REACTIONS OF ORGANIC SULPHUR-SULPHUR BONDS

A thesis presented for the degree of
Doctor of Philosophy in Chemistry
in the University of Canterbury,
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by

J.W. Mitchell

1971
Acknowledgements

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Abstract

Rates of cleavage reactions of substituted diaryl disulphides have been measured in 60% aqueous t-butanol at 30.0°C using cyanide ion, sulphite ion and hydroxide ion as nucleophiles.

Variation of substituents on the leaving group (thiophenoxide) gives results which correlate well with pK's of the appropriate thiophenoxides.

Variation of substituents on the aryl group attached to the sulphur atom where the nucleophilic substitution is taking place gives very unusual substituent effects. –R para groups have a decelerating effect and +R para groups an accelerating effect on the rate of the reaction, even though the Hammett p (measured from the meta points) is positive. An explanation of these effects, involving participation of the d orbitals of the sulphur atom during a nucleophilic substitution, has been given.
INTRODUCTION

Organic molecules containing a sulphur-sulphur bond are very widely distributed in nature, and reactions involving cleavage or formation of this bond are important in many biological processes.

Much research has recently been done on compounds in which one of the sulphur atoms has a valency of 4 or 6, namely thiolsulphinates (1), thiosulphonates (2), sulphynyl sulphones (3) and α-disulphones (4). Disulphides (5) are much more widely distributed in nature,

and this thesis describes a study of the chemistry of disulphides and, in particular, their reactions with nucleophilic reagents.
DISULPHIDES IN NATURE

Lipoic acid (6), in protein-bound form, has been recognized as a growth factor and a requirement for pyruvate oxidation by certain microorganisms.

The hormones insulin, vasopressin (diuretic) and oxytocin (lactogenic) are all believed to owe their activity, at least in part, to reactions of their disulphide groups, which occur as part of the cystine aminoacid residue (7).

The high proportion of cystine cross-links in proteins such as wool and hair is the reason for the hardness of these structures compared with other types of
protein. Cleavage and reformation of the cystine sulphur-sulphur bonds is the basis of the processes of permanent setting of hair and the pleating of wool fabrics. In the leather industry hair is removed from hides by use of a nucleophilic reagent to cleave the cystine sulphur-sulphur bonds, giving a product soluble in the alkaline medium used.

It is thought that irreversible denaturation of proteins such as serum albumin is a chain reaction initiated by a sulphydryl group involving formation of new sulphur-sulphur cross-links between protein chains.

Radiation damage to enzymes and other protein materials can occur through homolysis of their disulphide bonds. Sulphur compounds have been established as radiation protection agents.

CLEAVAGE OF THE SULPHUR-SULPHUR BOND

HOMOLYTIC CLEAVAGE

Disulphides are attacked by radical reagents (e.g. triphenylmethyl radical) according to the general equation 1.

\[
\text{RSSR} + R^+ \rightarrow \text{RSP}^+ + \text{RS}^- \tag{1}
\]

Sulphinyl sulphones decompose very readily in dioxan
at 50° via homolysis of the sulphur-sulphur bond, and disulphides, although less reactive, have been shown to dissociate according to equation 2 under photolytic conditions.

\[ \text{RSSR} \text{ by } 2\text{RS}^- \]  

Unsymmetrical diaryl disulphides have been shown to dissociate homolytically at 170° or in boiling dioxan to give symmetrical disulphides.

**ELECTROPHILIC CLEAVAGE**

Parker and Kharasch proposed a general mechanism for cleavages of the sulphur-sulphur bond by an electrophile involving formation of a sulphenium ion (equation 3).

\[ \text{RSSR} + \text{E}^+ \rightarrow \text{RSE} + \text{RS}^+ \]  

More recently it has been shown that many reactions previously thought to proceed by equation 3 may in fact be nucleophilic substitutions assisted by an electrophile. Addition of an electrophilic reagent to one sulphur atom creates an excellent potential leaving group and enables the sulphur-sulphur bond to be cleaved by a relatively weak nucleophile. For example, the isotopic exchange between thiophenol and diphenyl disulphide is specifically catalysed by HCl, HBr and HI, with relative catalytic effects of 1, 100, and 10,000. Reaction scheme 4 is a
possible mechanism.

$$RSSR + IX \rightarrow RSSR + X^- \quad + \quad RSSR + X^- \quad H$$

$$X^- \quad RS - SR \rightarrow RSX + RCH \quad H$$

**NUCLEOPHILIC CLEAVAGE**

For the purposes of the following discussion nucleophilic displacement is defined as replacement of a leaving group by a nucleophile. Nothing is implied about timing of the bond making and bond breaking steps. An $S_N^2$ displacement implies that bond making and breaking is a one step process. Formation of a metastable intermediate occurs when the nucleophile-sulphur bond is formed with no corresponding breakage of the sulphur-leaving group bond. This mechanism will involve two transition states (equation 5).

$$N: + Y-X \rightarrow N-Y-X \rightarrow N-Y-X$$

$$N-Y-X \rightarrow N-Y-X \rightarrow N-Y-X$$

Cleavage of the sulphur-sulphur bond by nucleophiles is complicated by the fact that many such reagents (notably hydroxide ion) are basic enough to initiate α- or β-elimination processes which may compete with or even exclude
the normal displacement reaction. In principle the mechanism involved could be characterised by the products of the reaction, but often the primary products undergo further reactions to make assignment of a mechanism less clear-cut.

In general it has been shown\textsuperscript{13} that dialkyl disulphides will react with hydroxide ion via a displacement reaction unless

(a) there is a negatively charged group in the molecule close to the disulphide bond,
(b) attack via displacement is sterically hindered, or
(c) protons $\alpha$ or $\beta$ to the disulphide bond are especially labile.

(A) $\alpha$-ELIMINATION

There is ample evidence\textsuperscript{14} to show that protons $\alpha$ to a divalent sulphur atom are appreciably acidic. Initial loss of such hydrogens in the reaction of disulphides with hydroxide would favour an elimination process (equation 6). This is the probable mode of decomposition of dithiodiacetic acid (8), 2,2'-dithiodipropionic acid\textsuperscript{13} (9) and dibenzyl disulphide\textsuperscript{15}.

\begin{align*}
RCH_2SSR & \quad \text{OH}^- \quad \text{R} - \text{CH} - S - \text{SR} \rightarrow \text{R} - \text{CH} = S + \text{RS}^- \\
R - \text{CH} = S & \quad \text{OH}^- \quad \text{R} - \text{CH} = O + S^2^-(6)
\end{align*}
A more detailed study has shown, as expected, that electron-withdrawing substituents X (equation 7) increase the amount of α-elimination products relative to displacement products.

\[
\begin{align*}
(x - &\text{O})_2 \underset{\text{CH-S-S}}{\text{CH-S-S}} \underset{\text{Y}^{\text{iPrONa/iPrOH}}}{\text{Y}} \\
(\text{X} - &\text{O})_2 \underset{\text{C=S}}{\text{C=S}} + \underset{\text{Y}}{\text{Y}} \quad (7)
\end{align*}
\]

(B) **β-ELIMINATION**

Although cystine reacts with hydroxide ion by a displacement mechanism, there is evidence that in a protein, where loss of a proton β to the disulphide bond is more favourable, alkaline decomposition occurs through a β-elimination process (equation 8).
Such a mechanism accounts for the formation of lanthionine (10) and lysinoalanine (11) in the alkaline hydrolysis of cystine-containing proteins. A careful analysis for these two amino acids led Miro and Garcia-Dominguez to postulate

\[
\begin{align*}
\text{HC} & \text{ CH} \text{ S} \text{ SR} \quad \text{OH}^- \\
\text{CH} & \text{ CH} \quad \text{S} \quad \text{SR}
\end{align*}
\]

(8)

\[
\text{C} = \text{CH}_2 + -S - \text{SR}
\]

a variety of mechanisms for cleavage of the S-S bond in the cystine residue: $\beta$-elimination for hydroxide ion attack, $S_N2$ for cyanide, and a mixture of the two mechanisms for sulphide.

(C) **NUCLEOPHILIC DISPLACEMENT**

Displacement is the most common type of reaction of nucleophiles with divalent sulphur compounds. In this reaction the nucleophile displaces a group which has less affinity for sulphur (or is less 'S-nucleophilic').

\[
Y^- + \text{RSX} \rightarrow \text{RSY} + X^-
\]
Edwards and Pearson\textsuperscript{20} have discussed the factors determining the relative reactivities of nucleophiles towards different substrates. A substrate shows a certain susceptibility to both the basicity and polarisability of the nucleophile. A large amount of rate data is correlated by equation \textsuperscript{9}\textsuperscript{21}, where \( k/k_0 \) is the rate relative to that obtained with water as a nucleophile, \( P \) is a polarisability term, \( H \) is a basicity term, with \( \alpha \) and \( \beta \) being determined by experiment for each substrate. Polarisability rather than basicity appears to be most important for substitutions at divalent sulphur, as is evident from the following order of reactivity given by Parker and Kharasch\textsuperscript{11}.

\[
\begin{align*}
R_2C^- > AlH_4^- > PO(OH)_2^- > P(OR)_3, RAsO(OH)^- > R_3N > \\
RCH_2S^- > R_2P, R_2As > C_6H_5S^-, CN^- > SO_3^-> OH^- > \\
RSO_2^- > SCN^- > Br^- > Cl^- 
\end{align*}
\]

This order is understandable since, when a nucleophile attacks divalent sulphur - an atom with outer orbitals projecting some distance from the nucleus - polarisation of the nucleophile's bonding electrons can occur in the nucleophile-S direction, while the non-bonding electrons on the nucleophile can be polarised in the direction away from
the sulphur atom. These two factors permit closer approach of nucleophile and sulphur atom by reducing Pauli exclusion repulsion effects.20

In the case of cleavage of a disulphide bond, the nucleophile may attack at either of the two sulphur atoms. If the disulphide is unsymmetrical, attack at these positions will lead to different products:

\[ \text{R-S-S-R} + \text{N}^- \rightarrow \text{R-N + R'S}^- \quad (10) \]
\[ \text{R-S-S-R} + \text{N}^- \rightarrow \text{R'SN + RS}^- \quad (11) \]

Formation of the more stable (less basic) mercaptide is favoured,22 but steric effects are also important.23 Hiskey and Harpp24 have shown that in the presence of an efficient mercaptide scavenger cleavage at the more positively polarised sulphur atom (i.e., to give the less stable mercaptide) is favoured. This is explained by the fact that the reactions are readily reversible. Formation of the more stable products soon predominates over formation of the kinetically more favourable products.

Fava and coworkers have established25-27 that the steric requirements for substitution at divalent sulphur closely parallel those for \( \text{S_N}_2 \) substitution at carbon. They cite this as evidence that displacement reactions at sulphur proceed with nucleophile, sulphur atom and leaving
group in a linear configuration (12).

\[
\begin{align*}
R & \\
\mid & \\
\text{Nu} & \text{---} \text{S} & \text{---} \text{L}
\end{align*}
\]

Pryor and Smith\textsuperscript{28} have warned against attaching too much mechanistic significance to this similarity in rate profiles, but it is generally accepted that attack by a nucleophile occurs at the back side of the sulphur atom. In all the ionic substitution reactions where stereochemistry has been investigated, the central sulphur undergoes a net inversion\textsuperscript{28}.

There are two possible mechanisms for the displacement reaction at sulphur.

(a) $S_N^2$

If only the sulphur $3s$ and $3p$ orbitals are involved in the transition state the situation is the same as for $S_N^2$ substitutions at carbon, i.e. because there are no vacant, easily accessible orbitals on the carbon the entering and leaving group utilise the same $p$ orbital and are therefore as collinear as possible with the reaction centre. In such a case bond making and breaking must be synchronous to some extent. Any buildup of charge on the reaction site in
the transition state will be small, its value and sign being dependent on the timing of the bond making and breaking processes.

(b) **Intermediate formation**

Formation of dsp³ hybrid orbitals on the sulphur atom would result in a trigonal bipyramidal intermediate (13) with the central sulphur atom bearing an appreciable quantity (up to one unit) of negative charge.

\[
\begin{array}{c}
R \\
\text{Nu} \rightarrow \text{S} \rightarrow \text{L}
\end{array}
\]

In such a structure, more electronegative substituent groups will tend to form bonds with orbitals of lowest s character. Since the entering and leaving groups are usually the most electronegative, they will form axial (pd) bonds, while the two lone pairs and the organic moiety will occupy the equatorial (sp²) positions. ClF₃, SF₄ and PCl₅ are among the stable molecules isoelectronic with this type of intermediate.
Arguments for and against intermediate formation

Most of the data available for nucleophilic substitutions at sulphur can be explained in terms of an $S_N^2$ mechanism, but analogy with the other second-row elements silicon and phosphorus, where such intermediate formation is generally accepted $^{30,31}$, and the exceptionally high rates of nucleophilic substitutions at sulphur compared with oxygen or carbon $^{32}$ have made an intermediate an attractive proposal.

Ciuffarin and Fava $^{12}$ have argued that the similarity of steric requirements for substitution at carbon and sulphur is evidence that d-orbitals are not involved in the transition state, as a transition state involving d-orbitals need not be linear (nucleophile or leaving group could occupy an equatorial position in (13)). For example, 1-silabicyclo-[2,2,2]-octyl chloride (14) has been found to react with hydride ion at the same rate as the open-chain compound.

