Essential features for antioxidant capacity of ascorbic acid (vitamin C)

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Abstract
Vitamin C or ascorbic acid is an indispensable micronutrient for human health found principally on citrus species such as lemon and orange fruits and vegetables. It was involved in the production of proteins such as collagen. Its biochemical mechanism is related to its antioxidant capacity; however, its function at the cellular level is still unclear. Several theoretical studies about antioxidant and redox mechanisms for ascorbic acid were suggested; however, no derivative was proposed. Thereby, an electronic study of antioxidant capacity for ascorbic acid derivatives was performed using theoretical chemistry at the DFT/B3LYP/6-311 + + (2d,2p) level of theory. Simplified derivatives show that enol hydroxyls are more important than any other functional group. The vicinal enolic hydroxyl on β position is more important for antioxidant capacity of ascorbic than hydroxyl on α position. According to our molecular modifications, the keto-alkene compound showed the best values when compared to ascorbic acid in some molecular characteristics. No lactone derivatives have superior application potential as antioxidant when compared with ascorbic acid. Several structures are possible to be proposed and were related to spin density contributions and the increase of chemical stability. New promising structural derivatives related to ascorbic acid can be developed in the future.

Keywords Ascorbic acid · Antioxidant mechanism · Pharmacophore · DFT · Redox capacity

Introduction
Ascorbic acid (AA) or vitamin C is an essential micronutrient for human health, acquired mainly through citrus fruits, such as lemon and orange, and vegetables, with antioxidant activity and involved in the production of proteins such as collagen, although its function at the cellular level is still unclear [1, 2]. Its deficiency can cause hemorrhagic condition (scurvy) of the skin and gums with an attack on collagen in the connecting tissues [3, 4].

Chemically, the structure (Fig. 1) is composed of a lactone ring (in red) and two enolic hydroxyls (in green), in addition to a primary and a secondary alcohol group (in blue). The two intermolecular hydrogen bonds contribute substantially to the stability and chemical qualities of the molecule [5]. The enolic form of α-ketolactone, known as (R)-3,4-dihydroxy-5-((S)-1,2-dihydroxyethyl)-furan-2(5H)-one, is easily oxidized in the form of diketo (dehydroascorbic acid) and converted to oxalic acid, diketogulonic acid, or threonic acid [5]. AA is an electron donor and therefore a reducing agent, resulting from all its known physiological and biochemical actions. It has an ability to donate a hydrogen atom and form a relatively stable ascorbyl free radical, thanks to its low electron potential and resonance stability. Yet, it donates two electrons from a double bond between the second and third carbons of the 6-carbon molecule. In addition, it plays a role in purifying reactive oxygen species (ROSs) and nitrogen, superoxide, and ozone, among others, maintaining the intracellular redox balance and minimizing the oxidative damage caused by these free radicals [1, 3, 5–9].

AA has been widely used in the treatment and prevention of cancer, although its clinical results are still inconclusive. At low concentrations, it has an antioxidant role, preventing oxidation, which induces apoptosis [1, 10]. Physiological
concentrations of ascorbate demonstrated inhibition of LDL oxidation and a synergistic action with vitamin E preventing lipid oxidation of cell membranes [1, 11, 12].

Based on their activity, antioxidants can be categorized as enzymatic and non-enzymatic. Enzymatic antioxidants work by breaking down and removing free radicals. To understand the mechanism of action of antioxidants, it is necessary to understand the generation of free radicals and their damaging reactions [13].

AA changes to the ascorbate radical by donating an electron to the lipid radical to terminate the lipid peroxidation chain reaction. The pairs of ascorbate radicals react quickly to produce an ascorbate molecule and a dehydroascorbate molecule (without antioxidant activity), the latter being converted back to ascorbate by the addition of two electrons, probably due to the action of oxidoreductase [13, 14].

Despite the instability of ascorbic acid in solution has been known for almost a century, the kinetics and mechanism of degradation, along with the influence of experimental conditions are still debated and controversial. Product studies indicate that, under aerobic conditions in an aqueous environment, the stages of degradation of the formal oxidation of two electrons by molecular oxygen produce dehydroascorbic acid, which is hydrolyzed to diketogluconic acid and subsequently transformed into a variety of products [14–16].

