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Metalloporphyrin Peroxo Complexes of Iron(III), Manganese(III), and Titanium(IV). Comparative Studies Demonstrating That the Iron(III) Complex Is Extremely Nucleophilic

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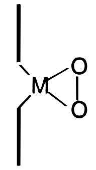
Peroxo Fe(III), Mn(III), and Ti(IV) porphyrin complexes were reacted with a variety of electron-rich and electron-poor organic substrates in order to compare their reactivities with those of other known metalloperoxide complexes. The peroxoiron(III) porphyrin complex was unreactive with electron-rich substrates such as tetramethylethylene, cyclohexene, triphenylphosphine, or butyllithium but was quite reactive with electron-poor substrates such as 2-cyclohexen-1-one and 2-methyl-1,4-naphthoquinone. The peroxomanganese(III) porphyrin complex was unreactive with these electron-poor olefins but did react with the strongly electron-deficient olefin tetracyanoethylene. The peroxotitanium(IV) porphyrin complex was unreactive with both electron-rich and electron-poor olefins, as well as butyllithium, but did quantitatively oxidize triphenylphosphine to triphenylphosphine oxide. These results lead to the conclusion that the peroxo Fe(III) porphyrin complex is significantly more nucleophilic than the analogous Mn(III) and Ti(IV) complexes and than several well-known nucleophilic non-porphyrin peroxometal complexes.

Cytochrome P450 enzymes catalyze oxygenations of a wide variety of organic substrates using dioxygen itself as the oxygen atom source.[1] Mechanisms proposed for these enzymes all invoke initial formation of a ferric heme peroxo complex, formulated as either $[(\text{porphyrin})\text{Fe}^{\text{III}}\text{O}_2]^-$ or its protonated form $(\text{porphyrin})\text{Fe}^{\text{III}}\text{OOH}$.[2−6] After formation of the peroxo intermediate, three distinctly different modes of reaction were proposed to account for the different types of reactivity observed for different P450 enzymes, i.e., (a) heterolytic O−O cleavage to generate a $(\text{porphyrin})\text{Fe}^{\text{V}}{=}\text{O}$ or $(\text{oxidized porphyrin})\text{Fe}^{\text{IV}}{=}\text{O}$ high-valent oxo species, (b) homolytic O−O cleavage to generate a $(\text{porphyrin})\text{Fe}^{\text{IV}}{=}\text{O}$ species, and (c) direct nucleophilic attack by a ferric heme peroxo species on an enzyme-bound substrate. The last mechanism has been proposed for aromatase,[7−9] cytochrome P450-2B4,[10] and NO synthase.[11]

Synthetic metalloporphyrin peroxo complexes have been synthesized in several laboratories, and it is expected that studies of the reactivities of such complexes will ultimately lead to insights into the details of the cytochrome P450 enzymatic pathways. Several of these synthetic metalloporphyrin peroxo complexes have been well characterized with respect to their crystal structures, spectroscopic and magnetic properties,[12−15] and, in certain cases, reactivities.[16] The metalloporphyrin peroxides $[(\text{TPP})\text{MnO}_2]^-$ and $(\text{TPP})\text{TiO}_2$ have been structurally characterized; both complexes form the following side-on geometry:



On the basis of EXAFS,[17] magnetic susceptibility, Mössbauer, and EPR studies,[15] it is very likely that the analogous iron complexes possess the same geometry. Studies of Fe(III) and Mn(III) porphyrin peroxo complexes have demonstrated a high degree of nucleophilic character in their reactions with acyl halides,[18,19] aldehydes,[20,21] carbon dioxide,[22] and electron-deficient olefins.[23] We recently reported that [(PPIXDME)-

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$Fe^{III}O_2]^-$ (PPIXDME = protoporphyrin IX dimethyl ester) is also able to directly transfer an oxygen atom to electron-deficient olefins such as 2-cyclohexen-1-one or 2-methyl-1,4-naphthoquinone.[23,24] This nucleophilic oxygen transfer mimics the direct nucleophilic attack on an enzyme-bound substrate proposed for certain of the P450 enzymes.

We report here a study of the relative reactivities of a series of Fe(III), Mn(III), and Ti(IV) porphyrin peroxo complexes in *direct* reactions with a variety of electron-rich and electron-poor organic substrates. The dramatic differences in the reactivities of these species allow us to rank these metalloporphyrin complexes with respect to their relative reactivities and to compare them with some of the non-porphyrin transition metal peroxo complexes. We find that the ferric porphyrin peroxo complex is by far the most nucleophilic of these complexes and therefore conclude that peroxo heme intermediates in enzymatic systems likewise have a high degree of nucleophilic character and will react with an appropriate substrate, if the substrate has unhindered access to the peroxo ligand. We also propose a classification scheme for the relative nucleophilic reactivity of a number of porphyrin and non-porphyrin transition metal peroxo complexes.

