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Plausible Mechanisms of the Fenton-Like Reactions, M = Fe(II) and Co(II), in the Presence of RCO₂[−] Substrates: Are OH• Radicals Formed in the Process?

Haya Kornweitz,^{*,†} Ariela Burg,[‡] and Dan Meyerstein^{†,§}

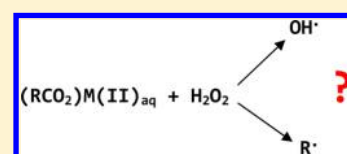
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S Supporting Information

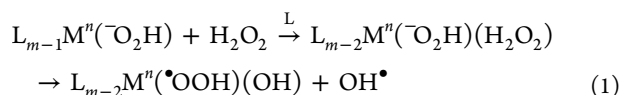
ABSTRACT: DFT calculations concerning the plausible mechanism of Fenton-like reactions catalyzed by Fe(II) and Co(II) cations in the presence of carboxylate ligands suggest that hydroxyl radicals are not formed in these reactions. This conclusion suggests that the commonly accepted mechanisms of Fenton-like reactions induced oxidative stress and advanced oxidation processes have to be reconsidered.



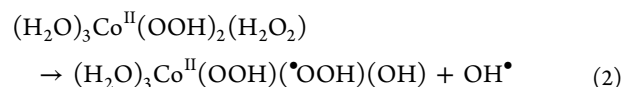
INTRODUCTION

In 1894, Fenton reported that $Fe(H_2O)_6^{2+}$ catalyzes the oxidation of tartaric acid by H_2O_2 .¹ Since then the reaction of $Fe(H_2O)_6^{2+}$ with H_2O_2 , which initiates this catalytic process is called “the Fenton reaction” and the reactions of low valent transition-metal complexes M^mL_m , where $M = Fe^{II}$ or other low valent transition metal cations, with H_2O_2 or other peroxides are called “Fenton-like reactions”. These reactions are of major importance as it is commonly accepted that they cause aging and a large variety of diseases,^{2–8} what is called oxidative stress (note: refs 2–16 are some recent reviews and clearly do not represent a full literature survey.) Furthermore, these reactions are involved in a variety of advanced oxidation processes, AOPs,^{9–15} and synthetic catalytic processes.¹⁶

Till recently it was accepted that Fenton-like reactions require a low valent transition-metal complex, M^mL_m , that can be oxidized and that the active intermediate formed is either the OH^\bullet radical or the $L_{m-1}M^{n+2}=O$.^{17,18} However, recently it was reported that also $Al(H_2O)_6^{3+}$, i.e., a cation with a single oxidation state, catalyzes the formation of OH^\bullet radicals from H_2O_2 .¹⁹ This was explained by the disproportionation reaction:²⁰

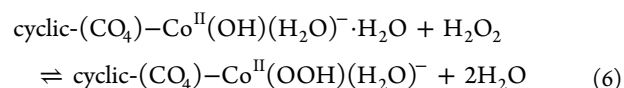
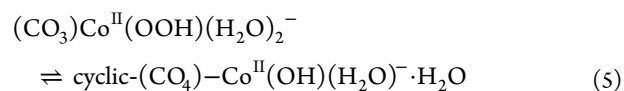
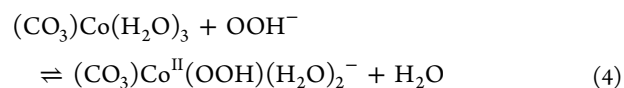
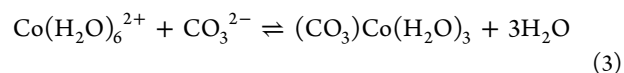


Similar reactions were reported for $M = Ga, In, Sc, Y, La, Be, Zn,$ and Cd .^{21,22} It should be pointed out that no kinetic evidence for the number of peroxide molecules bound to the central cation is available.^{19,21,22} In parallel, it was shown that the Fenton-like reaction of $Co(H_2O)_6^{2+}$ proceeds via the binding of three H_2O_2 molecules to the cobalt(II) ion forming the transient $(H_2O)_3Co^{II}(OOH)_2 \cdot (H_2O)_2$ ²³ that decomposes via:²³



i.e., also for low valent transition-metal complexes that have a high oxidation potential the radical formation does not involve the oxidation of the central cation. In other words the ligated H_2O_2 oxidizes the HO_2^- ligand bound to the same central cation. Furthermore, it was recently shown that the role of bicarbonate/carbonate as a catalyst of the Co^{II} catalyzed Fenton-like reaction is a multifacet one.²⁴ The major result is that the active species formed is not the OH^\bullet radical or the $M^{n+2}=O$ as commonly assumed^{17,18} but the $CO_3^{\bullet-}$ anion radical.²⁴ This radical anion is a very strong oxidizing agent, $E^\circ = 1.5$ V,²⁵ but considerably weaker than OH^\bullet and therefore considerably more selective in its redox processes.²⁶

