Polyhaloporphyrins: Unusual Ligands for Metals and Metal-Catalyzed Oxidations

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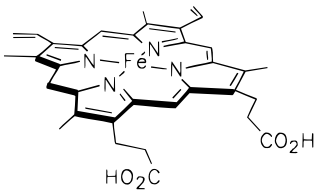
Introduction

Porphyrins together with their reduced analogs the chlorins and bacteriochlorins, their acyclic congeners the bile pigments and phytocyanins,[1] and other tetrapyrrolic macrocycles such as vitamin B_{12} and factor F_{430} serve as cofactors for a wide variety of biochemical processes. These materials, which are all highly colored, have been called the pigments of life.[2]

The most abundant naturally occurring porphyrin is iron protoporphyrin (**1**), known as heme. Heme is the prosthetic group for a large number of heme proteins which at first sight appear to have diverse unrelated biochemical functions[1] (Figure 1). Some of the most interesting and certainly the most widely studied of all heme proteins are the cytochromes P-450, so named because of the strong absorption they exhibit at 450 nm when reversibly inhibited by the coordination of CO[3] (reaction b, Figure 2). Figure 2 shows the catalytic cycle of P-450s, where it can be seen that they combine features of the three classes of heme proteins in that they bind dioxygen (reaction c), transport electrons (reactions a, d), and in so doing produce the equivalent of peroxide bound to ferric iron (intermediate **F**). Intermediate **G** undergoes O−O bond cleavage with the loss of water to give the active oxidizing agent (**J**).

Studies to determine the mechanisms of heme proteins are complicated by the protein. Since the chemistry (the making and breaking of bonds) takes place at the iron porphyrin (heme), biomimetic chemists have studied metalloporphyrins, *in vitro*, unencumbered by any biological superstructure. Most naturally occurring porphyrins are peripherally substituted by eight alkyl or alkenyl residues, as occurs with heme (**1**). Such compounds of this type often require time-consuming synthesis, or extensive purification from natural sources, and so a synthetic class of porphyrins, the *meso*-tetraarylporphyrins, including *meso*-tetraphenylporphyrin (**2a**, TPP),[4] which are easy to make, are commonly used as mimics of the natural systems. These porphyrins were first prepared, in low yields, by Rothemund from pyrrole and



Heme (1)

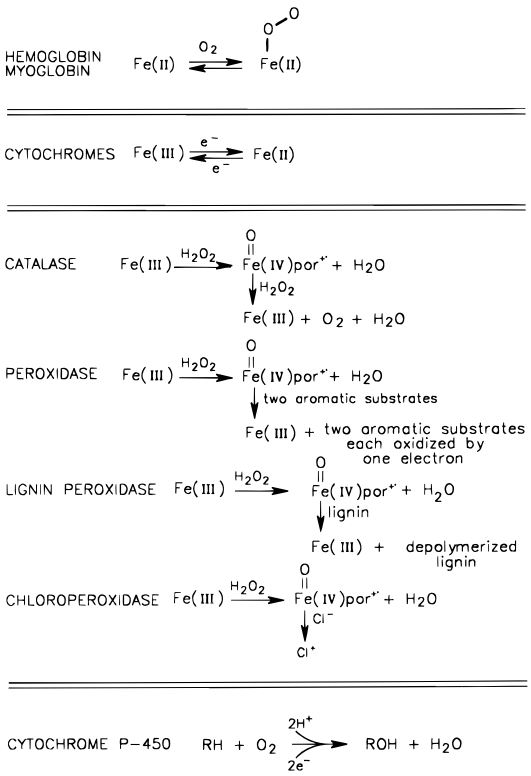


FIGURE 1. A brief summary of the principal reactions of heme proteins.

Teddy G. Traylor (1925−1993) never graduated from high school, but after the war, where he served in the Merchant Marine, he received his Ph.D. at UCLA with Saul Winstein and then was a postdoctoral fellow with Paul Bartlett at Harvard. He was the first organic chemist hired at UCSD, where he was a pioneer in organometallic chemistry. Teddy was the first to publish papers on superstructured porphyrins, and his research on oxygen binding and P-450 chemistry was seminal for the past two decades. His love of chemistry was surpassed only by his love of life. We are sorry that he is not with us to still enjoy them.

David Dolphin was born in London, England, at the beginning of the Second World War. After obtaining his undergraduate and graduate degrees at the University of Nottingham, he was a postdoctoral fellow with R. B. Woodward at Harvard and then joined the faculty there in 1966. In 1973 he joined the University of British Columbia, where he has been acting Dean of Science and is the NSERC/QLT Industrial Research Professor in Photodynamic Technology. He is also the V.P. of Technology Development at QLT PhotoTherapeutics, a Vancouver-based biotechnology company that is the world leader in photodynamic therapy.

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† University of British Columbia.
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(1) *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978/79; Vols. 1−7.
(2) Battersby, A. R. *Science* **1994**, *264*, 1551−1557.
(3) This paper as originally submitted to the Editor cited more than 100 references, which occupied fully one-third of the paper. In order to meet the space criteria of *Accounts*, we have chosen, where possible, to cite only recent references. A recent monograph gives an excellent up-to-date review of many areas touched upon here. *Cytochrome P-450: Structure, Mechanism and Biochemistry*, 2nd ed.; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1995.
(4) Even the trivial names of porphyrins are frequently complex. In this review the major porphyrins are abbreviated as follows: TPP = *meso*-tetraphenylporphyrin (**2a**) etc. as shown for structures **2**−**14**.

