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A DFT study on the structure and radical scavenging activity of newly synthesized hydroxychalcones

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Quantum-chemical computations based on the density functional theory have been employed to study the relation between the structure and the radical scavenging activity of six newly synthesized hydroxychalcones. The three main working mechanisms, hydrogen atom transfer (HAT), stepwise electron-transfer-proton-transfer, and sequential-proton-loss-electron-transfer (SPLET), were investigated, and the O–H bond dissociation enthalpy, ionization potential, proton dissociation enthalpy, and electron transfer energy parameters were computed in the gas phase and in solvents using PCM model. The geometry structure, radical, electron character, and the frontier molecular orbital were analyzed to explore the key factors that influence the radical scavenging activity of the hydroxychalcones. Results indicated that 3,4-dihydroxychalcone (6) possessing the catechol functionality is expected to be more efficient hydrogen atom and proton donor than others. The theoretical results confirm the important role of the B-ring and shed light on the role of the o-dihydroxy (catechol) moiety in the antioxidant properties of hydroxychalcones. In addition, the calculated results are in good agreement with experimental values. It was found that HAT is the most favored mechanism for explaining the radical-scavenger activity of hydroxychalcone in the gas phase, whereas SPLET mechanism is thermodynamically preferred pathway in aqueous solutions. Copyright © 2012 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this paper.

Keywords: DFT; hydroxychalcones; ionization potential; O–H bond dissociation enthalpy; proton dissociation enthalpy; radical scavenging activity

INTRODUCTION

Free radicals can result in the food souredness, the oil rottedness, and the most of industrial product aging. Moreover, free radicals are implicated in numerous pathological conditions such as inflammation, metabolic disorders, cellular aging, reperfusion damage, atherosclerosis, and carcinogenesis.[1–5] Therefore, there is increasing interest in the protective and preventive function of foods and their constituents against oxidative damage caused by free radicals.

Phenolic antioxidants are a potent compound applied in the fields of commerce and biology to inhibit the material oxidation. Based on the studies of the antioxidant mechanism in the experiment and theory, it was universally considered that the radical scavenging abilities of these compounds depend greatly on the number and arrangement of phenolic hydroxyl groups. In the last two decades, theoretical methods, especially the density functional theory (DFT) method, have been successfully used to evaluate chemical properties and to elucidate the structure–activity relationship (SAR) for phenolic antioxidants.[6–15] Moreover, the study of the electronic and molecular properties is of great importance to understand the mechanism of the antioxidant activity of these compounds.

Chalcones (or 1,3-diaryl-2-propen-1-ones) belonging to flavonoid family are largely distributed in plants, fruits, and vegetables (see Fig. 1). They are precursors of open chain flavonoids and isoflavonoids, which are abundant in edible plants.[16] The presence of a α,β-unsaturated bond and the absence of the central C-ring are two specific characteristics of chalcones, making these compounds chemically different from the other flavonoids. Chalcone and its derivatives have attracted increasing attention due to numerous pharmacological applications. They have displayed a broad spectrum of pharmacological activities, such as antimalarial,[17,18] anticancer,[19] antiprotozoal,[20] anti-inflammatory,[21] antibacterial,[22] antifilarial,[23] antifungal,[24] antimicrobial,[25] larvicidal,[26] anticonvulsant,[27] and antioxidant[28,29] activities. Moreover, they have also shown inhibition of the enzymes, especially mammalian alpha-amylase,[30] cyclo-oxygenase,[31] and monoamine oxidase.[32]

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a

2-Hydroxychalcone (**1**) 3-Hydroxychalcone (**2**) 4-Hydroxychalcone (**3**)

2-Hydroxy-3-methoxychalcone (**4**) 3-Hydroxy-4-methoxychalcone (**5**) 3,4-Dihydroxychalcone (**6**)

b

n-Coumaric acid (**CoumA**) Ferulic acid (**FA**) Caffeic acid (**CA**) Chroman C1 (**CrC1**)
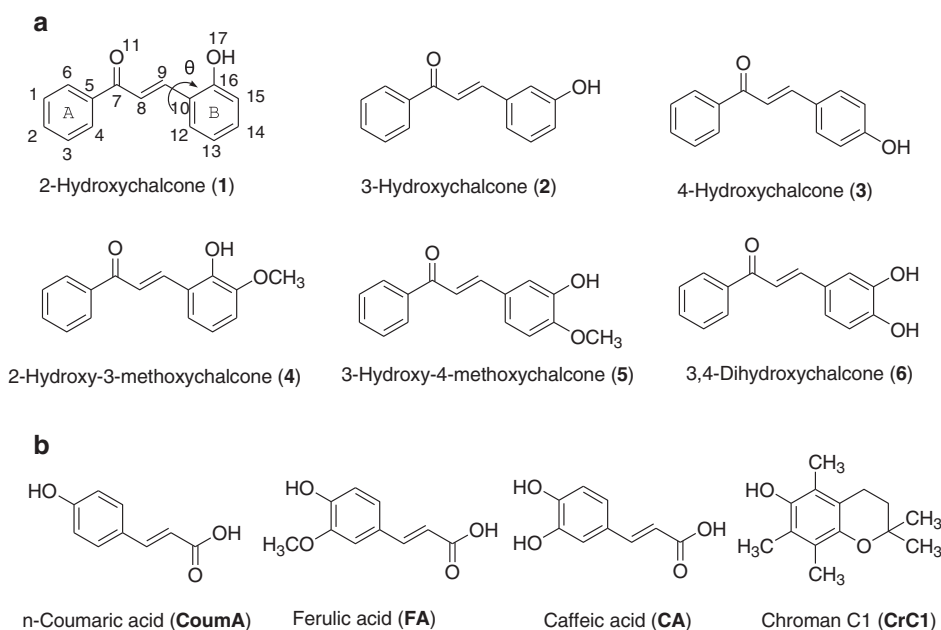
Figure 1. Structures of the hydroxychalcones **1–6** (a) and related compounds (b)

