Theoretical Study of the Reduction Mechanism of Sulfoxides by Thiols

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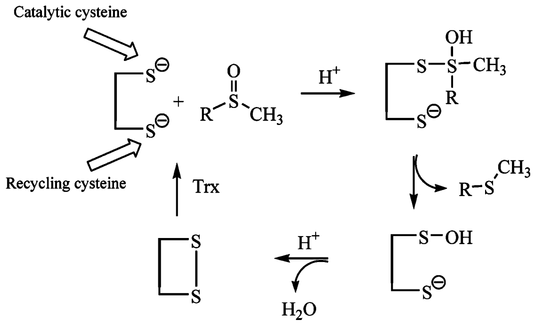
Theoretical computations have been carried out to investigate the reaction mechanism of the sulfoxide reduction by thiols in solution. This reaction is a suitable model for enzymatic processes involving methionine sulfoxide reductases (Msrs). Recent investigations on the Msr mechanism have clearly shown that a sulfenic acid intermediate is formed on the catalytic cysteine of the active site concomitantly to the methionine product. In contrast, experimental studies for the reaction of a number of thiols and sulfoxides in solution did not observe sulfenic acid formation. Only, a disulfide was identified as the final product of the process. The present study has been carried out at the MP2/6-311+G(3d2f,2df,2p)//B3LYP/6-311G(d,p) level of theory. The solvent effect in DMSO has been incorporated using a discrete−continuum model. The calculations provide a basic mechanistic framework that allows discussion on the apparent discrepancy existing between experimental data in solution and in the enzymes. They show that, in the early steps of the process in solution, a sulfurane intermediate is formed the rate of which is limiting. Then, a proton transfer from a second thiol molecule to the sulfurane leads to the formation of either a sulfenic acid or a disulfide though the latter is much more stable than the former. If a sulfenic acid is formed in solution, it should react with a thiol molecule making its experimental detection difficult or even unfeasible.

Introduction

The reduction reaction of sulfoxides by thiols is of considerable biochemical interest because it can be viewed as the simplest model for enzymatic reactions involving the methionine sulfoxide reductases (Msr).[1−17] Msrs are repair enzymes that reduce free or protein-bound methionine sulfoxide (MetSO) oxidized by reactive oxygen or nitrogen species. The enzymatic reaction mechanism has recently been investigated. The overall reaction is depicted in Scheme 1.[4,17] The catalytic cysteine reacts with MetSO to yield a sulfenic acid intermediate which has been evidenced by chemical and spectroscopic methods.[4,8] At this stage, the reduced substrate is released. Then, the enzymatic reaction proceeds through formation of an intra-disulfide bond upon the attack of the recycling cysteine to the sulfenic acid intermediate. Finally, the oxidized form of Msrs is recycled by thioredoxin. In some Msrs, like MsrA in *E. coli*, a third cysteine could be involved in the recycling process.[17] In all Msrs studied so far, the limiting step is associated to the thioredoxin-recycling process, whereas the rate of formation of the intra disulfide bond is governed by that of the sulfenic acid intermediate.[17]

The reduction of sulfoxides by thiols is also interesting from the point of view of synthetic chemistry. It has attracted attention since many decades because of high yields, mild experimental conditions, the ease of purification and the use of the sulfoxide (namely, dimethyl sulfoxide, DMSO) also as the solvent.[21−28] Both acids and bases, in particular aliphatic amines, catalyze the reaction.[24,26] Catalytic effects by halogen−hydrogen halides,[26] metals,[29−31] and alumina[32] have also been investigated. Early kinetic studies by Wallace[22] and Wallace and Mahon[23] indicated that the activation energy correlated with the pK_a of the thiol. Moreover, while the reaction was found to be overall second order, in the excess of one of the reagents, pseudo-first-order kinetics was observed. On the basis of these findings, the authors proposed a reaction mechanism that involves initial formation of a thiol−sulfoxide adduct of sulfurane type followed by reaction of this intermediate with a second thiol molecule according to eqs 1−2.

SCHEME 1



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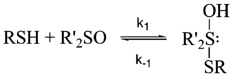
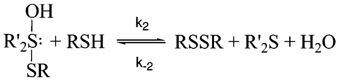


$$RSH + R'_2SO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R'_2\overset{\overset{OH}{|}}{\underset{\underset{SR}{|}}{S}}: \qquad (1)$$



$$R'_2\overset{\overset{OH}{|}}{\underset{\underset{SR}{|}}{S}}: + RSH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} RSSR + R'_2S + H_2O \qquad (2)$$

It was also shown that k_{-2} is negligible and that $k_2 \gg k_1$.

The proposed mechanism raises questions since (1) the assignment of a sulfurane intermediate was based on kinetic studies but not on direct structural information, and (2) it excludes the formation of a sulfenic acid intermediate in contrast to recent conclusions derived from enzymatic reaction studies.

Sulfenic acid intermediate, if formed, should react with methanethiol in the medium making their experimental detection difficult. Indeed, sulfenic acids[33−39] are highly reactive species and only a few sulfenic acids could be isolated and identified. In particular, they can be detected when they are part of a large molecule,[38,39] such as a protein,[40,41] which hinders their accessibility. Sulfenic acids may however be stabilized in a number of ways (see for instance ref 42), namely, by conversion into a sulfenate or a thiosulfinate, after reacting with another sulfenic acid.

