Pergamon

Tetrahedron, Vol. 53, No. 36, pp. 12287-12298, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00560-7

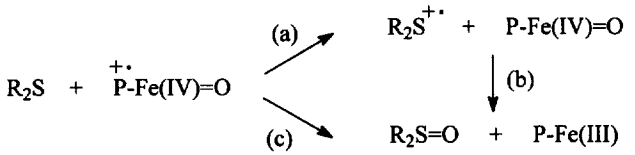
Oxidations of Benzyl and Phenethyl Phenyl Sulfides. Implications for the Mechanism of the Microsomal and Biomimetic Oxidation of Sulfides

Enrico Baciocchi,* Osvaldo Lanzalunga and Bruno Pirozzi

Dipartimento di Chimica, Universita' di Roma "La Sapienza" and Centro CNR di Studio sui Meccanismi di Reazione, Piazzale Aldo Moro 5, 00185, Roma, Italy

Abstract: The study of the oxidation of 4-methoxyphenethyl phenyl sulfide and 3,4-dimethoxyphenethyl phenyl sulfide with potassium 12-tungstocobalt(III)ate [Co(III)W] suggests that in the radical cations of 3,4,5-$(MeO)_3PhCH_2SPh$ (**4**) and 2,4,6$(MeO)_3PhCH_2SPh$ (**5**) the positive charge is not localized on the sulfur atom, but in the benzylic aromatic ring. Nevertheless, in the biomimetic and microsomal oxidation of **4** and **5** the products observed are exclusively sulfoxides and sulfones, which appears in contrast with a mechanism involving the formation of an intermediate sulfide radical cation followed by a fast oxygen rebound. A direct oxygen transfer mechanism seems most likely.

The sulfoxidation of sulfides catalyzed by hemoproteins (particularly, cytochrome P-450 and peroxidases) is a subject of current interest, especially with respect to the possible role of sulfide radical cations as reaction intermediates.[1,2] Accordingly, it is generally accepted that these oxidations are initiated by the transfer of one electron from the sulfide to the iron(IV) oxo porphyrin radical cation, therefrom indicated as $Por^{+\cdot}$-Fe(IV)=O, which is suggested to be the active species in these reactions.[3] As illustrated in Scheme 1 (paths a and b), the sulfoxide is then formed by reaction of the radical cation with Por-Fe(IV)=O (oxygen rebound).



Scheme 1

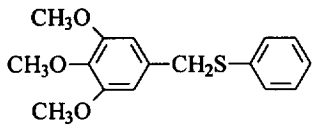
Indeed, there is little doubt that this mechanism holds in the oxidation of sulfides by horseradish peroxidase (HRP). Recently, we found clear evidence for the formation of sulfide radical cations in this reaction and were also able to give an estimate of the rate of the oxygen rebound step.[4] Accordingly, formation of the expected benzylic products was observed in the oxidation by HRP of benzyl phenyl sulfides which when converted into radical cations can undergo C-S bond cleavage, forming benzyl carbocations.

Less defined appears instead the situation for what concerns the mechanism of the oxidation of sulfides by cytochrome P-450. The electron transfer mechanism of Scheme 1 was proposed in the eighties by Oae and his associates, who suggested that it also operates in the oxidation of sulfides catalyzed by iron(III) porphyrins, which are good models of cytochrome P-450.[1a] However, the evidence supporting this mechanism is not unequivocal. Thus, the finding that the oxidation rate is increased by electron donating substituents in the sulfide by no means proves an ET mechanism. Apart from the fact that the ρ^+ of the S-oxygenation promoted by a reconstituted system with purified cytochrome P-450 is extremely small (-0.16), it can be mentioned that the epoxidation of alkenes catalyzed by models of cytochrome P-450 also exhibits a negative ρ^+ value (-1.9),[5a] yet the intermediacy of radical cations in this reaction seems very unlikely.[5b] More important, perhaps, is the observation that when $ArSCH_2X$ sulfides (X is a strong electron-withdrawing group) were studied, fragmentation products were also obtained, attributed to the deprotonation of the radical cation in competition with the oxygen rebound step. However, it cannot be excluded that, due to the presence of the electron-withdrawing group weakening the adjacent C-H bond, a hydrogen atom transfer reaction (leading to the same fragmentation products) takes place in competition with sulfoxidation. Thus, at present, whereas an electron transfer mechanism is possible, also viable is a direct oxygen transfer mechanism from the iron oxo porphyrin radical cation to the neutral sulfide, as shown in Scheme 1, path c.