Since backside attack is impossible at the bridgehead position, an intermediate involving a hydride-silicon-
chloride angle of about 90° has been postulated. The analogous carbon compound is extremely unreactive towards nucleophiles.

Several investigations using Hammett or similar correlations have been made to determine the extent of charge buildup on the sulphur atom in the transition states of displacement reactions. The exchange of labelled sulphite with phenyl and benzyl thiosulphates in water (equation 12) has been studied\textsuperscript{12} and Hammett $\rho$ values of

$$R - S - SO_3^- + SO_3^- \rightarrow R - S - SO_3^- + SO_3^- $$ (12)

+0.85 and +0.58 respectively were determined. These small positive values indicate a very small buildup of negative charge on the reaction site in the transition state.

Brown and Hogg\textsuperscript{33}, working on alkaline hydrolysis of sulphenic esters (equation 13) and Kice and Anderson\textsuperscript{34}, working on cyanide cleavage of aryl thiosulphates (equation 14) found even smaller variations in rate with changes of

$$X - \overset{\text{O}}{\overset{\text{O}}{\overset{\text{NO}_2}{\overset{\text{SO}}{\text{R}}}}} + \text{OH}^- \rightarrow [X - \overset{\text{O}}{\overset{\text{O}}{\overset{\text{NO}_2}{\overset{\text{SO}}{\text{H}}}}}] + \text{OR}^- $$ (13)

Further decomposition

$$X - \overset{\text{O}}{\overset{\text{O}}{\overset{\text{S}}{\overset{\text{SO}_3^-}{\text{R}}}}} + \text{CN}^- \rightarrow X - \overset{\text{O}}{\overset{\text{O}}{\overset{\text{SCN}}{\text{R}}}} + \text{SO}_3^- $$ (14)
substituents on the aromatic ring - the rate constants they obtained varied randomly with the substituent used. It has been suggested\(^{12}\) that the negative charge residing on the sulphur atom of an intermediate such as (13) would not need to be dispersed by electron-withdrawing groups in the organic moiety, since it is easily accommodated by a low-lying d orbital. However, p values for substitution in similar systems at silicon are uniformly high\(^{30}\), ranging from +2.70 (alkaline methanolysis of \( \text{R}_3\text{SiOMen} \)) to +4.30 (alkaline ethanolysis of \( \text{R}_2\text{SiH} \)). (\( \text{R}_2 = \alpha\text{-napthylphenylmethyl}, \text{Men} = \text{menthyl} \)).

A study of the reaction of various oxygen nucleophiles with phenyl trimethylphenylsulphenate esters (equation 15) led Senatore, Giuffarina and Pava\(^{35}\) to conclude that an \( \text{S}_\text{N}2 \)

\[
\text{RO}^- + \text{R}_3\text{CSOR}^! \rightarrow \text{R}_2\text{CSOR} + \text{R'O}^- 
\]

(15)

type of mechanism operated. Bronsted coefficients (i.e. slope of a plot of log \( k \) versus \( pK_a \)) for entering and leaving groups were found to be +0.25 and -0.97 respectively. These figures appear to indicate a fairly substantial positive charge on the reaction centre in the transition state. Such a picture is certainly not typical for substitutions at sulphur and the authors suggested that several factors, the most important being the bulk of the triphenylmethyl group, are responsible for the predominance
of bond-breaking over bond-making in the transition state in this particular case.

From this evidence the best conditions for formation of an intermediate would appear to be a good nucleophile, a poor leaving group and a highly electronegative and unhindered reaction centre. Some of these conditions are met in the following two cases in which pentacoordinate intermediates have been proposed.

Firstly, the mechanistic scheme below, involving two equilibrating intermediates, has been suggested to explain the reaction products of alkyllithiums with sulphonium salts.\(^{36}\)

\[
\begin{align*}
\text{Ph}_3S^+ + \text{PhLi} & \quad \rightleftharpoons \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \\
\text{Ph}_3S^+ + \text{RLi} & \quad \rightleftharpoons \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \\
\text{RPh} + \text{PhSPh} + \text{PhPh} + \text{RSPh}
\end{align*}
\]
Secondly, the presence of either a pentacoordinate intermediate (15) or an ion-pair intermediate (16) has been proposed to explain the kinetics of the reaction of amines with sulphenyl chlorides (equation 16). The chlorine atom in (15) is reluctant to leave as chloride until a proton is removed from the nitrogen atom.

\[
2RNH_2 + R'SCl \rightarrow RNHER' + RNH_2Cl
\]  

(16)

The purpose of the work described in this thesis was to investigate the mechanism of nucleophilic displacements at sulphur, in particular cleavage of disulphide bonds. Substituent effects have been studied with several series of aromatic disulphides, using three nucleophiles, to obtain information about charge distribution in the transition state for the reaction with emphasis on the possibility of the presence of an intermediate.
# RESULTS

Cleavage of Symmetrical Disulphides with Cyanide Ion

## Table 1

<table>
<thead>
<tr>
<th>Substituent</th>
<th>λ (nm)*</th>
<th>$10^2 k \text{ (l mole}^{-1} \text{sec}^{-1})$</th>
<th>log $k/k_0$</th>
</tr>
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<tbody>
<tr>
<td>p-NMe$_2$</td>
<td>275</td>
<td>2.70</td>
<td>-0.985</td>
</tr>
<tr>
<td>p-NH$_2$</td>
<td>265</td>
<td>2.06</td>
<td>-1.104</td>
</tr>
<tr>
<td>m-NH$_2$</td>
<td>269</td>
<td>6.52</td>
<td>-0.603</td>
</tr>
<tr>
<td>p-MeO</td>
<td>270</td>
<td>9.85</td>
<td>-0.425</td>
</tr>
<tr>
<td>m-CH$_3$</td>
<td>270</td>
<td>14.6</td>
<td>-0.253</td>
</tr>
<tr>
<td>p-CH$_3$</td>
<td>270</td>
<td>15.9</td>
<td>-0.217</td>
</tr>
<tr>
<td>H</td>
<td>270</td>
<td>26.2</td>
<td>0</td>
</tr>
<tr>
<td>p-F</td>
<td>265</td>
<td>384</td>
<td>1.167</td>
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<tr>
<td>p-Cl</td>
<td>277</td>
<td>565</td>
<td>1.334</td>
</tr>
<tr>
<td>p-Br</td>
<td>278</td>
<td>587</td>
<td>1.351</td>
</tr>
<tr>
<td>m-Cl</td>
<td>277</td>
<td>875</td>
<td>1.525</td>
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<tr>
<td>m-Br</td>
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<tr>
<td>m-COCH$_3$</td>
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<td>p-COCH$_3$</td>
<td>358</td>
<td>1230</td>
<td>1.672</td>
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<tr>
<td>p-CN</td>
<td>328</td>
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<td></td>
</tr>
<tr>
<td>m-NO$_2$</td>
<td>403</td>
<td>Too fast to measure</td>
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</tr>
<tr>
<td>p-NO$_2$</td>
<td>435</td>
<td></td>
<td></td>
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</tbody>
</table>

*Wavelength at which reaction was monitored.*
Cleavage of Substituted Phenyl-\(p\)-aminophenyl Disulphides with Cyanide Ion

Table 2

<table>
<thead>
<tr>
<th>Substituent</th>
<th>(\lambda)(nm)</th>
<th>(10^2k) (M(^{-1})sec(^{-1}))</th>
<th>log (k/k_0)</th>
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</thead>
<tbody>
<tr>
<td>(p)-NH(_2)(x0.5)</td>
<td>265</td>
<td>1.03</td>
<td>-0.773</td>
</tr>
<tr>
<td>(m)-CH(_3)</td>
<td>270</td>
<td>4.17</td>
<td>-0.165</td>
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<tr>
<td>(m)</td>
<td>270</td>
<td>6.10</td>
<td>0</td>
</tr>
<tr>
<td>(m)-Br</td>
<td>278</td>
<td>28.3</td>
<td>0.667</td>
</tr>
<tr>
<td>(p)-Br</td>
<td>278</td>
<td>29.0</td>
<td>0.677</td>
</tr>
<tr>
<td>(p)-NO(_2)</td>
<td>435</td>
<td>659</td>
<td>2.034</td>
</tr>
</tbody>
</table>
Cleavage of Substituted Phenyl-p-acetylphenyl Disulphides with Cyanide Ion

Tables 3, 4 and 5 contain rate constants for total decomposition ($k_T$) and corrected values for decomposition leading to formation of the less basic thiophenoxide ($k$).

Table 3

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$\lambda$ (nm)</th>
<th>$k_T$ (l.mole$^{-1}$sec$^{-1}$)</th>
<th>$k$</th>
<th>$\log k/k_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$m$-NH$_2$</td>
<td>358</td>
<td>1.10</td>
<td>1.02</td>
<td>-0.332</td>
</tr>
<tr>
<td>$m$-CH$_3$</td>
<td>358</td>
<td>1.79</td>
<td>1.66</td>
<td>-0.121</td>
</tr>
<tr>
<td>$p$-OCH$_3$</td>
<td>358</td>
<td>2.44</td>
<td>2.32</td>
<td>0.025</td>
</tr>
<tr>
<td>H</td>
<td>358</td>
<td>2.36</td>
<td>2.19</td>
<td>0</td>
</tr>
<tr>
<td>$m$-Br</td>
<td>358</td>
<td>12.37</td>
<td>8.91</td>
<td>0.609</td>
</tr>
<tr>
<td>$p$-Br</td>
<td>358</td>
<td>11.95</td>
<td>9.75</td>
<td>0.648</td>
</tr>
<tr>
<td>$p$-COCH$_3$</td>
<td>358</td>
<td>12.30</td>
<td>6.15</td>
<td>0.448</td>
</tr>
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</table>
Cleavage of Substituted Phenyl-\( \text{p-} \)nitrophenyl Disulphides with Hydroxide Ion

**Table 4**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>( \lambda ) (nm)</th>
<th>( 10^2 k_T (\text{mole}^{-1}\text{sec}^{-1}) )</th>
<th>( k )</th>
<th>( \log k/k_0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-( \text{NH}_2 )</td>
<td>435</td>
<td>1.285</td>
<td>1.285</td>
<td>-0.436</td>
</tr>
<tr>
<td>m-( \text{NH}_2 )</td>
<td>435</td>
<td>2.00</td>
<td>1.955</td>
<td>-0.273</td>
</tr>
<tr>
<td>m-( \text{CH}_3 )</td>
<td>435</td>
<td>2.65</td>
<td>2.33</td>
<td>-0.198</td>
</tr>
<tr>
<td>p-( \text{OCH}_3 )</td>
<td>435</td>
<td>3.48</td>
<td>3.48</td>
<td>0.023</td>
</tr>
<tr>
<td>H</td>
<td>435</td>
<td>4.32</td>
<td>3.67</td>
<td>0</td>
</tr>
<tr>
<td>p-( \text{Br} )</td>
<td>435</td>
<td>25.2</td>
<td>21.6</td>
<td>0.769</td>
</tr>
<tr>
<td>m-( \text{Br} )</td>
<td>435</td>
<td>28.5</td>
<td>19.1</td>
<td>0.716</td>
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<tr>
<td>p-( \text{COCH}_3 )</td>
<td>435</td>
<td>37.7</td>
<td>24.4</td>
<td>0.822</td>
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<tr>
<td>p-( \text{NO}_2 )</td>
<td>435</td>
<td>93.8</td>
<td>46.9</td>
<td>1.106</td>
</tr>
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</table>
Cleavage of Substituted Phenyl-p-acetylphe... with Sulphite Ion

Table 5

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$\lambda$(nm)</th>
<th>$k_T$ (l. mole$^{-1}$ sec$^{-1}$)</th>
<th>$k$</th>
<th>log $k/k_0$</th>
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<tr>
<td>$m$-$\text{NH}_2$</td>
<td>358</td>
<td>1.62</td>
<td>1.43</td>
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<tr>
<td>$m$-$\text{CH}_3$</td>
<td>358</td>
<td>1.21</td>
<td>0.972</td>
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<td>$H$</td>
<td>358</td>
<td>2.36</td>
<td>1.885</td>
<td>0</td>
</tr>
<tr>
<td>$p$-$\text{CH}_3$O</td>
<td>358</td>
<td>2.27</td>
<td>2.20</td>
<td>0.067</td>
</tr>
<tr>
<td>$m$-$\text{Br}$</td>
<td>358</td>
<td>6.17</td>
<td>3.46</td>
<td>0.263</td>
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<td>$p$-$\text{Br}$</td>
<td>358</td>
<td>5.35</td>
<td>3.59</td>
<td>0.279</td>
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<td>$p$-$\text{COCH}_3$</td>
<td>358</td>
<td>7.44</td>
<td>3.72</td>
<td>0.294</td>
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</table>
**Selectivity of Nucleophilic Cleavage**

The extent (given as a percentage) to which the more electron-withdrawing portion of the disulphide is ejected as thiophenoxide is reported for results in tables 3, 4 and 5.