### Methodology

All the calculations were performed with the Gaussian 09 molecular package [17]. The PM3 geometries [18] were optimized with the DFT/B3LYP hybrid density functional [19–21] by using the 6–311 + +G(2d,2p) basis set [22]. Based on lowest energy structures of neutrals (Mol or AA), cation free radicals (Mol•+ or AA•+), semiquinones (Mol• or AA•), and anion free radicals (Mol•−), four antioxidant mechanisms were explored. Reactive species such as cation free radical (RS•+) or semiquinone (RS•) are disassembled by means of electron or hydrogen scavenging. Usually, the single electron transfer (SET) and the hydrogen atom transfer (HAT) are the main antioxidant mechanisms; however, there are many others [23]. The ionization potential (IP) was calculated as the energy difference between a neutral molecule (Mol) and its respective anion free radical (1). The SET was calculated, as showed in Eq. 2, as a difference between ascorbic acid neutral and cation free radical (AA and AA•+) minus all other derivatives (Mol and Mol•+) [24–30]. The sequential proton lost electron transfer (SPLET) values were calculated as the difference between semiquinone (Mol•) and its respective anionic form (Mol−) (3). The bond dissociation energy of enol moiety (BDEOH) was calculated as the energy difference between a neutral molecule (Mol) and its respective semiquinone plus hydrogen (4). The HAT was calculated, as showed in Eq. 5, as a difference between ascorbic acid (AA) minus all other derivatives (Mol). The single electron acceptance (SEA) values were calculated as the difference between anion free radical (Mol−) and its respective quinone form (Molq) (6).

\[
\begin{align*}
\text{IP} & = \text{EMol}^{+} - \text{EMol} \\
\text{SET} & = (\text{EAA}^{+} + \text{EMol}) - (\text{EAA} + \text{EMol}^{+}) \\
\text{SPLET} & = \text{EMol}^{+} - \text{EMol}^{-} \\
\text{BDE}_{\text{OH}} & = (\text{EMol}^{+} + \text{EH}^{-}) - (\text{EMol}) \\
\text{HAT} & = (\text{EAA}^{+} + \text{EMol}) - (\text{EAA} + \text{EMol}^{+}) \\
\text{SEA} & = \text{EMol}^{+} - \text{EMolq}^{-}
\end{align*}
\]

All theoretical antioxidant mechanisms for ascorbic acid and its related derivatives are shown in Fig. 2, i.e., through electron transfer to the neutral (a), and anion forms (b), by hydrogen transfer (c), and by way of accepting to the electrons in quinone forms (d) [31].

In this study, the molecular modifications of ascorbic acid (1) are compared with their simplified derivatives by using molecular simplification on furanone system (2–5) and compared to furan ring derivatives (6–7), cycle-pentane derivatives (8–10), and lactone analogues (11–16). These compounds are showed in Fig. 3.

### Results and discussion

#### Molecular simplification

From the theoretical results described in Table 1, the ionization potential (IP) and single electron transfer (SET) values...
have indicated a lesser variation between ascorbic acid (1) and derivative 5 of 193.51 and 202.15 kcal/mol, when compared to compounds (2 and 3) without a hydroxyl (211.49 and 206.14 kcal/mol) or non-hydroxylated (210.17 kcal/mol) as observed in molecule 4, linked to the lactone ring. The same trend was observed for the transfer of a hydrogen, with enolic bond dissociation energy (BDE\textsubscript{OH}) values of 80.97 and 86.24 kcal/mol for ascorbic acid (1) and 82.75 and 87.20 kcal/mol for derivative 5, considering the \( \beta \) and \( \alpha \) position of the enolic group. In addition, according to the BDE\textsubscript{OH} values, 2 and 3 compounds showed the importance of the diol system due to the increase of BDE\textsubscript{OH} values to 91.70 and 99.99 kcal/mol. This agrees to IP values and explains the higher value of 210.17 kcal/mol for the PI of derivative 4 of ascorbic acid, which does not have the enolic hydroxyls.

According to these results, the 3,4-dihydro-furan-2-one system (5) is the most important and essential group for the antioxidant effect observed in ascorbic acid [32–34]. Consequently, similar structures that can be more potent than ascorbic acid in free radicals scavenging were proposed through molecular modifications [24, 27].

**Molecular modification on lactone**

Some molecular modifications were performed on the lactone ring including (i) the molecular simplification by removal of primary and secondary alcohol from the...
Fig. 3 Chemical structures of ascorbic acid (1) and its simplified derivatives (2–16)

