

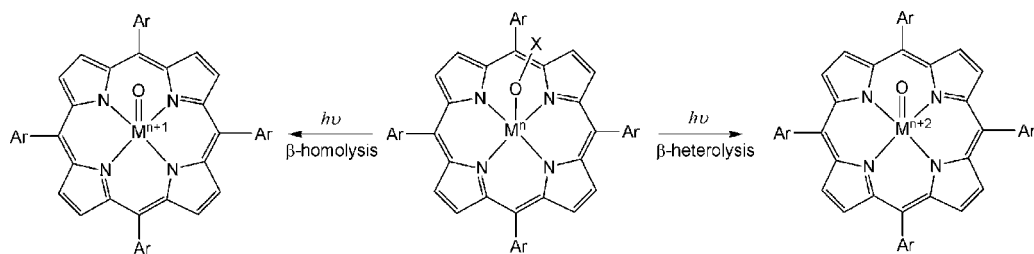
Laser Flash Photolysis Generation of High-Valent Transition Metal–Oxo Species: Insights from Kinetic Studies in Real Time

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CON SPECTUS



High-valent transition metal–oxo species are active oxidizing species in many metal-catalyzed oxidation reactions in both Nature and the laboratory. In homogeneous catalytic oxidations, a transition metal catalyst is oxidized to a metal–oxo species by a sacrificial oxidant, and the activated transition metal–oxo intermediate oxidizes substrates. Mechanistic studies of these oxidizing species can provide insights for understanding commercially important catalytic oxidations and the oxidants in cytochrome P450 enzymes. In many cases, however, the transition metal oxidants are so reactive that they do not accumulate to detectable levels in mixing experiments, which have millisecond mixing times, and successful generation and direct spectroscopic characterization of these highly reactive transients remain a considerable challenge. Our strategy for understanding homogeneous catalysis intermediates employs photochemical generation of the transients with spectroscopic detection on time scales as short as nanoseconds and direct kinetic studies of their reactions with substrates by laser flash photolysis (LFP) methods. This Account describes studies of high-valent manganese– and iron–oxo intermediates. Irradiation of porphyrin–manganese(III) nitrates and chlorates or corrole–manganese(IV) chlorates resulted in homolytic cleavage of the O–X bonds in the ligands, whereas irradiation of porphyrin–manganese(III) perchlorates resulted in heterolytic cleavage of O–Cl bonds to give porphyrin–manganese(V)–oxo cations. Similar reactions of corrole– and porphyrin–iron(IV) complexes gave highly reactive transients that were tentatively identified as macrocyclic ligand–iron(V)–oxo species. Kinetic studies demonstrated high reactivity of the manganese(V)–oxo species, and even higher reactivities of the putative iron(V)–oxo transients. For example, second-order rate constants for oxidations of *cis*-cyclooctene at room temperature were $6 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ for a corrole–iron(V)–oxo species and $1.6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for the putative tetramesitylporphyrin–iron(V)–oxo perchlorate species. The latter rate constant is 25 000 times larger than that for oxidation of *cis*-cyclooctene by iron(IV)–oxo perchlorate tetramesitylporphyrin radical cation, which is the thermodynamically favored electronic isomer of the putative iron(V)–oxo species. The LFP-determined rate constants can be used to implicate the transient oxidants in catalytic reactions under turnover conditions where high-valent species are not observable. Similarly, the observed reactivities of the putative porphyrin–iron(V)–oxo species might explain the unusually high reactivity of oxidants produced in the cytochrome P450 enzymes, heme–thiolate enzymes that are capable of oxidizing unactivated carbon–hydrogen bonds in substrates so rapidly that iron–oxo intermediates have not been detected under physiological conditions.

Introduction

Catalytic oxidation processes are key technologies for chemical synthesis in the pharmaceutical and petrochemicals industries, and transition metal complexes are the central theme for a large num-

ber of homogeneous oxidation catalysts.^{1,2} Many of these catalysts were designed to mimic the predominant oxidation catalysts in Nature, the cytochrome P450 enzymes.^{3,4} Homogeneous oxidation catalysts typically contain one of a vari-

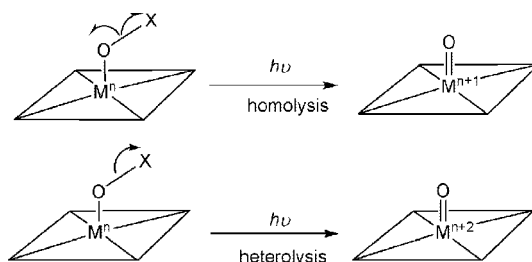
ety of transition metals, including iron, manganese, ruthenium, chromium, rhodium, or osmium, in macrocyclic (porphyrins and corroles)^{5–7} or “clamp”-like (salens)⁸ ligands, and the oxidizing power is provided by sacrificial oxidants such as hydrogen peroxide or a peroxy acid.

