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Mechanism of the Oxidation of Sulfides by Dioxiranes: Conformational Mobility and Transannular Interaction in the Oxidation of Thianthrene 5-Oxide

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Received September 23, 2004

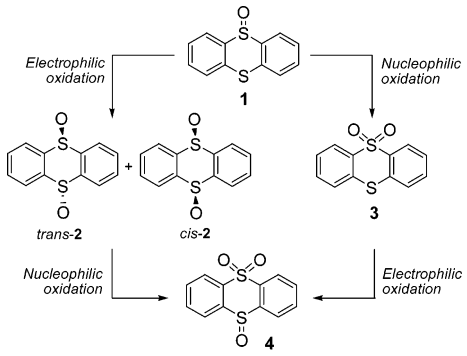
The detailed study of the oxidation of thianthrene 5-oxide (**1**) with methyl(trifluoromethyl)dioxirane (**5b**) in different solvents and in the presence of ^{18}O isotopic tracers is reported. Thianthrene 5-oxide (**1**) is a flexible molecule in solution, and this property allows for transannular interaction of the sulfoxide group with the expected zwitterionic **7** and hypervalent 10-S-4 sulfurane **9** intermediates formed in the oxidation and biases the course of the reaction toward the monooxygenation pathway.

Introduction

In studies of the oxidation of chemical and biochemical systems, it is very important to know the electronic character of the oxidant. Adam et al.[1] introduced the use of thianthrene 5-oxide (**1**) as a general mechanistic probe to determine the electrophilic or nucleophilic character of a given oxidant. With this probe, electrophilic oxidants should prefer to react with the sulfide moiety of **1** to yield disulfoxide **2**, while nucleophilic oxidants should preferably react at the sulfoxide sites of **1** and **2** to give sulfones **3** and **4**, respectively (Scheme 1). Oxidants are classified as either electrophilic or nucleophilic according to the χ_{SO} value, a parameter defined by the ratio of oxidation at the SO site to total oxidation. The advantages claimed[1] for this mechanistic probe are the presence of sulfide and sulfoxide moieties in the same molecule, the lack of exchange in the oxidation products, and the existence of the probe molecule in a single geometry folded along the axis defined by the sulfur atoms and the pseudoequatorial oxygen atom.

Since the first report in 1984,[1d] the mechanistic probe thianthrene 5-oxide has been used extensively to determine the electronic nature of many classes of oxidants such as peroxometal complexes,[2] metalloporphyrin catalysts,[3] hemoprotein oxidizing species,[4] heteropolyoxometalate oxidants,[5] dimethylphenylsilylhydrotrioxide,[6] dialkylperoxonium intermediates,[7] carbonyl oxides,[1] peracids,[8] dioxiranes,[9] and several metal oxidants.[10]

SCHEME 1. Thianthrene 5-Oxide Mechanistic Probe



X_{SO} = *Nucleophilic oxidation / Total oxidation* = = (**3** + **4**) / [**3** + **2** + 2 (**4**)]

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10.1021/jo0483062 CCC: $27.50
Published on Web 12/01/2004

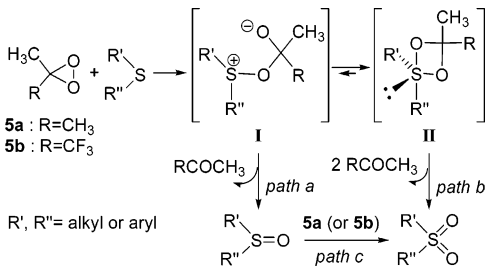

FIGURE 1. Proposed mechanism[13] for the oxidation of sulfides with dioxiranes **5**.

Notwithstanding its wide use in organic chemistry,[1−10] some results of the application of this probe have been controversial. For example, dimethyldioxirane (**5a**) has been classified as a nucleophilic[9] oxidant, in contrast to all of the experimental evidence available, which gave rise to a lively controversy[11] concerning the mechanistic details of the oxidation of sulfides and sulfoxides by dioxiranes **5**. Later, Adam et al. reexamined[12] their results regarding the oxidation of **1** with **5a** and extended the application of the probe to the case of methyl(trifluoromethyl)dioxirane (**5b**). They then discovered[12] that *trans*-thianthrene 5,10-dioxide (*trans*-**2**) was the main reaction product and reclassified **5a** and **5b** as strong electrophilic oxidants. The χ_{SO} values for **5a** and **5b** measured at 0 °C were 0.10 and 0.13, respectively, which resolved the preceding conflict.

The classification of an oxidant according to the value of its χ_{SO} parameter is based on the results of the oxidation of **1** by the investigated oxidant, with the assumption that it follows a sequential mechanism in which sulfides are first oxidized to sulfoxides and these, in a second step, are oxidized to sulfones. However, we have reported that such a sequential mechanism is not operative in the case of dioxirane **5b**.[13] Our studies have demonstrated the direct formation of sulfones in the reaction of simple sulfides with **5b** and provide clear evidence for the involvement of a 10-S-4 sulfurane intermediate (Figure 1). The mechanism involves an initial electrophilic attack of the sulfur atom by the dioxirane to give the zwitterionic species **I**, which in a reversible cyclization step gives rise to the hypervalent intermediate **II**. The β-elimination of trifluoroacetone from **II** leads to the formation of sulfoxides, while further oxidation of the hypervalent intermediates **II** by **5b** gives the corresponding sulfones. Sulfones are the main products in these reactions since the hypervalent sulfur adducts **II** undergo oxidation by **5b** faster than their parent sulfides. In general, the value of the sulfone/sulfoxide ratio decreases with factors that prevent the cyclization of **I** or that favor the opening of the cyclic sulfurane **II**.

This mechanistic scheme is fully consistent with the observed experimental results such as, for instance, the preferred formation of sulfones in polar aprotic solvents regardless of the presence of excess sulfide in the medium or, remarkably, the dramatic reversal of this trend in protic solvents or in the presence of acidic additives. Solvent effects and isotopic labeling of the products can be explained by characteristic ligand exchange reactions[14] of the hypervalent 10-S-4 species **II**. The differences found in the behavior of **5a** and **5b** in the oxidation of sulfides can be easily explained by the difference in the stability of the corresponding hemiacetalic zwitterionic intermediate **I** in each case. In fact, the classical sequential mechanism in which sulfides are oxidized first to sulfoxides and then to sulfones is just a particular case of our mechanism that applies when the β-elimination of ketone from the zwitterionic intermediate **I** occurs faster than cyclization to give the 10-S-4 hypervalent sulfur adduct **II**.

Regarding the oxidation of thianthrene-5-oxide (**1**), the mechanism depicted in Figure 1 predicts that dioxygenation compound **4** is formed as the main oxidation product of **1** with **5b**. However, Adam et al.[12] studied this reaction and reported that the monooxygenation product *trans*-**2** was formed instead. The apparent disagreement between the predictions based on our mechanism[13] and the low χ_{SO} values reported[12] for dioxiranes **5** in the application of the mechanistic probe **1** prompted us to examine this reaction in depth.

In a forthcoming paper,[15] we report on the measurement of the apparent dipole moment and the ^{1}H NMR spectra of **1** in different solvents which evidence the conformational mobility of **1** in solution. We have shown that thianthrene 5-oxide (**1**) switches between two limiting boat conformations that are folded along the axis defined by the sulfur atoms whose relative populations depends on the polarity of the solvent. However, the "mechanistic probe" thianthrene 5-oxide (**1**) has been used to date in the belief that it is a rigid molecule. Recently, Deubel[16] reported, based on density functional calculations, moderate ring inversion barriers for **1** and suggested that this could have important consequences regarding the reactivity of **1**.

