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Iron(II)-Induced Generation of Hydrogen Peroxide from Dioxygen: Induction of Fenton Chemistry and Ketonization of Hydrocarbons

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The combination of Fe^{II}(DPAH)$_2$ (DPAH$_2$ = 2,6-dicarboxypyridine) and O$_2$ in a 2:1 pyridine/acetic acid solution results in a rapid autoxidation to produce HOOH and Fe^{III}(DPA)(DPAH) (k_1, 1.8 ± 0.5 M^{-1} s^{-1}). The resultant HOOH reacts with excess Fe^{II}(DPAH)$_2$ via a nucleophilic addition to give a Fenton reagent [(DPAH)$_2^-$Fe^{II}OOH + pyH$^+$] (**1**) that reacts with (a) excess Fe^{II}(DPAH)$_2$ to give Fe^{III}(DPA)(DPAH) [k_2, (2 ± 1) × 10^3 M^{-1} s^{-1}], (b) excess c-C$_6$H$_{12}$ and PhSeSePh (a carbon radical trap) to give c-C$_6$H$_{11}$SePh [kinetic isotope effect (KIE) ($k_{\text{c-C}_6\text{H}_{12}}$/$k_{\text{c-C}_6\text{D}_{12}}$), 2.2], and (c) excess O$_2$ to form an adduct [**1**(O$_2$)], which reacts with excess c-C$_6$H$_{12}$ via an intermediate [(DPAH)$_2$Fe^{IV}(OH)(OOC$_6$H$_{11}$)] (**6**) and Fe^{II}(DPAH)$_2$ to give c-C$_6$H$_{10}$(O) (KIE, 2.0) and Fe^{III}(DPA)(DPAH) [32 mM Fe^{II}(DPAH)$_2$, O$_2$ (1 atm, 3.4 mM), and 1 M c-C$_6$H$_{12}$ yield 6 mM c-C$_6$H$_{10}$(O)].

Introduction

In a 2:1 pyridineacetic acid [(py)$_2$HOAc] solution the Fe^{II}(DPAH)$_2$ complex (DPAH$_2$ = 2,6-pyridinecarboxylic acid) activities dioxygen (O$_2$) to ketonize methylenic carbons and to dioxygenate acetylenes, arylolefins, and catechols.[1,2] The dioxygenation of catechols by the Fe^{II}(DPAH)$_2$/O$_2$ system parallels that of the *catechol dioxygenase* enzymes (non-heme iron proteins),[3] and this system may be a useful model for the dioxygenase enzymes. The product profile also is close to that for the Fe^{II}(PA)$_2$/HOOH system in the same (py)$_2$HOAc solvent, and the reactive intermediate may have a similar formulation for the two systems.[4,6] When the (py)$_2$HOAc solvent is replaced with acetonitrile (MeCN) or 3:1 MeCN/py, the Fe^{II}(DPAH)$_2$/O$_2$ combination does not react with hydrocarbon substrates. However, the addition of PhNHNHPh causes the system to become a hydrocarbon monooxygenase (c-C$_6$H$_{12}$ → c-C$_6$H$_{11}$-OH),[7] which parallels the catalytic chemistry of monooxygenase proteins.

The ketonization of methylenic carbon [e.g., c-C$_6$H$_{12}$ → c-C$_6$H$_{10}$(O)] during the autoxidation of Fe^{II}(DPAH)$_2$ was originally attributed to a binuclear-iron–O$_2$ reactive intermediate,[1,2] but subsequent work,[5,6] has shown this speculation to be wrong. Related studies have demonstrated that a one-to-one combination of Fe^{II}(PA)$_2$ (PAH = picolinic acid) [or Fe^{II}(DPAH)$_2$] and HOOH reacts as a Fenton reagent,[8] whereas 1-to-20 combinations catalytically transform methylenic carbons to ketones [e.g., c-C$_6$H$_{12}$ → c-C$_6$H$_{10}$(O)].[4-6] The Fe^{III}Cl$_3$/HOOH, ^{18}O$_2$/c-C$_6$H$_{12}$/(py)$_4$HOAc system yields products [c-C$_6$H$_{10}$(^{18}O) and c-C$_6$H$_{11}$^{18}OH] that have incorporated O$_2$,[9] which also is true for the Fe^{II}(PA)$_2$/HOOH, O$_2$/c-C$_6$H$_{12}$ system (oxygenated Fenton chemistry).[6,10]

