

Review

What Are the Oxidizing Intermediates in the Fenton and Fenton-like Reactions? A Perspective †

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† This perspective is dedicated in honor of Professor Dov Lichtenberg on his 80th birthday.

Abstract: The Fenton and Fenton-like reactions are of major importance due to their role as a source of oxidative stress in all living systems and due to their use in advanced oxidation technologies. For many years, there has been a debate whether the reaction of $\text{Fe}^{\text{II}}(\text{H}_2\text{O})_6^{2+}$ with H_2O_2 yields OH^\bullet radicals or $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$. It is now known that this reaction proceeds via the formation of the intermediate complex $(\text{H}_2\text{O})_5\text{Fe}^{\text{II}}(\text{O}_2\text{H})^+ / (\text{H}_2\text{O})_5\text{Fe}^{\text{II}}(\text{O}_2\text{H}_2)^{2+}$ that decomposes to form either OH^\bullet radicals or $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$, depending on the pH of the medium. The intermediate complex might also directly oxidize a substrate present in the medium. In the presence of $\text{Fe}^{\text{III}}_{\text{aq}}$, the complex $\text{Fe}^{\text{III}}(\text{OOH})_{\text{aq}}$ is formed. This complex reacts via $\text{Fe}^{\text{II}}(\text{H}_2\text{O})_6^{2+} + \text{Fe}^{\text{III}}(\text{OOH})_{\text{aq}} \rightarrow \text{Fe}^{\text{IV}}=\text{O}_{\text{aq}} + \text{Fe}^{\text{III}}_{\text{aq}}$. In the presence of ligands, the process often observed is $\text{L}_n(\text{H}_2\text{O})_{5-n}\text{Fe}^{\text{II}}(\text{O}_2\text{H}) \rightarrow \text{L}^{\bullet+} + \text{L}_{n-1}\text{Fe}^{\text{III}}_{\text{aq}}$. Thus, in the presence of small concentrations of HCO_3^- i.e., in biological systems and in advanced oxidation processes—the oxidizing radical formed is $\text{CO}_3^{\bullet-}$. It is evident that, in the presence of other transition metal complexes and/or other ligands, other radicals might be formed. In complexes of the type $\text{L}_n(\text{H}_2\text{O})_{5-n}\text{M}^{\text{III/II}}(\text{O}_2\text{H}^-)$, the peroxide might oxidize the ligand L without oxidizing the central cation M. OH^\bullet radicals are evidently not often formed in Fenton or Fenton-like reactions.

Keywords: OH^\bullet ; $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$; $\text{CO}_3^{\bullet-}$; pH effect; reactive oxidizing species



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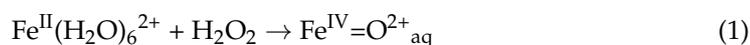
1. General Remarks

In 1894, Mr. Fenton reported that $\text{Fe}^{\text{II}}(\text{H}_2\text{O})_6^{2+}$ catalyzes the oxidation of tartaric acid by H_2O_2 [1]. No mechanism of this process was suggested by Mr. Fenton. Since then, the reaction $\text{Fe}^{\text{II}}(\text{H}_2\text{O})_6^{2+} + \text{H}_2\text{O}_2$ has been called the Fenton reaction and the reactions $\text{M}^{\text{n}}\text{L}_m + \text{ROOR}'$ —where M is either Fe or another low-valent transition metal, L is either H_2O or another ligand, and R and R' are either H or another substituent—are called Fenton-like reactions.

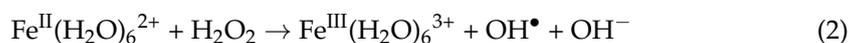
The Fenton and Fenton-like reactions are of major importance due to two reasons:

1. They are considered to be the major source of oxidative stress in all living systems.
2. They are used in the advanced oxidation technologies/processes that are of major importance in the environmental removal of pollutants.

