The Chemistry of the Thiol Group
Edited by Saul Patai

The chemistry of the thiol group

Part 1

Edited by

SAUL PATAI
The Hebrew University, Jerusalem

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Jerusalem, May 1974 SAUL PATAI

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CHAPTER 1

General and theoretical aspects of the thiol group

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I. PHYSICAL PROPERTIES

Physical properties may be divided into two broad classes: those that involve energy or more precisely energy differences, and those that represent molecular properties other than energy. Most of the physical and chemical measurements we shall discuss in this part are related to energy differences (cf. sections I.B to I.F). Other molecular properties such as quadrupole moment and diamagnetic susceptibility will not be discussed at length, but the theory of dipole moments will be presented in some detail since they have a direct bearing on the charge distribution within a molecule.

The purpose of this section is to show that there is no fundamental difference between corresponding oxygen and sulphur compounds, such as alcohols and thiols. Some observed variations that appear to represent qualitative changes, in reality only reflect a difference in the magnitude of the experimentally observed properties.

A. Standard States and Relative Energies

In order to discuss physical measurements that involve energy differences (i.e. a transition from one state to another) it may be appropriate to define commonly used energy units and reference states. The most commonly used energy units are shown in Table 1. It should be noted

TABLE 1. Conversion table for the most frequently used energy units

	$\frac{\text{Hartree}}{\text{particle}}$	$\frac{\text{eV}}{\text{particle}}$	$\frac{\text{cm}^{-1}}{\text{particle}}$	$\frac{\text{kcal}}{\text{mole}}$
Hartree/particle	1	27·210	219,470	627·71
eV/particle	$3{\cdot}6752 \times 10^{-2}$	1	8,066·0	23·069
cm^{-1}/particle	$4{\cdot}5563 \times 10^{-6}$	$1{\cdot}2398 \times 10^{-4}$	1	0·00286
kcal/mole	$1{\cdot}5931 \times 10^{-3}$	$4{\cdot}3348 \times 10^{-2}$	$3{\cdot}4964 \times 10^{2}$	1

that the Hartree unit is independent of fundamental constants such as h, m or e.

Energy is always measured with respect to a *standard state* established by convention.

Historically the *Thermodynamic Standard State* was the first one to be established although today it is only used by thermodynamicists. In this convention the standard state of a substance is defined as the state as it occurs at 25°C and 1 atmosphere pressure, and is arbitrarily set at zero.

Molecular energies or heats of formation* are then expressed with reference to this standard state. The major disadvantage of this convention is that many substances are not gaseous diatomic molecules in their standard states and therefore the numerical results often cannot be directly related to simple concepts. Consider, for example,

$$\tfrac{1}{2}\,O_2 + H_2 \longrightarrow H_2O \quad \Delta H_f = -57{\cdot}11 \text{ kcal/mole} \tag{1a}$$

$$\tfrac{1}{8}\,S_8 + H_2 \longrightarrow H_2S \quad \Delta H_f = -4{\cdot}18 \text{ kcal/mole} \tag{1b}$$

The heats of formation[1] cannot be used as a direct measure of stability since $\Delta H_f(H_2S)$ is calculated relative to H_2 and S_8.

The ΔH_f values derived in equations (1a) and (1b) imply that the two H—O bonds in H_2O are very much more stable than the bonds in O_2 and H_2, while two H—S bonds are only slightly more stable than the bonds in the starting materials, S_8 and H_2. Thus in this convention the energy differences reveal that one bonding arrangement is more stable than the other but they cannot be related to bond strengths. It is obvious that one should know the bond strengths in the initial states in order to be able to interpret a heat of formation in these terms. Alternatively one may choose another standard state in which there is absolutely no bonding in the initial state.

For this reason the *Chemical Standard State* is more practical because the energy difference is expressed with respect to the separated atoms and therefore has immediate relevance to the concepts of chemical bonding.

Consider again the formation of H_2O and H_2S but this time, the reactants are the separated atoms:

$$2\,H + O \longrightarrow H_2O \quad \Delta E = -216{\cdot}96 \text{ kcal/mole} \tag{2a}$$

$$2\,H + S \longrightarrow H_2S \quad \Delta E = -172{\cdot}1 \text{ kcal/mole} \tag{2b}$$

These energy differences (which are the sum of the dissociation energies[1]) immediately reveal that chemical bonding will stabilize H_2O by about 45 kcal/mole more than H_2S. What can be said about the sum of two bonds can also be said about the individual bonds[1]:

$$2\,H + O \xrightarrow[\text{kcal/mole}]{-101{\cdot}36} H{-}O + H \xrightarrow[\text{kcal/mole}]{-115{\cdot}6} H_2O \tag{3a}$$

$$2\,H + S \xrightarrow[\text{kcal/mole}]{-81{\cdot}4} H{-}S + H \xrightarrow[\text{kcal/mole}]{-90{\cdot}7} H_2S \tag{3b}$$

* Although molecular energies are calculated from $\Delta E = \Delta H - P\Delta V$, the work term is usually small and for qualitative comparisons the approximation $\Delta E \approx \Delta H$ is valid.

The limitations of these thermochemical equations must be realized. They only state that when H_2O or H_2S is formed from the constituting atoms, then 216·96 or 172·1 kcal/mole is released respectively and, for example, these energy values should not be regarded as arising exclusively from the formation of two bonds.

Even the assumption that only the valence electrons will undergo redistribution when the molecule is formed but the inner cores remain unchanged, involves a great deal of approximation. The relatively recent developments in photoelectron spectroscopy (ESCA) have convincingly shown that core electrons are bound to the nucleus to a different degree depending on the chemical environment. For this reason one should really include both the valence and core electrons in the calculations and choose a standard state where the electrons are not bound to the nuclei.

The *Quantum Chemical Standard State* assumes the separated nuclei and electrons to be the energy zero and the energies are expressed in terms of Hartree atomic units (or hartree in short). From its definition, the unit is related to the ground state of the hydrogen atom in such a way that

$$E_H = -\tfrac{1}{2} \text{ hartree.} \tag{4}$$

The energetics associated with the formation of H_2O and H_2S with respect to the different standard states are illustrated in Figure 1.

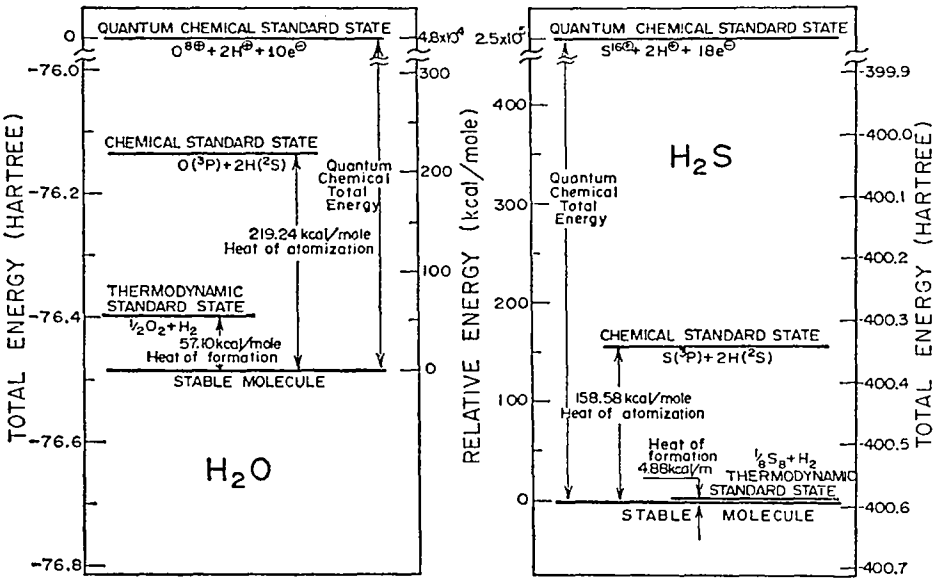


FIGURE 1. Energies of formation of H_2O and H_2S with respect to the thermodynamic, chemical and quantum chemical standard states.

The total molecular energy calculated on the quantum chemical scale is the sum of the atomic energies, E_{atoms}, the energy of atomization, E_{dissoc} (i.e. the sum of dissociation energies) and the zero point vibrational (ZPV) energy, E_{ZPV}:

$$E_{\text{total}} = E_{\text{atoms}} + E_{\text{dissoc}} + E_{\text{ZPV}} \tag{5}$$

The energy of an atom is the sum of all of its ionization potentials, 8 in the case of oxygen and 16 in the case of sulphur. (The energy of the hydrogen atom, equal to its single ionization potential, is the basic unit of energy on the atomic scale, as shown in equation 4.) The energy of atomization or total dissociation energy is calculated by the individual dissociation energies as indicated by equations (3a) and (3b), or, in a general form,

$$E_{\text{dissoc}} = \sum_{i=1}^{\text{all bonds}} D_0^{(i)} \tag{6}$$

The zero point vibration energy (E_{ZPV}) is defined by the following equations:

$$E_{\text{ZPV}}\ (\text{cm}^{-1}) = \frac{1}{2} \sum_{i=1}^{\text{all modes}} \nu_i\ (\text{cm}^{-1}) \tag{7a}$$

$$E_{\text{ZPV}}\ (\text{hartree}) = 4{\cdot}5563 \times 10^{-6}\ E_{\text{ZPV}}\ (\text{cm}^{-1}) \tag{7b}$$

The experimental vibrational frequencies[2–4] and dissociation energies reported for HO, H_2O, HS and H_2S are summarized in Table 2. The calculations of the total energies are shown in Table 3 and illustrated in Figure 2.

TABLE 2. Fundamental vibrational frequencies and dissociation energies of the hydrides of oxygen and sulphur

Molecular species	Vibrational frequencies (cm^{-1})			Dissociation energies (kcal/mole)	
	ν_1	ν_2	ν_3	$D_0^{(1)}$	$D_0^{(2)}$
HO	3735·2	—	—	101·27	—
H_2O	3657·1	1594·8	3755·8	117·97	101·27
HS	2702	—	—	81·43	—
H_2S	2614·6	1182·7	2627·5	75·21	81·43

TABLE 3. Calculation of molecular total energies[a] (E_c) from experimental data

Energy components	HO	H_2O	HS	H_2S
Atomic energy	−75·6162	−76·1162	−399·6977	−400·1977
Atomization energy	−0·1613	−0·3492	−0·1297	−0·2503
Zero point vibrational energy	−0·0085	−0·0205	−0·0062	−0·0146
Total energy	−75·7860	−76·4859	−399·8336	−400·4626

[a] In Hartree atomic units.

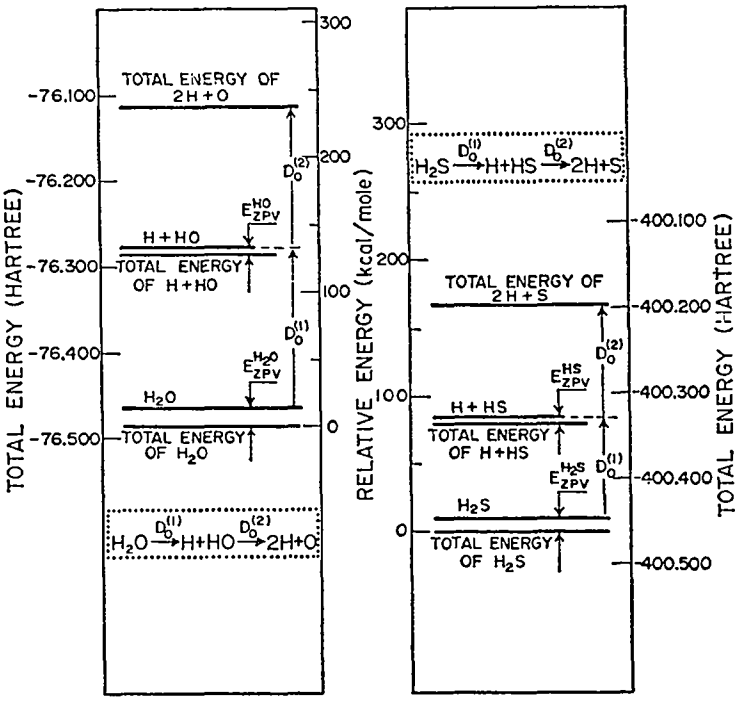


FIGURE 2. Total energy levels of H+O, OH, H_2O, S, SH and H_2S on the quantum chemical scale.

B. Bond Energies and Molecular Vibrations

In any calculation of molecular energy, it is necessary to consider the implication of changes in molecular geometry. Here too, atomic units prevail: the atomic unit of length is 1 bohr (Bohr a.u.) which is the radius of the Bohr orbit for the ground state hydrogen atom (1 bohr = 0·52917 Å).

When quantum chemical calculations are carried out, the molecular geometry is specified by the x, y, z coordinates of the constituting atoms. Bond lengths and bond angles have to be converted therefore to Cartesian coordinates using standard trigonometric relationships. The two-dimensional examples of H_2O and H_2S are shown in Figure 3 while equilibrium bond lengths and bond angles are summarized in Table 4.

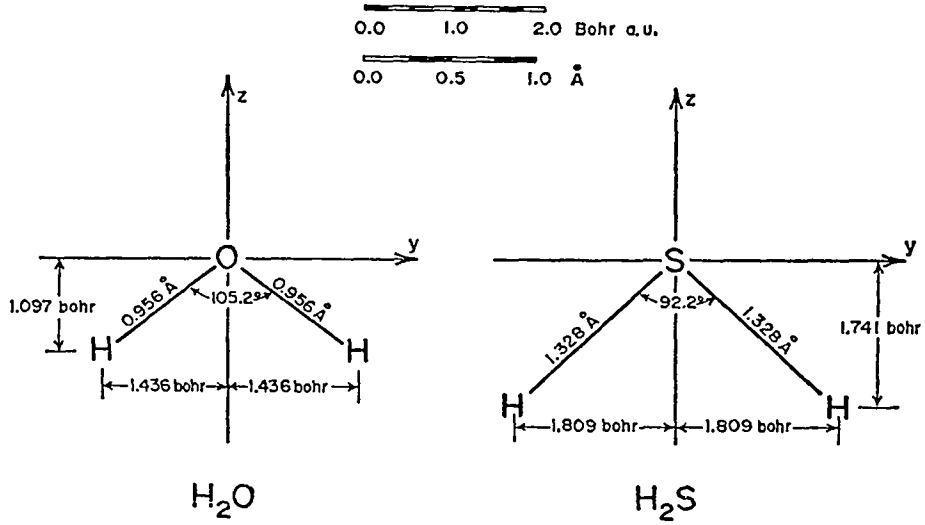


FIGURE 3. Bond lengths, bond angles and x, y, z coordinates of H_2O and H_2S.

TABLE 4. Selected bond lengths (r_e) and bond angles (ϕ_e) of some simple compounds containing the O—H and S—H functional groups

Bond length or angle		X = O	X = S
r_e	X—H	0·9706 Å	1·35 Å
	HX—H	0·956 Å	1·328 Å
	CH_3X—H	0·956 Å	1·329 Å
ϕ_e	H—X—H	105·2°	92·2°
	C—X—H	105·9°	100·3°

When the energy (E) is computed as a function of molecular geometry a potential curve $E(q)$, a potential surface $E(q_1, q_2)$, or a potential hypersurface $E(q_1, q_2, q_3, \ldots)$ is obtained for one, two or more independent variables respectively. No experimental potential energy surface

$E(r_{SH}, \phi_{HSH})$ associated with the geometrical changes in H_2S is available at this time. In such an energy surface the two independent variables are *bond-stretch* (r_{SH}), involving the symmetrical stretch of both bonds, and *bond-bend* (ϕ_{HSH}), implying an opening (and closing) of the bond angle.

A potential curve is simply a cross-section of a potential surface. Considering H_2O and H_2S, the potential curves associated with the in-plane-inversion[5] $E(\alpha)$ of each surface are shown in Figure 4. The two

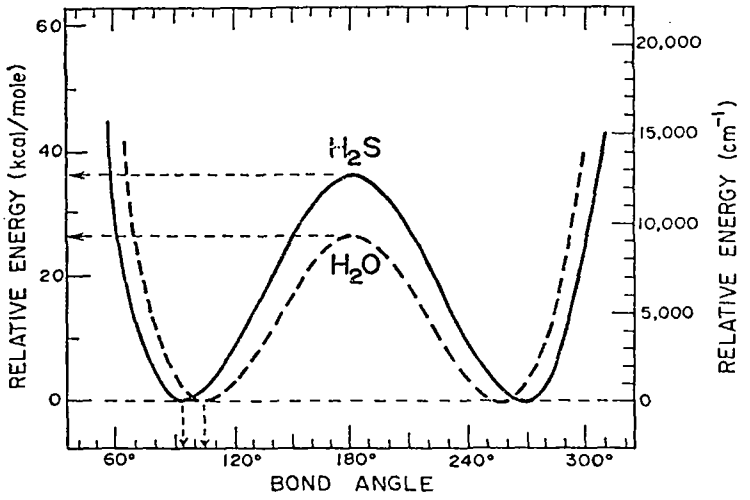


FIGURE 4. Inversion potential energy curves $E(\alpha)$ of H_2O and H_2S.

cross-sections along the symmetric stretching mode $E(r)$ of H_2O and H_2S are analogous to those shown in Figure 5.

The stretching potential can be fairly well represented by the Morse function:

$$E(r) = E_e + D_e\{1 - \exp[-\beta(r - r_e)]\}^2 \tag{8}$$

where E_e is total energy of the molecule at the equilibrium geometry (at the minimum of the potential curve), D_e is the bond energy which is the sum of the dissociation energy (D_0) and zero point vibrational energy E_{ZPV}:

$$D_e\,(\text{kcal/mole}) = D_0\,(\text{kcal/mole}) + 0{\cdot}00286 E_{ZPV}\,(\text{cm}^{-1}) \tag{9}$$

and r_e is the equilibrium bond length. The parameter β is a composite constant as defined by equation (10):

$$\beta = \sqrt{\frac{k}{2D_e}} \tag{10}$$

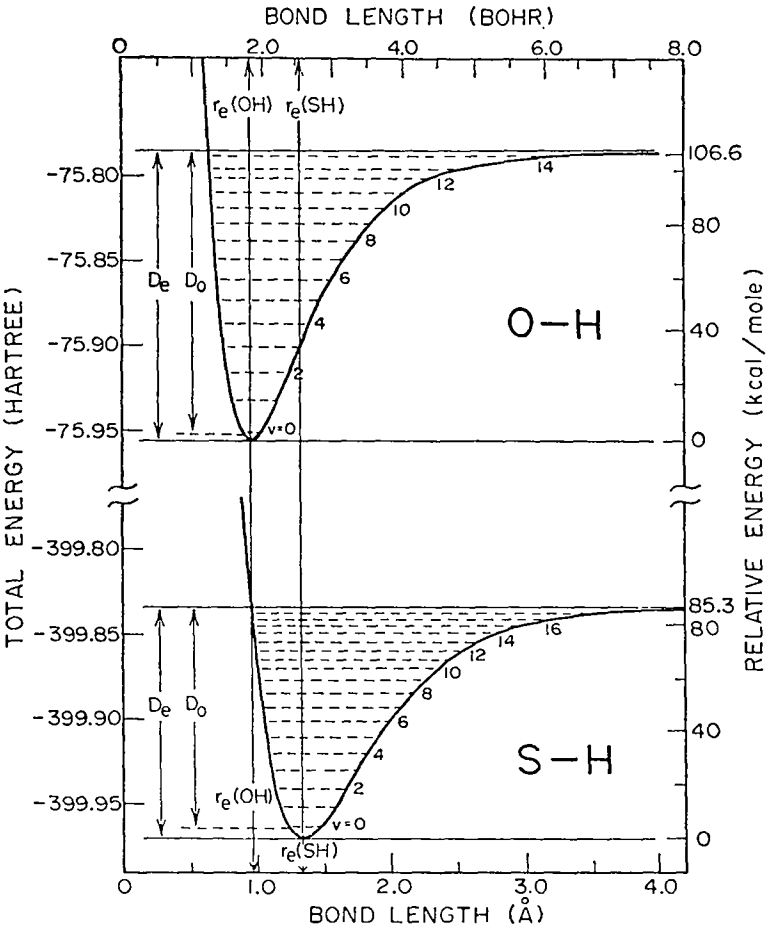


FIGURE 5. Stretching potential curves $E(r)$ of OH and SH.

The harmonic force constant k appearing in equation (10) is related to the vibrational frequency (ν) and to the reduced mass (μ):

$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}} \tag{11}$$

These quantities are summarized for HO and HS in Table 5 and were used for plotting the stretching potentials presented in Figure 5. Note that if the motions were really harmonic then the vibrational levels would be equispaced with a separation of $\Delta E = hc\omega_e$ (where ω_e is ν in the previous notation) corresponding to the following term scheme, where v is the vibrational quantum number:

$$E_{vib}\ (\mathrm{cm}^{-1}) = \omega_e(v+\tfrac{1}{2}) - \omega_e x_e(v+\tfrac{1}{2})^2 + \omega_e y_e(v+\tfrac{1}{2})^3 \ldots \tag{12}$$

TABLE 5. Morse potential parameters for OH and SH radicals

Parameter (unit)	OH	SH
E_e (hartree)	−75·7860	−399·8336
ω_e (cm^{-1})	3735·2	2702
$\omega_e x_e$ (cm^{-1})	82·8	60
E_{ZPV} (hartree)	0·0085	0·0062
D_0 (kcal/mole)	101·27	81·43
D_e (kcal/mole)	106·61	85·32
μ (Aston mass unit)[a]	0·948374	0·977325
k (millidynes/Å)	7·791	4·201
β (bohr^{-1})	1·2138	0·9963
r_e (bohr)	1·8342	2·551

[a] The atomic weights as expressed in Aston mass units were taken from the *C.R.C. Handbook of Chemistry and Physics*, 47th edition, pp. B6, B7 and B10. Published by the American Rubber Co., Cleveland, Ohio.

where $\omega_e x_e \ll \omega_e$ and $\omega_e y_e \ll \omega_e$. The introduction of correction terms for an harmonic motion alters the ZPV energy and the force constant value only slightly but has a substantial effect on higher vibrational levels.

For diatomic molecules there is only one mode of vibrational motion, stretching (or contracting) of the bond. For polyatomic molecules containing N atoms there are $3N-6$ coordinates for vibrational modes, 3 for translational and 3 for rotational modes. Vibrational modes for diatomic and triatomic molecules are illustrated in Figure 6.

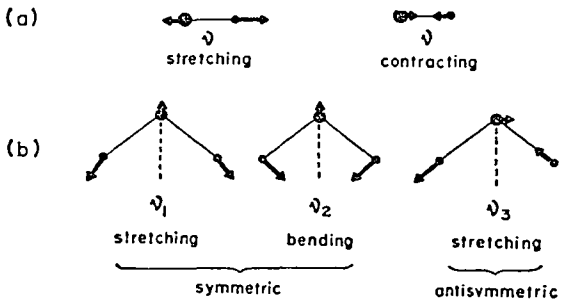
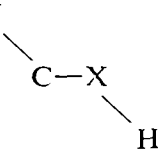


FIGURE 6. Vibrational modes of diatomic (a) and triatomic (b) molecules.

The situation is more complicated for CH_3—OH and CH_3—SH which have 12 vibrational modes of motion. Out of the 12 vibrational modes, 8 are symmetric with respect to the  (X = O or S) plane of

the molecule and 4 are antisymmetric with respect to that plane. The 4 antisymmetric vibrational frequencies are usually close in value to 4 of the symmetric modes; in fact they may show up as degenerate vibrations*.

For this reason an appropriate labelling is desirable. Frequencies associated with symmetric modes are designated by an unprimed or primed symbol ν_i or ν'_j and those corresponding to antisymmetric modes are symbolized by a double prime, ν''_j. Sometimes ν'_j and ν''_j are so close that they cannot be resolved and therefore they appear as a doubly degenerate mode. This is the case for ν'_5 and ν''_5 of CH_3OH and CH_3SH, shown in Table 6.

TABLE 6. Fundamental vibrational frequencies (cm^{-1}) of methanol and methylthiol

No.	X = O or S	Frequency	$CH_3—O—H$[a]	$CH_3—S—H$[b]
1	X—H	ν_1	3682	2869
2	C—H	ν_2	2844	2607
3	CH_3	ν_3	1477	1335
4	C—X	ν_4	1034	704
5	C—H	ν'_5	2977	3010
6		ν''_5	2977	3010
7	CH_3	ν'_6	1430	1475
8	CH_3	ν''_6	1455	1430
9	CH_3 rocking	ν'_7	1056	957
10	CH_3 rocking	ν''_7	1171	1060
11	XH bending	ν'_8	1340	803
12	XH twisting	ν''_8	270[c]	200 (?)[d]
E_{ZPV} (cm^{-1}) $= \frac{1}{2}\sum\nu_i$			10,856·5	9730·0
E_{ZPV} (hartree) $= 4{\cdot}5563 \times 10^{-6} E_{ZPV}$ (cm^{-1})			0·0489	0·0438

[a] Taken from G. H. Herzberg, *Molecular Spectra and Molecular Structure*, Vol. II, p. 335.

[b] Taken from G. H. Herzberg, *Molecular Spectra and Molecular Structure*, Vol. III, p. 630.

[c] This frequency is associated with the —OH torsion. The barrier to this internal rotation is 1·07 kcal mole (cf. section I.F).

[d] No frequency is available for this vibrational mode. The value quoted here is estimated from the barrier height of internal rotation (0·70 kcal/mole) which is smaller than that of methanol (cf. footnote *c*).

* These vibrations would be perfectly degenerate if the molecule had a linear geometry about X in $CH_3—X—H$ (i.e. angle CXH = 180°).

The frequencies given in Table 6 allow the calculation of zero point vibration energies (E_{ZPV}) which are also included in Table 6. With the aid of E_{ZPV} the total molecular energy can be calculated provided the dissociation energies are known. For CH_3—SH these are:

$$\left.\begin{array}{rcll} CH_3{-}SH & \longrightarrow & CH_3{+}SH & D_0^{(1)} = 73{\cdot}29 \text{ (reference 4)} \\ CH_3 & \longrightarrow & CH_2{+}H & D_0^{(2)} = 113{\cdot}04 \text{ (reference 4)} \\ CH_2 & \longrightarrow & CH{+}H & D_0^{(3)} = 97{\cdot}58 \text{ (reference 4)} \\ CH & \longrightarrow & C{+}H & D_0^{(4)} = 80{\cdot}05 \text{ (reference 6)} \\ SH & \longrightarrow & S{+}H & D_0^{(5)} = 81{\cdot}43 \text{ (reference 6)} \end{array}\right\} \quad (13)$$

$$E_{\text{dissoc}} = \sum_{i-1}^{\text{all bonds}} D_0^{(i)} = 445{\cdot}39 \text{ kcal/mole} = 0{\cdot}7096 \text{ hartree}$$

Thus the total energy for CH_3SH may be calculated from equation (5). The energy value and its components are listed in Table 7. The corresponding values for CH_3—OH are also included for comparison.

TABLE 7. The calculation of the experimental molecular total energy[a] values (E_e) for CH_3OH and CH_3SH

Components	CH_3OH	CH_3SH
Total atomic energy (E_{atoms})	−114·976	−439·058
Dissociation energy (E_{dissoc})	−0·766	−0·710
Zero-point vibration energy (E_{ZPV})	−0·049	−0·044
Experimental total energy (E_e)	−115·791	−439·812

[a] In Hartree atomic units.

Having computed the total energy values (E_e), it may be appropriate to compare the stretching potentials of C—S and S—H in methanethiol and the corresponding C—O and O—H stretching potentials in methanol. In order for this it is necessary to convert the Morse potential from the Quantum Chemical Standard State as defined by equation (8) to a modified chemical standard state where the infinitely separated radicals $\cdot CH_3 + \cdot SH$ or $CH_3S\cdot + \cdot H$ represent the energy zero (E_∞). The conversion

to this standard state can be achieved by subtracting the energy of the separated radicals (E_∞) from both sides of equation (8):

$$\Delta E = E - E_\infty = E_e - E_\infty + D_e\{1 - \exp[-\beta(r - r_e)]\}^2 \quad (14)$$

Since

$$D_e = E_\infty - E_e \quad (15)$$

and $E_e < E_\infty$, then

$$\Delta E = -D_e + D_e\{1 - \exp[-\beta(r - r_e)]\}^2 \quad (16)$$

and there is no need to calculate the total energy values of the various radicals in order to evaluate every E_∞ for the different dissociation reactions. The parameters necessary to plot the Morse potentials for the C—S, S—H, C—O and O—H bonds are summarized in Table 8 and the shapes of the potential curves are shown in Figure 7.

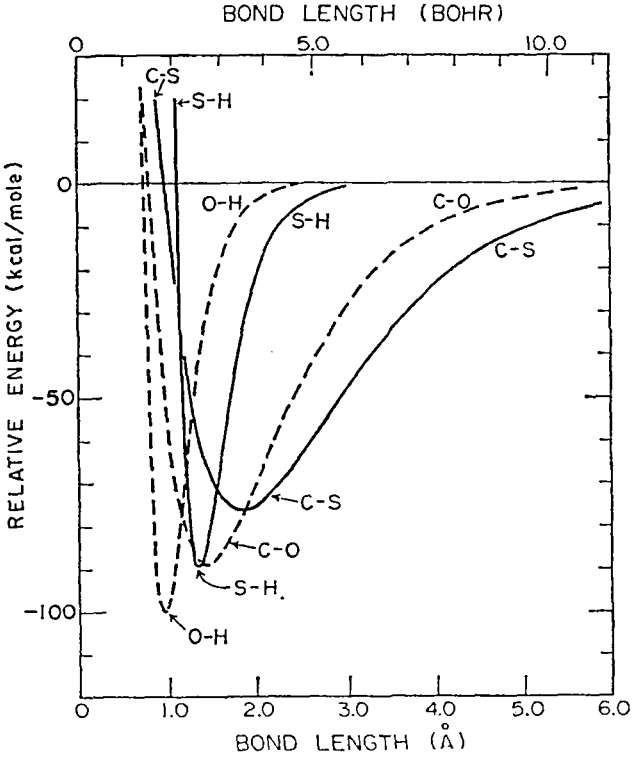


FIGURE 7. Potential curves for CS, SH, CO and OH.

TABLE 8. Morse potential parameters for two modes of motion in CH_3OH and CH_3SH

Parameter (unit)	CH_3OH		CH_3SH	
	C—O	O—H	C—S	S—H
μ (Aston mass unit)	0·243025		0·244884	
E_e (hartree)	−115·792		−439·812	
D_0 (Kcal/mole)	89	100	76	90
ν (cm^{-1})	1034	3682	704	2869
D_e (Kcal/mole)	89·0042	100·0150	76·0029	90·0117
k (millidyne/Å)	0·15328	1·94360	0·07160	1·18907
β ($Å^{-1}$)	0·35212	1·18285	0·26043	0·97523
r_e (Å)	1·428	0·956	1·818	1·329

C. Electronic Excitations

Visible and ultraviolet spectra are usually classified as electronic spectra because they involve transitions from one electronic state (normally the ground state) to another electronic state (usually a low-lying electronic excited state). These electronic states are characterized by a particular electronic configuration which in turn can be viewed as an occupancy scheme of molecular orbitals. Consequently the interpretation of electronic spectra is normally given in terms of molecular orbitals.

The molecular orbitals (MO) obtained by self-consistent field (SCF) calculations are symmetry adapted and are frequently referred to as canonical molecular orbitals (CMO). Ultraviolet excitation and molecular ionization phenomena are best explained in terms of CMO, hence the symmetry-adapted nature of these SCF orbitals is of some importance. The CMO representation of the valence electron shells of H_2O and H_2S is shown in Figure 8.

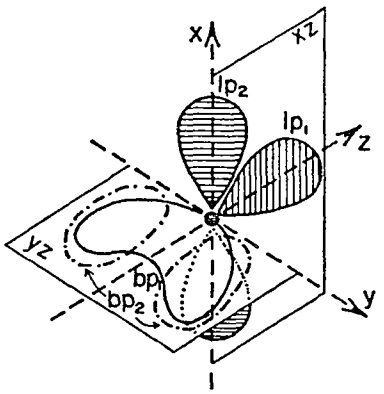


FIGURE 8. Canonical molecular orbitals of H_2S or H_2O.

Inspection of Figure 8 shows that one lone pair (lp_1) and one bonding pair (bp_1) are fully symmetric since these mathematical functions do not change sign either by rotation about the z axis or by reflection through the xz or yz plane. These symmetric orbitals are labelled a_1. On the other hand, there are two other orbitals which may be classified as antisymmetric and these will be labelled b. The second lone pair (lp_2) is antisymmetric and is labelled b_1. The second bonding pair (bp_2) is antisymmetric with respect to reflection through the xz plane or rotation about the z axis; this orbital is classified b_2. It might be added that in the familiar organic classification, orbitals a_1 and b_2 may be called σ-orbitals while orbital b_1

could be labelled as a π-MO. The composition of CMO in terms of the set of AO is clearly indicated for the 4 valence electron pairs (occupied MO) and for the 2 lowest-lying unoccupied (or virtual) MO in Figure 9.

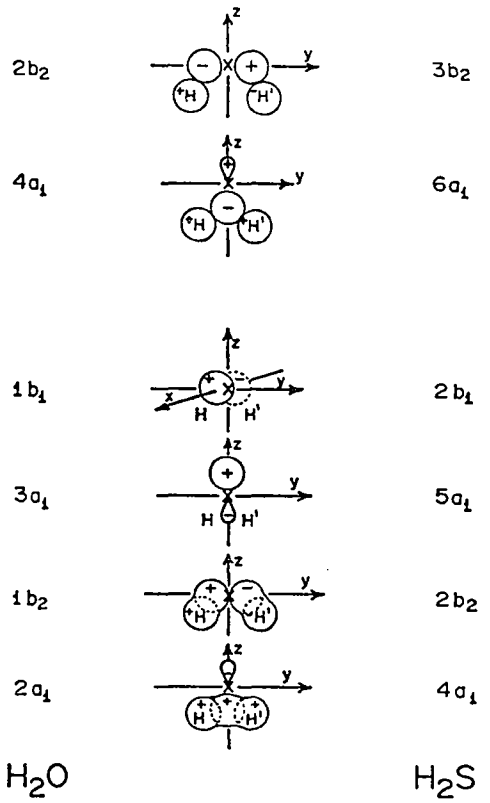


FIGURE 9. Four highest occupied and two lowest unoccupied molecular orbitals in H_2O and H_2S.

The energy values associated with these MO (orbital energies) are illustrated in a semi-quantitative fashion in Figure 10. The following explanatory comments might be useful:

(i) The number (1, 2, 3, ..., etc.) that precedes the symmetry classification (a_1, b_1, b_2) is the sequence number of the orbitals in that particular representation. The notation is analogous to $1\sigma, 2\sigma, 3\sigma$..., etc. and the orbital labelled with a smaller serial number has a lower (larger negative) orbital energy value: $\varepsilon(1a_1) < \varepsilon(2a_1) < \varepsilon(3a_1) < \ldots$.

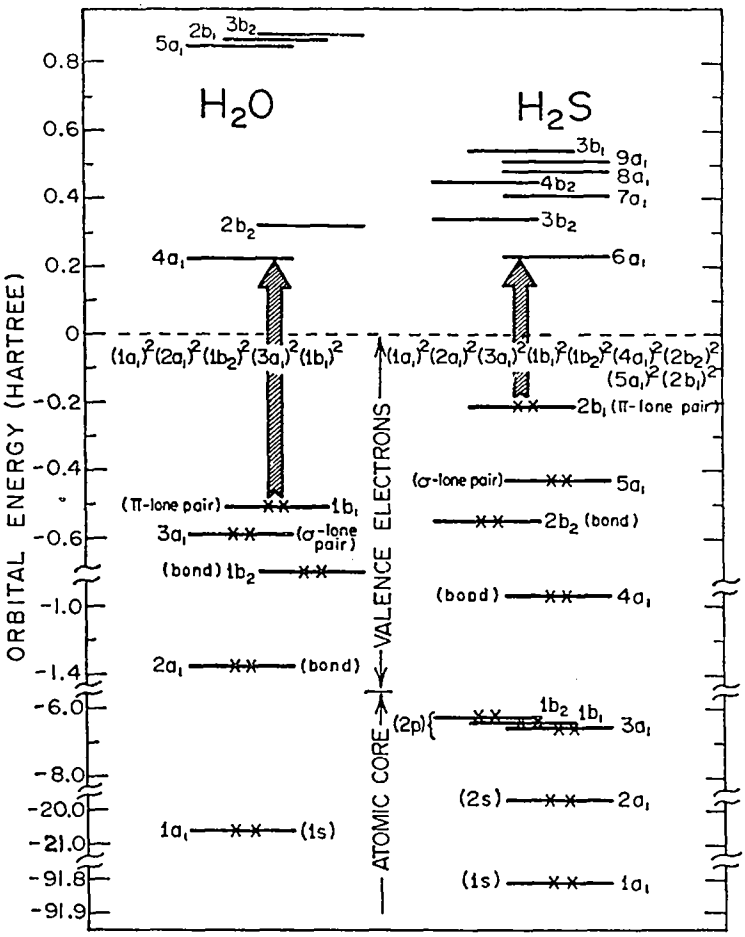


FIGURE 10. Molecular orbital energies of H_2O and H_2S.

(ii) There are more electrons in H_2S than in H_2O therefore the corresponding orbitals in the valence electron shell have different sequence numbers. The equivalence is noted below:

H_2O		H_2S
$2a_1$	. . . . .	$4a_1$
$1b_2$	. . . . .	$2b_2$
$3a_1$	. . . . .	$5a_1$
$1b_1$	. . . . .	$2b_1$
$4a_1$	. . . . .	$6a_1$

(17)

(iii) The sulphur core is more extensive than the oxygen core. These atomic orbitals of sulphur will become molecular orbitals as shown by the following equivalence:

$$\left.\begin{array}{ll} 1s & \ldots\ldots 1a_1 \\ 2s & \ldots\ldots 2a_1 \\ 2p_z & \ldots\ldots 3a_1 \\ 2p_x & \ldots\ldots 1b_1 \\ 2p_y & \ldots\ldots 1b_2 \end{array}\right\} \qquad (18)$$

An inspection of Figure 8 will reveal why the three $2p$ orbitals (i.e. p_z, p_x and p_y) have different symmetry properties (a_1, b_1 and b_2). More important is the fact that these three molecular orbitals ($3a_1$, $1b_1$ and $1b_2$) are not pure atomic orbitals ($2p_z$, $2p_x$ and $2p_y$) because their energy values are different (cf. right-hand side of Figure 10) while the original $2p$ atomic orbitals have the same energy value. This is further evidence that core electrons do change in the course of molecule formation. Consequently the assumption that they do not, and therefore they may be neglected, is only a zero-order approximation.

(iv) Most important is the fact that the orbitals that describe the valence electrons in H_2S are higher on the orbital energy scale than the corresponding orbitals for H_2O (cf. equation 17). This means that the valence electrons of H_2S are 'looser' and consequently more readily available than those of H_2O. This is reflected in some physical properties such as basicity, nucleophilicity etc. and is the basis for the rationale of the u.v. spectra of the thiol group in comparison to the OH group.

(v) Finally, these MO, presented in Figure 10, were obtained for the ground electronic configurations in which each of the lowest orbitals is occupied by a pair of electrons. These electronic configurations for H_2O and H_2S may be written as follows:

$$\begin{array}{lll} H_2O: & & (1a_1)^2|(2a_1)^2(1b_2)^2(3a_1)^2(1b_1)^2 \\ H_2S: & (1a_1)^2(2a_1)^2(3a_1)^2(1b_1)^2(1b_2)^2| & (4a_1)^2(2b_2)^2(5a_1)^2(2b_1)^2 \\ & \leftarrow\!\!-\text{atomic core}-\!\!\rightarrow & \leftarrow\!\!-\text{valence electrons} \end{array} \qquad (19)$$

Electronic excitation involves the promotion of an electron from one of the highest-filled MO to the low-lying but otherwise empty MO. This is illustrated by the heavy arrow in Figure 10 and corresponds to the

following change in the electronic configuration:

$$\left.\begin{array}{ll} H_2O: & \ldots(1b_2)^2(3a_1)^2(1b_1)^2 \xrightarrow{\Delta E(H_2O)} \ldots(1b_2)^2(3a_1)^2(1b_1)^1(4a_1)^1 \\ H_2S: & \ldots(2b_2)^2(5a_1)^2(2b_1)^2 \xrightarrow{\Delta E(H_2S)} \ldots(2b_2)^2(5a_1)^2(2b_1)^1(6a_1)^1 \end{array}\right\} \quad (20)$$

where ΔE is the corresponding excitation energy observed in the form of an absorption spectrum. The excitation energies (ΔE) for H_2O and H_2S are illustrated in Figure 11 and the actual spectra[7-8] of H_2S and CH_3SH are shown in Figure 12.

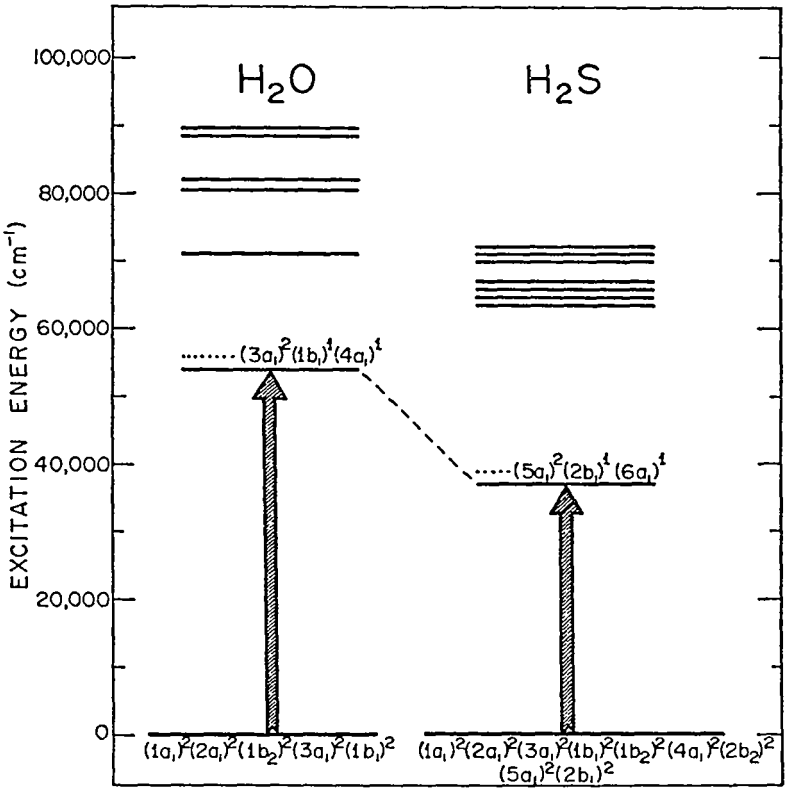


FIGURE 11. Ground and excited electron configurations in H_2O and H_2S.

Although Figure 12 includes the absorption spectrum of CH_3SH, a discussion of the excitation pattern of this compound will only be given in section III.B. It is clear however that substitution of sulphur for oxygen in RXH causes a larger shift towards low energy absorption than substitution of H by CH_3 is capable of causing. This is also illustrated

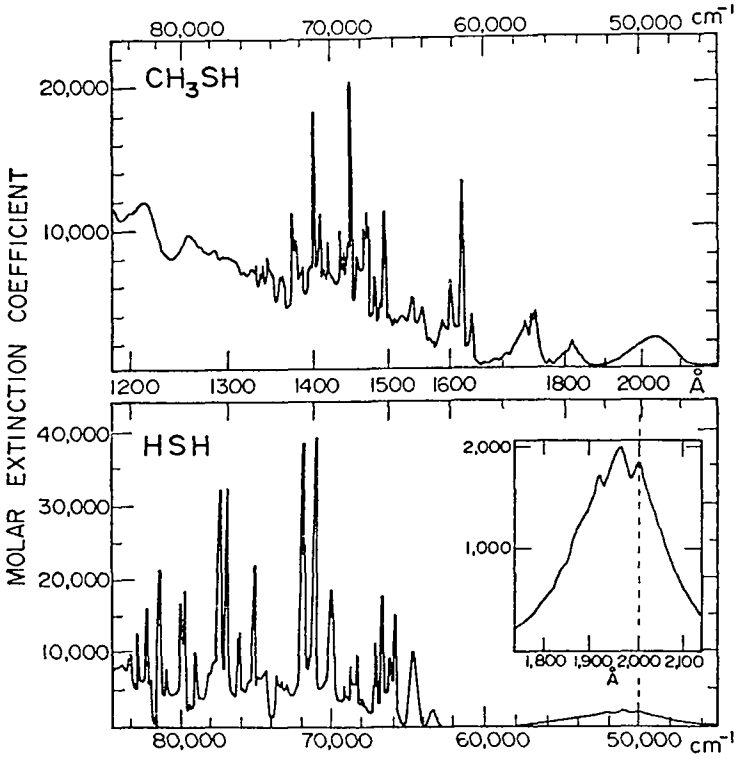


FIGURE 12. Absorption spectra of H_2S and CH_3SH.

in Table 9. The spectral shift in ROH, when R = H is changed to R = CH_3, has also been noticed[9] before.

Finally, it should be pointed out that the most favoured geometry for an excited state of a molecule is usually different from that of its ground state. For diatomic molecules this generally implies an increase in the

TABLE 9. First electronic excitation energies[a] of H_2O, H_2S and CH_3SH

Molecule	Excitation energy (ΔE)		Wavelength
	eV	cm^{-1}	λ (Å)
H—O—H	6·87	53,800	1860
H—S—H	4·59	37,000	2700
CH_3—S—H	4·46	36,000	2780

[a] Values were taken from reference 4.

bond length. The changes of the bond length upon excitation for HO and HS are 0·97→1·01 Å and 1·35→1·44 Å respectively. For more complicated molecules not only one but all bond lengths may change and bond angles are normally altered as well. For example, in *some* excited states of H_2S, the bond angle is 180°. The theoretical conformational analysis of the low-lying excited states of CH_3SH will be discussed in section III.B.

D. Ionization Potentials and Electron Affinities

The ionization potential (IP) is the energy *absorbed* when an electron is removed from a molecule (M) while the electron affinity (EA) is the energy *released* when an electron is captured by a molecule (M):

$$M^- \xleftarrow{EA} M \xrightarrow{IP} M^+ \tag{21}$$

EA is frequently specified as a positive number even though in the thermodynamic sense the energy released is always negative. In order to avoid confusion the thermodynamic convention will be used here, i.e. the energy difference is positive if consumed (endothermic process) and negative if liberated (exothermic process).

It should be noted that the process of ionization will increase the positive charge by 1 and electron capture will decrease the positive charge by 1. Consequently EA of a species (M) is the negative, in the arithmetical sense, of the IP of the corresponding species having a charge smaller by +1 (i.e. M^-). This is illustrated by the following equation and the corresponding set of equivalences:

$$\ldots M^{2-} \underset{EA^-}{\overset{IP^{2-}}{\rightleftharpoons}} M^- \underset{EA}{\overset{IP^-}{\rightleftharpoons}} M \underset{EA^+}{\overset{IP}{\rightleftharpoons}} M^+ \underset{EA^{2+}}{\overset{IP^+}{\rightleftharpoons}} M^{2+} \ldots \tag{22}$$

$$\left.\begin{aligned} &\vdots \\ EA^- &= -IP^{2-} \\ EA &= -IP^- \\ EA^+ &= -IP \\ EA^{2+} &= -IP^+ \\ &\vdots \end{aligned}\right\} \tag{23}$$

IP and EA values may be calculated from the heats of formation (ΔH_f^0) of the ions involved. These are listed in Table 10 for monatomic species such as oxygen and sulphur together with the relevant IP and EA values[10]. It may be noted that the IP of the sulphur species are always lower than the corresponding IP of the oxygen species *because the valence*

TABLE 10. Heats of formation (ΔH_f^0) [a] ionization potentials (IP) and electron affinities (EA) of oxygen and sulphur atoms as well as their ions

Oxygen	ΔH_f^0	$\Delta\Delta H_f^0$ (kcal/mole)		Sulphur	ΔH_f^0	$\Delta\Delta H_f^0$ (kcal/mole)	
	kcal/mole	IP	EA		kcal/mole	IP	EA
O^{8+}	47,210·0	—	−20,119·0	S^{8+}	20,507·0	—	−7,584·0
O^{7+}	27,091·0	20,119·0	−17,046·0	S^{7+}	12,923·0	7,584·0	−6,481·9
O^{6+}	10,045·0	17,046·0	−3,184·1	S^{6+}	6,441·1	6,481·9	−2,031·6
O^{5+}	6,860·9	3,184·1	−2,626·1	S^{5+}	4,409·5	2,031·6	−1,672·8
O^{4+}	4,234·8	2,626·1	−1,784·8	S^{4+}	2,736·7	1,672·8	−1,092·14
O^{3+}	2,450·0	1,784·8	−1,266·91	S^{3+}	1,644·56	1,092·14	−809·74
O^{2+}	1,183·09	1,266·91	−810·535	S^{2+}	834·82	809·74	−541·234
O^{+}	372·555	810·535	−313·969	S^{+}	293·586	541·234	−240·336
O	58·586	313·969	−33·386	S	53·25	240·336	−47·55
O^{-}	25·2	33·386	—	S^{-}	5·70	47·55	—

[a] Values were taken from reference 10.

electrons in sulphur experience a smaller effective nuclear charge than the valence electrons of oxygen.

The heats of formation for species containing the OH or SH groups are given in Table 11 and the corresponding IP and EA values are summarized in Table 12. A number of conclusions may be drawn from

TABLE 11. Heats of formation[a] (ΔH_f^0) of selected oxygen- and sulphur-containing neutral and charged species

Charge	O	OH	H—OH	CH_3—OH
+1	372·555[b]	313·35[c]	233·81[f]	203·38[f]
0	58·586[b]	9·29	−57·10[c]	−48·08[b]
−1	25·2[c]	−32·9[c]	−77·86[g]	?
Charge	S	SH	H—SH	CH_3—SH
+1	293·586[b]	276[d]	235[d]	212·32[f]
0	53·25[b]	34·4[c]	−4·81[b]	−5·46[e]
−1	5·70[g]	−25·58[g]	?	?

[a] In kcal/mole.
[b] Reference 10.
[c] Reference 11.
[d] Reference 12.
[e] Reference 13.
[f] Calculated from the IP and ΔH_f^0 of the corresponding neutral molecule. The IP value was taken from reference 1.
[g] Calculated from the EA and ΔH_f^0 of the corresponding neutral molecule. The EA value was taken from reference 1.

TABLE 12. Ionization potentials (IP) and electron affinities (EA)[a] of selected oxygen- and sulphur-containing species

Species	IP	EA
	kcal/mole	
O	313·97	−33·39
OH	304·06	−42·19
H_2O	290·91	−20·76
CH_3OH	251·46	?
S	240·34	−47·55
SH	241·60	−59·98
H_2S	239·81	?
CH_3SH	217·78	?

[a] The values were calculated as difference in heats of formation. The corresponding heats of formation values are summarized in Table 11.

these results. First of all the IP of oxygen compounds are larger than those of the corresponding sulphur compounds. This means that the valence electrons of sulphur are more readily available and thus, in a sense, the sulphur compounds are more basic. On the other hand, the EA values for oxygen compounds are considerably higher than those of the corresponding sulphur species, therefore in the case of negatively charged species the oxygen analogues are more basic. Another point of interest is that the values reported for the oxygen-containing compounds have a greater spread than those observed for the sulphur analogues. This implies that the substituent adjacent to the heteroatom creates a smaller perturbation on the electronic structure of the S atom than on that of the O atom. These points are clearly illustrated in Figure 13.

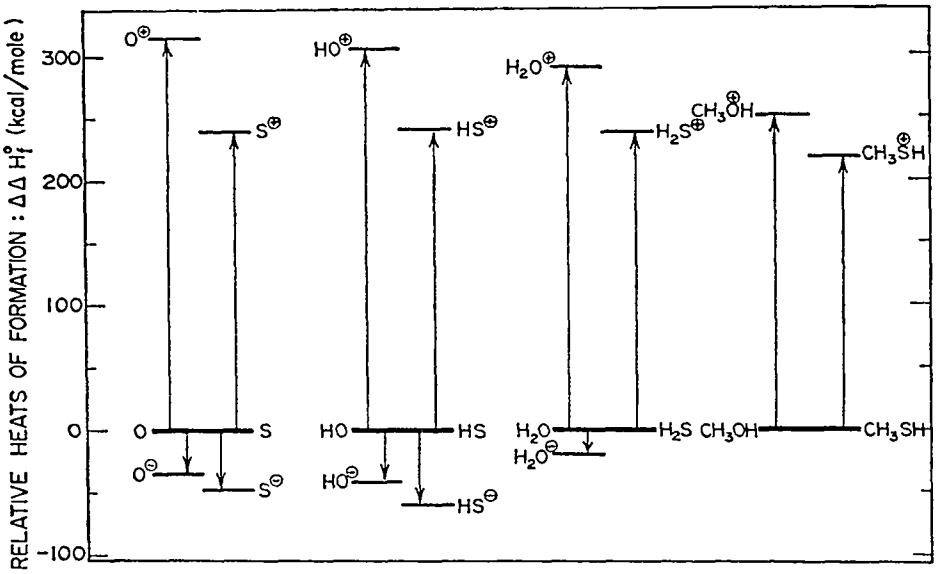


FIGURE 13. Ionization Potentials (IP) and Electron Affinities (EA) of O and S containing species. (The IP and EA values are expressed as relative heats of formation: $\Delta\Delta H_f^o$).

The ions generated by electron capture or ionization are separate entities and consequently may have different molecular geometries and spectroscopic constants with respect to the neutral species. These values are summarized in Table 13 for ions derived from HO and HS. The corresponding Morse potentials for the six species involved are presented in Figure 14.

TABLE 13. Heats of formation[a] and spectroscopic constants[b] of HO, HS and their ions

	HO^-	HO	HO^+
ω_e (cm^{-1})	3735 ± 560	3735·21	2955
$\omega_e X_e$ (cm^{-1})	74·7	82·81	74
r_e (Å)	0·9702	0·9706	1·0289
ΔH_f° (kcal/mole)	$-32·9 \pm 1·0$	$+9·290 \pm 0·3$	$+313·3 \pm 2·5$
D_0 (kcal/mole)	107·6	101·27	114·5
E_e (hartree)	−75·8434	−75·7860	−75·2999
	HS^-	HS	HS^+
ω_e (cm^{-1})	(2702)	2702	(2130)
$\omega_e X_e$ (cm^{-1})	—	60	—
r_e (Å)	(1·33)	1·3397	(1·4)
ΔH_f° (Kcal/mole)	−25·58	$+34·4 \pm 4$	+276·
D_0 (Kcal/mole)	87·67[c]	81·43	64·6
E_e (hartree)	−399·9229	−339·8336	−399·4475

[a] Taken from Table 11.
[b] Taken from references 2, 3, 6 and 14.
[c] Estimated from the following cycle: $D_0^{HS^-} = D_0^{HS} + (EA^{HS} - EA^S) = 5·53 + (2·60 - 2·33) = 3·80$ eV → 87·67 kcal/mole.

It is clear from this figure that, similarly to u.v. excitation, vertical and non-vertical transitions for both ionization and electron capture should be distinguished. The vertical ionization potential (IP_v) is always higher than the adiabatic ionization potential (IP_a) while a vertical electron capture involves a smaller electron affinity than that of the adiabatic process. This is because the anion has a slightly shorter bond length than the neutral species while the bond length of the cation is considerably longer.

The localization of the electron removed by ionization or gained by electron capture is frequently a matter of some controversy. It is quite reasonable to assume that the incoming electron, in the course of electron capture, will occupy the lowest empty orbital available because such an orbital occupancy corresponds to the electronic ground state of the anion thus ensuring maximum energy release. On the other hand, the ionization process is much more complicated. It is true that the loosest electron, occupying the highest energy MO, is the easiest to remove, but it is also true that when the ionization process involves very high energies then the more tightly bound electrons, corresponding to the lower energy MO, may be removed to yield the corresponding molecule-ion. It should be noted,

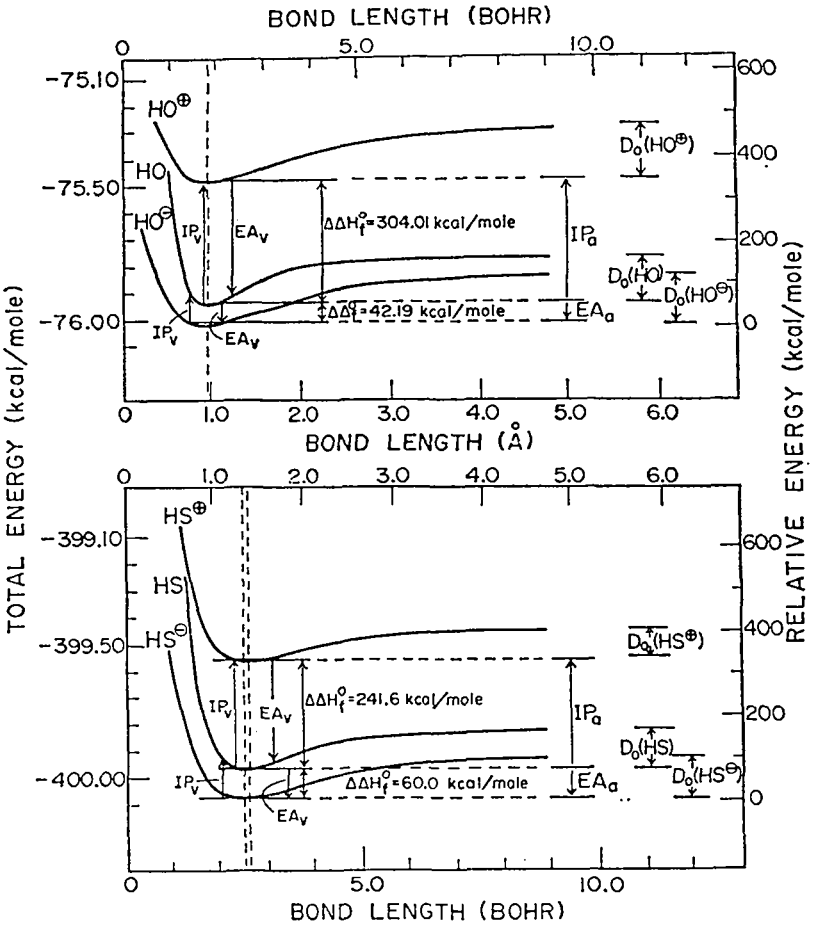


FIGURE 14. Morse potentials for OH, SH and their ions.

however, that while the former molecule-ion represents the electronic ground state, the latter corresponds to an electronic excited state of the same molecule-ion.

It should probably be emphasized that both the neutral parent molecule (e.g. H_2S) and the radical ion (e.g. H_2S^+) have their own excited state manifolds (cf. Figure 11 for H_2S) but only the first excited states of H_2S are shown in Figure 15. Electronic excitations, associated with transitions within either one of these manifolds, occur within the visible, u.v. or far u.v. range. On the other hand, the ionization energy begins somewhere in the far u.v. domain and extends into the frequency range of X-radiation. This branch of spectroscopy (involving transitions to ionized states) is

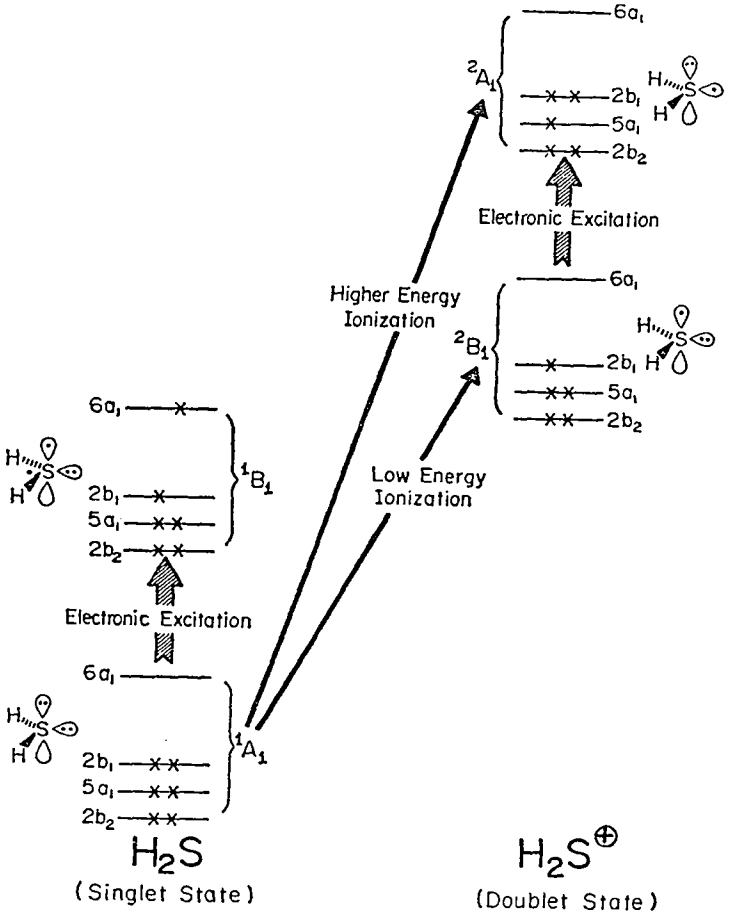


FIGURE 15. Molecular orbitals involved in electronic excitation and ionization processes in H_2S.

called photoelectron spectroscopy or ESCA (electron spectroscopy for chemical analysis). When X-rays are used, the innermost electrons (K or L shell) may be removed in the course of the ionization process. In general even these high energy ionization potentials vary with the chemical environment.

To use H_2S as an example, the two non-equivalent lone pairs corresponding to the CMO $2b_1(\pi$-lone pair) $5a_1(\sigma$-lone pair) should be considered as the two orbitals from which it is easiest to remove electrons. The principles discussed in the previous paragraph are illustrated schematically in Figure 15. The actual energy levels involving these two

ionized states compared with the electronic excitation pattern of the neutral parent molecule (H_2S) are summarized in Figure 16.

The spectra associated with the first two transitions[15]: $^2B_1 \leftarrow {}^1A_1$ and $^2A_1 \leftarrow {}^1A_1$ are combined in Figure 17. The ionization energies[16] associated

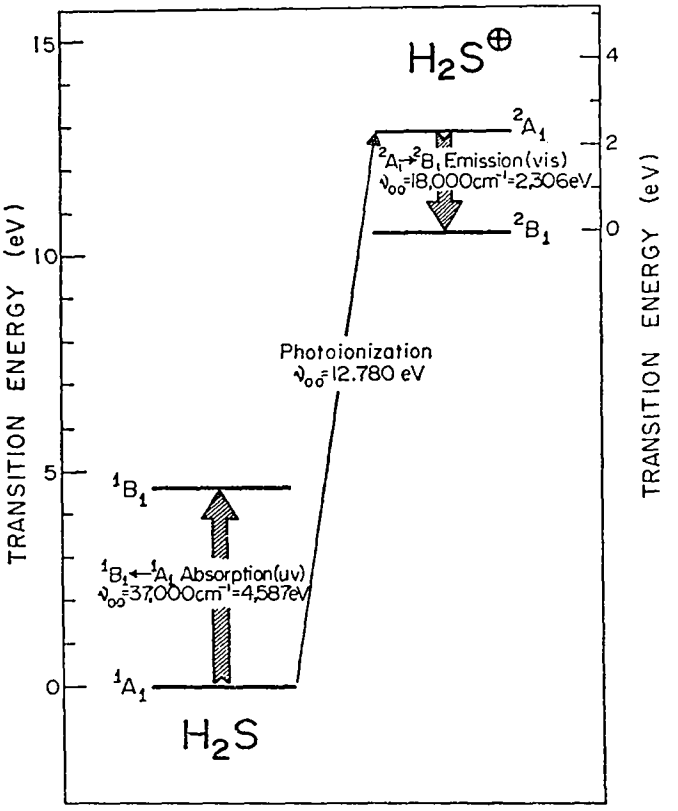


FIGURE 16. Ground and excited state energy levels involved in electronic excitation and ionization processes in H_2S.

with the first three states ($^2B_1$, $^2A_1$ and $^2B_2$) of H_2O, H_2S and H_2Se are summarized in Table 14. However the emission spectrum[17] for H_2S^+ associated with the $^2A_1 \rightarrow {}^2B_1$ transition will not be discussed here at length. Its energetics are clearly indicated however in Figure 16.

The photoelectron spectrum of CH_3SH has not been studied in as much detail as the ionization spectrum of H_2S. This is understandable because CH_3SH is much more complicated than H_2S. In the case of H_2S, the first two ionizations (cf. Figures 15, 16 and 17) are associated with the

removal of an electron from one or the other of the non-equivalent lone pairs, and only the third ionization (removal of an electron from the b_2-type MO) was related to the two SH bonds, according to Figure 9 and

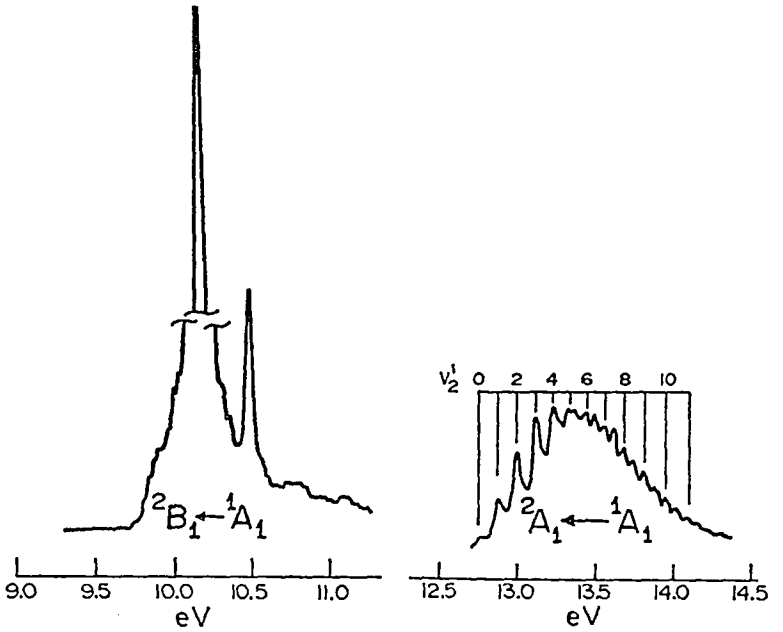


FIGURE 17. The $^2B_1 \leftarrow {}^1A_1$ and $^2A_1 \leftarrow {}^1A_1$ photoelectron band system of H_2S using the helium 584 Å line. In the $^2A_1 \rightarrow {}^1A_1$ transition the second (i.e. bending) vibrational quantum numbers associated with the ionized upper state ($^2A_1$) are designated v_2'.

Table 14. In the case of CH_3SH several bonding electrons fall in the low energy ionization potential range[18], as illustrated by Figure 18.

TABLE 14. Adiabatic ionization energies[a] of H_2X as measured from photoelectron spectra (X = O, S or Se)

$H_2X^+ \leftarrow H_2X$	H_2O	H_2S	H_2Se
$^2B_1 \leftarrow {}^1A_1$	12·61	10·43	9·93
$^2A_1 \leftarrow {}^1A_1$	13·70	12·81	12·17
$^2B_2 \leftarrow {}^1A_1$	17·22	14·79	13·61

[a] In eV.

Unfortunately the photoelectron spectrum of CH_3SH in the high energy range is not available; its ionization potential[19], associated with the sulphur $2p$ electron, is 162·7 eV.

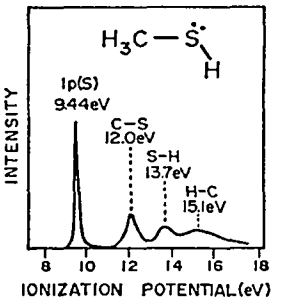


FIGURE 18. The photoelectron spectra of CH_3SH.

E. Proton Affinities, Hydrogen Affinities and Hydride Affinities

The most obvious species to include in a systematic study of molecular affinities are H^+, H and H^-. Consequently the proton affinity (A_{H^+}), hydrogen affinity (A_H) and hydride affinity (A_{H^-}) may be defined in the following way, where M may be any (charged or uncharged) species:

$$\left.\begin{aligned} M+H^+ &\xrightarrow{A_{H^+}} MH^+ \\ M+H &\xrightarrow{A_H} MH \\ M+H^- &\xrightarrow{A_{H^-}} MH^- \end{aligned}\right\} \tag{24}$$

These affinities may then be calculated from the corresponding heats of formation (ΔH_f^0):

$$\left.\begin{aligned} A_{H^+} &= \Delta H_f^0(MH^+) - \{\Delta H_f^0(M) + \Delta H_f^0(H^+)\} \\ A_H &= \Delta H_f^0(MH) - \{\Delta H_f^0(M) + \Delta H_f^0(H)\} \\ A_{H^-} &= \Delta H_f^0(MH^-) - \{\Delta H_f^0(M) = \Delta H_f^0(H^-)\} \end{aligned}\right\} \tag{25}$$

The heats of formation (ΔH_f^0) of some selected oxygen and sulphur compounds are summarized in Table 15. The corresponding proton, hydrogen and hydride affinities are listed in Table 16.

It is significant that hardly any A_H and A_{H^-} values are available. When a closed shell system such as RSH is combined with H or H^-, difficulties arise with respect to the accommodation of the 3 or 4 non-bonding electrons in the $R\ddot{S}H_2$ and $R\ddot{S}H^-$ systems. The situation is

TABLE 15. Heats of formation (ΔH_f^0)[a,b] of selected oxygen- and sulphur-containing neutral and charged species[c]

Species X:	O^+	O	OH	H—OH	CH_3—OH
X	372·555	58·586	9·29	−57·10	−48·08
XH^+	?	313·35	233·81	144·1	142·16
XH	313·35	9·29	−57·10	?	?
XH^-	9·29	−32·9	−77·86	?	?
Species X:	**S^+**	**S**	**SH**	**H—SH**	**CH_3—SH**
X	293·586	53·25	34·4	−4·81	−5·46
XH^+	?	276·	235·	182·43	170·
XH	276·	34·4	−4·81	?	?
XH^-	34·4	−25·58	?	?	?

[a] kcal/mole.
[b] Values were taken from references 1, 10, 11, 12 and 13.
[c] $\Delta H_f^0(H^+) = 365{\cdot}236$; $\Delta H_f^0(H) = 51{\cdot}631$; $\Delta H_f^0(H^-) = 34{\cdot}2$.

TABLE 16. Proton affinities (A_{H^+}), hydrogen affinities (A_{Π}) and hydride affinities (A_{H^-}) [a] of selected sulphur- and oxygen-containing compounds

Species	A_{H^+}	A_{Π}	A_{H^-}
O^+	—	−110·8	−329·1
O	−110·5	−110·9	−125·7
OH	−140·7	−118·0	−121·4
H_2O	−164·0[b]	—	—
CH_3OH	−175·0	—	—
Species	**A_{H^+}**	**A_{Π}**	**A_{H^-}**
S^+	—	−69·2	−293·4
S	−142·5	−70·5	−113·0
SH	−164·6	−90·8	—
H_2S	−178·0[b]	—	—
CH_3SH	−189·8	—	—

[a] In kcal/mole.
[b] Taken from reference 20.

somewhat simpler in the protonated species $R\ddot{S}H_2^+$ where only one lone pair is present. While the latter is pyramidal, the geometry of the former two species cannot be predicted from experimental or theoretical considerations. Intuitively, however, one may predict for $R\ddot{\underset{\cdot\cdot}{S}}H_2^-$ a T-shaped arrangement associated with a 5-electron pair (trigonal bipyramid) situation as the most favoured geometry. This is illustrated in Figure 19.

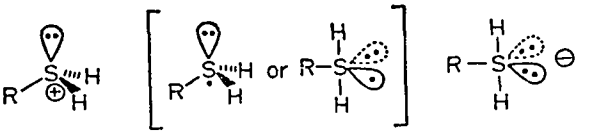


FIGURE 19. Probable conformations of RSH_2^+, RSH_2 and RSH_2^-.

It is even more difficult to be decisive about the neutral $R\ddot{\underset{\cdot}{S}}H_2$ species. Since it may be generated by ionization of $R\ddot{\underset{\cdot\cdot}{S}}H_2^-$ or by electron capture of RSH_2^+, its geometry may resemble either one of the charged analogues.

Since proton affinities are quite readily available in comparison to the hydrogen and hydride affinities, it may be appropriate to consider successive protonations, for example:

$$RS^- \xrightarrow[A_{H^+(RS^-)}]{H^+} RSH \xrightarrow[A_{H^+(RSH)}]{H^+} \overset{+}{R}SH_2 \qquad (26a)$$

The relevant data are summarized in Table 17.

TABLE 17. Proton affinity values[a] (kcal/mole) of some oxygen- and sulphur-containing species

	R = H	R = CH_3
R—O^-	−390	−384
R—S^-	−340	?
ROH	−164	−175
RSH	−178	−190

[a] Note that the following range is generally applicable for neutral molecules (M) and mononegative ion (M^-):

$$-100 \text{ kcal/mole} < A_{H^+}(M) < -250 \text{ kcal/mole}$$
$$-300 \text{ kcal/mole} < A_{H^+}(M^-) < -450 \text{ kcal/mole}$$

On inspection, the proton affinities observed for oxygen and sulphur compounds (ROH and RSH) as well as those of their anions (RO^- and

RS^-) reveal a definite trend. This is particularly meaningful if it is realized that the proton affinity of a neutral compound (e.g. RSH) is a measure of its *gas phase basicity* while the negative of the proton affinity of the corresponding anion (RS^-) is a measure of the *gas phase acidity* of the neutral molecule (RSH):

$$\left.\begin{array}{l} RSH \xrightarrow[-A_{H^+}(RS^-)]{\text{gas phase acidity}} RS^- + H^+ \\ H^+ + RSH \xrightarrow[A_{H^+}(RSH)]{\text{gas phase basicity}} RSH_2^+ \end{array}\right\} \quad (27)$$

The energetics of equation (27) are illustrated in Figure 20 for the cases of H_2O and H_2S. From Figure 20 and the data in Table 17 it must be

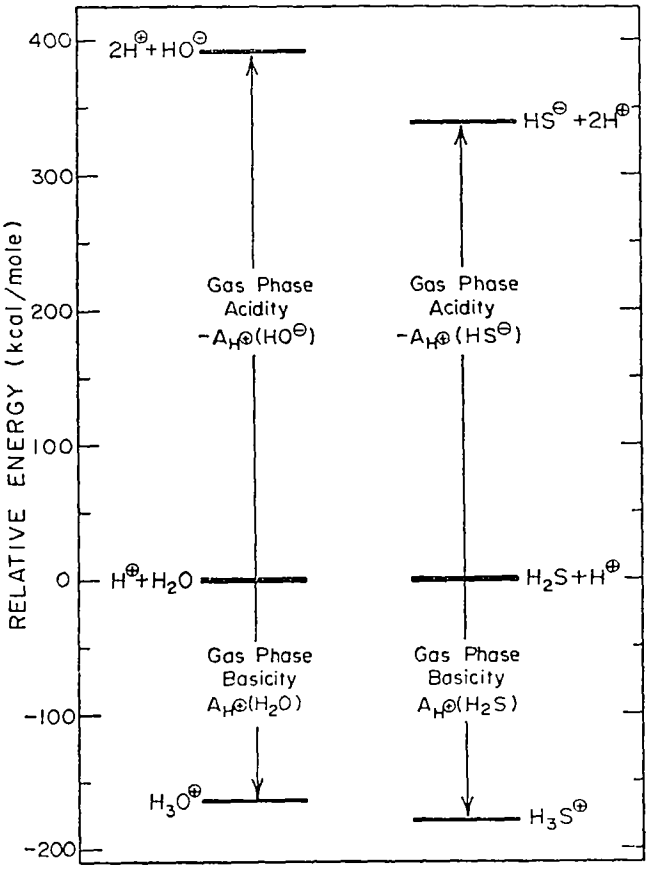
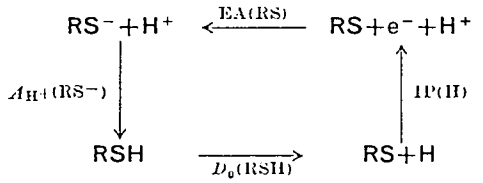


FIGURE 20. Relationship between proton affinity, A_{H^+}, gas phase acidity and basicity for H_2S and H_2O.

concluded that RSH compounds are more acidic and more basic in the gas phase than the corresponding oxygen analogues*.

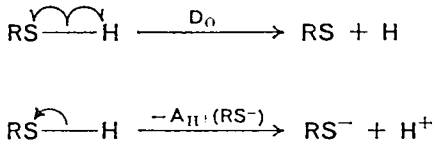
It should be pointed out that protonation almost always (even in the case of CH_4) lowers the energy of the system, that is, the calculated proton affinity is negative. (Consequently deprotonation always raises the energy level of the system.) For this reason one cannot correlate gas phase acidity (or basicity) with solution acidity (or basicity) because solvation may markedly alter the situation with respect to the gas phase. However, gas phase acidity and basicity measurements are suitable for correlation with molecular structure since solvation does not mask the energy change in the course of proton capture or ejection.

It may be appropriate at this stage to relate proton affinity to other parameters such as dissociation energy (D_0) and ionization potential (IP). This can most conveniently be done in terms of thermochemical cycles such as the following for RSH:



(28)

The parameters involved in equation (28) for H_2O and H_2S are summarized in Table 18 and those of the corresponding Morse potentials associated with free radical and ionic dissociation

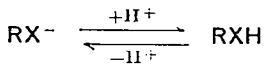


(29)

are summarized in Table 19. The actual Morse potentials are shown in Figure 21.

* It should be noted that here we are comparing two *unrelated* protonation–deprotonation processes:

rather than the traditionally considered *related* acid–base processes:



Consequently the above statement, concerning the relative gas-phase acidity and basicity of RSH compounds with respect to ROH, is not contradictory.

TABLE 18. Calculation of proton affinities (A_{Π^+}) from dissociation energies (D_0), ionization potentials (IP) and electron affinities (EA) for HO^- and HS^-

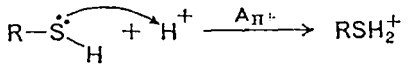
	X = O	X = S
D_0 (HX—H)	115·6	90·7
IP (H)	313·9	313·9
EA (HX)	−42·2	−60·0
A_{Π^+} (HX^-)	−387·3	−344·6

TABLE 19. Morse potential parameters for the free radical and ionic dissociation of H_2S

Parameter (unit)	HS—H → HS + H	HS—H → HS^- + H^+
μ (Aston unit)[a]	0·49609	0·49609
r_e (Å)	1·328	1·328
ω_e (cm^{-1})[b]	2627·5	2627·5
E_{ZPV} (hartree)[c]	0·00599	0·00599
E_e (hartree)	−400·4626	−400·4626
D_0 (kcal/mole)	90·7	344·6
D_e (kcal/mole)[d]	90·71	344·61
β ($Å^{-1}$)[e]	1·2663	0·6497

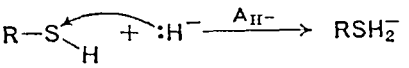
[a] $1/\mu = (2/m_\Pi) + (1/m_s)$.
[b] $k = (2\pi\omega_e)^2 \mu$.
[c] E_{ZPV} (cm^{-1}) = $\frac{1}{2}\omega_e$ (cm^{-1}).
[d] D_e (kcal/mole) = D_0 (kcal/mole) + 0·00286E_{ZPV} (cm^{-1}).
[e] $\beta = \sqrt{(k/2D_e)}$.

Finally, the proton affinity can be compared with the hydride affinity in another context. In protonation, the sulphur of the thiol group acts as a nucleophile (Lewis base):



(30)

while in the case of hydride attack, sulphur acts as an electrophile (Lewis acid):



(31)

From the data presented in Table 16, one may conclude that A_{H^-} is always negative. However, these data are limited to simple systems (e.g. S^+ and S) of open electron shells. The thiol group, on the other hand, has a closed electron shell and therefore the approach of another closed electron shell (H^-) could easily be repulsive, giving rise of a positive A_{H^-} value. While the latter process (cf. equation 31) may be an important model in

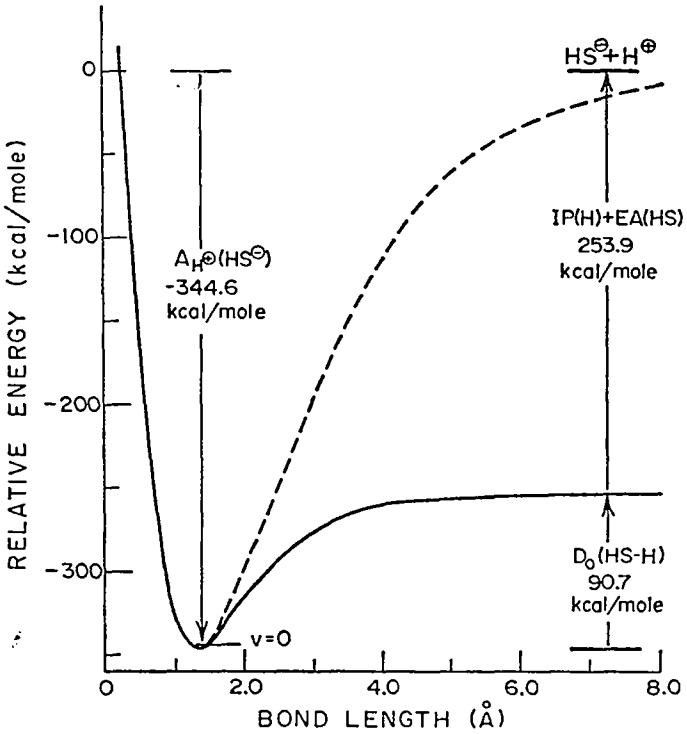


FIGURE 21. Morse potentials for the free radical and ionic dissociation of H_2S.

relation to nucleophilic substitution on divalent sulphur, it is quite probable that preferential attack by the nucleophile (base) will take place at the relatively acidic proton of the thiol group of mercaptans:

$$RS\overset{\curvearrowleft}{-}H\overset{\curvearrowright}{+}:H^- \longrightarrow RS^- + H_2 \qquad (32)$$

F. Stereochemistry

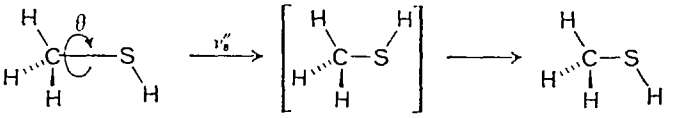
The primary aim of stereochemistry is the description of the three-dimensional structure of molecules. Although the molecular structure is determined only when all bond lengths and angles (or the x, y, z co-ordinates of all the atoms) are specified, more than one conformation can

often be written. For example methanethiol can exist in two forms:

(33)

Staggered (S) CH_3SH Eclipsed (E) CH_3SH

Only the staggered arrangement is stable but it is possible to change this structure to the transient eclipsed structure by rotating the SH group about the C—S bond. This mode of motion is associated with the vibrational frequency ν_8'' given in Table 6.

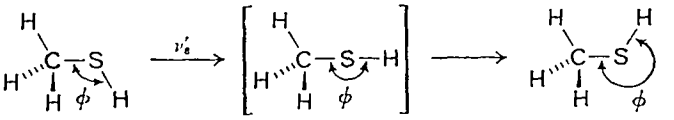


(34)

S E S

Note that no bond length or bond angle has been formally altered in going from one conformation to another; only the angle (θ) of internal rotation (or C—S torsion or SH twist) has been changed.

There is another way to change to staggered (S) conformation to the eclipsed (E) one but this involves a change in the CSH bond angle (ϕ). This mode of motion is associated with the vibrational frequency ν_8' (cf. Table 6) and the S→E conversion proceeds through a linear (L) transition state:



(35)

S L E

The energetics of these two modes of motion, described by equations (34) and (35), may be characterized by two separate potential energy curves $E(\theta)$ and $E(\phi)$ respectively, illustrated in Figure 22. The experimentally determined barrier height[21] for the rotational potential $E(\theta)$ is in the range[22] 1·06–1·46 kcal/mole and the currently accepted value is 1·27 kcal/mole. The barrier for the in-plane inversion described by equation (35) has not been measured. The one used in Figure 22 (32 kcal/mole) is that of CH_3OH but the corresponding value for CH_3SH is probably higher, as may be judged from the ν_8' values (cf. Table 6) sa well as the barriers shown for H_2O and H_2S in Figure 4. But even in this approximate presentation (Figure 22) it is easy to see that the barrier to rotation is more than an order of magnitude smaller than that to the

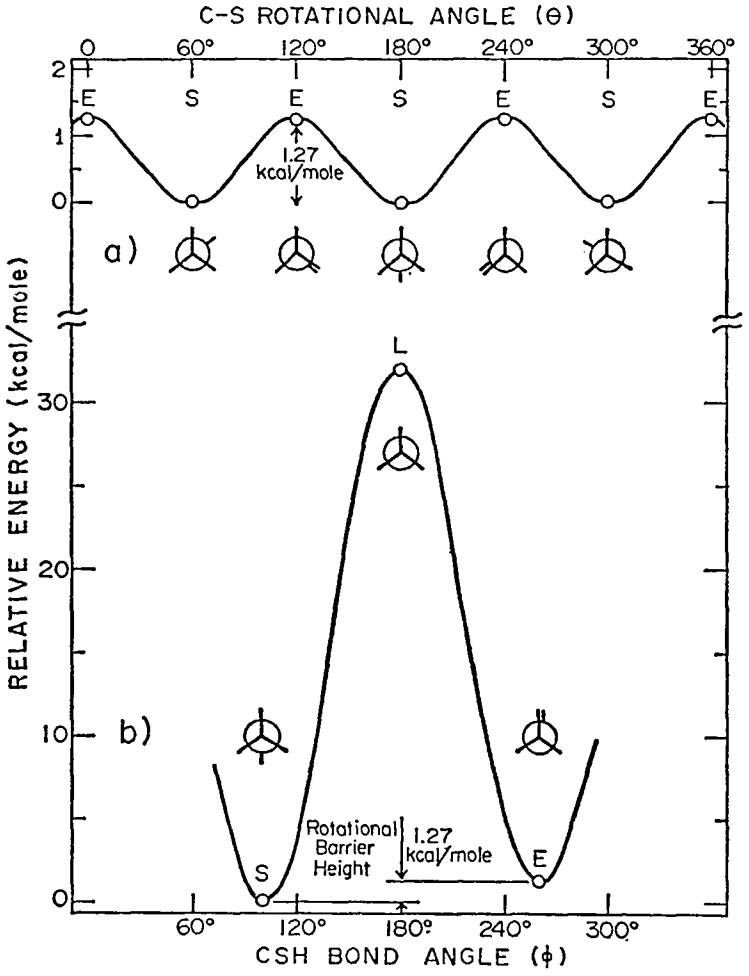
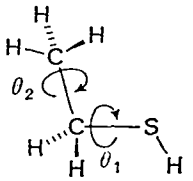


FIGURE 22. Potential energy curves for (a) C—S torsion and (b) C—S—H in-plane-inversion in CH_3SH.

in-plane inversion. The equilibrium bond angles (ϕ_e) about the sulphur and oxygen atoms for some simple representative compounds are summarized in Table 4. Since rotation about a single bond (such as C—S) and the in-plane inversion about an atom (such as S) are two independent variables, the simultaneous variation of θ and ϕ yields a potential surface $E(\theta, \phi)$. The two cross-sections of that surface, $E(\theta)$ and $E(\phi)$, correspond to the two potential curves shown in Figure 22.

For molecules larger than CH_3—SH there are several barriers to rotation. In fact every single bond between two atoms which are connected in a non-linear fashion to other atoms has a positive energy barrier to rotation.

Therefore, neither $CH_3—S^-$ nor the linear (L) structure $CH_3—S—H$ has a barrier to rotation, while $CH_3—SH$ (S or E) has one, and $CH_3—CH_2—SH$, two barriers to rotation (a double rotor):



(36)

If the two independent rotational modes of motion are labelled as θ_1 and θ_2 then an energy surface $E(\theta_1, \theta_2)$ is generated, having cross-sections $E(\theta_1)$ and $E(\theta_2)$ which will exhibit the characteristic barrier height. A segment of such a surface is illustrated schematically in Figure 23. When

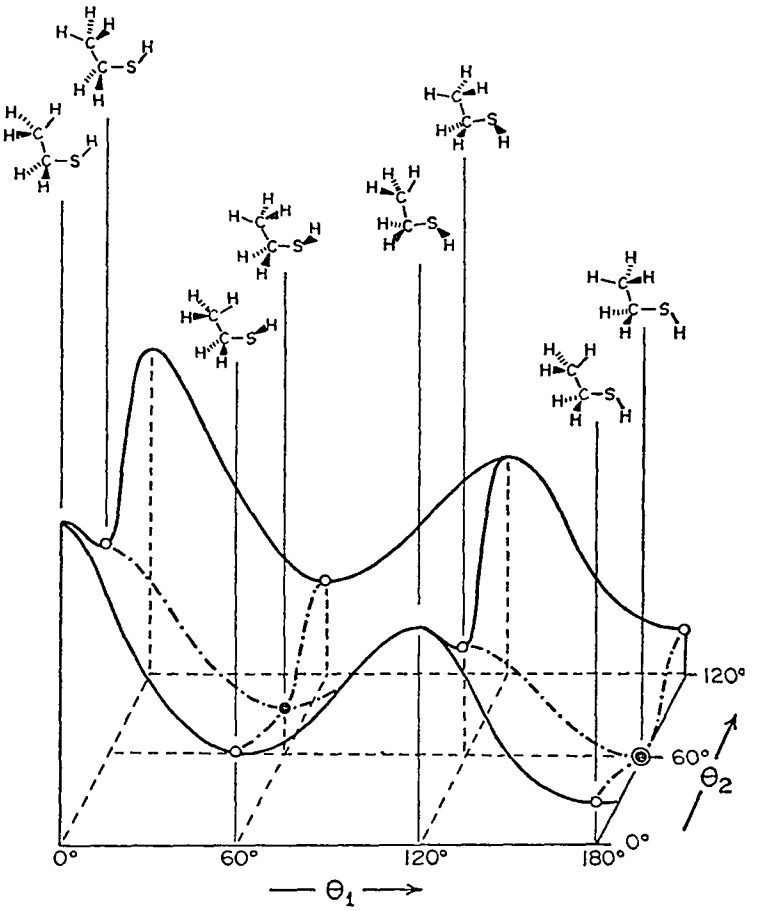


FIGURE 23. Potential energy surface for two rotational modes in CH_3CH_2SH.

the two potential curves $E(\theta_1)$ and $E(\theta_2)$ meet at their maxima there is a maximum point on the surface and when they meet at their minima there is a minimum point on the surface. However, when the two potential curves meet in such a way that one is at its maximum while the other is at its minimum, a saddle point occurs. If the two potential curves are identical there is only one kind of minimum, maximum and saddle point. However, if the two potential curves have different barrier heights as is the situation for the present double rotor, then there are two kinds of minima, two different maxima and four distinct saddle points. This situation is clearly indicated for CH_3CH_2SH in Figure 23.

It is seen from structure (36) that methyl rotation (θ_2) will produce a three-fold barrier similarly to that shown in Figure 22a, but that —SH rotation (θ_1) will necessarily yield a two-fold barrier. This represents a potential curve where $E(0° \rightarrow 180°)$ is the same as $E(360° \rightarrow 180°)$; or, more precisely, $E(180-\alpha) = E(180+\alpha)$. The combination of a two-fold

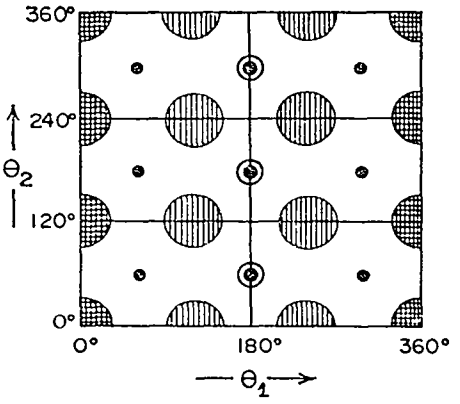


FIGURE 24. Spatial arrangement of the six segments of the conformational energy surface of a double rotor. (The minimum is designated by a dot and the low minimum is specified by a circled dot. The singly shaded area indicates the low maximum while the doubly shaded area shows the region of the high maximum.)

and a three-fold barrier implies a surface in which the segment shown in Figure 23 is repeated six times. The spatial arrangement of the six segments of the full surface is illustrated in Figure 24.

The experimentally measured barrier heights[22] for some simple ROH and RSH compounds are summarized in Table 20.

TABLE 20. Experimental barriers[a] to rotation for simple ROH and RSH compounds

Species	Rotational angle[b]	Barrier to rotation	
		X = O	X = S
CH_3—XH	θ	1·07	1·27
CH_3CH_2—XH	θ_1	0·8	1·64
CH_3—CH_2XH	θ_2	0·77	3·31

[a] Values were taken from reference 22 and are given in kcal/mole.
[b] Variable used in Figures 22–24.

G. Dipole Moment

Dipole moment is a quantity that measures charge separation and is defined as the mathematical product of the net charge (δ) and the distance between the charges ($\delta+$ and $\delta-$):

$$\begin{array}{ccc} \delta- & & \delta+ \\ S & \cdots\cdots & H \\ & \longleftarrow\ r\ \longrightarrow & \end{array} \qquad (37)$$

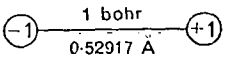
$$\vec{\mu} = |\delta|\vec{r} \qquad (38)$$

Since r is a vectorial quantity, whose direction is established by convention, μ will be a vector as well. In the definition of the *chemical dipole moment*, r points from the positive charge to the negative charge and the dipole moment vector points in the same direction. In the *physical dipole moment* the vector points in the opposite direction.

$$(\delta-)\ S \cdots\cdots H\ (\delta+) \qquad (39)$$

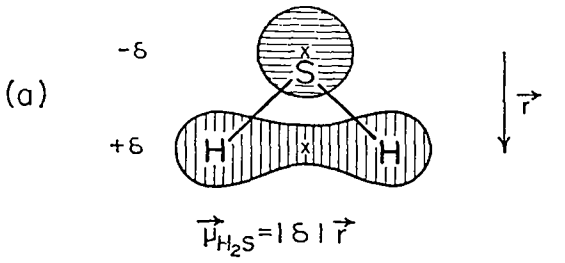
(chemical dipole: ←; physical dipole: →)

Theoretical chemists use the physical convention and express the computed dipole moment in atomic units. The magnitude of 1 atomic unit of dipole moment is equivalent to unit charges (+1 and −1) separated by 1 bohr:



$$\begin{aligned} \mu = |\delta| \times |r| &= 1 \times 1 \text{ bohr} \\ &= (4{\cdot}80 \times 10^{-10} \text{ esu}) \times (0{\cdot}52917 \times 10^{-8} \text{ cm}) \\ &= 2{\cdot}54 \times 10^{-18} \text{ esu.cm} \\ &= 2{\cdot}54 \text{ Debye} \end{aligned} \qquad (40)$$

Whenever a polyatomic molecule is considered, the dipole moment describes the separation between the positive and negative centroids of charge as illustrated in Figure 25a. Using ordinary plane trigonometry



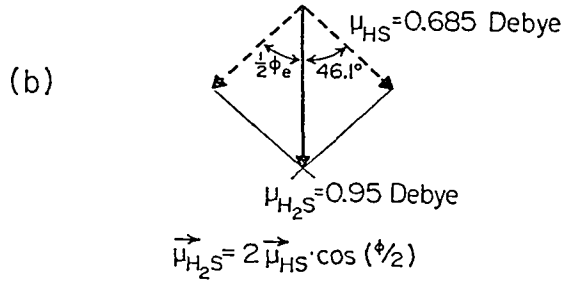


FIGURE 25. (a) Positive and negative centres of charge in H_2S. (b) Resolution of the overall dipole moment into bond moments.

one can resolve the overall dipole moment into bond moments as illustrated in Figure 25b. The computation of these bond moments from first principles will be discussed in section IV.

The overall or molecular dipole moments of HOH, CH_3OH, HSH and CH_3SH are shown in Figure 26. Unfortunately only the absolute value (1·26 Debye) of the dipole moment of CH_3SH is known[23] and its direction is not known. Nevertheless, its direction is not expected to deviate a great deal from the bisector of the CSH angle.

Two conclusions can be drawn from these dipole moment values. First, substitution of CH_3 for H hardly affects the dipole moment. Secondly, there appears to be no fundamental difference between H_2O and H_2S or CH_3OH and CH_3SH.

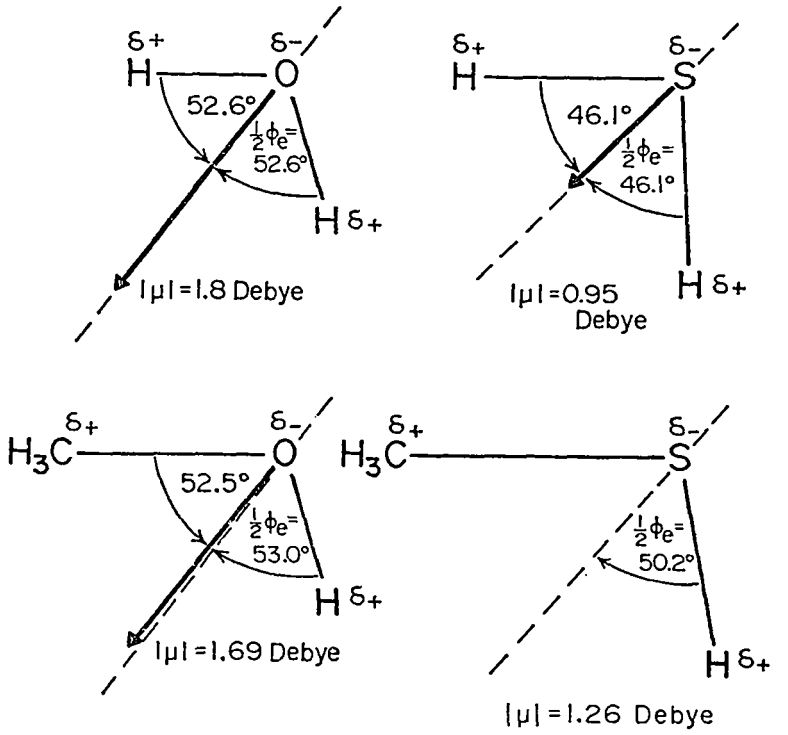


FIGURE 26. Dipole moments of H_2O, H_2S, CH_3OH and CH_3SH.

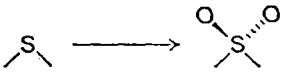
H. Concluding Remarks

In the preceding sections it has been shown that the differences in the physical properties of corresponding hydroxyl and thiol compounds are surprisingly consistent. Thus the vibrational and electronic excitations, as well as the ionization potentials, are lower for sulphur compounds; SH-containing compounds are more acidic and more basic in the gas phase than the corresponding oxygen analogues; the barriers to rotation about the C—S bond and the in-plane inversion about the S atom are higher in comparison to those of the corresponding oxygen compounds; on the other hand, the dipole moment values indicate that the charge separation in RSH compounds is smaller than that of ROH compounds.

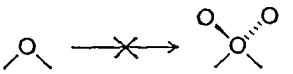
It is reasonable therefore to conclude that *there is no fundamental difference between analogous oxygen and sulphur compounds, such as alcohols and thiols. If so, then the observed differences are only in magnitude and do not arise from a qualitative change.*

The fact that divalent sulphur undergoes many reactions which are unknown for the oxygen analogue is not inconsistent with this conclusion.

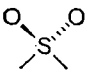
For example, divalent sulphur may be converted to a higher oxidation state and this is impossible for divalent oxygen:



(41a)



(41b)

At first sight, this appears to be a 'fundamental' difference. However, it is not unreasonable to assume that this apparent discrepancy arises solely from thermodynamic causes, i.e. that the hypothetical  moiety is relatively unstable with respect to the  group and therefore cannot be synthesized or even detected as an intermediate species in some reactions.

The notion of d orbital participation has frequently been involved in order to explain observed differences between oxygen and sulphur compounds. It will be shown (section II.F) that the mathematical importance of this, as well as that of higher polarization functions, in the computation of molecular energies cannot be identified with some 'chemical importance'.

II. THEORY

In this part some fundamental concepts of Quantum Chemistry will be reviewed (sections A and B) and the Hartree–Fock (HF) or non-empirical SCF–MO theory (section C) discussed in detail. Special emphasis will be given to the types and sizes of basis sets used in modern *ab initio* computations. It will be shown in the subsequent section (D) how this theory may be used to calculate physical properties, outlined in Part I, associated with the ground, ionized or excited states of thiols and related compounds. Localized molecular orbitals (LMO) and the mathematical equivalence of LMO and CMO (canonical molecular orbitals) obtained from the SCF calculations in a completely delocalized form will be presented in section E.

Finally, the role of polarizing functions (e.g. 3*d* AO on sulphur) is discussed (section F). It will be shown that *these polarizing functions* (*d*, *f*, *g*, ...) *have mathematical significance because they are members of a*

complete set. However, when calculations are performed with and without d-orbitals through an arbitrary truncation one cannot attribute the difference observed between two incomplete basis sets to the chemical significance of d-orbitals.

A. The Schrödinger Equation and the Variation Theorem

Just as a chemical structure uniquely defines the chemical system in question (e.g. CH_3SH) for an experimentalist, so does the Hamiltonian operator for a theoretician.

The total Hamiltonian operator ($\hat{H}$) includes the molecular geometries as well the energetic interactions of the particles (electrons and nuclei) that constitute the molecule. It can be partitioned into electronic ($\hat{H}^e$) and nuclear ($\hat{H}^n$) contributions which in turn consist of kinetic and potential energy terms:

$$\hat{H} = \hat{H}^e + \hat{H}^n = \hat{H}^e_{kin} + \hat{H}^e_{pot} + \hat{H}^n_{kin} + \hat{H}^n_{pot} \tag{42}$$

Since Molecular Quantum Mechanics is almost always used within the framework of the Born–Oppenheimer approximation, the nuclei are assumed to be fixed. However, if there is no nuclear motion the nuclear kinetic energy will be zero and the nuclear potential energy operator becomes a scalar quantity because all the internuclear distances (R_{IJ}) are constant:

$$\hat{H}^n_{pot} = \sum_{I,J}^{\substack{\text{all}\\ \text{nuclear}\\ \text{pairs}}} \frac{Z_I Z_J}{R_{IJ}} = \text{constant} \tag{43}$$

$\hat{H}^n_{pot}$ is a constant for one particular molecular geometry; however, a conformational change will yield another value for $\hat{H}^n_{pot}$.

Z_I and Z_J are the atomic numbers for nuclei I and J. Since the nuclear Hamiltonian ($\hat{H}^n$) is already defined to be a constant, as a consequence of the Born–Oppenheimer approximation, therefore our primary concern is

$$E^n = \hat{H}^n = \text{constant} \tag{44}$$

the calculation of the electronic energy (E^e) because the total energy (E^t) of the system is given by the sum of the nuclear repulsion (E^n) and the electron attraction (E^e):

$$E^t = E^n + E^e \tag{45}$$

However, the calculation of the electronic energy (E^e) is much more complicated than that of the nuclear repulsion energy (E^n) specified by equations (43) and (44). To calculate the electronic energy (E^e) one needs

to solve the Schrödinger equation characteristic of the chemical system (such as CH_3SH) in question:

$$\hat{H}^e \Psi^e = E^e \Psi^e \tag{46}$$

The electronic Schrödinger equation (equation 46) describes the distribution of all the electrons (26 in the case of CH_3SH) in the field of all the nuclei (e.g. S^{16+}, C^{6+} and 4 H^+) that constitute the chemical system. Consequently the Hamiltonian operator ($\hat{H}^e$) includes all electrons and their interactions with all the nuclei:

$$H^e = H^e_{kin} + H^e_{pot} \tag{47a}$$

$$= \sum_{\mu=1}^{\text{all electrons}} \left(-\tfrac{1}{2}\nabla_\mu^2 - \sum_{I=1}^{\text{all nuclei}} \frac{Z_I}{r_{I\mu}} \right) + \sum_{\mu,\nu}^{\text{all electron pairs}} \frac{1}{r_{\mu\nu}} \tag{47b}$$

$$= \sum_{\mu=1}^{\text{all electrons}} h_\mu + \sum_{\mu,\nu}^{\text{all electron pairs}} g_{\mu\nu} \tag{47c}$$

In equation (47b) the first term ($\sum -\frac{1}{2}\nabla_\mu^2$) corresponds to the kinetic energy and the last two are the overall potential energy components. The first of these, ($\sum Z_I/r_{I\mu}$), is the nuclear–electron attraction and the last term, ($\sum 1/r_{\mu\nu}$), corresponds to the electron–electron repulsion. The combination of the first two terms into $\sum h_\mu$ is practical because this is frequently referred to as a one-electron operator yielding the so-called one-electron energy (E_1) and the last term ($\sum g_{\mu\nu}$) is a two-electron operator associated with the two-electron energy (E_2). Consequently the electronic energy (E^e) may be written as follows:

$$E^e = E_1 + E_2 \tag{48}$$

Since the nuclear repulsion term (E^n) is associated with a 'no-electron operator' (equations 43 and 44) it may be labelled by E_0. Correspondingly, the total energy of the system (equation 45) may be written as follows:

$$\left.\begin{aligned} E^t &= E_0 + E_1 + E_2 \\ E^t &= E_0 + E_1^{kin} + E_1^{pot} + E_2 \end{aligned}\right\} \tag{49}$$

Since the electronic Hamiltonian $\hat{H}^e$ is a many-electron operator which describes the interactions of all the electrons, the same applies to the total electronic energy E^e:

$$\left.\begin{aligned} \hat{H}^e &= \hat{H}^e(1,2,\ldots) \\ E^e &= E^e(1,2,\ldots) \\ \Psi^e &= \Psi^e(1,2,\ldots) \end{aligned}\right\} \tag{50}$$

The electronic wavefunction Ψ^e, which is obtained as the solution of the Schrödinger equation, (46), is a many-electron wavefunction which depends on the coordinates of all the electrons $(1,2,\ldots)$ as explicitly stated in equation (50).

Only the Hamiltonian, which uniquely defines the chemical system, is known in the Schrödinger equation which must be solved for both the wavefunction Ψ^e and the corresponding energy E^e. This is accomplished *via* the variational theorem which states that any arbitrary trial wavefunction yields an arbitrary energy value which is higher than the true energy, i.e. is always an upper limit to the true energy. This implies that an improvement in the wavefunction will always lower the energy and as the trial wavefunction approaches the true wavefunction, the exact energy is approached:

$$\left.\begin{aligned} \Psi^e_{\text{arbitrary}} \equiv \Psi^e_a &\longrightarrow \Psi^e \\ E^e_{\text{arbitrary}} \equiv E^e_a &\longrightarrow E^e \end{aligned}\right\} \tag{51}$$

It is therefore possible to set up a variational procedure in which the wavefunction is systematically varied in such a way that the total energy is minimized.

The actual calculation within the framework of the *variational theorem* is carried out on the integrated form of the Schrödinger equation:

$$E^e_a = \frac{\int \Psi^e_a(1,2,\ldots)\,\hat{H}^e(1,2,\ldots)\,\Psi^e_a(1,2,\ldots)\,d\tau_1\,d\tau_2\ldots}{\int \Psi^e_a(1,2,\ldots)\,\Psi^e_a(1,2,\ldots)\,d\tau_1\,d\tau_2\ldots} \equiv \frac{\langle \Psi^e_a | \hat{H}^e | \Psi^e_a \rangle}{\langle \Psi^e_a | \Psi^e_a \rangle} \tag{52a}$$

This is simplified if the wavefunction is normalized so that the denominator of (52a) is unity:

$$E^e_a = \langle \Psi^e_a | \hat{H}^e | \Psi^e_a \rangle \tag{52b}$$

This minimization of E^e means the differentiation of both sides of equation (52) with respect to some internal variable in Ψ^e_a. This procedure, however, requires an explicit knowledge of the construction of function Ψ^e_a.

B. The Principles of Constructing Many-electron Wavefunctions

The Schrödinger equation has, at least in principle, infinite solutions. The lowest of these corresponds to the electronic ground state while the rest represent the manifold of electronic excited states. For this reason a subscript **u** will be introduced to specify the electronic state in question

and the superscript **e** will be omitted since only the electronic energies and wavefunctions will be considered:

$$\hat{H}(1,2,\ldots)\Psi_u(1,2,\ldots) = E_u(1,2,\ldots)\Psi_u(1,2,\ldots) \tag{53}$$

The most convenient way to construct Ψ_u is to write Ψ_u as a linear combination of electronic configurations Φ_v,

$$\Psi_u(1,2,\ldots) = \sum_v a_{uv}\Phi_v(1,2,\ldots) \tag{54}$$

where one of the electronic configurations corresponds to the ground electronic configuration and all the others are excited electronic configurations.

An abbreviated notation for the ground electronic configurations of H_2O and H_2S was given in equation (19) and the generation of the first excited configurations for H_2O and H_2S was described in equation (20). These electronic configurations were constructed from molecular orbitals and differ from each other by their occupancy. This is clearly illustrated for the first two configurations of H_2S and H_2S^+ in Figure 15. When these electronic configurations are superimposed according to equation (54) for a given state **u**, there is a set of mixing coefficients a_{uv} which is different from that of any other state. For example, consider the ground and first excited states:

$$\Psi_0(1,2,\ldots) = a_{00}\Phi_0(1,2,\ldots) + a_{01}\Phi_1(1,2,\ldots) + \ldots \tag{55}$$

$$\Psi_1(1,2,\ldots) = a_{10}\Phi_0(1,2,\ldots) + a_{11}\Phi_1(1,2,\ldots) + \ldots \tag{56}$$

The leading coefficient for the ground state, (55) is a_{00} (all the others are much smaller) while the largest coefficient for the first excited state, (56) is a_{11}. The corresponding configurations Φ_0 and Φ_1 are those illustrated in equations (19) and (20) respectively. This method of expansion is frequently referred to as Configuration Interaction (CI)*.

This expansion of an unknown wavefunction such as Ψ in terms of a set of known functions such as Φ is the most powerful method of constructing wavefunctions because the coefficients of the linear combinations (a_{uv}) can be varied within the framework of the variation theorem. Furthermore, when the expansion is complete (i.e. the summation is over the infinite possible terms in equation 54), the solution Ψ_u is the exact wavefunction which yields the exact energy E_u.

* If the configurations are constructed from atomic orbitals (AO) rather than molecular orbitals (MO) the expansion method is called the valence bond (VB) theory.

It would be tempting to assume that when the summation in equation (54) involves infinite terms then the calculated energy, (E_u), will be numerically equal to the experimentally measured total energy as expressed with respect to the Quantum Chemical Standard State. The fact that it is not so is simply a consequence of the Hamiltonian operator which does not include relativistic effects. For this reason the solution of equation (54), using a complete (i.e. infinite term) CI wavefunction yields a limiting value of the calculated property. This limit is usually referred to as the *Non-Relativistic Limit* (NRL). The difference in energy between the experimental energy (E_{exp}) and the energy computed at the non-relativistic limit (E_{NRL}) is called the relativistic correction (E_{rel}):

$$E_{exp} = E_{NRL} + E_{rel} \tag{57}$$

The relativistic energy (E_{rel}) is zero for hydrogen and relatively small for the light elements: $E_{rel}(C) = -0{\cdot}0138$ hartree and $E_{rel}(O) = -0{\cdot}0494$ hartree. However, its magnitude increases with the atomic number and for sulphur for example it is $-1{\cdot}0530$ hartree.

More important than the actual magnitude of E_{rel} is the fact that, to a high degree of approximation, the relativistic correction remains constant during a chemical reaction. Consequently, the molecular relativistic energy (E_{rel}^{mol}) may be calculated simply as the sum of the atomic relativistic energies ($E_{rel}^{atom(i)}$):

$$E_{rel}^{mol} = \sum_{i}^{\substack{\text{all}\\ \text{atoms}}} E_{rel}^{atom(i)} \tag{58}$$

For H_2O, H_2S, CH_3OH and CH_3SH the calculation is particularly simple because E_{rel} of hydrogen is zero:

$$\left.\begin{aligned} E_{rel}^{H_2O} &= -0{\cdot}0494 &&= -0{\cdot}0494 \text{ hartree} \\ E_{rel}^{H_2S} &= -1{\cdot}0530 &&= -1{\cdot}0530 \text{ hartree} \\ E_{rel}^{CH_3OH} &= -0{\cdot}0494 - 0{\cdot}0138 &&= -0{\cdot}0632 \text{ hartree} \\ E_{rel}^{CH_3SH} &= -1{\cdot}0530 - 0{\cdot}0138 &&= -1{\cdot}0668 \text{ hartree} \end{aligned}\right\} \tag{59}$$

Since most systems under investigation involve electronic ground state molecules, attention is naturally focused on the electronic ground state wavefunction:

$$\Psi_0(1, 2, 3, \ldots) = \sum_{v} a_{0v} \Phi_v(1, 2, 3, \ldots) \tag{60}$$

As shown in equation (55), from this large (in theory infinite) number of electronic configuration functions Φ_v, there is one configuration Φ_0 which

occurs with the heaviest weight and this is often used as a reasonably good approximation to Ψ_0:

$$\Psi_0(1,2,3,\ldots) \approx \Phi_0(1,2,3,\ldots) \tag{61}$$

If the expansion is thus truncated then the calculated properties will approach another limit which is normally referred to as the *Hartree–Fock Limit* (HFL). The energy value computed at the Hartree–Fock limit (E_{HFL}) is higher than that obtained for the non-relativistic limit (E_{NRL}),*

$$E_{\mathrm{NRL}} < E_{\mathrm{HFL}} \tag{62}$$

and the difference between these two quantities is called the correlation energy (E_{cor}) which is attributed to electron–electron correlation:

$$E_{\mathrm{NRL}} = E_{\mathrm{HFL}} + E_{\mathrm{cor}} \tag{63}$$

This means that a single configuration (Hartree–Fock) wavefunction for the ground state, Φ_0^{HF}, recovers no correlation energy when the wavefunction is used to calculate the total energy according to equation (52b):

$$E_{\mathrm{HFL}} = \langle \Phi_0^{\mathrm{HF}} | \hat{H} | \Phi_0^{\mathrm{HF}} \rangle \tag{64}$$

On the other hand, if the complete (i.e. infinite) CI expansion of the ground state wavefunction (Ψ_0^{NRL}) could be generated according to equation (54) then the energy at the NRL (E_{NRL}), which is the sum of E_{HF} and E_{cor}, (63), could be calculated:

$$E_{\mathrm{NRL}} = \langle \Psi_0^{\mathrm{NRL}} | \hat{H} | \Psi_0^{\mathrm{NRL}} \rangle \tag{65}$$

Consequently a limited CI expansion yields an energy lower than E_{HFL} but not as low as E_{NRL}. Since CI expansions are still very much under investigation it would be unwise at this time to use this method to study chemical systems as large as CH_3SH. Consequently attention will be focused on the Hartree–Fock limit.

The correlation energy that separates E_{HFL} from E_{NRL}, (63), is associated with the electron pairing that exists in a chemical system. Consequently the magnitude of E_{cor} increases with the number of electron pairs involved. Since hydrogen has only a single electron its correlation energy is zero. The E_{cor} values for C and O atoms are $-0{\cdot}1581$ and $-0{\cdot}2575$ hartree respectively, while E_{cor} for sulphur is correspondingly greater ($-0{\cdot}6400$). If one calculates E_{HFL} according to equation (64)

* In other words E_{NRL} is a larger negative number than E_{HFL}. Since both of these numbers are negative we might say that $|E_{\mathrm{NRL}}| > |E_{\mathrm{HFL}}|$.

then by combining equations (57) and (63) the total energy may be obtained as the sum of the three components:

$$E_{\text{exp}} = E_{\text{HFL}} + E_{\text{cor}} + E_{\text{rel}} \tag{66}$$

Values of E_{exp} (in Hartree atomic units) for H, C, O and S atoms are:

$$\left.\begin{aligned} E_{\text{exp}}\,(\text{H}) &= -0{\cdot}5000 &&= -0{\cdot}5000 \\ E_{\text{exp}}\,(\text{C}) &= -37{\cdot}6886 - 0{\cdot}1581 - 0{\cdot}0138 &&= -37{\cdot}8605 \\ E_{\text{exp}}\,(\text{O}) &= -74{\cdot}8093 - 0{\cdot}2575 - 0{\cdot}0494 &&= -75{\cdot}1162 \\ E_{\text{exp}}\,(\text{S}) &= -397{\cdot}5047 - 0{\cdot}6400 - 1{\cdot}0530 &&= -399{\cdot}1977 \end{aligned}\right\} \tag{67}$$

It should be noted (cf. equation 5 and Table 10) that the sum of all the ionization potentials of an atom is also equal to the experimental energy:

$$E_{\text{exp}}^{\text{atom}} = \sum_{i}^{\substack{\text{all} \\ \text{electrons}}} \text{IP}\,(i) \tag{68}$$

When molecular relativistic energy was discussed, it was pointed out that its estimation is relatively simple because it is the sum of atomic energies (cf. equation 58). Unfortunately the same is not true for the molecular correlation energy,

$$E_{\text{cor}}^{\text{mol}} < \sum_{i}^{\substack{\text{all} \\ \text{atoms}}} E_{\text{cor}}^{\text{atom}\,(i)} \tag{69}$$

because a molecule always contains more electron pairs than the corresponding atoms. (Note that the above inequality implies that the left-hand side: $E_{\text{cor}}^{\text{mol}}$ is a larger negative number than the right-hand side.)

Consider the formation of H_2S from S + 2 H. The electronic configurations of the sulphur and hydrogen atoms are:

$$\left.\begin{aligned} &\text{Sulphur} && (1s)^2\,(2s)^2\,(2p)^6\,(3s)^2\,(3p)^4 \\ &\text{Hydrogen} && (1s)^1 \end{aligned}\right\} \tag{70}$$

According to Hund's rule, the electronic ground $(3p)^4$ configuration of sulphur implies that three electrons occupy the trio of $3p$ orbitals $(3p_x)^1\,(3p_y)^1\,(3p_z)^1$ and the fourth electron will pair up with one of them, creating an electron pair and leaving two unpaired electrons. Similarly there are two odd electrons in the two hydrogen atoms before H_2S is formed:

(71)

Thus when the molecule is formed *two new electron pairs* are created, which are therefore responsible for the inequality (69). If an average value for the correlation energy correction (ΔE_{cor}^{bond}) associated with each bond formed can be assigned, then the inequality (69) can be converted to an approximate equality (72) provided the number (n) of new electron pairs (i.e. new bonds) formed is known:

$$E_{cor}^{mol} = \sum_{i}^{all} E_{cor}^{atom\ (i)} + n\,\Delta E_{cor}^{bond} \tag{72}$$

Substituting an average value for the bond correlation energy

$$\Delta E_{cor}^{bond} = -0{\cdot}065 \text{ hartree} \tag{73}$$

into equation (72) for the case of H_2S,

$$E_{cor}^{mol} = -0{\cdot}6400 - 2 \times 0{\cdot}065 = -0{\cdot}770 \text{ hartree} \tag{74}$$

Now that the relativistic correction, (59), the correlation energy, (74), and the experimental total energy (cf. equation 5 and Table 3) are known, the HFL for H_2S can be calculated:

$$E_{HFL}^{mol} = E_{exp}^{mol} - (E_{cor}^{mol} + E_{rel}^{mol}) \tag{75}$$

$$E_{HFL}^{H_2S} = -400{\cdot}4626 - (-0{\cdot}770 - 1{\cdot}053) = -398{\cdot}640 \tag{76}$$

The calculations of E_{HFL} for HO, HS, H_2O and H_2S are summarized in Table 21 and the components of the total energies of CH_3OH and CH_3SH are given in Table 22.

TABLE 21. Estimation of the Hartree–Fock limit for HO, H_2O, HS and H_2S

Component	HO	H_2O	HS	H_2S
Hartree–Fock energy (E_{HFL})	−75·414	−76·049	−398·076	−398·640
Correlation energy (E_{cor})[a]	−0·323	−0·388	−0·705	−0·770
Relativistic energy (E_{rel})	−0·049	−0·049	−1·053	−1·053
Experimental energy (E_{exp})[b]	−75·786	−76·486	−399·834	−400·463

[a] Taken from Table 3.
[b] Taken from Table 7.

The wavefunction Φ_0 specified in equation (61), which is capable of reproducing the HFL, should now be considered. This many-electron function is constructed from one-electron space functions ϕ_r which are atomic orbitals (AO) in the case of an atom and molecular orbitals (MO) in the case of a molecule. Due to the fact that electrons are indistinguishable, the proper form of Φ_0 must be a determinant, as shown by Slater.

TABLE 22. The breakdown of the experimental energy of CH_3OH and CH_3SH into theoretical components

Component	CH_3OH	CH_3SH
Hartree–Fock energy (E_{HFL})	−115·127	−437·762
Correlation energy (E_{cor})[a]	−0·602	−0·984
Relativistic energy (E_{rel})	−0·063	−1·067
Experimental energy (E_{exp})[b]	−115·791	−439·813

[a] $E_{cor}^{mol} = \sum E_{cor}^{atom} - 0{\cdot}186$. The value of $n\,\Delta E_{cor}^{bond}$ was calculated for CH_3OH and also used for CH_3SH.
[b] Taken from Table 7.

For a closed electronic shell of $2M$ electrons the total electronic wavefunction can be written in the form referred to as a Slater determinant:

$$\Phi_0(1,2,3,\ldots,2M) = 1/\sqrt{(2M)!} \times \begin{vmatrix} \phi_1(1)\alpha(1) & \phi_1(1)\beta(1) & \ldots & \phi_M(1)\alpha(1) & \phi_M(1)\beta(1) \\ \phi_1(2)\alpha(2) & \phi_1(2)\beta(2) & \ldots & \phi_M(2)\alpha(2) & \phi_M(2)\beta(2) \\ \vdots & \vdots & & \vdots & \vdots \\ \phi_1(2M)\alpha(2M) & \phi_1(2M)\beta(2M) & \ldots & \phi_M(2M)\alpha(2M) & \phi_M(2M)\beta(2M) \end{vmatrix} \tag{77}$$

According to the Pauli exclusion principle there are two orbitals for every electron, one with α spin and one with β spin. It is customary to abbreviate this determinant by quoting only the diagonal elements:

$$\Phi_0(1,2,\ldots,2M) = \mathrm{Det}\,|\phi_1(1)\alpha(1)\ \ \phi_1(2)\beta(2)\ \ \ldots\ \ \phi_M(2M-1)\alpha(2M-1)\ \ \phi_M(2M)\beta(2M)| \tag{78}$$

The normalizing factor should formally be included in equation (78) but is not usually written explicitly. This may further be simplified by dropping the electron labels $(1,2,\ldots,2M)$ and the spin functions α and β. Writing ϕ_μ for the spatial orbital corresponding to α spin and $\bar{\phi}_\mu$ for the same orbital corresponding to β spin,

$$\Phi_0 = \mathrm{Det}\,|\phi_1\bar{\phi}_1 \ldots \phi_M\bar{\phi}_M| \tag{79}$$

This expression can be further abbreviated by emphasizing the double occupancy of the orbitals in such a way that $\phi_\mu\bar{\phi}_\mu$ is replaced by $(\phi_\mu)^2$

$$\Phi_0 = (\phi_1)^2(\phi_2)^2 \ldots (\phi_{M-1})^2(\phi_M)^2 \tag{80}$$

This general expression is equivalent to the formal specification of the electronic configurations for H_2O and H_2S given in equation (19).

In the CI method the unknown many-electron wavefunction Ψ_u were obtained as linear combinations of known many-electron functions Φ_v, and the unknown one-electron functions ϕ_p, or molecular orbitals (MO), can be obtained by an analogous approach. These unknown delocalized MO (ϕ_p) are normally obtained as linear combinations (LC) of sets of known localized functions (η_i). Historically, these known one-electron functions (η_i) were atomic orbitals (AO), hence the abbreviation LCAO–MO has been coined:

$$\phi_p = \sum_{i=1}^{N} C_{pi}\eta_i \tag{81}$$

A set of η is usually referred to as the basis set of the MO calculation and N (the total number of η used) is called the size of the basis set. However, these η need not be genuine AO, in fact any arbitrary set of functions which satisfy certain mathematical requirements may be used. For this reason it is more appropriate to refer to a set of η basis functions rather than to atomic orbitals. Although nowadays MO are generated by linear combinations of some arbitrary sets of basis functions, the LCAO abbreviation remains for historical reasons. It can be shown that as N (i.e. the number of basis function: BF used) grows towards infinity the MO (ϕ_p) obtained will become the so-called *Hartree–Fock Molecular Orbitals* (HFMO) and properties calculated with the aid of the ground configuration wavefunction $\Phi_0(1, 2, 3, \ldots, 2M)$ which is constructed from these HFMO do indeed approach the *Hartree–Fock Limit*. The procedure of finding the coefficients (C_{pi}) which transform a set of η to a set of ϕ is an iterative technique called the *Self-Consistent Field* (SCF) method which will be discussed in the next section.

C. The Non-empirical SCF–MO Theory (the Hartree–Fock problem)

The main conclusions of sections II.A and II.B may be summarized as follows:

(i) The wavefunction which describes the electronic ground state of a $2M$ electron system has the form of a $2M \times 2M$ determinant:

$$\Phi_0 \equiv \Phi_0(1, 2, \ldots, 2M) = 1/\sqrt{(2M)!} \times \begin{vmatrix} \phi_1(1)\alpha(1) & \phi_1(1)\beta(1) & \ldots & \phi_M(1)\alpha(1) & \phi_M(1)\beta(1) \\ \phi_1(2)\alpha(2) & \phi_1(2)\beta(2) & \ldots & \phi_M(1)\alpha(2) & \phi_M(2)\beta(2) \\ \vdots & \vdots & & \vdots & \vdots \\ \phi_1(2M)\alpha(2M) & \phi_1(2M)\beta(2M) & \ldots & \phi_M(2M)\alpha(2M) & \phi_M(2M)\beta(2M) \end{vmatrix} \tag{77}$$

(ii) The Hamiltonian for the $2M$ electron system may be written as

$$\hat{H} \equiv \hat{H}(1, 2, \ldots, 2M) = \sum_{\mu=1}^{2M} \hat{h}_\mu + \sum_{\mu=\nu}^{M(2M-1)} \hat{g}_{\mu\nu} \tag{47}$$

(iii) The energy, after substitution of Φ_0 and $\hat{H}$ into equation (63b), is

$$E^c = \langle \Phi_0 | \hat{H} | \Phi_0 \rangle \tag{82}$$

Integrating out the spin variables, this energy expression becomes

$$\begin{aligned} E^c = 2 \sum_p^M & \langle \phi_p(1) | \hat{h}_1 | \phi_p(1) \rangle \\ & + \sum_p^M \sum_q^M [2 \langle \phi_p(1)\, \phi_q(2) | \hat{g}_{12} | \phi_p(1)\, \phi_q(2) \rangle \\ & \qquad - \langle \phi_p(1)\, \phi_p(2) | \hat{g}_{12} | \phi_q(1)\, \phi_q(2) \rangle] \end{aligned} \tag{83}$$

where the two-electron integrals (the last two terms in the above equation) are the Coulomb and exchange integrals. Note that in the Coulomb integrals, electron **1** is associated with orbital ϕ_p and electron **2** is associated with orbital ϕ_q. This distinction between Coulomb and exchange terms becomes clearer in the electron density formalism where orbitals associated with electron **1** are collected in front of the operator while those associated with particle **2** are written behind the operator:

$$\begin{aligned} E^c = 2 \sum_p^M & \langle \phi_p(1) | \hat{h}_1 | \phi_p(1) \rangle \\ & + \sum_p^M \sum_q^M [2\{\phi_p(1)\, \phi_p(1) | \phi_q(2)\, \phi_q(2)\} - \{\phi_p(1)\, \phi_q(1) | \phi_p(2)\, \phi_q(2)\}] \end{aligned} \tag{84}$$

Note that in order to distinguish the electron density formalism (84) from the traditional notation (83) the brackets were changed from $\langle | \, | \rangle$ to $\{ | \, \}$ and the electron–electron repulsion operator $\hat{g}_{\mu\nu}$ was omitted.

Expression (84) can be conveniently presented in abbreviated form,

$$E^c = 2 \sum_p^M h_{pp}^\phi + \sum_p^M \sum_q^M (2J_{pq}^\phi - K_{pq}^\phi) \tag{85}$$

where J_{pq} and K_{pq} symbolize the Coulomb and exchange integrals respectively. The superscript ϕ indicates that these matrix representatives are in the MO basis.

At this stage, it should be pointed out that the diagonal elements of the Coulomb and exchange integrals are identical:

$$J_{pp} = K_{pp} \tag{86}$$

The J and K integrals are conveniently expressed as pseudo one-electron integrals by defining pseudo one-electron hermitian operators $\hat{J}_p$ and $\hat{K}_p$ such that

$$J^{\phi}_{pq} = \langle \phi_p | \hat{J}_q | \phi_p \rangle = \langle \phi_q | \hat{J}_p | \phi_q \rangle \tag{87}$$

$$K^{\phi}_{pq} = \langle \phi_p | \hat{K}_q | \phi_p \rangle = \langle \phi_q | \hat{K}_p | \phi_q \rangle \tag{88}$$

This is also applicable for G_{pq} which is defined as

$$G^{\phi}_{pq} = \langle \phi_p | 2\hat{J}_q - \hat{K}_q | \phi_p \rangle = \langle \phi_p | \hat{G}_q | \phi_p \rangle \tag{89}$$

The energy expression (85) may therefore be written as

$$E^{e} = \sum_{p}^{M} \langle \phi_p | 2\hat{h} + \sum_{q}^{M} \hat{G}_q | \phi_p \rangle \tag{90}$$

and the orthonormality condition for the MO basis is

$$S_{pq} = \langle \phi_p | \phi_q \rangle = \delta_{pq} \tag{91}$$

According to the Variation Theorem the energy may be optimized by variation of ϕ_p.

To obtain an analytical expression for δE, each ϕ_p is varied by an infinitesimal amount $\delta\phi_p$ and subsequently this equation derived for δE is set equal to zero. This procedure is applicable for S_{pq}; since $S_{pq} = \delta_{pq}$, its derivative is automatically zero:

$$\left.\begin{aligned} \delta E &= 0 \\ \delta S &= 0 \end{aligned}\right\} \tag{92}$$

When the expression obtained for δE, from equation (90), and the expression obtained for δS_{pq}, from equation (91) are appropriately combined, the following relationship is obtained:

$$\langle \phi_p | \hat{h} + \sum_{q} \hat{G}_q | \phi_p \rangle = \langle \phi_p | \phi_p \rangle \varepsilon_p \tag{93}$$

where ε_p is the orbital energy associated with the pth MO. The operator $\hat{h} + \sum \hat{G}_q$ is frequently called the Fock operator, $\hat{F}$, therefore the above equation may be simplified to the following form:

$$\langle \phi_p | \hat{F} | \phi_p \rangle = \langle \phi_p | \phi_p \rangle \varepsilon_p \tag{94}$$

However, the MO are orthonomal ($\langle \phi_p | \phi_p \rangle = 1$) therefore

$$\langle \phi_p | \hat{F} | \phi_p \rangle = \varepsilon_p \tag{95}$$

The expansion of ϕ in terms of the known set of AO (81) which may be written in matrix notation as

$$\boldsymbol{\phi} = \boldsymbol{\eta}\mathbf{C} \tag{96}$$

and

$$\boldsymbol{\phi}^{\dagger} = \mathbf{C}^{\dagger}\boldsymbol{\eta}^{\dagger} \tag{97}$$

is then substituted into equation (95) and the *Hartree–Fock matrix equation* over the AO basis is obtained:

$$\mathbf{C}^{\dagger}\mathbf{F}^{\eta}\mathbf{C} = \mathbf{C}^{\dagger}\mathbf{S}^{\eta}\mathbf{C}\boldsymbol{\varepsilon} \tag{98}$$

where

$$\mathbf{F}^{\eta} = \mathbf{h}^{\eta} + 2\mathbf{J}^{\eta} - \mathbf{K}^{\eta} \tag{99}$$

and

$$S_{ij}^{\eta} = \langle \eta_i | \eta_j \rangle \tag{100}$$

The molecular integrals quoted in equation (99) have the usual one-electron or pseudo one-electron form:

$$h_{ij}^{\eta}(1) = \langle \eta_i(1) | \hat{h} | \eta_j(1) \rangle \tag{101}$$

$$J_{ij}^{\eta}(1) = \sum_{k=1}^{N}\sum_{l=1}^{N} \{\eta_i(1)\,\eta_j(1) | \eta_k(2)\,\eta_l(2)\}\,\rho_{kl} \tag{102}$$

$$K_{ij}^{\eta}(1) = \sum_{k=1}^{N}\sum_{l=1}^{N} \{\eta_i(1)\,\eta_k(1) | \eta_j(2)\,\eta_l(2)\}\,\rho_{kl} \tag{103}$$

where ρ_{kl} is the k,lth element of the density matrix:

$$\boldsymbol{\rho} = \begin{pmatrix} C_{11} & C_{12} & \cdots & C_{1M} \\ C_{21} & C_{22} & \cdots & C_{2M} \\ \vdots & \vdots & & \vdots \\ C_{N1} & C_{N2} & \cdots & C_{NM} \end{pmatrix} \begin{pmatrix} C_{11} & C_{21} & \cdots & C_{N1} \\ C_{12} & C_{22} & \cdots & C_{N2} \\ \vdots & \vdots & & \vdots \\ C_{1M} & C_{2M} & \cdots & C_{NM} \end{pmatrix} \tag{104}$$

Thus

$$F_{ij}^{\eta} = \langle \eta_i | \hat{h} | \eta_j \rangle + \sum_{k}^{N}\sum_{l}^{N} [2\{\eta_i\,\eta_j | \eta_k\,\eta_l\} - \{\eta_i\,\eta_k | \eta_j\,\eta_l\}]\,\rho_{kl} \tag{105}$$

In terms of the AO E^{e} can be written as

$$E^{e} = 2\sum_{i=1}^{N}\sum_{j=1}^{N} \rho_{ij} h_{ji}^{\eta} + 2\sum_{i=1}^{N}\sum_{j=1}^{N} \rho_{ij} J_{ji}^{\eta} - \sum_{i=1}^{N}\sum_{j=1}^{N} \rho_{ij} K_{ji}^{\eta} \tag{106}$$

The solution of the Hartree–Fock equation, (98), for the coefficient matrix **C** and for the molecular orbital energy matrix $\boldsymbol{\varepsilon}$ involves the following computational procedure.

(i) Two matrices, the overlap matrix (**S**) and the Fock matrix (**F**) are required. The elements of the **S** matrix may be computed directly but the

elements of the **F** matrix, F_{ij}, are assembled according to equation (105). It is clear however that F_{ij} depend on the density matrix ρ which, in turn, is computed from the coefficient matrix **C** according to equation (104). Thus the final **F** matrix cannot be assembled until the Hartree–Fock problem is solved: yet this cannot be solved until the **F** matrix is set up.

(ii) This leads to an iterative process where **C** is initially assumed and **F** is calculated in terms of this arbitrary **C**. When the approximate Fock matrix is assembled, the Hartree–Fock equation is solved, yielding a new coefficient matrix. This coefficient matrix can now be used to compute a new **F** matrix and the Hartree–Fock problem may be solved for the second time.

This iterative process is called the *Self-Consistent Field* (SCF) method. In the course of the SCF procedure the total energy (E^e) is lowered in each iterative cycle and the convergence to any desired accuracy is measured by the difference between the energy values associated with two successive iterations ($\Delta E_n^e = E_{n-1}^e - E_n^e$). The overall SCF process is illustrated in Figure 27.

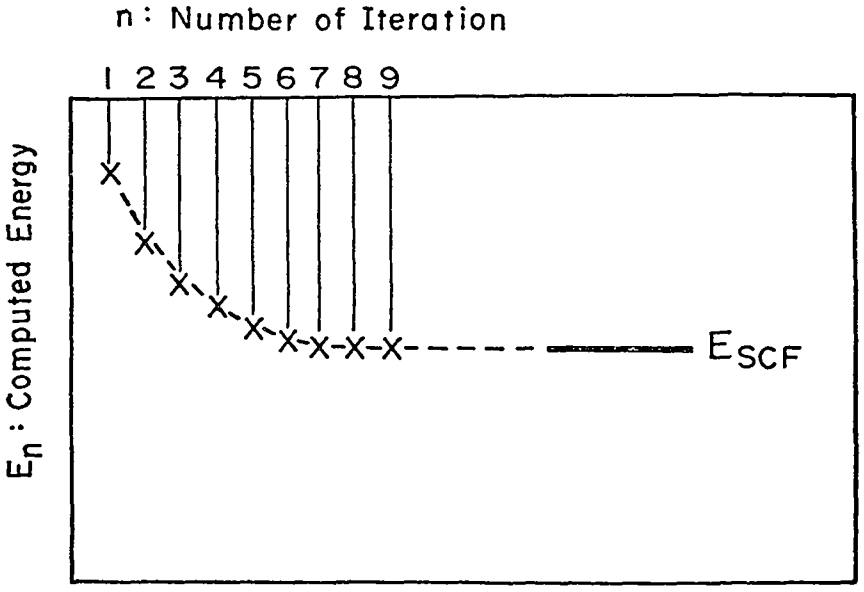


FIGURE 27. Minimization of the total energy E by the SCF method of successive iterations.

The most fundamental decision involved in these calculations is the choice of the types of basis functions η. Two types of functions are widely used, depending on the size of the system. One is the exponential type

functions (ETF), frequently called Slater type orbitals (STO), the other is the Gaussian type functions (GTF) sometimes referred to as Gaussian type orbitals (GTO). The most important difference between these two types of η is that in the former one the function decays exponentially to the first power of r while in the latter the decay takes place to r^2.

$$\begin{aligned} &\text{ETF (STO)} \quad \eta_E = N_E r^{(n-1)} e^{-\zeta r} S_{l,m}(\theta, \phi) \\ &\text{GTF (GTO)} \quad \eta_G = N_G r^{2(n-1)} e^{-\zeta r^2} S_{l,m}(\theta, \phi) \end{aligned} \tag{107}$$

Figure 28 shows 1s type examples for both of these. The three different s-GTF shown (heavy lines) have numerically different orbital exponents

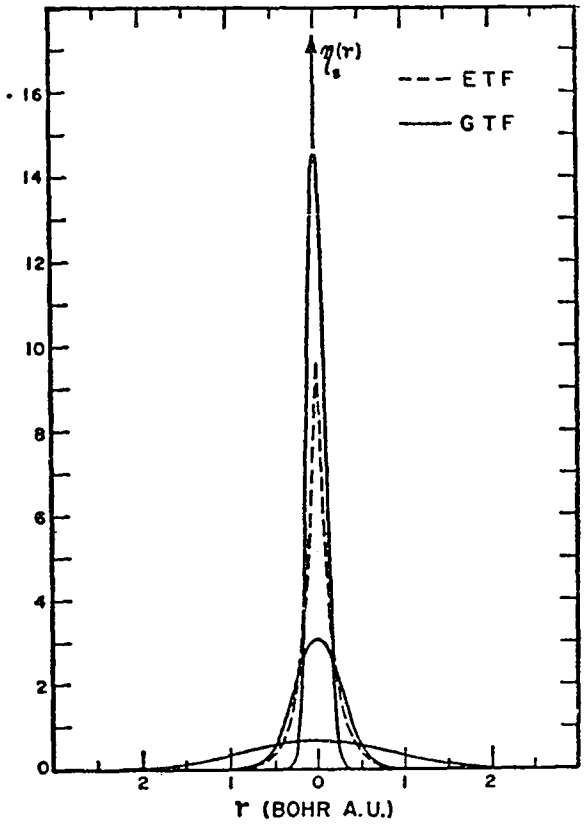


FIGURE 28. Exponential type functions (ETF) and Gaussian type functions (GTF) for 1s orbitals.

(ζ). On the whole, ETF are more accurate and are widely used for small systems. For larger molecules, computational difficulties arise and GTF are more practical.

However, for complex systems such as H_2S of CH_3SH the size of the GTF basis set becomes unmanageable since three times as many GTF than ETF are necessary to approach the Hartree–Fock Limit (HFL). For this reason, these primitive GTF are contracted to approximate ETF and this *contracted AO basis set*, which is very much reduced in size, is used for the SCF calculation.

The traditional basis sets are the *minimal* (or single zeta) *basis* and the *double zeta basis*. These are specified in the following way:

Minimal basis

$$\left.\begin{array}{ll} \text{H} & 1s \\ \text{C, N, O, F} & 1s,\ 2s,\ 2p_x,\ 2p_y,\ 2p_z \\ \text{Si, P, S, Cl} & 1s,\ 2s,\ 2p_x,\ 2p_y,\ 2p_z,\ 3s,\ 3p_x,\ 3p_y,\ 3p_z \end{array}\right\} \quad (108)$$

Double zeta basis

$$\left.\begin{array}{ll} \text{H} & 1s,\ 1s' \\ \text{C, N, O, F} & 1s,\ 1s',\ 2s,\ 2s',\ 2p,\ 2p' \\ \text{Si, P, S, Cl} & 1s,\ 1s',\ 2s,\ 2s',\ 2p,\ 2p',\ 3s,\ 3s',\ 3p,\ 3p' \end{array}\right\} \quad (109)$$

In the latter notation $2p$ and $3p$ stand collectively for $2p_x, 2p_y, 2p_z$ and $3p_x, 3p_y, 3p_z$. The term 'double zeta' originates from the fact that the primed and unprimed orbitals such as $1s\ 1s'$ differ only in their orbital exponents ζ and ζ'.

When primitive GTF are contracted they usually form either the minimal basis set or the double zeta basis set. It should be emphasized that a double zeta basis set is considered mandatory in order to obtain significant results, and more extensive than double zeta basis sets are not uncommon. The SCF energy values of H_2S computed with the aid of different basis sets are summarized in Table 23 and are compared to the Hartree—Fock limit in Figure 29. Unfortunately no calculations beyond the non-empirical Hartree–Fock framework have been reported in the literature.

Finally, it might be appropriate to call attention to the relationship between the total energy value and molecular orbital energies. From equations (85) and (97), the total energy of the system may be written in the following simplified form:

$$E^e = 2\sum_{p}^{M} h^{\phi}_{pp} + \sum_{p}^{M}\sum_{q}^{M} G^{\phi}_{pq} \quad (110)$$

TABLE 23. SCF energy values of H_2S computed from different basis sets

Reference	S—H (bohr)	<HSH	Basis[a]	E (hartree)	Code[b]
Rauk *et al.*, *Can. J. Chem.*, **46**, 1205 (1968)	2·5228	92·25°	Ext. GTF	−381·03894	a
Hopkinson *et al.*, *J. Chem. Phys.*, **49**, 3596 (1968)	2·523	92·5°	Ext. GTF	−381·0391	b
Hillier *et al.*, *Chem. Phys. Lett.*, **4**, 163 (1969)	2·510	92·2°	Ext. GTF	−394·516	c
Schwartz, *J. Chem. Phys.*, **51**, 182 (1969)	2·523	92·25°	Ext. GTF	−396·9005	d
Moccia, *J. Chem. Phys.*, **37**, 910 (1962)	2·509	89°	One centre	−397·5888	e
Moccia, *J. Chem. Phys.*, **40**, 2186 (1964)	2·509	89°	One centre	−397·5891	f
Boer *et al.*, *J. Chem. Phys.*, **50**, 989 (1969)	2·509	92·2°	Min. ETF	−397·8415	g
Kari, to be published	2·4	95·84°	Ext. GTF	−398·34005	h

[a] For the definition of Extended GTF basis and One centre expansion see the original papers.
[b] See Figure 29.

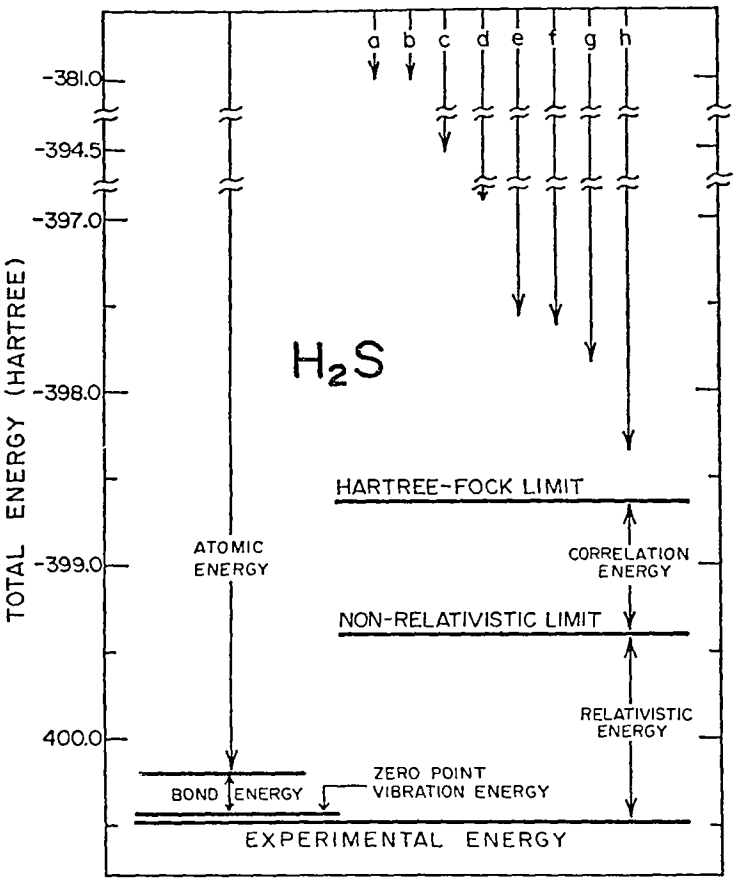


FIGURE 29. SCF energy values computed from GTO (a-d, h), one centre (e, f) and minimal STO (g) basis sets, and the Hartree–Fock limit for H_2S.

where the second term corresponds to the electron–electron repulsion. However, the introduction of the Fock operator (cf. equations 93–95) allows the substitution

$$F^{\phi}_{pp} = h^{\phi}_{pp} + \sum_{q}^{M} G^{\phi}_{pq} \tag{111}$$

or its equivalent:

$$h^{\phi}_{pp} = F^{\phi}_{pp} - \sum_{q}^{M} G^{\phi}_{pq}$$

Thus the total energy will assume the following form:

$$E^{c} + 2\sum_{p}^{M} F^{\phi}_{pp} - \sum_{p}^{M}\sum_{q}^{M} G^{\phi}_{pq} \tag{112}$$

However, equations (94) and (95) imply that

$$\varepsilon_p = \langle \phi_p | \hat{F} | \phi_p \rangle = F^{\phi}_{pp} \tag{113}$$

because the MO are orthonormal. Therefore the final relationship between E^e and ε is the following:

$$E^e = 2 \sum_{p}^{\substack{\text{all}\\ \text{occupied}\\ \text{MO}}} \varepsilon_p - \sum_{p,q}^{\substack{\text{all}\\ \text{occupied}\\ \text{MO pairs}}} G^{\phi}_{pq} \tag{114}$$

This equation clearly indicates that the *total energy is not simply twice the sum of the occupied orbital energies* and a correction has to be introduced for the electron–electron repulsion $\sum G_{pq}$.

D. Applications of the Non-empirical SCF–MO Theory

The theory outlined thus far applies to the ground electronic state. It would be appropriate at this point to recapitulate the major concepts outlined above, and then describe how they may be applied to study ground state properties and to calculate excited state properties.

The HF method and the various semi-empirical theories require the solution of a matrix equation which gives the coefficient matrix (**C**) needed to construct the MO from the AO (cf. equations 81, 96 and 115):

$$(\phi_1 \phi_2 \cdots \phi_M \,\vdots\, \phi_{M+1} \cdots \phi_N) = (\eta_1 \eta_2 \cdots \eta_N)$$

occupied MO → ← virtual MO

$$\times \begin{pmatrix} C_{11} & C_{12} & \cdots & C_{1M} & \cdots & C_{1N} \\ C_{21} & C_{22} & \cdots & C_{2M} & \cdots & C_{2N} \\ \vdots & \vdots & & \vdots & & \vdots \\ C_{N1} & C_{N2} & \cdots & C_{NM} & \cdots & C_{NN} \end{pmatrix} \tag{115}$$

The first M occupied molecular orbitals are then used to describe the $2M$ electrons in their ground electronic configuration, as illustrated in Figure 10 for the case of H_2O and H_2S. These M occupied MO are used to build a determinental many-electron wavefunction as specified by equation (77).

The Ground State within the MO theory is represented by the ground electronic configuration Φ_0. The total molecular energy is the sum of nuclear repulsion (E^n) and electronic attraction (E^e_0) (equation 45), and the electronic energy in turn is computed from the molecular wavefunction Φ_0 (cf. 77 and the Hamiltonian operator 46):

$$E^e_0 = \langle \Phi_0 | \hat{H} | \Phi_0 \rangle \tag{52b}$$

In terms of matrix elements (over the MO basis) the total electronic energy may be written

$$E_0^e = \langle \Phi_0 | \hat{H} | \Phi_0 \rangle = \sum_p^M \left\{ 2h_{pp}^{\phi} + \sum_q^M (2J_{pq}^{\phi} - K_{pq}^{\phi}) \right\} \tag{85}$$

while the orbital energies have the following form:

$$\varepsilon_p = h_{pp}^{\phi} + \sum_q^M (2J_{pq}^{\phi} - K_{pq}^{\phi}) \tag{116}$$

The total energy E_0^t may be computed for any desired geometry of the molecule. Consequently when one internal coordinate (q), such as bond length or bond angle, is varied, one obtains a potential curve:

$$E_0^t = E_0^t(q) \tag{117}$$

When two internal coordinates (q_1 and q_2) are varied simultaneously the result is a potential energy surface

$$E_0 = E_0(q_1, q_2) \tag{118}$$

and in the case of more than two independent variables ($q_1, q_2, q_3, \ldots$) a hypersurface is generated:

$$E_0 = E_0(q_1, q_2, q_3, \ldots) \tag{119}$$

Equations (117)-(119) are analogous to the potential functions discussed in section I.B which were obtained by analysing experimental data, but the present expressions refer to the variation of the total energy obtained by MO calculations.

These energy hypersurfaces (119), surfaces (118) or curves (117) are suitable for studying molecular conformations or stereochemical relationships. They are also the essential starting points for vibrational analysis which involves the calculation of force constants (120) and interaction force constants (121) as second derivatives

$$k_r = \frac{\partial^2 E_0^t}{\partial q_r^2} \tag{120}$$

$$k_{rs} = \frac{\partial^2 E_0^t}{\partial q_r \partial q_s} \tag{121}$$

The calculation of relative stabilities (ΔE) always involves the calculation of two energy values associated with two situations A and B. For example, proton affinity (A_{H^+}) is the difference between the energy of the protonated and non-protonated species.

The ionized state (a molecule-ion with loss of an electron from one of the 'bonding orbitals' (b) is a doublet state). The electronic configuration ${}^2\Phi_b$ is formed by suppressing one of the rows and one of the columns of the ground state determinant (77) and assuming that the remainder is unchanged. The energy of this doublet state may be computed from this wavefunction {a $(2M-1)\times(2M-1)$ determinant} as given below:

$$
\begin{aligned}
{}^2E_b &= \langle {}^2\Phi_b | \hat{H} | {}^2\Phi_b \rangle \\
&= \underbrace{2\sum_{p}^{M} h_p^{\phi} + \sum_{p}^{M}\sum_{q}^{M}(2J_{pq}^{\phi} - K_{pq}^{\phi})}_{E_0} \underbrace{- h_b^{\phi} - \sum_{q}^{M}(2J_{bq}^{\phi} - K_{bq}^{\phi})}_{-\varepsilon_b} = E_0 - \varepsilon_b
\end{aligned}
\tag{122}
$$

The ionization energy, may therefore be written:

$$
{}^2\Delta E_b = ({}^2E_b - E_0) = -\varepsilon_b \tag{123}
$$

This means that the ionization potential ${}^2\Delta E_b$ associated with the removal of an electron from orbital b is the negative of the orbital energy ε_b. Since the orbital energy is, in general, a negative quantity, the ionization potential is a positive number.

The above result (equation 123) is frequently referred to as *Koopmans' Theorem*.

The excited states are approximated by excited configurations, within the framework of MO theory, just as the ground state is approximated by ground configurations. Therefore, the description of one of the electrons requires that an 'antibonding': (a) or 'virtual' orbital be SUBSTITUTED into the determinental wavefunction to replace the 'bonding' (b) or 'occupied' MO. Apart from this substitution $\Phi_{b\to a}$ is analogous to Φ_0.

To calculate the excitation energy (ΔE), the energies of the ground configuration ($E_0 = \langle \Phi_0 | H | \Phi_0 \rangle$) and the excited configuration ($E_1 = \langle \Phi_1 | H | \Phi_1 \rangle$) must be computed. This illustrated by Figure 30. It

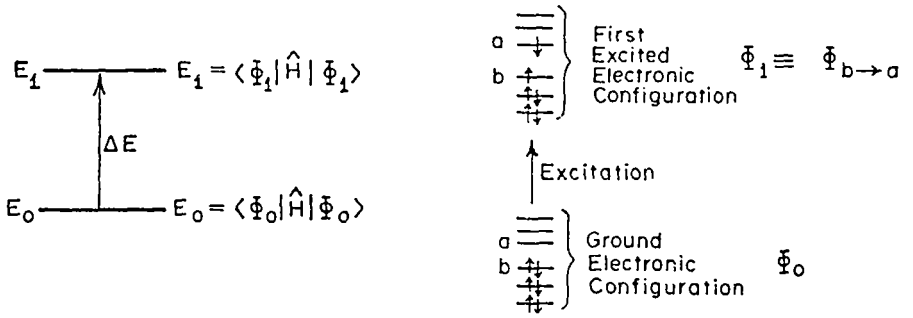


FIGURE 30. The generation of an excited electronic configuration for a closed shell system of $2M$ electrons.

is necessary, however, to distinguish between singlet and triplet configurations upon excitation from orbital b to orbital a as illustrated in Figure 31. Because these wavefunctions have the same form, we may

FIGURE 31. Singlet and triplet excited configurations.

denote them as $^{1,3}\Phi_{b\to a}$:

$$
\begin{aligned}
^{1,3}E_{b\to a} &= \langle {}^{1,3}\Phi_{b\to a}|\hat{H}|{}^{1,3}\Phi_{b\to a}\rangle \qquad (124)\\
&= \underbrace{\sum_{\substack{p\\ \text{all } b\\ \text{but not } a}}^{M}\left\{2h_p^\phi + \sum_{\substack{q\\ \text{all } b\\ \text{but not } a}}^{M}(2J_{pq}^\phi - K_{pq}^\phi)\right\}}_{E_0} \underbrace{-h_b^\phi - \sum_q^M (2J_{bq}^\phi - K_{bq}^\phi)}_{-\varepsilon_b}\\
&\quad \underbrace{+h_a^\phi + \sum_q^M (2J_{aq}^\phi - K_{aq}^\phi)}_{+\varepsilon_a} - (J_{ba}^\phi - K_{ba}^\phi) \pm K_{ba}^\phi
\end{aligned}
$$

where the $\pm$ signs represent the singlet and triplet states respectively. Thus

$$^{1,3}E_{b\to a} = E_0 + (\varepsilon_a - \varepsilon_b) - (J_{ba} - K_{ba}) \pm K_{ba} \qquad (125)$$

or, in detail,

$$
\left.
\begin{aligned}
^1E_{b\to a} &= E_0 + (\varepsilon_a - \varepsilon_b) - J_{ba} + 2K_{ba}\\
^3E_{b\to a} &= E_0 + (\varepsilon_a - \varepsilon_b) - J_{ba}
\end{aligned}
\right\} \qquad (126)
$$

The excitation energy values may be written as

$$
\left.
\begin{aligned}
^1\Delta E_{b\to a} &\equiv (^1E_{b\to a} - E_0) = (\varepsilon_a - \varepsilon_b) - J_{ba} + 2K_{ba}\\
^3\Delta E_{b\to a} &\equiv (^3E_{b\to a} - E_0) = (\varepsilon_a - \varepsilon_b) - J_{ba}
\end{aligned}
\right\} \qquad (127)
$$

E. The Concept of Localized Molecular Orbitals (LMO)

The molecular orbitals which produce a Fock matrix in the canonical (diagonal) form are known as canonical molecular orbitals (CMO).

These CMO are delocalized over the whole molecule irrespectively whether they belong to the σ or the π representations and are symmetry adapted, i.e. they form the basis for the irreducible representation of the point group determined by the symmetry of the molecule (cf. Figures 9 and 32). On the other hand, the otherwise equivalent localized molecular orbitals (LMO) are governed by the stereochemistry of molecular bonding (cf. Figure 32).

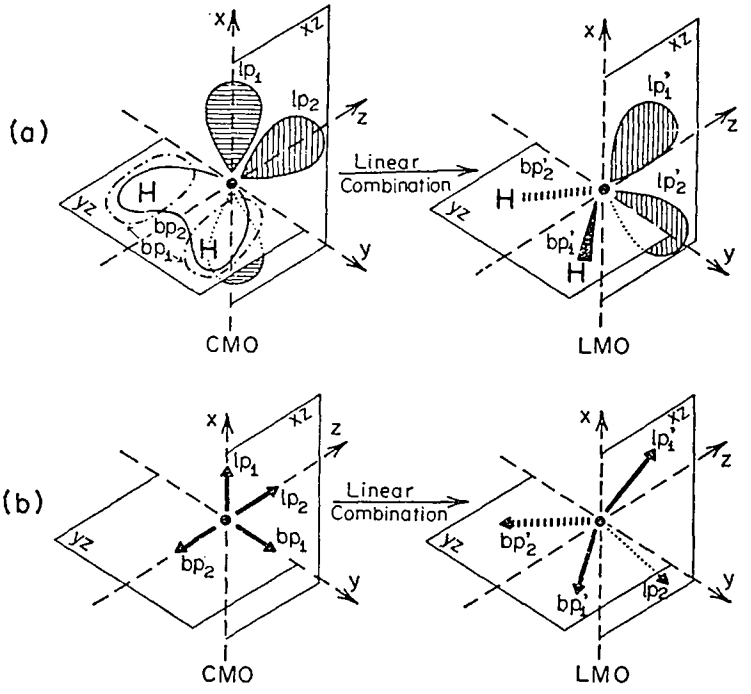


FIGURE 32. Molecular orbital (a) and vector (b) representation of the two bonding and two lone electron pairs of H_2O or H_2S and the relation between canonical molecular orbitals (CMO) and localized molecular orbitals (LMO).

To illustrate, consider the valence electron shell of H_2S or H_2O: both contain 8 valence electrons, which form 4 electron pairs, *i.e.* 2 bonding pairs and 2 lone pairs. It is customary in experimental chemistry to think in terms of LMO. In this representation the two bonding pairs correspond to two equivalent bonds which coincide with the plane formed by the three atoms of H_2O or H_2S. On the other hand, the two lone pairs are envisaged as two equivalent non-bonded orbitals in a plane perpendicular to the plane formed by the three atoms in question. This

representation is illustrated in Figure 32a where the constituting atoms of the molecule are placed in the *yz* plane of a right-handed Cartesian coordinate system.

If the molecular orbitals (both CMO and LMO) are symbolized by vectors, then a linear combination of the CMO will yield the LMO and *vice versa*. Labelling the lone pairs by *lp* and the bonding pairs by *bp*, and specifying the LMO by a prime while the CMO are unprimed the following relationships may be written,

$$\left.\begin{aligned} bp'_1 &= (1/\sqrt{2})(bp_2 + pb_1) \\ bp'_2 &= (1/\sqrt{2})(bp_2 - bp_1) \\ lp'_1 &= (1/\sqrt{2})(lp_2 + lp_1) \\ lp'_2 &= (1/\sqrt{2})(lp_2 - lp_1) \end{aligned}\right\} \tag{128}$$

and combined into one equation:

$$(bp'_1 \quad bp'_2 \quad lp'_1 \quad lp'_2) = (bp_1 \quad bp_2 \quad lp_1 \quad lp_2)\begin{pmatrix} 1/\sqrt{2} & -1/\sqrt{2} & 0 & 0 \\ 1/\sqrt{2} & 1/\sqrt{2} & 0 & 0 \\ 0 & 0 & 1/\sqrt{2} & -1/\sqrt{2} \\ 0 & 0 & 1/\sqrt{2} & 1/\sqrt{2} \end{pmatrix} \tag{129}$$

If no distinction is made between *bp* and *lp*, and denoting CMO by ϕ and LMO by ψ, then the following transformation may be written:

$$(\psi_1 \quad \psi_2 \quad \psi_3 \quad \psi_4) = (\phi_1 \quad \phi_2 \quad \phi_3 \quad \phi_4)\begin{pmatrix} 1/\sqrt{2} & -1/\sqrt{2} & 0 & 0 \\ 1/\sqrt{2} & 1/\sqrt{2} & 0 & 0 \\ 0 & 0 & 1/\sqrt{2} & -1/\sqrt{2} \\ 0 & 0 & 1/\sqrt{2} & 1/\sqrt{2} \end{pmatrix} \tag{130}$$

Examining the transforming 4×4 matrix in equation (130) it can be concluded, in agreement with other CMO→LMO transformations, that it is a unitary matrix (**U**),

$$\boldsymbol{\psi} = \boldsymbol{\phi}\mathbf{U} \tag{131}$$

which has far-reaching consequences. Firstly, the inverse of a unitary matrix ($\mathbf{U}^{-1}$) is its adjoint $\mathbf{U}^{\dagger}$ (the transpose for orbitals which are real, rather than complex functions):

$$\mathbf{U}^{-1} = \mathbf{U}^{\dagger} \tag{132}$$

This means that the **U** matrix may be used for the transformation in both directions (i.e. CMO → LMO and LMO → CMO):

$$\boldsymbol{\phi} = \boldsymbol{\psi}\mathbf{U}^{-1} = \boldsymbol{\psi}\mathbf{U}^{\dagger} \tag{133}$$

Secondly, a unitary transformation such as CMO → LMO specified in equations (129)-(131) does not change the orthonormality of the basis set. This is equivalent to rotation of the n-dimensional space, which may be defined by any basis. Thus the four-dimensional space, in the present case, can equally be defined by ϕ_1, ϕ_2, ϕ_3 and ϕ_4 or ψ_1, ψ_2, ψ_3 and ψ_4. This means that the LMO basis representation of the four-electron pair problem of H_2S is equivalent to that of the CMO basis.

Thirdly, it can be shown that whenever the many-electron wavefunction $\Phi_0(1, 2, \ldots)$, which is normally constructed in terms of CMO, is changed in such a way that LMO: ψ can be written instead of CMO: ϕ in the Slater determinant (77) then the new wavefunction generated, $\Phi_0'(1, 2, \ldots)$ is identical to the original function $\Phi_0(1, 2, \ldots)$. This means that the total electronic energies E_0^e computed from (52b) for Φ_0 and Φ_0' are numerically identical.

For a molecule that has less symmetry than H_2S it is not possible to construct, by inspection, the **U** matrix which transforms CMO to LMO (131). Therefore it is usual to modify the LMO in order to compute the **U** matrix for a general case. Since LMO, like chemical bonds, are separated from each other while all the CMO are spread over the molecule (i.e. CMO are delocalized) it is clear that the most objective localization procedure that could be employed would involve the construction of orbitals which are 'separated' from each other as much as possible, without having to stipulate in advance the location of these orbitals in space. Such a localization would require only that the definition of 'separation' be decided upon *ab initio*. The Edmiston–Ruedenberg method of separating the orbitals involves maximization of the 'total self-repulsion', i.e. the diagonal elements of the electron–electron repulsion.

The electron–electron repulsion term, i.e. the two-electron contribution (E_2) to the total energy

$$E^t = E_0 + E_1 + E_2 \tag{49}$$

results from the two-electron operator ($\hat{H}_2 = \sum r_{\mu\nu}^{-1}$) of the total Hamiltonian:

$$\hat{H} = \hat{H}_0 + \hat{H}_1 + \hat{H}_2 \tag{134}$$

Considering the case of closed electron shells only,

$$E_2 = 2\sum_{p}^{M}\sum_{q}^{M} J_{pq}^{\phi} - \sum_{p}^{M}\sum_{q}^{M} K_{pq}^{\phi} \tag{135}$$

The diagonal elements of both the Coulomb and exchange integrals can be combined since they are equal (cf. equation 86), while the off-diagonal elements remain separate:

$$E_2 = \sum_p J^{\phi}_{pp} + 2\sum_p \sum_{(q\neq p)} J^{\phi}_{pq} - \sum_p \sum_{(q\neq p)} K^{\phi}_{pq} \tag{136}$$

It is important to note that in equation (135) both terms are invariant under any unitary transformation of the MO basis (i.e. their numerical values are identical for both delocalized and any localized MO). However, in equation (136), neither of the terms is invariant under a unitary transformation of the basis set. In fact, it is this characteristic property which has been used as the localization criterion in the method of Edmiston and Ruedenberg. The object of this localization method is to maximize the 'self-repulsion', i.e. the first term on the right-hand side of the latter equation. This term is referred to as the localization sum:

$$J_0 = \sum_p J^{\phi}_{pp} = \sum_p K^{\phi}_{pp} \tag{137}$$

As the value of J_0 increases, the orbitals become more localized. The unitary matrix that maximizes the diagonal elements while simultaneously minimizing the off-diagonal elements of the **K** matrix may be obtained by a Jacobi type diagonalization:

$$\mathbf{K}^{\psi} = \mathbf{U}^{\dagger}\mathbf{K}^{\phi}\mathbf{U} \tag{138}$$

This matrix **U** is to be used to transform the CMO to the LMO in a unitary (orthogonal) transformation:

$$\boldsymbol{\psi} = \boldsymbol{\phi}\mathbf{U} \tag{131}$$

Some results obtained for CH_3SH and CH_3OH will be presented in section IV.

F. The Notion of d-orbital Participation

In the terminology of quantum chemistry, '*completeness*' *means* '*infinite*'. This was made clear in the theory of CI expansions (54), (55), (56) and the related concepts, where it was shown that the non-relativistic limit (NRL) can only be achieved when the CI expansion includes an infinite number of excited configurations $\Phi_v(1, 2, 3, \ldots)$:

$$\Psi_0^{\mathrm{NRL}}(1, 2, 3, \ldots) = \lim_{N\to\infty} \sum_{v=1}^{N} a_{0v}\Phi_v(1, 2, 3, \ldots) \tag{139}$$

The same is applicable to the expansion of MO in terms of AO. The molecular Hartree–Fock (HF) orbitals (ϕ) can only be generated if they

are expanded in terms of an infinite number of AO (η) (cf. equation 81):

$$\phi_p^{\mathrm{HF}}(1) = \lim_{N\to\infty} \sum_{i=1}^{N} C_{pi}\eta_i(1) \tag{140}$$

The discussion of basis set size implied that both the minimal basis (108) and double zeta basis (109) represent a severe truncation of the complete expansion (140).

Since all the AO consist of both radial and angular parts (107) the infinite set should refer to all types of AO. In other words, an infinite *s* basis (i.e. $1s, 2s, 3s, 4s, \ldots$) does not represent a complete basis. An infinite *sp* basis (i.e. $1s, 2s, 3s, 4s, \ldots; 2p, 3p, 4p, \ldots$) is better but still not complete. The complete AO basis should, in principle, include an infinite number of all angular types AO (i.e. $s, p, d, f, j, h, \ldots$). To state this slightly differently, *all AO have mathematical importance because they are members of the complete basis set.*

To illustrate this point, consider the H^- ion[24]. Different expansions including more and more *s*-functions (orbitals) until no further improvement was observed (*s*-limit), or more and more *p*-functions (*p*-limit) and so on, revealed that a very large number of functions was required to compute wavefunction $\Psi_0(1,2)$ in the limiting sense. This is clearly illustrated in Figure 33. Inspection of Figure 33 reveals that there is a substantial lowering of the total energy on going from the *s*-limit to the *p*-limit, and a considerably smaller (but still appreciable) decrease on going from the *p*-limit to the *d*-limit; however, the effect virtually disappears when the *g*-limit is passed. This may be taken as *the numerical measure of the mathematical importance of the* so-called *polarization functions*, i.e. the *p*, *d*, *f* and *g* orbitals for the case of hydrogen nucleus. However, it is traditionally unthinkable to associate chemical significance to these higher angular orbitals associated with the hydrogen nucleus. Nevertheless the chemical significance of 3*d*-AO (the role of *d*-orbital participation in bonding) on sulphur is widely debated.

It should be noted that, in connection with equations (139) and (140), the importance of polarization functions may be assessed from two different approaches corresponding to two different levels of sophistication. In one case, the magnitude of the coefficients of the polarization functions (such as 3*d*-AO on S) in the expansion of the *M* occupied MO (cf. equation 140) may be taken as the numerical measure of their mathematical importance. Only the first *M* occupied MO (i.e. $\phi_1, \phi_2, \ldots, \phi_{M-1}, \phi_M$) need be considered because these are the ones used in the construction of the many-electron MO wavefunction (77), $\Phi_0(1, 2, \ldots, 2M)$, as specified by equation (115). It should be emphasized that this wavefunction is still

above the HFL which can only be reached if the MO expansion (140) is complete (i.e. the summation is infinite, including $s, p, d, f, g, \ldots$ functions).

At the next level of sophistication, when the HFL is transcended (but the NRL has not been reached), the magnitude of the expansion coefficients a_{0v} of the various excited configurations, $\Phi_v(1, 2, \ldots, 2M)$ in

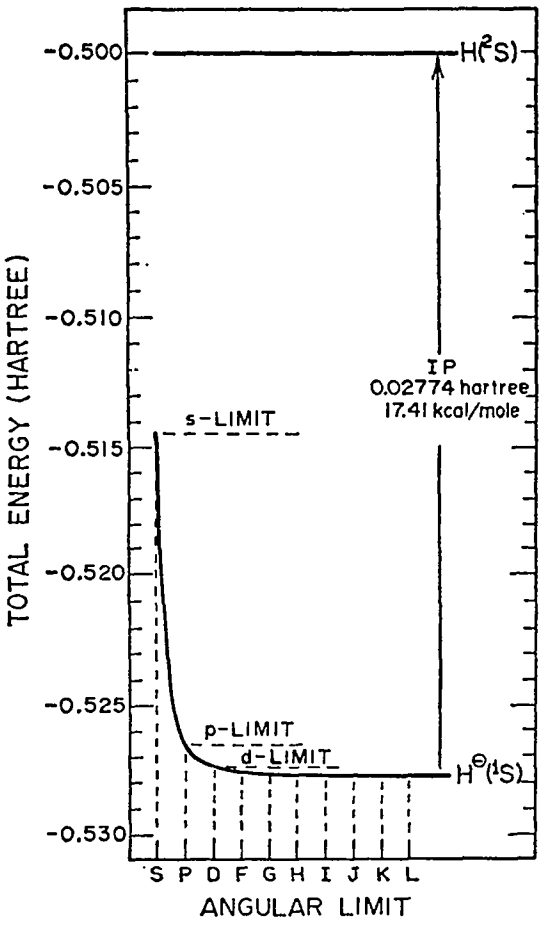


FIGURE 33. The dependence of the energy and the ionization potential on the angular limit for the hydride ion.

the CI expansion (139) should be considered. These excited configurations contain some of the virtual orbitals ($\phi_{M+1}, \phi_{M+2}, \ldots$) shown in equation (115). While this approach is relevant to the more sophisticated wave-

functions (cf. the case of H^- in Figure 33) only the former approach can be investigated at this time, since no wavefunction that transcends the HFL has been computed for any RSH compounds, including H_2S (cf. Figure 29).

As an illustration consider the successive protonation of HS^- and HO^-:

$$\left.\begin{aligned} HS^- &\xrightarrow{A_H+(HS^-)} H_2S \xrightarrow{A_H+(H_2S)} H_3S^+ \\ HO^- &\xrightarrow{A_H+(HO^-)} H_2O \xrightarrow{A_H+(H_2O)} H_3O^+ \end{aligned}\right\} \quad (26b)$$

The total energy values for these six species were computed with an *s*, *sp*, *spd* and *spdf* basis. The results are tabulated in Table 24 and 25 and

TABLE 24. SCF total energies computed for HO^-, H_2O, H_3O^+, HS^-, H_2S and H_3S^+ with *s*, *sp*, *spd* and *spdf* basis sets

Species	Basis[a,b]	Total energy (hartree)	
		X = O	X = S
HX^-	*s*	—	—
	sp	−75·344942	−398·067184
	spd	−75·360793	−398·085385
	spdf	−75·366723	−398·092297
H_2X	*s*	—	−323·244244
	sp	−75·997291	−398·624697
	spd	−76·026374	−398·672209
	spdf	−76·032596	−398·676781
H_3X^+	*s*	−72·112493	−328·899043
	sp	−76·288849	−398·833932
	spd	−76·304651	−398·927379
	spdf	−76·315642	−398·931469

[a] The hydrogen atoms were represented by a $1s\,1s'$ basis which in turn was contracted from four primitive $1s$-GTF.

[b] The *s*, *sp*, *spd* and *spdf* stand for the type of AO basis set used for the heteroatom (O and S). For details see equation (143a) in the next section.

plotted in Figure 34. The two sets of proton affinities are plotted in Figure 35 and clearly indicate how the mathematical importance of the higher angular polarization functions diminishes in the two systems.

TABLE 25. Proton affinity values for HO^-, H_2O, HS^- and H_2S calculated from the SCF total energies involving *sp*, *spd* and *spdf* basis sets

Reaction	Basis[a,b]	Proton affinity (kcal/mole)	
		X = O	X = S
$HX^- + H^+ \rightarrow H_2X$	*sp*	−409·49	−349·96
	spd	−417·79	−368·36
	spdf	−417·98	−366·89
$H_2X + H^+ \rightarrow H_3X^+$	*sp*	−183·01	−131·34
	spd	−174·68	−160·17
	spdf	−177·67	−159·87

[a] The hydrogen atoms were represented by a 1*s* 1*s*′ basis which in turn was contracted from four primitive 1*s*-GTF.

[b] The *sp*, *spd* and *spdf* stand for the type of AO basis set used for the heteroatom (O and S). For details see equation (143a) in the next section.

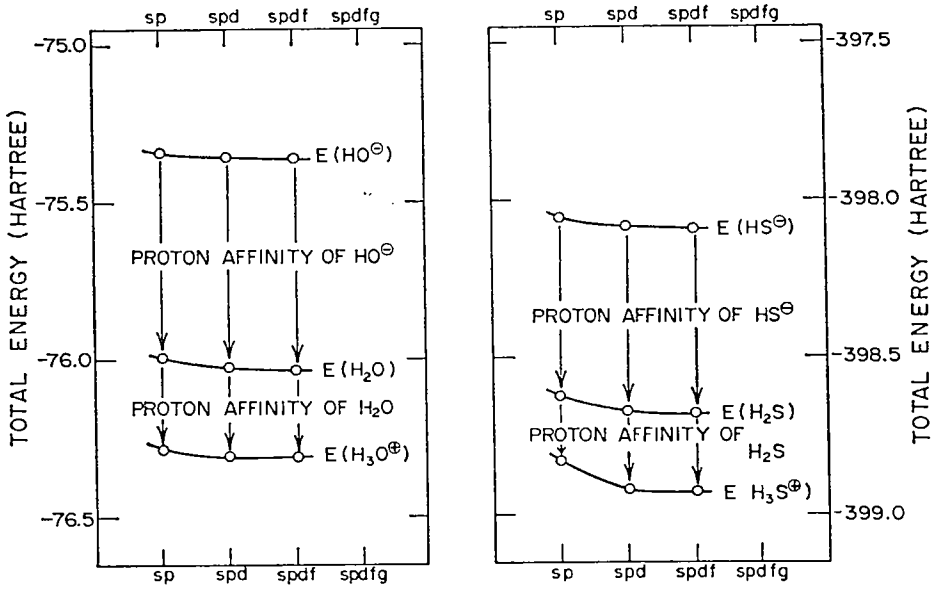


FIGURE 34. Total energies of HO^-, H_2O and H_3O^+ as well as HS^-, H_2S and H_3S^+ computed with *sp*, *spd* and *spdf* basis sets.

It should be made clear, however, that these one-electron functions (orbitals) are mathematical objects and while they may have mathematical importance one should not attribute chemical significance to these mathematical objects.

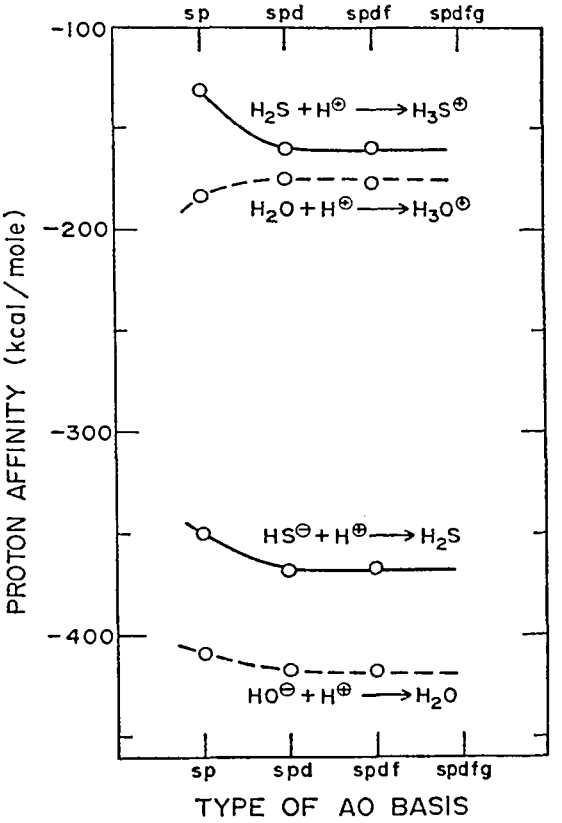
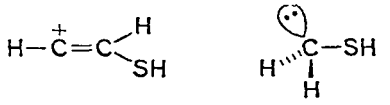


FIGURE 35. Effect of angular polarizing functions on computed A_{H^+} values of HS^-, H_2S, OH^- and H_2O.

III. CALCULATIONS OF MOLECULAR WAVEFUNCTIONS AND ENERGIES

The theoretical principles outlined in section II will now be applied to the computation of physical properties such as optimum geometries, ionization potentials, etc. described in section I. The calculations are centred around three families of compounds containing the —SH group. The *pre-thiol family* includes HS, H_2S and H_3S in their neutral and ionic forms. In the *thiol family* only the first member, CH_3SH, will be treated explicitly, and

compared with the corresponding oxygen analogue (CH_3OH). In addition to geometry optimization, ionization potentials will be calculated from Koopmans' theorem, and electronic excitation patterns will be treated within the framework of the virtual orbital technique. *Special structures* involving the thiol group will be limited to species which have either a carbonium ion centre or a carbanion centre adjacent to SH:



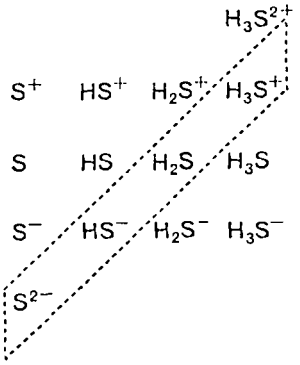
(141)

The overall purpose of section III is to demonstrate that accurate Hartree–Fock type molecular calculations are now technically feasible. The study of electron pairing and unpairing phenomena (dissociation, excitation) requires the generation of molecular wavefunctions that transcend the Hartree–Fock limit and these are currently under investigation; nevertheless, Molecular Quantum Chemistry is sufficiently advanced so as to be a practical research tool even for systems as large as RSH.

A. A Study on the Pre-thiol Family (HS, H_2S, H_3S)

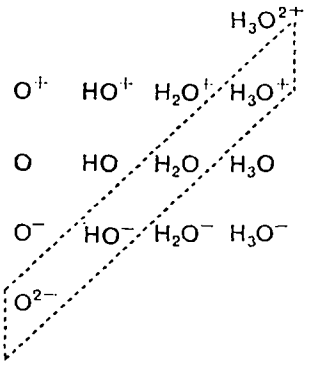
As shown in section II.C (cf. equations 108 and 109) the choice of the basis set is crucial to the results of the calculations: this was clearly shown for H_2S in Table 23 and Figure 29. Consequently, meaningful comparisons between different species can only be made from calculations using the *same basis set.*

The calculations described here are unpublished results of R. E. Kari[27]. This study covers the following set of sulphur-containing species:



(142a)

For comparison the corresponding hydrides of oxygen were treated in an analogous manner:



(142b)

The compounds framed with the broken line represent those with closed electronic shells. The basis sets used are summarized below:

H: (4*s*, 1*p*) primitive GTF ⟶ [2*s*, 1*p*] contracted BF
O: (10*s*, 5*p*, 1*d*) primitive GTF ⟶ [4*s*, 2*p*, 1*d*] contracted BF
S: (12*s*, 9*p*, 2*d*) primitive GTF ⟶ [6*s*, 4*p*, 2*d*] contracted BF

(143a)

For the species under investigation, this represents the following basis set sizes:

O: (31 GTF) ⟶ [16 BF]
HO: (38 GTF) ⟶ [21 BF]
H_2O: (45 GTF) ⟶ [26 BF]
H_3O: (52 GTF) ⟶ [31 BF]
S: (51 GTF) ⟶ [30 BF]
HS: (58 GTF) ⟶ [35 BF]
H_2S: (65 GTF) ⟶ [40 BF]
H_3S: (72 GTF) ⟶ [45 BF]

(143b)

The potential surfaces $E(r, \phi)$ generated by variation of the X—H bond length (r) and the HXH bond angle (ϕ) were calculated for H_2O and H_2S. The energy minima (E_e) associated with the equilibrium bond lengths (r_e) and bond angles (ϕ_e) of the various species studied are summarized in Table 26 for sulphur and Table 27 for oxygen.

TABLE 26. Equilibrium bond lengths (r_e), angles (ϕ_e) and energies (E_e) of sulphur species

Species	Shape	r_e (bohr)	ϕ_e (degree)	E_e (hartree)
$S^+(^4S)$	—	—	—	−397·13724
$S(^3P)$	—	—	—	−397·48234
$S^-(^2P)$	—	—	—	−397·48338
$S^{2-}(^1S)$	—	—	—	−397·15319
HS^+	linear	2·553	—	−397·72978
HS	linear	2·516	—	−398·07660
HS^-	linear	2·526	—	−398·09162
H_2S^+	bent	2·537	80·00	−398·33991
H_2S	bent	2·507	79·36	−398·68932
H_2S^-	bent	2·8	124·39	−398·54725[a]
H_3S^{2+}	pyramidal	2·616	116·37	−398·24991
H_3S^+	pyramidal	2·555	97·83	−398·96247
H_3S	pyramidal	2·8	120·00	−399·08559[a]
H_3S^-	pyramidal	2·8	120·00	−398·99616[b]

[a] This energy is to the lowest value computed to date.

[b] This energy corresponds to the minimum energy at a S—H bond length of 2·8 bohr. The minimum interpolated energy is expected to decrease by approximately 0·005 hartree.

TABLE 27. Equilibrium bond lengths (r_e), angles (ϕ_e) and energies (E_e) of oxygen species

Species	Shape	r_e (bohr)	ϕ_e (degree)	E_e (hartree)
$O^+(^4S)$	—	—	—	−74·355627
$O(^3P)$	—	—	—	−74·793186
$O^-(^2P)$	—	—	—	−74·748716
$O^{2-}(^1S)$	—	—	—	−74·277585
HO^+	linear	1·9	—	−74·982651
HO	linear	1·8	—	−75·399762
HO^-	linear	1·8	—	−75·366488
H_2O^+	bent	1·856	115·72	−75·636920
H_2O	bent	1·793	110·87	−76·038620
H_2O^-	bent	1·949	105·53	−75·834169
H_3O^{2+}	planar	1·999	120·00	−75·503960
H_3O^+	pyramidal	1·826	113·74	−76·323726
H_3O	pyramidal	1·956	112·96	−76·438160
H_3O^-	planar	>2·2	120·00	−76·288587[a]

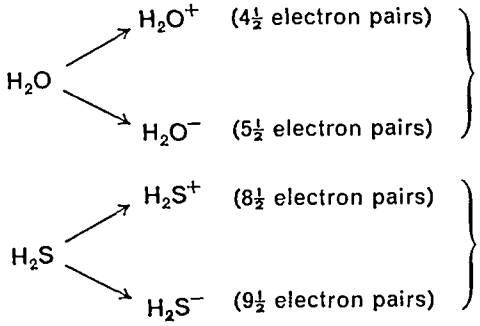
[a] Lowest energy computed to date.

These total energy values may be used to evaluate ionization potentials (IP) and electron affinities (EA) and the results are summarized in Table 28.

TABLE 28. Calculated ionization potentials and electron affinities for some hydrides of oxygen and sulphur

Species	IP (kcal/mole)		EA (kcal/mole)	
	X = O	X = S	X = O	X = S
X^+	—	—	−274·7	−216·6
X	274·7	216·6	−27·9	−0·65
X^-	27·9	+0·65	295·7	207·3
X^{2-}	−295·7	−207·3	—	—
HX^+	—	—	−261·8	+217·7
HX	261·8	+217·7	20·9	−9·4
HX^-	−20·9	+9·4	—	—
H_2X^+	—	—	252·2	−219·3
H_2X	252·2	219·3	128·3	89·3
H_2X^-	128·3	−89·3	—	—
H_3X^{2+}	—	—	−514·6	−447·3
H_3X^+	514·6	447·3	−71·8	550·4
H_3X	71·8	+77·3	>93·9	−571·6
H_3X^-	−93·9	−56·1	—	—

The relative energies are illustrated in Figure 36. Systematic errors are unavoidable since in most of the species studied, ionization and electron capture involve a difference in electron pairing. This is particularly true for the generation or destruction of closed electronic shell systems such as H_2O and H_2S:



(144a)

(144b)

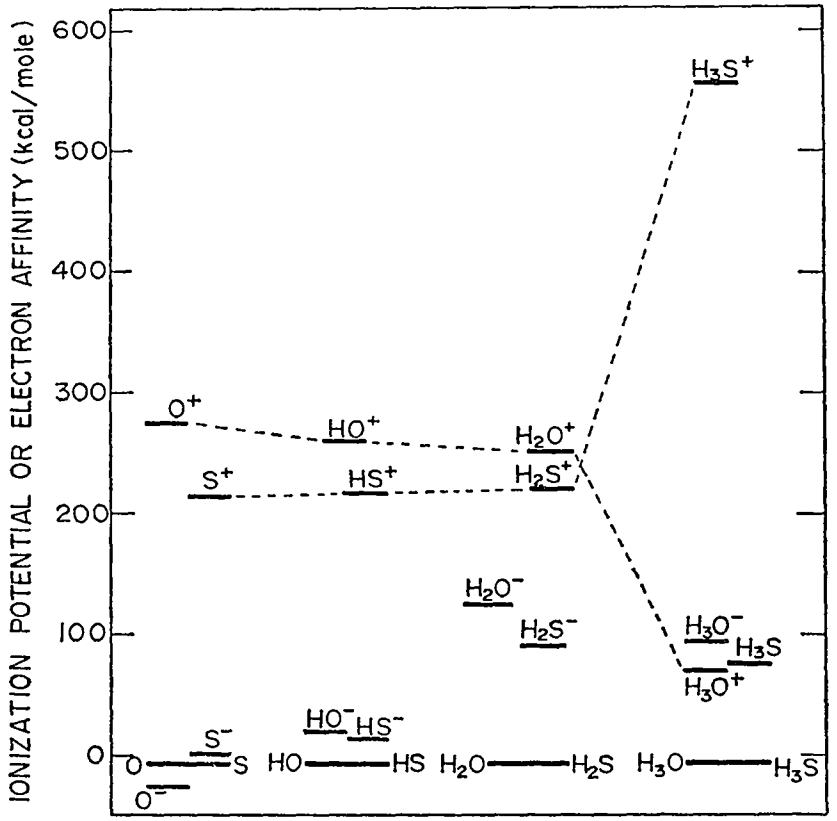


FIGURE 36. Calculated ionization potentials and electron affinities of oxygen and sulphur species.

In such cases a correction should be made for the change in correlation energy when a new electron pair is formed or an old pair is destroyed. Consequently better numerical accuracy may be anticipated when one goes beyond the Hartree–Fock method in the computation of molecular wavefunctions.

The correlation between experiment and theory is expected to be somewhat better in the case of proton affinities since the total number of electron pairs remains unchanged. However, the hydrogen affinity (A_H) of the neutral species again involves a change in electron pairing since it is opposite, in the arithmetical sense, to the dissociation energy:

$$H\ddot{S}\cdot + 2H \underset{D_0(H_2S)}{\overset{A_H(HS)}{\rightleftharpoons}} H_2\ddot{S} + \cdot H \underset{D_0(H_3S)}{\overset{A_H(H_2S)}{\rightleftharpoons}} H_3\ddot{S}\cdot \qquad (145)$$

The numerical values computed for A_{II^+}, A_{II} and A_{II^-}, are summarized in Table 29 and some of these results are illustrated in Figure 37.

TABLE 29. Proton, hydrogen and hydride affinities[a] calculated for some oxygen and sulphur species

Species	A_{II^+}[b]		A_{II}[c]		A_{II^-}[d]	
	X = O	X = S	X = O	X = S	X = O	X = S
X^+	—	—	−81·2	−37·7	−401·0	−335·3
X	−118·9	−155·3	−68·4	−60·6	−133·4	−128·1
X^-	−408·7	−372·4	−75·4	−44·0	—	—
HX^+	—	—	−98·3	−70·6	−408·4	−347·9
HX	−148·9	−165·3	−88·6	−72·2	−18·3	−41·0
HX^-	−421·9	−375·2	−18·8	−26·4	—	—
H_2X^+	84·9	56·5	−118·7	−49·8	−248·6	< −213·7
H_2X	−179·0	−171·5	61·6	−40·4	< 97·5	< 61·8
H_2X^-	−379·1	−337·9	< 27·1	−30·6	—	—

[a] In kcal/mole units.
[b] $E(H^+) = 0{\cdot}000000$ hartree.
[c] $E(H) = -0{\cdot}497639$ hartree.
[d] $E(H^-) = -0{\cdot}405271$ hartree.

B. A Study on Methanethiol (CH_3SH)

At the time of writing, Hartree–Fock type calculations have not been reported for CH_3SH and the results presented here are from the computations of M. H. Whangbo and B. Schlagel[28]. A double zeta quality basis set was used, similar to that specified in equation (143) with the inclusion of a pair of *d*-GTF of different exponents. This set amounted to 101 primitive GTF contracted to 48 basis functions (BF).

Partial molecular geometry optimization revealed that the optimum CSH angle is in the vicinity of 96·5° and the optimized C—S bond length, 1·872 Å is longer than the experimental value which is 1·818 Å. The molecular geometry is shown in Figure 38.

Calculations were performed for both the staggered and eclipsed conformations. The height of the barrier to rotation, 1·17 kcal/mole, calculated from the experimental C—S bond length, was slightly higher that that obtained from the optimized bond length, 0·97 kcal/mole. The results are summarized in Table 30 together with the corresponding energy values calculated for CH_3OH from experimental geometry.

The orbital energies associated with the eclipsed and staggered conformations of CH_3OH and CH_3SH are summarized in Table 31. Within

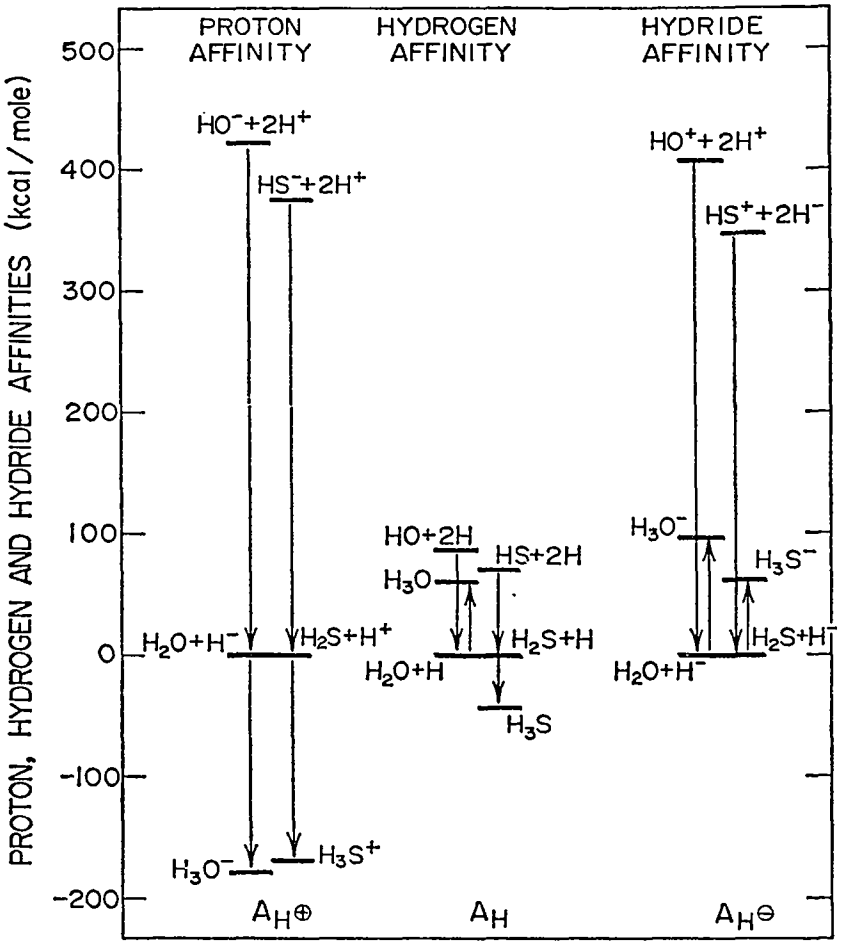


FIGURE 37. Calculated proton (A_{H^+}), hydrogen (A_H) and hydride (A_{H^-}) affinities of oxygen and sulphur species.

TABLE 30. Computed total energies and rotational barriers of CH_3OH and CH_3SH

Species	E (hartree)		Barrier
	Eclipsed	Staggered	(kcal/mole)
CH_3OH [a]	−115·00875	−115·01105	1·44
CH_3SH [b]	−437·68919	−437·69073	0·97

[a] Experimental geometry[29].
[b] Partially optimized geometry[28].

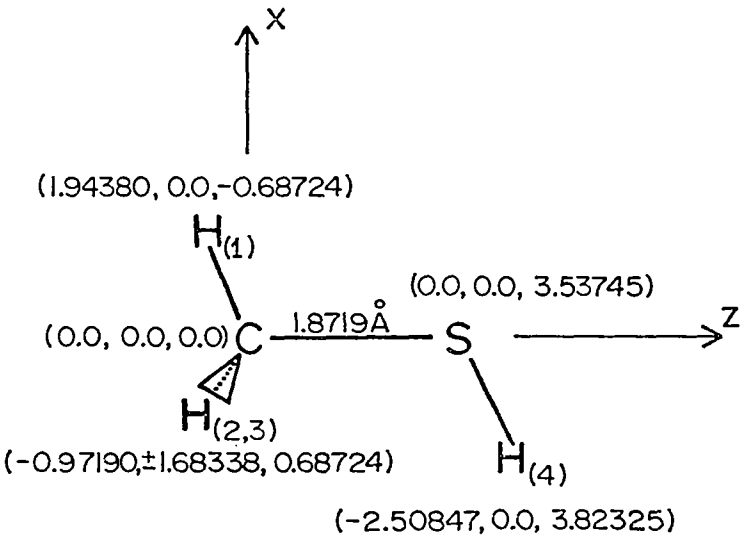


FIGURE 38. Molecular geometry of CH_3SH.

TABLE 31. Orbital energies hartree computed for the eclipsed and staggered conformations of CH_3OH and CH_3SH

MO	CH_3OH		CH_3SH	
	0°	60°	0°	60°
1	−20·531783	−20·532533	−91·96534	−91·965675
2	−11·280679	−11·280775	−11·266883	−11·267462
3	−1·353551	−1·353568	−8·9491544	−8·9494419
4	−0·936375	−0·936391	−6·6399092	−6·6401872
5	−0·679710	−0·678044	−6·6384849	−6·6387849
6	−0·623833	−0·625994	−6·6354987	−6·6357505
7	−0·591505	−0·591341	−1·0303167	−1·0304695
8	−0·489680	−0·488619	−0·87427031	−0·87453325
9	−0·444756	−0·446377[a]	−0·60598683	−0·60453979
10	0·257629	0·266977	−0·58928040	−0·58981474
11	0·368244	0·368324	−0·52748499	−0·52924918
12	0·377213	0·377850	−0·45293414	−0·45341008
13	0·383792	0·380672	−0·35663566	−0·35653279[b]
14			0·20405157	0·21035037
15			0·21685684	0·21873453
16			0·31367763	0·32879325
17			0·35502071	0·35012325

[a] IP (Koopmans' theorem) = 0·446 hartree = 12·14 eV = 280·0 kcal/mole.
[b] IP (Koopmans' theorem) = 0·357 hartree = 9·71 eV = 224·1 kcal/mole.

the framework of Koopmans' theorem (123) the negative of these orbital energies can be taken as an estimate of molecular ionization potentials. The highest filled MO energies correspond therefore to the lowest ionization potentials and are calculated to be 280·0 Kcal/mole and 224·1 kcal/mole for CH_3OH and CH_3SH respectively. These represent upper limits to the true values (Table 12) but nevertheless the trend

$$IP\,(CH_3OH) > IP\,(CH_3SH) \tag{146}$$

is observed in theory as well as experiment.

Excitation energies were calculated within the framework of the virtual orbital technique (127) which also yields upper bound values. The results again follow the expected trend, i.e. the energy levels of CH_3SH are predicted to be lower than those of CH_3OH. This is clearly illustrated in Figure 39 which summarizes calculated singlet (S_1, S_2) and triplet (T_1, T_2)

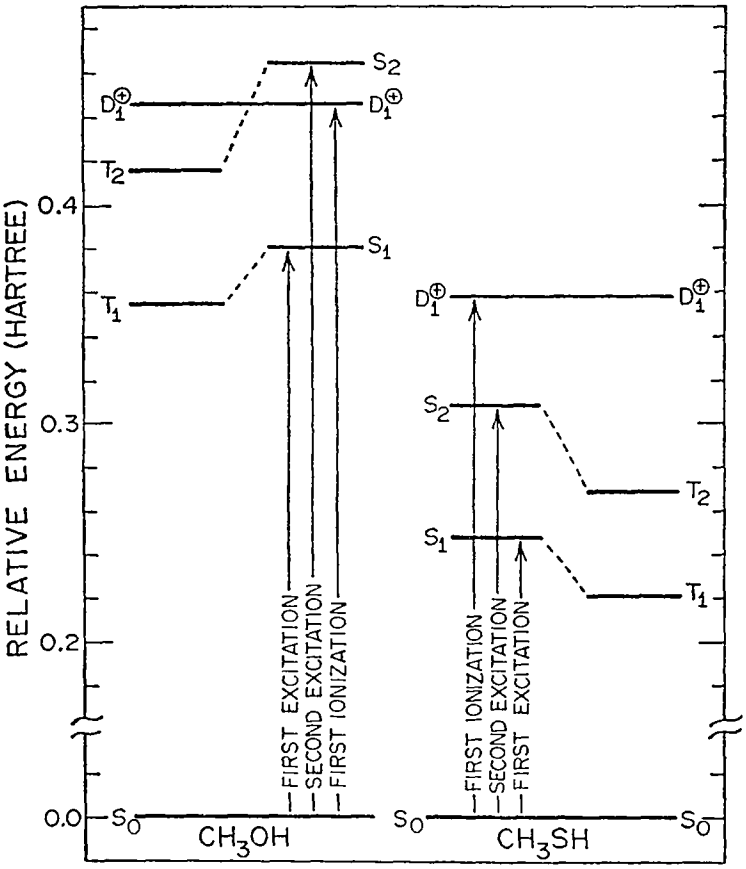


FIGURE 39. Singlet (S) and triplet (T) excitation and doublet (D^+) ionization energies for the staggered conformations of CH_3OH and CH_3SH.

excitation and doublet (D_1^+) ionization energies for the staggered conformations of CH_3OH and CH_3SH.

Excited state conformations of CH_3SH, illustrated in Figure 40, were derived from the excitation energies of both the staggered and eclipsed conformations which are summarized in Table 32. Figure 40 shows that

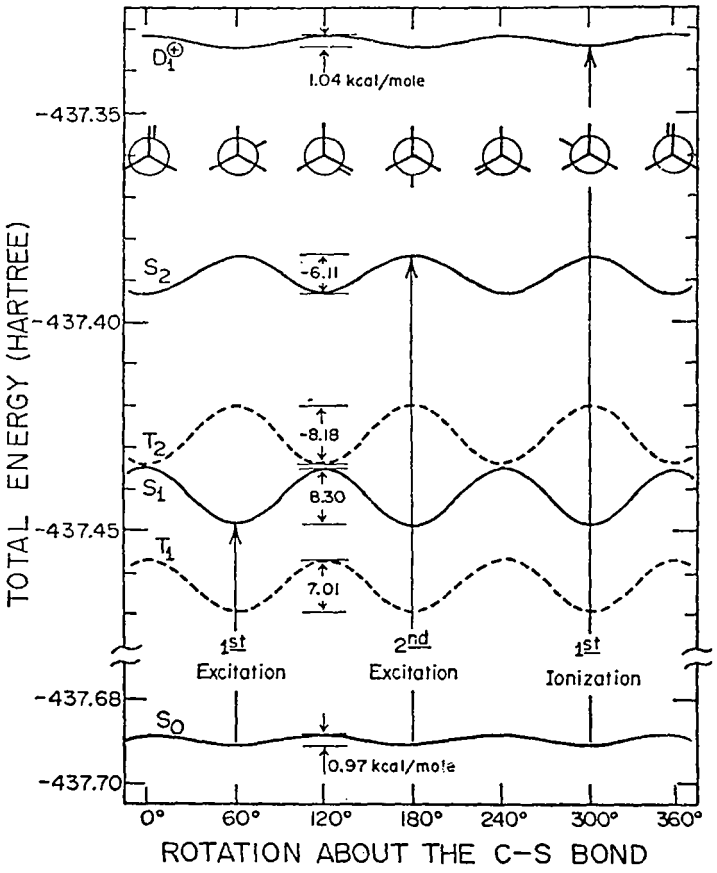


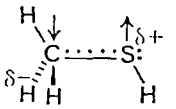
FIGURE 40. Ground and excited state conformations of CH_3SH.

the rotational barrier heights in the low-lying excited states are very much higher than those in the ground state, although the magnitudes of these differences are probably overestimated by the calculations. Undoubtedly a CI wavefunction that properly describes the unpaired electrons in the excited states would produce somewhat lower barrier heights. The most reasonable explanation for this phenomenon is that in

TABLE 32. Total energies and barriers to rotation computed for the ground (S_0), some low lying singlet (S_1, S_2), triplet (T_1, T_2) and first ionized doublet (D_1^+) states of CH_3SH and CH_3OH

Species	State	Total energy (hartree)		Barrier
		Eclipsed	Staggered	(Kcal/mole)
CH_3SH	D_1^+	−437·33255	−437·33420	1·04
	S_2	−437·39345	−437·38371	−6·11
	T_2	−437·43351	−437·42048	−8·18
	S_1	−437·43481	−437·44803	8·30
	T_1	−437·45747	−437·46863	7·01
	S_0	−437·68919	−437·69073	0·97
CH_3OH	D_1^+	−114·56395	−114·56465	0·44
	S_2	−114·55775	−114·54705	−6·72
	T_2	−114·60475	−114·59505	−6·09
	S_1	−114·62875	−114·63205	2·07
	T_1	−114·65075	−114·65705	3·95
	S_0	−115·00875	−115·01105	1·44

the excited state, the promoted electron creates a partial bond that hinders rotation:



(147)

This implies that in the excited states the charge separation is opposite (or at least changes in the opposite sense) to that of the ground state. It is not surprising, therefore, that *in some excited states the molecule assumes a geometry different from that of the ground state.* For example, the eclipsed configuration of CH_3SH is adopted in the S_2 and T_2 states (cf. Figure 40).

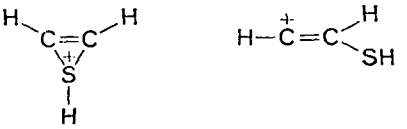
Similar observations were reported for the cases of CH_3OH[29] and FCH_2OH[36] and it seems therefore that such a phenomenon is not restricted to the thiol group.

C. *Special Structures involving the —SH Functional Group*

When a carbonium ion is generated adjacent to the —SH group, two alternative structures can arise *via* neighbouring group participation: a cyclic and linear cation. Although the phenomenon is applicable to both saturated and unsaturated systems only the latter, the vinyl cation problem,

is presented here. The calculations[30] were performed by V. Lucchini using a mixed basis set: minimal at C and H and double zeta at sulphur.

The fundamental problem is the relative stabilities of the cyclic structure and the linear cation.

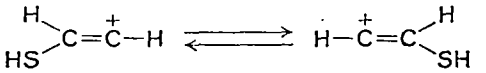


(148)

There are four *a priori* possibilities:

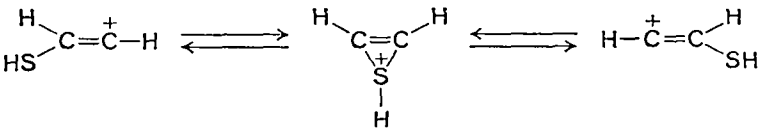
(a) only the cyclic ion is thermodynamically stable, therefore there is only one minimum on the energy hypersurface;

(b) only the linear ion is thermodynamically stable and the cyclic ion is a transient species only: this situation corresponds to an energy hypersurface with two equivalent minima associated with the two equivalent linear structures:



(149)

(c) both the linear and the cyclic structures are thermodynamically stable but the vinyl cation is more stable than the thiirenium ion. This represents a situation that corresponds to an energy surface having three minima: two equivalent lower minima and a higher one.



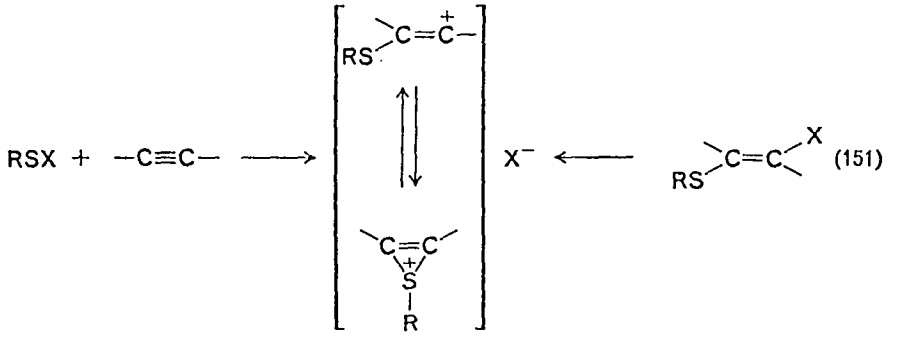
(150)

(d) the reverse of the previous situation, where the cyclic structure is more stable (lower minimum) than the linear structure (higher minima).

These four cases (a–d) are illustrated in Figure 41 (p. 89).

When the actual SCF computations are performed along the assumed reaction coordinate, the results reveal that the cyclic structure is more stable than the linear one, case (d). The computed energy curve is shown in Figure 42. (Note that Figure 42 shows only the right-hand side of the qualitative curve, Figure 41d.)

While these results were computed for the β-thiovinyl cation, they nevertheless explain some stereochemical aspect of the solvolyses of certain unsaturated compounds and the addition of RSX to acetylenes:

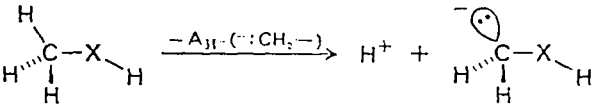


(151)

Another structure of special interest is one where the —SH group is adjacent to a carbanion centre. This corresponds to a tautomer of the thiolate ion just as the oxygen analogue is a tautomer of the corresponding alcoholate ion:

(152)

Since these structures are isoelectronic and isoprotic with H_2NOH and H_2NSH the conformational effects of the lone electron pairs are expected to be similar. Another point of interest is the effect of an adjacent SH or OH group on the gas phase acidity of the C—H bond:



(153)

Computations were carried out by L. M. Tel on CH_3OH[31], CH_3SH[32] and their corresponding anions, $^-$:CH_2—OH and $^-$:CH_2—SH. A double zeta quality basis set was used throughout the work but the geometry was not optimized; in fact, the bond angles about the carbon atom in the carbanions were assumed to be tetrahedral. Consequently the calculations can only indicate trends and not actual values in the energy differences.

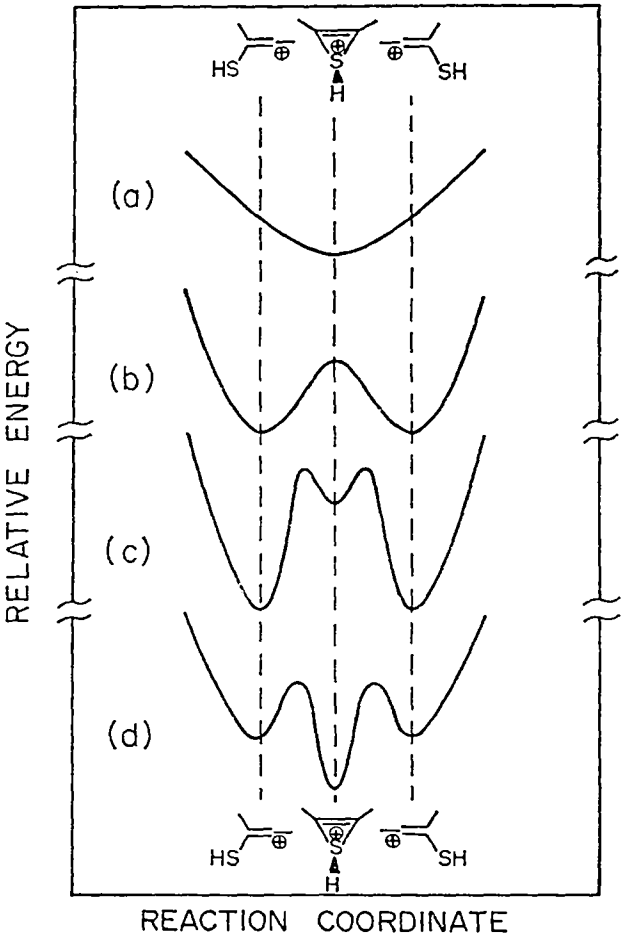


FIGURE 41. Potential energy curves of $C_2H_2SH^+$ assuming (a) only the cyclic structure is stable; (b) only the linear structure is stable; (c) the vinyl cation is more stable than the thiirenium ion; (d) the thiirenium ion is more stable than the vinyl cation.

The numerical data are summarized in Table 33 and illustrated in Figure 43. There are two stable structures in both carbanions corresponding to the Y and W arrangements* of the protons in $^-$:CH_2—OH the Y structure is more stable than the W structure while the situation is the opposite in the case of $^-$:CH_2—SH. This is clearly indicated in Figure 43.

* Y conformation:  . W conformation: 

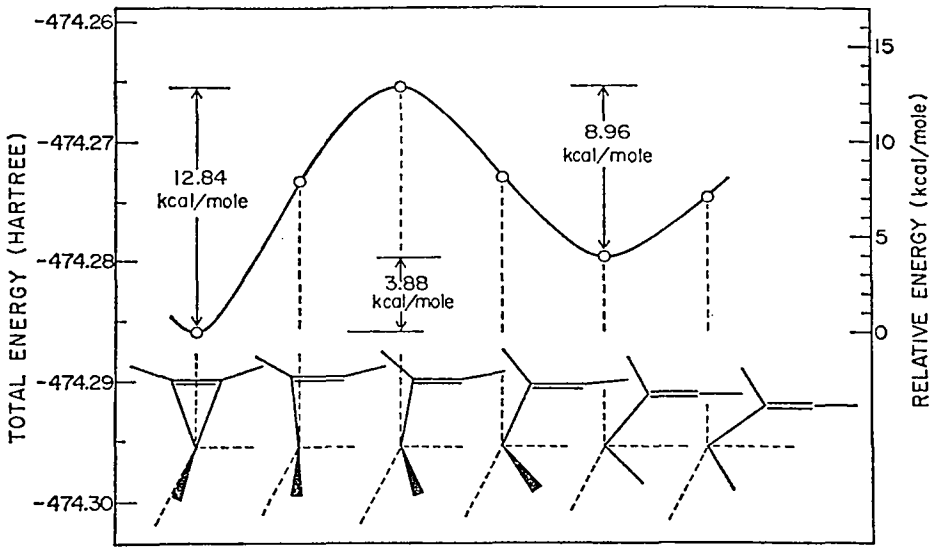


FIGURE 42. SCF potential energy curve of $C_2H_2SH^+$.

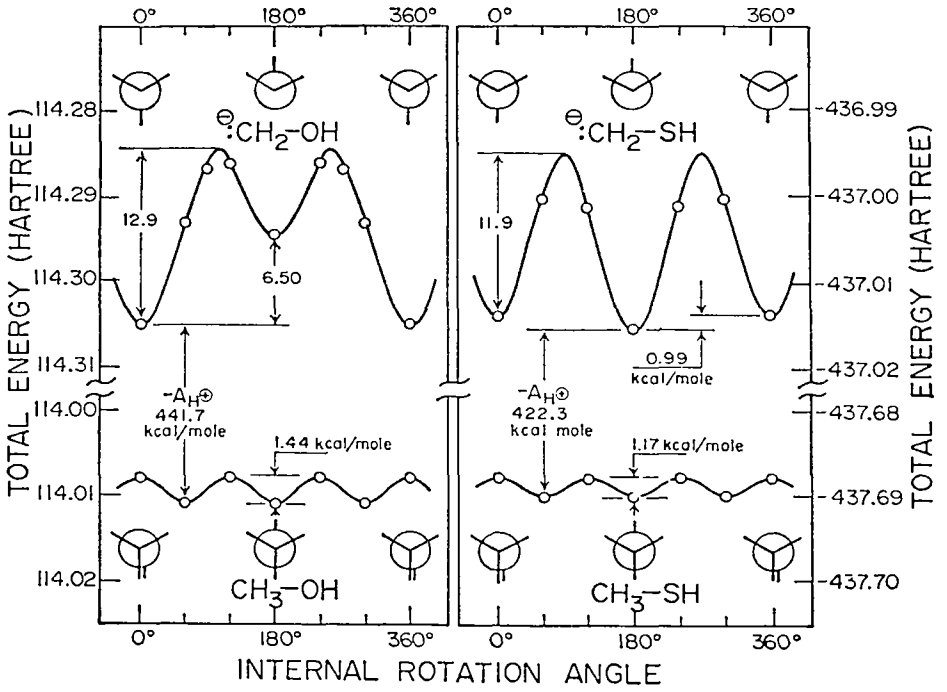


FIGURE 43. Total energies of $^-$:CH_2SH, CH_3SH, $^-$:CH_2OH and CH_3OH as a function of angle of internal rotation.

TABLE 33. Conformational energies of $^{-}$:CH_2OH, CH_3OH, $^{-}$:CH_2SH and CH_3SH

Species	Rotational angle			
	0°	60°	120°	180°
$^{-}$:CH_2—OH	−114·30505	−114·29316	−114·28616	−114·29469
CH_3OH	−115·00875	−114·01105	—	—
$^{-}$:CH_2—SH	−437·01398	−437·00044	−437·00131	−437·01555
CH_3—SH	−437·68839	−437·69026	—	—

The corresponding gas phase acidities, also shown in Figure 43, are the following:

$$\left.\begin{aligned} -A_{H^+}(^{-}:CH_2{-}OH) &= 0{\cdot}70370 \text{ hartree} = 441{\cdot}7 \text{ kcal/mole} \\ -A_{H^+}(^{-}:CH_2{-}SH) &= 0{\cdot}67284 \text{ hartree} = 422{\cdot}3 \text{ kcal/mole} \end{aligned}\right\} \quad (154)$$

Although these values indicate that the C—H bond next to an SH group is more acidic than that adjacent to OH, the numerical proton affinity values may change somewhat when the geometries are optimized.

At present, the gas phase acidity of the S—H bond in RS—H has not been calculated, but it is expected to be more acidic than that of the C—H bond since the CH_3—S^- tautomer is anticipated to be more stable than $^{-}$:CH_2—SH, by analogy to the CH_3—O^- and $^{-}$:CH_2—OH[31].

IV. ANALYSIS OF ELECTRON DISTRIBUTION

In this section the molecular wavefunctions will be analysed in order to obtain information about the electron distributions in CH_3OH and CH_3SH. The work was carried out by A. S. Denes and M. H. Whangbo using a double zeta quality basis set which did not include *d*-AO on sulphur. Any differences in the calculated properties of —OH and —SH are therefore not due to *d*-orbital participation on sulphur.

Population analyses and dipole moment values indicate that the charge separation in CH_3SH is not as extensive as that in CH_3OH. Furthermore, the valence electron shell sizes of the —OH and the —SH functional groups indicate that the magnitude of the electron density is more readily correlatable with physical properties than any other theoretical parameter: *it is suggested, therefore, that this parameter is the major factor which determines the differences in physical properties and chemical behaviour of alcohols and thiols.*

A. Charge Distribution and Dipole Moment

One way of expressing the separation of net charges in a molecule is by performing a Mulliken population analysis[33] on the computed wavefunction. This involves the following procedure. Every MO is doubly occupied and is built from atomic orbitals. A population matrix **P** is generated by analysing how the two electrons associated with each MO are distributed among the constituting atomic orbitals:

$$\mathbf{P} = 2\rho\mathbf{S} \tag{155}$$

where **S** and ρ are defined by equations (100) and (104) respectively. The populations are generated in terms of orthogonalized AO and the dimensions of the **P** matrix ($N \times N$) are the same as those of the AO basis (N).

The **P** matrix gives 'orbital by orbital' populations where the off-diagonal elements are frequently referred to as 'overlap populations'. The summation of those P_{ij} elements associated with a given atom A (both AO i and j are located on the same atom) reduces the 'orbital by orbital' population matrix **P** (cf. Figure 44) to an 'atom by atom'

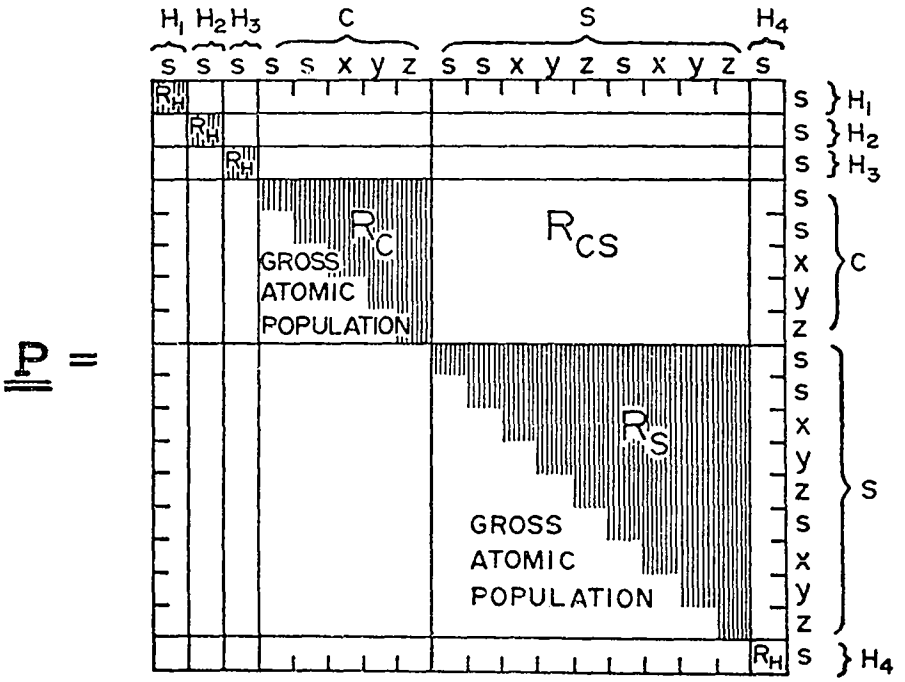


FIGURE 44. Orbital by orbital population matrix **P** for CH_3SH.

population matrix **R** (cf. Figure 45):

$$R_{AB} = \sum_{i}^{\substack{\text{AO on}\\ \text{atom A}}} \sum_{j}^{\substack{\text{AO on}\\ \text{atom B}}} P_{ij} \tag{156}$$

$\underline{\underline{R}} =$

H_1	H_2	H_3	C	S	H_4	
R_{H_1}	R_{HH}	R_{HH}	R_{HC}	R_{HS}	R_{HH}	H_1
	R_{H_2}	R_{HH}	R_{HC}	R_{HS}	R_{HH}	H_2
		R_{H_3}	R_{HC}	R_{HS}	R_{HH}	H_3
			R_C	R_{CS}	R_{CH}	C
				R_S	R_{SH}	S
					R_{H_4}	H_4

FIGURE 45. Atom by atom population matrix R for CH_3SH.

Note that R_{AB} is the number of electrons shared by atom A and atoms B therefore the sum $R_{AA}+\frac{1}{2}\sum' R_{AB}$ gives the total number of electrons for atom A. The second term, $\frac{1}{2}\sum' R_{AB}$ is necessary because only half of the shared electrons belong to A. The net charge (Q_A) associated with atom A is then given by

$$Q_A = Z_A - \left(R_{AA} + \tfrac{1}{2}\sum_{B}^{\substack{\text{all}\\ \text{atoms}}}{}' R_{AB}\right) \tag{157}$$

where Z_A is the nuclear charge of atom A and the summation is over all the atoms labelled B.

The charges for CH_3OH and CH_3SH computed with the aid of double zeta quality basis sets are shown in Figure 46. The values for the —OH and —SH groups are particularly significant since the δ^- charge on heteroatoms may be viewed as a measure of base strength and/or nucleophilicity while the δ^+ charge on H is associated with the acidic (electrophilic) character of the proton.

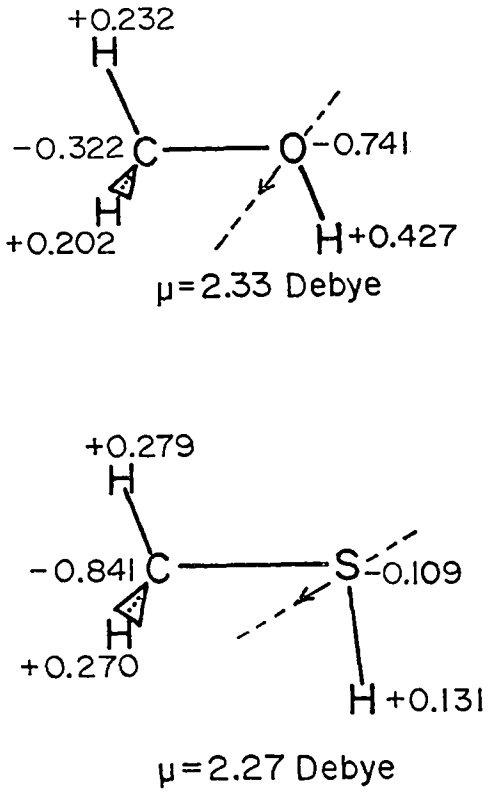


FIGURE 46. Net charges associated with the individual atoms in CH_3OH and CH_3SH. The ◁ sign signifies *two* H atoms, one in front of and one behind the plane of the paper, and *each* of these two has the positive charge shown.

Group charges between CH_3— and —SH (or —OH) can be obtained by summing the partial charges associated with the atoms of a functional group. The values are shown below:

$$\left.\begin{array}{c} +0{\cdot}314 \quad -0{\cdot}314 \\ CH_3{-}OH \\ -0{\cdot}022 \quad +0{\cdot}022 \\ CH_3{-}SH \end{array}\right\} \tag{158}$$

These charge separations may be interpreted as a measure of the electronic effects exerted by the functional groups —OH and —SH.

Another measure of charge separation is the dipole moment. Its operator is $\vec{r}$, which is also included in the classical definition (cf. equation 40), and since it operates on all electronic coordinates, the electronic dipole moment (μ_e) is computed as the expectation value of $\sum \vec{r}_i$ for the total electronic wavefunction:

$$\mu_e = \langle \Phi_0(1,2,\ldots,2M) | \sum_{i=1}^{2M} \vec{r}_i | \Phi_0(1,2,\ldots,2M) \rangle \tag{159}$$

If the total wavefunction $\Phi_0(1,2,\ldots,2M)$ is constructed in terms of localized molecular orbitals, ψ (equation 144),

$$\mu_e = \sum_{i=1}^{M} 2\langle \psi_i(1) | r_1 | \psi_i(1) \rangle = \sum_{i=1}^{M} \mu_e^i \tag{160}$$

then the summation includes all the 'bond moments' μ_e^i. The electronic component of the molecular dipole moment is the same if it is computed in terms of the CMO basis, ϕ,

$$\mu_e = \sum_{j=1}^{M} 2\langle \phi_j(1) | r_1 | \phi_j(1) \rangle \tag{161}$$

but the individual components over the LMO basis, μ_e^i (cf. equation 160), lend themselves to an easier visual interpretation.

The net results obtained for CH_3OH and CH_3SH are shown in Figure 46 and the components of this physical dipole (39) are summarized in Table 34.

TABLE 34. Computed dipole moment values[a] of CH_3OH and CH_3SH [b]

Dipole component	Eclipsed	Staggered	
	CH_3OH	CH_3OH	CH_3SH
μ_x (a.u.)	0·776	0·364	−0·515
μ_y (a.u.)	0·000	0·631	0·000
μ_z (a.u.)	−0·554	−0·559	−0·731
$\lvert\mu\rvert$ a.u.	0·955	0·918	0·895
$\lvert\mu\rvert$ Debye	2·43	2·33	2·27

[a] 1 a.u. of dipole moment = 2·54 Debye.
[b] Values for eclipsed CH_3SH have not been calculated.

B. Electron Density Contours

The electron density D_p associated with the pth MO is defined as $|\phi|^2$ or, more precisely, as $\phi, \phi^\dagger$:

$$D_p(x,y,z) = \phi_p(x,y,z)\,\phi^\dagger(x,y,z) \tag{162}$$

where $\phi^\dagger$ is the transpose of ϕ. The density may be calculated at any point (x,y,z) of the three-dimensional physical space in terms of the AO basis $\{\eta\}$ and the MO coefficient matrix $\mathbf{C}$:

$$D_p \equiv \phi_p\,\phi_p^\dagger = f_p(\eta_1\,\eta_2 \cdots \eta_N) \begin{pmatrix} C_{1p} \\ C_{2p} \\ \vdots \\ C_{Np} \end{pmatrix} (C_{1p}\,C_{2p} \cdots C_{Np}) \begin{pmatrix} \eta_1 \\ \eta_2 \\ \vdots \\ \eta_N \end{pmatrix}$$

$$= f_p(\eta_1\,\eta_2 \cdots \eta_N) \begin{pmatrix} \rho_{11}^p & \rho_{12}^p & \cdots & \rho_{1N} \\ \rho_{21} & \rho_{22} & \cdots & \rho_{2N}^p \\ \vdots & \vdots & & \vdots \\ \rho_{N1}^p & \rho_{N2}^p & \cdots & \rho_{NN}^p \end{pmatrix} \begin{pmatrix} \eta_1 \\ \eta_2 \\ \vdots \\ \eta_N \end{pmatrix} \tag{163}$$

where $\boldsymbol{\rho}^p$ is the density matrix of the pth MO. When summed up over all occupied MO, it yields the total density matrix $\boldsymbol{\rho}$ specified by equation (104):

$$\rho_{ij} = \sum_{p=1}^{M} \rho_{ij}^p \tag{164}$$

Thus D_p may be written in the following abbreviated notation:

$$D_p(x,y,z) = f_p\,\boldsymbol{\eta}(x,y,z)\,\boldsymbol{\rho}^p\,\boldsymbol{\eta}(x,y,z)$$

$$= f_p \sum_{i=1}^{N} \sum_{j=1}^{N} \eta_i(x,y,z)\,\rho_{ij}^p\,\eta_j(x,y,z) \tag{165}$$

Note that the factor f_p is the integrated spin part of the orbital, which is 2 if the orbital is doubly occupied, 1 if it is singly occupied and 0 if it is empty. The sum of the M doubly occupied MO densities is then

$$D(x,y,z) = \sum_{p=1}^{M} D_p(x,y,z) = 2 \sum_{i=1}^{N} \sum_{j=1}^{N} \eta_i(x,y,z)\,\rho_{ij}\,\eta_j(x,y,z) \tag{166}$$

The problem is simply to calculate the individual orbital electron density values D_p at every intersection of a given mesh around the molecule. In practice, 1600 points, that is, a 40×40 mesh, provide a fine

enough grid for a 10×10 bohr^2 (nearly 5×5 Å^2) area. Special purpose programs may be used to interpolate electron densities so that the density contours may be recorded by a two-dimensional (X, Y) plotter connected to the computer[34].

If the coefficient matrix **C** transforms the AO basis to the CMO basis then the densities of the CMO are generated. If the coefficient matrix however connects the AO to LMO then the LMO densities are obtained.

CMO densities associated with CH_3SH are similar to those of CH_3OH[35]. The LMO densities for CH_3OH and CH_3SH are illustrated in Figures 47 and 48 respectively. These density contours are analogous in many ways to the LMO plots obtained for FCH_2OH[36].

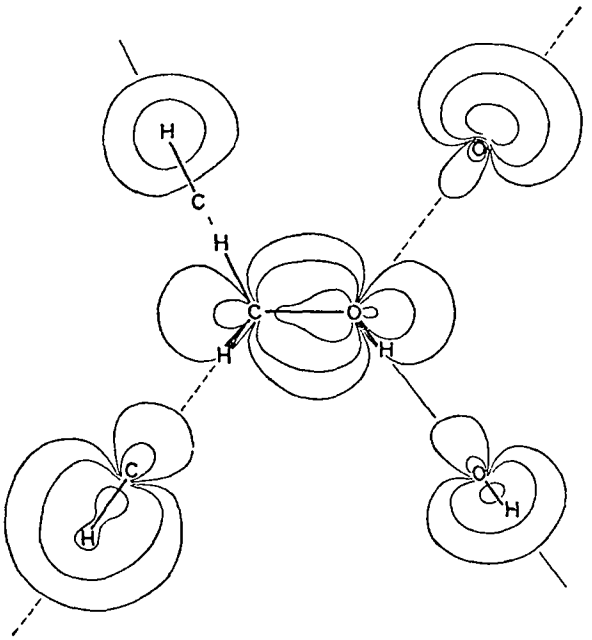


FIGURE 47. Localized molecular orbital density contours of CH_3OH. The LMO of the lone pairs and bonding pairs are projected out for ease of presentation.

C. *The Sizes and Shapes of Electron Pairs and Functional Groups*

An electron pair 'a' may be described by a localized molecular orbital ψ_a. The expectation values of the first (r) and the second (r^2) moment operators, in terms of these LMO, may be used to define the centroids of charge and the sizes and shapes of the electron pairs respectively[37].