In synthetic and natural catalysts, high-valent transition metal–oxo transients are implicated as the active oxidizing species.⁹ In some cases, metal–oxo species can be observed spectroscopically by rapid mixing or by production of low-reactivity analogues,^{10,11} but in many cases, the reactive metal–oxo species does not accumulate to detectable quantities, and the actual oxidizing species remains speculative. In the case of the P450 enzymes, for example, the putative oxidant is an iron(IV)–oxo porphyrin radical cation that has not been observed under turnover conditions.^{12,13} The lack of kinetic and mechanistic information complicates studies of transition metal oxidation catalysts, and indeed, the nature of the active oxidants in homogeneous processes typically is inferred from product studies. The successful generation and characterization of the reactive metal–oxo species provides insight into chemical models of the enzyme-like oxidants and ultimately should aid in catalyst development for selective oxidation of organic substrates in industrial processes.

Recently, we developed laser flash photolysis (LFP)-induced ligand cleavage reactions for production of high-valent transition metal–oxo derivatives.^{14–18} Unlike conventional chemical oxidations performed with mixing methods that have a ca. 1 ms minimum lag time, the photochemical approach produces metal–oxo species essentially instantly, and direct kinetic studies of fast reactions are relatively easy. In this Account, we describe our progress in the development of photochemical methods that lead to generation of a variety of high-valent metal–oxo species and kinetic studies of their oxidation reactions in real time. We also demonstrate that comprehensive kinetic studies can provide mechanistic insight as to the identities and reactivities of the active oxidants in the catalytic processes.

The concept of photoinduced ligand cleavage reactions is illustrated in Scheme 1. The precursor complexes have metal in the n oxidation state and an oxygen-containing ligand. Photolysis can result in homolytic cleavage of the O–X bond in the ligand to give an $(n + 1)$ oxidation state metal–oxo species or heterolytic cleavage of the O–X bond in the ligand to give an $(n + 2)$ oxidation state metal–oxo species. In practice, the metal–oxo species are monitored by UV–visible spectroscopy methods with temporal resolutions of <10 ns. Kinetics are measured in real time in single-turnover experiments using a large excess of reductants to achieve pseudo-

SCHEME 1. Photoinduced Ligand Cleavage Reactions for Production of High-Valent Transition Metal–Oxo Species

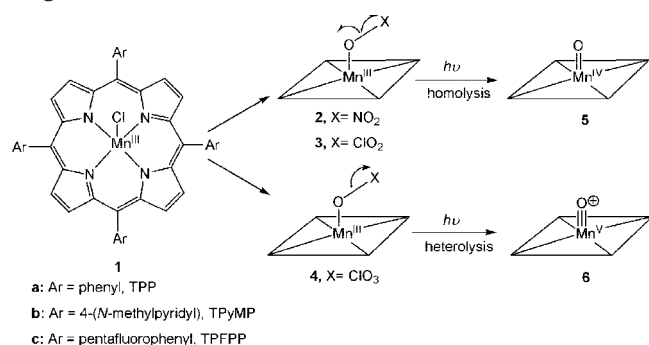


first-order kinetic conditions. Rate constants for reactions with reductants are determined from kinetic measurements with various concentrations of substrate; the second-order rate constant is the slope of the line in a plot of k_{obs} versus concentration of substrate.

High-Valent Manganese(V)– and Manganese(IV)–Oxo Porphyrin Complexes

Synthetic manganese porphyrin complexes were developed as models for cytochrome P450 enzymes.^{1,5} Reactive porphyrin manganese(V)–oxo derivatives were proposed as the key intermediates in catalytic processes for decades,^{19,20} but they eluded detection until 1997 when Groves and co-workers reported the synthesis of the first manganese(V)–oxo porphyrin complex.²¹ Subsequently, two additional examples of manganese(V)–oxo porphyrins were reported.^{22,23} In contrast, the well characterized manganese(IV)–oxo derivatives are less reactive than manganese(V)–oxo species and unlikely to be the active oxidants in manganese porphyrin-catalyzed oxidations.^{24–26} Our initial LFP studies focused on the photochemistry of manganese complexes, in large part due to early reports by Suslick and co-workers.²⁷ Porphyrin–manganese(III) nitrates were reported to give porphyrin–manganese(IV)–oxo species with continuous irradiation,²⁸ and irradiation of porphyrin–manganese(III) perchlorates or periodates in the presence of organic compounds gave oxidized substrates, presumably via manganese(V)–oxo species.²⁹ We were able to produce both porphyrin–manganese(IV)–oxo species and porphyrin–manganese(V)–oxo species as a function of the identity of the ligand,^{14,15} as summarized in Scheme 2.

We employed three porphyrin–manganese systems that encompass the range of reactivities of these intermediates as controlled by the electron demands of the macrocycle ligand. Reactions of chlorides **1** with silver salts gave nitrate (**2**), chlorate (**3**), or perchlorate (**4**) complexes. Photolyses of nitrate complexes **3** with 355 nm light gave porphyrin–manganese(IV)–oxo species **5** by homolytic cleavage of the ligand O–N bond in the ligand as expected.²⁸ Photolyses of the chlorate complexes **3** also gave oxo species **5** in a much more efficient photoreac-

SCHEME 2. Photochemical Formation of Porphyrin Manganese–Oxo Intermediates

tion.¹⁵ The identities of porphyrin–manganese(IV)–oxo species **5** from LFP were confirmed by preparing the same species by chemical oxidation.

