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A R T I C L E S

Metal [ML$_x$; M = Fe, Cu, Co, Mn]/Hydroperoxide-Induced Activation of Dioxygen for the Oxygenation of Hydrocarbons: Oxygenated Fenton Chemistry

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Earlier Accounts have discussed the electron-transfer reduction of dioxygen (O_2),[1] the formation and reactivity of superoxide ion ($O_2^{\bullet -}$),[2] and the nucleophilic character of hydroxide ion (HO^-, Lewis base and one-electron reductant).[3] The first two describe the propensity of nucleophilic $O_2^{\bullet -}$ to disproportionate via Brønsted acids (HA, including H_2O) to hydrogen peroxide (HOOH) and O_2. The one-electron-reductant character of HO^- that is discussed in the third led to the discovery of HO^--induced reduction of (a) O_2 to $O_2^{\bullet -}$,[4,5] (b) S_8 to $S_3^{\bullet -}$,[6] anthraquinone (AQ) to $AQ^{\bullet -}$,[7] and $(TPP)Fe^{III}(py)_2^+$ (TTP = tetraphenylporphyrin; py = pyridine) to $(TPP)Fe^{II}(py)_2$.[8] Thus, the present Account is the culminating chapter in a 40-year odyssey with the chemistry of O_2 and its reduction products ($O_2^{\bullet -}$, $HOO^{\bullet}$, HOOH, HOO^-, $HO^{\bullet}$, HO^-, H_2O).[9,10]

During the past five years we have come to appreciate that the primary reactivity of hydroperoxides (HOOR; R = H, *t*-Bu) is nucleophilic and is centered at the H−OOR bond. Thus, although the O−O bond energy of HOOH (ΔH_{DBE} = 51 kcal mol^{-1})[11] is much smaller than that for the H−OOH bond (89 kcal mol^{-1}) [and the bond energy for the *t*-BuO−OBu-*t* bond is even smaller (38 kcal mol^{-1})], the active center of hydroperoxides is the H−OOR bond as a nucleophile in relation to the Brønsted basicity of the solution matrix and the electrophilicity of the substrates. Hence, dialkyl peroxides (e.g., *t*-BuOOBu-*t*), in contrast to hydroperoxides (ROOH), are unreactive with electrophilic substrates [e.g., SO_2, $Fe^{II}Cl_2$ (Fenton chemistry), *n*-BuI, and HOCl ($^1O_2$ generation with HOOH)].

The nucleophilic character of hydroperoxides follows from three considerations:[3,12]

(a) Although HOO^- is a weaker Brønsted base [$(pK_a)_{HOOH} = 11.8)$] than HO^- [$(pK_a)_{H_2O} = 15.7$], it is a much stronger Lewis base [$(E_{ox})_{HOO^-} = +0.20$ V vs NHE vs $(E_{ox})_{HO^-} = +1.89$ V [the more negative, or less positive, the potential the more basic; with the electron (e^-) at the reduction potential of the solvent the ultimate Lewis base, −2.93 V vs NHE for H_2O]. Relative to the Lewis basicity of H_2O [$(E_{ox})_{H_2O,pH5} = +2.43$ V], that for HOOH [$(E_{ox})_{HOOH,pH5} = +1.01$ V] also is much greater.[12]

(b) Because all nucleophiles are dependent on solvent basicity, anhydrous HOOH in base-free media (e.g., dry MeCN) is unreactive (e.g., HOOH toward SO_2).

(c) The nucleophilicity (Nu) of a Lewis base (nucleophile, N) is equal to its oxidation potential [$(E_{ox})_N$] minus the bond-formation free energy [$(-\Delta G_{BF})_{N-E'}$ for the N−E′ bond] that results from its reaction with an electrophile [E; electrophilicity (El) equals $(E_{red})_E$]:

$$\mathrm{N} + \mathrm{E} \rightarrow \mathrm{N{-}E'}\ (+\mathrm{X}) \qquad -\Delta G_{\mathrm{reac}} \tag{1}$$

($-\Delta G_{BF}$) (for nucleophilic displacement reactions)

$$\mathrm{Nu} = (E_{\mathrm{ox}})_{\mathrm{N}} - [(-\Delta G_{\mathrm{BF}})_{\mathrm{N-E'}}/23.1\ \mathrm{kcal\ eV^{-1}\ mol^{-1}}] \tag{2}$$

$$\mathrm{El} = (E_{\mathrm{red}})_{\mathrm{E}} \tag{3}$$

The free energy for the reaction of a nucleophile with an electrophile (eq 1) can be determined with the

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relation

$$-\Delta G_{\mathrm{reac}} = (\mathrm{El} - \mathrm{Nu}) \times 23.1\ \mathrm{kcal\ mol^{-1}} = [(E_{\mathrm{red}})_{\mathrm{E}} - (E_{\mathrm{ox}})_{\mathrm{N}}]23.1 + (-\Delta G_{\mathrm{BF}})_{\mathrm{N-E'}} \qquad (4)$$

Fenton Chemistry. The traditional formulation of the one-to-one primary step for Fenton reagents [$\mathrm{Fe^{II}(OH_2)_6}^{2+}$/HOOH in H_2O at pH 2] depicts the production of free hydroxyl radical ($\mathrm{HO^\bullet}$):[13-17]

$$\mathrm{Fe^{II}(OH_2)_6}^{2+} + \mathrm{HOOH} \xrightarrow[\text{pH 2}]{k_5} (\mathrm{H_2O})_5{}^{2+}\mathrm{Fe^{III}OH} + \mathrm{H_2O} + \mathrm{HO^\bullet} \qquad (5)$$

$$k_5 = 41\ \mathrm{M^{-1}\ s^{-1}}$$

With this assumption, the subsequent reactions of Fenton reagents have been based on the primary chemistry of $\mathrm{HO^\bullet}$ (generated by radiolysis of H_2O or photolysis of HOOH),[18] which reacts with iron(II)

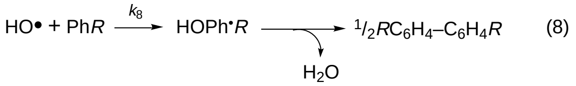
$$\mathrm{HO^\bullet} + \mathrm{Fe^{II}(OH_2)_6}^{2+} \xrightarrow{k_6} (\mathrm{H_2O})_5{}^{2+}\mathrm{Fe^{III}OH} + \mathrm{H_2O} \qquad (6)$$

$$k_6 = 3 \times 10^8\ \mathrm{M^{-1}\ s^{-1}}$$

and aliphatic (RH) and aromatic (PhR) hydrocarbons[18]

$$\mathrm{HO^\bullet} + \mathrm{RH} \xrightarrow{k_7} \mathrm{R^\bullet} + \mathrm{H_2O} \qquad (7)$$

$$k_7 = 1.1 \times 10^8\ \mathrm{M^{-1}\ s^{-1}}\ (\mathrm{CH_4}),\ 1.8 \times 10^9\ \mathrm{M^{-1}\ s^{-1}}\ (\mathrm{C_2H_6}),\ 3.7 \times 10^9\ \mathrm{M^{-1}\ s^{-1}}\ (\text{c-}\mathrm{C_5H_{10}},\ \text{cyclopentane})$$



$$\mathrm{HO^\bullet} + \mathrm{Ph}R \xrightarrow{k_8} \mathrm{HOPh^\bullet}R \xrightarrow[-\mathrm{H_2O}]{} {}^{1}\!/_{2}R\mathrm{C_6H_4{-}C_6H_4}R \qquad (8)$$

$$k_8 = 3.0 \times 10^9\ \mathrm{M^{-1}\ s^{-1}}\ (\mathrm{PhCH_3},\ 97\%\ \text{aryl addition}),\ 7.5 \times 10^9\ \mathrm{M^{-1}\ s^{-1}}\ (\mathrm{PhCH_2CH_3},\ 85\%\ \text{aryl addition})$$

