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Unexpected Superoxide Dismutase Antioxidant Activity of Ferric Chloride in Acetonitrile

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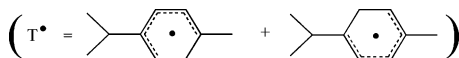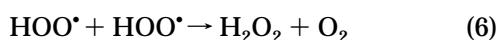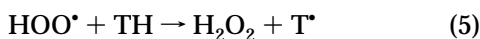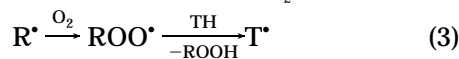
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Abstract: The azobis(isobutyronitrile)-initiated autoxidation of γ-terpinene in acetonitrile at 50 °C yields only *p*-cymene and hydrogen peroxide (1:1) in a chain reaction carried by the hydroperoxyl radical, HOO• (Foti, M. C.; Ingold, K. U. *J. Agric. Food Chem.* **2003**, *51*, 2758−2765). This reaction is retarded by very low (μM) concentrations of $FeCl_3$ and $CuCl_2$. The kinetics of the $FeCl_3$-inhibited autoxidation are consistent with chain-termination via the following: Fe^{3+} + HOO• ⇌ $[Fe^{IV}\text{-OOH}]^{3+}$ and $[Fe^{IV}\text{-OOH}]^{3+}$ + HOO• → Fe^{3+} + H_2O_2 + O_2. Thus, $FeCl_3$ in acetonitrile can be regarded as a very effective (and very simple) superoxide dismutase. The kinetics of the $CuCl_2$-inhibited autoxidation indicate that chain transfer occurs and becomes more and more important as the reaction proceeds, i.e., the inhibition is replaced by autocatalysis. These kinetics are consistent with reduction of Cu^{2+} to Cu^+ by HOO• and then the reoxidation of Cu^+ to Cu^{2+} by both HOO• and the H_2O_2 product. The latter reaction yields HO• radicals which continue the chain.

We have recently shown that the azobis(isobutyronitrile) (AIBN)-initiated autoxidation of the monoterpene, γ-terpinene (TH), yields *p*-cymene (Cy) as the only organic product:[1]
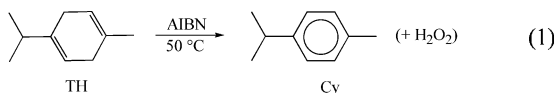
The oxidation chains are initiated by the peroxyl radicals produced by AIBN, reactions 2 and 3, and carried by the hydroperoxyl radical,[1] reactions 4−6.

$$\text{AIBN} \xrightarrow[\Delta]{k_d} [R^\bullet + N_2 + R^\bullet]_{cage} \xrightarrow[-N_2]{e} 2e\,R^\bullet \quad (2)$$

$$R^\bullet \xrightarrow{O_2} ROO^\bullet \xrightarrow[-ROOH]{TH} T^\bullet \quad (3)$$

$$T^\bullet + O_2 \rightarrow Cy + HOO^\bullet \quad (4)$$

$$HOO^\bullet + TH \rightarrow H_2O_2 + T^\bullet \quad (5)$$

$$HOO^\bullet + HOO^\bullet \rightarrow H_2O_2 + O_2 \quad (6)$$

Kinetic analysis of the above reactions yields the equation

$$R_{Cy} = \frac{k_5}{(2k_6)^{0.5}} \times (2ek_d)^{0.5} \times [AIBN]^{0.5} \times [TH]^{1.0} \quad (7)$$

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(1) Foti, M. C.; Ingold, K. U. *J. Agric. Food Chem.* **2003**, *51*, 2758−2765.

where R_{Cy} is the measured (by UV)[1] rate of formation of Cy and e is the efficiency of cage escape of the initial geminate pair of radicals produced by AIBN, reaction 2. The experimental rate law was in good agreement with eq 7, viz.,[1]

$$R_{Cy}/\text{M s}^{-1} = \{(4.4 \pm 0.3) \times 10^{-4}\}[AIBN]^{0.52\pm0.09}$$
$$[TH]^{0.95\pm0.08} \quad (8)$$

