

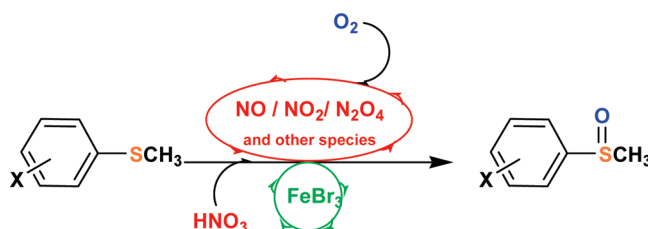
Mechanism of the Selective Sulfide Oxidation Promoted by HNO₃/FeBr₃

Claudio O. Kinen, Laura I. Rossi,* and Rita H. de Rossi*

Instituto de Investigaciones en Físico Química de Córdoba (INFIQC), Departamento de Química Orgánica,
Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, X5000HUA
Córdoba, Argentina

ritah@fcq.unc.edu.ar; lauraros@fcq.unc.edu.ar

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The oxidation of aryl methyl sulfides containing electron withdrawing and electron donating groups (*p*-NO₂, *p*-CHO, *p*-NCS, *p*-Br, H, *p*-CH₃, *p*-OCH₃) was carried out in homogeneous solution in acetonitrile in the presence of catalytic amounts of HNO₃ and FeBr₃. The FeBr₃ is required for the reaction to proceed for compounds with strongly electron withdrawing groups (*p*-NO₂ and *p*-CHO) but is not necessary in the case of all the other compounds, although in the latter cases the yield decreases considerably. The rate of the reaction was measured as a function of substrate, FeBr₃ and HNO₃ concentration. From the experimental data a mechanism is suggested where there are two reaction pathways, one involving the formation of a ternary complex between the substrate, FeBr₃ and NO₃⁻ and one involving a complex formed between the sulfide and the HNO₃. From these complexes HNO₂ is generated, which then combines with HNO₃ to yield N₂O₄, initiating a catalytic cycle where the sulfide is oxidized and O₂ from the air is stoichiometrically consumed.

Introduction

Sulfoxides and other organosulfur compounds are important synthetic intermediates in organic chemistry¹ and are valuable in the preparation of biologically and pharmaceutically relevant materials.^{2,3} One of the oxidation reactions found in pharmaceutical research and production is that of a sulfide to a sulfoxide, which is achieved with a very wide variety of reagents.³ When there are several different functional groups present in a molecule as in esomeprazole,⁴ a sulfoxide-containing drug, chemoselective transformations are of great significance. This has often been difficult in sulfoxidation

chemistry because oxidations of other functional groups can take place simultaneously.⁵ Furthermore, sulfoxides can undergo overoxidation to sulfones and therefore it is important that the catalyst has a low reactivity toward the sulfoxides.⁶

Considering the interest in the development of synthetic methods for the selective conversion of sulfides to sulfoxides,^{7,8}

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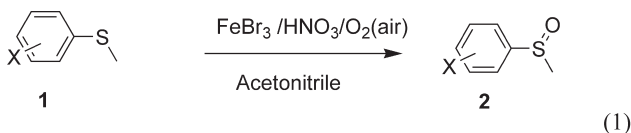
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we are currently engaged in the study of reaction methodologies to achieve chemoselective sulfoxidation reactions.^{9,10} In a previous paper,¹¹ we reported on the synthesis, characterization, and catalytic activity of several cyclodextrin-FeBr₃ (CD-Fe) complexes. We found that CD-Fe complexes, in the presence of a catalytic amount of [Fe(NO₃)₃·9H₂O] as oxidant, reacted with sulfides giving excellent yields of the corresponding sulfoxides. Furthermore, these complexes can be reused several times. These reactions were performed by recycling the solid CD-Fe complexes while the substrate, iron(III) nitrate, and the organic solvent were renewed.^{11b}

Complexes with cyclodextrins are of particular interest because of the possibility of inducing enantiomeric excess.¹² We reported that substrates with various highly oxidizable functions such as isothiocyanate or aldehyde remain unchanged under the reaction conditions used.¹⁰ In addition, the methodology proposed for the oxidation of sulfides fulfills several of the green chemistry principles since the oxidant is oxygen from the air, the reactions are highly selective producing minimum waste, and the catalyst is a noncontaminating metal.¹³

To obtain more insight into the mechanism of these reactions, we performed a kinetic study of the sulfoxidation reaction of sulfides **1a–g** (eq 1) in acetonitrile using catalytic amounts of FeBr₃ and HNO₃ as oxidation promoters. The results clearly indicate that the oxygen from the air is the species used in stoichiometric amounts whereas FeBr₃ plays a prominent role in the initiation of the process. On the other hand, HNO₃ is involved in the initiation and in the catalytic cycle. Furthermore, FeBr₃ is needed for substrates with strongly electron withdrawing groups while the reactions of sulfides with donor groups proceeds to products even in the absence of FeBr₃.