As an important part of chalcones family, hydroxychalcones are an object of attracted continuously growing interest among the scientists. In the last decade, a large number of literatures have been published on the beneficial effects of hydroxychalcones, especially the antioxidant activity.[33–39] These experimental results have shown that hydroxychalcones are efficient for the scavenging of various radicals including DPPH radical. Moreover, some of them, such as 2,3,4,6-tetrahydroxychalcone, exhibit more potent radical-scavenging activity than vitamin C and α-tocopherol.[37]

In addition to the experiment-derived qualitative SARs, a few theoretical investigations mainly based on DFT have also been performed on the antioxidant activity of hydroxychalcones to elucidate the SARs. Moa et al.[40] calculated O–H bond dissociation energies (BDE) and ionization potentials (IPs) of butein and isoliquiritigenin at the B3LYP/6-311++G(2d,2p) level using quantum theory of atoms in molecules. It was indicated that these hydroxychalcones bear a significant radical-scavenging activity similar to those of natural hydroxybenzoic and cinnamic acids. Cotelle et al.[41] investigated the redox properties of a series of hydroxychalcones by cyclic voltammetry and theoretical calculation. Kozlowski and co-workers[42] have reported a detailed study of conformational, electronic, and antioxidant properties of a series of natural hydroxychalcones by B3P86/6-31+G** calculations. Their results demonstrated the importance of the H atom transfer (HAT) mechanism to explain their capacity to scavenge the free radicals. Furthermore, the active sites were identified as the 6-OH group and the 3,4-dihydroxy-catechol. The calculated results obtained by Chen et al.[43] showed that the 2,4,3′,4′-tetrahydroxychalcone (butein) can serve as a powerful antioxidant against DPPH radical.
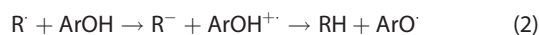
On the basis of what was previously mentioned, it is evident that further research studies are needed and would be useful to fully understand the antioxidant capability of hydroxychalcones. Very recently, the antiradical activity of six hydroxychalcones and a number of related compounds (see Fig. 1) was determined by a chemiluminescence method using the scavenging of peroxide
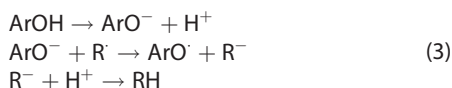
radicals ROO· + ArOH → ROOH + OAr (with the rate constant k_7) in a model reaction of diphenylmethane (RH) oxidation.[44] Meanwhile, the structures and energies of the reagents and intermediates were determined by semi-empirical quantum chemical (PM3, PM6) calculations. The paper has shown that compound **6**, which have a catechol structure, exhibited high antioxidant activity.

The aim of this work is to study the structural and electronic properties of these hydroxychalcones and their radicals at DFT level, in order to further shed light on the structure-radical scavenging activity relationship of these compounds and provide new clue for antioxidant development. Specifically, the homolytic bond dissociation enthalpy (BDE) of O–H bonds, adiabatic IP, O–H heterolytic BDE [proton dissociation enthalpy (PDE)], electron transfer energy (ETE), HOMO orbital distribution, and spin density in free radicals were calculated. With the current work, we hope to highlight the potent antioxidant activities of hydroxychalcones and stimulate the interest for further studies and exploitation in food or pharmaceutical applications.

THEORETICAL AND COMPUTATIONAL METHOD

According to the literature, there are at least three mechanisms reported for the radical scavenging processes of phenolic antioxidants (ArOH)[8,12,45,46]: (i) a direct HAT to the radical (R·), Eqn 1; (ii) stepwise electron-transfer-proton- transfer (ET-PT), Eqn 2; (iii) sequential-proton-loss-electron-transfer (SPLET), Eqn 3.

$$R· + ArOH → RH + ArO· \tag{1}$$

$$R· + ArOH → R^- + ArOH^{+·} → RH + ArO· \tag{2}$$

$$ArOH \rightarrow ArO^- + H^+$$
$$ArO^- + R^· \rightarrow ArO^· + R^- \qquad (3)$$
$$R^- + H^+ \rightarrow RH$$

In HAT, the reactivity of an ArOH can be estimated by calculating the O–H BDE, where the lower the BDE value, the higher the expected activity. The first step in mechanism 2 (ET-PT) is an electron-transfer reaction, whose corresponding controlling parameter is the adiabatic IP of ArOH; molecules with the lower IP values are expected to have higher activity. The PDE is involved in mechanism 3, where the ETE of ArO^- is another controlling parameter. Thus, in the present study BDE, IP, PDE, and ETE values were used as the main molecular descriptors to elucidate the radical scavenging activity of the investigated compounds.

