DFT for exploring the antioxidant potential of homogentisic and orsellinic acids

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Abstract: In recent years, much attention has been focused on the antioxidant potential of different phenolic acids. But still no theoretical investigation is reported on the antioxidant potential of Homogentisic and Orsellinic acids. In this study, computational investigation based on the density functional theory (DFT) has been carried out to understand the antioxidant potential of Homogentisic and Orsellinic acids. The bond dissociation enthalpy (BDE) of O-H, spin densities and electronic properties such as dipole moment, ionization potential, electron affinity, HOMO and LUMO energies, electronegativity, electrophilic index, energy gap, softness and hardness have been calculated. These properties show that both phenolic acids are good antioxidants. Comparison of BDE of Homogentisic and Orsellinic acids with many other phenolic acids also indicate the good antioxidant potential of these compounds. Homogentisic acid has very high antioxidant potential due to the presence of semiquinone structure. This study will be helpful for the better utilization of these compounds in pharmaceutical and food industry.

Keywords: Homogentisic acid, Orsellinic acid, density functional theory, antioxidant potential and bond dissociation enthalpy.

INTRODUCTION

Antioxidants are very important compounds which scavenge the free radical produced during different oxidation reactions. An outstanding characteristic of radicals is their property of having very high chemical reactivity, because of the availability of unpaired electrons, which elucidate their common biological activities (Nikolic, 2006). The free radicals formed during the reactions are able to cause damage to nucleic acids, amino acids, lipids, proteins and carbohydrates through mechanism of oxidation and results in many diseases and aging processes (Visioli *et al.,* 1998). Phenolic acids are distinguished as potent antioxidant compounds (Nikolic, 2006).

To highlight the importance of phenolic acids as antioxidants both theoretical and experimental research is being carried out. The applications of these compounds in biological and pharmaceutical materials are due to their capacity of scavenging free radicals (Markovic *et al.,* 2009).

Now a day, theoretical studies on antioxidant potential of different phenolic acids is the area of wide research (Mohajeri and Asemani, 2009; Jiaheng *et al.,* 2011; Huai *et al.,* 2005; Lithoxoidou *et al.,* 2004). But still antioxidant activity of simple phenolic acids such as Homogentisic and Orsellinic acids is not explored. Homogentisic acid (2, 5-dihydroxyphenylacetic acid) is present in strawberry-tree named *Arbutus unedo* honey (Paolo *et al.,* 1999). It can also be found in both the bacterial plant pathogen *Xanthomonas campestris* (Goodwin *et al.,* 1994) as well as in the yeast *Yarrowia lipolytica* (Alexandra *et al.,* 2001). Orsellinic acid can be extracted from lichens (Nolan *et al.,* 1940). Oxidation of orcyl aldehyde also used for the preparation of Orsellinic acid (Kang *et al.,* 2003).

From few years, DFT has been widely applied for exploring the antioxidant potential of the phenolic compounds. Theoretical investigation provides information about the antioxidant activity in very less time, easily and economically, with reasonable accuracy.

Basically there are three mechanisms through which different phenolic acids can scavenge free radical: hydrogen atom transfer (HAT), single-electron transfer-proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET) (Wright *et al.,* 2001).

The present study is carried out to predict the antioxidant potential of Homogentisic and Orsellinic acids. According to our information, this is the first investigation related to antioxidant potential of these acids. Before this no theoretical study has been carried out to check the antioxidant activity of Homogentisic and Orsellinic acids.

In present study, equilibrium geometries of the Homogentisic, Orsellinic acids and their free radicals were obtained to explain their antioxidant potential. BDE of O-H, spin densities, electronic properties such as dipole moment, electron affinity, HOMO and LUMO energies, electronegativity, electrophilic index (ω), energy gap,

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softness, ionization potential (IP) and hardness have been calculated.

