Acc. Chem. Res. **1991**, *24*, 243-249 **243**

N-Acetylcalicheamicin γ_1^I has been linked to an internalizable MoAb (7F11C7) specific for the human milk fat globule membrane antigen present on a variety of carcinomas. This MoAb conjugate caused tumor regression of the MX-1 and Lung 78 nonsmall lung carcinoma xenographs and resulted in long-term tumor free survivors in both murine models.[41] These very promising results suggest that it may be possible to prepare MoAb–calicheamicin conjugates that will be suitable for clinical treatment of human carcinomas.

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Reactions of Hydroperoxides with Metallotetraphenylporphyrins in Aqueous Solutions

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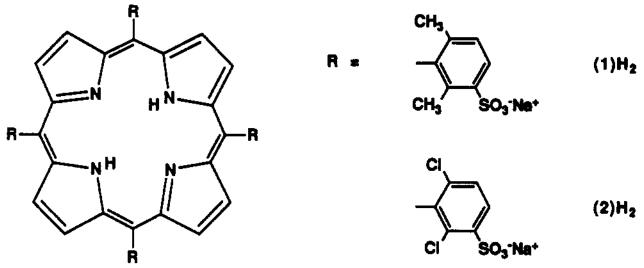
A marked renewal of interest in the mechanisms of reaction of metal ions with hydroperoxides[1] has come about due to interest in the biochemical reactions of peroxidases[2] with alkyl hydroperoxides and catalases[3] with hydrogen peroxide. Interest also stems from the finding that organic molecules in the presence of hydroperoxides and cytochrome P-450s[4] are oxidized to products that are comparable to those obtained in biochemical reactions that generate unidentified oxidants by stepwise reaction of $1e^- + O_2 + 1e^-$ with the Fe^{III} moiety of cytochrome P-450. This Account describes our studies of the reaction of hydroperoxides with Fe(III) and Mn(III) tetraphenylporphyrins in aqueous solution. It is in water that conditions (ionic strength, acidity, ligand species concentration) are best controlled and data (kinetic, electrochemical, etc.) are interpretable. A synopsis of our studies in organic solvents has been provided in a recent review.[5]

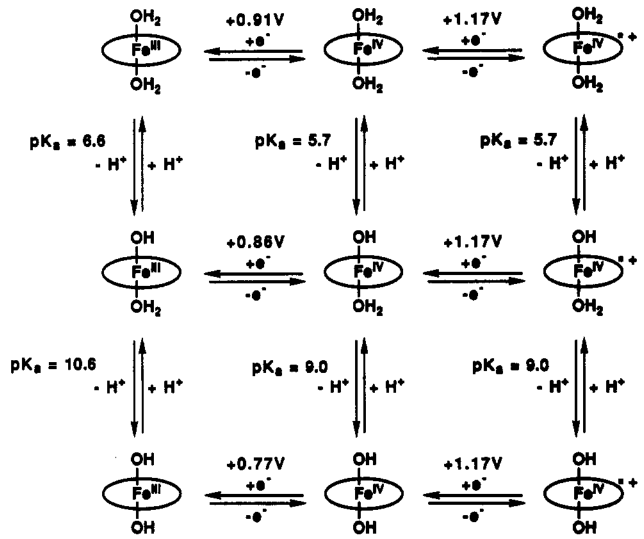
We have prepared and used the water-soluble Fe(III) and Mn(III) complexes of *meso*-tetrakis(2,6-dimethyl-3-sulfonatophenyl)porphyrin, $(1)H_2$, and *meso*-tetrakis(2,6-dichloro-3-sulfonatophenyl)porphyrin, $(2)H_2$ (Chart I). The Fe(III) and Mn(III) complexes of $(1)H_2$ and $(2)H_2$ are abbreviated as $(1)Fe^{III}(X)_2$, $(1)Mn^{III}(X)_2$, $(2)Fe^{III}(X)_2$, and $(2)Mn^{III}(X)_2$, respectively, where X = H_2O and HO^- axial ligands.[6-8] These metal complexes do not form μ-oxo dimers nor do they aggregate due to steric hindrance by the eight ortho substituents (CH_3 or Cl). Due to the four *m*-sulfonate substituents (Chart I), $(1)Fe^{III}(X)_2$, $(1)Mn^{III}(X)_2$, $(2)Fe^{III}(X)_2$, and $(2)Mn^{III}(X)_2$ exist as mixtures of four atropisomers. The electronic environments of the metal centers of a set of atropisomers have been shown to be comparable.

Dynamics, Electrochemical, and Product Studies with $(1)Fe^{III}(X)_2$ and $(2)Fe^{III}(X)_2$

Chart I



Scheme I



Pertinent Information Obtained from Electrochemical Studies with $(1)Fe^{III}(X)_2$ in Water.[9] The pK_a and $E^{\circ\prime}$ values of Scheme I were calculated from appropriate Nernst–Clark plots of potentials (E_m) for

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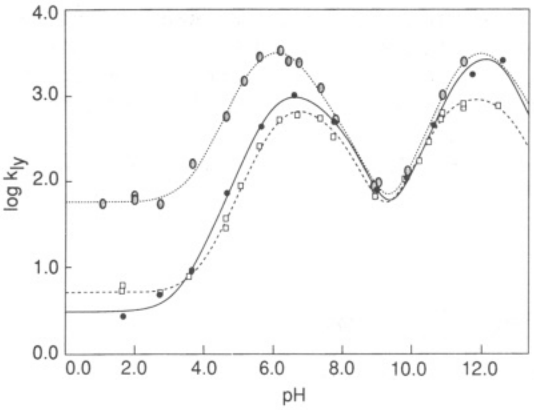

Figure 1. At any constant pH, the reaction of an iron(III) porphyrin with a hydroperoxide is characterized by an apparent second-order rate constant, k_{1y}. Plots of log k_{1y} vs pH are shown for the reaction of $(1)\mathrm{Fe^{III}(X)_2}$ with $\mathrm{(Ph)_2(CO_2Me)COOH}$ (···), $\mathrm{(Ph)(Me)_2COOH}$ (—), and $\mathrm{Me_3COOH}$ (- - -). The points are experimental (ref 11), and the lines fitting the points were generated from an equation (refs 10 and 12) derived from Scheme II with an assumption of steady state in the intermediates $\mathrm{IIH_2}^+$, IIH, and II^-.

stepwise $1e^-$ oxidation of $(1)\mathrm{Fe^{III}(X)_2}$ vs pH. Concerning the iron(IV) species: (i) the $\mathrm{p}K_{a1}$ and $\mathrm{p}K_{a2}$ values are lower than those for the iron(III) species due to the greater electropositive character of Fe(IV); (ii) the $E^{\circ\prime}$ potentials for $1e^-$ oxidation of the three Fe(IV) species are essentially identical; and (iii) the $\mathrm{p}K_{a1}$ values for $(1)\mathrm{Fe^{IV}(H_2O)_2}$ and $(1^{\bullet+})\mathrm{Fe^{IV}(H_2O)_2}$ are essentially the same as are the $\mathrm{p}K_{a2}$ values for $(1)\mathrm{Fe^{IV}(HO)(H_2O)}$ and $(1^{\bullet+})\mathrm{Fe^{IV}(HO)(H_2O)}$. These findings support a similar electron density of the Fe(IV) moieties in both Fe(IV) porphyrin and Fe(IV) porphyrin π-cation radical states with identical $\mathrm{H_2O}$ and $\mathrm{HO^-}$ ligation.