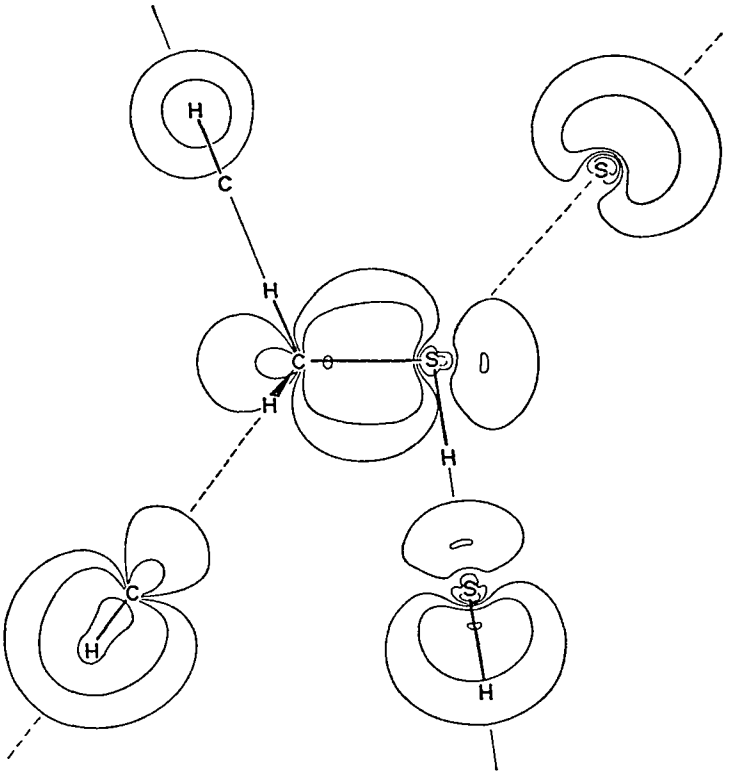


FIGURE 48. Localized molecular orbital density contours of CH_3SH. The LMO of the lone pairs and bonding pairs are projected out for ease of presentation.

The centroid of charge, with respect to an arbitrary coordinate system, is given in terms of the components (x_a, y_a, z_a) of the first moment $\langle r \rangle_o$:

$$\left.\begin{aligned} x_a \equiv \langle x \rangle_o &= \langle \psi_a | x | \psi_a \rangle \\ y_a \equiv \langle y \rangle_o &= \langle \psi_a | y | \psi_a \rangle \\ z_a \equiv \langle z \rangle_o &= \langle \psi_a | z | \psi_a \rangle \end{aligned}\right\} \tag{167}$$

where the subscript o indicates that the centroid of charge is expressed with respect to the origin of the arbitrary coordinate system. The following geometrical relationship holds for the distance of the centroid of charge (R_a) measured from the arbitrary origin:

$$R_a = |\langle r \rangle_o| = \sqrt{\langle x \rangle_o^2 + \langle y \rangle_o^2 + \langle z \rangle_o^2} = \sqrt{x_a^2 + y_a^2 + z_a^2} \tag{168}$$

The size of an electron pair 'a' may then be defined as the expectation value of a spherical quadratic (second moment) operator (r^2) evaluated at the centroid of charge (R_a) defined by the coordinates x_a, y_a, z_a:

$$\left.\begin{aligned}\langle r^2\rangle_{R_a} &= \langle (x-x_a)^2\rangle + \langle (y-y_a)^2\rangle + \langle (z-z_a)^2\rangle \\ &= \langle x^2\rangle_0 - 2x_a\langle x\rangle_0 + x_a^2 + \langle y^2\rangle_0 - 2y_a\langle y\rangle_0 + y_a^2 + \langle z^2\rangle_0 \\ &\quad - 2z_a\langle z\rangle + z_a^2 \\ &= \langle x^2\rangle - 2x_a^2 + x_a^2 + \langle y^2\rangle_0 - 2y_a^2 + y_a^2 + \langle z^2\rangle_0 - 2z_a^2 + z_a^2\end{aligned}\right\} \quad (169)$$

or:

$$\left.\begin{aligned}\langle r^2\rangle_{R_a} &= \langle x^2\rangle_0 + \langle y^2\rangle_0 + \langle z^2\rangle_0 - (x_a^2 + y_a^2 + z_a^2) \\ &= \langle x^2\rangle_0 + \langle y^2\rangle_0 + \langle z^2\rangle_0 - R_a^2 \\ &= \langle r^2\rangle_0 - R_a^2 \\ &= \langle r^2\rangle_0 - \langle r\rangle_0^2\end{aligned}\right\} \quad (170)$$

where $\langle r^2\rangle_0$ is the second moment of a given LMO, ψ_a, with respect to the arbitrary origin:

$$\langle r^2\rangle_0 = \langle \psi_a | r^2 | \psi_a \rangle \quad (171)$$

It is more practical, however, to collect the x, y and z components as shown below, in order to have an explicit expression for the components labelled $\langle x^2\rangle_{R_a}$, $\langle y^2\rangle_{R_a}$ and $\langle z^2\rangle_{R_a}$:

$$\left.\begin{aligned}\langle r^2\rangle_{R_a} &= \langle r^2\rangle_0 - R_a^2 = \langle r^2\rangle_0 - \langle r\rangle_0^2 \\ &= \{\langle x^2\rangle_0 - \langle r\rangle_0^2\} + \{\langle y^2\rangle_0 - \langle y\rangle_0^2\} + \{\langle z^2\rangle_0 - \langle z\rangle_0^2\} \\ &= \langle x^2\rangle_{R_a} + \langle y^2\rangle_{R_a} + \langle z^2\rangle_{R_a}.\end{aligned}\right\} \quad (172)$$

The shape of an electron pair 'a' may be identified with the three components of the size defined in equation (172), and these are characteristic of an ellipsoid[38]. However, the arbitrary coordinate system (x, y, z) may not be in alignment with major and two minor axes of the ellipsoid. Consequently it may be desirable to rotate the arbitrary coordinate system to a new one (x', y', z') which is now parallel to the major and minor axes of the ellipsoid. In this new coordinate system the size may be written in terms of its new components,

$$\langle r^2\rangle_{R_a} = \langle x'^2\rangle_{R_a} + \langle y'^2\rangle_{R_a} + \langle z'^2\rangle_{R_a} \quad (173)$$

which will uniquely define the shape of the electron pair but do not alter the numerical value of the size.

Both the spherical average, $\langle r^2\rangle_{R_a}$, which is a measure of size, and its components $\langle x'^2\rangle_{R_a}$, $\langle y'^2\rangle_{R_a}$ and $\langle z'^2\rangle_{R_a}$ which are related to the shape

(i.e. to the length of the major and minor axes of the ellipsoid), are graphically illustrated together with the centroid of charge $\langle r \rangle_o$, in Figure 49.

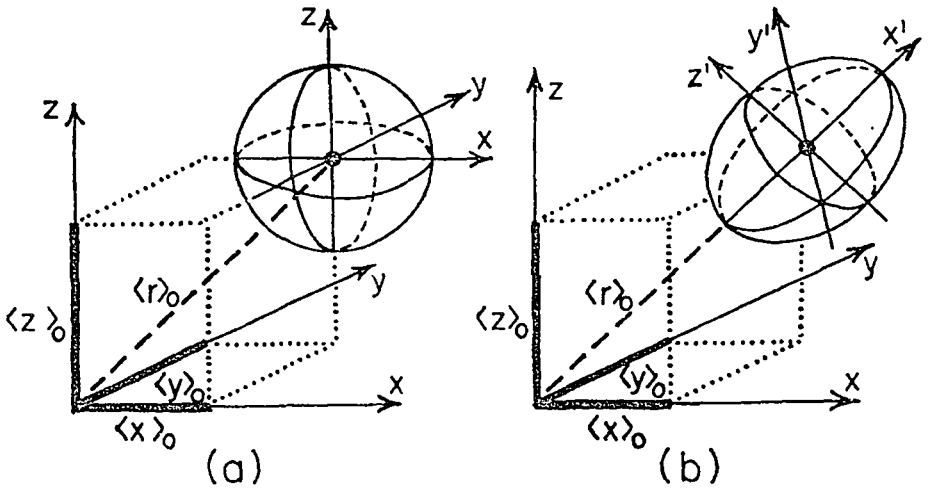


FIGURE 49. Spherical average, $\langle r^2 \rangle_{R_a}$ (a), and the ellipsoidal components, $\langle x'^2 \rangle_{R_a}$ $\langle y'^2 \rangle_{R_a}$ and $\langle z'^2 \rangle_{R_a}$, (b), of an electron pair, together with the centroid of charge, $\langle r \rangle_o$.

The centroids of charge, shapes and sizes of localized electron pairs in the staggered conformations of CH_3—OH and CH_3—SH are summarized in Tables 35 and 36 respectively. These values reveal that the lone pairs, associated with basicity or nucleophilicity of the heteroatoms and the X—H bonding pairs which are associated with acidity or electrophilicity of CH_3XH, are larger for the X = S case than X = O.

Since gas phase acidity and gas phase basicity are measured by energy differences, this means therefore that energy and size are correlatable. A similar conclusion may be drawn when the sizes of a group of electron pairs in a functional group are compared (cf. Table 37), particularly the valence shell sizes of the —OH and —SH functional groups as illustrated in Figure 50 (p. 103).

Since an experimental energy difference, ΔE_{exp}, such as bond energy, excitation energy, ionization potential, electron and proton affinity, rotational barrier height etc. is related to the theoretical energy difference, ΔE_{theor}, computed within the framework of quantum mechanics, and this in turn is a function of the electron density difference, $\Delta\rho$,

$$\Delta E_{exp} \approx \Delta E_{theor} = f(\Delta\rho) \tag{174}$$

TABLE 35. Centroids of charge, shapes and sizes of localized electron pairs in CH_3OH

Electron pair	Centroid (bohr)				Shape (bohr²)			Size[a]
	$\langle x \rangle$	$\langle y \rangle$	$\langle z \rangle$	$\langle r \rangle$	$\langle x'^2 \rangle$	$\langle y'^2 \rangle$	$\langle z'^2 \rangle$	$\langle r^2 \rangle^{\frac{1}{2}}$
O (core)	−0·000065	−0·000112	−1·349232	1·349232	0·025296	0·024304	0·023250	0·269909
C (core)	−0·000001	0·000001	−1·349333	1·349333	0·042665	0·041052	0·040646	0·352652
CO	0·024662	0·042716	0·296284	0·30059	1·296919	0·476314	0·473488	1·498906
CH_1	1·310329	0·006841	−1·810463	2·234901	1·131661	0·685893	0·665469	1·575760
$CH_{2,3}$	−0·649243	±1·138211	−1·810483	2·234924	1·121647	0·685902	0·665456	1·575754
OH	0·466559	0·808106	1·643307	1·889753	0·928661	0·463405	0·441244	1·353997
$lp_{1,2}$	0·316992	±0·487092	1·513811	1·621517	0·725605	0·490822	0·455927	1·293195

[a] $\langle r^2 \rangle^{\frac{1}{2}}$ *is the spherical average in Bohr atomic units.*

TABLE 36. Centroids of charge, shapes and sizes of localized electron pairs in CH_3SH

Electron pair	Centroid (bohr)				Shape (bohr²)			Size[a]
	$\langle x \rangle$	$\langle y \rangle$	$\langle z \rangle$	$\langle r \rangle$	$\langle x'^2 \rangle$	$\langle y'^2 \rangle$	$\langle z'^2 \rangle$	$\langle r^2 \rangle^{\frac{1}{2}}$
S (1s core)	0·000255	0·000000	3·537653	3·537652	0·007405	0·007277	0·007115	0·147640
C (1s core)	−0·000031	0·000000	0·000174	0·000177	0·043559	0·041894	0·041723	0·356618
S (L-shell)	0·127096	0·184350	3·533886	3·540972	0·101946	0·069227	0·068304	0·489365
	0·127228	−0·184249	3·533820	3·540906	0·101942	0·069235	0·068306	0·489370
	−0·127594	−0·000082	3·719974	3·721992	0·099694	0·071720	0·062149	0·483283
	−0·139106	−0·000019	3·354534	3·347416	0·100877	0·072731	0·061130	0·484497
CS	−0·009336	0·000000	1·763735	1·763759	2·387784	0·870793	0·865900	2·030881
CH_1	1·264048	0·000000	−0·435549	1·333756	1·200517	0·691568	0·686943	1·605934
$CH_{2,3}$	−0·639478	±1·101502	−0·484957	1·362872	1·141592	0·696491	0·686764	1·588976
SH	−1·643185	0·000000	3·728709	4·074717	1·764071	0·823971	0·823046	1·846912
$lp_{1,2}$	0·338915	±0·879760	3·834536	3·948734	1·430027	1·075888	1·052900	1·886481

[a] $\langle r^2 \rangle^{\frac{1}{2}}$ is the spherical average in Bohr atomic units.

TABLE 37. Group sizes in CH_3OH and CH_3SH

Group	Compound	$\langle x'^2 \rangle$	$\langle y'^2 \rangle$	$\langle z'^2 \rangle$	$\langle r^2 \rangle^{\frac{1}{2}}$ [a]
		bohr^2			bohr
CH_3— (valence shell)	CH_3OH	3·3950	2·0577	1·9664	2·7293
CH_3— (valence shell)	CH_3SH	3·4248	2·0895	2·0603	2·7522
—OH (valence shell)	CH_3OH	2·1768	1·4724	1·3677	2·2399
—SH (valence shell)	CH_3SH	4·2901	3·2277	3·158714	3·2675
—SH (L+valence shells)	CH_3SH	10·0103	7·5313	7·3703	4·9912

[a] $\langle r^2 \rangle^{\frac{1}{2}}$ is the spherical average.

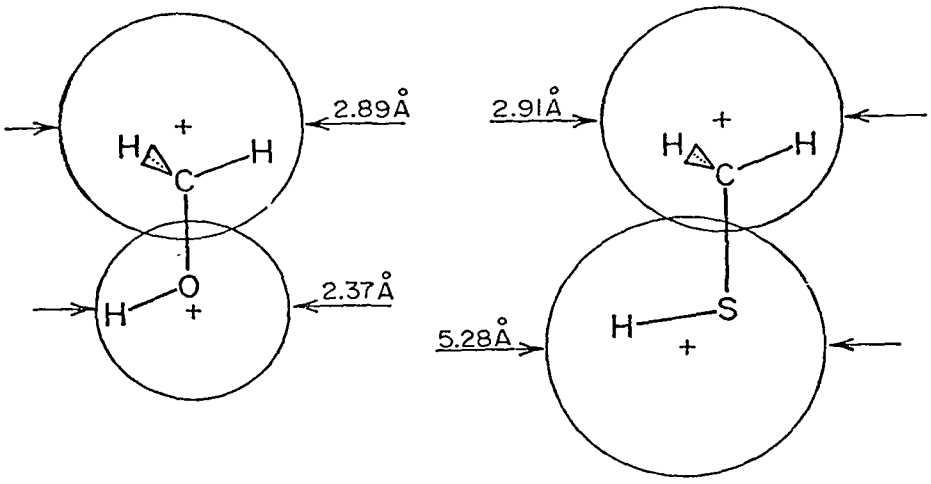


FIGURE 50. Valence shell sizes of the functional groups in CH_3SH and CH_3OH.

(cf. equation 106 for $E = E(\rho)$), it is immediately apparent that the most fundamental correlation in theoretical chemistry involves ΔE and $\Delta\rho$. A critical review of the four methods of analysing the electron distribution shows that:

(i) the Mulliken population analysis is too arbitrary,
(ii) the dipole moment value is too compact,
(iii) the electron density plots are too cumbersome to be of practical use.

It can therefore be concluded that *the 'size', i.e.* $\langle r^2 \rangle_{R_n}$, *of the electron cloud of a functional group such as* —*OH or* —*SH is the most convenient representative of the density* ρ *that should be correlated with those physical properties which involve energy or energy differences.*

V. CONCLUDING REMARKS

In this introductory chapter the general methods employed in the computations of molecular wavefunctions and energies were outlined (section II). Calculated energy differences (section III) for some representative —OH and —SH containing compounds were than compared with those physical properties which involve energy differences (section I).

According to one of the postulates of quantum theory the theoretical energy difference, ΔE_{theor}, should approach, in the limiting sense, the experimental energy difference when completeness is achieved in the computation:

$$\Delta E_{\text{exp}} = \lim_{N \to \infty} \Delta E_{\text{theor}} \tag{175}$$

Thus any discrepancy observed between ΔE_{theor} and ΔE_{exp} is due to a limited expansion ($N \ll \infty$) of the state wavefunction (Ψ) in terms of electronic configurations (Φ) as indicated by equation (139) or of the MO (ϕ) in terms of AO (η) as specified by equation (140).

Because only fairly limited expansions have been achieved in the case of RSH compounds some numerical discrepancy can be expected in the results reviewed in this chapter. However, the degree of such discrepancy varies with the nature of the problem. In some cases (e.g. conformational barrier heights or proton affinities) the correlation between ΔE_{exp} and ΔE_{theor} was encouraging, while in other cases (ionization potentials, hydrogen and electron affinities) the correlations were not very good.

Basically there are two possible reasons for the discrepancies: one is associated with the variation in the correlation energy and the other one is related to the numerical proximity of the SCF energy (E_{SCF}) to the energy at the Hartree–Fock limit (E_{HFL}). The former could be accounted for if an accurate expansion in the correlated wavefunction (i.e. $N \to \infty$ in equation 139 could be achieved), this, however, has not even been attempted for thiols. The latter problem could be eliminated with a complete expansion ($N \to \infty$ in equation 140) of the Hartree–Fock MO. Again, in the former case ΔE_{theor} would be identified with ΔE_{NRL} (the energy difference at the non-relativistic limit) while in the latter case

ΔE_{theor} could be equated with ΔE_{HFL} (the energy difference at the Hartree–Fock limit). In practice, through the SCF procedure, one obtains only near molecular Hartree–Fock wavefunctions and here we have to take ΔE_{SCF} as the value for ΔE_{theor}. This leads us to the following relation if we are concerned with an ionization phenomenon.

$$\Delta E_{\text{SCF}} \lesssim \Delta E_{\text{HFL}} < \Delta E_{\text{NRL}} \approx \Delta E_{\text{exp}} \tag{176}$$

The single inequality is due to the fact that in an ionization process two electrons are unpaired therefore the correlation energy of the radical ion (M^+) is less by about 0·065 hartree (cf. equation 73) than the correlation energy of the parent molecule (M). The double inequivalence in equation

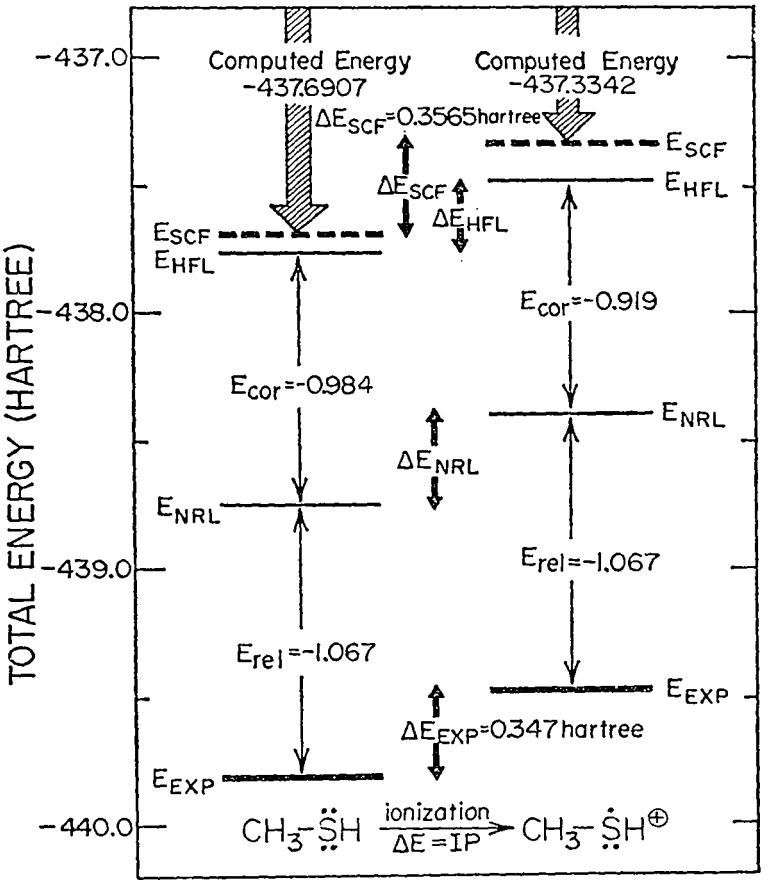


FIGURE 51. A comparison of theoretical energy differences (ΔE_{NRL}, ΔE_{HFL}, ΔE_{SCF}) with the experimental energy difference (ΔE_{exp}) associated with the ionization of CH_3SH.

(176) is due to the fact that the same basis set applied in the SCF calculations will produce energy values that approximate the HFL of M and M^+ to different degrees of accuracy. Note that the single inequality in this relation (176) is associated with the first reason and the double inequality is related to the second reason of discrepancy presented at the beginning of this paragraph. All those features are clearly illustrated in Figure 51 for the ionization process involving CH_3SH.

In contrast, the internal rotation in CH_3SH does not involve any electron unpairing therefore the correlation between the experimental

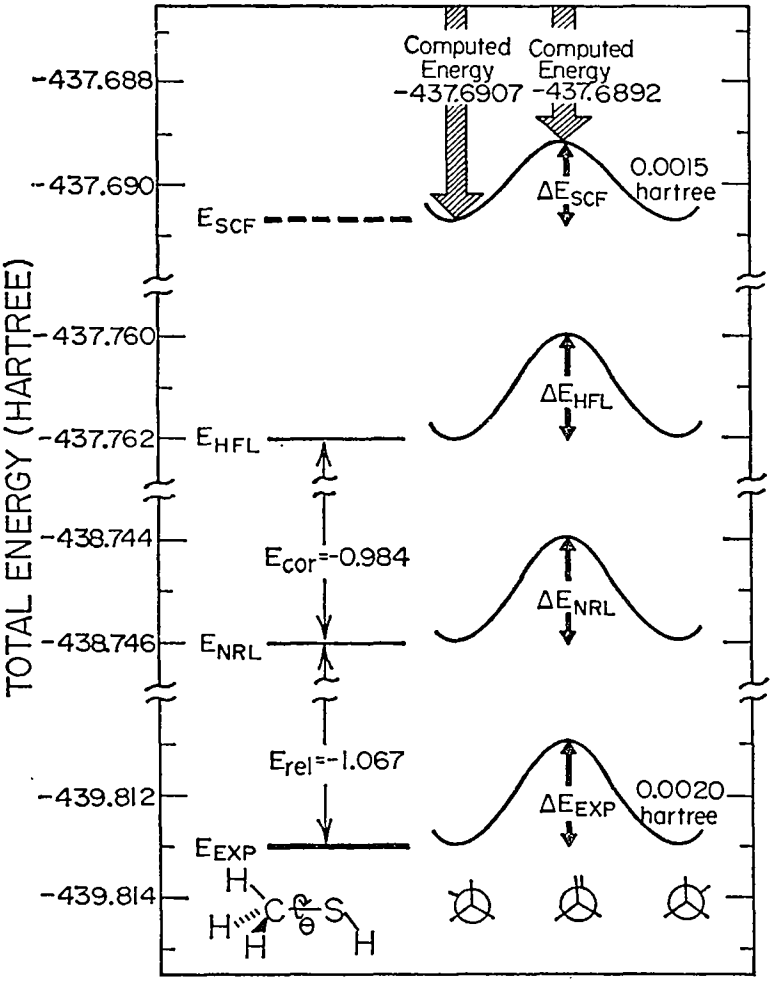


FIGURE 52. A comparison of theoretical energy differences (ΔE_{NRL}, ΔE_{HFL}, ΔE_{SCF}) with the experimental energy difference (ΔE_{exp}) associated with the internal rotation of CH_3SH.

(ΔE_{exp}) and theoretical (ΔE_{SCF}) barrier heights is expected to be considerably better:

$$\Delta E_{\text{SCF}} \approx \Delta E_{\text{HFL}} \approx \Delta E_{\text{NRL}} \approx \Delta E_{\text{exp}} \tag{177}$$

as illustrated in Figure 52. More important than the actual numerical accuracy in reproducing ΔE_{exp} by ΔE_{theor} is the fact that with present-day computer technology and programming capability an avenue has been opened to *calculate energy differences* (ΔE_{theor}) *from first principles*. The improvement in numerical accuracy ensuring $\Delta E_{\text{exp}} \approx \Delta E_{\text{theor}}$ for almost all chemical processes is surely to come with time.

However, numerical reproduction of ΔE_{exp} may not be the ultimate utility of quantum chemistry. In fact, the advancement of our fundamental understanding of a chemical problem is only partially tied to energy. It is the electron density (ρ) that defines the physical system and this is the quantity that determines everything else including the total energy:

$$E = E(\rho) \tag{178}$$

Since we can calculate ρ more accurately that ΔE some suitable analysis of ρ or $\Delta\rho$ is highly desirable. It has been shown that the size of electron pairs: $\langle r^2 \rangle_{R_a}$ or the size of a set of electron pairs which constitute a functional group, such as —OH or —SH, is related to ρ, yet it is a quantity that can easily be related to chemical concepts. It is therefore hoped that this quantity: $\langle r^2 \rangle_{R_a}$ will be successfully correlated with both the experimental and theoretical ΔE values.

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The Chemistry of the Thiol Group
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CHAPTER 2

Structural chemistry of the thiol group

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I. INTRODUCTION

In this section, an attempt is made to bring together such information as has been obtained on structures containing the thiol group, in the crystal, in solution and in the gas phase. In many ways the information obtained from studies on these three states is complementary. X-ray diffraction results usually provide definite and fairly precise answers on geometrical properties as they pertain in the solid state. Details such as bond lengths, bond angles, torsion angles and hydrogen bonding participation can usually be obtained from diffraction studies with a high degree of certainty. The method, however, suffers from the disadvantages that the molecules are in a high state of aggregation, are usually required by the nature of the crystal lattice to exist in a single conformation, and certain

intermolecular interactions that would be of less importance in the gas or in solution tend to be the major stabilizing influences. An additional disadvantage of X-ray analysis lies in its relative insensitivity to hydrogen atoms. This is clearly a major problem when dealing with a function such as the thiol group. When the hydrogen atom is bonded to a relatively 'heavy' atom like sulphur, its location in X-ray structure analysis becomes even more difficult. This limitation can be overcome by neutron diffraction studies as the scattering power of a hydrogen atom toward neutrons is much greater, yet the facilities for such studies are still not widely available, and the requirements in terms of crystal size, etc., are more stringent than is the case with X-ray diffraction. The lack of even a single neutron diffraction study on a compound containing a thiol group severely limits discussion of several topics in this review. Nevertheless, despite these several drawbacks, the X-ray diffraction method remains the method of choice for establishing detailed structural information on complex and moderately complex molecules.

Electron diffraction and microwave studies are able to provide highly accurate structural information on small molecules in the gas phase. These methods can also provide detailed results for bond lengths, angles and molecular conformation. However, their applicability is quite limited as to molecular complexity, and difficulty can be encountered when numerous conformers coexist.

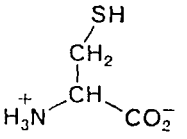
Infrared spectroscopic and nuclear magnetic resonance investigations on solutions cannot yield detailed bond lengths and angles, but can often produce important information on conformations, and they are well suited to examining molecular interactions and dynamic effects that are less susceptible to analysis by the diffraction techniques.

In this review of the structural chemistry of the thiol group, examples will be given of results obtained by all of the above methods. A necessarily short survey of the limited X-ray information on bond lengths, angles and conformations of molecules containing the thiol group will be followed by a somewhat critical description of certain structures that have been reported in the literature to contain thiol groups, but where considerable doubt can be raised on this point. That section then leads to a discussion of the relative occurrence of thiol : thione tautomers in the solid state. Next, there is a survey of the results obtained on simple thiols in the gas phase by electron diffraction and microwave methods and this is followed by a brief description of some of the results obtained by spectroscopic and resonance techniques in solution. Finally, there is a discussion of the hydrogen-bonding properties of sulphur both as a donor S—H···B and as an acceptor A—H···S. While there is considerable evidence regarding

the ability of sulphur to act as an acceptor and a fair amount of work has been done on its donor properties in solution, very little evidence has ever been gathered together on the hydrogen-bonding capabilities of the thiol group in the solid state.

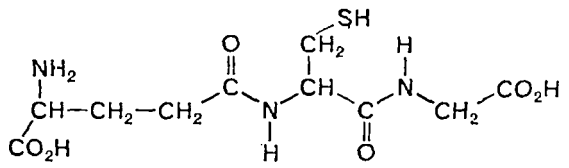
II. MOLECULAR DIMENSIONS AND CONFORMATIONAL INFORMATION OBTAINED FROM X-RAY CRYSTALLOGRAPHIC STUDIES

The literature relating to X-ray diffraction studies on molecules containing the thiol group is disappointingly, and rather surprisingly, meagre. Such work as does exist has been mainly on L-cysteine (**1**) and derivatives. To

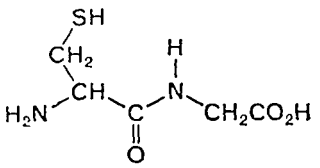


(1)

add to our disappointment, a great deal of this work has failed to reveal quite significant geometric details. X-ray analyses have been carried out on both the monoclinic[1] and orthorhombic forms[2] of L-cysteine; structures have also been determined for L-cysteine hydrochloride monohydrate[3], the 1 : 1 complex of L-cysteine ethyl ester hydrochloride and urea[4] and for the tripeptide, glutathione (**2**)[5]. The value of an early study on the dipeptide cysteylglycine (**3**) as the 2 : 1 sodium iodide complex[6] suffers



(2)



(3)

from a severe lack of experimental data and from a low degree of refinement.

The lengths obtained for the C—S bond in the various X-ray diffraction studies are listed in Table 1. To some extent, the reliability of these analyses can be gauged from the quoted *R*-factors. The *R*-factor, defined

TABLE 1. Molecular dimensions of the thiol group

	C—S (Å)	S—H (Å)	C—S—H (deg)	Method of data collection	Final *R*-factor	Ref.
X-ray diffraction results						
L-cysteine (**1**) (monoclinic)[a]	1·86 (1)[b] 1·77 (1)	—[c] —	—[c] —	Photographic[d]	0·127	1
L-cysteine (orthorhombic)[e]	1·811 (3)	—[c]	—[c]	Counter	0·037	2
L-cysteine hydrochloride monohydrate	1·801 (16)	—[c]	—[c]	Photographic	0·121	3
L-cysteine ethyl ester hydrochloride : urea (1 : 1)	1·772 (16)	—[c]	—[c]	Counter	0·092	4
Glutathione (**2**)	1·78 (3)	—[c]	—[c]	Photographic	0·21	5
Cysteylglycine : NaI[f] (2 : 1)	1·64	—[c]	—[c]	Photographic	0·14	6
Electron diffraction results						
Methanethiol (**4**)[g]	1·82 (1)	—	—			7
Ethane-1,2-dithiol (**5**)	1·819 (2)	1·40 (2)	90°30′ (3°12′)			8
Microwave analysis						
Methanethiol[h]	1·819 (5)	1·335 (10)	96°30′ (30′)			9
Sum of covalent[i] radii	1·81	1·41				12

[a] There are two crystallographically independent molecules in the monoclinic form of L-cysteine. The large discrepancy between the C—S lengths in the two molecules was attributed to the error that arises from neglect of proper treatment of anomalous dispersion in polar space groups; the space group was $P2_1$.

[b] The figures in parentheses given here and elsewhere in the review refer to the estimated standard deviations from the results of the analysis. If there are no significant systematic errors in the analysis, then, as a rough guide, one can say that there is one chance in a thousand that the value of the parameter given differs by as much as three times the estimated standard deviation from the true value of that parameter.

[c] The thiol hydrogen was not located.

[d] Towards the end of the data collection, some effects, attributed to oxidation of the sample, were noted.

[e] An abnormal value for the b_{33} component of the anisotropic temperature factor for sulphur was obtained. This anomaly may indicate disorder which may be responsible for the failure to locate the thiol hydrogen atom in an otherwise well-determined structure.

[f] Only very limited intensity data were recorded.

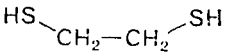
[g] Only the C—S length was given in the tabulation in reference 7. No details of the analysis were provided.

[h] This result is in good agreement with several earlier studies[10, 11].

[i] The values of the covalent radii were taken from reference 12.

as $\Sigma||F_{obs}|-|F_{calc}||/|\Sigma|F_{obs}|$, is a measure of the agreement between the observed structure amplitudes and those calculated on the basis of the model for the structure. With photographic data, *R*-factors less than 0·13–0·14 indicate fairly well-refined structures, while *R*-factors about 0·20 imply either that the measured intensities are quite inaccurate or that there is something significantly wrong with the structural model, although not to the extent that the overall molecular structure is incorrect. When the reflection data are measured by counters, usually on an automatic diffractometer, *R*-factors below 0·05 can be obtained in careful work. While there are certainly more reliable indicators of the accuracy of the results obtained from an X-ray analysis than the *R*-factor (which has gained a certain notoriety in this respect), it is still the most convenient and a reasonably reliable indicator of the overall quality of an analysis. If the results obtained from the more reliable X-ray analyses, i.e. those on the orthorhombic form of L-cysteine[2], on the hydrochloride salt of L-cysteine[3], and on the 1 : 1 urea complex[4], are compared with those obtained by electron diffraction[7,8] and microwave methods[9-11], and with the sum of the covalent radii for sulphur and carbon[12], then there is general agreement that the C(sp^3)—S bond length is in the range 1·77–1·82 Å. The agreement is even more impressive, if only the C—S length (1·811 (3) Å) from the most accurate X-ray analysis, that on the orthorhombic form of L-cysteine, is compared with the result (1·819 (5) Å) from the microwave data obtained on methanethiol (**4**) and with that (1·819 (2) Å) resulting from the electron diffraction study on ethane-1,2-dithiol (**5**). The very poor agreement between the C—S lengths in the

(4)

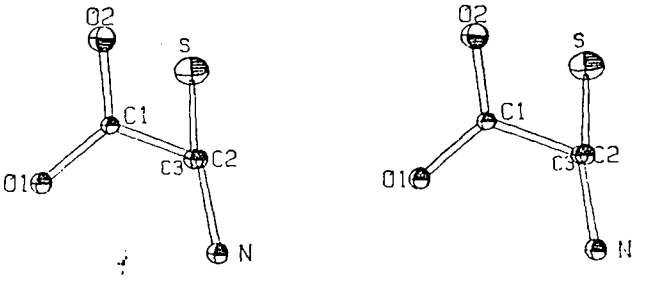


(5)

two molecules of L-cysteine in the monoclinic crystalline modification is possibly a result of a neglect of the dispersion effects encountered in polar non-centrosymmetric space groups, as was suggested by the authors[1]. However, there were some other disturbing factors about this analysis, such as apparent oxidation of the sample and the appearance of some large maxima and minima on the final difference map. There are no reliable X-ray data on C(sp^2)—S(H) or C(aromatic)—S(H) lengths.

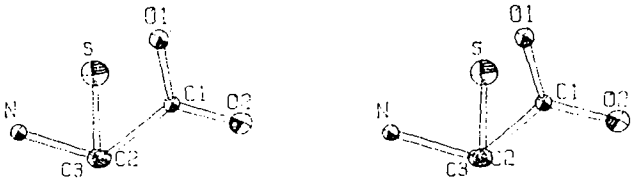
The thiol hydrogen atom was not located in any of the crystal structure determinations listed in Table 1. This is particularly surprising in the case of the orthorhombic form of L-cysteine[2] as all other hydrogen atoms were

(a)



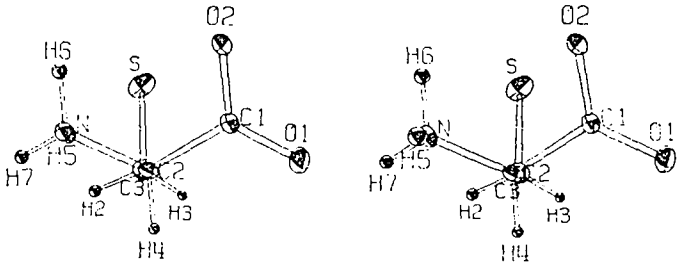
Monoclinic L – cysteine molecule B

(b)



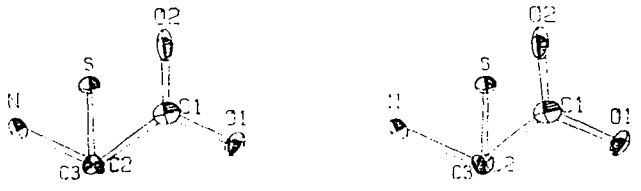
Monoclinic L – cysteine molecule A

(c)



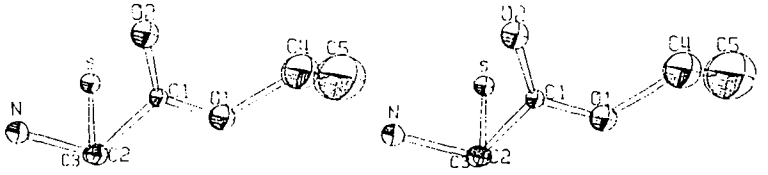
Orthorhombic L– cysteine

(d)



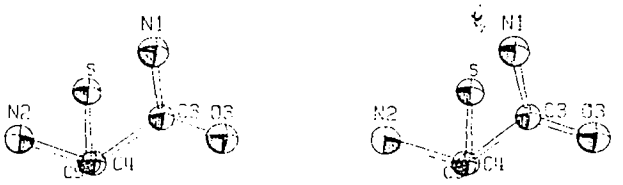
L- cysteine HCl Hydrate

(e)



L–cysteine ethyl ester hydrochloride : urea complex

(f)



Glutathione

FIGURE 1. Stereoscopic views projected along the $C_\beta—C_\alpha$ bond for various molecules containing the $\rangle C—CH_2—SH$ group. (a) Monoclinic form of L-cysteine (molecule B), (b) monoclinic form of L-cysteine (molecule A), (c) orthorhombic form of L-cysteine, (d) L-cysteine hydrochloride monohydrate, (e) L-cysteine ethyl ester hydrochloride : urea (1 : 1 complex) and (f) glutathione. These and subsequent stereoscopic views can best be seen with the aid of a simple stereoscopic viewer. They can also be seen by holding a small piece of cardboard normal to the paper between the right- and left-hand views, thus cutting off the right view from the left eye and vice versa. In the cases of the cysteine compounds, the atom numbering used in the original papers has been changed, where necessary, so that the $C_\beta—C_\alpha$ bond is $C_2—C_3$.

readily found. This analysis is certainly of a level of accuracy that one would not expect any difficulty in locating a hydrogen atom. There were some anomalies in the form of the temperature factor for the sulphur atom that might be attributed to some minor positional disorder for that atom and it is possible that the hydrogen atom does not occupy a unique position in the unit cell[2]. This possibility should be borne in mind when the hydrogen-bonding properties of the thiol group are discussed. Without information relating to the position of the thiol hydrogen atom, obviously nothing meaningful can be said about the S—H length, the C—S—H angle or the conformation found about the C—S bond from these X-ray analyses. A good quality neutron diffraction study on one or more of these structures would be particularly rewarding in providing information about the thiol hydrogen atom.

The conformations found about the C—C bond adjacent to the thiol group, however, do present some interesting results. Stereoscopic views of the projection down the C_β—C_α bond (α and β to the thiol group) for six of these molecules are shown in Figure 1. The exact values C(carboxyl)—C—C—S and N(amino)—C—C—S torsion angles are listed in Table 2.

TABLE 2. Torsion angles around the C—C bond adjacent to the thiol group

	τ[C(carboxyl)—C—C—S][a]	τ[N(amino)—C—C—S]	Ref.
L-cysteine (monoclinic), molecule B[b]	68·8°	−170·1°	1
L-cysteine (monoclinic), molecule A	−50·5°	72·6°	1
L-cysteine (orthorhombic)	−58·2°	65·4°	2
L-cysteine $HCl.H_2O$	−52·5°	64·9°	3
L-cysteine ethyl ester HCl : urea (1 : 1) complex	−44·8°	74·9°	4
Glutathione	−54·5°	71·8°	5
Cysteylglycine : NaI (2:1)	−57·8°	64·9°	6

[a] The torsion angle (A—B—C—D) is defined as positive if, when looking along the B—C bond, atom A has to be rotated clockwise to eclipse atom D.

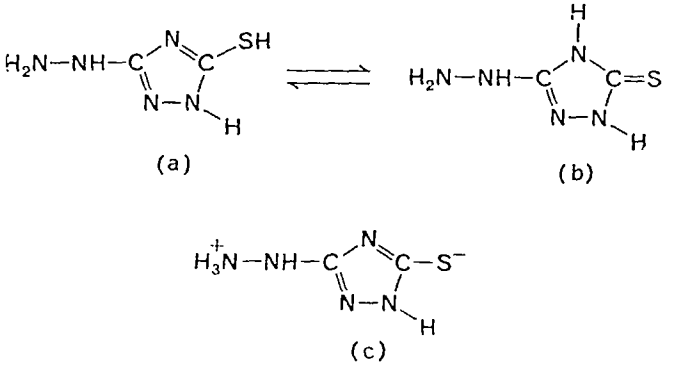
[b] There are two crystallographically independent molecules in this structure. Molecule A is the one with the sulphur atom labelled S(1) in reference 1, molecule B is the one with sulphur labelled S(11).

The C—S bond takes up an orientation that is *gauche* with respect to both the C—N(amino) and C—C(carboxyl) bonds, when projected along the C—C bond in the orthorhombic form of L-cysteine, in the L-cysteine hydrochloride salt, in the urea complex of the ethyl ester hydrochloride,

in glutathione, in the cysteylglycine : NaI complex, and in one of the two crystallographically independent molecules in the monoclinic form of L-cysteine. In all these cases the N(amino)—C—C—S torsion angle is somewhat greater than the C(carboxyl)—C—C—S torsion angle. The single exception to the *gauche* arrangement is found in the case of one of the molecules of the monoclinic form of L-cysteine. It has an arrangement with the C—NH_3^+ and C—S bonds in a nearly *anti* orientation. A possible explanation for this difference can be found in the crystal structure of the monoclinic form of L-cysteine[1]. As will be discussed later in this review, the molecule with the *anti* arrangement cannot be considered as a serious candidate for intermolecular S—H···B hydrogen bonding, whereas there is reasonable evidence that all the other molecules listed in Table 2 are so involved. However, the possibility for intramolecular hydrogen bonding does exist in the case of the molecule of L-cysteine (monoclinic) with the *anti* arrangement. Intuitively, the *anti* conformation around the C_β—C_α bond would have been thought to be more stable than a *gauche* arrangement, yet the evidence from crystallographic studies, at least on L-cysteine derivatives, does not support this view.

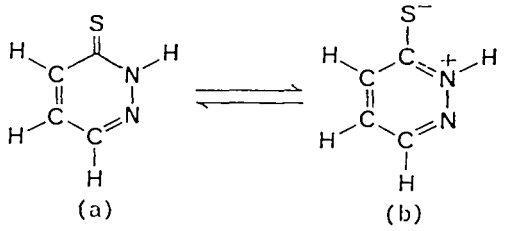
III. A DISCUSSION OF SOME STRUCTURES THAT HAVE BEEN REPORTED TO CONTAIN THE THIOL GROUP

The structure of 3-hydrazino-5-mercapto-1,2,4-triazole (**6**) was studied several years ago by Senko and Templeton[13]. This molecule can be represented by a tautomer with a thiol group (**6a**). Neutral forms with a thione group, such as **6b**, and zwitterionic forms such as **6c** would also be



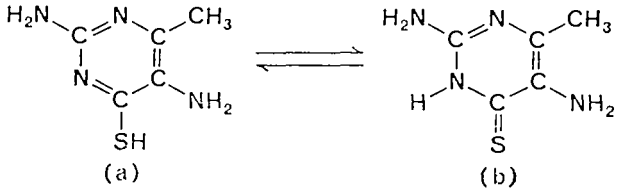
(6)

possible. The X-ray analysis did not indicate the positions of the hydrogen atoms, so the assignment as to which tautomer exists in the crystal had to be made on the basis of the observed molecular dimensions and intermolecular contacts. The molecular dimensions were not particularly helpful in making such a decision as the C—S bond length of 1·74 Å is intermediate between the lengths expected for a C—S single and C—S double bond[12,14]. However, the intermolecular contact of 3·24 Å between the terminal nitrogen of the hydrazino group and the sulphur atom was attributed by Senko and Templeton[13] to ionic rather than hydrogen bonding[15]. For this reason, they favoured a zwitterionic form (**6c**) rather than either of the neutral forms as representing the state of the molecule in the crystal. In a review of the hydrogen-bonding capabilities of sulphur, Srinivasan and Chacko[16] described both 3-hydrazino-5-mercapto-1,2,4-triazole and 2H-pyridaz-3-thione (**7**) as existing in zwitterionic tautomeric forms. However, there is little evidence from the X-ray study[17] on **7** to indicate that it exists in other than the neutral thione tautomeric form (**7a**).



(7)

The molecule of 2,5-diamino-4-mercapto-6-methylpyrimidine (**8**) was reported to exist in the crystal in the thiol form on the basis of an analysis of two projections, and co-ordinates were reported for the thiol hydrogen atom (although a two-fold disorder for the S—H group was invoked)[18].



(8)

As anisotropic thermal motion was not introduced into the model, some doubt as to the reliability of this location can reasonably be raised.

Inspection of the crystal structure (Figure 2) does not allow an unequivocal assignment of hydrogen bonding to be made and indeed suggests a structure with relatively little hydrogen bonding. On the basis of the

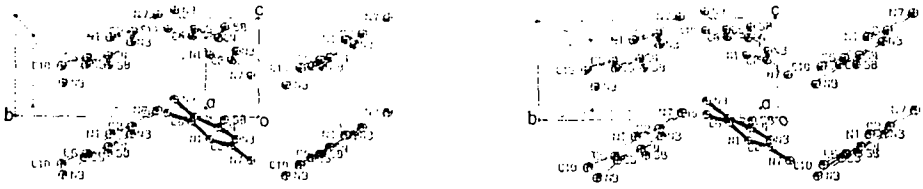
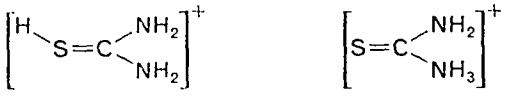


FIGURE 2. Stereoscopic view of the crystal structure of 2,5-diamino-4-mercapto-6-methylpyrimidine (8).

existing evidence, we feel that the case for a thiol group in this molecule remains to be established. Several structures involving the thione group (e.g. **8b**) could be written for this molecule.



(9)

The structure of thiourea nitrate (**9**) presents an interesting problem. The X-ray analysis performed by Feil and Loong[19] seemed to provide conclusive evidence that sulphur rather than nitrogen was protonated and that the cationic species was **9a** rather than **9b**. A difference map calculated to locate the hydrogen atoms, and presented by these authors[19], had a large positive peak near the sulphur atom. However, the resulting S—H distance seems unacceptably short (0.96 Å from the data collected with CuK_α radiation or 0·79 Å from those with MoK_α), when the values obtained from electron diffraction and microwave data are in the range 1·3–1·4 Å (Table 1). In addition, it was reported that the hydrogen atom attached to sulphur 'oscillated' during the refinement[19]. Furthermore, the C—S length of 1·735 (CuK_α) or 1·739 (4) Å (MoK_α radiation) is comparable to those found in thiourea and related compounds[20], and if representing a C=S—H bond, it certainly does not seem to have been much affected by protonation. The space group of the crystal is $P2_1/m$, which requires all the atoms to lie on a mirror plane[19]. If, however, there

was some disorder among the hydrogen positions, two *possible* different interpretations of the anomalies could be given.

1. The additional hydrogen atom is indeed bonded to the sulphur atom, but it does not lie in the mirror plane, but is statistically disordered between sites that are an equal distance above and below the plane. It is unlikely, however, that the proton is involved in hydrogen bonding as the closest S···O contact between molecules lying on adjacent mirror planes is 3·78 Å and the C—S···O angle is only 68°. Such an arrangement, however, would lead to a longer S—H bond and might provide an explanation for the difficulties encountered with this atom during the refinement.

2. A more radical re-interpretation would have the extra proton attached to one of the nitrogen atoms as in **9b**, with the consequence that the peak near sulphur was an artifact (there is an equivalently sized negative peak on the other side of the sulphur)[19]. Such an interpretation would require that one of the peaks on the mirror plane in the difference map that has been considered to represent a single hydrogen atom did in fact represent the midpoint between two hydrogen atoms attached to the one nitrogen, one of the hydrogen atoms being above the plane, the other being below the plane (Figure 3). This possibility would lead to a hydrogen bonding

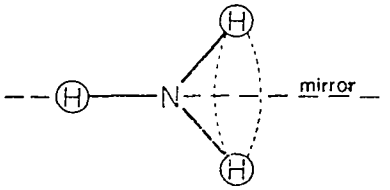


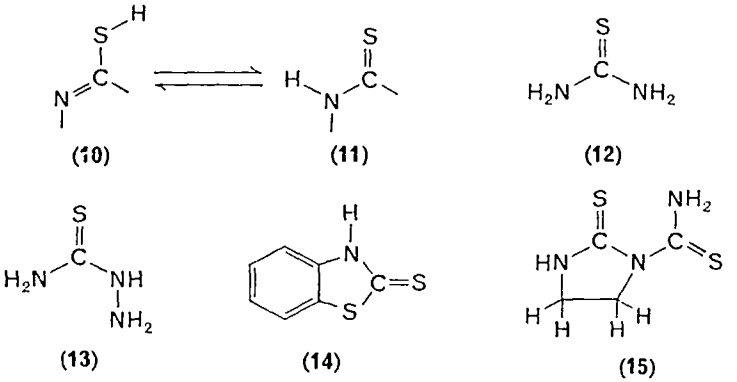
FIGURE 3. Representation of structure of $-NH_3^+$ group that could lead to accumulation of electron density on mirror plane.

arrangement between the N—H (thiourea) group and the nitrate ion at the equivalent position $(1-x, \frac{1}{2}+y, 1-z)$. In such an arrangement, the shortest N···O distance is 3·37 Å, but the N···N(nitrate) distance is 3·21 Å; the C—N···O and C—N···N angles are 86° and 95°.

These two structures are only *suggested* as possible explanations of the results. It is, of course, quite possible that the published structure is completely correct and that the thiol hydrogen has been placed artificially close to the sulphur atom. In this context, the structure of urea nitrate clearly has the oxygen atom protonated as demonstrated by both X-ray and neutron diffraction methods[21,22]. The crystals of urea nitrate and thiourea nitrate however, are not, isostructural and oxygen is much more electronegative than sulphur.

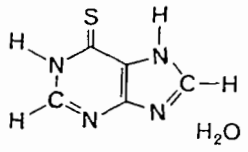
IV. RELATIVE OCCURRENCE OF THIOL : THIONE TAUTOMERS IN THE SOLID STATE

When there is the possibility of tautomerism between the thiol and thione forms (**10**) and (**11**), the thione form has been invariably found to be present in the solid state[20]. Compounds exemplified by thiourea (**12**)[23], thiosemicarbazide (**13**)[24], 2-mercaptobenzothiazole (**14**)[25], and 1-thiocarbamoylimidazolidine-2-thione (**15**)[26] all exist in the crystal as the tautomers containing the thione groups, as is clearly shown from X-ray



studies[27]. These conclusions have been reinforced by the precise location of the protons by electron[28] and neutron[29] diffraction studies on thiourea. A similar situation pertains among sulphur-containing nucleic acid bases. For example, 6-mercaptopurine monohydrate (**16**)[30], 2-mercapto-6-methylpurine monohydrate (**17**)[31], thiocytosine (**18**)[32], thioguanosine monohydrate (**19**)[33] and dithiouracil (**20**)[34] all exist in the thione tautomeric forms shown[35]. In the case of 6-mercaptopurine, this has the interesting consequence that while this molecule might have been anticipated to be a possible substitute for adenine (**21**) in polymeric nucleic acid structure, it is both an antagonist to nucleic acid synthesis and is an anti-tumour drug. It is tempting to speculate that this property is due in part to the inability of the 6-substituent to act as a hydrogen-bonding donor.

Most of the available evidence points to the predominance of the thione over the thiol form also in the liquid state and in solution. For example, the 2-, 6- and 8-thiopurines have been shown to exist mainly as the thione tautomers (**22–24**) in neutral solution by ultraviolet[36–38] and infrared[39,40] spectroscopy; tautomers with different nitrogen atoms protonated would also be possible. The electronic absorption spectra of thiopurines have also been interpreted using Pariser–Parr–Pople-type calculations and the



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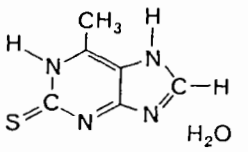

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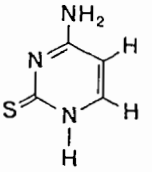

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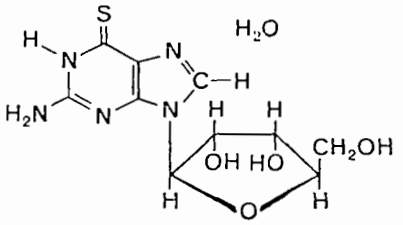

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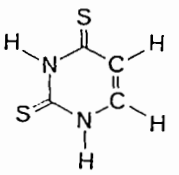

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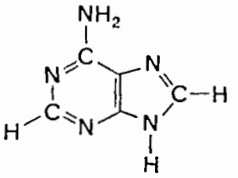

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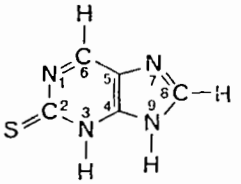

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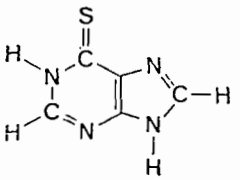

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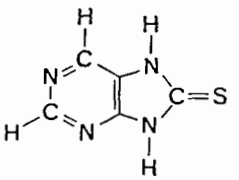
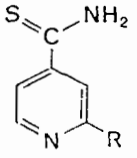


(24)

results of these calculations were in agreement with the existence of thione tautomers[41]. An infrared study on 2-(R-substituted)-isonicotinethioamides (**25**), where R = H, C_2H_5, $C_6H_5CH_2$, nicotinethioamide (**26**) and 6-(R-substituted)-2-picolinic acid thioamides (**27**) demonstrated that these compounds also existed as the thione form as shown, in both the liquid and solid states[42]. Furthermore, this finding is in agreement with the results of an X-ray study on isonicotinethioamide (**25**, R = H) carried out by Colleter and Gadret[43].



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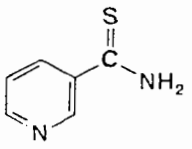

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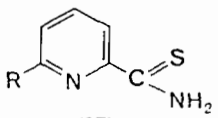
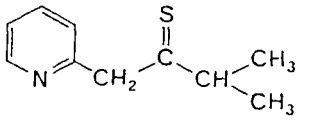


(27)

However, in certain cases the presence of thiol tautomers is observed. When the protons adjacent to the sulphur-bearing carbon atoms are quite labile, thioenol forms are observed. 2-Picolyl isopropyl thioketone (**28**) and α-thiobenzoylacetophenone (**29**) have been shown to exist as thioenol forms from the results of a p.m.r. study[44]. Various thiophenethiols, e.g. **30**, are stable with respect to the corresponding thione form (**31**) both in



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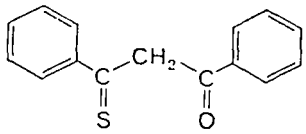

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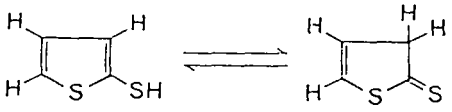


(30) (31)

the liquid state and in cyclohexane solution using p.m.r. spectra[45]. In this case the thione form would exhibit a loss of resonance energy in the heterocyclic ring. Later studies on thiophenethiols also confirmed the presence of the thiol proton[46]. An infrared examination[47] in the solid and liquid states combined with an n.m.r. study of ten mercaptoaldimine derivatives of thiophene revealed that the thione tautomer (**32**) was present in the solid, predominated in the liquid, but the amount of thiol tautomer (**33**) increased with increasing temperature. Thus, while thione tautomers are usually found, there are obviously some situations where the thiol form is preferred.

(32) (33)

V. ELECTRON DIFFRACTION AND MICROWAVE STUDIES ON MOLECULES CONTAINING THE THIOL GROUP

Here the situation is somewhat better than was the case with X-ray studies since there are several structural studies on molecules in the gas phase that contain thiol groups. Methanethiol (**4**) has been studied extensively by microwave methods[9–11,48,49] and there is also an early electron

diffraction study[7]. The most recent microwave data of Kojima[9] gave a C—S length of 1·819 (5) Å, an S—H length of 1·335 (10) Å and a C—S—H angle of 96°30′ (30′) (Table 1). The values for the C—S and S—H bonds are in excellent agreement with the sums of the accepted values for the covalent radii[12]; they are also in good agreement with those reported as a result of earlier microwave studies[10,11] on methanethiol, with the electron diffraction value for the C—S bond length (1·82 (1) Å) determined by Schomaker[7], and with the S—H length (1·32–1·34 Å) found in hydrogen sulphide[50]. While the C—S—H bond angle is much less than that found in the analogous oxygen group (where it is approximately tetrahedral), it is significantly larger than the H—S—H angle (92–93°) in hydrogen sulphide[50]. A small angle (2°10′ ± 30′) was found between the three-fold axis of symmetry of the methyl group and the direction of the C—S bond in **4**[9].

In addition to information on molecular structure, the microwave work provided measures of dipole moments[9,48,49] and the height of the barrier to internal rotation about the C—S bond[9–11,49,51]. The dipole moment parallel to the molecular axis, shown in Figure 4, is 1·33(3) D

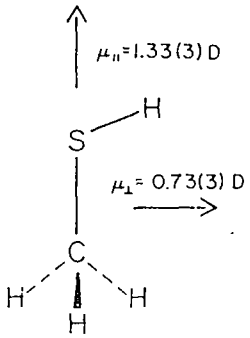
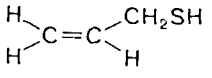


FIGURE 4. The molecule of methanethiol (**4**) showing the dipole moments parallel and perpendicular to the molecular axis. There is an angle of 2°10′ (30′) between the three-fold axis of the methyl group and the C—S bond.

whereas that perpendicular to the molecular axis, is 0·73 (3) D. These values are in good agreement with assumed bond dipole moments of H^+—S^- 0·68 D, C^+—S^- 1·00 D and H^+—C^- 0·40 D[9]. Estimates of the barrier to internal rotation range from a low of 0·70 to a high of 1·46 kcal/mole, the latter being determined from calorimetry[51]. However, on the basis of the most recent microwave study which took into account excited torsional states as well as the ground state, a value of 1·27 (3) kcal/mole was obtained[9]. A careful study of the vibrational spectra of CH_3SH

and CH_3SD in the gaseous and solid states by May and Pace[52] led to the assignment of bands in CH_3SH to the S—H stretching frequency (2605 cm^{-1}), the C—S—H bending frequency (802 cm^{-1}) and the C—S stretch (710 cm^{-1}). No absorption corresponding to rotation about the C—S bond could be observed. If the torsion barrier (1·27 kcal/mole) found by Kojima[9] is assumed, the frequency of this rotation should be 200 cm^{-1}. May and Pace[52] also carried out a normal co-ordinate analysis following their assignments. Similar calculations have recently been made by Gebhardt[53]. Both studies followed the molecular geometry deduced by Kojima[9].

The role of the thiol group in determining conformation in prop-2-ene-1-thiol (**34**) has been examined by microwave methods[51]. Several conformers



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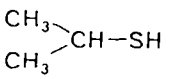


(35)

are possible as a result of rotation about the C—C and C—S bonds (Figure 5). The dipole moment was measured as 1·33 (3) D and it was possible to describe the structure in terms of standard bond lengths and angles. The most stable conformer is shown in Figure 5. It has one of the methylene hydrogen atoms arranged *trans* or *anti* to the single hydrogen

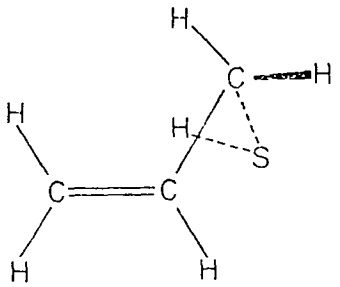


FIGURE 5. The most stable conformer of prop-2-ene-1-thiol (**34**).

on the central carbon atom and the best value for the C=C—C—S torsion angle was found to be $124 \pm 3°$ (Figure 6a), i.e. the thiol group is *gauche* with respect to the double bond. The thiol hydrogen atom is arranged such that the C—C—S—H torsion angle is 50° (Figure 6b). In contrast, 2-propanethiol (**35**) has been shown[55] to exist in two conformers about the C—S bond, one with the C—H and S—H bonds *anti* and the other with them *gauche*.

Ethane-1,2-dithiol (**5**) has been examined both by electron diffraction[8] and by spectroscopic methods[56]. The electron diffraction study yielded values of 1·819 (2) Å for the C—S, and 1·40 (2) Å for the S—H bonds, and a C—S—H angle of 90·5 (3·2)° (Table 1). While the angle is much smaller than that found in methanethiol, the high standard deviation for

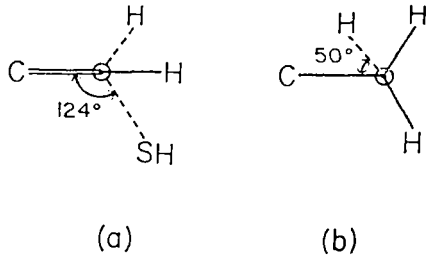


FIGURE 6. (a) Projection along the =C—C(SH) bond in the molecule of prop-2-ene-1-thiol (**34**), (b) projection along the C—S bond in **34**.

the value found for **5** does not imply that the difference must be significant. In this study, the S—H bond was *assumed* to be *anti* to the C—C bond, although this arrangement was not found in the case of prop-2-ene-1-thiol (**34**)[54]. Two conformers due to rotation about the central C—C bond were detected in the gas phase by the electron diffraction method. In the gas phase, there was 62% of the *anti* form and 38% of the *gauche* form of ethane-1,2-dithiol (Figures 7a and b)[8,57]. The energy difference between these two conformers was estimated to be 0·8 kcal/mole.

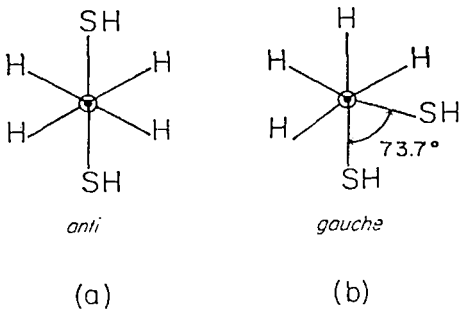


FIGURE 7. The *anti* and *gauche* conformers about the C—C bond in ethane-1,2-dithiol (**5**).

A spectroscopic study of **5** in both gaseous and crystalline states by Hayashi and coworkers[56] provides some interesting information on conformational possibilities. Correspondence between many of the spectral lines of **5** and those previously identified[58] for 1,2-dichloroethane allowed

many assignments to be made. In the gas phase, there is clear evidence for the existence of both *anti* and *gauche* conformers while upon crystallization the lines corresponding to the *gauche* conformer disappear. The positions of the S—H stretching, C—S—H bending, and C—S stretching modes are in general agreement with those observed for methanethiol. While no band corresponding to rotation about the central C—C bond was observed, a weak absorption, active in the Raman at 255 cm^{-1}, was assigned to the C—S torsion in the deuterated molecule $DSCH_2CH_2SD$, in the liquid state. Since the spectra recorded in the crystal show a mutual exclusion rule between the infrared and Raman spectra, the conformer in the crystalline state was judged to have a centre of symmetry. There are, however, two possible conformers with this symmetry (Figures 8a and b).

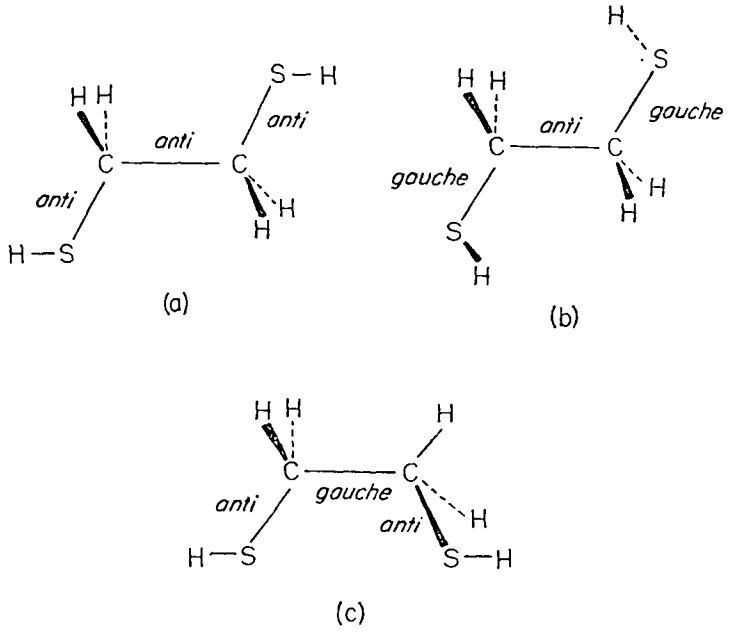


FIGURE 8. The rotational arrangements around the C—C and two C—S bonds in several conformations of ethane-1,2-dithiol (5).

One of these (Figure 8a) has an *anti* arrangement about the three bonds, S—C, C—C, C—S, while the other has a *gauche* arrangement about the two C—S bonds, but an *anti* arrangement around the central C—C bond. Likewise, an unequivocal assignment of the exact conformation of the species present in the gas phase and which disappears upon crystallization was not possible on the basis of the observed spectra, although the

principal species (there may be more than one) did have a *gauche* arrangement about the central C—C bond. However, when a normal co-ordinate analysis was carried out assuming that the form persisting in the crystal had C_{2h} symmetry (i.e. that shown in Figure 8a) and that the form in the gas phase which disappeared in the crystal had C_2 symmetry and was that shown in Figure 8c, the five constants for the various modes of vibration were consistent with results obtained in related structures. Thus, Hayashi and coworkers[56] believed that the two forms mainly present in the gas phase are those shown in Figures 8a and c, and that the form in the crystal is that in Figure 8a.

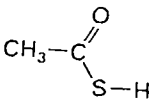
By measuring the relative intensities of the same vibrational mode in the two conformers (Figures 8a and c) at various temperatures, Hayashi and coworkers[56] estimated the energy difference between them to be 0·63 kcal/mole with the *anti* being the more stable; this result is in fair agreement with the value of 0·8 kcal/mole obtained from the electron diffraction experiment[8]. Hayashi and co-workers also estimated that the energy barriers to rotation about the C—C and C—S bonds were 4·8 kcal/mole and 1·7 kcal/mole, respectively; this latter value is somewhat greater than the 'best' value found for the C—S bond in methanethiol[9]. These authors[56] carried out a normal co-ordinate analysis on the molecule of **5** and obtained good agreement between observed and calculated frequencies.

Hayashi and coworkers[59] extended their studies on the spectra of molecules containing thiol groups to 2-chloro- and 2-bromoethanethiol (**36a** and **b**).

$$X{-}CH_2{-}CH_2{-}SH \qquad \begin{matrix}(\mathbf{36\,a})\ X = Cl \\ (\mathbf{36\,b})\ X = Br\end{matrix}$$

They had previously shown that in the crystal, ethane-1,2-dithiol exists in the single all *anti* form[56], whereas 2-chloroethanol exists in a single form with a *gauche* arrangement around the central C—C bond[60]. This latter finding was attributed to an internal O—H···Cl hydrogen bond. However, in the sulphur analogue, the *anti* arrangement around the central C—C bond was shown as the only conformer in the crystalline state and was found to be the most stable conformer in the gaseous and liquid states. Several conformers about the C—S bond were indicated in the gas and liquid[59]. There was no evidence from this study for intramolecular S—H···Cl hydrogen bonding analogous to that found in the oxygen compound. Mori and coworkers[61] studied rotational motion about the C—S bond in a number of alkanethiols and correlated this with intramolecular hydrogen bonding involving the thiol group.

Thioacetic acid (37) in the gas phase was the subject of an early electron diffraction study by Gordy[62]. He assumed that the S—H length was 1·34 Å, the S—C—O angle was 125° and that the molecule was planar apart from the hydrogen atoms of the methyl group. With these restrictions



(37)

placed on the geometry, he obtained values of 1·24 (4) Å and 1·78 (2) Å for the C=O and C—S bonds, respectively. He attributed the shortening of the C—S bond length when compared to the sum of the covalent radii to resonance effects involving the carbonyl group, which was somewhat lengthened. It was pointed out in the paper, however, that such resonance interaction was much less than in the case of esters or amides[62].

In summary, microwave spectroscopic and electron diffraction methods have provided more information on the geometry of the thiol group than has X-ray diffraction, particularly those aspects that involve knowledge of the location of the hydrogen atom. In favourable cases, infrared spectra can also be used to obtain qualitative information on subjects such as preferred rotational isomers, and also energy differences between different conformations.

VI. MAGNETIC RESONANCE INVESTIGATIONS OF CONFORMATION ON MOLECULES CONTAINING THIOL GROUPS

While nuclear magnetic resonance studies will not yield precise information on bond lengths and angles, they can give very valuable data on molecular conformation. Their value can, however, be dependent on some basic assignments of resonances to particular atoms and the results can in some instances be ambiguous. A few examples of the use of n.m.r in determining molecular conformation in thiol-containing compounds will be described.

An analysis of chemical shifts and spin–spin coupling constants for L-cysteine and some derivatives in various bonding situations was carried out by Martin and Mathur[63]. If the assignment of chemical shift to the two methylene protons adjacent to the thiol group was as made by Martin and Mathur, then the conformer with the thiol and carboxyl groups *anti* is favoured in solution (Figure 9a). In more acidic solutions, where the carboxylate group is protonated, the *anti* conformation, and the two *gauche* conformations shown in Figures 9b and c are nearly equally

populated. It is somewhat surprising that these results are so different from the information obtained from X-ray studies on the crystal, where the *gauche* conformation shown in Figure 9c is most commonly found (see section II of this review and Figure 1). If the initial assignment of chemical shifts was reversed, then different populations of conformers would result

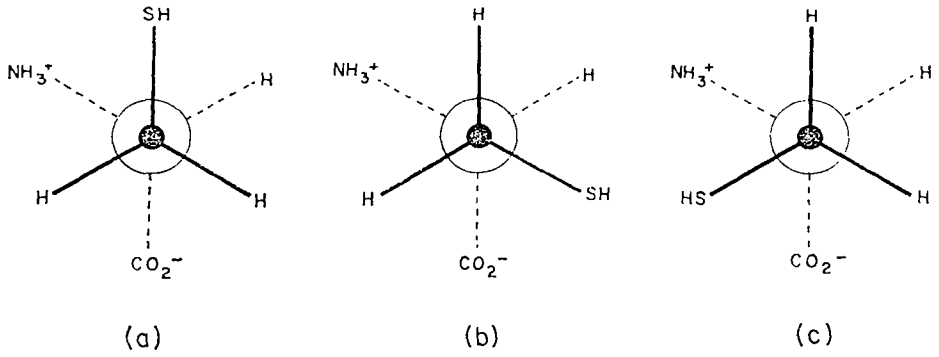
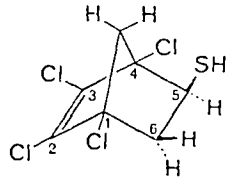


FIGURE 9. Three rotational conformers of L-cysteine considered by Martin and Mathur[63].

from this study. However, the same initial assignment also gave reasonable results in a more recent study of conformations in L-cystine and derivatives[64].

In contradiction to an earlier report[65], Eliel and Thill[66] showed that, on the basis of the p.m.r. chemical shifts, cyclohexanethiol exists in the conformation with the thiol group equatorial (**38**). This determination was made comparing the chemical shifts in cyclohexanethiol with those in *cis*- and *trans*-4-*t*-butylcyclohexanethiol. For (**38**), the equatorial conformation is favoured over the axial one by 0·9 kcal/mole.

(38)



(39)

The vicinal spin–spin H—C—S—H interactions and the long range H—S—C(5)—C(6)—H interactions were studied in the 1,2,3,4-tetrachloro-5-*exo*-thiobicyclo[2.2.1] heptane (**39**) molecule[67]. The results of this

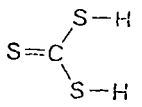
examination indicated that the preferred orientation of the C(6)—C(5)—S—H group was *anti*. A fairly comprehensive survey of S—H chemical shifts and H—S—C—H and H—S—C—C—H coupling constants for a number of aliphatic thiols was carried out recently by Marciacq-Rousselot[68]. These data were related to hydrogen bonding potential and molecular conformation.

VII. HYDROGEN-BONDING PROPERTIES OF SULPHUR

The hydrogen-bonding properties of sulphur in solution were considered generally by Pimentel and McClellan[69], while Hamilton and Ibers[70] discussed some aspects of hydrogen bonding involving sulphur in the solid state. A useful and more comprehensive review of the structural aspects of hydrogen bonding involving sulphur in the crystalline state was written by Srinivasan and Chacko[16]. This latter article provides the dimensions obtained from X-ray data for all systems, studied up to 1965, where sulphur may be implicated as either a donor or acceptor in hydrogen bonding.

The electronegativity value for sulphur on the Pauling scale is 2·5 compared to those for oxygen and nitrogen of 3·5 and 3·0[71]. Sulphur will thus be a less effective participant in hydrogen bonding than either an oxygen or a nitrogen atom. The very much less polar nature of the S—H bond as compared to the O—H bond appears to render sulphur a weak hydrogen bonding donor, at least in the crystalline state.

If S—H···B hydrogen bonding occurs in a crystal at all, it clearly represents a relatively weak interaction, and in no case is the evidence for its presence overwhelmingly conclusive. The structures of hydrogen sulphide[72] and trithiocarbonic acid (**40**)[73] may contain S—H···S hydrogen



(40)

bonds. After a critical examination of the crystallographic results for H_2S, Hamilton and Ibers[70] concluded that there is S—H···S hydrogen bonding in the tetragonal phase, stable below −168°C. While hydrogen atoms were not located, the S···S distance is 3·86 Å, and the S···S···S angle is 75°. There has been some doubt as to the appropriate values for the van der Waals radii of sulphur and hydrogen. The values given by Pauling[74] are 1·85 and 1·20 Å. Accumulated evidence from more recent studies[16,20,75] suggests that a value of 1·75 Å would be more appropriate for sulphur,

while, following a recent series of accurate neutron diffraction studies on amino acids, Hamilton[76] has concluded that the van der Waals radius of hydrogen should be 1·0 Å rather than 1·20 Å. If one assumes that the sum of the van der Waals radii of sulphur and hydrogen is 2·75 Å and that the covalent S—H bond length is 1·35 Å, then a minimum S···S contact of 4·10 Å might have been anticipated. Since the observed distance in H_2S is 0·24 Å *less* than this value, S—H···S hydrogen bonding seems to be implicated. In addition Hamilton and Ibers[70] made the point that the existence of several crystalline phases of H_2S is also indicative of weak intermolecular interactions such as might be anticipated when S—H···S hydrogen bonding exists. In the crystal of (**40**), S···S distances between 3·5 and 3·7 Å were found[73]. These distances were interpreted by the authors as S—H···S hydrogen bonding.

In the absence of exact knowledge of hydrogen atom positions, the following criteria can be adopted as necessary, although not sufficient conditions for hydrogen bonding. The S—H covalent bond is 1·35 Å, and the van der Waals radius for hydrogen is 1·0 Å[76]. Therefore the sulphur atom must lie within $(2{\cdot}35+r_B)$ Å of the atom B that is the potential hydrogen-bonding acceptor, with r_B being the van der Waals radius for that atom. In addition the C—S···B angle should be 95° ± (20–30°). These conditions can be appreciated from Figure 10. In addition, one would

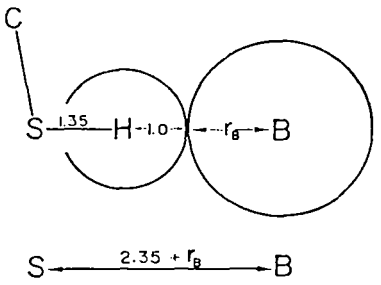


FIGURE 10. Schematic drawing showing the criteria for hydrogen bonding with the thiol group as donor. Atom B is the acceptor.

expect the S—H bond to take up either an *anti* or *gauche* arrangement around the C—S bond with respect to the C—C bond (Figure 11). Then the C—C—S···B projection angle should be approximately either ±60° or 180° (Figure 11) rather than 0° or ±120°. If these criteria are adopted, then hydrogen bonding with sulphur as a donor cannot be ruled out in the crystals of the two forms of L-cysteine[1,2], L-cysteine hydrochloride monohydrate[3], of the L-cysteine ethyl ester hydrochloride : urea (1 : 1) complex[4],

or of the tripeptide, glutathione[5]. These structures will now be examined in more detail.

A stereoscopic view of the crystal packing in L-cysteine hydrochloride monohydrate is shown in Figure 12. This view was drawn from the coordinates presented in reference 3. The hydrogen-bonding assignments involving the NH_3^+ group, the water molecule and the carboxylic acid group, as detailed by Ramachandra Ayyar[3], are indicated. None of the hydrogen atoms were located in this analysis, so the position of the thiol hydrogen atom is unknown. The shortest intermolecular distances involving sulphur are 3·50 Å to Cl^- and 3·43 Å to O(1) $[1-x, -\frac{1}{2}+y, \frac{1}{2}-z]$ [77]; the

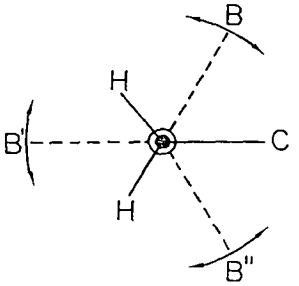


FIGURE 11. Schematic drawing of the projection down the C—S(H) bond showing the most probable orientations (B, B′ and B″) that could be adopted by the hydrogen-bonding acceptor.

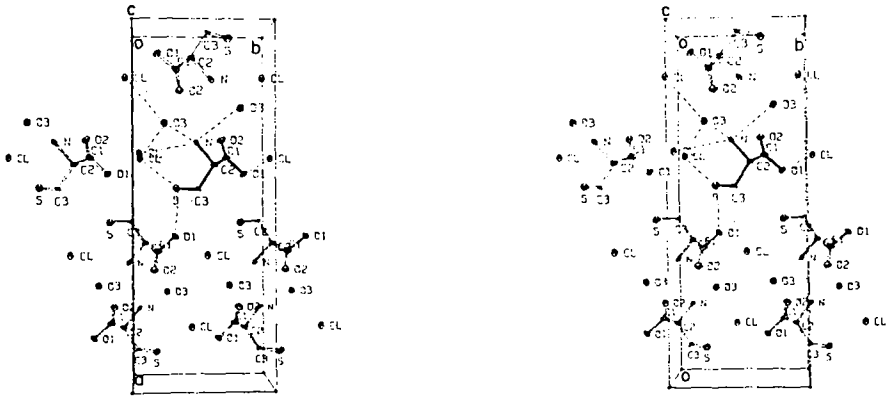


FIGURE 12. Stereoscopic view of the crystal structure of L-cysteine hydrochloride monohydrate. This view was drawn from the coordinates presented in reference 3. As in subsequent drawings the basic 'molecule' (in this case the two charged species and the water molecule) is shaded in black and the hydrogen bonding arrangements, including the more probable assignments involving the thiol group, are shown by discontinuous lines.

corresponding C—S···Cl^- and C—S···O(1) angles are 151° and 117°, respectively. While both Ramachandra Ayyar[3] and Srinivasan and Chacko[16] indicated that the S···Cl^- contact could be considered as S—H···Cl^- hydrogen bonding, the C—S···Cl^- angle seems to be inappropriate for such an interaction. In fact, the S—H···O interaction appears to merit more serious consideration as a hydrogen bond. Here the C—S···O angle is much more favourable for hydrogen bonding and the hydrogen atom could occupy a position that could lead to an H···O contact of about 2·1 Å. However, the C—C—S···O projection angle is 136°, a value that suggests the thiol hydrogen would have almost to eclipse one of the methylene hydrogen atoms; the C—C—S···Cl^- projection angle is −23°. The atom O(1) in the molecule at $x, -1+y, z$ appears to be a less probable acceptor for an S—H···O hydrogen bond (Figure 13).

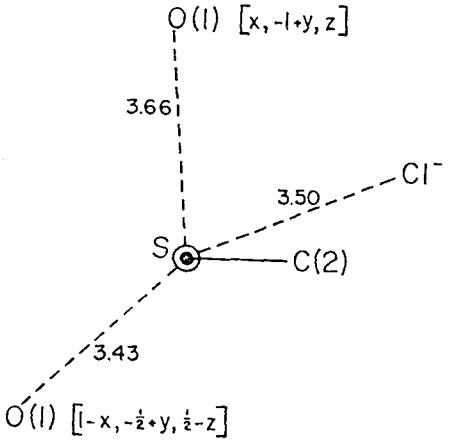


FIGURE 13. Projection along the C(α) or C(3)—S bond in the structure of L-cysteine hydrochloride monohydrate. The various possible S···B distances are shown in Å. The S···B contacts in this and similar subsequent drawings are proportional to the actual S···B length rather than that projected onto a plane perpendicular to the C—S bond. Atom numbering is that used in the original paper.

In Figure 14 is shown a stereoscopic view of the crystal structure of the 1 : 1 complex between L-cysteine ethyl ester hydrochloride and urea. This picture was drawn from the coordinates presented in reference 4. No parameters for the hydrogen atoms were given in the original paper. However, Haas was able to assign hydrogen bonds involving the three hydrogen atoms of the $-\overset{+}{N}H_3$ group and the four amino hydrogen atoms of the urea molecule[4]. He did not make any assignments of hydrogen

bonding involving the thiol hydrogen atom, although he said the 'sulphur atom is coordinated by a nitrogen, carbon, and two oxygen atoms in addition to the chloride ion'.

Sulphur has intermolecular contacts with several oxygen atoms and with a chloride anion; the S···O(2) $[1-x, \frac{1}{2}+y, 2-z]$, S···O(2) $[1-x, \frac{1}{2}+y, 1-z]$ and S···O(3) $[1-x, \frac{1}{2}+y, 1-z]$ distances are 3.38, 3·68 and 3·49 Å, respectively, while the S···Cl^- distance is 3·76 Å. The C—S···B

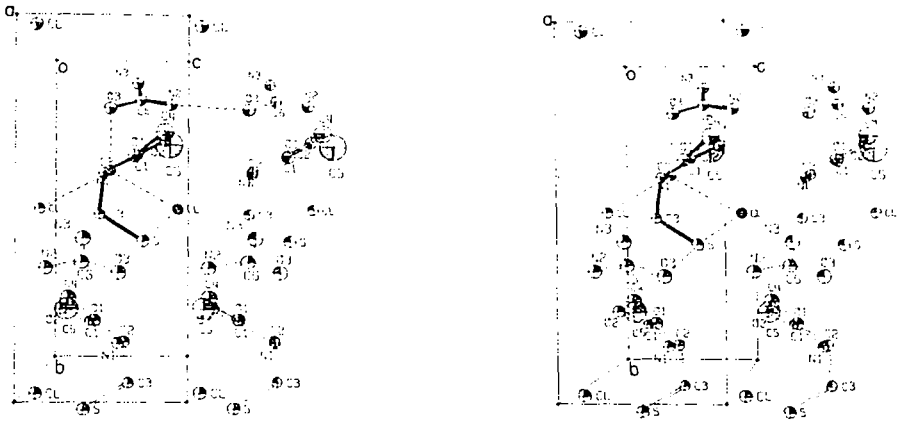


FIGURE 14. Stercoscopic view of the structure of the L-cysteine ethyl ester hydrochloride : urea complex. This picture was drawn from the coordinates presented in reference 4.

angles for these four possibilities are 166°, 74°, 86° and 98°. while the C—C—S···B projection angles are 169°, −174°, 126° and −47°. On the basis of the C—S···B angles, the two most probable candidates for S—H···B hydrogen bonding are O(3) $[1-x, \frac{1}{2}+y, 1-z]$ and Cl^-. The projection angles (a less stringent requirement) would tend to support the S—H···Cl^- assignment. A view of the geometry and the C—S bond is shown in Figure 15. Neither the author[4], nor Srinivasan and Chacko[16], who also examined this structure for S—H···B hydrogen bonding, made any specific assignments of hydrogen bonding involving the thiol group.

A stereoscopic view of the crystal structure of the orthorhombic form of L-cysteine is shown in Figure 16. This view was drawn from coordinates generously provided us by Dr. K. A. Kerr[2]. While the hydrogen atoms attached to carbon and nitrogen were readily positioned in this well-refined structure ($R = 0{\cdot}037$), the thiol hydrogen atom could not be located and the thermal vibrations of the sulphur atom seemed quite large as judged from the temperature parameters. These factors are suggestive of possible disorder in the region of the thiol group. The

closest contacts involving the sulphur are intramolecularly to H(6), attached to nitrogen, of 2·85 Å, and to O(2) of 3·495 Å and intermolecularly to O(2) at $[1\frac{1}{2}-x, 2-y, \frac{1}{2}+z]$ of 3·381 Å. There is also a contact between sulphur and O(1) at $[1-x, \frac{1}{2}+y, \frac{1}{2}-z]$ of 3·671 and

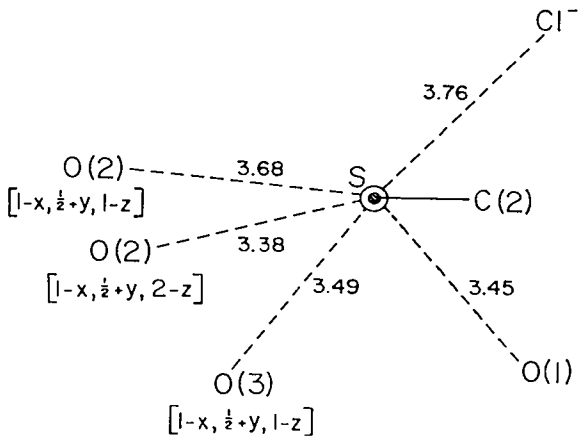


FIGURE 15. Projection along the C(3)—S bond in the structure of the 1 : 1 cysteine ethyl ester : urea complex. Atom numbering in this structure was changed to that used for other L-cysteine compounds in this review.

between sulphur and S at $[\frac{1}{2}-x, 2-y, -\frac{1}{2}+z]$ of 3·849 Å. The C—S···O(2), C—S···O(2) $[1\frac{1}{2}-x, 2-y, \frac{1}{2}+z]$, C—S···O(1) $[1-x, \frac{1}{2}+y, \frac{1}{2}-z]$, and C—S···S $[\frac{1}{2}-x, 2-y, -\frac{1}{2}+z]$ angles are 70·5°, 101·0°, 157·0° and 95·9°. The C—C—S···O(2), C—C—S···O(2) $[1\frac{1}{2}-x, 2-y, \frac{1}{2}+z]$, C—C—S···O(1) $[1-x, \frac{1}{2}+y, \frac{1}{2}-z]$ and C—C—S···S $[\frac{1}{2}-x, 2-y, -\frac{1}{2}+z]$ projection angles are 17·7°, −47·6°, 27·4° and 106·2°. Some of these dimensions are shown

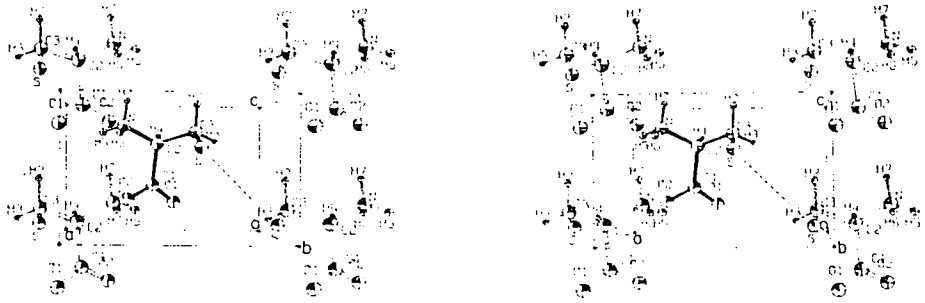


FIGURE 16. Stereoscopic view of the structure of the orthorhombic form of L-cysteine. This picture was drawn for the coordinates in reference 2. In this orientation, not all of the hydrogen bonding can be shown, e.g. the S···O(1) $[1-x, \frac{1}{2}+y, \frac{1}{2}-z]$ contact would be towards the viewer.

in Figure 17. From this information, a quite reasonable case can be made for S—H···O(2) [$1\frac{1}{2}-x, 2-y, \frac{1}{2}+z$] hydrogen bonding as suggested by the author[2].

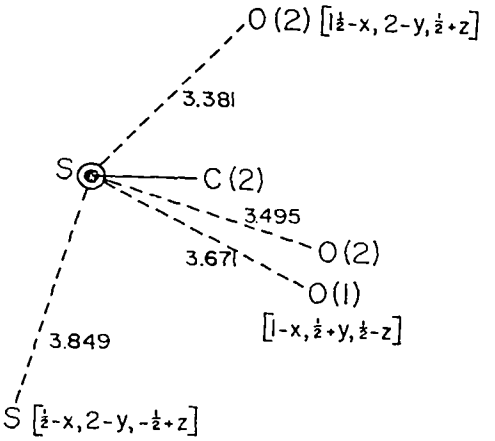


FIGURE 17. Projection along the C(3)—S bond in the orthorhombic form of L-cysteine.

As mentioned previously, there are two crystallographically independent molecules in the monoclinic form of L-cysteine[1]. A stereoscopic view of the packing of molecules in the crystal is shown in Figure 18, which was drawn from the coordinates presented in reference 1. Neither of the thiol

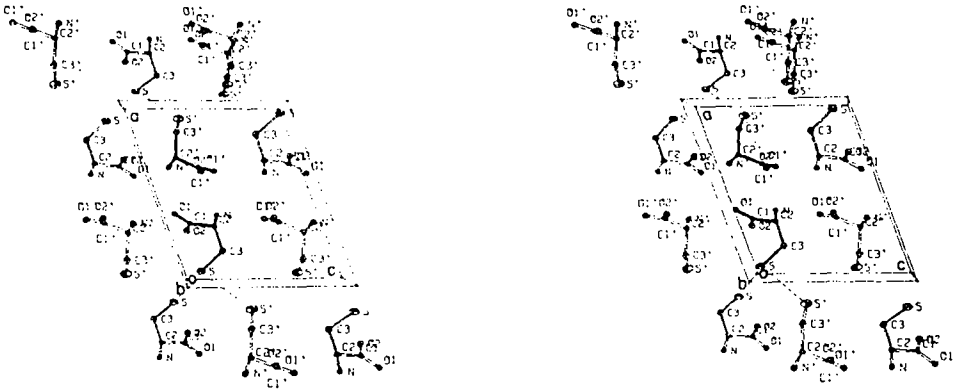


FIGURE 18. Stereoscopic view of the structure of the monoclinic form of L-cysteine. This picture was drawn from the coordinates presented in reference 1. The two crystallographically independent molecules are shaded, one being distinguished from the other by primes. One of the possible hydrogen-bonding assignments involving the thiol group of the 'unprimed' molecule is not shown as it is almost directly towards the viewer, i.e. the one to O(2) [$x, 1+y, z$].

hydrogen atoms was located in this analysis. No mention of hydrogen bonding was given in the original paper by Harding and Long[1]. There seems, however, to be reasonable geometric evidence that S (given as S(1) in reference 1) is involved in a hydrogen bond to O(2) at $[x, 1+y, z]$. The S···O distance of 3·48 Å meets the criterion of distance, the C—S···O angle is 96° and the C—C—S···O projection angle is −43°. On the basis of distance and C—S···S angle, one would also have to give serious consideration to possible S—H···S hydrogen bonding involving either S $[-x, -\frac{1}{2}+y, -z]$ or S′,S(11) in reference 1, at $[-1+x, 1+y, z]$. The S···S and S···S′ distances are 3·68 and 3·95 Å, respectively, and the C—S···S and C—S···S′ angles are 106° and 97°, respectively. However, the C—C—S···S and C—C—S···S′ projection angles are less favourable, being 106° and −135°, respectively. The projection along the C(3)—S bond is shown in Figure 19.

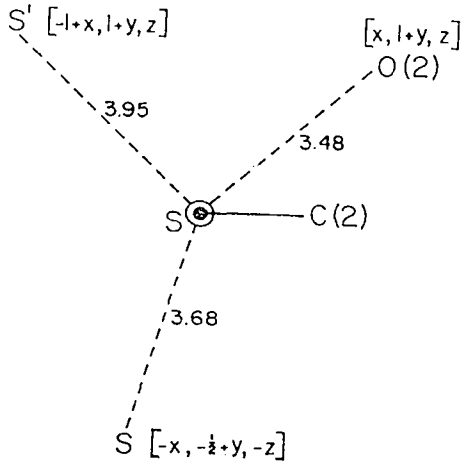


FIGURE 19. Projection along the C(3)—S bond in the 'unprimed' molecule in the monoclinic form of L-cysteine.

The evidence for intermolecular hydrogen bonding is much weaker in the case of atom S′. The only intermolecular contact that could even be considered as a hydrogen bond is the S′—H···S $[1+x, -1+y, z]$ interaction. The S′···S distance is 3·95 Å, the C(3′)—S′···S angle is 133°, and the C(2′)—C(3′)—S′···S projection angle is 99°. Naturally such an assignment would rule out the S—H···S′ hydrogen bonding possibility discussed in the previous paragraph. However, there is the possibility of intramolecular hydrogen bonding in this conformer. As described earlier, this molecule is unlike any other cysteine derivative in that the C—S bond

does not approximately bisect the projected N—C—C(carboxyl) angle (see Figure 1a). The intramolecular S′···O(2′) distance is 3·44 Å, the C—S···O angle is 69° and the C(2′)—C(3′)—S′···O(2′) torsion angle is −26° (Figure 20).

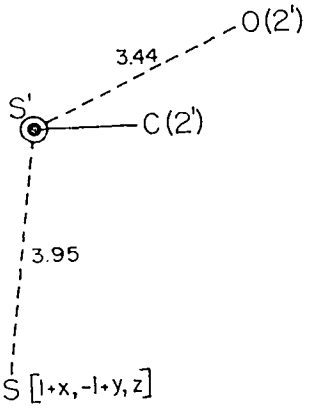


FIGURE 20. Projection along the C(3′)—S′ bond in the 'primed' molecule in the monoclinic form of L-cysteine.

A stereoscopic view of the crystal structure of glutathione is shown in Figure 21, which was drawn by us from the coordinates presented in reference 5. There are two S—H···O hydrogen bonding possibilities. One is to O(5) $[x, y, 1+z]$ with an S···O distance of 3·57 Å, a C—S···O angle of 83°, and a C—C—S···O projection angle of −74°. The other is to O(6) $[x, 1+y, 1+z]$, where there is an S···O distance of 3·53 Å, the C—S···O angle is 92° and the C—C—S···O projection angle is 99°. There

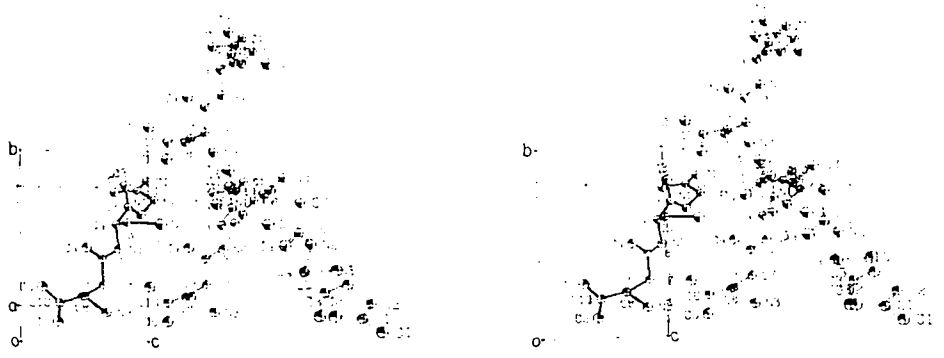


FIGURE 21. Stereoscopic view of the structure of glutathione. This picture was drawn from the coordinates presented in reference 5. Atom numbering here and in Figure 22 is that from the original paper.

is virtually no structural basis for making a judgement between these two alternatives. Either would seem to lead to quite reasonable S—H···O hydrogen-bonding arrangements, although the projection angle in the case of O(6) $[x, 1+y, 1+z]$ is somewhat unfavourable. The projection along the C(5)—S bond is shown in Figure 22.

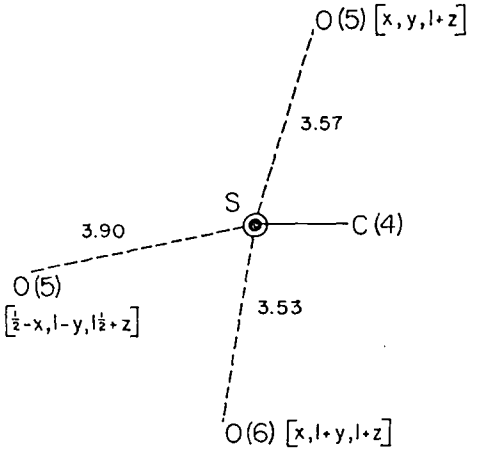


FIGURE 22. Projection along the C(5)—S bond in glutathione.

A view of the packing in the structure of the 2 : 1 cysteylglycine : NaI complex is shown in Figure 23. This picture was drawn by us from the coordinates presented in reference 6. Again, there are several possible hydrogen bonding assignments. The most probable appears to involve S—H···S hydrogen bonding. The S···S $[-x, \frac{1}{2}+y, \frac{1}{2}-z]$ distance is 3·62 Å, well below the 4·10 Å limit discussed earlier. The C—S···S angle

FIGURE 23. Stereoscopic view of the structure of the L-cysteylglycine : NaI complex. This picture was drawn from the coordinates presented in reference 6. Atom numbering used here and in Figure 24 is that from the original paper.

is 73° and the C—C—S···S projection angle is −174°. This assignment would lead to a series of S—H···S bonds along a column of molecules related by a screw axis. Another possibility would involve S—H···I⁻ hydrogen bonding. The S···I⁻ distance is 4·09 Å and the C—S···I⁻ angle is 100°. The van der Waals radius of I and the ionic radius of I⁻ are both 2·15 Å, so S···I⁻ distances of less than 4·50 Å would have to be considered as potential hydrogen bonding situations. The C—C—S···I⁻ projection angle is 83°. The projection along the C(4)—S bond is shown in Figure 24.

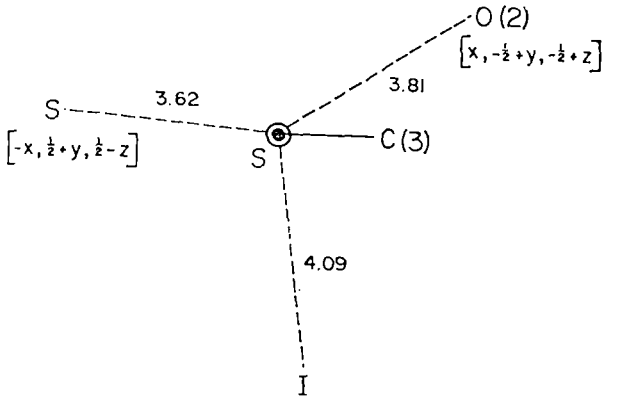


FIGURE 24. Projection along the C(4)—S bond in the 2 : 1 L-cysteylglycine : NaI complex.

While the above evidence for S—H···B hydrogen bonding is not overwhelmingly conclusive, in total it is persuasive. While neutron diffraction studies on some of these compounds would probably provide conclusive results, there are certainly reasonable indications from the crystal structure work that S—H···B hydrogen bonding does occur in solids. In some of the cases described, it appears that there is more than one possibility for hydrogen bonding. In such situations it is possible that there is disorder in the hydrogen position and two different types of hydrogen bonds exist. It is of special interest that the most probable hydrogen bonding assignments in the case of L-cysteine (monoclinic), L-cysteine (orthorhombic), and in the urea complex all lead to C—C—S···B projection angles in the range −26° to −47°.

Regardless of whether the thiol sulphur is a donor, there is a great deal of evidence that sulphur can act as the acceptor in hydrogen bonding in the solid state. Indeed, even if one accepts the more stringent requirements for A—H···S hydrogen bonding implicit in values of the van der Waals radii for sulphur and hydrogen of 1·75 and 1·00 Å[16,20,75,76], there is no doubt that this is a relatively important interaction in the

crystals of many compounds containing thione groups. This is dramatically demonstrated by surveys of the solid-state structures of sulphur-containing nucleic acid bases, nucleosides and nucleotides[33,78]. Out of thirteen published crystal structures of thionucleic acid bases or thionucleosides, only two (those of 4-thiouridine hydrate[79] and of the 1-methyl-4-thiouracil : 9-methyladenine complex[80]) did not exhibit A—H···S hydrogen bonding[33]. A list of these interactions taken from reference 33 is shown in Table 3. The A···S distances range from 3·133 (9) (A = oxygen) and 3·274 (8) (A = nitrogen) to 3·551 (2) Å (A = nitrogen); the H···S distances range from 2·27 (9) to 2·78 (8) Å; the A—H···S angles lie in the range from 120° to 176°.

In the cases of thioguanine and guanine[33], the replacement of the oxygen atom by a sulphur atom does not affect the general pattern of hydrogen bonding in the crystal, although where sulphur is involved the distances are necessarily longer and, presumably, the energy required to break the hydrogen bond is less. An earlier review by Donohue[78] is not restricted to nucleic acid components and surveys N—H···S hydrogen bonding in crystals described up to and including 1968. There are many subsequent examples with X—H···S bonds, for example, thiosemicarbazide[24], 2-mercaptobenzothiazole[25], 1-thiocarbamoylimidazolidine-2-thione[26] and 4,4′-dihydroxythiobenzophenone monohydrate[81]. It is worthy of note, however, that there is no evidence from the crystal structures of N,N′-diglycyl-L-cystine dihydrate[82], the hexagonal form of L-cystine[83], L-cystine dihydrochloride[84], or of L-cystine dihydrobromide[85] that the disulphide group in L-cystine acts as a hydrogen-bonding acceptor.

In solution, there is considerable evidence for participation of the thiol group in hydrogen bonding. Pimentel and McClellan[69] have summarized evidence cited by earlier workers both in favour of and against S—H···B hydrogen bonding in solution, and reached the conclusion that the S—H group did show specific hydrogen bonding association towards strong bases but that the relative weakness of the thiol group as a proton donor explained the absence of S—H···B hydrogen bonding in some systems. More recently, Marcus and Miller[86] have cited a number of papers wherein evidence was produced that the thiol group could act as a hydrogen bonding donor to oxygen, nitrogen, carbon and sulphur atoms, and possibly also to aromatic π-electrons. These authors[86] also studied the self-association of several thiols by n.m.r. techniques and concluded that hydrogen bonding plays an important part in such processes. A sampling of more recent work on the hydrogen bonding properties of the thiol group in solution suggests that in some systems there is S—H···B bonding but also that it does not always occur.

TABLE 3. Hydrogen bond distances and angles involving sulphur acceptors in crystal structures of thiopurines and thiopyrimidines

Compound	Distances (Å)			Donor—H—sulphur angle (deg)
	Donor atom	Donor—S	H—S	
6-Thioguanosine[a]	N(2)	3·274 (8)	2·39 (8)	145 (5)
6-Thioguanine[b]	N(2)	3·327 (5)	2·46 (4)	171 (3)
	N(7)	3·303 (5)	2·27 (4)	157 (3)
2-Thiocytidine[c]	N(4)	3·467 (5)	2·75 (5)	139 (4)
	O(water)	3·267 (5)	2·74 (5)	120 (4)
2,4-Dithiouracil,[d] atom S(2)	N(1)	3·335 (6)	2·78 (8)	157 (5)
2,4-Dithiouracil,[d] atom S(4)	N(3)	3·315 (6)	2·39 (8)	164 (5)
6-Mercaptopurine[e]	O(water)	3·373 (2)	2·58 (2)	162 (1)
6-Mercaptopurine riboside[f]	O(3′)	3·133 (9)	2·27 (9)	142 (5)
2-Mercapto-6-methyl-purine[g]	O(water)	3·26 (3)		
	N(1)	3·37 (3)		
2-Thiocytosine,[h] molecule A	N(4)	3·408 (2)	2·44 (2)	176 (1)
	N(4)	3·551 (2)	2·66 (2)	171 (1)
2-Thiocytosine,[h] molecule B	N(4)	3·345 (2)	2·41 (2)	176 (1)
	N(4)	3·466 (2)	2·58 (2)	168 (1)
2,4-Dithiouridine,[i] atom S(2)	O(5′)	3·218 (5)		
2,4-Dithiouridine,[i] atom S(4)	O(5′)	3·476 (5)		
	N(3)	3·330 (5)	2·41 (6)	158 (5)
3′-O-Acetyl-4-thiothymidine[j]	O(5′)	3·227 (6)	2·3 (1)	156 (7)
1-β-Arabinofuranosyl-4-thiouracil[k]	O(2′)	3·311 (5)	2·32 (7)	173 (6)
	O(3′)	3·343 (5)	2·45 (7)	142 (6)

[a] Reference 33.
[b] C. E. Bugg and U. Thewalt, *J. Amer. Chem. Soc.*, **92**, 7441 (1970).
[c] G. Hung-Yin Lin, M. Sundaralingam and S. K. Arora, *J. Amer. Chem. Soc.*, **93**, 1235 (1971).
[d] Reference 34.
[e] Reference 30.
[f] E. Shefter, *J. Pharm. Sci.*, **57**, 1157 (1968).
[g] Reference 31.
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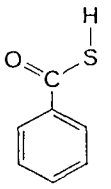
[i] G. Hung-Yin Lin and M. Sundaralingam, *Acta Crystallogr.*, B**27**, 961 (1971).
[j] W. Saenger and D. Suck, *Acta Crystallogr.*, B **27**, 2105 (1971).
[k] W. Saenger, *J. Amer. Chem. Soc.*, **94**, 621 (1972).

This table is taken from reference 33. Permission was kindly granted by the Editor of the *Journal of the American Chemical Society*.

The infrared spectra of a number of aliphatic carboxylic acids that also contain thiol groups were recorded and discussed by Saraswathi and Soundararajan[87]. They proposed that association through S—H···O hydrogen bonding occurs in the solid, yet is broken in solution. A combined infrared, ultraviolet and n.m.r. spectroscopic study[88] of thiolbenzoic acid (**41**) in solution provided little evidence for hydrogen-bonded dimerization of the type normally encountered in carboxylic acids. In a rather similar vein, no indications for intramolecular hydrogen bonding were detected in several thiols which also contained potential acceptor groups, but they were considered to be present in thiosalicyclic acid (**42**), even in acetonitrile solution[61]. Finally, an infrared study of nine thiophenols showed convincing evidence for intermolecular hydrogen bonding involving the S—H group, while in some *ortho*-substituted derivatives intramolecular hydrogen bonding was implicated[89].



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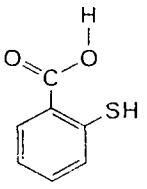

(42)

VIII. ACKNOWLEDGMENTS

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Note added in proof: Dr. K. A. Kerr has recently informed me of the results of a neutron diffraction study on the orthorhombic form of L-cysteine. These results indicate that the thiol hydrogen atom is disordered (60%, 40%) between two positions. At the first position it forms a hydrogen bond to $S[\frac{1}{2}-x, 2-y, -\frac{1}{2}+z]$, at the other it forms a hydrogen bond to O(2) $[1\frac{1}{2}-x, 2-y, \frac{1}{2}+z]$ (Figure 17). The S—H lengths were 1·30(2) and 1·25(3) Å, respectively. The results of the X-ray study on the orthorhombic form of L-cysteine have now appeared, K. A. Kerr and J. P. Ashmore, *Acta Crystallogr.*, **B29**, 2124 (1973). Results on another thiol-containing compound, L-β,β'-dimethylcysteine hydrochloride monohydrate have also been published, S. N. Rao, R. Parthasarathy, and F. E. Cole, *Acta Crystallogr.*, **B29**, 2373 (1973). In this latter investigation, the authors were unable to locate the thiol hydrogen atom.

The Chemistry of the Thiol Group
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CHAPTER 3

Thermochemistry of thiols

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I. INTRODUCTION

The thermochemistry of thiols is about a one-fourth part of the thermochemistry of sulphur compounds. Most of the data result from the work of three laboratories, namely, the Thermochemical Laboratory at the University of Lund, Sweden, the Bartlesville Petroleum Research Center in the U.S. Department of the Interior's Bureau of Mines, and the laboratory of Henry Mackle at the University of Belfast in Ireland.

The best method of determining the heats of combustion of sulphur compounds other than free radicals is generally recognized to be the rotating-bomb calorimeter method[1,2] that was developed in close to its present form in the 1950s. Since 1950 the currently accepted values of the enthalpies of formation of diatomic sulphur vapour[3] and of aqueous sulphuric acid[4,5] have been published. In addition, the last twenty years has seen a big improvement in the ease and accuracy of statistical mechanical calculation of entropies and heat capacities. Consequently, great care should be exercised when evaluating pre-1950 data. The recent activity in the sulphur thermochemistry field is particularly timely in view of the concern over the possible contribution to air pollution by sulphur oxides from combustion sources.

The thermochemical quantities under consideration are heat of formation ΔH_f^0, entropy S^0 and heat capacity C_p^0. Although the joule is now the

recommended unit of energy, English-speaking chemists and English language chemical journals still predominantly use the kilocalorie. The units used throughout this review will therefore be kcal/mole for ΔH_f^0, and cal/(mole-K) for S^0 and C_p^0.

II. MEASURED DATA

In spite of the recent flurry of activity in the field of thiol thermochemistry, there still is little data compared with that available for hydrocarbons. Perhaps the only advantage of so little data is that it is compact enough to be presented in a single table in a review article of this size, see Table 1. The arrangement of the table follows closely that used by Stull, Westrum and Sinke[6]. All of the compounds listed contain at least one carbon atom. In selecting values I have leaned heavily on recent reviews of thermochemical data by Stull, Westrum and Sinke[6], Cox and Pilcher[7], Domalski[8], El-Sabban and Scott[9] and an extensive new (1972) experimental effort by Good[10]. The values of ΔH_f^0 quoted by El-Sabban and Scott[9] differ from those of most other authors by $-15{\cdot}4$ kcal/mole per S atom because of a difference in reference states of sulphur. Thermochemical values for free alkylthio radicals are included in Table 1. Free radicals are too reactive for rotating-bomb calorimetry. Kinetic methods for determining heats of formation of alkylthio radicals are discussed in section IV.

In addition to the review monographs and the three main journals (*Journal of Chemical Thermodynamics*, *Journal of Chemical Engineering Data* and the new *Journal of Physical and Chemical Reference Data*), a vitally important key to the current literature is the *Bulletin of Thermodynamics and Thermochemistry* published annually by IUPAC. Most of the Bulletin's content is also on tape for mechanized searching. The Substance–Property Index is a good place to start a search. For each compound, this index gives the type of chemical thermodynamic property measured and a reference to another part of the Bulletin. This Bulletin reference is either a literature reference in the Bibliography of Recent Papers section or an abstract of work in progress at one of the 200 worldwide laboratories that contribute information to the Bulletin. The literature reference is usually both the original paper and a *Chemical Abstracts* reference.

III. ESTIMATION BY GROUP ADDITIVITY

Group Additivity is used to estimate thermochemical data that are lacking, to check measured data for consistency with those for chemically related compounds and to point out where further experiments are needed. The

TABLE 1. Thermochemical data for thiols

Formula	Name	State	ΔH_f^0 (kcal/mole)	Reference	S^0 (cal/mole-K)	Reference	C_p^0 (cal/mole-K)	Reference
CH_3S	Methylthio radical	g	29	13	57·6	14	9·9	14
CH_4S	Methanethiol	l	−11·09	6–8				
CH_4S	Methanethiol	g	−5·40	6, 7	60·96	6, 9	12·01	6, 9
C_2H_5S	Ethylthio radical	g	25	13	67·2	14	15·2	14
C_2H_6S	Ethanethiol	l	−17·53	6–7	49·48	6, 11	28·16	6, 11
C_2H_6S	Ethanethiol	g	−11·00	6, 7	70·77	6, 9	17·38	6, 9
$C_2H_6S_2$	1,2-Ethanedithiol	l	−12·83	7, 8				
$C_2H_6S_2$	1,2-Ethanethiol	g	−2·16	7				
C_3H_7S	*n*-Propylthio radical	g	18	13				
C_3H_7S	*i*-Propylthio radical	g	17	13	74·2	14	20·9	14
C_3H_8S	1-Propanethiol	l	−23·78	6–8	57·96	6	34·55	6
C_3H_8S	1-Propanethiol	g	−16·14	6, 7	80·40	6, 9	22·67	6, 9
C_3H_8S	2-Propanethiol	l	−25·22	6, 7	55·82	6	37·65	6
C_3H_8S	2-Propanethiol	g	−18·14	6, 7	77·51	6, 9	22·96	6, 9
$C_3H_8S_2$	1,3-Propanedithiol	l	−18·83	7, 8				
$C_3H_8S_2$	1,3-Propanedithiol	g	−6·95	7				
C_4H_9S	*n*-Butylthio radical	g	13	13				
C_4H_9S	*s*-Butylthio radical	g	12	13				
C_4H_9S	*i*-Butylthio radical	g	11	13				
C_4H_9S	*t*-Butylthio radical	g	9	13	77·2	14	26·8	14
$C_4H_{10}S$	1-Butanethiol	l	−29·70	6–8	65·96	6	41·20	6
$C_4H_{10}S$	1-Butanethiol	g	−20·98	6, 7	89·68	6	28·24	6
$C_4H_{10}S$	2-Butanethiol	l	−31·22	6, 7	64·87	6	40·91	6
$C_4H_{10}S$	2-Butanethiol	g	−23·09	6, 7	87·65	6, 9	28·56	6, 9
$C_4H_{10}S$	2-Methyl-1-propanethiol	l	−31·47	6, 7	63·66	6	41·16	6
$C_4H_{10}S$	2-Methyl-1-propanethiol	g	−23·17	6, 7	86·73	6, 9	28·34	6, 9

TABLE 1 (*cont.*)

Formula	Name	State	ΔH_f^0 (kcal/mole)	Reference	S^0 (cal/mole-K)	Reference	C_p^0 (cal/mole-K)	Reference
$C_4H_{10}S$	2-Methyl-2-propanethiol	l	−33·54	6, 7	58·90	6	41·84	6
$C_4H_{10}S$	2-Methyl-2-propanethiol	g	−26·12	6, 7	80·77	6, 9	28·90	6, 9
$C_4H_{10}S_2$	1,4-Butanedithiol	l	−25·12	7, 8				
$C_4H_{10}S_2$	1,4-Butanedithiol	g	−11·90	7				
$C_5H_{10}S$	Cyclopentanethiol	l	−21·34	6, 7	61·39	6	39·48	6
$C_5H_{10}S$	Cyclopentanethiol	g	−11·43	6, 7	86·38	6, 9	25·82	6, 9
$C_5H_{12}S$	1-Pentanethiol	l	−35·80	6–8	74·18	6, 11	48·12	6, 11
$C_5H_{12}S$	1-Pentanethiol	g	−26·24	6, 7	99·26	6, 11	33·75	6
$C_5H_{12}S$	2-Methyl-1-butanethiol	l	−36·83	10				
$C_5H_{12}S$	2-Methyl-1-butanethiol	g	−27·42	10				
$C_5H_{12}S$	2-Methyl-2-butanethiol	l	−38·84	6, 7				
$C_5H_{12}S$	2-Methyl-2-butanethiol	g	−30·30	6, 7	92·47	6, 9	34·29	6, 9
$C_5H_{12}S$	3-Methyl-1-butanethiol	l	−36·82	10				
$C_5H_{12}S$	3-Methyl-1-butanethiol	g	−27·40	7, 10				
$C_5H_{12}S$	3-Methyl-2-butanethiol	l	−37·87					
$C_5H_{12}S$	3-Methyl-2-butanethiol	g	−28·91	10				
$C_5H_{12}S$	2,2-Dimethyl-1-propanethiol	l	−39·46	10				
$C_5H_{12}S$	2,2-Dimethyl-1-propanethiol	g	−30·76	10				
$C_5H_{12}S_2$	1,5-Pentanedithiol	l	−30·99	7				
$C_5H_{12}S_2$	1,5-Pentanedithiol	g	−16·82	7				
C_6H_5S	Phenylthio radical	g	50	13				
C_6H_6S	Benzenethiol	l	15·32	6–8	53·25	6	41·36	6
C_6H_6S	Benzenethiol	g	26·80	6, 7	80·52	6, 9	25·06	6, 9
$C_6H_{12}S$	Cyclohexanethiol	l	−33·55	10	61·80	12	46·04	12
$C_6H_{12}S$	Cyclohexanethiol	g	−22·88	7, 10	87·19	9	31·82	9
$C_6H_{14}S$	1-Hexanethiol	l	−41·84	6–8	82·03	11	55·14	11

TABLE 1 (*cont.*)

Formula	Name	State	ΔH_f^0 (kcal/mole)	Reference	S^0 (cal/mole-K)	Reference	C_p^0 (cal/mole-K)	Reference
$C_6H_{14}S$	1-Hexanethiol	g	−30·89	6, 7	108·52	6, 11	39·21	6
$C_6H_{14}S$	2,3-Dimethyl-2-butanethiol	l	−44·61	10				
$C_6H_{14}S$	2,3-Dimethyl-2-butanethiol	g	−35·22	10				
$C_6H_{14}S$	2-Methyl-2-pentanethiol	l	−44·92	10				
$C_6H_{14}S$	2-Methyl-2-pentanethiol	g	−35·37	10				
C_7H_7S	Phenylmethylthio radical	g	55	13				
C_7H_8S	α-Toluenethiol	l	10·57	6, 7	53·25	6	41·36	6
C_7H_8S	α-Toluenethiol	l	8·73	10				
C_7H_8S	α-Toluenethiol	g	22·9	6, 7				
C_7H_8S	α-Toluenethiol	g	22·26	10				
$C_7H_{16}S$	1-Heptanethiol	l	−47·82	6, 7	89·71	11	61·98	11
$C_7H_{16}S$	1-Heptanethiol	g	−35·73	6, 7	117·76	6, 11	44·68	6
$C_{10}H_{22}S$	1-Decanethiol	l	−66·07	6, 7	113·08	11	83·75	11
$C_{10}H_{32}S$	1-Decanethiol	g	−50·65	6, 7	145·82	6	61·08	6

Group Additivity method is simple, fast and accurate, and is quickly gaining wide acceptance as the best method for estimation of thermochemical data.

Group Additivity postulates that chemical thermodynamic properties of molecules are made up of contributions from the individual groups that comprise the molecule. Group Additivity is therefore an extension of the series atom additivity, bond additivity, ..., and turns out to be an excellent compromise between simplicity and accuracy. For a detailed treatment of the additivity principle as applied to thermochemistry, see an early paper by Benson and Buss[15], and a more recent *Chemical Reviews* article[16]. The latter contains all the group values that could be derived from gas-phase thermochemical data for thiols up to 1969. The group values permit the estimation of ΔH_f^0 to an accuracy of better than ± 1 kcal/mole, S^0 to an accuracy of ± 1 cal/mole-K), and C_p^0 to an accuracy of $\pm 0{\cdot}5$ cal/(mole-K).

As an example of the power of Group Additivity for heats of formation, let us consider the six thiols whose heats of formation have been measured since 1969, and therefore do not appear in the *Chemical Reviews* paper*. In Table 2, the values for the six thiols measured by Good[10] are compared with estimates calculated for the present work using Group Additivity.

With only one exception, the fit between observed and estimated values, using no next-to-nearest neighbour interaction, is excellent.

TABLE 2. Comparison of observed heats of formation (in kcal/mole) with those calculated using Group Additivity

Compound	Obs.	Est.	Obs. − Est.
2-Methyl-1-butanethiol	−27·42	−27·24	−0·18
3-Methyl-1-butanethiol	−27·40	−27·24	−0·16
3-Methyl-2-butanethiol	−28·91	−29·36	0·45
2,2-Dimethyl-1-propanethiol	−30·76	−30·77	0·01
2,3-Dimethyl-2-butanethiol	−35·22	−36·55	1·33
2-Methyl-2-pentanethiol	−35·37	−35·17	−0·20
α-Toluenethiol	22·6	21·9	0·7

The Benson and Buss paper[15] contains bond contributions that permit estimation for thiols of ΔH_f^0 to ± 6 kcal/mole, S^0 and C_p^0 at 25°C to ± 3 cal/(mole-K). The accuracy of bond additivity is, therefore, not as

* There are two misprints in the *Chemical Reviews* entry for 3-methyl-1-butane-thiol. The estimated heat of formation should be −28·04 and the Δ should be +0·63 kcal/mole.

good as that of Group Additivity, but it is often good enough for a first-order approximation. Even atom additivity can be used for S^0 and C_p^0 at 25°C and has about the same accuracy as bond additivity. The Benson and Buss paper has the atom contributions.

The next step in developing Group Additivity is to extend it to the liquid phase. As yet there are no groups available for heats of formation of liquids. However, Group Additivity has been used[17] for the estimation of the heat capacities of liquids at 25°C with an improvement in precision from about ±4 to better than 1·5 cal/(mole-K). As an example, C_p^0 (liquid for the *n*-alkanethiols are shown in Table 3.

TABLE 3. Comparison of observed and estimated heat capacities of liquid *n*-alkanethiols

Thioalkane	C_p (liquid) observed	C_p (liquid) estimated by Group Additivity	ΔC_p obs. − est.	C_p (liquid) − C_p (gas)
Ethanethiol	28·2	27·1	1·1	10·8
1-Propanethiol	34·6	34·4	0·2	11·9
1-Butanethiol	41·2	41·6	−0·4	12·9
1-Pentanethiol	48·1	48·8	−0·7	14·4
1-Hexanethiol	55·1	56·1	−1·0	15·9
1-Heptanethiol	62·0	63·3	−1·3	17·3
1-Decanethiol	83·8	85·2	−1·4	22·7

If the required groups are not available, then C_p^0 of the liquid can be estimated to within a few cal/(mole-K), if the C_p^0 of the ideal gas is known, from ΔC_p^0 (liquid minus gas) = 12 cal/(mole-K). This rule breaks down for long straight chain molecules. The longer the chain, the worse the rule is obeyed, as is shown in Table 3.

IV. KINETICS AND THERMOCHEMISTRY

One of the main uses of thermochemistry, a well-developed science, is to help understand kinetics, which is still something of an art. The relationship between thermochemistry and kinetics has been treated in detail in a particularly useful monograph[18] by Benson. Therefore, only the main aspects will be discussed here, followed by specific cases of importance in thiol chemistry.

Most elementary chemical reactions obey the Arrhenius law over a limited temperature range, and so their rate constants can be broken down

into pre-exponential Arrhenius A-factors (or entropies of activiation) and activation energies (or heats of activation).

$$k = A\exp(-E/RT)$$

$$= \frac{eKT}{h}\exp(\Delta S_T^{0\ddagger}/R)\exp(\Delta H_T^{0\ddagger}/RT)$$

where k is the rate constant, A is the Arrhenius A-factor, E is the activation energy, R is the gas constant, T is absolute temperature, K is Boltzmann's constant, h is Planck's constant, $\Delta S^{0\ddagger}$ is the entropy of activation, and $\Delta H^{0\ddagger}$ is the heat of activation, and the subscript T is a temperature in the middle of the range. The entropy and heats changes at T are related to those at 298 K (25°C) by

$$\Delta H_T^{0\ddagger} = \Delta H_{298}^{0\ddagger} + \int_{298}^{T} \Delta C_p^{0\ddagger}\,dT$$

$$\Delta S_T^{0\ddagger} = \Delta S_{298}^{0\ddagger} + \int_{298}^{T} \frac{\Delta C_p^{0\ddagger}}{T}\,dT$$

where $\Delta C_p^{0\ddagger}$ is the standard state reaction heat capacity change. Although $\Delta C_p^{0\ddagger}$ is generally a function of temperature, for most purposes it may be taken as constant even over a wide temperature range. For example, Benson, Golden and Shaw[19] have recently shown that for the reaction A + BC → AB + C, where A, B and C are atoms, $\Delta C_p^{0\ddagger}$ is 3 ± 1 cal/(mole-K) from 200 to 4000 K.

There is another useful relation between Arrhenius parameters and thermochemistry. For example, in the reaction

$$CH_3 + RSH \rightleftharpoons CH_4 + RS \qquad (1)$$

it can be shown that the overall entropy change for the reaction ΔS_1^0 is related to the A-factor of the forward reaction A_1 and the A-factor of the reverse reaction A_{-1}, by $\exp(\Delta S_1^0/R) = A_1/A_{-1}$. Similarly, the heat of reaction ΔH_1^0 is related to the activation energy of the forward reaction E_1, and the activation energy of the back reaction E_{-1} by $\Delta H_1^0 = E_1 - E_{-1}$. Therefore, if the Arrhenius parameters of the forward reaction are known, the Arrhenius parameters for the back reaction can be calculated exactly from the known or estimated thermochemical properties of the reactants and products with no assumption necessary for transition state properties.

An important example of the interaction between thermochemistry and kinetics is the kinetic method for determining bond dissociation energies. This subject has been reviewed in detail by Kerr[20]. To take a specific case,

the bond dissociation energy of $CH_3S—H$ is the enthalpy, ΔH_2^0, of the reaction

$$CH_3SH \longrightarrow CH_3S+H \qquad (2)$$

$D(CH_3S—H) = \Delta H_2^0 \approx E_2 - E_{-2} = E_2$ with the reasonable assumption that E_{-2} is negligible. Thus the bond dissociation energy $D(CH_3S—H)$ can be obtained by measuring the activation energy for the reaction $CH_3SH \rightarrow CH_3S + H$. In practice the pyrolysis of CH_3SH does not occur by clean, unimolecular, S—H fission, so an alternative approach is used. The enthalpy of reaction ΔH_2^0, is also given by

$$\Delta H_2^0 = \Delta H_f^0(CH_3S) + \Delta H_f^0(H) - \Delta H_f^0(CH_3SH) \qquad (3)$$

Values for $\Delta H_f^0(H)$ and $\Delta H_f^0(CH_3SH)$ are known independently, so the problem is to find $\Delta H_f^0(CH_3S)$. Consider

$$PhCH_2SCH_3 \longrightarrow CH_3S+PhCH_2 \qquad (4)$$

$\Delta H_4^0 = \Delta H_f^0(CH_3S) + \Delta H_f^0(PhCH_2) - \Delta H_f^0(PhCH_2SCH_3) = E_4$. The $PhCH_2$—SCH_3 bond is the weakest bond in the molecule, so bond fission occurs primarily by reaction (4). From E_4 and known values of $\Delta H_f^0(PhCH_2)$ and $\Delta H_f^0(PhCH_2SCH_3)$, Mackle[21] obtained $\Delta H_f^0(CH_3S) = 30{\cdot}5$ kcal/mole, close to the currently accepted value[13] of 29 kcal/mole. Using this value of $\Delta H_f^0(CH_3S)$, the $CH_3S—H$ bond strength follows from known values of $\Delta H_f^0(H)$ and $\Delta H_f^0(CH_3SH)$.

However, it turns out the mechanisms and kinetics of decomposition of sulphur compounds are so complex that the kinetic method of determining bond strengths is less reliable than the electron impact method[13,21,22]*. Thus, instead of using kinetics as a basis for the thermochemistry, the thermochemistry is used to help understand the kinetics. The agreement in the preceding paragraph between the $CH_3S—H$ bond strength derived from the kinetic method and that derived from the electron impact method is due to compensating errors in E_4 and $\Delta H_f^0(PhCH_2)$ in the kinetic method.[20]

Sulphur—hydrogen bond strengths in thiols in Table 4 have been calculated from currently accepted heats of formation. The table shows that there is very little variation in the S—H bond strength in the alkanethiols. In benzenethiol, the S—H strength is reduced by benzylic-type resonance of 12 kcal/mole. H_2S is the zeroth member of the series, yet the bond strength is only slightly greater than for the other members. This is in marked contrast to the alcohols, where the O—H bond strength in water is 15 kcal/mole stronger than in methanol (see Table 5). It is also interesting

* See also the chapter on mass spectra in this volume.

TABLE 4. Sulphur—hydrogen bond strengths in thiols, calculated from heats of formation. All units are kcal/mole.

Alkanethiol	ΔH^0_{f298}(RSH)	ΔH^0_{f298}(H)	ΔH^0_{f298}(RS)	D(RS—H)
H_2S	−4·8	52·1	34	91
CH_3SH	−5·5	52·1	29	87
C_2H_5SH	−11·0	52·1	25	88
$CH_3(CH_2)_2SH$	−16·2	52·1	18	86
$(CH_3)_2CHSH$	−18·2	52·1	17	87
$CH_3(CH_2)_3SH$	−21·0	52·1	13	86
$(CH_3CH_2)(CH_3)CHSH$	−23·1	52·1	12	87
$(CH_3)_2CHCH_2SH$	−23·2	52·1	11	86
$(CH_3)_3SH$	−26·2	52·1	9	87
$C_6H_5CH_2SH$	21·9	52·1	55	85
Average alkylthio—hydrogen bond strength = 86·5 ± 1·5				
C_6H_5SH	26·7	52·1	50	75

Heats of formation of H, HS and H_2S are from Benson[18]. All others are from Fine and Westmore[13].

TABLE 5. A comparison of bond strengths (in kcal/mole) in thiols, alcohols and amines

Bond broken	Bond strength
HS—H	91
HO—H	119
H_2N—H	110
AlkS—H	87
AlkO—H	104
AlkNH—H	103
PhS—H	75
PhO—H	85
PhNH—H	86
Alk—SH	69
Alk—OH	91
Alk—NH_2	87
Ph—SH	86
Ph—OH	110
Ph—NH_2	104

The thiol data are from reference 13. The hydroxyl data are from references 22 and 23. The amino data are from references 23 and 24.

to note from Table 5 that the *S*—H bond in thiols is considerably weaker than the O—H bond in alcohols and the N—H bond in amines, and further that the C—S bond in thiols is much weaker than the C—O bond in alcohols and the C—N bond in amines. The consequence is, of course, that thiols are much less thermally stable than alcohols and amines.

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VI. REFERENCES

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The Chemistry of the Thiol Group
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CHAPTER 4

Preparation of thiols

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I. INTRODUCTION

The most direct method for the formation of thiols would be the insertion of sulphur into a carbon—hydrogen bond. This has no general synthetic application and is restricted to little more than a few nitrogen heterocyclic thiol syntheses.

In general, the preparations of alkanethiols can be considered separately from those of aromatic thiols. There are, in principle, methods available for both alkane and aromatic thiols, such as the reaction of organomagnesium and organolithium compounds with controlled quantities of sulphur;

$$R{-}m \xrightarrow{S_8} R{-}S{-}m \longrightarrow R{-}S{-}H$$

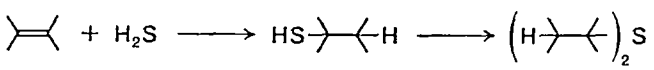
m=Li; MgX

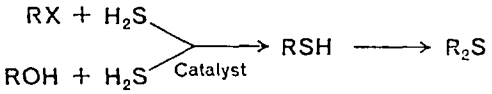
however, this particular procedure is seldom used for alkanethiols, except perhaps for *tert*-alkanethiols, which are difficult to prepare by other methods.

A. Alkanethiols

The most readily available starting materials for the preparation of alkyl derivatives are alkenes, alkyl halides and alcohols, the former two, in particular, are extensively used in thiol preparations although routes from the latter are also available. The simpler methods of preparation are, in theory, additions to alkenes and substitution of alkyl halides and alcohols by hydrogen sulphide. These methods are often used since the starting materials are available and cheap but unfortunately in these reactions

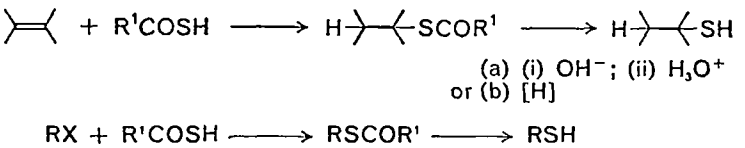
monosulphides are also significant products and their formation can be a decided disadvantage. To circumvent the formation of waste material from the hydrogen sulphide reactions, a number of less direct methods involving the use of other sulphur-containing compounds have been



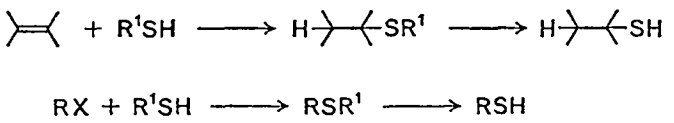


devised. Such methods of preparation of thiols must include hydrolysis, reduction or some bond cleavage of the intermediate. The disadvantage of the extra step must be weighed against the advantage of the cleaner and less wasteful reaction.

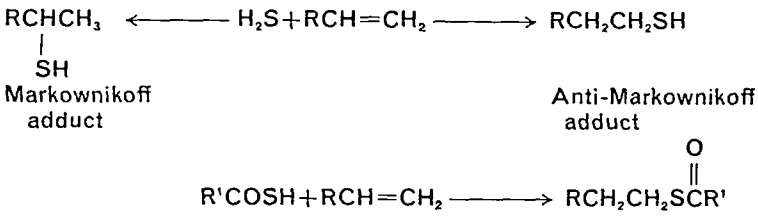
Among the indirect methods are reactions of both alkenes and alkyl halides with thiolcarboxylic acids—normally thiolacetic acid



and with thiols, R^1SH, containing an easily cleavable $R^1—S$ bond:



The stereospecificities of the thiolcarboxylic acid and thiol additions to alkenes are similar to that of the hydrogen sulphide additions (all being less stereospecific than that of hydrogen bromide) and so present no additional advantages or disadvantages on this account. The thiolcarboxylic acid additions, however, are less versatile than the hydrogen sulphide additions. From an alkene and hydrogen sulphide, either the Markownikoff product (via an ionic reaction) or the anti-Markownikoff product (via a free radical reaction), can be obtained in the presence of a suitable catalyst or agent, whereas the usual thiolcarboxylate would be the anti-Markownikoff adduct.



Among the other sulphur-containing compounds used with alkyl halides are thiourea, thiolsulphate ion, alkyl xanthate ion, trithiocarbonate ion, thiocyanate ion and less frequently phosphorothiolate ion and dialkyl dithiocarbamate ion (Table 1). The means of converting the intermediates

TABLE 1. Methods of formation of thiols, RSH, from alkyl halides, RX

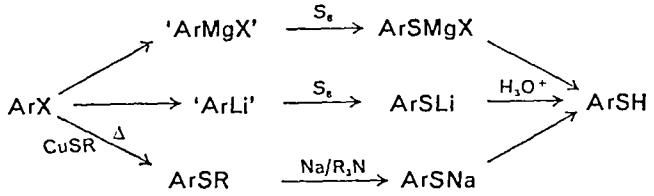
No.	Reagent	Intermediate	Conversion of intermediate into thiol
1	Sulphydryl ion		
2	Thiolcarboxylic acid, R^1COSH	$R-S-\overset{\overset{O}{\|}}{C}-R^1$	(a) (i) OH^- (ii) H_3O^+ (b) $LiAlH_4$
3	Thiol, R^1SH	$R-S-R^1$	(i) Na (ii) H_3O^+
4	Thiourea, $(NH_2)_2CS$	$R-S-C(=NH\cdot HX)-NH_2$ *iso*-Thiuronium salt	(i) Base (ii) H_3O^+
5	Alkyl xanthate ion, $R^1-O-\overset{\overset{S}{\|}}{C}-S-$	$R-S-\overset{\overset{S}{\|}}{C}-OR^1$ Xanthate	(a) (i) OH^- (ii) H_3O^+ (b) $LiAlH_4$
6	Thiosulphate ion, $S^2O_3^{2-}$	$R-S-SO_3^{2-}$ Bunté salt	H_3O^+
7	Trithiocarbonate ion $CS_3^{2-}(\leftarrow CS_2+S^{2-})$	$R-S-\overset{\overset{S}{\|}}{C}-S-$	(a) H_3O^+ (b) $LiAlH_4$
8	Phosphorothiolate ion, PSO_3^{3-} $(\leftarrow PSCl_3+3OH^-)$	$R-S-PO_3^{3-}$	H_3O^+
9	Dialkyl dithiocarbamate ion, $R_2^1N\cdot\overset{\overset{S}{\|}}{C}-S-(\leftarrow S_2C+OH^-+HNR_2)$	$R-S-\overset{\overset{S}{\|}}{C}-NR_2$	(i) OH^- (ii) H_3O^+
10	Thiocyanate ion, NCS^-	R—SCN	[H]
11	(i) Magnesium or lithium (ii) Sulphur	[R-m] R-S-m	H_3O^+

from these reactions, into thiols are indicated in the Table. These methods, coupled with that using organometallic compounds, provide a variety of routes for obtaining thiols from alkyl halides.

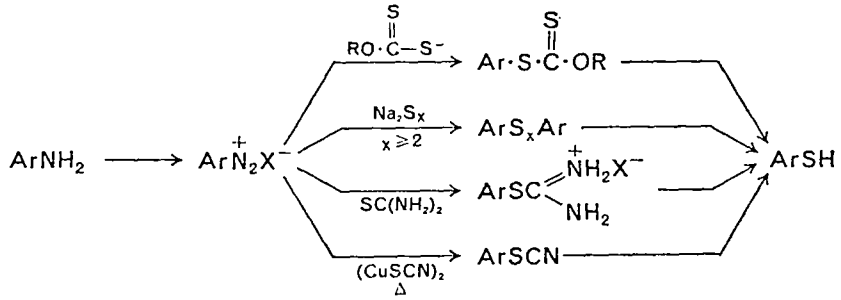
From alcohols, useful, but less direct methods than reaction with hydrogen sulphide are reaction with phosphorous pentasulphide and the prior conversion of the alcohol to a sulphonate or a sulphate before reaction with hydrogen sulphide.

B. Aromatic Thiols

Conversion of haloaromatics, which have strong electron-withdrawing groups present, into thiols can be achieved by the same methods available to alkyl halides; examples of such methods are reactions, with hydrogen sulphide ion, thiosulphate ion and thiourea. Simple haloaromatics cannot be so converted to thiols. However, there are available two useful routes for these compounds; that using organo-magnesium and -lithium compounds and that involving reaction with cuprous alkyl mercaptides and the subsequent cleavage of the so-formed alkyl aryl sulphides.



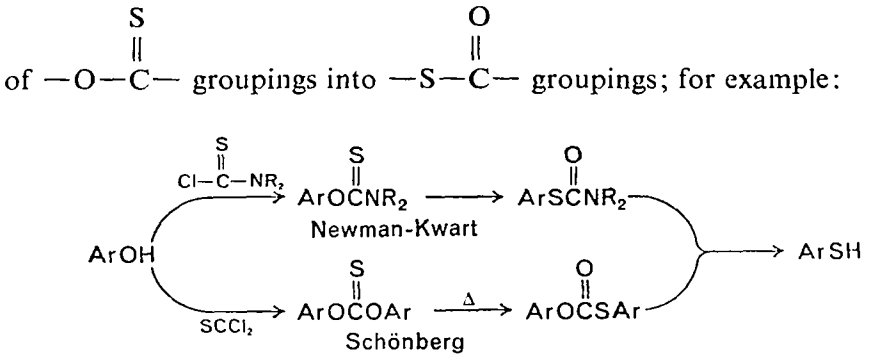
There are other general routes to aromatic thiols involving the conversion of other functional groups and substituents in the aromatic nucleus.



From primary aromatic amines, several variations are possible, each involving the reaction of the corresponding diazonium salt with a sulphur

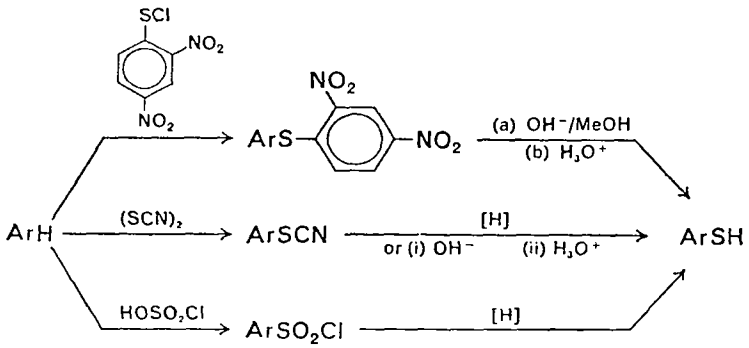
nucleophile. The oldest of these procedures is the xanthate reaction. This is still the most frequently used method, but all the others have considerable potential. The possibility of explosions with the xanthate variation and side reactions should turn more attention to the other methods.

Aromatic hydroxyl groups are also readily converted to thiol groups by fairly recently developed methods. These incorporate the conversions



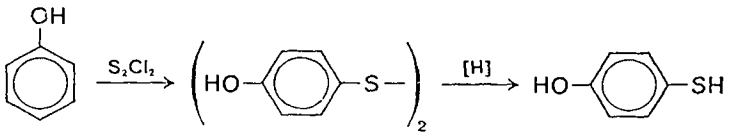
Of these two methods, that involving the Newman–Kwart rearrangement has had the most use and is now a well-established route to thiophenols from phenols.

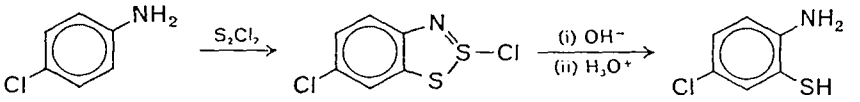
The usage of aromatic electrophilic substitutions by sulphur electrophiles provides another general type of method of formation of thiols (from



aromatic hydrocarbons with the overall replacement of hydrogen by the sulphydryl group). The limitations in these methods are that aromatics with electron-withdrawing groups will not react and only certain isomers can be produced. The reactions of sulphur dichloride with phenols and

anilines could also be included as other examples of electrophilic aromatic substitutions leading to thiol products.





All these methods are discussed in the body of the chapter. Also included in this chapter is a section on the conversion of monosulphides and disulphides to thiols.

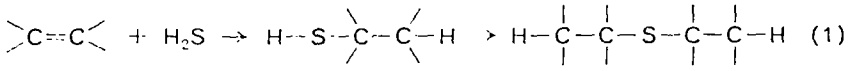
Functional substituted thiols have been prepared by the methods already outlined in this Introduction and given appropriate space in the body of the chapter. Specifically, a number of β-amino-, β-alkoxy- and β-thioalkoxy-thiols have been obtained from the cleavage of the appropriate 3-membered ring by hydrogen sulphide. Furthermore the formation of *gem*-dithiols from aldehydes and ketones is given attention.

Among the more recent reviews on thiol formation are references 1, 2a, 2b and 2c.

II. FORMATION FROM ALKENES

A. Hydrogen Sulphide Additions

This is in principle the simplest process for preparing alkanethiols. However, the further reaction of the initially formed thiol with the alkene, giving sulphides, severely limits the utility of this method[3], especially in those cases where the initially formed thiol is more reactive than H_2S towards the alkene [use of a 2·5 : 1 hydrogen sulphide to cyclohexene mole ratio at 150°C for 24 h led to cyclohexanethiol (2·5%) and dicyclohexyl sulphide (12%)][4].



Usually the use of a high hydrogen sulphide : alkene mole ratio favours the formation of the thiol[5]. Thus, in the photoinitiated reaction of hydrogen sulphide with 1-chlorocyclohexene with a reaction time of 4 hours, 18·6 and 65·0% chlorocyclohexanethiol products were obtained from mole ratios of hydrogen sulphide to alkene of 1 : 1 and 18 : 1 respectively.

Two isomeric thiols can in principle be formed from an unsymmetric alkene, e.g.

$$RCH{=}CH_2 \xrightarrow{H_2S} \underset{(1)}{RCHCH_3}(SH) + \underset{(2)}{RCH_2CH_2SH}$$

where **1** is termed the Markownikoff product and **2**, the anti-Markownikoff adduct. Equilibrium mixtures of the two thiols from the reaction of propylene and hydrogen sulphide were obtained at 200–300°C in the presence of a nickel catalyst[6]. At lower temperatures and generally when

$$\underset{\text{(2–3 parts)}}{CH_3CH(SH)CH_3} + \underset{\text{(1 part)}}{CH_3CH_2CH_2SH} \longleftarrow CH_3CH{=}CH_2 + H_2S$$

non-equilibrium situations prevail, one or other of the two thiols can be obtained in the higher yield by a suitable choice of a catalyst. The production of the Markownikoff compound is catalysed by a variety of materials, including metal sulphides[4,7] and oxides[8], acids[9] and sulphur[4,10]. Branched

$$RCH{=}CH_2 \xrightarrow[\text{catalyst}]{H^+} RCHCH_3 \xrightarrow{SH^-} RCH(SH)CH_3$$

chain alkenes react faster than straight chain and terminal alkenes in these ionic reactions[11].

The anti-Markownikoff adduct, **2**, is formed in a free-radical reaction[3a,12], catalysed by ultraviolet and other radiation and the usual

$$H_2S \longrightarrow HS^{\bullet}$$

$$RCH{=}CH_2 + HS^{\bullet} \longrightarrow RC^{\bullet}HCH_2SH$$

$$RC^{\bullet}HCH_2SH + H_2S \longrightarrow RCH_2CH_2SH + HS^{\bullet}$$

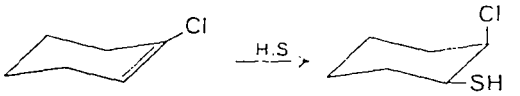
radical initiators; ultraviolet light has proved particularly useful[5b,13]. These reactions have been used for terminal, internal and cyclic alkenes.

In the oxygen-initiated addition of hydrogen sulphide to alkyl vinyl ethers, the rate of reaction decreased as the branching in the alkyl group increased. Furthermore, as the branching increased, so did the amount of the Markownikoff product, due to the increasing ease of oxidation of the vinyl ethers to acidic materials (which then act as Markownikoff

$$ROCH{=}CH_2 \xrightarrow{H_2S} ROCH_2CH_2SH \qquad (2)$$

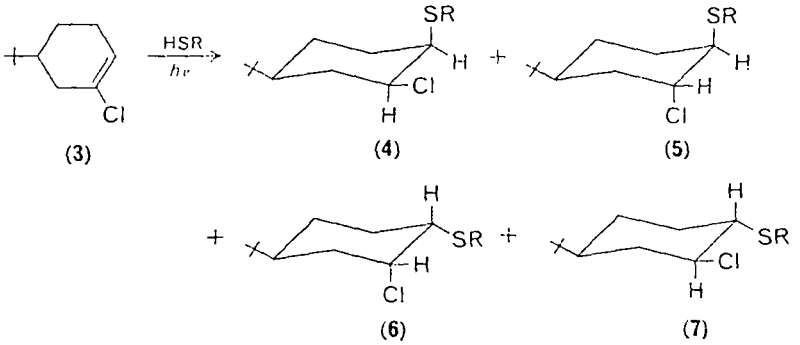
catalysts)[5a]. The ultraviolet light ($\lambda = 253{\cdot}7$ nm) initiated reaction of 1-butene with H_2S (1 : 2 mole ratio) at 0°C gave a mixture of *n*-butanethiol (85%) and di-*n*-butyl disulphide (15%); the authors mentioned that 80% of butene had reacted within minutes[13], under much more milder conditions than are required for the ionic process leading to 2-mercaptobutane. Longer wavelength radiation can also be used in the presence of photo-sensitizers, such as acetone, lead tetra-acetate and mercury compounds. γ-Radiation has also been successfully used[14]. Of all the chemical initiators, azonitriles are reported to be generally the most satisfactory[15]. Other chemical initiators occasionally fail; peroxides, for example, can oxidize H_2S to sulphur and the ionic process would then be favoured[12].

The stereochemistry of the products from the photo-induced radical reaction of hydrogen sulphide with 1-chlorocyclohexane[5b] has been investigated. The major thiol product was *cis*-chlorocyclohexanethiol



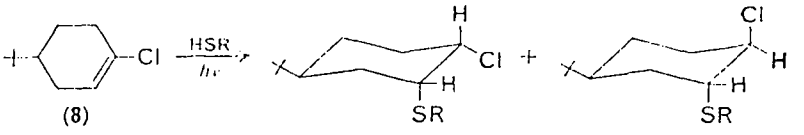
cis-chlorocyclohexanethiol

(85–90%); the remaining products being the *trans* isomer and mixed sulphides. The additions of hydrogen sulphide and thiols to 1- and 2-chloro-4-*t*-butylcyclohexenes in the presence of azobis*iso*butyronitrile have also been studied and the product ratios for the hydrogen sulphide and some thiol (for comparison) additions are given below[16]:

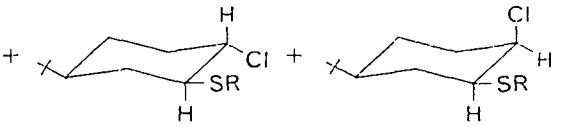


(3) (4) (5) (6) (7)

Yields at 5°C	(4)	(5)	(6)	(7)	$[H_2S]$: alkene
R = H	78·9%	2·2%	8·9%	10·0%	12 : 1
Me	82%	5%	6%	7%	10 : 1
COMe	74·6%	5·7%	13·1%	6·5%	10 : 1



(8) (9) (10)



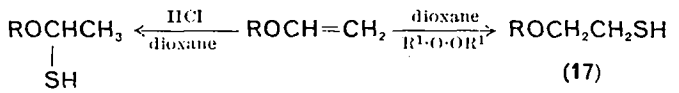
(11) (12)

Yields	(9)	(10)	(11)	(12)	
R = H	71·3%	1·2%	18·2%	9·3%	a 10 : 1
COMe	61·3%	4·5%	19·8%	14·8%	b 10 : 1

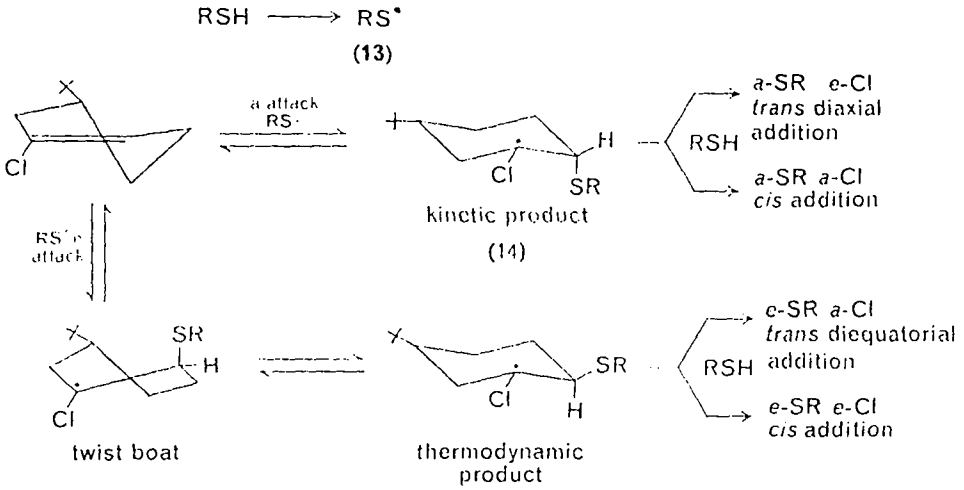
a at −50° C b at +60° C

Temperature and thiol concentration affected the product ratios, but *trans* diaxial anti-Markownikoff adducts always predominated in these reactions. The stereospecificities of the hydrogen sulphide and thiol additions are less than that for hydrogen bromide in which only 2-*cis*-chloro-4-*cis*-*t*-butyl cyclohexyl bromide was obtained. This difference is accounted for in terms of a reversal of the thiyl-radical addition step, the extent of which depends among other factors on the relative stabilities of the thiyl (**13**) and the thiyl-cyclohexyl radicals (**14** and **15**) and the rate of chain transfer (Scheme 1). (Such a reversal step is not important for the HBr reaction.) Bridged radicals were thought not to be important[16].

Modifications in the reaction media can readily change the type of addition. Thus catalytic amounts of hydrogen chloride dissolved in dioxane caused the formation from vinyl ethers and H_2S of **16**, while in the absence of hydrogen chloride, the peroxide impurities in the sample of dioxane used were sufficient to direct the formation to **17** [17].



(16) (17)



SCHEME 1. Reaction of thiols with 2-chloro-4-*t*-butylcyclohexene. *a* = *axial*; *e* = *equatorial*.

Reactions of allylamine with hydrogen sulphide under various conditions have been studied[18]. The reactants when irradiated with ultraviolet radiation did not give thiol products. However, at 85–95°C in an autoclave in the presence of azobis*iso*butyronitrile, a mixture of 1-amino-2-propanethiol (**18**) (4 parts) and 3-amino-2-propanethiol (**19**) (1 part) was

$$H_2S + CH_2{=}CHCH_2NH_2 \longrightarrow \underset{\displaystyle SH}{\underset{|}{CH_3CHCH_2NH_2}} + HSCH_2CH_2CH_2NH_2$$

(18) (19)

obtained. Amines are inhibitors of radical reactions and so the high yield of the Markownikoff adduct (**18**), under the radical conditions used, is understandable as is the lack of thiol products in the photochemical reaction. Good yields of the anti-Markownikoff adduct, (**19**), arise when salts of allylamine and hydrogen sulphide are reacted under radical conditions, since the amine salts are not inhibitors of radical reactions. The hydrogen chloride salt proved to be a better reagent than the acetic acid salt. Sulphides were also obtained in these reactions.

Alkenes, with electron-withdrawing groups such as carbonyl-[19,20,22], cyano-[21,25], nitro-[23], and carboxyl-[21,24] and ester-groups[24,25], are activated for nucleophilic attack by the thiolate anion and for such compounds, base catalysts are favoured.

TABLE 2. Base-catalysed additions of hydrogen sulphide to alkenes

No.	Alkene	Thiol	Catalyst	Yield (%)	Ref.
1	Mesityl oxide	$(H_3C)_2\underset{\displaystyle SH}{\underset{\vert}{C}}CH_2COCH_3$	—	60	19a
2	Methyl isopropenyl ketone	$CH_3COCH(CH_3)CH_2SH$	Et_3N	70	19b
3	Crotonic acid	$CH_3\underset{\displaystyle SH}{\underset{\vert}{C}}HCH_2CO_2H$	Et_2NH	53	21
4	Vinylacetic acid	$CH_3\underset{\displaystyle SH}{\underset{\vert}{C}}HCH_2CO_2H$	Et_2NH	38	21
5	Nitroethylene	$O_2NCH_2CH_2SH$	—	16	23
6	1-Nitro-2-methyl-prop-1-ene	$(CH_3)_2\underset{\displaystyle SH}{\underset{\vert}{C}}CH_2NO_2$	—	32	23

Vinylacetic acid (**20**) and crotonic acid (**21**) both give β-mercaptobutyric acid (**22**) on treatment with hydrogen sulphide in ethanol in the presence of diethylamine at 70°C in a sealed vessel[21]. Under these reaction conditions, **20** isomerizes to **21** before the reaction with hydrogen sulphide.

$$\underset{\textbf{(20)}}{CH_2{=}CHCH_2CO_2H} \longrightarrow \underset{\textbf{(21)}}{CH_3CH{=}CHCO_2H} \xrightarrow{H_2S;\,Et_2NH} \underset{\textbf{(22)}}{CH_3\underset{\displaystyle SH}{\underset{\vert}{C}}HCH_2CO_2H}$$

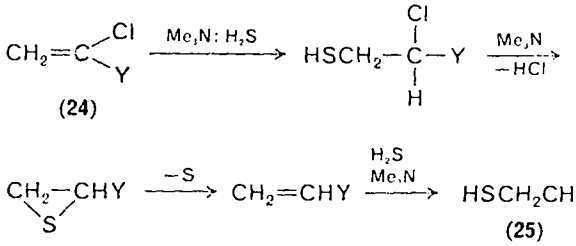
Acrylonitrile and crotononitrile on similar treatment solely produced the sulphides (**23**) and not the thiols.

$$\left(\begin{array}{c} \overset{\displaystyle S}{\overset{\Vert}{C}} \\ H_2N-C-CH_2-\underset{\displaystyle R}{\underset{\vert}{C}}H- \end{array}\right)_2 S \qquad R = CH_3 \text{ and } H$$

(23)

α-Chloromethyl acrylate (**24** with Y = CO_2Me), and hydrogen sulphide at −78°C and in the presence of trimethylamine gave a number of products, including β-mercaptomethyl propionate (**25**) in 15% yield[25]. The proposed

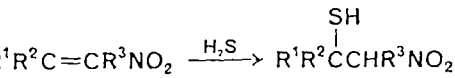
mechanism for the formation of **25** was by way of episulphide and alkene intermediates. α-Chloroacrylonitrile (**24** with Y = CN), reacted similarly.



(24)

(25)

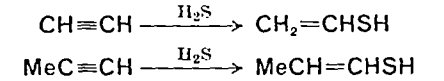
For the very activated nitroalkenes, such as $CH_2{=}C(NO_2)CH_3$ and $(CH_3)_2C{=}CHNO_2$, the basicity of the solvent, ethanol, was sufficient to effect the addition of hydrogen sulphide[23]. Much more sulphide products were obtained from primary alkenes than from branched alkenes. This was



(3)

rationalized by the primary thiols being more acidic than secondary or tertiary thiols, and creating less steric hindrance so that their reaction with alkenes are faster from both kinetic and steric factors. Methoxide ion and pyridine[26] have also been successfully used as catalysts.

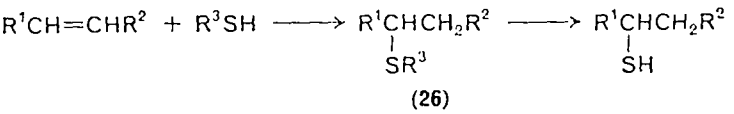
Additions to acetylenes have also been carried out under both photochemical[27,28] and X-ray initiation[29]. Thus at −78°C using a mercury lamp, acetylene and methylacetylene gave respectively vinyl thiol and a single geometric isomer of 1-propene-1-thiol, probably the *trans* compound[27]. Direct photolysis of acetylene at higher temperatures led to polymeric



material, $[CH_2{\cdot}CHSH]_n$[28]. X-Ray radiation[29] at room temperature gave vinyl thiols, divinyl sulphides, vicinal dithiols and also polymeric material.

B. Additions of Other Sulphur Acids

Additions of other sulphur acids to alkenes are frequently used in thiol preparations; the required thiol being obtained from the intermediate compounds after hydrolysis or dealkylation. Although an extra



(26)

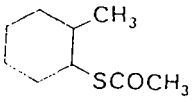
(4)

R^3 = alkyl, aralkyl or acyl

step is required compared to the direct hydrogen sulphide addition, there are advantages, one of which is that formation of waste sulphides [e.g. $(R^1CHCH_2R^2)_2S$] is prevented. The choice of R^3SH (equation 4) is governed by the ease of cleavage of the R^3—S bond in the unsymmetric sulphide (**26**). Of particular utility is thiolacetic acid and its additions to alkenes are next discussed.

I. Thiolacetic acid additions

Table 3. Addition of thiolacetic acid to alkenes

No.	Alkene	Product	Yield (%)	Ref.
1	4-Methyl-1-pentene	$CH_3CH(CH_3)CH_2CH_2CH_2SCOCH_3$	93·5	33
2	Oct-1-ene	n-$C_8H_{17}SCOCH_3$	100	34
3	Oct-2-ene	$CH_3CH(SCOCH_3)(CH_2)_5CH_3$ and $CH_3CH_2CH(SCOCH_3)(CH_2)_4CH_3$	100	34
4	Mesityl oxide	$(CH_3)_2C(SCOCH_3)CH_2COCH_3$	92	34
5	Allyl acetate	$SCH_2CH_2CH_2CO_2Et$ $\vert$ $COCH_3$	100	34
6	1-Methylcyclohexene		94	31
7	4-Oxo-2-pentenoic acid	2-Acetylthio-levulinic acid	95	36
8	α-Bromoacrylic acid	$CH_2C(Br)CO_2H$ $\vert$ $SCOCH_3$	92	37

Thiolacetic acid additions [$R^3 = CH_3C(=O)$, equation (4)] initially reported by Holmberg[30], are exothermic processes leading to the anti-Markownikoff adducts in good yields[31–34]. Photolysis and the usual radical initiators are frequently used.

$$XCH{=}CH_2 \longrightarrow XCH_2CH_2SCOCH_3 \longrightarrow XCH_2CH_2SH \qquad (5)$$

Hydrolysis of the thiolesters is normally achieved by alcoholic alkali (see p. 206). Several β-substituted thiols have been prepared by this method; the method is of particular importance for X = alkoxy and aryloxy[35], and for unsaturated acids and carbonyl compounds[34,36–38], e.g.

$$CH_3COCH{=}CHCO_2H \xrightarrow{CH_3COSH} CH_3COCH(SCOCH_3)CH_2CO_2H \longrightarrow$$

95%

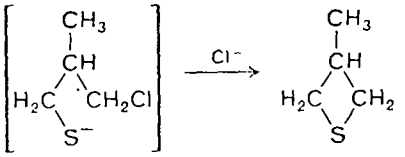
$$CH_3COCH(SH)CH_2CO_2H$$

Reference 36

However, for a β-chloro-alkene, the product normally isolated after alkaline hydrolysis of the thiolacetate was a cyclic sulphide[39–40] arising from an internal nucleophilic substitution in the intermediate thiolate, e.g.

$$CH_2{=}C(CH_3)CH_2Cl + CH_3COSH \xrightarrow{h\nu} CH_3COSCH_2CH(CH_3)CH_2Cl \xrightarrow{OH^-}$$

88%

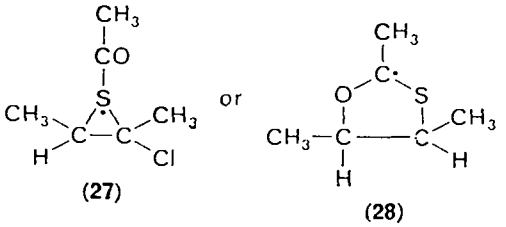


80%

For a series of pentenoic acids, the order of reactivity[38] towards thiolacetic acid was

$$CH_3CH_2CH{=}CHCO_2H < CH_3CH{=}CHCH_2CO_2H < CH_2{=}CHCH_2CH_2CO_2H$$

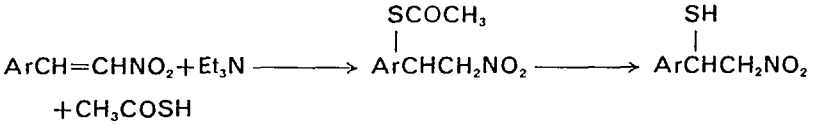
From either *cis*- or *trans*-2-chlorobut-2-enes, the same mixture of erythro- (10%) and threo- (90%) 2-acetylmercapto-3-chlorobutanes was obtained[40]; hydrolysis of the product mixture gave the episulphide. The same mixture of products from either reactant argues against bridged intermediates, such as **27** or **28**, and in favour of open intermediates which have time to equilibrate before reaction.



(27) (28)

Thiolacetic acid additions to cyclohexenes are less stereospecific than those of hydrogen bromide[16]. A reversal step was clearly shown by the isomerization of *cis*- and *trans*-2-chlorobutenes by catalytic quantities of thiolacetic acid[40]. In these reactions chlorobutyl thiolacetates must be formed reversibly, and eventually equilibrium concentrations of the two isomeric alkenes must be obtained. Other examples of the reduced stereospecificity of thiolacetic acid additions are given in references 39 and 40; e.g. only 85% *cis* with 15% *trans* adducts were obtained from 1-methylcyclohexene[41]. For a more detailed description of radical additions of thiolacetic acid to cyclohexenes, see reference 42.

Additions of thiolacetic acid to alkenes with strongly electron-withdrawing groups are catalysed by base[43], e.g.



2. Thiol additions

A detailed discussion of thiol additions to alkenes is outside the scope of this chapter: for reviews on this, see references 3a and 12. Dealkylation of sulphides to thiols is considered elsewhere in this chapter (section XIII).

III. FORMATION FROM ALCOHOLS

A. Using Hydrogen Sulphide

Direct reaction between hydrogen sulphide and alcohols normally requires the presence of a catalyst. Several processes involve basic catalysts, high temperatures and high pressures[44–46]. With basic alumina

$$ROH + H_2S \xrightarrow{\text{Catalyst}} RSH + H_2O$$

as the support, basic promoters favour thiol formation and acidic promoters give more dialkyl sulphides[47]. Kramer and Reid[48] gave details of the preparation of the lower thiols up to *iso*-amyl thiol in 35–52% yield from the passage of alcohol vapour and hydrogen sulphide over a heated thoria catalyst. Higher yields of thiols were obtained using a potassium tungstate/alumina catalyst system[49].

Triphenylmethanethiol has been obtained in 75% yield by passage of H_2S through a solution of the alcohol in acetic acid containing sulphuric acid[50] *. Probably, trityl hydrogen sulphate was initially formed, which then reacted with H_2S. Dialkyl sulphates and metal hydrogen sulphates have been known since 1834 to give thiols on reaction with H_2S[51]. A facile laboratory preparation of ethanethiol from ethanol, sulphuric acid and H_2S has been described by Reid[52]. Generally the yields of the lower thiols produced by this method are low—~25%, but the ready availability of the starting materials still makes this an attractive method. Sulphides and alkenes, especially at high pH, are also formed.

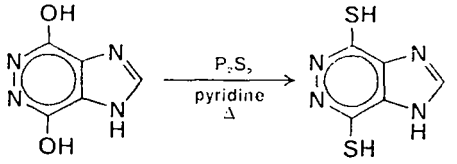
Sulphonates, too, have been used as starting materials[53]; e.g. octadecyl *p*-toluenesulphonate gave 76% thiol.

B. Using Phosphorus Pentasulphide

For alkanethiols, the formation from alcohols and phosphorus pentasulphide has been patented[55]. C_4–C_{16} alcohols can be converted to dialkyldithiophosphates, which on acid hydrolysis give the corresponding thiols. Yields greater than 70% can be obtained if the sulphides formed in the reaction are dealkylated to give thiols as well.

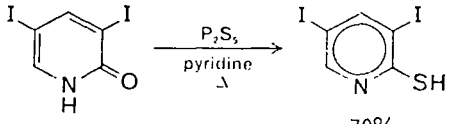
In the nitrogen-heterocyclic field, hydroxyl groups (or the carbonyls in the tautomeric amide groups) are readily converted to thiol units by phosphorous pentasulphide in the presence of pyridine. In such a way mercapto-imidazo-[4,5-d]-pyridazines[56,57], -pyridines[58], -purines[59,60] and -pyrimidines[61] can be obtained. Thiation and ring closure of 5-acetamido-2,4-diamino-6-hydroxy-pyrimidines also occur in a single step using P_2S_5.

* A better general method of preparation of tertiary thiols uses the reaction of HBr and thiourea on the alcohols[54].



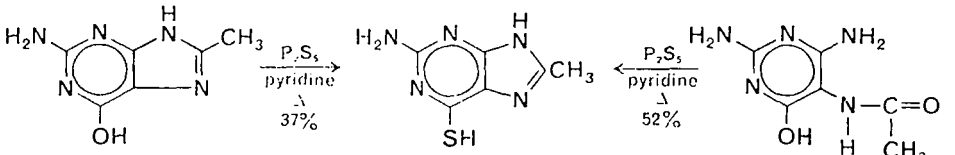
4,7-dihydroxyimidazo-[4,5-d]-pyridazine
Reference 56

79%



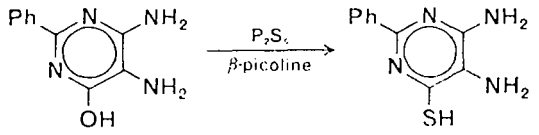
3,5-diiodo-2-pyridone
Reference 58

70%



2-Amino-6-hydroxy-8-methylpurine
Reference 60

5-Acetamido-2,4-diamino-6-hydroxy-pyrimidine



4,5-diamino-6-hydroxy-2-phenyl-pyrimidine
Reference 61

51%

IV. FORMATION FROM HALIDES AND HYDROGEN SULPHIDE

A. Alkyl Halides

Alkyl chlorides, bromides and iodides all react readily with metal hydrogen sulphides, frequently the sodium salt, in alcohol solution to give thiols[62]. Primary and secondary alkanethiols, for example, are prepared from the corresponding chlorides and NaHS, obtained by the action of

hydrogen sulphide either on alcoholic potassium hydroxide or on sodium ethoxide[63]. For thiols up to C_9, ethanol was found to be a good solvent, while for C_{10}–C_{18} compounds, a higher boiling alcohol, such an *n*-butanol, was a preferable solvent[64]. The higher mercaptans were produced in good yields from alkyl iodides and NaHS in an autoclave[65].

The higher mercaptans, particularly, are readily converted to disulphides by air oxidation especially in alkaline media and care to avoid this must be taken[65]. More significant general by-products are the dialkyl sulphides. The following equilibrium guarantees some formation of the sulphides. The equilibrium lies further to the right at higher temperature

$$2NaHS \rightleftharpoons Na_2S + H_2S$$

and so lower temperatures are to be preferred for thiol formation. From some halides, e.g. α-bromoketones, sulphides are predominantly formed[66] in reaction with the sulphydryl ion. Some difference between the use of sodium and potassium hydrogen sulphide has been reported; e.g. hexyl bromide in aqueous ethylene glycol gave at 155°C, 48% thiol and 29% sulphide with NaHS and with the same concentration of KHS, 19% thiol and 62% sulphide. The presence of H_2S or H_2SO_4 increased the yields of the thiol. In anhydrous glycol, 90% of hexanethiol was formed using NaHS[67] and the halide.

Another drawback in this procedure is the formation of alkenes[65,68]. A little cyclopentene was obtained as well as the thiol from the reaction of cyclopentyl bromide with KHS, while from cyclohexyl bromide, the major product was cyclohexene[68].

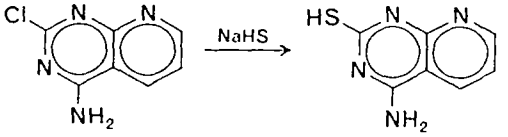
Tertiary aliphatic thiols are generally more difficult to prepare by this route, due to the ease of formation of the alkene. Triphenylmethanethiol has been obtained in 85% yield from the chloride and hydrogen sulphide in the presence of activated alumina[69].

α,ω-Dithiols were also obtained by this method from the dibromides, $Br(CH_2)_nBr$[70]. As well as the desired products and the usual impurities, polymeric sulphides and cyclic sulphides—especially for $n = 4$ and 5—were also obtained. Such was the amount of the cyclic tetra- and pentamethylene sulphides, that the dithiols are best prepared otherwise, namely *via* the isothiuronium method[70], see section VI. Heating the dihalide and hydrogen sulphide in a closed vessel has also been used[71].

An alternative approach is to treat the alkyl bromide or iodide with disodium disulphide in liquid ammonia to give the disulphide, which is cleaved by sodium. Thiols are obtained in good yields after acidification, e.g. $HSCH_2CH_2SH$ in 76% overall yield[72].

B. Heterocyclic Halides

Replacement of halogens in heterocyclic compounds by the sulphydryl group is also an easy reaction in several systems, e.g. pyridines[73], imidazo[4,5-d]pyridazines[74] and pyrido-[2,3-d]-pyrimidines[75]. With chloropteridine however, use of sodium sulphide in aqueous ethanol was preferred to NaHS, since the latter gave an addition complex[76]; a related complex was also obtained when thiourea was used.



2-mercapto-4-amino-pyrido-[2,3-d] pyrimidine

C. Aryl Halides

Nucleophilic replacements of halogen only proceed favourably under mild conditions if strongly electron-withdrawing groups are present in the aromatic compound. Thus halogens in halonitroaromatics, particularly those which are *ortho* or *para* to the nitro groups can be replaced by a

TABLE 4. Formation of thiols from reaction of aryl halides with metal sulphides

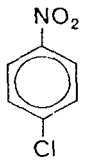
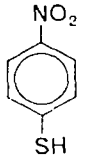
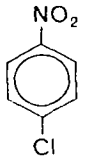
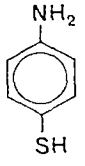
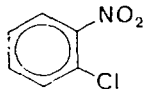
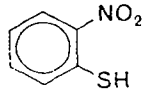
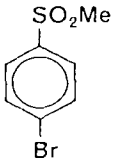
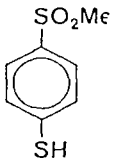
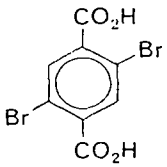
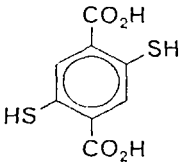
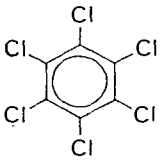
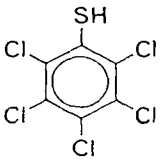
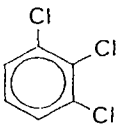
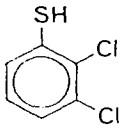
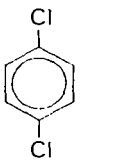
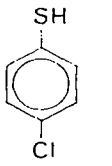
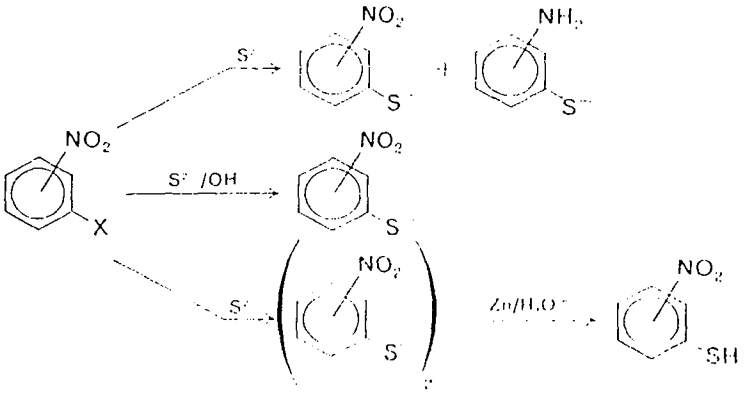
No.	Aryl halide	Thiol product	Method	Yield (%)	Reference
1			A	60–65	78
2			B	69	81
3			C	68	83

TABLE 4 (*cont.*)

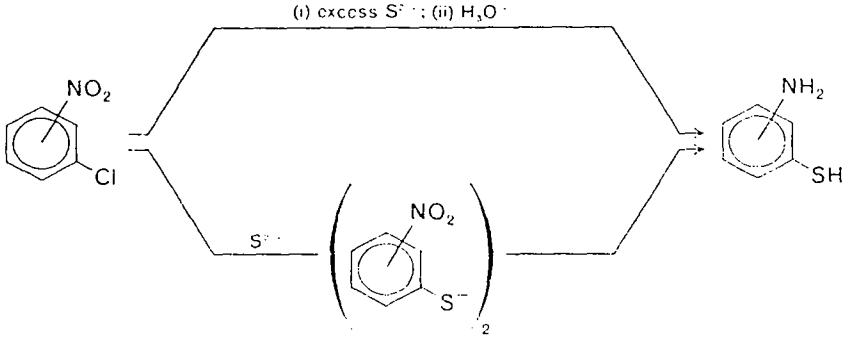
No.	Aryl halide	Thiol product	Method	Yield (%)	Reference
4			D	27	80
5			E	90	87
6			F	96	85
7			F	20	85
8			F	0	85

A. (i) Na_2S_2; (ii) OH^-; (iii) H_3O^+.
B. (i) Na_2S; (ii) HOAc.
C. (i) Na_2S_2; (ii) Zn/HOAc.
D. (i) Na_2S_2; (ii) glucose/OH^-; (iii) H_3O^+.
E. Cu, KSH.
F. (i) NaSH, liquid NH_3; (ii) H_3O^+.

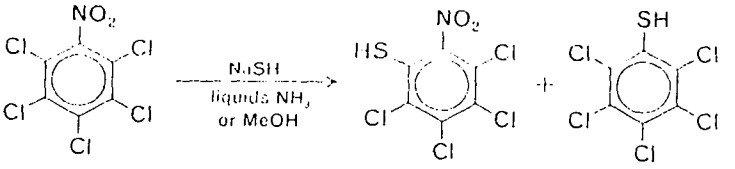
thiol unit. The direct route using sodium sulphide, followed by acid hydrolysis is possible[77], but substantial production of amino compounds limits the utility of this method for production of nitrothiophenols. Use of disodium disulphide in an alkaline medium appears to avoid the



disadvantage and good yields of the salts of nitrothiophenols are obtained in a single step[78]. Formation of di-(nitroaryl) disulphides from disodium-disulphide and their subsequent reduction to the thiophenol is an often used variation of this procedure[79,80]. Of course, the controlled simultaneous replacement of the halogen and reduction of the nitro group by sulphide ion is a good method of preparation of aminothiophenols[81,82] from halonitrobenzenes. Another possible pathway to prepare aminothiophenols from halonitrobenzenes is to obtain first the di-(nitrophenyl) disulphide and then reduce both the nitro and disulphide groups in one step[83].



Replacement of chloro and nitro groups in polychloronitrobenzenes by sulphydryl groups has been reported to occur in liquid ammonia and also in methanol[84]. Thus, pentachloronitrobenzene gives both 2,3,4,5-tetrachloro-6-nitrothiophenol and 2,3,4,5,6-pentachlorothiophenol. Polychlorobenzenes, $CCl_{6-x}H_x$ for $6 \leqslant x \leqslant 3$, also reacted with sodium hydrogen sulphide, either in liquid ammonia or methanol, to give the corresponding thiophenols[85], $CCl_{5-x}H_xSH$. Hexafluorobenzene reacted similarly[86], but

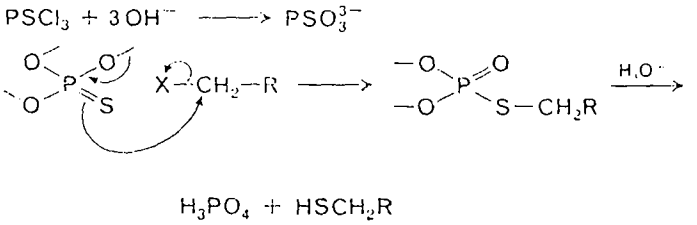


p-dichlorobenzene did not react, even in the presence of cupric acetate. The presence of the methanesulphonate group allows the nucleophilic replacement of bromide by the sulphydryl group in *p*-bromophenylmethyl sulphonate[80]. Both the halogens in 2,5-dibromoterephthalic acid were replaced directly by thiol groups[87], in the presence of copper.

In the absence of electron-withdrawing groups, forcing conditions are required to bring about reaction. Thus treating chlorobenzene with an excess of dry sodium sulphide in a polar organic solvent, such as 1-methyl-2-pyrrolidone or dimethyl acetamide at 300°C for some hours yields both thiophenol and diphenyl sulphide. Variations of the mole ratios of the reagents affect the product ratios, with approximately 50% of the thiophenol being the optimum yield[88]. Another patent describes the production of thiophenol from halobenzenes and hydrogen sulphide in the gas phase over a catalyst comprised of activated charcoal and a metal sulphide[89].

V. USING PHOSPHOROTHIOLATE ION

Treatment of alkyl halides, RX, by trisodium (or trilithium) phosphorothiolate and the acid hydrolysis of the alkyl-S-phosphorothiolate is a mild method of replacing X by SH [90]. The alkali metal phosphorothiolates are



best obtained by alkaline hydrolysis of thiophosphoryl chloride[90,91]. In such a way, 3-bromo-2-(bromoethyl)-propionic acid was converted at room temperature to the dithiol in 50% yield: i.e.

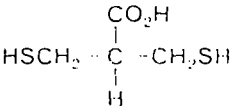
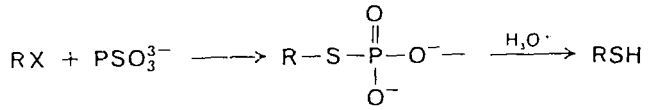
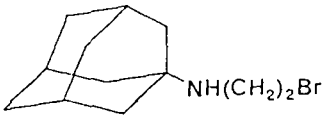
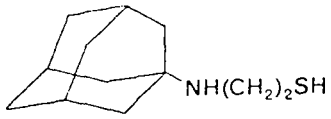


TABLE 5. Production of alkyl thiols from halides via phosphorothiolate intermediates



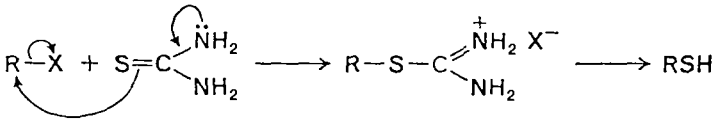
No.	Alkyl halide	Thiol	Yield (%)	Reference
1	$(BrCH_2)_2CHCO_2H$	$(HSCH_2)_2CHCO_2H$	50	90
2	$NH(CH_2)_3NH(CH_2)_2Br$ $\vert$ $(CH_2)_4$ $\vert$ $NH(CH_2)_3NH(CH_2)_2Br$	$NH(CH_2)_3NH(CH_2)_2SH$ $\vert$ $(CH_2)_4$ $\vert$ $NH(CH_2)_3NH(CH_2)_2SH$	80	92
3	$NH(CH_2)_2Br$ $\vert$ $(CH_2)_3$ $\vert$ $NH(CH_2)_4NH_2$	$NH(CH_2)_2SH$ $\vert$ $(CH_2)_3$ $\vert$ $NH(CH_2)_4NH_2$	74	92
4			88	93

Derivatives of 2-aminoethanethiols have been successfully prepared via the phosphorothiolate route[92,93].

VI. FORMATION *VIA ISO*-THIURONIUM SALTS: USE OF THIOUREA

A. S-Alkyl-iso-Thiuronium Salts from Alkyl Halides

This method, generally involving the reaction of a halide with thiourea to give an *iso*-thiuronium salt, and hydrolysis of the latter, is superior to that using hydrogen sulphide and alkyl bromides and iodides (but not



however chlorides), since it is experimentally simpler and no waste sulphides are formed. Mono- and di-thiols, from aliphatic as well as from aromatic halides, activated for nucleophilic attack, have been so prepared.

A variety of alkyl halides have been used as reagents, including haloalkylcarboxylic acids[95], tertiary alkyl halides[96] and unsaturated halides[97].

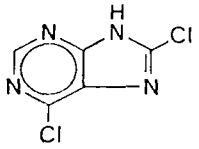
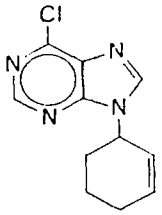
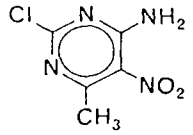
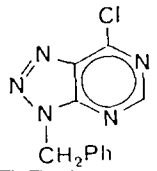
Older procedures[98] used alkaline hydrolysis, followed by steam distillation or ether/benzene extraction to collect the thiol from the reaction mixture. Details for such methods are given by Reid[94]. More recent developments include the use of a high boiling solvent (e.g. triethylene glycol) in which both to prepare the *iso*-thiuronium salt and to decompose it with a high boiling amine (e.g. tetraethylene pentamine)[99]. This modification gave good yields of alkanethiols (>68%) and α,ω-dithiols (>58%), except of ethane-1,2-dithiol. The di-*iso*-thiuronium salt of the latter on treatment with an amine eliminated ethylene sulphide which in turn reacted with the amine to give a substituted aminoethanethiol[99].

TABLE 6. Formation of thiols from halides *via iso*-thiuronium salts

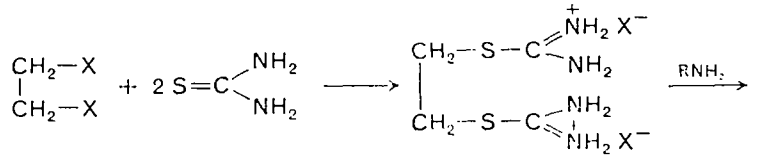
$$RX + SC(NH_2)_2 \longrightarrow R{-}S{-}C(=NH\cdot HX)(NH_2) \longrightarrow RSH$$

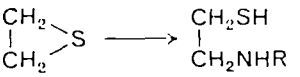
No.	Halide	Yield of thiol (%)	Method of decomposing *iso*-thiuronium salt	Reference
1	C_2H_5Br	68	Tetraethylene pentamine in ethylene glycol	99
2	n-C_3H_7Br	79	Tetraethylene pentamine in ethylene glycol	99
3	n-C_4H_9Br	77	Tetraethylene pentamine in ethylene glycol	99
4	n-$C_8H_{17}Br$	84	Tetraethylene pentamine in ethylene glycol	99
5	$Br(CH_2)_5Br$	80	Tetraethylene pentamine in ethylene glycol	99
6	$Br(CH_2)_4Br$	78	Tetraethylene pentamine in ethylene glycol	99
7	$Br(CH_2)_3Br$	58	Tetraethylene pentamine in ethylene glycol	99
8	$Br(CH_2)_2Br$	0	Tetraethylene pentamine in ethylene glycol	99
9	$Br(CH_2)_2Br$	60	$KOH/H_2O/\Delta$	100
10	2-Bromostearic acid	67	$OH^-/EtOH/\Delta$	95
11	$PhCH_2Cl$	almost 100	$NaHCO_3/\Delta$	101
12	p-$BrC_6H_4CH_2Br$	97–100 (p-$BrC_6H_4CH_2SH$)	DMSO/NaOH	102
13	9-Fluorenyl bromide	99	DMSO/NaOH	102

TABLE 6 (*cont.*)

No.	Halide	Yield of thiol (%)	Method of decomposing *iso*-thiuronium salt	Reference
14		97	EtOH/Δ	103
15		95·8	$OH^-/H_2O/\Delta$	105
16		100	EtOH/Δ	104
17		90	$OH^-/H_2O/\Delta$	107

However, alkaline hydrolysis of the di-*iso*-thiuronium salt has been successful[100]. Thermal decomposition of the *iso*-thiuronium salt in the presence of the mild bicarbonate ion has been reported[101].

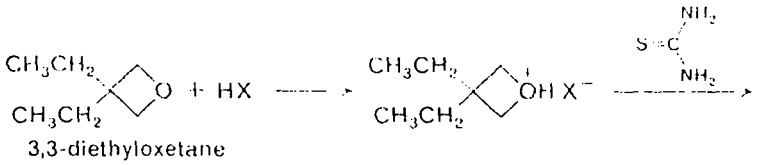




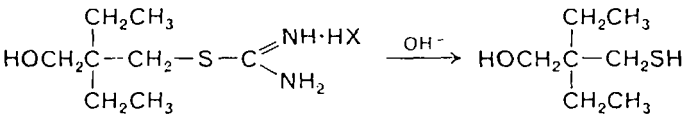
The use of dimethyl sulphoxide (DMSO) as the solvent enabled a single-step, high-yield preparation of aralkyl thiols to be made[102]. The

aralkyl halide and thiourea were stirred in DMSO at room temperature and on pouring into 10% aqueous sodium hydroxide the thiolate was formed. This mild method is useful for heat-sensitive compounds.

An interesting preparation of 3-mercapto-2,2-diethylpropan-1-ol involved the ring opening of an oxetane ring by thiourea in the presence of a strong acid[290]. Perchloric acid was the favoured acid, since its anion is poorly nucleophilic. (Hydrochloric acid also produced some $HOCH_2C(Et)_2CH_2Cl$.)



3,3-diethyloxetane

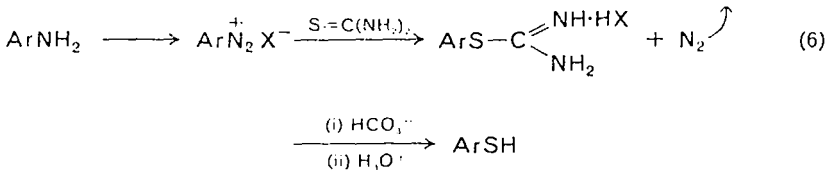


Extensive use has been made of the *iso*-thiuronium method in N-heterocyclic chemistry, e.g. for preparation of thiol derivatives of purines[103-106], pyrimidines[104] and azapurines[107]. The reactive pyrrolethiols have also been prepared *via* their *iso*-thiuronium salts[108].

B. S-Aryl-iso-Thiuronium Salts

1. From aryl halides and diazonium salts

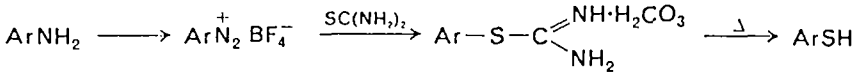
The decomposition of aryl *iso*-thiuronium salts to thiols has been variously reported[109-112]. A number of useful routes to aryl *iso*-thiuronium salts are available; the simple preparation from thiophenols and cyanamide can, of course, be neglected here. Nitrohalobenzenes[112-114] react directly with thiourea or tetramethylthiourea. When no electron-withdrawing groups are present, such a direct method fails. However,

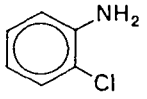
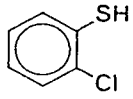
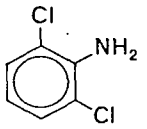
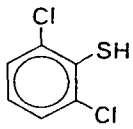
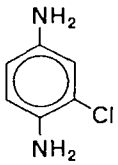
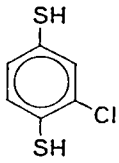
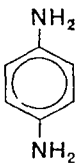
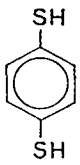


(6)

diazonium salts do give *iso*-thiuronium salts on reaction with thiourea[109-113] and so thiophenols can be prepared from anilines[109-111]. The method of Freidlina, Kopylova and Khasanova[112] of preparing aryl-*iso*-thiuronium

TABLE 7. Formation of aromatic thiols from aromatic amines *via* reaction of aryldiazonium salts with thiourea[109]



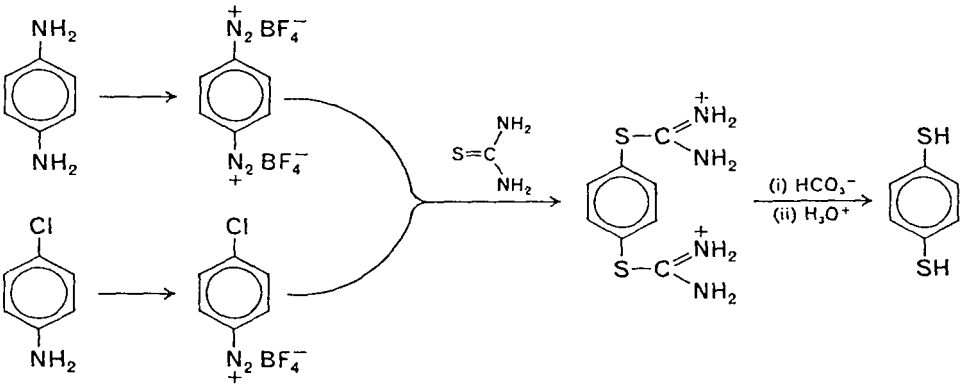
No.	Amine	Product	Yield (%)[a]
1			22
2			50
3			22
4			20

[a] Yield based on the diazonium tetrafluoroborate.

salts[112] involved aryldiazonium tetrafluoroborates (these were chosen as a result of their stability and the heterolytic nature of their reactions) and thiourea in an aqueous medium) while Kessler and coworkers[113] employed unspecified diazonium salts and tetramethylthiourea in the presence of cupric chloride; in the absence of the catalyst, no *iso*-thiuronium compound was obtained[115].

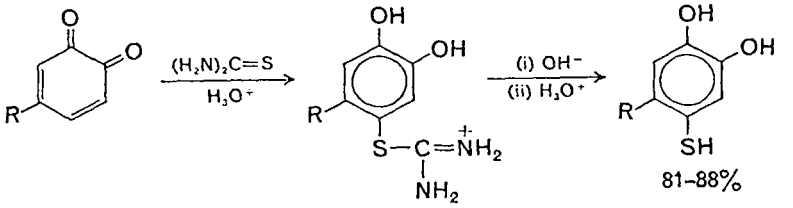
For the preparation of thiols[109-111], the S-aryl-*iso*-thiuronium salts need not be isolated but can be reacted *in situ* with bicarbonate ion: acidification

giving the thiols in yields ranging from 25 to 50%. The alternative decomposition of the *iso*-thiuronium salt by alkaline hydrolysis is inferior. The *p*-chloro group in a *p*-chlorobenzenediazonium salt is also reactive—due to the electron-withdrawing diazonium function—towards thiourea and so a *p*-di-*iso*-thiuronium compound can be obtained. Thus, benzene-1,4-dithiol can be prepared from either *p*-phenylenediamine or *p*-chloroaniline, although the former gives the better yield[109]. *o*- and *m*-Chloro-groups on the other hand are unaffected[109] by thiourea.



2. From addition to quinones

Two preparations of thiols from the reactions of thiourea with *p*- and *o*-benzoquinones have been reported[116-117]. The *o*-benzoquinones were prepared *in situ*.

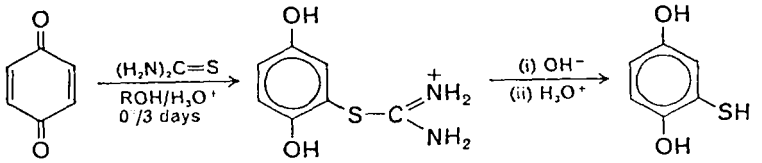


(7)

Reference 116.

80–90%

81–88%



(8)

Reference 117.

VII. FORMATION *VIA* BUNTÉ SALTS: USING THIOSULPHATE

A. From Halides

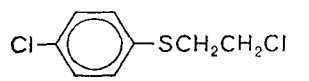
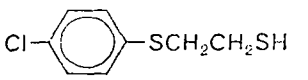
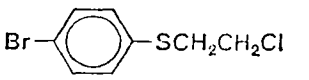
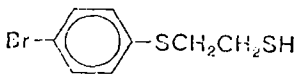
Acid catalysed hydrolysis of S-alkyl- and S-aryl-thiosulphates—Bunté salts[118]—is another particularly useful method of preparing thiols[119,120].

$$RX + S_2O_3^{2-} \longrightarrow R{\cdot}S{\cdot}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}O^- \xrightarrow{H_3O^+} RSH$$

The Bunté salts are conveniently obtained from halides—especially primary and secondary alkyl and aralkyl halides—in an aqueous or aqueous-organic medium; their hydrolyses are usually performed *in situ*

TABLE 8. Formation of thiols from halides *via* Bunté salts

$$RX + S_2O_3^{2-} \longrightarrow RSSO_3^- \xrightarrow{H_3O^+} RSH$$

No.	Halide	Thiol	Yield (%)	Reference
1	*n*-$C_9H_{19}Br$	*n*-$C_9H_{19}SH$	76·5	119
2	$Br(CH_2)_7Br$	$HS(CH_2)_7SH$	85	119
3	$PhCH_2CH_2Br$	$PhCH_2CH_2SH$	85	119
4	$PhCH{=}CHCH_2Br$	$PhCH{=}CHCH_2SH$	40	119
5	$O_2NC_6H_4CH_2Cl$ *o*-, *m*- and *p*-	$O_2NC_6H_4CH_2SH$	ca. 80	120
6			76	122
7			82	122

without prior isolation. Yields are generally good, but not however for 1,2-ethanedithiol[121], although β-arylthioethanethiols, $ArSCH_2CH_2SH$, were so prepared in good yields[122] from the corresponding halides.

A comparison of the *iso*-thiuronium and Bunté salt methods of preparing

$$PhNHCOCH\underset{|}{\overset{SH}{}}CH_3$$

β-mercaptopropionanilide, from the corresponding halide has been made[123]; higher yields were obtained from the latter. Normally, sodium thiosulphate is used due to its ready availability and

low cost. Thallous thiosulphate has, however, been recommended[124] especially as the thallous halides formed in the reaction are insoluble so enabling the Bunté salts to be easily collected, if required.

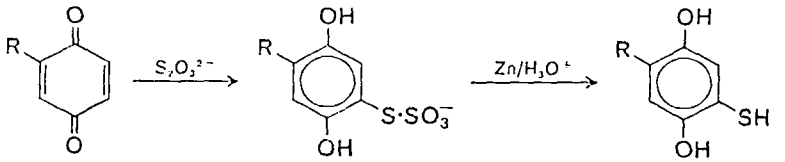
Some rates of formation and hydrolysis of Bunté salts have been measured. In the bimolecular reaction with thiosulphate, the reactivity of alkyl bromides[125] was in the order EtBr > *n*-PrBr > *iso*-PrBr and that of benzyl chlorides, p-$XC_6H_4CH_2Cl$ in aqueous diglyme, in the order $X = NO_2 > Cl > i\text{-}Pr > H$[126,127]; i.e. the more electron deficient the α-carbon the faster is the formation of the Bunté salt. Hydrolyses of Bunté salts are A-1 processes[128,129]:

$$R{-}S{-}SO_3^- + H^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} R{-}\overset{+}{\underset{\displaystyle H}{S}}{-}SO_3^- \xrightarrow{\text{slow}} RSH + SO_3$$

Only slight differences[128] in the rates of hydrolysis of simple S-alkyl-, S-aralkyl- and S-aryl-thiosulphates were found, e.g. for $RSSO_3^-$, the relative rates for R = Et:$PhCH_2$:Ph were 1 : 0·8 : 0·66.

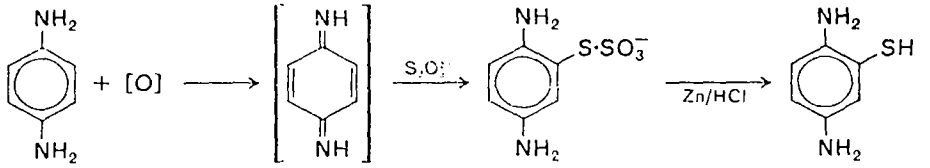
B. From Quinones and Related Compounds

Reaction of p-benzoquinones with thiosulphate led to 1,4-dihydroxyphenyl thiosulphates, which on reduction with zinc and hydrochloric acid gave the mercaptodihydroxybenzenes[130]. Other formations of aryl



R = H, Me and Ph

thiosulphates include the reaction of p-phenylenediamine with thiosulphate ion in the presence of chromate or dichromate[131,132]; mono-[131] or di- and tetra-[132] substituted derivatives are obtained depending on the conditions used, e.g.:



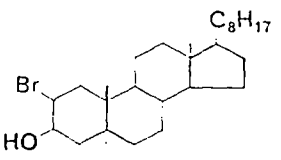
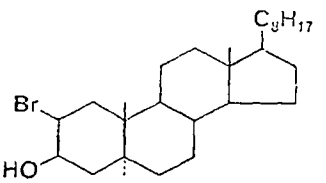
VIII. FORMATION *VIA* XANTHATES AND RELATED ESTERS

A. Xanthates from Alkyl Halides and Aromatic Diazonium Salts

Both alkane- and arene-thiols are obtained from the corresponding xanthates. The routes to each type of xanthate are however quite different: alkyl xanthates are normally prepared from alkyl halides[133-135], while aromatic derivatives are obtained from diazonium salts[136, 137, 139, 141], both routes involving an alkali metal alkylxanthate. Normally potassium

TABLE 9. Production of thiols from halides *via* xanthates

$$RX + {}^{-}S{-}\overset{\overset{O}{\|}}{C}{-}OR^1 \longrightarrow R{-}S{-}\overset{\overset{O}{\|}}{C}{-}OR^1 \longrightarrow RSH$$

No.	Halide	Thiol	Overall yield of thiol (%)	Agent to decompose xanthate
1	$CH_3CH_2CH_2Br$	$CH_3CH_2CH_2SH$	84[a]	$H_2NCH_2CH_2OH$
2	n-$C_{12}H_{25}Cl$	n-$C_{12}H_{25}SH$	85[a]	$H_2NCH_2CH_2NH_2$
3	$ClCH_2CH_2Cl$	$HSCH_2CH_2SH$	78[a]	$H_2NCH_2CH_2NH_2$
4	$PhCH_2Cl$	$PhCH_2SH$	85[a]	$H_2NCH_2CH_2NH_2$
5	α-Bromovaleric acid	α-mercapto-valeric acid	62[c]	NH_3
6	$PhCH_2CH_2Cl$	$PhCH_2CH_2SH$	73[b]	$LiAlH_4$
7	$PhC(=O)CH_2Br$	$PhCH(OH)CH_2SH$	64[b]	$LiAlH_4$
8	$PhC(=O)CH_2Br$	$PhCH(OH)CH_2SH$	87[c]	$LiAlH_4$
9	$PhCH(Cl)CO_2H$	$PhCH(SH)CH_2OH$	70[c]	$LiAlH_4$
10				$LiAlH_4$

[a] Yield based only on xanthate.
[b] Xanthate was isolated and purified.
[c] Xanthate was not isolated.

ethylxanthate is used but others have proved equally successful[134]. (The xanthates can be isolated but this is unnecessary.) The preparations of

$$RX + EtOC(=S)-S^-K^+ \longrightarrow RSC(=S)OEt \longrightarrow RSH \quad (9)$$

$$ArNH_2 \longrightarrow ArN_2^+X^- \longrightarrow ArSC(=S)OEt \longrightarrow ArSH \quad (10)$$

some alkali metal alkylxanthates, from alcohols and carbon disulphide in the presence of hydroxide ion, have been published[133].

$$ROH + OH^- + CS_2 \longrightarrow ROCS^- + H_2O$$

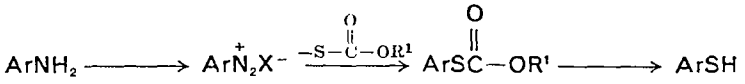
A warning about explosions resulting from heating solutions of aryl diazonium salts and potassium ethylxanthate has been given. However, a small amount of nickel acts as a catalyst in the formation of the aryl xanthate and its addition circumvents heating the mixture and so makes the procedure safer[138].

The reaction between diazonium salts and alkylxanthates does not only lead to aryl alkylxanthates, but also to diaryl dithiocarbonates, $(ArS)_2CO$, and alkyl alkylxanthates. The diaryl dithiocarbonates can also be reduced to thiols by $LiAlH_4$ [142].

Two general methods of production of thiols from xanthates are available. These methods are (a) hydrolysis under basic conditions and (b) reduction, particularly using lithium aluminium hydride. For aromatic compounds, hydrolysis of the xanthates by sodium (or potassium) hydroxide is normally used, since most substituents are inactive to the hydroxide ion, under the conditions needed for hydrolyses[136, 139, 140, 141]. In this way, many variously substituted thiophenols have been obtained.

Aliphatic compounds are generally more susceptible to nucleophiles, so that milder conditions than refluxing with hydroxide ion are preferred for hydrolysis[143, 144]. Aqueous ammonia has been successfully used and good yields of α-mercaptocarboxylic acids, and esters were obtained[143, 144]. Other nitrogen bases, including phenylhydrazine[133], 2-amino-ethanol[145] and ethylenediamine[146], have also been used. The latter is claimed to be a particularly effective and mild reagent requiring only short reaction times at low temperatures and at the same time having the added advantage of dissolving xanthates, which are insoluble in water. Yields of mono- and di-mercaptoalkanes are high (~80% in the hydrolysis step).

TABLE 10. Formation of aromatic thiols from aromatic amines via xanthates



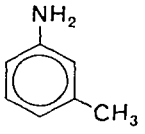
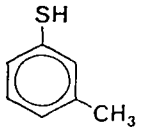
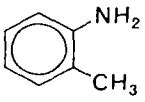
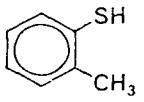
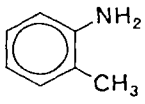
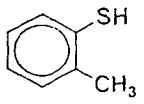
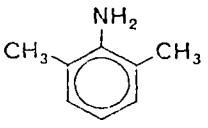
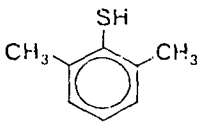
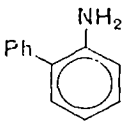
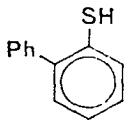
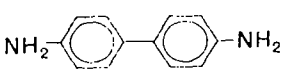
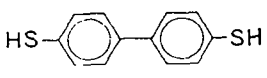
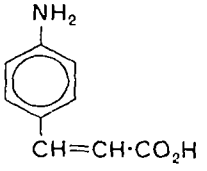
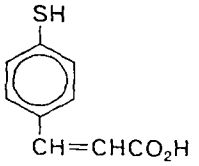
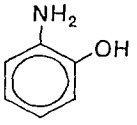
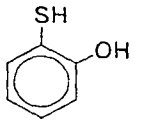
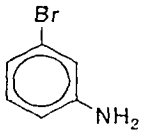
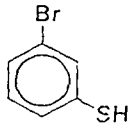
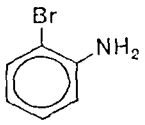
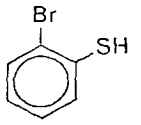
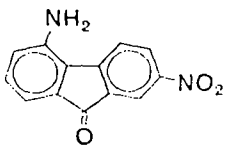
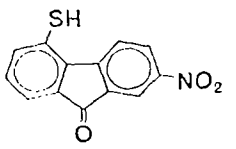
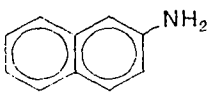
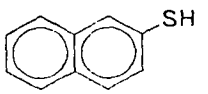
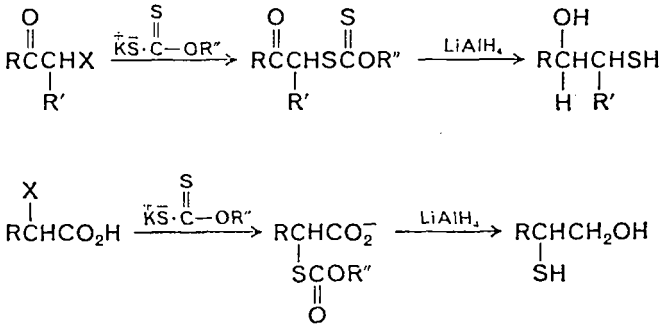
No.	Aniline	Thiol	Yield (%)	Agent for decomposing xanthates	Ref.
1			63–75	OH^-	136
2			89	$LiAlH_4$	147
3			37	OH^-	147
4			86	$LiAlH_4$	147
5			84	$LiAlH_4$	147
6			50	OH^-	141

TABLE 10 (*cont.*)

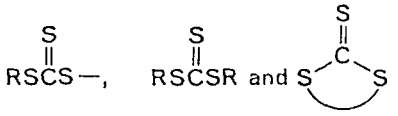
No.	Aniline	Thiol	Yield (%)	Agent for decomposing xanthates	Ref.
7			30	OH^-	229
8			64	$LiAlH_4$	134
9			50	OH^-	137
10			55	OH^-	137
11			45	OH^-	140
12			62	OH^-	175

Reduction of both alkyl- and aryl-xanthates by lithium aluminium hydride is particularly useful for compounds which are susceptible to an alkaline medium[134,147]. As air oxidation of thiols occurs in alkaline media, the lithium aluminium hydride method is immediately attractive for very easily oxidized thiols. A further general advantage, to offset against the cost and extra care required for lithium aluminium hydride reactions, is that the work-up is fairly simple. A specific advantage was found for hindered thiols, which were produced in much greater yields *via* $LiAlH_4$ reduction than by alkaline hydrolyses. Thus *o*-thiocresol was obtained from the ethyl xanthate in 89% yield by $LiAlH_4$ reduction and only in 37% yield by the hydroxide reaction[147]. A similar result was obtained in the preparation of *o*-phenylthiophenol. Djerassi and coworkers[134] further showed that a 64% yield of *o*-mercaptophenol was reproducibly obtained using $LiAlH_4$; from alkaline hydrolysis, variable yields of 30–70% were previously reported[148].

The presence of other easily reduced groups could limit the use of $LiAlH_4$ reductions although Djerassi and coworkers[134] used this method to advantage to prepare β-mercapto-ethanols from α-haloketones and acids in two-step syntheses.



B. *Trithiocarbonates*

Trithiocarbonates, 

are hydrolysed to thiols by acids[149] and bases[145,150,151] (not as good) as well as being reduced by lithium aluminium hydride[152,153].

The non-cyclic trithiocarbonates are prepared from alkyl halides and sodium trithiocarbonate[149,154,155,156], which is obtainable from sodium sulphide and carbon disulphide[155].

Martin and Greco[149] obtained particularly good yields of dithiols, such as 1,4-butanedithiol and β,β-'dimercaptodiethyl ether, but a much poorer

$$CS_2 + Na_2S \xrightarrow{H_2O} Na_2CS_3$$

$$RCl + Na_2CS_3 \longrightarrow NaSC(=S)SR \longrightarrow RSH + CS_2\uparrow$$

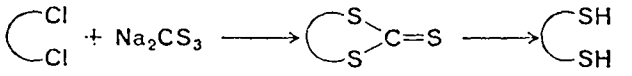
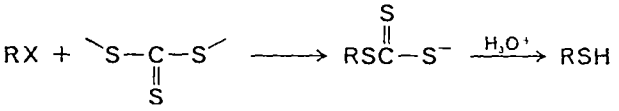


TABLE 11. Formation of thiols from halides *via* trithiocarbonates



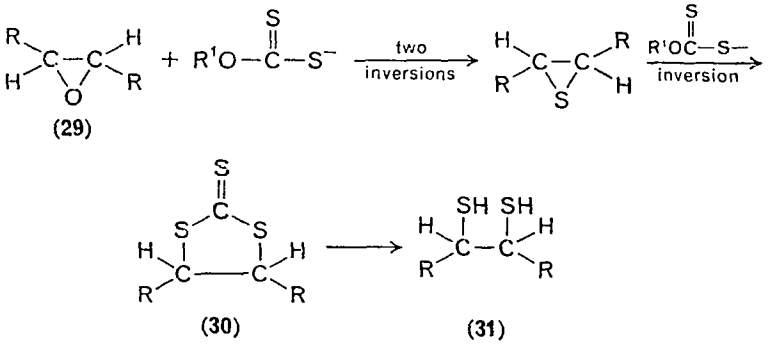
No.	Halide	Thiol	Yield (%)	Reference
1	CH_3CH_2Br	CH_3CH_2SH	85	154
2	$CH_3(CH_2)_5Br$	$CH_3(CH_2)_5SH$	79	154
3	$PhCH_2Cl$	$PhCH_2SH$ [a]	85	154
4	$PhCH_2Cl$	$PhCH_2SH$ [b]	25	149
5	$ClCH_2CO_2Na$	$HSCH_2CO_2H$	85	154
6	$ClCH_2CH_2OH$	$HSCH_2CH_2OH$	84	154
7	$ClCH_2CH_2Cl$	$HSCH_2CH_2SH$	84	145
8	$Cl(CH_2)_4Cl$	$HS(CH_2)_4SH$	61	149
9	$Cl(CH_2)_2O(CH_2)_2Cl$	$HS(CH_2)_2O(CH_2)_2SH$	77	149

[a] Intermediate trithiocarbonate produced in MeOH.
[b] Intermediate trithiocarbonate produced in H_2O.

yield of toluene-α-thiol, in their one-step synthesis from the appropriate halides. In all cases, hydrolysis of the trithiocarbonates was by acid. A Belgian Patent[154] reported, however, excellent yields of toluene-α-thiol and other simple and functionally substituted mono- and di-thiols from the acid-catalysed hydrolysis of trithiocarbonates. The better yield of toluene-α-thiol is most likely due to the use of an aqueous methanol solvent: the organic content would dissolve the halide better and so a more rapid reaction with the sodium trithiocarbonate would ensue. Dimethyl sulphoxide has been used as solvent for the formation of alkane- and nitroarene-thiols[156].

Preparations of cyclic trithiocarbonate include the treatment of epoxides[151,153,157,158] and episulphides[151,152,157,158] with alkyl xanthates. *Meso*- and D,L-isomers of 2,3-butanedithiol (**31**, R = Me) and related

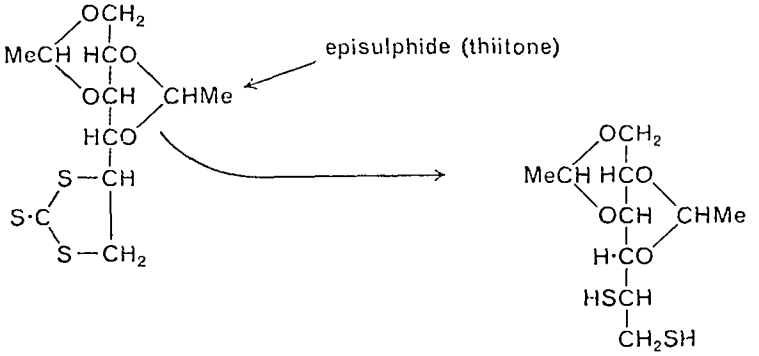
compounds were conveniently obtained by this route[152,153]. *Cis*- and *trans*-stilbene oxides (**29**, R = Ph) are converted to the *trans*- and *cis*-trithiocarbonates[153] (**30**, R = Ph; 4,5-diphenyl-1,3-dithiolane-2-thiones) respectively on reaction with potassium methylxanthate at room temperature in yields of 67 and 18%. Reduction of (**30**, R = Ph) by $LiAlH_4$ in tetrahydrofuran at reflux, followed by acidification, gave the D,L- and *meso*-α,α¹-stilbenedithiols in 40–50% yields.



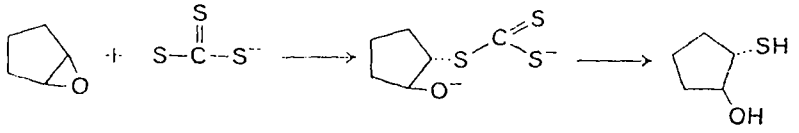
(29) (30) (31)

The advantage of the $LiAlH_4$ reductions of cyclic trithiocarbonates over other methods of preparing vicinal dithiols has been stressed[153]. Yields of ethane-1,2- (86%), propane-1,2- (75%) and cyclohexane-*trans*-1,2-thiols (90%) from $LiAlH_4$ reductions of cyclic trithiocarbonates were vastly superior to those obtained from base hydrolyses[151] of the same compounds. Iqbal and Owen[153] further pointed out that methods of preparing secondary vicinal dithiols from dihalides, such as the sodium hydrogen sulphide and potassium thiolacetate procedures, gave high yields of alkenes and such methods must be considered inferior to the $LiAlH_4$ reduction of cyclic trithiocarbonates.

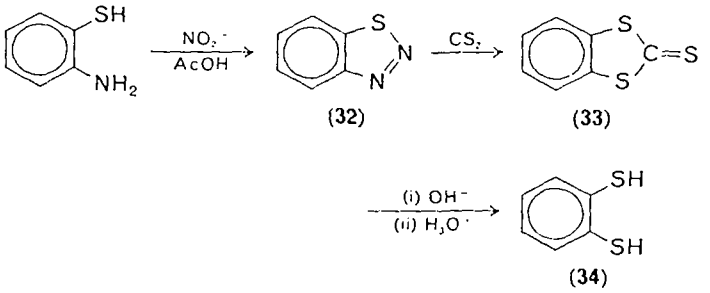
Good use of this method of preparing dithiols has been made in the carbohydrate field[153,157], e.g.



Not all epoxides, however, can be converted to the trithiocarbonates. Cyclopentene oxide, for example, unlike cyclopentene sulphide, did not give the trithiocarbonate on treatment with a xanthate but formed instead *trans*-2-mercaptocyclopentanol[153]. Strain is the likely explanation of this behaviour.



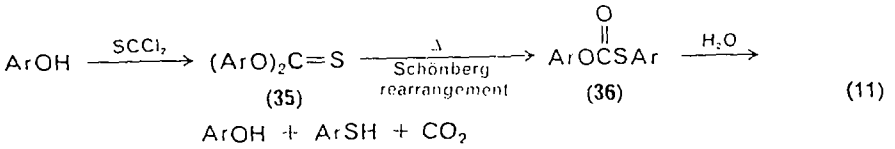
An interesting preparation of a cyclic trithiocarbonate—a dithiol-2-thione—in the aromatic field has been reported[159]. Diazotization of *o*-aminothiophenol in glacial acetic acid produced 1,2,3-benzothiadiazole (**32**), which on treatment with carbon disulphide under pressure gave 1,3-benzodithiol-2-thione (**33**). The latter, on base hydrolysis, gave, after acidification, benzene-1,2-dithiol (**34**).



(32) (33) (34)

C. *Via Thermal Rearrangement of Thioncarbonates and Thioncarbamates and Related Reactions*

Both thioncarbonates and thioncarbamates, available from phenols, undergo thermal rearrangement; the thioncarbonates (**35**) to the thiolcarbonates (**36**)—the Schönberg rearrangement[160-165]—and *O*-aryldialkylthioncarbamates (**37**) to S-aryldialkylthiocarbamates (**38**)—the Newman–Kwart rearrangement[165-174]. These rearrangements have been incorporated in thiophenol syntheses which provide the best general route from phenols



(35) (36) (11)

$$ArOH + ArSH + CO_2$$

$$ArOH \xrightarrow[(ii)\ R_2NCCl]{(i)\ Base} ArO\overset{\overset{S}{\|}}{C}NR_2 \xrightarrow[\text{Newman-Kwart rearrangement}]{\Delta} ArS\overset{\overset{O}{\|}}{C}NR_2 \xrightarrow[(ii)\ H_3O^+]{(i)\ OH^-} ArSH \quad (12)$$

(37) (38)

to thiophenols. (Although reactions of phenols with hydrogen sulphide under forcing conditions[176] and with phosphorous pentasulphide[177] do give some thiophenol, neither method can be considered as being a convenient or viable laboratory preparation.)

TABLE 12. Formation of thiols from phenols by use of dialkylthiocarbamyl chloride

$$ArOH + R_2NCCl \longrightarrow ArO\overset{\overset{S}{\|}}{C}NR_2 \xrightarrow{\Delta} ArS\overset{\overset{O}{\|}}{C}NR_2 \xrightarrow[(ii)\ H_3O^+]{(i)\ OH^-} ArSH$$

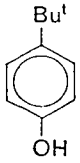
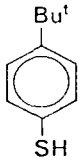
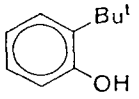
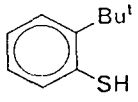
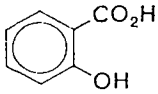
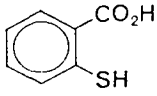
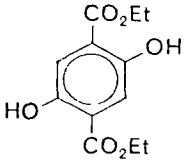
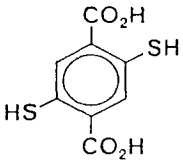
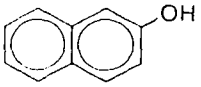
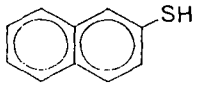
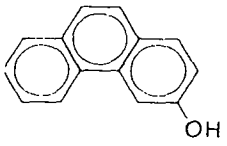
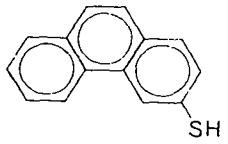
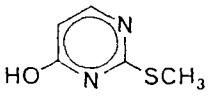
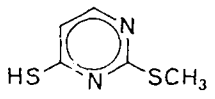
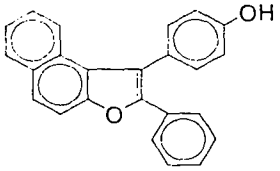
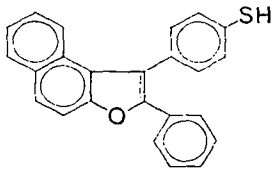
No.	ArOH	Thiol	Yield (%)	Conditions for formation of $ArOC(=S)NR_2$	Ref.
1			85[b]	NaH/D.M.F.	167
2			65[c]	Pyridine/xylene	173
3			92[b]	NaH/D.M.F.	167
4			85[b]	DABCO[a]/D.M.F.	87

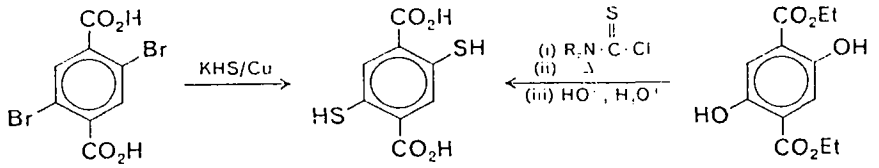
TABLE 12 (*cont.*)

No.	ArOH	Thiol	Yield (%)	Conditions for formation of $ArOC(=S)NR_2$	Ref.
5			52·5[c]	OH^-/T.H.F.	166
6			83[b]	NaH/D.M.F.	167
7			81[b]	NaH/D.M.F.	167
8			70[c]	NaH/D.M.F.	170

[a] DABCO = 1,4-diazabicyclo[2,2,2]octane.
[b] Yield of hydrolysis step. Yield of rearrangement step ~95–100%.
[c] Overall yield.

Of these two processes, that involving the Newman–Kwart rearrangement is the superior. Yields in each of three steps in the scheme are high; normally greater than 80%[87,166,167,170,173]. The preparation of diethyl thiocarbamyl chloride is described in *Organic Synthesis*[178], as well as its reaction with 2-naphthol to yield *O*-2-naphthyl-dimethylthioncarbamate[166].

The preparation of 2,5-dimercaptoterephthalic acid (**39**) has been achieved from the corresponding dibromoterephthalic acids and dihydroxy esters[87]. The yield obtained from the phenol conversion, using the

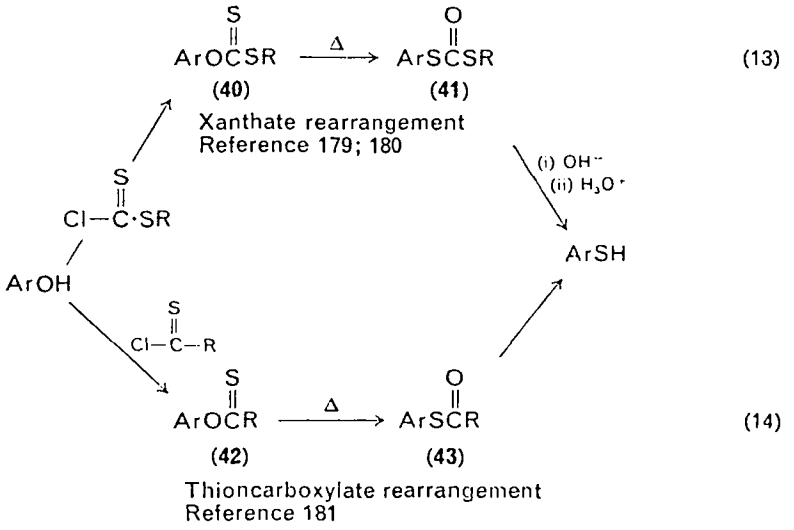


(39)

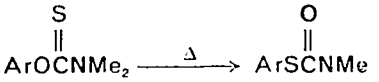
Newman–Kwart rearrangement, was greater than that from the halide, which involved nucleophilic substitution by SH^-.

Other related thermal rearrangements of $-\overset{\overset{S}{\|}}{C}-O-$ to $-\overset{\overset{O}{\|}}{C}-S-$ groupings are known, equations (13) and (14), but neither the xanthate nor the thioncarboxylate rearrangements have been utilized in thiophenol synthesis.

All four thermal rearrangements (equations 11–14) are unimolecular processes involving nucleophilic attack by sulphur on the aromatic ring

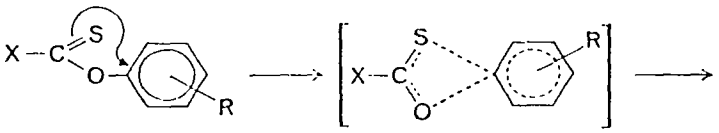


and pass through a cyclic transition state: electron-withdrawing substituents in the aromatic ring facilitate the reaction[163,174]. The rates of the rearrangements of aryl N,N-dimethylthioncarbamates in diphenyl ether

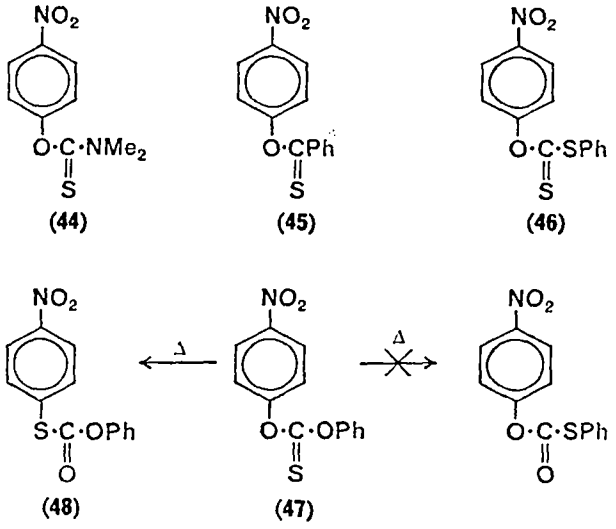


solution correlate well with the σ^- values of the *meta*- and *para*-substituents[174]. However in the absence of a solvent, the correlation was not so good[169]. Some steric acceleration[168] due to hindered rotation was noted for the rearrangements of *ortho*-substituted O-aryldialkylthioncarbamates.

The first-order rate constants for the rearrangement of *p*-nitrophenyl-N,N-dimethylthioncarbamate (**44**), *p*-nitrophenylthionbenzoate (**45**), O-*p*-nitrophenyl-S-phenyl dithioncarbonate (**46**) and *p*-nitrophenyl phenyl



thioncarbonate (**47**) in diphenyl ether at 200·5°C were $1{\cdot}21\times10^{-3}$; $1{\cdot}18\times10^{-4}$, $1{\cdot}06\times10^{-4}$ and $2{\cdot}34\times10^{-5}$ s^{-1} respectively[174]. This sequence is in accord with the inductive effects of the α substituents in the thiocarbonyl group. Unsymmetric diarylthioncarbonates, such as **47**, rearrange to the diarylthiocarbonates, such as **48**, in which the sulphur becomes bonded to the aryl ring containing groups with the greater electron-withdrawing ability.



By basic hydrolysis some disulphides can also be obtained from dithiocarbonates[182]. However, easy hydrogenation, for example, by zinc and acetic acid, see p. 221, does not make this a serious handicap. When

alkyl aryl thiolcarbonates, ArSC(O)R, are hydrolysed, some alkyl aryl sulphides are obtained especially when higher temperatures are used[183].

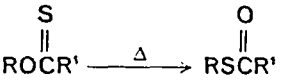
Hydrolysis and other reactions of thiolesters (**43**) have been shown to give thiols under varying conditions. This is dealt with in the next section.

D. Thiolesters: Formation and Conversion to Thiols

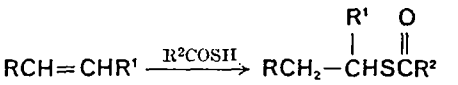
As briefly indicated in the previous section, the conversion of thiolesters to thiols is a convenient method of preparing the latter.

The thiolesters can be prepared in the following ways:

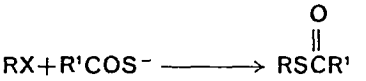
(a) Thermal rearrangement of thioncarboxylates:



(b) Addition of thiolcarboxylic acids to alkenes.

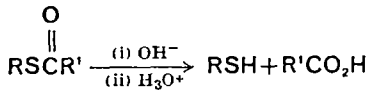


(c) Substitution of halide or sulphonate groups by thiolcarboxylate.



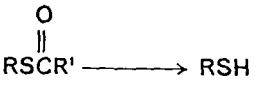
Methods (a) and (b) have been already mentioned (sections VIII.C and II.B.1 respectively). Method (c) is a straightforward nucleophilic substitution process. One strong recommendation for it is that no sulphide products[184] can be formed. Dimethylformamide has been used as the solvent with success for such reactions[185]. Normally, the sodium salt of thiolacetic acid is used.

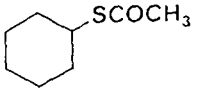
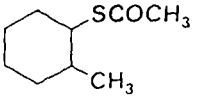
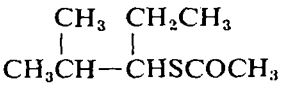
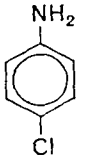
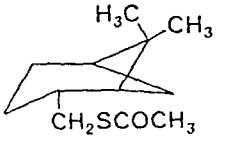
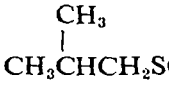
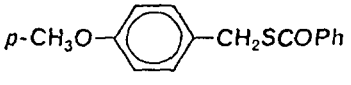
Conversion of thiolesters to thiols can be achieved by (i) basic hydrolysis, by (ii) reduction with lithium aluminium hydride, and by (iii) ultraviolet radiation. The first two are much more important than the third method. The very convenient method, of refluxing the thiolester with aqueous alcoholic potassium (or sodium) hydroxide and subsequent acidification, is often used[31,33,38,41]. Much milder conditions have been

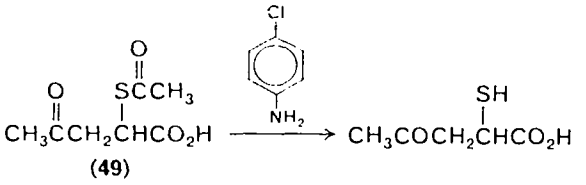


used occasionally. Thus[36], the weak base, *p*-chloroaniline, was used for the hydrolysis of the ester (**49**). Reaction of **49** in aqueous sodium hydroxide

TABLE 13. Hydrolyses of thiolcarboxylates to thiols

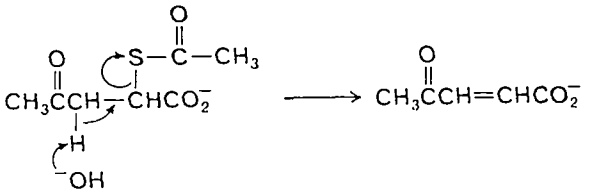


No.	Thiolacetate	Yield of thiol (%)	Hydrolysis conditions	Ref.
1		78	KOH/EtOH reflux	31
2		85	KOH/EtOH reflux	31
3		90·5	KOH/EtOH reflux	33
4	2-(Acetylthio)-levulinic acid	92		36
5	$HO_2C(CH_2)_4SCOCH_3$	83	$NaOH/H_2O$ reflux	38
6		83	KOH/H_2O reflux	41
7	$CH_3(CH_2)_3SCOPh$	45	$LiAlH_4/Et_2O$	189
8		41	$LiAlH_4/Et_2O$	189
9	PhSCOPh	96	$LiAlH_4$/dioxane	189
10		96	$LiAlH_4$/dioxane	189
11	Cholestanyl thiobenzoate	65	$LiAlH_4/Et_2O$	189



(49)

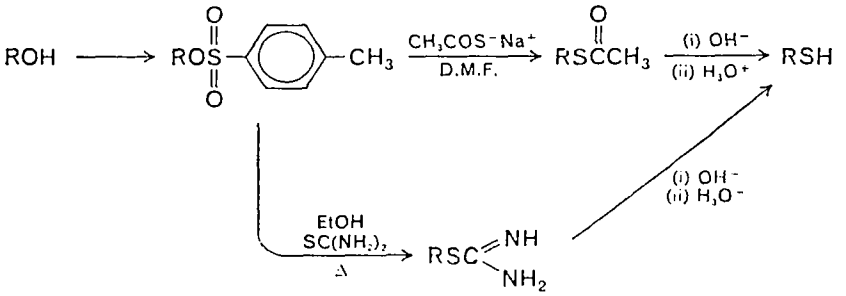
solution led to elimination of thiolacetic acid, resulting from the cleavage of the carbon—sulphur bond due to activation by the acetyl group:



Ammonia has also been used for aliphatic thiolacetates in the liquid phase[186]; thiols and acetamide were produced.