The resultant carbon radical ($\mathrm{R^\bullet}$) can (a) dimerize to R_2, (b) react with a second $\mathrm{HO^\bullet}$ to form ROH, and (c) in the presence of air, couple to O_2 to form $\mathrm{ROO^\bullet}$ (unreactive with saturated hydrocarbons; dimerizes to [ROOOOR] → ROOR + O_2 (when R is tertiary), $k_{\mathrm{d}} = 10^3-10^7\ \mathrm{M^{-1}\ s^{-1}}$).[15]

The kinetics for substrate reactivities with Fenton-generated "$\mathrm{HO^\bullet}$" usually are determined via the relative rate of disappearance of iron(II) (eq 6) to that of the substrate.[13] However, if Fenton reagents generate reactive intermediates (**X**) other than free $\mathrm{HO^\bullet}$, the reactivity of **X** with iron(II) and organic substrates will be different and may not produce free carbon radicals ($\mathrm{R^\bullet}$).

In 1989 we discussed the characteristics of a Fenton reagent in an organic solvent matrix [$\mathrm{Fe^{II}(PA)_2}$ (PAH = picolinic acid)/HOOH/(2:1 pyridine (py)/acetic acid (HOAc) (mol/mol))].[19] With one-to-one Fe(II)/HOOH stoichiometry (under an Ar atmosphere) the system reacted with hydrocarbons in a manner similar to that of traditional aqueous Fenton reagents [c-$\mathrm{C_6H_{12}}$ → (c-$\mathrm{C_6H_{11}}$)pyl (pyl = pyridyl, $\mathrm{C_5H_4N}$) (or c-$\mathrm{C_6H_{11}OH}$)]. As with all Fenton systems, the dominant product is *not* bicyclohexyl (c-$\mathrm{C_6H_{11}}$)$_2$, which is the major product from the reaction of $\mathrm{HO^\bullet}$ with cyclohexane (c-$\mathrm{C_6H_{12}}$). Table 1 summarizes the product profiles for two substrates (c-$\mathrm{C_6H_{12}}$, $\mathrm{PhCH_2CH_3}$) when combined with 1:1 or 1:20 mole ratios of ML_x (M = Fe, Co, Cu)/HOOH in the absence and the presence of O_2 (1 atm).[20-22] The kinetic isotope effect for cyclohexane [KIE, $k_{\text{c}-\mathrm{C_6H_{12}}}/k_{\text{c}-\mathrm{C_6D_{12}}}$] in relation to its major products is listed for the Fenton reagents under various reaction conditions. In contrast to the 1:1 $\mathrm{Fe^{II}(PA)_2}$/HOOH system [dominant product cyclohexylpyridyl, (c-$\mathrm{C_6H_{11}}$)pyl], the 1:20 system yields c-$\mathrm{C_6H_{10}(O)}$ (cyclohexanone) as the dominant product plus some (c-$\mathrm{C_6H_{11}}$)pyl or c-$\mathrm{C_6H_{11}OH}$. With the 1:1 systems in the presence of O_2 (1 atm), ketonization of methylenic carbon centers is dominant [c-$\mathrm{C_6H_{12}}$ → c-$\mathrm{C_6H_{10}(O)}$].

These[20-22] and related studies of cobalt(II)[23] and copper(I)[24] Fenton systems have confirmed that the metal/HOOH ratio is decisive with respect to reactivity and product profile. Thus, 1:1 ML_x/HOOH combinations of $\mathrm{Fe^{II}(bpy)_2}^{2+}$, $\mathrm{Fe^{II}(OPPh_3)_4}^{2+}$, $\mathrm{Co^{II}(bpy)_2}^{2+}$, and $\mathrm{Cu^{I}\,(bpy)_2}^{+}$ are not reactive with c-$\mathrm{C_6H_{12}}$, but 1:20 combinations yield substantial quantities of c-$\mathrm{C_6H_{10}(O)}$ as the dominant product [their 1:1 combination in the presence of O_2 also transforms c-$\mathrm{C_6H_{12}}$ to c-$\mathrm{C_6H_{10}(O)}$]. Clearly the latter conditions produce a different reactive intermediate than that from the 1:1 combination of classical Fenton chemistry.

The product profiles for a Fenton reagent [$\mathrm{Fe^{II}(PA)_2}$/HOOH/(2:1 py/HOAc (mol/mol))] with several organic substrates (RH or ArH) have been compared with those for free hydroxyl radical ($\mathrm{HO^\bullet}$) in an aqueous matrix.[19-22,25] In no case is substrate dimer R−R (dominant product for $\mathrm{HO^\bullet}$/saturated hydrocarbon reactions in the *absence* of O_2) or ROOR (dominant product for $\mathrm{HO^\bullet}$/saturated hydrocarbon reactions in the *presence* of O_2) detected in the product solutions.[18]

In the *absence* of O_2, (a) the Fenton systems yield (i) R(pyl) (alkylpyridyl) or ROH from saturated hydrocarbons (RH), (ii) PhOH from PhH, (iii) 3-hydroxypyridyl [3-HO(pyl)] from py, and (iv) $\mathrm{PhC(O)CH_3}$ from $\mathrm{PhCH_2CH_3}$, and (b) $\mathrm{HO^\bullet}$ yields (i) $\mathrm{R^\bullet}$→ R−R from RH, (ii) $\mathrm{HOP^\bullet H}$ → Ph−Ph from PhH, (iii) hydroxyl adduct

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Table 1. Comparison of Hydrocarbon (RH) Reactivities for Classical and Oxygenated Fenton Reagents with Those for Free Hydroxyl Radical ($HO^•$)