X = (a) *p*-NO₂, (b) *p*-CHO, (c) *p*-NCS

(d) *p*-Br, (e) H, (f) *p*-CH₃, (g) *p*-OCH₃

Results and Discussion

The kinetics of the sulfoxidation reaction of substrates **1a–g** in the presence of HNO₃/FeBr₃ in catalytic quantities was measured in different reaction vessels open or closed. It was determined that for the reaction to proceed to completion it was necessary to have a closed vessel with a volume that contained the required amount of oxygen for the stoichiometric oxidation reaction. If the closed vessel contained a small amount of O₂, the reaction did not proceed to

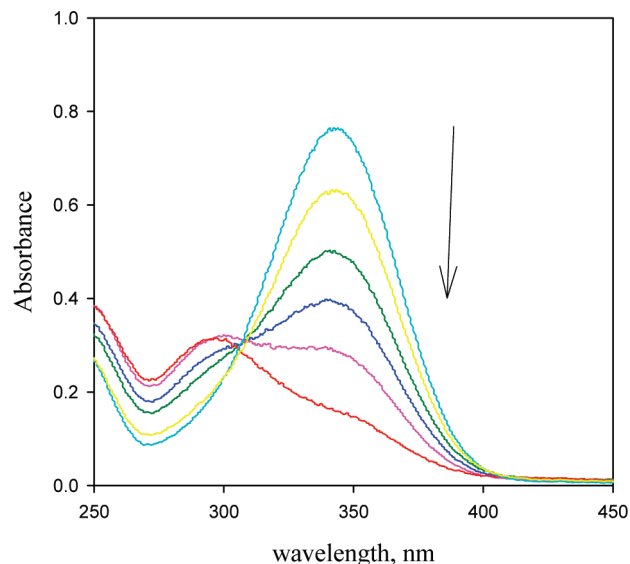


FIGURE 1. Spectra of **1a** (X = *p*-NO₂) as a function of time. The arrow indicates increasing time. The reaction contains **1a** = 1.3×10^{-3} M, HNO₃ (10%), and FeBr₃ (5%) in 2.6 mL of acetonitrile at 25 °C. The spectra were recorded after 500-fold dilution of the original solution in dichloromethane.

completion. The reactions carried out in open vessels did not give quantitative yields of the oxidation product. We suspect that this is because the nitrogen oxides, which are formed and which are required for the reaction, leave the solution in open vessels and therefore cannot take part in the catalytic cycle (see below). In all cases, the reaction gave the sulfoxide without any contamination by the corresponding sulfone or other products. The evolution of the reaction was determined by gas chromatography in some cases but in most instances the measurements were done by UV–vis spectrometry, following the decrease in absorption at the wavelength maximum of the sulfide (Figure 1 is representative). At the end of the reaction, the yield of product was determined by GC analysis. All reactions were run in duplicate and when the difference between the two runs was more than 10% they were discarded. Some of the reactions were followed by UV–vis and gas chromatography as well and the rate constants calculated were the same within experimental error.

Effect of the Substituents. The sulfoxidation reaction of sulfides **1a–g** was studied in the presence of FeBr₃ and in its absence, using 13% of HNO₃ as oxidation promoter. The results are summarized in Table 1. It can be seen that in the presence of FeBr₃ all substrates gave 100% reaction (entries 1–7, Table 1). On the other hand, in otherwise identical conditions but in the absence of FeBr₃, substrates with strongly electron withdrawing groups, such as *p*-NO₂ and *p*-CHO, did not react at all (entries 8 and 9, Table 1). The other substrates (entries 10–13, Table 1) reacted but the yield of the reaction was less than 100%, except for the one with the strongest electron donating group (entry 14, Table 1). It is interesting to note that for the substrates that reacted in the presence and in the absence of FeBr₃, the rate in the presence of the metal increased very little, so the rate constant ratios are 1.37, 1.09, 1.76, 1.51, and 1.55 for compounds with *p*-NCS (entries 3 and 10, Table 1), *p*-Br (entries 4 and 11,

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TABLE 1. Effect of the Substituents on the Oxidation of Aryl Methyl Sulfoxides **1a–g**^a

entry	substituent	Hammett σ^b	conversion (%) ^c	k_{obs} (10^{-2} min^{-1}) ^d	FeBr_3 (10^{-2} M)
1	<i>p</i> -NO ₂	+0.78	100	1.36	2.5
2	<i>p</i> -CHO	+0.42	100	1.56	2.5
3	<i>p</i> -NCS	+0.38	100	1.67	2.5
4	<i>p</i> -Br	+0.23	100	1.63	2.5
5	H	0.00	100	2.15	2.5
6	<i>p</i> -CH ₃	-0.17	100	2.65	2.5
7	<i>p</i> -OCH ₃	-0.27	100	2.80	2.5
8	<i>p</i> -NO ₂	+0.78	0	N.R.	
9	<i>p</i> -CHO	+0.42	0	N.R.	
10	<i>p</i> -NCS	+0.38	50	1.22	
11	<i>p</i> -Br	+0.23	53	1.52	
12	H	0.00	63	1.22	
13	<i>p</i> -CH ₃	-0.17	90	1.76	
14	<i>p</i> -OCH ₃	-0.27	100	1.81	

^aSolvent: acetonitrile, HNO₃ (13%), sulfide 0.509 M. ^bHammett σ constant taken from ref 15. ^cYield calculated by GC analysis. ^dObserved rate constant.

