Structural Chemistry (2020) 31:359–369
https://doi.org/10.1007/s11224-019-01411-z

ORIGINAL RESEARCH

DFT study of antioxidant molecules from traditional Japanese and Chinese teas: comparing allylic and phenolic antiradical activity

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Received: 7 March 2019 / Accepted: 5 August 2019 / Published online: 23 August 2019

Abstract

Quantum chemistry calculations were performed to compare the reactivity indexes obtained within the conceptual density functional theory of phenolic and allyl-phenolic molecules and investigated in order to elucidate their antioxidant activity. Selected molecules share allyl and OH phenolic moieties, which can donate hydrogen atoms to highly reactive oxidant species. As a result, they inhibit or decrease the oxidative cycle. The calculation of bond dissociation energy relates this capability, together with reactivity indexes of the radicals produced, in order to measure and compare their stability. These indexes indicate a clear difference between these sets of structures with higher stability manifested by the allyl-phenolic-produced radicals.

Keywords Conceptual DFT · Bond dissociation energy · Antioxidant · Radical · Asian tea · Allyl phenol

Introduction

Antioxidants are frequently known as playing a role in the reduction of symptoms of aging, cardiovascular illness, and neurodegenerative diseases, such as Alzheimer's and Parkinson's. Nowadays, these compounds are considered to be almost a panacea, promoting certain misconceptions in popular culture [1]. The first action of antioxidants is to reduce or neutralize reactive oxygen species (ROS) and thus decrease their oxidative process. Typical examples of ROS are OH, OOH, and NO_x radicals and O_2 singlet. These chemicals produce the so-called oxidative stress: resulting from an imbalance between the production of this oxidative species and its quenching by living beings. However, several biological processes implicate ROS; for example, the reduction of phagocytosis and ribonucleotides [2–4]. Phenolic- and allyl-derived compounds represent the main types of antioxidant molecules in experimental and computational studies. Both are arising from several natural vegetable sources [5]. Apart from the rigidity of their aromatic rings, phenolic compounds can also act as antioxidants because of the presence of hydroxyl and allyl groups [6, 7]. In addition to manifesting various biological activities, phenolic compounds often play crucial roles in food processing [8] which can be found in [9, 10] the form of complexes with other food components, such as protein and lipids, via hydrogen-bonding interactions. These components lead to changes in the physicochemical properties of the latter; for example, solubility, thermal stability, and digestibility. Some recent computational studies have been carried out on hydroxycinnamic acids [4], quercetin, and edaravone (both with DFT benchmark) [11], as well as catechin [12], flavones and flavonids [13], gallic acid [14], myricetin [13], pyranine [15], oxygenated terpenoids [16], and quinazoline derivatives [17]. Likewise, there are excellent reviews written about phenolic antioxidants [18, 19].

Plants represent an essential source of antioxidants, which are also commonly imbibed in tea. Asia is the leading producer of tea, and, in China and Japan, it is extensively utilized in their traditional medicine [20]. In Japan, these are called Kampo drugs, and their use recently has a boost because they have been mixed in modern medicine [21]. Besides, the antiviral activities of phenolic compounds from natural sources have been studied. For example, several phenolic compounds exhibit anti-HIV [22], can accomplish anti-tobacco mosaic virus activities, or even inhibit chikungunya and dengue virus replication [23]. Interestingly in [24], activities of phenolic

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11224-019-01411-z) contains supplementary material, which is available to authorized users.

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compounds against the encephalomyocarditis virus were evaluated, indicating the number of phenolic hydroxyl groups significantly affects antiviral activity. Substituents also affect the antiviral activity of the compounds. Moreover, the relative position of functional groups also plays a crucial role in viral inhibition activity. This paper focuses on molecules on phenolic and allyl functional groups, for which antioxidant activity has been reported [25] (see Chart 1 for the studied molecules). A few questions were proposed concerning these compounds. For example are the following: Which of these two functional groups increase antioxidant activity? Which is the better antioxidant? Does the presence of both enhance antioxidant capacity? Which moiety produces the most stable radical following an H atom donation? With these questions in mind, we calculated two proposed antioxidant mechanisms—hydrogen atom transfer and single electron transfer. The first one, which refers to hydrogen atom transfer (HAT) consists in that the antioxidant molecule donates an H atom to the ROS, neutralizing its reactivity. Bond dissociation enthalpy (BDE) measures this reactivity, which involves breaking the –H bond [26, 27]. For the present paper, we considered both results from the breakdown of the phenolic O-H bond and breakdown of the H-allyl bond. Generally, the computed BDE values can compare to the corresponding one from phenol, as a representative molecule.

$$\mathrm{AntOH} + \mathrm{R}^{\bullet} \rightarrow \mathrm{AntO}^{\bullet} + \mathrm{RH} \quad (1)$$

The second antioxidant mechanism studied in this paper is the Single Electron Transfer (SET). In this mechanism, there is a complete electron donation to the free radical. The viability of the mechanism relates to ionization energy (IE): in the case of an effective antioxidant, this quantity has a low value. Results are also usually compared to that of phenol [26]:

$$\mathrm{AntOH} + \mathrm{R}^{\bullet} \rightarrow \mathrm{AntOH}^{\bullet+} + \mathrm{R}^{-} \quad (2)$$

Antioxidant molecules manifest two critical features—the viability of electron donation to the free radical and the stability, or low reactivity, of the new radical formed by the antioxidant mechanism. BDE helps to measure the first one, as in thermodynamic terms, it shows how easily radical hydrogen donation is carried out by the antioxidant molecule. The second is related to conceptual DFT parameters, such as IE, hardness, electronegativity, and electrophilicity, thus measuring efficiency in terms of electron donation–acceptation. Concerning the stability and low reactivity of the radicals produced, we have calculated DFT reactivity indexes in order to analyze the chemical behavior of these species and compare phenolic and allylic radicals with well-known oxidant and antioxidant radicals.