Photolysis of perchlorate complexes **4** with 355 nm light gave distinctly different species than those from **2** and **3**, and we characterized these transients as porphyrin–manganese(V)–oxo derivatives **6**. Transients **6** were much more reactive than species **5** in self-decay reactions and in reactions with organic substrates. An important point for the identification of the intermediates **6** was that they could be formed by chemical oxidations of **1**, albeit as short-lived species or as mixtures with the manganese(IV)–oxo species.²¹ The formation of **6c** by chemical oxidation is especially noteworthy because the transient is so highly reactive in neat CH₃CN (0.7 ms lifetime) that it cannot be detected in mixing experiments. Somewhat surprisingly, **6c** was nearly 3 orders of magnitude less reactive in a mixture of water–acetonitrile.¹⁵

The ability to measure kinetics readily is a significant advantage for formation of the high-valent metal–oxo species by LFP methods instead of mixing methods, and we were able to measure rate constants for reactions of porphyrin–manganese(V)–oxo species **6** with variety of substrates.¹⁵ The reactivities in the series of transients **6** are consistent with expectations based on the electrophilic nature of high-valent metal–oxo complexes.³⁰ For any substrate, the reactivity order was **6c** > **6b** > **6a**. That is, the transient with the most electron demand by the porphyrin macrocycle (**6c**) was most reactive, and the transient with the least electron demand (**6a**) was least reactive. Representative rate constants for reactions of oxo species **6c** at ambient temperature in CH₃CN solvent are $k_{\text{ox}} = 6 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for reaction with *cis*-stilbene and $k_{\text{ox}} = 1.3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for reaction with ethylbenzene.

Rate constants for reactions of porphyrin–manganese(IV)–oxo species **5** also could be measured, but the mechanisms of these reactions were complex.¹⁵ For example, the reactions were effectively second-order in transient **5**, suggesting that **5**

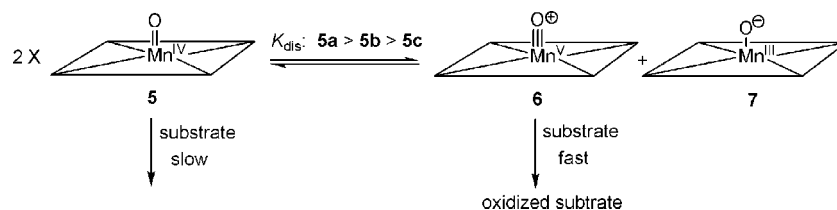
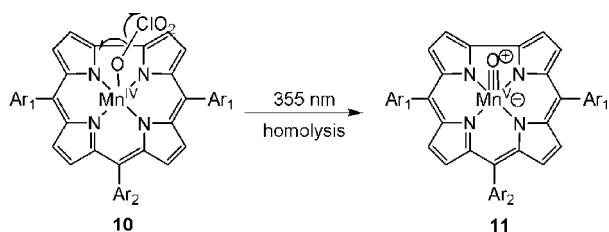
reacted in a disproportionation fashion to give **6** and a porphyrin–manganese(III) species (**7**) and that transient **6** was the actual oxidant in the reactions (Scheme 3). This conclusion was supported by the observation that the reactivity pattern for species **5** with any organic reductant evaluated was inverted from expectations based on electron demand from the macrocycle with **5a** being most reactive and **5c** least.³⁰ In Scheme 3, the equilibrium constant for formation of **6c** from **5c** was the least favorable ($K_{\text{dis}} = 0.002$), resulting in a small concentration of **6c** and slow overall reaction.¹⁵ The observable metal(IV)–oxo species gives the true oxidant, the manganese(V)–oxo species, which is present in undetectably low concentrations. With a larger equilibrium constant for disproportionation, however, $K_{\text{dis}} = 3.0$ for **5a**, the higher-valence **6a** was formed at appreciable concentrations in the first millisecond of the reactions and was detected. Fast disproportionation reactions of **5** were indicated by the second-order rate constants for disproportionation ($k = 3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for **5a** and $k = 1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for **5c**).

High-Valent Manganese(V)–Oxo Corrole Complexes

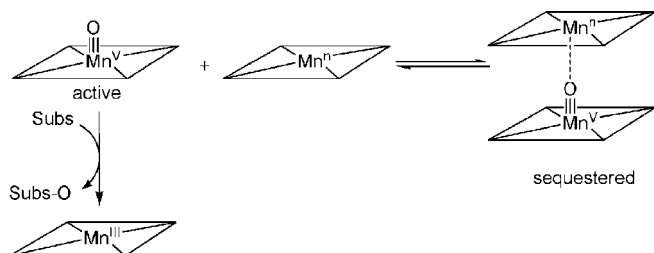
Due to the progress in the synthesis of 19-membered macrocyclic triarylcorroles,^{31,32} metallocorrole complexes attracted increased attention.^{6,7} Corrole ligands are trianionic, as opposed to dianionic porphyrin ligands, and corrole–metal–oxo species are inherently more stable than the porphyrin–metal–oxo analogues. Metallocorroles are less robust than metalloporphyrins because the π -system of the corrole is more electron-rich and prone to oxidative degradation.⁷ The first isolated and characterized corrole metal–oxo species was the relatively stable manganese(V)–oxo corrole produced by oxidation of the manganese(III) salt with chemical oxidants.³³