Kinetics of the Reactions of $(1)\mathrm{Fe^{III}(X)_2}$ and $(2)\mathrm{Fe^{III}(X)_2}$ with Alkyl Hydroperoxide and $\mathrm{H_2O_2}$.[6,7,10-12] Reactions were followed by use of 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) (ABTS) as a trap, which upon $1e^-$ oxidation provides $\mathrm{ABTS^{\bullet+}}$ (λ_{max} = 660 nm). Regardless of whether YO–OH bond scission is homolytic (eq 1a) or heterolytic (eq 2a), a single turnover of catalyst provides two $\mathrm{ABTS^{\bullet+}}$ species (eq 1b,c vs 2b). Reactions are first-order in (Porph)-$\mathrm{Fe^{III}(X)_2}$ and YOOH and zero-order in ABTS at constant pH values between pH 2 and 13 (eq 3).

$$(1)\mathrm{Fe^{III}(X)_2} + \mathrm{YOOH} \rightarrow (1)\mathrm{Fe^{IV}(X)_2} + \mathrm{YO^\bullet} \tag{1a}$$

$$(1)\mathrm{Fe^{IV}(X)_2} + \mathrm{ABTS} \rightarrow (1)\mathrm{Fe^{III}(X)_2} + \mathrm{ABTS^{\bullet+}} \tag{1b}$$

$$\mathrm{YO^\bullet} + \mathrm{ABTS} \rightarrow \mathrm{YOH} + \mathrm{ABTS^{\bullet+}} \tag{1c}$$

$$(1)\mathrm{Fe^{III}(X)_2} + \mathrm{YOOH} \rightarrow (1^{\bullet+})\mathrm{Fe^{IV}(X)_2} + \mathrm{YOH} \tag{2a}$$

$$(1^{\bullet+})\mathrm{Fe^{IV}(X)_2} + 2\mathrm{ABTS} \rightarrow (1)\mathrm{Fe^{III}(X)_2} + 2\mathrm{ABTS^{\bullet+}} \tag{2b}$$

$$-\mathrm{d[YOOH]}/\mathrm{d}t = k_{1y}[(1)\mathrm{Fe^{III}(X)_2}][\mathrm{YOOH}] \tag{3}$$

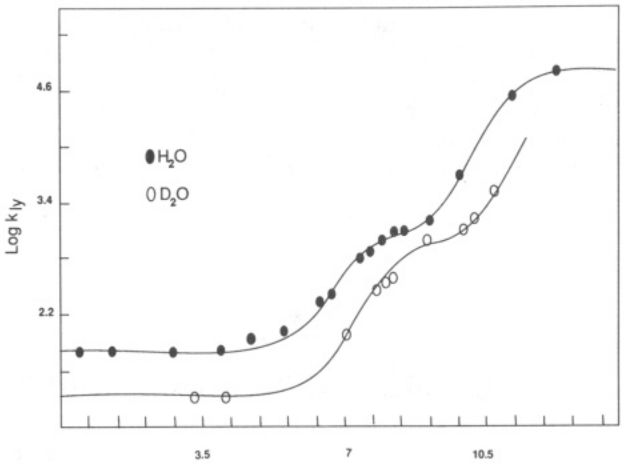

Figure 2. Plot of log k_{1y} vs pH(D) for the reaction of $(1)\mathrm{Fe^{III}(X)_2}$ with hydrogen peroxide in $\mathrm{H_2O}$ and $\mathrm{D_2O}$. The points are experimental (ref 7), and the lines were generated from an equation that assumes Scheme II and preequilibrium between starting states and the intermediates $\mathrm{IIH_2}^+$, IIH, and II^-. Values of solvent kinetic deuterium isotope effects ($k_{1y}{}^{\mathrm{H}}/k_{1y}{}^{\mathrm{D}}$) can be appreciated by a simple comparison of values of k_{1y} in $\mathrm{H_2O}$ and $\mathrm{D_2O}$ in the regions of independence of k_{1y} on pH(D). From ref 7.

The pH dependences of k_{1y} for the reactions of $(1)\mathrm{Fe^{III}(X)_2}$ with three alkyl hydroperoxide species are shown in Figure 1. Results with $(2)\mathrm{Fe^{III}(X)_2}$ are much the same. The pH dependence of k_{1y} for the reactions of $(2)\mathrm{Fe^{III}(X)_2}$ with hydrogen peroxide is shown in Figure 2. Results with $(1)\mathrm{Fe^{III}(X)_2}$ are much the same. Though the plots of Figures 1 and 2 differ in shape, the equations used to fit both were derived from Scheme II (by steady-state assumption in intermediates $\mathrm{IIH_2}^+$, IIH, and II^- for alkyl hydroperoxide and by preequilibrium assumption in the same intermediates for $\mathrm{H_2O_2}$).

The pH dependence of k_{1y} for alkyl hydroperoxide deserves additional comments. At low pH, k_{1y} is independent of acidity [$k_{1y} = k_1k_2/(k_2 + k_{-1})$, eq 4]. The plot of Figure 1 near neutrality results from the superimposition of the pH log k_{rate} profiles of the reactions of eqs 5 and 6. Equation 7 describes the pH dependence of k_{1y} at high pH. The ascending legs of the

$$[(1)\mathrm{Fe^{III}(H_2O)_2}]^+ \underset{k_{-1}}{\overset{k_1[\mathrm{YOOH}]}{\rightleftharpoons}} \mathrm{IIH_2}^+ \xrightarrow{k_2} \text{products} \tag{4}$$

$$[(1)\mathrm{Fe^{III}(H_2O)_2}]^+ \underset{k_{-1}}{\overset{k_1[\mathrm{YOOH}]}{\rightleftharpoons}} \mathrm{IIH_2}^+ \underset{+\mathrm{H^+}}{\overset{\overset{K_{a3}}{-\mathrm{H^+}}}{\rightleftharpoons}} \mathrm{IIH} \xrightarrow{k_4} \text{products} \tag{5}$$

$$(1)\mathrm{Fe^{III}(OH)(H_2O)} \underset{k_{-3}}{\overset{k_3[\mathrm{YOOH}]}{\rightleftharpoons}} \mathrm{IIH} \xrightarrow{k_4} \text{products} \tag{6}$$

$$[(1)\mathrm{Fe^{III}(OH)_2}]^- \underset{+\mathrm{HO^-}}{\overset{\overset{K_{\mathrm{D}}}{-\mathrm{HO^-}}}{\rightleftharpoons}} (1)\mathrm{Fe^{III}(OH)} \underset{k_{-5}}{\overset{k_5[\mathrm{YOO^-}]}{\rightleftharpoons}} \mathrm{II}^- \xrightarrow{k_6} \text{products} \tag{7}$$

