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Iron(II)-Induced Activation of Dioxygen for Oxygenation of Cyclohexene and Methyl Linoleate and Initiation of the Autoxidation of 1,4-Cyclohexadiene

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In general, iron-induced activation of dioxygen (O_2) requires either (a) that it be in a reduced state (HOOH; Fenton chemistries)[1−3] or (b) a reductant cofactor (O_2/DH_2 = PhNHNHPh, ascorbic acid, thiols, *cytochrome P-450 reductase*)[4] to facilitate hydrocarbon oxygenation. In a few cases, the organic substrate also acts as the reductant, e.g., *pyrocatechol dioxygenase*, which induces O_2 to transform catechol to muconic acid.[5,6] Hence, the discovery that iron(II) complexes catalytically activate O_2 for the direct oxygenation of cyclohexene and methyl linoleate came as a great surprise.

Here we report that coordinately unsaturated iron(II) complexes [$Fe^{II}(bpy)_2^{2+}$ and $Fe^{II}(OPPh_3)_4^{2+}$] in acetonitrile catalytically activate O_2 for the direct oxygenation of cyclohexene (c-C_6H_{10}) and methyl linoleate [$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7C(O)OCH_3$; RH] (Table 1). The product profiles for c-C_6H_{10} and methyl linoleate (MeL) indicate that (a) the 1.0 mM $Fe^{II}(bpy)_2^{2+}/O_2$ (1 atm)/4 M c-C_6H_{10} combination undergoes 230 turnovers within 1 h (the 0.1 mM/1 M c-C_6H_{10} system has 187 turnovers within 6 h) and (b) with 1 M MeL in place of c-C_6H_{10}, the combination undergoes 27 turnovers within 1 h (the 0.2 mM system has 123 turnovers within 6 h).

Cyclohexene. With 1 M c-C_6H_{10} as the substrate, (a) the use of air (0.2 atm O_2) in place of O_2 (1 atm) alters the c-$C_6H_8(O)$/c-C_6H_9OH (-one/-ol) product ratio from about 1.5 to about 0.9, but does not significantly reduce the rate of product formation; (b) larger catalyst concentrations (5 mM or greater) are less efficient; (c) the presence of 0.1% H_2O (56 mM) reduces the reaction efficiency by 30−50% (1% H_2O completely quenches the reaction, as does the presence of pyridine); and (d) the $Fe^{II}(bpy)_3^{2+}$ complex is not an effective catalyst [the $Fe^{II}(OPPh_3)_4^{2+}$ complex is about one-half as efficient as $Fe^{II}(bpy)_2^{2+}$, and the $Cu^{II}(OPPh_3)_4^{2+}$ complex is about one-tenth as efficient]. With 4 M c-C_6H_{10}, the initial rate of product formation is enhanced by a factor of 9 to give 230 mM product after 1 h.

Methyl Linoleate. With 1 M MeL as the substrate (contains one double allylic and two single allylic carbon centers), (a) about 3 times as much ketone (3 isomers plus a keto-epoxide; the double allylic center is about 3 times as reactive as the single allylic centers) is produced as alcohol (3 isomers, with the double allylic center about twice as reactive as the single allylic centers); (b) the initial rates of reaction are proportional to the catalyst concentration (up to 1 mM) and the partial pressure of O_2; (c) the alcohol/ketone product ratio is essentially the same for O_2 and air; and (d) the presence of 1% H_2O reduces the yield of alcohol by 50% but does not affect the yield of ketone.

The $Fe^{II}(bpy)_2^{2+}/O_2$/MeCN system is unreactive with 1 M 1-hexene, norbornene, methyl oleate, *cis*-stilbene, $PhCH_2CH_3$, and cyclohexane. However, with 4 M concentrations of the aliphatic olefins, limited amounts of ketone and alcohol products are observed.

