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Single or double hydrogen atom transfer in the reaction of metal – Associated phenolic acids with •OH radical: DFT study

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ABSTRACT

Results of quantum chemical calculations based on B3LYP/6-31+G* are reported for 3,4-dihydroxyphenylpyruvic acid (3,4-DHPPA), 3,4-dihydroxycinnamic acid (3,4-DHCA) and 3,4-dihydroxybenzoic acid (3,4-DHBA) chelated with Cu^{2+}, Mg^{2+} and Ca^{2+}. These results are discussed in regard to the capacity of these phenolic acids (PAs) to scavenge free radicals in the presence or the absence of a metal ion. The O—H bond dissociation enthalpies, the HOMO eigenvalues, the NBO charges and the structural changes are parameters that seem to be the best indicators of the antiradical property of these PAs. These parameters indicate that the antioxidant activity of the PAs are ordered as follows: 3,4-DHPPA > 3,4-DHCA > 3,4-DHBA. The C_7=C_8 double bond, and the $O_8H_8\cdots O_9$ intramolecular hydrogen bond present in the side chain are influential in determining this activity. We also showed that the chelation with a metal ion led to the oxidation of the PAs and the reduction of the metal ion, a behaviour evidenced by charge transfer from the PAs to the ion. This tendency is more pronounced for the copper ion for which we registered a charge transfer of roughly 1.02e. Chelation with a metal ion led to important structural changes at the site of chelation and contributed to the decrease of the Bond Dissociation Enthalpy (BDE). It greatly facilitated the hydrogen atom transfer and consequently enhanced the antioxidant activity of the PAs.

1. Introduction

For many years, many experiments showed that free radicals are used as life support though their presence in biological cells and tissues is dangerous. When the free radicals generated in the body are short and their concentration low, the body metabolism may be disorganized which might cause some diseases [1].

Natural antioxidants, phenolics in particular, have been under very close scrutiny as potential therapeutic agents against diseases caused by the metabolism disorder: inflammatory diseases, cardiovascular dysfunctions, diabetes, cancer, cataracts, atherosclerosis, arthritis and ageing [2–8]. It is also well-known that phenolic compounds or polyphenols constitute one of the most numerous or ubiquitously distributed group of plant secondary metabolites, with more than 8000 phenolic structures currently known [2,9]. Among phenolic compounds, phenolic acids (PAs) and their derivatives are widely present in plants (vegetables, fruits, grains and spices) many of them being metabolites, and several functions being attributed to them [9]. PAs may contribute to particular properties such as: the dark color, bitter taste and objectionable flavour of some fruits, leaves and seeds, and have been considered as possible agents that influence toxicological, nutritional, sensory and antioxidant properties of foods [9]. They may also activate or inhibit microbial growth, depending on their constitution and concentration [9–11]. PAs present antioxidant activity exert this property through their capacity to donate hydrogen atoms and electrons to inhibit reactive oxygen species that act like free radicals.

3,4-Dihydroxybenzoic acid (3,4-DHBA) and 3,4-dihydroxycinnamic acid (3,4-DHCA) are two phenolic acids previously studied by our research group [9,12]. Their interests are reported elsewhere [13–21]. In our previous works on these two PAs, the emphasis was put on their reaction with some free radicals like •OH, $•O_2^-$ and $•HO_2$. The nature of the transfer occurring during the interaction of these PAs with the mentioned free radicals was clarified. We also studied the behaviour of the antioxidant activity with the increasing number of phenolic OH bonded to the benzyl ring (from 1 to 3). We have concluded that the introduction of a second hydroxyl group at the ortho position of 4-hydroxybenzoic acid (or 4-hydroxycinnamic acid) enhances the antioxidant activity of the resulting molecular system, as obtained in the past by several authors working on phenolic compounds possessing the same moiety. In contrast, the introduction of two OH groups at ortho and

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meta positions as to give 3,4,5-trihydroxybenzoic acid, contributes to a decrease of the antioxidant activity.

3,4-Dihydroxyphenylpyruvic acid (3,4-DHPPA) is a fragment of quercetine. The keto tautomer of 3,4-DHPPA and its fully acetoxyphenylpyruvic acid were extensively investigated by Lindén et al. [22–24]. They studied the effect of 3,4-DHPPA on the metabolism of 3,4-dihydroxyphenyl-L-alanine (commonly known as L-DOPA) in isolated perfused rat liver. They showed that, in rat, 3,4-DHPPA was transaminated to L-DOPA. The latter being well-known as a drug used in the treatment of Parkinson's disease. Lindén and Niemi [25] also showed, in the light of experiment undertaken in isolated perfused rat liver that, 3,4-DHPPA decreased the initial hepatic extraction and extended the elimination half-life of L-DOPA when they were added simultaneously at the ratio 1:4 (L-DOPA:3,4-DHPPA) to the perfusate. It was also shown to be useful as food additive for people with chronic uremia [26]. Furthermore, 3,4-DHPPA was reported to be an alternative substrate for mammalian 4-hydroxyphenylpyruvate dioxygenase, which gives competitive inhibition versus 4-hydroxyphenylpyruvate [27,28]. The enol tautomer of 3,4-DHPPA, which was less studied compared to the keto tautomer, was pointed out by Milane [29] as being the fragment of quercetine responsible for its higher antioxidant activity.

