Theoretical Studies of the Reactions of the Sulfur–Sulfur Bond. 1. General Heterolytic Mechanisms

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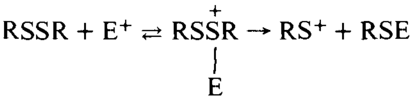
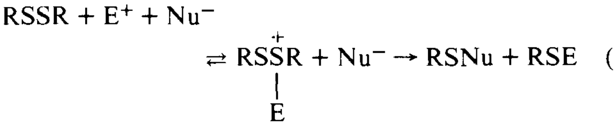
Abstract: The mechanisms of the electrophilic, nucleophilic, and concomitant reaction types of the disulfide bond have been studied based on ab-initio calculations in a double-ζ basis on model reactions of H_2S_2 with H^+, H_3O^+, H^-, F^-, Cl^-, OH^-, and SH^- as ions. The mechanisms are found to be somewhat different from what is generally assumed. The role of the electrophile is not to polarize the S–S bond but to increase the electron affinity of the LUMO (antibonding S–S orbital), thereby enhancing bond splitting by electron transfer from a nucleophile in the next reaction step, and to stabilize the end products. The cleavage of the S–S bond by the nucleophiles is found to proceed through a linear "push and pull" S_N2 mechanism without essential participation of the 3d orbitals on S. The reactivities are discussed for different initial conditions and the concomitant reactions are found to be more efficient than the nucleophilic and the electrophilic reactions, the latter having a high barrier. Evidence is found for a stable intermediate in the nucleophilic reaction. The calculated order for nucleophilicity of the anions in gas phase parallels their calculated basicity, in contrast to the experimental ordering. This indicates that the polarizability of the anions probably is less important than solvent effects in determining the nucleophilicity.

The relative ease by which the S–S bond can be broken and formed makes the study of its chemistry interesting and important not only to biochemistry and biology but also to organic and inorganic chemistry. Although much empirical data are available, a full understanding of the mechanisms underlying the chemistry of the disulfide bonds is still lacking. According to the present knowledge, the nonradical chemical reactions of the disulfides can be described in terms of three different reaction types[1-4]



$$\mathrm{RSSR} + \mathrm{E}^+ \rightleftarrows \mathrm{RS}\underset{\substack{|\\ \mathrm{E}}}{\overset{+}{\mathrm{S}}}\mathrm{R} \rightarrow \mathrm{RS}^+ + \mathrm{RSE} \qquad (1)$$



$$\mathrm{RSSR} + \mathrm{E}^+ + \mathrm{Nu}^- \rightleftarrows \mathrm{RS}\underset{\substack{|\\ \mathrm{E}}}{\overset{+}{\mathrm{S}}}\mathrm{R} + \mathrm{Nu}^- \rightarrow \mathrm{RSNu} + \mathrm{RSE} \qquad (2)$$

$$\mathrm{RSSR} + \mathrm{Nu}^- \rightarrow \mathrm{RS}^- + \mathrm{RSNu} \qquad (3)$$

being electrophilic, combined electrophilic and nucleophilic (commonly denoted as concomitant), and nucleophilic cleavage, respectively. The most important electrophiles[4,5] are H^+ and metal ions with high affinity for S like Ag^+ and Hg^{2+}, while the nucleophiles of interest cover a wide range like H^-, RS^-, CN^-, OH^-, R_3P and the halogen anions.[6] The mechanisms of these reactions are not understood in detail, nor is the question as to which mechanism is the dominating one under special conditions fully settled. Reaction types 1 and 3 have for a long time been considered as the mechanisms of S–S scission. More recently, evidence has accumulated indicating that (2) may strongly compete with (1) even with trace amounts of Nu^- present.[1,2] Most reactions previously classified as type 1 are thus likely to be of type 2. The presence of electrophiles are furthermore known to enhance type 3 reactions like in the cyanolysis of cystine.[19]

There has as yet been very little to be gained from theoretical studies as these almost exclusively have concentrated on the static properties of the S–S bond-like geometry and rotation barriers, whereas the reactivity has been discussed only peripherally. The aim of this study is thus threefold. By means of ab-initio calculations on selected model systems we will primarily attempt to gain further knowledge of the mechanisms behind the main reaction types 1–3. Our second aim is to elucidate the reason behind the very different efficiencies of these reactions in a given situation, and finally to compare the effect from different nucleophiles and electrophiles on the reactions.