	primary product (yield, mM ± 5%)[a]			
	$c\text{-}C_6H_{12}$		$PhCH_2CH_3$	
oxidant/solvent[b]		KIE[c]		$(k_{c-C_6H_{12}}/k_{PhCH_2CH_3})$[d]
$HO^•/H_2O$[e]	$c\text{-}C_6H_{11}^•$	1.0	$HOPh^•CH_2CH_3$	0.1
[1:1 $Fe^{II}(OH_2)_6^{2+}/HOOH]/H_2O$ (pH 2)[f]	$c\text{-}C_6H_{11}OH$	1.1	$PhCH(Me)OH$	
[1:1 $Fe^{II}(PA)_2/HOOH]/(py)_2HOAc$[g]	$(c\text{-}C_6H_{11})C_5H_4N$ (4)	1.7	$PhC(O)CH_3$ (2)	0.3
[1:1 $Fe^{II}(PA)_2/HOOH, O_2]/(py)_2HOAc$	$c\text{-}C_6H_{10}(O)$ (2)	2.1	$PhC(O)CH_3$ (4)	0.1
[1:20 $Fe^{II}(PA)_2/HOOH]/(py)_2HOAc$[h]	$c\text{-}C_6H_{10}(O)$ (27)	2.5	$PhC(O)CH_3$ (23)	0.2
	$(c\text{-}C_6H_{11})C_5H_4N$ (4)	1.7	$HOPhCH_2CH_3$ (5)	
[1:20 $Fe^{II}(PA)_2/HOOH, O_2]/(py)_2HOAc$	$c\text{-}C_6H_{10}(O)$ (15)	2.1	$PhC(O)CH_3$ (27)	0.1
[1:1 $Fe^{II}(PA)_2/HOOH]/MeCN$	$c\text{-}C_6H_{11}OH$ (3)		$PhC(O)CH_3$ (6)	0.1
[1:20 $Fe^{II}(PA)_2/HOOH]/MeCN$	$c\text{-}C_6H_{10}(O)$ (2)			
[1:20 $Fe^{III}Cl_3/HOOH]/MeCN$	$c\text{-}C_6H_{11}OH,Cl$ (24)	2.9	$PhCH(OH,Cl)CH_3$ (20)	0.2
	$c\text{-}C_6H_{10}(O)$ (8)	11	$PhC(O)CH_3$ (15)	0.1
[1:1 $Fe^{II}(bpy)_2^{2+}/HOOH]/MeCN$[i]	0			
[1:1 $Fe^{II}(bpy)_2^{2+}/HOOH, O_2]/MeCN$	$c\text{-}C_6H_{10}(O)$ (1)		$PhC(O)CH_3$ (2)	0.1
[1:20 $Fe^{II}(bpy)_2^{2+}/HOOH]/MeCN$[j]	$c\text{-}C_6H_{10}(O)$ (5)	4.0	$PhC(O)CH_3$ (14)	0.1
	$c\text{-}C_6H_{11}OH$ (4)	1.4		
[1:1:1 $Fe^{II}(OPPh_3)_4^{2+}/HOOH/HCl]/MeCN$[k]	$c\text{-}C_6H_{11}Cl$ (4)	1.8		
[1:20 $Fe^{II}(OPPh_3)_4^{2+}/HOOH]/MeCN$[j]	$c\text{-}C_6H_{11}OH$ (7)	1.9	$PhCH(Me)OH$ (21)	0.1
	$c\text{-}C_6H_{10}(O)$ (6)	>10	$PhC(O)CH_3$ (6)	0.2
[1:20 $Fe^{II}(O_2bpy)_2^{2+}/HOOH]/(MeCN)_4py$[j]	$c\text{-}C_6H_{10}(O)$ (12)	3.4	$PhC(O)CH_3$ (14)	0.2
[1:20 $Co^{II}(bpy)_2^{2+}/HOOH]/(MeCN)_4py$[j]	$c\text{-}C_6H_{10}(O)$ (20)	2.9	$PhC(O)CH_3$ (20)	0.2
[1:20 $Cu^{I}(bpy)_2^{+}/HOOH]/(MeCN)_4py$[l]	$c\text{-}C_6H_{10}(O)$ (12)	2.5	$PhC(O)CH_3$ (12)	0.2
[1:20 $Cu^{I}(bpy)_2^{+}/HOOH, O_2]/MeCN)_4py$[l]	$c\text{-}C_6H_{10}(O)$ (12)	2.4	$PhC(O)CH_3$ (12)	0.2

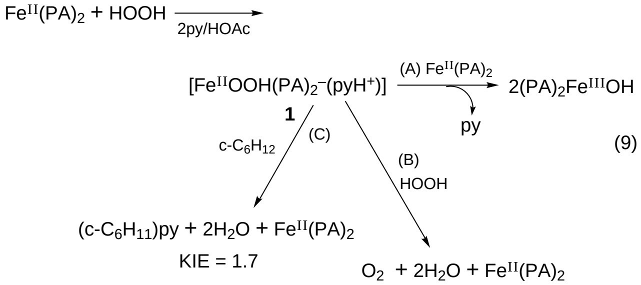
[a] Substrate and FeL_x combined in 3.5 mL of solvent, followed by the slow addition of HOOH (50%, in H_2O) to give 10 mM or 100 mM HOOH. The product solutions were analyzed by capillary-column gas chromatography and GC−MS after a reaction time of 3 h at 24 ± 2 °C. [b] Solvents: $(py)_2HOAc$, 2:1 mole ratio; $(MeCN)_4py$, 4:1 mole ratio. [c] Kinetic isotope effect, $k_{c-C_6H_{12}}/k_{c-C_6D_{12}}$. [d] Relative reactivity of $c\text{-}C_6H_{12}$ versus $PhCH_2CH_3$ (per CH_2 group). [e] Reference 18. [f] Reference 17. [g] 1:1 10 mM ML_x/10 mM HOOH. [h] 1:20 5 mM ML_x/100 mM HOOH. [i] 1:1 [$Fe^{II}(OPPh_3)_4^{2+}$, $Co^{II}(bpy)_2^{2+}$, and $Cu^{I}(bpy)_2^{2+}$]/HOOH also are unreactive with $c\text{-}C_6H_{12}$. [j] Reference 22. [k] Reference 36. [l] Reference 24.

$HOpy^•$ ($o/p = 2.0$) → pyl−pyl (2,2′-bipyridyl = bpy) from py, and (iv) $HOAr^•H \rightarrow Ar{-}Ar$ from $PhCH_2CH_3$. In the *presence* of O_2, the Fenton system yields ketones from the methylenic centers of hydrocarbons [RH; $c\text{-}C_6H_{12} \rightarrow c\text{-}C_6H_{10}(O)$], and $HO^•$ yields $ROO^• \rightarrow ROOR + O_2$ from RH.

Although $HO^•$ reacts with CH_4 ($k = 1.1 \times 10^8$ M^{-1} s^{-1}),[18] Fenton reagents are unreactive. Hydroxyl radical reacts with $Fe^{II}(bpy)_3^{2+}$ (bpy = 2,2′-bipyridyl) via aryl addition to give $(bpy)_2^{2+}Fe^{III}(bpy{-}OH)$ (bpy−OH = the hydroxyl derivative of bipyridyl) ($k = 9 \times 10^9$ M^{-1} s^{-1}),[18] but the 1:1 combination of $Fe^{II}(bpy)_2^{2+}$ and HOOH in MeCN is unreactive (Table 1).

