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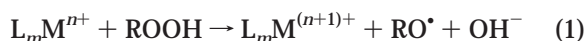
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COMMENTARY

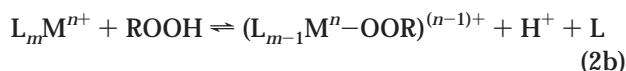
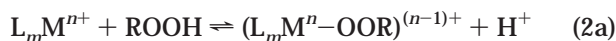
Comments on the Mechanism of the "Fenton-Like" Reaction

Recently, two commentaries on the mechanism of "Fenton-like" processes were published in this Journal.^{1,2} The major aim of these comments was to point out that low-valent transition metal ions with various attached ligands, $L_m M^{n+}$, react with ROOH (R = H or alkyl) to form $\cdot\text{OH}$ or $\text{RO}\cdot$ radicals via the so-called Fenton-like reaction:



These two commentaries^{1,2} argued against the conclusions of Sawyer et al.³ in an earlier Account that Fenton reagents do not produce $\cdot\text{OH}$ and $\text{RO}\cdot$ radicals. Though we agree that radicals are usually formed in Fenton processes, it is the aim of this commentary to point out some general mechanistic aspects for these processes, and to show that radicals may be formed via reactions that do not involve the formation of either $\cdot\text{OH}$ or $\text{RO}\cdot$ radicals.^{4,5}

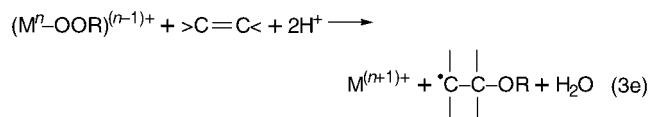
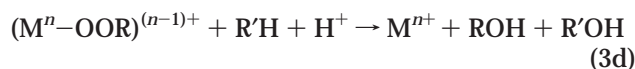
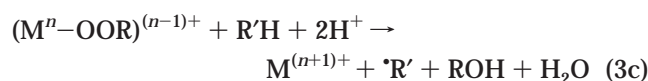
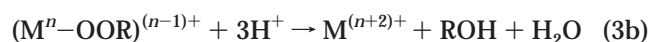
It has been shown,^{4,6} using the specific rate constants for reaction 1, the free energy gain in reaction 1, and the Marcus cross relation,⁷ that the reaction of most transition metal complexes with H_2O_2 cannot proceed in aqueous solution via an outer-sphere electron-transfer mechanism. Therefore, the first step in this process must be the formation of a transient complex between the metal complex and the peroxide:^{4,6,8}



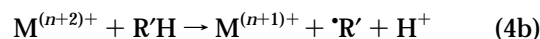
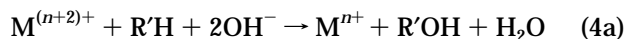
In the following discussion we shall assume that the transition metal peroxide complex is $(L_m M^n - \text{OOR})^{(n-1)+}$,

although the other possibilities are equally valid (for clarity purposes the nonparticipating ligands, L, will be omitted). The mechanistic requirement for the formation of these transient complexes might explain why the nonnucleophilic $(\text{CH}_3)_3\text{COOC}(\text{CH}_3)_3$, in contrast to $(\text{CH}_3)_3\text{COOH}$, does not react with FeCl_2 ,³ and why the reaction of $(\text{CH}_3)_3\text{COOC}(\text{CH}_3)_3$ with $\text{Cr}^{2+}_{\text{aq}}$ is extremely slow.⁹ There are cases where $(\text{CH}_3)_3\text{COOR}$ does react with $\text{Cr}^{2+}_{\text{aq}}$,⁹ which is a much stronger reducing agent than $\text{Fe}^{2+}_{\text{aq}}$, and has a higher rate of ligand exchange. In these cases $(\text{Cr}^{\text{II}} \cdot (\text{CH}_3)_3\text{COOR})^{2+}$ may be a plausible intermediate (reaction 2c), which decomposes fast into $(\text{CH}_3)_3\text{CO}\cdot$ and $(\text{Cr}^{\text{III}} - \text{OR})^{2+}$ (see below).