Table 1), H (entries 5 and 12, Table 1), *p*-CH₃ (entries 6 and 13, Table 1), and *p*-OCH₃ (entries 7 and 14, Table 1), respectively.

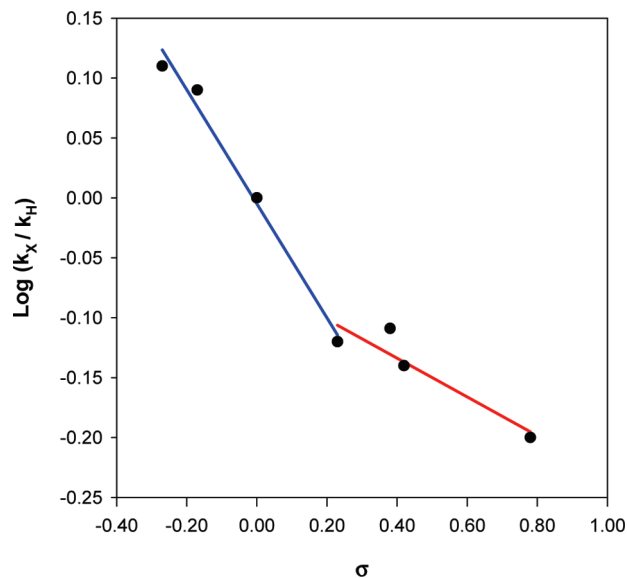
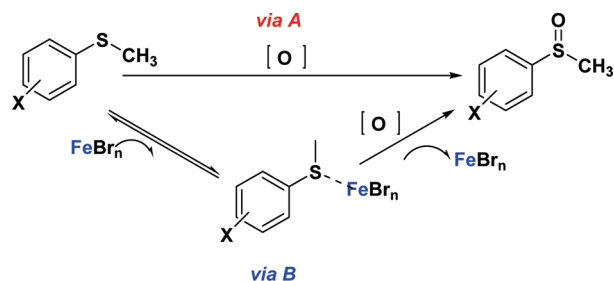


FIGURE 2. Hammett plot for the oxidation of sulfides **1a–g** 0.509 M in acetonitrile with 13% HNO₃ and 5% FeBr₃. The lines have been drawn as a visual aid.

A Hammett plot is shown in Figure 2 and it is clear that the plot is nonlinear. The nonlinearity of Hammett plots may indicate a change in mechanism or a change in rate determining step. Reactions that show an upward curvature indicate that more than one mechanism is operating.¹⁴ We suggest that the reaction takes place by two pathways, one that involves FeBr₃ and one that does not, as shown in Scheme 1.

On the other hand, the plot of the log of the rate constants vs. the oxidation potentials of the sulfur compounds is linear, as shown in Figure 3. It has been suggested that this type of dependence implies that the sulfoxidation reaction takes

SCHEME 1. Schematic Representation of the Two Pathways Suggested for the Sulfoxidation Reaction



place with the transfer of one electron from the sulfur atom to the oxidant species.¹⁶

To gain more insight into the mechanism of the reaction, the effect of change in the concentration of the reagents participating in the reaction on the rate constant was studied with substrates 1-methoxy-4-(methylsulfanyl)benzene **1g** and 4-(methylsulfanyl)benzaldehyde **1b** as representative of compounds with donor and acceptor groups, respectively.

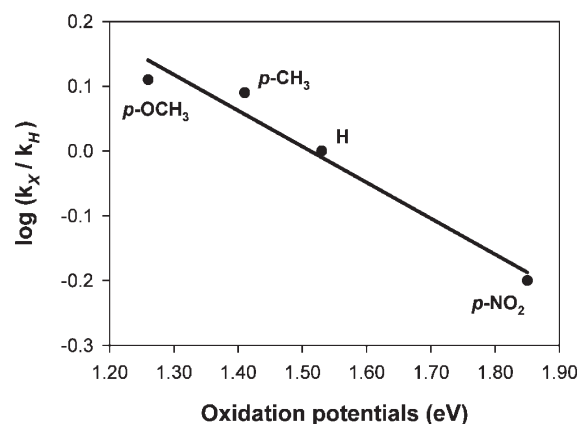


FIGURE 3. Log of the ratio of the rate constants for the sulfoxidation of **1** vs. oxidation potentials of the sulfides. (Oxidation potentials taken from the following: Watanabe, Y.; Iyanagi, T.; Oae, S. *Tetrahedron Lett.* **1980**, *21*, 3685).

Effect of the Reactant Concentrations on the Rate Constant. We took as the reference state the reactions conducted with the following concentrations: [substrate] = 0.509 M, [HNO₃] = 6.83×10^{-2} M, [FeBr₃] = 2.54×10^{-2} M, solvent (acetonitrile) = 2.6 mL. We performed experiments changing the concentrations of one of the reagents and keeping all the others constant.

Nitric Acid. Several experiments for each substrate were carried out changing the concentration of nitric acid in a range that gave measurable reaction rates, the maximum concentration being 0.1 M. It can be seen in Figure 4 that in both cases linear dependence of the observed rate constant with HNO₃ concentration was obtained, but the slope is slightly different, being smaller for the less reactive compound **1b**.

