# THE SCISSION OF THE SULFUR–SULFUR BOND[1]

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## I. Introduction

### A. Purposes and scope

The objectives of this review are: (*1*) to note the major current interests in the scission of the sulfur–sulfur bond; (*2*) to summarize and exemplify the classes of organic compounds that possess the sulfur–sulfur bond and are of interest to this review; (*3*) to summarize the existing literature on the scission of the sulfur–sulfur bond; and (*4*) to try to evaluate the known facts, in each aspect, in terms of reaction mechanisms.

The ionic scission of the sulfur–sulfur bond is emphasized. Only a brief section on homolytic (free-radical) scission, which cites the pertinent references to the latest literature, is included. In the other sections, however, the total literature was consulted.

The published work and ideas of Olav Foss (59, 60) were of special value in preparing this review. It was Foss who first clearly stated the conclusions (*a*) that in polythio compounds the sulfur atoms are in an unbranched chain (57) and (*b*) that many typical reactions of polythio compounds with anions ($SO_3^=$, $S_2O_3^=$, $CN^-$, etc.) are bimolecular nucleophilic substitutions on sulfur, which can be interpreted in terms of the base strengths of the displacing and displaced groups (56). These principles, together with others from the literature and some which have stemmed from the authors' own studies (135), have now been used to give a more coherent picture of the mechanisms involved in the ionic scissions of sulfur–sulfur bonds by nucleophilic reagents.

Studies of electrophilic ionic scission of sulfur–sulfur bonds also promise to become of interest, especially in view of recent work by Benesch and Benesch (15) and Moore and Porter (131). Here, again, some relatively simple ideas about mechanisms can assist in predicting results in new circumstances. The role of sulfenium ions in such reactions, a topic of particular interest to the authors (90), has been noted.

TABLE 1

*Classes of compounds containing sulfur–sulfur bonds**

| | |
|---|---|
| Disulfides | Aliphatic, RSSR or RSSR′, or aromatic, ArSSAr or ArSSAr′. Examples: Dimethyl disulfide; methyl ethyl disulfide; 2,3-dithiapentane; 1,2-dithiacyclopentane. |
| Polysulfides | $R(S)_nR$: methyl ethyl trisulfide; diethyl tetrasulfide, etc. The sulfur atoms in these compounds are unbranched (57). The "thia" nomenclature may also be used. Elemental sulfur, $S_8$, may also be included with this group (38). |
| Sulfenyl derivatives (90) | These include sulfenyl thiocyanates, RSSCN; "thiolsulfonate esters," $RSSO_2R'$, which are better viewed as sulfenyl sulfinates; Bunte salts, $RSSO_3Na$, which can be advantageously viewed as sulfenyl sulfites; sulfenyl monothiophosphates, $RSSPO(OR)_2$; sulfenyl thiosulfates, $RSS_2O_3^-$; and sulfenic anhydrides, which are now claimed to have the structures RS(O)SR† rather than RSOSR and may be considered as sulfenyl sulfenates. |
| Dialkylsulfonyl disulfides | $RSO_2SSSO_2R$ (60) |
| Polythionates | $^-O_3SS_nSSO_3^-$ (57) |
| Other classes | This review restricts itself to classes of sulfur–sulfur compounds in which at least one of the sulfur atoms is bivalent. Substances such as disulfones ($RSO_2SO_2R$), 1,2-disulfoxides [RS(O)S(O)R], etc., are not considered here. It may be noted, however, that an apparently unknown group of such compounds, namely, $RS(O)SO_2R$, should be attainable through reactions of the now conveniently prepared sulfinyl chlorides (39), RS(O)Cl, and sulfinate salts; i.e., $RSOCl + R'SO_2Na \rightarrow RS(O)SO_2R' + NaCl$. |

* For general references to these classes of sulfur compounds, *cf.* Houben-Weyl, *Methoden der organischen Chemie*, Vol. IX, G. Thieme, Stuttgart (1955).

† The products obtained by oxidizing disulfides with per acids are identical (187) with those obtained by hydrolyzing sulfenyl chlorides. The value of classing compounds such as thiolsulfonate esters, Bunte salts, and the others like them, as sulfenyl derivatives is that much of their chemistry, like that of sulfenyl halides, can be rationalized on the basis of nucleophilic displacement reactions from sulfur (56).

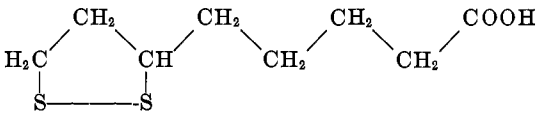
### B. CLASSES OF COMPOUNDS CONTAINING THE SULFUR–SULFUR BOND

While disulfides are generally considered as the preëminent class of compounds which contain the sulfur–sulfur bond, several others are also of interest. These are listed in table 1, with examples of nomenclature and with leading general references.

### C. CURRENT INTEREST IN THE SCISSION OF THE SULFUR–SULFUR BOND

Besides the many theoretical interests in the scission of the sulfur–sulfur bond, which are brought out in the following sections of this review, there are several significant areas of study in which knowledge of the sulfur–sulfur bond structure and of the mechanisms of cleavage is of central importance.

Biochemical interests include: (*1*) studies such as those of Ryle and Sanger (146) on the disulfide cross-links between the polypeptide chains of insulin; (*2*) the work of du Vigneaud, Ressler, Swan, Roberts, Katsoyannis, and Gordon (41) on the physiological activities of the lactogenic and diuretic hormones, oxytocin and vasopressin; (*3*) interest in the role of disulfide links in denaturation and subsequent coagulation of proteins (79), such as serum albumin; (*4*) investigations of the permanent setting of hair or wool (197); and (*5*) considerations of the role of $\alpha$-lipoic acid in the pyruvic acid cycle (139). The possible role of $\alpha$-lipoic acid (I) in photosynthesis—involving scission of the "strained" sulfur–sulfur bond—was put forward as an attractive hypothesis by Barltrop, Hayes, and Calvin (6), but this has not had experimental verification.



I

α-Lipoic acid

Industrially, reactions of disulfides which involve scissions of the sulfur–sulfur links are involved in their use as vulcanization accelerators (5, 94), radical initiators (145, 189), and chain-transfer agents in polymerization studies (5). The importance to rubber chemistry of the reactions of di- and polysulfides with olefins has been commented on recently by Bateman, Moore, and Porter (13). Some disulfides find use as agricultural chemicals, e.g., bis(*m*-nitrophenyl) disulfide, which acts as an anticoccideal agent in poultry (113).

In each of the above interests and applications, the processes involving the cleavage of the sulfur–sulfur bond are of first importance. Yet many of the fundamental questions concerning the physical and chemical properties of disulfides remain unanswered or incompletely resolved. An attempt to correlate and record the wealth of material which comes from so many diverse sources should therefore be of interest to many groups of workers.

## II. Stereochemistry of the Disulfide Bond

Disulfides exist only in the structure shown in formula II. Spectrochemical studies (95, 129), dipole moment measurements (191), electron and x-ray diffrac-

II III

tion studies (172), together with exchange reactions of disulfides using $S^{35}$ (195), have finally established that the branched structure (III) is not present in disulfides even in trace amounts.

The physical properties of sulfur compounds have been reviewed recently by Abrahams (1). The bond length between divalent sulfur atoms lies between 2.04 A. and 2.06 A. and the S—S—C valency angle varies from 103° to 107°. In noncyclic disulfides the dihedral angle between the two sulfur–carbon bonds is very nearly 90°. The structure of a typical aliphatic disulfide (dimethyl disulfide) according to Scott (164, 165) and Calvin (23) is shown in figure 1.

Pauling has discussed the distribution of valence electrons in disulfides and considers that the $\sigma$ bond joining the two sulfur atoms is nearly pure $p$ in character with the second lone pairs of electrons on each sulfur in the $3s$ orbitals, spherically distributed about the nucleus (136). The remaining pair of electrons on each sulfur exists as $3p$-$\pi$ electrons on the 90° axes. It is these $3p$-$\pi$ electrons which cause a barrier to rotation about the sulfur–sulfur bond of 10–14 kcal./mole (165). The barrier arises from the mutual repulsion between unshared $p$ electrons on adjacent sulfur atoms. This coulombic repulsion is maximal when the dihedral angle is 0° or 180°, and is least when the dihedral angle is 90°. It

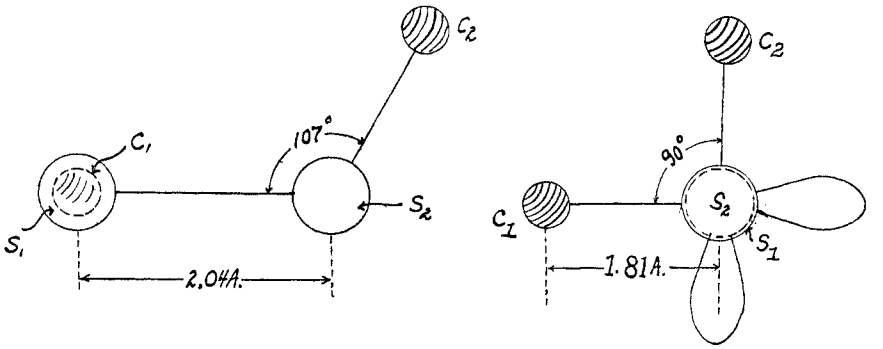



FIG. 1. Structure of dimethyl disulfide. The third nonbonding orbitals ($p_z$) are included only to show the orientation of the unshared electron pair, assuming no $s$ or $d$ hybridization.

has also been proposed (101) that overlap of the sulfur $3p$-$\pi$ electron pair with an available $3d$ orbital of the bond partner, to form a weak $pd$ $\pi$ bond, may stabilize the nonplanar configuration with a dihedral angle of 90°.

In view of the above model, in cyclic disulfides (of, say, three carbon atoms) the favorable geometric orientation of the sulfur–carbon bonds cannot be accommodated, partly as a result of resistance to rotation about the sulfur–sulfur bond (139). This is an important factor in considerations of the stability of cyclic disulfides, a subject which has received much attention in recent years, especially because of the interest in $\alpha$-lipoic acid (16, 25, 177).

The bond between two divalent sulfur atoms appears to be stronger than that between two oxygen atoms. The values of $D$(S—S) in dialkyl disulfides, hydrogen disulfide, and sulfur ($S_8$) lie in the range 50–70 kcal./mole (63, 81, 121, 166), while $D$(O—O) in dialkyl peroxides is about 40 kcal./mole (122).

## III. Analytical Procedures for Kinetic Studies

One of the major problems encountered in studying the ionic cleavage reactions of sulfur–sulfur bonds has been the application of a suitable analytical method for determining the concentration of either reactants or products, and hence the rate and/or equilibrium constant. In many cases reactions which equilibrate rapidly at room temperature are involved, so that the analytical method chosen must not upset the position of equilibrium, and, if rate constants are required, an effective means of stopping the reaction must be found. Spectrophotometric, polarimetric, and isotopic methods are most adaptable. Perhaps the most active workers in the search for suitable analytical methods have been Kolthoff, Stricks, and coworkers (96–99).

### A. SPECTROPHOTOMETRIC METHODS

Ryle and Sanger (146) studied disulfide exchange, using the reaction between cystine and bis(2,4-dinitrophenyl)cystine to form monodinitrophenyl cystine (mono-DNP). The bis(2,4-dinitrophenyl)cystine is soluble in ether, but the

mono(2,4-dinitrophenyl)cystine is not. The extent of exchange can be followed by measuring the absorption at 335 mμ in the aqueous phase after extraction with ether. Benesch and Benesch (15) used this same procedure. Schöberl and Ludwig (155) used a colorimetric method to estimate the thiol produced by the cleavage of some disulfides with cyanide or sulfite ions. Similarly, the cleavage of nitro-substituted aromatic disulfides by sulfite, cyanide, hydroxide, and alkyl mercaptide ions to displace nitro-substituted aromatic mercaptides can be followed from the optical density of the latter at 350–450 mμ (135). The reaction between $S_8$ and cyanide ion has been followed using the strong sulfur absorption between 250 and 300 mμ (9).

### B. POLARIMETRIC METHODS

These methods enabled Fredga to study the exchange between (+)-dithiodilactic acid and thiolactic acid (64). *l*-Cystine has an abnormally high optical rotation (140). This has been utilized in kinetic studies of the *l*-cystine–thioglycolic acid exchange (17), the racemization of *l*-cystine by cysteine (140), and cleavage of *l*-cystine by arylarsinites (33).

### C. ISOTOPIC METHODS

$S^{35}$ labelling has been used to study the kinetics of thiosulfate–tetrathionate exchange (47) and of thiol–disulfide exchange (50). Electrophoresis on paper impregnated with mercuric acetate gave an estimate of the concentrations of mixed $S^{35}$-labelled disulfides formed in thiol–disulfide exchange (42). Thus equilibrium constants and redox potentials for systems related to cystine/cysteine were evaluated.

### D. TITRIMETRIC METHODS

Stricks and Kolthoff investigated several titrimetric methods (97), and eventually titrated thiols amperometrically with mercuric chloride, using a rotating mercury pool electrode (99). In this way they estimated the disulfide linkages in bovine serum albumin (98). Cecil and McPhee (29) titrated thiols with silver nitrate, using silver or silver-thiol electrodes; using this method, McPhee (127) determined rate constants for the reaction of sulfite ion with disulfides related to cystine.

In some cases estimation of the displacing base rather than the displaced mercaptide is more simple. The reaction between triphenylphosphine and $S_8$ was followed by an iodometric titration of the unconsumed triphenylphosphine (11). This would not be suitable when oxidizable products, such as thiols, are formed.

### E. MISCELLANEOUS METHODS

Equilibrium constants for thiol–disulfide exchanges have been estimated using viscosity measurements (98). Stricks, Kolthoff, and coworkers (98) have also developed a polarographic method (174), which estimates the concentration of disulfides through their reduction and resulting half-wave potentials. This method gave the equilibrium constants for the exchange between cystine, oxidized glutathione, and dithiodiglycolic acid.

### F. IDENTIFICATION OF REACTION PRODUCTS

Identification before disproportionation (149), cyclization (153), or oxidation (135) is not always simple. Thiols can be identified by forming a sulfide derivative; Leandri and Tundo (106) and the authors (135) have shown that unsymmetrical disulfides are cleaved as in equation 1, by carrying out the reaction in the presence of an equimolar amount of 2,4-dinitrochlorobenzene and examining the sulfide produced (equation 2; Ar = 2,4-dinitrophenyl).

$$RS—SR' + OH^- \rightarrow RSOH + R'S^- \quad (1)$$

$$R'S^- + ArCl \rightarrow R'SAr + Cl^- \quad (2)$$

Similar methods have shown that a sulfinate rather than a mercaptide ion is displaced from thiolsulfones by alkali (107). The reaction between sulfide ion and disulfides was clarified in a similar way (123). In many cases reactions are carried out under nitrogen to avoid atmospheric oxidation of thiols (127, 135).

## IV. Homolytic Scission of the Sulfur–Sulfur Bond

While this review is concerned with the heterolysis of sulfur–sulfur bonds, convincing evidence exists that homolytic fission of the sulfur–sulfur bond in organic disulfides, in elemental sulfur, and in organic polysulfides occurs frequently. Pertinent evidence has been reviewed recently by Bateman, Moore, and Porter (13).