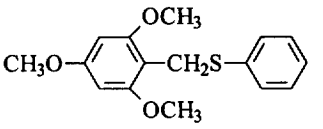
Few years ago, this problem was addressed by the same mechanistic approach used for our investigation on the oxidation catalyzed by HRP[4] and accordingly the microsomal and biomimetic oxidations of benzyl phenyl sulfide (**1**), 4-methoxybenzyl phenyl sulfide (**2**) and cumyl phenyl sulfide (**3**), all forming radical cations undergoing C-S bond cleavage, were studied.[6] In no case, did we find evidence for the formation of benzylic products and thus no support for the formation of radical cations was obtained by this work. The possibility that the oxygen rebound might occur to a rate much faster than that of the C-S bond cleavage step was considered unlikely as PES experiments suggested that in $\mathbf{2}^{+\cdot}$, the SOMO was located on the aromatic benzylic ring,[7] thus making unreasonable the hypothesis of a fast rebound step. However, more recent studies have cast doubts on this conclusion by indicating that in solution the location of the SOMO in $\mathbf{2}^{+\cdot}$ is probably on the sulfur atom.[8]

To remove this uncertainty we have now undertaken the study of the enzymatic and biomimetic oxidation of benzyl phenyl sulfides where certainly the SOMO resides on the benzylic aromatic ring. The compounds of choice were the sulfides **4** and **5**, where the three methoxy groups present in the benzylic

aromatic ring, should make it much easier to remove the electron from this ring rather than from the sulfur atom.

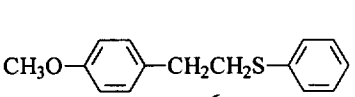


4

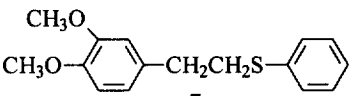


5

To check this point, we also investigated the oxidation of 4-methoxyphenethyl phenyl sulfide (**6**) and 3,4-dimethoxyphenethyl phenyl sulfide (**7**) promoted by a genuine one electron transfer oxidant potassium 12-tungstocobalt(III)ate, abbreviated as Co(III)W.[9] In **6** and **7**, the benzylic and thiophenoxy moieties are separated by a methylene group and different products are therefore expected depending on whether the SOMO of the intermediate radical cation is on the benzylic aromatic ring or on the sulfur atom. By this means, we should get information on the actual role of methoxy group(s) with respect to the SOMO localization in the radical cation, in solution. The results of this study are reported in this paper.



6



7

RESULTS AND DISCUSSION

Oxidations of 6 and 7 with Co(III)W.

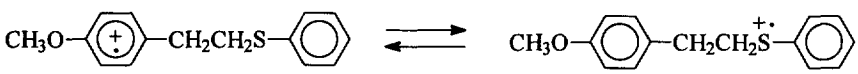
The oxidations of **6** and **7** with Co(III)W were carried out in a mixed AcOH-H_2O (70:30) solvent, where both Co(III)W and the substrate could be dissolved, at 55° C. The substrate : oxidant molar ratio ratio was 1 : 2, to keep overoxidation to a minimum, the substrate concentration being *ca* 0.06 M. Experiments were carried out in the presence and in the absence of AcOK, to look at possible effects of the presence of a basic species. At the end of the reaction (30 min-1h), the products were identified by NMR, GC-MS and HPLC, in most cases by comparison with authentic specimens. For details see the Experimental Part. Quantitative analyses of the products were performed by NMR, with the exception of the sulfoxides which were quantitated by HPLC. The material balance was always very good, ranging from 90 to 100%. All results are in Table 1.

Table 1. Reaction Products (%) in the Oxidation of $ArCH_2CH_2SPh$ by Co(III)W in AcOH : H_2O at 55 °C in the absence and in the presence of AcOK.

Ar	AcOK	Products (yield; %)[a]				
		ArCHO **8**	$ArCHXCH_2SPh$ **9**	$ArCH_2CH_2S(O)Ph$ **10**	$ArCH_2CHO$ **11**	$ArCH_2CHXSPh$ **12**
4-MeOPh	0.5M	1.2	9.8[b]	2.4	7.8	17.6 [c]
	-	2.4	25.0[b]	10.6	4.8	d
3,4-$(MeO)_2$Ph	0.5M	0.6	28.4[b]	0.8	0.6	1.6[c]
	-	0.8	28.8[b]	2.4	d	d