Because the Fe^{II}(PA)$_2$/HOOH-induced activation of O$_2$ for reaction with hydrocarbons (e.g., c-C$_6$H$_{12}$) yields results [including kinetic isotope effects ($k_{\text{c-C}_6\text{H}_{12}}$/$k_{\text{c-C}_6\text{D}_{12}}$)][6] that are essentially identical to those for the Fe^{II}(DPAH)$_2$/O$_2$ system, the latter may initially activate O$_2$ via generation of HOOH. This possibility has prompted the present investigation, which confirms that HOOH is the primary product from the combination of Fe^{II}(DPAH)$_2$ and O$_2$ in (py)$_2$HOAc.

Although there have been numerous suggestions that the autoxidation of reduced transition-metal complexes (Fe^{II}L$_x$, Co^{II}L$_x$, Mn^{II}L$_x$, and Cu^{I}L$_x$) generates HOOH,[11-13] we are not aware of previous experimental evidence for its in situ production by iron(II). The present results indicate that such generation may be reasonably common in biological systems and an important mechanism for oxygen toxicity.[14]

Experimental Section

Equipment. The reaction products were separated and identified with a Hewlett-Packard 5880 A Series gas chromatograph equipped with an HP-1 capillary column (cross-linked methyl silicone gum phase, 12 m × 0.2 mm i.d.) and by gas chromatography–mass spectrometry (Hewlett-Packard 5790A Series gas chromatograph with a mass-selective detector). A Vacuum Atmospheres glovebox was used for the storage, preparation and addition of air-sensitive and water-sensitive reagents.

A three-electrode potentiostat (Bioanalytical Systems Model CV-27) with a Houston Instruments Model 200 XY recorder was used to record the voltammograms. The experiments were conducted in a 15-mL electrochemical cell with provision to control the presence of O$_2$ with an argon-purge system. The working electrode was a Bioanalytical Systems glassy-carbon inlay (area, 0.09 cm^2), the auxiliary electrode a platinum wire, and the reference electrode a Ag/AgCl wire in an aqueous tetramethylammonium chloride solution that was adjusted to give a potential of 0.00 V vs SCE. The latter was contained in a Pyrex tube with cracked soft-glass tip, which was placed inside a luggin capillary.

Chemicals and Reagents. The reagents for the investigations and syntheses were the highest purity commercially available and were used without further purification. Burdick and Jackson "distilled in glass"

[●] Abstract published in *Advance ACS Abstracts,* December 1, 1993.

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grade acetonitrile (MeCN, 0.002% H_2O), pyridine (py, 0.007% H_2O), and glacial acetic acid (HOAc, ACS grade, Fisher) were used as solvents. High-purity argon was used to deaerate the solutions. All compounds were dried in vacuo over $CaSO_4$ for 24 h prior to use. Picolinic acid (PAH, 99%) and 2,6-pyridinedicarboxylic acid ($DPAH_2$, 99%) were obtained from Aldrich. Ferrous perchlorate (99+%) was obtained from GFS, and hydrogen peroxide (50% H_2O) and perchloric acid ($HClO_4$, 70%) were obtained from Fisher. The organic substrates included the following: Cyclohexane (Aldrich, anhydrous 99+%); cyclohexane-d_{12} (Aldrich, 99.5 atom % D).

Synthesis of $(Me_4N)PA$ and $(Me_4N)_2DPA$. Tetramethylammonium picolinate [$(Me_4N)PA$] and tetramethylammonium dipicolinate [$(Me_4N)_2$-DPA] were prepared by the neutralization of picolinic acid (PAH) and 2,6-pyridinedicarboxylic acid ($DPAH_2$) with tetramethylammonium hydroxide pentahydrate in acetonitrile (MeCN).[4] $(Me_4N)PA$ and [$(Me_4N)_2DPA$] were recrystallized from 95% MeCN/5% MeOH. The hygroscopic products were stored under vacuum.

$[Fe^{II}(MeCN)_4](ClO_4)_2$. The $[Fe^{II}(MeCN)_4](ClO_4)_2$ complex was prepared by multiple crystallizations of $[Fe^{II}(H_2O)_6](ClO_4)_2$ from MeCN.