Effect of the Sulfide Concentration. In this case the concentration of the substrate was changed from 0.3 to 1 M. The data are collected in Table 2 and in Figure 5.

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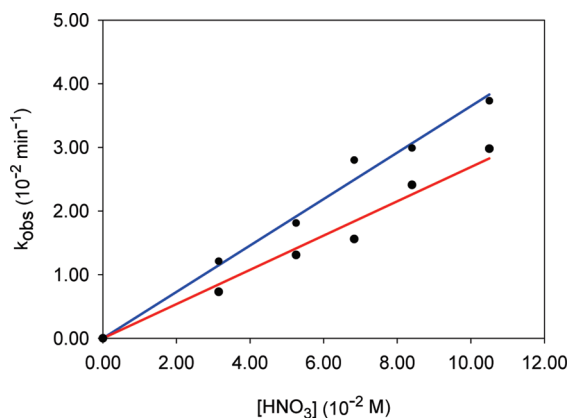


FIGURE 4. Effect of the concentration of HNO_3 on the rate of the reaction of compounds **1g** ($X = p\text{-OCH}_3$; blue line, slope 0.365) and **1b** ($X = p\text{-CHO}$; red line, slope 0.269). [Substrate] = 0.509 M, $[\text{FeBr}_3] = 2.54 \times 10^{-2}$ M.

TABLE 2. Effect of the Concentration of the Sulfide (**1b** or **1g**) on the Rate Constant for the Sulfoxidation Reaction

entry	[sulfide], M	% HNO_3^b	k_{obs} (10^{-2} min^{-1}) ^c	
			sulfide 1g	sulfide 1b
1	0.327	20.00	7.11	5.01
2	0.409	16.00	4.68	3.08
3	0.509	13.00	2.80	1.56
4	0.654	10.00	1.75	
5	1.089	6.00	0.65	0.08

^a $[\text{HNO}_3] = 6.83 \times 10^{-2}$ M, $[\text{FeBr}_3] = 2.54 \times 10^{-2}$ M; acetonitrile = 2.6 mL. The yield was in all cases 100% (determined by GC analysis). ^bPercentage of HNO_3 in moles with respect to the substrate. ^cRate constant determined by measuring the disappearance of the substrate with time; the value is the average of two or more determinations and the deviation is less than 10%.

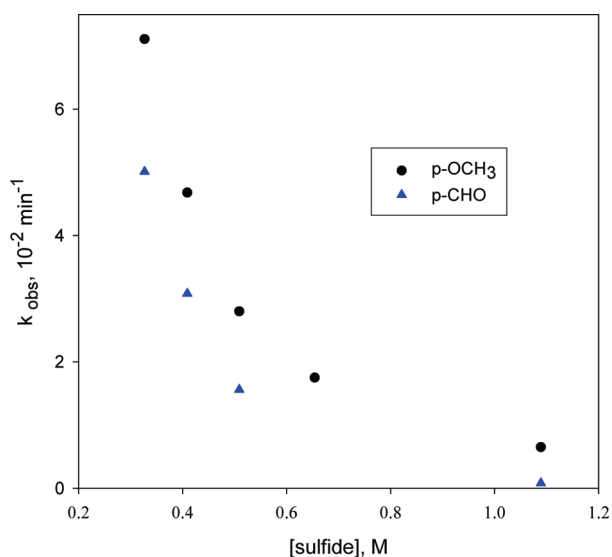


FIGURE 5. Effect of the substrate concentration on the rate of oxidation of sulfides (data from Table 2).

The observed inhibition of the reaction as the substrate concentration increases may be attributed to the facility of the sulfides to coordinate with the metal center and the

TABLE 3. Effect of the FeBr_3 Concentration on the Sulfoxidation Reaction of Sulfides **1b** and **1g**^a

Entry	$[\text{FeBr}_3]$, 10^{-2} M	% FeBr_3^b	k_{obs} (10^{-2} min^{-1}) ^c	
			sulfide 1g	sulfide 1b
1	0.00	0.00	1.81	no reaction
2	1.26	2.50	2.20	1.92
3	2.54	5.00	2.70	1.56
4	5.05	10.0	2.14	2.03
5	7.57	15.0	2.90	2.34

^a $[\text{HNO}_3] = 6.83 \times 10^{-2}$ M, [substrate] = 0.509 M; acetonitrile = 2.6 mL. The yield was 100%, except in entry 1. ^bPercentage of FeBr_3 in moles with respect to the substrate. ^cObserved rate constant determined by UV-vis spectrometry measurement of the disappearance of the substrate. The values are averages of at least two determinations and the deviation among them was less than 10%.

requirement of the formation of a ternary complex that involves the sulfide and the oxidant on the coordination sphere of the metal (see below).

It is interesting to note that in both cases the reaction rate decreases as the concentration of substrate increases in a nonlinear fashion, and the effect is even more noticeable for the less reactive substrate.

Effect of the FeBr_3 Concentration. In Table 3 the data are collected. It can be seen that for both substrates there was little variation of the rate when the percentage of FeBr_3 changed from 2.5% to 15%. However, the less reactive substrate **1b** required the presence of the metal in order to proceed, although once it was available the rate did not depend significantly on its concentration. These results show that compound **1g** can be oxidized without the participation of the metal, indicating that there is an alternative pathway as shown in Scheme 1.