As the method of choice, a DFT procedure was chosen at the B3LYP level, as a good compromise between feasibility of the method and accuracy.[7,8,14,46] All geometries of title compounds and their radicals were optimized without constraints, employing the DFT/B3LYP (UB3LYP for the resulting radicals) exchange-correlation functional and the 6-31G(d) basis set. Vibrational frequencies were obtained at the same level of theory, with the aim to characterize all structures as minima and to estimate zero-point energy corrections that were included into the electronic energies. Single-point energy (SPE) calculations using the 6-311++G(2d,2p) basis set were performed at B3LYP level on the 6-31G(d) optimized geometries and used to refine electronic energies. In the process of optimization of the structure of radicals, the spin contamination was monitored. No spin contamination was found for radicals, with the $<S^2>$ values being about 0.750 in all cases.

The molecular enthalpy at 298 K (H) is consisted of B3LYP/6-311++G(2d,2p) calculated SPE values and B3LYP/6-31G(d) thermal contributions to enthalpy (TCE, in which the vibrational contributions include zero-point vibrational energy). Then, the BDE values were calculated according to the formula $BDE = H_r + H_h - H_p$, where p, r and h indicate the parent molecule, the radical, and the H atom, respectively. The exact value of the electronic energy of the H atom (0.5 hartree) was used instead of the prediction by DFT methods. The enthalpy of the H atom at 298.15 K, including the translational and PV corrections, was 0.49764 hartree.[12] The IP values of neutral and anion forms were obtained according to the equation $IP = E(ArOH^{+·}) - E(ArOH)$ and $ETE = E(ArO^·) - E(ArO^-)$, respectively. ZPE was added to the electronic energy to obtain E_0 at 0 K. The PDE of the ArOH was calculated from the following equation, $PDE(ArOH) = H(ArO^-) + H(H^+) - H(ArOH)$. As previously proposed[47] gas-phase corrections were employed to calculate these parameters in the aqueous phase, since the vibrational frequencies calculation with PCM is computationally very demanding (and not very accurate) and thermal corrections are expected to be rather similar in the gas and solvated phases.

The HOMO orbital distribution and energy and the spin density were determined by using the (U)B3LYP/6-31G(d) level of theory for the fully optimized structure of the compounds. Solvent effects were computed on the single point level by using the integral equation formalism polarized continuum model.[48,49] PCM calculations were performed in water ($\varepsilon = 78.35$) to maximize the polarization effect as compared to vacuum calculations. Since in biological conditions antioxidants may also act in lipid membranes, the influence of the dielectric constant was also estimated using the benzene dielectric constant

($\varepsilon = 2.27$). This is assumed to give a reliable approximation of the polarizable conditions of a nonpolar medium such as lipid membrane. All calculations were performed by using Gaussian03 software package.[50]

RESULTS AND DISCUSSION

Conformational analysis and molecular geometries

The α,β-double bond of chalcone is always considered to exist in the trans configuration, since the cis configuration is unstable due to the strong steric effects between the B-ring and the carbonyl group. Then, two conformers arising from the torsion around C7–C8 bond must be taken into account: the s-cis and the s-trans compounds. Our previous calculations[51–53] have indicated that the s-cis conformer is more stable than the s-trans one, thus, we decided to focus on the s-cis conformer for compounds **1–6**.

The potential energy surfaces were obtained in relation to the torsion angle θ defined by the C8-C9-C10-C12 atoms (Fig. 1). The torsion angle θ was scanned in steps of 10° without constrains on all other geometrical parameters at the B3LYP/6-31G(d) level of theory in vacuo. The plots of the potential energy profile are shown in Fig. 2. The computations suggest that two minima (M_1 and M_2) are found for each hydroxychalcone studied, one at 0° (M_1) and the other at 180° (M_2) along the rotation of catechol or phenol moiety. The energy difference between the two conformers of each hydroxychalcone is very low, with the largest value of only 0.61 kcal/mol (see Table 1). The potential energy is maximum at 90°, and the barrier between the potential energy maximum and the minimum is in the range of 5.05 to 6.80 kcal/mol. Therefore, conversions between the two conformers can take place easily under normal conditions.

Based on the minimum energy conformations obtained from the energy scan, further geometry optimization was performed with the B3LYP/6-31G(d) method. The optimized structures of the most stable conformers of neutral form of hydroxychalcones are presented in Fig. 3. For comparison, the optimized structures of the related compounds, including *p*-coumaric acid (**CoumA**), caffeic acid (**CA**), ferulic acid (**FA**), and α-tocopherol analogue (**CrC1**), are also given in Fig. 3. The optimized geometrical parameters for neutral molecules and its radicals are shown in Tables S1–S3 in Supporting Information. From the data of bond distances and bond angles, it can be seen that no significant geometrical change has been observed when going from the neutral molecule to the phenoxy (ArO·) and cation (ArOH+·) radicals and the anion forms (ArO⁻). Most of the bond distances are exhibiting double bond character and at the same time shorter than single bonds. From the data of dihedral angle in Table S3, it can also be seen that the torsion angles between B-ring and the plane of enone system are nearly equal to 0°(180°), while the ones between A-ring and the plane of enone system are about 10°. The planarity of B-ring compared to the plane of enone system is further indication of possible extended conjugation and their stronger antioxidant activities, since the high scavenging activity of the molecule correlates with the planarity of the ring B, compared to the rest of the molecule.[54,55]