Following LFP strategies similar to those described above, photoinduced ligand cleavage reactions producing corrole–manganese(V)–oxo species were achieved (Scheme 4).¹⁶ One-electron oxidations³⁴ of corrole–manganese(III) salts (**8**) gave corrole–manganese(IV) chlorides (**9**) that reacted by ligand exchange with AgClO₃ to give the chlorate complexes **10**. As expected, laser photolysis of species **10** with 355 nm light resulted in homolytic cleavage of the ligand O–Cl bond to give corrole–manganese(V)–oxo species **11**, which had the same UV–visible spectra as the species formed by chemical oxidations.¹⁶

Kinetic studies of photogenerated species **11** showed that reactions of (Cor)Mn^V(O) are mechanistically complex. Most of the results could be explained by either of two models. In self-decay reactions and in reactions with substrates, the observed

SCHEME 3. Disproportionation of Manganese(IV)–Oxo Species**SCHEME 4.** Photochemical Formation of Corrole–Manganese(V)–Oxo Intermediates

- a:** Ar₁ = Ar₂ = phenyl, TPC
b: Ar₁ = pentafluorophenyl,
 Ar₂ = *p*-(methoxy)phenyl, BPFMC
c: Ar₁ = Ar₂ = pentafluorophenyl, TPFC

SCHEME 5. Proposed Model for Oxidations of Corrole–Manganese(V)–Oxo Intermediates

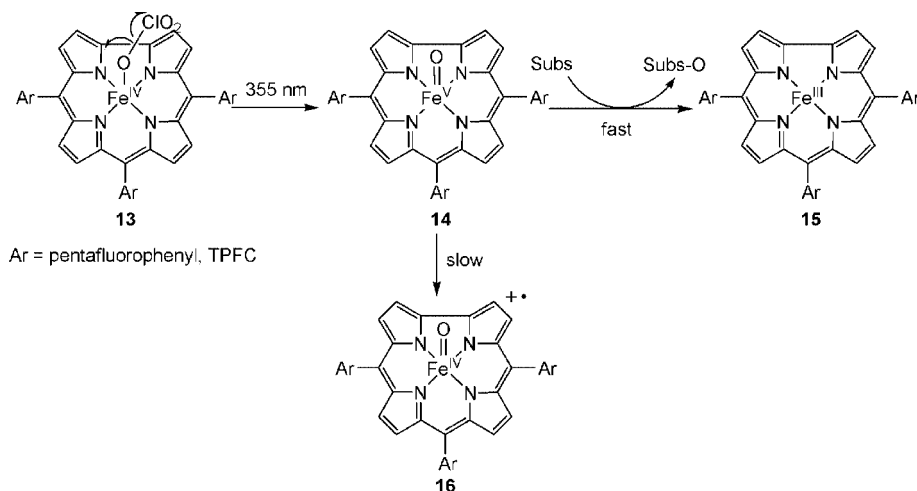
order of reactivity of (Cor)Mn^V(O) was **11a** (TPC) > **11b** (BPFMC) > **11c** (TPFC), which is inverted from that expected based on the electron demand of the ligands.³⁰ This suggests that the predominant oxidants in these systems could be corrole–manganese(VI)–oxo species formed by disproportionation but at concentrations too small for detection.³³ Importantly, however, the rate constants for oxidations by species **11** were inversely dependent on the concentration of the oxo species; specifically, they were partial order in oxo species **11**, with the effect that the oxidation reactions were slow for high concentrations of **11**. In fact, addition of any corrole–manganese species reduced the rate constants for oxidations by **11**. An alternative mechanistic hypothesis is that oxo species **11** is the actual oxidant, but it can complex with another molecule of **11** or another manganese species to produce a nonreactive, sequestered form of the oxidant (Scheme 5). Equilibrium dissociation of the sequestered complexes would result in partial kinetic order, as observed experimentally.¹⁶

Highly Reactive High-Valent Iron–Oxo Corrole Complexes

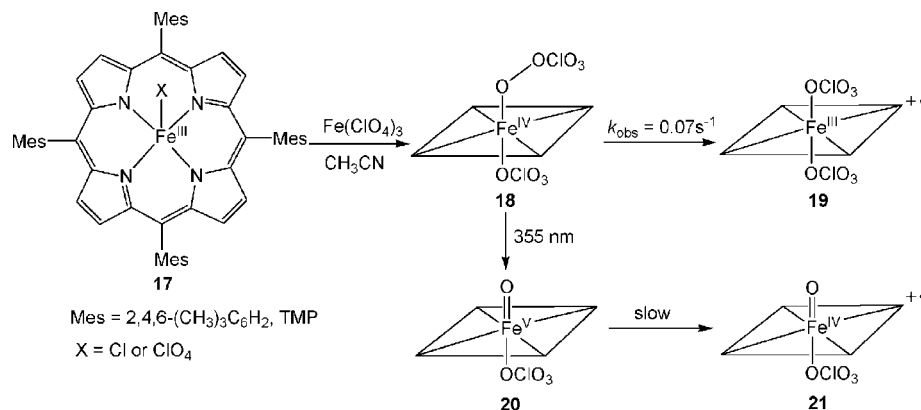
Among high-valent metal–oxo species, iron–oxo complexes have received particular interest because iron is the metal in a variety of oxidative enzymes in nature, including heme iron, nonheme iron, and diiron assemblies.^{3,11,35–38} Indeed, a recent issue of *Accounts of Chemical Research* was dedicated to this subject.³⁹ The readily accessible high oxidation state of iron is +4, and heme and nonheme iron(IV)–oxo species are well-known.^{11,40} High-valent iron(IV)–oxo porphyrin radical cations in heme-containing peroxidase and catalase enzymes (often termed compound I)³⁵ and in models¹⁰ have been characterized as the active oxidizing intermediates in catalytic cycles. Species with more highly oxidized iron such as nitridoiron(V) porphyrins are known,^{41,42} and a recent paper by Collins et al. reported spectroscopic evidence for an oxoiron(V) complex supported by a tetraanionic ligand with unprecedented reactivity.⁴³ An octahedral coordination complex of iron(VI) also was reported recently.⁴⁴

