Iron(III, II)-induced activation of dioxygen for the oxygenation of cyclohexene and related unsaturated hydrocarbons

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Abstract

Labile iron complexes [e.g., $[Fe^{III}(bpy)_2]^{3+}_{aq}$, $[Fe^{II}(bpy)_2]^{2+}_{aq}$, $[Fe^{III}(H_2O)_6]^{3+}_{aq}$ and $[Fe^{II}(H_2O)_6]^{2+}_{aq}$ in base-free aceto-nitrile activate dioxygen for the direct oxygenation of cyclohexene [to ketone, alcohol, and epoxide; $c\text{-}C_6H_{10} \xrightarrow{O_2} c\text{-}C_6H_8(O)$, $c\text{-}C_6H_9OH$, $c\text{-}C_6H_{10}$-epoxide] and related unsaturated hydrocarbons with allylic carbon centers. For example, the combination of 1 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}/O_2$ (1 atm)/1 M $c\text{-}C_6H_{10}$ yields 51 mM $c\text{-}C_6H_8(O)$, 42 mM $c\text{-}C_6H_9OH$, and 3 mM $c\text{-}C_6H_{10}$-epoxide within 24 h (about 100 catalyst turnovers − product molecules per catalyst molecule). With 1 mM $[Fe^{II}(H_2O)_6]^{2+}$ in place of $[Fe^{III}(bpy)_2]^{3+}$, the product yield is 35 mM $c\text{-}C_6H_8(O)$, 16 mM $c\text{-}C_6H_9OH$, and 0.1 mM epoxide. Under anhydrous conditions, the combination of 1 mM $[Fe^{II}(bpy)_2]^{2+}(MeCN)/O_2$ (1 atm)/2 M $c\text{-}C_6H_{10}$ in a 1-h reaction yields 48 mM $c\text{-}C_6H_8(O)$, 43 mM $c\text{-}C_6H_9OH$, and 3 mM $c\text{-}C_6H_{10}$-epoxide. Excess ligand or added H_2O inhibits the reaction rate, and 0.1 M H_3O^+, 0.3 mM α-tocopherol (vitamin E), or 1 mM 2,6-di-*tert*-butyl-4-methylphenol (BHT) completely suppresses product formation. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Although dioxygen (O_2, a biradical, 21 vol.% of the atmosphere) is an essential reagent in aerobic biology and the major factor in the degradation of organic molecules and polymers, it is essentially inert in the total absence of transition metals (free radicals by definition). Nature and the chemical process industries make use of O_2 via transition metal catalysts (enzymes) to (a) drive the biological heat engine (oxidative metabolism; ''cold combustion''), (b) dehydrogenate and oxygenate organic molecules, and thereby (c) facilitate the production of penicillin, hydroxylated tyrosine, muconic acid, methanol, nylon, and polyester (among

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many). Most biological catalysts are iron proteins plus several copper proteins, while industry uses mainly iron-, cobalt-, and silver-based catalysts. In contrast, trace quantities of dysfunctional iron and copper induce ''oxygen toxicity'', rancidification of fats and oils, and polymer degradation.

The reactivity of O_2 traditionally has been ascribed to its thermodynamic potential for electron transfer (with activation via electron transfer catalysts). However, on the basis of a series of chemical investigations, activated O_2 transforms organic substrates via H-atom and O-atom transfer [1–8], never via electron transfer. In the presence of O_2, Fenton systems [e.g., one-to-one Fe(II)/HOOH combinations] transform hydrocarbons to ketones and lesser amounts of alcohol, with all of the product oxygen derived from O_2 (oxygenated Fenton chemistry) [2–5]. The combination of Fe(II), O_2, and a donor molecule (DH_2; e.g., PhNHNHPh, ascorbic acid, $2PhCH_2SH$) (a) transforms hydrocarbons to alcohols and ketones, and (b) demethylates *N*-methyl anilines (model reaction system for *cytochrome P-450 monooxygenase / reductase*) [6,7] and (c) hydroxylates phenols (model reaction system for *tyrosine hydroxylase*) [8].

All of these (O_2)- activating systems (a) have a donor co-factor (e.g., HOOH, DH_2), (b) involve metal (M)/dioxygen (O_2) radical–radical coupling to weaken the O—O bond ($\Delta H_{DBE} = 119$ kcal mol^{-1} for O_2) [9] and thereby enhance the FeOO—H bond energy of substrate-derived (H·) atoms (or donor-derived) and the FeOO—R bond energy of substrate-derived carbon radicals ($R\cdot$), (c) are driven to exothermicity via formation of H_2O ($\Delta H_f = 221$ kcal mol^{-1}) [9] from two substrate H-atoms and one of the two O-atoms of O_2, and (d) appear to have a common reactive intermediate {[$L_x Fe^{IV}(OH)(OOR)$], **6**}.

With this background, we were surprised to discover that labile iron(II) complexes {e.g., $[Fe^{II}(bpy)_2]^{2+}$ and $[Fe^{II}(OPPh_3)_4]^{2+}$} catalytically activate O_2 (a) to transform (oxygenate) cyclohexene (c-C_6H_{10}) and methyl linoleate

$[CH_3(CH_2)_4CH{=}CH(CH_2)_7C(O)OCH_3]$ to their respective ketone, alcohol, and epoxide derivatives, and (b) to initiate the autoxidation of 1,4-cyclohexadiene (1,4-c-C_6H_8) to benzene [10]. Most schemes for ''oxygen toxicity'' and for the oxygenation of unsaturated fats and lipids [11,12] invoke initiation by free hydroxyl radical (HO·) or an iron(II)/HOOH combination (Fenton chemistry) [13]. Hence, the prospect that simple iron complexes are sufficient to activate ambient O_2 for this chemistry has important implications for strategies (a) to catalyze its constructive use and (b) to inhibit its toxic and degradative reactions (anti-oxidants).