"bell-shaped" plots are brought about by the increase of a reactant or intermediate concentration with increase in pH [IIH, eq 5; $(1)\mathrm{Fe^{III}(OH)(H_2O)}$, eq 6; $(1)\mathrm{Fe^{III}(OH)_2}$ + t-$\mathrm{BuOO^-}$, eq 7], whereas the descending portions are due to the concentrations of a reactant or intermediate {$[(1)\mathrm{Fe^{III}(H_2O)_2}]^+$, eq 5; IIH, eq 6; $(1)\mathrm{Fe^{III}(OH)}$, eq 7} becoming limited by increase in pH. The reactions of alkyl hydroperoxides with $(1)\mathrm{Fe^{III}(X)_2}$

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(8) Ultrafiltration is required to remove all traces of metal salts from metal(III) complexes of $(1)\mathrm{H_2}$ and $(2)\mathrm{H_2}$ and all water-soluble metalloporphyrins used for kinetic studies.

(9) Kaaret, T. W.; Zhang, G.-H.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 4652.

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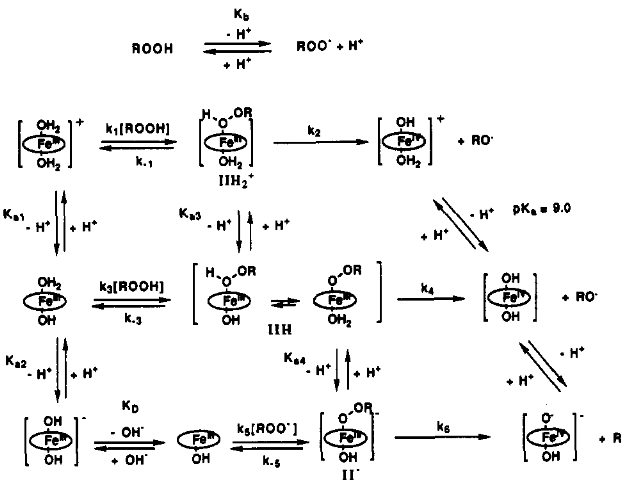
Scheme II



and $(2)Fe^{III}(X)_2$ are *not subject to general catalysis by oxygen or nitrogen (2,6-dimethylpyridines) acids nor bases.*

Consider the pH vs log k_{1y} profiles for reaction of H_2O_2 with $(1)Fe^{III}(X)_2$ and $(2)Fe^{III}(X)_2$ (Figure 2). The plateau regions at low, intermediate, and high pH relate to the rate-determining conversion of IIH_2^+, IIH, and II^- to products. As in the case of alkyl hydroperoxide, *general-acid or general-base catalysis is not observed with hydrogen peroxide in the presence of acids and oxygen bases.* In contrast to the case with alkyl hydroperoxide, *catalysis of the decomposition of* H_2O_2 *through* IIH_2^+ (eq 4) *is seen with buffers of 4-substituted 2,6-dimethylpyridines* (eq 8).[13] Decomposition of the intermediates IIH and II^- is not subject to catalysis by nitrogen bases or acids. A Bronsted plot of log k_{gb} (eq 8) for substituted 2,6-dimethylpyridines provides β value of ~0.1.

$$d[\text{product}]/dt = k_{gb}[(2)Fe^{III}(H_2O)(H_2O_2)][\text{nitrogen base}] \quad (8)$$

The dynamics for the reaction of the Fe(III) tetraphenylporphyrins with alkyl hydroperoxide-*d* and D_2O_2 have been investigated in D_2O. The deuterium *s*olvent *k*inetic *i*sotope *e*ffects (SKIEs) for reactions with both alkyl hydroperoxide and hydrogen peroxide are comparable. The SKIEs are k_2^H/k_2^D for decomposition of IIH_2^+ and k_4^H/k_4^D for decomposition of IIH. The finding that k_2^H/k_2^D values are >2 and <3 whereas k_4^H/k_4^D values are ~1.0 established that the *decomposition of* IIH_2^+ *represents general-base catalysis with water solvent as the catalyst,* whereas the reactions at intermediate pH (IIH decomposition) are not subject to such catalysis. Recall that 2,6-dimethylpyridine catalysis is important in the decomposition of IIH_2^+ but not IIH.

The kinetics for reaction of acyl hydroperoxide with $(1)Fe^{III}(X)_2$[14] and $(2)Fe^{III}(X)_2$[12] in aqueous solution have only been investigated between pH 2 and 7, to obviate hydrolysis of RCO_3H, and found to occur in the stopped-flow time range of milliseconds. The peracids employed were $PhCH_2CO_3H$, *n*-$C_5H_{11}CO_3H$, *p*-$NO_2C_6H_4CO_3H$, and *m*-$ClC_6H_4CO_3H$. *There could be detected no dependence of the second-order rate constants on pH or the concentrations of (oxygen base)/(oxygen acid) buffer.*

The Mechanism of Peroxide O–O Bond Cleavage as Shown by Products and Stoichiometries.[6,7,12,15,16] General agreement that the reactions of acyl hydroperoxide with Fe(III) porphyrins involve heterolytic O–O bond scission is based on bibenzyl not being a product (eq 9) when $PhCH_2CO_3H$ is used.