To get a deeper insight on the mechanism of this reaction, quantum chemistry calculations may be particularly useful. The aim of the present work is to make such a theoretical investigation for a model process in DMSO solution. Specifically, this paper considers the following aspects: (1) the potential energy surface of the chemical system is explored in deep detail, (2) the structures of possible reaction intermediates and transition structures are described, (3) the energetics of all possible reaction pathways are compared, and (4) the role of the solvent is analyzed. Though the mechanisms of acid-, base-, and enzyme-catalyzed reactions have not been considered in this study, the results reported for model compounds in DMSO solution provide a basic framework to interpret experimental data. For the sake of clarity, the nomenclature of sulfur compounds is summarized in a glossary at the end of the manuscript.

Computations, Methods, and Models

To keep the computational time within reasonable limits, we have investigated the model reaction methanethiol + DMSO in DMSO solution. Though there is no available experimental data for methanethiol, comparison with experiment can be made with thiols exhibiting a similar pK_a value since this property is well correlated with the reaction kinetic constant.[23] In particular, methanethiol and α-toluenethiol, for which experimental results are available, have close pK_as in water (10.3 and 10.5, respectively).[23,43]

The solvent has been modeled using a discrete−continuum model. The initial chemical system consists of one thiol molecule and two solvent molecules. Explicit inclusion of two DMSO solvent molecules was found to be important because the solvent can form strong hydrogen bonds with some reaction intermediates influencing in a crucial way their chemical properties. Moreover, being a proton acceptor, DMSO can participate to the reaction coordinate in proton-transfer processes. In the course of the reaction, a further thiol molecule has been incorporated to the system (see below). The polarizable continuum method developed in our laboratory[44−47] has been used (dielectric constant $\epsilon = 46.7$). We assume a molecular-shaped cavity and a multicentric multipole development of the reaction-field potential (up to 4th order). The cavity is defined by a scaled van der Waals surface with Bondi radii multiplied by a factor 1.308. All the geometries have been fully optimized at the B3LYP/6-311G(d,p) level of theory.[48,49] Harmonic frequencies have been computed at the same level for identifying the stationary points as minima or transition structures (TS). Besides, minima connected by the TSs have been verified via intrinsic reaction coordinate (IRC) calculations. Zero-point energies, thermal contributions to the enthalpy, and entropic terms have been computed in the usual way using the ideal gas approximation. Gibbs free energies are given relative to the initial complex after adding an empirical correction, as explained below.

To improve the accuracy on computed electronic energies, we have carried out MP2 single-point energy calculations on B3LYP optimized geometries. In that case, we use the extended basis set 6-311+G(3d2f,2df,2p) that is employed in the MP2 step of the CBS-QB3 method.[50] Unfortunately, in a few cases, this large basis set leads to solvation energy convergence problems. To avoid this difficulty and for the sake of homogeneity, MP2 calculations in solution have been done at the MP2/6-311G(d,p) level corrected by computations in gas phase at the MP2/6-311+G(3d2f,2df,2p) level according to

$$E_s(B) = E_s(A) + [E_g(B) - E_g(A)] \qquad (3)$$

where E_g (E_s) represents the electronic energy in gas-phase (solution) and A or B means MP2/6-311G(d,p) or MP2/6-311+G(3d2f,2df,2p) levels. This approximation has been tested in the case of the sulfurane intermediate described below, which plays a main role in the process, and shows the MP2/6-311+G(3d2f,2df,2p) energy to be very close to the approximated value obtained from eq 3 (difference 1 kcal/ mol).

The approximate MP2/6-311+G(3d2f,2df,2p) energies are used along the text and figures, unless otherwise stated. Corrections for basis set superposition error (BSSE) are not included in the energies presented below because with such a large basis set; BSSE has been found to represent a minor correction.

Electronic populations have been described in terms of a natural population analysis (NPA)[51] and Mayer bond orders.[52] All the calculations have been carried out using the Gaussian98 package.[53]

Results

As mentioned above, Wallace and Mahon[23] showed that the reaction in DMSO is pseudo-first order in thiol concentration. Since the whole process, as it is proposed, involves two thiol molecules, one may conclude that each thiol molecule concerns a different reaction step. This has been assumed in our calculations. For clarity of the presentation, the results will be separated in four parts devoted to: (1) the reaction of a thiol molecule with DMSO and the formation of a sulfurane reaction intermediate, (2) the analysis of the properties of the sulfurane intermediate, (3) the activation of the reaction intermediate OH group by a second thiol molecule, and (4) the formation of the products.

Only a few geometrical parameters for the main structures will be presented below. Cartesian coordinates are available as Supporting Information as well as a full description of the transition vectors in transition structures.

Methanethiol Reaction with DMSO. Though experimental measurements suggest that a sulfurane intermediate is formed at this reaction step, we have envisaged the formation of both a sulfurane and a sulfenic acid. In principle, these compounds might be obtained through concerted or stepwise processes. In

