

Ab-Initio MO Study of the Peracid Oxidation of Dimethyl Thiosulfinate

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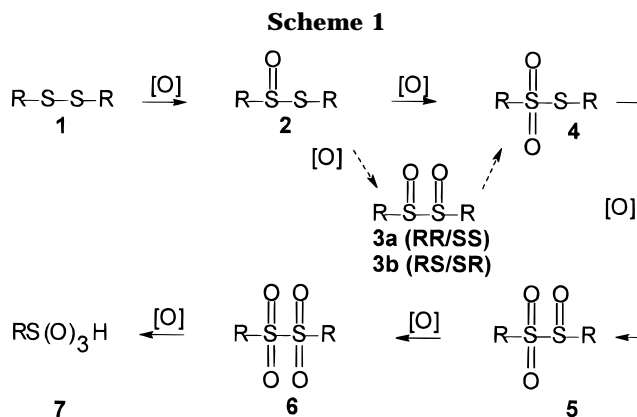
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The mechanism of oxidation of dimethyl thiosulfinate with performic acid was investigated theoretically at MO *ab-initio* level. Equilibrium geometries and transition states were optimized with two different basis sets (3-21G* and 6-31G*) and the inclusion of dynamic correlation correction at MP2 level. Along the possible reactions paths three different transition states were characterized, namely, those leading to the formation of the diastereomeric forms (*RR/SS* or *RS/SR*) of α -disulfoxide and that leading to the thiosulfonate. The calculated values of activation energies and free energies of activation, in the gas phase, fail to reproduce the observed chemoselectivity of oxidation reactions. However, when the formation of reaction clusters, or better, the inclusion of solvent effects (evaluated via SCFR method) is taken into account, one obtains a correct behavior that fits the experimental trend. The reaction path was also analyzed by employing the intrinsic reaction coordinate methodology in order to examine the transitory character of α -disulfoxide. The effect of acids in depressing the reactivity was also demonstrated.

Introduction

The oxidation of organic disulfides **1**, a widely studied chemical process, is thought to proceed via a number of stable intermediates (**2**, **4**, **5**, **6** in Scheme 1) leading to sulfonic acid **7** as the end product.¹ The experimental oxidation conditions can be controlled in order to increase the yield of the intermediates.² The formation of α -disulfoxides **3** in these reactions has been a source of controversy, since these elusive species have never been isolated and thiosulfonates **4** are the major products³ in the oxidation of alkyl and aryl thiosulfonates **2** (Scheme 1). The investigation of the presence of α -disulfoxide intermediates has been severely limited by their low stability and by the ease with which they transform into more stable species: however, clear evidence of their formation as reaction intermediates has been published.⁴ Freeman and Angeletakis, using the NMR technique, were the first to detect diastereomeric α -disulfoxides in their study of the low-temperature (-40 , -20 °C) *m*-chloroperoxybenzoic acid (MCPBA) oxidation of symmetrical alkyl thiosulfonates.⁵ The proposed mechanism⁴ for such reactions postulates the formation of α -disulfoxides in the preliminary step of the oxidation of **2** followed by rearrangement to **4** through homolytic S–S bond cleavage and head-to-tail recombination of the radicals.⁴ The “bond weakening effect” exerted by S=O when it is partner of an S–S bond has been noted⁶ and



has been ascribed to the relative stability of sulfinyl radicals.⁷ Although other reasonable mechanisms are possible, the proposed rearrangement of α -disulfoxides through homolytic S–S bond cleavage is supported by theoretical calculations.⁸ To date, the most stable α -disulfoxide has been observed in the electrophilic oxidation of bridged bicyclic thiosulfonates⁹ where the relatively rigid framework of the bicyclo backbone seems to strengthen the disulfide linkage.

