

ARTICLES

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 (O₂),¹ the formation and reactivity of superoxide ion (O₂^{•-}),² and the nucleophilic character of hydroxide ion (HO⁻, Lewis base and one-electron reductant).³ The first two describe the propensity of nucleophilic O₂^{•-} to disproportionate via Brønsted acids (HA, including H₂O) to hydrogen peroxide (HOOH) and O₂. The one-electron-reductant character of HO⁻ that is discussed in the third led to the discovery of HO⁻-induced reduction of (a) O₂ to O₂^{•-},^{4,5} (b) S₈ to S₃^{•-},⁶ anthraquinone (AQ) to AQ^{•-},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 O₂ and its reduction products (O₂^{•-}, HOO•, HOOH, HOO⁻, HO•, HO⁻, H₂O).^{9,10}

During the past five years we have come to appreciate that the primary reactivity of hydroperoxides (HOOH; R = H, *t*-Bu) is nucleophilic and is centered at the H–OOR bond. Thus, although the O–O bond energy of HOOH ($\Delta H_{\text{DBE}} = 51 \text{ kcal mol}^{-1}$)¹¹ is much smaller than that for the H–OOH bond (89 kcal mol⁻¹) [and the bond energy for the *t*-BuO–O*t*-Bu 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*-BuOO*t*-Bu), in contrast to hydroperoxides (ROOH), are unreactive with electrophilic substrates [e.g., SO₂, Fe^{II}Cl₂ (Fenton chemistry), *n*-BuI, and HOCl (¹O₂ generation with HOOH)].

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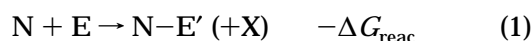
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The nucleophilic character of hydroperoxides follows from three considerations:^{3,12}

(a) Although HOO⁻ is a weaker Brønsted base [(p*K*_a)_{HOOH} = 11.8] than HO⁻ [(p*K*_a)_{H₂O} = 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 H₂O]. Relative to the Lewis basicity of H₂O [(*E*_{ox})_{H₂O}, 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 SO₂).

(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 [(- ΔG_{BF})_{N–E'} for the N–E' bond] that results from its reaction with an electrophile [E; electrophilicity (El) equals (*E*_{red})_E]:



(- ΔG_{BF}) (for nucleophilic displacement reactions)

