Ferric Hydroperoxides

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# $H_2O_2$ Oxidations Catalyzed by an Iron(III) Corrolazine: Avoiding High-Valent Iron–Oxido Species?**

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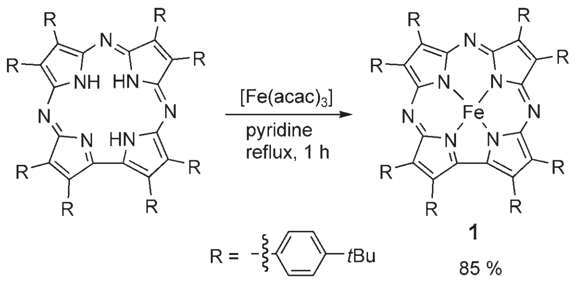
Oxidations catalyzed by iron porphyrins have received considerable attention because of their potential synthetic utility and because of their relevance to enzymatic, heme-catalyzed processes, such as those observed for cytochrome P450.[1] The key reactive intermediate in these systems is usually postulated as a high-valent iron–oxido porphyrin ([(porph$^{\bullet+}$)Fe$^{IV}$=O], Cpd I for P450), formed by oxidation of an iron porphyrin precursor with a variety of oxidants, including $O_2$, $H_2O_2$, PhIO, and mCPBA (3-chloroperoxybenzoic acid). When a peroxide or peracid is employed, iron–oxido formation is preceded by binding of the oxidant to the metal to produce [(porph)Fe$^{III}$–OOR] (R = H, alkyl, acyl), followed by O–O cleavage to give the high-valent intermediate. However, there is growing evidence that in both synthetic and biological systems, conditions may exist in which O–O cleavage is slow and [(porph)Fe$^{III}$–OOR] itself can function as an active oxidant. This concept has been debated for some time with regard to cytochrome P450 and the existence of a so-called second oxidant.[2] Although a two-state reactivity model involving different spin states of Cpd I seems to explain much of the data,[1b,2c,3] very recent findings for P450$_{BM3}$ suggest that a ferric hydroperoxy species is indeed responsible for the sulfoxidation of thioether substrates.[4]

Synthetic chemists have addressed these issues through the study of oxidation reactions catalyzed by iron porphyrins. Although formation of Cpd I-type intermediates is often facile, under certain conditions ferric peroxide precursors can oxidize substrates through either nucleophilic (Fe$^{III}$–$O_2^-$)[5] or electrophilic (Fe$^{III}$–$O_2$R)[6,7] mechanisms. Our group has been interested in a new approach to biomimetic oxidation reactions through the development of a novel class of porphyrinoid ligands called corrolazines (Cz), which are $C_\alpha$–$C_\alpha$ ring-contracted porphyrins with *meso* aza-substitution.[8] Corrolazines are structurally related to the older corrole class of compounds, and have the ability to stabilize high-oxidation-state transition-metal complexes, including high-valent metal–oxido species.[9] Thus, they are excellent candidates for studying metalloporphyrinoid oxidation reactions. For example, we have isolated a thermally stable Mn$^{V}$–oxido corrolazine [(Cz)Mn$^{V}$O] that is capable of oxygen-atom transfer and hydrogen-atom abstraction,[10] whereas the most stable Mn$^{V}$–oxido porphyrin decomposes after a few minutes at room temperature.[11]

Herein, we disclose the synthesis of the first iron corrolazine complex, [(TBP$_8$Cz)Fe$^{III}$] (**1**; TBP$_8$Cz = β-octakis-4-*tert*-butylphenylcorrolazinato). This complex is a highly potent and selective catalyst for the sulfoxidation of thioethers under mild conditions with $H_2O_2$ as the terminal oxidant. This result is of practical significance, because sulfoxidation catalysts are important for both chemical synthesis[12] and the decontamination of warfare agents.[13] Moreover, $H_2O_2$ is a desirable terminal oxidant because it is inexpensive and does not produce environmentally toxic byproducts. With regard to the mechanism of sulfoxidation, our expectation was that [(Cz)Fe] would access a Cpd I-type intermediate, given the stability of such high-valent species with the corrolazine ligand. To our surprise, the data taken as a whole do not support the participation of [(Cz)Fe=O] in the catalytic sulfoxidations, and instead point to an electrophilic [(Cz)Fe–OOH] intermediate analogous to that proposed for P450$_{BM3}$-catalyzed sulfoxidations.

