Theoretical Studies of the Reactions of the Sulphur–Sulphur Bond. Part 3.† R_3S_3 Ions as Intermediates in Thiol–Disulphide Exchange Reactions

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Ab initio calculations have been performed on model systems selected to clarify the reaction mechanisms and intermediate states in thiol–disulphide exchange reactions. Evidence is presented for formation of a weak $R_3S_3^-$ complex as intermediate in the exchange reaction $R^1SSR^2 + R^3S^- \longrightarrow R^1SSR^3 + R^2S^-$. The complex is linear and not a triangular ring as previously speculated and the excess charge is distributed solely on the peripheral sulphur atoms. The stability is almost insensitive to different R groups (H, CH_3). The complete reaction proceeds to liberate the weakest nucleophile which is also the most stable anion. However, the stability and nucleophilicity of the anions did not correlate with the charge densities on the anion as is often taken for granted. Evidence is also presented for a corresponding $R_3S_3^+$ complex as an intermediate in reactions like $R^1SSR^1 + R^2SCl \longrightarrow R^1SSR^2 + R^1SCl$. The complex is neither linear nor ring shaped but bent as for a regular trivalent sulphur atom; it has an almost neutral SSS region, and is likely to be quite stable.

An important class of reactions in biochemical sulphur chemistry is the exchange reactions of disulphides with sulphur-containing nucleophiles like thiolate anions (RS^-) or electrophiles like sulphenyl haldides (RSX) [reactions (i) and (ii)]. These reactions may formally be

$$R^1SSR^2 + R^3S^- \longrightarrow \underset{\text{(I)}}{[R^1SS(R^2)SR^3]^-} \longrightarrow R^1S^- + R^2SSR^3 \quad \text{(i)}$$

$$R^1SSR^2 + R^3SCl \longrightarrow \underset{\text{(II)}}{[R^1SS(R^2)SR^3]^+} + Cl^- \longrightarrow R^1SCl + R^2SSR^3 \quad \text{(ii)}$$

considered as proceeding through some intermediate state consisting of either a trisulphide anion (I) or a cation (II). Experimentally there is difficulty in following these reactions since both reactants and products are thiols and disulphides.

Substitution reactions on sulphur centres have been studied quite extensively, but nevertheless there seems to be only little information available on the mechanisms and particularly on the nature of the intermediate states. Questions like the possible stability, the structure, and the role of *d* orbitals in the transition states have been debated,[1-3] but most of the models are actually based on quite indirect information or speculation. The stability of $R_3S_3^+$ cations like $(CH_3)_3S_3^+$ seems to be rather well established,[4] whereas only weak experimental evidence is available for the existence of trisulphide anions like $G_3S_3^-$ (G = glutathione) with a possible half-life of several minutes.[5]

Quantum mechanical methods are especially suitable for investigations of transition states as the intermediate complexes may be studied regardless of their stability. Previous theoretical investigations on these kinds of reactions and complexes are scarce, but a recent model study of the reaction $H_2S_2 + F^-$ indicated that a transition state of the type $H_2S_2F^-$ with S–S–F linearly arranged probably could be stable.[6] This led us to suspect that the more interesting complex of H_2S_2 with HS^- probably also could be stable. In the present study, we thus report investigations on this complex, how different R groups may affect the complex and the complete reaction scheme (i), and finally on the nature of the intermediate $R_3S_3^+$ in reaction (ii) employing the model complex $H_3S_3^+$. A comment on the selection of model complexes may be appropriate in this context. Large R groups with several functional groups may of course strongly affect the chemistry of molecules containing disulphide and trisulphide groups. In this study, however, we restricted ourselves mainly to effects determined by the nature of the disulphide and trisulphide bond, and the small model systems we have chosen are relevant.

