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Metal [Fe(II), Cu(I), Co(II), Mn(III)]/hydroperoxide-induced activation of dioxygen ($\cdot O_2 \cdot$) for the ketonization of hydrocarbons: oxygenated Fenton Chemistry

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Contents

Abstract

Recent reports have established that Fenton chemistry involves the formation of hydroperoxide (ROOH) adducts (**1**) of reduced transition metals [iron(II), copper(I), and cobalt(II)] via nucleophilic addition {e.g. $Fe^{II}L_x + ROOH \overset{B}{\rightleftharpoons} [L_x^- Fe^{II}OOR, BH^+](\mathit{1})$} ($B = py$ or H_2O). These reactive intermediates (**1**) react with (a) excess catalyst ($Fe^{II}L_x$) to form $L_xFe^{III}OH(R)$; (b) excess ROOH to form O_2, H_2O and ROH; (c) excess hydrocarbon (*R*H) to form *R*OH (Fenton chemistry); and (d) ambient dioxygen (O_2) to form adducts of **1** {e.g. $\mathit{1}(O_2) = [L_x^- Fe^{III}(O_2)OO\mathit{R}(BH^+)]$ (**5**)}. (Note: All bracketed species are speculative, but consistent with the product profiles.) The latter (**5**) reacts selectivity with (a) methylenic carbon centers of hydrocarbons ($-CH_2-$) to form ketones [e.g. $c-C_6H_{12} \xrightarrow{5} c-C_6H_{10}(O)$] (oxygenated Fenton chemistry) and (b) arylolefins via dioxygenation [e.g. $\mathit{cis}-PhCH{=}CHPh \xrightarrow{5} 2PhCH(O)$]. The species **5** formed by *t*-BuOOH and O_2 with $Fe^{II}(PA)_2$ (in 2:1 py/HOAc) (PAH = picolinic acid; 2-carboxyl pyridine), $Fe^{II}(bpy)_2^{2+}$ (MeCN), $Fe^{II}(OPPh_3)_4^{2+}$ (MeCN), $Cu^I(bpy)_2^+$ (4:1 MeCN/py) and $Co^{II}(bpy)_2^{2+}$ (4:1 MeCN/py) ketonize the methylenic centers of hydrocarbons (e.g. c-C_6H_{12}, $PhCH_2CH_3$, c-C_6H_{10}). With the allylic centers of cyclohexene (c-C_6H_{10}) the various

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species **5** exhibit catalytic turnover of O_2 [e.g. 10 mM $Fe^{II}(bpy)_2^{2+}$/20 mM t-BuOOH yields 86 mM c-$C_6H_8(O)$ (4.3 O_2 turnovers per t-BuOOH)]. For analogous combinations with other complexes the turnover numbers are: $Fe^{II}(OPPh_3)_4^{2+}$, 3.0; $Fe^{II}(PA)_2$, 3.0; $Cu^{I}(bpy)_2^{+}$, 1.3; $Co^{II}(bpy)_2^{2+}$, 0.7; Mn^{III}(salen)(OAc), 8.0; $Mn^{III}(bpy)_2(OAc)_3$, 7.0. With $PhCH_2CH_3$ as the substrate the O_2-turnover numbers are: $Fe^{II}(PA)_2$, 3.2; $Fe^{II}(bpy)_2^{+}$, 1.8; $Fe^{II}(OPPh_3)_4^{2+}$, 1.9; $Cu^{I}(bpy)_2^{+}$, 1.4; $Co^{II}(bpy)_2^{2+}$, 0.9; Mn^{III}(salen)(OAc) (salen = Schiff base from two salicylaldehydes and ethylenediamine), 2.0; $Mn^{III}(bpy)_2(OAc)_3$, 1.6. The several species **1** react as hydroxylases (including aromatic substrates) and dehydrogenases, and species **5** react as ketonization agents and dioxygenases. With excess HOOH its ML_x-induced disproportionation to O_2 and H_2O results in production of species **5** without external sources of O_2.

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1. Introduction

The reaction chemistry of coordination complexes involves substitution by a more nucleophilic ligand, e.g.

$$Fe^{II}(OH_2)_6^{2+} + 3bpy \rightleftharpoons Fe^{II}(bpy)_3^{2+} + 6H_2O \qquad (1)$$

$$Fe^{II}(bpy)_3^{2+} + H_2Y^{2-} \rightleftharpoons Fe^{II}Y^{2-} + 2bpyH^{+} + bpy \qquad (2)$$

$$Fe^{II}(bpy)_3^{2+} + HOOH \rightleftharpoons [(bpy)_2^{+}Fe^{II}OOH(bpyH^{+})] \qquad (3)$$

In this set of displacement reactions bipyridine (bpy) is a stronger nucleophile than H_2O, EDTA (H_2Y^{2-}) stronger than bpy, and HOOH stronger than bpy, H_2O and the carboxylates of H_2Y^{2-}. As with all ligand-substitution reactions the more nucleophilic ligand displaces an existing ligand via a single-electron-transfer (SET) mechanism (the entering ligand transfers an electron via the metal center to the displaced ligand). This is analogous to the S_N2 mechanism for nucleophilic organic reactions [1]

$$HO^{-} + n\text{-}BuBr \xrightarrow{S_N2} HOBu\text{-}n + Br^{-} \qquad (4)$$

$$HO^{-} + Fe^{III}Cl_3 \rightarrow [HOFe^{III}Cl_3^{-}] \rightarrow HOFe^{III}Cl_2 + Cl^{-} \qquad (5)$$

$$2NH_3 + Ag^{I}Cl(s) \rightarrow Ag^{I}(NH_3)_2^{+} + Cl^{-} \qquad (6)$$

With saturated electrophiles (n-BuBr, Eq. (4)) the SET is to a less nucleophilic leaving group $N{:}^{-} + R{:}\ddot{\underset{..}{X}}{:}(E) \rightarrow N{:}R + {:}\ddot{\underset{..}{X}}{:}$

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 $(E_{red})_E$] [2]

$$N + E \rightarrow N - E'(+X) - -\Delta G_{reac} \qquad (7)$$

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

$$Nu = (E_{ox})_N - [(-\Delta G_{BF})_{N-E'}/23.1\ \text{kcal (eV)}^{-1}\ \text{mol}^{-1}] \quad (8)$$

$$El = (E_{red})_E \quad (9)$$

The free-energy for the reaction of a nucleophile with an electrophile (Eq. (7)) can be determined with the relation

$$-\Delta G_{reac} = (El - Nu)23.1\ \text{kcal mol}^{-1} = [(E_{red})_E - (E_{ox})_N]23.1 + (-\Delta G_{BF})_{N-E'} \quad (10)$$

Hence, the driving force for nucleophile/electrophile electron-transfer reactions is the redox potential for the nucleophile in the solution matrix ($HO^-/HO\cdot$, +0.92 V vs NHE in MeCN) [3] plus the nucleophile–substrate bond-formation free energy ($-\Delta G_{BF}$, n–Bu–OH; ~83 kcal mol^{-1}).

$$\text{Nucleophilicity} = (E_{1/2})_{ox} - (-\Delta G_{BF(N-E)}/23.1) \quad (11)$$

$$= (+0.92\ \text{V}) - [83\ \text{kcal mol}^{-1}/23.1\ \text{kcal mol}^{-1}\ (\text{eV})^{-1}]$$

$$= (+0.92 - 3.6)\ \text{V} = -2.70\ \text{V vs NHE}$$

$$[\text{n}-\text{BuBr} + e^- \rightarrow \text{n}-\text{Bu}\cdot + \text{Br}^-; E^{\circ\prime}, -2.0\ \text{V vs NHE}]$$

Thus, in MeCN reaction Eq. (4) is exothermic by about 16 kcal mol^{-1} [$-\Delta G_{reaction} = (El - Nu)$ eV = 0.7 V × 23.1 kcal mol^{-1} (eV)$^{-1}$ = 16 kcal mol^{-1}].

