Thianthrene 5-Oxide as a Probe for the Electronic Character of Oxygen-Transfer Reactions: Re-interpretation of Experiments Required[†,#]

Dirk V. Deubel

Contribution from the Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4[1]

deubel@ucalgary.ca

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The electronic character of oxidants, i.e., whether they attack substrates in an electrophilic or nucleophilic way, has extensively been investigated using thianthrene 5-oxide (SSO) as probe. The SSO molecule has a sulfide group, which is attacked by electrophilic oxidants, and a sulfoxide moiety, which is oxidized by nucleophilic oxidants. This density-functional study has been carried out in order to gain insight into the origin of the chemo- and stereoselectivity of SSO oxidation. It has been found that the *endo* and *exo* stereoisomers of the thianthrene oxides interconvert via ring-inversion with moderate energy barriers. Thus, the stereoselectivity of SSO oxidation has to be interpreted with caution. Furthermore, a topological electron-density analysis of thianthrene 5-oxide reveals that there is an area of charge depletion at the sulfoxide group. The location of this area indicates that the attack of nucleophilic oxidants on SSO is sterically hindered. Therefore, the SSO probe makes oxidants such as dioxiranes appear to be more electrophilic than they actually are.

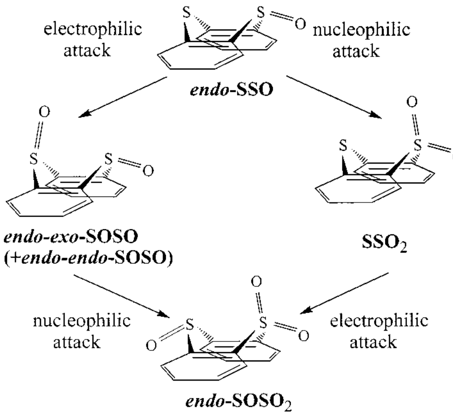
Introduction

It is useful for a rational design of catalysts for oxygen-transfer reactions to know whether the oxidant attacks the substrate in an electrophilic or nucleophilic way.[2] This information about the nature of the oxidant attack is defined as electronic character of oxygen-transfer reactions. One of the most valuable probes for the electronic character was introduced by Adam and co-workers:[3] the chemoselective oxidation of thianthrene 5-oxide (SSO). The SSO molecule contains both a sulfide group ("S site") and a sulfoxide group ("SO site", Scheme 1). Electrophilic oxidants preferentially attack the SSO molecule at the sulfide moiety, yielding 5,10-dioxides (SOSO), whereas nucleophilic oxidants transform the sulfoxide moiety to the sulfone (SSO_2). A subsequent oxidation of SOSO and SSO_2 gives $SOSO_2$, respectively. The reaction of an oxidant with SSO yields a mixture of oxidation products, the relative amount of which allows the classification of the oxidant on the X_{SO} scale:

$$X_{SO} = \frac{\text{"SO" oxidation}}{\text{total oxidation}} = \frac{y(SSO_2) + y(SOSO_2)}{y(SOSO) + y(SSO_2) + 2y(SOSO_2)}$$

y(P) is the yield of the oxidation product P. One obtains X_{SO} values on a scale between 0 and 1. A value of 0 indicates that only the sulfide moiety has been attacked and that the oxidant is highly electrophilic. An X_{SO} value of 1 shows that the thianthrene 5-oxide molecule has only been oxidized at the sulfoxide moiety and that the oxidant is nucleophilic. Beside the chemoselectivity (i.e., oxidation at the S site versus SO site), the stereoselectivity of SSO oxidation is of a considerable interest: Each sulfoxide moiety of SSO and its oxidation products has either an *endo* or an *exo* configuration (Scheme 1). The stereoselectivity provides insight into the role of steric properties

Scheme 1. Chemoselective Oxidation of *endo*-Thianthrene 5-Oxide (*endo*-SSO)



[†] Dedicated to Professor Dr. Jörg Sundermeyer.

