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Chemistry

Reviewing the effect of metal complexation upon the antioxidant/antiradical properties of L-ascorbic acid

Revisando o efeito da complexação de metais sobre as propriedades antioxidantes/antirradicais do ácido L-ascórbico

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ABSTRACT

L-ascorbic acid is a molecule used in the hydroxylation of various biochemical reactions in cells. Its main function is the hydroxylation of collagen, the fibrillar protein that gives resistance to bones, teeth, tendons and walls of blood vessels. Furthermore, it is a powerful antioxidant, being used to transform reactive oxygen species into inert forms. It is also used in the synthesis of some molecules that serve as hormones or neurotransmitters. In this review, a series of reactions are presented and discussed with the aim to discuss as some chemical parameters such as pH, redox potential, presence of different metal ions and ascorbic acid works effectively as a ligand. Several mechanisms are revisited and aspects as the effect of transition metals over the redox chemistry of acid is presented.

Keywords: L-ascorbic acid; Redox potential; Metal ligand

RESUMO

O ácido L-ascórbico é uma molécula utilizada na hidroxilação de várias reações bioquímicas nas células. Sua principal função é a hidroxilação do colágeno, a proteína fibrilar que dá resistência aos ossos, dentes, tendões e paredes dos vasos sanguíneos. Além disso, é um poderoso antioxidante, sendo utilizado para transformar espécies reativas de oxigênio em formas inertes. Também é usado na síntese de algumas moléculas que servem como hormônios ou neurotransmissores. Nesta revisão, uma série de reações são apresentadas e discutidas com o objetivo de discutir alguns parâmetros químicos como pH, potencial redox, presença de diferentes íons metálicos e o ácido ascórbico funciona efetivamente como um ligante. Vários mecanismos são revisitados e aspectos como o efeito dos metais de transição sobre a química redox do ácido são apresentados.