With reaction Eq. (5) the bond-formation free energy for Cl_2Fe^{III}–OH is 62 kcal mol^{-1} and $Fe^{III}Cl_3$ is reduced at +0.50 V vs NHE in acetonitrile (El). Hence, the nucleophilicity of HO^- in this reaction is given by the relation

$$\text{Nucleophilicity} = (E_{1/2})_{ox} - (-\Delta G_{BF(N-E)}/23.1) \quad (12)$$

$$= (+0.92\ \text{V}) - [62\ \text{kcal mol}^{-1}/23.1\ \text{kcal mol}^{-1}\ (\text{eV})^{-1}]$$

$$= (+0.92 - 2.68)\ \text{V} = -1.76\ \text{V vs NHE}$$

The reaction is exothermic by about 52 kcal mol^{-1} [$-\Delta G_{reaction} = (El - Nu)$ eV = 2.26 V × 23.1 kcal mol^{-1} (eV)$^{-1}$ = 52.2 kcal mol^{-1}].

Table 1 summarizes the oxidation potentials for nucleophiles and the reduction potentials for electrophiles in acetonitrile (MeCN) and in water [2]. The relative positions will be the same in other solvents, but nucleophiles that are stronger than HO^- will be "leveled" to its nucleophilicity in aqueous media. Under all conditions hydroperoxides (e.g. HOOH, *t*-BuOOH) are more nucleophilic than water (and alcohols), and peroxide anions are stronger nucleophiles than other oxy anions (HO^-, PhO^-).

Thus, hydroperoxides are favored relative to water in the ligand-centered

Table 1
Nucleophilicity and electrophilicity of molecules and ions (strongest or most reactive at top of listing)

Nucleophile	$(E_{1/2})_{ox}$ (V) (MeCN)	vs NHE (H_2O)	Electrophile	$(E_{1/2})_{red}$ (V) (MeCN)	vs NHE (H_2O)
e_{aq}^-	−3.9	+2.9	$H_2O^+\cdot$	+3.2	+2.7
$(TPP^-\cdot)Co^-$	−1.7		$Fe^{III}(bpy)_3^{3+}$	+1.3	+1.1
$(TPP^-\cdot)Fe^-$	−1.4		$HO\cdot$	+0.9	+1.9
$(TPP)Fe^-$	−0.8		$Fe^{III}(PA)_3$	+0.4	
$(TPP)Co^-$	−0.6		$(TPP)Fe^{III}(py)_2^+$	+0.4	
$O_2^-\cdot$	−0.7	−0.2	$(TPP)Fe^{III}Cl$	+0.2	
$PhCH_2S^-$	0.0		AQ (anthraquinone)	−0.6	
HOO^-	0.0	+0.2	$Co^{II}(bpy)_2^{2+}$	−0.6	
PhO^-	+0.3		O_2	−0.7	−0.2
Me_3N	+0.7		$Cu^I(bpy)_2^{2+}$	−0.9	
HO^-	+0.9	+1.9	$Fe^{II}(OPPh_3)_4^{2+}$	−0.9	
$MeC(O)O^-$	+1.5		$Fe^{II}(bpy)_2^{2+}$	−0.9	
PhOH	+1.7		CCl_4	−0.9	
Pyridine	+2.0		$Fe^{II}Cl_2$	−1.0	
Cl^-	+2.2	+2.4	H_3O^+	−1.6	−2.1
HOOH	+2.3	+0.9 (pH 7)	n-BuI	−1.9	
H_2O	+3.0	+2.3 (pH 7)	n-BuBr	−2.2	
			n-BuCl	−2.5	
			H_2O	−3.9	−2.9

nucleophilic substitution reactions of coordination chemistry

$$Fe^{III}(bpy)_3^{3+} + H_2O \rightarrow (bpy)_2^{2+}Fe^{III}-OH + bpyH^+ \quad (13)$$

$$Fe^{III}(bpy)_3^{3+} + HOOH \rightarrow (bpy)_2^{2+}Fe^{III}-OOH + bpyH^+ \quad (14)$$

$$(PA)_2Fe^{III}Cl + H_2O/py \rightarrow (PA)_2Fe^{III}-OH + pyHCl \quad (15)$$

$$(PA)_2Fe^{III}Cl + HOOH/py \rightarrow (PA)_2Fe^{III}-OOH + pyHCl \quad (16)$$

$$Fe^{II}(PA)_2 + HOOH/py \rightarrow [(PA)_2^-]Fe^{III}-OOH + pyH^+ \quad (17)$$

$$Fe^{II}(bpy)_2^{2+} + HOOH \rightarrow [(bpy)_2^+]Fe^{II}-OOH(bpyH^+) \quad (18)$$

The nucleophilic character of hydroperoxides follows from the fact that HOO^- is a much stronger Lewis base than HO^- [$(E_{ox})_{HOO^-} = +0.20$ V vs NHE vs $(E_{ox})_{HO^-} = +1.89$ V (pH 14)] [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 [$(E_{ox})_{H_2O, pH\ 5}$, +2.43 V], that for HOOH [$(E_{ox})_{HOOH, pH\ 5}$, +1.01 V] also is much greater [1,2].

2. Fenton chemistry

The traditional formulation of the one-to-one primary step for Fenton reagents [$Fe^{II}(OH_2)_6^{2+}$/HOOH in H_2O at pH 2] depicts the production of free hydroxyl radical ($HO\cdot$) [4–8]

$$Fe^{II}(OH_2)_6^{2+} + HOOH \xrightarrow[\text{pH } 2]{k_{19}} (H_2O)_5^{2+}Fe^{III}OH + H_2O + HO\cdot \qquad (19)$$

$k_{19} = 41\ M^{-1}\,s^{-1}$

With this assumption, the subsequent reactions of Fenton reagents have been based on the primary chemistry of $HO\cdot$ (generated by radiolysis of H_2O or photolysis of HOOH) [9], which reacts with iron(II) (all in aqueous media)

$$HO\cdot + Fe^{II}(OH_2)_6^{2+} \xrightarrow{k_{20}} (H_2O)_5^{2+}Fe^{III}OH + H_2O \qquad (20)$$