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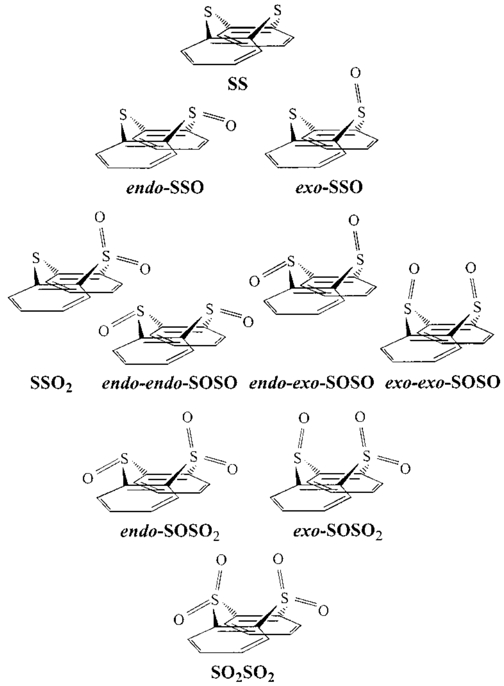
of oxidants.[4] In the past decade, the Adam probe has extensively been applied to many oxidants.[5]

Although the thianthrene 5-oxide probe is very popular in organic chemistry,[5] the origin of the stereo- and chemoselectivity of SSO oxidation has rarely been scrutinized. Bach and co-workers[6,7] performed quantum-chemical studies on the oxidation of dimethyl sulfide (DMS) and dimethyl sulfoxide (DMSO) with several oxidants, such as dioxiranes, carbonyloxides, and peroxy acids. For example, the activation barriers with dimethyldioxirane (DMDO) as oxidant were calculated at the B3LYP/6-31G(d) level to be 10.0 kcal/mol (DMS) and 9.6 kcal/mol (DMSO).[7] Since the two activation energies are very similar, DMDO should be both electrophilic and nucleophilic. However, for dimethyldioxirane, an X_{SO} parameter of about 0.10, depending on temperature, was obtained, indicating a highly electrophilic nature of dimethyldioxirane. According to this result, the activation barrier for the oxidation of DMSO with DMDO should be significantly higher than for the DMS oxidation. This puzzling contradiction can be resolved in the following way: (i) The SSO molecule has unique properties different from those of isolated sulfides and sulfoxides or (ii) the B3LYP/6-31G(d) level is not appropriate for energy calculations of sulfur compounds.[8,9] Therefore, we have performed the first density-functional study of thianthrene 5-oxide.[10]

Methods

For geometry optimizations, the three-parameter hybrid functional of Becke[11] together with the correlation functional of Lee, Yang, and Parr (B3LYP)[12] was employed as implemented in Gaussian 98.[13] The basis set 6-31G(d) was used.[14,15] Minima ($i = 0$) and transition states (TS, $i = 1$) on the potential-energy surfaces were characterized by the number i of imaginary frequencies. The zero-point-energy (ZPE) contributions are unscaled. Selected molecules were also investigated using the improved basis sets 6-311+G(d)[15−17] and 6-311++G(3d,2p)[17,18] as well as second-order Møller−Plesset perturbation theory (MP2),[19] respectively. Unless otherwise mentioned, geometries reported refer to the B3LYP/6-31G(d) level and energies refer to the B3LYP/6-311++G(3d,2p)//B3LYP/6-31G(d) level. For the interpretation of electron density, the atoms-in-molecules model (AIM)[20] was utilized.

Scheme 2. Thianthrene (SS) and Its Oxides



Results and Discussion

Molecular Geometries. Drawings of thianthrene (SS) and its oxides (*endo*-SSO, *exo*-SSO, SSO$_2$, *endo*-*endo*-SOSO, etc.) are shown in Scheme 2. The geometries of all molecules were fully optimized at the B3LYP/6-31G(d) level of theory. The structures theoretically predicted for the two stereoisomers of thianthrene 5-oxide (*endo*- and *exo*-SSO) are given in Figure 1; additional structural data of the molecules are listed in Table 1. These structures are very similar to the calculated geometries of thianthrene (SS) and of the other oxides. A good