The decomposition of $(M^n - \text{OOR})^{(n-1)+}$ may take place via one of the following reactions:



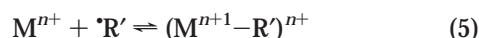
In addition, $M^{(n+2)+}$ (or $M^{n+2}=\text{O}$), formed in reaction 3b, can oxidize various substrates via reactions 4a and 4b.^{10,11} Thus, $(M^n - \text{OOR})^{(n-1)+}$ may act also as one-electron oxidants via reactions 3c, 3d, 3e, or 3b followed by 4b, and not only as two-electron oxidants as proposed by Walling.¹



The rates of reactions 3a–3e and 4a and 4b depend on the nature of M^{n+} , the ligand, the organic substrate and its

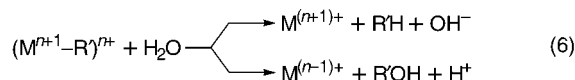
concentration, the solvent, and the pH.¹² Thus, organic radicals may be formed via (i) reaction 3a followed by the reaction of RO• with the substrate as proposed,^{2,11} (ii) reaction 3b followed by reaction 4b,³ (iii) reaction 3c,⁴ or (iv) reaction 3e. Organic radicals will not be formed if the decomposition of (Mⁿ-OOR)⁽ⁿ⁻¹⁾⁺ takes place via reaction 3d or reaction 3b followed by reaction 4a.

To determine whether hydroxyl radicals are involved in the Fenton reagent, sensitive tests have to be used.^{1,4,11,13} These tests have to take into account the reactions of the organic radicals with the metal ions present in the solution. The latter processes are considerably more complex than those suggested by Walling.¹ Most of these reactions do not proceed via an outer-sphere electron-transfer mechanism, and involve the formation of transient complexes with metal-carbon σ -bonds (reaction 5).^{1,4,12,14} The rate constants for the

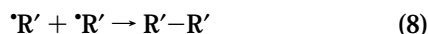


formation of many of these transient complexes with metal-carbon σ -bonds were reported.^{12,14} It has been shown that the ligands affect these rate constants considerably as most of these processes are controlled by the rate of ligand interchange of L_mMⁿ⁺.¹⁵

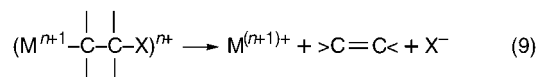
The mechanisms of the decomposition of the transient complexes with metal-carbon σ -bonds involve not only heterolysis (reaction 6),^{1,12} but also homolysis (reaction -5),¹²



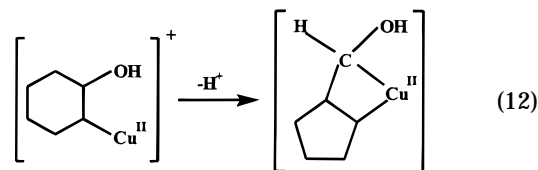
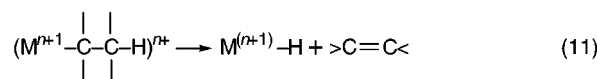
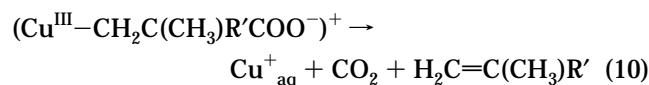
which might be followed by a variety of radical processes, e.g., reactions 7 and 8.^{12,14}



These reactions clearly affect the nature of the final products.¹² In addition, a β -elimination reaction may compete with both the heterolytic and homolytic cleavage of the σ -bond when a good leaving group, X (X = OR, NR₂, halide, etc.), is bound at the β position to the carbon-centered radical:¹⁶



Thus, for example, when (CH₃)₃COH is used as •OH scavenger, not only might (CH₃)₂C(CH₂OH)OH and ((CH₃)₂C(OH)-CH₂-)₂ be formed as proposed by Walling,¹ but (CH₃)₂C=CH₂ is often the major product, e.g., for L_mMⁿ⁺ = Fe^{II}(EDTA).¹¹ Other mechanisms of decomposition, which are often observed, include β -decarboxylation of (Cu^{III}-CH₂C(CH₃)-R'COO⁻)⁺ complexes (reaction 10),^{16,17} β -hydride shift reaction (reaction 11),¹⁸ and even a carbon skeleton rearrangement (reaction 12).¹⁹



Though all these reactions were extensively studied, it seems at present impossible to predict a priori the mechanism of decomposition of a given transient complex with a metal-carbon σ -bond.¹² Therefore, a detailed kinetic and product analysis is essential for each system to be used as a test for exploring the mechanism of a given Fenton reagent.