COMPUTATIONAL DETAILS

Density functional theory (DFT) was used in all the computational calculations. Computational calculations were performed with the Gaussian 09 W suite of programs (Frisch *et al.,* 2009). Lowest energy structures of the species were determined by conformational analysis. Geometry optimization was performed using B3LYP functional and 6-311G basis set. For the geometry optimization of parent molecule restricted approach was applied, while for the free radicals the unrestricted approach was used. For computational calculations of radicals H atom is removed from OH groups of optimized most stable structure of the neutral molecules. Vibrational frequencies were computed at the same level of theory for neutral molecule and radicals to estimate Zero point energies (ZPE), vibrational, rotational and translational contributions to enthalpy. The O-H bond dissociation enthalpy is calculated using following formula: BDE = $H_r + H_h - H_n$ where H_r is the enthalpy of the free radical produce after the removal of H, H_h is the enthalpy of hydrogen atom [-0.4962 Hartree] and H_n is the enthalpy of neutral molecule. We have computed dipole moment, HOMO and LUMO energies. We have also calculated the electronic properties such as ionization potential (IP) and electron affinities (EA), Hardness (η), Softness (S), Electro negativity (μ), Electrophilic index (ω) and energy gap (E_g). Following formulas were used to calculated electronic properties (Kohn *et al.,* 1996, Parr and Pearson, 1983).

Ionization potential (IP) = $-\varepsilon_{HOMO}$ (eV)
Electron affinity (EA) = $-\varepsilon_{LOMO}$ (eV)
Hardness (η) = (IP - EA)/2 (eV)
Softness (S) = 1/2η (eV)
Electro negativity (μ) = (IP + EA)/2 (eV)
Electrophilic index (ω) = $\mu^2/2\eta$
Energy gap (E_g) = $\varepsilon_{HOMO} - \varepsilon_{LOMO}$

RESULTS

In this study computational evaluation of antioxidant potential of Homogentisic acid and Orsellinic acid was carried out. Structures of Homogentisic acid and Orsellinic acid are given in fig. 1. Equilibrium geometries of Homogentisic acid and Orsellinic acid computed at B3LYP/6-311G level of theory are shown in tables 1, 2, 3 and 4. BDE and spin density of Homogentisic acid and Orsellinic acid are given in table 5. BDE and spin density are indicator of O-H bond strength and stability of free radical form by removal of H of hydroxyl group, respectively. Fig. 2 represents the semiquinone structure of Homogentisic acid radical 1. High antioxidant potential of Homogentisic acid is due to the semiquinone structure. Electronic properties such as ionization potential (IP) and electron affinities (EA), Hardness (η), Softness (S), Electro negativity (μ), Electrophilic index (ω) and energy gap (E_g)of Homogentisic and Orsellinic acid are given in table 6. MOMO and LUMO composition of Homogentisic acid, Orsellinic acid and their radicals are given in figs. 3, 4. We have compared the antioxidant of studied compounds with some phenolic acid. Comparison is graphically represented in fig. 5.

Table 1: Bond lengths (Å) of optimized structures of Homogentisic acid and their radicals

Bond parameters	Bond length (Å)		
	Neutral	2-OH	5-OH
C_1-C_2	1.409	1.458	1.418
C_2-C_3	1.399	1.453	1.415
C_3-C_4	1.390	1.370	1.370
C_4-C_5	1.397	1.411	1.444
C_5-C_6	1.389	1.404	1.435
C_1-C_6	1.396	1.376	1.381
C_1-C_7	1.480	1.483	1.485
C_2-O_8	1.380	1.274	1.365
C_5-O_9	1.388	1.370	1.285
C_7-O_{10}	1.233	1.233	1.230
C_7-O_{11}	1.373	1.368	1.371

Table 2: Bond lengths (Å) of optimized structures of Orsellinic acid and their radicals