Experimental Section

Materials and Methods. All reactions were performed under an inert atmosphere of helium in a Vacuum Atmospheres glovebox. Solvents were dried by distillation under an inert atmosphere from appropriate drying agents: calcium hydride for dimethylacetamide (DMA) and acetonitrile (CH_3CN); sodium/benzophenone for tetrahydrofuran (THF). Dimethylacetamide and acetonitrile were then further dried inside the glovebox by passage through neutral Woelm or Sigma activity grade Super I alumina. The solvent was stirred for 30 min with powdered potassium superoxide (KO_2, Aldrich) and filtered through more Super I alumina.[25] Electron spin resonance (ESR) spectra of the solvents showed no signal from dissolved superoxide. Tetramethylammonium superoxide ($(TMA)O_2$) was prepared by literature methods and determined to be greater than 95% pure by titration.[26] Kryptate 222 (K_{222}, MCB) was purified by recrystallization from heptane in the glovebox or was used as received. 18-Crown-6 (Aldrich) was recrystallized by literature procedures.[27] (TPP)FeCl and (TPP)-MnCl (TPP = tetraphenylporphyrin) were prepared by metalation of chlorin-free tetraphenylporphyrin (Mid-Century Chemical) by published procedures.[28] For the cyclohexene reactivity studies, (TMP)FeCl (TMP = tetramesitylporphyrin) was prepared by a modification of a published procedure[29] and metalated by the method of Adler.[28] All other studies used (TMP)FeCl obtained from Mid-Century Chemical. $(TPP)TiO_2$[30] was the generous gift of Dr. J.-M. Latour. Triphenylphosphine (BDH, analytical standard grade) was dried over phosphorus pentoxide and stored in the drybox. Triphenylphosphine oxide (Chemalog) was used as a standard in the identification of the oxidized substrate. Tetramethylethylene (Aldrich) was passed over basic alumina and checked for purity by ^1H NMR prior to use. Butyllithium (1.5 M in hexanes), tetracyanoethylene (TCNE), tetracyanoethylene oxide (TCNE oxide), and $Pt(PPh_3)_4$ were obtained from Aldrich. Deuterated chloroform and acetonitrile were obtained from Cambridge Isotopes.

Instrumentation. A Hewlett Packard 5890A gas chromatograph coupled with a Hewlett Packard Model 5970 mass selective detector was used for the GC-MS analyses. HPLC data were obtained using a Beckman Model 344 equipped with a Model 165 variable-wavelength detector. UV−vis spectra were recorded on a Cary 3 spectrophotometer (Varian). ^1H and ^{31}P NMR spectra were recorded on a Bruker 360 MHz spectrometer using $P(OMe)_3$ as an external standard for the ^{31}P measurements.

Reactions of the Metalloporphyrin Peroxide Complexes with Triphenylphosphine. The reactions of the peroxo metalloporphyrin complexes with triphenylphosphine were monitored by ^{31}P NMR and UV−vis absorption spectroscopies. In the reaction of the manganese or iron peroxo porphyrin complex, $(TPP)M^{III}Cl$, M = Fe or Mn (10 mg, 11 μmol), was added to a solution of KO_2 (2 equiv) and K_{222} (3 equiv) in CD_3CN (total volume = 1 mL, [peroxo metalloporphyrin complex] = 11 mM), and the mixture was stirred for 10−20 min. This solution was titrated with 5 equiv of triphenylphosphine, and the resulting ^{31}P NMR spectra were recorded after 1 h. Aliquots for UV−vis absorption analysis were removed after 15 min and analyzed using 0.1 mm cells. $(TPP)TiO_2$ (5 mg, 7.2 μmol) was dissolved in THF-d_8 (total volume = 1 mL, 7.2 mM), the solution was reacted with 5 equiv of triphenylphosphine, the mixture was analyzed as described above.

Reactions of the Metalloporphyrin Peroxide Complexes with Butyllithium. Molybdenum(VI) pentoxide hexamethylphosphoramide (MoO_5HMPA) was prepared by literature methods.[31] The peroxo complexes either were dissolved $(TPP)TiO_2$ or were prepared (Mn or Fe) in THF (1.85 mM); to this solution was added ≥1 equiv of butyllithium. After 5 min−1 h of stirring, excess acetic anhydride was added and the resulting solution was stirred for another 1 h. This mixture was then assayed for the formation of butyl acetate by GC.