**Table 6**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Table 3 (CN⁻ cleavage)</th>
<th>Table 4 (OH⁻)</th>
<th>Table 5 (SO₃⁻)</th>
</tr>
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<tr>
<td>p-NH₂</td>
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<td>100</td>
<td></td>
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<tr>
<td>m-NH₂</td>
<td>92.6</td>
<td>97.3</td>
<td>88.4</td>
</tr>
<tr>
<td>m-CH₃</td>
<td>93.0</td>
<td>88.0</td>
<td>80.6</td>
</tr>
<tr>
<td>p-OCH₃</td>
<td>95.3</td>
<td>100</td>
<td>97.0</td>
</tr>
<tr>
<td>H</td>
<td>93.0</td>
<td>84.7</td>
<td>80.1</td>
</tr>
<tr>
<td>p-Br</td>
<td>81.5</td>
<td>85.8</td>
<td>67.4</td>
</tr>
<tr>
<td>m-Br</td>
<td>72.0</td>
<td>67.0</td>
<td>56.4</td>
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<tr>
<td>p-COCH₃</td>
<td>50.0</td>
<td>64.7</td>
<td>50.0</td>
</tr>
<tr>
<td>p-NO₂</td>
<td></td>
<td>50.0</td>
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</tr>
</tbody>
</table>
DISCUSSION

Section 1

Cleavage of Symmetrical Disulphides with Cyanide Ion

A series of symmetrical diaryl disulphides was synthesised. Reaction rates of these compounds with cyanide ion (equation 17) were measured spectrophotometrically at the $\lambda_{\text{max}}$ of the thiophenoxide formed in 60% aqueous t-butanol containing 0.01M borax buffer at 30.0°C.

\[ R'\bigcdot O\bigcdot S\bigcdot S\bigcdot O\bigcdot R + \text{CN}^- \rightarrow R'\bigcdot O\bigcdot SCN + O\bigcdot S\bigcdot R^- \quad (17) \]

The reaction was first order in cyanide and disulphide and was studied using a large excess of cyanide to give pseudo first order conditions. Second order rate constants are reported in table 1.

Throughout this discussion the Hammett substituent constants used will mainly be the $\sigma^0$ constants first proposed by Taft$^{37}$. These constants are based on equilibria and reactions such as hydrolysis of phenylacetic esters where the reaction site is insulated by one or more CH$_2$ groups from direct resonance interaction with substituents on the aromatic ring. The $\sigma^0$ constants are useful in correlating reactions in which the resonance and inductive effects of substituents have the same relative importance.
Fig. 1

\[
\text{Reaction: } \text{R-S-S-R} + \text{CN}^- \rightarrow \text{R-S-SCN} + \text{R-S}^-
\]
in the ground state as in the transition state. They are the best available to illustrate the concept, to be introduced in later sections, of the resonance effect of a substituent working, in part, counter to its inductive effect.

A plot of \( \log \frac{k}{k_0} \) for the disulphide cleavages versus \( \sigma^0 \) is shown in Fig. 1. The meta points are correlated well by a straight line (correlation coefficient \( r = 0.994 \)) and the \( p \) value of this meta line is 4.18. The para points are more scattered, but a pattern does emerge. All the +R para points except para-methoxy lie above the line (i.e. they react faster than a \( p\sigma^0 \) relation predicts) and the only point below the meta line is p-acetyl, the only -R group in the series. This pattern of substituent effects is most unusual, but cannot be interpreted satisfactorily since it is made up of two separate components. The effects on reaction rate of para substituents in the thiocyanate-forming aromatic ring and of para substituents in the thiophenoxide-forming aromatic ring may be very different, each requiring a different set of sigma values. Accordingly discussion of deviations of para points will be left to later sections of the work, which have been designed to measure the nature and relative importance of these two components. This effect will be much less obvious in the case of meta substituents, since the variation between
different types of σ constant for a given meta substituent is usually very small. Thus, as long as the two component effects are independent (i.e., the ρ value for one component is not altered by substituents associated with the other component) there should be a meta correlation with the ρ value equal to the sum of the component ρ values.

The large positive ρ value (4.18) indicates a strong demand for stabilisation of negative charge in the transition state. Danehy and Parameswaran\(^3\) obtained a large substituent effect for the cleavage of diaryl disulphides with alkali, but their results could not be correlated quantitatively. An interesting comparison can be made for the same reaction at hexavalent sulphur. Conway\(^3\) has reacted diaryl α-disulphones with alkali (equation 18) and obtained a ρ value of 1.23. In this system the four electron-withdrawing oxygen atoms can stabilise the transition state

\[
\text{Ar} - \text{S} - \text{S} - \text{Ar} + \text{OH}^- \rightarrow \text{ArSO}_2^- + \text{ArSO}_2^- \tag{18}
\]

and the effect of changing the aryl substituents on the rate of reaction is relatively small.
Section 2

Cleavage of Substituted Phenyl-\(\text{p}\)-aminophenyl Disulphides with Cyanide Ion

A series of substituted phenyl-\(\text{p}\)-aminophenyl disulphides was synthesised. Reaction rates of these compounds with cyanide ion (equation 19) were measured under the same conditions used in Section 1.

\[
R\begin{array}{c}
\text{O}-\text{S}-\text{S}-\text{O} \\
\end{array}\begin{array}{c}
\text{NH}_2 + \text{CN}^- \rightarrow R\begin{array}{c}
\text{O}-\text{S}^- \\
\end{array}\begin{array}{c}
\text{NH}_2 \text{O} \\
\end{array}\text{SCN}
\end{array}
\]

(19)

Products resulting from cleavage at the other sulphur atom could not be detected. Second order rate constants are given in Table 2.

The small number of points used in this rate correlation and in the following sections using unsymmetrical disulphides is mainly a consequence of synthetic difficulties. Many of the unsymmetrical compounds, especially \(m\)-substituted ones, were oils and were very difficult to purify. In addition, two compounds showed inexplicable kinetic behaviour. The reaction of both \(m\)- and \(p\)-acetylphenyl \(p\)-aminophenyl disulphides with cyanide ion was shown to be first order in cyanide and second order in disulphide. An investigation of the reaction of the \(m\)-acetyl compound
\[
\text{H}_2\text{N}\text{C}_6\text{H}_4\text{S}-\text{S}^\text{R} + \text{CN}^- \rightarrow \text{H}_2\text{N}\text{C}_6\text{H}_4\text{SCN} + \text{R}_2\text{S}^-
\]

**Fig. 2**

\[
\log \frac{k}{k_0} \quad 2.4
\]

- **p-NO_2**
- **m-Br**
- **H**
- **m-Me**

**Fig. 3**

\[
\log \frac{k}{k_0} \quad 2.4
\]

- **p-NO_2**
- **m-Br**
- **H**
- **m-CH_3**

\[pK (\text{thiophenol})\]
showed that no products apart from the expected ones (p-aminophenylthiocyanate and m-acetylthiophenoxide) were formed. Cleavage with sulphite gave the normal pseudo first order kinetics. Replacement of the p-NH₂ group with a p-NMe₂ group removed the deviation - m-acetylphenyl-p-dimethylaminophenyl disulphide gave normal pseudo first order kinetics. Despite these difficulties the selection of points is still better than that used in any other study of the electronic requirements for substitution at sulphur. All such studies have been done with a small number of para points and no meta points.

The kinetic results are shown in Fig. 2 plotted against σ¹ values. The results include only two meta points and the H point with which to calculate a meta line. The p-nitro point is well off the meta line if a σ¹ value is used, so it appears probable that some -R resonance interaction occurs in this system. If σ values corresponding to this type of resonance interaction were available the ρ value could be calculated from all six points and not just three.

In Fig. 3 the kinetic results are plotted against the pK's of the appropriate thiophenols⁺⁴⁰. There is a good straight line correlation (r = 0.995) as might be expected from the structural similarity of the two systems. Breaking
an S-S rather than an S-H bond should not significantly alter the ability of the thiophenoxide-forming sulphur atom to participate in direct resonance interaction with aromatic substituent groups in the transition state. It is thus reasonable that the behaviour of the substituents in each system should be described by the same σ values.

Yukawa and Tsuno\textsuperscript{41} used equation 20 to correlate substituent effects for reactions in which direct resonance interaction is possible between substituent and reaction site. The quantity Δσ is either σ\textsuperscript{+}-σ or σ\textsuperscript{-}-σ, depending on the type of reaction, while r is constant for a given reaction, and is a measure of the extent of direct resonance interaction in the transition state. More recently\textsuperscript{42} they have suggested that r is a more meaningful measure of the extent of direct resonance interaction if σ\textsuperscript{0} values are used instead of σ values. The dissociation constants of substituted thiophenols (48% ethanol, 25°C) are very well correlated with equation 21\textsuperscript{42}.

\[
\log \frac{k}{k_0} = \rho(\sigma + r\Delta\sigma)
\]  

\[
pK - pK_0 = 2.56 (\sigma^0 + 0.52(\sigma^- - \sigma^0))
\]  

Accordingly, the only -R group for this set of kinetic results, p-nitro, has been given a σ value of
$\sigma^0 + 0.52(\sigma^- - \sigma^0) = 1.04$. A good straight line through all the points is then obtained with $\rho = 1.97$ and correlation coefficient $r = 0.996$. This $\rho$ value (the result of variation of the leaving group in the substitution reaction) shows that the leaving group has a considerable effect on the reaction rate, i.e. electron-withdrawing substituents have stabilised a substantial buildup of negative charge on the sulphur atom of the leaving group. The $\rho$ value is smaller than that obtained for $pK$'s of thiophenols (especially considering that using 60% $t$-butanol rather than the more polar 48% ethanol would tend to enhance the substituent effects slightly) indicating that the S-H bond is broken to a slightly greater extent than the S-S bond in the respective transition states for thiol dissociation and nucleophilic cleavage of disulphides.

Oae and coworkers\(^\text{43}\) obtained similar results when they changed the leaving group in the alkaline hydrolysis of aryl benzenethioisulphinates (equation 20), although only four substituents ($p$-CH$_3$, $p$-OCH$_3$, H and $p$-Cl) were used. They obtained a $\rho$ value of 2.1.

The fact that the S-S bond is appreciably broken in the transition state for these reactions eliminates the
possibility of a mechanism involving rate-determining formation of an intermediate (such as occurs in electrophilic aromatic substitution). In such a case there would not be a large effect on changing the leaving group.
$R\cdot-S\cdot-S\cdot-O\cdot-Ac + CN^- \rightarrow R\cdot-SCN + O\cdot-Ac\cdot-S\cdot$

Fig. 4

log $\frac{k_f}{k_0}$

-0.4 0 0.2 0.4 0.6

$\sigma^0$

p-Br ○ m-Br ○ p-Ac ○

p-MeO ○ m-Me ○ m-NH₂ ○ H

Fig. 5

log $\frac{k}{k_0}$

-0.4 0 0.2 0.4 0.6

$\sigma^0$

p-Br ○ m-Br ○ p-Ac ○

p-MeO ○ m-Me ○ m-NH₂ ○ H
Section 3

Cleavage of Substituted Phenyl-p-acetylphenyl Disulphides with Cyanide Ion

A series of substituted phenyl-p-acetylphenyl disulphides was synthesised. Rate constants for their reaction with cyanide ion (equation 21) were obtained as before.

\[
\begin{align*}
\text{R} & \text{S-S-O} & \text{COCH}_3 & \text{CN}^- & \text{R} & \text{S-S-SCN} & \text{+ S-O-COCH}_3 \\
\end{align*}
\]

(21)

In this reaction, products resulting from attack at the other sulphur atom (substituted thiophenoxide and p-acetylphenylthiocyanate) were detected. The method used for calculating rate constants gave the total rate of decomposition of disulphide (see Experimental) and product analysis, using u.v. extinction coefficients, enabled rate constants for equation 21 to be calculated. Both the total rate and corrected rate are reported in Table 3, and plots of log \( k/k_0 \) for each against \( \sigma^0 \) are shown in Figs 4 and 5.

The three meta points and the rate for the unsubstituted compound (Fig. 5) are well correlated with \( \sigma^0 \) values (\( r = 0.997 \)) and the \( \rho \) value for the line derived from these points is 1.70. Thus it appears that \( \rho \) values obtained from variation of substituents in one ring of the diphenyl disulphide/cyanide system are not influenced greatly by
substituents in the other ring, since the sum of the $\rho_{\text{meta}}$ values obtained from sections 2 and 3 (3.67) is close to that obtained for the reaction of the symmetrical compounds (section 1, $\rho = 4.18$).

The $\rho$ value of 1.70 obtained for the results in Fig. 4 indicates that a buildup of negative charge has taken place at the reaction site in the transition state. This is equally consistent with either an $S_N^2$ transition state with bond forming in advance of bond breaking (17) or a transition state for decomposition of an intermediate (18).

\[
\begin{array}{ccc}
\delta^- & \delta'^- & \delta''^- \\
\text{NC} & \text{S} & \text{SAr'} \\
\text{Ar} & & \\
\text{17} & & \\
\end{array}
\quad
\begin{array}{ccc}
\delta^- & \delta'^- \\
\text{NC} & \text{S} & \text{SAr'} \\
\text{Ar} & & \\
\text{18} & & \\
\end{array}
\]

$\delta^-, \delta'^-, \delta''$ etc. are different portions of negative charge - the overall charge on each structure is $-1$.