These considerations have prompted a systematic investigation of several iron(III) and iron(II) complexes in acetonitrile for the activation of O_2 to oxygenate cyclohexene and other unsaturated hydrocarbons. Again, to our surprise, iron(III) complexes are more effective catalysts {e.g., 1 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}$ yields 50% more product than 1 mM $[Fe^{II}(bpy)_2]^{2+}_{MeCN}$ [10] within a 1-h reaction time}. Apparently, the bound (HO·) group of the reactive form of the iron(III) catalyst [($L_x^{2+} Fe^{III}$–OH; approximate bond energy (ΔH_{DBE}), 53 kcal mol^{-1}] is reactive enough to abstract a substrate allylic hydrogen to form a carbon radical ($R\cdot$), which, within the collision complex, combines with O_2 and $Fe^{II}L_x^{2+}$ to form $[(L_x Fe^{III}$–OO–$R)]$ and thereby achieve exothermicity. Iron-hydroperoxo and alkylperoxo complexes like species 5 $((bpy)_2^{2+} Fe^{III}$–OO–$R))$ have been studied extensively during the last decade [14,15]. The existence of such complexes has been established and their role as catalytic intermediates in alkane and arene oxidation/hydroxylation and olefin epoxidation has been proposed [16–25]. Although the chemistry is radical-like, there is no evidence that the net product-forming pathways involve *free* oxy or carbon radicals. The role of the iron(III, II) catalysts, as free radicals, is probably to facilitate homolytic bond breakage and bond formation via metal oxygen radical/radical coupling, which facilitates HO–H and R–O radical/radical coupling.

2. Experimental

2.1. Equipment

The reaction products were separated and identified with a Hewlett-Packard 5880A Series gas chromatograph equipped with an HP-1 capillary column (cross-linked methyl silicone gum phase, 12 m $\times$ 0.2 mm i.d.) and by gas chromatography mass spectrometry (GC-MS; Hewlett-Packard 5790A Series gas chromatograph with a mass-selective detector). A three-electrode potentiostat (Bioanalytical Systems Model CV-50W) was used to record the voltammograms. The experiments were conducted in a 15 ml electrochemical cell with provision to control the presence of dioxygen 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 a cracked soft glass tip, which was placed inside a Luggin capillary [26].

2.2. Chemicals and reagents

The reagents for the investigations and syntheses were the highest purity commercially available and were used without further purification. The solvent for all of the experiments was Burdick and Jackson ''distilled in glass'' grade acetonitrile (MeCN, 0.002% H_2O). High-purity argon gas was used to deaerate the solutions. All compounds were dried in vacuo over $CaSO_4$ for 24 h prior to use. Ferric chloride [$Fe^{III}Cl_3$(aq), 98%] and 2,2′-bipyridine (bpy, 99 + %) were obtained from Aldrich. $Fe^{II}(ClO_4)_2 \cdot 6H_2O$ (99 + %) and $Fe^{III}(ClO_4)_2 \cdot 9H_2O$ (99 + %) were obtained from GFS, perchloric acid (HClO$_4$, 70%) from Fisher. The organic substances included cyclohexene (99%), ethyl benzene (99.8%), cumene (99%), 2,6-di-

tert-butyl-4-methylphenol (BHT) (99%), α-tocopherol (97%) and quercetin dihydrate (98%) which were obtained from Aldrich.

2.2.1. Synthesis of [Fe^{II}(MeCN)$_4$](ClO$_4$)$_2$

The [Fe^{II}(MeCN)$_4$](ClO$_4$)$_2$ complex was prepared by multiple recrystallizations of [Fe^{II}(H$_2$O)$_6$](ClO$_4$)$_2$ from MeCN [27,28].

2.2.2. Iron(II) bis(2,2′-bipyridine)

The [Fe^{II}(bpy)$_2$]$^{2+}_{MeCN}$ complex was prepared in situ by mixing [Fe^{II}(MeCN)$_4$](ClO$_4$)$_2$ in MeCN with a stoichiometric ratio of bipyridine. The other iron complexes were prepared in situ by mixing the iron salt with stoichiometric ratios of ligand in acetonitrile.

2.3. Methods

The investigations of O_2 activation by the iron complexes (0.1–5 mM) used solutions that contained 0.25–4 M substrate in 5 ml of MeCN. After 15 min, 1 h, or 24 h with constant stirring at room temperature (24 $\pm$ 2°C) under Ar or O_2 (0.2 or 1 atm), samples of the reaction solutions were injected into a capillary column gas chromatograph for analysis. In some cases, the reaction was quenched with water, and the product solution was 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. All experiments were performed three times. The presented values of concentration are the mean values of three independent experiments.

3. Results

In acetonitrile, simple iron(III) and iron(II) complexes catalytically activate dioxygen (O_2) to oxygenate cyclohexene (c-C$_6$H$_{10}$) to yield ketone [cyclohexene-3-one; c-C$_6$H$_8$(O)], alcohol [cyclohexene-3-ol; c-C$_6$H$_9$OH], and epoxide [cyclohexyl-oxide; c-C$_6$H$_{10}$O] (Table 1).

Table 1
Iron-induced activation of O_2 (1 atm) in acetonitrile for the oxygenation of cyclohexene (c-C_6H_{10}) to produce ketone [c-$C_6H_8(O)$], alcohol (c-C_6H_9OH), and epoxide (c-$C_6H_{10}O$)