Due to this prominence, a search in SciFinder for Fenton in 2021 results in 3286 references. The first mechanisms of the Fenton reaction were suggested in 1932 by two groups in parallel. Bray and Gorin [2] suggested that the mechanism is:



whereas Haber and Weiss [3,4] suggested that the mechanism of the Fenton reaction is:

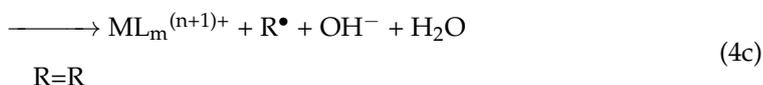
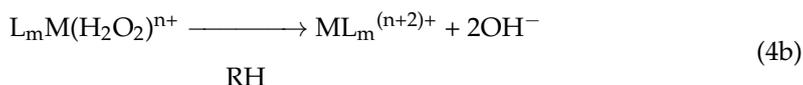


The debate whether the oxidizing intermediate formed in the Fenton reaction is $\text{Fe}^{\text{IV}} = \text{O}^{2+}_{\text{aq}}$ or OH^\bullet has lasted for many decades. Thus, even as recently as this year, it has been suggested that reaction (1) is the correct mechanism, at least in neutral solutions [5], and that (2) is the only process even at pH 5 [6].

The difficulty in differentiating between the two mechanisms stems from the fact that both OH^\bullet radicals and $\text{Fe}^{\text{IV}} = \text{O}^{2+}_{\text{aq}}$ react with organic substrates, usually by abstracting a hydrogen atom, and often form the same, or similar, radicals. Using EPR to quantify the relative yields of the radicals formed in order to decide whether their sources are OH^\bullet radicals often fails due to their different lifetimes [7]. This difficulty was overcome by measuring the final products formed when a mixture of two alcohols is present.⁸ This technique requires that the low-valent metal cation initiating the Fenton-like reaction has a fast ligand exchange rate, i.e., it does not fit $\text{Fe}^{\text{II}}(\text{H}_2\text{O})_6^{2+}$. Using this technique, it was shown that the reaction $\text{Cr}^{\text{II}}(\text{H}_2\text{O})_6^{2+} + \text{H}_2\text{O}_2$ proceeds via a mechanism analogous to reaction (2), whereas the reaction $\text{Cu}^{\text{I}}_{\text{aq}} + \text{H}_2\text{O}_2$ does not yield OH^\bullet radicals or $\text{Cu}^{\text{III}}_{\text{aq}}$ [8]. Furthermore, thermodynamic arguments [8] and kinetic arguments using the Marcus theory [9] indicate that the Fenton and Fenton-like reactions do not proceed via the outer sphere mechanism. Therefore, an inner sphere mechanism was proposed [8,9]:

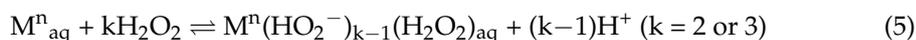


For simplicity, it will be assumed in that the complex formed is $\text{L}_m\text{M}(\text{H}_2\text{O}_2)^{n+}$. Reaction (3) might be followed by a variety of routes, e.g., [8,9]:



Naturally, $\text{L}_{m-1}\text{M}(\text{H}_2\text{O}_2)^{n+}$ might also directly oxidize different substrates, e.g., inorganic reducing agents.

It was later discovered that when the central cation M has a too high redox potential, e.g., Co(II) [10], or cannot be oxidized, e.g.: Al^{III} , Ga^{III} , In^{III} , Sc^{III} , Y^{III} , La^{III} , Be^{II} , Zn^{II} , and Cd^{II} [11–13], the binding of two or more peroxides to the central cation might lead to the formation of OH^\bullet radicals via disproportionation of the peroxides without involving oxidation of the central cation [10–13]:

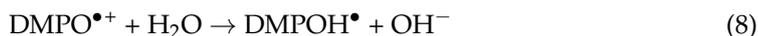


The observation that ligated H_2O_2 can oxidize a second ligated peroxide suggests that it might also oxidize other ligands. This was tested theoretically, by DFT [14], and experimentally for the oxidation of a carbonate ligated to Co^{II} [15], thus proving this possibility.

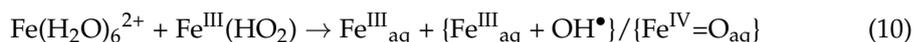
2. The Fenton Reaction Is ($\text{Fe}(\text{H}_2\text{O})_6^{2+} + \text{H}_2\text{O}_2$)

Efforts to determine whether the reaction $\text{Fe}(\text{H}_2\text{O})_6^{2+} + \text{H}_2\text{O}_2$ forms OH^\bullet radicals via following the formation of the DMPO- OH^\bullet adduct by EPR failed, as it was shown that even mild oxidants, e.g., $\text{Fe}^{\text{III}}_{\text{aq}}$, oxidize DMPO via [16]:





The rate constant of the Fenton reaction in acidic media is $k(\text{Fe}(\text{H}_2\text{O})_6^{2+} + \text{H}_2\text{O}_2) \sim 50 \text{ M}^{-1}\text{s}^{-1}$. The measured rate constants depend on the pH and on the ratio $[\text{H}_2\text{O}_2]/[\text{Fe}(\text{H}_2\text{O})_6^{2+}]$; the latter dependencies mainly stem from the observation that in the presence of excess H_2O_2 reactions (9) [17] and (10) [17,18] contribute to the observed rate constants [17].