This work aims to check the claim of Milane about the degree of antioxidant activity conferred to quercetine by 3,4-DHPPA [29]. It will also answer the following open questions: (i) Is the hydrogen atom (or the proton) transfer process facilitated by the chelation of these PAs with a metal center? In other words, what is the behaviour of the antioxidant activity of these phenolic acids after their chelation with some metal ions? (ii) Does the presence of the $C_7{=}C_8$ unsaturation, and/or $O_8H_8\cdots O_9$ hydrogen bond in the side chain of the phenolic acid increase its antioxidant activity? To our knowledge, this work represents the first attempt of the use of quantum chemical tools for the study of the interaction of phenolic acids with a free radical, such as $^{\bullet}$OH radical, in the presence of a metal ion.

In the following pages of this paper, details of calculations are given in Section 2. In Section 3 are presented the results and discussion, which consists of structural analysis, the details on charge transfer induced by metal chelation, the Bond Dissociation Enthalpy (BDE) and the Highest Occupied Molecular Orbital (HOMO) analysis, then the description of the reaction of the PAs with $^{\bullet}$OH radical. The article ends with the conclusions.

2. Computational methods

Geometry optimizations of 3,4-DHBA, 3,4-DHCA and 3,4-DHPPA molecular systems were carried out using the density functional theory (DFT) methods implemented in the Gaussian 03W computational package [30]. DFT was chosen because of the excellent compromise between the computational time and the description of electronic correlation. Furthermore, for molecular systems involving hydrogen bonds, DFT behaves better than the Hartree–Fock method. Throughout our calculations, the B3LYP hybrid functional of the DFT method, which consists of the Becke's three parameters exact exchange functional (B3) [31] combined with the non-local gradient corrected correlation functional of Lee–Yang–Parr (LYP) [32] was used. The standard split valence double zeta gaussian basis set 6-31G of Pople and coworkers [33], supplemented by a set of *d* polarization function [34] and a set of single diffuse *s* function [35], on heavy atoms, was chosen and used throughout the computational process. Full geometry optimization was carried out with no symmetry constraints up to convergence (largest component of nuclear gradient equal to 10^{-6} a.u./bohr and the change in total energy less than 10^{-7} a.u.). A subsequent vibrational frequency calculation was undertaken in order to confirm that the resulting equilibrium geometries were transition states, local or global minima on the potential energy surface. The natural bond orbital (NBO) technique [36] was used for charge calculations.

3. Results and discussion

3.1. Structure

The labelling and numbering of the optimized geometries of the molecular systems studied are presented in Fig. 1. An inspection of the geometrical parameters of the three molecular systems, 3,4-DHBA, 3,4-DHCA and 3,4-DHPPA, reveals that the side chain induces only small changes in the benzyl ring. The maximum bond length difference is 0.2 Å and the maximum bond angle difference is 5.4°. These changes localized at the C_7—C_1(phenyl) linking region concerns the C_1—C_7 bond length, and C_6—C_1—C_7, C_6—C_1—C_2, C_2—C_1—C_7 bond angles.

Let us now analyze the changes occurring on the bare structure of the above listed phenolic acids after their chelation with one of the following metal ions: Mg^{2+}, Ca^{2+} and Cu^{2+}. Our calculations show that, complexation of 3,4-DHBA, 3,4-DHCA or 3,4-DHPPA with Mg^{2+}, Ca^{2+} or Cu^{2+} does not lead to drastic evolution of structural parameters of the benzyl ring or the side chain. The maximum bond length and bond angle differences registered are 0.06 Å and 6°, respectively. It is worth mentioning that the changes occurring after the chelation with the metal ion only affects the site of chelation. We noticed that the C_3—O_3, C_4—O_4, O_3—H_3 and