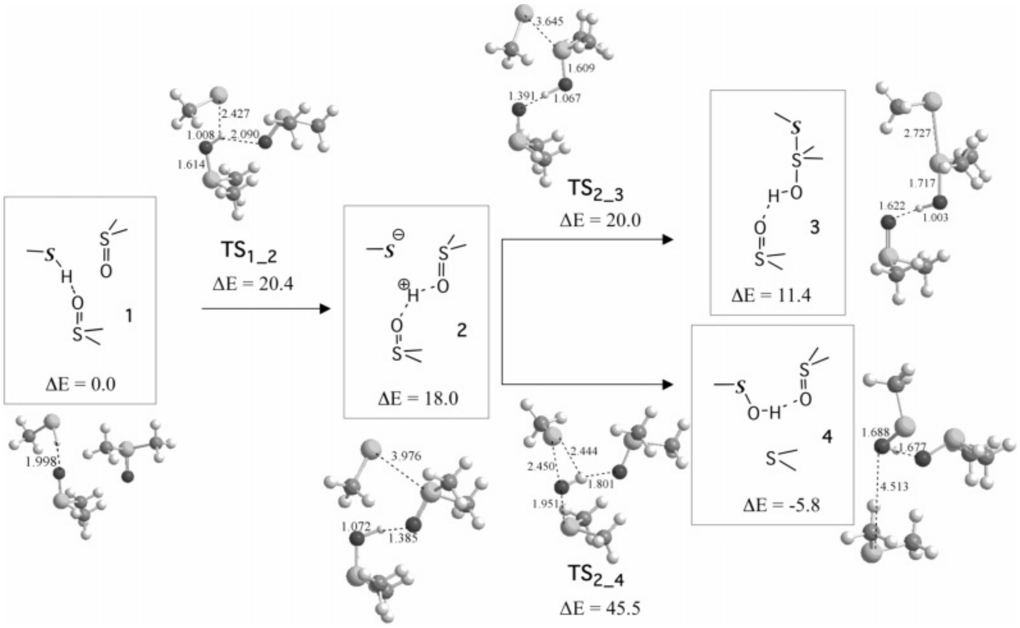


Figure 1. Schematic representation of the chemical species involved in stepwise reactions of methanethiol and DMSO and optimized structures at the B3LYP/6-311G** level (reactants, intermediates, transition structures) and approximate MP2/6-311+G(3d2f,2df,2p) energies in DMSO solution. Δ*E* includes the electrostatic free energy of solvation in the dielectric continuum and is given relative to complex 1. Values are in angstroms and kcal/mol.

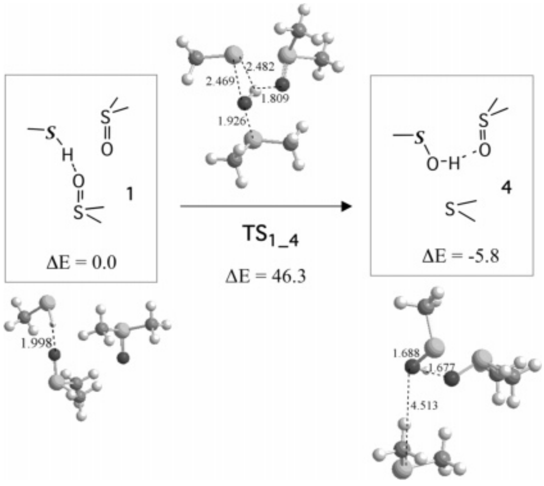


Figure 2. Schematic representation of the chemical species involved in the concerted reaction of methanethiol and DMSO to yield a sulfenic acid and optimized structures at the B3LYP/6-311G** level (reactants, intermediates, transition structures) and approximate MP2/6-311+G(3d2f,2df,2p) energies in DMSO solution. Δ*E* includes the electrostatic free energy of solvation in the dielectric continuum and is given relative to complex 1. Values are in angstroms and kcal/mol.

the stepwise process, an ion pair should initially be formed through proton transfer from the thiol to DMSO. In our computations, the reactants are described by a hydrogen-bonded complex involving methanethiol and two DMSO molecules. We then explore the potential energy surface of the complex looking for stationary points. Stepwise processes leading to either the sulfurane or the sulfenic acid have been obtained and are shown in Figure 1. A concerted process leading to sulfenic acid has also been identified and is represented in Figure 2. However, any transition structure for a direct formation of a sulfurane intermediate 3 from 1 could be located. Figures 1 and 2 include some optimized geometrical parameters as well as the predicted values for relative energies. Note that various conformations for the ion pair 2 have been obtained lying in a narrow energy range. For simplicity, we do not describe them in detail.

The predicted energies clearly suggest that formation of the sulfenic acid at this reaction step is very unlikely, the energies of TS$_{1\to4}$ or TS$_{2\to4}$ being quite high (both TSs exhibit similar energies). Rather, the sulfurane intermediate should be formed in a stepwise process $1 \rightarrow 2 \rightarrow 3$ that involves an activation energy of 20.4 kcal/mol in the first step and a fast recombination of the ions in 2 to form the adduct 3.

Since polar species are present, one may expect the solvent to play a crucial role in the process. Indeed, long-range electrostatic interactions are fundamental to stabilize the ion pair. Moreover, the analysis of the results shows that hydrogen bonds with the discrete DMSO molecule are very important too. This can be illustrated by looking at the geometries of intermediates 2, 3, and 4 in Figure 1. Structure 2 shows that the hydrogen bond distance between the transferred proton and the oxygen atom of the solvating DMSO is very short (1.385 Å) in agreement with the work by Fu et al.[54] Hydrogen-bond distances in 3 and 4 are larger (1.622 and 1.677 Å, respectively) but still correspond to strong interactions.

Hydrogen bonds in transition structures are also noticeable. TS$_{1\to2}$ merits some specific comments. As shown, proton transfer has already taken place in this transition structure. IRC calculations confirm that the reaction coordinate at the TS basically corresponds to a rearrangement of the DMSO solvent molecule that is necessary to stabilize the charge separation. Another interesting result concerns the reaction $1 \rightarrow 3$. A TS may be located in gas phase, whereas in solution, computations systematically lead to TS$_{1\to2}$ and show that, to a large extent, this is due to interactions with the explicit solvent DMSO molecule.

Properties of the Sulfurane Reaction Intermediate. We describe here some properties of the sulfurane molecule $CH_3S-S(CH_3)_2-OH$, which is present in complex 3. For the sake of comparison, we have carried out further calculations for the sulfurane species in gas phase. Results in solution correspond to the discrete−continuum model.