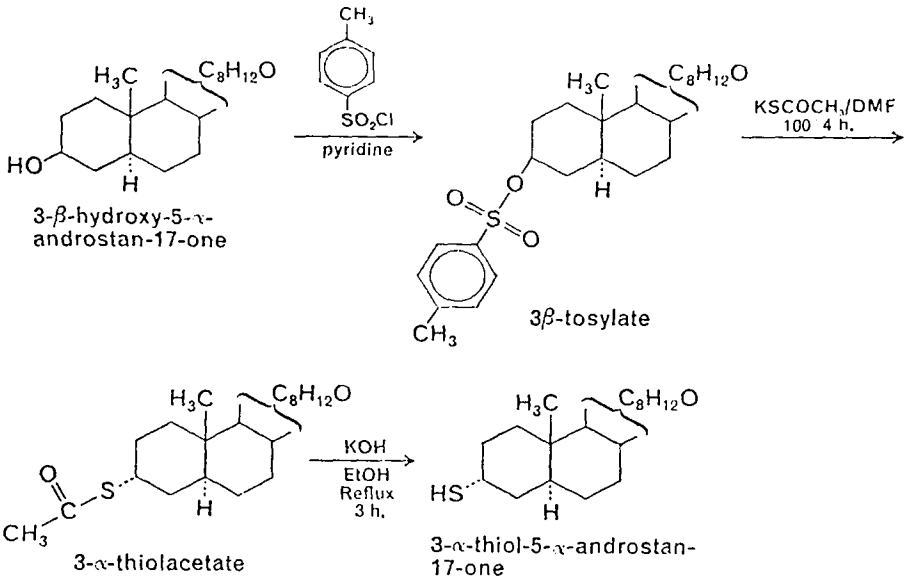
$$RSCOCH_3 + NH_3 \longrightarrow RSH + CH_3CONH_2$$

A route to thiols from alcohols incorporates the reaction of a sulphonate with thiolacetate, and the hydrolysis of the alkyl thiolacetate, so formed, with base. An inversion occurs in the reaction of the sulphonate with the



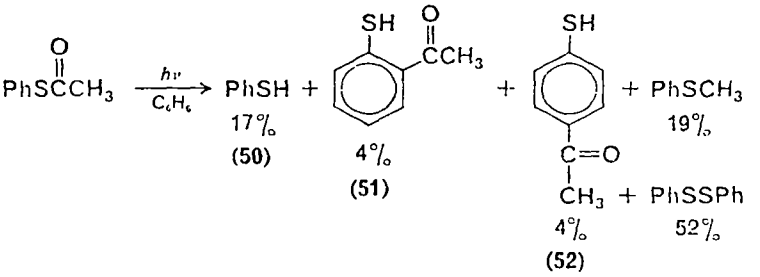
thiolacetate. In this way, thiols in the androstane, pregnane and cholestane series were prepared[187, 188]. Reaction of the sulphonate with thiourea was also used and this too led to inversion.

Reduction by lithium aluminium hydride, gives particularly good yields of thiols[189] from the thiolacetates. The reaction conditions are reported to be milder than those normally used for hydrolysis. Cholestanyl thiobenzoate afforded 3-mercaptocholestane in 50% yield by hydrolysis

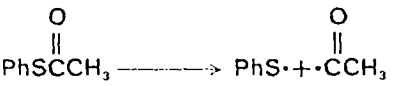


with sodium ethoxide, while 65% yield was obtained with lithium aluminium hydride.

Ultraviolet radiation of phenyl thiolacetate in benzene gave several products[190], among these were the indicated thiophenols. The amount of thiophenol (**50**) increased as the reaction time increased. The initial



reaction is the cleavage of the S—CO bond followed by hydrogen abstractions and other processes.



The report of the photolysis of *p*-tolyl thiolacetate[191] in cyclohexane solution, however, mentioned no thiol product.

E. Dithiocarbamates: Formation and Hydrolysis[192]

Alkyl and aralkyl chlorides and nitrochloroaromatics react with sodium

$$RCl + NaSCN(CH_3)_2 \xrightarrow{\text{acetone}} RSCN(CH_3)_2 \longrightarrow RSH$$

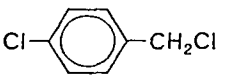
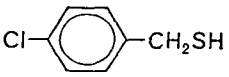
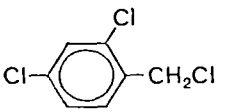
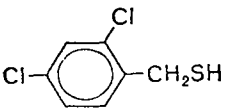
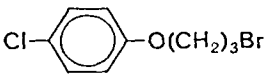
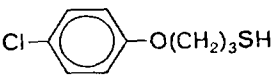
(53)

N,N-dimethyldithiocarbamate. The dithiocarbamate products are hydrolysed by base to thiols in good yields.

TABLE 14. Formation of thiols from halides by use of N,N-Dimethyldithiocarbamate ion[192].

$$RX + SCN(CH_3)_2 \longrightarrow RSCN(CH_3)_2 \longrightarrow RSH$$

(53)

No.	Halide	Yield of intermediate (53) (%)	Thiol	Yield of thiol based on (53) (%)
1	$PhCH_2Cl$	82	$PhCH_2SH$ $PhCH_2SH$	86%[a] 82%[b]
2		82		95[a]
3		94		88[a]
4	$PhCH_2CH_2Cl$	92	$PhCH_2CH_2SH$	66[a]
5	$CH_3(CH_2)_5Br$	86	$CH_3(CH_2)_5SH$	61[a]
6	$CH_3(CH_2)_{15}Br$	78	$CH_3(CH_2)_{15}SH$	65[a]
7		82		85[b]

[a] Decomposition of (53) catalysed by OH^-.
[b] Decomposition of (53) catalysed by NH_2NH_2.

The reagent, sodium N,N-dimethyldithiocarbamate, is readily obtained from carbon disulphide, dimethylamine and sodium hydroxide.

$$CS_2+NaOH+HN(CH_3)_2 \longrightarrow NaSC(=S)N(CH_3)_2$$

An advantage of this method is that the alkyl N,N-dimethyldithiocarbamates (53) are stable and easily purified: they are only hydrolysed in basic media. As well as hydroxide ion, hydrazine is effective, except for the *p*-nitrobenzyl and *p*-nitrophenyl compounds. Resinous material was obtained from attempts either to hydrolyse or to hydrazinolyse them. Another limitation was experienced with β-phenoxyethyl N,N-dimethyldithiocarbamate: phenols were obtained rather than the β-phenoxyethyl thiols.

$$ArOCH_2CH_2Cl \longrightarrow ArOCH_2CH_2-S-C(=S)-N(CH_3)_2 \xrightarrow[\text{or } OH^-]{H_2NNH_2} ArOH$$

IX. SULPHUR INSERTION REACTIONS OF ORGANOMETALLIC COMPOUNDS

Reactions of sulphur with organometallic compounds—particularly of the more electropositive elements—can lead to the metal salts of thiols[193,194]. This method, particularly using organomagnesium and organolithium compounds[195-199], has had considerable use; especially for formation of

$$R-m+S_8 \longrightarrow R-S-m \longrightarrow RSH \qquad (15)$$

aromatic thiols, since aliphatic thiols are more conveniently prepared by other ways. However, some *tert*-alkanethiols[200,201] and cycloalkanethiols[202] have been successfully prepared this way, starting from the alkyl halide. (These thiols are not so easily produced by the more regularly used alkanethiol preparations.)

Wruyts and Cosyns[203] in 1903 showed that sulphur reacted vigorously with organomagnesium halides to give magnesium mercaptides (m = 'MgX' in equation (15)) which on acid hydrolysis gave the thiols, disulphides and sulphides*. The method was later developed by Taboury[195] into a general one for the preparation of aromatic thiols. The

* The structures of organolithium[204] and organomagnesium compounds[205] are much more complex than suggested by the simple RLi and RMgX designations. However, such simple formulae will be used for convenience in this section without implying that these are in fact the compositions of the organometallic compounds.

reactions should be carried out under nitrogen and less than a stoichiometric amount of sulphur should be used, otherwise disulphides and monosulphides could be formed. The formation of *p*-fluorothiophenol

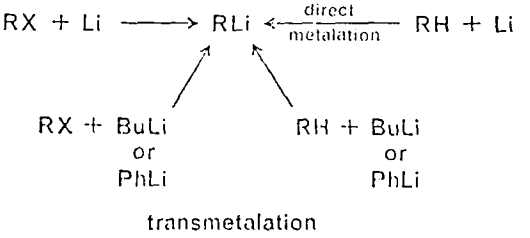
$$RMgBr + \tfrac{1}{8}S_8 \longrightarrow RSMgBr$$

$$2\,RSMgBr + \tfrac{1}{8}S_8 \longrightarrow RSSR + S(MgBr)_2$$

$$RSSR + RMgBr \longrightarrow RSMgBr + RSR$$

from *p*-bromofluorobenzene is a more recent example of this method[196]. Acid hydrolysis used to be the standard means of obtaining the free thiol from its magnesium salt; a more recently developed method is reduction by lithium aluminium hydride[206]. *m-tert*-Butylthiophenol was obtained in 83% yield from *m*-bromo-*tert*-butylbenzene using $LiAlH_4$ reduction, any disulphide produced during the reaction would also be converted to the thiol by lithium aluminium hydride and so help to give a high yield.

Reaction of organolithium compounds (m = Li in equation (15)) with sulphur also leads to good yields of thiophenols; for thiophenol itself, see reference 197. Formation of organolithium compounds is possible from halides and also from compounds with acidic hydrogens, either by direct metalation or by transmetalation reactions[207], which do not proceed so readily with magnesium. Thus, the organolithium route is the more versatile one of the two. 2-Thiophenethiol has been produced from both



organomagnesium[198,208] and organolithium compounds[199]. The starting materials for the organomagnesium routes were the bromide (overall crude yield 67%)[198] and the iodide (30% yield)[208] but thiophene itself

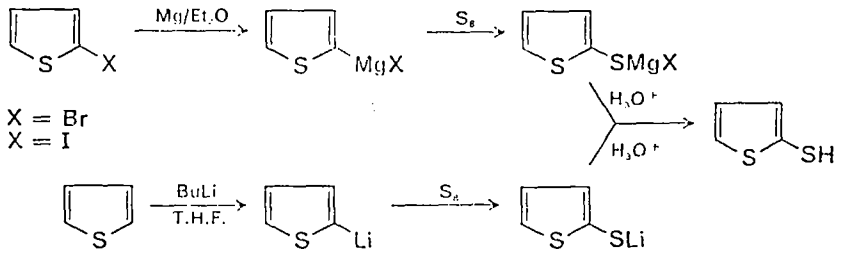
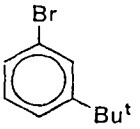
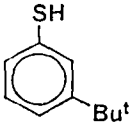
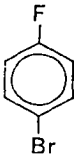
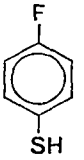
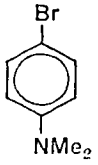
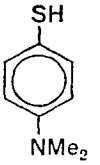
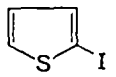
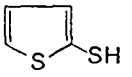
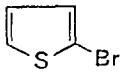
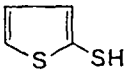
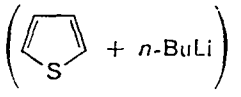
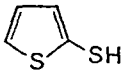


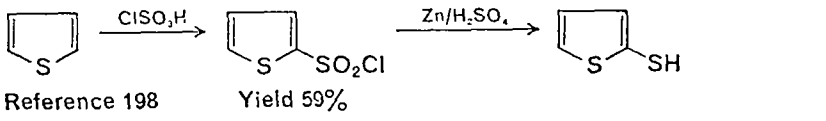
TABLE 15. Formation of thiols from organolithium and organomagnesium compounds with sulphur

$$RX \longrightarrow R{-}m \xrightarrow{S_8} R{-}S{-}m \xrightarrow{(H)} RSH$$

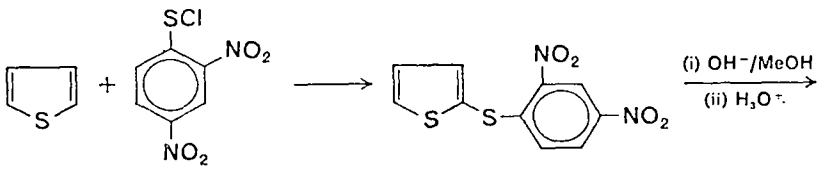
No.	RX	Metal used	Reagent for decomposition of R—S—m	Thiol	Yield (%)	Ref.
1	Bu^tCl	Mg	H_3O^+	Bu^tSH	70–75	200
2	Ph_3CBr	Mg	NH_4Cl	Ph_3CSH	70	201
3	PhBr	Mg	H_3O^+	PhSH	~30	195
4	PhBr	Li	H_3O^+	PhSH	62	197
5		Mg	$LiAlH_4$		83	206
6		Mg	H_3O^+		26	196
7		Li	H_3O^+		50	197
8		Mg	H_3O^+		30	208
9		Mg	H_3O^+		67	198
10			H_3O^+		65–70	199

was used in the lithium reaction[199] (65–70% yield). The β-hydrogens of thiophene are not sufficiently acidic to react directly and so the preparation of 3-thiophenethiol even through the organolithium route has to start from 3-halothiophenes. 3-Thiophenethiol[208,209] has been formed from 3-iodothiophene (via the organomagnesium reaction in a yield of 21%) and from 3-bromothiophene (via the organolithium route in a yield of 63%)[209].

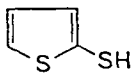
Comparisons of these organometallic procedures with some other methods of preparing 2-thiophenethiol indicate the usefulness of the former[210]. The other methods shown in equations (16) and (17) are discussed in sections X and XIII.



Reference 198 Yield 59% (16)

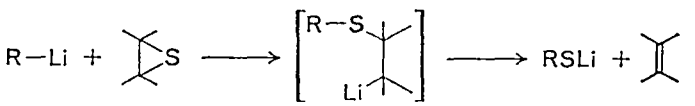


Reference 210



(17)

A modification of this reaction of organolithium compounds is that with thiiranes[211]. The lithium salt of a thiol and the alkene are formed in this reaction, in which the thiirane is merely being used as a controlled source



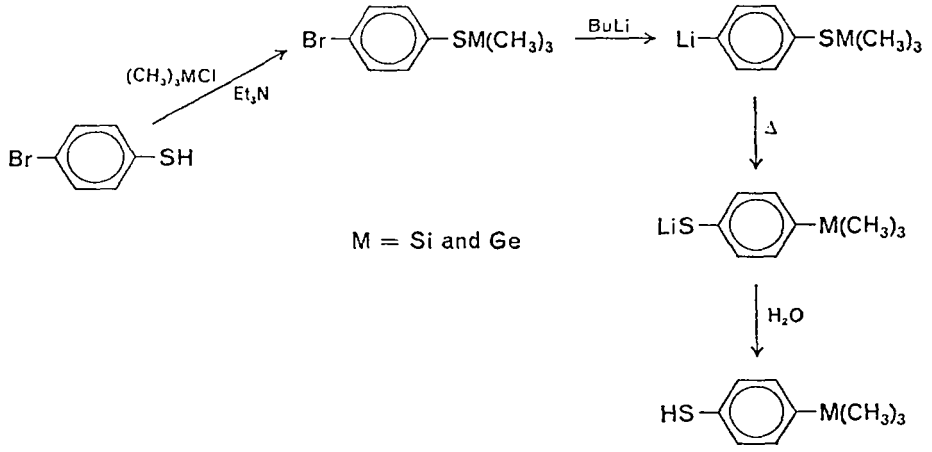
(18)

of sulphur. Thus, *n*-butyllithium and phenyllithium with cyclohexene sulphide gave, after hydrolysis, *n*-butanethiol (63% yield) and thiophenol (60%), respectively. The yields of thiols depend also upon the nature of the thiirane: for example, propylene sulphide gave thiophenol in 81% yield, considerably greater than that from ethylene sulphide, 51%. The

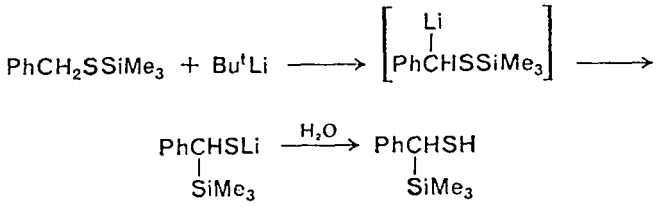
corresponding reactions of the organomagnesium compounds did not proceed so well. Only a 5% yield of *n*-butanethiol and no thiophenol at all were isolated from the reactions using cyclohexene sulphide, although in each case the amount of cyclohexene collected was high.

More electropositive elements than lithium and magnesium are not used, since their increased reactivity would make control of reactions difficult. The organometallic compounds of less electropositive elements require more vigorous conditions and the yields are normally low; for example, heating tetra-*p*-tolyltin with sulphur, 1 : 3 mole ratio, at 170°C in a sealed tube for 10 h gave only a 45% yield of di-*p*-tolyl-disulphide[212].

A thermal rearrangement in organosilicon and organogermanium compounds has been utilized in the formation of *p*-(trialkylsilyl)- and *p*-(trialkylgermanyl)-thiophenols[213,214]. The reaction represents an overall conversion from *p*-bromothiophenol.



Another interesting reaction of trialkylsilyl sulphides furnishes thiols. Thus, trimethylsilyl benzyl sulphide reacted with *tert*-butyllithium in tetrahydrofuran solution to give, after hydrolysis, > 79% α-(trimethylsilyl)-benzylthiol[215].



X. FORMATION AND REDUCTION OF SULPHONYL CHLORIDES AND RELATED COMPOUNDS

Reduction of sulphonyl chlorides is an effective method of producing thiols, especially of aromatic thiols. The method is not very frequently used for aliphatic thiols, since the aliphatic sulphonyl halides are not readily prepared (however, see reference 216). On the other hand, many aromatic derivatives are easily obtained by the chlorosulphonation of aromatics[230].

$$ArH + HOSO_2Cl \longrightarrow ArSO_2Cl \xrightarrow{[H]} ArSH$$

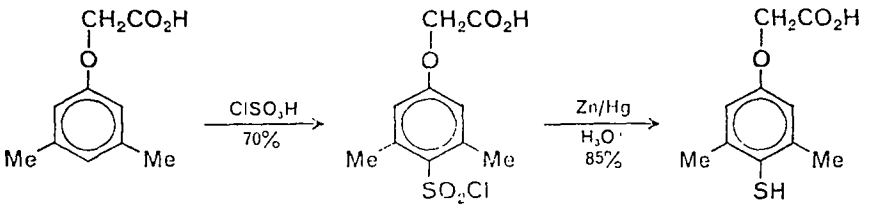
This method of preparing aromatic thiols generally does not suffer too much from disadvantages, for example, of side reactions and explosions, which is a particular hazard with the xanthate reaction with diazonium salts—although other reducible groups (e.g. nitro) may also be affected in the reduction stage. However, diborane has been found to be a safe reductant to use with nitroarylchlorosulphonates.

The alternative longer preparation

$$ArH + H_2SO_4 \longrightarrow ArSO_2OH \xrightarrow[PCl_5]{PCl_3 \text{ or}} ArSO_2Cl \xrightarrow{[H]} ArSH$$

is less frequently used[217-220].

Specifically, Marvel and coworkers[221] have described the production of 4-mercapto-3,5-dimethylphenoxyacetic acid (**54**) from 3,5-dimethylphenoxyacetic acid in a two-stage process in an overall yield of 60%.



(54)

Reduction of the sulphonyl chloride intermediate was by amalgamated zinc and sulphuric acid. The reversibility of the sulphonation step in acid media was clearly shown by some de-chlorosulphonation occurring during the reduction step with the formation of 3,5-dimethylphenoxyacetic acid[221]. The preparation and reduction of benzenesulphonyl chloride are described in *Organic Syntheses*[222a,b]. A single-step synthesis from aromatic compounds to thiols has been published: the aromatic compound and chlorosulphonic acid were allowed to react to completion, and the mixture was poured onto ice and sulphuric acid, to which zinc was carefully added.

TABLE 16. Formation of thiols from the reduction of sulphonyl chlorides

$RSO_2Cl \longrightarrow RSH$

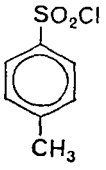
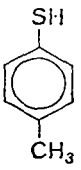
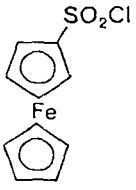
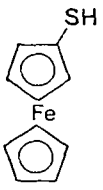
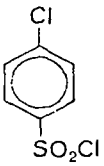
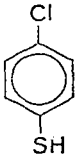
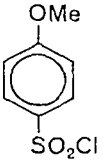
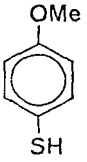
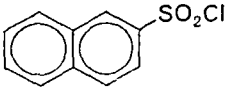
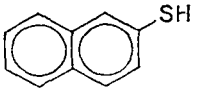
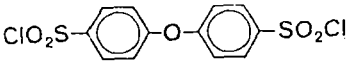
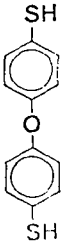
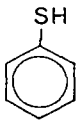
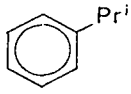
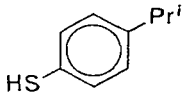
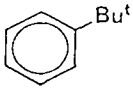
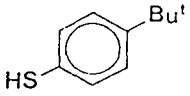
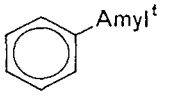
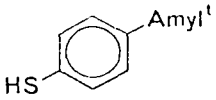
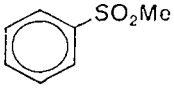
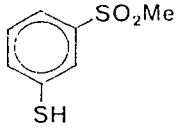
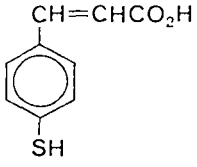
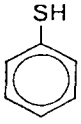
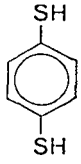
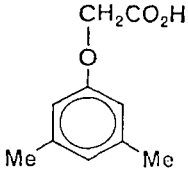
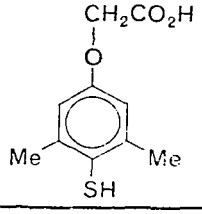
No.	RSO_2Cl	RSH	Yield (%)	Conditions	Ref.
1	*n*-$BuSO_2Cl$	*n*-BuSH	45	$LiAlH_4$	216
2			50 90 89 90	$LiAlH_4$ $LiAlH_4$ $LiAlH_4$ Red $P/I_2/CH_3CO_2H$	216 227 228 234
3			70	$LiAlH_4$ Zn/H_3O^+	217 226
4			91	Red $P/I_2/CH_3CO_2H$	234
5			63	Red $P/I_2/CH_3CO_2H$	234
6			89	Red $P/I_2/CH_3CO_2H$	234
7			85–90	Zn/H_3O^+	231

TABLE 17. Formation of thiols from aromatic hydrocarbons *via* aromatic sulphonyl chlorides

$$ArH \xrightarrow[(a)]{} ArSO_2Cl \xrightarrow[(b)]{[H]} ArSH$$

No.	Hydrocarbon	Conditions for stage (b)	Thiol	Overall yield (%) based on hydrocarbon	Ref.
1		Zn/H_3O^+		69	222
2		Zn/H_3O^+		60	224a
3		Zn/H_3O^+		60	224a
4		Zn/H_3O^+		32	224a
5		$LiAlH_4$		37	225
6	PhCH=CHCO$_2$H	Sn^{II}/H_3O^+		63	229
7		Zn/HgH_3O^+		22	231
8		$Zn/Hg/H_3O^+$		60	221

After a period of heating, the product was obtained by steam distillation[223]. From zinc/sulphuric acid reduction of sulphonyl chlorides, several alkyl-[224] and halogeno-thiophenols[224b,226] were obtained. The former group were produced in overall yields of 22–60%, based on the aromatic hydrocarbons.

Some other reducing agents have been used, including lithium aluminium hydride[216,218,225,227,228]; tin(II) chloride and acid[220,229,231]; tin and acid[219]; phosphine and base[232]; diborane, produced *in situ* from sodium borohydride and acid[233]; and red phosphorous with iodine[234,235].

To obtain thiols from sulphonyl chlorides by lithium aluminium hydride reduction requires the use of an excess of the reducing agent, otherwise sulphinic acids and disulphides may be formed, the sequence of reduction of sulphonyl chlorides to thiols being

$$RSO_2Cl \longrightarrow RSO_2H \longrightarrow RSOH \longrightarrow RSSR \longrightarrow RSH$$

However, these compounds can be further reduced simply on addition of more lithium aluminium hydride. Assuming that the stoichiometry of the reduction is:

$$2\,RSO_2Cl + 3\,LiAlH_4 \longrightarrow LiAlCl_2(SR)_2 + 6\,H_2 + 2\,LiAlO_2$$

$$LiAlCl_2(SR)_2 \xrightarrow{H_2O} RSH$$

then 23, 42 and 62% excesses of lithium aluminium hydride gave 71, 83 and 89% *p*-thiocresol respectively from *p*-toluenesulphonyl chloride[228]. Compounds, related to sulphonyl chlorides, which can also give thiols on reduction with lithium aluminium hydride, are sulphonic anhydrides and sulphonamides[231]; the latter react very slowly, however, and cannot be considered as a serious source of thiols. Another good general system for such reductions is red phosphorous and acetic acid in the presence of catalytic amounts of iodine[234-235].

Several of the other reductants have some particular and specific advantages. For example, diborane will reduce chlorosulphonyl groups preferentially and so nitrobenzenesulphonyl chlorides can be converted to the corresponding nitrothiophenols by diborane[233]. Stannous chloride reduction[229] of *p*-(chlorosulphonyl)-cinnamic acid to *p*-mercaptocinnamic acid gave 96% yield in contrast to zinc and acid reductions yielding only 22–26% of the thiol. Reductions by phosphines appear not to have much synthetic application for thiol formation. As well as thiols, disulphides and trithiophosphate esters are produced in yields dependent on the

conditions[232]. The presence of a base—pyridine was used as the solvent—was necessary. The best yields of thiols were obtained when an initial excess of phosphine was present; phosphine reduction of $PhSO_2Cl$, p-$CH_3C_6H_4SO_2Cl$, p-$BrC_6H_4SO_2Cl$ and p-$NO_2C_6H_4SO_2Cl$ led to 68, 56, 60 and 48% yields of the corresponding thiols respectively. When the phosphine was added in small portions gradually, the major products were the appropriate disulphides. The maximum yields of trithiophosphate esters were obtained in conditions intermediate between those reported above.

XI. THE FORMATION AND CONVERSION OF DISULPHIDES TO THIOLS

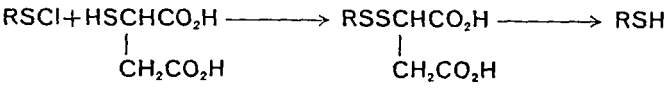
Conversion of disulphides to thiols can be achieved readily by reduction and by other sulphur—sulphur bond cleavage reactions. For a number of reasons, this is a very important conversion. Disulphides have been prepared in some cases in preference to the direct formation of thiols; the latter are subsequently prepared normally by reduction of the disulphides. A consideration in such indirect methods is that the disadvantage of the extra step in the synthesis must be more than offset by the reaction being more readily controlled, and producing greater yields than the direct route; for example, the reactions of alkyl halides[236,237] and aryl halides[238,239], activated for nucleophilic substitution by electron-withdrawing groups with disulphide ion have been preferred to reactions with the hydrogen sulphide ion, since these gave considerable amounts of waste sulphide products. Furthermore, rather than reacting aryldiazonium compounds with alkyl xanthates with the potential risk of explosions several authors have described the use of disulphide and polysulphide ions[206,240-242], in more reliable reactions:

$$2\ ArN_2^+ + S_n^{2-} \xrightarrow[n\geq 2]{} N_2\uparrow + ArS_nAr \xrightarrow{[H]} ArSH$$

Many procedures for thiol formation, for example, the *iso*thiuronium method (section VI), require base hydrolyses of the intermediates under vigorous conditions. Under such basic conditions, many thiols are particularly vulnerable to oxidation and considerable amounts of disulphide could be formed.

Air-oxidation of thiols on standing also leads to the formation of disulphides[243]. In some cases, the storage of disulphides is considered much wiser than storage of the thiols. Conversion of disulphides to thiols can be made whenever required. Kharasch and Parker[244] have recommended the

use of unsymmetric disulphides, formed almost quantitatively from α-mercaptosuccinic acid and the sulphenyl chloride derived from the particular thiol, RSH, as a useful method of storing very reactive thiols.

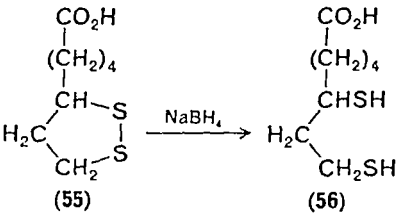


These unsymmetric disulphides are stable. The release of the desired thiol from the disulphide is readily obtained by some nucleophilic cleavage reaction (e.g. by CN^-; OH^-; see end of this section).

A considerable number of reagents and methods are available for reducing disulphides; these include lithium aluminium hydride[227,245-247]; sodium borohydride[248-250]; zinc and acid[251-256], or alcohol[257]; tin[251] and other metals[258] and acids; electrolytic reductions[259-261]; hydrogen sulphide and its metal salts[262-266]; ultraviolet radiation[267,268]; triorganophosphine[269-275]; glucose and base[80,276,277,295]; hypophosphorous acid—diselenide[278]; sodium in ammonia[279] and other solvents[280-283]. The ionic cleavage of sulphur—sulphur bonds in disulphides occurs with nucleophiles[239,244,284-289].

Lithium aluminium hydride reduces both diaryl and dialkyl disulphides readily in high yields to the thiols, after hydrolysis. Trisulphides are similarly reduced. Steric hindrance about the sulphur—sulphur bond can however restrict reduction[245].

Sodium borohydride was used[248] to reduce both (±) and (+) lipoic acids (**55**) to (±) and (+) dihydrolipoic acids (**56**) in excellent yields



(**55**) (**56**)

(≃90%). 2-Mercaptobenzothiazole[249] was prepared in 96% yield from the corresponding disulphide. Use of a Lewis acid, such as $AlCl_3$, with sodium borohydride leads to quantitative conversions of aryl, aralkyl and alkyl disulphides to thiols[250].

Several metal—proton donor-reducing systems have been successfully used. This is a long-established procedure[252] with the most frequently used combinations being tin[251] and zinc[251-253,256] in the presence of an acid. The almost quantitative determination of disulphides by amalgamated

TABLE 18. Preparation of thiols by reduction of disulphides

$$RSSR \xrightarrow{2[H]} 2\ RSH$$

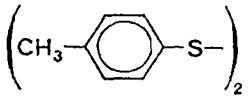
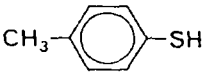
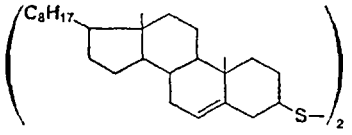
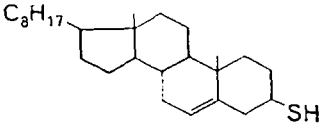
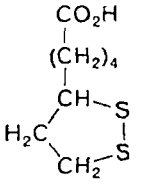
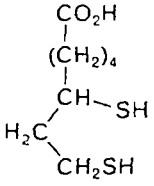
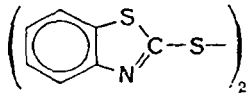
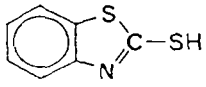
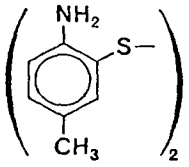
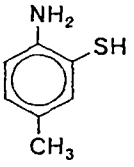
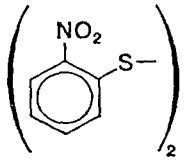
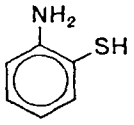
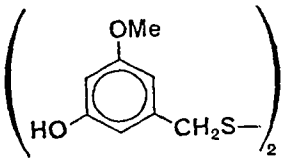
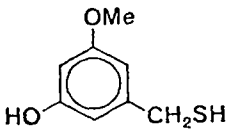
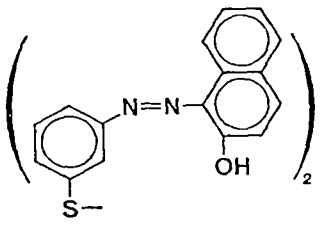
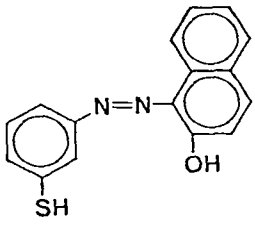
No.	Disulphide	Thiol	Yield (%)	Ref.
(a)	$LiAlH_4$ *reductions*			
1			75	227
2			88	227
3	$(n\text{-BuS})_2$	n-BuSH	96	245
4	$(PhS)_2$	PhSH	95	245
5	$(Bu^tS)_2$	Bu^tSH	0	245
6	$(Ph_2CHCHCH_2S)_2$ (OH)	$Ph_2CHCHCH_2SH$ (OH)	92	247
(b)	$NaBH_4$ *reductions*			
7			91	248
8			96	249
9	$(n\text{-BuS})_2$	n-BuSH	99	250
10	$(PhS)_2$	PhSH	99	250
11	$(PhCH_2S)_2$	$PhCH_2SH$	99	250
(c)	*Metal-acid reductions*			
12	$[CH_3(CH_2)_{11}S]_2$	$CH_3(CH_2)_{11}SH$	95 ($Zn/Hg/H_2SO_4$)	254

TABLE 18 (*cont.*)

No.	Disulphide	Thiol	Yield (%)	Ref.
13			45 (Zn/CH_3CO_2H)	251
14			90 (Zn/CH_3CO_2H)	256
15			59 ($Hg/Al/H_2O$)	258

(d) *Sodium sulphide reduction*

16			88	262

(e) *Triorganophosphine reductions*

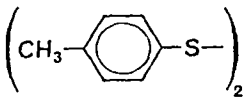
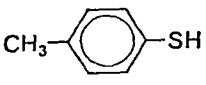
17	$(PhS)_2$	PhSH	~100 (PPh_3/MeOH H_2O/RT, 15 min)	269
18			~100 (PPh_3/MeOH H_2O/RT, 15 min)	269

TABLE 18 (*cont.*)

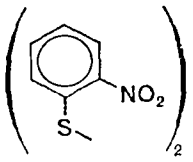
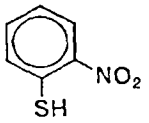
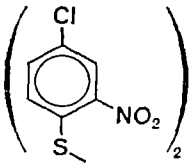
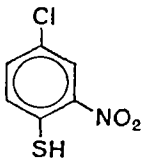
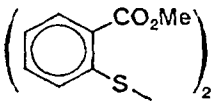
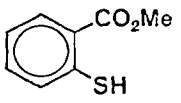
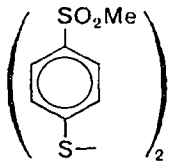
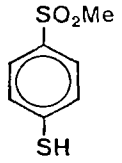
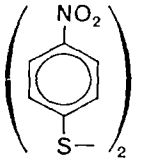
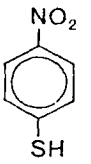
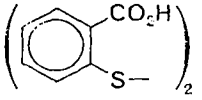
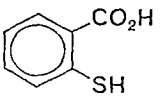
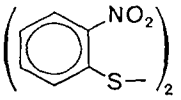
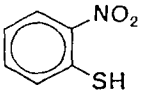
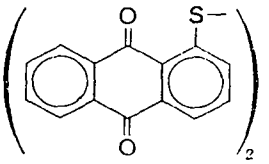
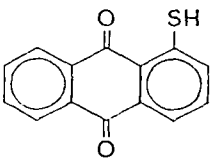
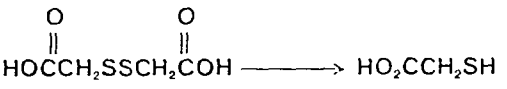
No.	Disulphide	Thiol	Yield (%)	Ref.
19			~100 (PPh_3/MeOH H_2O/RT, 15 min)	269
20			~100 (PPh_3/MeOH H_2O/RT, 15 min)	269
21			~100 (PPh_3/MeOH H_2O/RT, 15 min)	269
22	$(PhCH_2S)_2$	$PhCH_2SH$	40 (PPh_3/MeOH H_2O/20 h/RT) 95 (PPh_3/MeOH H_2O/reflux)	274 274
23	$(BuS)_2$	BuSH	93 (PPh_3/MeOH H_2O/reflux 6 h) 98 (PBu_3/MeOH H_2O/RT/1 h)	274 273
24	$(CH_3CH_2CH_2S)_2$	$CH_3CH_2CH_2SH$	73 (PPh_3/MeOH H_2O/reflux 4 h) 98 (PBu_3/MeOH H_2O/RT/1 h)	274 273
(f) *Glucose reductions*				
25			40	80

TABLE 18 (*cont.*)

No.	Disulphide	Thiol	Yield (%)	Ref.
26			32	80
27			—	276
28			—	276
29			—	277

zinc/acid reduction to thiols has been described[251]. Reduction of di(*o*-nitrophenyl) disulphide by zinc and acetic acid[256] is an efficient way of producing *o*-aminothiophenol. For some difurfuryl and dibenzyl disulphides, aluminium amalgam was used[258].

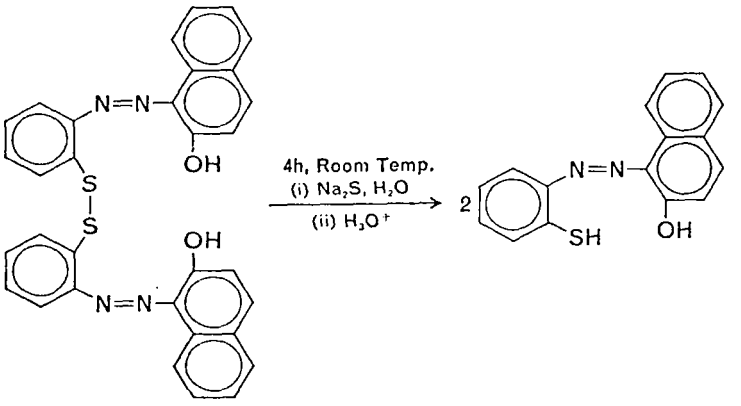
Cathodic reduction of cystine-^{35}S-hydrochloride to cysteine-^{35}S-hydrochloride has been achieved[259] in a very high yield. Electrolytic reduction was also used for dithio-diglycollic acid (**57**)[260], and for diphenyl disulphide[261].



(**57**)

Among the disulphides successfully reduced by sodium sulphide was[262] di-[*o*-(2-hydroxynaphthalene-1-azo)phenyl] disulphide (**58**). The yield of the

sodium salt of the thiol was 88%. Alcoholic potassium sulphide successfully reduced di-(4-methyl-3-bromophenyl) disulphide to the corresponding thiol after hydrolysis[265]. Reduction of both the nitro and disulphide groups



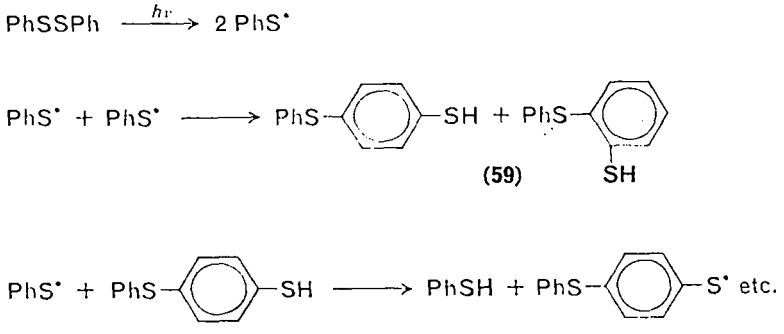
(58)

in di-(*o*-nitrophenyl) disulphide by an excess of ammonium hydrogen sulphide led, after acidification, to the formation of the hydrochloride of *o*-aminothiophenol[266].

Ultraviolet irradiation of solutions of disulphides in solvents able to act as proton donors[267] does lead to the corresponding thiols[267, 268, 291-294].

$$RSSR \xrightarrow{h\nu} RS\cdot \xrightarrow{R^1H} RSH + R^1\cdot \qquad (20)$$

In hydrogen-free solvents, such as carbon tetrachloride, or in weak hydrogen-donor solvents (e.g. toluene) diphenyl disulphide on irradiation also gave, in addition to thiophenol, the thiols (**59**) and polymeric thiol material[267]. The reaction scheme was envisaged to be:



The mean equivalent weight of thiol produced was intermediate between the molecular weight of thiophenol and of the mercaptodiphenyl sulphides. The yield of thiol products increased with longer irradiation times, e.g. in toluene solution, 7, 13, 17 and 22% conversion into thiols was obtained with irradiation times of 18, 42, 66 and 90 hours at 25°C. Dimesityl disulphide on similar photolysis in the presence of 9,10-dihydroanthracene was converted to mesitylenethiol in 78% yield[267]; anthracene was also formed. Di-*iso*butyl and di-*n*-butyl disulphides were also rapidly photolysed to thiols in cumene and other solvents at 35°C using a low pressure

$$Bu^iSSBu^i \xrightarrow{h\nu} 2\,Bu^iS^\bullet$$

$$Bu^iS^\bullet + PhC(CH_3)(H)-CH_3 \longrightarrow Bu^iSH + Ph\dot{C}(CH_3)_2$$

$$2\,Ph\dot{C}(CH_3)_2 \longrightarrow PhC(H_3C)(CH_3)-C(H_3C)(CH_3)-Ph$$

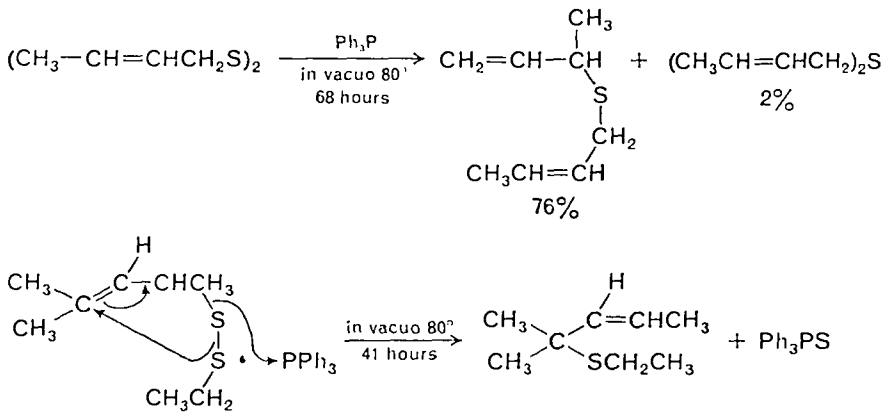
$$Ph\dot{C}(CH_3)_2 + Bu^iS^\bullet \longrightarrow PhC(CH_3)_2(SBu^i)$$

mercury arc; e.g. in cumene[268]. The yields of *iso*-butanethiol were in the region of 35%. Other solvents capable of acting as proton donors were also used; e.g. *iso*propyl ether (8% conversion) and tetralin (39% conversion). Other reports on the radical reactions of disulphides to thiols include that of di-*iso*-amyl disulphide[291] in refluxing tetralin and of diphenyl disulphide and di-(2-benzothiazyl) disulphide in the presence of tetralin, 9,10-dihydroanthracene or phenylcyclohexene at 260°C[292]. At these temperatures, some homolytic breakdown of the S—S bond occurs, at lower temperatures irradiation must be applied[293, 284].

$$ArSSAr + H_2O \xrightarrow[MeOH/H_2O]{Ph_3P/H_2O} 2\,ArSH + Ph_3PO$$

The reduction of diaryl disulphides to thiols by triphenylphosphine in aqueous methanol in the presence of an acid is a rapid and quantitative reaction at room temperature[269] and has even been recommended as an

analytical method for the determination of diaryl disulphides. The reaction is successful for a number of substituted diphenyl disulphides, including nitrophenyl compounds. In an anhydrous medium, diphenyl disulphide and related compounds were not reduced[271,272] by triphenylphosphine to thiols. Alkenyl disulphides reacted in the absence of solvent and water with triphenylphosphine in the dark at 80°C to give sulphides and triphenylphosphine sulphides[275], whereas dibenzyl disulphide did not react under similar conditions.



Similar reactions of these alkenyl disulphides occurred in solution[275], both in the presence and absence of water. Simple dialkyl disulphides are only sluggishly reduced by triphenylphosphine even in the presence of water and for these compounds the use of the more basic and nucleophilic tributylphosphine is recommended. Almost quantitative yield of thiols are obtained within 60 min at room temperature using this phosphine in aqueous methanol from dipropyl, dibutyl and dibenzyl disulphides[273].

Glucose in the presence of a base is another useful reductant of sulphur—sulphur bonds without affecting nitro groups[80,276,295].

Although hypophosphorous acid is a useful reductant for diselenides, it is not effective towards disulphides unless catalytic quantities of diselenides are also present. Thus, cystine and hypophosphorous acid in the presence of bis-(2-N,N-dimethylaminoethyl)diselenide gave 97% cysteine[278].

The last-mentioned reduction is also conveniently obtained using sodium in liquid ammonia[279]. Solvents other than ammonia have also been used for sodium reductions; ether[280] and xylene[281] being other frequently used solvents for thiol formation. Modifications of the basic process involved

the less reactive sodium amalgam[283] and the more reactive sodium–potassium alloy[281]. Both dialkyl and diaryl disulphides can be cleaved by sodium[281].

There are fairly recent reviews on the nucleophilic cleavage of aliphatic disulphides[285,286]. In the cleavage of unsymmetric disulphides, $RSSR^1$, it is the R unit with the more electron-withdrawing groups, which gives the thiolate ion initially[288]. Thus, the reaction is under thermodynamic control since the most stable RS^- is formed. The reactions should in fact be considered as equilibria; the position of equilibrium for a particular reaction depends on the nucleophile and the disulphide. Also, further

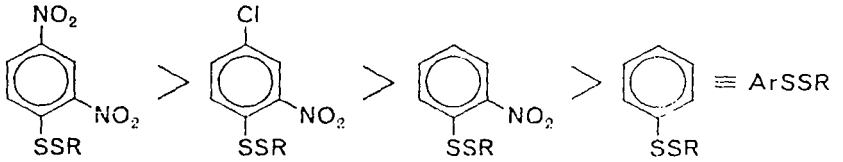
$$RSSR^1 + Nu^- \rightleftharpoons RS^- + [R^1SNu]$$

$Nu^- = EtS^-, PhS^-, CN^-, OH^-, SO_3^{2-}$ but not I^-, N_3^- or SCN^-

reactions of these initially formed products are possible. The sequence of S-nucleophilicity was found to be

$$EtS^- > PhS^- > CN^- > SO_3^{2-} > OH^- > N_3^- > SCN^- > I^-$$

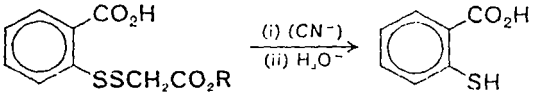
Clearly the sequence of nucleophilicity towards carbon and sulphur centres are different. From 2,4-dinitrophenyl ethyl disulphide (**60**, R = Et) in 85% aqueous acetone at 25°C, the reactions with OH^-, CN^- and N_3^- led to 85, 70 and 0% 2,4-dinitrobenzenethiol respectively[288]. The ease of cleavage of some disulphides by cyanide ion was in the sequence shown:



(**60**)

$$ArSSR \xrightarrow{CN^-} ArS^- + RSCN$$

Thus, electron-withdrawing groups in the aromatic molecules favour the cleavage reaction. The carboxylate group is also sufficiently electron withdrawing to enable cleavage of the S—S bond in **61** to occur by cyanide ion.



(**61**)

XII. THE FORMATION OF THIOCYANATES AND THEIR CONVERSION TO THIOLS

A. Formation of Thiocyanates

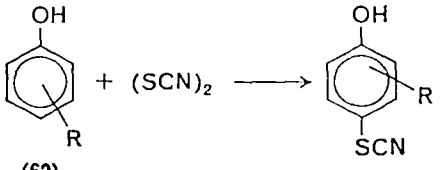
The most convenient preparation of alkyl and aralkyl thiocyanates is from the nucleophilic substitution of the corresponding halides, sulphates or sulphonates by thiocyanate ion[296-297, 299-302, 318, 319]. The yields are usually

$$RX + NCS^- \longrightarrow RSCN$$

at least 70%[301]. Some *iso*thiocyanates can also be formed[300], e.g. *t*-butyl chloride and thiocyanate ion at room temperature gave a mixture of both *t*-butyl thiocyanate and *t*-butyl *iso*thiocyanate[316]. Use of the reaction of sulphonates with thiocyanate ion was made in the preparation of cholesteryl thiocyanate[317]. Some sulphonate replacements by thiocyanate ion were observed to occur with inversion[302].

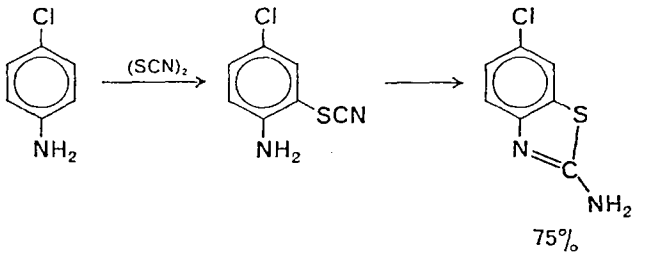
$$X_2 + NCS^- \longrightarrow XSCN \longrightarrow (SCN)_2$$

X = Br or Cl



(62)

Aromatic hydrocarbons having strong electron-donating groups, such as the hydroxy- and amino groups, even in the presence of NO_2, Cl, Br, CO_2Et, react with thiocyanogen or thiocyanogen halides to yield aryl thiocyanates[298, 303-307]. The thiocyanogen (or thiocyanogen halide) is



75%

normally formed *in situ* from a metal thiocyanate and either bromine or chlorine. Low temperatures must be employed to avoid the formation of polymeric thiocyanogen material. Since these are electrophilic reactions,

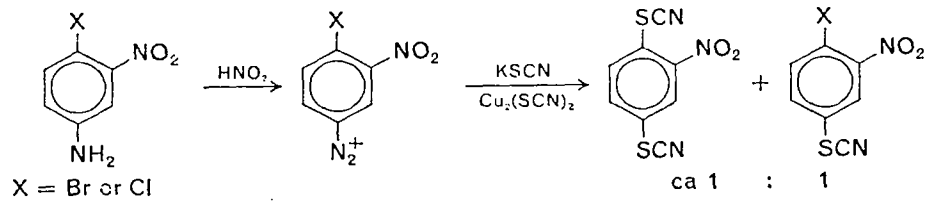
only certain isomers are obtainable: the thiocyanate goes almost exclusively into the *para* position to amino or hydroxyl groups; if this position is blocked, then *ortho* substitution will arise. Yields are very good, e.g. aniline gives 97% *p*-thiocyanatoaniline at 5°C in methanol[298]. When thiocyanation occurs *ortho* to the amino group, the final product could be an aminobenzothiazole[298].

In the presence of a Lewis acid catalyst, e.g. $AlCl_3$, even benzene can be thiocyanated[308]. For aromatic compounds, more deactivated than benzene towards electrophilic substitution, direct reaction with thiocyanogen fails even in the presence of a Lewis acid catalyst.

The Gatterman or Sandmeyer reactions of cuprous thiocyanates with diazotized amines are the more general routes to aryl thiocyanates[322, 309-311]. Ferric thiocyanate can also be used. The limitation in this method is the

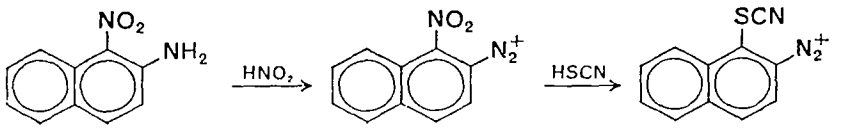
$$ArNH_2 \xrightarrow[HX]{HNO_2} Ar\overset{+}{N}_2X^- \xrightarrow[\Delta]{(CuSCN)_2} ArSCN$$

number of primary aromatic amines available. The halogen in *o*- and *p*-halobenzenediazonium salts can also be replaced by thiocyanate[312, 320, 321]. Thus diazotized 4-bromo- and 4-chloro-3-nitroaniline on treatment with potassium and copper(I) thiocyanates gave nitro-*p*-dithiocyanatobenzene as well as the 4-halogeno-3-nitrophenyl thiocyanate. Obviously the strongly electron-withdrawing diazonium group enables nucleophilic substitution of the halide to occur[312].



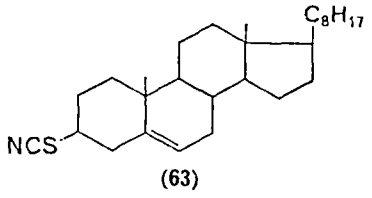
X = Br or Cl ca 1 : 1

The nitro group in the diazonium salts derived from 1-nitro-2-naphthylamine and 2-nitro-1-naphthylamine can also be replaced by thiocyanate in solutions containing HSCN [322].

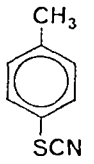


B. Reduction of Thiocyanates to Thiols

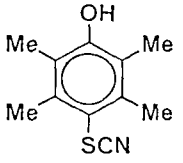
Reduction by lithium aluminium hydride in ether of such diverse compounds as cholesteryl thiocyanate (**63**)[227,297], *p*-tolyl thiocyanate (**64**)[227], 1-hydroxy-4-thiocyanato-2,3,5,6-tetramethylbenzene (**65**)[303] and 3-thiocyanatobenzothiazine (**66**)[116] proceed in good yield to the corresponding thiols.



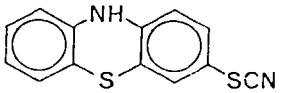
(63)



(64)

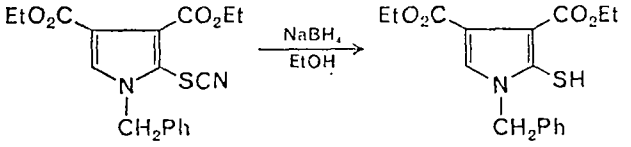


(65)



(66)

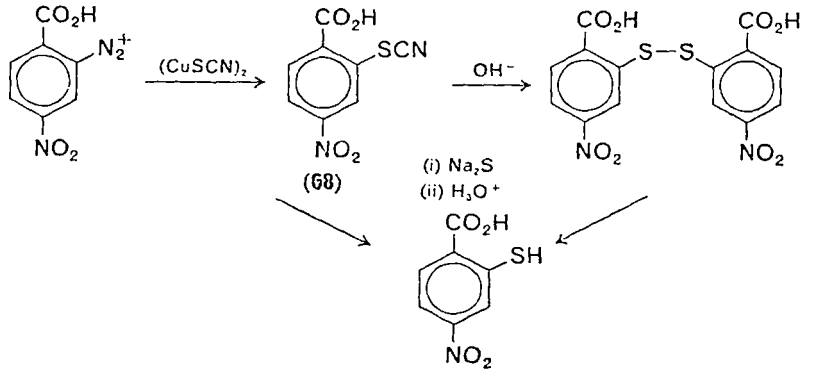
The milder reducing agent, sodium borohydride, was used as the reductant for diethyl 1-benzyl-2-thiocyanatopyrrole-3,4-dicarboxylate (**67**) without affecting the ester groups[304].

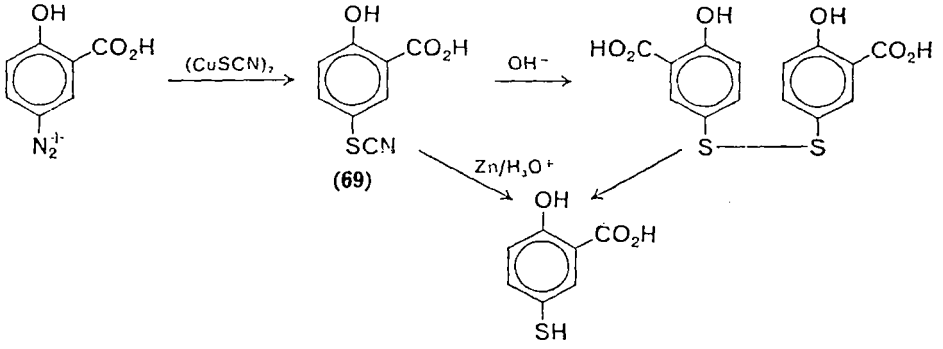


(67)

Sodium in liquid ammonia was successfully used to reduce both alkyl and aryl thiocyanates[307]; yields of greater than 70% were obtained for hydroxyaromatic thiols. However, halogeno- and nitro-groups are also affected by this system. In another patent, the alkaline hydrolysis of aryl thiocyanates was reported to give good yields of thiophenols. The alkaline hydrolysis of *p*-di-thiocyanatobenzene led to benzene-1,4-dithiol[312]. However, the action of alkali on aryl thiocyanates containing electron-withdrawing groups, for example **68** and **69**, led to the disulphide

instead[309,310]. Reduction of the thiocyanate can be otherwise achieved as indicated:





Other zinc and acid reductions have been described[313].

Acid-catalysed hydrolysis was successful for *p*-nitrobenzyl thiocyanate[314]; *p*-nitrobenzyl thiocarbamate was an intermediate in this reaction.

The reduction of 5-thiocyanato-uridine to 5-mercapto-uridine was achieved using dithiothreitol and also by the sodium dithionite–mercaptoethanol combination[315].

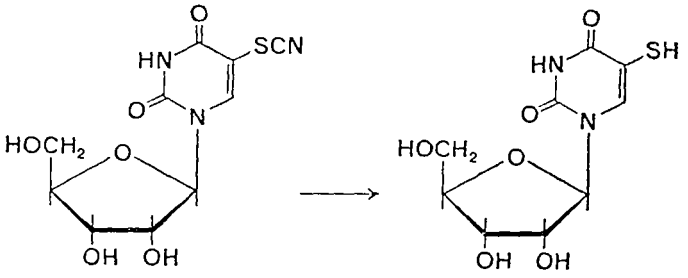


TABLE 19. Some representative examples of the formation of thiols by way of thiocyanates

(*a*) *From halides*

$$RX + NCS^- \longrightarrow RSCN \longrightarrow RSH$$

No.	Reagent	Thiol	Reductant of thiocyanate	Overall yield of thiol	Ref.
1	Chloresteryl chloride	Chloresteryl thiol	$LiAlH_4$	71%	297

(*b*) *From hydrocarbons*

$$ArH + (NCS)_2 \longrightarrow ArSCN \longrightarrow ArSH$$

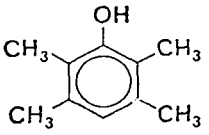
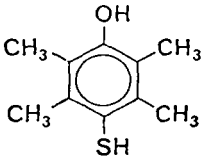
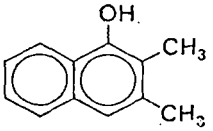
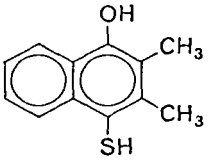
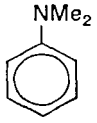
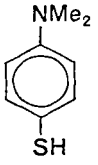
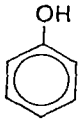
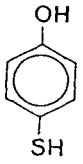
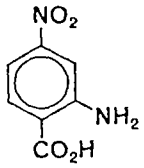
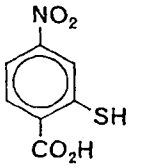
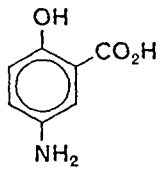
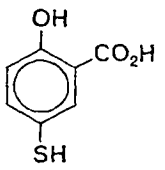
	Hydrocarbon	Thiol	Reductant of thiocyanate	Overall yield of thiol	Ref.
2			$LiAlH_4$	38%	303
3			$LiAlH_4$	39%	303
4			$Na/liqNH_3$	72%	307
5			OH^-	82%	306

TABLE 19 (*cont.*)

(*c*) *From anilines*

$$ArNH_2 \xrightarrow[HX]{HNO_2} ArN_2^+X^- \xrightarrow{(CuSCN)_2} ArSCN \longrightarrow ArSH$$

	Aniline	Thiol	Reductant of thiocyanate	Overall yield of thiol	Ref.
6			Na_2S/OH^-	23–30%	309
7			Zn/HCl	65%	310

XIII. DEALKYLATION OF SULPHIDES: CARBON—SULPHUR BOND CLEAVAGE

Cleavage of a carbon—sulphur bond in sulphides is an important reaction. Much of this importance is linked with the use of protecting groups for thiols. As the thiol grouping is extremely susceptible to attack, it is pertinent to protect it before carrying out modifications elsewhere in the molecule. Discussion of the various protecting groups available is given in Chapter 14. The following section is mainly concerned with preparation of thiols via sulphide formation.

Although formation of alkanethiols, RSH, from reaction of hydrogen sulphide with alkyl halides and sulphonates (section IV) and with alkanes (section II.A) is extensively used, there are some advantages in using thiols, R^1SH, rather than hydrogen sulphide to give sulphides, RSR^1, followed by dealkylation to RSH. If such an indirect route is taken then the ease of cleavage of the R^1—S bond must be much greater than the R—S bond. The longer methods have the particular advantage[323,324] over the more direct H_2S reactions in that no symmetric sulphide, RSR, can be formed; these symmetric sulphides being normally wasted. Particularly useful R^1 groups are the simple alkyl groups and, in particular, the benzyl group[323,324,325]. For instance, D,L-α-lipoic acid was obtained from ethyl 6,8-dibromo-octanoate in an overall yield of 67% *via* reaction with benzyl mercaptan,

followed by sodium in liquid ammonia cleavage and in a yield of 36% *via* the thiolacetate and its hydrolysis[324].

$$RBr \xrightarrow{PhCH_2SH} RSCH_2Ph \xrightarrow[(ii)\ H_3O^+]{(i)\ Na/liquid\ NH_3} RSH$$

$$\xrightarrow{CH_3COSH} R{\cdot}S{\cdot}\overset{\overset{O}{\|}}{C}{\cdot}CH_3 \xrightarrow[(ii)\ H_3O^+]{(i)\ OH^-} RSH$$

There are good reviews available on addition of thiols, R^1SH, to alkenes[3a,12], for other information regarding the selectivity of such additions, see reference 16: no details of such additions will be given here.

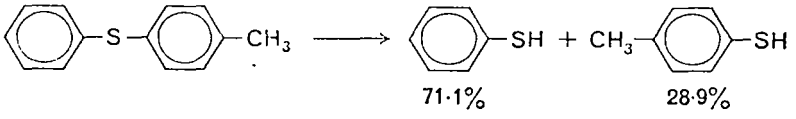
Conversion of aryl bromides to thiophenols can be achieved[326,327] by treating a halide with a cuprous mercaptide in boiling quinoline (200°C) for up to ten hours. The alkyl aryl sulphide formed can be cleaved to

$$ArBr + (CuSR)_2 \xrightarrow[quinoline]{\Delta} ArSR \xrightarrow[(ii)\ H_3O^+]{(i)\ Metal/Amine} ArSH$$

give the thiophenol in several metal–amine systems[328,329]. The best methods were using sodium in liquid ammonia and lithium in methylamine; a less effective system was sodium in pyridine. From the appropriate ethyl aryl sulphides, sodium in ammonia cleavage gave between 70 and 100% of the mercaptobenzenes.

The scope of the cuprous mercaptide reactions with organic halides in boiling quinoline is wide: mono-, di- and tri-alkylthiobenzenes; alkyl thiopyridines and thiophenes; simple dialkyl sulphides and alkenyl alkyl sulphides can all be prepared from the corresponding halogen derivatives and converted to the thiols. Tetra-, penta- and hexa-bromobenzenes, however, gave tars.

While cleavage of alkyl aryl sulphides by metal–amine systems always gave the aromatic thiol, no matter what the alkyl group was[328-331], cleavage of unsymmetric aryl sulphides gave in the majority of cases both thiols; e.g.



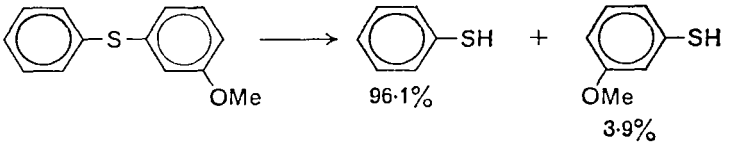
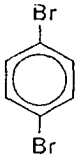
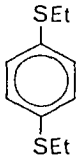
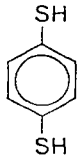
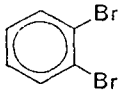
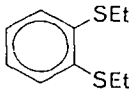
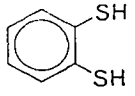
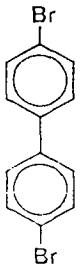
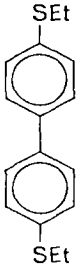
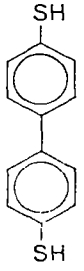
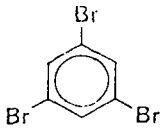
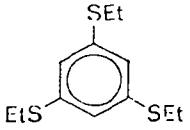
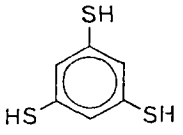


TABLE 20. Formation of thiols from aryl halides *via* reaction of cuprous alkyl sulphides[327, 328]

$$ArBr \xrightarrow{CuSR} ArSR \xrightarrow[(ii)\ H_3O^+]{(i)\ Na/R_3N} ArSH$$

No.	Aryl halide	Sulphide (Yield)	Thiol[a] (Yield)
1		 (96%)	 (98%, 85%[b])
2		 (58%)	 (72%)
3		 (94%)	 (97–99%)
4		 (35%)	 (85%)

[a] Yields based on sulphide (reduction by Na in liquid NH_3).
[b] Reduction by Na in pyridine.

For unsymmetric dialkyl sulphides, the ease of carbon—sulphur bond cleavage by lithium in methylamine was[330, 331] found to be

tert-alkyl > *sec*-alkyl > primary-alkyl

e.g.

$$n\text{-}C_4H_9SC_4H_9\text{—t} \longrightarrow n\text{-}C_4H_9SH + t\text{-}C_4H_9SH$$
$$97{\cdot}5\text{–}100\% \quad 0\text{—}2{\cdot}5\%$$

$$sec\text{-}C_4H_9SC_4H_9\text{-}t \longrightarrow sec\text{-}C_4H_9SH + t\text{-}C_4H_9SH$$
$$99{\cdot}5\% \quad 0{\cdot}5\%$$

$$n\text{-}C_4H_9SC_4H_9\text{-}sec \longrightarrow n\text{-}C_4H_9SH + sec\text{-}C_4H_9SH$$
$$50\% \quad 50\%$$

$$n\text{-}C_8H_{17}SC_4H_9\text{-}n \longrightarrow n\text{-}C_8H_{17}SH + n\text{-}C_4H_9SH$$
$$70\% \quad 30\%$$

The products also formed along with the thiols are hydrocarbons. The treatment of dibenzyl sulphide with lithium–methylamine did not lead to any thiol but instead to toluene and lithium sulphide arising from the facile cleavage of benzyl—sulphur bonds[330,331]:

$$PhCH_2SCH_2Ph \xrightarrow[MeNH_2]{Li} PhCH_3 + Li_2S$$

The mechanism of these reductions could involve both free radical (one-electron transfer) and carbanion (two-electron transfer) intermediates, each leading to different reaction rate sequences[331].

1 *electron transfer*

$$RSR' \xrightarrow{1e} RS^- + R'\cdot$$
$$[\text{Rate: } R' = Bu^t > Pr^i > Et > Me]$$

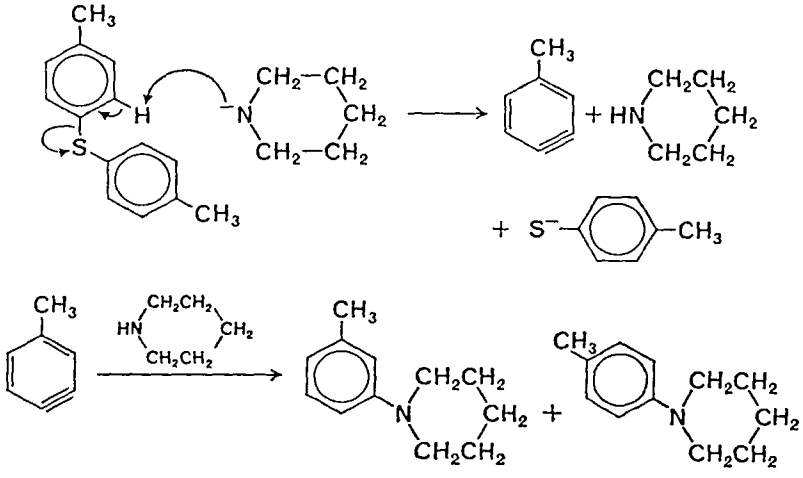
2 *electron transfer*

$$RSR' \xrightarrow{2e} RS^- + R'^-$$
$$[\text{Rate: } R' = Me > Pr^i > Bu^t]$$

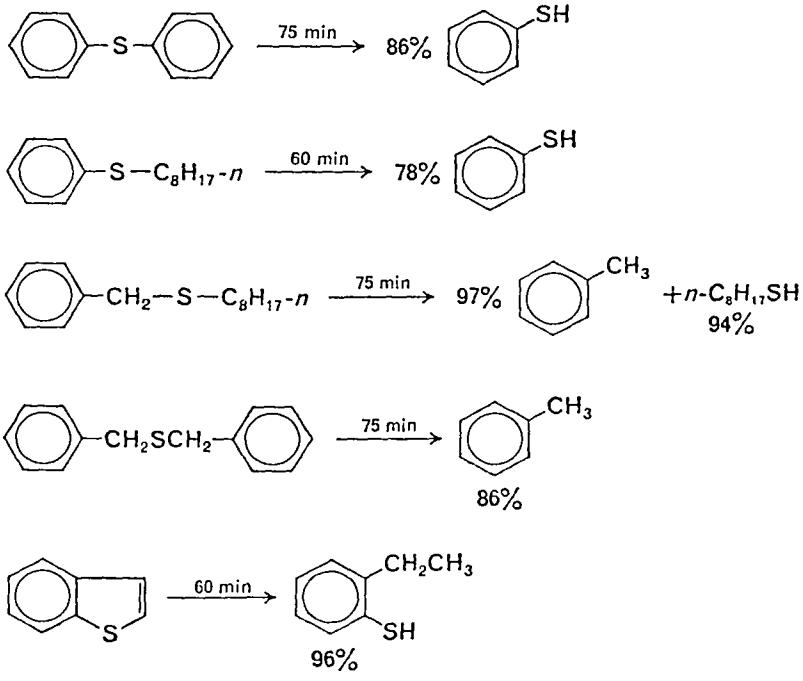
For other cleavages of sulphides, by sodium in ammonia see reference 332.

Related reductants are sodamide in piperidine[333,334] and calcium hexammine in ether[335]. Cleavage of diphenyl sulphide by sodamide in piperidine has been reported to give 91%[333] and 54%[334] thiophenol in two studies. N-Phenylpiperidine was also obtained. From di-*p*-tolyl sulphide, *p*-toluenethiol (54%) and N-*p*-tolylpiperidine were obtained and the cleavage mechanism was considered to be an aromatic S_N2 process and

not one involving arynes[334]. If arynes were involved, not only N-*p*-tolyl- but also N-*m*-tolyl-piperidine should be formed:



Calcium hexammine, prepared from calcium and ammonia, dissolved in ether, also reacted with sulphides at 0°C to give, after hydrolysis, thiols and hydrocarbons[335]; for example:



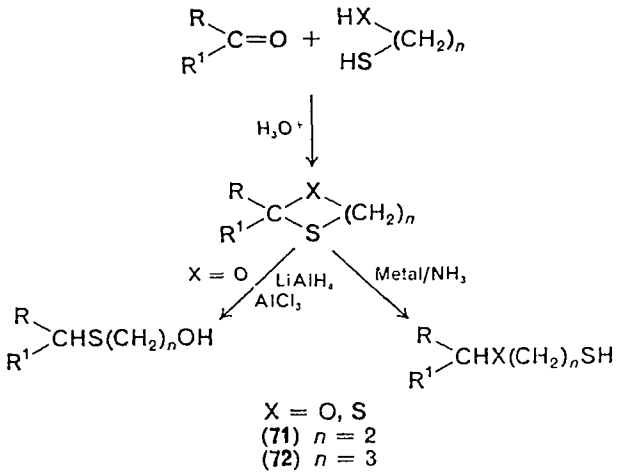
Ethylenic sulphides (e.g. **70**) are also cleaved by metal–liquid ammonia systems[336]. There is no concurrent reduction of the unsaturated bond nor loss of sulphur.

$$EtCH{=}CHSEt \xrightarrow{Li/NH_3} EtCH{=}CHSLi + C_2H_6$$

(70)

In the carbohydrate field, use has been made of the benzyl—sulphur bond cleavage by metal–amine systems to provide a route from an unsaturated compound to a thiol[337].

Use of metal-ammonia reducing combinations has been made in the synthesis of alkoxy- and thioalkoxy-thiols from thio-acetals and thio-ketals[338–342].



X = O, S
(71) $n = 2$
(72) $n = 3$

Metal–ammonia reductions of 1,3-oxathiolanes (**71**, X = O) and 1,3-oxathianes (**72**, X = O) are good methods of preparing β-alkoxyethane and γ-alkoxypropane thiols[338, 339, 342], whereas lithium aluminium hydride and aluminium chloride cleaves the carbon—oxygen bond in preference to the carbon—sulphur bond. The metal used can be any electropositive element; the sequence of increasing yield of product for various metals is

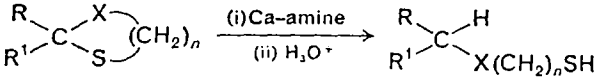
$$Ca > Li > Na > K$$

If either R or R^1 is a phenyl group, then alkylbenzenes are produced instead of the thiol product, e.g. 2-phenyl-1,3-oxathiolanes (**71**, X = O,

R^1 = Ph) on treatment with metal–ammonia[338,339,343]. This is due to the initially formed alkoxythiol, **73**, being easily cleaved by the reductant.

$$\underset{\underset{\mathbf{(73)}}{\mathbf{R}}}{\mathbf{PhCHOCH_2CH_2SH}} \xrightarrow[\text{(ii) } H_3O^+]{\text{(i) Ca–NH}_3} PhCH_2R + HO(CH_2)_2SH$$

TABLE 21. Formation of alkoxy- and thioalkoxy-thiols from Ca–amine reductions

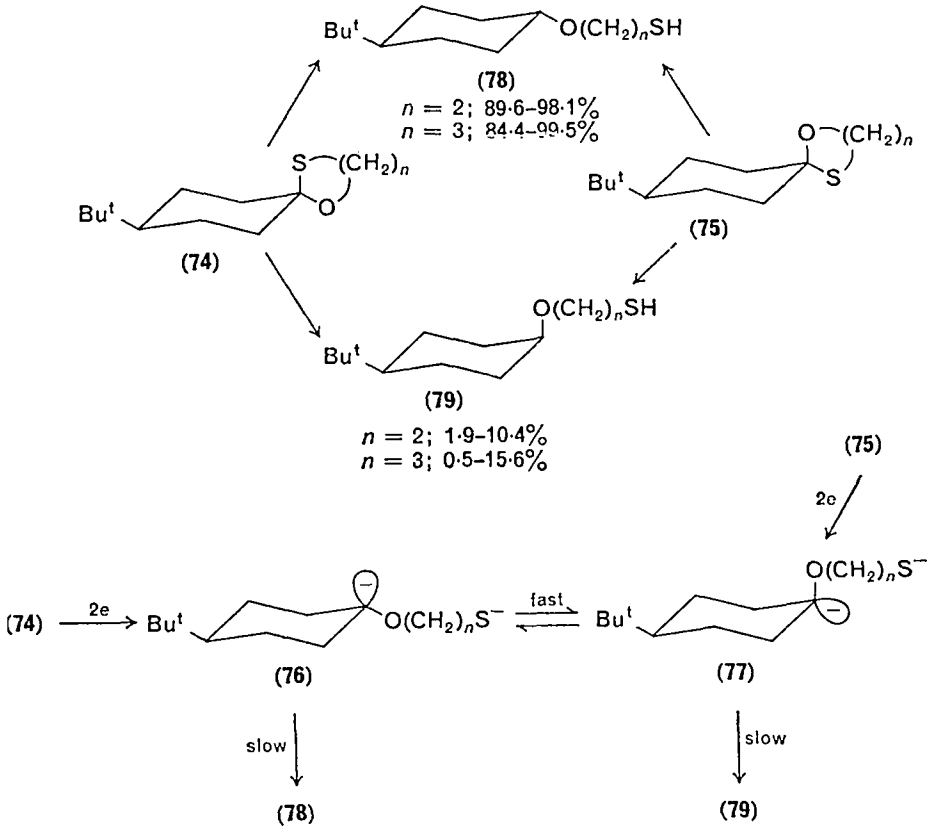


No.	R	R^1	X	*n*	Yield of thiol (%)	Reference
1	$(CH_3)_2CH$	H	O	2	7	338, 339
2	$PhCH_2$	H	O	2	73	338, 339
3	$PhCH_2$	CH_3	O	2	88	338, 339
4	$Ph(CH_2)_2$	CH_3	O	2	47	338, 339
5	Ph	H	O	2	0	338, 339
6	$-(CH_2)_4-$		O	2	25	338, 339
7	$-(CH_2)_5-$		O	2	49	338, 339
8	$(CH_3)_2CH$	H	S	2	85	338, 340
9	$-(CH_2)_5-$		S	2	85	338, 340
10	$PhCH_2$	H	S	2	94	340
11	$(CH_3)_2CH$	H	O	3	66	339
12	$-(CH_2)_4-$		O	3	85	339
13	$-(CH_2)_5-$		O	3	70	339
14	$(CH_3)_2CH$	H	S	3	85	340
15	$-(CH_2)_5-$		S	3	84	340

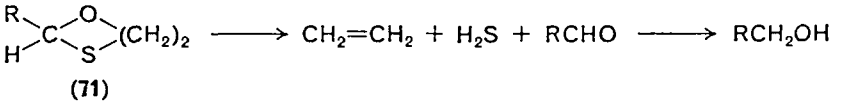
In general, oxathianes (**72**, X = O) give more thiol products than the corresponding oxathiolanes, (**71**, X = O); also acetals are not cleaved in as high a yield as are the ketals.

The stereochemistry of the metal–amine reaction has been thoroughly investigated using the pairs of isomeric thioketals derived from 4-*t*-butylcyclohexanone. The major products from each pair of isomers (**74** or **75**) were the thermodynamically more stable equatorial isomers (**78**). This suggests that the rates of interconversions of the dianions (or the radical anions)—**76** and **77**—are faster than the rates of protonation. The fact

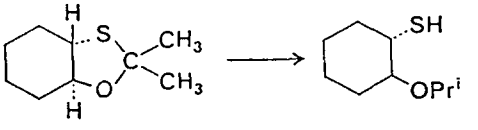
that slightly more axial products, **79**, are obtained from **75** indicates that some protonation occurred before complete equilibration.



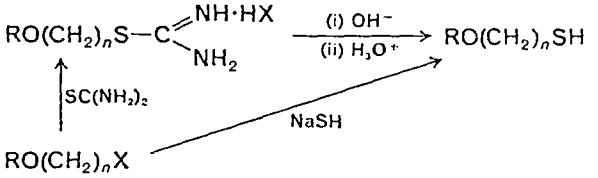
The lower yields of thio products from acetals are due to loss of olefin from **71**:



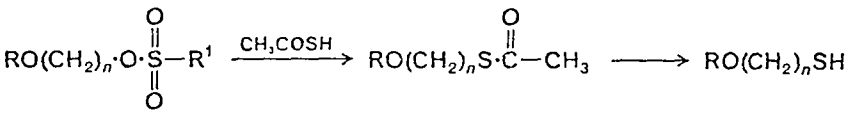
2,2-Dimethyl-*trans*-4,5-cyclohexano-1,3-oxathiolane gave the *trans*-thiol[341]:



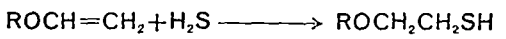
Other preparations of alkoxythiols, include reaction of alkoxyalkyl halides, $RO(CH_2)_nX$, either with thiourea, followed by alkaline hydrolysis of the *iso*-thiuronium salts[344] or with hydrogen sulphide ion[345,346]:



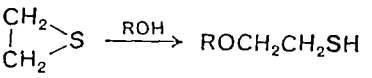
reaction of sulphonate esters with thiolacetic acid and subsequent alkaline hydrolysis[347]:



reaction of vinyl ethers[348] with hydrogen sulphide:



and reaction of thiiranes with alcohols[349]:

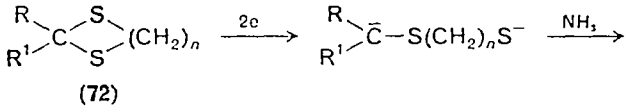


Cleavage of 1,3-dithiolanes (**71**, X = S) and 1,3-dithianes (**72**, X = S) similarly gave excellent yields of β-alkylthioethane- and γ-alkylthiopropane-thiols[338,340-342] (**80**). Yields are generally higher than for the

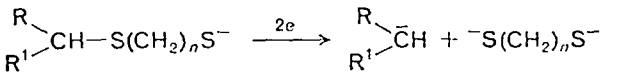
$$RR'CHS(CH_2)_nSH$$

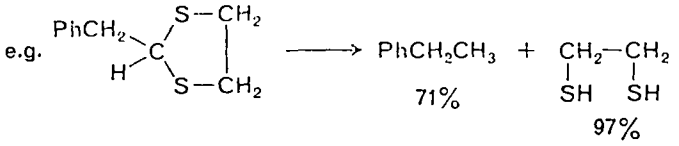
(80)

corresponding alkoxy compounds. Over-reduction to the dithiol and hydrocarbon can occur with R or R^1 = Ph or R = R^1 = H, but this can be controlled by use of a calculated quantity of the metal.

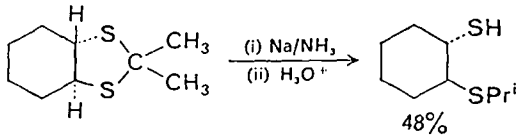


(72)

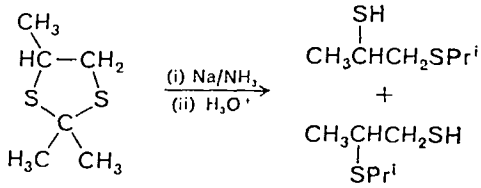




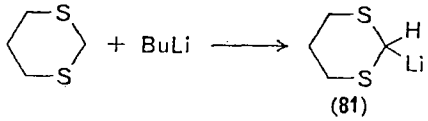
Brown, Iqbal and Owen[342] showed in their study that 2,2-dimethyl-*trans*-4,5-cyclohexano-1,3-dithiolan gave *trans*-2-*iso*-propylthiocyclohexanethiol:



and that 2,2,4-trimethyl-1,3-dithiolan gave a mixture of thiols:

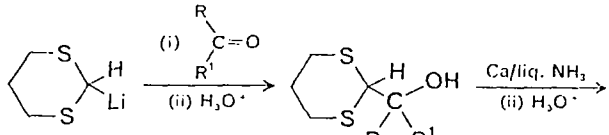


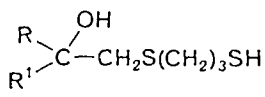
An extension of this method for the preparation of alkylthioalkanethiols utilized the fact that hydrogens on α-carbons to sulphur atoms are acidic and reactive towards organolithium compounds; e.g.



(81)

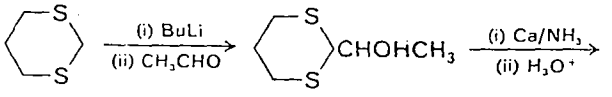
Reaction of the organolithium compound with an aldehyde or ketone will give (**82**). Calcium and ammonia reduction of (**82**) leads to the substituted γ-alkylthioalkanethiols (**83**). Thus, 1-(3-mercaptopropylthio)-2-





(83)

propanol was obtained in 83% by the following route[340].



$CH_3CHOHCH_2SCH_2CH_2SH$

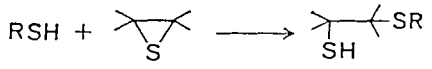
Other procedures for formation of β- and γ-alkylthioalkanethiols are available; these methods generally are less convenient than the metal–amine reductions and include the addition of hydrogen sulphide to vinyl

$$CH_2{=}CHSR + H_2S \longrightarrow HSCH_2CH_2SR$$

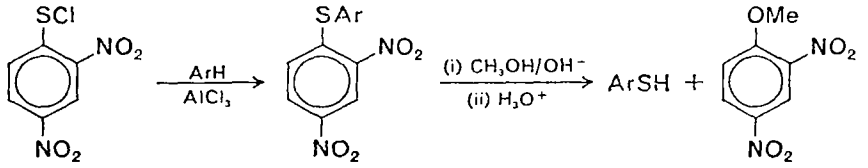
sulphides[353], the nucleophilic substitution of alkylthioalkyl halides[353]

$$[RS(CH_2)_nOH] \longrightarrow RS(CH_2)_nCl \xrightarrow{NaSH} RS(CH_2)_nSH$$

and the addition of thiols to thiiranes[349,354].



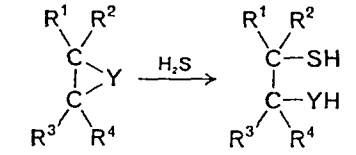
Another method of production of aromatic thiols using the intermediacy of sulphides is that of Kharasch and Swidler[355]. This procedure involves the electrophilic substitution of an aromatic hydrocarbon by 2,4-dinitrobenzenesulphenyl chloride and the nucleophilic cleavage of the sulphide so formed by methanolic hydroxide; the sulphur bond to the aryl ring with the most electron-withdrawing groups is the one cleaved. The yields of



thiophenols, p-XC_6H_4SH, were 80, 80, 79 and 76% for X = H, Me, Br and Cl respectively. The method is limited to aromatic hydrocarbons activated for electrophilic substitution. It was developed by Schuetz and Fredericks for thiophene- and thionaphthene-thiols[210]; the weaker Lewis acid, stannic chloride, was used as catalyst rather than aluminium chloride or ferric chloride, both of which caused extensive tar formation.

XIV. THIOL FORMATION FROM THE RING OPENING OF HETEROCYCLIC COMPOUNDS

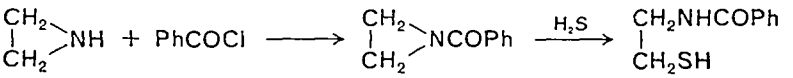
Ring opening of the three-membered heterocyclic compounds (**84**) by hydrogen sulphide gave β-substituted thiols.



Y = NR, O, S

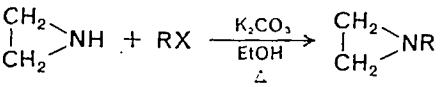
(**84**)

For ethyleneimine (**84**), Y = NH, $R^1 = R^2 = R^3 = R^4 = H$, reactions with hydrogen sulphide best occur at 0°C in dilute solutions to give yields of ~85% of β-aminoethanethiols[356]. N-benzoylaziridine (**84**, Y = NCOPh, $R^1 = R^2 = R^3 = R^4 = H$), prepared from ethyleneimine at 0°C[357], reacts similarly.

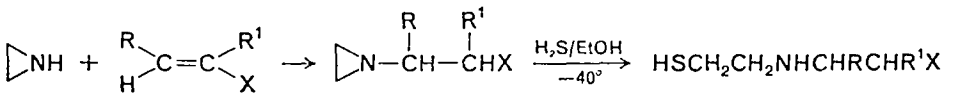


N-Substituted 2-aminoalkanethiols were prepared from 1-substituted aziridines and excess hydrogen sulphide in ethanol[358].

These compounds were produced from ethylenimine and an alkyl halide in the presence of potassium carbonate and ethanol.



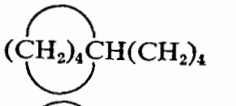
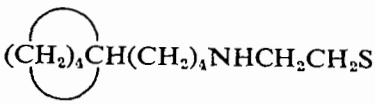
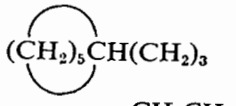
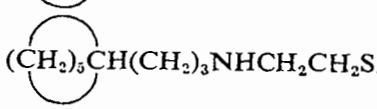
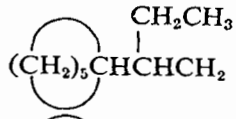
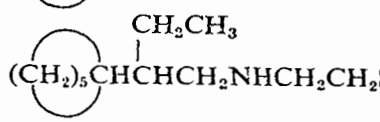
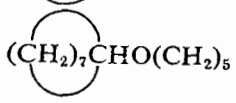
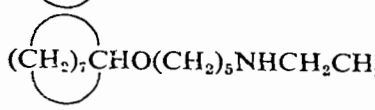
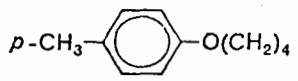
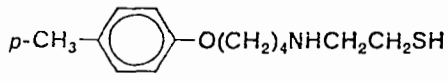
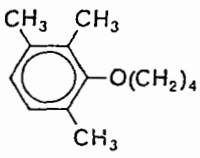
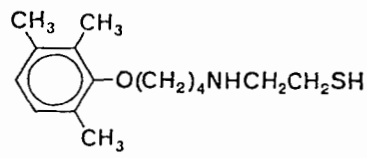
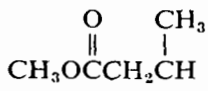
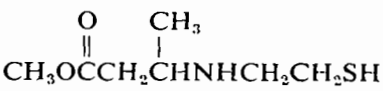
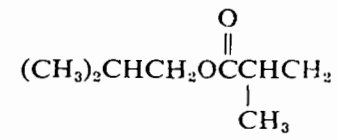
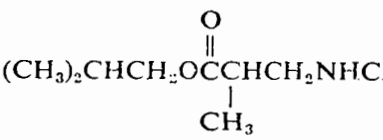
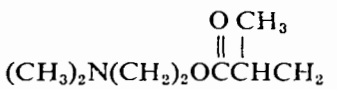
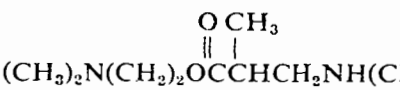
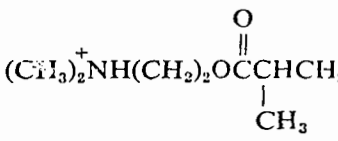
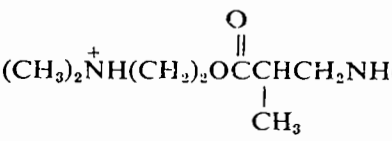
Another attractive route for functionally substituted β-mercaptoethylamines involves the catalysed additions of ethyleneimine to alkenes and cleavage of the product by hydrogen sulphide[359] at a low temperature.



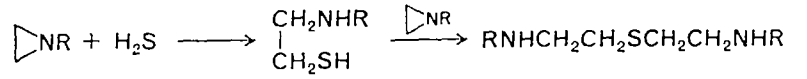
R,R' = H, alkyl, aryl or halide
X = CN, $COCH_3$, $COCH_2CH_3$, $CONH_2$, CONHR, CO_2R

The alkenes must have electron-withdrawing groups.

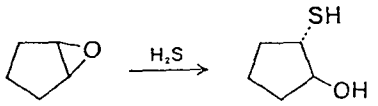
TABLE 22. Formation of thiols from hydrogen sulphide reactions of aziridines

No.	R	Thiol produced	Yield (%)	Ref.
1	H	$NH_2CH_2CH_2SH$	86	356
2	PhCO	$PhCONHCH_2CH_2SH$	55	357
3			22	358
4			11	358
5			60	358
6			51	358
7			38	358
8			60	358
9			76	359
10			71	359
11			54	359
12			60	359

In the reaction of hydrogen sulphide with the N-substituted aziridines, disulphides and monosulphides are also obtained. The latter are formed from reaction of the initially formed thiol with excess of ethylenimine.



For epoxides, (**84**, Y = O) cleavage by hydrogen sulphide in basic solution leads to the β-hydroxyalkanethiols[360,361]. From cyclopentene oxide, 64% *trans*-2-mercaptocyclopentanol[360] was obtained. Similarly[361],



cyclohexene oxide and potassium hydrogen sulphide reacted to give *trans*-2-mercaptocyclohexanol (44%) and the symmetric monosulphide (53%).

Ethylene oxide also reacted with sodium hydrogen sulphide to give the thiol and the sulphide[362].

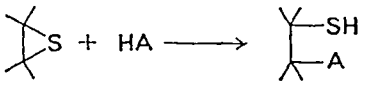
Formation of thiols from olefin sulphides (thiiranes) requires reaction with a proton donor, HX, and not exclusively hydrogen sulphide and so a range of β-substituted thiols are obtainable. Examples of such reactions (Table 23) include use of hydrogen sulphide[363], hydrogen sulphide ion[354], alkanethiols[349,354,363] and base, acetic acid[354,364], amines[354,365] and hydrogen chloride[354,363,366,367]. More polymer formation occurs with these reactions as compared to the oxide reactions.

Epoxides can be converted to the corresponding thiiranes by reaction with thiocyanate ion[363] or thiourea[361,368] especially with acid catalysts. The thiourea reaction gives β-hydroxy-*iso*-thiuronium salts as intermediates. Alkaline hydrolysis of these intermediates can lead to either thiiranes or β-hydroxythiols: the product depends on the hydrolysis conditions[368].

From the appropriate *iso*thiuronium salts, *trans*-2-hydroxycyclohexanethiol (71%) and *trans*-2-hydroxycyclopentanethiol (67%) were obtained as indicated above.

Cyclopentene sulphide cannot be readily obtained from the corresponding oxide; however, a convenient synthesis of thiiranes, including cyclopentene sulphide, is available by basic hydrolysis of the products obtained from alkenes and iodine thiocyanate[369].

TABLE 23. *Formation of thiols from ring opening of thiiranes*



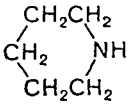
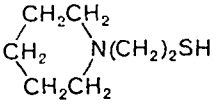
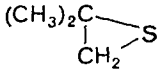
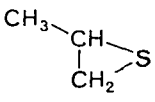
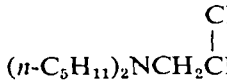
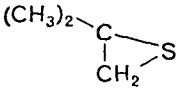
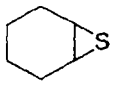
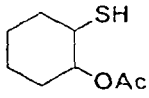
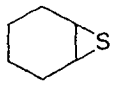
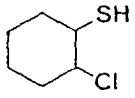
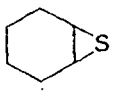
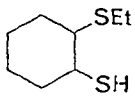
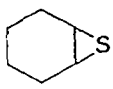
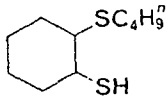
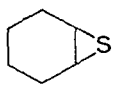
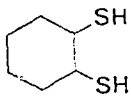
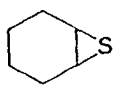
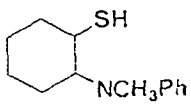
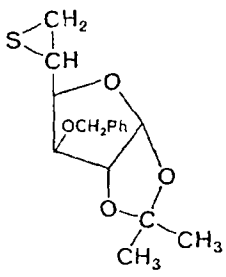
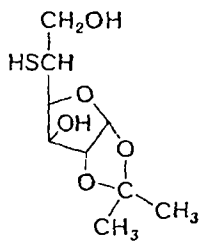
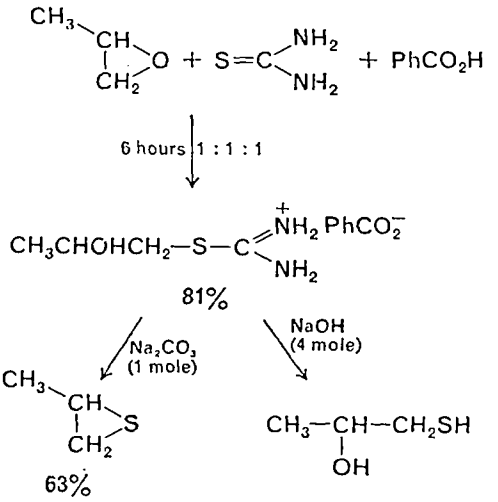
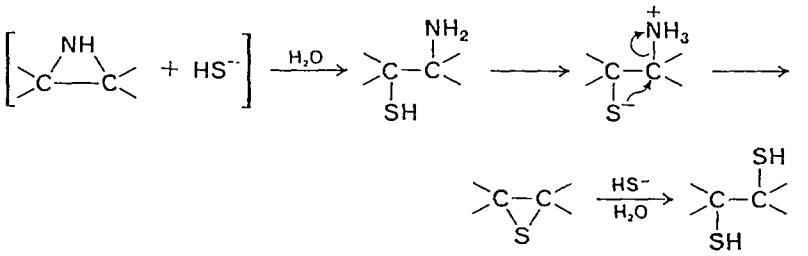
No.	Thiirane	HA	Thiol	Over-all yield	Ref.
1		HCl	$Cl(CH_2)_2SH$	93%	366
2		H_2S	$HS(CH_2)_2SH$	49%	363
3		n-$C_5H_{11}SH$	n-$C_5H_{11}S(CH_2)_2SH$	75%	363
4		$+n$-Bu_2NH	n-$Bu_2N(CH_2)_2SH$	70%	365
5		$PhNH_2$	$PhNH(CH_2)_2SH$	52%	365
6				77%	365
7		n-C_4H_9OH/BF_3	n-$C_4H_9OCH_2C(CH_3)_2SH$	20%	349
8		$(n$-$C_5H_{11})_2NH$		65%	365
9		$(n$-$C_5H_{11})_2NH$	$(n$-$C_5H_{11})_2NCH_2C(CH_3)_2SH$	27%	365

TABLE 23 (*cont.*)

No.	Thiirane	HA	Thiol	Over-all yield	R
10		HOAc		26%	
11		HCl		57% 82%	
12		EtSH/KOH		55%	
13		n-C_4H_9SH/BF_3		29%	
14		(i) KHS, (ii) H_3O^+		38%	
15		$PhNHCH_3$		50%	
16		(i) $\xrightarrow[Ac_2O]{KOAc/HOAc}$ (ii) Na/NH_3			



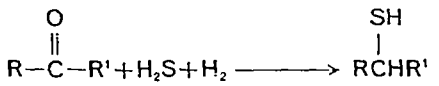
Neighbouring group participation by the thiolate ion can help bring about the displacement of the β-amino group in β-aminothiols to give thiiranes, which on further reaction produce dithiols.



Such thiiranes formed *in situ* can react further with hydrogen sulphide. Thus, 1-amino-2-propanethiol and excess ammonium hydrogen sulphide at 90°C gave 1,2-propanedithiol in 58% yield; furthermore, N-propylaziridine and an excess of ammonium hydrogen sulphide in an aqueous medium at 125°C produced the same dithiol in 42% yield[370].

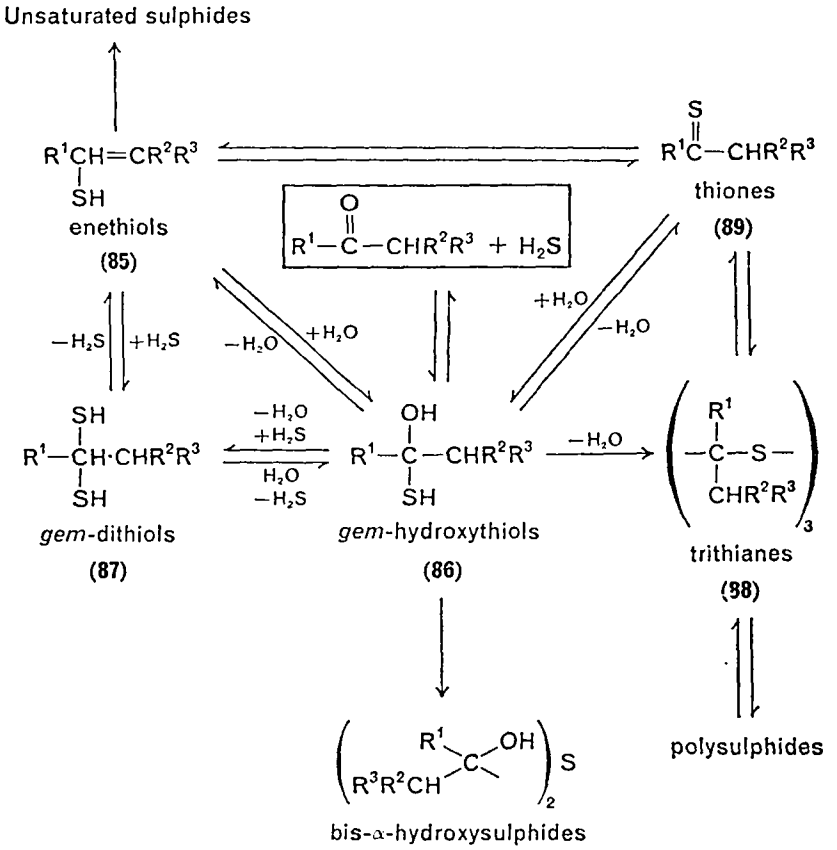
XV. THIOLS FROM ALDEHYDES AND KETONES

Catalytic reduction of aldehydes and ketones by hydrogen sulphide and hydrogen give thiols[371]. The catalysts are normally metallic sulphides, in particular cobalt and molybdenum polysulphides. Sulphur can be added



initially in place of the hydrogen sulphide since it is readily converted to hydrogen sulphide in the presence of the catalyst.

Reactions between hydrogen sulphide and aldehydes or ketones can lead, particularly in acid media, to a number of products, among which are enethiols (**85**), *gem*-hydroxythiols (**86**) and *gem*-dithiols (**87**). Trithianes (**88**) are, however, frequently obtained[372–375].

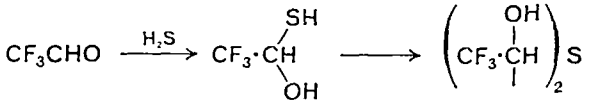


The initially formed products, the *gem*-hydroxythiols (**86**), are not normally isolated. However, for chloral, polyfluoro-ketones and -aldehydes and other carbonyl compounds, able to form stable *gem*-diols, such hydroxy thiols are isolatable[376,377]; e.g. CCl_3CHO gave at room temperature and at atmospheric pressure with an excess of hydrogen sulphide, 22% $CCl_3CH(SH)(OH)$; similarly CF_3CHO and CF_3COCF_3 gave 57% $CF_3CH(OH)(SH)$

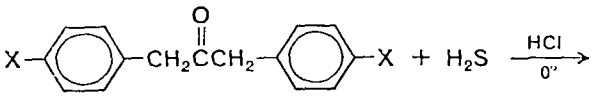
and 84% $CF_3\overset{\overset{OH}{|}}{C}CF_3$ respectively[377]. An excess of hydrogen sulphide

$\overset{\overset{SH}{|}}{}$

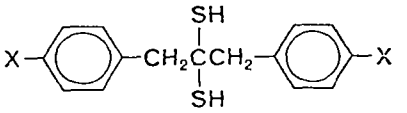
should be used to prevent sulphide formation.



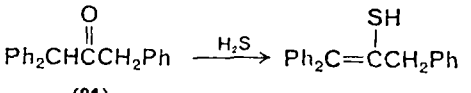
A study of the acid-catalysed reactions of aralkyl ketones with hydrogen sulphide has been made. In the presence of hydrogen chloride, 1,3-di-*p*-substituted-phenyl-2-propanones (**90**, X = H, OMe, Cl, but not NO_2) reacted with hydrogen sulphide in alcohol solution at 0–5°C to give the



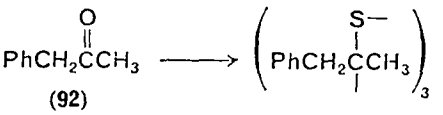
(90)



corresponding *gem*-dithiols[373,378,379]. That this is not a general reaction is clearly indicated by 1,1,3-triphenyl-2-propanone (**91**) giving 1,1,3-triphenyl-propene-2-thiol, while 1-phenyl-2-propanone (**92**) produced the 1,3,5-trithiane, on similar treatment. The reaction of adamantanone (**93**) with



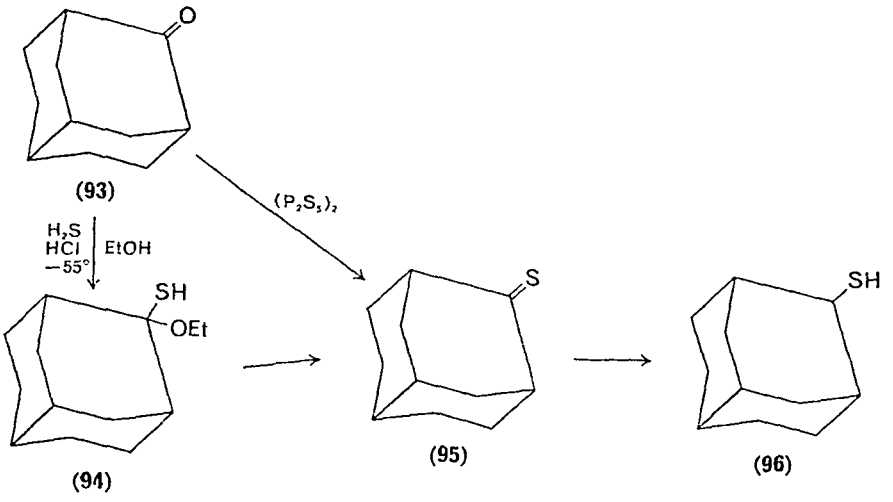
(91)



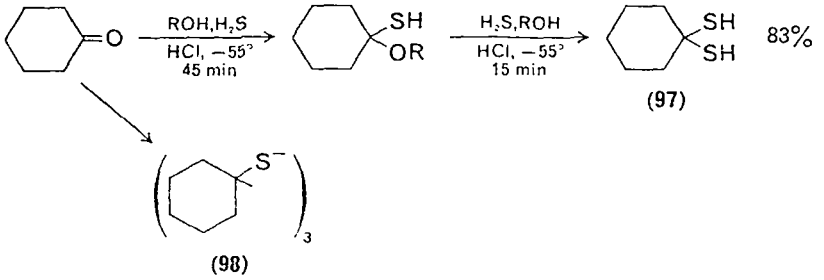
(92)

hydrogen sulphide in the presence of hydrogen chloride in ethanol solution at −55°C, however, gave 2-ethoxy-2-adamantanethiol (**94**) rather than the hydroxy derivative[380]; **94** on heating is converted to adamantanethione (**95**). The latter is reduced by sodium borohydride to

2-adamantanethiol (**96**). Adamantanethione can be formed directly from **93** by treatment with phosphorous pentasulphide.



Generally low temperature (−55°C) reactions of hydrogen sulphide with simple aliphatic acyclic and alicyclic ketones produce *gem*-dithiols[381]. For example, cyclohexanone and hydrogen sulphide in alcohol solution, saturated with hydrogen chloride, gave the *gem*-dithiol in 83% (**97**) *via* the intermediacy of the alkoxythiol.



At a higher temperature, (e.g. 0°C) the trithiane (**98**) was obtained instead[382]. The enethiol has also been reported to be obtained from the reaction of cyclohexanone with hydrogen sulphide[383]; however, this work has been more recently criticized[374].

The change in the amounts of *gem*-dithiols (**87**) and thiones (**89**) from reactions of simple aliphatic ketones and hydrogen sulphide in alcoholic hydrochloric acid as a function of temperature has been studied[384]. The maximum yields of the thione (60%) are found for reactions between −80

and −40°C; as the temperature is increased beyond −40°C, so yields of the thiones decrease. The maximum yields (60%) of the *gem*-dithiols are obtained between −25 and −20°C.

Basic catalysts have also had extensive use[385]. Thus cyclohexanone or cyclopentanone reacted with hydrogen sulphide, in the presence of morpholine, at 0°C to give the 1,1-cycloalkanedithiols in yields greater than 70%[385]. However, the yield of 2,2-propanedithiol from acetone was considerably less (30%). The use of *n*-butylamine as a catalyst in these reactions has been made[387]; in fact all amines appear capable of catalysing *gem*-dithiol formation[386]. The basic ketone, 1-methyl-4-piperidone, reacts without the need of additional amine catalysts[388].

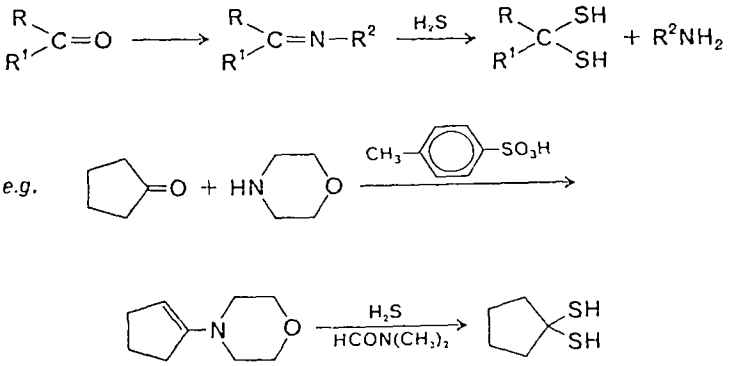
1,3-Diketones have been shown to give β-carbonylenethiols (**99**) whereas 1,2-diketones are reduced either to monoketones or to hydroxyketones[386].

$$RCOCH_2COR \xrightarrow{H_2S/amine} RCOCH{=}C(R)(SH)$$

(**99**)

In the absence of catalysts, heat and H_2S under high pressure (35–8500 atm) are required to bring about *gem*-dithiol formation in generally low yields[389]. Both aldehydes and ketones react but the former is more reactive.

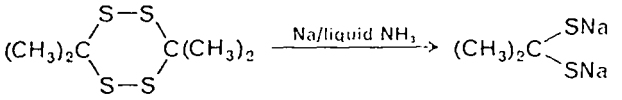
Other methods of preparing *gem*-dithiols also begin with carbonyl compounds. Ketimines and enamines have been prepared from the carbonyl compounds and subsequently reacted in ether solution with hydrogen sulphide at a low temperature; acidification frees the *gem*-dithiol[387,390–392]. While ketimines from aliphatic ketones as well as aliphatic aldimines do successfully give *gem*-dithiols, ketimines from alkyl aryl ketones and Schiff's bases of aromatic aldehydes do not[390].



Reference 364

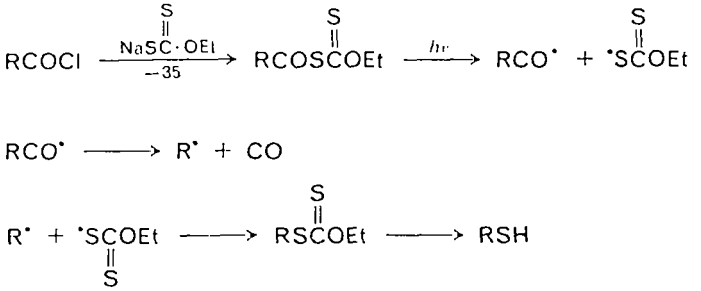
Use was made of dimethylformamide as solvent for reaction of morpholino derivatives of ketones with hydrogen sulphide[391] to give *gem*-dithiols; however, the use of the mixed dimethylformamide/ether solvent system led to trithianes[391].

Tetrathianes have also been used[393,394]. These compounds, prepared from ketones, are cleaved by sodium in liquid ammonia[393]. Evaporation of the ammonia, followed by acidification of the dithiol salt, gave the *gem*-dithiol. In contrast, cleavage of the tetrathiane by lithium aluminium hydride leads to a mono-thiol.

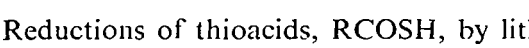


XVI. FORMATION FROM CARBOXYLIC ACID DERIVATIVES

a. Acyl Halides. A conversion of acyl halides to thiols[395] involves the photolysis of acyl xanthates, formed from the acyl halides. The alkyl xanthates thus produced, are hydrolysed to thiols.



b. Thioacids. Reductions of thioacids, RCOSH, by lithium aluminium hydride or sodium borohydride/aluminium trichloride lead to mixtures of the alcohols and thiols[396,397]. The sodium borohydride/aluminium trichloride reductant system is the better of the two for thiol formation.

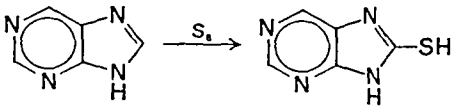


XVII. MISCELLANEOUS METHODS

A. Reaction with Sulphur

Several heterocyclic compounds react directly with sulphur. Purine (**100**), for example, reacted with sulphur at 245°C to give 8-mercaptopurine in 75% yield[398]. Amino- and methyl-substituted purines gave lower yields

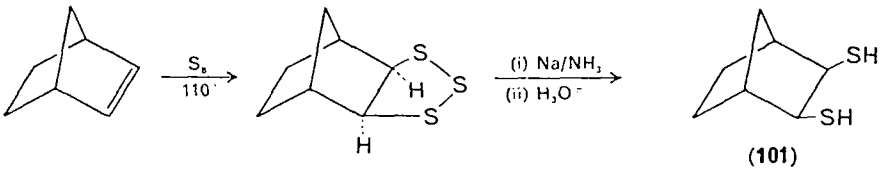
of mercapto products. Similarly benzimidazole and sulphur gave an 83% yield of 2-mercaptobenzimidazole.



(100)

Benzene also reacted with sulphur on strong heating but yields of thiol derivatives are too low to make the method a useful one[399]. When bromobenzene and sulphur are heated at 230–250°C for 2–3 h in a sealed tube, some diphenyl disulphide was obtained. Reduction by lithium aluminium hydride or zinc and hydrochloric acid gave thiophenol (29% yield). Chlorobenzene reacted more slowly and gave only a little thiophenol (< 1%) and some chlorothiophenols as well; thus attack at a ring hydrogen as well as at the halogen occurred[400].

Some alkenes also react with sulphur on heating, especially in the presence of an activator, such as ammonia, in dimethylformamide[401]. Thus, norbornene gave bicyclo[2,2,1]hepta-*exo*-*cis*-2,3-dithiol (**101**).



(101)

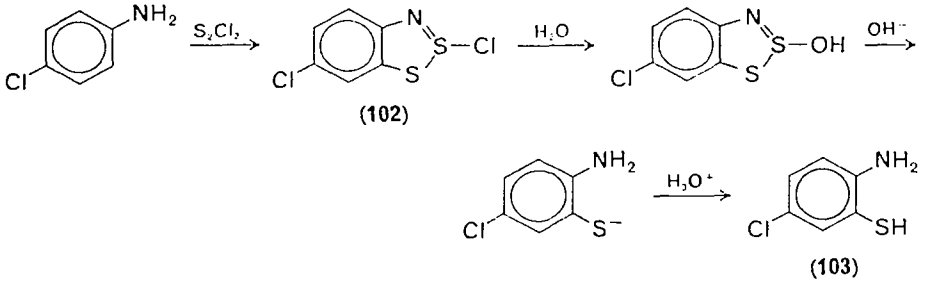
69%

B. Reaction with Sulphur Monochloride and Dichloride

Aromatic compounds, with strong electron-donating groups, react with sulphur mono- and di-chloride, in the presence of hydrogen sulphide to give disulphides. These can then be reduced to the thiophenol by the usual methods. Thus, *m*-cresol gave 3-methyl-4-mercaptophenol in good yield[402]. In another report phenols, on reaction with sulphur monochloride in carbon tetrachloride or toluene, gave crude disulphides, which were hydrogenated over a molybdenum disulphide catalyst to give mercaptophenols. The mercapto group generally is introduced at the *para* position to the hydroxyl group. Thus, phenol and 2,6-xylenol gave thiohydroquinone and 4-mercapto-2,6-xylenol in 19 and 49% yields respectively[403].

Reaction of aromatic amines with sulphur monochloride leads to thiazathiolium chlorides (**102**) which on alkaline hydrolysis produce

o-aminothiolates[404]. Amines must have a free *ortho* position. If the *para* position is also free, then substitution by chlorine at this site can also occur; thus, aniline can give 2-amino-5-chlorobenzenethiol (**103**). Nitro- and carboxyl-groups in the *para* position to the amine group can also be replaced by chlorine; however, bromo, methyl, methoxy and dimethylamino groups are not removed.



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The Chemistry of the Thiol Group
Edited by Saul Patai

CHAPTER 5

Detection and determination of thiols

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I. INTRODUCTION

As might be expected from the great reactivity of the thiol group and the wide distribution of thiols in natural materials, the literature dealing with the detection and determination of these compounds is extensive.

Broadly, the methods of determining the —SH groups depend on one or more of the following fundamental processes, i.e. oxidation of —SH to disulphide, mercaptide formation and alkylation. The amperometric and polarographic techniques depend in effect on mercaptide formation. Several colour reagents for —SH groups could be employed, the commonest being sodium nitroprusside. Other colorimetric procedures take advantage of the thiol–disulphide exchange reaction between aliphatic and aromatic thiols.

In the present monograph no attempt is made to obtain a comprehensive coverage of all the methods. The main purpose of this chapter is to describe principles underlying the methods and to indicate which are likely to be suitable.

The measurement of thiol groups in substances of biological origin is of prime importance, since it has been shown that the presence of these substituents is often necessary for the retention of biological activity. The analytical determination of cysteine (thiol group) and of cystine (disulphide group) in proteins is covered by several comprehensive reviews with well-documented analytical sections[8–15]. The literature references which are discussed here were chosen on the basis of application to problems which may be generally encountered in thiol chemistry.

The basic principles of the spectroscopic characterization (u.v., i.r., n.m.r., e.s.r.), of the —SH function are also included.

II. DETECTION

A. Qualitative Tests

Several qualitative tests for thiols are available and the procedures are extensively reported in books dealing with the identification of functional

groups[1-7]. Detailed analytical procedures for specific —SH-containing substances are also reported[3,4].

The commonest colour reagent for thiols is sodium nitroprusside $Na_2Fe(CN)_5NO$[5,8,16-18]. The solution of the —SH compound is adjusted to pH 9–11 with sodium carbonate or ammonia and a few drops of nitroprusside (5% solution) are added. If —SH groups or other powerful reducing agents are present, a pink-violet colour appears.

The exact composition of the colour complex is not known, but it is believed to involve a bond of the sulphur with the nitroso group of the nitroprusside. Alkyl sulphides also react with sodium nitroprusside, but the colour is more red than blue. Aryl sulphides do not give this test. Aromatic thiols will react with the reagent if ammonium hydroxide is substituted by sodium hydroxide[5,16].

Glutathione gives a red colour with sodium nitroprusside which can be used for quantitative estimation[19]. 2-Thiouracil is determined by the green colour with a modified sodium nitroprusside–hydroxylamine reagent. The reaction is also given by several other derivatives of uracil[20].

Thiol compounds reduce a solution of phosphotungstic acid with the formation of a blue colour[16,21,22]. The colour is stable for at least 6 h. Inorganic sulphides slowly develop colour. Potassium or sodium cyanide inhibit colour development.

The reaction between sodium azide and iodine takes place very slowly with the formation of iodide ions, but it can be accelerated by the presence of trace amounts of organic sulphur compounds, especially thiols and disulphides. By addition of an —SH compound to a solution of sodium azide and iodine, evolution of nitrogen is observed as well as the decolorization of the iodine solution[16].

The methylene blue reaction for hydrogen sulphide with dimethyl-*p*-phenylenediamine hydrochloride is of broad general applicability to —SH compounds including cysteine, glutathione and thiocresol. The reagent is used in acid solution in the presence of ferric ammonium sulphate. The colour is permanent[23,24]. Cysteine forms a blue colour with *p*-aminodimethylaniline and gives a dark red-violet colour with dimethyl-*p*-phenylenediamine hydrochloride in acid solution containing ferric ions. With 1,2-naphthoquinone-4-sulphonate cysteine gives a red colour[25].

The preparation of heavy metal salts is important both for the detection and determination (see section IV) of thiols. They react with lead or mercury salts of weak acids to form lead or mercury mercaptides (equation 1). Lead acetate or mercury cyanide are generally used for these tests[4-6].

$$RSH + M^+ \rightleftharpoons RSM + H^+ \qquad (1)$$

Sodium plumbite first forms yellow lead mercaptides, which are converted by sulphur to black lead sulphide and alkyl disulphides:

$$Pb(OH)_2 + 2\,RSH \longrightarrow Pb(SR)_2 + 2\,H_2O \quad (2)$$

$$Pb(SR)_2 + S \longrightarrow PbS + RSSR \quad (3)$$

A test based on the formation of mercury mercaptide according to equation (4) was described by Feigl and coworkers[26].

$$2\,RS^- + Hg(CN)_2 \longrightarrow Hg(SR)_2 + 2\,CN^- \quad (4)$$

Cyanide is sensitively detected through the blueing of filter paper moistened with a solution of copper ethylacetoacetate in chloroform. The test for alkali-soluble —SH compounds is specific provided that halogen ions are absent. The limits of identification are of the order of 2–5 μg.

Thiols may react with cupric ions in various ways. Sometimes water-insoluble, mostly dark coloured, cupric salts are produced. Another mode of reaction, which may occur in strong ammoniacal solution, leads to the production of black copper sulphide (e.g. cysteine). Along with this reaction, and sometimes predominating in the case of some thiol compounds, there is an initial redox reaction (equation 5). Subsequently,

$$2\,RS^- + 2\,Cu^{2+} \longrightarrow Cu_2^{2+} + RSSR \quad (5)$$

the cuprous ions may react with the —SH compound (equation 6). The water-insoluble copper (I) salts of thiol compounds are yellow, orange

$$Cu_2^{2+} + 2\,RS^- \longrightarrow Cu_2(SR)_2 \quad (6)$$

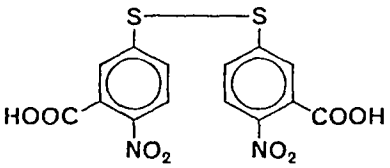
yellow or orange brown. The reaction takes place at room temperature with solid samples or with solutions in ammonia or alkali.

B. Spot Tests on Chromatograms

Few specific reagents are available for the detection of —SH-containing compounds on chromatograms. Sodium nitroprusside, platinic iodide[27,28], Feigl's sodium azide-iodine reaction[16,29,30], or various quinones[31] which are not specific for —SH groups have been used.

A rapid and sensitive technique has been developed for the identification and differentiation of thiols, disulphides and thioesters on thin-layer and paper chromatograms[32]. Thiols are detected as yellow spots after spraying chromatograms with an alcohol-buffer solution of the Ellman reagent,

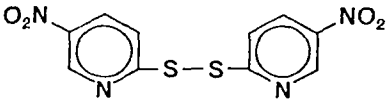
5,5′-dithiobis-(2-nitrobenzoic) acid (DTNB) (**1**) (see section V.A for a detailed discussion of the reaction between DTNB and thiols).



(1)

Disulphides can be detected after reduction to thiols with sodium borohydride and application of the DTNB spray reagent. Thioesters are hydrolysed by alkali and the resulting thiols are treated with DTNB.

A similar reagent, particularly suitable for paper and thin-layer chromatograms, 2,2′-dithiobis-(5-nitropyridine) (DTNP) (**2**)[33] was developed as a selective reagent for —SH groups (see also section V.B).



(2)

A quick t.l.c. test for the detection of —SH groups in the presence of other type of sulphur functional groups was described by Brown and Edwards[34].

Thiols show bleaching action on iodine used as the visualizing agent (equation 7). After exposure of the plates to iodine vapours, the thiols

$$2\,RSH + I_2 \longrightarrow RSSR + 2\,H^+ + 2\,I^- \qquad (7)$$

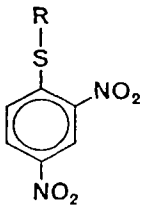
appeared as white spots on a tan background. This qualitative test for the presence of —SH groups can be used as a quick test, even in the presence of disulphide and carboxyl groups.

A visualizing reagent for —SH compounds in paper chromatography is a mixture of ceric ammonium nitrate and potassium permanganate[35]. The chromatogram is dipped in a solution of ceric ammonium nitrate in 0·5M nitric acid. Thiols (cysteine, cysteamine, thioglycollic acid) give a white spot in a yellow background.

C. Identification through Chemical Derivatives

Several solid derivatives are used for the identification of —SH compounds. Tables reporting the physical characteristics of such derivatives are available[1,5].

2,4-Dinitrochlorobenzene reacts with sodium salts of alkanethiols and aromatic thiols with the formation of well crystallized sulphides (3)[36,37] which can be further oxidized to the corresponding sulphones[38], thus enabling a second series of derivatives to be obtained. Paper[39] and gas[40] chromatography have been used for separation and identification of these derivatives.



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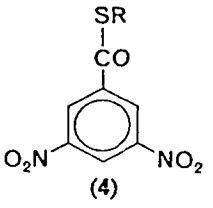

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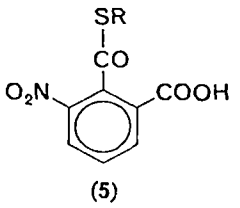

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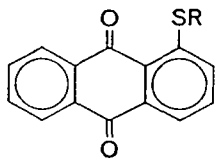


(6)

3,5-Dinitrothiobenzoates (4) are prepared from thiols and 3,5-dinitrobenzoyl chloride in a basic medium[41]. Thiols also react with 3-nitrophthalic anhydride giving 3-nitrophthalic thioesters (5)[41].

Solid thioether derivatives (6) may be prepared by reacting the —SH compound with sodium anthraquinone-α-sulphonate[42]. The thioether may be oxidized to the corresponding sulphone.

The mercury derivatives have been also used for the characterization of thiols. The preparation of solid derivatives from thiols using phenylmercury acetate was used by Howard and Baldry[43] by concentrating extremely dilute solutions of —SH compounds and analysing them by thin-layer chromatography.

III. OXIDIZING AGENTS

For analytical purposes the assumption is made that the oxidation proceeds according to equation (8). One mole of RSH should therefore be equivalent to 1 mole of a one-electron oxidant or $\frac{1}{2}$ mole of a two-electron oxidant.

$$2\,RSH \longrightarrow RSSR + 2\,H^+ + 2\,e \qquad (8)$$

Although the sensitivity of these methods is of a high order, especially the oxidation with ferricyanide, they lack specificity and the stoichiometry of the oxidation is unreliable[8]. In fact, oxidation proceeds quite easily beyond the disulphide stage. The extent to which this occurs depends on the molecular environment of the —SH groups, as well as on the nature of the oxidizing agent used, the pH, the concentration of reactants, the presence of metal ions, etc.

A known amount of the oxidizing agent may be added to the solution of which the —SH content is to be estimated and, after a suitable period of time, the amount of residual reagent is determined. If the oxidized and reduced forms of the reagent differ in colour, the reagent may be added as in conventional titrations and the end point estimated visually.

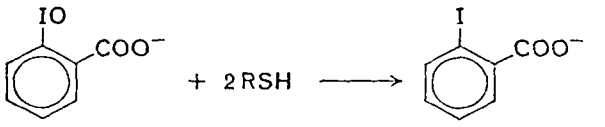
A number of oxidizing agents have been used or proposed for estimation of —SH groups. Among these are iodine, ferricyanide, perbenzoic acid, hydrogen peroxide, potassium permanganate and nitrous acid[8].

Ferricyanide[44–47] offers the particular advantage that it can be used for the estimation of as little as 10 μmoles of —SH (formation of prussian blue).

Sodium tetrathionate[48,49] is used for estimation of —SH groups, according to equation (9), the thiolsulphonate formed being titrated iodometrically.

$$2\,RSH + S_4O_6^{2-} \longrightarrow RSSR + 2\,S_2O_3^{2-} + 2\,H^+ \qquad (9)$$

At pH 7 the reaction of *o*-iodosobenzoate ion (7) with —SH groups can be written as in equation (10). The reaction does not appear to proceed



(7) (10)

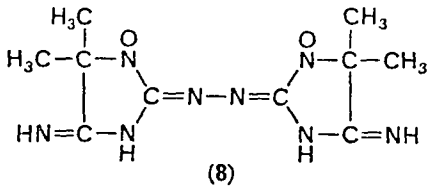
beyond the disulphide stage[50,51]. The usual procedure is to add an excess of the reagent and to determine the residual amount iodometrically according to equations (11) and (12). It is essential that the excess of

$$HOOCC_6H_4IO + 2\,I^- + 2\,H^+ \longrightarrow HOOCC_6H_4I + I_2 + H_2O \qquad (11)$$

$$I_2 + 2\,S_2O_3^{2-} \longrightarrow S_4O_6^{2-} + 2\,I^- \qquad (12)$$

reagent be kept as small as possible. Preliminary orienting tests may be made before the actual analysis is accomplished.

Porphyrindin (**8**)[8,52–55] has been used in the estimation of —SH groups in various biological substances.



(8)

The use of oxidizing agents for the determination of —SH groups in proteins is excluded since the nature of the oxidation products is uncertain, because the pairing of all —SH groups may not be sterically feasible in such large molecules with their limited conformational freedom[8].

IV. MERCAPTIDE FORMING AGENTS

The reaction of thiols with heavy metals leads to the formation of mercaptide derivatives. The reagents which have been used most successfully for the estimation of —SH groups are those which form highly undissociated mercaptides, namely, silver salts, mercury salts and organic mercury derivatives of the type RHgX.

Mercaptide formation could be reversed since the metal could be removed from an —SH group by using an excess of thiol. Reversible labelling of cysteine residues with heavy metals is extensively used in protein chemistry[56].

The solubility of the mercaptides in aqueous solution varies considerably. Silver derivatives usually are very insoluble, whereas those of mercury are often moderately soluble. The soluble ones are preferable from an analytical point of view, as errors from co-precipitation are avoided.

The most widely employed method for following these reactions analytically has been titration of the thiol with metal ions and the measurement of the excess by electrometric procedures.

A. Electrometric Procedures

Electroanalytical methods are well established in most branches of chemical research and have been used also in following the titration of —SH groups with mercury or silver ions to form undissociated mercaptides.

The electrometric determination of heavy metal ions is based on the fact that they are relatively easily reduced at a variety of electrodes. In amperometric titrations the voltage applied across the reference electrode and indicator electrode is constant, and the current increments are plotted against the volume of titrating reagent added.

Under well-defined conditions only a small residual current flows through the cell until all the —SH groups are blocked. The end point of the titration is then marked by the appearance of the diffusion current due to excess titrating reagent.

A plot of current *vs* the volume of added titrant gives two straight lines which intersect at the equivalence point (Figure 1). Near the equivalence point, equilibration is slow since both reactants are present

at very low concentrations. A very sharp inflexion is obtained with simple substances but with more complicated molecules such as proteins the removal of heavy metal ions from the solution is slower and the curve reaches linearity only gradually towards the end of the titration.

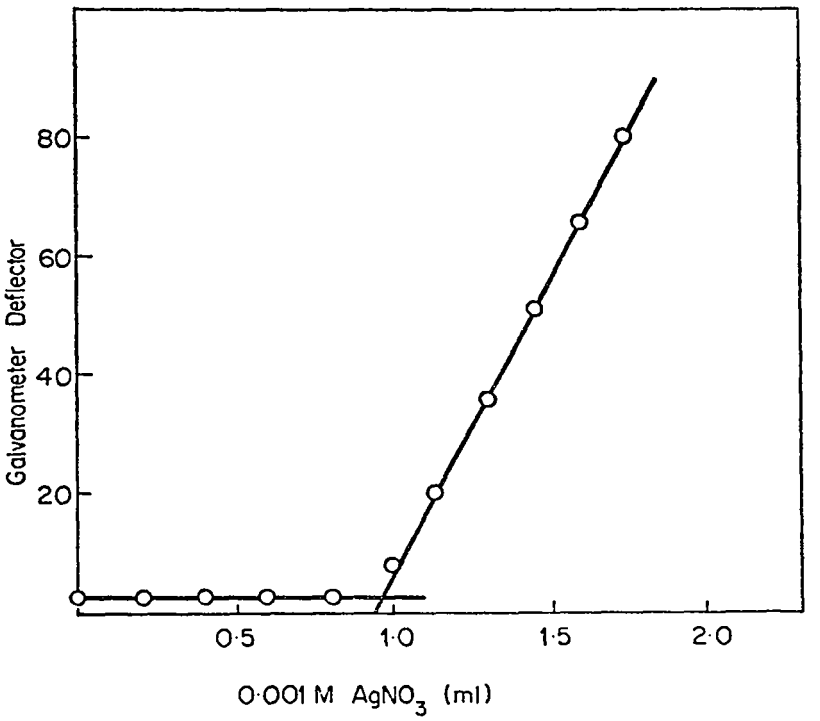


FIGURE 1. Example of an amperometric titration of 1·0 ml of 10^{-3}M glutathione with 10^{-3}M silver nitrate. (From R. and R. E. Benesch, 'Determination of —SH groups in Proteins', *Methods of Biochemical Analysis* (Ed. D. Glick), **10**, Interscience, 1962.)

Principles and practice of amperometric titrations can be found in standard books[57-60]. There are two types of electrodes in common use, namely the rotating platinum electrode and the dropping mercury electrode.

Mercaptide formation may also be followed by potentiometry. Potentiometric titration[61] is performed measuring the potential of a reversible electrode under equilibrium conditions. The potential is proportional to the logarithm of the concentration of the ion to which the electrode is reversible. Metal thiol electrodes, consisting of a mercaptide layer on the surface of the electrode, are employed, since they are reversible to thiol as well as to the metal ion.

I. Rotating platinum electrode

The indicator electrode is made from a short piece of platinum wire sealed into a piece of glass tubing which is filled with mercury. The electrode is rotated at speeds of about 800 r.p.m.

A general apparatus for amperometric titration is shown in Figure 2. The reference electrode could be prepared by mixing potassium iodide and

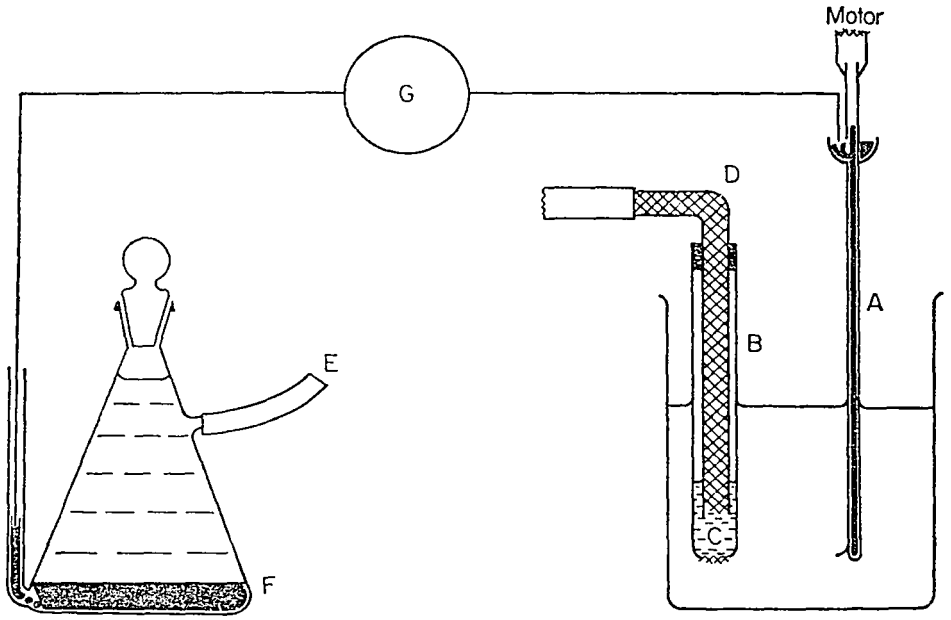


FIGURE 2. Apparatus for amperometric titration: A, rotating platinum electrode; B, agar-filled glass tube; C, electrolyte solution; D, glass tube; E, salt bridge; F, reference electrode; G, galvanometer. (From S. Siggia, *Quantitative Organic Analysis via Functional Groups*, Wiley, 1949.)

mercury iodide in potassium chloride solution. A layer of mercury serves as the electrode.

The rotating platinum electrode has a number of limitations. The surface of the electrode has a tendency to become poisoned by the sulphur compounds so that it becomes erratic or unresponsive, and must be therefore carefully cleaned prior to each titration. Another disadvantage of this electrode is its low over-voltage for hydrogen discharge. Hydrogen evolution will occur at the electrode, so that the number of reducible compounds which can be used as titrants is limited.

2. Dropping mercury electrode

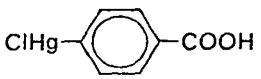
The limitations and disadvantages of the rotating platinum electrode are eliminated by using the dropping mercury electrode. This is simple to set up and operate, and one electrode will give several years of trouble-free service with little attention. Automatic recording polarographs are available commercially.

The dropping mercury electrode combines the unique advantages of a continuously renewed electrode surface of constant characteristics, but is about ten times less sensitive than the rotating platinum electrode.

Attempts have been made to combine the high sensitivity of the rotating platinum electrode with the reliability of the dropping mercury electrode by using a rotating mercury pool[62]. However, this is not simple to set up and maintain, and the advantage of a freshly formed surface of the mercury drops is lost. Nevertheless, the electrode has been used successfully for estimating thiol groups in simple thiols and in biological substances.

B. Mercury Compounds

Inorganic salts of mercury, HgX_2, form highly undissociated mercaptides. Since ambiguities can arise from the stoichiometry of the reaction (see below), alkylmercury derivatives of type RHgX are also used. There are numerous mercury derivatives available of differing molecular size, reactivity, solubility and specificity. Examples are alkylmercury compounds such as methylmercury iodide, mercurated alkylamides or phenylmercury compounds such as *p*-chloro-mercuribenzoic acid (*p*CMB) (**9**)[63].



(9)

All operations involving the use of metallic mercury, HgX_2 or RHgX, whether at the preparative or analytical level, should be carried out in a well-ventilated area, preferably under a fume hood[64, 65]. These precautions apply equally to work with all highly reactive —SH reagents particularly the volatile ones. All of these reagents are toxic on inhalation and have a vesicant action on the skin at high concentrations. **None must be pipetted by mouth.**

1. Inorganic mercury compounds

Mercury chloride shows a complex stoichiometry and reacts with simple thiols to give compounds of the type $(RS)_2Hg$, $(RS)_2Hg_2$ or $(RS)_2Hg_3$ depending upon the amount of excess mercury chloride present[66].

In spite of this, conditions may be chosen for the titration of simple thiols with a strict 1 : 2 stoichiometry, under which a sharp endpoint, corresponding to the formation of $(RS)_2Hg$ may be observed amperometrically[67,68]. The same is not true for the —SH groups of proteins, which according to the conditions used will produce mercaptides of the type RSHgX or $(RS)_2Hg$. The steric proximity of —SH groups in proteins is a critical factor in determining the stoichiometry of the reaction.

2. Alkylmercury compounds

In contrast to the situation that obtains with mercury chloride only one mole of —SH reacts with RHgX[69-71], giving to organic mercurials an outstanding advantage (equation 13):

$$R'SH + RHgX \longrightarrow R'SHgR + H^+ + X^- \qquad (13)$$

In using compounds of the type RHgX it is important to realize that if X is highly electronegative, e.g. fluoride, nitrate, sulphate or phosphate, the compounds behave largely as the salts RHg^+X^- and are more soluble in water and ethanol than in non-polar solvents. If X is chloride, bromide, iodide, acetate, cyanide, thiocyanate or hydroxide, the compounds are mainly covalent, volatile in steam and soluble in ether and benzene[12,14].

Although methylmercury iodide reacts more rapidly in alkaline solution than at pH 7, reaction still occurs sufficiently rapidly in neutral and acid solutions. Being a covalent compound the reagent has a limited solubility in water. Alternatively the more water-soluble CH_3HgCl or CH_3HgNO_3 may be used[14]. Methylmercury nitrate, which is very soluble, is best prepared in solution from methylmercury iodide by double decomposition with silver nitrate[72].

The end point in the reaction between —SH groups and organic mercury compounds has in general been determined by amperometric methods. The disappearance of —SH groups following addition of a mercury derivative has been also determined using nitroprusside indicator[8]. Alternatively, the excess mercurial could be determined colorimetrically[73]. The procedure consists of equilibrating the —SH sample with a solution of CH_3HgI dissolved in toluene and determining the excess left in the toluene layer by titrating with dithizone in the presence of amylamine and acetone. The very high solubility of CH_3HgI in the organic layer is a great advantage since, by minimizing the concentration of free reagent in the aqueous phase, it enhances the specificity of the method.

3. *p*-Chloromercuribenzoate (*p*CMB)

Several organic mercurials undergo spectral changes on reaction with thiols. However, thus far, *p*CMB[63,74] is the only mercurial which gives rise to an adequate increase in absorption in a useful spectral region as the result of mercaptide formation (Figure 3).

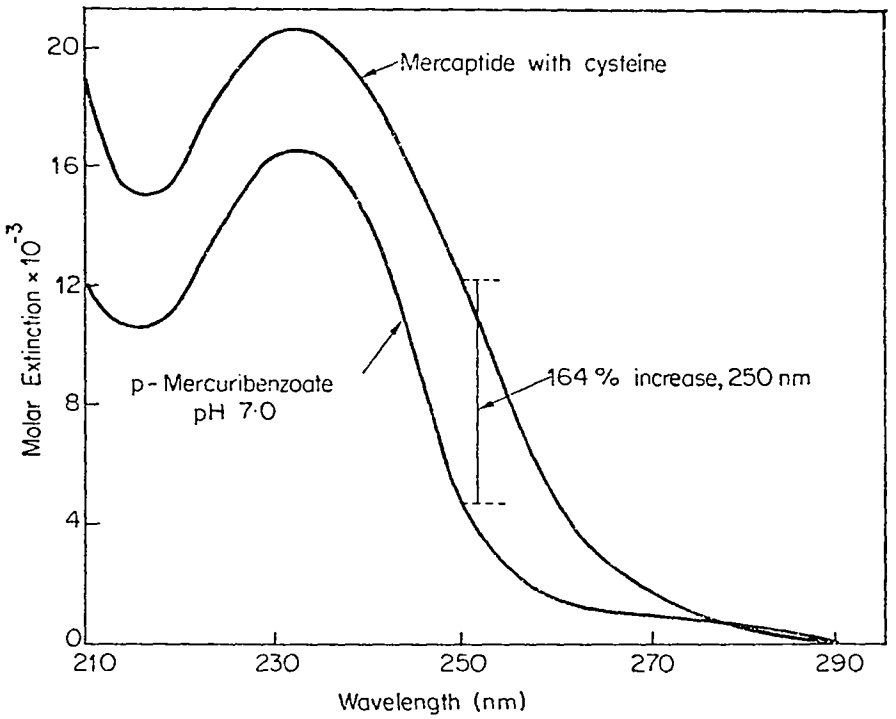


FIGURE 3. Absorbancy of *p*-chloromercuribenzoate and its mercaptide with cysteine in 0·05M phosphate, pH 7·0. (Reproduced by permission of the American Chemical Society from P. D. Boyer, *J. Amer. Chem. Soc.*, **76**, 4331 (1954).)

*p*CMB exhibits an absorption maximum at 233 nm with a molar absorptivity of $1{\cdot}69 \times 10^4$. On formation of a mercaptide, the molar absorptivity increases to $2{\cdot}2 \times 10^4$. However, a much larger difference in absorbance is observed between *p*CMB and its mercaptide in the region from 250 to 255 nm, which directly reflects the amount of reagent reacted.

The method of Boyer[63] is the only one which measures directly a property of the newly formed Hg—S bond, i.e. its u.v. absorption in the region of 250 nm. The technique used is to titrate the mercurial with the —SH compound until there is no further change in the absorption.

Instead of a single measurement with an excess of *p*CMB, the assay is therefore carried out in the form of a spectrophotometric titration.

Initial studies[8] with *p*CMB employed nitroprusside titration to detect the number of sulphydryl groups in proteins. Other methods[73] have determined the excess mercurial remaining after reaction with the protein either colorimetrically or amperometrically.

The spectrophotometric method using *p*CMB introduced by Boyer is one of the most generally useful techniques for determining —SH groups. *p*CMB has been extensively used with great success as a quantitative reagent for measuring —SH groups in proteins.

Problems concerning this analytical method should be mentioned. The extinction coefficient of the mercaptide formed could differ from protein to protein. Both components, reagent and protein, absorb strongly themselves at 250 nm. The observed differences may be small and, hence, adequate corrections must be made but may prove difficult.

C. Silver

Silver ion has certain advantages for thiol analysis and a great deal of work has been done with it[75-78]. The titrating metal ion is monovalent and can be standardized with a high degree of accuracy. It is easily reduced at a platinum or mercury electrode and is readily reversible at the silver electrode.

The reaction of silver with thiols has been most frequently followed by amperometric titration at the rotating platinum electrode. The procedure is sensitive (approximately 10^{-5}M —SH) and can be carried out in neutral aqueous solution.

Unfortunately, the stoichiometry of the reaction (equation 14) cannot always be relied upon, since the mercaptide formed (RSAg) can complex

$$RSH + Ag^+ \longrightarrow RSAg + H^+ \qquad (14)$$

additional silver. This co-ordination by the silver mercaptide depends greatly on the nature of the R residue to which the —SH group is attached. If this occurs to any extent under the conditions used for the estimation of the —SH groups, a positive error would result[79-82].

Substances which form stable complexes or insoluble salts with silver ions (e.g. cyanide, iodide, chloride, bromide and sulphide) are also expected to interfere. Possible steric hindrance to the access of the Ag^+ ion to the —SH groups should also be kept in mind.

These difficulties can be minimized by varying the pH or by using complexing agents for the heavy metal. The silver ion is converted to an

electro-reducible complex, so that all the heavy metal reagent is present either in the complex form or as the mercaptide.

Examples of this procedure are the use of ammonia, or tris-(hydroxymethylaminomethane) buffer. Sluyterman[83] has shown that the expected 1 : 1 stoichiometry between Ag^+ and cysteine can be obtained using imidazole buffers.

Kolthoff and Harris[84] described the amperometric titration of some aliphatic thiols with silver nitrate in 95% ethanol with ammonia and ammonium nitrate using the rotating platinum electrode. The silver ion was present as $Ag(NH_3)_2^+$ and therefore chloride ion did not interfere.

The potential on the indicator electrode was adjusted so that it was sufficiently negative to reduce $Ag(NH_3)_2^+$ but not oxygen.

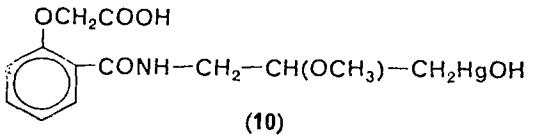
It has been shown[85] that the addition of an excess of standard potassium *p*-chloromercuribenzoate prior to the titration with silver nitrate effectively blocks the reaction with the $Ag(NH_3)_2^+$ ions. Such a procedure appears desirable as a test of the specificity of the titration when proteins, for example, are being analysed.

Recently, Gruen and Harrap[86,87] used a specific-ion electrode[88,89] which is highly selective to Ag^+ to observe the end point in the titration of thiols with Ag^+. The potential at the Ag/S specific-ion electrode depends only on the equilibrium activity of free Ag^+ (the only interfering species known is Hg^{2+}), whereas the current at the rotating platinum electrode depends on the dynamic reduction of any reducible species and may therefore not be as selective as the specific ion electrodes.

As Ag^+ was added to the thiol there was very little change in potential until the end point was almost reached (Figure 4). Beyond the end point, the potential rose rapidly due to the excess Ag^+. The end point was taken as the intersection between the linear baseline and the curve of potential *vs* excess Ag^+. The method was shown to be accurate ($\pm 2\%$) and found applicable also to the determination of —SH groups in proteins.

D. Other Mercaptide Forming Agents

Klotz and Carver[90] titrated thiols with salyrganic acid (**10**) using piperidine-2-azo-*p*-dimethylaniline as indicator. Combination of excess salyrganic acid with the indicator gave an increase in absorption at 550 nm.



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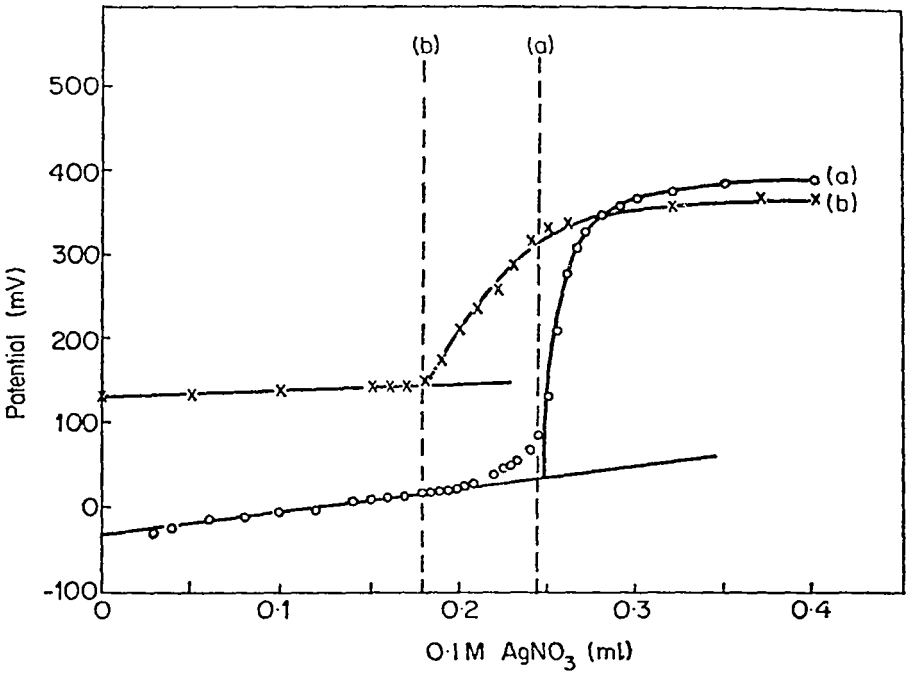
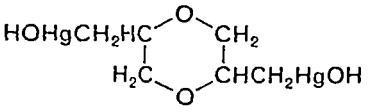


FIGURE 4. (a) Addition of 0·1M $AgNO_3$ to 0·2 ml 0·123M mercaptoethanol in 20 ml H_2O. (b) Addition of 1·0M $AgNO_3$ to 0·2 ml 0·088M glutathione in 20 ml H_2O. Vertical dashed lines indicate stoichiometric end points. (Reproduced by permission of Academic Press Inc., from L. C. Gruen and B. S. Harrap, *Anal. Biochemistry*, **42**, 377 (1971).)

Phenylmercury hydroxide, *o*-hydroxymercuribenzoic acid and various other mercury compounds have also been used[91].

A bifunctional mercury compound (**11**) was used in studies of human plasma albumin[92,93].



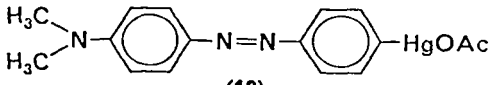
(**11**)

Coloured mercurials (**12–16**) have been employed extensively in biochemical work[94,95].

Klotz and coworkers[96,97] have used a coloured mercurial, 4-(*p*-dimethylaminobenzeneazo)phenylmercury acetate (**12**), which has an absorption peak at 458 nm.

1-(4-Chloromercuriphenylazo)-naphthol-2 (mercury orange) (**16**) has found an application as a histochemical reagent for its red staining and for

being very specific for —SH groups[98]. The reagent was applied in non-aqueous medium for the quantitative measurement of —SH groups, although the method is extremely time-consuming.



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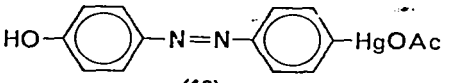

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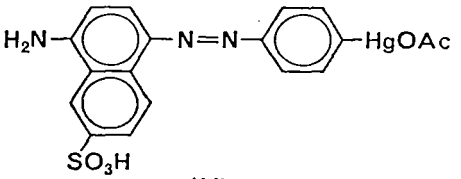

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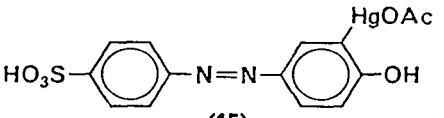

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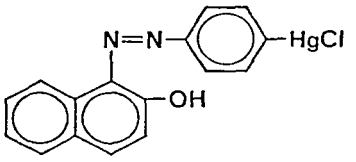
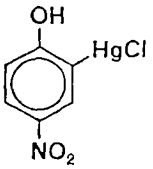


(16)

Mercury orange dissolved in a mixture of acetone and phosphate buffer reacts rapidly and specifically with —SH groups in proteins. The combined mercury orange is then eluted quickly in acidic acetone, which directly reflects the number of —SH groups. The procedure was applied for the measurement of —SH groups in both soluble and structural proteins.

The coloured mercurinitrophenol compounds[99,100] 2-chloromercury-4-nitrophenol (**17**), 2-chloromercury-4,6-dinitrophenol (**18**), 4-chloromercury-2-nitrophenol (**19**) and 2,6-dichloromercury-4-nitrophenol (**20**) have been used as chromophoric probes for thiol groups in proteins and other biologically interesting thiols. They bind specifically at the —SH groups, and the binding reaction induces pK changes and spectral changes of the nitrophenol moiety at certain pH values. The reagents allow



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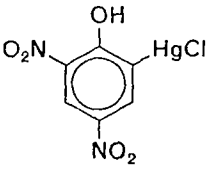

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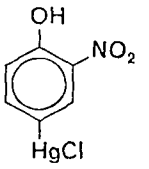

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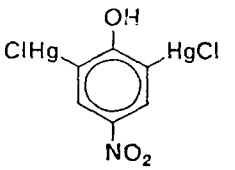


(20)

indication of the microenvironment at their site of reaction. Of the mercurinitrophenols, **18** gives the greatest spectral change at pH 3·3–6·5, and **17** at pH 6·5–9·0. The changes of molar extinction coefficients at 410 nm are in the region of 10^4.

The versatility of the mercurinitrophenols enables them to be used as 'reporter groups' indicating perturbations in biological macromolecules, in the determination of their tertiary structure, and as reagents for kinetic studies on the reactivity of the —SH groups[95,99].

V. COLORIMETRIC PROCEDURES

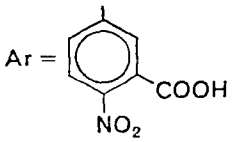
Most of the colorimetric procedures for the quantitative determination of —SH groups have been developed for the purpose of determining the cysteine content in proteins. The need for such colorimetric procedures has decreased with the advent of the various chromatographic methods for the separation of the constituent amino acids of hydrolysates.

A. Ellman's Reagent

The use of 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) (**21**) for the estimation of sulphydryl groups was introduced by Ellman[101] and the procedure is extensively used because of its ease and accuracy[102]. DTNB has a higher standard oxidation/reduction potential than aliphatic disulphides and will react with aliphatic thiols by an exchange reaction to form a mixed disulphide and one mole of 2-nitro-5-thiobenzoate (**23**) per mole of thiol group (equation 15). The mixed disulphide **22** could be in turn cleaved by the mercaptan according to equation (16).

$$\underset{\textbf{(21)}}{\text{RSH}+\text{ArSSAr}} \longrightarrow \underset{\textbf{(22)}}{\text{RSSAr}}+\underset{\textbf{(23)}}{\text{ArSH}} \qquad (15)$$

$$\underset{\textbf{(22)}}{\text{RSSAr}}+\text{RSH} \longrightarrow \text{RSSR}+\underset{\textbf{(23)}}{\text{ArSH}} \qquad (16)$$



However, whether reactions (15) or (15) and (16) occur, the same stoichiometry applies, namely, 1 mole of 2-nitro-5-thiobenzoate anion is formed per mole of —SH group. The anion **23** has an intense yellow colour with a molar absorptivity of 13,600$M^{-1}cm^{-1}$ at 412 nm.

With DTNB, a solution of 0·01 μmole of sulphydryl per millilitre gives an absorbance of 0·136 (1-cm light path) at 412 nm. Simple thiols, e.g. cysteine, give complete colour development within 2 min. The colour is not stable but slowly fades due to autoxidation (Figure 5). This can be delayed by the inclusion of EDTA in the reaction medium[103, 104].

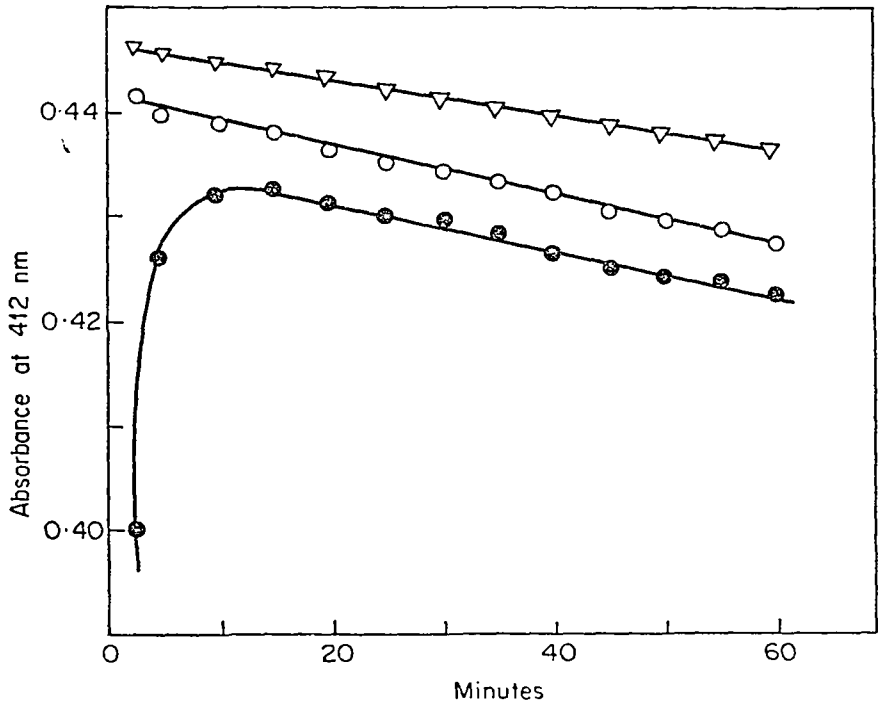


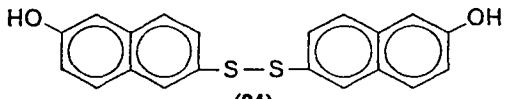
FIGURE 5. Time-dependent absorption of Ellman's reagent with glutathione (▽—▽), cysteine (○—○), and mercaptosuccinic acid (●—●). (Reproduced by permission of Springer Verlag, from H. Wenck, F. Schwabe, F. Schneider and L. Flohé, *Z. Anal. Chem.*, **258**, 267 (1972).)

Ellman's reagent has gained popularity rapidly especially in the field of protein chemistry. The reaction is specific for compounds containing a sulphur atom capable of existing as an anion at pH 8 such as cysteine, dodecanethiol, dithiobiuret, sodium sulphite, sodium thiocyanate, sodium thiosulphate, thioacetamide, thiopental and thiourea[103].

The colour obtained in the assay requires metal-free reagents. Therefore 10^{-4}M EDTA is generally included in the reagent solution[104]. In addition, in analysing the —SH content of proteins, the reaction is performed under denaturing conditions (urea, guanidinium hydrochloride) to expose buried —SH groups.

DTNB has also been used for the assay of sulphite and sulphide and as a reagent for the detection of various thiols on paper or thin-layer chromatograms[32].

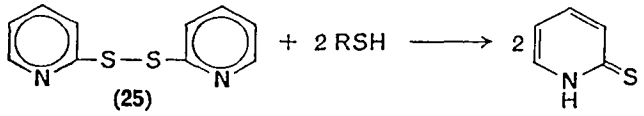
Bis-(*p*-nitrophenyl)-disulphide has been used by Maier[105] for the determination of thiols in foods, and the hydroxynaphthyl disulphide (**24**)[106,107] was used to bind a naphthyl residue to the —SH groups of proteins which was subsequently reacted with a diazotized amine.



(24)

B. Dithiodipyridine Derivatives

It has been shown that 2,2′-dithiodipyridine (**25**) and 4,4′-dithiodipyridine are excellent reagents for the determination of —SH groups, because of a shift in their absorption upon reaction with a thiol[108] (equation 17):



(25) (26) (17)

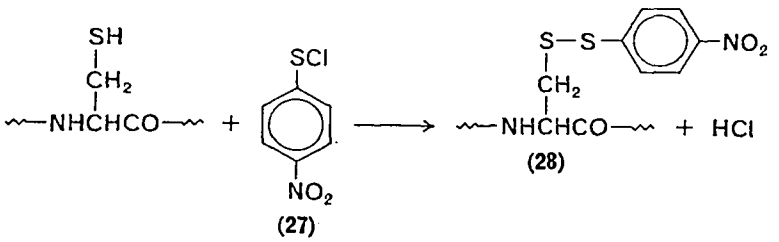
The pyridinethiol formed is virtually exclusively in the thiopyridone form (**26**) (2-thiopyridone has λ_{max} 343 nm and ε 7060 and 4-thiopyridone λ_{max} 324 nm and ε 19,800). This fact has the double advantage of causing a shift in the absorption and making the reaction essentially irreversible. These are useful alternatives to Ellman's reagent in the presence of substances which absorb in the region near 400 nm (e.g. heme-containing proteins). The method permits determination of less than 1·5 μg of —SH group with 2,2′-dithiopyridine and of less than 0·5 μg with 4,4′-dithiopyridine. Pyrimidine and thiazole disulphides were also tested in their utility as —SH reagents[109].

One compound, 2,2′-dithiobis-(5-nitropyridine) (**2**)[33], when treated with a thiol exhibits a wavelength shift into the visible range, and is suitable for

the visual detection of small amounts of thiols. This property can be applied to paper chromatography, electrophoresis, thin-layer chromatography and in general whenever visual detection of thiols is desired. Several —SH containing compounds were detected using 1–10 μg quantities.

C. Sulphenyl Halides

The reaction of sulphenyl halides with the —SH group of cysteine to form a mixed disulphide was usefully employed for titrating the cysteine residues in proteins[110]. The reaction of cysteine with *p*-nitrophenylsulphenyl chloride (*p*NPS-Cl) (**27**) is shown in equation (18).



(18)

Taking advantage of the ready cleavage in alkaline solution of alkyl-aryl disulphides (**28**) with formation of a thiophenol (*cf.* reference 111 for a discussion on the mechanism of the reaction), a method was developed involving labelling of the —SH-containing protein with *p*NPS-Cl in aqueous acetic acid. The *p*-nitrothiophenol moiety, covalently bound to the protein by a disulphide linkage, is then released by exposing the sample of *p*NPS-protein to alkaline media (0·1N NaOH). The highly coloured chromophore (ε 13,600 at 412 nm) was shown to be quantitatively released from the S-*p*NPS-derivatives (**28**) if deaerated solutions were employed. The method was tested with model compounds as well as with proteins[112].

D. Other Methods

The nitroprusside test could be adapted for quantitative determination of thiols[8]. The method is not specific for —SH groups, and substances like acetone, acetoacetate and creatinine also give a positive reaction. To obviate interference by traces of heavy metals 1 drop of 0·1M NaCN is added, so that the colour does not fade so rapidly.

The basis of Saville's method[113,114] is the ease of reaction of —SH groups at low pH with nitrous acid to give —S-nitroso derivatives (**29**)

(equation 19).

$$RSH + HNO_2 \longrightarrow \underset{(29)}{(RSNO)} + H_2O \qquad (19)$$

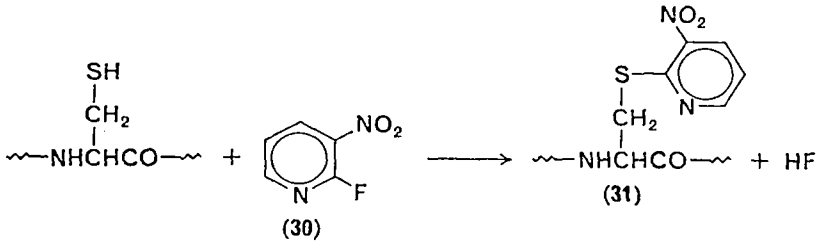
After removal of excess nitrous acid with ammonium sulphamate the S-nitroso derivative is catalytically decomposed by mercury ions to give nitrous acid again (equation 20). The amount of this acid liberated can be

$$(RSNO) + H_2O + Hg^{2+} \longrightarrow RSHg^{+} + HNO_2 + H^{+} \qquad (20)$$

ascertained by adding sulphanilamide. This gives a diazo compound which, on coupling with N-1-naphthylethylenediamine yields an intensely coloured magenta dye with an absorption maximum near 550 nm, the absorption of which is linearly related to the original thiol concentration.

The sensitivity (10^{-8}M thiol) and specificity of this method make it ideally suited for the measurement of the —SH content of living cells, tissues and biological fluids.

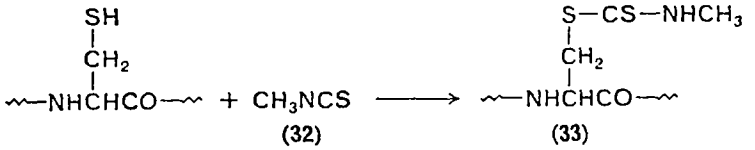
Circular dichroism measurements have been recently applied to the titration of —SH groups in peptide molecules[115]. By reaction of 2-fluoro-3-nitropyridine (**30**) with L-cysteine-containing peptides at pH 9, S-(3-nitro-2-pyridyl)-L-cysteine derivatives (**31**) are obtained (equation 21), which exhibit a positive Cotton effect at 365 nm.



(21)

The reaction was performed by adding increasing amounts of **30** to the solution of the —SH compound, and measuring the intensity of the band at 365 nm. The procedure was successfully tested with cysteine derivatives and glutathione.

Analogously, methyl isothiocyanate (**32**) was used[116] giving S-methyl-thiocarbamyl-L-cysteine derivatives (**33**) which show a positive Cotton effect at 320 nm (equation 22).



(22)

VI. ALKYLATING AGENTS

There is a wide choice of alkylating reagents for —SH groups which may be divided into two classes; (i) those with an 'active' halogen atom which reacts with the elimination of a halogen acid and (ii) those with an 'active double bond with which the reaction is an addition. In both cases, the rate of reaction falls off sharply below pH 6 suggesting that reaction is with RS^- and not RSH.

A. Carboxymethylation

A number of alkylating agents have been used in studies of —SH-containing substances, e.g. iodoacetate, iodoacetamide, iodoethanol, methyl iodide and other alkyl halides.

The most extensively studied and the most useful reagents are iodoacetamide and iodoacetic acid[117]. In general the amide is more reactive (equations 23 and 24):

$$RSH + ICH_2COOH \longrightarrow RSCH_2COOH + HI \quad (23)$$

$$RSH + ICH_2CONH_2 \longrightarrow RSCH_2CONH_2 + HI \quad (24)$$

The reaction of thiols with halogen compounds is a bimolecular nucleophilic substitution reaction, in which the reagent is the highly reactive thiolate ion[118].

The carboxymethylation technique is extensively used in protein chemistry. The protein reacts at pH 9 with an excess of iodoacetate in the presence of urea or guanidinium hydrochloride. The progress of the reaction may be ascertained by qualitative tests with a nitroprusside reagent. After exhaustive dialysis the carboxymethylated protein is hydrolysed in 6N HCl and the S-carboxymethylcysteine is assayed by ion-exchange chromatography on the amino acid analyser[119]. If iodoacetamide is used, the S-carboxamidomethylcysteine is converted by acid hydrolysis to the S-carboxymethyl derivative.

In the absence of precautions to exclude oxygen during acid hydrolysis, destruction of S-carboxymethylcysteine may amount to between 10% and 50%. The deaeration step is therefore extremely important and the use of a water pump is inadequate. Other steps may also introduce artificial peaks in the chromatograms and it is important to observe the recommended conditions in each detail.

Alkylating agents react also with amino, imidazole and even thioether groups of proteins under certain conditions. Many of the complications connected with the use of iodoacetic acid stem from the relatively small

difference in reactivity between —SH groups and other nucleophilic sites. Nevertheless the method is completely satisfactory for —SH groups, since S-carboxymethylcysteine is being assayed directly on the amino acid analyser.

Alternatively, the direct titration of the halogen acid formed by the reaction allows the determination of the thiol content[120,121]. This procedure is very sensitive, but is feasible only with simple thiols.

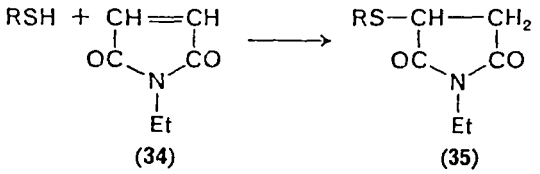
The H^+ ions liberated are measured at constant pH, the choice of this pH being crucial. The fact that the rate of the alkylation increases with increasing pH would make it desirable to choose a high pH. On the other hand, at pH values above 8, alkylation of $-NH_2$ groups becomes significant. The lowest pH at which the reaction proceeds at a reasonable rate should therefore be used, and this is generally found to be between 7·0 and 7·5.

The carboxymethylation reaction can be followed by oxidation of the liberated iodide with hydrogen peroxide and colorimetric estimation of the iodine formed[122].

Smythe[123] allowed the reaction to proceed in a bicarbonate–CO_2 buffer system and followed the evolution of CO_2 manometrically.

B. Addition to Double Bonds

N-Ethylmaleimide (NEM) (34) reacts rapidly with simple thiols at neutral pH, according to equation (25)[124–127].



(34) (35) (25)

NEM has received considerable attention because its absorption spectrum has a maximum at 300 nm which disappears when the reagent combines stoichiometrically with a compound containing an —SH group, as shown in Figure 6, allowing quantitative spectrophotometric determination.

NEM is of low reactivity in acid solution and unstable in alkali, so reaction is carried out by adding the thiol compound at pH 6–7.

The determination should be repeated using various amounts of —SH compound and allowing the reaction to proceed for various lengths of time. The reduction in optical density of the NEM is converted into a

reduction in concentration of the reagent by referring to the calibration curve.

A 10^{-3}M solution of NEM has an optical density of only ca. 0·62 at its wavelength maximum of 300–305 nm. Because of this and its limited

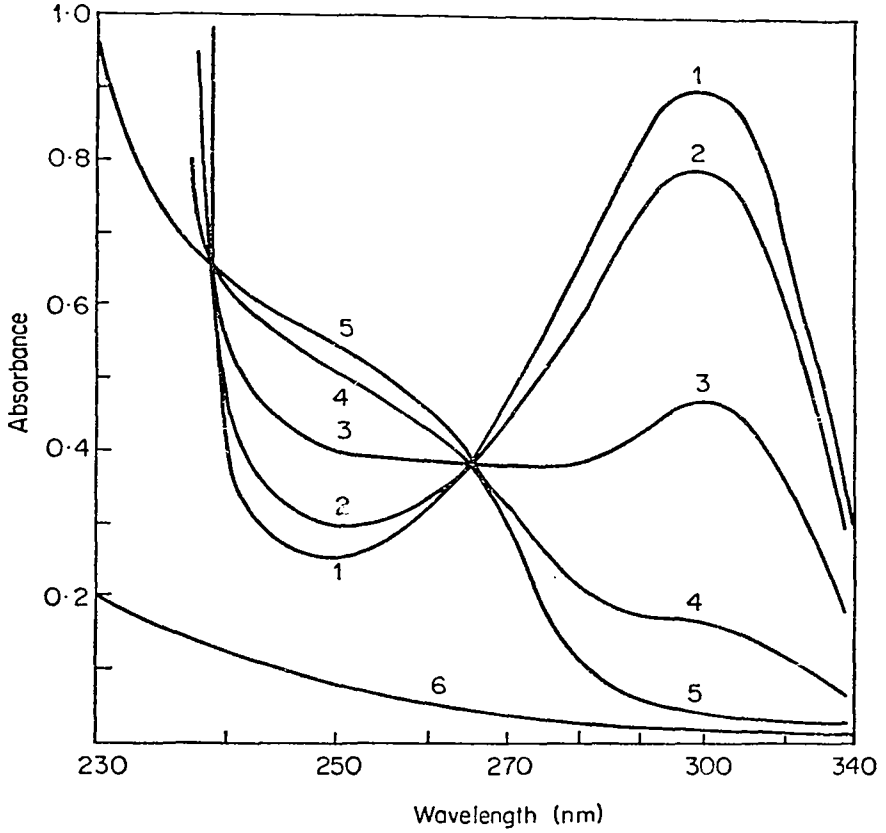
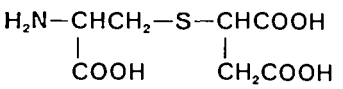


FIGURE 6. The absorption spectrum of N-ethylmaleimide ($1{\cdot}5 \times 10^{-3}$M) in phosphate buffer (0·1M, pH 6·0) in the presence of increasing amounts of cysteine. (1) Without cysteine; (2) $0{\cdot}15 \times 10^{-3}$M cysteine; (3) $0{\cdot}75 \times 10^{-3}$M cysteine; (4) $1{\cdot}27 \times 10^{-3}$M cysteine; (5) $1{\cdot}50 \times 10^{-3}$M cysteine; (6) $1{\cdot}50 \times 10^{-3}$M cysteine alone. (Reproduced by permission of the American Chemical Society from E. Roberts and G. Rouser, *Anal. Chem.*, **30**, 1291 (1958).)

reactivity as an —SH reagent, high concentrations of thiol are required in the estimation and the reaction must be carried out with an excess of NEM and solutions should be incubated before the reaction is complete.

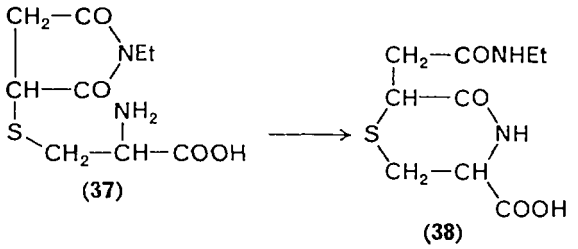
The reaction of NEM with thiols is also useful for chromatographic determinations. The product gives an intense red colour in alkaline solutions[128].

The method has been extensively used for the determination of cysteine in proteins[129-131]. In this case, the product (35) could be estimated either spectrophotometrically or, after acid hydrolysis in 6N HCl, as S-succinyl-cysteine (36) by automatic amino acid analysis.



(36)

The adduct of NEM with free cysteine (37) undergoes an intramolecular transamidation to 38 at pH 9 (equation 26)[132].



(37) (38) (26)

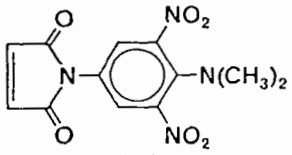
The formation of a stable alkyl derivative that resists acid hydrolysis is an important feature of this reagent.

Since proteins react more slowly with NEM than do simple thiols, a pretreatment of the protein sample with urea solution is suggested in order to expose the less reactive SH groups. Moreover, NEM is of limited —SH specificity and under the conditions used will combine slowly with other functional groups. Its use is therefore not to be recommended unless the more specific methods cannot be used.

Other substituted maleimides have proved useful, since they introduce a chromogenic substituent into biologically important substances, especially proteins. Such reagents allow modification of reactive —SH groups in the protein and ready detection of the appropriate peptide after proteolytic degradation and separation[136, 137].

These include, N-(4-dimethylamino-3,5-dinitrophenyl)maleimide (39)[133, 134] and N-(2,4-dinitrophenyl)maleimide (40)[135].

41 is not coloured but its derivatives with tetrazotized di-*o*-anisidine are, and give a sensitivity 100 times greater than NEM itself. 42 (X = O or S) is fluorescent and by reaction with —SH groups can introduce a fluorescent label into proteins.



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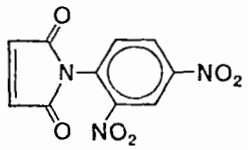

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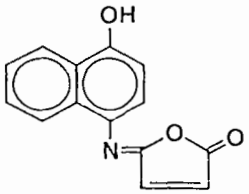

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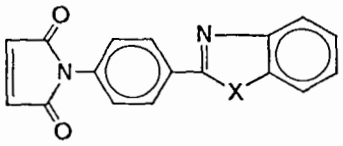
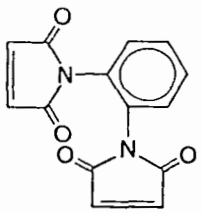


(42)

Several bifunctional maleimide derivatives (N,N'-(1,2-phenylene)-bismaleimide (**43**)[138], azophenyldimaleimide (**44**)[139], N,N'-hexamethylene-bismaleimide (**45**)[140], and bis(N-maleimidomethyl)ether (**46**)[141-143] have been used as cross-linking reagents in protein chemistry[144].



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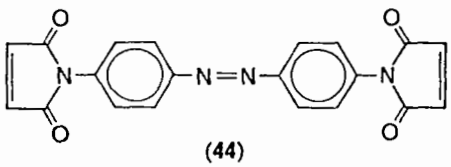

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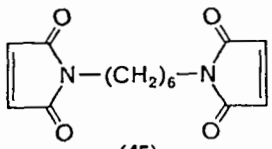

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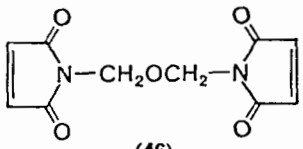


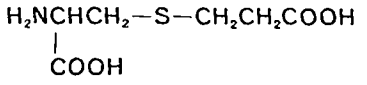
(46)

Acrylonitrile is another effective alkylating agent for thiols[145,146]. The reaction is quantitative resulting in cyanoethyl derivatives (equation 27).

$$RSH + CH_2{=}CHCN \longrightarrow RSCH_2CH_2CN \qquad (27)$$

Alkylation of protein sulphydryl groups with acrylonitrile is extensively used in protein chemistry for protein modification studies as well as for analytical purposes. Upon acid hydrolysis, the S-cyanoethyl derivative of

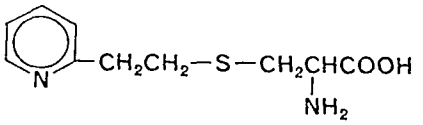
cysteine is converted to the S-carboxyethyl derivative **47** which is estimated by automatic amino acid analysis.



(47)

However, the method has its limitations since **47** is partially destroyed during acid hydrolysis of the proteins. On chromatograms of protein hydrolysates that contain a large amount of glutamic acid, **47** is not well resolved.

A reagent was therefore sought that would modify protein sulphydryl groups to yield a derivative which would be stable to acid hydrolysis and which could elute at a convenient position on an amino acid analyser. 2-Vinylpyridine meets all these requirements, and reacts specifically with thiol groups at pH 7·5, cysteine being converted to S-β-(2-pyridylethyl)-cysteine (PEC) (**48**)[147].

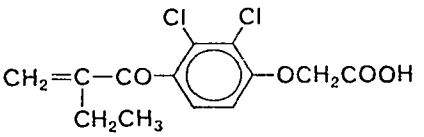


(48)

In addition to ion exchange chromatography[148], u.v. spectroscopy could also be employed for quantitative determinations. The PEC-residue has an absorption maximum at 263 nm with an extinction coefficient of 5000. Unfortunately, the molar extinction of the cysteine derivative was found to be solvent dependent and varying with the composition and molecular size of the protein.

2-Vinylquinoline with thiols produces a 2-quinolylethyl derivative which absorbs at 318 nm with a molar extinction of 10,000 in 0·1N acetic acid. Since proteins do not usually absorb at this wavelength, the reagent is useful for the determination of cysteine content in intact proteins. Optimal conditions for the reaction require equimolar concentration of 2-vinylquinoline to the SH groups and 4 h reaction time[149].

Ethacrynic acid was also employed as an —SH reagent in physiological studies[150, 151].



Ethacrynic acid

VII. RADIOCHEMICAL METHODS

Various disadvantages of the traditional methods of thiol group analysis are circumvented by the use of radiolabelled reagents. Radiochemical methods can be readily automated by means of scintillation counting, so that large numbers of samples can be estimated rapidly and precisely. Sensitivity is often the most important feature, especially in biochemical work.

The sensitivity of radiochemical methods is theoretically limited only by the specific activity of the reagent used. Extremely low levels of —SH may be estimated, i.e. less than one millimicromole of SH.

Mercaptide formation has been used in a direct labelling technique for estimation of thiol groups in insoluble proteins, such as wool fibres, using either [^{203}Hg]-phenylmercury acetate or [^{14}C]-methylmercury iodide. Samples containing [^{203}Hg] have to be combusted before counting by liquid scintillation, whereas they can be counted in the γ-counter in the solid state[152]. Samples containing ^{14}C were combusted to $^{14}CO_2$ and assayed by liquid scintillation counting.

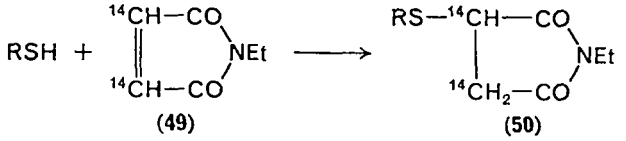
The excess radioactive reagent must be removed after reaction with the protein sample by dialysis or precipitation of the protein. The method therefore is not suitable for simple thiols.

Radioactive mercurial compounds have also been used for the autoradiographic detection of reactive protein thiol groups in haemoglobin chains[153]. It was found that insulin and ribonuclease (which contained disulphide and no thiol groups) did not bind the mercury compound, whereas with other proteins there was a general correlation between the —SH content and the autoradiography density.

Erwin and Pederson[154] used a sensitive gel filtration method for the determination of protein thiol groups with carboxyl-labelled [^{14}C]-*p*-chloromercuribenzoic acid ([^{14}C]*p*CMB). Unreacted reagent was separated by gel filtration using a Sephadex G25 column. The lowest level of protein assayed appeared to be 30–40 μg in 0·2 ml of incubation mixture.

^{14}C-Iodoacetic acid or ^{14}C-iodoacetamide have been extensively used in protein chemistry work[155,156]. Since side reactions with other amino acid side chains could occur (methionine, lysine, histidine and tyrosine) non-specifically bound radioactivity can easily amount to 10%.

Labelled N-ethylmaleimide (^{14}C-NEM) (**49**) has also received much attention. The reagent is commercially available and ^{14}C uptake can readily be measured[157–160]. Addition of ^{14}C-NEM to a thiol group (i.e. cysteine) results in the formation of labelled S-(ethylsuccinimido)-cysteine (**50**) (equation 28). On acid hydrolysis **50** is converted to S-succinyl-cysteine and ethylamine, both of which can be determined quantitatively

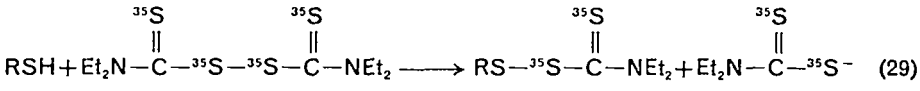


(49) (50) (28)

by means of amino acid analysis. Since unreacted NEM liberates ethylamine, care must be taken to remove all traces of excess reagent prior to hydrolysis. This allows a direct measure of the amount of cysteine in the protein that has reacted with the reagent.

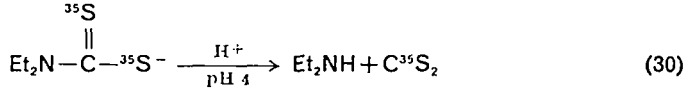
The limitations of the use of NEM as a thiol reagent for analytical purposes apply also in the case of ^{14}C-NEM, so that the procedure will be more useful for semi-quantitative than for precise analysis, and, in protein chemistry for locating SH sites in peptide fragments.

By reaction of [^{35}S]-tetraethylthiuram disulphide (TETD) (**51**) and protein thiol groups stoichiometric amounts of the [^{35}S]-diethyldithiocarbamate (**53**) ion are produced, according to equation (29)[161,162].



(51) (52) (53) (29)

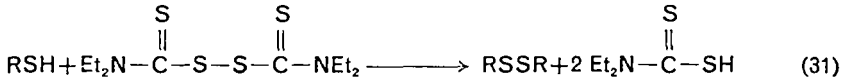
The dithiodicarbamate ion (**53**) has to be separated and allowed to decompose at pH 4 to give $C^{35}S_2$, which is trapped in alkaline piperidine and its radioactivity measured by liquid scintillation counting (equation 30).



(30)

The method was applicable to 10 μg quantities of protein and its precision was comparable to that of most existing methods.

Alkanethiols react differently and give alkyl disulphides according to equation (31).



(31)

A radiochemical procedure is described by Fletcher and Robson[163]. If acid hydrolysis of a protein is carried out in the presence of free [^{35}S]-cystine, the cystine found in the hydrolysate and all of its decomposition products, including cysteine, become uniformly labelled, i.e. they acquire the same specific activities by some kind of interchange mechanism.

VIII. MISCELLANEOUS

A. Total Sulphur

Several methods for the determination of total sulphur in organic compounds are available[164]. Oxidation of sulphur to sulphate is accomplished by oxygen, peroxides, potassium chlorate or fuming nitric acid. The determination of sulphate can be performed by gravimetric analysis or by titration with barium chloride using tetrahydroxyquinone or thorin as the indicators. The excess of barium chloride can be also determined by amperometric, conductometric or complexometric titration.

Organic sulphur may be also reduced to sulphide, the latter then being determined by iodometric titration[165].

Earlier methods for sulphur analysis are now superseded by the oxygen-flask combustion method of Schöniger[166]. The apparatus is extremely simple, consisting merely of an Erlenmeyer flask with a platinum combustion basket attached to the stopper.

B. Sulphides

Quantitative analysis of sulphides can be carried out by oxidation to sulphoxide with bromine in aqueous solution (equation 32)[167].

$$R_2S + Br_2 + H_2O \longrightarrow R_2SO + 2\,HBr \qquad (32)$$

Oxidation to the sulphoxide is rapid, whereas further oxidation to the sulphone is slow. Hence, it is possible to titrate directly with bromine. A standard acidified bromate–bromide solution can be used to form bromine *in situ* (equation 33).

$$BrO_3^- + 5\,Br^- + 6\,H^+ \longrightarrow 3\,Br_2 + 3\,H_2O \qquad (33)$$

The end point in the titration is detected by the first lasting colour of the excess free bromine. The end-point colour fades because of oxidation to sulphone, but so slowly that it can be detected without difficulty.

Aliphatic sulphides and iodine form a 1 : 1 complex which absorbs intensely in the ultraviolet[168]. Since the absorptivity of different compounds of the class varies somewhat the accuracy is less than 4%.

On oxidation with potassium permanganate or hydrogen peroxide, sulphides yield the corresponding sulphones, some of which, especially aromatic ones, have properties suitable for identification.

Another method uses the reaction of sulphides with alkyl halides, i.e. formation of sulphonium salts (equation 34)[169]. *p*-Bromophenacyl bromide

$$R_2S + R'X \longrightarrow R_2R'S^+X^- \qquad (34)$$

is employed as an alkylating agent. However, sulphides with branched chains either do not form *p*-bromophenacylsulphonium salts at all, or do so only in low yields[170].

A suitable method for identification of sulphides consists in their conversion to sulphilimines (55) on reaction with the sodium salt of sulphonylchloramine (54)[171].

$$R_2S + ArSO_2NClNa \longrightarrow R_2SNSO_2Ar + NaCl \qquad (35)$$

(54) (55)

Chloramine T is most convenient for identification purposes. The separation of *p*-nitrobenzenesulphonylsulphilimines by means of paper chromatography has been described[171].

C. Disulphides

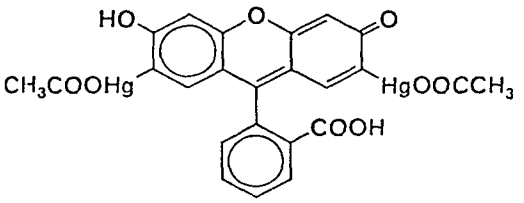
Disulphides are most conveniently estimated by conversion to thiols.

Disulphide samples containing thiols can be determined by first analysing the unreduced sample for thiol and then reducing the disulphide and determining the total thiol content; the disulphide content is obtained by difference.

The reaction between bromine and disulphides provides a method for the direct disulphide determination with accuracy and reproducibility[167]. However, the method (equation 36) has the disadvantage of being affected by a large number of interfering compounds.

$$RSSR + 5\,Br_2 + 4\,H_2O \longrightarrow 2\,RSO_2Br + 8\,HBr \qquad (36)$$

Mixtures of alkyl sulphides and disulphides can be determined by first obtaining the total of the two types by bromination and then determining the disulphide by reduction followed by determination of the thiol content.



(56)

Another direct assay for disulphide groups employs their quenching of the fluorescence of fluoroscein mercury acetate (56)[172]. In alkaline solution, thiols quench to only 5% of the extent of disulphides and their contribution can easily be eliminated, e.g. by alkylation with iodoacetate. The method is very sensitive (10^{-7}M) and gives values for the disulphide content of some proteins which agree well with the known values.

I. Cleavage of disulphides

We will now consider the methods available for splitting disulphide bonds.

a. Reduction. Disulphides can be easily reduced to the corresponding thiols, for example with zinc and sulphuric acid in acetic acid, or also with lithium aluminium hydride[173-176]. Zinc dust and magnesium were used for reducing oxidized glutathione. Kolthoff and coworkers[173] used both amalgamated zinc and diluted zinc amalgam for aliphatic disulphides. Sodium amalgam was used to reduce an acid solution of cystine[176].

Although it has been relatively little used, electrolytic reduction could also be successfully employed. Dohan and Woodward[177] described the reduction of oxidized glutathione in acid solution at a stirred mercury cathode. The voltage used was sufficient for hydrogen to be evolved.

Sodium borohydride has been also used successfully. The reduction is carried out in alkaline solution, and the excess borohydride is subsequently removed either by acidification or with acetone. This reduction was applied to proteins by Moore and coworkers[178] and the —SH groups produced were converted to the S-carboxymethyl derivative by reaction with iodoacetate. In some cases peptide bonds were also reduced; this side reaction can be minimized if the reduction is carried out in the presence of ethylenediaminetetraacetic acid.

The traditional method of reduction of protein disulphide groups is by treatment with high concentrations of thiols. Reagents that have been used are cysteine, reduced glutathione, β-mercaptoethanol[179], β-mercaptoethylamine[180] and thioglycollic acid[181].

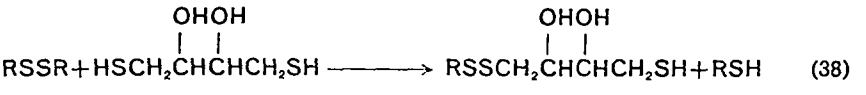
The reaction may be represented by equation (37) from which it is

$$RSSR + 2\,R'SH \rightleftharpoons 2\,RSH + R'SSR' \qquad (37)$$

obvious that in order to drive the reaction in the desired direction a considerable excess of thiol has to be added[182].

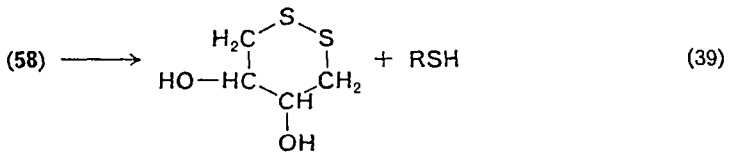
The reagent of choice for the reduction was β-mercaptoethanol until recently, when dithiothreitol (DTT) (57)[183,184] became commercially available. The use of DTT as a reducing agent for disulphides was first

described by Cleland, and the reagent bears his name (equations 38 and 39).



(38)

(57) (58)



(39)

(59)

The overall reaction proceeds nearly to completion because the formation of a 6-membered ring (**59**) containing a disulphide bridge is energetically favoured over the mixed disulphide.

The oxidation/reduction potential of DTT at pH 7 and 25°C is −0·33 V compared to −0·22 V for cysteine. These two values allow one to calculate an overall equilibrium constant of 10^4 for the reduction of cystine by DTT.

This reagent can be used at a much lower concentration than β-mercaptoethanol by virtue of its lower oxidation/reduction potential and its resistance to air oxidation. An additional advantage of DTT is its relative lack of the characteristic unpleasant thiol odour.

b. Sulphite treatment. When disulphides are treated with alkali sulphite, thiols and sulphenylsulphites (Bunte salts) (**60**) are formed (equation 40):

$$RSSR + SO_3^{2-} \longrightarrow RSSO_3^- + RS^- \qquad (40)$$

(60)

The reaction was extensively studied[185-188] and found to be reversible, so that the concentration of sulphite must be kept high. The equilibrium constants for many simple disulphides have been determined and found to be lower for those containing negatively charged groups than for neutral or positively charged molecules.

By mild oxidation (oxygen, sodium tetrathionate, iodosobenzene) RS^- is reconverted to RSSR so that the reaction with sulphite progresses to the quantitative conversion to $RSSO_3^-$. This may also be achieved by carrying out the sulphitolysis step in the presence of Cu^{2+} [189-191] (equation 41).

$$RSSR + 2\,Cu^{2+} + 2\,SO_3^{2-} \longrightarrow 2\,RSSO_3^- + 2\,Cu^+ \qquad (41)$$

Any thiol present will also be converted to S-sulphonate (equation 42).

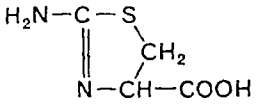
$$RSH + 2\,Cu^{2+} + SO_3^{2-} \longrightarrow RSSO_3^- + 2\,Cu^+ + H^+ \qquad (42)$$

Kolthoff and Stricks[192] have made these reactions the basis of an analytical method for thiols and disulphides. Reduction of cystine residues of proteins with dithiothreitol followed by treatment with an excess of sodium tetrathionate is the basis of the method of Inglis and Liu[193] for the determination of the half-cystine residues in proteins as S-sulphocysteine.

Cyanide will also react with disulphides in a similar way to sulphite (equation 43)[194].

$$RSSR + CN^- \longrightarrow RSCN + RS^- \qquad (43)$$

If the disulphides contain free amino groups, as with cystine, cyclic amidine derivatives (**61**) are formed[195–197].



(**61**)

Tri-*n*-butylphosphine (Bu_3P) is also a reductant for disulphide bonds (equation 44)[198–200].

$$RSSR + Bu_3P + H_2O \longrightarrow 2\,RSH + Bu_3PO \qquad (44)$$

Phosphorothionate (**62**) was used for the opening of disulphide bonds in proteins. The reaction is a nucleophilic heterolytic scission (equation 45)[201, 202].

$$RSSR + SPO_3^{3-} \longrightarrow RSSPO_3^{2-} + RS^- \qquad (45)$$

(**62**)

c. Oxidation. Thiols and disulphides are oxidized to sulphonic acid derivatives by a variety of strong oxidizing agents, such as hydrogen peroxide and various peracids, particularly performic acid[203].

The scission of disulphide bonds by oxidation with performic acid is a standard technique in protein chemistry[204], since its introduction by Sanger[205, 206] in researches with insulin. Cysteine and cystine residues are converted to cysteic acid, which, after acid hydrolysis of the protein sample, is determined by automatic amino acid analysis.

The performic acid reagent is made by mixing 5 volumes of 30% hydrogen peroxide and 95 volumes of 99% formic acid. The titre of peracid reaches a maximum after about 120 min and decreases slowly thereafter. Only freshly prepared reagent should be used.

Since the reaction is usually conducted with a 10-fold excess of reagent, removal of this excess from the protein must be accomplished under mild conditions. The most satisfactory approach is to reduce the excess reagent by ascorbic acid, sulphides or sodium sulphite. Alternatively, the reagent may be greatly diluted with water and the solution lyophilized[204].

Another possibility for the oxidative cleavage of disulphide bonds involves ozonization in 99% formic acid[207]. The yields of cysteic acid by this method using cystine as a model substance were as high as 98%. Photochemical oxidation[208] in the presence of cresol red or crystal violet as sensitizers proved also to be a useful technique for the quantitative conversion of cysteine to cysteic acid.

IX. SPECTROSCOPIC METHODS

A. Ultraviolet Absorption

The —SH chromophoric group in alkanethiols, characterized by the sulphur nonbonded electrons, has been extensively investigated both experimentally[209-221] (Table 1) and theoretically[209,210]. The u.v. spectra

TABLE 1. Electronic spectra of some aliphatic thiols

Compound	Solvent	λ_{max} (nm)	log ε_{max}	Reference
Hydrogen sulphide	Vapour	190–200	3·3	290, 210
	n-Hexane	190	3·2	211
Sodium sulphide	Water	230	3·7	212
Methanethiol	Vapour	204	3·4	209
		225–235	2·3	
Ethanethiol	Vapour	203	3·3	209
		225–235	2·3	
	n-Heptane	225–230	2·2	212
	Ethanol	195	3·1	211, 212
Propane-2-thiol	Cyclohexane	225–230	2·2	213
Butanethiol	Cyclohexane	225–230	2·2	213
	1N NaOH	240	3·7	214
Butane-2-thiol	Cyclohexane	225–230	2·1	213
2-Methylpropane-2-thiol	Vapour	205	3·5	209
Cyclohexanethiol	Cyclohexane	227	2·1	215
2,5-Hexanedithiol	Ethanol	224	2·4	217
2-Mercaptoethanol	pH 0·33	196	3·4	218
2-Mercaptopropan-1-ol	Ethanol	230	2·0	219
		206	2·7	
2-Mercaptopropionic acid	Ethanol	235	2·3	219
		206	2·8	
Cysteine	pH 0·41	190	3·4	218
	Water	199	not reported	220
	NaOH	235	3·5	221
5α-Cholestane-3α-thiol	Cyclohexane	229	2·1	216
5α-Mercaptocholestane-3β-yl acetate	Cyclohexane	225–235	2·2	216

of thiols exhibit an intense absorption band located near 200 nm accompanied by more complex absorption(s) of much lower intensity in the 220–240 nm region.

Owing to position and/or oscillator strength of these bands, the u.v. absorption technique is not a method of choice for detection and determination of saturated aliphatic thiols. Conversely, the u.v. spectra of aromatic thiols[222-228] well characterize this class of compounds, since they present a clearly defined maximum at 235–240 nm and a relatively weak and broad absorption from 265 to 295 nm which shows fine structure (Table 2). The effect of alkyl substituents in thiophenol appears to displace

TABLE 2. Electronic spectra of some aromatic thiols

Compound	Solvent	λ_{max} (nm)	log ε_{max}	Ref.
Thiophenol	Vapour	270–285	not reported	222
		235	not reported	222
		270·0–285·8 (10 bands)	not reported	223
	n-Hexane, cyclohexane, or 2,2,4-trimethyl-pentane	272, 280, 288	2·8, 2·8, 2·6	224
	n-Hexane	235	3·9	225
	i-Octane	270–290	2·7–2·9	226
		235	4·0	226
	Ethanol	237	4·0	227
(3-Methyl)thiophenol	Ethanol	239·5	3·8	228
(3-Methyl)thiophenolate	Ethanol	271	4·2	228
(4-Methyl)thiophenol	Cyclohexane	280, 286, 295	2·7–2·9	224
	Ethanol	237	4·0	228
(4-Methyl)thiophenolate	Ethanol	270·2	4·2	228
(4-*t*-Butyl)-thiophenol	Ethanol	238·6	4·0	228
(4-*t*-Butyl)-thiophenolate	Ethanol	270·2	4·2	228

the main absorption band to lower excitation energies[228]. In going from the thiols to the corresponding thiolates there is also a red-shift of the wavelength maximum accompanied by an increase in the oscillator strength[228].

The more intense band at 235–240 nm is very probably a charge-transfer band S(3pπ)$\rightarrow$ring(π^*), whereas the inflection band at 265–295 nm can be assigned with little doubt as the benzene analogue $^1L_b \rightarrow {}^1A$

transition. There has been considerable discussion on the involvement of sulphur 3d orbitals in π-bonding to the ring[224,229]. The most recent studies[224,230] seem to indicate that if there is any stabilization of the π orbitals by the use of sulphur 3d orbitals, it is very small and has little effect on orbital energies. The available data are consistent only with a perturbation of the benzene ring π orbitals *via* S(3pπ)—C(2pπ) bonding.

B. Infrared Absorption

1. S—H Stretching vibrations

The location of the S—H stretching absorption band has been extensively investigated (Table 3). It occurs as a sharp, easily recognized although rather weak band in the range 2600–2550 cm^{-1}. If allowance is made for these factors, the presence or absence of a band in this region can afford decisive evidence for the occurrence of a thiol group. Alkanethiols absorb towards the top of this range, aromatic thiols in the middle, and thioacids at the bottom.

Bell[231,232] was able to show that the bands near 2570 cm^{-1} in thiophenol and in the 4-thiocresol were absent from the corresponding sulphides. This early assignment was fully supported by later workers. Ellis[233] found the first overtone in the 5000 cm^{-1} region, Williams extended the series of thiols examined by Bell showing that all of them absorbed near 2600 cm^{-1}. Trotter and Thompson[235] and Sheppard[236] have each studied several simple thiols and compared them with the corresponding sulphides demonstrating in all cases the disappearance of the S—H absorption, which they assign as being in the range 2560–2590 cm^{-1}.

Hydrogen sulphide has its asymmetric SH mode at 2688 cm^{-1} [237]. This is an exceptional case, and organic thiols do not appear to absorb at higher frequencies than 2600 cm^{-1}. This has been confirmed by subsequent papers on this correlation[238,239]. From earlier studies it would seem that only very weak hydrogen bonds are formed in most thiols, although a few exceptional instances of relatively strong bonds are known.

Association of the SH link with the oxygen atoms of ethers, sulphones or carbonyl compounds does not result in frequency shifts of more than 10–20 cm^{-1} [240]. It is clear, both from the fact that some shifts occur and from the intensity changes, that hydrogen bonds are formed[241], but these are very weak so that thiolacetic acid does not dimerize in the liquid state[242]. Even with the ethyl ester of thiosalicylic acid, in which the —SH group is particularly well placed to form a strong intramolecular hydrogen bond, the frequency shift is only 23 cm^{-1}, as compared with *p*-thiochresol[239]. Also there is in general little change in the frequency of —SH absorption

TABLE 3. S—H Stretching bands of some thiols

Compound	νS—H (cm^{-1})	State or solvent	Ref.
Methanethiol	~2580	g	235
	2587	CCl_4	252
Ethanethiol	2582, 2577	CCl_4	252
	2573	g	235
Propane-1-thiol	2575	g	235
	2565	g	253
	2564	l	253
Propane-2-thiol	2576, 2562	CCl_4	252
Butane-1-thiol	2574	l	235
2-Methylpropane-1-thiol	2573	g	235
Butane-2-thiol	2567	g	235
2-Methylpropane-2-thiol	2570	g	235
	2573	CCl_4	252
2-Methylbutane-2-thiol	2591	l	254
Cyclohexanethiol	2571	l	255
(3-*N*,*N*-Diethylamino)propane-1-thiol	2584	C_6H_6, l	244
(3-*N*,*N*-Diphenylamino)propane-1-thiol	2584	C_6H_6	244
	2577	l	244
Ethane-1,2-dithiol	2350	l	248
Propane-1,1-dithiol	2522~2513	s	256
Propane-2,2-dithiol	2522~2513	s	256
Pentane-3,3-dithiol	2522~2513	s	256
Cyclohexane-1,1-dithiol	2522~2513	s	256
Thiophenol	2585	CCl_4	239
	2574, 2591	CCl_4	241
	2571, 2590	CCl_4	249
	2574	C_6H_6	249
2-Chlorothiophenol	2589	CCl_4	257
2-Bromothiophenol	2579	CCl_4	257
3-Chlorothiophenol	2590	CCl_4	257
	2583, 2589	CCl_4	249
3-Bromothiophenol	2591	CCl_4	257
4-Chlorothiophenol	2591	CCl_4	257
	2569, 2588	CCl_4	249
4-Bromothiophenol	2590	CCl_4	257
4-Iodothiophenol	2590	CCl_4	257
2-Mercaptobenzoic acid	2558	CCl_4	259
Ethyl-2-mercaptobenzoate	2542	l	239
4-Thiocresol	2565	CCl_4	239
Thiolacetic acid	2550	l	242
Dithioacetic acid	2481	l	245
Trithiocarbonic acid	2400	l	250
	2550, 2525	CS_2	250
Dimethyldithiophosphoric acid	2400	l	246
	2580	CCl_4	246
Diphenyldithiophosphinic acid	2420	s	247
	2560	$CHCl_3$	247

on passing from the liquid state to dilute solutions, so that self-association is not important[243, 244].

In a few instances, however, a reasonably strong hydrogen bond is formed. Thiophenol in pyridine shows its SH band about 80 cm^{-1} lower than usual[240], and mixtures with dialkyl sulphoxides show an even greater shift (about 100 cm^{-1})[239]. The shifts fall steeply in phenyl alkyl (70 cm^{-1}) and diaryl sulphoxides (48 cm^{-1}), in what seem to be disproportionately large steps, in relation to the small changes of polarity involved. The reason for these strong associations as compared with the weak effects with carbonyl, are not known. The increased polarity of the S=O bond would not seem sufficient in itself to explain this, as is emphasized by the fact that strong associations also occur with C=S and P=S links, which might be expected to be less polar than the carbonyl group. In contrast to thiolacetic acid, dithioacetic acid[245] is strongly associated and the S—H frequency falls by 80 cm^{-1} on passing from vapour to the liquid. With P=S links the association is even stronger and shifts of up to 180 cm^{-1} are reported[246-247]. Sweeney and coworkers[248] reported that ethane-1,2-dithiol absorbs at 2350 cm^{-1} in the liquid state, but this appears to be wholly exceptional.

These findings posed some interesting problems and more detailed studies of other examples of this effect, leading to better understanding of some of the basic factors which control hydrogen bond formation, have been carried out.

David and Hallam[249] showed that thiophenol exhibits a concentration-dependent shift in carbon tetrachloride suggesting intermolecular hydrogen bonding. In addition to an SH···S bonded structure the authors propose a dimeric SH···π bonded complex.

Intermolecular hydrogen bonding of the SH···S type was studied by dilution experiments on trithiocarbonic acid and its monoalkyl esters[250]. The S—H stretching frequency of the acid underwent a shift from 2400 cm^{-1} (bonded S—H) to 2550 and 2525 cm^{-1} (two rotational isomers for the free SH).

In the i.r. spectra of carbon tetrachloride solution of N-alkylated-β-amino thiols the band due to the stretching vibrations of the thiol group is found at 2555–2575 cm^{-1} in concentrated solutions (intermolecularly bonded S—H) and at 2620 cm^{-1} in dilute solutions (free S—H)[251]. In solutions of the compounds examined aggregates associated through —SH···N bonds are formed which break down when the concentration of the amino thiol is reduced to 10^{-2}–10^{-3}M.

Finally, evidence for rotational isomerism in aliphatic thiols has been suggested through the investigation of S—H stretching vibrations[252].

2. Other vibrations

The C—S stretching vibration of thiols appears in the i.r. as an absorption in the range 760–580 cm^{-1}. The weakness of this band and its variability in position render it of limited use in analytical work, especially since a number of skeletal vibrations occur in the same region. Identifications therefore have to be made with caution, and in fundamental studies have always been accompanied by Raman spectra in which the C—S stretching vibration appears as an intense band. Analytical studies on this band are therefore likely to be of value in a limited number of specialized cases.

The initial study in the vapour state of a group of thiols was made by Trotter and Thompson[235], who noted that considerable shifts in the C—S frequency resulted from relatively small changes in structure. This work was later extended by Sheppard[236] who compared i.r. and Raman spectra of a wider range of thiols and other C—S containing compounds. He was able to observe a progressive lowering of the frequency in primary, secondary and tertiary thiols, and throughout the series thiols → sulphides → disulphides.

This correlation has been further confirmed by studies on individual thiols such as cysteine and glutathione[258], dithioacetic acid[245], ethane-1,2-dithiol[248] and 2-mercaptoethanol[259].

C—S stretching, C—S—H and C—C—S bending and S—H torsional modes have been discussed in several papers dealing with conformational analysis of thiols[253–255, 260–263].

C. *Nuclear Magnetic Resonance*

Several examples of the n.m.r. of thiolic protons are available[264–267]. Chamberlain gives the range 8·4–8·8 ppm for aliphatic thiols and the value 6·4 ppm for thiophenol[264]. In one of the earlier studies on the application of n.m.r. to hydrogen bonding involving sulphur it was found that aliphatic and aromatic thiols undergo dimerization in carbon tetrachloride[265]. Compared to the proton chemical shifts in associated alcohols, 4·0 ppm upfield on dilution, the dilution shifts in mercaptans were small, 0·3–0·4 ppm.

Dilution shifts of the —SH proton magnetic resonance have been used to obtain hydrogen bonding dimerization constants of several thiols[266]. I.r. and p.m.r. techniques both have specific advantages in particular hydrogen-bonding applications. For thiols, i.r. evidence may be uniquely useful in identifying monomeric, dimeric and higher polymeric structures, and in distinguishing between cyclic and open dimers. However, it is

difficult to obtain correct thiol K_{ass} from i.r. data. On the other hand, p.m.r. thiol data, while blind to structure and subject to medium effects, are particularly suitable for determining K_{ass}.

A study was made of the downfield proton chemical shifts of the —SH group when hydrogen bonded to proton acceptor solvents[267]. The order of increasing complexation with several aliphatic thiols is:

$$(C_2H_5)_3N = (C_2H_5)_2O < (C_2H_5)_2S < (CH_3)_2S = C_2H_5OH <$$
$$< (CH_3)_2CO = \text{dioxane} < (CH_3)_2NCHO < (CH_3)_2SO < [(CH_3)_2N]_3PO$$

The δ_{SH} were in the range 0–1·4 ppm. The p.m.r. spectra of methanethiol and ethanethiol were analysed on the basis of nuclear grouping A_3B and A_3B_2C, respectively[268–270]. The spectra calculated agree well with those observed.

From coupling-constant arguments the rotamer populations in cysteine and its methyl ester have been established throughout the entire pH range[271–272].

A systematic study was conducted of the p.m.r. spectra of cysteine and glutathione[273]. The results indicate increased rigidity insofar as the rotation around the $C_\alpha—C_\beta$ bond of the cysteinyl residue of glutathione is concerned.

The ^{13}C n.m.r. spectra of glutathione and its oxidized form were measured by Jung and coworkers[274]. The most important results of these measurements are the large differences between the C_α and C_β shifts of cysteinyl and cystinyl residues in reduced and oxidized glutathione. The signal of C_β next to sulphur is shifted by 13 ppm to lower field whereas the signal of C_α is shifted by 3 ppm to higher field on transition from glutathione to its oxidized derivative.

A method utilizing ^{19}F n.m.r. as a tool for classifying thiols has been reported[275]. By the use of hexafluoroacetone (HFA) to introduce the probe group $\rangle C(CF_3)_2$, one obtains a ^{19}F n.m.r. signal corresponding to six atoms of fluorine per active hydrogen group. This method is consequently very sensitive, requiring only small quantities of the compounds to be examined. Adducts from thiols give bands which are effectively singlets because coupling of the $(CF_3)_2C\langle$ group to protons is small. Table 4 shows that the Δ' values (upfield chemical shifts in ppm relative to HFA) for primary and secondary thiols fall in the same range and hence are not distinguished by this method. The shielding effect of substituents near the thiol group affects as much as does the degree of substitution on the carbon to which —SH is attached. Hence even though a primary–secondary distinction cannot be made on the basis of Δ' for an unknown compound, it is often possible to detect closely related thiols separately

TABLE 4. Chemical shifts relative to hexafluoroacetone (HFA) for thiol adducts of HFA in ethyl acetate

	Δ′ (ppm)
1. Primary thiols	
Ethanethiol	0·95
Propane-1-thiol	0·92
Butane-1-thiol	0·93
2-Methylpropane-1-thiol	0·87
2-Mercaptoethanol (SH)	1·18
3-Mercaptopropanol (SH)	1·03
Ethyl thioglycolate	1·46
Toluene-α-thiol	0·68
2. Secondary thiols	
Propane-2-thiol	1·00
Butane-2-thiol	0·96
3. Tertiary thiols	
2-Methylpropane-2-thiol	1·51
4. Aromatic thiols	
Thiophenol	0·04

in a mixture because of different shielding effects and resulting different Δ′ values for each compound present. The Δ′ value for the single tertiary thiol which was tested is significantly larger than those for ordinary primary and secondary thiols. An unusually low Δ′ value is observed for thiophenol because of the downfield shift caused by the aromatic moiety.

Until recently all n.m.r. studies of sulphur compounds were indirect, i.e. the n.m.r. spectra were of neighbouring nuclei (^{1}H, ^{19}F, ^{13}C, etc.). While ^{32}S (natural abundance 99·24%) cannot be detected by n.m.r. due to its lack of nuclear spin, ^{33}S (natural abundance 0·76%) does have a nuclear spin ($I = \frac{3}{2}$). Although its sensitivity is only 0·226% that of ^{1}H, good environment-sensitive ^{33}S signals were reported for inorganic sulphur compounds[276]. The extension of this approach to thiols appears to be of interest.

D. *Electron Spin Resonance*

Free radicals produced by oxidation of thiols have long been considered of interest from the point of view of radiation damage and protection. Accordingly, a number of studies have been published discussing the nature of such sulphur radicals[273,277-287].

Thiols form free radicals of great stability when irradiated with γ- or x-rays or u.v. light in the solid state[277-282]. The e.s.r. spectra reported were broad lines, and had been assigned to various radical species with high

electron density on sulphur. The model of Kurita and Gordy[283], in which the electron density is concentrated in a nonbonding 3p orbital of the sulphur atom, accounted for the basic features.

Since the —SH group is a key functional group in a considerable number of biologically active polypeptides, the comparison of the behaviour of glutathione and free cysteine is of particular interest. In the case of x-ray irradiation of glutathione in the solid state the pattern at first resembles that of a mixture of the three amino acid components, cysteine, glutamic acid and glycine. However, unlike such a mixture, the spectrum due to glutathione alters with time until it closely resembles that of cysteine. These findings suggest that free radical centres are formed at each amino acid and then decay by migration to the —SH group[278]. The conclusion, which is supported by work with solid macromolecules[284, 285], is that this group is a preferred free radical trap.

In order to clarify whether the spectra obtained from the solid state reflect the nature of thiyl-free radicals in solution, several studies were undertaken[273, 286, 288]. In particular, as biological systems are usually in water at 37°C, it was felt that a systematic study of thiyl-free radicals in aqueous solution would give a better understanding of the significance of free radicals in biological processes[273]. In solution, although free radicals are not readily detected as they have only short half-lives, the e.s.r. spectra are similar to those obtained in the solid state. The important suggestion was made that in solution it will be possible to detect and identify the specific thiyl-free radical sites in proteins and their environment, whereas solid-state studies in general allow only gross identification of the presence or absence of sulphur-free radical sites.

X. CONCLUSION

We have above discussed the analytical techniques available for the identification and detection of thiols, as well as their spectroscopic characterization. The large number of methods which have been published over the years is perhaps the best indication of the technical difficulties that have been encountered. No single method has emerged which is superior to all others.

An instructive paper was recently published by Wenck and coworkers[288]. The authors made a comparative study of the most usual physico-chemical methods for the quantitative determination of —SH groups using compounds of different structure. Amperometric titration with $AgNO_3$, Ellman's and Boyer's (*p*CMB) methods, as well as potentiometric measurements were compared with respect to their applicability, reliability and susceptibility to interferences.

In Table 5 are reported the results of the analysis for the —SH content of a series of —SH-containing compounds using the four techniques mentioned above. Amperometric titration with $AgNO_3$ yields correct

TABLE 5. Comparative analysis for SH content. The results are presented as percentage, calculated on the basis of weighed amount of material taken as 100% (taken from Wenck and coworkers[288])

Compound	Potentio-metry	Ampero-metry	Boyer	Ellman
Glutathione	99·3	98·0	(100·0)[a]	(100·0)[a]
Mercaptosuccinic acid	99·3	96·6	99·0	100·0
Cysteine·HCl	99·0	139·0	101·0	99·0
Cysteamine·HCl	92·4	126·0	92·5	93·8
Cysteinamide·HCl	85·5	117·0	85·6	83·5
N-Acetylcysteine	95·5	92·6	96·3	98·6
N-Acetylcysteinamide	87·0	92·6	90·0	92·4
Homocysteine	97·0	112·0	98·0	100·0
4-Mercaptomethylimidazole·HCl	94·6	145·0	96·0	94·8
4-Mercaptoethylimidazole·HCl	99·2	133·0	99·5	101·5
1-Methyl-5-(2′-Mercaptoethyl)-imidazole·HCl	94·3	129·0	91·0	93·3
Cyclo-cysteinyl-glycine	97·0	96·5	96·0	99·3
N-Acetyl-cysteinyl-histidyl-aspartic acid	78·7	97·0	78·5	75·3
N-Acetyl-cysteinyl-γ-amino-butyryl-histidyl-γ-amino-butyryl-aspartic acid	88·7	103·8	88·5	87·4
2-Aminothiophenol·HCl	91·7	100·0	88·0	96·0
2-Mercaptoimidazole	97·2	142·5	—[b]	—[c]
1-Methyl-2-mercapto-4(5)-imidazolecarbonate methyl ester	94·4	—[d]	—[e]	—[c]
Ergothioneine	101·0	140·0	—[a]	—[c]
Glutathione + imidazole	—[b]	98·0	—[b]	—[b]

[a] Taken as standard.
[b] Not determined.
[c] No quantitative reaction.
[d] Not possible to calculate.
[e] Not soluble.

results only for certain types of compounds, since silver does not always combine in a 1 : 1 stoichiometry. Thiols which contain an additional amino or imidazole group bind additional silver. The Ellman's and Boyer's reagents give reliable results, but both require calibration by a

substance of known —SH content. Potentiometric measurement with the Ag/AgI electrode is a very suitable method for the determination of absolute —SH content, giving highly reproducible results for all the compounds tested.

XI. REFERENCES

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The Chemistry of the Thiol Group
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CHAPTER 6

The mass spectra of thiols

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I. INTRODUCTION

The mass spectra of thiols have often been compared to those of hydroxy compounds[1]. While there is much similarity, the differences are pronounced enough to warrant a special interest in the thiols. Yet, the effort

which has gone into research in this area is limited. Particularly lacking are theoretical discussions of thiol mass spectra from the point of view of the Quasi Equilibrium Theory (QET)[2], as well as experimental studies involving some of the more recently developed techniques, e.g. chemical ionization[3].

II. GENERAL CHARACTERISTICS OF THE MASS SPECTRA OF SH-COMPOUNDS

A. Aliphatic Thiols

The mass spectra of aliphatic thiols were obtained by Levy and Stahl[4] and correlations were found between the fragmentation pathways and the molecular structures. Haines and his coworkers[5–7] have also published the spectra of a number of other compounds of this type. A general characteristic is a fairly high abundance of the molecular ion (M^+) and the occurrence of an $M^+ + 2$ peak (due to ^{34}S) which allows easy identification of the molecular formula.

For the straight-chain primary thiols the molecular ion abundance lies between 4 and 100% of that of the base peak for carbon numbers up to C_{13} and the distinctive isotopic pattern of sulphur makes the presence of this element easily detectable. On the other hand, the base peaks especially for the higher members of the series are rarely due to the ions that contain sulphur but to the hydrocarbon fragments.

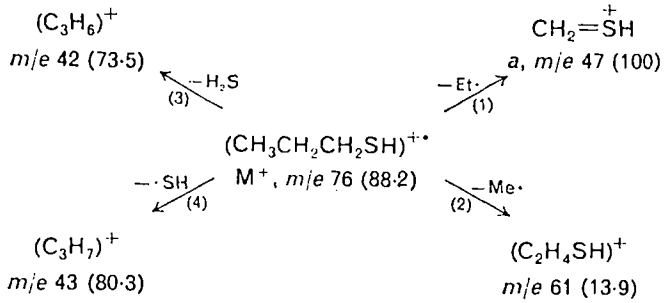


FIGURE 1. Proposed primary fragmentation reactions for n-C_3H_7SH; values in parentheses are intensities relative to base peak = 100.

A major decomposition path of the molecular ion is the α-cleavage (Figure 1, ion *a*, *m/e* 47), although other carbon—carbon bond cleavages occur as well, leaving in each case a sulphur-containing ionized fragment. Unfortunately secondary and tertiary thiols also give a rearrangement ion at *m/e* 47 which may be as large as 50% of the base peak abundance. The peak at *m/e* 61 is small in secondary and tertiary thiols, but the ion

formed by cleavage to lose the longest alkyl chain is large. The ratio of the intensities of the *m/e* 47 and 61 peaks remains remarkably constant at a value of about 2 for all primary straight-chain thiols greater than C_3 and this fact can be used for identification of such compounds.

Additional fragmentations involve H_2S elimination and a split off of the SH group. The various fragmentation reactions are exemplified for the case of n-C_3H_7SH, in Figure 1. The loss of H_2S results in the formation, in the case of primary thiols, of the olefinic ions at *m/e* M^+-34. This reaction is similar to that of primary alcohols which decompose to give M^+-H_2O ions. In the straight-chain C_4 thiol the elimination of H_2S produces the most abundant peak of the spectrum, but the intensity falls to about 5% of the base peak in the case of the C_{13} thiol. The mass spectra of secondary thiols contain more abundant peaks due to the loss of SH than of H_2S, in contrast to the behaviour of most of the primary thiols[4]. This phenomenon may be partly due to thermal effects[8].

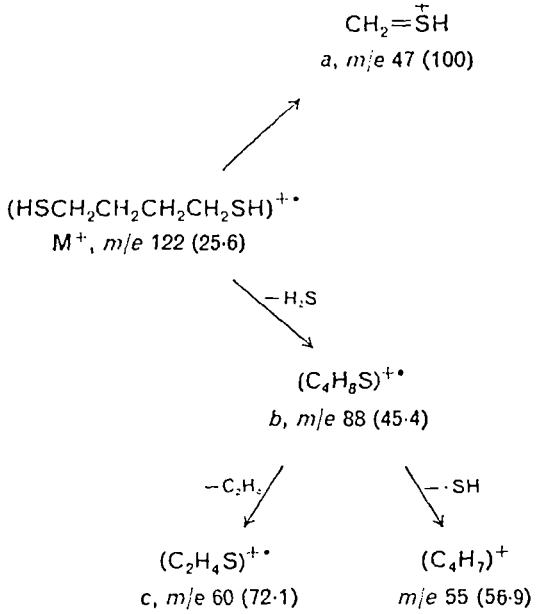


FIGURE 2. Proposed fragmentation scheme for 1,4-butanedithiol.

Deuterium-labelling experiments[8] have shown that contrary to the behaviour of alcohols, where the expulsion of H_2O takes place almost entirely *via* a 1,4-elimination, in the case of thiols 1,3-elimination of H_2S is almost as important as the 1,4-process. Other deuterium-labelling experiments[9] have shown that H atom eliminations from the methyl and

from the SH groups of CH_3SH take place at a 2 : 1 ratio (compared to a 6·7 : 1 ratio for the equivalent reactions in CH_3OH) and from the CH_2 versus the SH groups in the case of CH_3CH_2SH, at a ratio of 0·8 : 1.

Dithiols behave in a manner similar to thiols[10], as shown for 1,4-butanedithiol in Figure 2. The expulsion of ethylene, following H_2S elimination, is characteristic also of primary straight-chain monothiols[1(a),4].

B. Cycloaliphatic Thiols

Some spectra of cycloalkyl thiols were published in the A.P.I. catalogue of Mass Spectral Data[11]. These compounds yield a molecular ion of relatively great abundance as compared to those of corresponding alcohols. Among the spectra cited[11], the smallest M^+ peak is 26% of the base peak in the case of 1-methylcyclopentanethiol. The decomposition of this group of thiol compounds under electron bombardment is very similar to that of cycloalkyl alcohols, but the elimination of HS, H_2S and H_3S from the molecular ion proceeds more readily. The most abundant peak is due to the M^+-HS ion and its relative intensity is increased from 51% in the case of cis-2-methylcyclohexanethiol to 100% in 1-methyl-cyclopentanethiol.

The mass spectrometric behaviour of 17-oxoandrostane-3-thiols[12] is similar to that of the corresponding 3-hydroxy-steroids. Their spectra reveal the abundant molecular ion and M^+-H_2S peaks. There are no differences between mass spectra of 3α-SH and 3β-SH-steroid epimers of the androstane series[12].

C. Aliphatic Thiols with Additional Functional Groups

Mass spectra of thiols containing additional functional groups have been reported. That of 2-mercaptoethanol (Figure 3)[10,1(c)] deserves special attention in consideration of the relative influence of each functional group on the fragmentation pathway[13] (see section III). The intensity of the *m/e* 47 peak ($CH_2=\overset{+}{S}H$) is somewhat greater than that of the *m/e* 31 peak ($CH_2=\overset{+}{O}H$), but that may be partly due to reaction (9) (Figure 3)

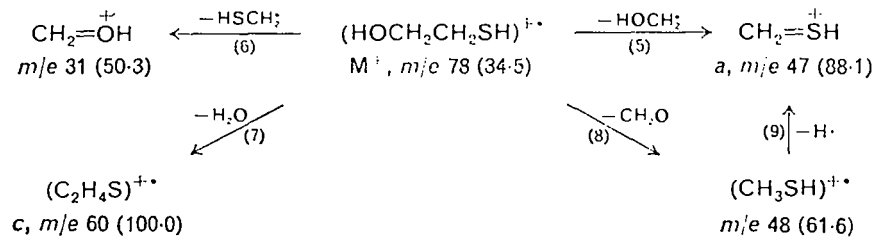


FIGURE 3. Proposed fragmentation scheme for 2-mercaptoethanol.

for which a 'metastable' ion has been observed[13]. Similar studies[14], at low ionizing energies, of bi-functional decanes, and in particular of 3-methoxy-8-mercaptodecane, have shown that nearly all fragments could be deduced from molecular ion species, ionized at one or the other functional group. Depending on the amount of the fragments produced by the ionization at the functional group it was possible to rank various substituents, according to their increasing influence on the fragmentation, as follows[14]:

$$COOH < Cl < Br < COOCH_3 < SH < CO < OCH_3 < I < SCH_3 < NHCOOCH_3 < NH_2 < NMe_2$$

In the mercaptoesters[15] of the general formula $HSCH_2COOR$, one of the most intense peaks is $(CH_2{=}SH)^{+\cdot}$(*a*) while in the secondary thiols, $CH_3CH(SH)COOR$, this shifts to $(CH_3CH{=}SH)^{+\cdot}$ (*d*, *m/e* 61). In each case these ions are formed by the elimination of $OR^{\cdot}$ followed by expulsion of CO. The McLafferty rearrangement produces an ion $(HSCH_2COOH)^{+\cdot}$ at *m/e* 92, while an elaborate skeletal rearrangement leads to formation of RS^+. The two proposed rearrangement mechanisms[15] are shown for $HSCH_2COOC_3H_7$ in Figure 4. The McLafferty rearrange-

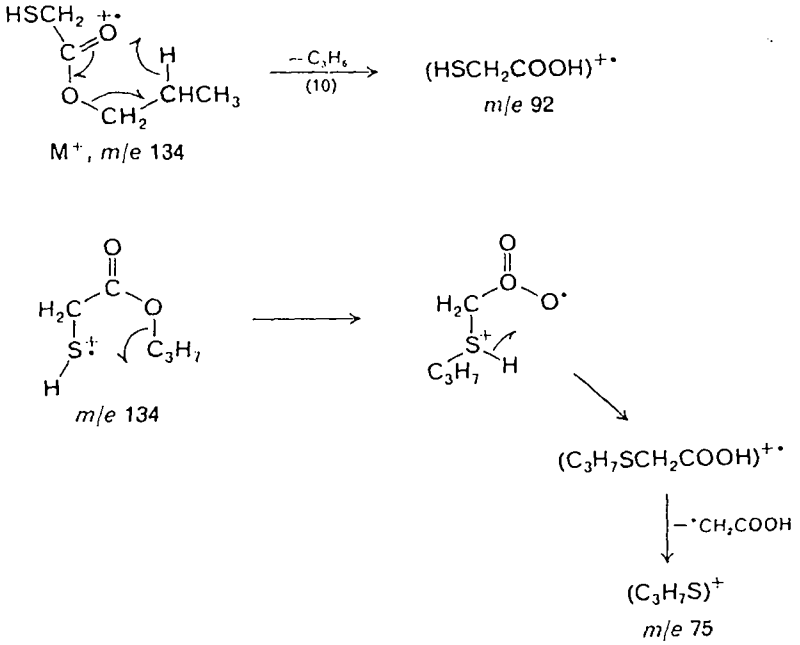


FIGURE 4. Proposed rearrangement reactions in *n*-propyl α-mercaptoacetate (reference 15).

ment (Figure 4, reaction 10) is peculiar in a way, since in acetates a similar reaction leads to the charged olefin and to the expulsion of neutral acetic acid[16]. The SH group apparently helps to retain the charge on the carbonyl-containing moiety, in the case of mercaptoesters.

D. Aromatic Thiols

Mass spectra of thiophenol, alkyl-substituted thiophenols, thiophenols with other functional groups in the nucleus, and thionaphthols have been determined[17]. Most of the major fragmentation reactions have been established by the metastable transitions. Those of thiophenol itself are shown in Figure 5. Deuterium labelling has demonstrated that over 50% of the H• atoms are eliminated from the SH group[1a].

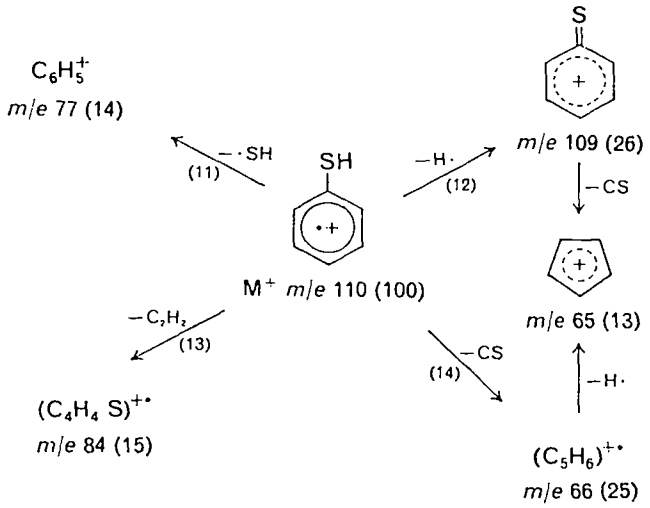
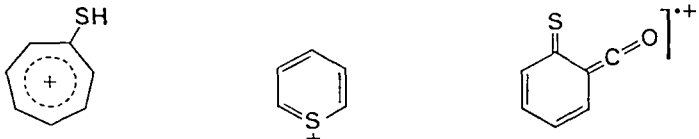


FIGURE 5. Fragmentations of thiophenol.

The spectra of thionaphthols and of aminothiophenols show a special feature, i.e. expulsion of a sulphur atom from the parent ion[17]. The driving force for this reaction is probably the formation of the stable naphthalene and aniline ions, respectively.

In the thiocresols the base peak is due to SH• elimination, since the stable tropylium ion, $C_7H_7^+$ (*m/e* 91) is formed, H atom elimination proceeds to a lesser extent, producing an SH-substituted tropylium ion, *e*[17]. The tropylium ion is also a base peak in benzyl mercaptan, H atom elimination being absent however[18].

In methoxythiophenols and aminothiophenols a $C_5H_5S^+$ ion appears[17], for which the thiopyrylium cation structure, *f*, has been proposed. In



e, *m/e* 123 *f*, *m/e* 97 *g*, *m/e* 136

methoxythiophenols this ion is formed by successive elimination of CH_3 and CO, while in the aminophenols it is formed by the successive elimination of H$^{\bullet}$ and HCN.

In thiosalicylic acid an 'ortho effect' is operating, and the facile elimination of water proceeds leading to the ion *g* [17].