Palavras-chave: Ácido L-ascórbico; Potencial redox; Ligante metálico

1 INTRODUCTION

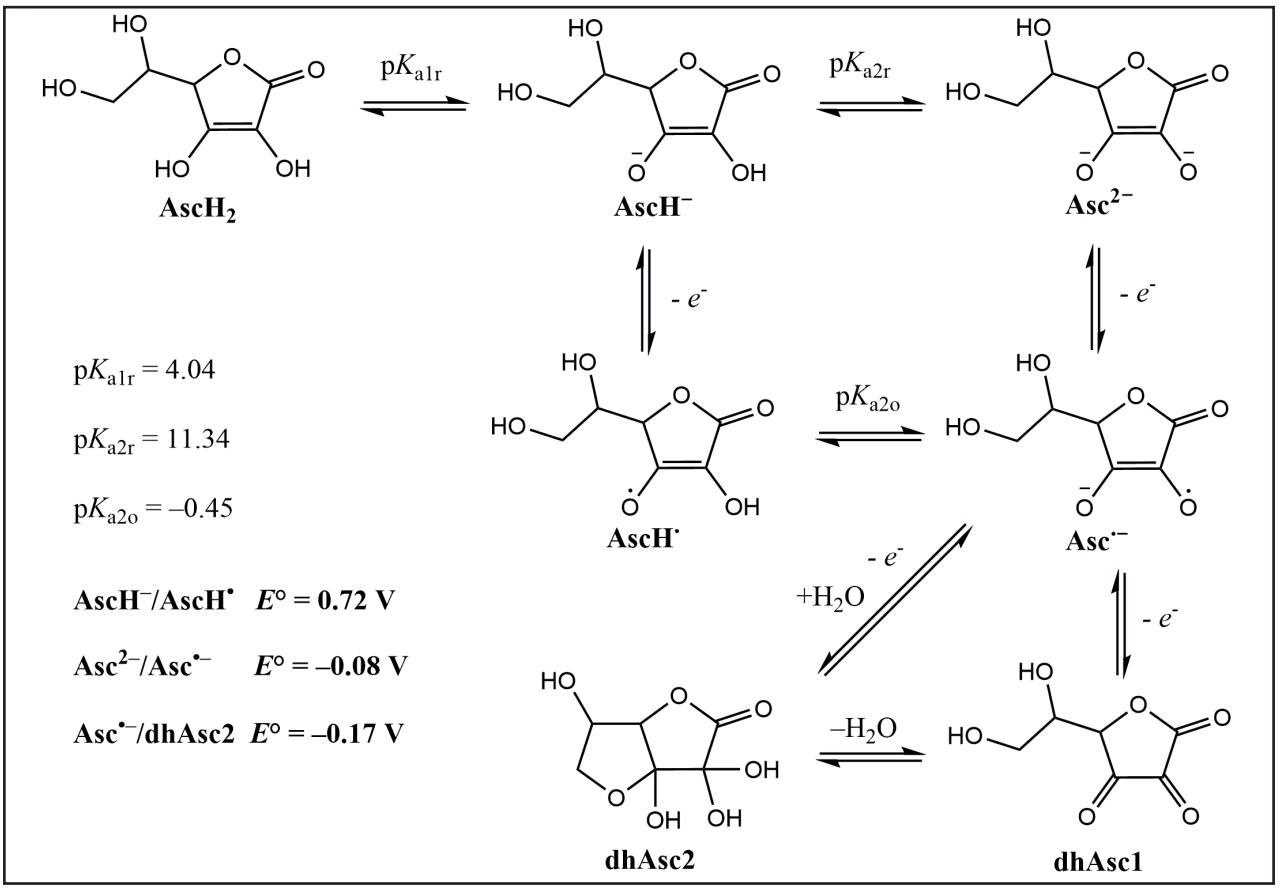
L-ascorbic acid ($AscH_2$) is among the most widely cited forms of water-soluble biological antioxidants. The ability to scavenge free radicals appears, in part, to involve one-electron oxidation where ascorbate serves as reductant towards radical species (Crans *et al.*, 2008). Reaction of $AscH_2$ with peroxyl or hydroxyl radicals typically yields radical intermediate species, which can be subsequently quenched as part of an overall antioxidant effect (Yin *et al.*, 2022). On the basis of the redox potential of $AscH_2$, radical intermediates seem to be formed with nearly equal facility during radical scavenging reactions (Tu, Njus and Schlegel, 2017). Nevertheless, $AscH_2$ is also known to act as a pro-oxidant in fats, particularly in aqueous fat systems (Kanner, Mendel and Budowski, 1977).

Metal ions appear to be involved in the pro-oxidant activity of $AscH_2$, as shown by the inhibition of such effect by metal chelating compounds as ethylenediaminetetraacetic acid (EDTA) or polyphosphates (Timoshnikov et al., 2022). Indeed, Fe^{3+} and Cu^{2+} have been reported to accelerate the pro-oxidant activity of $AscH_2$ towards lipids (Ritacca *et al.*, 2022).

The first standard reduction potential (E°) of $AscH_2$ is around 0.72 V, while the second one is around −0.17 V; this means that, even though it is a great anti-radical agent, it is not necessarily a good reducing agent. Free radicals are unstable and have a high E°, allowing electron transfer (ET) from $AscH_2$. Its antioxidant character is linked to the availability of electrons to reduce strong oxidizing agents, as free radicals, but it is not intended to behave as a strong reducing agent in the biological environment (Tu, Njus and Schlegel, 2017).

The antioxidant potential of $AscH_2$ comes from its ability to be converted into dehydroascorbate (dhAsc) through the abstraction of two protons and two electrons (Figure 1). This redox reaction provides the electrons needed to stabilize radicals, as well as the proton to balance charges (Nimse and Pal, 2015; Pehlivan, 2017).

Figure 1 – Possible mechanisms for the oxidation of $AscH_2$ to dhAsc



Source: Authors

It is very interesting to note that $AscH_2$ is an extremely efficient molecule which is adapted to function in the physiological environment. Figure 1 shows that, at a pH close to 7.0, $AscH_2$ appears almost entirely in its monoprotic $AscH^-$ form (pK_{a1r} = 4.04), while the pK_{a2r} value is 11.34. If $AscH^-$ ($AscH^-/AscH^{\cdot}$ $E°$ = 0.72 V) meets a strong enough oxidizing agent, it undergoes oxidation by transferring one electron, which results in $AscH^{\cdot}$ formation.