Sulfuranes[55−76] are intermediates in various oxidation−reduction reactions of sulfur compounds.[28,55,56,68] They bear a tetracovalent sulfur in the center of a trigonal bipyramidal structure with the more electronegative ligands at the apical positions.[59−62] The simplest sulfurane SH_4 seems to be an exception, calculations predicting a square pyramidal geometry.[63] The electronic structure of sulfuranes has been the subject of a number of theoretical studies.[64−66,75] In a very simplified approach, the S atom is supposed to be sp^2 hybridized. The remaining p orbital and the orbitals of the apical ligands combine to give an occupied bonding, an occupied nonbonding, and an empty antibonding molecular orbitals. Sulfur d orbitals are not needed for a qualitative description of the bonding, but their inclusion improves the results (e.g., bond orders[72,76]).

In the case of $CH_3S{-}S(CH_3)_2{-}OH$, d orbitals have a significant influence on the results. For instance, when full geometry optimization is carried out without d orbitals, the apical bond lengths become significantly longer (by about 0.15 Å). Indeed, in that case, the electronic structure agrees with a 3-center 4-electron bonding scheme. The apical ligands are, as expected, the most electronegative ones, i.e., $-OH$ and $-SCH_3$. Other arrangements of the sulfurane ligands have been envisaged. In most cases, geometry optimization leads either to the most stable structure or to system dissociation. Only one energy minimum involving an exchange between the apical $-SCH_3$ and the equatorial $-CH_3$ groups has been obtained though it is much less stable than 3 (by 21.2 kcal/mol).

It is noteworthy that solvent effects on the geometry of the sulfurane are quite large. The computed S−O and S−S distances in the gas phase are 1.905 and 2.410 Å, respectively. In DMSO solution, the S−O bond shortens to 1.717 Å and the S−S bond lengthens to 2.727 Å, indicating a marked tendency of the solvent to favor dissociation of 3 into $(OH)(CH_3)_2S^+$ and CH_3S^-. This is confirmed by the analysis of net atomic charges and bond orders in Table 1.

The S−S bond order is much weaker than the S−O bond, especially in solution. Most of the reactions of sulfuranes involves the cleavage of an apical bond yielding a sulfonium cation, $RR'R''S^+$.[61,69,71] In the case of $CH_3S{-}S(CH_3)_2{-}OH$, departure of the apical thiolate ligand seems more plausible than departure of the hydroxyl one. Indeed, if one compares the two dissociation processes

$$CH_3S{-}S(CH_3)_2{-}OH \rightarrow [CH_3S{-}S(CH_3)_2]^+ + OH^- \quad (4)$$

$$CH_3S{-}S(CH_3)_2{-}OH \rightarrow [(CH_3)_2S{-}OH]^+ + CH_3S^- \quad (5)$$

the second one is found to be favored by about 14 kcal/mol in DMSO solution (reaction free energies are 16.9 and 2.7 kcal/mol, respectively, using the discrete−continuum model and assuming the DMSO discrete solvent molecule interacting with the cations).

However, this scheme may be reversed when interactions with a proton donor are allowed due to the larger basicity of the hydroxyl compared to that of the thiolate. Thus, if one compares the processes

$$CH_3S{-}S(CH_3)_2{-}OH + H^+ \rightarrow [CH_3S{-}S(CH_3)_2]^+ + H_2O \quad (6)$$

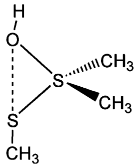
$$CH_3S{-}S(CH_3)_2{-}OH + H^+ \rightarrow [(CH_3)_2S{-}OH]^+ + CH_3SH \quad (7)$$

one finds that the first one is preferred by about 7 kcal/mol (reaction free energies are −21.3 and −14.1 kcal/mol, respectively, using the discrete−continuum model and the experimental[43] solvation energy of a proton in DMSO; besides the DMSO discrete solvent molecule is assumed to interact with the cations).

TABLE 1: NPA Atomic Charges (*q*) and Mayer Bond Orders (B) Computed for the Sulfurane $CH_3S{-}S(CH_3)_2{-}OH$ at the MP2/6-311+G(3d2f,2df,2p) level

	gas	DMSO solution
$q_{S(central)}$	0.885	1.085
q_O	−0.974	−0.929
$q_{S(apical)}$	−0.214	−0.586
B_{S-O}	0.931	1.243
B_{S-S}	0.628	0.220

SCHEME 2



According to these results, one can expect a marked pH influence on the sulfurane intermediate stability. Here, we are assuming a neutral medium, but proton transfer from a thiol molecule to the sulfurane is likely to occur and therefore such a process will be considered below. One should keep in mind however that in the process catalyzed by Msr enzymes, sulfenic acid formation occurs prior to participation of a second cysteine residue (see Scheme 1). The involvement of other residues able to stabilize the leaving hydroxyl group cannot be excluded but needs further investigation. In this paper, we have envisaged the possibility for the sulfurane species to lead to a sulfenic acid directly, i.e., without protonation of the hydroxyl group. Examination of the potential energy surface for structures of the type shown in Scheme 2 leads to location of a transition state exhibiting high activation energy (40.6 kcal/mol above intermediate 3). Thus, it is likely not operative in the chemical process.