$k_{20} = 3 \times 10^8\ M^{-1}\,s^{-1}$

and aliphatic (RH) and aromatic (PhR) hydrocarbons [9]

$$HO\cdot + RH \xrightarrow{k_{21}} R\cdot + H_2O \qquad (21)$$

$k_{21} = 1.1 \times 10^8\ M^{-1}\,s^{-1}$ (CH_4), $1.8 \times 10^9\ M^{-1}\,s^{-1}$ (C_2H_6),
$3.7 \times 10^9\ M^{-1}\,s^{-1}$ (c-C_5H_{10}; cyclopentane)

$$HO\cdot + PhR \xrightarrow{k_{22}} HOPh'R \underset{\downarrow\, H_2O}{\longrightarrow} \tfrac{1}{2}RC_6H_4{-}C_6H_4R \qquad (20)$$

$k_{22} = 3.0 \times 10^9\ M^{-1}\,s^{-1}$ ($PhCH_3$, 97% aryl addition),
$7.5 \times 10^9\ M^{-1}\,s^{-1}$ ($PhCH_2CH_3$, 85% aryl addition)

The resultant carbon radical ($R\cdot$) can (a) dimerize to R_2, (b) react with a second $HO\cdot$ to form ROH, and (c) in the presence of air, couple to O_2 to form $ROO\cdot$ {unreactive with saturated hydrocarbons; dimerizes to [ROOOOR]→ROOR + O_2 (when R is tertiary), $k_d = 10^3$–$10^7\ M^{-1}\,s^{-1}$} [6].

The kinetics for substrate reactivities with Fenton-generated "$HO\cdot$" usually are determined via the relative rate of disappearance of iron(II) (Eq. (20)) to that of the substrate [4]. However, if Fenton reagents generate reactive intermediates (X) other than free $HO\cdot$, the reactivity of X with iron(II) and organic substrates will be different and may not produce free carbon radicals ($R\cdot$).

In 1989 we discussed the characteristics of a Fenton reagent in an organic solvent matrix [$Fe^{II}(PA)_2$ (PAH = picolinic acid)/HOOH/2:1 pyridine (py)/acetic acid (HOAc) (mol/mol)] [10]. 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-C_6H_{12}→(c-C_6H_{11})pyl (pyl; pyridyl, C_5H_4N) (or c-$C_6H_{11}OH$)]. As with all Fenton systems, the dominant product is not bicyclohexyl (c-C_6H_{11})$_2$, which is the major product from the reaction of $HO\cdot$ with cyclohexane (c-C_6H_{12}).

Table 2 summarizes the product profiles for two substrates (c-C_6H_{12}, $PhCH_2CH_3$) when combined with 1:1 or 1:20 mol-ratios of ML_x(M = Fe, Co, Cu)/HOOH in the absence and the presence of O_2 (1 atm) [11–13]. The kinetic isotope effect for cyclohexane [*KIE*, $k_{c-C_6H_{12}}/k_{c-C_6D_{12}}$] in relation to its major products is listed for the Fenton reagents under various reaction conditions. In contrast to the 1:1 $Fe^{II}(PA)_2$/HOOH system [dominant product;

Table 2

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_6H_{12}			$PhCH_2CH_3$		
			[*KIE*][c]	$\{k_{c-C_6H_{12}}/k_{PhCH_2CH_3}\}$[d]		
$HO\cdot/H_2O$[e]	c-$C_6H_{11}\cdot$		[1.0]	$HOPh\cdot CH_2CH_3$		{0.1}
1:1 $Fe^{II}(OH_2)_6^{2+}$/HOOH]/H_2O(pH 2)[f]	c-$C_6H_{11}OH$		[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-$C_6H_{10}(O)$	2	[2.1]	$PhC(O)CH_3$	4	{0.1}
1:20 $Fe^{II}(PA)_2$/HOOH]/$(py)_2HOAc$[h]	c-$C_6H_{10}(O)$	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-$C_6H_{10}(O)$	15	[2.1]	$PhC(O)CH_3$	27	{0.1}
1:1 $Fe^{II}(PA)_2$/HOOH]/MeCN	c-$C_6H_{11}OH$	3		$PhC(O)CH_3$	6	{0.1}
1:20 $Fe^{II}(PA)_2$/HOOH]/MeCN	c-$C_6H_{10}(O)$	2				
1:20 $Fe^{III}Cl_3$/HOOH]/MeCN	c-$C_6H_{11}OH,Cl$	24	[2.9]	$PhCH(OH,Cl)CH_3$]	20	{0.2}
	c-$C_6H_{10}(O)$	8	[11]	$PhC(O)CH_3$	15	{0.1}
1:1 $Fe^{II}(PA)_2$/HOOH]/MeCN[i]	0					
1:1 $Fe^{II}(bpy)_2^{2+}$/HOOH,O_2]/MeCN	c-$C_6H_{10}(O)$	1		$PhC(O)CH_3$	2	{0.1}
1:20 $Fe^{II}(bpy)_3^{2+}$/HOOH]/MeCN[j]	c-$C_6H_{10}(O)$	5	[4.0]	$PhC(O)CH_3$	14	{0.1}
	c-$C_6H_{11}OH$	4	[1.4]			
1:1:1 $Fe^{II}(OPPh_3)_4^{2+}$/HOOH/HCl/MeCN[k]	c-$C_6H_{11}Cl$	4	[1.8]			
1:20 $Fe^{II}(OPPh_3)_4^{2+}$/HOOH]/MeCN[j]	c-$C_6H_{11}OH$	7	[1.9]	PhCH(Me)OH	21	{0.1}
	c-$C_6H_{10}(O)$	6	[> 10]	$PhC(O)CH_3$	6	{0.2}
1:20 $Fe^{II}(O_2bpy)_2^{2+}$/HOOH]/$(MeCN)_4py$[j]	c-$C_6H_{10}(O)$	12	[3.4]	$PhC(O)CH_3$	14	{0.2}
1:20 $Co^{II}(bpy)_2^{2+}$/HOOH]/$(MeCN)_4py$[j]	c-$C_6H_{10}(O)$	20	[2.9]	$PhC(O)CH_3$	20	{0.2}
1:20 $Cu^{I}(bpy)_2^{+}$/HOOH]/$(MeCN)_4py$[l]	c-$C_6H_{10}(O)$	12	[2.5]	$PhC(O)CH_3$	12	{0.2}
1:20 $Cu^{I}(bpy)_2^{+}$/HOOH,O_2]/$(MeCN)_4py$[l]	c-$C_6H_{10}(O)$	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 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 mol ratio; $(MeCN)_4py$, 4:1 mol ratio.

[c] Kinetic isotope effect, $k_{c-C_6H_{12}}/k_{c-C_6D_{12}}$.

[d] Relative reactivity of c-C_6H_{12} versus $PhCH_2CH_3$ (per CH_2-group).

[e] Ref. [9].

[f] Ref. [8].

[g] 1:1, 10 mM ML_x/10 mM HOOH.

[h] 1:20, 5 mM ML_x/100 mM HOOH.

[i] 1:1 [$Fe^{II}(OPPh_3)_4^{2+}$, $Co^{II}(bpy)_3^{2+}$ and $Cu^{I}(bpy)_2^{2+}$/HOOH] also are unreactive with c-C_6H_{12}.

[j] Ref. [13].

[k] Ref. [14].