BDE analysis

Table 2 presents the calculated BDE values in the gas phase and solvents (benzene and water). For a compound possessing more than one phenolic hydroxyl, its radical-scavenging activity is
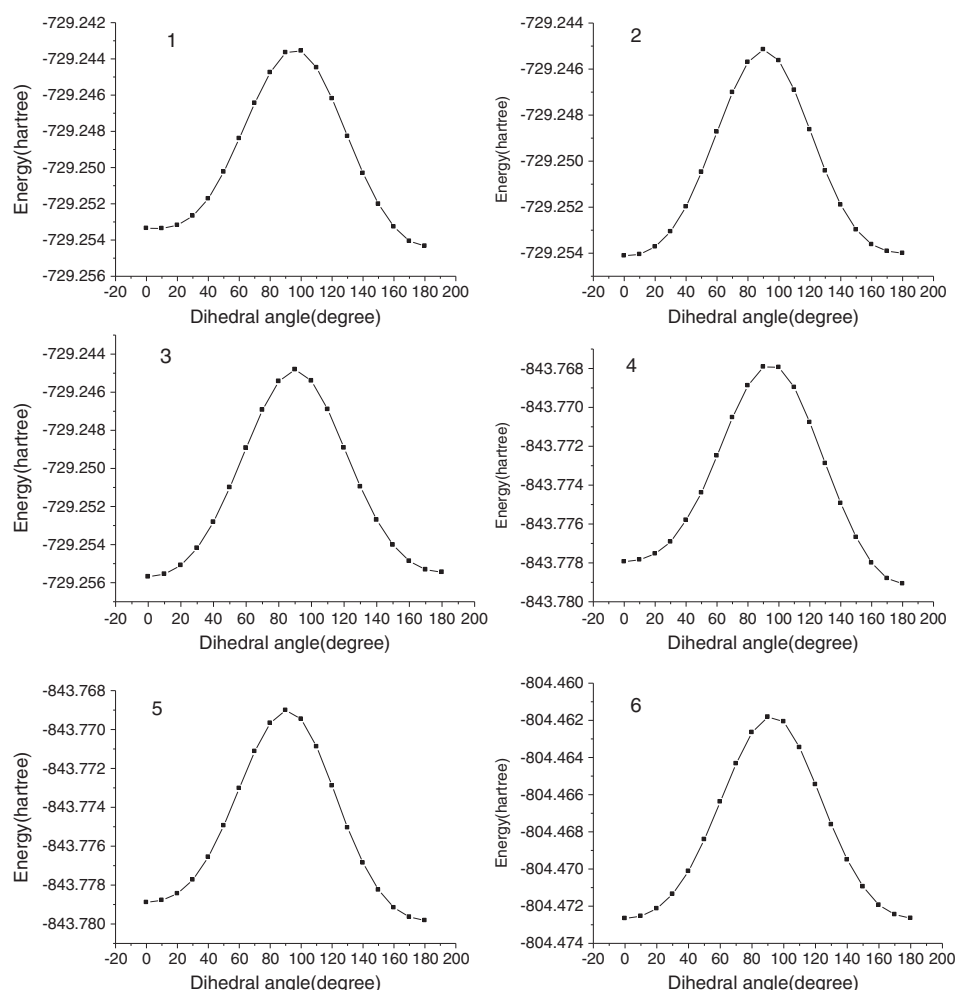
Figure 2. Potential energy curves of hydroxychalcones **1–6** calculated at the B3LYP/6-31G(d) level in the gas phase

Table 1. The energy as a function of torsional angle of the six hydroxychalcones at the B3LYP/6-31G(d) level

	M_1(hartree)	TS (hartree)	M_2 (hartree)	ΔE_1(Kcal/mol)[a]	ΔE_2(Kcal/mol)[b]
1	−729.25335	−729.24365	−729.25433	0.61	6.70
2	−729.25411	−729.24515	−729.2540	−0.07	5.55
3	−729.25569	−729.24481	−729.25545	−0.15	6.68
4	−843.14709	−843.13976	−843.1478	0.45	5.05
5	−843.77889	−843.76901	−843.77982	0.58	6.78
6	−804.47266	−804.46182	−804.47265	−0.01	6.80

[a]$\Delta E_1 = E_{M1} - E_{M2}$
[b]$\Delta E_2 = E_{TS} - E_{M2}$

determined by the one with the lowest O–H BDE. On the basis of the calculated O–H BDEs, the sequence of hydrogen donating ability of the hydroxychalcones is as follows: **6** > **3** > **4** > **1** > **5** > **2**, which is fully consistent with the order of antioxidant activity deduced from experimental rate constant.[44] In addition, the BDE value of **6** is comparable to those of **CrC1** and **CA**. This is also in line with the experimental results, i.e. the rate constant of compound **6** has the same order of magnitude as that in efficient antioxidants **CrC1** and **CA**.