The computations on the molecular systems involved in the reactions will be rather time consuming as these generally contain many electrons and have low or no symmetry. H_2S_2, being the smallest disulfide, is accordingly chosen as model for R_2S_2. As electrophile we use H^+ which by far is the most common and as nucleophiles we will study H^-, F^-, and to a somewhat lesser extent OH^-, Cl^-, and SH^-. The metal ions as electrophiles will be studied in a forthcoming paper. We stress that the effort will be laid on gaining qualitative understanding of the processes rather than obtaining quantitative results.

Details of the Calculation

All calculations were performed in the MO-LCAO-SCF framework using the program system MOLECULE.[7] As all molecules studied (except SH^+) are closed shell systems, the use of the Hartree–Fock approximation should be justified. The basis used was the medium size Gaussian set of Roos and Siegbahn,[8] being of the type 10s 6p 1d for second-row atoms, 7s 3p for first-row atoms, and Huizinaga's 4s basis[9] for H scaled by 1.25, all contracted to double ζ (plus polarization). The anions are somewhat more poorly described in this basis than the neutral molecules due to the additional diffuse charge, but this is not likely to influence any of the conclusions to be drawn concerning differences between the ions. The geometries of the reactants and products containing F^-, H^-, and SH^- were fully optimized whereas a partial optimization was performed on the molecules containing Cl^- and OH^-. The small error thereby introduced in the energies will not affect any of the conclusions to be drawn.

The aim of this study has not been to characterize the reaction paths on the complete potential surfaces but rather to compare qualitative differences between the various reaction types. This will be based on calculations in a few characteristic points on the surfaces and the total reaction energies. The calculated total energies for the stable molecules and the geometries used are reported in Table I and summarized as energies of reactions in Figure 1.

Protonation of the S–S Bond

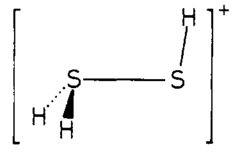
This reaction is common to the electrophilic and concomitant mechanism and it is believed[2,3] that its main purpose is partially to polarize and weaken the S–S bond and partially to make the RSE fragment a better leaving group by stabilizing

Table I. Total Energies and Geometries

No.	Mol	E, au	Geometry (bond distances in Å)[a]
1	H_2S_2	−795.94899	SS = 2.077 (O), SH = 1.336 (O), ∠SSH = 98.5° (O), ∠HSSH = 92.1° (O)
2	$H_3S_2^+$	−796.22924	SS = 2.104 (O), SH = 1.336 (O), SH+ = 1.340 (O), ∠SSH = 92.6° (O), ∠HSH = 95.4° (O), ∠HSSH = 131° (O)
3	HSF	−497.21624	SF = 1.640 (O), SH = 1.335 (O), ∠HSF = 96.2° (O)
4	H_2S	−398.55216	SH = 1.335 (O), ∠HSH = 93.5° (O)
5	HSOH	−473.25077	SO = 1.738 (O), ∠HSOH = 98° (O), SH = 1.336 (O1), ∠SOH = 94.8°, OH = 0.947
6	HSCl	−857.31090	SCl = 2.028 (O), SH = 1.335 (O3), ∠HSCl = 96.2° (O3)
7	H_3O^+	−76.18926	Planar (C_{3h}) OH = 0.960
8	H_2O	−75.88352	OH = 0.957, ∠HOH = 104.5°
9	HS^-	−397.95329	HS = 1.354 (O)
10	HS^+	−397.52526	HS = 1.351 (O), singlet state
11	OH^-	−75.17869	OH = 1.026 (O)
12	F^-	−99.16058	
13	Cl^-	−459.36534	
14	H^-	−0.42557	
15	HF	−99.81905	HF = 0.941 (O)
16	HCl	−459.92775	HCl = 1.275 (O)
17	H_2	−1.12691	HH = 0.738 (O)

[a] (O) denotes optimized parameters, (O*n*) denotes parameters optimized in molecule *n*.