Reactions of the Metalloporphyrin Peroxide Complexes with Cyclohexene. The reactions of the peroxo metalloporphyrin complexes with cyclohexene were monitored by GC and UV−vis absorption spectroscopies. (TMP)MnCl (20 μmol) or (TMP)FeCl (20 μmol) and a 5-fold molar excess of KO_2 were combined with 2.0 equiv of 18-crown-6 in CH_3CN (10 mL, [peroxo metalloporphyrin complex] = 2 mM), and the mixture was stirred for 30 min. The resultant mixture was then filtered through a 0.45 μm filter to remove undissolved KO_2, and the filtrate was stirred rapidly with 120 equiv of cyclohexene (250 μL in 5 mL of CH_3CN). The reaction of the titanium peroxo complex was performed in the same manner by dissolving the appropriate amount of the peroxo complex in tetrahydrofuran and stirring the solution with cyclohexene. Samples were analyzed by GC for the formation of cyclohexene oxide as well as cyclohexen-1-ol and cyclohexen-1-one. For spectral titrations, solutions of $(TPP)M^{III}Cl$, M = Fe and Mn (1 mM), were diluted to a final concentration of 1.7×10^{-5} M. Two equivalents of superoxide was added in each case, the formation of the peroxo complexes was verified by UV−vis absorption spectroscopy,[32,33] and then cyclohexene was added. Spectra were recorded several minutes after addition of the cyclohexene.

Reactions of the Metalloporphyrin Peroxide Complexes with Tetramethylethylene. To a 1 mM solution of $(TMP)MO_2^-$, prepared as described above, was added up to 100 equiv of tetramethylethylene by syringe. The mixture was then analyzed by UV−vis absorption spectroscopy using 0.1 mm cells.

Reactions of the Metalloporphyrin Peroxide Complexes with 2-Cyclohexen-1-one, 2-Methyl-1,4-naphthoquinone, and 2-Methyl-1,4-naphthoquinone Epoxide. $[(TMP)FeO_2]^-$ and the Mn analog were prepared as described above. $(TPP)TiO_2$ was dissolved in THF as described above. Two-equivalents of 2-cyclohexen-1-one (103 mM, 67 μL in CH_3CN) was added to 3.44 mM peroxo metalloporphyrin solutions (1 mL total volume), and the reactions were allowed to proceed, during which time aliquots were removed after approximately 10 and 30 min for GC-MS analysis. Prior to use, formation of the peroxo metalloporphyrin solutions was confirmed in each case by UV−vis spectroscopy. Two-equivalents of 2-methyl-1,4-naphthoquinone was added to the peroxo metalloporphyrin solutions, under inert atmosphere, at both 1 mM (58.1 mM, 34 μL in CH_3CN) and 0.1 mM

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(5.81 mM, 34 μL in CH_3CN) concentrations to give total volumes of 1 mL. UV−vis spectra were taken 10 and 30 min after addition of the substrate, and epoxide yields were determined by HPLC after 15 min and 1 h. Reactions of the peroxometal porphyrin complexes with the corresponding epoxide products was also investigated. 2-Methyl-1,4-naphthoquinone epoxide was prepared by a published procedure.[34] Two-equivalvent amounts of the epoxide (5.3 mM, 34 μL in CH_3CN) were added to 0.1 mM solutions of the peroxo metalloporphyrin complexes (total volume 1 mL). UV−vis spectra were taken 15 min and 1 h after addition of the epoxide, and the loss of epoxide was monitored by HPLC.

Reactions of the Metalloporphyrin Peroxide Complexes with Tetracyanoethylene and Tetracyanoethylene Oxide. Two-equivalent amounts of TCNE (29 μL, 78 mM in CH_3CN) were added to solutions of the peroxo metalloporphyrin complexes (1 mM, 1 mL total volume), and the mixtures were stirred for 10 min prior to analysis by UV−vis absorption spectroscopy. Reactions of the peroxo metalloporphyrin complexes with 2-equiv samples of TCNE epoxide (1 mg) were carried out analogously. Organic products were analyzed by GC-MS.

Reaction of $Pt(PPh_3)_2O_2$ with 2-Methyl-1,4-naphthoquinone. $Pt(PPh_3)_2O_2$ was prepared in $CDCl_3$ by a literature method,[35] and its ^{31}P NMR spectrum was recorded. To this solution was added 4 equiv of 2-methyl-1,4-naphthoquinone. The final concentration of the Pt complex was 5 mM. The ^{31}P NMR and ^{1}H NMR spectra of the reaction solution were recorded after approximately 10 min and 2 h.

