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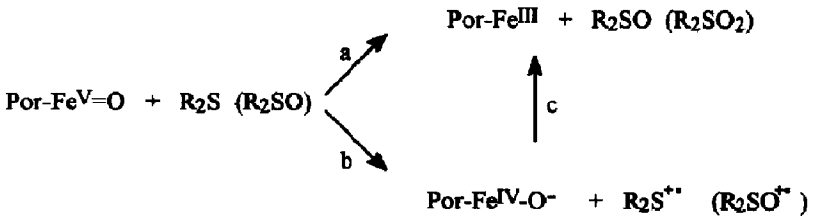
The Mechanism of Enzymatic and Biomimetic Oxidations of Aromatic Sulfides and Sulfoxides

Enrico Baciocchi*, Osvaldo Lanzalunga, Francesco Marconi

Dipartimento di Chimica, Università "La Sapienza" and Centro CNR di Studio sui Meccanismi di Reazione, P.le A. Moro 5, 00185 Rome, Italy.

Abstract: *Biomimetic and enzymatic oxidations of benzyl sulfides and sulfoxides lead to products (sulfoxides or sulfones) different from those obtained with bona fide electron transfer oxidations (products of C-H and/or C-S bond cleavage), which suggests the operation of an oxygen transfer mechanism.*

There is a continuous interest in the mechanism of enzymatic and biomimetic oxidation of organic substrates particularly concerning the possible role of electron transfer (ET) steps.[1] Thus, for the oxidation of sulfides and sulfoxides (to sulfoxides and sulfones, respectively) by microsomal cytochrome P-450 and the model compounds iron porphyrins, a mechanistic dichotomy has been envisaged. As shown in Scheme 1, this reaction can involve an oxygen transfer to sulfur from the iron-oxo complex (Por-Fe^{V}=O, Por = porphyrin) suggested[2] to be the active species both in the biomimetic and enzymatic oxidations (path a). Alternatively, an electron transfer step is also possible leading to a cation radical, which then collapses to products (path b and c). So far, no clear decision between these two reaction pathways has been possible,[3] even though a slight indication in favour of the electron transfer mechanism has been provided by Oae and his associates.[4]

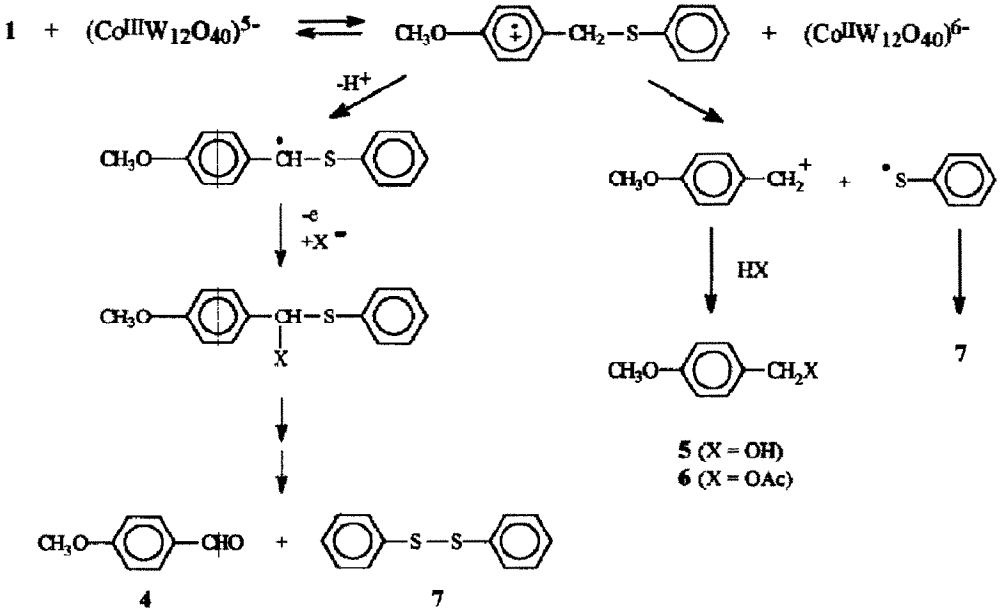


Scheme 1

To throw some light on this problem we have studied the oxidation of 4-methoxybenzyl phenyl sulfide (**1**), 4-methoxybenzyl phenyl sulfoxide (**2**) and 2-phenyl-2-propyl phenyl sulfide (**3**) by a bona fide ET oxidant, namely potassium 12-tungstocobalt(III)ate, $K_5(Co^{III}W_{12}O_{40})$,[5] and compared the results with those obtained in the oxidations of the same substrates catalyzed by microsomal cytochrome P-450 or by *meso*-(tetraphenylporphinato)iron^{III} chloride (TPPFe^{III}Cl).