Proposed Mechanism. Some relevant mechanisms proposed in the literature for the oxidation of sulfides can be grouped as follows:¹⁷ (a) oxidation initiated by electron transfer generating cation radicals,¹⁸ (b) concerted oxygen transfer from the oxidant species without the participation of intermediates,¹⁹ (c) mechanism initiated by the formation of a complex between the nonbonding electrons of the sulfur atom and the d orbitals of a transition metal,²⁰ and (d) reaction initiated by the interaction of the nonbonding electron pair of the sulfur atom and the π^* orbitals of the transition metal oxo-metallic complex.²¹ The last one is the more frequent mechanism when the oxidant species are organic or inorganic peroxides in the presence of transition metals as catalyst.

The sulfide oxidation to sulfoxide with use of nitrates as oxidant agent was reported several times. In 1961 the use of HNO_3 as oxidant was reported²² and the authors emphasize the use of HNO_3 as oxidant for its low cost and the possibility that the nitric oxides liberated could be reused in future oxidations. The proposed mechanism involves the direct reaction of the HNO_3 with the sulfide generating NO as product.

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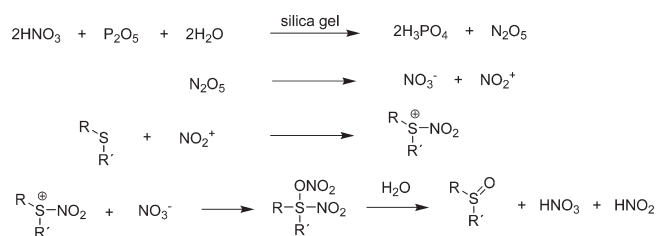
(18) Lepage, C.; Mihichuk, L.; Lee, D. *Can. J. Chem.* **2003**, *81*, 75.

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SCHEME 2. Mechanism Proposed for the Oxidation of Sulfides with HNO₃ and P₂O₅ Supported on Silica Gel²⁷


In a later work²³ it was determined that for the HNO₃ oxidation of sulfides the stoichiometric ratio sulfoxide/oxidant was three in the presence of oxygen and one in its absence (reactions carried out under N₂). In addition, they found that a product resulting from nitration of the aromatic ring of the substrate is formed and that the NO₂ substituted product²⁴ does not undergo oxidation under the reaction conditions employed, leading them to the conclusion that the oxidant species has an electrophilic nature.

It was reported that the oxidation of sulfides by HNO₃ under oxygen is catalyzed by Au halides²⁵ with very good chemoselectivity in the presence of several other functional groups. Dialkyl and diaryl sulfides were oxidized with cerium nitrate in acetic acid¹⁶ and it was found that the reactivity correlated very well with the oxidation potential of the sulfides, leading the authors to propose that sulfur radical cations were involved in the mechanism of the reaction.

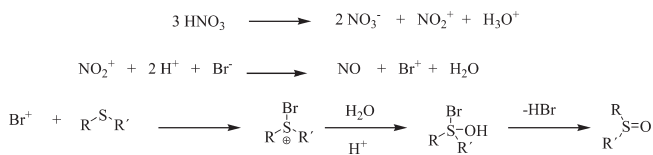
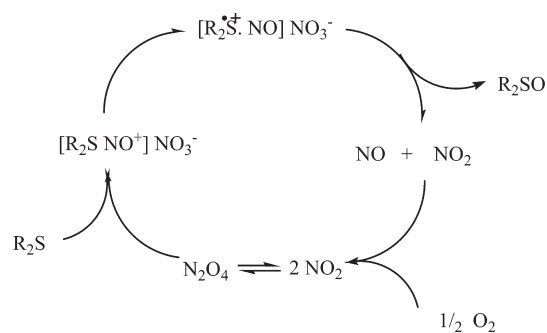
The combination of BiBr₃ and Bi(NO₃)₃ was proposed as the catalyst for the aerobic oxidation of sulfides²⁶ and the formation of a brownish gas suggested the formation of NO₂ as reduction product of the nitrate.

Transition metal bromides were proposed to act as redox mediators in the sulfoxidation of sulfides catalyzed by nitrates.⁹

It was reported that sulfides are selectively oxidized with 1 equiv of 64% HNO₃ in the presence of P₂O₅ supported on silica gel under solvent-free conditions. The suggested mechanism is outlined in Scheme 2.²⁷

Recently, a catalytic system that involves nitric acid supported on silica gel or polyvinylpyrrolidone (PVP) and sodium or potassium bromide was reported for the oxidation of sulfides to sulfoxides.²⁸ The authors proposed the mechanism shown in Scheme 3. It involves the autoxidation of nitric acid to yield nitronium ions (NO₂⁺), which in the presence of bromide ions yield bromonium ions.

The aerobic oxidation of sulfides in the presence of catalytic quantities of NO₂ takes place as shown in Scheme 4, and involves various intermediates derived from NO₂.²⁹ The authors suggest that the heterolytic dissociation of N₂O₄ to give NO⁺NO₃⁻ is favored in polar solvents and in the presence of sulfides in the reaction system.