Iron(II) Bis(picolinate) and Iron(II) Bis(dipicolinate). Solutions of $Fe^{II}(PA)_2$ and $Fe^{II}(DPAH)_2$ were prepared in-situ by mixing $[Fe^{II}(MeCN)_4](ClO_4)_2$ with stoichiometric ratios of the ligand anions.[15]

Methods. The investigations of O_2 and HOOH activation by the iron complexes (1–10 mM) used solutions that contained 1.0 M substrate in 3.5 mL of pyridine, HOAc, or various mole ratios of py/HOAc (usually 2:1). The reaction cell (10-mL glass vial) had 6 mL of head-space (O_2 at 1 atm, 44 mM), which provided a reservoir to maintain a constant solution concentration of O_2 (3.4 mM). For the activation of O_2, $Fe^{II}(DPAH)_2$ and substrate were combined in the solvent matrix prior to the addition of O_2 (1 atm, 3.4 mM).[1,15] For hydrogen peroxide activation, HOOH (50% in H_2O) was added to give 8–19 mM concentrations. The reactions were allowed to proceed for 1–18 h with constant stirring at room temperature (24 ± 2 °C) under Ar or O_2 (0.2 or 1 atm), after which samples of the reaction solutions (0.2–0.5 μL) were injected into a capillary-column gas chromatograph for analysis. In some cases the reactions were quenched with water and the product solutions extracted with diethyl ether. Product species were characterized by GC–MS. Reference samples were used to confirm product identifications and to produce standard curves for quantitative assays of the product species.

The kinetic isotope effect [KIE, k_H/k_D] was determined with a 1:1 cyclohexane/cyclohexane-d_{12} mixture (0.5 M/0.5 M) as the substrate; the KIE values were calculated from the product ratios of $c\text{-}C_6H_{10}(O)$/$c\text{-}C_6D_{10}(O)$, $(c\text{-}C_6H_{11})py$/$(c\text{-}C_6D_{11})py$, and $c\text{-}C_6H_{11}SePh$/$c\text{-}C_6D_{11}SePh$.

Results

The combination of $[Fe^{II}(MeCN)_4](ClO_4)$ with 2 equiv of $DPAH_2$ in 2:1 py/HOAc [$(py)_2HOAc$] yields $Fe^{II}(DPAH)_2$, which in the presence of O_2 is autoxidized to $Fe^{III}(DPA)(DPAH)$. Figure 1 illustrates that the $Fe^{II}(DPAH)_2$ complex is reversibly oxidized at +0.05 V vs SCE [$Fe^{II}(PA)_2$ is oxidized at +0.30 V under the same conditions and is unaffected by the presence of O_2; $Fe^{II}(DPA)$ is oxidized at +0.18 V].[4,15] The cyclic voltammogram for the $Fe^{II}(DPAH)_2/O_2$ combination (curve b, Figure 1) confirms that all of the iron is autoxidized to $Fe^{III}(DPA)$-(DPH) within 13 min (the initial rest potential of –0.15 V shifts to +0.12 V). An initial positive scan yields a new anodic peak at +1.25 V, which is characteristic of free HOOH in the presence of $Fe^{III}(DPA)(DPAH)$ (curve c, Figure 1). Under the limiting conditions of excess O_2 and 1 mM $Fe^{II}(DPAH)_2$ about 0.21 ± 0.05 HOOH is detected per $Fe^{III}(DPA)(DPAH)$ produced.

The rate of autoxidation of $Fe^{II}(DPAH)_2$ has been evaluated via potentiometry of the iron (II/III) couple. The results confirm that the reaction (a) is first-order each in $Fe^{II}(DPAH)_2$ and O_2 concentrations, (b) has a stoichiometric factor of four $Fe^{II}(DPAH)_2$ oxidized per O_2, and (c) has a apparent rate constant, k_1, of 2.3 ± 0.5 $M^{-1}\,s^{-1}$ ($k_1 = k_{obs}/4$). Because 1:1 $Fe^{II}(DPAH)_2$ [or $Fe^{II}(PA)_2$]/HOOH reacts 1000 times faster (k_2, 2×10^3 $M^{-1}\,s^{-1}$),[4] the $Fe^{II}(DPAH)_2/O_2$ system cannot accumulate HOOH.