The proposed mechanism is

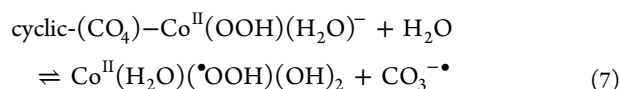


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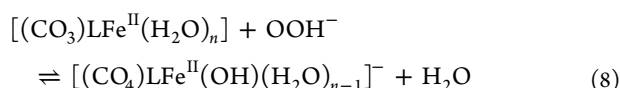
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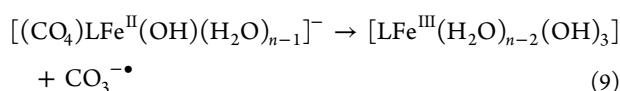


The mechanism involves the formation of cyclic-cobalt(II)-percarbonate as an intermediate. Also this result points out that a peroxide bound to a cation can oxidize another ligand bound to the same central cation. This finding is in accord with earlier reports on analogous processes.²⁷

It seemed of interest to explore, using DFT calculations, whether also other Fenton-like reactions proceed via analogous mechanisms. Of special interest are Fe^{II} complexes that might be present in biological systems, e.g., $\text{Fe}^{\text{II}}(\text{CO}_3)_{\text{aq}}$ as in the body HCO_3^- is present at considerable concentrations, 4–40 mM.²⁸ Then if indeed the Fenton-like reaction in biological systems proceeds via



followed by



One has to consider the possibility that oxidative stress is mainly initiated by $\text{CO}_3^{\bullet-}$ and not by OH^\bullet as is commonly accepted. Other carboxylic acids might also act as ligands of iron in biological systems.

In parallel it was decided to analyze whether the analogous reactions in the presence of Co^{II} , a cation with a high redox potential, proceed via similar mechanisms.

■ COMPUTATIONAL METHOD

All structures were calculated using DFT calculation. Optimizations in level of B3LYP/6-311+G** were performed using G09 program.²⁹ Frequencies were calculated for each structure in order to verify that the considered structure is indeed local minima.

Transition states were calculated using the Berny algorithm. IRC calculations were performed to follow the reaction path.

All reactions were in aqua solution. Solvation effects were calculated using the SMD method.³⁰

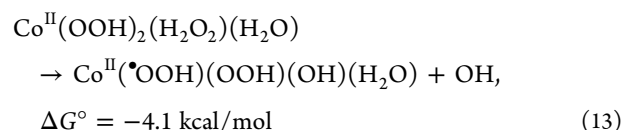
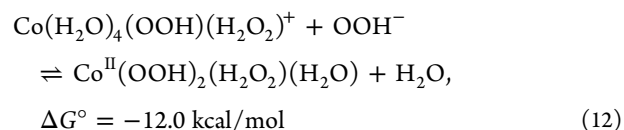
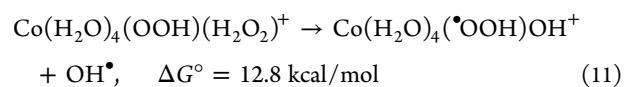
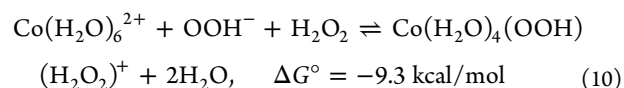
For each structure the free energy was calculated. This calculation takes into account the ZPE and thermal correction. The program's default standard state corresponding to an ideal gas at a standard pressure of 1 atm was changed to use either a standard state of 1 M (most species) or of 55.5 M (for water molecules). The values of free energy for each structure were used to calculate ΔG^0 values for relevant reactions.

ΔG^0 values were used to indicate the plausibility of the considered reaction. For the decomposition of $(\text{CO}_3)\text{Fe}^{\text{IV}}-(\text{OH})_3(\text{H}_2\text{O})^-$ also the activation energy of the two plausible mechanisms was calculated.