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

$$\text{El} = (E_{\text{red}})_{\text{E}} \quad (3)$$

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

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

oxidant/solvent ^b	primary product (yield, mM ± 5%) ^a			
	c-C ₆ H ₁₂		PhCH ₂ CH ₃	
	KIE ^c			(<i>k</i> _{c-C₆H₁₂} / <i>k</i> _{PhCH₂CH₃}) ^d
HO [•] /H ₂ O ^e	c-C ₆ H ₁₁ [•]	1.0	HOPh [•] CH ₂ CH ₃	0.1
[1:1 Fe ^{II} (OH ₂) ₆ ²⁺ /HOOH]/H ₂ O (pH 2) ^f	c-C ₆ H ₁₁ OH	1.1	PhCH(Me)OH	
[1:1 Fe ^{II} (PA) ₂ /HOOH]/(py) ₂ HOAc ^g	(c-C ₆ H ₁₁)C ₅ H ₄ N (4)	1.7	PhC(O)CH ₃ (2)	0.3
[1:1 Fe ^{II} (PA) ₂ /HOOH, O ₂]/(py) ₂ HOAc	c-C ₆ H ₁₀ (O) (2)	2.1	PhC(O)CH ₃ (4)	0.1
[1:20 Fe ^{II} (PA) ₂ /HOOH]/(py) ₂ HOAc ^h	c-C ₆ H ₁₀ (O) (27)	2.5	PhC(O)CH ₃ (23)	0.2
	(c-C ₆ H ₁₁)C ₅ H ₄ N (4)	1.7	HOPhCH ₂ CH ₃ (5)	
[1:20 Fe ^{II} (PA) ₂ /HOOH, O ₂]/(py) ₂ HOAc	c-C ₆ H ₁₀ (O) (15)	2.1	PhC(O)CH ₃ (27)	0.1
[1:1 Fe ^{II} (PA) ₂ /HOOH]/MeCN	c-C ₆ H ₁₁ OH (3)		PhC(O)CH ₃ (6)	0.1
[1:20 Fe ^{II} (PA) ₂ /HOOH]/MeCN	c-C ₆ H ₁₀ (O) (2)			
[1:20 Fe ^{III} Cl ₃ /HOOH]/MeCN	c-C ₆ H ₁₁ OH, Cl (24)	2.9	PhCH(OH, Cl)CH ₃ (20)	0.2
	c-C ₆ H 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-C ₆ H ₁₀ (O) (1)		PhC(O)CH ₃ (2)	0.1
[1:20 Fe ^{II} (bpy) ₂ ²⁺ /HOOH]/MeCN ^j	c-C ₆ H ₁₀ (O) (5)	4.0	PhC(O)CH ₃ (14)	0.1
	c-C ₆ H ₁₁ OH (4)	1.4		
[1:1:1 Fe ^{II} (OPPh ₃) ₄ ²⁺ /HOOH/HCl]/MeCN ^k	c-C ₆ H ₁₁ Cl (4)	1.8		
[1:20 Fe ^{II} (OPPh ₃) ₄ ²⁺ /HOOH]/MeCN ^j	c-C ₆ H ₁₁ OH (7)	1.9	PhCH(Me)OH (21)	0.1
	c-C ₆ H ₁₀ (O) (6)	> 10	PhC(O)CH ₃ (6)	0.2
[1:20 Fe ^{II} (O ₂ bpy) ₂ ²⁺ /HOOH]/(MeCN) ₄ py ^j	c-C ₆ H ₁₀ (O) (12)	3.4	PhC(O)CH ₃ (14)	0.2
[1:20 Co ^{II} (bpy) ₂ ²⁺ /HOOH]/(MeCN) ₄ py ^j	c-C ₆ H ₁₀ (O) (20)	2.9	PhC(O)CH ₃ (20)	0.2
[1:20 Cu ^I (bpy) ₂ ²⁺ /HOOH]/(MeCN) ₄ py ^j	c-C ₆ H ₁₀ (O) (12)	2.5	PhC(O)CH ₃ (12)	0.2
[1:20 Cu ^I (bpy) ₂ ²⁺ /HOOH, O ₂]/(MeCN) ₄ py ^j	c-C ₆ H ₁₀ (O) (12)	2.4	PhC(O)CH ₃ (12)	0.2

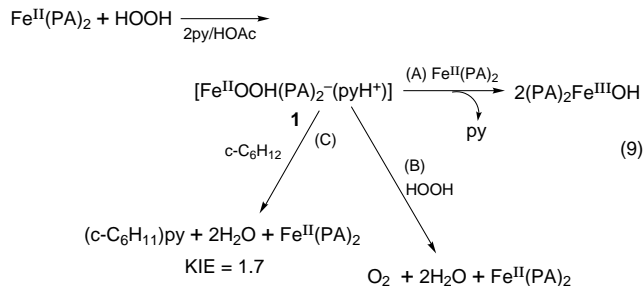
^a Substrate and FeL_x combined in 3.5 mL of solvent, followed by the slow addition of HOOH (50%, in H₂O) to give 10 mM or 100 mM HOOH. The product solutions were analyzed by capillary-column gas chromatography and GC-MS after a reaction time of 3 h at 24 ± 2 °C. ^b Solvents: (py)₂HOAc, 2:1 mole ratio; (MeCN)₄py, 4:1 mole ratio. ^c Kinetic isotope effect, *k*_{c-C₆H₁₂}/*k*_{c-C₆D₁₂}. ^d Relative reactivity of c-C₆H₁₂ versus PhCH₂CH₃ (per CH₂ 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}(OPPh₃)₄²⁺, Co^{II}(bpy)₂²⁺, and Cu^I(bpy)₂²⁺]/HOOH also are unreactive with c-C₆H₁₂. ^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 → Ar-Ar from PhCH₂CH₃. In the presence of O₂, the Fenton system yields ketones from the methylenic centers of hydrocarbons [RH; c-C₆H₁₂ → c-C₆H₁₀(O)], and HO[•] yields ROO[•] → ROOR + O₂ from RH.