Complex **1** was prepared by insertion of [Fe(acac)$_3$] (acac = acetylacetonate) into the metal-free macrocycle in pyridine heated at reflux (Scheme 1). The dark green crude product was purified by flash chromatography on silica gel to give **1** as a dark green solid (yield: 85%).[14] The iron oxidation state was probed by electron paramagnetic resonance (EPR) spectroscopy. The EPR spectrum of **1** in toluene/pyridine 9:1 at 77 K exhibited a signal typical of a low-spin axially ligated Fe$^{III}$ porphyrin with rhombic anisotropy ($g_1 = 1.90$, $g_2 = 2.20$, $g_3 = 2.39$). This spectrum confirms the assignment of the Fe$^{III}$ oxidation state and indicates that the iron center is coordinated by one or two pyridine ligands under these conditions. In the absence of pyridine, an



**Scheme 1.** Synthesis of [(TBP$_8$Cz)Fe$^{III}$] (**1**).

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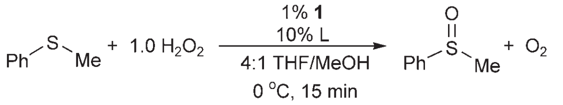
intermediate-spin Fe$^{III}$ EPR signal was observed (see the Supporting Information).[14] Interestingly, the stability of **1** contrasts what is known regarding Fe$^{III}$ corroles, which undergo spontaneous aerobic oxidation in the absence of strong axial ligands such as pyridine.[15]

When a $CH_2Cl_2$ solution of **1** was treated with an excess of $H_2O_2$, the characteristic dark green color of **1** bleached to pale yellow, suggesting destruction of the corrolazine chromophore. This observation is consistent with the activation of $H_2O_2$, leading to a reactive high-valent iron intermediate that subsequently undergoes rapid autodegradation. We therefore attempted to intercept this intermediate by the addition of organic substrates, with the goal of obtaining productive oxidation chemistry and avoiding self-destruction of the corrolazine catalyst. This strategy led to the discovery that **1** is a potent catalyst for the oxidation of sulfides to sulfoxides with $H_2O_2$ as the terminal oxidant (Table 1). The sulfoxidation of thioanisole occurred in 42 % yield (Table 1, entry 1), with only a trace amount of over-oxidized sulfone. The catalyst eventually bleached during this reaction however, prompting us to explore other conditions to improve catalyst stability. It was found that the addition of nitrogenous bases, such as pyridine, as co-catalysts dramatically improved the stability of **1**, causing the reaction to proceed with no evident catalyst degradation. The most successful co-catalyst of this type was *N*,*N*-(dimethylamino)pyridine (dmap; Table 1, entry 2). An EPR spectrum of the reaction mixture with dmap was nearly identical to that of the **1**-pyridine spectrum described above, indicating that **1** was axially ligated by dmap. Addition of nitrogen ligands to iron porphyrin/$H_2O_2$ oxidations has been shown to inhibit O–O homolysis, preventing the formation of $^{\bullet}$OH, which may be responsible for the destruction of **1**.[6a,b,16]

***Table 1:*** Quantification of oxidation products from $H_2O_2$ activation by **1**.



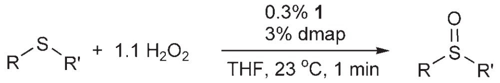
| Entry | L | Equiv PhSMe | Sulfoxide yield[a,b] [%] | $O_2$ yield[a,c] [%] |
|---|---|---|---|---|
| 1 | none | 1.0 | 42 | 10 |
| 2 | dmap | 1.0 | 82 | 10 |
| 3 | dmap | 0 | 0 | 98 |

