

Mechanism of S_H2 Reactions of Disulfides: Frontside vs Backside, Stepwise vs Concerted

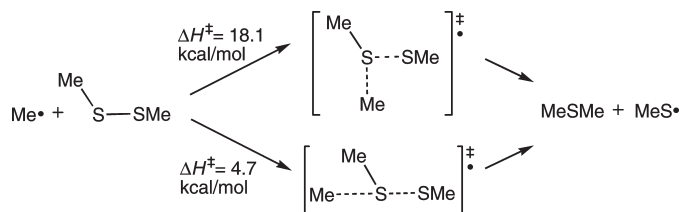
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Density functional theory calculations indicate that the S_H2 reactions of disulfides with alkyl or aryl radicals take place via concerted backside displacement. The activation energies for reactions of Me• with RSSR (R = Me, Et, ⁱPr, ^tBu) increase with the size of R, since larger R groups prevent the formation of an ideal geometry for SOMO–LUMO overlap. Frontside transition states can also be located, but these lie at least 11 kcal mol^{−1} above the corresponding backside transition states.

Introduction

Disulfides readily undergo substitution by both radicals and nucleophiles. These reactions are important in synthetic chemistry¹ and also play a role in the physiological chemistry of antioxidants and disulfide-containing proteins.² In principle, substitution at sulfur may take place via a variety of mechanisms. The mechanism of nucleophilic substitution of disulfides has been studied computationally by the groups of Bach,³ Bachrach,⁴ and Bickelhaupt,⁵ with an emphasis on the competition between S_N2 and addition–elimination mechanisms and their roles in biological thiolate–disulfide exchange reactions. The possibilities for radical substitution

are shown in Scheme 1. The incoming radical may approach from either the back side or the front side, and an intermediate sulfuranyl radical of the type [•]S(SR)RX might conceivably also be involved.

Radical substitution (S_H2) reactions of disulfides hold theoretical interest because it is not clear from orbital considerations whether backside attack or frontside attack should be preferred. If the radical attacks an S–S bond from the back side, the SOMO–LUMO interaction involves the in-phase, stabilizing overlap of the SOMO with the S–S σ^* orbital. If the radical attacks from the front side, the SOMO–LUMO interaction is less stabilizing because the SOMO is oriented toward a nodal surface of the σ^* orbital. The radical SOMO– σ_{SS} orbital interaction can stabilize either backside or frontside attack.

The stereochemistry of attack at divalent sulfur cannot be determined by use of the classical configurational-inversion diagnostic. Pioneering studies in the 1960s,^{6,7} which involved kinetic comparisons and are reviewed below, suggested that the nucleophilic and radical substitution reactions of S–S

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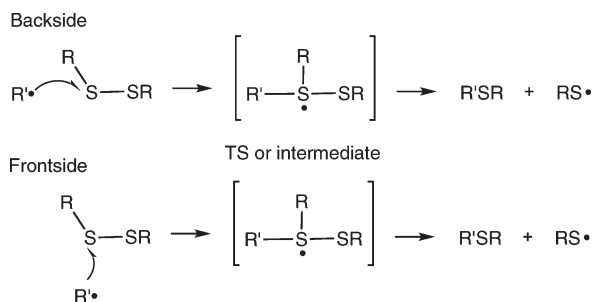
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SCHEME 1



compounds both follow S_N2 -like mechanisms. However, the question of mechanism has not been fully resolved.

Here we present a computational investigation of disulfide S_H2 reactions. Our results support the concerted backside mechanism. Density functional theory (DFT) calculations have been used to evaluate the quantitative factors governing backside and frontside attack.

