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Citric acid: A promising copper scavenger

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ABSTRACT

In this investigation, the capacity of citric acid as copper scavenger is analyzed. For the copper scavenger capacity, the formation of the chelate complexes is studied using the Gibbs free energies. The chelates may be formed since the formation reactions are all exergonic. The free radical scavenger ability of chelate complexes is investigated using the single electron transfer mechanism with the Full Electron Donor-Acceptor Map (FEDAM). Different acid-base species of citric acid are also studied as ˙OH inactivating ligands (OIL). The conclusion of this investigation is that metal chelation is viable for citric acid species and also that the formed chelates are efficient ˙OH scavengers. Therefore, it is possible to conclude that citric acid is promising for copper chelation therapy (metal scavenger). These results may be useful for further investigations concerning citric acid and can give ideas about the benefits of citric acid as an additive in food.

1. Introduction

Copper is one of the metal cofactors of several enzymes [1]. It has been considered as essential element for human body [2] but it can also be accumulated up to toxic levels. High concentration of Cu in the human body is related to oxidative damage of proteins, lipids and nucleic acids, [3–8] being the Wilson's disease the most dangerous disorder [9–16]. This condition is produced by the Haber-Weiss reactions that generate toxic hydroxyl free radicals [17] as shown in what follows

$$Cu(II) + O_2^{\cdot -} \rightarrow Cu(I) + O_2$$

$$Cu(I) + H_2O_2 \rightarrow Cu(II) + OH^- + {}^{\cdot}OH$$

To avoid the oxidative damage it is important to prevent copper accumulation. One way to do this is with chelating agents [18–24]. These agents were previously defined as metal scavengers to distinguish them from chelating agents with other purposes [25,26].

To recognize a good metal scavenger, a flow chart with the questions that should be answered was previously proposed [25]. According to that proposal, a good metal eliminator form stable chelate complexes and it is desirable that it also be a good free radical scavenger. The chelate complex should also act as an ˙OH inactivating ligand (OIL). OIL species prevent the damage caused by ˙OH by sequestering metal ions from reductants in Haber–Weiss reactions (OIL-1) or by deactivating ˙OH immediately as it is formed through Fenton-like reactions (OIL-2). In this investigation we analyze citric acid as copper scavenger following these ideas.

Citric acid is a weak organic acid. It is found in citric fruits and it is also an intermediate in the citric acid cycle that occurs in the metabolism of aerobic organisms. It plays numerous roles [27] and it is ubiquitous in nature (5% by weight of lemon juice is citric acid for example). The utilization of calcium contained in foods in higher organisms is regulated by citric acid.

Citric acid and its salts are used very often in everyday life. Along with others, it is commonly added to foods and cold drinks as an additive [28], in the production of cold drinks [29], to prevent lipid oxidation in frozen fish fillets [30], to assist phyto-extraction of chromium by sunflower [31] and to enhance the antioxidant defense system and chromium uptake [32]. However, there are sometime complications and the innocence of citric acid as food additive is not always real. It was recently reported that iron citrate complexes could be formed in the organism [33]; these complexes are toxic since they also generate free radicals. Authors reported that, in the absence of a pathological situation, citric acid is probably innocuous as additive but it may become dangerous under oxidative stress conditions or when there is an iron overload. In the presence of copper, it is not known if citric acid operates as pro-oxidant, producing Cu(I) that is a reactant of Haber-Weiss reactions that were previously mentioned.

From the theoretical point of view, there are previous studies about citric acid [34,35] but there are not investigations concerning its metal scavenger capacity, neither studies about its antioxidant activity. For this reason, in this work, we analyze the capacity of citric acid as copper

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scavenger following the steps previously reported [25]. These results may be useful for further investigations concerning citric acid and can give ideas about the danger or the benefits of citric acid as an additive in food.

2. Computational details

Gaussian09 was used for all the electronic calculations [36]. Geometry optimizations without symmetry constrains were carried at M06/6-31 + G(d,p) level of theory [37–41] and using the continuum solvation model density (SMD) with water to mimic a polar environment [42]. Harmonic analyses were calculated to verify local minima (zero imaginary frequencies). The metal scavenger capacity was investigated with the ΔG value for the following reaction:

$$[\text{Citric-xH}]^{-x} + [Cu(H_2O)_4]^{2+} \rightarrow \text{Cu-[Citric-xH-2H}_2\text{O}]^{-x+2} + 2H_2O \quad (1)$$

The free radical scavenger properties were studied by analyzing the single electron transfer (SET) mechanism. Vertical ionization energy (*I*) and vertical electron affinity (*A*) were obtained from single point calculations of the corresponding cationic and anionic molecules, using the optimized structure of the neutrals. Same level of theory was used in all computations. The Full Electron Donor-Acceptor Map (FEDAM), defined previously [43,44], is a useful graphic tool. In this map, *I* and *A* (Fig. 1) are plotted and allow classifying substances as either donors or acceptors of electrons. Electrons are transfer from good donor systems (down to the left of the map) to good electron acceptor systems (up to the right of the map).