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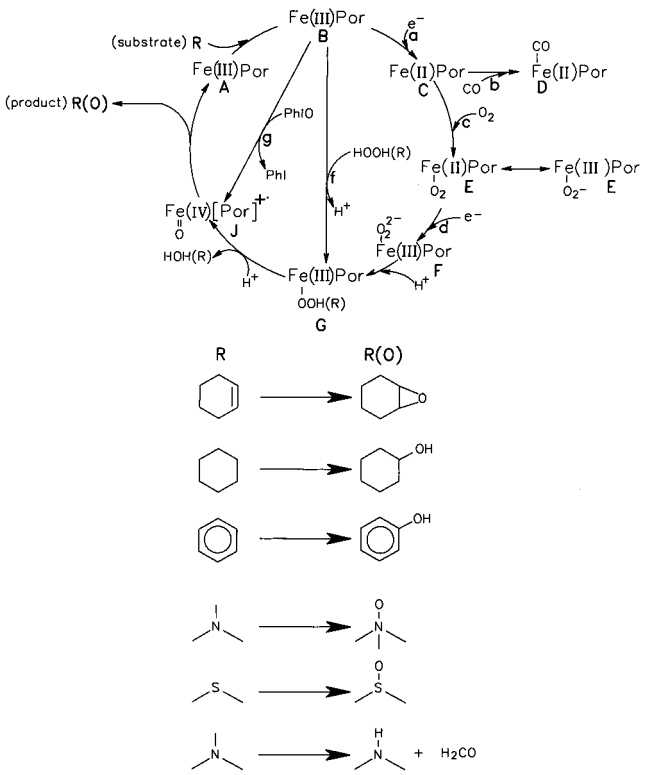
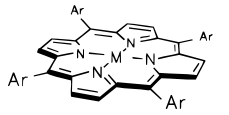


FIGURE 2. Catalytic cycle of cytochromes P-450. The resting enzyme A binds the substrate (R) to be oxidized. This brings about a change in the spin state of the heme to give intermediate B which accepts an electron to give the ferrous complex C. Reversible binding of CO gives D with a characteristic absorption at ~450 nm. Binding of dioxygen to D gives E, which upon a one-electron reduction (the rate-limiting step in the enzymatic cycle) gives F, which is formally ferric iron with bound peroxide. Protonation of F and then G and loss of water give the oxidizing intermediate J, which transfers the iron-bound oxygen atom to give the oxidized product [R(O)]. Listed beneath the catalytic cycle are the principal reactions catalyzed by the cytochromes P-450.

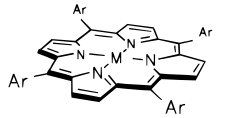
a benzaldehyde. Since then the synthetic routes have been greatly improved by Adler and Lindsay and their colleagues,[5] such that gram quantities are easily obtained. While the *meso*-tetraarylporphyrins are electronically similar to their β-octaalkyl counterparts, they are sterically quite different, with the four aryl (phenyl) groups being essentially orthogonal to the plane of the 18π-aromatic porphyrin macrocycle (Figure 3). This structural feature can be used to sterically protect the top and bottom faces of the porphyrin (and a coordinated metal and its attendant ligands).

Groves et al.[6] were the first to demonstrate cytochrome P-450-like activity in a model system using iron *meso*-tetraphenylporphyrin chloride (**2b**) and iodosylbenzene (PhIO) as a cooxidant; in their study it was shown that cyclohexene was converted to its epoxide and cyclohexane to cyclohexanol (eq 1). Other metalloporphyrins (including Cr, Mn, and Ru) were also shown to catalyze both epoxidation of olefins and hydroxylation of unactivated hydrocarbons, mimicking the natural reactions shown in Figure 2. Cooxidants such as hydrogen peroxide and alkyl hydroperoxides produce the active oxidant **J** (Figure 2) in a manner similar to the peroxide shunt mechanism (reaction f) whereas cooxidants such as iodosylbenzene parallel the oxygen atom shunt (reaction g). While these first-generation catalysts qualitatively reproduced most P-450 reactions, their catalytic activity was rapidly diminished by extensive destruction of the metalloporphyrin. However, second-generation catalysts such as iron *meso*-tetramesitylporphyrin chloride (TMPFeCl, **3b**) and iron *meso*-tetrakis(2,3,4,5,6-pentafluorophenyl)porphyrin chloride ((TPFPP)FeCl, **4b**), are able to resist, to some extent, oxidative destruction because of their steric and eletronic structures. Thus, both **3b** and **4b** showed the formation of a reasonably stable high-valent iron porphyrin radical cation[7] (related to **G**, Figure 2) and more effective catalysis of hydrocarbon oxidation.[8]

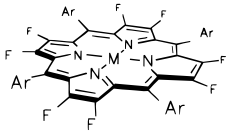
(1)



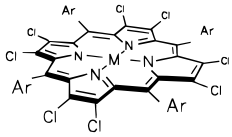
2 Ar = phenyl, TPP
3 = mesityl, TMP



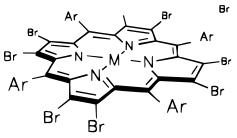
4 Ar = pentafluorophenyl, TPFPP
5 = 2,6-dichlorophenyl, TDCPP
6 = pentachlorophenyl, TPCPP



7 Ar = pentafluorophenyl, TPFP βF_8



8 Ar = pentafluorophenyl, TPFPβCl_8
9 = 2,6-dichlorophenyl, TDCPβCl_8
10 = pentachlorophenyl, TPCPβCl_8



11 Ar = phenyl, TPPβBr_8
12 = mesityl, TMPβBr_8
13 = pentafluorophenyl, TPFPβBr_8
14 = 2,6-dichlorophenyl, TDCPβBr_8

a M = 2H, **b** M = FeCl **c** M = MnCl
d M = Zn **e** M = $Ru(O)_2$

Pat and Ted Traylor, while on sabbatical leave in Dolphin's laboratory, showed that simple metalloporphyrins could be both sterically protected and electronically activated by placing chlorine atoms on the eight *o*-phenyl positions of TPP (Figure 3). Iron(III) *meso*-tetrakis(2,6-dichlorophenyl)porphyrin chloride (TDCPP)FeCl (**5b**) proved to be an unusually good catalyst for the epoxidation of alkenes.[9] Epoxidation was found to be very fast