Catalyst[a], (1 mM)	Products (mM, $\pm5\%$)[b]							
	1 M c-C_6H_{10}				2 M c-C_6H_{10}			
	one	ol	(ratio)[c]	epox	one	ol	(ratio)[c]	epox
$[Fe^{III}(bpy)_2]^{3+}_{aq}$; Ar[d]	0.2	2.0	(0.1)	0.0				
$[Fe^{III}(bpy)_2]^{3+}_{aq}$; air	4.9	8.4	(0.6)	0.0	5.1	10	(0.5)	0.0
$[Fe^{III}(bpy)_2]^{3+}_{aq}$	**51[21][e]**	**42[29][e]**	**1.2**	**3.1[0.5][e]**	**33**	**37**	**(0.9)**	**0.9**
$[Fe^{III}(bpy)_2]^{3+}_{aq}$	35[24][e]	38[30][e]	(0.9)	0.6[0.2][e]	31	36	(0.9)	0.5
$[Fe^{III}(bpy)_2]^{3+}_{aq}$/7 bpy	5.9	0.9	(6.6)	0.0				
$[Fe^{III}(bpy)_2]^{3+}_{aq}$/10 H_3^+O	45[10][e]	45[13][e]	(1.0)	0.0				
$[Fe^{III}(bpy)_2]^{3+}_{aq}$/2% H_2O	22[8.8][e]	31[13][e]	(0.9)	0.0	3.1	11	(0.3)	0.0
$[Fe^{III}(bpy)_2]Cl_{3\ aq}$	7.7	2.9	(2.8)	0.1	13	9	(1.5)	0.4
$[Fe^{III}(OH_2)_6]^{3+}$	**33[1.7][e]**	**12[0.6][e]**	**(2.8)**	**0.0**	**12[12][e]**	**23[15][e]**	**(0.5)**	**0.0**
0.05 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}$	26	13	(2.0)	0.0				
0.5 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}$	45[0.8][e]	38[14][e]	(1.2)	1.5[0.0][e]				
2 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}$	19[10][e]	24[18][e]	(0.8)	0.0				
$[Fe^{II}(bpy)_2]^{2+}$	**0.2**	**0.1**	**(2.0)**	**0.0**	**41[4.1][f]**	**37[13][f]**	**(1.1)**	**1.0**
$[Fe^{II}(bpy)_2]^{2+\ g}_{MeCN}$	21[e]	14[e]	(1.5)	1.6[e]	48[e]	43[e]	(1.1)	2.9[e]
$[Fe^{II}(bpy)_2]^{2+}_{MeCN}$; air[g]	18[e]	21[e]	(0.9)	0.9[e]				
$[Fe^{II}(OH_2)_6]^{2+}$	**35[5.4][e]**	**16[6.1][e]**	**(2.2)**	**0.1**	**10[10][e]**	**23[10][e]**	**(0.4)**	**0.0**
0.1 mM $[Fe^{II}(bpy)_2]^{2+}_{MeCN}$	5.6[e]	3.1[e]	(1.8)	0.2[e]				

[a] The catalyst complexes were prepared in situ by mixing $Fe^{III}(ClO_4)_3 \cdot 9H_2O$, $Fe^{II}(ClO_4)_2 \cdot 6H_2O$, or $Fe^{III}Cl_3 \times H_2O$ in MeCN with 2,2′-bipyridine.

[b] The combination of catalyst and c-C_6H_{10} in 5.0 ml of MeCN (25°C) was saturated with O_2 (1 atm) (or air) to initiate the reaction. After a reaction time of 24 h, the yield of products was assayed by capillary column GC. Presented data are the mean values of 3 independent experiments.

[c] Product ratio of c-$C_6H_8(O)$ per c-C_6H_9OH.

[d] The traces of O_2 were present.

[e] Reaction time, 1 h.

[f] Plus 2% H_2O.

[g] Ref. [10]; catalyst prepared in situ with $[Fe^{II}(MeCN)_4](ClO_4)_2$ in MeCN; 1 h reaction time. With 0.5 M c-C_6H_{10}, the yield is 3.7 mM c-$C_6H_8(O)$/1.8 mM c-C_6H_9OH/ratio, 2.0/0.3 mM epoxide.

The product profiles after 24 h reaction times indicate that the 1 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}$/$O_2$ (1 atm)/1 M c-C_6H_{10} combination is the most reactive [96 product/catalysts turnovers; with air (0.21 atm O_2), the reaction rate is reduced to 13 product/catalysts turnovers; with 0.05 mM catalyst, 39 mM of oxygenated product is produced in 24 h (780 product/catalyst turnovers); and with 2 mM catalyst, the reaction rate is reduced to 22 product/catalyst turnovers. However, in the presence of 2 M c-C_6H_{10}, 1 mM $[Fe^{II}(bpy)_2]^{2+}_{aq}$ is slightly more effective than 1 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}$ (79 vs. 71 product/catalyst turnovers). Likewise, the 1 mM $[Fe^{II}(H_2O)_6]^{2+}$/O_2 (1 atm)/1 M c-C_6H_{10} combination is more efficient than that with 1 mM $[Fe^{III}(H_2O)_6]^{3+}$ (51 vs. 45 product/catalyst turnovers). The presence of additional ligand (bpy or H_2O) inhibits the O_2/substrate reaction, but the addition of 10 mM H_3O^+ has a minor effect (the reaction is completely suppressed in the presence of 100 mM H_3O^+). Excess H_2O inhibits ketone production more than alcohol production. The stable, uncharged $[Fe^{III}(bpy)_2]Cl_3$ complex is almost an order of magnitude less efficient than $[Fe^{III}(bpy)_2]^{3+}_{aq}$ (Table 1). With the iron(III) catalysts, alcohol production is favored during the first hour of reaction. Lower partial pressures of O_2 reduce the ketone/alcohol product ratio, as does the initial presence of 2 M c-C_6H_{10} in place of 1 M substrate.

With 1 h reaction times, the $[Fe^{III}(bpy)_2]^{3+}_{aq}$ catalyst is no more effective than the water-free $[Fe^{II}(bpy)_2]^{2+}_{MeCN}$ complex; in fact, with 2 M c-C_6H_{10} as the substrate, the latter produces 40% more product in 1 h than the former does in 24 h. The co-production of H_2O clearly has a much greater inhibitory effect on $[Fe^{II}(bpy)_2]^{2+}$ than on the iron(III) catalysts.

In the presence of 0.1 mM BHT, the yield with the $[Fe^{III}(bpy)_2]^{3+}_{aq}$ catalyst is reduced to 25 mM c-$C_6H_8(O)$, 31 mM c-C_6H_9OH, and 0.6 mM epoxide; with 1 mM BHT, the oxygenation process is completely inhibited (as it is for all of the catalysts). The presence of 0.3 mM α-tocopherol (vitamin E) or 1 mM quercetin (3,5,7,3′,4′-pentahydroxyflavone) also completely inhibits the oxygenation process.