Table 1 Theoretical parameters for ascorbic acid and related derivatives

| Compound | IP    | SET | BDE$_{\text{OH}}^a$ | BDE$_{\text{OH}}^b$ | HAT | SPLET | BDE$_{\text{OH}}^c$ | SEA  |
|----------|-------|-----|---------------------|---------------------|-----|-------|---------------------|------|
| 1        | 193.51| 0   | 86.24               | 80.97               | 0   |       | 72.12              | 70.14| −68.41          |
| 2        | 211.49| 17.97| −                   | 91.70               | 10.73| 87.66 | −                  | −    |               |
| 3        | 206.14| 12.63| 99.99               | −                   | 19.02| 70.41 | −                  | −    |               |
| 4        | 210.17| 16.66| −                   | −                   | −    | −     | −                  | −    |               |
| 5        | 202.15| 8.63 | 97.20               | 82.75               | 1.78 | 79.36 | 69.90              | −60.43|               |
| 6        | 184.30| −9.20| 76.94               | 76.94               | −4.03| 35.75 | 59.59              | −35.75|               |
| 7        | 225.99| 32.48| 97.64               | 97.64               | 16.67| 79.36 | 71.97              | −79.36|               |
| 8        | 199.01| 5.50 | 94.48               | 89.77               | 8.80 | 55.72 | 72.73              | −55.72|               |
| 9        | 186.29| −7.21| 77.61               | 77.48               | −3.49| 46.60 | 63.02              | −46.60|               |
| 10       | 167.99| −25.51| 70.21              | 70.21               | −10.75| 25.65 | 59.98              | −26.44|               |
| 11       | 190.39| 8.63 | 79.76               | 79.76               | −1.20| 50.06 | 67.72              | 49.15 |               |
| 12       | 196.50| 2.98 | 86.36               | 82.41               | 1.44 | 62.83 | 70.76              | −59.36|               |
| 13       | 198.31| 4.80 | 89.38               | 79.92               | −1.04| 67.49 | 73.48              | −62.66|               |
| 14       | 191.68| −1.82| 87.56               | 78.45               | −2.51| 57.61 | 70.68              | −53.51|               |
| 15       | 190.66| −2.84| 88.68               | 79.59               | −1.37| 68.00 | 74.41              | −61.87|               |
| 16       | 193.48| −0.02| 85.67               | 82.59               | 1.62 | 63.29 | 70.59              | −59.28|               |

BDE$_{\text{OH}}$ values: abstraction of hydrogen for (a) α position, (b) β position, and (c) quinone formation

saturated chain, (ii) the removal of carbonyl for the formation of the ether in simplified ring (6), (iii) the addition of a second carbonyl in the δ position for the formation of the anhydride derivative (7), and (iv) the modification of the lactone group to obtain an aliphatic (8), olefinic ketone (9), dienolic, or non-lactone derivative (10).

According to these proposals, the absence of the carbonyl group decreased the values of IP and BDE$_{\text{OH}}$ to 184.30 and 76.94 kcal/mol (6), and the presence of an extra carbonyl increased these values to 225.99 and 97.64 kcal/mol (7). These results are accompanied by the lower SET and HAT values of −9.20 and −4.03 kcal/mol (6) and higher values of 32.48 and 16.67 kcal/mol (7), respectively. The presence of the keto-alkene group (9) showed the best values of IP and BDE$_{\text{OH}}$ (186.29 and 77.48 kcal/mol) when compared to the keto-alkane compound (8), whose values increased to 199.01 and 89.77 kcal/mol. These results are also accompanied by the lower SET and
HAT values of −7.21 and −3.49 kcal/mol for keto-alkene (9) and higher SET and HAT values of 5.50 and 8.80 kcal/mol for keto-alkane (9).

The same disposition was observed for the SPLET mechanism and for the quinone (MolQ) formation, revealing 6 and 9 derivatives have the best performance by the lowest values for these properties of 35.75 and 59.59 kcal/mol (6) and 46.60 and 63.02 kcal/mol (9), respectively. Finally, according to the single electron acceptance (SEA) values for the quinone derivatives, the presence of the carbonyl group is important for the best values of 35.75 and 59.59 kcal/mol (6) and 46.60 and 63.02 kcal/mol (9), respectively. Thus, the keto-alkene 9 can be a good strategy on design of potent antioxidant related to ascorbic acid.

The non-lactone or dienolic derivative (10) showed the best performance for electron and hydrogen transfer. The absence of lactone group decreased the values of IP and BDE$_{OH}$ to 167.99 and 70.21 kcal/mol. These results were related to the lowest SET and HAT values of −25.51 and −10.75 kcal/mol. They showed the same behavior for SPLET and quinone formation due to the lowest values of 25.65 kcal/mol and 59.98 kcal/mol, respectively. However, they have the worst performance to redox capacity and the lowest SEA value of −26.44. These results show that the dienolic moiety is essential for the best antioxidant capacity of ascorbic acid by electron or hydrogen transfers, and lactone moiety is involved in increased of electron accepting capacity of quinone derivatives.