Activation of the Sulfurane OH Group by a Second Methanethiol Molecule. Reaction of a second thiol molecule with the sulfurane is schematized in Figure 3. The pre-reactive hydrogen-bonded complex **5** formed by **3**, and CH_3SH is slightly bound. From **5**, the reaction proceeds by a low-barrier proton transfer from methanethiol to the sulfurane −OH group. This activates the cleavage of the sulfurane S−O bond, leading to the ion-pair complex 6. The latter may dissociate to the separated ions, thiosulfonium 7 and thiolate 8, plus a water molecule but, as shown in the next section, the ions may also react prior to dissociation. We have not tried to locate transition structures for the association/dissociation processes $3 + CH_3SH \rightarrow 5$ and $6 \rightarrow 7 + 8 + H_2O$ since the continuum model is not well adapted for such calculations. The hypothetical TSs are expected not to play a significant role anyway.

Formation of Products. The envisaged processes from 6 are summarized in Figure 4. In the products of these reactions, the explicit solvent DMSO molecule is assumed to interact with the water molecule or with the sulfenic acid because these species form the strongest hydrogen bonds.

Compound 9 (top reaction in Figure 4) is easily formed by the attack of the negatively charged sulfur atom of the thiolate on the positively charged sulfur atom of the thiosulfonium. We have not been able to locate the TS for this reaction. Indeed, our calculations suggest that the ion-pair complex 6 is metastable with the water molecule stabilizing the charge separation. A small perturbation of the system provokes the anion−cation

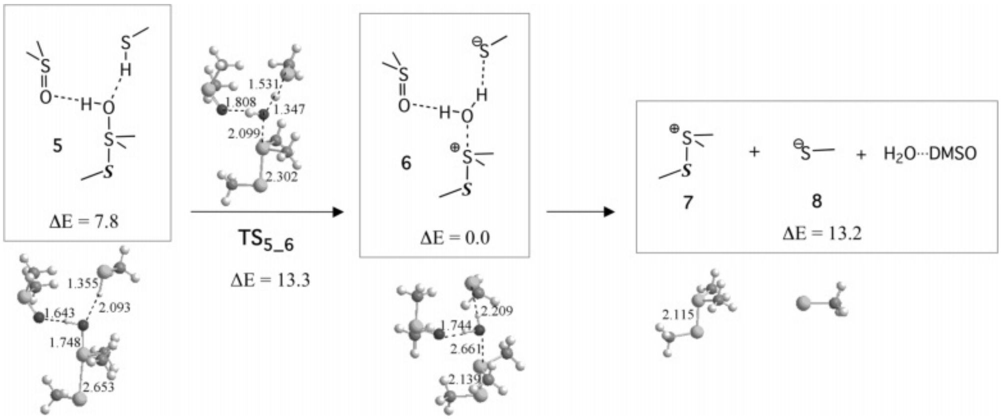


Figure 3. Schematic representation of the chemical species involved in the reaction of methanethiol with 3 and optimized structures (reactants, intermediates, transition structures) at the B3LYP/6-311G** level in DMSO solution and approximate MP2/6-311+G(3d2f,2df,2p) relative energies. Δ*E* includes the electrostatic free energy of solvation in the dielectric continuum and is given relative to separated 1 + CH_3SH. Values are in angstroms and kcal/mol.