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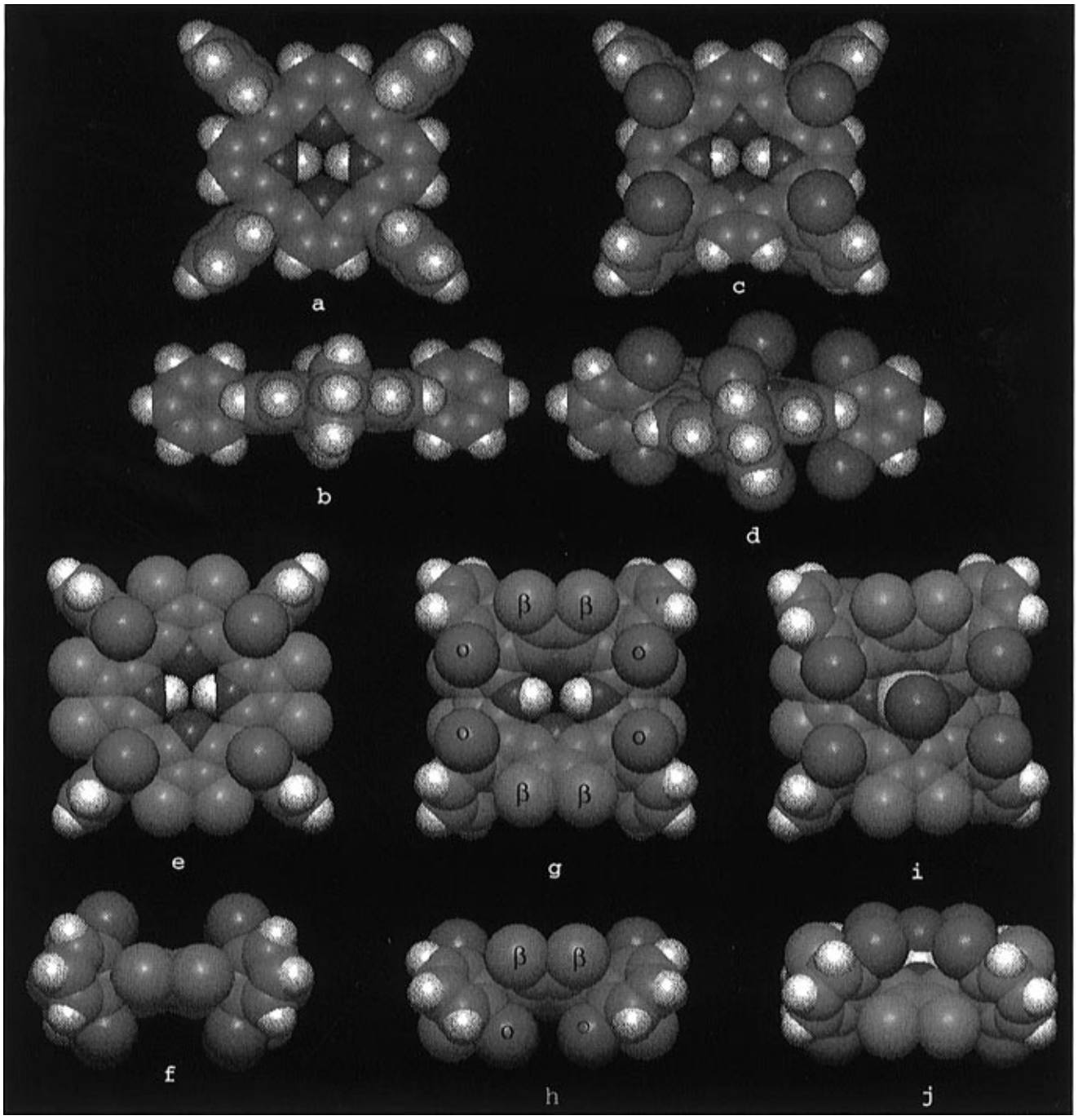
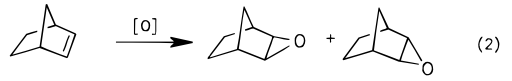


FIGURE 3. Structures a and b show the essentially flat *meso*-tetraphenylporphyrin 2a with phenyl groups which are nearly orthogonal to the plane of the porphyrin ring. Substitution of all eight *ortho* positions by chlorine gives 5a whose conformation is close to that of 2a (c, d). Substitution of all eight *β*-positions by chlorine gives 9a. The conformations shown in (e) and (f) are for the flat conformation where the *β*-chlorines (cyan in color) lie in the plane of the porphyrin and the eight *o*-chlorines sit above and below the porphyrin plane. Minimization of (e) gives (g) (and (h)), where the molecule adopts a saddle-shaped conformation. The conformation of the iron complex 9b is shown with an oxygen atom bound to the iron to represent the active oxidizing agent.

(300 turnovers/s for norbornene, eq 2), and very high



(2)

turnover numbers were obtained with iodosylpentafluorobenzene (PFIB) as cooxidant; minimal catalyst destruction was observed. However, less than 100 turnovers of alkane hydroxylation were achieved before significant catalyst degradation began.

Since the introduction of (TDCPP)FeCl (**5b**), our understanding of P-450 chemistry has benefited a great deal from studies using halogenated porphyrins as catalysts, and critical intermediates have been trapped and characterized. A number of groups including those of Bruice,[10] Gray,[11] Groves,[12] Lyons and Ellis,[13] Mansuy,[14] Meunier,[15] and Traylor[16] have made major contributions to these areas. We were able to suggest a common intermediate, as indicated in Figure 4, which could account for all of

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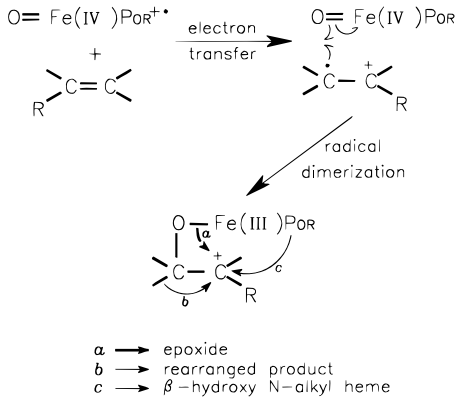

FIGURE 4. Electron transfer mechanism resulting in a PorFe^{III}−O−C−C^{+} intermediate which can rearrange in three separate ways to give the known products from the P-450-mediated oxidation of a terminal olefin.

the known reactions of cytochromes P-450 with terminal olefins, namely, epoxidation, rearrangement to ketones, and N-alkylation of heme.[17] However, there is considerable controversy in this area as discussed in a recently published seminal review of alkene epoxidation by high-valent (oxometallo)porphyrins.[10a] All of the available evidence from model studies suggested the O=Fe^{IV}Por$^{•+}$ (**G**, Figure 2) porphyrin π-cation radical[18] formulation for the P-450 oxidizing intermediate.[3] Recent work of Petsko[19] has shown the intermediacy of the iron−oxo complex (structure **J**, Figure 2) in cytochrome P-450$_{cam}$ and by inference in cytochromes P-450 in general.