Bond parameters	Bond length (Å)		
	Neutral	2-OH	4-OH
C_1-C_2	1.411	1.452	1.415
C_2-C_3	1.395	1.434	1.378
C_3-C_4	1.388	1.381	1.438
C_4-C_5	1.394	1.402	1.439
C_5-C_6	1.395	1.408	1.376
C_1-C_6	1.416	1.396	1.423
C_1-C_7	1.476	1.478	1.485
C_2-O_8	1.376	1.287	1.378
C_4-O_9	1.381	1.381	1.283
C_6-O_{10}	1.372	1.371	1.373
C_7-O_{11}	1.229	1.228	1.224
C_7-O_{12}	1.387	1.381	1.377

DISCUSSION

Conformational analysis

Conformations analysis plays a key role to explain the antioxidant potential of phenolic acids. Antioxidant potential of different O-H groups is mainly affected by neighboring groups and their geometries. The conformation is the first tool of interest to characterize the antioxidant capacity of Homogentisic and Orsellinic acids. Both Homogentisic and Orsellinic acids are planar.

Equilibrium conformations of these phenolic acids were calculated at B3LYP/6-31G level as described in tables 1, 2, 3 and 4. Conformation with smallest amount of energy was selected for the optimization and determination of selected parameters.

Table 3: Bond angles (^{0}) of optimized structures of Homogentisic acid and their radicals

Bond parameters	Bond angle (^{0})		
	Neutral	2-OH	5-OH
C_1-C_2-C_3	117	114	118
C_2-C_3-C_4	121	123	121
C_3-C_4-C_5	120	119	121
C_4-C_5-C_6	118	119	115
C_5-C_6-C_1	121	121	123
C_7-C_1-C_2	125	124	125
C_7-C_1-C_6	114	114	115
C_1-C_2-O_8	120	125	120
C_3-C_2-O_8	121	119	121
C_4-C_5-O_9	123	123	122
C_6-C_5-O_9	117	116	122
C_1-C_7-O_{10}	124	123	123
C_1-C_7-O_{11}	114	113	113
C_{10}-C_7-O_{11}	121	122	122

Table 4: Bond angles (^{0}) of optimized structures of Orsellinic acid and their radicals

Bond parameters	Bond angle (^{0})		
	Neutral	2-OH	4-OH
C_1-C_2-C_3	120	117	119
C_2-C_3-C_4	120	121	121
C_3-C_4-C_5	119	119	117
C_4-C_5-C_6	120	121	121
C_5-C_6-C_1	120	120	119
C_7-C_1-C_2	123	120	120
C_7-C_1-C_6	118	119	119
C_1-C_2-O_8	119	122	116
C_3-C_2-O_8	120	119	123
C_3-C_4-O_9	117	117	121
C_5-C_4-O_9	123	122	121
C_5-C_6-O_{10}	122	122	125
C_1-C_6-O_{10}	116	117	114
C_1-C_7-O_{11}	127	127	126
C_1-C_7-O_{12}	112	111	110
C_{11}-C_7-O_{12}	120	121	122

Table 5: BDE and spin densty of Homogentisic and Orsellinic acid

Parameter	Homogentisic acid		Orsellinic acid	
	2-OH	5-OH	2-OH	4-OH
DBEs	75.49	76.56	82.39	81.14
Spin density	0.466	0.524	0.559	0.504

From tables 1 and 2 it is clear that formation of free radicals from neutral molecules result in large change in bond lengths. Bond length change is prominent near O-atom from which H atom is abstracted. Tables 3 and 4 indicate the change in bond angle is due to the formation of free radicals.

Table 6: Electronic Properties of Homogentisic and Orsellinic acid

Parameters	Homogentisic acid	Orsellinic acid
Dipole moment	4.6	4.06
Ionization potential (IP) eV	5.69	6.01
Electron affinity (EA) eV	1.1	0.48
Hardness η	2.22	2.76
Softness (S)	0.22	0.18
Electro negativity (□)	3.39	3.25
Electrophilic index	2.58	1.91
Energy Gap E_g	4.58	5.53