RSE relative to RS^-. Both semiempirical calculations[10] on $(CH_3)_2S_2H^+$ and the ab-initio electrostatic potential[11] of H_2S_2 suggest a binding of the proton to one lone pair rather than a bridging bond between the sulfur atoms. This is supported by the calculated equilibrium structure of $H_3S_2^+$ which shows that the proton binds to one of the lone pairs almost parallel to the C_2 axis of H_2S_2 at a normal S-H distance from a somewhat distorted sp^3 sulfur atom. (See structure I and Table



I

1.) The common assumption that the electron withdrawal from the S-S bond due to the proton will weaken the bond is not supported, however. The S-S bond distance is indeed increased by 0.03 Å on protonation, but as much as 0.02 Å is due to the opening of the dihedral angle in H_2S_2 from 92 to 131° (at which the eclipsing of lone pairs and the electron deficient S-H bonds is almost at a maximum) and only 0.01 Å results directly from introducing H^+. The S-S overlap charges are furthermore equal in H_2S_2 and $H_3S_2^+$.

Semiempirical calculations of Yamabe et al.[10] have further supported the common conception of a polarized S-S bond in $RS^+S(E)R$ (so as to enhance the electron transfer from Nu^- in the concomitant reaction). The population analysis of $H_3S_2^+$ in the present calculation shows on the contrary that the S-S bond is not polarized at all (cf. Table II) and that the charge transferred to H^+ (0.69 e) mainly is taken from the hydrogen atoms. Of importance for the concomitant reaction, however, is that the electron affinity as described by the energy of the lowest vacant orbital (which is strongly S-S antibonding and into which the excess electron pair will go when Nu^- enters) drops sharply from +31.0 eV in H_2S_2 to −3.8 eV in $H_3S_2^+$. The S-S bond, which in itself is not considerably weakened upon protonation, will thus be more easily broken by the nucleophilic attack. It might be objected that some of the above conclusions are dependent on the special symmetry of $H_3S_2^+$ in which the electrophile is the same as the ligands of S. Calculations were performed on $(CH_3)_2S_2H^+$ in order to check this (using the same primitive Gaussian set but contracted to minimal basis). The conclusions were found to be equally valid for this system as seen from Table II. The major quantitative difference was that the LUMO is considerably lower in $(CH_3)_2S_2$ than in H_2S_2 (also valid in the double-ζ basis[11]).

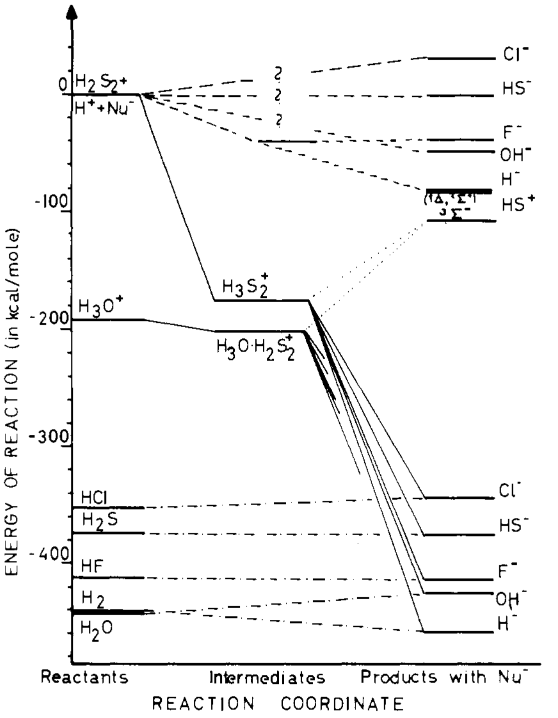


Figure 1. The calculated total energies of the reactions. The energy of H_2S_2 + H^+ + Nu^- is chosen as zero. The reaction types are indicated as: (—) concomitant, with dissociated H^+ + Nu^-; (- · · -) concomitant, with undissociated HNu; (···) electrophilic; and (- - -) nucleophilic.