The exact nature of this high-valent oxo−metal complex will depend on both the metalloporphyrin and the cooxidant. Groves and his colleagues have shown that "pure" metal−oxo species are generated for iron porphyrins, particularly **3b**, when activated with PhIO or NaOCl. Meunier's group have shown that iron and manganese porphyrins activated by $KHSO_5$ are metal−oxo-like species where the leaving group of the cooxidant is probably involved in the transition state during substrate oxidation. They have also shown that while oxomanganese(V) porphyrins have not yet been identified, ^{18}O exchange has been observed from both peroxy acid and persulfate. These observations require that the O−O bond has been broken, after which exchange between water and the reactive oxygen occurs, prior to substrate oxygenation.

There have been a number of reports from Bruice,[10] Mansuy,[14] Traylor,[16] and others[20] dealing with *meso*-tetrakis(2,6-dichlorophenyl)porphyrin (**5a**) as a ligand for metals such as Mn, Ru, and Cr in P-450-related reactions. Reasonable turnover numbers in alkane oxidation have been achieved in several systems mostly using Mn with a variety of cooxidants. For instance, (TDCPP)MnCl (**5c**) and sodium hypochlorite in the presence of 4-*tert*-butylpyridine and a phase transfer catalyst, benzyldimethylhexadecylammonium chloride, afforded more than 500 turnovers for cyclohexane oxidation before catalyst bleaching became noticeable.[21] When magnesium monoperoxyphthalate was used as a cooxidant in a similar system, a turnover rate of up to 24 cycles/min for cyclohexane was achieved.[22] This rate is even faster than that of the biological system, ~9 cycles/min.[23] Moreover, addition of a lipophilic carboxylic acid (benzoic acid) accelerated the rate of catalytic hydroxylation of cycloalkanes up to 125 cycles/min at 0 °C with up to 700 turnovers using a **5c**−H_2O_2 system,[24] a significant improvement from our original **5b**−PFIB system.

Unfortunately, far less acceleration with linear alkanes has been observed, where the reaction stopped after a few turnovers (12 for *n*-hexane) even though the catalyst remained intact and excess H_2O_2 was still present.[24] In addition, we showed that hydrocarbons tend to be overoxidized to ketones, with an alcohol to ketone ratio typically ranging from 2:1 to 5:1; **5b**−PFIB exhibited improved substrate specificity but fewer turnovers. Mansuy and co-workers have developed an efficient system using **5c**−H_2O_2 for the oxidation of hydrocarbons in the presence of a cocatalyst, imidazole (Im), which was found to act as both an axial ligand and a base catalyst. This system, **5c**−Im−H_2O_2, exhibits stereospecificity and regio- and chemo-selectivities identical to those of **5c**−Im−PhIO for selected substrates, indicating that similar active Mn−oxo species were present in both cases. Recently, they have shown that when imidazole was replaced by ammonium acetate, the catalytic activity of **5c**−H_2O_2 was

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further enhanced. Epoxidation with the latter system gave complete conversion with excellent yield, and hydroxylation of alkanes in yields up to 87% (based on H_2O_2) were observed. With this system even the poorly activated linear alkane heptane can be oxidized in 45% yield based on H_2O_2 (25% alcohol and 10% ketone). It is worth noting that the corresponding iron complex **5b** is an efficient catalyst for the decomposition of H_2O_2 (functioning as a catalase). Thus, H_2O_2 is often a poor choice as cooxidant in **5b**-catalyzed reactions, and the corresponding manganese catalyst (**5c**), which does not show catalase activity, is often superior.

While effective in the catalytic epoxidation of alkenes, destruction of the catalyst is noticeably severe during alkane hydroxylation using these second-generation catalysts. In order to generate more robust catalysts, it was decided independently, but simultaneously, in both our laboratories that halogenation of the β-porphyrin positions would provide the desired resistance to catalyst destruction. Chlorination of **5b** and iron *meso*-tetrakis(2,3,4,5,6-pentachlorophenyl)porphyrin chloride ((TPCPP)FeCl, **6b**) was carried out in Vancouver,[25] while bromination of (TDCPP)Zn (**5d**) was pursued in La Jolla.[26] These polyhalogenated metalloporphyrins (third-generation catalysts) have shown exceptional stabilities and efficiencies as catalysts for epoxidation and hydroxylation as well as exhibiting unusual spectroscopic properties. In addition to providing steric protection (Figure 3), perhalogenation of the porphyrin ring generates considerable electronic activation of the catalyst. While the eight chlorine atoms bonded to the *o*-phenyl groups change the redox potential of the Fe(III)/Fe(II) couple of (TDCPP)FeCl (**5b**) by only 60 mV compared to (TPP)FeCl (**2b**), the additional eight chlorines on the porphyrin ring in (TDCPβCl$_8$)FeCl (**9b**) move the potential by more than 500 mV compared to **2b**.[25] Since the catalytically active high-valent iron porphyrin radical cations in these model systems, and in P-450, function due to their electron deficiency, this additional ~12 kcal/mol makes for even more powerful catalysts.

Synthetic Procedures

Porphyrins and metalloporphyrins readily undergo aromatic electrophilic substitution. An appropriately substituted benzaldehyde will condense with pyrrole,[5] and the subsequent porphyrin, after metalation, can then be halogenated, nitrated, etc. at the porphyrin β-positions. Metal fluorides were used in the further fluorination of *meso*-tetrakis(2,3,4,5,6-pentafluorophenyl)porphyrin (**6a**).[27] Unfortunately, fluorination proves to be an irreproducible process, and better fluorination methods are still needed.

