Novel Model Sulfur Compounds as Mechanistic Probes for Enzymatic and Biomimetic Oxidations

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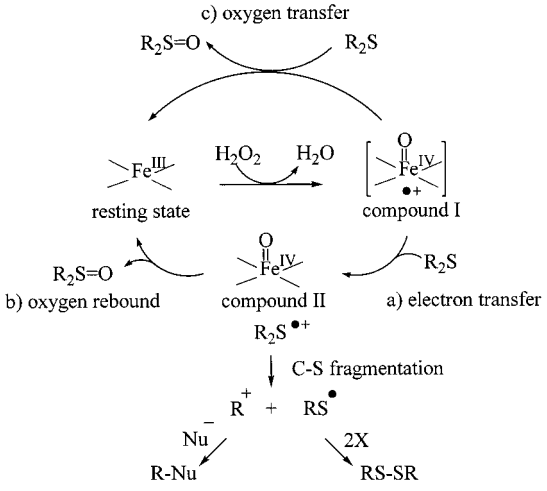
To test for the intermediacy of sulfide radical cations in biomimetic and enzymatic oxidations, the sulfides $PhSCH_3$ (**1a**), $PhSCH_2Ph$ (**1b**), $PhSCHPh_2$ (**1c**), $PhSCPh_3$ (**1d**), CH_3SCHPh_2 (**2**), $PhSCH_2CH{=}CH_2$ (**3**), $PhSCH_2CH{=}CHPh$ (**4**) and $CH_3SCH_2CH{=}CHPh$ (**5**) were studied, and their results were compared to those obtained for the corresponding chemical electron transfer (CET) and photoinduced electron transfer (PET) oxidations. The radical cations generated from **3**–**5** by CET in the presence of cerium(IV) ammonium nitrate (CAN) yielded only fragmentation products from the alkyl cations and the thiyl radicals ($RS^{\cdot}$), whereas $\mathbf{2}^{\cdot+}$ afforded both fragmentation and mainly α-deprotonation products. Photochemical treatment of the sulfides **1a** and **1b** with $C(NO_2)_4$ gave only the corresponding sulfoxides, while fragmentation was the main pathway for the photoreactions of **1c**, **2** and **5**, and for **1d** only this latter process was observed. These results support our selection of the sulfides $RSCHPh_2$, $RSCH_2CH{=}CHPh$ (R = Me, Ph) and $PhSCPh_3$ as models for the biomimetic and enzymatic studies. As evidenced by the sulfoxides and sulfones detected as unique products both in protic and in aprotic solvents, it is proposed that the mechanism of the biomimetic sulfoxidations of sulfides **1c** and **2**–**5** by $TPPFe^{III}Cl$ is direct oxygen transfer. Three enzymes – *Coprinus cinereus* peroxidase (CiP), horseradish peroxidase (HRP) and chloroperoxidase (CPO) – were studied in the oxidation of sulfides **1a**, **2**, **4** and **5**. The use of a racemic alkyl hydroperoxide in the CiP enzymatic oxidation of sulfides **5** and **2** yielded the corresponding sulfoxides (23 and 29%) and the aldehyde or benzophenone (5%), respectively. These results suggest the involvement of an ET process for the CiP-catalysed oxidation. Fragmentation products were observed in the enzymatic oxidation of sulfide **4** with HRP, which confirms the previously proposed ET mechanism. On the other hand, the CPO-enzymatic oxidation of sulfide **5** yielded only the corresponding sulfoxide, as would be expected for a direct oxygen-transfer or oxene mechanism.

Introduction

Enzymatic oxidation of sulfides to sulfoxides can be achieved by hemoproteins such as cytochrome P-450 and peroxidases.[1] Elucidation of the mechanism involved in these enantioselective sulfoxidations, valuable in asymmetric synthesis,[2] has attracted a great deal of attention during the past decade.[3–5] Two different mechanisms for this oxidation are possible, both of them involving the initial formation of the oxo(porphyrin)iron(IV) radical cation (compound I) through reaction between the enzyme and the peroxide.[1] This dichotomy is shown in Scheme 1. The so-called oxygen-rebound mechanism (paths *a* and *b*, Scheme 1), is triggered by electron transfer (ET) from the sulfide to the oxo(porphyrin)iron(IV) radical cation, with the generation of the corresponding sulfide radical-cation intermediate. Subsequent reactions between this radical cation and the oxo(porphyrin)iron(IV) complex result in the corresponding sulfoxide. The other possibility is a direct oxygen transfer from compound I to the neutral sulfide (path *c*, oxene mechanism, Scheme 1).



Scheme 1

There is currently general agreement that sulfoxidation by horseradish peroxidase (HRP)[3b,5a,5c] occurs through

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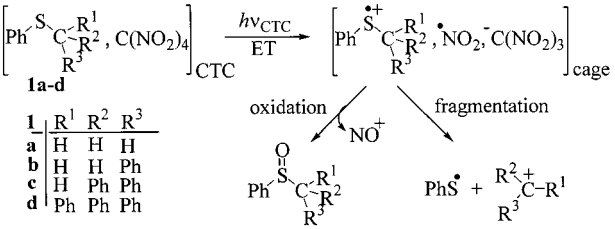
an ET process with the sulfide radical cations as intermediates. Although involvement of the radical cation was not confirmed for chloroperoxidase (CPO), a similar mechanism was initially advanced.[5a] Later, a direct oxygen transfer was assumed for this catalysed oxidation, instead of the ET mechanism as proposed for HRP.[5c] In contrast to the well studied mechanism for sulfoxidation with HRP, little is known about the mechanisms of this oxidation reaction when catalysed by other peroxidases. From a kinetic study, an oxygen-rebound mechanism was assumed for sulfoxidations of methyl phenyl sulfide by *Coprinus cinereus* peroxidase (CiP) and lactoperoxidase (LPO).[5d] On the other hand, since Oae's pioneering work,[3a] there is still controversy concerning the mechanism for cytochrome P-450 and the biomimetic models. In conflict with previous reports,[3b,3c,3d] an ET process has recently been proposed by Baciocchi[4] for the mechanism of the oxidation of aromatic sulfides catalysed by a water-soluble (porphyrin)iron. Furthermore, the participation of two distinct reactive intermediates, depending on the solvent and the oxidant, has been proposed for (porphyrin)iron(III) complex catalysed epoxidation reactions. Compound I, however, is the reactive species in protic solvents or under acid-catalysed conditions regardless of the oxidant.[6]

