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Enantioselective Sulfoxidation as a Probe for a Metal-Based Mechanism in H_2O_2-Dependent Oxidations Catalyzed by a Diiron Complex

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The catalytic properties of the diiron complex **1**, $Fe_2OL_4(H_2O)_2(ClO_4)_4$ with L = (−)-4,5-pinenebipyridine, a chiral bipyridine derivative, have been investigated. Complex **1** efficiently catalyzes the oxidation of aryl sulfides to the corresponding sulfoxides by hydrogen peroxide, with yields ranging from 45 to 90% based on the oxidant. Furthermore the reactions were enantioselective and produced a mixture of sulfoxide enantiomers with significant enantiomeric excesses. The largest ee value (40%) was found in the case of *p*-bromophenyl methyl sulfide. Optimal ee's were obtained in polar solvents and at low temperature (below 0 °C), when the excess of the oxidant was limited. The observation of (i) a saturation kinetics with respect to both sulfide and H_2O_2 concentrations, (ii) a linear Hammett correlation of the initial V_{max} values with σ_p values, for a series of *p*-substituted aryl methyl sulfides, (iii) iron−peroxo complexes, characterized by light absorption and Raman resonance spectroscopies, during reaction of complex **1** with H_2O_2, and (iv) a saturation kinetics with respect to sulfide during oxidation of sulfide into sulfoxide by the iron−peroxo complexes led us to propose that the iron−peroxo moiety is the actual oxygen atom donor to the substrate, thus explaining the enantioselective control of the catalytic reaction. These data demonstrate that oxidations by non heme diiron complexes can proceed through metal-based pathways and can thus be made stereoselective.

Introduction

An increasing number of monooxygenases have been found to use a non heme diiron active site, in which two ferric ions are bridged by an oxo (or hydroxo) ion and one or two carboxylates from glutamate or aspartate residues.[1] The prototype for this class of enzymes is methane monooxygenase found in methanotrophic bacteria.[2] In this case it is quite well established that molecular oxygen is activated by binding to the diferrous center,[3] yielding a diiron(III) peroxide species.[4] The subsequent cleavage of the peroxide O−O bond converts this first intermediate into a diiron(IV) complex, responsible for the transfer of an oxygen atom to methane.[4a,5] This mechanism is consistent with the ability of the enzyme to function with hydrogen peroxide as well, in the absence of a source of electrons.[6]

The discovery that the efficiency, the versatility, and the selectivity of oxidation reactions catalyzed by non heme diiron centers were actually rivaling those of heme-catalyzed reactions[7] and that both classes of enzymes seemed to operate through high-valent iron active oxygen species stimulated several lines of research. One was related to the question whether non heme diiron complexes had an intrinsic potential to activate molecular oxygen or peroxides and catalyze oxygen atom transfers to substrates. This question was investigated with the help of model complexes, containing the Fe(III)−O−Fe(III) unit, which actually proved to be excellent catalysts for the oxidation of hydrocarbons by alkyl hydroperoxides.[8] More recently we showed that this was also the case when hydrogen peroxide was used as the oxidant.[9] Even though yields and rates are generally rather low, except in the case when the substrate is covalently connected to the ligand,[10] there are also a few examples of O_2-dependent oxidations catalyzed by synthetic non

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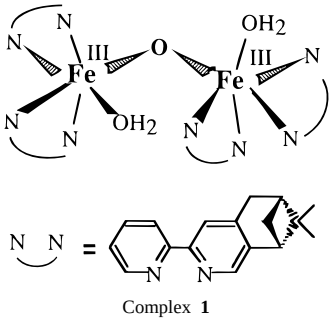
Chart 1. Schematic Representation of Complex **1**



Complex **1**

heme diiron complexes, in the presence of a reducing agent.[11] Furthermore, the model approach was extremely useful for characterizing key inorganic analogues to the enzyme active intermediates,[12] in particular the diiron(III) peroxide species[13] and more recently the only high-valent $Fe^{III}Fe^{IV}$ complex reported so far.[14]

The following important question was whether model non heme diiron complexes were also operating through metal-based pathways in which the active oxygen species is bound to the metal, during activation of peroxides and molecular oxygen. Until recently, the general dogma was that non heme iron-dependent reactions were essentially radical chain autoxidations. This concept is, in all probability, true when an alkyl hydroperoxide, such as *tert*-butyl hydroperoxide, is used as an oxidant, as recently shown by elegant studies from Ingold and Que.[15] However, this might not be the case with any oxidant and the question is investigated here for H_2O_2-dependent reactions.

Considering that direct evidence for the involvement of metal-based pathways would be the observation of a significant degree of stereoselectivity when the catalyst contains a chiral ligand, we synthesized complex **1**, $[Fe_2OL_4(H_2O)_2](ClO_4)_4$ (L = (−)-4,5-pinenebipyridine), which is an extension of our best previously reported bipyridine-based iron catalyst (Chart 1).[9] Here we show that complex **1** is a robust and efficient catalyst for the oxidation of sulfides by hydrogen peroxide and report mechanistic studies of the reaction. The sulfoxidation reaction is enantioselective, even though the selectivity is not large enough for preparative synthetic applications. Our data strongly support the notion that a non heme diiron complex-catalyzed oxygen transfer process can be, at least partly, metal-based. A reaction mechanism is proposed which may be useful if one wants to improve the selectivity of this system.

Experimental Section

Materials. Most of the reagents were of the best commercial grade and were used without further purification. On the other hand, the solvents benzonitrile, bromobenzene, and nitroethane were purified by distillation before use. Naphthyl methyl sulfide was prepared from the corresponding aryl thiol by alkylation with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and iodomethane[16] in toluene. Sulfoxides were prepared from the parent sulfide by sodium metaperiodate oxidation in methanol.[17] All these compounds were isolated by column chromatography on silica gel. The purity of the compounds was checked by GC, and they were identified by ^1H and ^{13}C NMR. The concentration of H_2O_2 was determined by iodometric titration.