With 1 M ethylbenzene ($PhCH_2CH_3$) as the substrate, the 1 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}/O_2$ (1 atm) system yields 7.2 mM acetophenone $[PhC(O)$-$CH_3]$ in a 24-h reaction {the $[Fe^{II}(bpy)_2]^{2+}_{aq}$ catalyst yields zero product}. In the presence of air (0.21 atm O_2), the iron(III) system yields 6.5 mM $PhC(O)CH_3$ in 24 h. With 1 M cumene $[PhCH(CH_3)_2]$, the iron(III)/1 atm O_2 system yields 16 mM $PhC(O)CH_3$, 15 mM $PhC(CH_3)_2OH$, and 12 mM PhOH in a 24-h reaction (respective yields after 1 h of reaction; 3.6, 6.5 and 0.0 mM). In the presence of air, the respective yields after a 24-h reaction are 6.4, 14 and 5.7 mM. The 1 mM $[Fe^{II}(bpy)_2]^{2+}_{aq}/1$ atm $O_2/1$ M $PhCH(CH_3)_2$ combination yields 21 mM $PhC(O)CH_3$, 33 mM $PhC(CH_3)_2OH$, and 1.8 mM PhOH in a 24-h reaction time. In the presence of air, this system gives respective yields of 3.8, 33 and 1.1 mM. Figs. 1 and 2 illustrate the oxidation/reduction character of the catalyst/substrate combinations in the absence and presence of O_2. In the absence of O_2, (a) $[Fe^{II}(bpy)_2]^{2+}_{aq}$ is completely unreactive and remains fully reduced, but (b) about 50% of 1 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}$ is reduced by the substrate within 5 min after combination with 2 M c-C_6H_{10} (Fig. 1A) to give c-C_6H_9OH (Table 1). In the presence of O_2, (a) most of the $[Fe^{II}(bpy)_2]^{2+}_{aq}$ remain in a reduced state
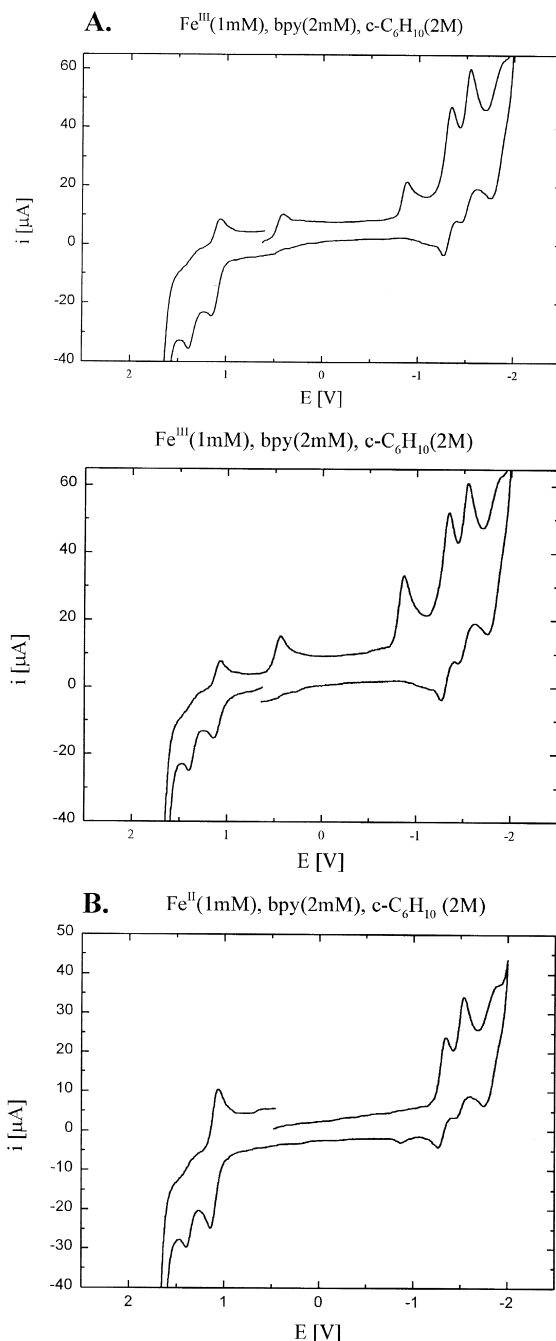
Fig. 1. Cyclic voltammograms in MeCN [0.1 M $(Et_4N)ClO_4$] for (A) 1 mM $[Fe^{III}(bpy)_2]^{3+}_{aq}$ in the presence of 2 M c-C_6H_{10} under an argon atmosphere and (B) 1 mM $[Fe^{II}(bpy)_2]^{2+}_{aq}$ in the presence of 2 M c-C_6H_{10} under an argon atmosphere. Cyclics were recorded within 3 min after mixing. Scan rate, 0.1 V s^{-1}, GCE (0.09 cm^2; SCE vs. NHE, +0.242 V).
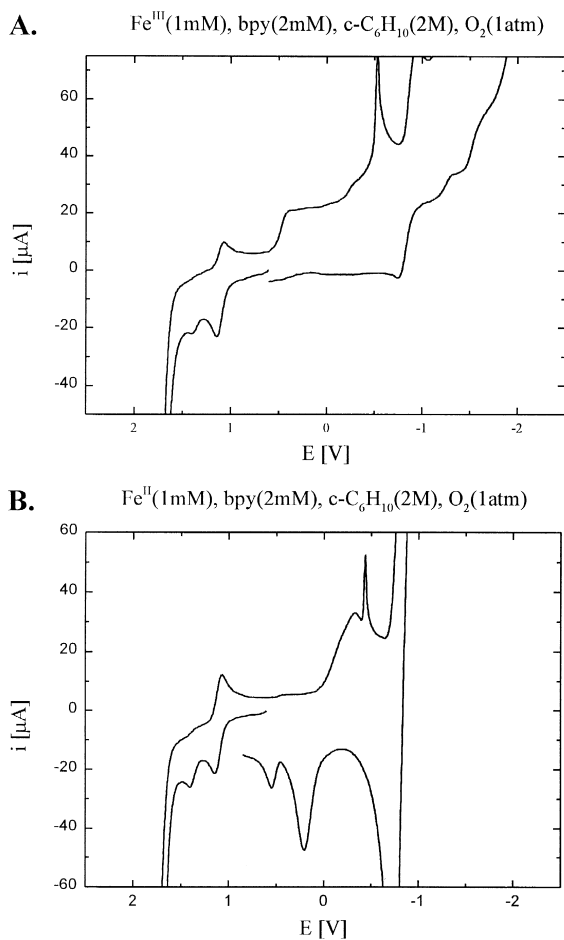
A.

B.

Fig. 2. Cyclic voltammograms in MeCN [0.1 M $(Et_4N)ClO_4$] for (A) 1 mM $[Fe^{III}(bpy)_2]_{aq}^{3+}$ in the presence of 2 M c-C_6H_{10} and O_2 (1 atm), and (B) 1 mM $[Fe^{II}(bpy)_2]_{aq}^{2+}$ in the presence of 2 M c-C_6H_{10} and O_2 (1 atm). Cyclics were recorded within 3 min after mixing. Scan rate, 0.1 V s^{-1}, GCE (0.09 cm^2; SCE vs. NHE, +0.242 V).

