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ORIGINAL ARTICLE

DFT-Based Quantum Chemical Studies on Conformational, Electronic and Antioxidant Properties of Isobavachalcone and 4-Hydroxyderricin

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Abstract Isobavachalcone and 4-hydroxyderricin which exhibit numerous biological activities are two major chalcone constituents isolated from the roots of *Angelica keiskei* KOIDZUMI. The conformational and antioxidant activity properties have been investigated by quantum chemical calculations based on the density functional theory, with the aim of verifying dominant antioxidant mechanisms. Three parameters of the O-H bond dissociation enthalpy (BDE), ionization potential (IP) and acidity in the presence of an implicit solvent for methanol are computed to estimate the antioxidant capacities. Results reveal that the order of antioxidant efficacies predicted by BDE and IP, different from that predicted by acidity, is in agreement with that obtained by experimental data. This demonstrates the importance of the hydrogen atom transfer and single electron transfer mechanisms to explain their capacities to scavenge 2, 2-diphenyl-1-picrylhydrazyl (DPPH) free radical.

Keywords Chalcones · Antioxidant activity · Density functional · Bond dissociation enthalpy · Ionization potential · Acidity

Introduction

Numerous chalcone derivatives have been identified in fruits, vegetables, and various natural plants. They are precursors in flavonoid biosynthesis. Many biological properties (anti-inflammatory, analgesic, antioxidant, antibacterial, antitumor, hypotensive and antidiabetic activities) have been reported to be associated with chalcone intake [1–7]. Recent studies have demonstrated that the extracted chalcones from the roots of *Angelica keiskei* KOIDZUMI exhibit a variety of biological activities [7–9]. It has been reported that most extracted chalcones bear prenyl group including isobavachalcone (IBC) and 4-hydroxyderricin (4-HD).

IBC can inhibit tumor promotion in vivo, inducing mitochondrial apoptosis and apoptotic cell death via the mitochondrial pathway in neuroblastoma cells without affecting normal neuronal cells. So it is taken as a potentially useful, safe and selective antitumor agent againstneuroblastoma cell lines [10–12]. 4-HD has hypotensive, lipid-regulatory and antimetastatic activities by producing elevation of the serum high density lipoprotein (HDL) level and a reduction of liver triglyceride levels in hypertensive rats [9, 13]. 4-HD can provide antibacterial activity against Gram positive pathogenic bacteria [1, 14], insulin-like activity by suppressing the elevation of blood glucose levels [4], antitumor-promoting activity in mouse skin carcinogenesis induced by 7,12-dimethylbenz [*a*] anthracene (DMBA) plus 12-*O*-tetradecanoylphorbol-13-acetate (TPA) [11]. 4-HD can also inhibit phenylephrine-induced vasoconstriction *in vivo* and possess potent cytotoxicity against two neuroblastoma cells (IMR-32 and NB-39) [12]. Several properties are correlated to their capacities to scavenge free radicals. Free radicals can lead to carcinogenesis, aging, inflammation and atherosclerosis through the reaction with cellular biological macromolecules [15, 16]. Therefore, the elucidation of antioxidant activity of the two chalcones is of prime importance for understanding other biological properties of *A. keiskei*.

The harmful action of free radicals ($R^{\bullet}$) can be alleviated by antioxidants (ArOH) through four potential mechanisms:the hydrogen atom transfer (HAT); single electron transfer (SET);

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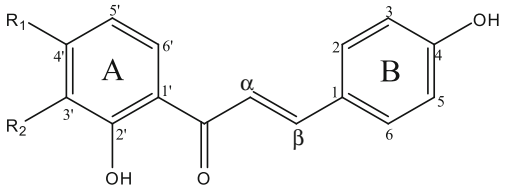

Isoliquiritigenin: R_1=OH, R_2=H

Isobavachalcone: R_1=OH, R_2=prenyl

4-Hydroxyderricin: R_1=OMe, R_2=prenyl

Fig. 1 Structures of the *s*-cis conformer of trans IBC and 4-HD; *s*-cis and *s*-trans represent the relative position of the C=O and C=C double bonds, with respect to the single bond

sequential proton-loss electron transfer (SPLET); proton-coupled electron transfer (PCET) [17–20].

$$\begin{aligned} &ArOH + R^{\cdot} \rightarrow ArO^{\cdot} + RH && (HAT/PCET)\\ &ArOH + R^{\cdot} \rightarrow ArOH^{\cdot+} + R^{-} && (SET)\\ &ArOH + R^{\cdot} \rightarrow ArO^{-} + RH^{+} \rightarrow ArO^{\cdot} + RH && (SPLET) \end{aligned}$$