As can be seen from Fig. 4, the spin densities of **2r**, **5r**, and **6r-b** radicals mainly distribute on the phenolic oxygen atom and the phenyl ring B, whereas in **1r**, **3r**, **4r**, and **6r-a** radicals, the spin densities delocalize not only on the phenolic oxygen and B-ring, but also on the enone system. This indicates that the spin densities in **1r**, **3r**, **4r**, and **6r-a** radicals are more delocalized, and thus these three radicals are more stable than other radicals. It must be stressed that the more delocalized the spin density in the radical leads more easily to the formation of the radical and makes the
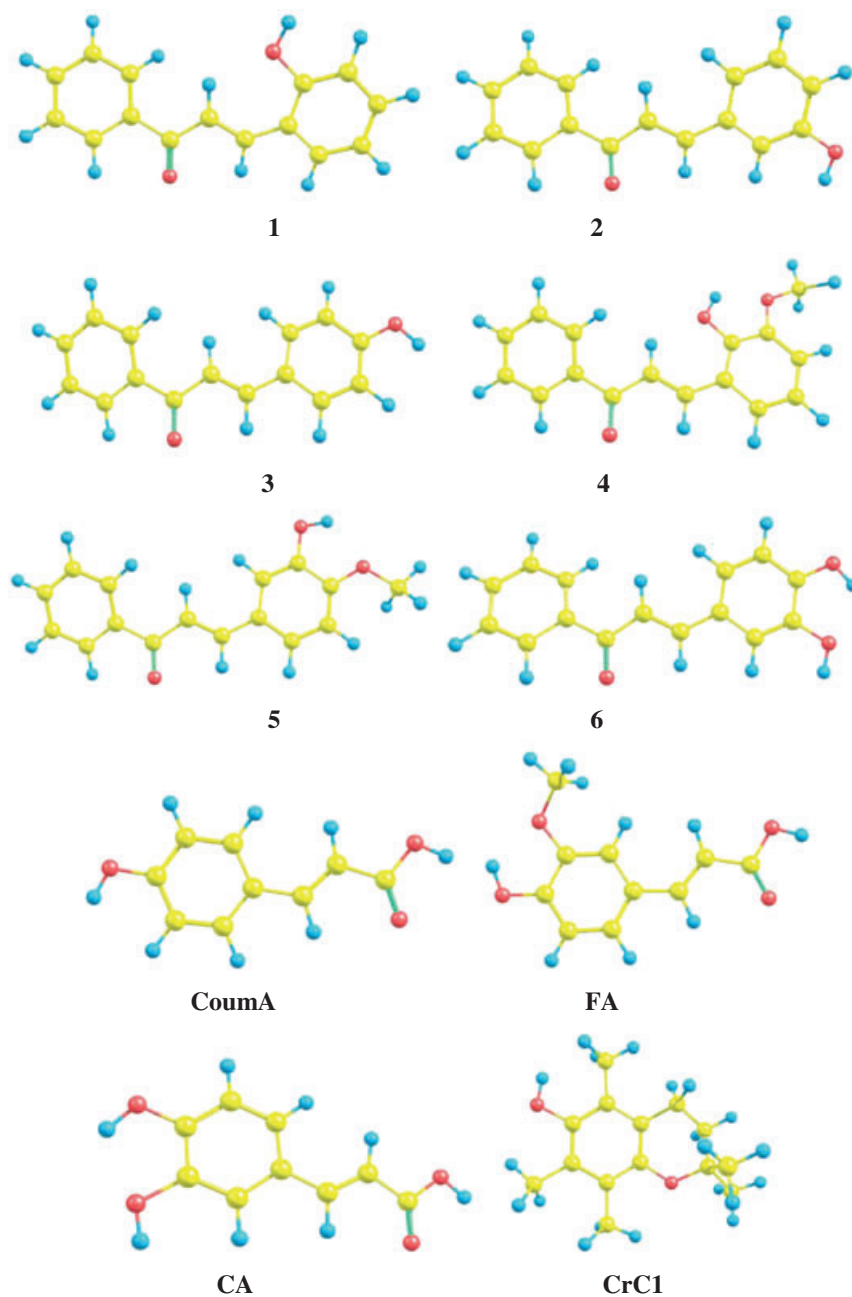
Figure 3. Optimized structures of hydroxychalcones **1–6** and the related compounds calculated at the B3LYP/6-31G(d) level in the gas phase

BDE lower.[56] Thus, the O–H BDE is lower in **1**, **3**, **4**, and **6** than other two molecules.

In the present study, compound **6**, bearing catechol group on the aromatic B ring, presented lower BDE values (76.5–81.0 kcal/mol), in comparison to those of other compounds bearing no such groups. Comparing **6** with **3**, we find that the presence of catechol group on aromatic rings decreases the O–H BDE by about 5 kcal/mol (Table 2). Such value was close to those computed for the simple catechol,[12] as well as the catechol moiety in the analogous **CA** (Table 2). This difference can be explained by the IHB effect and the ortho-hydroxyl electronic effect. The radical arising from H atom removal is stabilized by the formation of the IHB with the vicinal hydroxyl. According to our previous calculations on **6**,[53] the barrier height for the rotation of O–H in the radical is only ca. 5.8 kcal/mol;

hence, this rearrangement is energetically favorable. The latter ortho-hydroxyl electronic effect is rather simple and just results from the electron-donating property of the OH group. It is well known that electron-donating groups reduce the O–H BDEs for monophenols.[57]