(Fig. 2B) while oxygenating c-C_6H_{10} (Table 1, 79 product molecules per catalyst molecule in 24 h), and (b) about two-thirds of the $[Fe^{III}(bpy)_2]_{aq}^{3+}$ catalyst is in the reduced state (Fig. 2A) while oxygenating c-C_6H_{10} (Table 1, 71 product molecules per catalyst molecule in 24 h). Both systems, during the course of the reaction, exhibit a unique reduction peak at -0.3 V vs. SCE (Fig. 2) that is not observed with substrate-free solutions, and must be due to a catalyst/O_2/c-C_6H_{10} reactive intermediate that exhibits a multi-electron catalytic current. Analogous electrochemical behavior was observed for the (μ-oxo) di-aqua diiron(III) complexes with 2, 2′-bipyridine as a ligand in acetonitrile [29]. Electroreduction of the μ-oxo complexes leads to mononuclear iron (II) complex. The μ-oxo-bridged diiron(III) complexes are well known for the catalytic alkane oxidation and aromatic hydroxylation by hydroperoxides and dioxygen [16,30–36]. It was, however, established, that alkylperoxoiron(III) complexes are formed during oxidations catalyzed by μ-oxodiiron(III) complexes [16].

4. Discussion and conclusions

On the basis of the present electrochemical results (Figs. 1 and 2) and those from related studies [3,37–39], the dominant forms of the catalysts, their equilibria, and their oxidation–reduction processes can be assigned and are

Table 2
Equilibria and redox processes for the 1 mM $[Fe^{III}(bpy)_2]_{aq}^{3+}$ and $[Fe^{II}(bpy)_2]_{aq}^{2+}$ catalysts in acetonitrile

(1) $[Fe^{III}(bpy)_2(H_2O)]^{3+} \rightleftarrows (bpy)_2^{2+}Fe^{III}-OH\,(\mathbf{1}) + H_3O^+$

(2) $2(bpy)_2^{2+}Fe^{III}-OH(\mathbf{1}) \rightleftarrows (bpy)_2^{2+}Fe^{III}OFe^{III}(bpy)_2^{2+} + H_2O$, $K_f \sim 4$ mM^{-1}

(3) $[Fe^{III}(H_2O)_6]^{3+} \rightleftarrows (H_2O)_5^{2+}Fe^{III}-OH\,(\mathbf{1'}) + H_3O^+$

(4) $[Fe^{III}(bpy)_3]^{3+} + H_2O \rightleftarrows (bpy)_2^{2+}Fe^{III}-OH\,(\mathbf{1}) + bpyH^+$

(5) $(bpy)_2^{2+}Fe^{III}-OH\,(\mathbf{1}) + H_3O^+ + e^- \rightarrow [Fe^{II}(bpy)_2]^{2+}(\mathbf{2}) + 2H_2O\,E_{p,c}, +0.45$ V vs. SCE

(6) $(bpy)_2^{2+}Fe^{III}OFe^{III}(bpy)_2^{2+} + 2H_3O^+ + 2e^- \rightarrow Fe^{II}(bpy)_2^{2+}\,(\mathbf{2}) + 3H_2O\,E_{p,c}, -0.90$ V vs. SCE

(7) $2[Fe^{II}(bpy)_2(H_2O)_2]^{2+}(\mathbf{2}) - e^- \rightleftarrows [Fe^{III}(bpy)_3]^{3+} + [Fe^{II}(bpy)(H_2O)_4]^{2+}E_{1/2}, +1.05$ V vs. SCE

(8) $2(H_2O)_4^+Fe^{II}(bpy)^+ - 2e^- \rightarrow (H_2O)_3(bpy)^{2+}Fe^{III}OFe^{III}(bpy)(H_2O)_3^{2+} + 2H_3O^+E_{p,a}, +1.40$ V vs. SCE

(9) $(H_2O)_3(bpy)^{2+}Fe^{III}OFe^{III}(bpy)(H_2O)_3^{2+} + 2[Fe^{III}(bpy)_3]^{3+} \rightarrow 2(bpy)_2^{2+}Fe^{III}OFe^{III}(bpy)_2^{2+} + 2H_3O^+ + 3H_2O$

(10) $\{(bpy)_2^{2+}Fe^{IV}(OH)\,(OOC_6H_9),\,\mathbf{6}\} + 2H_3O^+ + 2e^- \rightarrow c$-$C_6H_8(O) + [Fe^{II}(bpy)_2]^{2+}(\mathbf{2}) + 4H_2O\,E_{p,c}, -0.3$ V vs. SCE

(hypothetical)

summarized in Table 2. In the absence of O_2, only the $(bpy)_{22+}Fe^{III}-OH$ (**1**) species is reactive with c-C_6H_{10} to produce its alcohol (Table 1 and Fig. 1A):

$$2(bpy)_2^{2+}Fe^{III}-OH(\textbf{1}) + c\text{-}C_6H_{10}$$
$$\rightarrow c\text{-}C_6H_9OH + 2Fe^{II}(bpy)_2^{2+} + H_2O. \quad (1)$$
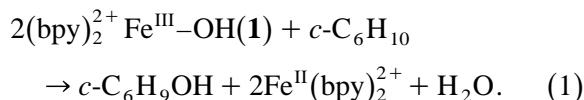
The initial step requires breakage of an allylic C−H bond in c-C_6H_{10} ($\Delta H_{DBE} = 83$ kcal mol^{-1}) [39] by **1** ($\Delta H_{DBE} = 53$ kcal mol^{-1}) [9,40,41] to form a water molecule.

$$(2)$$
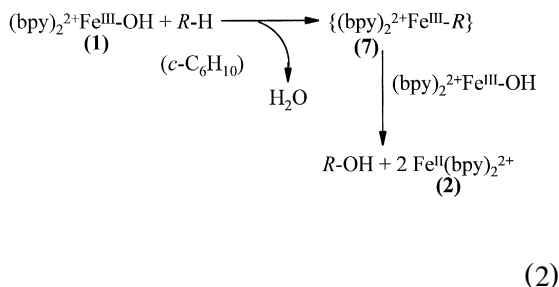
Because the total bond breakage energy ($\Delta H_{DBE} = 83 + 53 = 136$ kcal mol^{-1}) is greater than the free energy of bond formation for the HO−H bond ($-\Delta G_{BF} = 111$ kcal mol^{-1}) [9,41], for the observed process (Eq. 1) to occur at reasonable rates requires formation of an intermediate with an iron−carbon bond (species **7**, Eq. 2; $-\Delta G_{BF} \sim 25$ kcal mol^{-1}) [42]. The latter will react at diffusion-controlled rates with a second $[(bpy)_2^{2+}]Fe^{III}-OH$ to give the observed alcohol product (Eq. 2).