Complex **1** was synthesized by mixing 1 equiv of $Fe(ClO_4)_3 \cdot 9H_2O$ and 2 equiv of L in ethanol. A green solid was obtained. Anal. Calcd for $[Fe_2OL_4(H_2O)_2](ClO_4)_4 \cdot 4H_2O \cdot EtOH$ ($C_{70}H_{88}Cl_4Fe_2N_8O_{23}$): C, 50.03; H, 5.36; Cl, 8.45; Fe, 6.60; N, 6.60. Found: C, 49.95; H, 5.32; Cl, 8.90; Fe, 6.35; N, 6.29. UV−vis [CH_3CN, λ_{max}, ϵ]: 610 nm (160 $M^{-1} \cdot cm^{-1}$), 460 (sh, 1000), 350 (10 000). ^1H NMR (CD_3CN, δ in ppm): 25.3 ($H\alpha$ py), 18.7, 16.4, 14.6, 12.8 ($H\beta$ py), 8.3 and 7.7 ($H\gamma$ py). The chemical of these protons are similar to those of $Fe_2O(bipy)_4(H_2O)_2(ClO_4)_4$.[18]

Complex **1** was found to be optically active from its circular dichroism spectrum in acetonitrile [λ_{max} nm ($\Delta\epsilon$, $M^{-1} \cdot cm^{-1}$)]: 370 (0.28); 460 (−0.05).

Physical Methods. The 200 MHz ^1H NMR spectra were recorded on a AC200 Bruker spectrometer. Visible absorption spectra were recorded on a Kontron Uvikon 938 spectrophotometer. Gas chromatography (GC) was performed on a Perkin-Elmer Autosystem instrument connected to a Shimadzu Chromatopac CR6A with a FID detector, using an SE 30 column. Resonance Raman spectra were collected on an Acton AM-506 spectrometer (2400-groove grating) using Kaiser Optical holographic super-notch filter with a Princeton Instruments liquid-N_2-cooled (LN-1100PB) CCD detector with 4 cm^{-1} spectral resolution. Spectra were obtained by back-scattering geometry on liquid-N_2 frozen samples using 632.8 nm laser excitation from a Spectra Physics 2030-15 argon ion laser and a 375B CW dye (Rhodium 6G). Raman frequencies were referenced to indene.

Determination of the Enantiomeric Excess (ee). The reaction product, the sulfoxide, was purified by silica gel flash column chromatography. After evaporation of the reaction solution, the residue was suspended in hexane/ethyl acetate (1/1) and loaded onto the column. The remaining sulfide and the GC standard were both eluted first. Then, the sulfoxide was eluted with ethyl acetate. The product was characterized by ^1H NMR, and its purity was confirmed by GC. Determination of the optical yield was done using a chiral shift reagent: when ca. 1 equiv of (*R*)-(+)-2,2′-dihydroxy-1,1′-binaphthyl[20] was added to the sulfoxide in $CDCl_3$, the signal of the methyl group of the sulfoxide (for example for the phenyl methyl sulfoxide, δ 2.72 ppm, singlet) is changed into two signals (δ 2.66, δ 2.68 ppm) corresponding to the two enantiomers. Mathematic treatment by deconvolution of these signals was used to determine the ee value. The signal at higher field was assigned to the (*R*)-isomer. In some cases, the ee value was confirmed by comparing optical rotations with reported values. The estimated deviation on the ee value was found to be 10% of the measured value. The ee value was calculated as the average of three separated experiments.

Catalytic Oxidation of Sulfides by Hydrogen Peroxide. Standard conditions were as follows: 7.0 μmol of complex **1** (0.7 mM) was dissolved in acetonitrile containing 4.2 mmol of sulfide under argon atmosphere at 0 °C (final volume: 10 mL). The reaction was started by adding 70 μmol of H_2O_2 (ratio of complex **1**/sulfide/H_2O_2 = 1/600/10). After 10 min of stirring, 20 μmol of an internal standard

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(benzophenone or fluorenone) was added to the reaction mixture and the organic products were quantified by GC. Unambiguous identification of the products was made by comparison with pure compounds, prepared independently or commercially available. The following solvents have been used: benzonitrile ($\rho = 4.18$), acetonitrile ($\rho = 3.92$), acetone ($\rho = 3.65$), nitroethane ($\rho = 2.88$), bromopropane ($\rho = 2.20$), bromobenzene ($\rho = 1.70$), and methylene chloride ($\rho = 1.60$) ($\rho =$ dielectric constant values issued from the Chemical Handbook, 79th ed., CRC Press, David R. Lide, Ed.).

To study the effect of the sulfoxide on the reaction, the oxidation of naphthyl methyl sulfide by complex **1** (0.7 mM) and hydrogen peroxide (7.0 mM) was carried out under standard conditions (see above) in the presence of increasing amounts of methy phenyl sulfoxide (0−35 mM). The ee for naphthyl methyl sulfoxide was determined as described above.

Kinetic Studies. Kinetic experiments were carried out in acetonitrile at 20 °C. The reaction mixture contained complex **1**, phenyl methyl sulfide, and hydrogen peroxide in a total volume of 300 μL in a 0.1 cm optical path UV cell. Reactions were initiated by the addition of H_2O_2 and followed by the variation of the difference in absorption at a fixed wavelength λ between the sulfide and the corresponding sulfoxide. Initial rates were calculated by using the difference of molar extinction coefficients ($\Delta\epsilon$) between the sulfides and the corresponding sulfoxides [$\Delta\epsilon$ in $M^{-1}\cdot cm^{-1}$ (λ in nm)]: phenyl methyl sulfide, −7540 (254); *p*-methoxyphenyl methyl sulfide, −4080 (254); *p*-methylphenyl methyl sulfide, −4170 (254); *p*-bromophenyl methyl sufide, −6220 (254); *p*-nitrophenyl methyl sulfide, 3630 (250). A negative value indicates a decrease in absorbance during conversion of sulfide to sulfoxide.