E. Amino Acids and Peptides

The mass spectrum of cysteine can be easily obtained after either esterification of the carboxyl or acylation of the amino group both causing increased volatility. The spectrum of the cysteine ethyl ester has been reported by Biemann and coworkers[19], and some of its fragmentation reactions are shown in Figure 6. The major decomposition pathways of the

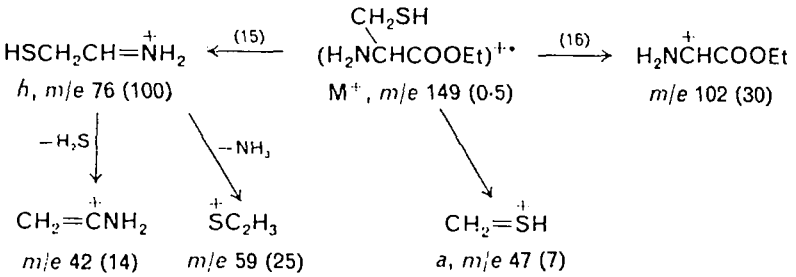
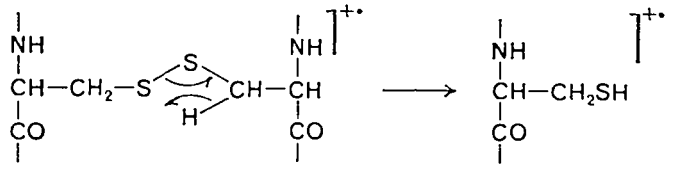


FIGURE 6. Some fragmentations of cysteine ethyl ester (reference 19).

molecular ion, reactions (15) and (16), are characteristic also of other amino acid ethyl esters, and produce the 'amino fragment' *h* (*m/e* 76) and the 'ester fragment' (*m/e* 102). The further elimination of H_2S from *h* is characteristic of cysteine, as is the ion *a*. Similar observations have been made in the case of the mass spectra of N-acetyl cysteine and of cysteine itself[20].

The mass spectrum of cysteine has also been studied using the field desorption method[20a]. It was found that both molecular (M^+) and protonated molecular ('quasimolecular') ($M^+ + 1$) ions are formed, the relative intensity being 50 and 100% respectively. In addition, above the 3% limit, only one fragment peak is present in the spectrum: $(M^+ + 1) - COOH_2$ which constitutes 15% of the base peak.

The mass spectra of esters of cystine-containing N-acyl peptides are actually those of the corresponding cysteine derivatives with unprotected SH groups. Under electron impact conditions, higher molecular weight compounds of this series do not form the molecular ion peak and very easily undergo S—S bond rupture accompanied by intramolecular transfer of a hydrogen[21,22].

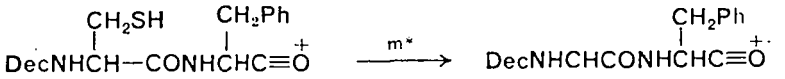


The cysteine peptides thus formed decompose further, under mass spectrometric conditions, according to 'the amino acid type' of fragmentation[22a]. This makes the determination of the amino acid sequence possible in cystine-containing peptides.

The transformation to the dehydroalanine residue is characteristic of the cysteine residue itself, as well as of the S-protected cysteine, the process being confirmed by a 'metastable' transition (m*).

$$\text{Decyl-Cys-Gly-OMe}]^{+\cdot} \xrightarrow{m^*} \text{Decyl-Ala-GlyOMe}(+H)]^{+\cdot}$$

Unlike the S-protected cysteine, the cysteine residue with a free mercapto group is prone to eliminate the side chain, the reaction being accompanied by migration of hydrogen. These rearrangements result in the formation of ions with *m/e* 46–48 mass units less than the mass numbers of the respective amino acid and aldimine fragments:



Therefore, the mass spectra of such peptides display a large number of additional peaks of which the most prominent are those due to the elimination of the entire side chain and to the transformation of cysteine (or cystine) to dehydroalanine residues. The general pattern of the mass spectrum becomes more complicated the larger the molecular weight of the peptide and, especially, the larger the number of its sulphur-containing amino acid residues. Moreover, the presence of cysteine (or cystine) residues greatly lowers the volatility of the compound leading to

considerable thermal destruction during the mass spectrometric determination. Finally, the presence of the sulphur-containing amino acids frequently leads to the absence of a number of sequence information peaks, which complicates still more the interpretation of the mass spectrum, limiting the applicability of the method.

Desulphurization considerably simplifies the mass spectrometric determination of the amino acid sequence of the sulphur-containing peptides, and at the same time extends the limits of the method[23]. It was found that quite good results can be obtained if the desulphurization is carried out in dimethyl-formamide solution at 20°C for 2 days in the presence of a tenfold amount by weight of the catalyst. Under such conditions cysteine (or S-substituted cysteine) residues are converted into alanine residue, while tryptophane, tyrosine, histidine, pyrimidylornithine and other amino acid residues are unaffected. It is convenient to use for desulphurization the N-acyl-peptide esters as they are much less absorbed by the Raney nickel than the free peptides, and the treatment of the reaction mixture is reduced to only filtration and evaporation, the product being suitable for mass spectrometry without purification. If the peptide contains an alanine residue as well as cysteine (or cystine) the Ni/Al alloy should be leached in D_2O so that the cysteine (cystine) residue is converted by the desulphurization process into deuterioalanine residue. It is also noteworthy that the temperature necessary to vaporize the desulphurized substance in the mass spectrometer is of about 100°C below that required for the sulphur-containing peptide[23].

F. Heterocyclic Thiols

Some of the fragmentation reactions already discussed occur in many heterocyclic thiols. Thus in 6-mercaptopurine, following the molecular ion peak, the next most intense peak is due to an SH elimination. This serves as proof that in the gas phase the molecule exists primarily as the mercapto tautomer, rather than in the thioketo form[24]. In 2-thenylthiol, the base peak is due to SH elimination[10] which leads to an ion at *m/e* 97, probably *-f*. The mass spectrum of 2-mercaptothiophen[25] differs slightly from that of thiophenol, the major difference being intensive elimination of H + CS which leads to an *m/e* 71 ion. The abundance of the latter is of about 90% of that of the molecular ion, which is, in turn, the base peak of the spectrum. Benzothiazole-2-thiol (Figure 7)[26] demonstrates the expulsion of a sulphur atom, previously encountered in thionaphthols, and of a CS group—characteristic also for thiophenols. In addition, the elimination of CS_2 becomes possible and important.

In the mass spectrum of 3-mercaptotetrahydropyran[27] the elimination of C-2 together with a SH group accompanied by ring contraction is the main feature. The molecular ion of 3-hydroxytetrahydropyran is decomposed in the same manner, but in the case of the 3-SH-analogue the peak due to this rearrangement is the most intense one in the spectrum.

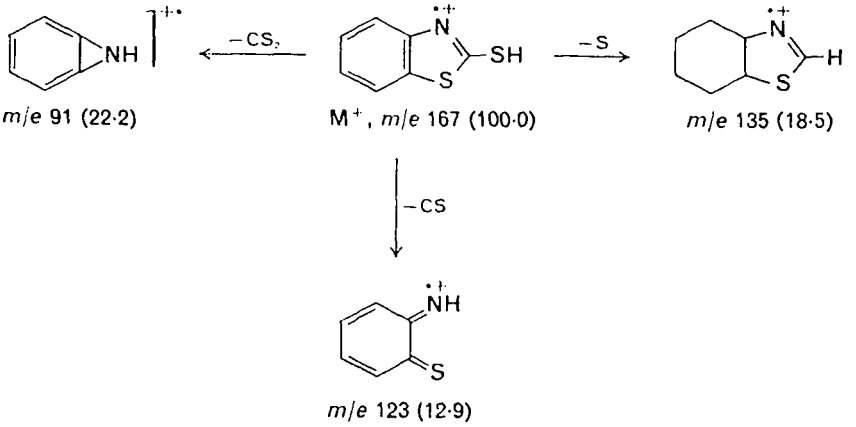


FIGURE 7. Fragmentation of benzothiazole-2-thiol.

III. ENERGETIC CONSIDERATIONS

A. Ionization Potentials: Charge Localization

The ionization potentials of the lower aliphatic thiols, thiolacetic acid and thiophenol have been determined by the very accurate method of photoionization[28] and are given in Table 1. The photoionization efficiency

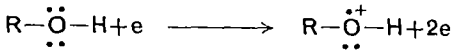
TABLE 1. Ionization Potentials (I.P.) of some thiols

Molecule	I.P. (eV)	ΔH_f (molecule ion) (kcal/mole)
Methanethiol	9·440 ± 0·005	212
Ethanethiol	9·285 ± 0·005	203
n-Propanethiol	9·195 ± 0·005	198
n-Butanethiol	9·14 ± 0·02	192
Thiolacetic acid	10·00 ± 0·02	—
Thiophenol	8·33 ± 0·01	217

curves of the aliphatic thiols rise sharply at threshold, indicating the coincidence of the vertical and adiabatic ionization potentials, i.e. the geometry of the ion in its electronic ground state is equal to that of the

molecule. This led to the conclusion of Watanabe and his coworkers[28], that the ionization involves the removal of one of the non-bonding electrons on the sulphur atom. The situation is quite different for aliphatic alcohols[28,29] where considerable vibrational structure has been observed in the ionization efficiency curves. This indicates extension of one or more of the bonds in the ion relative to the neutral molecule and shows that the electron removed has some bonding character.

It would thus seem that charge localization[30] which has been assumed for alcohols[31] as well as for thiols[1a] by writing the ionization processes as:



$$R-\ddot{O}-H+e \longrightarrow R-\ddot{O}^{+}-H+2e \qquad (17)$$

$$R-\ddot{S}-H+e \longrightarrow R-\ddot{S}^{+}-H+2e \qquad (18)$$

is considerably more justified for the thiols. This, in turn, is probably due to the fact that the ionization potential of the non-bonding electrons of sulphur is considerably lower than those of oxygen, and therefore also very much lower than the rest of the molecular electrons.

That the first Ionization Potential (I.P.) of CH_3SH corresponds to ionization of a lone-pair electron has recently[32a] been corroborated through the photoelectron spectrum of CH_3SH. In contrast to CH_3SH and to α-toluenethiol (benzylmercaptan), photoelectron spectroscopy has shown[32a] that the sulphur lone pair in thiophenol exhibits a considerable amount of π interaction with the benzene ring. The great advantage of photoelectron spectroscopy over photoionization and electron impact is the ease with which additional information concerning higher ionization potentials is obtained, i.e. those due to removal of more strongly bound electrons. In the case of CH_3SH the higher I.P.'s have been assigned and it has been shown[32a] that ionization occurs more readily from σ orbitals situated mainly in the C—S bond than the S—H bond.

The main features of the photoelectron spectra of aliphatic thiols appear also in the spectra of aliphatic alcohols[32b], but shifted to higher photon energies.

B. Appearance Potentials and Ionic Heats of Formation

Appearance potentials of ions from several simple thiols have been determined by electron impact methods[33-36]. They are represented in Table 2. These appearance potentials can be employed to calculate heats of formation of the product ions, e.g. for CH_2SH^+ from C_2H_5SH:

$$A.P.(CH_2SH^+)_{(C_2H_5SH)} = \Delta H_f(CH_2SH^+) + \Delta H_f(CH_3) - \Delta H_f(C_2H_5SH) \qquad (19)$$

TABLE 2. Appearance Potentials (A.P.) and heats of formation (ΔH_f) for ions from thiols

Ion	Source	A.P. (eV)	Neutral fragment	(ΔH_f) product ion, Kcal/mole	Reference
CHS^+	CH_3SH	15·8 ± 0·5	($H^\cdot + H_2$?)		33
$[CH_3S]^+$ [a]	CH_3SH	11·8 ± 0·05	$H^\cdot$	226	9
$[CH_3S]^+$ [a]	CH_3SH	11·2 ± 0·5	$H^\cdot$		33
CD_3S^+	CD_3SH	11·76 ± 0·1	$H^\cdot$	214	34
CD_2SH^+	CD_3SH	12·01 ± 0·1	$D^\cdot$	219	34
CH_2SH^+	C_2H_5SH	11·41 ± 0·1	$CH_3^\cdot$	220	34
CH_2SH^+	C_2H_5SH	11·3 ± 0·05	$CH_3^\cdot$	219	9
$C_2H_5^{+\cdot}$	C_2H_5SH	11·69	$SH^\cdot$	[b]	35
$[C_2H_5S]^+$ [a]	C_2H_5SH	11·5 ± 0·05	$H^\cdot$	203	9
$[C_2D_4SH]^+$ [a]	C_2D_5SH	11·85 ± 0·1	$D^\cdot$	210	34
CH_3CHSH^+	*iso*-C_3H_7SH	10·74 ± 0·1	$CH_3^\cdot$	197	34
n-$C_3H_7^+$	*n*-C_3H_7SH	11·12	$SH^\cdot$	[b]	35
t-$C_4H_9^+$	*t*-C_4H_9SH	9·96	$SH^\cdot$	[b]	35
CHS^+	C_6H_5SD	12·7 ± 0·2	*cyclo*-C_5H_4D ?	286	36
CDS^+	C_6H_5SD	12·7 ± 0·2	*cyclo*-C_5H_5 ?	286	36
cyclo-$C_5H_5D^+$	C_6H_5SD	11·9 ± 0·2	CS	[c]	36
$C_6H_5^+$	C_6H_5SD	13·3 ± 0·2	$SD^\cdot$	[c]	36
cyclo-$C_4H_4S^+$	C_6H_5SD	11·8 ± 0·2	C_2HD	232	36
cyclo-$C_4H_3DS^+$	C_6H_5SD	11·8 ± 0·2	C_2H_2	232	36
$C_6H_5S^+$	C_6H_5SD	12·2 ± 0·2	$D^\cdot$	254	36

[a] Exact structure of ion not specified.
[b] The appearance potential has been employed to calculate the heat of formation of the $SH^\cdot$ radical.
[c] The calculated heat of formation of the ion has served to prove the identity of the products.

therefore:

$$11.41 \times 23.063 \text{ kcal/mole} = \Delta H_f(CH_2SH^+) + 33.2 \text{ kcal/mole}^{37} - (-10.95 \text{ kcal/mole})^{37}$$

$$\Delta H_f(CH_2SH^+) = 219 \text{ kcal/mole}$$

The heats of formation of some of these sulphur-containing ions may be determined independently, by measuring the ionization potentials of the respective free radicals. The ionization potentials of the $SH^{\bullet}$, $CH_3S^{\bullet}$ and $C_6H_5S^{\bullet}$ free radicals have been determined[38]. The heats of formation of CH_3S^+ and $C_6H_5S^+$ thus obtained are in good agreement[39] with those listed in Table 2. Additional thermochemical information has been obtained from appearance potentials of sulphur-containing ions from sulphides[34,40-42]. The 'best' ionic heats of formation are listed in the NBS tables[39].

The heats of formation of the parent thiol ions are, of course, obtained directly from the ionization potentials of the thiols and from knowledge of the heats of formation of the neutral molecules. The ones which are known[39] are included in Table 1. The calculation is, e.g. for CH_3SH^+:

$$\begin{aligned}\Delta H_f(CH_3SH^+) &= \Delta H_f(CH_3SH) + \text{I.P.}(CH_3SH) \\ &= -5.34 \text{ kcal/mole}^{37} + 9.44 \times 23.063 \text{ kcal/mole} \\ &= 212.4 \text{ kcal/mole} \end{aligned} \quad (20)$$

C. *Structures of Sulphur-containing Ions*

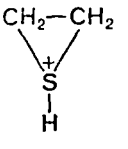
It has been assumed until now that the ion $m/e = 47$, having the elementary formula: $[CH_3S]^+$, has the structure *a*,

$CH_2{=}\overset{+}{S}H$ (*a*) $\qquad$ CH_3S^+ (*i*)

while, in fact, it could have either one of the two structures *a* or *i*. Similarly, the ion $m/e = 61$ having the composition $[C_2H_5S]^+$ may have five alternative structures:[34,9]

$[CH_3CH{=}SH]^+$ (*j*) $\qquad$ $[CH_3CH_2{-}S]^+$ (*k*) $\qquad$ $[CH_3S{=}CH_2]^+$ (*l*)

$[CH_2CH_2SH]^+$ (*m*)



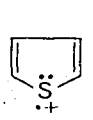
(*n*)

Deuterium-labelling experiments[34,9] have indicated the initial formation of *a*, as well as *i*, from CH_3SH, and the initial formation of *j*, as well as *k*, from CH_3CH_2SH. This does not mean that the ions, once formed, do not isomerize to a different structure; actually all ions of the same elementary composition may rearrange to give the same ('stable') structure. The heats of formation of ions *a* and *i* are very similar (in fact equal within the error limits of the experiments), being 220 kcal/mole and 214 kcal/mole, respectively[34] (Table 2). The same holds for the ions *j* and *k*, which have heats of formation of 197 kcal/mole and 202 kcal/mole respectively[34] (Table 2). The situation is quite different for the analogous oxygen-containing ions, where $CH_2{=}OH^+$ is much more stable than $CH_3{-}O^+$ and $[CH_3CH{=}OH]^+$ is in turn more stable than $[CH_3CH_2{-}O]^+$.

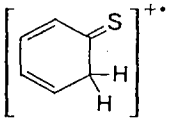
The near equality of the heats of formation of isomeric sulphur-containing ions makes it uncertain that the ions do, in fact, have the structure predicted from the structure of the neutral molecule[34,9]. On the other hand, identity of heats of formation does not prove that all ions have the same structure[34].

Assuming that ions having different structures will react differently with the same neutral molecule, one can determine ion structures by the technique of Ion Cyclotron Resonance (i.c.r.), for example[43]. Alternatively, isomeric ions should react differently via unimolecular decompositions. Thus, the oxygenated ions, analogous to $j \rightarrow n$, have been differentiated by Shannon and McLafferty[44], through their 'pure metastable' spectra.

Elucidation of the structures of sulphur-containing ions has to await the employment of either the i.c.r. or the metastable ion characterization technique.

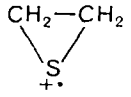


o, *m/e*=84



p

q



r

Derived ionic heats of formation have nevertheless been taken as proof for or against certain ionic structures. The ion $C_4H_4S^+$ from thiophenol, Figure 5, has a heat of formation[36] (Table 2) equal to that of the thiophene molecule ion[39]. It has thus been assumed[36] to have the cyclic structure, *o*. The ion $CH_4S^{+\bullet}$ formed by C_2H_4 elimination from $C_2H_5SCH_3$ has a derived heat of formation equal to that obtained by direct ionization of methyl mercaptan[34]. On the other hand, the ion $C_6H_6S^+$ formed by elimination of ethylene from ethylthiobenzene has a derived heat of formation[45] which

is in excess of the one obtained by direct ionization of thiophenol (Table 1) by about 30 kcal/mole. This has been taken as proof[45] for the formation of a thioketonic structure, *p*, from alkylthiobenzenes. Alternatively, the excess energy may be considered to be an energy of reorganization within the ethylene molecule, the ion still having the thiophenol, $C_6H_5\overset{\bullet+}{S}H$, structure[42]. It is interesting to speculate on the structures of some of the previously mentioned ions. For example, ion *b* (Figure 2) might have the tetrahydrothiophene ion structure, *q*, in which case ion *c* (Figure 2) might be the ethylene sulphide ion, *r*. There is no thermochemical evidence to corroborate this assumption.

D. Bond Energies

Ionic appearance potentials are very helpful for the determination of bond energies. For example, from the appearance potential of R^+ in RX, and knowing the ionization potential of the radical $R^\bullet$, one obtains the R—X bond energy:

$$D(R{-}X) = A.P.(R^+)_{RX} - I.P.(R^\bullet) \tag{21}$$

Thus, for methanethiol

$$\begin{aligned} D(CH_3S{-}H) &= A.P.(CH_3S^+)_{CH_3SH} - I.P.(CH_3S^\bullet) \\ &= 11{\cdot}76 \pm 0{\cdot}1 \text{ eV} - 8{\cdot}06 \pm 0{\cdot}1 \text{ eV} \\ &= 3{\cdot}7 \pm 0{\cdot}2 \text{ eV} \\ &= 85{\cdot}3 \pm 4{\cdot}6 \text{ kcal/mole} \end{aligned} \tag{22}$$

(from references 34, 38 and Table 1—neglecting deuterium isotope effects). On the other hand, the bond energy in the molecule-ion is

$$D(R^+{-}X) = A.P.(R^+)_{RX} - I.P.(RX) \tag{23}$$

which gives for methanethiol[31], $D(CH_3S^+{-}H) = 51$ kcal/mole. (These calculations assume that the products R^+ and $X^\bullet$ are formed in their electronic and vibrational ground states, without translational energy.)

The bond dissociation energy $D(CH_3{-}SH)$ has been determined in the following manner[38]:

The appearance potential of HS^+ from H_2S, via:

$$H_2S + e \longrightarrow HS^+ + H + 2\,e \tag{24}$$

is $A.P.(HS^+)_{H_2S} = 14{\cdot}43 \pm 0{\cdot}1$ eV. Therefore,

$$\begin{aligned} A.P.(HS^+) &= \Delta H_f(HS^+) + \Delta H_f(H) - \Delta H_f(H_2S) \\ 14{\cdot}43 \times 23{\cdot}06 \text{ kcal/mole} &= \Delta H_f(HS^+) + 52{\cdot}1 \text{ kcal/mole} - (-4{\cdot}82 \text{ kcal/mole}) \\ \Delta H_f(HS^+) &= 275{\cdot}9 \text{ kcal/mole} \end{aligned} \tag{25}$$

The ionization potential of the $SH^{\bullet}$ radical is I.P.$(HS^{\bullet}) = 10{\cdot}50 \pm 0{\cdot}1$ eV. Therefore,

$$\begin{aligned}\Delta H_f(SH^{\bullet}) &= \Delta H_f(SH^+) - \text{I.P.}(SH^{\bullet}) \\ &= 275{\cdot}9 \text{ kcal/mole} - 10.5 \times 23{\cdot}06 \text{ kcal/mole} \\ &= 33{\cdot}7 \text{ kcal/mole} \end{aligned} \tag{26}$$

Finally,

$$\begin{aligned}D(CH_3-SH) &= \Delta H_f(CH_3^{\bullet}) + \Delta H_f(SH^{\bullet}) - \Delta H_f(CH_3SH) \\ &= 32{\cdot}5 + 33{\cdot}7 - (-5{\cdot}4) \\ &= 71{\cdot}6 \text{ kcal/mole} \end{aligned} \tag{27}$$

Another bond dissociation energy in the methanethiol molecule-ion, which has been calculated[34] on the basis of equation (23), is $D(HSCH_2^+-H) = 57$ kcal/mole. This has been noted to be higher than most $D(XCH_2^+-H)$ bond energies[34,13], where $X \equiv OH$, NH_2, Cl or H. It would seem[34,1c] that sulphur is less effective in resonance stabilizing the structure $CH_2{=}X^+$ than are oxygen or nitrogen, for example.

E. Activation Energies and Fragmentation Pathways

According to the QET[2] the ions which comprise a mass spectrum are formed in a series of competitive and consecutive unimolecular reactions originating from the molecular ion. Consequently the abundance of any given fragment ion is determined by the relative rate of the reaction forming the ion and the rates of the reactions leading to further decomposition. These reaction rates depend, to a large extent, on the respective activation energies. To a first approximation, the activation energy is equal to the endothermicity of the reaction[2]. (This is certainly true for simple bond cleavages; in rearrangement reactions with a higher energy transition state there will be an additional contribution from the 'back activation energy'). Thus while there are no quantitative discussions available concerning the fragmentations of thiols, qualitative comparisons with the QET are possible, on the basis of the above acquired thermochemical information.

Harrison and coworkers[13] have shown that for competing fragmentation reactions (26a) and (26b), the relative abundances of $[R^1]^+$ and $[R^2]^+$ are

$$R^1R^2 \longrightarrow [R^1R^2]^+ \begin{cases} \nearrow [R^1]^+ + R^{2\bullet} & (26a) \\ \searrow [R^2]^+ + R^{1\bullet} & (26b) \end{cases}$$

determined by the relative values of the ionization potentials of the corresponding radicals $R^{1\bullet}$ and $R^{2\bullet}$. Since:

$$E_a(26a) = \text{I.P.}(R^1) + D(R^1-R^2) - \text{I.P.}(R^1R^2) \quad (27)$$

$$E_a(26b) = \text{I.P.}(R^2) + D(R^1-R^2) - \text{I.P.}(R^1R^2) \quad (28)$$

the activation energies, E_a for the two competing reactions, differ only by the ionization potentials of the radicals. The ionization potentials of $^{\bullet}CH_2SH$ and $^{\bullet}CH_2OH$ are almost equal[13], so that the relative intensities due to reactions (5) and (6) (Figure 3) in 2-mercaptoethanol are about equal, particularly at low ionizing voltages, when reaction (9) is not contributing to the formation of *a*.

Keyes and Harrison[34] have compared the energetics of ion formation and fragmentation in sulphur and oxygen compounds. In CH_3SH^+ and $C_2H_5SH^+$, the activation energies of S—H cleavage are only slightly lower than that for cleavage of an α C—H bond. Thus the two fragmentations should be competitive according to the QET and indeed they are (section II.A and references 9 and 34). On the other hand, the activation energies of O—H cleavage in CH_3OH^+ and $C_2H_5OH^+$ are considerably higher than those for an α cleavage. Since the rate of fragmentation strongly decreases with increasing activation energy, one would expect, according to the QET, only minor abundances of ions such as CH_3O^+ and $C_2H_5O^+$, and this is in agreement with the observed spectra[34].

Thermochemically derived activation energies also explain the observation that the parent ions of mercaptans are of greater abundance than the parent ions of the corresponding alcohols[34]. Figure 8 shows the situation in terms of the QET. The molecular ions are formed under electron impact

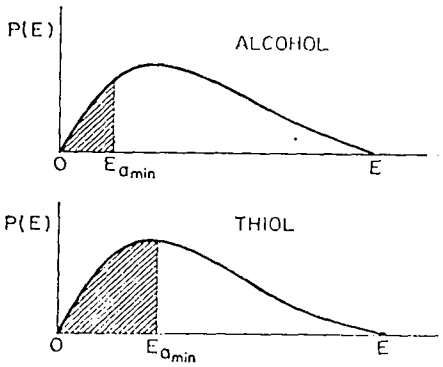


FIGURE 8. Hypothetical internal energy distributions (fraction of the parent-precursor ion with a particular internal energy content vs. energy) for an aliphatic alcohol and the analogous thiol.

with a distribution of internal energies. $P(E)$ gives, qualitatively, the fraction of molecule-ions formed with a certain internal energy E, as a function of E. $E = 0$ corresponds to the adiabatic ionization potential of the molecule, where the molecule ion is formed in its ground vibrational state. Now, as long as the internal energy E is lower than the lowest activation energy of any of the fragmentation reactions, $E_{a\,min}$ of the parent ion, the parent ion will not dissociate[46]. The relative intensity of the parent ion in the mass spectrum is thus obtained by the ratio of the shaded area underneath the $P(E)$ curve to the total area. Assuming that the $P(E)$ curves for a certain thiol and the corresponding alcohol are rather similar*, a change in the relative abundance of the parent ions is affected, by a shift in the lowest activation energy for fragmentation. For the alcohols, CH_3OH and C_2H_5OH, the lowest energy fragmentation is α cleavage, with an activation energy of 26 and 12 kcal/mole, respectively[34]. For the thiols, CH_3SH and C_2H_5SH, both α cleavage and cleavage of the bond to sulphur have approximately the same activation energy; however, this activation energy is in the range 45–57 kcal/mole[34], i.e. considerably higher than for the oxygen analogues.

The above observations probably hold qualitatively also for the higher homologues of the aliphatic thiols, although new fragmentations set in, in particular H_2S elimination (Figure 1).

The activation energies for reactions (1–4), in *n*-propanethiol, may be calculated on the basis of available thermochemical information[34,39] (Tables 1 and 2), as follows:

$$\begin{aligned}
E_a(1) &= \Delta H_f(CH_3S^+) + \Delta H_f(C_2H_5) - \Delta H_f(C_3H_7SH^+) \\
&= 218 + 25 - 198 = 45 \text{ kcal/mole} \\
E_a(2) &= \Delta H_f(C_2H_5S^+) + \Delta H_f(CH_3) - \Delta H_f(C_3H_7SH^+) \\
&\geqslant 210 + 33{\cdot}2 - 198 \geqslant 45 \text{ kcal/mole}\dagger \\
E_a(3) &= \Delta H_f(C_3H_6^+) + \Delta H_f(H_2S) - \Delta H_f(C_3H_7SH^+) \\
&= 229 - 4{\cdot}9 - 198 = 26{\cdot}1 \text{ kcal/mole} \\
E_a(4) &= \Delta H_f(C_3H_7^+) + \Delta H_f(HS) - \Delta H_f(C_3H_7SH^+) \\
&= 209 + 34{\cdot}1 - 198 = 45{\cdot}1 \text{ kcal/mole}
\end{aligned} \tag{29}$$

* These will probably be compared eventually in a more quantitative way, e.g. from energy deposition functions obtained from photoelectron spectroscopy[16]. The available photoelectron spectra[32] for ethanol and ethanethiol indicate that the $P(E)$ curves for these two molecules might indeed be very similar.

† The inequality sign is due to the uncertainty in the structure and heat of formation of $[C_2H_5S]^+$.

The calculated value $E_a(4)$ may be checked against the experimental value (Tables 1 and 2):

$$E_a(4) = \text{A.P.}(C_3H_7^+)_{n\text{-}C_3H_7SH} - \text{I.P.}(n\text{-}C_3H_7SH) =$$
$$= \quad 11{\cdot}12 \quad - \quad 9{\cdot}195 \quad = 1{\cdot}925 \text{ eV}$$
$$= 44{\cdot}4 \text{ kcal/mole} \qquad (30)$$

All activation energies for the primary reactions in *n*-propanethiol are still fairly high, which explains the relatively high parent-ion intensity (Figure 1). Those for reactions (1), (2) and (4) are comparable, which explains why the reactions are compatible. $E_a(3)$, for the H_2S elimination is considerably lower than the rest. This is in keeping with the observation that H_2S elimination is the major reaction for aliphatic thiols at low ionizing electron energies[1a]. The other reactions, which are simple bond ruptures, prevail in relative abundance at high ionizing energies over the H_2S elimination, which is a rearrangement reaction. This is expected, on the basis of the QET[46,47]. The rate constants for simple cleavage reactions rise faster with internal energy, E of the precursor ion, than do rearrangement reactions. There is, thus a certain internal energy at which the

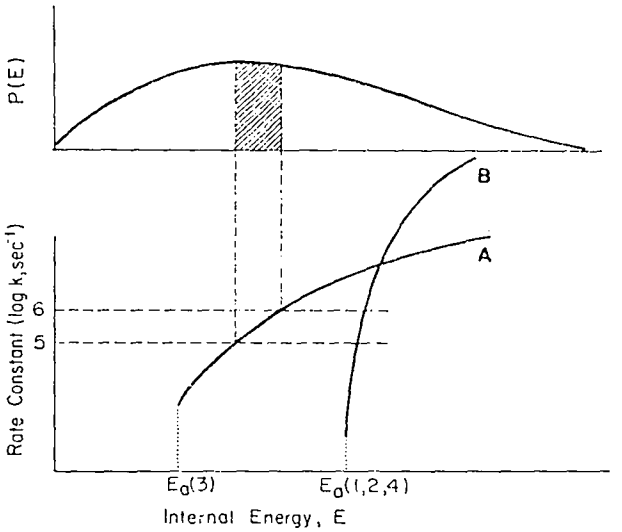


FIGURE 9. Lower curves: rates of two hypothetical unimolecular reactions as a function of internal energy of the precursor ions: A is a rearrangement, e.g. reaction (3) in *n*-C_3H_7SH, while B is a bond cleavage, e.g. any of the reactions (1), (2) or (4) in *n*-C_3H_7SH; upper curve: internal energy distribution in the precursor ions, i.e. fraction of the precursor ions with a particular internal energy content vs. energy. Adapted from ref. 47; the ratio of the shaded area to the total area underneath the P(E) curve, gives the relative abundance of the metastable ion, for reaction A, in the mass spectrum.

curves for $k(E)$ of two such reactions, e.g. (3) and (4), cross. Abundant metastable ions are expected only for the rearrangement reaction which possesses, on the one hand, the lowest activation energy, and for which, on the other hand, $k(E)$ rises slowly with E. The low activation energy ensures that in the range of rate constants characteristic for metastable ion formation, i.e. 10^5–10^6 s^{-1}, no competing fast reaction takes place in the ion-source. The slow rise of $k(E)$ ensures that a large portion of the $P(E)$ curve is covered in the range of energies E, for which $10^5 \leqslant k(E) \leqslant 10^6$ s^{-1}. This situation is exactly met by the H_2S elimination (Figure 9) in aliphatic thiols[47] and a strong metastable is observed ([metastable]/[daughter] = 0·76% in 1-heptanethiol).

IV. NEGATIVE IONS; DISSOCIATIVE ELECTRON CAPTURE PROCESSES AND ENERGETIC CONSIDERATIONS

The sulphur atom, as well as the SH· radical, possess high positive electron affinities of 2·077 eV[48] and 2·32 eV[49], respectively. It is thus not surprising that dissociative electron capture processes, e.g.

$$AB + e \longrightarrow A^- + B \tag{31}$$

are observed for thiols, where the negative charge resides on the sulphur-containing moiety. Dissociative electron capture processes are resonance processes, i.e. occur at discrete, well-defined energies or groups of energies. Thus, in order to observe them, the electron energy has normally to be in the range 0–10 eV. Generally also, the resonance peak maxima of the various negative ions from a certain molecule do not necessarily occur at the same energy and a certain negative ion may demonstrate several resonance peak maxima in its ionization efficiency curve. Such processes have been studied mass spectrometrically in methanethiol, thiophenol, benzylmercaptan and allylmercaptan[50]. Appearance potentials were determined for the various processes, and so have the energy positions and the relative intensities of the resonance maxima.

In methanethiol, the ions CH_3S^-, CH_2S^-, HS^- and S^- have been observed[50]. The ion of highest abundance and lowest appearance potential is CH_2S^-, via the process:

$$CH_3SH + e \longrightarrow CH_2S^- + H_2, \quad \text{A.P.} = 0{\cdot}33 \text{ eV} \tag{32}$$

Two maxima were observed in the ionization efficiency curve for CH_3S^- from CH_3SH, both were ascribed to

$$CH_3SH + e \longrightarrow CH_3S^- + H, \quad \text{A.P.} = 0{\cdot}58 \text{ eV} \tag{33}$$

The appearance potential of 0·58 eV, for the first resonance peak corresponds presumably to the formation of the products without excess energy. This can serve to estimate the electron affinity of the $CH_3S^{\bullet}$ radical, E.A.(CH_3S), as follows:

$$A.P.(CH_3S^-) = D(CH_3S{-}H) - E.A.(CH_3S) \quad (34)$$

We have already obtained $D(CH_3S{-}H) = 85{\cdot}3$ kcal/mole = 3·7 eV (section III.D), therefore:

$$0{\cdot}58 = 3{\cdot}7 - E.A.(CH_3S) \quad (35)$$

$$E.A.(CH_3S) = 3{\cdot}1 \text{ eV}$$

This value, as has been noted[50], seems rather high, in comparison with the electron affinities of the S and SH radicals, mentioned above.

The ions observed in thiophenol are[50]: $C_6H_5S^-$, SH^- and S^-. The ionization efficiency curve of $C_6H_5S^-$ is reproduced in Figure 10.

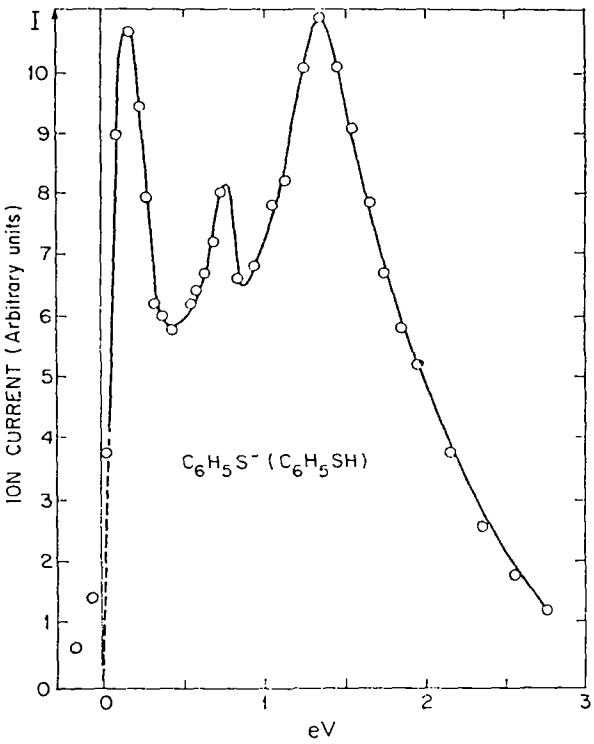


FIGURE 10. Ionization efficiency curve for $C_6H_5S^-$ from thiophenol: ion current (I) vs. electron energy; three resonance capture maxima are observed, all due to: $C_6H_5SH + e \rightarrow C_6H_6S^- + H$ with varying amount of internal excitation of the products (adapted from ref. 50).

In benzyl mercaptan the proposed reactions are[50]

$$C_6H_5CH_2SH+e \longrightarrow C_6H_5CH_2S^-+H \qquad (36)$$

(deuterium labelling has indicated that the H is lost from the SH group)

$$C_6H_5CH_2SH+e \begin{cases} \longrightarrow C_6H_5CHS^-+H_2 \\ \longrightarrow C_6H_5S^-+CH_3 \\ \longrightarrow C_3H_5S^-+? \\ \longrightarrow SH^-+C_6H_5CH_2 \\ \longrightarrow S^-+? \end{cases}$$

Similarly in allyl mercaptan[50],

$$CH_2{=}CHCH_2SH+e \begin{cases} \longrightarrow CH_2{=}CH{-}CH_2S^-+H \\ \longrightarrow CH_2{=}CH{-}CH{-}S^-+H_2 \\ \longrightarrow CH_3S^-+C_2H_3 \\ \longrightarrow CH_2S^-+C_2H_4 \\ \longrightarrow SH^-+CH_2{=}CH{-}CH_2 \\ \longrightarrow S^-+? \end{cases} \qquad (37)$$

It thus seems that H_2 elimination, following electron capture, becomes possible for those molecules which have a $-CH_2-$ group α to the SH. SH^- formation is an abundant process in benzyl mercaptan and allyl mercaptan, where the radical formed is stabilized by resonance. In both of these molecules one also observes skeletal rearrangements (at low yield).

V. ION-MOLECULE REACTIONS

Reactions between ions P^+ and molecules M, in the gas phase[51]:

$$P^+ + M \longrightarrow S^+ + N \qquad (38)$$

are of great interest. They have an important contribution to the understanding of basic chemical kinetics and chemical dynamics; their analytical applications are useful in molecular and ionic structure determinations through chemical ionization[3] and i.c.r. work[43]. Moreover, they can be said to open up a whole new ion-chemistry in the gas phase, devoid of interferences of solvents.

Due to the high rate constants[51] of those ion-molecule reactions which are exothermic, they take place within the ion-source of an ordinary mass spectrometer, even at fairly low pressures of $\sim 10^{-4}$ mm Hg. In order to

observe large percentage conversions of primary ions P^+ to secondary ions S^+, and in particular, in order to observe consecutive reactions, a special high-pressure ion source has to be employed.

A. Reactions of Positive Ions

Reactions of positive ions were studied in CH_3SH[33,52] and CD_3SH[52] in the pressure range 10^{-3}–10^{-1} mm Hg.

One of the most common ion-molecule reactions is proton transfer. Both the parent CH_3SH^+ ion (reaction 39) as well as the two forms CH_3S^+ and $CH_2{=}SH^+$ of the fragment CSH_3^+ were observed[52] to react *via* proton transfer with CH_3SH:

$$CH_3SH^+ + CH_3SH \longrightarrow CH_3SH_2^+ + CSH_3 \qquad (39)$$

$$\left.\begin{matrix} CH_2{=}SH^+ + CH_3SH\ (a) \\ CH_3S^+ + CH_3SH\ (b) \end{matrix}\right\} \longrightarrow CH_3SH_2^+ + CH_2S \qquad (40)$$

Deuterium-labelling experiments have indicated[52] that in reaction (39) the mercaptyl hydrogen is transferred approximately 35 times more readily than the methyl hydrogen and that in reaction (40a) with CD_2SH^+ the mercaptyl hydrogen is exclusively transferred. This, in effect, constitutes proof for the formation of structure *a*, without subsequent isomerization or hydrogen scrambling.

Under otherwise ordinary ion-source conditions, at elevated (20–40 μ) pressure, the protonated methanethiol ion, $CH_3SH_2^+$, constitutes about 90% of the total ionization[33,52]. At still higher pressures, two additional major ions appear, namely: $C_2H_5S^+$ and $C_2H_9S_2^+$. The former is absent at low ionizing electron energies, where the parent CH_3SH^+ is the only primary ion present[52]. It may be formed *via*[33]

$$CH_3S^+ + CH_3SH \longrightarrow C_2H_5S^+ + H_2S \qquad (41)$$

While $CH_3SH_2^+$ is a monosolvated proton, the ion $C_2H_9S_2^+$ is essentially a disolvated proton $(CH_3SH)_2H^+$. It is formed *via* a consecutive reaction of $CH_3SH_2^+$[33]:

$$CH_3SH_2^+ + CH_3SH \longrightarrow C_2H_9S_2^+ \qquad (42)$$

Most of the fragment ions of low abundance also react with methanethiol[33] eventually to produce $CH_3SH_2^+$. Some of them, e.g. HS^+, CHS^+, do so directly:

$$HS^+ + CH_3SH \longrightarrow CH_3SH_2^+ + S \qquad (43)$$

while others, e.g. S^+, react first via charge-transfer—another very common form of ion-molecule reactions:

$$S^+ + CH_3SH \longrightarrow CH_3SH^+ + S \qquad (44)$$

The product methanethiol ion, of the charge transfer step then reacts further (reaction 39) to produce the protonated methanethiol.

The relative concentrations of some ions in CH_3SH as a function of CH_3SH pressure are reproduced in Figure 11 from reference 33.

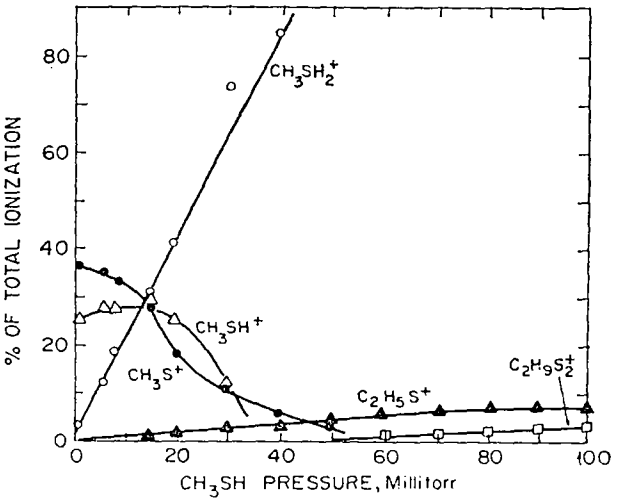


FIGURE 11. Relative concentrations of some ions in CH_3SH as a function of CH_3SH pressure (adapted from ref. 33).

B. Reaction Rate Constants

Reaction rate constants for ion-molecule reactions are normally expressed in units of cc/molecule·sec (these are easily converted to units of litre/mole·sec by multiplication by Avogadro's number and division by 1000). The reaction rate law for a typical ion-molecule reaction, e.g. (38) is

$$\frac{dI_{p^+}}{dt} = -kI_{p^+}[M] \qquad (45)$$

where I_{p^+} is the current of the primary ions measured at the ion collector (which is proportional to the concentration of P^+ in the ion source), k is the bimolecular rate constant for the disappearance of the primary ions and [M] is the concentration of neutral molecules in the ion-source (which

is proportional to the pressure of the reactant gas). Equation (45) may be integrated as a pseudo-first-order reaction to give[33]

$$\ln I_{p+} = -kt[M] + \ln I^0_{p+} \tag{46}$$

Primary ions are formed at the electron beam and they react on their way out towards the exit slit of the ion-source. The time, t, spent in the reaction chamber is given by[33]

$$t = \left(\frac{2dm}{Ee}\right)^{\frac{1}{2}} \tag{47}$$

where d is the distance from the ionizing electron beam to the exit hole of the source, E the field strength within the source, and m and e the mass and charge, respectively, on the ion*. For a given ion and field strength, t is fixed. The rate constant, k, can then be determined from the slope of a semi-logarithmic plot of the normalized primary ion intensities versus pressure (normalized intensities, i.e. $I_{p+}/\sum I$ are employed to take into account possible variations in collection efficiency with pressure).

Disappearance rate constants for CH_3SH^+ and CSH_3^+ (reactions 39 and 40) were thus obtained[52] at 10 eV nominal electron energy and 3·4 eV ion exit energy (the energy acquired up to the exit slit of the ion source, due to the existing field, E): $k_{39} = 11{\cdot}9 \pm 0{\cdot}6 \times 10^{-10}$ cc/molecule·sec and $k_{40} = 10{\cdot}4 \pm 0{\cdot}3 \times 10^{-10}$ cc/molecule·sec. These high rate constants are typical of exothermic ion-molecule reactions, which have no potential energy barrier, and take place at every close collision of the reaction partners. They thus reflect the collision rate, which is high in view of the strong, long-range, ion-induced dipole interaction[51, 53].

C. Reactions of Negative Ions

The following negative ion-molecule reactions[54] were postulated to occur in CH_3SH at 16 μ pressure in the ion-source of a time-of-flight mass spectrometer:

$$S^- + CH_3SH \longrightarrow CH_3S^- + HS \tag{48}$$

$$CH_3S^- + CH_3SH \longrightarrow HS^- + CH_3SCH_3 \tag{49}$$

$$S^- + CH_3SH \longrightarrow HS^- + CH_3S \tag{50}$$

It was difficult to establish the occurrence of these reactions with certainty, since the product ions are also formed by direct electron impact on CH_3SH. On the other hand, the occurrence of

$$CN^- + CH_3SH \longrightarrow SCN^- + CH_4 \tag{51}$$

was established[54] in a mixture of CH_3SH and ClCN.

* $d = \frac{1}{2}at^2$ where a is the acceleration; $eE = ma$.

These experiments suffer from the fact that they were carried out in a single ion-source. Much more information may be obtained, and the ambiguity concerning the identity of reactant and product ions may be removed, when a tandem mass spectrometer is employed[51,55]. It essentially consists of two mass spectrometers connected 'head to tail'. Reactant ions are mass and energy selected in the first-stage mass spectrometer and allowed to collide with neutral molecules in a collision chamber. The product ions of the ion-molecule reaction are then mass analysed in the second-stage mass spectrometer. The major advantage of a tandem instrument for the study of ion-molecule reactions is the capability for independent preparation of the ionic and neutral reactants.

A tandem mass spectrometer has been utilized to study reactions of negative ions with thiols, and the following reactions were reported[56]

$$OH^- + CH_3SH \longrightarrow CH_3S^- + H_2O \quad (52)$$

$$NH_2^- + CH_3SH \longrightarrow CH_3S^- + NH_3 \quad (53)$$

$$OH^- + CH_3CH_2SH \longrightarrow CH_3CH_2S^- + H_2O \quad (54)$$

$$NH_2^- + CH_3CH_2SH \longrightarrow CH_3CH_2S^- + NH_3 \quad (55)$$

An unsuccessful search was made for the following reactions:

$$SH^- + CH_3OH \longrightarrow CH_3O^- + H_2S \quad (56)$$

$$SH^- + CH_3CH_2OH \longrightarrow CH_3CH_2O^- + H_2S \quad (57)$$

$$SH^- + CH_3SH \longrightarrow CH_3S^- + H_2S \quad (58)$$

$$SH^- + CH_3CH_2SH \longrightarrow CH_3CH_2S^- + H_2S \quad (59)$$

D. Proton Affinities: Gas Phase Basicities and Acidities

Reactions (52–55) may be regarded as simple acid–base reactions in which the thiol is the acid or proton donor. The fact that reaction (52) is fast, in the direction shown, indicates that CH_3SH is a stronger acid than H_2O in the gas phase. The proton affinity of the negative ion R^- is a quantitative measure of the intrinsic (i.e. devoid of the influence of a solvent) acidity of the molecule RH[57]. The proton affinity of R^-, P.A.(R^-), is defined as the negative heat of reaction (60):

$$R^- + H^+ \longrightarrow RH \quad (60)$$

Thus,

$$P.A.(R^-) = D(RH) + I.P.(H) - E.A.(R) \quad (61)$$

The occurrence of reaction (52) indicates, in other words, that the proton affinity of OH^- is greater than that of CH_3S^-. This is mostly due to the fact that the HO—H bond is considerably stronger than the CH_3S—H bond, i.e. D(HO—H) > D(CH_3S—H). It may be partly due to the electron

affinity of CH_3S, E.A.(CH_3S) being greater than that of the hydroxyl radical.

Contrary to what is found in solution, the following acidity order has been established in the gas phase: $C_2H_5OH > CH_3OH > H_2O$[57]. Thus, for

$$OH^- + CH_3OH \rightleftharpoons CH_3O^- + H_2O \quad (62)$$

the equilibrium lies to the right in the gas phase and to the left in solution. This has recently[55] been verified by measuring the reaction rates, in a tandem mass spectrometer, in the forward, as well as the reverse directions. The fact that reactions (58) and (59) could not be observed in a tandem mass spectrometer[56] indicates the following gas phase acidity order: $H_2S > CH_3SH$, C_2H_5SH. This will still have to be verified, by showing that the reverse reactions of (58) and (59) are fast.

Related to the problem of intrinsic acidity in the gas phase is the problem of intrinsic basicity. This may be measured quantitatively by the proton affinity of the neutral molecule, M which is analogously defined to P.A.(R^-) as the negative heat of reaction (63):

$$M + H^+ \longrightarrow MH^+ \quad (63)$$

The original supposition was[58] that if an ion-molecule reaction occurs in the mass spectrometer, it must be exothermic. Thus, if

$$M_1H^+ + M_2 \longrightarrow M_2H^+ + M_1 \quad (64)$$

then P.A.(M_2) $\geq$ P.A.(M_1), or M_2 is a stronger base than M_1. Recently,[59] other methods have been devised to determine relative and absolute proton affinities of neutral molecules. These give P.A.(H_2S) = 170 kcal/mole and P.A.(CH_3SH) = 185 kcal/mole and yield the following order of gas phase basicity: $CH_3NH_2 > NH_3 > CH_3SH > CH_3OH > H_2S > H_2O$.

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The Chemistry of the Thiol Group
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CHAPTER 7

The optical rotatory dispersion and circular dichroism of thiols

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I. INTRODUCTION

The purpose of this chapter is to provide informations on the optical dissymetry effects[1] of compounds containing the thiol group. A brief comparison with alcohols is reported. Systems such as open-chain and cyclic thioethers are also discussed; however, for review articles dealing with optical rotatory properties of chromophoric derivatives[2] of thiols the reader is referred to references 3 and 4. Metal complexes will not be considered.

The advantages of circular dichroism (c.d.) over optical rotatory dispersion (o.r.d.) are well known[5–11], so that emphasis has been put mainly on c.d. studies. The nomenclature is that in common use[1].

II. ULTRAVIOLET ABSORPTION OF THIOLS AND THIOETHERS

Divalent sulphur is generally thought to participate in bonding *via* two σ bonds involving mainly two of the three 3p orbitals on the sulphur atom leaving the 3s orbital and the remaining 3p orbital to accommodate the four nonbonding electrons. The 3s nonbonding pair is much more tightly held by the sulphur atom than the 3p nonbonding pair. The replacement of hydrogen atoms in H_2S by electron-donating (alkyl) groups leads to a destabilization of these electron pairs[12].

The ultraviolet vapour spectrum of dimethyl sulphide[13,14] shows two main absorption bands in the region from 200 to 230 nm: a structured band around 220 nm, and a relatively structureless band at about 200 nm. These two bands have oscillator strengths of about 0·016 and 0·06, respectively.

Thompson and coworkers[13] have examined the vibrational structure of the 220 nm band and have assigned the frequencies to progressions and combinations of the symmetrical C—S—C stretch and the parallel methyl rock. This is consistent with an electric dipole allowed transition. On going from vapour to solution[13], the 220 nm band loses its structure and is blue shifted, so that it appears as a shoulder under the 200 nm absorption. There is a further blue shifting with increasing solvent polarity. In addition, the solution spectrum reveals a very weak transition on the long wavelength edge of the absorption with an ε_{max} of about 20. Apparently because of its very low intensity this band is masked in the vapour spectrum by the nearby much stronger 220 nm system.

In cyclic sulphides, the lowest energy transition undergoes a red shift as the C—S—C angle decreases on going from larger to smaller rings, and appears at about 265 nm in three-membered rings[14–16].

The spectrum of hydrogen sulphide[13] shows a band at 200 nm of approximately the same intensity as that in dimethyl sulphide. Cumper and coworkers[17] observed a band with roughly the same wavelength and intensity when the carbons bonded to sulphur were replaced by silicon and germanium, for example in $(Me_3Si)_2S$. The relative insensitivity of the position and intensity of this band to the nature of the atoms bonded to sulphur suggests an atomic-like transition.

In summary, the following low energy transitions have been observed in the X—S—Y system: a very weak band at about 240 nm, and two moderately strong bands at about 220 and 200 nm (another transition is known to exist at about 195 nm). In the course of what follows, according to Rosenfield and Moscowitz[18], we shall suggest the following assignments: (a) the very weak band at 240 nm is associated with an electric dipole forbidden, magnetic dipole allowed $b_1 \rightarrow b_2^*$ transition. This assignment is substantiated by its marked enhancement in intensity in the case of thiols and unsymmetrical alkyl sulphides. Moreover, it is strongly analogous to the $n \rightarrow \pi^*$ transition in carbonyl; (b) the band at 220 nm is associated with an electric dipole allowed $b_1 \rightarrow a_1^*$ transition; (c) the band at 200 nm is related to an atomic-like $b_1 \rightarrow 3d$ transition. The orbital b_1 is a nonbonding 3p orbital on the sulphur atom, b_2^* and a_1^* are orbitals antinodal in the plane of the C—S—C chromophore and antibonding between the sulphur and carbon atoms, and 3d represents a linear combination of sulphur 3d atomic orbitals. These assignments are based on symmetry arguments and considerations of the intensity of absorption and circular dichroism. It should be noted that the assignments proposed by Rosenfield and Moscowitz[18] are in disagreement with previous ones[13–16], which were based only on absorption data. Rosenfield and Moscowitz found that these previous assignments were less consonant with the optical activity data than their own. This emphasizes that o.r.d. and c.d. results can be useful for assigning electronic transitions.

III. OPTICAL DISSYMMETRY EFFECTS OF MONOCHROMOPHORIC THIOLS AND OPEN-CHAIN THIOETHERS

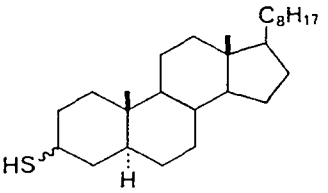
A. Monochromophoric Thiols

Optically active monochromophoric thiols (i.e. optically active compounds which contain only single C—C and C—H bonds in addition to the C—S—H group) have been poorly studied by o.r.d. and c.d. (Table 1).

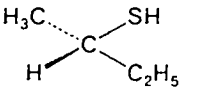
TABLE 1. Circular dichroism of monochromophoric thiols

Compound	Solvent	λ_{max} (nm)	$\Delta\varepsilon_{max}$	Ref.
(1) 5α-Cholestane-3α-thiol	Cyclohexane	235	−0·11	19
(2) 5α-Cholestane-3β-thiol	Cyclohexane	No maximum		19
(3) (2S)-2-Butanethiol	*n*-Heptane	233	+0·102	20

The chirospectroscopic properties of the cholestane-thiols **1** and **2** have been reported in a c.d. study of a range of 1,3-dithiolanes[19]. The α-derivative (**1**) exhibits a positive Cotton effect at 235 nm in the region of its longest-wavelength absorption (229 nm, $\varepsilon = 138$). Not surprisingly, the almost symmetrical β-derivative (**2**) showed no detectable c.d.



(**1**) 3α-SH
(**2**) 3β-SH



(**3**)

In an investigation on the relationship between optical rotatory power and optical purity of aliphatic compounds of the general formula $C_2H_5^*CH(CH_3)—X$ ($X = —SH$, $—SC_2H_5$) Salvadori and colleagues[20] reported the c.d. of (2S)-2-butanethiol (**3**), showing that the ultraviolet absorption band at the longest wavelength and corresponding to the shoulder in the 225–230 nm region is optically active. The Cotton effects associated with the 235 nm transition for **3** and its S-ethyl derivative (**24**) have opposite signs, despite the agreement found in the sign of rotation at 589 nm.

Finally, an o.r.d. study on a dithiol, namely (2S, 5S)-2,5-hexanedithiol, revealed a peak at 243 nm in *i*-octane and at 238 nm in ethanol[21]. It should be noted that the sign of rotation of this dithiol correlates with that found for (2S)-2-butanethiol (**3**). No o.r.d.–c.d. measurements of monochromophoric thiols are known below 230 nm.

In contrast to thiols, the c.d. of saturated chiral alcohols have been examined rather extensively[22–24]. Compounds containing hydroxy groups as the only substituent on a saturated hydrocarbon skeleton show no absorption maximum above 200 nm, and consequently aliphatic alcohols have been used extensively as solvents for the study of o.r.d. and c.d. In addition, it has been possible to disregard the presence of hydroxy substituents in work with compounds containing other chromophores, except for particular cases where there is interaction between a hydroxy group and a neighbouring chromophore. Saturated alcohols present a low intensity absorption maximum at 180–190 nm[23–25], which has been associated with the promotion of a nonbonding electron to an antibonding σ* group orbital, namely a $2p_{x,y} \rightarrow \sigma^*_{p_z}$ (in fact, the antibonding σ* level is composed largely of a p-orbital in these compounds, so that the

$n \rightarrow \sigma^*$ transition has the character of a forbidden $p_{x,y} \rightarrow p_z$ atomic transition). This situation presents similarities to that of thiols; however, a net difference exists in that in the case of alcohols it is not possible to invoke the participation of d electrons.

TABLE 2. Circular dichroism of some monochromophoric alcohols in *n*-hexane[22]

Compound	λ_{max} (nm)	$\Delta\varepsilon_{max}$
(4) 19-Nor-5α-cholestan-1β-ol	189	−0·25
(5) 19-Nor-5α-cholestan-2α-ol	190	−0·51
(6) 5α-Cholestan-2β-ol	198	+0·61
(7) 5α-Cholestan-3α-ol and four related compounds	187–188	−0·12 to −0·75
(8) 5α-Cholestan-3β-ol and four related compounds	187–189	−0·23 to −0·56
(9) 5α-Cholestan-4α-ol	191	−0·38
(10) 5α-Cholestan-6α-ol	196	+0·51
(11) D-Homo-5α-androstan-6α-ol	193	+0·38
(12) D-Homo-5α-androstan-11α-ol	193	−1·35
(13) D-Homo-5α-androstan-11β-ol	191	+2·86
(14) 5α-Androstan-11β-ol	188	+3·29
(15) 5α-Androstan-17β-ol	191	−2·12
(16) 5β-Cholan-12α-ol	203	+0·89
(17) 5α-Pregnan-20α-ol	193	+0·26
(18) 5α-Pregnan-20β-ol	203	+0·79
	193	−1·22
(19) 5α-17βH-Pregnan-20β-ol	188	−4·19
(20) exo-(1S, 3S)-Hydroxybornane	187	−2·32
(21) exo-(1R, 2R)-Hydroxybornane	189	+2·81
(22) (1S, 3S)-Hydroxypinane	187	+0·84
(23) (1R, 2R)-Hydroxypinane	188	−1·92

Table 2 illustrates the existence of well-defined Cotton effects for saturated alcohols in the region of the $n \rightarrow \sigma^*$ transition of their C—O—H group. The c.d. curves for the steroidal saturated hydrocarbons androstanes and cholestanes show the beginning of a Cotton effect below 190 nm but there is no maximum above 185 nm, and the maxima recorded in Table 2 must therefore be due to the hydroxy group. For many of the compounds listed in Table 2 Kirk and colleagues[22] have been able to predict the preferred conformation of the hydroxy group (assuming staggering about the C—O bond, with O—H occupying the least hindered position), and then to consider the relationship between the molecular geometry and the sign of the observed Cotton effect. Clearly, hydroxy Cotton effects

can no longer be ignored in c.d. studies of other chromophores which absorb below 200 nm.

A c.d. study of the self-association of (−)menthol and (−)borneol in heptane has been also reported[23]. The c.d. spectra near 200 nm consist of two bands of opposite sign.

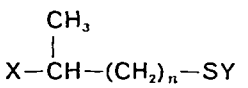
Vacuum-ultraviolet c.d. curves have been recorded for unsubstituted monosaccharides[24].

In summary, it is evident that the investigation of the thiol chromophore by optical dissymmetry effects has much farther to go before a fund of information approaching that available on the hydroxy chromophore is attained. The very fact, however, that the thiol system is somewhat more complex than hydroxy and, in particular, has d electrons involved in its transitions, makes this a potential source of new information and a promising area for further investigation.

Finally, no data concerning optical dissymmetry effects of —SeH- and —TeH-containing compounds have yet been published.

B. Monochromophoric Open-chain Thioethers

In 1968 Salvadori gave a fundamental contribution to the clarification of the problem of the optically active absorption bands in open-chain sulphides[26]. Dialkyl sulphides **24**, **27** and **28** have been shown to exhibit four optically active transitions in the region from 190 to 250 nm (Table 3). C.d. studies at low temperature and in the vapour phase clearly demonstrated that the best way to interpret the c.d. band at the longest wavelength for the aliphatic sulphides is to admit that an optically active transition is also present in the range 235–255 nm. The effect of a neighbouring asymmetric centre has been studied in these conformationally mobile systems. In general the intensity of the c.d. bands decreases with increasing distance between the sulphur atom and the asymmetric carbon atom; the corresponding electronic transitions are influenced in different ways by the asymmetric field variations connected with the structure of the compounds. The shift towards the visible observed in c.d. bands at 227–230 and 236–246 nm upon lowering the temperature shows that the hydrocarbon solvents cannot be considered 'inert solvents' with respect to the sulphide chromophore.



(24) $n = 0$; X = Et; Y = Et
(25) $n = 0$; X = Pr; Y = Et
(26) $n = 1$; X = Et; Y = Me
(27) $n = 1$; X = Et; Y = Et
(28) $n = 2$; X = Et; Y = Et

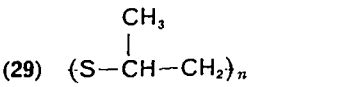
TABLE 3. Circular dichroism data for monochromophoric open-chain thioethers

Compound	Solvent	λ_{max} (nm)	$\Delta\varepsilon_{max}$	Ref.
(24) S-Ethyl-(2S)-2-mercapto-butane	*n*-Heptane	237	−0·276	20, 28
	n-Heptane	236	−0·26	26
		213	−2·25	
S-Ethyl-(2R)-2-mercapto-butane	*n*-Hexane	237	−0·23	27
		211	−1·60	
	Methanol	234	−0·24	27
		209	−1·10	
(25) S-Ethyl-(2R)-2-mercapto-pentane	*n*-Hexane	233	−0·25	27
		213	−1·59	
	Methanol	231	−0·28	27
(26) S-Methyl-(2S)-2-methyl-1-mercaptobutane	*n*-Heptane	242	not reported	28
(27) S-Ethyl-(2S)-2-methyl-1-mercaptobutane	*n*-Heptane	246	−0·02	26
		229	+0·09	
		206–210	−0·90	
		201	−1·16	
(28) S-Ethyl-(3S)-3-methyl-1-mercaptopentane	*n*-Heptane	251	−0·005	26
		230	+0·09	
		206–210	−0·50[a]	
		201	−0·74	

[a] Shoulder.

The c.d. properties of some open-chain thioethers have been also reported by Scopes and coworkers[27] (Table 3). The position and intensity of the Cotton effects exhibited by **24** are in agreement with those described by Salvadori[20,26,28] for the same compound. However, the signs have been reported to be opposite for the same enantiomer. This discrepancy could be due to the fact that Scopes and coworkers have obtained their c.d. spectra from optically impure samples of not unequivocal absolute configuration[27].

By complexing the sulphides **24** and **26** with Lewis acids the longest-wavelength Cotton effect completely disappears in the region above 235 nm[28]. These findings along with the solvent effects reported in Table 3 confirm that the transition responsible of the longest-wavelength c.d. band involves the promotion of a nonbonding electron on the sulphur atoms.



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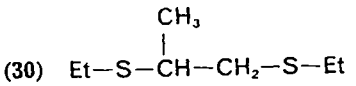


(30)

O.r.d. studies have often been useful for clarifying polymer conformations in solution. The o.r.d. curves of (−)poly(propylene-sulphide) (**29**) were anomalous in shape, having solvent-dependent troughs at 275–290 nm[29]. The optically active model compound (−)1,2-di(ethylthio)-propane (**30**) also shows anomalous rotatory dispersions and the patterns of the curves resemble those of the polymer. Accordingly, the Cotton effect of the latter must be attributed to the nature of the individual monomeric unit and not to the formation of any rigid helical conformation.

IV. OPTICAL DISSYMMETRY EFFECTS OF MONOCHROMOPHORIC THREE-MEMBERED RING THIOETHERS (EPISULPHIDES OR THIIRANES)

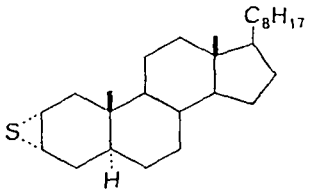
The chirospectroscopic properties of monochromophoric episulphides have been studied rather extensively[30–33], in view of the theoretical interest and potential stereochemical application of such information, particularly in the steroid field. In Table 4 are collected some relevant c.d. data of cholestane (**31–33**) and lanostane (**34, 35**) episulphides. The long wavelength Cotton effect is located in the 265 nm region, being associated with the very weak lower energy transition of the three-membered ring thioethers[14–16]. Of particular interest is the observation that while the u.v. extinction coefficients of the two epimeric episulphides **31** and **32** are very similar[30], their rotational strengths expressed in c.d. molar ellipticity differ by a factor of six, the more powerful 2α,3α-epimer (**31**) being characterized by a negative Cotton effect in contrast to the positive one of the 2β,3β-epimer (**32**)[30,31]. This pair represents an illustration where the small differences in electric dipole are not sufficient to have an important effect upon the extinction of the u.v. absorption maximum, but are reflected in the rotational strength because of the substantial magnetic dipole.

In several instances, either the sign or the rotational strength or both parameters have been utilized for purposes of differentiating between the position and/or configuration of the episulphide function in steroidal and triterpene molecules. At this point, it is relevant to note that the isolated episulphide group, like the isolated carbonyl group, represents a type of chromophore that has been classified as 'inherently symmetric'. Hence, whatever the nature of the relevant orbitals, their symmetry properties must reflect the inherent symmetry properties (e.g. reflection planes) of the *isolated* episulphide. The observed Cotton effects arise because of the dissymmetric molecular environment provided for the episulphide group by the rest of the steroid. This environment is determined to a large extent

by the position and orientation of the episulphide group in the steroid. Hence, the configuration of an incompletely characterized episulphide of a 5α-steroid, in which there is no substitution in the immediate vicinity of

TABLE 4. Circular dichroism of monochromophoric three-membered cyclic thioethers (episulphides or thiiranes)

Compound	Solvent	λ_{max} (nm)	$\Delta\varepsilon_{max}$	Reference
(31) 5α-Cholestan-2α,3α-episulphide	*i*-octane	268	−1·16	30
	Cyclohexane	268	−1·16	31
(32) 5α-Cholestan-2β,3β-episulphide	*i*-octane	264	+0·18	30
	Cyclohexane	264	+0·21	31
(33) 5α-Cholestan-3α,4α-episulphide	Dioxane	267	−1·40	30
(34) Lanostan-2α,3α-episulphide	Cyclohexane	267	−1·98	31
(35) Lanostan-2β,3β-episulphide	Cyclohexane	265	+0·58	31



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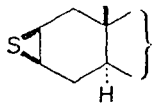

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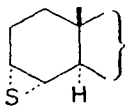

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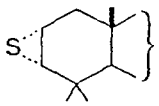

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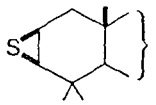


(35)

the episulphide group, can possibly be determined by comparison of its o.r.d. or c.d. curve with those reported in the literature[30-33].

A sector rule has been devised for the episulphide chromophore to account for the chirospectroscopic properties of steroidal episulphides[32, 33]

(Figure 1). Unfortunately, the exact nature of the transition involved is not definitely established, and, as a result, the rule does not rest on a firm theoretical foundation. Rather, it rests on the assumption that the transition at 265 nm is $n \rightarrow \sigma^*$, in which case the accessible sulphur d orbitals are not taken into account[16]. Nonetheless, the rule does appear to

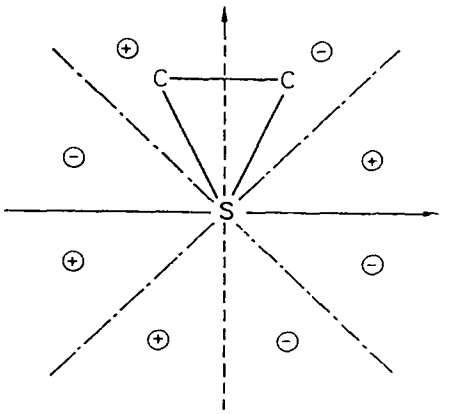


FIGURE 1. The episulphide sector rule.

enjoy a measure of success and should be examined more closely in systems other than steroidal[34].

Finally, a second optically active transition, whose solvent-dependent location falls in the 210–225 nm region[32], has been reported for steroidal episulphides.

V. OPTICAL DISSYMMETRY EFFECTS OF MONOCHROMOPHORIC FIVE-MEMBERED RING THIOETHERS (THIOLANES) AND SIX-MEMBERED RING THIOETHERS (THIANES)

The relatively rigid optically active thiolanes (8R,9R)-*trans*-2-thiahydrindan (**36**) and A-nor-2-thiacholestane (**37**) with known and opposite absolute configuration at the ring juncture have been synthesized and their optical rotatory properties investigated[18,35] (Table 5). Apparently, they seem to exhibit fewer optically active transitions than acyclic sulphides do[26]. In fact, **36** and **37** share two optically active transitions at 244 and 202 nm; in addition, compound **36** has an optically active transition centred at about 217 nm. The usefulness of the sulphide chromophore for stereochemical correlations has been confirmed following the observation

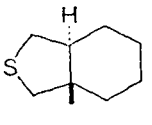
that the sign of the 244 nm band reflects the chirality of the neighbouring centres.

Whether the c.d. behaviour of cyclic sulphides can be expressed in terms of some spatial sign-determining rule analogous to the octant rule

TABLE 5. Experimental rotational strengths[a] (R) of monochromophoric thiolanes and thianes[18]

Compound	λ_{max} (nm)	R_{max}
36	244	−4·0
	217	+4·0
	202	−4·0
37	244	+4·0
	202	+4·0
38	233	−0·7
	215	−2·4
	202	+1·9
39	235	+1·8
	216	+1·3
	200	−1·4

[a] In units of 10^{-40} cgs.



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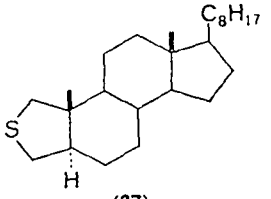

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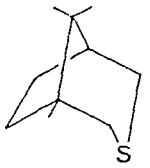

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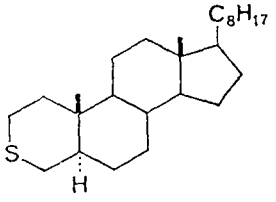


(39)

for the lowest-lying singlet transition in saturated ketones[36], and the quadrant rule for the lowest singlet in amides[37], awaits additional data on conformationally restricted and rigid systems. Following this line of approach, Rosenfield and Moscowitz[18] have carried out a theoretical and

experimental investigation on thiolanes **36** and **37**, and on two six-membered ring sulphides (thianes), namely 1,8,8-trimethyl-3-thiabicyclo-[3,3,1]-octane (**38**) and 3-thia-5-α-cholestane (**39**); in this study possible assignments for the three lowest-lying singlets in dialkyl sulphides have been proposed.

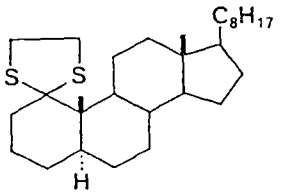
VI. OPTICAL DISSYMMETRY EFFECTS OF FIVE-MEMBERED RING DITHIOETHERS: 1,3-DITHIOLANES

The u.v. spectra of 1,3-dithiolanes exhibit a weak band at about 245 nm, corresponding to the $n \rightarrow \sigma^*$ transitions of the sulphur atoms[19,38,39]. Its optical activity is now demonstrated, as shown in the examples collected in Table 6. In the c.d. spectra two oppositely signed absorptions are generally seen, one between 260 and 280 nm, and the other, which is always more intense, between 235 and 250 nm[19,39].

To understand the spectra, the shape and symmetry of the dithiolane chromophore have been discussed[19]: (a) n.m.r. investigations of oxygen analogues of dithiolanes show that the ring undergoes pseudorotation

TABLE 6. Circular dichroism of five-membered ring dithioethers: 1,3-dithiolanes

Compound	Solvent	λ_{max} (nm)	$\Delta\varepsilon_{max}$	Reference
(40) 5α-Cholestan-1-one-ethylene-dithioketal	Dioxane	245	+3·60	39
(41) 5α-Cholestan-2-one-ethylene-dithioketal	Dioxane	263	+0·94	39
		240	−6·06	
(42) 5α-Cholestan-3-one-ethylene-dithioketal	Dioxane	261	+0·25	39
		239	−0·66	
	Cyclohexane	262	+0·05	19
		242	−0·25	
(43) 5α-Cholestan-6-one-ethylene-dithioketal	Cyclohexane	281	+0·03	19
		243	−3·69	
(44) 5α-Androstan-3-one-ethylene-dithioketal	Dioxane	262·5	+0·08	39
		235	−0·15	
(45) 5α-Androstan-16-one-ethylene-dithioketal	Dioxane	276	+0·11	39
		248	−4·09	
(46) 2,2-Ethylene-dithiocamphane	Cyclohexane	248	+4·75	19
(47) 1,1-Ethylene-dithio-3-methyl-cyclopentane	Cyclohexane	274	−0·12	19
		248–250	+1·24	
(48) 1,1-Ethylene-dithio-3-methyl-cyclohexane	Cyclohexane	264–265	+0·08	19
		239–240	−0·61	



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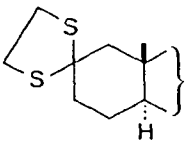

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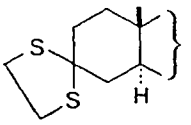

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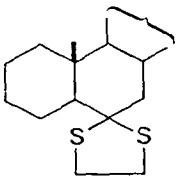

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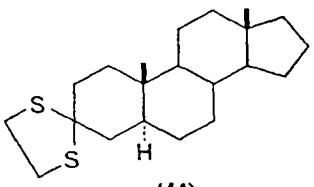

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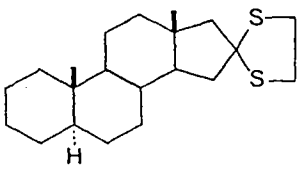

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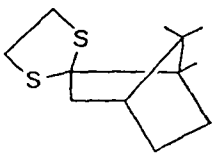

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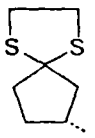

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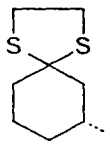
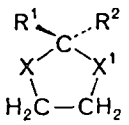


(48)

between the envelope and the two enantiomeric half-chair conformations, but no preference for the envelope form could be detected[40]. Therefore, although a 'time-average conformation' of a molecule exhibiting pseudo-rotation is not necessarily the same as the 'average conformation', the 1,3-dioxolane ring (and, by extension, the 1,3-dithiolane ring) appears to be planar and will possess C_{2v} symmetry if $R^1 = R^2$ in **49** (it would possess



(49)

X = X' = O
X = X' = S

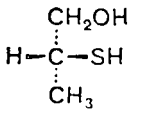
this symmetry also if it existed as the half-chair form, but not if it were in the envelope form); (b) however, it must be recalled that the spirodithiolanes are flexible compounds, which may undergo facile conformational twisting with accompanying reversing chirality, and any twist will give them an intrinsical optical activity; (c) in 1,3-dithiolanes, owing to the diffuse nature of the nonbonding 3p orbitals of sulphur there might be a net overlap of these orbitals, leading to several possible transitions[19]; the fact that only one absorption is seen in the u.v. spectra of 1,3-dithiolanes suggests that the degeneracy of the system is not seriously removed and that there must be only limited mixing between the electrons of the two sulphur atoms. On the other hand, the fact that 1,3-dithiolanes absorb at 15 nm longer wavelength than acyclic mercaptals has been attributed to increased overlap between sulphur orbitals[4]; and (d) a thorough analysis is further complicated by the undoubted importance of orbitals of sulphur other than 3p orbitals[13].

Notwithstanding these difficulties, Cookson and colleagues[19] have discussed the c.d. curves of 1,3-dithiolanes in terms of a simplified orbital diagram. Application of this approach to a number of 1,3-dithiolanes, with the interatomic distances and angles measured from Dreiding models, gave a fairly good qualitative interpretation of the c.d. spectra.

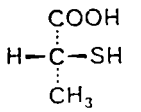
VII. OPTICAL DISSYMMETRY EFFECTS OF THIOLS AND OPEN-CHAIN THIOETHERS CONTAINING SOME ADDITIONAL CHROMOPHORES

A. Thiols

A study of (2R)-2-mercaptopropionic acid (**51**) and related compounds, in which sulphur and carboxy chromophores are present in the same molecule, has been reported by Scopes and coworkers[27]. The parent α-mercapto-carboxylic acid **51** shows two clear Cotton effects at 238–240 nm (positive) and 198 nm (negative) and one pronounced shoulder at 220 nm (Table 7). This may be compared with related (2R)-2-mercaptopropan-1-ol (**50**) which has a very small negative c.d. band at 235 nm



(**50**)



(**51**)

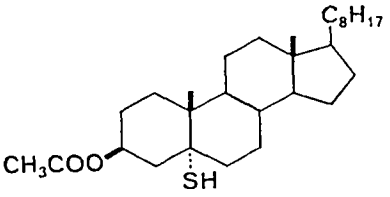
(226 nm in hexane) and a positive c.d. band at 198 nm[27]. The Cotton effect at 235–240 and 198 nm for the acid (**51**) and the alcohol (**50**) correspond to the absorption bands observed for these compounds in

TABLE 7. Circular dichroism of thiols containing additional chromophores

Compound	Solvent	λ_{max} (nm)	$\Delta\varepsilon_{max}$	Reference
(50) (2R)-2-Mercaptopropan-1-ol	*n*-Hexane	226	−0·13	27
		196	+1·50	
	Methanol	257	+0·004	27
		235	−0·023	
		198	+1·08	
(51) (2R)-2-Mercaptopropionic acid	*n*-Hexane	240	+2·10	27
		220	+1·48 sh	
		198	−2·26	
	Methanol	238	+1·66	27
		220	+0·91 sh	
		198	−1·90	
(52) 5α-Mercaptocholestan-3β-yl acetate	Cyclohexane	236–240	−0·23	19
(53) (S)-Cysteine	pH 1 (HCl)	208	+1·78	42
	pH 7 (phosphate buffer)	203	+2·34	42
	pH 13 (NaOH)	214	+3·74	42
	pH ca. 1 (HCl)	214	+1·22	45
	pH ca. 6 (water)	200	+1·54	45
(S)-Cysteine hydrochloride	Water	262	−0·0007	48
		201	+2·27	
	0·1N NaOH	277	−0·0025	48
		245	+0·403 sh	
		207	+3·27	
(54) N-Acetyl-(S)-cysteine	pH 1 (HCl)	263	+0·0114	48
		234	−0·338	
		206	+2·147	
	pH 13 (NaOH)	238	−1·44	48
(55) N-Acetyl-(S)-cysteine methylamide	pH 0·1 (HCl)	~268	~ +0·025	43
		~208	~ −2·3[a]	
(56) Reduced glutathione	Water	222	−1·10	9, 44
	pH 7·5 (phosphate buffer)	215	−1·80	48

[a] Refers to $\Delta\varepsilon$ at lowest wavelength reached: not a maximum.
sh = shoulder.

ethanol, which show a maximum at 206 nm and inflections at 235 and 230 nm respectively[27]. Although the two compounds (**50**) and (**51**) have the same configuration with respect to sulphur at the single asymmetric centre, the corresponding maxima at about 200 nm are of opposite sign. Comparison of the spectra shows that the effect of the sulphur chromophore



(**52**)

is dominant and the carboxy Cotton effect appears only as a shoulder at 220 nm in the c.d. curve of compound **51**. Thus, for compounds of the same absolute configuration with respect to sulphur the effect of replacing a primary alcohol group (compound **50**) by a carboxy group (compound **51**) is to invert the sign of the main c.d. Cotton effects, which are due to the sulphur chromophore and which have the dominant effect over the carboxy group.

In the case of c.d. spectra of cysteine (**53**) and its derivatives (**54–56**) (Figures 2 and 3, and Table 7), which are β-mercapto carboxy derivatives and have the —SH moiety separated from the asymmetric centre by one

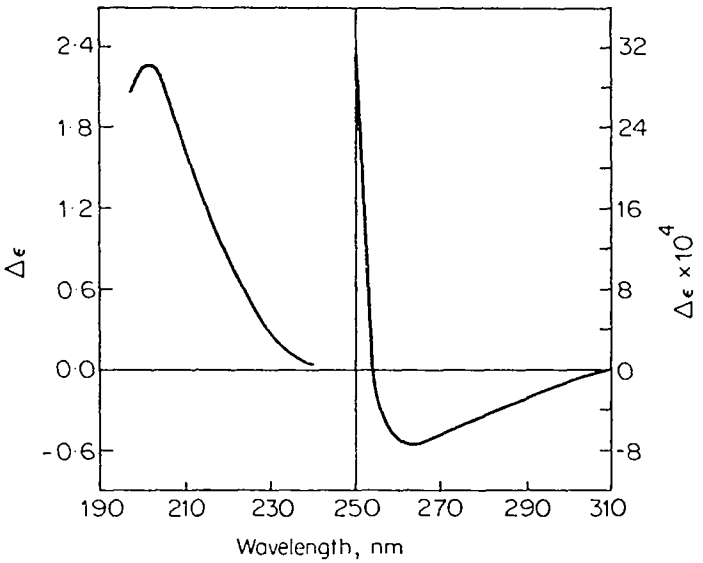


FIGURE 2. The c.d. spectrum of (S)-cysteine hydrochloride in water.

methylene group, the effect of the sulphur chromophore is much less relevant[9,42–45]. The spectra are basically similar to those observed for amino acids carrying an aliphatic side-chain[42,43,45,46] and appear to be dominated by the $n \rightarrow \pi^*$ transition of the CO—X (X = —OH, —NH—

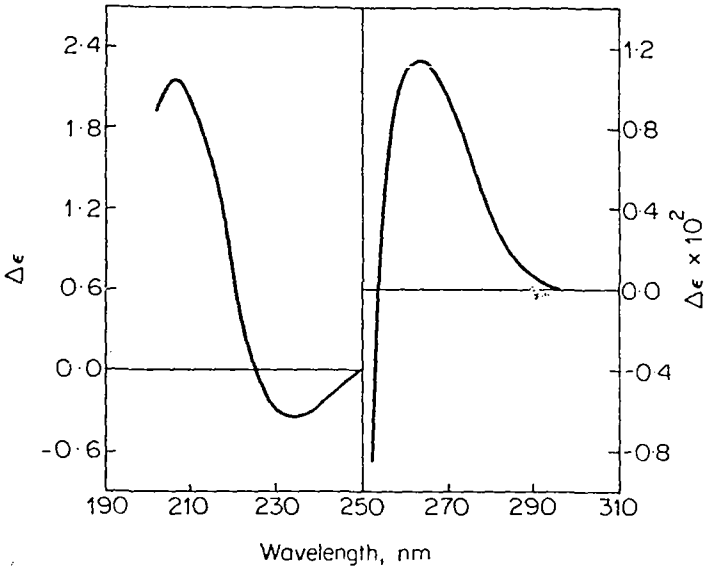
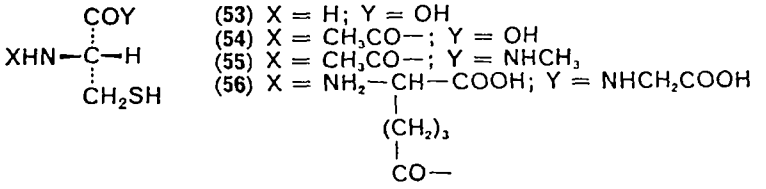


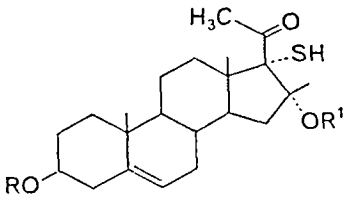
FIGURE 3. The c.d. spectrum of N-acetyl-(S)-cysteine at pH 1.

chromophores. In particular, the effect of replacing the —COOH group (**54**) for the —CONH— group (**55** and **56**) on the sign of the main c.d. band is noteworthy. The red shift of the wavelength maximum for the higher energy c.d. band in going from neutral to acid and alkaline pH, characteristic of aliphatic amino acids[42,45], is shown also by cysteine (Table 7).



The chiral-optical properties of steroidal thiols containing additional chromophores, such as —COOR, C=O and C=C (**52** and **57**), have also been investigated[19,47]. The results obtained[47] make it possible to conclude that sulphur-containing substituents, found in the α-position to the

20-C=O group in compounds of the pregnane series (**57**), in harmony with the octant rule[36], make a strong negative contribution to the c.d. intensity.



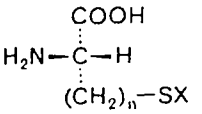
(**57**)

R = R' = H
R = R' = CH_3CO-

To our knowledge, no additional studies on —SH-containing compounds, in particular on $C_6H_5\underset{|}{(C)}_nSH$ ($n = 0, 1, \ldots$, etc.), have yet appeared in the literature.

B. Open-chain Thioethers

The four S-alkylated derivatives of (S)-cysteine (**59–62**) have very similar c.d. properties[45] (Table 8 and Figure 4). In aqueous solution two positive Cotton effects occur with maxima at 220 and 200 nm, respectively. In acid solution the two positive maxima occur again with a red shift of the 200 nm band. However, the relative magnitudes are changed; whereas in water the $\Delta\varepsilon$ value for the 200 nm band is about twice that for the 220 nm band, the reverse is true in acid. These bands have been ascribed to a transition of the sulphur atom, dissymmetrically perturbed by the centre



(**58**) $n = 2$; X = Me
(**59**) $n = 1$; X = Me
(**60**) $n = 1$; X = Pr
(**61**) $n = 1$; X = CH_2CH_2COOH
(**62**) $n = 1$; X = $CHCH_2COOH$ (with CH_3)

at C-2 (220 nm), and to the carboxyl $n \rightarrow \pi^*$ transition (200 nm)[45]. In (S)-methionine (**58**) the sulphur atom is separated from the asymmetric centre by one more methylene group than in **59**, and it is significant that the large 220 nm maximum is not observed, but a positive maximum at

TABLE 8. Circular dichroism data for some open-chain thioethers containing additional chromophores

Compound	Solvent[a]	λ_{max} (nm)	$\Delta\varepsilon_{max}$	Reference
(58) (S)-Methionine	pH ca. 6	198	+1·78	45
	pH ca. 1	205	+1·74	45
	pH 13	212	+0·81	42
	pH 7	228	−0·07	42
		200	+1·52	
		195	+1·36	
	pH 1	208	+1·53	42
	pH 7·5	227	−0·066	48
		199	+1·85	
	pH 1	249	−0·001	48
		206·5	+1·54	
(59) S-Methyl-(S)-cysteine	pH ca. 6	221	+1·07	45
		200	+2·60	
	pH ca. 1	223	+1·60	45
		207	+0·83 sh	
	pH 13	272	−0·005	48
		222	+1·25	
		210	+1·68[b]	
	pH 7·5	261	−0·015	48
		222	+1·23	
		201	+2·66	
	pH 1	258	−0·013	48
		223	+2·05	
		206	+1·02 sh	
(60) S-Propyl-(S)-cysteine	pH ca. 6	220	+0·84	45
		200	+2·11	
	pH ca. 1	223	+1·48	45
		202	+0·56	
(61) S-Carboxyethyl-(S)-cysteine	pH ca. 6	220	+0·93	45
		198	+2·34	
	pH ca. 1	222	+1·59	45
		202	+0·47 sh	
(62) S-β-Carboxyisopropyl-(S)-cysteine	pH ca. 6	220	+1·25	45
		199	+2·18	
	pH ca. 1	220	+2·00	45
		207	+0·69 sh	
(63) (S)-Djenkolic acid	pH ca. 6	200	+7·68	45
	pH ca. 1	217	+3·39	45
(64) N-Acetyl-(S)-djenkolic acid	pH ca. 6	205	+5·62	45
	pH ca. 1	208	+3·14	45
(65) S-Methyl-(2R)-2-mercapto-propionic acid	Methanol	271	−0·01	27
		240	+0·87	
		224	+0·80	

TABLE 8 (*cont.*)

Compound	Solvent[a]	λ_{max} (nm)	$\Delta\varepsilon_{max}$	Referen
		203	−0·73	
	n-Hexane	268	−0·15	27
		240	+0·67	
		221	+0·93	
		208	+0·56	
		197	−0·62	
	Methanol/NaOH	244	+0·34	27
		221	+0·42	
		212	−1·28[b]	
(66) S-Methyl-(2R)-2-mercapto-propionic acid methyl ester	Methanol	271	−0·02	27
		240	+1·18	
		221	+1·12	
		200	−1·06	
	n-Hexane	269	−0·04	27
		241	+1·83	
		229	+1·48 sh	
		203	−1·42	
(67) S-Methyl-(2R)-2-mercapto propan-1-ol	Methanol	255	+0·006	27
		231	−0·11	
		208	+0·37	
	n-Hexane	243	+0·009	27
		222	−0·26	
		208	+0·35	
(68) (R)-Methylthiosuccinic acid	Not indicated	235	+1·998	50
(69) (R) Ethylthiosuccinic acid	Not indicated	237–243	+1·62	50
(70) (R)-Propylthiosuccinic acid	Not indicated	244	+1·773	50
(71) (R)-Isopropylthiosuccinic acid	Not indicated	243–245	+0·92	50
(72) (R)-*n*-Butylthiosuccinic acid	Not indicated	239–243	+1·732	50
(73) (R)-*n*-Pentylthiosuccinic acid	Not indicated	237	+1·685	50
(74) 5α-Methylthiocholestan-3β-ol	Cyclohexane	238	−1·10	19
(75) 5α-Methylthiocholestan-3β-yl acetate	Cyclohexane	239–242	−0·22	19

[a] pH values were obtained thus:

pH 1 and ca. 1	HCl
pH ca. 6	water
pH 7 and 7·5	phosphate buffer
pH 13	NaOH

[b] Refers to $\Delta\varepsilon$ at lowest wavelength reached: not a maximum.
sh = shoulder.

about 200 nm, which confirms the (S)-configuration at C-2 for the four substituted cysteines[42,45,48] (Figure 4).

Compounds **63** and **64**, containing the $-S-CH_2-S-$ grouping, both gave positive Cotton effects at wavelengths similar to those for an alkyl-substituted cysteine[45]. The ellipticity values measured for **63** and **64** in water (Table 8), however, are of the order of magnitude usually associated with an inherently dissymmetric chromophore. This evidence implies that the system $-S-CH_2-S-$ is itself chiral, independently of any dissymmetric substitution.

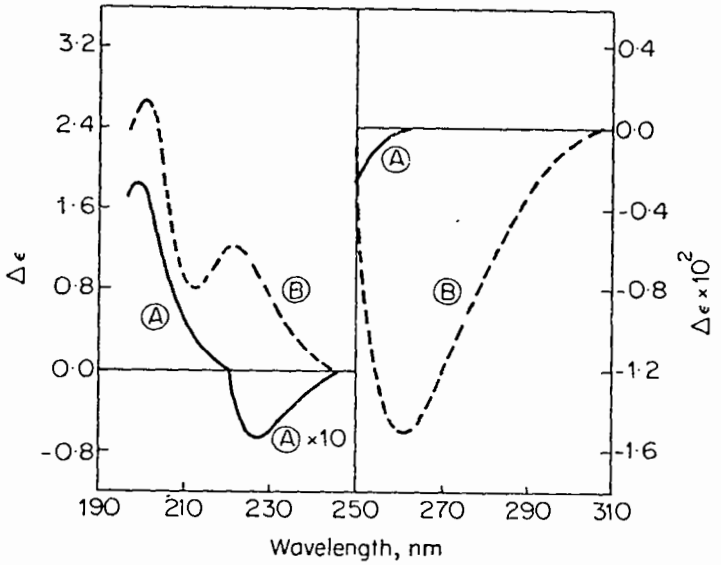
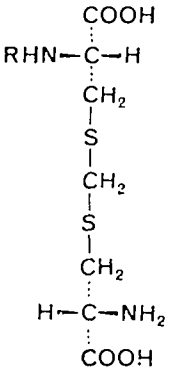


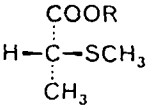
FIGURE 4. The c.d. spectra of (S)-methionine (A) and S-methyl-(S)-cysteine (B) in 0·2M phosphate buffer, pH 7·5.

S-Methyl-(2R)-2-mercaptopropionic acid (**65**) and its methyl ester (**66**) present very similar c.d. curves[27] (Table 8), which in contrast are remarkably different from that of the corresponding primary alcohol (**67**). As for the thiols (**50**) and (**51**), these results show a reversal in the sign of the major c.d. maxima accompanying the change from $-CH_2OH$ to $-COOH$ group. The data of Scopes and colleagues[27] on the longest wavelength c.d. band of **51** and **65** parallel the observation of Craig and Pereira on α-amino acids and α-hydroxy-acids[49], suggesting that coupling occurs between the carbonyl group in the carboxy chromophore and one of the nonbonding orbitals of the heteroatom attached to the asymmetric centre.

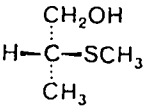
This coupling will only take place for a conformation in which the alkoxy-oxygen is close to the heteroatom. In addition, for the acid **65** and ester **66** there is a very large increase in ellipticity for all the c.d. bands investigated as the temperature is lowered to $-180°C$[27]. This finding is consistent with the great flexibility of these acyclic molecules.



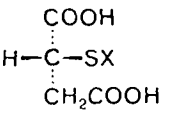
(**63**) R = H
(**64**) R = CH_3CO-



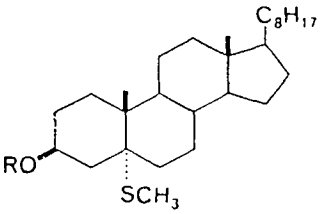
(**65**) R = H
(**66**) R = CH_3



(**67**)



(**68**) X = Me
(**69**) X = Et
(**70**) X = Pr
(**71**) X = *i*-Pr
(**72**) X = *n*-Bu
(**73**) X = *n*-Pe



(**74**) R = H
(**75**) R = CH_3CO-

Lastly, the alkylthiosuccinic acids **68–73** and the alkylthiocholestanes **74** and **75** all exhibit a Cotton effect at 235–245 nm associated with a transition within the sulphur chromophore[19,50].

Several poly-α-amino acids containing a sulphur atom in their side-chain have been investigated by o.r.d. and c.d.[51–55]. However, the analysis has not advanced sufficiently as yet to merit a detailed discussion.

Note added in proof: Since the completion of this article, several papers discussing the u.v., o.r.d., and c.d. spectra of alcohols[56], thiols[57-61], and thioethers[60-68] have appeared in the literature.

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The Chemistry of the Thiol Group
Edited by Saul Patai

CHAPTER 8

Acidity and hydrogen-bonding

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I. HYDROGEN BONDING

A. Introduction

A considerable proportion of the chemical literature continues to be concerned with studies of hydrogen bonding. Pimentel and McClellan following their standard work[1] in 1960 have reviewed the more recent literature[2], and a general review[3] stressing the theoretical aspects has appeared. Nevertheless hydrogen bonding involving thiols has received rather little attention due no doubt to the comparative weakness of the

interaction. Indeed until about 1960 there was doubt as to the existence of hydrogen bonding in thiols. Thus physical measurements such as cryoscopy[4] failed to detect their self-association and the boiling points, considerably lower than those of the corresponding alcohols, indicated less association than their oxygen analogues. However the modern use of spectroscopic techniques, mainly infrared and n.m.r., has shown the presence, albeit weak, of hydrogen bonding involving the SH group. In the former technique the formation of an H-bond S—H···B is in general accompanied by a decrease in the frequency of the SH stretching mode, and an increase in the bandwidth of this mode and an increase in its integrated intensity. In general, distinct bands are observed due to molecules in distinct environments as in monomer, dimer or polymer, so that the presence of such species can be determined in favourable cases. In p.m.r. spectroscopy hydrogen bonding involves a shift of the thiol proton resonance to lower field and the time-scale of the experiment is such that a single thiol band is observed whose position is a weighted average for the various hydrogen-bonded species present. From measurements of the variation of chemical shift with concentration equilibrium constants may be calculated. The two techniques are complementary and useful information has been obtained from each.

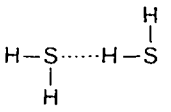
B. *Self-association*

1. Hydrogen sulphide

The boiling point of hydrogen sulphide[5] at −60°C is very much lower than that of water and indicates the considerably weaker intermolecular forces in liquid hydrogen sulphide than in water[6]. Nevertheless the p.m.r. shift of liquid hydrogen sulphide is 1·5 p.p.m. downfield from the position in the gas phase[7] showing the presence of association. In solid hydrogen sulphide evidence for weak S—H···S hydrogen bonding comes from the crystallographic studies of Harada and Kitamura[8]. There are several solid phases, a fact in itself suggestive of specific molecular interactions[9]. In the tetragonal phase stable below −168°C the S···S distance is 3·86 Å which is shorter by 0·5 Å than that expected from van der Waal's distances, and the S—S—S angle is 75°. This suggests[9] that the hydrogen sulphide molecule, with a bond angle of 92° in the isolated state is oriented so as to form two slightly bent hydrogen bonds to other sulphur atoms.

Infrared spectra of hydrogen sulphide in solid nitrogen matrices at 20 K have been recorded[10] and from an analysis of the SH stretching region assignments of bands to monomer, dimer and polymer species were made. Bands at 2632·6 cm^{-1} (ν_3) and 2619·5 cm^{-1} (ν_1) whose intensities increased

with increasing dilution of hydrogen sulphide in the matrix were attributed to monomer. The spectrum of the dimer indicates an open structure with a single hydrogen bond (**1**). Bands at 2631·1 and 2617·8 cm^{-1} are associated primarily with the proton acceptor molecule with bands at 2625·3 and



(1)

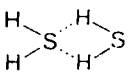
2580·3 cm^{-1} associated with the proton donor. The relative frequency shift on dimer formation was compared with that for matrix isolated water molecules with the result

$$(\Delta\nu/\nu)_{H_2S}/(\Delta\nu/\nu)_{H_2O} \simeq 0{\cdot}5$$

suggesting that in the nitrogen matrix the hydrogen sulphide hydrogen bond is approximately half as strong as the water hydrogen bond. The infrared spectra of hydrogen sulphide in carbon monoxide, argon and krypton matrices[11] similarly indicate the formation of an open-chain dimer. In the argon matrix absorptions due to higher multimers are generally broad and overlapping so that specific assignments are difficult although bands attributable to a trimeric species were found.

Infrared spectroscopy also provides evidence for the self-association of hydrogen sulphide in the gas phase at high pressure[12]. The results indicate[13] the formation of a dimer with an energy of about 1·7 kcal/mole.

A recent theoretical examination[14] of hydrogen bonding in hydrogen sulphide concludes that the CNDO method in its present form is not adequate to describe the properties of weak hydrogen bonds such as S···H—S. The predicted bond lengths are much too short while the bond energies are one or two orders of magnitude too high. *Ab initio* calculations give more acceptable results and indicate, in agreement with experimental evidence, that the linear form of the dimer (**1**) should be more stable than a bifurcated structure (**2**) or cyclic structure (**3**). The bond energy in the linear structure is predicted to be 0·7 kcal/mole. An earlier calculation[15] of the bond energy in the H_2S dimer, using the method of Pople[16], gave a bond strength of 1·8 Kcal/mole.



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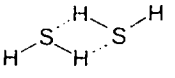

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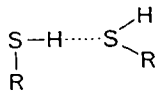
2. Aliphatic thiols and thiophenols

At one time self-association of aliphatic or aromatic thiols was thought to be unlikely. Thus molecular weights determined by the freezing-point method[4] showed no evidence of polymerization. Also calorimetric measurements indicated no heat of mixing when thiols were diluted with benzene[17] and dipole moment measurements[18] did not reveal any tendency to association. In addition early workers using the infrared method, limited by experimental inadequacies, were unable to detect any concentration effects on dilution of thiols with inert solvents and hence considered hydrogen bonding unlikely[19–21]. They were, however, able to detect the association of thiols with suitable oxygen- or nitrogen-containing solvents.

More recently infrared spectroscopy has provided definite evidence of self-association in thiols. Several groups of workers have found shifts of about 20 cm^{-1} in the SH stretching frequency as the concentration of thiol is varied. In the case of aliphatic thiols Bulanin and coworkers[22] found three factors indicative of hydrogen bonding. Thus as the concentration of thiol in carbon tetrachloride is increased the absorption frequency shifts from 2584 to 2564 cm^{-1}, the bandwidth increases from 25 to 58 cm^{-1} and the integrated absorption intensity increases by a factor of eight. The band at higher frequency was attributed to monomeric thiol molecules and that at lower frequency to associated species, the linear dimer (**4**) being thought most probable. Spurr and Byers[23] measured



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integrated intensities for the SH absorption of several thiols in carbon tetrachloride solutions. In accord with Bulanin's results they found that the band is formed of two components at about 2580 and 2560 cm^{-1} (see Figure 1). The variation of intensity with concentration could be accounted for on the basis of a monomer–dimer equilibrium and for all compounds studied the integrated absorption coefficient of the dimer was an order of magnitude greater than that of the monomer. Spurr and Byers assumed that both thiol groups in the dimer were hydrogen bonded, requiring a cyclic structure, and calculated equilibrium constants for the association process (Table 1, p. 385).

It is of interest that recently infrared spectra have been reported[24] for methanethiol and ethanethiol suspended in argon matrices at 20 K. In the

SH stretching region bands were identified due to thiols in the form of monomers (2600 cm^{-1}), linear dimers (2575 cm^{-1}) and cyclic tetramers (2551 cm^{-1}). The latter form (**5**) was found to be particularly stable for

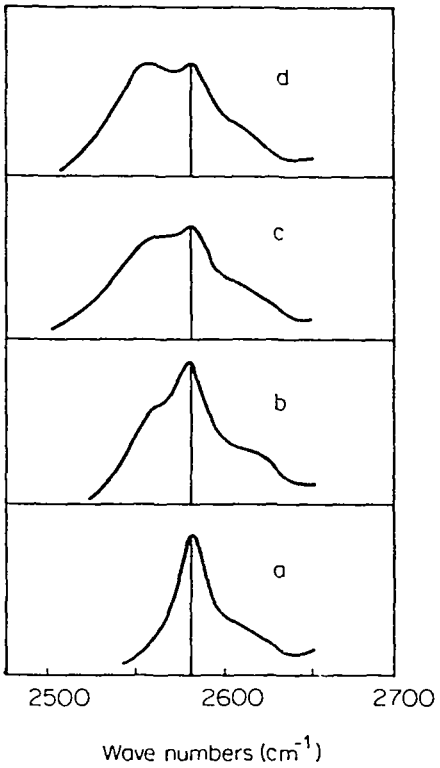
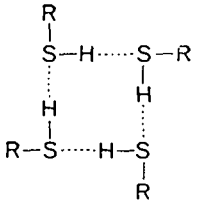


FIGURE 1. Infrared spectra of *t*-butanethiol in carbon tetrachloride: a, 0·125*M*; b, 3·08*M*; c, 6·99*M*; d, 9·20*M*, pure thiol. The bands at 2580 and 2560 cm^{-1} were attributed to monomer and dimer respectively. The shoulder at 2620 cm^{-1} is thought to be unconnected with SH absorption. Reproduced by permission from R. A. Spurr and F. H. Byers, *J. Phys. Chem.*, **62**, 425 (1958).

ethanethiol. In addition, the formation of dimers and more highly associated species from several aliphatic thiols has been confirmed recently[175] by low temperature measurements.



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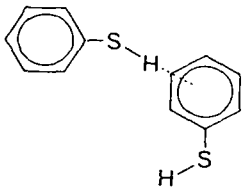


(6)

The effects of association in thiophenols were first noted by Josien and her coworkers[25]. In dilute solution in carbon tetrachloride the monomeric SH frequency is at 2591 cm^{-1}. As the concentration of thiophenol is increased a shoulder, attributed to dimer, is found at 2577 cm^{-1} while in the pure liquid a band at 2569 cm^{-1} is attributed to polymer. Evidence for association was also found in the case of mono-halogenated thiophenols[26]. Similarly David and Hallam[27] have given convincing demonstrations of the self-association of thiophenol and seven of its derivatives. They considered that the structure of the associate is most likely to be (**4**) although they raised the possibility that in thiophenols bonding may occur to the π-electrons of the benzene ring (**6**). Thus in dilute solutions of thiophenol in benzene where S—H $\cdots$ π interactions will occur the SH frequency is at 2574 cm^{-1}, similar to the position for self-associated thiophenol. Recent evidence suggests that both S—H$\cdots$S and S—H$\cdots\pi$ bonds are present[175].

P.m.r. spectroscopy has also been used to demonstrate the self-association of thiols. Hydrogen-bond formation results in deshielding of the hydrogen atom involved in the association giving rise to a shift to lower field[28]. Forsén[29] found that on dilution of ethanethiol with carbon tetrachloride a small upfield shift of 0·38 p.p.m. was obtained corresponding to cleavage of hydrogen bonds. The linear dependence of the shift on mole fraction of thiol, x_{SH}, was taken[30] to indicate a monomer–dimer equilibrium and from the slope an estimate for the dimerization constant K_D was obtained.

$$\frac{d\delta}{dx_{SH}} = 2K_D \Delta d, \quad \Delta d = \delta_D - \delta_M$$

The treatment is unsatisfactory in that although the monomer shift δ_M is determinable the value of δ_D, the shift of the dimer, is not known. Linear dilution shifts were also reported[31] for *n*-propanethiol, benzylthiol and thiophenol in carbon tetrachloride.

Similarly hydrogen bonds are broken on transfer of thiol from the liquid to the vapour phase. Measurements[32,33] with a series of aliphatic thiols showed that the shifts to high field accompanying the phase change were similar to those obtained on dilution of the liquid thiols with inert solvents (Table 1). The magnitude of the change, $\Delta\delta$, decreases with increasing chain length and with increasing chain branching which was interpreted as showing the greater hydrogen-bonding ability of the lower thiols. In addition, heating the liquid thiols was found[34] to give small shifts to high field of the thiol proton resonance indicative of hydrogen-bond breakage. The slopes $\Delta\delta/\Delta T$, in Hz/degree, were 0·16, 0·11, 0·10,

0·09 and 0·07 respectively for methane-, ethane-, *n*-propane-, *i*-propane- and *t*-butane-thiols and this was taken to be the order of decreasing hydrogen-bonding in the thiols.

The most comprehensive p.m.r. study is that of Marcus and Miller[35] who carried out a mathematical analysis of the dilution curves of seven thiols in inert solvents. They found, using Saunders and Hyne's approach,[36] that a monomer–dimer model gave best fit with the experimental results and their treatment yielded self-consistent values for the dimerization constant and dimer shift δ_D. In the case of thiophenol anomalies were observed due to the ring-current effect of the aromatic molecules. Thus as the concentration of thiophenol is increased the deshielding effect of hydrogen-bond formation is in part counteracted by the shielding ring-current effect of the aromatic rings so that a reduced dilution shift was obtained. This effect was overcome by the use of chlorobenzene as diluent so that the ring-current effect remained constant throughout. An alternative approach[37] when using carbon tetrachloride as diluent for thiophenols is to measure the thiol proton shift relative to that of the aromatic protons.

In Table 1 the association constants for dimer formation obtained by the n.m.r. method are compared with those obtained from infrared

TABLE 1. N.m.r. association shifts and calculated dimerization constants (K_D) for thiols

Thiol	$\Delta\delta$ (vapour)[a] (p.p.m.)	$\Delta\delta$ (CCl_4)[b] (p.p.m.)	K_D(n.m.r.)[c,f] (l/mole)	K_D(infrared)[d] (l/mole)
Methanethiol	0·49	0·40	—	—
Ethanethiol	0·37	0·38	0·0056	0·021
n-Propanethiol	0·28	0·26	0·0110	0·053
i-Propanethiol	0·26	0·22	0·0126	0·018
n-Butanethiol		0·23	0·0132	0·016
t-Butanethiol	0·24	0·19	0·0067	0·016
Cyclohexylthiol		0·22	0·0093	
Thiophenol		0·19[e]	0·0110	0·019

[a] This is the experimentally measured difference in chemical shifts between pure liquid and vapour, reference 32.

[b] This is the experimentally measured difference in chemical shift between pure liquid and dilute solution (references 32, 35).

[c] Reference 35.

[d] Reference 23.

[e] The solvent is chlorobenzene.

[f] Recent calculations[33] give values which increase from 0·04 l/mole for methanethiol to 0·1 l/mole for *t*-butanethiol. The enthalpy of dimer formation for methanethiol is reported as 1·85 kcal/mole.

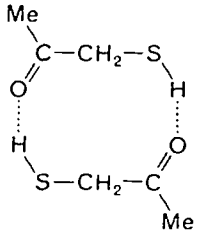
intensity measurements. The n.m.r. measurements do not depend on assumptions about the form of the dimer, e.g. linear or cyclic, but neither do they give information about its structure. The infrared data were calculated assuming a cyclic structure although on balance the evidence favours a linear structure. It is probably fair to say that these association constants should be regarded as giving the order of magnitude of the association rather than precise values. Somewhat anomalously the n.m.r. results for the aliphatic thiols indicate increasing association constants with increasing chain length whereas the association shifts, $\Delta\delta$, decrease with increasing chain length. However, as Marcus and Miller have noted[35], it does not necessarily follow that these quantities should be directly related.

The self-association of thiols is then considerably weaker than the corresponding self-association of alcohols and phenols[38,39]. The evidence suggests that the thiols are present in dilute solutions mainly as the monomers while in more concentrated solutions dimers, probably linear, are formed. In the pure liquids or solids polymeric forms may exist.

3. Other compounds

There is evidence[40] in the case of some aliphatic aminothiols for intermolecular association which breaks down only on dilution to about 10^{-2} mole/l. in carbon tetrachloride. The associated infrared shift of the SH band is 60 cm^{-1}. In this case it is almost certain that association occurs via S—H···N bonding. The self-association of thioamides, shown by cryoscopic measurements, has been attributed[41] to hydrogen bonding involving nitrogen and sulphur although the possibility remains that here N—H···N bonds alone are involved[23].

The self-association of aliphatic α- and β-mercaptoketones which is indicated by cryoscopic and infrared studies[42] almost certainly involves S—H···O=C interaction. Band shifts, $\Delta\nu_{SH}$, of about 20 cm^{-1} are observed and intensity measurements similar to those of Spurr and Byers[23] give association constants of ca. 0·1 l/mole. A cyclic structure (7) seems likely.



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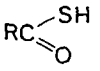
Thiobenzoic acid exists largely in the thiol form (**8**) rather than the thione form (**9**). A study[43] by spectroscopic and cryoscopic techniques shows that the tendency to associate is considerably reduced relative to



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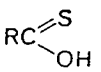


(9)

benzoic acid. Nevertheless, infrared spectra of both thiobenzoic and thioacetic acids in carbon tetrachloride solution present definite evidence for dimerization[44]. Bands at 1710 and 1690 cm^{-1} were attributed to carbonyl groups in the monomeric acid and dimer respectively. The latter band diminished on dilution and was absent in solution less concentrated than 1·4 mole/l. In the ν_{SH} region thioacetic acid shows a broad absorption at 2560 cm^{-1} attributed to dimer which diminishes in intensity on dilution and a band at 2585 cm^{-1} due to monomer. The most recent evidence[176] indicates formation of both open and cyclic dimers. A recent study[45] of self-association of thiobenzoic acid by the n.m.r. method indicates dimer formation. A surprisingly high enthalpy change of 6·5 kcal/mole is reported. The effects of substituents in the benzene ring on the dimerization constant and enthalpy change have also been reported[46]. A linear relationship with Hammett σ values was found.

The infrared spectrum of liquid dithioacetic acid shows a band, ν_{SH}, at 2481 cm^{-1} which is at considerably lower frequency than is found in the gas phase (2557 cm^{-1}) and indicates association[47]. Similarly[48,49] the spectra of trithiocarbonic acid, H_2CS_3, and related acids show large shifts in going from the pure liquid (ν_{SH}, 2400 cm^{-1}) to dilute solution in carbon disulphide (ν_{SH}, 2525, 2550 cm^{-1}).

An infrared study[50] of two phosphinodithioic acids, Et_2PSSH and Ph_2PSSH, indicates very strong association in the liquid state or in solution in carbon tetrachloride where a broad band is observed at 2420 cm^{-1}. In dilute solution the sharp monomer band is at 2560 cm^{-1}. The strong association in this case results from hydrogen bonding of the sulphydryl hydrogen with the polar P=S group. Similar strong association is found[51,52] in dialkyldithiophosphoric acids, $(RO)_2PSSH$, where dilution shifts of 140 cm^{-1} are again observed.

C. Thiols as Hydrogen-bonding Acids

Early evidence for the association of thiols with hydrogen-bond acceptors came from calorimetric measurements[17]. More recently the infrared hydrogen bond shifts, $\Delta\nu_{SH}$, have been measured for several

thiols in a variety of solvents (Table 2). The Badger–Bauer relationship[53,54] suggests that the relative frequency shift ($\Delta\nu/\nu$) on complex formation should give a measure of the strength of the hydrogen bond formed;

TABLE 2. Infrared frequency shifts $\Delta\nu_{SH}$ (cm^{-1}) for thiols with various hydrogen bond acceptors[a]

Acceptor	Thiophenol[b]	Hydrogen sulphide[c]	*t*-Butanethiol[d]	*n*-Propanethiol[e]
Carbon disulphide	14, 15	10	7	
n-Butyl bromide	15			
Ethyl iodide	24			
Benzene	14, 16, 17	12	5	
Mesitylene	27	20		
Acetonitrile	20, 25	11	8	
Acetone	29, 32	25	12	13
Dioxan	48, 51	37	20	16
Di-*n*-butyl ether	53	45		
Diethyl ether	48, 54	42	18	
Diphenyl sulphoxide	48			
Ethyl phenyl sulphoxide	70			
Diethyl sulphoxide	97			
Pyridine	128	115		60[f]
Triethylamine				123

[a] Shifts are measured relative to dilute solutions of the thiol in carbon tetrachloride.
[b] Reference 25, 19, 55, 56, 57.
[c] Reference 58.
[d] Reference 55.
[e] Reference 22.
[f] This value is for *n*-butanethiol (reference 19).

and in the case of hydroxyl groups plots of $\Delta\nu/\nu$ versus $-\Delta H$, the enthalpy change of association, are frequently linear[39]. Recent evidence[2] suggests that although the frequency shift can be used to estimate hydrogen-bond energies exact correlations involving different acid–base types are not always possible. The results in Table 2 indicate that for thiols the hydrogen-bond acceptors fall into a similar order to that found with other hydrogen-bond donors[1]. Thus the largest shifts, and thus probably strongest bonds, are formed with pyridine* and sulphoxides while the interaction with aromatics and alkyl halides is weak. Comparison of the thiols shows that

* Note added in proof: A detailed infrared study[177] of the association of thiols with pyridine and triethylamine confirms that the major interaction involves S—H···N bond formation.

in a given solvent a larger shift is obtained for thiophenol than for the less acidic aliphatic thiols and this may indicate some correlation between hydrogen bond strength and thiol acidity. For substituted thiophenols David and Hallam[56] have shown that a correlation exists between the solvent shift $\Delta\nu_{SH}$ and the pK_a value of the thiol measurement in methanol; the more acidic the thiophenol the larger the solvent shift.

N.m.r. spectroscopy has also been used to study the interactions of thiols with proton acceptors. The magnitude of the shift to low field of the thiol proton resonance produced on solution in basic solvents has been taken as a measure of the strength of the hydrogen bonds formed[59]. The largest shifts occurred in solutions of hexamethylphosphoramide and the following solvent order was found: hexamethylphosphoramide > dimethyl sulphoxide > dimethyl formamide > dioxan, acetone > ethanol, dimethyl sulphide > diethyl sulphide > diethyl ether, triethylamine. However, as Marcus and Miller[60], have pointed out the solvent shift is a complex quantity affected by at least five factors. For example, although hydrogen bonding generally results in proton deshielding giving a downfield shift, association with the π-electrons of benzene or end on with the nitrogen of acetonitrile will result in proton shielding and a shift to high field. They were, however, able to derive for weakly associated systems an expression relating the observed shift to the association constant indicating that under some circumstances the solvent shift may reflect the electron donating power of the solvent. Measurements with thiophenol and *n*-butanethiol in eighteen solvents ranging from acetone to aromatics indicated that the chemical shifts (in Hz, measured from tetramethylsilane) at infinite dilution are related by

$$\delta(\text{thiophenol}) = 2{\cdot}0\ \delta(n\text{-butanethiol}) - 58{\cdot}5$$

This then together with other evidence[17] suggests that stronger hydrogen bonds are formed by the more acidic thiophenol than by aliphatic thiols.

One of the few investigations of thiol hydrogen bonding in which thermodynamic parameters were determined involves the association of thiophenol with hydrogen-bond acceptors in carbon tetrachloride solution[61]. In dilute solutions the equilibrium may be represented simply as

$$\text{S—H} + \text{B} \underset{}{\overset{K}{\rightleftharpoons}} \text{S—H}\cdots\text{B}$$

It may be shown that when the base concentration, C_B, is in excess of that of the thiol the relative thiol shift, $\delta_{obs} - \delta_{monomer}$ is related to the equilibrium constant by

$$\frac{1}{\delta_{obs} - \delta_{monomer}} = \frac{1}{K.\Delta}\frac{1}{C_B} + \frac{1}{\Delta}$$

Here Δ is the chemical shift difference between complexed and monomeric thiol (not determinable experimentally, since at no stage is all the thiol complexed). Plots of $1/\delta_{obs} - \delta_{monomer}$ versus $1/C_B$ yield straight lines from whose slope value of Δ and K may be obtained. Plots at different temperatures obtained with dimethylformamide as hydrogen bond acceptor are shown in Figure 2. From the variation of K with temperature the

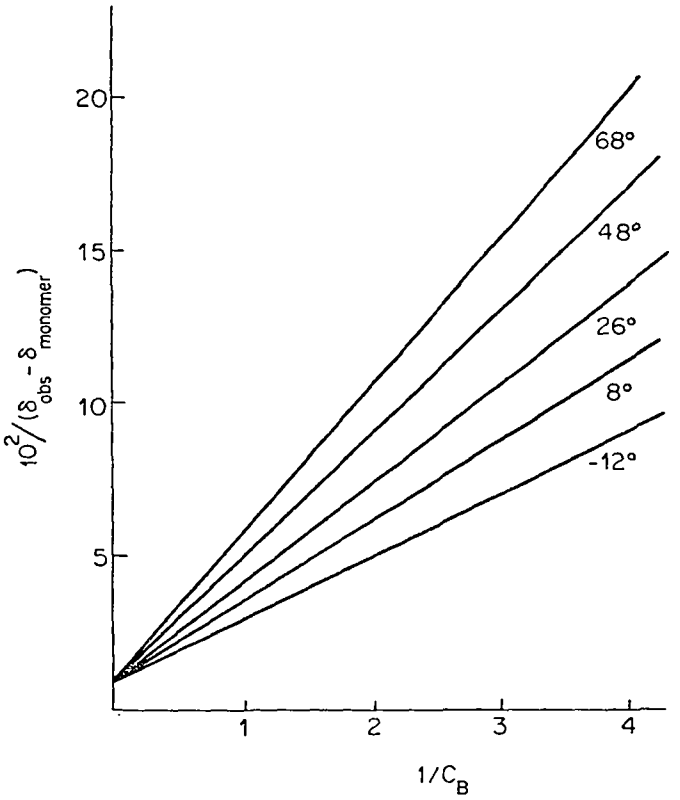


FIGURE 2. Variation of SH n.m.r. shift of thiophenol, $\delta_{obs} - \delta_{monomer}$ (Hz), with dimethylformamide concentration, C_B, in carbon tetrachloride solutions at various temperatures. See text for discussion. Reproduced by permission from R. Mathur, E. D. Becker, R. B. Bradley and N. C. Li, *J. Phys. Chem.*, **67**, 2190 (1963).

enthalpy of hydrogen-bond formation may be found. The results obtained with a series of bases are collected in Table 3.

The major limitation in the accuracy of these results arises from the small value of the intercept from which Δ is determined. There must be considerable error associated with the value of this quantity and hence

with the values of K obtained. The values of ΔH should, however, be more accurate since a change in the intercept would not appreciably affect the determination of ΔH. These results show that for these relatively strongly associated systems little correlation exists between association constant, K, and hydrogen bond shifts, Δ. In fact there appears to be an inverse

TABLE 3. Data for hydrogen bonding of thiophenol with various acceptors

Hydrogen acceptor	Δ (p.p.m.)	K (26°C) (l/mole)	$-\Delta H$ (kcal/mole)	Reference
Pyridine	1·1	0·22	2·4	61
N-Methylpyrazole	1·5	0·14	2·1	61
Tributylphosphate	1·8	0·43	2·0	61
Dimethylformamide	2·2	0·24	1·8	61
Benzene	−2·5[a]	0·039	0·5	61
N-Methylacetamide	2·2	0·14	0·9	62
Acetone	0·85	0·26[b]	3·2	63

[a] The shift is to high field due to the ring current effect in benzene.
[b] At 38°C.

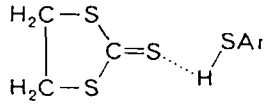
Recent results[33] give values of $K = 0{\cdot}24$ l/mole, $\Delta H = -1{\cdot}58$ kcal/mole for the association of methanethiol with hexamethylphosphoramide. Recent data[178] obtained by the n.m.r. method give values of $\Delta H \simeq -1$ kcal/mole, $\Delta S \simeq -8$ cal/deg. mole, for association of a series of aliphatic thiols with a variety of hydrogen-bond acceptors in carbon tetrachloride.

correlation between the enthalpy of association and Δ; thus the larger is the hydrogen bond shift the smaller is the heat evolved on association. However, it must be remembered that the values of Δ quoted are subject to considerable error. In a recent study[63] of hydrogen bonding of substituted thiophenols with acetone in carbon tetrachloride Russian workers have attempted to overcome this difficulty by measuring Δ directly. Their values for δ_{monomer} measured in dilute solution in carbon tetrachloride are no doubt accurate; however, the values for δ_{complex} obtained in acetone–carbon tetrachloride mixtures are unsatisfactory since the association constants are such that at no stage will complete conversion of thiol to hydrogen-bonded complex be achieved. At present it is unclear whether there exists a general correlation of wide applicability between the hydrogen bond shift, Δ, either in terms of association constant K or enthalpy change ΔH.

Evidence for the association (**10**) of several substituted thiophenols with the thione sulphur in ethylene trithiocarbonate is found[64] from

visible spectroscopy. Equilibrium constants of the order of 0·7 l/mole are reported.

Tetra-alkyl ammonium hydrosulphides, R_4NSH, have been prepared and are found to co-ordinate hydrogen sulphide at low temperatures[65,66]. The hydrogen bonded complexes so produced, $H_2S \cdot HS^-$, are found to



(10)

contain strong bonds with energies estimated variously in the range of 5 to 14 Kcal/mole. Calculations[67] using *ab initio* LCAO MO SCF techniques indicate that such a complex should indeed possess a very strong hydrogen bond. The most stable form is calculated to be a symmetric linear structure best represented as $(HS \cdots H \cdots SH)^-$ with a shortened S···S distance of 3·48 Å.

It is of interest to compare the relative hydrogen-bonding abilities of the thiol and hydroxyl groups[39]. The evidence suggests, despite the greater Brönsted acidities of thiols, that with a given base stronger hydrogen bonds are formed by alcohols and phenols than by the corresponding thiols. Thus to compare thiophenol and phenol[68]; enthalpies of association are considerably larger for the oxygen compound (with pyridine $-\Delta H = 9{\cdot}5$ Kcal/mole for phenol and 2·4 Kcal/mole for thiophenol), and infrared frequency shifts, $\Delta\nu/\nu$, are also considerably larger (again with pyridine, $\Delta\nu/\nu = 0{\cdot}15$ for phenol and 0·05 for thiophenol).

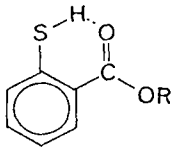
D. Intramolecular Hydrogen Bonding

Intermolecular and intramolecular hydrogen bonding are best distinguished spectroscopically from their concentration dependencies. Intermolecular association decreases with increasing dilution while intramolecular association is largely independent of concentration. A general review of intramolecular hydrogen bonding has been given[69].

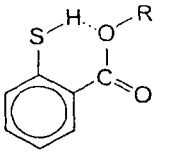
(11) (12)

Ortho-substituted thiophenols will exist in a mixture of *cis* (**11**) and *trans* (**12**) forms. In the absence of intramolecular association the *trans*

form would be expected, for steric reasons, to be favoured. However, if intramolecular hydrogen bonding occurs the *cis* isomer will have increased stability. Evidence for the intramolecular association of a number of *ortho*-substituted thiophenols comes from infrared spectroscopy. Thiosalicylic acid and its esters would appear to offer particularly good opportunities for such association[57] and examination of the ν_{SH} region indicates two bands both of which are at lower frequency than that expected (ca. 2585 cm^{-1}) for an unassociated thiol group. These bands which are at 2523 and 2556 cm^{-1} in the spectrum of the ethyl ester have been attributed[70] respectively to association with the carbonyl (**13**) or

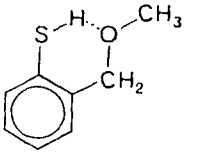


(13)



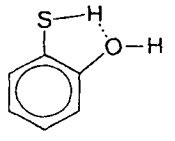
(14)

ethoxy (**14**) oxygen atoms. Examination of the carbonyl bands provides additional evidence for such associates and indicates that some intramolecular association persists even in the fairly basic solvent acetonitrile. The ether (**15**) shows in dilute solutions in carbon tetrachloride an intense band at 2560 cm^{-1} indicative of intramolecular association[70].

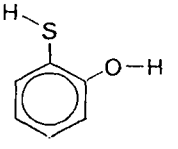


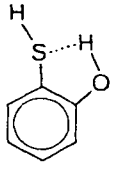
(15)

In the case of 2-hydroxythiophenol there is evidence[27] in inert solvents for a series of interactions involving intramolecular association of the thiol proton with oxygen (**16**) or hydroxyl proton with sulphur (**17**) as well as intermolecular association.



(16)
ν_{SH}—2547
ν_{OH}—3606



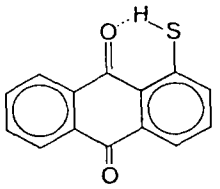


(17)
ν_{SH}—2595
ν_{OH}—3463

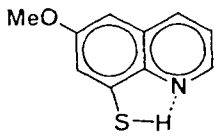
Similarly in the case of 2-aminothiophenol[27, 71 72, there is the possibility of intramolecular SH···N or NH···S bonding. The free ν_{SH} band is at 2559 cm^{-1} while that due to intramolecularly hydrogen-bonded thiol is at 2548 cm^{-1}. Examination of the amino frequencies indicates[72] that one NH always remains hydrogen bonded to sulphur so that a conformation with two internal hydrogen bonds seems possible.

Early studies indicated that 2-halogenothiophenols, in contrast to 2-halogenophenols, exist mainly in the unassociated *trans* form[26]. In addition studies[73, 179] of the intramolecular association of 2-nitrothiophenol by dipole moments and spectroscopy indicated considerably weaker hydrogen bonding than in the corresponding phenol. The infrared spectrum in carbon tetrachloride is reported[73] as showing two bands at 2555 and 2596 cm^{-1} attributed respectively to hydrogen bonded and free thiol groups. Solutions in acetone show a band at 2569 cm^{-1} due to association with the solvent. However, a recent investigation[74, 75] by infrared, n.m.r. and dipole moment measurements of thiophenols containing 2-halogen, 2-methoxy or 2-nitro substituents concludes that these compounds are present largely in the hydrogen-bonded *cis* form. The infrared results indicate that for these substituents intramolecular hydrogen bonding causes a large increase in intensity of the ν_{SH} absorption but little change in absorption frequency. Intramolecular association can also be discerned from the p.m.r. spectrum of these compounds in dilute solution in carbon tetrachloride. Such association causes a displacement to low field of the chemical shift of the SH protons.

There is chromatographic and spectroscopic evidence[76] for a weak intramolecular hydrogen bond in anthraquinone-1-thiol (**18**). Infrared spectra of 6-methoxy-8-mercaptoquinoline (**19**) show a concentration independent band at 2515 cm^{-1} indicating intramolecular association[77]. The SH···N bond enthalpies in a series of substituted 8-mercaptoquinolines are reported[78] to be in the range 2·4–3·1 kcal/mole.



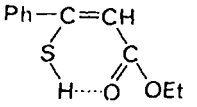
(18)



(19)

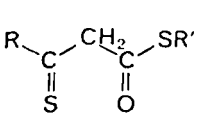
There have been relatively few reports of intramolecular hydrogen bonding in aliphatic thiols. The proximity of an oxygen atom might be expected to promote such association but an infrared investigation of 2- and 3-ethoxylalkylthiols, ethyl thioglycollate (CH_2SHCO_2Et) and other

esters found that little auto-association occurred[70]. However, some years ago Reyes and Silverstein[79] showed that ethyl thiobenzoylacetate exists largely in the intramolecularly hydrogen bonded enethiol form (**20**),

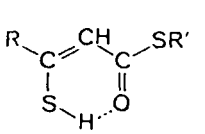


(**20**)

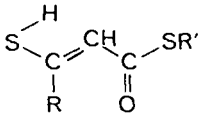
whose infrared spectrum shows a broad moderately strong thiol band at 2415 cm^{-1}. More recently many thiocarbonyl compounds have been found to contain a proportion of the enethiol form in tautomeric equilibrium with thioketone[80]. For example β-thioketoesters[81] and β-thioketothiolesters[82,83] can exist in three forms; the thioketo form (**21**) the hydrogen bonded *cis*-enethiol (**22**) and the *trans*-enethiol (**23**). The latter form is



(**21**)

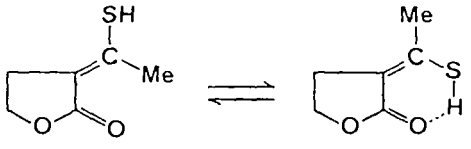


(**22**)



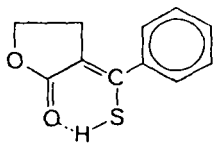
(**23**)

usually present only in very small concentration while the proportions of (**21**) and (**22**) depend on the solvent, more polar solvents giving a greater proportion of the thioketo tautomer. In the hydrogen bonded structure (**22**) the infrared absorption of the thiol group is at ca. 2420 cm^{-1} while the n.m.r. absorption is at low field ($\delta \simeq 7{\cdot}3$ p.p.m.). N.m.r. and infrared studies[80] of α-thioacyl-lactones and α-thioacylthiol-lactones show that the aliphatic compounds, for example (**24**), exist as equilibrium



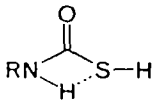
trans (**24**) *cis*

mixtures of *cis*- and *trans*-enethiol forms while the thioaroyl-lactones, for example (**25**), are present exclusively as intramolecularly bonded *cis*-enethiols

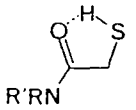


(**25**)

Spectroscopic studies of mercaptoacetamides[84] indicate the presence of intramolecular association. The infrared spectra suggest structure (**26**) when nitrogen is primary or secondary and (**27**) for tertiary substituted nitrogen.



(**26**)



(**27**)

II. THE ACIDITY OF THIOLS

A. *Introduction*

In this section the acidities of aliphatic and aromatic thiols are considered. Most measurements relate to water or other hydroxylic solvents at 25°C. Regrettably few determinations of enthalpies and entropies of ionization have been reported.

A recent general review[85] considered the effects of polar substituents on the ionization of acids. Internal effects intrinsic to the molecules concerned are distinguished from environmental effects resulting from interactions with the solvent. Hepler's work[174] with phenols indicates that for aqueous solutions near room temperature the change in Gibbs Free Energy of ionization (and hence the charge in pK) on substitution results largely from internal enthalpy effects. Changes in solute–solvent interactions are less important because the associated environmental enthalpy and entropy changes almost, or exactly, cancel. Changes in pK_a may then, in the absence of steric effects, be expected largely to reflect changes in polar effects of substituent groups. Changes in solute–solvent interactions are detected by changes in entropies of ionization.

B. *Aliphatic Thiols*

The acid dissociation constants in water of a number of aliphatic thiols have been determined. The most frequently used methods have been potentiometric titration and spectrophotometry[86]. The latter method takes advantage of the moderately strong ultraviolet absorption (λ_{max} at ca. 240 nm) of the thiolate anions[87] which enable their concentration to be determined. In general, the agreement between the values obtained by different groups of workers is not particularly good. This may in some cases be due to the unjustified neglect of activity coefficients which will result in rather large effects when dianions are formed as, for example,

with thioglycollic acid ($SHCH_2COOH$) and thiolactic acid ($SHCH_2CH_2$-$COOH$). The values collected in Table 4 are thought to be close to the thermodynamic values for the dissociation constants. Some measurements relating to alcohol–water solvent have also been reported[88,89].

The results in Table 4 show that the presence of electron-withdrawing groups tends to increase the acidity of thiols and a correlation with Taft's inductive parameters[90], σ^*, has been reported for a number of substituted methanethiols, RCH_2SH. The equation (1) is applicable[91,92] when σ^*

$$pK_a = 10{\cdot}22 - 3{\cdot}50\sigma^* \quad (1)$$

relates to the substituent RCH_2, or (2) when σ^* relates[93] to the substituent

$$pK_a = 10{\cdot}54 - 1{\cdot}47\sigma^* \quad (2)$$

R. The thiols are more acidic than the corresponding alcohols by between 5 and 6 pK units. However, the value of 1·47 for ρ^* the reaction constant is similar to that, 1·42, for the ionization of alcohols. It has been noted[91] that thiophenol ($pK_a = 6{\cdot}5$) and hydrogen sulphide are more acidic than is predicted from the inductive parameters. For the former compound this increased acidity is no doubt due to a resonance effect in which the negative charge on sulphur in the thiophenoxide ion is delocalized into the aromatic ring. The resulting enhancement in acidity was estimated as 1·6 pK units which is considerably smaller than the corresponding enhancement for phenol. The greater than predicted acidity of hydrogen sulphide was attributed to a steric effect on solvation, the SH^- ion being surrounded by a nearly symmetrical solvation shell which is diminished in the presence of an alkyl group.

The results in Table 4 show that the acidity of alkyl thiols decreases with increasing chain length and chain branching. This might be taken to indicate the intrinsic electron-releasing ability of alkyl groups. However, it should be noted that in the case of alcohols, measurements in the gas phase[103] give an acidity order *t*-butanol > ethanol > methanol which is the reverse of that found in water. Thus in the gas phase alkyl groups can stabilize alkoxide ions. Hence the acidity order found in solution may not represent the intrinsic acidities of the molecules. The reversal of the acidity order found in solution may result from steric inhibition to solvation of the larger anions.

The n.m.r. shifts of the SH groups of several aliphatic thiols at infinite dilution in carbon tetrachloride solution have been measured[109]. The shifts are affected by a number of factors including electronegativity, anisotropy, orientation and the number of α-carbon—carbon bonds.

TABLE 4. Acid dissociation constants for some thiols[a] in water at 25°C

Thiol	pK_a	Reference
CH_3SH	10·3	92
C_2H_5SH	10·5, 10·6, 10·61	94, 91, 95
n-C_3H_7SH	10·65	96
i-C_3H_7SH	10·86	95
n-C_4H_9SH	10·65	96
t-C_4H_9SH	11·05, 11·05, 11·2	92, 96, 95
t-$C_5H_{11}SH$	11·2, 11·35	96, 92
$HOCH_2CH_2SH$	9·43, 9·44, 9·6, 9·7	91, 97, 94, 95
$C_2H_5OCH_2CH_2SH$	9·38	91
$HOCH_2C(CH_3)_2SH$	9·85	92
$HOCH_2CH(OH)CH_2SH$	9·46	97
$HOCH_2CH_2CH(OH)CH_2SH$	9·5, 9·65	91, 98
$HSCH_2CH_2SH$	9·05	97
	10·56[b]	97
$HOCH_2CH(SH)CH_2SH$	8·62	97
	10·57[b]	97
$C_6H_5CH_2SH$	9·43	91
$CH_2{=}CHCH_2SH$	10·0	91
CH_3COCH_2SH	7·9	91
(2-pyridyl)CH_2SH	8·8	92
$CH_3CONHCH_2CH_2SH$	9·92	95
$^-O_2CCH_2SH$	10·53, 10·55, 10·68	99, 100, 95
	10·15[c], 10·22[c]	101, 102
$C_2H_5OCOCH_2SH$	7·93	91
CH_3OCOCH_2SH	7·7	94
$^-O_2CCH_2CH_2SH$	10·2, 10·4, 10·5, 10·8	94, 103, 104, 95
$C_2H_5OCOCH_2CH_2SH$	9·5	92
$^-O_2CCH_2CH(SH)CO_2^-$	11·14	105
	10·45[c]	105
$^-O_3SCH_2CH_2SH$	9·5	94
$^-O_3SCH_2CH(SH)CH_2SH$	8·93	105
	12·3[b]	106

[a] For additional data including values in alcohol–water mixtures, see reference 107.
[b] Second dissociation constant.
[c] In 0·1 mole/l potassium chloride.

However, in general, electron-withdrawing groups which tend to increase the acidity of the thiols give rise to a shift to low field. A correlation involving σ^* was found.

C. Hydrogen Sulphide

The acidity of hydrogen sulphide itself has been the subject of numerous investigations. The value of $pK_a = 7{\cdot}02$ for the first dissociation seems well established[96, 110]. A value of $pK_{a,2} = 15$ for the second dissociation

constant in water of 25°C has long standing[111]. However, more recent work[112] indicates greater acidity for the HS^- ion with values of ca. 14. Thus Widmer and Schwarzenbach[113] obtained a value of 14·15 in 1 mole/l potassium chloride from galvanic cell measurements, and Ellis and Golding[110] a value of 14·0 corrected to zero ionic strength from spectrophotometric measurements. In the latter case the decrease in absorption at 230 nm as the base concentration was increased in the range 0–1 mole/l was attributed to the progressive conversion of HS^- to S^{2-} ions. However, the most recent spectrophotometric measurements by Giggenbach[114] indicate that in alkaline solutions from which oxygen has been excluded no decrease in HS^- absorption occurs up to 5 mole/l aqueous base and that half conversion to the S^{2-} ion (with an absorption maximum at 250 nm) is achieved only in 15 mole/l base. In conjunction with previously reported values for the H_- acidity function a value of ca. 17·1 was derived for $pK_{a,2}$. It was suggested[114] that the previously observed decrease in absorption in less basic media resulted from loss of HS^- by oxidation rather than S^{2-} formation.

The properties of liquid hydrogen sulphide as a non-aqueous solvent have been reviewed[5]. The autoprotolysis constant has the value 25×10^{-34} at $-78°C$.

D. Aminothiols

Simple aminothiols such as 2-aminoethanethiol are protonated on nitrogen in acidic solution. The acidity of the thiol group in the cation is considerably greater than that of the ammonium group so formed so that a range of pH exists where the substrate is present mainly in zwitterionic form ($^-SCH_2CH_2NH_3^+$). In more basic solutions ionization of the ammonium group occurs. Some data relating to aqueous solutions are in Table 5; in addition some measurements have been reported for a methanol–water solvent[115]. The presence of the positive charge on nitrogen in solutions of 2-aminoethanethiol makes the acidity of the thiol group considerably greater than in, for example, ethanethiol. The results indicate that in compounds where the sulphur and nitrogen atoms are separated by two carbon atoms little variation in pK_a value is observed with the thiol group at a primary, secondary or tertiary carbon atom[116].

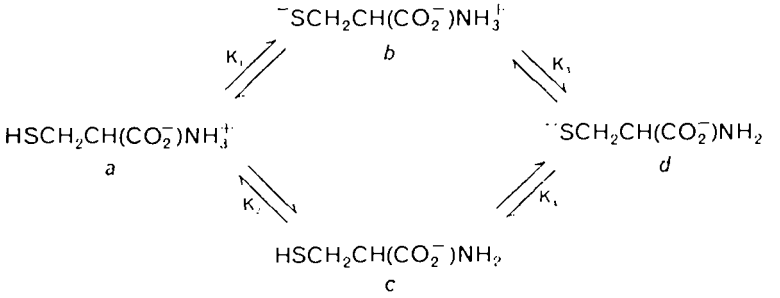
In some aminothiols the acidities of the SH and NH_3^+ groups are not well separated. In these cases potentiometric titration will give only a macroscopic dissociation constant. Benesch and Benesch[117] have shown that by using the ultraviolet absorption of the thiolate ions it is possible to measure the relative acidities of the thiol and ammonium groups and hence obtain specific ionization constants. Raman spectroscopy[118] and

TABLE 5. Acid dissociation constants of some aminothiols in water at 25°C

Parent	pK_a (SH)	pK_a (NH_3^+)	Reference
$HSCH_2CH_2NH_3^+$	8·35, 8·23, 8·19	10·75[a]	117, 95, 116
$HSCH(Me)CH_2NH_3^+$	8·10	10·12[a]	116
$HSCH(Et)CH_2NH_3^+$	8·19	10·91[a]	116
$PhCH_2CH(SH)CH_2NH_3^+$	8·00	11·04[a]	116
$(Me)_2C(SH)CH_2NH_3^+$	8·07	10·77[a]	116
$HSCH_2CH(Me)NH_3^+$	8·14	10·81[a]	116
$HSCH_2CH(CO_2^-)NH_3^+$	8·54	8·86	117, 120
$HSCH_2CH(CO_2^-)NH_2$	10·21	—	120
$HSCH_2CH(CO_2^-)NMe_3^+$	8·65	—	126
$HSCH_2CH(CO_2Et)NH_3^+$	7·45	6·77	117
$HSCH_2CH(CO_2Et)NH_2$	9·09	—	117
$HSCH_2CH(CONHCH_2CO_2^-)NH_3^+$	7·87	7·14	117
$HSCH_2CH(CONHCH_2CO_2^-)NH_2$	9·48	—	117
$(Me)_2CH(SH)CH(CO_2^-)NH_3^+$ (penicillamine)	8·17	8·61	127
$(Me)_2CH(SH)CH(CO_2^-)NH_2$	10·33	—	127

[a] This is the value for the second ionization of the parent.

calorimetric data[119] have also been used for this purpose. These methods have been put to good use in studies of the ionizations of cysteine[117, 120, 121], a molecule of biological importance. The overall ionization process is represented by the scheme:



The presence of the α-carboxyl group in cysteine results in an increase, relative to 2-aminoethanethiol, in the acid strength of the ammonium group, presumably because the inductive effect of the carbonyl group outweighs the electrostatic effect of the negative charge. Thus the acidity of the thiol group (pK_1 = 8·54) is only slightly greater than that of the

ammonium group ($pK_2 = 8{\cdot}86$). In more basic media the dianion is formed with $pK_3 = 10{\cdot}53$ and $pK_4 = 10{\cdot}21$. Modification of the carboxyl group of cysteine, as in the ethyl ester or the glycine peptide, results in a general increase in the acidity of the molecule (see Table 5). In these compounds where the negative charge is removed from the vicinity of the ammonium group, the acidity of the latter group is greater than that of the thiol group. The dissociation of a number of aminothiols including cysteine has been examined recently by ^{13}C n.m.r. spectroscopy and the results discussed in terms of the pH dependence of charge distribution within these molecules[122].

It has been shown recently[123] by use of relaxation techniques that for cysteine and related compounds anions *b* and *c* are rapidly interconverted by an intramolecular proton transfer process (relaxation time $2{\cdot}8 \times 10^{-9}$ s). For the systems studied the intramolecular proton exchange is faster by two or three orders of magnitude than the protolysis reactions.

It has been noted[124, 125] that the acidity of thiol groupings is sensitive to local structure both by way of inductive effects and also through medium effects. Hence in proteins where the SH group may be in the proximity of acidic or basic amino-acid side chains considerable variations in acidity may be found.

E. Thio Acids and Dithio Acids

The chemistry of thio acids (RCOSH) and dithio acids (RCS_2H) has been reviewed[49, 128]. In the case of the thio acids it appears that although there is a tautomeric equilibrium the thiol form predominates markedly over the thione form.

The acidities of several compounds have been measured (see Table 6). As expected the acidities of the thio acids are greater than those of the corresponding carboxylic acids. However, the difference in acidities is only ca. $1{\cdot}5\ pK$ units, which is much smaller than the difference in the acidities of thiols and alcohols. This small difference probably results largely from the smaller resonance stabilization of the $RCOS^-$ anion compared with that of RCO_2^-. The dithio acids are more acidic than the corresponding thio acids. Ethyl xanthic acid ($EtOCS_2H$) which is useful preparatively has been the subject of several investigations[129-132]. The free acid is unstable and extrapolation of measurements to zero time is necessary for the determination of the dissociation constant ($pK_a = 1{\cdot}55$).

The acidities of several hydroxy-substituted dithiobenzoic acids have been measured[133-136]. The acid strengthening effect of an hydroxy substituent *ortho* to the acid group may indicate internal hydrogen bonding

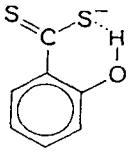
TABLE 6. Acid dissociation constants of thio acids and dithio acids in water at 25°C

Acid	pK_a	Reference
MeCOSH	3·33, 3·33, 3·41, 3·62	138, 139, 92, 95
n-PrCOSH	3·75	140
PhCOSH	2·48	138
HSOC·COSH	0·91	141
$^-$SOC·COSH	2·71	141
$MeCS_2H$	2·55	129
$EtOCS_2H$	1·51, 1·52, 1·55, 1·62	130, 131, 129, 132
H_2NCS_2H[a]	2·95	142
$EtSCS_2H$	1·55	129
$HSCS_2H$	2·7	143
$PhCS_2H$	1·92	133
$4\text{-}HOC_6H_4CS_2H$	2·58	133
$2\text{-}HOC_6H_4CS_2H$	1·55	134
$2,4\text{-}(OH)_2C_6H_3CS_2H$	1·91	133
$2,3,4\text{-}(OH)_3C_6H_2CS_2H$	1·72	133

[a] For some data on N-substituted dithiocarbamic acids see reference 144.

in the anion, (**28**), an effect which is important in the oxygen analogue, salicylic acid.

The acidities of thio acids and dithio acids have been compared in aromatic solvents by measurement of the extent of proton transfer to the indicator crystal violet[137]. In this relatively non-polar solvent ion-pairs are formed.



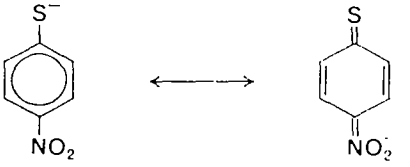
(**28**)

F. Thiophenols

The acidity of thiophenol in water ($pK_a = 6·50$)[92] is considerably greater than that of phenol ($pK_a = 9·99$)[39] although the difference in acidities is less than that between aliphatic thiols and alcohols. The greater resonance interaction of oxygen with the aromatic ring compared with sulphur probably accounts for the smaller difference. Surprisingly few pK_a values have been obtained for substituted thiophenols in water. This probably results from their low solubilities; however, the spectrophotometric method which requires very small concentrations should prove applicable. Values for the following substituents are reported as:

2-CO_2^-, $pK_a = 8{\cdot}88$[95], 8·6[145], 8·4[146], 8·2[107,147]; 3-CO_2^-, 6·25[107]; 4-CO_2^-, 5·80[95], 5·90[107]; 2-Me, 6·64[107]; 3-Me, 6·58[107]; 4-Me, 6·52[107]; 4-Cl, 5·9[107]; 4-SO_3^-, 5·7[148]; 4-NO_2, 4·5[149] and for C_6F_5SH, 2·68[149]. It should, however, be noted that in some cases measurements were made in solutions of fairly high ionic strength so that the values so obtained may differ somewhat from the thermodynamic ones.*

Considerably more data are available in mixed ethanol–water solvent systems where dissociation constants have been determined by Schwarzenbach and coworkers[150,151] using a hydrogen electrode. Others[152–154] have measured apparent acidity constants by determining with a pH meter the acidities of partially neutralized solutions of the substituted thiophenols. Data are collected in Table 7. In addition some data are available in methanol[155] or methanol–water mixtures[56]. For those substituents where resonance interaction or steric effects are not important a good correlation with Hammett σ constants is obtained. Values for the reaction constant ρ have been calculated[156] as 3·02 in 95% ethanol at 21°C, 2·62 in 48% ethanol at 25°C and 2·42 in 49% ethanol at 21°C. Chuchani and Frohlich[154] have calculated a value of 1·81 in 20% ethanol; however, recalculation using the methods of van Bekkum and coworkers[156] gives a value of 2·0.* It seems likely that the reaction constant in water will have a value close to 2·0 similar to that (2·23) governing the ionization of phenols[157]. For those substituents such as NO_2, SO_2Me, COMe which are capable of electron-withdrawing resonance interaction enhanced σ values are required[152,153]. This acid-strengthening effect no doubt results from the greater stabilization of the thiophenoxide anions (**29**) than the parent thiophenols. The stabilization of the anions from this source is, however, smaller than that observed in the case of phenols[152]. Thus $\sigma_{NO_2} = 1{\cdot}00$ for 4-nitrothiophenol and 1·24 for 4-nitrophenol.



(29)

The possibility of octet expansion of sulphur through electron-pair acceptor conjugation has been considered, e.g. **30**. This effect would be acid-weakening due to the greater stabilization of the parent thiophenol than the thiophenoxide ion. Bordwell and Boutan[158] found that the *para* resonance effects of some substituted thiophenols, and phenols (where

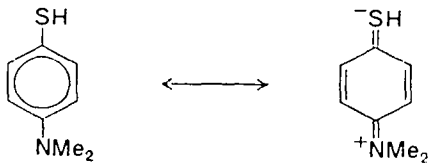
* Data for a number of substituted thiophenols in water have recently become available, and give a ρ value of 1·8. [P. De Maria, A. Fini and F. M. Hall, *J. Chem. Soc., Perkins II* 1969 (1973)].

TABLE 7. Acidities of thiophenols in ethanol–water mixtures at 20°C

Substituent	20–80 v/v EtOH–H_2O[a]	49–51 v/v EtOH–H_2O[b]	95–5 v/v EtOH–H_2O[c]
2-CO_2^-		10·69	13·4
2-NMe_2	10·18		
4-NH_2	7·47		10·45[g]
4-NMe_2	7·41	8·37[d]	
3-CO_2^-		8·07	10·25
4-CO_2^-		7·85	10·1
2-CO_2Me		8·46	10·0
4-OH		8·33	10·02
2-Me			9·87[g]
4-OMe	7·06	8·08	9·76, 9·71[g]
4-Me	7·08	8·07, 8·03[e]	9·66, 9·60[g]
3-Me	6·99	7·99, 7·96[e]	9·56
3-NMe_2	6·99	7·94[d]	
3-NH_2	6·95		
H	6·81	7·78, 7·76[e]	9·32, 9·28[g]
2-NHMe	6·77		
3-OMe	6·60	7·54	9·18, 9·14[g]
2-NH_2	6·54		9·02[g]
4-F			8·88[g]
4-Cl		7·06	8·45
4-Br		7·00, 6·99[e]	8·37
3-CO_2Me		6·98	8·40
4-I		6·99	8·32
3-COMe		6·93	8·35, 8·27[g]
3-Br	6·11	6·77[e]	8·22, 8·20[g]
3-Cl	6·07	6·85	8·15, 8·09[g]
3-I		6·85	8·08
4-CO_2Me		6·17	7·50
4-COMe		5·93	7·28, 7·47[g]
2-NO_2		5·99	7·46
3-NO_2		5·90[e]	
3-SO_2Me		5·88[e]	
4-SO_2Me		5·57[e]	
4-NO_2		4·99, 5·11[e]	6·42
4-NMe_3^+		5·60, 5·68[f]	6·35

[a] Reference 154.
[b, c] Reference 150, 151.
[d] Reference 158.
[e] Reference 152.
[f] Reference 159.
[g] Reference 153.

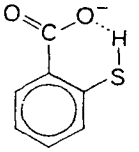
resonance of this type is not likely), were similar. They thus concluded that resonance interaction as in **30** must be negligible. However, a contradictory report[160] indicates a noticeable effect with NMe_2 and OMe substituents. The most recent evidence[154] shows that the effects of such resonance are small and not definitely proven.*



(30)

Recent measurements[160] show that bulky substituents in the 2-position of thiophenols lead to decreases in acidity due to steric effects. As in the case of phenols[39] the major effect is thought to be steric inhibition of solvation of the thiolate anions.

An unexpected solvent effect is found in the ionization of carboxyl-substituted thiophenols. In water the ionization of the thiol group is facilitated by *m*- or *p*-CO_2^- substitution. However, in ethanol–water mixtures this substituent is acid weakening. This change probably arises from the better solvation of the CO_2^- group by water than by the alcoholic solvents (cf. reference 85). The very weak acidity of the thiol group in thiosalicylic acid may indicate stabilization by intramolecular hydrogen bonding, **31**, an effect which is apparent with salicyclic acid[39]. Similarly the reportedly weakly acidic nature of 2-methoxycarbonyl thiophenol may result from intramolecular association as in **13** (R = Me).



(31)

The acidities of substituted thiophenols have also been investigated spectroscopically by use of infrared or n.m.r. methods. Thus the chemical shifts of the thiol resonances of eleven substituted thiophenols in dilute solution in carbon tetrachloride correlate well with Hammett σ values[109]. The shifts, measured in Hz downfield from TMS are given by

$$\delta_{SH} = -17{\cdot}0\sigma - 194{\cdot}4$$

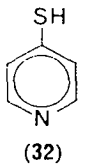
An enhanced value of σ is required for the 4-nitro substituent. The

* I.r. intensities indicate d-orbital electron acceptance when divalent sulphur is opposed by donor substituents. [N. C. Cutress, T. Grindley, A. R. Katritzky and R. D. Topsom, *J. Chem. Soc., Perkins II*, 263, (1974)].

correlation of infrared frequencies ν_{SH} of substituted thiophenols with σ values is less certain[161]. Miller and Krishnamurthy[162] found little correlation between these quantities. However, their data were drawn from two sources and the concentrations of thiols may have been too high so that hydrogen-bonded species were present. In contrast David and Hallam[56] found a reasonable correlation between frequency ν_{SH} and acid dissociation constant (pK_a) measured in methanol. However, they suggest that the best measure of proton donating power of an acid is the relative solvent shift $\Delta\nu/\nu$. Their method involves measuring the frequency ν_{SH} of a substituted thiophenol in a series of solvents ranging from carbon tetrachloride to di-*n*-butylether and plotting the quantities $\Delta\nu/\nu$ so obtained against the corresponding shifts for a reference acid in the same solvents. The slopes, S, so obtained give a measure of the relative acidities of the substituted thiophenols and correlate well with independently measured pK_a values.

G. Heteroaromatic Thiols

The study of mercaptopyridines is complicated by the presence of tautomeric equilibria. The ultraviolet spectra show clearly that in aqueous solution forms with the mobile hydrogen atom on nitrogen are favoured over those with hydrogen on sulphur[163,164]. Thus the spectra of mercaptopyridines closely resemble those of their N-methyl derivatives and are quite different from those of the S-methyl derivatives. For 2- or 4-mercaptopyridines (**32**) the tautomer with hydrogen on nitrogen can exist as a resonance hybrid with zwitterionic (**33**) or thioamide (**34**) forms and is



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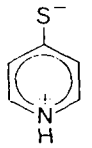

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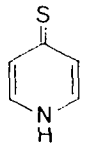
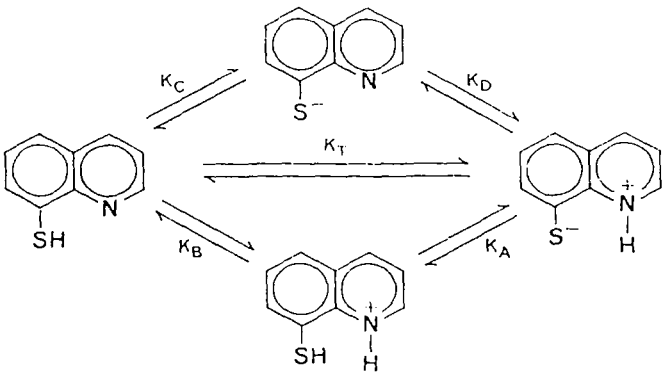


(34)

favoured by a factor of ca. 10^4. For 3-mercaptopyridine where the thioamide form is not present the ratio of tautomers is reduced from 10^4 to 150. Measurement of the acidities of these compounds thus yields values characteristic of proton loss from nitrogen rather than proton loss from sulphur.

A similar situation holds for mercaptoquinolines and mercaptoisoquinolines where again tautomers with hydrogen on nitrogen are favoured[164]. The macroscopic acidity constants of a series of substituted

8-mercaptoquinolines have been measured and interpreted according to the following scheme[165]:



If the reasonable assumption[166] is made that the value of K_B is equal to that for protonation of S-methyl-8-mercaptoquinoline then the five individual equilibrium constants can be found. The values are reported as $pK_A = 2{\cdot}07$, $pK_B = 3{\cdot}50$, $pK_C = 6{\cdot}84$, $pK_D = 8{\cdot}27$ and $K_T = 27$. The effects of ring substituents on these values have been discussed[165, 167, 168].

H. Deuterium Isotope Effects

Isotope effects on the ionization of the thiol groups of a series of compounds ranging in acidity from pentafluorothiophenol to thioglycollate ion have been measured[149]. The ratios of the dissociation constants, K_{H_2O}/K_{D_2O}, are in the range 2·0—2·5. The isotope effects are considerably smaller than those for the ionization of oxygen or nitrogen acids where $K_{H_2O}/K_{D_2O} = 2{\cdot}5$—$4{\cdot}5$. The relatively small magnitude of the isotope effect for thiols results from the low stretching and bending frequencies of the S—H bond and may provide a method of distinguishing thiols from oxygen or nitrogen acids. There is a small increase in the magnitude of the isotope effect with decreasing thiol acidity:

$$\Delta pK_a = 0{\cdot}26 + 0{\cdot}012pK_a$$

where pK_a is the value in water and ΔpK_a is the increase on going to deuterium oxide. This increase and the magnitude of the difference in the isotope effects of RSH and ROH provide evidence that isotope effects on the interaction of RS^- and RO^- with the solvent contribute to the observed effects.

I. Thermodynamics of Ionization

Relatively few enthalpies and entropies of ionization of thiols have been determined. The only systematic study appears to be that of Irving,

Nelander and Wadso[95] who measured ionization enthalpies calorimetrically. Data are collected in Table 8. The ionization enthalpies for the thiols studied are close to 6 kcal/mole except for thioacetic acid where the value is much smaller and close to that for carboxylic acids. There is

TABLE 8. Thermodynamic data for ionization of thiols in water at 25°C

Thiol	ΔG^0 (Kcal/mole)	ΔH^0 (Kcal/mole)	$-\Delta S^0$ (cal/deg.mole)	Ref.
EtSH	14·48	6·42	27	95
i-PrSH	14·82	5·38	31·7	95
t-BuSH	15·31	5·30	33·5	95
$HOCH_2CH_2SH$	13.26	6·21	23·7	95
	13·2	6·49	22·5	94
$AcNHCH_2CH_2SH$	13·54	6·26	24·4	95
		6·5		169
$(CO_2^-)CH_2SH$	14·58	6·28	27·8	95
	14·3	6·9	24·6	117
	14·2	7·4	23	94
$(CO_2^-)CH_2CH_2SH$	14·79	6·1	29·2	95
	14·2	7·3	23	94
$^+NH_3CH_2CH_2SH$	11·23	7·43	12·7	95
	11·4	6·08	17·6	94
$HSCH_2CH(CO_2^-)NH_3^+$	11·7	7·5	14	120
$HSCH_2CH(CO_2^-)NH_2$	14·1	6·4	25	120
CH_3COSH	4·94	0·56	14·7	95
$2\text{-}CO_2^-C_6H_4SH$	12·12	5·72	21·5	95

little correlation between the pK_a values for the thiols and ΔH^0 values. However, a linear relationship was found[95] between pK_a (or ΔG^0) and ΔS^0:

$$\Delta S^0 = -5{\cdot}92\ pK_a + 34{\cdot}1$$

The entropies of ionization will be affected by solute–solvent interactions. The stronger the solvent orientation at the anion the more negative the entropy change. Comparison of ethanethiol with 2-aminoethanethiol shows a much less negative value for the latter compound in which ionization gives a zwitterion. The entropies of ionization become more negative along the series EtSH, *i*-PrSh, *t*-BuSH a fact which has been attributed[95] to increasing solvent orientation in the disordered region outside the inner hydration shell of the acid anions.

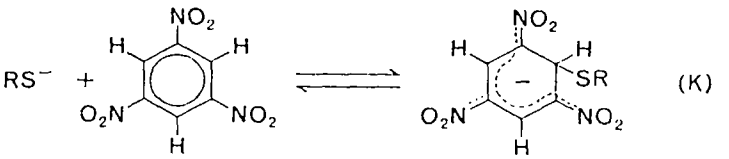
J. Carbon Basicities of Sulphur Bases

So far in this chapter the acidities of thiols have been considered with acid dissociation constants referring to the ionization of thiols to give a proton and thiolate ion. The reverse reaction, as shown below, effectively measures the affinity of a base for protons in the traditional Brönsted sense (proton basicity).

$$RS^- + H^+ \rightleftharpoons RSH \quad (K_a)^{-1}$$

It is, however, possible to compare the thermodynamic affinities of bases for other atoms and measure, for example, carbon basicities. These measurements are of interest both intrinsically and also because of their relevance to the kinetic reactivities (nucleophilicities) of the bases. It is well known that in nucleophilic substitution reactions sulphur bases are considerably more reactive relative to oxygen bases than would be expected from their Brönsted basicities[170, 171].

The carbon basicities of several sulphur bases have been compared by measuring[172] the equilibrium constants for σ-complex formation with activated aromatic compounds such as 1,3,5-trinitrobenzene:



(35)

The equilibrium constants, K, give a measure of the thermodynamic affinities of the sulphur bases for an aromatic carbon atom. In Table 9

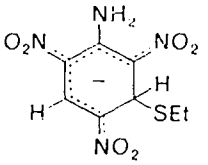
TABLE 9. Comparison of proton and carbon basicities of sulphur and oxygen bases[172]

	log K (σ-complex formation)	pK_a
MeO^-	1·15	15·5
PhO^-	$< -2·7$	10·0
EtS^-	3·54	10·6
PhS^-	0·29	6·5

the equilibrium constants measured in methanol for oxygen and sulphur bases are compared with the pK_a values measured in water. The results show that the carbon basicities decrease in the order $EtS^- > MeO^- >$

$PhS^- > PhO^-$ while the proton basicities are in the order $MeO^- > EtS^- > PhO^- > PhS^-$. The carbon basicities of methoxide and thiophenoxide ions are similar although the proton basicity of the oxygen base is about 9 log units larger. In terms of the theory of soft and hard acids and bases these results can be understood as the greater affinity of the soft polarizable sulphur bases for the soft carbon atom and the hard oxygen bases for the hard proton.

Comparison of the relative affinities of thioethoxide ions for carbon or hydrogen can also be made from measurements with 2,4,6-trinitroaniline[172]. The thioethoxide ion gives, almost exclusively, the adduct **36** resulting from covalent addition at a ring carbon atom. In contrast oxygen bases give a mixture of **37**, the anion formed by proton loss, and **38**, the σ-complex.



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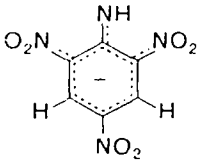

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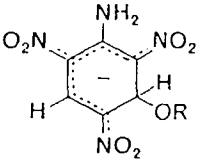

(38)

In a comparison of the carbon basicities of the hydroxide ion and thiophenoxide ion Bunnett, Hauser and Nahabedian[173] found that OH^- was bound about 10^3 times more tightly than PhS^- to the 9-position of 10-methyl-9-phenylacridinium ion.

Substituent effects on the carbon basicities of thiophenoxide ions have been measured[153] using the reaction with 1,3,5-trinitrobenzene. The general behaviour pattern is similar to that for the effects of substituents on proton basicities. The Hammett ρ values for the reactions in a solvent of 95/5 (v/v) ethanol water were found to be $-3{\cdot}33$ (carbon basicities) and $-3{\cdot}02$ (proton basicities).

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The Chemistry of the Thiol Group
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CHAPTER 9

Directing and activating effects

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I. INTRODUCTION AND GENERAL FEATURES

In this chapter we will discuss the electronic and proximity effects of the thiol group. This will be considered as a substituent in a molecule which reacts or is perturbed at a site other than the substituent itself. Therefore,

little attention will be paid to phenomena and reactions in which the thiol function is the primary centre of modification.

The proximity effects being discussed include those deriving from intramolecular participation of the thiol function in the reaction as well as those related to conformational equilibria involving thiol-substituted molecules.

The available literature is mainly concerned with the reactivity of the thiol function, whereas studies on its electronic properties, particularly from a quantitative point of view, are rather scarce; this is mainly due to the practical impossibility of avoiding strong involvement of the thiol group itself with the usual inorganic and organic reactants. In these cases it is difficult and therefore questionable to distinguish between the effects on reaction path and rate imparted by the thiol group itself and those due to its permanent or temporary modifications.

It has long since been recognized[1,2] that divalent sulphur groupings, such as thiol, owing to the unshared electrons on the sulphur atom are able to enter into conjugative interactions with electron-deficient sites or with electron-withdrawing unsaturated residues.

This resonance effect of the bivalent sulphur function, which involves contributions from a 2p–3p π-bond between carbon and sulphur, is smaller in magnitude than that of the oxygen analogues, since the latter requires contribution from a 2p–2p π-bond between oxygen and carbon. Furthermore, since the thiol group is polar and acidic, it can display inductive effects either as a thiol function or as a thiolate ion.

Besides the effects which can be attributed to the electronegativity and polarizability of the sulphur atom, a further one has been considered. This effect is possible, since the sulphur atom, as a second row element, may participate in resonance through structures having ten electrons: this is usually referred to as 'valence shell expansion'[3].

This hypothesis has been invoked to explain the anomalous behaviour of bivalent sulphur compared to oxygen, and especially the fact that hydrogen atoms in α-position to bivalent sulphur are much more acidic than in the corresponding oxygen derivatives[2,4]. Actually the greater acidity has been explained through the capability of sulphur, which has unoccupied 3*d*-orbitals, of expanding its valence shell through electron-pair acceptor type conjugation. In this way the higher stability of α-mercaptocarbanions may be explained as shown below:

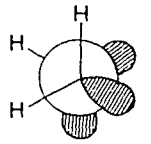
The introduction of this theory allowed many typical reactions and

properties of thiols to be interpreted assuming valence shell expansion without paying enough attention to alternative explanations. However, recent theoretical work[5] did cast serious doubt on this interpretation which had already been criticized on the ground of the energy values involved[6,7].

Wolfe and colleagues[5] studied by means of non-empirical molecular orbital calculations the carbanion of methane-thiol (**1**) and computed a three-dimensional energy surface for rotation about the C—S bond and inversion of the HCH angle.

$:\bar{C}H_2—SH$

(1)



(2)

The energy minimum is reached with the conformation (**2**) which maximizes gauche interactions between adjacent electron pairs without requiring significant contributions from the *d*-orbitals of sulphur. These conclusions are certainly quite reliable, since they have been obtained by means of a complete *ab initio* treatment.

II. POLAR EFFECTS

Various theories and parameters involving the electronegativity of atoms and groups are currently employed in organic chemistry to explain molecular properties. However, conformational effects have also to be introduced in order to predict correctly reaction pathways which could not be explained on the basis of electronic properties alone. In fact small variations of molecular geometry imparted by the environment or by substituents may strongly affect molecular properties[8] (see section V.D). Even though completely satisfactory theories about the dependence of chemical properties on electronic distribution and structural requirements have not yet been obtained, leading ideas[5] on this subject are at present being developed.

The thiol group attracts electrons from adjacent centres owing to its inductive effect (−I); on the other hand, the lone-pair electrons on the sulphur atom may interact with systems containing π bonds through the classical delocalizing models. Here no distinction will be made between permanent effects of polarization and temporary ones due to polarizability, although the latter is rather important for sulphur-containing groups[9]. Neither will a distinction be made between electrostatic interactions

operating through chemical bonds and interactions acting through space or through the solvent, which are often referred to as field effects.

In the following discussion which is concerned with polar effects of the thiol group the usual symbols already employed in this series of monographs will be used (cf., for instance, the chapters by Chuchani[10], and by Happer and Vaughan[11]).

A. Inductive and Related Effects in Saturated Systems

A possible method for providing an order of magnitude for the electron attractive effect of the thiol group is the comparison of the dipole moments in a homogeneous series of compounds (Table 1).

TABLE 1. Dipole moments of some representative compounds

Compound	$\mu \times 10^{18}$	Reference
CH_3F	1·81	12, 13
CH_3Cl	1·86	12, 13
CH_3OH	1·68	12, 13
CH_3NH_2	1·28	12, 13
CH_3SH	1·2	9

From the values of Table 1 the following sequence of inductive effects (−I) can be drawn:

$$F, Cl > OH > NH_2, SH$$

This relationship is not completely supported by the relative strength of the saturated acids substituted by the above reported groups, even when it is considered that the K_a value of glycine is affected by the electrostatic interaction between the carboxyl group and the basic amine nitrogen[14] (Table 2).

TABLE 2. K_a values of substituted acetic acids

Acid	K_a	Reference
$H_2N—CH_2COOH$	$4{\cdot}42.10^{-3}$	15
$F—CH_2COOH$	$2{\cdot}18.10^{-3}$	15
$Cl—CH_2COOH$	$1{\cdot}51.10^{-3}$	15
$HS—CH_2COOH$	$2{\cdot}1.10^{-4}$	16
$HO—CH_2COOH$	$1{\cdot}45.10^{-4}$	15

P.m.r. spectroscopy provided an alternative method for the evaluation of inductive effects. An electronegativity scale for substituent groups in ethyl derivatives (Table 3) has been deduced with this technique by Dailey and Shoolery[17] according to equation (1):

$$\text{electronegativity} = 0{\cdot}02315(\Delta CH_3 - \Delta CH_2) + 1{\cdot}71 \quad (1)$$

The electronegativity values found for the OH, SH, NH_2 and COOH groups are satisfactorily related[18] to the couplings between ring protons in monosubstituted benzenes.

TABLE 3. Relative electronegativity of some substituent groups[17]

Group	Electronegativity	Group	Electronegativity
—SH	2·45	$-C_6H_5$	2·70
—CN	2·52	—Br	2·94
—COOH	2·57	$-NH_2$	2·99
—CO—	2·61	—Cl	3·19
—S—	2·64	—OH	3·51
—I	2·68	—F	3·93

The reliability of these values of the electronegativity of polyatomic groups has been subsequently questioned[19], mainly because of the lack of a quantitative relationship with the σ^* values. However, the interaction between the molecular residue and the SH group does not have a simple character. An attempt to evaluate the whole effect induced by substituents on the sulphydryl proton resonance shift has been made by Marcus and Miller[20] for a large series of thiols. These authors discussed the p.m.r. spectra as a function of the effect of substituents on chemical shifts and spin–spin coupling constants. Owing to the complexity of the factors contributing to the proton magnetic shielding in aliphatic compounds, the correlation of ν_{SH} with σ^* was unsatisfactory. Nevertheless equation (2) gave a reasonable correlation even though its validity is restricted to aliphatic thiols.

$$\nu_{SH} = -47{\cdot}2\sigma^* - 73{\cdot}0 \quad (2)$$

Although the proton–proton coupling constants have been shown in some cases to be dependent on the electronegativity of substituents, in the case of aliphatic thiols the J values do not show[20] any regular substituent effects.

It should be noted that deshielding of the S–methyl protons can be related[21] to the number and magnitude of electronegative atoms bonded to sulphur (Table 4).

TABLE 4. Proton magnetic resonance chemical shifts (δ units) of representative sulphurated compounds[a]

Compounds	$-SCH_3$
CH_3SH	1·95
CH_3SCH_3	2·0
CH_3S-SCH_3	2·30
CH_3SCH_3 ‖ O	2·43
CH_3SOCH_3 ‖ O	2·46
CH_3SCl ‖ O	3·22[b]
O ‖ CH_3SCH_3 ‖ O	2·84
O ‖ CH_3SNH_2 ‖ O	2·92
O ‖ CH_3SCl ‖ O	3·52

[a] Taken from reference 21.
[b] Reference 22.

The following trend for CH_3-deshielding can be observed:

thiol $\cong$ sulphide < sulphoxide < sulphinate < sulphone < sulphonamide < sulphinyl halide < sulphonyl halide

Other relationships relative to inductive effects on sulphur atom and R groups in thiols and related compounds of the type $R(S)_nH$ have been found[23].

The effect of the substituent group upon the chemical properties of the SH function in thiols has been also investigated, through a correlation[24] between the acid dissociation constants of several thiols and Taft's inductive parameters (equation 3), where K is the ionization constant,

$$\log K = \sigma^* . \rho^* - \alpha \tag{3}$$

σ^* is Taft's inductive parameter and α is the logarithm of the ionization constant predicted for methyl mercaptan. This linear relationship ($\rho^* = 3{\cdot}402$; $\alpha = -10{\cdot}168$ moles l^{-1}) holds for a series of aliphatic thiols, but fails for hydrogen sulphide, probably because of a differential steric effect on solvation, and for thiophenol most likely because of resonance interactions stabilizing the thiophenolate ion.

It has to be considered that the mutual interaction between the SH group and hydrocarbon chain in aliphatic thiols has a not negligible conformational component[8]. This should not be neglected when the effects of the SH group on various molecules are investigated. In fact Krueger, Jan and Wieser[25] in an i.r. study on a series of alcohols were able to rationalize the relationship between $\nu_{(OH)}$ and $\nu_{(\alpha\text{-}CH)}$ by assuming the participation of an oxygen lone pair to a σ^*_{C-H} orbital on the adjacent carbon. Such an interaction enhances the stability of a definite conformer (see section V.D.) as it has been also observed for aliphatic amines. The authors also found analogous behaviour, even though to a lesser extent, for the corresponding aliphatic thiols. The degree of delocalization of lone pairs has the trend[25] N > O > S. This sequence is also followed in the participation of lone pairs in conjugative interactions in aromatic systems.

Finally, Taft and coworkers studied the effects of many substituents on fluorine n.m.r. intramolecular shieldings[26] and found the following order of inductive charge withdrawal:

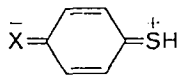
$$O^- < H, N(CH_3)_2 < SCH_3 < SH < OCH_3 < OH < Br < F$$

B. *Effects in Aromatic and Unsaturated Systems (Resonance Effects)*

As the divalent sulphur in the SH (or SR) group possesses lone-pair electrons, it may interact with an unsaturated system by overlapping of the lone-pair electrons with the p-orbital of the adjacent unsaturated carbon. This is the usual conjugative or +R resonance effect attributed to the divalent sulphur atom.

Much experimental evidence and some quantitative measurements indicate the conjugative ability of the thiol group. The conjugative power of SH is smaller[1] than that of OH and NH_2 groups.

Gordy[27], in an electron diffraction investigation of thioacetic acid (CH_3COSH), found a negligible amount (only about 6%) of double bond in the C—S linkage, this being indicative of a very small resonance effect between C—S and C=O bonds; this fact is even more noteworthy if compared with the large resonance effect observed when the sulphur atom is substituted by the more electronegative oxygen and nitrogen in esters and amides. The effect of the thiol group on σ-values for electron attracting substituents like *p*-CH_3SO_2 and *p*-NO_2 in benzene derivatives is indicative of a certain amount of resonance interaction as in **3**.



X = CH_3SO_2, NO_2

(3)

The acid-strengthening resonance effect in thiophenols (**3**) is absent in benzoic acids substituted by CH_3SO_2 and NO_2 groups. Furthermore, the progressively larger σ-values for *p*-CH_3SO_2 and *p*-NO_2 as determined from the dissociation constants of benzoic acids, benzenethiols, phenols and anilinium ions (Table 5) reflect the difference in the resonance interaction

TABLE 5. σ-Values for *p*-CH_3SO_2 and *p*-NO_2 groups obtained from acidity constants. The values 0·72 and 0·78 represent the limits of σ_I whereas 1·13 and 1·27 are those of σ^+

Acid	σ-values		Reference
	p-CH_3SO_2	*p*-NO_2	
X—C_6H_4COOH	0·72	0·78	28, 29
X—C_6H_4SH	0·82	1·00[a]	28, 28
X—C_6H_4OH	0·98	1·22	28, 1
X—$C_6H_4\overset{+}{N}H_3$	1·13	1·27	28, 29

[a] This figure compares well with that found in the oxidation of sulphides[30].

between the *p*-CH_3SO_2 and *p*-NO_2 groups in the dissociated and undissociated forms of the various acidic systems[1,28]. The data again show that the trend of the +R effect is N > O > S.

Lumbroso[31,32] has calculated the mesomeric moment μ_π of benzenethiol (0·44 D) and thioanisole (0·44 D) and found substantially smaller values

than for phenol (0·6 D) and anisole (0·8 D). This indicates that sulphur in this valence situation conjugates to a lesser extent than oxygen with the aromatic ring. On the basis of these observations, which are also supported by independent findings, the following trend for the resonance effect has been put forward[33]:

$$O > S > Se$$

Dipole moments[34] of substituted benzenethiols and thioanisoles, studied as interaction moments between the substituent groups, were found to be satisfactorily accounted for by the normal resonance structures **4** having a positively charged sulphur. Accordingly structures with ten electrons on sulphur atom (**5**) did not have to be invoked.

(**4**) X = NO_2, ... Y = $N(CH_3)_2$, ... (**5**)

Further experimental evidence on the conjugative power of the thiol group has been found by Marcus and Miller[20] by means of p.m.r. spectra in a series of benzenethiols. The resonance of the SH proton suffers an abnormal deshielding which cannot be explained in terms of inductive effects, nor considering the effect of the neighbouring hydrocarbon chain. This deshielding may result from direct conjugation of the SH grouping with the aromatic system, which induces a partial positive charge on the sulphur atom. The results with *ortho*-, *meta*- and *para*-substituted benzenethiols were therefore rationalized by these authors as due to a balance of electron-withdrawing inductive and electron-releasing conjugative effects of the SH group.

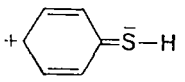
A comparison[28,35,36,37] between the acidity of aromatic and aliphatic thiols and that of the corresponding phenols and alcohols can also give an approximate indication about the +R effects showing again that the conjugative ability of the thiol group is smaller than that of the hydroxyl. Since the C=S double bond is formed to a lesser extent than the C=O double bond in thiophenol and phenol respectively, the resonance effect makes the hydroxyl much more acidic than the thiol group; therefore the difference in acidity between SH and OH sharply decreases in the aromatic compared to the aliphatic derivatives (Table 6).

In 1950 Robertson and Matsen[6], in discussing the ultraviolet spectra of phenol, aniline and thiophenol, noted that the position of thiophenol relative to phenol and aniline was anomalous. Among the suggestions made to explain this behaviour, participation of sulphur 3*d*-orbitals in

TABLE 6. pK's of SH and OH derivatives

Compounds	pK_a	Temperature, °C	Solvent	Method	Ref.
C_2H_5OH	~16	25	H_2O	extrap.	38
C_2H_5SH	10·50	20	H_2O	titrimet.	39
	10·88	25	H_2O	gas solubility	24
	10·61	25	H_2O	spectrophot.	40
C_6H_5OH	9·99	25	H_2O	titrimet.	41
$C_6H_5SH^{+\cdot}$	7·78	20	H_2O	titrimet.	39
	6·52	25	H_2O	spectrophot.	24

the resonance with the benzene ring was put forward. In this case a structure like (6) with a decet of electrons around sulphur should contribute to the resonance.



(6)

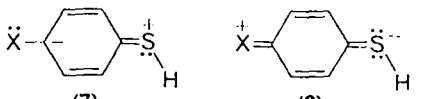
Other anomalous trends of the activating power of sulphurated groups in electrophilic aromatic substitutions had been already observed by Wheland and Pauling[42].

The different behaviour[43] of benzyl phenyl ether and benzyl phenyl sulphide towards aluminium bromide, as well as other differences in reactions between oxygen and sulphur derivatives (especially electrophilic aromatic substitutions), were explained in terms of sulphur valence shell expansion.

After this kind of conjugative pathway had been proposed, many papers appeared either supporting or contradicting the suggestion. The amount of such a conjugative effect $-R$ of bivalent sulphur has been thought[44] small or even negligible in the case of ionization of thio-substituted phenols and benzoic acids; the conclusion has been reached that only strongly electron-releasing groups such as carbanions may evoke a recognizable electron-pair acceptor-type conjugation in divalent sulphur groups.

However, this conclusion was later questioned by Beishline[45]. He objected that even though the observed effect might be rather small, the $(p-d)_\pi$ conjugation could still be considerable in extent, since the observed effect might be the result of the two opposite mechanisms $+R(p-p)_\pi$ and $-R(p-d)_\pi$ as shown in structures (7) and (8).

The $3d$ expansion has been assumed also to explain the behaviour of aminobenzenethiols in tritylation[46] (see further). Nevertheless, a re-investigation[47] of the effects imparted on the acidity of thiophenols and phenols by various substituents did not provide conclusive evidence on the valence shell expansion for the sulphur atom in this particular case.



(7) (8)

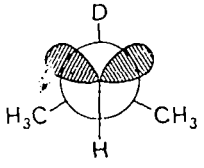
X = OCH_3, $N(CH_3)_2$

The trend which has been found for the CD stretching[25] in *iso*-propyl derivatives (**9–11**) can be understood on the basis of the inductive effects

$(CH_3)_2CDNH_2$ $(CH_3)_2CDOH$ $(CH_3)_2CDSH$

(**9**) (**10**) (**11**)

for the amine and the alcohol but not for the thiol. The relatively high $\nu_{(CD)}$ value of thiol has been tentatively explained as due to $3d$-electron acceptor properties of sulphur if (**12**) is assumed to be the most probable conformation.



(12)

In order to rationalize the results of an i.r. investigation on *ortho*-aminobenzenethiols, Krueger[48] advanced the hypothesis of the existence, besides the planar conformations, of another one with out-of-plane thiol group being stabilized by $3d$-conjugation of sulphur.

The participation of the sulphide function in both electron-releasing and electron-attracting conjugation in the ground state has also been postulated[49] in order to explain the properties of photoexcited states of aromatic sulphur compounds.

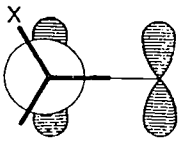
Goodman and Taft[50], in a series of substituent interference experiments explained the decreased intensity of the $^1L_b \rightarrow {}^1A$ transition in going from thiophenol to *p*-methylthiophenol in terms of a strong interaction between the π orbitals of the benzene ring and sulphur $3d$ orbitals. However, a reinvestigation[51] of the spectra indicated that there was a slight increase of intensity from the thiophenol to *p*-methylthiophenol, this being

indicative of a little involvement of the sulphur 3*d* orbitals and of a perturbation of the benzene ring π orbitals *via* S(3pπ)—C(2pπ) bonding. Recent photoelectron spectra[52] also supported this conclusion.

C. Hyperconjugation

A new type of hyperconjugation involving NH and OH bonds as electron donors has been presented[53]. This is theoretically possible also for SH bonds but an attempted application of the hyperconjugation theory to the sulphur series failed[54] to explain the results (see further) obtained for protodesilylation of substituted thioanisols and thiophenols.

By comparing the photoelectron spectra of allyl mercaptan (**13**) and propene (**14**) which exist only in the gauche form shown below, Schäfer and Schweig[55,56] could demonstrate that the hyperconjugative ability of the C—S bond of thiols (and sulphides) is nearly equal to that of the C—H bond. The conclusion was reached that the resulting interaction with π systems does not play any special role in contrast to what was found for C—Si hyperconjugation.



(**13**) X = SH
(**14**) X = H

III. CORRELATION BETWEEN STRUCTURE AND REACTIVITY

In this section attempts will be made to outline the linear free energy relationships existing for thiol-substituted molecules. The few sigma values deduced for the thiol group often show rather large differences. However, it has to be kept in mind how difficult it is to obtain quantitative information in reactions where the extremely reactive SH function is involved, as already outlined in the Introduction. In Table 7 sigma values are reported for SH and SCH_3 groups. The symbols to which reference is made in this section are those used by Wells[57].

A. The Hammett Substituent Constants

Rates and equilibria for hundreds of reactions have been correlated through Hammett's $\rho\sigma$ treatment, but this could not be applied for SH substituents. Table 7 show that only one σ value has been suggested for

TABLE 7. Some representative constants for SH and SCH_3 substituents

Group	σ	σ^+	Aliphatic σ_I	Aromatic σ_I	N.m.r. σ_I	σ^0	σ^0_R
m-SH	0·25[a]		0·25[c] 0·26[l]	0·30[n]	0·18[h]		
p-SH	0·15[a]	−0·365[d]					−0·15[g] −0·17[g]
m-SCH_3	0·14[f] 0·10[f] 0·16[f] 0·19[f] 0·15[i] 0·144[m]	0·158[o]	0·19[h]	0·21[n]	0·14[h]	0·13[i] 0·09[n]	
p-SCH_3	−0·047[b] 0·00[e] −0·01[f] −0·07[f] +0·16[f] +0·06[f]	−0·604[e, o]					−0·173[g]

[a] Reference 58; [b] reference 29; [c] reference 59; [d] reference 54; [e] reference 60; [f] reference 1; [g] reference 26b; [h] reference 26a; [i] reference 57; [l] reference 16; [m] reference 61; [n] reference 62; [o] reference 63.

m-SH and *p*-SH, this being a consequence of the difficulty of carrying out clean reactions on thiol derivatives. These values were actually calculated from the ionization constants in aqueous ethanol of thiol-substituted benzoic acids.

As can be seen from the data reported below[64], according to the Hammett relationship the thiol group is more electron-attracting than the hydroxyl and amino groups.

	NH_2	OH (OCH_3)	SCH_3	SH
σ *para*	−0·66	−0·37 (−0·268)	0·00	0·15
σ *meta*	−0·16	0·121 (0·115)	0·15	0·25

B. Electrophilic Substituent Constants

The only available value in the literature about the effect of the thiol group on the rate constant for an electrophilic aromatic substitution is that reported by Bailey and Taylor[51] which refers to protodesilylation.

In this case, owing to the electronic requirement in the transition state, the *p*-SH group displays an electron-releasing effect; the same behaviour, to even a larger extent, is also shown[60] by the *p*-SCH_3 group in a similar reaction.

The difference of activating power in electrophilic aromatic substitutions between the thiol substituent and other representative groups is supported by the following sequence of σ^+_{para} values:

$$NH_2\,(-1{\cdot}3) > OH\,(-0{\cdot}92) > SCH_3\,(-0{\cdot}60) > SH\,(-0{\cdot}37) > F\,(-0{\cdot}07)$$

This trend is in agreement with the relative conjugative abilities (+R) of these groups with aromatic systems.

Although not strictly pertinent, it should be noted here that the highest substituent sensitivity observed for a chemical process is that found by Taft, Martin and Lampe[65] for the reaction

$$CH_3X\,(g) + e^- \longrightarrow \overset{+}{C}H_2X\,(g) + 2\,e^- + H$$

In this case the substituent X is directly attached to the cation which makes the electron demand. Some of the results obtained are shown in Table 8. The substituent effect of X was given as stabilization energy

TABLE 8. Relative stabilization energies for monosubstituted methyl cations $\overset{+}{C}H_2X$

X	S.E., kcal/mole	X	S.E., kcal/mole
H	0·0	OH	60
F	26	SH	64
Cl	32	OCH_3	69
Br	51	SCH_3	74
I	53	NH_2	95

(S.E.) relative to the methyl cation $\overset{+}{C}H_3$ taken as zero. It should be noted that no ordinary substituent constant is able to correlate all the results except σ^+ for certain substituents (NH_2, F).

Taft[65] explained the larger S.E. for SCH_3 relative to OCH_3 and for SH relative to OH as resulting from the ability of the sulphur atom in answering to this extremely demanding situation in which the R effect involves 'only one predominant interaction mechanism', namely the π(p–p) interaction, while in the other cases (i.e. benzene derivatives including also σ^+ reactivities) this situation does not in general prevail.

C. Other Substituent Constants

Substituents interact with the benzene ring by both inductive and resonance mechanisms and the mutual interaction is clearly a function of both structure and substituent. Nevertheless Taft[59, 66, 67] found it convenient to divide the total effect of a substituent into inductive and resonance contributions:

$$\sigma = \sigma_I + \sigma_R$$

The source for the substituent constants σ_I is the following relationship:

$$\sigma_I(X) = 0{\cdot}45\sigma^*(XCH_2)$$

where σ^* constants are derived from the hydrolysis of substituted acetic acid esters.

In Table 7 are collected a few values of σ_I obtained from aliphatic and aromatic derivatives as well as those obtained from nuclear magnetic resonance shielding parameters. The latter should provide a good method for investigating substituent effects as the measurement depends on a transition that does not affect the chemical character of the substrate.

No σ^0 value[62], which as a rule differs only slightly from σ_{meta}, has been derived for the thiol group.

The resonance contribution of the thiol group to the reactivity σ_R^0[59, 68] in the aromatic series differs only slightly from the Hammett σ_{para} value.

IV. ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

A. General Considerations

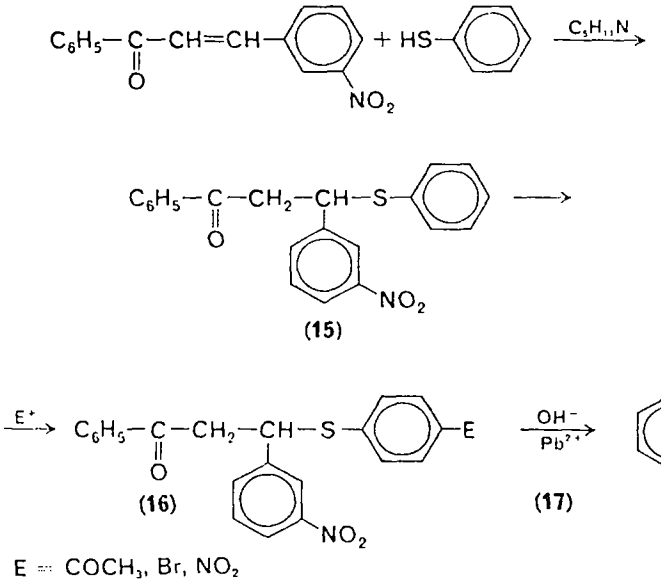
Several attempts have been made to carry out electrophilic substitution reactions on thiophenol and aryl thiols. Most of these reactions yielded transformation products of the SH group itself which seems to be in many cases more sensitive than the aromatic ring towards electrophilic reagents.

There is little quantitative information concerning the reactivity and mechanism of sulphur-containing substituted benzenes in electrophilic aromatic substitutions. Thiophenols, unlike phenols, have been found to undergo ordinary electrophilic substitution only in exceptional cases. As a general rule electrophilic reagents attack the sulphur atom and ring substitution is only rarely observed.

Attempts to nitrate or to brominate thiophenols give as a first step the disulphide[69-71] which may then undergo some nuclear substitution. Similarly, while bromination with N-bromosuccinimide of phenols and aromatic amines takes place in the ring, the same reaction with aromatic thiols leads to disulphides[72]. Other evidence for the low nuclear reactivity

of benzenethiols are the coupling of diazonium compounds with thiophenols to form diazo sulphides ArS—N=N—Ar[73-75] instead of mercaptoazobenzenes and the condensation of thiophenols with tertiary alcohols, in the presence of acid, to yield sulphides[76,77] instead of nuclear alkylation products. For this reason a number of methods have been developed to protect the thiol group in the course of the electrophilic substitution and to regenerate it again in the final product.

A rather general method for the preparation of electrophilically substituted thiophenols was developed by Herz and Tarbell[78]. They showed that the readily formed addition product (**15**) of a thiophenol and 3-nitrobenzalacetophenone can be acetylated, brominated and nitrated and that the substituted addition products (**16**) may be nearly quantitatively converted into the corresponding substituted thiophenol (**17**). This work provided the first general method for preparing a variety of substituted benzenethiols from benzenethiol precursors.



E = $COCH_3$, Br, NO_2

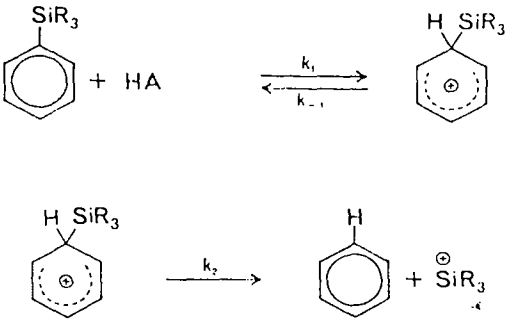
Other protective groups for electrophilic reactions in the benzenethiol series are the carboxymethyl[79,80], acetonyl, and cyanomethyl[81] groups, but these methods are less effective than that of Herz and Tarbell[78].

B. Protodesilylation

The most studied electrophilic aromatic substitution reaction of benzenethiols is protodesilylation, that is the acid-catalysed solvolytic cleavage of the aryl–silicon bond in aromatic compounds of the type

$ArSiR_3$. Many experiments[82] indicate that protodesilylation is an electrophilic substitution in which a solvated proton is the attacking[83,84] species.

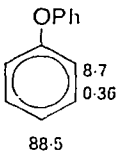
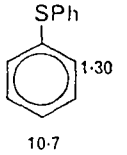
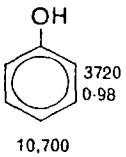
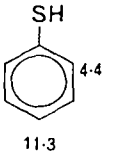
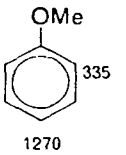
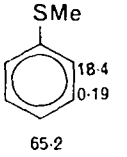
Most of the features of this substitution are consistent with the classical aromatic S_E2 mechanism proceeding through a σ complex.



Protodesilylation of arylthiols has been investigated by Bailey and Taylor[54] and the results are shown in Table 9.

The reactivity at the *ortho* and *para* positions of the sulphur-substituted organometallic compounds follows the order: SMe > SH > SPh.

TABLE 9. Partial rate factors and log f_0 : log f_p values for protodetrimethylsilylation[54] (methanol–aq. perchloric acid, 50°C)

Partial rate factors	log f_0 : log f_p	Partial rate factors	log f_0 : log f_p
	0·48		0·11
88·5		10·7	
	0·885		0·58
10,700		11·3	
	0·815		0·70
1270		65·2	

The data for protodesilylation fit very well the Yukawa-Tsuno equation with $\rho = 5{\cdot}0$ and $r = 0{\cdot}7$[85]. Use of this equation predicts $\sigma^{+}_{SH} = -0{\cdot}365$.

C. Reaction with Carbon Electrophiles

Since 1960 the major interest in the field of electrophilic substitution of benzenethiols concerns the direct alkylation of thiophenols.

1. Friedel–Crafts alkylation

In the case of aromatic thiols the most usually encountered alkylating agents are alkenes, alcohols, mercaptans and sulphides. Lewis acid catalysts used are $AlCl_3$, $AlBr_3$, AlI_3, $ZrCl_4$, $TiCl_4$, BF_3. Also mixtures of Lewis and Bronsted–Lowry acids have been used: BF_3–H_2O–HF, BF_3–H_3PO_4.

These reactions are the most complex among the usually occurring electrophilic aromatic substitutions. One factor leading to complexity is the number of intermediates which may be formed among the different reactants. In addition it should be noted that many alkylations may be only apparently direct since the initial formation of complexes of the various benzenethiols with alkylating catalysts has been postulated. Formation of these labile complexes evidently modifies the electronic character of the thiol (decreasing its nucleophilicity) and this might be an explanation of the lower susceptibility of the sulphur atom to be attacked by the electrophilic reagents in alkylations.

An important feature of the alkylation of thiophenols is that reagents and catalysts may be chosen so as to favour either *ortho*- or *para*-products:

(i) Boron fluoride does not form stable complexes with aromatic thiols[86], and $AlCl_3$, $AlBr_3$, AlI_3, $ZrCl_4$ and $TiCl_4$ are all soluble in the thiophenol[87].

(ii) Direct *t*-butylation of thiophenol based on boron trifluoride catalysed reaction with isobutylene[86] occurs exclusively in the *para* position. No *o*-*t*-butyl thiophenol can be detected. The same results can be obtained with *o*-thiocresol and 2,6-dimethylthiophenol. Thiophenols substituted in the *para* position do not yield ring-substituted products.

(iii) Often S-alkylation is competitive with ring alkylation.

(iv) Alkylation with propylene- or butene-BF_3 produces low yields of *iso*propyl or *sec*-butyl thiophenol and the substitution appears to be entirely *ortho*[86, 88, 89]. Other Lewis acid catalysts give essentially *ortho* substitution with propylene, cyclopropane, 1-butene, 2-butene, 1-pentene and ethylene[87].

(v) Alkylation with isobutylene $-BF_3-H_3PO_4$ converts thiophenol mainly into 4-*tert*-butylthiophenol with some *ortho* derivative[90].

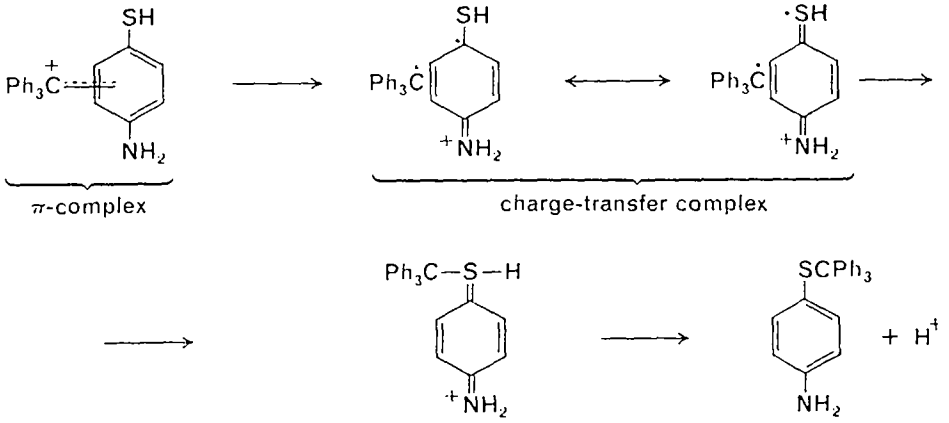
(vi) Dihydroxyfluoroboric acid as a catalyst directs the substituent both to the *ortho* and *para* positions[87].

Other alkylating procedures were described[91,92] but the properties of the resulting alkyl derivatives not given. Thiophenols with a tertiary alcohol or mercaptan in the presence of $AlCl_3$ give *p-tert*-alkyl substituted thiophenols[93].

2. Tritylation

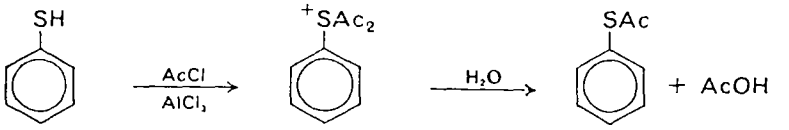
The triphenylmethyl cation has been shown to attack predominantly at the *para* position of anilines and phenols[94,95]. *Ortho*- and *meta*-aminophenols give the C-tritylated derivatives with the trityl group in the *para* position with respect to the amino group[96]. Tritylation of aromatic thiols gives trityl aryl sulphides and not nuclear substitution products[76,95]. Tritylation of each aminobenzenethiol isomer yields[97] only the corresponding trityl sulphide and no ring-substituted products.

The preference of the trityl cation (or an ion pair formed from triphenylmethanol) in attacking the sulphur atom has been taken[97] as an evidence of the expansion of the valence shell of sulphur. Re-examination[46] of the problem by means of Hückel MO calculation gave a series of reactivity indices which correctly predicted the point of attack by the triphenylmethyl carbonium ion in aminophenols but not in aminobenzenethiols. The latter reaction, which is an electrophilic attack of an alkyl ion on the electron-rich sulphur atom, was still explained[46] through valence shell expansion of sulphur and the following mechanism was proposed[46].

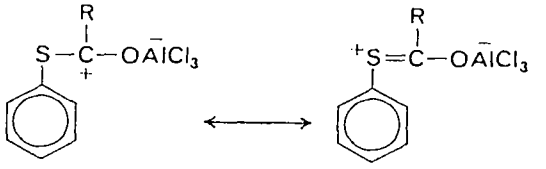


3. Acylation

No examples are known of direct nuclear acylation of arylthiols; attempts[98] to acetylate benzenethiol gave only the phenylthioacetate. This was tentatively explained[98] in terms of the following mechanism:



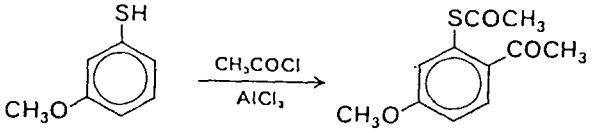
Alternatively the intervention of a co-ordination complex (**18**) between the catalyst and the oxygen of the acyl group was postulated[98].



(18)

The partial positive charge on sulphur would in this case prevent nuclear acylation.

Only if a strong activating group such as, e.g. methoxy, is present in the arylthiol (**19**), can nuclear acetylation be observed[99] (**20**). In this case, however, the electrophilic substitution is clearly dominated by the methoxy group.



(19) (20)

An attempted Fries reaction[100] with thiolesters was unsuccessful.

Ring acylation of thiols was successfully achieved only as described in section IV.A.

4. Reaction with carbon tetrachloride

While in the presence of chloroform and alkali phenol undergoes the Reimer–Tiemann reaction, benzenethiol gives, in the same conditions, phenyl orthothioformate, $HC(SPh)_3$[101].

When heated with carbon tetrachloride and alkali, benzenethiol gives[102] a poor yield of thiosalicylic acid together with a large quantity of its disulphide; no *para*-isomers were detected but a detailed study of the reaction is still lacking.

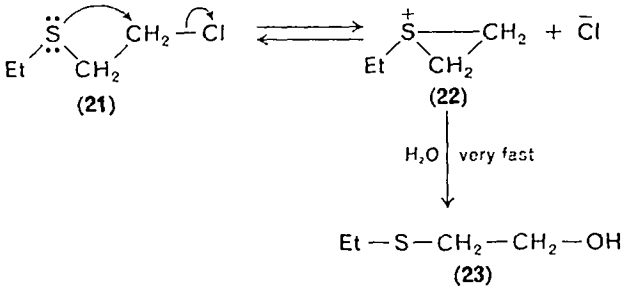
V. PROXIMITY EFFECTS

A. *Neighbouring Group Participation by the Thiol Group in Nucleophilic Substitutions*

It is well known that groups not directly bonded to the reaction centre may strongly affect the rate and the stereochemical course of aliphatic nucleophilic substitutions, particularly if they possess unshared electrons. This phenomenon was named 'neighbouring group effect' by Winstein[103], who later[104] proposed the term 'anchimerism' and called reactions which are accelerated by neighbouring group participation 'anchimerically assisted'.

The kinetic result of this assistance in nucleophilic substitutions is that substituents on β, γ or δ-carbon slow down the rate much less than expected on the basis of their $-I$ effect or, alternatively, accelerate the reaction more than expected on the basis of their $+I$ effect.

Typically, β-chloroethyl ethyl sulphide (**21**) $ClCH_2CH_2SCH_2CH_3$, is hydrolysed, in aqueous dioxane, 10,000 times more rapidly[105] than the corresponding ether $ClCH_2CH_2OCH_2CH_3$. This rate difference is far too large to be attributed to modifications in electronic or steric effects. The proposed mechanism for this solvolysis of sulphides[105-108] is an internal bimolecular displacement of chlorine by the polarizable sulphur atom (but not by oxygen in the corresponding ethers) to give an intermediate thiiranium ion (**22**)[109]; this species may either revert to the reactant by attack of the chloride ion or react with water to give the hydroxysulphide (**23**).



The relative neighbouring group effect of various β-substituents follows the order[110]:

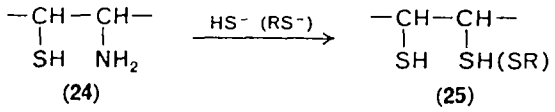
$$O^- > SH, SR > NR_2 > I > Br > OR$$

It must be noted that, with the exception of O^-, all these substituents have a $-I$ effect.

From the stereochemical point of view, neighbouring group participation in nucleophilic substitution results in a prevailing retention of configuration.

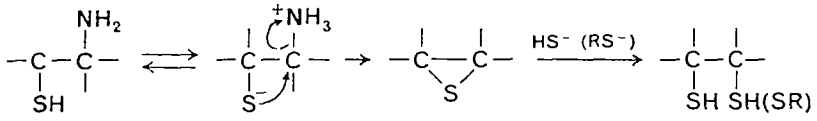
Finally, neighbouring group participation may lead to molecular rearrangement when the neighbouring group remains bonded to the reaction centre while breaking away from the atom to which it was originally attached[111].

In contrast to the sulphide group, only few quantitative data are known on anchimeric assistance of thiol groups in nucleophilic substitutions. A classical example of this effect is given by the reaction of β-amino thiols (**24**) with bisulphide ions or thiolates to give dithiols or mercaptothioethers (**25**)[112].



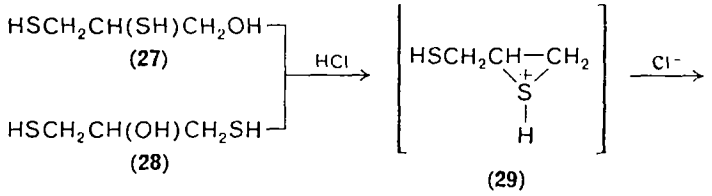
(**24**) (**25**)

Convincing evidence indicates the intermediacy of an episulphide derived from a nucleophilic intramolecular displacement of ammonia by the negative sulphur atom of (**26**).

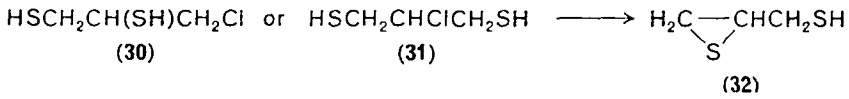


(**26**)

Transient formation of episulphides was also observed[113] during the distillation of simple β-amino thiols (equation 4).



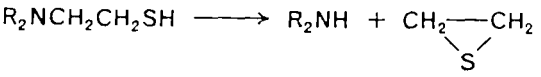
(**27**) (**28**) (**29**)



(**30**) (**31**) (**32**)

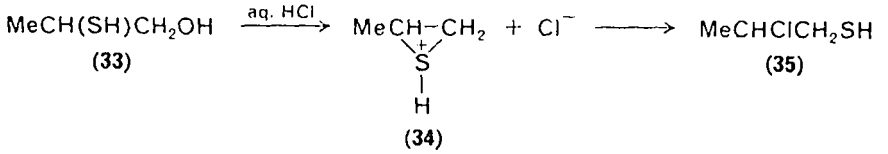
Treatment of 2,3-dimercaptopropanol (**27**) or 1,3-dimercaptopropan-2-ol (**28**) with hydrochloric acid followed by addition of sodium hydrogen carbonate gives[114] the episulphide (**32**), probably through the intermediacy

of a cyclic sulphonium ion (**29**) and subsequent attack of chloride ion to give the mercaptopropyl chlorides (**30**) or (**31**).

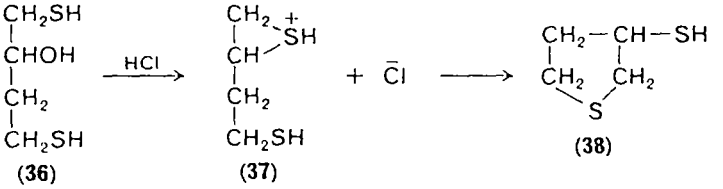


(4)

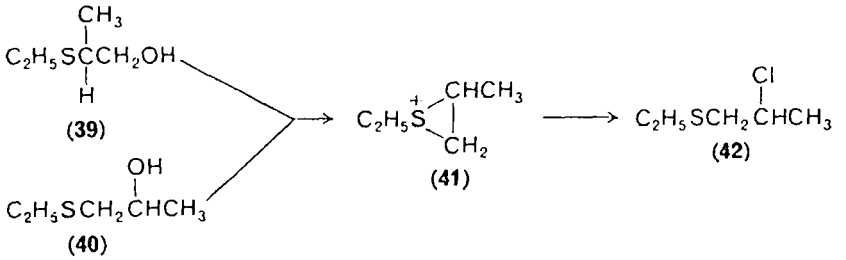
Another example of neighbouring group participation by the thiol group, also involving a molecular rearrangement, is given[115] in the reaction scheme shown below.



A rearrangement is also observed[114] in the reaction of 1,4-dimercaptobutan-2-ol (**36**) with hydrochloric acid; in this case the final product is the 3-mercaptothiolane (**38**).



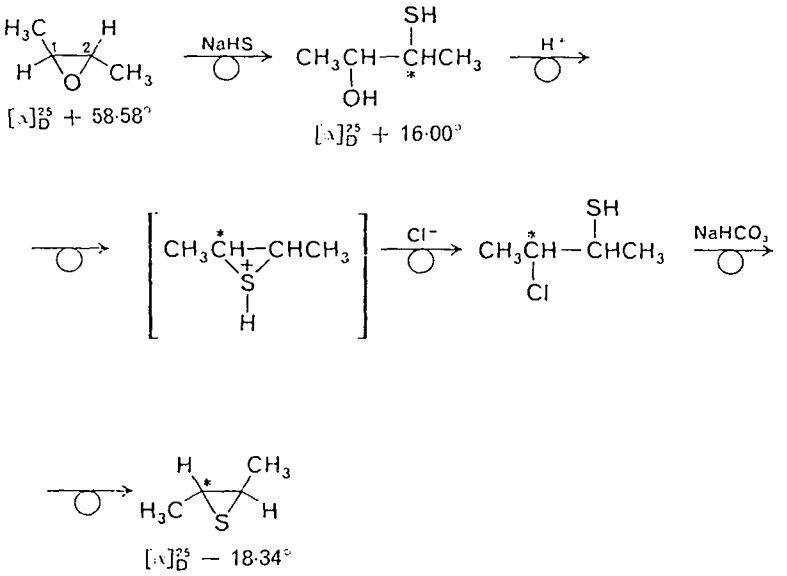
The existence of a cyclic sulphonium ion produced in nucleophilic substitution reactions involving hydroxyl or halogen substituents in the β-position with respect to a thiol or sulphide group had been postulated[116] since 1946, in order to explain the formation of the same 2-chloro-*n*-propyl ethyl sulphide (**42**) either from ethyl 2-hydroxyisopropyl sulphide (**39**) or from ethyl 2-hydroxy-n-propyl sulphide (**40**) when these are allowed to react with hydrochloric acid or thionyl chloride.



Evidence for such a mechanism was also found[117] in the case of δ-hydroxysulphides with the final formation of a five-membered ring.

A similar cyclic sulphonium ion was also postulated[118] to explain the features of solvolytic reactions of β-chloroethyl sulphide.

The results of a stereochemical investigation[119] also support neighbouring group participation of sulphide or thiol groups in nucleophilic substitution reactions.



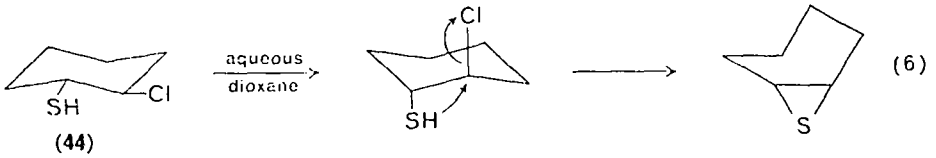
The final episulphide, although optically impure, displays a large negative rotation. Since three inversions occur at C_1 and one at C_2 (centres of inversion are identified by an asterisk), it can be concluded that the whole process results in a net configuration inversion at both carbon atoms of the starting epoxide.

It is worth mentioning that β-halogenothiols are fairly unstable and are the starting materials for a general synthetic method[120] for the preparation of episulphides based upon the intramolecular substitution of the halogen atom by the thiol group.

The solvolysis of the 2-chlorocyclohexanethiols in aqueous dioxane has been investigated in detail[121]. Rates of solvolysis of both *cis*- and *trans*-isomers suggest different kinds of neighbouring group participation. The behaviour of the *cis*- (**43**) and of the *trans*-isomer (**44**) has been explained as resulting from H-participation (equation 5) in the first case, and as a consequence of SH-participation (equation 6) in the second. In the case of the *cis*-isomer, the kinetically measured product was the final ketone and

not the intermediate thione which is assumed to be rapidly hydrolysed in aqueous dioxane. Conversely the *trans*-isomer, supposed to react in the diaxial conformation, is solvolysed into the episulphide which is sufficiently stable to be kinetically detected.

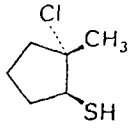
(43) (5)



(44) (6)

It should be noted that the *cis*-isomer (**43**) reacts less rapidly than *cis*-2-chlorocyclohexanol, thus suggesting that the driving force for H-participation is smaller; on the contrary the *trans*-isomer (**44**) reacts, as expected, much more rapidly than *trans*-2-chlorocyclohexanol indicating that SH participation is more effective than OH participation.

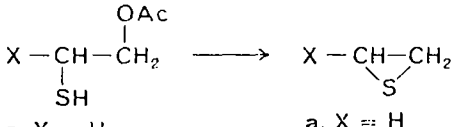
The solvolysis of the chlorocyclopentanethiol (**45**) was also investigated[121] and SH-participation detected.



(45)

This represents an unusual case in which the solvolysis of a tertiary chloroderivative does not proceed through a S_N1 mechanism.

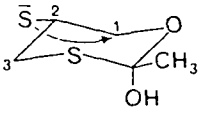
The neighbouring group effect of the thiol group is enhanced when a *vicinal* dithiol system is adjacent to the reaction centre. In fact the cyclization of 2,3-dimercaptopropyl acetate (**46b**) is much easier[122] than that of 2-mercaptoethyl acetate (**46a**).



a, X = H
b, X = CH_2SH (46)

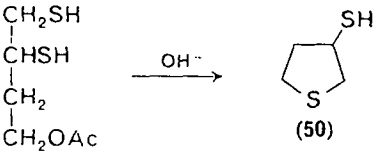
a, X = H
b, X = CH_2SH (47)

A possible explanation of the neighbouring group assistance brought about by a *vicinal* dithiol system has been given by Owen[122] and is based on the assumption that the thiol group at C_3 of (**46b**) interacts with the carbonyl carbon to form either a chelate or a true addition compound (**48**). The C_2—S^- bond (in the shown equatorial conformation) would then be co-planar with the bond system C_2—C_1—O as well as *trans* with respect to the C—O bond, a favourable situation for displacement.



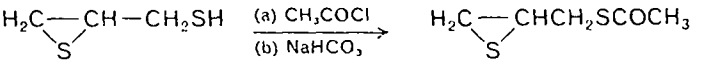
(**48**)

The peculiar reactivity of a *vicinal* dithiol group is also evident in the acyl derivatives of 3,4-dimercaptobutanol (**49**) which cyclize to give 3-mercaptothiophan (**50**)[123,124] while neither 3- nor 4-mercaptobutyl-acetate undergoes any cyclization.



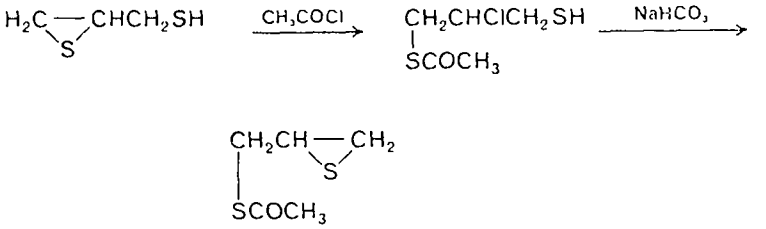
(**49**) (**50**)

A molecular rearrangement, not easily detectable, occurs in the acylation reaction of 3-mercaptopropylensulphide (**51**).

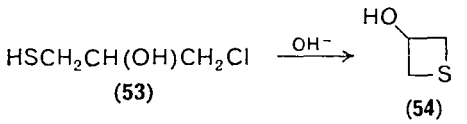


(**51**) (**52**)

It has been demonstrated[125], by isolating the intermediate 2-chloro-3-mercaptoacetylpropanethiol, that the final S-acyl derivative is obtained through the preliminary attack of acetyl chloride upon the thiirane ring followed by internal nucleophilic substitution of the halogen by the thiol group.



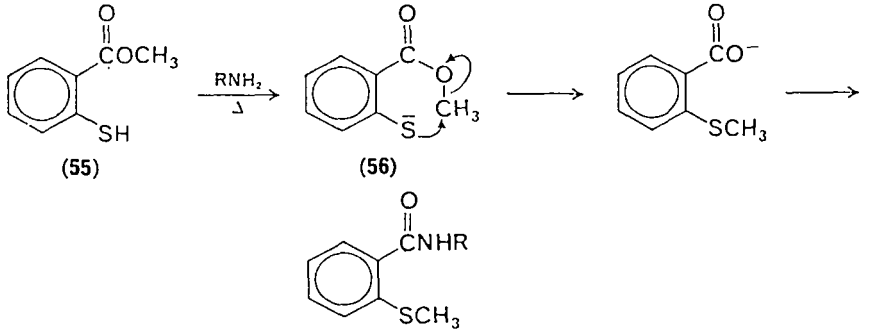
Intramolecular nucleophilic substitutions also occur in 3-mercapto-substituted halogen derivatives (53) leading to the formation of thietane (54)[125].



(53) (54)

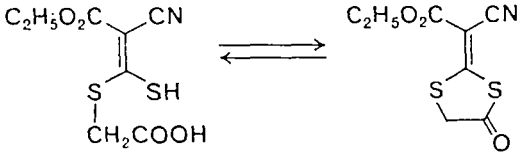
While the intramolecular sulphur→oxygen migration of an acyl group is quite usual[123,124], less well-known is the oxygen→sulphur migration of an alkyl group[126] which has been observed during the thermal reaction of methyl 2-mercaptobenzoate (55) with primary aliphatic amines.

This rearrangement has been explained through an intramolecular S_Ni type mechanism in which the migration of the methyl group involves a six-membered transition state (56)[126].



(55) (56)

Another example of interaction between a thiol and a carboxyl group has been found[127] in compound (57).



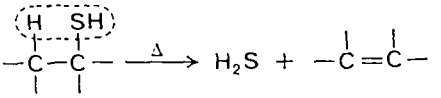
(57) (58)

Ethyl 4-oxo-1,3-dithiolan-2-ylidenecyanoacetate (58) is soluble in alkali and it could be shown that this is not due to enolization but to ring-opening so that the conclusion has been reached that the cyclization is an easy reversible process.

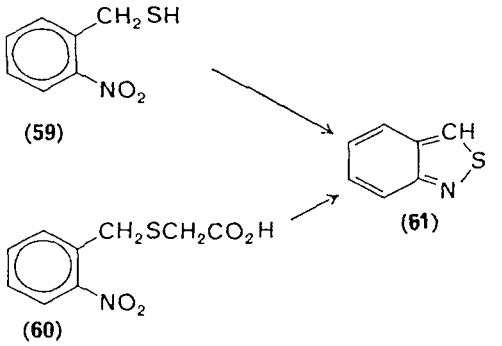
B. Other Proximity Effects

While thiols with no hydrogen atoms on the β-carbon give by thermal decomposition the carbon radical, ethanethiol and ethylene-thiol

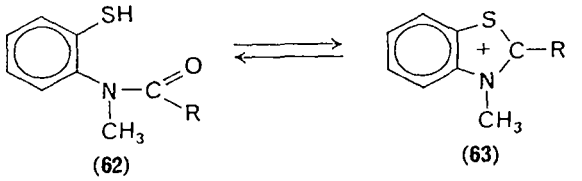
decompose according to a molecular mechanism for which the assistance of the thiol group in eliminating the hydrogen atom on the β-carbon was proposed[128].



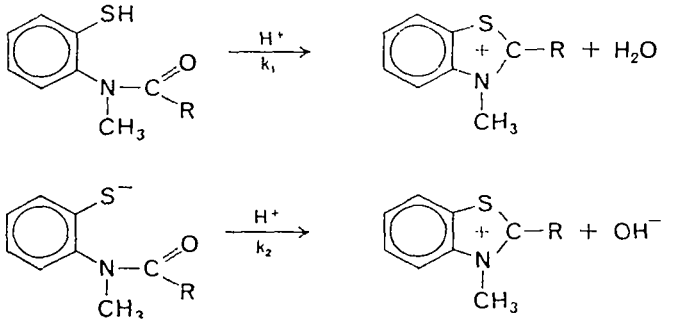
While *m*- and *p*-nitrophenylmethanethiols do not appreciably react in hot alkaline solutions, *o*-nitrophenylmethanethiol (**59**) reacts vigorously with strong aqueous alkali giving thioanthranil (**61**). The same cyclic product is obtained by alkaline hydrolysis of α-(*o*-nitrobenzylthio)acetic acid (**60**)[129]. In marked contrast, *o*-nitrobenzyl alcohol reacts very slowly[130].



The cyclization of *o*-(N-acyl-N-methylamino) benzenethiols (**62**) into 2,3-benzothiazolium ions (**63**) has been quantitatively studied[131] and the



following cyclization pathways have been put forward.



C. Acid–Base Equilibria

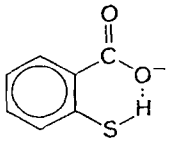
The best known example of the proximity effect of a thiol group involving an acid–base reaction can be found within the mercaptobenzoic acid series where the *ortho*-isomer shows a higher acidity compared with that of the *meta* and *para* analogues[36].

o-mercaptobenzoic acid pK_a: 5·02 (ethanol 48·9%, 20°C)

m-mercaptobenzoic acid pK_a: 5·42 (ethanol 48·9%, 20°C)

p-mercaptobenzoic acid pK_a: 5·56 (ethanol 48·9%, 20°C)

Irving, Nelander and Wadsö[40] have systematically studied the thermodynamics of the ionization for a number of thiols in aqueous solutions. They found that the thiol group in *o*-mercaptobenzoic acid has a low $-\Delta S_i$ value which has been tentatively explained by the formation of an intramolecular hydrogen bond in the monoanion (**64**). This stabilization

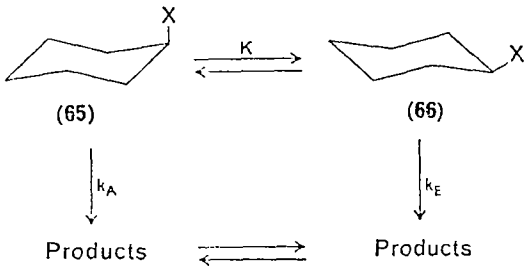


(**64**)

of the monoanion can explain the higher acidity of the *o*-mercaptobenzoic acid. On the other hand, the corresponding free carboxylic acid is not hydrogen-bonded[8] between the S-atom and the carboxyl group. An analogous explanation has been suggested also for the corresponding phenols[11, 132].

D. Effects of the Thiol Group on Conformational Equilibria

Simple monosubstituted cyclohexanes, and also a number of polysubstituted ones, may exist in two conformations[133], namely the axial (**65**) and the equatorial (**66**). If the rate of interconversion is fast compared with the rate of reaction, the reactivity of molecules of this kind clearly depends upon the reactivity of both conformers, as exemplified in scheme (7).



(7)

Eliel[134] derived a relationship (8) which shows that the specific reaction rate for a substituted cyclohexane depends on the equilibrium constant K and on the specific rate at which the individual conformers react.

$$k = (k_E K + k_A)/(K+1) \quad (8)$$

Another equivalent relationship was derived earlier by Winstein[135] for the same reacting system.

From equation (8) and the known rate constants it was possible to calculate the energy differences between equatorial and axial substituents. In Table 10 are collected some energy differences obtained by this and other methods.

TABLE 10. Free-energy differences between equatorial and axial substituents in monosubstituted cyclohexanes

Group X	$-\Delta G^0$, kcal/mole	Reference
OH	0·3–1·0	*a*, *b*
OCH_3	0·6–0·7	*a*, *b*
OC_2H_5	0·9–1·0	*a*, *b*
F	0·2	*a*, *b*
Cl	0·3–0·5	*a*, *b*
Br	0·2–0·9	*a*, *b*
I	0·3–0·4	*a*, *b*
SH	0·6–0·9	*b*
SC_6H_5	0·8	*a*, *b*
SAlk	0·4–0·7	*b*
SCH_3	0·7	*b*
S^-	1·3	*b*
CH_3	1·5–2·0	*a*, *b*

[a] Reference 133; [b] reference 136.

From the data of Table 10 it clearly results that the thiol group favours the equatorial conformation in cyclohexanethiol although a study[137] reported the axial conformer to be more stable by 0·4 kcal mole^{-1}.

The effect imported by the thiol group on conformational equilibria in open-chain alkanethiols has been also investigated by means of i.r. spectroscopy[8].

The i.r. spectral data of some alkanethiols in carbon tetrachloride are collected in Table 11.

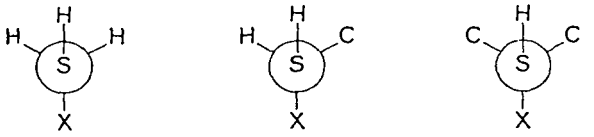
Shapes and frequencies of the bands are dependent on the nature of the alkyl group bonded to sulphur; the dependence is not attributable to any

molecular association, since thiols are monomeric at the concentrations used, the presence of rotational isomers around the C—S bond was invoked[8], by analogy with the corresponding alkanols[138].

TABLE 11. I.r. spectral data[8] of some alkanethiols in CCl_4

Compound	ν_{SH}, cm^{-1}	ε
CH_3SH	2586	—
C_2H_5SH	2578	2·2
n-C_4H_9SH	2578	2·2
i-C_3H_7SH	2577	3·0
s-C_4H_9SH	2577	2·7
t-C_4H_9SH	2572	2·1

The possible staggered conformations which can explain the variation of frequency are shown below.

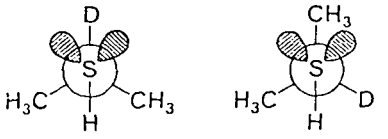


X = hydrogen or carbon

The existence of such an isomerism was demonstrated by Krueger, Jan and Wieser[25].

In Table 12 the i.r. spectral data for some primary, secondary and tertiary thiols and alcohols are summarized. These data are related to the possible conformers classified on the basis of the *trans* lone-pair/α-CH bond interactions. The assumption was made that two such interactions raise ν(SH) or ν(OH) about twice as much as does a single interaction[25].

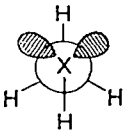
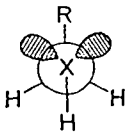
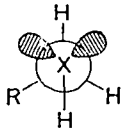
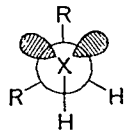
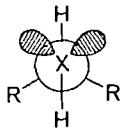
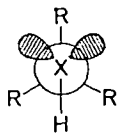
As an example the spectral data for 2-propanethiol-2-d_1 are indicative of the following conformational equilibrium



(67) (68)

The conclusion has been reached that conformer **67** dominates in dilute CCl_4 solution as well as in the pure liquid and gas phase. On the

TABLE 12. Conformations and corresponding ν(SH) and ν(OH) values in alkane-thiols and -ols (X = S, O)[25]

Compound	Number of interactions (lone-pair/α-CH)		
	Two	One	None
CH_3XH			
RCH_2XH			
R_2CHXH			
R_3CXH			
	Frequencies (cm^{-1})		
CH_3SH	2587		
C_2H_5SH	2582 sh	2577	
n-C_4H_9SH	2582 sh	2577	
i-C_3H_7SH		2576	2562 sh
s-C_4H_9SH		2578	2567 sh
t-C_4H_9SH			2573
t-$C_5H_{11}SH$			2572
CH_3OH	3643·8		
C_2H_5OH	3637·3	3627	
i-C_3H_7OH		3627·1	3617
t-C_4H_9OH			3616·9

sh = shoulder.

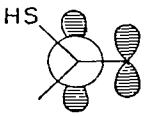
other hand the concentration of the more acidic form (**68**), with the possibility of a favourable lone pair/σ^*CD orbital interaction, which introduces some C⋯S double-bond character, is increased in dimethylsulphoxide solution.

The effect of the SH group in favouring definite conformers is also evident in *o*-aminothiophenols[48, 139–141].

By means of the microwave spectra of normal (**69**) and deuterated (**70**) allylmercaptan it has been demonstrated[142] that this thiol molecule exists

$CH_2{=}CHCH_2SH$ (**69**) $CH_2{=}CHCH_2SD$ (**70**)

only in the *gauche* form (**71**) with the thiol hydrogen relatively close to the π electrons of the double bond.



(**71**)

It should be remembered that allyl fluoride[143] and allyl cyanide[144] may exist both in the *cis* as well as in the *gauche* conformations, while for allyl alcohol[145], allyl chloride, bromide and iodide[146] the most stable conformation is the *gauche*. While the stability of the *gauche* form for the thiol (and the alcohol) can be attributed[142] to an electrostatic attraction between the π electrons and the acidic proton, in the other cases the higher stability of the *gauche* vs. the *cis* conformer has been attributed[147] to the size of the substituent on the methylene carbon.

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The Chemistry of the Thiol Group
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CHAPTER 10

Photochemistry of thiols

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I. INTRODUCTION

Investigations of the photochemical decomposition of thiols date back to 1938 and the work of Thompson and coworkers[1,2]. The mechanism tentatively proposed at that time for the photolysis of methanethiol consisted of the following three steps:

$$CH_3SH + h\nu \longrightarrow CH_3\dot{S} + \dot{H} \quad (1)$$

$$\dot{H} + CH_3SH \longrightarrow CH_3\dot{S} + H_2 \quad (2)$$

$$2\,CH_3\dot{S} \longrightarrow CH_3SSCH_3 \quad (3)$$

Although a great deal of work has been done since that time, and our understanding of the photochemistry of this class of compounds increased significantly, the simple sequence of reactions (1), (2) and (3) remains an

adequate description of the main mode of photochemical decomposition of this and other thiols†.

During the last few years the photochemistry of thiols has been investigated from several points of view—as a source of hydrogen atoms in the gas phase and in solution, as a source of thiyl, RS̈, radicals, and as a substrate whose photodecomposition can conveniently be examined from a theoretical point of view in the near ultraviolet region of the spectrum.

The absorption spectrum of ethanethiol in heptane solution is shown in Figure 1. The absorption characteristics of this compound are typical of the lower molecular weight thiols, with a weak band, $\varepsilon \approx 10^2$, around 2300–2400 Å, and a second, appreciably stronger absorption, $\varepsilon \approx 2 \times 10^3$, with a maximum around 2000 Å. Apart from a slight shift in the absorption maxima, the wavelength dependence of the absorption coefficient is essentially the same in the gas phase.