$$(\text{Porph})Fe^{III}(X)(PhCH_2CO_3) \rightarrow (\text{Porph})Fe^{IV}(X)_2 + PhCH_2CO_2^{\bullet} \quad (9)$$

$$PhCH_2CO_2^{\bullet} \rightarrow PhCH_2^{\bullet} + CO_2 \qquad \text{(very fast)}$$

$$2PhCH_2^{\bullet} \rightarrow (PhCH_2)_2$$

Homolysis of *t*-BuOOH and $Ph(CH_3)_2COOH$ (eq 1a) provides *t*-$BuO^{\bullet}$ and $Ph(CH_3)_2CO^{\bullet}$, respectively. Rate constants for fragmentation of such radicals (eq 10) are appreciable in water.[17] Acetone and acetophenone are

$$t\text{-}BuO^{\bullet} \rightarrow (CH_3)_2C{=}O + CH_3^{\bullet} \qquad k = 1.4 \times 10^6\ s^{-1} \quad (10)$$

products in reactions of *t*-BuOOH and $Ph(CH_3)_2COOH$, respectively, with $(1)Fe^{III}(X)_2$ and $(2)Fe^{III}(X)_2$. We have identified $CH_3^{\bullet}$ as an intermediate by spin trapping. The facile ($k = 2.3 \times 10^9\ M^{-1}\ s^{-1}$)[18] reaction of eq 11 is a portion of the so-called "rebound" mechanism for the hydroxylation of hydrocarbons by $(\text{Porph}^{\bullet+})Fe^{IV}(O)(L)$, cytochrome P-450,[19] chromate and permanganate.[20]

$$(\text{Porph})Fe^{III}(X)_2 + CH_3^{\bullet} \rightarrow (\text{Porph})Fe^{II}(X) + CH_3OH \quad (11)$$

From eqs 1a, 10, and 11 there follows eq 12 (where R = Ph and CH_3).

$$R(CH_3)_2COOH \xrightarrow{(1)Fe^{III}(X)_2} (R)(CH_3)C{=}O + CH_3OH \quad (12)$$

One-electron oxidation of ABTS by *t*-$BuO^{\bullet}$ is diffusion controlled in water.[17] Without ABTS, *t*-BuOOH yields $(CH_3)_2C{=}O$ (90%), CH_3OH (90%), and *t*-BuOH (15%). Therefore, *90% of t-BuOOH is converted to t-*$BuO^{\bullet}$*, which fragments to provide* $(CH_3)_2C{=}O$ *and*

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[13] The term $k_{gb}[(2)Fe^{III}(H_2O)(H_2O_2)][B:]$ is kinetically equivalent to the term $k_{ga}[(2)Fe^{III}(H_2O)(HO_2)][BH]$; B:/BH = 2,6-dimethylpyridine/2,6-dimethylpyridine·H^+. The choice of $k_{gb}[(2)Fe^{III}(H_2O)(H_2O_2)][B:]$ is based on the observation that the nonbuffer-catalyzed decomposition of $[(2)Fe^{III}(H_2O)(H_2O_2)]$ exhibits a solvent deuterium isotope effect of ~3 and that the solvent deuterium isotope for decomposition of $(2)Fe^{III}(H_2O)(HO_2)$ is ~1.2 (ref 3). In an earlier study of the reaction of $(1)Fe^{III}(X)_2$ with hydrogen peroxide (ref 2), it was concluded that both B: and BH species were catalysts. Recalculation of the experimental data by the procedure in ref 3 allows the assignment of a single term $k_{gb}[(1)Fe^{III}(H_2O)(H_2O_2)][B:]$.

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$CH_3^\bullet$. With increasing [ABTS], the yields of $(CH_3)_2C{=}O$ and *t*-BuOH approach 15% and 84%, respectively. Thus, *~15% of the t-BuO• intermediate cannot be trapped by ABTS, regardless of ABTS concentration.* Product yields are insensitive to pH (~4–11.5), buffer, ionic strength (with $NaNO_3$), or presence of O_2. Within limits of detection, *neither CH_4, C_2H_6, $(t\text{-}BuO)_2$, nor O_2 is a product.*

Lack of detection of $(t\text{-BuO})_2$ establishes eqs 13 and 14 to be of little consequence at the low [*t*-BuOOH] used. Dimerization of *t*-BuO• (eq 13) ($10^9\ M^{-1}\ s^{-1}$)[21]

$$2\,t\text{-BuO}^\bullet \rightarrow (t\text{-BuO})_2 \qquad (13)$$

$$2\,t\text{-BuOO}^\bullet \rightarrow (t\text{-BuOO})_2 \rightarrow (t\text{-BuO})_2 + O_2 \qquad (14)$$

must compete with its fragmentation (eq 10). The concentration of *t*-BuO•, at any time, is controlled by that of $(1)Fe^{III}(X)_2$ (~10^6 M), so bimolecular dimerization could not compete with unimolecular fragmentation. Equation 15 was also not competitive with unimolecular fragmentation of *t*-BuO• at the low [*t*-BuOOH] employed. Some *t*-BuOO• was detected by

$$t\text{-BuO}^\bullet + t\text{-BuOOH} \rightarrow t\text{-BuOH} + t\text{-BuOO}^\bullet \qquad (15)$$

spin trapping. This *t*-BuOO• is likely to result from the reaction of eq 16. Kinetic studies using high [*t*-BuOOH] are mechanistically useless because *t*-BuOOH becomes both the substrate and a trap for oxidation equivalents and much *t*-BuOO• is formed. The $(1)Fe^{IV}(X)_2$ and $(2)Fe^{IV}(X)_2$ intermediates (particularly the latter) accumulate at low [*t*-BuOOH] (vide infra).

$$(1)Fe^{IV}(X)_2 + t\text{-BuOOH} \rightarrow (1)Fe^{III}(X)_2 + t\text{-BuOO}^\bullet \qquad (16)$$

The 90% yields of $(CH_3)_2C{=}O$ and CH_3OH with *t*-BuOOH are not in accord with a heterolytic O–O bond cleavage. A heterolytic mechanism (Scheme III) can provide only 50% $(CH_3)_2C{=}O$ while homolysis (Scheme IV) provides $(CH_3)_2C{=}O$ and CH_3OH in 100% yield.

Scheme III

$$(1)Fe^{III}(X)_2 + t\text{-BuOOH} \rightarrow (1^{\bullet+})Fe^{IV}(X)_2 + t\text{-BuOH}$$

$$(1^{\bullet+})Fe^{IV}(X)_2 + t\text{-BuOOH} \rightarrow (1)Fe^{IV}(X)_2 + t\text{-BuOO}^\bullet$$

$$t\text{-BuOO}^\bullet \rightarrow t\text{-BuO}^\bullet + \tfrac{1}{2}O_2$$

$$t\text{-BuO}^\bullet \rightarrow (CH_3)_2C{=}O + CH_3^\bullet$$

$$(1)Fe^{IV}(X)_2 + CH_3^\bullet \rightarrow (1)Fe^{III}(X)_2 + CH_3OH$$

Scheme IV

$$(1)Fe^{III}(X)_2 + t\text{-BuOOH} \rightarrow (1)Fe^{IV}(X)_2 + t\text{-BuO}^\bullet$$

$$t\text{-BuO}^\bullet \rightarrow (CH_3)_2C{=}O + CH_3^\bullet$$

$$(1)Fe^{IV}(X)_2 + CH_3^\bullet \rightarrow (1)Fe^{III}(X)_2 + CH_3OH$$

Thus, *only a mechanism involving homolytic O–O bond scission can explain the yields of products in the reaction of $(1)Fe^{III}(X)_2$ and $(2)Fe^{III}(X)_2$ with t-BuOOH.*