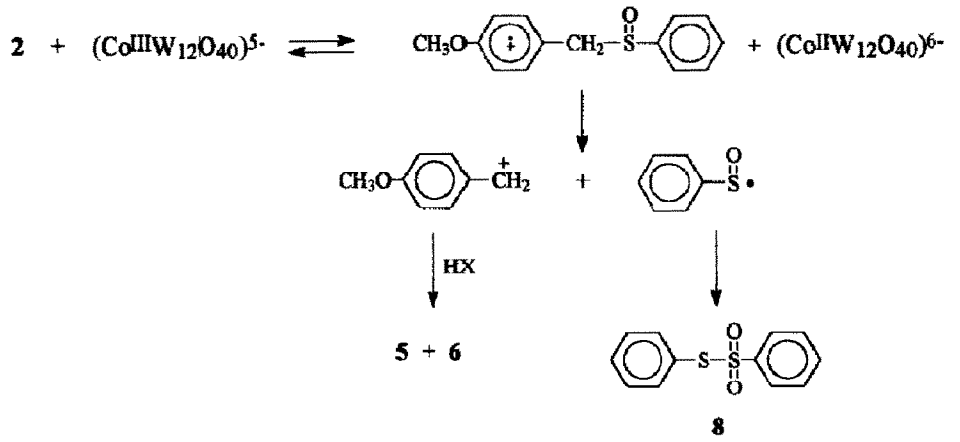
The reaction of **1** with $K_5(Co^{III}W_{12}O_{40})$ in AcOH:H_2O (70:30)[6] leads to 4-methoxybenzaldehyde (**4**), 4-methoxybenzyl alcohol (**5**), 4-methoxybenzyl acetate (**6**) and diphenyl disulfide (**7**). This result is reasonably interpreted on the basis of the formation of an intermediate radical cation, with the SOMO located on the methoxy bearing aromatic ring.[7] As illustrated in Scheme 2 (X = OH, OAc), the radical cation undergoes both C-H and C-S bond cleavage, the former being the major reaction path. In the deprotonation path an α-substituted derivative is first formed which, by oxidation, C-S bond cleavage and hydrolysis leads

to diphenyl disulfide and 4-methoxybenzaldehyde.[8] In the C-S bond cleavage route a benzyl carbocation and a phenylthiyl radical are formed, leading to the benzyl derivatives **5** and **6** and to diphenyl disulfide, respectively. No oxidation of **1** to give the sulfoxide **2** has been observed.



Scheme 2

The oxidation of **2** by the cobalt(III) complex[6] takes place with a reactivity comparable to that of **1** forming **5**, **6** and the thiosulfonate **8**. This result is in agreemennt with an ET mechanism shown in Scheme 3 (X = OH, OAc). Accordingly, **1** and **2** should have similar oxidation potential since the SPh and SOPh groups are not directly bonded to the aromatic ring where the SOMO is located.[7]

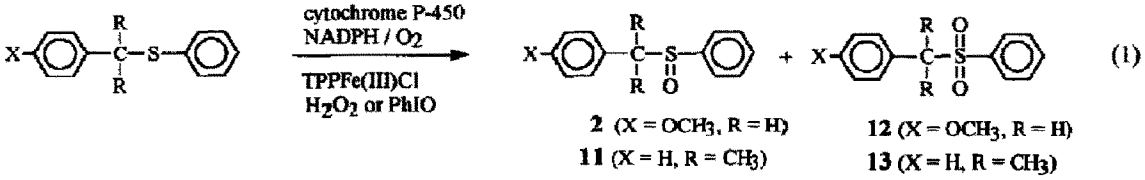


Scheme 3

It is noteworthy that $2^{+\cdot}$ undergoes only C-S bond cleavage, giving the benzyl carbocation and the phenylsulfinyl radical,[9] without any competition from C-H bond breaking. This is probably due to a much faster rate of C-S bond cleavage in $2^{+\cdot}$ than in $1^{+\cdot}$, in line with the well known greater stability of sulfinyl than thiyl radicals.[10] No oxidation of **2** to the corresponding sulfone has been observed.

Substantially similar results have been observed in the oxidation of 2-phenyl-2-propyl phenyl sulfide by $K_5(Co^{III}W_{12}O_{40})$.[6] 2-Phenyl-2-propanol (**9**) and 2-phenyl-2-propyl acetate (**10**) and the disulfide **7** are formed. In this case too the products can be rationalized on the basis of the formation of the radical cation $3^{+\cdot}$ with the SOMO now located on the sulfur atom,[7] which undergoes C-S bond cleavage producing the cumyl carbocation and the phenylthiyl radical. The former reacts with the solvent to form **9** and **10**, the latter dimerizes to the disulfide **7**. Again, no evidence for the formation of the corresponding sulfoxide has been found.