[l] Ref. [15].

cyclohexyl pyridyl, (c-C_6H_{11})pyl], the 1:20 system yields c-$C_6H_{10}(O)$ (cyclohexanone) as the dominant product plus some (c-C_6H_{11})pyl or c-$C_6H_{11}OH$. With the 1:1 systems in the presence of O_2 (1 atm), ketonization of methylenic carbon centers is dominant [c-$C_6H_{12} \rightarrow c$-$C_6H_{10}(O)$].

These [11–13] and related studies of iron(II)/HCl [14] and copper(I) [15] 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 $Fe^{II}(bpy)_2^{2+}$, $Fe^{II}(OPPh_3)_4^{2+}$, $Co^{II}(bpy)_2^{2+}$ and $Cu^{I}(bpy)_2^{+}$ are not reactive with c-C_6H_{12}, but 1:20 combinations yield substantial quantities of c-$C_6H_{10}(O)$ as the dominant product [their 1:1 combination in the presence of O_2 also transforms c-C_6H_{12} to c-$C_6H_{10}(O)$]. Clearly the latter conditions produce a different reactive intermediate than that from the 1:1 combination of classical Fenton chemistry.

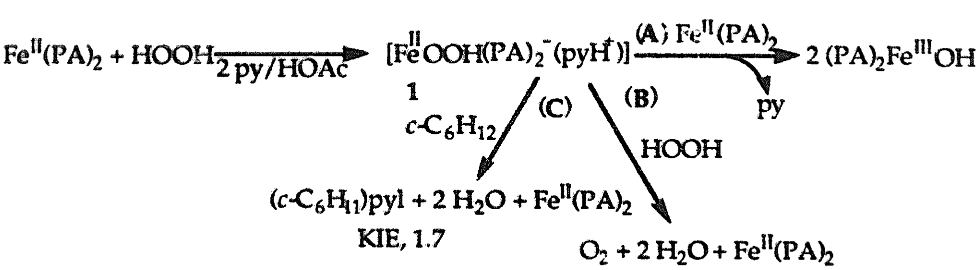
The product profiles for a Fenton reagent [$Fe^{II}(PA)_2$/HOOH/2:1 py/HOAc (mol/mol)] with several organic substrates (RH or ArH) have been compared with those for free hydroxyl radical (HO·) in an aqueous matrix [10–13,16]. In no case is substrate dimer (R–R) (dominant product for HO·/saturated-hydrocarbon reactions in the absence of O_2) or ROOR (dominant product for HO·/saturated-hydrocarbon reactions in the presence of O_2) detected in the product solutions [9].

In the absence of O_2, (a) the Fenton systems yield (i) R(pyl) (alkyl pyridyl) or ROH from saturated hydrocarbons (RH), (ii) PhOH from PhH, (iii) 3-hydroxy-pyridyl [3-HO(pyl)] from py, and (iv) $PhC(O)CH_3$ from $PhCH_2CH_3$; and (b) HO· yields (i) (R·→R–R) from RH, (ii) ($HO\dot{Ph}H \rightarrow Ph-Ph$) from PhH, (iii) hydroxyl adduct [$HO\dot{p}y(o/p, 2.0) \rightarrow pyl-pyl$] (bipyridyl; bpy) from py, and (iv) ($HOA\dot{r}H \rightarrow Ar-Ar$) from $PhCH_2CH_3$. In the presence of O_2, (a) the Fenton system yields ketones from the methylenic centers of hydrocarbons [RH; c-$C_6H_{12} \rightarrow c$-$C_6H_{10}(O)$], and (b) HO· yields (ROO·→ROOR+O_2) from RH.

Although HO· reacts with CH_4 ($k = 1.1 \times 10^8\ M^{-1}\ s^{-1}$) [9], 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, hydroxyl derivative of bipyridyl) ($k = 9 \times 10^9\ M^{-1}\ s^{-1}$) [9], but the 1:1 combination of $Fe^{II}(bpy)_2^{2+}$ and HOOH in MeCN is unreactive (Table 2).

In spite of the common belief that Fenton reagents ($Fe^{II}L_x$/HOOH) (L, ligand) produce free HO· (Eq. (19)), recent studies [11,17,18] and the results of Table 2 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}–O–OH(H_3O^+), **1**; "bound HO·"}] reacts directly with substrates [18]. Another study finds product profiles that are inconsistent with free HO· as the dominant reactive intermediate for a biological Fenton reagent [19].

The 1:1 $Fe^{II}(PA)_2$/HOOH combination in 2:1 py/HOAc is an effective Fenton reagent for organic substrates [10], and has reactivities and product profiles that are within the same mechanistic framework as those for traditional aqueous Fenton reagents [4]. Hence, the initial step is the reversible nucleophilic addition of HOOH to $Fe^{II}(PA)_2$ to give the primary reactive intermediate (**1**) [11–13] which reacts with (a) excess $Fe^{II}(PA)_2$ via path A ($k = 2 \times 10^3\ M^{-1}\ s^{-1}$) [10], (b) excess HOOH via



(23)

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 (cyclohexyl pyridyl) [aqueous Fenton systems produce $c\text{-}C_6H_{11}OH$ with a kinetic-isotope-effect (*KIE*) of 1.1 [8], and free HO· (pulse radiolysis) produces $c\text{-}C_6H_{11}\cdot$ with a *KIE* of 1.0 [9]. Although radical traps (e.g. PhSeSePh, $BrCCl_3$, Me_2SO) [9] 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. (23); Table 2). With 1M $c\text{-}C_6H_{12}$ the process of path **C** is facilitated via formation of an intermediate (**2**) that produces 2-$(c\text{-}C_6H_{11})$pyl and 4-$(c\text{-}C_6H_{11})$pyl

$$1 + c\text{-}C_6H_{12} + py \rightarrow \underset{\mathbf{2}}{\{(PA)_2Fe^{IV}(OH)[pyl(c\text{-}C_6H_{11})]\}} \rightarrow Fe^{II}(PA)_2 + (c\text{-}C_6H_{11})pyl + H_2O \qquad (24)$$

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 alkyl pyridyls (Rpyl) via $[(L_x^{2+})Fe^{IV}(pyR)(OH)]$ (**2**). When oxidized metal complexes [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. [12,13]

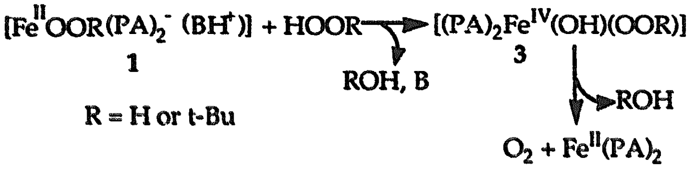
$$2Fe^{III}Cl_3 + HOOH \rightarrow 2Fe^{II}Cl_2 + O_2 + 2HCl \qquad (25)$$

The $Fe^{II}Cl_2$ product in turn forms $[Fe^{II}OOH(Cl_2^-)(H_3O^+)]$ (**1**), which reacts with $c\text{-}C_6H_{12}$ and $PhCH_2CH_3$ via $[Cl_2Fe^{IV}(OH)(R)]$ (**2**) to produce approximately 50:50 mixtures of ROH and RCl [13]. With HOOH and $c\text{-}C_6H_{12}$ the [*KIE*] value for **1** is 2.9 [13], and with *t*-BuOOH it is 4.3. The porphyrin catalyst $\{(Cl_8TPP)Fe^{II}$: [tetra(2,6-dichloro-phenyl)porphyrin]iron(II)} reacts with *t*-BuOOH to form $[(Cl_8TPP)Fe^{II}OOBu\text{-}t(H_3O^+)]$ (**1**), which reacts with $c\text{-}C_6H_{12}$ via $[(Cl_8TPP)Fe^{IV}(OH)(R)]$ (**2**) to produce ROH [$KIE = 5.0$] [12].