### A. HOMOLYSIS OF DISULFIDES

Disulfides react with radical reagents such as triphenylmethyl (162), metals (78, 126), nascent hydrogen (137), and hydrocarbon radicals involved in vinyl polymerizations (137). Such reactions can be generalized as in equation 3.

$$R\bullet + R'SSR\bullet \rightarrow RSR\bullet + R'S\bullet \quad (3)$$

Light-induced homolysis of the sulfur–sulfur bond in dialkyl and diaryl disulfides gives thiyl radicals (87, 124, 143, 144). A quantum yield of unity was found by Whitney and Calvin (194) for the photolysis of 1,2-dithiolane and 6,8-thioctic acid. Photolysis can be represented by equation 4.

$$RSSR \xrightarrow{h\nu} 2RS\bullet \quad (4)$$

Disulfides are very effective initiators of the polymerization of acrylonitrile (19) and styrene (52), but only under photolytic conditions (87). Halogen substituents on the aromatic nucleus promote dissociation of unsymmetrical diaryl disulfides in ultraviolet light (104). Nitro substituents do so to a lesser extent (104).

Much evidence has been advanced (13) which suggests thermal homolysis of the sulfur–sulfur bond at normal temperatures (30–150°C.), but this has been refuted in many cases (87, 116). Leandri and Tundo (104) report that unsymmetrical diaryl disulfides dissociate homolytically to give symmetrical disulfides when heated to 170°C. or when boiled in dioxane. Evidence that hot solutions of certain disulfides in toluene are paramagnetic does not necessarily establish

thermal homolysis, since excitation of the disulfide to a triplet state would produce a comparable effect (35). In any case, simple alkyl or aryl disulfides are not paramagnetic at temperatures up to 140°C. (70).

Bateman, Moore, and Porter (13), on the basis of an extensive literature survey, conclude that purely thermal homolysis of sulfur–sulfur bonds in organic di- and polysulfide molecules, and in elemental sulfur, at temperatures below 140°C. has not yet been conclusively demonstrated. Such fission occurs only when induced photochemically or by radical displacement reactions. Kharasch (87) and Lecher (115) advanced this view earlier, and regarded as inconclusive, or incorrect, evidence cited in favor of thermal homolysis under the conditions claimed.

### B. HOMOLYSIS OF ELEMENTAL SULFUR AND OF ORGANIC POLYSULFIDES

Liquid sulfur abruptly increases in molecular complexity at 150°C., a change which is attributed to the formation of a linear polymeric diradical form of sulfur, in equilibrium with $S_8$ rings (45, 70), i.e.,

$$S_8 + \cdot S \cdot_x \rightleftarrows \cdot S \cdot_{x+8} \tag{5}$$

Paramagnetic studies of liquid sulfur at 189°C. confirm this view (31), but Bateman, Moore, and Porter (13) consider it unlikely that diradicals of sulfur are present at appreciable concentrations below 140°C.

Unlike disulfides, sulfur (12) and organic polysulfides (87) inhibit the polymerization of vinylic monomers. This is due to homolysis of the sulfur–sulfur bond by the polymeric radical to give a radical which can not reinitiate polymerization (13).

$$R_nS \cdot_x \qquad (x > 1) \tag{6}$$

## V. Electrophilic Scission of the Sulfur–Sulfur Bond

It has long been known that disulfides are hydrolyzed in acid media (148, 168). In 1952, Lien, McCaulay, and Proell (118) proposed a mechanism (equations 7 to 10) for the acid-catalyzed interaction of alkyl disulfides with olefins, which postulated cleavage of the sulfur–sulfur bond via attack, on sulfur, by a proton and then by a carbonium ion.

$$RS{-}SR + H^+ \rightleftarrows [RS(H){-}SR]^+ \tag{7}$$

$$[RS(H){-}SR]^+ + CH_2{=}CH_2 \rightarrow RSCH_2CH_2^+ + RSH \tag{8}$$

$$RSCH_2CH_2^+ \rightarrow RS{-}SR \rightarrow RSCH_2CH_2SR + RS^+ \tag{9}$$

$$RS^+ + CH_2{=}CH_2 \rightarrow RSCH_2CH_2^+ \tag{10}$$

This work, however, attracted little attention to the possibility that fission of sulfur–sulfur bonds could occur generally by an electrophilic mechanism, until the simultaneous discovery of Moore and Porter (131) and Benesch and Benesch

(15) that arenesulfenyl chlorides enter into electrophilic reaction with symmetrical disulfides, to give unsymmetrical disulfides.

$$ArSCl + RS—SR \rightleftarrows ArSSR + RSCl \quad (11)$$

An examination of the literature now reveals that many reactions of disulfides can be formulated as in equation 12, where X is an electrophilic reagent.

$$RS—SR + X^+ \rightleftarrows RSX + RS^+ \quad (12)$$

### A. CLEAVAGE INDUCED BY PROTONS

Ryle and Sanger (146) discovered that disulfide exchange occurs in acid solution and is inhibited by added thiols (148). This led Benesch and Benesch (15) to suggest that interchange between cystine and bis(dinitrophenyl)cystine in acid solution occurs by an ionic chain reaction, initiated by protons (equation 13) and propagated by sulfenium ions (equations 14 and 15).

$$RS—SR + H^+ \rightleftarrows RS^+ + RSH \quad (13)$$

$$RS^+ + R'S—SR' \rightleftarrows R'S—SR + R'S^+ \quad (14)$$

$$R'S^+ + RS—SR \rightleftarrows R'S—SR + RS^+ \quad (15)$$

Added thiols inhibit this sequence by lowering the $RS^+$ concentration.

$$RS^+ + R'SH \rightleftarrows RS—SR' + H^+ \quad (16)$$

The extent of disulfide mixing is very sensitive to acid concentration and reaction 13 is apparently slow, since an induction period is observed. Equilibrium 13 lies well to the left, so that disulfide mixing is very slow in hydrochloric acid weaker than 9 *N* (15). The acid-catalyzed interaction of alkyl disulfides with olefins (118) (equations 7–10) is seen to be a similar process.

The sulfur–sulfur bond in cystine "disulfoxide" is cleaved in acid solution (185) to give cysteinesulfinic acid and the reactive sulfenium ion (15).

$$RS—\overset{\overset{O}{}}{\underset{\underset{O}{}}{S}}R + H^+ \rightleftarrows RS^+ + RSO_2H \quad (17)$$

Electrophilic scission of the sulfur–sulfur bond (equation 18) has been postulated for the acid-base catalyzed reactions of dimethylformamide with carboxyl-substituted alkyl disulfides related to cystine (157).

$$B{:}H^+ + RS—SCH_2R' \rightleftarrows \underset{H}{RS—SCH_2R'} + B{:} \rightleftarrows RSH + R'CH_2S^+ \quad (18)$$

then

$$R'CH_2S^+ + B{:} \rightarrow R'CH{=}S + B{:}H^+ \quad (19)$$

where $B = (CH_3)_2NCHO$.

Unpublished work by the authors has shown that unsymmetrical disulfides, such as 2,4-dinitrophenyl ethyl disulfide and 4-chloro-2-nitrophenyl ethyl disulfide, give symmetrical disulfides in quantitative yield when dissolved in concentrated sulfuric acid at room temperature. No reaction occurs in 12 *N* hy-

drochloric acid, but this may be due to the insolubility of the unsymmetrical disulfides in this reaction mixture. The mechanism is not known, but the first step may be:

$$ArS{-}SR + H^+ \rightleftarrows ArS^+ + RSH \tag{20}$$

### B. CLEAVAGE INDUCED BY SULFENIUM IONS

2,4-Dinitrobenzenesulfenyl chloride and trichloromethanesulfenyl chloride catalyze disulfide exchange between cystine and bis(dinitrophenyl)cystine (15). The sulfenyl chlorides form sulfenium ions in acid solution (88), so that the reaction can be represented generally as in equations 21 and 22.

$$RS^+ + R'S{-}SR' \rightleftarrows RS{-}SR' + R'S^+ \tag{21}$$

$$R'S^+ + R''S{-}SR'' \rightleftarrows R''S{-}SR' + R''S^+ \tag{22}$$

A similar reaction, in which a number of symmetrical disulfides (RSSR) react with 2,4-dinitrobenzenesulfenyl chloride or 4-carboxy-2-nitrobenzenesulfenyl chloride (ArSCl), in acetic acid at room temperature to give unsymmetrical disulfides, has been demonstrated by Moore and Porter (131), who propose the mechanism shown in equation 23. A polar mechanism involving separation of charges in the transition state would seem to be involved, since less polar solvents decrease the rate of exchange.

$$\begin{array}{ccccc} \overset{\delta+}{Ar}S{-}\overset{\delta-}{Cl} & & ArS{-}\overset{\frown}{Cl}^- & & ArSSR \\ + & \rightleftarrows & \uparrow & \rightarrow & + \\ R{-}\ddot{S}{-}\ddot{S}{-}R & & [R{-}\overset{+}{S}{-}S{-}R] & & RSCl \end{array} \tag{23}$$

Sulfenium ions also react with monosulfides to give disulfides, presumably by electrophilic attack on sulfur (130).

### C. CLEAVAGE INDUCED BY HALOGENS

Halogenation of disulfides to give sulfenyl halides (89) appears to be an electrophilic process, although, as in the halogenation of aromatic systems (82), a free-radical mechanism may also operate at elevated temperatures or under homolytic conditions. The reaction is greatly accelerated by Friedel–Crafts catalysts and by sulfuric acid (89). Sulfuryl chloride is a much more effective chlorinating agent than chlorine gas (92). These facts suggest, by analogy with aromatic halogenation, that chlorination involves electrophilic attack by a $Cl^+$ ion (equations 24 and 25).

$$\overset{\delta+}{Cl}{-}\overset{\delta-}{Cl} + RS{-}SR \rightarrow RSCl + RS^+ + Cl^- \tag{24}$$

$$RS^+ + Cl^- \rightarrow RSCl \tag{25}$$

Catalysis by concentrated sulfuric acid may be due to

$$RS{-}SR + H^+ \rightleftarrows RSH + RS^+ \tag{26}$$

then

$$RS^+ + Cl_2 \rightarrow RSCl + Cl^+ \quad (27)$$

and

$$Cl^+ + RS—SR \rightarrow RSCl + RS^+ \quad (28)$$

Bromination of disulfides is a similar process.

### D. CLEAVAGE INDUCED BY CARBONIUM IONS

Challenger and Taylor (31), during their study of biological methylations, have shown that betaine methylates disulfides to give a methyl monosulfide. The reaction is apparently an electrophilic attack by a methyl carbonium ion.

$$RS—SR + CH_3^+ \rightarrow RSCH_3 + RS^+ \quad (29)$$

In view of this reaction and the other examples of electrophilic scission of the sulfur–sulfur bond already discussed, Friedel–Crafts alkylations or acylations of disulfides should be possible. Sulfenium-ion mechanisms will be involved in these and related reactions.

### E. OXIDATION OF DISULFIDES

Oxidation of olefins by per acids is regarded as an electrophilic process (181). The active oxygen enters the olefin molecule as a cationic group ($OH^+$) at the same point as a positively polarized bromine atom does in heterolytic bromination (190). Divalent sulfur behaves very much like an ethylenic group (34), and it seems reasonable to regard the oxidation of disulfides by per acids as an electrophilic attack by $OH^+$ on sulfur (equation 30). The per acid oxidation of azo to azoxy compounds has also been compared with the per acid oxidation of disulfides (105).

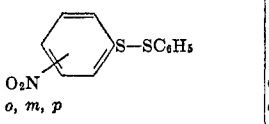
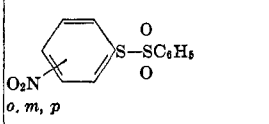
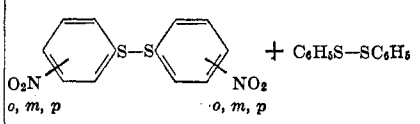
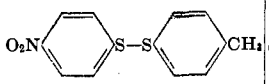
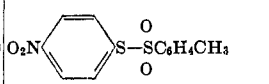
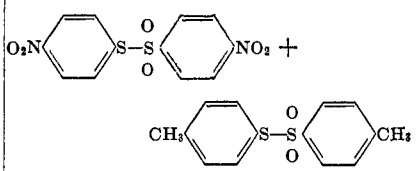
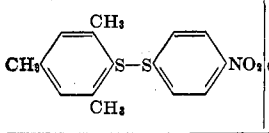
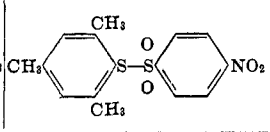
$$RS—SR' + 2R''CO_3H \rightarrow \underset{\underset{O}{\|}}{RS}—SR' + 2R''COOH \quad (30)$$

Although cleavage of the sulfur–sulfur bond is not involved in these reactions, some light is thrown on the polarization of the sulfur–sulfur bond and support is given to the explanation by Moore and Porter (131) for the orientation of products during the disulfide–sulfenyl chloride exchange. In the absence of steric effects, oxidation of unsymmetrical disulfides takes place at the sulfur atom furthest removed from an electron-withdrawing substituent. Some results obtained by Leandri and Tundo (105) are presented in table 2. It can be seen that oxidation takes place at the sulfur atom furthest removed from the electron-withdrawing nitro group, except in the case of 2,4,5-trimethylphenyl 4′-nitrophenyl disulfide, where presumably the steric effect of *o*-methyl groups hinders the approach of the $OH^+$ electrophile.

The electron density about the sulfur atoms in a disulfide RS—SR′, where

TABLE 2

*Oxidation of disulfides (105) by per acids*

| Disulfide | Asymmetric Product | Other Products |
|---|---|---|
|  |  |  |
|  |  |  |
|  |  | — |

R′ is more electron-withdrawing than R or sulfur, would thus appear to be as in formula IV.

$$\overset{\delta+}{\text{R}}\text{—}\overset{\delta+}{\text{S}}\text{—}\overset{\delta-}{\text{S}}\text{—R}'$$

IV

This is confirmed by results for the cleavage of disulfides by sulfenium ions.