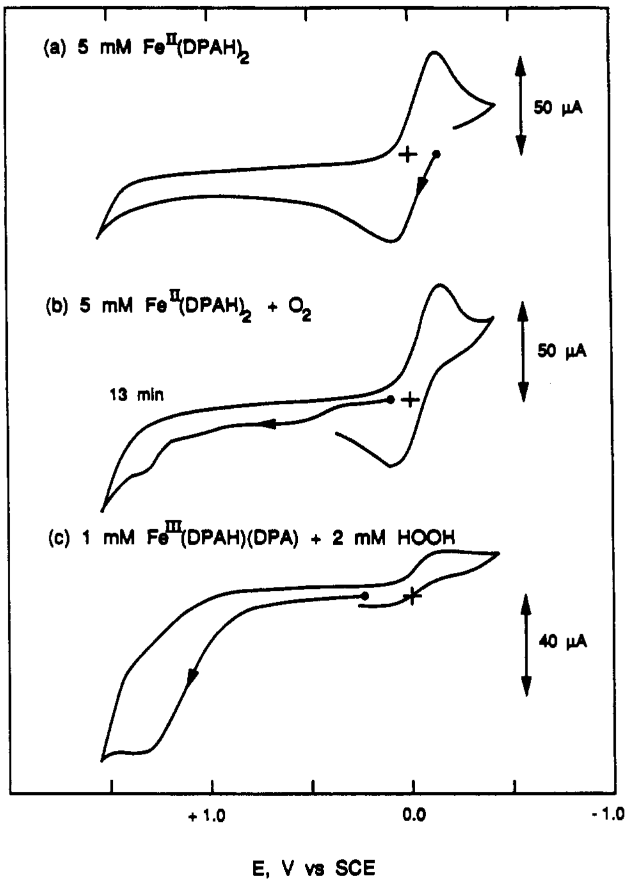

Figure 1. Cyclic voltammograms in $(py)_2HOAc$ [0.1 M $(Et_4N)ClO_4$] for (a) 5 mM $Fe^{II}(DPAH)_2$, (b) 5 mM $Fe^{II}(DPAH)_2$ in the presence of O_2 (1 atm, 3.4 mM), and (c) the combination of 1 mM $Fe^{III}(DPA)$-(DPAH) and 2 mM HOOH. Conditions: Glassy-carbon electrode (area, 0.09 cm^2); scan rate, 0.1 V s^{-1}; SCE vs NHE, +0.242 V.

Table 1. Concentrations of $c\text{-}C_6H_{10}(O)$ Produced from the Combination of 32 mM $Fe^{II}(DPAH)_2$, 1 M $c\text{-}C_6H_{12}$, and O_2 (1 atm, 3.4 mM) for Different py/HOAc Solvent Ratios and Reaction Times

pyr/HOAc, mole ratio	concn of $c\text{-}C_6H_{10}(O)$, mM (±5%)		
	10 min	3 h	8 h
pure py	3.3	4.9	4.7
3:1	4.5	5.4	5.0
2:1[a]	4.7	6.0	6.0
1:1	5.6	5.8	5.8
1:2	4.2	5.2	4.4
1:3	3.5	3.4	4.4
pure HOAc	0	0	0

[a] Addition of 32 mM $[(n\text{-}Bu)_4N]OH$ to the catalyst system reduced the yield 10–30%; addition of 32 mM $HClO_4$ had no detectable effect.

Reactivity with Hydrocarbon Substrates. Table 1 summarizes the effect of the solvent matrix on the reaction dynamics and product yield for the combination of 32 mM $Fe^{II}(DPAH)_2$, 1 M $c\text{-}C_6H_{12}$, and O_2 (1 atm). The rate of substrate ketonization is greater in 1:1 py/HOAc (yield within a 10-min reaction time), but the final yield is essentially the same for 1:1 and 2:1 py/HOAc. In the latter matrix the rate of $c\text{-}C_6H_{12}$ ketonization is first order each in $Fe^{II}(DPAH)_2$ and O_2 concentrations and the yield of $c\text{-}C_6H_{10}(O)$ is directly proportional to the initial concentration of $Fe^{II}(DPAH)_2$.[1]

The product profiles from the activation of O_2 or HOOH by $Fe^{II}(DPAH)_2$ in a $(py)_2HOAc$ matrix that contains 1 M $c\text{-}C_6H_{12}$ are summarized in Table 2. For the combination of 32 mM

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(15) The dominant form of these complexes in $(py)_2HOAc$ and DMF has been characterized by electrochemical and spectrophotometric measurements. In DMF $Fe^{II}(PA)_3^-$ is oxidized at –0.01 V vs SCE, $Fe^{II}(PA)_2$ at +0.15 V, $Fe^{II}(DPA)$ at +0.15 V, $Fe^{II}(DPAH)_2$ at –0.10 V, and $Fe^{II}(DPA)_2^{2-}$ at –0.31 V; $[(PA)_2Fe^{III}OH]_2$ is reduced at –0.65 V, and $(PA)_2Fe^{III}OFe^{III}(PA)_2$ at –0.85 V. In the presence of $Fe^{III}(DPA)(DPAH)$ in $(py)_2HOAc$, HOOH is oxidized at +1.25 V: Cofré, P.; Richert, S. A.; Sobkowiak, A.; Sawyer, D. T. *Inorg. Chem.* **1990**, *29*, 2645.