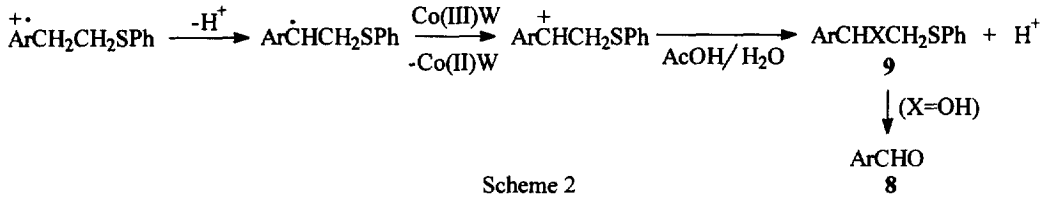
[a] Yields are referred to the oxidant considering a stoichiometry of 2:1 [Co(III)W/Substrate] in the formation of oxidation products. Average of two or more determinations. The error is ± 10%.
[b] Sum of the yields of **9**(X=OH) and **9**(X=OAc) .
[c] **12**(X=OAc).
[d] Under the limit of detection (0.2 %)

When the oxidation of **6** was carried out in the presence of AcOK, 4-methoxybenzaldehyde, **8(Ar=4-MeOPh)**, and the products of benzylic substitution **9(Ar=4-MeOPh, X=OAc, OH)** are formed along with the sulfoxide **10(Ar=4-MeOPh),** the acetoxy derivative **12(Ar=4-MeOPh, X=OAc)** and 4-methoxyphenylacetaldehyde, **11(Ar=4-MeOPh)**. Clearly, to reasonably account for these products requires the intervention of both the alkylaromatic (**6a**) and the sulfur centered (**6b**) radical cations, probably in equilibrium with one another,[10] as reaction intermediates.



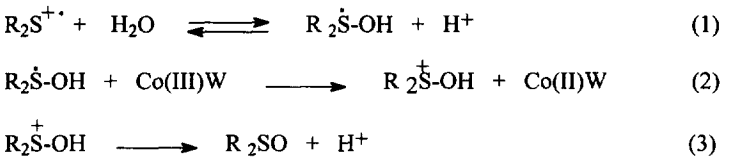
6a **6b**

Accordingly, deprotonation of the former radical cation at the benzylic position accounts for the formation of **9** and 4-methoxybenzaldehyde, as shown in Scheme 2, (Ar = 4-MeOPh). A benzylic carbon radical is formed undergoing oxidation by Co(III)W to a carbocation which reacts with water or acetic acid to give **9(Ar=4-MeOPh, X=OH, OAc)**. Oxidation of **9(Ar=4-MeOPh, X=OH)** leading to 4-methoxybenzaldehyde, a well known reaction involving C-C bond cleavage,[11] also occurs in part.

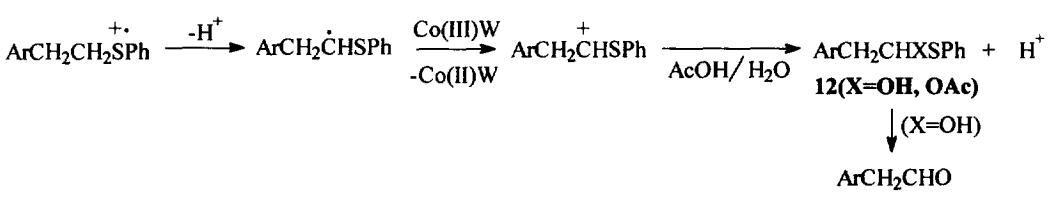


Scheme 2

The other products derive from the sulfur radical cation (**6b**). Thus, the sulfoxide is probably formed from **6b** *via* the mechanism already suggested for the sulfoxidation of the thianthrene radical cation (eqs. 1-3).[12] The oxidation of the sulfur centered radical by Co(III)W (eq. 2) can drive the process towards the sulfoxide formation.



For the formation of **11** and **12** the mechanism illustrated in Scheme 3 (Ar=4-MeOPh) can be suggested. Deprotonation of **6b** at the α to sulfur C-H bond leads to an α–thiophenoxy carbon radical which is then oxidized by Co(III)W to a carbocation. The latter reacts with AcOK to form **12(Ar=4-MeOPh, X=OAc)** and, probably, also reacts with the mixed solvent to give **12(Ar=4-MeOPh, X=OH)**, which however is not observed since it rapidly hydrolyzes to the aldehyde **11**. Accordingly, in the absence of AcOK, the same products but **12 (Ar=4-MeOPh, X=OAc)** were observed. Probably, under these conditions, the carbocation reacts predominantly with the water present in the mixed solvent to form **12(Ar=4-MeOPh, X=OH)** and therefrom **11**, as suggested above. It can also be noticed that in the absence of the base, deprotonation of **6b** at the C-H bond adjacent to sulfur is a relatively much less important process, which is probably due to the relatively low acidity of the C-H bond adjacent to the positively charged sulfur atom.