Reactivity of the Iron Peroxo Complex. The peroxo adduct can be generated at 0 °C mixing 0.2 mL (1.7×10^{-3} M) of hydrogen peroxide and 0.4 mL (1.7×10^{-4} M) of complex **1** in acetonitrile (final volume: 1.2 mL). Its decomposition in the presence of increasing amounts of phenyl methyl sulfide (0−85 mM) can be monitored by the decay of the absorbance at 700 nm as a function of time and was fitted with a pseudo-first-order kinetic law. The iron peroxo was quantified by using an approximative value of 1500 for the molar absorption coefficient at 700 nm. This value is in the range for coefficients of diiron complexes previously reported.[12,13,19]

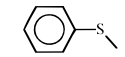
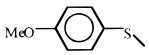
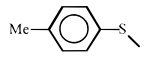
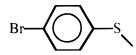
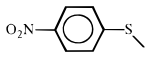
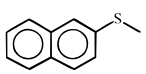
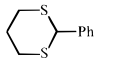
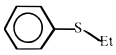
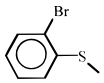
Results

Oxidation of Sulfides Catalyzed by Complex 1. As shown in Table 1, complex **1** was able to catalyze the oxidation of a great variety of aryl sulfides to sulfoxides by hydrogen peroxide, under anaerobic conditions. 2-Phenyl-1,3-dithiane, compound **7**, could also be oxidized, and oxidation occurred only at one sulfur atom. No oxidation could be observed in the absence of complex **1**. The ligand alone in combination with H_2O_2 was ineffective as well.

Optimal yields based on the oxidant, the limiting reactant, after 5 min of reaction, ranged from 70 to 90%, except for *p*-nitrophenyl methyl sulfide, compound **5** (45%). They did not show any significant dependence on the temperature and the presence of air in the reaction mixture. These yields were obtained at 0 °C, with large excesses (250−600 equiv in Table 1) of the substrates and small excesses of H_2O_2 with respect to iron. Dismutation of the oxidant was thus minimized, binding of the product sulfoxide to iron limited (vide infra), and oxygen transfer to the substrate favored. These specific conditions explain the observed selectivity as only sulfoxides were formed with no further oxidation to sulfones.

The oxygen atom in the product sulfoxide was entirely derived from H_2O_2 and not from water as shown from labeling experiments in which the oxidation of phenyl methyl sulfide was performed under standard conditions but in the presence of $H_2{}^{18}O$ (1 M final concentration, 98% final labeling). No incorporation of ^{18}O in the sulfoxide could be detected by mass spectrometry. One should note that addition of water did not affect the rates and yields of the reaction.

Table 1. Oxidation of Prochiral Sulfides by Hydrogen Peroxide Catalyzed by complex **1**[a]

Sulfide		ee (%)		yield[b] (%)	
		PhIO	H_2O_2	PhIO	H_2O_2
	**1**	9	21	100	90
	**2**	9	11	70	70
	**3**		28		68
	**4**	7	40	90	90
	**5**	9	4	95	45
	**6**[c]		40		80
	**7**		15		60
	**8**		4		90
	**9**		26		80

[a] For the experimental conditions, see the Experimental Section. [b] Yield based on the oxidant after 10 min of reaction. [c] Only 250 equiv of sulfide was used.

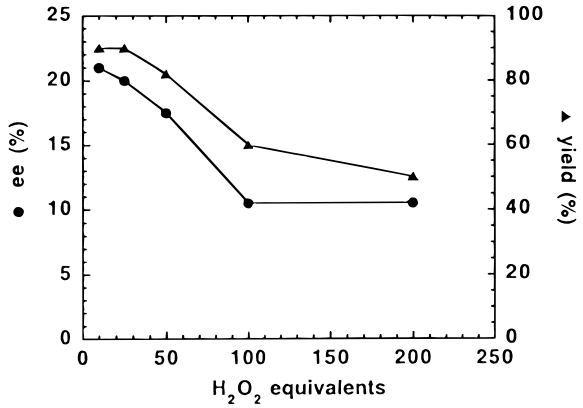


Figure 1. Effect of hydrogen peroxide concentration on enantiomeric excess (●) and yield (▲) based on oxidant in acetonitrile at 0 °C. Experimental conditions: [**1**] = 0.7 mM; **1**/phenyl methyl sulfide = 1/600.

Table 1 also shows that iodosylbenzene could be used as an oxidant and gave, under the same conditions, comparable yields (70−100%). In that case, oxidation of compound **5** was quantitative.

When the excess of H_2O_2 was slightly increased, whether it was added by a single injection (Figure 1) or by several aliquots of 10 equiv or slowly by syringe pumping, the yield based on the oxidant significantly decreased. However, the substrate could be almost totally converted in catalytic reactions with a large excess of H_2O_2. For example, with phenyl methyl sulfide as the substrate (substrate/catalyst = 100 (0.35 M)/1 (3.5 mM)), a

2-fold and 6-fold excess of H_2O_2 led to large substrate conversions (70% and 95%, respectively, compared to 5 and 20%, respectively, in the absence of the catalyst) within 5 min. This corresponds to up to 95 turnover numbers (mmol of oxidized product/mmol of catalyst). A second addition of the oxidant resulted in similar turnover numbers. However, the selectivity dropped as both the sulfoxide and the sulfone were formed (sulfoxide/sulfone = 90/10 and 55/45, respectively), as a consequence of the oxidation of the sulfoxide intermediate by the oxidant in excess. In fact, only the sulfide to sulfoxide conversion was catalyzed by complex **1** whereas the sulfoxide to sulfone conversion was not. Accordingly, during reaction of H_2O_2 with phenyl methyl sulfoxide (H_2O_2/substrate = 600/50 (0.175 M)), the corresponding sulfone was formed with a 60% yield, whether complex **1** was present or not in the reaction mixture.