SCHEME 3. Mechanism Proposed for the Oxidation of Sulfides by Nitric Acid Catalyzed by KBr²⁸

SCHEME 4. Proposed Mechanism for the Aerobic Oxidation of Sulfides with Catalytic Quantities of NO₂²⁹


Nitric oxide (NO) has been widely studied since it participates in many processes of great biological importance. Several iron complexes are involved in the metabolism of nitric oxide and many of them contain sulfur as ligands. It is well-known that S-nitrosothiols are responsible for the storage and transport of nitric oxide and related compounds and many NO receptors contain Fe and thiol groups that form ternary complexes Fe-sulfur-nitrosyl.³⁰

On the basis of the literature information mentioned above and our experimental results, we suggest the mechanism presented in Scheme 5. The proposed mechanism comprises an initiation step that may or may not involve FeBr₃, depending on the electronic nature of the substrates, and a catalytic cycle that is common to all substrates. In the initiation step the only oxidant present in the system is nitric acid, which must therefore be involved in this step.³¹ The relative participation of the pathways involving intermediates **3A** and **3B** depends on the electronic nature of the substituents on the aromatic ring. Compounds with strongly electron withdrawing groups such as NO₂ react only through the pathway involving intermediate **3B**. On the other hand, compounds with electron donating groups may react via intermediates **3A** and **3B** as well.

The sulfides are Lewis bases and their basicity increases with the presence of electron releasing groups in the aromatic ring. They can coordinate to the proton of the nitric acid, transforming the sulfur into an electrophilic species that may react with the nucleophilic nitrate generating intermediate **3A**. The later intermediate gives the sulfoxidation product and nitrous acid as reduction product derived from nitric acid.³²

(23) Ogata, Y.; Kamei, T. *Tetrahedron* **1970**, *26*, 5667.

(24) The substrate used in this study (ref 23) was diphenyl sulfide and the product of the nitration of the substrate was 4-nitrodiphenyl sulfide

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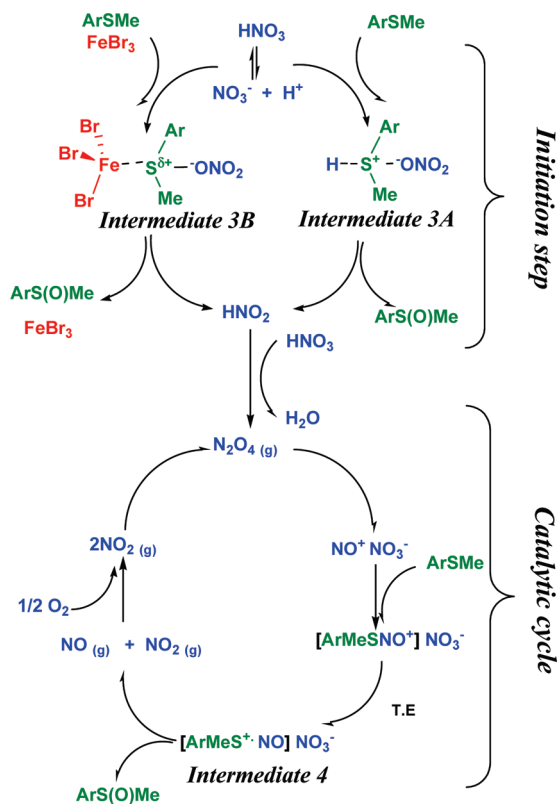
(29) Bosch, E.; Kochi, J. *J. Org. Chem.* **1995**, *60*, 3172.

(30) Szacilowski, K.; Chmura, A.; Stasicka, Z. *Coord. Chem. Rev.* **2005**, *249*, 2408.

(31) It is important to note that the sulfides are not oxidized in the absence of HNO₃.

(32) The formation of HNO₂ in these reactions was further supported by the fact that compounds having an aromatic amine produce azo derivatives. Unpublished results from our lab.

SCHEME 5. Suggested Mechanism for the Oxidation of Sulfides Promoted by Catalytic Amounts of HNO₃ and FeBr₃



On the other hand, the sulfides that contain electron attracting groups are probably not basic enough to be protonated by nitric acid, but they can coordinate to the Fe center. The coordinated sulfur is an electrophilic center that is able to react with the nitrate (intermediate 3B) leading to the sulfoxidation product and nitrous acid (Scheme 5).

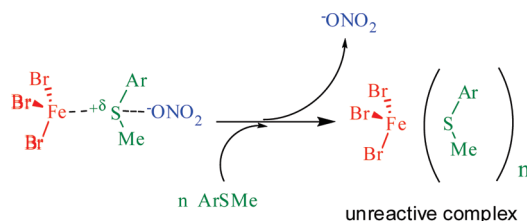
It is important to note that the sulfides have negative electron density on the sulfur atom but the sulfoxides have positive electron density. The change in charge on the sulfur may lead to its liberation from the coordination with the metal and therefore it becomes free to bind another sulfide molecule. Thus, only catalytic quantities of FeBr₃ are needed for the reaction to proceed.