The substituent effects of the para points in Fig. 5 are very unusual - in fact to this writer's knowledge similar effects have been reported in the literature only once. The $+R$ groups, $p$-bromo and $p$-methoxy, follow the results obtained for the symmetrical compounds (Fig. 1) in that they lie above the meta line (i.e. react faster than a $\rho^0$ relation would predict). The only $-R$ group, $p$-acetyl,
lies below the line and has an apparent $\sigma$ value of only 0.27, which is much lower than any common values which have been reported. The fact that the point lies below the line by an increment of almost exactly 0.30 (log 2) can be no more than coincidence; the overall rate obtained for the symmetrical $p$-acetyl compound must be divided by two to correct for the availability of two reaction sites. Furthermore, the same effect is still apparent if $\log k/k_0$ for the total rate of reaction of disulphide is plotted against $\sigma^o$ (Fig. 4), showing that the unusual effects do not arise from the method used for correcting the rate constants.

The reaction, therefore, is accelerated by inductive electron withdrawal, as expected, but also by conjugative electron release. In addition, it is retarded by conjugative electron withdrawal, so that interaction between substituents and reaction site appears to have an effect on the reaction rate opposite to the inductive interaction. There are a few reaction systems where this effect has been observed for electron-donating substituents. The best known is the dissociation of substituted phenols, a system aided by electron-withdrawing substituents. A plot of $pK_a$ versus $\sigma^o$ shows that the $p$-amino and $p$-methoxy points lie above the line (i.e., the phenoxide ions for these two cases are more stable than expected) and this is explained in terms of a saturation effect. There is no direct
resonance interaction in either the phenol or phenoxide, but the high concentration of negative charge on the phenoxide oxygen atom makes the indirect resonance interaction (inductive transfer from the carbon atom para to the +R group) less important than it is in the phenol.

Rate data for the ethanolyisis of aryl isothiocyanates (equation 22) was published by Browne and Dyson in 1931. A plot of their results against $\sigma^0$ shows that $\rho$ is positive and $+R$ substituents again lie above the meta line. A possible explanation of this would be that a cyclic transition state (19) is stabilised to some extent by $+R$ groups. Buildup of negative charge on the sulphur atom by $+R$ resonance (20) could favour formation of the $S-H$ bond.

Substituent effects quite similar to those obtained in this work have been found in the nucleophilic cleavage of the aryl-silicon bond of aryltrimethylsilanes in $H_2O/DMSO$. A good meta line (large positive $\rho$) is obtained with $+R$ para points above it and $p$-nitro, the only $-R$ point, below the line. These results have been explained in terms of
electrophilic assistance by the solvent at the carbon atom of the breaking aryl-silicon bond. +R and -R para substituents respectively encourage and discourage this electrophilic assistance.

None of these explanations will satisfactorily account for the deviations of the para points obtained in this work (Fig. 5). The explanation offered here involves the assumption of d-orbital participation during these nucleophilic displacement reactions, and it attempts to rationalise the observed substituent effects in terms of the interaction of the substituent group with the 3d orbitals on the sulphur atom.

Although utilisation of d orbitals has long been used to explain the expansion of the valence shell of sulphur (and elements such as phosphorus, chlorine, bromine and iodine) there have been some serious objections. Firstly, calculations show that the free atom 3d orbitals in sulphur with a d^1 excited configuration, for example, are too large and diffuse to provide any significant contribution to molecular binding on overlap with bonding orbitals of another atom. Secondly, energies involved in promotion of an electron to a 3d orbital are large compared with the gain of energy on bond formation.
To overcome these objections, Craig, MacColl, Nyholm, Orgel and Sutton\textsuperscript{49} proposed a ligand field contraction theory. According to the theory the diffuse 3d atomic orbitals on sulphur contract under the influence of the field from electronegative ligands to dimensions which are favourable for overlap with the bonding orbitals of the ligands. In the case of $\text{SF}_6$, the promotion energy required to form the $d^{2}sp^{3}$ configuration has been shown to be adequately compensated for by the stability resulting from bond formation\textsuperscript{50}.

A consequence of the contraction of a loosely bound orbital is the increase of promotion energy into it from a more tightly bound orbital\textsuperscript{51}. It would appear, then, that in the diaryl disulphide/cyanide system, electron-withdrawing substituents on the aryl group attached to the reaction site would hinder d orbital participation during cyanide ion attack because of the extra promotion energy involved. Electron-donating substituents would expand the d orbital and reduce the promotion energy. From a pictorial point of view, one could imagine electron-withdrawing substituents contracting the d orbitals to a position where they are not quite as readily accessible to a nucleophile, and electron-donating substituents making the d orbitals more accessible. The only assumption involved here is that the d orbitals or diaryl disulphides are of suitable size and energy for
interaction to occur in the first place. This point, which could possibly be confirmed by theoretical calculations, cannot be verified from the results of this work.

It is therefore proposed that the observed substituent effects are a result of two opposing effects; electron-withdrawing substituents tend to disperse the buildup of negative charge on the central sulphur atom in the transition state, thereby accelerating the rate of reaction, but they also make the d orbitals less accessible by an orbital contraction effect, decelerating the rate of reaction. The fact that a straight line with positive $p$ value is obtained for the meta points indicates that for interaction between substituent and reaction site purely through $\sigma$ bonds the charge dispersal effect predominates over the d-orbital contraction effect. The deviations of para points from the meta line can be explained if the reverse holds for interaction through a $\pi$-bonding system, i.e.: the d-orbital contraction effect has more influence on the stability of the transition state than the charge dispersal effect.

This is represented diagrammatically in Fig. 6. The circles on the line represent meta points, X is a $+R$ group and Y a $-R$ group. If substituents $X$ and $Y$ had no resonance interaction with the reaction site, the situation would be the same as for meta substituents and they would lie on the meta
line, giving good correlation with $\sigma^0$ values (points x and y).

These points will be shifted off the line by the contribution to the reaction rate made by resonance interaction. Point y will have a decelerating contribution (A) from the d orbital contraction effect, and an accelerating contribution (B) from the charge dispersal effect. Point x will have an accelerating contribution (A') from the d orbital contraction effect, and a decelerating contribution (B') from the charge dispersal effect. To explain the
observed substituent effects A must be greater than B and
A' greater than B', i.e. the d orbital contraction effect
through π bonds must be greater than the charge dispersal
effect through π bonds.

Pauling\textsuperscript{52} has discussed the distribution of valence
electrons in disulphides and considers that the σ bond
joining the two sulphur atoms is nearly pure p in character,
with a lone pair of electrons on each sulphur in the 3s
orbitals, spherically distributed about the nucleus. The
remaining pair of electrons on each sulphur exists as 3p–π
electrons, with a dihedral angle of 90° between the
electron pairs (Fig. 7). This explains the C–S–S–C
dihedral angle of 90° in dialkyl disulphides\textsuperscript{53}, and the
barrier to internal rotation about the S–S bond of 10–14
kcal/mole.\textsuperscript{54}
The 3p electron pair appears to be ideally positioned for interaction with a π-electron system on the R group, but -R resonance interaction in the most favourable type of system (thiophenoxides) is not as extensive as in the corresponding oxygen compounds (phenoxides). It may well be, therefore, that in this less favourable system the sulphur 3p electrons are merely polarised under the influence of the aromatic π-electron system, rather than effectively delocalised. Such polarisation could lead to a significant change in size and shape of the d orbitals but little accompanying dispersal of charge from sulphur. The condition required for the π interaction, i.e. that the d orbital contraction effect is greater than the charge dispersal effect on the reaction rate, is then not unreasonable.

The number of points in the Hammett plot on which this theory is based is small, for reasons already outlined, but experimental errors are several orders of magnitude smaller than the deviations shown by the para points (see Experimental). To confirm the presence of these unusual substituent effects, a slightly different reaction system with a wider range of reactivities was studied and the results are discussed in the next section.
Section 4

Cleavage of Substituted Phenyl-p-nitrophenyl Disulphides with Hydroxide Ion

A series of substituted phenyl-p-nitrophenyl disulphides was synthesised. Most of these compounds reacted too quickly with cyanide ion for their rate constants to be measured, so the less reactive nucleophile, hydroxide ion, was used. Reaction rates were measured in 60% aqueous t-butanol at 30.0°C. The reaction forms thiophenoxide and, initially, sulphenic acid, which decomposes quickly to thiophenoxide and sulphinic acid (equation 23). Products resulting from attack at the other sulphur atom were obtained; rate constants for total reaction ($k_T$) and cleavage leading to formation of p-nitrothiophenoxide as primary product ($k$) are reported in Table 4. The corresponding graphs of log ($k/k_o$) versus $\sigma^0$ are shown in Figs 8 and 9.

\[ \text{RB-S-S-N}^2O_2^- + \text{OH}^- \xrightarrow{\text{slow}} \text{RB-SOH} + \text{S}^- \text{O-N}^2O_2^- \]

\[ \text{RB-S-O}_2^- + \frac{1}{2} \text{R-C-O}^- \]

(23)
\[
R^1S-S-R^2NO_2 + OH^- \rightarrow [R^1SOH] + O_2N-R^2S^-
\]
It can be seen that these results are very similar to those obtained for the cyanide ion cleavage of the p-acetyl series of disulphides. The meta points in Fig. 9 are well correlated by a straight line ($\rho = 1.89$, $r = 0.991$) while the para points deviate, following the same pattern as before. The $+R$ groups, (p-amino, p-methoxy and p-bromo) lie above the meta line, almost in a straight line of their own. The p-acetyl point is fractionally below the meta line, in contrast to its previous large deviation, but a large deviation is observed for the other $+R$ group, p-nitro. Again, if total reaction rate is plotted versus $\sigma^0$ (Fig. 8) the same deviations are observed. A fair correlation can be made with a line through all the points, shown in Fig. 9 ($\rho = 1.48$, $r = 0.961$), but treatment of the results in this way obscures the clear similarities between these and the previous results. In addition, it may be noted that for purposes of calculation of $\sigma$ values, while Jaffe$^55$ used sets of data with $r > 0.95$, van Bekkum, Verkade and Wepster$^44$ used only sets of data with $r > 0.98$.

The $\rho$ value of 1.89 obtained for the results in Fig. 9 is comparable with that obtained in two similar systems. Oae and coworkers$^{43,56}$ obtained a value of 2.1 for substitution by hydroxide at sulphenyl sulphur (equation 24) and 1.6 for substitution at sulphinyl sulphur (equation 25).
The number of points used for these Hammett plots was insufficient to show whether the pattern of substituent effects was the same as that observed in the work in this thesis.
\[
\text{Fig. 10}
\]

\[
\text{Fig. 11}
\]
Section 5

Cleavage of Substituted Phenyl-p-acetylphenyl Disulphides with Sulphite Ion

The series of disulphides used in Section 3 was reacted with sulphite ion in 60% aqueous t-butanol containing borax buffer at 30.0°C. An aryl thiosulphate and a thiophenoxide are formed (equation 26).

\[
\begin{align*}
R-S-S-O-COCH_3 + SO_3^- &\rightarrow R-S-SO_3^- + S-O-COCH_3 \\
\text{(26)}
\end{align*}
\]

Products resulting from attack at the other sulphur atom were obtained, and rate constants for total reaction \((k_T)\) and cleavage according to equation 26 \((k)\) are reported in Table 5. The corresponding graphs of \(\log k/k_0\) versus \(\sigma^0\) are shown in Figs 10 and 11. These results are rather difficult to interpret, as the meta points do not lie on a straight line. The same substituent effects as found with the other nucleophiles are observed if the \(m\)-methyl point is disregarded. This then gives a meta line through \(m\)-bromo, \(H\) and \(m\)-amino, with \(p\)-methoxy and \(p\)-bromo above the meta line and \(p\)-acetyl slightly below it, the \(\rho\) value being approximately 0.7. The value for \(m\)-methyl has been checked, however, and there is no valid reason for discarding it.
Figures for the relative amounts of cleavage in different directions (Table 6) show that this reaction is a little less specific (i.e. forms more of the minor products) than the cleavage using cyanide ion. This must mean that substituents in the leaving group have less opportunity to provide some stabilisation in the transition state, i.e. the S-S bond is not broken to as great an extent in the transition state for reaction with sulphite as it is with cyanide. Carrying this argument a step further, the O₃S-S bond cannot be formed to the same extent as the NC-S bond in their relative transition states, otherwise similar ρ values would be observed for the two reactions.
Conclusions

There was no way to kinetically distinguish between two different mechanisms for the substitution reaction at sulphur; namely, the $S_{N}^{2}$ process, and a process involving rate determining decomposition of an intermediate (equation 27).

\[
R - S - X + N^{-} \xrightarrow{K} N - S - X \xrightarrow{K} RSN + X^{-}
\]

(27)

The initial rate expression for equation 27 is given in equation 28.

\[
\text{In. Rate} = k K \frac{[RSX]_{0} [N]_{0}}{1 + [N]_{0} K}
\]

(28)

At a nucleophile concentration of $0.01 \text{M}$, the largest used in this work, $K$ would have to be about 10 for measurable deviations from second order kinetics. An equilibrium constant as large as this would mean that the intermediate should be detectable by physical methods. Ultraviolet spectra of reacting solutions, as far as could be ascertained, only contained absorptions attributable to disulphide and cleavage products.