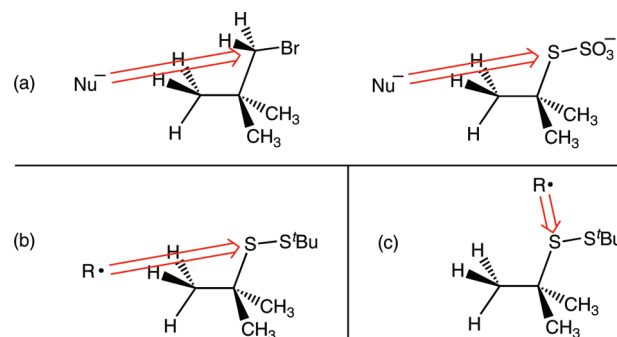
Background

Experimental studies of the stereochemistry of substitution at sulfur relied on the use of kinetic comparisons. Initially, Fava⁷ observed that the nucleophilic substitution reactions of alkyl thiosulfates $RS-SO_3^-$ with SO_3^{2-} ion showed a rate profile similar to those for the reactions of primary bromides RCH_2-Br with Br^- ion. By analogy, he proposed that the thiosulfates reacted via an S_N2 mechanism. The very slow rate of attack at the neopentyl-like sulfur of $^tBuS-SO_3^-$ was particularly indicative of backside attack (Scheme 2a).

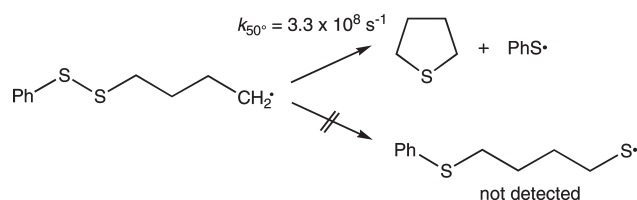
To examine radical substitution reactions at sulfur, one of us developed an extension of this kinetic analogy.⁶ The rate constants for the reactions of Ph^\bullet or $p-NO_2-C_6H_4^\bullet$ radicals with $MeSSMe$, $EtSSeEt$, $^iPrSS^iPr$, and $^tBuSS^tBu$ were measured and were found to correlate linearly, in a log–log plot, with those of Fava's thiosulfate S_N2 reactions. This suggested that the disulfides' S_H2 reactions followed an S_N2 -like mechanism. The reactions of $^tBuSS^tBu$ showed a neopentyl-type deceleration, consistent with the preference for backside attack (Scheme 2b) over frontside attack (Scheme 2c).

Bentrude⁸ subsequently performed a detailed kinetic study of the reactions of disulfides with a phosphoranyl radical and agreed that concerted backside attack was the most likely mechanism. Beckwith⁹ also favored a concerted backside mechanism, as it accounted for the exclusive formation of cyclic products that he observed during intramolecular reactions of alkyl radicals with disulfides (e.g., Scheme 3).

Bickelhaupt¹⁰ recently used density functional theory (DFT) calculations to study the backside vs frontside preferences in the nucleophilic substitution of Group 14 halides EH_3-Cl by Cl^- . For CH_3Cl , backside attack was preferred over frontside attack by $39.6 \text{ kcal mol}^{-1}$, while for SiH_3Cl , the preference was $17.3 \text{ kcal mol}^{-1}$. The D_{3h} backside

SCHEME 2. (a) Backside Attack Trajectories in S_N2 Reactions of Neopentyl Systems; (b) Backside Attack Trajectory in an S_H2 Reaction on a Neopentyl Disulfide; (c) Frontside Attack Trajectory in an S_H2 Reaction on a Neopentyl Disulfide

SCHEME 3



transition structure was a maximum on the potential energy surface for CH_3Cl , but a minimum for the heavier congeners.

There have been a number of computational studies concerning radical attack at sulfur,^{11–13} and these have dealt mainly with thiols and thioethers. Schiesser¹² found that sulfuranyl radicals such as H_3S^\bullet , H_2MeS^\bullet , and HMe_2S^\bullet (which could plausibly be formed by radical addition at sulfur) were not stable species at the MP2/6-31G** level. He also reported a systematic search of the MP2/DZP potential energy surface for $MeSH + Me^\bullet$, which produced no evidence for frontside attack.¹³