In this paper, we report on the oxidation of **1** with **5a** and **5b** in different solvents and in the presence of ^{18}O-isotope tracers. We propose here that the flexibility of **1** in solution allows transannular interactions between the sulfoxide oxygen atom and the reactive sulfur intermediates formed[13] after the initial attack of **5b** to the sulfide moiety in compound **1**, leading to monooxygenation products **2**. The relative population of the conformers of (**1**) in the equilibrium affects the composition of the oxidation products which depend to a large extent on the solvent polarity.

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TABLE 1. Product Distribution (%) in the Oxidation of Thianthrene 5-Oxide (SSO) (1) with Dioxiranes 5[a,b]

run	molar ratio **1/5**	solvent[c] (additive)	*trans*-**2**	**4**	*cis*-**2**	**3**	molar ratio **4/2**	molar ratio *trans***2**/cis-**2**
1[a]	5:1[a]	AC/DC	93.1		5.1	1.8		18.25
2	1:1	DC	77.4	18.0	4.3	0.3	0.22	18.00
3	3:1	DC	82.4	12.3	4.9	0.4	0.14	16.82
4	5:1	DC	86.1	8.8	4.8	0.3	0.10	17.94
5	1:1	CCl_4	42.2	47.1	10.1	0.7	0.90	4.18
6	3:1	CCl_4	54.0	31.9	13.0	1.0	0.48	4.15
7	5:1	CCl_4	63.9	19.7	15.1	1.2	0.25	4.23
8	1:1	DC/AN 15:85	78.6	19.7	1.4	0.3	0.25	56.14
9	3:1	DC/AN 15:85	86.9	11.1	1.6	0.4	0.13	54.31
10	5:1	DC/AN 15:85	90.3	7.3	1.6	0.8	0.08	56.44
11	5:1	DC/NM 15:85	89.1	10.1		0.8	0.11	
12	1:1	DC/TFE 15:85	91.7	3.6	4.6	0.1	0.04	19.93
13	3:1	DC/TFE 15:85	92.1	2.7	4.9	0.2	0.03	18.80
14	5:1	DC/TFE 15:85	93.6	1.3	5.0	0.1	0.01	18.72
15	3:1	AN/DC 90:10 (**6**, 50 equiv)	86.4	9.4	3.7	0.5	0.10	23.35
16	3:1	AN/DC 90:10 (**6**, 150 equiv)	88.2	7.4	4.0	0.4	0.08	22.05
17	3:1	AN/DC 90:10 (**6**, 250 equiv)	90.2	6.0	3.6	0.3	0.06	25.06
18	3:1	AN/DC 90:10 (**^{18}O-6**, 250 equiv)	89.7 (0.2)[d]	6.3	3.6 (4.4)[d]	0.4	0.07	24.92

[a] Reactions were carried out with **5b**, except that **5a** was used for run 1. [b] Reactions were carried out at 0 °C with an initial **1/5b** molar ratio of 5:1 and an initial substrate concentration of 0.01−0.05 M. Reactions were analyzed by HPLC. The values are the averages of at least three independent runs. [c] DC: dichloromethane, AC: acetone, AN: acetonitrile, TFE: 2,2,2-trifluoroethanol, NM: nitromethane. [d] Isotopic labeling was determined by HPLC/MS, and the eq $100 \times \{[(I + 2) - (I + 2)_{nat}]/[I + (I + 2)]\}$ was applied to the normalized relative intensities of the protonated molecular ions MH^+ (m/z = 249 for *trans*-**2** and *cis*-**2**).

Results and Discussion

Oxidation of Thianthrene 5-Oxide (1) with Dioxiranes (5). Oxidations were carried out at 0 °C by adding an aliquot of a solution of dioxirane[17] **5a** or **5b** in acetone or methylene chloride (initial concentration 0.01 M) to a solution of **1** in the corresponding solvent containing the additive indicated in each case. The results are shown in Table 1. Reaction mixtures were analyzed by HPLC and HPLC−MS under the conditions specified in the Experimental Section.

The oxidation of **1** with **5a** (run 1, Table 1) took place at the sulfide site, in good agreement with previous reports.[12] The reaction was highly stereoselective and led to the monooxygenation products *trans*-**2** and *cis*-**2** in a molar ratio of 18. Note the absence of detectable amounts of the double oxidation product **4** in this case.

While sulfones are the main oxidation products in the reaction of regular sulfides[13] with **5b** in polar aprotic solvents, the oxidation of **1** under similar conditions gives large amounts of the monooxygenation product **2**. Dioxygenation predominates, and **4** is only formed in reactions in carbon tetrachloride (run 5, Table 1). We observed significant differences in the distribution of the products under different reaction conditions. For instance, with an increase in the initial **1/5b** ratio from 1:1 to 5:1, the amounts of *trans*-**2** and *cis*-**2** obtained in methylene chloride increase at the expense of the formation of **4** (runs 2−4, Table 1). Under these conditions, the **4/2** ratio changes from 0.22 to 0.10. Interestingly, the *trans*-**2**/*cis*-**2** ratio remains nearly constant, with a value of 17 in several experiments (runs 2−4, Table 1). On the other hand, in other solvents such as carbon tetrachloride, acetonitrile, or nitromethane, we found significant differences in the **4/2** and/or *trans*-**2**/*cis*-**2** ratios (Table 1) depending on the reaction conditions. In carbon tetrachloride, the amount of dioxygenation product **4** increases with the concentration of **5b** (runs 5−7, Table 1). The **4/2** ratio was 0.90 for equimolar initial amounts of **1** and **5b**, while the use of a 5-fold excess of **1** led to a **4/2** ratio of 0.25 (runs 5−7, Table 1). In this solvent (CCl_4), the stereoselectivity measured by the value of the *trans*-**2**/*cis*-**2** ratio was only about 4. In contrast, in polar solvents such as acetonitrile and nitromethane, the oxidation of **1** follows the same pattern as in methylene chloride. While the observed **4/2** ratio in methylene chloride was similar to that in acetonitrile, the *trans*-**2**/*cis*-**2** ratio increased to 56 in the latter solvent (runs 8−10, Table 1). In nitromethane, the formation of *cis*-**2** was not detected (run 11, Table 1).

The amount of dioxygenation product **4** formed in 2,2,2-trifluoroethanol was 10 times less than that formed in methylene chloride (runs 12−14, Table 1). This solvent effect, although much less dramatic, follows the same trend as in the oxidation of simple sulfides.[13] Also, in this case, for greater values of the initial **1/5b** molar ratio, the **4/2** ratio decreases consistently within the series. On the other hand, the *trans*-**2**/*cis*-**2** ratio in 2,2,2-trifluoroethanol was about 19.

We also studied the oxidation of **1** with **5b** in acetonitrile with 50−250 equiv of 1,1,1-trifluoroacetone hydrate (**6**) added to the medium as a protic additive (runs 15−17, Table 1). Under these conditions, the **4/2** ratio decreased from 0.10 to 0.06 and the *trans*-**2**/*cis*-**2** ratio decreased to about 23, but this latter ratio remained roughly constant within the range of additive concentrations studied. This observation is somewhat unexpected if we consider the significant differences in the *trans*-**2**/*cis*-**2** selectivity found on going from methylene chloride to acetonitrile or nitromethane (runs 4, 10, and 11, Table 1).