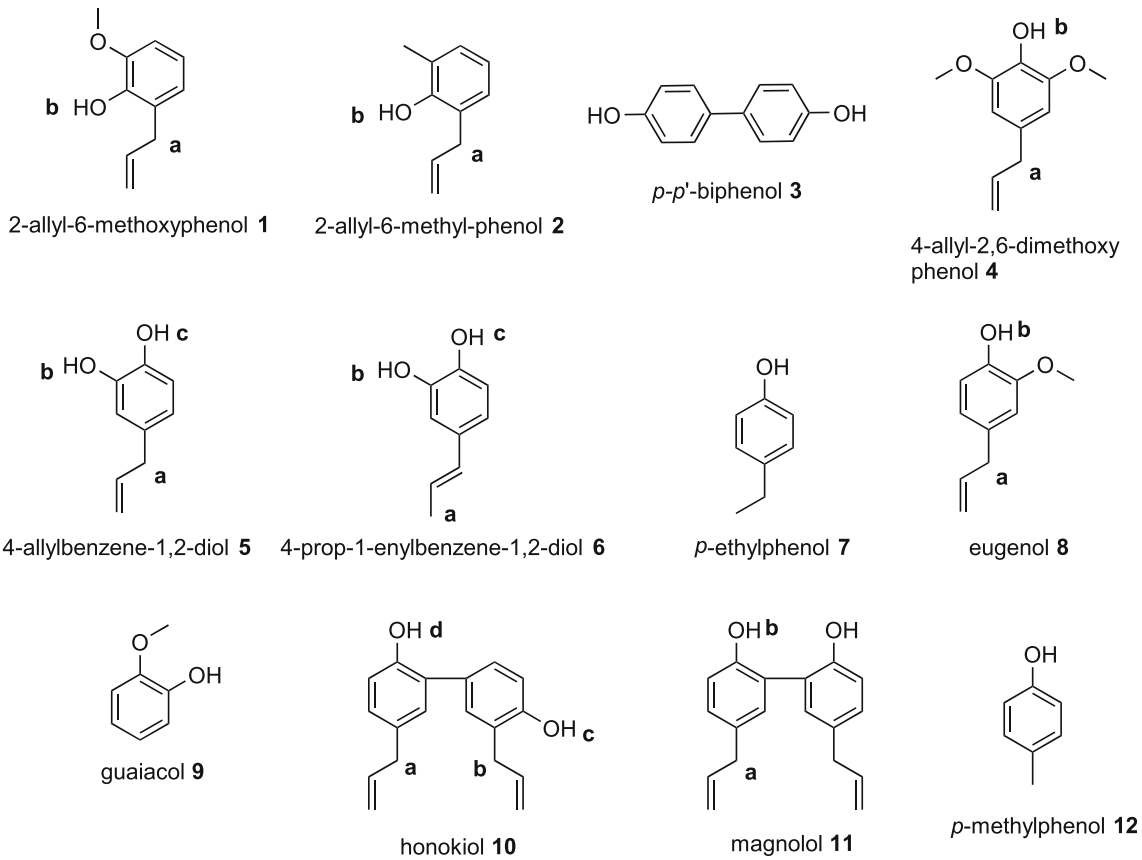

Chart 1 Antioxidant molecules from Asian tea

Computational details

We used Gaussian 09 software package for all computations [28]. Initial geometries were built using Avogadro molecular editor [29], thus generating the corresponding input file. All molecular geometries were optimized at the M05-2X [30, 31], employing the 6-311++G(d,p) basis set for all chemical species studied (non-radical, radical, anion, and cation). Frequency calculations were computed to characterize each of the neutral and radical species as minima over the potential energy surface and in order to evaluate the zero-point energy corrections included in BDE values. Calculated ionization energy (IE) and electron affinity (EA) were both vertical. In this way, $IE = E_{\text{cation}} - E_{\text{neutral}}$ and $EA = E_{\text{neutral}} - E_{\text{anion}}$. Calculation of BDE for OH and H-allyl bond dissociations was as follows: $BDE = H_{\text{r}} + H_{\text{H}} + H_{\text{neutral}}$. Here, H_{r} is the enthalpy of the radicals generated, H_{H} is the enthalpy of a hydrogen atom, and H_{neutral} is the enthalpy of a neutral molecule. We also applied B3LYP [32, 33] and LC-wPBE functional [34–36] (see supporting information) and CBS-QB3 methodology in order to compare and improve BDE energies [37]. CBS-n methods (CBS for complete basis set) are composite methods consisting of a sequence of geometric optimizations, calculating frequencies with a large basis set. They are usually followed by a series of single-point calculations, using higher level methods. Then, changing from a medium to smaller basis set, they apply an asymptotic extrapolation to reduce the error produced by the shortening of the basis sets employed [38]. CBS-QB3 is the medium-level method for this family that employs B3LYP/6-311G(2d,d,p) for geometry and frequency calculation and then a series of MP2, MP4, and CCSD(T) single points, as implemented in Gaussian 09. Previous works by us and other authors [11, 39] show a negligible influence on BDE and conceptual DFT indexes on the use of solvent effects, such as PCM (polarized continuum model). For this reason, we did not calculate them.