During this work (which was designed to reveal the mechanism by which TH inhibited the autoxidation of linoleic acid, LH),[1] we made the surprising discovery that *low concentrations* of ferric chloride or cupric chloride retarded the autoxidation of TH in acetonitrile. Our surprise was due to the fact that transition metal ions are well-known accelerators of the autoxidation of organic compounds, though in a few systems (generally involving high concentrations of transition metal ions) inhibition of the autoxidation is observed.[2] We therefore report on the $FeCl_3$- and $CuCl_2$-inhibited AIBN-initiated (1−15 mM) autoxidation of TH (10−160 mM) in acetonitrile at 50 °C, and deduce their most probable mechanisms of action.

In the presence of the metal chlorides, Cy was again[1] the sole organic product of reaction 1. The rate of Cy formation was the same for oxygen-saturated as for air-saturated solutions in the absence[1] and presence of the metal ions. However, the presence of low concentrations (μM) of both $FeCl_3$ and $CuCl_2$ greatly retarded the oxidation of TH, see Table 1 and Figure 1. With $FeCl_3$ there was an induction period followed by oxidation at an almost steady rate (see Figure 1 inset, curve B) for which the rate law was

$$R_{Cy}/\text{M s}^{-1} = \{(9.0 \pm 0.5) \times 10^{-7}\}$$
$$[TH]^{0.93\pm0.05}\frac{[AIBN]^{0.45\pm0.05}}{[FeCl_3]^{0.45\pm0.05}} \quad (9)$$

The rate of Cy formation during the induction period was very much lower than the steady rate described by eq 9, too low, in fact, to determine the order in $FeCl_3$. With $CuCl_2$, the induction period was short and the rate rather quickly approached the uninhibited rate (Figure 1 inset, curve C vs curve A). Rates measured 5 min after the reactants had been placed in a UV cuvette in the spectrophotometer preheated to 50 °C could be described by eq 10. The behavior of the two chlorides differs in more

$$R_{Cy}/\text{M s}^{-1} = \{(1.3 \pm 0.2) \times 10^{-9}\}$$
$$[TH]^{1.31\pm0.07}\frac{[AIBN]^{0.36\pm0.07}}{[CuCl_2]^{0.91\pm0.05}} \quad (10)$$

than their kinetic rate laws. Thus, at comparatively high concentrations ($\geq11\ \mu$M) copper chloride was able to *initiate* TH (ca. 65 mM) autoxidation to Cy *in the absence of AIBN* with a measurable (5 min) rate of 6.7×10^{-8} M s^{-1}, whereas $FeCl_3$ at this concentration did not induce measurable oxidation.

Of particular relevance for the present work is a 1963

TABLE 1. AIBN (8 mM)-Initiated Oxidation of 50 mM TH in Acetonitrile at 50 °C: Times Required to Produce 2.5 mM Cy (5% Reaction)[a] in the Absence and Presence of FeCl₃ or CuCl₂

[FeCl₃]/μM	time/s[b]	[CuCl₂]/μM	time/s[b]
0	800	0	800
0.31	1240	1.3	1210
0.61	1575	2.6	1500
1.21	2140	5.2	1920
2.38	3110	10.4	2100
4.58	3900		

[a] Evaluated spectrophotometrically at 273 nm from the quantity of *p*-cymene formed in solution (see Text). [b] Error ±10 s.
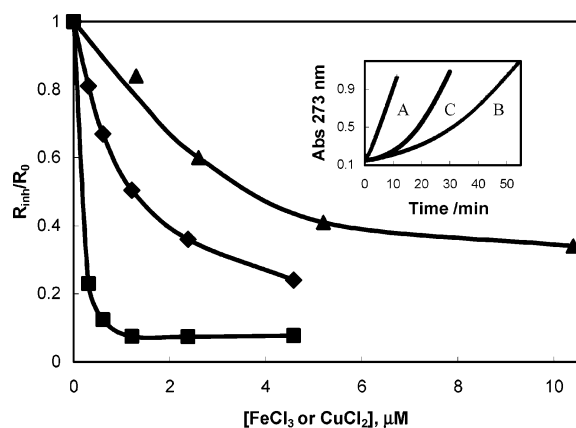