When O_2 is present, the same bond breakage energy is required (136 kcal mol^{-1}), but the bond formation free energy is enhanced via the apparent formation of the **5** bonds $[-\Delta G_{BF} = 15$ kcal mol^{-1} (est) and 20 kcal mol^{-1} (est)] [9,39,40] in place of the iron−carbon bond:

$$(bpy)_2^{2+}Fe^{III}-OH(\textbf{1}) + R\text{-}H + O_2$$
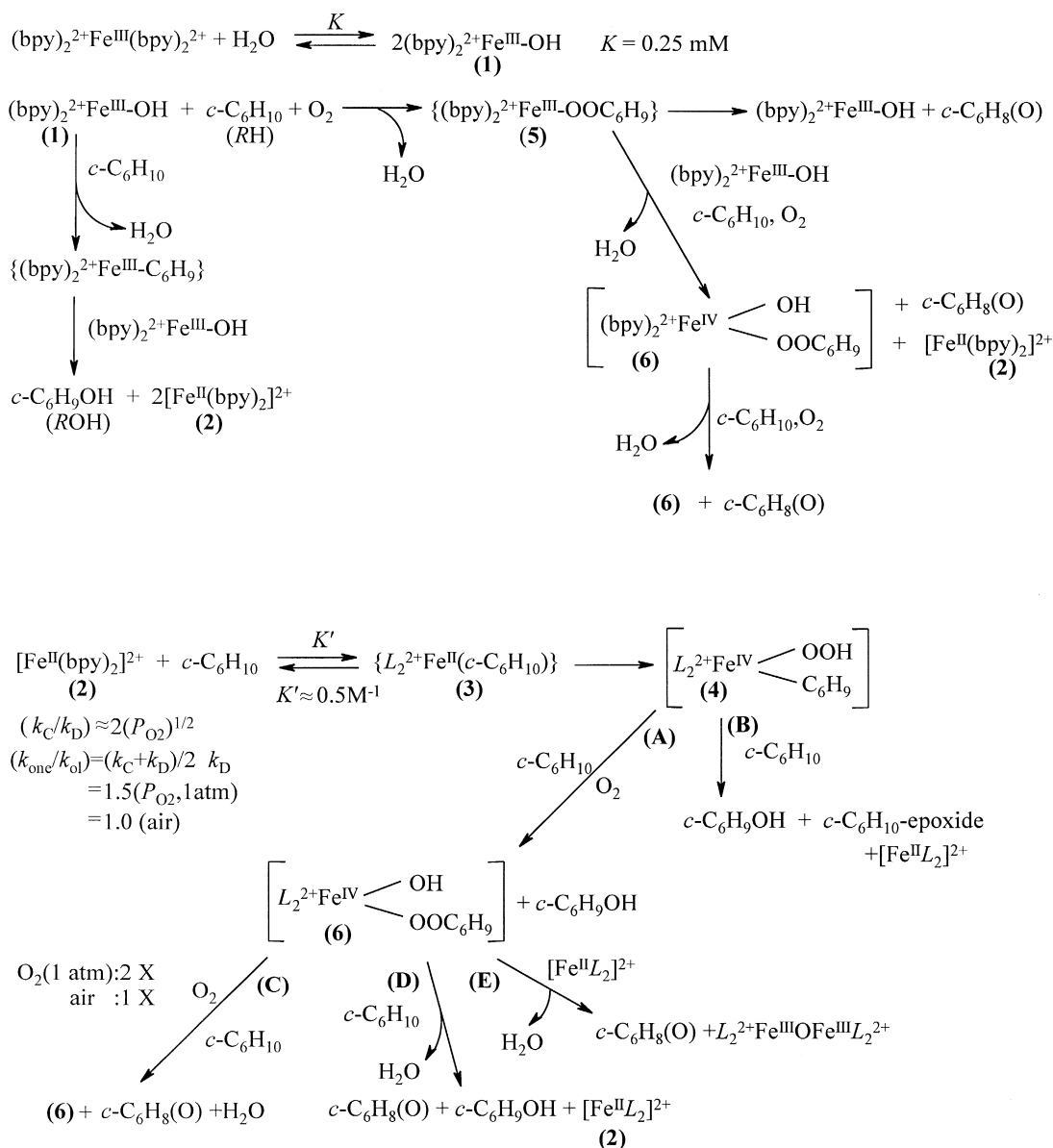$$\rightarrow (bpy)_2^{2+}Fe^{III}-OO-R(\textbf{5}) + H_2O. \quad (3)$$
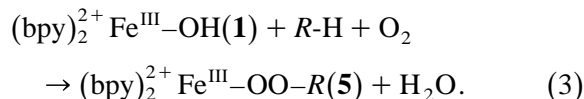
With these bond energy considerations, the process is exergonic by about 10 kcal mol^{-1}. Because the C−H bond energy of methylenic car-

bons in saturated hydrocarbons ($\Delta H_{DBE} = 96$ kcal mol^{-1}) [9] is 13 kcal mol^{-1} greater than that for the allylic C−H bonds of cyclohexene, the $[(bpy)_2^{2+}]Fe^{III}-OH/O_2$ system is unreactive with cyclohexane (c-C_6H_{12}).

Species **5** is believed to be a transient intermediate with several reaction pathways. Reasonable possibilities, which are outlined in Scheme 1, include (a) decomposition to ketone [c-$C_6H_8(O)$] and **1** and, the most probably, (b) reaction with the $(bpy)_2^{2+}Fe^{III}OH/c$-C_6H_{10}/O_2 combination to give ketone, $Fe^{II}(bpy)_2^{2+}$ (**2**), H_2O, and a reactive intermediate $\{(bpy)_2^{2+}\text{-}Fe^{IV}(OH)(OOC_6H_9)$, **6**$\}$. The latter (whatever its form) has been shown to facilitate multiple c-C_6H_{10}/O_2 turnovers to produce ketone via oxygenated Fenton chemistry [4,5] and has been postulated to be the reactive intermediate in an iron(II)/O_2/reductase (DH_2)/RH system [6].