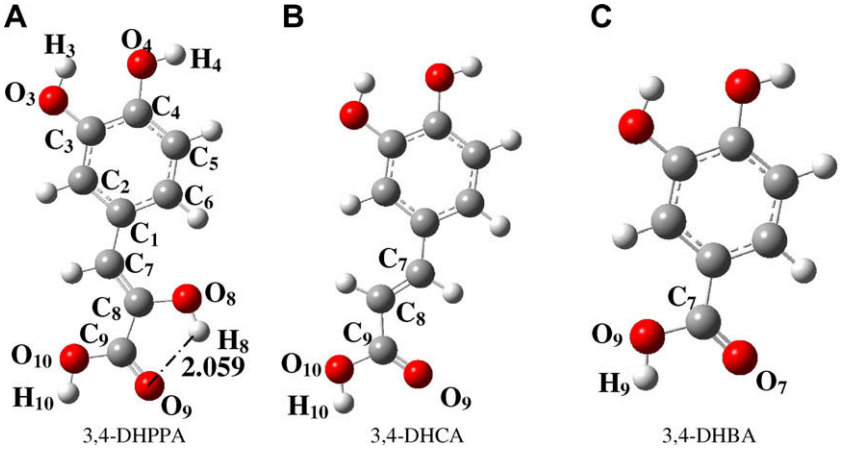

Fig. 1. Equilibrium geometries of 3,4-dihydroxyphenylpyruvic acid (A), 3,4-dihydroxycinnamic acid (B) and 3,4-dihydroxybenzoic acid (C) as derived from B3LYP/6-31+G* calculations.

O_4—H_4 bond lengths near the chelation site are substantially perturbed due to the strong interaction with the metal ion. The O—H bond lengths slightly increase from Ca^{2+} to Cu^{2+}, through Mg^{2+}, meaning that there exists a correlation between this O—H elongation and the electronegativity of the metal ion. One can keep in mind that, the more electronegative the metal ion, the longer the O—H bond. These elongations of O—H bonds upon metal ions chelation show that chelation weakens the O—H bonds and consequently facilitates hydrogen atom abstraction or proton transfer. As for O—H bonds, chelation of C—O bonds with Mg^{2+} or Ca^{2+} leads to an elongation ranging between 0.05 and 0.08 Å. In contrast, chelation with Cu^{2+} leads to slight elongation of C_3—O_3 and slight shortening of C_4—O_4, in the same range (roughly ±0.02 Å).

After a single hydrogen abstraction on a metal-associated phenolic acid, the perturbation occurs at the region of abstraction. First of all, we noticed that the metal ion came close to the oxygen atom where the hydrogen abstraction was done, and then, adopted a more important dissymmetric position with respect to O_3—C_3—C_4—O_4. This dissymmetry was more pronounced for copper and magnesium ions, so that the resulting complex was almost monodentate (see Table 1 and Fig. 2). After a double hydrogen abstraction at positions 3 and 4, we noticed a simultaneous shortening of C_3—O_3 and C_4—O_4 bonds. These two bonds almost became carbonyl (C=O) bonds, particularly for copper complexes. In addition, the resulting complexes were nearly bidentate. The M—O_3(O_4) distance, where M is the metal ion, was in the range: 1.91–1.98 Å for Mg^{2+}, 2.25–2.33 Å for Ca^{2+} and 2.01–2.14 Å for Cu^{2+}.

3.2. Charge transfer induced by metal chelation

In this work, we have three cases of metal ions (Mg^{2+}, Ca^{2+} or Cu^{2+}) chelating with phenolic acids at the oxygen atoms of the catechol functional group. Optimization of our models led to complexes in which the metal ions bore a charge. The values of these charges reported in Table 2, showed that the net charge carried by the metal ion was in the range: +(1.95–1.97)e for magnesium atom, +(1.60–1.89)e for calcium atom, and +(0.96–1.23)e for copper atom. Except for two cases, one for calcium atom (+1.60e) and the other for copper atom (+1.23e) in which we noticed a discrepancy, it could be considered that the metal ion carried approximately the same net charge. These values of the net charges of the metal ion confirmed that the latter has undergone a reduction while the substrate (phenolic acid) has undergone an oxidation. This shows a charge transfer from the substrate to the metal ion which increases with the electronegativity of the metal ion, and confirms that the metal ion plays an oxidation role towards the phenolic acid. This result turns out to be consistent with the observations done on quercetin, and reported by Fiorucci [37].

3.3. Bond Dissociation Enthalpy (BDE) and Highest Occupied Molecular Orbital (HOMO)

Knowing that the phenolic protons were more acidic than the carboxylic protons [9,12,38–40], the antioxidant potency of phenolic substances was connected to the phenolic O—H Bond Dissociation Enthalpy (featuring the facility of hydrogen abstraction). In this work, the O—H Bond Dissociation Enthalpy (BDE) was calculated as the difference in total enthalpy (the sum of the thermal corrected enthalpy and the total electronic energy) between the phenolic acids (3,4-DHBA, 3,4-DHCA or 3,4-DHPPA) and the corresponding radical (formed after hydrogen abstraction at a precise site), according to the following reaction:

$$ROH \rightarrow RO^{\bullet} + H^{\bullet} \quad (1)$$

The calculated BDE values for some radicals obtained after one (or two) phenolic hydrogen abstraction(s) are reported in Table 2. These values led to the conclusion that 3,4-DHPPA displays the ability of losing its phenolic hydrogens (at 3-OH or 4-OH positions) more easily than 3,4-DHCA or 3,4-DHBA. The BDE values for a single or a double hydrogen atom abstraction are ordered as follows: $BDE_{3,4\text{-DHPPA}} < BDE_{3,4\text{-DHCA}} < BDE_{3,4\text{-DHBA}}$, showing that the ordering for antioxidant activity of these phenolic acids is 3,4-DHPPA > 3,4-DHCA > 3,4-DHBA. This order may be explained by the presence of the C_7=C_8 double bond in the side chain of 3,4-DHCA, and the presence of both the C_7=C_8 double bond and the intramolecular hydrogen bond O_8—H_8···O_9 in the side chain of 3,4-DHPPA. The unsaturated double bond and the intramolecular hydrogen bond between O_8—H_8 and O_9 are influential in determining the antioxidant activity. They are responsible of a more important electron withdrawing from the benzyl ring to the side chain. This leads to the weakening of the phenolic O—H bonds, and consequently explains the smaller BDE calculated. These results support the findings of Soobrattee et al. [2] who proposed that the electron withdrawing of a single carboxyl functional group attached to phenol ring dampens the O—H donation capacity of the hydroxyl group. They are also consistent with the conclusions of Cuvelier et al. [42] who suggested that the presence of CH=CH—COOH group in cinnamic acids ensures greater efficiency than COOH group in benzoic acids. The difference between 3,4-DHPPA and 3,4-DHCA is the substitution of H_8 by O_8—H_8, which establishes the hydrogen bond O_8—H_8···O_9 between this O_8—H_8 group and the carbonyl C_9=O_9, the latter having a strong stabilizing effect in the resulting molecule. This may explain why the BDE of 3,4-DHPPA is smaller than that of 3,4-DHCA.

In the case of metal ion-associated phenolic acids, we noticed that chelation contributes to a decrease of the BDE. This decrease is more important for Mg^{2+} and Ca^{2+} and less important for Cu^{2+}. Interestingly, chelation with the first two metal ions (Mg^{2+} and Ca^{2+}) led to a small net charge transfer from the phenolic acid to the metal ion (roughly 0.04e for Mg^{2+} and 0.4e for Ca^{2+}), while for Cu^{2+} it led to an important net charge transfer (1.02e). For this reason, we have divided the metal ions chelated into two categories. The first category consists of Mg^{2+} and Ca^{2+} and the second one of Cu^{2+}. In the first category, we have registered a decrease of the BDE by 34.7 kcal/mol for 3,4-DHPPA+Mg^{2+}, and by 31.3 kcal/mol for 3,4-DHPPA+Ca^{2+}. We assigned the decrease of BDE to an increase of the antioxidant activity. This seems to be consistent with the more important elongation of O_3H_3 and O_4H_4 induced by chelation with Mg^{2+} and Ca^{2+}, which also means that chelation with Mg^{2+} and Ca^{2+} led to an important weakening of O_3H_3 and O_4H_4 bonds. In the second category, chelation induces oxidation of the phenolic acid moiety and the reduction of the metal ion, as well as the decrease of the BDE. These last three properties put together may be viewed to some extent as characteristics of increase of antioxidant and prooxidant activities of the molecule.

Molecular electron-donating ability was characterized by the Highest Occupied Molecular Orbital (HOMO) eigenvalues; the higher the HOMO eigenvalue, the higher the antioxidant activity [9,12,41]. The computed HOMO eigenvalues of 3,4-DHBA, 3,4-DHCA, 3,4-DHPPA, 3,4-OHBA, 3,4-OHCA and 3,4-OHPPA are reported in Table 1. These values show that E_{HOMO}(3,4-DHPPA) > E_{HOMO}(3,4-DHCA) > E_{HOMO}(3,4-DHBA) and E_{HOMO}(3,4-OHPPA) > E_{HOMO}(3,4-OHCA) > E_{HOMO}(3,4-OHBA). The comparison of the HOMO eigenvalues confirms that the ordering for antioxidant activity of these PAs is 3,4-DHPPA > 3,4-DHCA > 3,4-DHBA and 3,4-OHPPA > 3,4-OHCA > 3,4-OHBA. This order does not change upon chelation with a metal ion.

The ordering of antioxidant activity for the above listed PAs done on the basis of the HOMO eigenvalues was consistent with the one obtained using the BDE and the geometrical structure. These correlations agree with the conclusions of Zhang who

Table 1
Some selected bond lengths (Å) and bond angles (°) of (3,4-DHPPA, 3,4-OHPPA, 3,4-OOPPA) + (Mg^{2+}, Ca^{2+}, Cu^{2+}) as derived from B3LYP/6-31+G*.