Disulfides differ from these substrates in having a much weaker bond between sulfur and the leaving group. For example, the $S-X$ BDEs of $MeS-H$, $MeS-Me$, and $MeS-SMe$ are 87.4 ± 0.5 , 73.6 ± 0.8 , and $65.2 \pm 0.9 \text{ kcal mol}^{-1}$, respectively.¹⁴ However, sulfur is slightly more electronegative than carbon and hydrogen, the Pauling values being 2.58, 2.55, and 2.20, respectively.¹⁵ The first of these features favors concerted displacement, while the second slightly favors an intermediate sulfuranyl radical.¹⁶ Turecek et al.¹⁷ used B3LYP and MP2 calculations to study the reactions of hydrogen atom with $MeSSMe$ and 1,2-dithiolane. They found that backside attack took place with a barrier of 2 kcal mol^{-1} or less, but for $MeSSMe$ the reaction could also follow a frontside pathway with a barrier of 5–8 kcal

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mol^{-1} . Here we have used DFT calculations to explore the $\text{S}_{\text{H}2}$ reactions of disulfides with organic radicals, considering the backside/frontside and stepwise/concerted possibilities.

Computational Methods

Density functional theory calculations were performed at the B3LYP/6-31G(d) level¹⁸ in Gaussian 03.¹⁹ Species were characterized as minima or transition states on the basis of vibrational frequency analysis and IRC calculations.²⁰ Zero-point energy and thermal corrections were derived (unscaled) from the B3LYP/6-31G(d) frequencies. To assess the accuracy of B3LYP for the calculation of activation energies, data were also obtained for selected reactions using the high-accuracy CBS-QB3 method.²¹ The B3LYP/6-31G(d) values for $\Delta\Delta H^\ddagger$ (frontside–backside) for these cases lay within $1.2 \text{ kcal mol}^{-1}$ of the CBS-QB3 values. The B3LYP/6-31G(d) geometries of all species, and the CBS-QB3 data, are provided in the Supporting Information.

Results and Discussion

To explore the stereochemistry of radical attack on disulfides, we first calculated transition states for the reactions of Me^\bullet with various disulfides RSSR ($\text{R} = \text{Me}, \text{Et}, \text{Pr}, \text{Bu}, \text{Ph}$). For each disulfide, a backside transition structure was found, and the geometries are shown in Figure 1. Additional geometrical details are listed along with the activation and reaction energies in Table 1. Intrinsic reaction coordinate (IRC) calculations showed each backside TSs to lead to the products $\text{MeSR} + \text{RS}^\bullet$ (see below) and not to intermediate sulfuranyl radicals $^\bullet\text{S}(\text{SR})\text{RMe}$.

The TS for MeSSMe is representative. The forming bond length is 2.45 \AA and is oriented at an angle of 160° to the leaving group. The S–S bond has lengthened by 0.1 \AA relative to the reactant. The forming bond is 0.39 \AA longer than is found for the reaction of Me^\bullet with the thioether Me_2S , but the nonlinearity of approach is typical for radical attack at sulfur.^{11–13}

On going along the series from MeSSMe to $^\text{t}\text{BuSS}^\text{t}\text{Bu}$, the TSs become slightly more product-like, with shorter forming bonds and longer breaking bonds. There is little difference in the attack angles ($\angle\text{Me}^\bullet\text{–S–S}$) for MeSSMe and EtSSEt , but in the TSs for $^\text{t}\text{PrSS}^\text{t}\text{Pr}$ and $^\text{t}\text{BuSS}^\text{t}\text{Bu}$ the attack angles are smaller (155.9° and 146.6° , respectively) due to steric hindrance from the substituents.

These steric effects are responsible for the increase in activation enthalpies on going from MeSSMe to $^\text{t}\text{BuSS}^\text{t}\text{Bu}$. The contracted attack angles for the bulkier disulfides lead to poorer overlap between the Me^\bullet SOMO and the S–S σ^* orbital. S–S bond cleavage must therefore progress to a more advanced stage before interaction can be comparably stabilizing.