The proton is a very strong electrophile and the previous results consequently do not necessarily represent the proper effects from other electrophiles of interest. In an attempt to simulate the effect of covalently bound weaker electrophiles, a series of calculations was performed using "protons" with nuclear charges in the range 0 to +1.5 (geometry as in $H_3S_2^+$). Properties like the (non) polarization of the S-S bond, the S-S overlap charge, and the gross charge on H^+ were found to remain nearly constant (cf. Table II), while the cation affinity of H_2S_2 and the electron affinity of $H_2S_2E^+$ proved to be strongly dependent on Z. The orbital energy of the S-S* or-

Table II. Details of the Results for $R_2S_2E^+$

	Total energy, au	$\epsilon(SS^*)$	$p(SS)$	$q(E^+)$	$q(S_{E+})$	$q(S_H)$
$H_2S_2H^+$, $Z(H^+) = 1.5$	−796.747 59	−0.755	0.460	+0.28	+0.39	+0.14
$Z(H^+) = 1.0$	−796.229 24	−0.145	0.448	+0.31	+0.08	+0.02
$Z(H^+) = 0.6$	−796.029 80	−0.040	0.442	+0.26	−0.10	−0.06
$Z(H^+) = 0.3$	−795.963 62	+0.376	0.439	+0.14	−0.16	−0.12
$Z(H^+) = 0.0$	−795.944 90	+1.139	0.433	−0.03	−0.16	−0.18
$Z = 1.0^c$	−796.056 82	−0.130	0.261	+1.0	−0.60	+0.01
$[H_3OH_2S_2]^+$	−872.154 08[a]	−0.109	0.441	+0.37[b]	−0.03	−0.03
$(CH_3)_2S_2H^+$	−872.854 30[d]	−0.117	0.588	+0.29	+0.22	+0.17
$(CH_3)_2S_2^e$	−872.591 52[d]	+0.175	0.606			+0.02

[a] Total energy for $H_2S_2 + H_3O^+ = -872.138\ 25$ au and for $H_3S_2^+ + H_2O = -872.112\ 76$ au. [b] The charge of H between O and S. Total charge of H_3O^+ fragment = +0.51. [c] Proton without basis functions. [d] Minimal basis. [e] From ref 11.

bital becomes negative for $Z > 0.6$, which means that a rather strong electrophile is needed to get a positive electron affinity of $H_2S_2E^+$. Somewhat weaker electrophiles will probably be sufficient for $(CH_3)_2S_2E^+$.

Hard electrophiles on the other hand, like the cations of the 1 and 2 main groups, are expected to have a more ionic type of bonding to sulfur. This situation has been simulated by a proton ($Z = 1$) without basis functions to prevent charge transfer toward the ion. This is the only case where the S–S bond really is polarized (but opposite to the common assumption) and has a low overlap (cf. Table II) while the electron affinity is as in $H_3S_2^+$.

The calculated proton affinity of H_2S_2 (−175.8 kcal/mol, experimental value not known) is close to the proton affinity of H_2O (−192 kcal/mol in our basis without corrections for zero-point vibrations) and as H^+ of course is hydrated in aqueous solution; this raises the question whether $H_3S_2^+$ is a realistic model of protonated H_2S_2 in solution, at least for our purpose. Some informative calculations were accordingly performed on the $[H_3OH_2S_2]^+$ complex, indicating that the proton is roughly equally shared between H_2O and H_2S_2 and that the stability of the complex toward dissociation to $H_3O^+ + H_2S_2$ is of the order 10 kcal/mol (cf. Figure 1). The properties relevant for the reactivity, like electron affinity, S–S (non) polarization, and S–S overlap, were found to be essentially the same as for $H_3S_2^+$ with $Z = +1.0$ (cf. Table II). (The value of $Z = 1.0$ rather than a value more like the charge on H^+ in $[H_3OH_2S_2]^+$ (+0.37) is apparently necessary to allow for sufficient charge transfer from H_2S_2. If the "proton" affinity of H_2S_2 is to be equal the H_3O^+ affinity of H_2S_2, the nuclear charge of the "proton" will have to be ~0.3–0.4.) The hydration of H^+ thus seems to be an unnecessary complication of our model unless the cation affinity of R_2S_2 is discussed quantitatively.