Parameters	3,4-DHPPA	3,4-DHPPA + Mg^{2+}	3,4-DHPPA + Ca^{2+}	3,4-DHPPA + Cu^{2+}	3,4-OHPPA	3,4-OHPPA + Mg^{2+}	3,4-OHPPA + Ca^{2+}	3,4-OHPPA + Cu^{2+}	3,4-OOPPA	3,4-OOPPA + Mg^{2+}	3,4-OOPPA + Ca^{2+}	3,4-OOPPA + Cu^{2+}
Bond lengths												
C_1—C_2	1.41	1.42	1.42	1.43	1.42	1.44	1.44	1.44	1.37	1.42	1.41	1.42
C_2—C_3	1.39	1.38	1.38	1.37	1.38	1.36	1.36	1.36	1.46	1.38	1.39	1.44
C_3—C_4	1.41	1.39	1.39	1.42	1.47	1.43	1.44	1.49	1.56	1.52	1.53	1.54
C_4—C_5	1.39	1.39	1.39	1.40	1.45	1.42	1.42	1.46	1.47	1.44	1.45	1.46
C_5—C_6	1.39	1.39	1.39	1.38	1.37	1.38	1.37	1.35	1.35	1.35	1.35	1.36
C_1—C_6	1.41	1.42	1.42	1.43	1.44	1.44	1.44	1.47	1.48	1.49	1.49	1.47
C_1—C_7	1.46	1.44	1.45	1.42	1.44	1.42	1.42	1.40	1.45	1.41	1.42	1.41
C_9—O_{10}	1.35	1.33	1.34	1.32	1.35	1.33	1.33	1.32	1.34	1.32	1.32	1.32
C_8—C_9	1.48	1.51	1.50	1.52	1.48	1.52	1.32	1.54	1.49	1.53	1.52	1.54
C_7—C_8	1.35	1.37	1.36	1.40	1.37	1.40	1.39	1.41	1.36	1.40	1.39	1.42
C_9=O_9	1.23	1.21	1.21	1.21	1.22	1.21	1.21	1.21	1.22	1.21	1.21	1.21
C_4—O_4	1.38	1.42	1.44	1.37	1.25	1.31	1.30	1.24	1.22	1.27	1.25	1.23
C_3—O_3	1.37	1.43	1.44	1.38	1.34	1.43	1.42	1.34	1.22	1.30	1.28	1.24
O_3—Metal		2.00	2.32	2.11		2.01	2.42	2.53		1.91	2.25	2.08
O_4—Metal		2.01	2.31	2.15		1.87	2.19	1.94		1.97	2.33	2.13
O_3—H_3	0.969	0.977	0.976	0.975	0.986	0.976	0.975	0.977				
O_4—H_4	0.966	0.978	0.976	0.977								
O_8—H_8	0.975	0.980	0.994	0.991	1.000	0.980	0.998	0.994	0.971	0.998	0.994	1.003
Angles												
C_1—C_2—C_3	121.3	119.2	120.2	120.2	120.2	118.7	119.5	120.4	122.3	120.4912	120.7287	120.2978
C_2—C_3—C_4	119.4	121.6	121.3	120.2	121.6	123.5	123.0	120.6	117.1	118.8173	118.6231	118.8569
C_3—C_4—C_5	120.1	120.7	120.0	120.8	116.7	117.6	117.1	118.2	116.6	120.2107	119.5173	117.8614
C_4—C_5—C_6	120.5	118.6	119.5	119.6	120.9	120.3	120.8	120.4	121.5	118.7124	118.9485	120.5197
C_5—C_6—C_1	120.2	121.4	121.6	121.5	121.2	122.6	122.0	122.4	123.0			
C_6—C_1—C_2	118.4	118.2	117.6	118.5	119.1	118.3	118.1	119.2	119.8	119.7801	119.8282	119.3889
C_6—C_1—C_7	124.0	124.2	124.3	124.3	123.4	124.6	124.6	123.7	121.9	122.2889	121.8301	124.6708
C_1—C_7—C_8	129.3	127.9	127.4	128.9	129.7	128.7	128.7	128.7	129.8	129.4270	129.4617	128.8459
C_7—C_8—C_9	123.3	123.7	123.5	123.3	123.1	123.9	123.7	123.4	122.7	123.2137	123.0304	123.9094
C_8—C_9—O_{10}	116.0	114.4	114.9	113.8	115.7	114.0	114.3	113.7	115.6	113.8644	114.1783	113.2881
C_8—C_9=O_9	121.3	118.6	119.5	117.5	120.9	118.0	118.5	116.9	120.6	117.1365	117.7479	116.5356
C_9—O_{10}—H_{10}	106.9	109.5	108.7	110.5	107.3	110.1	109.7	111.0	107.6	110.7857	110.2247	111.4703
C_3—C_4—O_4	115.3	115.1	117.6	115.7	118.0	119.7	119.3	120.6	120.4	117.2653	117.1562	117.3299
C_4—O_4—H_4	110.8	112.1	108.6	113.2								
C_3—O_3—H_3	108.7	112.2	108.7	113.1	105.2	112.9	110.0	113.7				
O_3—C_3—C_2	119.8	123.7	121.7	124.6	122.5	123.8	123.5	127.0	122.7	125.4244	125.9782	123.1507
C_1—C_7—H_7	115.9	117.2	117.0	117.4	116.0	117.5	117.3	117.8	115.4	117.0165	116.6556	117.5322
C_7—C_8—O_8	124.0	123.8	124.1	123.3	124.2	123.4	123.6	124.5	125.1	124.7764	125.0294	123.5157
C_8—C_7—H_7	114.8	114.9	115.6	113.7	114.3	113.8	113.9	113.5	114.8	115.5419	113.8828	113.6219
C_9—C_8—O_8	112.7	112.6	112.7	112.7	112.1	112.2	112.3	111.9	112.6			
C_8—C_9—O_9	121.3	118.6	119.5	117.5	120.9	118.0	118.5	116.9	120.6	119.0862	117.7479	116.5356
O_9—C_9—O_{10}	122.7	127.0	125.6	128.7	123.4	128.0	127.3	129.5	123.8	126.3346	128.0739	130.1762

