Switching on the Nucleophilic Reactivity of a Ferric Porphyrin Peroxo Complex

Matthias Selke and Joan Selverstone Valentine*

Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, California 90095-1589

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The chemical reactivity of the peroxide ligand, O_2^{2-}, when bound to a metal ion is remarkably diverse. Nucleophilic and electrophilic reactivities, as well as protonation followed by homolytic and heterolytic O−O bond cleavage, have been observed in a variety of complexes,[1] but the factors dictating the particular mode of reactivity are often unclear. This subject is of great importance in attempting to understand mechanisms of metalloenzyme-catalyzed dioxygen activation, where such complexes have been invoked as key intermediates. In the case of the cytochrome P450 enzyme family, for example, most reactions appear to proceed by protonation of the peroxide ligand followed by O−O bond cleavage that occurs prior to attack on the enzyme-bound substrate.[2] However, in certain cases, these same enzymes appear to proceed by a different mechanism, which has been proposed to involve direct nucleophilic attack of the peroxide ligand.[3]

Our laboratory has for some time been studying ferric porphyrin peroxo complexes as synthetic analogues of intermediates that might occur in enzymatic reactions.[4] We have recently shown that the ferric porphyrin peroxo complexes $[Fe(P)O_2]^-$ (P = protoporphyrin IX dimethyl ester or tetramesitylporphyrin) are powerful nucleophiles capable of epoxidizing electron-deficient olefins.[5] Surprisingly, however, we found the ferric peroxo complex of the electron-deficient porphyrin 5,10,15,20-tetrakis-(pentafluorophenyl)porphyrin (F_{20}TPP) to be unreactive with such olefins.[5b] We now report that binding of an additional axial ligand to the ferric peroxo complex of the latter porphyrin dramatically increases the nucleophilicity and thus can act as a switch to turn on nucleophilic epoxidation reactions.

Binding of Axial Ligands to Electron-Deficient Ferric Porphyrin Peroxo Complexes. Addition of triphenylphosphine to acetonitrile or toluene solutions of $[Fe(F_{20}TPP)O_2]^-$, **1**, and $Fe(F_{20}TPP)Cl$, **2**, resulted in dramatic broadening and a slight shift perturbation of the phosphorus signal in the ^{31}P NMR,[5b] consistent with the formation of a very weak bond between the phosphine and the iron in both the peroxo and the chloro complexes. When a CD_2Cl_2 solution of complex **2** and excess PPh_3 was cooled to −60 °C, a small new peak at 12.6 ppm, in addition to the sharp signal for free PPh_3, was observed in the ^{31}P NMR spectrum. When the sample was warmed, this peak disappeared, and the signal of the free PPh_3 again broadened. Thus, the complex $Fe(F_{20}TPP)Cl(PPh_3)$ exists as a distinct species at − 60 °C in CD_2Cl_2, although only a very small fraction (<1% by integration of the phosphine signals) of the total ferric porphyrin complex consists of this diaxial species.[6]

In contrast to the above results, *no* broadening or shift perturbation of PPh_3 in solutions of **1** or **2** in neat DMSO was observed. Upon titrating up to 1 equiv of DMSO (relative to the concentration of the ferric porphyrin complex) to CD_3CN or toluene solutions of either **1** or **2** and 5 equiv of PPh_3, there was little change in the broad PPh_3 signal in the ^{31}P NMR spectrum. Using equal amounts of PPh_3 and DMSO decreased the line width of the phosphorus signal by nearly 50%, and when ≥4 times the equivalents of DMSO was added, only a sharp unperturbed signal for the PPh_3 was observed. Thus, the reversible binding of DMSO is competitive with that of PPh_3. Interestingly, methyl phenyl sulfoxide showed no binding ability to either complex **1** or **2**, presumably because of a steric effect.[7]

Effects of Axial Ligands on the Nucleophilicity of Electron-Deficient Ferric Porphyrin Peroxo Complexes. As we have previously reported, the electron-deficient peroxo complex **1** in acetonitrile is unreactive with electron-poor olefins such as 2-methyl-1,4-naphthaquinone (menadione), in contrast to peroxo complexes containing electron-rich porphyrin ligands such as $[Fe(TMP)O_2]^-$, **3**.[5b] However, when the reaction between **1** and menadione was carried out instead in neat DMSO and under strictly anaerobic conditions, the characteristic blood-red color of the peroxo complex disappeared instantaneously, a new porphyrin species with λ_{max} = 424 nm (Soret) and a pyrrole peak at 31 ppm in the paramagnetic ^1H NMR was formed,[8] and menadione epoxide was detected as the product by diamagnetic ^1H NMR. The formation of menadione epoxide occurred in excellent yield (60−70% based on the Fe complex as determined by ^1H NMR).[11]