An important extension of our LFP-induced ligand cleavage reactions was production of a highly reactive high-valent iron–oxo transient that was tentatively assigned as a corrole–iron–oxo complex.¹⁷ Iron(III) complexes are subject to photoreduction reactions that cleave a ligand–metal bond homolytically to give an iron(II) species,²⁷ but the photochemistry of iron(IV) complexes presents a reaction manifold similar to that of the manganese(IV) systems. The corrole–iron(IV) chlorate **13** is a metastable species prepared by ligand exchange from the corresponding chlorate (12). Photolysis of **13** gave a transient with a strong, sharp Soret absorbance, which, in view of its high reactivity and by analogy to the reactions of corrole–manganese species, was tentatively described as the corrole–iron(V)–oxo species **14** (Scheme 6). The same species apparently also was generated as a short-lived transient when the neutral corrole iron(III) complex **15** was mixed with 5 equiv of *m*-chloroperoxybenzoic acid (mCPBA) at –130 °C in butyronitrile solution, and further characterization by various spectroscopies will support or refute the assignment of an iron(V)–oxo structure.⁴⁵

SCHEME 6. Photochemical Formation of Corrole–Iron(V)–Oxo Intermediate



SCHEME 7. Photochemical Formation of a Highly Reactive Porphyrin–Iron–Oxo Intermediate



The high-energy iron(V)–oxo species **14** might isomerize to a more stable iron(IV)–oxo corrole radical cation (**16**) by internal electron transfer,⁴⁶ but isomerization of **14** to **16** apparently has a significant energy barrier such that **14** reacts with organic reductants faster than it isomerizes, and recent computational results support the existence of iron(V)–oxo species with corrole or corrolazine ligands.⁴⁷ The high-valent corrole–iron–oxo is remarkably reactive; for example, oxo species **14** reacts with ethylbenzene with a rate constant of $160 \text{ M}^{-1} \text{ s}^{-1}$, which is 6–7 orders of magnitude greater than that expected for reaction of an iron(IV)–oxo corrole radical cation.¹⁷

Highly Reactive High-Valent Iron–Oxo Porphyrin Complexes

By extension of the LFP studies to a porphyrin–iron complex, an apparent iron–oxo species with unprecedented high reactivity was prepared photochemically.¹⁸ From studies with corrole–iron species, we learned that photolysis of porphyrin–iron complexes with the metal in +4 oxidation

state might result in cleavage of an O–X bond in an oxygen-bound ligand to give iron–oxo species. Oxidation of tetramesitylporphyrin–iron(III) perchlorate (**17**) with $\text{Fe}(\text{ClO}_4)_3$ in CH_3CN gave short-lived (TMP) Fe^{IV} diperchlorate (**18**, Scheme 7), which was characterized by UV–visible, electron paramagnetic resonance, and NMR spectroscopies, as well as magnetic susceptibility measurements. Species **18** relaxed by internal electron transfer within ca. 10 s at ambient temperature to give the known iron(III) porphyrin radical cation (**19**). Photolyses of the first-formed intermediate **18** with 355 nm laser afforded a highly reactive transient (**20**) with strong, sharp Soret bands and a UV–visible spectrum unlike that of any known 5,10,15,20-tetramesitylporphyrinatoiron derivative. Transient oxo species **20** was remarkably reactive; representative rate constants for reaction of **20** at ambient temperature in CH_3CN are $k_{\text{ox}} = 2.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for *cis*-stilbene and $k_{\text{ox}} = 1.5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for ethylbenzene.¹⁸

Transient **20** appears to be a member of a new class of porphyrin–iron–oxo derivatives as deduced by its unique UV–visible spectrum and its very high reactivity. This species