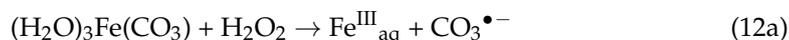
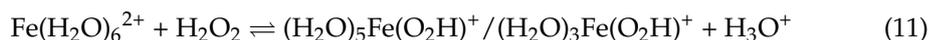


$$K_{10} = 7.7 \cdot 10^5 \text{ M}^{-1}\text{s}^{-1} \text{ at pH 1.0}$$

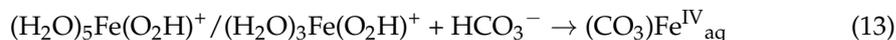
The nature of the products of reaction (10) were later determined [19] to be $\text{Fe}^{\text{III}}_{\text{aq}} + \text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$; thus, clearly in acidic solutions when $[\text{H}_2\text{O}_2]/[\text{Fe}(\text{H}_2\text{O})_6^{2+}] > 1$, a mixture of OH^{\bullet} radicals and $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ is formed.

Next, Bakac et al. developed a new procedure to differentiate between OH^{\bullet} radicals and $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ based on the different final products formed in the reactions of OH^{\bullet} radicals and $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ with DMSO, $(\text{CH}_3)_2\text{SO}$ [20]. This technique can only be used for iron. Using this technique, it was proved that, in acidic solutions, OH^{\bullet} radicals are formed by the Fenton reaction, whereas in neutral solutions, where $\text{pH} > 6$, the product is $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ [20]. This proves that the Fenton reaction under physiological conditions does not form OH^{\bullet} radicals: However, this statement is not correct for the acidic organelles, e.g., lysosomes [21] and some peroxisomes [22]. This conclusion is correct for reactions of $\text{Fe}(\text{H}_2\text{O})_6^{2+}$, but not for all Fenton-like reactions of $\text{Fe}^{\text{II}}\text{L}_m$, as seen below.

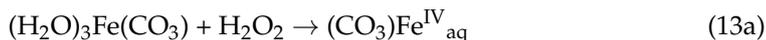
Recently, it was shown that the Fenton reaction is dramatically accelerated in the presence of low concentrations of bicarbonate well below those present in living cells [19]. The oxidizing transient formed under these conditions is the carbonate anion radical, $\text{CO}_3^{\bullet-}$ [19]. $\text{CO}_3^{\bullet-}$ is a strong oxidizing agent, $E^0(\text{CO}_3^{\bullet-}/\text{CO}_3^{2-}) = 1.57 \text{ V vs. NHE}$ [23] and is evidently somewhat stronger in neutral media. $\text{CO}_3^{\bullet-}$ is still a considerably weaker oxidizing agent than OH^{\bullet} radicals and is, therefore, more selective as a ROS [24,25]. The reactions occurring were proposed to be [19]:



Recent unpublished results [26] suggest that reaction (12) likely proceeds via:



and reaction (12a) likely proceeds via:



The $(\text{CO}_3)\text{Fe}^{\text{IV}}_{\text{aq}}$ thus formed might decompose via:



Substrate



The competition between reactions (14a) and (14b) depends on the substrate. Thus, for DMSO $k_{14a} \gg k_{14b}$, but for PMSO (phenyl-methyl-sulfoxide) $k_{14a} \sim k_{14b}$.

3. Fenton-like Reactions Involving $\text{Fe}^{\text{II}}\text{L}_m$

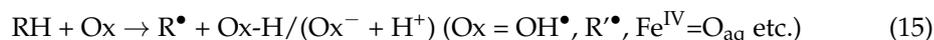
Two types of Fenton-like reactions have to be considered.

When ligands, L, different from H_2O are ligated to The Fe^{II} central cation, the effect of HCO_3^- on the mechanism, discussed above, can be included herein. It should be noted that the technique to distinguish between OH^\bullet radicals and $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$, developed by Bakac et al. [20], cannot always be applied here because the mechanism of the reaction $\text{LFe}^{\text{IV}}=\text{O}$ with DMSO is not known. The mechanism of the reactions of $\text{Fe}^{\text{II}}\text{L}_m$ with H_2O_2 for the following ligands was studied.