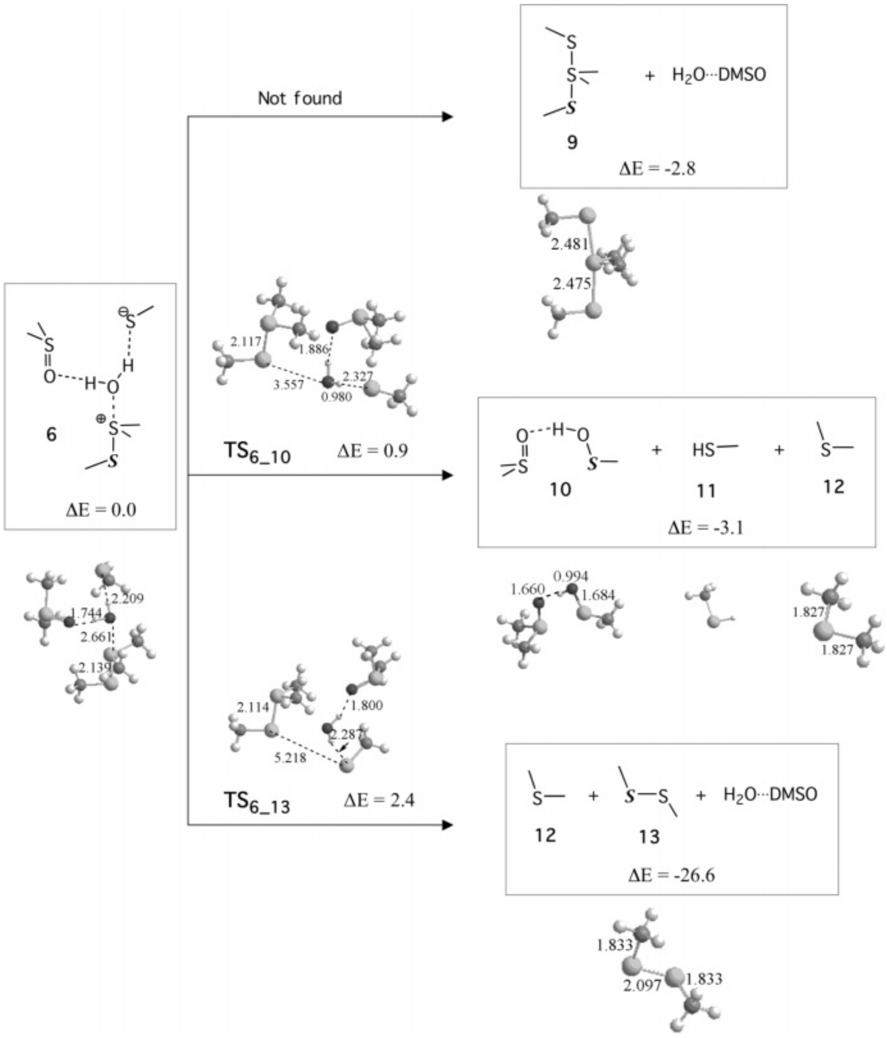


Figure 4. Schematic representation of the chemical species involved in various possible reactions of the thiolate, thiosulfonium ion and water and optimized structures at the B3LYP/6-311G** level in DMSO solution and approximate MP2/6-311+G(3d2f,2df,2p) relative energies. Δ*E* includes the electrostatic free energy of solvation in the dielectric continuum and is given relative to separated 1 + CH_3SH. Values are in angstroms and kcal/mol.

reaction and the formation of the sulfurane 9. The structure of 9 is similar to that of 3 and simply differs from it by a hydroxyl/thiolate group exchange. Experimentally, it is known that if a sulfurane has an alkoxy ligand, it can be exchanged readily with the alkoxy group of an alcohol.[57,61] Our results indicate that such a rapid exchange can also take place between −OH and −SR ligands in the presence of thiols. Sulfurane 9 should undergo further processes similar to those of sulfurane 3, and therefore it is not expected to be a final product of the reaction.

In another reaction mechanism (middle reaction in Figure 4), complex 6 leads to formation of a sulfenic acid 10, a thiol 11, and a thioether 12 by crossing the transition structure $TS_{6\rightarrow10}$.

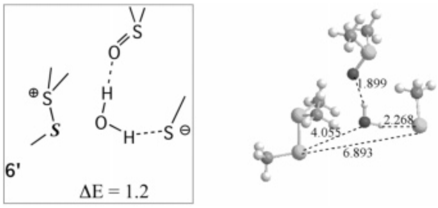
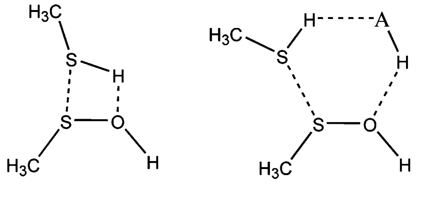


Figure 5. Structure 6′ is formed from reorientation of the species in 6 and is appropriate for the formation of a sulfenic acid 10, a thiol 11, and a thioether 12 shown in Figure 4 (middle reaction) and optimized structures at the B3LYP/6-311G** level in DMSO solution and approximate MP2/6-311+G(3d2f,2df,2p) relative energies. ΔE includes the electrostatic free energy of solvation in the dielectric continuum and is given relative to 1 + CH_3SH. Values are in angstroms and kcal/mol.

SCHEME 3



Non-assisted Assisted

Note however that IRC calculations have shown that this TS cannot be directly attained from 6. Some preliminary reorganization is needed so that: (1) the water molecule can donate a proton to the thiolate anion and (2) the forming OH^- can attack the neutral sulfur atom of the thiosulfonium cation in a S_N2 type reaction. A structure of this type (6′) is displayed in Figure 5. It lies at 1.2 kcal/mol above 6. The arrangement shown is not the only possible one, but we have not made a systematic search in this case**.** Neither the cleavage of the S−S bond nor the proton transfer from the water to the thiolate has started at $TS_{6\rightarrow 10}$. Both initiate spontaneously after crossing this TS, as detailed examination of the potential energy surface and IRC computations have revealed.

Sulfenic acids are rather reactive compounds. Thus, if a sulfenic acid is formed during the sulfoxide reduction reaction, it would rapidly disappear to form the disulfide product that is the experimentally observed species. In principle, one can imagine a condensation reaction with a thiol going through transition structures as indicated in Scheme 3. The process may undergo bifunctional catalysis in the presence of ancillary AH species, such as water or a second thiol molecule. Calculations for the nonassisted process in solution (using, as before, the discrete−continuum model) leads to a rather high activation energy ($\Delta E = 39.3$ kcal/mol with respect to a separated thiol and DMSO−sulfenic acid complex). Calculations for the assisted reaction show also that assistance by a second thiol molecule is not very efficient whereas assistance by water molecules may considerably reduce the barrier. Indeed, when a linear water trimer is considered as the ancillary AH species, the activation barrier is drastically reduced to 1.2 kcal/mol (relative to the separated species; neither zero-point energy nor thermal corrections are included in this value). Reactions involving more than one sulfenic acid molecule could be invoked too. For instance, computations show that two sulfenic acid molecules may react to give $(CH_3)-S-O-S-(CH_3)$ in the presence of a third sulfenic acid with an extremely low energy barrier ($\Delta E = 0.1$ kcal/mol). A detailed analysis of these processes is beyond the objectives of the present work and will not be considered further.

The third process in Figure 4 (bottom reaction) is of the S_N2 type and leads to the disulfide 13 and the thioether 12. Again, the transition structure $TS_{6\rightarrow 13}$ corresponds to a rearrangement of the complex 6 (actually, IRC calculations from this TS lead to conformation 6′ rather than 6). In the present case, it puts the sulfur atom of the thiolate in a suitable position for a nucleophilic attack on the neutral sulfur atom of the thiosulfonium cation. Bond cleavage and bond formation take place immediately after $TS_{6\rightarrow 13}$ crossing without any further energy barrier.