### F. MECHANISM OF ELECTROPHILIC SCISSION

Leandri and Tundo (112) considered the reaction between unsymmetrical disulfides and 2,4-dinitrochlorobenzene (ArCl), in the presence of sodium bicarbonate, to be a nucleophilic attack on ArCl by a disulfide molecule, polarized as shown in equation 31 and not as already shown in equation 7. Reaction 31, which proceeds exclusively as shown, represents such a reaction and has been studied by the authors (135) for purposes of comparison with the work of Moore and Porter (131).

$$\text{Ar—}\overset{\delta-}{\text{S}}\text{—}\overset{\delta+}{\text{S}}\text{—CH}_2\text{C}_6\text{H}_5 + \text{ArCl} \xrightarrow[\text{or } CN^-]{HCO_3^- (HOH)} \text{Ar—S—Ar} + \text{C}_6\text{H}_5\text{CH}_2\text{S}\begin{matrix}(OH)\\(CN)\end{matrix} \quad (31)^3$$

The exchange reaction between arenesulfenyl chlorides and disulfides (131) might be regarded as a similar reaction, involving displacement of chloride ion from the sulfenyl chloride by the polarized disulfide acting as a base towards sulfur (equation 32).

$$\text{ArS—}\overset{\delta-}{\text{S}}\text{—}\overset{\delta+}{\text{S}}\text{—CH}_2\text{C}_6\text{H}_5 + \overset{+-}{\text{ArSCl}} \rightleftarrows \text{ArS—SAr} + \text{C}_6\text{H}_5\text{CH}_2\text{SCl} \quad (32)$$

However, Moore and Porter could not observe any reaction between 2,4-dinitrophenyl benzyl disulfide and 2,4-dinitrobenzenesulfenyl chloride. They did propose the exchange shown in equation 33. This would confirm that disulfides of

[3] Ar = 2,4-dinitrophenyl in equations 31 to 36.

this type are polarized as shown in equations 7 and 33, and not as shown in equation 32.

$$\overset{\delta+}{\text{ArS}}\text{—}\overset{\delta-}{\text{SCH}_2\text{C}_6\text{H}_5} + \text{ArSCl} \rightleftarrows \text{ArS—SCH}_2\text{C}_6\text{H}_5 + \text{ArSCl} \quad (33)$$

Reaction 33 suggests that reactions 31 and 32 proceed by a different mechanism. Since it has been shown that reaction 31 proceeds only in the presence of bases (112, 135), the authors propose that the reaction of disulfides with ArCl is a two-step process. The first step (reaction 34) involves nucleophilic cleavage of the sulfur–sulfur bond (equation 40). The orientation of cleavage is governed by the relative base strengths of the two mercaptides available for displacement (page 600). The second step is sulfide formation (reaction 35).

$$\text{ArS—SCH}_2\text{C}_6\text{H}_5 + \text{OH}^- \rightleftarrows \text{ArS}^- + \text{C}_6\text{H}_5\text{CH}_2\text{SOH} \quad (34)$$

$$\text{ArS}^- + \text{ArCl} \rightarrow \text{ArSAr} + \text{Cl}^- \quad (35)$$

Assuming that the electron density about sulfur is as shown in equation 7, the exchange (reaction 31) and reactions 21 and 23 can be regarded as electrophilic attack on the least positive sulfur atom by a sulfenium ion (reaction 36), or by a covalently bound, polarized sulfenyl chloride (reaction 23) (131).

$$\overset{\delta-}{\text{ArS}}\text{—}\overset{\delta+}{\text{S}}\text{—}\overset{\delta+}{\text{CH}_2\text{C}_6\text{H}_5} + \overset{+}{\text{Ar'S}} + \text{Cl}^- \rightleftarrows \text{ArS}^+ + \text{Cl}^- + \text{Ar'S—SCH}_2\text{C}_6\text{H}_5 \quad (36)$$

## VI. Nucleophilic Scission of the Sulfur–Sulfur Bond

### A. Introduction

Several mechanisms, some of which are discussed below, have been proposed to explain the variety of products, the reactivity of structurally different compounds, and the anomalous behavior of hydroxide ion when the sulfur–sulfur bond is cleaved in the presence of a base. The most common, and the simplest, is displacement of a thioanion (56) from sulfur by a base which has a greater affinity for sulfur (is more "S-nucleophilic") than the displaced thioanion. Although Schiller and Otto (149), in 1876, had expressed reaction 37 as shown, it was not until Olav Foss (56) turned his attention to the subject that a clearer under-

$$\text{RS—SR} + \text{OH}^- \rightarrow \text{RSOH} + \text{RS}^- \quad (37)$$

standing was obtained. Foss realized that reaction 37 was simply a special case of nucleophilic displacement from divalent sulfur as in reaction 38, the only special feature being that two sulfur atoms are available for attack by a base

$$\text{—S—X} + \text{Y}^- \rightleftarrows \text{—S—Y} + \text{X}^- \quad (38)$$

$\text{Y}^-$. Nucleophilic displacements of this type are now well known. Such reactions as (*1*) the interconversions of sulfenic acid derivatives (93), i.e., sulfenyl chlorides (RSCl) or corresponding bromides (RSBr), thiocyanates, (RSSCN), "sulfenyl cyanides" (RSCN), sulfenyl sulfites ($\text{RSSO}_3^-$) and sulfenyl esters (RSOR), (*2*) the displacement from thiosulfate ion of sulfite by cyanide (9), triphenylphosphine (9), and labelled sulfite ions (60), and (*3*) the scission of $\text{S}_8$ by cyanide (57) and triphenylphosphine (11) can be interpreted in terms of the general equation 38, where $\text{Y}^-$ is a base with greater affinity for sulfur than $\text{X}^-$. Disulfides can,

for purposes of discussion, be regarded as sulfenyl mercaptides, and are simply more stable to Lewis bases than most sulfenic acid derivatives, because a mercaptide anion is more "S-nucleophilic" than many other bases and thus more difficult to displace.

### B. MECHANISMS OF REACTION

Wagner (188) has suggested that cleavage of the sulfur–sulfur bond involves a reversible $S_N1$ type disproportionation into ions (reaction 39), followed by reactions of the positively and negatively charged fission products. These secondary reactions depend on the structure of R and the strength of the carbon–sulfur bond.

$$RS—SR' \rightleftarrows RS + R'S^- \tag{39}$$

Reaction 39 requires that the rate of reaction be independent of the concentration of the base, but in all reactions, involving base-induced scission of the sulfur–sulfur bond, for which kinetic data are available (60), bimolecular reactions, following second-order kinetics, are observed. It is therefore felt that equations such as 40, based on equation 38, represent the nucleophilic cleavage of the sulfur–sulfur bond by a base $Y^-$, more generally than equation 39.

$$RS—SR' + Y^- \rightleftarrows RSY + R'S^- \tag{40}$$

In many reactions of bases with disulfides the equilibrium shown in equation 40 lies well to the left, either because $R'S^-$ is more S-nucleophilic than the base, $Y^-$, or because steric factors hinder attack by $Y^-$. In such cases other reaction paths, dependent on the structure of the disulfide and the nature of the base, are taken, as shown by the variety of products formed. Elemental sulfur (67, 77), hydrogen sulfide (150, 156), sulfinic acids (149), carbonyl compounds (150), carboxylic acids (66), thio acids (66, 150), monosulfides (179), and thiazolines (154) have all been isolated and identified. It is difficult, as some workers have done (67), to believe that all these products result from decompositions of sulfenic acids, or their derivatives, despite the variety of known products from such decompositions (91).

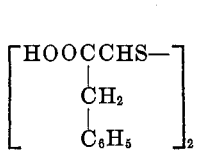
Two alternate mechanisms of scission other than that shown in equation 40 are based on the hypothesis that, in basic solutions, a proton can be removed from carbon under the activating influence of a nearby sulfur atom, aided by an electron-withdrawing substituent such as carboxyl. A third mechanism is based on displacement of sulfur from carbon, followed by decomposition of the resulting dimercaptide ion, as discussed below.

#### *1. Ionization of β-hydrogen*

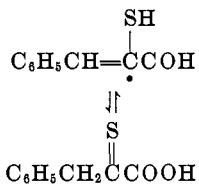
Spectrophotometric studies (140) reveal that molecules such as cystine may lose a β-hydrogen atom in basic solution. Hence Rosenthal (140) proposed equation 41 as the mechanism for the alkaline hydrolysis of molecules of this type. The key step is the acceptance by sulfur of the surplus electrons of the carbanion. The ability of sulfur to expand its valency in this manner is discussed on page 599. Carbonyl compounds and hydrogen sulfide are formed through hydrolysis of a thioaldehyde as shown.

$$RCH_2S{-}SR' + OH^- \rightleftarrows R\bar{C}HS{-}SR + H_2O \rightleftarrows RCH{=}\bar{S}{-}SR' \rightarrow \underset{\downarrow H_2O}{RCH{=}S} + RS^- \quad (41)$$
$$RCHO + H_2S$$

As an example of reaction 41, diphenyldithiodilactic acid (V) hydrolyzes to mercaptocinnamic acid (VI) (150), as shown in equation 73.

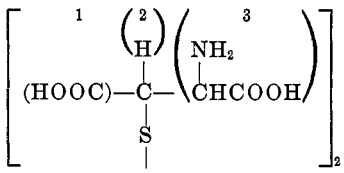


V



VI

Rosenthal (140) demonstrated the role of the $\beta$-hydrogen atom in the alkaline hydrolysis of disulfides in a striking way. Compound VII, as shown, is very labile in alkali, but if groups 1 and 2, or 2 and 3, are replaced by methyl groups, the



VII

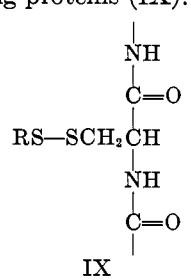
resulting compounds are stable to alkali; if only group 3 is substituted by methyl, however, the compound is still hydrolyzable, showing the importance of the presence of the $\alpha$-hydrogen substituent.

### *2. Ionization of $\alpha$-hydrogen*

Tarbell and Harnish (183) consider that mechanism 42, involving ionization of an $\alpha$-hydrogen atom, is the initial step for the alkaline hydrolysis of disulfides like VIII and have reviewed examples of such reactions.

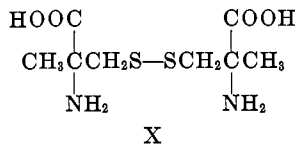
$$\underset{\text{VIII}}{RS{-}SCH_2\overset{\displaystyle X}{\overset{|}{C}}H{-}Y} + OH^- \rightleftarrows RS{-}SCH_2\overset{\displaystyle X}{\overset{|}{C}}{}^-{-}Y + H_2O \rightarrow RS{-}S^- + \overset{\displaystyle X}{\overset{|}{C}}{=}CH_2{-}Y \quad (42)$$
$$RS^- + S$$

Ionization is facilitated by electron withdrawal by X and Y. Such a situation is found in the cystine-containing proteins (IX).



IX

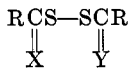
Swan (179) believes that the formation of lanthionine, $[HOOCCH(NH_2)CH_2]_2S$, from the hydrolysis of cystine has reaction 42 as the precursor, followed by a reverse $\beta$-elimination between the olefin and mercaptide (equation 75). Cystine can be cleaved by alkali at room temperature, whereas $\alpha,\alpha'$-dimethylcystine (X) is unaffected by boiling alkali after 3 hr. (180). This suggests that an acidic $\alpha$-hydrogen atom is required for reaction to take place.



X

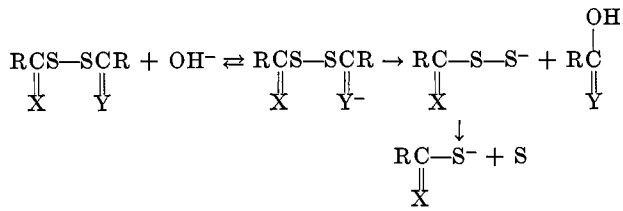
*3. Attack on carbon*

Disulfides like XI, in which X and Y are powerful electron-withdrawing, multivalent atoms such as oxygen, sulfur, or nitrogen, may have the $\alpha$-carbon atoms more susceptible to nucleophilic attack than their sulfur atoms (183). If carbon



XI

is attacked (equation 43), carboxylic acids and elemental sulfur would be formed when Y = oxygen in equation 43.



(43)

*4. Ionic displacement of mercaptides from sulfur*

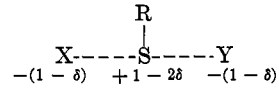
Mechanisms as represented in equations 41, 42, and 43 explain certain important examples of sulfur–sulfur bond cleavage by strongly alkaline bases, but since the ionic displacement mechanism has wider applications, this review gives that subject more detailed attention.

Such varied reactions as thiol–disulfide exchanges (44, 50, 64), alkylthiosulfate–sulfite exchanges (51), the reactions of elemental sulfur with cyanide (9) and triphenylphosphine (11), the cleavage of alkyl disulfides by sulfite ion (28) and aryl arsenites (33), and numerous reactions of polythionate ions (58) are all bimolecular, follow second-order kinetics, and involve ionic scission of the sulfur–sulfur bond, as shown by the products of reaction. Indeed, in all cases for which kinetic data are available, displacements from divalent sulfur are of the $S_N2$ type (60).

Fava, Iliceto, and Camera (49, 50, 51) have discussed the structure and charge distribution in the transition state for displacements at divalent sulfur. They suggest that the transition states for substitution at saturated carbon (37) and at

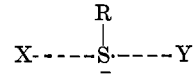
sulfur are similar, and that displacements from sulfur take place by a backside attack (49), so that the entering and leaving groups are in a straight line, as in XII. The two reactions thus have similar steric requirements, as discussed below.

Two suggestions have been made (51) as to the charge distribution in the transition state. The first involves only *s* and *p* orbitals of sulfur, with the central sulfur atom less negative than in the initial state (XII).




XII

The second, which the authors favor, utilizes the vacant *d* orbital of sulfur in a structure (XIII) in which the central sulfur has ten valence electrons with one pair in a 3*d* orbital. The configuration at the central sulfur is probably $sdp^3$, trigonal bipyramidal, with the vertices occupied by the entering and leaving groups (51). Here the central sulfur is more negative than in the initial state.

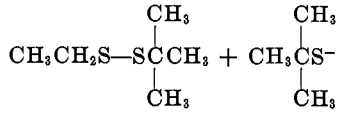



XIII

There is little evidence favoring either structure over the other. Fava, Iliceto, and Camera incline towards XII, but the authors consider XIII more likely, largely because of the greater susceptibility of sulfur to nucleophilic attack as compared to oxygen (60). Oxygen has no vacant *d* orbitals, but it is well known that the outer vacant *d* orbitals of sulfur are capable of being utilized in bond formation by accepting electrons from an external atom (132). Reaction 41 is an example of this (140). Longuet-Higgins (120) has shown that hybridization between *p* and *d* orbitals to give strongly directed $\pi$ bonds is theoretically very probable.

Steric factors are important in displacements at divalent sulfur. Methyl substituents on an $\alpha$-carbon atom hinder backside displacements at sulfur (49), just as methyl substituents in the ethyl, isopropyl, and neopentyl halides hinder backside displacement of halide ion from saturated carbon (37). Thus *tert*-butyl disulfide is very stable in the presence of bases (4), and the exchange of sulfite–*tert*-butylsulfenyl sulfite is slower than the sulfite–isopropylsulfenyl sulfite exchange by a factor of $10^3$ (49) (table 5). *tert*-Butyl mercaptide, $(CH_3)_3CS^-$, displaces ethyl mercaptide from diethyl disulfide (equation 44), but it will not displace ethyl mercaptide from ethyl *tert*-butyl disulfide (equation 45) (125). Steric resistance, of the neopentyl type, to formation of the transition state may explain this result (20).

$$CH_3CH_2S{-}SCH_2CH_3 + \textit{tert}\text{-}C_4H_9S^- \rightleftarrows CH_3CH_2S{-}SC_4H_9\text{-}\textit{tert} + CH_3CH_2S^- \quad (44)$$




(No reaction observed, although *tert*-butyl mercaptide exchange may occur) (45)

As discussed on page 607, the authors have used the "neopentyl" type of steric effect to explain the important observation of Schöberl and Ludwig (155) that disulfide linkages bound to tertiary carbon are not cleaved by bases such as cyanide and sulfite ion.