Two or more of these mechanisms can operate simultaneously during the antioxidant action since different OH groups are involved. Which mechanisms operate dominant also depends on the properties of radicals. $R^{\bullet}$ can be (i) the stable 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical, (ii) one of the most toxic hydroxyl radical, (iii) the peroxyl radical, and (iv) the carbon-centered $CH_3^{\bullet}CHOH$ radical. The stability of radicals from the three reactions ($ArO^{\bullet}$, $ArOH^{\bullet+}$ and ArO^{-}) prevents or slows down the chain radical reactions. In this situation, the O-H bond dissociation enthalpy (BDE), ionization potential (IP) [21, 22] and acidity are introduced to evaluate the antioxidant capacities and the relative importance of these mechanisms.

One paper [23] has reported the use of DFT/B3P86 [24–27] for the study of eleven natural chalcones, compared to the widely used B3LYP functional [27–29]. On that basis, here, we extend the use of the DFT/B3P86 methodology to the two chalcones to compare.

The purpose of this research is to rationalize experimental findings to scavenge 2, 2-diphenyl-1-picrylhydrazyl free radical, by employing computational method. To our knowledge, no theoretical study based on density functional theory has been performed on IBC and 4-HD. Hence, the conformational behavior is first analyzed. Since the O-H bond dissociation enthalpy (BDE), ionization potential (IP) and acidity are of particular importance to decide which mechanisms are the favored ones, we compute these quantities and compare them with the data available in the literature [23]. We hope our study may help the chemists find some indications for exploring high-effective and innocuous chalcone-type antioxidant.

Computational Methods

All calculations referred in this study were performed with the Gaussian 03 software package [30]. The geometries of neutral molecules were optimized at the B3P86 exchange-correlation potential [26, 27] level employing the 6–31+G (d, p) basis set. The geometries and energies of phenoxyl radicals, radical cations, and phenoxide anions were obtained at the same level of theory. Then frequency calculations were performed to characterize all their conformations as minima or saddle points and to evaluate the zero-point energy corrections which were included in all the relative energy values.

To study the solvent polarity effects on the BDE and IP, the self-consistent reaction field (SCRF) calculation has been performed using the conductor-like polarizable continuum