Scheme 3

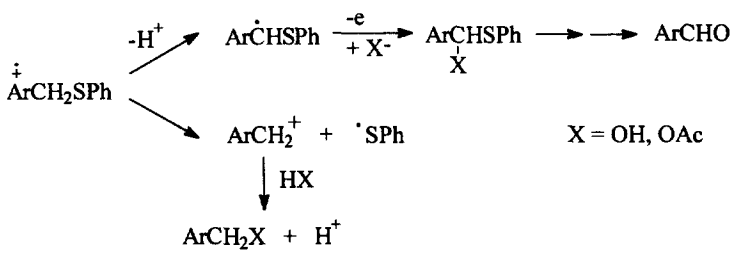
This result is in line with the recent finding that the deprotonation of thioanisole radical cation is very slow in water, but it undergoes a dramatic acceleration in the presence of OH^-.[8]

A clearly different situation is found in the oxidation of **7** where the benzylic substitution product **9[Ar=3,4-$(MeO)_2$Ph, X=OAc, OH]** are by far the major products accompanied by very small amounts of the other products listed in Table 1. Clearly this finding shows that now the radical cation is the one predominantly formed where the SOMO resides on the dimethoxy substituted benzylic aromatic ring, whereas the sulfur centered radical cation plays a very minor role. Accordingly, **9[Ar=3,4-$(MeO)_2$Ph, X=OAc, OH]** and 3,4-dimethoxybenzaldehyde derive from deprotonation of the benzylic radical cation as described in Scheme 2 [Ar = 3,4-$(MeO)_2$Ph], whereas **10**, **11** and **12** are formed by the sulfur centered radical cation as described above for **6b**. A similar situation is found in the absence of AcOK, where again the almost exclusive product is **9[Ar=3,4-$(MeO)_2$Ph, X=OH, OAc]** and only very small amounts of sulfoxide are formed.

In conclusion, the data presented above show that when only one methoxy group is present in the benzylic aromatic ring the sulfur centered radical cation and the radical cation with the SOMO on the benzylic moiety are formed in comparable amounts upon electron abstraction from the neutral parent. When two methoxy groups are present, however, the radical cation where the SOMO is on the benzylic aromatic ring is produced in much larger amounts than the sulfur centered radical cation.

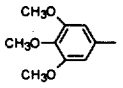
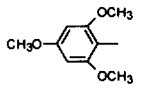
*Oxidation of **4** and **5** by Co(III)W*

On the basis of the results previously presented, there is little doubt that **4** and **5** should almost exclusively form radical cations with the SOMO residing on the benzylic aromatic ring, where as many as three methoxy groups are present. A further support to this conclusion comes from the observation[13] that the UV spectrum of $\mathbf{4}^{+\cdot}$ (λ_{max} at 430nm) closely resembles that of 1,2,3-trimethoxybenzene radical cation,[14] whereas it is drastically different from that of thioanisole radical cation (λ_{max} at 540 nm).[8] It follows that, both $\mathbf{4}^{+\cdot}$ And $\mathbf{5}^{+\cdot}$ should behave as alkylaromatic radical cations and not as sulfide radical cations.



Scheme 4

Table 2. Reaction Products (%) in the Oxidation of $ArCH_2SPh$ by Co(III)W in AcOH : H_2O at Room Temperature in the presence of AcOK.

Ar	base	Products (yield; %)[a]		
		ArCHO	$ArCH_2OH$	$ArCH_2OAc$
	AcOK 0.5M	19.0	2.8	8.0
	AcOK 0.5M	5.6	2.4	16.0

[a] Yields are referred to the oxidant considering a stoichiometry of 2:1 [Co(III)W/Substrate] in the formation of oxidation products (the stoichiometric ratio is however 1:1 in the case of the benzylic products alcohol and acetate). Average of two or more determinations. The error is ± 10%.

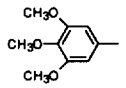
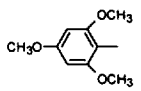
Thus, the products obtained in the oxidations with Co(III)W (reaction conditions are the same as those described above for **6** and **7** except for the temperature, see Experimental) and namely benzaldehydes, benzylic alcohols and acetates, as reported in Table 2, can be interpreted according to the mechanism illustrated in Scheme 4, where the radical cation undergoes deprotonation (leading to the corresponding benzaldehyde) and C-S bond cleavage (leading to the corresponding benzylic acetate and benzyl alcohol).[6,15]

It should however be noticed that small amounts of many other products were also obtained in the oxidations of **4** and **5**, which probably derive from reactions involving the very electron rich benzylic aromatic ring. As a matter of fact, it can react with the benzylic carbocation formed in the C-S bond cleavage step as well as undergo acetoxylation once formed the radical cation. An identification of these products (expected to be very difficult) was not considered worthwhile with respect to the aim of the present work.