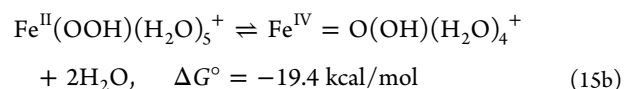
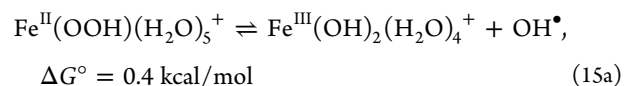
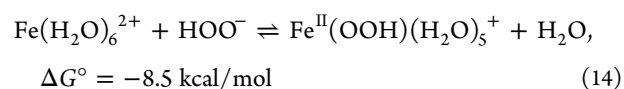
■ RESULTS AND DISCUSSION

Following our previously proposed mechanism, the plausible mechanisms of Fenton-like reactions catalyzed by $\text{M}^{2+}_{\text{aq}}$ ($\text{M} = \text{Co}, \text{Fe}$) in the presence of RCO_2^- ($\text{R} = \text{CH}_3, \text{NH}_2\text{CH}_2, \text{C}_6\text{H}_5$) in neutral solutions was studied. The free energy gain in the catalyzed reactions has to be compared with that obtained for the reactions of the $\text{M}(\text{H}_2\text{O})_6^{2+}$ cations with H_2O_2 . For cobalt these free energy values were previously reported²³ and are

here corrected for standard state 1 M (most species) or of 55.5 M (for water molecules):

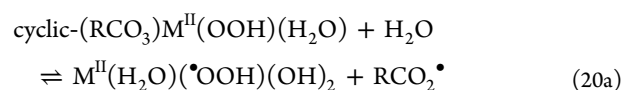
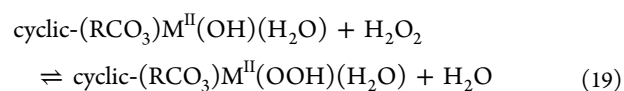
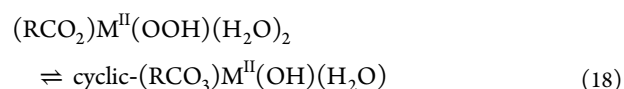
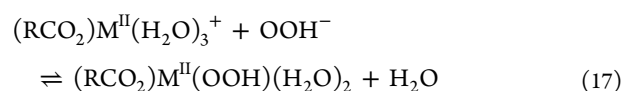
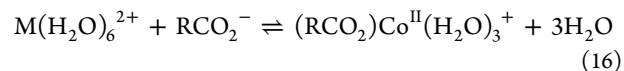


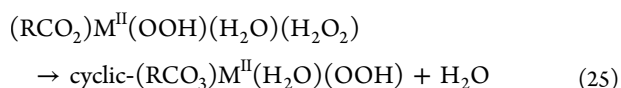
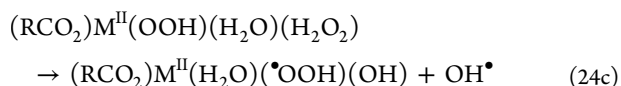
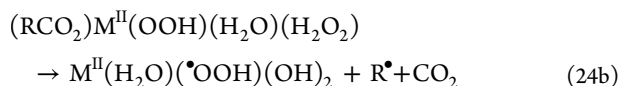
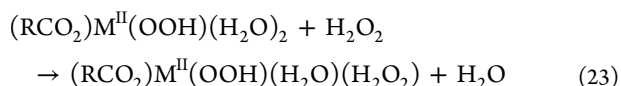
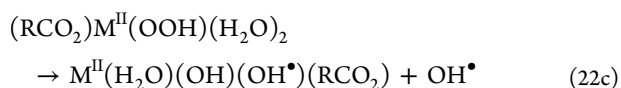
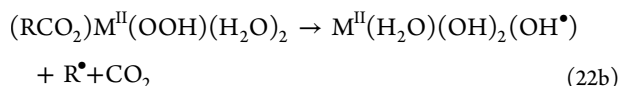
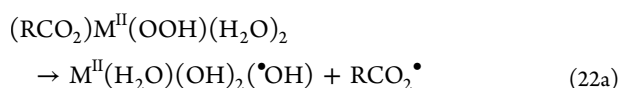
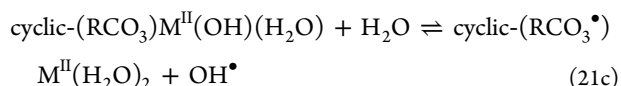
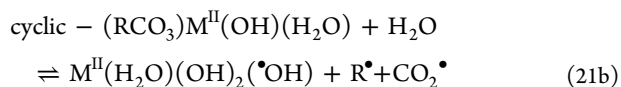
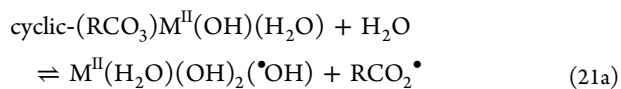
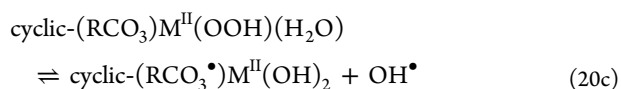
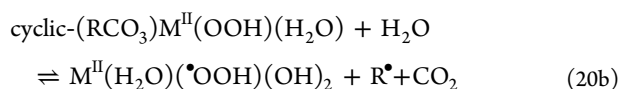
For iron the corresponding values were now calculated, remembering that only one peroxide is required for the Fenton reaction:



This result is in accord with a recent report that in neutral solution $\text{Fe}^{\text{IV}}_{\text{aq}}$ is the product of the Fenton reaction.^{31–37} However, it should be noted that under the experimental conditions of this study³¹ it is plausible that the reaction leading to the formation of the reactive intermediate is $(\text{H}_2\text{O})_5\text{Fe}^{\text{III}}(\text{OOH}) + \text{Fe}(\text{H}_2\text{O})_6^{2+}$,¹⁹ that is also claimed to form $\text{Fe}^{\text{IV}}_{\text{aq}}$.

The following reactions catalyzed by RCO_2^- were considered:





ΔG° values for $\text{M} = \text{Co}$ in kcal/mol are given in Table 1.

Structures of the cyclic species, considered in these reactions, are depicted in Figure 1. In all structures the bond length of $\text{Co}-\text{OC}$ is $2.07 \pm 0.03 \text{ \AA}$ and the bond length of $\text{Co}-\text{OOC}$ is $1.93 \pm 0.02 \text{ \AA}$.

The results presented in Table 1, point out that the ligation of RCO_2^- (reaction 16) followed by the ligation of OOH^- (reaction 17) are quite exothermic for all three acids, significantly more than reaction 10, and are therefore expected to be the first steps in the Fenton-like reaction. The following reaction may be one of three options: isomerization to form a bidentate percarboxylate ligand, reaction 18, direct dissociation to form radicals, reactions 22a,22b or addition of one more hydrogen peroxide molecule—reaction 23, as was observed for carbonate complexes.²⁴ For acetic acid and glycine, the free energy gain in the direct dissociation according to reaction 22a,22b is considerably larger than in the isomerization reaction 18 or in the further addition of H_2O_2 reaction 23. Reaction 22c is clearly not feasible. Therefore, the mechanism in these cases probably involves the direct dissociation of $(\text{RCO}_2)\text{Co}(\text{OOH})-$

Table 1. ΔG° Values in kcal/mol of Reactions 16–25 for $\text{M} = \text{Co}$

reaction no.	R= CH ₃	R = NH ₂ CH ₂	R = C ₆ H ₅
16	−11.8	−18.8	−10.2
17	−16.5	−9.6	−17.2
18	1.9	−1.85	−0.04
19	−6.83	−1.2	−4.2
20a	CH ₃ CO ₂ • is not stable	−23.6	0.2
20b	−11.03	−23.71	0.1
20c	9.1	10.8	11.7
21a	CH ₃ CO ₂ • is not stable	−22.5	−1.1
21b	−11.8	−24.0	−2.5
21c	103.0	102.6	113.0
22a	CH ₃ CO ₂ • is not stable	−17.6	6.0
22b	−12.9	−20.6	4.9
22c	19.8	19.5	14.3
23	4.0	4.0	3.8
24a	CH ₃ CO ₂ • is not stable	−25.5	−2.0
24b	−18.0	−28.8	−3.1
24c	6.3	6.3	7.0
25	−3.7	−1.8	−3.2