TABLE 1. Rate Constants for Reactions of Metal–Oxo Species^a

metal–oxo species	<i>cis</i> -stilbene	<i>cis</i> -cyclooctene	ethylbenzene
Porphyrin–Metal(IV)–Oxo Derivatives			
(TPP)Mn ^{IV} (O) (5a) ^b	1.2 × 10 ³		
(TPFPP)Mn ^{IV} (O) (5c) ^b	2.4 × 10 ²		
(TPFPP)Fe ^{IV} (O) ^{b,c}	2.1 × 10 ⁻²	1.8 × 10 ⁻²	
Corrole–Metal(V)–Oxo Derivatives			
(TPFC)Mn ^V (O) (11c)	9	4	
(TPFC)Fe ^V (O) (15)		6.0 × 10 ³	5.7 × 10 ²
Iron(IV)–Oxo Porphyrin Radical Cations			
(TMP ⁺)Fe ^{IV} (O)ClO ₄ (21) ^d	90	62	1.6
(TMP ⁺)Fe ^{IV} (O)Cl ^d	320	290	4.5
(TPFPP ⁺)Fe ^{IV} (O)ClO ₄ ^d	187	116	6.2
CPO compound I ^e	<i>f</i>		9.6 × 10 ²
Porphyrin–Metal(V)–Oxo Derivatives			
[(TPP)Mn ^V (O)] ⁺ (6a)	1.1 × 10 ⁴		<2.0 × 10 ³
[(TPFPP)Mn ^V (O)] ⁺ (6c)	6 × 10 ⁵	5.8 × 10 ⁵	1.3 × 10 ⁵
(TMP)Fe ^V (O)ClO ₄ (20)	2.0 × 10 ⁶	1.6 × 10 ⁶	1.2 × 10 ⁵

^a Second-order rate constants in units of M⁻¹ s⁻¹ for reactions at 22 ± 2 °C in CH₃CN, unless otherwise specified. Kinetics obtained from refs 14–18. ^b An apparent second-order rate constant is observed from reaction of the equilibrium population of (Porph)(metal)^V(O). ^c From ref 50. ^d The compound I analogues were prepared by mCPBA oxidation of the corresponding (TMP)Fe^{III}(ClO₄) and (TMP)Fe^{III}(Cl) salts, respectively, from ref 48. ^e The CPO compound I derivative was prepared by peroxyacetic acid oxidation of CPO in buffered solution (pH = 4.8), see ref 49. ^f Not detected.

reacts with typical organic substrates about 5 orders of magnitude faster than the iron(IV)–oxo radical cation analogue (**21**), suggesting that **20** cannot be a simple ligand-exchanged derivative of **21**. We speculate that **20** is an isomer of **21**, however, possibly one best described as an iron(V)–oxo species. Electronic excited states of porphyrin–metal complexes relax on the picosecond time scale, and a porphyrin–iron(V)–oxo species that existed in the millisecond time frame requires a high barrier for internal electron transfer from the porphyrin to the metal. Such a barrier that could “trap” the iron(V)–oxo species might result from a large degree of structure reorganization or atomic motions. Further spectroscopic characterization of this species will be necessary to provide a better understanding of its structure.

Reactivity Comparison between Metal–Oxo Species and Implications for P450 Enzymes

Our photochemical entries to high-valent metal–oxo species permit a wide variety of kinetic studies that were not possible previously. Table 1 contains some representative rate constants for comparisons of the reactivities of various metal–oxo species where the macrocyclic ligands are similar, either porphyrins or corroles. Table 1 also includes the rate constants of iron(IV) porphyrin radical cation (compound I analogues) that were obtained from more conventional kinetic studies.^{48–50}

Porphyrin manganese(V)–oxo derivatives are in the same formal oxidation state as the iron(IV)–oxo porphyrin radical

cation. When produced in CH₃CN, 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin–manganese(V)–oxo cation (**6c**) with a weak-binding counterion, either perchlorate or chlorate, reacts more than 3 orders of magnitude faster than the iron(IV)–oxo porphyrin radical cation. In the related corrole system, however, the iron(V)–oxo **15** is about 3 orders magnitude more reactive than the analogous corrole manganese(V)–oxo species. Moreover, this neutral corrole transient is at least 10 times more reactive than the positively charged iron(IV)–oxo porphyrin radical cation, although corrole metal–oxo complexes should be inherently much less reactive than the analogous porphyrin complexes.⁷ Similarly, the high reactivity of transient **20** is apparent by comparison of its rate constants to those for the compound I derivatives, and it reacts 4–5 orders of magnitude faster than the isomeric species (TMP⁺)Fe^{IV}(O)(ClO₄) (**21**) and its chloride analogue.

The high reactivity of the apparent iron(V)–oxo transients **15** and **20** relative to the compound I analogues might be important for understanding the oxidation reactions of cytochrome P450 enzymes. In biological systems, compounds I are formed in peroxidase and catalase enzymes by reaction of the resting enzyme with hydrogen peroxide.⁵¹ P450 enzymes are activated by a different sequence where the equivalent of hydrogen peroxide is formed in the presence of bound substrate by iron reduction, oxygen binding, a second reduction, and two protonation steps. The active oxidant in P450 enzymes under turnover conditions has not been detected, but by extension from other heme-containing enzymes, it is usually assumed to be a compound I species.^{12,13} The P450 enzymes contain a thiolate from cysteine as the fifth ligand to iron, and this thiolate is proposed to activate the compound I species strongly.³⁵ In a recent study, however, we found that the compound I derivative from chloroperoxidase (CPO), a heme–thiolate enzyme that gives an observable compound I derivative, oxidized ethylbenzene with a rate constant of $k \approx 960 \text{ M}^{-1} \text{ s}^{-1}$ and displayed no detectable reaction with lauric acid.⁴⁹ These kinetic results are not consistent with the oxidant in P450 enzymes being a compound I derivative because the active oxidant in P450 enzymes is so reactive that it does not accumulate to detectable levels. For example, low-temperature studies with cytochrome P450_{cam} indicate that the active oxidant hydroxylates the unactivated C–H bond at the 5-position of camphor faster than it is formed.⁵² Extrapolation of the low-temperature results suggests that the decay of the precursor to the active oxidant would have a rate constant at ambient temperature of $k \approx 1000 \text{ s}^{-1}$. Thus, the transient in P450_{cam} reacts with the unactivated C–H bond in camphor with a *smaller* barrier than