The situation is at least as complex in oxygenated solutions due to the reaction of the organic radical, •R', with O₂ to form peroxy radicals (reaction 13),²⁰



where •R' is formed via pathways i-iv as described above. Peroxy radicals may undergo a number of unimolecular processes (reaction 14). The most ubiquitous ones are HO₂•



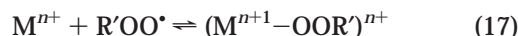
and O₂^{•-} eliminations, which are usually base-catalyzed, but intramolecular addition to the C=C double bond or H-abstraction has also been demonstrated.²⁰ Peroxy radicals, which do not decay in one of the unimolecular processes, disappear bimolecularly (reaction 15), where tertiary peroxy



radicals decay considerably more slowly than secondary and primary ones.^{14,20} R'OOOOR' is not stable, and often decomposes to yield O₂, alcohol, and aldehyde//ketone.²⁰ Peroxy radicals can also react with various organic solutes via reaction 16, and for this reaction to occur at an appreciable



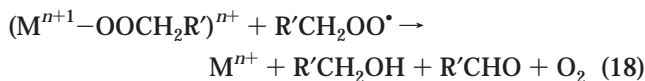
rate, the C-H bond energy of the donor must be sufficiently low.²⁰ Indeed, *k*₁₆ values for cyclohexane and cyclohexene were reported to be 0.048 and 6.1 M⁻¹ s⁻¹, respectively.² However, when R'OO• is formed in oxygenated Fenton reagents, it most probably reacts with the metal complex:



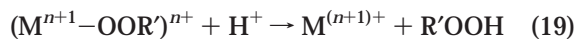
We note that (Mⁿ⁺¹-OOR')ⁿ⁺ is not the only product plausible, but is usually the major one.¹² The rate of reaction 17 is usually controlled by the rate of the ligand exchange, e.g., for Fe²⁺_{aq} *k*₁₇ ≈ 1 × 10⁶ M⁻¹ s⁻¹.^{14,21} It is expected that in less polar solvents the rate of the ligand exchange by the solvent will be even faster. Thus, in oxygenated Fenton reagents, reaction 17 is expected to compete efficiently with both reactions 15 and 16, and has to be considered when the product composition is discussed.

The decomposition of $(M^{n+1}-OOR')^{n+}$ may take place via the following processes a–e followed by oxidation of the substrate by $M^{(n+3)}=O$:

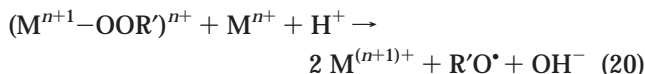
(a) homolysis of the M–O bond (reaction –17),
followed by reactions 15,²⁰ 16,²⁰ and/or 18²²



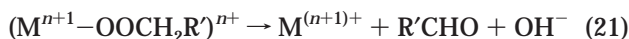
(b) heterolysis of the M–O bond¹²



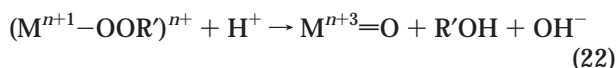
(c) Fenton-like reaction, e.g., reaction 20



(d) oxidation of the alkyl residue, e.g., reaction 21



(e) heterolysis of the O–O bond (reaction 22)



This last pathway has not been observed in aqueous solution. The transient complexes, $(M^{n+1}-OOR')^{n+}$, may also decompose via oxidation of the ligand and substrates present in the solution. If $(M^{n+1}-OOR')^{n+}$ decomposes mainly via homolysis of the M–O bond, then the formation of these transient complexes would not affect the nature of the final products as predicted through reactions 15 and 16. However, the experimental data, at least in aqueous solutions, indicate that reactions 19 and 20 are the major processes observed.