In summary: Fenton reagents do not produce (a) free HO·, (b) free carbon radicals (R·) or (c) aryl adducts (HO–Ar·). Early work [20] 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 cytotoxic agent than free HO· within the oxy-radical theory of aging and heart disease [21,22].

3. 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. (23)). 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) [12,13,15].



$$[Fe^{II}OOR(PA)_2^-(BH^+)] + HOOR \xrightarrow[ROH,\ B]{} [(PA)_2Fe^{IV}(OH)(OOR)] \xrightarrow{-ROH} O_2 + Fe^{II}(PA)_2 \qquad (26)$$

1 3

R = H or t-Bu

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-C_6H_{12} system yields 27 mM c-$C_6H_{10}(O)$ and 4 mM (c-C_6H_{11})pyl (the respective [*KIE*]-values are 2.5 and 1.7, Table 2). More than half of the HOOH is decomposed to O_2 (Eq. (26)). When *t*-BuOOH is used in place of HOOH the system yields 7 mM c-C_6H_{11}OOBu-*t* ([*KIE*]= 8.4), 11 mM c-$C_6H_{10}(O)$ ([*KIE*]=7.6) and 19 mM (c-C_6H_{11})pyl ([*KIE*]=4.6). Again, almost half of the *t*-BuOOH is decomposed to O_2 via Eq. (26). Combinations of $Fe^{II}(PA)_2$ and HOOH in the presence of O_2 transform c-C_6H_{12} to c-$C_6H_{10}(O)$ ([*KIE*], 2.1) as the only detectable product (Table 2).

Although 1:1 combinations of [$Fe^{II}(bpy)_2^{2+}$, $Fe^{II}(O_2bpy)_2^{2+}$, $Fe^{II}(OPPh_3)_4^{2+}$, $Co^{II}(bpy)_2^{2+}$ or $Cu^{I}(bpy)_2^{+}$]/HOOH in the absence of O_2 are unreactive with c-C_6H_{12}, they readily react in its presence to produce c-$C_6H_{10}(O)$. When their ratio is 1:20 ML_x/HOOH, most of the HOOH is transformed to O_2 via Eq. (26), which results in analogous Fenton-induced activation of O_2 for reaction with c-C_6H_{12} and $PhCH_2CH_3$ (Table 2).

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. (23)) to give $(PA)_2Fe^{III}OH$. In the presence of O_2 (with or without 1M c-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) [12]. These observations are compelling evidence that species **1** (formed from *t*-BuOOH) produces an O_2-adduct (**5**)

$$1 + O_2 \rightarrow [Fe^{III}(OOBu-t)(PA)_2^-(O_2)(pyH^+)]5[1(O_2)] \qquad (27)$$

which reacts with excess c-C_6H_{12} to produce c-$C_6H_{10}(O)$. The dioxygen adduct (**5**) appears to be the steady state primary reactive intermediate rather than species **1** on the basis of the enhanced [*KIE*] value for ketone formation {8.5 [for initial formation of **6**] vs 4.6 [for formation of (c-C_6H_{11})pyl]}. Table 3 summarizes the product profiles for several ML_x/*t*-BuOOH/O_2 (1 atm) combinations with c-C_6H_{12} and c-C_6H_{10}. In all cases the oxygen atoms that are incorporated in the product species come from O_2 [12].

The production of 16 mM PhC(O)Me by the 5 mM $Fe^{II}(PA)_2$/5 mM *t*-BuOOH/O_2/1M $PhCH_2CH_3$ system [12] indicates that (a) most

Table 3

Metal [ML_x; Me = Fe, Cu, Co, Mn]/t-BuOOH-induced activation of O_2 (1 atm) for the oxygenation of cyclohexane (c-C_6H_{12}) and cyclohexene (c-C_6H_{10}); oxygenated Fenton chemistry

ML_x	t-BuOOH (mM)	Solvent	Products (mM ± 5%)[a]						
			c-C_6H_{12} (1M)			c-C_6H_{10} (1M)			
			c-$C_6H_{10}(O)$	c-$C_6H_{11}OH$	Effncy[b] (%)	c-$C_6H_8(O)$	c-C_6H_9OH	c-$C_6H_{10}(O)$ (epoxide)	Effncy[b] (%)
5 mM $Fe^{II}(PA)_2$	5	2:1 py/HOAc	4	0	80	15	0	0	300
10 mM $Fe^{II}(PA)_2$	20	2:1 py/HOAc	12	0	60	45	2	0	235
20 mM $Fe^{II}(PA)_2$	20	2:1 py/HOAc	1	16[d]	85	0	5[d]	0	25
10 mM $Fe^{II}(bpy)^{2+}$	20	MeCN	4 (0)[c]	5 (0)[c]	45	86 (0)[c]	60 (2.5)[c]	0	730
10 mM $Fe^{II}(OPPh_3)_4^{2+}$	20	4:1 MeCN/py	4	6	50	60	35	0	475
10 mM $Fe^{III}Cl_3$	20	MeCN	5	4	45	71	69	0	700
1 mM $Fe^{II}(bpy)_2^{2+}$	0	MeCN	0	0	36	22	3		
5 mM $Cu^{I}(bpy)_2^{2+}$	20	4:1 MeCN/py	6	0	30	25	0	0	125
10 mM $Co^{II}(bpy)_2^{2+}$	10	4:1 MeCN/py	1	1	20	10	2	0	120
5 mM $Mn^{III}(bpy)_2(OAc)_3$	20	MeCN	0	0	0	139 (26)[f]	41 (14)[f]	5 (1)[f]	925 (200)[f]
5 mM Mn^{III}(salen) (OAc)	20	MeCN	0	0	0	159 (29)[f]	48 (12)[f]	6 (1)[f]	1070 (210)[f]
5 mM Mn^{III}(salen) (OAc)	20	2:1 py/HOAc	0	0	0	22	19	18	295
20 mM Mn^{III}(salen) (OAc)	20	2:1 py/HOAc	0	0	0	24	25	30	395

[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] Under an argon atmosphere.

[d] Product was (c-C_6H_{11})pyl.

[e] R–R dimer.

[f] Under air (0.2 atm O_2).

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** $[(PA)_2Fe^{IV}(OH)(OOR)]$ (three times as much product as initial *t*-BuOOH).

$$\underset{RH}{\mathbf{5} + PhCH_2CH_3} \xrightarrow[t\text{-BuOH}]{} \underset{\mathbf{6a}}{\{(PA)_2Fe^{IV}(OH)[OOCH(CH_3)Ph]\}} \xrightarrow[O_2]{PhCH_2CH_3} \mathbf{6a} + PhC(O)CH_3 + H_2O \qquad (28)$$

Cyclohexene (c-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 3).