*Enzymatic and biomimetic oxidation of **4** and **5***

The microsomal oxidations of **4** and **5** were carried out by incubating the substrates with phenobarbital induced rat liver microsomes. In both cases the reactions were started by addition of NADPH generating system. The biomimetic oxidations were carried out in acetonitrile, using FeTPPCl as the catalyst, imidazole as the porphyrin ligand and H_2O_2 as the oxidant. Products analyses were performed by NMR and liquid chromatography (further details are in the Experimental Part) and the results are collected in Table 3

Table 3. Reaction Products (%) in the Oxidation of $ArCH_2SPh$ with Phenobarbital Induced Rat Liver Microsomes or with H_2O_2 Catalyzed by FeTPPCl in MeCN.

Ar	Oxidizing System	Products (yield; %)[a]	
		$ArCH_2SOPh$	$ArCH_2SO_2Ph$
	Microsomal P450[b]	4.2	2.8
	$FeTPPCl/H_2O_2$[c]	64.9	5.4
	Microsomal P450[b]	d	d
	$FeTPPCl/H_2O_2$[c]	61.1	11.5

[a] Yields are referred to the starting material. Average of two or more determinations. The error is ± 10%.
[b] No products were formed when either NADPH generating system or microsomes were omitted.
[c] No products were observed in the absence of FeTPPCl.
[d] Under the limit of detection (0.2 %).

The first notation is that no products whatsoever were obtained in the microsomal oxidation of **5**. This was attributed by us to the too small solubility of **5** in the reaction medium. Concerning the other reactions, the data in Table 3 show that in all cases sulfoxides and sulfones are the observed reaction products. No evidence for the formation of benzylic as well as of other fragmentation products was obtained, at complete variance with what observed in the oxidations promoted by Co(III)W.

Clearly, this result is very important as it shows that in these reactions sulfoxides can be formed also from sulfides which upon electron transfer *should not form a sulfur centered radical cation*. Thus, it seems unlikely that the absence of fragmentation products is due to an extremely fast rate of the oxygen transfer between P-Fe(IV)=O and the sulfur of the radical cation (Scheme 1, path b). Accordingly, a fast rate for this step can reasonably be suggested when the SOMO of the radical cation is on the sulfur atom, but not certainly when the positive charge is delocalized on the aromatic ring as well as on the methoxy groups. Thus, the data in our hands suggest that the biomimetic and microsomal oxidations of sulfides most probably occur by a direct oxygen transfer from the iron-oxo complex to the sulfur atom of the neutral substrate (Scheme 1, path c).

EXPERIMENTAL SECTION

Methods. ^{1}H-NMR spectra were recorded on a Bruker AC300P spectrometer in $CDCl_3$. GC-MS analyses were performed on a HP5890 GC (OV1 capillary column, 12m x 0.2 mm) coupled with a HP5970

MSD. GLC analyses were performed on a Varian 3400 GC (OV1 capillary column, 25m x 0.2mm) and Varian Vista 6000 (OV1701 capillary column, 30m x 0.35 mm). HPLC analyses were carried out on a Hewlett Packard 1050 liquid chromatograph fitted with a UV-Vis detector operating at 230 nm (Supelcosil LC-18 column, 25 cm x 4.6 mm).

Starting Materials. The solvents AcOH (CARLO ERBA) and CH_3CN (CARLO ERBA-HPLC grade) and high purity commercial samples of thiophenol, 2-Phenylethyl chloride, 2-(4-methoxyphenyl)ethyl chloride, 2-(3,4)dimethoxyphenyl)ethanol, 3,4,5-trimethoxybenzyl chloride, 2,4,6-trimethoxybenzaldehyde, cobaltous acetate tetrahydrate, potassium acetate, sodium tungstate dihydrate, potassium persulfate, tetraphenylporphyrin iron(III) chloride (FeTPPCl) were used as received. 2-(3,4-dimethoxyphenyl)ethyl chloride was obtained from 2-(3,4)dimethoxyphenyl)ethanol using thionyl chloride and pyridine. Potassium 12-tungstocobalt(III)ate was prepared as described in literature.[9]

2-(4-methoxyphenyl)ethyl phenyl sulfide (**6**), 2-(3,4-dimethoxyphenyl)ethyl phenyl sulfide (**7**), 3,4,5-trimethoxybenzyl phenyl sulfide (**4**) were prepared by reaction of the corresponding phenethyl or benzyl chloride with thiophenol in refluxing acetone in the presence of anhydrous K_2CO_3 as previously described.[16] 2,4,6-Trimethoxybenzyl phenyl sulfide (**5**) was obtained by treating 2,4,6-trimethoxybenzyl alcohol (obtained after reduction of the corresponding benzaldehyde with $NaBH_4$) with excess thiophenol in the presence of trace amounts of *p*-toluenesulfonic acid in benzene. All compounds were purified by chromatography on silica gel columns eluting with light petroleum ether-ethyl acetate (5:1) and characterized by ^1H NMR and GC-MS.