In spite of the common belief that Fenton reagents ($Fe^{II}L_x$/HOOH) (L = ligand) produce free $HO^•$ (eq 5), recent studies[20,26,27] and the results of Table 1 provide clear evidence that free $HO^•$ is not the dominant reactant, and that with highly stabilized iron(II) complexes [Fe^{II}(diethylenetriaminepentaacetate) and Fe^{II}(EDTA)] a nucleophilic adduct {(EDTA)$Fe^{II}OOH$(H_3O^+)], **1**; “bound $HO^•$”} reacts directly with substrates.[27] Another study finds product profiles that are inconsistent with free $HO^•$ as the dominant reactive intermediate for a biological Fenton reagent.[28]

The 1:1 $Fe^{II}(PA)_2$/HOOH combination in 2:1 py/HOAc is an effective Fenton reagent for organic substrates,[19] and has reactivities and product profiles that are within the same mechanistic framework as those for traditional aqueous Fenton reagents.[13] Hence, the initial step is the reversible nucleophilic addition of HOOH to $Fe^{II}(PA)_2$ to give the primary reactive intermediate **1**,[20−22] which reacts with (a) excess $Fe^{II}(PA)_2$ via path A, (b) excess HOOH via path B to give O_2, and (c) excess $c\text{-}C_6H_{12}$ via path C to give ($c\text{-}C_6H_{11}$)pyl (cylohexylpyridyl) [aqueous Fenton systems produce $c\text{-}C_6H_{11}OH$ with a kinetic isotope effect (KIE) of 1.1,[17] and free $HO^•$ (pulse radiolysis) produces $c\text{-}C_6H_{11}^•$ with a KIE of 1.0].[18] Although radical traps (e.g., PhSeSePh, $BrCCl_3$, Me_2SO)[18] often are used to “prove” that free carbon radicals are formed by “free $HO^•$” from Fenton reagents, these also react with nonradicals (e.g., the intermediate of path C, eq 9; Table 1).



In summary, Fenton reagents *do not produce* (a) free $HO^•$, (b) free carbon radicals ($R^•$), or (c) aryl adducts ($HO{-}Ar^•$). Early work[29] has demonstrated that the primary chemistry of HOOH is nucleophilic addition, even in matrices as weakly basic as water at pH 2. Hence, Fenton reagents [reduced electrophilic transition-metal complexes ($Fe^{II}L_x$, $Cu^{I}L_x$, and $Co^{II}L_x$)] must have a primary step of nucleophilic addition to the metal center to give **1** (the reactive intermediate of Fenton reagents). The efficient and selective reactivity of **1** (Fenton chemistry) makes it a more reasonable

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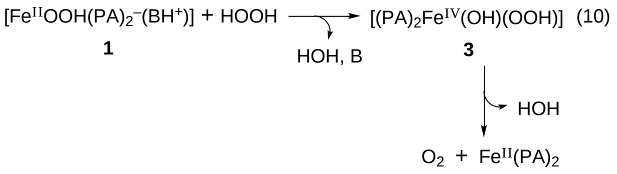
cytotoxic agent than free $HO^•$ within the oxy radical theory of aging and heart disease.[30,31]

Oxygenated Fenton Chemistry. When excess HOOH (or *t*-BuOOH) is combined with transition-metal metal complexes, it becomes the dominant substrate for the initially formed Fenton intermediate **1**, (eq 9). This reaction facilitates the disproportionation of hydroperoxides via species **3** (rapid in the case of HOOH and much slower in the case of *t*-BuOOH).[21,22,24]



$$\underset{\mathbf{1}}{[\mathrm{Fe^{II}OOH(PA)_2^-(BH^+)}]} + \mathrm{HOOH} \xrightarrow[\mathrm{HOH,\ B}]{} \underset{\mathbf{3}}{[\mathrm{(PA)_2Fe^{IV}(OH)(OOH)}]} \xrightarrow{\mathrm{HOH}} \mathrm{O_2 + Fe^{II}(PA)_2} \quad (10)$$

Note: Reactive intermediates (e.g., ***1*** *and* ***3****) are within square brackets because their formulations are hypothetical (although chemically reasonable, supported by electrochemical measurements,[21] and consistent with the product profiles). Also, the Roman numeral superscripts represent the number of covalent bonds (covalence), not the electronic charge of the metal.*[9]

Hence, a system with excess HOOH initially produces its own O_2 atmosphere. For example, the 5 mM $Fe^{II}(PA)_2$/100 mM HOOH/1 M $c\text{-}C_6H_{12}$ system yields 27 mM $c\text{-}C_6H_{10}(O)$ and 4 mM $(c\text{-}C_6H_{11})pyl$ (the respective KIE values are 2.5 and 1.7, Table 1). More than half of the HOOH is decomposed to O_2 (eq 10). When *t*-BuOOH is used in place of HOOH, the system yields 7 mM $c\text{-}C_6H_{11}OOBu\text{-}t$ (KIE = 8.4), 11 mM $c\text{-}C_6H_{10}(O)$ (KIE = 7.6), and 19 mM $(c\text{-}C_6H_{11})pyl$ (KIE = 4.6). Again, almost half of the *t*-BuOOH is decomposed to O_2 via eq 10. Combinations of $Fe^{II}(PA)_2$ and HOOH in the presence of O_2 transform $c\text{-}C_6H_{12}$ to $c\text{-}C_6H_{10}(O)$ (KIE = 2.1) as the only detectable product (Table 1).

Although 1:1 combinations of $[Fe^{II}(bpy)_2{}^{2+}$, $Fe^{II}(O_2\text{-}bpy)_2{}^{2+}$, $Fe^{II}(OPPh_3)_4{}^{2+}$, $Co^{II}(bpy)_2{}^{2+}$, or $Cu^{I}(bpy)_2{}^{+}]$/HOOH in the absence of O_2 are unreactive with $c\text{-}C_6H_{12}$, they readily react in its presence to produce $c\text{-}C_6H_{10}(O)$. When their ratio is 1:20 ML_x/HOOH, most of the HOOH is transformed to O_2 via eq 10, which results in analogous Fenton-induced activation of O_2 for reaction with $c\text{-}C_6H_{12}$ and $PhCH_2CH_3$ (Table 1).

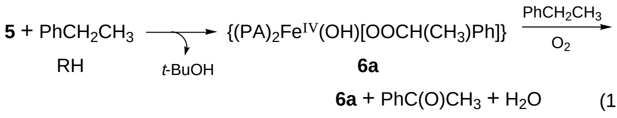
The 9 mM $Fe^{II}(PA)_2$/9 mM *t*-BuOOH system in the absence of O_2 and substrate reacts via a Fenton process (path A, eq 9) to give $(PA)_2Fe^{III}OH$. In the presence of O_2 (with or without 1 M $c\text{-}C_6H_{12}$) there is no evidence for free $Fe^{II}(PA)_2$ in the reaction matrix (no electrochemical oxidation, but a two-electron per iron irreversible reduction).[21] These observations are compelling evidence that species **1** (formed from *t*-BuOOH) produces an O_2 adduct (**5**) which reacts with

$$\mathbf{1} + O_2 \rightarrow \underset{\mathbf{5}}{[Fe^{III}(OOBu\text{-}t)(PA)_2{}^-(O_2)(pyH^+)]} \quad (11)$$

excess $c\text{-}C_6H_{12}$ to produce $c\text{-}C_6H_{10}(O)$. The dioxygen adduct **5** appears to be the steady state primary reactive intermediate rather than species **1** on the basis of (a) the enhanced KIE value for ketone formation {8.5 vs 4.6 [for formation of $(c\text{-}C_6H_{11})pyl$]}.