Results

I. Reactions of (porph)$Ti^{IV}O_2$, [(porph)$Mn^{III}O_2$]$^-$, and [(porph)$Fe^{III}O_2$]$^-$ with Electron-Rich Substrates. (a) Reactions with Triphenylphosphine. The titanium peroxo porphyrin reacted rapidly and stoichiometrically with triphenylphosphine to give 1 equiv of triphenylphosphine oxide, identified by HPLC and ^{31}P NMR, and 1 equiv of (TPP)$Ti^{IV}O$, identified by its UV−vis spectrum. It was previously reported that the peroxotitanium porphyrin can be photochemically induced to oxygenate a variety of organic substrates;[36,37] therefore, we also carried out the reaction with triphenylphosphine in the dark in order to ascertain if the reaction observed was photochemically driven. Again the spectrum indicated that the sole component of the reaction mixture was the oxotitanium porphyrin, and the yield of triphenylphosphine oxide was 87% ± 2% as measured by ^{31}P NMR. From these results, we conclude that the oxidation of triphenylphosphine is a characteristic reaction of the peroxotitanium porphyrin complex and does not require light. The reaction is illustrated in eq 1; UV−vis spectra of the peroxo Ti porphyrin complex before and after the addition of phosphine are shown in Figure 1.

$$\text{(porphyrin)}Ti^{IV}O_2 + PPh_3 \rightarrow \text{(porphyrin)}Ti^{IV}{=}O + Ph_3PO \qquad (1)$$

In contrast to the titanium complex, the iron and manganese peroxo porphyrins did not react with triphenylphosphine. Spectrophotometric titrations demonstrated that the peroxo complexes were unaffected by the addition of triphenylphosphine: when either the iron or the manganese peroxo complex was titrated with 1−5 equiv of substrate, there was virtually no UV−vis spectral change. This lack of reactivity was observed in a variety of solvents, including DMSO, DMA, CH_3CN, and THF, and for both tetraphenyl- and tetramesityl porphyrins. In addition, no triphenylphosphine oxide was detected by ^{31}P NMR after 1 h, in a solution containing either 20 mM [(TMP)FeO_2]$^-$ or 20 mM [(TMP)MnO_2]$^-$ and 5 equiv of triphenylphosphine.

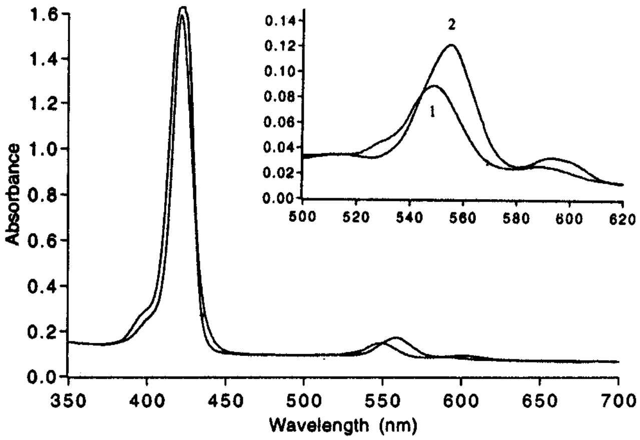

Figure 1. UV−vis spectra for the reaction of Ti^{IV}(TPP)O_2 with triphenylphosphine in THF. Spectrum 1 corresponds to the peroxotitanium porphyrin complex, while spectrum 2 corresponds to the product formed upon reaction with 5 equiv of triphenylphosphine. The UV−vis absorption spectrum of the porphyrin product is identical to that of Ti^{IV}(TPP)O.

(b) Reactions with Butyllithium. According to the procedure described by Regen and Whitesides,[38] the peroxo complexes were reacted with butyllithium, and the extents of the reactions were assayed by gas chromatography. In this assay, the butoxy anion formed by the oxidation of the butyl anion by the peroxo complex reacts with acetic anhydride to give butyl acetate. (TPP)TiO_2 was reacted with butyllithium according to the published procedure. When butyllithium was added, the solution immediately turned from pink to dark green. Only trace amounts of butyl acetate were seen when the reaction was quenched with acetic anhydride. In none of the reactions was the yield of butyl acetate more than 6%. The iron peroxo complex was reacted with butyllithium and acetic anhydride in a similar fashion. No butyl acetate was observed despite the addition of a large excess of butyllithium, nor was it observed when the reaction was followed for an extended period of time. The reaction was also monitored by UV−vis spectroscopy, which indicated that the butyllithium reduced the Fe(III) initially to a species similar to the ferrous hydroxo complex.

The reactivity of the manganese peroxo complex was similar to that of the iron; i.e., no butyl acetate was formed under the reaction conditions. MoO_5HMPA was used as a control and was observed to yield 1 equiv of butyl acetate/equiv of peroxide ligand under identical conditions.