Citric acid (neutral and deprotonated) may act as pro-oxidant producing Cu(I) that is one of the important reactants of the Haber-Weiss reactions. Therefore, it is important to analyze the following reaction:

$$[\text{Citric-xH}]^{-x} + [Cu(H_2O)_4]^{2+} \rightarrow [\text{Citric-xH}]^{-x-1} + [Cu(H_2O)_4]^{1+} \quad (2)$$

3. Results and discussion

As pointed out in the introduction, citric acid is a weak organic acid. The pKa values are 3.1, 4.8 and 6.4 (see Fig. 2). This means that, under physiological conditions (pH equal 7.4), citric acid is deprotonated in a high percentage. For this reason, in this study we investigated all possible structures, neutral and deprotonated. The optimized geometries are reported in Fig. 2 and, as expected, they are quite similar.

To analyze the metal chelation process, copper atom was bonded at several positions of the citric acid (neutral and deprotonated). Gibbs free energies were obtained according to Eq. (1). Fig. 3 reports the most stable structures of the compounds with copper and the corresponding values of ΔG. Bond distances are similar and all the reactions are exergonic, indicating that they are thermodynamically viable. The most exergonic reaction is for $[\text{Citric-3H}]^{-3}$. In all cases, there is an important electrostatic component in the interaction of copper atom with citric acid. For this reason, when the global negative charge of the citric acid increases, a raise of the electrostatic interaction with positive copper atoms is produced. In fact, as the global negative charge of the citric acid increases, the exergonicity also augments.

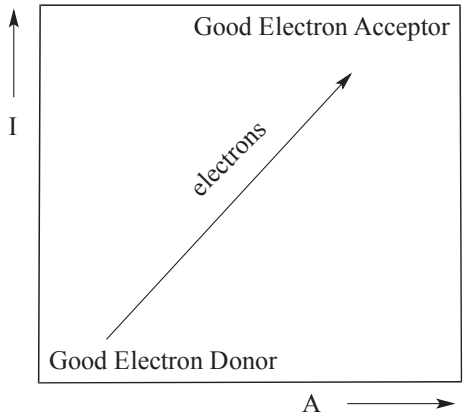

Fig. 1. Full Electron Donor-Acceptor Map.

The second step to recognize a good metal scavenger is to know the efficiency of the molecule as free radical scavenger. To investigate this, the SET mechanism was used for citric acid (neutral and anionics). Fig. 4 reports the FEDAM for citric acid species and ˙OH. As expected, $[\text{Citric-3H}]^{-3}$ is the best electron donor. Citric acid species are down to the left, with respect to ˙OH. Therefore, they are able to give an electron to the free radical and consequently they are good free radical scavengers.

Metal chelation is viable for citric acid species and also these species are efficient free radical scavengers. Therefore, it is possible to conclude that citric acid is promising for copper chelation therapy (metal scavenger).

To analyze OIL-2 mechanism it is necessary to investigate the capacity of the chelates to act as ˙OH scavengers. To answer this question we analyzed the SET mechanism with the results of Fig. 4. Chelate species are down to the left at the FEDAM, whilst ˙OH is up to the right. Therefore copper compounds can also donate an electron to the free radical but they are better electron acceptors and worse electron donors than the citric acid species without copper. Citric acid species are better free radical scavengers but chelate compounds with copper can also act as ˙OH scavenger.

To analyze the OIL-1 mechanism, the reduction of the Cu(II) chelates was investigated. Two possible reductants were considered: (i) the superoxide radical anion ($O_2^{\cdot -1}$) and the ascorbate anion (Asc^{-1}). $O_2^{\cdot -}$ is involved in the first step of the Haber–Weiss recombination and Asc^{-1} is frequently used mixed with copper to induce oxidative conditions in vitro. The Gibbs free energies (ΔG) for the reactions of these two reductants with the Cu(II) chelates (having citric acid species as ligands) are reported in Table 1. The ΔG values for the reactions with "free" copper are also provided in this table, as references.

Free Cu(II) ions were modeled coordinated to water molecules because this model is more adequate to represent this species, under physiological conditions, than the naked ion. It was modeled in an almost square-planar four coordinate geometry, since it has been reported to be the most likely arrangement for this ion in aqueous solution [45,46] For consistency purposes, the hydrated Cu(I) ions were modeled with four water molecules albeit in this case the linear two-coordinate configuration is preferred [47–49]. Thus, in this model, Cu(I) is actually coordinated to two water molecules, while the other two are solvating the system.