In conclusion, one can state that radicals are intermediates in most Fenton reagents, at least in aqueous solutions. However, this does not mean that hydroxyl radicals are the active intermediates in these processes. The mechanisms of Fenton-like processes are extremely complex, and it is not surprising that different conclusions about the identity of the oxidizing intermediate were reached for different reagents and substrates. For example, careful studies in well-designed systems show that hydroxyl radicals are the major products in the reaction of Cu^{+}_{aq} with H_2O_2 in the presence of aromatic compounds,²³ whereas they are not formed in the presence of alcohols.^{4,5} Similar examples can be found in the literature for Fe^{2+}_{aq} reacting with H_2O_2 in the presence of different substrates.^{24,25}

The experimental results point out that there is no general answer to the question of whether hydroxyl radicals are being formed in Fenton-like processes. A detailed mechanistic study of each system has to be carried out to address this point. This is nearly impossible for biological systems.

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References

- (1) Walling, C. Intermediates in the reaction of Fenton type reagents. *Acc. Chem. Res.* **1998**, *31*, 155.
- (2) MacFaul, P. H.; Wayner, D. D. M.; Ingold, K. W. A radical account of "oxygenated Fenton chemistry". *Acc. Chem. Res.* **1998**, *31*, 159.
- (3) Sawyer, D. T.; Sobkowiak, A.; Matsushita, T. Metal $\{ML_x; M = Fe, Cu, Co, Mn\}$ /hydroperoxide-induced activation of dioxygen for oxygenation of hydrocarbons: Oxygenated Fenton chemistry. *Acc. Chem. Res.* **1996**, *29*, 409.
- (4) Masarwa, M.; Cohen, H.; Meyerstein, D.; Hickman, D. L.; Bakak, A.; Espenson, J. H. The reaction of low valent transition metal complexes with hydrogen peroxide. Are they "Fenton-like" or not? 1. The case of Cu^{+}_{aq} and Cr^{2+}_{aq} . *J. Am. Chem. Soc.* **1988**, *110*, 4293.
- (5) Johnson, G. R. A.; Nazhat, N. B.; Saadala-Nazhat, R. A. Reactions of the aquocopper(I) ion with hydrogen peroxide: evidence against hydroxyl free radical formation. *J. Chem. Soc., Chem. Commun.* **1985**, 407.
- (6) Goldstein, S.; Meyerstein, D.; Czapski, G. The Fenton reagent. *Free Radical Biol. Med.* **1993**, *15*, 435.
- (7) Marcus, R. A.; Sutin, N. Electron transfer in chemistry and biology. *Biochim. Biophys. Acta* **1985**, *811*, 265.
- (8) Sawyer, D. T. Metal $[Fe(II), Cu(I), Co(II), Mn(III)]$ hydroperoxide-induced activation of dioxygen for the ketonization of hydrocarbons: oxygenated Fenton Chemistry. *Coord. Chem. Rev.* **1997**, *165*, 297.
- (9) Hyde, M. R.; Espenson, J. H. Kinetics and mechanism of the formation of organochromium(III) complexes in the reaction of organic peroxides with Chromium(II). *J. Am. Chem. Soc.* **1976**, *98*, 4463.
- (10) Groves, J. T.; Van der Puy, M. Spectroscopic aliphatic hydroxylation by an iron-based oxidants. *J. Am. Chem. Soc.* **1974**, *96*, 5274.
- (11) Luzzatto, E.; Cohen, H.; Stockheim, C.; Wieghardt, K.; Meyerstein, D. Reactions of low valent transition metal complexes with hydrogen peroxide. Are they "Fenton-like" or not? 4. The case of $Fe(II)L$, $L = EDTA; HEDTA$ and $TCMA$. *Free Radical Res. Commun.* **1995**, *23*, 453.
- (12) Meyerstein, D. Reactions of aliphatic carbon-centered and aliphatic peroxy radicals with transition metal complexes as a plausible source for biological damage induced by radical processes. In *Metal ions in Biological systems*; Sigel, A., Sigel, H., Eds.; Marcel Dekker: New York, in press; see also references therein.
- (13) Goldstein, S.; Meyerstein, D.; Czapski, G. A reconsideration of the hydroxylation of salicylate as an assay for $\cdot OH$ radicals identification. In *The Oxygen Paradox*; Davies, K. J. A., Ursini, F., Eds.; CLEUP University Press: Padova, Italy, 1985; p 169.
- (14) Mallard, W. G.; Ross, A. B.; Helman, W. P. *NIST Standard Reference Database 40, Version 3.0*, 1998.
- (15) Van Eldik, R.; Cohen, H.; Meyerstein, D. Ligand interchange controls many oxidations of divalent first-row transition metal ions by free radicals. *Inorg. Chem.* **1994**, *33*, 1566.
- (16) Goldstein, S.; Czapski, G.; Cohen, H.; Meyerstein, D. Hydroxyl radical induces decarboxylation and deamination of 2-methylalanine catalyzed by copper ions. *Inorg. Chem.* **1992**, *31*, 2439.