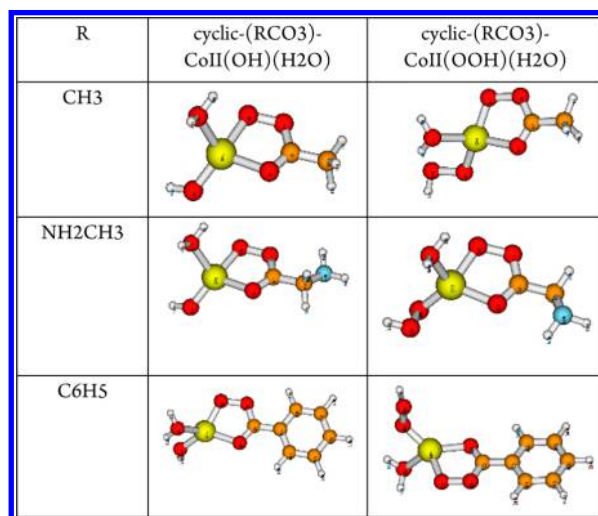


Figure 1. Cyclic structures in reactions 10–19, $\text{M} = \text{Co}$. Key: Co, yellow; C, brown; H, white; O, red.

$(\text{H}_2\text{O})_2$ ($\text{R} = \text{CH}_3, \text{NH}_2\text{CH}_2$) to radicals. As the radical R^\bullet is formed in this reaction in close proximity to the ligated hydroxyl radical the rebound reaction to form ROH is plausible.

For benzoic acid ΔG° values for reactions 22a,22b, and 23 are positive; however, reaction 22b cannot be excluded as the small endothermicity might be compensated by the follow up radical reactions. Alternatively $(\text{C}_6\text{H}_5\text{CO}_2)\text{Co}(\text{OOH})(\text{H}_2\text{O})_2$ can isomerize to form the per-carboxylate complex, reaction 18 as the free energy gain of this reactions is \sim zero. Reaction 18 would be followed by reactions 19, which is slightly exoergic, and 20b, which is thermo-neutral. Some contribution of reaction 21b in competition with 22b cannot be ruled out. However, the thermodynamically most plausible mechanism in this system is reaction 17 followed by reactions 18 and 19. The results clearly indicate that the benzoate is a considerably weaker catalyst to the Fenton-like reaction than the aliphatic carboxylates.

Table 2. ΔG^0 Values in kcal/mol of Relevant Reaction for M = Fe

reaction no.	R = CH ₃	R = NH ₂ CH ₂	R = C ₆ H ₅	R = O [−]
16	−13.6	−18.8	−6.7	−12.9
17	−8.3	−9.7	−17.6	−15.7
18	−5.0	−0.9	−1.2	−12.0
22a	CH ₃ CO ₂ • is not stable	−428	−24.8	−43.1
22b	−38.0	−46.1	−20.3	−
22c	−9.7	−9.1	−7.5	−16.2
23	−2.0	2.6	3.1	0.7

A comparison of the reactions in the presence of the three carboxylic acids with the reactions in their absence, reactions 10–13 points out the following items.

- As in the presence of carbonate, also the carboxylates catalyze the formation of radicals, i.e., the formation of radicals does not require the binding of three hydrogen-peroxide molecules to the central cobalt cation.
- In all the reactions studied, the oxidation of the central Co(II) cation does not occur.
- A comparison to the catalysis of the reaction by bicarbonate/carbonate ions points out that the addition of two hydrogen peroxide molecules to the central cobalt cation is not always necessary in the presence of the carboxylates.
- Furthermore, the formation of the peracids is less favored in the presence of the carboxylates than in the presence of carbonate. Furthermore, this isomerization is not always an essential step to the formation of radicals.

Finally it should be noted that the cobalt induced Fenton-like reactions are catalyzed by all these carboxylates forming a variety of radicals. This conclusion has to be considered when AOPs catalyzed by cobalt cations are designed.

In biological systems, the most important Fenton reaction catalysts are Fe(II)/Fe(III) complexes that require only one peroxide to oxidize the central cation; therefore calculations were performed for reactions 16–18 and 22a for M = Fe. The calculated ΔG^0 values are summed up in Table 2. In addition to acetate, benzoate and glycine calculations were performed for carbonate (R = O[−]); such calculations were performed previously for Co²⁺ but not for Fe²⁺ ions.²⁴ Reaction 23 was considered too in order to ensure that calculations as well as experiments exclude the route of a second peroxide addition. ΔG^0 values for the relevant reactions are summed up in Table 2. (ΔG^0 values for all the reactions 16–25 are given in Table S-1).

ΔG^0 values of reactions 16 and 17 are considerably more negative than the ΔG^0 value of reaction 14, and 15b (except for R = C₆H₅) pointing out that the ligation of RCO₂[−] followed by the ligation of OOH[−] are the first steps in the Fenton-like reaction in the presence of these carboxylates. Furthermore, the decomposition of (RCO₂)Fe^{II}(OOH)(H₂O)₂ is more exothermic than reaction 15a and therefore the carboxylates are expected to catalyze the Fenton-like reactions.