Isotopic Tracer Experiments. The involvement of a hypervalent 10-S-4 sulfurane **II** intermediate in the oxidation of simple sulfides was clearly demonstrated[13] by ^{18}O-tracer isotopic experiments. We designed a series

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of parallel experiments to disclose whether the oxidation of **1** follows the same reaction mechanism. A 3-fold excess of **1** was treated with **5b** at 0 °C in acetonitrile/methylene chloride solution containing labeled trifluoroacetone hydrate (**6**-^{18}**O**, 49 atom % labeled) (250 equiv) (run 18, Table 1), which was obtained in situ by mixing equimolar amounts of $H_2{}^{18}O$ (Aldrich, 98 atom % labeled) and 1,1,1-trifluoroacetone in acetonitrile/dichloromethane solution at 0 °C. The incorporation of isotopic tracer into the oxidation products was determined by HPLC−MS and ascertained by GC−MS analysis.

The oxidation of **1** under these conditions led to a 4.4 ^{18}O atom % incorporation into the *minor* (3.6%) monooxygenation product *cis*-**2** and a 0.2 ^{18}O atom % incorporation into the main (89.7%) product *trans*-**2**. The presence of labeled **4** could not be detected. The incorporation of isotopic tracer is remarkably low compared to the results we obtained previously with simple sulfides under similar conditions.[13] In that study, methylphenylsulfide yielded 23 ^{18}O atom % labeled methylphenylsulfoxide and 6 ^{18}O atom % labeled methylphenyl sulfone.[13] The low isotopic tracer incorporation seen here indicates that hypervalent intermediates are involved in the oxidation of **1** with **5b**, but also suggests that some other factor(s) severely reduce the efficiency of the intermediate trapping process.

Conformational Mobility. The experimental results summarized above bring to our attention the following relevant issues in the oxidation of **1** with **5b**: (i) the main reaction is the stereoselective monooxygenation of the sulfide moiety, in clear contrast to the oxidation of simple sulfides, where dioxygenation prevails under identical reaction conditions; (ii) increasing the solvent polarity or introducing protic solvents or additives disfavors the formation of **4**; (iii) the *trans*-**2**/*cis*-**2** isomer ratio is solvent-dependent, and (iv) ^{18}O-label incorporation occurs almost exclusively in the *minor* monooxygenated product *cis*-**2**.

According to our mechanism[13] depicted in Figure 1, the formation of either mono- or dioxygenated products depends on the equilibrium constant between the zwitterionic and hypervalent intermediates **I** and **II** and the relative values of the rate constants for the β-elimination of ketone from **I** and the oxidation of the hypervalent intermediate **II** to give sulfone. The irregular behavior shown by **1** in this oxidation may be attributed to the particular structure of this compound, which inhibits the cyclization of **I** to **II** or favors the displacement of the equilibrium between these two species toward **I**.

The most striking structural feature of **1** is the endocyclic character of the sulfide and sulfoxide moieties. However, this by itself does not explain the unexpected reactivity of **1**, since the reaction of cyclic sulfides with **5b** also yields sulfones as the main product. The oxidation reactions of strained episulfides[18] or fenothiazine[13a] are examples of this behavior. Moreover, the direct conversion of episulfides into sulfones through a sulfurane intermediate is a trick for obtaining cyclic sulfones[18] with the sulfur atom embedded in a three-membered ring. It has also been reported [14] that the stability of sulfuranes actually increases when the hypervalent sulfur atom belongs to a five- or six-membered ring. In some cases, cyclic sulfuranes can be isolated and characterized.[14]

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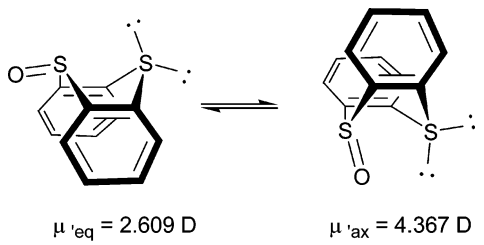

FIGURE 2. Conformational equilibrium of **1** in solution.

These data allowed us to exclude the possibility that geometric considerations might preclude the formation of the corresponding cyclic 10-S-4 sulfurane intermediate type **II** in the oxidation of **1** and prompted us to consider the effect of the sulfoxide group on the reactivity. In our previous study,[13] we found that, although the value of the sulfone/sulfoxide ratio decreases in the oxidation of simple sulfides in the presence of sulfoxides, sulfones are the main oxidation product in reactions performed in the presence of a 5-fold excess of DMSO in the medium.[13] In contrast, in the oxidation of **1** with an equimolecular amount of **5b** in methylene chloride, the **4/2** ratio was as low as 0.22 (run 2, Table 1). This ratio depends on the solvent and has a maximum value of 0.90 for the stoichiometric oxidation of **1** in carbon tetrachloride (run 5, Table 1). Consequently, the formation of **2** in preference to **4** cannot be related to any *intermolecular* interaction between the sulfoxide group in **1** and the postulated reaction intermediates type **I** and/or **II**. Therefore, we examined the possibility of a *transannular* interaction between the sulfoxide group and the proposed intermediates **I** and/or **II** promoted by the conformational mobility of **1**. Although early studies[19] indicated that related compounds such as the parent thianthrene and its dioxides *trans*-**2** and *cis*-**2** show conformational mobility in solution, this factor has been systematically ignored in the previous use of **1** as a mechanistic probe since it was described as a single conformation represented by the rigid boat structure $\mathbf{1}'_{\mathbf{eq}}$, with the oxygen atom placed at the bowsprit position.

In a forthcoming paper,[15] we provide evidence for the conformational mobility of **1** on the basis of apparent dipolar moment measurement and ^{1}H NMR spectra. Compound **1** can be depicted in two equilibrating boat-type limit conformations with the oxygen atom placed either in a pseudoequatorial ($\mathbf{1}'_{\mathbf{eq}}$) or pseudoaxial ($\mathbf{1}'_{\mathbf{ax}}$) position (Figure 2). Switching between these limit conformations occurs through a planar form by flapping of the aromatic rings. Only the flagpole oxygen atom in conformation $\mathbf{1}'_{\mathbf{ax}}$ has the correct orientation to originate *transannular* interactions with the opposite sulfur atom. The sulfoxide moiety in conformation $\mathbf{1}'_{\mathbf{eq}}$ is sterically crowded by the presence of the aromatic *peri*-C−H bonds. In conformation $\mathbf{1}'_{\mathbf{ax}}$, electronic repulsion exists between the flagpole sulfoxide group and the *cis* electron lone pair of the sulfide-type opposite sulfur atom. Theoretical

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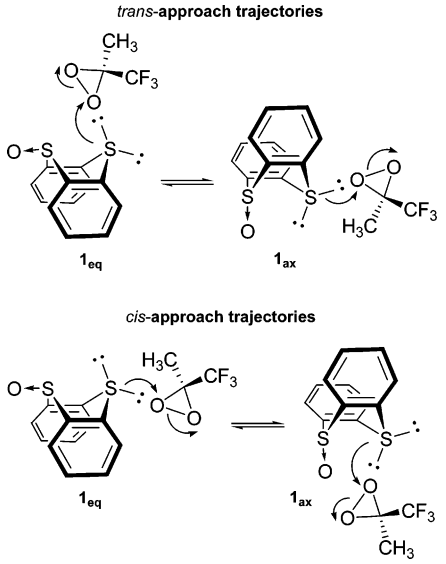