Another interesting aspect of the low-temperature MCPBA oxidation of symmetrical alkyl thiosulfonates (with R = *neo*-C₅H₁₁, CH₃, *t*-C₄H₉, *n*-C₃H₇, *i*-C₃H₇, *n*-C₄H₉ in Scheme 1) is the *absence* of thiosulfonates in the initial product mixture,⁵ thus confirming that sulfinyl sulfur is more reactive toward peroxybenzoic acid, as observed in previous kinetic studies.¹⁰

The relative degree of nucleophilicity of a sulfide with respect to its sulfoxide has been examined theoretically by Bach and co-workers¹¹ at MO *ab-initio* level: the authors stressed the importance of solvent effects to

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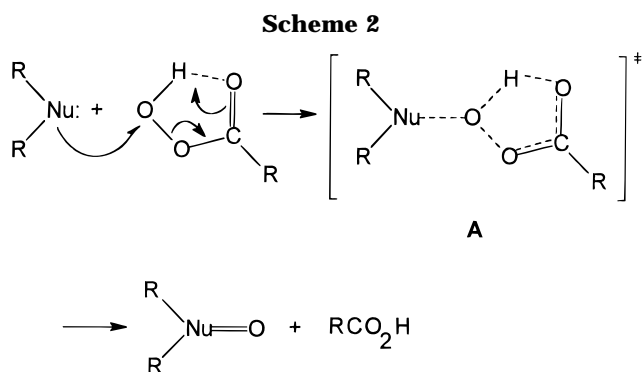
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reproduce the correct reactivities, since the gas-phase intrinsic reactivities are virtually identical.

In order to examine the mechanism of the peracid oxidation of thiosulfates **2**, we need to refer to the widely accepted description¹³ of the oxidation of atoms bearing lone pairs. A large number of reactions of peroxy acids with reducing agents can be regarded as a nucleophilic attack on the electrophilic oxygen of the intramolecularly hydrogen-bonded form of the peroxy acid, forming the activated complex of type **A**, Scheme 2, where Nu denotes a generic nucleophile.

On the basis of the proposed mechanism, the following general features would be expected for these reactions: (a) second-order reaction kinetics, first order in the nucleophile and peroxy acid; (b) an increase in the reaction rate by electron-donating groups on the nucleophile (increased nucleophilicity), and the opposite effect when such groups are located on the peroxy acid (decreased electrophilicity); (c) negative activation entropies due to the remarkable rigidity of the transition state; (d) relatively low activation energies (ca. 12–16 kcal/mol).¹²

Theoretical studies have shown that the ability of peroxy acids to release an electrophilic oxygen of the peroxide group involves overlap control, *i.e.*, the attack of a nucleophile on the lowest vacant orbital (LUMO) of the O–O bond.¹³ Moreover, frontier orbital theory¹⁴ postulates that the nucleophilic properties of the reducing agent are related to the highest occupied molecular orbital (HOMO); according to this theory, the position most likely to be attacked by an electrophilic reagent is that more populated by the two electrons occupying the HOMO in the ground state. As a consequence, transition states would be highly oriented.

The aim of this paper is to study theoretically, at MO *ab-initio* level, the oxidation mechanism of dimethyl thiosulfinate by performic acid in order to examine the factors governing the nature of the oxidative process at molecular level and to investigate the routes of formation of the elusive α -disulfoxides and of thiosulfonates.

Computational Method

The level of theory that is required to describe the ground-state cleavage of the O–O bond in oxidation reactions adequately has been a matter of lengthy debate, since the single-determinant Hartree–Fock cleavage (HF) wave function affords a poor description of the potential energy surfaces involving O–O bond breaking. Dynamic correlation at the Møller–

Plesset (MP2) level seems able to provide reliable geometries, while static correlation corrections are not as important as was thought initially.¹⁵ We optimized the equilibrium and transition-state structures at the MP2/3-21G* and MP2/6-31G* levels. Transition states were characterized by means of frequency analysis at the MP2/3-21G* level and were found to be first-order saddle points. The model chosen referred to a gas-phase reaction, and solvent effects were calculated via the self-consistent reaction field (SCRF) facility using the isodensity surface polarized continuum model (IPCM) implemented on a GAUSSIAN 94 package.¹⁶ We performed calculations with the smaller 3-21G* basis set as well in order to compare the results with those obtained with the implemented 6-31G* basis set, since for reactions in more complex systems, normally investigated experimentally, the latter becomes prohibitively time consuming. Also, we wanted to check whether indicative information can be gained at such a lower level of theory.