The calculation for electrophilicity requires electronegativity and hardness. For an N electron system with a potential external $v(r)$ and total energy E, the partial derivative of the energy, related to the number of electrons at a constant potential, defines electronegativity. In a finite difference approximation, this is equivalent as half of the sum of IE and EA [40]:

$$\chi = \left(\frac{\partial E}{\partial N}\right)_{\nu(r)} \approx \frac{IE + EA}{2} \tag{3}$$

Chemical hardness calculation was according to the definition proposed by Parr and Pearson: differentiating chemical potential to the number of electrons, at constant energy potential. The latter can approximate to half of the difference between IE and EA [41]. In order to symmetrize with electronegativity, the product multiplies by one half, as noted by Pearson [42]:

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{\nu(r)} \approx \frac{IE - EA}{2} \tag{4}$$

The calculation for the electrophilicity index is as:

$$\omega = \frac{\chi^2}{2\eta} \tag{5}$$

IE and EA can also be used to calculate the electrodonor (ω^-) and electroacceptor (ω^+) indexes as proposed by Gázquez and co-workers [43]. Electrodonating power measures the propensity of donating charge, as defined by the following:

$$\omega^- \approx \frac{(3IE + EA)^2}{16(IE - EA)}, \tag{6}$$

whereas the definition for electroaccepting power or the propensity to accept electrons (ω^+) is as follows:

$$\omega^+ \approx \frac{(IE + 3EA)^2}{16(IE - EA)} \tag{7}$$

Low values for ω^- are understood to indicate a greater capacity to donate charge, whereas high values for ω^+ imply the greater capacity to accept a charge.

Plotting electrodonating and electroaccepting powers results in a donor–acceptor map, DAM, as proposed by Martínez [44]. This map, normalized with F as a model for suitable electron acceptor, and Na as a good electron donor, gives a useful graphic indicator. This comparison was therefore performed using computational values for F and Na atoms, at the same level of theory for the molecules studied. Thus, for any compound L, electron acceptance index is defined as follows:

$$Ra = \frac{\omega_L^+}{\omega_F^+}$$

If $Ra = 1$, L is a compound with an electron acceptor efficiency similar to F. If $Ra > 1$, L represents a more effective electron acceptor than F. Finally, if $Ra < 1$, L represents a less effective electron acceptor than F. Similarly, electron donation index is defined as follows:

$$Rd = \frac{\omega_L^-}{\omega_{Na}^-}$$

If $Rd = 1$, then L represents an electron donor with similar efficiency to Na. If $Rd > 1$, L is a less effective electron donor than Na. Likewise, if $Rd < 1$, L is a more effective electron donor than Na. Plotting Ra and Rd is the right way of visualizing the antioxidant scheme using MAP (Fig. 1). The graph

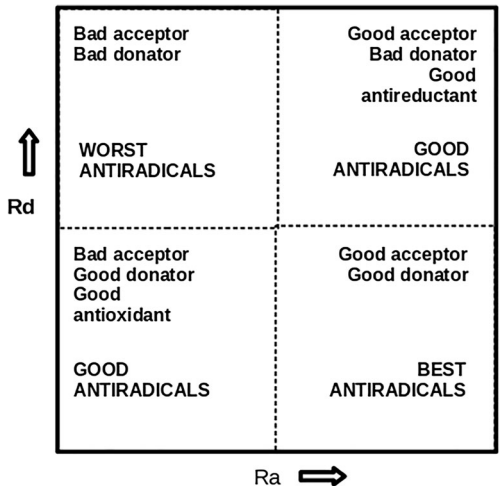

Fig. 1 Donor acceptor map (DAM) diagram. Four regions are distinguished and described in detail by Martinez. Dashed lines separating regions are only indicative, to clarify the image

has four central regions: the worst antiradical activity locates within the zone with poor donor and acceptor capacity. Two regions with good antiradical behavior correspond to bad acceptor but good donator and suitable acceptor but bad donator. Finally, the best antiradical zone stands for both suitable acceptor and donator.

Results

To accompany the study, we choose a couple of representative structures to compare the antioxidant capacity of the rest of the molecules. Lower limit corresponded to phenol, while the upper one to 2,2-diphenyl-picrylhydrazyl (DPPH). This molecule produces a very stable radical that is very well-known in antioxidant assays. The stabilization of DPPH radical is due to the distribution of the free electron over the whole molecule. The resulting species are hard to dimerize, which is contrary to most of the radicals [5]. Other molecules suggested for comparison are 2-propenyl-benzene and 1-propenyl-benzene. These molecules contrast with the collection proposed as they are non-phenolic compounds. The main structural difference in the case of these allyl and phenolic moieties is the non-planarity of the allyl moiety and phenolic ring. The latter can thus refer to as poor stabilization on the part of the unpaired electron between the ring and the allyl functional group. However, as shown in the subsequent texts, the calculated antioxidant parameters for allylic molecules are very similar and even better than the phenolic ones.

BDE of studied molecules

One of the most commonly utilized methods for defining antioxidant activity in computational chemistry is the calculation of BDE. This parameter can display the ability of electron and hydrogen donation in terms of the facility with which the X-H bond can break. A lower value for this energy indicates an increase in the possibility of hydrogen donation, resulting in the stabilization of other radicals in the oxidant cycle. The functionals and CBS-QB3 methods utilized yield a very similar tendency for BDE. The presentation of numerical results for calculations is in Table 1. Notably, recommending experimental BDE for phenol is 88.3 kcal mol^{-1} [45], and CBS-QB3 and M05-2X are the methods with values nearest to this. M05-2X also proved to be an excellent functional alternative to expensive methods, as it is similar to CBS-QB3 and experimental values are available. Moreover, it has been tested and benchmarked, particularly for antioxidant activity, and for the reaction kinetics of radicals [46]. In general, both B3LYP and LC-wPBE have similar values and are lower by approximately 3 kcal mol^{-1}, when compared to M05-2X or CBS-QB3.

