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Investigation of comparative shielding of Morin against oxidative damage by radicals: A DFT study

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Abstract: This article describes theoretical study of comparative radical scavenging activity of polyphenolic flavonoid (Morin). The molecular and electronic characteristics have been computed using density functional theory approach with B3PW91/6-31G (d,p) and B3PW91/6–311G (d,p) levels of theory. The computational calculation of bond dissociation enthalpy magnitudes for all the OH sites clearly represents the frequent abstraction of proton from OH site adjacent to carbonyl groups on B ring. The molecular descriptors and frontier molecular studies confirm the higher reactivity of B and C rings as compared to A-ring of the studied flavonoid molecule.

Subjects: Chemistry; Material Science

Keywords: Morin; flavonoid; DFT; antioxidant; ionisation potential; electrophilicity

1. Introduction

Flavonoids are free-radical scavengers, usually placed under the subheading of vitamin P section of natural antioxidants (Harborne, 1980; Middleton & Kandaswami, 1994). They are ubiquitous group of polyphenolic substances present in most plants, concentrated in seeds, fruit skin or peel, bark, flowers, at an average, a dried green tea leaf contain 30% flavonoids in weight (Birjees Bukhari, Memon, Mahroof Tahir, & Bhanger, 2008; Harborne, 1986; Mohammed-Ziegler, Holmgren, Forsling, Lindberg, & Ranheimer, 2004; Sadasivam & Kumaresan, 2011). The antioxidant capacity of Flavonoids is much stronger than those of vitamin C and vitamin E (Manach, Scalbert, Morand, Remesy, & Jimenez, 2004). They enhance the function of vitamin C by improving its bioabsorption, protecting it from oxidation, and have associated with a variety of biochemical and pharmacological properties, including antibacterial, antiallergic, antimutagenic, anti-carcinogenic, antiviral, antineoplastic, anti-inflammatory, anti-thrombotic, vasodilator activity, scavenger and antioxidant activities believed to be beneficial to human biomechanical and biochemical system (Middleton, Kandaswami, & Theoharides, 2000; Rasulev, Abdullaev, Syrov, & Leszczynski, 2005; Souza & De Giovani, 2005). Furthermore, flavonoids are effective metal-ion chelators

ABOUT THE AUTHOR

Nasarul Islam received his master's degree in Natural Sciences (Chemistry) at Department of Chemistry from the University of Kashmir-India. He completed his PhD with Dr. Altaf Hussain Pandith on DFT studies of chiro-optic electronic system using DFT. After completing PhD, he joined College of Engineering, Zakura Campus, University of Kashmir. Presently he is working as DR D. S. Kothari's postdoctoral research fellow at Guru Nanak Dev University, Amritsar, Punjab. His research focuses on the basic DFT calculation related to molecular electronic structures.

Nasarul Islam

PUBLIC INTEREST STATEMENT

Antioxidants are substances that may protect your cells against the effects of free radicals. The body produces a range of its own protective antioxidants. However, best antioxidant sources are fruits and vegetables, as well as products derived from plants. In this work, I have studied the comparative proton abstraction from the available OH sites on the naturally occurring Flavonoid (Morin). Morin have been found associated with various pharmacological activities including antibacterial, anti-inflammatory, anti-thrombotic and antioxidant.

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Figure 1. Sketch and the atom numbering of the studied compound with rotational energy profile.
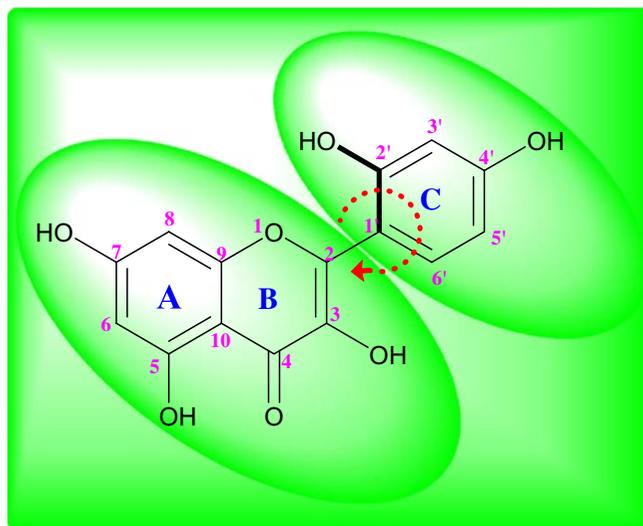
(Boudet, Cornard, & Merlin, 2000; Chen, Sun, Cao, Liang, & Song, 2009; Fernandez, Mira, Florencio, & Jennings, 2002; Thompson, Williams, & Elliot, 1976). Thus, the ability of flavonoids in scavenging hydroxyl radicals, superoxide anions and lipid peroxy radicals may be one of the most significant roles of these compounds and underlies many of the above activities in the body. A multitude of substitution patterns on the two benzene rings (A and C) of the basic existing molecular structural framework in nature (Figure 1) and variations in their heterocyclic rings give rise to flavonols, flavones, catechins, flavanones, anthocyanidins and isoflavones (Billes & Mohammed-Ziegler, 2007; Engelmann, Hutcheson, & Cheng, 2005; Goodwin, 1976; Harborne & Mabry, 1982).