Table 2 summarizes the product profiles for several ML_x/*t*-BuOOH/O_2 (1 atm) combinations with $c\text{-}C_6H_{12}$, $c\text{-}C_6H_{10}$, and $PhCH_2CH_3$. In all cases the oxygen atoms that are incorporated in the product species come from O_2.[21]

The production of 16 mM PhC(O)Me by the 5 mM $Fe^{II}(PA)_2$/5 mM *t*-BuOOH/O_2/1 M $PhCH_2CH_3$ system[21] indicates that (a) most of the oxygen in the product comes from O_2 and (b) the reaction is initiated by species **5**, but (c) the catalytic cycle is carried by species **6** $[(PA)_2Fe^{IV}(OH)(OOR)]$ (3 times as much product as initial *t*-BuOOH).



$$\underset{\mathrm{RH}}{\mathbf{5} + \mathrm{PhCH_2CH_3}} \xrightarrow[t\text{-BuOH}]{} \underset{\mathbf{6a}}{\{\mathrm{(PA)_2Fe^{IV}(OH)[OOCH(CH_3)Ph]}\}} \xrightarrow[\mathrm{O_2}]{\mathrm{PhCH_2CH_3}} \mathbf{6a} + \mathrm{PhC(O)CH_3 + H_2O} \quad (12)$$

Cyclohexene $(c\text{-}C_6H_{10})$ has similar reactivity in the 10 mM $Fe^{II}(bpy)_2{}^{2+}$/20 mM *t*-BuOOH/O_2 system with at least 4 O_2 turnovers per *t*-BuOOH (Table 2).

Scheme 1 outlines a set of reaction paths that are consistent with the product profiles for Fenton chemistry [1:1 ML_x/HOOH (or *t*-BuOOH)] and its activation of O_2. The species **3** that is formed from *t*-BuOOH is long lived [decomposes slowly to O_2 and *t*-BuOH (eq 10)], and thereby can react with $c\text{-}C_6H_{12}$ to form $c\text{-}C_6H_{11}OOBu\text{-}t$. Because the KIE value for its formation is 8.4, the reactive intermediate must involve a pathway other than that for Fenton chemistry {path C [KIE = 4.6] (Table 2 and Scheme 1)}. The product is only observed with *t*-BuOOH (and not HOOH), which is consistent with the longer lifetime of **3** when formed from excess *t*-BuOOH.

With 20:1 HOOH(Bu-*t*)/$Fe^{II}(PA)_2$ ratios, substantial fractions of the HOOH(Bu-*t*) are decomposed to O_2 via species **3** (eq 10) (rapidly for HOOH and slowly for *t*-BuOOH). This internally generated O_2 in turn combines with **1** to form **5**, which accounts for the production of ketone (rather than ROOBu-*t*) in O_2-free systems of *t*-BuOOH. Electrochemical results[21] confirm that excess *t*-BuOOH with $Fe^{II}(PA)_2$ undergoes a sustained disproportionation to O_2 and formation of **5** [same reduction peak as for 1:1 $Fe^{II}(PA)_2$/*t*-BuOOH in the presence of O_2]. A similar set of observations and rationalizations has been presented for incorporation of O_2 derived from *t*-BuOOH in a Fe(III)/*t*-BuOOH/$c\text{-}C_8H_{16}$/(10:1 py/HOAc) system.[32]

Other iron(II) complexes $[Fe^{II}(bpy)_2{}^{2+}$, $Fe^{II}(OPPh_3)_4{}^{2+}$, $Fe^{II}Cl_2]$ undergo initial nucleophilic addition by HOOH to form an analogue of species **1**. For the $Fe^{II}L_x{}^{2+}$ complexes in pure MeCN this is a cationic reactive intermediate $[(L_x{}^+)Fe^{II}OOH(H_3O^+)]$ that reacts with excess HOOH to form **3**, which decomposes to O_2 and reacts with substrates. In the presence of O_2 **1** reacts with $c\text{-}C_6H_{12}$ to form **6b**, which reacts with a second $c\text{-}C_6H_{12}$ to produce $c\text{-}C_6H_{10}(O)$ and $c\text{-}C_6H_{11}OH$ (Scheme 1).

The presence of pyridine in the solvent matrix causes the primary reactant to be $[(L_x{}^+)Fe^{II}OOH(pyH^+)]$ (**1**), which reacts with aliphatic substrates (RH) to produce alkylpyridyls (Rpyl) via $[(L_x{}^{2+})Fe^{IV}(pyR)(OH)]$ (**2**). When oxidized metal complexes

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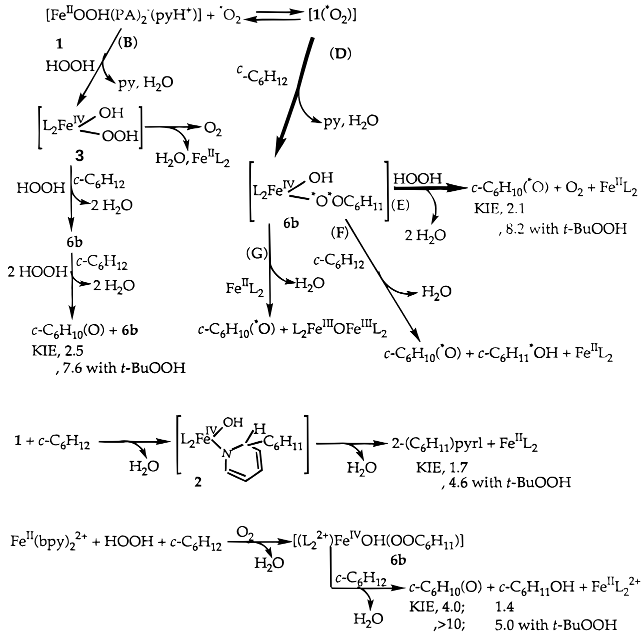
Table 2. Metal [ML_x; M = Fe, Cu, Co, Mn]/*t*-BuOOH-Induced Activation of O_2 (1 atm) for the Oxygenation of Cyclohexane (c-C_6H_{12}), Cyclohexene (c-C_6H_{10}), and Ethylbenzene ($PhCH_2CH_3$): Oxygenated Fenton Chemistry

			products (mM ± 5%)[a]									
			c-C_6H_{12} (1 M)			c-C_6H_{10} (1 M)				$PhCH_2CH_3$ (1 M)		
ML_x	[*t*-BuOOH] (mM)	solvent	c-C_6H_{10}(O)	c-C_6H_{11}OH	effncy[b] (%)	ketone c-C_6H_8(O)	alcohol c-C_6H_9OH	epoxide c-C_6H_{10}(O)	effncy[b] (%)	PhC(O)CH_3	PhCH (Me)OH	effncy[b] (%)
5 mM $Fe^{II}(PA)_2$	5	2:1 py/HOAc	4 [7.6][c]	0	80	15	0	0	300	16	0	320
10 mM $Fe^{II}(PA)_2$	20	2:1 py/HOAc	12	0	60	45	2	0	235	34	0	170
20 mM $Fe^{II}(PA)_2$[d]	20	2:1 py/HOAc	1	16[e] [4.6][c]	85	0	5[f]	0	25	13	3	80
10 mM $Fe^{II}(bpy)_2^{2+}$	20	MeCN	4 (0)[d] [>10][c]	5 (0)[d] [4.8][c]	45	86 (0)[d]	60 (2.5)[d]	0	730	35	11	230
10 mM $Fe^{II}(OPPh_3)_4^{2+}$	20	4:1 MeCN/py	4 [10][c]	6 [5.2][c]	50	60	35	0	475	38	16	270
10 mM $Fe^{III}Cl_3$	20	MeCN	5 [>10][c]	4 [4.3][c]	45	71	69	0	700	16	9	125
5 mM $Cu^{I}(bpy)_2^{2+}$	20	4:1 MeCN/py	6 [8.8][c]	0	30	25	0	0	125	28	0	140
5 mM $Mn^{III}(bpy)_2(OAc)_3$	20	MeCN	0	0	0	139 (26)[g]	41 (14)[g]	5 (1)[g]	925 (200)[g]	32	0	160
5 mM Mn^{III}(salen)(OAc)	20	MeCN	0	0	0	159 (29)[g] (5)[d]	48 (12)[g] (1)[d]	6 (1)[g]	1070 (210)[g]	40	0	200
5 mM Mn^{III}(salen)(OAc)	20	2:1 py/HOAc	0	0	0	22	19	18	295	14	7	105
20 mM Mn^{III}(salen)(OAc)	20	2:1 py/HOAc	0	0	0	24	25	30	395	23	9	160
10 mM $Mn^{III}(OPPh_3)_4(OAc)_3$	20	2:1 py/HOAc	0	0	0	111	12	3	630	25	0	125