MP2/3-21G* calculated frequencies were employed for estimating ΔH^\ddagger and ΔG^\ddagger at 295.15 K.

IBM AIX RS/6000 workstation and CRAY C90 computer were employed.

Results and Discussion

Dimethyl thiosulfinate (**2a**) and performic acid (**8**) were chosen as model compounds for the more complex reagents (*i.e.*, symmetrical alkyl and aryl thiosulfonates and *m*-Cl-perbenzoic acid) employed in the reactions studied experimentally; **2a**, besides being a model compound, is actually a widely-used reagent in such reactions. In order to save computational resources the simpler hydrogen-substituted thiosulfinate (HSS(O)H) might be used but, as stated previously, on parent systems,¹¹ the omission of substituents larger than hydrogen on the substrates is likely to give unreliable results and to lead to misleading mechanistic conclusions. The methyl substituents have proved¹¹ to be crucial for theoretical studies of this type.

Equilibrium structures were fully optimized at the MP2/3-21G* and MP2/6-31G* levels, and the geometries are reported in Figure 1. As can be seen, the values reported show a good agreement between the two levels of theory.

In order to locate the activated complexes, we adopted the reaction mechanisms reported in the literature¹³ for parent reactions. For the oxidation of sulfides (R_1R_2S) to sulfoxides ($R_1R_2S=O$), kinetic studies¹⁷ suggest an activated complex of type **A**. The mechanism is a nucleophilic attack of the sulfur atom on the electrophilic oxygen of the peroxy acid (“electrophilic” oxidation); the reactions do not undergo acid catalysis and are not subject to salt effects. As regards the oxidation of sulfinyl sulfur ($R_1R_2S=O$), two types of mechanisms have been proposed:¹³ type 1 is similar to that suggested for the oxidation of sulfides, while type 2 involves a nucleophilic attack of the peroxy anion on the sulfur atom (“nucleo-

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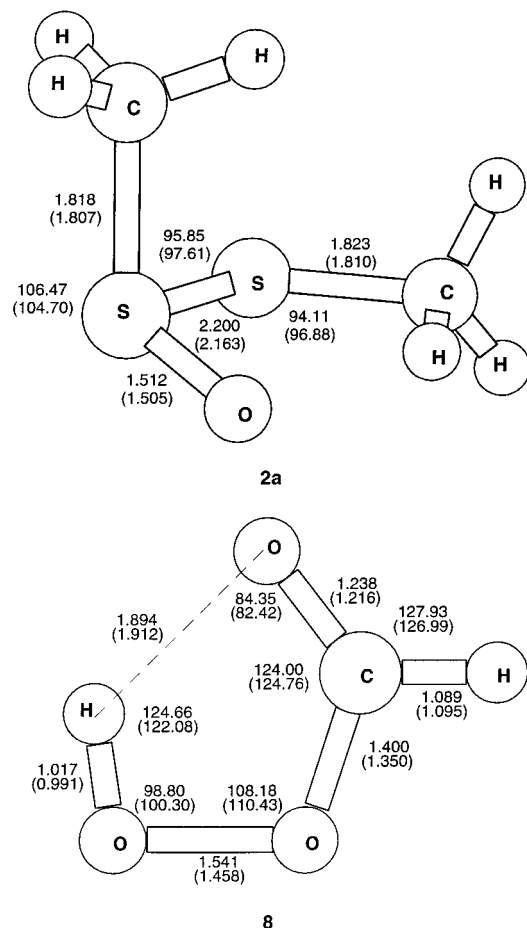


Figure 1. Key features of the optimized MP2/3-21G* and MP2/6-31G* (values are shown in parentheses) geometries of the reactants. Bond lengths in Å, angles in degrees.

philic" oxidation), also called "alkaline" oxidation. In neutral or slightly acidic solutions, however, peracid oxidation seems to prefer the attack of type 1). The lower reaction rates have been rationalized as being due to the lower nucleophilicity of sulfur of sulfoxide.¹⁸