In the reaction of hydrogen peroxide with $(1)Fe^{III}(X)_2$, rate-controlling O–O bond homolysis can be followed by a second $1e^-$ transfer (eq 17). The oxidation of the Fe(IV) species by HO•, within the solvent cage, is thermodynamically favored on the basis of reduction potentials (eq 18).[22] This is not true when HO• is replaced by alkyl-O•.

$$(1)Fe^{III}(H_2O)(H_2O_2) \rightarrow \{(1)Fe^{IV}(H_2O)(HO)\,{}^\bullet OH\} \qquad (17a)$$

$$[(1)Fe^{IV}(H_2O)(HO)\,{}^\bullet OH] \rightarrow (1^{\bullet+})Fe^{IV}(H_2O)(HO) + HO^- \qquad (17b)$$

$$(1)Fe^{IV}(H_2O)(HO) \rightarrow (1^{\bullet+})Fe^{IV}(H_2O)(HO) + e^- \qquad (+1.17\ V\ SCE) \qquad (18)$$

$$HO^- \rightarrow HO^\bullet + e^- \qquad (+1.65\ V\ SCE)$$

Identifiable Oxidation States of Fe Porphyrin.[12,14,16] Heterolytic O–O bond scission in reaction of acyl hydroperoxide with Fe(III) tetraphenylporphyrins yield Fe(IV) tetraphenylporphyrin π-cation radicals as immediate products. However, due to eq 19 (>$10^6\ M^{-1}\ s^{-1}$) only $(1)Fe^{IV}(X)_2$ and $(2)Fe^{IV}(X)_2$ are observed. In contrast, *t*-BuOOH, $(Ph)(Me)_2COOH$, and $(Ph)_2(CH_3OCO)COOH$ provide Fe(IV) species only in the presence of O_2. On saturating anaerobically in CO, a portion of the catalyst is trapped (>$10^6\ M^{-1}\ s^{-1}$)[23] as a tetraphenylporphyrin Fe(II) carbon monoxide complex (eq 20) during reaction with alkyl hydroperoxide. The 10% $(1)Fe^{II}(X)_2$ and 20% $(2)Fe^{II}(X)_2$ trapped as CO complexes underrepresents the fraction of catalyst that passes through the Fe(II) state as the reaction of eq 20 must compete with that of eq 21. Also, $(Porph)Fe^{II}(X)(CO)$ is subject to oxidation. Equation 21 accounts for the lack of observation of $(Porph)Fe^{IV}(X)_2$ in the absence of O_2 [$(Porph)Fe^{II}(X)_2$ is converted to $(Porph)Fe^{IV}(X)_2$ by O_2].[24] Formation of $(1)Fe^{II}(X)$ and $(2)Fe^{II}(X)$ can be attributed to the reaction of eq 22 (also see third reaction of Scheme IV).

$$(1^{\bullet+})Fe^{IV}(X)_2 + (1)Fe^{III}(X)_2 \rightarrow 2\,(1)Fe^{IV}(X)_2 \qquad (19)$$

$$(1)Fe^{II}(X)\ \text{or}\ (2)Fe^{II}(X) + CO \rightarrow (1)Fe^{II}(X)(CO)\ \text{or}\ (2)Fe^{II}(X)(CO) \qquad (20)$$

$$(Porph)Fe^{II}(X)_2 + (Porph)Fe^{IV}(X)_2 \rightarrow 2(Porph)Fe^{III}(X)_2 \qquad (21)$$

$$(1)Fe^{III}(H_2O)(OH) + CH_3^\bullet \rightarrow (1)Fe^{II}(H_2O) + CH_3OH \qquad (22)$$

Titration of $(1)Fe^{III}(X)_2$ (pH 5–7) and $(2)Fe^{III}(X)_2$ (pH 2–12) with *t*-BuOOH in the presence of O_2 yields $(1)Fe^{IV}(X)_2$ and $(2)Fe^{IV}(X)_2$, although such titration with H_2O_2 does not provide $(1)Fe^{IV}(X)_2$ or $(2)Fe^{IV}(X)_2$. [The $(2)Fe^{IV}(X)_2$ species is quite stable (detectable for 100 h at pH 6).] These observations are explained by the reduction of Fe^{IV} species by alkyl hydroperoxide and H_2O_2 (eqs 23 and 24, respectively) with the latter reaction being particularly rapid. The reduction of Fe(III) tetraphenylporphyrins by $O_2^{\bullet-}$ is diffusion controlled.[25]

$$(1)Fe^{IV}(X)_2 + t\text{-BuOOH} \rightarrow (1)Fe^{III}(X)_2 + t\text{-BuOO}^\bullet \qquad (23)$$

$$(1)Fe^{IV}(X)_2 + H_2O_2 \rightarrow [(1)Fe^{III}(X)_2O_2^{\bullet-}] \rightarrow (1)Fe^{II}(X)_2 + O_2 \qquad (24)$$

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The Influence of Hydroperoxide Substituents on Rate Constants.[11,14] Figure 1 shows that k_{ly} values for the reactions of $(CH_3)_3COOH$ and $(Ph)(CH_3)_2COOH$ with $(1)Fe^{III}(X)_2$ are virtually identical between pH 2 and 10 and differ only a little at high pH. Values of k_{ly} for $(Ph)(CH_3)_2COOH$ and $(Ph)_2(CH_3OCO)COOH$ are almost superimposable in the pH range 8–12. The greatest difference is at the plateau at low pH where k_{ly} $[=k_1k_2/(k_{-1} + k_2)]$ relates to the decomposition of the IIH_2^+ species (Scheme II). On heterolytic O–O bond scission (eq 2a) of $(R')(R'')(R''')COOH$, the leaving group is the substituted methanol $[(R')(R'')(R''')COH]$. The pK_a values for t-BuOH (16.7), $(Ph)(CH_3)_2COH$ (15.5), and $(Ph)_2(CH_3OCO)COH$ (11.1) can be calculated from the pK_a of CH_3OH (15.5),[26] the ρ^I value for the pK_a values of substituted methanols (−8.2 to −8.4),[27,28] and the σ_I values for CH_3 (−0.05), Ph (+0.1), and CO_2CH_3 (+0.34). A plot of log $k_1k_2/(k_{-1} + k_2)$ vs pK_a of $(R')(R'')(R''')COH$ has slope $\beta_{lg} \sim -0.22$. Complexing of $(R')(R'')(R''')COOH$ by $(1)Fe^{III}(H_2O)_2$ to provide the reactive species IIH_2^+ involves the terminal oxygen of the hydroperoxide. The pK_a's of the least electron deficient t-BuOOH and most electron deficient $(Ph)_2(CH_3OCO)COOH$ differ by about only 0.4 units. Therefore, the values of the equilibrium constants (k_1/k_{-1}) for complexation of alkyl hydroperoxide with $(Porph)Fe^{III}(X)_2$ are expected to be much the same for the three alkyl hydroperoxides, and the β_{lg} of −0.22 relates to the breakdown of the IIH_2^+ complexes. Analysis of the kinetic data for the decomposition of IIH complexes suggests that the β_{lg} value is even smaller. Thus, *there is a marked insensitivity to polar effects in the reaction of alkyl hydroperoxide with* $(1)Fe^{III}(X)_2$.