Enantioselective Sulfoxidations. In experiments with limiting H_2O_2, we observed a significant degree of enantioselectivity during catalytic sulfide oxidation to sulfoxide (Table 1). In all cases the *R*-(+)-sulfoxide enantiomer was the major product as determined by polarimetric and spectroscopic (^{1}H NMR) methods.[20] In the case of compound **7**, the absolute configuration of the corresponding sulfoxide was not determined. Enantiomeric excesses (ee's) were rather low but in some cases could reach 40%. Iodosylbenzene gave much lower ee's (less than 10%). The ee's were much more sensitive to the nature of the substituents on the phenyl ring of phenyl methyl sulfide when H_2O_2 was used as the oxidant. However, there was no clear correlation with the electronic effects of these substituents. Finally, only racemic mixtures of sulfoxides were obtained when TBHP was used as an oxidant (data not shown).

The enantiomeric excesses were very much dependent on the solvent and the temperature but not on the presence of air. As shown in Figure 2A, there is large increase of the selectivity as the polarity of the solvent increases with the highest numbers obtained with benzonitrile as the solvent and the lowest with dichloromethane, during catalytic oxidation of phenyl methyl sulfide by H_2O_2. Figure 2A shows that there is the same effect of solvent polarity on the reaction yields which varied from about 10% to 100%. Figure 2B shows that ee's decreased as the reaction temperature increased with a larger effect of the temperature above 0 °C. Consequently, the reactions were run at 0 °C, under standard conditions (Table 1).

Finally, as shown in the case of phenyl methyl sulfide, the ee value decreased with increased H_2O_2 (Figure 1). This was not due to some racemization of the sulfoxide product, since a mixture of *R* and *S* enantiomers of phenyl methyl sulfoxide (*R* > *S*, ee = 20%) retained the same proportion of these enantiomers during incubation with complex **1** and H_2O_2. This was not due either to the small proportion of uncatalyzed production of racemic sulfoxide at large excess of H_2O_2. With 200 equiv of H_2O_2, 100 equiv of sulfoxide was produced in the presence of complex **1** (Figure 1) compared to 10 equiv in the absence of complex **1** (data not shown). This could not account for the 20% to 10% drop of the ee value.

Stability of the Catalyst. At the end of the reaction, the light-absorption spectrum of the catalyst was significantly different from that of the initial complex, indicating a modification of the complex. However it did not display the absorption band at 520 nm characteristic for the mononuclear tris(bipyridine)-iron-(II) complex. This inactive complex was usually found to irreversibly accumulate during reaction of peroxides with analogues of complex **1** containing unsubstituted bipyridine or phenanthroline ligands.[8a] Isolation of the final complex, demetalation, and analysis of the organic component by ^{1}H NMR spectroscopy demonstrated that the ligand was intact.

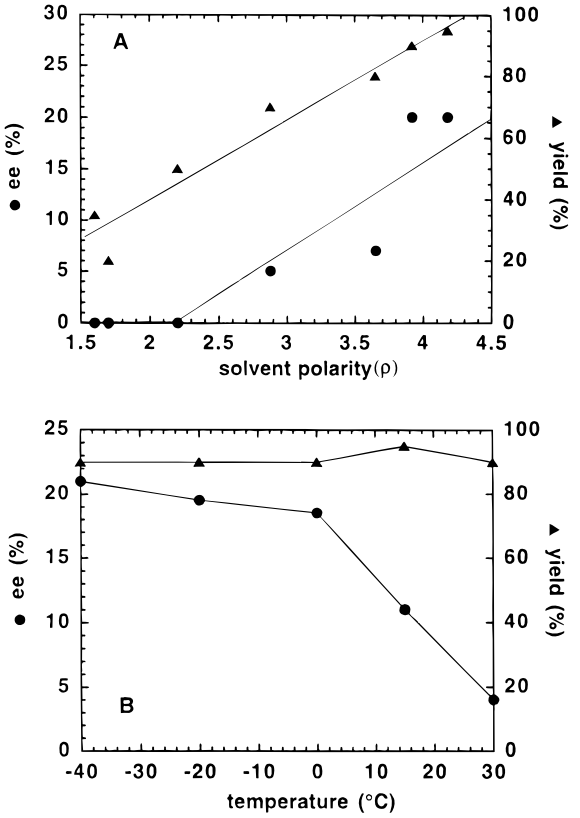


Figure 2. Effect of the solvent polarity at 0 °C (A) (ρ = dielectric constant) and temperature in acetonitrile (B) on the enantiomeric excess (●) and yield (▲). Experimental conditions: [**1**] = 0.7 mM; **1**/phenyl methyl sulfide = 1/600.

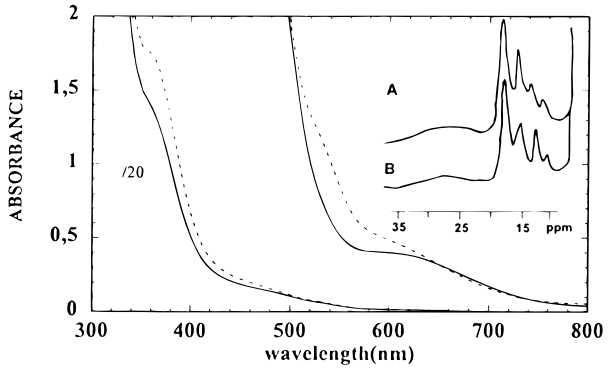


Figure 3. UV−visible spectrum of complex **1** (solid line) and complex **1** with 10 equiv of phenyl methyl sufoxide (dashed line). Inset: ^{1}H NMR spectrum of ligand *m*-proton resonances of complex **1** without (A) and with 10 equiv of phenyl methyl sulfoxide (B).