Three different transition states were located on the potential energy surface for the electrophilic attack, with the peroxide bond oriented close to the direction of the sulfur lone pairs, that of sulfinyl sulfur being p type and that of sulfinyl sulfur being sp^3 hybrid type. Owing to the chiral character of the sulfinyl sulfur, two α -disulfoxides will be formed, *i.e.* the diastereomers *RS/SR* (*meso*) and *RR/SS* (*d,l*) and two transition states, **TS-1_{RS}** and **TS-1_{RR}** (Figure 2) are present. In the reaction path leading to the thiosulfonate derivative, the **TS-2** activated complex (Figure 2) was located.

In all the activated complexes, the transition vectors are dominated by the shortening of the S...O distance and the elongation of the O—O bond, suggesting a similar mechanism for all the processes, namely, the transfer of an electrophilic hydroxyl cation (OH^+) from the peracid to the nucleophilic substrate. Proton transfer to the departing group occurs after the barrier is crossed (demonstrated also with intrinsic reaction coordinate (IRC) calculations¹⁶). The fact that the O—H bond is not broken in the transition state seems to explain why the reaction with peracids is not subjected to acid catalysis. Oxidation of sulfides to sulfoxides by hydrogen peroxide

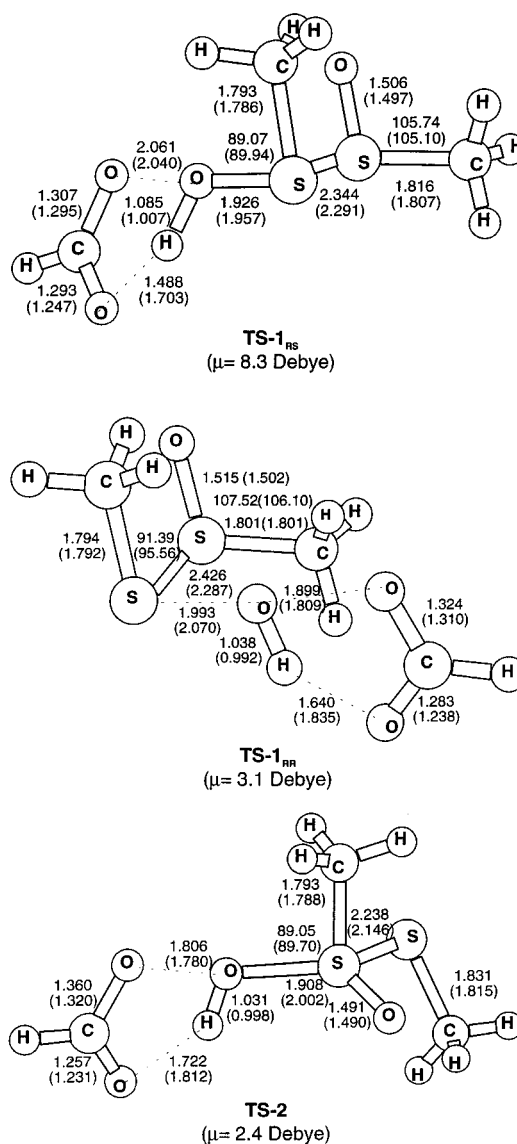


Figure 2. Key features of the optimized MP2/3-21G* and MP2/6-31G* (in parentheses) geometries of **TS-1_{RS}**, **TS-1_{RR}**, and **TS-2**. Bond lengths in angstroms, angles in degrees.

and alkyl hydroperoxides undergoes acid catalysis;¹⁹ the catalyst HA is believed to assist the attack of the O—O bond, thereby forming the transition state which allows ring formation of peracids, in the planar *syn* form, allows a 1,4 intramolecular proton migration. While they act as "self-catalysts", peroxy acids are normally 10^3 times more reactive than alkyl hydroperoxides.¹³

Activation barriers, calculated from isolated reactants, are reported in Table 1. For sulfide and sulfoxide oxidation, similar calculated gas-phase reactivities were obtained independently of the basis set used and the activation parameters describe a competitive attack of the peroxy acid on different nucleophiles. This gas-phase model thus fails to reproduce the observed chemoselectivity for sulfinyl oxidation.