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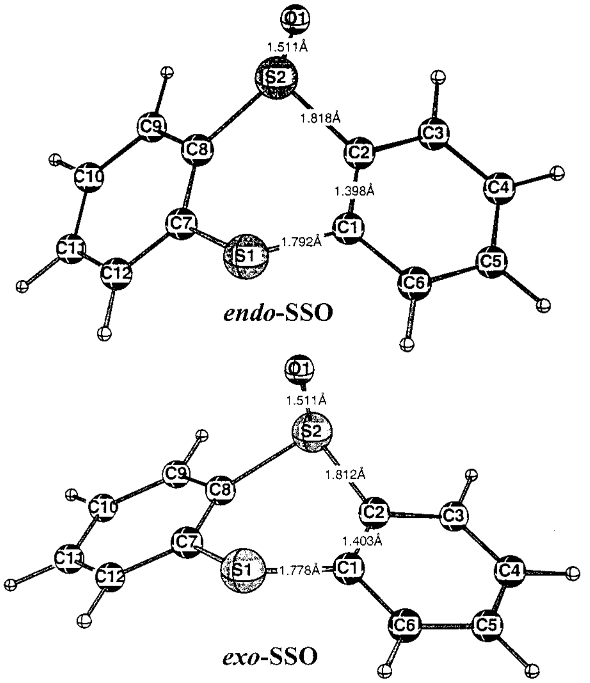

Figure 1. Optimized geometries (B3LYP/6-31G(d)) of *endo*-thianthrene 5-oxide (*endo*-SSO) and *exo*-SSO.

agreement of the theoretically predicted structures with X-ray data of SS, SSO_2, and SO_2SO_2 was achieved; the calculated C−SO and S−O bond lengths are longer than the experimental values by about 0.02 Å.[21] The molecules have folded geometries, which can be understood considering basic concepts: If thianthrene was planar, it would contain an antiaromatic 1,4-dithiin moiety with 8 π electrons. Furthermore, the VSEPR model[22] and Bent's rule[23] favor C−S−C angles less than the tetrahedron angle in SS and its oxides, respectively, which are confirmed by the data provided in Table 1.

Relative Energies. Since the oxidation of thianthrene 5-oxide with an oxidant yields a mixture of several oxidation products, it is interesting to learn the relative energies of the molecules. The energies of thianthrene (SS) and its oxides calculated at the B3LYP/6-31G(d) are listed in Table 2, respectively. The values refer to the isomer which is lowest in energy. Additional calculations of the energies of selected molecules using the improved basis set 6-311++G(3d,2p) have led to small changes (Table 2). We predict that the sulfone SSO_2 is more stable by 24.7 kcal/mol than the disulfoxide with the lowest energy (*endo*-*endo*-SOSO). This energy difference between SSO_2 and *endo*-*endo*-SOSO was previously calculated at the PM3 level to be only 9.1 kcal/mol,[4] arising from an inaccurate description of hypervalent molecules at semiempirical levels of theory.[24] Furthermore, the calculationsreveal that the *endo* configuration of a sulfoxide moiety is in general more stable than the *exo* configuration by about 4 kcal/mol.[25] For example, *endo*-SSO is more stable than *exo*-SSO by 3.8 kcal/mol. The formation of two sulfoxide groups with *exo* configuration requires an additional energy of about 4 kcal/mol. For example, *endo*-*exo*-SOSO is more stable by 8.6 kcal/mol than *exo*-*exo*-SOSO (Table 2).

On the Stereoselectivity of SSO Oxidation. In a recent experimental study,[4] the relative amount of the disulfoxides (*endo*-*endo*-SOSO and *endo*-*exo*-SOSO; *exo*-*exo*-SOSO was not reported) was discussed in detail in order to gain insight into the role of steric properties of several oxidants in the oxidation process. Nobody has doubted these interpretations. Chiral sulfoxides are commonly applied as chiral auxiliaries[27] and the activation energies for the *direct* inversion of sulfoxides are very large, for instance 47.8 kcal/mol for DMSO. However, the thianthrene 5-oxide molecule does not consist of an isolated sulfide group and an isolated sulfoxide group: The two sulfur moieties of SSO are embedded in a heteroanalogous anthracene molecule, and, in this section, we scrutinize whether an interconversion of the stereoisomers via ring inversion is feasible. Figure 2 shows the optimized transition-state geometry for TS(*endo* → *exo*-SSO). The theoretically predicted energies of the TS for ring inversion of all thianthrene oxides are also given in Table 2; they refer to the most stable isomer. The calculations reveal that the activation energies are low, for example 7.4 kcal/mol for TS(*endo* → *exo*-SSO). The barriers depend rather on the relative energies of the corresponding isomers than on the number of oxo groups at the sulfur moieties. For the transformation of *exo*-*exo*-SOSO to *endo*-*endo*-SOSO, the barrier is only 1.6 kcal/mol. Note that ring inversion does not neccessarily lead to a different product, e.g., *endo*-*exo*-SOSO inverted gives the same molecule.