1,4-Cyclohexadiene. The $Fe^{II}(bpy)_2^{2+}/O_2$/MeCN system initiates the autoxidation of 1,4-c-C_6H_8 (with two double allylic carbon centers; ΔH_{DBE} = 73 kcal mol^{-1})[7] and benzaldehyde [PhCH(O); ΔH_{DBE} = 87 kcal mol^{-1}].[7] The combination of 0.5 mM $Fe^{II}(bpy)_2^{2+}/O_2$ (1 atm)/1 M c-C_6H_8 yields 0.37 M PhH, 6 mM c-C_6H_7OOH, and 1 mM PhOH within 3 h; with 1 M PhCH(O), the system produces 0.37 M PhC(O)OH within 3 h. As in the case of c-C_6H_{10} and methyl linoleate, the presence of 0.1% H_2O quenches the initiation rate by 30−40%; 1% H_2O completely inhibits the initiation. The use of air (0.2 atm O_2) in place of O_2 (1 atm) reduces the initiation rate by 40%, and the $Fe^{II}(bpy)_3^{2+}$ complex is inactive. The initiation of the catalyst-independent autoxidation of c-C_6H_8 to benzene and H_2O appears to depend on the initial formation of c-C_6H_7OOH, which, in combination with $Fe^{II}(bpy)_2^{2+}$, becomes a Fenton reagent (and in combination with O_2 an oxygenated Fenton reagent to produce PhOH from c-C_6H_8).[3,8]

Although the iron(II)-induced formation of the hydroperoxide of c-C_6H_{10} is an attractive proposition (which would lead to subsequent oxygenated Fenton chemistry and the observed product profiles), we have not been able to detect even trace amounts. Furthermore, water does not have a deleterious effect on oxygenated Fenton chemistry, whereas it is a serious inhibitor with the present system.

Given the preceding observations of catalyst activity, substrate dependence, and O_2 dependence, a reasonable interpretation is that the primary step is the reversible formation of a substrate adduct of a coordinately unsaturated iron(II) complex in a base-free solvent, with subsequent incorporation of O_2 to produce oxygenated products. Product water and alcohol cause the catalyst to become coordinated, saturated, and inactive:

$$2Fe^{II}(bpy)_2^{2+} + 4H_2O \rightarrow Fe^{II}(bpy)_3^{2+} + Fe^{II}(bpy)(OH_2)_4^{2+} \tag{1}$$

The last entries in Table 1 give the product profiles for an $Fe^{II}(bpy)_2^{2+}$/*t*-BuOOH/O_2 system (oxygenated Fenton chemistry)[3] after a 3 h reaction time. These are closely similar to those for the $Fe^{II}(bpy)_2^{2+}/O_2$ system, but c-C_6H_{10} does not yield any epoxide. An earlier study[3] has shown that the oxygen atoms in the c-C_6H_9OH and c-$C_6H_8(O)$ products come from O_2 and not *t*-BuOOH, which may account for the equivalent product profiles. Here this Fenton system, in its reaction with c-C_6H_{10}, exhibits substantial O_2 turnovers beyond the 20 mM *t*-BuOOH [86 mM c-$C_6H_8(O)$ and 60 mM c-C_6H_9OH]. A hydroperoxide-independent intermediate [$L_2^{2+}Fe^{IV}(OH)(OOC_6H_9)$, **6**] has been proposed to account for this excess product yield.[3]

These considerations lead us to propose a set of reaction paths for the $Fe^{II}(bpy)_2^{2+}/O_2$ reaction with c-C_6H_{10} that are consistent with the product profiles and experimental observations (Scheme 1). The unique and selective reactivity of c-C_6H_{10} (relative to other olefins) appears to be due to adduct formation prior to reaction with dioxygen to give **11**. The latter in turn reacts with another O_2/c-C_6H_{10} to give **6** and c-C_6H_9OH (path A) or c-C_6H_{10} to give c-C_6H_9OH and epoxide (path B). Species **6** appears to be identical to the species **6** of oxygenated Fenton chemistry[3] and of iron(II)/reductant-induced activation of dioxygen.[4] In the present system, **6** can react with (a) another O_2/c-C_6H_{10} to give **6** and c-$C_6H_8(O)$ (path C) or (b) c-C_6H_{10}