In order to gain better mechanistic understanding of such complex enantioselective sulfoxidations, substrates that will undergo competitive processes such as C−S bond cleavage or α-deprotonation more rapidly than formation of the sulfoxide in the oxygen-rebound mechanism are essential. Such substrates would allow the intermediacy of the postulated sulfur-centred radical cations to be assessed (Scheme 1). Up to now, the sulfides used for testing for the participation of a sulfide radical cation in the mechanism have been methyl phenyl sulfide (**1a**), benzyl phenyl sulfide (**1b**) and their derivatives.[3−5]

We had previously studied the generation and reactivity of sulfide radical cations through photochemical reactions with tetranitromethane [$C(NO_2)_4$].[7] These reactions proceed through initial formation of a charge-transfer complex, followed by light-induced, dissociative electron transfer to afford a triad of reactive species: the sulfur-centred radical cation, the radical nitrogen dioxide, and the nitroform anion (Scheme 2). Coupling of the first two species and subsequent loss of nitrosyl cation gives the corresponding sulfoxide. Alternatively, C−S bond cleavage can occur to produce a thiyl radical and a carbocation, the radical dimerising to the corresponding disulfide, and the cation being trapped by a nucleophile. Competition between *oxidation* and/or *fragmentation* depends markedly on the substrate structure (Scheme 2).Thus, in the photooxidation reactions of **1a** and **1b** in the presence of $C(NO_2)_4$, only the sulfoxides are obtained, which is ascribed to a fast oxygen transfer from the nitroxide radical to the sulfur-centred radical cation in the solvent cage. Under similar conditions, however, **1c** undergoes both sulfoxidation and C−S bond scission, while **1d** only experiences fragmentation.



Scheme 2

In view of these findings, we regard the sulfides **1c**−**d**, as well as the methyl derivative **2**, as appropriate model substrates with which to study the mechanisms of biomimetic oxidation of sulfides. With these substrates, it is to be expected that C−S bond cleavage should be more efficient than sulfoxidation in the oxygen-rebound process. Other sulfur models under study are the allyl phenyl sulfide derivatives **3**−**5**, for which it is likely that $\mathbf{4}^{\bullet+}$ or $\mathbf{5}^{\bullet+}$ should be prone to C−S bond fragmentation to give the stabilised cinnamyl cation intermediate. With some of these model sulfides we have tested for the intermediacy of the sulfur-centred radical cations in enzymatic oxidation with CiP, HRP and CPO. Here we report the results of our detailed study of the chemical electron transfer (CET), photoinduced electron transfer (PET) with $C(NO_2)_4$, biomimetic and enzymatic oxidations of the sulfides **1c**, **1d** and **2**−**5**.

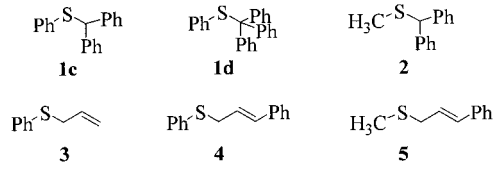


Figure 1. Structure of the sulfur models employed

Results and Discussion

Chemical Electron Transfer − Oxidation by CAN

The results obtained from treatment of sulfides **2**−**5** with CAN in acetonitrile under nitrogen are summarised in Table 1. These CET reactions generate the sulfur-centred radical cations, which fragment into the thiyl radicals and the corresponding carbocation as intermediates, affording the disulfides and products of nucleophilic attack on the carbocation as main products. Sulfide **2**, when oxidised by CAN (Table 1, Entry 1), mainly affords products originating from α-deprotonation[8] of the sulfur radical cation (benzophenone), together with, to a minor extent, fragmentation products originating from the benzhydryl cation and dimethyl disulfide. Sulfide **3**, on the other hand, mainly yields the fragmentation product diphenyl disulfide, with the sulfoxide and sulfone derivatives being observed only in trace amounts (Table 1, Entry 2). When sulfides **4** and **5** were reacted with CAN in CH_3CN for 30 min, complex mixtures of fragmentation products were found. Although

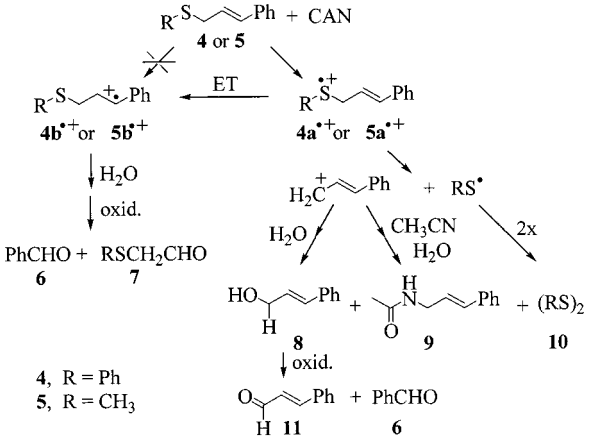
Table 1. Oxidation of sulfides by chemical electron transfer with CAN and photoinduced electron transfer with $C(NO_2)_4$