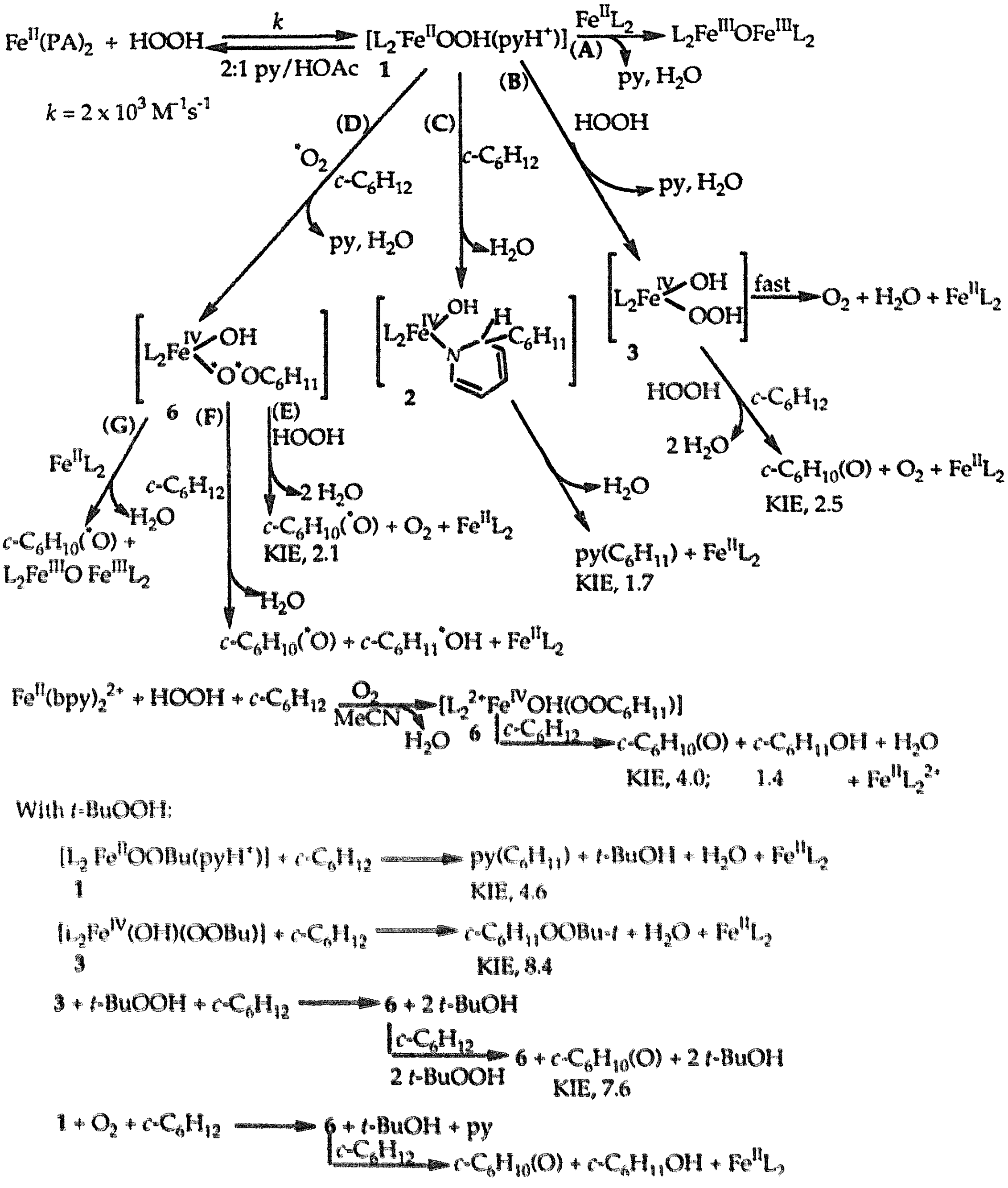
Scheme 1 outlines a set of reaction paths that are consistent with the product profiles for Fenton chemistry and oxygenated Fenton chemistry [1:1 ML_x/HOOH (or *t*-BuOOH)/$^*O_2$] with cyclohexane (c-C_6H_{12}) as the substrate. The species **3** that is formed from *t*-BuOOH (rather than HOOH) is about 100 times longer lived [decomposes to O_2 and *t*-BuOH (Eq. (26))], and thereby can react with c-C_6H_{12} to form c-C_6H_{11}OOBu-*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] and Table 3). 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. (26)) (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 [12] 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-C_8H_{16}/(10:1 py/HOAc) system [23].

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-C_6H_{12} to form **6**, which reacts with a second c-C_6H_{12} to produce c-C_6H_{10}(O) and c-C_6H_{11}OH (Scheme 1).

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 [13]). The reactivity parameters for [$Co^{II}(bpy)_3^{2+}$] [13] and [$Cu^{I}(bpy)_2^{+}$] [15] are similar and in accord with the proposition that all of these complexes activate HOOH initially via a species **1**, which reacts with hydrocarbon substrates (RH) via path **C** to form species **2**. In general, the reactivity parameter [*KIE*] has smaller values for the path-**C** step than for the path-**D** step of Scheme 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 either with excess HOOH



Scheme 1. Fenton Chemistry and the activation of dioxygen (Oxygenated Fenton Chemistry)

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 3].

$$2c-C_6H_{12}+O_2^{*}+t-BuOOH \xrightarrow[Fe^{II}L_x]{} c-C_6H_{10}(O^{*})+c-C_6H_{11}O^{*}H+t-BuOH+H_2O \qquad (29)$$