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Table 1. Activation of O_2 by $Fe^{II}(bpy)_2{}^{2+}$ for the Oxygenation of Cyclohexene (c-C_6H_{10}) and Methyl Linoleate [$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7C(O)OCH_3$] in MeCN {One Hour Reaction Time; P_{O_2}, 1 atm (or 0.2 atm)} [Yields at 10-Min Reaction Time]

A. Cyclohexene

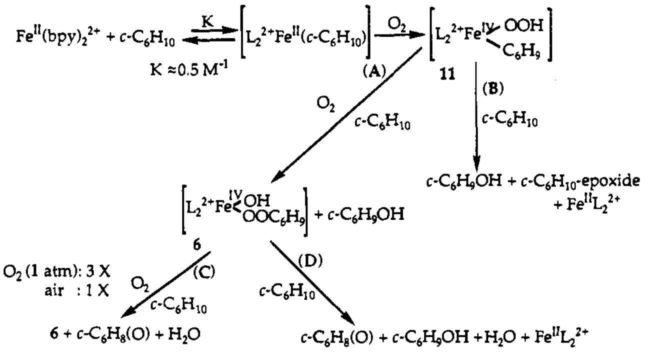
		products (mM, ±5%)[a]			
$Fe^{II}(bpy)_2{}^{2+}$ (mM)	c-C_6H_{10} (M)	c-$C_6H_8(O)$	c-C_6H_9OH	c-C_6H_{10}-epoxide	-one/-ol ratio (air)
0.1	1.00	5.6	3.1	0.2	1.8
0.2 (air)[b]	1.00	7.9 (9.4)	4.3 (10)	0.4 (0.3)	1.9 (0.9)
0.5[c,d] (air)[b]	1.00	13 (14)	9.5 (15)	0.8 (0.9)	1.3 (1.0)
1.0 (air)[b]	1.00	21 (18) [4.1]	14 (21) [3.5]	1.6 (0.9) [0.6]	1.5 (0.9)
	0.25	0	0	0	
	0.50	3.7	1.8	0.3	2.0
	0.75	9.2 [1.3]	5.0 [1.0]	0.7 [0.2]	1.9 [1.3]
	2.00	48 [14]	43 [15]	2.9 [0.8]	1.1 [1.0]
	4.00	113 [35]	111 [40]	6.6 [2.2]	1.0 [0.9]
2.0 (air)[b]	1.00	15 (14)	8.6 (15)	1.1 (0.6)	1.8 (0.9)
10.0 (+20 mM*t*-BuOOH)[e]	1.00	86	60	0.0	1.4

B. Methyl Linoleate (RH, 1 M)

	products (mM, ±5%)[a]		
$Fe^{II}(bpy)_2{}^{2+}$ (mM)	R′(O) [3 isomers + keto-epoxide]	ROH [3 isomers]	-one/-ol ratio (air)
0.2 (air)[b]	4.5 [1.1/0.9/2.5/0.0] (0.4)	3.7 [1.5/1.3/0.9] (0.7)	1.2 (0.6)
0.5 (air)[b]	20 [3.2/4.2/8.3/4.2] (5.4)	4.5 [0.6/0.9/3.0] (1.7)	4.4 (3.2)
1.0 (air)[b]	20 [3.8/2.4/10/3.2] (5.7)	6.5 [1.0/3.0/2.5] (2.9)	3.1 (2.0)
2.0 (air)[b]	20 [3.2/4.8/8.4/3.7] (3.9)	4.1 [0.4/1.3/2.4] (3.5)	4.5 (1.1)
5.0[f] (air)[b]	12 [3.0/2.6/5.8/0.9] (0.0)	3.9 [1.1/1.4/1.4] (3.3)	3.1 (0.0)
10.0 (+20 mM *t*-BuOOH)[e]	36 [7.3/6.5/16/5.1]	12 [0.8/5.8/5.6]	3.0

