Regular Article

A Theoretical Study on the Structure-Radical Scavenging Activity of Some Hydroxyphenols

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Antioxidants are made for the struggle and reconstruction of the damaged cells, because of their ability in destroying the free radicals. On account of their importance, a theoretical procedure was applied for the study of the molecular structure and radical scavenging activity of six hydroxyphenols which have been introduced as antioxidant compounds. All geometry structures were optimized by M06-2X, MPWB1K with 6-311++G (d, p) basis in the gas phase and solvent using the CPCM model. Three probable mechanisms for the antioxidant activities have been presented and analyzed. According to bond dissociation enthalpy (BDE) and ionization potential (IP) values, hydrogen atom transfer (HAT) mechanism is a more reasonable path for antioxidant activity. The contribution of the HOMO-LUMO orbitals and spin density distribution have been calculated for evaluating of the previous data. Finally, based on the comparison of the experimental and the calculated data, BDE mechanism showed the best agreement.

INTRODUCTION

Free radicals are molecules or atoms which have an unpaired electron, so they are very unstable materials. They tend to bond with other species for increasing their stability [1]. Free radicals are created by breaking a bond of the stable molecules. There are different mechanisms to reduce free radical effects in the biological systems and antioxidants play an important role in the destruction of the free radicals *via* these mechanisms [2,3]. Antioxidants destroy free radicals and boost the immune against all kinds of diseases [4]. ROS (reactive oxygen species), known as the famous free radicals, destruct and damage the proteins, lipids and DNA [5]. Antioxidants are substances that prevent the free radical formation in the cells. A pairing process of the antioxidant and free radical makes it less harmful. Antioxidants can be divided into two categories

[6]: First class is the inhibitor antioxidants, which can reduce the reaction rate by the free radical chain reactions and the second class is the chain-breaking antioxidants, which prevent the spread of the oxidation reactions.

Phenolic compounds are introduced as one of the biggest classified substances which have been produced by several biosynthetic pathways. In the phenolic compounds, a hydroxyl group (OH) is directly bonded to an aromatic hydrocarbon group. Phenolic compounds are a large group of the antioxidant compounds [7,8]. Some of the phenolic compounds have been applied in the food industry due to their organoleptic properties [9]. It has been experimentally confirmed that H-atom abstraction from the phenols by a free radical might take place through different mechanisms [10].

In general, free radicals are inactivated through two principal mechanisms by antioxidants [11]. The first mechanism [12] is called hydrogen atom transfer, HAT (Eq. (1)). The HAT is concentrated on the proton and electron

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motion in a single kinetic step from one group to another [13]. The HAT mechanism shows radical polarity while they have nucleophilic or electrophilic tendencies [14].

$$X^{\cdot} + AH \longrightarrow XH + A^{\cdot} \qquad (1)$$
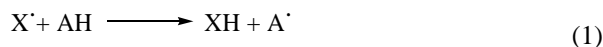
The second mechanism is BDE which is usually named homolytic bond dissociation enthalpy. This means the chemical bond energy required to break one mole of the bonding atoms to give separated atoms with fifty percent of the shared electrons. The bond dissociation energy shows the bond strength [15-16]. Therefore, a chemical compound which has the strongest OH bond will hardly react with the free radicals.

In the hydrogen atom transfer mechanism, one hydrogen atom of OH group is transferred from the phenolic compound to the free radical [17], according to Eq. (2).

$$ArOH + DPPH^{\cdot} \xrightarrow{(HAT)} ArO^{\cdot} + DPPH\text{-}H \qquad (2)$$
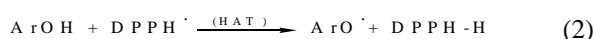
The HAT is an elemental chemical qualitative change utilized in many enzymatic systems [18]. One hydrogen atom of OH group is transferred from the phenol (ArOH) to a free radical, resulting in an organizing a phenoxyl radical (ArO$^{\cdot}$). Bond dissociation energy employs as an energetic parameter to measure of this mechanism, so the compounds with the weakest OH bond react more quickly with free radicals [19].