The moderate ring-inversion barriers for thianthrene 5-oxide and the subsequent oxidation products have an important consequence for the interpretation of the stereoselectivity of SSO oxidation. If the activation energy for the oxidation of SSO at the sulfide moiety is comparable to the ring-inversion barrier, the stereoselectivity of SSO oxidation should be interpreted with caution. The energy profile for ring inversion of thianthrene 5-oxide has been calculated using various basis sets and using the MP2 ab initio method. These results listed in Table 3 confirm the low ring-inversion energy.

Despite the larger thermodynamic stability of a sulfoxide with the *endo* configuration compared to the *exo* configuration, an electrophilic attack on the SSO molecule preferentially yields *endo*-*exo*-SOSO instead of *endo*-*endo*-SOSO,[28] which has to be explained by kinetic rather than thermodynamic reasons: During an attack at the *endo* position of the S site of SSO, the oxidant is probably repelled from the hydrogen atoms of the benzo

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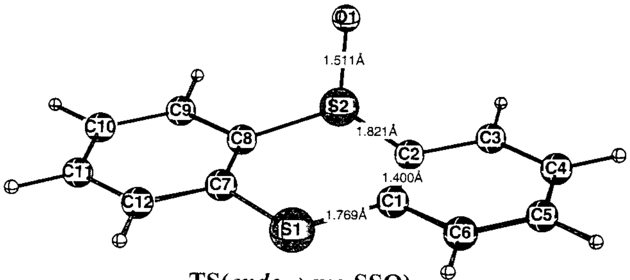
Table 1. Selected Structural Parameters (B3LYP/6-31G(d)) of *endo*-Thianthrene 5-Oxide (*endo*-SSO), *exo*-SSO, and the Transition State for Ring Inversion

		Distances [Å]					Angles [deg]					
mol/TS	PG	S1−C1	S2−C2	S2−O1	C1−C2	S1−S2	S1−S2−O1	C1−S1−C7	S1−C1−C2	C1−C2−S2	C2−S2−C8	C2−S2−O1
endo-SSO	C_s	1.792	1.818	1.511	1.398	3.221	159.0	99.9	120.8	119.7	96.0	108.6
exo-SSO	C_s	1.778	1.812	1.511	1.403	3.365	84.6	102.1	123.1	122.8	96.7	108.3
TS	C_s	1.769	1.821	1.511	1.400	3.604	117.9	106.5	126.6	129.1	102.0	108.4

Table 2. Calculated Relative Energies E_{rel} (kcal/mol) at the B3LYP/6-31G(d) and B3LYP/6-311++G(3d,2p)//B3LYP/6-31G(d) Levels for Thianthrene (SS) and Its Oxides (i = 0) and the Transition States TS for Ring Inversion (i = 1)[a]

molecule	PG	i^b	E_{rel}^c	E_{rel}^d
SS	C_{2v}	0	0.0 (0.0)	
TS(SS)	D_{2h}	1	5.5 (5.3)	
endo-SSO	C_s	0	0.0 (0.0)	0.0
exo-SSO	C_s	0	5.3 (5.2)	3.8
TS(*endo* → *exo*-SSO)	C_s	1	9.7 (9.4)	7.4
SSO_2	C_s	0	0.0 (0.0)	0.0
endo-endo-SOSO	C_{2v}	0	23.5 (22.4)	24.7
endo-exo-SOSO	C_s	0	27.5 (26.3)	28.0
exo-exo-SOSO	C_{2v}	0	37.1 (35.9)	36.6
TS(SSO_2)	C_{2v}	1	5.5 (5.1)	3.9
TS(*endo-exo*-SOSO)	C_{2h}	1	38.0 (36.7)	37.7
TS(*endo-endo* → *exo-exo*-SOSO)	C_{2v}	1	40.3 (38.7)	38.2
endo-$SOSO_2$	C_s	0	0.0 (0.0)	
exo-$SOSO_2$	C_s	0	8.7 (8.6)	
TS(*endo* → *exo*-$SOSO_2$)	C_s	1	12.6 (12.2)	
SO_2SO_2	C_{2v}	0	0.0 (0.0)	
TS(SO_2SO_2)	D_{2h}	1	6.3 (5.9)	