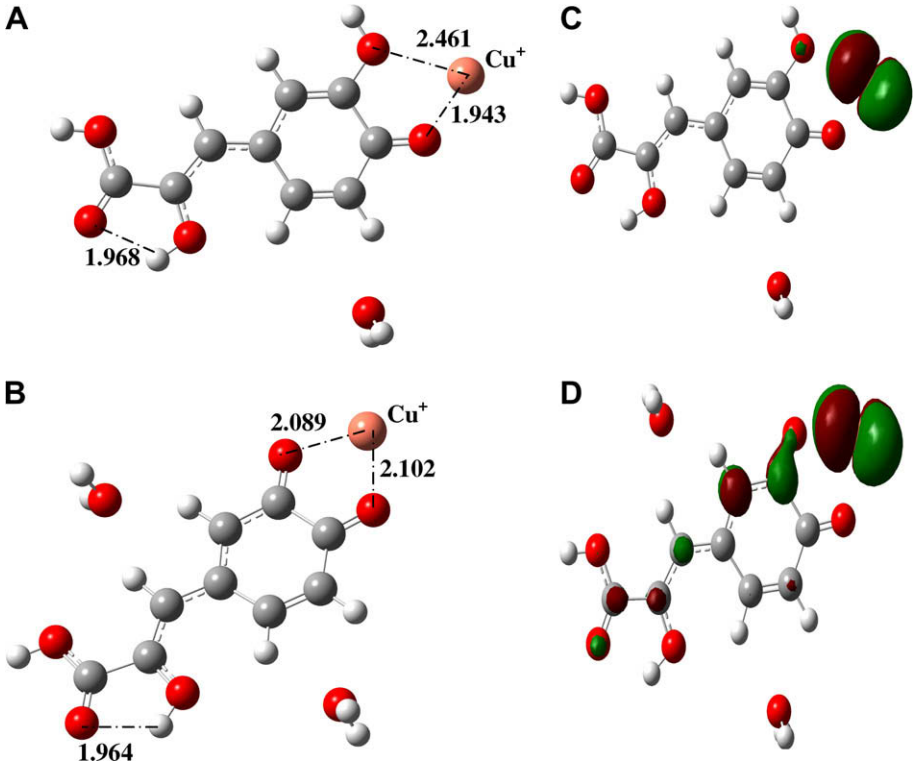

Fig. 2. Equilibrium geometries of the structures resulting from the reaction of 3,4-DHPPA with one •OH radical (A) or two •OH radicals (B), in the presence of an explicit Cu^{2+} ion. •OH radical(s) is (are) put nearby the attacked site(s) and the optimization is undertaken without restriction upon convergence. Calculations are made at the B3LYP/6-31+G* level. The corresponding HOMO distributions are given in (C) and (D), respectively for one and two •OH radical attacks.

showed in a recent review article [43] that there exists a good correlation between the BDE and many structurally relevant parameters.