The best line in a plot of log of the pH-independent second-order rate constants for the reaction of p-$NO_2C_6H_4CO_3H$, m-$ClC_6H_4CO_3H$, $C_6H_5CH_2CO_3H$, and n-$C_5H_{11}CO_3H$ with $(1)Fe^{III}(X)_2$ vs the pK_a of the carboxylic acid leaving groups accommodates the log rate constant vs pK_a point for the very reactive alkyl hydroperoxide $(Ph)_2(CN)COOH$. The value of β_{lg} equals about −0.6. *The heterolytic O–O bond cleavage that accompanies the reaction of acyl hydroperoxides* [*and apparently* $(Ph)_2(CN)COOH$] *with* $(1)Fe^{III}(X)_2$ *is sensitive to polar effects of substituents.* Linear free energy plots of log k_{ly} vs pK_a of leaving groups which include acyl and alkyl hydroperoxide exhibit a marked break at pK_a 11, suggesting a change in mechanism.

The Influence of Porphyrin Structure. Across the entire pH range, k_{ly} values for the reactions of t-BuOOH with $(2)Fe^{III}(X)_2$ exceed the k_{ly} values for reaction with $(1)Fe^{III}(X)_2$ by, at most, only 2.5–3.8-fold.[10,12] Thus, replacing the eight o-CH_3 substituents of (1)-$Fe^{III}(X)_2$ by o-Cl substituents provides only a minor difference in reactivity toward t-BuOOH. It has been established that electronic substituent effects on the four phenyl moieties of tetraphenylporphyrins are not readily conveyed to the porphyrin ring due to the out-of-plane disposition of phenyl and porphyrin rings.[29]

The Influence of Fe(III) Ligation on Reactivity.[10] The reaction of Fe(III) with t-BuOOH in H_2O and D_2O in the pH(D) range 1–4 has been examined with ABTS being used as a trapping agent. As observed in reactions with Fe(III) porphyrins (eqs 1 and 2), two $ABTS^{\bullet+}$ are formed for each t-BuOOH consumed. The reaction of t-BuOOH with Fe^{III} in this pH(D) range is insensitive to pH, and $k_{ly}^H/k_{ly}^D = 2.0$. This similarity in the pH independence of rate constants and deuterium SKIEs for the reaction of Fe^{III} and $(1)Fe^{III}(H_2O)_2$ with t-BuOOH and the reaction of H_2O_2 with $(2)Fe^{III}(H_2O)_2$ suggests a common mechanism. The rate of reaction of $Fe^{III}(H_2O)_n$ with t-BuOOH is 5-fold greater than the rate for reaction of $(1)Fe^{III}(H_2O)_2$ with t-BuOOH. It is likely that *the sole kinetic advantage of ligation of Fe(III) by tetraphenylporphyrins* $(1)H_2$ *and* $(2)H_2$ *is to keep the* Fe^{III} *in solution at neutral and alkaline pH.*

Summation of Findings with $(1)Fe^{III}(X)_2$ and $(2)Fe^{III}(X)_2$. The Mechanism of Hydroperoxide Reactions

Oxidative oxygen transfer with acyl hydroperoxide involves heterolytic O–O bond scission (eq 2a). The following observations may be brought to bear on the reaction of alkyl hydroperoxides with $(1)Fe^{III}(X)_2$ and $(2)Fe^{III}(X)_2$: (i) reactions are not subject to general-acid nor general-base catalysis at any pH by either oxygen or nitrogen acids or bases; (ii) rate-determining decomposition of intermediate IIH_2^+ (Scheme II) displays a deuterium SKIE >2 whereas the decomposition of IIH or II^- does not; (iii) products and product stoichiometry are pH independent; (iv) product stoichiometry can only be explained via homolytic O–O bond cleavage (eq 1a); and (v) there is a marked insensitivity of rate constant to inductive withdrawal in the homolytic reaction of alkyl hydroperoxide as compared to the heterolytic reaction of acyl hydroperoxide. These findings point to the reactions of eqs 25–27 for alkyl hydroperoxide. The slow steps are a, and formation of the thermodynamic products (Scheme I) is via protonation (b). The reaction of eq 25a (but not 26a or 27a)

$$(Porph)Fe^{III}(YOOH)(H_2O) \rightarrow (Porph)Fe^{IV}(OH)(H_2O) + YO^{\bullet} \quad (25a)$$

$$(Porph)Fe^{IV}(OH)(H_2O) + H^+ \rightarrow (Porph)Fe^{IV}(H_2O)_2 \quad (25b)$$

$$(Porph)Fe^{III}(YOO)(H_2O) \rightarrow (Porph)Fe^{IV}(OH)_2 + YO^{\bullet} \quad (26a)$$

$$(Porph)Fe^{IV}(OH)_2 + H^+ \rightarrow (Porph)Fe^{IV}(OH)(H_2O) \quad (26b)$$

$$(Porph)Fe^{III}(YOO)(OH) \rightarrow (Porph)Fe^{IV}(O)(OH) + YO^{\bullet} \quad (27a)$$

$$(Porph)Fe^{IV}(O)(OH) + H^+ \rightarrow (Porph)Fe^{IV}(OH)_2 \quad (27b)$$

exhibits a deuterium SKIE indicating solvent general-base catalysis. We propose preassociation of H_2O with complexes YOOH (Chart II).