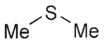
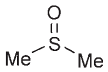
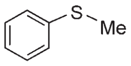
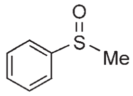
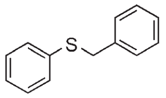
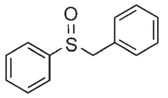
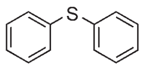
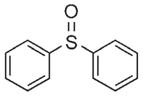
[a] Yields are based on $H_2O_2$ and are an average of at least three data points. [b] Determined by GC relative to an internal standard. [c] Determined by $\Delta V$ measured with a gas buret (see the Supporting Information).

An examination of the yield of sulfoxide in Table 1, entry 2 suggested that even under the best conditions, a significant amount of $H_2O_2$ was either unreacted or potentially being consumed by a competing pathway. Exposure of the headspace of the sulfoxidation reaction to an alkaline pyrogallol solution indicated the presence of $O_2$,[17] pointing to iron-catalyzed disproportionation of $H_2O_2$ (catalase behavior). The yield of $O_2$ was quantified, and when both oxidation products are considered, 92 % mass balance for $H_2O_2$ is obtained. When thioanisole was omitted from the reaction (Table 1, entry 3), the volume of dioxygen produced accounted for 98 % of the amount expected from disproportionation of $H_2O_2$, indicating that **1** performs as a highly efficient catalase mimic in the absence of other substrates. The importance of the axial ligand as a co-catalyst in both oxidative pathways is clear from all of the data in Table 1: in the absence of dmap, a significantly lower total yield of oxidation products (sulfoxide + $O_2$) is obtained, and the catalyst is completely degraded by the end of the reaction (entry 1), whereas in the presence of dmap, **1** is recovered intact (Table 1, entries 2 and 3), and the oxidation reactions proceed to completion.

Optimization of reaction conditions (e.g. solvent, temperature) revealed that highly efficient sulfoxidations take place in pure THF at room temperature (Table 2). These reactions require low catalyst loadings (0.3 mol %) and proceed at a rapid rate, achieving more than 300 turnovers per minute. As seen in Table 2, a variety of sulfides with both aryl and alkyl substituents were smoothly converted into the corresponding sulfoxides, with negligible over-oxidation to sulfones.

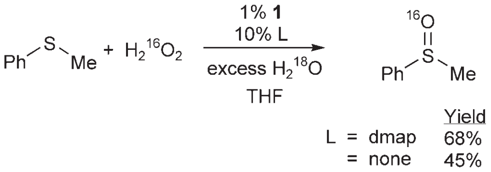
***Table 2:*** Sulfide oxidation with $H_2O_2$ catalyzed by **1**.



| Entry | Sulfide | Product | Yield[a] [%] |
|---|---|---|---|
| 1 |  |  | 88 |
| 2 |  |  | 98 |
| 3 |  |  | 85 |
| 4 |  |  | 83 |

[a] Determined by GC relative to an internal standard.