The transition structures $TS_{6\rightarrow 10}$ and $TS_{6\rightarrow 13}$ are only slightly above the complex 6. Therefore, the corresponding reactions are expected to be extremely fast and competing. This finding is in agreement with previous studies in the literature[77−81] on S_N2 reactions for compounds containing S−S bonds. When the leaving group is neutral, the cleavage of the S−S bond is very easy.

Discussion

Free-Energy Profile. As said in the computational section, complex 1 is taken as a free-energy reference. Analysis of translational, rotational, and vibrational contributions suggested however that G must be corrected for this complex due in particular to significant underestimation of the entropy. Indeed, computing accurate G values of low-bound complexes is a difficult task that would require ad hoc statistical mechanics simulations. In the present work, we have rather adopted a pragmatic approach using an empirical correction that has been obtained as follows. We first compute the free energy for the ionization process $1 \rightarrow CH_3S^- + H^+(DMSO)_2$ in DMSO solution (assuming the ions separated at infinite). By use of standard techniques, the free energy of this model reaction amounts 15.3 kcal/mol that is expected to be smaller than the experimental ionization energy. The experimental pK_a of methanethiol in DMSO is not available, but it may be estimated from the reported value for α-toluenethiol, 15.3.[54] The corresponding free energy of ionization is 20.9 kcal/mol. The difference (5.6 kcal/mol) may basically be ascribed to the computational error for the entropy of complex 1. For the other structures, no correction has been added but one should note that for those species displaying weak interactions with the solvent DMSO molecule (like 5, 6, and $TS_{5\rightarrow 6}$), the computed free-energy values might be a little overestimated.

With this correction, the free-energy profile (at 298 K) for the whole reaction path is schematized in Figure 6. Let us summarize the process. Initially, proton transfer occurs from the thiol to the sulfoxide generating an ion-pair complex stabilized by the solvent. The ions recombine to form the sulfurane 3. This intermediate can accept a proton from a second thiol molecule, and the process leads to the formation of a sulfonium cation, a thiolate anion, and a water molecule. The latter reacts quite easily to form, depending on the relative orientation of the species, a new sulfurane compound, a sulfenic acid, or a disulfide. As shown, the calculations predict that the first step should be the rate-limiting one since the corresponding transition state is the highest one along the reaction path (29.6 kcal/mol). The activation energies of all the steps following the first one are substantially smaller. Note however that the transition state for the third step ($TS_{5\rightarrow 6}$) lies only slightly below the highest TS (29.0 vs 29.6 kcal/mol).

The larger stability predicted for the disulfide is consistent with the experimental fact that it is the only observed product in the case of the reaction in solution. The sulfurane 9 and the sulfenic acid 10 are shown in Figure 6 for comparison. Though

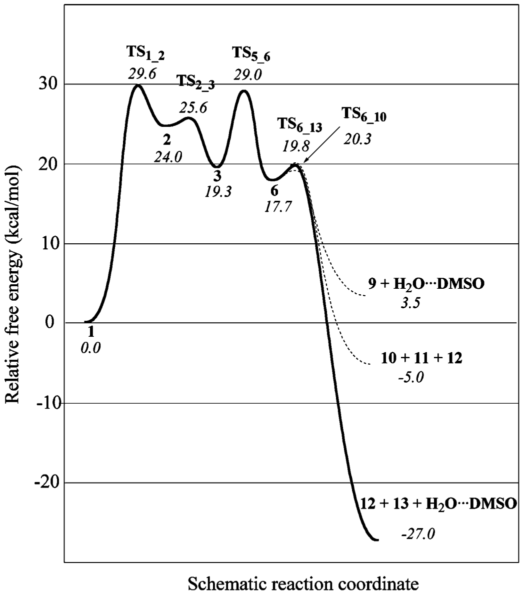


Figure 6. Free-energy profile for the reduction of DMSO by methanethiol in DMSO solution. The *x*-axis represents a schematic reaction path combining several coordinates for individual steps. Approximate MP2/6-311+G(3d2f,2df,2p) relative energies (in italics, in kcal/mol) using optimized structures at the B3LYP/6-311G** level and eq 3. The hydrogen-bonded structure 5 ($\Delta G = 23.7$ kcal/mol) is not included for simplicity. It lies between 3 and $\mathrm{TS}_{5\to6}$.

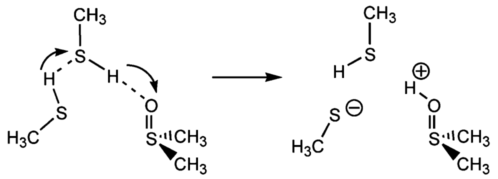
our theoretical study suggests that these intermediates could be formed in the process, they should rapidly react making their experimental detection in solution difficult or even unfeasible.

Comparison with Experimental Data in Solution. Kinetic studies by Wallace and Mahon[23] proposed the reaction mechanism summarized in eqs 1 and 2. The authors deduced a negligible value for k_{-2} and obtained $k_2 \gg k_1$. Qualitatively, our calculations are in very good agreement with these experimental findings. We show however that the formation of the intermediate 3 (eq 1) actually involves two steps, ionization, which is rate-determining, and ion recombination, which is a fast reaction.

Experimental data for methanethiol was not reported, but as noted in the Introduction, results for α-toluenethiol should be a good approximation. The measured pseudo-first-order rate constant, k', at 100 °C with DMSO being the reagent in excess was 4.03 10^{-5} s^{-1}.[23] Since the reaction was shown to be first order in DMSO concentration, the true kinetic constant k corresponding to the second-order reaction is derived from $k' = k\cdot$[DMSO]. Taking [DMSO] as the concentration of the pure liquid ([DMSO] = 14.1 mol L^{-1}) and using transition state theory, the experimental free energy of activation is estimated to be 31.4 kcal/mol for α-toluenethiol, which is in satisfactory agreement with our computed value 29.6 kcal/mol for methanethiol considering the different approximations made. Note also that these values correspond to different temperatures. An estimation of the free energy of activation at 100 °C gives 30.5 kcal/mol (assuming the same dielectric constant and empirical correction to free energy that the one used above).