for reaction of CPO compound I with the activated C–H bond of ethylbenzene.

In a similar manner, iron(IV)–oxo porphyrin radical cation species are thought to be the active oxidizing species in systems that employ porphyrin–iron(III) salts as catalysts with terminal oxidants such as *m*-chloroperoxybenzoic acid or iodosobenzene.⁵³ Unactivated C–H bonds in hydrocarbons can be oxidized under turnover conditions, but isolated iron(IV)–oxo radical cations do not exhibit adequate reactivity for hydrocarbon oxidation reactions.^{48,54} For example, compound I analogues oxidize benzylic C–H bonds sluggishly (Table 1). It is noteworthy for iron(IV)–oxo porphyrin radical cations that the kinetic effects of changing electron demand in the aryl groups of the porphyrin or the identity of the counterion are minor.⁴⁸ Thus, the high reactivity obvious under turnover apparently requires a profoundly different nature of the oxidants.

The dichotomy between the observed small rate constants for oxidation reactions effected by iron(IV)–oxo porphyrin radical cations and the very fast oxidation reactions of porphyrin–iron catalysts and P450 enzymes was noted previously, and alternate oxidants to compound I species were discussed.^{55,56} It is possible that the active oxidant in P450 enzymes is not a compound I species but an iron(V)–oxo transient similar to those we formed photochemically.¹⁸ The thiolate axial ligand in the P450 enzyme might further activate an iron(V)–oxo species by 2–3 orders of magnitude, similar in magnitude to the effect of the thiolate ligand in CPO compound I reactions.⁴⁹ Heterolytic cleavage of an O–X bond in a precursor complex could produce a high-energy iron(V)–oxo species that reacts with bound substrate faster than it isomerizes to a more stable compound I derivative.⁴⁶ In this model, internal electron transfer might occur when reactive substrates are not present or as side reaction.

The Reactive Oxidants in Homogeneous Oxidation Catalysis

One objective of our studies is to identify the oxidants during catalytic turnover conditions with transition metal catalysts. Identifying the kinetically competent oxidants could lead to better control of the catalytic oxidation reactions, especially in terms of selectivities. In a typical catalytic reaction, however, the concentrations of active oxidants do not build up to detectable concentrations. Moreover, as our studies of porphyrin–manganese(IV)–oxo species **5**,¹⁵ corrole–manganese(V)–oxo species **11**,¹⁶ and porphyrin–iron(IV)–oxo species⁵⁰ indicate, a high-valent metal–oxo species detected in a reaction might not be the true oxidant in the system.

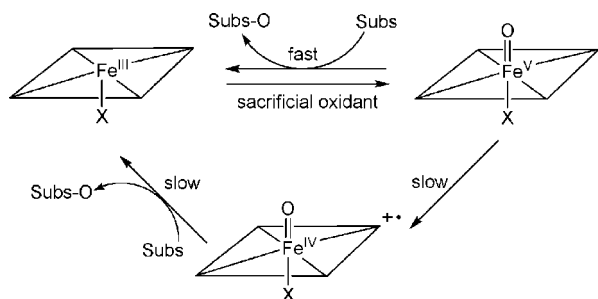
TABLE 2. Comparison of Competition Catalytic Oxidations with Ratios of Absolute Rate Constants

substrates ^a	oxidant	method	k_{rel}^b
Manganese–Oxo Oxidations			
<i>cis</i> -stilbene/Ph ₂ CH ₂	(TPFPP)Mn ^V (O), 6c	LFP kinetic ratio	4.7
	(TPFPP)Mn ^{III} Cl /PhIO	competition	4.6
	(TPFPP)Mn ^{III} Cl /mCPBA	competition	6.5
PhEt/PhEt- <i>d</i> ₁₀	(TPFPP)Mn ^V (O), 6c	LFP kinetic ratio	2.3
	(TPFPP)Mn ^{III} Cl /PhIO	competition	2.1
	(TPFPP)Mn ^{III} Cl /mCPBA	competition	2.6
<i>cis</i> -stilbene/Ph ₂ CH ₂	(TMPyP)Mn ^V (O), 6b	LFP kinetic ratio	7.5
	(TMPyP)Mn ^{III} Cl/mCPBA	competition	8.8
Iron–Oxo Oxidations			
<i>cis</i> -stilbene/Ph ₂ CH ₂	(TMP)Fe ^V (O)ClO ₄ , 20	LFP kinetic ratio	13
	(TMP ⁺)Fe ^V (O)ClO ₄ , 21^c	kinetic ratio	69
	(TMP)Fe ^{III} ClO ₄ /mCPBA	competition	22
<i>cis</i> -stilbene/PhEt	(TMP)Fe ^V (O)ClO ₄ , 20	LFP kinetic ratio	17
	(TMP ⁺)Fe ^V (O)ClO ₄ , 21^c	kinetic ratio	56
	(TMP)Fe ^{III} ClO ₄ /mCPBA	competition	18
<i>cis</i> -cyclooctene/ <i>trans</i> -stilbene	(TMP)Fe ^V (O)ClO ₄ , 20	LFP kinetic ratio	1.0
	(TMP ⁺)Fe ^V (O)ClO ₄ , 21^c	kinetic ratio	18
	(TMP)Fe ^{III} ClO ₄ /PhIO	competition	3.7