The ultraviolet absorption of simple alkanethiols has been interpreted by Clarke and Simpson[3] who have characterized both transitions in the near u.v. as non-Rydberg. The longer wavelength band is ascribed to the transition of a non-bonding sulphur atom to an antibonding molecular orbital, while an electron transition from a bonding C—S orbital to an antibonding H—S orbital is suggested as the origin of the shorter wavelength absorption. Most of the general investigations of thiol photochemistry have involved primarily photolysis in the lower energy band. However, it is apparent from the spectrum that if an unfiltered light source is used at $\lambda > 2000$ Å, excitation to both states may be occurring. One recent study to be discussed below (cf. section II.B) indeed has indicated that there are likely significant differences in the detailed photochemistry of thiols in the two bands.

Thermochemical characteristics of thiols are also an important factor influencing mechanistic interpretations of their photochemistry. The C—S bond is the weakest linkage in the molecule, for example,

$$D(CH_3—SH) = 73 \text{ kcal/mole}$$

while the S—H bond is 88 ± 5 kcal/mole in the lower molecular weight alkanethiols[4]. Despite this energy difference the main mode of decomposition in the photochemical system is S—H cleavage. The lability of the

† The photochemistry of H_2S is not discussed in this Chapter. Although many of its characteristics are similar to those of thiols, in many respects it is more appropriately treated as a sulphide. A concise summary with references to the important reactions in the photodecomposition of H_2S is contained in a recent report on the flash photolysis of H_2S by R. B. Langford and G. A. Oldershaw, *J. Chem. Soc. Faraday Trans.*, **68**, 1550 (1972).

sulphydryl hydrogen, compared to carbon—hydrogen bonds in the thiol molecule and other species which might be added to the system, e.g. olefins, makes it the virtually exclusive site of abstractive attack in the thiol molecule. When other species that might be susceptible to radical attack are also present, the lability of the S—H bonds renders it vulnerable

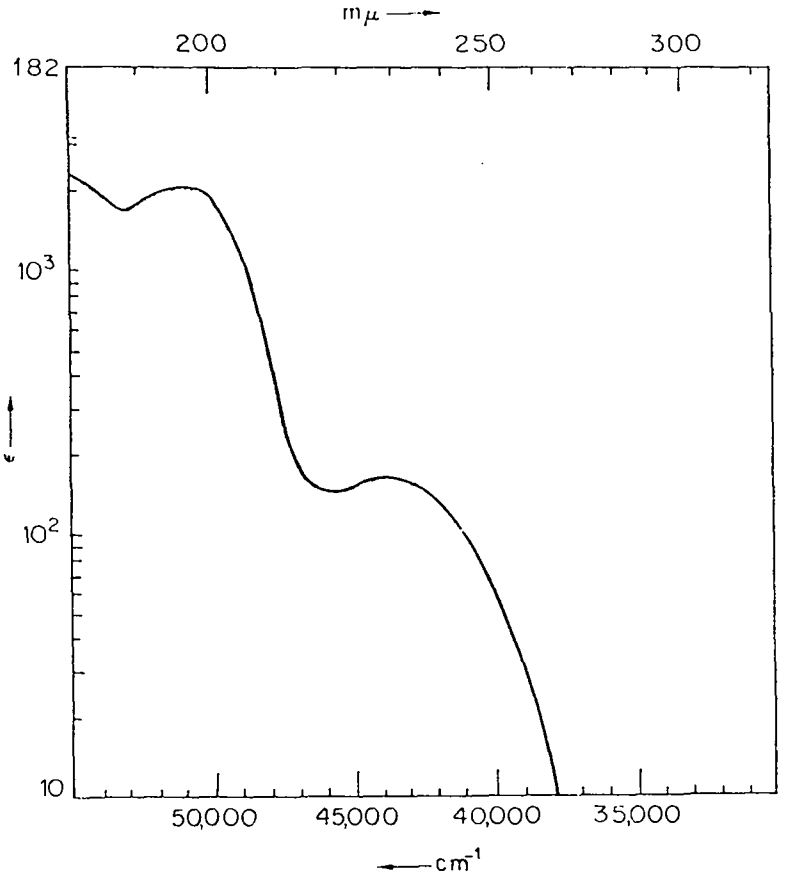


FIGURE 1. Ultraviolet absorption spectrum of ethanethiol in heptane solution. Reproduced by permission from *DMS UV Atlas of Organic Compounds*, Vol. IV, Verlag Chemie, Weinheim; Butterworths, London (1967).

in that case as well. This high reactivity is reflected in appreciably lower activation energies for H-atom removal from thiols as compared to other hydrogen donors. Finally, the low S—H bond energy gives rise to appreciable amounts of excess energy in the primary photochemical process leading to the formation of H-atoms with excess energy.

II. GAS PHASE PHOTODECOMPOSITION OF THIOLS

A. *Photolysis of Methanethiol*

The first quantitative study of the photochemical decomposition of alkanethiols in the vapour phase was an investigation of the CH_3SH system carried out by Inaba and Darwent[5]. In that study an unfiltered mercury arc was employed so that the photolysing wavelengths covered the 2000–2600 Å range, although the incident radiation was concentrated in the region near 2537 Å. When the decomposition was restricted to less than 0·3%, H_2 and CH_4 were the only noncondensable gases observed. No attempt was made to analyse for other reaction products.

It was suggested that CH_4 results from secondary reactions and that hydrogen production is via reaction (1) as the primary process, followed by abstraction in reaction (2). Experiments with CH_3SD produced entirely D_2 and no H_2 or HD, eliminating possible involvement of the methyl hydrogens in either the primary process or the subsequent abstraction reaction. When ethylene is added to the system H-atoms can be scavenged by the process

$$\dot{H} + C_2H_4 \longrightarrow \dot{C}_2H_5 \qquad (4)$$

and by kinetic analysis of the observed rates of hydrogen formation in the presence and absence of the olefin, a rate constant ratio, k_2/k_4, of 1·7 was obtained at room temperature. An activation energy of 4·6 kcal/mole for reaction (2) was obtained from temperature studies.

More recently Steer and Knight[6] studied the photolysis of CH_3SH vapour at 2537 Å at pressures from 5 to 800 Torr and investigated in detail the effects of temperature and a number of addends.

A unique aspect of that work was the confirmation of the presence of thiyl radicals in the system through the observation of methyl thionitrite, CH_3SNO, as a product when the photolysis was conducted in the presence of nitric oxide. The thionitrite is formed via reaction (5),

$$CH_3\dot{S} + NO \longrightarrow CH_3SNO \qquad (5)$$

but is a relatively unstable compound. If the pressure of nitric oxide exceeds 20 Torr, a chain reaction giving nitrogen appears to become important and evidently continues for some time after the termination of the photochemically induced decomposition. Thus it is difficult to utilize CH_3SNO yields to measure quantitatively methylthiyl radical production. However, observation of significant amounts of this product is strong evidence for reaction (1) as the primary process in this system.

Since the higher molecular weight thionitrites are considerably more stable than CH_3SNO, the technique of photolysing other thiols in the

presence of NO may be a valuable tool in determining thiyl radical yields. It is an area that could profitably be investigated.

In the photolysis of pure CH_3SH, Steer and Knight found CH_3SSCH_3, H_2S and CH_4 as products and determined their yields under a variety of experimental conditions. Figure 2 shows the rate of formation of these

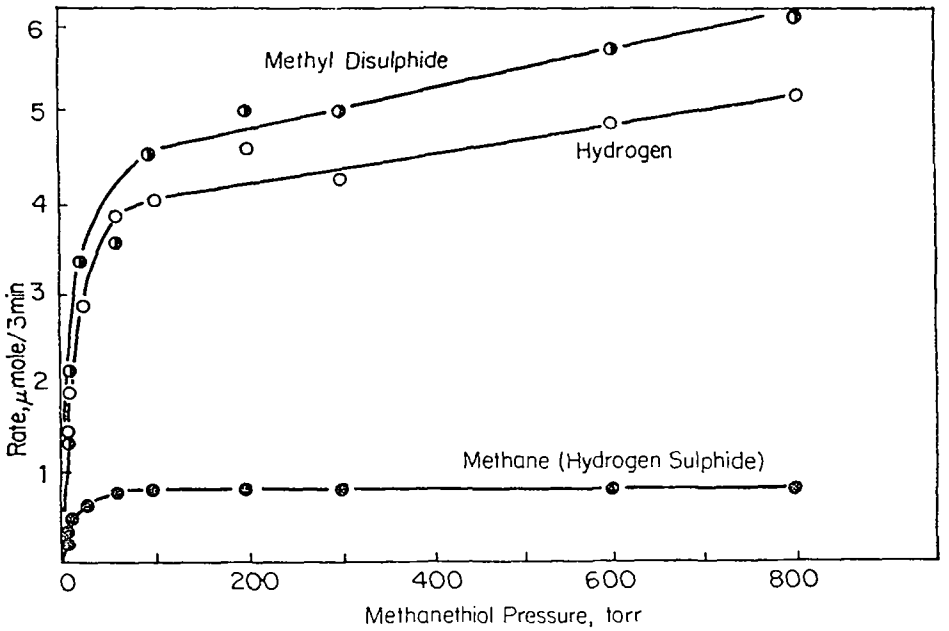


FIGURE 2. Rate of formation of CH_3SSCH_3, H_2 and CH_4 as a function of methanethiol pressure in the photolysis of CH_3SH at 2537 Å and 25°C. The yields of H_2S are the same within experimental error as those of methane. Reproduced by permission from R. P. Steer and A. R. Knight, *J. Phys. Chem.*, **72**, 2145 (1968).

products as a function of methanethiol pressure. The sharp increase in yields over the low pressure range is readily ascribed to increasing light absorption by the thiol. Under the conditions of these experiments the absorption should be complete at pressures less than *ca.* 75 Torr. The increase in rates beyond this pressure constitutes an important characteristic of thiol photolyses that has not been definitively resolved to date. To demonstrate that the observed increase in the rates of H_2 and CH_4 formation is not associated with absorption effects, quantum yields (Φ) were measured as a function of pressure and the data obtained are shown in Figure 3. Thus although the value of $\Phi(H_2)$ at zero pressure is unity, the value evidently increases with pressure. Furthermore, the yield of CH_4 [and of H_2S whose yields are not shown in the figure] does not extrapolate

to zero. The latter observation would tend to indicate an additional primary process,

$$CH_3SH + h\nu \longrightarrow \dot{C}H_3 + \dot{S}H \qquad (6)$$

is occurring, followed by hydrogen atom abstraction by CH_3 and SH radicals. However, the fact that the quantum yield of $H_2 + CH_4$ is greater

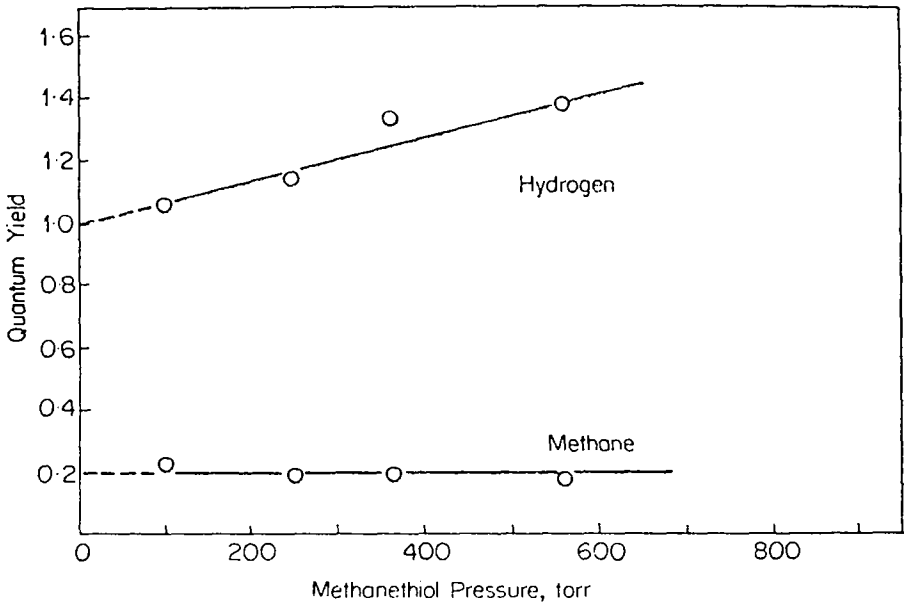


FIGURE 3. Quantum yields of H_2 and CH_4 as a function of methanethiol pressure in the photolysis of CH_3SH at 2537 Å and 25°C. Reproduced by permission from R. P. Steer and A. R. Knight, *J. Phys. Chem.*, **72**, 2145 (1968).

than unity, even at $P = 0$, suggests that additional sources of one or both of these products are important.

These authors suggested that process (1) is the sole significant primary step and that CH_4 and H_2S are formed through the following sequence in which * indicates an excited species:

$$2\,CH_3\dot{S} \rightleftharpoons CH_3SSCH_3^* \qquad (7)$$

$$CH_3SSCH_3^* + CH_3SH \longrightarrow CH_3SSCH_3 + \dot{C}H_3 + H\dot{S} \qquad (8a)$$

$$CH_3SSCH_3^* + CH_3SH \longrightarrow CH_3SSCH_3 + CH_3SH^* \qquad (8b)$$

$$CH_3SSCH_3^* + M \longrightarrow CH_3SSCH_3 + M^* \qquad (9)$$

$$\dot{C}H_3 + CH_3SH \longrightarrow CH_4 + CH_3\dot{S} \qquad (10)$$

$$H\dot{S} + CH_3SH \longrightarrow H_2S + CH_3\dot{S} \qquad (11)$$

$$CH_3SH^* + M \longrightarrow CH_3SH + M \qquad (12)$$

When CF_4 was added to the system as a thermalizing addend, it was found that H_2 yields were unaltered, while those of CH_4 were significantly reduced as predicted by this mechanism.

An alternative explanation of the observations made in that study may be considered if the quantum yields determined by Steer and Knight are larger than the true values. Both primary processes, (1) and (6), could be occurring, the latter through an excited state of sufficient longevity to be susceptible to collisional deactivation. Such a sequence would explain all observations, apart from the quantum yields. There is ample evidence from other thiyl radical systems that reaction (7) is important, but whether a process such as reaction (8a) makes a significant contribution is open to question, particularly in view of more recent work on the ethanethiol system to be discussed below.

The major features of the dependence of product yields on pressure of added ethylene in this system are readily explained. As shown in Figure 4 the hydrogen yield decreases through scavenging of H-atoms by the olefin in reaction (4). Methyl ethyl sulphide formation and the continued formation of ethyl disulphide are explainable on the basis of reactions (1), (2) and (4) and the sequence:

$$\dot{C}_2H_5 + CH_3SH \longrightarrow C_2H_6 + CH_3\dot{S} \tag{13}$$

$$C_2H_6 + xC_2H_4 \xrightarrow{CH_3SH} \text{higher alkanes} + CH_3\dot{S} \tag{14}$$

$$2\,CH_3\dot{S} \rightleftharpoons CH_3SSCH_3^* \xrightarrow{M} CH_3SSCH_3 \tag{15}$$

$$CH_3\dot{S} + C_2H_4 \rightleftharpoons CH_3S\dot{C}_2H_4 \tag{16}$$

$$CH_3S\dot{C}_2H_4 + CH_3SH \longrightarrow CH_3\dot{S} + CH_3SC_2H_5 \tag{17}$$

A kinetic treatment of the mechanism yields the following expression for the quantum yield of methyl ethyl sulphide formation.

$$\Phi(CH_3SC_2H_5) = (1/I_a)^{\frac{1}{2}} \frac{k_{16}k_{17}[CH_3SH][C_2H_4]}{k_{15}^{\frac{1}{2}}(k_{-16} + k_{17}[CH_3SH])} \tag{18}$$

where I_a is the absorbed intensity. This predicts, as observed (Figure 4), that the rate and quantum yield of formation of the sulphide are linearly dependent on olefin pressure. A similar analysis of the hydrogen yields indicates that there is a simple competition for H-atoms between reactions (2) and (4) and the rate constant ratio can be evaluated from the data as $k_2/k_4 = 2{\cdot}32 \pm 0{\cdot}11$ compared to the value of 1·7 obtained by Inaba and Darwent[5].

Graham and coworkers have utilized the photolysis of methanethiol to determine a number of absolute values for the rate constants for the addition of CH_3S radicals to olefins. In a study[7] of the photolysis of

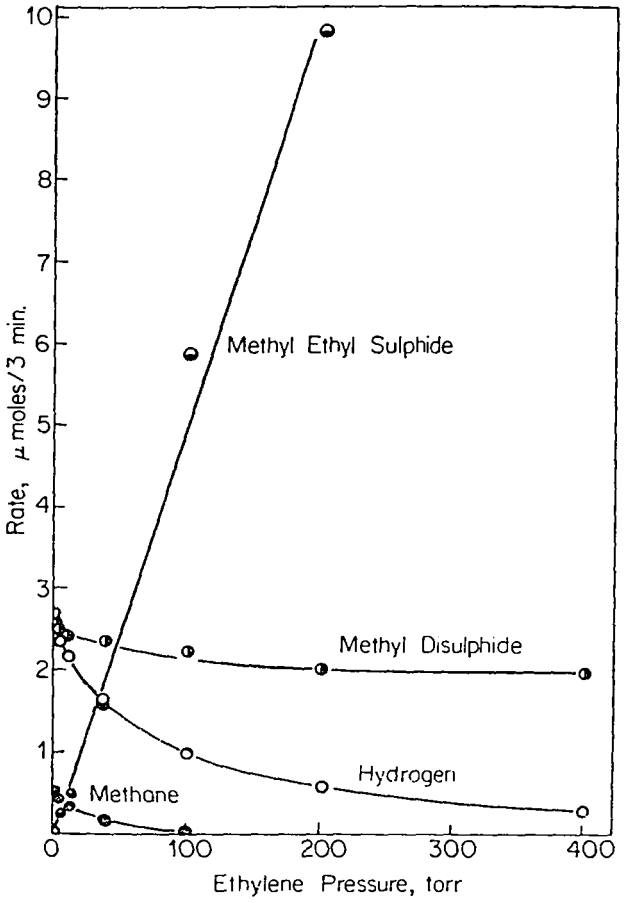


FIGURE 4. Rates of formation of $CH_3SC_2H_5$, CH_3SSCH_3, H_2 and CH_4 as a function of pressure of added C_2H_4 in the photolysis of 25 Torr of CH_3SH at 2537 Å and 25°C. Reproduced by permission from R. P. Steer and A. R. Knight, *J. Phys. Chem.*, **72**, 2145 (1968).

CH_3SH with *cis*- and *trans*-butene-2, they demonstrated that the isomerization of the olefin, which arises because of the reversibility of the addition process, reaction (16), occurs at a much faster rate than does the addition sequence producing the sulphide product. Additional investigations[8,9] of the addition reaction have provided data which permit the calculation of

values for k_{16} with several olefins. The kinetic treatment is based on a mechanism comprised essentially of reactions (1) through (4) and (16) and (17). The computation requires a value for the rate constant for reaction (3), thiyl radical recombination. Using the rotating sector intermittent illumination technique a value of $k_3 = 2{\cdot}5 \times 10^9$ litre/mole sec was found. The calculated rate constant values, in litre/mole sec, for reaction (16) are as follows: $7{\cdot}9 \times 10^4$ for acetylene, $4{\cdot}8 \times 10^5$ for ethylene and $1{\cdot}6 \times 10^6$ for butene-2. In the kinetic analysis of their results these authors also took into account the fact that an appreciable fraction of the incident radiation is absorbed and therefore the primary rate of radical production is not uniform throughout the reaction vessel.

Yamashita and Lossing[10] studied the $Hg(^3P_1)$-photosensitized decomposition of CH_3SH at low pressures of the thiol in a fast flow system, using 8 Torr helium as carrier, coupled to a mass spectrometer. The yields of the main products obtained, in moles formed per CH_3SH decomposed, were as follows: CH_3SSCH_3 [0·131], CH_3SCH_3 [0·138], H_2S [0·385], C_2H_6 [0·175], CH_4 [0·066] and H_2 [0·136]. The product CH_3SSH was also detected but could not be determined quantitatively. The inordinately large hydrogen sulphide yield was thought to be due to secondary reactions within the mass spectrometer and is not of photochemical origin. Making use of a technique developed for this type of reaction system it was possible to establish the nature of the primary radicals. Added $Hg(CD_3)_2$ was decomposed simultaneously in the flow system and provided a clean source of CD_3 radicals. Under these conditions formation of CH_3SCD_3 and CD_3SH could be observed, arising via the processes

$$CD_3 + CH_3S \longrightarrow CD_3SCH_3 \qquad (19a)$$

$$CD_3 + SH \longrightarrow CD_3SH \qquad (19b)$$

On the basis of the relative yields of the two deuteriated products, these authors suggested that reaction (6), involving C—S bond cleavage, accounts for about 10% of the primary decomposition in the sensitized decomposition, which must originate with a triplet state of the thiol.

Further evidence of a duality of primary processes in the methanethiol system, although at higher energy wavelengths, has been obtained recently by Callear and Dickson[11] who examined the flash photolysis of CH_3SH at 1950 Å and observed absorption spectra due to all three possible primary radicals, $CH_3\dot{S}$, $\dot{C}H_3$ and $\dot{S}H$. They established that these species did not arise from secondary processes and determined that the ratio of C—S to S—H bond cleavage at 1950 Å is 1 : 1·7.

B. Photolysis of Ethanethiol

Two recent investigations of the gas phase photodecomposition of C_2H_5SH by White and coworkers[12] and by Steer and Knight[13] are in essential agreement on the principal features of the reaction, with the exception of the exact value for the quantum yield of hydrogen formation.

The observed products for this system are H_2, C_2H_4, C_2H_6, H_2S and $C_2H_5SSC_2H_5$. The general characteristics of the reaction can be explained on the basis of a mechanism entirely analogous to that proposed for methanethiol. The key element of uncertainty is the origin of $\dot{C}_2H_5$ and $\dot{S}H$ radicals in the system.

Steer and Knight used acetone as an actinometer at 2537 Å and reported $\Phi(H_2) = 0{\cdot}97 \pm 0{\cdot}3$ independent of thiol or addend pressure. They therefore suggested that ethyl and $\dot{S}H$ radicals arise from the disulphide sensitized decomposition of the thiol:

$$2\,C_2H_5\dot{S} \longrightarrow C_2H_5SSC_2H_5^* \tag{20}$$

$$C_2H_5SSC_2H_5^* + C_2H_5SH \longrightarrow \dot{C}_2H_5 + \dot{S}H + C_2H_5SSC_2H_5 \tag{21}$$

The reduction in the yields of products coming from $\dot{C}_2H_5$ and $\dot{S}H$ radicals, that is observed when the pressure in inert addends is increased, is explainable on the basis of $C_2H_5SSC_2H_5^*$ molecules being collisionally deactivated.

White and coworkers, on the other hand, made use of both HBr and HI actinometry at 2537 Å and found $\Phi(H_2) = 0{\cdot}82 \pm 0{\cdot}02$, independent of C_2H_5SH pressure. They therefore proposed that the primary decomposition may proceed by two routes,

$$C_2H_5SH + h\nu \longrightarrow \dot{C}_2H_5^* + \dot{S}H \tag{22}$$

$$C_2H_5SH + h\nu \longrightarrow C_2H_4 + H_2S \tag{23}$$

in addition to the predominant primary step,

$$C_2H_5SH + h\nu \longrightarrow C_2H_5\dot{S} + \dot{H}^* \tag{24}$$

The subsequent reactions of the primary product radicals were proposed as follows:

$$\dot{H}^* + C_2H_5SH \longrightarrow C_2H_5\dot{S} + H_2 \tag{25}$$

$$\dot{H} + C_2H_5SH \longrightarrow C_2H_5\dot{S} + H_2 \tag{26}$$

$$\dot{C}_2H_5^* + C_2H_5SH \longrightarrow C_2H_6 + C_2H_5\dot{S} \tag{27}$$

$$\dot{C}_2H_5 + C_2H_5SH \longrightarrow C_2H_6 + C_2H_5\dot{S} \tag{28}$$

$$\dot{S}H + C_2H_5SH \longrightarrow H_2S + C_2H_5\dot{S} \quad (29)$$

$$C_2H_5\dot{S} + C_2H_5\dot{S} \longrightarrow C_2H_5SSC_2H_5 \quad (30)$$

$$\dot{H}^* + C_2H_5SH \longrightarrow \dot{C}_2H_5 + H_2S \quad (31)$$

$$\dot{C}_2H_5^* + C_2H_5SH \longrightarrow C_2H_4 + C_2H_6 + \dot{S}H \quad (32)$$

$$\dot{H}^* + M \longrightarrow \dot{H} + M \quad (33)$$

$$\dot{C}_2H_5^* + M \longrightarrow \dot{C}_2H_5 + M \quad (34)$$

This mechanism ascribes the pressure dependence of C_2H_6, C_2H_4 and H_2S to the participation of hot hydrogen atoms and hot ethyl radicals. These species, which attain energy in the primary process because of the difference between the excitation energy of absorption and the lower bond energy in the molecule, will be increasingly thermalized in the presence of inert addends at concentration [M], or by increasing pressure of the thiol itself. Thus the steady state treatment of the reaction sequence yields, for example, the following expression for $\Phi(C_2H_6)$:

$$\Phi(C_2H_6) = \Phi_{22} + \frac{k_{30}[C_2H_5SH]\Phi_{24}}{(k_{24}+k_{30})[C_2H_5SH]+k_{33}[M]} \quad (35)$$

and the predicted decline in ethane yields with pressure has been observed in both investigations. White and coworkers also photolysed $C_2H_5SSC_2H_5$ (known to give excited disulphide molecules[14]) in the presence of C_2H_5SH at wavelengths where only the disulphide absorbs and found no products arising from $\dot{C}_2H_5$ or $\dot{S}H$ radicals, thus providing additional evidence against a process such as reaction (21).

Because of the more detailed determinations of quantum yields by White and coworkers, their values must be considered to be more reliable than those reported by Steer and Knight. Consequently, the mechanism given above, which is otherwise consistent with all of the other data from both studies, is, on the basis of the available data, the more plausible one.

The investigation of White and coworkers[12] also included a study of the photolysis at 2140 Å. The results indicate that at this shorter wavelength reactions (22) and (23) account for a larger proportion, *ca.* 20%, of the primary decomposition, a characteristic of the reaction reflected principally in a reduced hydrogen quantum yield of 0·75. Thus although the effect is not particularly pronounced, it appears that the absorption band centred at 2000 Å may be due to the transition leading to C—S bond cleavage. This suggestion is consistent with these authors' results and those obtained in the flash photolysis study[11].

C. Energy Partitioning in the Primary Process—Production of Translationally Excited Hydrogen Atoms

Two reports that appeared in 1967 aroused considerable interest in the question of the energetics of the primary photochemical decomposition of thiols in the gas phase. Gann and Dubrin[15] studied the flash photolysis of H_2S at 2138 Å in the presence of C_4D_{10} and interpreted the formation of HD as resulting from the preferential attack by translationally excited, 'hot', hydrogen atoms on the deuteriated addend, since thermalized H-atoms would be expected to be scavenged here by the H_2S. In another study, Kuntz[16] examined the reactions of hydrogen atoms from the photolysis of H_2S, CH_3SH and C_2H_5SH with ethylene and observed a surprising pressure dependence of the rate constants normally evaluated in that kind of system. Although not all of the data could be explained in that way, some of the results strongly indicated the presence of hot hydrogen atoms.

Since that time White and coworkers have used effectively the method of Gann and Dubrin, replacing C_4D_{10} by D_2 as the energy-sensitive detector, to establish not only the participation of hot hydrogen atoms, but also the partitioning of the energy at various wavelengths between RS and H fragments. Experimentally the rates of H_2 and HD formation are measured as a function of $[RSH]/[D_2]$ in the presence and absence of thermalizing addends. The results can be interpreted kinetically on the basis of the following mechanism, for the methanethiol photolysis[17].

$$CH_3SH + h\nu \longrightarrow CH_3\dot{S} + \dot{H}^* \quad (36)$$

$$\dot{H}^* + CH_3SH \longrightarrow H_2 + CH_3\dot{S} \quad (37)$$

$$\dot{H}^* + D_2 \longrightarrow HD + \dot{D} \quad (38)$$

$$\dot{H}^* + CH_3SH \longrightarrow \dot{H} + CH_3SH \quad (39)$$

$$\dot{H}^* + D_2 \longrightarrow \dot{H} + D_2 \quad (40)$$

$$\dot{H}^* + M \longrightarrow \dot{H} + M \quad (33)$$

$$\dot{H} + CH_3SH \longrightarrow H_2 + CH_3\dot{S} \quad (2)$$

$$\dot{D} + CH_3SH \longrightarrow HD + CH_3\dot{S} \quad (41)$$

$$2\,CH_3\dot{S} \longrightarrow CH_3SCH_3 \quad (3)$$

$$\dot{H} + D_2 \longrightarrow HD + \dot{D} \quad (42)$$

The expression for $2[H_2]/[HD]$ product ratios obtained from the steady-state treatment of the mechanism is

$$\frac{2[H_2]}{[HD]} = \frac{(k_{37}+k_{38})[CH_3SH]}{k_{37}[D_2]} + \frac{k_{40}}{k_{38}} + \frac{k_{33}[M]}{k_{38}[D_2]} \tag{43}$$

which predicts that $2[H_2]/[D_2]$ should be a linear function of the ratio of thiol to deuterium concentrations. This linear dependence was in fact observed in this and all other thiol systems studied. In the absence of thermalizing gas, $[M] = 0$, the intercept yields k_{40}/k_{38}, while in the presence of M at a constant $[M]/[D_2]$ ratio the intercept is

$$k_{40}/k_{38} + (k_{33}/k_{38})[M]/[D_2].$$

As a general criterion in systems of this kind, the observation of a non-zero intercept in the plot of the left-hand side of equation (43) as a function of thiol : deuterium concentrations indicates the participation of hot hydrogen atoms. Furthermore, comparison of k_{33}/k_{38} ratios gives an indication of the relative efficiencies of various thermalizing addends.

Using this technique, for example, White and Strum[18] showed that in the photolysis of CH_3SH at 2537 Å, $k_{40}/k_{38} = 5{\cdot}3 \pm 0{\cdot}47$ while at 2288 Å the rate constant ratio is $1{\cdot}96 \pm 0{\cdot}12$ indicating that H-atoms produced at the shorter wavelength have appreciably more energy.

If the variation in $2[H_2]/[HD]$ with reactant ratio $[CH_3SH]/[D_2]$ is compared with that produced by photolysing HBr or HI in the presence of D_2 under the same conditions, the partitioning of the excess energy in the primary process between the thiyl radical and hydrogen atom can be evaluated. The observed variation in $2[H_2]/[HD]$ in the case of the HBr or HI experiments serves as a calibration point since the initial translational energy, E_0, of the H-atoms formed in those systems can be computed unambiguously.

In terms of the kinetic treatment of the mechanism listed above, if k_{40}/k_{38} is represented as I_0 (the intercept of the $2[H_2]/[HD]$ *vs.* $[HX]/[D_2]$ plots, where X = RS, Br or I) then the quantity $(I_0+1)^{-1}$ which is equal to $[HD]/([H_2]+[HD])$ represents the fraction of H-atoms that react while still translationally excited, in the limiting case of pure D_2. Thus a plot of $(I_0+1)^{-1}$ for the case of HBr (or HI) *vs.* E_0 serves as a calibration curve from which the value of E_0 for H-atoms produced by RSH species can be computed when the value of $(I_0+1)^{-1}$ for that system has been determined. Furthermore, E_{max}, the maximum energy which the H-atoms can receive from the primary process involving thiols can be calculated through equation (44),

$$E_{max} = (M_{RS}/M_{RSH})(h\nu - E_{D(RS-H)}) \tag{44}$$

where M_{RS} and M_{RSH} are the molecular masses of the thiyl radical and thiol respectively, and E_D is the S—H bond strength in the thiol, and thence $(E_{max} - E_0)$ gives the residual energy in the thiyl radical.

The technique may be illustrated by reference to Figures 5 and 6 which give the plot corresponding to equation (43) for the photolysis of

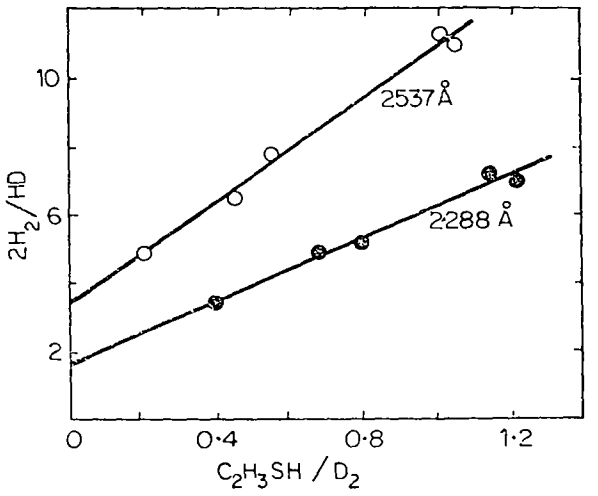


FIGURE 5. The variation of $2[H_2]/[HD]$ as a function of the ethanethiol : deuterium concentration ratio in the photolysis of C_2H_5SH–D_2 mixtures at 2537 Å and 2288 Å. Reproduced by permission of the *Journal of Chemical Physics* and the authors from J. M. White, R. L. Johnson and D. Bacon, *J. Chem. Phys.*, **52**, 5212 (1970).

ethanethiol–deuterium mixtures[19] and a plot of $(I_0+1)^{-1}$ for the photolysis of HBr in the presence of D_2[18]. The values of $(I_0+1)^{-1}$ in Figure 6 indicated for $\lambda = 2288$ Å and $\lambda = 2537$ Å were computed from the observed intercepts in the $2[H_2]/[HD]$ plots in Figure 5, and show that the value of E_0 for the hydrogen atoms from the C_2H_5SH photolysis is 1·0 eV at 2537 Å and 1·35 eV at 2288 Å. The corresponding E_{max} values, calculated from equation (44), are 1·03 eV (2537 Å) and 1·57 eV (2288 Å). Thus the energy partitioning ratio $R_E = E(RS)/E_0(H)$ may be determined for this system as 0·03 at 2537 Å and 0·15 at 2288 Å. There is no doubt that the majority of the carry-over energy from the primary process in these systems resides in the translationally excited hydrogen atoms formed therein. The energy partitioning ratios calculated from the data of White and coworkers[19,20,21] for methanethiol and ethanethiol are summarized in Table 1.

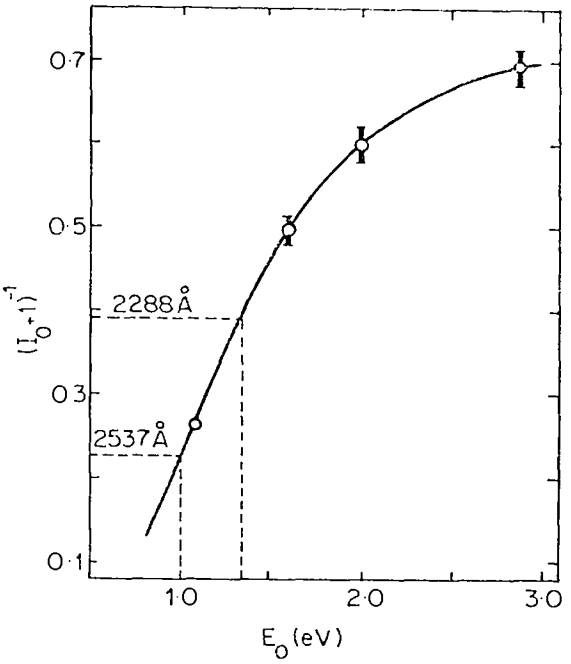


FIGURE 6. Dependence of the function $(I_0+1)^{-1}$ (see test) on the initial translational energy, E_0, of H-atoms as determined in the photolysis of HBr–D_2 mixtures. The graph also indicates the $(I_0+1)^{-1}$ values measured in the photolysis of ethanethiol at 2537 Å and 2268 Å and the corresponding values of E_0. Reproduced by permission of the *Journal of Chemical Physics* and the authors from J. M. White, R. L. Johnson and D. Bacon, *J. Chem. Phys.*, **52**, 5212 (1970).

TABLE 1. Wavelength dependence of the energy partitioning ratio R_E in the photolysis of thiols

Thiol	Wavelength (Å)	$R_E = E(RS)/E_0(H)$	Reference
CH_3SH	2537	0·18	20
CH_3SH	2288	0·28	20
CH_3SH	2138	0·39	20
CH_3SH	1849	1·51	20
C_2H_5SH	2537	0·03	19
C_2H_5SH	2288	0·15	19
C_2H_5SH	2138	0·30	21
C_2H_5SH	1849	1·60	21

The data in Table 1 indicate that the energy partitioning ratio is much the same for both thiols, and that the excitation energy of the thiyl radical is becoming more important as the wavelength of the photolysing light is decreased. These trends are consistent with the known similarity of the absorption spectra of CH_3SH and C_2H_5SH and the suggestion outlined earlier that a second excited state becomes progressively more important at shorter wavelengths.

The possible implications of the formation of translationally excited hydrogen atoms in thiol photolyses with respect to the use of such systems to study the addition of H-atoms to olefins have been investigated by Steer and Knight[22]. In that context the reactions to be considered in the general case of $RSH + C_2H_4$ mixtures are:

$$RSH + h\nu \longrightarrow R\dot{S} + \dot{H} \tag{45a}$$

$$RSH + h\nu \longrightarrow R\dot{S} + \dot{H}^* \tag{45b}$$

$$\dot{H} + RSH \longrightarrow H_2 + R\dot{S} \tag{46}$$

$$\dot{H}^* + RSH \longrightarrow H_2 + R\dot{S} \tag{47}$$

$$\dot{H} + C_2H_4 \longrightarrow \dot{C}_2H_5 \tag{4}$$

$$\dot{H}^* + C_2H_4 \longrightarrow \dot{C}_2H_5 \tag{48}$$

$$\dot{C}_2H_5 + RSH \longrightarrow C_2H_6 + R\dot{S} \tag{49}$$

$$\dot{H}^* + M \longrightarrow \dot{H} + M \tag{33}$$

In the absence of deactivating addend, the kinetic treatment of the above sequence yields, from a measurement of the yield of H_2 as a function of olefin pressure, the rate constant ratio k_{47}/k_{48}. Values of $2{\cdot}32 \pm 0{\cdot}11$ for the CH_3SH—C_2H_4 system[6] and $2{\cdot}00 \pm 0{\cdot}05$ for the C_2H_5SH system[22] were found. Prior to the appreciation of the role of hot hydrogen atoms, these ratios were interpreted, however, as those for thermalized H-atoms, i.e. k_{46}/k_4. Steer and Knight examined the photolysis of 25 Torr of ethylene and of either methanethiol or ethanethiol as a function of added CO_2 pressure up to 1400 Torr. The observed decreases in hydrogen production resulting from thermalization of H*-atoms in reaction 33 are shown in Figure 7. If the same kinetic analysis is carried out using the high pressure results, under which conditions presumably only thermalized H-atoms are involved in the addition and abstraction processes, the rate constant ratios found are $k_{46}/k_4 = 1{\cdot}15 \pm 0{\cdot}10$ (methanethiol) and $1{\cdot}05 \pm 0{\cdot}05$ (ethanethiol). A series of comparable experiments at 2288 Å showed that

this technique is incapable of detecting the differences in energy of H-atoms formed at various wavelengths that were detected and measured by White and co-workers.

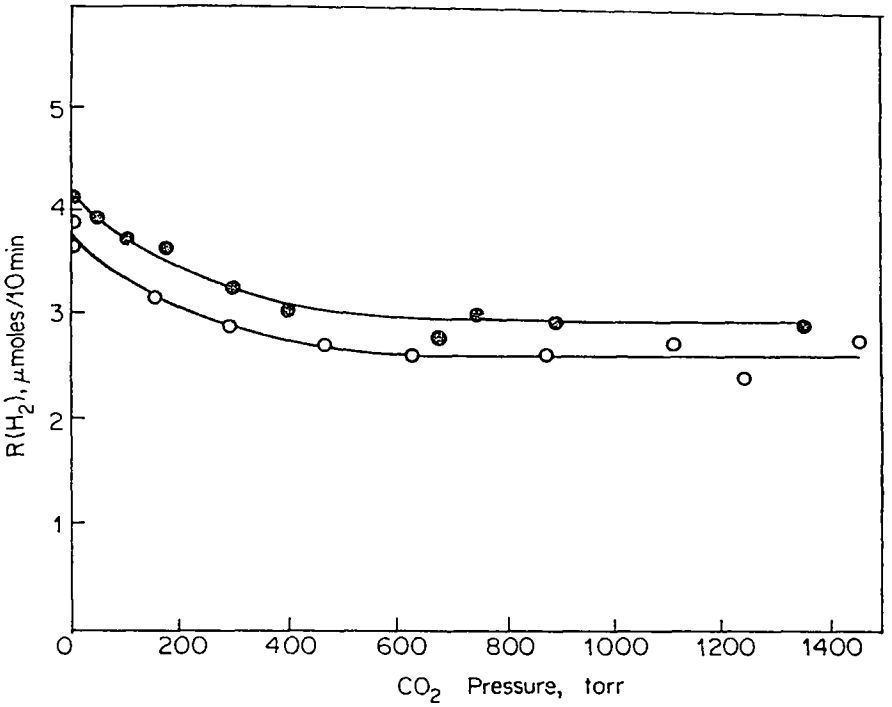


FIGURE 7. Rate of formation of H_2 as a function of added CO_2 in the photolysis of mixtures of 25 Torr C_2H_4 and 25 Torr of CH_3SH, ●, or 25 Torr C_2H_5SH, ○. Reproduced by permission of the National Research Council of Canada from the *Canadian Journal of Chemistry*, **46**, 2878 (1968).

III. CONDENSED PHASE PHOTOLYSES

Thiols have been photodecomposed both as pure liquids and in solution in investigations primarily designed to study the reactions of the hydrogen atoms and thiyl radicals formed. In condensed phase it has generally been assumed that the only significant primary process is S—H bond cleavage. A recent study of the photolysis of neat liquid ethanethiol indicates that to be the case[23].

The accumulated evidence on the chemical and kinetic behaviour of thiol photolysis indicates that subsequent reactions of the two primary fragments are essentially independent. In pure thiols, H-atoms react

exclusively in process (2) to form H_2 and an additional $R\dot{S}$ species. If a hydrogen donor, QH, is added, H-atom abstraction from that species will compete with reaction (2), abstraction from RSH. The hydrogen atoms that so react will already have been thermalized in the liquid and furthermore, possible complicating reactions involving RS or Q radicals either do not appear to be significant or can be taken into account in a simple way in the kinetic analysis. Thiyl radicals will react with themselves, the combination process (3), or with the addend. Their reaction with the parent thiol has no net effect and $R\dot{S}$ radicals are not involved in subsequent reactions with hydrogen atoms.

In general, however, it has been only in recent years, since the overall characteristics of thiol photolyses have been established that these systems have been utilized as a method for the controlled production of hydrogen atoms and thiyl radicals.

A. Photolysis of Liquid Mercaptans

Since the pioneering work of Thompson[1,2] the investigation of the photolysis of pure liquid mercaptans has received very little attention. Recently Carlson and Knight[23] studied the photolysis of pure liquid C_2H_5SH at 2537 Å. Hydrogen and ethyl disulphide were the only products detected. The rates of formation of both products were the same within experimental error and linearly dependent on exposure time. Using the photolysis of methyl disulphide–ethyl disulphide mixtures as a secondary actinometer to determine the absorbed intensity in the system[24], the quantum yield values of $\Phi(H_2) = \Phi(C_2H_5SSC_2H_5) = 0{\cdot}25$ were determined. On the basis of the observed simplicity of the products, the decomposition can adequately be explained on the basis of the simple reaction sequence:

$$C_2H_5SH + h\nu \longrightarrow C_2H_5\dot{S} + \dot{H} \qquad (50)$$

$$\dot{H} + C_2H_5SH \longrightarrow H_2 + C_2H_5\dot{S} \qquad (26)$$

$$2\,C_2H_5\dot{S} \longrightarrow C_2H_5SSC_2H_5 \qquad (51)$$

The equivalence of hydrogen and disulphide yields also rules out the possibility of thiyl radical disproportionation via

$$2\,C_2H_5\dot{S} \longrightarrow C_2H_4S + C_2H_5SH \qquad (52)$$

as a possible complicating factor when the thiol photolysis is exploited as an H-atom or thiyl radical source.

B. *Thiols as H-atom Sources in Solution*

There is a great deal of interest in the reactions of hydrogen atoms both theoretically because of the fundamental importance of the $H + H_2$ reaction in absolute rate theory[25,26] and because of the identification of the significant role of H-atoms, resulting from irradiation of aqueous solutions, in processes in radiation biology[27,28].

Pryor and coworkers have recently examined the photolysis of thiols in solution from this point of view and have developed two methods whereby rate constants for reactions of the general type

$$\dot{H} + QH \xrightarrow{k_H} H_2 + \dot{Q} \tag{53}$$

can be evaluated. In what will be referred to here as Method I[29,30,31] a thiol, tritium labelled at tracer levels in the sulphydryl position, RSH^T, is photolysed in the presence of QH, an organic molecule with one or more abstractable hydrogen atoms, at various [RSH]/[QH] ratios. In the usual procedure the thiol : hydrogen donor ratio is varied over a tenfold range and the activity of the thiol and of the hydrogen donor with tritium incorporated, QH^T, is measured. The results are interpreted on the basis of the following reaction sequence for the case of *n*-propanethiol as RSH:

$$PrSH^T + h \longrightarrow Pr\dot{S} + \dot{H} \tag{54}$$

$$\dot{H} + PrSH \longrightarrow H_2 + Pr\dot{S} \tag{55}$$

$$\dot{H} + PrSH \longrightarrow H_2 + C_2H_5\dot{C}SH \tag{56}$$

$$\dot{H} + QH \longrightarrow H_2 + \dot{Q} \tag{57}$$

$$\dot{H} + QH \longrightarrow (HQH) \text{ or } (HQH)^T \tag{58}$$

$$C_2H_5\dot{C}SH + PrSH \longrightarrow PrSH + Pr\dot{S} \tag{59}$$

$$C_2H_5\dot{C}SH + PrSH^T \longrightarrow Pr^TSH + Pr\dot{S} \tag{60}$$

$$PrSH + \dot{Q} \longrightarrow Pr\dot{S} + QH \tag{61}$$

$$PrSH^T + \dot{Q} \longrightarrow Pr\dot{S} + QH^T \tag{62}$$

The atoms produced in the primary process are predominantly H-atoms as shown since the tritium is at tracer levels only. HQH and HQH^T are any addition product complex which the hydrogen donor may form with hydrogen or with tritium atoms. Pr^TSH represents the thiol with tritium incorporated into the side chain. The rate constants for reaction 60 and 62 are written, respectively, as $k_{59}I_{59}$ and $k_{61}I_{61}$, where the I factors are the kinetic isotope effects on the two reactions—abstraction of tritium *vs* hydrogen.

The kinetic analysis of the mechanism gives the following rate expression:

$$\frac{(t)\,[\mathrm{PrSH}]_0/[\mathrm{QH}]_0}{A_{\mathrm{QH}}/A^0_{\mathrm{PrSH}}} = \frac{(k_{57}+k_{58})/k_{54}}{k_{57}I_{61}} + \frac{(k_{55}+k_{56})/k_{54}[\mathrm{PrSH}]_0}{k_{57}I_{61}[\mathrm{QH}]_0} \qquad (63)$$

in which t is the photolysis time in sec, A_{QH} and A^0_{PrSH} are the molar specific activities of the $\mathrm{QH^T}$ produced in the experiment and the initial thiol respectively. A plot of the left-hand side of equation (63) *vs* $[\mathrm{PrSH}]_0/[\mathrm{QH}]_0$ gives a straight line with slope inversely proportional to $k_{57}I_{61}$—the product of the rate constant for H-atom attack on QH and the kinetic isotope factor in reactions (61) and (62). A further refinement which takes into account possible variations in absorbed light intensity from experiment to experiment involves measurement of the molar specific activity of the side-chain-labelled thiol, $\mathrm{Pr^TSH}$. By comparison of the results of the analysis using equation (63) and an analogous expression involving $A_{\mathrm{Pr^TSH}}$, values of $k_{57(\mathrm{rel})}I_{61}$, compared to $k_{56}I_{59}$ can be obtained. The method has the disadvantage that it can be applied only to QH species for which the Q—H bond energy is appreciably stronger than the S—H bond in thiols. If such is not the case then abstraction from QH by species other than H-atoms may occur and lead to deceptively large yields of tritiated QH.

Method II developed by Pryor and coworkers[29,30,32] makes use of a somewhat simpler system. A deuteriated thiol, usually *t*-BuSD, is photolysed in the presence of the hydrogen donor QH and the amounts of HD and D_2 produced are measured mass spectrometrically.

At small percent conversions the only reactions, in addition to the primary dissociation into alkylthiyl radicals and H-atoms, that must be considered are

$$\dot{\mathrm{D}} + \mathrm{RSD} \longrightarrow \mathrm{D_2} + \dot{\mathrm{RS}} \qquad (64)$$

$$\dot{\mathrm{D}} + \mathrm{RSD} \longrightarrow \dot{\mathrm{R}}'\mathrm{SD} + \mathrm{HD} \qquad (65)$$

$$\dot{\mathrm{D}} + \mathrm{QH} \longrightarrow \dot{\mathrm{Q}} + \mathrm{HD} \qquad (66)$$

where $\dot{\mathrm{R}}'\mathrm{SD}$ is the radical produced when a hydrogen atom is abstracted from the alkyl group in the thiol. For purposes of comparison of *hydrogen*-atom reactions, k_{66} is expressed as $k_{57}I$ where I is the isotope effect on reactions (57) and (66), hydrogen and deuterium abstracting from QH. The kinetic treatment thus gives

$$\frac{[\mathrm{HD}]}{[\mathrm{D_2}]} = \frac{k_{65}}{k_{64}} + \frac{k_{57}I}{k_{64}}\frac{[\mathrm{QH}]}{[\mathrm{RSD}]} \qquad (67)$$

Plots of $[\mathrm{HD}]/[\mathrm{D_2}]$ as a function of $[\mathrm{QH}]/[\mathrm{RSD}]$ were found to be linear and thus values of $k_{57}I/k_{64}$ could be obtained.

In both methods the variation in the isotope effect with QH will evidently influence the relative rates of attack computed from these data. For k_D/k_H its values are close to unity[33]. For the tritiated systems, Pryor and Kneipp[34] have measured the effect for a variety of QH species and utilized these values to compute a series of $k_{H(rel)}$ values correct for the isotope effects. A few representative values are listed in Table 2, along with relative

TABLE 2. Relative rate constants for the attack of H-atoms on hydrogen donors

Hydrogen donor	k_H(relative)		
	Method I[a]	Method II[a]	Radiolysis[b]
Hexane	1	1	1
Nonane	1·4	2·2	1·7
2,3-dimethylbutane	2·1	2·2	3·1
Tetrahydrofuran	9·1	8·2	7·7

[a] See text, data of Pryor and coworkers.
[b] Data from radiolysis of aqueous solutions, ref. 33.

rate constants obtained in studies of the radiolysis of aqueous solutions. The data in Table 2 are representative of the kind of agreement between the thiol photolysis method and the radiolysis data in the case of all substrates except the alcohols. The origin of the large differences in the data for ROH species (for example, 1·9 *vs* 13 for k_H for *i*-propanol) have not yet been explained.

The methods of Pryor and coworkers thus provide an additional useful technique for the determination of values of the rate constants of these reactions of considerable practical importance. It is instructive to note that their utility originates with the relative simplicity of the thiol photolysis in the condensed phase and the appreciable lability of the sulphydryl hydrogen.

C. *Thiols as Thiyl Radical Sources in Solution*

Thiols have been widely investigated as a source of thiyl radicals for the chain process in which RS species are added to unsaturated hydrocarbons. The systems studied have been primarily thermal reactions, frequently catalysed by peroxides. These results have been summarized elsewhere[35,36,37]. Photochemical initiation of the chain process has been examined less widely[38,39].

Recently Carlson and Knight photolysed ethanethiol–methyl disulphide mixtures and studied the chain exchange reaction between thiyl radicals and the disulphide[23]. Thiyl radicals produced by the thiol photolysis attack the disulphide to form a new disulphide and eventually convert the methyl disulphide, present initially at about 10% concentrations, to CH_3SH.

The conversion involves the following steps:

$$C_2H_5SH + h\nu \longrightarrow C_2H_5\dot{S} + \dot{H} \quad (50)$$

$$CH_3SSCH_3 + h\nu \longrightarrow 2\,CH_3\dot{S} \quad (68)$$

$$C_2H_5\dot{S} + CH_3SSCH_3 \longrightarrow C_2H_5SSCH_3 + CH_3\dot{S} \quad (69)$$

$$C_2H_5\dot{S} + C_2H_5SSCH_3 \longrightarrow C_2H_5SSC_2H_5 + CH_3\dot{S} \quad (70)$$

$$CH_3\dot{S} + C_2H_5SH \longrightarrow CH_3SH + C_2H_5\dot{S} \quad (71)$$

Reactions (69) and (70) are the chain propagating steps in the sequence, with the $CH_3\dot{S}$ radicals produced therein giving rise to the final 'product', CH_3SH. The participation of the chain reaction is indicated by the value of $\Phi(CH_3SH) = 151$ in the initial stages of the reaction. As the reaction period increases, the yield of $C_2H_5SSCH_3$ passes through a maximum and there is a concomitant increase in $\Phi(C_2H_5SSC_2H_5)$. The chain exchange process has been investigated in detail in disulphide mixtures previously[24].

D. Other Condensed Phase Studies

Caspari and Granzow[40] studied the flash photolysis of 2-mercaptoethanol, benzenethiol and cysteine hydrochloride in aqueous solution. The transient spectra observed, with $\lambda_{max} = 420$ nm were identical to those found in the pulse radiolysis of these substrates and were identified as arising from the $R\dot{S}\bar{S}R$ radical anion. For 2-mercaptoethanol and cysteine hydrochloride the predominant species in solution at the pH values involved is the RS^- anion. The primary photochemical process was suggested to be the production of thiyl radicals via electron detachment from that species as

$$RS^- + h\nu \longrightarrow R\dot{S} + e^- \quad (72)$$

For benzenethiol the molecular form of the thiol is also important and there the primary process is

$$RSH + h\nu \longrightarrow R\dot{S} + \dot{H} \quad (45a)$$

The observed transient arises from the attack of the thiyl radicals so formed on the RS^- anion. The concentrations are controlled via the equilibrium

$$R\dot{S}\bar{S}R \rightleftharpoons R\dot{S} + RS^- \longrightarrow \text{products} \quad (73)$$

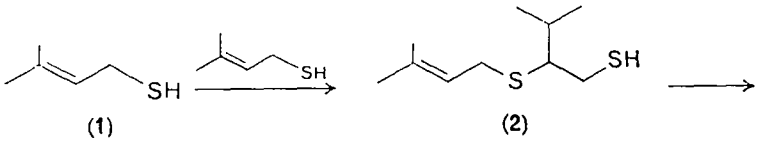
Since the transient spectra fade via first-order kinetics, the equilibrium must be predominantly in favour of the left-hand side of process (73).

A number of investigations of the photolysis of thiols in the solid state have produced ultraviolet and e.p.r. spectral evidence for the formation of thiyl radicals. Rosengren[41] photolysed ethanethiol, 2-propanethiol and 1-butanethiol in an isopentane–3-methylpentane matrix at 77 K and observed an ultraviolet absorption band centred around 4000 Å. The absorption was ascribed to the thiyl radical formed in the primary process. The initially formed hydrogen atoms diffuse away from the parent thiol, leaving the thiyl radical trapped in the matrix. The RS absorption spectrum disappears on warming to room temperature and subsequent chemical analysis showed the presence of significant amounts of disulphide.

Volman and coworkers[42] examined the e.p.r. spectra obtained from ultraviolet exposure of a series of samples of thiols and other S-containing substrates at 77 K, including methanethiol and CH_3SD and their aqueous solutions. The resonances obtained were attributed to the thiyl radical produced in the primary process at 2537 Å.

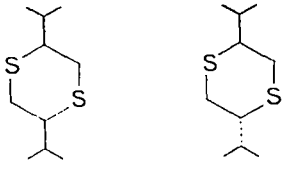
Skelton and Adam[43] carried out a similar e.p.r. study but in addition compared the behaviour of the same thiols under γ-irradiation. Thiyl radical e.p.r. spectra were observed only in the photolysed samples. Wan[44] photolysed triphenylmethanethiol in benzene solution at 77 K and found two e.p.r. spectra, one ascribed to the $Ph_3C\dot{S}$ radical suggested to be the main primary fragment, and the other assigned to the $Ph_2\dot{C}_6H_6CSH$ radical produced via H-atom abstraction from the substrate.

Very little attention has been paid to unsaturated thiols, most of which are relatively unstable. A recent report[45] indicates that one such thiol, γ,γ'-dimethylallylthiol (**1**) is sufficiently stable to be investigated. Irradiation of **1** in *n*-hexane solution under N_2 gives quantitative conversion of **1** to **3** via



(1) (2)

(74)



(3c) (3t)

As the irradiation time is increased the proportion of **2** in the products decreases so that at 97% conversion, **2** is reduced to trace proportions and **3c** and **3t** comprise 20 and 75% respectively of the analysable products.

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The Chemistry of the Thiol Group
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CHAPTER 11

The radiation chemistry of thiols

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I. INTRODUCTION

High energy radiation interacts with matter causing ionization and excitation, followed by ion–molecule reactions, charge neutralization and dissociation of molecules giving rise to the formation of free radicals. Thus the radiation chemistry of thiols is essentially free radical chemistry, with the thiyl radical, $RS^{\bullet}$, as the most important intermediate species. The thiols which have been most studied are for two main reasons those of biological interest. Firstly the —SH group is very reactive towards free radicals and consequently molecules containing thiol groups play a dominant role in radiation–biological processes. Secondly, it was found in the 1940's that some aminothiols when added to *in vivo* systems gave considerable protection against the harmful effects of ionizing radiation. As thiols occur in nature, mainly as aminoacid residues of peptide-containing molecules, cysteine, $NH_3^+CH(CO_2^-)CH_2SH$, has been the thiol most closely studied. Cysteamine (2-mercaptoethylamine) was early on found to be highly protective and has also been studied extensively. Studies of the basic radiation chemistry of these and related thiols, in aqueous solutions, alone, or in mixtures with model compounds of biological importance have been most informative, and the gap between radiation chemistry and radiation biology has closed considerably in the last five years. Much current work is now centred on large biologically active molecules.

As the radiolysis of a thiol frequently produces the corresponding disulphide as the major product, and as both thiol and disulphide groups are present together in biological systems, some discussion on the radiation chemistry of the disulphide group is an essential part of this chapter.

Radiation chemistry yields are usually expressed as *G*-values, the number of molecules (or radicals) formed (or destroyed) per 100 eV of

energy absorbed by the system. The equation

$$G(-\mathrm{RSH}) = 2\,G(\mathrm{RSSR}) + G(\mathrm{H_2S})$$

implies that disulphide and H_2S are the only sulphur-containing products formed in a particular experimental study.

II. AQUEOUS SOLUTIONS OF THIOLS–OXYGEN-FREE

A. Radiolysis of Aqueous Solutions

The absorption of high energy radiation by water results in the formation of radical and molecular products[1], and for fast electrons or γ-radiation may be represented by reaction (1) where the stoichiometry is expressed in G-values[2]. The exact mechanism of the formation of these products is

$$G_{-\mathrm{H_2O}} \longrightarrow G_{\mathrm{H}}\mathrm{H} + G_{\mathrm{H^+_{aq}}}\mathrm{H^+_{aq}} + G_{\mathrm{e^-_{aq}}}\mathrm{e^-_{aq}} + G_{\mathrm{H}}\mathrm{H} + G_{\mathrm{OH}}\mathrm{OH} + G_{\mathrm{H_2}}\mathrm{H_2} + G_{\mathrm{H_2O_2}}\mathrm{H_2O_2}$$

or

$$4{\cdot}2\,\mathrm{H_2O} \longrightarrow 2{\cdot}7\,\mathrm{H^+_{aq}} + 2{\cdot}7\,\mathrm{e^-_{aq}} + 0{\cdot}6\,\mathrm{H} + 2{\cdot}7\,\mathrm{OH} + 0{\cdot}45\,\mathrm{H_2} + 0{\cdot}7\,\mathrm{H_2O_2} \qquad (1)$$

still a matter of research and discussion, but it is clear that at about 100 ns after the absorption of the high energy particle the above products have formed and diffused away sufficiently from the particle track to react with solutes in low concentration ($\leqslant 10^{-3}$M) with effectively homogeneous kinetics. The fraction of the incident energy absorbed by the solute is negligibly small for dilute solutions. The situation is therefore different from that found in photochemistry where all the photon energy is absorbed by direct solute–photon interaction. As its concentration is increased above about 10^{-3}M a reactive solute may progressively interfere with spur reactions, reacting with the primary radical products or their precursors during the stage of 'spur diffusion kinetics', and thus alter the radical and molecular yields.

In dilute solutions of a thiol, RSH, it should be possible to explain the radiation chemistry in terms of the reactions of RSH with OH, e^-_{aq} and H at low conversions, but as the radiation products accumulate, competition between these and RSH for the radicals will occur, leading to secondary products. Thus 'initial yields' of products are normally measured experimentally in mechanistic investigations. When a second solute is also present, e.g. O_2, competition for the primary products will occur, and the intermediates formed from RSH may also react with this added solute. The pH of the solution is also important because H^+_{aq} may compete with RSH for e^-_{aq}, and in addition the actual form, and hence the reactivity, of the thiol may change with pH in a manner depending on its acid dissociation constants.

B. Reactions of Thiols with Primary Radicals

1. Hydroxyl radical

The hydroxyl radical reacts rapidly with thiols, product analysis indicating the thiyl radical to be the main product as in reaction (2). This

$$RSH + OH \longrightarrow RS^{\bullet} + H_2O \qquad (2)$$

is supported by the work of Armstrong and Humphries[3], who generated $OH^{\bullet}$ radicals from Ti^{3+}–H_2O_2 solutions and reacted them with thiols in a flow system. The e.s.r. spectrum corresponded to that of a thiyl radical. Rate constants for various thiols are listed in Table 1. Jayson, Stirling and

TABLE 1. Rate constants for the reaction of OH with RSH[a]

Thiol	pH	Method[b]	$10^{-9}k$, l mol^{-1} s^{-1}	Reference
Cysteamine	1·4	CNS^-	15	4
Cysteamine	6·5	CNS^-	13	4
Cysteamine	9	CNS^-	13	4
Cysteine	6·5	CNS^-	13	5
Mercaptoethanol	7	CNS^-	25	6
Mercaptoethanol	11	CNS^-	6·2	6
Mercaptoethanol	6·5	CNS^-	17	7
Mercaptoethanol	6·5	$Fe(CN)_6^{4-}$	6·1	7
Mercaptoethanol	6·5	$PhNO_2$[c]	5	7
Methyl mercaptan	7	CNS^-	31	6
Methyl mercaptan	11	CNS^-	9·4	6
t-Butyl mercaptan	7	CNS^-	17	6
Glutathione	6·5	CNS^-	12	5
Homocysteine	7	PNDA[d]	1·7	8

[a] Normalized to rate constants given in reference 9.
[b] Pulse radiolysis except for homocysteine.
[c] Using $k_{OH+PhNO_2} = 4{\cdot}7 \times 10^9$ l mol^{-1} s^{-1}.
[d] *p*-Nitrosodimethylaniline—steady-state radiolysis.

Swallow obtained a higher figure for mercaptoethanol with thiocyanate ion as competition scavenger than with ferrocyanide ion or nitrobenzene[7], and other figures in the table using CNS^- could also possibly be too high. At pH 9 or 11 the thiols listed would be mainly in their thiolate ion form. In the case of mercaptoethanol and methyl mercaptan at pH 11 new transients seen by pulse radiolysis, and not observed at lower pH, were tentatively attributed to radicals obtained by hydrogen atom abstraction from the α-carbon atom with respect to sulphur[6]. Recent e.s.r.-radiolysis studies also give evidence for some H-abstraction from carbon in mercaptocarboxylic acids[10].

2. Aquated electron

The aquated electron reacts rapidly with thiols in near-neutral solutions to give H_2S and the parent hydrocarbon as the major detectable products, according to reactions (3) and (4). Values of $G(H_2S)$ and $G(RH)$ of

$$RSH + e^-_{aq} \longrightarrow R^\bullet + HS^- \quad (3)$$

$$R^\bullet + RSH \longrightarrow RH + RS^\bullet \quad (4)$$

between 2·5 and 3·0 have been reported for cysteine[11,12,13], cysteamine[14], methyl mercaptan[15], and homocysteine[8] for thiol concentrations in the range 10^{-3}–5×10^{-2}M. Lower values of 2·3 have been reported for glutathione (10^{-2}M)[16], and 4-aminobutane-1-thiol (10^{-3}M)[17], while very much lower values of 1·4 and 1·7 for 10^{-2}M and 10^{-1}M mercaptoethanol[7] have been found. The authors in the latter case suggest that nearly half the e^-_{aq} are reacting by reaction (5):

$$e^-_{aq} + HOCH_2CH_2SH \xrightarrow{H^+} HOCH_2CH_2S^\bullet + H_2 \quad (5)$$

but the reason for this difference is not understood.

Reported rate constants for the reaction of e^-_{aq} with thiols are listed in Table 2. In pulse radiolysis studies the rate of disappearance of e^-_{aq} is measured directly, whereas in product-yield–scavenger studies, the RSH–e^-_{aq} adduct could in principle transfer the electron to a scavenger, or not yield H_2S quantitatively, thus leading to low values. The figures for cysteine at low and high pH call for comment. Trumbore and coworkers suggest that the fully protonated form of cysteine, carrying an overall positive charge, reacts faster than does the zwitter-ion form[18], while the 100-fold decrease at pH 11·6 found by Braams[20] would be due to the cysteine being present as the thiolate ion, RS^-. It was found in a much earlier study[21] that $G(H_2S)$ drops as the pH is increased above 8, and the thiolate ion is probably unreactive towards e^-_{aq}.

3. Hydrogen atom

In acidic solutions aquated electrons with protons yield hydrogen atoms by reaction (6), and these, together with those formed directly ($G_H = 0{\cdot}6$), may react with the thiol. Armstrong and coworkers have

$$e^-_{aq} + H^+_{aq} \longrightarrow H \quad (6)$$

shown that lowering pH increases $G(H_2)$ and decreases $G(H_2S)$[15], but even under conditions where all e^-_{aq} are scavenged by H^+_{aq} some H_2S is still produced. Thus it appears that H may react by reaction (7) or reaction

TABLE 2. Rate constants for the reaction of e^-_{aq} with RSH

Thiol	pH	[RSH], M	Measured quantity	Technique[a]	$10^{-9}k$, l mol^{-1} s^{-1}	Reference
Cysteine	0·7–0·8	10^{-3}	$G(H_2)$	$[H^+]$	11	15
Cysteine	7	—	$G(H_2S)$	$[NO_3^-]$	4·4	12
Cysteine	7	—	$G(H_2S)$	[acetone]	5·4	12
Cysteine	0·5, 1	10^{-3}–10^{-1}	$G(H_2)$	[RSH]	30	18
Cysteine	5–6	10^{-2}	$G(H_2S)$	$[NO_3^-]$	11	11
Cysteine	5–6	10^{-2}	$G(H_2S)$	[acetone]	11	11
Cysteine	7	3×10^{-3}	$G(H_2S)$	$[O_2]$	4	19
Cysteine	6·3	—	$[e^-_{aq}]$	p.r.	8·7	20
Cysteine	11·6	—	$[e^-_{aq}]$	p.r.	0·075	20
Cysteamine	6·9	—	$[e^-_{aq}]$	p.r.	20	20
Glutathione	8·25	—	$[e^-_{aq}]$	p.r.	3·2	20
Penicillamine	6·5	—	$[e^-_{aq}]$	p.r.	5·1	20
Mercaptoethanol	5·7–9	—	$[e^-_{aq}]$	p.r.	12	7
Mercaptoethanol	10	—	$[e^-_{aq}]$	p.r.	10	6
Methyl mercaptan	7	—	$[e^-_{aq}]$	p.r.	7·5	6
Methyl mercaptan	0·7–8	5×10^{-2}	$G(H_2)$	$[H^+]$	18	15
t-Butyl mercaptan	7	—	$[e^-_{aq}]$	p.r.	3	6
Homocysteine	7	3×10^{-3}	$G(H_2S)$	$[O_2]$	4·3	8
4-Aminobutane-1-thiol	7	10^{-3}	$G(H_2S)$	$[O_2]$	4	17

[a] p.r. stands for pulse radiolysis. In the other cases the competitive electron scavenging technique was used, the compound whose concentration was varied being indicated.

(8) with the R$^{\bullet}$ abstracting H from a second thiol molecule, reaction (4).

$$H + RSH \longrightarrow H_2 + RS^{\bullet} \quad (7)$$

$$H + RSH \longrightarrow H_2S + R^{\bullet} \quad (8)$$

Trumbore has pointed out[18] that reactions (9) and (10) provide a possible alternative route for the formation of H_2S. No evidence that clearly separates the possibilities has been reported.

$$H + RSH \longrightarrow HS^{\bullet} + RH \quad (9)$$

$$HS^{\bullet} + RSH \longrightarrow H_2S + RS^{\bullet} \quad (10)$$

The rate constant ratio k_7/k_8 (or k_7/k_9) has been determined from $G(H_2)$ and/or $G(H_2S)$ measurements. The following figures have been obtained at room temperature: cysteine, 3·5[22] and 3·7[23]; cysteamine, 2·7[14]; mercaptoethanol, ~5[7]. By bubbling H atoms formed by an electric discharge into a solution of cysteine Navon and Stein obtained a value of about 5[24].

C. Mechanism

The products of the radiolysis of a thiol in the absence of O_2 are the disulphide, H_2 and H_2S. The generally accepted mechanism established for cysteine by Armstrong[11,15,22] and by Trumbore[12,18] is:

$$e^-_{aq} + H^+_{aq} \longrightarrow H \quad (6)$$

$$e^-_{aq} + RSH \longrightarrow R^{\bullet} + HS^- \quad (3)$$

$$H + RSH \longrightarrow RS^{\bullet} + H_2 \quad (7)$$

$$H + RSH \longrightarrow R^{\bullet} + H_2S \quad (8)$$

$$OH + RSH \longrightarrow RS^{\bullet} + H_2O \quad (2)$$

$$R^{\bullet} + RSH \longrightarrow RH + RS^{\bullet} \quad (4)$$

$$RS^{\bullet} + RS^{\bullet} \longrightarrow RSSR \quad (11)$$

The evidence for this mechanism comes from the effect of pH on $G(-RSH)$, $G(H_2S)$ and $G(H_2)$, the equality of $G(H_2S)$ and $G(RH)$ at all pH, the sulphur mass-balance $G(-RSH) = 2G(RSSR) + G(H_2S)$, and reasonable agreement of $G(-RSH)$ with the values calculated on the above mechanisms in the extreme where all e^-_{aq} react with RSH according to reaction (3). At any pH the relationship

$$G(-RSH) = G_{OH} + G_{e^-_{aq}} + G_H + G(H_2S)$$

holds if the mechanism is correct, and from simple competition kinetics,

$$G(H_2S) = G_{e_{aq}^-}\frac{k_3[RSH]}{k_3[RSH]+k_6[H^+]}+G_{e_{aq}^-}\frac{k_6[H^+]}{k_3[RSH]+k_6[H^+]}\frac{k_8}{k_7+k_8}+G_H\frac{k_8}{k_7+k_8}$$

At low pH we therefore have

$$G(-RSH) = G_{OH}+(G_{e_{aq}^-}+G_H)\left(1+\frac{k_8}{k_7+k_8}\right)$$

and in neutral solution

$$G(-RSH) = G_{OH}+2\,G_{e_{aq}^-}+G_H\left(1+\frac{k_8}{k_7+k_8}\right)$$

The rate constant ratio k_7/k_8 reported in the previous section was obtained by assuming the above mechanism. Taking the figure of 3·5 for this ratio for cysteine, and the radical yields given in reaction (1), $G(-RSH) = 6{\cdot}7$ in acidic and 8·8 in neutral solution respectively.

In all thiols studied, $G(-RSH)$ figures decrease with decreasing thiol concentrations, the decrease being greater than may be expected from rate constant data. The same general mechanism appears to apply to the thiols cysteamine[14], glutathione[16], homocysteine[8] and 4-aminobutane-1-thiol[17], although the values of $G(-RSH)$ were a little low for complete scavenging in some cases.

As mentioned in section II.B.2 mercaptoethanol behaves differently in that only about half the aquated electrons give rise to H_2S[7]. Bronsted acids can react with e_{aq}^- and convert them to H, but the pK_a of the thiol group in mercaptoethanol is not lower than for other thiols, and the explanation must lie elsewhere.

A further reaction which should be considered when deducing mechanism from product yields is that of H_2O_2 with thiols (12):

$$2\,RSH+H_2O_2 \longrightarrow RSSR+2\,H_2O \qquad (12)$$

This reaction is slow in acidic solution, and $G(H_2O_2) = G_{H_2O_2}$ is found. However, in neutral and alkaline solution the rate can be appreciable and the reaction must be allowed for[11]. It has been shown that the reaction involves a nucleophilic attack of the thiolate ion on hydrogen peroxide, the rate being found proportional to $[RS^-]$ in studies on cysteamine[14] and cysteine[25] in which pH was varied.

D. Transients

1. Pulse radiolysis studies

Pulse radiolysis studies have shown the presence of a transient species when thiols are irradiated at a pH where some ionization of the thiol group has occurred. These species have an absorption band from

approximately 350 to 500 nm with a maximum at 400–450 nm and an extinction coefficient of the order of 10^4 l mol^{-1} cm^{-1}.

The first detailed study was on cysteamine by Adams and coworkers[4], who showed that the transient was not RS$^\bullet$ as they had first suspected but RS$\bar{S}$R formed by reaction of the thiyl radical with the thiolate ion in an equilibrium reaction (13). Evidence for this came from studying both

$$RS^\bullet + RS^- \rightleftharpoons RS\bar{S}R \qquad (13)$$

cystamine and cysteamine solutions. In pure solutions of the disulphide the rate of formation of the transient matched the rate of decay of the aquated electron, and the addition of nitrous oxide drastically reduced the amount formed. N_2O scavenges e^-_{aq} to produce OH radicals, reaction (14).

$$e^-_{aq} + N_2O \xrightarrow{H^+} OH + N_2 \qquad (14)$$

The decay of absorption was always exponential, suggesting electron attachment to the disulphide followed by dissociation, reactions (15) and (−13). In cysteamine solution N_2O increased the amount of transient

$$e^-_{aq} + RSSR \longrightarrow RS\bar{S}R \qquad (15)$$

$$RS\bar{S}R \longrightarrow RS^\bullet + RS^- \qquad (-13)$$

formed immediately after the pulse, showing OH radicals to be the precursor in this case. The rate of growth of transient was slower than the rate of reaction of thiol with OH radicals (as measured by CNS^- competition scavenging) but increased with thiol concentration. The maximum absorbance obtained after the electron pulse increased with increasing thiol concentration and pH, i.e. with increasing RS^- concentration, implying the equilibrium (13). This was confirmed by the decay kinetics, which were second-order and much slower than the first-order decay (−13). The second-order rate constant decreased with increasing thiol concentration and pH, implying that the rate of disappearance was controlled by dimerization of free thiyl radicals (reaction 11):

$$RS^\bullet + RS^\bullet \longrightarrow RSSR \qquad (11)$$

Similar results have been found for cysteine[25,26], mercaptoethanol[6,7], various alkyl mercaptans[6], H_2S[27], and penicillamine[28].

Further study of the second-order decay of RS$\bar{S}$R as a function of pH and thiol concentration showed that reaction (16) was also important[29], and this was confirmed during further work on cysteine[30].

$$RS^\bullet + RS\bar{S}R \longrightarrow \text{Products} \qquad (16)$$

The products are presumably RSSR and RS^-. Rate constants reported for reactions (11) and (16) are $\geqslant 10^9\,l\,mol^{-1}\,s^{-1}$.

The equilibrium constants for reaction (13) have been determined from either the rate constants of the forward and back reactions or from dependence of maximum absorbance after the pulse upon concentration and pH, and are shown in Table 3 together with reported extinction coefficients and absorption maximum for $RS\bar{S}R$.

Weaker absorptions at shorter wavelengths have been reported and assigned to the thiyl radical for penicillamine[28] at pH 5 ($\lambda_{max} = 330$ nm, $\varepsilon = 1{\cdot}2 \times 10^3\,l\,mol^{-1}\,cm^{-1}$) and for mercaptoethanol[7] at pH 6 ($\lambda_{max} = 360$ nm, $\varepsilon = 1{\cdot}3 \times 10^2\,l\,mol^{-1}\,cm^{-1}$), and tentatively to the radicals $HOCH_2\dot{C}HS^-$ and $^{\bullet}CH_2S^-$ for mercaptoethanol and methyl mercaptan[6] respectively at pH 12 ($\lambda_{max} = 300$ nm).

2. E.s.r. studies

Transient intermcdiates in radiolysis can also be detected by e.s.r., and this technique has been developed by Fessenden and his coworkers[32]. A radical must build up to some minimum concentration to be detected, and must not have too great a linewidth.

The radical formed by dissociative electron capture, postulated from stable product analysis, has been detected directly for the mercapto-àcetate ion[10]. A spectrum consisting of a 21·2-G triplet with $g = 2{\cdot}0032$ has been attributed to the radical $^{\bullet}CH_2CO_2^-$ at pH 12·4 and 8·6 and shown to have e_{aq}^- as a precursor because N_2O prevented its formation. Increasing $^-SCH_2CO_2^-$ concentration decreased the signal, this being taken as evidence for reaction (4). The OH radical was shown to abstract hydrogen from carbon as well as sulphur since the mercaptoacetate ion at pH 12·4 gave a 13·4-G doublet with $g = 2{\cdot}0086$, attributed to $\bar{S}\dot{C}HCO_2^-$. This could not be detected at pH 8·6, and it was thought the doubly-charged anion lowered the recombination rate sufficiently for its concentration to build up to detectable amounts. The radicals $^-S\dot{C}HCH_2CO_2^-$ and $^-SCH_2\dot{C}(NH_2)COO^-$ were detected in alkaline solutions of 3-mercapto-propionate and cysteine respectively, abstraction from the β-carbon atom with respect to sulphur in the latter case being attributed to the extra stability of a tertiary radical.

No thiyl radicals were detected in these studies, possibly because such radicals could react with thiolate anions, reaction (13), and that the G-factor of $RS\bar{S}R$ might cause such line broadening to make it un-detectable.

TABLE 3. Data on $RS\bar{S}R$

Thiol	K_{13}, l mol^{-1}	k_{13}, l mol^{-1} s^{-1}	k_{-13}, s^{-1}	ε_{max}, l mol^{-1} cm^{-1}	λ_{max}, nm	Reference
Cysteamine	6×10^3	$4{\cdot}9 \times 10^9$	8×10^5	$8{\cdot}9 \times 10^3$	410	4, 29
Cysteamine	—	—	$3{\cdot}5 \times 10^5$	$9{\cdot}0 \times 10^3$	415	105
Cysteine	$9{\cdot}5 \times 10^3$	$3{\cdot}1 \times 10^9$	$3{\cdot}2 \times 10^5$	—	420	30
Cysteine	—	—	$2{\cdot}9 \times 10^5$	$\geqslant 8{\cdot}8 \times 10^3$	420	105
Penicillamine	$2{\cdot}5 \times 10^2$	—	$1{\cdot}5 \times 10^6$	$7{\cdot}5 \times 10^3$	450	28
Penicillamine	—	—	$1{\cdot}3 \times 10^6$	$7{\cdot}3 \times 10^3$	450	105
Glutathione	—	—	3×10^5	5×10^3	420	31
Glutathione	—	—	$1{\cdot}5 \times 10^5$	8×10^3	420	105
Mercaptoethanol	$1{\cdot}7 \times 10^3$	—	—	$8{\cdot}3 \times 10^3$	420	6
Hydrogen sulphide	$2{\cdot}5 \times 10^4$	—	—	$\sim 10^4$	380	27
Cysteine methyl ester	—	—	$1{\cdot}9 \times 10^5$	$8{\cdot}3 \times 10^3$	420	105
2-Mercaptoacetic acid	—	—	$2{\cdot}4 \times 10^6$	$9{\cdot}5 \times 10^3$	400	105
3-Mercaptopropanoic acid	—	—	$2{\cdot}7 \times 10^6$	$1{\cdot}5 \times 10^4$	420	105

E. Derivatives of Thiols

1. Disulphides

The OH radical reacts rapidly with disulphides, rate constants greater than 10^9 l mol^{-1} s^{-1} being reported for cystine[33] and cystamine[34]. There is little direct evidence for the immediate products, the reaction being written as (17) by Purdie for cystine and penicillamine disulphide[35,36], and as (18)

$$RSSR + OH \longrightarrow RSOH + RS^{\bullet} \quad (17)$$

$$RSSR + OH \longrightarrow RS\overset{+}{S}R + OH^{-} \quad (18)$$

by Jayson and Owen and coworkers for cystamine[37,38], with the cation undergoing bond cleavage in subsequent reactions. The formation of an adduct $RS\dot{S}(OH)R$ with a significant lifetime has also been proposed[39]. Purdie has shown that the OH radical also leads to the formation of trisulphides[35,36] and has postulated a second set of products from OH attack, reaction (19). The sulphenic acid, from reaction (17), can react

$$RSSR + OH \longrightarrow RSSOH + R^{\bullet} \quad (19)$$

with RSH produced from e^{-}_{aq}, reaction (20), or disproportionate, reaction (21), while the trisulphide is also a product of radiation-produced thiol, reaction (22)[36].

$$RSOH + RSH \longrightarrow RSSR + H_2O \quad (20)$$

$$RSOH + RSOH \longrightarrow RSH + RSO_2H \quad (21)$$

$$RSSOH + RSH \longrightarrow RSSSR + H_2O \quad (22)$$

It has been shown that the presence of chloride ion (hydrochloride salts of aminothiols are often used) in acidic solution decreases S—S cleavage and increases ammonia yields with cystine[40]. (Ammonia is a major product of both e^{-}_{aq} and OH attack on amino acids and peptides not having thiol or disulphide groups[41].)

The aquated electron reacts rapidly with disulphides, rate constants of $1{\cdot}3 \times 10^{10}$, 2×10^{10}, 9×10^9 and $6{\cdot}4 \times 10^9$ l mol^{-1} s^{-1} for cystine, cystamine, homocystine and glutathione disulphide, respectively, at pH 6–7 being reported[20]. As discussed in section II.D.1 the adduct $RS\bar{S}R$ is first formed, and in the absence of other solutes breaks down to $RS^{\bullet}$ and RS^{-}.

H atoms have been reported to react with cystine with a rate constant of 5×10^9 l mol^{-1} s^{-1} and to produce cysteine[24], reaction (23). A transient

$$RSSR + H \longrightarrow RSH + RS^{\bullet} \quad (23)$$

intermediate, believed to be RSŠHR, has been reported by Simic and Hoffmann[31] on pulse radiolysis of glutathione disulphide at pH 1 with λ_{max} of 330 nm and extinction coefficient of 600 l mol^{-1} cm^{-1}. The same transient was seen at pH 3·7 where e^-_{aq} would react directly with the disulphide, and thus it was postulated that H atom addition, and protonation of the electron adduct gave the same product[31] *.

$$RSSR + H \longrightarrow RS\dot{S}HR \quad (24)$$

$$RS\bar{S}R + H^+ \longrightarrow RS\dot{S}HR \quad (25)$$

Product yields in oxygen-free solutions of disulphides are low because of concurrent oxidation and reduction. RSOH (or RS^+) and RSH effectively give back the starting material, reactions (17), (15) and (20).

2. Large molecules of biological interest

In the previous sections reactions associated with the thiol or disulphide groups themselves have been mainly discussed, although some of the molecules mentioned do have other functional groups which show varying degrees of reactivity towards the primary radiolysis products of water. However, product analysis shows that in these cases reactions at other sites in the molecule are at the most only minor, the high reactivity of the —SH and —S—S— groups being the dominating factor.

Recently work has been done on enzymes which contain both thiol and/or disulphide groups[42], including lysozyme[43,44], trypsin[45] and papain[46]. In each case pulse radiolysis shows an absorption at 400–430 nm associated with RSŠR, and shown to have e^-_{aq} as precursor. Sixty per cent of e^-_{aq} are estimated to react with the cystine residue in trypsin[45] and perhaps only 25% in the case of papain[46] where 20% of the adducts decayed with a half-life of about 30 μs, the remainder having a lifetime longer than 0·05 s showing it to be very stable. It was noted that there are three disulphide bridges in papain, and it is possible that electron transfer from one of these to other groups could occur in a time too short to allow detection.

OH attack is shown to occur mainly not at free thiol groups, but at tyrosine residues for papain[46] and tryptophan residues for lysozyme[43] and

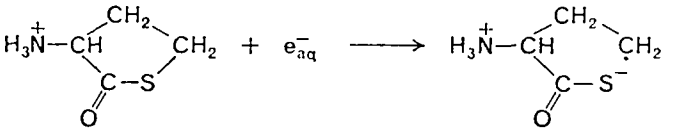
* Shafferman has since shown that this assignment of the transient to RSŠHR is incorrect, and that the species seen was the thiyl radical of glutathione, RS$^{\bullet}$ [106]. For glutathione disulphide he measured k_{15}, k_{23} and k_{25} as $2{\cdot}7 \times 10^9$, $1{\cdot}1 \times 10^{10}$ and $2{\cdot}6 \times 10^{10}$ l mol^{-1} s^{-1} respectively. Further work by Hoffman and Hayon is in agreement with Shafferman's conclusions[105] and these authors also give λ_{max} and extinction coefficients for other thiyl radicals together with more extensive figures for k_{15} including their pH dependence.

trypsin[45], and that loss of enzyme acitivity may be associated with this for lysozyme, although this loss of activity has recently also been attributed to polymerization through intermolecular —S—S— bond formation[47].

A comparison of pulse radiolysis transient yields and final values of $G(-\text{tryptophan})$ and $G(\text{RSH})$ for trypsin shows that a reconstitution or back reaction occurs, as final yields are low[45]. Oxygen prevented this back reaction. Recent work on ribonuclease shows the same general features as the enzymes mentioned above[107].

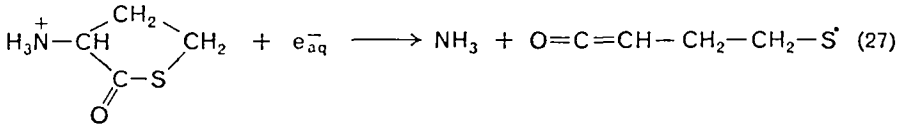
3. Thiolactone

Homocysteine lactonizes readily in acidic solutions, and a study of the aqueous radiation chemistry of this thiolactone was undertaken to see how bonding of the sulphur to a carbonyl carbon modifies its reactivity to the aquated electron[48]. (The normal H atom abstraction from sulphur by OH cannot occur.) The dissociative electron capture reaction which gives H_2S in the case of free thiols can be formulated:

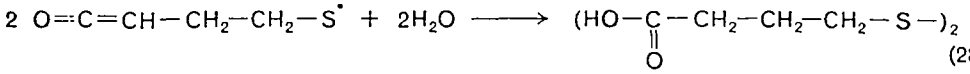


(26)

Resonance stabilization of the thiocarboxylate group might have been expected to favour this reaction. The aquated electron reacted fast with the thiolactone, $k = 3{\cdot}6 \times 10^{10}\,\text{l mol}^{-1}\,\text{s}^{-1}$, but it was found that reductive deamination occurred, this being the typical reaction for amino acid derivatives[41]. 4,4′-Dithiodibutyric acid was found to be a product, and the following steps involving ring opening were postulated:



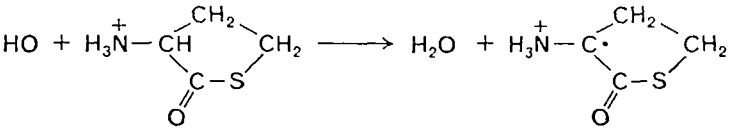
(27)

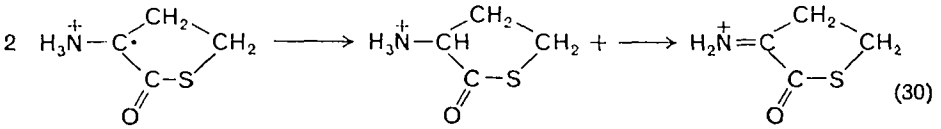


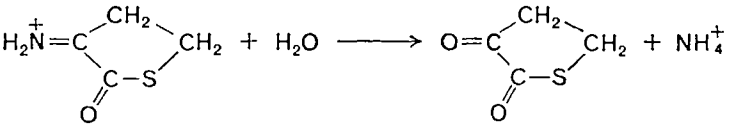
(28)

The OH radical leads to oxidative deamination and ketoacid formation in a manner similar to that for amino acids[41]. This shows that H atom

abstraction occurs from the tertiary carbon atom, rather than from that α to sulphur, as found in e.s.r. studies with cysteine[10].


(29)


(30)


(31)

F. Reactions with Secondary Radiation-produced Radicals

Many organic radicals will abstract hydrogen from the thiyl group, reaction (4) being one example. Where the organic radical has been produced by H atom abstraction by OH or H, this hydrogen transfer from thiol restores the molecule to its original form, and effectively protects it from radiolysis damage. This topic is dealt with more fully in section VI on radiation protection.

Inorganic radicals, formed from the reaction between anions and OH can also oxidize thiols to free thiyl radicals. The species $(CNS)_2^-$, Br_2^-, Cl_2^- and I_2^- (formed by radiolysis of N_2O-saturated solutions of CNS^-, Br^-, Cl^-, I^-) are reduced by cysteine with rate constants of $0{\cdot}5\text{–}8{\cdot}5 \times 10^8$ l mol^{-1} s^{-1}, and the rate constants for (CNS_2^-), Br_2^- and I_2^- increase by approximately a factor of 10 when the thiol is converted to the thiolate anion[49]. (Cl_2^- exists only in acidic solution.) CO_3^- is also reduced rapidly by the thiolate anion of cysteine[49].

Whereas thiols may be oxidized, disulphides may be reduced by electron transfer from radicals. Willson has shown by pulse radiolysis[50] that the electron adduct of the lipoate anion $[\overline{S—SCH_2CH_2\dot{C}H}(CH_2)_4CO_2^-]$ is formed in the reaction of lipoate with $(CH_3)_2\dot{C}OH$, $CH_3\dot{C}HOH$, CO_2^- and the electron-thymine adduct with rate constants of $1\text{–}6 \times 10^8$ l mol^{-1} s^{-1}.

Thiyl radicals themselves react with disulphides leading to new products where two different alkyl groups are present[51,39].

$$RS^{\bullet}+RSSR' \longrightarrow RSSR+R'S^{\bullet} \qquad (32)$$

III. AQUEOUS SOLUTIONS OF THIOLS—CONTAINING OXYGEN

A. *Products and Yields*

Cysteine has been the most extensively studied thiol in oxygenated aqueous solutions. Although reported yields vary from group to group the following general features have been found:

1. Oxygen lowers $G(H_2)$ and $G(H_2S)$ and increases $G(H_2O_2)$ with respect to oxygen-free yields.

2. At low doses, and provided [RSH] $\geqslant \sim 10^{-3}$M the disulphide cystine is still the only major sulphur-containing product, but large doses do result in higher oxidation products being formed.

3. Increasing cysteine concentration increases yields, this effect being greater when the free base is used instead of the hydrochloride (Table 4 shows figures from different research groups) and at pH $\leqslant 5$, there is an approximately equimolar increase in hydrogen peroxide and disulphide. Oxygen concentration has little effect on the yields.

TABLE 4. Variation in $G(-RSH)$ or $2G(RSSR)$ with [RSH] for oxygenated cysteine solutions

[RSH], M	$2G$(RSSR)		$G(-RSH)$						
10^{-4}	5·5	5·6							
3×10^{-4}	10	9·5	7·6	7·6		7		13	
5×10^{-5}					5		15		
10^{-3}		15	15	8·2	7	9	20	20	14
3×10^{-3}	18	18		9·2	10	11	36	24	
10^{-2}			24						
O_2	air[a]	air	air	air	air	1 atm[b]	1 atm	1 atm	air
pH	1	3	0–1	1·35	4	3–4	7	7	7
Reference	23	52	53	25	54	25	19	25	53

Note: Dose rate $0{\cdot}8\text{–}1{\cdot}4\times10^{18}$ eV l^{-1} s^{-1}.

[a] Equilibrated with air at 1 atm.

[b] Equilibrated with oxygen at 1 atm.

4. As the pH is raised above 5 a marked increase in $G(-RSH)$ and G(RSSR) occurs, but $G(H_2O_2)$ does not increase until the pH is greater

than 7, and then the value of $G(H_2O_2)$ is less than that of $G(RSSR)$[25]. Figure 1 illustrates this.

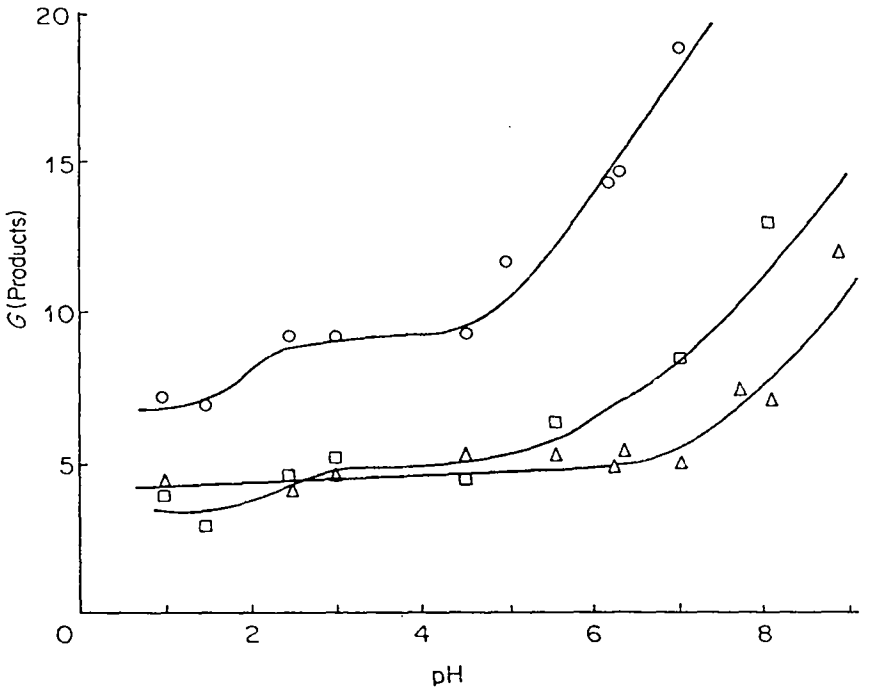


FIGURE 1. G(Products) as a function of pH for 10^{-3} M cysteine saturated with oxygen[25].

$\circ = G(-RSH)$ $\square = G(RSSR)$ $\triangle = G(H_2O_2)$

Mercaptoethanol has been studied[7] in the pH range 0–5·8, and oxygen increases both G(RSSR) and $G(H_2O_2)$, while increasing the thiol concentration from 10^{-2}M to 10^{-1}M causes a major increase as shown in Table 5.

TABLE 5. Product yields from aerated aqueous mercaptoethanol solution[a]

[RSH], M	pH	Aeration	$G(H_2O_2)$	G(RSSR)
10^{-2}	3·1	None	0·56	3·45
10^{-2}	3·1	Air	6·5	6·5
10^{-1}	3·3	None	0·45	4·4
10^{-1}	3·0	Air	36·1	36·1

Note: Dose rate $7{\cdot}8 \times 10^{16}$ eV l^{-1} s^{-1}.

[a] Taken from Table 1, reference 7.

Cysteamine[14] was found to differ from the above two thiols in that little disulphide and hydrogen peroxide were formed at low pH, whereas at higher pH the yields were at least qualitatively similar to those of cysteine. Figure 2 illustrates these points. Presumably products with sulphur in a higher oxidation state than in cystamine are formed in acidic solution.

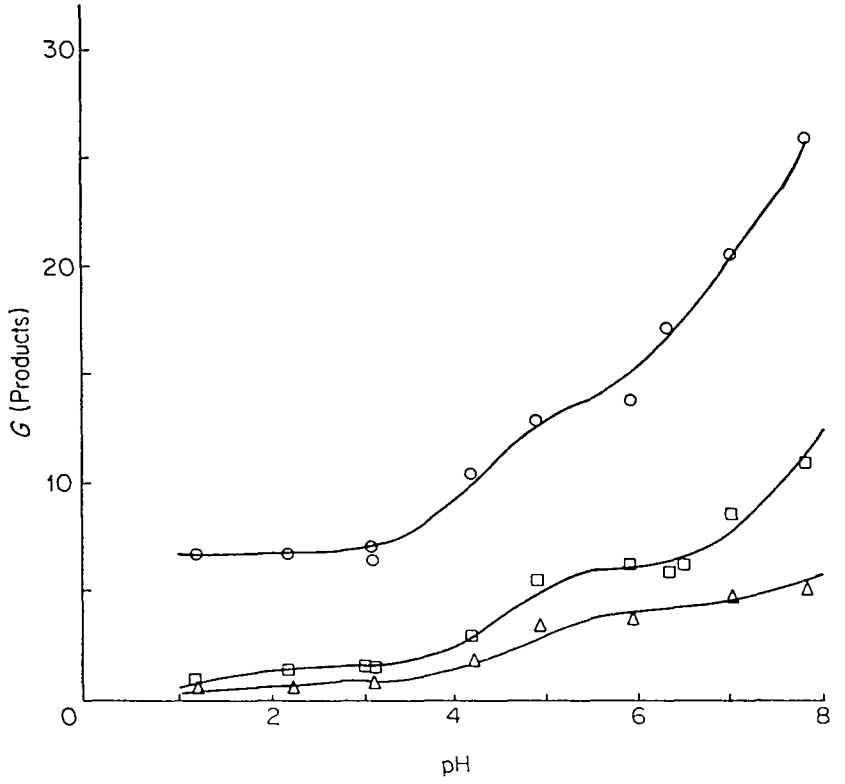


FIGURE 2. G(Products) as a function of pH for aerated 10^{-3} M cysteamine[14].
○ = $G(-\mathrm{RSH})$ □ = $G(\mathrm{RSSR})$ △ = $G(H_2O_2)$

Very high yields of disulphide from some n-alkyl mercaptides with G(RSSR) up to 650 have been reported[55]. Quantitative product yields are however difficult to obtain at pH > 8 because of autoxidation, and because the thermal reaction between hydrogen peroxide and thiol proceeds at an appreciable rate.

Disulphides have been studied in the presence of oxygen by Purdie[35,36,39,51,56] and Owen and coworkers[37,38,57,58]. Sulphonic acids become a major product, Owen consistently reporting higher yields than Purdie, who finds significant amounts of sulphinic acids are still formed.

B. Effect of Oxygen on Radical Reactions

1. Competition for primary radicals

Oxygen does not react with OH except at high pH[59] where the latter exists as O^-. As thiols are readily autoxidized in alkaline solution no detailed studies of oxygenated solutions at high pH have been reported. However, oxygen reacts rapidly with both H and e^-_{aq} to give HOO• and O_2^- with rate constants k_{33} and k_{34} of 2×10^{10} and $1{\cdot}88\times10^{10}$ l mol^{-1} s^{-1} respectively[59], and would be expected to lower $G(H_2)$ and $G(H_2S)$ with

$$H + O_2 \longrightarrow HOO^{\bullet} \qquad (33)$$

$$e^-_{aq} + O_2 \longrightarrow O_2^- \qquad (34)$$

respect to oxygen-free solutions. This has generally been found. Al-Thannon found for example that air lowered $G(H_2)$ from 3·10 to 0·65 in 10^{-4}M cysteine solution and from 3·4 to 3·06 for 10^{-2}M cysteine[23], competition being less effective at the higher thiol concentration as expected. Competition between O_2 and RSH for e^-_{aq} has been used by the Auckland group[8,17,19] to determine k_3 for various thiols at pH 7 (Table 2). Neglecting H_2S from reaction (8) and by plotting $1/G(H_2S)$ against $[O_2]/[RSH]$,

$$G(H_2S) = G_{e^-_{aq}} \frac{k_3[RSH]}{k_3[RSH]+k_{34}[O_2]}$$

or

$$\frac{1}{G(H_2S)} = \frac{1}{G_{e^-_{aq}}}\left(1+\frac{k_{34}[O_2]}{k_3[RSH]}\right)$$

k_3 can be found. This technique of determining rate constant ratios by competitive scavenging is common in radiation chemistry.

It has been found for mercaptoethanol that oxygen lowers $G(H_2S)$ much more than would be expected from the known values of k_3 for this thiol determined by measuring the rate of disappearance of e^-_{aq} by pulse-radiolysis and k_{34}, and it has been suggested that the electron adduct of the thiol might be sufficiently long-lived to transfer partially the electron to oxygen before dissociating, reactions (35) and (36)[7]. Barton considered

$$e^-_{aq} + HOCH_2CH_2SH \longrightarrow HOCH_2CH_2SH^- \qquad (35)$$

$$HOCH_2CH_2SH^- + O_2 \longrightarrow HOCH_2CH_2SH + O_2^- \qquad (36)$$

that the reason Winchester's figure for k_3 for cysteine[19] was only about half that measured directly by pulse radiolysis[20] might be due to similar reactions, but by re-analysing Winchester's results where both [RSH] and

$[O_2]$ were varied, he showed this not to be the case[25]. Again it appears as though the reaction between e^-_{aq} and mercaptoethanol is somewhat anomalous.

2. Reaction of HOO• with RSH

The hydroperoxy radical has a pK_a of 4·88 and thus it exists as HOO• in acidic solutions and as its conjugate base, O_2^-, in neutral and alkaline solution[60]. By studying the formate ion–oxygen–cysteine system as a function of pH Barton has found that HOO• does not react with cysteine, but that O_2^- does[25,30]. In the absence of thiol, reactions (37), (38) and (39) in addition to (33) or (34) occur, giving a yield of hydrogen peroxide,

$$OH + HCOOH\ (HCOO^-) \longrightarrow H_2O + {}^\bullet COOH\ (CO_2^-) \quad (37)$$

$$^\bullet COOH\ (CO_2^-) + O_2 \longrightarrow CO_2 + HOO^\bullet\ (O_2^-) \quad (38)$$

$$2\,HOO^\bullet\ (O_2^-) \longrightarrow H_2O_2 + O_2 \quad (39)$$

$G(H_2O_2) = G_{H_2O_2} + \frac{1}{2}(G_{OH} + G_{e_{aq}^-} + G_H) = 3{\cdot}7$. If the peroxy radical abstracts H from the thiol, the yield of H_2O_2 should increase as each OH, e^-_{aq} or H now gives rise to one molecule of H_2O_2

$$HOO^\bullet + RSH \longrightarrow H_2O_2 + RS^\bullet \quad (40)$$

$$O_2^- + RSH \xrightarrow{H^+} H_2O_2 + RS^\bullet \quad (41)$$

and $G(H_2O_2) = G_{H_2O_2} + G_{OH} + G_{e_{aq}^-} + G_H = 6{\cdot}7$. In solutions where [HCOOH]≫[cysteine], Barton found $G(H_2O_2) = 3{\cdot}7$ and $G(-RSH) = 0$ in acidic solution, these increasing to 6·2 and 5·8 respectively as the pH is raised to 5·1. From this work he estimated k_{41} as $1{\cdot}8 \times 10^4\ l\,mol^{-1}\,s^{-1}$ within a factor of five. Using the same method cysteamine was also found[19] to be unreactive towards HOO•.

The reason for the enhanced reactivity of O_2^- probably lies in the free energy of protonation of the peroxide anion (pK_a of $H_2O_2 = 11{\cdot}8$). On bond strength figures, reaction (40) would be nearly thermoneutral[61,62].

3. Reaction of RS$\bar{S}$R with oxygen

The transient RS$\bar{S}$R has been found to react with oxygen in pulse radiolysis studies of cystine[30] and lipoate[50] with rate constants of $4{\cdot}3 \times 10^8$ and $9 \times 10^8\ l\,mol^{-1}\,s^{-1}$ respectively. Oxygen enhanced the rate of first-order decay, the increase in rate being proportional to oxygen concentration. The reaction is thought to involve electron transfer from disulphide to oxygen, reaction (42).

$$RS\bar{S}R + O_2 \longrightarrow RSSR + O_2^- \quad (42)$$

4. Reaction of thiyl radicals with oxygen

It has been assumed that oxygen reacts with the thiyl radical according to reaction (43) when possible mechanisms for thiol radiolysis in the

$$RS^{\bullet} + O_2 \longrightarrow RSOO^{\bullet} \qquad (43)$$

presence of oxygen have been postulated[13, 52, 62], but direct evidence for this reaction has only been found recently and is limited. Purdie found oxygen inhibited reaction (32) and concluded that oxygen reacts with the thiyl radical[39, 51]. When neutral and slightly alkaline solutions of cysteine saturated with N_2O were irradiated it was found that oxygen markedly decreased the amount of $RS\bar{S}R$ formed immediately after the pulse as well as greatly increasing its rate of decay by reaction (42). This decrease was considered to be caused by competition between RS^- and O_2 for the thiyl radicals, reactions (13) and (43), and assuming such competition, and plotting A^0_{max}/A_{max} against $[O_2]/[RS^-]$, a value of $k_{43} = 8 \times 10^9\ l\,mol^{-1}\,s^{-1}$ was found, A^0_{max} and A_{max} being the maximum absorbances after the pulse in the absence and presence of oxygen respectively[30].

Swallow and coworkers found a weak absorption with λ_{max} at 560 nm when mercaptoethanol was irradiated in acidic oxygen-saturated solutions[7]. From the variation in the amount formed on changing mercaptoethanol concentration and pH it was concluded that the transient was $HOCH_2CH_2SOO^{\bullet}$ and that it had an extinction coefficient of $180 \pm 35\ l\,mol^{-1}\,cm^{-1}$. A weak transient, λ_{max} at 530 nm, was also detected by Packer on irradiating acidic cysteine solutions in the presence of oxygen, the amount formed increasing slightly with cysteine concentration and more definitely with oxygen concentration. The decay kinetics were complex, but decays were rapid with half-lives of a few microseconds decreasing as the pulse length (i.e. dose) increased, suggesting radical–radical reactions[64]. The data were not inconsistent with the transient being $NH_3^+CH(CO_2^-)CH_2SOO^{\bullet}$.

5. Reaction of alkyl radicals with oxygen

Dissociative electron capture by thiol leads to an alkyl radical, reaction (3). Oxygen, by competing for e^-_{aq} lowers the yield of alkyl radicals, and as it adds to them rapidly, reaction (44), should further lower the yield of

$$R + O_2 \longrightarrow ROO^{\bullet} \qquad (44)$$

alkane by preventing H atom transfer from an unreacted thiol molecule, reaction (4). No data that show the fate of such alkylperoxy radicals have

been reported. If they abstract H from the thiol group an alkyl hydroperoxide would form, but none has been identified, and anyway may be reduced in the presence of thiol. Serine, the expected reduction product from cysteine, is formed in low yield[53].

C. Mechanisms

1. Cysteine

For cysteine there appear to be three regions of pH involving distinctly different mechanistic features[25], namely 0–5, 5–7 and >7.

The pH region 0–5 has been studied by several research groups. Recently Barton[25] has collected all the available data and carried out calculations on the 'extra' product yields due to oxygen. From the known rate constants for reactions (2), (3), (6), (7), (33) and (34) he calculated the initial values of $G(RS^{\bullet})$, $G(HOO^{\bullet})$ and $G(O_2^{-})$. Considering the equilibrium between $HOO^{\bullet}$ and O_2^{-}, and assuming that reactions (39) and (41) but not (40) occurred, and that each $RS^{\bullet}$ radical gave rise to half a molecule of cystine, RSSR, he determined $G(-RSH)$, $G(RSSR)$ and $G(H_2O_2)$ arising from these reactions. There is a small possible error as the fate of $R^{\bullet}$ in the presence of oxygen is not known. Subtracting these values from the experimental yields, he obtained the 'extra' product yields which he labelled $G(-RSH)_c$, $G(RSSR)_c$ and $G(H_2O_2)_c$ as the results seemed best explained by a short chain-type mechanism. The essential facts to emerge were that $G(RSSR)_c \sim G(H_2O_2)_c$ for all sets of data; that $G(RSSR)_c$ was proportional to (dose-rate)$^{-\frac{1}{2}}$ from the results of Al-Thannon[23]; and that these 'extra' yields increased slowly with increasing cysteine concentration. He postulated the following scheme:

$$RS^{\bullet} + O_2 \longrightarrow RSOO^{\bullet} \qquad (43)$$

$$RSOO^{\bullet} + RSH \longrightarrow RSOOH + RS^{\bullet} \qquad (45)$$

as the propagating steps, and

$$RS^{\bullet} + RS^{\bullet} \longrightarrow RSSR \qquad (11)$$

$$RS^{\bullet} + RSOO^{\bullet} \longrightarrow RSSR + O_2 \qquad (46)$$

$$RSOO^{\bullet} + RSOO^{\bullet} \longrightarrow RSSR + 2\,O_2 \qquad (47)$$

as possible termination steps. Reaction (45) must be relatively slow as the 'chain' yields are very small[63], and in view of the fact that reaction (40)

does not occur[25,30] this seems reasonable. Reactions (48), or (49) and (20), account for the equality of $G(RSSR)_c$ and $G(H_2O_2)_c$. Owen and Brown

$$RSOOH + RSH \longrightarrow RSSR + H_2O_2 \quad (48)$$

$$RSOOH + H_2O \longrightarrow RSOH + H_2O_2 \quad (49)$$

$$RSOH + RSH \longrightarrow RSSR + H_2O \quad (20)$$

found a slow post-irradiation increase in cystine at pH ~ 4·5 and suggest that reaction (48) was slow[52], but Barton was unable to reproduce their results[25].

The relatively low 'chain' yields imply that oxygen which reacts fast with the thiyl radical does not get reduced, and reaction (47) is proposed to account for this. As a result of his disulphide studies Purdie[39] has suggested that RSOO$^\bullet$ radicals react together according to reaction (50), the

$$RSOO^\bullet + RSOO^\bullet \longrightarrow RSO_2SR + O_2 \quad (50)$$

product being a dioxide, not a peroxide. Assuming the dioxide would be reduced to disulphide by thiol, reaction (50) would lead to a considerable increase in G(RSSR) without a corresponding increase in $G(H_2O_2)$, contrary to what is observed. The possibility of reaction (43) being reversible and giving rise to an equilibrium between RS$^\bullet$ and RSOO$^\bullet$ comes from the observation that the maximum absorbance at 530 nm following a pulse of electrons in acidified cysteine solution increased with increasing oxygen concentration at concentrations where reaction (43) would be complete were it a fast irreversible reaction[64]. The decay, assuming the transient to be RSOO$^\bullet$, was too fast for it to occur by reactions (11) and (−43) alone. Purdie[57] has measured G(cystine) in oxygenated solutions of the mixed disulphide of cysteine and cysteamine as a function of this disulphide concentration. Oxygen and the disulphide compete for cysteinyl radicals from reaction (17), cystine arising from the latter reaction (32). He proposes reaction (46) to account for the fact that G(cystine) has a value of 1·5 when extrapolated to zero mixed disulphide concentration, implying that reaction (43) does not go to completion.

The mechanism requires the 'chain' yield to be proportional to cysteine concentration, but the dependence is much less than first-order. A first-order decay of RSOO$^\bullet$ in competition with reactions (45) and (47) would account for this, but a possible reaction is difficult to visualize, and it is concluded that the mechanism is not yet fully understood. A reaction such as (51) is also possible in acidic solution.

$$RSOO^\bullet + HOO^\bullet \longrightarrow RSOOH + O_2 \quad (51)$$

In the pH region 5–7 $G(RSSR)_c$ increases with pH while $G(H_2O_2)_c$ remains almost constant. The increase in $G(RSSR)_c$ has tentatively[25] been attributed to reaction (52) being much faster than (45), and the divergence

$$RSOO^{\bullet} + RS^{-} \xrightarrow{H^{+}} RSOOH + RS^{\bullet} \qquad (52)$$

of $G(RSSR)_c$ and $G(H_2O_2)_c$ to the fact that the intermediate sulphenyl hydroperoxide is reduced to water by cysteine as the pH increases, reactions (53) and (20).

$$RSOOH + RSH \longrightarrow 2\,RSOH \qquad (53)$$

A different chain reaction at pH > 7, involving $RS\bar{S}R$ and producing equimolar amounts of cystine and H_2O_2 was postulated by Packer and Winchester[13], and direct evidence for reactions (42) and (41) was subsequently found[30]. Barton suggests that the two competing chain reactions,

$$RS^{\bullet} + RS^{-} \longrightarrow RS\bar{S}R \qquad (13)$$

$$RS\bar{S}R + O_2 \longrightarrow RSSR + O_2^{-} \qquad (42)$$

$$O_2^{-} + RSH \xrightarrow{H^{+}} H_2O_2 + RS^{\bullet} \qquad (41)$$

(13), (42), (41) and (43), (52) with (53) and (20) best explain the experimental yields in this higher pH region.

2. Other thiols

As mentioned in section III.A, mercaptoethanol and cysteamine are the only other thiols that have been studied in any detail. As Table 5 shows, increasing mercaptoethanol concentration in acidic solution substantially increases $G(RSSR)$ and $G(H_2O_2)$, and a mechanism similar to that proposed above for cysteine has been postulated[7].

As no detailed product analysis has been done no mechanism for the radiolysis of cysteamine in strongly acidic solution can be postulated. However, it is of interest to note that both Owen[38] and Purdie[51] obtain higher yields of taurine ($NH_3^{+}CH_2CH_2SO_3H$) from oxygenated cystamine radiolysis than they do the corresponding sulphonic acid from other disulphide solutions. Possibly $NH_3^{+}CH_2CH_2SOO^{\bullet}$ is readily oxidized by $HOO^{\bullet}$ or H_2O_2 at low pH. Sims [14] has calculated 'chain' or 'extra' yields over the pH range in a similar manner to Barton, and finds that $G(RSSR)_c \sim G(H_2O_2)_c$ at pH of about 4, with both increasing as the pH is further increased, $G(RSSR)_c$ rising faster than $G(H_2O_2)_c$. Thus at higher pH the mechanisms for cysteamine and cysteine would appear to be essentially the same.

3. Disulphides

Owen considers sulphonic acids are formed by reactions (18), (54) and (55), his values of $G(RSO_3H)$ being close to G_{OH}. His values of $G(H_2O_2)$ are consistent with reactions (42) and (39) being important[38]. In his

$$RSSR + OH \longrightarrow RS\overset{+}{S}R + OH^- \quad (18)$$

$$RS\overset{+}{S}R + O_2 \longrightarrow [RSSR^{\bullet}O_2]^+ \longrightarrow RSO_2^+ + RS^{\bullet} \quad (54)$$

$$RSO_2^+ + OH^- \longrightarrow RSO_3H \quad (55)$$

earlier papers[35] Purdie considered the sulphonic acid to come from reaction (56), but after further work[51] has suggested that it may be formed

$$RSOH + O_2^- \longrightarrow RSO_2^- + H \quad (56)$$

by reaction (57). Both authors also consider a number of other reactions to explain the various products and yields.

$$RSO_2^{\bullet} + RSOH \longrightarrow RSO_3H + RS^{\bullet} \quad (57)$$

4. Conclusions

It is clear from the above discussion that more work is needed before a definitive understanding of the reactions involved in the radiolysis of oxygenated solutions of thiols and disulphides is achieved. The variations in yields with experimental conditions, the distinctly different yields from different thiols or disulphides under similar conditions, and the analytical problems in determining yields of sulphur compounds in various oxidation states makes this a complex and difficult field to work in.

IV. THIOLS IN THE LIQUID STATE

Only two studies of thiols irradiated in the pure liquid state have been reported. It was of interest to compare ethanethiol[65] with ethanol where the main products, in addition to H_2, are ethylene glycol and acetaldehyde, which come partly from $CH_3\dot{C}HOH$ as precursor[66]. In ethanol the α-C—H bond is weaker than the O—H bond, whereas in the thiol the relative strengths are reversed. $G(H_2)$ was 7·1, greater than for ethanol (possibly because of the lower ionization energy of ethanethiol), and of the main products $C_2H_5S—SC_2H_5$ contributed 80%, and $C_2H_5SC_2H_5$, 15%. No butane-2,3-dithiol or thioacetaldehyde were found[65]. No mention was made of H_2S, a product that might be expected in view of the sulphide yield.

For thiophenol[67] G values found were: H_2, 4·2; PhS—SPh, 4·6; C_6H_6, 1·4; H_2S, 0·44; PhSPh, 0·049. Hentz considered that reaction (58), involving the parent positive ion and equivalent to that occurring in liquids exhibiting hydrogen-bonding, would be unimportant, and thought reactions (59) and (60) unlikely on thermodynamic grounds although electron capture to give $PhSH^-$ as an intermediate could well occur.

$$\dot{PhSH}^+ + PhSH \longrightarrow PhS^\bullet + PhS^+H_2 \quad (58)$$

$$PhSH + e^- \longrightarrow Ph^\bullet + SH^- \quad (59)$$

$$PhSH + e^- \longrightarrow PhS^- + H \quad (60)$$

As dissociation of the lowest triplet excited state was not possible, he concluded that breakdown occurred from the lowest excited singlet state following charge neutration of the parent ion, with S—H cleavage and to a lesser extent Ph—S cleavage the only important processes. (Johnsen[65] also considered the equivalent of reaction (58) to be less important with ethanethiol, and that the difference from ethanol may well be attributed to the much weaker hydrogen bonding as well as to the relative bond strengths mentioned above.) In benzene–thiophenol mixtures, energy transfer from benzene to thiophenol was shown to occur, leading to products similar to those from pure thiophenol. By using deuterated benzene it was shown that very few H atoms arose from benzene radiolysis. Prior to this work it was not entirely clear whether the very low values of $G(H_2)$ found in aromatic systems implied a low yield of H atoms or were due to the fact that they add to the aromatic ring. Thiophenol was the first aromatic compound studied which gave an appreciable yield of H_2, and this work clearly shows the dominating role that the —SH group exerts when it is present in a molecule, H-abstraction from sulphur preventing the usual ring addition almost entirely.

V. THIOLS IN THE SOLID STATE

A. Pure Compounds

1. Product analysis

Most solid state studies have involved only e.s.r. measurements of the radicals produced on irradiation. However, Garrison and coworkers[68] have irradiated dry degassed cysteine at room temperature, dissolved the irradiated solid in water and analysed the products, finding the following yields: $G(H_2) = 3{\cdot}1$; $G(H_2S) = 1{\cdot}5$; $G(NH_3) = 1{\cdot}8$; G(cystine) = 5·0; $G(NH_2$-free compounds) = 1·0; G(total carbonyl compounds) $\leqslant 0{\cdot}1$. In aqueous solution the —SH group appears to be the locus of all significant

reactions as the predominant reactions for amino acid derivatives[41], reductive and oxidative deamination (the latter leading to carbonyl compounds), are negligible. It was of interest to see if this was the case in the solid state also. As the results show oxidative deamination was absent, but reductive deamination competes with loss of HS^-. The following steps were postulated:

$$RSH \longrightarrow RS^{\bullet} + H^+ + e \quad (61)$$

$$RSH \longrightarrow RS^{\bullet} + H \quad (62)$$

reaction (61) involving proton transfer from the radical ion to a neighbouring group, and (62) dissociation of an excited molecule, followed by

$$H^{\bullet} + RSH \longrightarrow H_2 + RS^{\bullet} \quad (7)$$

$$H^{\bullet} + RSH \longrightarrow H_2S + NH_3^+CH(\dot{C}H_2)CO_2^- \quad (63)$$

$$e^- + RSH \longrightarrow NH_3 + {}^{\bullet}CH(CH_2SH)CO_2^- \quad (64)$$

$$e^- + RSH \longrightarrow H_2 + NH_2CH(CH_2S^{\bullet})CO_2^- \quad (65)$$

$$e^- + RSH \longrightarrow H_2S + NH_2CH(\dot{C}H_2)CO_2^- \quad (66)$$

$$RSH + \dot{C}H(CH_2SH)CO_2^- \longrightarrow RS^{\bullet} + CH_2(CH_2SH)CO_2^- \quad (67)$$

$$RSH + NH_2CH(\dot{C}H_2)CO_2^- \longrightarrow RS^{\bullet} + NH_2CH(CH_3)CO_2^- \quad (68)$$

$$2\,RS^{\bullet} \longrightarrow RSSR \quad (11)$$

It was suggested that dimerization of thiyl radicals to give disulphide occurred mainly on dissolution of the irradiated solid. In the case of cysteamine hydrochloride, where there is no carbonyl group to trap the electron prior to deamination, it was found that $G(NH_3) < 0{\cdot}1$. In spite of this $G(H_2S)$ was only 1·2, lower than for cysteine, but the value of $G(H_2)$ of 5·1 was much higher. This is the same situation as was found for mercaptoethanol[7] but not for cysteamine itself[14] in aqueous solution.

2. E.s.r. studies

Several e.s.r. studies have been made on single crystals of cysteine hydrochloride monohydrate. On irradiation with 1·5 MeV electrons at 77 K Akasaka[69] observed an isotropic doublet as the main radical species with a high anisotropic but axial symmetric g factor, and attributed this to the $^{\bullet}SCH_2CH(COOH)NH_3^+Cl^-$ radical, as found by Kurita and Gordy for cystine[70]. Remarkable broadening was observed on warming and at

225 K the spectrum had almost disappeared, although this was not due to radical decay as the spectrum reappeared on cooling[69]. Wheaton and Omerod[71] used ^{60}Co γ-irradiation at 77 K and then warmed or illuminated their crystal with u.v. light. They observed six radicals, four of which were $RS^{\bullet}$. Their initial spectrum was a triplet, which Akasaka did not see, probably because his electron beam warmed the crystals above 77 K. Conformational changes on warming lead to interaction between spin on the sulphur atom and neighbouring —SH groups to give large anisotropies in the spectroscopic splitting factor g. Warming also gave higher radical concentrations suggesting to them that the original damage was not paramagnetic. Further warming beyond 200 K caused nearly complete disappearance of radicals suggesting that the thiyl radicals in fact dimerized in the solid state.

Recent work by Budzinski and Box[72] has shown that 77 K is not a sufficiently low temperature to stabilize the primary radicals initially formed and have found evidence for electron capture by the carboxyl group, providing direct evidence for Garrison's mechanism[68]. They were able to get better defined spectra with penicillamine hydrochloride than with cysteine, and reported detailed work on this compound. At 4 K they observed three radical species, two due to oxidation which they assigned to a chlorine atom and to $^{\bullet}SC(CH_3)_2CH(NH_3^+Cl^-)COOH$ and one due to reduction, $HSC(CH_3)_2CH(NH_3^+Cl^-)\dot{C}(OH)O^-$ formed by electron capture. On warming to 200 K, hole transfer from the chlorine atom occurred to give a different thiyl radical, and the initial thiyl radical underwent a change in conformation to give the same radical. The electron adduct also underwent a conformational change and then on further warming deamination occurred to give the radical $HSC(CH_3)_2\dot{C}HCOOH$. On further warming to 275 K this radical abstracted hydrogen from sulphur to give another thiyl radical, and those already formed underwent a further conformational change, so that at room temperature thiyl radicals were the only type present. Presumably dissociative electron capture by the —SH group would give a radical which would also abstract H from thiol, so although this radical was not observed, this work was not in disagreement with Garrison's mechanism. Box also had a higher yield of radicals from oxidation than from reduction, supporting Garrison's dissociation reaction, as H atoms would abstract hydrogen from the thiyl group. The anisotropy of the thiyl radical was again observed. In agreement with the previous work, the final thiyl species observed at ambient temperature has undergone bending of the carbon–carbon bond α to the sulphur atom.

Ramsbottom, Pintar and Forbes[73] have studied the radical recombination in irradiated polycrystalline cysteine HCl monohydrate at temperatures 340–390 K. Above 333 K a second phase, glassy in nature, was found to form and it was presumed that this was caused by free water molecules around lattice imperfections because irradiated samples had a greater percentage of this new phase. This phase which was absent in anhydrous samples would contain no radicals, and the observed decay was of radicals in the crystalline phase. The decay exhibited second-order kinetics over 4–5 half-lives and an activation energy of 50 kJ mol^{-1} (12 kcal mol^{-1}). They concluded that the decay mechanism involved dimerization of thiyl radicals and that H atom transfer between the thiol group and thiyl radicals could occur above 378 K. The half-life at 375 K was approximately 200 min, and these results would seem to throw doubt on Omerod's observation[71] that radicals decayed at 200 K.

Clear ethanethiol glasses[74,75] have been irradiated at 77 K. A deep orange colour formed, and an absorption maximum at 430 nm was observed. Bleaching with visible light caused the colour to fade to clear yellow, with λ_{max} at 405 nm. E.s.r. measurements before bleaching showed two species, one attributed to $C_2H_5S^{\bullet}$ and the other to an ionic radical. It was the latter that disappeared on bleaching and the peak at 405 nm was attributed to $C_2H_5S^{\bullet}$. Initial yields[75] were given as $G(C_2H_5S^{\bullet}) = 0{\cdot}5$ and $G(\text{ion}) = 2{\cdot}9$.

A series of alkyl mercaptans[76–78] have been irradiated at 77 K. The thiyl radical, RS$^{\bullet}$, is the predominant species for molecules with three or less carbon atoms, but the relative concentration of alkyl radicals increases with the size of the alkyl group.

Disulphides have also been studied. The final stable radical from a single crystal of L-cystine hydrochloride is an RS$^{\bullet}$ radical[70], but irradiation as 4 K gives $RS\overset{+}{S}R$ and $RS\overset{-}{S}R$, the former having an optical absorption maximum at 550 nm and the latter at 420 nm[79]. Some RS$^{\bullet}$ is also produced at 4 K. Both $RS\overset{+}{S}R$ and $RS\overset{-}{S}R$ are present in the dark at 77 K, but light causes all of $RS\overset{+}{S}R$ and about half $RS\overset{-}{S}R$ to decay without a concurrent increase in RS$^{\bullet}$ radicals[80]. In the dark $RS\overset{+}{S}R$ disappears in about 30 min at 125 K but $RS\overset{-}{S}R$ is stable at this temperature.

In studies of peptides and proteins containing sulphydryl and disulphide groups irradiation at 77 K leads to non-S radicals, but on warming migration of spins to sulphur occurs and the stable radicals at higher temperature are thiyl radicals[81,92]. Other forms of energy transfer must also occur as the concentration of thiyl radicals eventually formed is higher than the total radical concentration at 77 K.

B. Frozen Solutions and Glasses

The radicals formed on irradiating frozen aqueous solutions of cysteamine at 77 K and their behaviour on annealing have been studied by e.s.r.[83, 84] Solutions of pH less than 2 before freezing formed thiyl radicals on annealing to 178 K, but these thiyl radicals could not be detected when the pH of the initial solutions was greater than 3. At higher pH increases in radical yield and in radical stability to annealing occur and these increases follow the ionization curve of the —SH group. The radicals here were tentatively attributed to $RS\bar{S}R$.

The absorption spectra of species formed on γ-irradiation of methyltetrahydrofuran and hydrocarbon glasses containing thiols and disulphides[85] at 77 K show that $RS\bar{S}R$ radicals are formed by electron capture and that $RS^{\bullet}$ radicals are formed on warming by H atom abstraction by solvent radicals. The electron scavenger CCl_4 inhibited formation of the former but not the latter. In contrast Skelton and Adam[86] were unable to detect thiyl radicals when simple mercaptans in glassy 3-methylpentane were γ-irradiated, although thiyl radicals were formed and were stable at room temperature when the same glasses were photolysed.

VI. RADIATION PROTECTION BY THIOLS

A. Mechanisms

The phenomenon of chemical protection of mammals against the harmful effects of ionizing radiation was discovered in 1949, and aminothiols or compounds that could give rise to free thiol groups were found to be the most active. Much work on synthesizing and testing new compounds of this class has been undertaken. The phenomenon of protection has been the subject of a book[87]. Whereas most compounds containing thiol or disulphide groups act as protecting agents in laboratory studies, only some of them are effective in the body, problems of solubility, transport, toxicity and other factors outside the province of physical chemistry being involved. Only simple chemical theories and work related to them are discussed here.

That the mechanism of protection is partly chemical (i.e. involving fast free radical reactions) rather than biochemical (i.e. involving slow reactions of protecting agents with the biologically important molecules prior to or after irradiation as suggested, for example, in the mixed disulphide theory[88, 89]) has been shown by mixing cysteine with bacteria[90]

or lysozyme[91] in a rapid flow system. Protection was found with a pre-irradiation mixing time as short as 4 ms but no protection was found if mixing occurred 5 ms after irradiation.

There are two simple mechanisms for this chemical protection, 'competition scavenging' and 'repair'. In both of these the thiol is thought to prevent or reduce damage caused by attack of free radical precursors on the biological solute, the so-called 'indirect action'. As cells are 60–80% water there is little doubt that these precursors are OH, H, or e^-_{aq}, and the number of them reacting with the biological substrate is reduced by competitive scavenging of the thiol, yielding thiyl radicals. These are relatively unreactive towards the biological molecules and consequently damage is reduced. Where the primary radicals do react directly with the substrate a free radical formed by H atom abstraction is a likely product and further reactions of this may lead to permanent biological damage. In the repair mechanism the thiol is thought to transfer a hydrogen atom from sulphur to the radical, restoring the biological molecule to its original form and replacing it by the innocuous thiyl radical.

The repair mechanism can also operate where a radical has been formed by H atom loss after a direct ionization of a biological molecule, and energy transfer, especially to a disulphide group, is also a possibility.

Evidence for these mechanisms has come from radiolysis experiments, including e.s.r. measurements on model systems.

B. Solution Studies

Adams and coworkers have made quantitative measurements on both possible mechanisms, using monomers[92] and polymers[29] as model substrates and cysteamine as the protecting agent. On pulse irradiating mixtures of alcohols and cysteamine they found $RS\bar{S}R$ to be formed in two reactions, one of these being complete 3 μs after the pulse with the other slower reaction occurring during the next 10–100 μs. Increasing the alcohol concentration at fixed cysteamine concentration decreased the amount of $RS\bar{S}R$ formed 3 μs after the pulse, showing normal competitive kinetic behaviour, reactions (2) and for methanol (69), but the total

$$OH + RSH \longrightarrow H_2O + RS^{\bullet} \qquad (2)$$

$$OH + CH_3OH \longrightarrow H_2O + {}^{\bullet}CH_2OH \qquad (69)$$

amount finally formed remained the same. The rate of formation of $RS\bar{S}R$ in the slower reaction was independent of alcohol concentration

but was proportional to cysteamine concentration, suggesting the repair reaction (70) was being observed. (Recent work on the γ-radiolysis of

$$^{\bullet}CH_2OH + RSH \longrightarrow CH_3OH + RS^{\bullet} \qquad (70)$$

isopropanol in D_2O substantiates this since it was found that addition of thiol induces deuteration of the alcohol and lowers the yield of acetone[93].) Analysis of the oscillograms of growth of $RS\bar{S}R$ yielded 'repair' rate constants for a series of alcohols, the values ranging from $1{\cdot}8 \times 10^7$ l mol^{-1} s^{-1} for *t*-butanol to 42×10^7 l mol^{-1} s^{-1} for isopropanol[92]. Using polyethylene oxide (PEO) polymers of varying molecular weights, the same two kinetic pathways of $RS\bar{S}R$ formation were again observed, and repair rate constants of $5\text{–}10 \times 10^6$ l mol^{-1} s^{-1} were found. With high molecular weight PEO reactions of PEO radicals with RS$^{\bullet}$ and $RS\bar{S}R$ were also detected. pH studies on both monomer and polymer systems showed the thiolate anion barely repaired the radicals, if at all[29].

The repair mechanism does not appear to function where attack occurs on pyrimidine bases. Here primary radicals add to the 5:6 double bond and hydrogen transfer to the intermediate radical would complete an addition across this bond. This reaction has been shown to occur between cysteine and the protonated electron-adduct of cytosine[91], and in this case cysteine increases $G(-\text{cytosine})$ by blocking the reconstitution reaction which occurs between OH-adduct and electron-adduct. Adams[92] found the rate constants for reaction between cysteamine and the OH-adducts of allyl alcohol, thymidine and uracil to be less than 10^7 l mol^{-1} s^{-1}, his findings being confirmed very recently in a pulse radiolysis study using e.s.r. to detect transient intermediates[95]. Both cysteamine and cysteine were used and the corresponding rate constants for uracil and thymine being shown to be less than 10^6 l mol^{-1} s^{-1}. For these compounds all protection was due to thiol scavenging of OH. This technique gave figures comparable to Adams's for repair of alcohol radicals[92], and also showed the repair mechanism functioned for dihydrothymine.

There is evidence that radicals other than primary ones can add to pyrimidine bases and hence damage DNA function, and it has been shown that thiols can prevent this by repairing the intermediate radicals prior to their attack on the base[96]. The repair mechanism has also been shown to operate in e.s.r.-flow studies of biochemical molecules where OH radicals are generated chemically[97].

Studies of protection of two enzymes, lysozyme[44] and papain[98], have been made in aqueous solution, and in addition to scavenging protection,

a reaction between cysteine and the OH-adduct of lysozyme has been observed[44]. A slow post-irradiation repair reaction was found for papain[98], probably involving cysteine as a reducing agent.

In some systems it is found that the presence of oxygen lowers the protection given by added thiol[99], an explanation being that oxygen reacts with the substrate radical in an irrepairable step in competition with the hydrogen transfer reaction with thiol. Pulse radiolysis studies with cysteamine were not inconsistent with this[92].

C. Solid State Studies

E.s.r. studies in the solid state also give considerable evidence for the repair mechanism of thiols. Mention of migration of spins to sulphur in proteins and from solvent to thiol in glasses has been made in section V. In a simple model system a single crystal of 2-aminobutyric acid HCl containing 2% of cysteine HCl was irradiated. The main radical detected at 220°K was $CH_3CH_2\dot{C}HCOOH$, but on warming to room temperature the free thiyl radical appeared, implying transfer of H from the thiol[100]. Work prior to 1965 has been reviewed[101] and many systems involving mixtures of thiols and model compounds or biological material in the dry or glassy state have been studied since and have provided clear examples of the repair mechanism. However the factors controlling transfer of spin to the added thiols are complex, as recent work by Milvy has shown[102,103].

VII. ADDITION OF THIOLS TO OLEFINS

Radiolysis of mixtures of thiols and olefins in the absence of oxygen leads to anti-Markovnikov addition across the double bond in a long chain reaction involving free radicals. The propagation steps for a terminal olefin are:

$$RS^{\bullet} + R'CH{=}CH_2 \longrightarrow R'\dot{C}H{-}CH_2SR \qquad (71)$$

$$RSH + R'\dot{C}H{=}CH_2SR \longrightarrow R'CH_2{-}CH_2SR + RS^{\bullet} \qquad (72)$$

This reaction is not specific to radiolysis, and the initiating free radicals may also be generated thermally or photochemically. The general field of free radical addition of thiols to unsaturated compounds has recently been reviewed[104].

Thiols may be formed by radiolysis of H_2S with olefins, the mechanism being similar to that above, but as the thiol formed undergoes loss of hydrogen by radical abstraction more readily than H_2S, a mixture of thiol and sulphides is likely to be formed.

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The Chemistry of the Thiol Group
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CHAPTER 12

Synthetic uses of thiols

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I. INTRODUCTION

The use of thiols in the synthesis of bivalent organosulphur compounds is well known[1]. Thiols can be converted to sulphides, disulphides, sulphonium salts, sulphoxides, sulphones, sulphonic acids, thioacetals and thioacids; these transformations being effected generally by nucleophilic displacement, addition, oxidation or condensation reactions involving the sulphur function. In the above cases a thiol is used in the preparation of a new compound containing sulphur and this is often the main purpose for effecting the reaction. In this chapter we have chosen not to cover *per se* these types of reactions; certain of these reactions are covered in various detail in other chapters in this volume. We have chosen instead to treat reactions in which a thiol is an important and necessary reagent, being incorporated into the molecule to promote the desired transformation, following which the sulphur function is removed to yield the final reaction product. The thiol, therefore, functions in an accessory role in the synthetic transformation. An example is the conversion of a carbonyl group to a

methylene group by Raney nickel desulphurization of an intermediate thioacetal; the thioacetal being prepared by reaction of a thiol with the ketone or aldehyde.

Examples of a thiol functioning in a synthetic transformation involving only one step are minimal. Most cases covered in this chapter require more than one step with several steps being involved in the conversion of the reactant, *via* reaction with a thiol, into the final product. This necessitates that the thiol be transformed into a bivalent organosulphur derivative, i.e. a sulphide, thioacetal or a higher oxidized sulphur function such as a sulphone or sulphonium salt, followed by subsequent conversion to final product. Thus, many of the reactions covered could be considered as examples of the synthetic use of sulphides, sulphones, etc., equally as well as synthetic uses of thiols[2]. The general criteria used in selection of reactions for the chapter have been: (a) a thiol has been or readily could be used in preparation of the intermediate organosulphur derivative, (b) the purpose of the transformation is not the preparation of an organosulphur derivative, thus (c) the sulphur function is normally and conveniently removed to give the final product.

The following reactions have been excluded as being beyond the scope of this chapter: the variety of synthetically useful reactions of dimethyl sulphoxide (DMSO) and dimethyl sulphide, which include reactions involving dimsyl anion, oxidation reactions involving DMSO, methylene transfer reactions of corresponding sulphonium methylides, and reaction of stabilized sulphonium ylids normally prepared from dimethyl sulphide[3].

II. DITHIOACETALS

The formation of a dithioacetal as an intermediate in organic synthesis is not new to most chemists. However, in recent years there has been a continuing improvement in the methods of preparation as well as the subsequent reactions. The early use of the dithioacetal group as a means to reduce carbonyl functions with Raney nickel has been expanded to extensive use as a protecting group, methylene blocking group and as an intermediate in the preparation of complex hydrocarbons, olefins, aldehydes and ketones.

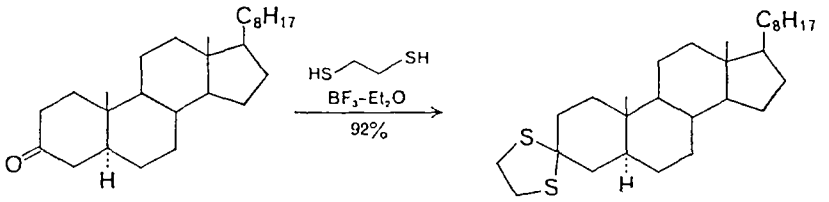
A. Carbonyl Protection

The protecting ability of dithioacetals has become well established[4]. These groups are stable towards both mild acid and mild base and show reasonable stability towards such varied reagents as lithium aluminium hydride, chromium trioxide and Grignard reagents[5]. However, the method

has rarely been utilized because of the difficulty in regenerating the carbonyl. Recent developments in this area should change the situation and give dithioacetals a prominent place in synthetic organic chemistry.

I. Preparation

Early workers reacted the ketone with an excess of the thiol in the presence of an acid catalyst such as zinc chloride[6], hydrogen chloride[7,8] or *p*-toluenesulphonic acid[9] to prepare dithioacetals. The results were erratic and the yields often disappointing. The use of boron trifluoride etherate has led to consistently better results[8,10]. This method is particularly effective when the thiol is used for the solvent of the ketone as the boron trifluoride etherate is added. Ethanedithiol and propanedithiol are usually the thiols of choice forming 1,3-dithiolanes and 1,3-dithianes respectively. For example, the 1,3-dithiolane of cholestane-3-one (equation 1) can be prepared in high yield by this method[10]. Occasionally the choice



(1)

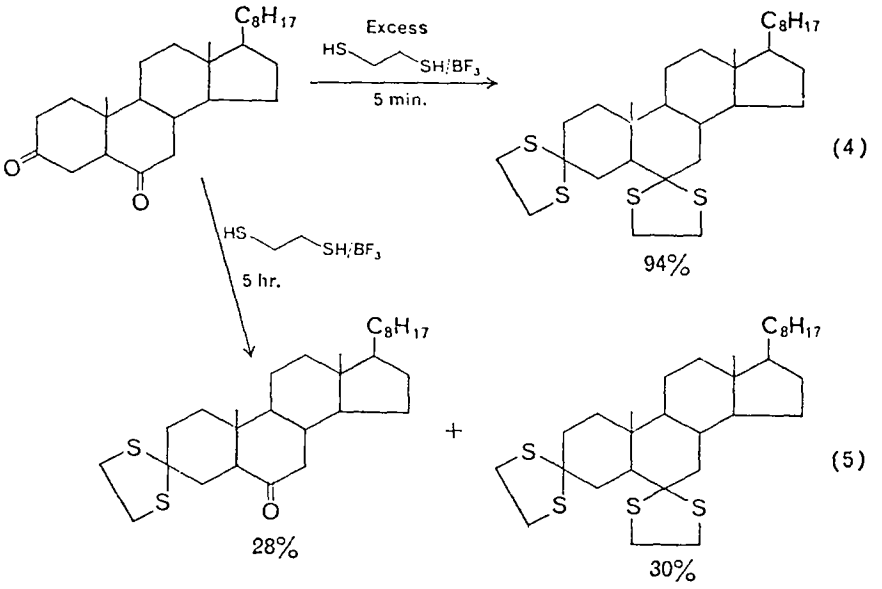
of solvent is very important and it has been noted that a more acidic medium such as acetic acid may be useful in accelerating product formation and reducing side reactions[11]. A newer method involving the use of alkyl orthothioborates gives nearly quantitative yields of the dithioacetals of simple aldehydes and ketones (equation 3) under neutral conditions[12]. The orthothioborates are easily prepared from sulphurated sodium borohydride (equation 2) but the use of dithiols would seem to be excluded.

$$NaBH_2S_3 + EtSH \longrightarrow (EtS)_3B + H_2 + (EtS)_2 + NaS_3H \qquad (2)$$

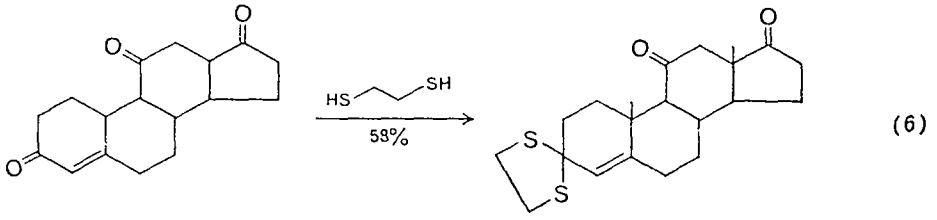
$$CH_3CH_2\overset{\overset{O}{\|}}{C}CH_3 + (EtS)_3B \longrightarrow CH_3CH_2\overset{\overset{Et\ \ Et}{S\ \ S}}{\underset{}{C}}CH_3 + B_2O_3 \qquad (3)$$

In the formation of 1,3-dithiolanes of di- and tricarbonyl compounds, there is considerable selectivity. Normally one does obtain a mixture of the monodithiolane contaminated by varying amounts of the bisdithiolane

but separation is generally not difficult. Apparently the formation of two isomeric and hard-to-separate monothiolanes is seldom a problem. Cholestane-3,6-dione with excess ethanedithiol gives a high yield of the bis-1,3-dithiolane (equation 4) in just 5 min[10]. Restricting the quantity of thiol and extending the reaction time led to a mixture containing a reasonable yield of the cholestane-3,6-dione-3-(1,3-dithiolane) (equation 5)[10].

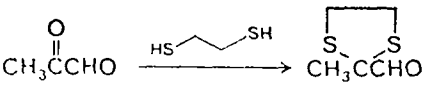


Where the nature of the carbonyls of a dicarbonyl compound differ greatly, one isomer of the monodithiolane may become the only product. In the conversion of 4-androstene-3,11,17-trione to 4-androstene-3,11,17-trione-3-(1,3-dithiolane) no bis- or trisdithiolane was observed (equation 6)[9]. The condensation of an equimolar amount of 1,2-ethanedithiol with



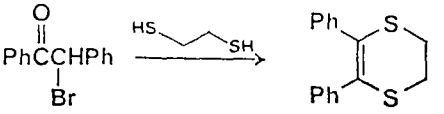
(6)

an α-keto aldehyde such as pyruvaldehyde leads to the formation of 1,3-dithiolane-2-carboxaldehydes[13] with little or none of the isomeric 1,3-dithiolan-2-yl ketones being observed (equation 7).



(7)

Although the formation of dithioacetals generally is a simple reaction, side reactions become prevalent when a reasonable leaving group is in the α-position to the carbonyl or to a conjugated double bond. In the reaction of 2-bromo-2-phenylacetophenone with ethanedithiol, 2,3-diphenyl-5,6-dihydro-1,4-dithiin (equation 8) was obtained[14,15]. Similarly, the dihydrodithiin (**1**) was obtained from 6-β-acetoxy-4-cholesten-3-one (equation 9)[3]. Additional examples exist for the formation of dihydro-1,4-dithiins *via* halides[16], epoxides[17] and even amides[18].



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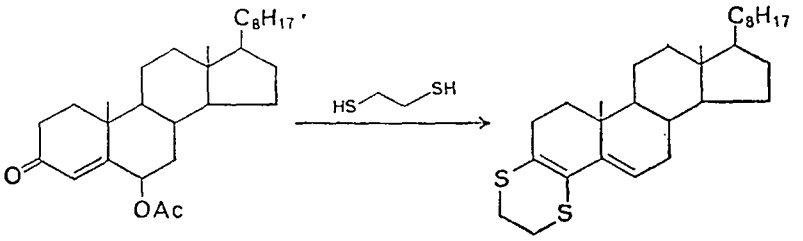
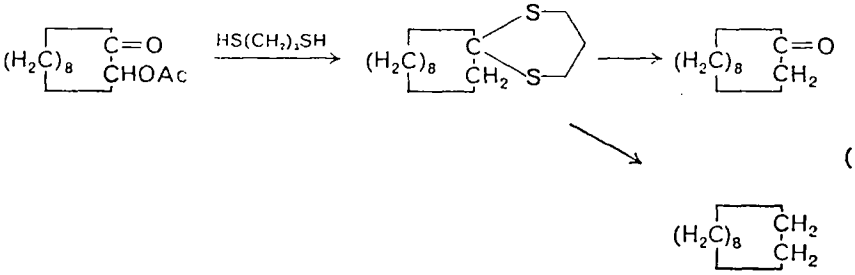


(9)

(1)

Under slightly different conditions, using 1,3-propanedithiol, acyloins and acyloin acetates lead to the formation of 1,3-dithianes where hydrogen has replaced the hydroxyl or acetoxyl group[19]. Hydrolysis to the ketone provides a method of converting acyloins to ketones and desulphurization allows conversion of acyloins to hydrocarbons (equation 10). Reduction of 1,1-dimethyl-5-hydroxysila-4-cycloheptanone gave 1,1-dimethylsila-4-cycloheptanone by this method (equation 11)[20]. A similar reaction is believed to be involved in the action of D-proline reductase[21].



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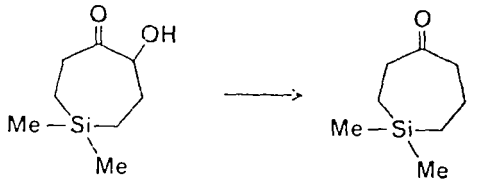


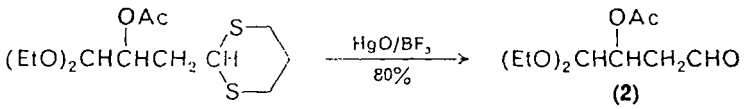
(11)

Numerous other examples of dithioacetal formation, including selective formations, have been well documented[4,22-24], but the above suggest the scope.

2. Removal

Early workers relied completely on the use of heavy metal salts in the hydrolysis of dithioacetals. The initial use of mercuric chloride with cadmium carbonate in hydroxylic medium[25,19] was modified and generally improved by the substitution of mercuric oxide for the cadmium carbonate[26,27]. However, in some cases the results of this method of hydrolysis have been disappointing. This is especially true in the recovery of aldehydes and steroidal ketones from their dithioacetals. Recently, numerous new methods of hydrolysis have emerged significantly changing the stature of dithioacetals as blocking groups.

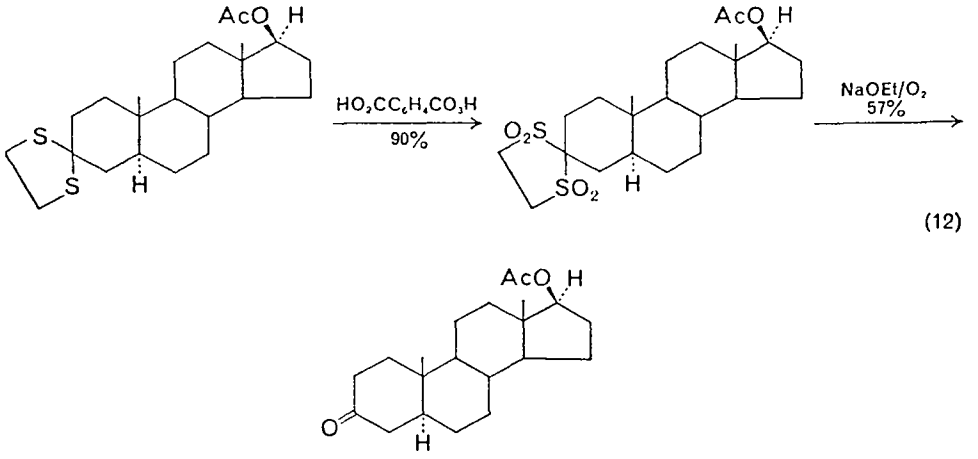
The use of mercuric oxide and boron trifluoride etherate in aqueous tetrahydrofuran gave good yields of aldehydes[28], even those such as **2** where mercuric chloride only destroyed the starting material. This method has also proved useful in carbohydrate chemistry[29,30,31].



(2)

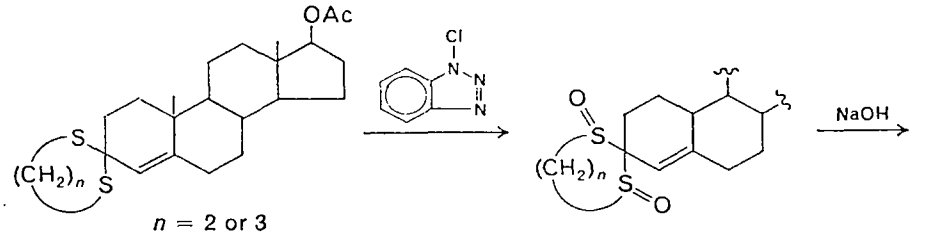
Oxidation of 1,3-dithiolanes with monoperphthalic acid[32] or hydrogen peroxide[33] gives ethylenedisulphones in high yields. These compounds are stable in acid, but are easily decomposed with base in the presence of oxygen to give the original carbonyl group. Thus, 17β-hydroxy-5α-androstan-3-one-3-(1,3-dithiolane) acetate was converted to the disulphone, which in the presence of sodium ethoxide and oxygen gave the original ketone (equation 12)[32]. Besides the fact that this method is effective in the steroid series, there are the advantages of being able to hydrolyse acid-sensitive compounds or work in acid media without fear of decomposing the blocking group.

The use of a mild oxidizing agent such as 1-chlorobenzotriazole[34] with 1,3-dithiolanes and 1,3-dithianes leads to the formation of disulphoxides.



(12)

The disulphoxides generally are not isolated but are decomposed with sodium hydroxide to the ketone[35]. The reaction works well in the steroids, with 17β-acetoxytestosterone (3) easily being regenerated from its dithioacetal (equation 13).



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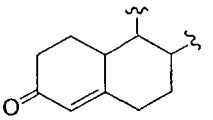
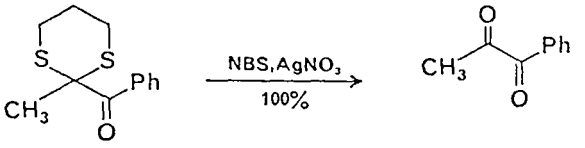


(3)

Oxidative hydrolysis of 1,3-dithianes using N-halosuccinimides has been extensively investigated[36]. The yields were consistently high when using N-bromosuccinimide (NBS), usually in acetonitrile. Unlike earlier methods 2-acyl-1,3-dithianes were efficiently hydrolysed to 1,2-dicarbonyl compounds. For example, 1-phenyl-1,2-propanedione was prepared in quantitative yield from the 2-benzoyl-2-methyl-1,3-dithiane (equation 14). Silver salts often aid the reaction, but it has been noted[3] that NBS in the

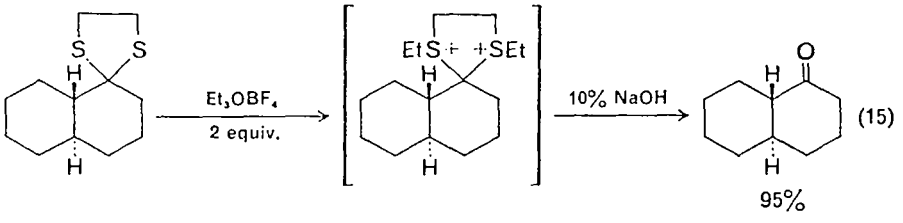
presence of silver ion reacts with double bonds. However, N-chlorosuccinimide (NCS) even with silver nitrate is compatible with double bonds and still gives comparable yields.



(14)

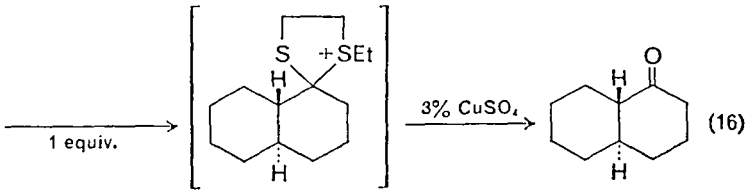
A few other methods for hydrolysis of 1,3-dithianes have recently been discovered but have not been thoroughly investigated. Use of sodium N-chloro-*p*-toluenesulphonamide (chloramine-T) leads to the corresponding ketones in consistently high yields[37]. The procedure requires only short reaction times in aqueous alcohol and should prove to be a very powerful method.

Alkylation of 1,3-dithiolanes with two equivalents of triethyloxonium tetrafluoroborate leads to bissulphonium salts. Treatment with 10% sodium hydroxide gives excellent yields of the corresponding ketones[38]. If only one equivalent of the oxonium salt is used, the resulting monosulphonium salt gives the ketone in high yield if a mild oxidizing agent such as copper sulphate or hydrogen peroxide is present. Equations (15) and (16) demonstrate the effectiveness of this method in the recovery of *trans*-1-decalone.



(15)

95%

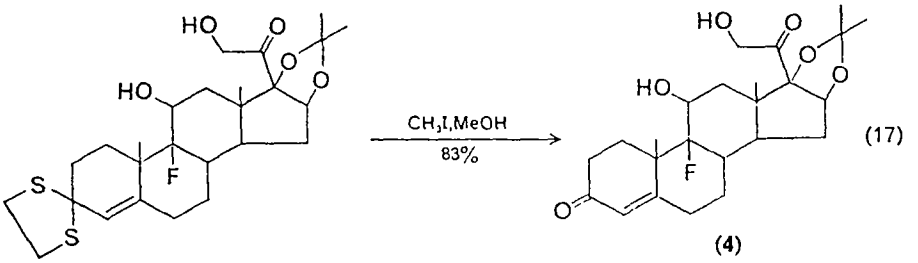


(16)

89%

The sulphonium salt also seems to be involved in a procedure using methyl iodide in aqueous alcohol[39]. Mild conditions and high yields are typical. That the reaction is quite selective is apparent from the hydrolysis

of the 1,3-dithiolane of 9-fluoro-11β,16α,17,21-tetrahydroxypregn-4-ene-3,20-dione-16,17-acetonide (**4**) in high yield (equation 17).

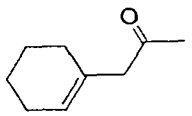
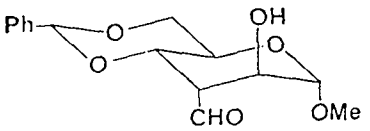


(17)

(4)

Some further representative examples of the hydrolysis of dithioacetals are given in Table 1.

TABLE 1. Hydrolysis of dithioacetals to carbonyl compounds

Dithioacetal of	Reagent	Yield, %	Reference
Cholestan-3-one	Chloramine-T	75	37
	1-Chlorobenzotriazole	50	35
	Monoperphthalic acid	52	32
	(1) $Et_3O^+BF_4^-$; (2) NaOH	81	38
Cyclohexanone	Chloramine-T	95	37
	(1) $Et_3O^+BF_4^-$; (2) $CuSO_4$	81	38
	$HgO—BF_3$	25	28
Fluorenone	Chloramine-T	86	37
PhCH=CHCHO	$HgO—BF_3$	86	28
$Ph_3SiC(=O)CH_3$	$HgCl_2$, aq. acetone–benzene	82	40
$CH_3CH_2CH(CH_3)CH_2C(=O)Ph$	$HgCl_2$, HgO, aq. MeOH	70	41
	NCS, $AgNO_3$	94	36
	$HgO—BF_3$	80	29, 30
$PhCH_2C(=O)CO_2Et$	NBS, acetone	78	36

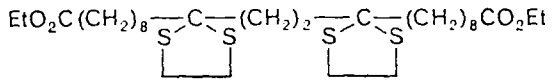
B. Carbonyl Reduction

Since the Raney nickel desulphurization of dithioacetals to the corresponding methylene was first observed by Wolfrom[42], the reaction has become one of the most reliable and mild ways of reducing the carbonyl group. Outstanding reviews can be found concerning the application of nickel desulphurizations to all types of organosulphur compounds[22,23] as well as a detailed discussion of the mechanism[43]. However, a brief mention of the scope of the reaction as well as some of the more recent modifications seems in order.

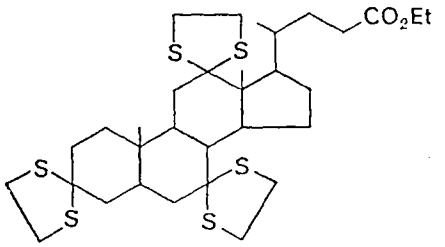
1. Reduction to saturated hydrocarbons

Typically desulphurization reactions are carried out with a large excess of Raney nickel. The reaction is not truly catalytic in nature since the hydrogen used to replace the sulphur usually comes from hydrogen retained by the metal during its preparation. In addition the nickel is consumed by the combination with the sulphur to form nickel sulphide. In practice a minimum ratio of 2·6 : 1 for nickel atoms to sulphur atoms is necessary[44].

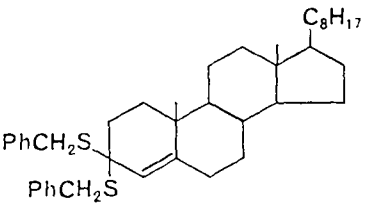
The Raney nickel catalyst is prepared through the action of aqueous alkali on a nickel–aluminium alloy. The conditions employed allow the preparation of the catalyst with a specific activity. Furthermore, the catalyst may be deactivated by refluxing with hydrogen acceptors, by degassing or by ageing. For details the reader is referred to the reviews mentioned above.



(5) (87%)



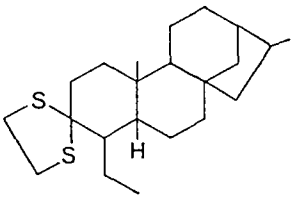
(6) (86%)



(7) (92%)

Although desulphurizations are very successful on most dithioacetals, a few have been somewhat unsatisfactory. Compounds **5**[45], **6**[6] and **7**[6] are typical of the high yields which often accompany desulphurizations. On

the other hand, *n*-heptanal diethylthioacetal gave only 40% yield of heptane[42] and compound **8** gave only 33% of desulphurized product[23]. Other functional groups generally do not affect the results. Desoxytetrahydrohelenaline (**9**) gave the desired product quantitatively[23] and isatin 1,3-dithiolane (**10**) gave oxindol without complication[23].



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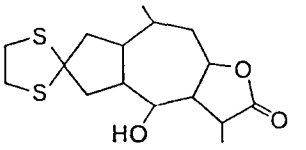

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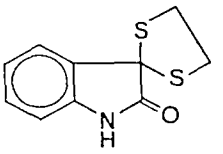
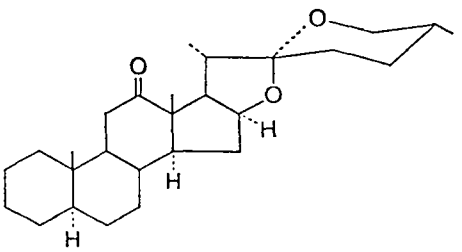


(10)

A recent modification in the use of Raney nickel may greatly enhance its utility. Industrial use of the standard procedure has been limited by the necessity to use such large quantities of the very expensive Raney nickel. It now appears that the use of the nickel–aluminium alloy itself in formic acid leads to very efficient desulphurizations with Ni/S ratios of only 0·2[44]. High proportions of the aluminium seem to give the best results, apparently because of the ability of the aluminium to regenerate the active nickel catalyst. Similar results were obtained using nickel or cobalt salts in the presence of auxiliary metals such as aluminium or iron.

The use of deuterium oxide and sodium deuterium oxide in the preparation of Raney nickel leads to the formation of deutero Raney nickel suitable for replacing dithioacetals with deuterium[46,47]. The method suffers from some scrambling of the isotope often leading to products of low isotopic purity. Deuteration of (25R)-5α-spirostan-12-one (**11**) by this



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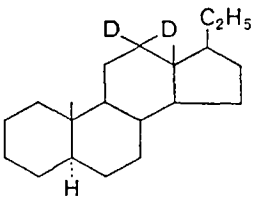
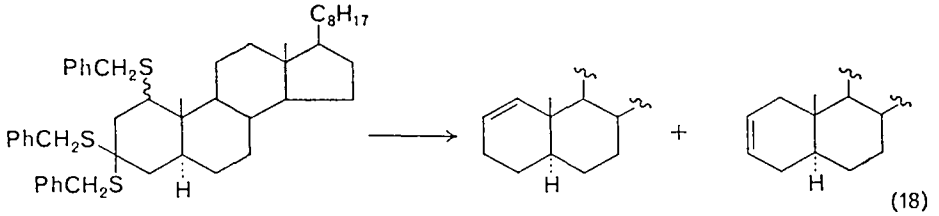


(12)

method led to an isotopic mixture consisting of 4% d_0, 44% d_1, 49% d_2 and 3% d_3 products[48]. At times fairly pure products are obtained, such as the preparation of 12,12-d_2-pregnane (**12**) with 76% d_2[49].

2. Reduction to olefins

The formation of an olefin during desulphurization was first noted when 1,3,3-tribenzylthiocholestane gave a mixture of cholest-1-ene and cholest-2-ene (equation 18) with Raney nickel deactivated by boiling in acetone[50]. Similar conditions gave predominantly olefin with the 1,3-dithiolane from 14β-$\Delta^{5,7,9}$-anthraergostatriene-15-one (equation 19)[51].



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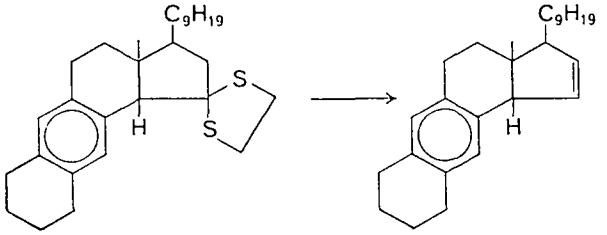
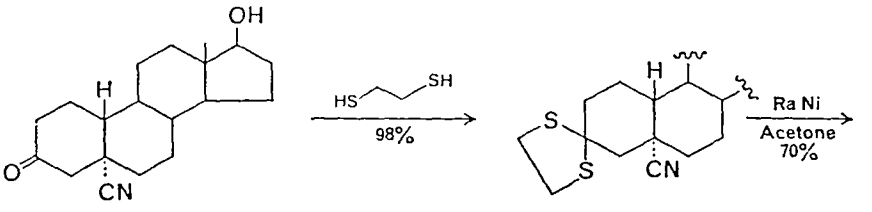


(19)

More extensive investigations[46,52] have led to the use of W-2 Raney nickel in refluxing acetone to obtain olefins in 55–75% yields based on starting ketone. Even the synthesis of dienes from α,β-unsaturated ketones was successful[52]. Using this method 5α-cyano-17β-hydroxyestran-3-one was converted to the corresponding olefin (equation 20)[53]. Surprisingly, the 5β-cyano isomer gave low yields in the first step and no olefin in the second step. Both the *cis*- and *trans*-isomers in the 2-keto-10-cyano series have been converted to olefins[54,55]. Other examples of this reaction include the conversion of dihydrogedunin (**13**) to the olefin[56] and the partial formation of olefin from 17-norphyllocladan-16-one (**14**)[57]. Groups in the α-position to the ketone may be lost during the reaction as seen by the formation of 5α-cholest-2-ene as the sole product from 2α-chloro-5α-cholestan-3-one[58].



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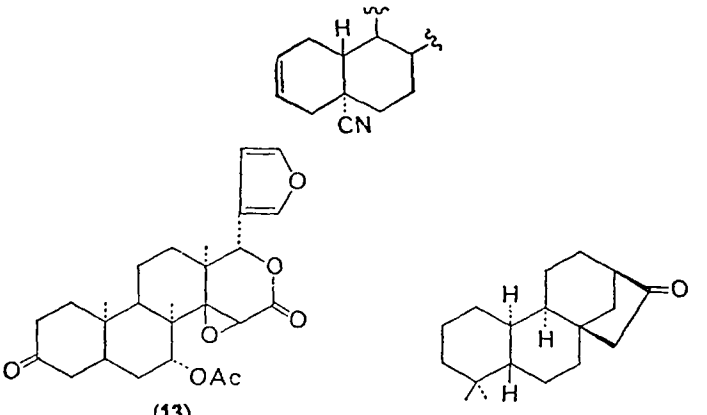
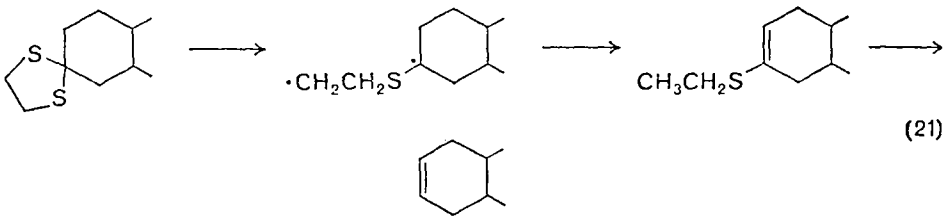


(13) (14)

The mechanism of this reaction seems to involve formation of a diradical intermediate which, if the concentration of hydrogen radicals is low, gives the thioenol ether[46]. Further desulphurization gives the olefin (equation 21). If the alkyl radical is responsible for the $C_{(2)}$ hydrogen



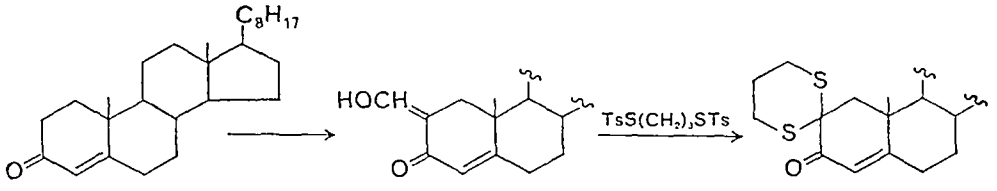
(21)

abstraction, it would seem necessary that it remain near the reaction site so that homolysis takes place before addition of hydrogen from the catalyst. Analogy with studies of the mechanism of desulphurization in monothioacetals[59] and thiazolidines[60] suggests that the abstraction may very well come from an external radical.

C. Methylene Blocking Group

In the presence of ethyl formate and sodium methoxide, the most reactive methylene group of a ketone is converted to its hydroxymethylene

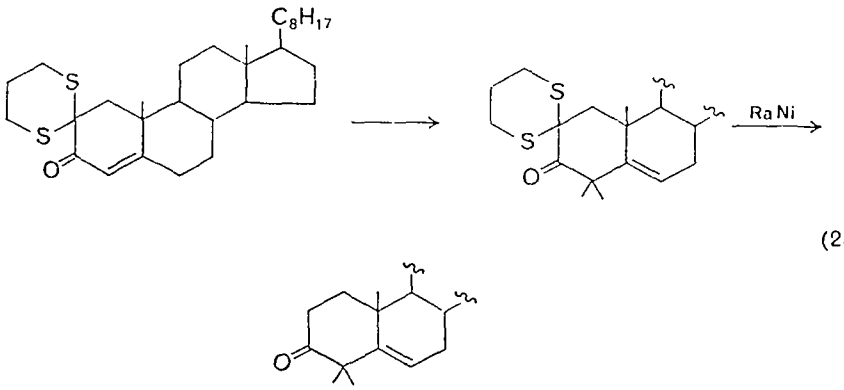
derivative[61]. Further reaction with the ditosylate of propane-1,3-dithiol[62] leads to the formation of the 1,3-dithiane[63] (equation 22). Thus the active position of the ketone is effectively blocked with a group easily removed by Raney nickel.



(22)

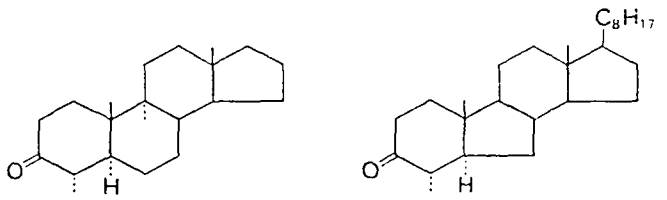
I. Alkylations

The presence of the dithioacetal does reduce the reactivity of the ketone toward alkylations at its other available positions[64], but nevertheless the sequence has been effectively utilized. This is clearly demonstrated by the formation of 4,4-dimethylcholestenone by this procedure (equation 23)[63]. Other examples of the successful use of this method include the



(23)

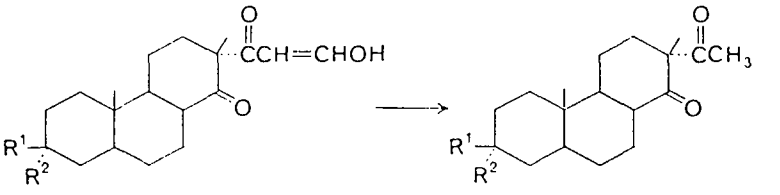
preparation of 4α,9α-dimethyl-5α-androstan-3-one (**15**)[65] and 4α-methyl-B-nor-5α-cholestan-3-one (**16**)[66].



(15) (16)

2. Decarbonylations

The formation of 1,3-dithianes from hydroxymethylene compounds, which are enol tautomers of β-keto aldehydes, has been shown to be useful in itself. When followed by desulphurization the net reaction is the decarbonylation to the ketone. This has been used to advantage in the formation of the methyl ketone (**17**)[67] in equation (24). Similarly the methyl ketone (**18**) was formed from its hydroxymethylene derivative[68].

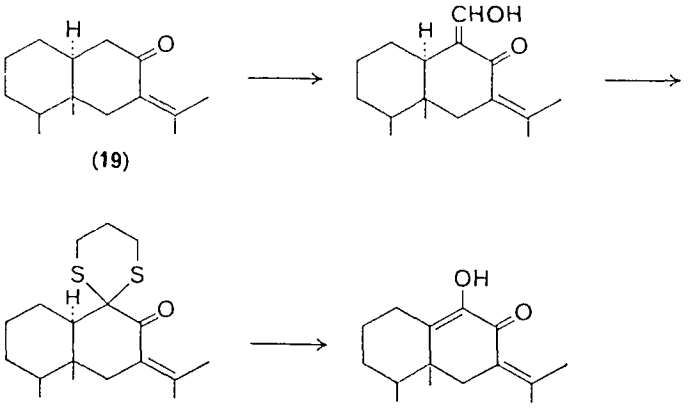


(24)

(**17**) R^1 = OAc, R^2 = H
(**18**) R^1 = CO_2Me, R^2 = Me

3. Formation of dicarbonyl compounds

The treatment of the intermediate 1,3-dithiane, either before or after alkylation with reagents such as mercuric chloride–cadmium carbonate (see section II.A.2) gives hydrolysis to the carbonyl. Thus *trans*-fukinone (**19**) was converted to (+)-hydroxyeremophilone (**20**) (equation 25)[69]. In *cis*-fukinone, the 1,3-dithiane could not be formed from the 1-hydroxymethylene fukinone, presumably for steric reasons.



(**19**)

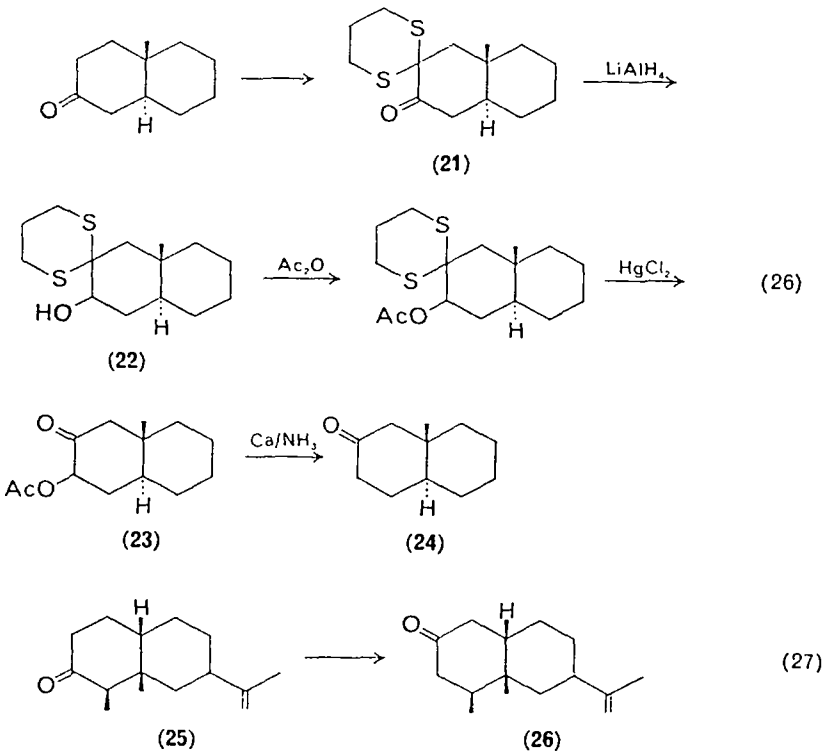
(**20**)

(25)

4. Ketone transposition

Modification of the above sequence to include reduction of the original ketone before hydrolysis is the basis for a new method of ketone transposition[70]. For example, the keto 1,3-dithiane (**21**) was prepared in the

usual manner followed by reduction of the carbonyl with lithium aluminium hydride to the alcohol (**22**). Conversion to the acetate and hydrolysis of the dithiane with mercuric chloride led to the keto acetate (**23**). Reduction with calcium in ammonia resulted in the formation of the new methyl decalone (**24**) in 58% overall yield (equation 26). The same



(26)

(27)

sequence was used to convert decalone (**25**) into the isomeric decalone (**26**) in 46% overall yield (equation 27). These conversions have been shown to take place with complete stereochemical integrity. Alternative methods of removing the carbonyl from the keto 1,3-dithiane so far have not been satisfactory.

5. Selective carbon—carbon bond cleavage

Keto 1,3-dithianes are susceptible to nucleophilic attack at the carbonyl with subsequent cleavage occurring preferentially between the carbonyl and the dithiane functions[71]. In the one instance reported, the keto dithiane (**27**) was cleaved with sodium methoxide in dimethyl sulphoxide to acid (**28**). The explanation as to why the acid is formed instead of the

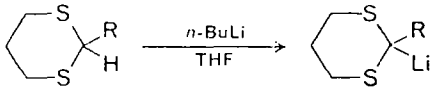
methyl ester is not apparent. The reaction conditions are mild and do not seem to put serious limitations on the nature of the rest of the molecule. Most importantly, after cleavage, the 1,3-dithiane grouping is suitable for many conversions such as reduction, alkylation, acylation or hydrolysis.

(27) (28) (28)

D. Synthetic Applications of 2-Lithio-1,3-dithianes

Corey and Seebach have reported[72] the use of 2-lithio-1,3-dithianes as useful reagents in organic synthesis. The method involves the use of 1,3-propanedithiol, which is caused to react with an aldehyde to yield the 1,3-dithiane (equation 29). Lithiation of the dithiane, normally with *n*-butyllithium in tetrahydrofuran at lowered temperatures, gives the 2-lithio-1,3-dithiane (equation 30). The R group can be alkyl, aryl or hydrogen.

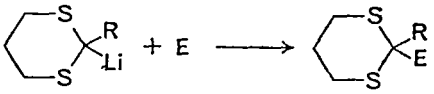
(29)



(30)

2-Lithio-1,3-dithianes have been shown[73] to undergo reaction with a variety of electrophiles, E, to give substituted dithianes (equation 31). Removal of the dithioketal function generates the newly synthesized carbonyl compound (equation 32) having the group E substituted for the aldehydic hydrogen of the original aldehyde. The dithioketal is most often hydrolysed using the mercuric chloride : mercuric oxide method[26] or by oxidative hydrolysis with N-halosuccinimides[27]. It is possible also to remove the dithioacetal function by desulphurization (Raney Ni) to yield the corresponding methylene derivative (equation 33). For a general treatment of removal of the dithioacetal function, see section II.A.2.

2-Lithio-1,3-dithiane reagents are in effect masked nucleophilic acylating agents and can be considered equivalent to the presently unknown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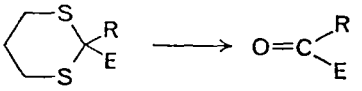
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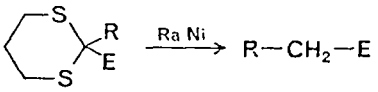
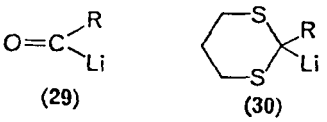

(33)

acyllithium reagent (**29**). Thus, by use of a thiol, the carbonyl carbon of an aldehyde can be transformed from an electrophilic site to the nucleophilic centre in the lithiated dithiane derivative (**30**). The ability of sulphur to


(34)

(29) (30)

stabilize carbanions α to the sulphur atom is significant in the readily accomplished lithiation of 1,3-dithianes. The preparation and reactions of 2-lithio-1,3-dithianes have been reviewed[73].

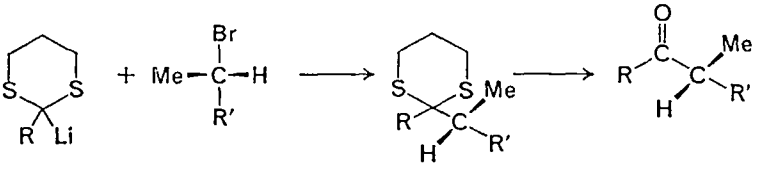
The following is a general outline of the various types of reactions that these reagents are known to undergo, including a comprehensive treatment of reactions reported since the review article by Seebach[73].

I. Reaction with alkyl halides

2-Lithio-1,3-dithianes undergo alkylation at the 2-position upon reaction with alkyl halides. This reaction appears to be S_N2 in nature as it is applicable to primary and secondary alkyl halides[72], occurs most readily with alkyl iodides[72], and with optically active secondary halides gives inverted products[74]. It has been shown[41,72] that reaction with optically active alkyl halides provides a useful route for the preparation of optically active aldehydes or ketones (equations 35 and 36).

Cycloalkylation has been effected by reaction with α,ω-dihaloalkanes to give, upon hydrolysis, cyclic ketones[72,75] (equation 37). Likewise, the

dithiane derivatives of α,β-unsaturated aldehydes undergo hydrochlorination followed by cycloalkylation to yield substituted cyclopropanes (equation 38)[76c]. Cyclic 1,3-diones are available[72] by the



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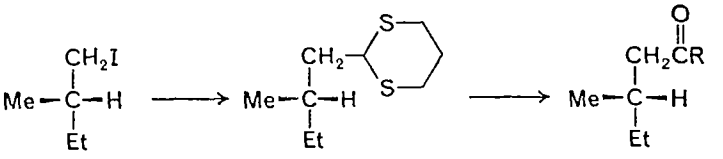
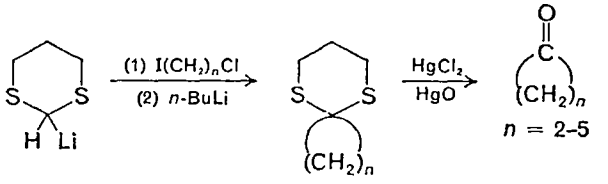


(36)

alkylation of the bis-dithiane **31** (equation 39). It also has been observed that the use of α,ω-dibromoalkanes in cycloalkylation reactions is complicated by formation of sulphonium salts (equation 40), a reaction not observed with use of α-chloro-ω-iodo or α,ω-dichloroalkanes.



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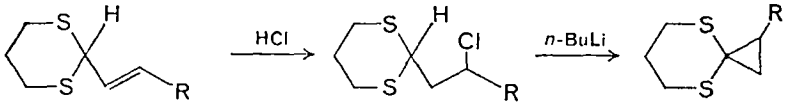

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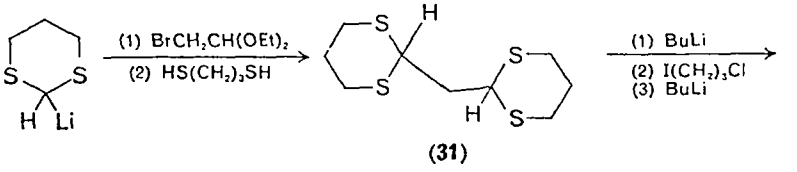

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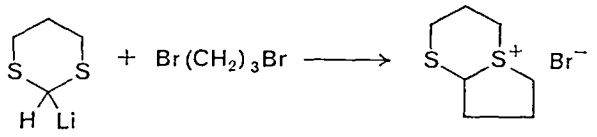
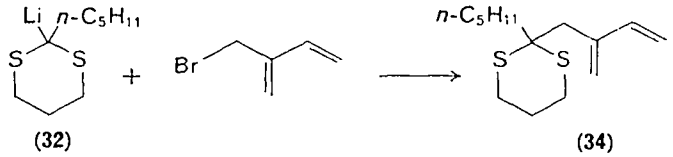


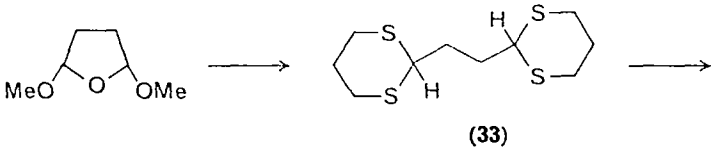
(40)

Corey and coworkers[76a], in a synthesis of prostaglandins, prepared diene **34** by alkylation of the lithiodithiane **32** with 2-bromomethyl-1,3-butadiene (equation 41). A synthesis of jasmone (**35**), in an overall yield of 50%, has been reported by Ellison and Woessner[76b] in which the bisdithianylethane **33** was sequentially alkylated, followed by hydrolysis and cyclization (equation 42). A similar route for preparation of 4-hydroxy-2-cyclopenten-1-ones has been reported[77]. This method appears to provide a general route to 1,4-diketones *via* 1,3-dithianes.



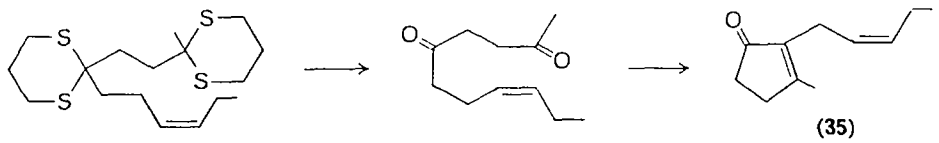
(32) (34)

(41)



(33)

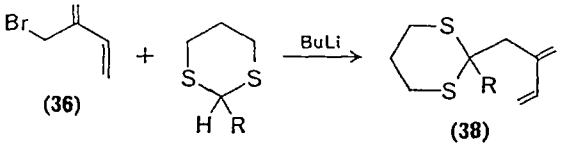
(42)



(35)

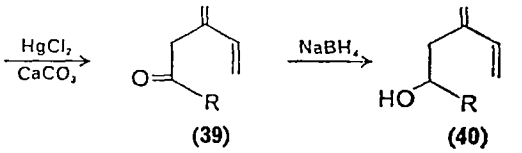
The synthesis of the monoterpene components **40** of the sex attractant of the bark beetle has been accomplished[78] as outlined in equation (43). The alkylation of the dithiane **37** was a key step in the synthesis since efforts to prepare **40** by addition of the magnesium or lithium derivatives of the bromoalkene **36** to the appropriate aldehyde failed.

Hylton and Boekelheide[79] prepared the cyclophanedione **43** by alkylation of the bisdithiane **41** followed by hydrolysis. An improved procedure for the preparation of **41** has been reported[80].

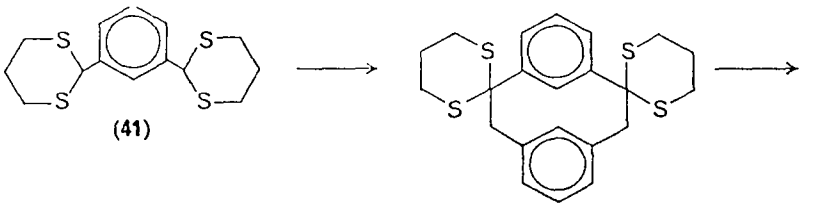


(36) (37) (38)

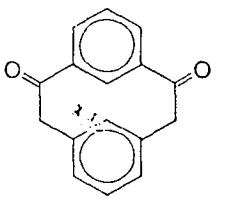
$R = -CH_2CH(CH_3)_2$ or $-CH{=}C(CH_3)_2$ (43)



(39) (40)



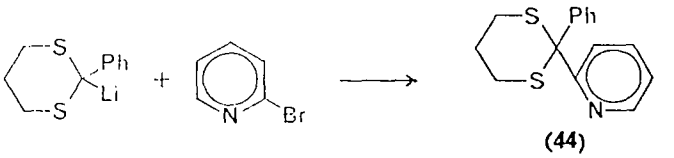
(41) (42) (44)



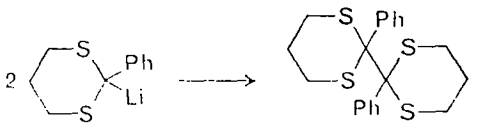
(43)

2. Reaction with aryl halides

Treatment of 2-lithio-2-phenyl-1,3-dithiane with 2-bromopyridine gave the substituted pyridine **44** in 50% yield[81]. However, reaction with 2,4-dinitrobromobenzene gave none of the substitution product, but rather compound **45** resulting from oxidative dimerization of the dithiane



(44) (45)

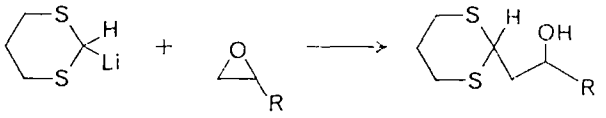


(45) (46)

moiety[81]. Such oxidative dimerizations (see section II.D.7) of 2-lithio-1,3-dithianes are known and have been reported[72] to occur with nitro compounds.

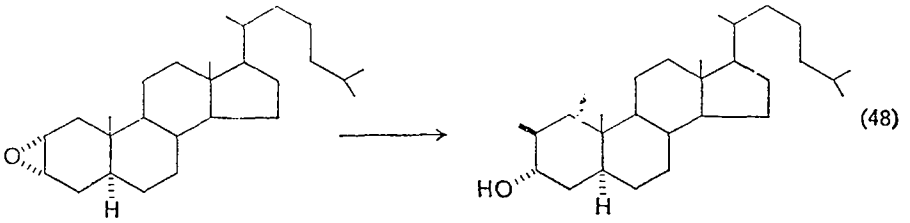
3. Reaction with epoxides

Epoxides effect alkylation of 2-lithio-1,3-dithianes[72,75] (equation 47); opening of the epoxide ring occurs in the fashion typical of reactions with nucleophiles. The reported yields are in the range of 70–95% and appear to be free of side reactions common with other organometallic reagents[73].



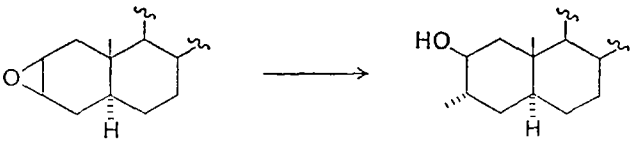
(47)

Recently, Jones and Grayshan[82-84] have reported the reaction of lithiodithiane derivatives with steroidal epoxides to effect preparation of modified steroids. Treatment of 2α,3α-oxiranyl-5α-cholestane (**46**) with 2-lithio-1,3-dithiane, followed by desulphurization, yielded the 2β-methyl-3α-cholestanol **47** (equation 48). Conversely, reaction with the epimeric epoxide **48** furnished 3α-methyl-5α-cholestan-2β-ol (**49**) (equation 49)[82].



(48)

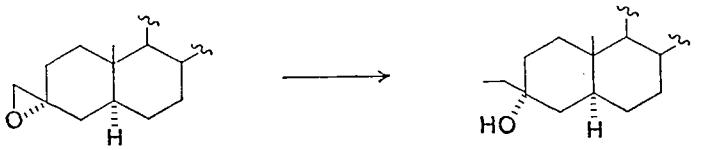
(46) (47)



(49)

(48) (49)

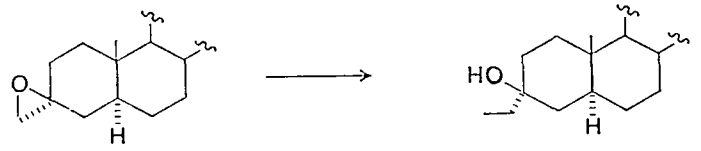
The spiroepoxide **50**, prepared from 5α-cholestan-3-one, was cleanly converted to the 3β-ethyl derivative **51**; the 3α-ethyl derivative **53** was obtained in an analogous manner from the epimeric spiroepoxide **52**[83] (equation 51). Similar results were obtained[34] when this method was applied



(50)

(51)

(50)

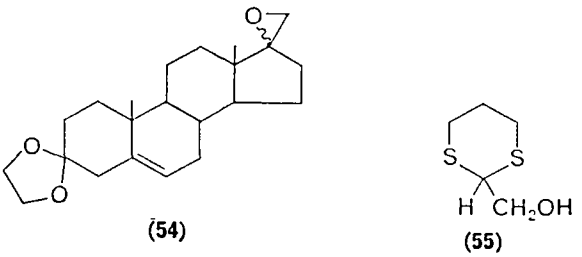


(52)

(53)

(51)

to the epimeric spiroepoxide **54**. This method appears to be the most suitable synthetic route to these modified steroids. However, attempts to utilize the lithium derivative of 2-hydroxymethyl-1,3-dithiane (**55**), or the corresponding tetrahydropyran derivative, to prepare corticoid steroids were unfruitful[84].

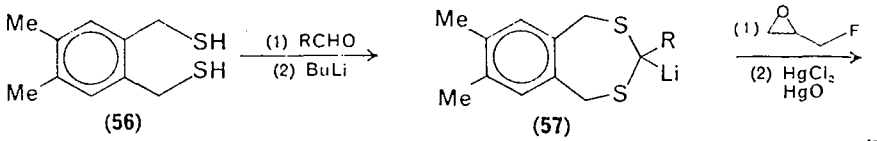


(54)

(55)

(52)

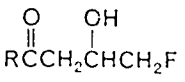
The preparation of some γ-fluoro-β-hydroxyketones (**58**) by reaction of epifluorohydrin with the lithio derivative **57** has been reported[85]. The dithioacetals prepared from dithiol **56** are reported to be crystalline, odourless compounds[86], therefore some advantage may be purported for their use.



(56)

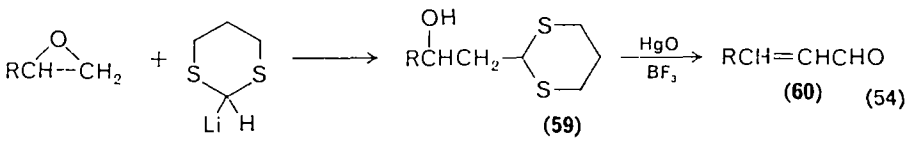
(57)

(53)



(58)

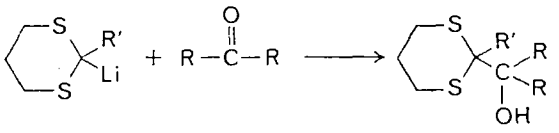
A synthesis[28] of α,β-unsaturated aldehydes has been effected by reaction of 2-lithio-1,3-dithiane with epoxides (equation 54). It was found that treatment of the dithianyl alcohol **59** with mercuric oxide–boron trifluoride caused dehydration and hydrolysis to give the α,β-unsaturated aldehyde **60** in good yield. Standard methods for removal of the thioacetal function were not successful in these cases.



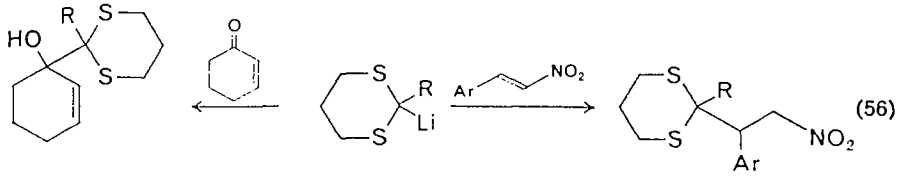
(59) (60) (54)

4. Reaction with aldehydes and ketones

2-Lithio-1,3-dithianes add to the carbonyl group of aldehydes and ketones to provide mercaptal derivatives of α-hydroxy aldehydes or ketones[72] (equation 55). The yields are normally quite high. Reaction with α,β-unsaturated ketones has been observed[72,87] to give only 1,2-addition; however, Seebach and Lietz have reported[88] 1,4-addition to occur in reactions with α,β-unsaturated nitro derivatives (equation 56). In the case

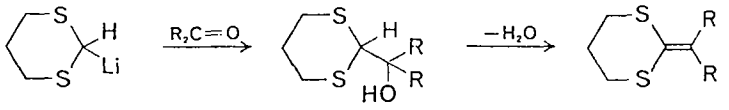


(55)



(56)

where R′ = H, the addition product obtained from reaction with a ketone can be converted by dehydration to a ketene thioacetal (equation 57).



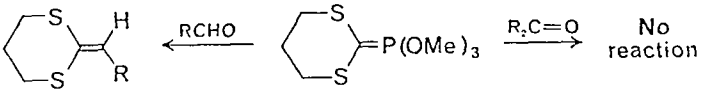
(57)

Ketene thioacetals also are readily available[89,90] by a Wittig-type reaction of 2-lithio-2-trimethylsilyl-1,3-dithiane (**61**) with aldehydes or

ketones. The dithiane **61** is prepared[40,91] by reaction of 2-lithio-1,3-dithiane with trimethylchlorosilane followed by lithiation (see section II.D.6). A method employing the phosphite ylid **62** to prepare ketene thioacetals by reaction with aldehydes, but not ketones, has been reported[92] (equation 59).

(58)

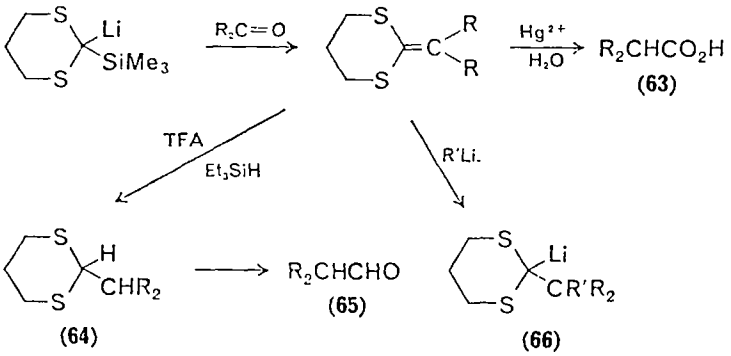
(61)



(59)

(62)

Ketene thioacetals should prove to be useful synthetic intermediates. Hydrolysis[92] of ketene thioacetals yields carboxylic acids (**63**), while protonation–hydride transfer using trifluoroacetic acid-triethylsilane, as reported by Carey and Neergaard[93], provides the thioacetal (**64**) of the homologous aldehyde (**65**).

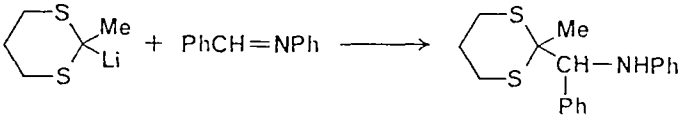


(60)

(63) (64) (65) (66)

Alkyllithium reagents are known[94] to add to ketene thioacetals to give 2-lithio-1,3-dithianes **66** in which R′ has become attached to the ethylidene carbon. Both **64** and **66** are capable of undergoing further reactions available to 2-lithio-1,3-dithianes. Therefore, it should be possible in principle to convert an aldehyde, RCHO, to any of the following *via* the corresponding ketene dithioacetal: RCH_2CO_2H, RCH_2CHO, RR′CHCHO, RR′CHCOR″, and RR′R″CCOR‴.

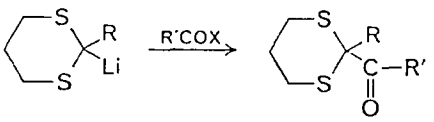
Imines, being nitrogen analogues of carbonyl compounds, are reported[72] to undergo addition with 2-lithio-1,3-dithianes to yield amines (equation 61).



(61)

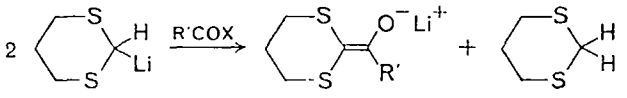
5. Reaction with acylating agents

Acylation of 2-lithio-1,3-dithiane derivatives occurs in satisfactory yields only when a dilute solution of the dithiane derivative is added at −78°C to a solution containing a 20–100-fold excess of the acylating agent[72,73] (equation 62). The above conditions are necessary to circumvent reaction of a molecule of the reactive lithiodithiane with a molecule of previously formed 2-acyldithiane. This method offers, by subsequent removal of the dithioketal function, a route for the preparation of 1,2-dicarbonyl compounds.



(62)

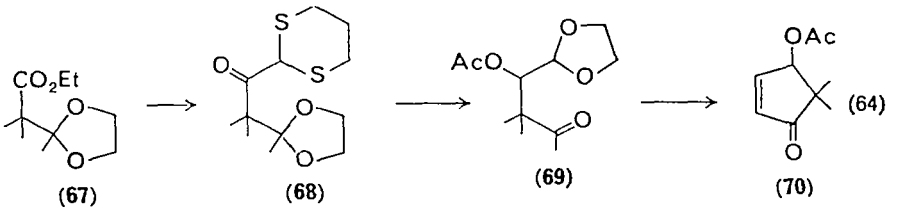
Acylating agents that have been employed[72] are carbon dioxide, alkyl chloroformates, alkyl formates, acid chlorides, esters, benzonitrile and dimethylformamide; the expected acylation products from reaction with the above reagents were formed in each case. However, the N,N-dimethylamide derivatives of higher carboxylic acids did not yield acylated product as in the case of dimethylformamide[73]. When R = H (equation 63), it was necessary to employ two equivalents of the lithiodithiane due to product enolate formation.



(63)

In the total synthesis of illudin M, Matsumoto and coworkers[95] prepared the cyclopentenone **70** by reaction of 2-lithio-1,3-dithiane with

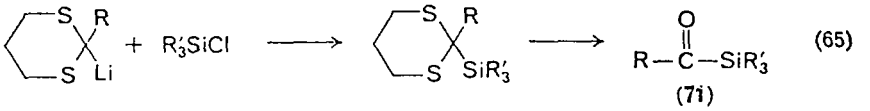
the ester **67** to give **68**. Reduction, acetylation and removal of the dithioacetal function gave **69**, apparently formed by an intramolecular transketalization reaction.



(67) (68) (69) (70)

6. Silylation and related reactions

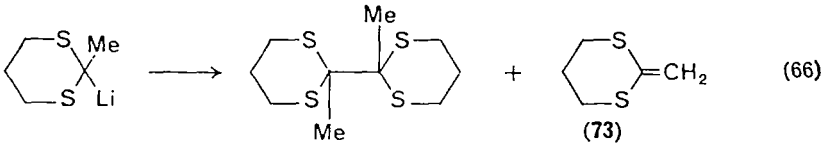
2-Lithio-1,3-dithianes react with trialkyl- and triaryl-chlorosilanes to give the 2-silylated derivatives (equation 65). This method was used in the preparation[10,91] of the previously unknown α-silylketones **71**. Germanylation and stannylation also can be accomplished with the corresponding trialkylhalo derivatives[40].



(71)

7. Oxidative dimerization

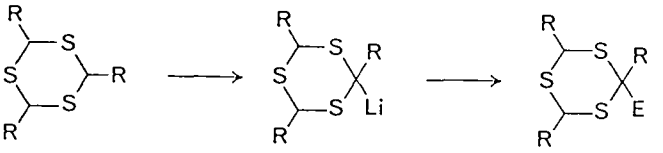
Treatment of 2-lithio-1,3-dithianes with iodine, cupric salts, 1,2-dibromoethane, or nitro compounds effects oxidative dimerization[73] to give the dimer **72** plus a small amount of the 2-methylene derivative **73**.



(72) (73)

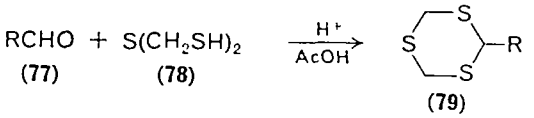
8. Reactions using 1,3,5-trithianes

1,3,5-Trithianes (**74**) undergo lithiation[41,73] with an equivalent of *n*-butyllithium to yield the 2-lithio derivatives, which substances undergo the usual reactions (equation 67) as with 2-lithio-1,3-dithianes. Since additional active hydrogens are present in 1,3,5-trithianes, dimethylation has been observed in some cases[73].



(74) R = H or alkyl (75) (76) (67)

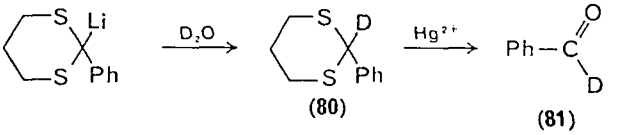
An alternate route not involving 2-lithio-1,3,5-trithianes for the preparation of 2-substituted-1,3,5-trithianes recently has been reported[96]. This method involves reaction of an aldehyde **77** with the dithiol **78** to yield the 2-substituted trithiane **79**.



(77) (78) (79) (68)

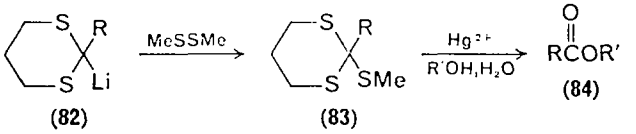
9. Miscellaneous applications

A convenient preparation of 1-deuterioaldehydes (**81**) *via* 2-lithio-1,3-dithianes has been reported by Seebach and coworkers[27] (equation 69). This method appears to be superior to previously reported methods for the preparation of 1-deuterioaldehydes.



(80) (81) (69)

Treatment of 2-lithio-1,3-dithiane derivatives with methyl disulphide yields the orthothioformate **83**, which upon hydrolysis in alcoholic solvents furnishes an ester[97]. This method may provide a useful route for the conversion of sensitive aldehydes to esters and carboxylic acids.



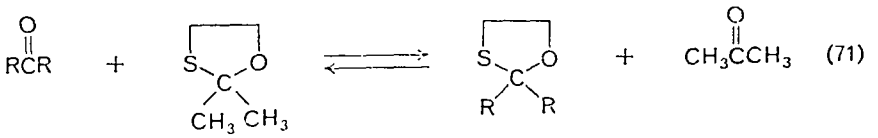
(82) (83) (84) (70)

III. MONOTHIOACETALS

The use of monothioacetals in organic synthesis has not been nearly so extensive as the use of dithioacetals. Generally prepared as 1,3-oxathiolanes and 1,3-oxathianes, the group is resistant toward dilute base and lithium aluminium hydride[14]. Regeneration of the carbonyl is easily accomplished.

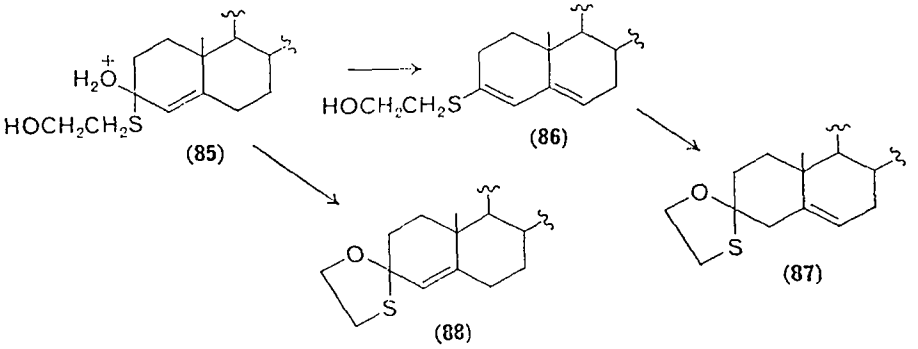
A. Preparation

Condensation of 2-mercaptoethanol or 3-mercaptopropanol with ketones is usually achieved with the aid of an acid catalyst. Hydrogen chloride has been used[98] but more common agents are boron trifluoride[10], freshly fused zinc chloride[99] or *p*-toluenesulphonic acid[100]. An exchange method between 2,2-dimethyl-1,3-oxathiolane or 2,2-dimethyl-1,3-oxathiane and a non-volatile ketone leads to formation of the new monothioacetal and acetone[100]. The equilibrium is displaced by continuous distillation of the acetone formed (equation 71). With saturated ketones, mostly steroids, the yields of the above methods are comparable and are usually in the 60–90% range. With α,β-unsaturated ketones, the yields were significantly lower[100].



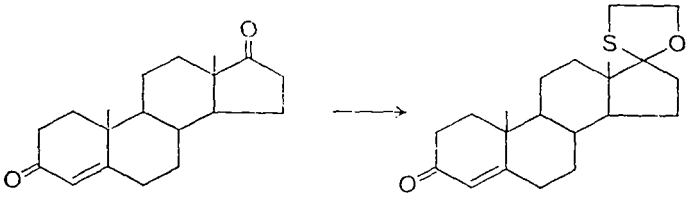
(71)

Unlike the case of 1,3-dithiolane formation, 1,3-oxathiolanes from α,β-unsaturated ketones show a shift of the double bond. It has been proposed[100] that intermediate **85** may undergo nucleophilic attack by the hydroxyl leading to unrearranged product **88**. Alternatively, dehydration would give the conjugated diene **86**, to which the hydroxyl could add giving the rearranged product **87**. Obviously, with ethanedithiol nucleophilic attack of the sulphur must predominate, while with the less nucleophilic hydroxyl, prior dehydration occurs. This is in agreement with the fact that with ethanediol the resulting ketal shows a shifted double bond.



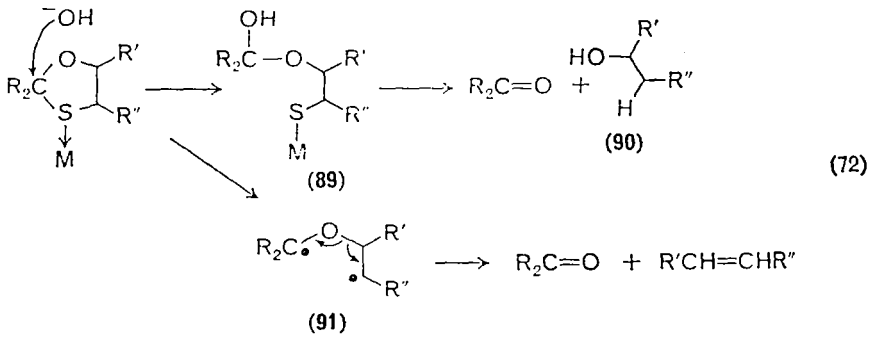
The reduced reactivity of α,β-unsaturated ketones towards 3-mercaptoethanol allows preferential formation of the hemithioacetal of an unconjugated carbonyl present in the molecule. One example of this general

phenomenon is given below in which 4-androstene-3,17-dione was converted to the 17-(1,3-oxathiolane) with zinc chloride catalysis[99]. With *p*-toluenesulphonic acid catalysis, the 3,17-bis(1,3-oxathiolane) could be formed in low yield.



B. Removal

Unlike 1,3-dithiolanes, treatment of 1,3-oxathiolanes with Raney nickel gives regeneration of the carbonyl group[99]. Thus, protection of a carbonyl by condensation with 2-mercaptoethanol allows regeneration in high yields under neutral conditions. Surprisingly, in the usual alcohol or acetone solvent, the ketonic oxygen is not from the oxathiolane. Apparently, association of the sulphur with the electron-deficient metal (equation 72) causes activation of the ring followed by attack of a hydroxide, either from the media or combined with the metal, to give the hemiketal **89**. Normal work-up cleaves the hemiketal which, with further desulphurization, leads to formation of the ketone and the alcohol **90**[59,101]. Solvents such as benzene may also be used and under the right conditions lead to high yields of the ketone[101]. In nonpolar solvents,

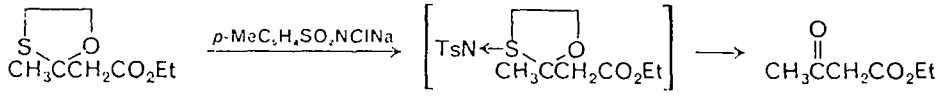


(72)

ionic intermediates are presumably not involved and the diradical (**91**) is the accepted intermediate[59,101]. The desulphurization of 1,3-oxathianes behaves similarly with the ketone being the major product[101]. Additional information may be found in the previously mentioned reviews[22,23,43].

The hydrolysis of 1,3-oxathiolanes with acid[102,103] or mercuric ion[101] also provides a suitable procedure for regenerating the ketone. The mechanism involved appears similar to that with Raney nickel, but with a proton or mercuric ion taking the place of the nickel.

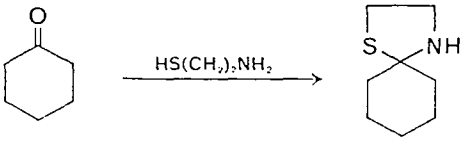
The most recent method of removal of the 1,3-oxathiolane group is by the use of N-chloro-*p*-toluenesulphonamide(chloramine-T)[104] in water, methanol or ethanol (equation 73). Again basically the same mechanism appears involved with prior association of the sulphur to form an unstable sulphilimine. The reaction times are short (2 min), conditions are mild and yields are high (85–100%).



(73)

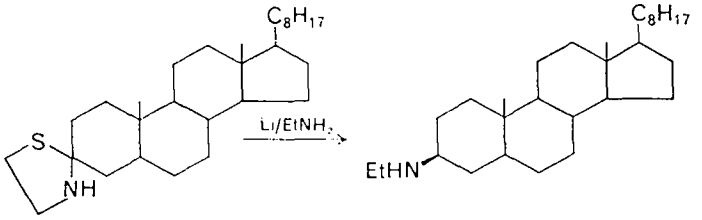
IV. THIAZOLIDINES

Just as 2-mercaptoethanol will condense with ketones to produce 1,3-oxathiolanes, so will 2-mercaptoethylamine react to produce thiazolidines[60]. Usually *p*-toluenesulphonic acid is used as a catalyst in benzene with yields being quite good, 94% in the case of cyclohexanone (equation 74). The uses of the thiazolidines have not been throughly



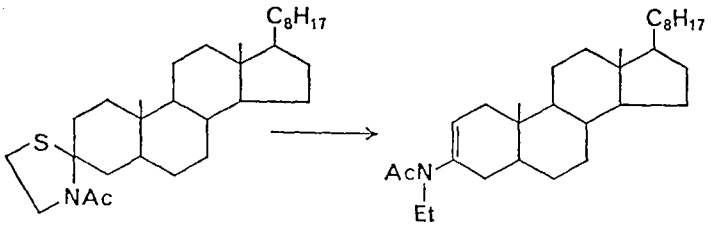
(74)

investigated, but it appears that they offer no advantages over previously mentioned protecting groups. Although Raney nickel desulphurization gives unsatisfactory yields of the starting ketone, lithium in ethylamine offers promise in the preparation of amines. 3β-Ethylamino-5α-cholestane was prepared in 87% yield[60] when desulphurized in this manner (equation 75).



(75)

More thoroughly investigated has been the desulphurization of N-acetylated thiazolidines to form acetylated enamines. Thus 31-day-old Raney nickel in benzene gives a 90% yield of 3-(N-ethylacetamido)-5α-cholest-2-ene (equation 76) from the corresponding N-acetylthiazolidine [60, 105]. The conditions for this reaction are rather sensitive to solvent



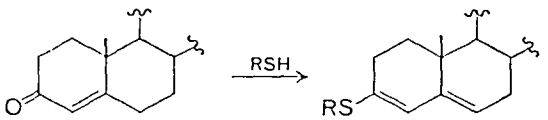
(76)

and catalyst age. The unsaturated amide is the favoured product in benzene with aged catalyst, but with fresh catalyst the major product in acetone is the ketone and in ethanol the saturated amide. The mechanism of desulphurization is believed[60] to be similar to the first step in the formation of olefins from 1,3-dithiolanes (see section II.B.2).

V. THIOENOL ETHERS

A. Carbonyl Protecting Group

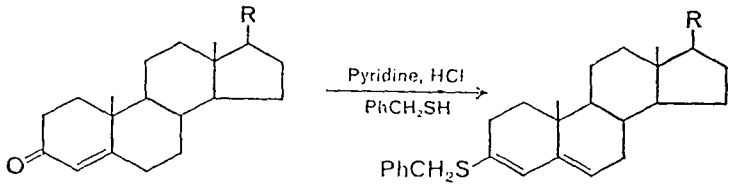
It has been noted (see section III.A) that protecting reagents such as 2-mercaptoethanol react preferentially with the saturated carbonyl when it is in the presence of an α,β-unsaturated carbonyl. Thioenol ethers are equally useful because they are formed almost exclusively from α,β-unsaturated carbonyls (equation 77).



(77)

Normally the reaction of thiols with carbonyls, saturated or unsaturated, leads to the formation of dithioacetals when acid catalysts such as zinc chloride or *p*-toluene-sulphonic acid are present (see section II.A.1). Occasionally, under special reaction conditions thioenol ethers have been formed using these same catalysts[106, 107], but never in the presence of acid-sensitive substituents. Pyridine hydrochloride as the catalyst has been successfully used to give excellent yields of the thioenol ethers of Δ^4-3-ketosteroids even in the presence of sensitive groups[108]. Thus, desoxycorticosterone acetate (**92**) was converted to its 3-benzylthioenol ether

(93) in 60% yield (equation 78). The selectivity of the reaction using these conditions is very high. Unlike the case with zinc chloride, progesterone (94) with pyridine hydrochloride and benzyl mercaptan gives no observable reaction at $C_{(20)}$ with the only product being progesterone 3-benzyl thioenol ether (95)[108].

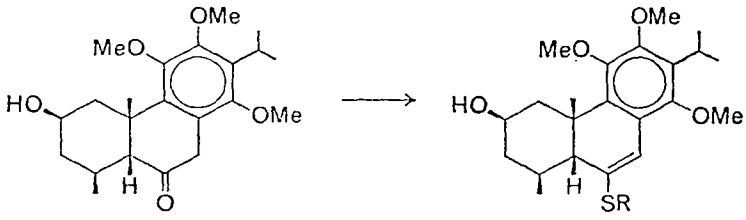


(78)

(92) R = $COCH_2OAc$
(94) R = $COCH_3$

(93) R = $COCH_2OAc$
(95) R = $COCH_3$

Other condensing agents which have proved useful under certain conditions are boron trifluoride[8], formic acid with *p*-toluenesulphonic acid[8] and hydrochloric acid in acetic acid[8,107]. One unusual example of a thioenol ether formed from a saturated ketone has been reported using hydrogen chloride as the catalyst[109]. In this case, compound **96** was converted to either its benzylthioenol ether **97** or its ethylthioenol ether **98** (equation 79). Benzyl mercaptan normally seems to be the reagent of choice in most conversions because of its easily crystallized products.

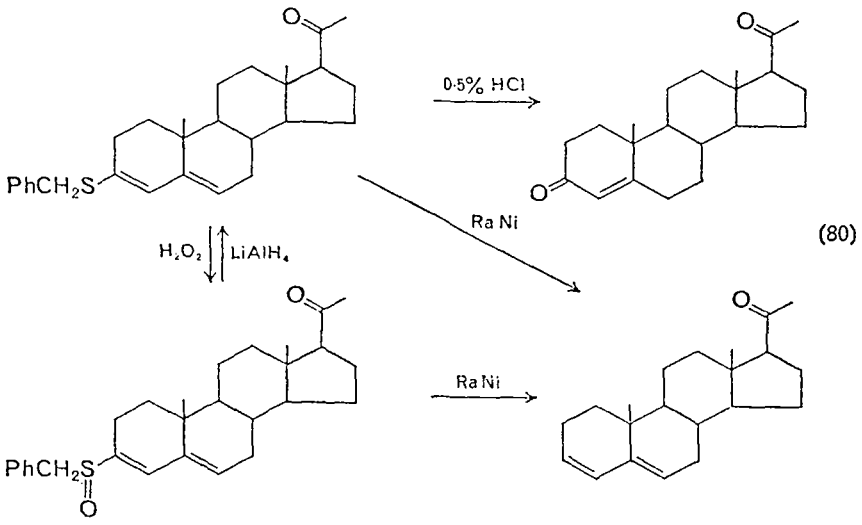


(79)

(96)

(97) R = $PhCH_2$—
(98) R = Et

The thioenol ethers are stable towards base[8] and lithium aluminium hydride[106,108], but are reconverted to the parent compound on dilute acid hydrolysis. Raney nickel desulphurization can be used to form the diene[108]. Hydrogen peroxide oxidation will convert the acid-labile thioenol ether to an acid-stable sulphoxidoenol ether[8,108]. The sulphoxidoenol ether may be desulphurized with Raney nickel to the diene, or with lithium aluminium hydride reconverted to the thioenol ether for hydrolysis to the α,β-unsaturated ketone[108]. These reactions are depicted in equation (80).

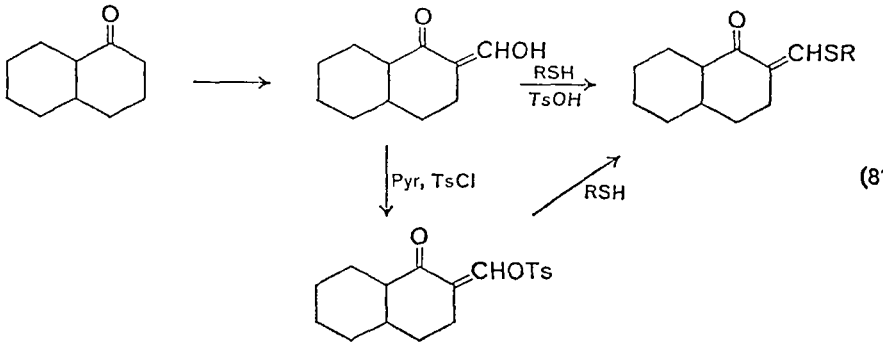


(80)

B. Methylene Blocking Group

In the continuing search for the ideal methylene blocking group, considerable effort has been expended in looking at derivatives of hydroxymethylenes. These are readily prepared from a ketone, ethylformate and sodium methoxide[61].

Ireland and Marshall[64] found that alkanethiols form very versatile derivatives with hydroxymethylenes. The reaction with a thiol, accompanied by a *p*-toluensulphonic acid catalysed water separation, leads to formation of the corresponding thioenol ether (equation 81). If acid-labile substituents are present, a procedure involving displacement from an intermediate tosylate (**99**) by the thiol is used. Although other thiols

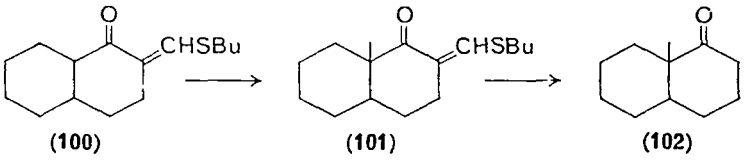


(81)

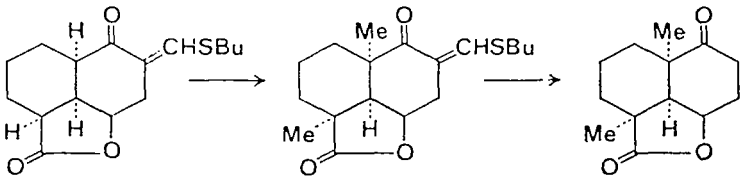
(**99**)

have been used, *n*-butanethiol appears to be the most convenient in this reaction. The yields of the thioenol ethers from hydroxymethylenes are generally greater than 80% using the acid catalysed method and only slightly lower with the basic pyridine procedure.

Alkylations of the protected ketones are very facile. The thioenol ether generally need only be left in contact with the base a few minutes before addition of the alkyl halide. Such short contact with the base allows easy isolation of the alkylated, blocked ketones[64]. Thus, 2-*n*-butylthiomethylene-1-decalone (**100**) was converted to 9-methyl-2-butylthiomethylene-1-decalone (**101**) in 85% yield. This procedure was used in the difficult dimethylation of **103** to give the lactone **104**.



(100) (101) (102) (82)



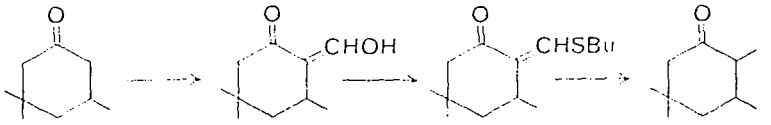
(103) (104) (105) (83)

Although the *n*-butylthiomethylene group is subject to acid hydrolysis, basic conditions for hydrolysis have been developed[64] and these seem to be preferred in actual practice. A typical procedure uses a mixture of a 25% aqueous potassium hydroxide solution with ethylene glycol heated at reflux. In this manner thioenol ether **101** was converted to 9-methyl-1-decalone (**102**) in 78% yield[64] (equation 82). The rare use of acid hydrolysis is exemplified by the use of concentrated hydrochloric acid to hydrolyse the blocked lactone (**104**) to **105** (equation 83)[110]. Additional examples of conversions using a thioenol ether intermediate are shown in Table 2.

C. Monomethylation via Reduction

Just as the blocking of active sites to permit alkylations on less reactive sites has been a recurring problem, so has the problem of preventing polyalkylations on reactive sites. The use of the alkylthiomethylene group offers a convenient intermediate from which monomethylated products are prepared by desulphurization with Raney nickel. In this way, 2,3,5,5-tetramethylcyclohexanone was prepared[119] in 58% overall yield from

3,3,5-trimethylcyclohexanone (equation 84). The same procedure was used[120] in the conversion of 7-oxobicyclo[3.2.1]octane to the 6-methyl derivative (equation 85). Similarly, 10-carbethoxy-2,7,7-trimethyl-*cis*-



(84)

TABLE 2. Alkylation of ketones using thioenol ethers as a methylene blocking group

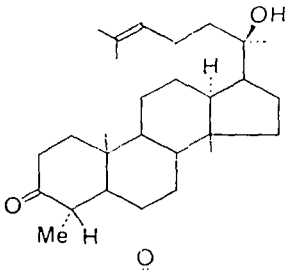
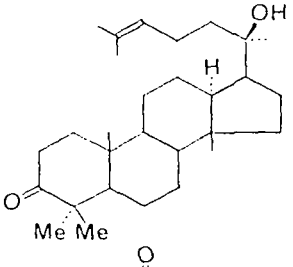
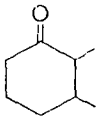
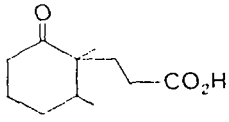
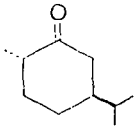
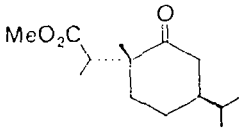
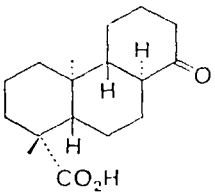
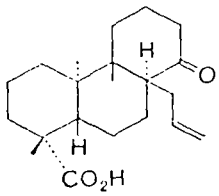
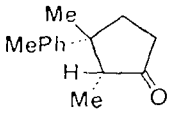
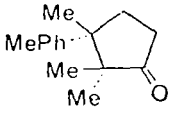
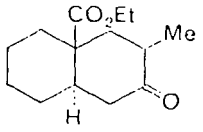
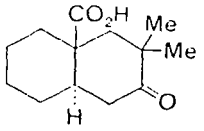
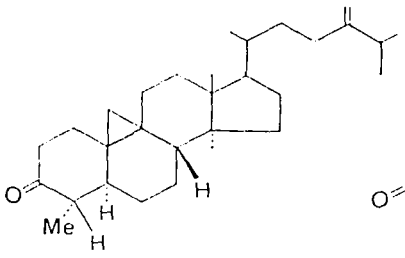
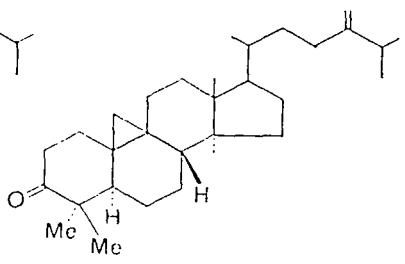
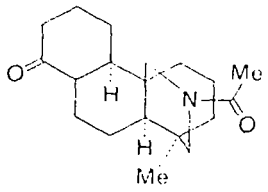
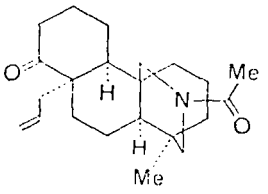
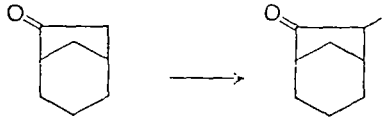
Reactant	Product	Overall yield, %	Reference
		73	111
		60	112
		62	113
		82	114
		31	115

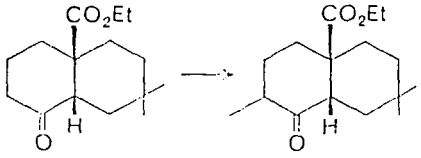
TABLE 2 (*cont.*)

Reactant	Product	Overall yield %	Reference
		62	116
		35	117
		36	118

decal-1-one (equation 86) was prepared in 73% overall yield using this method[121]. In those cases where partial reduction of the carbonyl accompanies desulphurization, the crude mixture is oxidized before purification[119].

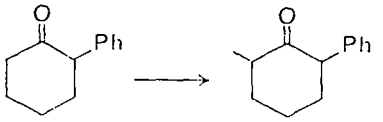


(85)



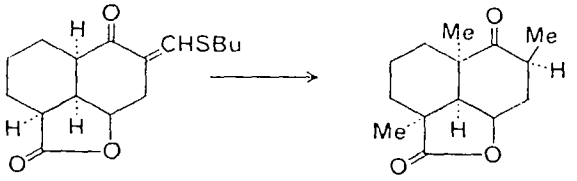
(86)

The methylation of a very active but substituted position is easily avoided by the alkylthiomethylene approach. A high yield of 6-phenyl-2-methylcyclohexanone was obtained from 6-phenylcyclohexanone (equation 87)[64,122].



(87)

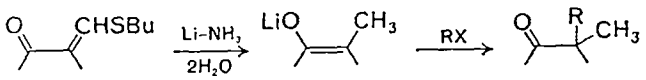
Of course, the use of the alkylthiomethylene group first for blocking and later as a route to monomethylation further expands its utility. Thus, compound **103** was methylated and desulphurized to give the trimethyl derivative **106**[110].



(103) (106)

D. Geminal Alkylation

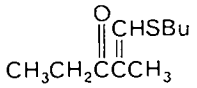
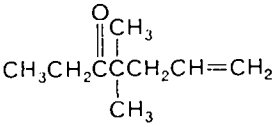
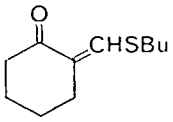
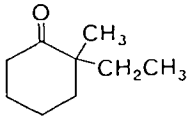
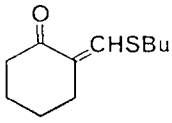
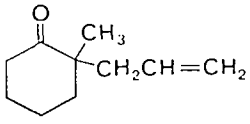
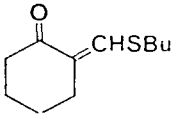
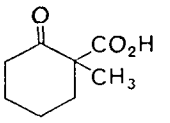
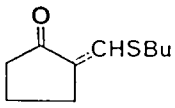
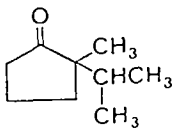
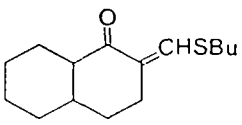
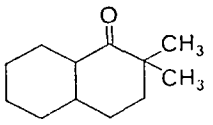
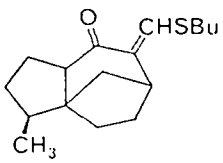
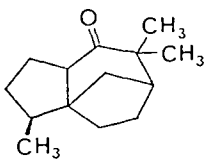
In attempting alkylations leading to highly substituted ketones, careful choice of methods is required to avoid difficulties. Selective geminal alkylations can be achieved by blocking all other available sites, but this is not always possible as with α,α,α′-trisubstituted acetones. An interesting new method has evolved incorporating the lithium–ammonia reduction of *n*-butylthiomethylene derivatives of ketones to their methyl-substituted enolate anions with subsequent alkylation[123]. This reduction–alkylation leads to the introduction of one methyl group and a second variable geminal substituent at any position which will condense with ethyl formate (equation 88). Reaction times as brief as 30 s plus the use of water



(88)

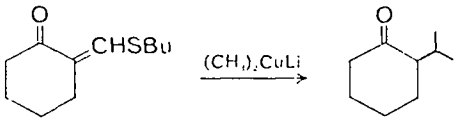
as a proton donor minimize any over-alkylation. Table 3 lists some typical conversions using this procedure.

TABLE 3. Geminal alkylation of ketones *via* thioenol ether derivatives

Ketone derivative	Product	Yield from *n*-butylthio-methylene derivative, %	Reference
		82	123
		75	123
		85	123
		56	123
		40	123
		70	123
		69	128

E. Symmetrical α-Branched Alkylation

The reaction of dialkylcopper lithium reagents with α,β-unsaturated ketones leads to selective conjugate addition[124]. It has been observed that *n*-butylthiomethylene derivatives undergo a double conjugate addition, with loss of the alkylthio group, upon reaction with dimethylcopper lithium. Thus, dimethylcopper lithium reacts with 2-*n*-butylthiomethylene-cyclohexanone to give almost quantitatively 2-isopropylcyclohexanone (equation 89)[123]. This reaction should prove useful for the preparation of ketones having a symmetrically branched alkyl substituent in the α-position.