Electrophilic Scission

This reaction type was for a long time considered to be the only mechanism of any importance for electrophiles reacting with disulfides. The RS^+ ion produced in the presumed rate-determining step has rarely been observed, however, and there is now evidence[1] indicating that a majority of the reactions previously classified as electrophilic scissions are likely to be of the concomitant type with the solvent or contaminating anions as nucleophiles.

The formation of HS^+ ($^3\Sigma^-$ ground state) is from our calculations[12] endothermic by as much as 60–70 kcal/mol (cf. Figure 1). The highly reactive RS^+ ion is supposed to have the following fate[5]:

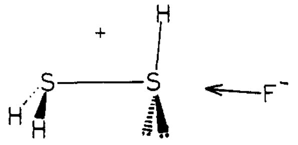
$$2RS^+ + 2OH^- \rightarrow 2RSOH \rightarrow RSH + RSO_2H \qquad (4)$$

Although the reaction sequence eq 1 + 4 in the next section is shown to be exothermic, it will thus nevertheless have a high barrier against cleavage of the S–S bond. This may explain why eq 1 + 4 probably are so rarely observed except when steric hindrance prevents (2) or (3) as in Bunte salts, $RSSO_3^-$.

Concomitant Scission

In recent years, considerable experimental evidence has accumulated indicating that low concentrations (10^{-4}–10^{-6} M) of nucleophiles can often exert dramatic catalytic effect on the rates of reactions previously classified as electrophilic scissions.[1] The concomitant mechanism, although not understood in detail, has been proposed[13] as responsible for this. It is believed, but as yet not fully settled, to be a quite general mechanism functioning for a wide variety of nucleophiles.

In our study, F^- is adopted as the nucleophile in the model reaction $H_3S_2^+ + F^- \rightarrow H_2S + HSF$. The results show that F^- preferably will approach H_2SSH^+ in the SSH plane (i.e., in between the lone pairs on S) on the opposite side of the S–S bond (see structure II). Figure 2 shows the length of the S–S bond to be broken as a function of the bond to be formed in the different reactions studied. Although a limited number of calculations and convergency problems resulted in very few points, the results nevertheless clearly demonstrate that the S–S bond breaks at an early stage with the main part of the reaction energy liberated during the incoming phase. The H_2S and HSF fragments are neutral (within ±0.03e) already at a S–F distance ~0.75 Å longer than in HSF, so that the excess charge on F^- is transferred to $H_3S_2^+$ at an early stage although F^- is not a particularly soft ion. The variations of the orbital energies and the populations furthermore suggest that the electron pair in the S–S bond in $H_3S_2^+$ is transformed into a lone pair on H_2S, being consistent with the "push and pull" mechanism originally proposed[14] for S_N2 displacement reactions on sp^3 C.



II

To get an idea of how different nucleophiles will influence the rate of the reaction, the total energy of reaction was calculated for $Nu^- = Cl^-, OH^-, SH^-$, and H^-;[15] see Figure 1. The concomitant reaction is generally seen to occur without any barriers and to be strongly exothermic with the nucleophilicity of the anions ordered as $H^- > OH^- > F^- > HS^- > Cl^-$.

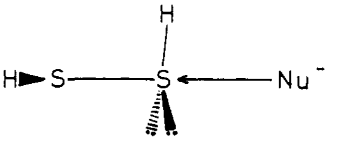
This picture is drastically changed, however, if the concentration of X^- is low in strongly acidic media. Then H^+ and X^- will not exist as free ions but as HX, and the reaction energies will have to be changed by the endothermicities of HX

$\rightarrow H^+ + X^-$, which are of the same order. The corrected reaction energies are thus almost zero (cf. Figure 1), deriving indirect experimental support from the fact that these reactions are believed to be slower. It is not justifiable to order the nucleophiles in this case on the basis of our calculations, except to note that the reaction with OH^- is now very likely endothermic while the reaction with SH^- is of zero energy by symmetry. But in any case the concomitant reactions are considerably more favorable than the corresponding electrophilic reaction with H_3O^+.