Table 1 Bond dissociation enthalpies for hydrogen atom of phenolic molecules from rosemary obtained at DFT-Method/6-311++G(d,p) level. Values in kcal/mol

Molecule	M05-2X	CBS-QB3	%inh[a]
2-Allyl-6-methoxy phenol 1a	78.16	81.22	
1b	83.27	82.94	
2-Allyl-6-methyl phenol 2a	81.67	85.82	75.7
2b	84.01	84.11	
4-4′-Biphenol 3	85.34	85.62	88.3
4-Allylbenzene-1,2-diol 4a	78.12	81.72	91.3
4b	83.07	83.42	
4-Allylbenzene-1,2-diol 5a	74.79	78.71	
4-Prop-1-enyl benzene-1,2-diol 5b	77.85	77.93	
5c	78.54	78.75	
6a	79.78	83.31	
6b	76.08	74.54	
6c	79.27	78.73	
Ethylphenol 7	85.52	85.4	53.9
Eugenol 8a	74.81	78.76	85.0
8b	80.19	80.32	
Guaiacol 9	80.67	81.57	35.9
Honokiol 10a	81.61	86.85	76.9
10b	78.29	82.43	
10c	84.28	85.42	
10d	83.94	84.87	
Magnolol 11a	75.27	78.37	63.6
11b	88.82	89.04	
p-Methylphenol 12	85.36	85.26	
2-Propenyl benzene 13	80.17	82.76	
Phenol 14	87.55	87.09	
1-Propenyl benzene 16	82.47	85.22	

[a] Experimental values of percentage of inhibition of lipid oxidation using TBARS. Values from Ref. [25]

Values for M05-2X and CBS-QB3 have a disparity to hydrogens from allyl moieties, by approximately 3 kcal mol^{-1}. The calculation of BDE for simple allyl phenols presented for comparison purposes concurs well with experimental values, with 88.4 kcal mol^{-1} for prop-2-enylbenzene and 78.9 kcal mol^{-1} for (*E*)-1 phenylpropene [47]. In contrast, the results presented here for 1-phenylpropene are higher than those for prop-2-enylbenzene. However, experimental values represent the mean or average energies of the broken hydrogen bonds attached to the functional groups and can scarcely compare to energies calculated accurately here. BDE results are higher for simple phenolic compounds, such as phenol, *p*-ethyl-phenol, *p*-methyl phenol, or guaiacol. Considering the phenolic diol systems, the hydrogen bond formation between adjacent oxygens has lower BDE for catechol structures induced by a hydrogen bond formation [48]. Similarly, the presence of allyl or extra phenyl functional groups attached to a phenolic ring produces a lower BDE than that of phenol, for at least one type of hydrogen. Interesting cases are guaiacol and eugenol, for which BDE for allyl hydrogen decreases. The experimental data we consulted from TBARS corroborates our finding that the presence of the allyl group increases antioxidant capacity [25]. In these reports, the tendency for antioxidant activity is 4-allyl-2,6-dimethoxyphenol > 4_4biphenol > eugenol > 2-allyl-6-methyl_phenol > honokiol > magnolol > *p*-ethylphenol > guaiacol, as made apparent in Table 1 by the percentage of lipid oxidation inhibition. A possible explanation regarding the lower values for allyl hydrogen BDE compared to those of hydroxyl groups refers to the difference in electronegativity between carbon and oxygen. The latter appears to be more plausible than stabilization of the radical because of geometrical (planar) reasons. The geometry of the allyl in non-radical and radical structures has poor coplanarity with the aromatic ring (XYZ coordinates of the molecules studied are available in the Supplementary Information). In this way, electronic delocalization of the unpaired electron in the yielded radical seems unsuitable.

IE of antioxidants

Ionization energy is a popular tool for measuring antioxidant capacity utilized in computational chemistry (Table 2) [26]. This index may indicate the possibility of an electron donation from the antioxidant to highly oxidative species, thus breaking the oxidant cycle. Usually, it compares to that of phenol as a representative phenolic molecule. Lower IE means greater capacity for electron donation. We also calculated the IE of DPPH and used this as an example of a good antioxidant molecule. DPPH can produce a very stable radical, and its properties may be useful for contrasting the antioxidant properties of the studied set of molecules [49]. The tendency is similar to BDE: that is, simple phenolic systems, such as phenol and allylphenols, have the highest IE. The representative antioxidant, DPPH, has an IE of 8.1 eV; therefore, molecules with a similar or lower IE title as good electron donors. Honokiol is the molecule with less IE, followed by 4-prop-1-enyl benzene-1,2-diol 6; 4–4′-biphenol, 4-allyl-2,6-dimethoxy phenol; and 2allyl-6-methoxy phenol. The rest of the studied molecules are not as efficient electron donors as DPPH; however, they are more efficient compared to phenol or simple allylphenols.

EA of antioxidants

Results for EA are in Table 2. The representative antioxidant, DPPH, has the highest EA with 2.0 eV, whereas the lowest values are for phenol, *p*-ethylphenol, and *p*-methyl phenol with − 1.4 eV, followed by allyl phenols (− 0.8 eV). Magnolol has a calculated EA of − 0.4 eV whereas, for the rest of molecules, EA values are close to − 0.7 eV. EA can clarify the electron-accepting behavior of a molecule. In this case, pure phenolic compounds are bad at accepting electrons whereas, in contrast, DPPH manifests good electron-accepting behavior, indicated by its positive EA. Due to the negative values of EA, the molecules studied are not suitable electron acceptors. The latter is made evident in the donor–acceptor map displayed in the subsequent texts.