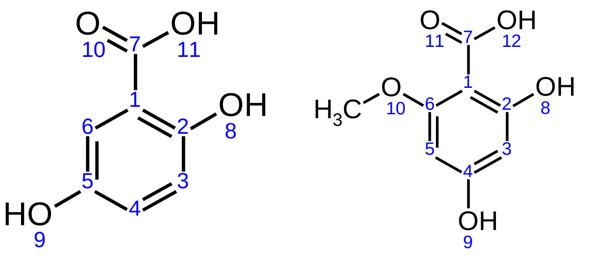


Fig. 1: Structures of (a) Homogentisic acid and (b) Orsellinic acid

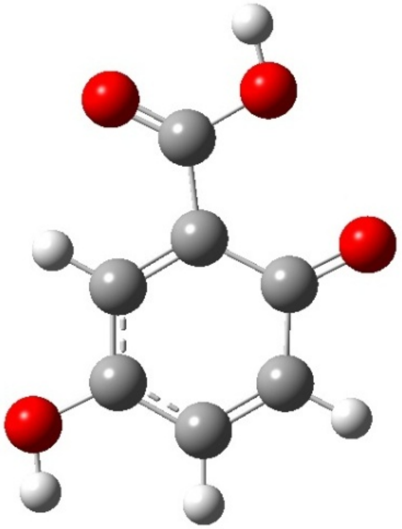
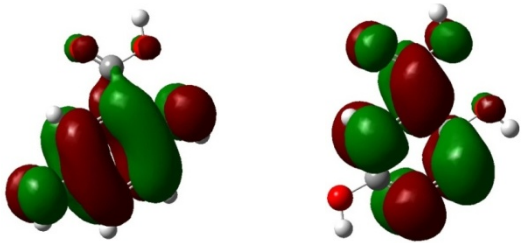


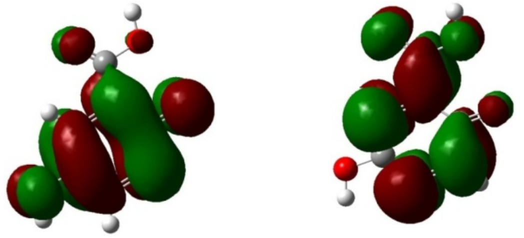
Fig. 2: Semiquinone structure of Homogentisic acid radical 1

Bond dissociation enthalpy (BDE)

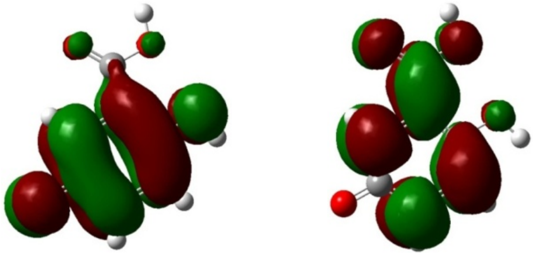
The hydrogen donating capacity of phenolic compounds and their free radicals are characterized by an important parameter i.e. bond dissociation enthalpy. The bond dissociation enthalpy is related to the breaking of O-H bond i.e. removal of H, with the help of this tool the stability of hydroxyl bonds can be estimated (Hong *et al.*, 2009). Lower BDE indicates the high antioxidant potential. Table 5 presents gas phase BDEs.



Neutral HOMO Neutral LUMO



2-OH, HOMO 2-OH, LUMO



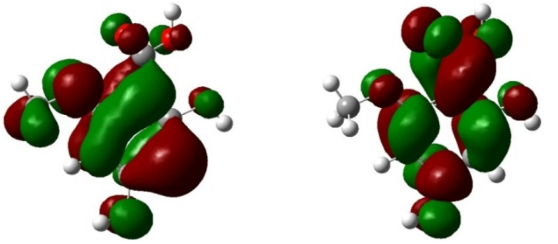
5-OH, HOMO 5-OH, LUMO

Fig. 3: MOMO and LUMO composition of Homogentisic acid and radicals.