COMPUTATIONALS

The calculations were performed within the MO–SCF–LCAO framework using the program system MOLECULE.[7] Two Gaussian basis sets were used, one of medium size denoted A and one large basis denoted B. Basis A is the (10,6,1) set for S and (7,3) set for C of Roos and Siegbahn [8] with Huzinaga's [9] 4*s* basis for H scaled by 1.25, all contracted to double zeta (plus polarization). Further details can be found elsewhere.[10] Basis B consists of the (12,9) basis of Veillard *et al.*[11] for S augmented by two *d* orbitals of exponents 2.0 and 0.54, the (9,5) basis of Huzinaga and Dunning,[12] for C augmented by a *d* orbital of exponent 0.63,[8] and Huzinaga's 4*s* basis for H scaled by 1.25 extended by a *p* orbital of exponent 0.8. This was contracted to double zeta with all polarization functions free.

Rather extensive geometry optimizations were required in a few of the molecules while only partial optimization was necessary in others. The selection of parameters to be optimised was based on previous experience from sulphur systems.[6,10,13] Errors in the total energies due to non-optimal geometries have been estimated based on calculated structures and force constants in similar systems. All optimizations were performed using basis A. The calculations with basis B were performed with the geometry obtained in basis A.

RESULTS AND DISCUSSION

Nucleophilic Reactions.—The transition state. Nucleophilic reactions of type A are usually fast and spontaneous near pH 7 with bimolecular kinetics (S_N2), but the mechanism has not yet been established.[14] The reactions are generally considered to be thermodynamically

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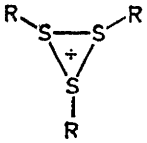
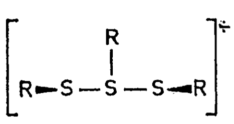
† Part 2, ref. 19.

controlled, *i.e.* by the difference in stability of the reactants and the products or by the difference in nucleophilicity of the thiolate anions involved. The reaction presumably proceeds through the formation of the intermediate complex (I). It is possible that such a complex could be formed as a distinct entity rather than as a transition state, although direct evidence for this seems unavailable at present. A half-life of several minutes has been proposed for such a complex $G_3S_3^-$ (G = glutathione) in the reduction of GS^- by GSSG.[5] It is proposed that the structure is triangular in order to account for electron sharing by the sulphur atoms needed in the proposed reduction mechanism.

As a model complex for $R_3S_3^-$ we considered $H_3S_3^-$ and later exchanged some of the hydrogens with CH_3 groups to see the effects of substituents with different electron-withdrawing properties. Two different structures of $H_3S_3^-$ were considered, one triangular (III) and one open (IV). The SS distance, SSS angle, and HSSH dihedral angle was optimised in the open complex (the rest of the parameters kept as in H_2S_2).[6] A planar equilateral structure was considered for the triangular case and was found to be almost 120 kcal mol^{-1} above the open complex in energy. Although this triangular structure was not pursued in any detail, this practically rules out the ring form of $R_3S_3^-$ as interesting, at least in this context. It is not even sure whether the triangular complex is electronically stable, *i.e.* represents a local minimum on the potential surface.


(III)


(IV)

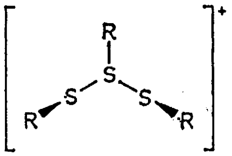

(V)

TABLE 1

Calculated total energies and optimised structural parameters of sulphides. A and B denotes the basis set used in the calculations

	Basis	$-E$ (a.u.)	Optimised parameters
H_2S_2	A [a]	795.9490	SS 2.077 Å, ∠HSSH 92.1°, ∠SSH 98.5°, SH 1.336 Å
H_2S_2	B [b]	796.194	
CH_3SSH	A	834.9374	SS 2.070 Å, ∠HSSC 87.8°
$(CH_3)_2S_2$	A	873.9251	SS 2.060 Å, ∠CSSC 86.3°
$H_3S_3^-$ linear	A	1 193.9261	SS 2.470 Å, ∠SSS 184.5°, ∠HSSH 89.5°
$H_3S_3^-$ linear	B	1 194.3076	
$H_3S_3^-$ ring	A	1 193.7326	
$H_3S_3^+$ linear	A	1 193.5950	SS 2.055 Å, ∠SSS 133.2°, ∠HSSH 90.7°
$H_3S_3^+$ ring	A	1 193.313	
$(CH_3)S_3H_2^-$	A	1 232.9046	
$(CH_3)_2S_3H^-$	A	1 271.8829	
CH_3S^-	A [b]	436.9297	CS 1.890 Å
CH_3S^-	B	437.1255	
HS^-	A [b]	397.9533	SH 1.360 Å
HS^-	B	398.1043	

[a] From ref. 6. [b] From ref. 10.