An identical spectrum, with the low-energy band significantly blue-shifted but still with the high-energy transition at 350 nm, characteristic for the oxo-to-iron charge transfer (Figure 3), was obtained by addition of a few equivalents of phenyl methyl sulfoxide to complex **1**. The ^{1}H NMR spectrum of the catalyst was also slightly modified by addition of the sulfoxide (Figure 3). We could not detect any spectral modification in the case of *p*-nitrophenyl methyl sulfoxide, under comparable conditions. Altogether these data show that basic sulfoxides can displace the H_2O ligands and bind to the diiron complex without altering its dinuclear structure. Thus a stable diiron(III) sulfoxide complex was formed during oxidation reactions as a result of binding of the sulfoxide product to complex **1**. When the

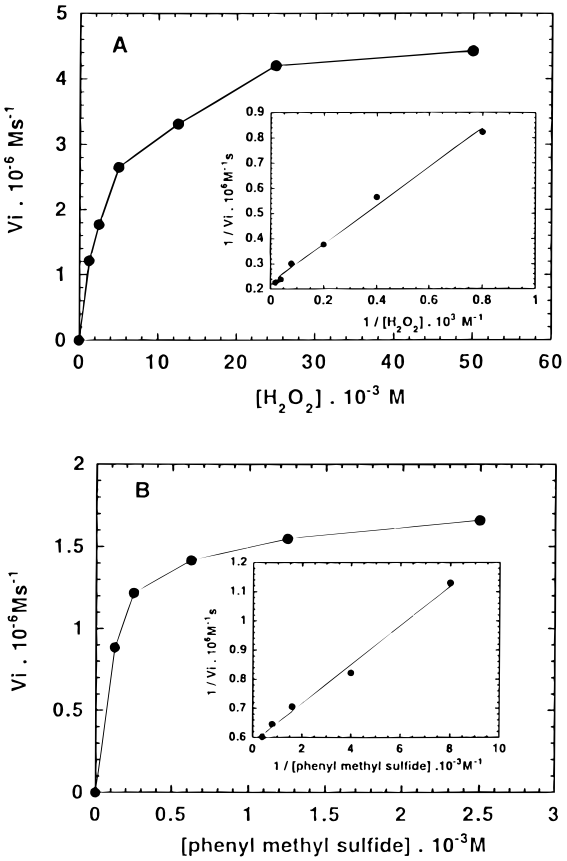


Figure 4. Initial rate of phenyl methyl sulfoxide formation as a function of hydrogen peroxide (A) and substrate (B) concentrations in acetonitrile at 20 °C. Experimental conditions: [**1**] = 5 × 10^{-5} M; **1**/phenyl methyl sulfide = 1/50 (A); [**1**] = 2.5 × 10^{-5} M; **1**/hydrogen peroxide = 1/50 (B). Inset: Reciprocal plots of the observed initial rates as a function of hydrogen peroxide (A) and substrate (B) concentrations.

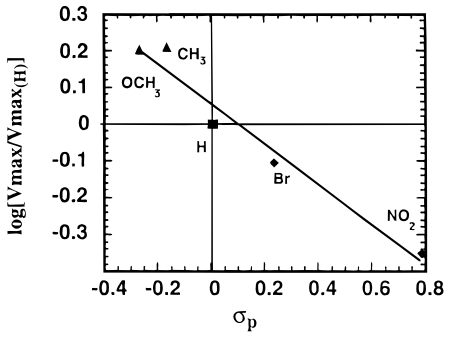


Figure 5. Hammett plot for the oxidation of *p*-substituted aryl methyl sulfides in acetonitrile at 20 °C. Experimental conditions: [**1**] = 5 × 10^{-5} M; **1**/sulfide = 1/50.

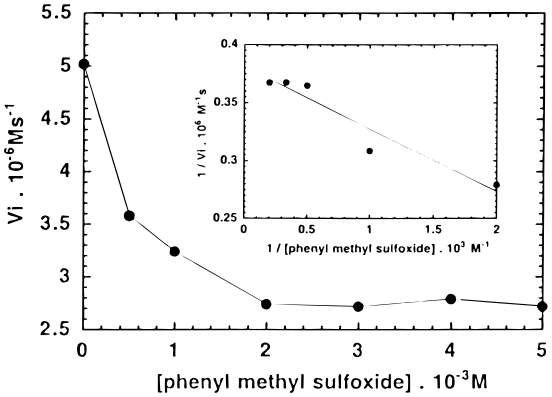


Figure 6. Inhibition of phenyl methyl sulfide oxidation by the product phenyl methyl sulfoxide at 20 °C in acetonitrile. Increasing amounts of sulfoxide were added before addition of the oxidant. Experimental conditions: [**1**] = 1.0 mM; **1**/H_2O_2/sulfide = 1/15/15.

modified catalyst was isolated from the reaction mixture and the diiron unit separated from the sulfoxide by precipitation in diethyl ether, the initial catalytic activity was fully recovered, as tested in a second oxidation assay.

Mechanistic Studies: Reaction Kinetics. The initial rate of phenyl methyl sulfide oxidation was determined at 20 °C from the formation of the sulfoxide during the first 15 s, assayed by UV spectrophotometry (see Experimental Section). The range of substrate concentrations accessible was limited because of the intensity of sulfoxide absorption in the UV region. A short reaction time was selected in order to avoid complications due to accumulation of the sulfoxide and possible inactivation of the catalyst; within 15 s of reaction, less than 1 turnover was achieved even for the largest substrate concentrations (Figure 4). In Figure 4A it is shown that the initial reaction rate increased as the concentration of H_2O_2 increased but reached a plateau at high oxidant concentration. The observed saturation kinetics and the fact that the initial rates followed typical Michaelis−Menten kinetics, with double reciprocal plots of the results giving a straight line, likely implies the binding of H_2O_2 to the complex during the reaction. From the results shown in Figure 4A an apparent K_m value of 3.5 mM for H_2O_2 could be obtained.

The same kinetic analysis was applied to the dependence of the initial rates on the concentration of the substrate, with H_2O_2 concentration kept at 2.5 mM, a nonsaturating concentration (Figure 4B). Again a saturation kinetics with respect to sulfide concentration was observed and the double reciprocal plot of the results showed a line, indicating that also the sulfide bound to the complex during the reaction. An apparent K_m value of 0.1 mM could be deduced from these data.

Furthermore, the initial reaction rates were linearly correlated to the concentration of the diiron catalyst (data not shown), suggesting that the active species retained its dinuclear structure throughout the oxidation reaction. This was further supported by the fact that no EPR signal characteristic for mononuclear species could be observed, when the reaction was monitored by EPR spectroscopy.