Conceptual DFT indexes of antioxidants

Hardness, electronegativity, and electrophilicity are also in Table 2. Hardness measures the resistance on the part of the

Table 2 Ionization energies, electron affinities, hardness, electronegativity, and electrophilicity for the molecules studied at M05-2X/6-311++G(d,p) theory level

Molecule	IE	EA	η	χ	ω
2-Allyl-6-methoxy phenol 1	7.94	− 0.85	4.39	3.55	1.43
2-Allyl-6-methyl phenol 2	8.32	− 0.78	4.55	3.77	1.56
4–4′-Biphenol 3	7.83	− 0.67	4.25	3.58	1.51
4-Allyl-2,6-dimethoxy phenol 4	7.93	− 0.75	4.34	3.59	1.49
4-Allylbenzene-1,2-diol 5	8.20	− 0.68	4.44	3.76	1.59
4-Prop-1-enyl benzene-1,2-diol 6	7.81	− 0.68	4.24	3.57	1.50
Ethylphenol 7	8.34	− 1.40	4.87	3.47	1.23
Eugenol 8	8.21	− 0.77	4.49	3.72	1.54
Guaiacol 9	8.55	− 0.78	4.66	3.88	1.61
Honokiol 10	7.70	− 0.76	4.23	3.47	1.42
Magnolol 11	8.21	− 0.43	4.32	3.89	1.75
P-Methylphenol 12	8.38	− 1.40	4.89	3.49	1.25
2-Propenyl benzene 13	9.00	− 0.86	4.93	4.07	1.68
Phenol 14	8.73	− 1.45	5.09	3.64	1.30
DPPH 15	8.07	2.00	3.04	5.03	4.17
1-Propenyl benzene 16	8.45	− 0.87	4.66	3.79	1.54

chemical potential to change the number of electrons [42]. The latter means that phenol with the greatest hardness is less likely to change electronic distributions, and it is also the structure that manifests least antioxidant activity. Likewise, DPPH is the least hard molecule, thus increasing the possibility that will change its electronic distribution, confirming that this molecule is a more efficient antioxidant. There is a tendency for the simple phenolic structures like allylbenzenes, guaiacol, *p*-ethylphenol, and p-methyl phenol to manifest hardness similar to that of phenol (higher than 4.7 eV), whereas the rest of the studied structures have low values. Therefore, a lower hardness than phenol characterizes antioxidant activity for these molecules. There is a noticeable relationship between the number of hydroxyl groups and hardness values, as apparent in Table 2. Excepting DPPH and phenol compounds (which are the extreme values), the lowest values for hardness belong to honokiol, 4-prop-1-enyl benzene-1,2-diol, and 4–4′-biphenol, which have two hydroxyl groups. In contrast, the highest values of hardness belong to 2-propenyl benzene and ethylphenol, which have zero and a single OH group. This index may relate to the relationship between the number of hydroxyl groups and antiviral activity reported in Refs. [22, 24]. Electronegativity values do not tend in the way hardness does. However, interestingly, DPPH has the highest value, and there is no clear difference concerning the rest of the structures studied. There is also no relationship between the OH number and this index, as evidenced in Table 2: honokiol has two OH groups and has the lowest value for electronegativity. Likewise, ethylphenol, *p*-methylphenol, and 2allyl-6-methoxy phenol have a single OH and low values for hardness.

In contrast, compounds with the highest values of electronegativity, including DPPH, are 2-propenyl benzene, magnolol, and guaiacol, which have zero, two, and one OH groups, respectively. For the set of molecules studied, electronegativity may not be the best tool for analyzing these structures. A similar case shows electrophilicity, which is the highest value obtained for DPPH, with no apparent difference to the rest of the structures studied. Relatively high electronegativity and electrophilicity, in the case of phenol, may be indicative of a good antioxidant. However, there is no significant difference between these values and the molecules studied.

Donor–acceptor maps for antioxidants

The values plotted for the set of compounds studied (Fig. 2) place them in the zone of good antiradical behavior with the suitable donor but bad electron-accepting capacity. The value for Rd slightly above 1 shows a capacity of electron donation superior to the Na atom [44]. The set of molecules studied has very similar DAM values, even approaching that of phenol. In contrast, DPPH occurs as a molecule with one of the best

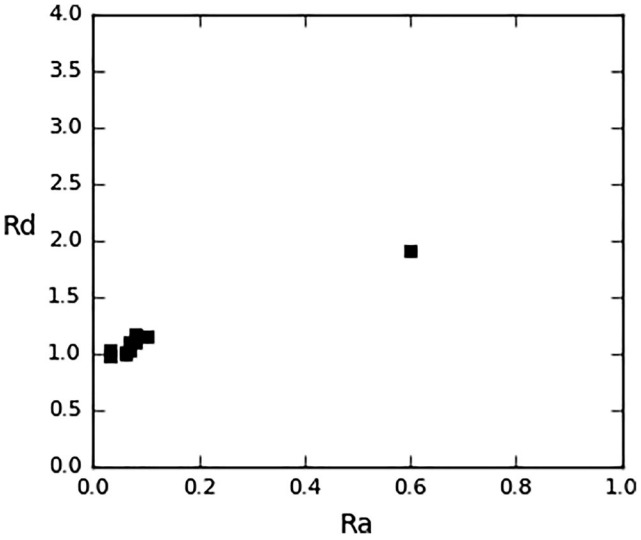

Fig. 2 Donor–acceptor map for molecules studied during the gas phase. Points on the left, most of them hard to distinguish, are the antioxidants studied here and classify as good antiradical. The isolated point to the right represents DPPH shown to be one of the best radicals according to the scheme proposed by Martínez

antiradical behavior; that is, good electron donor and acceptor capacities. Low values of hardness also corroborate this dual behavior on the part of DPPH.