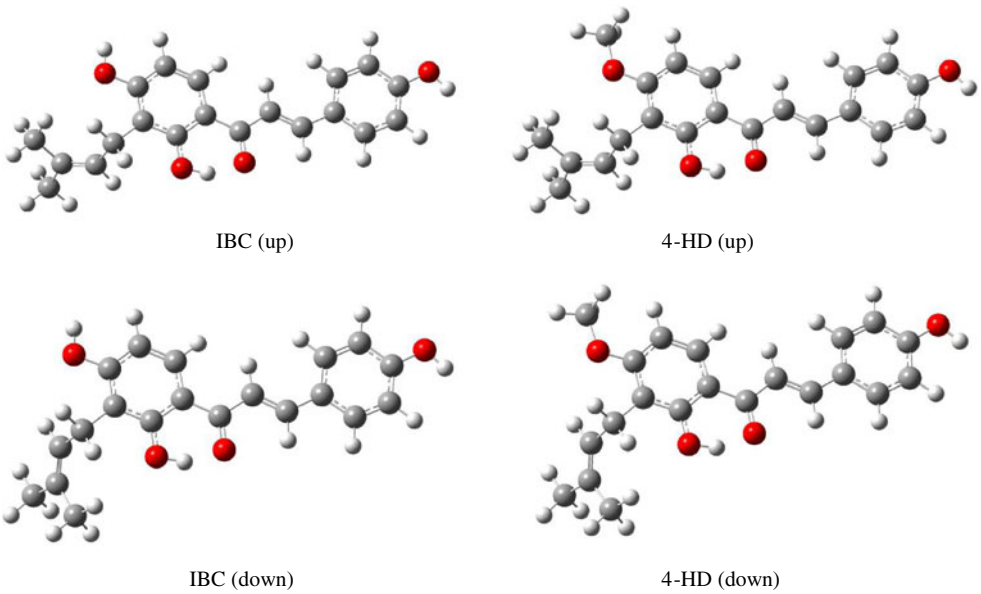

Fig. 2 Optimized geometries of IBC and 4-HD including up and down conformations

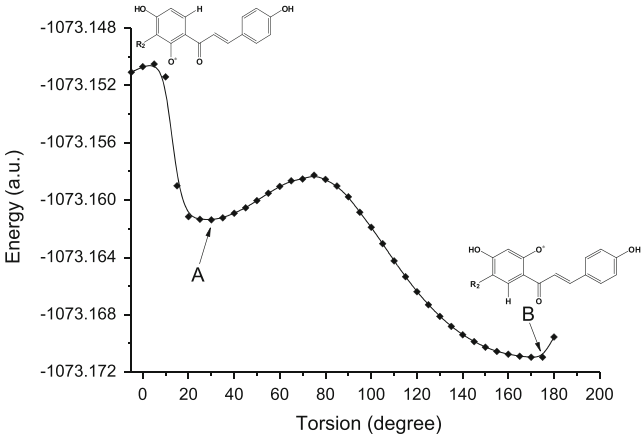

Fig. 3 Potential curve of the O-C-$C_{1'}$-$C_{2'}$ torsion angle in the 2′-OH radical formed after hydrogen abstraction for compound IBC

model (C-PCM) [31–34] with COSMO model (KLAMT) [34, 35] set of solvation radii to build the cavity for the solute in its gas-phase equilibrium geometry. Solvent effects on the acidity was computed in the framework of the self-consistent reaction field polarizable continuum model (SCRF-PCM) [31, 36, 37], using the UAHF [38] set of solvation radii to build the cavity for the solute. The dielectric constant of 32.63 was chosen to perform calculations in the presence of an implicit solvent for methanol. The PCM model calculates the free energy in solution composed of the electrostatic (G_{el}) together with non-electrostatic energies ($G_{n\text{-}el}=G_{disp}+G_{rep}+G_{cav}$).

Enthalpy was obtained from the sum of electronic and zero-point energies in this research, not considering the thermal correction to enthalpy. The O-H bond dissociation enthalpy ($H_{ArO\bullet}+H_{H\bullet}-H_{ArOH}$) for each OH groups and ionization potential ($H_{ArOH\bullet+}-H_{ArOH}$) were computed at 298.15 K, respectively. The gas-phase acidity at 298.15 K was computed as enthalpy difference between the anion (ArO^-) and its neutral species (ArOH), since the enthalpy of proton is zero and not considered. In the condensed phase, the acidity was computed in terms of total free solvation energy (ΔG in kcal.mol^{-1}) which is defined as the sum of electronic, non-electrostatic and zero-point energies.

Table 2 Relative energies for different radicals of IBC and 4-HD in methanol

	ΔE/(kcal.mol^{-1})	
	IBC	4-HD
2′-ArO$^\bullet$	11.5	11.3
4′-ArO$^\bullet$	3.9	—
4-ArO$^\bullet$	0	0

$$\Delta H_{(\text{acidity})} = H(\text{ArO}^-)\text{–}H(\text{ArOH})$$
$$\Delta G_{(\text{acidity})} = G(\text{ArO}^-) + G(\text{H}^+)\text{–}G(\text{ArOH})$$

The relative p$K_a$in methanol between various antioxidants and phenol is calculating using

$$\Delta \text{p}K_a = \Delta(\Delta G)\Big/1.37$$

Results and Discussion

Conformational Study

It has been reported that there are two conformers known as the *s*-cis and *s*-trans forms existed in the trans configuration of chalcones. Previous study has demonstrated that the *s*-cis conformer of trans-chalcone seems to be fully planar, whereas the *s*-trans conformer to be nonplanar for chalcones with 2′-OH group, and there are no changes in the BDE values from the *s*-cis to the *s*-trans chalcone [23]. Thus, we only focus on the *s*-cis conformer of the two chalcones for research because the *s*-cis conformer is more stable than the *s*-trans one. Figure 1 gives structures of the *s*-cis conformer of trans IBC and 4-HD. The prenyl chains have two positions with respect to the plane of the molecules: up or down. Figure 2 shows the optimized geometries of IBC and 4-HD including the two conformations. The

Table 1 Bond dissociation enthalpy (BDE) values in the gas phase for the two conformers of IBC and 4-HD with different OH substitutions

	BDE/(kcal.mol^{-1})		
	2′-OH	4′-OH	4-OH
IBC[a]	106.8	86.7	83.8
IBC[b]	106.6	86.7	83.8
4-HD[a]	107.0	—	83.6
4-HD[b]	106.8	—	83.6

[a] BDE values computed from the up conformer. [b] BDE values computed from the down conformer.