Although the kinetic results are quite compatible with rate-determining decomposition of an intermediate (rate determining formation of an intermediate is ruled out
because of the considerable leaving group effect demonstrated in Section 2) it is unlikely that an intermediate utilising \( sp^2-dp \) hybrid orbitals and accommodating a full negative charge on the sulphur atom (13) is involved. The low \( \rho \) values obtained for nucleophilic substitutions at sulphur, in contrast to the high values obtained for similar processes at silicon, are particularly good evidence that complete participation of a \( d \) orbital to give an intermediate of type (13) does not occur. At the end of Section 5, it was proposed that the O\( _2 \)S-S bond is not completely formed in the transition state for the reaction of disulphides with sulphite ion. It therefore appears that the reaction is an \( S_N2 \) type of process with participation by \( d \) orbitals to stabilise any buildup of charge at the reaction centre. The structure of the transition state would lie somewhere between (20), where no \( d \) orbitals are involved, and (21), where complete \( dsp^3 \) hybrids have been formed. This transition state would be associated with an energy minimum (point \( X \)) in a reaction profile diagram
(Fig. 10), but this minimum would not be deep enough to give the intermediate species any degree of stability.

![Reaction Co-ordinate](image)

**Fig. 10**

It was mentioned in the introduction that buildup of negative charge on the reaction site, which would encourage d-orbital participation, would be favoured by good nucleophiles. The results of this work show that hydroxide, the least reactive nucleophile, is associated with the highest \( \rho \) value, indicating the largest buildup of negative charge. This is almost certainly due to the highly polarisable nature of sulphite and cyanide ions. An excess of charge on the central sulphur atom in the transition state of a
nucleophilic substitution could be partly accommodated on the "nucleophile end" of the transition state.

The unusual substituent effects observed in this work are considered to be real. The explanation offered for them cannot be tested by the small amount of relevant kinetic data at present in the literature\textsuperscript{12,33,34,56}, as such data consists of small selections of points using only \textit{para} substituents. Further work will be required to ascertain whether this type of effect is a general one for nucleophilic attack at divalent sulphur.
**Experimental**

All u.v. measurements were carried out on a Shimadzu MPS-50L spectrophotometer with an electronically thermostatted cell holder. Mass spectra were measured on an AEI MS-902, n.m.r. spectra on a Varian A-60, and infrared spectra on either a Shimadzu IR-27G or Perkin-Elmer 337. Infrared and n.m.r. spectra of all compounds prepared were consistent with assigned structures unless otherwise stated. Melting points are uncorrected. 'Sorbsil' silica was used for column chromatography. Thin layer chromatograms were developed with mixtures of petroleum ether (50°-70° fraction), benzene and chloroform, and were visualised with iodine vapour. New compounds are underlined at their first mention in the experimental section.
General Procedure for Kinetic Runs

The general equation for the reactions studied is

\[ \text{RSSR} + \text{Nu}^- \rightarrow \text{RSNu} + \text{R'S}^- \]  \hspace{1cm} (29)

The reaction was monitored by following the change in u.v. absorption with time at \( \lambda_{\text{max}} \) for \( \text{R'S}^- \). Use of sulphite and cyanide as nucleophiles was complicated by the equilibria

\[ \text{CN}^- + \text{H}_2\text{O} \rightarrow \text{HCN} + \text{OH}^- \]  \hspace{1cm} (30)

\[ \text{SO}_3^{2-} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{SO}_3^- + \text{OH}^- \]  \hspace{1cm} (31)

No attempts were made to measure the extent of these equilibria in 60% aqueous t-butanol but kinetics were measured in the presence of a buffer (0.01M borax) to ensure that the quantities \( \frac{[\text{CN}^-]}{[\text{HCN}]} \) and \( \frac{[\text{SO}_3^{2-}]}{[\text{H}_2\text{SO}_3^-]} \) were constants for all runs. In water

\[ \frac{[\text{CN}^-]}{[\text{HCN}]} \quad \text{and} \quad \frac{[\text{SO}_3^{2-}]}{[\text{H}_2\text{SO}_3^-]} \]

are about 0.7 and 100 respectively at the pH of the buffer (9.2) and it was assumed that in aqueous t-butanol solvent these ratios would still be such that the concentration of free nucleophile would be high enough to satisfy the
requirements of pseudo first order kinetics. Competition by hydroxide in the reactions of disulphides with cyanide and with sulphite can be ruled out; the kinetic results obtained in this work show that hydroxide ion reacts by a factor of about $10^3$ times slower than the other two nucleophiles.

The following procedure was followed in carrying out a kinetic run. An aqueous solution of nucleophile (2 ml), containing buffer in the case of sulphite and cyanide, was pipetted into a flask in a thermostat bath. To this was added a solution of the disulphide in $t$-butanol (3 ml). The resultant solution was swirled and transferred as quickly as possible to a thermostatted 1 cm silica cell, and measurement of absorbance commenced. Rate constants reported are the average of at least three runs.
Calculation of Rate Constants

All reactions were carried out under pseudo first order conditions, i.e.

\[ [\text{Nu}^-] \gg [10 \text{RSSR}'] \].

Use was made of the Guggenheim method\(^5^7\) for obtaining first order rate constants. This entailed plotting 
\[ \log (A_t + A_t - A_t) \] against \( t \), where \( A_t \) is the absorbance of the reacting solution at time \( t \) and \( A_t \) is any time interval greater than the half life of the reaction. The slope of the resultant straight line is 
\[ \frac{k_1}{k_1 [\text{Nu}^-]} \] 
where \( k_1 \) is the pseudo first order rate constant. \( \frac{k_1}{k_1 [\text{Nu}^-]} \) then gives a true second order rate constant.

Adjustment for Unsymmetrical Disulphides

A nucleophile can cleave an unsymmetrical disulphide in two ways, and the rate constant required here is that for cleavage in a given direction.

\[ \text{RSSR}^- + \text{N}^- \quad k_1 \quad \text{RGN} + \text{R'S}^- \quad (32) \]

\[ \text{RSSR}^- + \text{N}^- \quad k_2 \quad \text{R'SN} + \text{RS}^- \]

In all cases where cleavage in two directions was observed, one of the disulphide substituent groups was either \( p \)-nitro or \( p \)-acetyl. \( p \)-Nitrothiophenoxide and \( p \)-acetylthio­phenoxide absorb free from any interference from other
reaction products, at 435 and 353 nm respectively, and reactions were monitored at these wavelengths.

Consider the case where the reaction is being monitored at $\lambda_{\text{max}}$ for $R'S^-$. 

$$- \frac{d[R'S^-]}{dt} = k_1[RSSR'] + k_2[RSSR']$$

$$= k[RSSR'] \text{ where } k = k_1 + k_2$$

Integrating $[RSSR'] = [RSSR']_0 e^{-kt}$

$$\frac{d[R'S^-]}{dt} = k_1[RSSR']$$

$$= k_1[RSSR']_0 e^{-kt}$$

Integrating $[R'S^-]_t = [R'S^-]_0 + \frac{k_1}{k} [RSSR']_0 (1 - e^{-kt})$

$$[R'S^-]_{t+\Delta t} = [R'S^-]_0 + \frac{k_1}{k} [RSSR']_0 (1 - e^{-k(t+\Delta t)})$$

$$[R'S^-]_{t+\Delta t} - [R'S^-]_t = \frac{k_1}{k} [RSSR']_0 (e^{-kt} - e^{-k(t+\Delta t)})$$

$$= \frac{k_1}{k} [RSSR']_0 (1 - e^{-k\Delta t}) e^{-kt}$$

$$\log([R'S^-]_{t+\Delta t} - [R'S^-]_t) = -kt + \text{constant}.$$ 

As only $R'S^-$ absorbs at the analytical wavelength

$$[R'S^-]_t = E_t/\epsilon$$
where $\varepsilon$ is the extinction coefficient of $R'S^-$ and $E$ is the absorbance of the solution.

\[
\therefore \log (E_{t+\Delta t} - E_t) = -kt + \text{constant}'.
\]

Thus the rate constant measured by the Guggenheim plot is $k = k_1 + k_2$. The two rate constants can be obtained if the final product distribution is known.

\[
\frac{k_1}{k_2} = \frac{[R'S^-]}{[RS^-]}
\]

Measurements of concentration of $p$-nitrothiophenoxide and $p$-acetylthiophenoxide were made directly using known extinction coefficients. Knowledge of the initial disulphide concentration then made it possible to calculate the relative amounts of each product as long as the disulphide had decomposed completely according to the required stoichiometry. Representative reactions with each nucleophile were carried out without any detectable amount of disulphide present at the finish of the reaction.

A complication arose in the analysis of competing reactions with hydroxide ion as nucleophile. Cleavage with hydroxide ion involves formation of the unstable sulphenic acid\textsuperscript{15}, which decomposes to give thiophenoxide and sulphuric acid. The reaction scheme below shows the origin of the various products formed by cleavage of an
unsymmetrical disulphide. Let the proportion of cleavage in a given direction be $\alpha\%$ and the initial $[\text{RSSR}']$ be $c_1$. Concentrations of individual species are shown in brackets.

If the equilibrium absorbance reading at $\lambda_{\text{max}}$ for $\text{RS}^-$ is $\Lambda_\infty$ and the extinction coefficient for $\text{RS}^-$ at this wavelength is $c$, with none of the other components absorbing at this wavelength, then

$$\frac{\Lambda_\infty}{c} = \frac{\alpha c_1}{100} + \frac{\frac{1}{2}(100-\alpha)c_1}{100}$$  \hspace{1cm} (35)$$

and $\alpha$ can be determined, making calculation of the rate constant for cleavage in one direction possible.
**Typical Calculation**

**Compound** - \( m \)-tolyl-\( p \)-acetylnaphenyl disulphide

(concn. = 5.32 x 10\(^{-5}\)M).

\( \lambda = 358 \text{ nm (} \varepsilon_{358} \text{ for } p \text{-acetylthiophenoxide.} = 20,800) \)

**Nucleophile** - sulphite (concn. = 5.60 x 10\(^{-2}\)M).
<table>
<thead>
<tr>
<th>$t$ (min)</th>
<th>$D_t$</th>
<th>$D_{t+8}$</th>
<th>$D_{t+8} - D_t$</th>
<th>$\log(D_{t+8} - D_t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.268</td>
<td>0.870</td>
<td>0.602</td>
<td>0.220</td>
</tr>
<tr>
<td>0.25</td>
<td>0.343</td>
<td>0.871</td>
<td>0.528</td>
<td>-0.277</td>
</tr>
<tr>
<td>0.50</td>
<td>0.406</td>
<td>0.873</td>
<td>0.467</td>
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</tr>
<tr>
<td>0.75</td>
<td>0.464</td>
<td>0.874</td>
<td>0.410</td>
<td>-0.387</td>
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<tr>
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<td>0.876</td>
<td>0.364</td>
<td>-0.439</td>
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<tr>
<td>1.25</td>
<td>0.554</td>
<td>0.877</td>
<td>0.323</td>
<td>-0.491</td>
</tr>
<tr>
<td>1.50</td>
<td>0.594</td>
<td>0.977</td>
<td>0.283</td>
<td>-0.548</td>
</tr>
<tr>
<td>1.75</td>
<td>0.627</td>
<td>0.878</td>
<td>0.251</td>
<td>-0.600</td>
</tr>
<tr>
<td>2.00</td>
<td>0.656</td>
<td>0.878</td>
<td>0.222</td>
<td>-0.653</td>
</tr>
<tr>
<td>2.25</td>
<td>0.685</td>
<td>0.878</td>
<td>0.193</td>
<td>-0.714</td>
</tr>
</tbody>
</table>

A graph of $\log(D_{t+8} - D_t)$ versus $t$ is a straight line, slope $0.218$. 
2nd order rate constant = \( \frac{0.218 \times 2.303}{5.60 \times 10^{-3} \times 60} \) \( \text{mol}^{-1}\text{sec}^{-1} \).

= 1.495 \( \text{mol}^{-1}\text{sec}^{-1} \).

Time scale on u.v. machine needs a correction factor of 0.830.

Rate const. = 1.240

Measured \( D_\infty \) = 0.890

\( D_\infty \) if reaction had formed 100% \( \beta \)-acetylthiophenoxide

= 5.32 \times 10^{-5} \times 20,800

= 1.110

:. Rate const. for cleavage to give \( \beta \)-acetylthiophenoxide

= \( \frac{1.240 \times 0.890}{1.110} \)

= 0.994 \( \text{mol}^{-1}\text{sec}^{-1} \).

N.B. Errors in these determinations are discussed later in the experimental section.
Reagents

Disulphide solutions were made up by dissolving the disulphide (weighed on a Cahn balance) in t-butanol in a standard flask, and were used within 48 hours.

Cyanide solutions were made up by dissolving AnalaR potassium cyanide (weighed on a Cahn balance) and AnalaR borax (sufficient to make the solution 0.025 M) in distilled water in a standard flask and were used within eight hours.

Sulphite solutions were made up by dissolving AnalaR sodium metabisulphite and AnalaR borax (sufficient to make the solution 0.025 M) in distilled water. Solutions were standardised within several hours of use by reaction with a known excess of iodine and back-titration with thiosulphate.$^{58}$

Hydroxide solutions were made up by dissolving AnalaR potassium hydroxide in distilled water and were standardised within a few hours of use by titration with sulphuric acid.

t-Butanol was solvent grade, redistilled, b.p. 81-82.5°.
Errors

Symmetrical Disulphides

**AnalaR KON** is guaranteed not less than 96% pure, but the same jar of cyanide was used to make up all solutions, so that errors involved here would be systematic. The fact that cyanide is present in the protonated form to some extent is also a systematic error of unknown magnitude.

The largest contributions to random errors came from

(i) Pipetting of reaction solutions.
(ii) Temperature variation. The cell thremostatting system was not reliable to better than ±0.1°C.
(iii) Manual plotting of kinetic results. Most straight lines were very good and uncertainty here would not be greater than ±1%.