Comparing **4** with **1**, or **5** with **2**, we find that the introduction of the electron-donating methoxy group in the o-position of 2-OH or 3-OH has almost no effect on the O–H BDE. As can be seen from Table 2, the 2-OH group of **4** exhibited a BDE lower by only about 1 kcal/mol than that of **1**. This is in agreement with the experimental results. Among the phenolic hydroxyls at different positions, the hydroxyl at position 4 in compound **3** has lower BDE than that of O2-H in **1** and O3-H in **2** obtained both in the gas phase and in aqueous solution, which shows that the hydrogen atom in O4-H is more active than those in O2-H and

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Table 2. The O–H BDE, IP, PDE, and ETE (in kcal/mol) values of hydroxychalcones **1–6** and the related compounds. The rate constant from experimental measurement are also included for comparison

Comp.		BDE			IP		PDE[b]		ETE		$K(M^{-1} s^{-1})$[a]
	radical	gas	benzene	water	gas	water	gas	water	gas	water	
1	2-OH	83.1	83.8	85.4	183.1	141.4	327.6	44.4	67.7	108.4	3.9×10^4
2	3-OH	86.2	86.6	87.8	182.0	140.3	337.4	49.2	62.5	105.7	1.1×10^4
3	4-OH	81.9	82.6	84.1	176.4	134.8	326.3	44.0	69.8	107.8	1.1×10^5
4	2-OH	82.0	82.6	83.7	174.6	135.8	330.4	45.5	65.3	105.4	2.4×10^4
5	3-OH	84.8	85.1	86.1	170.8	131.7	337.8	51.0	60.6	102.1	1.2×10^4
6	3-OH	79.3	80.9	83.5	172.9	133.4	328.4	47.5	64.5	103.1	8.7×10^6
	4-OH	76.5	78.2	81.0			321.8	43.4	68.3	104.6	
CoumA		83.4			183.1						2.2×10^4
FA		83.1			180.4						3.6×10^6
CA		74.9			178.8						4.6×10^6
CrCl		73.1			154.2						7.6×10^6
phenol		85.0			191.6						-

[a]Rate constant[44]
[b]The enthalpy values of 1.48 and −245.05 kcal/mol are used for H$^+$ in the gas phase and water, respectively.[60,61]
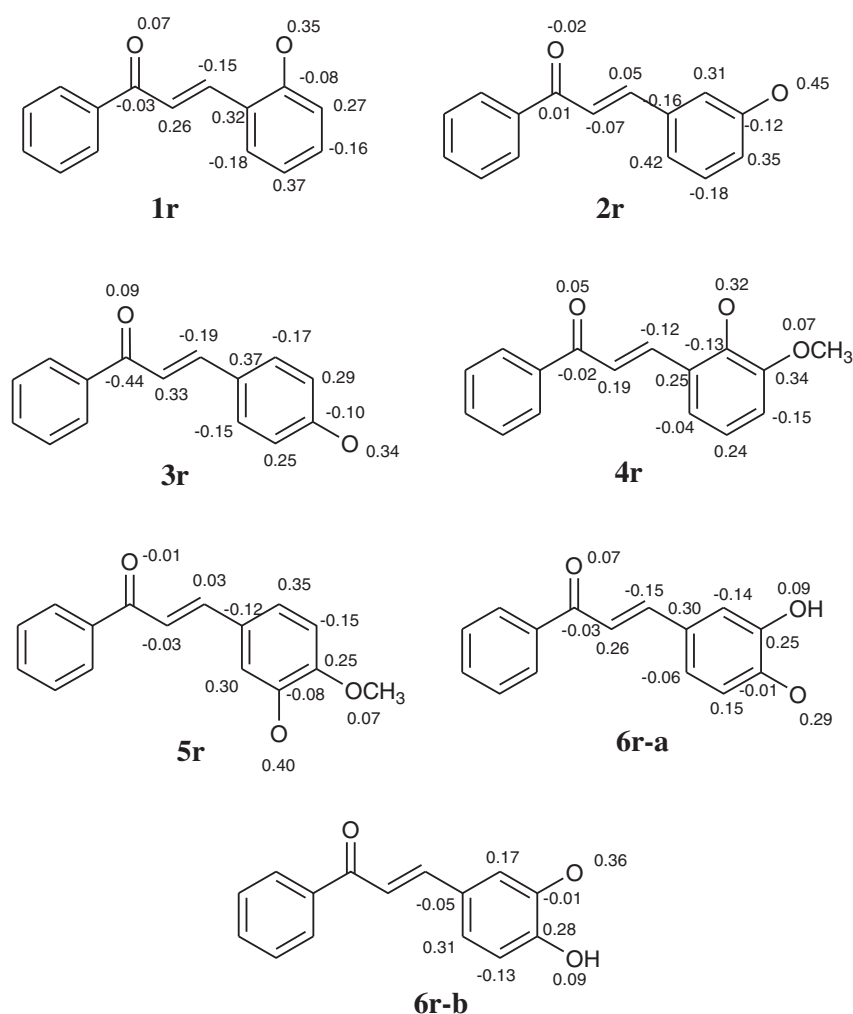
Figure 4. The spin density in phenoxy radicals of hydroxychalcones **1–6** in the gas phase computed at uB3LYP/6-31G(d) level of theory. Only the sites with values higher than 0.01 are shown

O3-H. Indeed, the BDE values (Table 2) for the phenolic hydroxyls at different positions give the following sequence: 4 < 2 < 3. As shown in Fig. 4, the value of spin density on the phenolic O-atom follows the order of O4 < O2 < O3. This order conforms to BDEs of the hydroxyls in the relevant positions, having indicated a good relationship between H-abstraction and unpaired electron delocalization.