As shown in Figure 5, it is obvious that during sulfoxidation of *p*-substituted aryl methyl sulfides V_{max} values increased with the increase of the electron-donating ability of the substituent. A linear Hammett correlation of the V_{max} values with σ_p values rather than with σ^+ values, with a negative slope ($\rho = -0.55$, $R = 0.98$), was obtained. This is consistent with a concerted mechanism in which an electrophilic active oxygen species is attacked by a nucleophilic sulfide, with the electron-rich substrates displaying the highest reactivity.

Binding of the sulfoxide to the diiron complex decreased its catalytic activity. This is shown from the observed inhibition of the catalytic sulfoxidation reactions by increasing amounts of the product sulfoxide (Figure 6). However, the reaction could not be totally inhibited by the sulfoxide as shown from the saturation behavior of the inhibition with regard to sulfoxide concentration. We also observed that sulfoxide binding to the catalyst affected the stereoselectivity of the reaction. As shown in Figure 7, there is a concentration-dependent loss of the stereoselectivity of the oxidation of naphthyl methyl sulfide by increasing amounts of phenyl methyl sulfoxide, with the ee dropping from 40% to about 20%. There again, the curve in

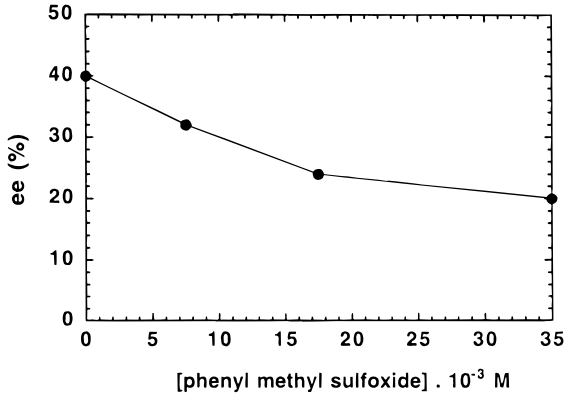


Figure 7. Enantiomeric excess of naphthyl methyl sulfoxide as a function of phenyl methyl sulfoxide concentration, added before addition of hydrogen peroxide at 20 °C in acetonitrile. Experimental conditions: [**1**] = 0.7 mM; **1**/naphthyl methyl sulfide = 1/250.

Figure 7 shows a plateau, reflecting a saturating effect with respect to sulfoxide concentration.

Mechanistic Studies: A Peroxo−Diiron(III) Intermediate. It has been previously shown that peroxides can bind to non heme mononuclear or dinuclear iron complexes.[12,13,21] In agreement with the saturation behavior of the catalytic system studied here with respect to H_2O_2 concentration (vide supra) we suspected a peroxo−iron complex to be implicated in the sulfoxidations.

This complex could be detected in the absence of the substrate when complex **1** (0.75 mM) was treated with 10 equiv of H_2O_2 in acetonitrile at −40 °C. The reaction actually yielded a new broad light absorption band at around 700 nm, a transition assigned to a peroxo-to-iron charge transfer (Figure 8C). EPR analysis of the reaction mixture revealed the presence of a minor amount (less than 5%) of a low-spin $S = {}^1/_2$ mononuclear complex, proving that iron was essentially in the diferric EPR-silent form (data not shown).

When excited at 632.8 nm, the reaction mixture in either acetonitrile or CH_2Cl_2 exhibited resonance-enhanced Raman features at 868, 806, 618, and around 483 cm^{-1}, all of which shift to lower frequency upon introduction of $H_2{}^{18}O_2$ (Figure 8A). Since iron peroxide complexes typically exhibit a ν(O−O) at 800−900 cm^{-1},[2a,13a,13c,22] the spectrum in Figure 8A suggests that there is more than one peroxo species formed in the reaction. Indeed, the observed shift of −44 and −48 cm^{-1} for the features at 806 and 868 cm^{-1}, respectively, with $H_2{}^{18}O_2$ is consistent with O−O vibrations for two peroxo species. Excitation profile studies show that the 868 and 483 cm^{-1} features are associated with one chromophore and that it is red shifted relative to the chromophore associated with the 806 and 618 cm^{-1} features. The former pair of vibrations is similar to those associated with (μ-1,2-peroxo)diiron(III) complexes,[13] while the latter pair resembles the Raman features of a recently characterized mononuclear low-spin Fe−OOH intermediate (790 and 632 cm^{-1}).[23] Therefore, the Raman studies show that at least two peroxo species are generated in the reaction mixture.

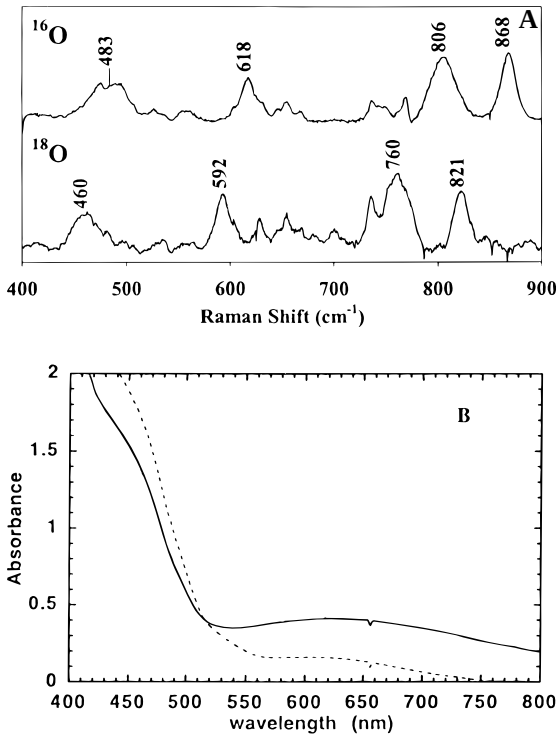


Figure 8. (A) Resonance Raman spectra of complex **1** with ^{16}O- and ^{18}O-labeled H_2O_2, taken with 632.8 nm laser excitation in CH_3CN. (B) UV−visible spectra of complex **1** (dashed line) and complex **1** with 5 equiv of hydrogen peroxide (solid line) in acetonitrile.