Once in radical form, it becomes a strong base, promptly losing the second proton (pK_{a2o} = −0.45 against pK_{a2r} = 11.34). The $Asc^{\cdot-}$/dhAsc pair is a much more efficient reducer ($E°$ = −0.174 V), easily transferring the second electron to the substrate.

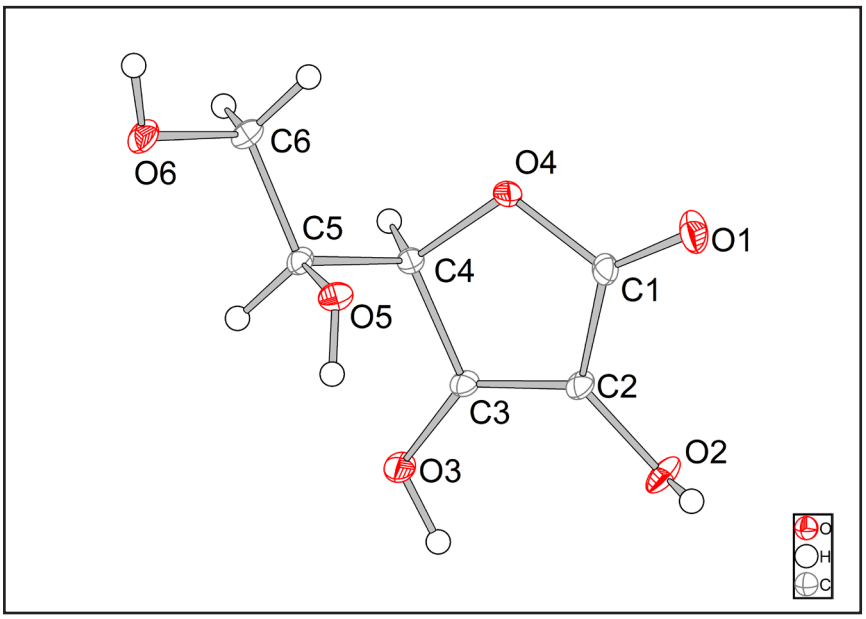
When deprotonated, $AscH_2$ functions as an O-donor base with low polarizability, a hard base according to the hard and soft acids and bases (HSAB) theory; it easily forms complexes with various metal ions present in solution, mainly transition metals

showing high oxidation states (e.g. Fe^{3+}, Co^{3+}, Cu^{2+}, Cr^{6+}, V^{5+}). Complexation occurs because the $AscH^-$ and Asc^{2-} species must donate electronic density to the metal ions, forming a stable complex. Interaction with the metallic center totally changes the expected redox behavior of $AscH_2$.

2 L-ASCORBIC ACID AS A LIGAND

In the nearly 90 years since its discovery (1928), $AscH_2$ has become "the most famous yet least understood of the vitamins". The crystal structure of $AscH_2$ (Figure 2) has been reported by Hvoslef in 1964 (Hvoslef 1964). Despite being a simple molecule, its biochemistry is poorly understood owing to a quite complicated redox chemistry, which makes it both an interesting and intriguing reducing agent in inorganic systems. Many solution studies have since been carried out on reactions between $AscH_2$ and metal ions. The important work of Martell has established the catalytic role of metals in $AscH_2$ oxidation (Martell, 1982).

Figure 2 – Crystal structure of L-ascorbic acid



Source: Martell, 1982

As a weak diprotic acid (pK_{a1} = 4.25 and pK_{a2} = 11.79), the monoanion ($AscH^-$) is formed at pH 4–5 with deprotonation of O(3)–H, and the dianion (Asc^{2-}) is formed at pH 11–12 with deprotonation of the O(2)–H. The mono-anionic form is more stable due to the delocalization of the negative charge between the oxygen atoms at positions 1 and 3. Although $AscH_2$ has numerous donor atoms to promote the formation of a metal complex, interaction of $AscH^-$ with metals mainly occurs monodentately through the O(3) atom, or by chelation via O(3) and O(2), depending on the nature of the metal cation and the solution pH. Multiple other bonding modes have been proposed in the solid state, including the participation of the carbonyl oxygen and side chain OH groups.