Although HO[•] reacts with CH₄ (*k* = 1.1 × 10⁸ M⁻¹ s⁻¹),¹⁸ Fenton reagents are unreactive. Hydroxyl radical reacts with Fe^{II}(bpy)₃²⁺ (bpy = 2,2'-bipyridyl) via aryl addition to give (bpy)₂²⁺Fe^{III}(bpy-OH) (bpy-OH = the hydroxyl derivative of bipyridyl) (*k* = 9 × 10⁹ M⁻¹ s⁻¹),¹⁸ but the 1:1 combination of Fe^{II}(bpy)₂²⁺ 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-(H₃O⁺), **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 O₂, and (c) excess c-C₆H₁₂ via path C to give (c-C₆H₁₁)pyl (cylohexylpyridyl) [aqueous Fenton systems produce c-C₆H₁₁OH with a kinetic isotope effect (KIE)



of 1.1,¹⁷ and free HO[•] (pulse radiolysis) produces c-C₆H₁₁[•] with a KIE of 1.0].¹⁸ Although radical traps (e.g., PhSeSePh, BrCCl₃, Me₂SO)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 work²⁹ 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^IL_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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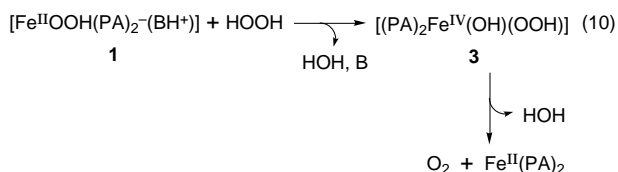
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cytotoxic agent than free HO• within the oxy radical theory of aging and heart disease.^{30,31}

Oxygenated Fenton Chemistry. When excess HOOH (or *t*-BuOOH) is combined with transition-metal 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}

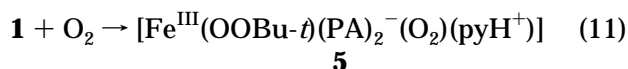


*Note: Reactive intermediates (e.g., **1** and **3**) are within square brackets because their formulations are hypothetical (although chemically reasonable, supported by electrochemical measurements,²¹ and consistent with the product profiles). Also, the Roman numeral superscripts represent the number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

Hence, a system with excess HOOH initially produces its own O₂ atmosphere. For example, the 5 mM Fe^{II}(PA)₂/100 mM HOOH/1 M *c*-C₆H₁₂ system yields 27 mM *c*-C₆H₁₀(O) and 4 mM (*c*-C₆H₁₁)pyl (the respective KIE values are 2.5 and 1.7, Table 1). More than half of the HOOH is decomposed to O₂ (eq 10). When *t*-BuOOH is used in place of HOOH, the system yields 7 mM *c*-C₆H₁₁OOBu-*t* (KIE = 8.4), 11 mM *c*-C₆H₁₀(O) (KIE = 7.6), and 19 mM (*c*-C₆H₁₁)pyl (KIE = 4.6). Again, almost half of the *t*-BuOOH is decomposed to O₂ via eq 10. Combinations of Fe^{II}(PA)₂ and HOOH in the presence of O₂ transform *c*-C₆H₁₂ to *c*-C₆H₁₀(O) (KIE = 2.1) as the only detectable product (Table 1).

Although 1:1 combinations of [Fe^{II}(bpy)₂]²⁺, Fe^{II}(O₂-bpy)₂²⁺, Fe^{II}(OPPh₃)₄²⁺, Co^{II}(bpy)₂²⁺, or Cu^I(bpy)₂²⁺/HOOH in the absence of O₂ are unreactive with *c*-C₆H₁₂, they readily react in its presence to produce *c*-C₆H₁₀(O). When their ratio is 1:20 ML_x/HOOH, most of the HOOH is transformed to O₂ via eq 10, which results in analogous Fenton-induced activation of O₂ for reaction with *c*-C₆H₁₂ and PhCH₂CH₃ (Table 1).

The 9 mM Fe^{II}(PA)₂/9 mM *t*-BuOOH system in the absence of O₂ and substrate reacts via a Fenton process (path A, eq 9) to give (PA)₂Fe^{III}OH. In the presence of O₂ (with or without 1 M *c*-C₆H₁₂) 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 O₂ adduct (**5**) which reacts with

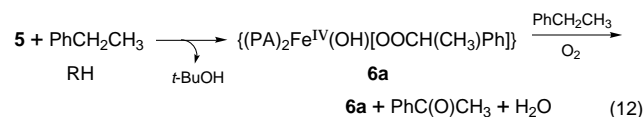


excess *c*-C₆H₁₂ to produce *c*-C₆H₁₀(O). The dioxygen adduct **5** appears to be the steady state primary reactive intermediate rather than species **1** on the

basis of (a) the enhanced KIE value for ketone formation {8.5 vs 4.6 [for formation of (*c*-C₆H₁₁)pyl]}.