Polyhalogenated Metalloporphyrins as Catalysts for Oxidation Reactions

Oxidations with Oxygen Donors. The following examples illustrate the improved catalytic activities of the third-generation metalloporphyrins where the porphyrin ring is fully halogenated. The effectiveness of iron(III) complexes as catalysts can be seen in Table 1, where Mansuy's group compared the hydroxylation of heptane. The total yield of heptanols was significantly improved using (TDCPβCl$_8$)FeCl (**9b**) or (TDCPβBr$_8$)FeCl (**14b**) compared to **5b** (βCl$_8$ and βBr$_8$ indicate β-octachloro and β-octabromo substitution on the porphyrin). Furthermore, they showed that the chemoselectivity of the third-generation catalysts for alkane (hydroxylation) over alkene (epoxidation) was enhanced as seen by the marked decrease of the epoxide to alcohol (including ketone) ratio in a competitive experiment (Table 1).

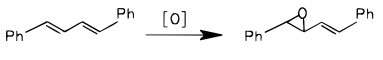
Table 1. Comparison of Heptane Hydroxylation Catalyzed by the Second- and Third-Generation Catalysts[a]

	heptane total yield (%)	epoxide:(alcohol + ketone)
catalyst **5b**	38	8.2
catalyst **9b**	80	2.8
catalyst **14b**	78	2.9

[a] From ref 14, heptane:PhIO:cat. = 800:20:1 in CH_2Cl_2, [catalyst] = 2 mM, 1 h at 20 °C; yields based on the PhIO consumed.

We studied the kinetics of the cyclohexane oxidation in another system [solvent $CH_2Cl_2/CF_3CH_2OH/H_2O$ (90:9:1), catalyst **14b**, oxidant PFIB], where a bimolecular rate constant of around 10^4 M^{-1} s^{-1} was observed. This means that these hydroxylation reactions can be carried out to completion in seconds to minutes. These fast rates and high yields are unprecedented in metalloporphyrin chemistry! It is especially noteworthy that the product selectivity for cyclohexanol is also very high: when the reaction is carried out to 1% conversion of cyclohexane, the yield of cyclohexanol, based upon the consumed PFIB, is 93%[16d] with a 37:1 ratio of alcohol to ketone. An even greater specificity was observed with norbornane hydroxylation catalyzed by **14b**, giving an 82% yield of alcohol (including <1% ketone) with an exo:endo ratio of 6.7:1. The stereochemistry of the observed exo:endo product formation is close to that of the P-450 enzyme-catalyzed reaction (exo:endo = 3.3:1).

A striking example of the effect of halogenation on the reactivity of the oxoferryl porphyrin π-cation radical is seen in the competition between bond cleavage of *t*-BuOOH (to give *t*-BuOH) and alkene epoxidation. We showed[16a,b] that whereas the catalytic oxidant made from (TMP)FeCl (**3b**) reacts with 1,4-diphenyl-1,3-butadiene and *tert*-butyl hydroperoxide with about the same rate ($k_{ep}/k_{hp} \approx 1.0$; k_{ep} = rate of epoxidation, k_{hp} = rate of *t*-BuOO$^\bullet$ formation), the corresponding (TPFPP)FeCl (**4b**) reacts much faster with the alkene ($k_{ep}/k_{hp} > 100$) (eqs 3 and 4). These rates account for the epoxidation yields



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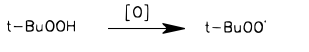

(4)

using H_2O_2 or *t*-BuOOH with **4b**, (TPFPβF$_8$)FeCl (**7**), and (TDCPβBr$_8$)FeCl (**14b**). In addition, the use of electronegative substituents on the porphyrin gives the same results with H_2O_2 (as an inexpensive source of oxidant) as obtained with PFIB. Meunier showed that molybdenum

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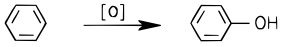
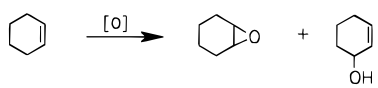
complexes of **12a** and a dodecachloro derivative of **3a** gave a 30% yield for the epoxidation of cyclooctene in ethyl acetate at 70 °C.[15e] Epoxidation with (TPFPβF$_8$)FeCl (**7b**) was reported to give a 100% yield of epoxide based upon H_2O_2 consumed, without catalyst degradation, showing that very high turnover numbers may be achieved.[27]

Aromatic hydroxylation is a well-known reaction of P-450, which gives rise to the NIH shift. Similar reactions can be observed with our catalysts. Mansuy showed that hydroxylation of anisole by (TDCPβBr$_8$)MnCl (**14c**) gave a 70% yield of hydroxyanisole (in the presence of imidazole) based on H_2O_2. A lower yield but higher regiospecificity (95% *para*) was observed with **5c**. An increase in total yield but decrease in regioselectivity has also been observed with these catalysts for heptane hydroxylation, and has been attributed to a change in the nature and intrinsic reactivity of the high-valent metal−oxo species. Hydroxylation of benzene to phenol (eq 5) occurred with 55 turnovers over 2 h using (TPFPβF$_8$)FeCl (**7b**) at room temperature. No destruction of the catalyst was observed during this reaction.[27]



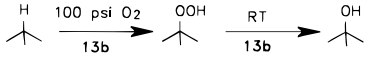
(5)

Oxidations Using Molecular Oxygen without a Reductant. Nature has learned how to activate heme proteins with both exogeneous hydrogen peroxide and "peroxide" generated by the *in situ* reduction of dioxygen. Chemists have been less successful in modeling P-450 systems using dioxygen and reducing agents.[28] However, the use of dioxygen, especially in the absence of reducing agents, has enormous industrial potential, and our polyhaloporphyrins appear to be meeting some of this potential. The most successful epoxidation using a metalloporphyrin and dioxygen, prior to the introduction of perhalogenated porphyrins, was the reaction of ruthenium(VI) *meso*-tetramesitylporphyrin, (TMP)Ru(O)$_2$ (**3e**).[12a] Groves showed that reaction with this catalyst afforded 16−45 turnovers over 24 h, but the catalyst tended to be deactivated by product coordination and by formation of the inactive Ru(II)−CO complex. However, the Ru(VI) complex of the perfluoroporphyrin (**7e**) in pure cyclooctene at 100 °C under oxygen gave thousands of turnovers in the same period.[29] Iron perfluoro-*meso*-tetraphenylporphyrin (TPFPβF$_8$)FeCl (**7b**) catalyzes the oxidation of cyclohexene to the corresponding epoxide and the allylic hydroxylation product using dioxygen under mild conditions (eq 6).