(RCO₂)Fe^{II}(OOH)(H₂O)₂ can either isomerize according to reaction 18, or add a second hydrogen peroxide according to reaction 23 or dissociate to radical products according to reactions 22a, 22b and 22c. All the ΔG^0 values are negative, but the values of reactions 22a, 22b are considerably more negative for all the ligands R studied, therefore it is expected that this is the first step toward the oxidation of the central Fe(II). The product of reaction 22a is RCO₂•, which releases CO₂ and

forms R. For carbonate, R = O[−], the product is CO₃•[−]; there is no further dissociation and no release of CO₂.

The complex M^{II}(H₂O)(OH)₂(OH•) formed in reactions 22a and 22b (and in reactions 21a, 21b). This radical complex is stabilized since the electronic density of the unpaired electron is spread on three oxygen atoms, as shown in Tables 3 and 4. In

Table 3. Mulliken Atomic Spin Densities of M^{II}(H₂O)(OH)₂(OH•)

		M ^{II} (H ₂ O)(OH) ₃	
		atomic spin densities	
no. of atom	atom	M = Co	M = Fe
1	O	0.05	0.03
2	M	2.96	4.11
3	O	0.28	0.26
4	O	0.35	0.29
5	O	0.35	0.27
6	H	0.00	0.01
7	H	0.00	0.01
8	H	0.00	0.00
9	H	0.00	0.00
10	H	0.00	0.01
sum of atomic spin densities		4	5

Table 4. Mulliken Atomic Spin Densities of M^{II}(H₂O)(•OOH)(OH)₂

		M ^{II} (H ₂ O)(OOH)(OH) ₂	
		atomic spin densities	
no. of atom	atom	M = Co	M = Fe
1	O	0.05	0.03
2	M	3.06	4.07
3	O	0.24	0.23
4	O	0.31	0.30
5	O	0.29	0.29
6	H	0.00	0.01
7	O	0.05	0.05
8	H	0.00	0.00
9	H	0.01	0.01
10	H	0.00	0.00
11	H	0.00	0.00
sum of atomic spin densities		4	5

Table 3 values of Mulliken atomic spin densities for the radical products M^{II}(H₂O)(OH)₂(OH•) are given. In Table 4 the same values are given for M^{II}(H₂O)(•OOH)(OH)₂. Also this complex is stabilized due to the distribution of the spin on three oxygen atoms. Structures of these radical complexes are given in Figure 2.

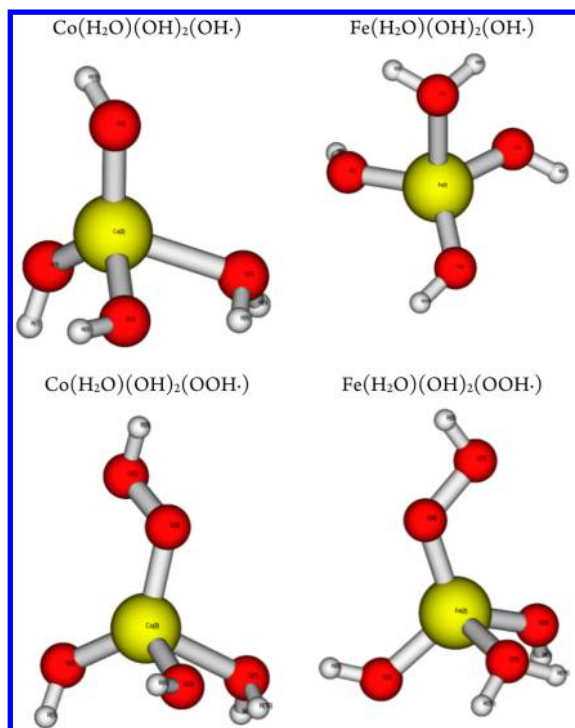
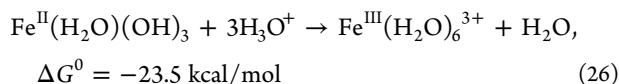