The following features characterize H_2O_2 reaction: (i) a deuterium SKIE >2 at low pH(D) (associated with decomposition of IIH_2^+, Scheme II); (ii) no catalysis by oxygen bases or acids; and (iii) general-base catalysis of decomposition of IIH_2^+ by 2,6-dimethylpyridines with Bronsted $\beta = 0.1$. Features i and ii are as seen with alkyl hydroperoxide. A $\beta = 0.1$ indicates an early transition state and little dependence of k_{gb} on the

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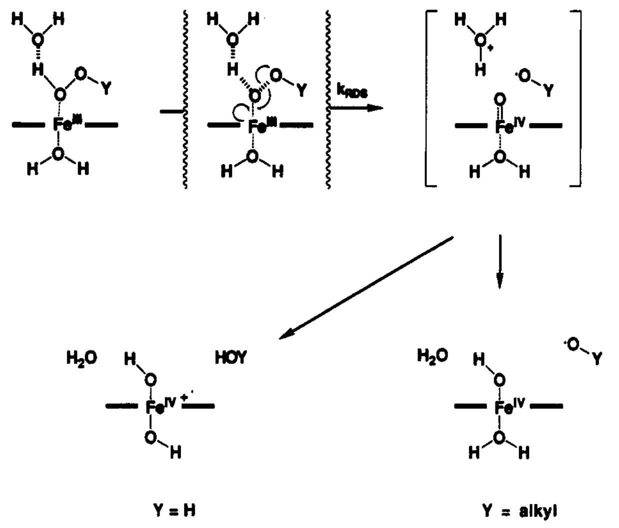
Chart II



Scheme V[a]

<u>Association</u>

$(2)Fe^{III}(H_2O)(X) + (CH_3)_3COOH \longrightarrow (2)Fe^{III}(X)((CH_3)_3COOH)$ (A)

<u>Caged Reactions</u>

$(2)Fe^{III}(X)((CH_3)_3COOH) \longrightarrow \wr (2)Fe^{IV}(O)(X), {}^{\bullet}OC(CH_3)_3 \wr$ (B)

$\wr (2)Fe^{IV}(O)(X), {}^{\bullet}OC(CH_3)_3 \wr \longrightarrow \wr (2)Fe^{IV}(O)(X), CH_3^{\bullet}, O{=}C(CH_3)_2 \wr$ (C)

$\wr (2)Fe^{IV}(O)(X), CH_3^{\bullet}, O{=}C(CH_3)_2 \wr \longrightarrow (2)Fe^{III}(H_2O)(X) + CH_3OH + (CH_3)_2CO$ (D)

<u>Non - Caged reactions</u>

$(2)Fe^{III}(X)((CH_3)_3COOH) \longrightarrow (2)Fe^{IV}(O)(X) + (CH_3)_3C{-}O^{\bullet}$ (E)

$(CH_3)_3C{-}O^{\bullet} \longrightarrow (CH_3)_2C{=}O + CH_3^{\bullet}$ (F)

$(2)Fe^{IV}(O)(X) + CH_3^{\bullet} \longrightarrow (2)Fe^{III}(H_2O)(X) + CH_3OH$ (G)

<u>Following reactions</u>

$(2)Fe^{III}(H_2O)(X) + CH_3^{\bullet} \longrightarrow (2)Fe^{II}(X)(H_2O) + CH_3OH$ (H)

$2 \times (2)Fe^{II}(H_2O)(X) + O_2 \longrightarrow (2)Fe^{III}(X){-}O{-}O{-}Fe^{III}(X)(2)$ (I)

$(2)Fe^{III}(X){-}O{-}O{-}Fe^{III}(X)(2) \longrightarrow 2\,(2)Fe^{IV}(O)(X)$ (J)

$(2)Fe^{II}(H_2O)(X) + (2)Fe^{IV}(O)(X) \longrightarrow 2\,(2)Fe^{III}(H_2O)(X)$ (K)

<u>Peroxide Oxidation</u>

$(2)Fe^{IV}(O)(X) + (CH_3)_3COOH \longrightarrow (2)Fe^{III}(H_2O)(X) + (CH_3)_3COO^{\bullet} + H^+$ (L)

$(CH_3)_3COO^{\bullet} \longrightarrow (CH_3)_3CO^{\bullet} + 1/2\,O_2$ (M)

$(CH_3)_3CO^{\bullet} \longrightarrow (CH_3)_2C{=}O + CH_3^{\bullet}$ (N)

[a] X = H_2O or OH^-. From ref 12.

basicity of the catalyst. This would explain the weak base H_2O (at 55 M) acting as a general-base catalyst (Chart II). The lack of catalysis by oxyanion bases for the reaction of H_2O_2 (and alkyl hydroperoxide) may then be explained by eq 28. The value of C may be

$$\log k_{gb} = \beta pK_a + C \tag{28}$$

greater for 2,6-dimethylpyridines than for carboxylates due to the greater solvation of carboxylates and/or to electrostatic repulsion of negatively charged carboxylates. Shielding by an electrostatic effect is a real possibility. The relationship of pK_{a1} of $(1)Fe^{III}(H_2O)_2$ to ionic strength (Guntelberg–Debye–Huckel expression)[30] suggests that the *m*-sulfonate substituents of $(1)Fe^{III}(X)_2$ invoke a charge of −2 at the Fe^{III} center.

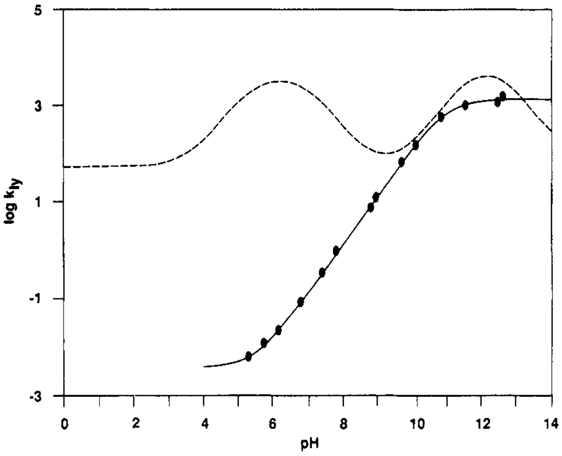
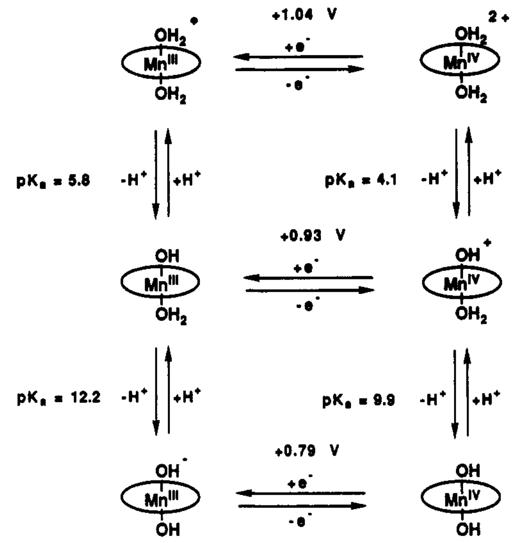


Figure 3. Comparison of the log k_{1y} vs pH profiles for the reaction of $(Ph)_2(CO_2Me)COOH$ with $(1)Fe^{III}(X)_2$ (dashed line without points, line copied from Figure 1) and with $(1)Mn^{III}(X)_2$. The dark points on the profile for $(1)Mn^{III}(X)_2$ are experimental, and the line was generated with the assumptions of Scheme VI and steady state in the intermediates IIH and II^-. The difference in the sensitivity of the apparent second-order rate constants (k_{1y}) for the reaction of iron(III) and manganese(III) porphyrins is directly related to the differences in the pH dependences of potentials for $1e^-$ oxidation of $(1)Fe^{III}(X)_2 \rightarrow (1)Fe^{IV}(X)_2$ and $1e^-$ oxidation of $(1)Mn^{III}(X)_2 \rightarrow (1)Mn^{IV}(X)_2$ (compare Schemes I and VII).