FIGURE 3. Approach trajectories of **5b** on to the conformations $\mathbf{1}_{eq}'$ and $\mathbf{1}_{ax}'$.

calculations[16] show the existence of two potential energy minima that correspond to these conformations, $\mathbf{1}_{eq}'$ being 3,8−6,8 kcal mol^{-1} more stable than $\mathbf{1}_{ax}'$ and predict an activation energy of 3.8−7.4 kcal mol^{-1} for the ring inversion of **1**. MOPAC PM3 semiempirical calculations give values of 2.609 and 4.367 D for the dipole moments of $\mathbf{1}_{eq}'$ and $\mathbf{1}_{ax}'$, respectively. Accordingly, we have found[15] that the relative populations of each conformer depend on the polarity of the solvent, the more polar conformer $\mathbf{1}_{ax}'$ being favored in the more polar solvent.

Therefore, to explain the singular reactivity of **1** with **5b** we must take into account the stereoelectronic factors in the course of the reaction for both limit conformations and especially the involvement of *transannular* interactions between the flagpole oxygen and the reacting sulfide group.

Zwitterionic Intermediates: Stereochemistry and Transannular Interactions. The conformational equilibrium described above and the presence of two diasterotopic sulfide lone electron pairs allow us to define two limit approach trajectories for **5b** to attack the sulfide-type sulfur atom in **1**. We will define these approaches as *cis*-trajectory and *trans*-trajectory (Figure 3) according to the position of the sulfoxide oxygen. Molecular models show that the *trans*-trajectory in conformation $\mathbf{1}_{eq}'$ occurs relatively free from steric hindrance, while the *cis*-attack is hindered by aromatic C_1−H and C_9−H bonds. Consequently, conformation $\mathbf{1}_{eq}'$ is expected to preferably react with **5b** by the lone electron pair *trans* to the sulfoxide S−O bond (Figure 3).

This prediction is supported by the results of the oxidation of *cis*-**2** and *trans*-**2** with peroxometal complexes.[2a] In this case, the value of the rate constant ratio $k_{ax}'/k_{eq}' = 3$ was attributed to the steric hindrance by aromatic *peri* C−H bonds of the equatorial approach of the reagent to the substrate. Moreover, it should be emphasized that oxidations with dioxiranes are particularly sensitive to steric effects. On the other hand, the pseudoaxial orientation of the oxygen atom in conformation $\mathbf{1}_{ax}'$ will prevent the approach of **5b** to the *cis* electron pair of the sulfide moiety while the *trans*-trajectory, shielded by the C_1−H and C_9−H bonds of the aromatic rings, is the less-hindered approach in this case. These qualitative considerations suggest the preference of a *trans*-attack for both conformers. In addition, $\mathbf{1}_{eq}'$ and $\mathbf{1}_{ax}'$ should show roughly the same reactivity toward the equatorial attack.

In the first step, the electrophilic attack of the sulfide moiety in **1** by **5b** occurs with the formation of a covalent S−O bond to give a set of zwitterionic intermediate isomers *cis*-**7** and *trans*-**7** (Scheme 2). The two limit conformations $\mathbf{7}_{ax}'$ and $\mathbf{7}_{eq}'$ for each stereoisomer differ with regard to the orientation of the sulfoxide oxygen atom (pseudoaxial or pseudoequatorial). As described above, formation of the *trans*-**7** couple should be preferred independent of the conformation, $\mathbf{1}_{ax}'$ or $\mathbf{1}_{eq}'$, of the starting substrate.

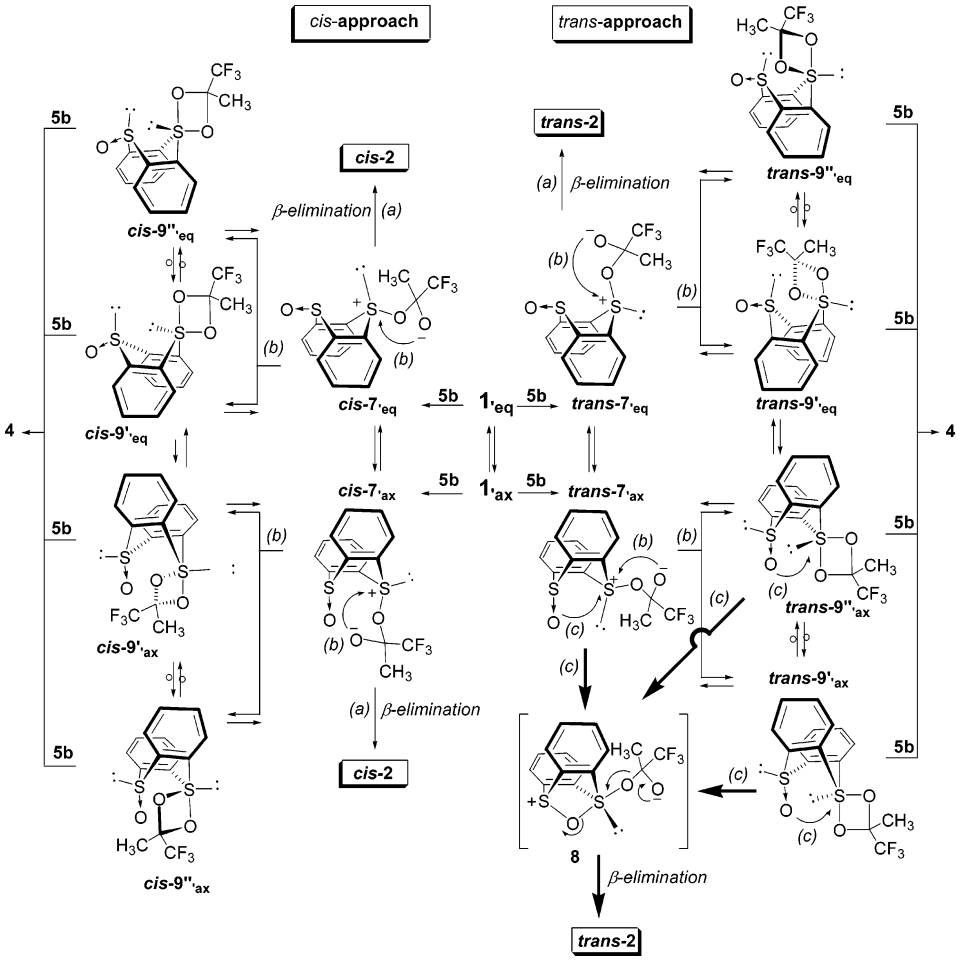
According to the general mechanism[13] depicted in Figure 1, β-elimination of trifluoropropanone from **I** affords sulfoxide while intramolecular interaction of the alkoxysulfonium sulfur atom and the alkoxide oxygen atom derived from **5b** should give rise to the formation of hypervalent sulfur intermediates **II**. These reaction routes are indicated in Scheme 2 as via *a* and *b*. However, the oxidation of **1** is quite complex compared to the oxidation of simple sulfides, since the alkoxysulfonium sulfur atom in *trans*-**7** has two proximate nucleophiles with which it can interact; i.e., the alkoxide oxygen (via *b*, Scheme 2) and the transannular sulfoxide oxygen atoms (via *c*, Scheme 2). Isomer *trans*-$\mathbf{7}_{ax}'$ is particularly well-suited for transannular interaction (Scheme 2) to give a hypervalent sulfur intermediate **8**. This reaction seems very likely to occur if we consider that **8** results from attack on the sulfonium−sulfur atom by the entering nucleophile following a trajectory *antiperiplanar* to the best electron-acceptor bond, that is, the covalent S−O bond.[20] Species **8**, due to the apical disposition of the oxygenated ligands, will be prone to undergo β-elimination of 1,1,1-trifluoroacetone, with simultaneous scission of the hypervalent S−O bond involving the transannular sulfoxide group (Scheme 2). The orientation of the oxygen atom transferred relative to the flagpole sulfoxide oxygen atom in *trans*-$\mathbf{7}_{ax}'$ remains unchanged during the transannular interaction process. Isomer *trans*-$\mathbf{7}_{eq}'$ could follow the same reaction path after ring inversion. According to our mechanism, the formation of **8** promotes the β-elimination of 1,1,1-trifluoroacetone and constitutes a route to the monooxygenation of **1**, which is not seen in the oxidation of simple sulfides.