Radicals

The low reactivity of the produced radical is also a characteristic of a good antioxidant. Calculation of conceptual DFT parameters for the formed radicals helped to analyze this. Radicals derived from phenol, propenyl benzene, and allylbenzene served as examples of low antioxidant activity, whereas the radical obtained from DPPH was an example of a good antioxidant. Other attempts to clarify the nature of radicals by the conceptual DFT were reported, for example, the comparison of these parameters with that of molecules previously assumed to have low reactivity [50] or analyzing a broad set of structures in order to build a scale of reactivity and a particular property, such as hardness or electrophilicity [51, 52]. The main goal of this paper is to analyze radicals of molecules with the phenolic and allylbenzene moieties and compare their stability via conceptual DFT parameters. The calculated numerical data shows a significant difference between phenolic and allylbenzene radicals with low reactivity in the case of these last ones. Concerning ionization energy in Fig. 3, the analyzed radicals show similar values to the parent non-radical structures. This energy indicates the possibility of obtaining an extra electron from radical to oxidative species. The highest IE value is for phenol radical with 9.0 eV. The stable radical from DPPH has a slightly higher IE than benzene allyl radicals, which have the lowest values of any molecules studied. Highly reactive radicals, such as OOH and

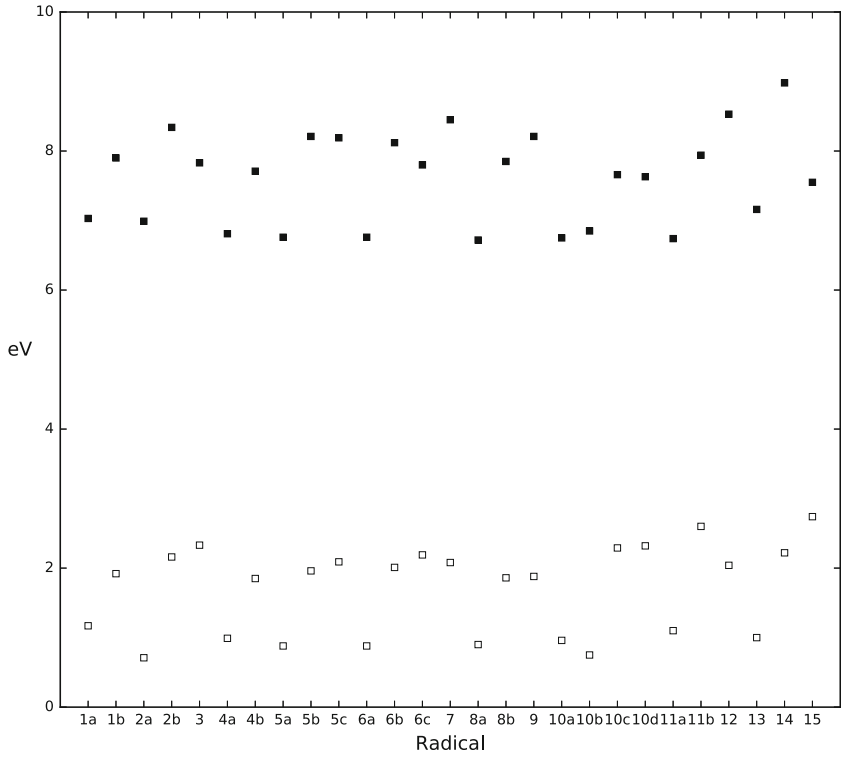

Fig. 3 Graph of ionization energy (full squares) and electron affinity (open squares) for the studied radicals. The labels on the x-axis correspond to those in Chart 1 and Table 1. DPPH radical label is 15. The tendency is as follows: lower values for allyl radicals and higher ones for phenolic radicals, for both properties

OH, were reported previously to have higher IE (12.8 and 16.2 eV, respectively) [39]. Thus, for the set of molecules studied, a low IE is indicative of a radical with low reactivity. A similar trend occurs with EA (Fig. 3), lower values by approximately 1 eV for allyl radicals compared to phenolic ones (close to 2 eV). In this case, DPPH has shown a similar EA to phenol (2.2 and 2.7 eV, respectively).

Concerning hardness (Fig. 4), there is no significant difference between allylic and phenolic radicals. However, it is noticeable that DPPH has the lowest values,