3.4. Reaction of phenolic acids with •OH radical

According to our previous works on hydroxybenzoic acids [9] and hydroxycinnamic acids [12], the BDE for 3-OH position is greater than that for 4-OH position. This showed that the hydrogen atom at position 4-OH on the catechol functional group might be easily detached upon an interaction with a free radical. Moreover, experiments undertaken on hydroxybenzoic acids and their derivatives by Yassin and Marynick [38] and reported later by Meffert et al. [39], and Gimon et al. [40], revealed that phenolic hydrogen atoms were more acidic than the carboxylic one. In regard to this, our observations are restricted to the •OH radical attack at 4-OH position (for a single hydrogen atom transfer), and at 3-OH and 4-OH sites (for a double hydrogen atom transfer), in presence of a metal ion. We will present below only the case of the copper ion in which we have observed an important charge transfer (of roughly 1.02e). The interaction of the phenolic acid with one free •OH radical, in the presence of Cu^{2+} metal ion is summarized by Eq. (2):

$$ROH + {}^{\bullet}OH + Cu^{2+} \rightarrow RO^{+} + H_2O + Cu^{+}. \quad (2)$$

A careful inspection of the resulting structures after the •OH radical attack revealed a shortening of the C_4—O_4 bond which became 1.246 Å, and the complete detachment of the hydrogen H_4. This detached hydrogen atom was then rapidly attached to the •OH radical by a reaction of addition so as to form a water molecule. After the formation of H_2O, the site C_4—O_4 became hydrophobic and pushed the H_2O molecule very far i.e. at a distance above which there exists no interaction between H_2O molecule and the C_4—O_4 site (see Fig. 2(A)). The same behaviour was observed for two •OH radicals attacking 3,4-DHPPA at sites 3-OH and 4-OH. C_3—O_3 and C_4—O_4 bonds became short, almost double (i.e. C_3═O_3 (1.242 Å), C_4═O_4 (1.236 Å)) and showed also a hydrophobic character, so that they pushed both water molecules very far (see Fig. 2(B)).

The NBO net charge carried by the copper atom was +0.97e for a single hydrogen atom abstraction and +0.98e for a double hydrogen atom abstraction. In addition, the phenoxyl moiety bore a net charge of roughly +1e and water molecules were neutral. These net charge values were nearly the same for the chelation of copper with 3,4-DHBA or 3,4-DHCA (see Table 2). It could thus be considered that throughout the process of hydrogen atom (or proton) transfer, the substrate remained oxidized and the copper atom had a formal oxidation state of +1. By considering this result together with the BDE, HOMO and structural analysis, it could be said that the copper atom played its oxidizing role before the reaction and along the reaction mechanism. This behaviour was in agreement with that observed on copper–associated quercetin by Fiorucci et al. [37]. The key role played by copper was also supported by the HOMO distribution which was highly localized on this metal ion (see Fig. 2(C and D)).

As far as the structures resulting from the reaction of 3,4-DHPPA, 3,4-DHCA or 3,4-DHBA with •OH are concerned, we noted that the presence of the metal ion facilitates this reaction and consequently contributes to an increase of the antioxidant activity.

4. Conclusion

In this paper, we have used the B3LYP/6-31+G* theoretical method to study the influence and the role of metal ions on the antioxidant activities of some phenolic acids (3,4-dihydroxybenzoic acid (3,4-DHBA), 3,4-dihydroxycinnamic acid (3,4-DHCA), and 3,4-dihydroxyphenylpyruvic acid (3,4-DHPPA)), as well as

Table 2
Bond Dissociation Enthalpy (BDE) for single hydrogen atom transfer (SHAT) and double hydrogen atom transfer (DHAT) as derived from B3LYP/6-31+G* calculations using the sum of electronic energy (Ee) and thermal corrected enthalpy (TCE); the NBO charge (q/e) carried by the metal ion, the HOMO eigenvalue (eV).