FIGURE 1. AIBN (8 mM)-initiated autoxidation of TH (50 mM) in acetonitrile at 50 °C in the presence of different concentrations of FeCl₃ during the induction period (■), after the induction period (◆), and different concentrations of CuCl₂ 5 min after the start of the reaction (▲). The metal ion inhibited rates, R_{inh}, are plotted relative to the rate in the absence of metals, R_0. Inset: Growth in the 273-nm absorbance, due to Cy formation, as a function of time under the above experimental conditions in the absence of metal ions (A), in the presence of 2.4 μM FeCl₃ (B), and in the presence of 5.2 μM CuCl₂ (C).

report by Hammond et al.[3] in which it is shown that 0.05–2 mM FeCl₃ gave well-defined induction periods in the AIBN-initiated autoxidation of cumene and Tetralin in chlorobenzene at 70 °C.

The rates of these FeCl₃-inhibited autoxidations were independent of the oxygen partial pressure. As Hammond et al.[3] pointed out, this means that the actual chain-breaking process must involve the peroxyl radicals and not the carbon-centered radicals, all carbon-centered radicals being trapped by dioxygen. That is, chain-breaking was not due to the ligand transfer oxidation of the carbon-centered radicals (eq 11, with $MX_n = FeCl_3$), a process first reported by Minisci[4] for X = halide and

$$R^• + MX_n \rightarrow RX + MX_{n-1} \qquad (11)$$

(2) There are at least two books[2a,b] and some reviews[2c–f] which discuss (in whole or in part) transition metal-catalyzed autoxidations of organic liquids and include mention of some odd exception where autoxidations are inhibited by metal ions. (a) Emanuel, N. M.; Denisov, E. T.; Maizus, Z. K. *Liquid-Phase Oxidation of Hydrocarbons*; Plenum Press: New York, 1967. (b) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (c) Ingold, K. U. *Chem. Rev.* **1961**, *61*, 563–589. (d) Ingold, K. U. In *Metal Catalysed Lipid Oxidation*; Svenska Institutet för Konserveringsforskning (SIK) Rapport, 1968, No. 240, pp 11–41. (e) Marcuse, R.; Fredeiksson, P.-O. In *Metal Catalysed Lipid Oxidation*; SIK Rapport, 1968, No. 240, pp 97–103. (f) Howard, J. A. In *Peroxyl Radicals*; Alfassi, Z. B., Ed.; Wiley: New York, 1997; Chapter 10.

(3) Hammond, G. S.; Mahoney, L. R.; Nandi, U. S. *J. Am. Chem. Soc.* **1963**, *85*, 737–741.

pseudohalide ions in the presence of iron or copper salts. Kochi[5] has shown that these reactions are extremely rapid and it has been pointed out by Minisci and Fontana[6] that ferric and cupric halides are among the most effective traps for alkyl radicals. Since the competing trapping by dioxygen, reaction 12, is diffusion-controlled,[7] at the concentrations of O₂ and FeCl₃ used by Hammond et al.,[3] reaction 11 does not compete with reaction 12. Hammond et al.[3] also found that the addition

$$R^• + O_2 \rightarrow ROO^• \qquad (12)$$

of a small amount of the hydroperoxide derived from the two substrates, i.e., cumene hydroperoxide or Tetralin hydroperoxide, increased the induction periods to such an extent that their end was not observed. In contrast, the addition of *tert*-butyl hydroperoxide did not increase the induction periods. Moreover, the autoxidation of cyclohexene was not inhibited by FeCl₃ but was strongly inhibited by the addition of FeCl₃ and Tetralin hydroperoxide.[3] These workers[3] also confirmed an earlier report[8] that, in benzene, FeCl₃ catalyzed the decomposition of cumene hydroperoxide to phenol and acetone,[9] reaction 13.