In the third mechanism which is the single electron transfer (SET), Eq. (3), antioxidants through the single electron transfer process, give one electron to the free radical [20].

$$X^{\cdot} + AH \longrightarrow X^{-} + AH^{+} \qquad (3)$$

In this mechanism, the ionization potential would have been found as energy per charge unit needed to remove one electron from a given atom or molecule to an infinite distance, which is usually expressed in Volts and known as the ionization potential [21] (Eq. (4)).

$$ArOH^{\cdot+} + DPPH^{-} \xrightarrow{(IP)} ArO^{\cdot} + DPPH\text{-}H \qquad (4)$$
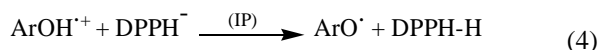
In particular, ionization potential (IP) is related to ionization energy (IE) term. It means the energy required to remove electrons from an atom. This quantity was sometime called ionization potential, the energy required to remove an electron from a neutral atom, named as the first ionization potential. The potential related to the removal of the second electron from a singly ionized atom or molecule is called the second ionization potential, and so on [22,23]. Therefore, by the calculation of BDEs and IPs, interesting information about the effectiveness and the activity of the phenolic antioxidants is obtained. Figure 1 shows the radical inhibitory activity found against DPPH$^{\cdot}$ expressed as EC50 values.

The objective of this study is evaluating the antioxidant activity of some phenolic compounds by using density functional theory method. The importance of these phenolic compounds is their antibacterial activity found against DPPH$^{\cdot}$ (Fig. 1).

COMPUTATIONAL METHODS

Computational chemistry is a powerful tool to demonstrate and examine the reaction mechanisms with radical characters. All calculations were carried out using density functional theory as implemented in Gaussian 09 package [25] at 298.15 K and 1.00 atm.

In the DFT calculations, famous functionals of B3LYP, M05-2X, M06-2X and MPWB1K within 6-311++G (d,p) basis set were used and theoretical data were compared with the experimental ones. These levels of the theory have provided specific information on the geometry, harmonic vibrational frequencies, thermodynamic and kinetic parameters. The solvent effect of ethanol was included in all calculations, implicitly, with the framework of self-consistent reaction field polarizable continuum model (SCRF-PCM) [26].

The scavenging efficiency of the antioxidants depends on some factors such as spin density, HOMO (highest occupied molecular orbital) energy, bond dissociation energy and ionization potential.

In the HAT mechanism of the Phenolic derivatives (Eq. (5)), ArOH activity may be computed by two OH bond dissociation enthalpies (Eq. (6)). A lower BDE value correlates with the most favorite activity.
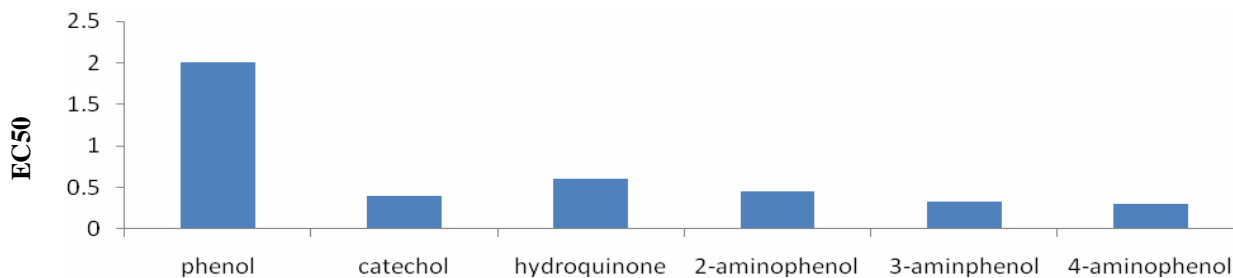
Fig. 1. Radical inhibitory activity of the phenolic compounds against DPPH [24].

$$R^{\cdot} + ArOH \longrightarrow RH + ArO^{\cdot} \qquad (5)$$
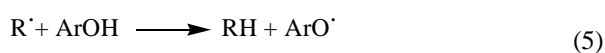
$$BDE_{(O\text{-}H)} \quad = \quad H_{(ArO^{\cdot})} + H_{(H^{\cdot})} - H_{(ArOH)} \quad (6)$$

In Miertus *et al*.'s work [27], BDE values of the O-H bond were evaluated from the enthalpy of the reactants and products. Total electronic enthalpy of the H atom was considered as 0.5 Hartree. According to Eq. (7), electron migrates from the phenolic compounds to the radical. If a molecule has a high IP or BDE value, it is considered as a molecule with lower activity. The IP values can be obtained by Eq. (8):

$$R^{\cdot} + ArOH \longrightarrow R^{-} + ArO^{\cdot +} \qquad (7)$$
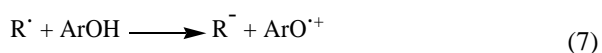
$$IP \quad = \quad {}^{\cdot}E_{0\,(ArO^{\cdot +})} - E_{0\,(ArOH)} \qquad (8)$$

where $E_{0\,(ArO+^{\circ})}$ is the total energy of the cation radical and E_{0} (ArOH) demonstrates the total energy of the phenolic molecules.