(6)

Lyons and Ellis[13] reported an efficient oxidation of isobutane to *tert*-butyl alcohol at room temperature under 100 psi of oxygen using (TPFPβBr$_8$)FeCl (**13b**) as catalyst. Oxidation of isobutane proceeded with over 90% selectivity to *tert*-butyl alcohol, and the turnover number reached more than 13 000 (eq 7). This catalyst is twice as efficient



(7)

as **4b**, and the catalytic activity remained constant for 74 h. This extraordinary activity has been suggested by Lyons and Ellis and co-workers to arise from the ability of the catalyst to form a highly active iron−oxo intermediate mimicking P-450 chemistry, but without the requirement of a coreductant! Subsequent studies from Gray's laboratory have shown[11] that formation of iron−oxo species via the proposed homolytic cleavage of a peroxo-bridged dimer is very unlikely given the stability of the ferrous oxidation state in this system (Fe(III)/Fe(II) = 0.31 V vs SCE). A radical-chain autoxidation mechanism is likely operative where the role of **13b** is to generate radicals by catalyzing the decomposition of alkyl hydroperoxides. Indeed **13b** has been shown by Lyons and Ellis to be an exceptionally efficient catalyst (>100 cycles/s) for *tert*-butyl hydroperoxide decomposition to *tert*-butyl alcohol at ambient temperature (eq 7). Moreover, the catalytic activity found for alkane oxidation can be completely inhibited by addition of a radical trapping agent. Computer modeling of this system, based on a radical-chain autoxidation mechanism, accounts closely for the activity and product distribution for both alkane oxidation and alkyl hydroperoxide decomposition.[30]

Oxidation of cyclohexene using **13b** and iodosylbenzene gives a 77% yield of the epoxide via the intermediacy of a high-valent metal−oxo complex. However, cyclohexene and **13b** with dioxygen at room temperature gave mainly allylic oxidation products (49% alcohol and 44% ketone) with 73 turnovers in 24 h. Gray and his colleagues noted that this latter observation suggests the intermediacy of allylic alkylperoxides (from free radical autoxidation) and their decomposition by the iron porphyrin catalyst.

Biomimetic Catalysis

Since it would appear that all heme proteins, which serve as oxidants, function via a similar high oxidation state (i.e., O=Fe^{IV}[Por]$^{\bullet+}$), it is clear that the diverse chemistry these enzymes exhibit must be due to the modulation imposed by the protein via coordination to the iron and the spatial definition of the active site. The polyhalogenated metalloporphyrins constitute a universal "heme enzyme" devoid of the restraints of an active site. We might anticipate that given the appropriate substrate our catalysts should mimic much of the known oxidative reactions of heme proteins using either electron or oxygen atom transfer routes.

Lignin, the second most abundant biopolymer on Earth, has a wide variety of substructures (including biphenyl and phenyl ether linkages). Rather than generating a very large number of different enzymes to cleave all of the many substructures, another class of heme proteins (the lignin peroxidases) bring about lignin degradation by single-electron transfer reactions.[31] This is most easily demonstrated by comparing the reactions of

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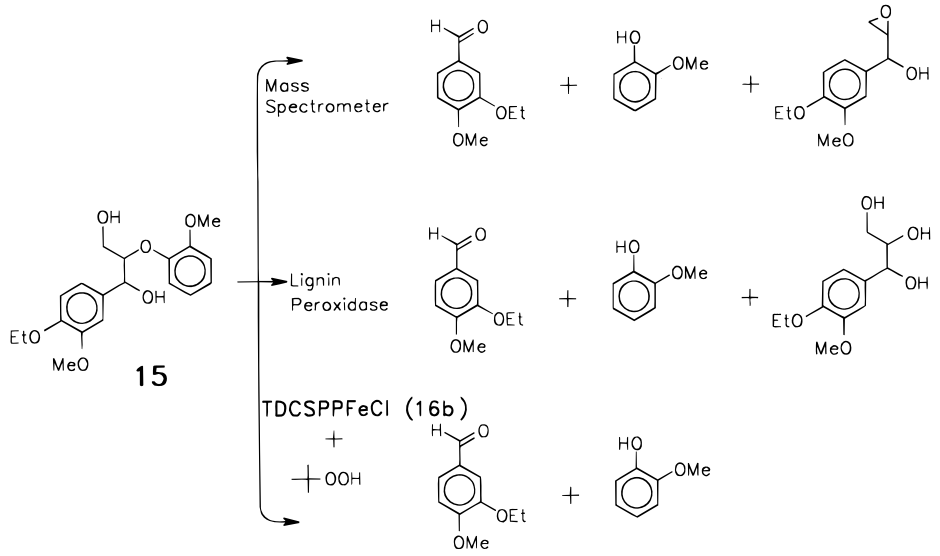
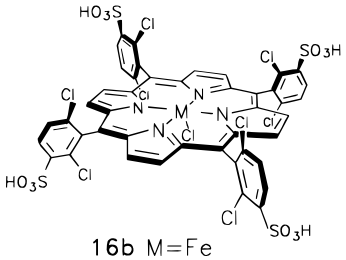
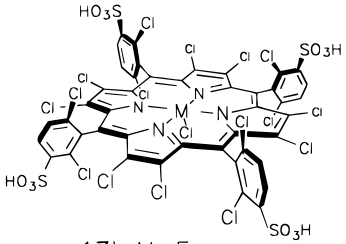


FIGURE 5. A comparison of the one-electron oxidation of the dimeric lignin model compound 15 by the mass spectrometer, lignin peroxidase, and a polyhalogenated iron porphyrin (16b) and *tert*-butyl hydroperoxide.