In contrast, a similar transannular interaction in *cis*-$\mathbf{7}_{ax}'$ is unlikely due to stereoelectronic considerations (Scheme 2). The attack on the alkoxysulfonium sulfur atom by the flagpole oxygen atom would be in this case *antiperiplanar* to the lone electron pair, which would consequently be forced to the unfavorable apical position in the resulting 10-S-4 sulfurane.[14] Accordingly, transannular interactions should not promote the β-elimination of trifluoroacetone in *cis*-**7**.

Hypervalent Intermediates: Stereochemistry and Transannular Interactions. On the other hand, by

(20) (a) Zhang, J.; Saito, S.; Koizumi, T. *J. Org. Chem.* **1998**, *63*, 9375. (b) Zhang, J.; Saito, S.; Koizumi, T. *J. Am. Chem. Soc.* **1998**, *120*, 1631. (c) Martin, J. C.; Balthazor, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 152. (d) Balthazor, T. M.; Martin, J. C. *J. Am. Chem. Soc.* **1975**, *97*, 5634. (e) Tullock, C. W.; Coffman, D. D.; Muetterties, E. L. *J. Am. Chem. Soc.* **1964**, *86*, 357.

SCHEME 2. Reaction Pathways in the Oxidation of 1 with 5b



analogy with the case of regular sulfides, the sulfonium and alkoxide moieties of **7** should interact to yield a set of hypervalent sulfurane intermediates (via *b*, Scheme 2). These intermediates are named *trans*-**9′**$_{ax}$, *trans*-**9′**$_{eq}$, *cis*-**9′**$_{ax}$, and *cis*-**9′**$_{eq}$ according to the relative orientations of the covalent sulfurane S−O bond and the sulfoxide oxygen atom. The attack on the sulfonium-sulfur atom by the entering nucleophile follows in this case a trajectory *antiperiplanar* to the sulfur−carbon bond. Thus, the alkoxide oxygen atom in the parent **7** and one of the aryl groups are the apical ligands integrated in the hypervalent bond of **9** in the resulting trigonal bipyramid (TBP), while the unreacted lone electron pair occupies an equatorial TBP position.[14] Excluding from our consideration the methyl and trifluoromethyl substituents in the sulfurane ring, each isomer **9** can be depicted in two limit conformations, **9′** and **9″**, which are mirror images of each other and related by pseudorotation[14] around the hypervalent sulfur atom (Scheme 2). Although the apical and equatorial oxygen atoms in the cyclic sulfuranes **9** are exchanged by pseudorotation, *cis*−*trans* isomerization cannot occur since it would involve an arrangement with the lone electron pair in an apical position.[14] Consequently, the *cis* or *trans* orientation of the covalent TBP-equatorial S−O bond relative to the sulfoxide oxygen atom is defined in the diastereoselective oxidation of **1′**$_{eq}$ and **1′**$_{ax}$ and remains unchanged throughout the pseudorotation process.

Any eventual fragmentation of sulfuranes **9** to give sulfoxides **2** will take place through **7** by dissociation of the strongly polarized hypervalent S−O bond and with the negative charge density at the oxygen atom acting as a driving force to promote the β-elimination of 1,1,1-trifluoropropanone (Scheme 2 and Figure 1). It is important to emphasize that on the basis of regular sulfurane chemistry only the apical S−O bond will be broken, and hence, the oxygen atom incorporated in this way into **2** must originate from the covalent S−O bond in the parent sulfurane **9**. The *cis*−*trans* configurational stability of these intermediates ensures that sulfoxide *trans*-**2** arises in any case from *trans*-**7** while *cis*-**7** is the precursor of sulfoxide *cis*-**2**.

It is possible to consider a conformational equilibrium for these intermediates similar to the ring flapping in **1** by inversion of the boatlike sulfurane conformations (Scheme 2). This equilibrium would allow the conformational exchange of *trans*-**9′**$_{eq}$ with *trans*-**9′**$_{ax}$ and *cis*-**9′**$_{eq}$ with *cis*-**9′**$_{ax}$. In the second case, the most favorable conformation is *cis*-**9′**$_{eq}$ due to the repulsive interaction of the flagpole oxygen atoms in the structure *cis*-**9′**$_{ax}$. For sulfuranes *trans*-**9**, it is hard to predict the position of the equilibrium based on a simple inspection of the models.

We must also consider the involvement of the transannular sulfoxide group in the sulfoxide-assisted decomposition of **9**. This possibility depends on the orien-

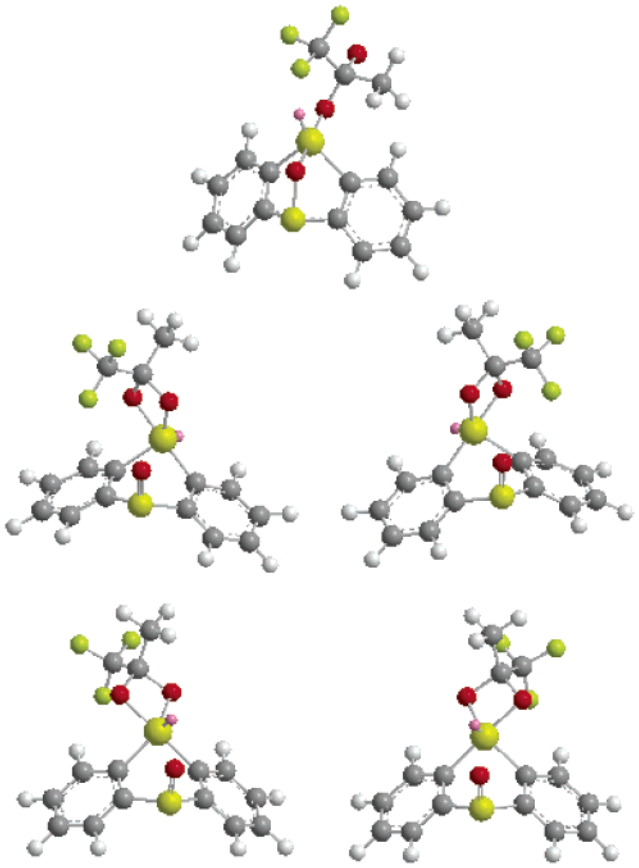
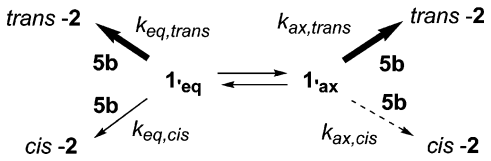