One aspect of the base-induced cleavage of the sulfur–sulfur bond which has not previously been considered in detail is that disulfides have two divalent sulfur atoms from which displacement can be made. With symmetrical disulfides this need not be considered, but with unsymmetrical disulfides (RSSR′) the interesting question arises as to which sulfur atom behaves as an electropositive center, and which sulfur is displaced as mercaptide. Two reactions are possible.

$$RS—SR' + Y^- \rightleftarrows RSY + R'S^- \quad (46)$$

$$RS—SR' + Y^- \rightleftarrows RS^- + R'SY \quad (47)$$

It has been shown that if $R'S^-$ has greater anionic stability than $RS^-$ only reaction 46 is observed (106, 135). Apparently the bond-breaking step governs the orientation of cleavage rather than the electron density about the individual sulfur atoms (135). Electron withdrawal by R′ lowers the base strength of $R'S^-$, favoring reaction 46.

The following examples (135), in which Ar = 2,4-dinitrophenyl, illustrate the above argument:

$$ArS—SCN + CN^- \rightarrow ArSCN + SCN^- \quad (48)$$

$$ArS—SCH_2CH_3 + CN^- \rightarrow ArS^- + CH_3CH_2SCN \quad (49)$$

$$ArS—SC_6H_5 + C_6H_5S^- \rightarrow ArS^- + C_6H_5S—SC_6H_5 \quad (50)$$

$$4\text{-}O_2NC_6H_4S—SC_6H_5 + CN^- \rightleftarrows 4\text{-}O_2NC_6H_4S^- + C_6H_5SCN \quad (51)$$

In equation 48 the thiocyanate ion has less affinity for sulfur than $ArS^-$ or cyanide ion, so that reaction proceeds rapidly as shown. In reactions 49 and 50 $ArS^-$ is the weakest base and is displaced exclusively, but not as rapidly as $SCN^-$ in reaction 48. 4-Nitrophenyl mercaptide is displaced in reaction 51, but cleavage is slower than in reaction 48 or reaction 49 because this mercaptide is more S-nucleophilic than $ArS^-$ or $SCN^-$ and is displaced less readily by any stronger base.

### C. EFFECT OF VARYING THE BASE IN THE IONIC DISPLACEMENT REACTION

Nucleophilic displacements from sulfur take place when the attacking base has a greater affinity for sulfur than the displaced group (56). The affinities of a base for sulfur (S-nucleophilicity) and for carbon (C-nucleophilicity) (178) are not necessarily parallel. The polarizability of the atom forming a new bond with sulfur or carbon seems to be a more important factor in displacements at sulfur. As will become apparent, elements of the third or fourth period of the Periodic Table—such as phosphorus, sulfur, and arsenic, which have readily polarizable electrons—have a greater tendency to form bonds with sulfur than do elements of the second period, such as oxygen and nitrogen. The effect may be associated with the ability of the larger elements to form *pd* bonds with sulfur in the transition state.

TABLE 3

*Displacement from divalent sulfur; S-nucleophilicity of* Y *in the reaction:*

$$RSX + Y^- \rightleftarrows RSY + X^-$$

(The groups, Y, are listed in order of approximate decreasing strength as S-nucleophiles)

| | |
|---|---|
| $R_3C^-$, $AlH_4^-$ | Grignard reagents cleave diethyl disulfide at room temperature (8). The carbon-sulfur bond is not broken by other bases (183). $LiAlH_4$ reduces dibenzyl disulfide in ether at room temperature (3). |
| $AsO(OH_2)^-$, $PO(OR)_2^-$ | Both displace ethyl mercaptide from diethyl disulfide in polar solvents (55, 75). |
| $P(OR)_3$, $RAsO(OH)^-$ | Both displace ethyl mercaptide from diethyl disulfide (16) and cystine (33). Tabled as shown because of the principles that (*a*) an anion is more nucleophilic than a neutral group and (*b*) R decreases the nucleophilicity of arsenic. |
| $R_3N$ | Cleaves diisopropyl disulfide at high temperature (142). |
| $RCH_2S^-$ | If R is hydrocarbon, it is displaced by the above bases. |
| $R_3P$, $R_3As$ | $R_3P$ does not displace ethyl mercaptide (161). $R_3P$ cleaves diphenyl disulfide in boiling benzene (161). $R_3As$ reacts rapidly with elemental sulfur (102). |
| $C_6H_5S^-$, $CN^-$ | See table 4. |
| $SO_3^-$ | See table 4. Displaces $o$-$O_2NC_6H_4S^-$ (135) and $HOOCCH_2S^-$ (29). |
| $OH^-$ | Displaces $o$-$O_2NC_6H_4S^-$ less readily than $SO_3^-$ (135). Displaces $HOOCCH_2S^-$ (180). |
| $COOHCH_2S^-$ | See above. |
| $o$-$O_2NC_6H_4S^-$, $p$-$O_2NC_6H_4S^-$, 2,4-$(NO_2)_2C_6H_3S^-$ | Displaced by $OH^-$ (135). |
| $RSO_2^-$ | Displaced from 2,4-$(NO_2)_2C_6H_3SSR$ (107a). |
| $S_2O_3^-$, $(NH_2)_2C{=}S$, $RSO_2S^-$, $(CH_3O)_2P(O)S^-$, $SCN^-$ | This order demonstrated by Foss (55). |
| $Br^-$, $Cl^-$ | Displaces $Cl^-$ from RSCl and is displaced by $SCN^-$ (93). |

Some of the most effective S-nucleophiles are the so called "anthioanions." This name was proposed by Foss (55) for anions which have such an affinity for sulfur that they form a stable thioanion when they react with elemental sulfur. Well-known anthioanion–thioanion pairs are: cyanide–thiocyanate, sulfite–thiosulfate, phosphine–phosphine sulfide, sulfinate–thiosulfinate, sulfide–polysulfide, and arsine–arsine sulfide. Hydroxide ion also reacts with elemental sulfur to give thiosulfate ion and polysulfides, supposedly through disproportionation of the unknown $SOH^-$ ion (60). Thioanions, in general, have less affinity for sulfur than anthioanions and are displaced from sulfur by the latter. Such reactions involve scission of the sulfur–sulfur bond.

Following a procedure suggested by the work of Olav Foss (60), the authors have surveyed a number of displacements from divalent sulfur by different bases. Table 3 lists the bases considered in the following pages, arranged in decreasing order of displacing power. The table is purely qualitative, and no doubt contains examples which will be modified by future work, but the authors believe, in the absence of steric effects in the group R and of special interactions of R with sulfur (as in SCN), that a group high in the table will displace any group below it from divalent sulfur. Similar tables, based on redox potentials, have been set

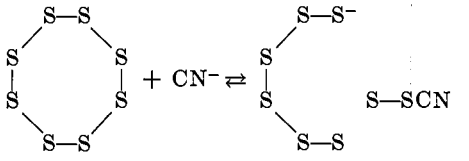
up (60) to demonstrate the base strength of thioanions. Table 3, based on known displacement data, is rather more extensive.

### D. SPECIFIC REACTIONS

#### *1. Cleavage induced by cyanide ion*

Cyanide ion can be regarded as a modified carbanion in its reactions with sulfur. Carbanions are amongst the most S-nucleophilic bases known (table 3), but in cyanide ion the negative character of carbon is reduced by resonance with the triply bound nitrogen atom. Cyanide ion, however, displaces many bases from sulfur, including some mercaptides, although, as will be seen, mercaptides are generally slightly more powerful bases towards sulfur.

The cyanide ion is a typical anthioanion (56) and readily forms thiocyanate with elemental sulfur. Bartlett and Davis (9) have shown that ring opening of $S_8$ by cyanide ion (equation 52) is the initial and rate-determining step in a second-order process. This confirmed a mechanism proposed by Foss (55), in which reactions of bases with $S_8$ can be regarded as a nucleophilic attack on sulfur, with ionic scission of the sulfur–sulfur bond. The reaction with cyanide ion is completed by successive displacements of thiocyanate by cyanide ion, and so on, removing one more sulfur atom each time.




(52)

$$^{-}S—S_5—S—SCN + CN^{-} \rightarrow {}^{-}S—S_5—SCN + SCN^{-}, \text{ etc.} \qquad (53)$$

Other reactions in which cyanide ion shows its affinity for sulfur are the following.

##### (a) Direct displacement of mercaptide

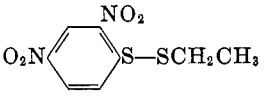
Cyanide has been reported as not reacting with diphenyl disulfide (192) and the forward reaction (equation 54) has been demonstrated (133). However, if 2,4-dinitrochlorobenzene is present to remove phenyl mercaptide as it is formed,

$$C_6H_5SCN + C_6H_5S^{-} \rightarrow C_6H_5SSC_6H_5 + CN^{-} \qquad (54)$$

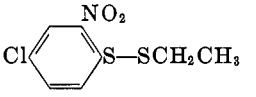
steam distillation of a sodium cyanide–diphenyl disulfide reaction mixture gives a 25 per cent yield of phenyl thiocyanate (135).

Spectrophotometric measurements of reaction 54 indicate that appreciable quantities of phenyl mercaptide are present at equilibrium if an excess of cyanide ion is present (135). However, the equilibrium is favored in the forward direction with equimolar quantities of reactants, suggesting that phenyl mercaptide is slightly more S-nucleophilic than cyanide ion (135). If electron-withdrawing substituents are on the aromatic nucleus, cyanide ion readily displaces substituted aryl mercaptides from divalent sulfur. Thus, the disulfides XIV to XIX are all rapidly cleaved by sodium cyanide (equation 55) at room temperature in aqueous

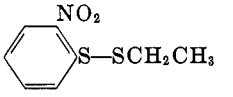
alcohol (135). The formation of the substituted aryl mercaptide rather than ethyl or phenyl mercaptide in reaction 55 confirms that the base strength of the displaced mercaptide governs the orientation of scission of the sulfur–sulfur bond.



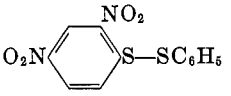
XIV



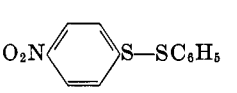
XV



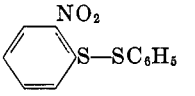
XVI



XVII



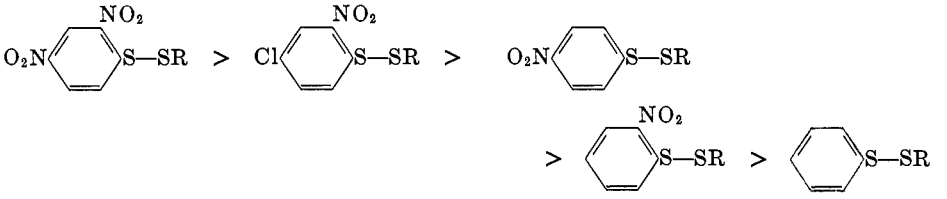
XVIII



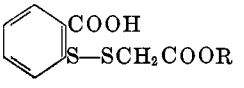
XIX

$$\mathrm{ArS{-}S{-}}\begin{cases}\mathrm{C_6H_5}\\ \text{or}\\ \mathrm{C_2H_5}\end{cases} + \mathrm{CN^-} \rightarrow \mathrm{ArS^-} + \begin{matrix}\mathrm{C_6H_5SCN}\\ \text{or}\\ \mathrm{CH_3CH_2SCN}\end{matrix} \qquad (55)$$

Susceptibility to cleavage by cyanide ion (and other bases) decreases markedly in the series of disulfides shown below (135), in which R is less electron-withdrawing than *o*-nitrophenyl.



Schöberl (158) has found that disulfides such as XX when treated with sodium cyanide give thiosalicylic acid in good yield. This result shows that electron



XX

withdrawal by an *o*-carboxylate group is sufficient to decrease the S-nucleophilicity of phenyl mercaptide below that of cyanide ion. It may be that an ortho neighboring-group effect is also assisting cleavage.

(b) Direct displacement of other thioanions

Cyanide, being a strong S-nucleophile, displaces many anions from sulfur. The sulfur–sulfur bond is cleaved in the following reactions of cyanide ion with the substances listed.

Thiocyanogen (170):

$$\mathrm{NCS{-}SCN + CN^- \rightarrow NC{-}SCN + SCN^-} \qquad (56)$$

Thiocyanogen thiosulfate (55):

$$\mathrm{NCS{-}SSO_3^- + CN^- \rightarrow {^-O_3S{-}SCN} + SCN^-} \qquad (57)$$

Thiosulfate (55):

$$SSO_3^- + CN^- \rightarrow SCN^- + SO_3^- \quad (58)$$

Sulfenyl thiocyanates (55):

$$RS{-}SCN + CN^- \rightarrow RSCN + SCN^- \quad (59)$$

Sulfenyl sulfinates (167):

$$RS{-}\overset{\overset{O}{\|}}{S}R + CN^- \rightarrow RSCN + RSO_2^- \quad (60)$$
$$\underset{\underset{O}{\|}}{}$$

Alkylsulfenyl sulfites (53):

$$RS{-}SO_3^- + CN^- \rightarrow RSCN + SO_3^- \quad (61)$$

These reactions all appear to be examples of the general mechanism for ionic scission of the sulfur–sulfur bond (equation 62). In the examples cited, $XS^-$ of reaction 62 is a much weaker base than $RS^-$ or $Y^-$.