HOMO analysis and spin density calculations were carried out using the M06-2X and MPWB1K functionals, in the gas phase and solution, respectively. Spin density is calculated in an automatic way within the spin-unrestricted wave functions to have a correct multiplicity. It also can be used to restrict the open shell types of radical calculations.

RESULTS AND DISCUSSION

BDE Calculations

Optimized structures of the studied phenol derivatives at the M06-2X/6-311++G(d,p) level of theory are presented in Fig. 2. It is noteworthy that for the calculation of radicals and cation radicals, the unrestricted density functions have been applied.

After optimization of all structures, their bond dissociation energies are calculated and compared with the experimental data and are reported in Table 1. The BDE mechanism is suitable to describe the O-H bond breaking, which corresponds to the bond breaking into the radical. Therefore, the bond dissociation energy reflects the stability of the radicals.

According to Table 1 and Fig. 3, the M06-2X level of theory shows the best agreement with the experimental data of the BDE. Considering Table 1, it reveals that the BDE value of 4-aminophenol is the lowest and it has the strongest hydrogen donating ability than other derivatives. This means that, the phenolic compounds having a lower antioxidant activity possess a higher degree of BDE. When the H atom is abstracted from the OH groups, the radicals make the most stable construction of the native molecules. As a result, among the compounds possessing more than one hydroxyl or aminophenol group, the structure which corresponds to the lowest bond dissociation energy, shows the best radical scavenging activity. Accordingly, the hydrogen donating ability is as follows: 4-aminophenol > 2-aminophenol > hydroquinone > catechol > 3-aminophenol > phenol.

The influence of ethanol as the solvent on the calculated BDE has been considered. Because ethanol is a common solvent in food colorings and flavorings and medicinal preparations. Low electrophilicity of the oxygen atom in the polar OH part of the ethanol molecule enables it to form hydrogen bonding with the other molecules. Table 2 shows the ethanol effect as a solvent on the calculated BDE.

2-Aminophenol   3-Aminophenol   4-Aminophenol

Catechol   Hydroquinone   Phenol
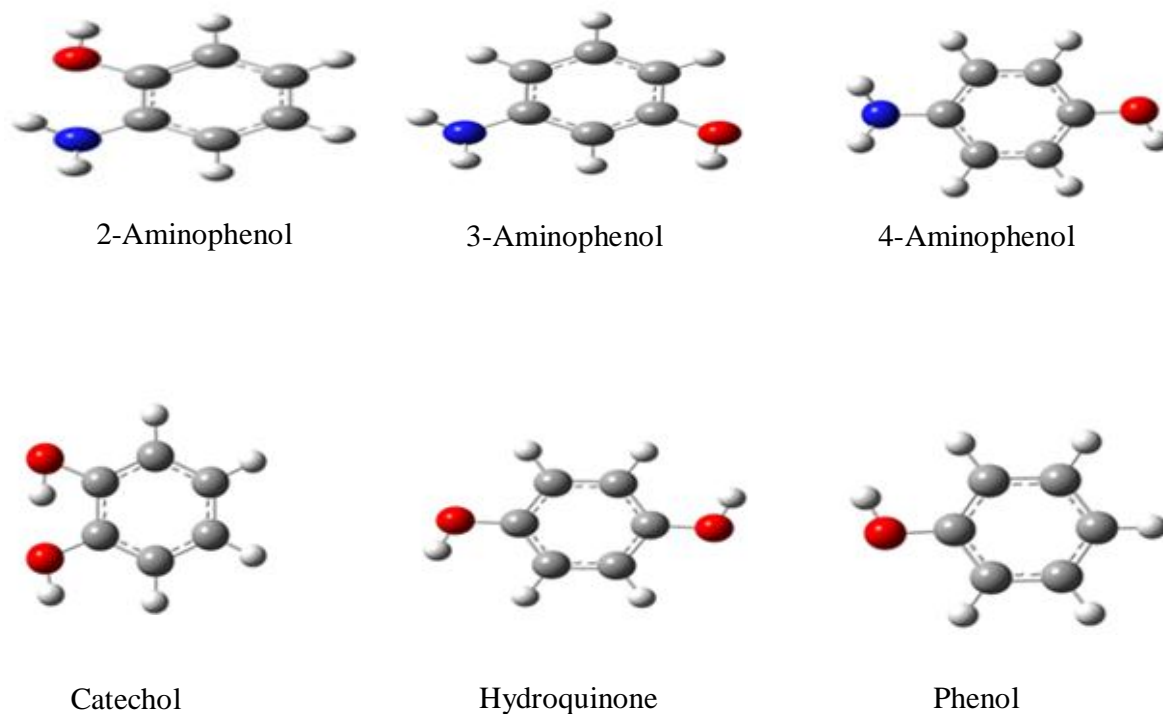
Fig. 2. Optimized structures of hydroxyphenols at the M06-2X/6-311+ + G(d,p) level in the gas phase.