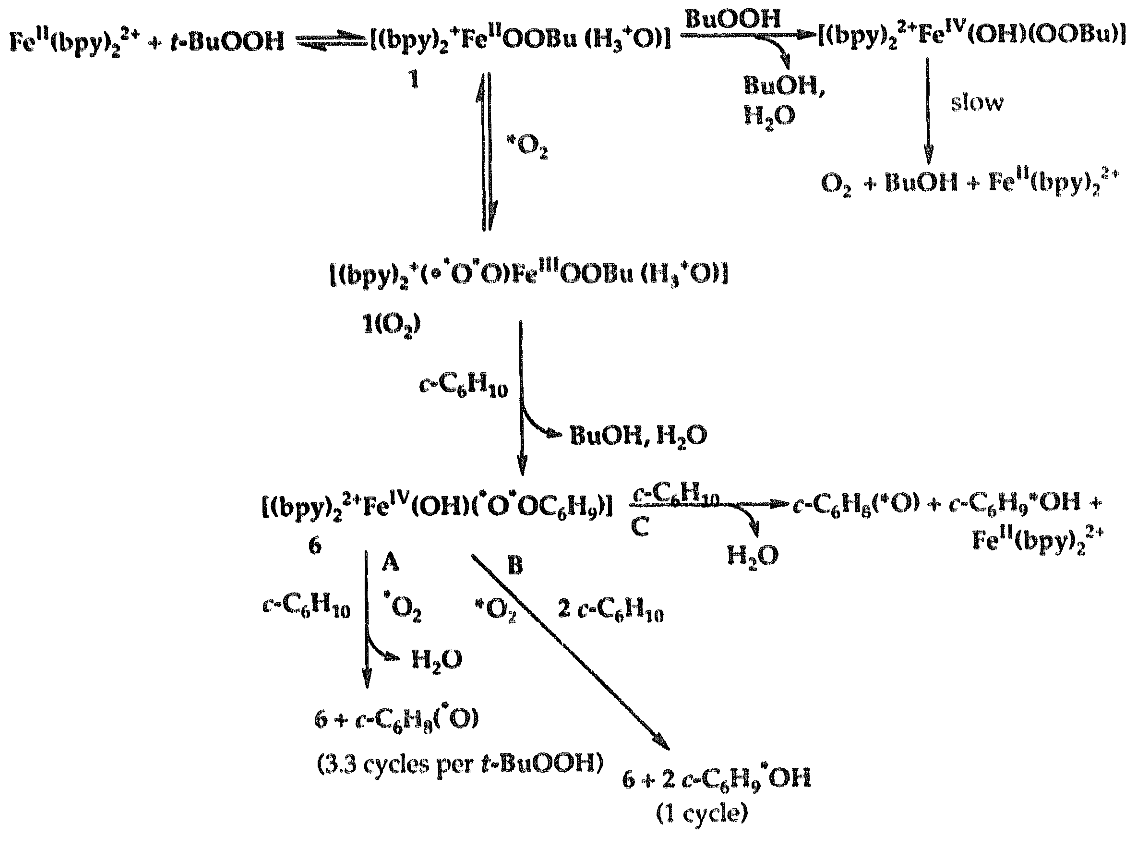
Results [23] for a $Fe^{III}(NO_3)_3/t$-BuOOH/$^{18}O_2/c$-C_8H_{16} system in acetonitrile establish that the O-atoms in the c-$C_8H_{14}(O)$ and c-$C_8H_{15}OH$ products are from O_2. This supports the stoichiometry of Eq. (29) [10:20 $Fe^{II}L_x/t$-BuOOH systems are 20–80% efficient (ketone per t-BuOOH, Table 3)].

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. (29), Table 3), species **6** must activate O_2 for reaction with the substrate [turnovers per $Fe^{II}L_x \geq (t\text{-BuOOH}/Fe^{II}L_x)$]

$$\underset{\mathbf{6b}}{[L_xFe^{IV}(OH)(OOC_6H_9)]} \xrightarrow[O_2]{c-C_6H_{10}} \mathbf{6b} + \underset{2-\text{cyclohexene}-\text{one}}{c-C_6H_8(O)} + H_2O \qquad (30)$$

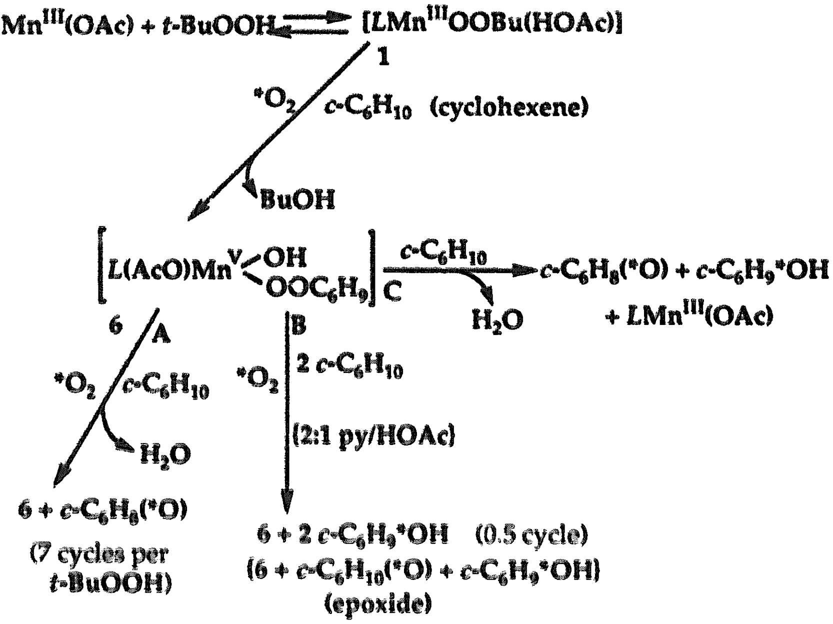
Hence, the 10 mM $Fe^{II}(bpy)_2^{2+}$/20 mM t-BuOOH/c-C_6H_{10} system has at least 3 O_2 turnovers via path E, which is similar to the 1.4 O_2 turovers per copper for the 5 mM $Cu^{I}(bpy)_2^{+}$/5 mM t-BuOOH/$PhCH_2CH_3$ system [15]. Likewise, the 10 mM $Fe^{II}(OPPh_3)_4^{2+}$/20 mM t-BuOOH/1 M c-C_6H_{10} system has almost 2 O_2 turnovers via Eq. (30) [12]. Scheme 2 outlines a set of reaction paths that are consistent with the product profiles with c-C_6H_{10} as the substrate.

Perhaps the most dramatic example of oxygenated Fenton chemistry is the



Scheme 2. Proposed pathways and intermediates for the metal/hydroperoxide-induced activation of O_2 for the ketonization of cyclohexane (c-C_6H_{10}).

$Mn^{III}L_x$/*t*-BuOOH-induced activation of O_2 for reaction with *c*-C_6H_{10} (Table 3) [24]. With (salen)Mn^{III}OAc (salen; Schiff base of two salicylaldehydes 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 three. However, whereas the ketone [*c*-C_6H_8(O), 2-cyclohexene-one] 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 3. 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 3 are not effective Fenton catalysts.



Scheme 3. $Mn^{III}L_x$/*t*-BuOOH-induced activation of O_2 for the oxygenation of olefins.

Thus, transition-metal complexes [ML_x; $Fe^{II}L_x$, $Mn^{III}L_x$, $Cu^{I}(bpy)_2^{+}$ and $Co^{II}(bpy)_3^{2+}$] 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; Scheme 1, Scheme 2 and Scheme 3). Analysis of the results in Table 2 and Table 3 confirms that the catalytic efficiency for the various species **6** depends on the metal, its ligand, the hydroperoxide (HOOH or *t*-BuOOH), the solution matrix, and the substrate. Hence, the $Fe^{II}(PA)_2$/HOOH/(2 py/HOAc) system provides the most potent reactive intermediates (**1** and **5**; smallest [*KIE*], 1.7 and 2.1, respectively for *c*-C_6H_{12}), but has low reaction efficiencies because HOOH acts as a competitive substrate. In contrast, the Mn^{III}(salen)(OAc)/*t*-BuOOH/MeCN system is not an effective Fenton reagent, nor an oxygenated Fenton reagent with *c*-C_6H_{12}. However, with *c*-C_6H_{10} as the substrate it is by far the most efficient oxygenated Fenton reagent (8.2 ketones [*c*-C_6H_8(O)] and 2.4 alcohols [*c*-C_6H_9OH] produced per *t*-BuOOH). Table 4 summarizes the relative reaction efficiencies (ketone per hydroper-