[a] ZPE-corrected values are given in parentheses. [b] Number of imaginary frequencies. [c] B3LYP/6-31G(d). [d] B3LYP/6-311++G(3d,2p)//B3LYP/6-31G(d).



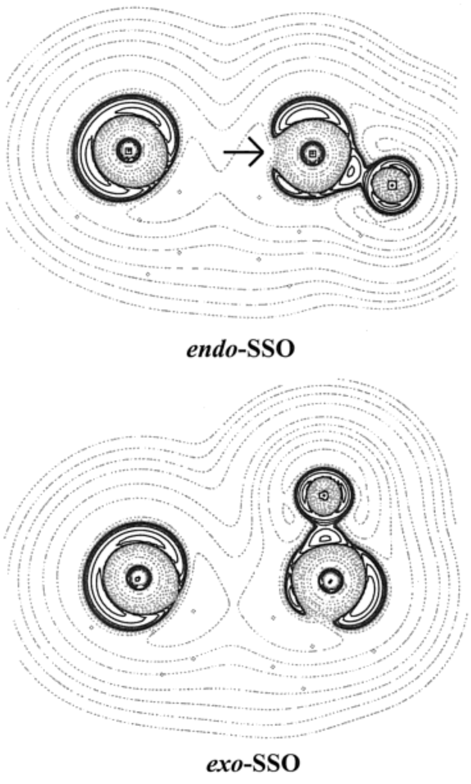
TS(*endo*→*exo*-SSO)

Figure 2. Optimized geometry (B3LYP/6-31G(d)) of the transition state for the ring inversion of SSO.

Table 3. Calculated Relative Energies for Thianthrene 5-Oxide (SSO) and 1,4-Dithiin 1-Oxide (DTO) Isomerization

		E_{rel}		
model	method	*endo*	*exo*	TS
SSO	B3LYP/6-31G(d)	0.0	5.3	9.7
SSO	B3LYP/6-31G(d) + ZPE	0.0	5.2	9.4
SSO	B3LYP/6-311+G(d)//B3LYP/6-31G(d)	0.0	4.7	9.0
SSO	B3LYP/6-311+G(d)	0.0	4.7	9.0
SSO	B3LYP/6-311++G(3d,2p)//B3LYP/6-31G(d)	0.0	3.8	7.4
SSO	MP2/6-31G(d)	0.0	6.8	11.4
DTO	B3LYP/6-31G(d)	0.0	−0.1	5.9
DTO:SSO[a]	ONIOM (B3LYP/6-31G(d):PM3)[a]	0.0	−0.2	3.8

[a] High level:low level of the ONIOM hybrid model.



endo-SSO

exo-SSO

Figure 3. Contour-line diagrams of the Laplacian $\nabla^2\rho$ of electron density in the S−S−O plane of *endo*-SSO and *exo*-SSO. Solid lines, $\nabla^2\rho < 0$; dashed lines, $\nabla^2\rho > 0$.

moieties (i.e., the H atoms at C6 and C12 in *endo*-SSO, Figure 1). Unfortunately, systematic geometry optimizations of transition states for the reaction of thianthrene 5-oxide with any oxidant are presently not computationally feasible because the molecules are too large. Therefore, we considered 1,4-dithiin 1-oxide (DTO) as a simple model for SSO and calculated the energy profile for the ring inversion of DTO. The results are also given in Table 3. The computations show that the *exo* isomer of DTO is predicted to be more stable than the corresponding *endo* isomer. Thus, 1,4-dithiin 1-oxide is useless as a model for SSO in theoretical investigations. The application of a hybrid model, such as ONIOM,[29] is also not appropriate.