Table 2. Autoxidation of $Fe^{II}(DPAH)_2$ for the in Situ Generation of HOOH and Induction of Fenton Chemistry with c-C_6H_{12} (1 M) in $(py)_2HOAc$

system[a]	products (mM, ±5%)[b] [KIE][c]
(a) 32 mM $Fe^{II}(DPAH)_2/O_2$ (1 atm, 3.4 mM)	
w 10 mM PhSeSePh	*c*-C_6H_{12}SePh (2) [2.2]
wo 10 mM PhSeSePh	*c*-C_6H_{10}(O) (6) [2.0]
(b) 8 mM $Fe^{II}(DPAH)_2$/8 mM HOOH/Ar (1 atm)	
w 10 mM PhSeSePh	*c*-C_6H_{11}SePh (2) [2.4]
wo 10 mM PhSeSePh	(*c*-C_6H_{11})py (3) [1.8]
wo 10 mM PhSeSePh/O_2 (1 atm)	*c*-C_6H_{10}(O) (2) [2.0]
(c) 9 mM $Fe^{II}(PA)_2$/9 mM HOOH/Ar (1 atm)	
w 10 mM PhSeSePh	*c*-C_6H_{11}SePh (8) [2.4]
wo 10 mM PhSeSePh	(*c*-C_6H_{11})py (4) [1.7]
wo 10 mM PhSeSePh/O_2 (1 atm)	*c*-C_6H_{10}(O) (2) [2.1]
(d) 19 mM $Fe^{II}(PA)_2$/19 mM HOOH/Ar (1 atm)	
w 10 mM PhSeSePh	*c*-C_6H_{11}SePh (17); *c*-C_6H_{10}(O) (1)
wo 10 mM PhSeSePh	(*c*-C_6H_{11})py (6) [1.7]; *c*-C_6H_{10}(O) (1)

[a] Substrate (1 M *c*-C_6H_{12}) and $Fe^{II}(DPAH)_2$ [$Fe^{II}(MeCN)_4(ClO_4)_2$ added to 2 equiv of $DPAH_2$] combined in 3.5 mL of pyridine/HOAc (2:1 mol ratio) followed by the addition of O_2 (1 atm, 3.4 mM) (or HOOH) in a reaction cell with 6 mL of head space (1 atm O_2, 4 mM). Reaction time and temperature: 1–18 h at 24 ● 2 °C. *w* = with and *wo* = without. [b] The product solutions were analyzed by capillary-column gas chromatography and GC–MS (either by direct injection of the product solution or by quenching with H_2O and extracting with diethyl ether). [c] KIE = kinetic isotope effect ($k_{c\text{-}C_6H_{12}}/k_{c\text{-}C_6D_{12}}$); product ratios from a 0.5 M *c*-C_6H_{12}/0.5 M *c*-C_6D_{12} substrate.

$Fe^{II}(DPAH)_2$ and O_2 (1 atm, 3.4 mM),[4] 6 mM c-C_6H_{10}(O) (kinetic isotope effect, 2.0) is the only detectable product, and with 10 mM PhSeSePh (a carbon-radical trap) present phenylselenization results to give 2 mM c-C_6H_{11}SePh (Table 2a). For a one-to-one combination of 8 mM $Fe^{II}(DPAH)_2$ and 8 mM HOOH with c-C_6H_{12} in the absence of O_2 the only detectable product is (c-C_6H_{11})py; 2 mM c-C_6H_{11}SePh is the main product when PhSeSePh is present. In the presence of O_2 the product is c-C_6H_{10}(O) (Table 2b). Thus, the $Fe^{II}(DPAH)_2$/c-C_6H_{12}/O_2 combination parallels the $Fe^{II}(DPAH)_2$/c-C_6H_{12}/(HOOH, O_2) system for ketonization, and the $Fe^{II}(DPAH)_2$/c-C_6H_{12}/PhSeSePh/O_2 combination parallels the $Fe^{II}(DPAH)_2$/c-C_6H_{12}/PhSeSePh/HOOH system for phenylselenization. The results for a one-to-one $Fe^{II}(DPAH)_2$/HOOH combination (without and with O_2 present) to produce (c-C_6H_{11})py, c-C_6H_{11}SePh, and c-C_6H_{10}(O) are the same as those for the $Fe^{II}(PA)_2$/HOOH system (Table 2b,c).