Table 2 summarizes the product profiles for several ML_x/*t*-BuOOH/O₂ (1 atm) combinations with *c*-C₆H₁₂, *c*-C₆H₁₀, and PhCH₂CH₃. In all cases the oxygen atoms that are incorporated in the product species come from O₂.²¹

The production of 16 mM PhC(O)Me by the 5 mM Fe^{II}(PA)₂/5 mM *t*-BuOOH/O₂/1 M PhCH₂CH₃ system²¹ indicates that (a) most of the oxygen in the product comes from O₂ 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).



Cyclohexene (*c*-C₆H₁₀) has similar reactivity in the 10 mM Fe^{II}(bpy)₂²⁺/20 mM *t*-BuOOH/O₂ system with at least 4 O₂ 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 O₂. The species **3** that is formed from *t*-BuOOH is long lived [decomposes slowly to O₂ and *t*-BuOH (eq 10)], and thereby can react with *c*-C₆H₁₂ to form *c*-C₆H₁₁OOBu-*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 O₂ via species **3** (eq 10) (rapidly for HOOH and slowly for *t*-BuOOH). This internally generated O₂ in turn combines with **1** to form **5**, which accounts for the production of ketone (rather than ROOBu-*t*) in O₂-free systems of *t*-BuOOH. Electrochemical results²¹ confirm that excess *t*-BuOOH with Fe^{II}(PA)₂ undergoes a sustained disproportionation to O₂ and formation of **5** [same reduction peak as for 1:1 Fe^{II}(PA)₂/*t*-BuOOH in the presence of O₂]. A similar set of observations and rationalizations has been presented for incorporation of O₂ derived from *t*-BuOOH in a Fe(III)/*t*-BuOOH/*c*-C₆H₁₆/(10:1 py/HOAc) system.³²

Other iron(II) complexes [Fe^{II}(bpy)₂²⁺, Fe^{II}(OPPh₃)₄²⁺, Fe^{II}Cl₂] undergo initial nucleophilic addition by HOOH to form an analogue of species **1**. For the Fe^{II}L_x²⁺ complexes in pure MeCN this is a cationic reactive intermediate [(L_x⁺)Fe^{II}OOH(H₃O⁺)] that reacts with excess HOOH to form **3**, which decomposes to O₂ and reacts with substrates. In the presence of O₂ **1** reacts with *c*-C₆H₁₂ to form **6b**, which reacts with a second *c*-C₆H₁₂ to produce *c*-C₆H₁₀(O) and *c*-C₆H₁₁-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_x²⁺)Fe^{IV}(pyR)(OH)] (**2**). When oxidized metal complexes

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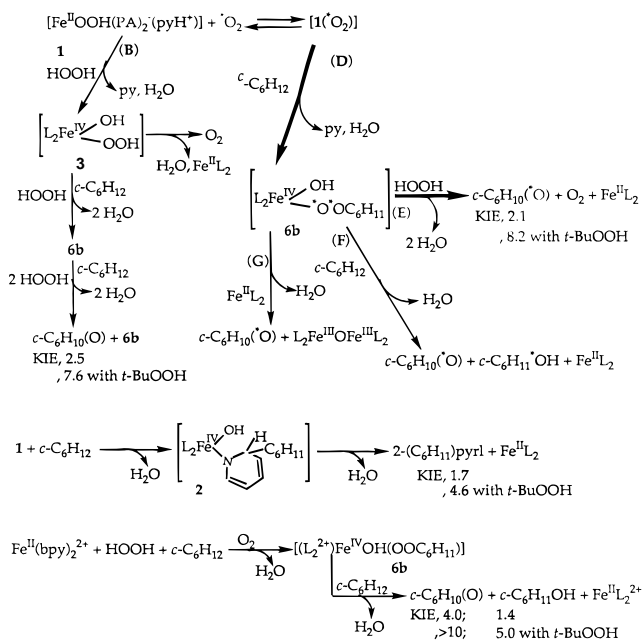
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Table 2. Metal [ML_x; M = Fe, Cu, Mn]/*t*-BuOOH-Induced Activation of O₂ (1 atm) for the Oxygenation of Cyclohexane (c-C₆H₁₂), Cyclohexene (c-C₆H₁₀), and Ethylbenzene (PhCH₂CH₃): Oxygenated Fenton Chemistry