$$PhCMe_2OOH \xrightarrow{FeCl_3} PhOH + Me_2CO \qquad (13)$$

It was also shown that this reaction was very fast in chlorobenzene.[3] Since an ortho-alkylated phenol would be expected from the FeCl₃-catalyzed decomposition of Tetralin hydroperoxide, but no phenol could be fromed from *tert*-butyl hydroperoxide or cyclohexene hydroperoxide, it was concluded[3] that the inhibition of autoxidation of the two alkylaromatic hydrocarbons by FeCl₃ was due to peroxyl radical trapping by the phenols[11] generated from their hydroperoxides, i.e.,

$$ROO^• + ArOH \rightarrow ROOH + ArO^• \qquad (14)$$
$$ROO^• + ArO^• \rightarrow \text{nonradical products} \qquad (15)$$

In principle, an analogous mechanism could be invoked to explain the FeCl₃-inhibited autoxidation of TH.[12] Such an explanation would require the Cy product to be oxidized to *p*-methylcumene hydroperoxide, which is then converted to *p*-cresol. However, oxidation of Cy during the early stages of the reaction can be ruled out both on kinetic grounds and by experiment. In the early stages of TH oxidation not only is [Cy] ≪ [TH][13] but also the rate constants for hydrogen atom abstraction from cumene

(4) Minisci, F. *Angew. Chem.* **1958**, *70*, 599.

(5) Kochi, J. K. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Chapter 11.

(6) Minisci, F.; Fontana, F. *Tetrahedron Lett.* **1994**, *35*, 1427–1430. See also: Ingold, K. U.; MacFaul, P. A. In *Biomimetic Oxidation Catalyzed by Transition Metal Complexes*; Meunier, B., Ed.; Imperial College Press: London, UK, 1999; Chapter 2.

(7) Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095–5099.

(8) Kharasch, M. S.; Fono, A.; Nudenberg, W. *J. Org. Chem.* **1950**, *15*, 748–752.

(9) The cumene hydroperoxide/FeCl₃ reaction has recently been put to synthetic use.[10]

(10) Liguori, L.; Bjorsvik, H.-R.; Fontana, F.; Bosco, D.; Galimberti, L.; Minisci, F. *J. Org. Chem.* **1999**, *64*, 8812–8815.

(11) Or a ferric phenoxide.[3]

(12) TH autoxidation was inhibited by 0.3–5 μM FeCl₃, concentrations well below the minimum concentration of 50 μM used by Hammond et al.[3] to inhibit the autoxidation of cumene and Tetralin.
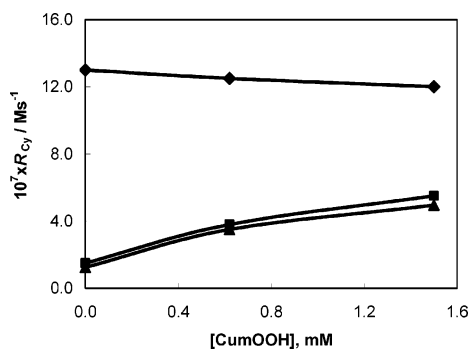
FIGURE 2. Rates of the AIBN (8.3 mM)-initiated autoxidation of TH (40 mM) in acetonitrile at 50 °C in the presence of different concentrations of cumene hydroperoxide and $FeCl_3$. Key: ◆, $[FeCl_3] = 0$; ■, $[FeCl_3] = 4.5$ μM; ▲, $[FeCl_3] = 18$ μM.
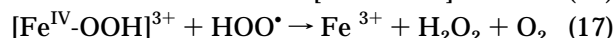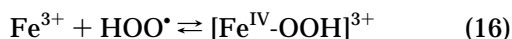
(a model for Cy) and TH by peroxyl radicals strongly favor the latter reaction, viz., at 50 °C $k(ROO^\bullet + cumene)$ = 0.7 M^{-1} s^{-1} [14] and k_4 ($HOO^\bullet + TH$) = 2800 M^{-1} s^{-1}.[1] Experimentally, with 50 mM [TH], 8 mM [AIBN], and 1 μM $FeCl_3$ in acetonitrile at 50 °C, the rate of autoxidation was unaffected by the deliberate addition of 10 mM Cy (which is about three times the amount produced in 30 min in the absence of $FeCl_3$). Furthermore, the addition of cumene hydroperoxide to AIBN-initiated autoxidations of TH in acetonitrile *increased* the rates of $FeCl_3$-inhibited reactions, rather than producing a further decrease in rate, see Figure 2.