Discussion and Conclusions

The $Fe^{II}(PA)_2$ complex in $(py)_2HOAc$ is reversibly oxidized at +0.30 V vs SCE to $(PA)_2Fe^{III}(OAc)$[4,15] but is unreactive with O_2. In contrast, the $Fe^{II}(DPAH)_2$ complex is oxidized at a less positive potential

$$Fe^{II}(DPAH)_2 + py \underset{-0.10\text{ V}}{\overset{+0.05\text{ V vs SCE}}{\rightleftarrows}} Fe^{III}(DPA)(DPAH) + pyH^+ + e^- \quad (1)$$

and is rapidly autoxidized by O_2 to $Fe^{III}(DPA)(DPAH)$ (Figure 1).[15]

The shift of 0.25 V indicates that (a) $Fe^{II}(DPAH)_2$ is a better reductant, (b) the stability constant for $Fe^{III}(DPA)(DPAH)$ is about 10^4 times greater than that for $Fe^{III}(PA)_2(OAc)$, and (c) the latter is due to an entropic chelate effect for the intramolecular formation of $Fe^{III}(DPA)(DPAH)$ (about 6 kcal mol^{-1}).[16]

Addition of O_2 to $Fe^{II}(DPAH)_2$ results in its rapid autoxidation and the production of HOOH {Figure 1, about 25% efficient [HOOH per two $Fe^{II}(DPAH)_2$]}.

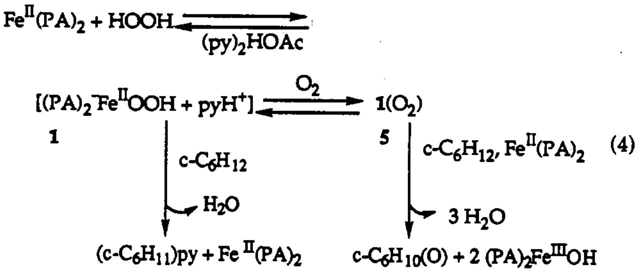
$$Fe^{II}(DPAH)_2 + O_2 \underset{(py)_2HOAC}{\overset{k_1}{\rightleftarrows}} [(DPAH)_2Fe^{IV}(O_2)] \xrightarrow{Fe^{II}(DPAH)_2} 2Fe^{III}(DPA)(DPAH) + HOOH \quad (2)$$

The resultant HOOH reacts with excess $Fe^{II}(DPAH)_2$ 1000 times faster, which precludes accumulation of HOOH.

$$Fe^{II}(DPAH)_2 + HOOH \overset{k_2}{\rightleftarrows} [(DPAH)_2^{-}Fe^{II}OOH + pyH^+] \xrightarrow{Fe^{II}(DPAH)_2} 2Fe^{III}(DPA)(DPAH) + 2H_2O \quad (3)$$

With significant $Fe^{II}(DPAH)_2$ concentrations all of the initially formed HOOH is consumed, but as iron(II) is depleted via the reactions of eqs 2 and 3 HOOH persists during the latter stage of the autoxidation (Figure 1).

The combination of $Fe^{II}(PA)_2$ and HOOH activates O_2 for the ketonization of c-C_6H_{12} (KIE, 2.1 for HOOH) (Table 2c).[6]



(4)

In the absence of O_2 the $Fe^{II}(PA)_2$/HOOH system gives (c-C_6H_{11})py as the major product.[5,6,8] The $Fe^{II}(DPAH)_2$/HOOH system is equally effective in the activation of O_2 for the ketonization of methylenic carbons (Table 2b). The $Fe^{II}(DPAH)_2/O_2$/c-C_6H_{12} system (KIE, 2.0) (Table 2a) has the same reactivity as the $Fe^{II}(DPAH)_2$/HOOH, O_2/c-C_6H_{12} system to give c-C_6H_{10}(O) as the only detectable product (KIE, 2.0). This is compelling evidence the $Fe^{II}(DPAH)_2/O_2$ combination generates HOOH, which combines with excess $Fe^{II}(DPAH)_2$ to form **1** and activate excess O_2 for the ketonization of c-C_6H_{12} (eq 4).