Scheme VI



Scheme V accommodates the findings of these studies for the reaction of $(1)Fe^{III}(X)_2$ and $(2)Fe^{III}(X)_2$ with *t*-BuOOH. The fragmentation of *t*-BuO• within the intimate pair $[(1)Fe^{IV}(X)_2\,t\text{-BuO}^{\bullet}]$ is proposed to account for the 15% of *t*-BuO• that cannot be trapped by ABTS.

Comparison of the Reactions of Mn^{III} and Fe^{III} Porphyrins with Hydroperoxides[31,32]

A number of interesting conclusions can be reached from a comparison of the log k_{1y} vs pH profiles for the reaction of $(1)Mn^{III}(X)_2$ and $(1)Fe^{III}(X)_2$ with $(Ph)_2(CH_3OCO)COOH$, *t*-BuOOH, $Ph(CH_3)_2COOH$, and

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H_2O_2. First, values of k_{1y} for $(1)Fe^{III}(X)_2$ and $(1)Mn^{III}(X)_2$ are comparable only at high pH (II^- decomposition). As the pH decreases, $(1)Fe^{III}(X)_2$ becomes a much better catalyst (Figure 3). These differences in pH dependences of k_{1y} relate to the pH dependences of $E°'$ potentials for $(1)Fe^{III}(X)_2$ (Scheme I) and $(1)Mn^{III}(X)_2$ (Scheme VI) species. Thus, $E°'$ for $1e^- + (1)Mn^{IV}(OH)_2 \rightarrow (1)Mn^{III}(OH)_2$ and $1e^- + (1)Fe^{IV}(OH)_2 \rightarrow (1)Fe^{III}(OH)_2$ differ by but 30 mV ($\Delta\Delta G° = 0.5$ kcal/mol), and k_{1y} for reactions of $(1)Mn^{III}(OH)_2$ and $(1)Fe^{III}(OH)_2$ with hydroperoxides are comparable (Figure 3). The $E°'$ for $1e^-$ reduction of $(1)Mn^{IV}(OH)(H_2O)$ exceeds that for $(1)Fe^{IV}(OH)(H_2O)$ by 70 mV ($\Delta\Delta G° = 1.6$ kcal/mol), whereas $E°'$ for $1e^-$ reduction of $(1)Mn^{IV}(H_2O)_2$ is more positive than that for $(1)Fe^{IV}(H_2O)_2$ by 130 mV ($\Delta\Delta G° = 3.0$ kcal/mol) and the reaction of $(1)Mn^{III}(H_2O)_2$ with hydroperoxide cannot be determined over spontaneous decomposition of hydroperoxide. General catalysis with $(Porph)Fe^{III}(X)_2$ catalysts is seen only with the IIH_2^+ species (Scheme II), and reactions through the IIH_2^+ species cannot be detected with $(Porph)Mn^{III}(X)_2$ catalysts. It is, therefore, not surprising to find that the reactions of hydroperoxides with $(1)Mn^{III}(X)_2$ and $(2)Mn^{III}(X)_2$ are not subject to general-acid/base catalysis by H_2O, (oxygen base)/(oxygen acid) pairs, not (nitrogen base)/(nitrogen acid) pairs at any pH.

The ratios of the rate constants, at a given pH, for the reactions of $(Ph)_2(CH_3OCO)COOH$, *t*-BuOOH, and $Ph(CH_3)_2COOH$ with $(1)Mn^{III}(X)_2$ and $(1)Fe^{III}(X)_2$ are comparable, suggesting hydroperoxide O–O bond homolysis. This is supported by the products obtained from reaction of *t*-BuOOH with $(1)Mn^{III}(X)_2$.

With imidazole, $(1)Mn^{III}(X)_2$ forms a monoligated species which reacts with alkyl hydroperoxides (eq 29) with a rate constant, k_{Im}, exceeding k_{1y} for the reaction with $(1)Mn^{III}(X)_2$ by 10–100-fold.

$$-d[YOOH]/dt = k_{Im}[(1)Mn^{III}(X)(\text{"imidazole"})][YOOH] \quad (29)$$

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Second-Moment Scaling and Covalent Crystal Structures

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In recent years the molecular orbital theory, originally developed to study small organic and inorganic molecules, has been successfully applied to the study of the infinite arrays of atoms found in extended solids.[1] In much of this work, arguments based on simple quantum mechanical models have been used to account for the structures and properties of these large and at times dauntingly complex chemical systems. Clear examples of this approach can be found in the work of J. K. Burdett, R. Hoffmann, and M. H. Whangbo. Their contributions have been reviewed recently.[1] The research reported in this Account is heavily influenced by the viewpoints of the aforementioned researchers.

In this Account we show how a modified Hückel theory allows one to make accurate predictions about the structures of covalently bonded extended solids. This modification was suggested independently in earlier work by D. G. Pettifor and R. Podloucky and in work by J. K. Burdett and me.[2] The modification itself has recently been investigated with renewed vigor by D. Pettifor's group and our own group at Michigan.[2] We call our method second-moment scaling. In order to understand the basis of second-moment scaling, we consider first the Hückel theory as it was originally applied to unsaturated hydrocarbons.

Hückel Theory

In Hückel theory one assumes that the principal force governing covalent bonds is the overlap of the respective atomic orbitals. Formally, this corresponds to solving the equation $H\psi = E\psi$, where the off-diagonal elements of the Hückel Hamiltonian, H_{ij}, follow the Wolfsberg–Helmholtz approximation,[3] $H_{ij} = KS_{ij}(H_{ii} + H_{jj})$, S_{ij} is the overlap integral, K is a proportionality constant, and the H_{ii} values are taken from compendiums of atomic parameters.[4] In this Account we will generally assume that the S_{ij} values depend on the orientations and distances of the respective atomic orbitals.

One of the best known applications of Hückel theory is for unsaturated hydrocarbon ring systems such as the cyclopropenium cation (1), benzene (2), and the hypothetical cyclobutadiene dianion **3**. It is well-known that the triangular form, 1, is stable only as a cation and the hexagonal form, 2, is stable as a neutral molecule, while

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