ML _x	[<i>t</i> -BuOOH] (mM)	solvent	c-C ₆ H ₁₂ (1 M)			c-C ₆ H ₁₀ (1 M)			PhCH ₂ CH ₃ (1 M)		
			c-C ₆ H ₁₀ (O)	c-C ₆ H ₁₁ OH	effncy ^b (%)	ketone c-C ₆ H ₈ (O)	alcohol c-C ₆ H ₉ OH	epoxide c-C ₆ H ₁₀ (O)	effncy ^b (%)	PhC(O)CH ₃	PhCH(OH)Me
5 mM Fe ^{II} (PA) ₂	5	2:1 py/HOAc	4 [7.6] ^c	0	80	15	0	0	16	0	320
10 mM Fe ^{II} (PA) ₂	20	2:1 py/HOAc	12	0	60	45	0	0	34	0	170
20 mM Fe ^{II} (PA) ₂ ^d	20	2:1 py/HOAc	1	16 ^e [4.6] ^c	85	0	0	0	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	0	0	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	0	0	38	16	270
10 mM Fe ^{II} Cl ₃	20	MeCN	5 [> 10] ^c	4 [4.3] ^c	45	71	0	0	16	9	125
5 mM Cu ^I (bpy) ₂ ²⁺	20	4:1 MeCN/py	6 [8.8] ^c	0	30	25	0	0	28	0	140
5 mM Mn ^{III} (bpy) ₂ (OAc) ₃	20	MeCN	0	0	0	139 (26) ^g	0	5 (1) ^g	32	0	160
5 mM Mn ^{III} (salen)(OAc)	20	MeCN	0	0	0	159 (29) ^g (5) ^d	0	6 (1) ^g	40	0	200
5 mM Mn ^{III} (salen)(OAc)	20	2:1 py/HOAc	0	0	0	22	19	18	14	7	105
20 mM Mn ^{II} (salen)(OAc)	20	2:1 py/HOAc	0	0	0	24	25	30	23	9	160
10 mM Mn ^{II} (OPPh ₃) ₄ (OAc) ₃	20	2:1 py/HOAc	0	0	0	111	12	3	25	0	125

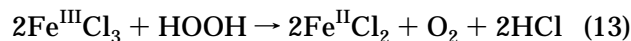
^a The product solutions were analyzed by capillary-column gas chromatography after a reaction time of 3 h at 24 ± 2 °C. ^b Efficiency for product formation; mM of products per mM of *t*-BuOOH (100% represents one product species per *t*-BuOOH). ^c Kinetic isotope effect, KIE = $k_{c-C_6H_{12}}/k_{c-C_6D_{12}}$. ^d Under an argon atmosphere. ^e The product was (c-C₆H₁₁)py. ^f R-R dimer. ^g Under air (0.2 atm of O₂).

Scheme 1. Oxygenated Fenton Chemistry^a



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

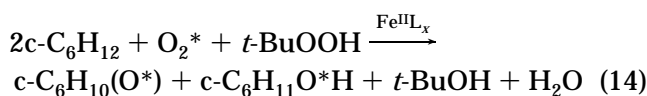
[e.g., Fe^{III}Cl₃, Fe^{III}(PA)₃, Cu^{II}(bpy)₂²⁺] are used, the initial event appears to be reduction by HOOH, e.g.^{21,22}

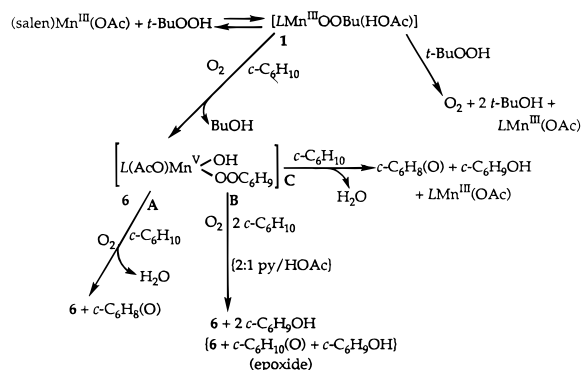


The Fe^{II}Cl₂ product in turn forms [Fe^{II}OOH(Cl₂⁻(H₃O⁺))] (1), which reacts with c-C₆H₁₂ and PhCH₂CH₃ via [Cl₂-Fe^{IV}(OH)(R)] (4) to produce approximately 50:50 mixtures of ROH and RCl.²² With HOOH and c-C₆H₁₂ the KIE value for 1 is 2.9,²² and with *t*-BuOOH it is 4.3. The porphyrin catalyst [Cl₈TPP]Fe^{II} reacts with *t*-BuOOH to form [(Cl₈TPP)Fe^{II}OOBu-*t*(H₃O⁺)] (1), which reacts with c-C₆H₁₂ via [(Cl₈TPP)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-C₆H₁₂ range from 5.4 to 8.4).²² The reactivity parameters for [Co^{II}(bpy)₂²⁺]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.