Table 1. Calculated BDE (kcal mol^{-1}) for the Working Sets in the Gas Phase

Compounds	B3LYP	M052X	M062X	MPWB1K	Experimental [27]	QSPR [28][a]
Phenol	78.6	48.1	86.9	41.3	84.0	82.2
Catechol	77.9	113.2	82.4	18.0	77.3	78.7
Hydroquinone	78.8	112.3	81.7	2.3	77.9	78.8
2-Aminophenol	70.6	106.3	77.9	18.0	77.0	77.5
3-Aminophenol	71.5	116.8	86.4	29.4	82.9	80.3
4-Aminophenol	74.1	108.4	77.8	20.2	74.9	76.4

[a]Quantitative Structure-Property Relationship (QSPR).
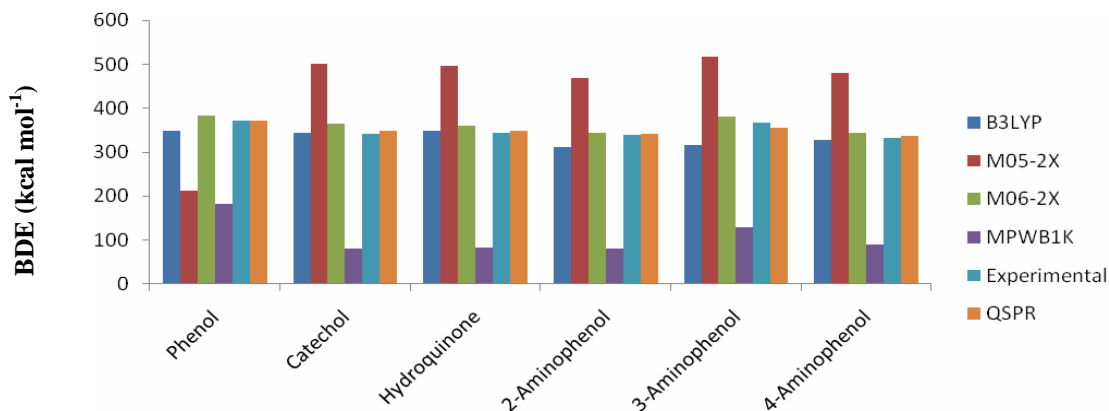
Fig. 3. Pictorial view of the calculated BDE (kcal mol^{-1}) for the working sets in the gas phase.

Table 2. Calculated BDE (kcal mol^{-1}) in Ethanol

| Compounds	B3LYP	M05-2X	M06-2X	MPWB1K	Experimental [12]
Phenol	40.4	45.3	42.6	80.8	80.2
Catechol	21.9	26.6	23.2	74.9	72.8
Hydroquinone	21.0	25.5	22.1	73.6	78.5
2-Aminophenol	16.2	25.5	22.1	67.7	70.4
3-Aminophenol	30.0	35.1	32.5	78.2	-
4-Aminophenol	20.0	24.7	21.5	67.1	75.5

Comparison between the experimental data and the calculated BDEs at the MPWB1K functional shows a better agreement on CPCM procedure. Figure 4 indicates a pictorial representation of the data in Table 2. However, the values of the BDE in ethanol relative to the gas phase show that the phenolic-based antioxidants have a higher ability in hydrogen transfer in ethanol, which can be described in the theory of the solute-solvent interactions and polarizing effects of the ethanol.

Considering Table 2 and Fig. 4, the antioxidant activities are according to:

4-aminophenol > 2-aminophenol > hydroquinone > catechol > 3-aminophenol > phenol.