Entry	Oxid.	R^1SR^2 (R^1 = Me, Ph)	Convn.	Product yields [%][a] Fragmentation				Oxidation	
				$R^1_2S_2$	R^2OH	**11**	**6**	SO	SO_2
1	CAN[b]	**2**	78	24	7[c]	–	15	–	–
2		**3**	48	5	–	–	–	[d]	[d]
3		**4**	73	8	5	9	16	–	–
4		**5**	73	19	7[e]	3	19	–	–
5[f]		–	14	–	–	5	9	–	–
6[g]	$Ar_3N^{\cdot+}$	**5**	99	15	23[e]	3	5	–	–
7[h]	$C(NO_2)_4$ [i]	**1a**	100	–	–	–	–	100	–
8[h]		**1b**	100	–	–	–	–	100	–
9[h]		**1c**	100	73	7[j]	–	–	23	–
10[h]		**1d**	100	94	90	–	–	–	–
11		**2**	100	[k]	74	–	–	4	22
12[l]		**2**	100	[k]	17	–	–	–	74
13		**5**	62	[k]	3	2	12	7	5

[a] Fragmentation products were quantified by GC analysis by an internal standard method and oxidation products by ^1H NMR spectroscopy. The degree of conversion was determined by quantification of the unchanged sulfide. [b] Reactions were carried out in CH_3CN in the presence of 1 equiv. of CAN over 30 min under N_2. [c] Together with Ph_2CO (52%) and $Ph_2CHNHCOCH_3$ (5%). [d] Only traces of the corresponding sulfoxides and sulfones were detected. [e] Together with 2% of **9**. [f] Control experiment with alcohol **8** as substrate. [g] The reaction was performed with 1 equiv. of $(p\text{-}BrC_6H_4)_3N^{\cdot+}$ $SbCl_6^-$ as oxidant. [h] Ref.[7] [i] Reactions were carried out in CH_3CN unless otherwise indicated, in the presence of 1 equiv. of $C(NO_2)_4$ under N_2 and with irradiation at λ = 419 nm for 30 min. [j] Together with Ph_2CO (6%), $Ph_2CHNHCOCH_3$ (25%) and $Ph_2CHC(NO_2)_3$ (41%), from ref.[7] [k] Not quantified. [l] In CH_2Cl_2.

much effort was devoted to improving the recovery of the volatile compounds from the product mixtures, the mass balances of these reactions were lower than expected (for quantification, the internal standard was added at the outset of the reaction; Table 1, Entries 3 and 4).

Sulfides **4** and **5** are oxidised at sulfur to yield the radical cations $\mathbf{4a}^{\cdot+}$ and $\mathbf{5a}^{\cdot+}$, which in turn produce $\mathbf{4b}^{\cdot+}$ and $\mathbf{5b}^{\cdot+}$ through a hole transfer to the double-bond functionality (Scheme 3). Direct oxidation of the double bond by CAN ($E_{1/2}$ = 1.61V)[9] may be regarded as negligible, since styrene was not oxidised by CAN in a control experiment under the same experimental conditions. This is consistent with a half-wave oxidation potential of styrene ($E^{ox}_{1/2}$ = 2.05 V),[10] which is higher than those of the sulfides **4** and **5** (E^{ox}_p = 1.56 V and 1.38 V, respectively).[11] These values were obtained vs. SCE in acetonitrile. Fragmentation of $\mathbf{4a}^{\cdot+}$ and $\mathbf{5a}^{\cdot+}$ yielded the cinnamyl cation and thiyl radicals. Nucleophilic attack on the cation by the solvent or water (present as traces) afforded the amide **9** and the alcohol **8**. Dimerisation of the thiyl radicals resulted in the corresponding disulfides **10**. Alternatively, the radical cations $\mathbf{4b}^{\cdot+}$ and $\mathbf{5b}^{\cdot+}$ afforded the aldehydes **6** and **7** by oxidative cleavage (Table 1, Entries 3 and 4). This C−C bond fragmentation is probably the result of nucleophilic reaction of water (present as traces) with the radical cations $\mathbf{4b}^{\cdot+}$ and $\mathbf{5b}^{\cdot+}$ to afford vicinal diols, which are further oxidised to the aldehydes **6** and **7**.[12] A similar oxidative fragmentation of 1-aryl-1-cycloalkenes has been observed previously with use of CAN in MeOH.[13] Furthermore, the formation of benzaldehyde as a side product in the epoxidation of styrene and derivatives, through C−C bond fragmentation, has previously been described for enzymatic oxidation with peroxidases,[14] and also in electrocatalytic oxidation by a high-valent (porphyrin)ruthenium cation radical.[15]



Scheme 3

The allylic alcohol **8** was not stable under the experimental conditions, and further oxidation of **8** by CAN yielded the aldehydes **11** and **6**, the latter through oxidative cleavage of the double bond[16] (Table 1, Entry 5). A mixture of the epoxide, cinnamyl aldehyde and benzaldehyde was obtained during the enantioselective oxidation of cinnamyl alcohol with catalysis by Mn^{II}- and Ru^{III}-substituted polyoxometalates.[17] Furthermore, oxidation of cinnamyl alcohol by transition metal cations in zeolites as catalysts also affords benzaldehyde in variable yields as a side product.[18] Similar results were obtained with use of Magic Blue [(*p*-

$BrC_6H_4)_3N^{\cdot+}$ $SbCl_6^-$] as oxidant in place of CAN (Table 1, Entry 6).