Stability of complexes is generally less than might have been expected. The formation constants of the 1:1 complexes are in the range of 10 to $10^{3.6}$ (Martell, 1982). The values are quite small, possibly as a result of the low negative charge on the ligand anion. Jabs and Gaube determined the ligand field parameters of the $AscH^-$ ligand and suggested that ascorbate should take an intermediate position in the spectroscopic series, around H_2O and O^{2-} and just before the fluoride ligand in the nephelauxetic series (Jabs and Gaube, 1986). Later, Cieslak-Golonka and co-workers calculated crystal field parameters of some chromium ascorbate complexes for octahedral and tetragonal symmetries from diffuse reflectance spectra (Adach, Janyst and Cieślak-Golonka, 1995). They found that the Dq values are in the 1600–1800 cm^{-1} region and larger in solution, typical of oxygen ligands.

Nearly all the work on transition metal pure ascorbate complexes has been performed with the first-row metals and on powdered samples. Since no single crystal data is available, the structural assignments have generally been deduced from UV-vis, NMR, IR and magnetic measurements. Due to the unstable nature of the molecule and hydrolytic instabilities of the complexes, there have not been many reports on the isolation of solid complexes of $AscH_2$. The proposed structures of the pure ascorbate complexes have been the subject of the most controversy in the absence of X-ray crystal data.

The first systematic synthesis and isolation of binary ascorbate complexes with redox-inert transition metals have been described by Jabs and Gaube (JABS and GAUBE, 1984). Complexes of the type $M(AscH)_n \cdot xH_2O$ (M = TiO^{2+}, Cr^{3+}, Mn^{2+}, Co^{2+}, Ni^{2+} and Zn^{2+}) were obtained through the reaction:

$$MSO_4 + Ba(OH)_2 + 2AscH_2 \rightarrow M(AscH)_n \cdot xH_2O + BaSO_4 + 2H_2O \quad (2.1)$$

Since then, complexes with highly oxidized transition metals have been investigated by other authors. In these cases, the metal center is generally reduced by $AscH_2$ via an inner-sphere reaction. Ferrer and co-workers demonstrated that the primary complexes generated by the interaction of dhAsc with metal ions are not stable and irreversibly hydrolyze to diketogulonic acid complexes of the related metal (Ferrer, Williams and Baran, 1998).

3 EFFECT OF TRANSITION METALS OVER THE REDOX CHEMISTRY OF L-ASCORBIC ACID

Complexation of $AscH_2$ with metal ions having E° greater than 0.72 V, e.g., Co^{3+}, Cr^{6+} and V^{5+} (Table 1), promotes ET from $AscH_2$ to the metal, leading to dhAsc formation. Usually, dhAsc is irreversibly hydrolyzed to diketogulonic acid (Figure 1) (Ferrer, Williams and Baran, 1998; Kontoghiorghes *et al.*, 2020). In this scenario, there is a reduction in the concentration of $AscH_2$ in the medium, leading to an underestimated measurement of the antioxidant activity, for example. Some of the known redox complexation reactions of $AscH_2$ are:

3.1 High oxidation state metals: Co(III), Cr(VI) and V(V)

Complexation of $AscH_2$ with metal ions having *E*° greater than 0.72 V, e.g., Co^{3+}, Cr^{6+} and V^{5+} (Table 1), promotes ET from $AscH_2$ to the metal, leading to dhAsc formation. Usually, dhAsc is irreversibly hydrolyzed to diketogulonic acid (Figure 1) (Ferrer, Williams and Baran, 1998;

Kontoghiorghes *et al.*, 2020). In this scenario, there is a reduction in the concentration of $AscH_2$ in the medium, leading to an underestimated measurement of the antioxidant activity, for example. Some of the known redox complexation reactions of $AscH_2$ are:

$$3AscH^- + 2Cr(VI) \rightarrow 3dhAsc + 2Cr(III) + 3H^+ \quad (3.1.1)$$

$$AscH^- + Co(III) \rightarrow dhAsc + Co(II) + H^+ \quad (3.1.2)$$

$$AscH^- + V(V) \rightarrow dhAsc + V(IV) + H^+ \quad (3.1.3)$$

3.2 Redox inert transition metals: Zn(II), Cd(II), and Al(III)

Interaction of these metals with $AscH_2$ has been assessed in the solution and solid phases (Zümreoglu-Karan, 2006). Complexes with general formula $M^{n+}(AscH^-)_n \cdot xH_2O$ show good stability without any ET from $AscH_2$ to the metal center (Cesario *et al.*, 2017; Davies, 1992). The complex stability can affect the species distribution and, consequently, the availability for redox reactions.