As regards the formation of diastereomeric α -disulfoxides, *RR/SS* attack seems to be favored by at least 3 kcal/

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Table 1. Gas Transition-State Parameters and Condensed-Phase Activation Energies (kcal/mol)^{a-c}

phase	TS	MP2/3-21G*			MP2/6-31G*		
		ΔE^\ddagger	ΔH^\ddagger	ΔG^\ddagger	ΔE^\ddagger	ΔH^\ddagger	ΔG^\ddagger
gas	TS-1_{RS}	11.82	11.26	22.72	12.30	11.74	23.20
	TS-1_{RR}	6.48	6.70	19.64	9.56	9.78	22.72
	TS-2	6.43	6.94	18.34	9.94 (13.68)	10.45	21.85
condensed $\epsilon = 4.83$	TS-1_{RS}	4.13			6.78		
	TS-1_{RR}	7.61			11.55		
	TS-2	8.74			11.67 (12.55)		
$\epsilon = 9.08$	TS-1_{RS}	2.27					
	TS-1_{RR}	7.79					
	TS-2	9.20					
$\epsilon = 32.7$	TS-1_{RS}	0.39					
	TS-1_{RR}	7.94					
	TS-2	9.60					

^a Values calculated with respect to isolated reactants. ^b In parentheses, the values calculated with respect to reactant cluster **10**. ^c Thermodynamic properties refer to 298.15 K and 1 atm of pressure. Frequencies calculated at MP2/3-21G* level were employed.

mol (Table 1). NMR studies⁵ on the oxidation of dimethyl thiosulfinate (**2a**) by MCPBA suggest that the *RR/SS* form is the initial product. Monitoring the NMR signals of the product mixture at -40°C , it has been noted⁵ that the *upfield* resonance assigned to the *RS/SR* (**3b**) diastereomer decreases much faster than the corresponding *downfield* resonance of the *RR/SS* (**3a**) form: this should imply⁵ that **3b** stereomutates to **3a** and/or decomposes or rearranges to other products.⁵ We calculated the relative stability of α -disulfoxide diastereomers: **3a** was found to be 10.67(6.12) kcal/mol more stable than **3b** at the MP2/3-21G*(MP2/6-31G*) level. We also noted that, although use of the 6-31G* basis set causes all the barriers, particularly those for **TS-1_{RR}** and **TS-2**, to increase, the mechanistic conclusions drawn are no different from those obtained at using 3-21G* basis set. The calculated activation entropies (-38.44 , -43.40 , and -38.24 cal mol⁻¹ K⁻¹ for **TS-1_{RS}**, **TS-1_{RR}**, and **TS-2** paths respectively) are negative as required by the highly oriented transition states, as reported previously for similar reactions.¹²

Reactant clusters, considered as ground states for the oxidation reaction, formed by complexation of HCO₃H with dimethyl sulfide and dimethyl sulfoxide have been reported by Bach and co-workers.¹¹ In order to obtain a qualitative picture of the region of the reaction path, we started from the optimized transition states and scanned three channels along the S...O distance as the reaction coordinate with single-point energy calculations at the MP2/3-21G* level. The approximate reaction profiles obtained with this approach are reported in Figure 3. Moving from the minima on the profiles, we tried to locate the clusters by means of the analytical gradient method.¹⁶ The search failed in all the cases considered owing to the energy surface being very flat and the dispersion forces small. As a matter of interest, we then calculated the classical activation barriers with respect to the minima of the curves, considered as reactant complexes, obtaining values of 16.17, 10.48, and 11.65 kcal/mol for the three different paths, respectively (it is important to note that these values are only *upper limits* to the real energies). Even the results of this approach show that gas-phase reactivities are of comparable magnitude; the attack to form the *RR/SS* α -disulfoxide seems to be slightly favored (by ~ 1 kcal/mol) and the minimum relative to the thiosulfonate is the lowest one (Figure 3). At the MP2/6-31G* level, only the cluster (**9**) (Figure 4) leading to **TS-2** was definitely characterized, and its stabilization energy relative to isolated reactants