On the Chemoselectivity of SSO Oxidation. To obtain information about the electronic structure of the SSO molecule, a topological analysis of electron density ρ was performed;[20] we focus on the Laplacian $\nabla^2\rho$. In Figure 3 (top), the contour-line diagram of $\nabla^2\rho$ in the S−S−O plane of *endo*-SSO is plotted. The left side of the plot represents the sulfide moiety of *endo*-SSO and the right side shows the SO moiety of the molecule. Solid lines refer to values of $\nabla^2\rho < 0$ and indicate areas of the concentration of negative charge, wheras dashed lines represent values of $\nabla^2\rho > 0$ indicating areas of charge depletion. The analysis reveals that the sulfide group

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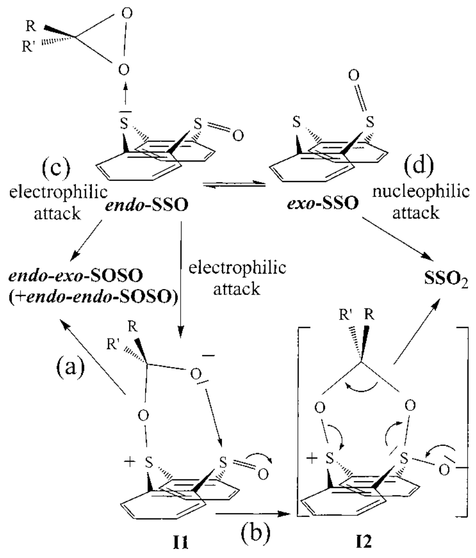
(29) (a) Maseras, F.; Morokuma, K. *J. Comput. Chem.* **1995**, *16*, 1170. (b) Humbel, S.; Sieber, S.; Morokuma, K. *J. Chem. Phys.* **1996**, *105*, 1959. (c) Svensson, M.; Humbel, S.; Froese, R. D. J.; Matsubara, T.; Sieber, S.; Morokuma, K. *J. Phys. Chem.* **1996**, *100*, 19357.

(left) is shielded by continuous areas of charge concentration (solid lines); the two lone pairs can be identified in the contour-line diagram. The electronic structure at the SO moiety (right) is very interesting: There is an area of charge depletion marked with an arrow.[30] Note that nucleophilic oxidants will preferentially attack the SSO molecule here. However, this area of charge depletion does not point into "free space" but to the sulfide moiety. Therefore, a nucleophilic oxidant with an unsuited molecular shape cannot approach the sulfoxide moiety well. One might remark that only the reactant was analyzed here and that the effect on the activation barrier for the nucleophilic SSO oxidation cannot exactly be estimated. One should consider Bach's theoretical studies on sulfide and sulfoxide oxidation with several oxidants.[6,7] In these studies, the calculated geometries of reactant clusters initially formed by oxidants and dimethyl sulfoxide were reported. These geometries clearly indicate that a nucleophilic attack of an oxidant on the SSO molecule does occur at the position marked with the arrow (Figure 3). The results of the present work show that, if the activation energies for the oxidation of sulfides and sulfoxides by an oxidant are comparable, the oxidation of the sulfoxide moiety of SSO by this oxidant is unfavored. The ordering of reagents on the X_{SO} scale will scarcely be affected, but the scale itself is partially shifted toward an artificial electrophilic character of the oxidants.

The contour-line diagram of $\nabla^2\rho$ in the S−S−O plane of the other stereoisomer, *exo*-SSO, is also shown in Figure 3 (bottom). According to the $\nabla^2\rho$ plot for the *exo* form, this isomer rather than *endo*-SSO seems to behave like a usual sulfoxide concerning a potential nucleophilic attack: A nucleophilic oxidant has a more or less free access to the area of charge depletion at the sulfoxide moiety though there might also be a repulsion of oxidants that are sterically demanding from the hydrogen atoms of the benzo moieties. Note that the electronic-structure analyses presented here refer to the molecules in the gas phase. In the presence of donating solvents, thianthrene 5-oxide might be preferentially solvated at the areas of charge depletion, which additionally influences the stereo- and chemoselectivity of SSO oxidation.