Total random error involved in these results would be about ±3%.

Unsymmetrical Disulphides

There was greater uncertainty in these results because the extent of cleavage in different directions had to be measured. About an extra 3% of random error is involved through measurements of initial disulphide concentration, measurement of $D_\infty$, and measurement of the extinction coefficient of the appropriate thiophenoxide. In addition,
any impurity of a given percentage in the disulphide will be reflected in a final result which is too large by approximately the same percentage.
Reactions of Disulphides with Cyanide Ion

Identification of Reaction Products

(a) Aqueous Ethanol Solvent

Study of the kinetics was originally attempted using aqueous ethanol as solvent. The reaction did not obey first order kinetics in this solvent or in aqueous methanol. This was shown to be a consequence of decomposition of phenyl thiocyanate, a product of the reaction. Phenyl thiocyanate reacts with sodium ethoxide$^{59}$ to form sodium thiophenoxide, ethyl phenyl sulphide and diphenyl disulphide. Apparently the concentration of ethoxide ions produced due to the basicity of KCN is high enough to cause this reaction to take place when phenyl thiocyanate is produced by cyanide cleavage of diphenyl disulphide.

Phenyl thiocyanate, prepared by the method of Gattermann and Haussknecht$^{60}$, (0.8g), was left to react overnight with a saturated solution of KCN in ethanol (80 ml) at room temperature. The solution was poured into 500 ml water and extracted three times with chloroform. The chloroform layer was dried with MgSO$_4$ and evaporated. A gas chromatogram of the resultant oil showed a complex mixture of products. Samples of the three most plentiful compounds (relative peak areas $\approx 4:3:1$) were collected by preparative GLC. The most abundant compound had a retention time and
infrared spectrum identical to diphenyl disulphide, and the next two had n.m.r. spectra consistent with the structures of ethyl phenyl sulphide and ethyl benzene sulphenate respectively.

(b) **Aqueous t-Butanol Solvent**

The reaction products of four disulphides were investigated here. Diphenyl disulphide was used as a representative example, products from di-(p-acetylphenyl) disulphide were studied because of the apparently abnormally slow rate of reaction of that compound, and p-aminophenyl-m-acetylphenyl disulphide showed abnormal kinetics. Products from m-tolyl-p-aminophenyl disulphide were studied because this compound was the most likely of the p-aminophenyl series of disulphides to give products resulting from attack of cyanide at both sulphur atoms.

(i) **Diphenyl Disulphide**

Diphenyl disulphide (25 mg) was dissolved in t-butanol (60 ml) and mixed with a solution of KCN (400 mg) in water (40 ml). The mixture was left for 1 hour, diluted to 500 ml with water and extracted with chloroform. The chloroform extract was analysed by g.l.c. Two peaks appeared and these had the same retention times on an S.E.30 column as authentic samples of phenyl thiocyanate and diphenyl disulphide.
The procedure was repeated, but conc. HCl (5 ml) was added to the solution before extraction with chloroform. An additional peak appeared in the gas chromatogram of the chloroform extract, with the same retention time as an authentic sample of thiophenol.

(ii) Di-$(p$-acetylphenyl) disulphide

Di-$(p$-acetylphenyl) disulphide (50 mg) was dissolved in $t$-butanol (40 ml) and potassium cyanide (300 mg) dissolved in aqueous 0.025 M borax (16 ml) was added. Water (10 ml) was added to make the solution homogeneous. After one hour the mixture was poured into water (600 ml), acidified with HCl, and extracted three times with chloroform. The chloroform extract was shown by t.l.c. to contain only starting material (presumably formed by aerial oxidation of $p$-acetylthiophenol) and $p$-acetylphenylthiocyanate, which was identified by comparison of t.l.c. and g.l.c. properties with those of an authentic sample, made from $p$-aminoacetophenone by the method of Overberger and Lebovits.

(iii) $m$-$Tolyl$-$p$-aminophenyl disulphide

$m$-$Tolyl$-$p$-aminophenyl disulphide (30 mg) was dissolved in $t$-butanol (70 ml) and a solution of potassium cyanide (1 g) in aqueous 0.025 M borax (70 ml) was added. After ten minutes the mixture was poured into water (400 ml) and extracted three times with chloroform. The components of the chloroform extract were shown by t.l.c. to be unchanged.
disulphide, \(m\)-thiocresol, di-(\(m\)-toly) disulphide (presumably formed by aerial oxidation of the thiol) and \(p\)-amino-phenylthiocyanate, which was identified by comparison of t.l.c. \(R_f\) value with that of an authentic sample, made from aniline by the method of Kaji\(^{62}\).

(iv) \(p\)-Aminophenyl-\(m\)-acetylphenyl disulphide

\(p\)-Aminophenyl-\(m\)-acetylphenyl disulphide (9 mg) was dissolved in \(t\)-butanol (70 ml) and a solution of potassium cyanide (500 mg) in aqueous 0.025 M borax solution (50 ml) was added. After 5 min. the mixture was poured into 400 ml water and was extracted three times with chloroform. The chloroform layer was shown by t.l.c. to contain only \(p\)-aminophenylthiocyanate. The aqueous layer was acidified and extracted three times with chloroform. The chloroform layer was shown by t.l.c. to consist of a mixture of \(m\)-acetylthiophenol and di-(\(m\)-acetylphenyl) disulphide (presumably formed by aerial oxidation of the thiol).
Slope of Gugg. plot (x 20)

Fig. 12

$[\text{KCN}] (x10^4 \text{ M})$
Reaction Order

Di-(p-acetylphenyl) disulphide is used as a representative example (di-(p-methoxyphenyl) disulphide gave the same results) while the results for the abnormal reaction of p-aminophenyl-m-acetylphenyl disulphide with cyanide are also reported.

(i) Di-(p-acetylphenyl) disulphide

The fact that good straight lines were obtained from Guggenheim plots of absorbance data was considered sufficient indication that the reaction was first order in disulphide. The reaction was shown to be first order in cyanide by measuring the slope of a Guggenheim plot at various cyanide ion concentrations (Table 7, Fig. 12).

| Table 7 |
|---|---|---|---|---|---|---|
| **Disulphide concentration constant** |  |
| KCN concentration (x10^4 M) | 5.19 | 6.64 | 8.66 | 9.89 | 14.0 | 19.5 |
| Guggenheim Slope | 0.206 | 0.242 | 0.310 | 0.361 | 0.523 | 0.700 |
(ii) p-Aminophenyl-m-acetylphenyl disulphide

Reaction order was measured here by estimation of initial rates. The u.v. absorption curve was extrapolated back a short distance to zero time and the initial slope was measured. True initial rates in mole,$t^{-1}, sec^{-1}$ have not been calculated; initial slopes only are quoted. The results of Table 8 and Fig. 13 show that the reaction is first order in cyanide, since the initial rates are proportional to cyanide ion concentration. The results of Table 9 and Fig. 14 show that the reaction is second order in disulphide, since the square root of the initial rate is proportional to disulphide concentration.

Table 8

<table>
<thead>
<tr>
<th>Disulphide concentration constant</th>
<th>1.85</th>
<th>2.44</th>
<th>2.78</th>
<th>3.70</th>
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<tr>
<td>KCN concentration ($x 10^2$ M)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial slope</td>
<td>0.50</td>
<td>0.64</td>
<td>0.80</td>
<td>0.97</td>
</tr>
</tbody>
</table>
**Initial Slope (x 10)**

![Graph](image)

- **Fig. 13**

- **Fig. 14**

- \[(\text{Initial Slope})^{\frac{1}{2}} (x 10)\]
Table 9

<table>
<thead>
<tr>
<th>Disulphide concn. (x $10^5$ M)</th>
<th>2.46</th>
<th>3.25</th>
<th>3.69</th>
<th>4.92</th>
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<tbody>
<tr>
<td>Initial Slope</td>
<td>0.176</td>
<td>0.266</td>
<td>0.328</td>
<td>0.736</td>
</tr>
<tr>
<td>(Initial Slope)$^{1/2}$</td>
<td>0.420</td>
<td>0.516</td>
<td>0.572</td>
<td>0.857</td>
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</tbody>
</table>
Reaction of Disulphides with Hydroxide Ion

Reaction Products

The stoichiometry of this reaction (equation 36) was established as far back as 1876, and Danehy and Parameswaran have established the identity of the products in aqueous ethanol.

\[ \text{RSSR} + \text{OH}^- \rightarrow [\text{RSOH}] + \text{RS}^- \]

(36)

The success of the method used for correcting rate constants obtained from cleavage of substituted phenyl-p-nitrophényl disulphides (p. 11) depends on p-nitrothiophenoxide being the only species absorbing at 435 nm. To check this, p-nitrobenzenesulphinic acid was synthesised and its extinction coefficient in basic solution at 435 nm was measured. It was found to be 1.6, which is insignificant compared with 14,500 for p-nitrothiophenoxide.

Reaction Order

A Guggenheim plot of the absorbance curve of di-(p-nitrophenyl) disulphide with hydroxide ion at 435 nm gave a straight line, indicating that the reaction was first
Fig. 15

Slope of Gugg. plot

\[ [\text{OH}^-] \times 10^3 \text{M} \]
order in disulphide. Rate constants for various hydroxide ion concentrations (Table 10, Fig. 15) showed that the reaction was first order in hydroxide ion. If sulphenic acid is accepted as the initial cleavage product it appears that its decomposition is a fast step compared with cleavage. This is to be expected as sulphenic acids can only be isolated in special circumstances$^{64,65}$.

**Table 10**

<table>
<thead>
<tr>
<th>Disulphide Concentration Constant</th>
<th>$[OH^-](x 10^3 M)$</th>
<th>3.14</th>
<th>6.28</th>
<th>8.37</th>
<th>12.56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guggenheim plot slope</td>
<td>0.091</td>
<td>0.157</td>
<td>0.210</td>
<td>0.280</td>
<td></td>
</tr>
</tbody>
</table>
Reaction of Disulphides with Sulphite Ion

Reaction Products

By analogy with the known reaction of diaryl disulphides\(^{23}\), the products of reaction of sulphite ion with diaryl disulphides were assumed to be aryl thiosulphate and thiophenoxide (equation 37).

\[
\text{ArSSAr} + \text{SO}_3^- \rightarrow \text{ArSSO}_3^- + \text{ArS}^- \quad (37)
\]

Examination of the u.v. spectrum of the reaction of sulphite ion with di-(\(\text{p}\)-acetylphenyl) disulphide showed exactly one mole of thiophenoxide formed at the completion of the reaction per mole of disulphide.

Reaction Order

Guggenheim plots of the absorbance curves of all the reactions used gave straight lines, indicating that the reaction was first order in disulphide. The data in Table 11, plotted in Fig. 16, indicated that the reaction was first order in sulphite.
Slope of Gugg. plot

Fig. 16
Table 11

<table>
<thead>
<tr>
<th>([SO_3^-]) (x 10^3 M)</th>
<th>1.43</th>
<th>2.50</th>
<th>3.57</th>
<th>5.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guggenheim plot slope</td>
<td>0.094</td>
<td>0.180</td>
<td>0.253</td>
<td>0.338</td>
</tr>
</tbody>
</table>
Synthesis of Symmetrical Disulphides

Several different synthetic routes were used to make the series of symmetrical disulphides. These compounds were usually prepared from the appropriate thiols by oxidation (e.g. with iodine or hydrogen peroxide). The required thiols were normally prepared either from the aryl diazonium salts, via the aryl xanthate or by replacement of halogen of an aryl halide with sulphide. Apart from oxidation of thiols, other methods used for synthesis of disulphides were

(a) Reduction of sulphonyl chlorides

(b) Oxidation of phenylmercaptoacetic acids.

Diphenyl Disulphide

Thiophenol (5g, Fluka AG purum) was added to 2N NaOH (50 ml) in a beaker in an ice bath. 30% H₂O₂ (7 ml) was added with stirring. Crude diphenyl disulphide was extracted from the mixture with ether and recrystallised from ethanol. Yield, 2.8g (60%), m.p. = 60° (lit. 61°).
Di-(m-tolyl) Disulphide

m-Thiocresol was prepared from m-toluidine (13.5g) by the method of Tarbell and Fukushima66. The product (5g) was dissolved in 2N NaOH (100 ml) and 30% H₂O₂ (10 ml) was added slowly with stirring. The resultant oil (4.2g, 30% overall) was separated, and pure di-(m-tolyl) disulphide was obtained as a pale yellow oil by preparative g.l.c. It had M⁺ 246.0547, calc. for C₁₄H₁₄S₂ 246.0537.

Di-(p-tolyl) Disulphide

This compound was prepared by the procedure used for the meta compound, with p-toluidine as starting material. Recrystallisation from methanol gave a white solid, m.p. 45-6° (lit.72 48°), 30% overall yield.

Di-(p-aminophenyl) Disulphide

This compound was prepared from p-chloronitrobenzene by the method of Price and Stacy73. It had m.p. 75° (lit.73 75-6°).