$$RS{-}SX + Y^- \rightleftarrows RSY + XS^- \quad (62)$$

Some reactions of the type shown in equation 63 are summarized in table 4. The table can be used to estimate the relative S-nucleophilicity of cyanide ion

$$RSY + CN^- \rightleftarrows RSCN + Y^- \quad (63)$$

TABLE 4

*Examples of the equilibrium:* $XSY + CN^- \rightleftarrows XSCN + Y^-$

| Reaction | S-Nucleophilicity | Reference |
|---|---|---|
| $C_6H_5S{-}SC_6H_5 + CN^- \rightarrow C_6H_5SCN + C_6H_5S^-$ | $C_6H_5S^- \approx CN^-$ | (135) |
| $C_6H_5SCN + C_6H_5S^- \rightarrow C_6H_5S{-}SC_6H_5 + CN^-$ | $C_6H_5S^- > CN^-$ | (133) |
| $C_6H_5CH_2S{-}SCH_2C_6H_5 + CN^-$: no reaction | $C_6H_5CH_2S^- > CN^-$ | (128) |
| $NCS{-}SCN + CN^- \rightarrow NCSCN + SCN^-$ | $CN^- > SCN^-$ | (170) |
| $O_3S{-}SSCN + CN^- \rightarrow {}^-O_3S{-}SCN + SCN^-$ | $CN^-, S_2O_3^- > SCN^-$ | (55) |
| $SCN^- + \overset{*}{C}N^- \rightarrow \overset{*}{S}CN^- + CN^-$ (very slow) | | (2) |
| $SCN^- + P(C_6H_5)_3$: no reaction | | (9) |
| $SP(C_6H_5)_3 + CN^-$: no reaction | $CN^- \approx P(C_6H_5)_3$ | (9) |
| $SSO_3^- + CN^- \rightarrow SO_3^- + SCN^-$ | $CN^- > SCN^-, SO_3^-$ | (55) |
| $RS{-}S_2O_3^- + CN^- \rightarrow RSCN + S_2O_3^-$ | $CN^- > S_2O_3^-$ | (55) |
| $RSSCN + CN^- \rightarrow RSCN + SCN^-$ | $CN^-, RS^- > SCN^-$ | (55) |
| $ArSSCH_2CH_3 + CN^- \rightarrow ArS^- + CH_3CH_2SCN$ | $CN^- > 2,4\text{-}(NO_2)_2C_6H_3S^-$ | (135) |
| $2\text{-}O_2NC_6H_4SSCH_2CH_3 + CN^- \rightarrow RS^- + CH_3CH_2SCN$ | $CN^- > o\text{-}O_2NC_6H_4S^-$ | (135) |
| $CH_3CH_2S{-}SCH_2CH_3 + CN^-$: no reaction | $CH_3CH_2S^- > CN^-$ | (135) |
| $C_6H_5S{-}\overset{\overset{O}{\|}}{S}{-}C_6H_5 + CN^- \rightarrow C_6H_5SCN + C_6H_5SO_2^-$ | $CN^-, C_6H_5S^- > C_6H_5SO_2^-$ | (167) |
| $(HOOCCHS{-})_2 + CN^-$: no reaction | "Neopentyl" steric effect | (155) |
| $(HOOCCH_2S{-})_2 + CN^- \rightarrow HOOCCH_2SCN + HOOCCH_2S^-$ | $CN^- > CH_2COOH > S^-$ | (128) |
| $RSSO_3^- + CN^- \rightarrow RSCN + SO_3^-$ | $CN^- > SO_3^-$ | (53) |
| $RSSP(OCH_3)_2 + CN^- \rightarrow RSCN + (CH_3O)_2OPS^-$ | $CN^- > (CH_3O)_2\overset{\overset{O}{\|}}{O}PS^-$ | (55) |
| $R_2NCS{-}SCNR_2 + CN^- \rightarrow R_2NCS^- + R_2NCSCN$ | $CN^- > R_2NCS^-$ | (26) |

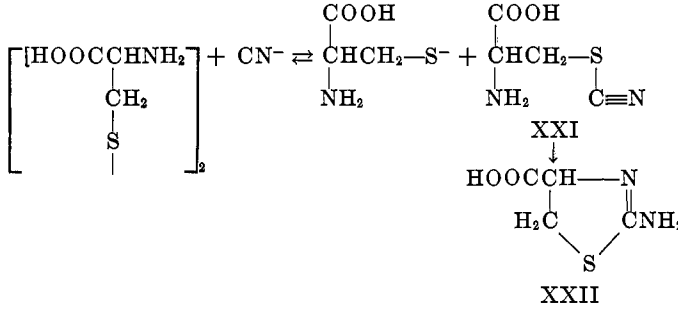
and a number of bases $Y^-$. Resonance in the structure $RSC{\equiv}N$ may be one reason why cyanide ion is so rarely displaced from divalent sulfur.

(c) Displacement aided by cyclization

Simple dialkyl disulfides do not react with cyanide ion (23), but often do so when carboxyl and/or amino groups are present in the molecule. Thus Ludwig (155) obtained one mole of thiol per mole of disulfide from the reaction of potassium cyanide with cystine and related disulfides. Windus and Turley (196) claim to have isolated cysteine and cyanocysteine from cystine, using lime and sodium cyanide. They also observed thiocyanate ions in the mixture.

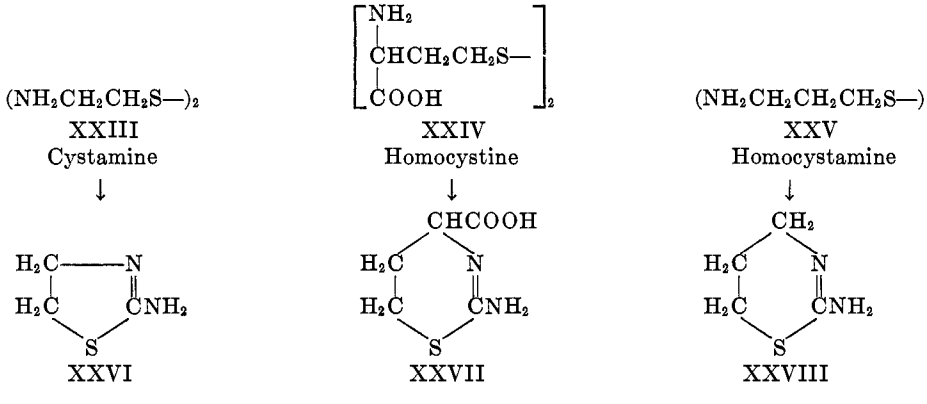
These reactions are not simply a hydrolysis of the disulfide in the alkaline cyanide solution, since Fraenkel-Conrat (62) has shown that at 35°C. and pH 5, hydrocyanic acid slowly cleaves cystine to give cysteine in yields not exceeding 50 per cent. Although cyanocysteine was not isolated, the reaction was regarded as a hydrocyanolysis.

Schöberl, Kawohl, and Hamm have recently reëxamined the reaction between cystine and cyanide ion (153, 154) and shown that cyanocysteine (XXI) cyclizes to 2-aminothiazoline-4-carboxylic acid (XXII), as shown in equation 64.



(64)

Other disulfides, such as cystamine (XXIII), homocystine (XXIV), and homocystamine (XXV), which have suitably situated amino groups, yield cyclic products (XXVI to XXVIII) together with the corresponding mercaptide (152).

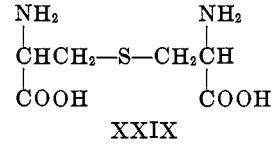


Normally, disulfides of the type $XCH_2S{-}SCH_2X$ do not react with cyanide ion as in equation 40, unless X is a strongly electron-withdrawing group and thus

$XCH_2S^-$ is less S-nucleophilic than cyanide ion. In the above examples, where an amino group is a substituent, the formation of stable thiazolines and similar cyclic derivatives forces an equilibrium such as shown in equation 64 to the right, despite the fact that in some cases the mercaptide displaced from the disulfide is a stronger base than cyanide ion.

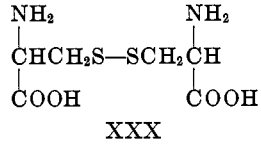
(d) Secondary displacement of thiocyanate ion

Swan (179) has isolated lanthionine (XXIX) from the cystine–potassium cyanide reaction and shown that eight other cystine derivatives give appreciable yields of the corresponding monosulfide under similar conditions.

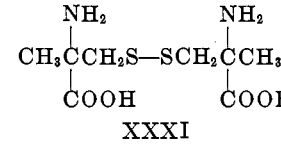


XXIX

Swan originally proposed (179) that the first step in lanthionine formation was ionization of an $\alpha$-hydrogen atom in the basic cyanide solution, followed by $\beta$-elimination, in a mechanism analogous to that proposed by Tarbell (183); *cf.* equation 42 for the reaction of alkali with cystine. However, he later demonstrated (180) that cystine (XXX) and $\alpha,\alpha'$-dimethylcystine (XXXI) are almost indistinguishable in their reactions with cyanide ions, making it unlikely that removal of an $\alpha$-hydrogen atom affects such reactions.

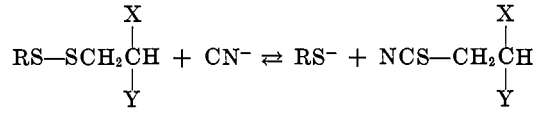


XXX

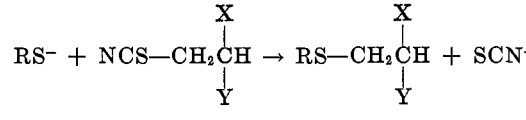


XXXI

The authors consider that monosulfide formation could be a secondary reaction (equation 66), occurring after the normal nucleophilic displacement (equation 65).

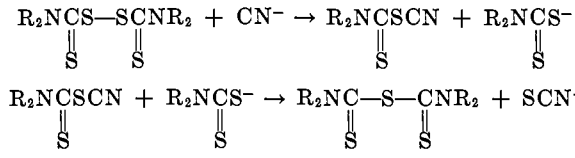


(65)



(66)

A displacement such as that shown in equation 66 would explain the presence of thiocyanate ion in the reaction mixture (196). The observations of Cambron (26), who showed that reactions 67 and 68 proceed as shown, also support this explanation.



(67)



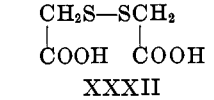
(68)

Displacements of thiocyanate from carbon by mercaptide, as in equations 66 and 68, are most likely when facilitated by electron-withdrawing substituents. For this reason, the yields of lanthionine from reaction 66 are greater when the cystine is in the protein form (IX), with X and Y (in equation 66) as —CONH— and —NHCO—, respectively, than in the free form (XXX), when X and Y are —COOH and —$NH_2$, respectively.

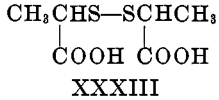
### (e) The "neopentyl" steric effect

Schöberl and Ludwig (155) established the important fact that where the sulfur atom of a disulfide is linked to a secondary or tertiary carbon atom, then that disulfide is particularly stable to most bases, including cyanide ion. Thus dithiodiglycolic acid (XXXII) is readily cleaved by cyanide, whereas dithiodilactic acid (XXXIII) is stable in cyanide solutions.

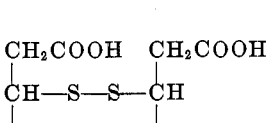
Other disulfides with secondary or tertiary carbon atoms attached to sulfur, such as succinic acid disulfide (XXXIV), substituted dithiodiglycolic acids (XXXV), and penicillamine disulfide (XXXVI) are also stable to cyanide ion (160).



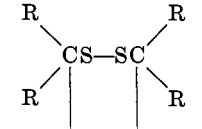
XXXII
Dithiodiglycolic acid



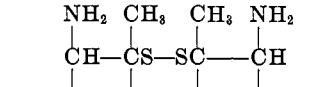
XXXIII
Dithiodilactic acid



XXXIV
Succinic acid disulfide



XXXV



XXXVI
Penicillamine disulfide

These results can be explained by steric hindrance to backside attack at sulfur (page 600), caused by the substituents on the $\alpha$-carbon atom. Another good example of this effect is the failure of *tert*-butylsulfenyl thiocyanate to react with cyanide ion, as reported by Himel and Edwards (58a). In view of the great difference in the S-nucleophilicity of cyanide vs. thiocyanate ion, this provides a revealing example of the importance of the steric factor.

### (f) Summary

It would appear that cyanide ion is not a sufficiently strong base to displace aliphatic mercaptides from sulfur unless aided by some secondary process, such

as cyclization of products, electron withdrawal by groups such as —COOH, —NHCO—, or CONH—, neighboring-group participation from carboxyl and/or amino, or ring strain in a cyclic disulfide such as in dithiolane. In the absence of special effects from R, equilibrium 69 lies well to the left.

$$RCH_2S—SCH_2R + CN^- \rightleftarrows RCH_2SCN + RCH_2S^- \quad (69)$$

Cyanide ion is only slightly less S-nucleophilic than phenyl mercaptide and will displace suitably substituted aryl mercaptides from sulfur.

*2. Cleavage induced by bases whose nucleophilic atom is oxygen*

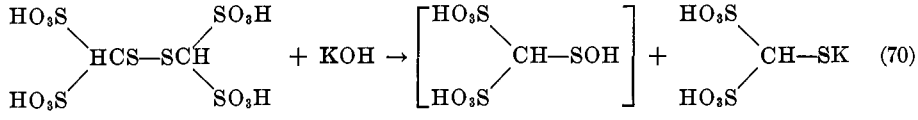
Hydroxide ion is the most common oxygen base, but other alkoxides such as ethoxide ion (69) cleave the sulfur–sulfur bond. Discussion will be confined to cleavage by hydroxide ion, but the principles apply equally well to other simple alkoxides. Hydroxide ion hydrolyzes elemental sulfur to thiosulfate and polysulfides (60), which presumably result from the disproportionation of the unstable $SOH^-$ ion.

Simple dialkyl disulfides are very stable to alkali. Schöberl and Wagner (160) have reviewed the data on hydrolysis of the sulfur–sulfur bond in disulfides, and conclude that only diaryl disulfides, disulfides with carbonyl functions, or disulfides with unsaturated groups at the $\alpha$-carbon atom are hydrolyzed. The reaction is not clean and hydrogen sulfide, sulfur, sulfinic acids, carbonyl compounds, carboxylic acids, and thio acids have all been observed as products.

Hydroxide ion (table 3) is not a strong displacing base at sulfur (135), so that despite the instability of RSOH and its decomposition to stable products (93), the direct displacement mechanism (equation 37) is rarely observed in reactions of aliphatic disulfides with hydroxide ion. Hydroxide ion is a strong base towards hydrogen and carbon, however, so that some of the alternate modes of scission (page 597) of the sulfur–sulfur bond are observed. Most of the known examples of scission can be classified according to the mechanisms already discussed. Examples of these mechanisms are given below.

(a) Direct displacement of mercaptide

Backer (4) reported the formation of the sulfenic acid XXXVII from reaction 70, but the evidence is not conclusive and in no other example of hydrolysis of a disulfide has a sulfenic acid been isolated. Their existence as intermediates has often been postulated (160), however, and can be inferred from the formation of sulfinic and sulfonic acids in the reaction mixture (149).




XXXVII (70)

Direct displacement of mercaptide, as in reaction 37, would appear to be involved in the cleavage of 2,4-dinitroaryl disulfides (ArS—SR) by alkali (135). Even bicarbonate solutions displace 2,4-dinitrophenyl mercaptide ($ArS^-$) from ArS—SR, if 2,4-dinitrochlorobenzene is present to capture $ArS^-$ as it is formed (112). Aryl disulfides containing less highly electron-withdrawing substituents react slowly with hydroxide ion, and diphenyl disulfide is cleaved only at elevated temperatures (149). Diaryl disulfides containing carboxyl substituents give mercaptides with alkali (158, 169). It appears likely that a direct neighboring-group interaction between $—COO^-$ and S may be involved. Unsymmetrical aryl disulfides are hydrolyzed so that the least S-nucleophilic mercaptide is displaced, in accord with the general ionic displacement mechanism. In such reactions, hydroxide ion is less S-nucleophilic than cyanide or sulfite ions (135).

Unsubstituted disulfides are cleaved by alkali only with difficulty. Diphenyl disulfide and phenyl ethyl disulfide give benzenesulfinic and ethanesulfinic acids, as well as mercaptans and disulfides, when heated with alkali at temperatures greater than 100°C. (149). Price (138) completely decomposed diethyl disulfide with alkali at 150–180°C., but only partial hydrolysis took place under reflux. Apparently, at elevated temperatures decomposition of ethanesulfenic acid displaces an equilibrium such as shown in equation 71 completely to the right. Decompositions of sulfenic acids explain why, in some cases, hydroxide ion appears to be a stronger base, relative to, for example, cyanide ion, than it actually is.

$$CH_3CH_2S—SCH_2CH_3 + OH^- \rightleftarrows [CH_3CH_2SOH] + CH_3CH_2S^- \qquad (71)$$

Sulfinates are displaced from "sulfenyl sulfinates" ($RSSO_2R'$) by alkali (equation 72) (107). A sulfinate ion is less S-nucleophilic than hydroxide ion or a mercaptide ion (table 3), so it is displaced exclusively and rapidly.