The inability of cumene hydroperoxide + $FeCl_3$ to inhibit autoxidation under our conditions was confirmed by using linoleic acid, rather that TH, as the oxidizable substrate. It was found that autoxidation was accelerated by $FeCl_3$ alone and was further accelerated, in a dose-dependent manner, by the addition of cumene hydroperoxide (see Supporting Information, Figure S1). The accelerating effect of cumene hydroperoxide on the rates of the $FeCl_3$-modulated, AIBN-initiated autoxidation of TH and linoleic acid in acetonitrile at 50 °C contrasts with Hammond's[3] finding that the AIBN-initiated autoxidation of cyclohexene in *chlorobenzene* at 70 °C is strongly inhibited by $FeCl_3$ plus Tetralin hydroperoxide, though it is not inhibited by $FeCl_3$ alone. This difference must be attributed to a solvent effect with the rate of the $FeCl_3$-catalyzed conversion of alkylaromatic hydroperoxides to phenols being much faster in chlorobenzene than in acetonitrile. In this connection, it is interesting to note that in the first publication on reaction 13, Kharasch et al.[8] reported that this reaction was fast in benzene (where the $FeCl_3$ is a strong Lewis acid) and that the reaction did not occur in alcohol (where the $FeCl_3$ is a weak Lewis acid).

Having eliminated two potential explanations for inhibition of AIBN-initiated autoxidation of TH by $FeCl_3$ and $CuCl_2$, viz. (i) trapping of the T$^\bullet$ radical (no oxygen pressure dependence) and (ii) trapping of the chain carrying hydroperoxyl radical[1] by *p*-cresol formed in situ, we are forced to conclude that inhibition is due to direct reactions of the metal ions with the $HOO^\bullet$ radical. There is, in fact, a wealth of evidence indicating that peroxyl

radicals can complex reversibly with transition metal ions.[2,16] Inhibition resulting from complex formation could, in principle, be due to a decrease in the rate constant for chain propagation by the complexed $HOO^\bullet$ (reaction 5) or an increase in the rate constant for chain termination (reaction 6). The latter appears the more probable in view of the very low (μM) concentration of $FeCl_3$ and $CuCl_2$ required to produce substantial inhibition of the autoxidation of TH (cf. inhibition of hydrocarbon and lipid autoxidation by peroxyl radical trapping phenols at μM concentrations).[2a,c,f]

With $FeCl_3$, chain termination by reactions 16 and 17 (which ignore the ligands on the iron)[17] yields the kinetic rate law for inhibition of TH autoxidation given in eq 18, which is in excellent agreement with experiment, eq 9.
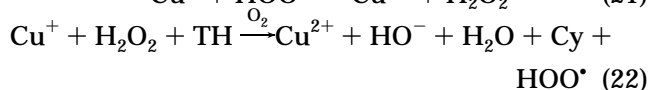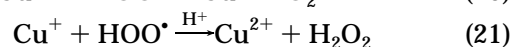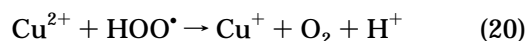
$$Fe^{3+} + HOO^\bullet \rightleftharpoons [Fe^{IV}\text{-}OOH]^{3+} \qquad (16)$$

$$[Fe^{IV}\text{-}OOH]^{3+} + HOO^\bullet \rightarrow Fe^{3+} + H_2O_2 + O_2 \quad (17)$$

$$R_{Cy}/M\ s^{-1} = k_5(2ek_d)^{0.5}\left(\frac{k_{-16}}{k_{16}k_{17}}\right)^{0.5}[TH]\frac{[AIBN]^{0.5}}{[Fe^{3+}]^{0.5}} \quad (18)$$