Products. Product structures were demonstrated as follows: 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde, 2,4,6-trimethoxybenzaldehyde and 3,4,5-trimethoxybenzylalcohol, comparison with authentic specimens (commercial products). 4-Methoxyphenethyl phenyl sulfoxide, 3,4-dimethoxyphenethyl phenyl sulfoxide, 3,4,5-trimethoxybenzyl phenyl sulfoxide, 2,4,6-trimethoxybenzyl phenyl sulfoxide, 3,4,5-trimethoxybenzyl phenyl sulfone, 2,4,6-trimethoxybenzyl phenyl sulfone, 1-(4-methoxyphenyl)-2-(phenylthio)ethanol, 1-(4-methoxyphenyl)-2-(phenylthio)ethyl acetate, 3,4,5-trimethoxy-benzyl acetate and 2,4,6-trimethoxybenzyl acetate, comparison with authentic specimens (sinthethized according to literature procedures).[17-19] 4-Methoxyphenylacetaldehyde **11(Ar=4-MeOPh)**, 2-(4-Methoxyphenyl)-1-(phenylthio)ethyl acetate **12(Ar=4-MeOPh, X=OAc)**, 1-(3,4-Dimethoxyphenyl)-2-(phenylthio)ethanol **9[Ar=3,4-$(MeO)_2$Ph, X=OH]** and 1-(3,4-dimethoxyphenyl)-2-(phenylthio)ethyl acetate **9[Ar=3,4$(MeO)_2$Ph, X=OAc]** were isolated from the oxidation in a preparative scale of **6** and **7** with Co(III)W in AcOH/H_2O (7/3) in the presence of AcOK 0.5M and characterized on the basis of the following spectral data. **11(Ar=4-MeOPh)** [NMR δ 9.73-9.71 (t, 1H, CHO), 7.13-6.88 (m, 4H, ArH), 3.80 (s, 3H, OCH_3), 3.63-3.62 (d, 2H, CH_2); MS *m/z* (rel. intensity) M^+ 150,121(100),91,78,77,51]; **9[Ar=3,4-$(MeO)_2$Ph, X=OH]** [NMR δ 7.43-6.79 (m, 8H, ArH), 4.70-4.65 (q, 1H, CH), 3.86 (2s, 6H, OCH_3), 3.32-3.07 (m, 2H,

CH_2), 2.9 (s, 1H, OH); MS *m/z* (rel. intensity) M^+ 290,272,167(100),139,124,109,108,77,65,51]; **9[Ar=4-(MeO)$_2$Ph, X=OAc]** [NMR δ 7.40-6.80 (m, 8H, ArH), 5.86-5.81 (q, 1H, CH), 3.86 (2s, 6H, OCH_3), 3.47-3.19 (m, 2H, CH_2), 2.02 (s, 3H, $COCH_3$); MS *m/z* (rel. intensity) M^+ 332,272,241,209,167(100),165, 139,91,77,51]; **12(Ar=4-MeOPh, X=OAc)** [NMR δ 7.5-6.8 (m, 8H, ArH), 6.27-6.23 (q, 1H, CH), 3.78 (s, 3H, OCH_3), 3.10-2.97 (m, 2H, CH_2), 1.98 (s, 3H, $COCH_3$)]. The formation of **11[Ar=3,4-(MeO)$_2$Ph]** and **12[Ar=3,4-(MeO)$_2$Ph, X=OAc]** in the reaction of **7** with Co(III)W/AcOK was deduced on the basis of the presence, in the NMR spectrum of the crude product, of an A_2X [δ 9.74-9.71 (t, 1H, CHO), 3.63-3.62 (d, 2H, CH_2)] and an ABX [δ 6.29-6.25 (q, 1H, CH), 3.11-2.88 (m, 2H, CH_2)] system, closely corresponding to those observed for **11(Ar=4-MeOPh)** and **12(Ar=4-MeOPh, X=OAc)**, respectively. Moreover, the presence of **11[Ar=3,4-(MeO)$_2$Ph]** was confirmed by GC-MS analysis [MS *m/z* (rel. intensity) M^+ 180,166,151(100),135,107,77,65,51]. Both **11[Ar=3,4-(MeO)$_2$Ph]** and **12[Ar=3,4-(MeO)$_2$Ph, X=OAc]** were formed in so small amounts as to make impossible their isolation from the reaction mixture.