- $\text{L} = \text{PO}_4^{3-} / \text{HPO}_4^{2-}$ [20]. The results suggest that the Fenton reaction in the presence of phosphate in neutral solutions yields OH^\bullet radicals and not $(\text{PO}_4^{3-})_m\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ [20].
- $\text{L} = \text{edta}$ [22]. The reaction $\text{Fe}^{\text{II}}(\text{edta})^{2-} + \text{H}_2\text{O}_2$ was studied at $\text{pH} > 5.5$ using the technique developed by Masarwa et al. [8]. The results indicate that OH^\bullet radicals are the product of this reaction [27].
- $\text{L} = \text{nta}$, $\text{nta} = \text{N}(\text{CH}_2\text{CO}_2^-)_3^{3-}$ [28]. The reaction $\text{Fe}^{\text{II}}(\text{nta})^- + \text{H}_2\text{O}_2$ was studied. Surprisingly, though edta and nta are very similar ligands, the results differ considerably. The results suggest that the major product of the $\text{Fe}^{\text{II}}(\text{nta})^- + \text{H}_2\text{O}_2$ is a $(\text{nta})\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ complex [28]. The yields of the final products are pH dependent [28].
- $\text{L} = \text{citrate}$ [29]. The reaction of $\text{Fe}^{\text{II}}(\text{citrate})^-$ with H_2O_2 was studied. This reaction is of importance because $\text{Fe}^{\text{III}}(\text{citrate})$ is a major component of the non-transferrin iron mobile pool [30]. The results indicate that the reaction $\text{Fe}^{\text{II}}(\text{citrate})^- + \text{H}_2\text{O}_2$ in neutral solutions does not yield OH^\bullet radicals. The results do not answer the question whether a $\text{Fe}^{\text{IV}}(\text{citrate})_{\text{aq}}$ species is a transient formed by this reaction. When low concentration of HCO_3^- are added to this system, the kinetics and final products are changed dramatically, indicating that the $\text{CO}_3^{\bullet-}$ radical anion is a major product of the reaction under these conditions [29].

The results presented in this section indicate that the mechanism of the Fenton-like reactions of $\text{Fe}^{\text{II}}\text{L}_m$ complex dramatically depend on the nature of the ligand. Therefore, one cannot assume that Fe^{II} complexes with analogous ligands react via the same mechanism.

When different peroxides are used as oxidants in the Fenton-like reaction, such as in biological systems, the most important peroxides are the ROOH compounds, where R is an alkyl. The ROOH peroxides are formed in biological systems, mainly in lipids, via the chain reaction [30,31]:



Therefore, the mechanism of the reaction $(\text{CH}_3)_3\text{COOH} + \text{Fe}(\text{H}_2\text{O})_6^{2+}$ was studied. The results indicate that in this system $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ is also formed in neutral solutions in the absence of bicarbonate. In the presence of low concentrations of bicarbonate, $\text{CO}_3^{\bullet-}$ radical anions are the product of this Fenton-like reaction [32].

The $\text{S}_2\text{O}_8^{2-}$ and HSO_5^- peroxides are of major importance in advanced oxidation technologies [33–36]. Therefore, the mechanisms of the reactions $\text{Fe}(\text{H}_2\text{O})_6^{2+} + \text{HSO}_5^- / \text{S}_2\text{O}_8^{2-}$ were studied. The results indicate that in acidic media, $\text{SO}_4^{\bullet-}$ radical anions are the active oxidizing species formed, in neutral solutions, $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ is formed, and in the presence of low concentrations of bicarbonate, $\text{CO}_3^{\bullet-}$ is the oxidizing intermediate formed [26].

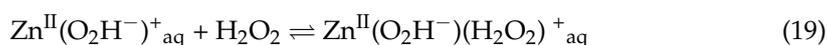
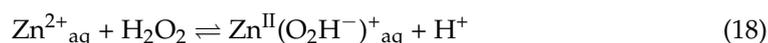
4. Other Fenton-like Reactions

Fenton-like reactions are reported for most low-valent transition metals and even for cations that are not involved in redox processes [11–13]. Herein, only Fenton-like reactions

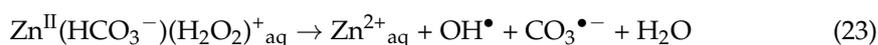
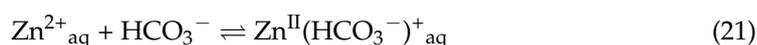
involving Cu^I [37] and Zn^{II} [38–41] that are of biological importance and Co^{II}, due to its role in advanced oxidation technologies [15], are discussed.