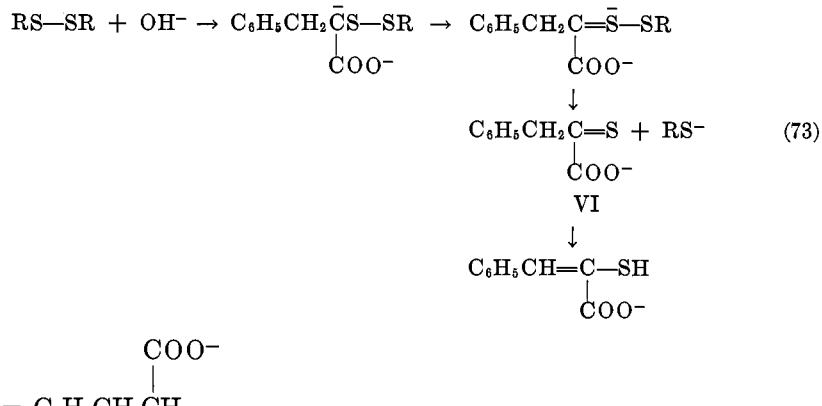
$$RS—\overset{\overset{O}{}}{\underset{\underset{O}{}}{S}}R' + OH^- \rightarrow RSOH + R'SO_2^- \qquad (72)$$

(b) Ionization of acidic hydrogen

With an ion like hydroxide, which is a strong base towards hydrogen yet relatively weaker towards sulfur, removal of a proton as in equation 41 or 42 may take place concurrently with direct displacement from sulfur. If equilibrium 37 is well to the left, reactions 41 and 42 may be the only modes of cleavage. The particular reaction (reaction 37, 41, or 42) will depend on the structure of the disulfide.

(i) Ionization from disulfides with carboxyl groups on carbon alpha to sulfur

Schöberl and Eck (151) isolated α-mercaptocinnamic acid from the alkaline hydrolysis of diphenyldithiodilactic acid. This product can be explained by a mechanism such as shown in equation 73, based on equation 41, in which an acidic hydrogen atom on the α-carbon atom is ionized (140).

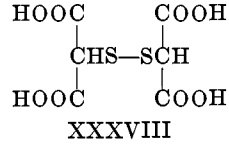


(73)

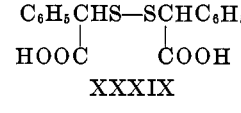
where R = $C_6H_5CH_2\underset{\displaystyle COO^-}{\underset{|}{C}}H$.

In general, a thioketone (VI) is hydrolyzed to hydrogen sulfide and carbonyl compounds as in equation 41.

Reactions such as reaction 41 could explain why disulfides such as dimalonic acid disulfide (XXXVIII), succinic acid disulfide (XXXIV), dithiodilactic acid (XXXIII), dithiodiglycolic acid (XXXII), and diphenyldithiodiglycolic acid (XXXIX), which have activating carboxyl groups and labile hydrogen atoms on the carbon adjacent to sulfur, give carbonyl compounds and mercaptides on hydrolysis (151). It is significant that succinic acid disulfide is cleaved by hydroxide ion but not by cyanide ion (160). Since cyanide ion is generally more "S-nucleophilic" than hydroxide ion (table 3), this result confirms that the hydroxide ion reaction is not occurring via direct ionic displacement of mercaptide. Cyanide ion, being a weak base towards the proton, does not react as shown in equation 41, nor does it react via equation 40, since steric effects interfere (page 599).



XXXVIII



XXXIX

Disulfides with $\alpha$-carboxyl groups but no $\alpha$-hydrogen are not cleaved by alkali under mild conditions (140). Presumably at higher temperatures direct displacement of mercaptide from sulfur might take place.

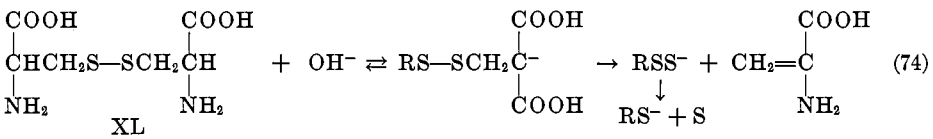
(ii) Ionization from disulfides with carboxyl groups on $\beta$-carbon

Many of the biologically important disulfides, notably cystine, have carboxyl groups two carbon atoms removed from sulfur. Rosenthal (140) believes that such disulfides are also cleaved as in equation 41, and that the ability of sulfur to expand its valency is sufficient to labilize a proton on the carbon atom adjacent to sulfur, without assistance from an $\alpha$-carboxyl group. The fact that diethyl disulfide is stable to alkali (138) makes this latter hypothesis unlikely, however.

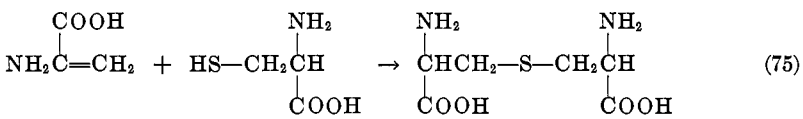
Swan (180) has observed that $\alpha,\alpha$-dimethylcystine (X) is stable to alkali,

whereas cystine (XL) is readily hydrolyzed. For this reason, he favors mechanism 42 (179) for the alkaline hydrolysis of disulfides related to cystine.

Lanthionine is produced from the hydrolysis of cystine possibly as shown in equations 74 and 75 (180).




(74)




(75)

It would seem to the authors that scission as in equation 74 is an alternative mechanism for the reaction of cystine with alkali, and that the direct displacement mechanism (equation 37) also occurs in conjunction with reaction 74. This latter conclusion is based on the fact that sulfite ion, which is only slightly more S-nucleophilic than hydroxide ion (table 3), will displace cysteine from cystine via the direct displacement reaction.

### (c) Displacement of dimercaptide from carbon

Tarbell and Harnish have recently reviewed the reactions, with alkali, of disulfides with unsaturated groups on the carbon adjacent to sulfur (183). A nucleophilic attack on carbon to displace dimercaptide ion (equation 37) is proposed. The mechanism shown in equation 43 would explain the formation of elemental sulfur and of oxygen compounds (160) in reactions of this type.

### (d) Summary

Hydroxide ion is a weaker base towards sulfur than cyanide ion, sulfite ion, or alkylmercaptide ion. Direct displacement of a mercaptide ion from sulfur by hydroxide ion occurs only if the displaced mercaptide is a weak base or at very high temperatures ($>100°C.$). Ionization of a proton under the labilizing influence of sulfur and a carboxyl group promotes cleavage of disulfides containing carboxyl substituents. A variety of products are formed in such reactions, depending on the structure of the disulfide.

## *3. Cleavage induced by bases whose nucleophilic atom is sulfur*

### (a) Sulfide ion

Certain reactions of elemental sulfur are remarkably catalyzed by trace amounts of sulfide ion (100), and the reaction between sulfide ion and sulfur to give polysulfide ions is well known (60). The reactions no doubt involve nucleophilic attack on sulfur, and scission of the sulfur–sulfur bond if the sulfur is in the cyclic ($S_8$) form.

Lukashevich and Sergeeva (123) identified a number of mercaptides and polymercaptides from the reaction (equation 76) between sulfide or polysulfide ions and some diaryl disulfides, including diphenyl disulfide. Otto and Rössing (134) also demonstrated the formation of elemental sulfur and polysulfide ions in such reactions. The steps may be formulated as in equations 76 to 79.

$$RS—SR + S_n^{=} \rightleftarrows RS^- + RS_{n+1}^- \quad (76)$$

$$RS—SR + S^{=} \rightleftarrows RSS^- + RS^- \quad (77)$$

$$RS—S^- \rightarrow RS^- + S \quad (78)$$

$$RS—S^- + S^{=} \rightarrow RS^- + S_2^{=} \quad (79)$$

Diphenyl disulfide is readily cleaved by sodium sulfide in methanol (123), suggesting that sulfide ion is more S-nucleophilic than cyanide, sulfite, or hydroxide ion. Dutcher, Johnson, and Bruce (40) postulated the disulfide linkage in the antibiotic gliotoxin on the basis of its reaction with sulfide ion.

### (b) Sulfite ion

The sulfite ion ($SO_3^{=}$) has the base strength of its negatively charged sulfur atom reduced by resonance with multiply bound oxygen atoms, so that it is not as powerful a base towards sulfur as the sulfide ion. Nevertheless, it reacts rapidly with elemental sulfur to form thiosulfate ion (57), and desulfurates polysulfides (46, 57, 128). These latter reactions involve displacement of a mercaptide by sulfite (equation 80), followed by successive displacement of thiosulfate by sulfite ion (equation 81), and finally displacement of thiosulfate by the mercaptide displaced in the first step (equation 82) (57).

$$RSSSSR + SO_3^{=} \rightleftarrows RSSSSO_3^- + RS^- \quad (80)$$

$$RSSSSO_3 + SO_3^{=} \rightleftarrows RSSSO_3^- + S_2O_3^{=} \quad (81)$$

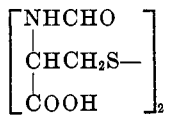
$$RSSSO_3^- + RS^- \rightleftarrows RSSR + S_2O_3^{=} \quad (82)$$

Since thiosulfate is by far the least S-nucleophilic (table 3) of all the ions which could be involved in this reaction, the equilibrium lies completely to the right. Sulfite ion desulfurates polythionates by successive displacements of thiosulfate ion from sulfur in an analogous way (56).

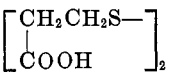
Diphenyl (192) and dibenzyl (128) disulfides are not cleaved by sulfite ion, but dialkyl disulfides containing suitably situated amino or carboxyl groups react as in equation 83 to give mercaptides and sulfenyl sulfites. Thus, sulfite has been shown to cleave cystine (XL) (29, 32, 155, 175), diformylcystine (XLI) (29),

$$RS—SR + SO_3^{=} \rightleftarrows RS^- + RSSO_3^- \quad (83)$$

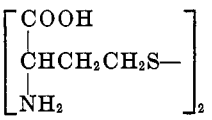
oxidized glutathione (29, 176), dithiodipropionic acid (XLII) (127), homocystine (XLIII) (127), cystamine (XLIV) (155), and dithiodiglycolic acid (XXXII) (128, 155, 176). The expected mercaptides were observed in each case.



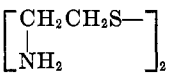
XLI



XLII



XLIII



XLIV

The reactions with the above disulfides are simple bimolecular reversible displacements (127, 176) and kinetic data are available in most cases (29, 127). The reaction rates were very sensitive to pH changes, since at low pH values the less S-nucleophilic bisulfite ion is formed. The rate also decreased considerably as the net charge in the vicinity of the sulfur–sulfur bond was changed from positive ($NH_3^+$) to negative ($—COO^-$) (29).

Kolthoff and coworkers (175, 176) have calculated the equilibrium constants for reactions of similar disulfides with sulfite and hydroxide ions, and found that the reactivity of the disulfides—oxidized glutathione (GSSG), cystine (CSSC), and dithiodiglycolic acid (TSST)—decreased in the order:

$$\text{GSSG} > \text{CSSC} > \text{TSST with sulfite ion}$$

$$\text{TSST} > \text{GSSG} > \text{CSSC with hydroxide ion}$$

This result supports the conclusion (page 611) that cleavage of this type of disulfide by hydroxide ion proceeds via a different mechanism from direct displacement (equation 40) by bases such as sulfite and cyanide ions.

Aryl disulfides (ArSSR) containing very powerful electron-withdrawing aryl groups (e.g., 2,4-dinitrophenyl) are rapidly cleaved by sulfite ion, but mononitro-substituted aryl disulfides give mercaptide only slowly (135). This led the authors to believe that sulfite ion is less S-nucleophilic than cyanide ion (135). The orientation of cleavage is such as to give the least basic mercaptide ($ArS^-$), confirming that the general displacement mechanism (equation 40) is operative.

As might be expected, a "neopentyl type" steric effect, analogous to that discussed for cyanide ion (page 607), is observed in displacements by sulfite ion from divalent sulfur (51). Thus, dithiodiglycolic acid (XXXII) is readily cleaved by sulfite ion (155), whereas dithiodilactic acid (XXXIII) does not react (128). In addition, disulfides with their sulfur atoms bound to tertiary carbon do not react with sulfite ion (155). The "neopentyl" steric effect in displacements at

$$RS—SO_3^- + \overset{*}{S}O_3^= \rightarrow RS—\overset{*}{S}O_3^- + SO_3^= \qquad (84)$$

divalent sulfur was observed by Fava, Iliceto, and Pajarro (49, 51) in the exchange shown in equation 84. They concluded that the mechanism of this reaction was similar to that for displacement at saturated carbon, since the exchange

TABLE 5

*Steric effect of methyl groups on displacements at sulfur-sulfite exchange (equation 84)*

| R* | $CH_3$— | $CH_3CH_2$— | $(CH_3)_2CH$— | $(CH_3)_3C$— |
|---|---|---|---|---|
| $\frac{100k_2\dagger}{k_{2(CH_3)}}$ | 100 | 50 | 0.7 | 0.0006 |

* In equation 84.

† Second-order rate constant.

was first order in each reactant and very dependent on pH and ionic strength. The steric effect of R in reaction 84 can be seen in table 5.