^a The more rapidly reacting substrate is listed first. ^b Relative ratios of absolute rate constants from LFP results with photogenerated metal–oxo species or from kinetic results with chemically formed compound I derivatives, or product ratios from competitive oxidations with metalloporphyrin catalysts at ambient temperature in CH₃CN solvent (refs 15 and 18). ^c From ref 48.

One method to test the identity of the oxidants under turnover conditions is to compare the selectivity found in competitive oxidation reactions (one oxidant presented with two reductants) to the ratio of absolute rate constants found in direct kinetic studies of the same reductants. If the ratio of products in the competitive oxidation reaction is the same as the ratio of absolute rate constants, then one can infer that the same oxo species is active under catalytic and single-turnover conditions. For example, the ratio of rate constants for reaction of porphyrin–manganese(V)–oxo species **6c** and **6b** with organic substrates is similar to the ratio of products found in competitive catalytic oxidations (Table 2).¹⁵ Differences in inherent reactivities of the reductants obviously influence the ratio of products, but the close match between the ratios of absolute rate constants and the ratios of products from the competition experiment strongly suggests that species **6c** and **6b** were the active oxidants in the catalytic oxidation reactions, even though they could not be detected during the reactions.

The situation with iron–oxo species is quite different. Table 2 also lists some results^{18,48} from competition studies with iron catalysts and the ratios of absolute rate constants for reactions of the same substrates with the putative tetramesityliron(V)–oxo transient **20** and its compound I analogue **21**. One concludes that a compound I derivative is unlikely to be the sole active oxidant under turnover conditions with the tetramesitylporphyrin system. The ratios of rate

SCHEME 8. Possible Reaction Model for Porphyrin–Iron(III)-Catalyzed Oxidations

constants for oxidations by the compound I analogue **21** are larger than the observed product ratios from competition studies, suggesting that the compound I analogue is less reactive (higher selectivity) than the species formed in the catalytic reactions. For transient **20**, however, the ratios of absolute rate constants are similar to or even slightly smaller than the observed ratios of products. It appears possible that transient **20** was the major, but possibly not the only, active oxidant under turnover conditions.

The interesting possibility thus exists that Scheme 8 might describe catalytic oxidation reactions under turnover conditions. Reaction of the porphyrin–iron(III) salt with the sacrificial oxidant might give a porphyrin–iron(V)–oxo species that is the major oxidant of substrate. In a slow competing process, the porphyrin–iron(V)–oxo species might relax to a compound I derivative that also serves as an oxidant. When reactive substrates were not present, compound I derivatives might be the only observable products because the porphyrin–iron(V)–oxo species are too short-lived and do not accumulate to detectable concentrations.

If this reaction model is reasonable, then it is possible that catalytic oxidations could involve two active oxidants that have different reactivities and selectivities in, for example, competition reactions. Thus, the results in Table 2 are consistent with a multiple oxidant model. Much evidence has accumulated in recent years that multiple oxidants can be involved in oxidations by ligand–metal catalysts under turnover conditions, although the identities of the multiple oxidants are speculative points.^{57–60} We suggest that the model in Scheme 8 presents a possible explanation for such results when ligand–iron catalysts are employed.

Concluding Remarks

In this Account, we show that the photoinduced ligand cleavage method is a powerful technique for production of high-valent metal–oxo complexes. The inherent good temporal resolution of laser flash photolysis methods permits the production, spectral characterization, and kinetic studies of reac-

tive intermediates that cannot be observed by chemical oxidations in mixing experiments. Previously unknown high-valent iron–oxo species, possibly iron(V)–oxo derivatives, apparently already have been produced by photoinduced ligand cleavage reactions. Further characterizations of these new transients and related species will be necessary to provide important structural information, but the assignment as iron(V)–oxo species seems to be most consistent with spectroscopic and kinetic results obtained thus far. The results from kinetic studies in real time permits comparison of reactivities of various metal–oxo species, providing important information for understanding the transients for the high energy demanding oxidations of hydrocarbons catalyzed by cytochrome P450 enzymes. It is noteworthy that the putative porphyrin–iron(V)–oxo transient¹⁸ displayed the appropriate level of reactivity for the oxidant in a catalytic process under turnover conditions, and the kinetic results suggest that iron(V)–oxo species might be the oxidants in cytochrome P450 enzymes.

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FOOTNOTES

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