(c) Reactions with Cyclohexene and Tetramethylethylene. Cyclohexene has two different modes of reactivity with oxygen transfer reagents, i.e., allylic oxidation and epoxidation. The former is characteristic of a radical mechanism, producing primarily the allylic oxidation products cyclohexen-1-ol and cyclohexen-1-one, and the latter of a non-radical, or atom transfer, pathway, which typically produces high yields of the epoxide. No epoxide was detected in the [(TMP)FeO_2]$^-$ reaction with cyclohexene, and only a trace (<1%) was detected in the (TPP)TiO_2 reaction. [(TMP)MnO_2]$^-$ produced 2.4% of the epoxide over a period of 1 h, but no further increase in the epoxide level occurred over time. The levels of 2-cyclohexen-1-one and 2-cyclohexen-1-ol were also quite low in all cases (<1% for Ti and not detectable for Mn and Fe). The UV−vis spectra of the metalloperoxide porphyrin complexes were

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Table 1. Comparative Reactivities of Peroxo Fe(III), Mn(III), and Ti(IV) Porphyrin Complexes with Electron-Deficient Olefins

peroxo metalloporphyrin complex	yield,[a] %	
	2-cyclohexen-1-one epoxide	2-methyl-1,4-naphthoquinone epoxide
$[\mathrm{Fe^{III}(TMP)O_2}]^-$ [b]	23 ± 2	76 ± 8
$[\mathrm{Mn^{III}(TMP)O_{2]}}^-$ [b]	<1	5 ± 1
$\mathrm{Ti^{III}(TMP)O_2}$[c]	<1	<0.5
$\mathrm{KO_2}$ control[b]	<3	8 ± 1
$\mathrm{H_2O_2/KHCO_3}$ control[b]		5 ± 1

[a] Yields based on 3.44 mM porphyrin (or oxidant in the controls) used to make the peroxo complexes. [b] These reactions were carried out in $\mathrm{CH_3CN}$. [c] These reactions were carried out in THF.

essentially unchanged after addition of either cyclohexene or the more electron-rich olefin tetramethylethylene. No tetramethylethylene oxide was detected for any of the metalloperoxide porphyrin complexes by GC-MS over a period of 30 min. Thus none of the metalloporphyrin peroxo complexes we examined demonstrated significant reactivity toward these electron-rich olefins.

II. Reactions of Ti(IV), Mn(III), and Fe(III) Porphyrin Peroxo Complexes with Electron-Deficient Substrates. (a) Reactions with 2-Cyclohexen-1-one, 2-Methyl-1,4-naphthoquinone, and 2-Methyl-1,4-naphthoquinone Epoxide. Since the metalloporphyrin peroxo complexes showed little tendency to react with electron-rich substrates, the ability of these complexes to react with electron-deficient olefins and quinones was assessed. Addition of 2 equiv of 2-cyclohexen-1-one to 3.4 mM solutions of the Mn and Ti peroxo porphyrin complexes (or 2 equiv of 2-methyl-1,4-naphthoquinone to 0.1 mM solutions of these peroxo metalloporphyrin complexes) caused essentially no change in the UV−vis spectra after 10 min. The yields of the products, i.e., 2-cyclohexanone epoxide, determined by GC-MS, and 2-methyl-1,4-naphthoquinone epoxide, determined by HPLC, are shown in Table 1. No detectable level of 2-cyclohexanone epoxide (i.e., <1%) was seen after 10 and 30 min. A small amount of 2-methyl-1,4-naphthoquinone epoxide (5% ± 1%) was observed for the $[\mathrm{(TMP)MnO_2}]^-$ reaction after 30 min, but none was detected for $\mathrm{(TPP)TiO_2}$ (i.e., <0.5%). In contrast, 0.1 mM peroxoiron tetramesitylporphyrin gave much higher yields of 2-methyl-1,4-naphthoquinone epoxide (76% ± 8%) and was the only complex that epoxidized 2-cyclohexen-1-one (23% ± 2%).[23] When the peroxo Fe and Mn porphyrin complexes were reacted with 2-methyl-1,4-naphthoquinone epoxide (2 equiv) under the same conditions, the losses of epoxide after 1 h were similar, i.e., 19% ± 2% for reaction with the peroxo Fe porphyrin and 14% ± 2% for reaction with the peroxo Mn porphyrin. $\mathrm{(TPP)TiO_2}$ was unreactive with 2-methyl-1,4-naphthoquinone epoxide. We conclude that the large difference in epoxide yields (Table 1) observed is due to inherent differences in reactivity with the olefin and not with the epoxide product.