The open form of $H_3S_3^-$ (found to be electronically stable) turned out to be almost linear (4.6° off) and had a HSSH dihedral angle as in H_2S_2 (see Table 1). Thus S prefers a transition state with the entering and the leaving groups linearily arranged, an idea that has been gradually emerging both from experimental[1-3] and theoretical[6] data. The low *d* orbital occupancy of *ca.* 0.05 e or less in the present calculations once again[15] confirms that *d* orbitals are not vital in the binding of most sulphur complexes although that seems to be quite a common view.[16] The long SS distance of 2.470 Å compared with 2.077 Å in H_2S_2 really mirrors the fact that these bonds are being formed or broken in the intermediate complex. This becomes even more evident when the stability of $H_3S_3^-$ relative to the reactants (or products) H_2S_2 and HS^- is considered. In basis A the stability was calculated to be 14.9 kcal mol^{-1} (see Table 2).

TABLE 2

Calculated charge distributions, ionization potentials (ε_{HOMO}), and stabilities of linear $R_3S_3^{+,-}$ complexes. For $H_3S_3^+$ ε_{LUMO} is the electron affinity

	Basis	q ($S_{peripheral}$)	q ($S_{central}$)	ε_{HOMO} (a.u.)	ΔE/ kcal mol ^{1}
$H_3S_3^-$	A	-0.619	-0.066	-0.102	-14.9
$H_3S_3^-$	B	-0.558	$+0.021$	-0.123	-5.8
$(CH_3)S_3H_2^-$	A	-0.611	-0.059	-0.101	-8.7
$(CH_3)_2S_3H^-$	A	-0.465	-0.078	-0.088	-9.9
				ε_{LUMO}	
$H_3S_3^+$	A	$+0.101$	-0.062	-0.188	

As the geometries of the reactants were completely optimised, this is a lower limit to the value in this basis. However, considering the concentration of excess charge in $H_3S_3^-$ and especially in HS^-, it is likely that these anions are somewhat poorer described than H_2S_2 in basis A. The calculations were accordingly repeated in basis B which is better balanced in this respect, and the stability was then reduced to 5.8 kcal mol^{-1}. This value should not be interpreted as the true stability of the intermediate complex due to the approximations inherent in the model (neglect of correlation, zero-point vibrations, solvent effects, *etc.*), but as indicating that a very weak complex may be formed between disulphides and thiolate anions.

A look at the electronic structure of $H_3S_3^-$ reveals how this low stability comes about. The excess charge is distributed with essentially 0.5—0.6 e on each of the peripheral sulphur atoms, the central sulphur being neutral. The excess charge may thus be distributed all over the molecule even in the linear form of $R_3S_3^-$, so it is not necessary to invoke a triangular structure for this reason like Painter and Hunter did for $G_3S_3^-$.[5] The orbital being responsible for this special charge distribution is the highest occupied MO (HOMO). This orbital is concentrated exclusively on the sulphur atoms, it is strongly SS-antibonding (but it does not have a node at the central S), and it has an eigenvalue of -2.35 eV, thus being able to keep its extra electron. The strong distinction between the central and peripheral sulphur atoms as far as the electron distribution goes, suggests that substituents with different electron donating or accepting properties may change the stability of $R_3S_3^-$ depending on the site of the substitution.