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(6) Unfortunately this experiment could not be carried out with complex **1**, as the ferric peroxo complexes cannot be prepared in methylene chloride and as the freezing point of acetonitrile is too high to prevent rapid exchange between free and coordinated phosphine on the NMR time scale. It is possible that the chloride ligand of complex **2** is substituted by the phosphine, leading to a complex $[Fe(F_{20}TPP)(PPh_3)]^+Cl^-$ rather than the bisaxially coordinated species.

(7) PM3 calculations of methyl phenyl sulfoxide predict that the conformation in which the plane of the phenyl ring is *parallel* to the S═O bond is preferred by 4.4 kcal to that in which the plane is perpendicular to the S═O bond. The former preferred arrangement almost certainly blocks the approach toward the porphyrin moiety.

(8) The spectral data for the porphyrin product is consistent with a ferrous species.[9] We believe that the initial porphyrin product is the ferric OH complex, as is the case in the nucleophilic epoxidation reactions of ferric porphyrin peroxo complexes containing electron-rich porphyrin ligands, and that formation of the ferrous complex is due to a secondary reaction. Support for this conclusion is our observation that the ferric OH complex $Fe(F_{20}TPP)$-OH, prepared either from $Fe(F_{20}TPP)Cl$ and concentrated KOH in benzene[10] or by decomposition of $[Fe(F_{20}TPP)O_2]^-$ under air in CH_3CN, was instantaneously converted to the same ferrous species upon dissolving it in DMSO.

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(11) The ^1H NMR spectrum of the menadione epoxide obtained from the reaction with **1** was identical to that of menadione epoxide prepared from menadione and basic H_2O_2. The yield obtained represents a low estimate of the actual yield, as the epoxide product is quite unstable under the experimental conditions.

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Table 1. Spectral Properties of Ferric Porphyrin Peroxo Complexes

porphyrin complex/solvent	UV/vis (nm)	UV/vis (Q-bands) (nm)	^{1}H NMR (pyrrole protons) (ppm)[a]
$[Fe(F_{20}TPP)O_2]^-$, **1**, in DMSO-d_6[a]	432	538, 558, 589, 612 (sh)	63.0
$[Fe(F_{20}TPP)O_2]^-$, **1**, in CD_3CN	430[b]	538, 559, 588 (sh), 610 (sh)[b]	65.0
$[Fe(TMP)O_2]^-$, **3**, in CD_3CN	434[b]	549 (sh), 568, 595 (sh), 612[b]	63.5
$[Fe(TMP)O_2]^-$, **3**, in 65% DMSO-d_6:35% CD_3CN[c]	437	547 (sh), 565, 595 (sh), 612	64.5

[a] This work. [b] Reference 5b. [c] This complex cannot be prepared in neat DMSO due to the insolubility of the starting Fe(TMP)Cl complex in DMSO. Therefore, a solution of this complex was prepared in CD_3CN and then diluted with DMSO.

Approximately 20% (by vol.) of DMSO was necessary to obtain significant reactivity between **1** and menadione, when a 3 mM solution of **1** in acetonitrile containing 5 equiv of menadione was titrated with DMSO.[12] This result is not surprising as the coordination of either PPh_3 or DMSO appears to be quite weak; the equilibrium greatly favors the uncoordinated species, as shown by the low-temperature ^{31}P NMR studies. The nucleophilic reactivity of complex **1** is only observed when a large amount of DMSO (20% by vol.) is present, presumably an amount sufficient to drive the equilibrium to the bis-axially coordinated $[Fe(F_{20}TPP)O_2(DMSO)]^-$ complex. By contrast, addition of methyl phenyl sulfoxide to acetonitrile solutions of **1** did not promote any nucleophilic reactivity, indicating that the remarkable reactivity of **1** observed in DMSO is not due to a simple solvent effect, but rather that coordination of a second axial ligand is a prerequisite to obtain this reactivity.[13]