The reaction of Cu^I with H₂O₂ was long thought to yield OH• radicals [42], but it was later shown that the active oxidizing agent is Cu^I(H₂O₂) [8] or Cu^{III}_{aq} [43]. It was also proposed that the reaction of Cu^I with S₂O₈²⁻ yields Cu^{III}_{aq} [44]. Conversely, it was proposed that the reactions of Cu(II) with HSO₅⁻ and S₂O₈²⁻ yield Cu^{III}_{aq} and SO₄•⁻ [45].

Surprisingly, Zn²⁺_{aq} and Zn^{II}-complexes were shown to be involved in the formation of reactive oxygen species (see references [38–41] for example.). However, no chemical mechanism initiating this process was forwarded. One possible mechanism is that suggested by Shul'pin et al. [13]. According to this mechanism, the reactions involved are:

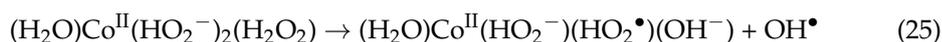
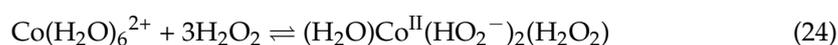


As the steady state concentration of H₂O₂ in biological media is very low, the probability that two H₂O₂ will bind to the same Zn²⁺_{aq} is low. Therefore, it is tempting to propose that the process leading to the formation of reactive oxygen species catalyzed by Zn²⁺_{aq} is:



These two plausible mechanisms must be studied experimentally to prove one or both of them.

The reaction Co(H₂O)₆²⁺ + H₂O₂ to yield OH• radicals is endothermic due to the high redox potential of the Co^{III/II} couple [10]. However, it was shown that the following reactions replace the simple Fenton-like reaction [14]:



In the presence of bicarbonate, the complex *cyclic*-(CO₄)Co^{II}(HO₂⁻)₂(H₂O) is formed. This complex decomposes via [15]:



The reaction of HSO₅⁻ with Co(H₂O)₆²⁺ and with Co^{II}(P₂O₇)(H₂O)₂²⁻ require more than one peroxymonosulfate to form radicals [46].

Finally, it should be pointed out that it is likely that ligands other than carbonate, with the proper redox potential, might also be oxidized directly by peroxides [14].

5. Heterogeneous Fenton-like Processes

A variety of heterogeneous catalysts react with H₂O₂ in Fenton-like processes. Thus, ZnO-nanoparticles induce the formation of reactive oxygen species in biological systems. However, this is attributed to the dissolved Zn²⁺_{aq} ions [39] and is, therefore, not truly heterogeneous.

The most important heterogeneous catalysts of Fenton-like processes have iron atoms/cations as the active participants, e.g., zero-valent iron [47], MFe₂O₄ (e.g., Fe₃O₄ [48] and MgFe₂O₄ [49]), and LaFeO₃ [50]. These systems are used in advanced oxidation processes and not in biological ones. Therefore, their mechanisms are not discussed herein.

6. Concluding Remarks

The major conclusions of this perspective are:

- I. The reaction $\text{Fe}^{\text{II}}(\text{H}_2\text{O})_6^{2+} + \text{H}_2\text{O}_2$ yields OH^\bullet radicals as the active oxidizing agent in acidic solutions when $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})_6^{2+}] > [\text{H}_2\text{O}_2]$, a mixture of OH^\bullet radicals and $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ in acidic solutions when $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})_6^{2+}] < [\text{H}_2\text{O}_2]$, $\text{Fe}^{\text{IV}}=\text{O}_{\text{aq}}$ in neutral solutions, and $\text{CO}_3^{\bullet-}$ in solutions containing even low concentration of HCO_3^- , i.e., under physiological conditions.
- II. It is important to note that mechanisms of the reactions $\text{H}_2\text{O}_2 + \text{Fe}^{\text{II}}\text{L}_m(\text{H}_2\text{O})_k$, where L are ligands different than water, depend dramatically on the properties of L. Thus, one must study the mechanism for each ligand separately.
- III. The study of the mechanisms of Fenton-like reactions with other peroxides requires separate studies.
- IV. The mechanisms of Fenton-like reactions of other low-valent metal cations differ from each other and thus require separate studies.

Therefore, it must be concluded that the mechanism of each Fenton-like reaction should be studied before concluding which oxidizing transient is formed in that reaction.

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