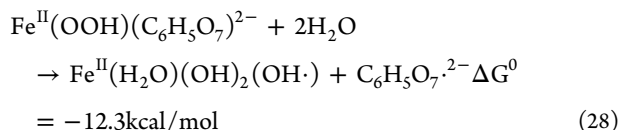
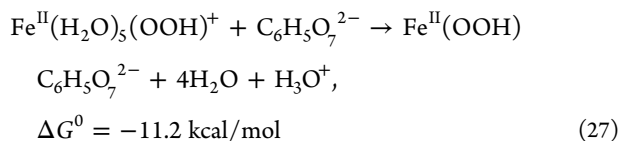
Figure 2. Structures of $M^{\text{II}}(\text{H}_2\text{O})(\cdot\text{OOH})(\text{OH})_2$ and $M^{\text{II}}(\text{H}_2\text{O})(\text{OH})_2(\cdot\text{OH})$: M, yellow; C, brown; H, white; O, red.

It was experimentally proved that Co^{II} is not oxidized during Fenton-like reaction,²⁴ but Fe^{II} is oxidized to Fe^{III} . An intramolecular electron transfer occurs according to eq 26:



In biological systems, no free $\text{Fe}^{\text{III/II}}_{\text{aq}}$ exists. Most of the iron(III) ions in the mobile pool are present as citrate or ATP complexes.³⁸ The Fenton reaction is then initiated by the reduction of these complexes. Therefore, the ΔG^0 values of reactions 27–31 were calculated.

The first steps are forming a complex between $\text{Fe}^{\text{II}}(\text{H}_2\text{O})_5(\text{OOH})^-$ and citric acid—reaction 27. Citrate is a tridentate ligand, the structure of the complex formed is shown in Figure 3. This reaction is followed by reaction 28.



$\text{Fe}^{\text{II}}(\text{H}_2\text{O})(\text{OH})_2(\cdot\text{OH})$ is converted to $\text{Fe}(\text{H}_2\text{O})_6^{3+}$ according to reaction 26.

The final product $\text{C}_5\text{H}_4\text{O}_5^{2-}$ is gained by further oxidation of $\text{C}_6\text{H}_5\text{O}_7^{2-}$, either by Fe^{3+} ions—reaction 29—or by another peroxide—reactions 30a,30b. Oxidation of $\text{C}_6\text{H}_5\text{O}_7^{2-}$ by Fe^{3+} produces $\text{C}_5\text{H}_4\text{O}_5 + \text{CO}_2$, the known final products of the oxidation of citrate. In the presence of excess of peroxide the oxidation might occur via reactions 30a or 30b.

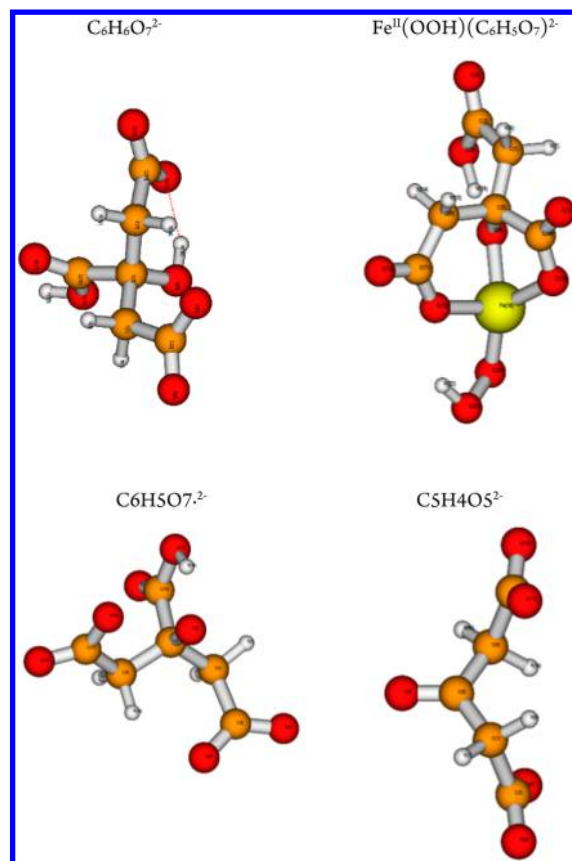
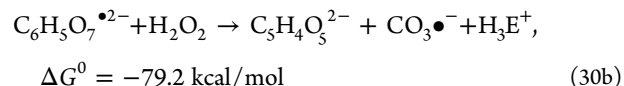
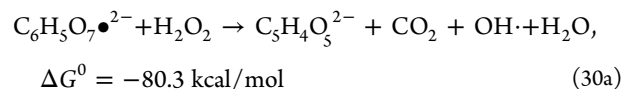
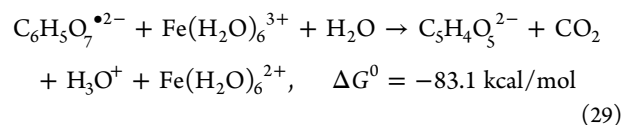


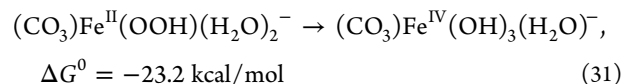
Figure 3. Structures of reactants and products of reactions 27–30. Key: M, yellow; C, brown; H, white; O, red.