The reaction of PhSSPh with Me^\bullet has a lower barrier than those of the dialkyl disulfides. This is probably due mainly to

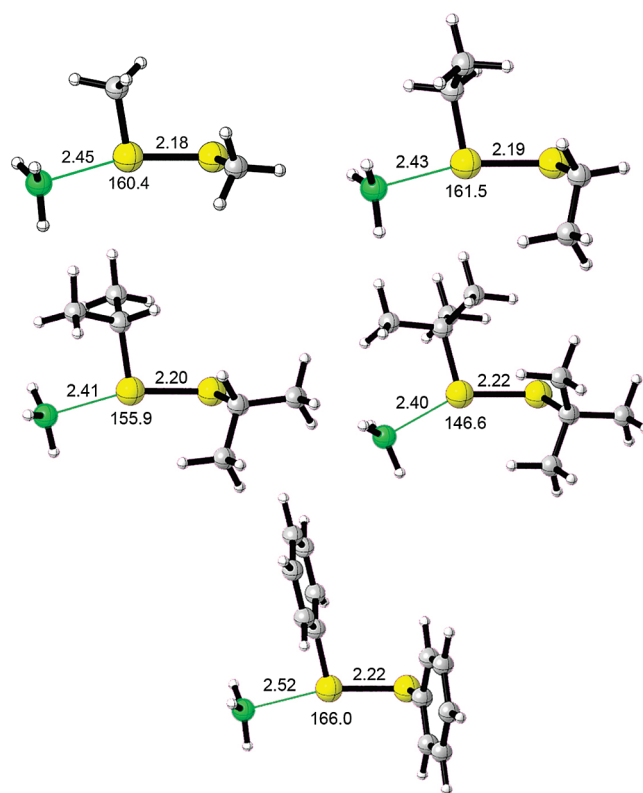


FIGURE 1. Transition structures for backside attack of Me^\bullet (green) on disulfides.

the lower dissociation energy of the S–S bond in PhSSPh .²² The TS for PhSSPh has a longer forming bond (2.52 \AA) and a considerably more linear attack angle (166.0°) than those of the dialkyl disulfides.

Concerted backside TSs were also found for reactions of disulfides with other carbon-centered radicals, including $^\bullet\text{CH}_2(\text{CN})$, $^\bullet\text{CH}_2(\text{OMe})$, and Ph^\bullet . The TSs for substitution by Ph^\bullet are earlier than those for Me^\bullet . For Ph^\bullet , the forming bonds are $0.04\text{--}0.12 \text{ \AA}$ longer than with Me^\bullet and the breaking bonds are $0.04\text{--}0.05 \text{ \AA}$ shorter.

Several previous studies have examined the possibility that intermediate sulfuranyl radicals may be formed during $\text{S}_{\text{H}2}$ reactions at divalent sulfur.^{17,23–25} The simplest sulfuranyl radical, SH_3^\bullet , is a transition state at many levels of theory, although QCISD calculations with a Hay–Wadt pseudo-potential²⁶ on sulfur describe it as a shallow minimum.²⁴ An SH_3^\bullet radical with a lifetime of $0.2\text{--}2.8 \mu\text{s}$ has been detected by mass spectrometry, following electron capture by SH_3^+ ,^{23,25a} but it seems likely^{25a} that this short-lived species is an excited state. In the disulfide series, mass spectrometric studies have characterized “adducts” of H^\bullet with MeSSMe and 1,2-dithiolane, which B3LYP and MP2

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TABLE 1. Transition-State Geometries, Activation Energies, and Reaction Energies for S_{H2} Reactions of the Methyl Radical with Disulfides^a

	RSSR		Transition State				ΔH^\ddagger	ΔS^\ddagger	ΔG^\ddagger	ΔH
	S–S (Å)	\angle CSSC (°)	Me*–S (Å)	\angle Me*S–S (°)	S–S (Å)	\angle CSSC (°)				
MeSSMe	2.08	87.2	2.45	160.4	2.18	84.1	4.7	–28.4	13.2	–5.6
EtSSEt	2.09	96.3	2.43	161.5	2.19	96.8	5.0	–29.3	13.7	–15.0
^t PrSS ^t Pr	2.08	89.4	2.41	155.9	2.20	93.4	7.4	–28.9	16.1	–13.6
^t BuSS ^t Bu	2.09	111.5	2.40	146.6	2.22	117.1	9.1	–30.8	18.3	–14.6
PhSSPh	2.12	82.9	2.52	166.0	2.22	81.8	3.1	–29.0	11.7	–24.3