IP Calculation

Single electron migration is an important process in calculation of the ionization potential. The antioxidant
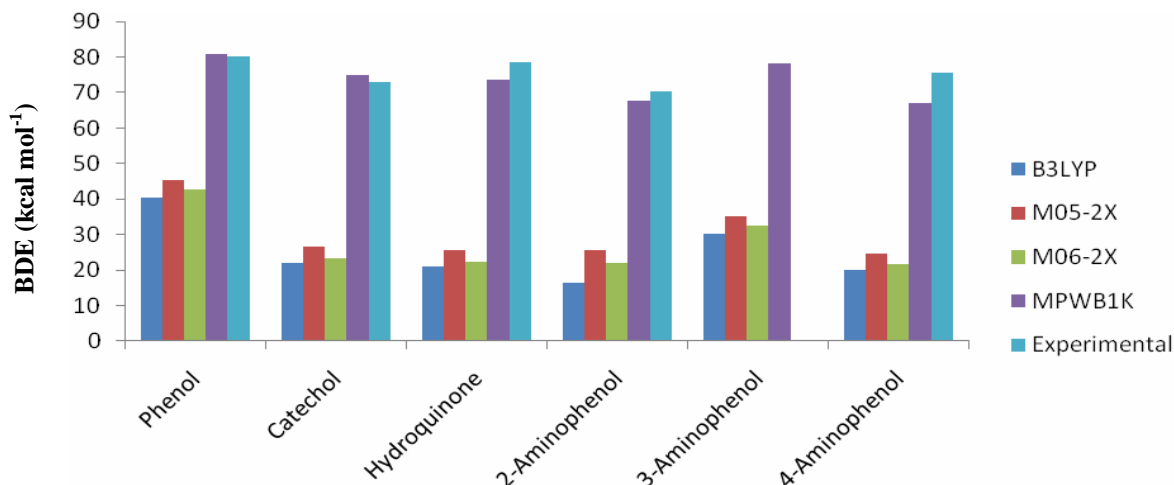
Fig. 4. Graphical presentation of the working sets of Table 2.

Table 3. Comparison Between the Calculated BDE and IP Values (kcal mol^{-1}) in the Gas Phase and Ethanol

Compound	BDE		IP	
	Ethanol	Gas phase	Ethanol	Gas phase
Phenol	80.8	86.9	392.4	601.0
Catechol	74.9	82.4	386.6	581.5
Hydroquinone	73.6	81.7	385.3	577.3
2-Aminophenol	67.7	77.9	372.2	559.9
3-Aminophenol	78.2	86.4	390.0	593.8
4-Aminophenol	67.1	77.8	378.8	557.0

activity can be correlated with electron donation. In the other words, a molecule with higher values of the IP shows the lower antioxidant activity. Theoretical values of the IP in the phenol derivatives in the gas phase and ethanol have been reported in Table 3.

Considering Table 3, it is confirmed that ethanol has affected the IP values, greatly. This behavior is completely different from the BDE mechanism in which the ethanol did not show a great important effect, while the IP values are very surprising in the ethanol. This is because of the charge separation process which is largely sensitive to the polarity of ethanol. The topological parameters accelerated by the substitutes, affect on the BDE whereas the structure of the whole molecule will affect on the IP values [29]. In the IP mechanism, an electron transfer from a neutral substrate results in a cation radical/anion radical formation. The

Table 4. Calculated HOMO Energy (a.u.) Level at the 6-311++G(d,p) Level of the Theory

Compound	HOMO	
	Gas phase	Ethanol
Phenol	-0.284	-0.203
Catechol	-0.270	-0.189
Hydroquinone	-0.265	-0.182
2-Aminophenol	-0.252	-0.175
3-Aminophenol	-0.259	-0.179
4-Aminophenol	-0.247	-0.168

calculated IP values for the studied phenol derivatives are as follows:

2-aminophenol > 4-aminophenol > hydroquinone > catechol > 3-aminophenol > phenol

Molecular Orbital Analysis

In the molecular orbital analysis, it is always focused on the electrons as the most fundamental entity in the chemical reactions; HOMO and LUMO. HOMO orbitals are important to approximate the free radical scavenging activity of the phenolic antioxidants. Because a molecule with higher HOMO energy level displays a proper electron distribution ability.

The HOMO energy levels of the studied phenols have been calculated at the M06-2X and MPWB1K/6-311++G(d,p) level of theory and are reported in Table 4.