(b) Reactions of of $[\mathrm{(TMP)FeO_2}]^-$ and $[\mathrm{(TMP)MnO_2}]^-$ with Tetracyanoethylene and Tetracyanoethylene Oxide. Addition of 2 equiv of TCNE to $\mathrm{(TPP)TiO_2}$ (1 mM) led to no change in the UV−vis spectrum after 30 min; an immediate change occurred, however, upon addition of TCNE to 1 mM solutions of either $[\mathrm{(TMP)FeO_2}]^-$ or $[\mathrm{(TMP)MnO_2}]^-$. Malononitrile was the only organic product formed in the reaction, as confirmed by comparison of the GC-MS fragmentation pattern with that of a standard.

To determine if TCNE oxide, if it were formed, would be stable to the reaction conditions, we added 2 equiv of TCNE oxide to a 1 mM solution of $[\mathrm{(TMP)FeO_2}]^-$. The UV−vis spectrum of the resulting solution indicated that $[\mathrm{(TMP)FeO_2}]^-$ reacted very rapidly with TCNE oxide to give unknown products. Likewise, addition of 2 equiv of TCNE or TCNE oxide to a 1 mM solution of $[\mathrm{(TMP)MnO_2}]^-$ immediately led to dramatic changes in the UV−vis spectrum indicating the same unknown products.

Reaction of $\mathrm{Pt(PPh_3)_2O_2}$ with 2-Methyl-1,4-naphthoquinone. Since $\mathrm{Pt(PPh_3)_2O_2}$ is a classic nucleophilic peroxometal complex whose reactivity with tetracyanoethylene and related electron-deficient olefins has been well characterized,[39] we investigated its reactivity with 2-methyl-1,4-naphthoquinone in order to compare its nucleophilic reactivity with that of the peroxo metalloporphyrin complexes. No 2-methyl-1,4-naphthoquinone epoxide was detected (by ^{1}H NMR) upon mixing $\mathrm{Pt(PPh_3)_2O_2}$ with 4 equiv of 2-methyl-1,4-naphthoquinone in $\mathrm{CDCl_3}$. The spectrum of the starting material did not change after addition of the platinum peroxo complex: the ^{31}P NMR spectrum of the mixture showed the characteristic triplet of the platinum peroxo complex [$\delta = 15.3$ ppm (t, $J(^{195}\mathrm{Pt{-}P}) = 4083$ Hz); lit.[40] 16.4 ppm (t, $J(^{195}\mathrm{Pt{-}P}) = 4059$ Hz)]; a small amount of $\mathrm{PPh_3O}$ was also present. The ^{31}P NMR spectrum did not change during a 2-h period, except that the peak for triphenylphosphine oxide (29.2 ppm) increased somewhat, as would be expected in a $\mathrm{CDCl_3}$ solution containing trace amounts of water.[40] Hence we conclude that the platinum peroxo complex does not readily react with 2-methyl-1,4-naphthoquinone.

Discussion

Classification of Metalloperoxide Complexes According to Their Reactivities with Electron-Rich vs Electron-Poor Substrates. Peroxo complexes of transition metals can generally be classified as either electrophilic or nucleophilic with respect to their reactivities with organic substrates.[41−44] Electrophilic species have been characterized by their ability to oxidize the butyl anion to the butoxide anion[38] and the sulfide moiety of thianthrene 5-oxide (SSO) to sulfoxide.[43,44] Reactivity with triphenylphosphine to give triphenylphosphine oxide can also be used to assess the electrophilicity of such complexes.[45] The strongest electrophiles in such reactions are typically those peroxo complexes of metal ions with low numbers of electrons in d orbitals, such as Mo(VI), W(VI), and Cr(VI), which are all d^0. Complexes of metal ions with a high number of d electrons, such as Pt(II) (d^8) and Ir(III) (d^6), are found to have little electrophilic character. The electrophilic peroxo metal complexes frequently are found to be more reactive with electron-rich olefins.[46,47]

Sheldon and van Doorn[39] have reported that some peroxometal complexes derived from group VIII metal complexes are nucleophilic: they react readily with the extremely electron-poor olefin TCNE. Reactivity toward activated carbonyls, such as acyl halides, also appears to be characteristic of nucleophilic peroxo metalloporphyrin complexes.[18,19] Our results indicate that the reactivity of peroxo complexes with electron-deficient

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olefins such as 2-cyclohexen-1-one and 2-methyl-1,4-naphthoquinone can also be used to classify the reactivities of these complexes. We have found that only those peroxo complexes of extremely strong nucleophilic character react rapidly and in high yield with 2-cyclohexen-1-one and 2-methyl-1,4-naphthoquinone. Thus these two substrates allow us to discriminate between different degrees of nucleophilic character in the peroxoiron and peroxomanganese porphyrin complexes. We have classified the peroxotitanium porphyrin complex as a weak electrophile, despite its lack of reactivity with the butyl anion[25] and cyclohexene, because it is able to oxidize triphenylphosphine and because it is completely unreactive with electron-deficient olefins, including TCNE.