Sulfite ion is less basic towards sulfur than cyanide ion or triphenylphosphine, since it is displaced from divalent sulfur by these bases, as in reactions 85 to 87. It will displace thiosulfate or thiocyanate ion, however, as in reactions 88 and 89, respectively.

$$RS{-}SO_3^- + CN^- \rightarrow RSCN + SO_3^= \quad (53) \qquad (85)$$

$$S{-}SO_3^- + CN^- \rightarrow SCN^- + SO_3^= \quad (9) \qquad (86)$$

$$S{-}SO_3^- + P(C_6H_5)_3 \rightarrow (C_6H_5)_3PS + SO_3^= \quad (9) \qquad (87)$$

$$RSS_2O_3^- + SO_3^= \rightarrow RSSO_3^- + S_2O_3^= \quad (55) \qquad (88)$$

$$RSSCN + SO_3^= \rightarrow RSSO_3^- + SCN^- \quad (55) \qquad (89)$$

(c) Thiosulfate ion

Thiosulfate ion is not a powerful S-nucleophile. It is displaced from divalent sulfur by cyanide (reaction 90), sulfite (reaction 91), and mercaptide (reaction 92) ions, but will displace thiocyanate (reaction 93), *O,O*-dialkylthiophosphates, alkanesulfenyl sulfinates, and thiourea from sulfur (58, 85). These reactions are typical examples of reaction 38, i.e., displacements of a weaker base by a stronger base. In equations 90 to 94, the equilibria lie to the right.

$$RSS_2O_3^- + CN^- \rightleftarrows RSCN + S_2O_3^= \qquad (90)$$

$$RSS_2O_3^- + SO_3^= \rightleftarrows RSSO_3^- + S_2O_3^= \qquad (91)$$

$$RSS_2O_3^- + RS^- \rightleftarrows RS{-}SR + S_2O_3^= \qquad (92)$$

$$RSSCN + S_2O_3^= \rightleftarrows RSS_2O_3^- + SCN^- \qquad (93)$$

$$RS{-}S{-}\overset{\overset{NH}{\|}}{C}{-}NH_2 + S_2O_3^= \rightleftarrows RSS_2O_3^- + {}^-S{-}\overset{\overset{NH}{\|}}{C}{-}NH_2 \qquad (94)$$

Thiosulfate ion will displace sulfite ion, but only if the sulfite ion is removed from the equilibrium (reaction 95) by strong acid (36) or formaldehyde (61). In this way sulfur chains can be built up (58).

$$SSO_3^= + SSO_3^= \rightleftarrows S{-}SSO_3^= + SO_3^= \qquad (95)$$

### (d) Sulfinates

Sulfinate ions, $RSO_2^-$, will react with elemental sulfur to give thiolsulfonates ($RSO_2S^-$) (56), but are not powerful S-nucleophiles, since they are displaced from divalent sulfur by mercaptides (reaction 96) (167),

$$RS—SO_2R' + R''S^- \rightleftarrows RSSR'' + R'SO_2^- \quad (96)$$

by cyanide ion (167),

$$RS—SO_2R' + CN^- \rightleftarrows RSCN + R'SO_2^- \quad (97)$$

and by sulfite ion (56).

$$RSO_2S^- + SO_3^= \rightleftarrows S_2O_3^= + RSO_2^- \quad (98)$$

The orientation of cleavage of the sulfur–sulfur bond is always as shown, confirming that mercaptides ($RS^-$) are more S-nucleophilic than sulfinate ions ($R'SO_2^-$).

Gibson and Loudon (71) found that in reaction 99, where R′ = nitrophenyl,

$$RS—SO_2R' + R''SO_2^- \rightleftarrows RSSO_2R'' + R'SO_2^- \quad (99)$$

$R''SO_2^-$ was a more effective displacing base in the order of R″:

*p*-chlorophenyl > phenyl > ethyl

This would be expected if the base strengths of $R'SO_2^-$ and $R''SO_2^-$ governed the rate and extent of displacement, i.e., if the reaction were an ionic displacement like reaction 40.

### (e) Thiol–disulfide exchange reactions

The interactions between thiol and disulfide groups have been of particular interest to biochemists. For example, studies of the chemistry of some proteins (80, 86), wool (22), and hair waving (193) processes, and of the stress relaxation of polysulfide rubbers (171) have all been intimately concerned with the cleavage of a sulfur–sulfur bond by a mercaptide ion.

The denaturation of proteins by urea involves thiol–disulfide interchange (80). Disulfide cross-links between protein molecules are formed from interaction of a free thiol group in one molecule with an intramolecular disulfide link in another. This links two protein molecules, and gives a free thiol group which is capable of continuing the coagulation. Studies of the denaturation of ovalbumin (65, 76) and bovine plasma albumin (79) have been based on this principle.

#### (i) Mechanism

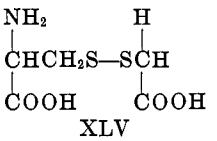
Until quite recently, reactions between mercaptides and disulfides were treated as oxidation-reduction processes, despite the observation by Lecher (114) in 1920 that an exchange takes place. It is now generally accepted (18, 23, 60) that reactions like reaction 100 are rarely true oxidation-reductions, in the sense of radical scission of the sulfur–sulfur bond, but are more often a two-step ionic displacement (reactions 101 and 102) of $XS^-$ by the more basic $X'S^-$ (X denotes any group capable of forming an anion $XS^-$ and a disulfide XSSX).

$$XS—SX + 2X'S^- \rightleftarrows X'S—SX' + 2XS^- \quad (100)$$

$$XS—SX + X'S^- \rightleftarrows XS—SX' + XS^- \quad (101)$$

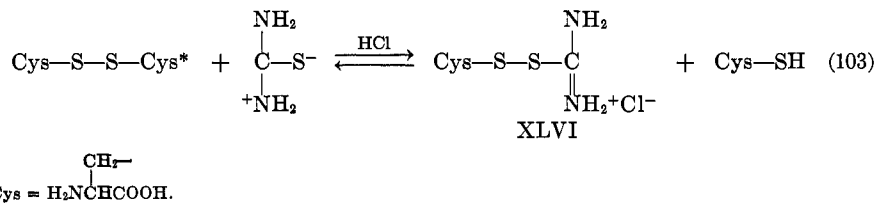
$$XS—SX' + X'S^- \rightleftarrows X'S—SX' + XS^- \quad (102)$$

Mixed disulfides are often isolated in reactions such as 100, thus confirming the two-step ionic process. Bersin and Steudel (17) suggested that an unsymmetrical disulfide (XLV) was the intermediate in the reaction between *l*-cystine and thioglycolic acid, but assumed incorrectly (98) that the intermediate was unstable and rapidly gave cysteine and dithiodiglycolic acid. This reaction is of some interest, since the combined cystine in keratin can be converted to com-



XLV

bined cysteine in the presence of a large excess of a thiol such as thioglycolic acid (72). Mixed disulfides have also been isolated from the base-catalyzed reaction between cystine and bis-2,4-dinitrophenylcystine (148), from the interchange between cysteine and penicillamine disulfide (182), and from the exchanges of aromatic disulfides with the free thiol groups present in tissue protein (7). Toennies (184) showed that the unsymmetrical disulfide (XLVI) was an intermediate in the reaction between thiourea and cystine to give cysteine. He proposed a two-step ionic process for which the first step was as shown in equation 103.



XLVI

(103)

* Cys = $H_2NCHCOOH$.

Thiol–disulfide exchanges do proceed by a free-radical mechanism in some cases. One example is the exchange between $S^{35}$-labelled thiocresol and ditolyl disulfide in xylene as solvent (74). The rate was independent of the thiol concentration and proportional to the square root of the disulfide concentration. Catalysis by ultraviolet light was observed.

Disulfide–disulfide interchanges (equation 104) as well as thiol–disulfide ex-

$$XS—SX + X'S—SX' \rightleftarrows 2XS—SX' \quad (104)$$

changes proceed in two ways: (*a*) by homolytic scission of the sulfur–sulfur bond to give short-lived sulfenyl radicals; (*b*) by ionic scission of the sulfur–sulfur bond, promoted by bases which generate mercaptides ($XS^-$).

Bertozzi, Davis, and Fettes (18) have examined a number of reactions like the one shown in equation 104 and conclude that the ionic process is far more common.

Unsymmetrical diaryl disulfides redistribute to symmetrical disulfides in non-ionizing solvents when irradiated with ultraviolet light or heated to 170°C. (110). This reaction, the reverse of reaction 104, would appear to be an example of homolytic scission of the sulfur–sulfur bond.

The ionic disulfide–disulfide interchanges [(b) above] are strongly catalyzed by trace amounts of thiols (125) and by increasing alkalinity of the solution. The reactive species is no doubt a mercaptide ion ($XS^-$ or $X'S^-$) generated by ionic cleavage (reaction 40) of either XS—SX or X'S—SX' (24). Assuming that XS—SX is more readily cleaved than X'SSX', base catalysis of the product of reaction 104 by $Y^-$ can be expressed by the following equations:

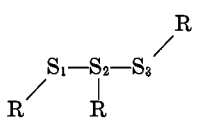
$$XS—XS + Y^- \rightleftarrows XSY + XS^- \quad (105)$$

$$X'S—SX' + XS^- \rightleftarrows XS—SX' + X'S^- \quad (106)$$

$$XSY + X'S^- \rightleftarrows XS—SX' + Y^- \quad (107)$$

McAllan, Cullum, Dean, and Fidler (125) have shown that interchange between equimolar quantities of a number of pairs of linear aliphatic disulfides gave the random distribution of products 1:2:1, with the unsymmetrical disulfide predominating. With branched aliphatic disulfides, notably *tert*-butyl systems, the unsymmetrical disulfide predominated.

Fava, Iliceto, and Camera (50) have proposed that the transition state in thiol–disulfide exchange has the three sulfur atoms in a straight line, with the attached groups as in formula XLVII. As in all nucleophilic displacements at divalent sulfur, a backside attack is involved (49). The charge distribution in




XLVII

XLVII should be as in one of the two possible transition states for displacement at sulfur (page 599).

Some quantitative studies of thiol–disulfide exchange have been made. Fredga (64) followed the reaction between (+)-dithiodilactic acid and thiolactic acid in neutral solution, and concluded that the mercaptide ion was the reactive entity. This was confirmed by Fava and Iliceto (48), who showed that the exchange between $S^{35}$-labelled *n*-butyl mercaptan and di-*n*-butyl disulfide was negligible in absolute ethanol, faster in aqueous alcohol, and very rapid if the sodium salt of the *n*-butyl mercaptan is used. In both these instances, and in other cases for which kinetic data are available (17, 60), the reactions followed a bimolecular course.

Fava, Iliceto, and Camera (50) have measured rate constants for the exchange reaction between $S^{35}$-labelled mercaptides and their corresponding unlabelled disulfides. Their results are summarized in table 6.

Of special interest is the slow reaction of the *tert*-butyl system, presumably because of "neopentyl type" steric hindrance to formation of the transition state.

TABLE 6

*Rate constants at 25°C. in methanol for the exchange:*

$$\overset{*}{R}S^- + RSSR \rightleftarrows RS\text{—}\overset{*}{S}R + RS^-$$

| R | $k_2$ | R | $k_2$ |
|---|---|---|---|
| | *l. mole*$^{-1}$ *sec.*$^{-1}$ | | *l. mole*$^{-1}$ *sec.*$^{-1}$ |
| $CH_3CH_2CH_2CH_2$— | 0.26 | $C_6H_5$— | 0.49 |
| $CH_3(CH_2)_4CH_2$— | 0.26 | | |
| $(CH_3)_3C$— | $1 \times 10^{-7}$ | | |
| | | $CH_3CH_2CH_2CH_2$— +  | 1400 |

TABLE 7

*Examples of reactions 101 and 102*

| Reaction | Reference |
|---|---|
| 1. $RS^- + {}^-O_3S\text{—}S\text{—}SO_3^- \rightleftarrows RSS_2O_3 + S_2O_3^- \xrightleftharpoons{RS^-} RS\text{—}SR + S_2O_3^-$ | (55) |
| 2. $RS^- + NCS\text{—}SCN \rightleftarrows RSSCN + SCN^- \xrightleftharpoons{RS^-} RS\text{—}SR + SCN^-$ | (116) |
| 3. $\overset{*}{S}\text{—}SO_3^- + {}^-O_3S\text{—}SSSO_3^- \rightleftarrows {}^-O_3S\text{—}\overset{*}{S}\text{—}SO_3^- + S_2O_3^- \xrightleftharpoons{\overset{*}{S}_2O_3^-} {}^-O_3S\overset{**}{S}SSO_3^-$ | (47) |
| 4. $ROC\text{—}S^- + [(CH_3O)_2OPS^-]_2 \rightleftarrows ROC\text{—}S\text{—}SPO(OCH_3)_2 + (CH_3O)_2OPS^-$ (S; S) | (54) |
| 5. $S\text{—}SO_3^- + NH_2CS\text{—}SCNH_2 \rightleftarrows NH_2CS\text{—}SSO_3^- + NH_2CS^- \xrightleftharpoons{S_2O_3^-} {}^-O_3S\text{—}S\text{—}S\text{—}SO_3^- + NH_2CS^-$ (O; O; O; O; O) | (147) |
| 6. $S\text{—}SO_3^- + NCS\text{—}SCN \rightleftarrows {}^-O_3S\text{—}S\text{—}SCN + SCN^- \xrightarrow{S_2O_3^-} {}^-O_3SSSSO_3^- + SCN^-$ | (85) |

A steric effect of this type is common to nucleophilic displacements at divalent sulfur, and confirms the general ionic displacement mechanism (equation 40) for thiol–disulfide exchange. The reactivity of the strained 1,2-dithiolane molecule is significant because of the interest in such ring systems in photosynthesis (6) and in the pyruvic acid oxidation cycle (119, 139).

Besides the simple organic thiol–disulfide exchanges, numerous reactions, which can be expressed as in equations 101 and 102, are known in which negatively charged sulfur behaves as an S-nucleophile and displaces another thioanion from divalent sulfur. Many of these reactions have been regarded as oxidations, but, as pointed out by Foss (60), they are equally well explained by the exchange mechanisms of table 7.

The oxidations of xanthates (27), thiobenzoate (26), and dithiobenzoate (27) to their disulfides by tetrathionate, and by bis(dimethoxy phosphinyl) disulfide (54), are also two-step ionic displacements and thiol–disulfide exchanges in a wider sense (60).

### (ii) S-nucleophilicity of mercaptides

Reactions 101 and 102 are equilibria with the position of equilibrium determined by the S-nucleophilicity of $XS^-$ and $X'S^-$. There is a close correspondence

TABLE 8

*Electrode potentials (55) vs. the normal hydrogen electrode for the systems:*

$2XS^- \rightleftarrows XS—SX + 2\epsilon$

| Reactant | Electrode Potential | Reactant | Electrode Potential |
|---|---|---|---|
| | *volts* | | *volts* |
| $SCN^-$ | +0.77 | $(NH_2)_2CS$ | +0.42 |
| $(CH_3O)_2OPS^-$ | +0.56 | $S_2O_3^=$ | +0.2 |
| $CH_3SO_2S^-$ | +0.54 | $RS^-$ | 0 |
| $[(CH_3)_2CHO]OPS^-$ | +0.50 | | |

between the ease of oxidizing $XS^-$ to XS—SX and the S-nucleophilicity of the mercaptide (55). It is found that the lower the electrode potential of the system $2XS^-/XS—SX$, the greater the base strength of $XS^-$. Table 8 gives some oxidation-reduction potentials collected by Foss (55).

Foss (55) showed that unsymmetrical disulfides (RS—SX)—where R = *o*-nitrophenyl or 2-nitro-5-methylphenyl and XS is a group of table 8—underwent a series of displacements (equation 108) with thiocyanate, *O*,*O*-dialkyl thiophosphate, thiosulfonate, thiosulfate, xanthate, and mercaptide ions. A readily oxidized thioanion, i.e., one low in table 8, displaced any thioanion above it, which was less readily oxidized.

$$RS—SX + X'S^- \rightleftarrows RS—SX' + XS^- \qquad (108)$$

Table 8 successfully predicts that mercaptides will displace thiocyanate, thiosulfate, and other weakly basic thioanions from sulfur, but the most interest is in reactions where a mercaptide ion, $RS^-$, displaces another mercaptide ion, $R'S^-$, from sulfur. For the organic thiol–disulfide couples commonly encountered in biochemical problems, the potential is small and varies little from that of cysteine/cystine (i.e., +0.074 v.) (42, 98). Thus the equilibrium constants for reactions such as thioglycolic acid–cystine exchange and cysteine–glutathione exchange are close to unity (42, 98). Apparently both the displacing and the displaced mercaptides are of similar S-nucleophilicity.