It was found that chelation by the citric acid species fully turn off the Cu(II) reduction by Asc^{-1}, since the corresponding reactions are all endergonic. These results suggest that citric acid will behave as an efficient antioxidant, via OIL-1, in experiments using Cu/Asc^{-1} mixture to induce oxidation. On the contrary, the Cu(II) reduction by $O_2^{\cdot -1}$ is predicted to be only partially inhibited, because in this case the corresponding reactions were found to be less exergonic than for free copper, but still thermochemically viable. Therefore, citric acid might downgrade the ˙OH production in biological systems, but the inhibition will not be complete. These results indicate that the efficiency of citric acid as an OIL-1 antioxidant would depend on the strength of the reductant. Moreover, since $O_2^{\cdot -1}$ is expected to be the most likely reductant under physiological conditions, in biological systems citric acid would be more efficient as an OIL-2 antioxidant.

In the presence of copper, citric acid (neutral and de-protonated)

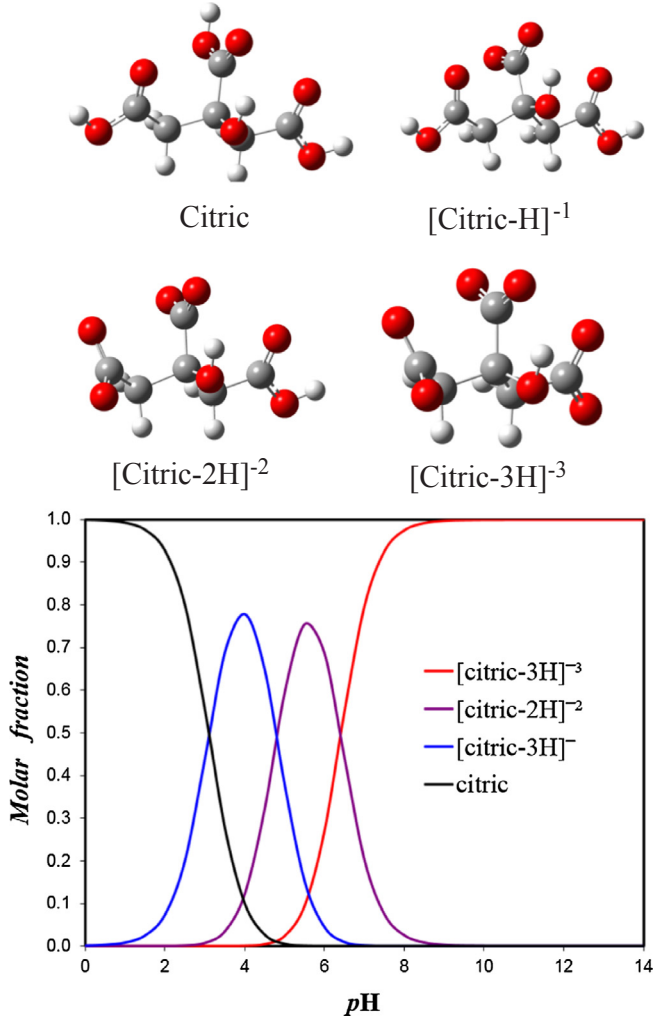

Fig. 2. Distribution diagram and optimized structures of citric acid (neutral and the deprotonated species).

may act as pro-oxidant producing Cu(I), one of the reactants of Haber-Weiss reactions. If this were the case, then citric acid should not be considered as a good metal scavenger in biological systems. We investigate the Cu(II) reducing ability of citric acid (neutral and de-protonated) and Table 2 reports the correspondent Gibbs free energies. All the reactions are endergonic and therefore they are not thermodynamically viable. With these results, it is possible to say that citric acid is not able to reduce Cu(II), thus it is not a pro-oxidant and it will not promote ˙OH production via the Haber-Weiss reactions.

4. Conclusions

According with all the results presented here, the best copper scavenger is $[Citric\text{-}3H]^{-3}$. This is a promising result since most citric acid under physiological conditions will be present in this form.

Citric acid will behave as an efficient antioxidant, via OIL-1, in experiments using Cu/Asc^{-1} mixture to induce oxidation. The Cu(II) reduction by $O_2^{\cdot -1}$ will be only partially inhibited, since the corresponding reactions are less exergonic than for free copper. Therefore, citric acid might downgrade the ˙OH production in biological systems.

Moreover, citric acid will not reduce Cu(II), thus it is not a pro-oxidant and it will not promote ˙OH production via the Haber-Weiss reactions.