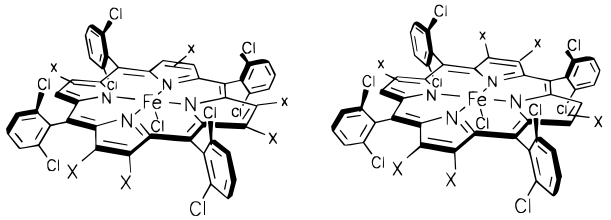
the dimeric model lignin substructure (**15**) in the mass spectrometer[32] and in the presence of lignin peroxidase. Both systems bring about the one-electron oxidation of **15**, after which well-known fragmentation patterns follow to give monomeric products which differ only as a result of the presence or absence of water (Figure 5). Water soluble iron *meso*-tetrakis(2,6-dichloro-3-sulfophenyl)-porphyrin chloride (**16b**) prepared by sulfonation of **9a**



16b M=Fe
c M=Mn



17b M=Fe
c M=Mn



19 X=NO_2

with oleum[25] gives a product distribution similar to that of the enzyme with **15** (Figure 5). Indeed, the polyhalogenated metalloporphyrins **16b**,**c** and **17b**,**c** mimic all of the known bond cleavage reactions of the lignin peroxidases including $C_\alpha-C_\beta$ cleavage, β-O-4 bond cleavage, dealkoxylation, hydroxylation of benzylic methylene groups, glycol formation from $C_\alpha-C_\beta$ double bonds, and aromatic ring cleavage reactions.[33]

It is perhaps not too surprising that the polyhalogenated metalloporphyrins can closely mimic relatively simple chemistry such as lignin degradation initiated by single-electron transfer reactions, but this mimicking extends to even more complicated and demanding systems. There are many mammalian liver microsomal cytochromes P-450 whose principal function is to metabolize (oxidatively) hydrophobic and xenobiotic materials to make them water soluble and thus excretable. Many of these enzymes can be induced in the liver, but even the induced enzymes metabolize a wide variety of substrates with the result that mammalian metabolism of drugs (which is principally oxidative and principally of P-450 in origin) gives rise to numerous metabolites.

Mansuy and his colleagues showed that oxidation of the analgesic lidocaine (**18**) catalyzed by **5c** with various cooxidants gave three of the known mammalian metabolites (Figure 6). Meunier and his colleagues produced two of the known metabolites of SR 48117 (an antagonist of vasopresin V_{1a} receptors) using a sulfonated analog of **5c** and magnesium monoperphthalate as cooxidant. We were surprised that more of the known metabolites were not produced in the above reactions since these catalysts are, after all, a naked P-450 devoid of any restrictions of an active site and ought, in principal, to give all of the known mammalian P-450 metabolites. This is indeed the case, since in our hands the oxidation of lidocaine with **17b** and various cooxidants gave not only **all** of the known metabolites but three additional compounds whose struc-

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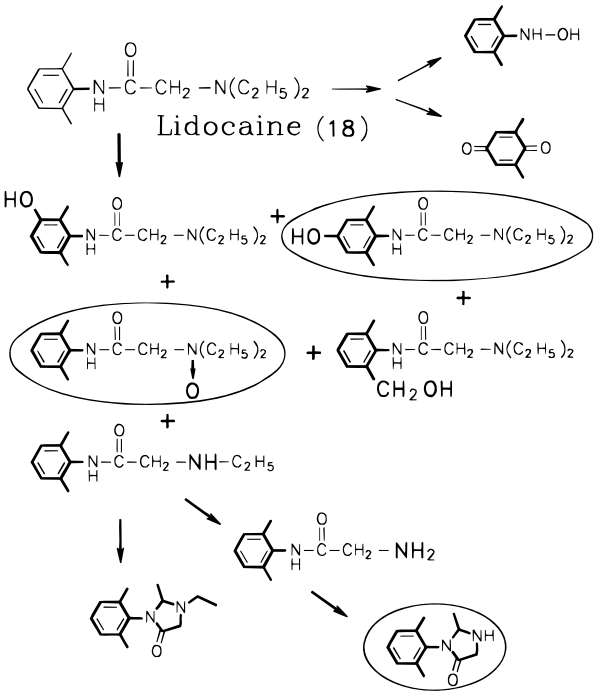

FIGURE 6. Oxidation of lidocaine (18) using 17b as catalyst. The oxidized groups are shown bold, and the "new" metabolites are circled.

tures suggest that they could also be mammalian metabolites (Figure 6).[34] The same production of all the known and some additional mammalian metabolites was found when we examined the oxidation of aminopyrene. Moreover, changing the reaction conditions allowed us to prepare several of the metabolites on a practical scale. These polyhalogenated metalloporphyrins thus have the potential to act as a universal cytochrome P-450 and can be used to predict (and prepare), *in vitro*, mammalian drug metabolites that are produced *in vivo*.

Catalysts with Electron-Withdrawing Groups Other Than β-Halogens

Metalloporphyrins bearing other electron-deficient groups besides halogens should, in principle, be good catalysts for the oxidation of alkenes and alkanes. Mansuy has prepared complexes with β-substituents such as $-NO_2$, $-CN$, and $-SO_3H$, and porphyrins with *meso*-polyfluoroalkyl groups have been prepared.[35] Iron porphyrins bearing 4−7 β-nitro groups show very interesting properties as oxidation catalysts. Mansuy's group found that iron *meso*-tetrakis(2,6-dichlorophenyl)-β-hexanitroporphyrin chloride (**19**), present as a mixture of six regioisomers, catalyzed the hydroxylation of heptane with PhIO to a total yield of 66%; of more significance is the fact that epoxidation of alkenes with H_2O_2 can be carried out to complete conversion in less than 1/2 h at room temperature. This catalyst is significantly better than **10f** for the oxidation of alkanes by O_2 at 90 °C. It is also twice as efficient as **14f** in the oxidation of cyclohexane and 8 times better than **14f** in the case of heptane hydroxylation.