- (17) Masarwa, M.; Cohen, H.; Saar, J.; Meyerstein, D. Metal induced decarboxylation of aliphatic free radicals. I. Kinetics of the reactions of copper(I) and copper(II) with the 2-methyl-2-carboxylic acid-propyl free radical in aqueous solutions. A pulse radiolysis study. *Isr. J. Chem.* **1990**, *30*, 361.
- (18) Luzzatto, E.; Cohen, H.; Meyerstein, D. Acetaldehyde as the product of reaction of the free radical $\cdot\text{CH}_2\text{-CH}_2\text{NH}_3^+$ with Fe(II) complexes. An alternative mechanism for the formation of carbonyl groups in metal catalyzed oxidations by amines. *J. Inorg. Biochem.* **1993**, *5*, 225.
- (19) Masarwa, M.; Cohen, H.; Meyerstein, D. Mechanism of oxidation of the 2-hydroxycyclohexyl radical to cyclopentanecarbaldehyde by copper ions in aqueous solutions. *Inorg. Chem.* **1991**, *30*, 1849.
- (20) von Sonntag, C.; Schuchmann, H.-P. Peroxyl radicals in aqueous solution. In *Peroxyl Radicals*; Alfassi, Z. B., Ed.; Jon Wiley & Sons: New York, 1997; p 173.
- (21) Khaikin, G. L.; Alfassi, Z. B.; Huie, R. E.; Neta, P. Oxidation of ferrous and ferrocyanide ions by peroxyl radicals. *J. Phys. Chem.* **1996**, *100*, 7072.
- (22) Solomon-Rapaport, E.; Masarwa, A.; Cohen, H.; Meyerstein, D. On the chemical properties of the transient complexes $\text{L}_m\text{M}^{n+1}\text{-OOR}$. Part 1. The case of (2,3,9,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetrane)(H_2O) $\text{Co}^{\text{III}}\text{-OOCH}_3^{2+}$. Submitted for publication. The rate constant for the reaction of $\text{LCo}^{\text{III}}\text{-OOCH}_3$ with $\text{CH}_3\text{OO}\cdot$ has been determined to be $(3 \pm 2) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.
- (23) Eberhardt, M. K.; Ramirez, G.; Ayala, E. Does the reaction of Cu^+ with H_2O_2 give OH radicals? A study of aromatic hydroxylation. *J. Org. Chem.* **1989**, *54*, 5922.
- (24) Wink, D. A.; Nims, R. W.; Saavedra, J. E.; Utermahlen, Jr., W. E.; Ford, P. C. The Fenton oxidation mechanism: Reactivities of biologically relevant substrates with two oxidizing intermediates differ from those predicted for the hydroxyl radical. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 6604.
- (25) Eberhardt, M. K.; Colina, R. The reaction of OH radicals with dimethyl sulfoxide. A comparative study of Fenton's reagent and the radiolysis of aqueous dimethyl sulfoxide solutions. *J. Org. Chem.* **1988**, *53*, 1071.

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