Turecek[8] and Jenks and co-workers[9] have found a strong basis-set dependence of the energy profile of other sulfoxide-related reactions. Therefore, we have performed energy calculations at the B3LYP/6-311++G(3d,2p)//B3LYP/6-31G(d) level. The results in Table 2 have shown that there are small corrections of the relative energies for the isomers of SSO, subsequent oxidation products, and the ring-inversion transition states. We have also calculated the activation energies for the oxidation of DMS and DMSO with dimethyldioxirane (DMDO) at the same level of theory (B3LYP/6-311++G(3d,2p)//B3LYP/6-31G(d)). The values predicted at the B3LYP/6-31G(d) level are 10.1 (DMS) and 9.6 kcal/mol (DMSO).[7] At the higher level, these activation energies significantly change: 4.1 (DMS) and 8.1 (DMSO) kcal/mol, indicating a preference for the sulfide oxidation by DMDO. Note that experimental free-enthalpy values might be higher than these small energies. For bimolecular reactions, there are considerable translational and rotational entropy contributions to the activation free energy.[24]

Scheme 3. Reaction Pathways for the Oxidation of SSO with Dioxiranes: Mechanisms a and b, Postulated by Adam (Ref 4), and Direct Oxygen-Transfer Mechanisms c and d



On the Solvent Dependence of the Chemoselectivity of SSO Oxidation with Dioxiranes. Adam and co-workers[4] pointed out the peculiar solvent dependence of the chemoselectivity of SSO oxidation by dioxiranes: For protic-polar solvents added to CH_2Cl_2, the X_{SO} value significantly decreases from about 0.1 to 0, i.e., a smaller amount of the sulfone is formed. This result was explained by a competition between two mechanisms (a) and (b) shown in Scheme 3:[4] The initial step of the latter mechanism is also an electrophilic attack by the oxidant, however, with the product detected being the sulfone SSO_2. The results of this study provide another explanation of the astonishing solvent dependence of SSO oxidation with dioxiranes: a competition between the mechanisms (c) and (d), see Scheme 3. After ring inversion, *exo*-SSO can be attacked at the *endo* position of the sulfoxide moiety by the dioxirane (d); note that the ring-inversion energy and barrier are also solvent-dependent.

Conclusions

(i) The use of the thianthrene 5-oxide (SSO) system is beyond dispute. The application of the Adam probe showed, for example, that dioxiranes and carbonyloxides are different compounds.[5a] However, experimentalists employing SSO for a probe for the electronic character of oxygen-transfer reactions should be aware of its unique properties.

(ii) The stereoselectivity of SSO oxidation (i.e., the formation of *endo* and *exo* isomers) must be interpreted with caution since the stereoisomers of the thianthrene oxides interconvert via low ring-inversion barriers.

(iii) The chemoselectivity of SSO oxidation (i.e., the attack at the sulfide or at the sulfoxide site) should also carefully be interpreted. A topological electron-density analysis of thianthrene 5-oxide shows that there is an area of charge depletion at the sulfoxide group. The location of this area indicates that a nucleophilic attack

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[30] Nucleophilic and electrophilic properties of carbene and carbyne complexes were also examined using the Atoms-in-Molecules analysis: (a) Vyboishchikov, S. F.; Frenking, G. *Chem.—Eur. J.* **1998**, *4*, 1428. (b) Vyboishchikov, S. F.; Frenking, G. *Chem.—Eur. J.* **1998**, *4*, 1439.

of oxidants on SSO is sterically hindered, compared to the oxidation of dimethyl sulfoxide.

(iv) Large basis sets at the sulfur atoms are required to obtain accurate energies.

(v) The presence of solvents may significantly influence the equilibrium between the stereoisomers and their electronic structure.

(vi) The results of this study will encourage to develop additional probes for the electronic character of oxygen-transfer reactions. Recently, a quantum-chemical probe has been proposed:[31] Charge decomposition analysis (CDA)[32] applied to transition states of olefin epoxidation suggests that dioxiranes are less electrophilic oxidants than peroxy acids, which in turn are less electrophilic than transition metal peroxo complexes.[31]

Supporting Information Available: Calculated reaction energies for dimethyl sulfide (DMS) and dimethyl sulfoxide (DMSO) oxidation with hydrogen peroxide and for isodesmic oxygen-transfer reactions of thianthrene oxides with DMS, DMSO, and dimethyl sulfone (DMSO$_2$). This material is available free of charge via the Internet at http://pubs.acs.org.

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