Nucleophilic Scission

The most extensively studied and best known reactions of the disulfides are probably the nucleophilic scissions where a thiol anion RS^- is displaced. The mechanism is most likely to be S_N2, but details on how the reaction proceeds have not been established. A survey of these reactions has given the following rough order of S nucleophilicity:[5,6] $H^- > RS^- > R_3P > CN^- > OH^- > SCN^- > Br^- > Cl^-$.

As nucleophiles in our model study, we have used H^- (which is a very strong nucleophile in aprotic solvents like DMSO[15]) and to some extent F^- being on the other extreme of the reactivity scale. The results reveal a mechanism very much like that of the concomitant reactions. H^- appears to approach H_2S_2 in the SSH plane and proceed through a linear $S–S–H^-$ state with bond formation ahead of bond breaking (see structure III). As in the concomitant reaction, the electron pair in the S–S bond is transformed into a lone pair on H_2S.



III

The geometry of the intermediate state and the importance of d orbitals in this context have been subject to much discussion.[2,3] Our results confirm the general belief of a trigonal-bipyramid configuration on the sulfur center with the entering and leaving groups in apical positions. The fact that the d occupation on S is essentially unaltered and low (~0.1 e) during the reaction, that the charge on S is somewhat lower (~0.1 e) in the intermediate states than in the reactants and the products, and that the entering and leaving is linear shows that d orbitals are not essential in order to understand the mechanism.

The calculations on F^- reveal the existence of a stable intermediate complex of the type $[HS–S(H)–F]^-$ being at least 6 kcal/mol lower in energy than the products. The structure was not further refined except being found to be linear, but the very existence of the complex is interesting as it supports the idea that a similar complex with RS^- also might be stable. Such a complex, $G_3S_3^-$ (G = glutathione), with a possible half-life of several minutes, has been proposed[16] as essential in a possible mechanism of the oxidative phosphorylation in which GSH is oxidized by cytochrome *c* in the presence of GSSG. The thiol disulfide exchange also presumably proceeds through a stable intermediate complex of the type $R_3S_3^-$.[5] Stronger evidence cannot be advanced without further studies, however.

The calculations with F^- also allow a direct comparison of the efficiencies of the concomitant and the nucleophilic mechanisms in cleaving the S–S bond. Figure 2 clearly demonstrates that the S–S bond is considerably weaker at a certain S–F distance in the concomitant reaction than in the nucleophilic reaction. In the latter mechanism the S–S bond is broken at a later stage of the reaction.

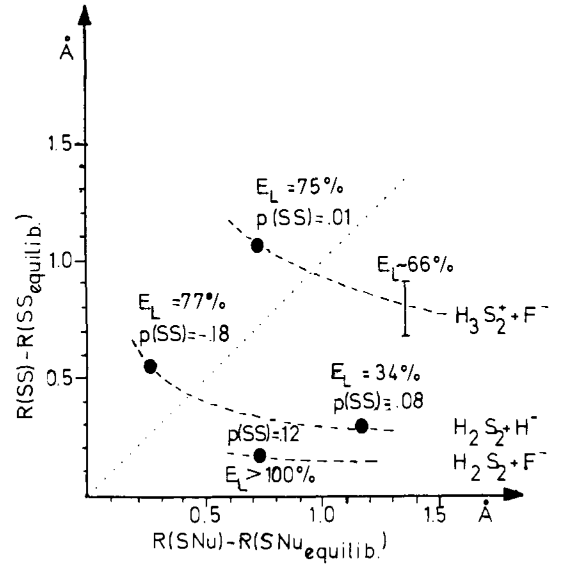


Figure 2. The length of the S–S bond as a function of the length of the S–Nu bond to be formed in reactions 2 and 3. The distances are relative to the calculated equilibrium distances in the reactants and the products. The S–S overlap populations p(SS) and the energy liberated E_L in % of the total reaction energies are given.