[a] The combination of $Fe^{II}(bpy)_2{}^{2+}$ and 1 M c-C_6H_{10} (or methyl linoleate, c-C_6H_8, PhCH(O), and other substrates) in 5.0 mL of MeCN (25 °C) was saturated with O_2 (1 atm) to initiate the reaction. The $Fe^{II}(bpy)_2{}^{2+}$ complex was prepared in situ by mixing $[Fe^{II}(MeCN)_4](ClO_4)_2$ in MeCN with 2 equiv of 2,2′-bipyridine. After the indicated reaction times, the yield of products was assayed by capillary column GC and/or GC-MS. Control experiments (i) without catalyst, (ii) without O_2, and (iii) without substrate each resulted in no reaction and no products. [b] With air in place of O_2 (1 atm); the yields are given in parenthesis. [c] With c-C_6H_{10}, c-C_6H_8, PhCH(O), and other substrates, the presence of 0.1% H_2O (v/v) reduced the yields by 30−40%; with 1% H_2O, no products were detected after 3 h. [d] With 0.5 mM $Fe^{II}(OPPh_3)_4{}^{2+}$ in place of $Fe^{II}(bpy)_2{}^{2+}$, the product yields are reduced 30−50%. [e] Results with an oxygenated Fenton system, ref 3. [f] With methyl linoleate, the presence of 1% H_2O reduced the alcohol yield by 50% but did not affect the ketone yields.

Scheme 1. Iron(II)-Induced Activation of O_2 for the Oxygenation of Cyclohexene (c-C_6H_{10})

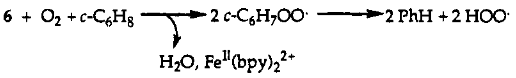


alone to give c-$C_6H_8(O)$ and c-C_6H_9OH (path D). The results of Table 1A indicate that with O_2 at 1 atm, path C is followed three times before path D terminates a cycle to give three ketones and two alcohols (-one/-ol ratio, 1.5). With air (0.2 atm O_2), path C is followed one time before path D to give two ketones and two alcohols (-one/-ol ratio, 0.9); 0.1 atm O_2 gives a ratio of 0.8.

The results of Table 1B indicate that MeL has reaction paths similar to those for c-C_6H_{10}, but with the complication of two single allylic ($\Delta H_{DBE} = 85$ kcal mol^{-1}) and one double allylic ($\Delta H_{DBE} = 75$ kcal mol^{-1}) centers.[7] When the latter forms **6**, it occasionally may collapse to give the observed keto-epoxide:

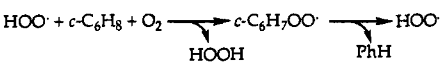
$$\mathbf{6} \rightarrow \text{MeL-keto-epoxide} + H_2O + Fe^{II}(bpy)_2{}^{2+} \qquad (2)$$

When c-C_6H_8 reacts to form **11** (analogous to c-C_6H_{10} and MeL; Scheme 1), the latter collapses to give the observed c-C_6H_7OOH. The latter becomes an oxygenated Fenton reagent[3] to produce intermediate **6** and PhOH. Species **6** in turn reacts with O_2/c-C_6H_8 to produce HOO•:



$$\mathbf{6} + O_2 + c\text{-}C_6H_8 \xrightarrow[\quad H_2O,\ Fe^{II}(bpy)_2{}^{2+}]{} 2\ c\text{-}C_6H_7OO^{\cdot} \longrightarrow 2\ PhH + 2\ HOO^{\cdot} \qquad (3)$$

which is the carrier of the observed catalysis-independent autoxidation,



$$HOO^{\cdot} + c\text{-}C_6H_8 + O_2 \xrightarrow[\quad HOOH]{} c\text{-}C_6H_7OO^{\cdot} \xrightarrow[\quad PhH]{} HOO^{\cdot} \qquad (4)$$

An earlier study of the $Fe^{II}(bpy)_2{}^{2+}$/reductant/O_2-induced initiation of the autoxidation of c-C_6H_8 concluded that an equivalent species **6** is the initiating intermediate.[4]

The formation of a hydroperoxide from c-C_6H_8 may be relevant to the peroxidation of lipids by O_2 via iron−bleomycin[9,10] and lipoxygenase.[11] Likewise, the results for the $Fe^{II}(bpy)_2{}^{2+}$/O_2/MeL system (Table 1B) are pertinent to metal/O_2-induced toxicity, rancidification of fats and oils, and the oxy radical theory of aging and heart disease.[12,13]

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