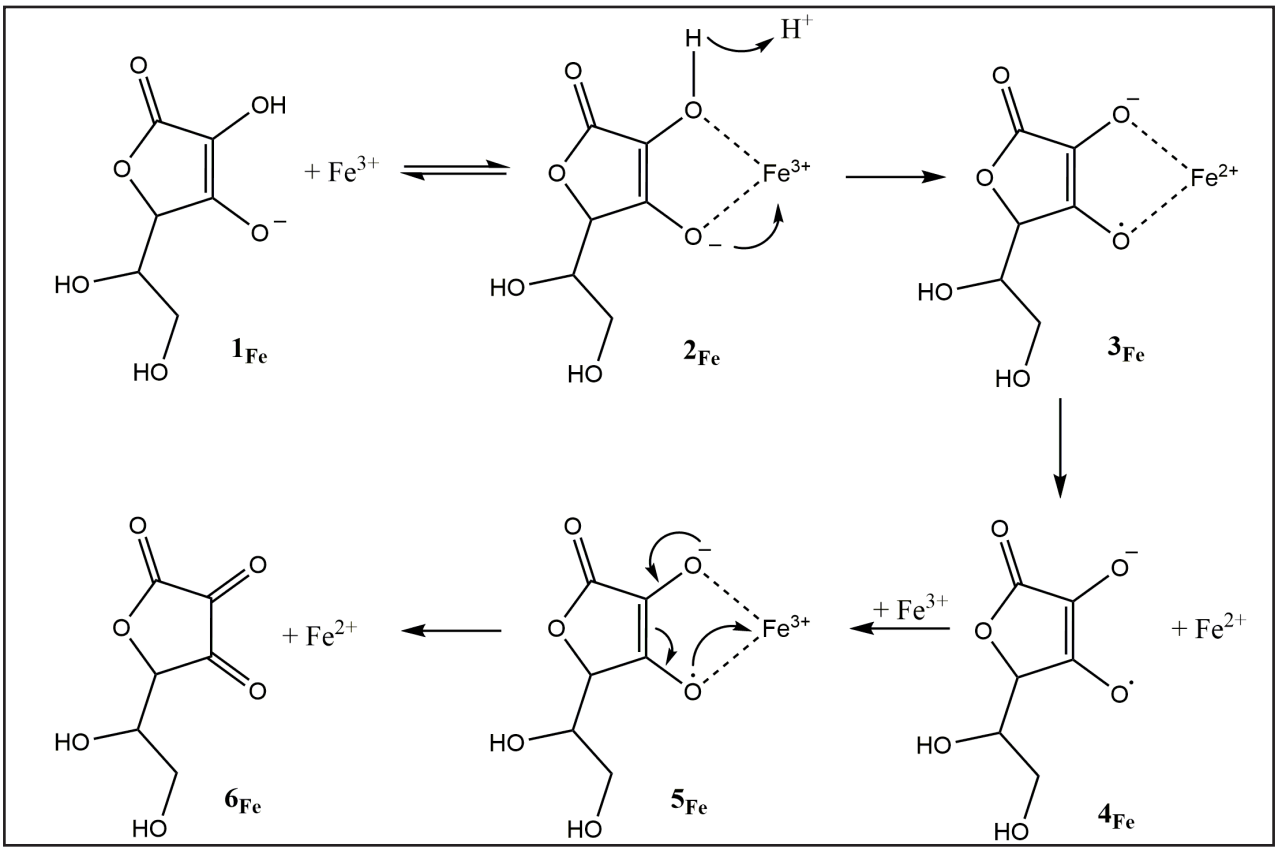
A recent study with cichoric acid evaluated the effects of metal complexation on the antioxidant activity of the molecule, via radical scavenging capacity. Results showed a slight increase in radical inhibition for complexes with redox inert metals (Na^+ and Zn^{2+}) (Swiderski *et al.*, 2020). Nonetheless, to the best of the authors' knowledge, the effect of complexation upon the antioxidant activity of $AscH_2$ has not yet been investigated.