FIGURE 4. Selected molecular models for intermediate sulfuranes **8** and **9**.

tation of the sulfoxide oxygen atom relative to the covalent S−O bond in **9**. Sulfurane *trans*-**9**$'_{ax}$ fulfills the stereoelectronic requirements[14,20] to undergo this process (see Scheme 2 and Figure 4). The nucleophilic substitution through an associative mechanism on hypervalent 10-S-4 species[14] proceeds in the equatorial plane along a trajectory *anti* to the best acceptor equatorial bond to give a new pentacoordinate hypervalent intermediate with the new ligand at the equatorial position. The apical leaving group in this hypervalent intermediate is subsequently lost with the simultaneous rearrangement of ligands. In the case of sulfuranes *trans*-**9**$'_{ax}$, this process leads to *trans*-**2** through the intermediate species **8** (Scheme 2). In this way, the resulting new sulfoxide will incorporate the TBP-equatorial oxygen atom corresponding to the covalent S−O bond in the parent sulfurane *trans*-**9**$'_{ax}$. Consequently, the transannular oxygen-assisted opening of *trans*-**9**$'_{ax}$ yields exclusively *trans*-**2**. Conversely, stereoelectronic restraints prevent a similar transannular interaction in *cis*-**9**, since the attack of the sulfurane moiety by the sulfoxide oxygen atom would be in this case *antiperiplanar* to the lone electron pair (Scheme 2). As a consequence, this mechanism cannot contribute to the formation of *cis*-**2**.

The oxidation of sulfuranes **9** by **5b** leads to the formation of sulfone **4**. While the product **4**/**2** ratio decreases as the **1**/**5b** ratio increases, the *trans*-**2**/*cis*-**2** isomers ratio remains roughly unchanged (see Table 1). These data suggest that the double-oxygenation product **4** is obtained by oxidation of both sulfuranes *trans*-**9** and

SCHEME 3. Simplified Kinetic Scheme



cis-**9**. The unexpectedly poor conversion to **4** suggests the importance of routes leading to the formation of intermediate **8**, i.e., direct trapping of the zwitterionic alkoxysulfonium intermediate *trans*-**7**$'_{ax}$ by the transannular sulfoxide and sulfoxide-assisted ring-opening of *trans*-**9**$'_{ax}$ (Scheme 2).

Solvent Effects. According to our model, the *trans*-**2**/*cis*-**2** isomer ratio will be solvent-dependent, since the polarity of the solvent modifies the position of the conformational equilibrium of **1** and each conformer differs in reactivity toward **5b**. If we do not consider the formation of sulfone **4**, the kinetic course of the reaction can be simplified as depicted in Scheme 3. This system can be analyzed in terms of the Curtin−Hammett principle[21] provided that the values for the rate constants for the exchange of conformers **1**$'_{ax}$ and **1**$'_{eq}$ are much higher than those for the formation of the alkoxysulfonium intermediates **7**. To further simplify, we assume that **1**$'_{ax}$ undergoes only *trans*-attack.

The rate equations can be written as follows:

$$\mathrm{d}[\textit{trans}\text{-}\mathbf{2}]/\mathrm{d}t = k_{ax,t}[\mathbf{1}'_{ax}][\mathbf{5b}] + k_{eq,t}[\mathbf{1}'_{eq}][\mathbf{5b}] \quad (2)$$

$$\mathrm{d}[\textit{cis}\text{-}\mathbf{2}]/\mathrm{d}t = k_{eq,c}[\mathbf{1}'_{eq}][\mathbf{5b}] \quad (3)$$

and

$$\mathrm{d}[\textit{trans}\text{-}\mathbf{2}]/\mathrm{d}[\textit{cis}\text{-}\mathbf{2}] = (k_{ax,t}[\mathbf{1}'_{ax}] + k_{eq,t}[\mathbf{1}'_{eq}])/k_{eq,c}[\mathbf{1}'_{eq}] \quad (4)$$

By integration of this expression, considering that $K_{SSO} = [\mathbf{1}'_{ax}]/[\mathbf{1}'_{eq}]$, we have

$$[\textit{trans}\text{-}\mathbf{2}]/[\textit{cis}\text{-}\mathbf{2}] = (k_{ax,t}/k_{eq,c})\,K_{SSO} + k_{eq,t}/k_{eq,c} \quad (5)$$

If we assume that the reactivity of the pseudoequatorial electron pair is the same in conformations $\mathbf{1}_{ax}$ and $\mathbf{1}_{eq}$ ($k_{ax,t}/k_{eq,c} = 1$), then we have

$$[\textit{trans}\text{-}\mathbf{2}]/[\textit{cis}\text{-}\mathbf{2}] \approx K_{SSO} + k_{eq,t}/k_{eq,c} \quad (6)$$

On the basis of this equation, the diastereoselectivity of the oxidation reaction depends directly on the conformational equilibrium constant K_{SSO} and the relative oxidation rate of the diasterotopic lone electron pairs of the sulfide moiety in **1**$'_{eq}$. Note that the attack of **1**$'_{eq}$ by **5b** to give *trans*-**2** is the fastest process in Scheme 3, while the route to this compound from **1**$'_{ax}$ is hindered by the *peri*-C−H bonds. If we assume that the ratio $k_{eq,t}/k_{eq,c}$ is not significantly dependent on the solvent, according to eq 6 the conformational equilibrium (K_{SSO}) determines the *trans*-**2**/*cis*-**2** isomer ratio observed for each solvent.

(21) Seeman, J. I., *Chem. Rev.* **1983**, *83*, 83

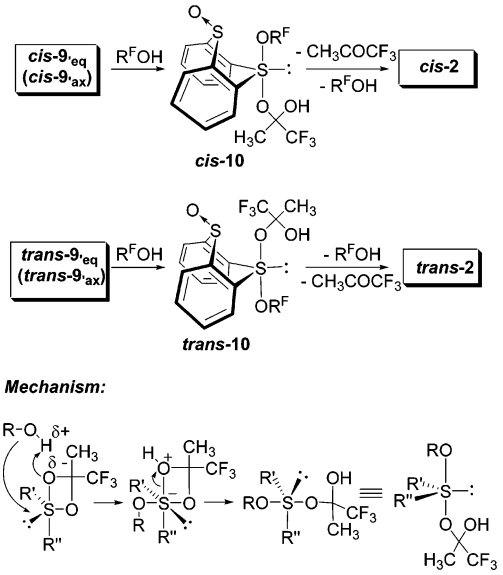
In compound **1**, the conformational equilibrium is displaced toward the conformer $\mathbf{1}_{ax}$ when the polarity of the solvent increases as shown by dipole moment and ^{1}H NMR measurements.[15] Consequently, according to our model, the *trans*-**2**/*cis*-**2** product ratio decreases in less-polar solvents, which is in good agreement with the experimental results (see Table 1). For instance, with an initial **1**/**5b** ratio of 5:1, the values found for the *trans*-**2**/*cis*-**2** isomer ratio in acetonitrile ($\mu = 3.92$ D), methylene chloride ($\mu = 1.14$ D), and carbon tetrachloride ($\mu = 0.0$ D) were 56.17, 17.59, and 4.22, respectively. For comparison, in the reaction of **1** with **5a** in acetone solution ($\mu = 2.69$ D), the *trans*-**2**/*cis*-**2** ratio was 18.25.