It was possible to accumulate the Fe−peroxo complexes (80−90%) at 0 °C in acetonitrile by reaction of complex **1** with 10 equiv of H_2O_2 and to monitor its reaction with phenyl methyl sulfide. The rate of the decay of the 700 nm absorption band was measured at 0 °C as a function of the concentration of added sulfide. The traces could be fitted with a first-order kinetic law, with respect to the iron−peroxo complex, and the calculated k_{obs} values for different concentrations of sulfide are reported in Figure 9. A saturation behavior was observed at high concentrations of sulfide (Figure 9) strongly suggesting that the substrate bound to the iron complex and that the ternary iron−peroxo−sulfide complex was a key reaction intermediate, within which oxo transfer takes place. Furthermore, we checked that sulfoxide formation followed the decomposition of the peroxo complex.

Discussion

It is generally accepted that mononuclear heme enzymes, such as cytochrome P450-dependent monooxygenases, and dinuclear non heme iron enzymes, such as methane monooxygenase, catalyze oxidation reactions through metal-based pathways involving high-valent iron intermediates. This property provides them with the ability to control the regio-, chemo-, and stereoselectivity of enzyme reactions.

With cytochrome P-450 model complexes, i.e., iron porphyrins, it has been shown that the porphyrin ring provides unique electronic properties which make the generation and the utilization of high-valent iron−oxo intermediates possible. Enantioselective catalytic oxidations of substrates by iodosylbenzene have been reported in the case of synthetic chiral iron porphyrins.[24]

The field of non heme diiron-dependent oxidations is more recent, and to our knowledge there is only one example of a synthetic high-valent complex, containing an $Fe^{IV}Fe^{III}$ center,

(21) (a) Ménage, S.; Wilkinson, E. C.; Que, L., Jr.; Fontecave, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 203. (b) Kim, J.; Larka, E.; Wilkinson, E. C.; Que, L., Jr. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2048. (c) Nguyen, C.; Guajardo, R. J.; Masharak, P. K. *Inorg. Chem.* **1996**, *35*, 6273. (d) Lubben, M.; Meetsma, A.; Wilkinson, E. C.; Feringa, B.; Que, L., Jr. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1512.
(22) Brennan, B. A.; Chen, Q.; Juarez-Garcia, C.; True, L., Jr. *Inorg. Chem.* **1991**, *30*, 1937.
(23) Ho, R. Y. N.; Roelfes, G.; Feringa, B. L.; Que, L., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 264.

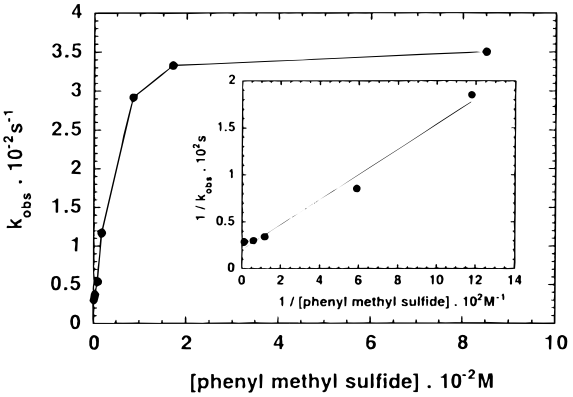


Figure 9. First-order rate constant (k_{obs}) of the decay of the complex **1** as a function of sulfide concentration at 0 °C in acetonitrile. The reaction was monitored spectrophotometrically at 700 nm, the LMCT band characteristic of the iron peroxo complex. Experimental conditions: [**1**] = 2×10^{-4} M; **1**/hydrogen peroxide = 1/10.

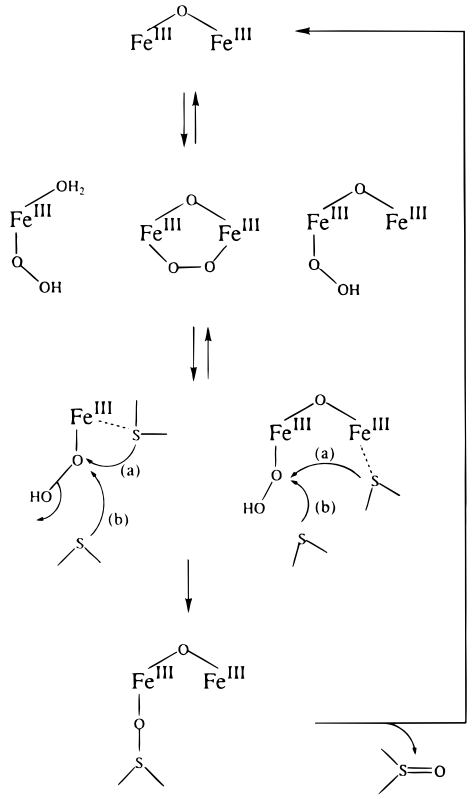
obtained by reaction of a diiron(III) complex with H_2O_2.[14] This new oxidant has the potential to oxidize cumene and ethylbenzene.[25] This unambiguously proves that oxidizing equivalents can be stored on model diiron centers, even in a non heme environment, for further utilization in oxidation reactions. Furthermore, there are now a large number of catalytic systems, based on non heme diiron(III) complexes, which proved to be active during oxidation of alkanes and sulfides by peroxides and peracids.[8,26] However, there was no example of enantioselective oxidations, probably because most systems reported so far used alkyl hydroperoxides as the oxidant. In that case, it is now clearly established that the reaction mainly proceeds through iron-catalyzed homolytic cleavage of the peroxide O−O bond and radical chain autoxidation processes, i.e., mechanistic conditions which do not allow a stereochemical control of the reaction.[15]

Our results reported here and in a preliminary communication[9b] show that a robust diiron catalyst, containing a chiral bipyridine ligand, could catalyze an enantioselective oxidation of sulfides to sulfoxides. The highest ee values we obtained (40%) are clearly not large enough to make this system useful for preparative applications yet. One should note however that these numbers are comparable to those obtained with systems based on chiral iron porphyrins.[24] Nevertheless, they are significant enough to unambiguously show that oxidations catalyzed by non heme diiron complexes can proceed through metal-based pathways, at least with H_2O_2 as the oxidant.