In the preliminary study of iron(II)-induced activation of O_2 for the oxygenation of cyclohexene $\{[Fe^{II}(bpy)_2]^{2+}/O_2/c$-$C_6H_{10}\}$ [10], the rate of product formation was shown to be: (a) first-order in catalyst concentration up to 1 mM, but inhibited by larger concentrations; (b) zero for c-C_6H_{10} concentrations less than 0.5 M, but approximately first-order for concentrations above 1.0 M; and (c) inhibited by the presence of H_2O [0.1% H_2O (56 mM) reduced the reaction efficiency by 30–50%; 1% H_2O completely quenched the reaction as did the presence of 100 mM pyridine]. The results for $[Fe^{III}(bpy)_2]_{aq}^{3+}$ and $[Fe^{II}(bpy)_2]_{aq}^{2+}$ (Table 1) confirm that the presence of H_2O inhibits reaction with c-C_6H_{10}. In the presence of 1 M c-C_6H_{10}, the $[Fe^{II}(H_2O)_6]^{2+}$ complex is more efficient than $[Fe^{II}(bpy)_2]_{MeCN}^{2+}$; the opposite is observed for 2 M c-C_6H_{10}.

The results summarized in Table 1 and electrochemical data (Figs. 1 and 2) confirm that during the course of the oxygenation reaction, the reduced iron complex (**2**) is the effective catalyst. Although **1** is a much more effective initiator, it is reduced to **2** via its initiation reactions (Scheme 1). The unique and selective reactivity of c-C_6H_{10} when all of the catalysts

$$(bpy)_2^{2+}Fe^{III}(bpy)_2^{2+} + H_2O \underset{K}{\rightleftharpoons} 2(bpy)_2^{2+}Fe^{III}\text{-}OH \qquad K = 0.25 \text{ mM}$$
$$(1)$$

$$(bpy)_2^{2+}Fe^{III}\text{-}OH + c\text{-}C_6H_{10} + O_2 \longrightarrow \{(bpy)_2^{2+}Fe^{III}\text{-}OOC_6H_9\} \longrightarrow (bpy)_2^{2+}Fe^{III}\text{-}OH + c\text{-}C_6H_8(O)$$
$$(1) \qquad\qquad (RH) \qquad\qquad\qquad (5)$$

$$(bpy)_2^{2+}Fe^{III}\text{-}OH$$
$$c\text{-}C_6H_{10}, O_2$$

$$c\text{-}C_6H_{10} \searrow H_2O$$

$$\{(bpy)_2^{2+}Fe^{III}\text{-}C_6H_9\}$$

$$\left[(bpy)_2^{2+}Fe^{IV}\begin{array}{c}\text{OH}\\\text{OOC}_6\text{H}_9\end{array}\right] + c\text{-}C_6H_8(O)$$
$$(6) \qquad\qquad + [Fe^{II}(bpy)_2]^{2+}$$
$$(2)$$

$$(bpy)_2^{2+}Fe^{III}\text{-}OH$$

$$c\text{-}C_6H_9OH + 2[Fe^{II}(bpy)_2]^{2+}$$
$$(ROH) \qquad\qquad (2)$$

$$H_2O \swarrow \Bigg\downarrow c\text{-}C_6H_{10}, O_2$$

$$(6) + c\text{-}C_6H_8(O)$$

$$[Fe^{II}(bpy)_2]^{2+} + c\text{-}C_6H_{10} \underset{K'\approx 0.5M^{-1}}{\overset{K'}{\rightleftharpoons}} \{L_2^{2+}Fe^{II}(c\text{-}C_6H_{10})\} \longrightarrow \left[L_2^{2+}Fe^{IV}\begin{array}{c}\text{OOH}\\\text{C}_6\text{H}_9\end{array}\right]$$
$$(2) \qquad\qquad\qquad\qquad (3) \qquad\qquad\qquad (4)\quad (B)$$

$$(k_C/k_D) \approx 2(P_{O2})^{1/2}$$
$$(k_{one}/k_{ol}) = (k_C + k_D)/2\ k_D$$
$$= 1.5(P_{O2}, 1\text{atm})$$
$$= 1.0\ (\text{air})$$

$$(A) \quad c\text{-}C_6H_{10} \Big/ O_2$$

$$c\text{-}C_6H_9OH + c\text{-}C_6H_{10}\text{-epoxide} + [Fe^{II}L_2]^{2+}$$

$$\left[L_2^{2+}Fe^{IV}\begin{array}{c}\text{OH}\\\text{OOC}_6\text{H}_9\end{array}\right] + c\text{-}C_6H_9OH$$
$$(6)$$

$$O_2(1\text{ atm}):2\ X$$
$$\text{air}\ :1\ X \quad O_2\Big/(C) \qquad (D) \quad (E) \quad [Fe^{II}L_2]^{2+}$$
$$c\text{-}C_6H_{10} \qquad c\text{-}C_6H_{10} \searrow \qquad \searrow H_2O \quad c\text{-}C_6H_8(O) + L_2^{2+}Fe^{III}OFe^{III}L_2^{2+}$$
$$H_2O$$

$$(6) + c\text{-}C_6H_8(O) + H_2O \qquad c\text{-}C_6H_8(O) + c\text{-}C_6H_9OH + [Fe^{II}L_2]^{2+}$$
$$(2)$$

Scheme 1. Iron(III)-induced activation of O_2 for the oxygenation of cyclohexane ($c\text{-}C_6H_{10}$).

are initially in the reduced form appears to be due to adduct formation $\{(bpy)_2^{2+}Fe^{II}(c\text{-}C_6H_{10})$, **3**$\}$ prior to reaction with O_2 to give $\{(bpy)_2^{2+}Fe^{IV}(OOH)(C_6H_9)$, **4**$\}$ (Scheme 1). The apparent formation constant (K') for **3** is approximately 0.5 M^{-1} (Table 1) [10]. On the basis of reasonable estimates of $-\Delta G_{BF}$ [9,40,41], formation of intermediate **4** is exoer-

gonic by 7 kcal mol^{-1}; in turn, it reacts with (a) $O_2/c\text{-}C_6H_{10}$ to give $\{(bpy)_2^{2+}Fe^{IV}(OH)\text{-}(OOC_6H_9)$, **6**$\}$ and $c\text{-}C_6H_9OH$ (path A, Scheme 1; estimated to be a 23 kcal mol^{-1} exergonic reaction), or (b) $c\text{-}C_6H_{10}$ to give $c\text{-}C_6H_9OH$, epoxide ($c\text{-}C_6H_{10}O$), and **2** (path B, Scheme 1; estimated to be a 10 kcal mol^{-1} exergonic reaction).