^a B3LYP/6-31G*, enthalpies, and free energies in kcal mol^{–1} and entropies in eu at 298.15 K.

calculations showed to have very long S–S distances of ca. 3 Å.¹⁷ To check for the possible intermediacy of sulfuranyl radicals during S_{H2} reactions, we carried out a QCISD calculation on [•]S(SH)H₂ with the Hay–Wadt pseudopotential on sulfur.²⁷ This led to a structure similar to those described for MeSSMe and 1,2-dithiolane,¹⁷ which is best viewed as a van der Waals complex of H₂S and HS[•]. The S–S distance in the complex is 3.61 Å, the central sulfur is pyramidal, and the HS[•] sulfur has a spin density of 1.0. B3LYP/6-31G(d) calculations provide a similar, although tighter, van der Waals complex. B3LYP calculations indicate that the S_{H2} reactions of disulfides with Me[•] also proceed through these types of complexes.

In contrast to previously studied sulfur systems,^{11–13} it also proved possible to locate frontside TSs for the S_{H2} reactions of disulfides. For the reaction of Me[•] with MeSSMe, three frontside TSs were found, and these are shown in Figure 2. They represent alternative trajectories by which the Me[•] radical may approach. The Me[•] radical forms a dihedral of approximately 180°, 135°, or 0° with the leaving SMe group. The values of ΔH^\ddagger for the frontside TSs are 18.1–22.2 kcal mol^{–1}, compared with 4.7 kcal mol^{–1} for the backside TS. The entropies of activation for frontside attack are approximately 3 eu more negative than for backside attack. The forming C–S bonds are shorter than for backside attack (by 0.11–0.37 Å), while the breaking S–S bonds are slightly longer (by ~0.05 Å). The attack angles range from 83° to 93°, as expected for the interaction of the radical with one of the sulfur 3p orbitals. Similar frontside TSs were located for the other disulfides. As was found for backside attack, IRC calculations showed that each frontside TS leads to displacement of MeS[•].

The ability of disulfides to react via frontside TSs provides a point of difference from thioethers and thiols. An S–S bond weakens more dramatically than an S–C or S–H bond when electron density is removed from a sulfur lone pair. This facilitates the concerted ejection of the product radical RS[•]. However, although frontside TSs can be located on the potential energy surface, they are unlikely to contribute significantly to the reaction. The three frontside TSs for Me[•] + MeSSMe lie 13.4–17.5 kcal mol^{–1} above the backside TS. The strong backside preference in radical attack on disulfides contrasts with the behavior of related Group 14 compounds, where backside and frontside pathways have been shown to have similar activation energies.²⁸ For example, whereas the frontside TS for reaction of Me[•] with HSSH lies 16.4 kcal mol^{–1} above the backside TS, the frontside TSs for reaction with H₃SiSiH₃, H₃GeGeH₃, and H₃SnSnH₃ lie

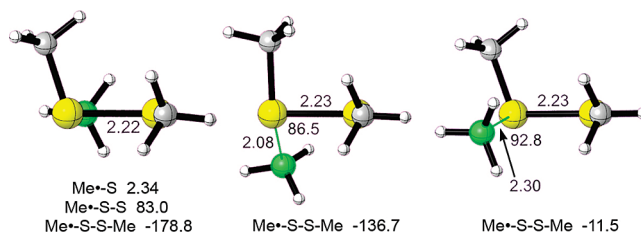


FIGURE 2. Transition structures for frontside attack of Me[•] (green) on MeSSMe.

only 1.6, 2.9, and 1.3 kcal mol^{–1} above the TS for backside attack, respectively.²⁹

A third type of transition state was found for the reaction of Me[•] with MeSSMe. In this TS, the Me[•] radical approaches at an angle of 97° to the S–S bond and with a Me[•]–S–S–Me dihedral of 88°. The Me[•] radical is almost collinear with the Me substituent at the site of attack, and the TS leads to cleavage of the S–C bond rather than the S–S bond. The activation energy for S–C cleavage is 16.0 kcal mol^{–1}, which is 2 kcal mol^{–1} lower than for frontside S–S cleavage.