Table 4
Relative reaction efficiencies (ketone/hydroperoxide) for the ketonization of cyclohexane (c-C_6H_{12}), cyclohexene (c-C_6H_{10}) and ethyl benzene ($PhCH_2CH_3$) via metal/hydroperoxide-induced activation of O_2^a

$c-C_6H_{12}$:HOOH:$Fe^{II}(PA)_2 > Co^{II}(bpy)_2^{2+} > Cu^{I}(bpy)_2^{+} > Fe^{II}(bpy)_2^{2+} \sim Fe^{II}(OPPh_3)_4^{2+}$							
(K/HP)	0.4 [2.1]^b	0.2 [2.9]^b	0.1 [2.4]^b	0.05 [4.0]^b	0.05 [>10]^b		
(Alc/HP)	0.0	0.0	0.07 [1.1]^b	0.04 [1.4]^b	0.07 [1.9]^b		
$t-$BuOOH:$Fe^{II}(PA)_2 > Cu^{I}(bpy)_2^{+} > Fe^{II}(bpy)_2^{2+} \sim Fe^{II}(OPPh_3)_4^{2+} > Co^{II}(bpy)_2^{2+}$							
(K/HP)	0.8 [7.6]^b	0.3 [8.8]^b	0.2 [>10]^b	0.2 [10]^b	0.1 [9.6]^b		
(Alc/HP)	0.0	0.1 [>8]^b	0.25 [4.8]^b	0.31 [5.4]^b	0.03 [6.3]^b		
$c-C_6H_{10}$:HOOH:$Co^{II}(bpy)_2^{2+} > Fe^{II}(PA)_2 \sim Cu^{I}(bpy)_2^{+} > Fe^{II}(bpy)_2^{2+} > Fe^{II}(OPPh_3)_4^{2+}$							
(K/HP)	0.2	0.1	0.1	0.05	0.03		
$t-$BuOOH:$Mn^{III}(salen)(OAc) > Mn^{III}(bpy)_2(OAc)_3 > Mn^{III}(OPPh_3)_4(OAc)_3 > Fe^{II}(bpy)_2^{2+} > Fe^{II}(PA)_2 > Cu^{I}(bpy)_2^{+} > Co^{II}(bpy)_2^{2+} Fe^{II}(OPPh_3)_4^{2+}$							
(*K*/*HP*)	8.0	7.0	5.6	4.3	3.0	1.3	0.7
(*Alc*/*HP*)	2.4	2.1	0.6	3.0	1.8	0.0	
$PhCH_2CH_3$:HOOH:$Fe^{II}(PA)_2 > Co^{II}(bpy)_2^{2+} > Fe^{II}(bpy)_2^{2+} > Cu^{I}(bpy)_2^{+} > Fe^{II}(OPPh_3)_4^{2+}$							
(*K*/*HP*)	0.8	0.2	0.15	0.1	0.05		
$t-$BuOOH:$Fe^{II}(PA)_2 > Mn^{III}(salen)(OAc) > Fe^{II}(OPPh_3)_4^{2+} > Fe^{II}(bpy)_2^{2+} > Mn^{III}(bpy)_2(OAc)_3 > Cu^{I}(bpy)_2^{+} > Co^{II}(bpy)_2^{2+} Mn^{III}(OPPh_3)_4(OAc)_3$							
(*K*/*HP*)	3.2	2.0	1.9	1.8	1.6	1.4	0.9
(*Alc*/*HP*)	0.0	0.0	0.8	0.6	0.0	0.0	0.2

[a] Data from Refs. [11–13].

[b] Kinetic-isotope-effect; $[KIE] = k_{c-C_6H_{12}}/k_{c-C_6D_{12}}$.

oxide) for the several systems with cyclohexane, cyclohexene and ethyl benzene. Although the various species **5** and **6** formed via HOOH are more reactive than those formed via t-BuOOH (the former have much smaller *KIE* values), the latter have much larger efficiencies (HOOH is a much more reactive competitive substrate than t-BuOOH).

4. Summary

Hydroperoxides (ROOH) in solution react as nucleophiles towards electrophilic substrates [SO_2; RX; HOCl; transition-metal complexes ($Fe^{II}L_x$, $Cu^{I}L_x$, $Mn^{III}L_x$, $Co^{II}L_x$)] [25]. In contrast, dialkyl peroxides (ROOR) [with a weaker O–O bond (ΔH_{DBE} 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 towards 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 {**5** [**1**(O_2)]}. Table 5 lists proposed formulations for the reactive

Table 5
Proposed formulations for the reactive intermediates for Fenton chemistry (**1**) and oxygenated Fenton chemistry {**5** [**1**(O_2)] and **6**}

1:	$\{[(PA)_2^-]Fe^{II}OOH(Bu)[pyH^+]\}$	$\{[(Cl)_2^-]Fe^{II}OOH(Bu)[H_3O^+]\}$
	2py/HOAc	MeCN
5 [**1**(O_2)]:	$\{[(PA)_2^-](\cdot OO)Fe^{III}OOH(Bu)[pyH^+]\}$	$\{[(Cl)_2^-](\cdot OO)Fe^{III}OOH(Bu)[H_3O^+]\}$
	$\{(bpy)_2^+(\cdot OO)Fe^{III}OOH(Bu)[H_3O^+]\}$	$\{(bpy)_2(O_2)Cu^{III}OOH(Bu)[H_3O^+]\}$
	$\{(bpy)_2^+(\cdot OO)Co^{III}OOH(Bu)[pyH^+]\}$	$\{(bpy)_2(AcO)_2(\cdot OO)Mn^{IV}OOBu[HOAc]\}$
		$\{(salen)(\cdot OO)Mn^{IV}OOBu[HOAc]\}$
6:	$[(PA_2Fe^{IV}(OH)(OOR)]$ $[Cl_2Fe^{IV}(OH)(OOR)]$	$[(bpy)_2^{2+}Fe^{IV}(OH)(OOR)]$
	$[(bpy)_2^+Cu^{III}(OH)(OOR)]$	$[(bpy)_2^{2+}Co^{IV}(OH)(OOR)]$
	$[(bpy)_2(AcO)_3Mn^V(OH)(OOR)]$	$[(salen)(AcO)Mn^V(OH)(OOR)]$

RH = c-C_6H_{12} (cyclohexane), c-C_6H_{10}(cyclohexene), $PhCH_2CH_3$ (ethyl benzene)
PAH = picolinic acid (2-carboxyl pyridine)
salen = Schiff base (ethylenediamine plus 2 salicylaldehydes)

intermediates for Fenton chemistry (**1**) and oxygenated Fenton chemistry {**5** [**1**(O_2)] and **6**} within the present study. Each of these reactive intermediates (**1**, **5**, **6**) includes a stabilized hydroxyl group (HO) that (a) is less reactive than free HO· and (b) gives products from organic substrates via the internal formation of an intermediate with an iron–carbon bond [or Fe(pyl)–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**, **5**, **6**] 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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