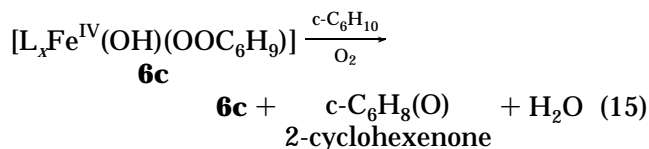
With excess O₂ most of the species 1 react with substrates (RH) via path D to form species 6, which in the case of c-C₆H₁₂, reacts initially with either excess HOOH via path E or excess c-C₆H₁₂ via path F, and finally with excess Fe^{II}L_x via path G (Scheme 1). Thus, the various species 1 (Fenton intermediates) catalyze the incorporation of O₂ into the ketone and alcohol products [e.g., Fe^{II}(bpy)₂²⁺/*t*-BuOOH, O₂/c-C₆H₁₂, Table 2].



Scheme 2. Mn^{III}L_x/t-BuOOH-Induced Activation of O₂ for the Oxygenation of Olefins


Results³² for a Fe^{III}(NO₃)₃/t-BuOOH/¹⁸O₂/c-C₈H₁₆ system in acetonitrile establish that the O atoms in the c-C₈H₁₄(O) and c-C₈H₁₅OH products are from O₂. 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 CH₂ groups [PhCH₂CH₃ and the allylic carbons of cyclohexene (c-C₆H₁₀)], species **6** becomes a catalyst for the activation of O₂. When the reaction efficiency for such substrates is >100% (ketone per t-BuOOH, eq 14, Table 2), species **6** must activate O₂ for reaction with the substrate [turnovers per Fe^{II}L_x ≥ t-BuOOH/Fe^{II}L_x].



Hence, the 10 mM Fe^{II}(bpy)₂²⁺/20 mM t-BuOOH/c-C₆H₁₀ system has at least 3 O₂ turnovers via path E, which is similar to the 1.4 O₂ turnovers per copper for the 5 mM Cu^I(bpy)₂⁺/5 mM t-BuOOH/PhCH₂CH₃ system.²⁴ Likewise, the 10 mM Fe^{II}(OPPh₃)₄²⁺/20 mM t-BuOOH/1 M c-C₆H₁₀ system has almost 2 O₂ turnovers via eq 15.²¹

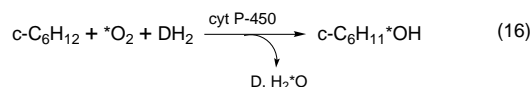
Perhaps the most dramatic example of oxygenated Fenton chemistry is the Mn^{III}L_x/t-BuOOH-induced activation of O₂ for reaction with c-C₆H₁₀ (Table 2).³³ With (salen)Mn^{III}OAc (salen = the Schiff base of salicylaldehyde and ethylenediamine) in MeCN more than 10 product molecules are produced per 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-C₆H₈(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-C₆H₁₂, 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.

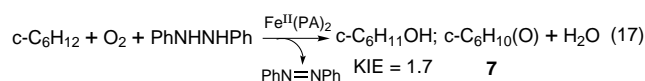
Thus, transition-metal complexes [ML_x = Fe^{II}L_x, Mn^{III}L_x, Cu^I(bpy)₂⁺, and Co^{II}(bpy)₂²⁺] undergo nucleophilic addition by hydroperoxides (HOOH or t-BuOOH) to form [L_xMOOH(BH⁺)] (**1**), which in the presence of O₂ oxygenates hydrocarbons and related organic substrates via species **6** (oxygenated Fenton chemistry, Schemes 1 and 2).

Relationship to Gif Chemistry. The substrate reactivities and product profiles with Gif chemistry³⁴ 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}Cl₃/HOOH combination rather than species **1**(O₂) [from an iron(II)/HOOH/O₂ 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 invariably reduces iron(III) complexes [Fe^{III}Cl₃, 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 reactivities 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^{•+})Fe^{IV}=O]⁹ (por = porphyrin) and the proposed intermediate [(H₂O)Cl₃Fe^V=O] from the 1:1 Fe^{III}Cl₃/HOOH combination (under base-free conditions),³⁵ both of which epoxidize olefins [e.g., cyclohexene (c-C₆H₁₀)] (only detected product). In contrast **1**(O₂) [from Fe^{II}(PA)₂/HOOH/O₂] transforms c-C₆H₁₀ to its ketone [c-C₆H₈(O)] as the only detected product. With *cis*-PhCH=CHPh the [(H₂O)Cl₃Fe^V=O] intermediate produces mainly epoxide (57% of product), while **1**(O₂) 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 [(H₂O)Cl₃Fe^V=O] intermediate from the 1:1 Fe^{III}Cl₃/HOOH combination is not formed in basic media (>100 mM H₂O or py in MeCN).³⁵