The highest ee values were obtained with H_2O_2 as the oxidant. Iodosylbenzene gave much lower values, suggesting that these two systems proceeded by different mechanisms. No enantioselectivity could be observed with TBHP, confirming the radical mechanism of TBHP-dependent oxidations.

We found that a major drawback of this system was the inhibition of the reaction by the product sulfoxide (Figure 6). This was due to the rather tight binding of the sulfoxide to the diiron center. This interaction also led to an attenuation of the stereochemical control of the reaction by the metal center (Figure 7). All these data are likely to explain the decrease of both yields and ee values with increased H_2O_2 (Figure 1).

Scheme 1. Proposed Mechanism of Sulfide Oxidation Catalyzed by Complex **1** with (a) and (b) Corresponding to Different Nucleophilic Attack Pathways (see text)



The data reported here can be interpreted with the following mechanism shown in Scheme 1. The first intermediate is proposed to be an iron peroxo complex. In fact, several structures could account for the light-absorption band at 700 nm, observed when H_2O_2 was added to complex **1** at low temperature. One is a (μ-peroxo)diiron(III) complex. Several structurally characterized analogues of such a complex have been recently reported.[13,19] Scheme 1 shows other possible structures: dinuclear and mononuclear complexes in which the peroxide is bound to one iron atom by a monodentate binding mode. Accordingly, a small amount of $S = {}^1/_2$ ferric complex was transiently observed by EPR spectroscopy in the absence of substrate. That several iron peroxide complexes were present in acetonitrile solutions containing complex **1** and hydrogen peroxide was shown from the presence in the resonance Raman spectrum of two ^{18}O sensitive features in the 800−900 cm^{-1} range characteristic for the Fe-bound peroxide vibrations. The species characterized by the 868 and 483 cm^{-1} features might be a (μ-oxo)(μ-peroxo)diferric complex as comparable features were found in the case of the $[Fe_2O(O_2)(6\text{-Me3-TPA})_2](ClO_4)_2$ complex previously reported.[19] The second peroxo complex is characterized by vibrations at 806 and 618 cm^{-1} and may be associated with a mononuclear iron peroxide complex[23] or an (η^1-peroxo)diferric complex (see Scheme 1). Further studies are required to better define it. At present it is difficult to determine whether one or both peroxo species are responsible for enantioselective substrate oxidation.

The second proposed intermediate is a ternary complex in which both the peroxide and the sulfide are bound to the complex. This can be achieved within the dinuclear structure (one substrate bound at one iron and the second at the other) or within the mononuclear one.

(24) (a) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (b) Naruta, Y.; Tani, F.; Maruyama, K. *Tetrahedron Asymmetry* **1991**, *2*, 533. (c) Chiang, L.-C.; Konishi, K.; Aida, T.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1992**, 254.
(25) Kim, C.; Dong, Y.; Que, L., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 3635.
(26) Kodera, M.; Shimakoshi, H.; Kano, K. *J. Chem. Soc., Chem. Commun.* **1996**, 1737.

The combination of the following data strongly support the notion that oxygen transfer from the peroxide to the sulfide occurs within this ternary complex: (i) The kinetics of sulfide oxidation are characterized by a saturation behavior with respect to both H_2O_2 and sulfide concentrations. (ii) The iron peroxide complex, generated at low temperature, reacts with phenyl methyl sulfide, as shown from the decay of its characteristic 700 nm band after addition of the sulfide, with a kinetics which is also characterized by a saturation behavior with respect to sulfide concentration.

The linear Hammett correlation we have obtained shows that the highest reactivity is observed with electron-rich sulfides. Furthermore, no incorporation of ^{18}O could be detected when the reaction was performed in the presence of $H_2{}^{18}O$. We thus propose that the monooxidation of sulfides catalyzed by complex **1** proceeds by a nucleophilic attack of the sulfide to the peroxide followed by H_2O release, within the iron peroxide sulfide complex (pathway a). This is in agreement with the observed solvent effect (Figure 2). The resulting sulfoxide is found bound to iron at the end of the catalytic cycle and should be released for the next cycle. This becomes more and more difficult as more sulfoxide accumulates after several cycles, thus explaining the inhibition of the reaction by the product.

The proposed mechanism explains why the reaction can be enantioselective as the transfer of the oxygen atom occurs within the iron coordination sphere (pathway a). However, the catalyst does not allow an optimal stereochemical control of the reaction probably because the chiral center is too far away from the reaction center. It is also very likely that a significant amount of the sulfoxide derives from the attack of free sulfide molecules on Fe-bound peroxide, a pathway which is likely to be less stereochemically controlled (pathway b). This intermolecular reaction could represent the major pathway when sulfide is replaced by the product sulfoxide for binding to the catalyst. It might account for the part of the sulfoxidation reaction that is hardly inhibitable by excesses of sulfoxide (Figure 6) and whose enantioselectivity is hardly decreased by increased additions of sulfoxide (Figure 7).

This work and the proposed mechanism identify a number of issues which remain to be solved if one wants to improve this new catalytic system, in particular in terms of higher enantiomeric excesses. Certainly new ligands which bring the chiral center closer to the reaction site have to be studied. Furthermore methods to prevent the product sulfoxide from binding to the catalyst should be found. Nevertheless, further investigation is warranted into this type of complex which together with hydrogen peroxide generates an iron peroxo complex with the potential for enantioselective oxidations.

Acknowledgment. This work was supported by the National Institutes of Health (Grant GM38767). R.Y.N.H. acknowledges a National Institutes of Health postdoctoral fellowship (Grant GM-17849).

Supporting Information Available: CD spectrum of complex **1** in acetonitrile. This material is available free of charge via the Internet at http://pubs.acs.org.

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