Microsomal Preparation. The liver microsomes were obtained from Male Sprague Dawley rats pretreated with sodium phenobarbital (300 mg/Kg of body weight, each day for 7 d) according to a procedure reported in the literature.[20]

Oxidation with Potassium 12-tungstocobalt(III)ate. The oxidation procedure was as follow: a solution of the substrate (0.3 mmol) in 5 ml of AcOH/H_2O (7/3), in the presence or in the absence of AcOK (2.5 mmol), was degassed with argon in a 10 ml Schlenk tube. After thermal equilibration at 55 °C (oxidation of **6-7**) or at room temperature (oxidation of **4-5**) the reaction was started by rapid addition of 0.15 mmol of cobalt(III) complex under Ar atmosphere. Reaction time was 30 min for **5**, **6** (in the presence of base) and **7**, 1 h for **4** and **6** (in the absence of base). Workup was performed as already described[9] and the residue was subjected to analysis. The reaction products and the yields referred to the oxidant are reported in Table 1 (oxidations of **6** and **7**) and in Table 2 (oxidations of **4** and **5**). Diphenyl disulfide was also observed among the reaction products in all the experiments.

Quantitative determinations were performed by HPLC (MeOH/H_2O=4/1, flow rate 1ml/min) and ^{1}H-NMR. The material balance was between 90% and 100%.

Biomimetic Oxidation. FeTPPCl (6.5 μmol) and imidazole (30 μmol) were added to a solution of substrate (0.125 mmol) in 5 ml of CH_3CN, H_2O_2 30% (0.25 mmol) was added and the reaction mixture was stirred under argon atmosphere at room temperature for 30 min. At the end of the reaction an internal standard and 10 ml of H_2O were added, the mixture extracted with ether and analyzed by ^{1}H-NMR. Only sulfoxides and sulfones were produced. Reaction products and the yields referred to the starting material are reported in Table 3. Blank experiments were carried out in the absence of the metalloporphyrin, no products were observed in the absence of the catalyst.

Enzymatic Oxidation. In the microsomal oxidation, phenobarbital-induced rat liver microsomes (28 mg protein), NADPH generating system (5 μmol of $NADP^+$, 50 μmol of glucose-6-phosphate, 50 μmol of $MgCl_2 \times 6H_2O$, 10 units of glucose-6-phosphate dehydrogenase) and **4-5** (20 μmol) were incubated in 5 ml of phosphate buffer (pH 7.4, 0.1 M) at 36 °C for 2 h. The substrates had a limited solubility, therefore the reaction mixture, except for the NADPH generating system, was preincubated for 10 min at 36 °C. Reaction products were extracted as reported before[1a] and analyzed by HPLC ($MeCN/H_2O$=88/12, flow rate 1ml/min). In the oxidation of **4** the products observed were the corresponding sulfoxide and sulfone. The yields, referred to the starting material, are reported in Table 3. In the oxidation of **5** no products were observed after the incubation. Blank experiments, carried out in the absence of microsomes or of NADPH generating system lead to the complete recovery of the starting material and no formation of oxidation products.

Acknowledgements. Thanks are due to the Ministry for the University and the Scientific and Technological Research (MURST) and to the National Research Council (CNR) for financial support. Thanks are also due to Professor L. Vittozzi and his group (Istituto Superiore di Sanita', Rome) for kindly providing us with rat liver microsomes.

REFERENCES AND NOTES

1. (a) Watanabe, Y.; Numata, T.; Iyanagi, T.; Oae, S *Tetrahedron Lett.* **1980**, *21*, 3685-3688; Watanabe, Y.; Numata, T.; Iyanagi, T.; Oae, S. *Bull. Chem. Soc. Jpn.*, **1981**, *54*, 1163-1170; Oae, S.; Watanabe, Y.; Fujimori, K. *Tetrahedron Lett.* **1982**, *23*, 1189-1192; Watanabe, Y.; Iyanagi, T.; Oae, S. *Bull. Chem. Soc. Jpn.*, **1982**, *55*, 188-195; Oae, S.; Mikami, A.; Matsuura, T.; Ogawa-Asada, K.; Watanabe, Y.; Fujimori, K.; Iyanagi, T. *Biochem. and Biophys. Res. Commun.* **1985**, *131*, 567-573; Cashman, J. R.; Olsen, L. D. *Mol. Pharmacol.* **1990**, *38*, 573-585; Pautet, F. Barret, R.; Favre, L.; Daudon, M. *Pharmazie* **1988**, 437. (b) Takata, T.; Tajima, R.; Ando, W. *Phosphorus and Sulfur*, **1983**, *16*, 67; Cashman, J. R.; Proudfoot, J.; Ho, Y.-K.; Chin. M. S.; Olsen, L. D. *J. Am. Chem. Soc.* **1989**, *111*, 4844.
2. Dunford, H. B., Stilman, J. S. *Coord. Chem. Rev.* **1976**, *19*, 187; Ortiz de Montellano, P. R. *Ann. Rev Pharmacol. Toxicol.* **1992**, *32*, 89; Kobayashi, S.; Nakano, M.;Goto, T.; Kimura, T.; Schaap, A. P. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 166; Kobayashi, S.; Nakano, M.; Kimura, T.; Schaap, A. P. *Biochemistry* **1987**, *26*, 5019-5022; Doerge, D. R. *Arch Biochem. Biophys.* **1986**, *244*, 678; Doerge, D. R.; Cooray, N. M.; Brewster, M. E. *Biochemistry* **1991**, *30*, 8960; Harris, R. Z.; Newmyer, S. L.; Ortiz de Montellano, P. R. *J. Biol. Chem.* **1993**, *268*, 1637; Ozaki, S.-I.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1994**, *116*, 4487; Ozaki, S.-I.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1995**, *117*,