In striking contrast with the above results, the oxidations of **1** and **3** catalyzed by microsomal cytochrome P-450[11] or by $TPPFe^{III}Cl$, using H_2O_2 in CH_3CN or PhIO in CH_2Cl_2 as oxidants,[12] have exclusively produced a mixture of the corrisponding sulfoxides and sulfones (eq. 1), in line with previous observations concerning the oxidations of aliphatic and aromatic sulfides under the same oxidation conditions.[3,4,13]



2 (X = OCH_3, R = H) **12** (X = OCH_3, R = H)
11 (X = H, R = CH_3) **13** (X = H, R = CH_3)

(1)

Presumably, sulfoxides are oxidized to sulfones in the reaction medium and indeed we have found that the sulfoxide **2** is converted to the corresponding sulfone when oxidized by either microsomal cytochrome P-450 or $H_2O_2/TPPFe^{III}Cl$ or $PhIO/TPPFe^{III}Cl$. In no case evidence for the formation of fragmentation products, deriving from C-H and/or C-S bond cleavage, as observed in the ET reactions of **1-3**, has been obtained.

Clearly, these results lend no support to the hypothesis that cation radicals are involved in these biomimetic and enzymatic oxidations of sulfides and sulfoxides. On the other hand, the possibility that fragmentation products are not observed since the collapse of the radical cation with the reduced form of the iron-oxo complex (path c in Scheme 1), is faster than any other reaction is also unlikely. Accordingly, while this hypothesis would be at least in principle reasonable when the SOMO, and therefore the positive charge resides on the sulfur atom, it does not seem plausible when, as seen above in the case of $1^{+\cdot}$ and $2^{+\cdot}$, the positive charge is located on the aromatic ring bearing the methoxy group and no direct interaction between this charge and the sulfur atom is possible.

In conclusion, our data favour a direct interaction between the iron-oxo complex and the sulfur atom. An oxygen transfer is therefore the most likely mechanism.

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6. The oxidation procedure was as follow: the substrate (0.45 mmol) was treated with 0.7 mmol of cobalt(III) complex in 10 ml of AcOH/H_2O (7/3), in the presence of AcOK 0.5 M (oxidation of **3**), at 40 °C under Ar atmosphere. Oxidation of **1** gave **4** (16%, referred to the recovered material), **5** (4%), **6** (2%) and **7** (11%), oxidation of **2** gave **5** (28%), **6** (10%) and **8** (18,5%);oxidation of **3** gave **9** (6%), **10** (3%) and **7** (4%). The material balance was between 93% and 99%. Products were identified by comparison with authentic specimens. Analyses have been performed by HPLC, GLC, GC-MS and ^{1}H-NMR.
7. A He(I)/He(II) photoelectron spettroscopy study of a number of benzyl phenyl sulfides (to be published elsewhere) has clearly shown that in 4-methoxybenzyl phenyl sulfide cation radical the SOMO is located on the aromatic ring. The same conclusion holds for $2^{+\cdot}$ and in line with this **1** and **2** have quite close oxidation potentials (8.05 eV and 8.20 eV respectively). For benzyl phenyl sulfide cation radical the SOMO is on the sulfur atom and this conclusion also applies for $3^{+\cdot}$.
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11. Rat liver microsomes (40 mg protein), NADPH generating system (10 μmol of $NADP^+$, 100 μmol of G6P, and 12 units of G6P-DH) and substrate (0.1 mmol) were incubated in 7 ml of phosphate buffer (pH 7.4, 0.1 M) at 36 °C for 2 h. Reaction products were extracted as described in ref. 4. Only sulfoxides and sulfones were detected as reaction products: oxidation of **1** gave **2** (18%, referred to the recovered material) and **12** (5%); oxidation of **2** gave **12** (14%); oxidation of **3** gave **11** (38%) and **13** (41%).
12. *With PhIO:* TPPFe^{III}Cl (3 μmol) was added to a solution of sulfide (0,12 mmol) in 5ml of CH_2Cl_2 at -12 °C. PhIO (0,12 mmol) was added and the reaction mixture was stirred under Ar atmosphere for 30 min. Only sulfoxides and sulfones were detected as reaction products: oxidation of **1** gave **2** (39%) and **12** (22%); oxidation of **2** gave **12** (92%); oxidation of **3** gave **11** (44%) and **13** (18%).
With H_2O_2: TPPFe^{III}Cl (0.0125 mmole) and imidazole (0.025 mmole) were added to a solution of substrate (0.25 mmol) in 7 ml of CH_3CN, H_2O_2 30% (0.5 mmol) was added at room temperature and the reaction mixture was stirred under argon atmosphere for 30 min. Also in this case only sulfoxides and sulfones were produced: oxidation of **1** gave **2** (58%) and **12** (26%); oxidation of **2** gave **12** (80%); oxidation of **3** gave **11** (57%) and **13** (10%). Yields are referred to the recovered material.
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