Table 3 Bond dissociation enthalpy (BDE) values at 298 K of IBC, 4-HD as well as ILG with different OH substitutions in methanol

	BDE/(kcal.mol^{-1})		
	2′-OH	4′-OH	4-OH
ILG	100.9	91.8	85.7
IBC	95.9	88.3	84.4
4-HD	95.5	—	84.2

Table 4 The frontier molecular orbital energies and energy gap between them (ΔE); the ionization potential (IP) of IBC, 4-HD, as well as ILG in methanol

	E_{HOMO}/(eV)	E_{LUMO}/(eV)	ΔE/(eV)	IP/(kcal.mol^{-1})
ILG	−6.75	−3.02	3.73	149.8
IBC	−6.64	−2.97	3.67	147.4
4-HD	−6.59	−2.94	3.65	146.3

energy of the down conformer for IBC is calculated to be higher by 0.14 kcal/mol than that of the up conformer, while this value is 0.03 kcal/mol for 4-HD. Although the down conformer is less stable, the difference in stability is too small to exclude the presence of such species in the actual system.

Significant geometrical changes have been observed when forming the 2′-OH (2′-ArO$^{\bullet}$) radical obtained after hydrogen abstraction of IBC and 4-HD, while no changes are found for the other radicals. The potential curve as a function of the O-C-$C_{1'}$-$C_{2'}$ torsion angle in the 2′-OH radical of IBC, obtained by scanning it in steps of 5° from −5° to 180°, is plotted in Fig. 3. It can be observed that two types of conformational isomers (A and B) existed in the 2′-OH radical of IBC. The B conformer with a torsion angle of ~175° is nearly planar, whereas the A conformer is nonplanar, with a torsion angle of ~30°, which can be attributed to steric hindrance between the 2′-O and the O atom of the carbonyl group after the loss of hydrogen bonding. The B conformer is more stable than A by 6.0 kcal/mol and a barrier of 8.0 kcal/mol is found when going from B to A form.

BDE Evaluation

BDE values of the up and down conformers in gas phase are calculated to study the possible influence of the chain conformation on the BDE of substituted hydroxyl groups since the two conformations coexist at room temperature. Table 1 compares the BDE values calculated for both up and down conformers of IBC and 4-HD. They are identical except for the 2′-OH, which shows that the conformation has no influence on the BDE of 4-OH and 4′-OH. Thus, we decided to focus on the up conformer for research when it is more stable.

The relative energies of different radicals obtained after abstraction of a hydrogen atom from each OH group of IBC and 4-HD in methanol are collected in Table 2. The most stable radical arising from both IBC and 4-HD is the 4-ArO$^{\bullet}$, the radical 4′-ArO$^{\bullet}$ for IBC is separated in energy by 3.90 kcal/mol. A remarkably high relative energies are found for the radical 2′-ArO$^{\bullet}$ with values of 11.5 and 11.3 kcal/mol for IBC and 4-HD, respectively, since the radicalization of 2′-OH group involves the breaking of the hydrogen bond established with the O atom of the neighboring carbonyl group.

Table 3 lists the calculated BDE values of IBC and 4-HD in methanol, with different OH substituted groups, these values of isoliquiritigenin (ILG) are also given for purposes of comparison. They are increased by ~1 kcal/mol for the 4-OH and 4′-OH groups when going from the gas phase to the methanol solution, which can be attributed to the interaction potential between the continuum and the molecule. This interaction is increased in the molecule due to the presence of an additional polar OH group compared to the radical. In the case of the 2′-OH group, the BDE values are decreased by ~11 kcal/mol, resulted from the inter-hydrogen bonding existing between the carbonyl group and the OH group in methanol. This competition effect weakens the intra-hydrogen bonding interaction between the 2-OH and the carbonyl group compared to the gas phase. Since the condensed phase seems to be more reflective of real situations as the vacuum phase barely considering ideal state, the BDE values in methanol are well analyzed.

The lowest BDE values are obtained by abstraction of a hydrogen atom from the 4-OH group in the B ring.