Related Systems for O₂ Activation. Nature oxygenates hydrocarbon substrates via a combination of a monooxygenase catalyst (e.g., cytochrome P-450), O₂, and a reductase (DH₂, e.g., dihydroflavin).³⁶



In a recent study³⁷ we have been able to mimic this chemistry with a combination of a transition-metal complex, O₂, and a reductant, e.g.



The ratio of alcohol to ketone increases as the DH₂/Fe^{II}(PA)₂ ratio increases. In the interpretation of the results we have proposed a reactive intermediate for

(33) Matsushita, T.; Sawyer, D. T. *Bioorg. Med. Chem.*, submitted for publication.

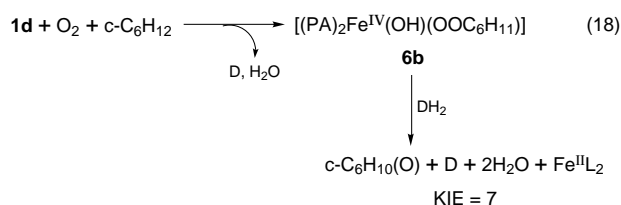
(34) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504–512.

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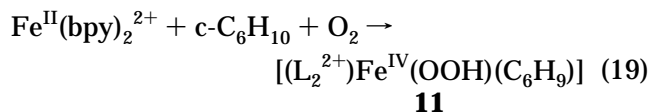
(37) Sawyer, D. T.; Liu, X.; Redman, C.; Chong, B. *Bioorg. Med. Chem.* **1994**, *2*, 1385–1395.

alcohol production $[(PA)_2Fe^{IV}(OOH)(DH), \mathbf{1d}]$ that is closely similar to that for Fenton chemistry ($\mathbf{1}$, eq 9); with $c\text{-C}_6\text{H}_{12}$, species $\mathbf{1d}$ and $\mathbf{1}$ have the same KIE value, 1.7. The production of ketone appears to involve species $\mathbf{1d}$, O_2 , and $c\text{-C}_6\text{H}_{12}$ in a process that produces the same intermediate ($\mathbf{6b}$) as oxygenated Fenton chemistry.

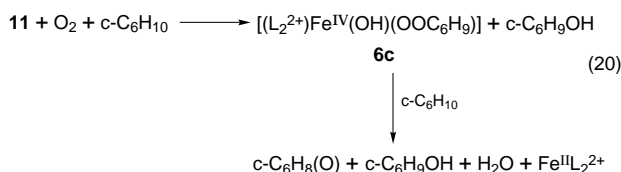


However, the oxygenated Fenton system has a KIE value of 2.1, which confirms that the rate-determining step involves the dioxygen adduct $\mathbf{1}(O_2)$ (eq 11 and Scheme 1), a more robust reactant than that of eq 18.

In another recent study³⁸ we discovered that coordinately unsaturated iron(II) complexes can activate O_2 for the oxygenation of cyclohexene ($c\text{-C}_6\text{H}_{10}$) to produce ketone, alcohol, and epoxide. Apparently in the initial step the substrate acts as a reductant (DH_2 , eq 17) to form $\mathbf{11}$



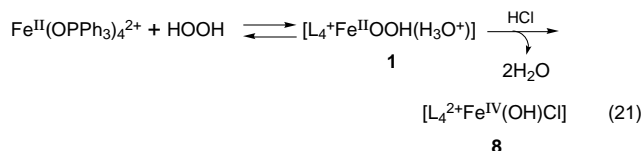
The latter in turn reacts with a second substrate and O_2 , apparently to produce a reactive intermediate that is analogous to that for oxygenated Fenton chemistry.



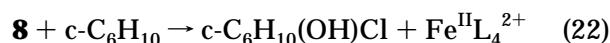
Hence, three different O_2 activating systems appear to involve a common reactive intermediate (species $\mathbf{6}$; eqs 15, 18, and 20) in their oxygenation of $c\text{-C}_6\text{H}_{10}$.