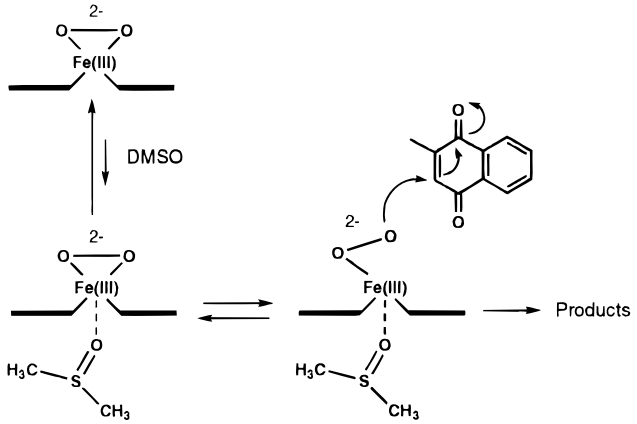
Despite the astonishing contrast between the reactivity of **1** in acetonitrile and in DMSO, the spectral properties of complex **1** in either solvent were found to be very similar, as is also the case for the peroxo complex of the electron-rich porphyrin ligand tetramesitylporphyrin (TMP) (see Table 1).

Nitrogen bases such as pyridine and 1-methylimidazole were also attempted as second axial ligands, but these compounds led only to reduction of the ferric porphyrin peroxo complexes to ferrous species; no evidence for binding was ever obtained.

Discussion. It has generally been assumed that the reactivity of peroxo complexes depends mainly upon the distribution of electrons between the metal and the peroxo ligand and, in some cases, upon the strength of the O−O bond.[14] We suggest here an additional factor that may be important: an equilibrium between the closed triangular form of the peroxo ligand and an open peroxo ligand. Ring opening of the peroxo ligand has

previously been suggested for nucleophilic reactions of peroxo complexes derived from group VIII transition metals with SO_2,[15] CO,[16] and tetracyanoethylene.[17] The equilibrium depicted in Scheme 1 may also explain the remarkable reactivity of the Re-

Scheme 1. Epoxidation of an Electron-Deficient Olefin by the Ferric Perfluorinated Peroxo Complex in DMSO



(VII) complex $Re(O_2)_2(O)CH_3$ prepared by Herrmann et al.,[18] which exhibits both electrophilic and nucleophilic reactivities.[19] The steric crowding at the rhenium atom may promote dissociation of one end of the peroxo ligands, thereby leading to nucleophilic reactivity, while the electrophilic reactions may go through a pathway involving a closed peroxo ligand, similar to other d^0 transition metal complexes.[20]

In the case of ferric porphyrin peroxo complexes, our results suggest that axial ligands can act as a switch to push the triangularly bound peroxo complex open and make the peroxo ligand much more nucleophilic. Since the spectral properties of complex **1** in acetonitrile and DMSO are very similar, it is apparent that only a very small amount of the open peroxo complex could exist in solution, but reaction with menadione would drive this equilibrium all the way to the right (see Scheme 1).

Dawson et al. proposed in 1976 that the axial thiolate ligand bound to the iron atom of the heme moiety in cytochrome P450 weakens the O−O bond of the putative hydroperoxide intermediate in P450 through electron donation, thereby facilitating heterolytic O−O bond cleavage.[21] A number of model systems have been developed to show how an axial base can cause either homolytic or heterolytic O−O bond cleavage of ferric hydroperoxy porphyrin complexes via a "push−pull" mechanism.[22] However, so far, little is known about the role that axial ligands may play in selecting the nucleophilic mode of reactivity in the enzyme. On the basis of the results of this study, it seems possible that the axial ligand in the enzyme may also act as a switch togenerate an open peroxo complex, leading to nucleophilic attack on substrate, as has recently been suggested by Graham-Lorence et al.[3d] to be occurring in the aromatization step in cytochrome P450 aromatase as well as in cytochrome P450 2b4.[3c]

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(12) Slow changes also took place at lower DMSO concentrations, as evidenced by a decrease in the Soret absorption of the peroxo complex, but these changes occurred too slowly to discriminate between possible nucleophilic reactions and other decomposition pathways of the relatively unstable peroxo complex.

(13) Up to 40% (by molarity) of methyl phenyl sulfoxide were added to acetonitrile solutions of **1** in the presence of a 2-fold excess of menadione. Except for dilution effects, there was no change in the UV/vis spectrum of the peroxo complex.

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