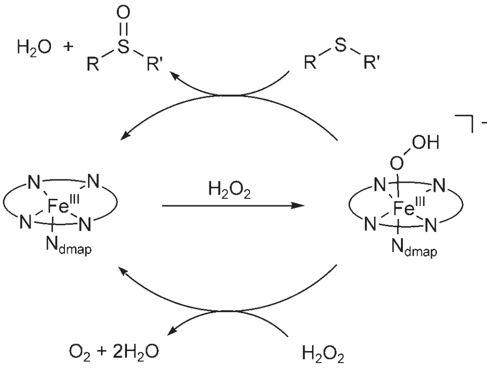
Having found optimal catalytic conditions, spectroscopic measurements of the reaction mixtures were made with the goal of determining the resting state of the catalyst. A high-valent iron–oxido species can be expected to exhibit distinctly different EPR and UV/Vis spectra from its Fe$^{III}$ precursor.[18] The EPR data of catalytic reaction mixtures with PhSMe as the substrate showed evidence for only a (Cz)Fe$^{III}$–dmap adduct, with no indication of any other EPR-active iron corrolazine species.[19] In addition, no changes were observed by UV/Vis when $H_2O_2$ was added to **1**/dmap/PhSMe at room temperature, or when the sulfoxidation reaction was performed at −78 °C. In previous work on metalloporphyrins, the presence of a reactive metal–oxido species during catalytic oxidations has been inferred by the incorporation of $^{18}O$ into organic products after addition of $H_2{}^{18}O$.[18b,20] When the oxidation of thioanisole catalyzed by **1**/dmap was performed in the presence of a large excess of $H_2{}^{18}O$, the only reaction product detected by gas chromatography–mass spectrometry (GC–MS) was $PhS(^{16}O)Me$ (Scheme 2). Because axially ligated dmap may inhibit incorporation of $H_2{}^{18}O$ into an iron–oxido species, the experiment was also performed in the absence of dmap. No $^{18}O$ incorporation into methylphenyl sulfoxide was detected in either case.



***Scheme 2.*** $^{18}O$-exchange experiment. No $^{18}O$ is incorporated into sulfoxide.

One of the hallmarks of authentic iron–oxido porphyrins is the ability to epoxidize alkenes. Although **1** was a very efficient sulfoxidation catalyst, no conditions for **1** were found in which an oxygen atom could be transferred from $H_2O_2$ to an alkene (epoxidation), even when a relatively reactive substrate such as *cis*-cyclooctene was employed.[21] This lack of reactivity with **1**/$H_2O_2$, coupled with the spectral and isotopic-exchange data discussed above, suggest the reactive species in **1**/$H_2O_2$ oxidations is not a high-valent iron–oxido corrolazine.

A logical mechanistic alternative to an Fe=O-type oxidant is an electrophilic $Fe^{III}$ hydroperoxide, as shown in Scheme 3.[22] Although the disproportionation of $H_2O_2$ to $O_2$ by iron porphyrins is well known,[23] this reaction is believed to occur exclusively through an iron–oxido intermediate, and to our knowledge, catalase-like activity of an Fe–OOH adduct has not been described.[24] Although we cannot rule out the possibility of leakage of a small amount of catalyst **1** to an iron–oxido species, the combined data support the hypothesis that $[(TBP_8Cz)Fe^{III}{-}OOH]$ is the active oxidant for both sulfoxidation and catalase activity. No evidence for a high-valent iron–oxido intermediate was obtained under any conditions, despite the expected stability of such a species with the corrolazine platform.[25]



***Scheme 3.*** Proposed catalytic cycle.

We have prepared the first iron corrolazine and found it to be a highly efficient sulfoxidation catalyst with $H_2O_2$, as well as an active catalase mimic. In $P450_{BM3}$ oxidations, it is suggested that thioethers are kinetically competent to intercept $Fe^{III}{-}OOH$ prior to formation of Cpd I, whereas less reactive substrates such as hydrocarbons are not.[4] Support for this proposal in a synthetic system comes from the results for **1**/$H_2O_2$ oxidations, in which thioether substrates appear competent to intercept a $[(Cz)Fe^{III}{-}OOH]$ species prior to formation of a Cpd I-type intermediate or disproportionation of $H_2O_2$.

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[21] Addition of mCPBA to **1** at −78 °C produces a new species by UV/Vis and EPR that is capable of epoxidizing alkenes. Characterization of this species is currently underway.

[22] Another alternative, free radical oxidation, is unlikely on the basis of the lack of benzyl alcohol and/or benzaldehyde observed in the oxidation of benzylphenyl sulfide (Table 2, entry 3). The radical cation formed by one-electron oxidation of this substrate undergoes rapid C–S cleavage. See: E. Baciocchi, O. Lanzalunga, B. Pirozzi, *Tetrahedron* **1997**, *53*, 12287–12298.

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