Di-(m-aminophenyl) Disulphide

Di-(m-nitrophenyl) disulphide (20g, Aldrich Chem. Co.) was added to a solution of sodium sulphide nonahydrate (100g) in water (250 ml). The mixture was refluxed for 5 hours, cooled and filtered. The filtrate was saturated with NaCl,
acetic acid (35 ml) was added, and the solution extracted three times with ether. The ether layer was dried with sodium sulphate and distilled to give m-aminothiophenol (8.6g, 55%) b.p. 123-5°/8mm.

m-Aminothiophenol (0.5g) was dissolved in ethanol (10 ml) and 6% \( \text{H}_{2}\text{O}_2 \) (5 ml) was added. The solution was distilled with water (50 ml) and extracted with ether. The ether layer was dried with sodium sulphate and evaporated down to give an oil (0.4g), which could not be induced to crystallise, even after purification on an alumina column. Di-\((m\text{-aminophenyl})\) disulphide dihydrochloride was obtained when conc. HCl was added to an ethanol solution of the oil; after recrystallisation from ethanol/aqueous HCl, it had m.p. 215-220°C (dec.). Yield, 0.1g (20%), mass spectrum \( m^+ \ 248.0439 \), \( \text{C}_{12}\text{H}_{12}\text{N}_2\text{S}_2 \) requires 248.0441. The parent ion observed in the mass spectrum was the diamine, not the diamine dihydrochloride.

Di-\((\text{p-}N,\text{N-dimethylaminophenyl})\) Disulphide

1. \( \text{N},\text{N-Dimethyl-p-phenylenediamine} \). Dimethylaniline (19g) in 1:1 aq. HCl (100 ml) was cooled below 0° and \( \text{NaNO}_2 \) (11g) in water (30 ml) was added with stirring, keeping the temperature below 0°. The resultant precipitate was filtered off, washed with dilute HCl and added to 40 ml water at
Portions of this mixture and powdered zinc (about 45g required in total) were then added alternately to 100 ml conc. HCl. Near the end of the addition a further 30 ml conc. HCl was added. When reduction was complete a pale pink solution was obtained and this was filtered, neutralised with sodium carbonate and extracted five times with ether. A dark brown oil (9g) was obtained. It had an infrared spectrum consistent with the structure of N,N-dimethyl-p-phenylenediamine.

2. p-N,N-Dimethylaminothiophenol. The oil from the previous preparation was diazotised in HCl solution below 0°C and was run into a solution of potassium ethyl xanthate (20g) in water (60 ml) at 40-45°. After one hour the resultant oil was separated by ether extraction and refluxed for 3 hr with potassium hydroxide (20g), ethanol (40 ml) and water (20 ml). The resultant solution was acidified with 1:4 aqueous sulphuric acid and neutralised with sodium acetate (100g). It was then extracted three times with ether and the ether layer evaporated down. Heating two thirds of this residue to 200° under 6 mm pressure yielded a distillate of p-N,N-dimethylaminothiophenol (0.15g, 1.5%), m.p. 32-36° (lit. 33.5-37°).

3. Di-(p-N,N-dimethylaminophenyl) Disulphide. The other one third of the residue, after repeated recrystallisation
from methanol, gave di-(p-dimethylaminophenyl) disulphide, m.p. 145-146.5° (lit.75 118°c). N.m.r. (CDCl₃) δ 2.95 (6H, singlet; OCH₂), 7.05 (4H, quartet; ArH). Mass spectrum and infrared were consistent with the structure, although the mass spectrum showed a small peak at 336.

Di-(p-methoxyphenyl) Disulphide

p-Methoxythiophenol (6.0g, 25%) was prepared from 20g distilled p-anisidine by the method of Tarbell and Fukushima66. The thiol was dissolved in ethanol (50 ml) and a 1 M aqueous solution of iodine in excess potassium iodide was added until a permanent iodine colour appeared. The solution was diluted to 300 ml with water and was extracted twice with ether. The ether layer was washed with 7% aqueous sodium thiosulphate solution, dried and the ether evaporated off. The resultant yellow oil solidified on standing and was recrystallised from methanol to give di-(p-methoxyphenyl) disulphide, m.p. 36-7°C (lit.76 44°C), 3.5g (60%).

Di-(p-bromophenyl) Disulphide

Phenylmercaptoacetic acid was prepared by the method of Uyeda77. It was used to make di-(p-bromophenyl) disulphide by the method of Walker and Lieb70, m.p. 93-4° (lit.70 95-6°).
**Di-(m-bromophenyl) Disulphide**

To m-bromothiophenol (8g, prepared from m-bromoaniline by the method of Schwarzenbach and Egli\(^6\)) and 10% NaOH (50 ml), 30% \( \text{H}_2\text{O}_2 \) (6 ml) was added slowly with stirring in an ice bath. The solution was extracted with ether, the ether layer was washed with 3% KOH solution, dried with MgSO\(_4\), and evaporated down to give crude di-(m-bromophenyl) disulphide (5g, 60%). A pure sample (yellow oil) was obtained by preparative g.l.c. It had \( M^+ 373.8436 \), \( C_{12}H_8Br_2S_2 \) requires 373.8435.

**Di-(p-chlorophenyl) Disulphide**

p-Chlorobenzenesulphonyl chloride (11.5g, prepared from chlorobenzene by the method of Ullmann and Korsett\(^7\)) was dissolved in acetic acid (45 ml) and 63% HBr (6 ml). Red phosphorus (1.8g) was added and the mixture stirred at 75°C for 1 hr, diluted with water (200 ml) and extracted with ether. The ether layer was washed twice with 5% NaOH and the solvent taken off. Recrystallisation from methanol gave pure di-(p-chlorophenyl) disulphide, m.p. 70-71°C (lit.\(^7\) 71-2°C), 2.8g (35%).
Di-(m-chlorophenyl) Disulphide

1. Sodium m-chlorobenzenesulphonate. Copper sulphate crystals (60g), sodium chloride (20g) and water (200 ml) were heated to 60° and a concentrated solution of sodium metabisulphite (10g) in water was added. The resultant precipitate of cuprous chloride was filtered off and dissolved in conc. HCl (80 ml) and water (100 ml). Metanilic acid (38g) was mixed with conc. HCl (80 ml) and water (50 ml). The mixture was diazotised below 5°C with NaNO₂ (15.5g) in water (35 ml). The cold solution was filtered and the filtrate run into the cuprous chloride solution, keeping the temperature between 25° and 30°. The resultant solution was then warmed on a steam bath until evolution of nitrogen ceased, sodium hydroxide pellets (30g) carefully added, and the solution heated to near boiling point and saturated with NaCl; cooling in an ice-salt bath gave sodium m-chlorobenzenesulphonate as a solid. This was filtered off, recrystallised from water and dried at 100°. Yield, 22g (60%).

2. m-Chlorobenzenesulphonyl Chloride. Powdered sodium m-chlorobenzenesulphonate (10g) mixed with powdered phosphorus pentachloride (6g) in a 100 ml flask with a condenser was heated at 180°C for 20 hr, with stirring after 4 hr and 8 hr. The resultant pasty mass was poured into water
(100 ml) and extracted with CCl₄. Vacuum distillation of the CCl₄ layer gave m-chlorobenzenesulphonyl chloride (3.8 g, 40%).

3. **Di-(m-chlorophenyl) Disulphide.** m-Chlorobenzenesulphonyl chloride (3.8 g) was dissolved in acetic acid (15 ml) and 63% HBr (2 ml). Red phosphorus (0.6 g) was added and the mixture stirred at 75° for 1 hr. Dilution with water (100 ml) and extraction with ether gave an oil (2.6 g) which was shown by g.l.c. to be about 70% disulphide. A pure sample of **di-(m-chlorophenyl) disulphide** (yellow oil) was obtained by preparative g.l.c. It had M⁺ 285.9419, C₁₂H₈Cl₂S₂ requires 285.9444.

**Di-(p-fluorophenyl) Disulphide**

p-Fluorothiophenol (5 g, Aldrich Chem. Co.) was dissolved in ethanol (50 ml) and a 1 M solution of iodine and excess potassium iodide added until the iodine colour was permanent. The mixture was diluted with water (200 ml) and extracted with ether. The ether layer was washed with 1% Na₂S₂O₅, 3% NaOH and water, and was distilled to give **di-(p-fluorophenyl) disulphide** as a yellow oil, b.p. 138-141°/3 mm, 4.0 g (80%). The product shows only one peak on an E.E.30 analytical g.l.c. column.
Di-(p-acetylphenyl) Disulphide

This compound was prepared from phenylmercaptoacetic acid according to the method of Walker and Lieb, m.p. 96-7° (lit. 71 97-8°).

Di-(m-acetylphenyl) Disulphide

m-Nitroacetophenone was prepared from acetophenone by the method of Corson and Hazen and reduced to m-aminoacetophenone by the method of Morgan and Moss. m-Aminoacetophenone was converted to m-acetyltiophenol by the method of Schwarzenback and Egli. The crude thiol obtained was dissolved in ethanol and oxidised with 7% aqueous \( \text{H}_2\text{O}_2 \) solution. Crude disulphide was obtained in 30% yield by dilution with water and extraction with ether; pure \text{di-(m-acetylphenyl) disulphide} was obtained as a yellow oil by preparative g.l.c. It had \( \text{M}^+ 302.0427, \text{C}_{16}\text{H}_{14}\text{O}_2\text{S}_2 \) requires 302.0435.

Di-(p-cyanophenyl) Disulphide

p-Toluenesulphonyl chloride (100g) was powdered and added to ammonia solution (S.G. 0.880, 300 ml). The mixture was heated to boiling and cooled. The crude product was filtered off and recrystallised from water. After 1½ hr drying at 100°, there was obtained p-toluenesulphonamide, (91g, 99%). m.p. 137.5-138.5° (lit. 67 138.5-139°).
p-Toluenesulphonamide (91g) was dissolved in a solution of water (250 ml) and NaOH (15g). It was heated to 70° in an oil bath and potassium permanganate (161g) was added carefully with vigorous mechanical stirring at such a rate that the temperature did not rise above 90°. The resultant MnO₂ was filtered off and washed three times with 5% NaOH. The total filtrate was acidified with HCl, the resultant precipitate being filtered off and recrystallised from water to give p-carboxybenzenesulphonamide (68.5g, 65%) m.p. 264° (dec.) (lit. 283° (dec.))

Powdered p-carboxybenzenesulphonamide (5g) was mixed with powdered POCl₃ (11g) and was heated in an oil bath at 220° until all the POCl₃ had distilled off. The resultant product was washed with water and purified on an alumina column. Recrystallisation from petroleum ether/benzene gave p-cyanobenzenesulphonyl chloride, m.p. 105-108° (lit. 110°), 0.85g (17%).

Di-(p-cyanophenyl) disulphide was made from p-cyano-benzenesulphonyl chloride by the method of Bauer and Cyerman. It had m.p. 170-170° (lit. 172-3°).

Di-(m-nitrophenyl) Disulphide

This compound was purchased from Aldrich Chem. Co. It was used without further purification m.p. 79-80°.
**Di-(p-nitrophenyl) Disulphide**

This compound was purchased from Aldrich Chem. Co. Recrystallised from toluene, it had m.p. 180-1° (lit.71 181-2°).
Synthesis of Unsymmetrical Disulphides

There appeared initially to be no problem in making unsymmetrical disulphides as there are two reactions in the literature which report good yields. These are

(a) Reaction of a thiol with a sulphenyl chloride\textsuperscript{84}.

(b) Consecutive reaction of two thiols with diethyl azodicarboxylate.\textsuperscript{85}

However, unsymmetrical aromatic disulphides readily disproportionate (via radical formation\textsuperscript{10}) to form a mixture of symmetrical and unsymmetrical compounds. Factors which have been shown to assist this rearrangement are heat, light, solvent (e.g. acetone) and an active solid phase (e.g. alumina). Both the above general reactions usually produced significant quantities of symmetrical products, and this made purification of the unsymmetrical compounds difficult, as many of these were low-melting solids or oils.

Crystalline unsymmetrical disulphides were stable as long as they were not exposed to too much light, but the oils were stable for a few days only, even in the dark. They were stable on silica t.l.c. plates, and t.l.c. appears to be the only reliable method of indicating the purity of these compounds. Column chromatography on silica proved to be a very useful preliminary purification step in preparations where large quantities of symmetrical
disulphides had formed as by-products. Recrystallisation (at dry ice/acetone temperature in the case of oils) was then carried out on the purest fractions obtained from the columns.