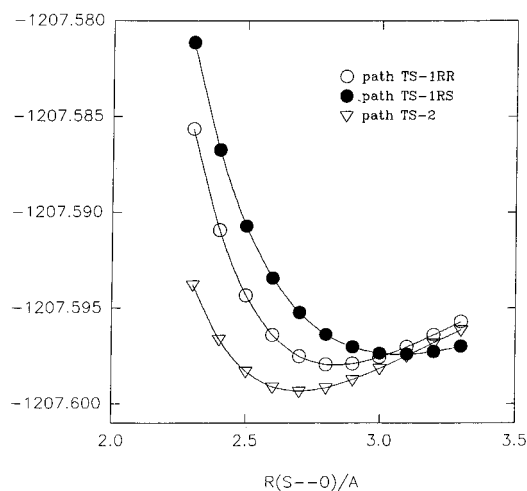


Figure 3. Approximate reaction paths (MP2/3-21G*) for the formation of reactant clusters (see text).

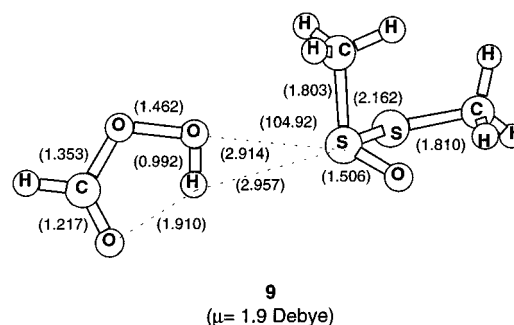


Figure 4. Key features for reactant cluster (MP2/6-31G*) leading to **TS-2**.

amounts to 3.74 kcal/mol. Taking **9** as the ground state for the path leading to **TS-2**, the correct order of reactivities is reproduced (Table 1). However, the fact that similar clusters were not located at the levels of calculations employed in the entrance channels of the paths leading to **TS-1** transition states does not definitely exclude their eventual existence. From our results stems the suggestion that these "hypothetical clusters" are probably less stabilized than **9** (at least for **TS-1_{RR}**), as the failure of the optimization attempts seem to suggest, and the "hypothetical barriers" are thus lower than that for **TS-2**.

Comparison between the **TS** geometries calculated at the MP2/6-31G* and MP2/3-21G* levels, respectively,