(89)

F. α, β-Unsaturated Aldehydes

Ketones with blocking groups of the isopropoxymethylene type are readily converted to α,β-unsaturated aldehydes by reduction followed by acid-catalysed rearrangement[125,126]. However, the use of this blocking group has the drawback of being moisture-sensitive and of having a deactivating effect on the other α-position. Fortunately, the *n*-butylthio-methylene grouping does not suffer from these drawbacks and is still readily converted to the α,β-unsaturated aldehyde[64,127]. Thus 2-*n*-butyl-thiomethylene-6,6-dimethylcyclohexanone (**107**) is reduced with lithium aluminium hydride and the resulting alcohol hydrolysed in acid to the α,β-unsaturated aldehyde **110**[129]. The alcohol **111** typically makes up

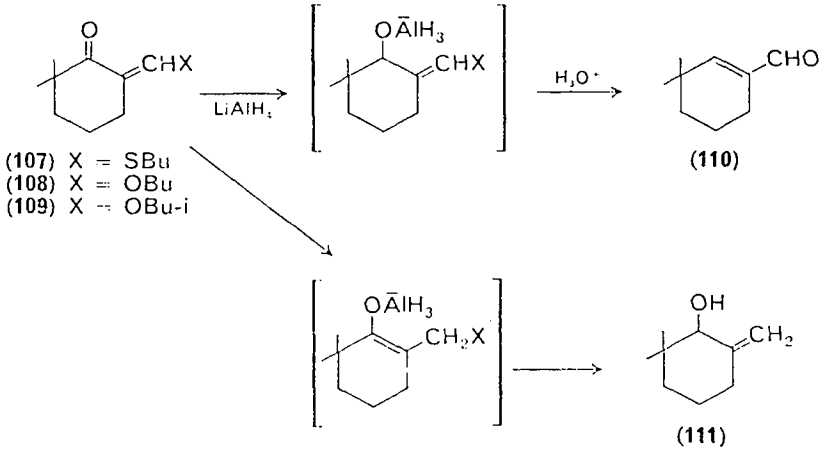
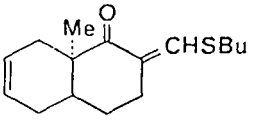
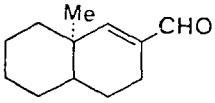
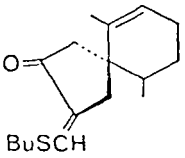
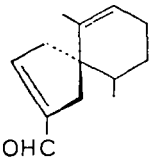
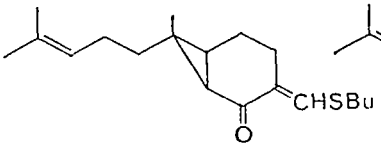
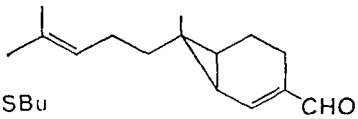
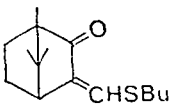
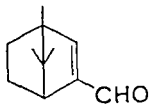
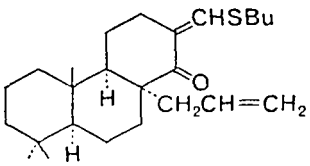
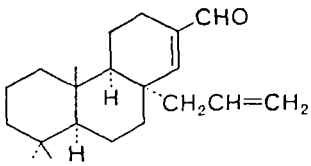
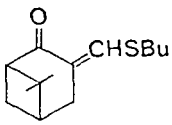
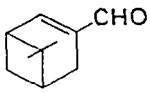


TABLE 4. Preparation of α,β-unsaturated aldehydes by $LiAlH_4$ reduction of α-*n*-butylthiomethylene ketone derivatives

Ketone derivative	Product	Yield from *n*-butylithio-methylene, %	Reference
		63	127
		81	131, 132
		—	133
		—	130
		38	134
		52	135

about 5% of the product. A comparison of the *n*-butylthiomethylenes with butoxy- and isobutoxymethylenes (**108** and **109**) shows[119,129] that the latter two are significantly more prone to 1,4-addition leading to alcohols such as **111**. The use of lithium aluminium hydride instead of the originally suggested sodium borohydride[127] also seems to minimize the 1,4-addition[130]. Table 4 provides some further examples of this reaction.

VI. SULPHUR EXTRUSION REACTIONS

Reactions in which a sulphur atom that bridges or interconnects two carbon groups is extruded with formation of a carbon—carbon bond between the two carbon groups is termed a sulphur extrusion reaction (equation 90). These types of reactions have proven to be of synthetic utility and are treated in this section.

$$R-S-R \longrightarrow R-R + S \qquad (90)$$

Thiols can serve as reagents in the extrusion reaction by being converted to a sulphide or a corresponding higher oxidized derivative upon which the extrusion process is effected. While for many of the cases covered in this section the organosulphur compound used in the extrusion reaction was not prepared directly from a thiol, the potential exists for thiols to be utilized in these types of reactions.

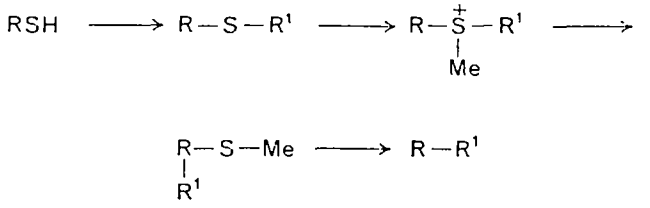
A. Stevens Rearrangement of Sulphonium Salts

The Stevens rearrangement of a sulphonium salt[136] involves treatment of the salt with base and leads to migration of a group from sulphur to an adjacent carbon atom (equation 91). Analogous Stevens rearrangement of ammonium salts[137] and the related Wittig rearrangement[137] of ethers are well known.

$$R-\overset{+}{S}(R)-CH_2R^1 \xrightarrow{\text{base}} R-S-CHR^1(R) \qquad (91)$$

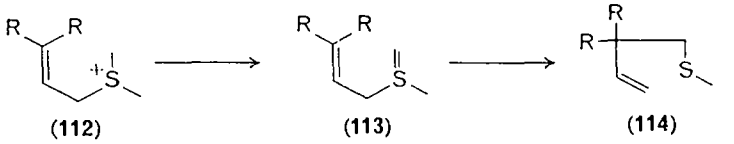
The sulphonium salts used in the Stevens rearrangement need not be prepared initially from a thiol; however, this is feasible and is often the case. This method, therefore, allows the conversion of a thiol to a sulphonium salt, followed by rearrangement with concomitant carbon—carbon bond formation. Removal of the sulphur moiety following rearrangement permits, in effect, a thiol to function in a reaction that leads to bond formation between two R groups that originally were attached to sulphur (equation 92).

The Stevens rearrangement of sulphonium salts is known to proceed through the intermediacy of the corresponding sulphonium ylid[138]. There appears to be two distinct mechanistic pathways, depending upon the structure of the ylid, leading to rearranged product. Rearrangement of



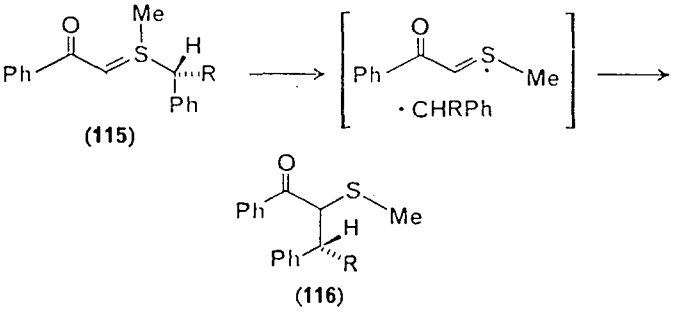
(92)

allyl sulphonium salts[139] (**112**), proceeding via the ylid **113**, has been shown[140] to occur by a [2,3] sigmatropic reaction (equation 93); a minor amount of product also arises by what is equivalent to a [1,2] shift[140]. These rearrangements are examples of what appear to be a general class of electrocyclic reactions of sulphonium ylids[141].



(93)

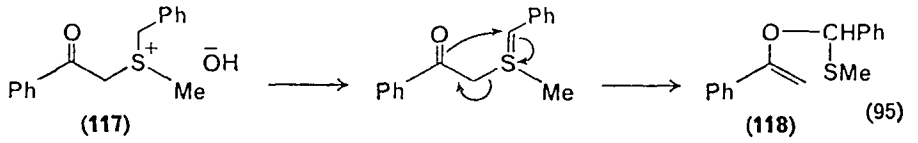
A second type of rearrangement involves ylids derived from non-allyl sulphonium salts. Baldwin and coworkers[142] have reported that rearrangement of the sulphonium ylid **115** in toluene at reflux temperatures occurs by a radical pair mechanism (equation 94), in which the benzyl group migrates with predominant retention of configuration to yield **116**.



(94)

Thompson and Stevens[143], in their first paper on the rearrangement of sulphonium salts, reported obtaining the sulphide **116** upon treatment of **117** with sodium methoxide. However, more recent work has shown[138, 144]

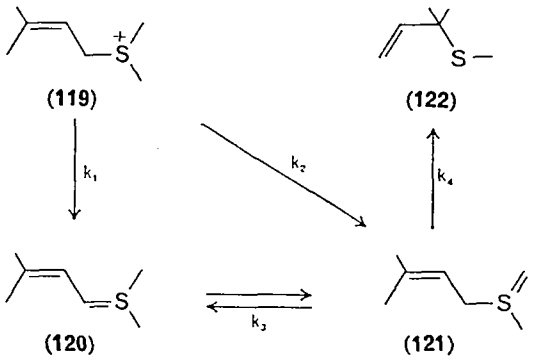
the product to be enol ether **118**, apparently formed by an electrocyclic reaction (equation 95) as described above for allyl sulphonium salts. It appears that if reaction conditions permit or favour the [2,3] sigmatropic pathway, this is the favoured course of the reaction.



(95)

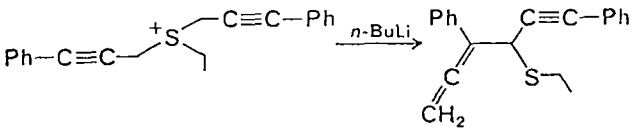
I. Rearrangement of allyl sulphonium salts

Several workers[139] independently reported application of allyl sulphonium salts in the Stevens rearrangement. Bates and Feld[139a] were able to show that even though the ylid **120** was formed at a faster rate than ylid **121** ($k_1 > k_2$), the formation of product **122** from **121** was also fast



(96)

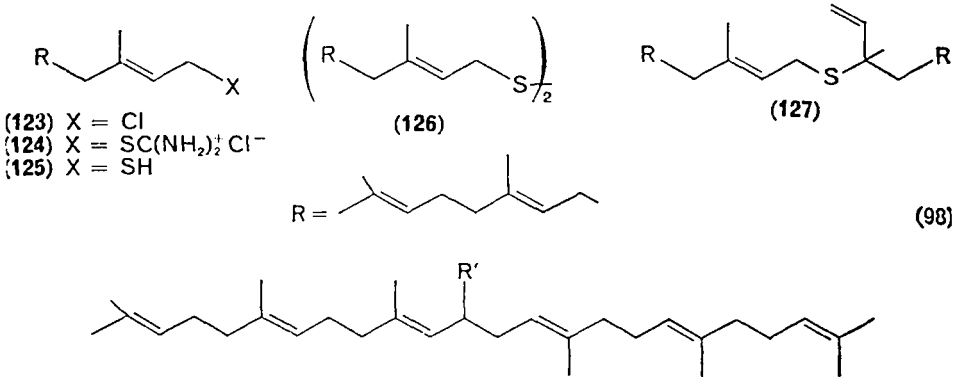
($k_4 > k_3$). While most of the rearrangements occur in good yield, the reaction of $CH_2{=}CH{-}CH_2S^+(Ph)_2$ gave a multicomponent product mixture[139c]. The acetylenic bond [145] also undergoes reaction leading to allenes as products (equation 97), however, $HC{\equiv}C{-}CH_2{-}\overset{+}{S}Me_2$ leads to the formation of a polymer[145b].



(97)

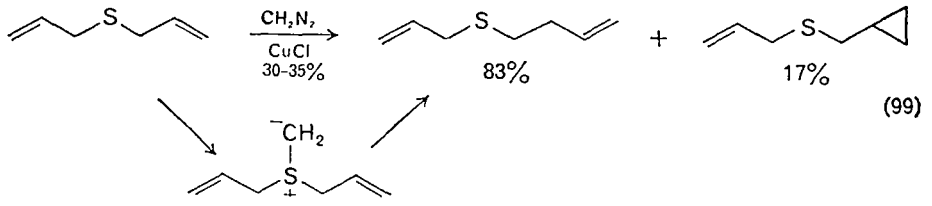
The Stevens rearrangement has been applied most elegantly in the synthesis of squalene (**129**)[146] and other isoprenoid substances[139,147]. Farnesyl chloride (**123**) was converted to an unstable disulphide **126** *via*

hydrolysis of the thiouronium salt **124** and oxidation of the resulting thiol **125**. The disulphide **126** was transformed[148] by treatment with triphenylphosphine to farnesyl nerolidyl sulphide **127**. Conversion of sulphide **127** to the sulphonium salt with trimethyloxonium tetrafluoroborate was unsuccessful; however, treatment with generated benzyne effected arylation and rearrangement to give 12-phenylthiosqualene (**128**). Reductive removal of the phenylthiol group with lithium in liquid ammonia furnished squalene (**129**)[146]. The synthesis of squalene *via*



rearrangement of sulphonium salts was described[139,147] as a possible model for biosynthesis of isoprenoid natural products. Recent work[149] has established that this is not the biogenetic pathway leading to squalene.

Reaction[150] of allyl sulphides with diazomethane furnishes products resulting from rearrangement of the presumed intermediate ylid along with some olefin insertion product (equation 99). Similar products are obtained from reaction of allyl sulphides with dichlorocarbene[151].



2. Rearrangement of non-allyl sulphonium salts

Boekelheide and coworkers[152] have found the Stevens rearrangement with subsequent elimination of the sulphur moiety a general method for the synthesis of cyclophanedienes or the corresponding tautomeric

dihydropyrenes. Thus, reaction of *m*-xylylene dimercaptan with *p*-xylylene dibromide gave the dithiacyclophane **130** in 30% yield. Methylation, followed by treatment of the sulphonium salt with sodium hydride, yielded an isomeric mixture of the Stevens rearrangement product **131**. Methylation of **131** and subsequent E_2 elimination of the sulphonium salt furnished in good yield [2.2]metaparacyclophane-1,9-diene (**132**)[152c] (equation 100). Compounds prepared by this method are listed in Table 5. The Stevens rearrangement–elimination sequence is the current method of choice for the preparation of these strained cyclic molecules.

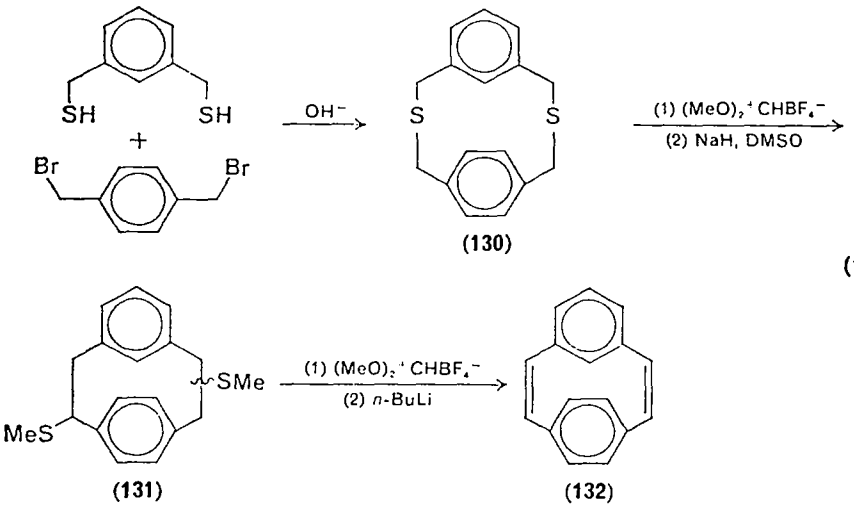
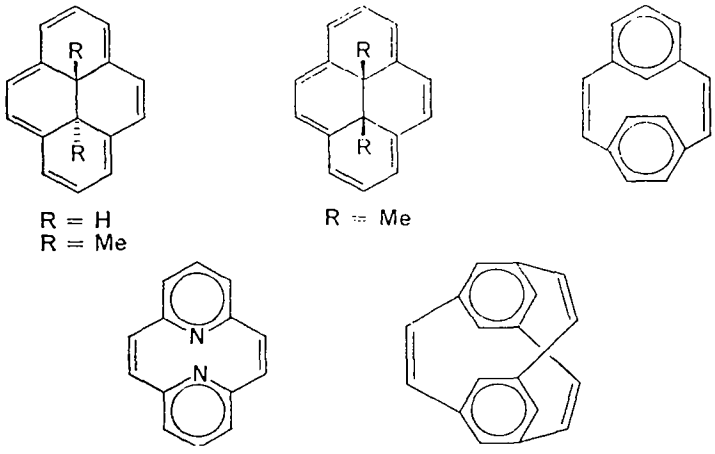
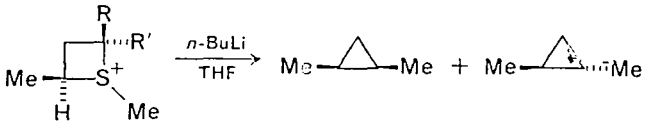


TABLE 5. Compounds prepared by Bockelheide and coworkers using the Stevens rearrangement–elimination sequence[152]



Trost and coworkers[153] have investigated the reaction of thietanonium salts (equation 101) with *n*-butyllithium to give cyclopropanes. The yields of cyclopropanes are only about 25%; however, high stereoselectivity was observed in the reactions. These desulphurization reactions, however, are not proposed[153] to proceed by a Stevens rearrangement.



(101)

R = Me, R' = H	10%	90%
R = H, R' = Me	87%	13%

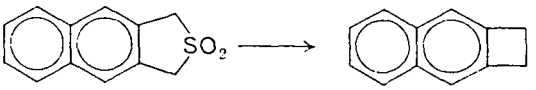
B. Extrusion of Sulphur Dioxide

1. Pyrolysis of sulphones

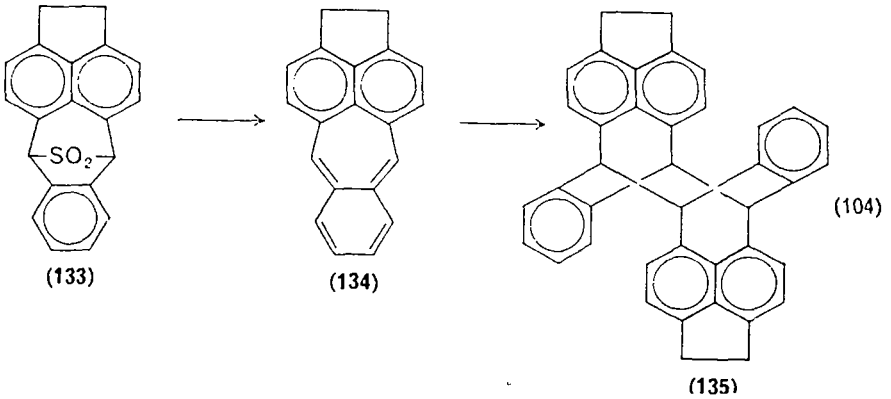
Sulphones are known[154] to undergo loss of sulphur dioxide upon thermolysis with formation of a new carbon—carbon bond between the atoms originally attached to sulphur (equation 102).

$$R{-}SO_2{-}R' \xrightarrow{\Delta} R{-}R' + SO_2 \qquad (102)$$

Cava and coworkers[155] employed this method in the synthesis of benzo- and naphthocyclobutenes (equation 103). When the sulphone **133** was pyrolysed, the dimer **135** of acepleiadene **134** was formed[156]. The spirobenzocyclobutene **137** was prepared in low yield by pyrolysis of the disulphone **136**[157].



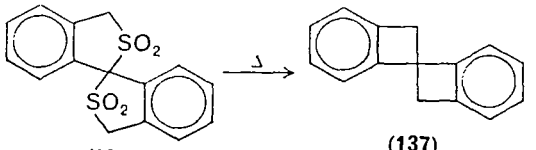
(103)



(133) (134) (135)

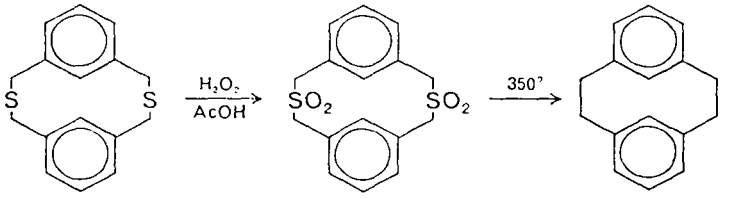
(104)

Extrusion of sulphur dioxide, therefore, appears to be a useful method for the formation of C—C bonds, bond formation often occurring intramolecularly to yield ring compounds. Cava also observed that extrusion of sulphur dioxide could be effected photolytically[158].



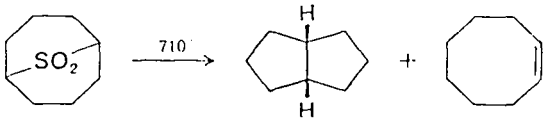
(136) (137) (105)

Vögtle has used a similar approach involving dithiacyclophane **138** intermediates for the preparation of a series of cyclophanes[159]. Extrusion of sulphur was effected by thermolysis of the corresponding sulphones **139** (equation 106); however, the yields in this step were generally low. Cyclophanes prepared by this method are listed in Table 6.



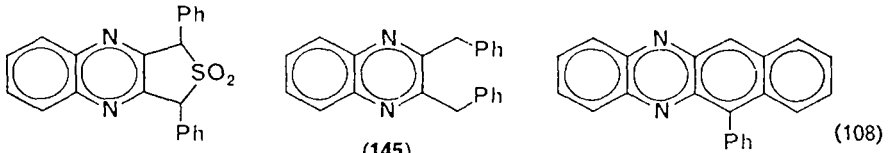
(138) (139) (140) (106)

Upon pyrolysis of sulphone **141**, a mixture of bicyclic compound **142** and cyclooctene **143** was obtained[161].



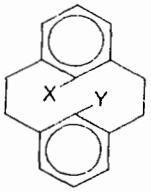
(141) (142) 45% (143) 10% (107)

Pyrolysis of the quinoxaline **144** lead to the formation of mixtures in which **145** and **146** were the major products. None of the desired product, diphenylcyclobuta[b]-quinoxaline, was observed[162].

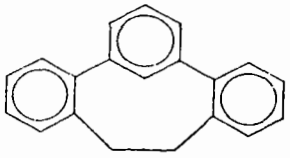


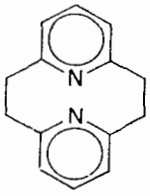
(144) (145) (146) (108)

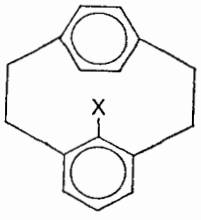
TABLE 6. Cyclophane derivatives prepared by sulphone thermolysis[159, 160]



X	Y
H	H
H	F
F	F
H	Cl

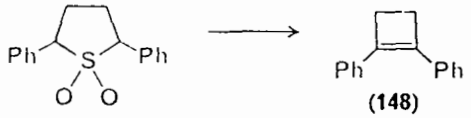






X = H or F

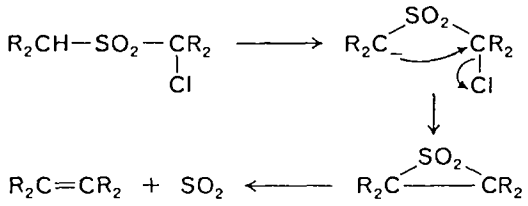
The conversion of the sulphone **147**, upon treatment with ethyl magnesium bromide, to 1,2-diphenylcyclobutene (**148**) in moderate yield has been reported[163]. Reactions of other sulphones gave mixtures of olefins[164].



(147) (148) (109)

2. Ramberg–Bäcklund reaction

Extrusion of sulphur dioxide occurs when an α-halosulphone possessing an α′ hydrogen is treated with base; the resulting product is an olefin (equation 110). This reaction, known as the Ramberg–Bäcklund reaction, effects joining by an olefinic bond of the two groups initially attached to the sulphone function. The mechanism of the reaction has been discussed in recent reviews[165].



(110)

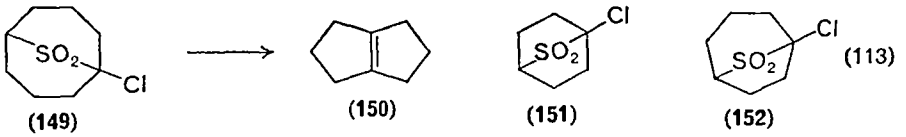
Homologization of an olefin has been accomplished[166] by a sequence (equation 111) involving radical addition of hydrogen sulphide, chloromethylation of the resulting thiol, oxidation to the sulphone and application of the Ramberg–Bäcklund reaction. Use of other aldehydes in place of formaldehyde in the chloromethylation step led to lower yields of olefin[166b].

$$R_2C{=}CH_2 \xrightarrow[h\nu]{H_2S} R_2CHCH_2SH \xrightarrow[HCl]{CH_2O} R_2CHCH_2SCH_2Cl \longrightarrow$$
$$R_2CHCH_2SO_2CH_2Cl \longrightarrow R_2CHCH{=}CH_2 + SO_2 \qquad (111)$$

The fact that exchange of the α′-hydrogen occurs at a faster rate than elimination of the α-chloro group allows the synthesis of deuterated olefins when the reaction is carried out in D_2O (equation 112)[166b].

$$R_2CSO_2CH_2R \xrightarrow[D_2O]{NaOD} R_2CSO_2CD_2R \longrightarrow R_2C{=}CDR \qquad (112)$$
$$\quad\;\; | \qquad\qquad\qquad\quad |$$
$$\quad\;\; Cl \qquad\qquad\qquad\quad Cl$$

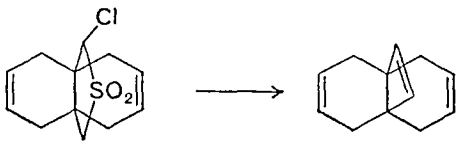
The Ramberg–Bäcklund reaction has proven[5,161] to be the method of choice for the preparation of $\Delta^{1,5}$-bicyclo[3.3.0]octene (**150**). The α-chloro sulphones **151** and **152** failed to give, however, the desired bicyclic olefins.



(113)

(149) (150) (151) (152)

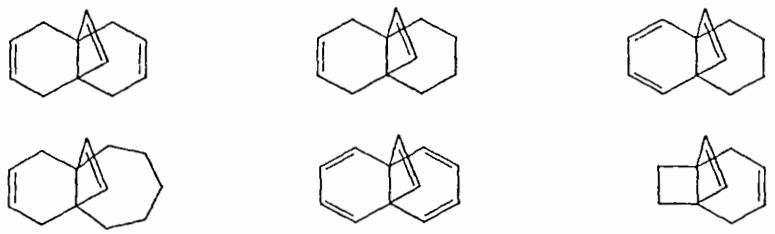
Paquette and coworkers[167] have synthesized some unsaturated propellanes by use of the Ramberg–Bäcklund reaction. Thus, treatment of the α-chloro sulphone **153** with potassium *t*-butoxide in THF led to the formation of [4.4.2]propella-3,8,11-triene (**154**). Propellanes prepared by this method are listed in Table 7.



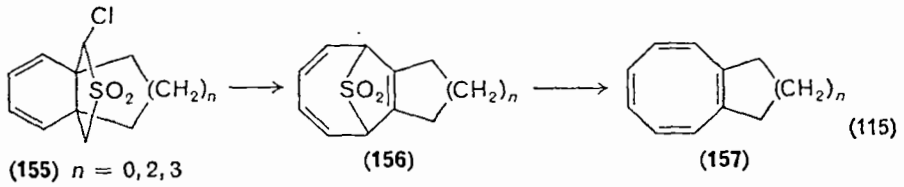
(114)

(153) (154)

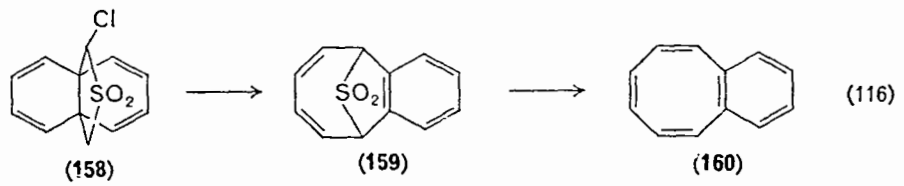
TABLE 7. Propellanes prepared by the Ramberg–Bäcklund reaction[167]



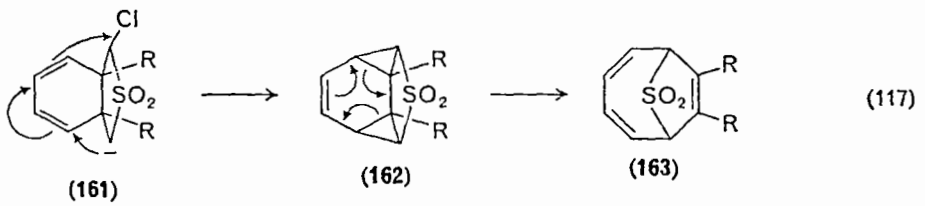
An usual course of the reaction has been observed[168] in which α-chloro sulphones **155** and **158** yielded the cyclooctatriene-bridged sulphones **156** and **159**. Photolysis of **156** and **159** led to formation of the corresponding cyclooctatetraenes **157** and **160**. This rearrangement is thought[168] to proceed by a bishomoconjugative 1,8 displacement (**161**) of the chloro group to give the dicyclopropylsulphone **162**, followed by a $[\sigma 2_s + \sigma 2_s + \pi 2_s]$ electrocyclic process to yield the cyclooctatriene **163** (equation 117).



(155) $n = 0, 2, 3$ (156) (157) (115)



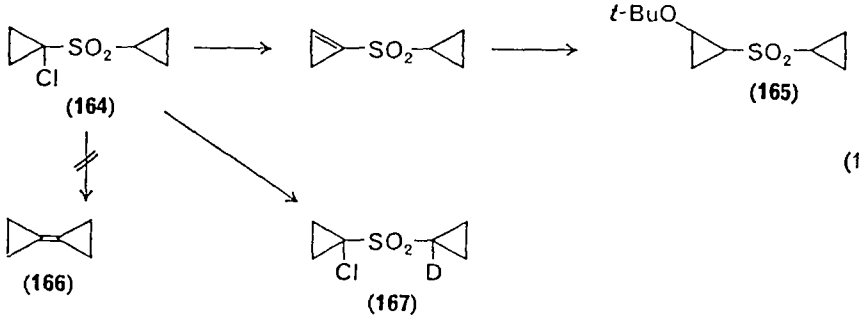
(158) (159) (160) (116)



(161) (162) (163) (117)

Attempts to prepare bis-cyclopropylidene (**166**) by treatment of the sulphone **164** with potassium *t*-butoxide in THF did not cause

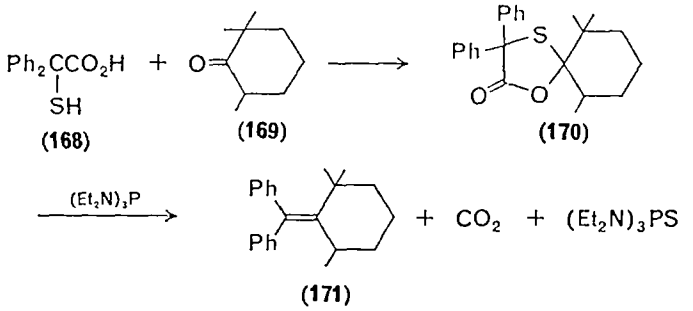
elimination of sulphur dioxide, but rather E_2 elimination of chloride followed by conjugate addition of alcohol to the unsaturated sulphone to give **165**[169]. This result is probably due to the unreactive nature of cyclopropyl halides towards displacement; the requisite carbanion was apparently formed at the α' carbon as evidenced by formation of **167** upon hydrogen–deuterium exchange.



(118)

C. Miscellaneous Extrusion Reactions

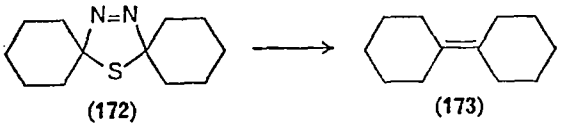
Barton and coworkers[170] have developed novel twofold extrusion processes for the synthesis of hindered olefins. For example, when the oxathiolan-5-one **170**, prepared from thiobenzilic acid (**168**) and ketone **169**, was treated with tris-(diethylamino)phosphine an 80% yield of the hindered olefin **171** was obtained[170a]. This method, however, only appears to be applicable if a phenyl group is present to facilitate loss of carbon dioxide.



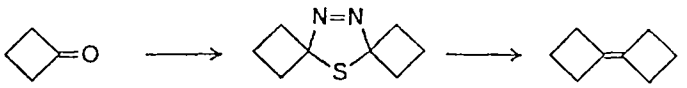
(119)

A second example[170b] of a twofold extrusion reaction is the formation of bis-cyclohexylidene (**173**) upon treatment of the azosulphide **172** with triphenylphosphine. The azosulphide **172** was prepared by reaction of cyclohexanone with hydrogen sulphide and hydrazine followed by oxidation with lead tetraacetate. This method has been employed[171] for the synthesis of bis-cyclobutylidene (equation 121).

The extrusion of the sulphoxide function has been observed[172] upon treatment of benzylic sulphoxides with phenyllithium; however, isomeric

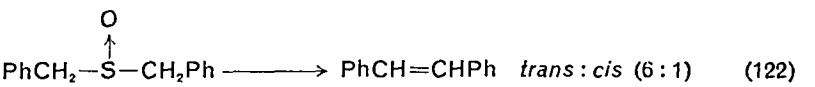


(172) (173) (120)



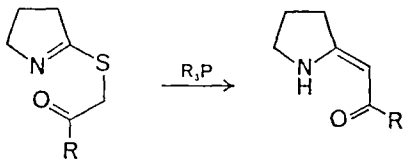
(121)

product mixtures of olefins are normally obtained (equation 122). Episulphides are reported to be intermediates in the reaction.



(122)

Eschenmoser and coworkers have developed an elegant sulphur extrusion reaction in conjunction with the synthesis of vitamin B_{12}[173]. While the enamide sulphide employed in the reaction is obtained from a thioamide, mention is made here as this method proved to be most valuable in the vitamin B_{12} synthesis. A general scheme for the sulphur extrusion reaction is shown below (equation 123).



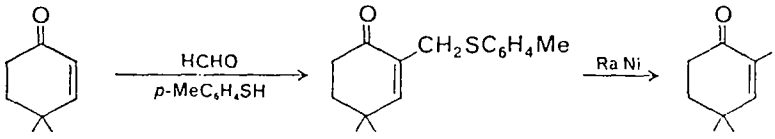
(123)

VII. MISCELLANEOUS SYNTHETIC USES OF THIOLS

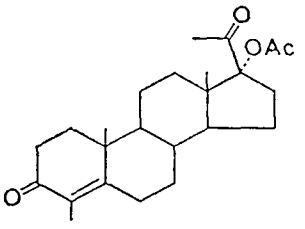
A. Methylation of α, β-Unsaturated Ketones

Methylation of α,β-unsaturated ketones under normal conditions usually leads to a mixture of as many as four products, the monomethyl, dimethyl, trimethyl and tetramethyl derivatives (the latter two being β,γ-unsaturated)[174,175]. A method which minimizes this problem and leads to generally high yields of α-methyl-α,β-unsaturated ketones has been developed[175]. The unsaturated ketone is condensed with formaldehyde and *p*-toluenethiol in the presence of triethylamine to give the α-*p*-toluenethiomethyl-α,β-unsaturated ketone. Desulphurization with deactivated Raney

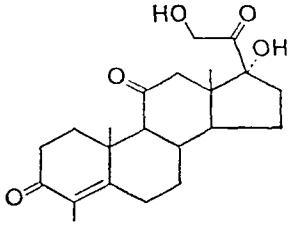
nickel gives the desired monomethyl product. A simple example of the use of this method is the conversion of 4,4-dimethyl-2-cyclohexenone to 2,4,4-trimethyl-2-cyclohexenone[176] in 60% overall yield (equation 124). Compounds **174** and **175** are two of the numerous successful examples of products from this reaction in the steroid field[175].



(124)



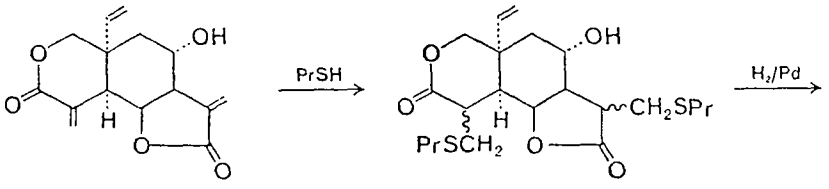
(174)



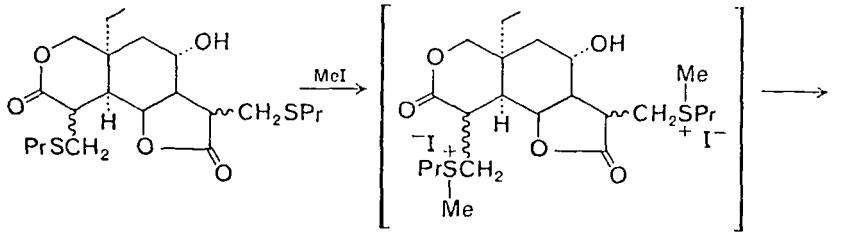
(175)

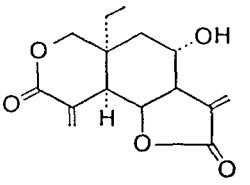
B. Blocking of Conjugated α-Methylene Groups in Esters

During a recent study of vernolepin (**176**), selective hydrogenation of the vinyl group was desired[177]. It was found that if the vernolepin was stirred with 1-propanethiol in pH 9·2 buffer the bis-1-propanethiol adduct (**177**) was obtained. After hydrogenation, the protecting group could be removed by methylation to the sulphonium salt followed by hydrolysis (equation 125). That the α-methylene groups need not be in a lactone ring was demonstrated[178] by the zinc–copper couple reduction of elephantopin *via* the bis-1-propanethiol adduct to deoxyelephantopin (equation 126). Although the overall yield was only 5%, this conversion could not be effected without saturating the conjugated methylene of the lactone unless this site was blocked.

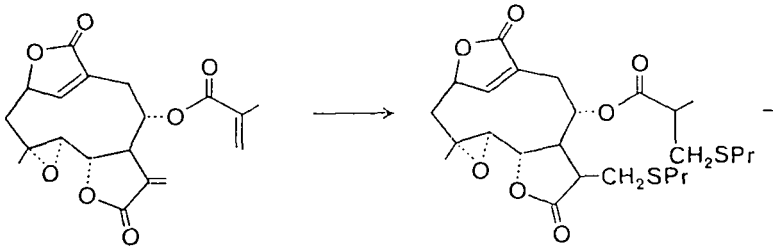


(176) (177)

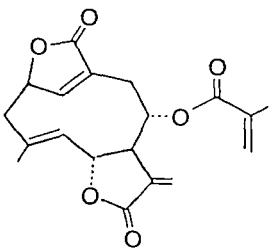




(125)



(126)

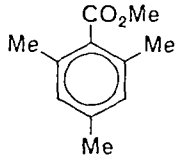


C. Cleavage of Sterically Hindered Methyl Esters

It was shown in a mechanistic study by Vaughan and Bauman[179] that sodium *n*-propyl mercaptide in dimethylformamide would cleave esters by an S_N2 process. However, the modification of the conditions to use lithium *n*-propyl mercaptide in hexamethylphosphoramide has greatly enhanced the effectiveness of the reaction[180]. The reaction is usually run by dissolving the ester in a mercaptide reagent of known concentration prepared by the action of lithium hydride on 1-propanethiol (equation 127). The hindered esters which have been investigated (with the yields of the

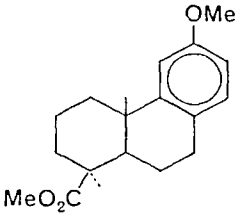
$$RCOCH_3 \xrightarrow[HMP]{LiSC_3H_7} RCOH + CH_3SC_3H_7 \qquad (127)$$

acid, shown in parentheses) include methyl mesitoate (**178**), methyl triisopropyl acetate (**179**), methyl O-methylpodocarpate (**180**) and methyl 3β-acetoxy-5-androstene-17β-carboxylate (**181**).

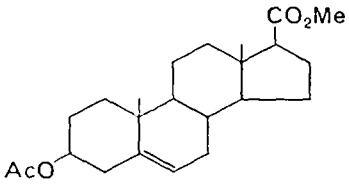


(178) (100%)

(*i*-Pr)$_3$CCO$_2$Me
(179) (99%)



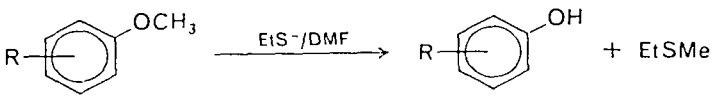
(180) (100%)



(181) (92%)

D. Cleavage of Aryl Methyl Ethers

When acid-sensitive groups are present on an ether which is to be cleaved, nucleophilic reagents offer the alternative to the usual strong acid cleavage. The discovery[181] that ethyl mercaptide ion in hot dimethylformamide effects a rapid cleavage of aryl ethers provides a nucleophilic method of great promise (equation 128). The substituents on the aromatic ring include 3-methyl-2-*t*-butyl-, 4-bromo-3-methyl-[181] and those of compound **180**[180]. In all the cases studied the yields were nearly quantitative.

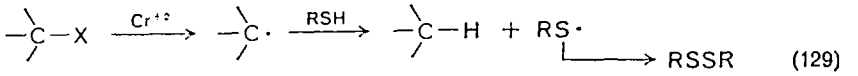


(128)

E. Dehalogenations

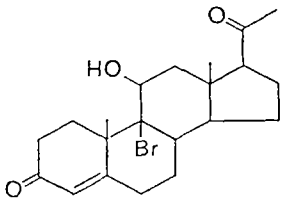
It has been noted that halogen compounds (usually bromides or iodides) are reduced by chromous ion in the presence of a hydrogen donor[182]. Although numerous donors have been tried, thiols seem superior to all

others. This reaction probably involves a radical mechanism similar to that shown in equation (129). Thus compounds **183**[182] and **184**[183a] were

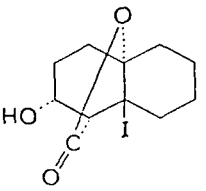


(129)

dehalogenated with chromous acetate in the presence of any of the simple thiols in yields exceeding 80%.

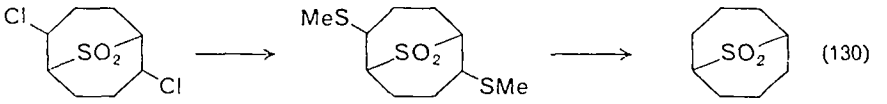


(183)



(184)

An example[193b] of the use of a thiol to effect hydrogenolysis is shown by removal of the chloro groups in the chlorosulphone **185** by nucleophilic displacement with methyl mercaptide to give **186**, followed by Raney nickel desulphurization. Attempts to remove the chloro groups by use of other reducing agents failed.

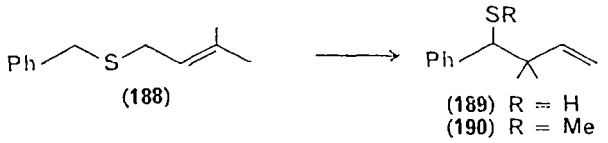


(185) (186) (187) (130)

F. Use of α-Sulphenyl Carbanions

The generation of a carbanion α to sulphur is a known process and has been of synthetic use. Some recent work of current interest is reported herein.

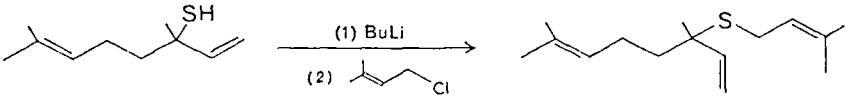
Treatment of the allyl benzyl sulphide **188**, as reported by Rautenstrauch[184], with *n*-butyllithium effects a [2,3] sigmatropic rearrangement to give good yield of thiol **189**. Addition of methyl iodide to the reaction mixture furnishes the sulphide **190**. The synthesis of isoprenoids related to squalene has been accomplished using this method; however, a mixture (≈2 : 3) of geometrical isomers was obtained showing the non-stereospecificity of this procedure[184] (equation 132). This rearrangement is related to the [2,3] sigmatropic rearrangement of allyl sulphonium salts (section VI.A.1), and of allyl ethers.



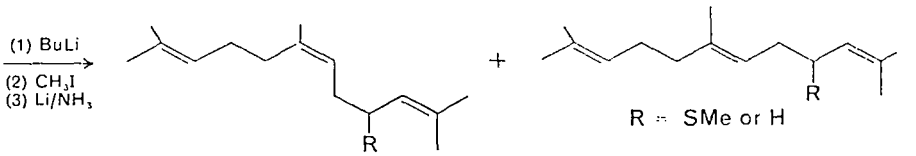
(188)

(189) R = H
(190) R = Me

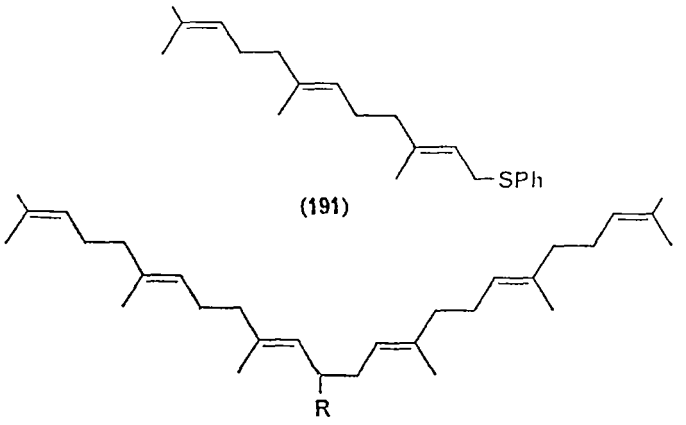
(131)



(132)



Alkylation of carbanions derived from allyl thioethers has been used by Biellmann and Ducep[185] as an excellent method for the synthesis of squalene (**193**). Farnesyl phenyl sulphide (**191**), upon treatment with *n*-butyllithium in THF followed by alkylation with farnesyl bromide, gave 12-phenylthiosqualene (**192**) in 82% yield. Treatment of **192** with lithium in ethylamine gave squalene (**193**) in 70% yield (equation 133). It has been shown that no isomerization of the double bond adjacent to the carbanion occurs during the reaction; however, substitution of an alkyl group at the allylic carbon renders this method inoperative[185]. Application of this method in the synthesis of pentacyclic triterpenoids has been reported[186].

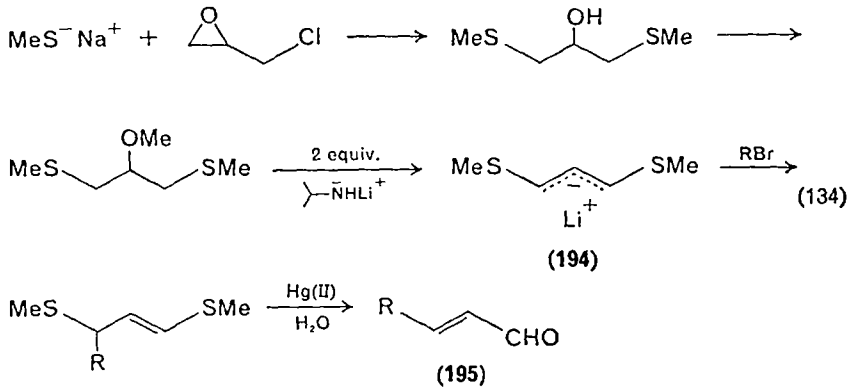


(191)

(133)

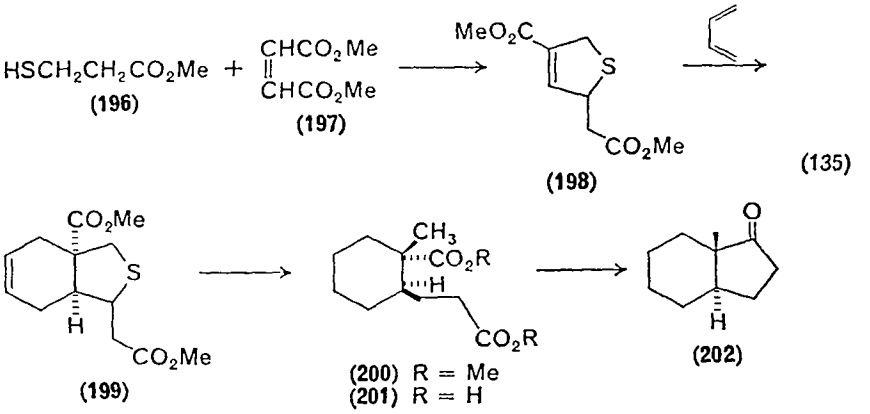
(192) R = PhS
(193) R = H

Corey and coworkers[187] have reported the use of 1,3-bis(methylthio)allyllithium (**194**) as a useful reagent for introduction of a —CH=CH—CHO unit into a molecule. The lithium reagent **194** was prepared from methanethiol as shown in equation (134). Alkylation of **194** with an alkyl halide or epoxide, followed by hydrolysis employing Hg(II) salts, yields an β-alkyl-α,β-unsaturated aldehyde **195**. The use of **194** in the synthesis of prostaglandin F_2 has been reported[188].



G. Synthesis of trans-Fused Bicyclic Ring Systems

Stork and Stotter[189] have reported the use of a thiol derivative in a stereospecific synthesis of *trans*-fused bicyclic ring compounds. The dihydrothiophene **198** was prepared in three steps from methyl β-mercaptopropionate (**196**) and dimethyl maleate (**197**). Diels–Alder addition of **198** to butadiene yielded **199**, which gave the diacid **201** upon Raney nickel desulphurization and hydrolysis. Cyclization of the diester **200** would give a *trans*-fused hydrindane **202**.



H. Synthesis Using Methyl Methylthiomethyl Sulphoxide

A synthesis of aldehydes employing methyl methylthiomethyl sulphoxide (**203**) has been reported[190]. The sulphoxide **203** was prepared[191] by reaction of methanethiol with formaldehyde to give formaldehyde mercaptal, followed by oxidation with one equivalent of hydrogen peroxide in acetic acid (equation 136). Treatment of **203** with sodium hydride in tetrahydrofuran generated the corresponding carbanion, which upon alkylation with an alkyl halide yielded the substituted sulphoxide **204**. Hydrolysis of **204** occurred under mild acidic conditions to give aldehyde **205** and dimethyl disulphide (equation 137). This method has proven useful for the synthesis of labile aldehydes[190].

$$CH_3SCH_2SCH_3 \xrightarrow[AcOH]{H_2O_2} CH_3SCH_2\overset{O}{\overset{\uparrow}{S}}CH_3 \quad \textbf{(203)} \qquad (136)$$

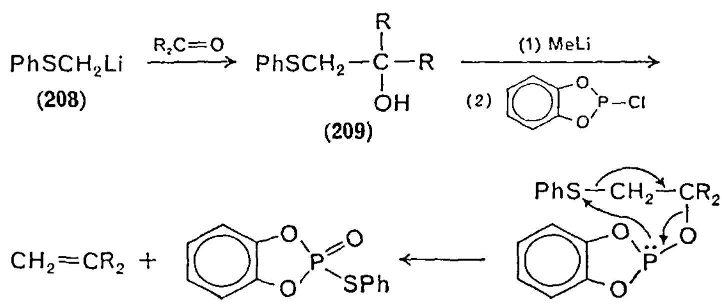
$$\underset{\textbf{(203)}}{MeSCH_2SOMe} \xrightarrow[(2)\ RX]{(1)\ NaH} \underset{\textbf{(204)}}{MeS\underset{R}{\underset{|}{C}}HSOMe} \xrightarrow{H^+} \underset{\textbf{(205)}}{RCHO} \qquad (137)$$

Methyl methylthiomethyl sulphoxide also undergoes condensation with aromatic aldehydes[190] to give 1-methylsulphinyl-1-methylthio-2-arylethylenes (**206**). Hydrolysis of **206** provides a useful route for the preparation of phenylacetic acid derivatives (**207**).

$$\underset{\textbf{(203)}}{MeSCH_2SOMe} \xrightarrow[Triton\ B]{ArCHO} \underset{\textbf{(206)}}{(Ar)(H)C{=}C(SMe)(SOMe)} \xrightarrow[ROH]{H^+} \underset{\textbf{(207)}}{ArCH_2CO_2R} \qquad (138)$$

I. Olefin Synthesis

A synthesis of olefins has been effected[192] by the reaction scheme outlined below (equation 139). Reactions of the lithium derivative **208** with

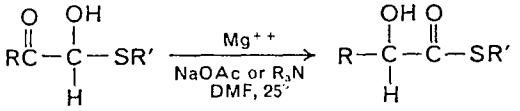


(139)

a carbonyl compound leads to the alcohol **209**, which upon sequential treatment with methyllithium and *o*-phenylene phosphorochloridite yielded olefin in yields of 70–90%. A similar olefin synthesis using sulphoxides in place of sulphides has been reported[193].

J. Preparation of α-Hydroxythiolesters

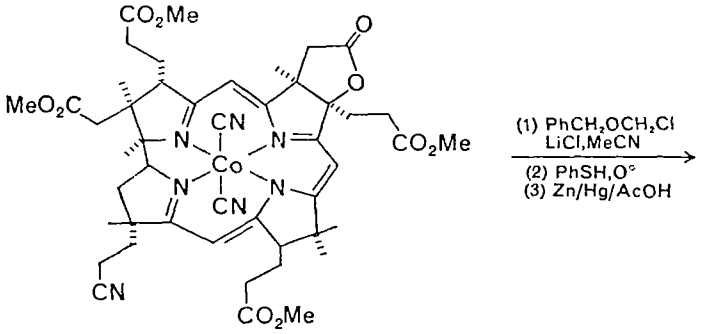
The conversion of α-ketohemimercaptals to α-hydroxythiolesters (equation 140) is mentioned as an alternate route for the preparation of α-hydroxycarboxylic acids[194]. This rearrangement, which in effect exchanges a hydroxyl and carbonyl group, requires catalysis by a metal ion and a base and proceeds in high yield.



(140)

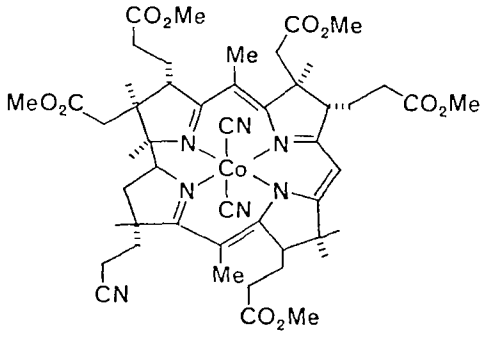
K. Methylation

In the Woodward–Eschenmoser synthesis of vitamin B_{12}, methylation of the corrin ring was carried out using chloromethyl phenyl sulphide



(210)

(141)

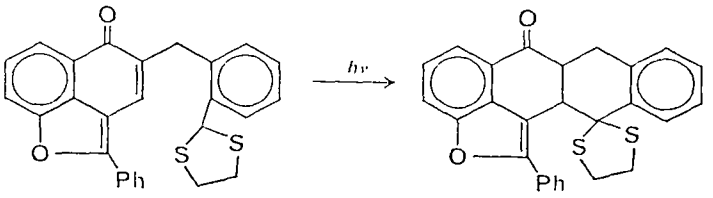


(211)

followed by reduction with Raney nickel[195]. Likewise, methylation at the 5 and 15 positions of the important intermediate **210** was effected by treatment with benzyl chloromethyl ether, thiophenol and zinc amalgam to give **211**[196].

L. Photocyclization of Dithioacetals

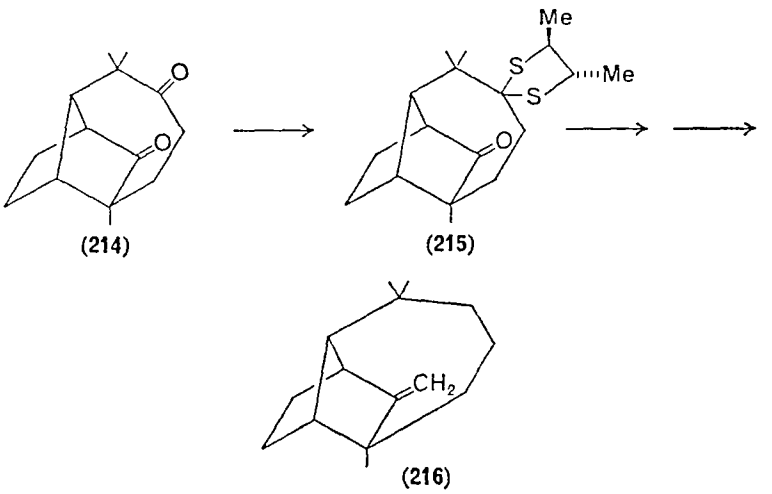
Barton and coworkers[197] have reported photocyclization of the dithioacetal **212** to give the tetracycle **213** in good yield. The reaction is applicable also with the monothioacetal and the ethylene acetal.



(212) (213) (142)

M. Resolution of Ketones

Corey and coworkers[26] have used an optically active dithiol as a reagent for the resolution of ketones. For example, in the total synthesis[198] of longifolene (**216**), the ketone **214** was converted into a diasteromeric mixture by reaction with L(+)-2,3-butanedithiol. Following resolution, the desired isomer **215** was subsequently converted to (+)-longifolene (**216**).



(214) (215) (143)

(216)

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The Chemistry of the Thiol Group
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CHAPTER 13

Biochemistry of the thiol group

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I. INTRODUCTION*

The stench of a rotten egg or the smell of smouldering hair should be enough to convince anyone that reduced sulphur is prevalent in biological materials. Essentially all of the divalent sulphur in living systems can be considered as an organic thiol or a derivative thereof. A wide spectrum of biological phenomena is believed to be somehow dependent on thiols and thiol derivatives. In fact the functional group concept, as it has been developed in biochemistry, has been largely concerned with thiols. No other chemical entity has been subjected to more experimental scrutiny or generated more mechanistic speculation by the biochemist.

Two factors probably account for this great fascination with thiol function. The first is the relative ease with which the reactions of this group can occur at moderate temperature and neutral pH. Other biologically available functionalities are not nearly so reactive under physiological conditions. The thiol is therefore usually a prime candidate for the functional centre of almost any biological molecule. The second factor is the ease and specificity with which the thiol can be modified. Certainly more specific reagents are available for sulphydryl groups and

* The following abbreviations are employed in this chapter: ACP, acyl carrier protein; ADP, adenosine diphosphate; AMP, adenosine monophosphate; APS, adenosine phosphosulphate; ATP, adenosine triphosphate; CoA or CoASH, coenzyme A; FAD, flavin adenine dinucleotide; $FADH_2$, reduced flavin adenine dinucleotide; FH_4, tetrahydrofolic acid; FMN, flavin mononucleotide; GDP, guanosine diphosphate; GSH, glutathione; GSSG, disulphide of glutathione; GTP, guanosine triphosphate; HiPIP, high potential iron protein; ITP, inosine triphosphate; m-RNA, messenger ribonucleic acid; NAD^+, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; $NADP^+$, nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide dinucleotide phosphate; NHI, nonhaem iron; PAP, phosphoadenosine phosphate; PAPS, phophoadenosine phosphosulphate; SAM, S-adenosyl methionine; TPP, thiamine pyrophosphate; t-RNA, transfer ribonucleic acid.

since thiol roles are more frequently tested for, they are more frequently found. In the majority of cases the nature of the thiol involvement has remained largely undefined although postulates are more than ample. There are now enough well-characterized examples of specific thiol participation in catalytic, structural and protective roles to establish it as one of the most important functional groups in biochemistry.

Two facets of thiol group biochemistry will be considered in this chapter. The first concern is the metabolic transformations of the sulphur whereas the second aspect is the functional roles in which thiols or thiol derivatives participate. Fortunately there is a high degree of specialization among thiol biochemicals and each function can pretty well be equated with a particular class of thiol or thiol derivative. Thus the organization of the material has taken the form of a taxonomic listing of biologically important thiols. It begins with the small and relatively simple thiol amino acids, progresses through peptide and nucleotide cofactors, protein-bound prosthetic groups and finishes with complex thiol proteins.

Within this framework the biochemical formation, reaction and significance of thiols, dithiols, disulphides, persulphides, thioesters, thioethers, sulphonium ions and metallothiol complexes are discussed. Energy trapping, electron transport, acyl and alkyl group transfer, structural stabilization and detoxification are among the functional areas in which the thiol group is indispensable.

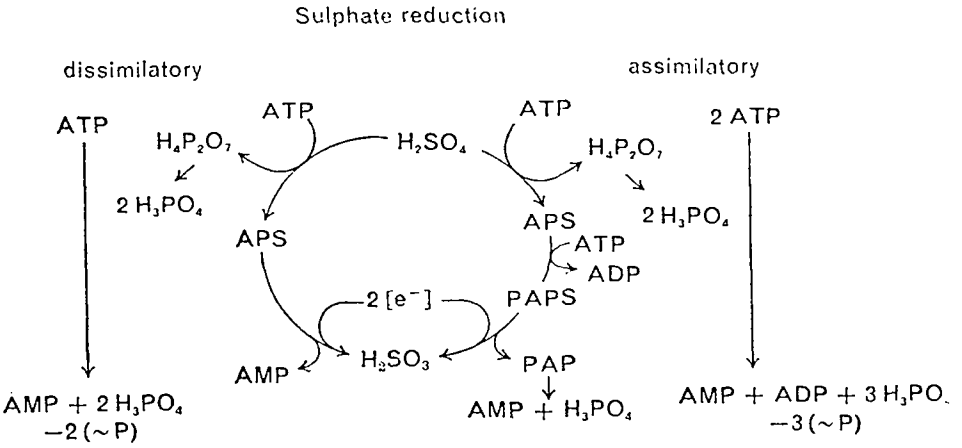
II. THIOL METABOLISM

A. Reduction of Sulphate to Divalent Sulphur[1,2,3]

Most sulphur entering the biosphere is in the form of inorganic sulphate. In order to form organic thiol compounds, the sulphate must be reduced to sulphide. Sulphate reduction is carried out by plants and a variety of microorganisms. Animals are not capable of reductive sulphate assimilation and are therefore dependent on dietary sources for reduced sulphur. Two forms of biological sulphate reduction are commonly differentiated. The assimilatory type of sequence operates on a relatively small scale and supplies an organism's need for sulphur amino acids. It is the type of system found in the majority of sulphate reducing organisms. The dissimilatory pathway is found in a small number of microorganisms which link the reduction of sulphate to the oxidation of organic metabolites for energy production. Actually the reaction pathways for sulphur are quite similar in both the assimilatory and dissimilatory organisms with the differences residing primarily in the mechanisms utilized for supplying the reducing equivalents.

I. Sulphate reduction to sulphite

In both assimilatory and dissimilatory sequences sulphate is first reduced to sulphite or some enzyme-bound equivalent. The pathways for this apparently simple two-electron reduction are actually quite complex and differ somewhat between assimilatory and dissimilatory organisms. Sulphate first reacts with adenosine triphosphate (ATP), pyrophosphate is eliminated, and a mixed organophosphate-sulphate anhydride, adenosine phosphosulphate (APS), is formed. A rapid hydrolysis of pyrophosphate serves to drive the reaction, but the process is still not thermodynamically favourable and APS does not accumulate significantly. APS is directly reduced in dissimilatory organisms with the production of adenosine monophosphate (AMP), and sulphite. In the assimilatory pathway APS reacts with an additional ATP to produce phosphoadenosine phosphosulphate (PAPS); phosphate being added to the 3′ hydroxyl group of the ribose. Only through this coupling to the expenditure of a third 'high energy phosphate bond' * does the sulphate activation system become thermodynamically favourable. PAPS is then reduced, generating sulphite and releasing phosphoadenosine phosphate (PAP). The assimilatory and dissimilatory modes of sulphate reduction are summarized below with the biological energy consequences expressed as consumption

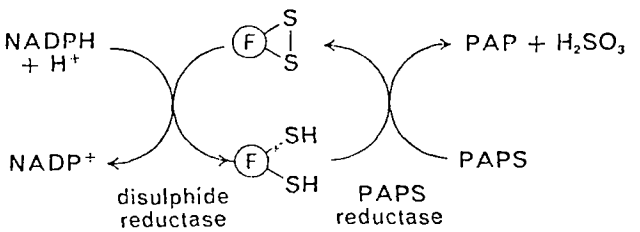


* The phosphate anhydride bonds of ATP are the energy quanta of biochemical systems, their highly exergonic free energy of hydrolysis being coupled to endergonic processes. They are commonly referred to as 'high energy phosphate bonds', a terminology used to imply a high transfer potential and not a high bond energy in the usual chemical sense. The number of high energy phosphate bonds expended in a biosynthetic sequence is a measure of the energetic cost of that process to the cell.

of high energy phosphate bonds, these being symbolized in the scheme below as (~P). While it is not obvious why these differing modes for sulphate reduction are employed by assimilatory and dissimilatory organisms the advantage of a less 'expensive' pathway for those bacteria which utilize sulphate reduction for ATP production can be appreciated.

The system supplying electrons for the reduction of sulphate to sulphite is most clearly worked out in the case of the assimilatory pathway. The ultimate electron donor is reduced nicotinamide adenine dinucleotide phosphate (NADPH), but three separate protein factors are involved. One of these is a heat-stable protein factor of about 10,000 molecular weight, represented in the scheme below as Ⓕ. The active centre of this factor is a disulphide which is reduced by NADPH through the action of one of the heat-labile enzyme fractions. The resulting dithiol form of the heat-stable factor then serves as reductant for PAPS. This is catalysed by a second enzyme, the true PAPS reductase.

Sulphate reductase pathway



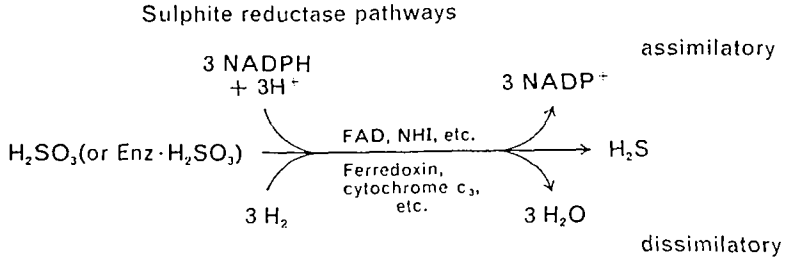
This is an example of a class of biological reductions mediated through low molecular weight protein dithiol–disulphide cofactors, the thioredoxins, to be discussed in a subsequent section. It has also been suggested that the dithiol might act as a carrier for a bound form of sulphite and that free sulphite is not actually involved in the overall reduction sequence[4].

In dissimilatory organisms the APS reductase system is less well defined. In *Desulphovibrio* electron flow from hydrogen appears to proceed through a ferredoxin (or flavodoxin) and cytochrome-cc'_3 electron transport sequence, somehow coupled to ATP synthesis[5].

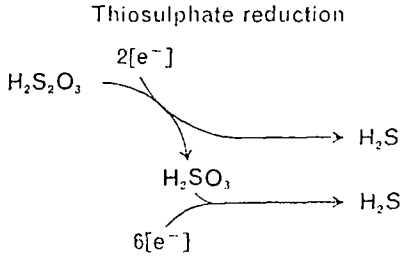
2. Sulphite reduction to sulphide

The six-electron reduction of sulphite to sulphide occurs as a single reaction with no evidence for any intermediate stages. A single enzyme or multienzyme aggregate appears to be responsible for this reaction. Although its exact nature may vary somewhat from species to species it is a complex enzyme containing a number of electron transport cofactors.

The yeast sulphite reductase contains flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), nonhaem iron (NHI) and possibly haem iron[6]. All of these carriers presumably participate in the passage of electrons from NADPH to sulphite. In dissimilatory organisms the electron-transporting system involves ferredoxin and cytochrome c_3, but a concerted six-electron reduction of sulphite to sulphide also occurs. Just how one- and two-electron transport carriers can provide for a six-electron reduction without any intermediate reduction states is unclear. This problem is not unique to sulphur reduction as a similar six-electron step occurs in the reduction of nitrite to ammonia.



Thiosulphate can also serve as a sulphide source, but it does not seem to play a critical role in the sulphur metabolism of most organisms. The two sulphurs are not equivalent and the reaction sequence is best viewed as an initial two-electron reduction to sulphide and sulphite with the sulphite then proceeding to sulphide through the sulphite reduction systems.



B. Metabolism of Cysteine and Other Thiols

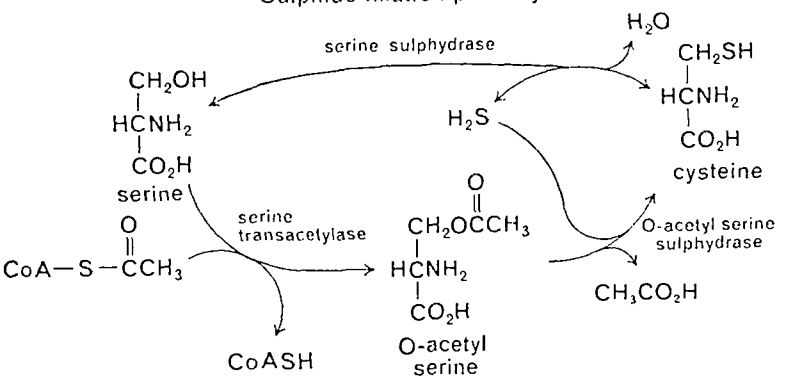
1. Sulphide assimilation[1,2]

Sulphide entry into organic linkage is through a reaction with serine to form cysteine, the central compound of intermediary thiol metabolism. There has been some controversy over just how the sulphide sulphur is

condensed with serine. It presently appears that two different enzyme sequences are possible and both may operate in some organisms.

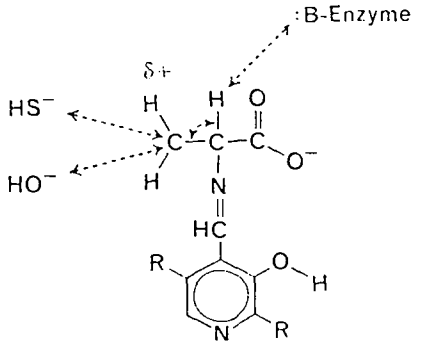
These are contrasted in the scheme below.

Sulphide fixation pathways



With the direct H_2S–H_2O interchange enzyme, serine sulphydrase, the reaction is completely reversible. Pyridoxal phosphate participates as an essential cofactor which suggests a mechanism involving a pyridoxamine–Schiff base intermediate. By stabilizing an electrophilic centre at the side chain carbon a nucleophilic substitution could be facilitated.

Serine sulphydrase intermediate



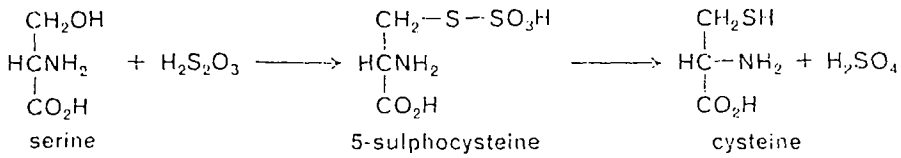
The reversibility of this reaction would allow this enzyme to participate in either sulphuration or desulphuration of cysteine and its real role *in vivo* remains somewhat doubtful.

The other system for sulphide assimilation involves a coupled hydrolysis of acetyl coenzyme A. This enzyme system can only operate in the direction of cysteine synthesis and would ensure the effective trapping of

most available sulphide for this purpose. The acetylation of the serine hydroxyl also provides an effective leaving group so that one might envisage an enzyme-mediated direct nucleophilic displacement mechanism. Pyridoxal cofactors are not thought to participate in the O-acetyl serine sulphydrase reaction, although this remains an unsettled question. The enzymes of the O-acetyl serine pathway are responsive to the metabolic needs of the cell being repressed by cysteine in *Escherichia coli*. There is a biochemical generalization that critical biosynthetic pathways such as this are normally coupled to high energy bond expenditure which guarantees effective utilization of nutrients. Such considerations make it likely that this is the normal biosynthetic route. Similar systems have not been found in all organisms capable of sulphide incorporation however, so an important role of the direct sulphide–hydroxyl exchange system in cysteine synthesis cannot be excluded. There is evidence for a similar system in chick embryo involving a serine phosphate rather than the acetate[7].

Cysteine formation through the addition of thiosulphate to serine or O-acetyl serine may play a role in the sulphur metabolism of some organisms. The reactions involved are similar in form to those described above, with S-sulphocysteine serving an intermediary role. Since thiosulphate is not generally considered to be on the main line of inorganic sulphur metabolism this probably represents an adaptation to certain special environments.

Cysteine formation from thiosulphate



2. Cysteine oxidation[1,2]

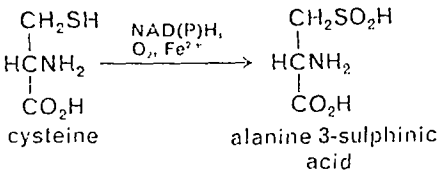
The balance of the 'sulphur cycle' requires that reduced sulphur derivatives eventually be reoxidized to sulphate. A number of photosynthetic and chemosynthetic organisms have the ability to utilize reduced sulphur, particularly H_2S, as critical electron donors for ATP production, but these pathways are not of enough general importance to consider here. Pathways are known for the production of sulphide from cysteine, and it is also clear that the oxidation of sulphide can occur in animals with production of sulphate and thiosulphate. What is not certain is to just what extent specific enzyme reactions are involved. The nonenzymatic

oxidation of sulphite is promoted by a variety of normal cellular constituents, but it is felt that direct sulphide oxidation is of little consequence for animals. Sulphide is an exceedingly toxic material, precluding its normal accumulation in significant amounts and the principal 'detoxification' route seems to be fixation into organic thiol compounds rather than oxidation.

All organic thiols and thiol derivatives are quite susceptible to aerobic oxidation yielding a variety of oxy-derivatives. Actually the biological significance of most of these sulphoxide derivatives is unknown. In certain instances, there are mechanisms to reduce sulphoxides back to divalent sulphur compounds. β-Lipoic acid, an active factor in bioassays, proved to be a sulphoxide derivative of this disulphide cofactor which was generated during purification[8]. Its biological activity implies that it can be reduced to the normal form of the cofactor. A methionine sulphoxide reductase system from yeast has been studied extensively and found to resemble the PAPS reductase and ribonucleotide reductase systems in that electron transport was mediated by a heat-stable protein disulphide factor[9]. Thus, there does seem to be some ability to salvage partially oxidized thiol derivatives, but it is uncertain how widespread this capacity might be.

The only thiol oxidation reaction to oxy-derivatives of general biochemical significance is that of cysteine to alanine 3-sulphinic acid (cysteine sulphinic acid)[1,10]. This is thought to be the initial reaction in the

Cysteine oxidase reaction

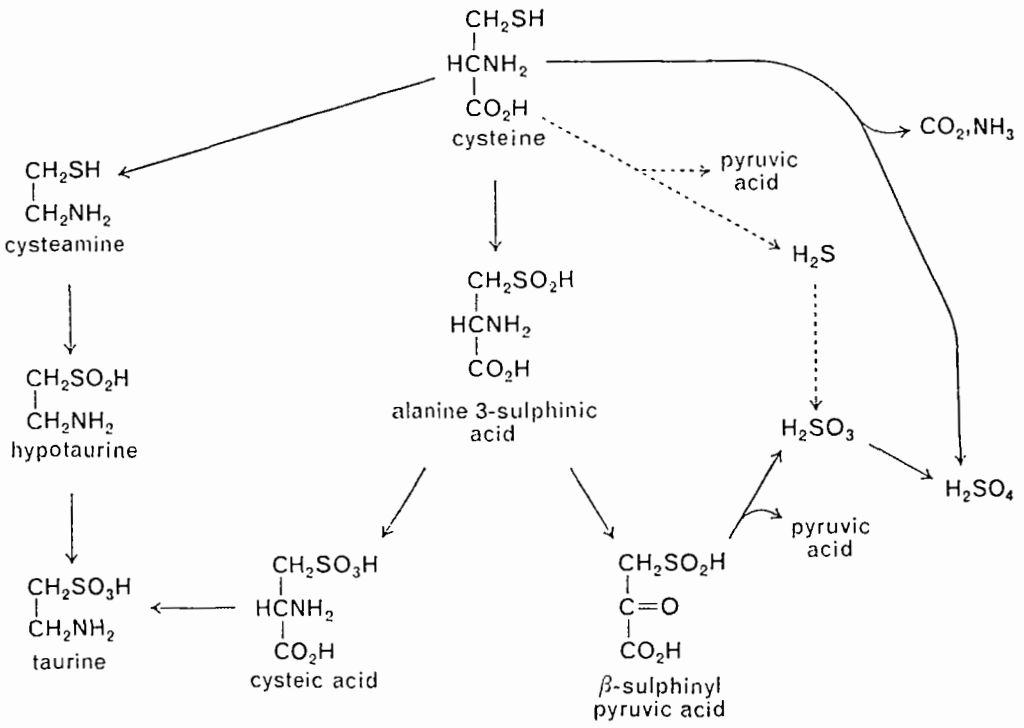


cysteine alanine 3-sulphinic acid

main pathway for the utilization of cysteine sulphur for sulphate production. Relatively little is known about the details of this oxidation process. Some form of reduced nicotinamide coenzyme, ferrous iron, and possibly other cofactors are required by an enzyme from the soluble fraction of rat liver. There is little information on mechanistic details or possible intermediate states. Cysteine sulphinic acid is further converted to what has been presumed to be β-sulphinyl pyruvic acid and ultimately to inorganic sulphite. This is then oxidized to sulphate. Cysteic acid and taurine may also arise from cysteine sulphinic acid.

There is also a mitochondrial system for cysteine oxidation to sulphate in which there are no known intermediates. It has been suggested that this system is important in cysteine metabolisms and the production of sulphate from sulphur amino acids. A sulphite oxidase deficiency has been reported in the human[11]. Since virtually no sulphate ions occurred in the urine, this would imply an obligatory role for this enzyme in the cysteine to sulphate conversion, and cast doubt on the role of the mitochondrial system. However, the sulphite oxidase is also a mitochondrial enzyme and might function in both pathways. A possible defect in cysteine oxidation has also been considered in another genetic disease, cystinosis. The cysteine to sulphate oxidation has, however, been shown to be normal in the liver of such patients[12]. Greater understanding of these processes should be forthcoming in conjunction with such studies on human genetic disease. The possible routes for the enzymatic oxidation of cysteine sulphur to oxy-acid derivatives are summarized below.

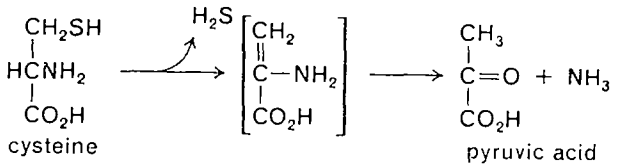
Possible cysteine oxidation pathways



3. Cysteine desulphuration[1,10]

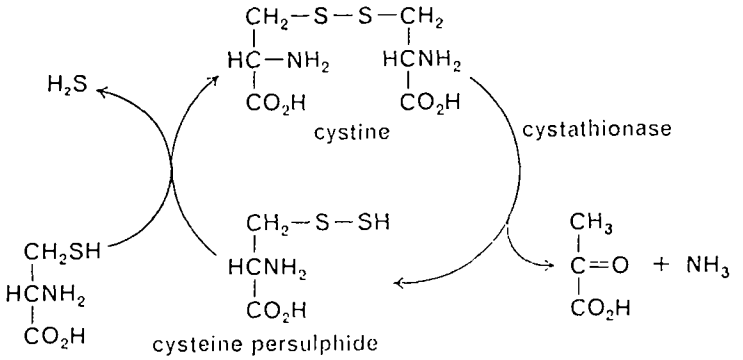
Desulphuration (desulphydration) of cysteine may play a role in thiol catabolism, but there is considerable confusion concerning the existence of a distinct cysteine desulphydrase.

Cysteine desulphydrase reaction



There is no doubt that such a reaction, catalysed by a pyridoxal phosphate-dependent enzyme, can occur in biological systems. It is quite possible, however, that this only represents a side reaction of other enzymes. Cystathionase, for example, will act on cystine with the elimination of a cysteine persulphide and pyruvate. The persulphide then reacts with cysteine to eliminate sulphide and regenerate cystine. The complete cycle would constitute a cysteine desulphydrase activity.

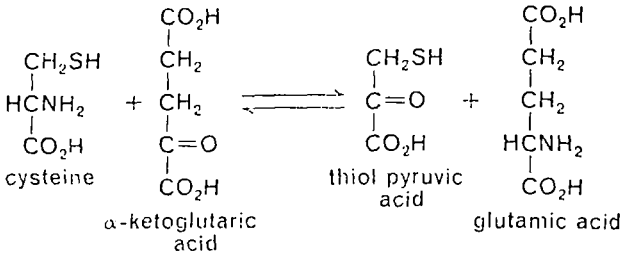
Cysteine desulphydrase activity via cystathionase and cystine



Cystathionase also has a low level of direct cysteine desulphydrase activity. Tryptophanase and tryptophan synthetase are other enzymes capable of carrying out the cysteine desulphydrase reaction. Such considerations have cast doubt on this biological significance of this reaction, although strong arguments have been presented for a true cysteine desulphydrase in *Salmonella*[13].

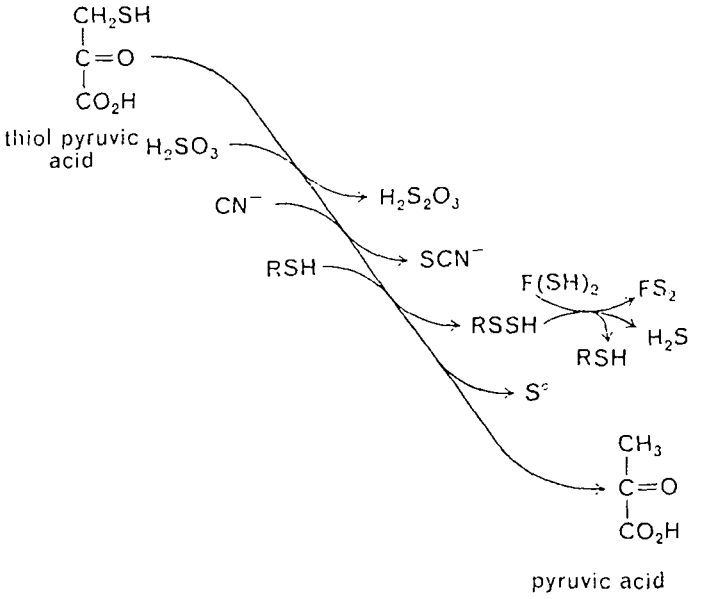
Another route for the removal of the thiol group from cysteine is through the intermediate formation of thiol pyruvic acid, which is the α-keto acid derived from cysteine by transamination:

Cysteine transaminase reaction



The product can be acted on by an enzyme which transfers sulphur to a variety of acceptors *in vitro* to generate thiosulphate (and thiosulphonates), thiocyanate and organic persulphides[1, 10, 14]. A direct desulphuration to sulphide does not appear to occur but a further reaction of persulphide with dithiol carriers would provide this product. The generation of elemental sulphur can also occur under certain circumstances. The thiol pyruvate sulphurtransferase is though to act through an enzyme persulphide

Reactions of thiol pyruvate sulphurtransferase

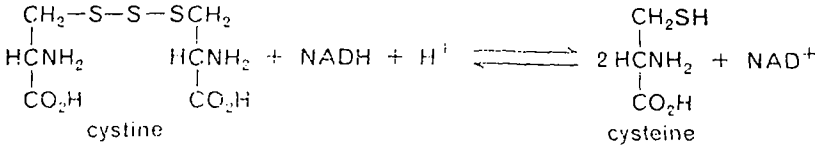


intermediate and will be considered further in a subsequent section. Thiol pyruvate can also be reduced to thiol lactate and decarboxylated to mercaptoethanol.

4. Cysteine–cystine interconversion[12]

While it is doubtful if cystine, the disulphide of cysteine, has any critical biological role as such, it is an ubiquitous constituent of aerobic systems resulting from the facile oxidation of cysteine. It also can arise from the digestion of protein disulphides. Cystine is relatively insoluble and if allowed to build up tends to form crystalline precipitates within the cell. There is normally little of the disulphide in cells, while in the blood the oxidized form dominates. One method for the reduction of cystine to cysteine is *via* a nicotinamide coenzyme-linked dehydrogenase. Glutathione

Cysteine dehydrogenase reaction



cystine cysteine

also has a critical role in cystine reduction. While this reduction occurs readily without enzymes, it is stimulated by the enzyme cystine–glutathione transhydrogenase.

$$2\,GSH + \text{cystine} \longrightarrow GSSG + 2\,\text{cysteine}$$

This latter system appears to be the one dominant in cystine reduction by mammalian cells.

Two human genetic diseases are known which involve this disulphide amino acid. In one, cystinuria[15], there is a transport defect in the intestine and kidney. This results in abnormally high levels of cystine in the urine and can result in the precipitation of cystine crystals and kidney stone formation. In cystinosis[12], cystine crystals form within cells and eventually cause severe kidney damage. The nature of the primary biochemical lesion is unknown; all known cystine reduction systems of the cell appear to be normal.

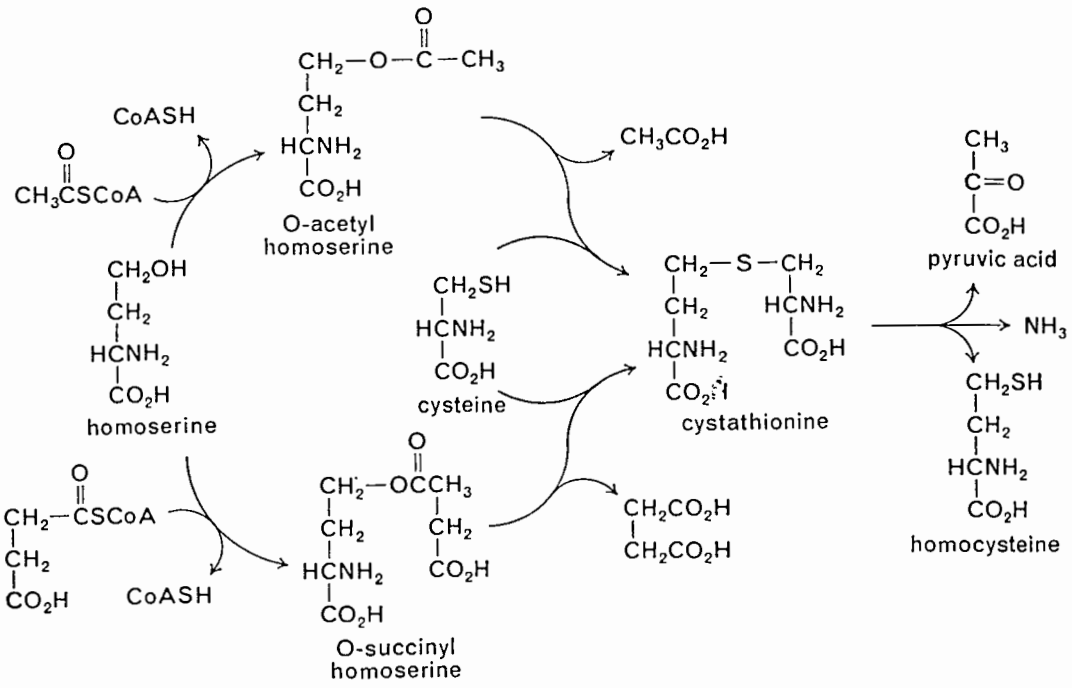
5. Transsulphuration *via* cystathionine[1,2,16]

Cysteine also donates its sulphur to form homocysteine and eventually the second critical sulphur amino acid, methionine. Methionine is the S-methyl ether of homocysteine, a cysteine analogue with one additional

carbon in the chain. Transsulphuration from cysteine occurs in bacteria, plants, yeast and fungi, but not in animals. The latter rely on dietary sources of methionine. It is actually the homocysteine portion which is required but this does not normally occur in significant quantities.

The carbon skeleton of homocysteine is derived from the corresponding hydroxy amino acid, homoserine. The hydroxyl of homoserine is acylated with either a succinyl (bacteria) or acetyl (yeast, fungi, plants) group derived from the corresponding coenzyme A derivative. The O-acyl substituent is then displaced by the thiol group of cysteine producing a mixed thioether, cystathionine. This in turn undergoes a pyridoxal phosphate dependent β-elimination to homocysteine, pyruvate and

Homocysteine Biosynthesis

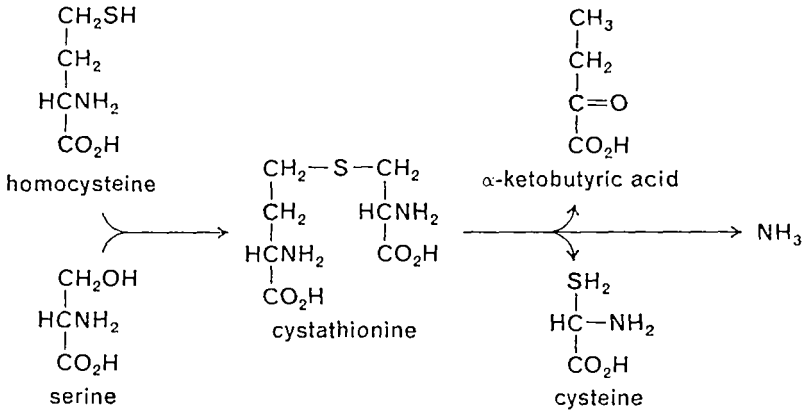


ammonia. Homocysteine is then methylated to methionine by pathways to be discussed later. Cystathionine is generally only a trace metabolite, but occurs in reasonably high concentrations (25–50 mg/100 gm) in brain[17]. A direct formation of homocysteine from homoserine (or O-acyl homoserine) and hydrogen sulphide has also been observed in extracts of some organisms. Whether this is only a side reaction of the cystathionine

synthesis system or is a physiologically important route for assimilation of sulphide is uncertain.

In animals homocysteine arises from methionine through its role as a methyl donor, as will be discussed in a subsequent section. It may either be reutilized for methionine production or degraded. In animal tissues the degradative pathway plays a major role in sulphur nutrition[18]. Much of the cysteine sulphur, and through it sulphate, can be derived from dietary methionine. The transsulphuration from homocysteine to produce cysteine is very much like that in the other direction. It also involves cystathionine but is not a reversal of the synthetic pathway. Quite different reactions are involved. Homocysteine reacts with serine to produce the

Homocysteine catabolism



thioether intermediate. Unlike the route from cysteine and homoserine, no O-acylation step has been implicated. Instead, the homocysteine–serine-condensing enzyme probably requires pyridoxal phosphate as a coenzyme, although this is not unequivocally established.

Cystathionine cleavage in the mammalian transsulphuration system produces cysteine, α-ketobutyrate and ammonia by what is believed to be a pyridoxal-catalysed γ-elimination reaction. Again this reaction is quite similar to the cystathionine cleavage by the other pathway; only the direction of cleavage is different. Actually the bacterial cystathionase is capable of cleaving the thioether in either direction, although that producing homocysteine is dominant. This implies that even the enzyme-bound intermediates are similar and the binding specificity of the particular enzyme site is crucial in ensuring the proper reaction.

Particular interest in this pathway arises from the findings of human genetic diseases associated with each step[19]. Lack of the first enzyme,

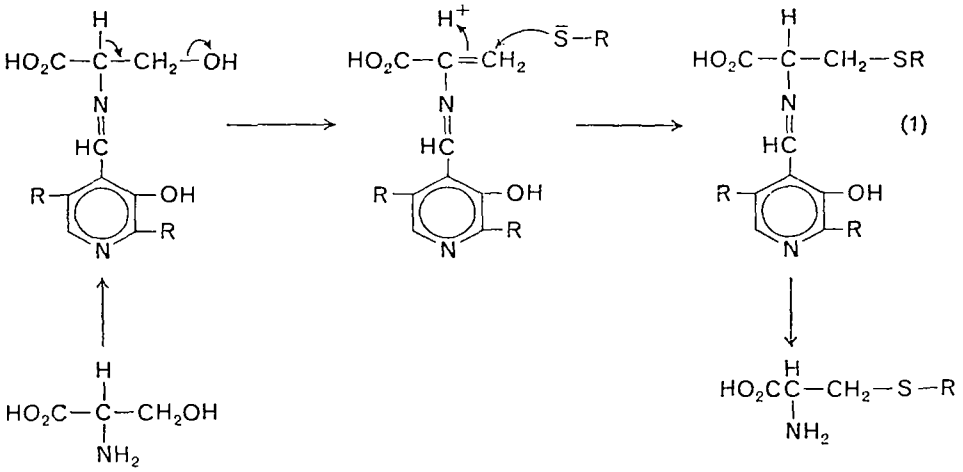
cystathionine synthase, results in homocystinuria[20]. This is one of the most common genetic disorders of amino acid metabolism and is exceeded in frequency only by phenylketonuria. In this disease, homocysteine cannot be metabolized and its disulphide, homocystine, builds up and is excreted. The disorder is often associated with severe symptoms including mental retardation. Actually two distinct autosomal recessive forms of homocystinuria can be differentiated: one type is susceptible to treatment with vitamin B_6 (pyridoxine). Since pyridoxine is the precursor of pyridoxal phosphate, such therapeutic results strongly support a critical role for this coenzyme in the cystathionine synthase. It also implies that, in at least some homocystinurics, the biochemical defect is in coenzyme formation or binding. In the vitamin B_6-unresponsive patients the mutation must affect some other aspect of the enzyme. Actually only a small proportion of the daily methionine intake by homocystinuria patients can be accounted for by the excreted homocysteine and the study of this disease may greatly enhance our knowledge of thiol metabolism. For example, it appears that homocystinurics can make cystathionine to some extent from cysteine and homoserine, a reaction generally believed impossible in animals.

Cystathioninuria, a deficiency of cystathionase, is a much rarer and less clearly defined disorder[17]. While the disease has frequently been associated with mental retardation, this may only reflect the type of individual with which testing most frequently occurs. Patients with normal mental function are also known. Nonetheless, the high levels of cystathionine in brain and the mental defects associated with its faulty metabolism, have led to speculation that this thioether has some special role in nervous function. In tissues from at least one patient, there was evidence that the defect was in pyridoxal phosphate binding by cystathionase and that normal enzyme activity could be achieved at abnormally high levels of coenzyme. This is often quoted as the classical example of a binding or 'K_m' mutant, but not all patients with the disorder give the same effect.

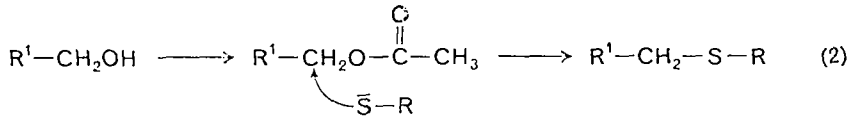
These reactions which lead to homocysteine formation in some creatures and its utilization in others are undoubtedly representative of a general thiol group transfer mechanism. The initial condensation of the donor thiol, most commonly cysteine, with some suitably reactive receptor generates a thioether. The differences in the requirement for O-acylation when starting from serine and homoserine may reflect two completely different mechanisms for this thiol substitution reaction. In the case of serine, the removal of the hydroxyl as hydroxide and the stabilization of an electrophilic centre on the side-chain carbon can be achieved through the pyridoxal phosphate–amino acid adduct. A similar example is in the carbon–carbon condensation between serine and imidazole in tryptophan

synthesis. When homoserine is the receptor a different activation system appears to be necessary. While pyridoxal coenzymes can facilitate γ-elimination of hydroxide from the homoserine structure, stabilization of an electrophilic centre at the appropriate position cannot occur. By first acylating the hydroxyl of homoserine a suitable leaving group for an enzyme-facilitated nucleophilic displacement reaction is created. The two possible mechanisms for formation of a thioether intermediate for trans-sulphuration are shown below. The thioether then breaks down by the

Possible mechanisms for thioether formation



(1)



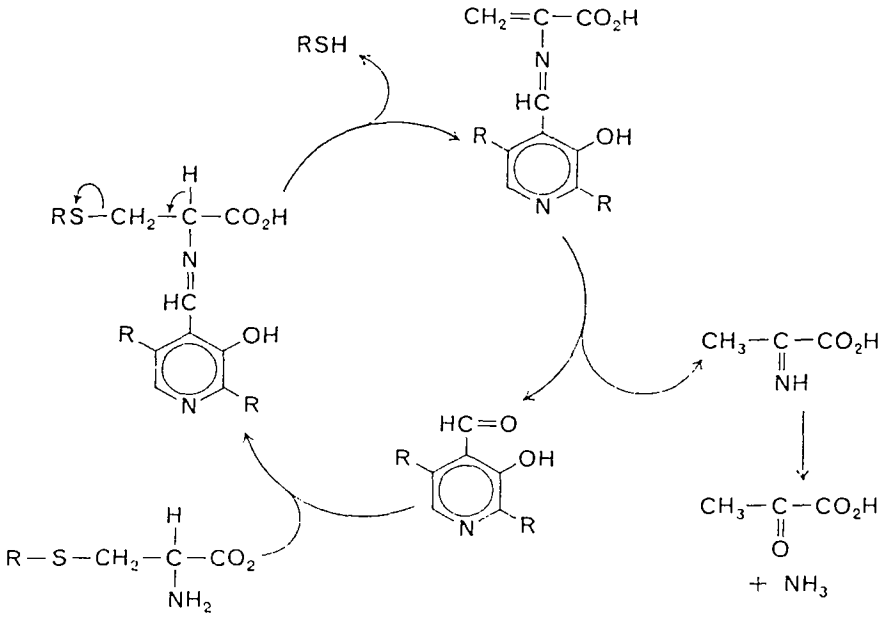
(2)

elimination of a thiolate to complete the transsulphuration sequence. Typically this would be a β-elimination from the cysteine structure potentiated by a pyridoxal phosphate stabilized intermediate as depicted below.

It also appears that thiol pyruvate can serve as sulphur donor for some biological transsulphurations. The thiol nucleotides which occur in small quantities in certain nucleic acids appear to derive their sulphur, at least in part, from thiol pyruvate rather than directly from cysteine[21]. While these reactions have not been extensively studied as yet, ATP is required possibly to activate a group for intermediate thioether formation. Pyruvate elimination could then proceed through an enolate or an intermediate enzyme-bound Schiff base.

A diverse variety of divalent sulphur compounds is found throughout nature. These are often found in small quantities or in restricted species and little is known about their metabolism. It is generally presumed that they all ultimately derive their sulphur from cysteine. Thus more examples of transsulphuration reactions will be described, and it is likely that

β-Elimination from a cysteine thioether



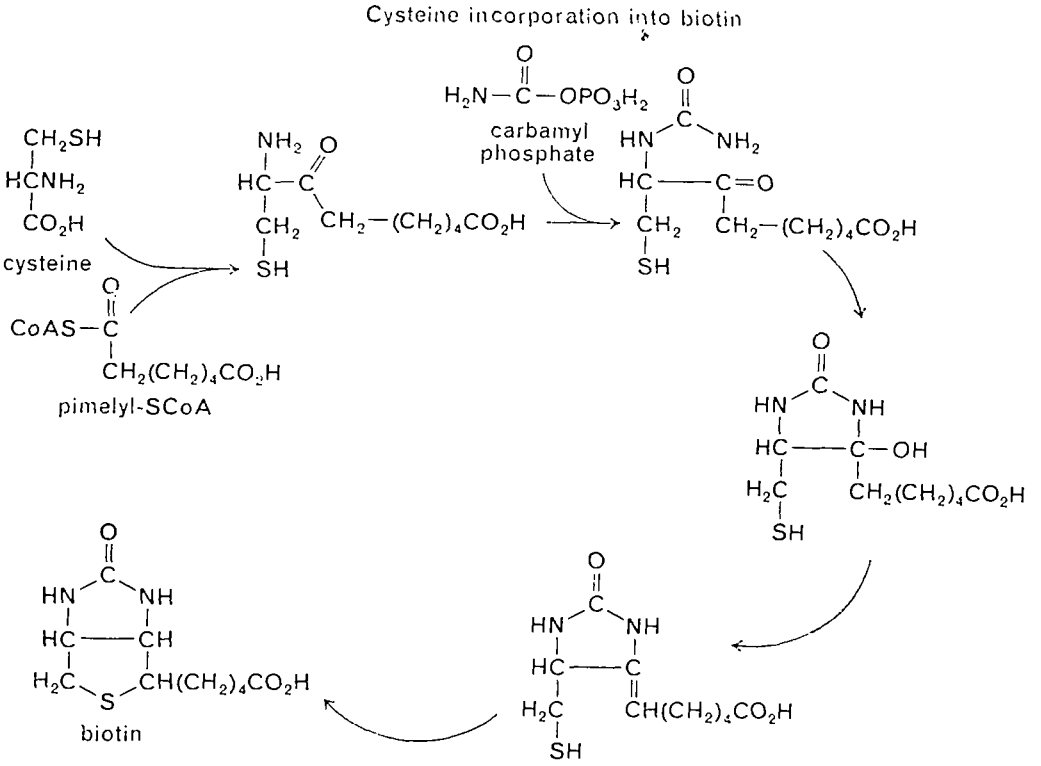
mechanisms involving mixed thioether intermediates will frequently be implicated. Another general route for transsulphuration may be through enzyme-bound persulphides. The existence of such intermediates in the rhodanese and thiol pyruvate sulphur transferase reactions seems reasonably established, although there are no examples of their being involved in the formation of organic thiols.

6. Thiol formation by cysteine incorporation

Thiol groups enter some biologically important thiol compounds by the direct incorporation of cysteine itself. Most frequently this involves peptide bond formation. The incorporation of cysteine into proteins does not differ from any other amino acid involving activation as an amino acid adenylate, transfer to a specific transfer ribonucleic acid (t-RNA), and assembly by ribosomal enzymes as coded by messenger ribonucleic acid (m-RNA). It should be pointed out that cystine, the 'two-headed'

disulphide amino acid, is not directly incorporated, but arises in proteins by oxidation of two cysteine residues after assembly of the chain. The formation of glutathione and pantetheine also involves peptide bond formation to cysteine, but the mechanism of formation is quite different from the nucleic acid-coded protein synthesis. These pathways will be included in the discussions of the thiol coenzymes.

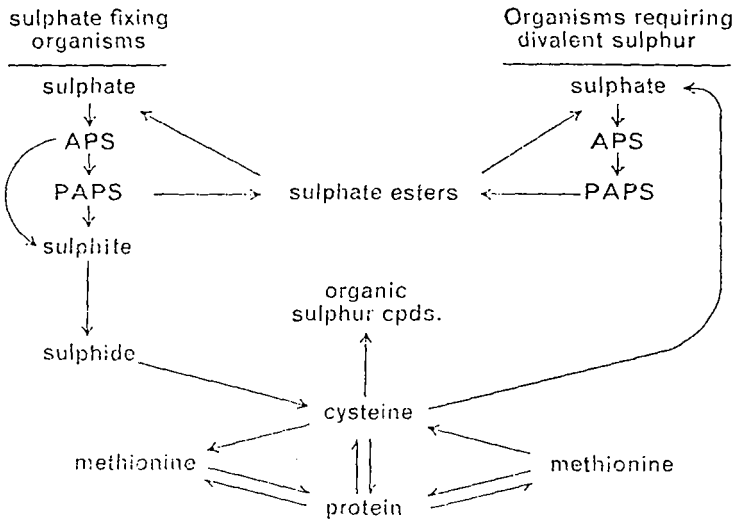
An example in which a portion of the cysteine carbon chain is incorporated directly is one of the proposed routes for biotin synthesis by microorganisms[22]. An acyl coenzyme A derivative of pimelic acid condenses with cysteine, eliminating CO_2. Reaction with carbamyl phosphate leads to the formation of an ureido ring system. The thiol then forms a cyclic thioether by addition to a double bond resulting from dehydration.



Cysteine is the pivotal compound in thiol metabolism. Sulphate and other oxidized forms of sulphur are reduced to the level of sulphide, which enters organic linkage as cysteine. There is no other direct sulphuration pathway of any significance. All biological thiols and subsequently

derivatives such as disulphides, thioesters, thioethers and sulphonium salts derive sulphur through cysteine. This is accomplished either by transsulphuration or by incorporation of the cysteine structure directly. The sulphur metabolism in organisms capable of sulphate fixation and those requiring preformed sulphur amino acids is summarized below.

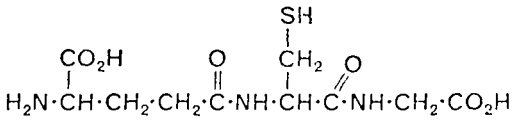
Outline of sulphur metabolism



III. BIOLOGICAL THIOLS AND THEIR FUNCTION

A. Glutathione[23, 24, 25]

While cysteine is the central compound of organic thiol metabolism, a tripeptide derivative, glutathione, is probably the most ubiquitous single thiol compound. Much fascinating biochemical history surrounds this molecule and it has served as the subject of two published volumes[23, 25]. Still, remarkably little is really known concerning its biological importance.



Glutathione (γ-glutamyl cysteinyl glycine)

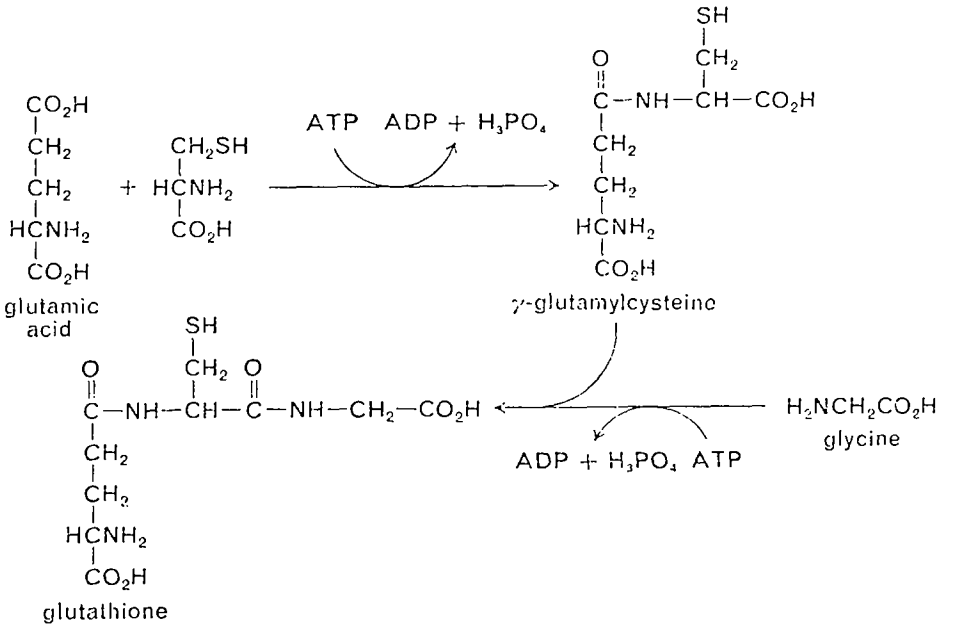
Since glutathione occurs throughout the biological world, it is felt that it must satisfy some critical cellular need. The most likely general function is maintaining a reduced cellular environment. Glutathione can also serve

a variety of additional roles. This peptide functions as cofactor for certain enzymes and it may serve as a γ-glutamyl donor in the synthesis of other γ-glutamyl derivatives. Glutathione is involved in the detoxification of certain organic toxins by some species. There have also been suggestions of special roles for glutathione or its derivatives in brain function and in cell division.

I. Biosynthesis and degradation[24, 26]

Glutathione is assembled from glutamic acid, cysteine and glycine in a protein-directed synthesis. Glutamic acid reacts with cysteine in the presence of ATP to yield ADP, inorganic phosphate and γ-glutamyl cysteine. In a second step the γ-glutamyl cysteine is condensed with glycine to give glutathione. A considerable amount of glutathione synthesis

Biosynthesis of glutathione

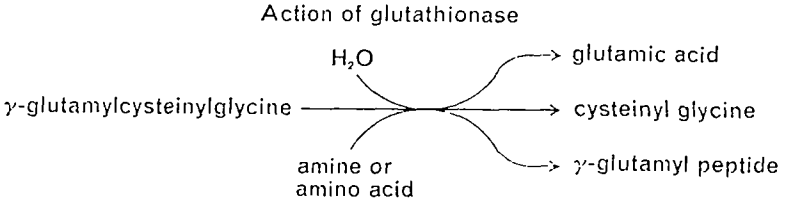


occurs in some cells. Liver may contain 10 mM glutathione which turns over every 2 to 10 h. Such high rates of synthesis and breakdown only add to the mystery of glutathione's importance.

A human disease associated with impaired glutathione synthesis has been reported[27]. Red blood cells from this patient lacked the second enzyme of the synthetic sequence, but the activities of enzymes involved

in glutathione utilization were all normal. Red blood cell glutathione was only reduced to 10–20% of normal. This implies either that the enzyme defect is tissue specific and other tissues can supply some glutathione to the red cell or that the cell produces a less stable enzyme which had become inactivated by the time of analysis. Aside from their intrinsic medical interest, such natural mutants can be expected to provide considerable information about the biochemistry of glutathione. For example, this person was reasonably normal with problems only appearing under stress. This is surprising if the defect was really general and the roles of glutathione are as critical as suggested. On the other hand, an increased sensitivity of this individual's red cells to oxidative stress favours an anti-oxidant role for glutathione.

One special enzyme, that cleaving the γ-glutamyl bond, is involved in glutathione degradation. This enzyme, usually referred to as glutathionase, also has γ-glutamyl transpeptidase activity under certain assay conditions.



It is unclear if the transpeptidation activity represents a way for glutathione to serve as a synthetic γ-glutamyl donor or is simply an insignificant transferase activity typical of many hydrolases. This enzyme probably also participates in mercapturic acid formation[28], and this can be viewed as a variation of the direct hydrolysis reaction in which a substituted glutathione is substrate.

2. Maintenance of the reduced cell[24]

Glutathione can be oxidized to its disulphide by oxygen, oxidized electron transport carriers, free radicals and a variety of disulphides. While most of these reactions are facilitated by enzymes, they also can occur spontaneously. It must be assumed that the ease of nonenzymatic oxidation is an important attribute in the protection of other cellular constituents. The idea that glutathione serves to keep thiols in a reduced state is a direct extension of its usefulness in maintaining extracted enzyme systems in a functional form. The nonenzymatic disulphide interchange reaction of glutathione is facile and a number of enzymatic activities promoting such reactions have also been described.

Disulphide interchange reaction of glutathione (GSH)

$$2\,GSH + RSSR \rightleftharpoons GSSG + 2\,RSH$$

Glutathione reductase is an ubiquitous enzyme to be discussed mechanistically in the section on dithiol enzymes. Through its action, metabolic reducing power generated as reduced pyridine nucleotides can be coupled to the maintenance of the reduced environment.

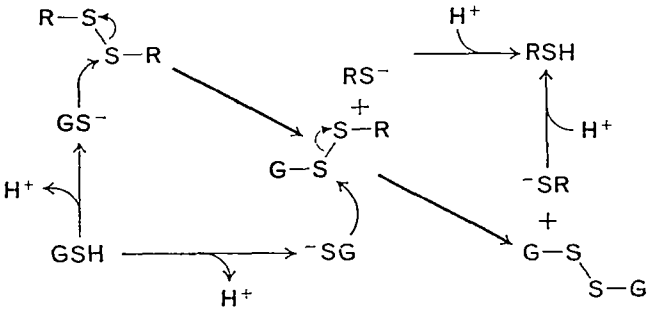
Glutathione reductase reaction

$$GSSG + NADPH + H^+ \rightleftharpoons 2\,GSH + NADP^+$$

Crucial thiols such as cysteine and coenzyme A and the numerous cellular enzymes requiring thiol groups for proper function are kept reduced by the high glutathione levels within cells. Oxidized glutathione in turn is reduced by glutathione reductase and NADPH-generating systems.

Glutathione-mediated disulphide reductions whether enzyme mediated or spontaneous probably proceed through an intermediate mixed disulphide *via* a thiolate displacement mechanism.

Disulphide interchange mechanism



Relatively high glutathione concentration would be required to ensure complete reduction. Some glutathione bound as a mixed disulphide is found in cellular proteins as would be expected from this scheme, but it is uncertain if this actually existed within the cell or was produced on extraction.

A few systems are known in which glutathione serves as a reductant for molecules other than disulphides[10, 24]. Probably the most critical of these in animals is the glutathione peroxidase of the red cell. Along with catylase this enzyme is responsible for destroying peroxides and thereby preventing lipid peroxidation and haemoglobin inactivation. The

Glutathione peroxidase reaction

$$2\,GSH + H_2O_2 \longrightarrow GSSG + 2\,H_2O$$

functional importance of this reaction can be deduced from the effects of genetic disorders such as erythrocyte glucose-6-phosphate dehydrogenase deficiency. Where there is a lack of NADPH production the inability to maintain glutathione in the reduced form results in decreased red cell stability and haemolytic anaemias[29].

Related to this is the action of glutathione as a free radical scavenger in protection against radiation damage[25]. Thiols readily react with free radicals producing thiol radicals which eventually combine to disulphides. It is felt that the ease of this reaction and the ready availability of glutathione minimizes damage to critical biological structures by the free

Glutathione reaction with free radicals

$$GSH + HO^{\bullet} \longrightarrow GS^{\bullet} + H_2O$$

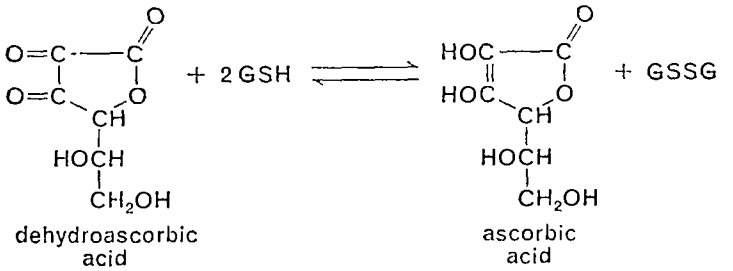
$$2\,GS^{\bullet} \longrightarrow GSSG$$

radicals produced by ionizing radiation. Some consider one important mechanism of cellular ageing to be a slow accumulation of radiation-induced damage. Glutathione might therefore be considered also to have an anti-ageing role.

3. Other electron transport roles[24, 25]

Plants have an enzyme system linking the oxidation of glutathione to the reduction of dehydroascorbic acid. A similar enzyme may occur in animal tissues, although in this case a facile non-enzymatic reaction could possibly account for the observed activity. The plant enzyme provides a

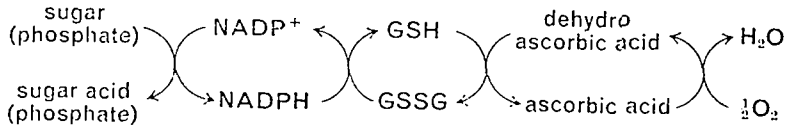
Dehydroascorbate reductase reaction



pathway whereby oxidized ascorbate can be reduced thereby enhancing its potential as an antioxidant. The full appreciation of the biological significance of this reaction suffers from the almost complete ignorance of the role of ascorbic acid. Coupled with a NADPH-linked glutathione reductase, the NADP reduction activity of the pentose shunt enzymes, and

a dehydroascorbic acid oxidase, a complete respiratory chain for the oxidation of glucose is possible. Its actual operation if it occurs at all appears restricted to the earliest phases of plant development.

Glutathione-ascorbic acid respiratory chain

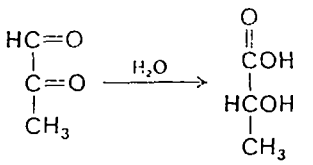


Glutathione is also the reductant for an organo-nitrate ester-reducing enzyme from liver. This so-called nitroglycerin reductase reacts with glycerol, erythritol or mannitol nitrates to yield free alcoholic hydroxyls and nitrite ions. The normal physiological substrate for this system is unclear. While its study has provided interesting enzymology it has not yielded any insight into the biological significance of glutathione.

4. Use as an enzyme cofactor

The best established functional role for glutathione is as a cofactor in certain enzymatic processes. The most extensively studied example is the glyoxylase system[24,30]. This catalyses an internal oxidation–reduction, or dismutation, of certain α-keto aldehydes to α-hydroxy acids.

Glyoxylase reaction

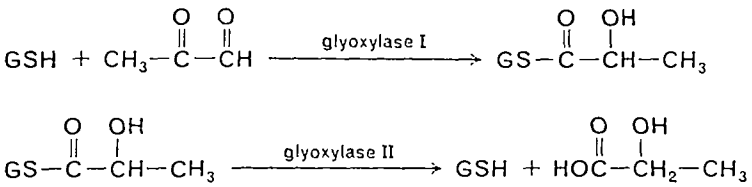


The idea that this system played a crucial role in carbohydrate metabolism forms an important, but now largely forgotten, aspect of the history of biochemistry[24]. The discovery of the importance of glutathione in the glyoxylase reaction was, in fact, the critical finding which has relegated this reaction to its present metabolic obscurity. In muscle preparations the glyoxylase system was found to be inoperative without added glutathione. However, glycolytic activity continued precluding any direct role for glyoxylase in this important metabolic process. While the bulk of intermediary metabolism has been traced out in the intervening forty years, glyoxylase function remains undefined. At present it is assigned a detoxification role in protecting against α-keto aldehydes, although

Szent-Györgyi has proposed that the glyoxylase system may be important in the control of cell division[31].

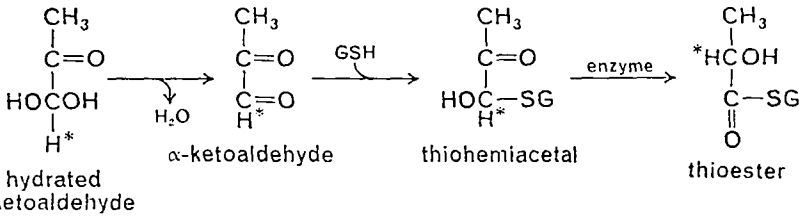
The glyoxylase reaction is promoted by two enzymes found in almost all living creatures. The first protein catalyses the condensation of the α-keto aldehyde with glutathione followed by an internal disproportionation producing a thioester of an α-hydroxy acid. A second enzyme cleaves the thioester regenerating glutathione.

Glyoxylase system



The present conception of the glyoxylase I mechanism involves a non-enzymatic condensation of the thiol of glutathione with the α-keto aldehyde to produce a thiohemiacetal. The enzyme then promotes an intramolecular hydride migration generating an α-hydroxy acid-thioester. The original aldehydic hydrogen is retained in the final product. It has been compared to the Cannizzaro and benzilic acid rearrangements of organic chemistry.

Glyoxylase I mechanism



The second enzyme of the glyoxylase system, the thioesterase, is specific for thioesters of glutathione and its analogues. Thioester hydrolysis and transacylation will be discussed in subsequent sections.

At one time glutathione was also thought to constitute part of the active centre of glyceraldehyde 3-phosphate dehydrogenase[32] with similar thiohemiacetal and thioester intermediates. While the analogous involvement of an enzyme thiol in the enzyme reaction has been well established, an analysis of the amino acid sequence at the active site of the enzyme has shown that glutathione is not a part of the enzyme[33]. Glutathione does

appear to have a valid role in a similar reaction, that of formaldehyde dehydrogenase[24].

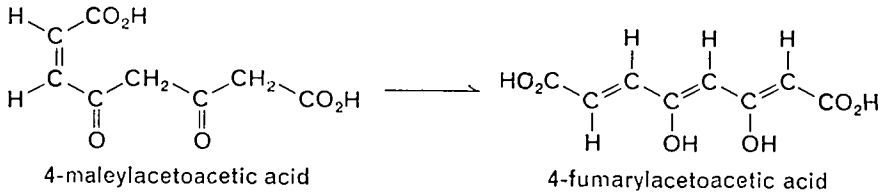
Formaldehyde dehydrogenase reaction

$$H_2C{=}O + NAD^+ + H_2O \longrightarrow HCO_2H + NADH + H^+$$

formaldehyde — formic acid

Glutathione also acts as coenzyme for a completely different type of reaction, the isomerization of maleylacetoacetate to fumarylacetoacetate[25].

Maleylacetoacetate isomerase reaction



4-maleylacetoacetic acid — 4-fumarylacetoacetic acid

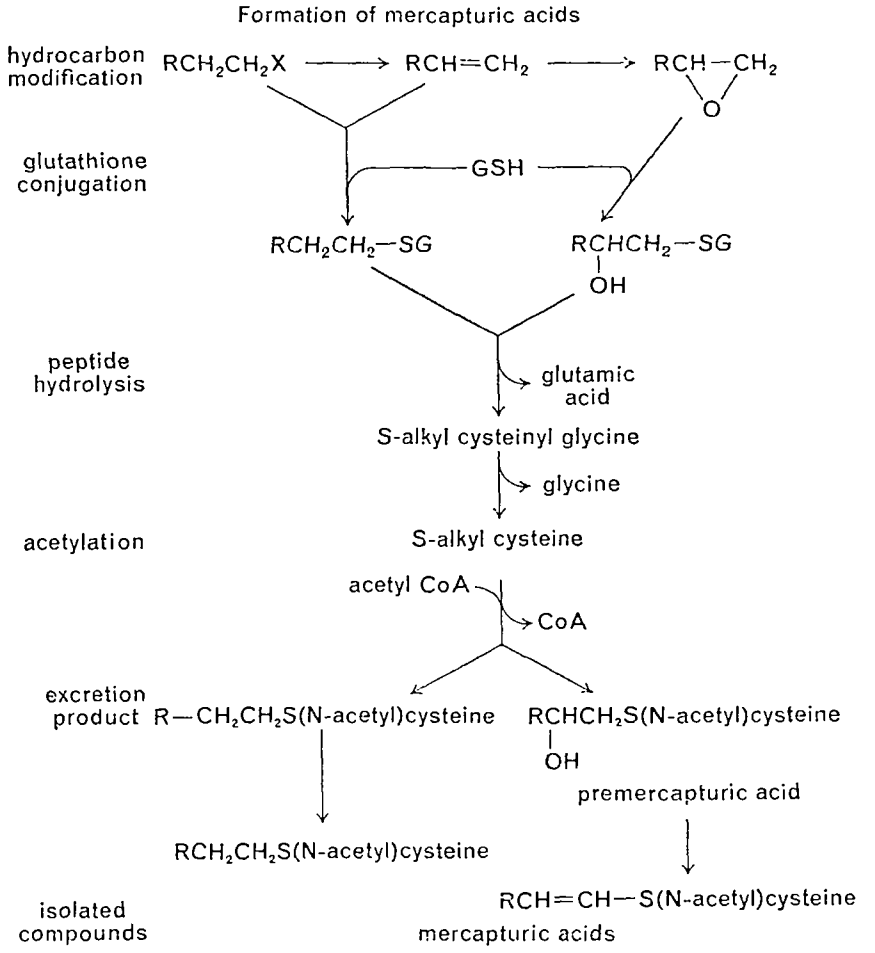
The reaction is thought to proceed through a reversible addition of the thiol to the double bond. Glutathione can catalyse the isomerization of this and other α-β-unsaturated acids even in the absence of enzyme. A glutathione addition product can be isolated with such substrates but does not appear to be a true intermediate in the enzymatic process, as it is not acted on by the enzyme. An enzyme-bound adduct is thus implicated.

5. Mercapturic acid formation and detoxification[10, 28]

Glutathione is involved in the conjugation of certain toxic hydrocarbons by the liver. These are eventually excreted as mercapturic acids, S-substituted N-acetyl-cysteines. Such compounds have been isolated from the urine of many animals including man.

Benzene, halobenzenes, naphthalenes and a variety of other aromatic or unsaturated hydrocarbons are conjugated by reaction with glutathione. Many of these compounds readily react with thiols nonenzymatically, and their rapid sequestration would be critical in protecting the functional thiols of the cell. A group of enzymes concentrated in the liver and kidneys, the glutathione-S transferases, catalyse the condensation with glutathione. Cysteine or other biological thiols do not serve as acceptors. After formation of the hydrocarbon adduct the glutathione peptide bonds are hydrolysed and the cysteine residue is N-acetylated before excretion. In many cases the product actually excreted is a so-called premercapturic acid which contains a hydroxyl adjacent to the thioether substituent. Water is eliminated during isolation to produce the mercapturic acid. The

frequent occurrence of an α-hydroxy substituent suggests that the hydrocarbon has undergone epoxidation of a double bond prior to reaction with glutathione. The condensation reaction would then involve an attack on the epoxide ring by a thiolate. Direct addition of the thiol to a double bond or even halogen displacement may also occur in certain cases giving rise to metabolic products without α-hydroxy substituents.

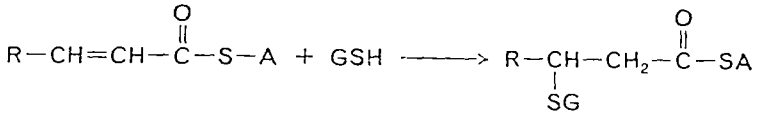


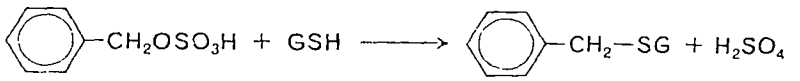
In humans mercapturic acid formation appears less significant than detoxification pathways involving glucuronide or sulphate ester formation, but is of considerable importance in other species. Halobenzenes which can cause liver damage lead to mercapturic acid formation in the rat, while non-toxic compounds such as *p*-dibromobenzene do not. Such facts strongly support the idea that this pathway has a detoxification role.

Mercapturic acid production seems to have first call on the sulphur amino acid reserves and serious deficiency states can be induced in rats by hepatotoxic hydrocarbons. Diets high in cysteine and methionine will protect against the liver damage. Some mercapturic acid production may also result from reaction of protein thiol groups with the hydrocarbons, hydrolysis of the protein to the S-substituted cysteine and its N-acylation. However, the vast majority is formed via the glutathione adducts if the hydrocarbon dose is not so great as to deplete the glutathione reserves of the liver.

The intermediate production of aralkyl sulphate esters or thioacyl derivatives prior to conjugation with glutathione seems likely for certain types of compounds since enzymes of the following types have been characterized[34,35].

Glutathione conjugation via thioesters and sulphates





Mercapturic acid formation has been shown to occur in a variety of mammals, birds, reptiles, amphibians and fish. Insects also form glutathione conjugates but do not N-acylate the eventual S-substituted cysteine derivatives to any great extent. It is also possible that the S-carboxyalkylcysteines of plants have a similar genesis. Mercapturic acid formation is certainly one of the best studied and documented protective functions for glutathione.

Thus, in spite of many years of investigation and speculation, no universal functional role has been established for glutathione which would explain its broad distribution and high concentration in biological systems. The most satisfying concept is that the glutathione system establishes the reduced state of the cell, at least in so far as preventing the oxidation of cellular thiols. In fact the thiol protective effect is multi-faceted. Glutathione preferentially reacts with agents of all types which otherwise would inactivate thiol metabolites, coenzymes and proteins. If inappropriate disulphide formation should occur, activity can be restored by the disulphide interchange. Whether such a general protective action is the universal glutathione role has been difficult to prove, and the

concept has been gently derided by labelling it the euphoristic theory of glutathione action (see reference 24).

While the overriding function of glutathione may be protective, a number of more specific roles have evolved. It serves as a coenzyme for certain enzymatic processes, and it may moderate critical rearrangements of cellular architecture. If for no other reason glutathione could be regarded as the most important cellular thiol on a purely quantitative basis, and it is likely that it has functions of correspondingly critical significance.

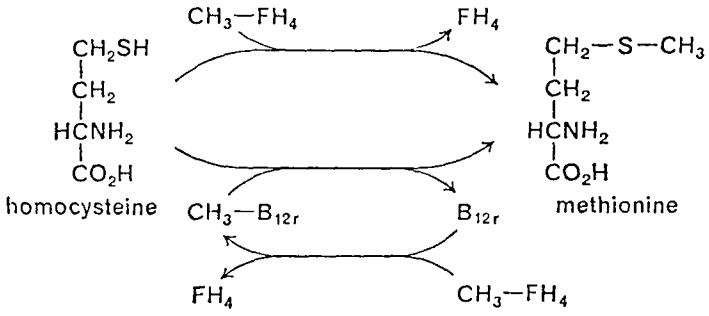
B. Methionine and S-Adenosyl Methionine[36,37]

The biological importance of the second thiol amino acid, homocysteine, is as the thioether and sulphonium ion derivatives. The free thiol occurs only as a metabolic intermediate. Methionine, the methyl thioether, is one of the twenty amino acids utilized for protein synthesis. Our concepts of the special significance of methionine in protein structure and function are only beginning to be developed, and will not be considered here. N-Formyl methionine also has the distinctive role of being a chain initiator in protein synthesis[38]. The most extensively studied form of this thiol is S-adenosyl methionine or SAM, the sulphonium ion cofactor. This is the principal methylating reagent of biological systems and other alkyl transfers from the sulphonium ion are also known.

1. Methylation of homocysteine

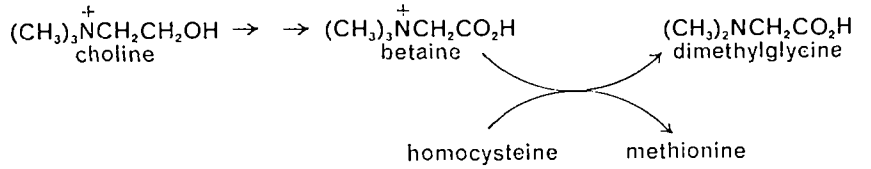
Methylation of homocysteine to methionine can be accomplished by one of several sequences. A major route is from a N^5-methyl-tetrahydrofolic acid ($CH_3—FH_4$) derivative. In some organisms a coenzyme derivative of vitamin B_{12} is also required, where it functions in its reduced form (B_{12r} in the following scheme) as an intermediate methyl carrier:

Methylation of homocysteine by folic acid derivatives



Animals also derive methyl groups from dietary choline, which can partially substitute for the methionine nutritional requirement. An oxidation product of choline, betaine, is the actual methyl donor to homocysteine. This probably represents a salvage pathway for methyl groups in the catabolism of choline, but it can be of considerable importance if the capacity for *de novo* methyl synthesis is limited.

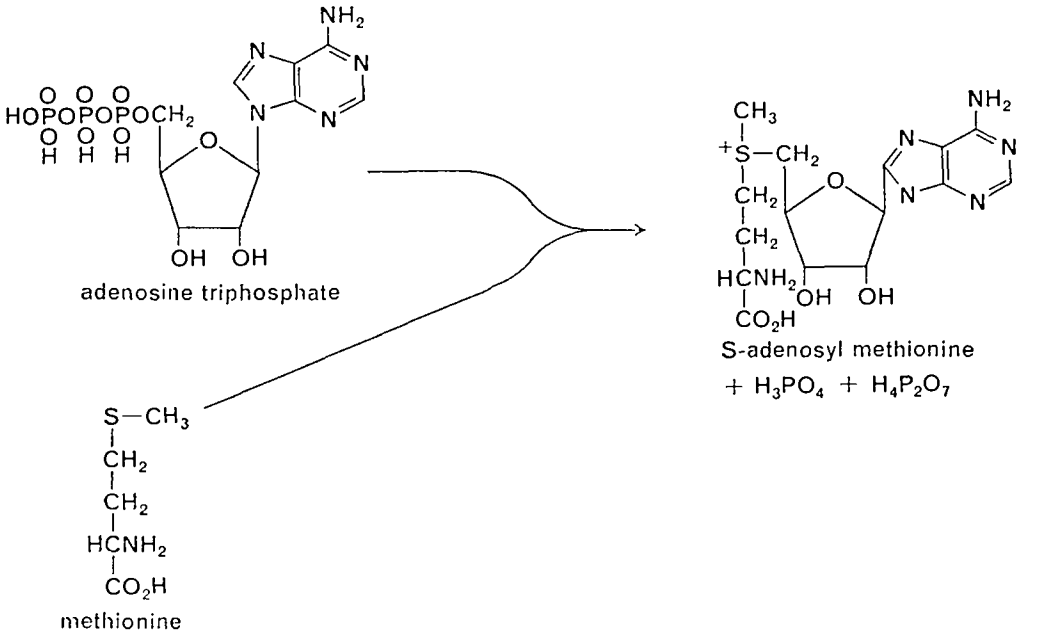
Choline as a methyl group source



2. S-Adenosyl methionine and transmethylation

Methionine reacts with ATP to produce S-adenosyl methionine (SAM) with the release of both an orthophosphate and pyrophosphate residue.

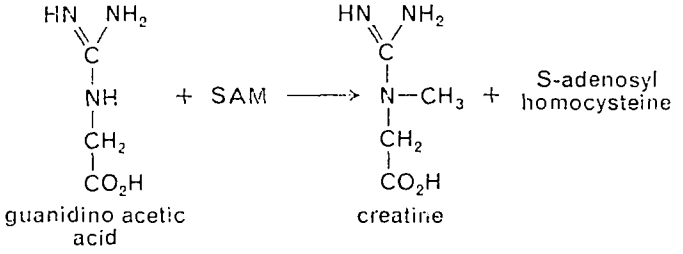
Biosynthesis of S-adenosyl methionine

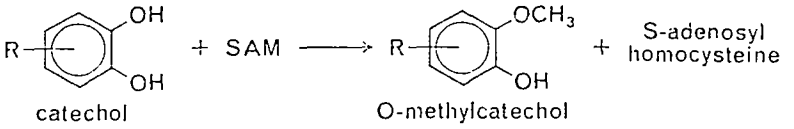


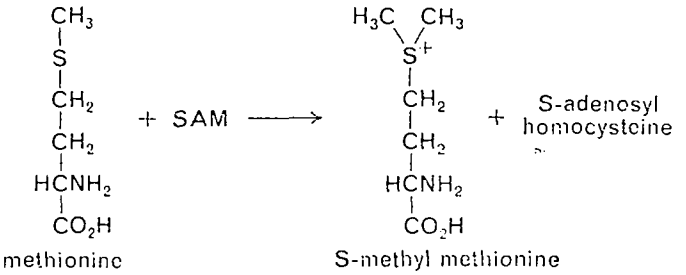
This sulphonium compound, often referred to as 'active methyl', serves as a methyl donor for biological synthesis. The list of compounds which derive methyl groups by transmethylation from SAM is extensive and

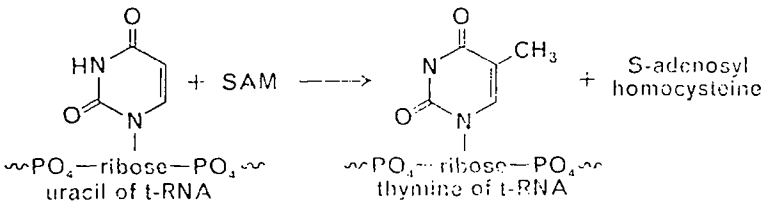
includes many types. Oxygen, nitrogen, sulphur and carbon atoms can act as acceptor. A few representative reactions are indicated below.

Typical methylation reactions



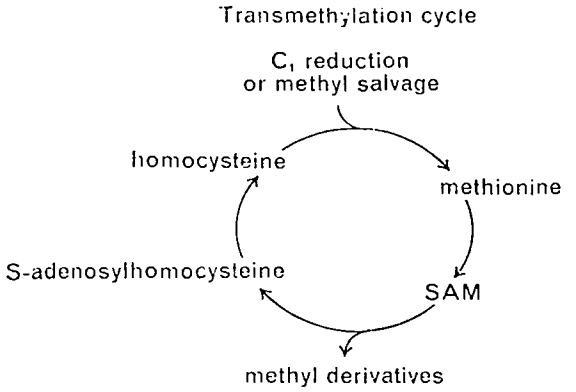






The S-adenosyl homocysteine produced in the transmethylation reactions is generally cleaved to adenosine and homocysteine. The latter can be degraded as previously discussed or be remethylated to methionine and eventually regenerate S-adenosyl methionine. Thus the operation of a methionine cycle provides a route whereby one-carbon metabolites reduced through the tetrahydrofolic acid sequence provide methyl groups for biosynthetic pathways. Certain other sulphonium compounds such as

S-methyl methionine and dimethyl β-propiothetin are apparently capable of serving as methylating agents in some organisms but do not have the general biological significance of S-adenosyl methionine.

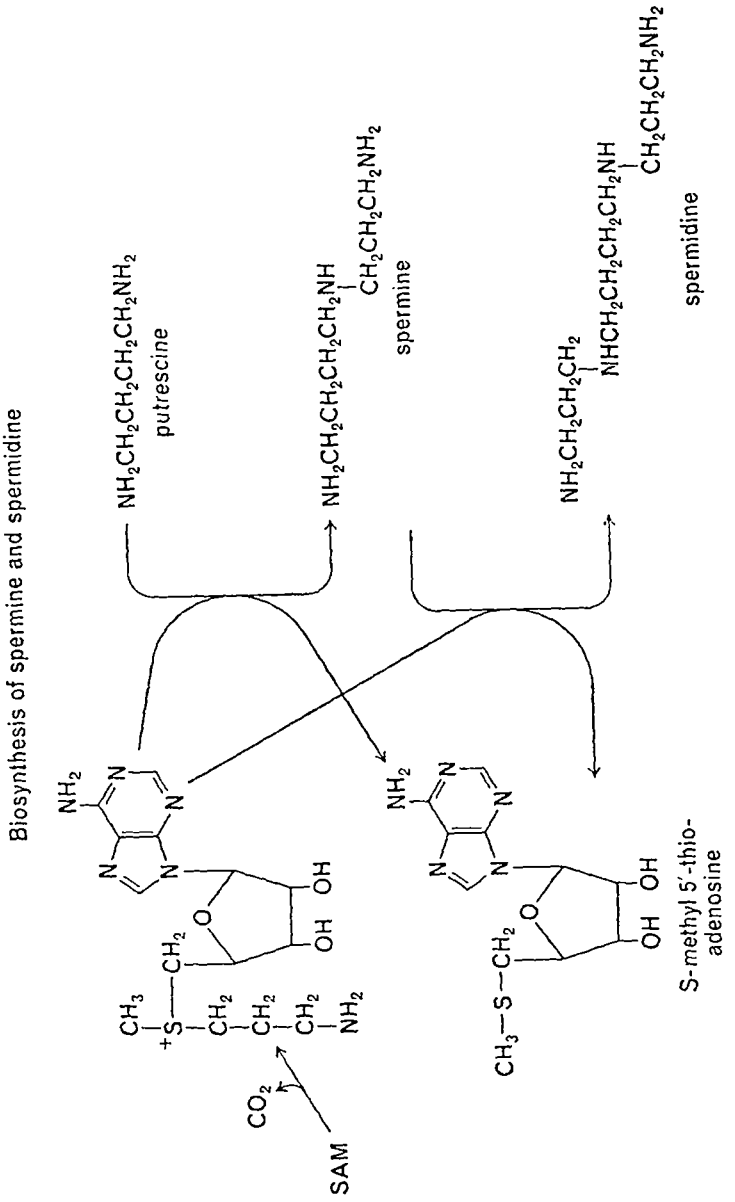


3. Other sulphonium ion alkylations

Methyl transfer is not the only kind of alkylation that can be effected by the sulphonium centre. The best studied example is the synthesis of the polyamines spermine and spermidine, important counter ions for nucleic acids. S-Adenosyl methionine undergoes a decarboxylation of the homocysteine side chain producing a thiopropyl amine derivative. The propyl amine residue then is transferred, first to one and then to the other amino group of putrescine yielding in turn spermine and spermidine[39].

S-Adenosyl methionine provides an interesting example of how thiol derivatives can promote what are normally considered to be difficult organic reactions. Few alkylating reagents employed by the chemist are compatible with the conditions of biochemical systems. Sulphonium ions can however be readily formed under biological conditions and are sufficiently stable in an aqueous environment to have their reaction controlled by enzyme specificity. The wide biological distribution of S-adenosyl methionine-mediated transmethylation attests to the fact that alkylation through sulphonium ion intermediates is among the most ancient biological group transfer reactions.

The chemical rationalization for the alkyl-transferring capacity of the sulphonium (and other 'onium') compounds is that the positively charged sulphur induces a partial positive charge on the immediately adjacent carbon atom. Such a positive carbon centre then becomes susceptible to nucleophilic attack. The thioether serves as an excellent leaving group particularly if a relatively nonpolar reactive centre is envisaged. Reactions involving S-adenosyl methionine as a methyl donor at neutral pH, generally


Biosynthesis of spermine and spermidine
putrescine
spermine
spermidine
SAM
S-methyl 5'-thio-adenosine

have favourable free energies of -7 (or more) kilocalories per mole. Thus, the intermediary role of SAM in biological transmethylations and occasionally in other transalkylation reactions reflects both thermodynamic and mechanistic attributes of sulphonium ions. Sulphonium ion reactions in turn constitute one of the fundamental functional roles of a thiol in biological systems.

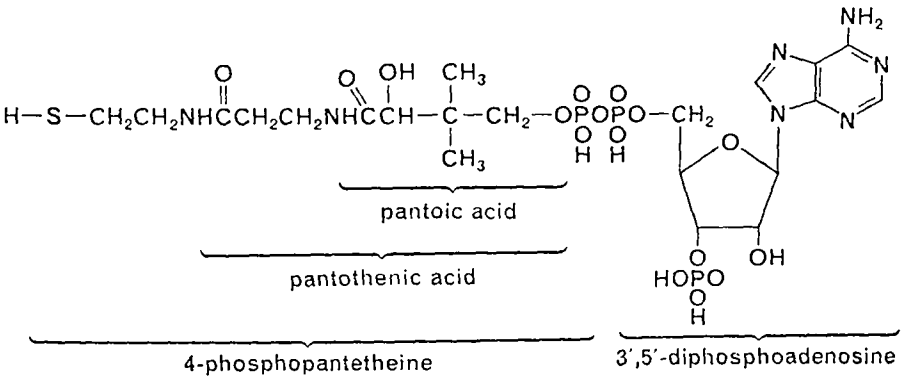
C. Pantetheine Cofactors

The most clearly defined functional role of cellular thiols is that of coenzyme A and related cofactors[40,41,42]. Coenzyme A was first recognized as a carrier for activated acyl groups. The general sequence for acylation in biological systems is acyl activation to a thioester followed by acyl transfer to form amides, esters and acid anhydrides. In addition the thioester linkage enhances the carbonyl nature of the carboxylate group leading to a variety of reactions within the acyl carbon chain. Recently it has been recognized that the phosphopantetheine portion of the coenzyme A molecule also occurs in proteins, where it serves a similar role. A great deal of mechanistic information has been accumulated on enzyme reactions mediated by the thioesters of coenzyme A and related structures[43]. This is one of the areas in which the physical organic chemists' approach to biochemistry has proved most fruitful.

1. Biosynthesis of coenzyme A[44]

Coenzyme A is a complex organic molecule with a nucleotide portion of adenine, ribose and phosphoryl groups linked through a pyrophosphoryl bridge to an unusual peptide, pantetheine. This structure has a branched-chain dihydroxy acid, pantoic acid, linked to β-alanine which in turn is bonded to thioethylamine. In spite of the complexity of the coenzyme A

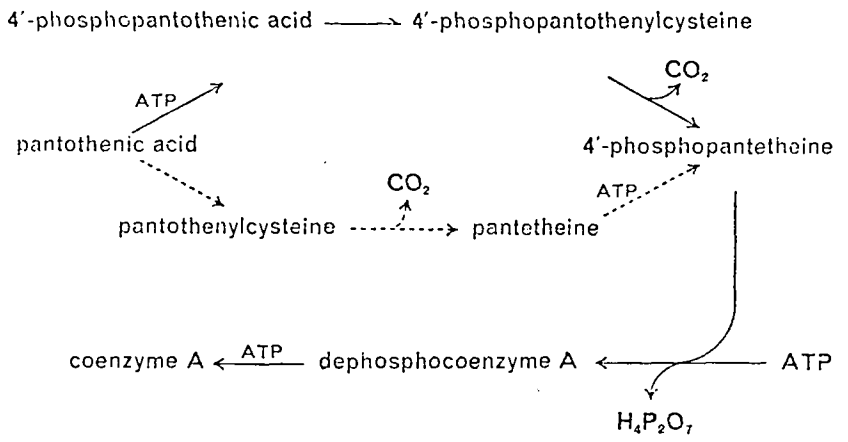
Coenzyme A



molecule our understanding of its function relates only to the fact that it is a thiol. The remainder of the molecule is presently relegated to imparting water solubility to acyl derivatives and providing highly specific structures for enzyme binding. In fact its catalytic function in several enzyme systems can be met by various simple N-acyl cysteamine models, although enzyme affinity is considerably lowered. While viewing coenzyme A simply as a thiol is generally recognized as being a gross oversimplification, evidence of any functional significance for other structural elements is sparse.

In microorganisms the pantoic acid carbon chain is derived from valine and 'active formaldehyde' and the β-alanine from aspartic acid. Higher organisms are unable to synthesize the pantothenic acid portion of the molecule and it is a required vitamin. Pantothenic acid is first phosphorylated to 4-phosphopantothenic acid and then condensed with cysteine to produce 4′-phosphopantothenyl cysteine. The cysteine residue then undergoes decarboxylation to 4′-phosphopantetheine. An adenylate is transferred from ATP to generate dephospho coenzyme A and a final phosphorylation of the 3′-hydroxyl of ribose provides the biologically active molecule. A slightly different sequence was thought to operate at one time, and still may be possible in some organisms. It differs only in that condensation with cysteine and the decarboxylation precedes the phosphorylation of the pantothenic acid hydroxyl group.

Biosynthesis of coenzyme A



Coenzyme A can readily be oxidized to an inactive disulphide in air and mixed disulphides with other thiols such as cysteine and glutathione are also readily formed. In fact any reagent used to probe for enzyme thiols

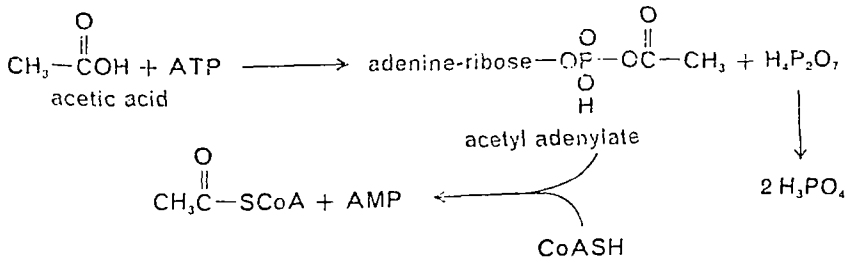
will also react with coenzyme A making studies of protein thiols much more difficult in coenzyme A-requiring systems.

2. Formation of coenzyme A thioesters[10,11]

In its biological function the sulphydryl group of coenzyme A is converted to a thioester. The acid is almost always a carboxylic acid although there have been some indications that coenzyme A thiophosphate esters might play a role in certain reactions. Thioesters have a sufficiently large negative free energy of hydrolysis to place them among the so-called 'high energy' compounds of biochemical energetics. Their synthesis must be driven by exergonic metabolic processes. Actually coenzyme A thioesters participate in the metabolic energy exchange system serving as an intermediate repository for the biochemical energy quanta represented by the squiggle (~) bond. Thioesters are formed by nucleoside triphosphate-dependent reactions, by oxidative processes or by thiolytic cleavage of β-keto thioesters. The coenzyme A derivative can donate the acyl to amino, thiol, hydroxyl and carbanion centres in energetically favourable reactions. It can also drive the formation of pyrophosphate linkages of nucleoside triphosphates. Coupled with this high reactive potential of the thioester is an amazing kinetic stability. Spontaneous decomposition mechanisms are not available in an aqueous environment at neutral pH and physiological temperatures. Such a situation is biochemically ideal, a high reactivity which can be completely controlled by enzymatic catalysis.

The direct route of acyl coenzyme A synthesis from a free carboxylic acid is catalysed by a group of nucleoside triphosphate-requiring enzymes, collectively known as thiokinases. The general mechanism, as exemplified for acetate activation by acetyl thiokinase, proceeds as follows. The carboxylic acid is first activated by acetyl adenylate formation with the displacement of pyrophosphate from ATP. While the initial reaction is fully reversible, subsequent action of pyrophosphatase drives the reaction

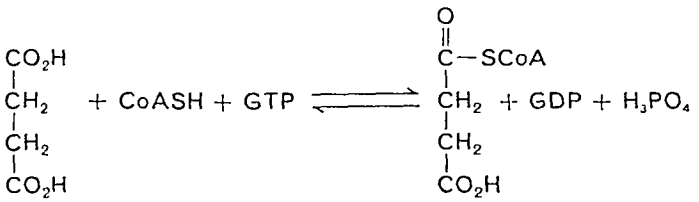
Acyl thiokinase reaction via an acyladenylate



process. The thiol of coenzyme A then displaces adenylic acid in a second step to produce the acetyl thioester.

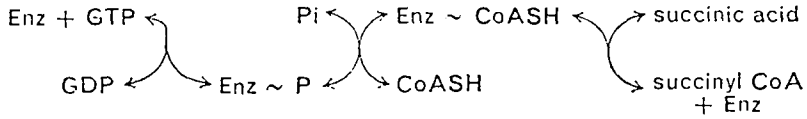
Acyl adenylate intermediates seem the general rule for acyl activation, but alternate mechanisms are known. An example is the succinyl thiokinase reaction[45]. The mammalian enzyme system utilizes guanosine triphosphate (GTP) or inosine triphosphate (ITP), although similar ATP-requiring enzymes are known from plants and bacteria. In addition to the coenzyme A derivative, a nucleoside disphosphate and inorganic phosphate are produced.

Succinyl thiokinase reaction



The products suggest activation as a phosphoryl rather than as a nucleotidyl derivative. Both succinyl phosphate and thiophosphoryl coenzyme A have been suggested as intermediates. However, neither is included, at least as a freely dissociable intermediate, in current formulations of this reaction. An enzyme-bound phosphoryl histidine intermediate is thought to be involved, as is some sort of activated enzyme–CoA complex. Many aspects of the enzyme mechanism are still in doubt, but the sequence below is consistent with most available data.

Proposed succinylthiokinase mechanism



This mode of thioester formation is not as energetically favourable as that involving pyrophosphate release and its eventual cleavage. This probably reflects different biological roles for the two types of thiokinases. Succinyl thiokinase and probably other nucleoside diphosphate–inorganic phosphate type enzymes normally operate in the other direction, with thioacyl coenzyme A driving the synthesis of nucleoside triphosphate. One type of enzyme system produces coenzyme A thioesters efficiently at the expense of nucleoside triphosphate, while the other helps to couple metabolic processes to the synthesis of high energy phosphates.

Another way to generate particular acyl coenzyme A derivatives is at the expense of others. The succinyl–acetoacetyl coenzyme A transferase reaction is an important example.

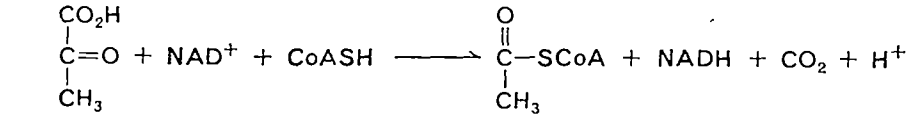
Acyl interchange reaction

succinyl-S-CoA + acetoacetic acid $\rightleftharpoons$ succinic acid + acetoacetyl-S-CoA

An intermediate enzyme–coenzyme A complex in which the energy of the thioester bond is preserved has been demonstrated. Here the coenzyme A thioester is involved in a transfer reaction quite different from its usual acyl donor role. Functionally this enzyme allows metabolically generated coenzyme A derivatives to be utilized directly for carboxylic acid activation, without intermediary formation of nucleoside triphosphates.

A metabolically important route for the generation of acyl coenzyme A derivatives is through the oxidation of α-keto acids. The α-keto acid dehydrogenase complexes, of which pyruvate dehydrogenase complex is typical, are large multienzyme aggregates. They carry out a complex reaction sequence to be discussed in section III.D on lipoic acid. The overall reaction given below is an oxidative decarboxylation coupled to thioester formation.

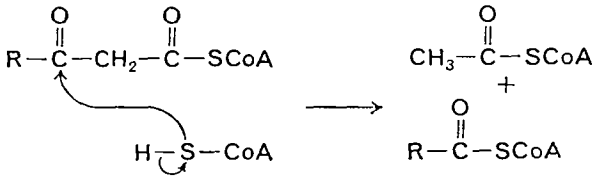
Pyruvate decarboxylase-dehydrogenase reaction



pyruvic acid acetyl CoA

The final process for coenzyme A thioester synthesis is by the thiolytic cleavage of β-keto acyl coenzyme A derivatives. The thiolase reaction is the principal metabolic process for degrading the hydrocarbon chain of fatty acids.

β-ketofatty acyl CoA thiolase reaction

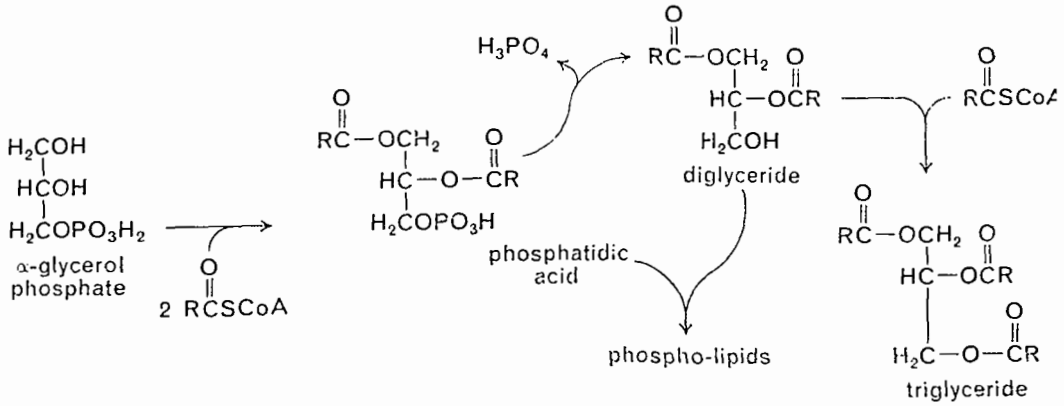


3. Reactions of coenzyme A thioesters[42,43]

Examples of acylation by acyl coenzyme A derivatives are numerous[41]. The quantitatively most important example is the transfer of fatty acyl

residues from coenzyme A in the synthesis of glycerides. In this case the acyl acceptors are the hydroxyl groups of glycerol derivatives and the products are oxygen esters. Acyl coenzyme A hydrolases can also be

Pathways for glycerol lipid synthesis

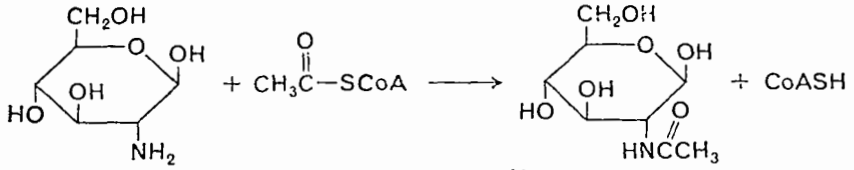


looked upon as acyl O-transferases of a special type with water acting as acceptor.

Acyl-coenzyme A hydrolase reaction

Transfer from an acyl coenzyme A derivative to a nitrogen nucleophile is also quite common. Typical is the N-acetylation of the amino sugars such as glucosamine. The conversion of palmityl coenzyme A to palmit-

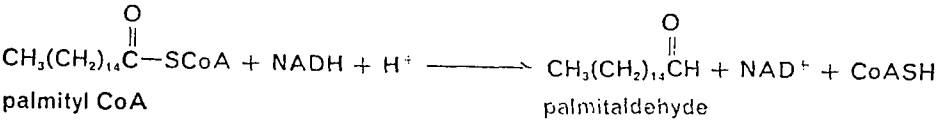
Glucosamine Acetylation



aldehyde by reduced pyridine nucleotide can be considered, at least formally, as an acyl transfer reaction. Here the acyl acceptor can be envisaged as a hydride ion derived from NADH.

Reactions where phosphate, thiol and even cyanide accept the substituent from acyl coenzyme A derivatives have been described in biological

Acyl coenzyme A reductase reaction

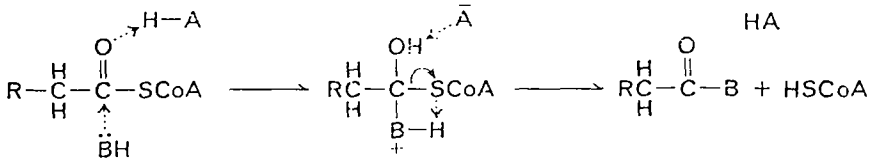


systems. Carbon is also an important acyl acceptor, generally reacting as a resonance-stabilized carbanion. Examples are the Claisen type ester condensation reactions to be discussed in section III.E.1.

The increased acyl transfer potential of thioesters as compared to corresponding oxygen esters is explained as being due to less double bond character in the bridging bond. The unpaired sulphur electrons do not have as high a tendency towards double bond formation as those of oxygen, and less electron delocalization or resonance stabilization of the bonding system is possible. This results in a longer and more easily displaced linkage. The lack of resonance with the ester sulphur also results in an enhanced electrophilic character of the carbonyl carbon. Thus, attack by nucleophiles at this position is facilitated.

The general mechanism for acyl transfer reactions from thioesters is envisaged as a nucleophilic attack at the positively polarized carbonyl carbon, accompanied by or followed by thiol elimination.

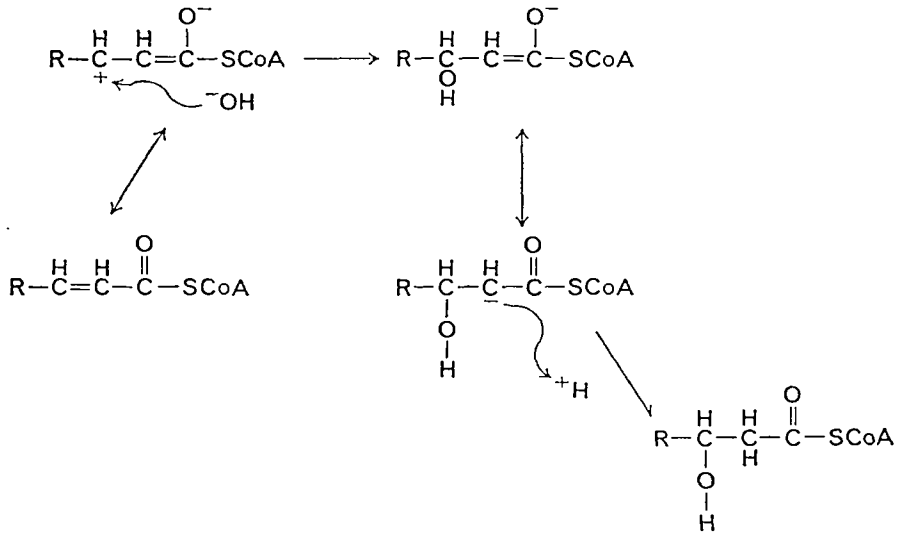
General transacylation mechanism from acyl coenzyme A



It is supposed that the enzyme participates by providing general acid and general base groups which facilitate the attack of the entering nucleophile, the departure of the thiolate and the polarization of the carbonyl. An intermediate acylated enzyme may occur in some reactions but this can simply be envisioned as a case where binding centre, catalytic groups and the initial attacking nucleophile are all provided by the enzyme.

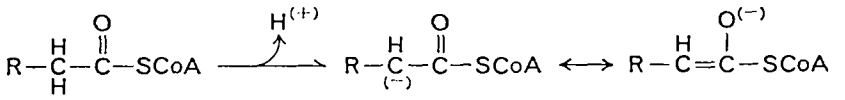
Coenzyme A thioesters can also promote nucleophilic attack at the β-carbon in α,β-enoyl derivatives. In these cases an electrophilic centre is stabilized at the β-carbon by resonance with the carbonyl system. This could be particularly favoured by hydrogen bonding or protonation of the carbonyl oxygen by an enzyme. An example is the enoyl coenzyme A hydratase reaction of fatty acid degradation.

β-substitution in α,β-enoyl coenzyme A thioesters



α-Activation is the other crucial aspect of thioester and acyl coenzyme A biochemistry. The formation of the thioester considerably increases the ketone-like character of the carbonyl group of the carboxylic acid. In addition to increasing the electrophilic behaviour of the carbonyl carbon, it enhances the acidity of the hydrogens at the α-position. This is normally attributed to the possibility for resonance stabilization involving the enolate anion.

Enolate stabilization in coenzyme A thioesters

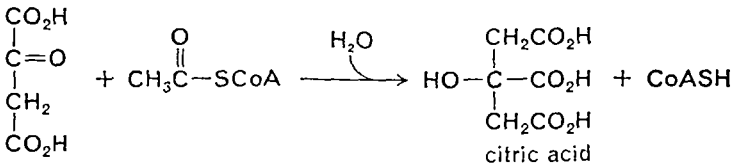


Enolate ion formation allows coenzyme A-bound acyl groups to serve as nucleophiles and to react at electrophilic centres. This permits thioesters to participate in the formation or degradation of carbon—carbon linkages by mechanisms analogous to the aldol condensation or more specifically the Claisen type ester condensation. There are few available mechanisms for carbon—carbon bond formation or cleavage which can be employed under biological reaction conditions, and pathways which depend on coenzyme A thioesters for this purpose are widespread.

The classic example is the reaction by which acetate carbon enters the tricarboxylic acid cycle, the citrate synthase reaction. Extensive mechanistic studies have established the involvement of the enolate of the acetyl

thioester in the enzyme reaction[42]. Exchange of the acetate hydrogens of acetyl coenzyme A with deuterium or tritium in the solvent is catalysed by the enzyme under conditions in which the condensation cannot occur.

Citrate synthase reaction

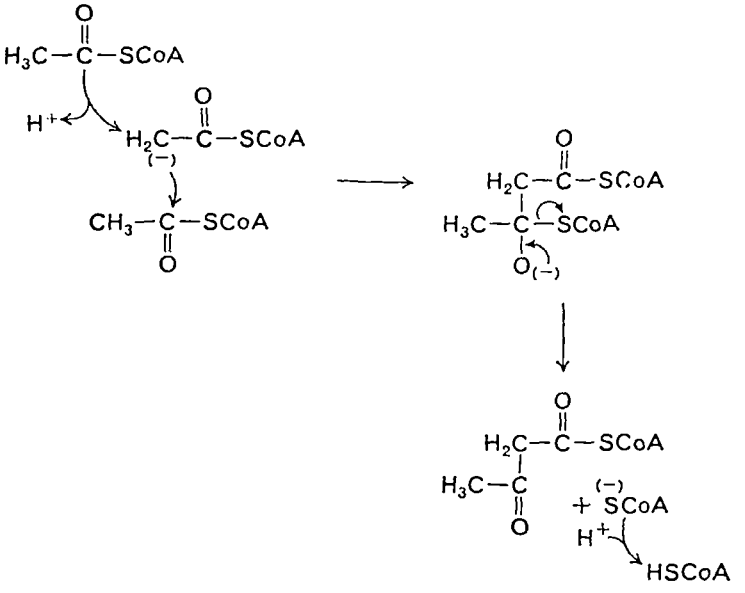


oxaloacetic acid citric acid

Initially this was not observed, exchange only being measurable when oxaloacetate was also present. This absence of exchange is now believed to result from a need to have oxaloacetate bound to the enzyme before the proper catalytic configuration can be achieved. This function can be served by certain other dicarboxylic acids which are not capable of undergoing the condensation reaction and the exchange activity has been demonstrated. A coenzyme A-facilitated enolization mechanism seems firmly established.

An example in which reactivity of both the attacking nucleophile and the electrophilic acceptor is dependent on the special character of acyl thioesters is in the condensation of two acetyl coenzyme A units to form acetoacetyl coenzyme A. This is the reverse of the thiolase reaction

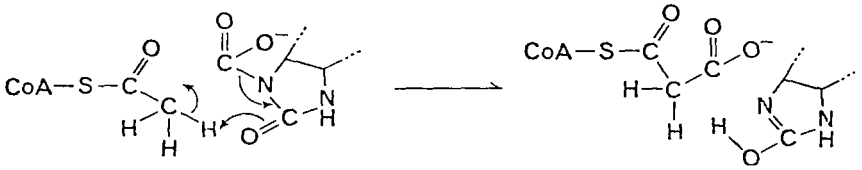
Condensation of two acetyl coenzyme A units



discussed previously. The actual mechanism of this reaction may involve an initial transfer of one acetyl grouping to an enzyme thiol prior to condensation, but the general reaction scheme is unchanged as thioacyl activation would still be involved.

α-Carbon activation is also involved in the biotin-mediated carboxylation of acetyl coenzyme A to malonyl coenzyme A, a critical and distinctive step in fatty acid biosynthesis[16]. Carbon dioxide is initially attached to a ureido carbon of biotin and then transferred to the methyl carbon of acetyl coenzyme A. A concerted mechanism for this transfer has been suggested rather than a pre-equilibrium enolization of the acetyl coenzyme A on the basis of the stereochemistry of the condensation[42]. The proposed reaction sequence is an example of how concerted substitution on the α-carbon of thioesters could be facilitated.

Mechanism of acetyl coenzyme A carboxylation

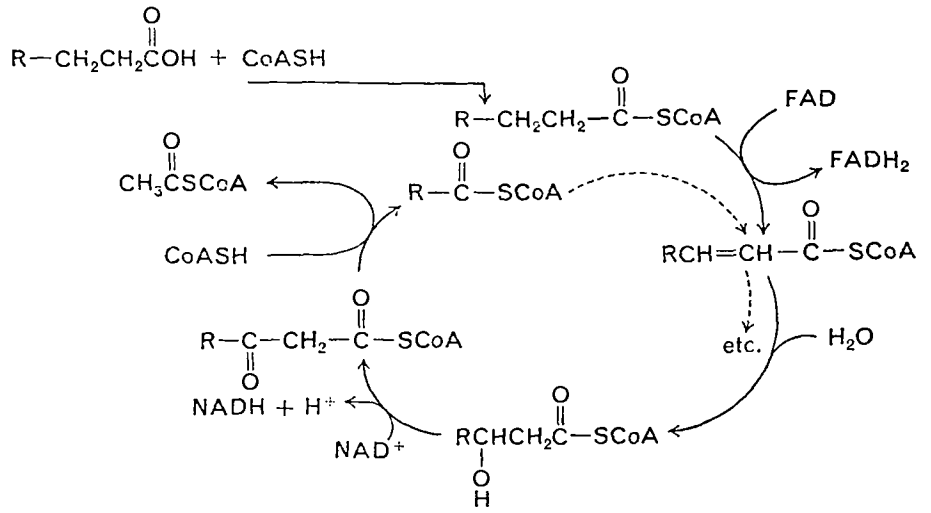


The thioester promotes the acidity of the α-hydrogens favouring hydrogen-bonded interaction with the ureido oxygen. In this case the promoting base and the electrophilic centre being attacked are part of the same structure, permitting a concerted electronic rearrangement without the necessity of an actual enolate ion. Since similar advantageous arrangements of reacting and catalytic functions are possible on enzymes, it is conceivable that other examples may also circumvent the pre-equilibrium enolate formation which would be predicted from analogy to solution chemistry. This does not alter the concept that thioesters facilitate such reactions by enhancing the acidity of α-hydrogens.

A convenient way to summarize the reactions of coenzyme A thioesters is by reviewing the β-oxidation pathway for fatty acids[46]. Fatty acid activation occurs by acylation of the coenzyme A thiol by way of an acyl adenylate. This is then dehydrogenated to an α,β-enoyl acyl coenzyme A derivative by a flavin-dependent dehydrogenase. The ability of the adjacent carbonyl to provide resonance stabilization of the product appears to be an important aspect of this reaction. Such flavin-dependent dehydrogenations occur in other reaction sequences, but only where carbonyl resonance stabilization is possible. Water adds to the α,β-enoyl thioester to generate a β-hydroxy fatty acid derivative, a reaction facilitated by β-carbonium ion stabilization in enoyl thioesters. The β-hydroxyl is next

reduced to a β-keto group. Such nicotinamide coenzyme-linked reductions to alcohols are common and no special advantage can be ascribed to the thioester. Thiolytic cleavage of the β-keto thioester releases acetyl coenzyme A and leaves a fatty acid derivative two carbons shorter than the original. The desaturation, hydration, dehydrogenation, thiolation sequence is repeated to reduce the chain by two carbons at a time with almost every step dependent on the unique properties of coenzyme A thioesters.

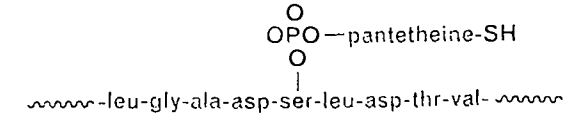
Fatty acid oxidation spiral



4. Phosphopantetheine proteins

Protein-bound phosphopantetheine has been found in recent years to be involved in acyl binding and reaction in much the same manner as coenzyme A [47]. A 77 amino acid protein was isolated from *E. coli* which acted as an acyl carrier in fatty acid synthesis. This protein completely lacked cysteine or other thiol amino acid, yet functioned by binding various acyl intermediates as thioesters. The reactive centre was phosphopantetheine linked to the protein through a phosphodiester bridge to serine. Similar acyl carrier proteins, or ACPs, have now been isolated from a variety of organisms and extensively characterized. An active ACP protein chain has even been prepared synthetically. ACP *per se* has been

Phosphopantetheine linkage in *E. coli* acyl carrier protein



difficult to demonstrate in higher organisms in which the intermediates of fatty acid synthesis are bound to high molecular weight complexes. It is reasonably certain that protein-bound phosphopantetheine is involved however, and an analogous protein cofactor is believed to be present in a tightly bound form. Phosphopantetheine prosthetic groups are now also known to function in other pathways.

Coenzyme A is the precursor of the enzyme-bound phosphopantetheine. The prosthetic group is added to the prosthetic group free protein (apo-ACP), by a phosphoryl transfer reaction employing coenzyme A as donor, yielding the functional complex protein, holo-APC:

Attachment of 4-phosphopantetheine to protein

$$\text{apo-ACP} + \text{coenzyme A} \longrightarrow \text{holo-ACP} + \text{3',5'-adenosine diphosphate}$$

The phosphopantetheine prosthetic group of ACP, fatty acid synthetase complexes, and presumably other enzyme systems, turn over rapidly, possibly as part of a cellular control mechanism. A specific phosphodiesterase cleaves holo-ACP to 4'-phosphopantetheine and the apoprotein:

Removal of 4-phosphopantetheine from protein

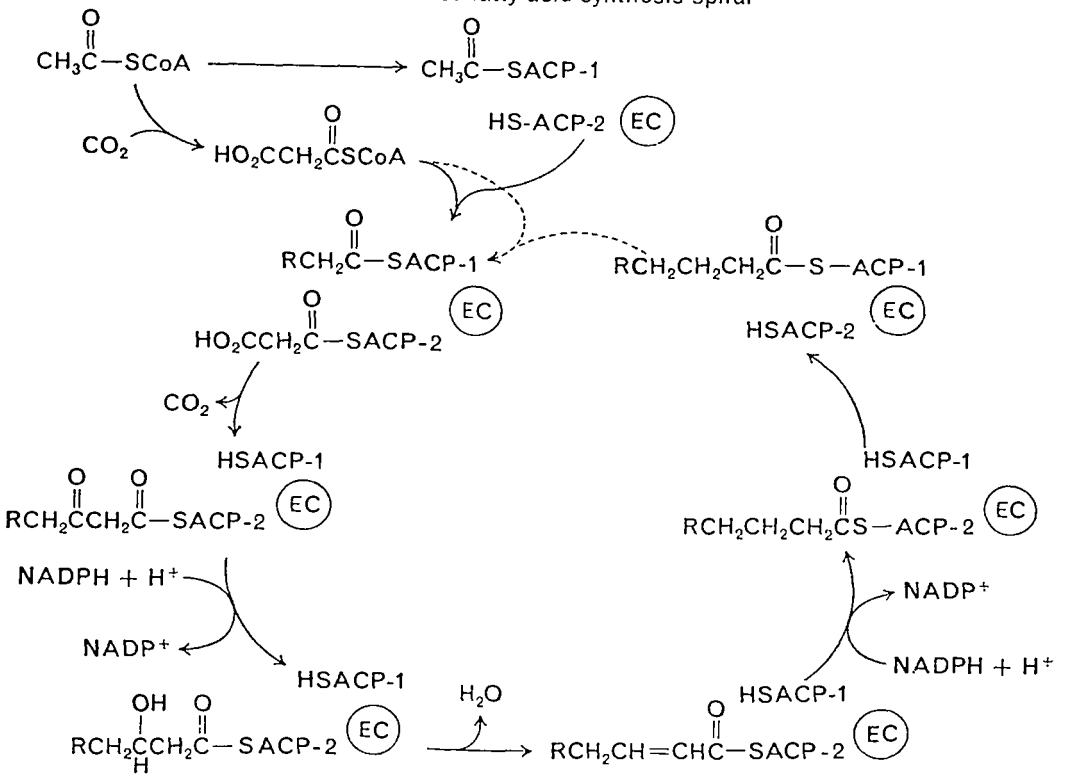
$$\text{holo-ACP} \xrightarrow{H_2O} \text{4-phosphopantetheine} + \text{apo-ACP}$$

The role of phosphopantetheine linked to protein is analogous to that in coenzyme A. Mechanistically fatty acid synthesis is pretty much a reversal of the β-oxidation pathway discussed earlier. There are however a few minor and one major differences. ACP rather than coenzyme A derivatives participate in synthesis and a nicotinamide coenzyme rather than a flavin cofactor is involved in double bond reduction. The major difference is that in the chain-elongating thioester condensation reaction the attacking nucleophilic carbon derives from a malonyl rather than an acetyl thioester. As indicated previously, malonyl coenzyme A is produced from acetyl coenzyme A by a biotin- and ATP-dependent CO_2 fixation reaction. Both acetyl and malonyl groupings are transacylated to ACP for fatty acid synthesis. Enzyme thiols, in addition to those of the phosphopantetheine prosthetic group, are also implicated in the process. In the yeast system, at least, a thioacyl linkage to a cysteinyl residue participates at one stage.

A turn of a generalized fatty acid synthesis spiral is presented below where the intermediate carriers are represented as ACP units tightly bound to a multienzyme complex, (EC).

Specific details vary somewhat from species to species, but this scheme illustrates a typical phosphopantetheine protein involvement.

Generalized fatty acid synthesis spiral



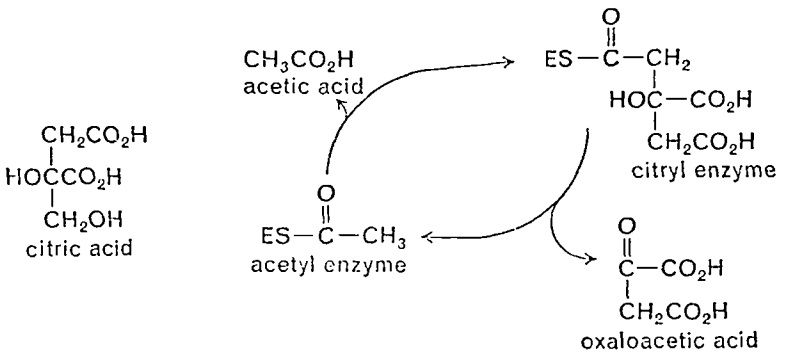
Acetyl coenzyme A transfers its substituent to ACP-1 of the synthetase complex where it serves as the start of the growing chain. A subsequent acetyl coenzyme A unit is carboxylated to malonyl coenzyme A and transferred to ACP-2. The acetyl (or higher homologue) segment then reacts with the malonyl methylene carbon accompanied by the release of CO_2 and freeing the thiol of ACP-1. The β-keto derivative of ACP-2 is then reduced to the β-hydroxy, dehydrated to the α,β-enoyl and reduced to the saturated fatty acid derivative. The acyl group is next transferred to ACP-1. With the entry of a new malonyl unit on ACP-2 the sequence repeats and the chain is built up two carbon units at a time. No intermediates are released from the complex until the long-chain fatty acid is completed. The fatty acyl linkage is then transferred from ACP-1 to coenzyme A for use in the synthesis of complex lipids. A direct utilization of the ACP thioester for acylation of lipids probably occurs in some systems.

The point of note is the special role of the malonyl thioester in the chain elongation process. The presence of the additional carboxylate group

adjacent to the methylene carbon increases the stabilization of a carbanion at this position. This further facilitates proton dissociation and attack at the carbonyl of the other ACP-bound thioester. The concerted loss of CO_2 renders the reaction essentially irreversible and provides a thermodynamic situation favourable for chain elongation.

Multienzyme complexes responsible for the assembly of the cyclic polypeptide antibiotics, gramicidin and tyrocidine, also contain protein-bound phosphopantetheine. This presumably participates in the enzyme-directed peptide bond assembly as an amino acyl carrier. Citrate lyase catalyses the cleavage of citrate to oxaloacetate and acetate without the involvement of coenzyme A. This has posed somewhat of a dilemma since thioester activation is considered mechanistically important in the oxaloacetate–acetate condensation sequence and presumably should also be necessary for decondensation. Recent evidence implies that the enzyme contains a phosphopantetheine unit which is acetylated in the active enzyme[48]. The reaction is envisaged as an acyl exchange with citrate, releasing acetate and generating a citryl thioenzyme. This then undergoes a thioester-promoted decondensation releasing oxaloacetate and re-generating the S-acetyl enzyme.

Proposed citrate lyase mechanism



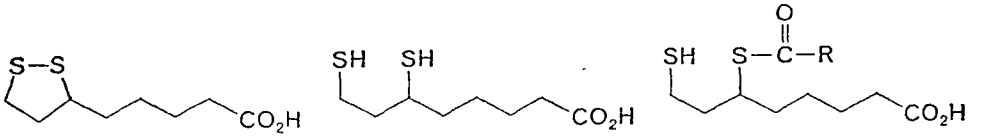
Thus the biological importance of the phosphopantetheine group as a catalytic centre is widespread. Numerous examples of the role of coenzyme A are known and the list of phosphopantetheine enzyme centres is growing. The principal reactive element is the thiol, although other attributes of the unique peptide will undoubtedly prove important. The thiol serves as the site of thioester formation and its particular chemical attributes facilitate acyl transfer, carbon chain modification and condensation reactions. The phosphopantetheine thiol represents the most

extensively investigated example of this functional group in biochemical processes.

D. Lipoic Acid[8,49]

Lipoic acid is a five-membered cyclic disulphide ring with a five-carbon carboxylic acid chain. When reduced it provides a constrained dithiol centre. This disulphide–dithiol cofactor is covalently bound to one of the enzymes in a multienzyme complex which catalyses oxidative decarboxylation of α-keto acids. In the course of the reaction three forms of the prosthetic group participate; the cyclic disulphide, the dithiol and a thioester of the dithiol form.

Forms of lipoic acid in α-keto acid decarboxylase-dehydrogenase

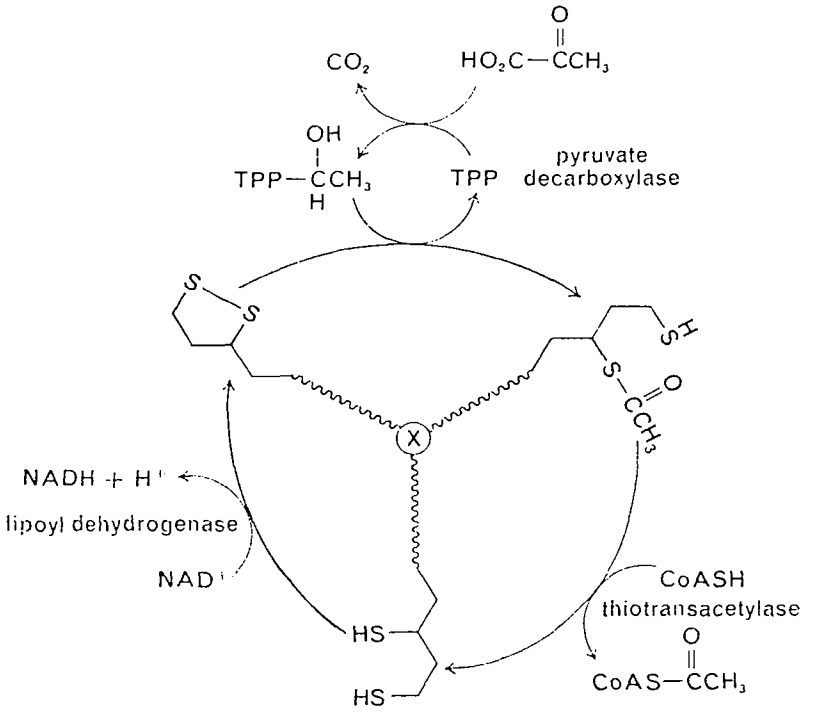


lipoic acid dihydrolipoic acid 6-S-acyl dihydrolipoic acid

The reactions of the α-keto acid decarboxylase system occur in a highly organized complex of enzymes which utilizes a number of cofactors in addition to lipoic acid[50]. It has been proposed that a long flexible arm resulting from the amide linkage of the lipoyl carboxylate to an ε-amino group of a protein lysine permits the disulphide–dithiol centre to swing from one active site to another within the confines of the complex. The lipoic acid centre therefore may serve a physical transport role within its special environment, in addition to its chemical participation in the reaction sequence. In the initial reaction of the α-keto acid system a thiamine pyrophosphate-mediated decarboxylation results in a thiamine–aldehyde adduct. This is oxidized by the lipoic acid disulphide and the resulting acyl transferred from thiamine to the thiol at carbon-6 of the dihydrolipoyl residue. A second enzyme of the complex then transfers the thioacyl from the dithiol to coenzyme A. This system thus provides one of the major routes for acyl coenzyme A production from sugar and amino acid metabolites. At the reactive centre of the third enzyme of the complex the lipoyl disulphide is regenerated by oxidation of the dithiol by a nicotinamide coenzyme. The dihydrolipoyl dehydrogenase is an unusual flavoprotein which will be discussed subsequently as an example of a dithiol–disulphide electron transfer protein.

Lipoic acid links two of the major biochemical roles of thiol groups, being both involved in electron transfer and the generation of high

Action of lipoic acid in pyruvate decarboxylase complex



energy thioester bonds. By positioning the two thiol groups in a close relationship specific oxidation is facilitated. The presence of strain in the five-membered dithiolane ring system also may be an important aspect of lipoic acid biochemistry, but its functional significance has remained moot.

There are relatively large amounts of lipoic acid and dihydrolipoyl dehydrogenase in photosynthetic tissues. Their presence still lacks a satisfactory explanation in terms of a particular functional role. Proposals implicating the lipoate dithiolane ring system in primary energy trapping or in the transfer and utilization of chlorophyll-trapped energy has not gained any real acceptance[51].

Photosynthetic carbon dioxide fixation into α-keto acids has recently been found to be the major pathway in some organisms. The process appears to be essentially a reversal of the mitochondrial oxidative decarboxylation process[52]. The photoreduction is mediated through a ferredoxin system similar to the photosynthetic nicotinamide coenzyme reductase. The involvement of lipoic acid has not yet been shown, but it would be expected and could provide the long-sought role of lipoate in photosynthesis.

The really unique reaction of the lipoate centre in α-keto acid metabolism is the oxidative thioester formation from a thiamine-coordinated 'active aldehyde'. Thiol transacetylase and dithiol–disulphide oxidation reduction roles are well-known attributes of other biological thiols. Unfortunately mechanistic studies on this reductive acylation of a cyclic disulphide have so far received little attention. Proposals that a lipoic acid–thiamine pyrophosphate compound was the functional entity in α-keto acid oxidation have been completely abandoned, but data supporting this concept remain unexplained. Investigations in this area might have some relevance for the reductive acylation process.

Enzyme systems have been found for the formation and hydrolysis of the lipoyl amide linkage at appropriate lysine ε-amino groups of enzymes[49]. The lipoic acid is activated by ATP to form a lipoyl adenylate, possibly as an enzyme-bound form, which then transfers the lipoyl group to the protein amino group.

Attachment and release of enzyme-bound lipoic acid

$$\text{lipoic acid} + \text{ATP} \longrightarrow \text{lipoyl-AMP} + H_4P_2O_7$$

$$\text{lipoyl-AMP} + H_2N\text{-protein} \longrightarrow \text{lipoyl-}\overset{H}{N}\text{-protein} + \text{AMP}$$

$$\text{lipoyl-}\overset{H}{N}\text{-protein} \xrightarrow{H_2O} \text{lipoic acid} + H_2N\text{-protein}$$

The specific cofactor attachment and removal system could reflect an effective enzyme control mechanism. At present there is no evidence that such a control is manifest within cells, and these reactions must be viewed as synthetic and degradative processes.

It should be noted that most enzyme studies concerning this disulphide–dithiol coenzyme have actually been carried out with either free lipoic acid or lipoamide and not a protein-bound cofactor. While this has been a pragmatic necessity, certain reserve should be maintained in extrapolating from such studies to the protein-bound prosthetic group.

The only established lipoic acid function is that in the α-keto acid decarboxylase–dehydrogenase complexes, although several examples of this type of enzyme with varying substrate specificities are known. Other examples of lipoic acid enzymes have been sought, but other dithiol–disulphide enzymes have been shown to be free of lipoic acid residues. Sulphoxide derivatives of lipoic acid are easily isolated, and their possible biological function has also been suggested. However, presently accepted dogma dismisses the more oxidized forms of lipoic acid as artifacts of air oxidation during isolation.

E. Thiol Proteins[53-56]

A large number of functional proteins are known in which substitution of some or all of the thiols of cysteine residues interferes with activity. Most frequently this is only a reflection of a requirement for the thiol in maintaining a proper configuration or subunit interaction. In some cases a thiol group is believed to exist in or near the active site and possibly play a role in substrate or cofactor binding. In a few enzymes the cysteine thiol is known to play a critical role in the catalytic process. In all of these cases enzyme activity or other biological function can be influenced by reaction of the protein with thiol-specific reagents. The diverse spectrum of chemicals used to probe for thiol function in biological reaction systems will not be discussed here, nor will the limits of their supposed specificity. Other sources should be consulted for information on these fascinating but overly extensive topics[57-59]. It is probably important to point out, however, that a variety of types of chemicals are commonly employed including metal ions, organometallics, alkylating agents, and disulphide oxidants. Sometimes quite different results are achieved with different agents. Furthermore, their specificity for thiol functions is not complete. Thus evidence for thiol groups based on thiol-specific reagents must always be viewed with caution. Only in those cases where there is strong collaborating evidence can indications for thiol function be considered secure.

Those proteins for which the thiol has no known specific function are not really of interest for the present discussion since no particular aspect of thiol chemistry can be related to the biological activity. Most of the emphasis will be reserved for thoses cases where the thiol group participation in the reaction is clearly established. Examples where thiol involvement is merely postulated will be mentioned only if they represent particularly interesting possibilities of thiol function.

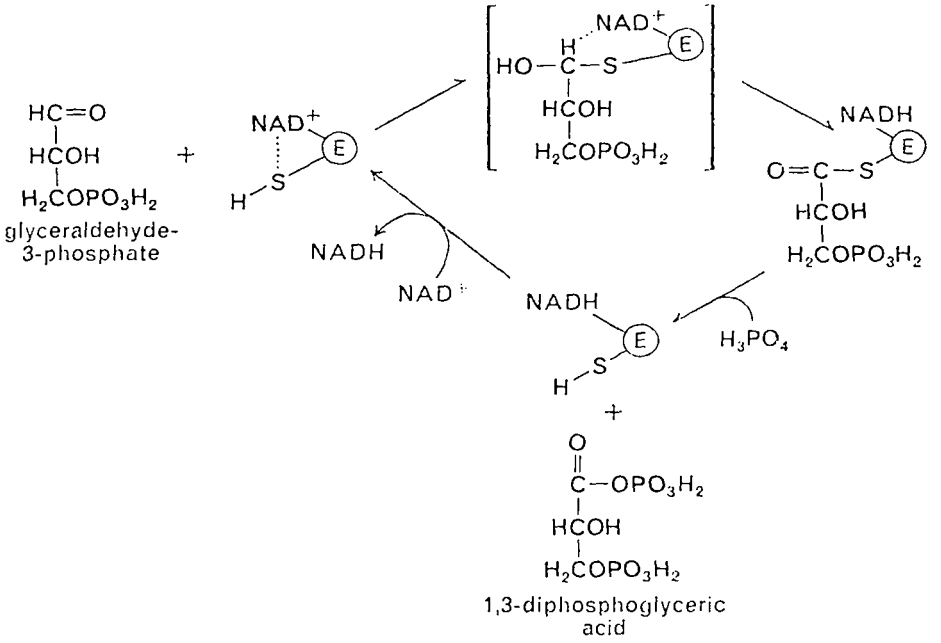
1. Thioester enzyme intermediates

Glyceraldehyde phosphate dehydrogenase probably holds the distinction of being the classic thiol enzyme in the minds of most biochemists[60,61]. The thiol is believed to be involved in the initial attachment of the aldehyde substrate as a thiohemiacetal. The enzyme-bound thiohemiacetal is then oxidized by NAD^+ generating an enzyme-bound thioester. In more sophisticated proposals for this mechanism the nicotinamide cofactor interacts with the active centre thiol as a charge transfer type of complex. This facilitates the reaction of the thiol with the carbonyl of the substrate. The thiol addition and the electron transfer to nicotinamide occur

simultaneously so that the thiohemiacetal actually does not build up as true steady state intermediate.

The thioester of phosphoglyceric acid is generated as an enzyme-bound reaction intermediate. It possesses a highly negative free energy of hydrolysis and is capable of driving ATP synthesis. The freely reversible interaction of a thiol with an aldehyde carbonyl followed by oxidation of the thiohemiacetal has provided the cell with a mechanism for trapping part of the energy released in the conversion of an aldehyde to an acid. The enzyme-bound thioester undergoes phosphorolysis in the normal course of events, freeing the enzyme thiol and producing 1,3-diphosphoglyceric acid. This enzyme system is fully reversible and the thioester intermediate can be generated from the acyl phosphate.

Glyceraldehyde phosphate dehydrogenase reaction

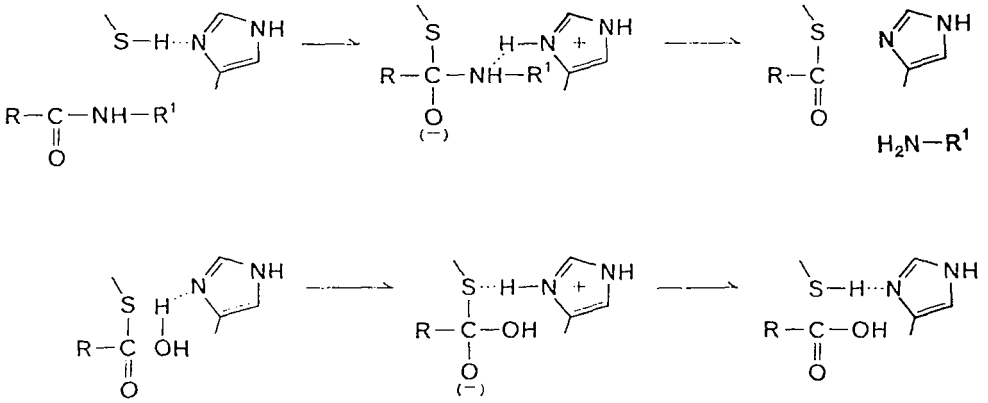


Treatment of the enzyme with acyl phosphate in the complete absence of reduced cofactor has allowed the thiol enzyme derivative to be prepared and separated from its reaction mixture. This in turn has permitted considerable characterization of the enzyme thiol. No special cofactor is involved. The thiol of a cysteine residue from the main peptide chain of the enzyme provides the reactive centre[33]. This enzyme demonstrates that the acyl transfer role of thioesters in biological systems is not restricted to phosphopantetheine and dihydrolipoate derivatives. The reactions of the

enzyme thioester are analogous with the transacylations to phosphate and hydride ion described previously (section III.C.3). Acyl transferase reactions to hydroxylamine, arsenate, methylmercaptan and even a nitrogen within the enzyme itself can be demonstrated with acylated glyceraldehyde phosphate dehydrogenase. These reactions probably have no biological significance but have proven useful in substantiating and characterizing the thioester intermediate.

The thiol enzyme for which the most detailed mechanistic formulations have been proposed is papain[62, 63]. In this enzyme a cysteine thiol group appears to function in the same manner as the serine hydroxyl of other proteases and esterases. In the hydrolysis of proteins by this plant protease there is an intermediate formation of an acyl thiol, which is subsequently cleaved by water.

Mechanism of papain proteolysis

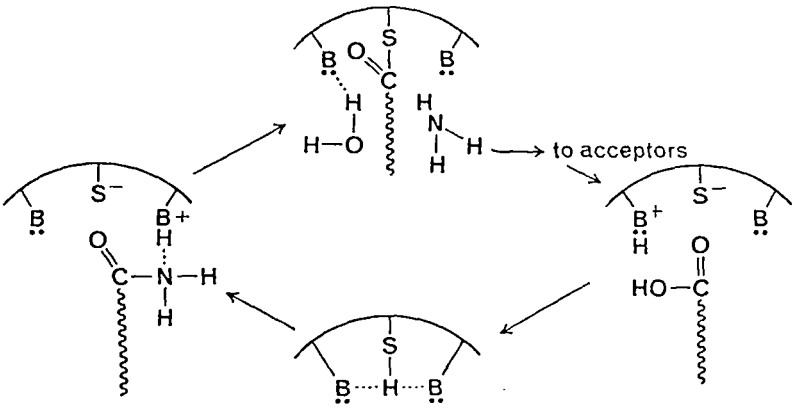


Imidazole from an enzyme histidine and possibly an enzyme carboxylate group are thought to participate in the reaction. X-ray crystal analysis of the protein[64] has established that a cysteine at position 25 and a histidine at position 159 are so positioned that they can participate in a hydrogen-bonded reactive centre. An aspartic acid at position 158 is also close enough to influence the reaction. The papain-active-centre thiol shows exceedingly rapid rates of reaction with certain thiol reagents. This suggests an enhanced nucleophilic character due to interaction with the imidazole and possibly other functional groupings in the reactive centre. The participation of a cysteine thiol in papain and other plant proteases must be considered unusual from the standpoint of thiol chemistry. Acyl transfer from amide nitrogen to sulphur is not considered thermodynamically reasonable, except under unusual circumstances. In this regard it is interesting to note that the active-centre serine hydroxyl of the

bacterial protease, subtilisin, can be chemically converted to a thiol and still retain certain enzymatic activities[65]. This stresses the critical importance of the proper juxtaposition of appropriate reactive groupings as opposed to the precise chemical attributes of any single functional group in enzymatic catalysis.

An intermediate formation of a thioester, facilitated by adjacent acid and base groups, has also been proposed as a general mechanism for glutamine-mediated amination reactions[66]. The apparent function of glutamine in such reactions is to provide a source of unhydrated ammonia at the reactive centre. This is accomplished by hydrolysis of the amide with the following type of mechanism being suggested:

Proposed reactions for ammonia generation from glutamine



Thus thioacyl cysteines appear to participate in the catalytic function of diverse types of enzymes, even when the conservation of a high energy bond is not the prime consideration.

2. Persulphide enzyme intermediates[1,67]

Rhodanese provides an example of a thiol enzyme of a somewhat different type. This enzyme, which is widely distributed throughout nature, catalyses the formation of thiocyanate from thiosulphate and cyanide. This reaction probably does not represent the true biological

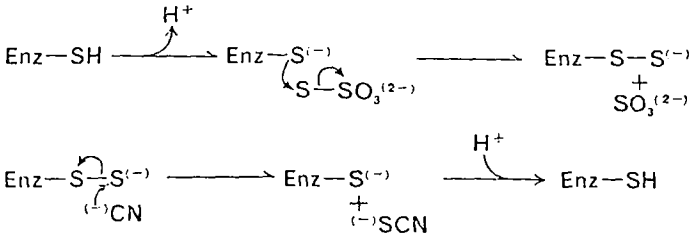
Rhodanese reaction

$$HSSO_3H + {}^{(-)}CN \longrightarrow {}^{(-)}SCN + H_2SO_3$$

action of the enzyme, although it could provide a system for the detoxification of cyanide. The reaction is more likely only a convenient means for the *in vitro* assay of some uncharacterized sulphur-transferring

system. The proposed mechanism involves an initial transfer of sulphur from the donor to an enzyme thiol group producing an enzyme persulphide. The persulphide sulphur is then displaced by the acceptor-regenerating enzyme thiol.

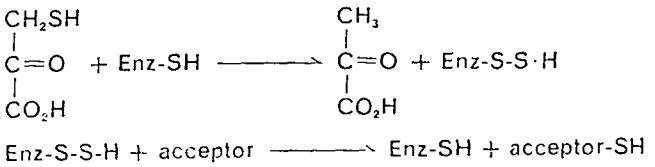
Persulphide enzyme mechanism for rhodanese



Some doubt that enzyme persulphide *per se* exists in the enzyme intermediate has been indicated, but at least an enzyme-stabilized equivalent of persulphide seems generally accepted. A release of the intermediate persulphide sulphur from the enzyme can be effected by heat or trichloroacetic acid treatment.

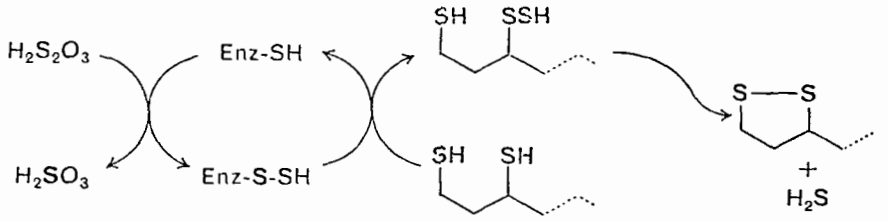
The enzyme transferring sulphur from 3-mercapto pyruvate appears to have a similar mechanism, involving a persulphide-like enzymatic intermediate. The possible role of this enzyme in transsulphuration from cysteine has been discussed earlier.

Thiol pyruvate transsulphurase reaction



In the presence of disulphide-reducing agents there is a production of sulphide from persulphide enzyme intermediates. Dihydrolipoate (or more likely a protein-bound form) may be a natural acceptor substrate for such enzymes. Only one optical isomer reacted in the rhodanese system, suggesting the presence of a specific binding site. It was presumed that one of the dihydrolipoyl thiols acted as the sulphur acceptor with a subsequent release of sulphide through displacement by the adjacent thiol. Therefore these enzymes may normally function in reductive desulphuration. Alternatively, transsulphuration by way of the enzyme persulphide may be the important biological process. It has been proposed that rhodanese, and by inference other enzyme persulphide transferases, may be the

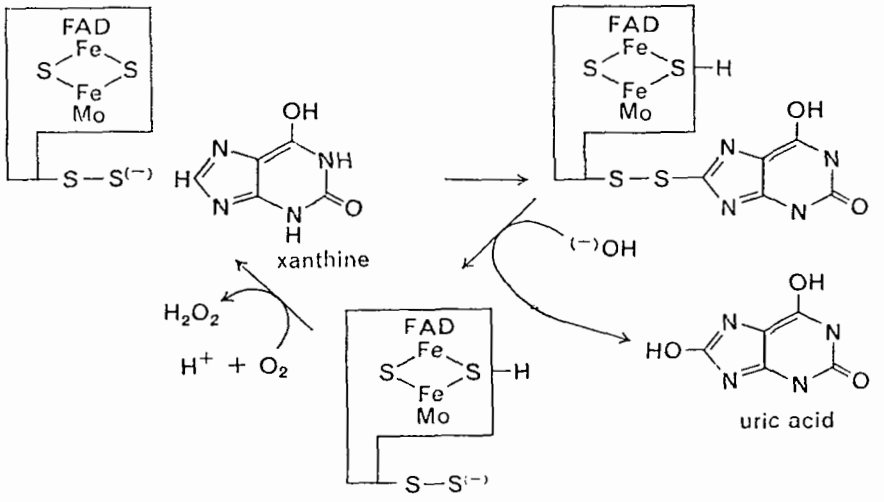
Possible persulphide mediated desulphydration mechanism



immediate donor of the 'labile sulphide' for the biosynthesis of nonhaem iron proteins such as ferredoxin[68].

Evidence for the presence of a persulphide group in the active form of xanthine oxidase has recently been presented, and a direct catalytic role for the group is proposed[69]. Thus protein persulphides may play a significant functional group role in their own right.

Proposed role of persulphide in xanthine oxidase

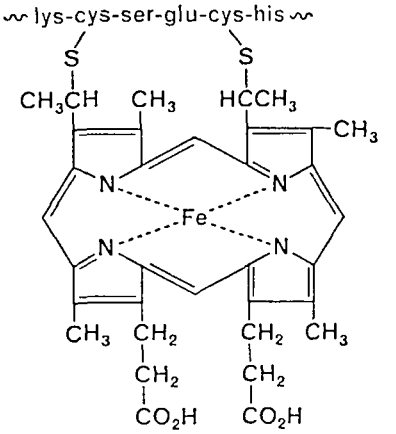


3. Thiol-binding centres

Another way thiols can participate in enzyme reactions is by binding substrates or coenzymes at the active site. A clear differentiation between involvement in catalytic and binding functions is seldom possible, but a binding role is presumed when protection of the critical thiol is afforded by the presence of substrate and no specific catalytic role is suspected. There are only a few proven examples of thiol substrate binding other than those already discussed in which a precise catalytic role is also proposed.

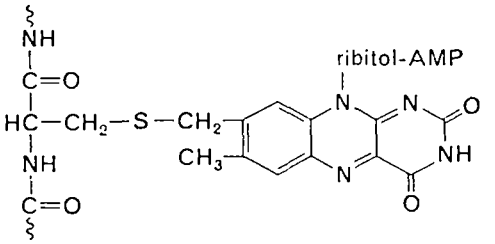
The clearest examples of thiol-binding centres are those in which the linkage is covalent. Attachment of the haem group to the cytochrome c protein occurs through two cysteine thiol residues[54]. The sulphydryls add across the double bond of two vinylic side chains of the iron tetrapyrrole, providing thioether bridges between the protein and the prosthetic group.

Haem linkage to human cytochrome c



The binding of a flavin prosthetic group to hepatic monamine oxidase has recently been reported to involve a thiol[70]. FAD is linked as a thioether formed between a cysteine and a methyl substituent on the dimethyl isoalloxazine. While binding is generally conceived to be a reversible process and these cases must be viewed as an extreme, they do provide clear examples of the general concept.

Flavin binding to monamine oxidase



A frequently postulated binding role for thiols is in the attachment of metals to metalloproteins[71]. The involvement of thiol ligands will influence the strength and specificity of metal-complexing centres and in this way could affect the structure and function of proteins in rather specific ways.

Polythiol metal-binding sites will be discussed in section III.F.4, but single thiols acting in conjunction with oxygen and nitrogen ligands are also quite important.

Loss of titratable thiol in the presence of zinc and the magnitudes of the stability constants for a series of enzyme–metal complexes has implicated a nitrogen–sulphur metal-binding centre in bovine carboxypeptidase. However, no cysteine side chains were found within the zinc coordination sphere on X-ray crystallographic analysis, casting considerable doubt on these conclusions[72]. A thiol has also been implicated in metal binding by human carbonic anhydrase, but the complete lack of cysteine in the bovine enzyme makes this contention somewhat uncertain since zinc binding by both enzymes is very similar. Metallothiol centres may themselves act as binding sites. A metal ion bridge is thought to be involved in nicotinamide coenzyme binding by alcohol dehydrogenase and there is evidence that the protein centre includes a thiol.

Most claims for thiol participation in binding are based on protection of sulphydryl groups by the presence of the ligand or on lack of binding if thiol groups have been blocked. Unfortunately, it has become increasingly obvious that such evidence does not necessarily mean that the thiol is directly involved or even that it is near the binding site. Attachment of substrate can simply mask an otherwise uninvolved thiol, or can induce a conformational shift which alters thiol reactivity. Conversely, the integrity of distant thiol groups may be necessary for the proper binding configuration of the protein. Their derivatization could produce structural rearrangements which would eliminate binding and activity in distant parts of the molecule. In fact, certain enzyme activities can be enhanced by thiol substitution, implying that the thiol effect must be taking place away from the active centre. Early studies showed that substitution of sulphydryl groups on haemoglobin altered the nature of the oxygen binding and eliminated haem–haem interactions[51]. This would now be explained as being due to alterations in subunit interaction since it is known that thiols are not in or near the oxygen-binding site[73].

4. Thiols and disulphides in protein structure[51]

The most common thiol role is participation in the overall structural integrity of proteins. Except for the special case of the disulphide linkage this can be viewed as a rather nonspecific and passive function. This is not to imply that in any given circumstance that another amino acid side chain might serve as effectively as cysteine or methionine, but rather to point out that these amino acids are no more critical in their place than are any other in theirs. From an experimental standpoint there is one

special significance of the sulphydryl group in protein structure. It is the ease and specificity with which it can be modified. The list of enzymes which have their activity influenced by thiol-specific reagents far exceeds the number for which a defined role in binding or catalysis can be established. In most of these cases it must be concluded that the thiol reagent sensitivity represents the loss of some critical structural feature upon thiol modification.

It is also not surprising that quite contradictory effects can sometimes be achieved with various thiol reagents since these introduce different bulk, ionic charge or hydrogen-binding capabilities at the site of substitution.

While offering little information on the active structure of proteins, modification of these 'structural' sulphydryl residues has been helpful to the biochemist in many instances[74]. As examples one can cite the increasing success of thiol reagents in dissociating subunit enzymes and releasing tightly bound cofactors without destroying covalent linkages. When the thiol blocking agent can subsequently be removed, as is the case with organic mercurials, the reassembly of functioning units can sometimes be achieved.

It is as the disulphide that the structural importance of the thiol in proteins can best be appreciated[75]. Covalent disulphide bonds provide bridges that are much stronger than the hydrophobic and hydrogen-bonded interactions believed responsible for initial protein folding. The real uniqueness of the thiol–disulphide structural system lies in the ease with which it may be formed, broken down and reformed under reasonable biological conditions. The principal method for the making and breaking of protein disulphides is by disulphide interchange. This process, as mediated by glutathione, can be coupled to cellular redox systems by a specific reduced nicotinamide coenzyme–disulphide reductase. Thus, protein disulphide structure can be formed, be rearranged and broken up by systems involving low molecular weight thiol–disulphide couples.

However, a major disulphide contribution to structures within the cell is made unlikely by the observation that disulphide bonds are relatively rare in intercellular proteins. In fact we have already discussed the possible role of glutathione in maintaining protein thiols in the reduced state. It is really with proteins that operate outside the cell that one finds the great importance of disulphide-stabilized structures. One can reasonably rationalize this fact in two ways. Since the protein must operate without the protective environment of the cell, random disulphide formation would eventually occur. By initially fixing most thiols as disulphides in an active configuration the chances for deleterious random disulphide formation

would be reduced. Another view would contend that extracellular proteins must survive and function in a much more variable and hostile environment than cellular enzymes. They therefore require greater rigidity and an ability to function even if partially damaged. These attributes are afforded by disulphide cross linking. Both explanations probably have some truth with the inevitability of disulphide formation and the increase in structural stability once formed contributing to the importance of this system. Since many of the most abundant and best studied proteins are extracellular many examples are known in which functional structure is dependent on disulphide bridges. Only a few examples illustrating certain generalizations will be discussed.

It is important to remember that the position of disulphide bonds cannot be directly specified by the genetic code and disulphide formation must occur subsequent to the assembly of the peptide chain. There is now strong evidence for the idea that the initial three-dimensional folding of a protein is totally a consequence of the primary amino acid sequence. The same is true for the association of subunits into functional complexes. It is only after weak interactions have brought about a highly favoured configuration that the disulphide formation occurs to 'lock in' the protein structure. Disulphide cross linking does not create form, but only fixes what was initially dictated by the linear peptide sequence and weak bonding forces.

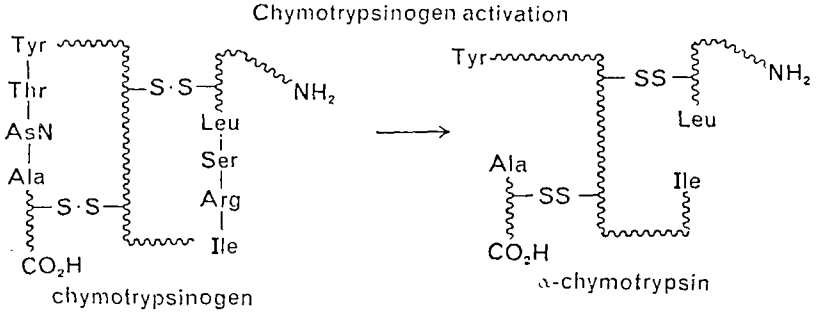
The exact nature of the oxidant for the normal biogenesis of disulphides is uncertain. Low molecular weight protein disulphide–dithiol electron transport carriers are implicated. The cytological localization of the process is more certain. A membrane-bound microsomal enzyme which catalyses a protein disulphide interchange is probably responsible for assembly of disulphide-stabilized structures. This activity is most prevalent in those cells which are producing and excreting disulphide-stabilized proteins. The enzyme occupies a position on the microsomal membranes at or near the site for ribosome binding. It is therefore directly available to act on the newly assembled peptide chains. Assay of this enzyme depends on its ability to reform the active, disulphide-stabilized, structure of ribonuclease from a randomly cross-linked material. Of the 105 possible disulphide combinations, only one is proper and active. Actually this one 'correct' structure can reform in reasonably high yield if oxidation conditions are properly controlled. The microsomal disulphide interchange enzyme facilitates the process by promoting rearrangement of inappropriate disulphide patterns. The interchange capacity of the system is important because it allows the newly formed protein to achieve its best and presumably proper folding pattern even if some premature oxidation

might occur. It also seems reasonable to assume for the present that this same enzyme is responsible for the initial oxidation of the thiols on the newly synthesized protein. Since this probably involves an intramolecular disulphide exchange with a disulphide–dithiol redox carrier no new catalytic capacity need be involved. The exclusive association of this disulphide interchange activity with rough endoplasmic reticulum is consistent with the idea that disulphide proteins only occur extracellularly. These are the cellular structures believed responsible for assembly and vacuolization of excretory proteins.

It is also possible that disulphide bond formation and rearrangement occurs after excretion of the protein from its cell of synthesis in some cases. This would best account for assembly of very large sulphur-rich aggregates such as hair. Exact cross linking fidelity is probably not so critical in these cases and complete assembly of such large cross-linked meshworks within a cell is clearly impossible.

The most dramatic examples of the importance of disulphides for biological function are found among enzymes which are initially produced as inactive precursor proteins. Chain folding and disulphide bonding patterns reflect the primary peptide structure of this inactive zymogen molecule. Activation usually involves the cleavage of peptide bonds and sizeable peptide segments may be removed[76]. The protein arrangement is no longer one that would form spontaneously. The maintenance of the active structure is completely dependent on the disulphide linkages.

Chymotrypsinogen, as synthesized by the pancreatic cells, is a single polypeptide chain which can maintain its native configuration if the disulphide links are reduced. Activation, by a series of peptide bond cleavages, eventually results in three separate polypeptide segments held together by disulphides, as indicated diagrammatically below. Destruction



of the disulphide links now results in separation of subunits. Reassembly cannot occur and activity is completely and irreversibly lost.

An example involving another familiar protein is the biosynthesis of insulin[77]. This hormone is assembled as a continuous chain of 73 amino acids. Subsequent to folding and the establishment of disulphide bonds, a 22-amino-acid segment is removed from the centre of the protein. This provides the two-standard, disulphide cross-linked structure of the active molecule. Thus one general function which can clearly be assigned to disulphides is the maintenance of appropriate structure after secondary protein modifications have occurred.

A closely related role for disulphide bridging is in 'freezing' subunit arrangements[76]. The four peptide chains of the typical antibody molecule are held together in proper position by disulphide bonds. A vast variety of individual antibodies can coexist in the blood without any mixing of subunits. If the disulphide bonds holding the chains together are reduced, the proper type of subunit interaction can be maintained under certain experimental conditions. However an interchange of subunits can now occur. The presence of the disulphide bridges in the native structure ensures that subunits forming the two identical and highly specific binding sites will remain together in the general circulation. While such subunit assemblies must be formed by spontaneous and reversible interactions at their point of synthesis, they can be prevented from undergoing subsequent rearrangement by disulphide bonding.

Large disulphide-linked aggregates are found in hair and related animal keratins[78,79]. In fact the cardinal characteristic of wool, nails, horns, feathers, etc. is their high sulphur content. The basic keratin system is believed by most to be composed of two protein subtypes. One type forms filamentous fibrils which are wound arrays of protein strands. Differing arrangements of fibres and patterns of protein folding distinguish the α- and β-keratins. Fibril proteins are rather low in cysteine content and hydrogen bonding and hydrophobic interactions impart their strong fibre-forming tendencies. The keratin fibres are embedded in a protein matrix having no recognizable order. The matrix proteins are extremely rich in cysteine and also enriched in serine, threonine and proline. The high sulphur proteins are extensively crosslinked to each other, and to the sulphur-poor fibrous constituents through disulphide bonds. The sulphur-rich fraction probably does not represent a single protein but rather a mixture of related proteins. The nature of this mixture and the amounts of the individual constituents vary with the type of structure formed (hair, feather, horn, etc.) and to some extent with the diet of the animal. Newly synthesized hair proteins are actually soluble, but by 4 to 6 hours they can no longer be extracted into water and by 18 to 20 hours much of the material cannot even be solubilized by urea. This suggests that assembly

of the crosslinked disulphide meshwork occurs long after the initial peptide assembly is completed. The high sulphur proteins have been extremely hard to study because of the difficulty in dissolving them without modifying backbone structures. The biochemistry of this complex system is only beginning to be unravelled, principally by chemists interested in modification of the basic structures for textile or cosmetic application. However, there is little doubt that disulphide bonds constitute the principal structural feature of hair and other keratin assemblies.

Another area in which a critical functional role for protein disulphides has been suggested is in the action of the polypeptide hormones[80]. A small cyclic disulphide loop is a common feature in many of these molecules. This has drawn attention as a possible site for hormone binding to the target cell. The greatest amount of evidence supporting this idea concerns the action of antidiuretic hormone or vasopressin. The hormone is bound in the kidney by a thiol-cleavable bond, and no such interaction occurs with other tissues. Thiol reagents prevent binding, and reduction of the hormone's disulphide causes inactivation. Diuretic effects can be achieved by a wide variety of compounds which share an ability to react with thiols. The idea of a disulphide loop being a site for attachment to a target thiol by disulphide interchange is attractive and may prove to be a generally significant disulphide function.

Almost all proteins contain some cysteine, but in only a minority of these can the thiol group be assigned a definite role. Nonetheless the list of thiol functions in proteins is long and clearly exemplifies the importance of this group in biological systems.

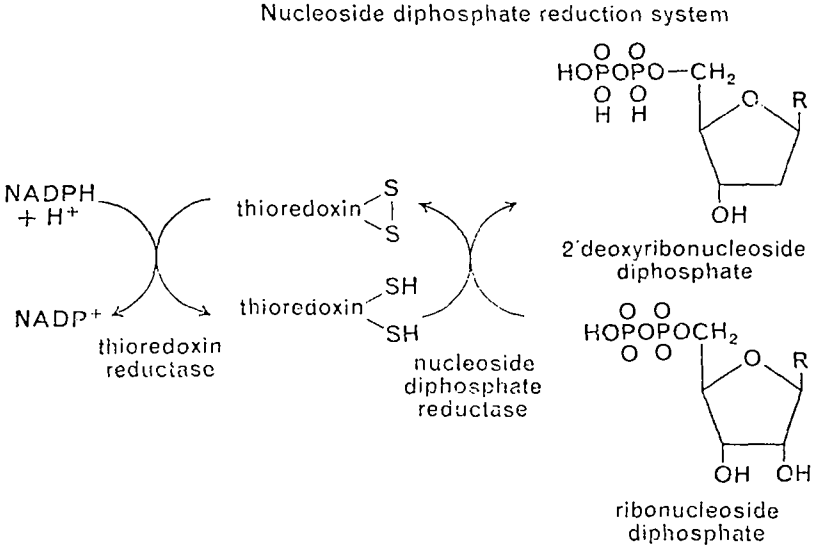
F. Dithiol and Polythiol Proteins[82]

A special type of thiol functional group can be achieved by constraining more than one thiol group into a polythiol centre. An example has already been considered, lipoic acid, where the presence of two thiols on the same carbon chain facilities a dithiol–disulphide redox system. A similar functional centre can be created by the close positioning of two cysteine thiols through appropriate secondary and tertiary folding of a polypeptide chain. Inhibition by arsenite or by cadmium has been considered to be indicative of a dithiol involvement in enzyme action. Unfortunately, a lack of knowledge about the precise chemical specificity of these dithiol reagents has left most suggestions of an enzyme dithiol in doubt. Several examples have now been supported by direct thiol assay or active site isolation, strengthening the dithiol enzyme concept. Recent studies on dithiol criteria should increase confidence in specific reagents when used appropriately[83], but also emphasize the deficiencies in the way such

criteria have often been applied. The division between mono- and dithiol functions is quite arbitrary. However, it does emphasize that something more than just a summation of two independent groups is achieved by making it possible for them to act in concert.

I. Thioredoxins[83]

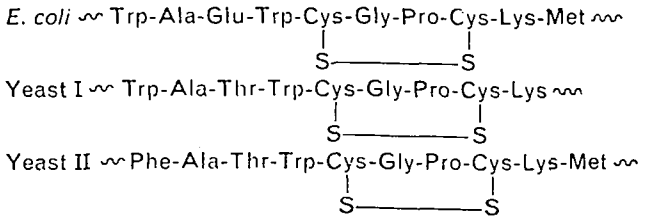
A dithiol protein, thioredoxin, functions in the transport of electrons from reduced nicotinamide adenine dinucleotide phosphate (NADPH) to ribonucleotides in the biosynthesis of 2′-deoxyribonucleotides. A thioredoxin type carrier is involved in both vitamin B_{12} dependent and independent type systems. Thioredoxin is frequently described as a polypeptide cofactor rather than an enzyme because its activity is not destroyed



by heating, and the molecular weight is relatively low (approximately 12,000). As such it is only one example of a class of small proteins carrying reactive centres which have been recognized in recent years.

Thioredoxin from *E. coli* contains only two cysteine residues which are linked as a disulphide in the oxidized form of the molecule. These residues are separated by two intervening amino acids, glycine and proline, providing a small polypeptide as the functional centre of the molecule. When two thioredoxins from yeast and the one from *E. coli* were compared, the amino acid sequences were identical in the immediate vicinity of the disulphide–dithiol centre, and quite similar for a considerable distance beyond.

Sequencies of thioredoxin active centres

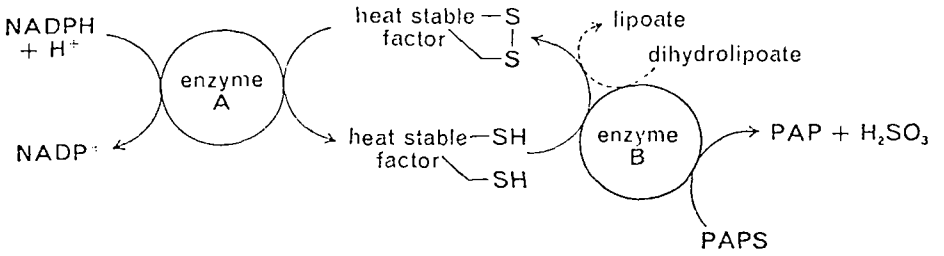


The thioredoxins appear to have a highly specific relationship with the enzyme carrying out their reduction. Yeast thioredoxin for example is not reduced by the thioredoxin reductase from *E. coli*. In contrast reduced thioredoxins may donate electrons to a variety of acceptors. Reduced thioredoxin is a good general disulphide reductant. In combination with its reductase a disulphide reductase system is formed which is capable of reducing lipoic acid, oxidized glutathione and other similar structures. In these cases the thioredoxin–disulphide redox system does not appear to require additional enzymatic components.

Reducing equivalents from a given thioredoxin can be donated to a variety of reductase enzymes. They are not specific for the nucleotide reductase or for enzymes from the same organism. Reduced yeast thioredoxin will serve as reductant for methionine sulphoxide reductase, sulphate reductase and the *E. coli* nucleoside diphosphate reductase. Heat-stable protein cofactors are known to be involved in each of these systems.

The sulphate reductase factor which has already been mentioned was the first of these polypeptide dithiol–disulphide cofactors to be recognized[3]. In this case the reduction of PAPS to PAP and sulphite was shown possible with a dithiol reductant such as dihydrolipoate or with NADPH and two protein components. One of the protein factors was not inactivated by heating. Incubation of the two protein fractions with NADPH generated

Electron transport system for sulphate reduction



approximately two moles of thiol associated with the heat-stable component. The heat-labile reductase enzyme could not of itself reduce lipoamide or other disulphides.

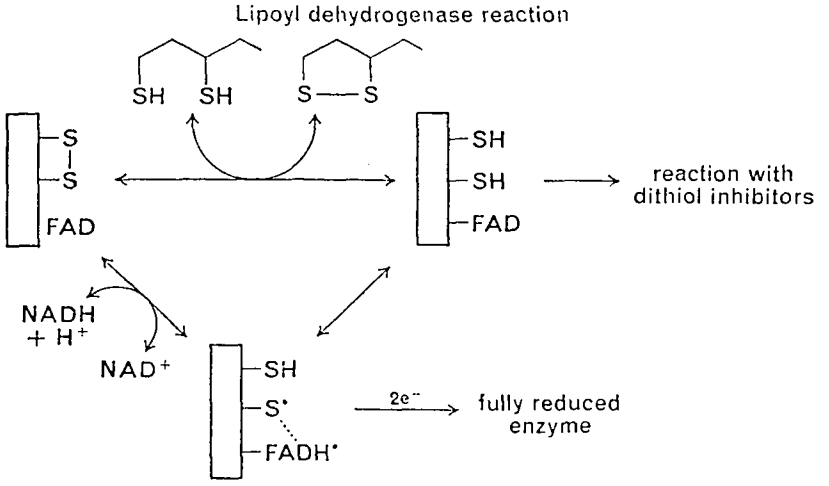
There is a growing literature on similar electron transport systems and it seems likely that such small protein disulphide–dithiol factors will be found to have a general biological role. It seems reasonable to refer to all cofactors of this type as thioredoxins, emphasizing that this is a class of compounds of similar but not identical structures which can show a high degree of specificity for a given organism or reaction.

2. Dithiol–flavin enzymes[86]

Disulphide–dithiol redox centres are also found in a number of high molecular weight electron-transporting enzymes. Most extensively studied of these are the group of flavoproteins which carry electrons between disulphide cofactors and nicotinamide nucleotides. These include lipoyl dehydrogenase, glutathione reductase and the thioredoxin reductases. These enzymes are unique in utilizing a combined flavin–disulphide centre for the oxidation of reduced nicotinamide coenzyme. Each reactive enzyme centre is composed of a disulphide formed from two cysteine sulphydryls and a tightly bound flavin adenine dinucleotide (FAD). Upon reduction by reduced nicotinamide cofactor the two-electron equivalents are shared between the dithiol and the flavin prosthetic groups. A fully reduced four-electron enzyme containing a dithiol and $FADH_2$ does not occur during the normal catalytic cycle. The reduced enzyme site is envisaged as some sort of mixed free radical with one electron on sulphur and the other in the flavin system. This is not a conventional flavin semi-quinone and the possibility of a charge transfer complex between the active elements of the redox centre has been proposed. Complete electron transfer to the dithiol centre and reduction of the disulphide substrate through a disulphide interchange sequence completes the catalytic cycle.

These dithiol–flavoproteins transport electrons over a redox potential range considerably more reducing than is associated with free flavin and most other types of flavin enzymes. By acting in conjunction with the protein dithiol centre, flavin is transformed into a much more powerful reducing agent.

The sequences of the dithiol active centres of two enzymes of this type from *E. coli* have recently been reported[87,88]. The lipoyl dehydrogenase dithiol peptide has four amino acids intervening between the two cysteines and is rich in hydrophobic amino acids. This has been taken as a reflection of a highly hydrophobic pocket at the catalytic centre, as had been implicated by model substrate studies. The thioredoxin reductase dithiol



centre has only two residues between the cysteines. The dithiol peptide of thioredoxin itself is the same size as that of its reductase but the sequences are quite distinct.

Amino acid sequences of dithiol-disulphide centres

Lipoyl dehydrogenase ~ val-cys-leu-asn-val-gly-cys-ilu-pro-ser
S——————S

Thioredoxin reductase ~ ala-cys-ala-thr-cys-asp-gly-phe ~
S———S

Amino acid sequences of the known dithiol–disulphide redox centres provide little hope that any specific peptide structure will be found associated with this particular activity. Even the size of the disulphide ring systems vary, so one must conclude that it is the overall folding of the protein which is responsible for the correct juxtaposition of the functional elements.

3. Other dithiol enzymes[82]

The presence of dithiol centres at the active sites of a variety of additional enzymes has been proposed on the basis of inhibition studies. For example, the investigations on aldehyde dehydrogenase represent one of the earliest uses of arsenite as a dithiol diagnostic reagent. The overall data strongly support the presence of a polythiol site as a general feature of aldehyde oxidases, but its functional role has not been established. Because of the ease of thioacetal formation a dithiol would make a chemically attractive

aldehyde binding site. The failure to find lipoic acid as a part of these enzymes makes it likely that the dithiol centre arises from the juxtaposition of cysteine thiol residues.

The light-emitting luciferase system from fireflies has been extensively studied and there is strong support for a functional dithiol[89]. The extensive thiol involvement in fatty acid biosynthesis has already been indicated, and some enzyme components have characteristics expected of dithiol centres. There are many additional systems where there is some evidence for dithiol involvement, but proof for a clear functional role of a dithiol is lacking.

4. Polythiol metal-binding centres[90]

A polythiol centre can serve as a highly specific metal ion binding site. For example, polythiol ligands have come to be thought of as relatively selective for cadmium. Actually a number of important metal ions including mercury, zinc, lead, copper and iron bind quite well at such centres[91]. The order of relative binding affinities for polythiol chelates is different from those involving nitrogen or oxygen ligands. Cadmium, mercury and to a lesser degree zinc form the most avid complexes.

The polythiol metal complexes can provide functional centres with unique properties, an example being the nonhaem iron proteins to be discussed in the next section. They also are capable of serving rather distinctive structural roles, since the binding of metals can influence the overall configuration of the protein. Studies on cadmium and zinc binding to thiol-substituted dextran polymers showed that these metals can actually organize polythiol-binding centres and might appreciably change the folding of a polypeptide chain[90].

Metals with a high affinity for multithiol coordination thus could serve to generate and stabilize particular protein conformations. Several examples of structurally important metal–polythiol interaction have recently appeared. *E. coli* aspartate transcarbamylase, the subject of extensive investigations concerned with mechanisms for enzyme control, has been shown to contain zinc. Zinc binding appears to occur at a dithiol centre. The metal is required to maintain the regulatory subunit in a configuration suitable for binding to the catalytic subunit[92]. Histidine ammonia-lyase is dependent on cadmium when enzyme disulphides have been reduced, and this has been shown to be due to the formation of a metallo-dithiol complex[93]. The reactive thiols appear to be contributed by separate subunits and the complex formation establishes an appropriate interaction of the individual components. In the oxidized enzyme, these thiols are linked as a disulphide and this form of metal ion activation is

not required. In bovine superoxide dismutase the proper conformation for the binding of an active site copper ion is maintained by a distinct zinc-binding centre[94]. Two sulphydryl groups per zinc are uncovered on removal of this metal implicating a dithiol-binding site. Metal binding at specific dithiol or polythiol sites could constitute a general mechanism for stabilizing protein conformation or facilitating interaction between subunits.

A cadmium-rich protein, metallothionein, has been isolated from kidney and other tissues[91]. It is a small protein of about 7000 molecular weight and is exceedingly rich in thiol groups. One out of every four to five amino acids is cysteine, and three thiols are involved in each cadmium-binding site. The biological importance of metallothionein is unknown. The simplest role envisaged is scavenging toxic metal ions which might otherwise interfere with critical enzymatic processes. Metallothionein from kidneys of patients treated with mercurial diuretics contained increased amounts of mercury which could reflect a toxic ion sequestering action of the protein. Another interpretation might be that metallothionein is an undegradable and unexcretable end product. It might have been derived from a thiol-rich centre of a protein(s) which had been inactivated by cadmium. The isolated material would merely be the accumulating debris of toxic insult. A somewhat intermediate viewpoint would ascribe a normal trace metal-binding role to metallothionein. A similar constituent has been isolated from liver and contains primarily zinc and copper. If the protein's normal function was the storage or mobilization of these two critical trace metals, cadmium would interfere because of its avid binding. This would eventually lead to inactive cadmium- (or mercury-) saturated forms such as those isolated from the kidney. Whatever its role, metallothionein is an excellent example of polythiols serving as selective metal-binding sites.

5. Iron–sulphur redox proteins[95,96]

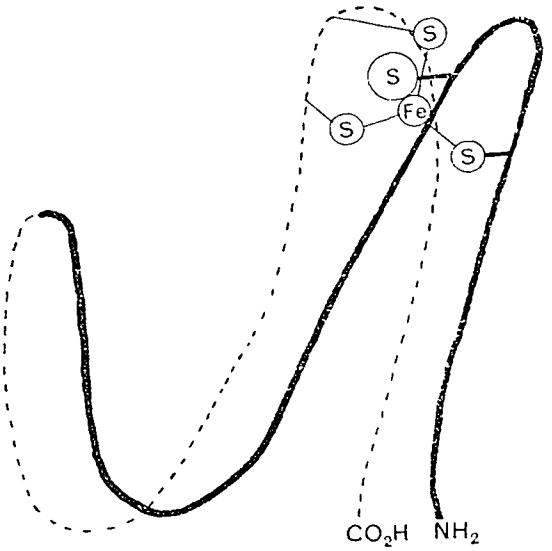
One rapidly advancing area of thiol biochemistry involves a group of iron–sulphur redox proteins, most commonly referred to as the nonhaem iron proteins. This designation derives from the fact that more iron was present in electron transport complexes than could be accounted for by the haem content. In the investigation of bacterial nitrogen fixation a low molecular weight iron containing protein was isolated which functioned as an electron transport carrier. This was named ferredoxin. An unusual characteristic was that when the protein was treated with acid to release iron, hydrogen sulphide was also produced. A component of the photosynthetic nicotinamide coenzyme reductase system was recognized as

having similar properties and has come to be referred to as plant ferredoxin. Adrenodoxin, putidaredoxin, rubredoxin and high potential iron-protein are additional nonhaem iron electron transport proteins of a similar character. A variety of high molecular weight electron transporting enzymes also have been found to have nonhaem iron centres. A triad of characteristics has come to be associated: (1) a tightly bound iron, not accountable for as haem iron; (2) an unusual e.p.r. signal in the vicinity of $G = 1{\cdot}96$, not characteristic of typical iron chelates; and (3) the release of iron on acidification accompanied by the unmasking of protein thiol groups and the generation of hydrogen sulphide. While each of these characteristics is not always demonstrable, they have served to delineate a heretofore unrecognized redox centre of wide distribution.

An intense effort by physicists, physical chemists, biochemists, inorganic chemists and X-ray crystallographers has now defined the common attribute of the nonhaem iron proteins. It is an iron centre tetrahedrally coordinated by four sulphur ligands. A number of variations within this theme are recognized. The simplest case is found to be rubredoxin from *Clostridium pasteurianum*, a 6000 molecular weight protein whose exact electron transport function is unknown.

A single iron atom is bound by four cysteine sulphurs with no acid labile sulphur being involved. A detailed crystallographic analysis of this molecule has been carried out, the general features of which are indicated below[97].