Let us now consider the products of the reaction. Our study predicts the formation of sulfenic acid 10 and disulfide 13 in competing reactions. The disulfide is the most stable species, and if thermodynamic control would apply, only this species should be observed. However, the sulfenic acid is substantially more stable than 6 and backward reaction appears to be unlikely. In the experimental work of Wallace and Mahon,[23] the only reported product was the disulfide although it is not clear whether the authors tried to identify a sulfenic acid or not. Hence, the calculations agree with experimental data in predicting 13 as the major reaction product but points out to a possible formation of a secondary product 10.

SCHEME 4



Proton Relay Mechanism, Bifunctional Catalysis. The rate-determining step in the sulfoxide reduction reaction involves the ionization of the system through a proton transfer process from the thiol to the sulfoxide. This process may substantially be favored by proton relay mechanisms and bifunctional catalysis. A typical process is illustrated in Scheme 4, where we assume that two methanethiol molecules are involved in DMSO protonation. The structures of the complex and of the proton-transfer TS have been optimized. The computed activation energy is 19.6 kcal/mol that may be compared with the corresponding value for the nonassisted process in Figure 1, 20.4 kcal/mol. Computation of the activation free energy in solution is not straightforward for the same reasons as those presented above for the nonassisted ionization mechanism. However, one may obtain a rough evaluation of the bifunctional catalytic effect by computing the quantity

$$\delta\Delta G^{\ddagger} = G(\mathrm{TS_{Ass}}) - G(\mathrm{TS_{1\to2}}) - G(\mathrm{CH_3SH}) + G(\mathrm{DMSO})$$

where $\mathrm{TS_{Ass}}$ and $\mathrm{TS_{1\to2}}$ represent the transition structures for the assisted proton-relay (Scheme 4) and nonassisted (Figure 1) mechanisms, respectively. The expression is rigorous in the gas phase provided the molecules are assumed to be separated at infinity in the reactant state and can be considered to be a reasonably good approximation for the process in solution. Our computations lead to a free energy barrier decrease of $\delta\Delta G = -1.7$ kcal/mol. A comparable effect may be expected if water molecules or other chemical species bearing bifunctional groups are present in the reaction medium.

We shall not describe here the details of the subsequent steps for the assisted reduction reaction. In principle, one could expect the formed ions to recombine and form a sulfurane intermediate, as in the nonassisted process above. Our calculations show sulfurane formation from the ions in Scheme 4 to be a feasible reaction though it requires a larger activation free energy than sulfurane formation from the ions in 2. In the latter structure, the explicit solvent DMSO molecule provides a significant stabilization effect. Such an interaction is absent in the system shown in Scheme 4 where it is replaced by the interaction of the ions with an extra thiol molecule. Thus, an increase in thiol concentration may lead to a change of the reduction process kinetics due to two main factors: (1) decrease of the activation entropy associated to the proton relay mechanisms and (2) modification of the solute–solvent intermolecular interactions. Obtaining quantitative results for a given [DMSO]/[methanethiol] ratio would need taking into account the interactions with the solvent in a more rigorous way although due to increasing system complexity such a study might also require to combine quantum mechanical calculations with statistical simulations.

Conclusions

The calculations carried out in this work confirm the experimental result that the reduction of sulfoxides by thiols in

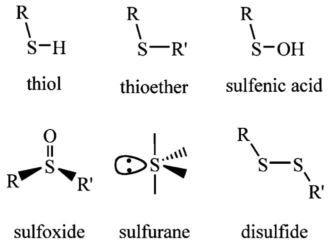
DMSO solution basically involves the slow formation of a sulfurane intermediate followed by a fast decay of this intermediate into the products. The computed activation free energy for the model reaction methanethiol + DMSO (29.6 kcal/mol) is close to the experimental valued for the reaction of DMSO with α-toluenethiol (31.4 kcal/mol, deduced here from reported kinetic constants at 100 °C). Nevertheless, our study provides further insight in the reaction mechanism that appears to be more complicated. First, the sulfurane intermediate is formed in a stepwise reaction after ionization of the thiol−sulfoxide system, proton transfer being rate determining. Once formed, the sulfurane rapidly reacts with another thiol molecule. Sulfonium and thiolate ions are formed at this step that recombine to form sulfenic acid or disulfide, the latter being much more stable than the former.

In the catalytic mechanism of Msrs, a sulfenic acid intermediate has clearly been shown to be formed. Therefore, it is probable that the sulfenic acid was not reported in the experimental chemical study because it undergoes a fast decay into a disulfide species due to the presence of thiol. In that context, comparison of enzymatic and in solution processes is not straightforward. For instance, it is not clear which chemical group in the enzymatic process could play the activation role postulated for the second thiol molecule in the solution process (Figure 3). What is certain is that the recycling cysteine is not involved since the sulfenic acid intermediate is efficiently formed in its absence. Hence, understanding the mechanism in the active site of Msr enzymes deserves further investigation.

Glossary

Scheme 5 summarizes the nomenclature of sulfur compounds appearing in this study.

SCHEME 5



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Supporting Information Available: Cartesian coordinates of all the optimized structures and transition vectors in transition structures are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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