Effects of different R *groups*. To investigate the influence of different substituents on $R_3S_3^-$, calculations were performed with methyl groups either on the central or peripheral S, *i.e.* on $HSS(CH_3)SH^-$ and $CH_3SS(H)SCH_3^-$. The S_3 structure was fixed as in $H_3S_3^-$ and linearity was tested. The stabilities thus obtained were 8.7 and 9.9 kcal mol^{-1}, respectively. Rather conservative error estimates (0.10 Å in SS, 0.05 Å in SC, and 5° in SSS) based on the calculated force constants of $H_3S_3^-$ and previous experience from structural determination of sulphides yield an error of 2.5—3 kcal mol^{-1} in basis A. The stabilities of the methylated complexes are thus equal and very close to that of the non-methylated $H_3S_3^-$. The size of these systems prevents calculating the corresponding stabilities in basis B, but an idea of how that would have changed the relative stabilities of the methylated complexes may be obtained by comparing the corresponding proton affinities for CH_3S^- and HS^- as done in Table 3. A change to basis B lowers both proton affinities by 10—13 kcal mol^{-1}, so introducing a methyl group does not essentially change the relative stabilities. As the stability of $H_3S_3^-$ in basis B was 5.8 kcal mol^{-1}, it is reasonable to suggest that the corresponding values for the methylated complexes will be of the same size, but likely closer to zero.

TABLE 3

Calculated proton affinities E(P.A.) and charges on S, q(S), in RS^- from ref. 13

	Basis	E(P.A.) kcal mol ^{1}	q(S)
HS	A	375.8	−0.963
HS^-	B	362.8	−0.949
CH_3S^-	A	380.6	−0.804
CH_3S^-	B	370.9	−0.784

At first it may seem a bit surprising that methylation does not affect the stability of the $R_3S_3^-$ complex although it changes the charge distribution somewhat (to be discussed below). However, a closer look at the electronic structure of $R_3S_3^-$ reveals why this is so. Contrary to what may be expected, the R groups do not interact directly with the antibonding SSS orbital. This orbital is essentially the same in all complexes, it is exclusively confined to the sulphur atoms as in $H_3S_3^-$ and it has essentially the same ionization potential (see Table 2). The methyl groups do, however, take *ca.* 0.15 e away from each of the peripheral S but leave the (neutral) charge on the central S unchanged. These redistributions occur in the lower lying orbitals, however, so the excess electron is still distributed as in $H_3S_3^-$ although the substituents change the total charge on the peripheral S atoms.

Total reaction energies. As the intermediate complex (I) in reaction (i) has a low stability which is rather unaffected by different substituents, this implies that the way R groups may direct the reactions is by changing the stabilities of reactants and products or equivalently, the total energies of the reactions. Traditionally this is rationalized by stating that the most stable anion will be liberated. By furthermore assuming this to be the weakest nucleophile, this means that the stronger nucleophile will replace the weaker in $RSSR^1$.

In order to assess the nucleophilicity of different RS^- ions, we use the previous experience that the (gas-phase) nucleophilicity of anions towards sulphur centres correlates nicely with the proton affinities of the anions.[6] Now, methyl groups (relative to H) are usually known to reduce the proton affinities of ions like RO^- and R_2N^-.[17,18] For RS^- ions on the other hand, methyl is seen from Table 3 to increase the proton affinity somewhat; this is in fact most pronounced in basis B. CH_3S^- is thus predicted to be a slightly stronger sulphur nucleophile than HS^-, the latter thus being expected to be liberated. On the other hand CH_3 is known to be electron withdrawing in systems with excess charge (see Table 3 and ref. 17). Traditionally this would be taken to account for CH_3S^- (and not HS^-) being the most stable ion and accordingly being liberated.

Two different but traditionally accepted ways of considering the problem thus lead to contradictory predictions of the products. To resolve this, we have calculated the energies of all possible reactions of the type (iii) R^1—R^3 being any combinations of H and CH_3.