Metal chelation is viable for citric acid species and also these species are efficient free radical scavengers. Therefore, it is possible to conclude

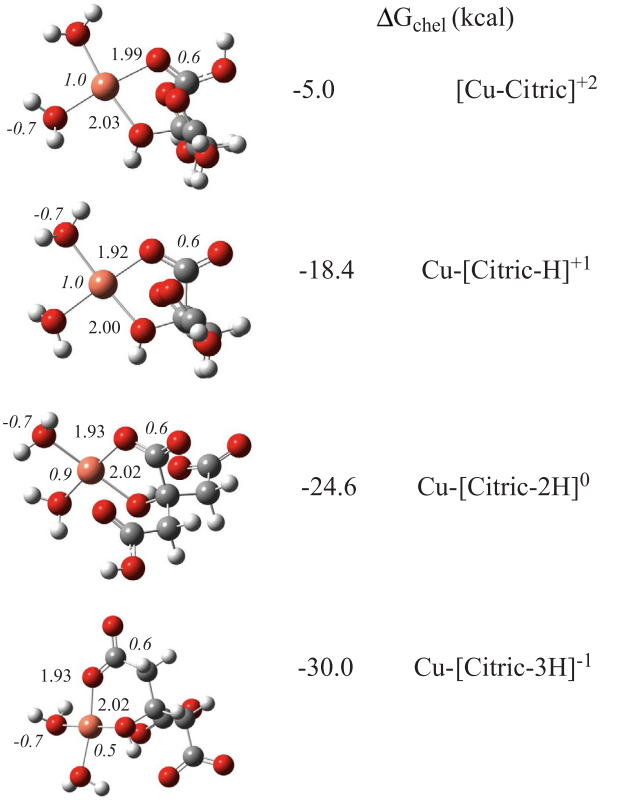

Fig. 3. Most stable structures of compounds with copper and citric acid (neutral and deprotonated). Mulliken atomic charges are reported in *italics*.

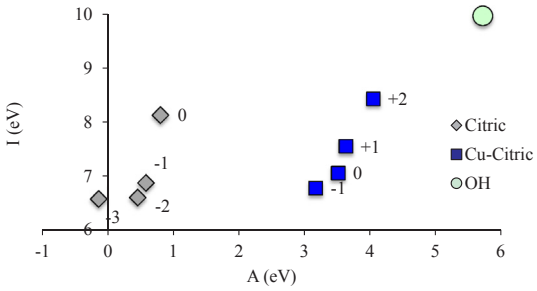

Fig. 4. FEDAM for citric acid species and OH free radical. Chelate species are also included.

Table 1
Gibbs free energies (kcal/mol, at 298.15 K) of the reactions of Cu(II) – citric acid with the superoxide radical anion ($O_2^{\cdot -1}$) and the ascorbate anion (Asc^{-1}) as reductants.

	$O_2^{\cdot -1}$	Asc^{-1}
$[Cu(H_2O)_4]^{+2}$	−26.2	−2.2
$[Cu\text{-}Citric]^{+2}$ $2H_2O$	−18.1	4.5
$[Cu\text{-}[Citric\text{-}H]]^{+1}$ $2H_2O$	−11.4	11.2
$[Cu\text{-}[Citric\text{-}2H]]^{0}$ $2H_2O$	−10.2	12.4
$[Cu\text{-}[Citric\text{-}3H]]^{-1}$ $2H_2O$	−5.4	17.2

that citric acid is promising for copper chelation therapy (metal scavenger). In this sense, citric acid is not only safe as food additive but also it may improve the quality of the food.

Table 2
Gibbs free energies (kcal/mol, at 298.15 K) of the reactions of Cu(II) and citric acid (neutral and de-protonated) to produces Cu(I) and the correspondent free radical.

Reaction	ΔG
$[Citric] + [Cu(H_2O)_4]^{2+} \rightarrow [Citric]^{\cdot +1} + [Cu(H_2O)_4]^{1+}$	59.9
$[Citric\text{-}H]^{-1} + [Cu(H_2O)_4]^{2+} \rightarrow [Citric\text{-}H]^{\cdot 0} + [Cu(H_2O)_4]^{1+}$	8.7
$[Citric\text{-}2H]^{-2} + [Cu(H_2O)_4]^{2+} \rightarrow [Citric\text{-}2H]^{\cdot -1} + [Cu(H_2O)_4]^{1+}$	27.5
$[Citric\text{-}3H]^{-3} + [Cu(H_2O)_4]^{2+} \rightarrow [Citric\text{-}3H]^{\cdot -2} + [Cu(H_2O)_4]^{1+}$	4.0

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