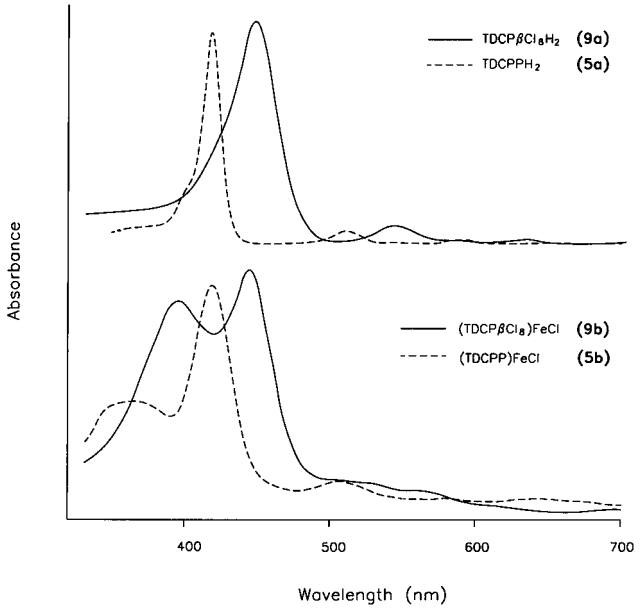

FIGURE 7. Optical spectra (CH_2Cl_2) of the free base porphyrins 5a and 9a and their iron chloride complexes 5b and 9b.

Heterogenous Catalysis

We have shown that perhalogenated metalloporphyrins can also be polymerized or be attached to a variety of solid supports. The *meso*-tetrakis(2,3,4,5,6-pentafluorophenyl)-porphyrins **4b** and **7b** will react with sodium sulfide alone or in the presence of perfluorobiphenyl in DMF to give cross-linked polymers. These polymers are effective catalysts for norbornene oxidation, giving quantitative yields with an exo:endo ratio of 12:1 and giving a 70% yield for cyclohexane hydroxylation with an alcohol:ketone ratio of around 50. Although the yield for hydroxylation does not exceed 80% in this case, catalyst can be recovered with the same activity for up to seven cycles.

Mansuy and Meunier have attached perhalogenated metalloporphyrins to various supports such as silica and montmorillonite and found these systems to be good catalysts for alkane hydroxylation and alkene epoxidation.

Conformational Changes

The presence of eight β-halogen substituents greatly modifies the structure of the normally "flat" tetrapyrrolic ring. Gray and Meunier have determined X-ray structures of several polyhalogenated porphyrins and their metal derivatives and have shown that these compounds adopt a ruffled or a saddle-shape structure for their porphyrin cores (Figure 3). Semiempirical quantum calculations on H_2TPPBr_8 (**11a**) indicated an increased stability of ~15 kcal/mol between the planar structure and the optimized saddle shape, and we find that **9a** is minimized to give a saddle-shape structure with each *meso*-aryl group tilted in order to minimize the strong steric interactions between the *meso*-aryl and β-halogen groups whereas **5a** displays a nearly planar porphyrin ring with four essentially orthogonal *meso*-phenyl groups (Figure 3). The optical transitions of these distorted compounds are red-shifted compared to those of the planar structures (Figure 7). Experimental studies and electronic structure calculations show that electron-density patterns of the HOMOs and

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Table 2. Fe(III)/Fe(II) Redox Potential of (Por)FeCl (vs SCE)

(Por)FeCl	$E_{1/2}$ (V vs SCE)	(Por)FeCl	$E_{1/2}$ (V vs SCE)	(Por)FeCl	$E_{1/2}$ (V vs SCE)
2b[a]	−0.37	**8b**[b]	0.28	**13b**[c,d]	0.31
4b[b]	0.07	**9b**[a]	0.10	**13b(py)$_2$**[c,d]	0.82
5b[a]	−0.34	**10b**[b]	0.27		
	0.044				

[a] From ref 25b. [b] From ref 13. [c] From ref 11. [d] Vs Ag/AgCl, 1 M KCl.

LUMOs in flat *meso*-tetraphenylporphyrins are maintained in the saddle-shaped (D_2) systems. However, while the ground state of monooxidized **2d** ($Zn^{II}TPP^{\bullet+}$) is $^2A_{2u}$, the ground states of monooxidized **4d** and **13d** are $^2A_{1u}$ and $^2A(^2A_{1u})$.[36]

Partial β-halogenation appears to raise the oxidation potentials of halogenated porphyrins. However, the redox potentials of perhalogenated porphyrins are also affected by conformational distortions which will raise the energy of the HOMO and thus decrease the oxidation potential of porphyrins.[36,37] Despite the expectation that increased halogenation raises the oxidation potential of the porphyrin, octahalogenated macrocycles are found to be more readily oxidized than the corresponding tetrahalogenated derivatives due to the distortion of the tetrapyrrole rings.[37] The stability and reactivity of iron porphyrins increase with the redox potentials of the Fe(III)/Fe(II) couple, and halogenation of iron porphyrins causes a large positive shift in their redox potentials (Table 2).

Conclusion

β-Substitution of halogen on the porphyrin periphery has a similar but more pronounced effect than substitution on the phenyl rings. The redox potentials of both the porphyrin ring and coordinated metal are raised.

The main differences observed between the catalytic properties of the iron porphyrins of the second (phenyl-substituted) and the third generation (porphyrin-substituted) are due, at least in part, to an increase in the electrophilicity and accessibility of the active oxidizing species.[38] Similarly, because the electron deficient iron−oxo complexes are much better electron acceptors, they will be more powerful oxidants than the corresponding species derived from simple TPP complexes. Thus, these complexes are intrinsically more robust catalysts for the most difficult of oxidations, namely, alkane hydroxylation. We anticipate that the stability and high catalytic activity of the perhalogenated metalloporphyrins will ensure their place in the ever expanding armory of synthetic chemists.

This work was supported by the Natural Sciences and Engineering Research Council of Canada.

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