7056; Perez, U.; Dunford, H. B. *Biochim. Biophys. Acta* **1990**, *1038*, 98; Colonna, S.; Gaggero, N.; Carrea, G.; Pasta, P. *J. Chem. Soc Chem. Commun.* **1992**, 357.

3. Ortiz de Montellano, P. R. *Cytochrome P-450: Stucture, Mechanism and Biochemistry;* Second edition, Plenum: New York. 1995; *Peroxidases in Chemistry and Biology*; Everse, J., Everse, K. E., Giishman, M. B., Eds.; CRC Press: Boca Raton, 1991.
4. Baciocchi, E.; Ioele, M.; Lanzalunga, O.; Malandrucco, M.; Steenken, S. *J. Am. Chem. Soc.* **1996**, *118*, 8973-8974.
5. (a) Groves, J. R.; Watanabe, Y. *J. Am. Chem. Soc.* **1986**, *108*, 507; (b) Ostovic, D.; Bruice, T. C. *Acc. Chem. Res.*, **1992**, *25*, 314.
6. Baciocchi, E.; Lanzalunga, O. Marconi, F. *Tetrahedron Lett.* **1994**, *35*, 9771-9774.
7. To be published.
8. Baciocchi, E.; Ioele, M.; Steenken, S. *J. Phys. Chem.*, in press.
9. Eberson, L. *J. Am. Chem. Soc.* **1983**, *105*, 3192; Baciocchi, E.; Crescenzi, M.; Fasella, E.; Mattioli, M. *J. Org. Chem.* **1992**, *57*, 4684.
10. A fast equilibrium between **6a** and **6b** is suggested by the observation that the total yield of products from **6b** relative to that from **6a** increases in the presence of AcOK (Table 1). The base shifts the equilibrium towards **6b** by probably favouring the deprotonation from the α to sulfur C-H bond more than the deprotonation from the benzylic C-H bond of **6a**.
11. Gravel, D.; Farmer, L.; Ayotte, C. *Tetrahedron Lett.* **1990**, *31*, 63; Ci, X.; Whitten, D. G. in *Photoinduced Electron Transfer;* Fox, M. A.; Chanon, M. Eds.; Elsevier: Amsterdam, 1988; Part C, pp 567.
12. Jones, G.; Huang, B.; Griffin, S. F. *J. Org. Chem.* **1993**, *58*, 2035-2042.
13. Data from a pulse radiolysis study. To be published.
14. O'Neill, P.; Steenken, S.; Schulte-Frohlinde, D. *J. Phys. Chem.* **1975**, *79*, 2773-2779.
15. Baciocchi, E.; Fasella, E.; Lanzalunga, O.; Mattioli, M. *Angew. Chem.* **1993**, *105*, 1100; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1071.
16. Russell, G. A.; Pecoraro, J. M. *J. Am. Chem. Soc.* **1979**, *101*, 3331-3333; Baciocchi, E.; Intini, D.; Piermattei, A.; Rol, C.; Ruzziconi, R. *Gazz. Chim. Ital.* **1989**, *119*, 649-652.
17. Ruff, F.; Kucsman, A. *J. Chem. Soc. Perkin Trans. II*, **1985**, 683-687.
18. Behzadi, A.; Owen, L. N. *J. Chem. Soc. Perkin I*, **1973**, 2733-2737.
19. Knüsli, E. *Gazz. Chim. Ital.* **1949**, *79*, 621.
20. Ade, P.; Soldaini, B.; Castelli, M. G.; Chiesara, E.; Clementi, F.; Fanelli, R.; Funari, E.; Ignesti, G.; Marabini, A. *Ecotoxicol. Envir. Safety,* **1984**, *8*, 423.

(*Received* 27 *February* 1997; *accepted* 15 *April* 1997)