$$R^1SSR^2 + R^3S^- \longrightarrow R^1SSR^3 + R^2S^- \qquad \text{(iii)}$$

Apart from the obvious zero-energy reactions in which reactants and products are equal, the reactions will be included in either (iv) or (v). The geometries were optimised in the most important parameters [at least R(SS) and $\angle R^1SSR^2$ in R^1SSR^2 and R(SR) in RS^-] ensuring that the calculated reaction energies $\Delta E_{(iv)}$ -7.5 and $\Delta E_{(v)}$ -7.1 kcal mol^{-1} are significantly negative (but not different). This implies that both reactions (iv) and (v) will proceed to the right with liberation of HS^-. This furthermore implies that HS^- is more stable than CH_3S^- although it has the highest electronic charge on S (0.96 *versus* 0.80 e in basis A). Accordingly, one is forced to conclude that the energies of protonation, nucleophilicity, or stability of sulphur ions do not necessarily correlate with the charge densities on the anions as often assumed in simpler models but previously shown to be wrong for alcohols and amines.[17,18]

$$HSSH + CH_3S^- \rightleftharpoons HSSCH_3 + HS^- \qquad \text{(iv)}$$

$$CH_3SSH + CH_3S^- \rightleftharpoons CH_3SSCH_3 + HS^- \qquad \text{(v)}$$

Intermediates in Electrophilic Reactions.—The second important category of reactions in which trisulphide ions are postulated to occur are the electrophilic substitution reactions of which (ii) is an example. Only recently has strong evidence for the existence of $R_3S_3^+$ actually been reported, but the highly hygroscopic nature of the salts has prevented their isolation and characterization.[4] Much of the interest in this kind of ions is due to their role as sulphenylium ion (RS^+) transfer agents towards double and triple bonds. Such agents are convenient especially as the existence of free RS$^+$ ions is highly questioned.[1,4] Despite the failure to characterize (CH$_3$)$_3$S$_3^+$ (the only R$_3$S$_3^+$ ion experimentally investigated so far) the n.m.r. study ruled out a triangular S$_3$ structure as a likely form of the complex.

The experience from previous theoretical studies of H$_2$S$_2$E^{n+} complexes[19] is that the preference of triangular over open-chain structure of SSE partly depends on the nature of electrophile. For bivalent ions like Be^{2+} where both forms are found stable the calculated energy difference determining the thermodynamic stability is rather low (*ca.* 12 kcal mol^{-1} in the gas phase) in favour of the open structure. For monovalent ions like H$^+$ on the other hand, the open structure was the only stable configuration found, the triangular structure being a saddle point on the potential surface. In the present investigation we calculated the open-chain structure of H$_3$S$_3^+$ by optimising the SS distance, the SSS bending angle, and the HSSH dihedral angle. Structure (V) (see later) was found to be stable while the lowest closed-shell configuration of triangular H$_3$S$_3^+$ [equiliteral, planer, R(SS) 2.45 Å not optimised] was as much as 7—8 eV above the open-chain form (see Table 1). So the triangular form may be ruled out as uninteresting in this context, confirming the observation of Capozzi *et al.*[4]

The detailed structure of the open-chain form (V) as reported in Table 1 shows the S$_3$ group to be bent with a SSS angle of 133°, which is more like a regular trivalent S in H$_2$S$_2$E^{n+} (92—105°).[13] While all H$_2$S$_2$E^{n+} ions previously investigated have longer calculated SS bonds than H$_2$S$_2$ (2.077 Å), the SS bond length in H$_3$S$_3^+$ was found to be 2.055 Å. Geometrically, H$_3$S$_3^+$ thus resembles S$_3^{2-}$ [R(SS) 2.063 Å, SSS 114.9°][20] with three protons added. The charge distribution is very much like that of H$_3$S$_2^+$ in the sense that the positive charge mainly is distributed among the hydrogens, $q(\mathrm{H}) = +0.26$ e — 0.34 e, while the sulphur atoms are almost neutral, $q(\mathrm{S}_{\mathrm{central}}) = -0.06$ e and $q(\mathrm{S}_{\mathrm{peripheral}}) = +0.10$ e. The electron affinity of 5.1 eV is the highest found in any H$_2$S$_2$E$^+$ complex we have studied so far. We have always found the HOMOs to be SS bonding in this type of complexes, but H$_3$S$_3^+$ is the only case where the HOMO is delocalized onto the electrophile. These observations combined with the short SS bond very likely indicate that H$_3$S$_3^+$ is quite a stable complex at least in the gas phase.

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