Photoinduced Electron Transfer. Oxidation with $C(NO_2)_4$

The photochemical oxidations of the sulfides **2** and **5** with $C(NO_2)_4$ were performed in order to evaluate the possibility of competition between oxidation and C−H or C−S bond cleavage in the photochemically generated sulfide radical cations. Table 1 summarises these and the previously reported results for sulfides **1a**−**d**.[7]

Oxidation and/or *fragmentation* products are observed in the photochemical reactions of the sulfides **1a**−**d**, **2** and **5** with $C(NO_2)_4$. The PET reactions of **1a** and **1b** give only the corresponding sulfoxides (oxidation), but the main reaction observed on photoirradiation of **1c**, **2** and **5** in the presence of $C(NO_2)_4$ is fragmentation, while for **1d** only this latter process is observed. The competition between the in-cage coupling of the sulfur-centred radical cation intermediates and the nitrogen dioxide radical with respect to *oxidation* and their *fragmentation*, depends on the substrate structure and the solvent. Thus, the driving force behind the carbon−sulfur bond cleavage in the sulfide radical cation intermediate mirrors the stabilization of the carbenium ion produced through phenyl and allylphenyl conjugation (i.e., the established sequence $PhCH_2^+ < Ph_2CH^+ \approx PhCH{=}CHCH_2^+ < Ph_3C^+$ for such fragmentation processes dominates in these orders). For sulfide **2** the *oxidation*/*fragmentation* product ratio depends on the solvent (Table 1, Entries 11 and 12). *Fragmentation* is thus the main pathway in the polar CH_3CN, while in-cage coupling to afford *oxidation* products is favoured in the non-polar CH_2Cl_2.

These results clearly demonstrate that the fragmentation of $PhSMe^{\cdot+}$ or $PhSCH_2Ph^{\cdot+}$ is slower than that of $RSCHPh_2^{\cdot+}$, $RSCH_2CH{=}CHPh^{\cdot+}$ (R = Me, Ph) and $PhSCPh_3^{\cdot+}$, suggesting that sulfides **1c**, **1d**, **2** and **5** should be better choices than sulfides **1a** or **1b** as model compounds and so are used in this report.[19]

Biomimetic Sulfoxidation by $TPPFe^{III}Cl$

Biomimetic sulfoxidations were carried out in CH_3CN, with H_2O_2 as oxygen source and $TPPFe^{III}Cl$ [(5,10,15,20-tetraphenylporphyrin)iron chloride] as catalyst. The results are listed in Table 2. For the sulfides **1c** and **2**−**5** the corresponding sulfoxides and sulfones were obtained in CH_3CN, without even traces of C−S or C−H bond fragmentation products being observed. In CH_2Cl_2, the reaction of sulfide **1c** was slower and afforded only the sulfoxide. No products were observed in the absence of $TPPFe^{III}Cl$ and with the porphyrin itself. With phenyl triphenylmethyl sulfide (**1d**) no products had been formed after 48 h either in CH_3CN or in CH_2Cl_2, with a sulfide/catalyst molar ratio of 6:1 or even when the reaction was performed with $FeTPP^{III}OH$[20] as catalyst. We also investigated [tetrakis(pentafluorophenyl)porphyrin]iron chloride ($TPFPPFe^{III}Cl$) as catalyst in the oxidation reaction of sulfide **2** with H_2O_2. The metal and porphyrin reduction potentials of halogenated (porphyrin)iron compounds are anodically shifted from those of $TPPFe^{III}Cl$, favouring a possible ET mechanism.[21] Nevertheless, only the sulfoxide derivative was obtained in this reaction, without deprotonation or fragmentation products (Table 2, Entry 5).

Table 2. Biomimetic sulfoxidation with $TPPFe^{III}Cl$

Entry[a]	Sulfide	Conditions		Product yields [%][b]		
		Solvent	Time [h]	Conversion	SO	SO_2
1	**1c**	CH_3CN	24	100	20	63
2	**1c**	CH_2Cl_2	48	53	49	−
3[c]	**2**	CH_3CN	2	78	76	4
4[c]	**2**	CH_3CN	24	100	71	28
5[c][d]	**2**	CH_3CN	2	59	52	−
6[c][e]	**2**	CH_3CN/ CH_2Cl_2	2	55	45	−
7[c][f]	**2**	CH_3OH/ CH_2Cl_2	2	89	90	−
8	**3**	CH_3CN	0.5	100	8	90
9[g]	**4**	CH_3CN	0.5	95	58	37
10[g]	**4**	CH_3CN	2	100	47	53
11[c]	**5**	CH_3CN	2	77	65	8
12[c][e]	**5**	CH_3CN/ CH_2Cl_2	2	79	69	6
13[c][f]	**5**	CH_3OH/ CH_2Cl_2	2	84	64	2

[a] Reactions were carried out in 5 mL of the indicated solvent with 25 mM of the sulfide at room temperature (ca. 20 °C), in a sulfide/H_2O_2/catalyst ratio of 20:40:1. [b] Quantified by GC analysis by the internal standard method, unless otherwise indicated. The conversion was determined by quantification of the unchanged sulfide. [c] Yield determined by ^1H NMR spectroscopy. [d] $TPFPPFe^{III}Cl$ as catalyst. [e] CH_3CN/CH_2Cl_2 ratio 1:1. [f] CH_3OH/CH_2Cl_2 ratio 3:1. [g] Quantified by HPLC.

It had previously been reported that the oxo(porphyrin)iron(IV) cation radical (Compound I) is generated as a reactive oxidising intermediate in (porphyrin)iron(III) complex-catalysed epoxidation reactions with *m*-chloroperoxybenzoic acid (*m*CPBA) as oxidant in protic solvents (mixtures of CH_3OH and CH_2Cl_2) or under acid catalytic conditions, while the reactive intermediate in aprotic solvents (mixtures of CH_3CN and CH_2Cl_2) is a hydroperoxy iron(III) complex.[6] In order to evaluate the possibility of participation of an oxidising intermediate other than compound I, sulfoxidation reactions of sulfides **2** and **5** were performed in the reported previously protic and aprotic solvent mixtures (Table 2, Entries 6, 7, 12 and 13) and in the presence of $HClO_4$ as acid catalyst.[22] There were no differences between the two solvent mixtures and CH_3CN in the oxidation product distributions. These results are in agreement with those previously reported by Nam, for (porphyrin)iron(III)-catalysed epoxidation reactions with H_2O_2 as oxidant, which afforded similar results regardless of the solvent mixture used.[6] It can be concluded that the radical cation compound I is the oxidising species generated in the current study.