The phenylselenization reactions of Table 2 also support the conclusion that the $Fe^{II}(DPAH)_2/O_2$ combination initially generates HOOH. Thus, the $Fe^{II}(DPAH)_2$/HOOH/PhSeSePh system in $(py)_2HOAc$ yields c-C_6H_{11}SePh from c-C_6H_{12} (KIE, 2.4) [analogous to $Fe^{II}(PA)_2$/HOOH],[8] as does the $Fe^{II}(DPAH)_2/O_2$/PhSeSePh system (2.2). The HOOH generated from $Fe^{II}(DPAH)_2$ and O_2 is activated by the excess $Fe^{II}(DPAH)_2$ to give the product.

$$Fe^{II}(DPAH)_2 + HOOH + c\text{-}C_6H_{12} + {}^1/_2PhSeSePh \rightarrow Fe^{III}(DPA)(DPAH) + c\text{-}C_6H_{11}SePh + 2H_2O \quad (5)$$

The cyclic voltammograms for the $Fe^{II}(DPAH)_2/O_2$ combination also indicate the presence of in-situ generated HOOH (+1.25-V peak, Figure 1).[15]

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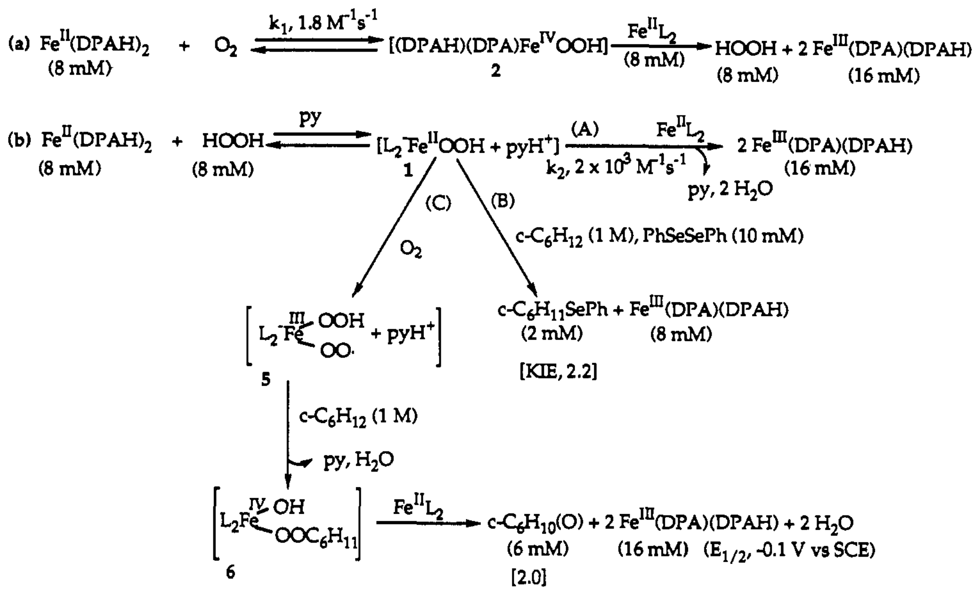
Scheme 1. $Fe^{II}(DPAH)_2$-Induced Generation of HOOH from O_2[a]



[a] Model: 32 mM $Fe^{II}(DPAH)_2$, O_2 (1 atm, 3.4 mM), and 1 M $c\text{-}C_6H_{12}$ in $(py)_2HOAc$.

Reaction schemes for the production of HOOH from $Co^{II}(bpy)_2{}^{2+}/O_2$ and $Cu^{I}(tpy)_2{}^{+}/O_2$ combinations via binuclear μ-peroxo complexes have been proposed.[17,18] These propositions are supported by electrochemical and spectroscopic results, but similar studies of the $Fe^{II}(DPAH)_2/O_2$ system do not provide any support for the formation of a binuclear intermediate during the HOOH generation cycle (the electrochemistry indicates that the iron remains mononuclear, Figure 1).[15]