Species **6** appears to be identical to the species **6** of oxygenated Fenton chemistry [4,5] and of iron(II)/reductant (DH_2)-induced activation of O_2 [6], and is believed to be the intermediate that is reduced at -0.3 V vs. SCE (Fig. 2B and Table 2) during steady-state reaction [3,16]. The product profiles of Table 1 and from the preliminary study $\{[Fe^{II}(bpy)_2]_{MeCN}^{2+}/O_2/c\text{-}C_6H_{10}\}$ [10] indicate that **6** can react with (a) another $O_2/c\text{-}C_6H_{10}$ combination to give **6** and $c\text{-}C_6H_8(O)$ (path C, Scheme 1); (b) $c\text{-}C_6H_{10}$ alone to give $c\text{-}C_6H_8(O)$, $c\text{-}C_6H_9OH$, and **2** (path D), or a reduced catalyst (e.g., **2**) to give $c\text{-}C_6H_8(O)$ and inactive oxidized iron {e.g., $(bpy)_2^{2+}\text{-}Fe^{III}OFe^{III}(bpy)_2^{2+}$} (path E). The results of Table 1 indicate that with O_2 at 1 atm, path C is followed two to three times {two times for $[Fe^{II}(bpy)_2]_{MeCN}^{2+}$} before path D terminates a **6**-to-**6** cycle to give three to four ketones and two alcohols (-one/-ol ratio, 1.5–2.0). With air (0.2 atm O_2) and $[Fe^{II}(bpy)_2]_{MeCN}^{2+}$, path C is followed one time before path D to give two ketones and two alcohols (-one/-ol ratio, 0.9); 0.1 atm O_2 gives an -one/-ol ratio of 0.8 (if Scheme 1 is an accurate representation of the catalytic chemistry, complete suppression of path C would give an -one/-ol ratio of 0.5) [10]. With 0.5 M $c\text{-}C_6H_{10}/[Fe^{II}(bpy)_2]_{MeCN}^{2+}/O_2$ (1 atm), path C is followed three times before path D to give four ketones and two alcohols (-one/-ol ratio, 2.0) [10]. The presence of H_2O in the coordination sphere {e.g., $[Fe^{II}(bpy)_2](H_2O)_2^{2+}$ and $[Fe^{II}(H_2O)_6]^{2+}$} favors the **6**-to-**6** cycle (path C) three times prior to path D.
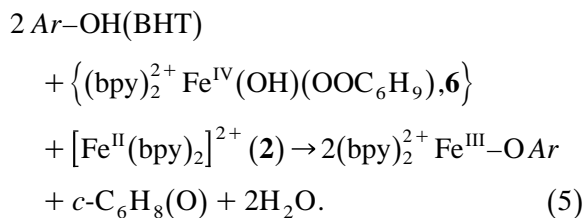
When $[Fe^{III}(bpy)_2]_{aq}^{3+}$ is the catalyst, the initial dominant process is reduction to $[Fe^{II}(bpy)_2]_{aq}^{2+}$ and production of alcohol (Eq. 2). Because the latter is a more basic ligand than H_2O, it has a similar inhibitory effect on path C to that of excess water (as does excess bipyridine, Table 1). Subsequent product formation appears to involve solely reduced catalyst $\{[Fe^{II}(bpy)_2]_{aq}^{2+}\}$.

The inhibitory effect of antioxidants (e.g., BHT or vitamin E, Ar–OH) appears to be stoichiometric with respect to iron catalyst (com-plete suppression for one-to-one combinations for all catalysts). A reasonable possibility is that BHT reacts with **1** to form an inactive oxidized catalyst:

$$Ar\text{–}OH(BHT) + (bpy)_2^{2+}Fe^{III}\text{–}OH(\mathbf{1})$$
$$\rightarrow (bpy)_2^{2+}Fe^{III}\text{–}OAr + H_2O. \qquad (4)$$
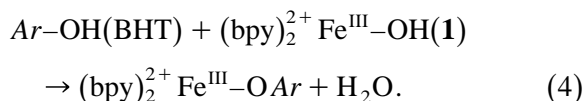
Species **6** also should be highly reactive with BHT or vitamin E; one possibility would be to also deactivate **2**:

$$2\,Ar\text{–}OH(BHT)$$
$$+ \left\{(bpy)_2^{2+}Fe^{IV}(OH)(OOC_6H_9),\mathbf{6}\right\}$$
$$+ \left[Fe^{II}(bpy)_2\right]^{2+}(\mathbf{2}) \rightarrow 2(bpy)_2^{2+}Fe^{III}\text{–}OAr$$
$$+ c\text{-}C_6H_8(O) + 2H_2O. \qquad (5)$$

Hence, the apparent means by which BHT is an effective ''anti-oxidant'' is to functionalize the iron catalysts into an unreactive form {e.g., $(bpy)_2^{2+}Fe^{III}\text{-}OAr$}. This, in turn, leads to the suggestion that the search for other effective inhibitory agents should focus on those that inactivate iron catalysts via the chemistry of Eqs. 4 and 5.

The iron(III, II)-induced activation of O_2 for the oxygenation of allylic carbon centers (Table 1) makes such systems more reasonable cyto-toxic agents than the non-selective free hydroxyl radical (HO·) within the oxy-radical theory of aging and heart disease [11,12]. In the preliminary study [10], the reactivity and product profiles with the $[Fe^{II}(bpy)_2]_{MeCN}^{2+}/O_2$ system for methyl linoleate closely paralleled those for $c\text{-}C_6H_{10}$, which indicates that cyclohexene is a good model substrate for unsaturated fatty acid esters and there oxygenation via iron(II, III)/O_2 combinations.

Acknowledgements

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