3.3 Special cases, formation of catalytical systems: Cu(II) and Fe(III)

The $E°$ for the redox pair $Fe^{3+} + e^- \rightleftharpoons Fe^{2+}$ is 0.77 V, which is relatively high and indicates that reduction of Fe^{3+} is thermodynamically favorable; however, it is unusual to find Fe^{2+} ions in oxidizing environment, as in the presence of O_2. Fe^{3+} has a semi-

filled d orbital ($3d^5$), ensuring greater stability compared to Fe^{2+} ($3d^6$), especially when complexed with intermediate or weak field ligands which promote a smaller unfolding of the crystalline field, thus stabilizing the high spin species. The easiness with which Fe^{2+} is quickly oxidized to Fe^{3+}, in the presence of O_2, provides a catalytic system that promotes $AscH_2$ oxidation, even with trace amounts of Fe^{3+} in the medium (Kontoghiorghes *et al.*, 2020; Martell, 1982). Interaction of iron complexes with $AscH_2$ form powerful catalysts for Fenton reactions which behave as pro-oxidants, as seen in the proposed mechanism illustrated in Figure 3 (Yuan *et al.*, 2021).

Figure 3 – Proposed mechanism for the catalytic oxidation of $AscH_2$ by Fe^{3+}

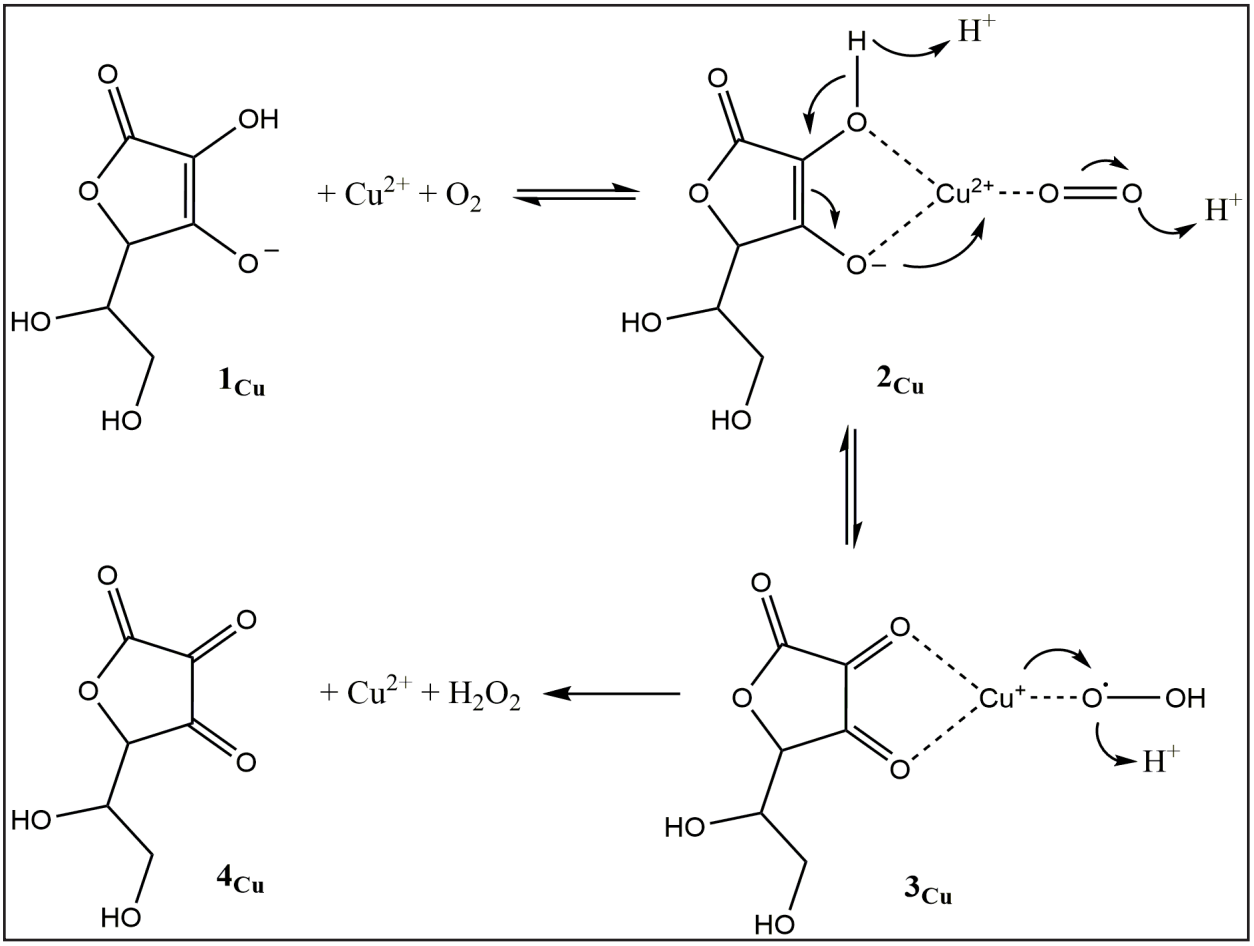


Source: Yuan *et al.*, 2021

The Cu^{2+} cation is a classic case of the Jahn-Teller effect with a greater stabilization of the d_{z^2} orbital in the $3d^9$ configuration. Cu^+, in turn, has a full filled subshell ($3d^{10}$) which can also provide stability to the monovalent cation. Nevertheless, since it is a

soft acid (HSAB theory), Cu^{+} needs an equally soft base, little polarizable, as an S-donor base in order to form a stable complex. In an aqueous medium, the hydration enthalpy for Cu^{+} is so high that the cation is quickly oxidized to the divalent state (Khan and Martell, 1967). The redox behavior of Cu^{2+} in aqueous solution promotes the catalytic oxidation of $AscH_2$ with hydrogen peroxide formation (Martell, 1982), as seen in the proposed mechanism depicted in Figure 4.