Table III. Proton Affinities (in kcal/mol) as Calculated from Table I and Corrected for Differences in Zero-Point Energies

	Calcd PA	Zero-point corr[a]	Corr PA	Exptl
H^-	440.1	6.3	433.8	400[22]
OH^-	442.3	~9.5	~432.8	390[23]
F^-	413.2	4.3	408.9	368[24]
HS^-	375.8			337[25]
Cl^-	352.9	4.3	348.6	327[24]
H_2O	191.9	5.3[21]	186.6	168[26]
H_2S_2	175.8			

[a] Compiled from Herzberg, "Spectra of Diatomic Molecules", 2nd ed, Van Nostrand, Princeton, N.J., 1950.

The reaction energies of the different nucleophiles may easily be obtained from the corresponding concomitant values by adding the endothermicity of $H_2S \rightarrow HS^- + H^+$ (375.8 kcal/mol). The reaction with Cl^- thus becomes endothermic, F^-, OH^-, and H^- exothermic, and of zero energy with HS^- (by symmetry).

Nucleophilic Reactivity

The experimental ordering (which at best is a rough one) of the S nucleophilicity of the anions does not follow their basicity. This is usually interpreted in the way that the polarizability of the nucleophiles, in addition to basicity, also is an important factor determining the nucleophilicity.[6] Our calculated order of nucleophilicity[20] ($OH^- > F^- > HS^- > Cl^-$) differs from the experimental ($HS^- > OH^- > Cl^- > F^-$) mostly in that the first and second row elements are interchanged, but it exactly parallels the calculated basicity or proton affinity of the anions as reported in Table III. The calculated order applies to the gas phase, and so far nucleophilicity is correlated to the calculated reaction energies; polarization of the anions is not necessary to explain the ordering. The main difference in solution is likely to arise from the different affinity of the ions for the solvent, which is larger for first row atoms than for second row atoms. In aqueous solution, this difference for F^- and Cl^- may be of the order 50 kcal/mol[17] which may be sufficient to change the ordering.[18] It thus seems fair to conclude that affinity for the solvent may be as important as polarizability in determining the nucleophilic character of an anion.

Conclusions

Our studies of the reaction types 1-3 show that the detailed mechanisms are somewhat different from what is generally assumed. The effect of the electrophile on R_2S_2 is not to polarize or weaken the S-S bond (unless the electrophile is electrostatically bound) but to prepare the S-S scission in the next reaction step by enhancing the approach of nucleophiles and to transform RS(E) into a better leaving group. The preparation is achieved by a considerable increase in the electron affinity of the disulfide as seen from the lowering of the orbital energy of the LUMO. The strongly S-S antibonding character of this orbital will thus greatly facilitate the bond scission when the excess electron is transferred from the nucleophile. The hydration of the proton proved not to be essential for studies of these effects. The electrophilic scission mechanism 1 was found to be highly endothermic while the concomitant mechanism 2 was found to proceed without any barrier and with large exothermicity. Even for small concentrations of nucleophiles the concomitant mechanism was found to be superior to the electrophilic mechanism. The nucleophilic reaction types 3 have much smaller reaction energies than the concomitant reactions and proceed through an asynchronous (early formation) S_N2 mechanism without essential participation of d orbitals. The concomitant and nucleophilic reactions exhibit the same "push and pull" mechanism in splitting the S-S bond. The difference in efficiencies is due to the previously mentioned effect of E^+ to enhance the electron transfer from Nu^- to the antibonding S-S orbital. Stable intermediates may be formed in the nucleophilic reactions.

The main factor that determines the nucleophilic character of an anion toward sulfur was found to be the basicity as expected. Contrary to the common conception, however, polarization was found to be of less importance, while the solvent affinity may prove to be essential.

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(12) A rough estimate of the energy of the $^3\Sigma^-$ ground state of HS^+ (but sufficient for our purpose) is obtained as the calculated energy of a closed shell system (yielding a mixture of $^1\Delta$ and $^1\Sigma^+$) minus the calculated $^1\Delta - {}^3\Sigma^-$ splitting of 1.16 ± 0.1 eV from P. E. Cade, *Can. J. Phys.*, **46**, 1989 (1968).

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