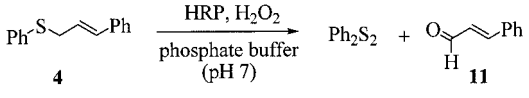
The sulfides **2**−**5** were found to be more reactive than **1c** and **1d**, with the reactions being complete in under 2 h in the cases of the allyl derivatives **3** and **4**. In contrast, 24 h were necessary for complete conversion of **1c**, while **1d** was unreactive. The reactivity thus decreased as the steric hindrance of the sulfide increased, making the approach to the

oxo(porphyrin)iron(IV) more difficult. On the other hand, highly chemoselective sulfoxidation was observed in the (porphyrin)iron(III) complex-catalysed reactions of the sulfides **3**−**5** containing a double bond.[23] Oxidation of **3** thus afforded the sulfone (90%) as main product after half an hour, while sulfide **5** yielded mainly the sulfoxide (69%), with the sulfone as a minor product (6%) (Table 2, Entries 8 and 12). No effort to optimise these reactions was made.

The finding of sulfoxides and sulfones as oxidation products from the sulfides **1c** and **2**−**5** in the presence of both porphyrins, the absence of fragmentation or α-deprotonation products from a possible sulfide radical cation intermediate, the fact that the same results were obtained both in protic ($MeOH/CH_2Cl_2$) and in aprotic ($MeCN/CH_2Cl_2$) solvents, together with the lack of reactivity of the sulfide **1d**, suggest that these biomimetic oxidations do not take place through ET from the oxoiron radical cation to the sulfide, as has been recently proposed.[4] This process should not be significantly affected by steric hindrance, as would be expected for a direct oxygen transfer, which requires a close approach of the sulfur atom to the oxoiron centre in Compound I. The results reported here thus suggest that the mechanism involved in these biomimetic sulfoxidations is a direct oxygen transfer rather than an ET pathway, which would imply sulfide radical cations as intermediates.

Enzymatic Sulfoxidation

We have studied different enzymatic systems: horseradish peroxidase (HRP), *Coprinus cinereus* peroxidase (CiP) and chloroperoxidase (CPO). These results are presented in Table 3. Sulfoxidation by HRP has been proposed to take place through an oxygen-rebound mechanism (ET process).[3b,5a,5c] In order to test the behaviour of the selected sulfides as model compounds for our studies, oxidation by HRP was carried out with H_2O_2 as oxidant in a phosphate buffer (pH 7). As a control experiment, we repeated the reported sulfoxidation of methyl phenyl sulfide (**1a**), the sulfoxide being obtained in a 45% yield (Table 3, Entry 1). In contrast, no oxidation was observed with the substrates **1c**, **1d** and **2**, even when the reaction was performed at 40 °C. These results were in part to be expected, as a result of the very low solubilities of these sulfides in aqueous media and the apparently poor substrate acceptance by the enzyme. The reaction of the less bulky sulfide **4** was performed at room temperature. Although this reaction proceeded at a low level of conversion, the fragmentation products diphenyl disulfide and cinnamyl aldehyde **11** were observed and quantified (Table 3, Entry 2) by GC-MS analysis [Equation (1)]. In addition, the sulfide was completely recovered in the enzyme-free control experiment.



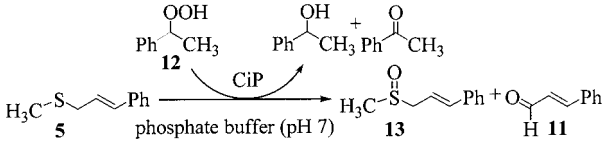
(1)

The enzyme CiP was recently shown to perform the enantioselective oxidation of sulfides.[5d,24] Different approaches to avoiding inactivation of the enzyme by excess H_2O_2 have been followed, including continuous addition of the oxygen donor,[5d] the use of an alkyl hydroperoxide,[24] and generation of H_2O_2 in situ by oxidation of glucose with molecular oxygen, catalysed by a glucose oxidase.[25] Although a kinetic study of the enzymatic oxidation of methyl phenyl sulfide by CiP has previously been reported,[5d] no further mechanistic studies have been performed with this enzyme.

In order to avoid deactivation of the enzyme by H_2O_2, the enzymatic oxidations with CiP were carried out at pH 7 in the presence of two oxygen donors: H_2O_2 (added in small aliquots every 10 min) and a weaker oxidising agent such as *tert*-butyl hydroperoxide. No sulfoxide or fragmentation products were found for the enzymatic reactions of sulfides **3** or **4**, at least at the detection limit of the GC assay. Alternatively, a racemic alkyl hydroperoxide (**12**)[24] was used. As a control experiment the reaction of sulfide **1a** was first performed, and afforded only the sulfoxide in 20% yield (Table 3, Entry 3).