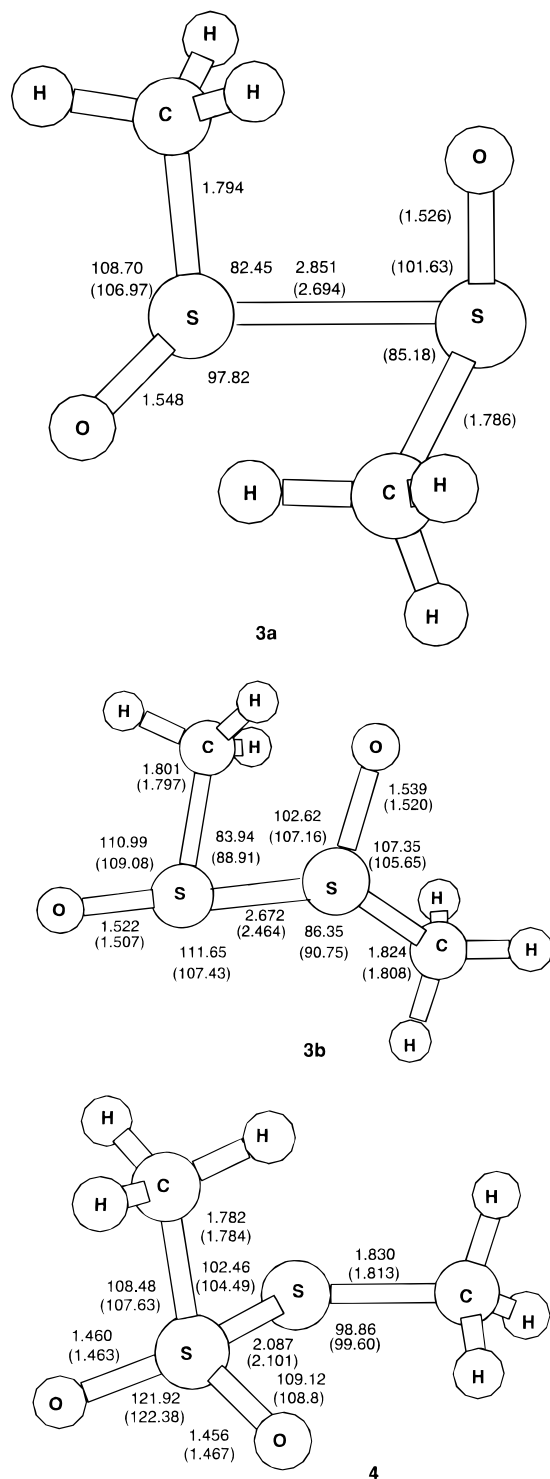


Figure 5. Key features of the optimized MP2/3-21G* and MP2/6-31G* (in parentheses) geometries of **3a**, **3b**, and **4**. Bond lengths in angstroms, angles in degrees.

shows that they are very similar to each other; at MP2/6-31G* level the three activated complexes tend to have similar structures. In **TS-1** transition states the S-S distances are significantly longer than those in the **TS-2** transition state, which suggests that in α -disulfoxides S-S bond breaking can occur after the barrier is crossed (at the MP2/6-31G* level in **TS-2** the R_{S-S} is even slightly shorter than in the reagent **2a**). In fact, optimizing the geometry of the compounds formed beyond the barrier, *vic* α -disulfoxides *RR/SS* (**3a**) and *RS/SR* (**3b**) and thiosulfonate (**4**) (Figure 5) at MP2/3-21G* (6-31G*) level,

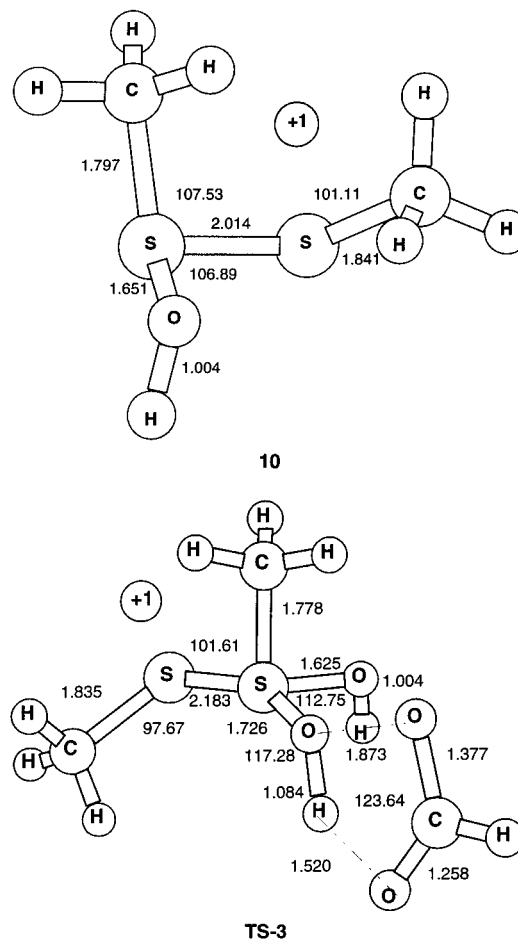


Figure 6. Key features of the optimized MP2/3-21G* geometries of protonated thiosulfinate and **TS-3**. Bond lengths in angstroms, angles in degrees.