Both pathways generate nitrous acid, which in the presence of nitric acid forms the colorless gas N₂O₄,²³ the first intermediate produced in the catalytic cycle. This gas is in equilibrium with the product of homolytic dissociation (2NO₂) or heterolytic dissociation (NO⁺NO₃⁻), the latter being the predominant species in polar solvents.²³

The oxidation of sulfides by nitrosonium ion has been reported and the proposed mechanism for these reactions involves the coordination of the NO⁺ to the sulfide followed by an electron transfer to generate the radical cation of the sulfide²⁹ (intermediate 4). The intermediate decomposes generating the sulfoxide, NO, and NO₂. The NO combines with O₂ from the air present in the system yielding NO₂(g). The combination of two molecules of NO₂ gives N₂O₄, which continues the catalytic cycle.

The involvement of O₂ in the reaction is evident from the fact that the yield of reactions carried out in closed systems is very much dependent on the volume of the reaction system.

SCHEME 6. Displacement of NO₃⁻ by the Sulfide in the Ternary Complex



When the volume was small, such that the amount of O₂ present was less than the stoichiometric amount, the reaction did not proceed to completion. The formation of NO₂ was evident from the observation of the evolution of a brownish gas.

The observed inhibition of the reaction when the sulfide concentration increased may be explained by considering the reaction shown in Scheme 6 where the sulfide displaces the NO₃⁻ from the ternary complex forming an unreactive complex. In addition, when the substrate concentration increases, the amount of free HNO₃ decreases and therefore it is not available to initiate the catalytic cycle; this may be the reason for the decrease in rate in the reactions that do not require FeBr₃.

The formation of a ternary complex between the sulfide, FeBr₃, and nitrate was demonstrated spectroscopically by measuring the change in absorption with time at the wavelength maximum of FeBr₃ (388 nm). Since the absorbance of FeBr₃ is smaller than that of any sulfide used in this work, in order to do measurements at this wavelength it was necessary to dilute the solutions 5 times less than for solutions where the disappearance of the sulfide was followed (259–314 nm). Therefore the change in absorption cannot be measured at the two wavelengths (259–314 and 388 nm) in the same solution. With use of sulfide **1g** (X = *p*-OCH₃), during the first 25 min there is a significant increase in absorbance at λ = 388 nm. There was no change in the absorbance between 25 and 100 min and thereafter the absorbance decreases (see Figure 6).

These results indicated that during the first 25 min a new species accumulated and it remained unchanged until the first 100 min; at this time, the sulfoxidation reaction finished and the absorbance started to decay.

The species absorbing at 388 nm could be a complex between sulfide and FeBr₃, a complex formed between nitric acid and FeBr₃, or a ternary complex formed with the three compounds. To determine the nature of the species we mixed solutions of FeBr₃ and sulfide at concentrations similar to those used in the experiment described above and we did not see any change in the spectrum at λ = 388 nm, which discounts the formation of a complex between sulfide and FeBr₃. On the other hand, when solutions of nitric acid and FeBr₃ were mixed, the absorbance at λ = 388 nm decreased in a similar way to that observed for the reaction described above after about 100 min (see Figure 6). The observed decrease in absorbance at 388 nm is attributed to the ionic exchange between FeBr₃ and HNO₃ to yield Fe(NO₃)₃ and HBr.³³

(33) Cotton, F. A.; Wilkinson G. *Química Inorgánica Avanzada*, 3rd ed.; Editorial Limusa: Mexico City, Mexico, 1990; pp 905–924.

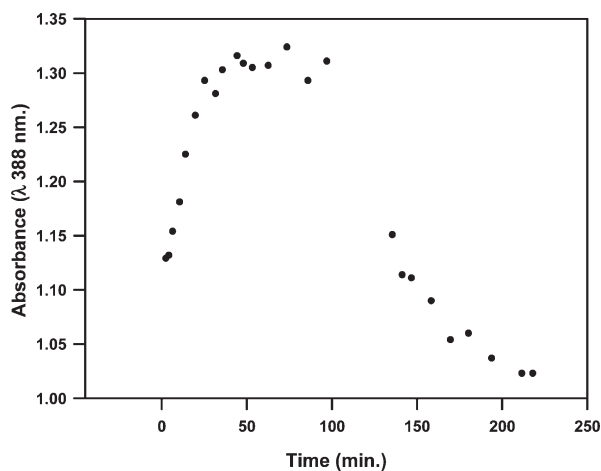


FIGURE 6. Change in absorbance with time for the sulfoxidation reaction at 388 nm. Solvent: acetonitrile (2.6 mL), HNO₃ (13%), FeBr₃ (5%), sulfide **1g** (X = *p*-OCH₃) 0.509 M. The reaction solution was diluted 100-fold before measurement.

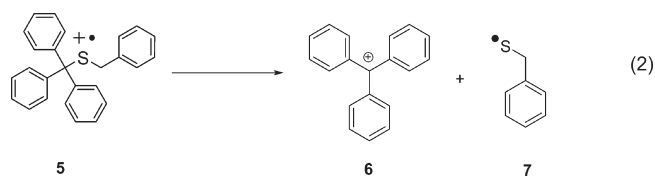
From experiments mentioned above we conclude that a ternary complex is formed.

In a similar reaction carried out with **1b** (X = *p*-CHO) there is also an increase in the absorbance at $\lambda = 388$ nm but the time required to reach the maximum is approximately 45 min, i.e., almost twice that required for the other substrate. This observation is consistent with the mechanism suggested where substrates having electron withdrawing groups react only through the pathway that involves the ternary complex and therefore it is consumed as soon as it is formed. (See Figure S1 in the Supporting Information).