Equation 18 can be rewritten by putting $k_{inh} = k_{16}k_{17}/k_{-16}$, where k_{inh} represents the *effective* inhibition rate constant, i.e.,

$$R_{Cy}/M\ s^{-1} =$$
$$\frac{k_5(2ek_d)^{0.5}}{k_{inh}{}^{0.5}}[TH]\frac{[AIBN]^{0.5}}{[Fe^{3+}]^{0.5}} = \frac{k_5[TH]R_i^{0.5}}{(k_{inh}[Fe^{3+}])^{0.5}} \quad (19)$$

where $R_i = 2ek_d[AIBN]$ is the rate of chain initiation by AIBN.[18] Thus, *ferric chloride catalytically and effectively traps the chain-carrying hydroperoxyl, the conjugate acid of the superoxide radical anion.*[17] *Ferric chloride in acetonitrile acts, therefore, as a superoxide dismutase (SOD).* This contrasts with the situation in water where iron (aquo-iron) is not an effective SOD.[20,21]

With $CuCl_2$, the rate law (determined after 5 min of reaction), eq 10, has an order in TH greater than 1.0. This indicates that inhibition is accompanied by a chain-transfer step. Termination via reactions 20 and 21, together with chain transfer (presumably mediated by $HO^\bullet$ radicals) via reaction 22, appears most plausible.[22]

$$Cu^{2+} + HOO^\bullet \rightarrow Cu^+ + O_2 + H^+ \qquad (20)$$

$$Cu^+ + HOO^\bullet \xrightarrow{H^+} Cu^{2+} + H_2O_2 \qquad (21)$$

$$Cu^+ + H_2O_2 + TH \xrightarrow{O_2} Cu^{2+} + HO^- + H_2O + Cy +$$
$$HOO^\bullet \quad (22)$$

Applying the usual steady-state approximation to the radicals and Cu^+ yields the rate expression[25]

(13) Due to the spontaneous oxidation of TH, *p*-cymene is usually present in mM concentrations even in distilled, neat TH.

(14) Based on a measured rate constant of 0.18 M^{-1} s^{-1} at 30 °C[15] and an assumed Arrhenius preexponential factor of $10^{8.5}$ M^{-1} s^{-1}.

(15) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1967**, *45*, 793−802.

(16) Goldstein, S.; Meyerstein, D. *Acc. Chem. Res.* **1999**, *32*, 547−550.

(17) In addition, the following discussions deal only with reaction of the $HOO^\bullet$ radical. We used "dry" acetonitrile in our experiments, but cannot rule out contributions to the overall chemistry from its conjugate base, superoxide. We also note that TH is not converted in measurable yield into an epoxide under our experimental conditions although $FeCl_3/H_2O_2$ in dry acetonitrile is an epoxidation catalyst with 1,4-cyclohexadiene yielding 5% epoxide and 95% benzene, see: Sugimoto, H.; Sawyer, D. T. *J. Org. Chem.* **1985**, *50*, 1784−1786.

$$R_{Cy} = k_5[TH]$$
$$\left(\frac{R_i k_{21} + \{(R_i k_{21})^2 + 8R_i k_{20}k_{21}k_{22}[TH][Cu^{2+}][H_2O_2]\}^{0.5}}{4k_{20}k_{21}[Cu^{2+}]} \right) \quad (23)$$

Equation 23 is consistent with the autoacceleration observed in the CuCl$_2$-inhibited, AIBN-initiated oxidation of TH in acetonitrile (see Figure 1 inset, curve C). At the beginning of the reaction when there is no H$_2$O$_2$ present, eq 23 simplifies to eq 24, while later when the H$_2$O$_2$ concentration has become significant, it simplifies to eq 25.