The Thiol-Sulphenyl Chloride Reaction

\[ RSH + R'SCl \rightarrow RSSR' + HCl \] (38)

Some of the preparations using this reaction were carried out with ether as solvent, and the products included appreciable amounts of symmetrical compounds. It was later found that using acetic acid as solvent gave virtually 100% reaction to unsymmetrical products. However, isolation of the products from acetic acid was difficult. Rearrangement occurred if the acetic acid solution was added to water and then extracted with ether. The best procedure was to remove acetic acid at room temperature with a vacuum pump. Addition of another solvent for recrystallising purposes usually caused some disproportionation, but often the compound remained pure enough to recrystallise successfully without using column chromatography.
Reaction of Thiols with Diethyl Azodicarboxylate

\[ R'SH + \text{eti}O_2C-N=N-\text{CO}_2\text{et} \rightarrow \text{eti}O_2C-N=N-\text{CO}_2\text{et} \quad (39) \]

\[ R'SH + \text{eti}O_2C-N=N-\text{CO}_2\text{et} \rightarrow \text{RSR'} + \text{eti}O_2C-N=N-\text{CO}_2\text{et} \quad (40) \]

If an amino group is required on the unsymmetrical disulphide, the sulphenyl chloride reaction cannot be used because sulphenyl chlorides react with amines to form sulphenamides.

\[ \text{RSCl} + \text{R'NH}_2 \rightarrow \text{RSNHR'} + \text{HCl} \quad (41) \]

This difficulty is overcome by using diethyl azodicarboxylate as shown in equations (39) and (40). The products from all the reactions carried out by this method contained large amounts of symmetrical compounds. The literature quoted reaction times in hours, but both of the thiol addition reactions appeared to be complete within a matter of seconds, and yields decreased with long reaction times when an aminothiol was the first thiol to be added. This reaction was less satisfactory than the sulphenyl chloride reaction, but had the advantage that the extra synthetic step, conversion of thiol to sulphenyl chloride, was not needed.
Yields and Product Purity

Analytical data was not found helpful as a measure of purity of the unsymmetrical disulphides, as in most cases impurities were approximately equal amounts of the appropriate symmetrical disulphides. All compounds used for kinetic studies were pure to t.l.c. on silica unless otherwise stated. Verification of the identity of the compound was done by mass-measurement of the parent ion in the mass spectrum. No attempt was made to estimate yields in each synthesis, the main object being to obtain enough pure compound for kinetics.
General Synthetic Procedure

Thiol-Sulphenyl Chloride Reaction

Solutions of equimolar quantities (about 1 millimole) of the two reactants were mixed in a total volume of about 20 ml of solvent. Reaction was instantaneous, as shown by the disappearance of the strong orange or yellow colour of the sulphenyl chloride.

Reaction of Thiols with Diethyl Azodicarboxylate

Solutions of equimolar quantities (about 1 millimole) of a thiol and diethyl azodicarboxylate were mixed in a total volume of about 15 ml of solvent. After 2-3 minutes an equivalent amount of the second thiol in about 6 ml of solvent was added.
Individual Syntheses of Unsymmetrical Disulphides

p-Acetylphenyl Series of Disulphides

Phenyl-p-acetylphenyl Disulphide

p-Acetylthiophenol was prepared in 45% yield from p-aminoacetophenone by the method of Schwarzenback and Egli, b.p. 110-115°/8 mm.

Phenylsulphenyl chloride was prepared from diphenyl disulphide by the method of Lecher et al.

p-Acetylthiophenol was reacted with phenylsulphenyl chloride in acetic acid. The unsymmetrical product was isolated by dilution of the reaction mixture with water and extraction with ether. Phenyl p-acetylphenyl disulphide, purified by silica column chromatography and recrystallisation from n-pentane (dry ice/acetone temperature), had m.p. 62-3°, M+ 260.0328, C14H12S2O requires 260.0330.

m-Tolyl-p-acetylphenyl Disulphide

Di-(m-tolyl) disulphide (7.75g) was dissolved in dry CCl4 (50 ml) in a flask in an ice-salt bath, and dry chlorine was bubbled in for 15 min. The resultant orange-red solution was distilled to give m-tolylsulphenyl chloride (5.87g, 60%), b.p. 100-108°/12 mm.

p-Acetylthiophenol was reacted with m-tolylsulphenyl chloride in ether. The unsymmetrical product was purified
by silica column chromatography and was recrystallised from ether/n-pentane (dry ice/acetone temperature) to give pure m-tolyl-p-acetylphenyl disulphide, m.p. 37-39°, M⁺ 274.0482, C₁₅H₁₄O₂S₂ requires 274.0485.

p-Methoxyphenyl-p-acetylphenyl Disulphide

p-Methoxythiophenol was reacted with diethyl azodicarboxylate in ether. p-Acetylthiophenol was added and the unsymmetrical disulphide was isolated by silica column chromatography. Recrystallisation from ether/n-pentane gave p-methoxyphenyl-p-acetylphenyl disulphide, m.p. 56-57°, M⁺ 290.0426, C₁₅H₁₄O₂S₂ requires 290.0435.

m-Aminophenyl-p-acetylphenyl Disulphide

p-Acetylthiophenol was reacted with diethyl azodicarboxylate in ether. m-Aminothiophenol was added and the unsymmetrical disulphide was isolated by silica column chromatography. A t.l.c. plate of the purest fraction of m-aminophenyl-p-acetylphenyl disulphide (amorphous solid, m.p. 82-85°) showed traces of symmetrical compounds, but any recrystallisation attempts resulted in decomposition, so this fraction was used for kinetics. It had M⁺ 275.0415, C₁₄H₁₂N₂O₂S₂ requires 275.0438.

m-Bromophenyl-p-acetylphenyl Disulphide

m-Bromothiophenol (9.2g) was dissolved in dry CCℓ₄ (30 ml) in a flask in an oil bath at 60°C. Dry chlorine
was bubbled through the solution for $1\frac{1}{2}$ hr, and distillation then gave m-bromophenylsulphenyl chloride (6.7 g, 60%), b.p. 105-112°/6 mm.

m-Bromophenylsulphenyl chloride was reacted with p-acetyltthiophenol in acetic acid, and the solvent was removed at room temperature with a vacuum pump. The unsymmetrical product was obtained by silica column chromatography and recrystallisation from ether/pentane (dry ice/acetone temperature). m-Bromophenyl-p-acetyltphenyl disulphide was a yellow oil at room temperature, $M^+ 337.9439$, $C_{14}H_{11}BrO_2$ requires 337.9435.

p-Bromophenyl-p-acetyltphenyl Disulphide

p-Bromothiophenol was prepared from p-bromoaniline in 25% yield by the method of Schwarzenbach and Egli. p-Bromothiophenol was reacted with diethyl azodicarboxylate in ether. p-Acetyltthiophenol was then added and p-bromophenyl-p-acetyltphenyl disulphide was isolated from the mixture by silica column chromatography. When recrystallised from ether/pentane it had m.p. 61-63°, $M^+ 337.9429$, $C_{14}H_{11}BrO_2$ requires 337.9435.
**p-Aminophenyl Series of Disulphides**

**Phenyl-p-aminophenyl Disulphide**

p-Aminothiophenol was prepared from p-chloronitrobenzene by the method of Gilman and Gainer. 68

Thiophenol was reacted with diethyl azodicarboxylate in ether and p-aminothiophenol was then added to the reaction mixture. **Phenyl-p-aminophenyl disulphide**, isolated by silica column chromatography as a yellow oil, could not be recrystallised. It showed traces of impurity on silica t.l.c. and was about 95% pure on g.l.c. (S.E.30 column). It had $M^+$ 233.0318, $C_{12}H_{11}NS_2$ requires 233.0333.

**m-Tolyl-p-aminophenyl disulphide**

m-Thiocresol was reacted with diethyl azodicarboxylate in ether and p-aminothiophenol was added to the reaction mixture. **m-Tolyl-p-aminophenyl disulphide** was isolated by silica column chromatography. The yellow oil obtained, which was pure to silica t.l.c., could not be recrystallised. It had $M^+$ 247.0502, $C_{13}H_{13}NS_2$ requires 247.0489.

**m-Bromophenyl-p-aminophenyl Disulphide**

m-Bromothiophenol was reacted with diethyl azodicarboxylate in ether and then p-aminothiophenol was added to the mixture. **m-Bromophenyl-p-aminophenyl disulphide**, isolated as a yellow oil by silica column chromatography,
could not be recrystallised. It showed trace impurities to silica t.l.c. and was about 95% pure on g.l.c. (G.E.30 column). It had $M^+ = 310.9419$, $C_{12}H_{10}BrNS_2$ requires 310.9437.

**p-Bromophenyl-p-aminophenyl Disulphide**

p-Bromothiophenol was reacted with diethyl azodicarboxylate in ether and p-aminothiophenol was added to the mixture. p-Bromophenyl-p-aminophenyl disulphide was isolated by silica column chromatography and recrystallised from petroleum ether, m.p. 77-78.5°, $M^+ = 310.9413$, $C_{12}H_{10}BrNS_2$ requires 310.9437.

**m-Acetylphenyl-p-aminophenyl Disulphide**

m-Acetyltiophenol was reacted with diethyl azodicarboxylate in ether and p-aminothiophenol was added to the mixture. m-Acetylphenyl-p-aminophenyl disulphide was isolated by silica column chromatography and recrystallised from ether/n-pentane, m.p. 94-95°, $M^+ = 275.0439$, $C_{14}H_{13}NOS_2$ requires 275.0439.

**p-Nitrophenyl-p-aminophenyl Disulphide**

p-Nitrothiophenol was prepared by the method of Price and Stacy. It was reacted with diethyl azodicarboxylate in ether and p-aminothiophenol was added to the mixture. p-Nitrophenyl-p-aminophenyl disulphide was isolated by column chromatography and recrystallised from ether/n-pentane, m.p. 118-120°, $M^+ = 278.0180$, $C_{12}H_{10}N_2O_2S_2$ requires 278.0183.
p-Nitrophenyl Series of Disulphides

Phenyl-p-nitropheno;yl Disulphide

Di-(p-nitrophenyl) disulphide (5g) was suspended in dry 50% CCl₄/CHCl₃ (35 ml) at 80°C and dry chlorine was bubbled through for 2 hr. The resultant red solution was distilled to give p-nitrophenylsulphenyl chloride (3.3g, 55%), b.p. 124-6°C/0.75 mm, m.p. 40.5-41.5°C (lit. 88 52°C).

p-Nitrophenylsulphenyl chloride was reacted with thiophenol in acetic acid and the acetic acid was taken off at room temperature with a vacuum pump. The resultant phenyl-p-nitrophenyl disulphide was recrystallised from petroleum ether, m.p. 57.5-58°C (lit. 85 58-9°C).

m-Aminophenyl-p-nitrophenyl Disulphide

p-Nitrothiophenol was reacted with diethyl azodicarboxylate in benzene, and then m-aminothiophenol was added to the mixture. The m-aminophenyl-p-nitrophenyl disulphide was isolated by silica column chromatography and recrystallised from ether/m-pentane, m.p. 88-89.5°C, M⁺ 278.0185, C₁₂H₁₀N₂S₂O₂ requires 278.0184.

p-Methoxyphenyl-p-nitrophenyl Disulphide

p-Methoxythiophenol was reacted with p-nitrophenylsulphenyl chloride in acetic acid and the acetic acid was taken off at room temperature under vacuum. The resultant p-methoxyphenyl-p-nitrophenyl disulphide was recrystallised
from ether/\text{n}-pentane, m.p. 69-71°, M^+ 293.0196, C_{13}H_{11}NO_3S_2 requires 293.0180.

\textit{m-Bromophenyl-\textit{p}-nitrophenyl Disulphide}

\textit{m-Bromothiophenol} was reacted with \textit{p-nitrophenyl-sulphenyl chloride} in acetic acid and the acetic acid was removed at room temperature under vacuum. The resulting \textit{m-bromophenyl-\textit{p}-nitrophenyl disulphide}, recrystallised from petroleum ether (dry ice/acetone temperature), had m.p. 35-7°, M^+ 340.9170, C_{12}H_{8}BrNO_2S_2 requires 340.9180.

\textit{p-Bromophenyl-\textit{p}-nitrophenyl Disulphide}

\textit{p-Bromothiophenol} was reacted with \textit{p-nitrophenyl-sulphenyl chloride} in acetic acid and the acetic acid was removed at room temperature under vacuum. The resulting \textit{p-bromophenyl-\textit{p}-nitrophenyl disulphide}, recrystallised from petroleum ether/benzene, had m.p. 94.5-96°, M^+ 340.9162, C_{12}H_{8}BrNO_2S_2 requires 340.9180.

\textit{p-Acetylphenyl-\textit{p}-nitrophenyl Disulphide}

\textit{p-Acetylthiophenol} was reacted with \textit{p-nitrophenyl-sulphenyl chloride} in acetic acid and the acetic acid was removed at room temperature under vacuum. The resultant \textit{p-acetylphenyl-\textit{p}-nitrophenyl disulphide}, recrystallised from methanol, had m.p. 78.5-80°, M^+ 305.0147, C_{14}H_{11}NO_3S_2 requires 305.0180.
**m-Tolyl-p-nitrophenyl Disulphide**

*m*-Thiocresol was reacted with *p*-nitrophenylsulphenyl chloride in acetic acid and the acetic acid removed at room temperature under vacuum. The resultant *m*-tolyl-*p*-nitrophenyl disulphide was recrystallised from ether/*n*-pentane (dry ice/acetone temperature) until t.l.c. showed only traces of impurities. It was a yellow oil at room temperatures, and had $M^+$ 277.0224, $C_{13}H_{11}NO_2S_2$ requires 277.0231.
Synthesis of p-Nitrobenzenesulphinic Acid

p-Nitrobenzenesulphonyl chloride was prepared by the method of Gialdi et al.\textsuperscript{89}

p-Nitrobenzenesulphonyl chloride (1g) was stirred vigorously with sodium sulphite crystals (2.5g) in water (7 ml). Potassium hydroxide solution was added periodically to keep the mixture alkaline. After two hours the starting material had dissolved and the resultant solution was acidified with conc. HCl. The resultant precipitate was filtered off and recrystallised from aqueous HCl to give p-nitrobenzenesulphinic acid (0.3g, 35\%), m.p. 150-160° (dec.) (lit.\textsuperscript{16} 120° or 159°), (Found: C, 38.5; H, 2.7; S, 17.1. Calc. for C\textsubscript{6}H\textsubscript{5}NO\textsubscript{4}S: C, 38.5; H, 2.8; S, 16.9%).
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