Previously, Bickelhaupt¹⁰ applied the activation strain model of reactivity to analyze the preference for backside over frontside attack in S_{N2} reactions. In this model (which we have referred to as the distortion/interaction model³⁰), an activation barrier (ΔE^\ddagger) is divided into two components: the distortion energy ΔE_{dist} associated with converting the reactants separately to their TS geometries, and the energy of interaction ΔE_{int} between the distorted reactants in the TS. The high energy of the frontside pathway for S_{N2} reactions of EH₃–Cl (E = C, Si, Ge, Sn, Pb) was traced primarily to the much greater distortion in the frontside transition structure.¹⁰ The interaction energy was also less favorable due to weaker orbital overlap.

A distortion/interaction analysis of the TSs for reaction of Me[•] with MeSSMe indicates that the backside vs frontside preference is controlled primarily by ΔE_{int} . The values of ΔE_{dist} and ΔE_{int} for the backside TS are 2.8 and 0.4 kcal mol^{–1}, respectively, while for the lowest energy frontside TS they are 7.0 and 9.4 kcal mol^{–1}. The net interaction is repulsive in both TSs, and this term only becomes attractive at a later stage of reaction. Backside attack involves a more favorable interaction of the radical SOMO with the

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(27) QCISD calculations were performed using Basis Set G of ref 24b. Spin densities were calculated by Mulliken analysis.

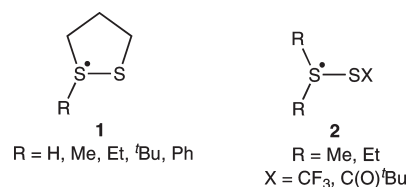
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S–S σ^* orbital (LUMO), while frontside attack involves a smaller interaction of this type, plus many repulsive steric and electrostatic interactions in the more crowded frontside transition state.

Attack via a frontside pathway should in principle be less disfavored for electron-deficient attacking radicals. Calculations on $\cdot\text{CH}_2(\text{CN})$ are consistent with this, but the effect on $\Delta\Delta H^\ddagger$ (frontside–backside) is quite small: $\Delta\Delta H^\ddagger$ is 13.0 kcal mol⁻¹, compared with 13.4 kcal mol⁻¹ for Me \cdot . For Ph \cdot , the value of $\Delta\Delta H^\ddagger$ is 11.4 kcal mol⁻¹. Changing from a dialkyl disulfide to a diaryl disulfide produces a similar small change in $\Delta\Delta H^\ddagger$: for the reaction of Me \cdot with PhSSPh, the value of $\Delta\Delta H^\ddagger$ is 11.8 kcal mol⁻¹.

All of the S_H2 reactions of disulfides with alkyl and aryl radicals that we have studied proceed via concerted displacement. Several sulfuranyl radicals of the type $\cdot\text{S}(\text{SX})\text{R}_2$ have been characterized spectroscopically, including **1** and **2**,^{31,32} but these are stabilized by entropic factors or the presence of an electronegative substituent, respectively. At the B3LYP/6-31G(d) level, acyclic sulfuranyl radicals of the type $\cdot\text{S}(\text{SR})\text{RX}$ (R, X = alkyl) are not stable minima. If X is a very electronegative group, such as OH or PhO, a T-shaped radical Me(MeS)(RO)S \cdot (R = H, Ph) can be located, in which the MeS and RO groups are axial. However, for simple organic attacking radicals, the S–S bond is too

weak for an intermediate adduct to be found as a minimum on the potential energy surface.



Conclusions

B3LYP calculations are in agreement with the previous proposal⁶ that S_H2 reactions of disulfides with alkyl or aryl radicals follow an S_N2-like pathway. Both backside and frontside transition states exist on the potential energy surface, but the frontside TSs have prohibitively high energies. The preference for backside attack is due to the less repulsive interaction between the reactants at the TS, which enables the backside TS to be reached with a smaller degree of reactant distortion than the TS for frontside attack.

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Supporting Information Available: B3LYP/6-31G* geometries for all species, CBS-QB3 data, and a complete citation for ref 19. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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