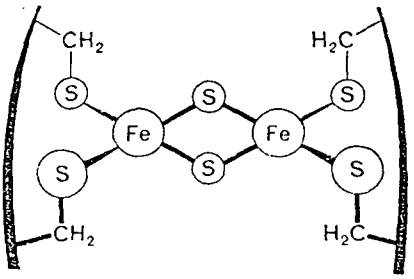
Iron binding site of rubredoxin



The peptide chain can be roughly described as a bent hairpin. The iron-binding centre consists of two small dithiol peptide segments. These dithiol centres are quite distant in the linear peptide sequence occurring in the end halves of the two legs of the hairpin. The peptide folding transforms these into a compact tetrathiol iron-binding centre. While this simplified description does great injustice to the details of the X-ray structure analysis, it serves to illustrate the critical features of the metal-binding centre. It also draws attention to a possible relationship of the iron–sulphur proteins to the disulphide–dithiol redox carriers considered previously.

The more typical iron–sulphur centre contains two iron atoms, two sulphides and four cysteine sulphurs[98]. It is believed that each iron is surrounded by four sulphur ligands in an approximate tetrahedral array. Every iron is coordinated by two sulphurs from cysteine and two from sulphide, with each of the sulphides binding both irons. The general structure of the two-iron redox centre is depicted below.

Proposed structure of a two-iron centre



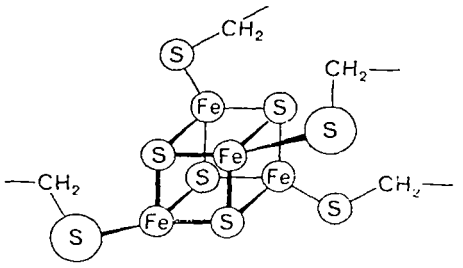
Another arrangement for an iron–sulphur redox centre is found in HiPIP (high potential iron–protein) from *Chromatium* and the bacterial ferredoxins[99,100]. These structures have been elegantly established by X-ray crystallography. The redox centre contains four iron atoms, four sulphide sulphurs and four cysteine sulphurs from the protein. Each iron is again surrounded by four sulphur ligands in an approximate tetrahedral arrangement, but each sulphide sulphur now interacts with three irons. The irons are bonded to three sulphides and one cysteine sulphur. The iron–sulphur array is roughly cubical with the corners being either a sulphide sulphur or an iron linked to the protein shell.

Bacterial ferredoxin actually contains eight irons and eight labile sulphides, but these are arranged as two distinct four-iron clusters.

Iron–sulphur proteins participate as one electron carriers, even those with reactive sites containing four irons. Each centre rather than each

iron must be counted as an electron transport unit. Only the bacterial ferredoxin acts as a two-electron acceptor and even in this case it is really two Fe_4S_4 one-electron centres acting independently.

Arrangement of the Fe_4S_4 nonhaem iron centre



Iron–sulphur prosthetic groups of a similar nature are also implicated in more complex higher molecular weight electron-transferring enzymes. Examples such as xanthine oxidase have been extensively examined and the type of iron–sulphur centre seems analogous to those in the lower molecular weight cofactors. For the present at least the nonhaem iron centres of complex electron transport chains can also be envisaged as enzyme polythiol sites generated by the juxtaposition of two protein dithiol sequences. Coordinated within this tetrathiol cavity is an iron–sulphide core.

What is it about divalent sulphur which results in such unique and biologically useful complexes of iron? The special feature of these prosthetic groups is that the iron is held in what approximates a tetrahedral complex, while all common iron complexes with oxygen and nitrogen ligands are octahedral. Tetrahedral iron–oxygen complexes are known, but only as high molecular weight networks where there seems to be a requirement for a condensed packing. One critical difference in the sulphur ligand could simply be effective size. Since the outer orbitals of sulphur are occupied it might be difficult to pack six ligands around an iron. The less crowded tetrahedral arrangement would therefore be favoured. The capacity of sulphur for expansion of the valence shell also might be considered of importance for moving electrons into and out of the complex and for delocalizing electrons in the reduced complex. The intense research activity currently focused on these iron–sulphur proteins ensures that our understanding of this aspect of thiol biochemistry will improve rapidly.

The variety of oxidation–reduction carriers having a dithiol centre as a part of their structure suggests a possible evolutionary relationship.

Dithiol–disulphide redox roles in primitive systems would have favoured the development of dicysteinyl peptides, restraining two thiols in close proximity. Thioredoxin type molecules would have evolved from these small prototype dithiol peptides. Similar centres would also have developed as parts of more complex enzymes. The binding of a flavin coenzyme near a dithiol centre could eventually have produced the combined disulphide–flavoprotein centre with its special redox properties.

The propensity for dithiols to bind metals would have led to a further evolution of function. Metal–protein bridging may have preceded disulphides as a method of holding proteins in effective organization particularly before the oxidizing environment developed. Iron–sulphur complexes had redox potentials different from other iron carriers and the dithiol. They eventually developed into the powerful reducing system of the ferredoxins by combining two dithiol ligands around one iron. Simple iron sulphide aggregates were also incorporated giving rise to the two iron-two sulphide and four iron-four sulphide variants. As more iron–sulphur atoms condensed into a single site, the redox possibilities increased and the iron–sulphur centre became involved in the variety of different redox roles seen today.

Cytochrome C might also have arisen from a dithiol redox protein as the haem-binding centre is nothing more than a dithiol peptide. While such speculations on the evolution of biomolecules are only mental games, they point out how the dithiol can be modified to carry out a variety of related functions.

IV. CONCLUSION

The thiol and its simple derivatives represent an exceedingly important and versatile functional centre in biological molecules. A number of basic metabolic processes are dependent on the particular chemical characteristics of thiol derivatives. It is difficult to imagine how metabolism might have evolved without the rich supply of thiols which probably were available in the 'primordial soup'. Actually thiols or their derivatives participate in so many biological reactions that one is amazed to find they have no indispensable role in the central dogma of molecular biology. Self-replication, transcription and translation rely only periferally on thiols. It is in the realms of catalysis and structure, the domains of the enzymologist and protein physical chemist, that the thiol is of central importance.

Thiols have been of foremost importance in the development of the functional group concept in biochemistry. Because of its ease of

manipulation the thiol, particularly that of glutathione, has fascinated the biochemist. All manner of roles have been suggested but most of these have not been proven, and many are totally forgotten. Still the chemical approach to biochemistry and the attempt to explain how biological reactions occur in terms of model organic systems had much of its initial success in explaining thiol-mediated reactions. The sulphur of the thioester provides activation for acyl transfer, and an intermediate in amide and ester hydrolysis. It facilitates α-hydrogen dissociation and provides a mechanism for carbon–carbon condensation and chain modifications. Reduction of carboxylic acids is preceded by thioester formation. Energy released by oxidative metabolism is trapped as a thioester, a form suitable for driving the synthesis of ATP.

The disulphide and certain thiol–metal ion derivatives serve as carriers of electrons and function in biological redox reactions of diverse types. Thiols and their metal derivatives provide strong binding centres for substrates and cofactors. They often help maintain proper protein configurations and subunit interactions. The disulphides of extracellular proteins are of profound structural importance. They make relatively permanent the arrangements of peptide chains initially established by weaker bonding forces. Often they become totally responsible for holding the active structure together, particularly where covalent modification of the protein chain is involved in activation. Animal keratins are particularly rich in sulphur, deriving their inertness from extensive disulphide cross linking.

The sulphonium ion serves as an alkylating reagent. The bulk of biological methylations proceed through S-adenosyl methionine. Persulphides, thiophosphates, thiocyanates and thiosulphonate derivatives have been postulated to have significant functional roles. The plant kingdom in particular is full of strange thiols and thiol derivatives which impart characteristic tastes and smells. Their functions are unknown, but could range from insect attractant to water repellent. Vitamins such as thiamine and biotin have heterocyclic sulphur which can be viewed as thiol derivatives. Even the simplest thiol of all, sulphide, finds a critical biochemical involvement in the iron–sulphur electron transport centres.

Thiols provide the living systems with a link to their genesis in a reducing environment. Glutathione helps maintain the cellular interior in a state in which enzyme activities evolved in the absence of oxygen can still function. Protection from all sorts of injurious agents, detoxification and anti-radiation roles can be added to complete the listing of thiol functions in biological systems. The intense fascination of the biochemist with the thiol functional group can certainly be appreciated.

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* The aim of this chapter is to present a general coverage of the biochemistry of thiols rather than a review of recent advances. As such this is a departure from the usual coverage of material in this volume. The biochemical literature encompassed by this subject is immense, and many excellent reviews, monographs and symposia have been devoted to certain aspects of the topic. If possible referencing has been restricted to these secondary sources, since it was presumed that an interested reader would prefer to see these before proceeding to original material. It has of course been necessary to cite also primary literature when no suitable secondary source could be found. The article cited, however, is usually one of the most recent in that area and not necessarily the most pertinent to the subject being discussed. No attempt was made to include a comprehensive coverage of even the recent literature, but often typical papers have been cited in order to provide a reasonable point of entry to the literature of rapidly expanding areas. This heavy reliance on secondary sources and the desire to present the material in as generalized a form as possible have done great injustice to original data and to its original interpretations in many cases. It is also realized that many excellent papers and ideas have been ignored or completely missed. While this is regrettable, the scope of the subject probably makes it inevitable, and only a simple apology can be offered.

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CHAPTER 14

Protection of the thiol group

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I. INTRODUCTION

The thiol group readily undergoes a variety of chemical reactions (e.g. oxidation, alkylation, acylation), so there is a need to protect it while other sites in the molecule are undergoing chemical changes. This can be done by converting the thiol group to a derivative which is stable under the reaction conditions to be employed, and from which the thiol group can be regenerated without affecting the rest of the molecule.

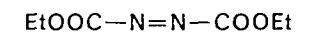
The great interest in thiol-protecting groups is due mainly to the significant development in the chemical synthesis of peptides, polypeptides and proteins. It is important to note that only one kind of a protecting group is needed to protect the various cysteine thiols during a protein synthesis. This results from the spontaneous refolding of proteins which takes place upon reoxidation of their sulphydryl groups produced by reduction of the protein with mercaptoethanol. This phenomenon was observed first with ribonuclease where the reoxidized molecule retained its full biological activity[1] and extended to a large number of proteins (e.g. insulin, lysozyme).

We shall try in this chapter to concentrate on the processes involved in the formation and deblocking of various types of protecting groups.

II. DISULPHIDES AS A PROTECTING GROUP

Disulphides are much less prone to participate in organic reactions (e.g. oxidation, alkylation, acylation) then the corresponding free thiol[2], and as such could serve as a protection for the thiol group. Furthermore, in some cases the removal of some protecting groups results in the formation of the disulphide first (e.g. sections III. B,C; V. A,C) which, later on, is reduced to the free thiol.

Disulphides are obtained by oxidation of the corresponding thiols, by a variety of reagents, e.g. oxygen, hydrogen peroxide, iodine, bromine, hypohalites, ferric chloride, nitrous oxide, sulphonyl chloride[3], diethyl azocarboxylate (**1**)[4], N-bromosuccinimide[5], tetranitromethane[6], peroxy-



(**1**)

acetyl nitrate[7]. The free thiols are obtained from the disulphides by reduction, which again may be carried out by a large variety of reagents, e.g. tin and acid, sodium in xylene, ether or liquid ammonia, lithium aluminium hydride, sodium borohydride, sodium dithionate and various organic thiols[8]. The most widely used thiols are thioglycolic acid and mercaptoethanol. Of special interest among the thiols used is dithioerythritol (**2**)[9], which is a powerful reducing agent and reduces disulphides in much lower concentration than other mercaptans (e.g. mercaptoethanol) presumably due to the formation of a stable six-member ring containing a disulphide bond. Disulphides could also be reduced to free thiols by means of electrolytic reduction[8] as well as by water soluble phosphines (e.g. trihydroxymethylphosphine, tricarboxymethylphosphine) which were recently used for disulphide cleavage in proteins[10].

$$R-S-S-R + HSCH_2-CHOH-CHOH-CH_2SH \longrightarrow RSH + \underset{(2)}{R-S-S-CH_2-CHOH-CHOH-CH_2SH}$$

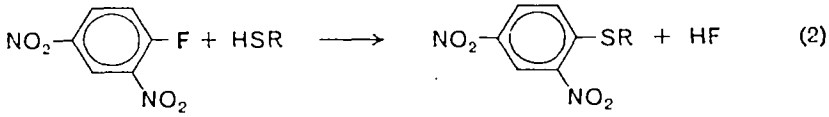
$$\longrightarrow RSH + \text{(cyclic disulphide)} \qquad (1)$$

A much more detailed discussion of the reduction of disulphides to mercaptans is given in Chapter 4 on the preparation of thiols.

III. THIOETHERS

Simple saturated aliphatic thioethers are generally not easily cleaved to yield the free thiols[11]. However, there are some exceptions in which the alkyl radical of an alkyl-phenyl-thioether is cleaved by means of sodium in liquid ammonia, lithium in dimethylamine[12] or lithium in monomethylamine[13] to give the corresponding thiophenols. (See Chapter 4.)

2,4-Dinitrophenyl-thioethers are cleaved under very mild conditions ('thiolysis' of the thioether), with mercaptoethanol at pH 8[14]. These derivatives are obtained by reacting the thiol with 2,4-dinitrofluorobenzene in presence of base.



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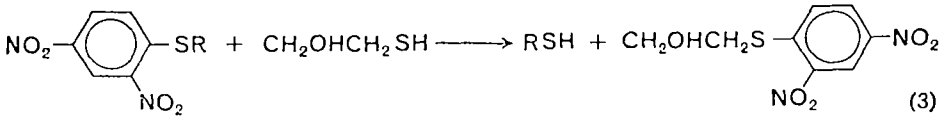

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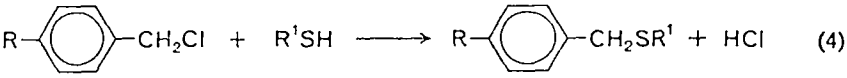
A. Benzyl Derivatives

The best known, and most widely used sulphydryl protecting group is the benzyl group. Benzylation takes place by reacting benzyl chloride in the presence of base with the thiol in aqueous or non-aqueous media (reaction 4; R = H)[15,16]. The reaction could take place also with the sodium



(4)

mercaptide using liquid ammonia as solvent[17]. The protecting group is removed by reductive cleavage with sodium in liquid ammonia[17,18,19]. In cases in which the benzyl thioether is insoluble in liquid ammonia, reductive cleavage can be achieved by using sodium in boiling butanol[20] or sodium in boiling ethanol[21]. It is of importance to note that sometimes desulphurization occurs during the cleavage with sodium in liquid ammonia[22].

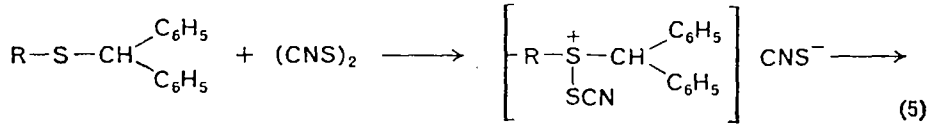
Due to the large lowering of the Pd or Pt catalyst efficiency caused by the sulphur which is present in a thioether form, the reductive cleavage of the benzyl group from the thioether cannot be achieved by catalytic hydrogenation. It has been shown that sufficient catalyst efficiency is retained for the reductive cleavage of the *p*-nitrobenzyl group, presumably due to the labilization of the CH_2—S bond by the strong inductive effect of the nitro group. The *p*-nitrobenzyl protecting group, which is introduced by reacting *p*-nitrobenzyl chloride with the thiol (reaction 4; R = NO_2), is removed by hydrogenation under atmospheric pressure, using 10% Pd on charcoal as a catalyst[23]. It has been shown that this reaction is not a general one and it does not take an unequivocal course since e.g. S-*p*-nitrobenzyl-cysteine gives S-*p*-aminobenzyl-cysteine and similarly benzyloxycarbonyl-S-*p*-nitrobenzyl-cysteinylglycine gives benzyloxycarbonyl-S-*p*-aminobenzyl-cysteinylglycine[24]. Recently it has been shown that the *p*-aminobenzyl group could be cleaved from the thioether by using 10% $HgSO_4$ solution in 5% H_2SO_4 (Hopkin's reagent)[25]. Thus the *p*-nitrobenzyl group could be removed in a two-step reaction involving first reduction to the corresponding *p*-aminobenzyl derivative and then removal of the *p*-aminobenzyl group by acidic $HgSO_4$ solution.

While the benzyl protecting group is stable towards acidic cleavage under normal conditions, introduction of a methoxy group at the *p* position will increase its tendency to acidic cleavage. Thus the *p*-methoxybenzyl group which is introduced in the usual manner (reaction 4; R = OCH_3)[26] is removed by means of trifluoroacetic acid[26] or anhydrous hydrogen fluoride[27].

B. Diphenylmethyl Derivatives

Reaction of thiols with diphenylmethyl chloride gives the diphenylmethyl (or benzhydryl) thioethers[28]. It has been shown that the thioether could be obtained in high yield by reacting the thiol with diphenylmethanol in the presence of BF_3 etherate[29]. The diphenylmethyl protecting group is removed either by trifluoroacetic acid or *via* reductive cleavage using sodium in liquid ammonia[28]. The diphenylmethyl thioether could also be cleaved by thiocyanogen using trifluoroacetic acid–acetic acid as a

solvent[30]. One pathway for this reaction may be *via* formation of a sulphonium salt intermediate (3) which can eject a stabilized carbonium ion and sulphenylthiocyanate, the latter reacting further with another molecule of thioether or with free thiol to yield the disulphide (reaction 5). The formation of free thiols from sulphenylthiocyanates directly or *via* the disulphide is discussed in Chapter 4. An alternative possibility is that the protecting group is split in the acidic solvent and the free thiol thus formed reacts with thiocyanogen to give sulphenylthiocyanate (reaction 6).



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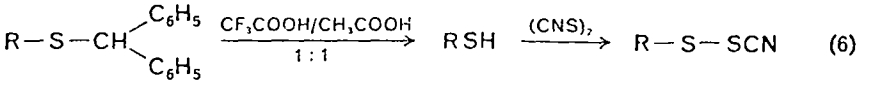
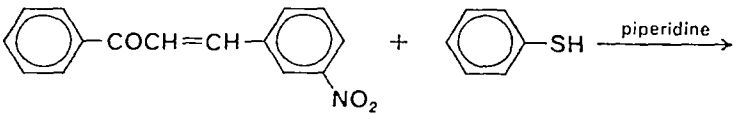


(6)

Another protecting group which could be included in this class is a thioether obtained by reacting the thiol with *m*-nitrobenzalacetophenone in the presence of piperidine (reaction 7); the protecting group is removed



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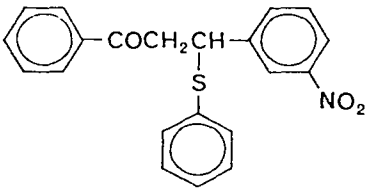


by treatment with basic lead acetate[31]. This group is used to protect the sulphydryl moiety of thiophenol and substituted thiophenols during electrophilic substitution reactions on the benzene rings[31].

C. Triphenylmethyl Derivatives

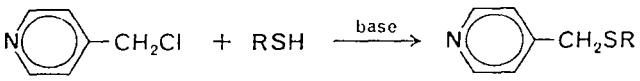
The triphenylmethyl (trityl) derivatives are obtained by reacting the appropriate thiol with triphenylmethyl chloride[28,32,33], or with triphenyl

methanol and BF_3 etherate[29]. Similarly to the diphenylmethyl thioether, the triphenylmethyl thioether is cleaved by sodium in liquid ammonia to give the free thiol[34], however, contrary to the diphenylmethyl thioether, the triphenylmethyl group could also be cleaved from the thioether by heavy metal ions. Moreover, trityl thioethers are more susceptible to acid hydrolysis as well as to thiocyanogen oxidation than the corresponding diphenylmethyl derivatives.

Although the removal of the triphenylmethyl group by trifluoroacetic acid[28] and hydrogen chloride in chloroform[33] is reported, there are cases in which acidic cleavage (e.g. by means of trifluoroacetic acid, hydrogen bromide in glacial acetic acid, *p*-toluene sulphonic acid) indeed removed the protecting group but the product obtained did not possess any free sulphydryl group[35,36]. It seems that the best acidic reagent to use is hydrochloric acid in aqueous acetic acid[36]. The heavy metal ions used for the removal of the triphenylmethyl group from the thioether are Ag^+ and Hg^{2+}. Initially, methanolic silver nitrate solution in the presence of pyridine was used[28]. Later it has been shown that there are cases in which better cleavage yields are obtained by using mercuric acetate[35,36], in other cases silver nitrate gives the best results[37] and in some cases both reagents give about the same yields[38]. It seems that the cleavage yield depends upon the whole molecule in question, and the metal of choice could be found only experimentally. The triphenylmethyl moiety is removed from the thioether very easily by oxidation with thiocyanogen in the presence of sodium acetate. The sulphenylthiocyanate which is obtained reacts with free thiol or with another molecule of the thioether to form unsymmetrical or symmetrical disulphides which can be reduced later to the free thiol[39]. The removal of the triphenylmethyl group by the thiocyanogen is so easy that it can even be removed in the presence of a diphenylmethyl thioether, without any cleavage of the latter compound[40].

D. Picolyl Derivatives

Contrary to catalytic hydrogenation which usually fails in the presence of thiols or thioethers, electrolytic reduction at a mercury cathode takes place without difficulty[41]. Among the thioethers which could be cleaved by electrolytic reduction are the 4-picolyl thioethers. These derivatives are obtained by reacting the free thiol with freshly distilled 4-picolyl chloride in the presence of base. The thioether is completely stable towards acidic



(8)

cleavage, and no cleavage could be detected after its storage for 7 days in trifluoroacetic acid or in hydrogen bromide in acetic acid. The protecting group could be removed by electrolytic reduction at a mercury cathode in 0·5N sulphuric acid solution[42].

This protecting group was recently used in the synthesis of L-cystinyl-bis-glycine[42].

E. Acetamidomethyl Derivatives

The acetamidomethyl thioether is obtained by reacting a 10% excess of acetamidomethanol (**4**) with the thiol at pH 0·5. The protecting group is very stable in the pH range of 0–13 as well as towards concentrated strong

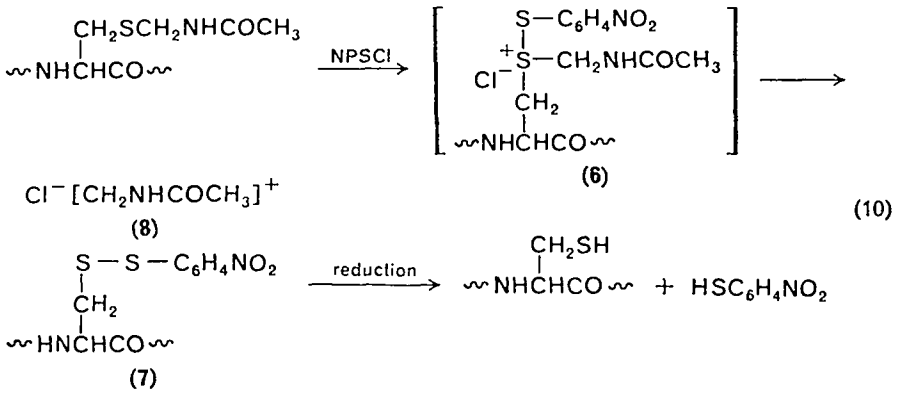
$$\underset{\textbf{(4)}}{CH_3CONHCH_2OH} + \underset{\textbf{(5)}}{\overset{+}{N}H_3CH(CH_2SH)COO^-} \xrightarrow{pH\ 0{\cdot}5} {}^+NH_3CH(CH_2SCH_2NHCOCH_3)COO^- \qquad (9)$$

acids (e.g. trifluoroacetic acid, hydrogen bromide in glacial acetic acid, anhydrous hydrofluoric acid). It is removed from the thioether by using two equivalents of mercuric ions at pH 4[43].

In the case of cysteine (**5**) the product obtained is contaminated by cystine and also by thiazolidine carboxylic acid (obtained by reaction of cysteine and formaldehyde, the latter arising from hydrolytic decomposition of acetamidomethanol, see section VI). However, the product could easily be purified by using ion exchange columns[44]. On the other hand, anhydrous conditions should avoid the decomposition of the acetamidomethanol and indeed a reaction using hydrogen fluoride as a solvent results in quantitative yield of the pure product[45].

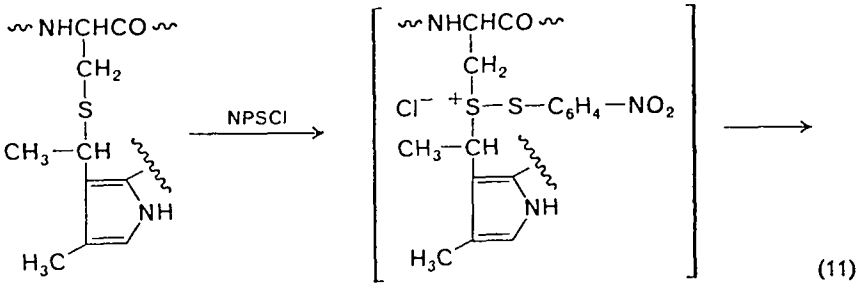
An elegant method for the cleavage of the protecting group has been discussed recently[46]. It is based on the observation that sulphenyl halides are reacting with unsymmetrical thioethers giving disulphides among other products, depending upon the structure of the thioethers. Reaction of 2-nitrophenylsulphenyl chloride (NPSCl) with acetamidomethyl cysteine residue would form a thiosulphonium ion (**6**) which decomposed to the mixed disulphide derivative (**7**) and to (**8**). The thiol function is then regenerated from the disulphide derivative by the usual reduction procedure (see section II).

The reaction of sulphenyl halides with thioethers seems to be a general procedure for the cleavage of a thiol protecting group, provided that a stable cation could be ejected from the thiosulphonium ion intermediate. Thus the thioether linkages between the haem group and the cysteine



(10)

residue in horse heart cytochrome C was rapidly and quantitatively cleaved by 2-nitrophenylsulphenyl chloride[47]. The cleavage is successfully effected due to the easy formation of the carbonium ion (**9**), stabilized by the conjugated porphyrin system. This haem cleavage procedure is a very useful alternative to the available methods[48].



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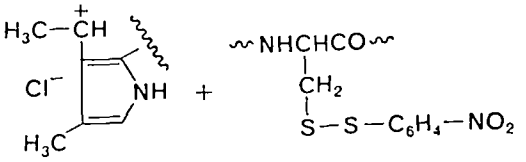
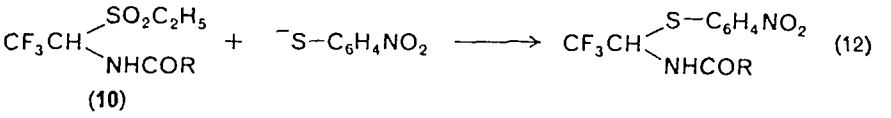


(9)

F. β, β, β-*Trifluoro-α-acylaminoethyl Derivatives*

Only one work has been reported using this protecting group[49]. The thioether is obtained by an exchange reaction of the thiol with *β,β,β*-trifluorocthyl-α-ethanesulphonyl-α-N-acylamine (**10**). In the case of

R = $C_6H_5CH_2O$, the protecting group is removed by hydrogen bromide in acetic acid followed by adjusting the pH to 9–10. While some protected

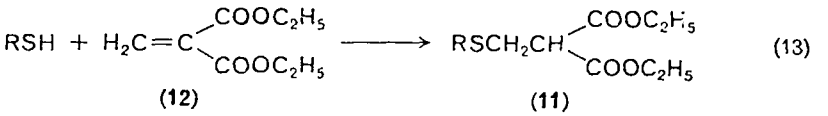


(10) (12)

cysteine derivatives were prepared[49], the removal of the protecting group from those derivatives is not reported. Some more work should be carried out on this protecting group before it gains any use.

G. β, β-Diethoxycarbonylethyl Derivatives

Another protecting group which has not yet gained a wide use is the β,β-diethylcarbonylethyl group. The thioether (**11**) is obtained by the addition of the thiol to diethyl methylenemalonate (**12**). The protecting



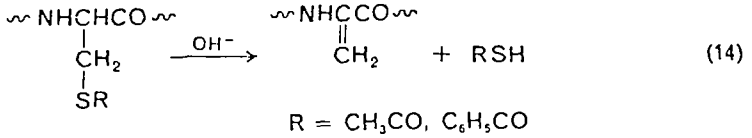
(12) (11) (13)

group is stable towards acidic reagents (e.g. trifluoroacetic acid, hydrogen bromide in acetic acid) but is cleaved by 1N KOH solution *via* β-elimination[50]. This protecting group was used to protect the thiol group of cysteine during the synthesis of glutathione[51].

IV. THIOESTERS

A. Acetyl and Benzoyl Derivatives

The acetyl and benzoyl derivatives are obtained by the reaction of the corresponding acyl chloride with the thiol[52]. These thioesters are in effect 'active esters' prone to attack by nucleophiles in general and very susceptible to dilute base. The protecting groups are removed completely by very dilute alkali within 20 min, but with dilute ammonia solution only 50% cleavage occurs during the same time. The hydrolytic cleavage is accompanied by a β-elimination as a side-reaction, especially in cysteine derivatives (reaction 14). This side-reaction can be avoided in low



R = CH_3CO, C_6H_5CO (14)

molecular weight peptides when the protecting group is removed by methanolysis with sodium methoxide in methanol[52]. Since the extent of β-elimination is related to the polarity of the solvent used, it has been shown that in the case of large peptides which are soluble only in highly polar solvents β-elimination occurs during methanolysis too[53].

The acetyl and benzoyl thioesters are stable towards aqueous acids as well as towards trifluoroacetic acid. While the benzoyl group is stable towards 2N hydrochloric acid in glacial acetic acid, the acetyl group is cleaved under those conditions[52].

B. Benzyloxycarbonyl Derivatives

These derivatives are obtained by reacting benzyloxycarbonyl chloride with a thiol[54]. Contrary to the N-benzyloxycarbonyl derivatives they are stable towards hydrogen bromide in acetic acid[52,55] but they are cleaved by phosphonium iodide in acetic acid[54] or by boiling trifluoroacetic acid[52]. The protecting group is removed by methanolysis and ammonolysis, but those cleavage reactions proceed much slower than in the case of the corresponding acyl derivatives. The protecting group is removed very easily by ammonolysis using concentrated aqueous ammonia solution[52] as well as by methanolysis using fivefold excess of sodium methoxide.

C. Urethane Derivatives

The best known protecting group of this class is the ethylcarbamoyl which is obtained by the reaction of ethyl isocyanate with the thiol[56]. The protecting group is stable in acidic and neutral solutions but is

$$C_2H_5NCO + HSR \longrightarrow \underset{H}{C_2H_5NCOSR} \qquad (15)$$

cleaved easily in basic solution (e.g. aqueous and anhydrous ammonia solution, dilute sodium hydroxide solution, dilute sodium methoxide solution in methanol)[57]. No β-elimination could be detected when ethylcarbamoyl cysteine derivatives were treated with 1N sodium hydroxide solution to yield the unprotected cysteine derivatives[57]. This is contrary to the behaviour of the corresponding benzoyl and acetyl derivatives where considerable β-elimination is observed. It has been shown recently that the ethylcarbamoyl moiety is removed by treatment with heavy metal ions (Hg^{2+}, Ag^{+})[58].

An interesting protecting group of this class is the β-(N-acyl-N-methylaminoethyl)carbamoyl group. The isocyanate (**13**), which reacts

with the mercaptan to give the thiourethane, is obtained *via* the following route[59].

$$CH_2{=}CHCN + CH_3NH_2 \longrightarrow CH_3NHCH_2CH_2CN \xrightarrow{Ba(OH)_2} CH_3NHCH_2CH_2COOH \xrightarrow{RY}$$

$$\underset{R}{CH_3NCH_2CH_2COOH} \xrightarrow{HN_3} \underset{R}{CH_3NCH_2CH_2CON_3} \xrightarrow{\Delta} \underset{R}{CH_3NCH_2CH_2NCO} \quad \textbf{(13)} \qquad (16)$$

$R = C_6H_5CH_2OCO$, $Y = Cl$.

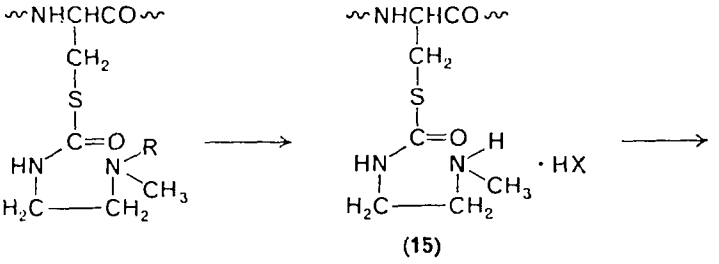
$R = (CH_3)_3COCO$, $Y = N_3$.

Reaction of **13** with cysteine will give β-(N-acyl-N-methylaminoethyl) carbamoyl cysteine (**14**). The acyl group, which is a urethane-type

$$\underset{R}{CH_3NCH_2CH_2NCO} + {}^{+}NH_3CH(CH_2SH)COO^{-} \longrightarrow {}^{+}NH_3CH(CH_2SCONHCH_2CH_2NRCH_3)COO^{-} \qquad (17)$$

(14)

protecting group of the β-amino group, is removed by the usual means[60] to give the ammonium salt (**15**). Upon neutralization of the salt there is an intermolecular nucleophilic attack of the β-amino group on the carbonyl group, followed by cleavage and formation of the free mercaptan



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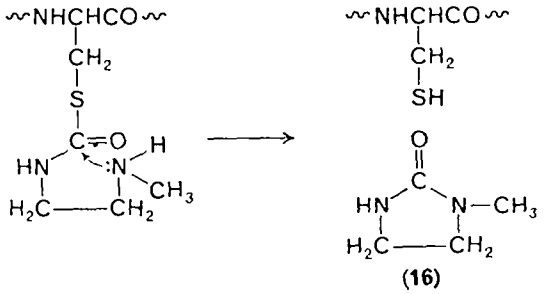


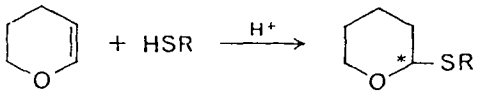
(16)

and 1-methyl-2-imidazolidone (**16**). This protecting group was recently used to protect the thiol group of cysteine during the synthesis of oxytocine[59].

V. SEMITHIOACETALS

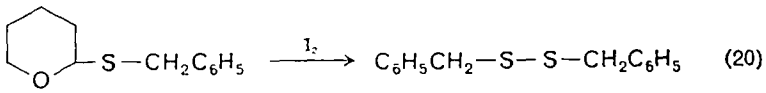
A. Tetrahydropyranyl Derivatives

The tetrahydropyranyl derivatives are prepared by reacting the free thiol with 2,3-dihydropyrane in the presence of acid as a catalyst[61,62]. A disadvantage in using this protecting group is the introduction of a new asymmetric centre (*) to the molecule. The protecting group is removed by hydrolysis with very dilute acid[61], by the action of aqueous



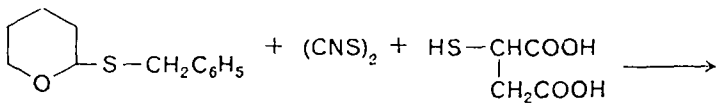
(19)

silver nitrate solution[63], or by reaction with iodine[64]. In the latter case the disulphide (which could be reduced to the free thiol) is obtained, e.g. benzyl tetrahydropyranyl sulphide reacts with iodine to give dibenzyl disulphide. A similar cleavage is observed by the action of thiocyanogen:



(20)

benzyl tetrahydropyranyl sulphide reacts with thiocyanogen in the presence of $ZnCl_2$ and mercaptosuccinic acid to form the disulphide (**17**)[64]. The cleavage of this sulphide by electrophiles is presumably due to the



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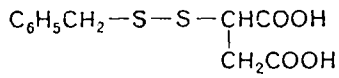
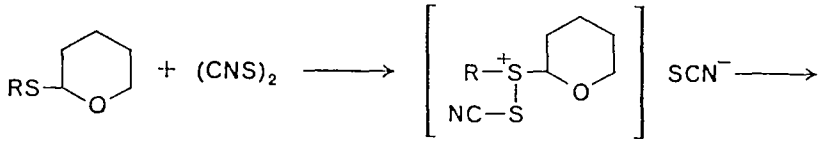


(17)

fact that the intermediate sulphonium salt (**18**) can eject a stabilized carbonium ion (see sections III.B, III.E) and the sulphenyl thiocyanate

reacts further with thiols or certain sulphides to produce unsymmetrical or symmetrical disulphides.



(18) (22)

$$RSSCN + R'SH \longrightarrow \underset{\displaystyle R-S-S-CN}{R-S-S-R'} + HSCN$$

B. Benzylthiomethyl and Phenylthiomethyl Derivatives

These derivatives were obtained by the reaction of various thiols with benzylthiomethyl chloride in methanol[65]. It was found that products obtained by this route are difficult to purify and the method of choice now

$$C_6H_5CH_2SCH_2Cl + HSR \longrightarrow C_6H_5CH_2SCH_2SR \qquad (23)$$

is reduction of a symmetrical disulphide by means of sodium in liquid ammonia, followed by addition of the freshly distilled benzylthiomethyl chloride[66]. The protecting group is stable in acidic media (e.g. hydrogen bromide in acetic acid) but is removed by mercuric acetate solution in 80% formic acid[66]. The usefulness of this group as a thiol protecting group was demonstrated in the synthesis of glutathione[67].

The phenylthiomethyl ($C_6H_5SCH_2-$) protecting group is obtained and removed in an identical way to that of the benzylthiomethyl group[66].

C. Isobutyloxymethyl Derivatives

Isobutyloxymethyl derivatives are obtained by reaction of isobutyloxymethyl chloride with thiols[66]. These are more sensitive to acid than the corresponding benzylthiomethyl derivatives. The isobutyloxymethyl

$$(CH_3)_2CHCH_2OCH_2Cl + HSR \longrightarrow (CH_3)_2CHCH_2OCH_2SR \qquad (24)$$

group is cleaved by hydrogen bromide in acetic acid[66], BF_3 etherate or trifluoroacetic acid[68], but it is stable towards 2N hydrochloric acid in 50% acetic acid[66] or 12N hydrochloric acid in acetone[68]. The isobutyloxymethyl sulphide is decomposed to some extent by 2N sodium hydroxide[66], but it is stable towards hydrazine hydrate in boiling ethanol[68].

The protecting group can be cleaved by thiocyanogen similarly to the triphenylmethyl, diphenylmethyl and tetrahydropyranyl groups[68].

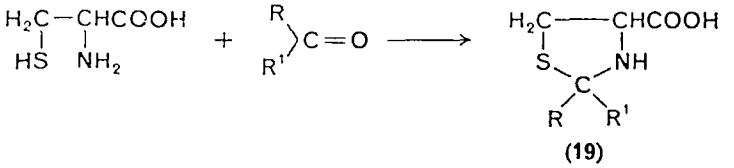
The reactivity of the isobutyloxymethyl group towards thiocyanogen lies between that of the triphenylmethyl and the diphenylmethyl group. The difference in reactivity is not sufficient to allow the selective oxidative cleavage of the triphenylmethyl group in the presence of the isobutyloxymethyl moiety, or the cleavage of the isobutyloxymethyl group in the presence of the diphenylmethyl moiety[68].

VI. HETEROCYCLIC RINGS

A. Thiazolidine Derivatives

Cysteine and cysteine derivatives (like other β-aminothiols) react with aldehydes and ketones to form thiazolidine derivatives[69].

The best known derivatives of this class are thiazolidinecarboxylic acid (**19**, $R = R^1 = H$) (or thioproline) and 2,2-dimethylthiazolidinecarboxylic acid (**19**, $R = R^1 = CH_3$) which are formed by the reaction of



(25)

(19)

cysteine with formaldehyde or acetone respectively[69-71]. The protecting group can be removed by mild acid hydrolysis[69-71]. In the case of thiazolidinecarboxylic acid, oxidation with iodine yields the disulphide which can be easily reduced to the free mercaptan[69]. The protecting group can be removed from 2,2-dimethylthiazolidinecarboxylic acid by aqueous mercuric chloride solution[70,71].

VII. ACKNOWLEDGEMENTS

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The Chemistry of the Thiol Group
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CHAPTER 15

Rearrangements involving thiols

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I. INTRODUCTION

This chapter deals with rearrangement reactions which involve thiols either as starting materials or as products. However, because of the high reactivity of thiols in both nucleophilic and free radical reactions, they are actually involved in many cases as transient species only. Such cases, in which the intermediacy of thiols is evident or highly probable, are also included here.

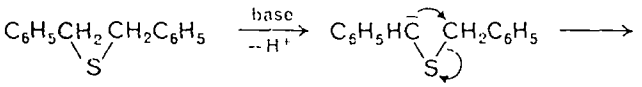
Only few rearrangements involving thiols, particularly those which are of synthetic importance or are related to biochemical processes, have been thoroughly investigated. It was not the aim of this chapter to unearth and list all the rearrangements which have been reported in the literature, but rather to group and describe, with illustrative examples, the most important types.

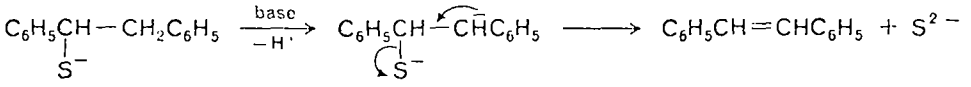
II. GROUP MIGRATIONS FROM AND ONTO THIOLS

A. *Alkyl Migrations*

1. Sulphur to carbon

Migrations of alkyl groups from oxygen to negatively charged carbon (Wittig rearrangement) are well known[1]. The analogous rearrangement of sulphides, which would lead to isomeric thiols, has not yet been observed. A Wittig-like mechanism was however used to explain the formation of stilbene from dibenzyl sulphide and strong base, assuming the intermediacy of the thiol (**1**) which eliminates sulphide ion[2].

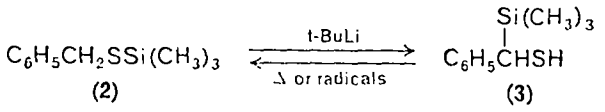




(**1**)

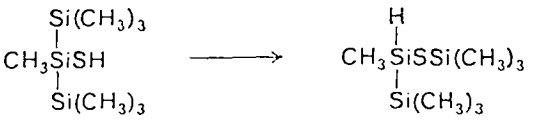
Trialkylsilyl groups, on the other hand, migrate very readily under Wittig conditions. Benzylthiotrimethylsilane (**2**) on treatment with tert-butyllithium is rapidly converted to α-trimethylsilyl toluene-α-thiol (**3**) in almost quantitative yield.

The reverse rearrangement (**3**→**2**) occurs on heating **3** at 190°C under the influence of radical catalysis. A similar rearrangement, which involves



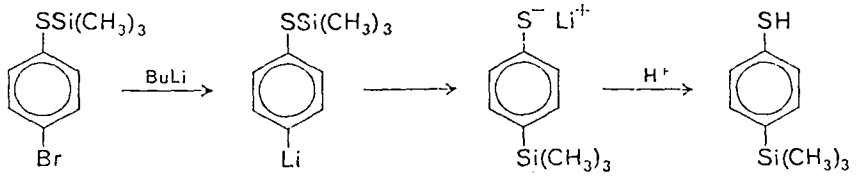
(2) (3)

radical induced migration of trialkylsilyl groups from silicon to sulphur (**4**→**5**) was also reported[4].



(4) (5)

Migration of trialkylsilyl and germanyl groups from sulphur to aromatic carbon was also observed[5]. Lithiation of 4-bromo-S-trimethylsilyl-benzenethiol (**6**) yields the lithium salt of 4-trimethylsilylbenzenethiol (**7**). The mechanism has not been investigated and it has not been established whether an intra- or intermolecular process is involved.

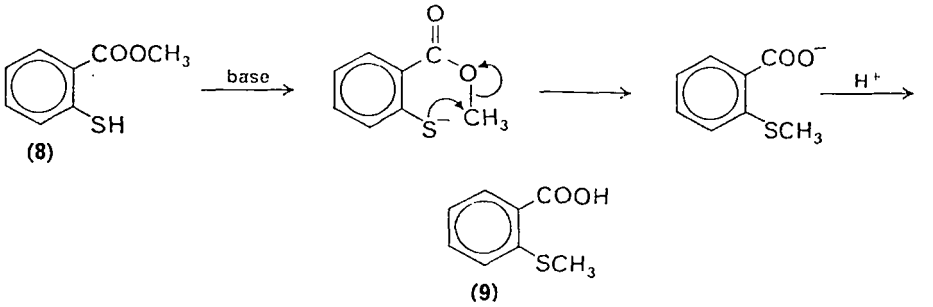


(6) (7)

2. Sulphur to oxygen

Oxygen—alkyl bonds are easily cleaved by thiol salts[6]. An intramolecular reaction of this type would result in migration of an alkyl group from oxygen to sulphur. Indeed, treatment of methyl 2-mercaptobenzoate (**8**) with alkali gives 73% of 2-methylthiobenzoic acid (**9**)[7].

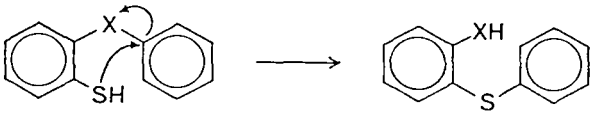
With benzylamine, **8** yields the benzylamide of **9**, probably through dehydration of the benzylamine salt.



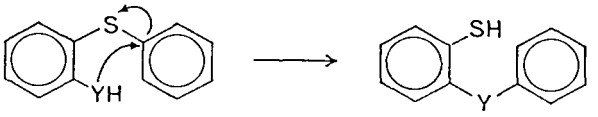
(8) (9)

B. *Aryl Migrations (the Smiles Rearrangement)*

The Smiles rearrangement is defined as an aromatic nucleophilic displacement in which the nucleophile and the leaving group are joined, usually by being *ortho*-substituents on an aromatic ring. The result is a migration of an aryl group from one heteroatom to another. The thiol group can be involved in the Smiles rearrangement either as the nucleophile (equation 1) or as the displaced group (equation 2).



(1)

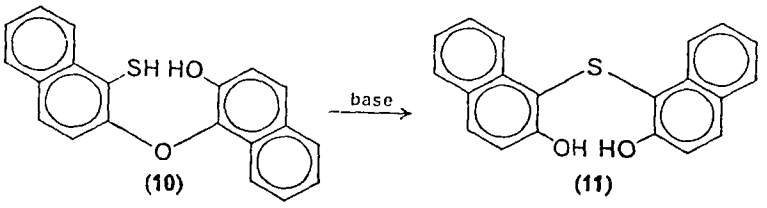


(2)

A recent review[8] describes in detail the mechanistic and synthetic aspects of the reaction and also presents a tabular survey of all Smiles rearrangements which appeared in the literature.

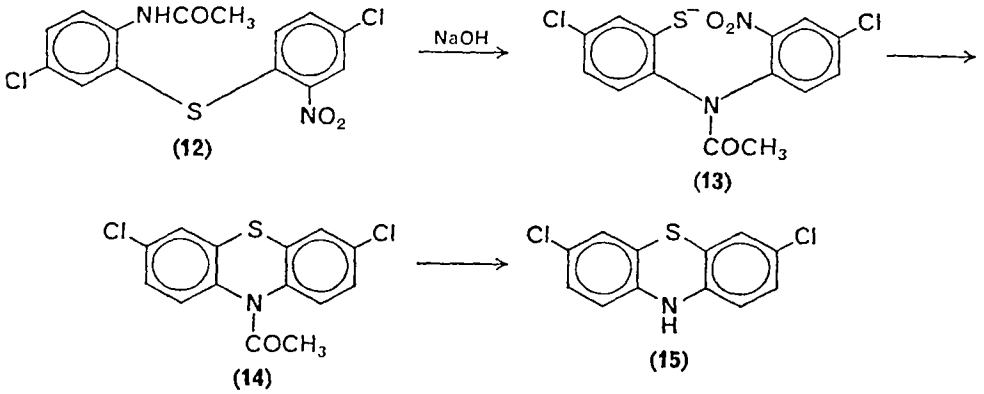
Because of the high nucleophility of the thiol group and its anion, it is to be expected that reactions of the type shown in equation (1) would be of a wide scope. However, only a small number of examples were reported, mostly by Smiles[9], and all involve the conversion of mercaptodiaryl ethers to hydroxydiaryl sulphides. In this manner 2-hydroxy-1′-mercapto-1,2′-dinaphthyl ether (**10**) yielded 2,2′-dihydroxy-1,1′-dinaphthyl ether (**11**).

Reactions of the type shown in equation (**2**) have attracted much more attention, as they present the easiest and the most direct synthetic route to the medically important phenothiazines[10]. Almost all the rearrangements reported in the literature are of 2-acylamino-2′-nitrodiphenyl sulphides which yield phenothiazines on treatment with base. A typical



(10) (11)

one[11] is that of the sulphide (**12**). Its rearrangement led initially to the thiol salt (**13**) and subsequently the thiol group displaced the nitro group to give **14**. The acyl group is usually hydrolysed under the reaction conditions and the phenothiazine (**15**) was obtained in one step. Isolation of the intermediate N-arylphenothiazines was reported in several cases[12,13].



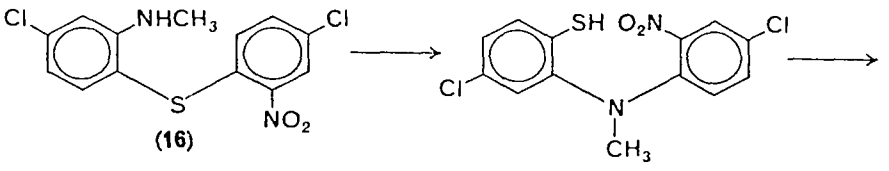
(12) (13) (14) (15)

Although the phenothiazines could have been formed by a direct displacement of the nitro group by the amide, the positions of the substituents in the products establish the mechanism shown and the intermediacy of thiols.

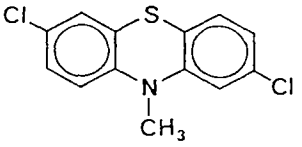
A closely related reaction is the rearrangement of N-alkylaminodiaryl sulphides, which yield N-alkylphenothiazines on heating in boiling quinoline or aniline[14]. Compound **17** was thus obtained from **16** (57% yield).

Contrary to previous reports it was recently found[15] that 2-amino-2′-nitrodiphenyl sulphide (**18**) also rearranged on heating at 190°C alone or in dimethylacetamide to give the phenothiazine **19**. The dibenzothiophen **20** was also formed as a by-product.

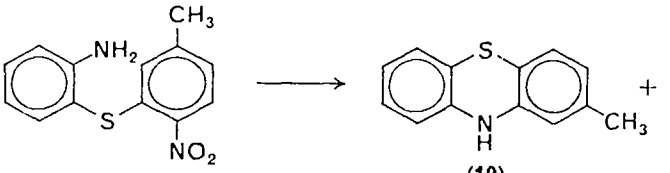
The rearrangement of pyridyl sulphides is particularly interesting, as it was found to occur also under acidic conditions[16]. 3-Amino-3′-nitro-2,2′-dipyridyl sulphide (**21**) gives 2-mercapto-3′-nitro-3,2′-dipyridylamine (**22**) in nearly quantitative yield on short treatment with hydrochloric acid.



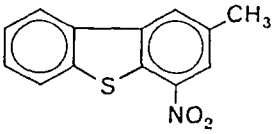
(16)



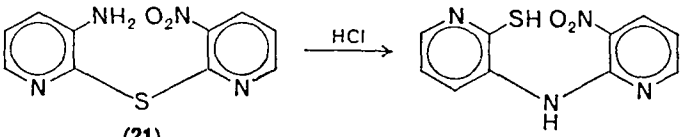
(17)



(18) (19)

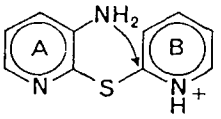


(20)

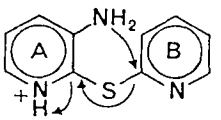


(21) (22)

The catalytic effect of the acid can be explained by protonation of either pyridine ring. Protonation of ring B (**23**) makes it more susceptible to nucleophilic attacks, while protonation of ring A (**24**) stabilizes the leaving group.

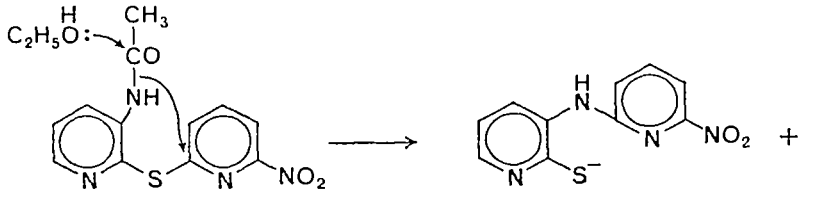


(23)



(24)

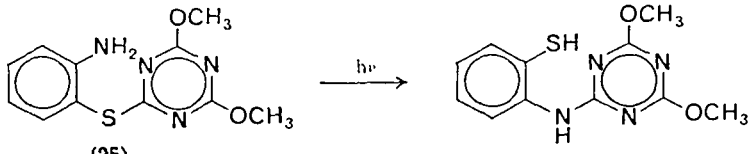
The thermal rearrangement of dipyridyl sulphides proceeds much easier than that of diphenyl sulphides and is highly solvent-dependent: it is rapid in boiling ethanol, slower in water and does not occur at all in benzene or dimethylsulphoxide[16]. It was also observed that 2-acylamino-pyridyl sulphides rearrange faster than the corresponding 2-amino derivatives. These facts suggest solvent participation such as shown in equation 3.



(3)

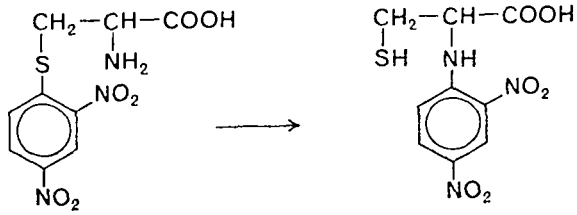
$H^+ + CH_3COOC_2H_5$

The photochemical Smiles rearrangement was also reported recently. An example involving a thiol is the conversion of **25** to **26** on irradiation in ethanol[17].



(25) **(26)**

Migrations of 2,4-dinitrophenyl groups from aliphatic thiols are also known. Migration to nitrogen occurs[18] in the cysteine derivative **27** at pH 7, and migration to oxygen in compound **28** on treatment with base[19].



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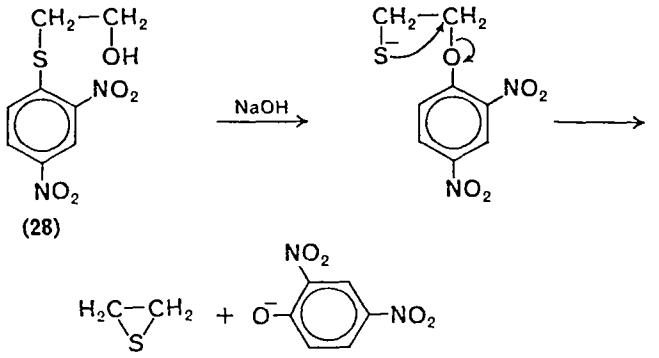
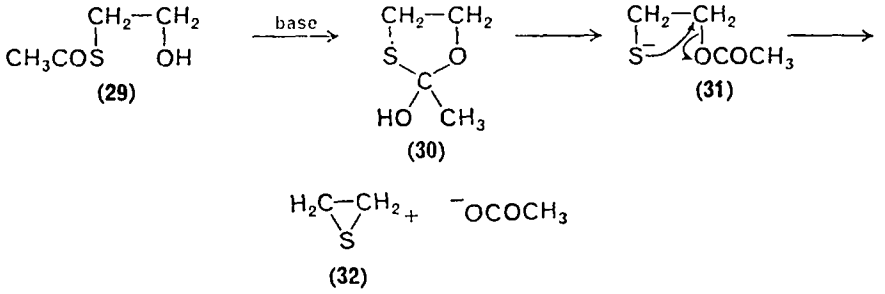


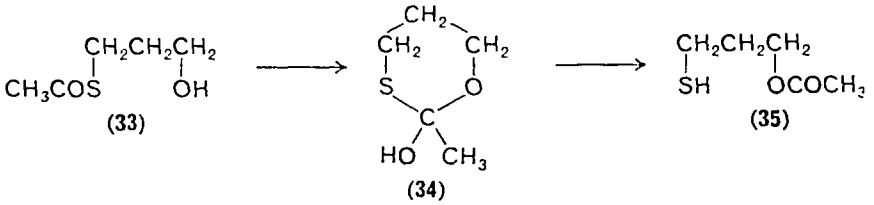
C. Acyl Migrations

1. Sulphur to Oxygen

Acetyl transfer from thiol to hydroxyl groups occurs readily, under basic conditions, in the series $RCOS(CH_2)_nOH$ when n is 2 or 3, but not when n is 4. S-Acetylmercaptoethanol (**29**) thus yields thiiran (**32**) as a result of acetate ion elimination from the rearranged product **32**[20,21].



S-Acetyl-3-mercaptopropanol (**33**) yields, under the same conditions, 3-mercaptopropyl acetate (**35**) which is stable and isolatable.

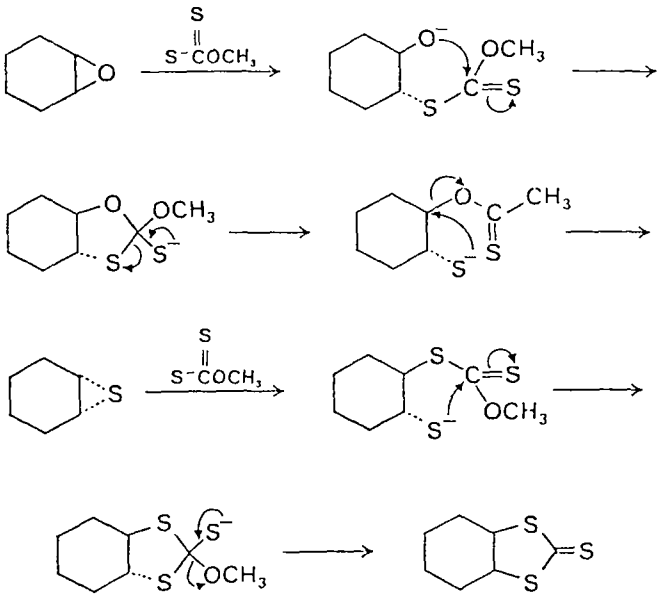


The importance of the distance between the thiol and the hydroxy groups implicates intermediate ring formations (**30** and **34**) during the

migrations. It can be expected that a five-membered ring intermediate would provide the optimum ring size for the transfer, and indeed compound **29** rearranges 30 times faster than **33**[23].

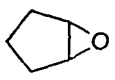
A kinetic study of the rearrangement of **33** to **35** showed that the equilibrium constant is 56 (at 39°C, 0·3 ionic strength), corresponding to a difference of free energy of 2500 kcal/mole between esters and thiol esters[24].

A similar rearrangement which involves migration of the thionoalkoxy group is assumed to occur during the reaction of xanthate salts with epoxides, which leads to trithiocarbonates[25]. The proposed mechanism[26,27] is presented in equation (4).

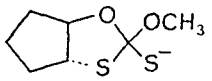


(4)

Evidence for the mechanism is provided by the fact that cyclopentene oxide (**36**) does not react[28], as its rearrangement would require the existence of the intermediate **37** which possesses two *trans*-fused five-membered rings. The thiiran **38**, however, reacts smoothly and gives **39**. This striking difference in behaviour can probably be attributed mainly

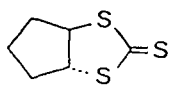


(36)



(37)

(38)

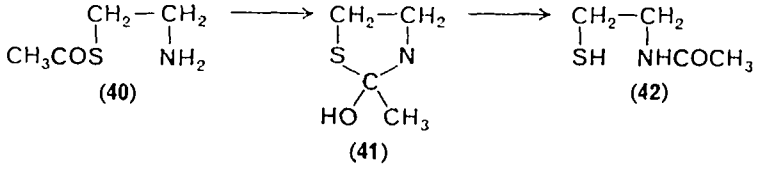


(39)

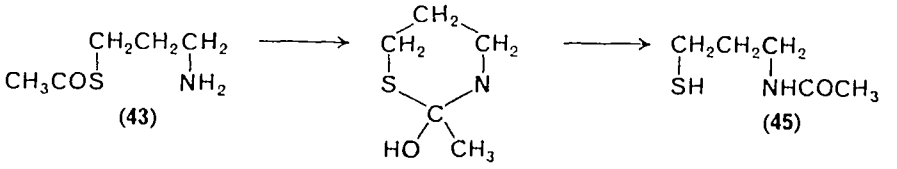
to the much greater nucleophilicity of the thiol anion, but ring closure may also be facilitated by an enhanced ease of deformation of bond angles when oxygen is replaced by sulphur.

2. Sulphur to Nitrogen

The migration of an acyl group from a thiol to an amino group is analogous to the migration to hydroxyl described above, and proceeds through the corresponding cyclic intermediates. S-Acetyl-2-aminoethanethiol (**40**) rearranges in this manner very readily to 2-acetamidoethanethiol (**42**) *via* the thiazolidine **41** and S-acetyl-3-aminopropanethiol (**43**) rearranges to 3-acetamidopropanethiol (**45**) via **44**[29].



(40) (41) (42)



(43) (44) (45)

These rearrangements take place even in acidic media and, as expected, the rearrangement of **40** proceeds much faster than that of **43** (at pH 5, rate ratio 1 : 100). The rearrangement of S-acetyl-4-aminobutanethiol (**46**) to **47**, which would require a seven-membered ring intermediate, occurs at a measurable rate only at pH > 8 and is much slower. On increasing the distance between the thiol and the amino group, no rearrangement was observed and treatment of **48** or **49** with base results only in hydrolysis of the acetyl group

$$CH_3COS(CH_2)_4NH_2 \xrightarrow{\text{base}} HS(CH_2)_4NHCOCH_3$$

(46) (47)

$CH_3COS(CH_2)_6NH_2$ (48) $CH_3COS(CH_2)_{10}NH_2$ (49)

A kinetic study on the reaction **40** → **41** → **42**[34,35] confirmed the intermediacy of **41**. All the reaction steps were assumed to be equilibria, and equilibrium constants and rate constants were determined. Of particular interest is the pH effect. The migration rate exhibits an inverse dependence on hydrogen ion concentration at low pH (2·5–3), a plateau region (pH 3–4·5) which is ascribed to general base catalysis by H_2O and then general base catalysis by OH^- at higher pH (> 5)[23]. A detailed mechanism which accounts for all the data and includes protonation equilibria was proposed[23].

S-Benzoyl-2-aminoethanethiol and its N-alkyl derivatives (**50**) rearrange immediately on liberation from the hydrobromide salts[30]. However, besides the expected 2-benzamidoethanethiols (**51**) small amounts of N,S-dibenzoyl-2-aminoethanethiols (**52**) were also obtained, which indicates that the intramolecular acyl migrations were followed by transthiolesterifications[31] from the starting materials **50** to the rearranged products **51**. The transesterifications must be accompanied by elimination of 2-aminoethanethiols (**53**) and although attempts to isolate **53a** and **53b** from the reactions of **50a** and **50b** failed, **50c** afforded all three products

$$\underset{\textbf{(50)}}{C_6H_5COSCH_2CH_2NHR} \longrightarrow \underset{\textbf{(51)}}{HSCH_2CH_2NR(COC_6H_5)} + \underset{\textbf{(52)}}{C_6H_5COSCH_2CH_2NR(COC_6H_5)} + \underset{\textbf{(53)}}{HSCH_2CH_2NHR}$$

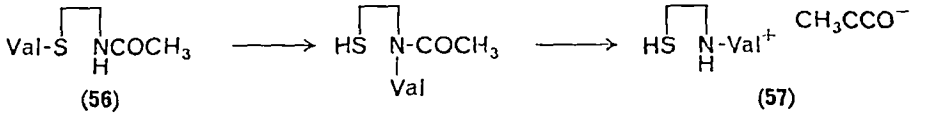
a, R = H

b, R = ethyl

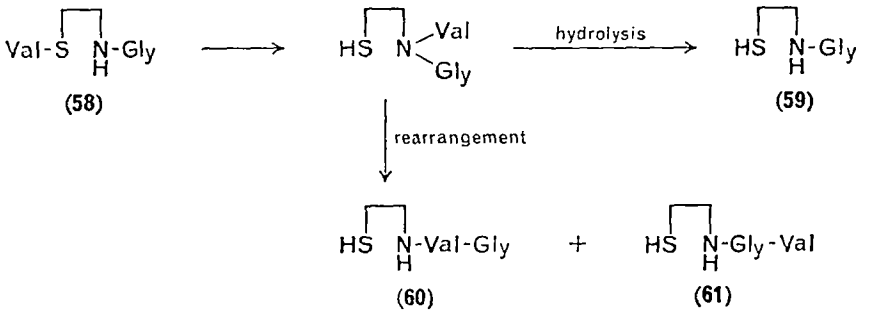
c, R = cyclohexyl

Applications by the rearrangement to peptides were studied by Wieland[29,32,33]. Migrations of α-aminoacyl groups are very rapid and the rearrangement of S-glycylcystamine **54** to the N-glycyl derivative (**55**) was complete at pH 5·2 in 2 min. Under basic conditions α-aminoacyl groups migrate from sulphur even to amides, to give diacylimines. These undergo a very facile hydrolysis and lose one acyl group (**56** → **57**), or if possible rearrange further *via* N → N acyl migrations to give tripeptides. 5-Valyl-N-glycylcystamine (**58**) for example yielded a mixture which contained N-glycylcystamine (**59**), N-valylglycylcystamine (**60**) and N-glycylvalylcystamine (**61**).

(54) (55)



(56) (57)

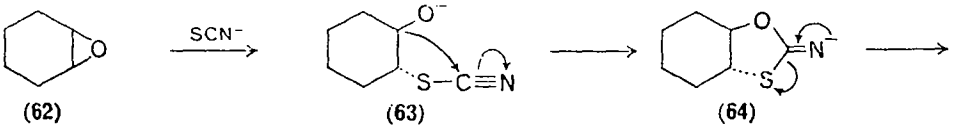


(58) (59) (60) (61)

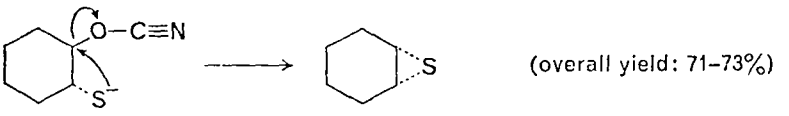
D. Migrations of Nitrogen-containing Species

1. Cyano group migrations

One of the most important syntheses of thiirans[36] is the direct conversion of oxirans to thiirans with thiocyanate salts[37]. The mechanism proposed[38,39] is opening of the oxirane (**62**) to hydroxy thiocyanate (**63**), rearrangement to mercapto cyanate (**65**) through the cyclic intermediate **64** and finally elimination of cyanate ion to give the thiiran **66**.



(62) (63) (64)



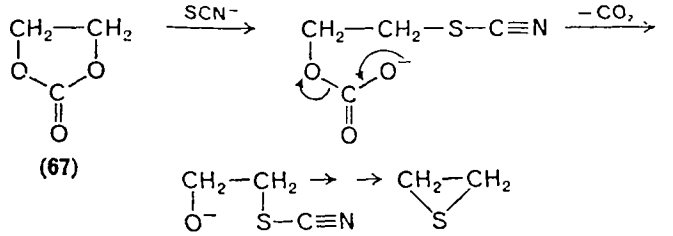
(65) (66)

(overall yield: 71–73%)

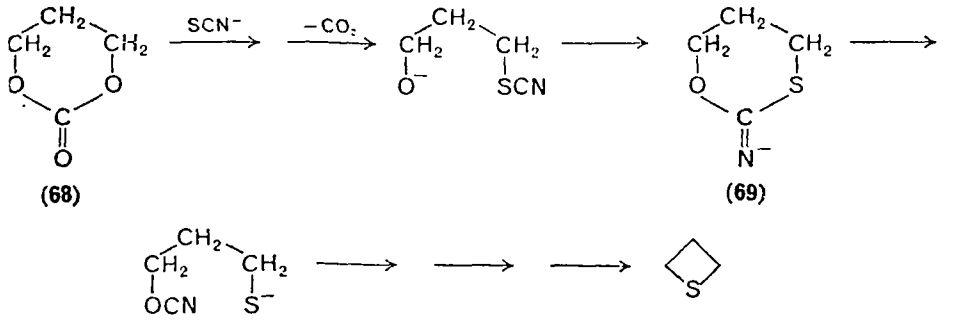
This mechanism was substantiated by isolation of the *p*-nitrobenzoyl derivative of the cyclic intermediate **64**, and by the observation that inversion occurred at each asymmetric carbon[40], as the mechanism demands that the resultant thiiran possess a configuration opposite to that of the starting oxirane.

Cyclopentane oxide does not react under customary reaction conditions because of the considerable strain required to form a cyclic intermediate analogous to **64**. However, on employing harsher conditions 20% of the corresponding thiiran could be obtained[41].

A modification of the above reaction, which proceeds via the same intermediate, is the reaction of thiocyanate salts with ethylene carbonates (**67**)[42].



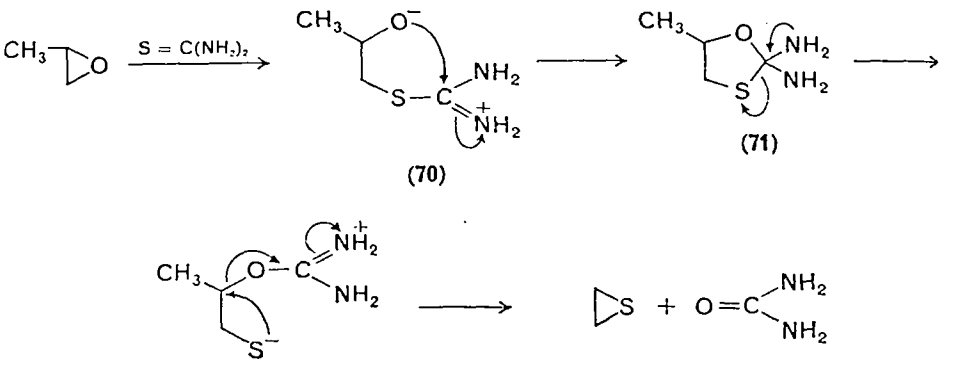
Propylene carbonates (**68**) react as well to give thietans[43], thus the rearrangement can proceed also *via* the six-membered ring intermediate **69**.



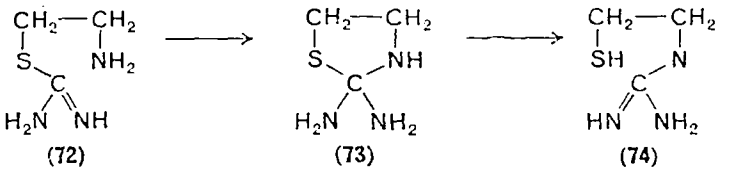
2. Amidino group migrations

This rearrangement is assumed to occur during the conversion of oxirans to thiirans by reaction with thiourea[44] (equation 5).

The β-hydroxyisothiouronium salt **70** can be isolated in the presence of acid[44,45] and react further on addition of base. The importance of the cyclic intermediate **71** is evident from the failure of cyclopentene oxide to react.



In a similar manner the amidino group migrates[46] from S to N. S-(2-Aminoethyl)isothiouronium salts (**72**) rearrange, at neutral pH, to 2-mercaptoethylguanidine (**74**). Both starting materials and products are in this case isolatable as hydrobromide salts. The reaction was shown[47] to involve the cyclic intermediate **73**.



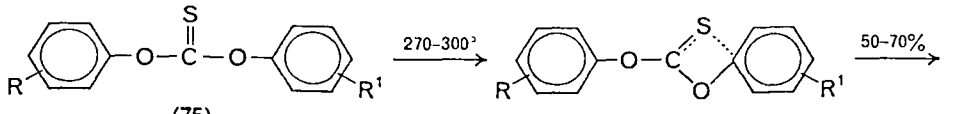
S-(3-aminopropyl)isothiouronium salts rearrange in the same manner to (3-mercaptopropyl)guanidines through a six-membered cyclic intermediate[46].

III. REARRANGEMENTS OF THE O-THIOACYL SYSTEM TO THE S-ACYL SYSTEM

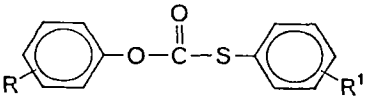
A. Rearrangements which Proceed through a Four-membered Cyclic Transition State

The first reported rearrangement of this type was the thermal isomerization of diarylthioncarbonates (**75**) to diarylthiolcarbonates (**77**)[48,49].

An examination of a large series of compounds[50] showed that when R and R′ are electron-withdrawing substituents, rate accelerations are experienced, and in unsymmetrically substituted thioncarbonates the rearrangement occurs primarily in the direction of the ring bearing the more electron-withdrawing substituents. The reaction thus originates from the nucleophilic character of the sulphur. A kinetic study[51] showed that



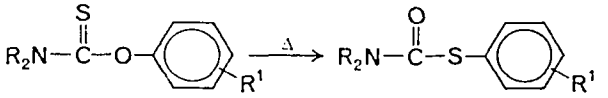
(75) (76)



(77)

the reaction is first order and all these data indicate that the rearrangement consists of an aromatic nucleophilic displacement in which the ring migrates from O to S via a four-membered cyclic transition state (**76**). Since this mechanism requires no solvation, the reaction could be carried out also in the gas phase (440°C, short periods) and yields were improved[52]. The reaction can serve as an efficient preparation method for aromatic thiols by hydrolysis of the products **77**.

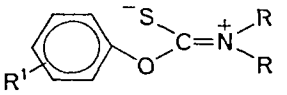
N,N-Dialkylthioncarbamates (**78**) rearrange similarily to thiolcarbamates (**79**). This isomerization is faster and proceeds at lower temperatures and in higher yields (usually above 90%)[53,54].



(78) (79)

The four-membered cyclic mechanism is supported by substituent effects and kinetic results[53,55]. No crossover products were found on heating a mixture of two thioncarbamates.

Steric rate enhancement due to hindered rotation was found to be present in ortho-substituted compounds in this series[56]. The relatively low temperature required results from increased nucleophilicity of the sulphur, since the polarization is assisted by the dialkylamino group, towards the zwitterionic form **80**.



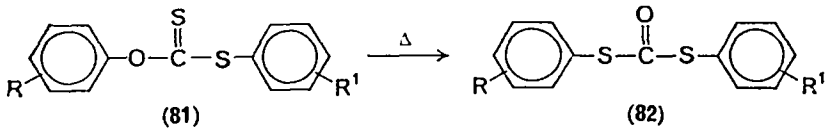
(80)

A stronger electron-donating inductive effect of R should promote the nucleophilic character of the sulphur further, and indeed the rearrangement rate was found to increase in the order[55]:

$$R = i\text{-}C_4H_9 > n\text{-}C_3H_7 > C_2H_5 > CH_3$$

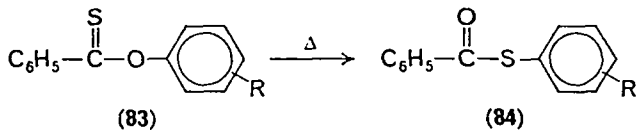
The reaction was utilized for the synthesis of aromatic thiols[53] and sulphonic acids[57] by hydrolysis or oxidation of the rearranged products.

The heating of xanthates usually results in β-elimination and formation of olefins (Chugaev reaction[58]). However, when there is no β-hydrogen at the alcohol moiety, rearrangement takes place. A kinetic study of the influence of substituents on the reaction rate of a series of diaryl xanthates to diaryl dithiocarbonates (**81**→**82**) again indicates a four-membered cyclic transition state[59]. A similar transition state is indicated, by the same



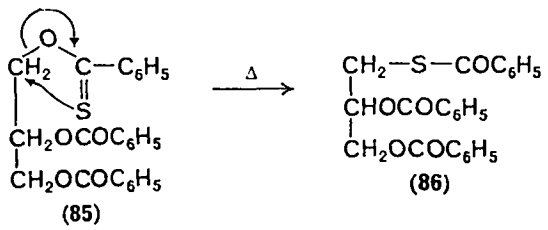
(81) (82)

kind of evidence, for the rearrangement of aryl thiobenzoates (**83**) to aryl thiolbenzoates (**84**)[60].



(83) (84)

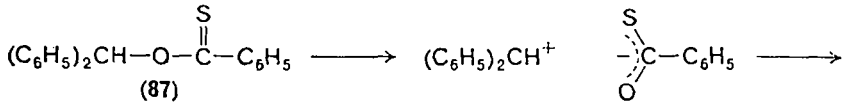
The rearrangement of alkyl thiobenzoates had also been reported in certain cases[61]. An application of this reaction is the thermal conversion of thionesters of glycerol to esters of thioglycerol (**85**→**86**)[62].



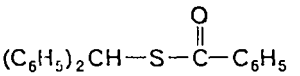
(85) (86)

B. Rearrangements which Proceed through Dissociation and Return

O-Alkyl thionesters rearrange easily to thiolesters when the alkyl group can form relatively stable carbonium ions. Benzhydryl thioncarbonate (**87**) yields **88** on heating in ethanol[63] and the suggested mechanism is a dissociation to a ion pair, the return of which occurs *via* the sulphur because of the greater nucleophility of the sulphur compared to the oxygen.

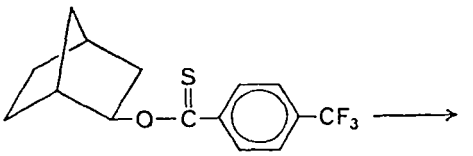


(87)

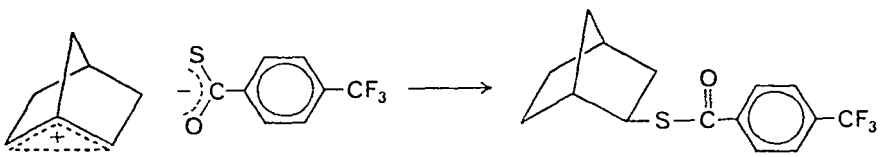


(88)

A study of the rearrangement of the optically active exo-norbornyl thiobenzoate **89** to **90** showed that the rate of racemization was equal to the rate of the disappearance of **89**. This indicates that no return *via* the oxygen occurs[64].

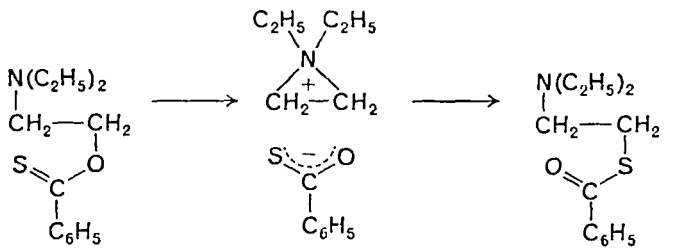


(89)



(90)

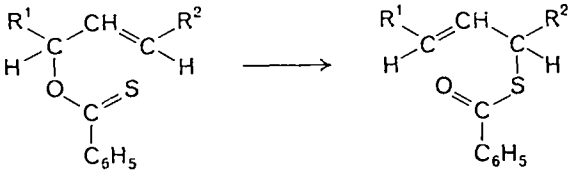
The dissociation, and hence the rearrangement, may be caused by neighbouring group participation in the formation of the cation. An example is the rearrangement of the thionester **91**[65].



(91)

C. Rearrangement of Allyl Thionesters

Allyl thionbenzoates (92) rearrange[66] to allyl thiolbenzoates (93), accompanying an allyl shift, on heating to 100°C.



(92) (93)

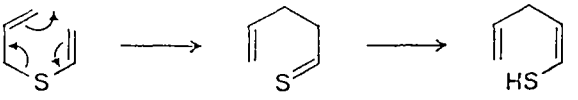
This isomerization is very little influenced by the medium and occurs only ca. ten times faster in acetic acid than in cyclohexane. This low sensitivity to the ionizing power of the solvent indicates that allyl thionesters rearrange by a mechanism which involves very little change in charge separation between the ground state and the transition state. Thus a cyclic concerted mechanism is more probable than dissociation to ion pairs. This conclusion was confirmed by deuterium isotope effect measurements[67].

Allyl thioncarbamates[68] and allyl xanthates[65] also rearrange easily in the same manner.

IV. THE THIO-CLAISEN REARRANGEMENT

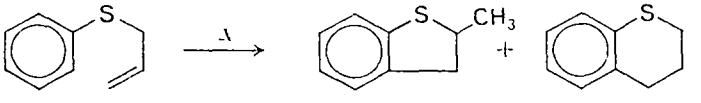
A. The Rearrangement of Allyl Aryl Sulphides

The thio-Claisen rearrangement is a [3,3]sigmatropic process, which consists of synchronous cleavage of a carbon—sulphur bond and formation of a new carbon—carbon bond (equation 6).



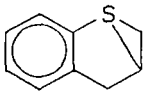
(6)

The thiols formed usually do not survive under the reaction conditions and cyclize to five- and six-membered rings. Heating of allyl phenyl sulphide (94) in high boiling amines[69,70] or carboxylic acids[71] yields 2-methyl-2,3-dihydrobenzothiophene (95) and thiachroman (96). The two products are not interconvertible under these conditions.

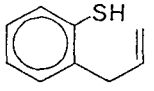


(94) (95) (96)

Although a different reaction pathway, which involves the thiiran **97** as intermediate, has been proposed[72,73], the intermediacy of 2-allylbenzenethiol (**98**) and therefore the correctness of the concerted mechanism has been rigorously established. In the presence of methyl iodide the methylthio derivative **99** was isolated[74]. Furthermore, compound **98** was synthesized independently[72] and was shown to undergo a facile cyclization to give both **95** and **96**. When cyclized under the rearrangement conditions, the proportions of the products from **98** were identical with those obtained directly from **94**[74].



(97)



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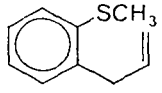
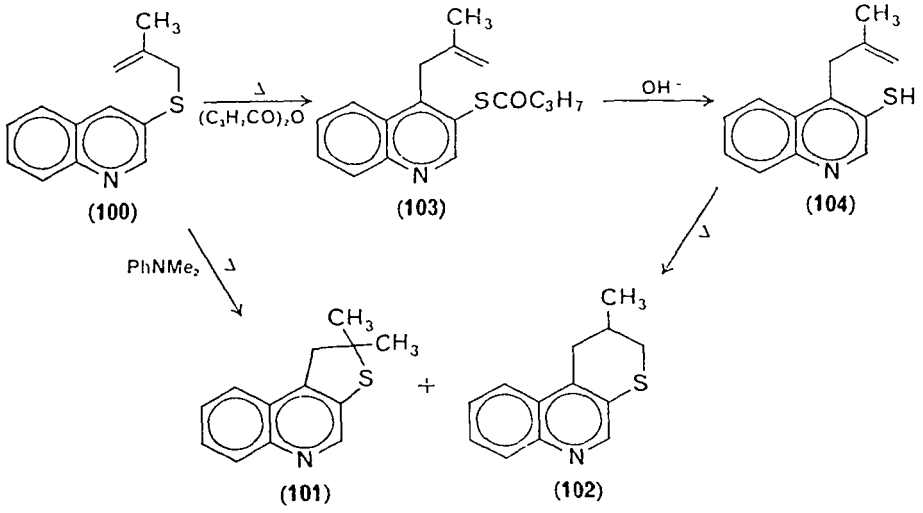


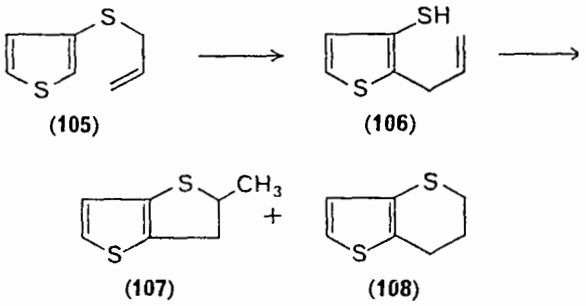
(99)

Definitive evidence for the sole intermediacy of 2-allylarenethiols was obtained from work on the rearrangements of allyl quinolyl sulphides[75–77]. For example, 3-methallylquinolyl sulphide (**100**), which rearranges in dimethylaniline to **101** and **102**, gave in butyric anhydride quantitative yield of the butyryl derivative (**103**) of the Claisen product **104**. Compounds **100** and **104** yielded **101** and **102** in the same proportions when heated under identical conditions.



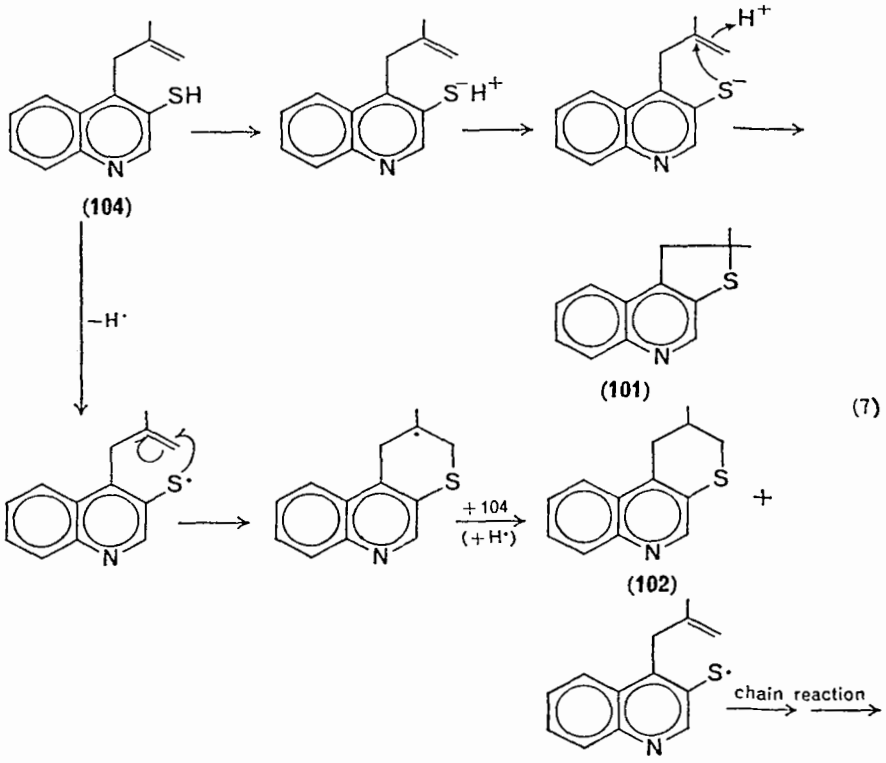
(100) (103) (104) (101) (102)

Similar results were observed in the thiophene series[78]. In the rearrangement of allyl 3-thienyl sulphide (**105**) to **107** and **108**, the intermediate 2-allylthiol **106** has been isolated for the first time directly from the reaction mixture.



(105) (106) (107) (108)

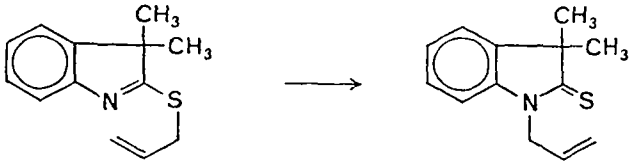
The five-membered ring products result from the normal (Markownikoff) internal addition of the thiol group to the double bond, whereas the six-membered ring products result from abnormal (anti-Markownikoff) addition, which is characteristic of a free radical process. The formation of both heterocycles thus indicates competitive thermally induced heterolytic and homolytic fissions of the thiol S—H bond (equation 7). The cyclization mechanisms were verified[79] by a detailed examination of the thermal behaviour of **104**. Product **102** was formed almost exclusively



(7)

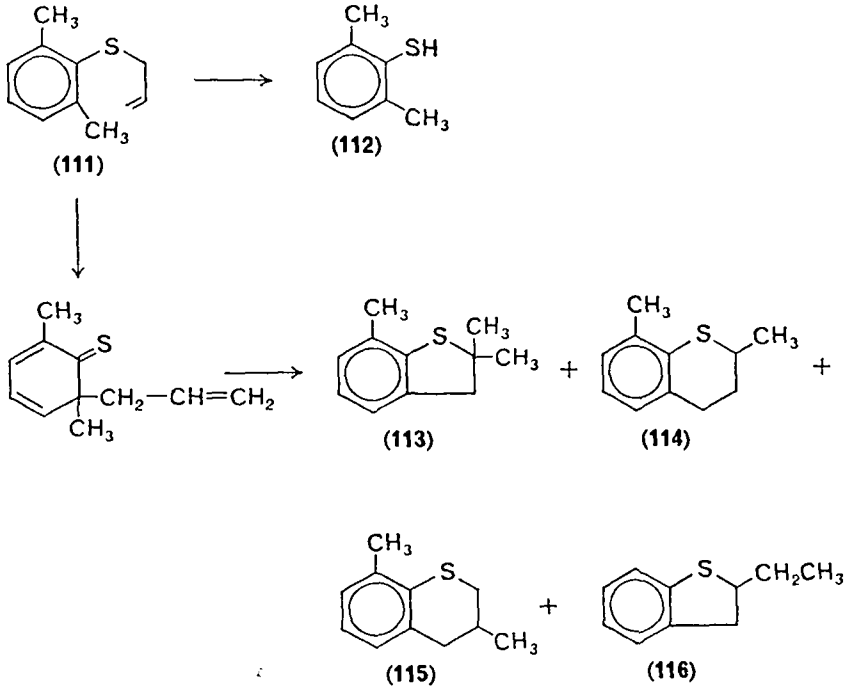
under free radical initiation. The intervention of free radical intermediates was also evident from e.s.r. monitoring of the reaction.

Cyclization does not occur when the thione initially formed in the rearrangement cannot tautomerize to the corresponding enethiol. The indolenine **109** for example rearranges to **110** which shows no tendency to cyclize[80].



(109) **(110)**

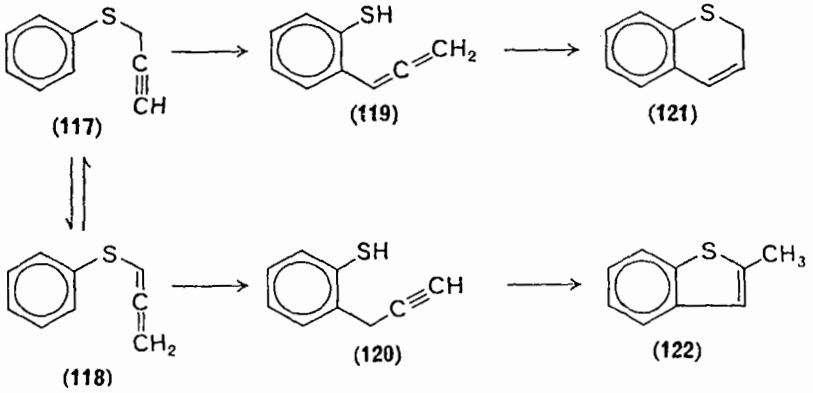
When the two *ortho*-positions are blocked, no *para*-Claisen products are observed. Heating of allyl 2,6-dimethylphenyl sulphide (**111**) yields a cleavage product **112** and four cyclic materials (**113–116**) which probably result from *ortho*-rearrangement followed by 1,3- and 1,4-methyl migrations[81].



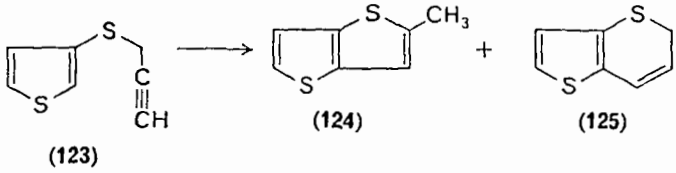
(111) **(112)** **(113)** **(114)** **(115)** **(116)**

B. The Rearrangement of Prop-2-ynyl Aryl Sulphides

This reaction also yields both five and six-membered cyclic products, but has been shown to consist of two parallel processes[82]. Prop-2-ynyl phenyl sulphide (**117**) on heating initially isomerizes to phenyl allenyl sulphide (**118**) and both **117** and **118** undergo the thio-Claisen rearrangement to the allenic (**119**) and acetylenic (**120**) thiols respectively. Subsequent cyclization yields the final products, 2H-thiachromene (**121**) and 2-methylbenzothiophene (**122**).



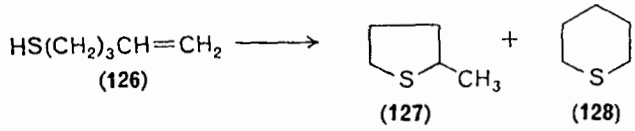
The rearrangement of prop-2-ynyl-3-thienyl sulphide (**123**) proceeds in the same manner to give **124** and **125**[83].



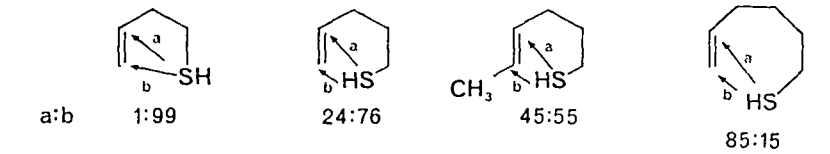
V. INTERNAL ADDITIONS, ELIMINATIONS AND RING-CHAIN TAUTOMERISMS

A. Intramolecular Additions to Double Bonds

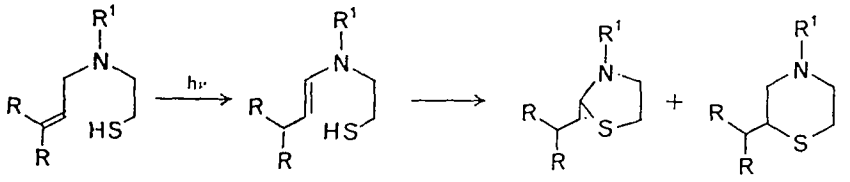
The cyclization of *ortho*-allylbenzenethiols has already been discussed in connection with the thio-Claisen rearrangement. It has been shown that ionic and free radical processes operate simultaneously to give five- and six-membered heterocycles respectively[79]. Similar dual pathways were observed in the cyclization of 5-mercapto-1-pentene (**126**) which gave both **127** and **128**[84].



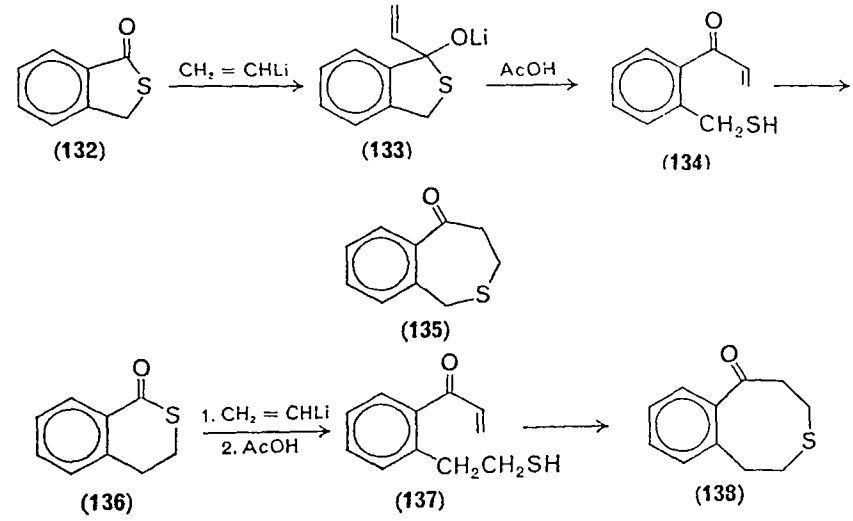
Free radical cyclization (Bz_2O_2 catalysis) of a series of simple mercapto-olefins gave the following product ratios[85].



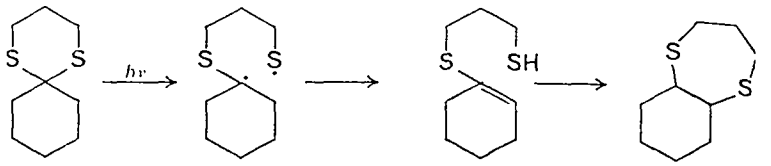
Different results were observed in nitrogen-containing chains. Ultraviolet irradiation of N-allyl-2-aminoethanethiols (**129**) gave mainly thiazolidines (**130**) when R was H and hexahydrothiazines (**131**) when R was methyl. These results can be rationalized by assuming an initial double-bond migration towards the nitrogen[86].



Reaction routes which include internal additions of thiols have been proposed for several rearrangement reactions. Addition of vinyllithium to thiophthalide (**132**) yielded, after acidification, 4,5,6,7-tetrahydro-2H-benzo[c]thiepin-5-one (**135**). The probable course is ring opening of the adduct **133** to the thiol **134** which cyclizes by conjugate addition to give **135**. The thiolactone **136** yielded **138** in an analogous manner *via* the thiol **137**[87].



Another example is the photolysis of mercaptoles. Compound **139** yielded the rearranged product **140** (*cis-trans* mixture, ratio 8 : 1). Its formation is best explained by a homolytic scission of the C—S bond, followed by hydrogen atom transfer and addition of the thiol to the double bond[88].



(139) (140)

B. Intramolecular Additions to Triple Bonds

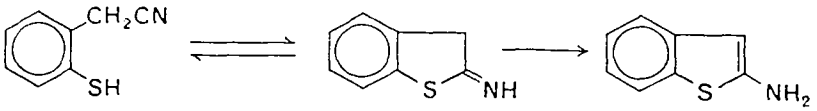
Cyclization of a series of acetylenic thiols under various conditions gave the following results[89] (Table 1, in %).

Although the polymerization was extensive in most cases, the analysis of the cyclic products clearly shows that in terminal acetylenes nucleophilic reaction leads mainly to exo-methylene-heterocycles, while free radical cyclization leads to unsaturated rings.

The cyclization of *ortho*-prop-2-ynylbenzenethiol has already been discussed in connection with the thio-Claisen rearrangement[82].

C. Cyclization and Ring-chain Tautomerism of Cyanothiols

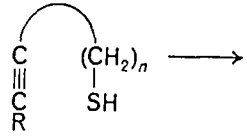
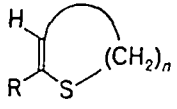
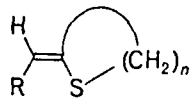
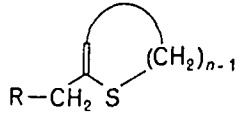
Cyanothiols cyclize irreversibly in cases in which the product exists predominately in its enamino form. *o*-Mercaptobenzylcyanide (**141**) thus cyclized to **142** which tautomerized to **143** and was shown to exist only in a cyclic form[90].



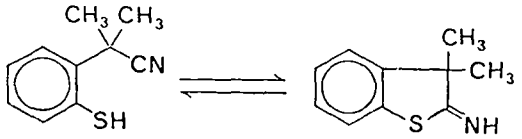
(141) (142) (143)

Compound **144**, on the other hand, cyclized to **145** in which the methyl substituents at position 3 preclude tautomerism to an enamine, and indeed its exists in the cyclic form only in neutral or acidic media. However, in basic solution it reacts as the open chain form **144**, and can be S-alkylated or oxidized to the corresponding disulphide[91].

TABLE 1. Cyclization of acetylenic thiols

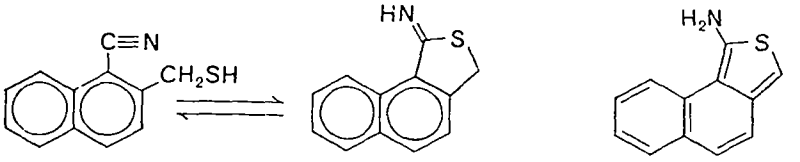
	R	Cyclization method					+ polymers
$n = 2$	H	h ν	traces	—	—		44
$n = 3$	H	Nu	—	25	—		not determined
	H	Δ	10	—	3		47
	H	Bz_2O_2	15	—	6		56
	H	h ν	48	traces	traces		43
	H	h ν-acetone	35	traces	traces		43
	CH_3	h ν	4	17	10		28
	C_6H_5	h ν	—	75	—		10
$n = 4$	H	Nu	—	20	—		not determined
	H	Δ	5	traces	—		80
	H	Bz_2O_2	28	traces	—		70
	H	h ν	38	traces	—		52
	H	h ν-acetone	51	traces	—		44
$n = 5$	H	h ν	23	—	—		51
$n = 6$	H	h ν	8	—	—		39

h ν, ultraviolet irradiation.
h ν-acetone, ultraviolet irradiation with acetone as sensitizer.
Δ, prolonged heating in cyclohexane.
Bz_2O_2, short heating; Bz_2O_2 added for free radical initiation.
Nu, nucleophilic cyclization by heating with NaOH.



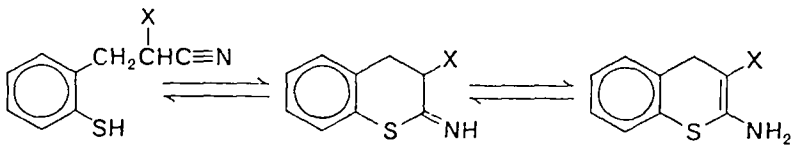
(144) (145)

The same ring-chain tautomerism is exhibited by the pair **146** ⇋ **147**. The cyclic form **147** exists as the imino tautomer, as aromatic stability would be disrupted by the *o*-quinoidal structural requirement of the enamino tautomer **148**[92].



(146) (147) (148)

In corresponding six-membered systems it was shown that **151b** and **151c** are the predominant forms, as a result of conjugation with the substituent X, and therefore they do not show tautomerism with the open forms **149**. It was speculated by the authors[93] that if X would be a hydrogen, the cyclic form might exist as **150a**, and would be in tautomerism with **149a**. However, this could not be demonstrated, due to the failure to synthesize **149a** or **150a**.



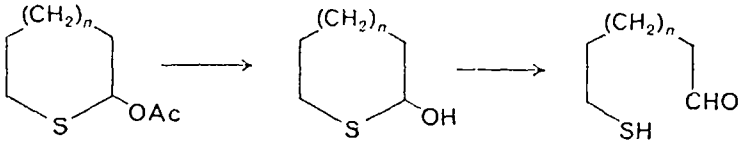
(149) a, x = H
b, x = $COOC_2H_5$
c, x = CN

(150) (151)

D. Ring-chain Tautomerism of Mercaptoaldehydes and Mercaptoketones

The order of stability of the cyclic form of hemithioacetals relative to the open chain form is parallel to that observed for hydroxyaldehydes[94]. 2-Hydroxytetrahydrothiophen (**152a**) and 2-hydroxyhexahydrothiopyran (**152b**) (prepared from the corresponding acetates) were shown, by spectral evidence, to exist in their cyclic forms both in the neat state and in their solutions in organic solvents. In aqueous solutions, however, they are

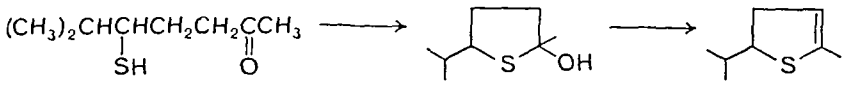
converted into the tautomeric mercaptoaldehydes **153a** and **153b** and can be titrated as thiols with aqueous iodine. The seven-membered ring **152c**, on the other hand, exists as such only in the solid state, but shows spectral properties ascribable to the open form **153c** in chloroform solution, indicating that tautomerism occurs in this case very readily[95].



(152) **a**, n = 0
b, n = 1
c, n = 2

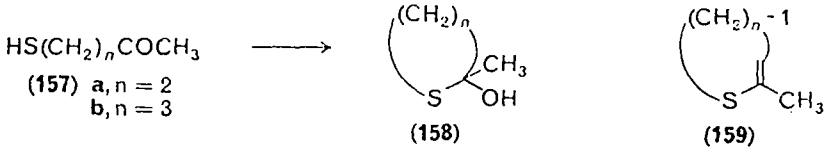
(153)

Similar results were obtained with mercaptoketones. The thiol **154** was prepared from open-chain precursors and cyclized spontaneously with loss of water to **156**. The possible intermediate **155** could not be isolated[96].



(154) (155) (156)

The unsubstituted mercaptoketones **157a** and **157b** were never isolated and isolation attempts led to the unsaturated heterocycles **159a** and **159b**, probably *via* the hemithioacetals **158a** and **158b**[96,97].

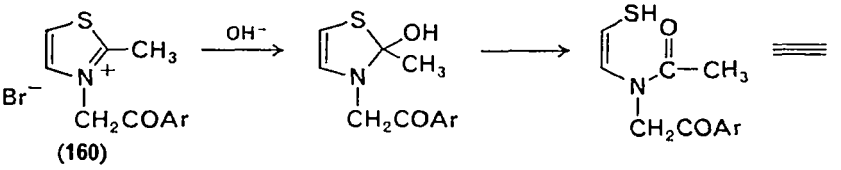


(157) **a**, n = 2
b, n = 3

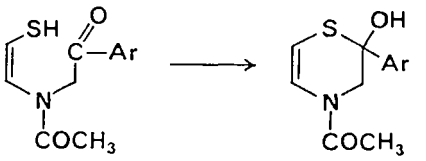
(158) (159)

Internal thiol–carbonyl interactions were extensively investigated in the field of thiosugars, and were applied to the syntheses of the thiofuranose[98], and thiopyranose[99,100] and thioseptanose[101,102] systems.

Ring opening and closure involving mercaptoketones were assumed to occur during the unexpected formation of 4-acetyl-2,3-dihydro-2-hydroxy-2-phenyl-4H-1,4-thiazine (**161**), on treating 2-methyl-3-phenacylthiazolin bromide (**160**) with base[103].

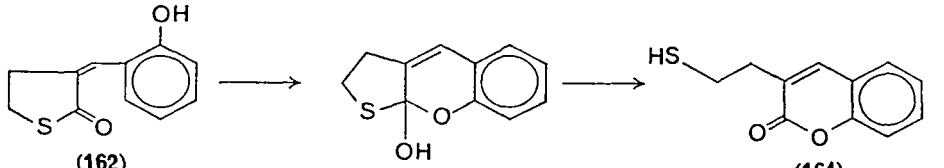


(160)



(161)

Another interesting example exists in the photochemical rearrangement of α-(*o*-hydroxybenzylidene)-γ-butyrothiolactone (**162**) to 3-(2-mercaptoethyl) coumarin (**164**). The rearranged product **163** is stabilized by ring opening, as the carbonyl group formed becomes a part of the coumarin system[101].

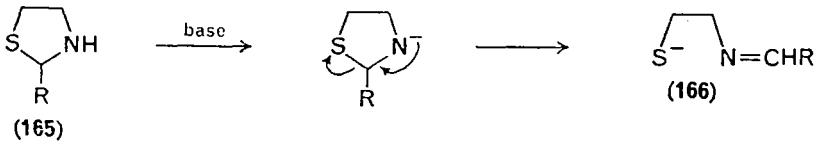


(162) (163) (164)

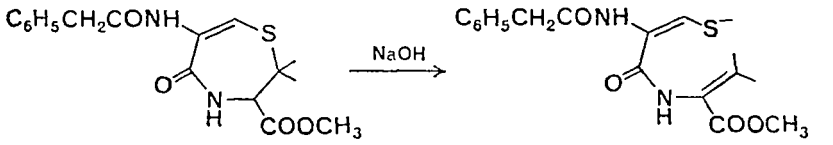
E. Ring Openings of Cyclic Sulphides to Unsaturated Thiols

1. β-Eliminations

This reaction has been observed mainly in nitrogen-containing systems. The proton elimination can occur either from a β-nitrogen atom or from a β-carbon. 2-Arylthiazolidines (**165**) are thus opened to the iminothiols **166**[105] and the tetrahydro-1,4-thiazepine **167** is opened to the enethiol **168** which is unstable, but could be trapped. The corresponding

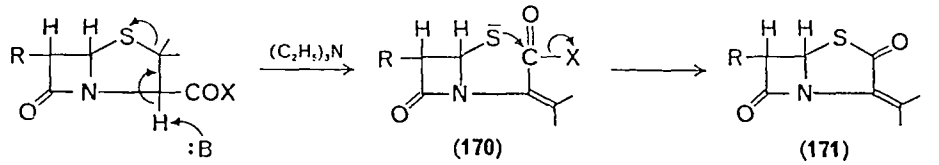


(165) (166)



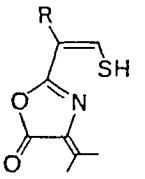
(167) (168)

perhydrothiazepine is opened by base at a much slower rate, and the resulting thiol is isolatable[106]. Rearrangements of this type are most common in penicillin chemistry. An example is the rearrangement of penicillins with an activated carboxyl group **169** to anhydropenicillins (**171**), in which the first step is β-elimination to the thiol (**170**)[107].



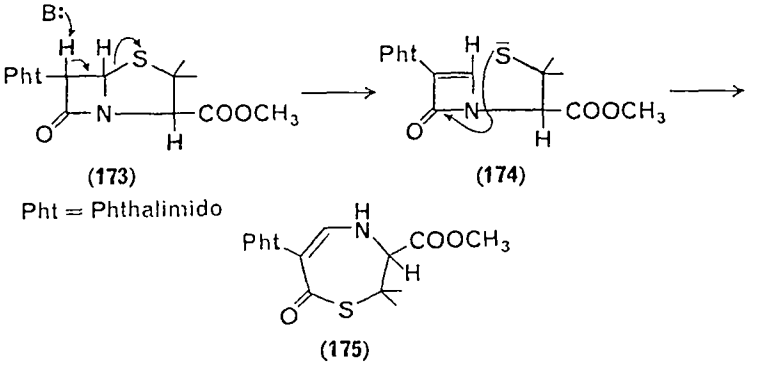
(169) (170) (171)

The intermediate **170** could, in certain cases, be trapped as its acyl derivative[108]. In another instance the carboxyl group reacted with the lactam ring leading to the oxazole **172**[109].



(172)

Another type of penicillin rearrangement is that which starts with proton elimination from C-6. Such mechanism explains the epimerization at C-6 on treating phthaloylpenicillin methyl ester (**173**) with sodium hydride[110]. The first step is the opening of the thiazole ring to the thiol salt **174** which recyclizes to **173** with epimerization. Support for this mechanism was provided by the isolation of the thiazepine **175** as a by-product[111].

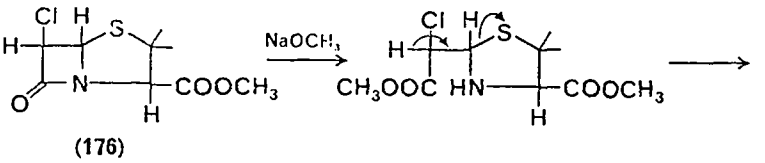


(173) (174)

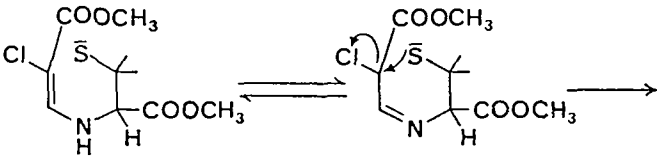
Pht = Phthalimido

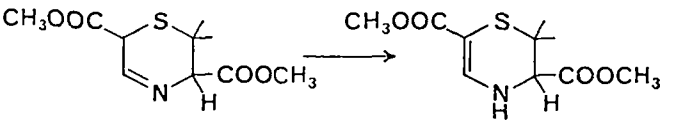
(175)

Another interesting penicillin rearrangement which involves β-elimination and a thiol intermediate is that of methyl 6α-chloropenicillate (**176**) to the 1,4-thiazine **177**, through the pathway shown[112]. Ring opening



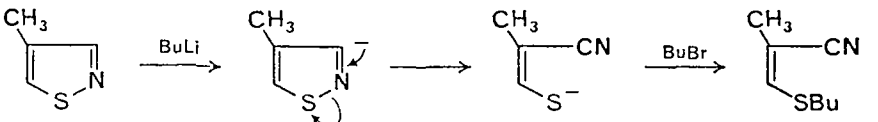
(176)





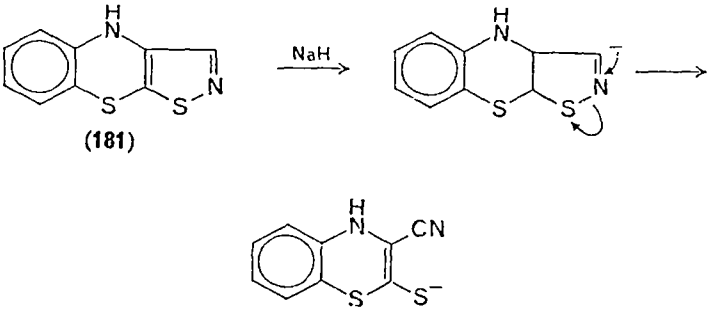
(177)

by β-elimination occurs also in the fully aromatic isothiazole system. During the lithiation of 4-methylisothiazole (**178**), which occurred mainly at position 5, the nitrile **180** was also formed as a by-product. The mechanistic pathway is probably lithiation at position 3, ring opening to the thiol salt **179** and alkylation by butyl bromide present in the reaction mixture[113].



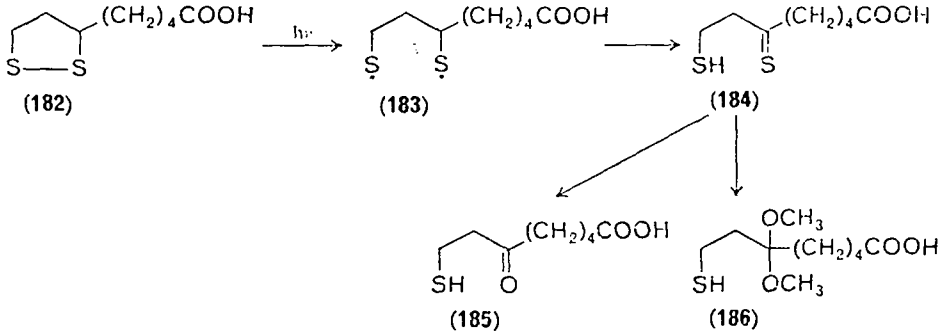
(178) (179) (180)

Similar openings were observed on treating condensed isothiazoles (**181**) with base[114].



2. Homolytic fissions followed by hydrogen transfer

The results of several photolysis reactions of sulphur-containing rings can be rationalized by postulating this process. One example is the photolysis of lipoic acid (**182**)[115] which yielded **185** (in water) or **186** (in methanol). The proposed mechanism is a homolytic scission of the S—S bond to the diradical **183** and migration of the tertiary hydrogen atom as a radical, to form the thionthiol **184** which reacts with the solvent. A similar mechanism which involves a primary homolytic cleavage of a C—S bond was assumed to occur in the photolysis of mercaptols[88].

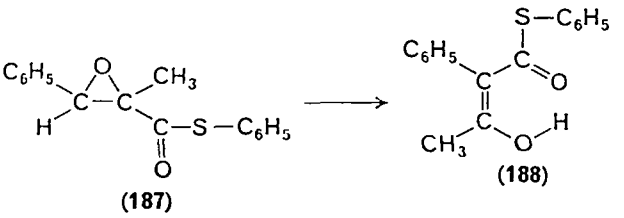


VI. MISCELLANEOUS REARRANGEMENTS

A. Migration of a Thiol Ester Group

The only case in which this type of migration occurs is the acidolytic ring opening of epoxides[116]. Phenyl α-methyl-*trans*-β-phenylthiolglycidate (**187**) gave, upon treatment with boron trifluoride etherate, 45% yield of the enol tautomer of phenyl α-phenylacetothiolacetate (**188**).

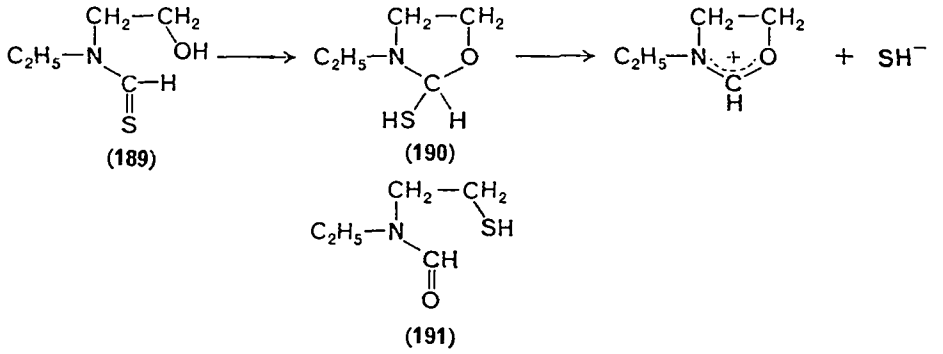
The tendency of the thiol ester group to migrate in this particular case is not surprising, since the unusual migration of the carbethoxy group in the corresponding glycidic ester was observed previously[117].



(187) (188)

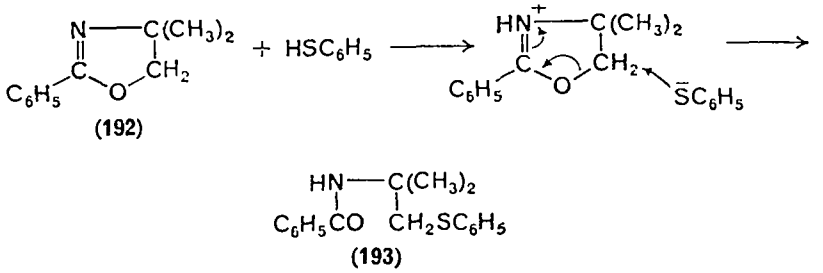
B. Dissociation and Return of the Hydrosulphide Ion

A rearrangement which proceeds through this mechanism was observed during the preparation of N-(β-hydroxyethyl)-N-ethyl-thioformamide (**189**). An isomer, N-(β-mercaptoethyl)-N-ethylformamide (**191**), was obtained as a side product and it was shown[118] that **191** was formed from **189**. The probable course is a cyclization of **189** to 1-ethyloxazolidine-2-thiol (**190**) and attack of the hydrosulphide ion at C-4. This mechanism is



(189) (190) (191)

supported by a previous report on the ring opening of oxazolidines by thiols (**192** → **193**)[119].



(192) (193)

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The Chemistry of the Thiol Group
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CHAPTER 16

Thiols as nucleophiles

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I. INTRODUCTION

The thiols act as nucleophiles in two basic types of reaction, involving either substitution or addition to a multiple bond such as C=C

$$RSH+AB \longrightarrow RSA+HB \quad (1)$$

or

$$RS^-+AB \longrightarrow RSA+B^- \quad (2)$$

$$RSH+\rangle C=C\langle \longrightarrow RSC-CH \quad (3)$$

In reactions of the type 1 the HB generated may fracture the S—A bond formed; for example the silicon—sulphur bond in H_3SiSCF_3 is susceptible to fracture by HI.

$$H_3SiSCF_3+HI \longrightarrow H_3SiI+CF_3SH$$

The substitution reactions discussed in this review will be restricted primarily to the thiolate anion, RS^- acting as a nucleophile. This may be present initially when a metal thiolate, such as silver(I) or lead(II), is employed, or may be generated in solution in the presence of a base such as sodium hydroxide or trimethylamine. The acidity of the thiol is important if the RS^- anion acts as a nucleophile in a neutral thiol solution. Thiolate nucleophiles can be obtained in non-aqueous solution by treatment of thiol esters, such as CH_3COSR, with strong non-nucleophilic bases[1], or by hydrolysis of thiourea derivatives[2].

The substitution type reaction is not restricted to substitution at a carbon atom, either aliphatic or aromatic, but includes the main group and transition elements. Several examples will be given of the varieties of the use of thiolates as nucleophiles, and although most of these reactions are

general, some of the illustrative examples will be drawn from the chemistry of halogenated thiols, in which the author is particularly interested. The review will generally be restricted to monofunctional thiols, and usually excludes dithiols, thio acids, etc.

Various reviews have been written on parts of this topic and these will be referred to at appropriate places in the text. The alkoxide nucleophiles have been investigated considerably more than the thiolate nucleophiles, and conversely selenolates significantly less than thiolates. In general the order of nucleophilic strength increases in the series alcohols, thiols and selenols, although sulphur-containing nucleophiles are generally less basic than their oxygen analogues.

The nucleophilic reactivities towards cations of several nucleophiles has been reviewed[3]. A parameter N_+ which is characteristic of the nucleophile system and independent of the cation has been defined as

$$\log [K_n/K_{\mathrm{H_2O}}] = N_+$$

where K_n is the rate constant for reaction of a cation with a specific nucleophilic system (i.e. a given nucleophile in a given solvent), $K_{\mathrm{H_2O}}$ is the rate constant for reaction of the same cation with water in water. This generalization can successfully be applied to the reactions of various nucleophiles with various cations. It has been suggested that the N_+ values are related to the solvation energies of the nucleophiles[4]. In all the reactions studied, values of N_+ are highest for the benzenethiolate anion. Comparable values for the reactions of nucleophiles with *p*-nitro- (Malachite Green) are, solvent in brackets, MeOH (MeOH), 0·5; MeO^- (MeOH), 7·5; N_3^- (MeOH), 8·5; CN^- (DMSO), 8·6; PhS^- (MeOH), 10·7; PhS^- (DMSO), 13·1. Unfortunately data are not currently available to correlate analogous oxygen, sulphur and selenium nucleophiles by this method.

A considerable range and variety of thiols have been employed as nucleophiles. Some thiols are unstable in basic solution, but can be employed as their thiolate salts. Examples of this type of thiol include trifluoromethanethiol and pentafluorobenzenethiol. The trifluoromethanethiolate anion readily loses fluoride in solution in an irreversible reaction[5], but the mercury derivative, $Hg(SCF_3)_2$, effectively acts as a source of

$$(SCF_3)^- \longrightarrow CSF_2 + F^-$$

nucleophilic trifluoromethanethiolate ions. The pentafluorobenzenethiolate anion decomposes in basic solution in air. The reaction probably proceeds initially with the oxidation of the thiolate to the disulphide, which is then

attacked nucleophilically by the thiolate.

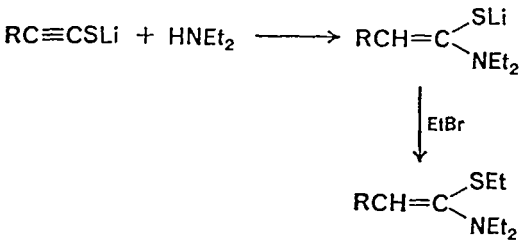
$$2\ C_6F_5S^- \xrightarrow{air} C_6F_5SSC_6F_5 + 2\ e$$

$$2\ C_6F_5S^- + C_6F_5SSC_6F_5 \longrightarrow C_6F_5SC_6F_4SSC_6F_4SC_6F_5 + 2\ F^-$$

The product, termed perfluoropoly(phenylene sulphide)[6], has been characterized by chemical analysis and molecular weight[7].

Some thiolates, such as pentachlorobenzenethiolate, show no nucleophilic reactivity[8].

Other interesting thiols that have been studied include the silylalkanethiols, such as $(EtO)_3SiCH_2CH_2CH_2SH$[9], and $(Me_3SiO)_2MeSi(CH_2)_3SH$[10]. A series of syntheses based on the alkynethiolates has been reported[11]. In some reactions the C≡C bond is retained, but in others it reacts, e.g.



The stereochemistry of the thiol is important. Steric effects have been used to explain the differences in rates of reactivity of RC_6H_4SH (R = H, 2-*t*-Bu, 4-*t*-Bu) in addition reactions with N-ethyl maleimide or displacement of 2,4-$(O_2N)_2C_6H_3S^-$ from 2,4-$(O_2N)_2C_6H_3SSEt$[12].

In some circumstances the electrophiles studied are susceptible to the thiolate anion causing both substitution or addition. An example is $HC{\equiv}CCMeHalCO_2Et$[13]. In this case the thiolate can also act as a reducing agent. The reducing properties of the thiols will only be commented on when it is incidental to substitution or addition. The reducing power of thiolates, however, means that the electrophiles employed generally do not contain a group that is readily reduced, such as the nitro group. When simultaneous substitution and addition occur, the reaction will be discussed in the substitution section, particularly in compounds containing C≡C bonds.

This review is divided into two main sections; substitution reactions and addition reactions. Sometimes the classification of a particular reaction is somewhat arbitrary. Dealkylation reactions, some of which can superficially appear to be neither substitution nor addition reactions, are basically substitution reactions and a section is devoted to these reactions, including both aliphatic and aromatic examples.

II. SUBSTITUTION REACTIONS

A. *Aliphatic Substitution*

1. Introduction

Simple thiolate substitution of an aliphatic compound can be represented by the equation

$$RX + R^1S^- \longrightarrow RSR^1 + X^-$$

where the group X may be a halogen, methoxy (discussed mainly under dealkylation), methanesulphonate, tosyl, etc.

Examples of the reactions of alkyl and acyl halides are[14]:

$$CH_2Cl_2 + Pb(SC_6F_5)_2 \longrightarrow CH_2(SC_6F_5)_2 + PbCl_2$$

$$ClCH_2CH_2Cl + Pb(SC_6F_5)_2 \longrightarrow (CH_2SC_6F_5)_2 + PbCl_2$$

$$2\,PhCOCl + Pb(SC_6F_5)_2 \longrightarrow 2\,PhCOSC_6F_5 + PbCl_2$$

An inert solvent is usually used but liquid ammonia has been used in the reaction of alkyl chlorides with sodium hydrogen sulphide[15,16]. The compound $(PhS)_3CH$ was formed in the reaction of the benzenethiolate anion and dibromocarbene, prepared from $PhHgCBr_3$ in benzene at 80°C. The postulated initial step was the addition of the electrophile Br_2C: to the sulphur nucleophile, forming an anion intermediate which picked up a proton yielding $PhSCHBr_2$. Subsequent nucleophilic replacement of bromine by the thiolate gave the product[17], $(PhS)_3CH$.

Polymers are formed when dithiols react with dihaloalkanes. Condensation of *p*-$HSCH_2C_6H_4CH_2CH(Me)C_6H_4CH_2SH$-*p* with dihaloalkanes gives polymers[18] such as $H(SCH_2C_6H_4CH_2CH(Me)C_6H_4CH_2S(CH_2)_m)_n$Hal. Two different monofunctional high molecular weight chlorides (R^1Cl and R^2Cl) react with the difunctional thiol, $(CH_2SH)_2$, in the presence of triethylamine to give primarily the symmetrical bisulphides, $(R^1SCH_2)_2$ and $(R^2SCH_2)_2$, and only very small yields of the unsymmetrical bisulphide $R^1SCH_2CH_2SR^2$ [19].

Recently copper(I) salts including thiolates have been studied as nucleophiles. Copper(I)butanethiolate and copper(I)cyanide in DMF did not react with *t*-butyl chloride or benzyl chloride, but halogenoaromatic compounds react under similar conditions. When the reactions were repeated in the presence of thiourea or quinoline, the expected products, di-*t*-butyl sulphide, valeronitrile and phenylacetonitrile, were obtained. The thiourea or quinoline probably act as ligands and bind strongly to the copper, forming the ion $(CuL_4)^+$, leaving the counterion (e.g. BuS^- from CuSBu) available for normal nucleophilic attack[20].

2. Reactions with electrophiles of the type $RM(CH_2)_nX$ and $RMCHX_2$

a. Displacement of halogen. Alkylthio-substituted acetic acids can be obtained from monochloracetic acid and a thiol[21],

$$ArOCH_2SH + ClCH_2CO_2H \longrightarrow ArOCH_2SCH_2CO_2H$$

Derivatives of 1,1,1-trifluoroacetone may be prepared similarly[22],

$$CF_3COCH_2Cl + RSH \xrightarrow{Et_3N} CF_3COCH_2SR \quad (R = Et, Bu, Ph)$$

Organotin derivatives containing the $RSCH_2Sn(IV)$ group can readily be obtained in the reactions of RSNa and $BrCH_2Sn\lessgtr$ or $RSCH_2Li$ and $ClSn\lessgtr$, the former method being preferred. Compounds containing both Sn—S and Sn—C bonds can be prepared[23],

$$RSNa + (BrCH_2)_2SnBr_2 \longrightarrow (RSCH_2)_2Sn(SR)_2$$

A similar reaction involves replacement of the Cl in $RR^1NP(O)(CH_2Cl)_2$ and $(ClCH_2)_2P(O)OPh$ or tosyl in $4\text{-}MeC_6H_4SO_3CH_2P(O)Ph_2$ with $(SR^2)^-$,[24,25]. Substituted trialkylphosphine oxides or sulphides, $(RSCH_2CH_2)_3PX$ (X = O, S) can be prepared analogously[26,27], from a thiolate anion and $(ClCH_2CH_2)_3PX$.

b. Displacement of sulphonyl groups. Ready replacement of the methanesulphonate group by the benzenethiolate group from bismethanesulphonates of 3-arylthiopropane-1,2-diols, 2-arylthiopropane-1,3-diols and 1-arylthiopropane-2-ols has been reported[28,29].

$$p\text{-}MeSC_6H_4SCH_2CH(OSO_2Me)CH_2(OSO_2Me) + PhS^- \longrightarrow p\text{-}MeSC_6H_4SCH_2CH(SPh)CH_2(SPh)$$

The reaction proceeded via a direct S_N2 substitution except when rearrangement occurred, which was only partially observed in the reaction

$$p\text{-}MeOC_6H_4SCH_2CH(Me)OSO_2Me + PhS^- \longrightarrow p\text{-}MeOC_6H_4SCH_2CH(Me)SPh + p\text{-}MeOC_6H_4SCHMeCH_2(SPh)$$

The cyclic intermediate $\overset{+}{C}H(Me)S\overset{+}{A}rCH_2X^-$ is postulated. It is impossible to detect whether rearrangement or direct substitution occurred in the reaction

$$PhSCH_2CH(OSO_2Me)Me + SPh^- \longrightarrow PhSCH(Me)CH_2SPh + MeSO_3^-$$

The nitro groups were reduced in derivatives of 2,4-dinitrobenzene.

The trifluoromethanesulphonyl group is displaced in *p*-tolylsulphonylmethyltrifluoromethanesulphonate in the S_N2 reaction with nucleophiles, such as benzenethiolate[30],

$$p\text{-}MeC_6H_4SO_2CH_2O_3SCF_3 + PhS^- \longrightarrow p\text{-}MeC_6H_4SO_2CH_2SPh + CF_3SO_3^-$$

In the reaction of 2,2-dialkyl-3-(tosyloxy)propionaldehydes with benzene- or methane-thiolates the tosyl group is displaced and it is postulated that the attack originates at the carbon atom of the carbonyl group[31].

$$Me_2C(CHO)CH_2OTs + RS^- \longrightarrow Me_2C(CHO)CH_2SR$$

The carbon—sulphur bond is fractured in the reaction of *p*-toluenesulphonyl cyanide with sodium ethanethiolate in ethanol. Other thiols, not thiolates, can also fracture the carbon—sulphur bond[32].

$$p\text{-}TolSO_2CN + EtS^- \longrightarrow EtSCN$$

3. Reactions of electrophiles of the type $Ar(CH_2)_nX$

The chlorine kinetic isotope effect in nucleophilic displacement at saturated carbon in *para*-substituted benzyl chlorides, with thiolate and analogous oxygen nucleophiles, has been examined[33]. The reactions proceed via a concerted transition state.

$$R'S^- + RCl \longrightarrow [R'S \sim R \sim Cl] \longrightarrow RSR' + Cl^-$$

As the *para*-substituent changes from more electron donating to more electron withdrawing, the relative importance of bond breaking and bond making in the transition state alters. With methoxide and benzenethiolate nucleophiles the chlorine isotope effect (K_{35}/K_{37}) increases in the order $p\text{-}NO_2 < H < p\text{-}MeO$, indicating greater bond breaking as the *para*-substituent becomes more electron withdrawing. For both oxygen and sulphur nucleophiles the isotope effect decreases with increase in basicity, PhO^- *vs* MeO^-, and PhS^- *vs* *n*-BuS^-, indicating less bond cleavage at the transition state with the stronger nucleophile. In comparison between oxygen and sulphur the reaction is slower with the oxygen nucleophiles (presumably owing to solvation) and the isotope effect is smaller, suggesting not only that the bond breaking is less, but also that the oxygen is a stronger nucleophile.

In a Hammett equation study of the reactions of 1,1-diaryl-2,2,2-trichloro- and 1,1-diaryl-2,2-dichloro-ethane with benzenethiolate, two types of reactions were observed. For one type, the ρ-value for the benzenethiolate-promoted dehydrochlorination of $(p\text{-}XC_6H_4)_2CHCCl_3$ in

ethanol at 65°C was 2·11, while for the S_N2 substitution of benzenethiolate for chlorine in $(p\text{-}XC_6H_4)_2CHCHCl_2$ forming $(p\text{-}XC_6H_4)_2C{=}CHSPh$ as the sole organic product[34], the ρ-value was 0·41:

$$(p\text{-}XC_6H_4)_2CHCHCl_2 + 2\ PhS^- \longrightarrow (p\text{-}XC_6H_4)_2C{=}CHSPh + 2\ Cl^- + PhSH$$

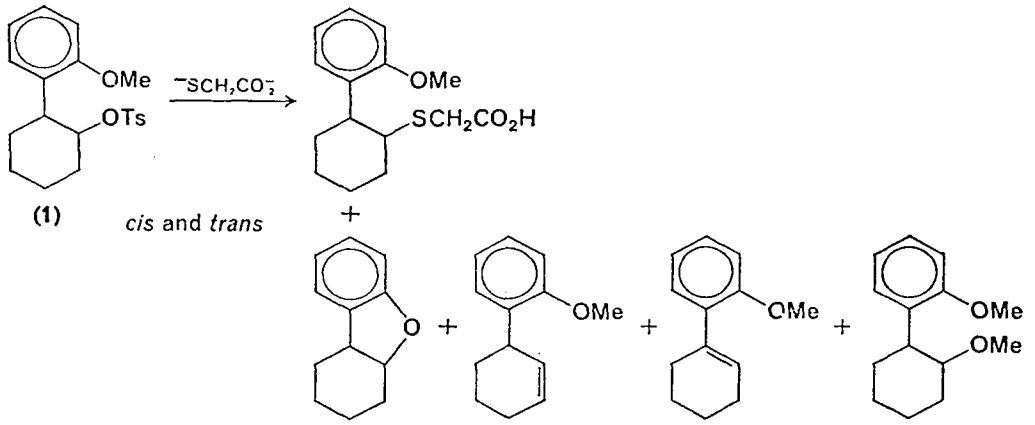
The potential insecticide $m\text{-}RSCH_2C_6H_4O_2CNHMe$ (R = Me, Et, *i*-Pr) can be prepared from methyl isocyanate and $m\text{-}RSCH_2C_6H_4OH$, which in turn is obtained from $m\text{-}ClCH_2C_6H_4OH$[35],

$$m\text{-}ClCH_2C_6H_4OH + EtSH \xrightarrow[MeONa]{MeCN} m\text{-}EtSCH_2C_6H_4OH$$

Heterocyclic derivatives can be used as electrophiles. The hydrochloride of 3-chloromethylpyridazine reacted with sodium benzenethiolate in toluene, replacing the Cl by SPh[36].

4. Reactions with cyclic compounds

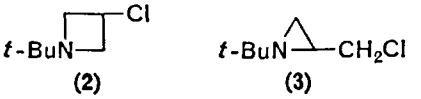
Replacements of substituents by a thiolate group occurs in several cyclic compounds. Several products are found in the reaction of 2-phenylcyclohexyl-*p*-toluenesulphonate (**1**) with the dipotassium salt of mercaptoacetic acid in methanol, corresponding to simple replacement, neighbouring



group replacement forming a furan derivative, elimination forming an olefin and solvolysis. The actual products depend on the reactant ratio, anion : tosylate; the furan is formed when the ratio is 2 : 1, but at 50 : 1 simple displacement occurs. The tosyl group is more readily replaced than the aromatic methoxy[37].

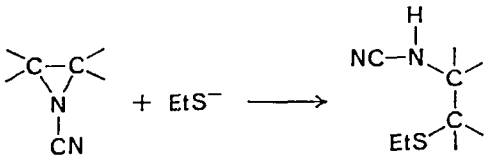
In the nitrogen heterocyclic systems, 1-*t*-butyl-3-chloroazetide (**2**) and 1-*t*-butyl-2-chloromethylarizidine (**3**) react with thiolate anions giving

simple replacement of the chlorine, although other nucleophiles give

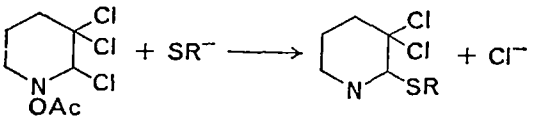


(2) (3)

partial hydrolysis and cyanide converts (3)→(2) (as its cyanide)[38]. The ethanethiolate anion and various other nucleophiles have been used for ring opening of N-cyanoaziridine in steroids, such as 2β,3β-(cyanoimino)-cholestane[3]:



Displacement of the 2-chlorine of 2,3,3-trichloro-1-acetylpiperidine (4) occurs with various nucleophiles, including alkoxides and thiolates[40],

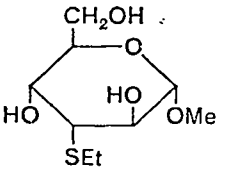


(4)

R = Me, Et, *i*-Pr, Bu, *sec*-Bu, Ph

Cleavage of the C—N bond occurs when 1-[β-(phenylsulphonyl) ethyl]-piperidine hydrochloride or methiodide is treated with aromatic thiols in aqueous dioxane and sulphonyl sulphides are formed. An elimination–addition mechanism is proposed[41].

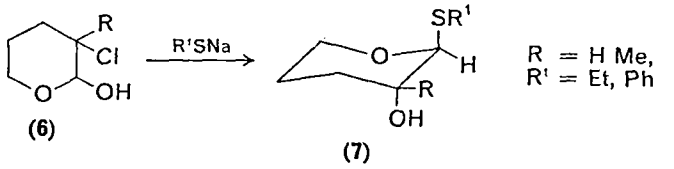
Treatment of methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-gluco-pyranoside with ethanethiol/sodium methoxide and methanol gives 100% yield of methyl 3-S-ethyl-3-thio-β-D-altropyranoside (5). The S-benzyl



(5)

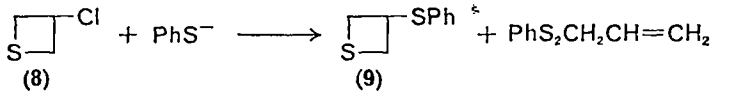
analogue is prepared similarly[42]. In the reactions of chlorohydrin derivatives (6) with thiolates the chlorine is also replaced by thiolate giving,

for instance, *trans*-3-hydroxy-2-ethylthio-tetrahydropyran (**7**). When R = H, the product is 45% diaxial and 55% dicquatorial[43].



(6) (7)

The ring is partially fractured in the treatment of 3-chlorothietane (**8**) with the benzenethiolate anion. A mixture containing 30% of phenyl-3-thietanyl sulphide (**9**) and $PhS_2CH_2CH{=}CH_2$ was obtained. The latter



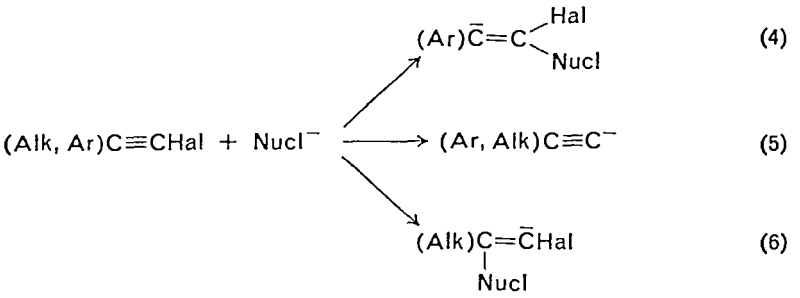
(8) (9)

was also prepared from PhSCl and $HSCH_2CH{=}CH_2$. The reaction probably proceeds[44] via the formation of the cations $H_2C{=}CHCH_2S^+$ and  . The C—S bond is fractured in 2-dialkylamino-1,3-dithiolium perchlorate (**10**) when treated with the ethane-thiolate anion in DMF. Quite different products are found with the ethoxide ion as a nucleophile, involving attack on the 2-carbon atom as opposed to attack on the 4-carbon atom with the ethanethiolate anion[45].

5. Reactions with RC≡CX, $R^1R^2C{=}CR^3X$ and $R^1R^2C{=}NX$

The reactions described in this section will be concerned primarily with the replacement of a group X with a group RS, and not addition reactions.

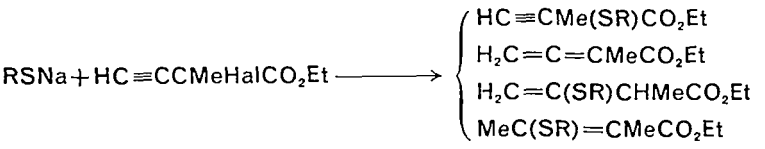
a. Alkyne derivatives. Three different routes are proposed for the reaction of acetylenes with nucleophiles[46],



The intermediates react further to give (Alk,Ar)C≡CNuCl. With thiolate nucleophiles (EtS^- and PhS^-), Hal = Cl, Br, I, the mechanism is restricted to attack on the halogen (5), but attack on the carbon is also observed in the reaction of EtS^- and ArC≡CCl. The second-order rate constants in methanol–water mixtures for *meta*- and *para*-substituted 1-bromo-2-phenylacetylenes correlate well with Hammett σ constants; $\rho = 1{\cdot}15$. A linear correlation was also observed between $\log K_2$ and pK_a of the corresponding thiols.

The rate constants for the reaction of $p\text{-}ZC_6H_4C{\equiv}CHal$ (Z = Me, H, Cl; Hal = Cl, Br) with $p\text{-}MeC_6H_4S^-Na^+$ in DMF, forming $p\text{-}ZC_6H_4C{\equiv}CSC_6H_4SMe\text{-}p$ have been measured. Attempts to trap the ion $p\text{-}ZC_6H_4C{\equiv}C^-$ were unsuccessful. These results have, however, been interpreted differently from those presented in the previous paragraph, and an addition–elimination mechanism is favoured, involving the formation of $p\text{-}ZC_6H_4\bar{C}{=}CHal(SC_6H_4Me\text{-}p)$ and fast elimination of Hal^- to give the product[47].

Various products were obtained from the reaction of sodium thiolate with the acetylene derivative HC≡CCMeHalCO$_2$Et (Hal = Cl,Br), where the thiolate replaced the halogen, acted as a reducing agent or added across an acetylenic or ethylenic bond[13].



R = Et, *t*-Bu, Ph; Hal = Cl, Br

The proportion of the reduction products, especially when Hal = Br, increased with the basicity of the nucleophile and its concentration.

The reactions of 1,3-dihalopropynes (**11**) with nucleophiles, amines and thiols have been studied[48]. Heterocyclic thiols are used as potassium salts in aqueous methanol.

$$Hal^1C{\equiv}CHCH_2Hal^2 + RS^- \longrightarrow Hal^1C{\equiv}CCH_2SR$$

(11)

(Hal¹ = Cl, Hal² = I(**a**); Hal¹ = Hal² = I(**b**) or Br)

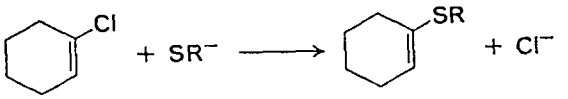
The reactions of **11a** or **11b** with other thiols RSH (R = ethyl, *i*-butyl, phenyl, or benzyl), in the presence of potassium hydroxide, however, gave deiodination and the corresponding dialkyl, diphenyl or dibenzyl disulphide, which could in most cases be isolated quantitatively,

$$IC{\equiv}CCH_2I + PhCH_2S^- + PhCH_2SH \longrightarrow HC{\equiv}CCH_2I + (PhCH_2S)_2 + I^-$$

The only thiols forming iodoacetylenic sulphides were heterocyclic thiols having a tautomeric thiolactam structure.

b. Alkene derivatives. Substitution reactions of nucleophiles with ethylenic substrates have been recently reviewed, and the similarity with aromatic nucleophilic substitution emphasized. The possible mechanisms of these reactions have been discussed[49, 50].

A simple example of substitution in a vinyl halide is the preparation of thiol derivatives of 1-cyclohexene from the thiol and sodamide in THF with chloro-1-cyclohexene (**12**)[51].



(12)

Vinyl bromides react with copper(I) thiolates, both aliphatic and aromatic, to give vinyl sulphides. Vinyl bromides studied include β-bromostyrene and 1-bromo-2-methyl-1-propene. This method of synthesis of thioethers is claimed to be superior to that using sodium thiolates and most other reported methods[52]. 1,2-Dibromoethylene gives a mixture of *cis* (18%) and *trans* (42%) 1,2-diphenylthioethylene with copper(I) benzenethiolate, but with copper(I) ethanethiolate ethylthioacetylene is formed with the elimination of hydrogen bromide[52],

$$BrHC{=}CHBr + CuSEt \longrightarrow HC{\equiv}CSEt + HBr + CuBr$$

When substitution occurs in an ethylene derivative, it is of interest to observe whether the original configuration is retained. Several reactions of ethylene compounds where configuration is retained have been examined. Some are shown below.

$$HalCH{=}CHCO_2Et + EtS^- \longrightarrow EtSCH{=}CHCO_2Et \text{ [53]} \quad (Hal = Cl, Br, I)$$

$$R^1(R^2S)C{=}CR^1(OSO_2R^3) + R^4SH \longrightarrow R^1(R^2S)C{=}CR^1(SR^4) + R^3SO_3H \text{ [54]}$$

In the former reaction, mixtures of isomers are formed when the ethoxide ion is used as a nucleophile. In the latter reaction, when a thiolate instead of a thiol is used as the nucleophile, the electropositive carbon of the trinitrobenzene residue is attacked forming a sulphide and ketone[54].

$$Ph(p\text{-}ClC_6H_4S)C{=}C(Ph)OSO_2R + p\text{-}ClC_6H_4S^- \longrightarrow Ph(p\text{-}ClC_6H_4S)CHCOPh + p\text{-}ClC_6H_4SR$$

$$(R = 2,4,6\text{-}(NO_2)_3C_6H_2)$$

In some reactions such as

$$(PhSO_2)HC{=}CFH + PhS^- \longrightarrow (PhSO_2)HC{=}C(SPh)H + F^-$$

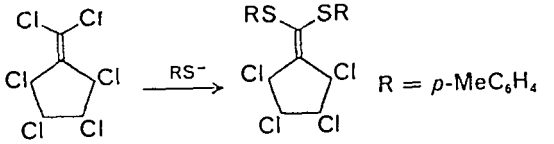
the *trans* reactant gives the *trans* product, but the *cis* reactant gives *cis* and *trans* products in a 3 : 1 ratio[55].

When several halides are present, as in trifluorochloroethylene, replacement of a fluorine with a thiolate occurs:

$$CF_2{=}CFCl + PhSNa \longrightarrow (PhS)CF{=}CFCl + NaF$$

Butanethiol reacts similarly with $CF_2{=}CFHal$ (Hal = Cl, Br), and $CF_2{=}CCl_2$ forming $BuSCF{=}CFHal$ and $BuSCF{=}CCl_2$ respectively[56]. In the compound $AcNHCH{=}CCl_2$ the butanethiolate ion can replace one of the chlorine atoms or add across the double bond, forming $AcNHCH{=}CCl(SBu)$ and $AcNHCH(SBu)CHCl_2$ respectively[57].

Other interesting examples of this type of reaction include that of hexachlorofulvene (**13**) with $p\text{-}MeC_6H_4S^-$ in the presence of triethylamine[58].



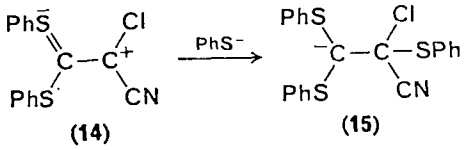
(13)

Various acrylonitrile derivatives have been examined. The configuration is retained in the reaction of 3-halomethacrylonitriles with sodium

ethanethiolates, and an addition–elimination mechanism is proposed[59]. 3,3-Di(thiophenyl)acrylonitriles can be prepared in the reaction

$$Cl_2C{=}CR(CN) + 2\ PhS^- \longrightarrow (PhS)_2C{=}CR(CN) \quad (R = H, Me, CN, Ph)$$

When R = Cl, the product is mainly $(PhS)_2C{=}C(Cl)CN$, together with trace amounts of $(PhS)_2C{=}C(SPh)CN$. Displacement of the α-Cl is unusual. This has been attributed to the high nucleophilic character of the anion, increased positive charge on the α-carbon atom (**14**) and stabilization of the intermediate (**15**) by the benzenethiol group[60]. Reactions of



(**14**) (**15**)

other acrylic acid derivatives with thiolates can give nucleophilic replacement, or the thiol can be oxidized to the disulphide[61].

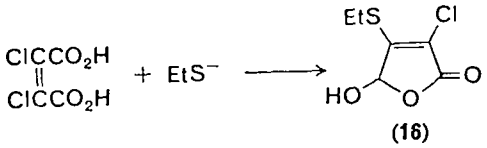
$$MeC(R){=}CBrCO_2Et + PhSNa \longrightarrow MeC(R){=}C(SPh)CO_2Et$$

(R = EtS, *t*-BuS, PhS, EtO)

$$MeC(SEt){=}CBrCO_2Et + EtS^-/EtSH \longrightarrow MeC(SEt){=}CHCO_2Et + EtSSEt + Br^-$$

The rate constants for the addition of butanethiol to ethyl acrylate have been measured by iodometry over a wide pH range. Below pH 4 it is assumed that the reaction is initiated by the neutral molecule, but at pH > 7 the anion BuS^- started the reaction[62].

Cyclization occurs when dichloro- and dibromo-maleic acids react with thiols in the presence of triethylamine forming 2-halo-3-mercaptomalealdehydic (**16**) derivatives[63], e.g.



(**16**)

c. Imine derivatives. Displacements in compounds having C=N bonds have been observed. One of the simplest types of reaction is that of $ClCH_2CNO$, which can be converted into *o*-(thiocyanomethylthio)-benzamide, an antibacterial, by refluxing with the sodium salt of

o-mercapto-benzamide[64]. Iminoboranes react with thiols forming alkylthio iminoboranes[65],

$$Cl_3C(Br)C{=}NBMeBr + RSH \longrightarrow Cl_3CC(SR){=}NH\cdot BMeBr_2$$

$$Cl_3CC(SR){=}NH\cdot BMeBr_2 \xrightarrow{Et_3N} Cl_3CCSR{=}NH + Br_2(Me)B\cdot NEt_3$$

The bromine on the boron may react further

$$Cl_3CC(SPh){=}NH\cdot BMeBr_2 + PhSH \longrightarrow Cl_3CC(SPh){=}N(H)\cdot BMeBr(SPh)$$

$$Cl_3CC(SPh){=}N(H)\cdot BMeBr(SPh) \xrightarrow{\text{Distillation, } -HBr} Cl_3CC(SPh){=}N{-}B(Me)SPh$$

Similar reactions are observed with 1,1-dibromo-4-(*p*-nitrophenyl)- and -(*p*-chlorophenyl)-2,3-diazabuta-2,3-dienes and aliphatic or aromatic thiols, resulting from the thiolysis of one or two bromine atoms[66],

$$p\text{-}O_2NC_6H_4CH{=}N{-}N{=}CBr_2 + p\text{-}ClC_6H_4SH \xrightarrow[C_6H_6]{NEt_3} p\text{-}O_2NC_6H_4CH{=}N{-}N{=}CBr(SC_6H_4Cl\text{-}p)$$

B. *Aromatic Substitution*

1. Introduction

Aromatic nucleophilic substitution with a thiolate anion can be represented as

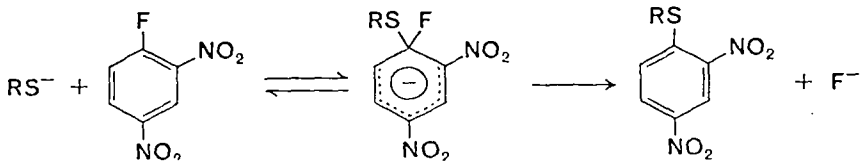
$$ArX + RS^- \longrightarrow ArSR + X^-$$

where X^- is usually a stable ion, such as a halide. When more groups or atoms that may be replaced are present initially multiple substitution can occur. Nucleophilic aromatic substitution is usually discussed in the annual volumes of *Organic Reaction Mechanisms*. Reviews of aromatic nucleophilic substitution usually mention *inter alia* the thiolate as a nucleophile. One review has been devoted to the behaviour of sulphur reagents in nucleophilic aromatic substitution[67], and also discusses substitution in benzenethiazoles. A book has also been published on nucleophilic substitution[68].

While the reactions of the corresponding oxygen-containing nucleophiles have been studied in considerable detail, there is a relative paucity of data

on the thiolates as nucleophiles in aromatic substitution. Few kinetic data are available. Any data show that the RS^- is a better nucleophile than its oxygen analogues, although this has been questioned[67].

The reactions of various halonitrobenzenes with thiolates have been studied in more detail. A comprehensive review of the activating effects of the nitro group in aromatic substitution[69] covers the literature up to the middle of 1967. This review discusses primarily the displacement of halogen, although displacement of other groups such as hydrogen, nitro, alkoxy, aryloxy, and sulphonate are also considered. The relative rates of the reaction of 1-X-2,4-dinitrobenzenes with piperidine in MeOH at 0°C decreases in the series $F \gg NO_2 \gg OSO_2C_6H_4CH_3\text{-}p \gg SOC_6H_5 \sim Br \sim Cl > SO_2C_6H_5 \sim OC_6H_4NO_2\text{-}p > I$. A similar sort of series can be expected when the thiolate anion is used as a nucleophile. The reaction of nitro compounds with nucleophiles occurs primarily via an addition–elimination mechanism, involving a Meisenheimer complex.



Obvious variables in such a reaction are the stereochemistry of the entering group, the stability of the intermediate Meisenheimer complex, and the effect of the leaving group. A thermochemical approach concluded that the decomposition of the Meisenheimer complex was rate determining[70], however, this is not in accord with the leaving group lability[71]. As cleavage of the carbon—fluorine bond is acid catalysed, it has been concluded that the rate-determining step is the formation of the Meisenheimer complex rather than its decomposition[72]. Substitution of 2,4-dinitrochlorobenzene with 2,3,5,6-tetrafluorobenzene thiolate gives replacement of the chlorine[73]. A detailed discussion of the thermodynamics of the reaction of MeS^- and PhS^- with 1-X-2,4-dinitrobenzene has been reported[68, 70].

The nucleophilic activity is $PhS^- > MeS^-$ for the reaction with 1-iodo-2,4-dinitrobenzene, but $MeS^- > PhS^-$ for *p*-fluoronitrobenzene[68]. Data on the reaction of substituted halogenobenzothiazoles show that there are appreciable steric effects in the cases of α branching (methyl > ethyl > *i*-propyl > *t*-butyl), whereas β and ω branching do not cause any steric effect and influence the reaction rates only slightly because of their typical electronic effects[67]. The mobility of the leaving halogen, derived from kinetic data with various halogenonitrobenzenes, is $F > Cl > Br > I$[74].

The intermediate Meisenheimer complexes have been reviewed[75, 76], and

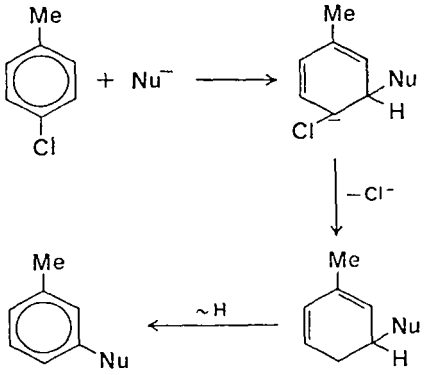
the work of Crampton is important in this area[77, 78, 79]. Further reference should be made to the chapter in this book by M. R. Crampton.

When substitution occurs in polyhalogenated aromatic compounds, such as the pentafluorobenzene derivatives, C_6F_5X, the extent of the replacement of F or X by the nucleophile and the product orientation must be determined.

A detailed study of the orientation and reactivity in the nucleophilic replacement reactions of aromatic polyhalo-compounds has been published[80]. This involves study of the stability of the Wheland type intermediates (**17**, **18**) where Nu is a nucleophile. The formation of *meta*

(17) (18)

products with a nucleophile may be rationalized by the scheme involving a carbene intermediate[81],



Most activating groups cause primarily *para* substitution but some *ortho* substitution may occur. Deactivating groups, such as NH_2, O^-, or S^- will cause *meta* substitution[68]. The solvent plays an important role in determining the relative amounts of *ortho* and *para* substitution. Solvents with dielectric constant lower than about 30 cause some *ortho* substitution, whereas solvents of dielectric constant greater than 30 cause almost exclusive *para* substitution. This has been attributed to increasing ionic dissociation of the nucleophile in the higher dielectric constant solvents[82, 83]. Presumably the formation of *meta* substitution products in solvents of

low dielectric constant does not involve the formation of the thiolate anion as an active entity.

Thiolates can also cause dehalogenation of various halogen compounds, such as 2-bromo-3-nitro-thiophene[84] and 2- and 4-halo-1-naphthols[85].

2. Substitution in hexahalobenzenes

Pentafluoro- and pentachloro-benzenethiols can readily be prepared by the reaction of a hydrogen sulphide anion, SH^-, with hexafluoro- and hexachlorobenzene respectively[6,86]. No dithiols can be produced in this reaction. Due to the basic medium employed the thiol formed will be present as its thiolate anion, which is not readily attacked further nucleophilically. Using hexafluorobenzene and excess hydrogen sulphide perfluoropoly(phenylene sulphide) may be isolated[6]. When the hydrogen sulphide anion is replaced by a thiolate as a nucleophile, multiple replacement of fluorine or chlorine can occur. The products of these reactions can be summarized:

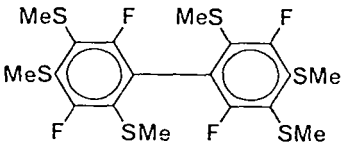
$$C_6Hal_6 + SR^- \longrightarrow C_6Hal_5SR \quad (19)$$
$$C_6Hal_4(SR)_2 \quad (20)$$
$$C_6Hal_3(SR)_3 \quad (21)$$
$$C_6Hal_2(SR)_4 \quad (22)$$
$$C_6Hal(SR)_5 \quad (23)$$
$$C_6(SR)_6 \quad (24)$$

The reaction of hexafluorobenzene with various nucleophiles (R = Me[87], Et[87], Ph[87,73], *p*-HC_6F_4[73], *p*-$NH_2C_6F_4$[73]) in ethylene glycol and/or pyridine as a solvent has been studied. The products obtained are **19**, **20** and **22**. The compounds **21**, **23** and **24** have not been isolated, but **21** must be present as intermediate in the conversion of **20** to **22**. The orientation of the products has been deduced from ^1H and ^{19}F n.m.r. spectra[87], or chemical oxidation and Raney nickel degradations[73]. The compound **20** has the two RS groups *para*, whereas the compounds $C_6F_2(SMe)_4$, $C_6F_2(SEt)_4$, $C_6F_2(SMe)_2(SPh)_2$, and $C_6F_2(SPh)_4$ have the two fluorines *para*[8,73]. When 2-mercaptoethanol was used as a nucleophile, the sulphur atom rather than the oxygen acted as the nucleophile and 1,2,4,5-tetrafluoro-3,5-bis-2-hydroxyethylthiobenzene was isolated[88].

This work has also been extended to decafluorobiphenyl where each ring is substituted once or three times:

$$C_6F_5C_6F_5 + SR^- \longrightarrow RSC_6F_4C_6F_4SR \quad (25)$$
$$(RS)_3C_6F_4C_6F_4(SR)_3 \quad (26)$$

The predominant product is **25** when R = Et or Ph, but when R = Me, the mono- and tri-substituted products are formed. The orientation of **25** is *p*-(RS)$C_6F_4C_6F_4$(SR)-*p*[87] and that of **26** is probably[87]



Substitution of hexachlorobenzene with various nucleophiles has also been studied [87,89]. No monosubstituted products were isolated.

$$C_6Cl_6 + SR^- \longrightarrow p\text{-}(RS)_2C_6Cl_4 + p\text{-}Cl_2C_6(SR)_4$$

The orientation of the disubstituted product has been deduced by alternate synthesis, whereas that of *p*-$Cl_2C_6(SR)_4$ has only been derived intuitively[89]. Attempts to use the $C_6Cl_5S^-$ anion as a nucleophile to form the sulphide $(C_6Cl_5)_2S$ have failed[8].

The obvious extension of this work to hexabromobenzene has been investigated, where it is found that the SMe^- anion will not react[8]. Study of the reactions of other nucleophiles with hexabromobenzene leads to photodebromination and some nucleophilic substitution[90]. Pentabromobenzenethiol has recently been prepared from the pentabromophenyl Grignard reagent and sulphur[91].

A somewhat analogous system is pentafluoropyridine where substitution with hydrogen sulphide anion, or benzenethiolate, occurs *para* to the nitrogen. The thiol formed reacts with pentafluoropyridine to give the corresponding sulphide[83,92]. 2,3,5,6-Tetrachloropyridine thiol is prepared similarly from pentachloropyridine and the hydrogen sulphide anion in ethylene glycol[93].

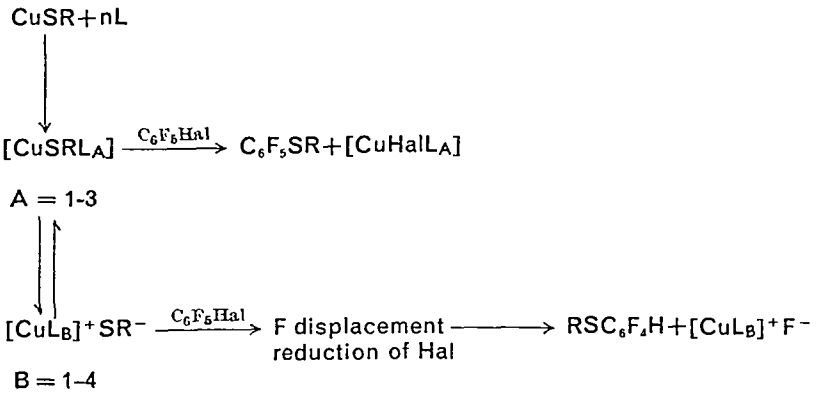
3. Substitution in mixed hexahalobenzenes

For the series of monosubstituted halopentafluorobenzenes such as C_6F_5Hal, it is of interest to observe which halogen is replaced initially.

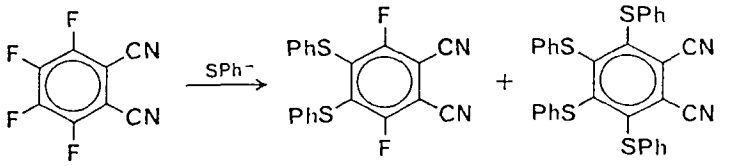
Bis(pentafluorophenyl)sulphide, $(C_6F_5)_2S$, may be prepared from bromopentafluorobenzene and copper(I) pentafluorobenzenethiolate in DMF[94]. The use of the copper salt eliminates the need to generate the pentafluorobenzenethiolate anion, $C_6F_5S^-$, in basic solution. The copper-assisted nucleophilic displacement reactions of halopentafluorobenzenes have been studied[95]. The reaction of CuSBu with C_6F_5Br gave two products

$$C_6F_5Br + CuSBu \longrightarrow \underset{\textbf{(27)}}{C_6F_5SBu} + \underset{\textbf{(28)}}{BuSC_6F_4H}$$

The ratio of the products depended on the solvent employed. In DMF product **27** was formed exclusively, whereas product **28** involving halogen reduction was formed in various solvents in the presence of thiourea, although thiourea alone does not react with bromopentafluorobenzene. In similar experiments using chloropentafluorobenzene no reaction occurred in the absence of thiourea, but when it was added exclusive fluorine replacement occurred without chlorine reduction. With iodopentafluorobenzene and copper(I) benzenethiolate and urea, rapid reduction of the iodine occurred together with multiple fluorine replacement resulting in the formation of 2,4-difluoro-1,3,5-tris(phenylthio)benzene; pentafluorobenzene gave essentially the same products under the same conditions. The formation of product **27** without further substitution suggests that species such as $C_6F_5(Br)(SBu)$ may be ligated to the copper. A reaction scheme has been postulated involving the participation of the solvent, and the thiolate anion acting as a reducing agent,



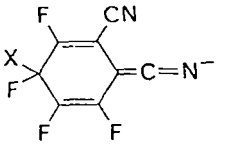
Nucleophilic substitution of tetrafluorophthalonitrile (**29**) with the benzenethiolate anion gives replacement of two or four fluorine atoms, but not the nitrile groups.



(**29**)

In solvent water the tetrasubstituted product is formed, but in methanol the ratio of disubstituted to tetrasubstituted is about 8 : 1 [96]. The formation of 4- and 5-disubstitution product rather than the anticipated 3- and 6- is similar to that observed in analogous reactions, and may be due to the

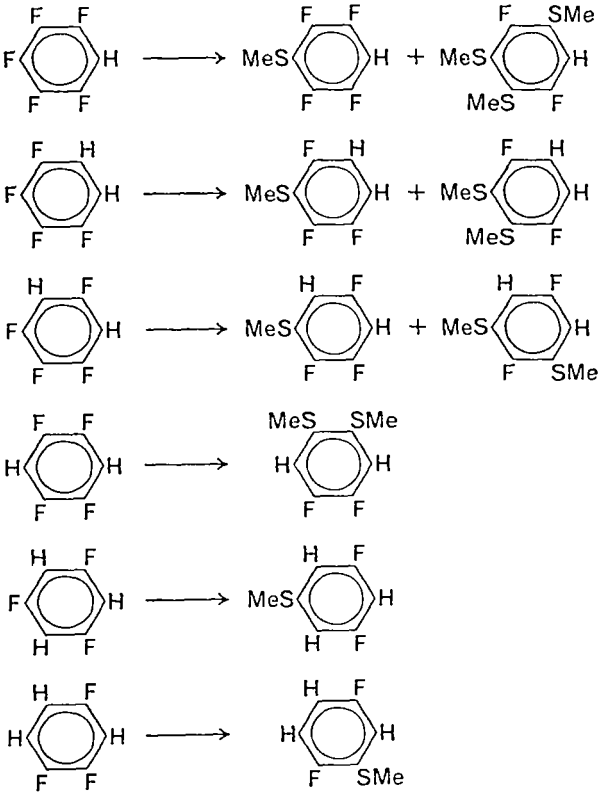
formation of a more stable *para* than *ortho* intermediate (**30**). The orientation of the product has been deduced from its ^{19}F n.m.r. spectrum.



(30)

4. Substitution in halobenzenes

The reactions of various fluorobenzenes with thiolate anions have been investigated in ethylene glycol/pyridine mixtures. The results are shown below using the methanethiolate anion as a nucleophile[8].



Product orientations have been deduced from ^{1}H and ^{19}F n.m.r. No reaction occurred with any difluorobenzene or fluorobenzene. Under these conditions the maximum substitution observed requires there to be two fluorine atoms still in the nucleus. Changing the solvents it is possible

to replace the fluorine in fluorobenzene or bromine in bromobenzene by a thiolate group, for example in HMPA/THF solvent mixtures using EtSNa, BuSNa or PhSNa in the presence of $NaNH_2$, the sulphides C_6H_5SR are formed[97-100]. An ideal solvent was found to be HMPA–THF in the ratio 1 : 5[99]. Similar reactions involving replacement of one or two aromatic halogens with potassium benzenethiolate or potassium thioresorcinolate have been observed in pyrrolidine as solvent[101].

Reaction of pentafluorobenzene with copper(I) benzenethiolate gives 2,4-difluoro-1,3,5-tris(phenylthio)benzene. This orientation is not inconsistent with the ^{19}F n.m.r.[95]. The fluorine *para* to the hydrogen in pentafluorobenzene has been replaced by a variety of nucleophiles, such as *p*-$HC_6F_4S^-$ forming *p*-$HC_6F_4SC_6F_4H$-*p*[73].

No thiolate substitution of *p*-dichlorobenzene, 1,2,4,5-tetrachlorobenzene, or pentachlorophenylanisole in alcohol was observed[89] Substitution of 2,3,4- and 2,4,5-trichlorobenzonitrile, 2,3-, 2,5- and 3-4-dichlorobenzonitrile and *o*- and *p*-chlorobenzonitriles with sodium hydrogen sulphide in liquid ammonia afforded the cyanothiophenols. Preferential replacement of the *p*-Cl was observed. *Meta*-chlorobenzonitrile did not undergo nucleophilic substitution under these conditions, but was rather hydrolysed by the water present in the NaSH [102].

In the naphthalene derivatives 1-fluoro- and 1-bromo-naphthalenes and 2-fluoro- and 2-bromo-naphthalenes reacted with *n*-butanethiolate in DMSO to give good yields of *n*-butyl 1-naphthyl sulphide and *n*-butyl 2-naphthyl sulphide respectively. *t*-Butanethiolate reacted similarly[103].

5. Substitution in miscellaneous polyhalogenated aromatics

The reaction of nitro and amino fluorobromobenzenes of the type *o*-XC_6F_4Br and *p*-XC_6F_4Br where X = NO_2 or NH_2 with the pentafluoro benzenethiolate anion, in its copper(I) salt, resulted in the replacement of the bromine[82]. The pentafluorobenzenethiolate anion or the anion of 2,3,5,6-tetrafluoro-4-mercaptopyridine, replaced the fluorine *ortho* or *para* to the nitro group in nitropentafluorobenzene. *Para* substitution only occurred in solvents of high dielectric constant, such as DMF and acetonitrile, whereas in solvents of low dielectric constant, such as ether, mixed replacement of *ortho*- and *para*-fluorine was observed[82, 83]. Increasing ionization of the thiol is postulated to cause predominantly *para* substitution.

6. Substitution in monohalogenated benzene derivatives

This section includes compounds such as 1-fluoro-2-nitrobenzene, where the fluorine atom is activated by the nitro group. The reactions of halonitrobenzenes with thiolate nucleophiles have been reviewed[69]. The

fluorine atom may easily be replaced in 1-fluoro-2-nitrobenzene by 2,3,5,6-tetrafluorobenzenethiolate forming *o*-nitrophenyl-2,3,5,6-tetrafluorophenyl sulphide, but polymerization of the pentafluorobenzenethiolate anion occurred when it was employed as the nucleophile[104]. Replacement of halogen in the cyclic derivatives such as 1- and -2-fluoro- and -chloro-anthraquinones[105], and various halo-1,2,3-benzothiazoles[106], is also observed.

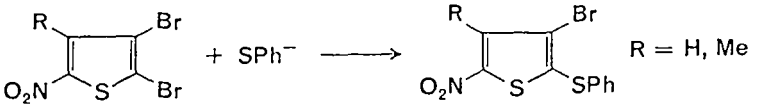
Considerable use has been made of the copper(I) benzenethiolate and butanethiolate in the preparation of thioethers. A large series of compounds of general formula $(RS)_nX$, $n > 1$, R = Ph or Bu, and X is an aryl group, have been prepared from the copper(I) thiolates and aryl halides (aryl bromides only reacted with the butanethiolate)[52,107].

7. Substitution in heterocyclic compounds

This type of reaction is essentially similar to that of replacement of an aromatic halogen by a thiolate group. Halogen compounds studied include 3,4-dimethyl-5-bromo-2(N,N-dimethylaminomethylene)-2H-pyrrole[108] and chlorofuro-[2,3-d]pyridazines[109]. Copper(I) alkylthiolates have been used to form thioethers with 2-bromothiophene, 2-bromopyridine and 2-bromofuroic acid, the latter with concomitant decarboxylation[52].

The rate and activation parameters have been determined for the reaction of potassium methanethiolate with various 2-fluoro- and bromo-pyridines. Although an *ortho*-methyl group did not activate the 2- position in 2-bromo- or 2-fluoro-pyridine towards attack by the methanethiolate ion, deactivation of the *ortho* rather than the *para* position was observed. At 110°C for the bromo-compounds K_o-Me : K_p-Me = 3·9, while K_o-Br : K_p-Br = 2·2. The results have been compared with those obtained using methoxide and benzenethiolate anions in methanol. The relative rates observed in HMPA are the same as those in methanol[110]. Thiophenol reacts faster than its anion with a bromopyridine, in methanol, due to a rapid acid–base pre-equilibrium in which the pyridine is protonated. An *o*-MeO substituent accelerates the replacement of Br, and a small increase is also noted on going from MeOH to DMSO as solvent[111].

In 2,3-dibromo-5-nitrothiophenes (**31**) the 2-bromo group is replaced by the benzenethiolate anion



(31)

The *meta* methyl group increases the reactivity towards nucleophiles of the 2-bromine by increasing the Reinheimer and Bunnett effect of the 3-bromine on the activated 2-bromine[112].

Nucleophilic substitution of 2-chloro-4,6-bis(isopropylamino)-S-triazine with sodium methanethiolate in methanol gave prometryne (**32**) in 90% yield. The reaction is second order and the activation energies were 20·26 and 27·24 kcal/mole in *i*-propanol and methanol respectively[113,114].

(32)

8. Substitution of groups other than halogen

The rate constants for the replacement of various groups X in *p*-$XC_6H_4SO_2CF_3$ by NaSPh in methanol decreased in the order

$$X = SO_2CH_3 > NO_2 > F > Cl$$ [115].

The element effect of atoms or groups increased with increasing activation and polarizability of the aromatic system.

Nitro groups in heterocyclic compounds can be replaced by thiolate groups. 5-Phenylmercapto-2-furaldehyde is obtained from 5-nitro-2-furaldehyde and benzenethiolate. Thiolates will not, however, react with halogenofurfural[116]. One nitro group in 3,4-dinitrothiophene may be replaced by a benzenethiolate group, but rearrangement occurs and phenyl-2-(4-nitrothienyl) sulphide is formed[117]. Sodium benzenethiolate or benzeneselenate gives replacement of either one but not both of the nitro groups in 2,3-dinitrothiophene[118].

Displacement of a thiolate group occurs in 2-methylthio- and 2-ethylthio-4[1(3)H] pyrimidines at the 2 position in greater than 70% yield, using a thiol in basic solution. A 5-halo and 6-amino substituent hindered the reaction but a 1-methyl or 6-hydroxy group facilitated it by influencing the tautomerism[119].

C. Dealkylation Reactions

A dealkylation reaction can be defined as the removal of an alkyl group, and its subsequent replacement by hydrogen, or the removal of an alkyl group from an ammonium salt with the formation of an amine, e.g.

$R_2\overset{+}{N}Me_2Cl^- + PhS^-Na^+ \longrightarrow R_2NMe$ (reference 120)

$p\text{-}CH_3C_6H_4OCH_2\overset{+}{N}Me_3I^- + HSR \longrightarrow p\text{-}CH_3C_6H_4OCH_2SR$ (reference 121)

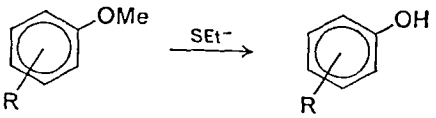
$Et_3Me\overset{+}{N}(CH_2)_2\overset{+}{N}MeEt_2\,2\,I^- + PhSH \longrightarrow PhSMe$ (reference 121)

The method can be used preparatively. Other examples include the selective demethylation of triethylmethylammonium chloride with sodium benzenethiolate[122]. A somewhat analogous reaction is observed in the reaction of alkoxytri(dimethylamine)phosphonium chloride (33) with thiolates forming a phosphine oxide and sulphide[23].

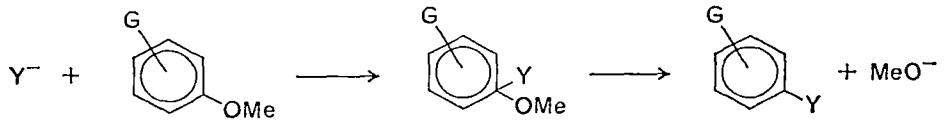
$$PhCH_2OP^+(NMe_2)_3Cl^- + PhSH(Et_3N) \xrightarrow{60^\circ C} OP(NMe_2)_3 + PhCH_2SPh + Et_3NH^+Cl^-$$

(33)

The method is not restricted to group V derivatives and can easily be applied to oxygen esters and ethers. The use of various nucleophiles in this type of reaction has been discussed[124]. The main advantage of this technique for the demethylation of ethers with ethanethiolate in a solvent such as DMF is that a relatively low temperature is required and the group R may be acid sensitive[124-126].



The thiolate is generated *in situ* from sodium hydride and the corresponding thiol[124]. Aryl methyl ethers with strong electron-withdrawing substituents (G) require milder conditions for cleaving the ether linkage, but these compounds are also likely to suffer substitution of the aromatic carbon with strong carbon nucleophiles[127].

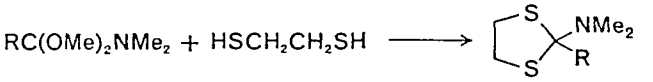


Using methyl ethers of di- and tri-hydric phenols, selective monodemethylation occurs, e.g. resorcinol monomethyl ether is obtained from resorcinol dimethyl ether and sodium ethanethiolate in DMF. An exception is pyrogallol trimethyl ether which afforded pyrogallol 1-monomethyl ether in high yield[124]. Methylene ethers, such as methylenedioxybenzene, can be quantitatively converted to catechol, via the intermediate formation of ethyl *o*-hydroxyphenoxymethyl sulphide[126].

This method, using ethanethiolate, has been extended to esters[126]. The cleavage of methyl esters by lithium propanethiolate in HMPA, an S_N2 reaction, has been reported. The lithium salt reacts very much faster than the sodium salt[128]. The benzenethiolate and propanethiolate anions have

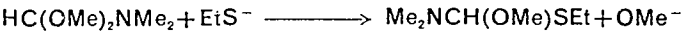
also been used in the conversion of esters to the corresponding acid or its sodium salt[129,130]. Examples include the conversion of *p*-anisate into *p*-hydroxybenzoic acid and methyl *p*-chlorophenoxyacetate to *p*-chlorophenol[126]. The latter is an example of the cleavage of an aryloxyacetate. However hydrolysis of *p*-nitrophenylacetate with both simple and polyfunctional thiols proceeds at a rate dependent upon the thiolate ion concentration. The initial products are *p*-nitrophenol and the thiol ester. Thermodynamic parameters E_a, ΔH^*, ΔF^* and ΔS^* have been found to be 8·0, 7·4, 16·7 kcal/mole and −30·7 e.u. respectively for the reaction of cysteine with *p*-nitrophenylacetate (29·6°C)[131].

The two methoxy groups in amide acetals can be replaced by a dithiol forming 1,3-dithiolanes (**34**),

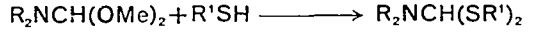


(34)

Replacement of only one methoxy group is found in the reaction of DMF-dimethyl sulphate mixture (presumably forming $HC(OMe)_2NMe_2$) with sodium ethanethiolate,

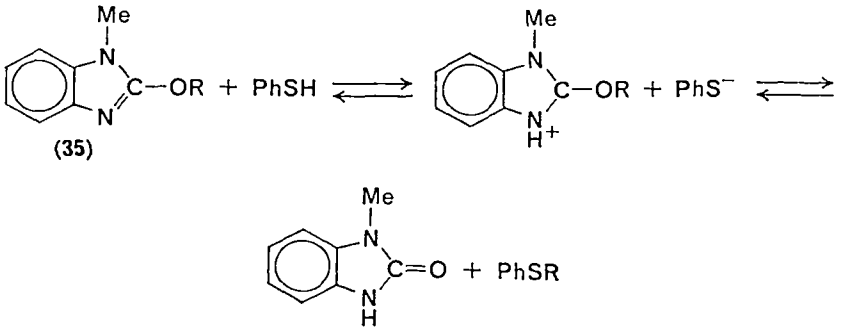


but thiols themselves displace both methoxy groups[132]. Other formamide mercaptals have also been used to form amide mercaptals, where R_2N = piperidine and R^1 = Me, C_6H_{13}, C_7H_{15} and $PhCH_2$[133].



An interesting extension of this type of reaction is the transalkylation reaction between 2-alkoxy-1-methylbenzimidazole (**35**) and benzenethiol. The kinetics of this reaction indicate a rapid acid–base equilibrium, followed by an S_N2 attack at the ether saturated carbon by the PhS^- ion[134].

A somewhat analogous reaction is observed in the reaction of the mixed anhydride, acetic formic anhydride, with thiophenol in pyridine, where 93% of the thioformate, HCOSPh, and 7% of the thioacetate, MeCOSPh, are formed[135].



The thiolate anion acts both as a dealkylating agent and a reducing agent with p-$CH_2{=}CHOC_6H_4NO_2$. The yields of the various products are shown.

$$p\text{-}CH_2{=}CHOC_6H_4NO_2 \xrightarrow[\text{abs. EtOH}]{\text{NaSBu}} \begin{cases} 50\%\ BuSC_6H_4N(O){=}NC_6H_3SBu\text{-}p \\ 3\%\ BuSC_6H_4N{=}NC_6H_4SBu\text{-}p \\ 25\%\ p\text{-}CH_2{=}CHOC_6H_4N(O){=}NC_6H_4OCH{=}CH_2\text{-}p \end{cases}$$

When this reaction was studied under electrophilic conditions with the thiol in Et_2O/SO_2 or in a sealed tube with a free radical initiator, different reactions ensued, including addition across the C=C bond[136].

D. Reactions with Main Group Elements

1. Introduction

Thiols and thio-β-diketone derivatives of the elements have been reviewed, and compared with the alkoxides[137]. The alkali and alkaline earth metal salts of the thiols are probably ionic and can be prepared in numerous ways. In the aqueous phase, the excess water is removed by azeotropic distillation with toluene[138,139]. Alternatively using other solvents, salts or solvated salts can be isolated[7,140,141]. The crystal structures of the alkali metal thiolates, MSMe (M = Li, Na, K), have been reported and are of the same type as the corresponding alkoxides[142].

The thiol derivatives of the other main groups elements are often prepared from their halides using the thiol in the presence of a hydrogen halide acceptor or by using a metal thiolate, such as lead, where R is a main group element.

$$RHal + R'SH + Et_3N \longrightarrow RSR' + Et_3NH^+Hal^-$$

$$2\ RHal + Pb(SR')_2 \longrightarrow 2\ RSR' + PbHal_2$$

2. Group II

Few thiolate derivatives of beryllium are known. Di(*t*-butylthio)triberyllium tetra-*t*-butoxide, $(t\text{-BuS})_2Be_3(OBu\text{-}t)_4$, has been obtained from dichlorotriberyllium tetra-*t*-butoxide, $Cl_2Be_3(OBu\text{-}t)_4$, and lithium butanethiolate[143]. Other beryllium thiolates are prepared by reaction of a thiol with dialkylberyllium or dialkyneberyllium and do not involve a thiolate anion as an intermediate[144,145]. Various other compounds such as thiomagnesium alkyls[146] and dimethyl(methylthio)aluminum[147] are obtained analogously.

3. Boron

Reviews have been published about the problems and results of boron–sulphur chemistry[148], and organic boron–sulphur compounds[149]. The trialkylthio- or arylthioboranes can readily be prepared from boron trihalide and a metal thiolate:

$$3\ Pb(SC_6F_5)_2 + 2\ BCl_3 \longrightarrow 2\ B(SC_6F_5)_3 + 3\ PbCl_2 \quad \text{(reference 14)}$$

$$3\ Hg(SCF_3)_2 + 2\ BBr_3 \longrightarrow 2\ B(SCF_3)_3 + 3\ HgBr_2 \quad \text{(reference 150)}$$

In the latter reaction the mixed products $Hal_xB(SCF_3)_{3-x}$ ($x = 1,2$; Hal = Cl, Br) can also be isolated. Mixed arylakylthioboranes such as bis(ethylthio)phenylborane may be prepared analogously from dichlorophenylborane and lead ethanethiolate[151], or using the thiol in the presence of triethylamine[152]:

$$BrBMe_2 + HSPh + NEt_3 \longrightarrow PhSBMe_2 + Et_3\overset{+}{N}HBr^- \quad \text{(reference 152)}$$

Interesting new compounds of the type $M[RS(BH_3)_2]$ have recently been reported to be formed in the reaction of a metal thiolate with diborane in THF. The compound $K[EtS(BH_3)_2]$ has been isolated and some of its reactions studied[153].

$$KSEt + B_2H_6 \longrightarrow K[EtS(BH_3)_2]$$

4. Group IV

The reactions of thiolates with various carbon compounds are discussed elsewhere in this chapter.

Thiol derivatives of silicon, germanium, tin and lead can readily be prepared from a halide, usually chloride, and a thiol in the presence of a hydrogen halide acceptor or a metal thiolate. Various illustrative examples

are shown below:

$$H_3SiBr + NaSMe \longrightarrow MeSSiH_3 + H_4Si + solids$$
(reference 154)

$$H_3MI + NaSPh \longrightarrow H_3MSPh + NaI \quad (M = Si, Ge)$$
(references 155, 156)

$$Pb(p\text{-}SC_6F_4C_6F_4S\text{-}p) + Ph_3MCl \longrightarrow p\text{-}Ph_3MSC_6F_4C_6F_4SMPh_3\text{-}p \quad (M = Sn, Pb)$$
(reference 157)

$$Ph_3MHal + C_6F_5SH + Py \longrightarrow Ph_3MSC_6F_5 + PyH^+Cl^-$$
(reference 158)

$$GeCl_4 + 4\ RSH + 4\ NH_3 \longrightarrow Ge(SR)_4 + 4\ NH_4Cl\downarrow$$ (reference 159)

$$(ArO)_nSiCl_{4-n} + Ar'SH + Et_3N \longrightarrow (ArO)_nSi(SAr')_{4-n}$$ (reference 160)

Thiols can displace ammonia from silizanes[7].

$$(Me_3Si)_2NH + 2\ C_6F_5SH \longrightarrow 2\ Me_3SiSC_6F_5 + NH_3$$

The silicon analogue of the methanethiolate and methaneselenate anions, H_3SiS^- and H_3SiSe^-, are formed in the reaction of trisilylamine and hydrogen sulphide or selenide,

$$(SiH_3)_3N + H_2Y \longrightarrow (H_3Si)_2Y + NH_4^+(YSiH_3)^- \quad (Y = S,Se)$$

The trimethylammonium salt can also be formed.

$$4\ Me_3NH(HS) + 3\ SiH_3Br \longrightarrow 3\ Me_3NHBr + (SiH_3)_2S + 2\ H_2S + Me_3NH(SSiH_3)$$

The salts of the anion H_3SiS^- are stable at room temperature[161]. Similar anions Ph_3MS^- (M = Ge, Sn, Pb), presumably present in the lithium derivatives Ph_3MSLi, are well characterized and have been used in the synthesis of unsymmetrical sulphides[162].

$$Ph_3MSLi + Ph_3M'Cl \longrightarrow Ph_3MSM'Ph_3 \quad (M \text{ and } M' = Ge, Sn, Pb)$$

The derivatives such as $Et_2Sn(SNa)_2$ can be prepared from Et_2SnCl_2 and Na_2S, and react with chloro compounds to give the corresponding organotin thiol derivative[163],

$$Et_2Sn(SNa)_2 + 2\ BzCl \longrightarrow Et_2Sn(SBz)_2 + 2\ NaCl$$

The compound $(RSCH_2)_2Sn(SR)_2$ can be obtained by replacement of bromine bonded to carbon and tin in $(BrCH_2)_2SnBr_2$ by its reaction with the sodium thiolate RSNa [23].

5. Group V

The thiol-substituted amines such as sulphenamides and tris-(alkanesulphenyl) amines are often prepared from sulphenyl chlorides and ammonia[164,165], and never from nitrogen trichloride and a thiolate anion or a thiol. Chloramines react with thiols to produce symmetrical disulphides[166].

$$Me_2NCl + 2\,PhSH \longrightarrow PhSSPh + Me_2NH_2^+Cl^-$$

However methyl-N-chlorobenzimidate (**36**) and benzenethiol form N-benzoylbenzenesulphenamide (**37**). The reaction may proceed through the formation of the unknown PhCON=SHPh as an intermediate[167].

$$\underset{\textbf{(36)}}{PhC(OMe)=NCl} + PhSH \longrightarrow \underset{\textbf{(37)}}{PhCONH(SPh)} + MeCl$$

The kinetics of the reaction of diazonium ions $XC_6H_4N_2^+$ with benzenethiolate anions show that initially the *syn*-diazo thioether is formed rapidly, which is followed by the slower *syn-anti* isomerism. Only in the cases of *p*-nitro- and *p*-cyano-benzenediazonium ions is it possible to distinguish between the first and second reactions. Using benzenediazonium ion and the *p*-Me- and *p*-OCH_3-substituted ions with benzenethiolate, first-order kinetics were observed over the entire range of the reaction. It is postulated that there the rate-determining step is formation of the *syn*-diazothioether, followed by its rapid isomerization to the *anti*-diazothioether[168].

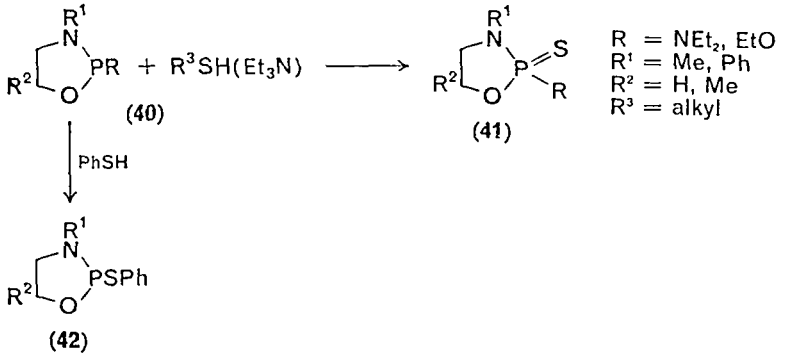
The simple alkyl and aryl-thio phosphorus derivatives, $(RS)_3P$, $(RS)_3PO$ and $(RS)_3PS$, can readily be prepared from phosphorus trichloride (or phosphorus pentachloride), phosphoryl chloride or thiophosphoryl chloride, and the corresponding lead thiolate[11,140,169]. Partially substituted compounds, such as $Cl_xP(SCF_3)_{3-x}$, are sometimes formed[170]. Substituted derivatives $R_2P(SR^1)$ and $RP(SR^1)_2$ can be prepared from the corresponding halide and lead thiolate[14,140,171]. Various mixed fluorophosphoranes, such as $MePF_2(SEt)_2$, can be prepared from $MePF_4$ and ethanethiol or its sodium salt[172].

p-Nitrophenyl methylphosphonic acid (**38**) reacts with thiolate nucleophiles leading to the formation of thiophosphonic esters (**39**), although the

$$\underset{\textbf{(38)}}{MeP(O)(OC_6H_4NO_2\text{-}p)O^-} + RS^- \xrightarrow{pH \sim 11} \underset{\textbf{(39)}}{MeP(O)(SR)O^-} + p\text{-}O_2NC_6H_4O^-$$

formation of some disulphide complicates the reaction[173]. Thiophosphites are also formed in the reaction of sodium thiolates or thiol/triethylamine with acetyl phosphite[171].

Reactions involving fracture of P—O or P—N bonds and displacement of EtO and Et_2N groups in various 1,3,2-oxaazaphospholanes (**40**) (R = EtO, Et_2N) with thiols in the presence of triethylamine have been examined[175]. Aliphatic thiolates used their sulphur in reaction with **40** to form 50–60% oxaazaphospholane 2-sulphide (**41**), whereas benzene thiol formed 78% 2-phenylthio-N-phenyl-1,3,2-oxaazaphospholane (**42**) (R^1 = Ph; R^2 = H). Similar derivatives (**40**; R = R^3S) are readily prepared from **40** when R = Cl, on treatment with a thiol in the presence of triethylamine[175].



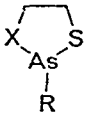
The thiolate group may be added to phosphorus acting as a ligand, for example in the preparation of (ethyldimethylthiophosphinite)pentacarbonyl molybdenum[176],

$$(ClR_2P)Mo(CO)_5 + EtSH \xrightarrow[Et_3N]{\text{hexane}} (EtSMe_2P)(CO)_5Mo + Et_4NHCl$$

The thiol derivatives of arsenic can be prepared by similar methods to those used for phosphorus[14,141]. Various mixed derivatives such as BuPhAsSPr can be prepared from BuPhAsI and PrSNa in absolute ethanol[177]. Displacement of an OEt group may occur in PhAsCl(OEt), but this reaction may involve rearrangement of an unstable intermediate PhAs(OEt)SBu[178].

$$2\ PhAsCl(OEt) + 2\ BuSH + 2\ Et_3N \longrightarrow PhAs(SBu)_2 + PhAs(OEt)_2 + 2\ Et_3\overset{+}{N}HCl^-$$

Derivatives of heterocyclic arsenic compounds can be prepared, e.g.



when X = O and R = Cl, the reaction with PhSNa gave R = SPh, but when X = S the reaction with PhSNa in benzene gave $As(SPh)_3$, along with ethylene arsenite[178].

Derivatives of antimony(III), $Sb(SR)_3$, can be prepared analogously[14, 141], or from antimony trichloride and thiols in the presence of ammonia[179]. Antimony(V) derivatives have been prepared[180], e.g.

$$Me_3SbCl_2 + 2\,MeSH + 2\,Et_3N \xrightarrow{-60^\circ} Me_3Sb(SMe)_2 + 2\,Et_3\overset{+}{N}H\,Cl^-$$

These compounds are thermally unstable, decomposing to Me_3Sb and MeSSMe. The unstable Me_4SbSR analogues can be prepared from pentamethylantimony and a thiol at low temperature[181].

Bismuth thiolates can be prepared in reactions similar to those used to prepare metal thiolates[7].

6. Group VI

Attempts to prepare compounds of the type RSOSR containing a single-bonded system RS—O—SR failed, and possible rearrangement of this as an unstable intermediate occurred[182].

$$4\,CF_3SCl + 2\,Ag_2O \longrightarrow CF_3SSCF_3 + CF_3SO_2SCF_3 + 4\,AgCl$$

The reactions of chlorine monoxide with thiols or thiolates have not been investigated.

The thiolate anion can play a very important role in the thiol–disulphide interchange.

Various derivatives of sulphur may be prepared by the reaction of sulphur monochloride, sulphur dichloride or sulphenyl halides with thiolates; the products depend on the reactant stoichiometry.

$$(C_6F_5S)_2Pb + SCl_2 \longrightarrow C_6F_5SSSC_6F_5 + PbCl_2 \quad \text{(reference 183)}$$

$$Ph_3CSH + SCl_2 \xrightarrow{-78^\circ C} Ph_3CSSCl + HCl \quad \text{(reference 184)}$$

$$(C_6F_5S)_2Pb + S_2Cl_2 \longrightarrow C_6F_5SSSSC_6F_5 + PbCl_2 \quad \text{(reference 183)}$$

$$(EtS)_2Pb + 2\,C_6F_5SBr \longrightarrow 2\,C_6F_5SSEt + PbBr_2 \quad \text{(reference 185)}$$

$$RSH + ClCOSCl \longrightarrow RSSCOCl + HCl \quad \text{(reference 186)}$$

Symmetrical disulphides are formed in the reaction of a thiol with an azide in the presence of copper(I). The reaction probably proceeds through the formation of a sulphenamide which is decomposed by the thiol[187].

$$2R^1SH + RN_3 \longrightarrow RNHSR^1 + N_2$$

$$RNHSR^1 \xrightarrow{R^1SH} RNH_2 + R^1SSR^1$$

Unsymmetrical disulphides can be formed by the decomposition of a sulphenamide with a thiol[188-190].

$$RSNEt_2 + PhSH \longrightarrow RSSPh + Et_2NH \quad (R = Me, Ph) \quad \text{(reference 188)}$$

The cleavage of the N—S bond in N(thiosulphenyl)phthalimide with thiols yields an unsymmetrical trisulphide[189,191]. Unsymmetrical disulphides are also formed in the thiolate anion fracture of the C—S bond in ethyl thiocyanate in DMF; small amounts, less than 10%, of the symmetrical disulphides are formed[192].

$$EtSCN + RS^- \longrightarrow EtSSR + CN^- \quad (R = n\text{-}C_9H_{19},\ PhCH_2,\ Ph)$$

Attempts to prepare derivatives of sulphur(IV) or sulphur(VI) by the reaction of thionyl or sulphonyl chloride with lead thiolate failed, as the sulphur(II) derivative and sulphur dioxide were formed[14,182],

$$2\,(C_6F_5S)_2Pb + 2\,SOCl_2 \longrightarrow 2\,[C_6F_5S\cdot SO\cdot SC_6F_5] + 2\,PbCl_2$$

$$\downarrow$$

$$2\,C_6F_5SSC_6F_5 + SO_2 + S$$

$$(CF_3S)_2Hg + SO_2Cl_2 \longrightarrow [CF_3S\cdot SO_2\cdot SCF_3] + HgCl_2$$

$$\downarrow$$

$$CF_3SSCF_3 + SO_2$$

Other reactions of thiolate anions with sulphur(IV) and sulphur(VI) include the reaction with arylsulphonylsulphones

$$n\text{-}BuS^- + ArS(O)S(O)_2Ar \longrightarrow n\text{-}BuSS(O)Ar + ArSO_2^- \quad \text{(reference 193)}$$

and the reaction with the trithionate ion,

$$PhS^- + {}^-O_3SSSO_3^- \xrightarrow{K_a} PhS{-}SSO_3^- + SO_3^{2-}$$

$$\swarrow K_c \qquad K_b \searrow SO_3^{2-}$$

$$S_2O_3^{2-} + PhSSPh \xrightarrow[SO_3^{2-}]{K_d} PhSSO_3^- + S_2O_3^{2-}$$

The rate-determining step is K_a, and added formaldehyde eliminates the K_b and K_d paths, leaving PhSSPh[194].

Very few thiolate derivatives of selenium, and virtually none of tellurium, are known. Attempts to prepare $R_2Se(SC_6F_5)_2$ or $Me_2Te(SC_6F_5)_2$ from the dialkyl (or aryl) selenium dichloride, dimethyltellurium dichloride and lead pentafluorobenzenethiolate resulted in the formation of the disulphide, $C_6F_5SSC_6F_5$, and the dialkyl (or aryl) selenium, R_2Se, or Me_2Te. The chlorides Se_2Cl_2 and $TeCl_2$ yielded only the disulphide and selenium or tellurium[14]. Tellurium—sulphur and —selenium bonds have been formed in the reaction of organotellurium bromides with benzenethiol or benzeneselenol[195],

$$o\text{-}HCOC_6H_4TeBr + PhMH \longrightarrow o\text{-}HCOC_6H_4TeMPh \quad (M = S, Se)$$

7. Group VII

Attempts to prepare simple sulphenyl fluorides from thiolates and fluorine have not been reported, but are unlikely to be successful due to the oxidizing powers of fluorine[196] or chlorine monofluoride[197] causing oxidation of the sulphur(II)

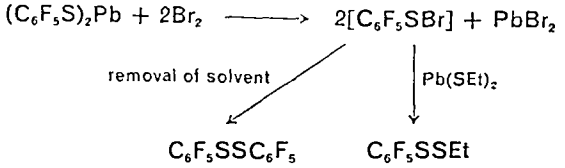
$$(CF_3)_2S + F_2 \xrightarrow{-78^\circ C} (CF_3)_2SF_2 \quad \text{(reference 196)}$$

Attempts to prepare trifluoromethanesulphenylfluoride resulted in the formation of trifluoromethylsulphur trifluoride and bis(trifluoromethyl)-disulphide[198].

Conversely sulphenyl chlorides can readily be prepared by the action of chlorine on a metal thiolate.

$$(C_6F_5S)_2Pb + 2\,Cl_2 \longrightarrow 2\,C_6F_5SCl + PbCl_2 \quad \text{(reference 185)}$$

Sulphenyl bromide can be obtained analogously in solution, but removal of the solvent caused decomposition[185],



The thiolate anion is quantitatively oxidized by iodine to the disulphide[185], and this method, involving the formation of an unstable sulphenyl iodide, is the basis of the iodometric determination of mercapto groups in a number of compounds[199].

$$(C_6F_5S)_2Pb + 2\,I_2 \longrightarrow 2\,[C_6F_5SI] + PbI_2$$

$$\downarrow$$

$$C_6F_5SSC_6F_5 + I_2$$

The thiolate anion is an intermediate in the oxidation of a thiol by iodine[200].

E. Reactions with Transition Metal Derivatives

1. Simple transition metal derivatives

This section will be primarily restricted to the derivatives and reactions of monofunctional thiols. The dithiol derivatives of the transition metals are a rapidly expanding area of research and have been reviewed several times recently[201-204]. Other polyfunctional thiols, such as monothioglycol, (with Ag(I)[205] and In(III)[206]), α-mercaptopropionic acid[207,208] and thioethanolamine[209,210], have been extensively studied and will not be discussed further. It is however noteworthy that interesting complexes of the type Ag_2SR^+, AgSR and $Ag(SR)_2^-$[205], $In(SR)_n^{(3-n)+}$ (n = 1, 2, 3, 4; R = $HOCH_2CH_2$)[206], and $\{Cd[NiL_2]_2\}^{2+}$ and $\{Ag[NiL_2]_2\}^+$ (L = H_2NCH_2-CH_2SH)[209] are formed.

Simple transition metal mercaptides, such as $Ni(SR)_2$ or $Hg(SR)_2$, are usually prepared by reactions not involving the thiolate anion as a nucleophile[7,141,211]. Occasional use is made of thiolates, for instance in the preparation of chromium(III) methanethiolate, where sodium methanethiolate was reacted with chromium chloride in excess of dimethyl disulphide under dry nitrogen and irradiated to yield the desired product, which can also be prepared by other photochemical methods[212]. Cobalt thiolates, $[Co(SR)_2]_n$, may be prepared from cobalt acetate in methanol with a basic solution of the thiol[213]. Some biochemical applications of thiolate anions are important. The binding of thiols to Co(II) corrins has been studied by e.s.r. where it has been shown that the thiols, thiolates and sulphides bind to the cobalt. The binding of Co(II) B_{12} complexes to thiols and sulphides will necessitate a re-examination of the methyl-transferring enzymes in which thiols are known to be important[214].

The continuous oxidation of thiols involved in the sweetening of light naphtha, with air to the disulphides using cobalt phthalocyanine complexes as catalysts, involves the formation of a stable complex between the thiolate ions and the metallocyanine catalyst[215].

The kinetics of various reactions involving thiolates and platinum complexes have been studied. The rate of reaction of *trans*-$[Pt(py)_2Cl_2]$

with nucleophiles Y is given by the equation

$$\text{rate} = K_1[\text{complex}] + K_2[\text{complex}][Y]$$

A reactivity sequence $PhS^- \gg MeO^- > N_3^-$ etc. was deduced[216]. The kinetic behaviour of *trans*-$[Pt(PEt_3)_2RCl]$ (R = Ph, *o*-Tol) with different entering groups, including PhS^-, has been examined. The rate was found to be independent of the reagent concentration in solvents (solv) such as methanol or DMSO[217].

$$\textit{trans}\text{-}[Pt(PEt_3)_2(o\text{-Tol})Cl] \underset{\text{slow}}{\overset{+\text{solv}}{\rightleftharpoons}} \text{intermediate} \overset{+Y}{\rightleftharpoons} \textit{trans}\text{-}[Pt(PEt_3)_2(o\text{-Tol})Y] + Cl^-$$

2. Complex ions

Various complex ions of the type $[M(SR)_2]^-$ and $[M(SR)_4]^{2-}$ have been reported. These complexes can be formed readily when R = Ph[218], C_6F_5[218-220], C_6Cl_5[140,221] and the metal M may be Co(II), Pd(II), Pt(II), Zn(II), Cd(II), Hg(II), Cu(I), Ag(I) or Au(I). The complex ions are usually prepared by the reaction of an alkali metal thiolate with an appropriate metal salt. The anions may be isolated as their salts with potassium, tetramethyl- or tetrabutyl-ammonium, or tetraphenyl-arsonium cations. The electronic spectra of these systems have been analysed[218,222] and the nature of the bonding discussed[223]. The SC_6F_5 ligand is intermediate between NCO^- and NCS^- in the spectrochemical series, about the same as I^- in the nephelauxetic (cloud expanding) series (reflecting the decreasing covalency of the ligands), and the optical electronegativity $\chi_{opt}(SC_6F_5)$ is $2{\cdot}5 \sim 2{\cdot}6$[222]. However other data have been interpreted to give slightly different spectrochemical and nephelauxetic series[218]. The data for several ligands have been discussed and various deductions made. High ligand electro-negatives, χ_L, are associated with high coordination numbers and high complex symmetries, whereas ligands with lower values of χ_L promote lower coordination numbers and distorted symmetries. This has been rationalized in terms of the charge balance requirements of the metal ion and the covalence of the metal ligand bond[223].

Similar complex ions, stabilized as the tetraalkyl ammonium salts, have been prepared from tetrafluorobenzene-1,2-dithiol (H_2tfdt). The complex ions formed were $[Mtfdt_2]^-$ (M = Fe(III), Co(III), Ni(III)), and $[Mtfdt_3]^{2-}$ (M = Mo(IV) and Pt(IV))[224].

3. Organometallic compounds

This section is concerned primarily with organometallic transition metal complexes.

Cyclopentadienyltitanium thiolates have been prepared in benzene solution from the corresponding chloride and several thiols in the presence of triethylamine in good yields[225].

$$(\pi\text{-}C_5H_5)_2TiCl_2 + 2\ RSH + 2\ Et_3N \longrightarrow (\pi\text{-}C_5H_5)_2Ti(SR)_2 + 2\ Et_3NH^+Cl^-$$

The compound $(\pi\text{-}C_5H_5)_2Ti(SR)_2$ (R = Me, Ph) has also been prepared from $(\pi\text{-}C_5H_5)_2TiCl_2$ and NaSR[226]. Attempts to prepare $(\pi\text{-}C_5H_5)_2Ti(SCF_3)_2$ from $(\pi\text{-}C_5H_5)_2TiCl_3$ and $AgSCF_3$ resulted in the formation of $(\pi\text{-}C_5H_5)_2TiF_2$[227], and several unsuccessful attempts have been made to prepare $(\pi\text{-}C_5H_5)_2Ti(SC_6F_5)_2$[228].

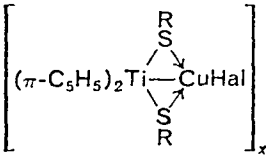
The extremely unstable mono-π-cyclopentadienyltitanium tri(benzenethiolate) has also been reported[229],

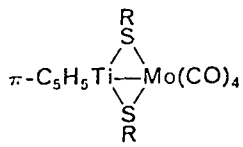
$$\pi\text{-}C_5H_5TiCl_3 + 3\ HSPh + 3\ NEt_3 \longrightarrow \pi\text{-}C_5H_5Ti(SPh)_3 + 3\ Et_3NH^+Cl^-$$

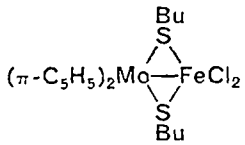
If a 1 : 1 reactant stoichiometry is used, the stable compound $\pi\text{-}C_5H_5TiCl_2(SPh)$ is readily isolated and can be purified by vacuum sublimation. The derivatives of zirconium, $(\pi\text{-}C_5H_5)_2Zr(SPh)_2$ and $(\pi\text{-}C_5H_5)_2Zr(SePh)_2$, have been prepared analogously from $\pi\text{-}C_5H_5ZrCl_2$ and the thiol or selenol in the presence of triethylamine[230].

Various other analogous compounds, such as $(\pi\text{-}C_5H_5)_2Nb(SR)_2$ (R = Me, Ph[231]) and $(\pi\text{-}C_5H_5)_2M(SR)_2$ (M = Mo, W[232]) can be obtained from the corresponding chloride and sodium thiolate.

The compounds of the type $(\pi\text{-}C_5H_5)_2M(SR)_2$ (M = Ti, Mo, W, Nb) have been found to have extremely interesting properties[231, 233, 239]. They can act as bidentate ligands forming complexes, some of which may contain metal—metal bonds, e.g.







Various other organometallic thiolate complexes may be formed by using thiolates.

$$[(\pi\text{-}C_5H_5)Ni(n\text{-}Bu_3P)_2]^+Cl^- + Na^+SR^- \rightarrow [(\pi\text{-}C_5H_5)Ni(n\text{-}Bu_3P)SR] + NaCl + n\text{-}Bu_3P$$

where the thiolate anion can be derived from aliphatic or aromatic thiols[240, 241]. Dithiol derivatives can also be obtained[242].

$$2[(\pi\text{-}C_5H_5)Ni(n\text{-}Bu_3P)_2]^+Cl^- + NaS(CH_2)_nSNa \longrightarrow$$
$$(\pi\text{-}C_5H_5)(n\text{-}Bu_3P)NiS(CH_2)_nSNi(n\text{-}Bu_3P)(\pi\text{-}C_5H_5) \quad (n = 2, 4, 6)$$

Other reactions involving thiols, such as the reaction

$$(\pi\text{-}C_5H_5)_2Ni + HSR \longrightarrow (\pi\text{-}C_5H_5)NiSR + C_5H_6$$

$$\downarrow \text{ fast}$$

$$(\pi\text{-}C_5H_5)Ni\begin{matrix}\diagup R \\ S \\ \diagdown S \\ \diagup R\end{matrix}Ni(\pi\text{-}C_5H_5)$$

which has been studied kinetically, do not involve the thiolate anion, but rather the thiol itself, the sulphur of which bonds initially to the nickel[243].

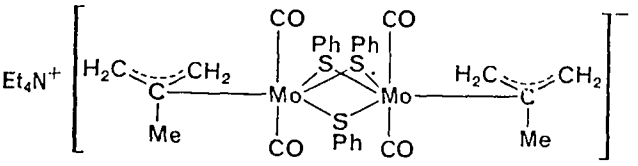
Various CF_3S derivatives have been prepared using silver trifluoromethanethiolate, and its reactions with certain norbornadiene and tetraphenylcyclobutadienemetal complexes studied[244]. The reaction of the norbornadiene derivative $C_7H_8PtCl_2$, with $AgSCF_3$ in dichloromethane solution resulted in the replacement of both chlorine atoms with CF_3S groups to give the white crystalline $C_7H_8Pt(SCF_3)_2$. However, in the analogous reaction of $C_7H_8PdCl_2$ with CF_3SAg, addition of CF_3S groups to the norbornadiene ligand occurred to give two yellow crystalline products, $[(C_7H_8SCF_3)Pd]_2Cl_2$ and $[(C_7H_8SCF_3)Pd]_2(Cl)(SCF_3)$, which are novel nortricyclic derivatives. Reaction of the tetraphenylcyclobutadiene complex $[Ph_4C_4PdBr_2]_2$ with $AgSCF_3$ gave the golden-red $Ph_4C_4Pd(SCF_3)_2$ formulated as a monomeric 16-electron tetraphenylcyclobutadiene complex, but the reaction of $Ph_4C_4Co(CO)_2Cl$ with $AgSCF_3$ gave the binuclear complex $[Ph_4C_4Co(CO)SCF_3]_2$.

The molybdenum complexes $[\pi\text{-}C_5H_5Mo(NO)X]_2$, $[\pi\text{-}C_5H_5Mo(NO)X_2]_2$ and $[\pi\text{-}C_5H_5Mo(NO)(I)(SCH_2Ph)]_2$, X = I, SCH_2Ph, or SPh, have been obtained from the iodide $[\pi\text{-}C_5H_5Mo(NO)I_2]_2$ by reaction with the appropriate thiolate anions under differing conditions[245]. The structures of the analogous chromium compounds $[\pi\text{-}C_5H_5Cr(NO)SPh]_2$ show that the SPh groups act as bridges between the two chromium atoms[246].

Several molybdenum derivatives can be prepared using a thiolate. A stable monomeric π-allyl molybdenum derivative has been obtained by the metathesis[247]:

$$\pi\text{-}C_3H_5Mbipy(CO)_2Cl + TlSC_6F_5 \longrightarrow \pi\text{-}C_3H_5Mbipy(CO)_2SC_6F_5 \quad (M = Mo, W)$$

A dinuclear π-allylmolybdenum complex has been obtained by treatment of its trichloroanalogue with sodium thiolate[248].



Various other mixed cyclopentadienyl carbonyl complexes can be prepared using a thiolate:

$$\left.\begin{array}{l}\pi\text{-}C_5H_5W(CO)_3Cl + NaSR \\ \pi\text{-}C_5H_5W(CO)_3Cl + RSH + Et_3N\end{array}\right\} \longrightarrow \pi\text{-}C_5H_5W(CO)_3SR \quad (R = Me, Ph)$$

(reference 249)

$$\pi\text{-}C_5H_5Fe(CO)_2Br + NaSEt \longrightarrow \pi\text{-}C_5H_5Fe(CO)_2SEt$$ [250]

(reference 250)

4. Carbonyl compounds

Sulphur-containing metal carbonyls have been reviewed, and there is a section concerning mercapto compounds[247]. While several mercapto carbonyl complexes are known which can be prepared from the thiol itself or the disulphide some preparations involve the use of the thiolate anion. The complex ions $[M(CO)_5SC_6F_5]^-$ (M = Cr, Mo, W) can readily be prepared from the pentacarbonyl and sodium pentafluorobenzenethiolate[251]. The square planar complexes, *trans*-$[M(SC_6F_5)(CO)(PPh_3)_2]$ are obtained from thallium(I) pentafluorobenzenethiolate and the complexes $[MCl(CO)(PPh_3)_2]$ (M = Ir, Rh)[252]. The complex $[Ir(SC_6F_5)(CO)(PPh_3)_2]$ will add another mole of pentafluorobenzenethiol in benzene to form $[IrH(SC_6F_5)_2(CO)(PPh_3)_2]$, and also readily adds oxygen, forming $[Ir(SC_6F_5)(O_2)(CO)(PPh_3)_2]$[252].

The yellow diamagnetic anions $[Cr_2(CO)_{10}SR]^-$ (R = H, Me, Et, Ph) are formed on oxidation of aqueous $Na_2[Cr_2(CO)_{10}]$ by RSH, accompanied by the evolution of hydrogen, but when RSH is thio-*p*-cresol the mononuclear anion $[Cr(CO)_5SR]^-$ (R = C_6H_4Me) is isolated[253]. The monomeric carbonyl derivatives $M(CO)_5SR^-$ can be prepared by using the mercury thiolates; only a small amount of the dimeric species is obtained [254]. The

$$M_2(CO)_{10}^{2-} + Hg(SR)_2 \longrightarrow 2\,M(CO)_5SR^- + Hg$$

ions $[M_2(CO)_{10}SR]^-$ (M = Cr, Mo, W), stabilized as their bis(triphenylphosphine)iminium derivatives, are obtained in reactions of the type

$$2\,Cr(CO)_6^- + SMe^- \xrightarrow[THF]{u.v.} Cr_2(CO)_{10}SMe^- + CO$$

but this reaction does not give as good yields as the reaction of $M(CO)_5Cl^-$ with organotin thiolates[255].

Various carbonyl derivatives containing the SCF_3 group can be obtained using silver trifluoromethanethiolates. Some reactions are summarized below[227]:

$$Mn(CO)_5Br + AgSCF_3 \longrightarrow [CF_3SMn(CO)_4]_2$$

$$Re(CO)_5Br + AgSCF_3 \longrightarrow [CF_3SRe(CO)_4]_2 + CF_3SRe(CO)_5$$

$$\pi\text{-}C_5H_5Fe(CO)_2I + AgSCF_3 \longrightarrow CF_3SFe(CO)_2(\pi\text{-}C_5H_5)$$

$$C_3H_5Fe(CO)_3I + AgSCF_3 \longrightarrow CF_3SFe(CO)_3C_3H_5$$

$$\pi\text{-}C_5H_5Cr(NO)_2Cl + AgSCF_3 \longrightarrow CF_3SCr(NO)_2(\pi\text{-}C_5H_5)$$

$$C_3F_7Fe(CO)_4I + AgSCF_3 \longrightarrow [C_3F_7Fe(CO)_5SCF_3]_2 \quad \text{(reference 256)}$$

Other complexes can be obtained using mercury(II) trifluoromethanethiolate[257].

$$Mn_2(CO)_8P(CF_3)_2I + Hg(SCF_3)_2 \longrightarrow Mn_2(CO)_8P(CF_3)_2SCF_3$$

The compounds $[\pi\text{-}C_5H_5Mo(NO)HalSR]_2$ (Hal = Br, I), $[\pi\text{-}C_5H_5Mo(NO)(SR)]_2$ and $[\pi\text{-}C_5H_5Mo(NO)(SR)_2]_2$ containing bridging sulphur ligands can readily be prepared from $[\pi\text{-}C_5H_5Mo(NO)Hal_2]$ (Hal = Br, I) and the thiol or its sodium salt by replacing one and two halogens respectively[258]. Other dimeric compounds with bridging thiolate groups, such as $[Rh(CO)_2(SPh)]_2$, are readily obtained from benzenethiol and $[Rh(CO)_2Cl_2]^-$ in ethanol. However, analogous compounds such as $[Rh(CO)(SR)_2Hal]$ (Hal = Cl, R = Et, Pr; Hal = Br, R = Et) may be polymeric[259]. Bridging thiolates are also present in the iron compounds, $(CO)_3Fe(SEt)_2Fe(CO)_3$ obtained from $Fe_2(CO)_6(COPh)_2$ and EtSH in hexane[260].

Carbene complexes $(CO)_5CrC(SR)R^1$ (R = Me, Et, Ph; R^1 = Me, Ph) and $(CO)_5WC(SMe)Me$ are readily obtained by nucleophilic displacement of OMe from $(CO)_5MC(OMe)R^1$ (M = Cr, W) with a thiol[261].

III. ADDITION REACTIONS

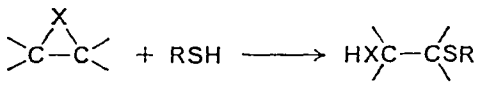
A. Introduction

The addition of a thiol or a thiolate to an unsaturated compound A=B can be represented as

$$A{=}B + RSH \longrightarrow RSA{-}BH \text{ or } HA{-}BSR$$

Two products are possible, depending on whether the RS group adds to A or B. This will obviously be affected by the nature of atoms forming the

multiple bond and, possibly, by the other groups present in A and B. Addition reactions can occur in cyclic systems, such as epoxides or thioepoxides, involving fracture of the ring



It is, among other things, of interest to ascertain the nature of the addition product.

Most of the addition reactions observed occur by a radical mechanism. This type of reaction has been reviewed[262], and two chapters in this book are concerned with radical reactions of thiols. This discussion will exclude all reactions that occur via the formation of radicals. Considerably less study has been made of ionic additions of thiolates to unsaturated systems than that of radical additions.

B. Reactions with Olefins

Sulphides are formed when a thiol adds onto an olefinic bond. Most of the reactions reported correspond to anti-Markownikoff addition, but this is probably a free radical mechanism, which also occurs in the presence of minute traces of peroxides. With carefully purified reagents in the presence of acid, Markownikoff addition occurs[263a]

$$Me_2C{=}CHMe + RSH \longrightarrow Me_2C(SR)CH_2Me$$

The kinetics of the addition of benzenethiol and substituted benzenethiols to derivatives of phenylvinylsulphone have been studied[264,265]. In 50% aqueous ethanol at 25°C the reaction was second order, first order in the sulphone and in the thiolate anion.

$$XC_6H_4SH \rightleftharpoons XC_6H_4S^- + H^+$$

$$XC_6H_4S^- + YC_6H_4SO_2CH{=}CH_2 \xrightarrow{\text{slow}} YC_6H_4SO_2C^-HCH_2SC_6H_4X$$

$$YC_6H_4SO_2C^-HCH_2SC_6H_4X \xrightarrow{H^+\ \text{fast}} YC_6H_4SO_2CH_2CH_2SC_6H_4X$$

Hammett treatment showed that substitution in the phenyl ring of the sulphone influenced the reaction more than substitution in the thiol, indicating that the transition state resembles a carbanion intermediate[264]. The second-order rate constant for the nucleophilic addition of p-$MeC_6H_4S^-$ to phenyl vinyl sulphone has been detected at 0–45°C, the energy, free

energy of activation and entropy being 16·0 kcal/mole, 16·6 kcal/mole and −4 e.u. respectively[265].

Allyl alcohol and *n*-BuSH give *n*-$BuSCHMeCH_2OH$ in the presence of 5% elementary sulphur as a catalyst and an initial pressure of hydrogen of about 30 atmospheres, but allyl alcohol and *t*-BuSH form *t*-$BuS(CH_2)_3OH$ under free-radical conditions[266]. The compound $MeS(CH_2)_3SMe$ has been prepared from allyl chloride, first by $MeS^{\bullet}$ addition and then MeS^{-} substitution[266].

Activated thiols will add to *p*-isopropenylphenol in chloroform solution in the presence of *p*-toluenesulphonic acid giving a Markownikoff addition product,

$$p\text{-}HOC_6H_4CMe{=}CH_2 + RSH \longrightarrow p\text{-}HOC_6H_4CMe_2(SR)$$

$$(R = CH_2CO_2R',\ (R'O)_2PS,\ CH_2CONHC_{10}H_7)$$

Thioacetic acid gave an anti-Markownikoff addition product. Simple thiols did not react even in the presence of catalysts, except under pressure and irradiation. With benzenethiol and *p*-chlorobenzenethiol the unusual addition of the *para*-hydrogen occurred[267].

$$p\text{-}HOC_6H_4CMe{=}CH_2 + C_6H_5SH \longrightarrow p\text{-}HOC_6H_4CMe_2C_6H_4SH\text{-}p$$

A few other examples of this type of addition, in the presence of a catalyst, are found in the patent literature[267].

Simple Markownikoff addition of thiol to the C=C bond occurs in some carbohydrate derivatives[268], and to dimethyl maleate[269].

C. Reactions with Acetylenes

Thiols do not add less readily to acetylenes than to olefins. The addition occurs at high temperatures in the presence of a base[263a].

$$HC{\equiv}CH + R'SH \longrightarrow CH_2{=}CH(SR)$$

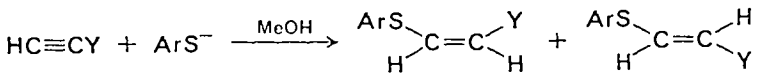
A second molecule of thiol may be taken up

$$RSCH{=}CH_2 + RSH \longrightarrow RSCH_2CH_2SR$$

If addition occurs across an acetylenic bond, there is the possibility of formation of *cis* and *trans* isomers. Phenyl acetylene reacts with ethanethiol in the presence of an alkali catalyst at 100–225°C. Progressively larger amounts of the *trans* isomer were formed as the temperature increased, reaching a maximum of 71% *trans* at 200°C. A rapid *cis–trans* isomerism accompanies the vinylation reaction[270].

$$EtSH + Ph{\equiv}CH \longrightarrow (EtS)CH{=}CHPh$$

The degree of *trans* stereoselectivity for nucleophilic additions of *p*-toluenethiol derivatives to negatively substituted acetylenic compounds (Y=CN; $SO_2C_6H_4Me$-*p*, $C_6H_4NO_2$-*p*, CO_2Me, $CONH_2$, COMe) in methanol is dependent on the nature of the activating group Y, and



decreases where Y is capable of delocalizing the adjacent incipient negative charge[271]. In the tertiary amine-catalysed addition of thiols to ethyl propiolate, it has been shown that the amount of *trans* addition product in the reaction mixture increased as the acidity of the thiol. Similar additions to hexafluoro-2-butyne and trifluoromethylacetylene showed that with both trifluoromethyl-activated acetylenes *trans* addition was predominant. However only 5% *trans* was obtained in the reaction of cyclohexanethiol and trifluoromethyl acetylene[272].

Addition reactions have been studied with various substituted acetylenes such as the Markownikoff additions

$$PhOC{\equiv}CH + EtSH \xrightarrow{Na(NH_3)} 52{\cdot}3\%\ H_2C{=}C(OPh)SEt$$

and anti-Markownikoff additions of thiols to phenoxyacetylene, depending on the solvent employed[273],

$$PhOCH{\equiv}CH + RSH \xrightarrow{Et_2O} PhOCH{=}CHSR \quad (R = Et, Bu)$$

Addition to trifluoromethylacetylenes has been studied with thiols in the presence of sodium ethoxide or triethylamine[274]:

$$RSH + XC{\equiv}CCF_3 \longrightarrow (RS)XC{=}CHCF_3 \quad (R = Et, HOC_2H_4, Bu, Ph;\ X = Cl, Br, Et, CF_3, H, Et_2N)$$

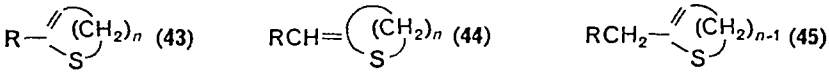
Addition can also occur in systems containing ethylenic and acetylenic bonds, and nucleophilic addition occurs primarily across the acetylenic bond:

$$RSH + F_3CC{\equiv}CCHRCR^1{=}CR^2R^3 \longrightarrow F_3CCH{=}C(SR)CHRCR^1{=}CR^2R^3$$

The latter compound isomerizes to $F_3CCH_2C(SR){=}CRCR^1{=}CR^2R^3$. In the free radical addition compounds such as $F_3CC{\equiv}C(CH_2)_3SMe$ were isolated[275].

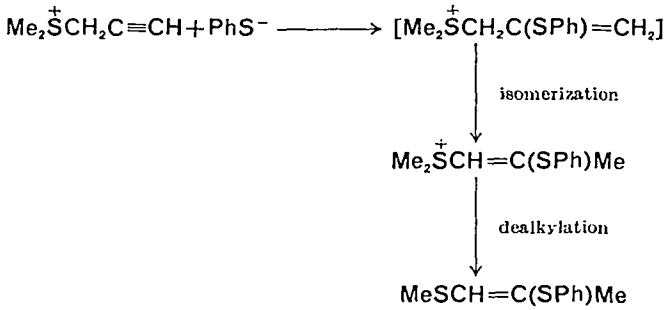
Thiols containing an acetylenic bond may cyclize. The heterocyclization of acetylenic thiols, $RC{\equiv}C(CH_2)_nSH$, has been studied under nucleophilic

and free radical conditions forming products (43), (44) and (45). Compound **44** is the main product of the nucleophilic attack when R = H, and mixtures of all three are formed under free radical conditions[276].



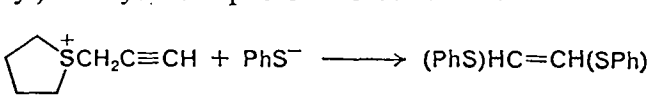
The addition of thiols to acetylenic bonds in compounds with a formal negative or positive charge has been examined. Aromatic thiols react with $HO_2CC{\equiv}CCO_2K$ giving (phenylthio)fumaric acids, which were cyclized in the presence of sulphuric acid to thiachromonecarboxylic acids[276a].

Two products are formed when the benzenethiolate anion reacts with dimethylprop-2-ynylsulphonium bromide, $Me_2\overset{+}{S}CH_2C{\equiv}CH\ Br^-$. The reaction is postulated to proceed through the formation of an allenic system $\overset{+}{S}C{=}C{=}C$. The initial product, not isolated, isomerizes, and may subsequently be dealkylated with excess thiolate:



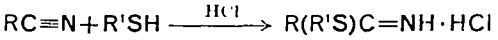
The methanethiolate anion also adds to the ethylenic bond of the dealkylated product and some trisulphide is formed:

A similar reaction is observed with the benzenethiolate anion and 1-(prop-2-ynyl)tetrahydrothiophenium bromide[276b].



D. Reactions with Nitrile Groups and Azomethine Bonds

In acidic solution nitriles undergo an addition reaction with thiols forming iminothioesters[263b]

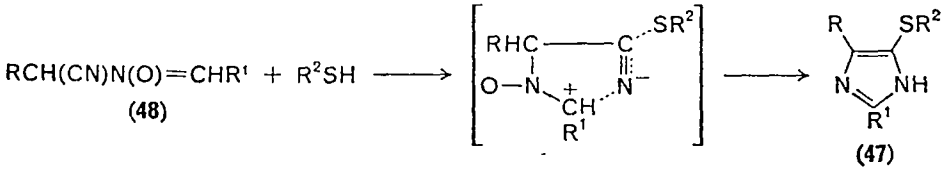


The examples of this type of reaction in the recent literature are somewhat limited. The simplest is the formation of cyanoformimidic acid (**46**) by reaction of cyanogen with a thiol in an inert solvent in the presence of amines or metal hydroxides[277],

$$RSH + (CN)_2 \longrightarrow HN{=}C(CN)SR$$

(46)

2,4,5-Trisubstituted imidizoles (**47**) can be obtained from thiols and N-(1-cyanoalkyl)alkylidenimine-N-oxides (**48**). This reaction involves a cyclization reaction, proceeding through the initial addition of the thiol to the C≡N bond[278].



(48) **(47)**

Addition of thiols across an azomethine bond occurs resulting in the formation of a carbon—sulphur bond, an example is the formation of N-benzylidene-*o*-nitroaniline (**49**)[279],

$$o\text{-}O_2NC_6H_4N{=}CHPh + p\text{-}MeC_6H_4SH \longrightarrow o\text{-}O_2NC_6H_4NHCH(Ph)SC_6H_4Me\text{-}p$$

(49)

Thiophenol reacts with diphenyl-ketene-(*p*-bromophenyl)imine (**50**) causing reduction of the aromatic bromine and fracture of the C=N bond[280],

$$Ph_2C{=}C{=}NC_6H_4Br\text{-}p + PhSH \xrightarrow{169^\circ C} Ph_2C{=}C(SPh)_2 + PhNH_2 \cdot HBr$$

(50)

E. Reactions with Carbonyl and Thiocarbonyl Groups

Thiols can react with ketones to give a hemithioacetal:

$$R^1R^2CO + RSH \rightleftharpoons R^1R^2C(OH)SR$$

Further reaction readily gives the thioacetal, although a catalyst is sometimes required[263c]:

$$R^1R^2C(OH)SR + RSH \rightleftharpoons R^1R^2C(SR)_2 + H_2O$$

Thioacetals may be thermally decomposed to the corresponding thione:

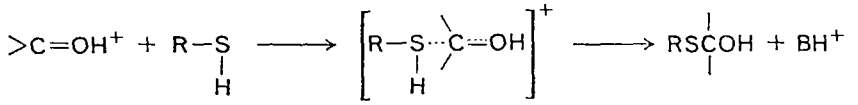
$$R^1R^2C(SR)_2 \longrightarrow R^1R^2CS + R_2S$$

The hemithioacetal can also be reduced by excess thiol to the sulphide[263a]:

$$2\,R^1SH + RCH(OH)SR^1 \longrightarrow RCH_2SR^1 + R^1_2S_2 + H_2O$$

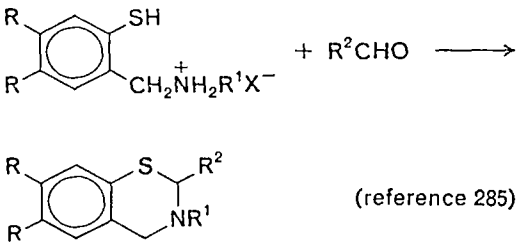
The equilibria between propanethiol and simple carbonyl compounds have been studied in CH_2Cl_2: the resulting α-hydroxysulphides may be converted into the thioacetals where the equilibrium constants are less than 10^2, by addition of an acid catalyst (BF_3 or HCl). Examples of aldehydes and ketones whose values of K are less than 10^2 are MeCHO, Me_2CO; those having K values greater than 10^2 are CCl_3CHO, $(CF_3)_2CO$[281].