$$R_{Cy} = \frac{k_5[TH]R_i}{2k_{20}[Cu^{2+}]} \quad (24)$$

$$R_{Cy} = \frac{k_5[TH]^{1.5}R_i^{0.5}k_{22}^{0.5}[H_2O_2]^{0.5}}{(2k_{20}k_{21}[Cu^{2+}])^{0.5}} \quad (25)$$

Thus, as the reaction progresses the order in [TH] increases from 1.0 toward 1.5, the order in R_i decreases from 1.0 toward 0.5, and the order in [CuCl$_2$] changes from −1.0 toward −0.5. The failure of theory to exactly match eq 10 (for which rates were measured at a single 5-min time point rather than at equal [H$_2$O$_2$], i.e., equal TH to Cy conversion) is hardly surprising.

Unlike FeCl$_3$, CuCl$_2$ is *not* a SOD in the AIBN/TH/acetonitrile system. The CuCl$_2$ only functions as an antioxidant at the start of the reaction where [H$_2$O$_2$] is low because the reduction of Cu^{II} to Cu^I in reaction 20 allows chain-transfer via reaction 22 to compete with the chain-terminating reoxidation of Cu^I to Cu^{II} by the HOO$^{\bullet}$ radical, reaction 21. This difference in the behavior of the two metals is concordant with the reported rate constants for relevant reaction *in water*. Thus, k_{20} (for Cu$^{II}_{aq}$) = 1 × 10^9 M^{-1} s^{-1},[21] which implies that the expected [Cu^I-OOH]$^{2+}$ intermediate is much too short-lived to enter into a bimolecular, chain-terminating step with a second HOO$^{\bullet}$ radical (analogous to reaction 17). In contrast, the overall reaction

$$Fe^{3+}_{aq} + HOO^{\bullet} \rightarrow Fe^{2+} + O_2 + H^+ \quad (26)$$

is slow with $k_{26} < 10^3$ M^{-1} s^{-1},[21] consistent with a prolonged lifetime for the initial [Fe^{IV}-OOH]$^{3+}$ complex (reaction 16), which permits the subsequent chain-ending reaction 17 with a second HOO$^{\bullet}$ radical. Moreover, the fast reduction of Cu^{2+} to Cu$^+$ by HOO$^{\bullet}$ will, as the H$_2$O$_2$ concentration builds up, be followed by chain transfer, reaction 22, induced by the rather fast reaction 27 ($k_{27} = 4.7 \times 10^3$ M^{-1} s^{-1}).[21]

$$Cu^+_{aq} + H_2O_2 \rightarrow Cu^{2+} + HO^- + HO^{\bullet} \quad (27)$$
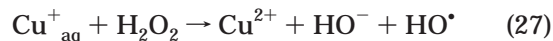
If any Fe^{2+} is actually formed by unimolecular decomposition of [Fe^{IV}-OOH]$^{3+}$ (to Fe^{2+}, O$_2$, and H$^+$) it is roughly 2 orders of magnitude less reactive than Cu$^+$ in converting H$_2$O$_2$ into HO$^{\bullet}$ radicals ($k_{28} \approx 50$ M^{-1} s^{-1})[28,29]

$$Fe^{2+}_{aq} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO^{\bullet} \quad (28)$$
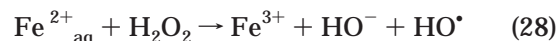
Experimental Section

Acetonitrile and all the other chemicals were of the purest grade commercially available and were used as received except for AIBN, which was recrystallized from methanol and stored at −20 °C. The kinetics were monitored on a Perkin-Elmer Lambda 25 UV/VIS double ray spectrometer; the GC-MS analyses were done on a Hewlett-Packard 5890 interfaced to a Hewlett-Packard 5971A Mass Selective Detector (DB-5 capillary column, 30 m × 0.25 mm, film thickness 0.25 μm).