Neither the $[(TPP)Mn^{III}O_2]^-$ nor the $[(TPP)Fe^{III}O_2]^-$ complex reacted with triphenylphosphine under conditions identical to those used for the reaction with $(TPP)TiO_2$. While the titanium complex can form a stable oxo complex, this is not an option for the manganese and iron complexes, since the corresponding unprotonated oxo complexes of Fe(III) and Mn(III), if they were formed as products, would be expected to be less stable than the peroxo complees themselves. While hydroxo complexes of manganese(III) and iron(III) porphyrins are stable, the corresponding oxo complexes are not, because of the inability of these metal ions to stabilize the oxide ligand through π-bonding from filled oxygen p orbitals to empty d orbitals of π symmetry on the metal.[2,3] The absence of a favorable reaction pathway presumably accounts for the lack of reactivity of triphenylphosphine with either of these metalloporphyrin peroxides.

Ferrous porphyrins react with dioxygen to form μ-peroxo dimeric porphyrin complexes which react with triphenylphosphine to give triphenylphosphine oxide.[14,48] This sequence has been shown to proceed not by a direct reaction of the peroxide ligand but by prior O−O bond cleavage to give an Fe(IV) oxo complex, $PFe^{IV}{=}O$, which is the species responsible for the transfer of an oxygen atom to the phosphine.

All of the metalloporphyrin peroxide complexes studied reacted with butyllithium, but none of these reactions led to the formation of lithium butoxide. Thus it appears that butyllithium reacts with the Fe, Mn, and Ti metalloporphyrin moieties faster than it does with the bound peroxo ligands. Therefore no information regarding the inherent electrophilicity of the peroxo ligand can be obtained in these cases. It is interesting to note that, while butyllithium is a more exothermic oxygen scavenger than triphenylphosphine thermodynamically $[\Delta H_f(LiBu) - \Delta H_f(LiOBu) = 390 \pm 15$ kJ/mol[49] vs $\Delta H_f(Ph_3P) - \Delta H_f(Ph_3PO) = 323.4 \pm 4.9$ kJ/mol],[50] it fails to react with the peroxo moiety of $(TPP)TiO_2$, while triphenylphosphine does react.

Classification Scheme. Table 2 illustrates the classification scheme that we have devised for metalloperoxide complexes on the basis of their observed relative reactivities with electron-rich and electron-poor substrates. Class I nucleophiles react not only with extremely electron-deficient substrates, such as tetracyanoethylene (this work) and acyl halides,[19] but also with enones and quinones.[23] The only metalloperoxide complexes known to transfer oxygen directly to these latter substrates are those which contain a d^5 iron(III) metal such as $[(TMP)FeO_2]^-$.[23]

Table 2. Classification Scheme for Nucleophilic and Electrophilic Peroxo Complexes[a]

←increasing nucleophilicity		increasing electrophilicity→	
class I nucleophile	class II nucleophiles	class II electrophile	class I electrophiles
$[Fe^{III}(porph)O_2]^-$	$[Mn^{III}(porph)O_2]^-$	$Ti^{IV}(TPP)O_2$	$Mo^{VI}O_2$
	$Pt^{II}(PPh_{3)2}O_2$		$Cr^{VI}O_2$
	$Ir(CO)I(PPh_{3)2}O_2$		$V^{V}O_2$
			$Ti^{IV}O_2$

[a] Substrates oxidized by class I nucleophiles: TCNE, acyl halides, CO_2, enones, quinones. Substrates oxidized by class II nucleophiles: TCNE, acyl halides, CO_2. Substrates oxidized by class I electrophiles: triphenylphosphine, electron-rich olefins. Substrates oxidized by class II electrophiles: triphenylphosphine.