[a] The product solutions were analyzed by capillary-column gas chromatography after a reaction time of 3 h at 24 ± 2 °C. [b] Efficiency for product formation; mM of products per mM of *t*-BuOOH (100% represents one product species per *t*-BuOOH). [c] Kinetic isotope effect, KIE = $k_{c-C_6H_{12}}/k_{c-C_6D_{12}}$. [d] Under an argon atmosphere. [e] The product was (c-C_6H_{11})py. [f] R−R dimer. [g] Under air (0.2 atm of O_2).

Scheme 1. Oxygenated Fenton Chemistry[a]



[a] Note: The formulations for reactive intermediates are within square brackets because they are short-lived and hypothetical.

[e.g., $Fe^{III}Cl_3$, $Fe^{III}(PA)_3$, $Cu^{II}(bpy)_2^{2+}$] are used, the initial event appears to be reduction by HOOH, e.g.[21,22]

$$2Fe^{III}Cl_3 + HOOH \rightarrow 2Fe^{II}Cl_2 + O_2 + 2HCl \quad (13)$$

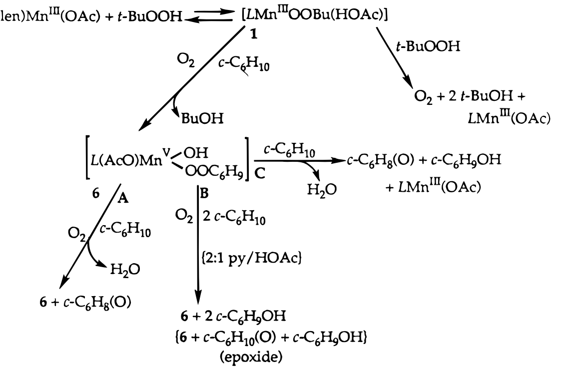
The $Fe^{II}Cl_2$ product in turn forms [$Fe^{II}OOH(Cl_2^-(H_3O^+)$] (**1**), which reacts with c-C_6H_{12} and $PhCH_2CH_3$ via [Cl_2-Fe^{IV}(OH)(R)] (**4**) to produce approximately 50:50 mixtures of ROH and RCl.[22] With HOOH and c-C_6H_{12} the KIE value for **1** is 2.9,[22] and with *t*-BuOOH it is 4.3. The porphyrin catalyst [$(Cl_8TPP)Fe^{II}$] reacts with *t*-BuOOH to form [$(Cl_8TPP)Fe^{II}$OOBu-*t*(H_3O^+)] (**1**), which reacts with c-C_6H_{12} via [$(Cl_8TPP)Fe^{IV}$(OH)(R)] (**4**) to produce ROH [KIE = 5.0].[21]

With excess HOOH or *t*-BuOOH the primary reactive intermediates **1** disproportionate HOOH (rapidly) and *t*-BuOOH (slowly) via path B and species **3** (Scheme 1). For the conditions of excess *t*-BuOOH and substrate (RH), species **3** reacts with RH to produce ROOBu-*t* (the KIE values for c-C_6H_{12} range from 5.4 to 8.4).[22] The reactivity parameters for [$Co^{II}(bpy)_2^{2+}$][22] and [$Cu^{I}(bpy)_2^{+}$][24] are similar and in accord with the proposition that all of these complexes activate HOOH initially via species **1**.

With excess O_2 most of the species **1** react with substrates (RH) via path D to form species **6**, which in the case of c-C_6H_{12}, reacts initially with either excess HOOH via path E or excess c-C_6H_{12} via path F, and finally with excess $Fe^{II}L_x$ via path G (Scheme 1). Thus, the various species **1** (Fenton intermediates) catalyze the incorporation of O_2 into the ketone and alcohol products [e.g., $Fe^{II}(bpy)_2^{2+}$/*t*-BuOOH, O_2/c-C_6H_{12}, Table 2].

$$2c\text{-}C_6H_{12} + O_2^* + t\text{-BuOOH} \xrightarrow{Fe^{II}L_x} c\text{-}C_6H_{10}(O^*) + c\text{-}C_6H_{11}O^*H + t\text{-BuOH} + H_2O \quad (14)$$

Scheme 2. $Mn^{III}L_x$/*t*-BuOOH-Induced Activation of O_2 for the Oxygenation of Olefins



Results[32] for a $Fe^{III}(NO_3)_3$/*t*-BuOOH/$^{18}O_2$/c-C_8H_{16} system in acetonitrile establish that the O atoms in the c-C_8H_{14}(O) and c-C_8H_{15}OH products are from O_2. This supports the stoichiometry of eq 14 [10:20 $Fe^{II}L_x$/*t*-BuOOH systems are 20–80% efficient (ketone per *t*-BuOOH, Table 2)].

For substrates with weak C–H bonds in their CH_2 groups [$PhCH_2CH_3$ and the allylic carbons of cyclohexene (c-C_6H_{10})], species **6** becomes a catalyst for the activation of O_2. When the reaction efficiency for such substrates is >100% (ketone per *t*-BuOOH, eq 14, Table 2), species **6** must activate O_2 for reaction with the substrate [turnovers per $Fe^{II}L_x \geq$ *t*-BuOOH/$Fe^{II}L_x$].

$$\underset{\mathbf{6c}}{[L_xFe^{IV}(OH)(OOC_6H_9)]} \xrightarrow[O_2]{\text{c-}C_6H_{10}} \mathbf{6c} + \underset{\text{2-cyclohexenone}}{\text{c-}C_6H_8(O)} + H_2O \quad (15)$$

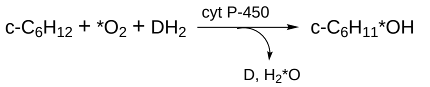
Hence, the 10 mM $Fe^{II}(bpy)_2^{2+}$/20 mM *t*-BuOOH/c-C_6H_{10} system has at least 3 O_2 turnovers via path E, which is similar to the 1.4 O_2 turovers per copper for the 5 mM $Cu^I(bpy)_2^+$/5 mM *t*-BuOOH/$PhCH_2CH_3$ system.[24] Likewise, the 10 mM $Fe^{II}(OPPh_3)_4^{2+}$/20 mM *t*-BuOOH/1 M c-C_6H_{10} system has almost 2 O_2 turnovers via eq 15.[21]