Chlorinated Fenton Chemistry. The preceding discussions confirm that the $Fe^{II}(bpy)_2^{2+}$ and $Fe^{II}(\text{OPPh}_3)_4^{2+}$ complexes are not effective 1:1 $Fe(II)/\text{HOOH}$ Fenton reagents.^{21,22} However, in the presence of HCl they [as well as $Fe^{II}(\text{OH}_2)_6^{2+}$ and $Fe^{III}\text{Cl}_3$] induce (a) the chlorohydroxylation of olefins, (b) the chlorination of saturated hydrocarbons (Table 1), (c) the epoxidation of $cis\text{-PhCH=CHPh}$, and (d) the hydroxylation of benzene (PhH).³⁹

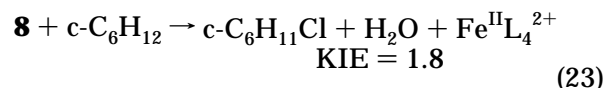
Because the dominant chemical characteristic of HOOH is nucleophilic addition (see preceding sections), this is a reasonable initial step in the iron(II)-induced activation of HOOH/HCl , with subsequent reaction of $\mathbf{1}$ with HCl to give the reactive intermediate (HCl acts as a H atom donor and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



which chlorohydroxylates olefins.



The reaction of species $\mathbf{8}$ with saturated hydrocarbons ($c\text{-C}_6\text{H}_{12}$) to give the chloro derivative as the only detectable product



is consistent with its formulation in eq 21. Thus, the stabilized HO^\bullet of $\mathbf{8}$ attacks a C–H bond of the substrate to give a carbon radical that is stabilized via bond formation with the iron center $[(L_4^{2+})Fe^{IV}(c\text{-C}_6\text{H}_{11})\text{Cl}]$ 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 $Fe^{III}\text{Cl}_3/\text{HOOH}/\text{MeCN}$ system reacts with $c\text{-C}_6\text{H}_{12}$ to yield approximately equal amounts of $c\text{-C}_6\text{H}_{11}\text{OH}$ and $c\text{-C}_6\text{H}_{11}\text{Cl}$ [apparently via an iron(V) reactive intermediate $[\text{Cl}_3\text{Fe}^V(\text{OH})_2]$ ($\mathbf{9}$); KIE = 2.9 ± 0.3].^{22,35} The smaller kinetic-isotope-effect value for $\mathbf{8}$ indicates that it is significantly more reactive than species $\mathbf{9}$ [that is, the Fe–OH bond in $\mathbf{8}$ is weaker than that in $\mathbf{9}$ (lower valence electron density)]. Thus, the pathways of eqs 21–23 might be classified as *chlorinated Fenton chemistry*.

In the presence of $cis\text{-PhCH=CHPh}$, species $\mathbf{8}$ appears to act as an effective epoxidizing agent, possibly first being transformed to $[(L_4^{2+})Fe^{IV}(\text{O})]$ by elimination of HCl . Although the $Fe^{II}(\text{OPPh}_3)_4^{2+}/(\text{HOOH}/\text{HCl})/\text{H}_2\text{O}$ system hydroxylates benzene with an impressive 38% efficiency, essentially the same efficiency is achieved for systems without HCl .²⁵ Hence, species $\mathbf{1}$ (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 $\mathbf{8}$ is much more reactive than HOCl (the biological oxidant from myeloperoxidase)⁴⁰ with organic substrates in an aqueous matrix. The uncontrolled formation of $\mathbf{8}$ 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 ($\text{Fe}^{\text{II}}\text{L}_x$, $\text{Cu}^{\text{I}}\text{L}_x$, $\text{Mn}^{\text{III}}\text{L}_x$, $\text{Co}^{\text{II}}\text{L}_x$)]. 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., $\text{Fe}^{\text{II}}(\text{PA})_2$], 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 $\text{Fe}^{\text{II}}(\text{bpy})_2^{2+}$ {[$(\text{bpy})_2^+$] $\text{Fe}^{\text{II}}\text{OOH}(\text{H}_3\text{O}^+)$, **1**} reacts with 1 equiv of HCl to give the reactive intermediate for chlorinated Fenton chemistry {[$(\text{bpy})_2^{2+}$] $\text{Fe}^{\text{IV}}(\text{OH})\text{Cl}$ } (**8**). Each of these reactive intermediates (**1**, **1(O₂)**, **8**) includes a stabilized hydroxyl group (HO) that (a) is less reactive than free HO[•] 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[•]. 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[•]. 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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