Peroxidation of γ-Terpinene in the Absence and Presence of FeCl$_3$ or CuCl$_2$. Solutions of γ-terpinene (final concentration 10−160 mM) and AIBN (final concentration 1−15 mM) in acetonitrile were mixed 1:1 (v/v) in a UV-cuvette (optical path, 1.0 cm) saturated with air or oxygen at 1 atm and quickly heated to 50 °C. Thereafter, the cell compartment was maintained at 50 °C and the absorbance at 273 nm (corresponding to a maximum *p*-cymene absorbance) was monitored over time as previously described.[1] Excellent straight lines ($R^2 = 0.97$−0.99) of absorbance vs time were usually obtained whose slopes (divided by 390 M^{-1} cm^{-1}) gave the rate of reaction, d[Cy]/dt in M s^{-1}. In the case of the metal-inhibited oxidations, 10−80 μL aliquots of a concentrated solution of FeCl$_3$ (final concentration 0.3−5 μM) or CuCl$_2$ (final concentration 1−8 μM) in acetonitrile were added along with the other reactants before saturating the solutions with O$_2$ or air. The reaction orders for AIBN, γ-terpinene, FeCl$_3$, or CuCl$_2$ were obtained by changing the concentration of the pertinent species while keeping the others constant. Acetonitrile was employed in these oxidations to solubilize the two metal chlorides which were employed at concentrations sufficiently low that their own UV absorptions did not interfere with measurements of Cy formation.

Note Added after ASAP Posting. The formal oxidation number of iron in the complex [Fe^{IV}-OOH]$^{3+}$ in eqs 16 and 17 and the TOC graphic was incorrect in the version posted ASAP October 24, 2003; the corrected version was posted October 28, 2003.

(18) From the values in acetonitrile at 50 °C of $k_4 = 2800$ M^{-1} s^{-1},[1] $2ek_d = 2.0 \times 10^{-6}$ s^{-1},[19] and the numerical factor of the experimental eq 9, it is possible to calculate that FeCl$_3$ inhibits reaction 1 with a $k_{inh} = 1.9 \times 10^{13}$ M^{-2} s^{-1}.

(19) Foti, M. C.; Ruberto, G. *J. Agric. Food Chem.* **2001**, *49*, 342−348.

(20) For an excellent review of models of superoxide dismutases see ref 21. Effective model SODs generally contain Cu, Fe, or Mn chelated by a multidentate ligand, with the Mn complexes generally being the most active.
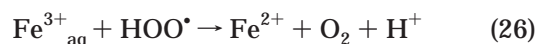
(21) Cabelli, D. E.; Riley, D.; Rodriguez, J. A.; Valentine, J. S.; Zhu, H. In *Biomimetic Oxidations Catalyzed by Transition Metal Complexes*; Meunier, B., Ed.; Imperial College, Press: London, UK. 1999; Chapter 10.

(22) Hydrogen atom abstraction by the HO$^{\bullet}$ radical will partition approximately 80% in favor of the 50 mM TH (for which a reasonable model is 1,4-cyclohexadiene, $k = 7.7 \times 10^9$ M^{-1} s^{-1})[23] and approximately 20% in favor of the ca. 19 M acetonitrile ($k = 5.5 \times 10^6$ M^{-1} s^{-1}).[24] Of course, the 20% of radicals formed by H-atom abstraction from the acetonitrile will rapidly add oxygen and the resultant peroxyl will abstract from TH to yield T$^{\bullet}$.

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(25) Analogous kinetics have been observed in the phenol-inhibited, AIBN-initiated autoxidation of Tetralin.[26,27] Termination involves reactions 14 and 15 (Ar = Ph) and chain transfer the following reaction: PhO$^{\bullet}$ + RH → PhOH + R$^{\bullet}$. Kinetic analysis with some simplifying assumptions[26,27] yields an inhibited oxidation rate proportional to [Tetralin]$^{1.5}$[AIBN]$^{0.5}$/[PhOH]$^{0.5}$.

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