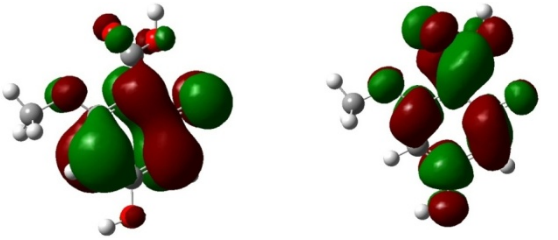
The value of BDE for Homogentisic acid is lower than that of Orsellinic acid. These results show that Homogentisic acid is a better antioxidant than Orsellinic acid. The BDE value for 2-OH of Homogentisic acid is lower than that for 5-OH. But in case of Orsellinic acid, BDE value for 2-OH is greater than that for 4-OH. BDE for 2-OH of Homogentisic acid (75.49) is lower than BDE of 2-OH of Orsellinic acid (82.39). This is due to the presence of semiquinone structure in 2-OH radical of Homogentisic acid. This semiquinone structure is responsible for the stability of 2-OH radical of Homogentisic acid and results in the lower value of BDE. Very low spin density of 2-OH radical of Homogentisic acid also support the presence of semiquinone structure.

Spin density

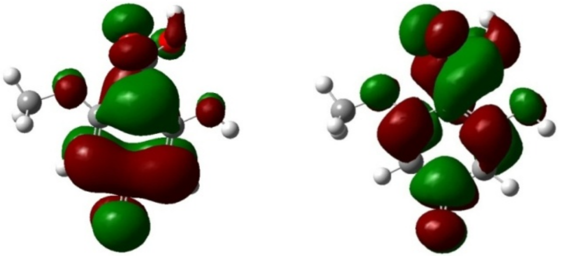
The spin density of phenolic acids is important parameter for the description of stability of free radicals formed from phenolic acids. Therefore, spin densities of the radicals of Homogentisic and Orsellinic acids were calculated in order to find difference in the reactivity of various OH groups and ultimately difference in the BDE of phenolic acids. It was concluded that the radical having higher spin density delocalization, easier is the formation of radical and lower is the value of bond dissociation enthalpy (Parkinson *et al.,* 1999). The values of spin densities are presented in table 5.



Neutral HOMO Neutral LUMO



2-OH, HOMO 2-OH, LUMO



4-OH, HOMO 4-OH, LUMO

Fig. 4: MOMO and LUMO composition of Orsellinic acid and radicals.

For Homogentisic acid, the spin density appears to be more delocalized for the radical originating from 2-OH than those from 5-OH. Spin population is 0.466 on the O-atom in the 2 -OH radicals of Homogentisic acid and it is 0.524 for the same compound in the 5-OH position. This in turn results in lower BDE value of 2-OH than that of the 5-OH. BDEs are slightly different from each other but spin densities are different in large extent. The small differences in the BDE cannot be explained only on the basis of the spin density magnitude of O-atom. Less spin density of O atom in 2-OH radical of Homogentisic acid is due to the presence semiquinone structure, which is absent in 5-OH radical. For Orsellinic acid spin population of O-atom in the 2 -OH radical is 0.559 and that of 4-OH radical is 0.504 and the difference in the spin population is only 0.055.

Electronic properties

All the electronic properties of Homogentisic and Orsellinic acids are given in table 6. The charge density and bond properties of phenolic acids can easily be calculated through the dipole moment of molecules. The reactivity index can be calculated with the help of dipole moment of bonds. The dipole moment of Homogentisic acid is 4.60D and that of Orsellinic acid is 4.06 D. The values of dipole moment for Homogentisic and Orsellinic acids indicated that both phenolic acids are quite polarized and verify their solubility in polar solvents.

The ionization potential can give the idea about energy necessary to eject an electron from a molecule. From higher values of ionization potential of a molecule, it can be concluded that the molecule do not lose electrons easily (Chang, 2001). The electron affinity can be expressed as the amount of energy released when an electron absorbed by a neutral molecule. The greater electronic affinity of a molecule/atom means to absorb the electrons easily (Chang, 2001). The chemical hardness can be defined as the resistance to charge transfers (Parr and Yang, 1989). The electronegativity can be measured as the capacity to attract electrons in a chemical bond, but in DFT it is expressed as the minus of chemical potential (Parr and Yang, 1989).