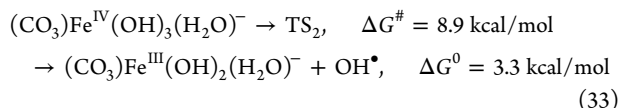
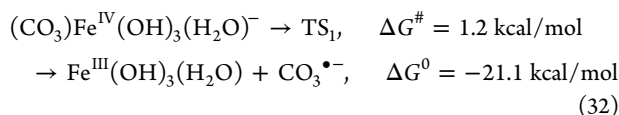
In reaction 30a the produced radical is $\text{OH}\cdot$ and in reaction 30b the produced radical is $\text{CO}_3^{\cdot-}$. These two reactions are thermodynamically equally favorable but mechanistically reaction 31 is difficult to envisage.



The structures of the reactants and products of reaction 27–30 are depicted in Figure 3.

This manuscript is based mainly on thermodynamics, but in order to get some insight on kinetic effects, the mechanism of the dissociation of $(\text{CO}_3)\text{Fe}^{\text{II}}(\text{OOH})(\text{H}_2\text{O})_2^-$ was studied. The product of the dissociation of $(\text{CO}_3)\text{Fe}^{\text{II}}(\text{OOH})(\text{H}_2\text{O})_2^-$ is either $\text{CO}_3^{\cdot-}$ or $\text{OH}\cdot$. The first step of this dissociation is reaction 31 followed by reaction 32 or reaction 33:





The barrier of reaction 32 is almost zero while the barrier of reaction 33 is 8.9 kcal/mol. The conclusion is that the favored reaction is 32 where $\text{CO}_3^{\bullet-}$ radicals are formed.

The structures of $(\text{CO}_3)\text{Fe}^{\text{IV}}(\text{OH})_3(\text{H}_2\text{O})^-$, TS1 and TS2 are given in Figure 4. The bond length of Fe–OCO₂ in

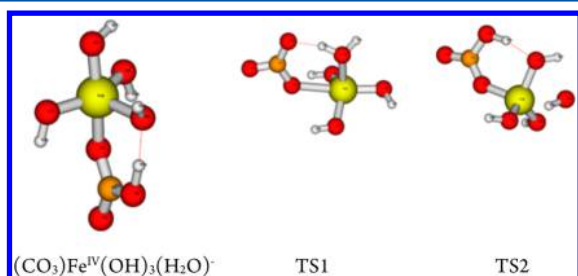


Figure 4. Structures of $(\text{CO}_3)\text{Fe}^{\text{IV}}(\text{OH})_3(\text{H}_2\text{O})^-$, TS1, and TS2: Fe, yellow; C, brown; H, white; O, red.

$(\text{CO}_3)\text{Fe}^{\text{IV}}(\text{OH})_3(\text{H}_2\text{O})^-$ is 1.91 Å, this bond is extended in TS1 to 2.11 Å. The bond length of Fe–OH in $(\text{CO}_3)\text{Fe}^{\text{IV}}(\text{OH})_3(\text{H}_2\text{O})^-$ is 1.86 Å, this bond is extended in TS2 to 2.55 Å.

CONCLUDING REMARKS

The results presented suggest that in the presence of carboxylate ligands the Fenton-like reactions catalyzed by either Fe(II) or Co(II) cations do not form hydroxyl radicals. This suggests that radicals with considerable lower oxidation potentials, than commonly assumed, often induce oxidative stress and advanced oxidation processes.

These radicals are naturally considerably more selective in their reactions than hydroxyl radicals. The oxidation of other ligands, e.g. glycosides, bound to the central cation by a ligated peroxide is clearly plausible. It should be noted that this mechanism is an alternative explanation to the site specific mechanism proposed in the literature.^{39,40}

ASSOCIATED CONTENT

Supporting Information

Table S-1, ΔG^0 values for all the reactions 16–25, M = Fe(II). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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