Figure 4 – Proposed mechanism for the catalytic oxidation of $AscH_2$ by Cu^{2+}, with hydrogen peroxide formation



Source: Martell, 1982

Table 1 – Selected standard reduction potentials for some transition metals (Lide, 2004)

Redox reaction	E°	Redox reaction	E°
$Cu^{2+} + e^- \rightleftharpoons Cu^+$	0.15	$Co^{3+} + e^- \rightleftharpoons Co^{2+}$	1.92
$Fe^{3+} + e^- \rightleftharpoons Fe^{2+}$	0.77	$Co^{2+} + e^- \rightleftharpoons Co$	−0.28
$Ni^{2+} + 2e^- \rightleftharpoons Ni$	−0.26	$O_2 + 2H^+ + 2e^- \rightleftharpoons H_2O_2$	0.69
$Cr^{3+} + e^- \rightleftharpoons Cr^{2+}$	−0.41	$VO_2^+ + 2H^+ + e^- \rightleftharpoons VO^{2+} + H_2O$	0.99
$Al^{3+} + 3e^- \rightleftharpoons Al$	−1.62	$Cr_2O_7^{2-} + 14H^+ + 6e^- \rightleftharpoons 2Cr^{3+} + 7H_2O$	1.36

4 CONCLUSION

Metal ions affect the reaction mechanism and antioxidant potentials. $AscH_2$, one of the most classic antioxidant agents studied in the literature, suffers a strong influence in the presence of metal ions forming stable metal complexes.

Based on this logic, it would be interesting to have more experimental tests in future works, mainly evaluating the complexation chemistry for $AscH_2$; in spite of having been studied for a long time, there is no clear information in the literature with respect to characterization of crystals, for instance. In addition, there are no studies assessing the antioxidant activity of $AscH_2$ complexes, especially regarding complexes with fixed oxidation states; those are known complexes, but their antiradical potentials have not yet been evaluated.

Interference of traces of metals is also very relevant, since the ability to act as a reducing agent can lead $AscH_2$ to promote the reduction of Fe^{3+} to Fe^{2+}, for example, thus catalyzing Fenton reactions and resulting in an apparent pro-oxidant activity.

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