There was no reaction between sulfide **3** and the hydroperoxide **12** with CiP as catalyst; allyl phenyl sulfide (**3**) was recovered in 90% yield, together with the acetophenone and the 1-phenylethanol derived from the hydroperoxide **12**, in 40% and 60% yields respectively. In the absence of the enzyme, a 16% yield of sulfoxide was obtained (Table 3, Entries 4 and 5). These results suggest that, when the substrate is not accepted by the enzyme, catalase activity of the latter is expressed, the hydroperoxide being converted into the corresponding alcohol and ketone derivatives. Such behaviour has also been reported previously.[24]

The *Coprinus cinereus* enzyme accepted the methyl phenyl sulfides (**1a**) but not the allyl phenyl sulfide (**3**). It had previously been reported that elongation of the alkyl chain strongly reduced the reactivity and selectivity of CiP-catalysed sulfoxidation of ethyl tosyl sulfide relative to that of **1a**.[24] These observations prompted us to investigate cinnamyl methyl sulfide (**5**) and methyl diphenylmethyl sulfide (**2**) as more appropriate probes. The sulfide **5**, with the racemic hydroperoxide **12** as oxygen source, yielded the corresponding sulfoxide **13** and aldehyde **11** [Equation (2)] in the CiP-catalysed oxidation (Table 3, Entry 6). The absence of double bond oxidation products (epoxidation and carbon−carbon bond cleavage)[14a] indicates the chemoselectivity of the CiP reaction, which only affords oxidation on the sulfur atom with concomitant fragmentation of the corresponding radical cation.



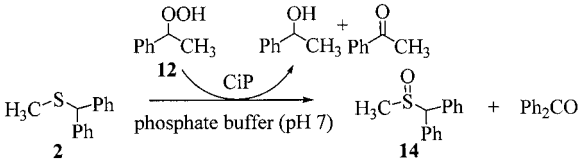
(2)

The oxidation of sulfide **2** by CiP resulted in the sulfoxide **14** and benzophenone [Equation (3)] (Table 3, Entry 8).

Table 3. Enzymatic sulfoxidation by HRP, CPO and CiP

Entry[a]	Sulfide	Enzyme	Sulf./Enzyme (mol ratio)	ROOH/Sulf. (mol ratio)	Time [h]	Convn.[b] [%]	Product yields[c] [%]
1	**1a**	HRP[d]	400:1	H_2O_2, 1:1	3	48	sulfoxide (45)
2	**4**	HRP[d]	400:1		3	5	Ph_2S_2 (3), **11** (4)
3	**1a**	CiP	150:1	**12**, 2.2:1	4	25	sulfoxide (20)
4	**3**	CiP	150:1		4	0[e]	–
5	**3**	–	–		4	18	sulfoxide (16)
6	**5**	CiP	200:1		4	83	sulfoxide (23), **11** (5)
7	**5**	–	–		4	36	sulfoxide (29)
8	**2**	CiP	200:1		4	67	sulfoxide (29), Ph_2CO (5)
9	**2**	–	–		4	52	sulfoxide (52)
10[f]	**2**	–	–		4	20	sulfoxide (20)
11[g]	**2**	–	–		4	0	–
12[h]	**5**	CPO	62700:1	H_2O_2, 2:1	2	24	sulfoxide (7.4)

[a] The reactions were performed at room temperature and in 1 M phosphate buffer (pH = 7), unless otherwise indicated. [b] The conversion was determined by quantification of the unchanged substrate. [c] The products were quantified by GC or ^{1}H NMR analyses with an internal standard method. [d] 0.1 M phosphate buffer (pH = 7). [e] Sulfide **3** recovered in a 90%. [f] 10% CH_3CN as co-solvent. [g] 50% CH_3CN as co-solvent. [h] Reaction performed at 37 °C and in 0.1 M citrate buffer (pH = 5).

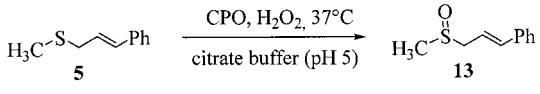


(3)

In the absence of catalyst, both sulfides **5** and **2** were oxidised by **12** to the corresponding sulfoxides (Table 3, Entries 7 and 9). When the uncatalysed reaction of sulfide **2** was performed with acetonitrile as co-solvent (10%), the yield of the corresponding sulfoxide was considerably decreased, and with 50% acetonitrile there was no reaction at all (Table 3, Entries 10 and 11). These results suggest that the high sulfoxidation yield observed in the absence of the enzyme can be ascribed to better solubilisation of the sulfide **2** into the hydrophobic **12** than in the aqueous medium.[26]

As a control experiment we performed a recovery assay of the sulfide **5** from a solution of CiP (sulfide/enzyme ratio of 200:1). After the usual workup by extraction of the aqueous solution with diethyl ether, only 87% of **5** was quantified by GC. The low mass balances observed for the CiP-catalysed reactions of sulfides **2** and **5** can therefore be explained by low product recovery from the reaction mixture emulsions.

In order to compare CiP with other enzymes, we finally examined the sulfide probes **3**, **4** and **5** with CPO. Although **3** and **4** were not reactive, sulfide **5** afforded a 7.4% yield of the sulfoxide **13** on enzymatic oxidation with CPO after 2 h (Table 3, Entry 12) [Equation (4)]. Only 73% of sulfide **5** quantified by GC and NMR was recovered from a CPO solution (sulfide/enzyme ratio of 62700:1), which is responsible for the low mass balances observed in the enzymatic reaction.



(4)

The occurrence of ET[27] depends on the oxidation potential of the sulfide and on the nature of compound I, due to the thermodynamics of the reaction and the reorganisation parameter (λ) respectively, the latter being determined by the nature of the active site. For a given sulfide, the character of the process will be determined by the active site. Peroxidases are all hemo enzymes, and HRP and CiP have considerable homology in the tertiary structures of their active sites:[28] a distal and an axial histidine are present in both enzymes,[29] whereas in CPO a glutamate and a cysteine are found.[30] It is believed that protonation of the distal ligand is a concomitant process in the formation of compound II, which is an intermediate in the oxygen-rebound step (ET process).[31] For CiP and HRP, with distal histidine ligands, this process is favoured. In contrast, CPO has an acidic glutamate distal residue, avoiding this protonation pathway, and the ferryl oxygen is more accessible and makes direct oxygen transfer to the sulfide possible.[32] Furthermore, the binding site in HRP is sterically restricted, thus favouring an ET process.[33]