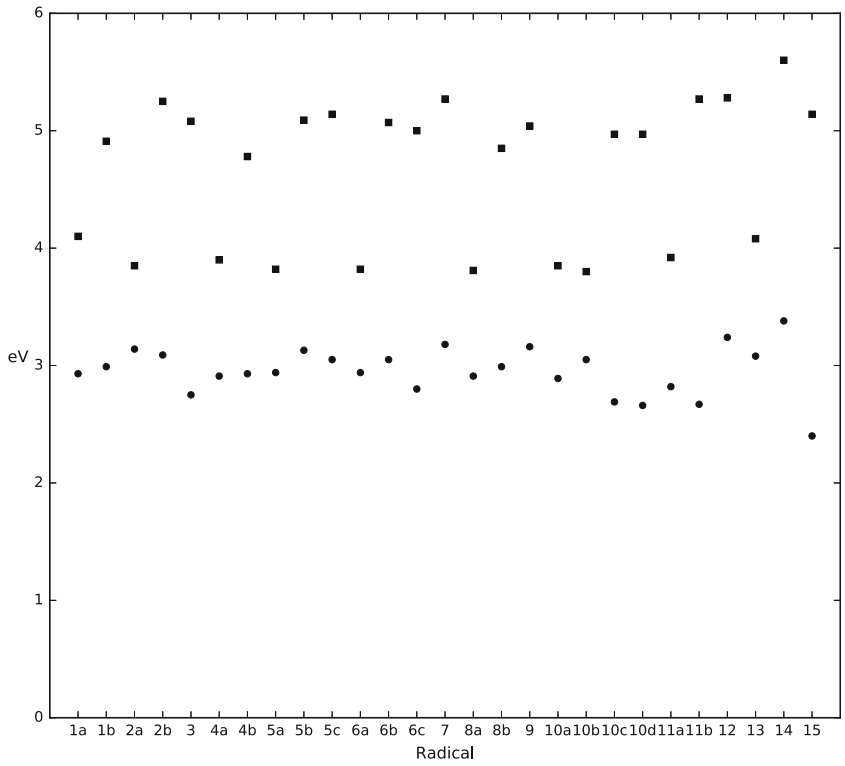

Fig. 4 Graph showing electronegativity (squares) and hardness (circles) for radicals studied. The labels on the *x*-axis correspond to those of Chart 1 and Table 1. DPPH radical label is 15. Concerning electronegativity, the tendency is as follows: lower values for allyl radicals and higher ones for phenolic radicals. There is no clear tendency for hardness

whereas phenol has the highest ones (3.4 and 4.4 eV, respectively) for this index. This information referring to the stability and low reactivity of DPPH contrasts with oxidative OOH and OH radicals, with hardness values of 6.3 and 7.2 eV. Likewise, electronegativity (Fig. 4) shows a similar tendency to IE, with a difference of approximately 1 eV between phenolic and allylic radicals with the highest value for phenol (5.6 eV). Low electronegativity characterizes to low reactivity radicals, in comparison to oxidant radicals OOH and OH, which have an electronegativity of 6.6 and 8.9 eV, less than that of phenol.

The electrophilicity (Fig. 5) for the radicals studied also shows a difference between allylic and phenolic radicals of approximately 1 eV. These values were even more in some cases, with the allyl radicals showing the lowest values. DPPH and phenol have relatively high electrophilicity values. The latter indicates that allylic radicals have insufficient capacity for accepting more electrons, especially compared to phenyl radicals or even DPPH radicals. Highly reactive radical OH has same electrophilicity as DPPH (5.5 eV), whereas OOH has a lower value (3.6 eV). As there is no apparent difference between the radicals studied and prototype molecules, electrophilicity is not a very good indicator for clarifying tendencies among the radicals studied.

Frontier molecular orbitals

The study of the antioxidant properties of the molecules was also made analyzing the highest occupied molecular orbital HOMO. The lower the energy in this orbital, the higher the possibility to donate an electron. Also, qualitatively, the electron density of HOMO can offer a view of the electron-donating site region. As a complement, the electron density of LUMO can show the electron-accepting area of high oxidative radicals in the molecule. The HOMO values for the molecules studied here (Fig. 6) cannot be entirely associated with their antioxidant character, as this should depend on the specific reaction. For example, magnolol 11 manifests a high percentage of lipid oxidation inhibition (see Table 1). However, it presents the lowest HOMO values (− 7.6 eV), which are very similar to those of other compounds, such as *p*-ethylphenol 7 and *p*-methylphenol 12 (− 7.5 eV). They are known to be weak oxidation inhibitors. Even eugenol 8 (− 7.5 eV), which can be cataloged as a weak antioxidant, shows a good percentage of lipid oxidation inhibition. These values imply that HOMO values may still manifest good antioxidant behavior on the part of molecules, despite the relatively high energy of this orbital. It also shows that they represent good antioxidants in terms of their percentage of lipid oxidation inhibition. From a qualitative perspective, HOMO is mainly located over aromatic rings and hydroxyl moiety but concentrates poorly over the allyl group, with 4-prop-1-enylbenzene-1,2-diol 6 representing the only exception. The poor coplanarity of the allyl and benzene fragments explains this exception. As a result, there is a lower extension of electronic delocalization of the double bond near the benzene cycle. Concerning the electron density of the HOMO of the hydroxyl group, this may show the region of the available electron or H atom from

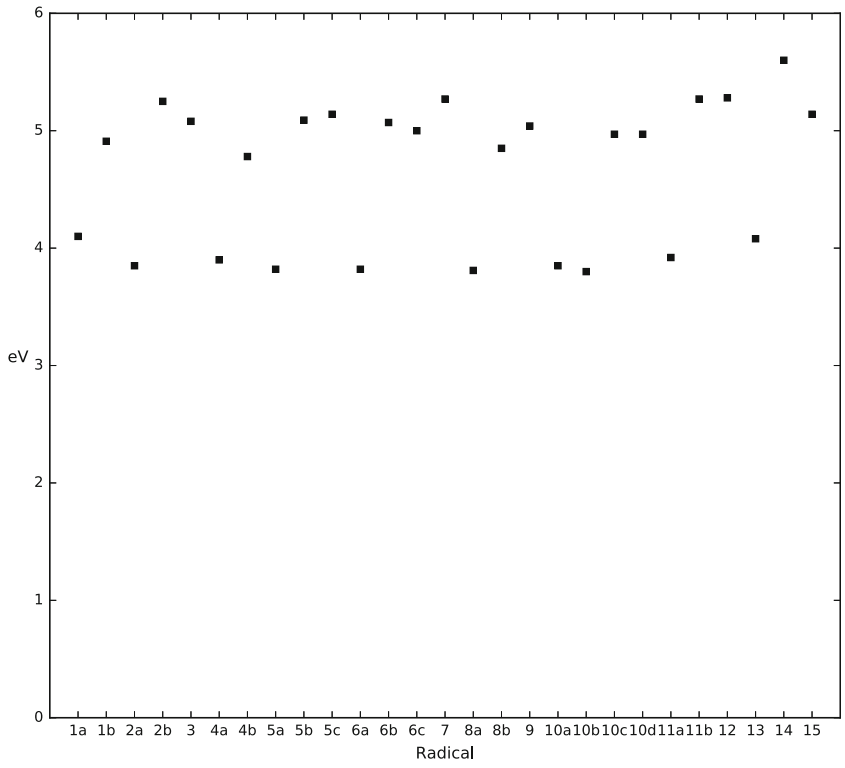

Fig. 5 Graph showing electrophilicity for radicals studied. The labels on the *x*-axis correspond to those in Chart 1 and Table 1. DPPH radical label is 15. The tendency is as follows: lower values for allyl radicals and higher ones for phenolic radicals