Molecular system	Ee + TCE	BDE_{SHAT}	BDE_{DHAT}	q/e	$-E_{HOMO}$
H	−0.4950				
3,4-DHBA	−571.1529				6.37
3,4-$OHBA_4$	−570.5252	83.27*			6.53
3,4-$OHBA_4$	−570.5388	74.74			6.61
3,4-$OOBA_{34}$	−569.9262		148.54		7.43
3,4-DHCA	−648.5230				6.18
3,4-$OHCA_4$	−647.8998	80.50*			6.26
3,4-$OHCA_4$	−647.9136	71.80			6.31
3,4-$OOCA_{34}$	−647.2979		147.57		7.31
3,4-DHPPA	−723.7421				5.82
3,4-$OHPPA_4$	−723.1217	78.74*			5.80
3,4-$OHPPA_4$	−723.1358	69.87			5.90
3,4-$OOPPA_{34}$	−722.5220		144.47		6.99
3,4-DHBA + Ca^{2+}	−1248.1579			1.965	13.31
3,4-$OHBA_4$ + Ca^{2+}	−1247.5567	66.64		1.958	14.20
3,4-$OOBA_{34}$ + Ca^{2+}	−1246.9592		131.01	1.955	14.53
3,4-DHCA + Ca^{2+}	−1325.5310			1.964	12.16
3,4-$OHCA_4$ + Ca^{2+}	−1324.9501	53.94		1.954	13.12
3,4-$OOCA_{34}$ + Ca^{2+}	−1324.3523		118.48	1.949	13.61
3,4-DHPPA + Ca^{2+}	−1400.7631			1.963	11.56
3,4-$OHPPA_4$ + Ca^{2+}	−1400.1926	47.45		1.950	12.35
3,4-$OOPPA_{34}$ + Ca^{2+}	−1399.5989		109.37	1.944	13.31
3,4-DHBA + Mg^{2+}	−770.6043			1.887	13.88
3,4-$OHBA_4$ + Mg^{2+}	−770.0085	63.32		1.882	14.86
3,4-$OOBA_{34}$ + Mg^{2+}	−769.4100		128.30	1.869	15.51
3,4-DHCA + Mg^{2+}	−847.9811			1.773	13.01
3,4-$OHCA_4$ + Mg^{2+}	−847.4082	48.88		1.873	13.88
3,4-$OOCA_{34}$ + Mg^{2+}	−846.8117		117.62	1.858	14.29
3,4-DHPPA + Mg^{2+}	−923.2198			1.596	12.60
3,4-$OHPPA_4$ + Mg^{2+}	−922.6547	44.00		1.863	13.12
3,4-$OOPPA_{34}$ + Mg^{2+}	−922.0641		104.06	1.846	14.12
3,4-DHBA + Cu^{2+}	−2210.8060			0.969	15.67
3,4-$OHBA_4$ + Cu^{2+}	−2210.1928	74.15		1.024	15.89
3,4-$OOBA_{34}$ + Cu^{2+}	−2209.5530		165.05	1.229	16.71
3,4-DHCA + Cu^{2+}	−2288.2118			0.961	14.48
3,4-$OHCA_4$ + Cu^{2+}	−2287.6019	72.14		0.987	14.80
3,4-$OOCA_{34}$ + Cu^{2+}	−2286.9721		156.75	0.995	14.83
3,4-DHPPA + Cu^{2+}	−2363.4614			0.960	13.90
3,4-$OHPPA_4$ + Cu^{2+}	−2362.8588	67.53		0.973	14.86
3,4-$OOPPA_{34}$ + Cu^{2+}	−2362.2274		153.14	0.995	14.72

BDE, Bond Dissociation Enthalpy in kcal/mol.
H, Hydrogen atom.
3,4-DHBA, 3,4-dihydroxybenzoic acid.
3,4-DHCA, 3,4-dihydroxycinnamic acid.
3,4-DHPPA, 3,4-dihydroxyphenylpyruvic acid.
3,4-$OHBA_4$, 4-quinone corresponding to hydrogen abstraction at position 4 of the 3,4-DHBA.
3,4-$OHCA_4$, 4-quinone corresponding to hydrogen abstraction at position 4 of the 3,4-DHCA.
3,4-$OHPPA_4$, 4-quinone corresponding to hydrogen abstraction at position 4 of the 3,4-DHPPA.
3,4-$OOBA_{34}$, 3,4-quinone corresponding to hydrogen abstraction at positions 3 and 4 of the 3,4-DHBA.
3,4-$OOCA_{34}$, 3,4-quinone corresponding to hydrogen abstraction at positions 3 and 4 of the 3,4-DHCA.
3,4-$OOPPA_{34}$, 3,4-quinone corresponding to hydrogen abstraction at positions 3 and 4 of the 3,4-DHPPA.
* Calculated in the geometry for which the hydrogen atom H_3 is not in between O_3 and O_4 ($H_3—O_3—C_3—C_4 = 180°$).

the changes occurring in their structures after their reactions with the •OH radical in the presence of a metal ion.

The computed O—H bond dissociation enthalpies, and the HOMO eigenvalues have shown that the antioxidant activity of the phenolic acids studied is ordered as follows: 3,4-DHPPA > 3,4-DHCA > 3,4-DHBA and this result confirms that the presence of the $C_7=C_8$ unsaturation, and/or $O_8H_8\cdots O_9$ intramolecular hydrogen bond in the side chain of the phenolic acid increases the antioxidant activity of the molecular system.

The calculated NBO charges clearly confirm that the chelation of a metal ion induces simultaneously the oxidation of the substrate and the reduction of the metal ion. This oxidation is evidenced by charge transfer from the substrate to the metal ion, particularly in the case of Cu^{2+} where the formal charge transferred is roughly 1.02e. This oxidizing role of the metal ion remains before and throughout the process of hydrogen atom transfer. Furthermore, the chelation of a metal ion with a phenolic acid greatly facilitates the reaction of the resulting complex with a free radical.

Knowing that solvents have an important influence on the antioxidant activity of flavonoids and phenolic acids (what is not the aim of this study), we intend to publish in a forthcoming article, an extended work specially devoted to the details of the solvent effects on the activity of PAs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.theochem.2008.12.046.

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