Comparing the behavior of the two substrates, we can see that in the substrate with an electron donor group (**1g**) the ternary complex is formed at the beginning of the reaction and its concentration stays constant until the oxidation reaction is complete. With the substrate having an electron withdrawing group (**1b**) the concentration of the ternary complex increases slowly and reaches a maximum, but then it decreases as the reaction proceeds.

These results are consistent with the proposed mechanism since the main reaction pathway for the substrates with electron donating group involves the complex formed with nitric acid. On the other hand, for the substrates with electron withdrawing groups the main reaction pathway is that involving the ternary complex; therefore, it is formed and degraded during the oxidation reaction.

The formation of radical cations has been postulated on the basis of the linear dependence of the oxidation of aryl methyl sulfides with oxidation potentials.²⁹ To find additional evidence for the participation of radical cations in the reaction mechanism, we carried out an experiment under the same reaction conditions (5% FeBr₃ and 13% HNO₃ in acetonitrile) but using triphenyl benzyl sulfide as a substrate. It is known that the radical cation of this substrate **5** gives mainly the fragmentation products **6** and **7** due to the stability of the trityl cation **6** (eq 2).³⁴



The reaction was followed by UV-vis spectroscopy and TLC. Both techniques indicated that most of the substrate remained unchanged for 120 min; however, there were absorption bands that appeared 5 min after the start of the reaction with $\lambda_{\text{max}} = 412$ and 435 nm (Figure S2, Supporting Information). These bands are coincident with those corresponding to the trityl cation.³⁵ Upon the addition of nucleophiles such as HO⁻ or I⁻, the bands at 412 and 435 disappeared, which gives further support to the presence of the trityl cation in the solution.

For the reactions that require the presence of FeBr₃, it may be that the metal is required in the initiation step as shown in Scheme 5 and/or in the catalytic cycle. To check for the latter possibility we carried out an experiment using NO₂ as oxidant for sulfide **1b** (see the Supporting Information). In this case the sulfide was obtained in quantitative yield indicating that the FeBr₃ is not needed for the catalytic cycle.

Conclusions

It was shown that the oxidation of aryl methyl sulfides with strong electron donating groups takes place in the presence of catalytic amounts of HNO₃ in acetonitrile. The same reaction takes place with compounds having electron withdrawing groups but in this case the presence of a catalytic amount of FeBr₃ is required in addition to the nitric acid. It is suggested that the mechanism has an initiation step where HNO₂ is formed and that this species enters into a catalytic cycle that involves the formation of a radical cation of the sulfide. The oxidant species which is consumed in stoichiometric amounts is O₂ from the air. The Fe(III) metal is not involved in the catalytic cycle; it only participates in the initiation step and this may be the reason why the use of complexes of FeBr₃ with several chiral ligands, including cyclodextrin, did not lead to enantioselective oxidation. The oxidation reaction of sulfides with catalytic amounts of FeBr₃ and HNO₃ is highly chemoselective, proceeds at a convenient rate at 25 °C, and must be carried out in a closed system to prevent the gaseous species derived from HNO₃ from leaving the system.

Experimental Section

All reagents were commercial materials and their purity was checked by NMR spectroscopy with a 400 MHz instrument.

Kinetic Procedures. The reactions were carried out in a bottle containing a side arm with a septum to take samples. The required amount of FeBr₃ was weighed in the reaction vessel and the sulfur compound dissolved in 1.3 mL of acetonitrile was added. The HNO₃, also dissolved in 1.3 mL of acetonitrile, was then added and this time was taken as the zero time for the reaction. All solutions were kept in a temperature-controlled bath at 25 °C. The reaction was continuously stirred with a magnetic stirrer.

(34) Peñeñory, A.; Adam, W.; Argüello, J. *J. Org. Chem.* **1998**, *63*, 3905.

(35) Acar, M.; Yagci, Y.; Schnabel, W. *Polym. Int.* **1998**, *46*, 331.

To follow the reactions, two different techniques were used: UV–vis and gas chromatography. For the UV–vis experiments, 2 μL of the reaction was dropped on 10 mL of dichloromethane. The dilution stops the reaction and the spectrum was determined at the selected times. The reactions were followed by measuring the decrease in absorbance of the substrate at its wavelength maximum. The data were fitted to a monoexponential equation and the pseudo-first-order rate constant was calculated.

For the gas chromatography method, 0.1 mL of the reaction solution was taken at different reaction times and dropped on 0.5 mL of dichloromethane containing an internal standard previously selected. Then 0.5 mL of water was added to eliminate the FeBr_3 and HNO_3 . The two layers were separated, the organic layer was dried with anhydrous MgSO_4 , and the samples were analyzed by gas chromatography using a capillary column of ZB-5 (5% phenyl polysiloxane) 30 m \times 0.25 mm \times 0.25 μm .

The two methods gave comparable results, but the UV–vis method is simpler and therefore most of the reactions were followed by this method.

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Supporting Information Available: UV–vis spectrum of the reaction of **6** and experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.