Class II nucleophiles include those non-porphyrin metalloperoxide complexes that contain a high number of electrons in the d orbitals of the metal, as in the d^8 metal complexes formed by the group VIII metals such as Pt(II) and Pd(II). These complexes are known to react with highly electron-deficient substrates such as tetracyanoethylene[38,39] and acyl halides.[51] Our studies indicate, however, that $(Ph_3P)_2PtO_2$ does not react with 2-methyl-1,4-naphthoquinone. While the reactivity of the d^6 complex $(Ph_3P)_2Ir(CO)(O_2)I$ has not been studied with class I substrates, we place it in class II because it is known to react with TCNE but to be less nucleophilic than $(Ph_3P)_2PtO_2$.[38,39] Also included in this category is the d^4 porphyrin complex $[(TMP)MnO_2]^-$, which reacts with tetracyanoethylene (this work) and acyl halides[18] but does not react to any appreciable extent with 2-cyclohexen-1-one or 2-methyl-1,4-naphthoquinone. All of the class I and class II nucleophiles are unreactive toward electron-rich substrates such as cyclohexene, the butyl anion, and triphenylphosphine.

Class I electrophiles react with butyllithium, at low temperature, to give the butoxide anion; many also react with electron-rich olefins such as cyclohexene to give the corresponding epoxides. Examples of such electrophilic d^0 peroxometal complexes are those which contain Mo(VI) or W(VI),[38,43,44,46,47] Cr(VI),][38] V(V),[46,47] and Ti(IV).[52,53] Class II electrophiles, such as the d^0 complex $(TPP)TiO_2$, react *neither* with electron-deficient nor with electron-rich olefins but do oxidize triphenylphosphine to triphenylphosphine oxide.

Unusual Reactivity of Peroxo Fe(III) and Mn(III) Porphyrin Complexes with TCNE. Nucleophilic (dioxygen)metal complexes such as $(Ph_3P)_2MO_2$ (M = Pd, Pt) readily add to tetracyanoethylene to form cyclic peroxy adducts which have been characterized by IR and NMR.[39] Both $[(TMP)Fe(O_2]^-$ and $[(TMP)MnO_2]^-$ react actively with tetracyanoethylene but they react rapidly with tetracyanoethylene oxide as well, so we are unable to determine if the epoxide is formed as an intermediate in this reaction. Nevertheless, the known nucleophilic reactivity of $[(TMP)FeO_2]^-$ and $[(TMP)MnO_2]^-$ with other electron-deficient olefins and the known reactivity of TCNE with other nucleophilic metal peroxide complexes make us confident that the initial step of the reaction involves nucleophilic attack of the peroxometal complex on the electron-deficient bond, as shown in eq 2.

The Remarkable Nucleophilicity of the Peroxoiron(III) Complex. It has been proposed,[54] on the basis of charge-iterative extended Hückel (IEH) calculations, that the relative energies of the orbitals of $[(TMP)MnO_2]^-$ are unusual relative

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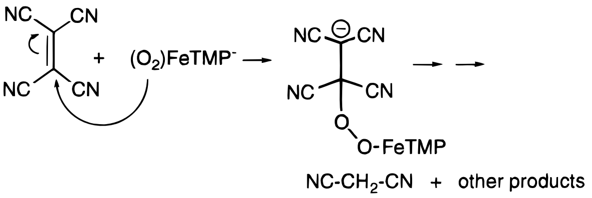

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to other Mn^{III} porphyrin complexes due to the large out-of-plane metal displacement and strong d$-O_2$ π_g orbital mixing. The lowest unoccupied molecular orbital in the d^4 $[(TMP)MnO_2]^-$ complex is thought to be a 43% d_{yz} + 47% O_2 π_{gz} hybrid. However, in the d^5 $[(TMP)FeO_2]^-$ complex, this same orbital would be occupied by a single electron, which would thus have a high degree (47%) of peroxo orbital character. Occupancy of this orbital by the fifth d electron may explain why the peroxo Fe(III) porphyrin complexes are so extraordinarily nucleophilic as compared to their Mn(III) analogs.

Conclusion. Determination of the relative reactivities of Fe(III), Mn(III), and Ti(IV) porphyrin peroxo complexes with electron-rich and electron-poor substrates has allowed us to classify these complexes and to compare them with several well-characterized non-porphyrin metal peroxo complexes. We conclude that the iron(III) peroxo complexes are by far the most nucleophilic of the known metalloporphyrin peroxo complexes and that they are probably among the most nucleophilic of all metal peroxo complexes, porphyrin or non-porphyrin. This conclusion is supported by the observation by Rana and Meares[55,56] that non-porphyrin ferric peroxo EDTA complexes tethered to proteins are highly reactive and cause cleavage of peptides by a mechanism whose first step is nucleophilic attack on a peptide carbonyl. The extraordinarily high nucleophilic character of ferric porphyrin peroxo complexes demonstrated here also lends strong support to mechanisms proposing nucleophilic attack by peroxo heme intermediates in enzymes such as aromatase,[7,8] cytochrome P450-2B4,[10] and NO synthase[11] and suggests that other examples of such enzymatic reactions should be sought.

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