Based on the results in Table 4, 4-aminophenol has the lowest HOMO energy level, whereas phenol has the highest one. These results are in accordance with the calculated BDE values. HOMO energy levels increase in ethanol compared to those in the gas phase. The lowest HOMO energy level corresponds to the largest BDE. Therefore, a linear correlation between the HOMO energy level and bond dissociation energy is expected.

Figure 5 shows the different distributions of the HOMOs

on the position and number of substituted OH groups. In 4-aminophenol and 2-aminophenol, which have the OH groups on *para* and *meta* positions, respectively, the HOMOs are almost localized on the active part of the molecule, while in hydroquinone and catechol, they are centered on the NH groups which have the greatest influence on the antioxidant activity. Hence, the radical scavenging activity in agreement with the gas phase is: 4-aminophenol > 2-aminophenol > 3-aminophenol > hydroquinone > catechol > phenol, respectively.

Spin Density Distribution Analysis

Spin density is the number of nuclear dipoles per volume unit, and a key parameter in destroying the free radicals. It is determined as the total electron density of one definite spin, minus the total electron density of the electrons of other spins. Spin density is frequently estimated as the stability of the free radicals and antioxidant inhibitory properties. In general, for the phenoxyl free radicals, substituents can delocalize this spin density and stabilize the free radical. This effect is dominated for the *para* and *ortho* positions where the spin density value is the highest. The oxygen atom at the *para* position may be involved in the π-electron system and delocalizes the spin density [30]. According to Table 5, 2-aminophenol radical has the lowest

2-Aminophenol **3-Aminophenol** **4-Aminophenol**

Catechol **Hydroquinone** **Phenol**
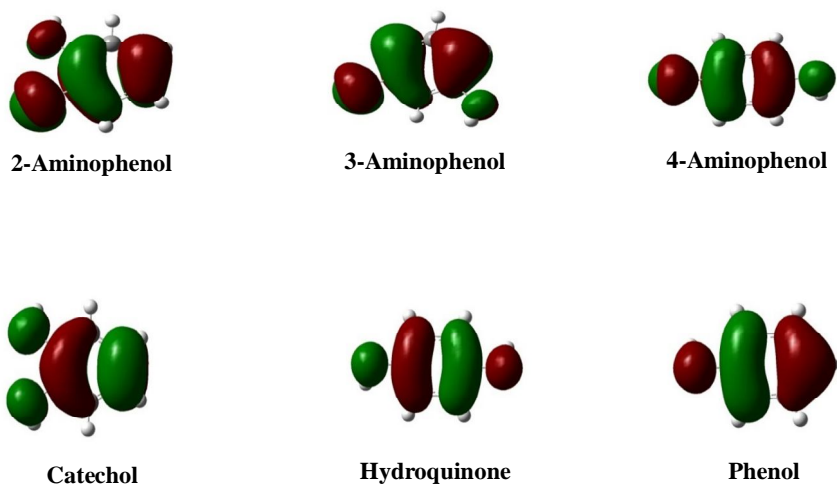
Fig. 5. 3D-view of the HOMO for different hydroxyphenols in the gas phase at the M06-2X/6-311 ++ G(d,p) level.

Table 5. Spin Density Distribution on the Phenoxy Radicals of the Studied
Hydroxyphenols in the Gas Phase and Ethanol

Radical	Spin density	
	Gas phase	Ethanol
Phenol	0.416	0.339
Catechol	0.383	0.303
Hydroquinone	0.386	0.297
2-Aminophenol	0.314	0.243
3-Aminophenol	0.386	0.276
4-Aminophenol	0.358	0.260

spin density in the gas phase and ethanol, whereas the phenol radical has the highest one. Spin density values are smaller in the solvent than those in the gas phase. This means that the spin density can be considered as a function of the medium polarity, and the results correspond to the BDE values.

CONCLUSIONS

In the present work, DFT method has been applied to

study the structure-activity relationship for a group of the phenolic compounds. All calculations have been carried out in the gas phase and in solution to estimate the values of the BDE and IP for the O-H bond breaking. Moreover, HOMO analysis and spin density distribution have been investigated. According to different analyses, the BDE mechanism is a more reasonable path for describing the radical scavenging activity of hydroxyphenols. Therefore, the HAT mechanism, intramolecular H bonds with the oxygen radical, is preferred because it is independent of phase conditions and it has lower energy than the IP mechanism. This means that BDE and antioxidant activities have a good correlation. Hence, The HAT mechanism is a reasonable path for calculating the radical-scavenging activity of antioxidants.

ACKNOWLEDGEMENTS

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