When solvents were taken into consideration, an increase of 1.3–4.5 kcal/mol was obtained for BDE values when computation was carried out in polar water. Smaller differences (0.3–1.7 kcal/mol) were found in the nonpolar benzene. Such a result has previously been reported for structurally related aurones[54] and trans-resveratrols,[7] i.e. an increasing of the BDE values in going from the gas phase to solvent. It is noticeable that the order of BDE values calculated for the solvent phase is the same as that for the gas phase.

Results presented in Table 2 show that the BDEs computed in the gas phase (76.5–86.2 kcal/mol) are similar to or smaller than those of cinnamic acid antioxidants such as **CoumA** (83.4 kcal/mol), **FA** (83.1 kcal/mol), and **CA** (74.9 kcal/mol) calculated at the same level of theory. This indicates that most of the phenolic hydroxyls were of comparable or better hydrogen donating ability than the cinnamic acid antioxidants. In addition, the BDE of 4-OH group in **6** that is the most active (76.5 kcal/mol in the gas phase) is similar to that of **CrC1** (73.1 kcal/mol), a model for the antioxidant α-tocopherol lacking the phytl ($C_{16}H_{33}$) tail.

IP analysis

As reported above, antioxidants may also act according to the ET-PT mechanism. In this case, IP is an important physical factor indicating the range of electron donation. The IPs of hydroxy-chalcones in the gas phase as well as in water are presented in Table 2. As can be seen from Table 2, the compound exhibiting the lowest value of gas-phase IP is **5** (170.8 kcal/mol), followed by **6** (172.9 kcal/mol), **4** (174.6 kcal/mol), **3** (176.4 kcal/mol), **2** (182.0 kcal/mol), and **1** (183.1 kcal/mol). Similarly, as in the gas phase, the computations performed in water reveal that **5** has the highest electron donating ability whereas the ability of **1** to this process is smallest. By comparison, we found that the trend for calculated IP values is different from that of BDE values. This discrepancy can be attributed to the fact that BDE is affected by the local phenomena induced by the substituents, whereas IP value is affected by the structure of the whole molecule.[12]

When the solvent effect was taken into account, a significant influence of water medium on IP values was observed (Table 2). This is not unexpected because it is well known that cation radicals are charged and quite sensitive to the polarity of various solvents. The values of this antioxidant factor in water medium are dramatically lower than in the gas phase. For instance, IP value of **5** that is the most active, changes from 170.8 to 131.7 kcal/mol, in going from the gas phase to the water medium.

As shown in Table 2, the IP values in the gas phase of **1–6** are about 10–22 kcal/mol lower than that of phenol (191.6 kcal/mol) calculated at the same level of theory. Such a difference is rather small in comparison to those reported for other flavonoids, which usually have 30–40 kcal/mol lower IP value than that of phenol.[58] This suggests that when the electron transfer mechanism predominates for the scavenging of free radicals, hydroxychalcones **1–6** are not expected to be as efficient as other flavonoids. In addition, the IPs of **1–6** are similar to or
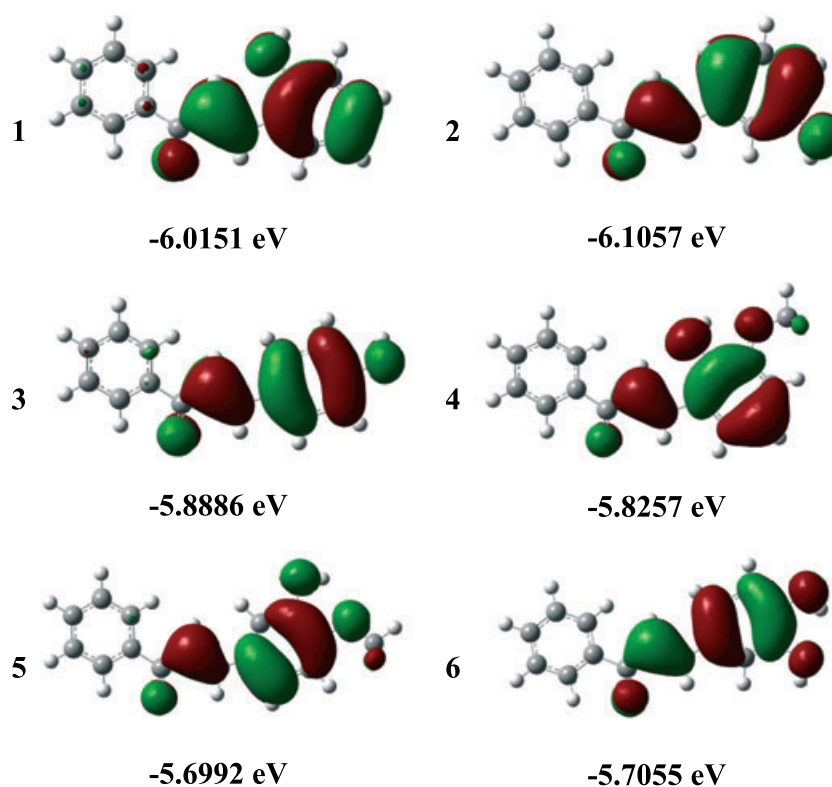