The electrophilic index used to find the electrons affinity and measures maximum electron flow between a donor and an acceptor (Parr *et al.,* 1999). table 6 clearly described the chemical potential values. These can also advocate their good antioxidant potential. Another important factor to be calculated is the energy gap. The energy gap of Homogentisic acid is calculated as 4.58 eV and that of Orsellinic acid is 5.53 eV. The difference between the energy gap of Homogentisic and Orsellinic acids is 0.95 eV. The energy gap differences between these two phenolic acids are moderate; it suggests that both the phenolic acids could be good antioxidant.

HOMO-LUMO composition of neutral and radical species

Literature survey clears that no literature is quoted to describe the HOMO and LUMO compositions of these phenolic acids related to the antioxidant activity. The HOMO and the LUMO energies of Homogentisic and Orsellinic acids and their neutral and radical species are presented in figs. 3 and 4.

The HOMO energies of Homogentisic acid and Orsellinic acid are computed as 5.69 eV and 6.01 eV respectively. While the LUMO energies of Homogentisic acid and Orsellinic acid are calculated as 1.10 eV and 0.48 eV respectively The high energy gap (5.53 eV) of Orsellinic acid as compared with Homogentisic acid (4.58) may be due to its blue-shifted absorption spectrum. Some prominent variations are present in the electronic properties of these phenolic acids. Due to the higher delocalization of charge density over the whole molecule there are no measurable differences between the LUMO compositions of Homogentisic acid and Orsellinic acid. Few differences are detected for HOMOs of these phenolic acids.

We have compared the antioxidant potential of Homogentisic and Orsellinic acids with some good phenolic acid antioxidants. This comparison was based on BDE values of phenolic acids. Fig. 5 demonstrated the comparison graphically. From fig. 5 it was clear that Homogentisic acid is very good antioxidant. Orsellinic acid has reasonable antioxidant activity. For the better utilization of these compounds in pharmaceutical and food industry further research is required. This study is an initiative in this regard. This study will catch the attentions of scientists for the development of new antioxidants.

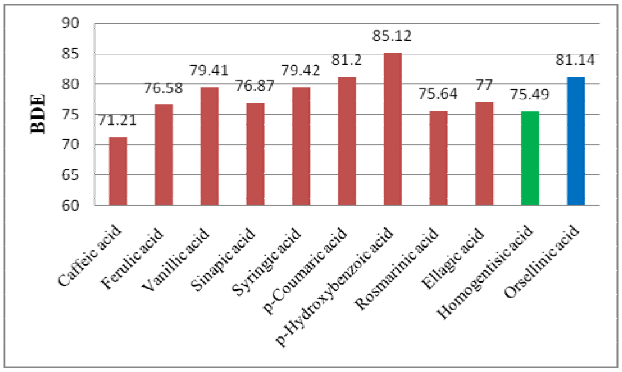


Fig. 5: Comparison of BDEs of some phenolic acid with Homogentisic acid and Orsellinic acid (Mohajeri and Asemani, 2009, Jiaheng *et al.,* 2011, Huai *et al.,* 2005).

CONCLUSION

In this research work, we have study the antioxidant potential of Homogentisic acid and Orsellinic acid by using DFT calculations. This study was aimed to determine the geometrical and energetic characteristics to find the factors affecting the antioxidant activity. Two prime indicators of antioxidant activity (BDE and IP) were calculated. Moreover, electronic properties such as dipole moment, electron affinity, HOMO and LUMO energies, electronegativity, electrophilic index, energy gap, softness and hardness have been calculated. Among these two phenolic acids, Homogentisic acid is a better antioxidant than Orsellinic acid. Comparison of BDE with other phenolic acid antioxidants indicates that these acids have good antioxidant potential. It is hoped the present study will provide information about antioxidant potential of these acids. On basis of this information Homogentisic acid and Orsellinic acid can be used in better way in field of food and pharmacy.

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