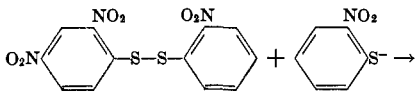
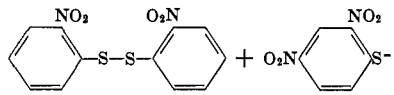
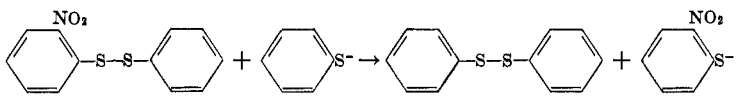
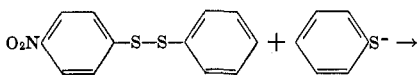
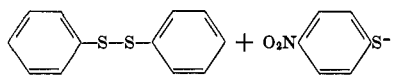
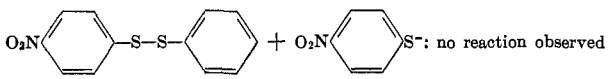
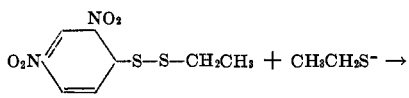
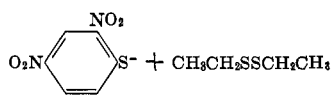
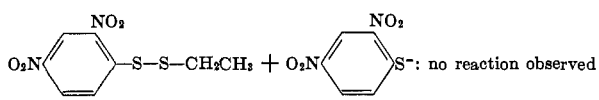
The mercaptides may be of similar S-nucleophilicity because, in the examples cited above, they are all of the type $RCH_2S^-$, where R is insulated from sulfur by a $—CH_2—$ group, so that relatively small changes in R do not greatly affect the base strength of sulfur. Exchanges involving aromatic mercaptides and disulfides (ArSSR) present a different picture, however. Where sulfur is directly attached to an aromatic nucleus, differences in the base strength of sulfur, as substituents on Ar are changed, are more pronounced (111), and equilibrium constants for exchange are not close to unity. If differences of base strength are large enough, a mercaptide–disulfide exchange (equation 101) may proceed exclusively in one direction (135), as in the examples of table 9.

It should be remembered in evaluating table 9 that electron withdrawal and conjugation with sulfur decrease the base strength of an aromatic mercaptide (111, 135). Steric effects may prevent equilibration as in the ethyl *tert*-butyl disulfide–*tert*-butyl mercaptide exchange (125).

TABLE 9

*Disulfide exchange reactions in alcoholic solvents*

(Reactions proceed at least 90 per cent to the right, if equimolar quantities of reactants are used)

| Reaction | Reference |
|---|---|
|  | |
|  | (123) |
|  | (123) |
|  | |
|  | (135) |
|  | (135) |
|  | |
|  | (135) |
|  | (135) |

*4. Cleavage induced by bases whose nucleophilic atom is nitrogen*

Secondary amines, such as diethylamine (10), strongly catalyze the ring opening of $S_8$ via an ionic displacement. The reaction with triethylamine has also been discussed (10, 84).

$$(C_2H_5)_3N: + S_8 \rightarrow (C_2H_5)_3\overset{+}{N}—SS_6S^- \qquad (109)$$

Diisopropyl disulfide is cleaved by isopropylamine to give isopropyl mercaptan (142), and pyridine and aniline cleave 4,4′-dicarboxydiphenyl disulfide (169) to give the corresponding mercaptan. In no case was the other cleavage product identified. The reactions are probably of the type:

$$RS—SR + R_3N \rightleftarrows R_3\overset{+}{N}SR + RS^- \qquad (110)$$

Triethylamine cleaves the dimethyl ester of cystine but not the dimethyl ester of $\alpha,\alpha'$-dimethylcystine (*cf.* formula X and reference 180). Lanthionine dimethyl ester is produced in the former reaction, and this, together with the $\alpha$-hydrogen effect, suggests that the reaction is not a direct displacement (equation 40) of cysteine methyl ester from sulfur, but is analogous to the reaction of cystine with alkali (equations 74 and 75), where the first step is ionization of an $\alpha$-hydrogen atom under the strongly basic conditions.

Diethylamine displaces thiocyanate ion from thiocyanogen (117) and from 2-nitrobenzenesulfenyl thiocyanate (116) (equation 111). All the products of these reactions were identified and accounted for.

$$2\text{-}O_2NC_6H_4S\text{—}SCN + (C_2H_5)_2NH \rightarrow 2\text{-}O_2NC_6H_4SN(C_2H_5)_2 + HSCN \qquad (111)$$

*5. Cleavage induced by bases whose nucleophilic atom is phosphorus*

Phosphorus appears to have a strong affinity for sulfur, presumably because of its high polarizability (21) and size, enabling it to utilize the empty 3*d* orbital of sulfur more effectively than can, for example, atoms such as oxygen and nitrogen in the second period in the Periodic Table.

Trialkyl phosphites react readily with diethyl disulfide (161), a disulfide which is stable to most other bases. The reaction is a typical displacement (reaction 40) of ethyl mercaptide from sulfur

$$(CH_3CH_2O)_3P + CH_3CH_2S\text{—}SCH_2CH_3 \rightarrow CH_3CH_2S^- + CH_3CH_2\overset{+}{S}P(OCH_2CH_3)_3 \qquad (112)$$

followed by deëthylation of the phosphonium product by ethyl mercaptide (83).

$$CH_3CH_2\overset{+}{S}P(OCH_2CH_3)_3 + CH_3CH_2S^- \rightarrow CH_3CH_2SCH_2CH_3 + CH_3CH_2S\overset{O}{\overset{\|}{P}}(OCH_2CH_3)_2 \qquad (113)$$

Triphenylphosphine attacks sulfur ($S_8$) to form triphenylphosphine sulfide via a series of ionic displacements (11) analogous to those for the reaction between cyanide ion and $S_8$ (page 602). Triphenylphosphine is a less powerful base than trialkyl phosphites, for Schönberg and Barakat (161) showed that although several simple dialkyl and diaryl disulfides, including diphenyl disulfide, were cleaved by triphenylphosphine in boiling benzene, diethyl disulfide was not cleaved. They formulated a free-radical mechanism, but the authors agree with Foss (60) and Challenger and Greenwood (30) that an ionic displacement (equation 114) is more likely.

$$(C_6H_5)_3P + RS\text{—}SR \rightarrow (C_6H_5)_3\overset{+}{P}\text{—}SR + RS^- \rightarrow RSR + (C_6H_5)_3PS \qquad (114)$$

Here, as in equation 113, dealkylation of the intermediate by mercaptide gives the reaction the appearance of a simple desulfuration (which it is not).

Triphenylphosphine will displace sulfite ion from thiosulfate ion (reaction 115) in a reaction which follows second-order kinetics (9). Triphenylphosphine does not displace cyanide ion from thiocyanate ion (9), but neither does cyanide ion

displace triphenylphosphine from triphenylphosphine sulfide (9). The authors conclude that triphenylphosphine and cyanide ion have comparable S-nucleophilicities, with the former slightly more powerful, since it displaces phenyl mercaptide from diphenyl disulfide (161).

$$SSO_3^- + (C_6H_5)_3P \rightarrow (C_6H_5)_3PS + SO_3^- \quad (115)$$

*O,O*-Dialkylphosphites, $(RO)_2OP^-$, very rapidly cleave the sulfur bonds in $S_8$ (55). Foss (55) has suggested that they have a greater affinity for sulfur than cyanide ion does.

From the above discussion the authors tentatively propose the following order of decreasing S-nucleophilicity:

$$PO(OR)_2^-, P(OR)_3 > CH_3CH_2S^- > PR_3 > CN^-$$

*6. Cleavage induced by bases whose nucleophilic atom is arsenic*

Trivalent arsenic has a strong affinity for sulfur, as might be expected for a large, highly polarizable atom of the fourth period. Arsines, e.g., triethylarsine, react readily with elemental sulfur to give arsine sulfides (102). Cohen, King, and Strangeways (33) have shown that *l*-cystine gives cysteine with sodium arylarsinites. The reaction is bimolecular, and is presumably a nucleophilic displacement on sulfur (58).

$$RS{-}SR + R'AsO(OH)^- \leftrightarrows RS\overset{\displaystyle OH}{\underset{\displaystyle O}{\overset{|}{\underset{\|}{As}}}}R' + RS^- \quad (116)$$

Subsequent hydrolysis of the pentavalent arsenic intermediate

$$RS\overset{\displaystyle O}{\underset{\displaystyle OH}{\overset{\|}{\underset{|}{As}}}}R' + H_2O \rightarrow RSH + R'AsO(OH)_2 \quad (117)$$

gives the reaction the appearance of an oxidation-reduction. Gutman (75), in his study of the "oxidation" of sodium arsenite to sodium arsenate by disulfides, benzenesulfenyl thiocyanate, sodium ethylthiosulfate (or sodium ethylsulfenyl sulfite), and ethyl *p*-toluenethiolsulfonate (or *p*-toluenesulfenyl sulfinate), apparently did not propose that the reaction could be explained (60) as nucleophilic attack on divalent sulfur (equation 118), followed by hydrolysis of the arsenic intermediate to arsenate ion and mercaptide (equation 119).

$$\left.\begin{matrix} RS{-}SR \\ RS{-}SCN \\ RS{-}SO_3^- \\ RS{-}SO_2R' \end{matrix}\right\} + AsO(OH)_2^- \rightarrow RS{-}AsO(OH)_2 + \left\{\begin{matrix} RS^- \\ SCN^- \\ SO_3^- \\ R'SO_2^- \end{matrix}\right. \quad (118)$$

then

$$RSAsO(OH)_2 + H_2O \rightleftarrows RSH + AsO(OH)_3 \quad (119)$$

It is significant that sodium arsenite displaced cyanide ion from NCSCN, and ethyl mercaptide from diethyl disulfide (75). This suggests that the arsenite ion

is more S-nucleophilic than $CN^-$ or $C_2H_5S^-$, and at least of comparable strength to triethylphosphite (table 3).

*7. Cleavage induced by bases whose nucleophilic atom is hydrogen*

Trevoy and Brown (186) have proposed that reductions of organic compounds by lithium aluminum hydride can be regarded as displacements of oxygen, nitrogen, or halogen by hydrogen, the reaction being initiated by nucleophilic attack of aluminohydride ions on carbon. This concept was extended to sulfur compounds by Bordwell and McKellin (20), who propose that the reductions of disulfides (3, 173), sulfenyl chlorides (173), sulfenyl thiocyanates (173), sulfinic acids (173), sulfoxides (20), sulfonyl chlorides (173), arylsulfonates (173), thiolsulfonates (173), and sulfones (20) by lithium aluminum hydride are displacements of chlorine, oxygen, or sulfur by nucleophilic attack of aluminohydride ions on sulfur.

The reactions are apparently ionic displacements of the general type shown in equation 38 (with $Y^- = AlH_4^-$), and in the reduction of disulfides and sulfenyl thiocyanates a sulfur–sulfur bond is cleaved. A "neopentyl type" steric effect (page 607) is observed, confirming the ionic displacement mechanism, for the reduction of *tert*-butyl disulfide (3) and *tert*-butyl sulfone (20). These compounds are relatively inert to lithium aluminum hydride, but other simple dialkyl and diaryl disulfides such as diphenyl, dibenzyl, and di-*n*-butyl disulfides, are rapidly and quantitatively reduced to the mercaptan by lithium aluminum hydride in ether at room temperature (3). This would suggest that the aluminohydride ion is a strong S-nucleophile, of at least the strength of a carbanion (table 3).

*8. Cleavage induced by bases whose nucleophilic atom is carbon*

Negatively charged carbon is a strong S-nucleophile and carbanions will displace most other bases from sulfur (table 3). This might have been inferred from the fact that the carbon–sulfur bond is rarely cleaved via nucleophilic displacement on sulfur, except when the displacing base is another carbanion (183). Foss (58) has proposed an ionic displacement mechanism, involving carbanions, for the reaction of elemental sulfur with Grignard reagents to give mono-, di-, or polysulfides.

$$S_8 + \overset{\delta-}{R}—\overset{\delta+}{Mg}X \rightarrow RS_8^-$$

$$RS_8^- + RMgX \rightarrow RS_xR + S_{8-x}^{=} \qquad (120)$$

or

$$RS_8^- + RMgX \rightarrow RS^- + RS_7^-$$

Leandri and Tundo (109) have demonstrated that disulfides, such as diphenyl disulfide and 4,4′-dimethoxydiphenyl disulfide, which are stable to cyanide and sulfite ions, are readily cleaved by diphenylsulfonylmethane in alkaline solution. A carbanion would appear to be the displacing base, as shown in equation 121. Unsymmetrical disulfides are cleaved so that the least basic mercaptide is dis-

$$(C_6H_5SO_2)_2CH^- + RS—SR \rightarrow RSCH(SO_2C_6H_5)_2 + RS^- \qquad (121)$$

placed, as is found in all reactions proceeding via the ionic displacement mechanism shown in equation 40.

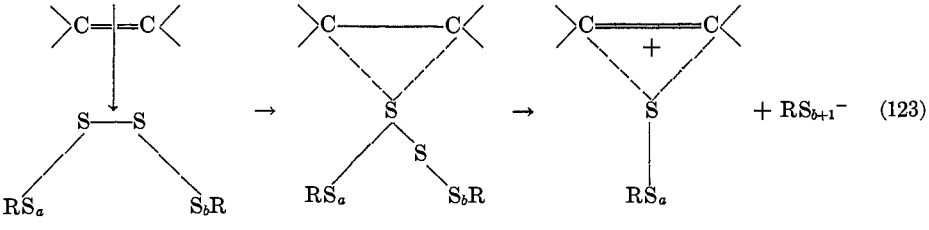
Schönberg, Stephenson, Kaltschmidt, Pettersen, and Schulten (162) demonstrated that phenyllithium and sodium triphenylmethide cleave diphenyl disulfide and di-*p*-tolyl disulfide to give sulfides and mercaptides (reaction 122). The reactions can be regarded also as displacements from sulfur by a carbanion.

$$RS—SR + C_6H_5^- \rightarrow RSC_6H_5 + RS^- \qquad (122)$$

Alkyl- and arylmagnesium bromides (RMgBr) cleave diethyl disulfide (8, 198) and diphenyl disulfide (198) to give the corresponding mercaptides. An ionic displacement of mercaptide by $R^-$ would explain this result. Apparently carbanions are in general more S-nucleophilic than ethyl mercaptide.

### *9. Olefinic double bonds as displacing bases*

Bateman, Moore, and Porter (13) regard the reaction of olefins with sulfur and polysulfides at 140°C. as a polar chain reaction. The $\pi$ electrons of the olefin interact with sulfur, and the very strong affinity of carbanions for sulfur (table 3) causes displacement of a thioanion. They propose the following mechanism for the reaction with polysulfides such as $RS_aSSS_bR$.




(123)

The bridged persulfonium ion then decomposes to complex polysulfides, including cyclic structures. Presumably a related reaction could occur with a suitable disulfide.

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