1 -6.0151 eV

2 -6.1057 eV

3 -5.8886 eV

4 -5.8257 eV

5 -5.6992 eV

6 -5.7055 eV

Figure 5. The orbital distribution and energy of HOMO for neutral forms of hydroxychalcones **1–6** computed at B3LYP/6-31G(d) level of theory in the gas phase

smaller than those of cinnamic acid antioxidants under investigation, but these values are higher than that of **CrC1**.

HOMO orbital distribution

When describing the free-radical scavenging activities of phenolic antioxidants, parameters such as the energy and distribution of the HOMO orbital are also useful. The molecules with a higher energy of the HOMO orbital have stronger electron donating ability. Based on our calculations (Fig. 5), hydroxychalcone **5** provided the highest HOMO energy, followed by **6**, **4**, **3**, **1**, **2**. This clearly confirms that **5** has the strongest electron-donating capability among the title compounds. Moreover, the predicted electron-donating capability order according to HOMO energies was found to be the same as that for IPs. Analysis of HOMO orbital distribution in Fig. 5 shows that HOMOs of the six compounds present similar distribution. The HOMO orbitals are mainly localized on 3-phenyl-propenal and phenolic oxygen atom. These results show that ring B and the enone are responsible for the free radical activities.

Antioxidant mechanisms

According to Wright et al.,[12] the mechanism dominating the antioxidant activity of a certain phenolic compound can be inferred from the relative values of its IP and BDE with respect to phenol (ΔIP and ΔBDE, respectively). Wright et al. believe that up to about ΔIP $= -36$ kcal/mol and for values of ΔBDE $\approx$ 10 kcal/mol, the mechanism is dominated by HAT, but for ΔIP above that point, reactions tend to be predominantly ET. From our calculations (Table 2), it is observed that the ΔIP values in the gas phase are in the range of 10–22 kcal/mol, whereas the ΔBDE values range from -8.5 to 1.2 kcal/mol. Therefore, HAT mechanism may be more likely for the dominant antioxidant mechanism of the hydroxychalcones in the gas phase.

From Table 2, it can be seen that the calculated gas-phase PDE of considered molecules are significantly higher than the O–H BDE and IP values. These results further indicate that from the thermodynamic point of view, HAT represents preferred reaction pathway in the gas phase. Due to the high solvation enthalpies of proton, PDEs obtained in water are far away lower than that obtained in the vacuum. The differences between PDE in gas and water phase are ranging from 278.4 to 288.2 kcal/mol for all investigated compounds. Moreover, for each compound, values of PDEs related to all phenolic protons in water are lower than those of BDEs and IPs. Thus, in such polar solvent, SPLET is the preferred mechanism. Computed ETEs of anion species are significantly lower than those of neutral species (IPs) in the two media. Furthermore, all ETEs are higher in water than in the gas phase. In the case of water phase, all ETEs are higher than PDE, while in the case of the gas phase, all ETEs are lower than PDE.

Overall, among the three mechanisms, HAT is thermodynamically preferred in the gas phase, and SPLET is thermodynamically preferred pathway in water. However, it should be kept in mind that the relative importance of HAT, ET-PT, or SPLET is not only determined by microenvironmental features (lipid phase, aqueous phase) but also governed by the characteristics of the scavenged radical.[59]

CONCLUSION

In this work, a DFT-based method has been applied to study the radical scavenging activity of a series of hydroxychalones. The O–H BDEs, adiabatic IPs, PDEs, and ETEs have been computed both in the gas phase and in solutions. In addition, other descriptors such as HOMO orbital distribution and spin density have also been presented.

The introduction of electron-donating groups for the molecules decreases the BDE values. The theoretical results confirm the important role of the B-ring and shed light on the role of the catechol moiety in the antioxidant properties of hydroxychalcones. Solution- and gas-phase hydrogen donating ability deduced from the BDE values follow the same trend, **6** > **3** > **4** > **1** > **5** > **2**, which is fully consistent with the experimental order obtained from kinetic measurement. The solvent influence was relatively weak on the BDEs, indicating that difference in reactivity between compounds **1** and **6** will be very similar in polar solution and in nonpolar medium such as lipid membranes. The results reveal that the trend for calculated IP values is different from that of BDE values. Moreover, the IP and ETE values depend significantly on the phase because of the stabilization of charged species by polar solvents. The obtained results also indicate the HAT is the most favored mechanism for explaining the radical-scavenger activity of hydroxychalcone in the gas phase, whereas SPLET mechanism is thermodynamically preferred pathway in aqueous solutions.

SUPPORTING INFORMATION

The calculated values of the key bond lengths and angles for the hydroxychalcones investigated (Tables S1–S3).

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