The value of the equilibrium constant K_{SSO} in *n*-hexane has been estimated[15] as 0.45 on the basis of the averaged dipolar moment measured in this solvent and the dipolar moments calculated for each conformer. If we assume that the value of the equilibrium constant K_{SSO} is similar in *n*-hexane and carbon tetrachloride ($K_{SSO} = 0.45$) and if we substitute this value and the average value (4.18) of the *trans*-**2**/*cis*-**2** ratio (runs 5−7 in Table 1) into eq 6, we can estimate the reactivity of the pseudoequatorial lone pair of $\mathbf{1_{eq}}$, measured by the value of ratio $k_{eq,t}/k_{eq,c}$, to be 3.73 times the reactivity of the pseudoaxial pair. This estimation agrees well with the differences in the steric constraints for each diasterotopic electron pair and also with experimental data reported by other authors[2b] concerning the oxidation of **1** with other oxidants.

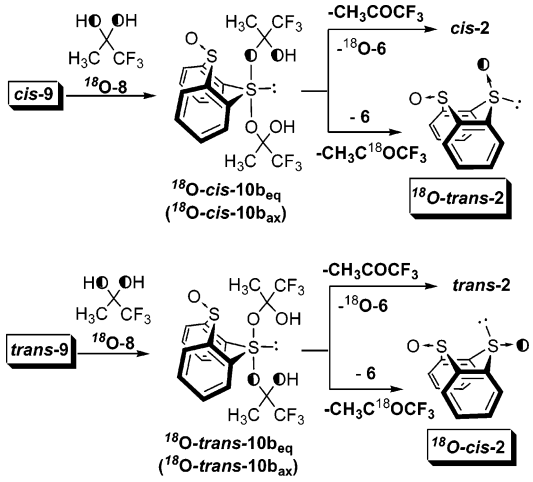
Our model also explains why the **4**/**2** ratio depends on the solvent and decreases when the polarity increases. Polar solvents favor ionization of the hypervalent S−O bond, which precedes the β-elimination of trifluoroacetone to give the monooxygenation product **2**. Conversely, a more efficient oxidation of **9** is achieved in apolar solvents, with a corresponding increase in dioxygenation product **4**.

Effect of Acidic Additives and Isotope Labeling of *cis*-2. Sulfuranes characteristically react with acids to give ligand exchange processes at the hypervalent sulfur atom.[14,22] We have previously used[13] this typical reaction to detect sulfuranes **II** as intermediates in the oxidation of simple sulfides by isotopic labeling. The reaction mechanism involves protonation of the highly basic apical oxygen ligand in the TBP structure followed by nucleophilic addition of alcohol *anti* to the best electron acceptor TBP-equatorial bond. Loss of the apical substituent and rearrangement gives a new 10-S-4 sulfurane (Scheme 4). Now, let us consider the reaction of **1** with **5b** in the presence of 2,2,2-trifluoroethanol. Ligand exchange in **9** will give a set of secondary 10-S-4 sulfuranes **10a** that are asymmetrically substituted in the TBP-apical positions. The former equatorial alkoxy substituent of hemiacetal nature in sulfurane **9** derived from dioxirane **5b** is now placed at an apical position of **10a**, and its relative stereochemistry with regard to the sulfoxide oxygen atom is preserved during the ligand exchange reaction (Scheme 4). Sulfuranes **10a** should

SCHEME 4. Ligand Exchange Reactions



SCHEME 5. Isotopic Tracer Incorporation



decompose readily by β-scission with a loss of trifluoroacetone into the corresponding sulfoxide **2**. Also under these conditions, *cis*-**2** and *trans*-**2** are produced selectively from *cis*-**9** and *trans*-**9**, respectively (Scheme 4).

Alternatively, secondary sulfuranes **10a** could be oxidized further by a second equivalent of **5b** to give sulfone **4**. However, **10a** will be less reactive toward **5b** than **9** since it has two apical alkoxy ligands which more efficiently delocalize the electron density.[13] Consequently, less sulfone **4** is obtained under these conditions (see Table 1).

On the other hand, the reaction of **1** and **5b** in acetonitrile in the presence of ^{18}O-trifluoroacetone hydrate (**^{18}O-6**) (run 18, Table 1) is very selective and gives **^{18}O-*cis*-2** as the main labeled product. The above considerations regarding the stereochemistry of the oxidation and subsequent ligand exchange reaction allow us to explain this result. Ligand exchange between sulfuranes *trans*-**9** and *cis*-**9** with **^{18}O-6** will produce new *stereospecifically labeled* sulfuranes **^{18}O-10b**, which differ in the orientation of the labeled ligand (Scheme 5). In this particular case, both TBP-apical ligands have an identical hemiacetal nature and are equally well suited to transfer

(22) (a) Adzima, L. J.; Duesler, E. N.; Martin, J. C. *J. Org. Chem.* **1977**, *42*, 4001. (b) Martin, L. D.; Martin, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 3511. (c) Martin, J. C.; Franz, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 583. (d) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604. (e) Franz, J. A.; Martin, J. C. *J. Am. Chem. Soc.* **1973**, *95*, 2017. (f) Martin. J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 5003. (g) Perozzi, E.; Martin, J. C. *J. Org. Chem.* **1977**, *42*, 3222.

oxygen to the sulfur by the β-elimination of ketone. In this way, **^{18}O-*trans*-2** is formed exclusively from sulfurane *cis*-**9** while **^{18}O-*cis*-2** is derived from sulfurane *trans*-**9**. The proportion of labeled **^{18}O-*cis*-2** observed in the oxidation of **1** is low compared with the formation of labeled sulfoxides in the oxidation of simple sulfides with **5b** under similar reaction conditions.[13] This strongly suggests again that the transannular interaction of the sulfoxide moiety with the reaction intermediates *trans*-**7** and *trans*-**9** is very efficient and prevails over the intermolecular ligand exchange reaction with **^{18}O-6**.

Sulfuranes derived[22g] from thianthrene, fenothiazine, and oxathiazine with alkoxy groups at the TBP-apical positions exist as mixtures of conformers in rapid equilibrium. In the case of sulfuranes **10b**, the conformational equilibrium will be displaced toward the conformation with the sulfoxide oxygen atom in the pseudoequatorial position. In any case, geometric considerations in **10b** preclude the transannular displacement of ligands by the nucleophilic sulfoxide oxygen since, as stated above, the attack on the hypervalent sulfur by the nucleophile cannot occur *antiperiplanar* to the lone electron pair in the TBP arrangement. The hemiacetal ligands in sulfuranes **^{18}O-10b** are diasterotopic and, probably, the elimination of 1,1,1-trifluoroacetone from the ligand facing the aromatic C−H will be rapid since it proceeds with a relief of steric strain. Interestingly, we observed a decrease in the *trans*-**2**/*cis*-**2** ratio in oxidations carried out in acetonitrile in the presence of **^{18}O-6** (runs 8−10 and 15−18, Table 1). This fact strongly suggests that sulfurane **^{18}O-10b** offers another way to obtain *cis*-**2** from *trans*-**9**.