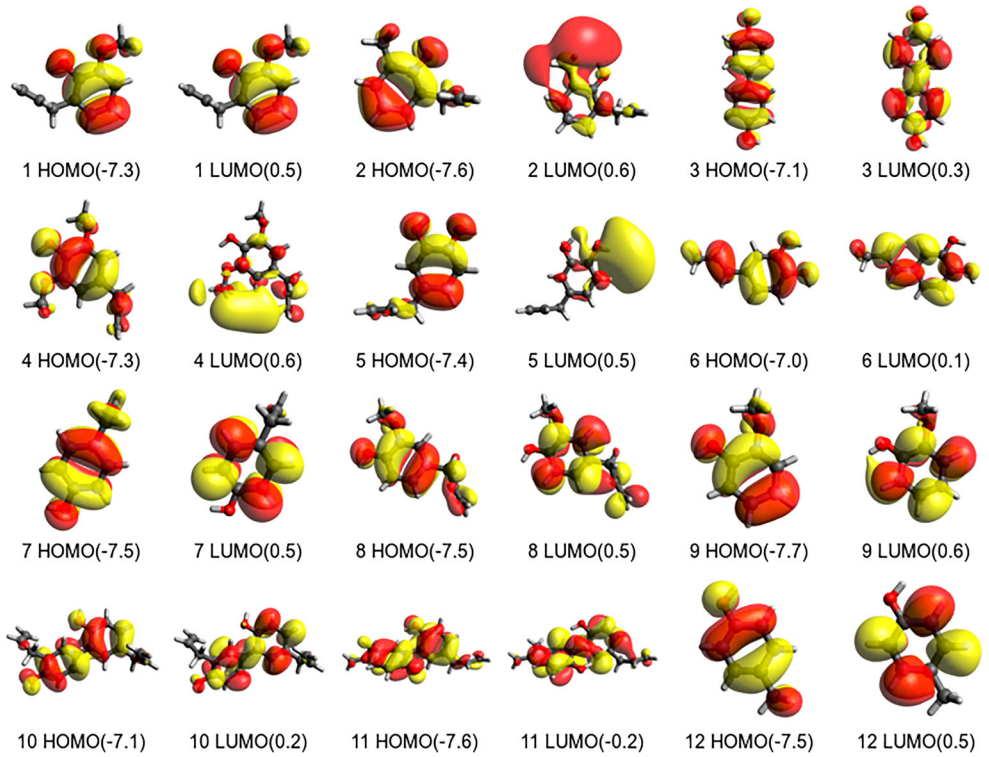

Fig. 6 Graphs showing frontier molecular orbitals for molecules studied. Structures are numbering as in Chart 1. Values are in eV

this and the consequent stabilization of the yielded radical by the aromatic ring. Contrastingly, LUMO locates mainly over the allyl group, aromatic ring, and the rest of the organic functional groups. This location characterizes zones of the molecules in a way similar to electron acceptors. The difference between the hydroxyl group as an electron donor and the allyl as an electron acceptor is apparent.

Conclusion

The following facts should be emphasized for the studied molecules:

HAT mechanism for allyl-type hydrogen displays an antioxidant capacity, which is as good as that of hydroxyl-phenolic, showing similar BDE values or even lower ones in the case of some allyl compounds.

IE tends to show lower values for molecules with more functional groups attached to the aromatic ring. It is well-established that electron donor groups reduce the IE of catechols [53]. In this study, both allyl and hydroxy groups are the functional groups of electron donors. The latter allows us to associate that the reduction of IE is mainly influenced by this fact, as evident in the results for ionization energy. Moreover, allyl-benzene compounds and phenol tend to have high IE values.

Concerning DFT indexes for molecules, interestingly DPPH is characterized by low hardness, high electronegativity, and high electrophilicity. Similarly, IE and EA show DPPH to be a good electron acceptor–donor. In contrast, phenol exhibits high hardness, low electronegativity, and low electrophilicity. Bearing this in mind, all of the antioxidants studied manifest good antioxidant activity. However, as DFT indexes present very similar values for the molecule set, it is difficult to discern or detect a tendency. Notwithstanding, all antioxidants studied manifest good antioxidant activity.

Concerning the radicals yielded following hydrogen donation, DFT indexes for allyl radical show lower IE, electronegativity, and electrophilicity than hydroxy-benzene radicals. Comparing these compounds to highly oxidative radicals, such as OOH and OH that have relatively high IE and electronegativity, the radicals studied show poor reactivity and therefore good stability, with allyl radicals being the most stable. Likewise, the hardness of radicals studied is low compared to OOH and OH, corroborating the idea of the stability of the radicals analyzed.

Acknowledgments Financial support by PRODEP/DSA/511/18-9169 UDG-PTC-1436, CONACyT-Mexico by grant 52827, and ProSNI program of Universidad de Guadalajara is acknowledged. DAH thanks the "Programa de Repatriaciones y Retenciones 2017" of CONACyT-Mexico and Universidad de Guadalajara. The authors gratefully acknowledge the computing time granted by LANCAD and CONACYT on the supercomputer Yoltla/Miztli/Xiuhcoatl at LSVP UAM-Iztapalapa/DGTIC UNAM/CGSTIC CINVESTAV.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this article.

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