R_{S-S} equilibrium distances of 2.851 (2.694), 2.672 (2.464), and 2.087 (2.101) Å, respectively, were obtained, which indicates that α -disulfoxide is most probably an unstable compound. Significant information could be obtained by testing the stability of the Hartree-Fock wave functions; real-RHF \rightarrow real-UHF instabilities were found only for **3a,b** (root = -0.108, -0.084 au, respectively), which shows that a more flexible wave function is needed to describe these systems properly. A comparative⁶ study of the S-S bond stability in disulfides, thiosulfonates, and α -disulfoxides with a multiconfigurational wave function (CASSCF) has shown that in *vic*-disulfoxides the bond appears to be much weaker than in the other molecules (BDE(1) 43.5, BDE(2) 18.0, and BDE(3a) 1.0 kcal/mol) and that the "equilibrium" distance turns out to be about 4 Å. In α -disulfoxides the S-S bond most probably undergoes homolytic breaking as soon as it is formed. In order to support this conclusion, we performed an IRC (intrinsic reaction coordinate)¹⁶ at the 3-21G* level starting from the structure of **TS-1_{RR}** and moving toward the products: R_{S-S} increases along the reaction coordinate, thus showing that homolytic cleavage occurs.

It has previously been noted on parent systems¹¹ that solvent interactions in the condensed phase should determine selectivity at the level of the different transition states. In the reactions studied here, the dipole moment of **TS-1_{RS}** is greater than those of the other transition states (Figure 2). As a consequence, an increase in solvent polarity should stabilize **TS-1_{RS}** more than **TS-1_{RR}** and **TS-2**, thus lowering the activation

barrier for sulfide oxidation. Starting from this premise, we calculated the solvent effect with the IPCM solvation model on the transition states by simulating solvents of increasing dielectric constants (4.83, 9.8, and 32.7 corresponding to CHCl_3 , CH_2Cl_2 , and CH_3OH solvents, respectively) and with MP2/3-21G* gas-phase geometries. Single-point energy calculations showed that, at the three values of dielectric constant, the following stabilizations occur: **TS-1_{RS}** 15.65, 19.11, and 22.48 kcal/mol; **TS-1_{RR}** 6.83, 8.25, and 9.60 kcal/mol; **TS-2** 5.65, 6.78, and 7.84 kcal/mol. Solvent interactions stabilize **TS-1_{RS}** significantly. Solvent effects were also calculated for the isolated reagents at different dielectric constants. At the MP2/6-31G* level the solvent effect was calculated only for the dielectric constant of 4.83, corresponding to CHCl_3 , a solvent widely employed for these reactions. Classical activation barriers obtained by these approaches are reported in Table 1. Solvent effects significantly lower the activation energy for path **1-RS**: the decrease in the barrier is proportional to the solvent polarity. Only a slight increase is found for the other barriers considered and is more evident in the case of the pathway leading to the thiosulfonate product. At the MP2/6-31G* level this trend is confirmed. The observed chemoselectivity of sulfide-to-sulfoxide oxidation is thus likely to be a consequence of the fact that solvation greatly lowers the energy of the transition state for sulfinyl sulfur oxidation.

We have so far ignored the ability of the highly polarized S=O group to form hydrogen bonds with protic solvents: hydrogen-bonded sulfoxides are expected to be poorer nucleophiles than the unsolvated ones. Addition of acids in fact depresses the reactivity of sulfoxides toward peroxy acids.^{17,18} In order to verify the decrease

in nucleophilicity of the protonated species, which should at the same time confirm the electrophilic nature of the attack, we optimized the geometry of the O-protonated thiosulfinate **10** (Figure 6) at the MP2/3-21G* level. Following the electrophilic attack of performic acid on sulfinyl sulfur, as described above, we located the activated complex **TS-3** (Figure 6), which is 14.55 kcal/mol less stable than the reactants: the energy required to reach the transition state is thus more than twice that required for the attack on the unprotonated thiosulfinate (**TS-2**, in Figure 2) (6.43 kcal/mol).

A final consideration regards the basis set effect. Although optimized geometries are similar at the level of the two basis set employed, significant variations were found for the activation barriers. Consistently higher values were found at the MP2/6-31G* level. The mechanistic conclusions derived at the two levels of theory are nevertheless in qualitative agreement.

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Supporting Information Available: Table of Cartesian coordinates, total energies for reactants, products, transition states and reactant cluster (MP2/3-21G* and MP2/6-31G*), and table of SCRF total energies for reactants and transition states (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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