**Lactone analogues**

The exchange of oxygen for nitrogen, sulfur, or selenium on lactone analogues (10–16) did not show superior potential as an antioxidant when compared to ascorbic acid (1) by electron or hydrogen transfer mechanism. The IP values for lactam (11) and sulfur (15) derivatives through electron transfer were 190.39 kcal/mol and 190.36 kcal/mol, respectively. These results were accompanied by the lower SET values of −3.11 and −2.84 kcal/mol. Some derivatives had lower BDE$_{OH}$ values when compared to ascorbic acid except for compounds 12 and 16 (82.41 and 82.59 kcal/mol). All compounds (11–16) showed better values by SPLET mechanism. However, only lactam (11) derivative demonstrated the best value of BDE$_{OH}$ in the quinone formation (67.72 kcal/mol).

All SEA values by quinone reduction were lower and lactam (11) is the least reactive compound when compared to ascorbic acid. Its SEA value was of −49.15 kcal/mol. Thus, the lactone derivatives can be a good strategy for the development of antioxidant related to ascorbic acid.

**Spin density contributions**

The spin density calculations of free radical cations of ascorbic acid and some simplified derivatives that are related to the simplified lactone derivative 5 (Fig. 4) showed that 1,2-dienolic system has concentrated the greatest contributions. This region can be associated to the most nucleophilic moiety of all molecules. However, these spin density contributions are asymmetric since the largest contributions are in α carbon (0.25–0.36) when compared to β carbon (0.18–0.26). The only exceptions were compounds 10 and 11, which had the largest contribution to carbon β (0.30–0.34). Likewise, these spin density contributions are also asymmetric for the enol oxygens because the largest contributions are in the oxygen of α position (0.15–0.21) when compared to the oxygen in the β position (0.09–0.16). The compounds 6 and 7 are exceptions in these cases, which have a symmetric contribution in both oxygens (0.14–0.21).

In accordance with these results, the spin density contribution is the key to increasing free radical stability. Our
results showed that 2,3-dihydroxy-cyclopenta-2,4-dienone 9 is more stable than 3,4-dihydroxy-5H-furan-2-one 5. In fact, this molecule has an electronic behavior among all other related compounds. The extra spin density contribution in the alkene carbon is very expressive (0.27), decreasing all contributions on 1,2-dienolic system.

Likewise, these results agreed with the calculations of the spin density contributions of all compounds studied here for the semiquinone forms obtained after the loss of hydrogen from the β-position hydroxyl (Fig. 5). The spin density contributions are expressive over α carbon (0.46–0.53) when compared to β carbon (0.02–0.03). Also, the greater contributions were concentrated in the α oxygen (0.21–0.31) when compared to β oxygen (0.13–0.17) and are responsible for the asymmetry for the enol oxygens obtained in the spin density results. The exception of these cases is precisely the compound 9, which exhibits an inverse contribution, whose contributions in the α oxygen is greater than in the β oxygen (0.17–0.12).

**Chemical stability**

The spin density contributions are an excellent parameter to qualitatively determine the chemical stability of a free radical, so the most stable radicals are related to the largest number of resonance structures [35–39].

According to Fig. 6, our simplified derivative of ascorbic acid, 2,3-dihydroxy-cyclopenta-2,4-dienone 9, is the most stable derivative when compared to simplified derivative of ascorbic acid, 3,4-dihydroxy-5H-furan-2-one 5. These structures were based on the semiquinone forms of these two derivatives after homolytic dissociation of enolic hydrogen at the β-position.

Additionally, several structures could be proposed from the effects of 1,3 and 1,5 replacements of the radical charge, as well as the prototropic rearrangement among enol and keto groups. None of the other simplified derivatives of ascorbic acid showed the same performance when comparing chemical reactivity between electron and
Consent for publication  Yes.

Conflict of interest  The authors declare no competing interests.

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Conclusion

According to our obtained theoretical results, the ketoalkene compound showed the best values when compared to ascorbic acid. However, it is surprising the superiority of the redox property of ascorbic acid in comparison to the derivatives proposed in this work. The 3,4-dihydro-furan-2-one system is the most important and essential group for the antioxidant effect observed in ascorbic acid. Molecular modification on lactone has generated to the most interesting compounds. No similar lactone derivatives have shown superior application than ascorbic acid. 2,3-Dihydroxy-cyclopenta-2,4-dienone was the most potential core as antioxidant. Several structures are possible to be proposed based on the effects of the 1,3 and 1,5 replacements of the radical charge, as well as the prototropic rearrangement among enol and keto groups, and are related to spin density contributions and the increase of chemical stability. Except for SEA, all suggested molecules showed better values for the studied parameters. In this sense, it is possible that the best natural compounds that act as antioxidants have an average value for all properties, and ascorbic acid can be act by several antioxidant mechanisms.

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Declarations

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