For the horseradish enzyme, the result obtained with sulfide **4** supports an ET process as previously reported, in which the radical cation of the sulfide fragments, ultimately to yield the disulfide and the aldehyde [Equation (1)]. The fact that products derived from the sulfur radical cation intermediates were obtained in both CiP-catalysed reactions of sulfides **5** and **2** (fragmentation or α-deprotonation products), clearly also indicated the participation of an ET pathway in these enzymatic processes. On the other hand, the formation only of an oxidation product in the CPO-catalysed reaction of sulfide **5** could be attributable to oxygen rebound being faster than the C–S bond cleavage or to a direct oxygen transfer. In view of our results for the PET oxidation of sulfides with $C(NO_2)_4$ and those previously reported for this enzyme, direct oxygen transfer (oxene mechanism) appears more plausible for this enzymatic sulfoxidation by CPO. This mechanism would be expected to be sensitive to steric hindrance, as observed in the change

in reactivity on going from $PhSCH_2CH=CH_2$ (**3**) and $PhSCH_2CH=CHPh$ (**4**) to $CH_3SCH_2CH=CHPh$ (**5**). The observed difference between CiP/HRP and CPO may thus arise from differences in their active sites.

Conclusion

The sulfides $PhSCH_2CH=CHPh$ (**4**), $CH_3SCH_2CH=CHPh$ (**5**) and CH_3SCHPh_2 (**2**) have been shown to be suitable probes for biomimetic and enzymatic mechanism studies, since their sulfur radical cations undergo fragmentation or α-deprotonation as alternatives to the oxidation step. Although the reaction conversions in the enzymatic sulfoxidation are low, principally due to poor solubility of the sulfide substrates in the aqueous medium and poor acceptance by the enzymes, the formation of fragmentation or α-deprotonation products is clear evidence of an ET mechanism. Thus, by a product study of the oxidation of these sulfide probes, it is possible to test for the participation of an ET process in the oxidation reaction.

The biomimetic sulfoxidations by $TPPFe^{III}Cl$ and the enzymatic one by CPO involve a direct oxygen-transfer or oxene mechanism (Scheme 1, pathway c). The HRP-catalysed oxidation of the sulfide **4** as model substrate yielded fragmentation products, which confirm the ET mechanism for this enzymatic sulfoxidations (Scheme 1, pathway a, b). Finally, the use of the racemic secondary aryl alkyl hydroperoxide **12** in the CiP-catalysed oxidation of **5** and **2** gave the corresponding sulfoxides with the aldehyde **11** and benzophenone, from fragmentation and α-deprotonation respectively. These results clearly show that sulfoxidation proceeded by an oxygen-rebound mechanism (Scheme 1, pathway a, b).

Experimental Section

Methods: ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, with a Bruker AC 200 spectrometer, and spectra are reported in δ (ppm) relative to Me_4Si and $CDCl_3$, respectively, in $CDCl_3$ as solvent. Gas chromatographic analyses were performed on a Hewlett Packard 6890 A with a flame-ionization detector, with a HP-5 30 m capillary column of a 0.32 mm × 0.25 μm film thickness or a HP1 column (5 m × 0.53 × 2.65 μm film thickness). GS/MS analyses were carried out with a Shimadzu GC-MS QP 5050 spectrometer, on a 25 m × 0.2 mm × 0.33 μm HP-1 column. HPLC analyses were carried out with an LKB Bromma instrument, with use of the 2141 detector (detection was performed at 254 nm) and the 2249 pumping system, on a 4.0 × 250 mm Spherisorb ODS2 column.

Materials: The commercially available compounds were used as received. CH_3CN, CH_2Cl_2 and CH_3OH were distilled under vacuum and stored over molecular sieves (4 Å). The 1-phenylethyl hydroperoxide (**12**) was prepared from the corresponding alcohol by treatment with 85% H_2O_2, by the previously reported procedure.[34] $TPPFe^{III}Cl$, HRP (Sigma, type VI) and CPO from *Caldariomyces fumago* (Sigma) were used. CiP was kindly provided by Novo Nordisk. Sulfides **1c**−**d**,[7] **2**,[35] **3**,[36] **4**[36,37] and **5**,[37] were obtained by standard procedures and exhibited physical properties identical to those reported in the literature. Diphenylmethyl phenyl sulfoxide,[7] diphenylmethyl methyl sulfoxide (**14**),[38] allyl phenyl sulfoxide,[39] cinnamyl phenyl sulfoxide,[40] diphenylmethyl phenyl sulfone,[41] diphenylmethyl methyl sulfone,[41a] allyl phenyl sulfone,[42] cinnamyl phenyl sulfone[42,43] and cinnamyl methyl sulfone[44] were prepared by oxidation (of the sulfide) with 1 or 3 equivalents of dimethyldioxirane,[45] and exhibited physical properties identical to those reported in the literature. The amide **9** was obtained according to the literature.[46] All products were characterised by ^1H and ^{13}C NMR and mass spectrometry.

Cinnamyl Phenyl Sulfoxide: Solid (m.p. 90−92 °C) (ref.[40] m.p. 91.5−92 °C). ^1H NMR (200 MHz, $CDCl_3$, 30 °C): δ = 3.57−3.76 (m, 2 H, CH_2), 5.97 (dt, ^3J = 15.9, 7.6 Hz, 1 H, $CH_2-CH=CH$), 6.40 (d, ^3J = 15.9 Hz, 1 H, $CH_2-CH=CH$), 7.17−7.60 (m, 10 H, Ar H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 30 °C): δ = 60.4, 116.0, 124.5, 126.6, 128.3, 128.7, 129.2, 131.3, 136.2, 138.6, 143.0 ppm.