Table 5 The acidity values in gas phase and methanol of IBC, 4-HD, and ILG

		Acidity/(kcal.mol^{-1})		Relative acidity/(kcal.mol^{-1})		Relative pK_a in methanol/(kcal.mol^{-1})
		Gas	Methanol	Gas	Methanol	
phenol	OH	345.1	186.2	0.0	0.0	0.0
ILG	2′-OH	351.0	185.0	5.9	−1.2	−0.87
	4′-OH	328.7	172.2	−16.4	−14	−10.2
	4-OH	321.3	169.6	−23.8	−16.6	−12.1
IBC	2′-OH	349.7	187.6	4.6	1.4	1.0
	4′-OH	326.5	173.8	−18.6	−12.4	−9.0
	4-OH	321.1	169.7	−24	−16.5	−12.0
4-HD	2′-OH	351.0	184.6	5.9	−1.6	−1.2
	4-OH	321.6	169.6	−23.5	−16.6	−12.1

Thus, BDE values for the 4-OH group are used to characterize the antioxidant capacities. Seen from Table 3, ILG has the largest BDE value, while no significant difference is found for IBC and 4-HD. Since the smaller the BDE value is, the easier the hydrogen abstraction will be, the order of antioxidant efficacies predicted by BDE is 4-HD ≥ IBC>ILG. Results indicate that the substitutions of prenyl and methoxyl groups on the $C_{3'}$ and $C_{4'}$ positions make the BDE values for the 4-OH group smaller, or the substitutions increase the antioxidant efficacies.

IP Evaluation

Although the phenols usually react with free radicals through a HAT process, we also performed calculations on the second possible mechanism. An electron removed from the frontier molecular orbital HOMO of the parent molecules gives rise to radical cation species. Table 4 lists the frontier molecular orbital (HOMO, LUMO) energies and energy gap between them in the gas phase. It has been concluded that the abstraction of an electron becomes easier for 4-HD and IBC compared to ILG, this is because the higher the HOMO energy is, the smaller the energy gap is, the easier an electron abstraction will be. The calculated IP values of IBC, 4-HD and ILG in methanol medium are also collected in Table 4. It can be seen that 4-HD has the smallest IP value, and ILG has the largest one. The order of antioxidant efficacies predicted by IP is 4-HD>IBC>ILG, since the smaller the IP value is, the easier the electron abstraction will be.

Acidity Evaluation

The third possible mechanism is not exhaustively studied, but the determination of the acidity of these chalcones is an important thermodynamic parameter to be taken into account, rather than systematically excluded for any biological system. The absolute and relative acidities in gas phase and methanol of IBC, 4-HD and ILG are collected in Table 5. The relative pK_a values with respect to phenol in methanol are also given as further information. It can be seen from Table 5 that the 4-OH position is the most favored deprotonation site, followed by the 4′-OH position. The less acidic group is the 2′-OH one because the deprotonation of this position leads to disappearance of the hydrogen bond and brings on the electronic repulsion between the negative charge of the deprotonated oxygen and the neighboring carbonyl oxygen. It has been concluded that the order of antioxidant efficacies predicted by acidity is 4-HD=ILG ≥ IBC, since no significant change is found in acidity values.

Reaction with DPPH Radical

The reactions of IBC and ILG with DPPH radical have been experimentally reported by Luo et al. [16] and Kozlowski et al. [23]. The concentrations are 5.0×10^{-5} M and 5.0×10^{-3} M for IBC and ILG, respectively, when DPPH radical scavenging rate is 11 %. On the basis of obtained results, it can be concluded that IBC has higher antioxidant capacities than ILG in the DPPH radical scavenging assay. This matches results concerning the evaluation of O-H bond dissociation enthalpy and ionization potential. We can conclude that the dominant processes are HAT and SET, in the case of the reactions of these chalcones against DPPH radical.

Conclusions

In summary, we investigated two chalcone constituents isolated from *A. keiskei* based on density functional theory, by which we explained effects of substitutions of prenyl and methoxyl groups on the antioxidant efficacies and confirmed which mechanisms play dominant roles. Two conformers could coexist at room temperature. We have demonstrated that there are no changes in the BDE of 4-OH and 4′-OH, while minor change is found for the 2′-OH going from the down to the up conformations. The parameters of O-H bond dissociation enthalpy, ionization potential and acidity are computed to estimate the antioxidant capacities. The role of the phenol moiety (4-OH) is confirmed for explaining the antioxidant properties of the two chalcones, similar to those found for other chalcones that are characterized by the presence of the phenol moiety in the B ring. It is important to note that the substitutions of prenyl and methoxyl groups make the BDE values for the 4-OH group smaller, and the raise in HOMO energy makes IP values smaller. The order of antioxidant efficacies predicted by BDE and IP is in agreement with that obtained by experiments. This demonstrates the importance of the HAT and SET mechanisms to explain their capacities to scavenge DPPH radical. However, knowledge of theoretical calculations may be helpful in assessing potential *in vivo* antioxidant activity of *A. keiskei*.

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