Perhaps the most dramatic example of oxygenated Fenton chemistry is the $Mn^{III}L_x$/*t*-BuOOH-induced activation of O_2 for reaction with c-C_6H_{10} (Table 2).[33] With (salen)Mn^{III}OAc (salen = the Schiff base of salicylaldehyde and ethylenediamine) in MeCN more that 10 product molecules are produced per *t*-BuOOH. When the solvent is changed to 2:1 py/HOAc, the overall efficiency is reduced by a factor of 3. However, whereas the ketone [c-C_6H_8(O), 2-cyclohexenone] is the dominant product in MeCN, in py/HOAc approximately equal amounts of epoxide, alcohol, and ketone are produced (about 4 product molecules per *t*-BuOOH). A set of reaction paths that are consistent with the product profiles and reaction dynamics are outlined in Scheme 2. Species **1** is unreactive with c-C_6H_{12}, and the system is ineffective when *t*-BuOOH is replaced by HOOH. The Mn(II) analogues of the complexes in Table 2 are not effective Fenton catalysts.

Thus, transition-metal complexes [ML_x = $Fe^{II}L_x$, $Mn^{III}L_x$, $Cu^I(bpy)_2^+$, and $Co^{II}(bpy)_2^{2+}$] undergo nucleophilic addition by hydroperoxides (HOOH or *t*-BuOOH) to form [$L_xMOOH(BH^+)$] (**1**), which in the presence of O_2 oxygenates hydrocarbons and related organic substrates via species **6** (oxygenated Fenton chemistry, Schemes 1 and 2).

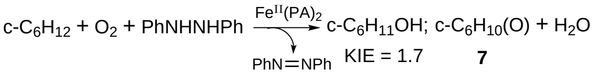
Relationship to Gif Chemistry. The substrate reactivities and product profiles with Gif chemistry[34] are closely similar to those with oxygenated Fenton chemistry. However, the proposed reactive intermediate is an iron(V)–oxene [L_xFe^V=O] species that results from a $Fe^{III}Cl_3$/HOOH combination rather than species **1(O_2)** [from an iron(II)/HOOH/O_2 combination]. We believe that [L_xFe^V=O] is an unreasonable candidate on several grounds: (a) In our experience the presence of excess HOOH in a py/HOAc matrix invaribly reduces iron(III) complexes [$Fe^{III}Cl_3$, $Fe^{III}(PA)_3$, $Fe^{III}(OAc)_3$] [in contrast, with excess $Fe^{II}(PA)_2$ relative to HOOH (at the end of a reaction cycle for Fenton chemistry and oxygenated Fenton chemistry) it is oxidized via path A of eq 9]. As a result, for 1:20 FeL_x/HOOH conditions the same substrate reactivites are observed independent of the valence state of the iron, and as the $Fe^{II}(PA)_2$/HOOH ratio becomes 2:1 all of the Fe(II) is oxidized. (b) The closest analogues to [L_xFe^V=O] are compound I of horseradish peroxidase [$(por^{\bullet +})Fe^{IV}$=O][9] (por = porphyrin) and the proposed intermediate [$(H_2O)Cl_3Fe^V$=O] from the 1:1 $Fe^{III}Cl_3$/HOOH combination (under base-free conditions],[35] both of which epoxidize olefins [e.g., cyclohexene (c-C_6H_{10})] (only detected product). In contrast **1(O_2)** [from $Fe^{II}(PA)_2$/HOOH/O_2] transforms c-C_6H_{10} to its ketone [c-C_6H_8(O)] as the only detected product. With *cis*-PhCH=CHPh the [$(H_2O)Cl_3Fe^V$=O] intermediate produces mainly epoxide (57% of product), while **1-(O_2)** produces mainly PhCH(O) and no epoxide. Thus, the product profiles for Gif chemistry are more consistent with oxygenated Fenton chemistry than those to be expected for the proposed reactive intermediate [L_xFe^V=O]. (c) Also, in our experience the [$(H_2O)Cl_3Fe^V$=O] intermediate from the 1:1 $Fe^{III}Cl_3$/HOOH combination is not formed in basic media (>100 mM H_2O or py in MeCN).[35]

Related Systems for O_2 Activation. Nature oxygenates hydrocarbon substrates via a combination of a monoxygenase catalyst (e.g., cytochrome P-450), O_2, and a reductase (*D*H_2, e.g., dihydroflavin).[36]



$$c\text{-}C_6H_{12} + {}^*O_2 + DH_2 \xrightarrow[D,\ H_2{}^*O]{\text{cyt P-450}} c\text{-}C_6H_{11}{}^*OH \quad (16)$$

In a recent study[37] we have been able to mimic this chemistry with a combination of a transition-metal complex, O_2, and a reductant, e.g.



$$c\text{-}C_6H_{12} + O_2 + PhNHNHPh \xrightarrow[PhN=NPh]{Fe^{II}(PA)_2} c\text{-}C_6H_{11}OH;\ c\text{-}C_6H_{10}(O) + H_2O \quad (17)$$

KIE = 1.7 **7**

The ratio of alcohol to ketone increases as the *D*H_2/$Fe^{II}(PA)_2$ ratio increases. In the interpretation of the results we have proposed a reactive intermediate for

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alcohol production [$(PA)_2Fe^{IV}(OOH)(DH)$, **1d**] that is closely similar to that for Fenton chemistry (**1**, eq 9); with c-C_6H_{12}, species **1d** and **1** have the same KIE value, 1.7. The production of ketone appears to involve species **1d**, O_2, and c-C_6H_{12} in a process that produces the same intermediate (**6b**) as oxygenated Fenton chemistry.

$$\begin{tikzcd} \mathbf{1d} + O_2 + c\text{-}C_6H_{12} \arrow[r, "D,\ H_2O"'] & \underset{\mathbf{6b}}{[(PA)_2Fe^{IV}(OH)(OOC_6H_{11})]} \arrow[d, "DH_2"] \\ & c\text{-}C_6H_{10}(O) + D + 2H_2O + Fe^{II}L_2 \\ & \text{KIE} = 7 \end{tikzcd} \qquad (18)$$

However, the oxygenated Fenton system has a KIE value of 2.1, which confirms that the rate-determining step involves the dioxygen adduct **1(O_2)** (eq 11 and Scheme 1), a more robust reactant than that of eq 18.

In another recent study[38] we discovered that coordinately unsaturated iron(II) complexes can activate O_2 for the oxygenation of cyclohexene (c-C_6H_{10}) to produce ketone, alcohol, and epoxide. Apparently in the initial step the substrate acts as a reductant (DH_2, eq 17) to form **11**

$$Fe^{II}(bpy)_2{}^{2+} + c\text{-}C_6H_{10} + O_2 \rightarrow \underset{\mathbf{11}}{[(L_2{}^{2+})Fe^{IV}(OOH)(C_6H_9)]} \qquad (19)$$

The latter in turn reacts with a second substrate and O_2, apparently to produce a reactive intermediate that is analogous to that for oxygenated Fenton chemistry.

$$\begin{tikzcd} \mathbf{11} + O_2 + c\text{-}C_6H_{10} \arrow[r] & \underset{\mathbf{6c}}{[(L_2{}^{2+})Fe^{IV}(OH)(OOC_6H_9)]} + c\text{-}C_6H_9OH \arrow[d, "c\text{-}C_6H_{10}"] \\ & c\text{-}C_6H_8(O) + c\text{-}C_6H_9OH + H_2O + Fe^{II}L_2{}^{2+} \end{tikzcd} \qquad (20)$$

Hence, three different O_2 activating systems appear to involve a common reactive intermediate (species **6**; eqs 15, 18, and 20) in their oxygenation of c-C_6H_{10}.