The kinetics of the formation of the hemithioacetal in 50% ethanol–water have shown that the reaction is acid catalysed and does not involve a thiolate anion, probably proceeding via the formation of the protonated ketone[282],



Other studies of rate and equilibrium constants of the formation and breakdown of hemithioacetals (MeCHO + PhSH, or AcSH, or *p*-$NO_2C_6H_4SH$) reveal a diffusion-controlled rate-determining step, with proton transfer in some sense concerted with cleavage and formation of the C—S bond[283]. A general base-catalysed mechanism involves attack of the RS^- anion on the carbonyl group[284].

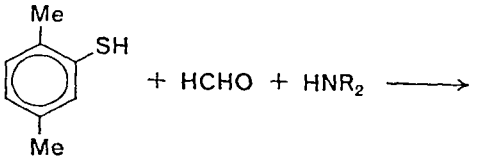
The addition reaction can be utilized synthetically, as is illustrated in the examples where further reaction with amines occurs.

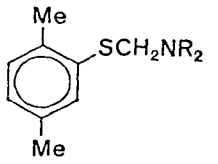


(reference 285)

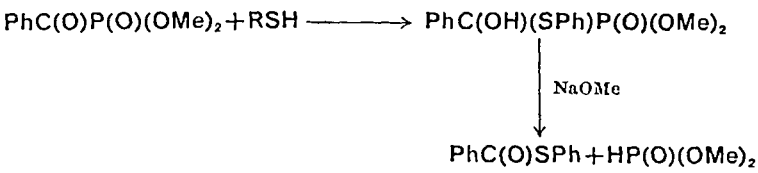
The phosphorus containing ketone $PhC(O)P(O)(OMe)_2$ does not react with sodium thiolate, but will react with the thiol in the presence of

magnesium bromide forming the thioester, upon fracture of the carbon—phosphorus bond[287].

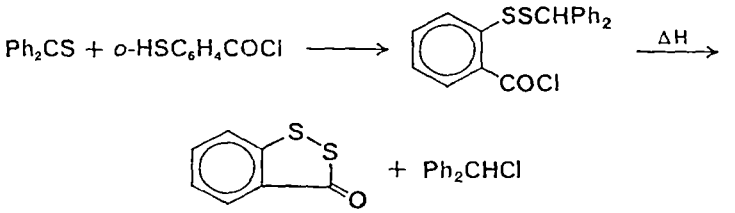




(reference 286)



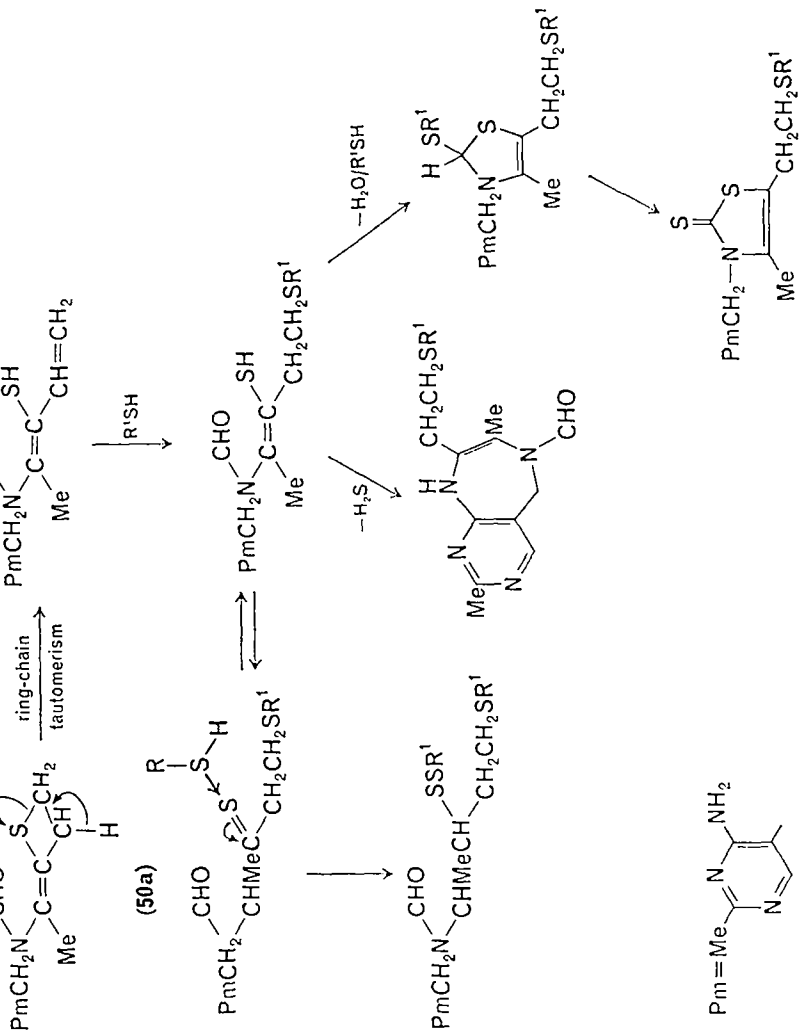
Analogous reactions occur with thiones, as illustrated by the example[288]:



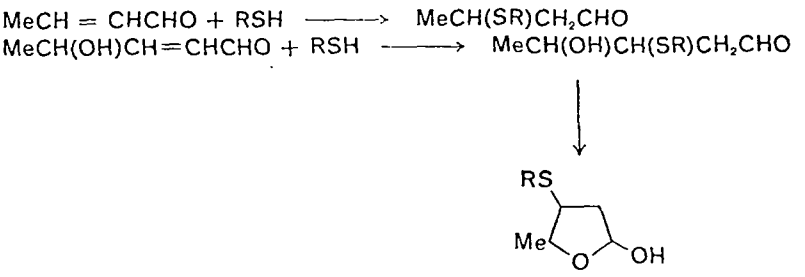
F. Reactions Involving Conjugated Systems

With a conjugated system similar to the type C=C—C=X, where X can be C,N,O, it is of interest to observe where addition of a thiol occurs. The majority of reactions involve addition across the C=C bond, but exceptions are found.

Several products are obtained from the reaction of thiols with thiamine anhydride (**50a**). A conjugated system is postulated as an intermediate with initial 1,2 addition. The reaction products depend subtly on the pH[289].

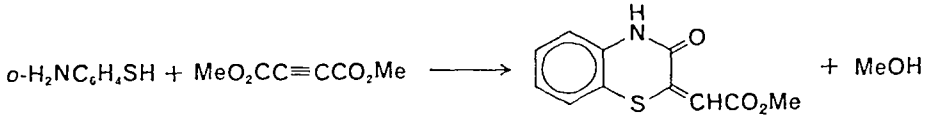

ring-chain
tautomerism
R'SH
(50a)
−H₂O/R'SH
−H₂S
Pm=Me

Reactions of the conjugated aldehydes, crotonaldehyde and 4-hydroxy-2-pentenal, with a C=C—C=O bond system, in aqueous solution with thioglycollic acid, either as its sodium salt or ethyl ester, give addition across the C=C bond. The 4-hydroxy-2-pentenal adduct cyclizes to the hemiacetal,

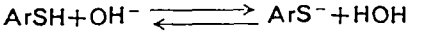


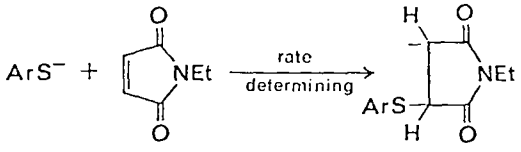
The kinetics have been studied and show that with thioglycollic acid derivatives between pH 1·5 and 2·5 the RS^- ion and RSH react, but at pH > 2·5 the RS^- anion is the reactive entity. A reaction mechanism has been derived[290].

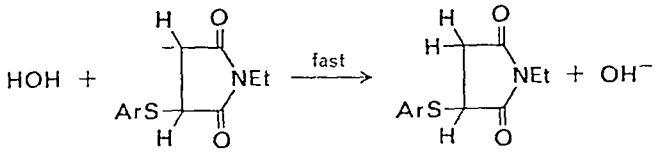
1,4-Addition of thiols in basic solution to the C=C—C=O bond system in α,β unsaturated ketones, such as 4-benzylidene-1-butyl-pyrrolidine-2,3-dione, has been observed, forming with benzenethiol in piperidine, 1-butyl-3-hydroxy-4(α-phenylthiobenzyl)-3-pyrrolin-2-one[291]. Addition of thiols primarily to the C=C bond in C=C—C=O systems in quinones and lactones has been observed[292,293]. The reactions were studied in neutral or alkaline solution and probably involve attack by the thiolate anion. In compounds containing both carbonyl or carboxyl groups and acetylenic triple bonds, addition occurs primarily across the acetylene bond. Cyclization of the initial product so formed is also observed[294].



The addition of thiols to N-ethylmaleimide within the pH range 5–7 in 95% ethanol has been studied[295]. The reaction proceeds via the mechanism

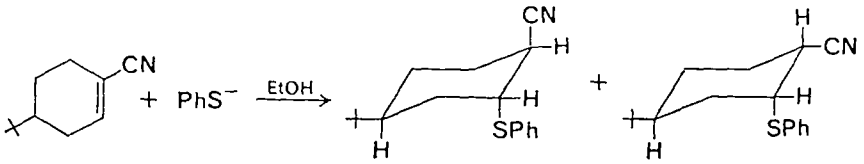






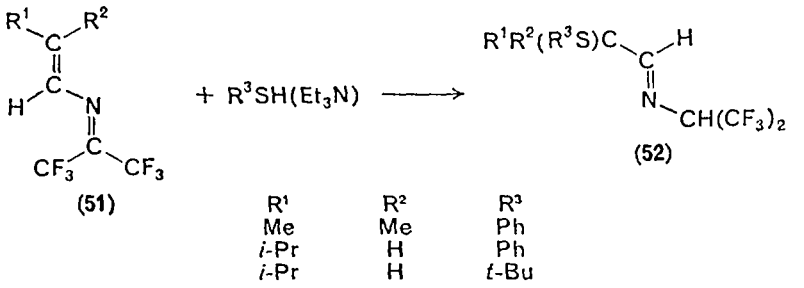
Attack by the neutral thiol could not be detected. The rate of attack of *ortho*-alkyl-substituted benzenethiolate anions upon the olefinic bond is sensitive to the bulk of the alkyl group. Two effects can be distinguished:
(1) inihibition of solvation of the thiolate anion, which increases its nucleophilicity (rate accelerating), and
(2) steric interference between the thiolate nucleophile and the olefin in the transition state (rate retarding). Net steric acceleration is observed in the nucleophilic addition to an activated double bond of *o*-*t*-butylbenzenethiolate which is an order of magnitude more reactive than the other alkylbenzenethiols studied. The implications of these results as regards hydrophobic bulk effects in enzymatic reactions involving mercaptide functions have been discussed[295].

The addition of the benzenethiolate anion to 4-*t*-butyl-1-cyanocyclohexene, containing formally a —C=C—C≡N bond system, occurs across the C=C bond. In ethanol two products are obtained both containing axial phenylthio groups, but in THF some equatorial SPh is also formed[296],



Addition reactions occur in C=C—C=N conjugated systems. Various products are formed in the reaction of thiols, in the presence of triethylamine, with N-[1,1,1,3,3,3-hexafluoroisopropylidene]-2,2-dialkylvinylamine (**51**)[297]. 1,4-Addition, forming products of orientation (**52**), occurs

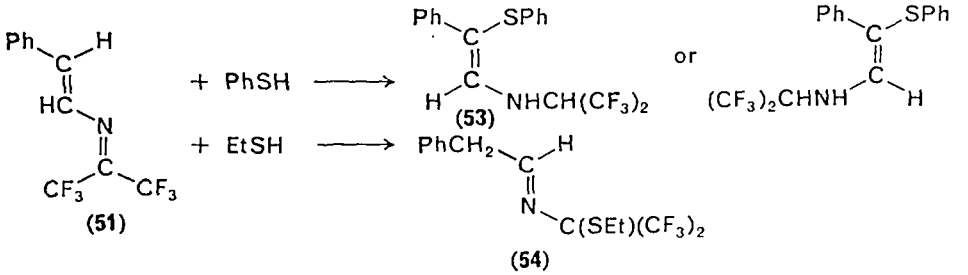
with *t*-butanethiol and benzenethiol:



(51) (52)

R^1	R^2	R^3
Me	Me	Ph
i-Pr	H	Ph
i-Pr	H	*t*-Bu

The reaction of benzenethiol with **51** when R^1 = Ph and R^2 = H gives an enamine **53**; a differently orientated 1,4-addition product **54** is obtained with ethanethiol.



(51) (53) (54)

Addition across a conjugated C=N—C=O system is the mechanism postulated for the reaction of the 2,2-dichlorovinylamine derivatives of $RCONHCH{=}CCl_2$ with BuSH in the presence of a small amount of alkaline, although the reaction appears superficially to be addition across a C=C bond:

$$MeCONHCH{=}CCl_2 + BuSH \longrightarrow MeCONHCH(SBu)CHCl_2$$

Initially a conjugated C=N—C=O system is formed and the thiol gives 1,4-addition[298]:

$$Cl_2C{=}CHNHCOMe \longrightarrow [CHCl_2CH{=}N{-}C(Me){=}O] \xrightarrow{BuSH/KOH} CHCl_2CH(SBu)N{=}C(Me)OH \longrightarrow CHCl_2CH(SBu)NHCOMe$$

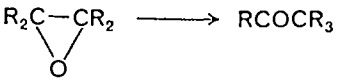
G. Reactions with Alkylene Oxides and Sulphides

Alkylene oxides undergo ring-opening reactions with a wide variety of substances:

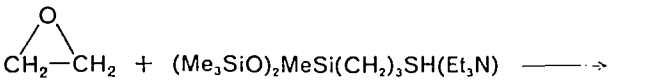
$$RCH{-}CH_2 \;(\text{O}) + HA \longrightarrow RCHOHCH_2A \text{ or } RCH(A)CH_2OH$$

Under basic or neutral conditions when R is an electron-donating group, the main product is that formed by attack at the least substituted carbon atom, namely $RCHOHCH_2A$. The A^- ion probably attacks before the C—O bond is completely broken. Thiols react to form hydroxythioethers.

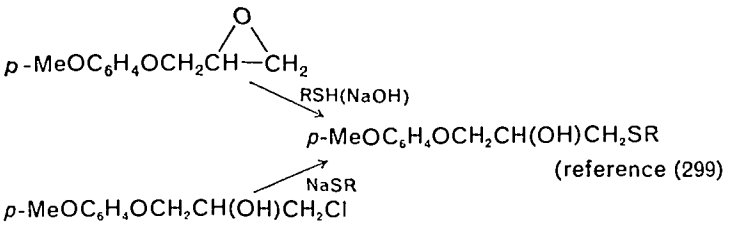
The alkylene oxides are thermally unstable and form the isomeric aldehydes or ketones:



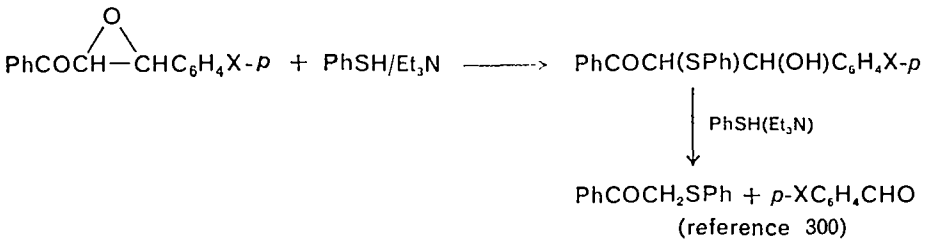
The products of the reactions of thiols or thiolate ions with alkylene oxides may correspond to addition across the C—O bond, or reactions of the isomeric aldehyde or ketone if the temperature is sufficiently high. Simple addition is observed in reactions such as



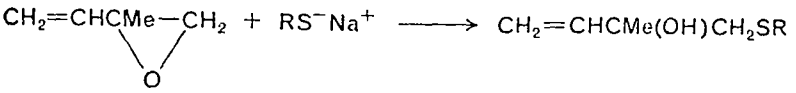
$(Me_3SiO)_2MeSi(CH_2)_3SCH_2CH_2OH$ (reference (10)



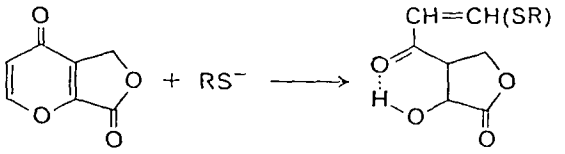
In other reactions both the C—O and C—C ring bonds are cleaved, and the intermediate product corresponding to addition across the C—O bond can be isolated:



The C—O ring is opened by thiolates, in preference to addition to the carbon—carbon double bond in the butylene derivative[301].

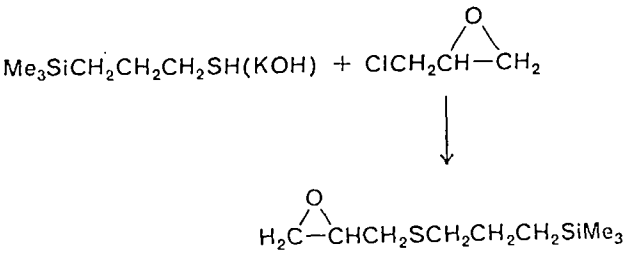


Large epoxide rings may also be opened by hydrogen sulphide[302,303]. The C—O bond is broken when dehydroisopatuline (**55**) reacts with thiolates[304], forming hydroxy-3-(*trans*-3-mercaptoacryloyl)but-2-en-4-olides (**56**).

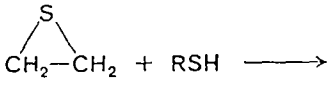


(**55**) (**56**)

In compounds containing both an epoxide ring and an aliphatic chloride, such as epichlorohydrin, the thiolate reacts preferentially with the aliphatic chlorine[305]

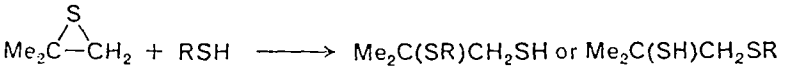


Various examples are known where an alkylene sulphide ring system is fractured by a thiol or thiolate, the reactions are essentially similar to those of the oxygen analogues. The thiol generated in the initial reaction may react further with the remaining cyclic sulphide[306].

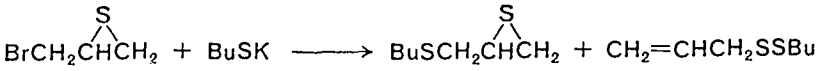


50-70%$RSCH_2CH_2SH$ and 20-30%$RSCH_2CH_2SCH_2CH_2SH$

Thiols can react with alkylene sulphides to form two products[263d],

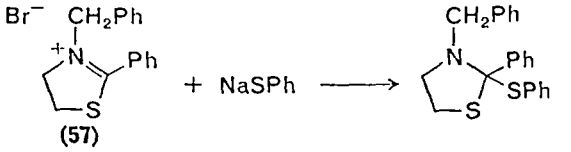


While thioepichlorhydrin reacts with potassium butanethiolate without ring fracture to form butylthioglycidyl sulphide, the products of the reaction with thioepibromohydrin include butylthioglycidyl sulphide and some of the disulphide, $CH_2{=}CHCH_2SSBu$, formed by fracture of the alkylene sulphide ring and subsequent dehydrobromination[307].



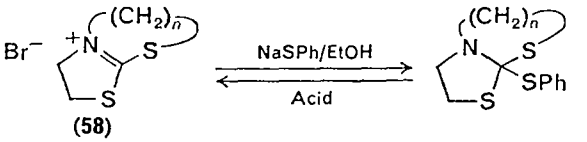
H. Reactions with Cyclic Compounds

Thiols will add across the C=N bond in cyclic systems, such as 3-benzyl-2-phenylthiazolinum bromide (**57**)[308],:



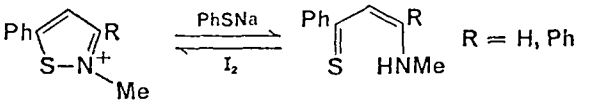
(**57**)

Similar addition occurs in the bicyclic compound (**58**):



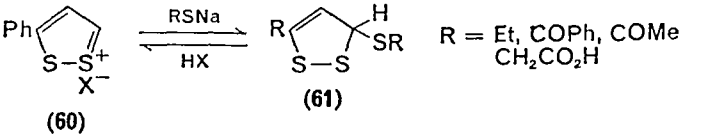
(**58**)

The benzenethiolate anion acts primarily as a reducing agent with 2-alkylisothiazolium salts (**59**); simple aliphatic thiols did not react[309].



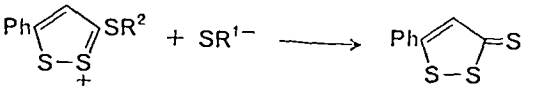
(**59**)

However, with 5-phenyl-1,2-dithiolium cation (**60**), unlike the isothiazolium cations, simple 5-adducts (**61**) were formed with a range of sulphur nucleophiles:



(**60**) (**61**)

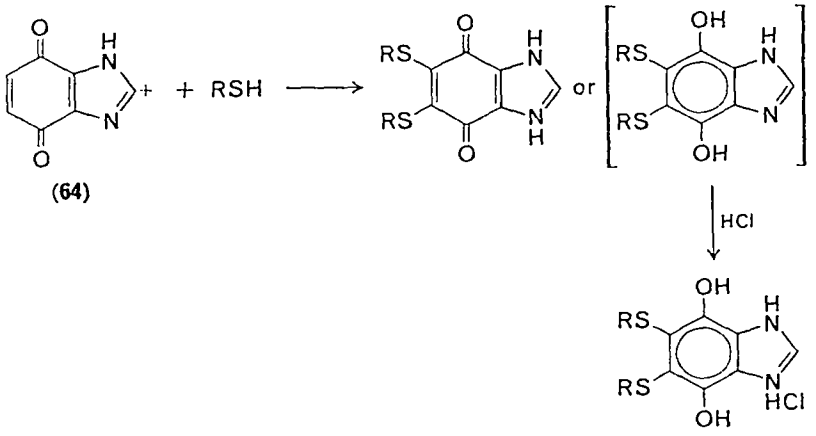
A similar 3-adduct was formed by only the ethanethiolate ion with 3,5-diphenyl-1,2-dithiolium salts. Other thiols, except ethanethiol, which did not react, convert to 3-alkylthio-5-phenyl-1,2-dithiolium cations (**62**) into 1,2-dithiole-3-thione (**63**).



(**62**) (**63**)

This is probably not a simple demethylation as no S-methylated nucleophiles were detected. The thione is also produced in the reaction of benzenethiolate anion with the 1,2-dithiolium cation with no S-alkyl substituent in the 3-position[309].

Two products, a disubstituted quinone or hydroquinone, are formed exclusively in the reaction of thiols with 4,7-benzimidazoledione (**64**) in methanol. The quinone is formed exclusively by aliphatic thiols and the hydroquinone when R=Ph, *p*-Tol, or $HOCH_2CH_2$[310].



(**64**)

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The Chemistry of the Thiol Group
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CHAPTER 17

Oxidation of thiols

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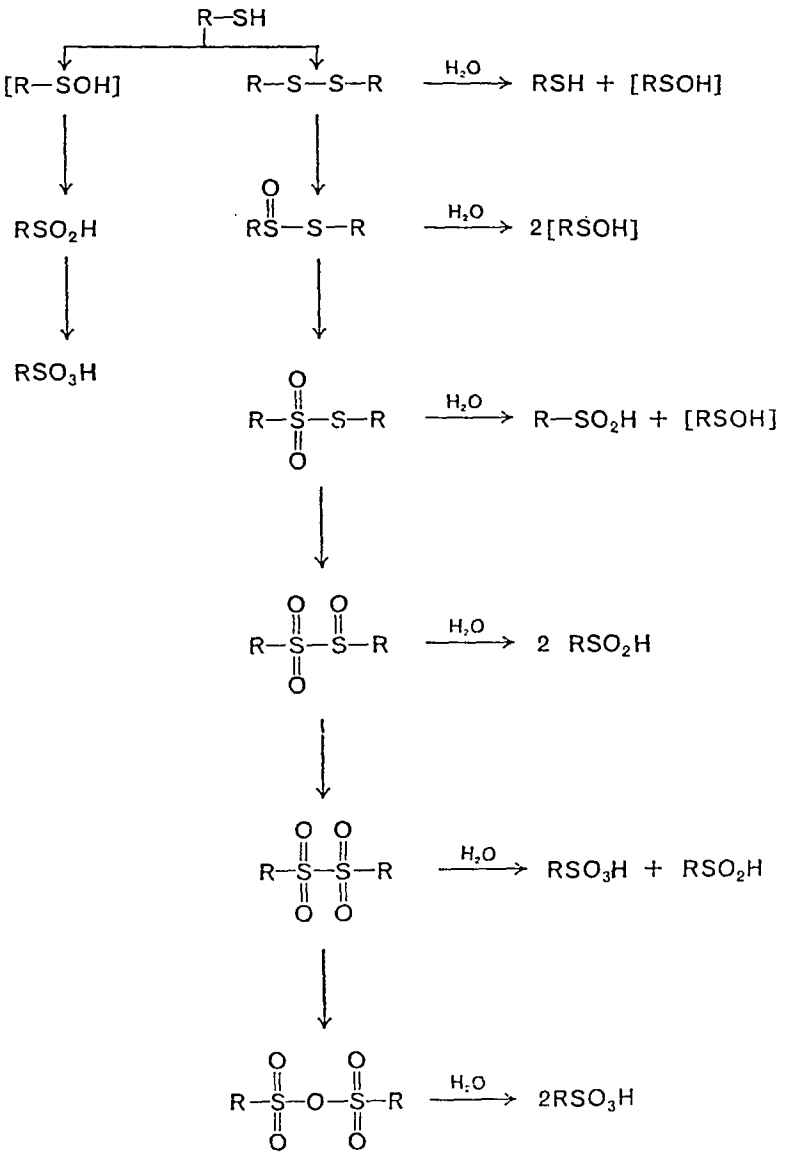
I. INTRODUCTION

Aliphatic and aromatic thiols are oxidized by a variety of reagents to disulphides and to higher oxidation products depending on the specific reaction conditions (Scheme 1).

The two oxidation chains are not as separate as indicated in the scheme since a number of interconversions are possible. They may be thought


R—SH
[R—SOH]
R—S—S—R
H₂O
RSH + [RSOH]
RSO₂H
RS—S—R
2[RSOH]
RSO₃H
R—S—S—R
R—SO₂H + [RSOH]
R—S—S—R
2 RSO₂H
R—S—S—R
RSO₃H + RSO₂H
R—S—O—S—R
2RSO₃H

SCHEME 1

to occur *via* the hydrolytic products which are shown on the right side of the Scheme. The sulphenic acid has been reported in brackets since its very high reactivity does not permit isolation except in very special cases (see section III.B).

Most of the reactions indicated in the scheme are reversible eventually through appropriate derivatives; however, true equilibria among pairs of the above-mentioned products are quite rare.

In this chapter we shall mainly deal with the oxidation of thiols to disulphides (equation 1).

$$2\,RSH \xrightarrow{[0]} RSSR + H_2O \qquad (1)$$

The subsequent stages of oxidation will be dealt with only in limited and specific cases. Attention has been mainly focused on the most commonly used chemical oxidizing agents.

Electrochemical and photochemical oxidations are also briefly discussed but for more comprehensive reviews on these subjects see the relevant chapters in this volume.

The literature, which is not comprehensively reviewed, has been covered up to the middle of 1972. References to some later published papers have been also made.

II. ELECTROCHEMICAL OXIDATION

Studies on the formally simple equilibrium (2) meet severe difficulties.

$$2\,RSH \rightleftharpoons RSSR + 2\,H^+ + 2\,e^- \qquad (2)$$

Polarographic studies (dropping mercury electrode, D.M.E.) have been limited by the chemical intervention of the mercury[1] whereas more recent work with noble metals electrodes has been hampered by absorption and/or passivation phenomena[2].

Much attention has been devoted to systems of biological interest and electrochemical methods for quantitative analysis of thiol and disulphide groups in simple organic compounds as well as in proteins have been reported[3-8].

The polarography of thiols is characterized by an anodic wave which often is well defined[1,9-11] although, as for instance in the case of cysteine, the shape of the polarogram depends strongly on pH and buffer[12]. Kolthoff and Barnum[12] showed that the anodic wave of cysteine is due to the formation of mercurous mercaptide (HgSR), i.e. to the oxidation of the electrode and not of the thiol. Complications may arise when the reaction product is insoluble in the medium and covers the electrode[12].

Thiols are also oxidized at a platinum electrode but at more positive potentials (see below).

The oxidation of the mercury electrode, the anodic potential of which is decreased by salt formation, appears to be quite general[1,9].

The values of $E_{\frac{1}{2}}$ do not change very much with the nature of the thiol at pH values high enough to ensure that all the thiols are in the anionic form[9] as shown in Table 1.

TABLE 1. Half-wave potential[a] and pK_a of mercaptans at pH 11·5 [9]

Thiol	$E_{\frac{1}{2}}$ (volts)[b]	pK_a
2-Mercaptoethylguanidine	−0·508	8·8
2-Mercaptopropylguanidine	−0·534	9·4
2-Mercaptoethylamine	−0·560	10·75
2-Mercaptoethanol	−0·537	9·6
Thioglycollic acid	−0·580	10·68
Cysteine	−0·580	10·28
Glutathione	−0·480	9·12

[a] At the dropping mercury electrode (D.M.E.).
[b] Referred to standard calomel electrode (S.C.E.).

The reduction of disulphides on D.M.E., the reverse of equation (2), appears to be a simpler reaction and in some cases a single cathodic wave was observed which behaves as required by a reversible process[9,10]; however, in many other cases evidence for irreversible processes was found[1,9,10]. Moreover, in some conditions cystine[1,13] as well as other disulphides[14] present a pre-wave.

Whereas the wave at higher potential appears to be due to a diffusion-controlled process, the pre-wave, as also shown by oscillographic polarography studies[13,14], depends on the absorption and reaction of the disulphide at the electrode.

The following equations were proposed to explain the process:

$$RSSR + Hg \longrightarrow RSSR \cdot Hg\ (ads.) \qquad (3)$$

$$RSSR \cdot Hg \longrightarrow (RS)_2Hg \qquad (4)$$

$$(RS)_2Hg + 2\,e^- + 2\,H^+ \longrightarrow 2\,RSH \cdot Hg \qquad (5)$$

$$2\,RSH \cdot Hg \longrightarrow 2\,RSH + Hg\ (desorb.) \qquad (6)$$

On platinum or gold electrodes, aqueous solutions of disulphides are not reduced and only the oxidation of thiols could be studied.

It was observed that cysteine as well as other thiols[2, 12, 15, 16] is oxidized, by a one-electron process, to cystine and the latter is further oxidized, probably, to cysteic acid. Strong absorption phenomena were observed.

In DMF solutions the redox reaction benzenethiol-diphenyl disulphide (equation 2, R = Ph) could be studied by cyclic voltammetry on an inert electrode from both directions. The results obtained indicate that the reactions are 'irreversible' and that the acid hydrogen of benzenethiol is converted to molecular hydrogen.

The authors[16] proposed that the following reactions occur at an inert electrode in solvents like DMF:

$$2\,RSH - 2\,e^- \longrightarrow RSSR + 2\,H^+ \qquad (2)$$

$$2\,RS^- - 2\,e^- \longrightarrow RSSR \qquad (7)$$

$$RSSR + 2\,e^- \longrightarrow 2\,RS^- \qquad (8)$$

$$2\,RSH + 2\,e^- \longrightarrow 2\,RS^- + H_2 \qquad (9)$$

It is noteworthy that diphenyl disulphide in the stated conditions[16] is not further oxidized, contrary to what is observed with cystine[2, 12, 15] in aqueous solutions.

However, at higher potentials the disulphide can be oxidized: in acetonitrile with sodium perchlorate as supporting electrolyte, diphenyl disulphide is oxidized to benzenesulphonic acid[17]. Possibly, in this case the perchlorate ion does intervene in a chemical reaction subsequent to the anodic process.

All schemes proposed for the oxidation of thiols to disulphides in a more or less explicit way imply the formation of thiyl radicals as intermediates.

The absence of any reaction of these radicals with the solvent suggests that the dimerization occurs at the electrode surface in a very fast process.

III. CHEMICAL OXIDATION

A. Oxidation by Peroxidic Compounds

The oxidation of thiols by hydrogen peroxide, alkyl hydroperoxides as well as peroxyacids is a well-known reaction in its qualitative aspects, but very little mechanistic study has been carried out[18, 19].

The initially formed product is in most cases the corresponding disulphide, which can be easily oxidized further by excess oxidant.

A particular example of overoxidation is the oxidative desulphurization of heteroaromatic thiols by hydrogen peroxide which may lead to the

formation of the corresponding hydrocarbon[20,21] or hydroxy derivative[22,23] depending upon the reaction conditions.

Because of the easy overoxidation, these reactions are scarcely used for preparative purposes. However, the oxidation of thiols to disulphides by peroxides attracted some interest in the patent literature connected with the general problem of hydrocarbon sweetening. More recently interest was revived by the suggested use of hydrogen peroxide as a selective oxidant and control of sulphide odours in sewage treatments and similar applications[24].

Aliphatic and aromatic thiols are easily oxidized to disulphides in aqueous or alcoholic solutions under both acid and alkaline conditions[25,26]. Higher molecular weight thiols are better oxidized as copper salts[27,28]. Particularly in the presence of aliphatic amines the oxidation is easily carried out also in hydrocarbon solvents[29].

In hydrocarbons, and more generally in aprotic solvents, lower molecular weight aliphatic peracids are quite effective in oxidizing thiols to disulphides.

A mechanistic study[18,30] of the oxidation of *o*-mercapto-phenylacetic acid in water in the pH range 2·44–7·17 by hydrogen peroxide showed that the rate of reaction (r) was independent of the thiol concentration, first order in H_2O_2 and inversely proportional to the square root of hydrogen ion concentration (equation 10).

$$r = k[H_2O_2]/[H^+]^{\frac{1}{2}} \tag{10}$$

The suggestion that the reaction was catalysed by traces of heavy metal ions was advanced on the basis of the acceleration observed on addition of ferrous ions and the depression of rates when EDTA in excess was added. In this case the kinetic expression also changed becoming first order in thiol concentration (equation 11).

$$r = k[H_2O_2]\,[RSH]/[H^+]^{\frac{1}{2}} \tag{11}$$

Further thorough studies would be necessary to define in detail the mechanism of these reactions. The limited evidence available is, however, consistent with the reasonable assumption that the reaction proceeds by a radical chain mechanism[31], probably initiated by heavy metal ions and involving thiyl radicals following a scheme similar to that proposed for the oxidation of mercaptans by molecular oxygen (see section IV).

The quite abundant literature on the oxidation of thiol groups in compounds of biological interest like glutathione, cysteine, etc., which has been recently reviewed[32], is also in line with the above conclusions.

B. Oxidation by Halogens

The products of the oxidation of thiols by halogens vary with the halogen and with the reaction medium.

In aqueous solvents chlorine and bromine react with thiols to give sulphonyl halides or sulphonic acids[33–36] (equations 12 and 13).

$$RSH+3\,X_2+2\,H_2O \longrightarrow RSO_2X+5\,HX \quad (12)$$

$$RSH+3\,X_2+3\,H_2O \longrightarrow RSO_3H+6\,HX \quad (13)$$

The same compounds are obtained starting with disulphides and there is evidence that at least in some conditions the latter are intermediates in the reaction (see below).

Under anhydrous conditions the following reactions have been observed[37] (equation 14–17):

$$RSH+X_2 \longrightarrow RSX+HX \quad (14)$$

$$RSX+X_2 \rightleftharpoons RSX_3 \quad (15)$$

$$RSX+RSH \longrightarrow RSSR+HX \quad (16)$$

$$RSSR+X_2 \rightleftharpoons 2\,RSX \quad (17)$$

Excess of halogen forms sulphur trihalides (equation 15). In the case of arylsulphur trichlorides the equilibrium is shifted to the left by increasing the temperature; with aliphatic derivatives containing a methylene group linked to sulphur the decomposition of the trichloride may lead to the formation of α-chlorinated sulphenyl chlorides[33] (equation 18).

$$RCH_2-SCl_3 \longrightarrow \underset{\displaystyle Cl}{\overset{\displaystyle |}{RCH-SCl}}+HCl \quad (18)$$

Careful hydrolysis of alkyl or aryl sulphur trihalides, in particular trichlorides, yields either sulphinic acid or sulphinyl halide[33,38,39]. The latter is obtained in good yields by reacting the trihalide with the stoichiometric amount of acetic acid[40] (equation 19).

$$RSX_3+CH_3COOH \longrightarrow RSOX+CH_3COX+HX \quad (19)$$

The reaction of thiols with halogens in aprotic not nucleophilic solvents can be, possibly, represented as in equation (20).

$$R-SH+X_2 \rightleftharpoons [R-\underset{\displaystyle X}{\overset{\displaystyle |}{\overset{+}{S}}}-H+X^-] \longrightarrow RSX+HX \quad (20)$$

Although there are no mechanistic studies in this area, schemes equivalent to equation (20) have been proposed for the halogenolysis of sulphides and other bivalent sulphur compounds[41–47]. The reaction goes to completion to the right with chlorine and bromine, but takes a more complex course with iodine. With fluorine the reaction yields higher oxidation products with extensive fluorination at the hydrocarbon moiety[48].

Sulphenyl halides are very prone to nucleophilic attack[33, 35, 49] (equation 21) and in particular excess mercaptan reacts with them to give the corresponding disulphide (equation 16).

$$RSX + NuH \longrightarrow RSNu + HX \qquad (21)$$

$$NuH = R_2NH, HSCN, ROH, RSH, \text{etc.}$$

The hydrolysis of sulphenyl halides is believed to form sulphenic acids (equation 22). These compounds, however, have never been isolated in this reaction; rather thiolsulphinate esters are formed by fast reaction of sulphenic acids with sulphenyl halides[50–53] (equation 23).

Disproportionation of sulphenic acids has also been suggested as a possible route for the formation of these compounds[49] (equation 24). The hydrolysis of sulphenyl halides under not carefully controlled conditions and particularly in concentrated solutions lead to disulphides and thiolsulphonates[54–59] because of the easy disproportionation of thiolsulphinates (equation 25).

$$RSX + H_2O \longrightarrow [RSOH] + HX \qquad (22)$$

$$[RSOH] + RSX \longrightarrow RS{-}S{-}R + HX \qquad (23)$$
$$\qquad\qquad\qquad\qquad\qquad\quad \| \quad O$$

$$2\,[RSOH] \longrightarrow R{-}S{-}S{-}R + H_2O \qquad (24)$$
$$\qquad\qquad\qquad\quad \| \quad O$$

$$2\,RS{-}S{-}R \longrightarrow R{-}S{-}S{-}R + RS{-}SO_2{-}R \qquad (25)$$
$$\quad \| \quad O$$

Some anthraquinone-sulphenic and -disulphenic acids and 1-methyluracil-4-sulphenic acid have been prepared by different routes[60–63]. In these compounds intramolecular hydrogen-bonded and tautomeric structures are suggested to stabilize the sulphenic derivatives[64–66]. Chemical and n.m.r. evidence for the existence of an aliphatic sulphenic acid in the

thermal decomposition of di-*t*-butyl sulphoxide has been reported[67] (equation 26).

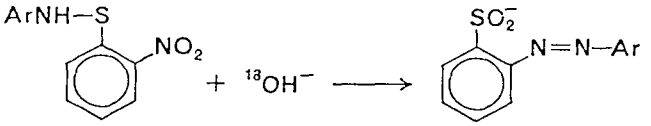
$$(CH_3)_3C-\overset{\overset{O}{\|}}{S}-C(CH_3)_3 \longrightarrow (CH_3)_3CSOH+(CH_3)_2=CH_2 \qquad (26)$$

Sulphenyl halides have been considered for a long time as a source of sulphenyl cations[49] (equation 27). However, unambiguous evidence on free sulphenyl cations is scarce and somewhat contradictory.

$$RSX \rightleftharpoons RS^+ + X^- \qquad (27)$$

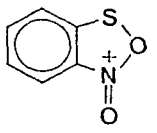
The substitutions at sulphenyl sulphur so far studied in detail occur *via* bimolecular mechanism[54] except, possibly, the very special case of 2,4,6-trimethoxybenzenethiol arylsulphonate which was reported to undergo unimolecular solvolysis[68].

On the other hand, evidence on the formation of a cationic species, thought to be the sulphenyl cation, by dissolving 2,4-dinitrobenzene sulphenyl chloride in concentrated sulphuric acid has been obtained[69-70]. However, the nature of the cation is not certain[71]. Moreover, the substrate chosen is, perhaps, not quite typical. Strong interaction between the *o*-nitro group and the sulphenyl sulphur are in fact shown by X-ray analysis of methyl *o*-nitrobenzenesulphenate ester[72] and also by the oxygen transfer from nitrogen to sulphur observed in the alkaline rearrangement of 2-nitrobenzenesulphenyl anilides[73] (equation 28).



(28)

This suggests that in the special case of *o*-nitrobenzene derivatives and similar species the cation formed might have the cyclic structure (**1**).



(1)

Finally, it has been reported that sulphur dichloride and trichloromethanesulphenyl chloride give 1 : 1 and 2 : 1 complexes with Lewis acids ($SbCl_5$, $AlCl_3$, $FeCl_3$) with a salt-like behaviour[74,75]. The instability of the complexes made a full characterization unfeasible.

Relevant to this point is the recent finding[76,77] that methane and ethane sulphenyl chloride form by addition of either BF_3 or SbF_5 in liquid SO_2 a dimeric cationic species (**2**) described as follows (equation 29):

$$2RSCl + BF_3 \longrightarrow R-S-\overset{+}{S}-R + BF_3Cl^- \qquad (29)$$
$$\qquad\qquad\qquad\qquad\quad Cl$$
$$\qquad\qquad\qquad\qquad\quad (2)$$

The same species seems to be formed in fluorosulphonic acid and 100% sulphuric acid as well[77]. Preliminary results also indicate that reaction 29 occurs with aromatic sulphenyl chlorides. The tendency of sulphur compounds to give species like (**2**) seems quite general: for example, disulphide and sulphenyl chloride in FSO_3H or 100% H_2SO_4 and in SO_2 with BF_3 or SbF_5 give a species analogous to (**2**)[77] (equation 30).

$$R-S-S-R + RSCl \xrightarrow{+BF_3} R-S-\overset{+}{S}-R + BF_3Cl^- \qquad (30)$$
$$\qquad\qquad\qquad\qquad\qquad\quad SR$$
$$\qquad\qquad\qquad\qquad\qquad\quad (3)$$

Furthermore, ions similar to (**3**) are postulated as intermediates in the interchange reaction of disulphides and sulphenyl chlorides[78,79], and intermediates like (**2**) should be involved in the reaction of disulphide with halogens (equation 17) which has to be considered an equilibrium reaction.

$$RSSR + X_2 \rightleftharpoons 2\,RSX \qquad (17)$$

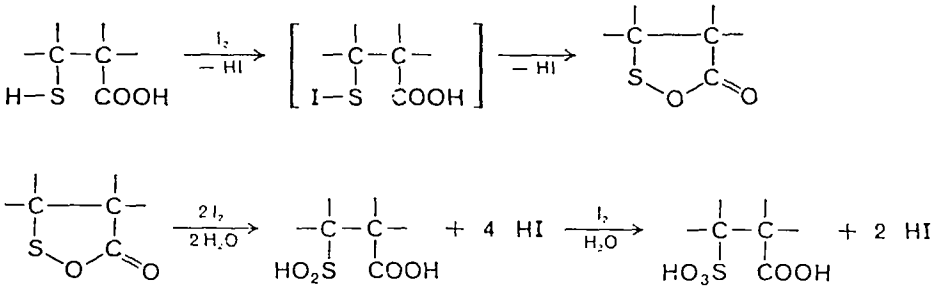
Equilibrium (17) is completely shifted to the right for X = Cl and largely to the left with X = I. The case of bromine is, as usually, intermediate. As a matter of fact very few sulphenyl iodides are known[80,81]. Apparently only sterically hindered derivatives are able to exist and also their stability, which may be reasonably great in dilute solution, is very low in concentrated solution or as pure material.

Since equilibrium (17) is shifted almost completely to the left in the case of X = I whereas reaction (14) goes to completion even with iodine, a method to titrate thiols based on the reaction in equation (31) has been

$$2\,RSH + I_2 \longrightarrow RSSR + 2\,HI \qquad (31)$$

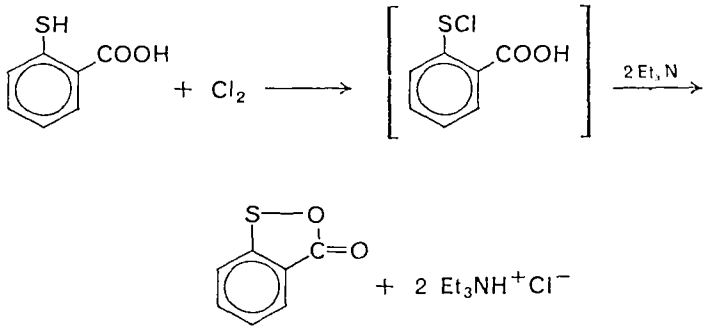
widely used. However, care has to be taken to use the appropriate conditions of pH and dilution to avoid overoxidation of the disulphide which may be a quite serious cause of error[82]. Thiols containing a β-carboxyl group are particularly susceptible to consume more than the iodine

required by equation (31). It was suggested that the carboxyl group intramolecularly attacks the initially formed sulphenyl iodide to form a sulphenic anhydride which may undergo further oxidation at sulphur (Scheme 2)[82,83]. This mechanism seems likely also in view of the recent



SCHEME 2

evidence of trapping *o*-sulphenobenzoic acid anhydride by reaction of *o*-mercaptobenzoic acid with chlorine in the presence of triethyl amine[84] (equation 32).



(32)

C. Oxidation by Dimethyl Sulphoxide and Other Sulphoxides

The oxidizing power of dimethyl sulphoxide (DMSO) as well as of other sulphoxides is well known and has been recently reviewed[85].

Yiannios and Karabinos[86] reported that thiols were selectively oxidized by DMSO to the corresponding disulphides in high yield with the concomitant reduction of DMSO to dimethyl sulphide (equation 33). Further

$$2\,RSH + (CH_3)_2SO \longrightarrow RSSR + (CH_3)_2S + H_2O \qquad (33)$$

studies, mainly by Wallace and coworkers[87-91] confirmed these early results. They studied the reaction of several thiols with DMSO and TMSO

(tetramethylene sulphoxide) in large excess and in the absence of solvent. In the stated conditions second-order kinetics[89] and strong catalysis by added amines (Table 2) were observed[90].

TABLE 2. Effect of amines on the oxidation rate of 1-dodecanethiol by TMSO at 100°C[90]

Amine	pK_a [a]	k, s^{-1}	Rel. rate
—	—	$7{\cdot}58 \times 10^{-6}$	1
N,N-Dimethylaniline	5·1	$1{\cdot}15 \times 10^{-5}$	1·5
2,6-Dimethylpyridine	6·6	$1{\cdot}64 \times 10^{-5}$	2·2
1-*n*-Dodecylamine	10·6	$6{\cdot}42 \times 10^{-4}$	84·4
Tri-*n*-butylamine	11·4	$2{\cdot}04 \times 10^{-3}$	269

[a] Reference 92.

These authors showed[89] that the rate of oxidation depends on the acidity of thiol and a correlation between the estimated pK_a of them and the energy of activation was suggested (Table 3).

The oxidation rates depend also on the structure of sulphoxide[89] (Table 4). As shown in Figure 1, a linear correlation of $\log k_{obs}$ with the recently evaluated pK_a in water of sulphoxides[93,94] does hold.

TABLE 3. Effect of thiol acidity on the oxidation with TMSO at 100°C[89]

Thiol	pK_a	k, s^{-1}	Rel. rate	E_a, kcal/mole
1-Dodecanethiol	13·5	$7{\cdot}8 \times 10^{-6}$	1	19·4
α-Toluenethiol	10·5	$1{\cdot}9 \times 10^{-4}$	25	13·7
o-Toluenethiol	8	$6{\cdot}6 \times 10^{-3}$	850	6·2
Benzenethiol	7	$4{\cdot}0 \times 10^{-2}$	5186	4·9

TABLE 4. Effect of sulphoxide basicity in the oxidation of α-toluenethiol at 100°C[89]

Sulphoxide	pK_a	$\log k$ [a]	Rel. rate
Diphenyl sulphoxide	−2·54[b]	−5·91	1
Phenyl methyl sulphoxide	−2·27[b]	−5·11	6·22
DMSO	−1·80[b]	−4·40	33·3
TMSO	−1·31[c]	−3·71	159

[a] k, sec^{-1}.
[b] Reference 93.
[c] Reference 94.

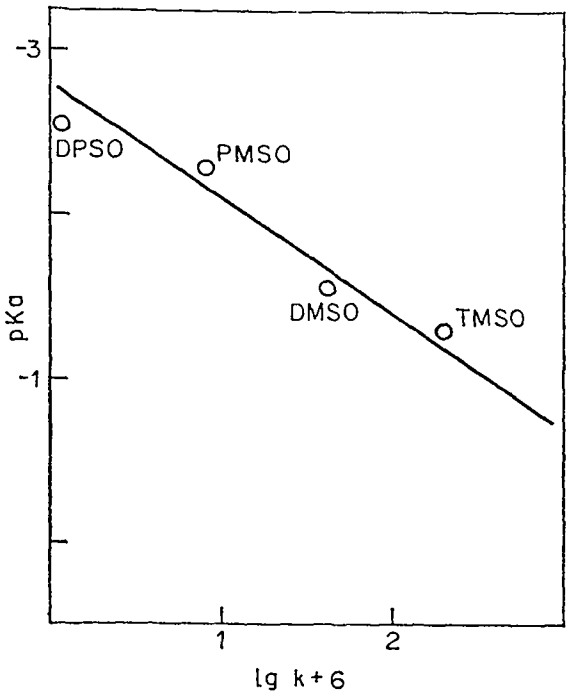
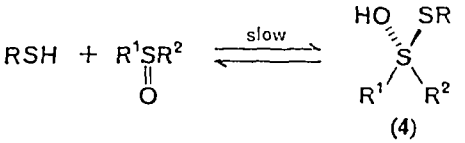


FIGURE 1. Correlation between the oxidation rates at 100°C of α-toluenethiol and the pK_a of the sulphoxides. pK_a values taken from the literature: diphenyl sulphoxide (DPSO), phenyl methyl sulphoxide (PMSO) and dimethyl sulphoxide (DMSO), reference 93; tetramethylene sulphoxide (TMSO), reference 94.

The authors[87-91] proposed that the slow step of the reaction is the formation of the adduct (**4**) (equation 34) followed by a fast reaction with a second molecule of thiol (equation 35). Similar mechanisms have been



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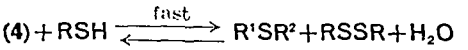
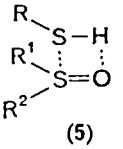


(35)

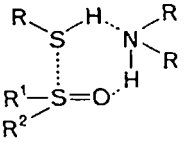
proposed for other sulphoxide-promoted oxidations[95-99] and the recent isolation of stable tetracoordinate sulphur compounds[100-103] makes this hypothesis quite likely.

However, the detailed mechanism could be more complicated as it is, in part, suggested by the phenomena of base and acid catalysis observed[90].

It may well be, as suggested[90], that four-centre (**5**) and five-centre (**6**) transition states are involved for the uncatalysed and amine-catalysed



(5)



(6)

reactions, respectively. Alternatively an acid–base interaction of the reagents (equation 36) to give an ion pair, followed by collapse of the latter to the adduct (**4**) (equation 37) could be postulated. This

$$RSH + R_2SO \rightleftharpoons RS^- + R_2\overset{+}{S}OH \qquad (36)$$

$$RS^- + R_2\overset{+}{S}OH \rightleftharpoons RS-\underset{\displaystyle R}{\overset{\displaystyle R}{\underset{|}{\overset{|}{S}}}}-OH \qquad (37)$$

(4)

resembles the mechanisms proposed for some nucleophilic substitutions by thiols of 2-chlorobenzimidazole[104] and chloroquinolines[105].

The reaction of (**4**) with the thiol to give the products (equation 35) may also be more complicated than depicted[106]. However, any hypothesis would be highly speculative in the absence of more detailed kinetic studies.

The oxidation of thiols with sulphoxides presents several attractive features like the simplicity of the reaction, the high yield and the selectivity of disulphide formation. It has to be noticed, however, that tertiary thiols do not react with sulphoxides or they give very little disulphide even in the presence of amine catalysts. Reaction temperatures higher than 100°C give rise to extensive decomposition[91].

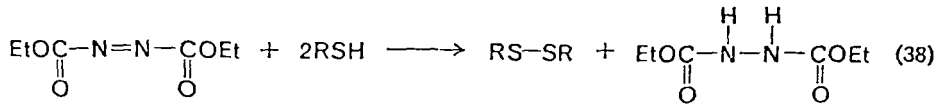
An interesting synthetic application of this reaction is the recovery of optically active sulphoxides from racemates when an optically active thiol is oxidized with more than the stoichiometric amount of the sulphoxide[107].

D. Oxidation by Other Organic Chemicals

Several organic compounds may oxidize thiols to disulphides or to products of further oxidation in a variety of experimental conditions. We shall briefly deal in this section with some of the more characteristic cases.

I. Diethyl azodicarboxylate

Diethyl azodicarboxylate oxidizes thiols to disulphides, in the dark at room temperature, with concomitant formation of diethyl hydrazodicarboxylate[108, 109] (equation 38).



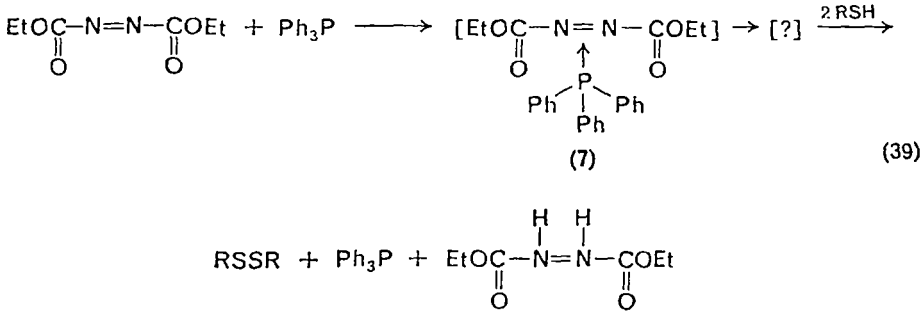
The reaction may also be carried out in refluxing anhydrous solvents. In Table 5 the results obtained for the oxidation of several thiols are

TABLE 5. Oxidation of thiols to disulphides with diethyl azodicarboxylate [109]

Thiol	Solvent	Temperature[a]	Time, h	Yield, %
Ethanethiol	None	R	48	90
2-Propanethiol	None	R	72	70
2-Propene-1-thiol	None	R	0·5	90
1-*n*-Dodecanethiol	Benzene	B	5	95
t-Dodecanethiol	Benzene	B	10	70
Benzenethiol	None	R	24	90
4-Nitrobenzenethiol	Ethanol	B	8	—
2-Aminobenzenethiol	Benzene	B	4	67
2-Naphthalenethiol	Chloroform	B	5	87
2-Mercaptobenzothiazole	Benzene	B	0·5	95

[a] R = room temperature; B = refluxing solvent.

reported. It was reported[110] that triphenylphosphine catalyses the reaction. Formation of a charge transfer complex (7) with the azo derivative as formulated below (equation 39) was suggested. It seems likely that radicals or radical ions intervene in the reaction.

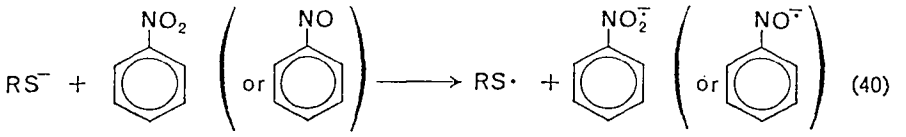


(39)

2. Nitroso and nitro-compounds

In basic medium thiols are oxidized to disulphides by nitrobenzene or nitrosobenzene[111-112] which are reduced mainly to azoxy and azobenzene.

E.s.r. experiments indicate the presence of stable radical anions derived by electron transfer from the thiol anion to the nitro or nitroso group (equation 40).



(40)

Other species may oxidize thiols to disulphides following a similar route. Among them azodicarbonamide[111], maleic anhydride[111] and 4-nitropyridine N-oxide[112] seem to be the most reactive ones.

3. Iodosobenzene

In refluxing dioxane, iodosobenzene and benzenethiol give rise to the formation of diphenyl disulphide in fairly good yield (76%)[113] (equation 41).

$$C_6H_5IO + 2\,PhSH \longrightarrow C_6H_5I + PhSSPh + H_2O \qquad (41)$$

Although extensive studies have not been made on this reaction, it may represent a general and convenient method for thiol oxidation.

4. Trimethylsulphoxonium iodide

When benenethiol reacts with trimethylsulphoxonium iodide in dimethylformamide at 100°C, phenyl methyl sulphide, diphenyl disulphide and dimethyl sulphide are formed[114].

The reaction seems to be quite complex. Formation of a labile adduct between the oxonium salt and the thiol is suggested (equation 42).

$$(CH_3)_3\overset{\overset{O}{\|}}{S}{}^+I^- + PhSH \longrightarrow [(CH_3)_3\overset{\overset{O}{\|}}{S}{}^+PhS^-] + HI \qquad (42)$$

Decomposition of this intermediate would lead to dimethyl sulphoxide and phenyl methyl sulphide (equation 43). Diphenyl disulphide should

$$[(CH_3)_3\overset{\overset{O}{\|}}{S}{}^+PhS^-] \longrightarrow CH_3\overset{\overset{O}{\|}}{S}CH_3 + PhSCH_3 \qquad (43)$$

arise either from the reaction of the thiol with dimethyl sulphoxide (see section III.C) or from oxidation by iodine (see section III.B) generated in

the reduction of dimethyl sulphoxide by hydrogen iodide[93] (equations 44 and 45).

$$(CH_3)_2SO + 2\,HI \longrightarrow (CH_3)_2S + H_2O + I_2 \quad (44)$$

$$2\,PhSH + I_2 \longrightarrow PhSSPh + 2\,HI \quad (45)$$

5. Halogen transfer agents

Several 'positive halogen' compounds, ZHal, like N-halo-succinimide N-chlorobenzotriazole, dichloroiodobenzene, etc., react with thiols to give sulphenyl halides or disulphides depending on the relative ratios of the reagents[37] (equations 46 and 47).

$$ZHal + RSH \longrightarrow ZH + RSHal \quad (46)$$

$$ZHal + 2\,RSH \longrightarrow ZH + HHal + RSSR \quad (47)$$

Among these compounds, 2,4,4,6-tetrabromo-cyclohexa-2,5-dienone has been reported to be particularly selective[115].

E. Oxidation by Metal Ions and Oxides

Ions and oxides of transition metals which may exist in different valence states have been shown to oxidize thiols. Most of the studies so far available on this topic deal with the oxidation by ferric ions; careful investigations with many other metals have been carried out as well. The catalytic effect of these metal ions on the auto-oxidation of thiols has been pointed out (see section IV). The intervention of metals in a number of redox enzymes in which the metal is bound to a thiol group at the active site of the enzyme has been also suggested.

1. Ferric ion

Complexes of Fe^{3+} as $Fe(CN)_6^{3-}$ and ferric octanoate, $[Fe(Oct)_3]$ quantitatively oxidize thiols to disulphides in the absence of oxygen (equation 48). This reaction has been largely employed in the synthesis of synthetic rubber[116].

$$2\,RSH + 2\,Fe^{3+} \longrightarrow RSSR + 2\,Fe^{2+} + 2\,H^+ \quad (48)$$

Oxidation of thiols by $Fe(Oct)_3$ has been carried out in acetone and xylene[117]. Kinetic studies indicate that the reaction follows a second-order rate law. It is suggested that disulphide arises from dimerization of thiyl radicals which are formed in the rate-determining reaction of thiol with $Fe(Oct)_3$ (equations 49, 50).

$$2\,RSH + 2\,Fe(Oct)_3 \longrightarrow 2\,RS\cdot + 2\,Fe(Oct)_2 + 2\,OctH \quad (49)$$

$$2\,RS\cdot \longrightarrow RSSR \quad (50)$$

The intermediacy of such radicals is exemplified by the reaction in the presence of alkenes. In this case formation of sulphide, probably arising from a chain reaction, is observed (equations 49, 51, 52). At constant

$$RSH + Fe(Oct)_3 \longrightarrow RS\cdot + Fe(Oct)_2 + OctH \quad (49)$$

$$RS\cdot + R^1CH{=}CH_2 \longrightarrow RSCH_2{-}\dot{C}HR^1 \quad (51)$$

$$RSCH_2{-}\dot{C}HR^1 + RSH \longrightarrow RSCH_2CH_2R^1 + RS\cdot \quad (52)$$

alkene and mercaptan concentrations the ratio of disulphide to sulphide formation decreases with decreasing metal ion concentration (Table 6).

TABLE 6. Effect of ferric octoanate concentration on the ratio disulphide : sulphide in the oxidation of 1-*n*-dodecanethiol[a] in the presence of 1-*n*-dodecene[117]

1-*n*-Dodecene / 1-*n*-Dodecanethiol	1-*n*-Dodecanethiol / $Fe(Oct)_3$	Dodecyl disulphide / Dodecyl sulphide
10	1	21
10	4	5·4
10	10	1·4
10	20	0·07

[a] 1-*n*-Dodecanethiol 0·2 M in xylene at 35°C.

It is suggested that this is related to the increased rate of formation and consequently the greater steady concentration of thiyl radicals at higher metal concentration which makes the dimerization reaction faster than the sequence of reactions leading to the sulphide.

Oxidation of thiols by $Fe(CN)_6^{3-}$ in alkaline and acid medium has been studied[118-122]. In both cases disulphide is the oxidation product; however, the reaction mechanism markedly differs. In the pH range 7–10·8 the rate of oxidation of *n*-octanethiol is pH dependent and exhibits a first-order dependence on $Fe(CN)_6^{3-}$, thiol and OH^-[118].

Cyanide ion depresses the rate but at higher cyanide concentration the rate of oxidation is practically independent from it.

Owing to the observed order in OH^- and since the rate increases with the pH, thiol anion is believed to be the reactive species.

Different mechanisms are proposed for this reaction depending upon the presence of added cyanide. A mechanism similar to that outlined in equations (49) and (50) is suggested for the oxidation in the presence of added cyanide, i.e. slow formation of thiyl radicals and fast formation of disulphide *via* dimerization of the radicals or further oxidation of them to

a cationic species (equation 53) which is neutralized by thiolate anion (equation 54).

$$RS\cdot + Fe(CN)_6^{3-} \longrightarrow RS^+ + Fe(CN)_6^{4-} \quad (53)$$

$$RS^+ + RS^- \longrightarrow RSSR \quad (54)$$

In the absence of added cyanide ion, a reversible substitution of a CN^- by an RS^- residue in the ferric complex has been postulated to be rate determining (equation 55).

Rapid decomposition of the sulphur-containing complex generates thiyl radical and pentacoordinate Fe^{2+} complex which reacts with the CN^- to give the ferrocyanide complex (equations 56 and 57).

Disulphide is then formed according to equation (50) or (53) and (54). Kinetic studies[119-122] of acid oxidation of thiols by ferricyanide, suggest

$$Fe(CN)_6^{3-} + RS^- \underset{\longleftarrow}{\overset{\text{slow}}{\longrightarrow}} [Fe(CN)_5RS]^{3-} + CN^- \quad (55)$$

$$[Fe(CN)_5RS]^{3-} \xrightarrow{\text{fast}} Fe(CN)_5^{3-} + RS\cdot \quad (56)$$

$$Fe(CN)_5^{3-} + CN^- \xrightarrow{\text{fast}} Fe(CN)_6^{4-} \quad (57)$$

that the reaction mechanism is quite complex. The rate law shows a second-order dependence on the $Fe(CN)_6^{3-}$ concentration and first on that of the thiol[119-121]. Inhibition by small amounts and catalysis by higher concentration of $Fe(CN)_6^{4-}$ is observed; the rate of oxidation is also dependent on the initial ferricyanide concentration and on the pH.

Several mechanisms[119-122] have been proposed for the acid oxidation of thiols by ferricyanide ions but since they are not fully established, we will not report them in detail.

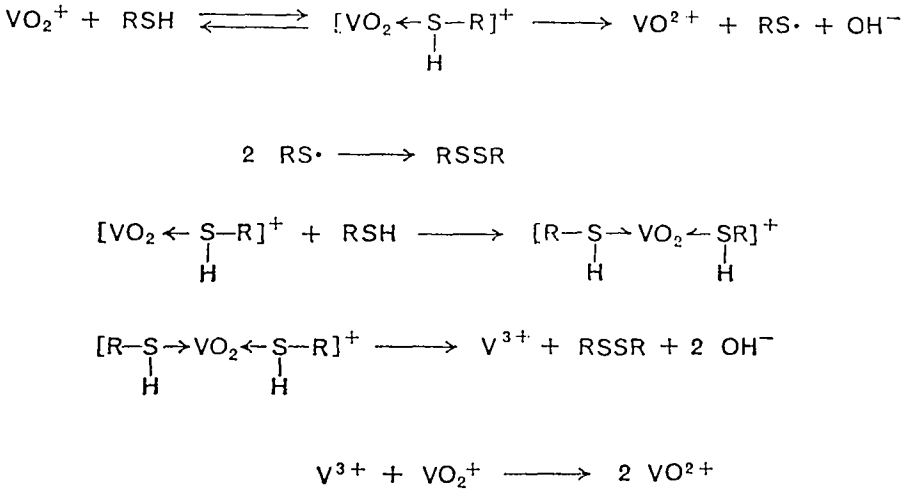
2. Other metal ions

Like ferric ions, other heavy metal ions in their higher oxidation states react with thiols to give the corresponding disulphides. Quite frequently complexation of thiols with the metal occurs followed by a one-electron transfer to give thiyl radicals which dimerize to disulphide. This is the case, for example, with Ce^{4+}, Co^{3+} and V^{5+} ions in acid solution[123-125].

The homolitic nature of such reactions was confirmed by an e.s.r. study of the Ce^{4+} oxidation of several thiols which showed the presence of thiyl radicals among other radical species. Thus primary thiols give a 1 : 2 : 1 triplet signal, secondary a 1 : 1 doublet and tertiary a single absorption line[126].

The nature and the stability of the complex formed depends upon the metal[123-125]. In the V^{5+} oxidation for instance, kinetic evidence and

formation of more than one mole of base suggest the intervention of two different complexes both leading to the disulphide but following separate paths[125] (Scheme 3).



SCHEME 3

The importance of the nature and stability of the complexes between metal ions and thiols is clearly indicated in the case of the oxidation with Mo^{5+} and Mo^{6+} of thioglycollic acid, cysteine and glutathione[127,128].

A detailed study shows that the kinetic equation may change with pH and with metal concentration as well as with the particular thiol. Indeed the mechanism of the reaction is not unique although some of the differences of the reaction features could be explained on the basis of different stability and nature of the complexes formed in the early stages of the reaction.

Other reaction paths are available at least in some special cases. For instance in the oxidation with manganic acetylacetonate[129], disulphide is believed to arise from reaction of a sulphenium ion with the thiol (equation 58) which implies that further oxidation of thiyl radicals to

$$RSH + RS^{+} \longrightarrow RSSR + H^{+} \qquad (58)$$

sulphenium ion is faster than dimerization. The intervention of thiyl radicals has been ruled out by the absence of addition products when the reaction is carried out in the presence of alkenes.

The difference in mechanism between the Fe^{3+} and the Mn^{3+} oxidation of thiols is probably due to the powerful ability of the latter in oxidizing the radical first formed[130].

Oxidation by cupric complexes in non-polar media is a more complex reaction, as shown by the formation of sulphide together with disulphide[117]. The former may arise from cupric thiolate (equation 59) or *via* desulphurization of the disulphide by copper ions.

$$Cu(SR)_2 \longrightarrow CuS + RSR \tag{59}$$

Lead tetraacetate is also able to oxidize thiols at low temperature to disulphides[131–134].

High yield of disulphide is obtained when one mole of lead tetraacetate is allowed to react with two moles of thiol[132] (equation 60).

$$2\,RSH + Pb(OAc)_4 \longrightarrow RSSR + Pb(OAc)_2 + 2\,AcOH \tag{60}$$

When the lead salt–thiol ratio is 0·25, lead mercaptide is formed together with disulphide and acetic acid[134] (equation 61).

$$4\,RSH + Pb(OAc)_4 \longrightarrow RSSR + Pb(SR)_2 + 4\,AcOH \tag{61}$$

Higher temperature and the presence of alcohols would cause further oxidation of the disulphide and formation of sulphinic esters[133].

3. Metal oxides

A large variety of metal oxides like MnO_2, PbO_2, CrO_3, Fe_2O_3, Co_2O_3, CuO[134–136] oxidize thiols to disulphides at low temperature in chloroform or xylene solution.

In the oxidation by lead dioxide, formation of an intermediate by addition of two molecules of thiol to the metal oxide has been suggested[134]. It may give the disulphide by decomposition (equation 62), or generate an intermediate lead tetramercaptide which decomposes giving disulphide (equations 63 and 64).

$$2\,RSH + PbO_2 \longrightarrow \left[\begin{array}{c} RS \\ RS \end{array}\!\!>\!Pb\!<\!\begin{array}{c} OH \\ OH \end{array}\right] \longrightarrow Pb(OH)_2 + RSSR \tag{62}$$

$$[(RS)_2\,Pb(OH)_2] + RSH \longrightarrow [Pb(SR)_4] + 2\,H_2O \tag{63}$$

$$[Pb(SR)_4] \longrightarrow RSSR + Pb(SR)_2 \tag{64}$$

Manganese dioxide is the most effective oxidizing agent among the above-mentioned oxides.

The nature of such reactions has been checked for MnO_2, Fe_2O_3, Co_2O_3, by carrying out the oxidation in the presence of an alkene. Formation of large amounts of thiol addition products to the double bond suggests intermediacy of thiyl radicals.

It was also observed that the rate of stirring affects the rate of the oxidation which suggests that the reaction is a diffusion-controlled process. Under these circumstances the greater ability of MnO_2 in oxidizing thiols is probably due to surface effects and more favourable absorption of thiols[136].

IV. OXIDATION BY MOLECULAR OXYGEN

The easy oxidation of thiols on exposure to air is well known as is the sensitivity of this reaction to catalysts[137] like metal ions, u.v. light and other initiators of radical reactions. It is also known that autooxidation of thiols is accelerated by bases.

The interest in this reaction from the industrial (sweetening of crude petroleum) and biological points of view notwithstanding, the mechanism of the autooxidation of thiols is not as yet satisfactorily understood.

We shall attempt in this section to review critically the more significant contributions, with the interpretations of the phenomena as offered by the authors.

A. Catalysis by Strong Bases

Cullis and coworkers[138] studied the oxidation of ethanethiol in aqueous alkaline solution under constant pressure of oxygen. They observed low reproducibility of the oxygen uptake rates even when careful precautions were taken to avoid the presence of adventitious impurities. Under their conditions (EtSH 0·3–0·5 M; NaOH 0·5–2 M; the base always in excess) the stoichiometry of the reaction was found, in agreement with other authors[137, 139, 140], to be:

$$4\,RSH + O_2 \longrightarrow 2\,RSSR + 2\,H_2O \qquad (65)$$

Dependence on the first power of both the oxygen pressure and the base concentration was also observed. The order in thiol was found to be about one at the beginning, decreasing to zero as the reaction progressed. The oxygen uptake rates were faster at the beginning and reached a stationary value after 20–30% reaction. Apparently the change in order with respect to thiol as well as the change in rate depends on the disulphide formed. Indeed, disulphide added at zero time suppresses the typical features of the initial reaction (Table 7). It is not clear which is the effect of disulphide. It is insoluble in water and hence a two-phase system results as soon as minor amounts of this product is formed. Partition of thiol between the two phases may be important and, possibly, be involved in the observed order in the base. With the minimum of base added, however, the thiol

should be already fully in the anionic form and hence an excess of base should not affect the rates.

The authors[138] emphasize the point that they cannot exclude even in their conditions that trace metal catalysis may still be active. Indeed the addition of sequestering agents like EDTA (ethylenediamine tetra-acetic

TABLE 7. Effect of diethyl disulphide and metal ion sequestering agents on the oxidation of ethanethiol[a] [138]

[EtSH], M	[Compound added]	M	Initial rate, mole l^{-1} s^{-1}	Final steady rate, mole l^{-1} s^{-1}
0·5	—	—	$1·7 \times 10^{-6}$	$1·0 \times 10^{-6}$
0·5	EDTA[b]	0·1	$3·3 \times 10^{-6}$	$2·0 \times 10^{-6}$
0·5	EN[c]	0·1	Undetectable	$1·1 \times 10^{-6}$
0·5	EtSSEt	0·5	—	$2·0 \times 10^{-6}$
0·0	EtSSEt	0·5	—	—[d]
0·5	EtSSEt	0·5	—	$1·1 \times 10^{-6}$
0·0	KCN + EtSSEt	0·25 + 0·5	—	—[d]
0·5	KCN	0·25	$1·2 \times 10^{-6}$	$2·3 \times 10^{-7}$[e]

[a] Oxygen pressure 700 mm Hg; temperature, 30°C.
[b] EDTA, ethylenediaminetetra-acetic acid.
[c] EN, ethylenediamine.
[d] Oxygen uptake *ca.* 0.
[e] Oxygen uptake after 10 days *ca.* 300%.

acid) and EN (ethylenediamine) causes contradictory results. Furthermore, added cyanide ion gives slower rates of oxygen uptake, and the reaction no longer yields disulphide but products of more profound oxidation (Table 7).

The same authors[138] studied, in the same conditions, the oxidation of a number of thiols and found the following sequence of reactivity:

$$n\text{-HexSH} > i\text{-BuSH} > n\text{-BuSH} > \text{EtSH} > \text{PhCH}_2\text{SH} > s\text{-BuSH} > \text{PhSH} > t\text{-BuSH}$$

The sequence does not appear simple. Steric effects could, perhaps, be responsible for the low reactivity of *t*-BuSH and electronic effects for that of benzenethiol. However, the authors' suspicions that the sequence could be partially determined by different amounts of adventitious catalytic impurities deserves careful attention.

The first-order dependence of the initial rate on thiol concentration as well as the base catalysis would indicate that thiolate ions play a particular role in the reaction.

Wallace and coworkers[140–143] had reached similar conclusions by studying the oxidation rates of several thiols. They also observed that the solvent has a quite large effect, which, in a general way, may be explained on the same basis. As shown in Table 8, the rate increases quite steadily on passing from alcoholic to non-protic and to dipolar aprotic solvents.

TABLE 8. Solvent effect on the oxidation rate of *n*-butanethiol[140]

Solvent	k, s^{-1} [a]	Rel. rate
Methanol	$5{\cdot}4 \times 10^{-5}$	1
Tetrahydrofuran	193×10^{-5}	36
Dioxane	482×10^{-5}	89
Diglyme	538×10^{-5}	100
Dimethylacetamide	1560×10^{-5}	289
Dimethylformamide	1795×10^{-5}	332

[a] 23·5°C, constant oxygen pressure 1 atm.

From data on relative rates of oxidation in methanol, ethanol and *t*-butanol in the presence of the corresponding alkoxides (Table 9) a correlation of the rate of oxidation with the pK_a of the alcohol was inferred[140]. However, on changing the cation, large variations in rates were observed (Table 9), strongly suggesting that ion-pairing phenomena are involved.

TABLE 9. Oxidation of *n*-butanethiol in alcoholic solvents at 23·5°C by molecular oxygen (1 atm)[140]

Alcohol	Base[a]	pK_a	k, s^{-1}
Methanol	NaOMe	15·5[b]	$5{\cdot}4 \times 10^{-5}$
Methanol	KOMe	—	$52{\cdot}2 \times 10^{-5}$
Ethanol	NaOEt	15·9[b]	$9{\cdot}6 \times 10^{-5}$
t-Butanol	NaOBu-*t*	19·2[c]	$35{\cdot}0 \times 10^{-5}$
t-Butanol	KOBu-*t*	—	$57{\cdot}8 \times 10^{-5}$
t-Butanol	RbOBu-*t*	—	$321{\cdot}7 \times 10^{-5}$
t-Butanol	CsOBu-*t*	—	$798{\cdot}3 \times 10^{-5}$

[a] Two-fold excess in respect to *n*-butanethiol.
[b] Reference 144.
[c] Reference 145.

All these facts are interconnected in the sense that both the size of the cation and the cation-solvating power of dipolar aprotic solvents have the effect of disrupting ion pairs and hence rendering the thiolate ion more

basic. The protic solvents, on the other hand, by hydrogen-bonding thiolate ions behave in the opposite way.

This latter point is illustrated[142] by the effect of added methanol on the oxidation rates of *n*-butanethiol in dimethylformamide (DMF) and di-(2-methoxyethyl)ether (diglyme) (Table 10).

TABLE 10. Effect of added methanol on the oxidation of *n*-butanethiol in DMF and diglyme at 23·5°C by molecular oxygen (1 atm)[142]

Methanol, %	DMF, %	Diglyme, %	k, s^{-1} [a]	Rel. rate
—	100	—	$1{\cdot}8 \times 10^{-2}$	334
25	75	—	$6{\cdot}1 \times 10^{-3}$	114
50	50	—	$1{\cdot}1 \times 10^{-3}$	21·3
75	25	—	$1{\cdot}5 \times 10^{-4}$	2·8
90	10	—	$6{\cdot}5 \times 10^{-5}$	1·2
—	—	100	$5{\cdot}4 \times 10^{-3}$	100
25	—	75	$2{\cdot}3 \times 10^{-3}$	43
50	—	50	$6{\cdot}1 \times 10^{-4}$	11
65	—	35	$1{\cdot}0 \times 10^{-4}$	1·9
100	—	—	$5{\cdot}4 \times 10^{-5}$	1

[a] Sodium methoxide as base.

The above results lead the authors[140–142] to propose the following scheme (Scheme 4) for the overall reaction:

$$RSH + B^- \rightleftharpoons RS^- + BH \quad (66)$$

$$RS^- + O_2 \longrightarrow RS\cdot + O_2^{\cdot-} \quad (67)$$

$$RS^- + O_2^{\cdot-} \longrightarrow RS\cdot + O_2^{2-} \quad (68)$$

$$2\,RS\cdot \longrightarrow RSSR \quad (69)$$

$$2\,O_2^{2-} + 2\,BH \longrightarrow \tfrac{1}{2}\,O_2 + 2\,B^- + 2\,OH^- \quad (70)$$

SCHEME 4

This scheme gives rise to some doubts which will be discussed further below. However, we wish to point out that reaction (70) is not essential in its present form since the protonation of O_2^{2-} would give H_2O_2. It, in turn, will be quickly destroyed by excess of mercaptan.

Large excess of base[146] and/or prolonged reaction times causes oxidation beyond the disulphide level in aqueous solutions. This phenomenon is more pronounced in dipolar aprotic solvents[141,147] where sulphonic acids

are produced together with minor amounts of disulphides (Table 11). However, disulphides are again the dominant product when a protic solvent is added (Table 12). No kinetic measurements were made for this

TABLE 11. Effect of solvent, base and temperature on the oxidation of *n*-butanethiol[141]

Solvent	Base[a]	Temperature, °C	Conversion of thiol, mole %, (time, h)	Sulphonic acid, mole %, in product	Disulphide, mole %, in product
HMPA[b]	KOH	23·5	97 (24·5)	95	3
HMPA	KOH	23·5	95 (21·5)	95	1
HMPA	KOH	80	100 (23)	100	—
HMPA	KOH	80	99 (6)	96	1
HMPA	NaOH	23·5	97 (24)	90	8
HMPA	NaOH	80	90 (18·5)	92	1
DMF[b]	KOH	23·5	98 (17·5)	88	9
DMF	NaOH	23·5	94 (18·5)	67	24
Tetra-methyl-urea	KOH	23·5	93 (23)	64	28
Pyridine	KOH	80	83 (18)	20	64

[a] Ratio base/thiol = 4.
[b] HMPA = hexamethylphosphoramide, DMF = dimethylformamide.

TABLE 12. Effect of added water on the product distribution in the oxidation of *n*-butanethiol in HMPA[a] at 23·5°C[141]

H_2O, vol. %	Thiol conversion, %	Sulphonic acid, mole % in product	Disulphide, mole % in product
10	96	54	41
20	99	48	52

[a] HMPA = hexamethylphosphoramide; constant oxygen pressure 1 atm.; ratio KOH/thiol = 4; reaction time = 5 h.

reaction since the systems were always heterogeneous, but based on the rate of oxygen uptake for several mercaptans (Figure 2), the order of reactivity seems to be *n*-butyl > phenyl > 2,2-di-*n*-pentyl-1-hexyl. This parallels the order of reactivity found for the oxidation in hydroxylic solvents[138, 142, 146]. It was suggested[141, 147] that sulphonic acids derive from

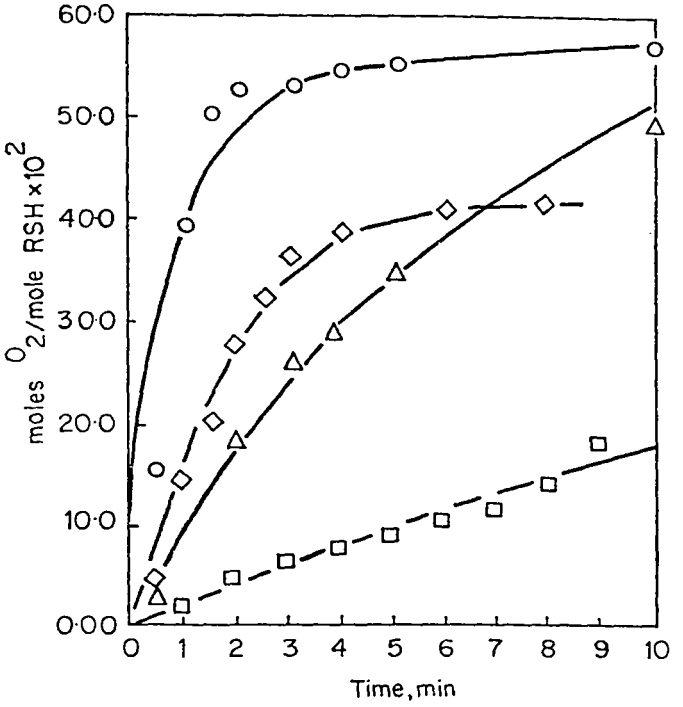


FIGURE 2. Effects of temperature and thiol structure on the oxygen uptake in HMPA (hexamethylphosphoramide)[141]. ○ 1-C_4H_9SH in KOH/HMPA (23·5°); △ C_6H_5SH in KOH/HMPA (23·5°); □ 1-$C_{16}H_{33}SH$ in KOH/HMPA (23·5°); ◇ 1-$C_{16}H_{33}SH$ in KOH/HMPA (80°). Reproduced by permission of the author and editor from *Tetrahedron*, **21**, 2271 (1965).

disproportionation of sulphenate ions formed by nucleophilic displacement at the S—S bond of the disulphide[148] (Scheme 5). This mechanism is

$$RS{-}SR + OH^- \rightleftharpoons RSOH + RS^- \quad (71)$$

$$RSOH + OH^- \rightleftharpoons RSO^- + H_2O \quad (72)$$

$$3\,RSO^- \longrightarrow RSO_3^- + 2\,RS^- \quad (73)$$

SCHEME 5

supported by the fact that disulphide may undergo base-catalysed oxidation in the same solvent system (Table 13) and that increasing amounts of water added to the aprotic solvent markedly favour the formation of disulphide (Table 12 and Figure 3). The protic component of the solvent, decreasing the activity of the base, would inhibit the

TABLE 13. Base-catalysed oxidation of disulphides in HMPA[a] [141]

Disulphide	Temperature, °C	Disulphide conversion, %	Time, h	Sulphonic acid, mole %	Thiol, mole %
Di-*n*-butyl disulphide	23·5	98	41	92	3
Di-*n*-butyl disulphide	80	96	45	97	—
Diphenyl disulphide	23·5	98	22	88	—
Diphenyl disulphide	80	98	22·5	99	—
Di-*o*-tolyl disulphide	80	98	23	98	—

[a] HMPA = hexamethylphosphoramide, ratio KOH/disulphide = 8.

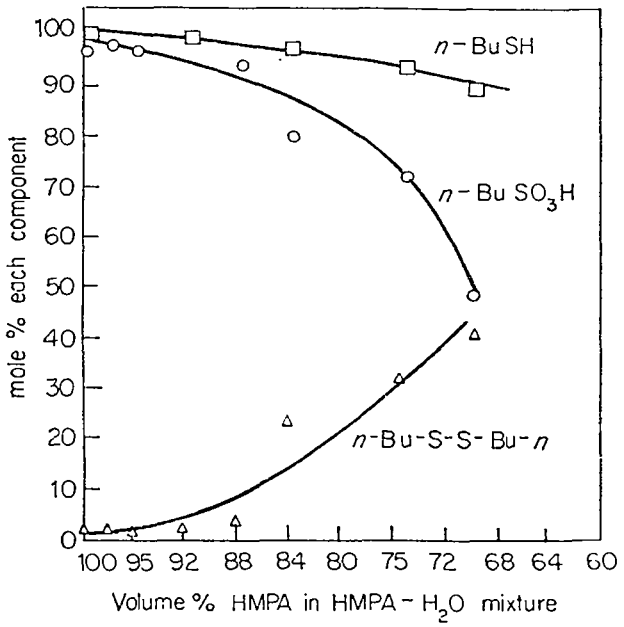


FIGURE 3. Effects of added water on thiol conversion and molar product distribution in the oxidation of *n*-butanethiol in HMPA at 80°C [141]. Ratio KOH/RSH = 4, reaction time 5 h. Reproduced by permission of the author and editor from *Tetrahedron*, **21**, 2271 (1965).

nucleophilic displacement at the disulphide linkage which is responsible for the further oxidation to sulphonic acid.

There is not, however, general agreement with this explanation. Indeed, direct oxidation of mercaptide ion to sulphonic acid was proposed by Berger[149] who considers the formation of disulphide as a side reaction.

Most of the work dealt with the oxidation of *n*-octanethiol but a few other thiols were briefly studied. The reactions were carried out in *t*-butanol with potassium *t*-butoxide as base under the assumption that in this solvent trace metal contaminations are less likely.

The oxidation under 1 atm pressure of oxygen gave sulphinic and sulphonic acids together with variable amounts of disulphide depending on the concentration of the base (Figure 4). Increasing amounts of base

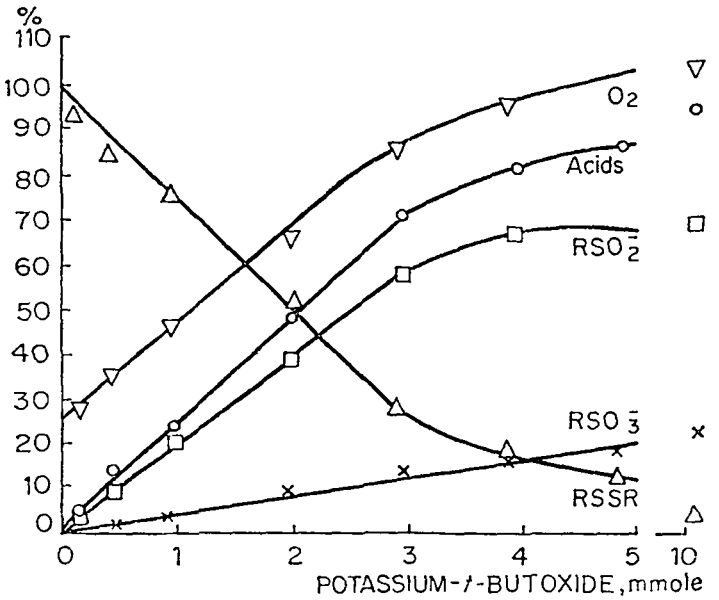


FIGURE 4. Oxidation of *n*-octanethiol in *t*-butanol at 25°C. Dependence of product distribution at complete conversion on potassium *t*-butoxide concentration[149]. *n*-Octanethiol 0·25 M (3 mmoles in 12 ml of *t*-BuOH); the products formed and oxygen uptake are referred to the mercaptan as (mmoles product/mmoles RSH) × 100; 'acids' refer to the sum of RSO_2^- and RSO_3^-. Reproduced by permission from *Rec. Trav. Chim.*, **82**, 773 (1963).

decrease the percentage of disulphide in the final products, thus suggesting a dependence of the distribution of products upon the extent of ionized mercaptan. Formation of disulphide and higher oxidation products are indeed processes which progress at different rates. Oxidation of *n*-octanethiol in the presence of insufficient base shows that in the earlier reaction stages formation of disulphide occurs almost quantitatively. This is even more evident for the oxidation of benzenethiol in which diphenyldisulphide is the only oxidation product up to 20–25% of reaction (Figure 5).

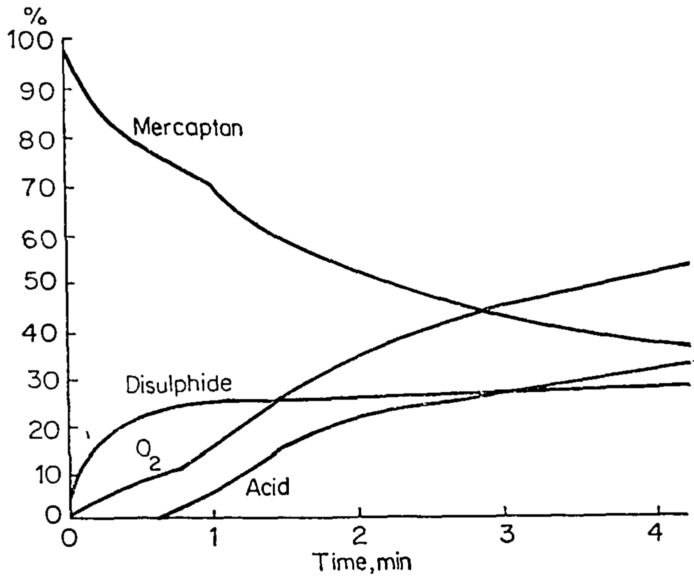


FIGURE 5. Oxidation of benzenethiol in *t*-butanol at 50°C. Distribution of products as a function of time. Benzenethiol 0·17 M; potassium *t*-butoxide 0·11 M; oxygen pressure 1 atm. Reproduced by permission from *Rec. Trav. Chim.*, **82**, 773 (1963).

Catalytic effects on the oxidation of benzenethiol by anthraquinone-1-sulphenic acid, *t*-butyl hydroperoxide and phenyl benzenethiolsulphinate have been observed. It was taken as evidence that sulphenate ion is a key intermediate in the reaction chain leading to the oxidized products. Indeed the above reagents may give rise to the sulphenate ion by ionization or by oxidation (equation 74) or by nucleophilic displacement[54] (equation 75).

$$RS^- + R'OOH \longrightarrow RSO^- + R'OH \tag{74}$$

$$\underset{\displaystyle \overset{|}{O}}{RSSR} + RS^- \longrightarrow RSO^- + RSSR \tag{75}$$

The overall reaction was rationalized[149] on the basis of Scheme 6. The results reported above and other observations including an analysis of the reaction kinetics lead the author[149] to suggest that the first step is the formation of a peroxysulphenate ion in the triplet state (equation 76) which may react with undissociated thiol, when present, to give, ultimately, disulphide (equation 77).

$$RS^- + O_2 \rightleftharpoons \underset{(8)}{[RSOO^{-*}]} \tag{76}$$

$$[RSOO^{-*}] + 4\,RSH \longrightarrow RS^- + 2\,H_2O + 2\,RSSR \tag{77}$$

Alternatively, by an intersystem crossing, **8** gives rise to a peroxysulphenate ion (**9**) which then initiates a chain reaction, probably a short chain, as reported in Scheme 6.

Initiation

$$RS^- + O_2 \rightleftharpoons (8) \longrightarrow \underset{(9)}{RSOO^-} \quad (78)$$

$$RSOO^- + RS^- \longrightarrow 2\,RSO^- \quad (79)$$

Propagation

$$RSO^- + O_2 \longrightarrow RS(=O)-O^- \quad (80)$$

$$RS(=O)-O^- + RS^- \longrightarrow RSO^- + RSO_2^- \quad (81)$$

Termination

$$RS(=O)-O^- + RSO^- \longrightarrow 2\,RSO_2^- \quad (82)$$

$$RS(=O)-O^- + RSO_2^- \longrightarrow RSO_2^- + RSO_3^- \quad (83)$$

$$RSOO^- + RSO_2^- \longrightarrow RSO^- + RSO_3^- \quad (84)$$

SCHEME 6

The above outlined scheme leads to the conclusion that completely ionized thiols would give exclusively sulphinic and sulphonic acids; nevertheless, the experimental results indicate formation of *ca.* 5% of disulphide in the oxidation of potassium benzenethiolate even with base in large excess. Since formation of disulphide would require the presence of undissociated thiol, other mechanisms must be operative. Again it is possible that the intervention of trace metal catalysis in the oxidation reaction has to be taken into account. Cullis, Hopton and Trimm[138] reported that copper ions in concentrations as low as 10^{-7} M are still active as catalysts and indeed it is very hard to detect metal ions at such low concentrations and to exclude adventitious impurities of this order of magnitude.

Another puzzling point of the mechanisms proposed to explain the autooxidation of thiols in basic solutions (in particular see Scheme 4) is the assumption that mercapto radicals dimerize almost quantitatively without interacting with the solvents in which the reaction was studied.

Although the dimerization of thiyl radicals has been found to be very fast (10^9–10^{10} $M^{-1}\,sec^{-1}$)[150] the very low concentration of such species could still make the search for an alternative path to disulphide formation rewarding. It may be worth mentioning that Caspari and Granzow[151] observed that mercapto radicals generated by flash photolysis in aqueous solutions give rise to a radical ion, possibly by interaction with an ionized thiol molecule (equation 85).

$$RS\cdot + RS^- \rightleftharpoons RS\overset{\cdot}{\underset{-}{S}}R \qquad (85)$$

Similar radical anions have been observed[150] as transient species in the reaction of various disulphides with hydrated electrons (equation 86) which eventually decay to give thiyl radicals and mercaptide ions (equation 85 from right to left).

$$RSSR + e^- \longrightarrow RS\overset{\cdot}{\underset{-}{S}}R \qquad (86)$$

A related observation was reported by Zweig and Hoffmann[152] who observed a one-electron reduction of naphthalene 1,8-disulphide, contrary to the more usual two-electron reduction of disulphides (see Section II) and also that the radical anion generated from this disulphide with sodium in 1,2-dimethoxyethane has an ESR spectrum characterized by a single line with 1·04 gauss separation from peak to peak, $g = 2{\cdot}0110$. The electrochemical generation of the same radical partially resolves the line into an overlapped 1 : 2 : 1 triplet, $a_H = 0{\cdot}4$ gauss. The lack of coupling of the unpaired electron with the aromatic π system indicates that the electron is localized on sulphur. This, in turn, suggests that disulphide radical ions may be a relatively long-living species and hence reaction intermediates. Indeed, under special experimental conditions[151] or with special geometrical constrictions[152] they live long enough to be physically detected.

B. Catalysis by Aliphatic Amines

Thiols and in particular aromatic thiols are acids strong enough to be partially transformed into their conjugate base by amines. It follows that the oxidation of thiols by molecular oxygen, which is much faster on the anion than on the undissociated thiol (see section III.A), may be catalysed by aliphatic amines acting simply as base (see, however, section III.D).

These catalysts have been used[29] in the oxidation of thiols in hydrocarbon solvents in which amines, but not the more basic alkali hydroxides, are soluble.

The hypothesis that the amine-catalysed oxidation of thiols is a particular case of the more general reaction of oxidation by molecular oxygen of thiolate ions is confirmed by the finding that arene-thiols, which are more acidic and hence more dissociated, are oxidized faster than arylalkane- and alkane-thiols in the presence of amines[143].

A special case of combination of amine catalysis and solvent effect is given[153] by the easy oxidation of aliphatic and aromatic thiols in tetramethylguanidine which acts both as base and as a dipolar aprotic solvent (see Table 14).

TABLE 14. Oxidation of thiols to disulphides in tetramethylguanidine at 23·5°C [a] [153]

Thiol	Disulphide yield, %	Reaction time, h
n-Propanethiol	82	19
i-Propanethiol	82	19
n-Pentanethiol	82	19
Cyclohexanethiol	72	16
α-Toluenethiol	12	43
Benzenethiol	80	19

[a] Constant oxygen pressure 1 atm.

C. Catalysis by Metal Ions

The addition of heavy metal salts to the basic aqueous solution of thiols increases the rate of oxygen uptake[154,155] as shown in Table 15. It may be easily realized that the catalytic activity varies with the metal ion. The oxidation gives, except for very special cases (see below), only disulphide without any contamination by products of further oxidation (Table 16). The stoichiometric relation of one mole of oxygen for four moles of thiol has always been observed (equation 65).

The results reported in Table 15 have to be considered to be only qualitative; indeed many of the metal ions listed give in the reaction medium slightly soluble oxides and hence formation of precipitates is observed. The addition of thiols to these non-homogeneous solutions causes changes in the amount, colour and possibly nature of the insoluble material. In some cases the nature of the precipitate formed was investigated; in particular $Co(SC_2H_5)_3$, $Pd(SC_2H_5)_2$, $TlSC_2H_5$, $Ni(SC_2H_5)_2$ and $(C_2H_5S)_3Ni(OH)$ were identified in the oxidation of C_2H_5SH catalysed by Co^{2+}, Pd^{2+}, Tl^{+} and Ni^{2+} respectively.

TABLE 15. Effect of metal ions on the oxidation of ethanethiol[a] [154]

Metal ion	Salt	Thiol conversion, %, after 1·5 h	$-d[O_2]/dt$ mole l^{-1} s^{-1} [b]
—	—	—	$1·7 \times 10^{-6}$
Ce^{4+}	$(NH_4)_2Ce(NO_3)_6$	12·8	$3·1 \times 10^{-6}$
UO_2^{2+}	$UO_2(NO_3)_2 \cdot 6H_2O$	11·8	$2·9 \times 10^{-6}$
VO^{2+}	$VOSO_4$ + aq·	11·5	$2·6 \times 10^{-6}$
Cr^{3+}	$Cr_2(SO_4)_3 \cdot K_2SO_4 \cdot 24\ H_2O$	6·4	$2·1 \times 10^{-6}$
Mo^{6+}	$(NH_4)_6Mo_7O_{24} \cdot 4\ H_2O$	13·9	$3·2 \times 10^{-6}$
W^{6+}	$Na_2WO_4 \cdot 2\ H_2O$	14·3	$3·4 \times 10^{-6}$
Mn^{2+}	$MnSO_4 \cdot 4\ H_2O$	11·4	$4·6 \times 10^{-6}$
Fe^{2+}	$FeSO_4 \cdot 7\ H_2O$	11·4	$3·6 \times 10^{-6}$
Fe^{3+}	Haemin (Fe = $1·5 \times 10^{-3}$ M)	90·0	$26·8 \times 10^{-6}$
Co^{2+}	$CoSO_4 \cdot 7\ H_2O$	35·7	$12·8 \times 10^{-6}$
Ni^{2+}	$NiSO_4$	45·7	$11·9 \times 10^{-6}$
Pd^{2+}	$PdCl_2$	4·8	$1·5 \times 10^{-6}$
Pt^{4+}	$PtCl_4$	12·2	$2·6 \times 10^{-6}$
Cu^{2+}	$CuSO_4 \cdot 5\ H_2O$	96·7	$26·8 \times 10^{-6}$
Ag^{+}	$AgNO_3$	5·7	$1·7 \times 10^{-6}$
Zn^{2+}	$ZnSO_4 \cdot 7\ H_2O$	17·5	$3·9 \times 10^{-6}$
Cd^{2+}	$3\ CdSO_4 \cdot 8\ H_2O$	13·9	$3·2 \times 10^{-6}$
Hg^{2+}	$HgCl_2$	6·1	$2·0 \times 10^{-6}$
Al^{3+}	$Al_2(SO_4)_3 \cdot K_2SO_4 \cdot 24\ H_2O$	11·8	$3·0 \times 10^{-6}$
Tl^{+}	Tl_2SO_4	10·3	$2·4 \times 10^{-6}$
Sn^{2+}	$SnCl_2 \cdot 2\ H_2O$	15·4	$2·2 \times 10^{-6}$

[a] Metal ion = 1×10^{-3} M unless otherwise stated; ethanethiol = 0·5 M; NaOH = 2 M; constant oxygen pressure, 700 mm Hg at 30°C.
[b] Rate of oxygen uptake.

TABLE 16. Oxidation of thiols catalyzed by copper, cobalt and nickel sulphate[a] [155]

Thiol	Copper[b]		Cobalt		Nickel	
	90% of reaction, h	Disulphide yield, %[c]	90% of reaction, h	Disulphide yield, %[c]	90% of reaction, h	Disulphide yield, %[c]
EtSH	1	100	4·5	101	4	96
n-BuSH	1·5	101	> 10	—	15	102
i-BuSH	1·5	102	6	100	12	99
s-BuSH	2	100	8	98	> 10	—
t-BuSH	> 10	—	> 10	—	> 10	—
n-HexSH	1·5	104	5	101	4·5	101
PhSH	> 10	—	> 10	—	> 10	—
$PhCH_2SH$	3	98	> 10	—	> 10	—

[a] Reaction conditions as in Table 15.
[b] 1×10^{-5} M.
[c] Referred to thiol.

It was suggested[156, 157] that a contribution to the catalysis could be given by undissolved metal complexes. However, a careful study on the effect of these insoluble materials in the case of copper, cobalt and nickel salts did not confirm this hypothesis[155, 158].

In Table 17 the rates of oxygen uptake of solutions containing the precipitates are reported together with those obtained from solutions filtered before and after addition of the thiol.

TABLE 17. Effect of actual dissolved metal on the oxidation of ethanethiol[a] [155, 158]

Metal ion	Initial rate of oxygen uptake, mole l^{-1} s^{-1}	Conditions[b]	Metal concentration in solution, M
Cu	$13{\cdot}2 \times 10^{-6}$	A	10^{-5} [c]
	$13{\cdot}2 \times 10^{-6}$	B	10^{-5}
	$13{\cdot}2 \times 10^{-6}$	C	10^{-5}
Co	$10{\cdot}3 \times 10^{-6}$	A	$1{\cdot}0 \times 10^{-3}$ [c]
	$7{\cdot}6 \times 10^{-6}$	B	$8{\cdot}9 \times 10^{-5}$
	$9{\cdot}9 \times 10^{-6}$	C	$6{\cdot}4 \times 10^{-4}$
	$10{\cdot}2 \times 10^{-6}$	D	$1{\cdot}0 \times 10^{-3}$
Ni	$15{\cdot}2 \times 10^{-6}$	A	$1{\cdot}0 \times 10^{-3}$ [c]
	$3{\cdot}4 \times 10^{-6}$	B	$1{\cdot}3 \times 10^{-5}$
	$14{\cdot}6 \times 10^{-6}$	C	$5{\cdot}3 \times 10^{-4}$
	$14{\cdot}8 \times 10^{-6}$	D	$1{\cdot}0 \times 10^{-3}$

[a] Reaction conditions as in Table 15.
[b] A: *no filtration*; B: *filtration before* addition of ethanethiol; C: filtration after addition of thiol; D: metal added as thiol complex.
[c] Concentration of metal ion added.

It is quite clear that precipitates, in this system, do not play any role. The oxygen uptake rates of solutions not filtered (A) and those of solutions filtered before (B) or after addition of the thiol (C) are almost the same within experimental errors. The lower rates observed when the filtration is carried out before addition of thiol (B) could be due to a lower solubility of hydroxides in respect to that of metal mercaptides. This is further confirmed by the fact that addition of metals as thiol complexes gives again the same rate of oxidation (D).

An evaluation of the relative efficiency of the metals listed in Table 15 as catalysts is hindered by several factors. First of all the concentration of the metal ions in solution is not known, except in a few cases (see Table 17); for example, the different rates observed with $FeSO_4$ and haemin complex

(Table 15) could in part be due to different solubility and hence concentration of the two catalysts. A second point is that the highest rates of oxygen uptake reported ($2{\cdot}7 \times 10^{-5}$) are near the diffusion-controlled rates.

In fact with copper salts, rates independent from stirring are obtained only at much lower concentration than those of other metal ions (Table 18). On the same line are the results reported in Table 19 which show that

TABLE 18. Dependence on shake rate of the oxidation of ethanethiol[a] catalysed by copper ions[155]

$[Cu^{2+}]$, M	Shake rate, cycles per minute	Rate of oxygen uptake[b]
10^{-3}	360	0·80
10^{-3}	380	1·23
10^{-4}	310	0·74
	360	0·84
	400	1·57
10^{-5}	310	0·60
	400	0·60

[a] Reaction conditions as in Table 15.
[b] Initial rates, expressed as percentage of final uptake/min.

TABLE 19. Effect of metal concentration on the oxidation of ethanethiol[a] [154]

Metal ion	Salt	Concentration of metal added, M	$\frac{-d[O_2]}{dt}$ mole l^{-1} s^{-1} [b]
Fe^{2+}	$FeSO_4 \cdot 7\,H_2O$	0	$2{\cdot}2 \times 10^{-6}$
		10^{-6}	$2{\cdot}2 \times 10^{-6}$
		10^{-5}	$3{\cdot}0 \times 10^{-6}$
		10^{-4}	$3{\cdot}5 \times 10^{-6}$
		10^{-3}	$5{\cdot}8 \times 10^{-6}$ I
			$3{\cdot}5 \times 10^{-6}$ F
		10^{-2}	$11{\cdot}5 \times 10^{-6}$ I
			$3{\cdot}7 \times 10^{-6}$ F
Fe^{3+}	Haemin	$1{\cdot}5 \times 10^{-3}$	$26{\cdot}8 \times 10^{-6}$
		$0{\cdot}6 \times 10^{-3}$	$11{\cdot}6 \times 10^{-6}$
Mn^{2+}	$MnSO_4 \cdot 4\,H_2O$	10^{-5}	$3{\cdot}2 \times 10^{-6}$
		10^{-4}	$3{\cdot}0 \times 10^{-6}$
		10^{-3}	$3{\cdot}2 \times 10^{-6}$ I
			$4{\cdot}8 \times 10^{-6}$ F
Cr^{3+}	Chrome alum	10^{-5}	$4{\cdot}2 \times 10^{-6}$ I
			$2{\cdot}3 \times 10^{-6}$ F
		10^{-3}	$2{\cdot}0 \times 10^{-6}$

[a] Reaction conditions as in Table 15.
[b] Rate of oxygen uptake. I = initial rate; F = final steady rate.

increasing concentrations of the metals do not increase in the expected way the rates of oxygen uptake; possibly because of saturation effects.

A typical feature often observed is that initial rates differ, and are frequently higher than final steady rates[154] (Figure 6, Table 19).

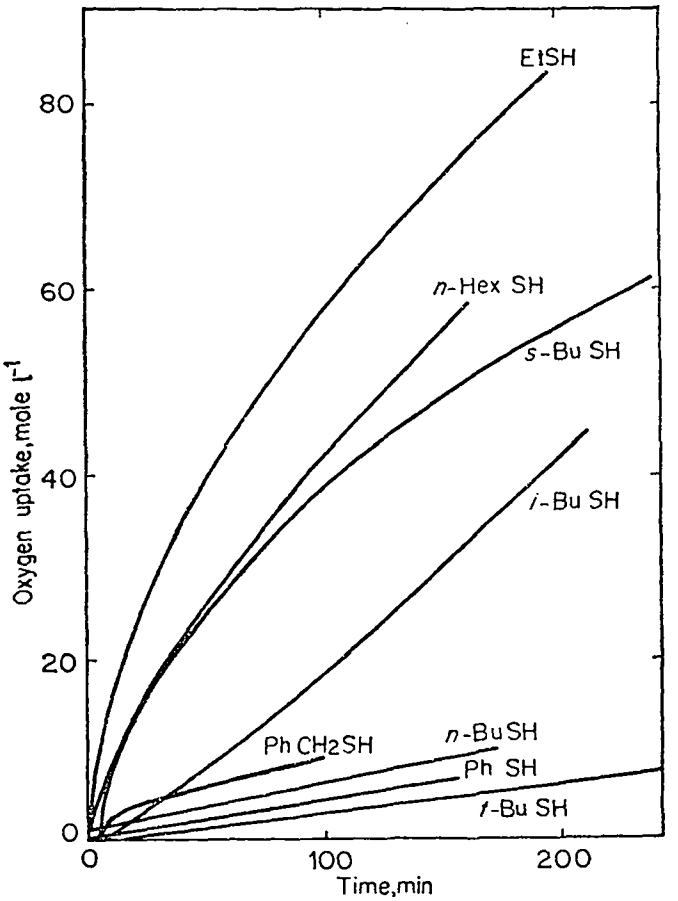


FIGURE 6. Oxidation of thiols catalysed by cobalt sulphate[154]. Reaction conditions as in Table 15. Reproduced by permission of the author and the Society of Chemical Industry from *J. Appl. Chem.*, **18**, 335 (1968).

The authors suggested that this change in rate is linked to the formation of disulphide which could compete with the thiol in coordination to the metal. Indeed the addition of disulphide at the beginning of the reaction depresses the initial rates but does not affect the final steady rate. Since the

disulphide is very little soluble in the reaction medium, its concentration in solution is expected to reach saturation quickly. Other effects due to the formation of a two-phase system could not be ruled out.

Among the most actively studied metals are copper, cobalt and nickel[154,155] and we shall devote to them a more detailed analysis. The rate of oxidation is zero order in thiol concentration for cobalt (see Figure 6) and for copper ions whereas in the case of nickel, first order in thiol was observed.

However, the rate of oxygen uptake does depend on the thiol: the relative rates vary with different metals but benzenethiol and *t*-butanethiol are always among the least reactive compounds. Probably this is related for benzenethiol to its greater acidity (i.e. its higher oxidation potential) and for *t*-butanethiol to steric hindrance to coordination on the metal.

A detailed analysis of the structural effect of thiols on their rate of oxidation is probably unrewarding because of several uncertainties like partition coefficients of the thiols and metal complexes between the aqueous and disulphide phases and, perhaps more important, the degree of contamination of the solutions by other heavy metals due to the well-known ability of metal mercaptides to distil together with thiols[159]. It has to be noticed that the nominal uncatalysed rate is not as small as could be expected in respect to the catalysed rates and that concentration of copper ions of the order of 1×10^{-5} M is more effective than that of other metals at the 'nominal' concentration of 1×10^{-3} M.

Pertinent to this point is the study of the effect of typical ligands on the rate of oxidation[158,160]. The results with ethylenediaminetetra-acetic acid (EDTA), ethylenediamine (EN) and CN^- are reported in Table 20.

The complexing agents always reduces the rate of oxygen uptake and the effect of CN^- is particularly large. This latter ion has also the effect of changing the course of the reaction since no disulphide, or at least only traces of it, is formed and more than the stoichiometric amount of oxygen is consumed.

Tests were made to ensure that the increase of oxygen consumption is not due to further oxidation of disulphides which appear to be stable in the reaction conditions even in the presence of CN^-.

The effect of complex ligands like porphirine, phthalocyanine, etc. has been studied by numerous authors particularly on biological systems[32,143].

Some data on studies with these ligands and simple alkane-thiols[161] are reported in Table 21.

It is interesting to observe that also in these cases, cyanide ion depresses the oxidation rates and that the rates of oxygen uptake with these metal complexes exceed in several cases the limiting rate of oxygen diffusion.

TABLE 20. Effect on the oxidation rates of ethanethiol of several ligands[a] [158]

[RSSR] M	[CN^-] M	[EDTA] M	[EN] M	Metal ion[b]	$\frac{-d[O_2]}{dt}$ mole l^{-1} s^{-1} [c]	Final O_2 uptake, % of theoretical	Notes
0	0	0	0	—	$2{\cdot}0 \times 10^{-6}$	101	
0·5	0	0	0	—	$2{\cdot}3 \times 10^{-6}$	—	
0	0·25	0	0	—	$0{\cdot}2 \times 10^{-6}$	302 (at 200 h)	No disulphide formed
0·5	0·25	0	0	—	$1{\cdot}0 \times 10^{-6}$	—	
0·5	0·25	0	0	—	zero	—	No thiol present
0	0	0	0	Cu^{2+}	$18{\cdot}3 \times 10^{-6}$	102	
0	0·25	0	0	Cu^{2+}	$0{\cdot}3 \times 10^{-6}$	—	No disulphide formed
0	0	0·1	0	Cu^{2+}	$11{\cdot}8 \times 10^{-6}$	101	
0	0	0	0·1	Cu^{2+}	$13{\cdot}5 \times 10^{-6}$	—	
0	0	0	0	Co^{2+}	$17{\cdot}7 \times 10^{-6}$ I $4{\cdot}3 \times 10^{-6}$ F	99	
0·5	0	0	0	Co^{2+}	$8{\cdot}8 \times 10^{-6}$ I $4{\cdot}4 \times 10^{-6}$ F	—	
0	0·25	0	0	Co^{2+}	$0{\cdot}6 \times 10^{-6}$	—	No disulphide formed
0	0	0·1	0	Co^{2+}	$7{\cdot}5 \times 10^{-6}$	103	
0	0	0	0·1	Co^{2+}	$0{\cdot}4 \times 10^{-6}$	—	Small amounts of disulphide formed
0	0	0	0	Ni^{2+}	$15{\cdot}3 \times 10^{-6}$	101	
0	0·25	0	0	Ni^{2+}	$1{\cdot}3 \times 10^{-6}$	—	No disulphide formed
0	0	0·1	0	Ni^{2+}	$3{\cdot}0 \times 10^{-6}$	—	No disulphide formed
0	0	0	0·1	Ni^{2+}	$2{\cdot}4 \times 10^{-6}$	99	No disulphide formed

[a] Reaction conditions as in Table 15.
[b] Added as sulphate: 1×10^{-3} M $CoSO_4$ and $NiSO_4$, 1×10^{-5} M $CuSO_4$.
[c] Rate of oxygen uptake. I = initial rate, F = final steady rate.

TABLE 21. Oxidation of ethanethiol[a] catalysed by metal complexes[161]

Metal	Metal complex	Concentration, M	Rate of oxygen uptake, k (mole l^{-1} s^{-1}) $\times 10^6$	
			No KCN	0·25 M KCN
Co	$CoSO_4 \cdot 7\ H_2O$	10^{-3}	10·3	1·1
	Phthalocyanine	$3{\cdot}5 \times 10^{-3}$	47·6	—
	Vitamin B_{12}	10^{-3}	80·4	0·7
Ni	$NiSO_4$ + aq.	10^{-3}	15·1	1·0
Cu	$CuSO_4 \cdot 5\ H_2O$	10^{-5}	13·2	1·2
	Phthalocyanine	$3{\cdot}5 \times 10^{-3}$	5·4	—
Fe	$FeSO_4 \cdot 7\ H_2O$	10^{-3}	4·0	1·1
	Phthalocyanine	$3{\cdot}5 \times 10^{-3}$	14·7	—
	Haemin	10^{-3}	17·1	14·7
—	—	—	1·0	0·2

[a] Reaction conditions as in Table 15.

This could be due to the ability of these complexes to co-ordinate molecular oxygen.

The suggestion was advanced that the metal-catalysed oxidation of thiols in alkaline media is based on an electron transfer from the metal in its higher oxidation state to the thiol *via* an inner-sphere process whenever the thiol may co-ordinate to the metal. Outer-sphere processes are suggested when strong complexing agents prevent the entering of thiol into the co-ordination sphere of the metal[161].

It may be worthwhile to notice that disulphide is formed in quantitative yields when no strong ligands are present otherwise products of further oxidation are obtained.

This puts some doubt on the hypothesis that disulphide formation stems from dimerization of free thiol radicals as indicated in the simplified mechanism (Scheme 7) reported below.

$$2\ M^{n+} + O_2 \longrightarrow 2\ M^{(n+1)} + O_2^{2-}$$

$$2\ RS^- + 2\ M^{(n+1)} \longrightarrow 2\ RS\cdot + 2\ M^{n+}$$

$$2\ RS\cdot \longrightarrow RSSR$$

$$O_2^{2-} + 2\ H_2O \longrightarrow H_2O_2 + 2\ OH^-$$

SCHEME 7

It could be suggested that disulphide is formed within the co-ordination sphere of the metal or in a step concerted with the release of thiyl radicals.

Indeed when, as in the case of cyanide complexes, it is assumed that the oxidation of thiols occurs by an outer-sphere process and hence thiyl radicals are formed as free particles in the solution, disulphide is at the most a minor reaction product and the thiols are oxidized to sulphinic or sulphonic acids.

Most proposed schemes assume that hydrogen peroxide is a by product and that it is consumed in a subsequent probably metal-catalysed fast reaction. Although this cannot be ruled out, it could also be that when the oxygen enters into the co-ordination sphere of the metal it is reduced in successive steps to water rather than released at an intermediate stage of reduction.

D. Catalysis by Organic Redox Systems

Hydroquinone (QH_2) and *p*-phenylenediamine derivatives in basic medium as well as other easily oxidizable species like the reduced forms of several dyes may act as catalysts in the autooxidation of thiols to disulphides.

The rate of oxygen uptake for the oxidation of *n*-hexanethiol in the presence of hydroquinone is characterized by an initial slow rate which increases up to a maximum and then decreases at longer reaction times[162]. The maximum rate at constant oxygen pressure is dependent upon the first power of base and of catalyst concentration (equation 87)

$$\frac{-dO_2}{dt} = k[QH_2]\,[OH^-] \tag{87}$$

The first step of the reaction is assumed to be the oxidation of the hydroquinone anion (QH^-) by the oxygen to generate the semiquinone (QH) (equations 88 and 89).

$$QH_2 + OH^- \rightleftharpoons QH^- + H_2O \tag{88}$$

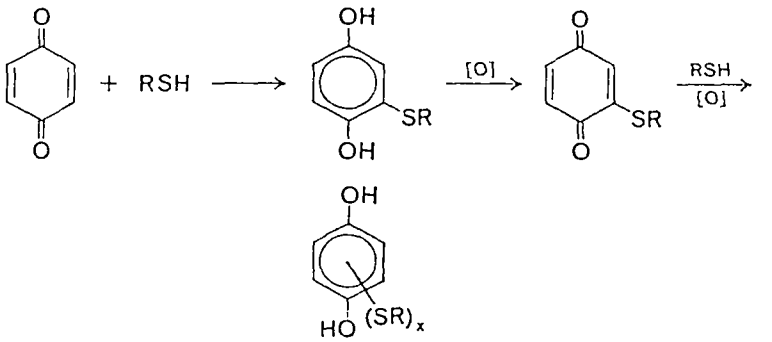
$$QH^- + O_2 \longrightarrow QH + O_2^{\cdot-} \tag{89}$$

The semiquinone then reacts with the thiol to give the corresponding thiyl radical (equation 90) which yields disulphide by dimerization.

$$QH + RS^- \longrightarrow QH^- + RS\cdot \tag{90}$$

The oxidation rates depend on the hydroquinone used as catalyst, but the catalytic power is not directly related to the oxidation rate of the catalyst[163]. However, the two sets of data are obtained in different conditions and in particular at largely different pH, and this could justify the discrepancies observed. Alternatively it is possible that the quinone is

first transformed into its mercapto derivative (equation 91) and that the substituted quinone is the true oxidizing species[162].

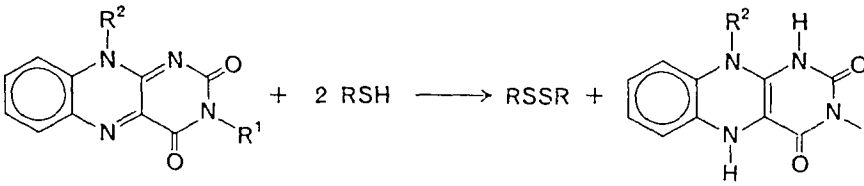


(91)

Studies of the oxidation of thiols with tetrasubstituted quinones not susceptible to further addition would shed light on this problem. Unfortunately data of this kind are not available in the literature.

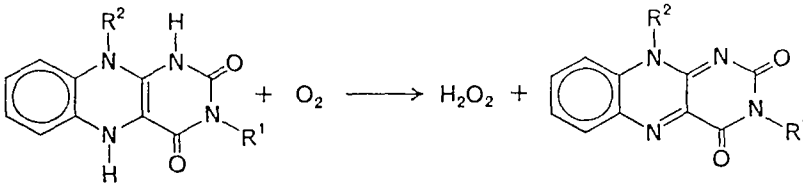
An identical mechanism has been proposed for the oxidation of thiols catalysed by phenylenediamine derivatives[164–166].

Flavine derivatives oxidize thiols to disulphides in the absence of oxygen with formation of dihydroflavines[167] (equation 92).



(92)

The reduced form of this dye may be reoxidized by molecular oxygen with regeneration of the oxidant and formation of hydrogen peroxide which is itself an oxidizing agent toward mercaptans (see section III.A) (equation 93).

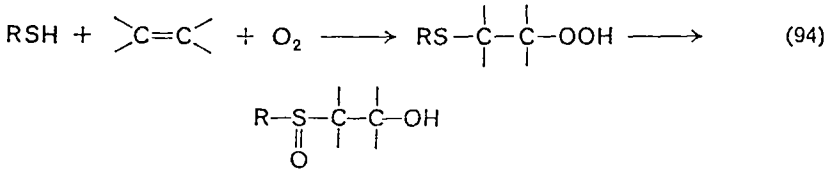


(93)

Other organic redox systems are good catalysts for the oxidation of thiols by molecular oxygen and probably act by similar mechanisms[32].

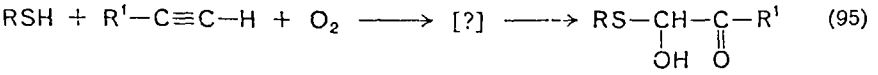
E. Co-oxidation

The autooxidation of thiols in the presence of alkenes takes a quite different course[143, 168]. They are in fact oxidized by oxygen to give, possibly by a chain reaction, β-thiohydroperoxides which eventually rearrange to β-sulphinyl alcohols (equation 94). Acetylene derivatives give under the



(94)

same conditions a similar reaction which may be represented by equation (95).

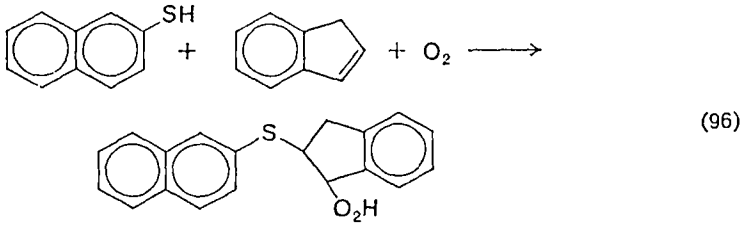


(95)

These reactions are usually called co-oxidation of thiols since an alkene (or an acetylene) is oxidized together with a thiol molecule. It has been reported that the rate of co-oxidation depends on the alkene and on the thiol, with aromatic derivatives reacting faster than the aliphatic ones. Catalysis by typical radical initiators has also been observed[143].

Kharash and coworkers[168] first proposed a hydroperoxysulphide intermediate in the formation of β-sulphinyl alcohols in the co-oxidation of thiols with olefins. This was later confirmed by detection of peroxy compounds[169] in the reaction mixture. Further studies led to the isolation of several hydroperoxysulphides when aromatic thiols were oxidized at low temperatures[170, 171].

An example of this class of compounds is the 2-(2-naphthylmercapto)-1-indanyl hydroperoxide (**10**) obtained[170] as a solid, melting at 70°C, by co-oxidation of 2-naphthalenethiol and indene (equation 96).



(96)

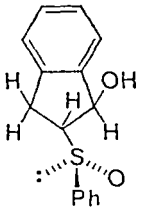
(10)

When the hydroperoxide intermediate formed in the co-oxidation of 2-naphthalenethiol and indene is allowed to decompose in the presence of 2-(4-chlorophenylmercapto)-1-indanol, none of the latter was oxidized. This would suggest an intramolecular transfer of the peroxidic oxygen at the sulphide sulphur.

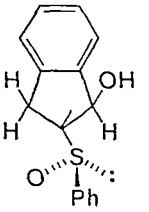
Further evidence on the intramolecular character of the oxygen transfer as well as on the stereochemistry of the co-oxidation process stems from a careful investigation by Szmant and Rigau[172, 173] on the reaction of benzenethiol with indene.

They isolated from the reaction and fully characterized three of the four possible diastereoisomeric 2-phenylsulphinyl-1-indanols and prepared the missing isomer by oxidation of *cis*-2-phenylmercapto indanol with hydrogen peroxide or with *m*-chloroperoxybenzoic acid.

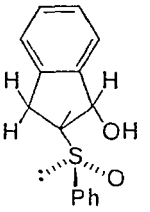
The four stereoisomers (only one enantiomer is reported) are listed below with the relative yields obtained in the co-oxidation in benzene solution.



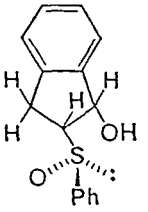
(11) m.p. 101° (60·3%)



(12) m.p. 158° (24·2%)



(13) m.p. 158° (15·6%)



(14) m.p. 146° (0·0%)

These results indicate that a 5·4 : 1 trans/cis mixture of hydroperoxides is formed and hence that in this system the co-oxidation is stereoselective rather than stereospecific as it was earlier suggested[143, 169, 171].

The formation of only three of the four possible sulphinyl isomers and the ratio in which they are formed appears to be clear evidence of the intramolecular character of the oxidation step.

In fact the molecular models of the *cis* and *trans* phenylmercapto indene hydroperoxides, precursors of compounds **11–14**, show that the *trans*

isomer may suffer intramolecular attack at sulphur from both sides through conformations of similar estimated energy and hence compounds **11** and **12** are formed in similar amounts. On the contrary in the case of *cis* hydroperoxide the conformation which would lead to compound **14** by direct oxygen transfer is not accessible requiring that the phenyl be above the indane ring. This may explain why only the *cis* isomer (**13**) is formed.

For the formation of the intermediate hydroperoxide the following mechanism based on a radical chain reaction may be formulated (equations 97–100)[168].

$$RSH \xrightarrow{O_2,\ u.v.\ light,\ etc.} RS\cdot \tag{97}$$

$$RS\cdot + \rangle C{=}C\langle \longrightarrow RS{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\cdot \tag{98}$$

$$RS{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\cdot + O_2 \longrightarrow RS{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OO\cdot \tag{99}$$

$$RS{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}O{-}O_2^{\cdot} + RSH \longrightarrow RS{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OOH + RS\cdot \tag{100}$$

When thiols and olefins are co-oxidized in the presence of an aliphatic amine, the end-products are 2-mercaptoethanols, disulphides and water[174,175] (equation 101).

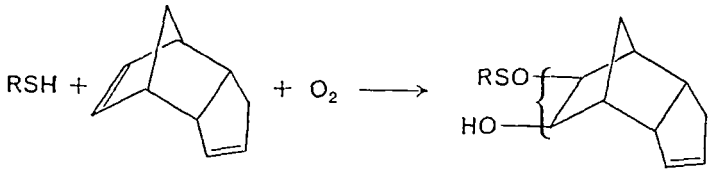
$$3RSH + \rangle C{=}C\langle + O_2 \xrightarrow{R_3N} RS{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OH + RS{-}SR + H_2O \tag{101}$$

This reaction may be explained in terms of an amine catalysed oxidation of the thiol[29] by the 2-mercaptoethylhydroperoxy intermediate.

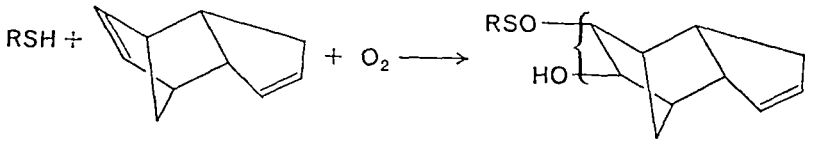
This was confirmed by the observation[174] that the complex of **10** with triethylenediamine oxidizes quantitatively benzenethiol to disulphide.

Olefins containing isolated double bonds with different reactivity towards thiyl radicals are selectively co-oxidized at the more reactive unsaturation centre[176]. This is the case of co-oxidation of *endo* and *exo* dicyclopentadienes with 4-chlorobenzenethiol (equations 102, 103). (The bracket indicates that the stereochemistry is unknown.)

Co-oxidation of thiols with 1,3-butadiene, the simplest conjugated diolefin, has been studied in the presence of *t*-butylamine[175]. Products derived from 1,2- and 1,4-addition were observed in the reaction with methane- and ethane-thiols, predominant 1,2-co-oxidation products were formed when benzene or *p*-toluenethiol were used (equation 104).



(102)



(103)

$$RSH + CH_2{=}CH{-}CH{=}CH_2 \xrightarrow[R_3N]{O_2} RS{-}CH_2{-}\underset{\displaystyle HO}{\underset{|}{CH}}{-}CH{=}CH_2 + RS{-}CH_2{-}CH{=}CH{-}CH_2{-}OH \tag{104}$$

The 1,2- versus the 1,4-addition to conjugated diolefins also depends on the structure of the diene[175, 177, 178]. 2,5-Dimethyl-2,4-hexadiene gives only 1,4-co-oxidation products[175] (equation 105) whereas 2,3-dimethyl-1,3-butadiene affords 1,2-oxidation products[177] (equation 106).

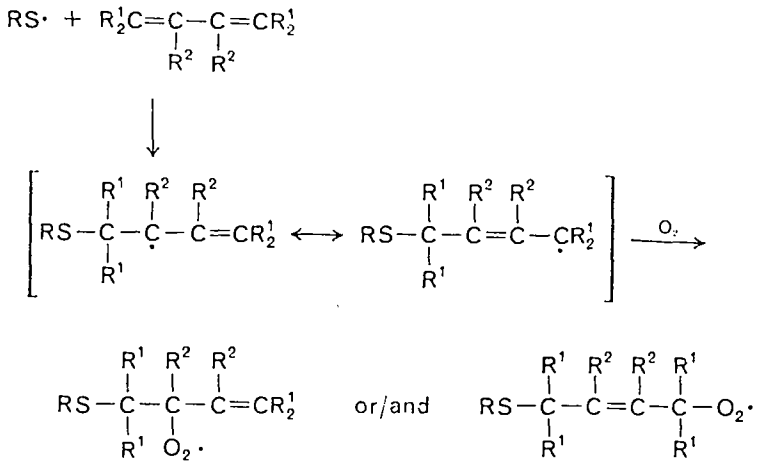
$$3RSH + (CH_3)_2C{=}CH{-}CH{=}C(CH_3)_2 + O_2 \xrightarrow{R_3N}$$

$$RS{-}\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}{-}CH{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}{-}OH + RSSR + H_2O \tag{105}$$

$$3RSH + CH_2{=}\underset{\displaystyle H_3C}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2 + O_2 \xrightarrow{R_3N}$$

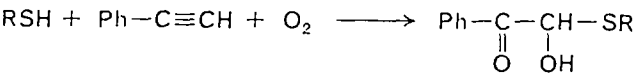
$$RS{-}CH_2{-}\underset{\displaystyle H{-}O}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2 + RSSR + H_2O \tag{106}$$

The scheme suggested for these reactions is similar to that proposed for the co-oxidation of simple alkenes. The thiyl radical attacks one of the terminal carbons to give an allyl radical followed by attack of oxygen at the 2 or 4 carbon depending on the relative stability of the two formal radicals (Scheme 8).



SCHEME 8

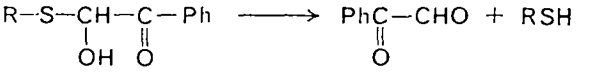
Co-oxidation of thiols and phenylacetylene with oxygen produces phenylglyoxal hemithioacetals[179] (equation 107).



(107)

The reaction occurs more easily than the co-oxidation with olefins. Benzenethiol and phenylacetylene react at reasonable rates even at temperatures below −70°C under u.v. irradiation. At this temperature a peroxidic compound which decomposes above −10°C to give the hemithioacetal is formed.

The products of co-oxidation of thiols and phenylacetylene are unstable and decompose to phenylglyoxal and thiol when vacuum distilled (equation 108).



(108)

The mechanism of the co-oxidation of acetylenes and thiols is not defined; however, a reaction sequence similar to that proposed for the co-oxidation with olefins has been suggested[179].

As reported above, the autooxidation is a quite general and important reaction. Beside the co-oxidation with olefins, which may be an undesired side reaction, oxidation of thiols by molecular oxygen represents a simple method of transforming these unstable compounds characterized by a

quite unpleasant smell into odourless and relatively stable compounds. It may also be a cheap method of synthesis of disulphides although care should be taken to avoid overoxidation. Furthermore, some thiols and their corresponding products of oxidation undergo easy base-promoted α-elimination leading to desulphurized compounds[180-182].

V. PHOTO-OXIDATION

Thiols undergo an easy photolytic reaction (see chapter 10 on photochemistry) which is in fact an oxidation of mercaptans to disulphides (equation 109).

$$2\,RSH \xrightarrow{h\nu} RSSR + H_2 \qquad (109)$$

The instability of thiols to light has been known for a long time[183] and there is a lively interest in the photolytic and radiolytic reactions with high energy radiations of thiols and sulphur compounds in general also because of the problem of biological effects of radiations[32, 184, 185].

Recent detailed work in the gas phase by Steer and Knight[186, 187], largely confirming earlier results[32, 184, 185, 188], showed that the primary photolytic process by irradiation at *ca.* 2500 Å for methane- and ethanethiols is the homolysis of the S—H bond (equation 110) to give thiyl radicals and hydrogen atom. The principal products of the reaction are molecular hydrogen and disulphides. The simple Scheme 9 was proposed for this reaction.

$$RSH \xrightarrow{h\nu} RS\cdot + H\cdot \qquad (110)$$

$$RSH + H\cdot \longrightarrow RS\cdot + H_2 \qquad (111)$$

$$2\,RS\cdot \longrightarrow RSSR \qquad (112)$$

SCHEME 9

Minor amounts of methane and hydrogen sulphide in the methanethiol reaction and of ethane, ethylene and hydrogen sulphide in the ethanethiol reaction were also formed. The authors[186, 187] propose that these products are not formed in a primary process, but they derive from reaction of the thiol with a disulphide molecule which has not yet transferred the excess of energy which it contains at the act of formation (Scheme 10).

$$2\,CH_3S\cdot \longrightarrow CH_3SSCH_3^* \qquad (113)$$

$$CH_3SSCH_3^* + CH_3SH \longrightarrow CH_3SSCH_3 + CH_3\cdot + HS\cdot \qquad (114)$$

$$CH_3\cdot + CH_3SH \longrightarrow CH_4 + CH_3S\cdot \qquad (115)$$

$$HS\cdot + CH_3SH \longrightarrow H_2S + CH_3S\cdot \qquad (116)$$

SCHEME 10

In the case of ethanethiol in addition to the processes corresponding to reactions (114)–(116), equation (117) was proposed to explain the formation of ethylene. Reaction (117), because of the larger rearrangement involved, should be slower than the equivalent of reaction (114),

$$C_2H_5SSC_2H_5^* + C_2H_5SH \longrightarrow C_2H_5SSC_2H_5 + C_2H_4 + H_2S \qquad (117)$$

as is in fact observed. Among the evidence presented by the authors[186,187] in favour of the mechanism of formation of hydrogen sulphide and hydrocarbons the decrease of the yields of these products with the pressure of added inert gas is especially convincing.

As far as the primary process (Scheme 9) is concerned the supporting evidence is overwhelming: addition of ethylene, for instance, decreases the yields of hydrogen and disulphide with concomitant formation of ethyl sulphide *via* addition of the thiyl radical to ethylene.

Flash photolysis studies[151] allowed the direct detection of thiyl radicals; these species were also detected by u.v. and e.s.r. when the photolysis was carried out in solid matrices[189–192].

Quite similar processes occur also in aqueous solutions, as well as in other solvents[151,183,184], sometimes complicated, however, by interaction of the radical initially formed (equation 110) with other species present. Indeed the photolysis of thiols has been used as a source of hydrogen atoms to study their reactions with several compounds[193].

Higher molecular weight thiols, particularly secondary and tertiary alkanethiols, may undergo other primary photolytic processes, in particular breaking of the carbon–sulphur bond[184,185]. In the majority of cases, however, the main path seems to be the sulphur–hydrogen bond breaking leading to the formation of thiyl radicals which may undergo in appropriate experimental conditions several reactions besides dimerization to disulphide (section IV). Carbon–sulphur bond fission may also occur when shorter wavelength light is used. Under these conditions more complex phenomena due to the production of particles with excess energy content have also been observed[194–197].

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The Chemistry of the Thiol Group
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CHAPTER 18

The synthesis and uses of isotopically labelled thiols

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I. INTRODUCTION

Isotopic labelling of thiols has been used in research disciplines ranging from atomic physics to forestry in the study of practically every atomic, molecular and biological process that thiols are known to undergo. In this review we will consider the changes that substitution of deuterium for the

hydrogen of the thiol group introduces into the translational, rotational and vibrational processes of thiols both in the ground and transition states. These perturbations have helped to elucidate some of the most fundamental structural and chemical properties of thiols. The low energy β-rays emitted by the thiol group when it is substituted with tritium or sulphur-35 allow the thiol group and its constituent atoms to be located in complex reaction mixtures. In this review we will consider the tracer applications of radio-isotope labelling in mechanistic studies of thiol reactions. However, we will also consider the use of tritiated and sulphur-35 labelled thiols in the optimization of industrial processes, as well as to trace the path that thiols follow in the body. We extend this review into these two areas of research which are usually considered to be beyond the research interests of the organic chemists for two reasons. First, the physiochemical phenomena which underlie these processes are the same as those encountered in the reaction vessel by the organic chemist. The same radical transfer reactions of thiols take place in the photochemical reaction vessel, synthetic rubber polymerization chambers, and within the body of an animal exposed to ionizing radiation. The relative lipid- as compared to water-solubility of a thiol determines not only the best procedure for its extraction from a reaction mixture but also whether the thiol will penetrate the lipoidal blood–brain barrier. Second, we have included these industrial and biological studies for the sake of the chemist who may want to extend his research on thiols to more industrially or biological significant problems. In total, we will cover processes as delicate as the passage of a thiol over a transition state or as intractile as the wearing down of steel. We will trace the flow of a thiol down the axon of a neuron and through the ecosystem of a forest.

II. MOTIONAL PROCESSES

The most fundamental chemical questions concerning the molecular weight, atomic co-ordinates and bond strengths of thiols have been answered in the most precise way by careful physical measurements of the translational, rotational and vibrational motions of thiols. Since in any one measurement the number of physical variables usually exceeds the observable parameters, meaningful physical parameters could not have been obtained if measurements had not been made on a series of isotopically substituted molecules. It is now common practice in molecular spectrometry to site a motional process from several isotopically labelled positions in a molecule. In the following sections, we will briefly describe the physical origin of the isotope effect in mass spectrometry, microwave

and infrared spectroscopy and review how it has been used to answer fundamental chemical questions concerning thiols.

A. Translation

Mass spectrometry is a relatively accurate and convenient method for the determination of the molecular weight of a molecule. Moreover, in the course of the measurement, the molecule often fragments to smaller molecular ions, whose molecular weights are also measured. Later the pattern of molecular fragments can be pieced together in a way that will reveal the structure of the thiol. However, very often fragments originating from different parts of a molecule will have the same mass and will not be distinguishable from each other. As we will see, isotopic labelling readily overcomes this problem and precisely traces the origin of molecule ion fragments.

When thiols enter the mass spectrometer, they are first ionized and partially broken into fragments. Both the molecular parent ion and the fragment ion carry a charge, e, by virtue of which they can be accelerated through a potential, V. When the ions emerge from the accelerating chamber they all possess the same kinetic energy, Mv^2, and potential energy, eV (where M is the mass and V the velocity of the ion). When this process is applied to a mixture of normal and heavier isotopically labelled thiols, both the light and heavy ions will emerge with the same energy, but the light molecules will be travelling faster than the heavy molecules. The accelerated ions next enter the magnetic sector of the spectrometer, where the magnetic field, H, exerts a centripetal force, HeV, on the ions which is exactly balanced by a centrifugal force, Mv^2/r, i.e. $HeV = Mv^2/r$ (where r is the radius of the ions trajectory through the magnetic field). The lighter, normal ions travel with a greater velocity v and experience a greater centripetal force, and an even greater centrifugal force, than the heavier isotopically labelled thiols. Accordingly, the path of the lighter ions will have a smaller radius. The difference in paths of the light and heavy ions facilitates their separation and analysis[1].

The two most labile bonds in a thiol, $R—CH_2—SH$, are the S—H and C—H bonds. However, removal of a hydrogen from the CH_2 or the SH group yields fragments with the same mass. Amos and coworkers[2] have used isotopic labelling to show that CD_3SH fragments to $[CD_2{=}SH]^+$ and $[CD_3S]^+$ in the ratio 2 : 1, while the ratio in CH_3CD_2SH is approximately unity. Upon ionization, benzenethiol-S-d_1 has been shown by Lawesson, Madsen and Schroll[3] to lose equal amounts of mercapto-deuterium and ring hydrogen. In a later section, we will show how separation of ion fragments using isotope labelling has made possible a

number of mass spectrometric studies of the bond energies of thiols and the thermodynamics of their bond cleavages.

B. Rotation

Microwave spectroscopy has proved to be a powerful technique, providing data on the structure and bonding of gaseous molecules. The interaction of the dipole moment of the molecule with a microwave field induces transitions between the rotational energy levels of the gaseous molecule. The microwave frequencies, at which the transitions occur, depend entirely on the moments of inertia of the molecule about its principal rotational axes. The moment of inertia is determined by the atomic masses and bond lengths and angles of the molecule. Usually the determination of one set of moments of inertia is not sufficient to give a unique set of molecular parameters. To obtain such a unique set of molecular parameters, measurements must be made on a series of molecules, in which isotopic substitution has been used to create a series of changes in atomic mass along the molecule. As microwave measurements are quite sensitive, thiols containing ^{13}C, ^{33}S and ^{34}S at natural abundance can be observed and used to provide a series of naturally occurring isotopically substituted molecules[4].

In the first application of microwave spectroscopy to a thiol, Solimene and Dailey[5] measured the 0_{00}–1_{01} transition in several isotopically substituted methane thiols, including $^{12}CH_3{}^{32}SH$, $^{13}CH_3{}^{32}SH$, $^{12}CD_3{}^{32}SH$, $^{12}CH_3{}^{33}SH$, $^{12}CH_3{}^{34}SH$ and $^{12}CH_3{}^{32}SD$. From these data they derived the moments of inertia and corresponding structural parameters of methanethiol. Kadzar, Abbason and Imanev[6] determined the structure of ethanethiol using $CH_2CH_2{}^{32}SH$ and $CH_2CH_2{}^{34}SH$. A more comprehensive set of molecular parameters for ethanethiol has been obtained by Hayaishi and coworkers[7] from the spectra of the *trans* and *gauche* isomers of CH_3CH_2SH, CH_2DCH_2SH (syn and anti), CH_3CD_2SH, $CH_3CH_2{}^{34}SH$ and CH_3CH_2SD.

In addition to rotating with the molecule as a whole, the methyl group of methane thiol can rotate against the thiol group along the C—S bond. The resulting modes of hindered rotation (i.e. torsional vibration) create an additional series of spectral lines. Solimene and Dailey[5], by measuring the intensity of the lower-lying excited torsional states relative to the ground state in CH_3SH and CD_3SH, determined that the potential barrier for hindered rotation is sinusoidal with a height of 1·06 kcal/mole. Later Kojima[8], measuring the $\Delta J = \pm 1$, $\Delta K = \mp 1$ lines in the ground state and the $\Delta J = 0$ lines in the first excited state of CH_3SH and $CH_3{}^{34}SH$ determined the potential barrier of methanethiol to be $444 \pm 10\ cm^{-1}$.

In similar measurements of CH_2DSH and CHD_2SH, Knopp, Daniel and Quade[9] showed that the staggered conformation for the methyl and thiol group corresponds to a threefold minima in the potential energy function for hindered rotation. Reddington[10] has found that the height of the potential barrier of CF_3SH and CF_3SD is quite close to that of CH_3SH. The fact that substitution of CF_3 for CH_3 has little effect on the height of the barrier rules out repulsion between non-bonded atoms as the source of the potential barrier. Measurements like these can be expected to continue to provide insight into the nature of the interaction between two internally rotating groups.

It is interesting to note that one of the first measurements of the electric nuclear quadrapole moment of ^{33}S was made by Bird and Townes[11] who on close examination of Solimene and Dailey's microwave spectrum of methanethiol noticed a group of three very weak doublets. They ascribed the doublets to the interaction of the electric quadrupole moment of natural abundance ^{33}S with the electric field of the molecule as a whole.

C. *Vibration*

Infrared spectroscopy can be used not only in a qualitative way to identify functional groups in a molecule, but also to provide precise data on the bond strengths. Before such calculations can be made, however, every observed spectral band must be assigned to one of the vibrational modes of the molecule. Such assignments can often be ambiguous. Replacing an atom in a molecule with one of its isotopes does not, to a high order of approximation, change the electronic structure of the molecule, and therefore does not alter the potential functions governing the vibrations of the atoms. However, the frequency of the vibration will be affected and will reveal itself in a shift of the vibrational band. The shift will be small, when the isotopically substituted atoms moves very little in a particular vibrational mode; but when the atom has a large amplitude of vibration in a mode, the shift will be large[12]. Plant, Tarbell and Whiteman[13] reported the first isotope shift observed in the vibrational spectrum of a thiol. They found that in benzenethiol and *n*-hexanethiol deuteration of the thiol groups shifted the bands at 2600 cm^{-1} to 1839 and 1870 cm^{-1}, respectively. Since then isotope shifts have helped elucidate the infrared spectra of several thiols. For example, CF_3SH displays a band at 906 cm^{-1}, which shifts to 699 cm^{-1} in CF_3SD. This large spectral shift has allowed the band to be assigned to the CSH bending mode; whereas a series of bands near 500 cm^{-1} shift very little upon isotopic substitution, verifying their assignment to the CF_3 deformation modes[10].

Takeoka[14] has used the isotope shifts observed in the infrared spectrum of cyclohexanethiol-S-d_1 to assign the observed bands to the proper vibrational modes. In addition, bands belonging to the axial and equatorial conformations of cyclohexanethiol could be distinguished. Furthermore, the changes in the relative concentration of the two conformers on going from the liquid to the plastic to the hard crystalline phases could be followed.

Once the vibrational bands of a molecule have been assigned to their proper modes, calculations can be made of the interatomic forces that bind atoms together to form a molecule. The strength of these interatomic forces is measured in terms of a force constant for a particular vibrational mode. When the atomic co-ordinates and masses of a molecule are known, a complete set of force constants can be used in a normal co-ordinate analysis using the Wilson *FG* matrix method[15], to obtain a set of calculated vibrational bands. The set of force constants is then adjusted so as to obtain the best fit between observed and calculated frequencies. As occurs in other spectroscopic measurements, the number of force constants often exceeds the number of observed frequencies in any one spectrum. Since the force field is independent of isotopic substitutions, the spectra of isotopically substituted molecules can be used to provide additional frequencies. A particularly good check of a force field is its ability to predict the spectra of isotopically substituted molecules. May and Pace[16,17] have obtained a force field for methanethiol based on the frequencies of CH_3SH and CH_3SD and microwave structural parameters. Their force field accurately predicts all the observed frequencies of the normal and isotopically labelled molecules. Hayaishi and coworkers[18] have obtained a reliable set of force constants for ethanedithiol from the frequencies of $HSCH_2CH_2SH$ and $DSCH_2CH_2SD$. Furthermore, they have shown that when *trans, trans, trans* and *trans, trans, gauche* conformations are assumed, the force field satisfactorily predicts the observed frequencies of *n*-propanethiol, β-thiamethylethane thiol, β-halogenoethane thiol and 1,2-dithiamethyl ethane.

III. CLEAVAGE OF THE S—H BOND

A. The Primary Hydrogen Isotope Effect and the Nature of the Transition State

In the previous section we saw how isotope labelling has played an indispensable role in the elucidation of the motional processes and structure determinations of thiols. In this section we turn to the dynamics of the rupture of the S—H bond. The chemical phenomenon of the

S—H bond cleavage is indeed only another motional process, in which the thiol hydrogen moves independently of the rest of the thiol molecule in a sort of extended S—H stretching mode. As we have seen, substitution of deuterium for the thiol hydrogen has a pronounced effect on the motion of a thiol, particularly the S—H bond stretching vibration. We might expect that deuterium substitution will greatly affect the dynamics of the S—H bond cleavage. In this section, after having reviewed the theoretical basis for primary hydrogen isotope effects[19,20], we will construct several transition state models for S—H bond cleavage[20], predict the isotope effect for each model, and compare these to the measured values. Finally, we will turn to the use of isotopic labelling to trace the fate of the thiol hydrogen after it has been abstracted from a thiol.

For the purpose of theoretical discussion, we consider that the thiol lies on a surface of potential energy, whose co-ordinates are the bond lengths and angles of the thiol molecule in the horizontal direction and potential energy in the vertical direction. The exact topography of the surface is determined by the electronic structure of the molecule. During the processes of S—H bond cleavage, the thiol can be thought of as travelling across the surface along a pathway of lowest energy, which will correspond to the S—H stretching mode. The highest point along this pathway of lowest energy is called the transition state. The rate at which S—H bond cleavage will occur depends primarily on the probability of a thiol reaching the transition state, RSH‡. If we consider that ground state and transition state molecules are in equilibrium, then the process can be characterized by an equilibrium constant $K^{\ddagger}$ (eqns. 1 and 2).

$$\mathrm{RSH} \rightleftharpoons \mathrm{RSH}^{\ddagger} \tag{1}$$

$$K^{\ddagger} = \frac{[\mathrm{RSH}^{\ddagger}]}{[\mathrm{RSH}]} = \frac{\prod Q^{0}_{\mathrm{products}}}{\prod Q^{0}_{\mathrm{reactants}}} \exp(\Delta E/RT) \tag{2}$$

Equilibrium constants can be expressed in terms of the motional processes of a molecule, i.e. in terms of the partition function of the reactant and the product, which in this case is the transition state, as seen in equation (2). The partition function, Q or Q^{0} (for unit volume of an ordinary molecule), denotes the probability of a molecule existing in any one particular motional state, summed over all the possible translational, rotational and vibrational states available to the molecule. The energies of the motional states are calculated taking the lowest classical state, as having zero energy. The exponential term in equation (2) corrects for the difference in energy between the reactant and transition states.

Having written $K^{\ddagger}$ in terms of motional states of the molecule, we are now prepared to ask how substitution of deuterium for the thiol hydrogen

will affect the probability of the thiol reaching the transition state $RSH^{\neq}$. Experimentally the question is posed in the ratio of the rate of the S—H bond cleavage over rate of S—D cleavage. These rates are largely determined by the equilibria in equations (3) and (4). As seen in equation (5) the hydrogen isotope effect can be written in terms of the partition functions for the light and heavy thiols.

A major advance in the theory of primary hydrogen isotope effects came when the approximation was made that substitution of deuterium for hydrogen does not greatly affect the classical properties of the molecule, such as the mass or moments of inertia and consequently neither the translational nor rotational partition functions[21]. This left only the quantum mechanical vibrational partition function as a source of the isotope effect. Writing the deuterium isotope effect in terms of the complete vibrational partition function, equation (6) is obtained, where $u_i = h\nu_i/kT$, ν_i is the frequency of the ith vibrational mode and N is the number of atoms in the molecule. The products and summations are

$$RSH \underset{\longleftarrow}{\xrightarrow{K_H^{\neq}}} RSH^{\neq} \tag{3}$$

$$RSD \underset{\longleftarrow}{\xrightarrow{K_D^{\neq}}} RSD^{\neq} \tag{4}$$

$$\frac{k_H}{k_D} = \frac{K_H^{\neq}}{K_D^{\neq}} = \frac{\Pi Q_H^{0\neq}}{\Pi Q_D^{0\neq}} \times \frac{\Pi Q_D^0}{\Pi Q_H^0} \tag{5}$$

$$\frac{k_H}{k_D} = \prod_i^{3N^{\neq}-7} \frac{1-\exp(-u_{i(D)}^{\neq})}{1-\exp(-u_{i(H)}^{\neq})} \times \prod_i^{3N-6} \frac{1-\exp(-u_{i(H)})}{1-\exp(-u_{i(D)})} \times \exp\left\{-\frac{1}{2}\left[\sum_i^{3N^{\neq}-7}(u_{i(H)}^{\neq}-u_{i(D)}^{\neq}) - \sum_i^{3N-6}(u_{i(H)}-u_{i(D)})\right]\right\} \tag{6}$$

taken over the $3N-6$ vibrational modes of the ground state and over $3N^{\neq}-7$ vibrational modes of the transition state, in which the vibrational mode corresponding to the reaction pathway (in our case the S—H stretch) is omitted. As seen in equation (6), an isotope effect will occur only when the deuterium participates in a vibrational mode, whose frequency changes on going from the ground to the transition state. We are now ready to characterize various transition states precisely in terms of what vibrational modes have changed, which is another way of locating the transition state on the potential surface.

The simplest model that can be chosen for the transition state is one in which the only vibrational mode that has changed is the S—H stretching mode. Since this vibrational mode is the reaction co-ordinate itself, it does not contribute to the isotope effect in the transition state. Molecular vibrations involving hydrogen generally have vibrational bands above 700 cm^{-1}, for which $\exp(-u)$ is 0·03 at 300 K and products involving this term will be close to unity. Equation (6) therefore reduces simply to

$$\frac{k_H}{k_D} = \exp\left[\tfrac{1}{2}(u_{RSH} - u_{RSD})\right] = \exp\left[\frac{hc}{2kT}(\bar{\nu}_{RSH} - \bar{\nu}_{RSD})\right] \tag{7}$$

where $\bar{\nu}$ is the wave number of the thiol stretching mode in the ground state. Using the literature value[16] for the thiol stretching mode of methanethiol, 2605 cm^{-1} and 1893 cm^{-1} for CH_3SH and CH_3SD respectively, a value of 5·5 is obtained for k_H/k_D. Using equation (8), this corresponds to a value of

$$\frac{k_T}{k_H} = 1{\cdot}11\left(\frac{k_D}{k_H}\right) \times 1{\cdot}44 \tag{8}$$

or 11·29 for k_H/k_T, the primary tritium isotope effect.

Weakening the S—H bond in the transition state must certainly reduce the frequency of the C—S—H bending mode. If we consider the extreme case in which the frequency has gone to zero, the product term $[1-\exp(-u^{\ddagger}_{i(D)})]/[1-\exp(-u^{\ddagger}_{i(H)})]$ of equation (6) approaches $u^{\ddagger}_D/u^{\ddagger}_H$, which can be approximated by $(m_H/m_D)^{\frac{1}{2}}$, where m refers to mass. Equation (6) now reduces to

$$\frac{k_H}{k_D} = \left(\frac{m_H}{m_D}\right)^{\frac{1}{2}} \exp\left\{\frac{hc}{2kT}[(\bar{\nu}_{SH\ stretch} - \bar{\nu}_{SD\ stretch}) + (\bar{\nu}_{CSH\ bend} - \bar{\nu}_{CSD\ bend})]\right\} \tag{9}$$

Using values of 802 cm^{-1} and 623 cm^{-1} for the bending modes of CH_3SH and CH_3SD,[16] k_H/k_D increases to a value of 5·9 and k_H/k_T to 11·42. We may then expect that weakening the C—S—H bending mode will tend to increase slightly the isotope effect.

In addition to unimolecular dissociation of the S—H bond, thiol bonds are often ruptured when an acceptor molecule (usually a free radical) abstracts hydrogen from the thiol. In this case, the transition state will contain the three-centre linear system S—H—A, where A is the acceptor atom. The stretching and bending modes of the C—S—H group of the ground-state thiol will make the same contribution to the isotope effect as they did in the unimolecular dissociation, and the S—H stretch will

remain the reaction co-ordinate. However, in the transition state a new linear stretching mode associated with the S—H—A system will have to be introduced. If S—H—A is asymmetric, i.e. A does not resemble sulphur, then the stretching mode shown in Figure (1a) will tend to weaken the isotope effect for either of two reasons: (1) for large u and $u^{\ddagger}_{SHA} > u^{\ddagger}_{SDA}$, the transition state vibration will detract from the contribution made by the ground state molecules or (2) for small u, $[1-\exp(u^{\ddagger}_{i(D)})]/[1-\exp(u^{\ddagger}_{i(H)})]$ will introduce the term m_D/m_H. On the other hand, when S—H—A is symmetric, the linear vibration introduced, Figure (1b), in which H does not move, will not contribute to the isotope effect.

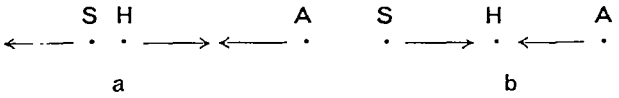


FIGURE 1. Stretching modes of the S—H—A system.

We might conceive of a reaction in which S—H bond cleavage occurs long before the thiol reaches the transition state, such as in the base-catalysed addition of RSH to an olefin, equations (10) and (11).

$$RSH + B \rightleftharpoons [RS^- HB^+] \tag{10}$$

$$[RS^- HB^+] + \rangle C{=}C\langle \longrightarrow RS{-}\overset{H}{\underset{|}{C}}{-}\overset{H}{\underset{|}{C}}{-}{+}B \tag{11}$$

Here isotope substitution exerts its effect on the rate of the reaction, *via* the pre-reaction equilibrium, equation (10). Rather than calculating the kinetic isotope effect for the reaction, we will want to obtain an expression for the ratio of the equilibrium reactions.

$$RSH + B \overset{K_H}{\rightleftharpoons} [RS\cdots HB] \tag{12}$$

$$RSD + B \overset{K_D}{\rightleftharpoons} [RS\cdots DB] \tag{13}$$

The ratio of equilibrium constants, K_H/K_D, for equations (12) and (13) is equivalent to the equilibrium constant $K_{H/D}$ for the isotope exchange equilibrium.

$$RSH + [RS\cdots DB] \overset{K_{H/D}}{\rightleftharpoons} RSD + [RS\cdots HB] \tag{14}$$

Expressing $K_{H/D}$ in terms of the vibrational partition functions we obtain

$$K_{H/D} = \frac{Q_{RSH}\, Q_{RSDB}}{Q_{RSD}\, Q_{RSHB}} \tag{15}$$

Equation (15) is simply the individual partition function ratio of isotopic substituted RSH Q_{RSH}/Q_{RSD}, divided by Q_{RSHB}/Q_{RSDB},

$$\frac{Q_{RSH}}{Q_{RSD}} = \Pi \frac{u_{RSD}}{u_{RSH}} \times \exp\left(\sum \frac{u_{RSH} - u_{RSD}}{2}\right) \times \Pi \frac{1-\exp(-u_{RSH})}{1-\exp(-u_{RSD})} \tag{16}$$

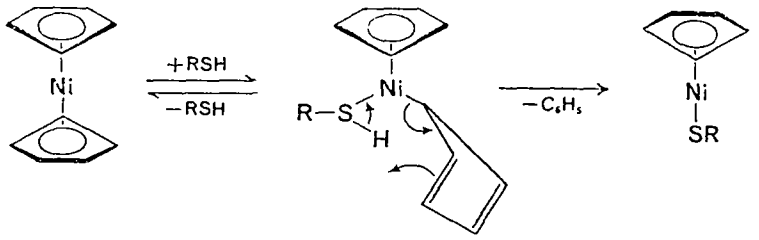
$$\frac{Q_{RSHB}}{Q_{RSDB}} = \Pi \frac{u_{RSDB}}{u_{RSHB}} \times \exp\left(\sum \frac{u_{RSHB} - u_{RSDB}}{2}\right) \times \Pi \frac{1-\exp(-u_{RSHB})}{1-\exp(-u_{RSDB})} \tag{17}$$

Just as in the case of the kinetic isotope effect, deuterium substitution is felt only in those vibrational modes that change on going from reactants to products.

The rate at which a particular reaction takes place is only partially accounted for by $K^{\ddagger}$. The rate of passage of a thiol over the potential barrier at the transition state is given by $\nu_i^{\ddagger}[RSH]$, in which $\nu_i^{\ddagger}$ is the frequency of the vibration that carries the thiol over the potential barrier and tears the S—H bond apart. The magnitude of $\nu_i^{\ddagger}$ is determined by the curvature of the potential surface near the transition state and since the curvature is concave downwards the frequency is imaginary, but has the same absolute value as if the surface were concave upwards, with a real vibrational frequency. The rate is influenced by two other parameters, which intimately depend on the topography of the potential surface. These are the transmission coefficient, i.e. the fraction of molecules passing over the barrier in the forward direction, and the percentage of tunnelling of the molecules under the potential barrier. These parameters are generally ignored or considered to introduce no isotope effect; however, in cases where large deviations from the predicted isotope effects are found, they have to be considered. The way in which these phenomena are affected by isotope substitution is an active field of theoretical study.

The observation of a large kinetic isotope effect indicates that isotopically substituted thiol hydrogen participates directly in a vibrational mode, whose frequency changes on going to the transition state, i.e. that S—H bond cleavage is an integral part of the transition state. The fact that a value for k_H/k_D of 2·80 was obtained for the addition of benzenethiol-S-d_1 to nickelocene, led Ellgen and Gregory[22] to propose the mechanism below for the reaction. Although the authors did not comment

on the rather low value of k_H/k_D, it would seem to indicate that the zero point energy lost on cleavage of the S—H bond is partially offset by the formation of the cyclopentadienyl hydrogen bond. The abstraction of



thiol hydrogen by the triphenylmethyl radical proceeds with an anomalous large value for k_H/k_T of 14·9, which was attributed by Lewis and Butler[23] to tunnelling through the potential barrier, which occurs when a barrier is symmetrical.

Dmuchovsky, Vineyard and Zienty[24] observed a quite unusual inverse isotope effect for k_H/k_D of 0·65 for the base catalysed addition of *n*-butanethiol-S-d_1 to maleic anhydride. While inconsistent with any model of a transition state involving S—H bond cleavage, the inverse isotope effect could be accounted for by postulating a pre-reaction equilibrium between butanethiol and triethylamine, much like the one in equations (10) and (11). In fact, substitution into equations (16) and (17) of 2566 and 1850 cm^{-1} for the S—H and S—D stretching frequency, respectively, and 3253 and 2380 cm^{-1} for the N—H and N—D stretches of the amine–thiol complex, yields an equilibrium isotope effect of 0·68[23].

Isotope equilibrium exchange constants for a number of thiol–water systems have been measured and the value $K_{H/D}$ is usually referred to as the equilibrium isotope separation factor, α. Haul and Blenneman[25] have measured α for $HSCH_2CH_2SD$ as a function of temperature and obtained $\ln \alpha = 262/T - 0{\cdot}1162$, which corresponds to a ΔH of −520 cal/mole. Sakodynskii, Babkov and Zhavoronkov[26] found that changing the structure and composition of a thiol had very little effect on α, which indicates that, during hydrogen exchange with water, changes in vibrational frequencies are restricted to the C—S—H bonds.

The measurement of kinetic isotope effects have provided insight into economically important industrial processes. Early in the course of the synthetic rubber programme it was found that the molecular weight of a polymer such as G R—S, could be quantitatively regulated by the addition of thiols to the polymerization system. Normally the polymerization occurs as in equation (18); however, a growing polymer can abstract a hydrogen

atom from thiol, thereby transferring the radical to the thiol and inactivating the polymer chain, equation (19).

$$M_n^{\bullet} + M \xrightarrow{k_2} M_{n+1}^{\bullet} \quad (18)$$

$$M_n^{\bullet} + RSH \xrightarrow{k_3} M_nH + RS^{\bullet} \quad (19)$$

The chain length of the polymer formed is proportional to the transfer constant k_3/k_2, which is the ratio of the specific rate of radical transfer to the specific rate of chain propagation[27]. Wall and Brown[28] measured the isotope effect $k_{t(H)}/k_{t(D)}$ of the chain transfer step in the butanethiol-S-d_1 mediated polymerization of styrene. A value of 4, somewhat less than the predicted value of about 6, was obtained. The low kinetic isotope effect indicated that either the loss of zero point energy of the S—H bond had been compensated by the formation of unusually strong bonds or that the reaction was complicated by the abstraction of butyl hydrogens as well as thiol hydrogen. Data such as these can often aid in the search for more efficient transfer agents.

B. Tracers of Atoms and Free Radicals during S—H Bond Cleavage

In addition to its use in probing the nature of transition states, labelling with heavy hydrogen is an indispensable aid in following the fate of thiol hydrogen in the reaction mixture. It distinguishes thiol hydrogen not only from the hydrogens of the reaction mixture as a whole, but also from other hydrogen atoms of the thiol, which may have been dissociated under the reaction conditions that led to the dissociation of the S—H bond.

Greig and Thynne[29] have measured the relative rates at which methyl radicals abstract hydrogen and deuterium from CD_3SH. The hydrogen of the SH bond was abstracted 120 times faster than the methyl deuterium. Riesz and Burr[30] have measured the relative amounts of D_2 and HD produced by the reaction of deuterium atoms with cysteine-S-d_1 and n-butanethiol-S-d_1. The yields of D_2 were 80 and 83%, respectively, indicating that atom abstraction occurred primarily from the —SD group. Volman, Wolstenholme and Hadley[31] irradiated CH_3SD at 77 K with 2537 Å light and detected e.s.r. signals originating from D• but not from H. This indicated, that if $\cdot CH_2SD$ radicals were observed in the irradiated sample, they could only have been formed by a secondary radical abstraction reaction. Keyes and Harrison[32] were able to study the two major pathways of thiols that occur in the ion chamber of the mass spectrometer. Unlabelled CH_3SH yields fragments which cannot be separated, but CD_3SH, equations (20) and (21), yields $[CD_3S^+]$ and $[CD_2{=}SH^+]$ ions, whose heat of formation were found to be 214 and

219 kcal/mole, respectively. The difference in the heats of formation indicate the relative ease with which hydrogen can be abstracted from a mercapto group as opposed to a methyl group. Deuterium labelling has revealed that the fragmentation of benzenethiol is considerably more

$$CD_3SH \xrightarrow{9{\cdot}54\ eV} e^- + [CD_3SH]^+ \xrightarrow{2{\cdot}22\ eV} [CD_3S^+] + H \qquad (20)$$

$$\searrow^{2{\cdot}47\ eV} [CD_2{=}SH^+] + D \qquad (21)$$

complex than that of methanethiol. Earnshaw, Cook and Dinneen[33] found that the fragment ions produced from benzenethiol-S-d_1 could be rationalized only by assuming that the parent ion $C_6H_5DS^+$ exists in two isomeric forms, an ionized benzenethiol (Figure 2a) and a cyclic seven-membered ion, in which the deuterium atom cannot be associated with any particular carbon atom (Figure 2b).

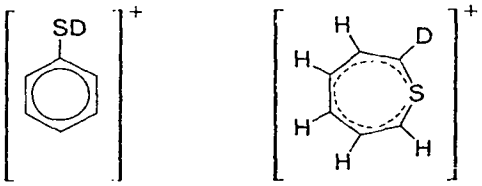


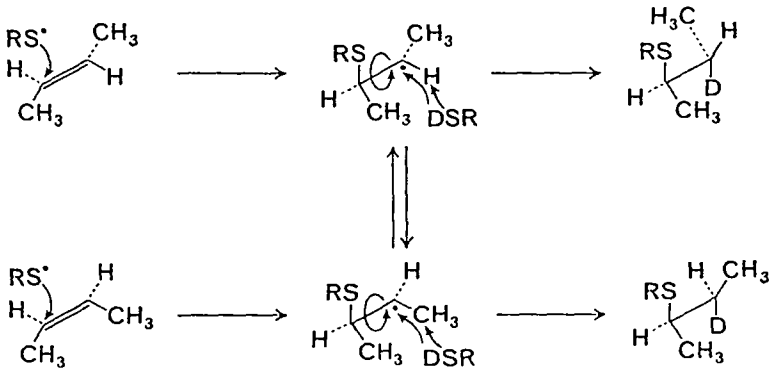
FIGURE 2. Isomeric forms of the $C_6H_5DS^+$ ion.

Labelling of the thiol group with heavy hydrogen can provide information concerning the nature of the hydrogen abstractor as well. The phenylethyl radical can exist as two isomers which can be interconverted by a 1,2 hydrogen migration (equation 22). Slaugh[34a] by

$$\begin{array}{ccc} PhCH_2\dot{C}H_2 & \rightleftharpoons & Ph\dot{C}HCH_3 \\ \downarrow PhST & & \downarrow PhST \\ PhCH_2CH_2T & & PhCHTCH_3 \end{array} \qquad (22)$$

allowing the radical to abstract hydrogen from benzenethiol-S-t_1 was able to mark the site of the radical with tritium. Methanethiol-S-d_1 adds across the double bonds of *cis*- and *trans*-2-butene to form identical mixtures of erythro- and threo-3-deuterio-2-(methylthio)butane. Skell and Allen[34b] found that the radical reaction takes place in two steps, the

addition of a methylthio radical to butene followed by the abstraction of deuterium from a molecule of CH_3SD by the 3-methylthio-2-butyl radical (equation 23). The fact that with deuterium labelling a mixture of threo



(23)

and erythro methylthiobutanes is obtained indicates that abstraction of thiol hydrogen is slower than the rate of rotation about the 2,3 carbon—carbon bond of the radical.

There are many exchange reactions that can be detected only with the use of isotopic labelling. One such reaction is hydrogen exchange between a thiol and a protic solvent. For example, Denisov, Kazakova and Ryl'tsev[35] studied mixtures of MeSH (or iso-BuSH) : MeOD and iso-BuSD : HOAc (or MeOH) to determine the relationship between the rate of hydrogen exchange and proton donor and acceptor properties. Sulphur-35 labelling was used by Dixon, Kornberg and Lund[36] in a study of the enzyme, malate synthetase, to determine whether the enzyme had a catalytic effect on exchange between coenzyme A-^{35}S and acetyl coenzyme A (equation 24)

$$CoA-{}^{35}SH + acetyl-S-Co \rightleftharpoons acetyl-{}^{35}S-CoA + CoA-S-H \qquad (24)$$

In the photolysis of the S—H bond it is possible to introduce into the thiol more than enough energy for the cleavage of the S—H bond. The very subtle question of whether upon bond cleavage this excess energy is channelled into the vibrational modes of the radical or into the translational energy of the dissociated hydrogen atom has been answered by White and coworkers[37,38] by a clever use of isotope labelling. Translationally excited hydrogen atoms displace deuterium from D_2 to form HD (equation 25) to an extent that is proportional to the energy of the hydrogen atom. By photolysing CH_3SH in the presence of D_2 and measuring the amount of HD produced, they found that the excess energy resided chiefly in the

translational mode of the hydrogen atom. Furthermore, hydrogen atoms formed at 2282 Å appeared to have on the average significantly more energy than those produced at 2537 Å.

$$\left.\begin{aligned} RSH &\xrightarrow{h\nu} RS + H^* \\ H^* + D_2 &\longrightarrow HD + D^* \end{aligned}\right\} \qquad (25)$$

IV. TRACING ^{35}S-LABELLED THIOLS IN BIOLOGICAL SYSTEMS

In the previous section we have seen how isotopic labelling has been used to trace the fate of thiol sulphur and hydrogen atoms in the course of chemical reactions. However, by far the greatest application of isotopic labelling in tracer studies of thiols has been in biochemical, biological and clinical studies which have sought to map out the path followed by various thiols in the body from the time of their administration to their excretion. While many of these studies have been performed by scientists other than chemists, the phenomena they probe are essentially physiochemical in nature. For this reason we have taken the liberty to extend the scope of this review to the biological applications of isotopic labelling of thiols. We have done this in the hope that it will familiarize the chemist working in an interdisciplinary group with the nature of a biological system from the point of view of tracer studies, for which he may be asked to design a chemical probe.

A. *Macromolecular Systems*

Before turning to body tracer studies, we might consider the application of ^{35}S-tracing to a few isolated biochemical systems. The only place thiopurines and thiopyrimidines occur in nature are in the tRNA's (transfer ribonucleic acid). The question that was immediately posed after their discovery was whether whole thiopurines and thiopyrimides are incorporated in tRNA at the time of chain assembly or whether at some later time sulphur is exchanged for oxygen at particular sites in assembled tRNA chains that are deficient in sulphur. Sulphur-35 labelling has played an indispensable role in the discovery of the cysteine tRNA sulphurtransferase enzymes, that were found to substitute the sulphur-35 of labelled cysteine for the oxygen in the 4-position of uridine[39], in tRNA chains deficient in thiol sulphur. Sulphur-35 labelling also revealed that in some cases β-mercaptopyruvate could also serve as a donor of sulphur[40].

Sulphur-35 labelling of the cysteine residues in a protein has often been used as a convenient way of tagging a particular protein in the study of a

macromolecular phenomenon. For example, the macromolecular machinery used in the bacterial cell for the synthesis of proteins initially consists of (1) a chain of mRNA (messenger ribonucleic acid), (2) around which is clamped a 30S and a 50S ribosome particle, which together form an active 70S ribosome complex, (3) to which is bound a f-Met-$tRNA_F$ (N-formyl-L-methionyl transfer ribonucleic acid) molecule, that will supply the first amino acid to be incorporated. It was believed that upon completion of the synthesis of the polypeptide chain, the 70S ribosome is released in a form that cannot be immediately re-used and that it must first be dissociated back into 30S and 50S subunits. A protein known as initiation factor F_3 was later found to be essential for the formation of the initiation complex, and lately its function has been revealed in a study that has employed ^{35}S-labelled F_3[41]. ^{35}S-F_3 was shown to bind readily to 30S particles, but to neither 50S particles nor the 70S complex. When the ^{35}S-F_3 charged 30S subunit is induced to a 50S subunit by increasing the Mg^{2+} concentration of the media, ^{35}S-F_3 is released. This suggested that when an initiation complex is formed from 50S and F_3-30S subunits, F_3 is released and is free to dissociate other used inactive 70S complexes into subunits that can subsequently reform active 70S complexes.

^{35}S-Labelling has also been used in a quantitative fashion to obtain data on the number of binding sites available to a labelled molecule in a particular macromolecular complex. For example, the 30S particle was found to have one site available for ^{35}S-F_3[41]. Arabinosyl—6-mercapto purine-^{35}S (ara—MP-^{35}S), a non-toxic suppressor of the homograft response, was found to bind the surface red blood cells with a minimum of $6{\cdot}7 \times 10^5$ sites on B red blood cells and $1{\cdot}2 \times 10^5$ sites on tanned sheep blood cells[42].

Turning to a very simple biological system, ^{35}S-labelling has proved to be quite efficient in visualizing the behaviour of viruses. Virus particles usually consist of a strand of nucleic acid contained in a sheath of coat protein. Upon infection of a cell at 37°C, the nucleic acid enters the cell leaving its coat protein bound to the cell surface, whereas at 4°C the nucleic acid prefers to remain on the cell surface with its coat on. This phenomenon has been visualized with Sendai virus, whose coat proteins have been labelled with cysteine-^{35}S[43]. Ten minutes after infection of human amnion cell culture, faint uniformly distributed grains appear in the autoradiographs of the infected cell, reaching a maximum after 60 min. The uniform distribution of grains suggested that the labelled viral component was absorbed onto, but had not penetrated into, the cell. This was supported by the fact that identical grain counts were obtained at 37°C and 4°C. Mechanical shearing is often sufficient to

knock coat proteins off the cell surface. This technique together with ^{35}S-labelling can be used to distinguish between viral components injected into and absorbed onto cells[44]. MS-2 RNA coliphages contain two species of proteins, a coat protein and a maturation protein. The latter is required for both phage absorption to the F-pili of the host *Escherichia coli* cell and for the reconstitution of the infectious phage. ^{35}S-labelled MS-2 phage was used to determine whether the maturation protein enters the cell together with RNA. After infection at 37°C and shearing, 300 cpm/10^9 cells remained associated with the cell, whereas at 4°C only 20 cpm/10^9 cells were obtained. This implied that during infection the maturation protein had penetrated beyond the F-pili of the *E. coli* cell.

B. Whole Body Systems

In the remaining part of this section, we will consider the fascinating use of ^{35}S-labelling to follow the path taken by various thiols in an organism. After ingestion or intravenous or intraperitoneal injection, thiols rapidly cross the gastro-intestinal barrier and enter the vascular system of the organism, where they are swept by the blood flow past the membranes, lipoidal structures that insulate the organs and cells from the blood stream. At this point the thiol is evenly distributed in the vascular system of all the organs of the animal and its fate from here on will be determined largely by its physiochemical properties.

If the thiol is relatively soluble in lipids, it will be able to penetrate the lipoidal membranes, and will freely pass in and out of cellular structures. For example, thiopental, a rapidly acting anaesthetic, has a high solubility in lipids; and this allows it readily to penetrate the lipid membranes of the brain. A combination of ^{35}S-labelling and autoradiography has shown that the distribution of thiopental-^{35}S in the brain itself is not uniform[45]. Once inside the brain the distribution of the thiol depends not so much on its lipid solubility, but on the pattern of blood flow in the cortex, geniculates, colliculi and white matter of the cat brain. In fact, thiopental-^{35}S autoradiography has been used as a means of studying the physiological territory of supply of cerebral blood vessels[46]. While thiopental is freely passing in and out of the brain, its concentration in other organs is rapidly equilibrating in accord with the lipid solubility of the thiol. Ocular tissues, like the blood–brain barrier, behave as a lipid membrane and ^{35}S-thiopental, with its high lipid solubility, experiences no delay in penetrating the uveal tissue[47]. This is in contrast to more ionizable drugs, like phenobarbitone, which slowly penetrate the uveal tissue, but once inside bind to pigmented molecules. Thiopental-^{35}S forms no such complexes and is rapidly swept out of the tissue by the blood flow. In

vital organs, such as the brain, lung and liver, ^{35}S-activity reaches its maximum level within 15 s after injection and decreases to a plateau by 2 min. The liver then commences thiopental uptake again, obtaining a peak after 5 min, while depot fat takes up thiol at a constant rate. By the time the animal awakes, most of the thiol is concentrated in the liver and depot fat. It is interesting to observe that the lipid solubility of thiopental that allowed it to penetrate the brain so rapidly has led to the termination of its anaesthetic action[48]. With time thiopental will gradually accumulate in the kidneys and will be excreted[49].

A rough idea of the path that a thiol follows in the body can be obtained by measuring its rate of its excretion *via* urine, faeces and respiratory air. ^{35}S-Labelling has allowed the following kind of data to be obtained: 70% of glutathione-^{35}S subcutaneously injected in a mouse is excreted in the urine within 18 h[50]; the radioactivity of ^{35}S-thiobarbiturates are excreted 70–90% in the faeces and up to 1% by respiration[51]; SKF 525-A (2-diethylaminoethyl 2,2-diphenylvalerate) prolongs the thiopental induced sleeping time in mice by delaying the urinary excretion of injected ^{35}S-labelled thiopental[52].

Often in the course of a thiol's travels through the body, it will encounter a compound with which it will form a complex. In contrast to thiopental, penicillamine-^{35}S rapidly enters the plasma after oral administration where it is bound to the serum albumin[53]. In this bound state, penicillamine is no longer able to pass through the semi-permeable membrane of the kidneys, which retards its excretion in the urine. Penicillamine-^{35}S subsequently becomes evenly distributed in the body fluids, affording the drug an opportunity to scavenge copper efficiently from the body fluids. The resulting widespread and long-lasting action of the thiol makes it the drug of choice in the treatment of Wilson's Disease.

Inside a cell, a thiol might form a stable complex with a particular cellular constituent. Cystamine-^{35}S does not seem to form any particularly marked complexes with the cell nuclei, mitochondria and microsomes of liver and spleen[54], while cysteamine-^{35}S forms a very tight complex with the dinucleoprotein, which cannot be disrupted by repeated water shock and extraction[55].

In addition to forming a complex with a particular cellular substance, the thiol may encounter an enzyme that will alter its chemical composition. A change in the structure of the thiol can profoundly alter its distribution within the body. One of the most striking examples of this phenomenon is the accumulation of 6-methyl-thiopurine ribonucleotide-^{35}S (6-MMPR) by erythrocytes. The ratio of radioactivity in the erythrocyte as compared to plasma is 40 : 1, whereas in the case of 6-mercapto-purine-^{35}S the ratio is 1 : 100, representing a 4000-fold difference between

the two compounds. The selective accumulation of 6-MMPR-^{35}S in erythrocytes has been attributed to its intracellular phosphorylation to the more ionizable and hence less diffusible ribonucleotide[56]. The fact that the behaviour of a thiol within an organism is largely determined by physical properties such as lipid as opposed to water solubility suggested that more efficient drugs might be designed on the basis of their solubility properties. An interesting experiment along this line was the conversion of the water-soluble, carcinostatic drug 9-(β-D-xylofuranosyl)—9H—purine 6-thiol (xyl—6-MP) to its triacetyl derivative (xyl—6-MP—TAC). It was hoped that the derivative, which is relatively insoluble in water, would be retained in the body longer than xyl—6-MP. Surprisingly, xyl—6-MP—TAC-^{35}S was excreted in the form of xyl—6-MP-^{35}S and sulphate-^{35}S even more rapidly than xyl—6-MP-^{35}S itself[57].

If the thiol does not bind tightly to a cellular constituent or encounter an enzyme into whose binding site it can fit, it will eventually be excreted in an unaltered form. In one of the earliest applications of ^{35}S-labelling of thiols in a biological tracer experiment, mercaptohistidine-^{35}S was administered to rats and boars to test whether a metabolic pathway exists for the conversion of mercaptohistidine to its betaine derivative, the naturally occurring ergothioneine. Ergothioneine did not take up radioactivity and 90% of the administered 2-mercaptohistidine-^{35}S was excreted in the urine by the twenty-first day[58,59].

Tracer studies such as those just described have found a particularly important application in the design of drugs that retard the growth of tumours and increase the survival times of afflicted animals, including man. One of the basic strategies that underlie the search for effective carcinostatic drugs is the design of a drug that has a high toxicity for tumour cells, while relatively non-toxic for the host animal. The fast turnover rate of tumour cells, and the demands that this places on the synthesis of purines and pyrimidines and their incorporation into DNA have proved to be the Achilles heel of the tumour cell.

One group of compounds that have proved to be particularly effective in interfering with DNA synthesis of tumour cells are the mercaptopurines and pyrimidines and their alkyl derivatives: 6-mercaptopurine (6-MP) blocks the *de novo* synthesis of purines[60]; 9-(β-D-arabinofuranosyl)—9H—purine—6-thiol (ara—6-MP) inhibits the incorporation of L-aspartic acid and orotic acid into DNA cystosine[61,62]; 9-(β-D-xylofuranosyl)—9H—purine—6-thiol (xyl—6-MP) inhibits the utilization of exogenously administered guanine[57]; the periodic acid oxidation product of 9-(β-D-ribosyl)—6-methyl—thio purine (MMPR—OP) blocks the incorporation of thymidine into DNA[63]. The effective clinical use of thiols

such as these depends on two phenomena: whether the thiol will selectively accumulate in tumour cells, while the remainder of the drug is rapidly flushed out of the body and whether the thiol is selectively metabolized by the tumour cell to a more toxic substance.

The correlation of therapeutic action with the distribution of a drug had already been found in one of the earliest tracer studies of a labelled thiol. The powerful antithyroid drug, 4-methyl-2-thiouracil-^{35}S, was distributed more or less evenly in the different organs of the cockerel, with only the thyroid gland, the pituitary gland and the fast-growing base of the feathershafts showing distinctly above normal concentrations[64]. ^{35}S-Labelling has continued to be an indispensable tool in studying both of these phenomena during the testing of thiol drugs.

Both 6-mercaptopurine and buthiopurine (δ-(purinyl-6)mercapto-valeric acid) are carcinostatic drugs. However, buthiopurine is 8 times less active, but 30 times less toxic on chronic administration than 6-mercapto-purine. The origin of this effect was thought to lie in the relative tissue distributions of the drugs, which were studied using ^{35}S-labelling[65]. Mercaptopurine-^{35}S passed rapidly through the gastro-intestinal barrier and flooded many tissues, especially the liver, lungs, spleen and heart, as compared to the more gradual accumulation of buthiopurine in these organs. This was thought to account for the higher toxicity of 6-mercapto-purine. In the tumour itself, 6-mercaptopurine achieved a high level of accumulation, which then fell off as a function of time; whereas, buthio-purine persisted at a lower level for a longer time. The lower level of buthiopurine in the tumour as compared to that of mercaptopurine is in correlation with the effectiveness of the two drugs.

The oxidation of the ribosyl moiety of MMPR to MMPR—OP completely changes the mode of action of the drug as well as its stability. MMPR—OP-^{35}S is no longer selectively concentrated in tissues, but is rapidly excreted in the urine, most of it unchanged. The rapid passage of the drug through the body spares the host animal. However, a small portion of the drug is bound to the ascite tumour membrane and is responsible for the drug's therapeutic effect. Although the drug is cleaved in part to methylthiopurine, intact MMPR—OP was assumed to be the active agent[63]. Ara—6-MP-^{35}S rapidly appears in the blood, after intra-peritoneal injection, where it is evenly distributed between plasma and red blood cells. At 3 min, the tumour cells already contained the largest percentage of the drug. By 30 min the drug is found in all tissues, except those beyond the blood–brain barrier. The concentration of the drug in the kidneys steadily increases with time, as the drug is cleared from the blood. The rapid clearance of the drug from the vital organs is thought

to account for its low toxicity. After 6 h 76% of the injected dose had been excreted, of which 87% could be accounted for as unchanged drug. The tumour cells themselves did not cleave ara—6-MP-^{36}S to 6-MP-^{35}S, nor appreciably converted it to the nucleotide, nor incorporated it into nucleic acids[61, 62].

6-Mercaptopurine-^{35}S is converted in the tumour cell to 6-methylthiopurine ribonucleotide. The ribonucleotide was shown to be much more efficient than the nucleotide of the parent compound, 6-MP, in inhibiting the enzyme, phosphoribosyl pyrophosphate amidotransferase, and subsequently bringing to a halt *de novo* purine synthesis in the tumour cell. The conversion of 6-MP follows the pathway 6-MP → MP nucleotide → 6-Me—MP nucleotide. Tumour cells lacking the enzyme hypoxanthine phosphoribosyl transferase, which is needed for the conversion to nucleotide, are spared the action of 6-MP. Compounds that would be active against 6-MP-resistant tumours have been actively sought, and those found include: 6-MeMP, MMPR—OP, ara—6-MP, 9-Me—6-MP and 9-Et—6-MP. ^{35}S-Labelling studies showed that these thiols are rapidly excreted unaltered[60, 61, 63, 66].

Till now we have considered the behaviour of thiols that are essentially foreign to the metabolism of the animal. However, perhaps the most sophisticated tracer techniques yet applied to the study of labelled thiols have been developed in the course of investigations of the utilization of a pulse-labelled cysteine in the on-going process of the synthesis of body proteins. After administration, ^{35}S-cysteine quickly enters the various amino acid pools of the body and is incorporated along with naturally occurring cysteine into the polypeptides synthesized in various tissues.

When amino acid sequencing techniques were first applied to proteins, the sequence Cys–Gly–Gly was found to occur with greater than chance frequency. This suggested that perhaps this sequence originated from glutathione, rather than from free amino acids. To check this, oviduct mince was incubated with glutathione labelled with ^{35}S in the cysteine residue and ^{14}C in the carboxyl group of the glycyl residue. The ovalbumin produced was hydrolysed and the specific activity of cysteic acid and glycine originating from the sequence Cys–Gly was compared to the activity of those amino acids from other positions in the polypeptide chain. The results indicated that glutathione played no specific role in the biosynthesis of the Cys–Gly sequence[67].

The rate of uptake of labelled cysteine into proteins has been extensively used as an indicator of the metabolic activity of tissues. ^{35}S-L-cysteine administered to mice was found to be preferentially incorporated into growing hair follicles and claws. In other forms of epithelia the rate of

incorporation was found to be related to the cell turnover rate end and in glandular cells to the rate of protein synthesis[68]. Bleeding caused an arrest or delay in the incorporation of cysteine-^{35}S into organ proteins, followed by a period of enhanced incorporation[69]. Zinc deficiency in rats impairs the incorporation of L-cystine-^{35}S in skin protein while enhancing the rate of incorporation of L-cystine-^{35}S into pancreas protein. This suggested that zinc is essential to the synthesis of skin keratin and collagen[70].

Many hormones are rich in cysteine and the tissues in which they accumulate can be easily recognized by a marked uptake of ^{35}S-L-cysteine. For instance, mature virgin mice, mature mice of both sexes and castrated males display a ^{35}S-labelled juxtamedullary X-zone in the brain, whereas normal adult male mice do not[71]. The neurosecretory system of the earthworm markedly accumulates cysteine-^{35}S[72]. The neurosecretory cells of rapidly developing female locusts and females in the second gonotropic cycle take up cysteine-^{35}S at a greater rate than either newly emerged or slowly developing females[73].

The neurosecretory system that has been studied in greatest detail is the brain's hypothalamo-hypophysial tract, that is concerned with the synthesis of the octapeptide hormones, oxytocin and vassopressin, and their secretion into the blood stream. Bargmann[74] and Schrarrer[75] have proposed that the neurophysial octapeptides are synthesized in the perikaryon of specialized nerve cells. They are subsequently bound to carrier proteins, the neurophysins, which are then organized into granules. These granules of neurosecretory material are then transported down the axon of the neuron and stored in the terminals of the nerve fibres. The release of the hormones into the blood vessels is accompanied by the dissociation of the hormone from the carrier protein. Morphologically[74,75,76], the system consists of two paired nuclei, the supraoptic and the paraventricular nuclei, which lie in the hypothalamus of the brain. The axons that extend from these parikaryons run through the hypothalamo-hypophysial tract and reach the neurohypophysis, where they terminate next to the basement membrane of the blood capillaries.

The neurosecretory material is rich in cysteine and can be spotted with histochemical reagents specific for S—H and S—S bonds. Histochemical staining has located neurosecretory material in the Golgi bodies of the parikaryon and stored in vesicles in the nerve terminals[74]. However, such staining techniques cannot detect the flow of hormones through the neurosecretory system, while the use of single pulses of ^{35}S-cysteine offers the possibility of observing the fascinating process of the flow of neurosecretory material through the cells of the secretory system.

In 1959 Sloper[77] first performed the now much repeated experiment of administering ^{35}S-labelled cysteine and methionine to rats and observing the appearance of radioactivity in various parts of the neurosecretory system. Labelled cysteine and methionine rapidly appeared in the supraoptic nuclei, and only later labelled cysteine, but not methione, appeared in the infundibular process of the neurophysis. This suggested that the supraoptic nuclei were actively engaged in protein synthesis, and one of these polypeptides, particularly rich in cysteine, had migrated to the neurophysis. Ficq and Flament-Durand[78] similarly observed that cystine-^{35}S appeared in the supraoptic and paraventricular nuclei within 5 min after administration of labelled cystine, and only 10 h later did labelled material appear in the neurohypophysis. Talanti and coworkers[79,80] have monitored as function of time elapsed after the administration of labelled cysteine the radioactivity that appears in the supraoptic and paraventricular nuclei, as well as in three sites along the hypothalamo-hypophysial tract and in the neurohypophysis. When one has such a set of data, stating as a function of time the amount of label present in an anatomical structure, a kinetic model of the system can be set up that consists of a number of discrete pools of compounds whose flow from compartment to compartment obeys simple mathematics. When Talanti and coworkers[79,80] analysed their data in terms of such a kinetic model, they could detect a component that first appeared in the supraoptic and paraventricular nuclei and slowly flowed through the hypothalamo-hypophysial tract to the neurohypophysis. Superimposed on the slow component was a rapidly abating pulse of radioactivity that moved through the hypothalamo-hypophysial tract at a constant speed of 0·6 mm/h without experiencing any delays. The fast component was thought to represent neurosecretory material, while the slow component represents structural proteins.

The identity of the labelled material that was seen to flow through the neurosecretory system was established only when the system was taken apart chemically. Sachs[81], by directly infusing highly labelled cysteine-^{35}S into the third ventricle of the brain of a dog, succeeded in isolating minute quantities of vasopressin-^{35}S. Vasopressin-^{35}S associated with the neurosecretory particle always had the lowest specific activity, whereas vasopressin-^{35}S found in the cell nuclei and in large granules had the highest specific activity. Norström and Sjöstrand[82] later showed in a very elegant experiment that following the injection of cysteine-^{35}S in the area of the supraoptic nuclei, radioactivity appeared in a group of proteins that migrated through the hypothalamo-neurohypophysial tract, at a speed of 2–3 mm/h. Approximately 90% of the radioactivity of these

soluble proteins was recovered in a single protein component. Norström, Hansson and Sjöstrand[83] later showed that when the microtubuli of the axons are depolymerized with colchinine, the amount of labelled material that reaches the hypothalamo-neurohypophysial tract and the neurohypophysis is considerably reduced.

Quite early in the course of these tracer studies it was noted that marked changes in the uptake of cysteine-^{35}S occur following periods of water deprivation. Wells[84] found that in rats thirst causes a marked increase in the uptake of radioactivity in the supraoptic nucleus and to a lesser extent in the paraventricular nucleus. Talanti[85] later observed that thirst accelerates the rate of disappearance of radioactivity from the supraoptic and paraventricular nuclei, as well as the disappearance of radioactivity from the neurohypophysis. These results indicated that thirst activates both the synthesis and release of neurosecretory hormones that regulate the function of the kidneys.

V. APPLICATION OF ^{35}S-TRACER STUDIES TO AGRICULTURAL SCIENCE AND INDUSTRY

Perhaps the largest system in which ^{35}S-labelling has been used to follow the distribution of a thiol was a 20 acre forested area that was aerially sprayed with Malathion-^{35}S during a study of the ecological transport of the insecticide[86]. Samples were taken in a number of ingenious ways. Air samples were taken on frosted glass discs suspended from helium balloons to measure the above canopy drift of the insecticide off the area. Samples of bark were taken to measure the settling out of the insecticide at different layers within the canopy. Soil samples were measured to determine the subsurface distribution. Samples collected on spotting enamel paper placed throughout the forest monitored the horizontal distribution of the insecticide. Samples from streams, insects, mammals, reptiles and birds indicated the initial and subsequent transport of the insecticide and its metabolities in the ecosystem.

The cream of cows which have consumed the weed, landcress, becomes tainted upon heat treatment with α-toluenethiol. In order to determine the efficiency of steam distillation for the removal of the taint, ^{35}S-labelled α-toluenethiol was added to cream. The measurement of radioactivity proved to be a convenient analytical method to determine the amount of thiol that remained in the cream[87].

The SH : SS ratio in gluten has been conveniently measured by assaying the relative ^{35}S-activity of NEMI-cysteine and cystine in gluten prepared

from dough that had been made from the flour of wheat that was grown on soil supplemented with sulphate-^{35}S [88].

The friction produced by a chrome-steel ball-bearing moving against discs and steel and brass creates a layer of FeS on the disc when it is lubricated with a mixture of cetane- and dodecane-thiol. The rate of formation of FeS and its subsequent wear were quantitatively measured by taking autoradiographs of the tracks of $Fe^{35}S$ left by the ball-bearing on the steel discs when dodecane thiol-^{35}S was added to the lubricant[89].

VI. ISOTOPE LABELLING AND COUNTING IN PRACTICE

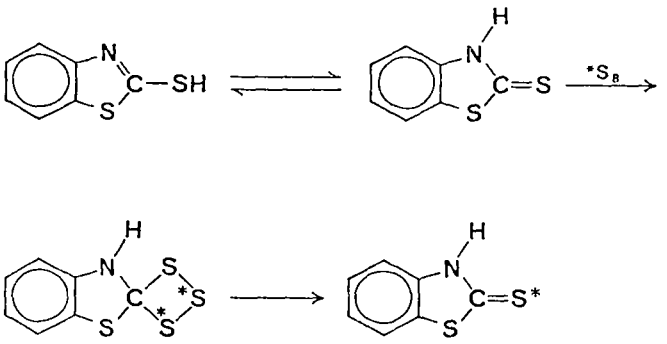
Having reviewed the phenomena that can be probed with isotopically labelled thiols, we now turn to the technical problems associated with the execution of an experiment using isotope labelling. While many of the isotopically labelled thiols discussed in this review are now commercially available, we will review the synthetic procedures that have been used in the past to incorporate deuterium, tritium and sulphur-35 into these thiols, in the hope that it will allow the researcher with a less common thiol to choose the best synthetic route to its preparation. Having prepared a ^{35}S-labelled thiol, various methods are available for the assay of its sulphur-35 activity. The method, best suited to a particular study, will depend on the accuracy desired, the level of sulphur-35 activity in the sample, and the nature of the medium in which the ^{35}S-labelled thiol is dispersed. These and the various auxiliary techniques used to prepare the sample for counting will be discussed. Finally, we will turn to various methodological and phenomenological considerations which have rendered past ^{35}S-labelling studies, especially in endocrinology, subject to criticism.

A. Synthetic Methods

Perhaps the simplest and most elegant method of labelling a thiol with ^{35}S would be to add a neutron to the nucleus of natural abundance ^{34}S by the nuclear reaction $^{34}S(n,\gamma)^{35}S$. To date, this method has not been used, probably because there is no effective way to prevent the heat generated by the nuclear reaction from decomposing the molecule.

If the sulphur in a thiol cannot be rendered radioactive itself, it might be exchanged for thermally activated radioactive ^{35}S atoms. For instance, the sulphur atoms of mercaptobenzothiazole exchange with ^{35}S recoil atoms generated *in situ* by the nuclear reactions, $Cl(n,p)^{35}S$ (where $C_6H_3Cl_3$ is used as the Cl source) or $^{34}S(n,\gamma)^{35}S$ where elemental sulphur

is the source of natural abundance ^{34}S [90]. The yield of ^{35}S-labelled mercaptobenzothiazole is ~2–5% for ^{35}S generated from ^{35}Cl and ~30% for ^{35}S from ^{34}S. It is not necessary to use ^{35}S recoil atoms to accomplish the exchange. It has long been known that during the heating of a solution of 2-mercaptobenzothiazole with sulphur-^{35}S, the sulphur of the mercapto group is exchanged for radio-sulphur[91]. Since the thiol group of mercaptobenzothiazole is in tautomeric equilibrium with the thion form, exchange is thought to occur by the addition of elemental sulphur to the C=S bond of the thio tautomer (equation 26). Morávek and Kopecky[92,93] have



(26)

found the exchange to be generally synthetically useful for the labelling of thiols that can exist in a tautomeric form. Table 1 lists the thiols that have been labelled in this way.

The exchange of labelled sulphur can be promoted by enzyme catalysts, instead of heating. Bird egg yolk[94] and the cysteine desulphydrase[95,96,97] that it contains catalyse the exchange of sulphur-35 from $Na_2{}^{35}S$ to L-cysteine, L-cystine and L-cysteic acid. In a typical experiment, 150 ml of a buffer solution containing 2 millimoles of cysteine–HCl, 2 millimoles of $Na_2{}^{35}S$ and 500 mg of cysteine desulphydrase preparation is incubated at 38°C for 15 h. A mixture of 74·4% cystine-^{35}S and 25·3% cysteine-^{35}S is obtained. L-Cystine-^{35}S is subsequently reduced electrolytically to cysteine-^{35}S. The total yield of L-cysteine-^{35}S obtained by isotope exchange is 70%.

Although isotope exchange by virtue of its simplicity and ability to form compounds of high specific activity is the method of choice for the labelling of tautomeric thiols, a synthetic method is often better suited to other thiols. For example, heating α-toluenethiol with sulphur-^{35}S in benzene at 135–140°C for 6–12 h, yields α-toluenethiol-^{35}S with a specific activity of only 2–9%. However, the synthesis of the compound from benzyl-magnesium chloride and sulphur-^{35}S yields α-toluenethiol-^{35}S

TABLE 1. Isotopically labelled thiols

Compound	Source of the isotope	Method of synthesis	Reference
Methanethiol-S-d_1	D_2O	Isotope exchange	16
Methanethiol-C-d_3	CD_3I	$+SC(NH_2)_2$	5
Methanethiol-^{35}S	Thiourea-^{35}S	$+(CH_3)_2SO_4$	110, 115
		$+CH_3I$	111
Ethanethiol-C_1-d_2	$LiAlD_4$	$+CH_3C{\equiv}S{-}OEt$	2
Ethanethiol-^{35}S	Hydrogen-sulphide-^{35}S	$+C_2H_4$	100
Ethanedithiol-S-d_2	D_2O	Isotope exchange	18
2-Mercaptoethanol	Hydrogen sulphide-^{35}S	$+ClCH_2CH_2OH$	112
β-Mercaptoacetic acid (thioglycollic acid)	Hydrogen sulphide-^{35}S	$+CH_2CH_2O$	112
	Thiourea-^{35}S	$+ClCH_2COOH$	117
	Dithioglycollic acid-$^{35}S_2$	H_2 reduction	124
β-Dimethylaminoethane-thiol-^{35}S	Thiourea-^{35}S	$+(CH_3)_2NCH_2CH_2Cl$	118
β-Diethylaminoethanethiol-^{35}S	Thiourea-^{35}S	$(CH_3CH_2)_2NCH_2CH_2Cl$	119
n-Butanethiol-S-d_1	DCl, D_2O	Isotope exchange	28, 24
n-Butanethiol-^{35}S	Thiourea-^{35}S	$+CH_3CH_2CH_2CH_2Br$	108
	Sodium hydrogen sulphide-^{35}S	$+CH_3CH_2CH_2CH_2Br$	116
iso-Butanethiol-^{35}S	Sulphur-^{35}S	$+(CH_3)_2CHCH_2MgBr$	104
2,3-Dimercaptosuccinic acid-^{35}S	$(^{35}SCH_2COOH)_2$	H_2 reduction	127
n-Hexanethiol-S-d_1	D_2O	$+CH_3(CH_2)_4CH_2SNa$	13
Cyclohexanethiol-S-d_1	D_2O	Isotope exchange	14
Benzenethiol-S-d_1	D_2O	$+C_6H_5SNa$	13
Benzenethiol-S-t_1	HTO	Isotope exchange	23
p-Halogen-benzene thiol-S-d_1	Methanol-O-d_1	$+XC_6H_4S{-}Si(CH_3)_3$	134
Benzenethiol-^{35}S	Sulphur-^{35}S	$+C_6H_5MgBr$	105
α-Toluenethiol-S-t_1	HTO	Isotope exchange	34

TABLE I (*cont.*)

Compound	Source of the isotope	Method of synthesis	Reference
α-Toluenethiol-^{35}S	Sulphur-^{35}S	+ $C_6H_5CH_2MgCl$	106
	Sulphur-^{35}S	Isotope exchange	98
	Sodium hydrogen sulphide-^{35}S	+ $C_6H_5CH_2Br$	108
p-Toluenethiol-^{35}S	Sulphur-^{35}S	+ $CH_3C_6H_3SMgBr$	108
2-Phenylethanethiol-^{35}S	Sulphur-^{35}S	+ $C_6H_5CH_2CH_2MgBr$	109
p-Methoxybenzenethiol-^{35}S	Carbon disulphide-^{35}S	+ *p*-$CH_3OC_6H_4N_2Cl$	108
p-Phenylbenzenethiol-^{35}S	Carbon disulphide-^{35}S	+ *p*-$C_6H_5C_6H_4N_2Cl$	108
α-Naphthalenethiol-^{35}S	Sulphur-^{35}S	+ α-$C_{10}H_7MgBr$	110
2-Mercaptobenzothiazole-$^{35}S_{2,3}$	Sulphur-^{35}S	+ C_6H_5NCS	162
2-Mercaptobenzothiazole-^{35}S	Sodium hydrogen sulphide-^{35}S	2-Chloromercapto-benzothiazole	122
	Sulphur-^{35}S	Isotope exchange	91
D,L-Cysteine-^{35}S	$C_6H_5COSCH_2CH(NHCOC_6H_5)CO_2CH_3$-^{35}S	Hydrolysis	
L-Cysteine	Sulphur-^{35}S or Sodium sulphide-^{35}S	Enzymatic isotope exchange	94, 95 96, 97
	SO_4^{2-}-^{35}S	Biosynthesis	127
α-Amino-β-mercaptobutyric acid	4-Carboxy-5-methyl-2-phenyl thiozoline-^{35}S	Acid hydrolysis	126
Thiopental-^{35}S (5-Ethyl-5(-1-methylbutyl)-2-thiobarbituric acid)	Sulphur-^{35}S	Isotope exchange	163, 164 165
Thiopyrimidines	Sulphur-^{35}S	Isotope exchange	166
2,4-Dithiouracil	Sulphur-^{35}S	Isotope exchange	93
4-Thiouracil	Sulphur-^{35}S	Isotope exchange	93
6-Methyl-2-thiouracil	Sulphur-^{35}S	Isotope exchange	167, 168, 93

TABLE 1 (*cont.*)

Compound	Source of the isotope	Method of synthesis	Reference
2-Thiouracil	Sulphur-^{35}S	Isotope exchange	166, 168, 93
4-Amino-2-thiouracil	Sulphur-^{35}S	Isotope exchange	93
6-Phenyl-2-thiouracil	Sulphur-^{35}S	Isotope exchange	93
2-Thio-6-azouracil	Sulphur-^{35}S	Isotope exchange	93
6-Amino-2-thiouracil	Sulphur-^{35}S	Isotope exchange	93
2-Thiobarbituric acid	Sulphur-^{35}S	Isotope exchange	93
6-Mercaptopurine	Sulphur-^{35}S	Isotope exchange	168, 93
	Barium sulphate-^{35}S	6-Chloropurine	123
2-Methyl-6-mercaptopurine	Sulphur-^{35}S	Isotope exchange	93
6-Thioguanine	Sulphur-^{35}S	Isotope exchange	168
6-Thioguanosine	Sulphur-^{35}S	Isotope exchange	93
6-Mercaptopurine riboside	Sulphur-^{35}S	Isotope exchange	93
2-Hydroxyl-6-mercaptopurine	Sulphur-^{35}S	Isotope exchange	93
6-Hydroxy-2-mercaptopurine	Sulphur-^{35}S	Isotope exchange	93
8-Mercaptoguanosine	Sulphur-^{35}S	Isotope exchange	93
2-Thioxanthine	Sulphur-^{35}S	Isotope exchange	168
Coenzyme-A-^{35}S	$^{35}SO_4^{2-}$	Biosynthesis	131
Glutathione-^{35}S	$^{35}SO_4^{2-}$	Biosynthesis	130
γ-Globulin-^{35}S	Cysteine-^{35}S	Biosynthesis	132
Insulin-^{35}S	Cysteine-^{35}S	Biosynthesis	129
Dysentery bacteria-^{35}S	Cysteine-^{35}S	Biosynthesis	133

with a specific activity of 27%[98]. There are a number of synthetic routes available for the synthesis of labelled thiols, ranging in specificity from high temperature and hot atom reactions to the biosynthesis of complex thiols, such as coenzyme A.

Thermolysis and recoil atom reactions yield quite complex mixtures of thiols. For example, when an equimolar mixture of C_2H_2—N_2—$H_2{}^{35}S$ was passed through an empty quartz tube C_3H_8, 0·00001%; C_4H_{10}, 0·001%; cyclobutane, 0·001%; ethanethiol, 0·1%; butanethiol, 0·2%; isobutanethiol, 0·2%; and many other unidentified products was obtained[99]. When a 1 : 1·3 mixture of $^{14}C_2H_4$ and $H_2{}^{35}S$ was heated for 10 h at 310°C at 20 atmospheres, $^{14}CH_3{}^{14}CH_2{}^{35}SH$ and $(^{14}CH_3{}^{14}CH_2)_2{}^{35}S$ were obtained in mole fractions of $3{\cdot}3\times10^{-4}$ and $3{\cdot}9\times10^{-4}$, respectively[100]. ^{35}S-Recoil atoms produced in a mixture of methane–HCl by the atomic reaction $^{35}Cl(n,p)^{35}S$, yield a mixture containing $H_2{}^{35}S$ and $CH_3{}^{35}SH$ as the major constituents[101]. The relative amounts of the products can be controlled by adjusting the concentration of Ar and NO, which serve as moderator and radical scavenger. Hot ^{35}S atoms formed by the neutron bombardment of CCl_4 react with a cyclopentane : cyclohexane mixture to give a mixture of ^{35}S-labelled thiophene, tetrahydrothiopyran, cyclopentanethiol, cyclohexanethiol, ethanethiol, proparethiol, butanethiol, dicyclopentyl sulphide and polymeric mercaptans and sulphides[102]. Neutron bombardment of a 1 : 1 mixture of CCl_4 and cyclohexane yields a reaction containing $C_6H_{11}SH$ and $C_5H_{10}S$ at levels of 3·5 and 8% of the total radioactivity, respectively; however, the majority of the activity is found in non-volatile products[103]. In practice, the more conventional synthetic methods used for the preparation of thiols in general are better suited to the preparation of labelled thiol, especially when the ^{35}S-labelled precursor is commercially available.

Thiomagnesium halides formed by the reaction of sulphur with a Grignard reagent can be decomposed to the corresponding thiols (equation 27). While the reaction has not been extensively used for the preparation of non-labelled arenethiols, it is particularly well suited to the

$$RX+Mg \longrightarrow RMgX \xrightarrow{^{35}S} R^{35}SMgX \xrightarrow{HX} R^{35}SH+MgX_2 \qquad (27)$$

synthesis of ^{35}S-labelled thiols, since the ^{35}S-labelled reactant, sulphur-^{35}S, is readily available. Among the ^{35}S-labelled thiols that have been prepared by this method are iso-butanethiol[104], benzenethiol[105], α-toluenethiol[98,106,107], *p*-toluenethiol[108], 2-phenylethanethiol[109] and α-naphthalenethiol[110]. Yields vary from 44 to 90%.

In recent years the method of choice for the preparation of thiols in the laboratory has become the addition of an alkyl-halide to thiourea to form

an S-alkylisothiouronium halide which is subsequently decomposed with alkali to the alkanethiol (equation 28). The reaction is easy to control and

$$RI + SC(NH_2)_2 \longrightarrow RSC(:NH)NH_2HI \longrightarrow RSH + H_2NCN \qquad (28)$$

the isothiouronium salts are stable and can be stored. The decomposition of S-methylisothiouronium sulphate, prepared from thiourea and dimethyl-sulphate, has been used as a convenient source of methanethiol-^{35}S in the course of a number of syntheses. The quaternization of thiourea with methyl iodide[111] has been reported to give higher yields than with dimethyl-sulphate. The ^{35}S-labelled precursor, thiourea-^{35}S, is prepared from H_2^*S by reaction with H_2O, NH_2CN, NH_4OH[112] or from $Ba^{35}S$ by treatment with H_2O, NH_4HCO_3 and a trace of powdered sulphur[113,114]. A number of ^{35}S-labelled thiols have been prepared in this way, including methane thiol-^{35}S[111,114,115], *n*-butanethiol-^{35}S[116], β-mercaptoacetic acid-^{35}S[117], dimethylaminoethanethiol-^{35}S[118], diethylaminoethanethiol-^{35}S[119] and 2-thiouracil-^{35}S[120]. Yields up to 90·5% have been reported.

In 1840 Regnault passed ethyl chloride into potassium hydrogen sulphide in a retort and obtained ethanethiol[121] (equation 29). This classical synthetic method has been used to prepare labelled thiols from $Na^{35}SH$ and organic halides. The thiols prepared by this method include

$$RCl + NaSH \longrightarrow RSH + NaCl \qquad (29)$$

n-butane-thiol-^{35}S[108], α-toluenethiol-^{35}S[108] and 2-mercaptobenzothiazole-^{35}S[122]. In variations on the method, 2-mercaptoethanol-^{35}S has been prepared from $H_2{}^{35}S$ and 2-chloroethanol[112] and 6-mercaptopurine was obtained by heating 6-chloropurine with $Ba^{35}SO_4$[123].

A standard method for making aromatic thiols from relatively unreactive aromatic halides is to convert them to the aromatic diazonium salt,

$$\left.\begin{aligned} RN_2Cl + KSCSOEt &\longrightarrow RSCSOEt + N_2 + KCl \\ RSCSOEt + H_2O &\longrightarrow RSH + COS + EtOH \end{aligned}\right\} \qquad (30)$$

which readily reacts with a xanthate, such as $EtOCS_2K$ (equation 30). ^{35}S-Labelled $EtOCS_2K$ has been prepared by treating Na_2S and sulphur-^{35}S with CS_2 to form uniformly labelled $NaCS_3$, which is then decomposed with HCl and the resulting CS_2-^{35}S passed through a EtOH/EtOK solution. Both ^{35}S-labelled *p*-methoxy- and *p*-phenyl-benzenethiol have been prepared from $EtOCS_2K$-^{35}S and the corresponding diazonium chloride[108].

When ^{35}S-labelled disulphides are available, the corresponding ^{35}S-thiol can be readily prepared by electrolytic or H_2 reduction (equation 31). β-Mercaptoacetic acid[121] and cysteine have been obtained in this way[125].

$$RSSR + H_2 \longrightarrow 2\,RSH \qquad (31)$$

Although the addition of H_2S to unsaturated bonds proceeds in quantitative yields, e.g. the addition of hydrogen sulphide to ethylene gives ethyl mercaptan with no by-products, the reaction has been used only once to prepare ethanethiol-^{35}S from H_2S-^{35}S and ethylene (equation 32)[100]. The addition of H_2S-^{35}S across strained heteroatomic bonds in

$$H_2S + \underset{\diagdown\,\diagup}{\overset{\diagup\,\diagdown}{CH_2CH_2}}X \longrightarrow HSCH_2CH_2XH \qquad (32)$$

small ring compounds has been used to prepare 2-mercaptoethanol[112] from ethylene oxide and 2-mercaptoethylamine from ethyleneimine[112].

In addition to these standard methods, a number of specialized reactions of limited scope have been used to prepare some biologically important ^{35}S-labelled thiols. For instance, 2-thiouracil-^{35}S has been prepared by the condensation of thiourea-^{35}S with $NaOCH{=}CHCO_2Et$[120]. α-Amino-β-mercaptobutyric acid-^{35}S was prepared by the acid hydrolysis of 4-carboxy-5-methyl-2-phenylthiazoline-^{35}S[126]. 2,3-Dimercaptosuccinic acid-$^{35}S_2$ was obtained by the hydrolysis of 2,3-bis(acetylthio)succinic acid-^{35}S[127]. D,L-Cysteine-^{35}S was obtained by the acid hydrolysis of $PhCOS{-}CH_2CH(HNCOC_6H_5)CO_2Me$[128].

However, as the biologically interesting thiols become more complex, biosynthetic routes would appear to be the method of choice for their synthesis, in spite of the inherent loss of ^{35}S isotope in the biological system and need for chromatographic separation of the isotopically labelled molecule from a complex biological mixture. L-Cysteine-^{35}S[129], glutathione-^{35}S[130] and coenzyme-A-^{35}S[131] have been obtained from labelled sulphate by biosynthetic routes, while complex polypeptides, such as γ-globulin[132] and insulin[129] have been obtained from organisms grown on cysteine-^{35}S. Even highly labelled whole organisms such as dysentery bacteria[133] have been grown on cysteine-^{35}S.

Deuterium and tritium labelling of the SH group can be carried out most conveniently by isotope exchange with D_2O or T_2O by simply dissolving the thiol in the labelled solvent, followed by evaporation. The thiols labelled by isotope exchange are, CH_3SD[5,16], $DSCH_2CH_2SD$[18], $CH_3(CH_2)_3SD$[24,28], $C_6H_{11}SD$[14], C_6H_5ST[23], $C_6H_5CH_2ST$[34]. Thiols have also been deuterated by the D_2O solvolysis of Na mercaptides, such as

$CH_3(CH_2)_5SNa$[13] and C_6H_5SNa[13] and by the reaction of MeOD with $XC_6H_4S—SiMe_3$ (X = halide)[134].

As in any synthesis employing radioisotopes, special care must be taken not to contaminate the laboratory. Special glassware which minimize the escape of the isotope are usually designed to meet the needs of a specific synthetic route. The preparation of thiols from radioactive sulphur and a Grignard reagent is a good illustrative example of the design of such vessels for an organic reaction and the subsequent extraction of the labelled compound with organic solvents[110].

An apparatus for the reaction of ^{35}S with a Grignard reagent is shown in Figure 3. The Grignard reagent is pipetted in tube A, ether is added and

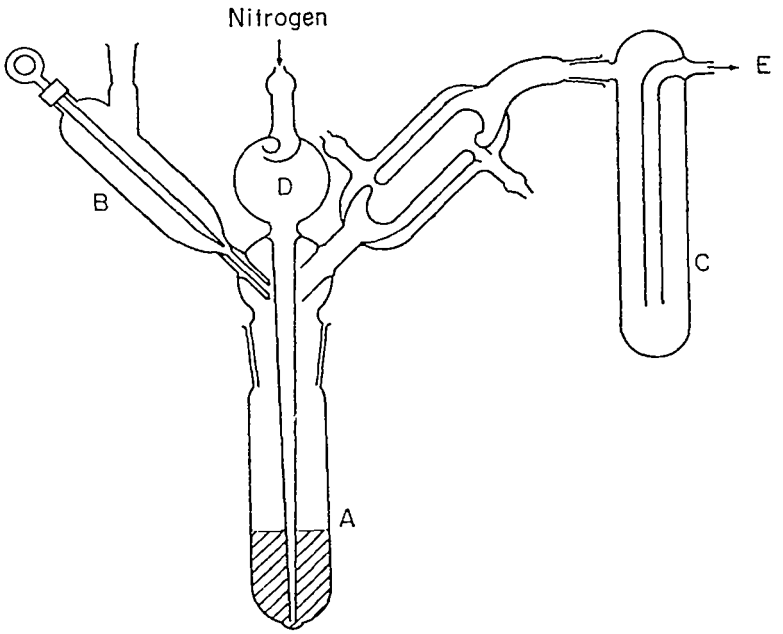


FIGURE 3. Reaction vessel used for Grignard reaction.

the apparatus is flushed with nitrogen. Sulphur-35 dissolved in xylene is added to the mixture from B and the reaction mixture is stirred under nitrogen at 0°C. The liquid air trap C protects the mixture from moisture, while tube D acts as a liquid trap in a case of a pressure backflow due to a pressure build-up in a series of aqueous sodium hydroxide traps connected at E. Upon completion of reaction the Grignard reagent is decomposed by addition of HCl.

The labelled thiol is extracted from the reaction mixture by rapidly transferring the reaction flask A to the apparatus shown in Figure 4. The extraction is carried out under a nitrogen atmosphere. By properly adjusting the traps, the reaction mixture is transferred from A to the separatory funnel G, to which ether is added through H. The two phases are agitated by the magnetic stirrer I, and the aqueous layer is returned to A and the ether layer to F. The aqueous layer is extracted with more

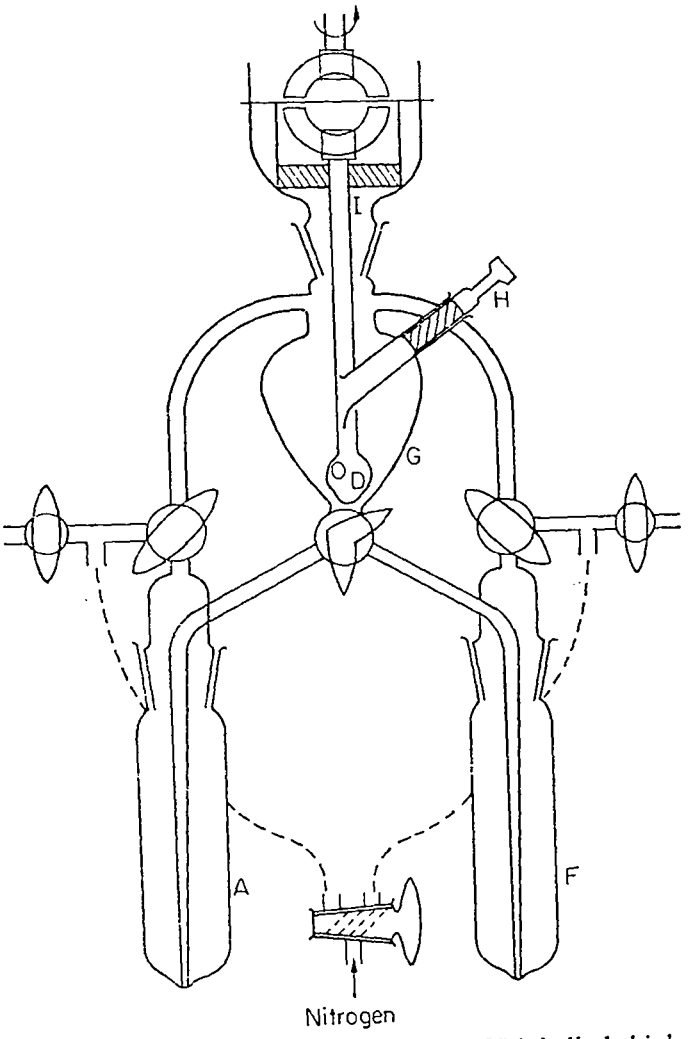


FIGURE 4. Vessel for the extraction of ^{35}S-labelled thiols.

portions of ether added through H. The thiol can be precipitated from the ether layer as the Na salt by simply extracting the aqueous layer with the 10% aqueous sodium hydroxide.

B. Counting Methods

The low energy β-rays emitted by ^{35}S can be counted in a number of different ways, including gas flow counting, liquid scintillation counting and autoradiography on photographic emulsions. The particular method chosen depends on the nature of the sample.

Perhaps the simplest counting procedure is to place the same on a planchet and assay its radioactivity under either a windowless gas flow counter or a mica end window counter. This method of counting has most often applied to $BaSO_4$-^{35}S[58,59,64] or benzidine sulphate-^{35}S[65], which is layered on the planchet. In addition, films of polymers[110], TCA precipitated proteins, whole blood[42], and red blood cell ghosts[42] labelled with ^{35}S have been counted in this way. Often the counting of a layer of material is complicated by the self-absorption of the radiation from the bottom of the sample. The self-absorption of radiation is generally standardized by preparing layers that are 'infinitely thick', e.g. 15–16 mg sulphate per cm^2. This ensures that radiation from the bottom of the sample is completely adsorbed. When ^{35}S to be counted is in the gas phase, as in SO_2 or H_2S, it can be introduced together with methane directly into a Geiger–Müller tube and counted at efficiencies of 95–96%[135]. Sulphur dioxide-^{35}S can be introduced up to 7·5 torr, whereas hydrogen sulphide-^{35}S can be counted at much higher partial pressures. A novel application of this type of counting was the measurement of β-activity of alkanethiols, as they emerge from a gas–liquid chromatograph, in which methane was used as the carrier gas[136].

A convenient and fast method of locating ^{35}S-labelled spots on thin-layer plates or on paper chromatograms is to pass the chromatogram under a windowless gas flow counter[39,92]. Radiochromatogram scanners of this type are commercially available and their design have been described[137,138]. However, for accurate determination of radioactivity the spot must be counted in a liquid scintillation counter.

Liquid scintillation counting has been used to assay the radioactivity of numerous ^{35}S-labelled compounds after they have been separated on TLC plates. However, the ^{35}S-labelled compound must first be located by radiochromatogram scanning, scraped off the plate and eluted off the absorbent into the counting solution. Alternatively, the absorbent together with the ^{35}S-labelled compound can be suspended in the counting

solution by Cab-O-Sil. Paper chromatograms, on the other hand, are usually cut into 1 cm strips which are eluted and counted in a toluene scintillator. Polyacrylamide gels have been embedded in 2% agar gel, mounted on a rubber plate and cut into 1 mm thick slices in a mechanical chopper. The strips are then placed in a liquid scintillator phial, extracted in 1 ml of toluene and subsequently counted[82]. Alternatively, gels were thickened with 10% glycerol and sliced in a dry-ice acetone–hexane bath[139]. The radioactivity of ^{35}S-labelled compounds, emerging from a liquid chromatograph, has been measured as they flow through a plastic scintillator spiral[140]. A number of liquid scintillator fluors particularly suited for the low energy β-rays of ^{35}S have been developed[141, 142, 143].

Autoradiography has been extensively used to locate radioactive areas on chromatograms. Usually the chromatogram is pressed against a no-screen X-ray film and allowed to develop[131]. The development time can extend over a period of weeks or months, which allows radioactive areas of very low activity to be detected[16].

Autoradiography is particularly well suited for determining the distribution of radioactivity in tissue. In principle, the distribution of radioactivity in a tissue could be assessed by gas flow counting, if the tissue was dissected, its parts weighed and uniformly spread as a dry film on a degassed planchet. However, very often it is difficult to identify exactly the part of the tissue that has been dissected. Furthermore, the fluids which surround the tissue in the body may often be very highly labelled and will contaminate the dissected specimen. The use of autoradiography readily overcomes these difficulties[77].

The methods of preparing the autoradiographs most commonly used in ^{35}S tracer studies are those of Doniach and Pelc[144] and Ullberg[145]. The choice of exposure time and counting methods has been discussed by Pelc[146]. The activity recorded on the photographic film can be determined either by directly counting silver grains[73] or by mounting the autoradiograph on a microscope slide and measuring the relative amount of light transmitted using a photocell at the ocular of a microscope[84]. The former is more accurate and the data are obtained in a form that can be treated by statistical methods, i.e. silver granules/μ^2 ($\pm$ S.E.M.). The absolute sensitivity of electron microscope autoradiography, i.e. ratio of developed grains to radioactive decays in the specimen, were determined for ^{35}S with Ilford L4 and Kodak NTE emulsions and found to be 1/21 for ^{35}S in a monomolecular layer[147]. The resolution that can be obtained depends on the photographic emulsion. The observed radioactivity depends on several physical factors, including the thickness of the sample, the nature of the tissue, the exposure time and the modalities of the

developing procedures[78]. Autoradiography has been used to follow the whole body distribution of ^{35}S in plants and animals[68], as well as the movement of ^{35}S down the axon of a nerve cell[77-80].

C. Sample Preparation

1. Wet ashing

The wet ashing technique was originally designed to convert sulphur contained in organic material into a form, such as $BaSO_4$, which could be layered on a planchet for gas flow counting. This was achieved by decomposing the sample with a mixture of HNO_3 and $HClO_4$[148], or a mixture of HCl and HNO_3 together with a copper salt catalyst[58,59,65], followed by the precipitation of SO_4^{2-} by barium. The method also lends itself to liquid scintillation counting when the $BaSO_4$ is suspended in a liquid scintillator solution that has been gelled by Cab-O-Sil[148]. Alternatively, the sample can be reduced to H_2S, which is subsequently absorbed in a solution of NaOH, and assayed in a liquid scintillation counter[149].

2. Oxygen flask combustion

The oxygen flask method converts organic sulphur to a form suitable for liquid scintillation counting. In principle, the sample is combusted in an oxygen atmosphere. Sulphur is converted to SO_2, which is trapped in a liquid scintillator solution. In practice, a good deal of development has gone into increasing the speed, efficiency and safety of the technique. The sample can be held in a number of ways, such as in a Pt basket[150,151] or a paper cup held by a Pt–Ir wire[152], or impregnated on a cotton pellet, placed in a paper cup that is held in a glass ring or watch-glass-type combustion platform[153]. The reaction vessel, which can be either a 2 l glass flask[151] (accommodating 20–200 mg of matter), a liquid scintillation phial (holding 10–15 mg)[152], or a plastic bag[153], is flushed with oxygen. The sample is ignited most often by focusing a light beam on a dark spot which has been made on the paper sample holder or by heating electrically the Pt sample holder. The sample is combusted and SO_2 is collected in a trapping agent such as phenylethylamine[153,154] or ethanolamine[155,156] in nine parts of methanol. The trapping solution is subsequently mixed with the liquid scintillator and counted. Usually the trapping agent, which is a flammable organic mixture, is added to the reaction vessel prior to ignition, and therefore poses a hazard when the sample is ignited. To avoid explosions, the reaction vessel is either cooled in dry-ice acetone to lower the volatility of the trapping solution or

alternatively the vessel is fitted with a balloon attached to the side-arm[151]. A non-flammable trapping solution consisting of a 1 : 1 : 2 mixture of toluene, triton X-100 and water has also been used[151]. The efficiency of counting which takes into account the recovery of radioactivity and the quenching of the scintillant by the trapping agent is usually 90–95%. In human samples, in which a large amount of material with a very low activity is combusted, a compromise must be struck between the counting rate and the quenching level. The large amounts of trapping agent that are required, quench the counting mixture, while dilution of the trapping agent reduces the counting rate to the background level of the counter[160].

3. Specialized techniques

In addition to the wet ashing and oxygen flask methods, a number of rather specialized techniques have been used to convert a sample to a form which can be sufficiently counted. Methanethiol-^{35}S has been added to $Hg(CN)_2$ and precipitated as $(MeS)_2Hg$ and counted under a gas flow counter[157]. ^{35}S-Labelled scintillation counting was carried out by an in-phial degradation by heating in a xylene solution containing *t*-butyl hydrogen peroxide and OsO_4[158]. Labelled H_2S released into the atmosphere by micro-organisms has been trapped on paper strips impregnated with basic lead acetate, which are subsequently treated with glyoxal, H_3PO_4 and zinc powder and counted in a Tracerlab counter[159].

D. Methodological Considerations

A number of important methodological considerations enter into the design of body tracer studies. The number of labelled thiol molecules that will be incorporated into a particular macromolecule or tissue depends on (1) the dilution of the isotope in the added molecule, (2) the pre-existing concentration of the compound in different organs and cells, (3) the presence of different precursors of the compound, (4) the turnover rate of the compound and its precursors, and finally (5) the rate of synthesis of the complex polypeptide into which it will be incorporated. Furthermore, in endocrine research, polypeptide hormones may be quickly metabolized and lead to an unspecified labelling sometimes difficult to detect. Hormones are usually physiologically active at very low concentrations, which requires that they be very highly labelled if they are to be observed at all[78]. As the metabolic pathways of cells are often ramified, in addition to the hormone, labelled sulphur may also be incorporated into structural proteins, lipid sulphatides, sulphonated mucopolysaccharides and water-soluble substances, such as cystine, methionine, glutathione, taurine and

inorganic sulphates. Labelled methionine can be used to determine the rate of accumulation of labelled sulphur in structural proteins, and labelled sulphate can be used to check the localization of sulphur in other compounds[77]. If the specific activity of the labelled polypeptide is to be determined then a technique such as autoradiography must be used in conjunction with quantitative cytochemical methods.

The interpretation of autoradiographs can be ambiguous, especially if the anatomy of the tissue furnishes few points of reference and the area to be counted is far from the cell nucleus. Often the shape of the cell may impede the exact determination of its centre[80].

Kinetic measurements of the rate of transport of a labelled compound in a tissue depend on the specification of the time and the site of entry of the labelled compound into the system. Ideally, one would like to inject the labelled compound directly into the system under study. However, the local application of the labelled substances introduces a serious risk of disturbing both the timing of precursor adsorption into the system and the rate of incorporation. There may be no way of knowing whether the true physiological circumstances are preserved. Furthermore, the local application of the labelled compound does not enhance the specificity of its incorporation in the polypeptide, as opposed to other uptake mechanisms[79]. Since the measurement of isotope accumulation requires that the animal be sacrificed, it is not possible to take consecutive samples from the same animal as a function of time. The kinetic measurements must therefore represent a picture of the mean behaviour of the isotope in a population of animals[80].

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