Cinnamyl Methyl Sulfoxide (13): Solid (m.p. 54−56 °C). ^1H NMR (200 MHz, $CDCl_3$, 30 °C): δ = 2.46 (s, 3 H, CH_3), 3.40−3.60 (m, 2 H, CH_2), 6.16 (dt, ^3J = 15.8, 7.6 Hz, 1 H, $CH_2-CH=CH$), 6.58 (d, ^3J = 15.8 Hz, 1 H, $CH_2-CH=CH$), 7.17−7.34 (m, 5 H, Ar H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 30 °C): δ = 36.6, 56.9, 116.3, 126.4, 128.2, 128.6, 135.8, 138.0 ppm. $C_{10}H_{12}OS$ (180.27): calcd. C 66.63, H 6.71, S 17.79; found C 66.54, H 6.62, S 17.86.

Cinnamyl Methyl Sulfone:[44] Solid (m.p. 113−114 °C). ^1H NMR (200 MHz, $CDCl_3$, 30 °C): δ = 2.90 (s, 3 H, CH_3), 3.89 (d, ^3J = 7.5 Hz, 2 H, CH_2), 6.29 (dt, ^3J = 15.9, 7.5 Hz, 1 H, $CH_2-CH=$ CH), 6.72 (d, ^3J = 15.9 Hz, 1 H, $CH_2-CH=CH$), 7.30−7.44 (m, 5 H, Ar H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 30 °C): δ = 39.2, 59.2, 115.6, 126.7, 128.8, 135.4, 139.1 ppm.

Methyl Diphenylmethyl Sulfone: Solid (m.p. 130−131 °C) (ref.[47] m.p. 127−128.5 °C). ^1H NMR (200 MHz, $CDCl_3$, 30 °C): δ = 2.72 (s, 3 H, CH_3), 5.35 (s, 1 H, CH), 7.33−7.66 (m, 10 H, Ar H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 30 °C): δ = 39.8, 74.5, 128.8, 128.9, 129.6, 132.7 ppm. MS (EI+): *m*/*z* (%) = 167 (100), 166 (43), 152 (24), 82 (16).

General Procedures for the Oxidation

Chemical Oxidation by CAN $[Ce(NH_4)_2(NO_3)_6]$: The sulfide (0.25 mmol) was added to a solution of CAN (137 mg, 0.25 mmol, unless otherwise indicated in Table 1) in degassed CH_3CN (5 mL). The reaction mixture was stirred for 30 min under nitrogen, water (15 mL) was added, and the mixture was extracted with diethyl ether (3 × 10 mL) and further analysed by GC, GC-MS and ^1H NMR spectroscopy.

Photochemical Oxidation with TNM $[C(NO_2)_4]$: The TNM (49 mg, 0.25 mmol) was added to a solution of the sulfide (0.25 mmol) in degassed CH_3CN or CH_2Cl_2 (5 mL) and the reaction mixture was irradiated for 180 min at λ = 419 nm under nitrogen. Water (10 mL) was added, and the mixture was extracted with diethyl ether (3 × 10 mL) and further analysed by GC and ^1H NMR spectroscopy.

Biomimetic Oxidation by $TPPFe^{III}Cl$:[3c] H_2O_2 (28 μL of a 8.93 M solution) was added to a solution of the sulfide (25 mM), the catalyst and imidazole as additive in the indicated organic solvent, with a sulfide/H_2O_2/catalyst ratio of 20:40:1. The mixture was stirred as required. The reaction was quenched by addition of sodium sulfite in water (10 mL), and the mixture was extracted with diethyl ether or CH_2Cl_2 (3 × 10 mL) and analysed by GC, GC-MS, HPLC and ^1H NMR spectroscopy.

Enzymatic Oxidation by HRP: Reactions were carried out in phosphate buffer (pH 7, 0.1 M, 6 mL) with a 5.7 mM final concentration of the sulfide, which was dissolved in methanol (1 mL) prior to addition to the phosphate buffer. HRP (0.1μmol, 4.4 mg) was then added to the sulfide solution. A solution of H_2O_2 in phosphate buffer (pH 7, 98 mM) was added in 10 aliquots (408 μL) every 10 min. The reactions were stopped by addition of sodium sulfite and extracted with diethyl ether (3 × 10 mL).

Enzymatic Oxidation by CiP: Reactions were carried out in phosphate buffer (pH 7, 0.1 M, 10 mL), with a 2.6 mM final concentration of the sulfide, which was dissolved in *tert*-butyl alcohol (1 mL) prior to addition to the phosphate buffer. An aqueous solution of CiP (0.10 mM) was added in two aliquots (4.2 mL). As a sign of enzyme purity, the absorbance ratio (A_{405}/A_{280}) was determined to be 2.1. The enzyme concentration was determined by use of a molar extinction coefficient of 109 $mM^{-1}\cdot cm^{-1}$ at 405 nm.[48] A solution of H_2O_2 in phosphate buffer (pH 7, 98 mM) was added in 16 aliquots (408 μL) every 10 min. The reactions were stopped by addition of sodium sulfite and extracted with diethyl ether (3 × 10 mL). The reactions with the alkyl hydroperoxide **12** as oxygen source were performed in phosphate buffer (pH 7, 1 M); the sulfide was dissolved in *tert*-butyl alcohol (1 mL) and the procedure according to ref.[14] was applied.

Enzymatic Oxidation by CPO:[49] The sulfide (0.21 mmol), dissolved in methanol (1 mL), and the CPO (3.3×10^{-6} mmol) were stirred in citrate buffer (pH = 5, 0.1 M, 20 mL), and the oxidant (0.42 mmol) in buffer solution (2 mL) was added during the first hour of reaction in 13 aliquots (150 μL) at 5 min intervals. The reactions were stopped by addition of sodium sulfite and the mixtures were extracted with diethyl ether (3 × 10 mL) and analysed by ^{1}H NMR spectroscopy.

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