The autoxidation of uncharged *meso*-tetraphenylporphyrinato)-iron(II) $[Fe^{II}(TPP)]$ initially forms a binuclear μ-peroxo species $[(TPP)Fe^{III}OOFe^{III}(TPP)]$ that dissociates homolytically to give an oxene product $[(TPP)Fe^{IV}=O]$.[19,20] This result implies that the generation of HOOH from $Fe(II)/O_2$ combinations does not occur via a binuclear peroxo complex. A more reasonable path involves an initial rate-limiting interaction between iron(II) and dioxygen to give a dioxygen–iron adduct $[(DPAH)_2Fe^{IV}(O_2)]$ (eq 2). The latter may undergo an internal arrangement to give $[(DPAH)(DPA)Fe^{IV}OOH]$ before it reacts with another iron(II) to generate HOOH and two $Fe^{III}(DPA)(DPAH)$.

Scheme 1 outlines a reasonable set of reaction pathways for the $Fe^{II}(DPAH)_2/O_2/c\text{-}C_6H_{12}$ system. The initial formation of an $[Fe^{II}(DPAH)_2](O_2)$ adduct (**2**, Scheme 1a) is reversible and rate limiting and is rapidly driven to completion by excess $Fe^{II}(DPAH)_2$ to produce HOOH [about 8 mM HOOH for 32 mM $Fe^{II}(DPAH)_2$] (Table 2). The resultant HOOH reacts with $Fe^{II}(DPAH)_2$ via nucleophilic addition to give **1** (Scheme 1b),[5] which reacts via (a) path A with $Fe^{II}(DPAH)_2$ to give $Fe^{III}(DPA)(DPAH)$;[4] (b) path B with $c\text{-}C_6H_{12}$ and PhSeSePh to give $c\text{-}C_6H_{11}SePh$ (Fenton chemistry),[8] and (c) path C with O_2 to form an adduct (**5**) that reacts with $c\text{-}C_6H_{12}$ via **6** to give $c\text{-}C_6H_{10}(O)$ (*oxygenated Fenton chemistry*;[10] 75% efficient in terms of the proposed stoichiometry of Scheme 1).[6] The 8 mM $Fe^{II}(DPAH)_2$/8 mM HOOH, $O_2/c\text{-}C_6H_{12}$ system (Table 2) appears to react via the same paths of Scheme 1b but is only 25% efficient (probably due to the large initial HOOH concentration, which favors its disproportionation).[6]

Thus, species **5** represents an *oxygenated Fenton reagent* that reacts with saturated hydrocarbons (RH) to form a carbon radical ($R^\bullet$) that is trapped by the bound dioxygen to give species **6**.[6,10]

$$\mathbf{5} + RH \rightarrow \mathbf{6} + H_2O \qquad (6)$$

With $Fe^{II}(PA)_2$/HOOH/RH systems species **6** reacts with either another substrate molecule [large $HOOH/Fe^{II}(PA)_2$ ratio] or the catalyst [small $HOOH/Fe^{II}(PA)_2$ ratio, at the end of the reaction cycle]:[10]

$$\mathbf{6} + RH \rightarrow R'(O) + ROH + H_2O + Fe^{II}(PA)_2 \qquad (7)$$

$$\mathbf{6} + Fe^{II}(PA)_2 \rightarrow R'(O) + 2Fe^{III}(PA)_2(OH) \qquad (8)$$

With the present system the latter condition [low $HOOH/Fe^{II}(DPAH)_2$ ratio] prevails (path C, Scheme 1b).

The entropic-energy gain that results from the ability of $Fe^{II}(DPAH)_2$ to provide the hydrogen atoms for the formation of HOOH (eq 2 and Scheme 1a) appears to be the reason for the unique, rapid autoxidation of $Fe^{II}(DPAH)_2$ to $Fe^{III}(DPA)(DPAH)$[15] {the unreactive $Fe^{II}(PA)_2$ complex ($E_{1/2}$, +0.2 V vs SCE)[6,15] would require HOAc in an autoxidation reaction $[2Fe^{II}(PA)_2 + 2HOAc + O_2 \rightleftarrows 2(PA)_2Fe^{III}OAc + HOOH]$}. A similar driving force should result from the site-specific binding of an iron(II) by a histidine and two aspartic-acid residues of a protein, which would induce the in-situ generation of HOOH, Fenton chemistry, and the substrate reactions of Scheme 1. This scenario is a more reasonable explanation of the apparent biological hazard of the reduced-iron/O_2 combination than is the generation of superoxide ion and free hydroxyl radical.[14]

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