Conclusions

The formation of monooxygenation products **2**, the dependence of the *trans*-**2**/*cis*-**2** ratio on the solvent and the selective labeling of the minor reaction product *cis*-**2** in ^{18}O-isotopic tracer experiments in the oxidation of the mechanistic probe thianthrene-5-oxide **1** with TFDO (**5b**) can be fully explained in terms of the mechanism we previously proposed[13] for the oxidation of sulfides with dioxiranes **5** (Figure 1). The conformational mobility of **1**, as demonstrated by dipole moment measurements and NMR experiments in different solvents, and which has been systematically ignored since its introduction as a mechanistic probe in 1984, allows us to envisage the interaction of the transannular sulfoxide group with the reactive intermediates formed on the sulfide moiety, which shifts the oxidation toward the formation of **2**.

The different reactivities of the diasterotopic electron lone pairs of the sulfide group in conformations $\mathbf{1'_{ax}}$ and $\mathbf{1'_{eq}}$ and the stereochemical course of the ligand exchange reaction in 10-S-4 sulfuranes allow us to account for the experimental results.

With regard to the application of SSO (**1**) as a mechanistic probe for assessing the electronic nature of an oxidant, our results show that the oxidation mechanism involved as well as the conformational mobility of **1** and the eventual neighboring group participation of the sulfoxide moiety cannot be disregarded otherwise the experimental results could lead to misleading interpretations. Therefore, the conclusions reached over the past two decades through the application of SSO mechanistic probe should be reconsidered.

Experimental Section

General Methods. Solvents and reagents were purified by standard procedures.[23] 9-Fluorenone recrystallized from ethanol was used as an internal standard for HPLC analysis. Thianthrene 5-oxide (**1**), thianthrene 5,10,10-trioxide (**4**), and thianthrene 5,5,10,10-tetraoxide (SO_2SO_2) were prepared by the oxidation of thianthrene with *m*-chloroperbenzoic acid.[2a] *trans*-Thianthrene 5,10-dioxide *(trans*-**2**) and *cis*-thianthrene 5,10-dioxide (*cis*-**2**) were prepared by the oxidation of **1** with hydrogen peroxide in acid media.[2a] Thianthrene 5,5-dioxide (**3**) was prepared by the oxidation of **1** with $KMnO_4$ in acetone.[2a] Dichloromethane solutions of methyl(trifluoromethyl)dioxirane (**5b**) free of 1,1,1-trifluoropropanone, and acetone solutions of dimethyldioxirane (**5a**) were prepared as previously reported.[16] Dioxirane solutions were carefully dried over anhydrous magnesium sulfate prior to use. 1,1,1-Trifluoropropanone for the synthesis of methyl(trifluoromethyl)dioxirane was purchased from Fluorochem and distilled from concentrated H_2SO_4 before use. Caroate triple salt 2 $KHSO_5$−$KHSO_4$−K_2SO_4 was purchased from Fluka. $H_2{}^{18}O$ (98 atom %) was purchased from Aldrich and used as received.

Product Analysis. HPLC analyses were carried out using a Lachrom (Merck-Hitachi) chromatograph equipped with a UV−vis detector at 254 nm and a RP-18 reversed-phase column (25 cm, 5 μm, 4.6 mm, 1.2 mL min^{-1}) with 64:34:2 methanol/water/acetonitrile as the eluent, as reported elsewhere.[12] Response factors for the reaction products were determined using 9-fluorenone as an internal standard (*trans*-**2**, 1.00; *cis*-**2**, 1.05; **3**, 0.10; **4**, 1.27; **1**, 0.65). HPLC−MS analyses were carried out in an Agilent HPLC 1100 equipped with a Zorbax C-18 column (15 cm, 5 μm, 2.1 mm, 0.2 mL min^{-1}, 64:34:2 methanol/water/acetonitrile, 254 nm) coupled to a quadrupolar mass spectrometer (Agilent MSD 1100) using $APCI^+$ as the ionization method (vaporizer at 350 °C, nitrogen flow at 4 l min^{-1}, nebulizer pressure at 60 psi, capillary voltage at 4000 V and corona discharge at 4 mA).

Reaction of Thianthrene 5-Oxide (1) with Dioxiranes 5b. General Procedure. A solution of thianthrene 5-oxide (**1**) and 9-fluorenone as an internal HPLC standard in 2 mL of the selected solvent (dichloromethane, carbon tetrachloride, acetone, acetonitrile, 2,2,2-trifluoroethanol, nitromethane) (initial concentration from 0.01 to 0.05 M), at 0 °C, was treated with an aliquot of a thermostated 0.06−0.08 M acetone solution of DMDO (**5a**) or a 0.3−0.6 M ketone-free methylene chloride solution of TFDO (**5b**) (ca. 0.20 M) (dioxirane initial concentration 0.01 M) (see Table 1). Reactions were carried out under an inert atmosphere in the dark. After 10 min, the solvents were removed under vacuum and the residue was redissolved in methanol/water/acetonitrile 64:34:2 and analyzed by HPLC and HPLC−MS under the conditions described above. Conversions were determined by comparison with the t_0 chromatograms; yields were calculated accordingly using the response factors of the products (see Table 1).

Reaction of Thianthrene 5-Oxide (1) with Methyl(trifluoromethyl)dioxirane (5b) in the Presence of 1,1,1-Trifluoropropanone-^{18}O Hydrate (6-^{18}O). 1,1,1-Trifluoro-2-propanone-*^{18}O* hydrate (**6**-*^{18}O*) was generated in situ by adding, at 0 °C under an inert atmosphere, 0.14 mL (7.5 mmol) of water-*^{18}O* (98 atom %) to a solution of 0.71 mL of 1,1,1-trifluoropropanone (7.5 mmol) in acetonitrile (2 mL) and dichloromethane (0.25 mL). The reaction mixture was vigorously stirred at 0 °C for 30 min and then analyzed by mass spectrometry (EI^+, 70 eV and 200 °C ion source temperature). Incorporation of the isotopic label was determined from the ion m/z = 95 $[CF_2COOH]^+$ by applying the equation

(23) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd Ed.; Pergamon: New York, 1998.

$$^{18}\text{O-atom } \% = 100 \times \{[(I+2) - (I+2)_{nat}] + [(I+4) - (I+4)_{nat}]/[I + (I+2) + (I+4)]\}$$

The values $(I + 2)_{nat}$ and $(I + 4)_{nat}$ were the averages of at least three independent analyses of 1,1,1-trifluoropropanone hydrate. To this solution were added 15 mg (0.065 mmol) of thianthrene 5-oxide (**1**) and then 0.36 mL of a thermostated and dried 0.06 M methylene chloride solution of TFDO (**5b**) free of 1,1,1-trifluoroacetone (0.022 mmol) at 0 °C. After 20 min, the solvents were removed under vacuum, and the residue was redissolved in methanol/water/acetonitrile 64:34:2 and analyzed at least three times by HPLC−MS under the conditions described above (see entry 18, Table 1).

Acknowledgment. Financial support from the Dirección General de Investigación (MCYT) Project BQU2003-00315 is gratefully acknowledged. We thank SCSIE (UV) and STI (UA) for access to instrumental facilities. J.R. thanks the Spanish Ministerio de Ciencia y Tecnología for a fellowship.

JO0483062