Chlorinated Fenton Chemistry. The preceding discussions confirm that the $Fe^{II}(bpy)_2{}^{2+}$ and $Fe^{II}(OPPh_3)_4{}^{2+}$ complexes are not effective 1:1 Fe(II)/HOOH Fenton reagents.[21,22] However, in the presence of HCl they [as well as $Fe^{II}(OH_2)_6{}^{2+}$ and $Fe^{III}Cl_3$] induce (a) the chlorohydroxylation of olefins, (b) the chlorination of saturated hydrocarbons (Table 1), (c) the epoxidation of *cis*-PhCH=CHPh, and (d) the hydroxylation of benzene (PhH).[39]

Because the dominant chemical characteristic of HOOH is nucleophilic addition (see preceding sections), this is a reasonable initial step in the iron(II)-induced activation of HOOH/HCl, with subsequent reaction of **1** with HCl to give the reactive intermediate (HCl acts as a H atom donor and reductant)

$$Fe^{II}(OPPh_3)_4{}^{2+} + HOOH \rightleftharpoons \underset{\mathbf{1}}{[L_4{}^{+}Fe^{II}OOH(H_3O^+)]} \xrightarrow[2H_2O]{HCl} \underset{\mathbf{8}}{[L_4{}^{2+}Fe^{IV}(OH)Cl]} \qquad (21)$$

which chlorohydroxylates olefins.

$$\mathbf{8} + c\text{-}C_6H_{10} \rightarrow c\text{-}C_6H_{10}(OH)Cl + Fe^{II}L_4{}^{2+} \qquad (22)$$

The reaction of species **8** with saturated hydrocarbons (c-C_6H_{12}) to give the chloro derivative as the only detectable product

$$\mathbf{8} + c\text{-}C_6H_{12} \rightarrow c\text{-}C_6H_{11}Cl + H_2O + Fe^{II}L_4{}^{2+} \quad \text{KIE} = 1.8 \qquad (23)$$

is consistent with its formulation in eq 21. Thus, the stabilized $HO^\bullet$ of **8** attacks a C−H bond of the substrate to give a carbon radical that is stabilized via bond formation with the iron center [$(L_4{}^{2+})Fe^{IV}(c\text{-}C_6H_{11})Cl$] prior to its collapse to product. This process is analogous to the proposed pathway for the hydroxylation of hydrocarbons by Fenton reagents.[20] In contrast, the $Fe^{III}Cl_3$/HOOH/MeCN system reacts with c-C_6H_{12} to yield approximately equal amounts of c-$C_6H_{11}OH$ and c-$C_6H_{11}Cl$ {apparently via an iron(V) reactive intermediate [$Cl_3Fe^V(OH)_2$] (**9**); KIE = 2.9 ± 0.3}.[22,35] The smaller kinetic-isotope-effect value for **8** indicates that it is significantly more reactive than species **9** [that is, the Fe−OH bond in **8** is weaker than that in **9** (lower valence electron density)]. Thus, the pathways of eqs 21−23 might be classified as *chlorinated Fenton chemistry*.

In the presence of *cis*-PhCH=CHPh, species **8** appears to act as an effective epoxidizing agent, possibly first being transformed to [$(L_4{}^{2+})Fe^{IV}(O)$] by elimination of HCl. Although the $Fe^{II}(OPPh_3)_4{}^{2+}$/(HOOH/HCl)/H_2O system hydroxylates benzene with an impressive 38% efficiency, essentially the same efficiency is achieved for systems without HCl.[25] Hence, species **1** (eq 16) appears to be the reactive intermediate.

Perhaps the most noteworthy attribute of the present systems is their ability to catalytically and selectively chlorohydroxylate olefins (via HOOH/HCl) without the use of HOCl or Cl_2. Also, effective chlorination of hydrocarbons by an HOOH/HCl combination in place of Cl_2 may have advantages in some syntheses. There should be substantial environmental benefits to the extent that HOOH/HCl can replace Cl_2/HOCl in synthetic and process chemistry.

A final point to ponder is whether the in vivo combination of dysfunctional iron, hydrogen peroxide, and HCl/Cl^- leads to the reactivity with organic substrates that is outlined in eq 21−23. The present results indicate that species **8** is much more reactive than HOCl (the biological oxidant from myeloperoxidase)[40] with organic substrates in an aqueous matrix. The uncontrolled formation of **8** in a biological matrix via chlorinated Fenton chemistry may be a more reasonable basis for the "oxy-radical" theory for aging and disease states (rather than the generation of free hydroxyl radicals).[30,31]

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Summary. Hydroperoxides (ROOH) in solution react as nucleophiles toward electrophilic substrates [SO_2; RX; HOCl; transition-metal complexes ($Fe^{II}L_x$, $Cu^{I}L_x$, $Mn^{III}L_x$, $Co^{II}L_x$)]. In contrast, dialkyl peroxides (ROOR) [with a weaker O−O bond (ΔH_{DBE} of about 40 kcal mol^{-1}) than that for ROOH (about 50 kcal mol^{-1})] are much less reactive and must be activated via homolytic dissociation of their O−O bond. Because all coordination complexes of metals (ML_x) have electrophilic metal centers with nucleophilic ligands, the primary chemistry of hydroperoxides toward them is nucleophilic addition and substitution. When the complex includes a reduced transition metal [e.g., $Fe^{II}(PA)_2$], nucleophilic addition yields the reactive intermediate for Fenton chemistry (**1**) and the precursor to the reactive intermediate for oxygenated Fenton chemistry [**1(O₂)**]. The nucleophilic HOOH adduct of $Fe^{II}(bpy)_2^{2+}$ {$[(bpy)_2^{+}]Fe^{II}OOH(H_3O^{+})$, **1**} reacts with 1 equiv of HCl to give the reactive intermediate for chlorinated Fenton chemistry {$[bpy)_2^{2+}]Fe^{IV}(OH)Cl$} (**8**). Each of these reactive intermediates (**1**, **1(O₂)**, **8**) includes a stabilized hydroxyl group (HO) that (a) is less reactive than free $HO^{\bullet}$ and (b) produces products from organic substrates via the internal formation of an intermediate with an iron−carbon bond (or an FeOO−carbon bond) that are different from those for free $HO^{\bullet}$. Thus, the metal-induced activation of hydroperoxides via nucleophilic addition (Fenton chemistry) is a highly disciplined “distant cousin” to the radical chemistry of free $HO^{\bullet}$. Hence, the specific reactivities of Fenton reactive intermediates [**1**, **1(O₂)**, **8**] are affected by the metal (Fe, Cu, Mn, or Co), the ligand, and the solution matrix. The more limited reactivity of Fenton systems is more than compensated for by their selectivity and unique ability to produce pure products.

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