Morin (3,5,7,2′,4′ pentahydroxyflavone) is a light yellowish natural plant dye, one of the most common flavonols present in nature that has attracted the attention of many researchers because of its biological and pharmaceutical properties (Basile et al., 2000; Marković et al., 2012; Wijeratne, Abou-Zaid, & Shahidi, 2006). The bioactivity of Morin is associated with its structural features also involved in complex formation with metals. Due to well-situated location of the 5-OH and 4-CO as well as 3-OH and 4-CO groups in a molecule, Morin forms chelate complexes with ions of p-, d- and f-electron metals (Ferrari, Pappano, Debattista, & Montaña, 2008; Panhwar, Memon, & Bhanger, 2010; Temerk, Ibrahim, & Kotb, 2009; Woźnicka, Kopacz, Umbreit, & Kłos, 2007). Ahmed and Hossan (1995) reported that Morin can react in slightly acidic 50% ethanol media with aluminium to give a deep yellow chelate which has an absorption maximum at 421 nm. They successfully applied this method to identify aluminium in human blood and urine. The specific fluorescence properties of Morin were studied in various $CH_3OH–H_2O$ and $CH_3CN–H_2O$ mixed solvents by Park et al. (2015). They reported that the rotational energy barrier for dihedral angle is minimum in S1 state as compared to S0 state and two different conformers exist in two solvent mixtures. Morin hydrate can frequently be used as a food preservative and has been shown to prevent lipid peroxidation in addition to its protective nature against oxyl-radicals (Caillet et al., 2007; Chinnam et al., 2010; Yu, Fong, & Cheng, 2006). The present investigation aims to study relative electronic properties through density functional theory (DFT) model chemistry, with the purpose of generating accurate information which enables to have better understanding of antioxidant activity of all hydroxy groups of the radical species formed after the removal of H-atoms from the neutral Morin skeleton.

2. Method

All calculations were accomplished with the Gaussian 03 package of programs (Frisch et al., 2004) and the full molecular geometry optimisations in the ground, radical and cationic state was studied by the DFT with the three-parameter hybrid functionals B3PW91 (Perdew, Burke, & Wang, 1996) correlation function using 6-31G (d,p) and 6-311G(d,p) basis set (Binkley, Pople, & Hehre, 1980; McLean

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& Chandler, 1980). All the parameters were allowed to relax and all the calculations converged to an optimised geometry for both neutral and their radicals, which corresponds to a true minimum, as revealed by the lack of imaginary values in the wave number calculations. Neutral molecules were treated as closed shell and radicals were solved by unrestricted open-shell approach. Polarised continuum model available in Gaussian 03 was employed for addressing solvent effects (Scalmani & Frisch, 2010).

3. Result and discussion

3.1. Conformation analysis

The conformational analysis is employed as first tool to unwrap the extent to which the behaviour of O–H groups in polyphenolic compounds is influenced by the electronic effect of both neighbouring and the overall geometry of the molecule. Scanning of torsion angle (τ) as defined by the O1-C2-C1′-C2′ was employed for determining the relative position of the rings B and C in Morin molecular framework (Figure 2). The torsion angle was scanned in steps by 30° from −150° to 150° without any constraint. Analysis of potential energy surface displays non-planarity in all Morin rotamers, with conformational absolute at 38.39° followed by a minimum at 68.31° with an energy difference of 10.43 kJ/mol. The potential energy is maximum at $\tau = 0°$ and the barrier between the potential maximum and minimum for rotation from $\tau = 0°$ to $\tau = 38.39°$ is 13.1 kJ/mol. This means that the rotation on this side requires a negligible amount of energy. The most important feature in these compounds is intramolecular hydrogen bonding. The geometrical features outcome from these computations (Figure 3) reveals existence of only one hydrogen bond that is between 3-OH (B ring) and the C4-O carbonyl group in neutral and radical species except in the case of 4′-OH radical, where an additional hydrogen bond is formed on onset of net stability of semiquinone we intermediate. The non-planarity of the flavonoid compound is attributed to steric repulsion between 3-OH and 2′-OH groups of B and C rings, respectively.

3.2. Bond dissociation energy, ionisation potentials and global descriptors

A phenolic compound can follow either of the two mechanisms for the radical scavenging, through which they can exert their antioxidant functions: hydrogen atom transferring, controlled by the bond dissociation enthalpy (BDE) of phenol (Equation 1), and electron donating ability, controlled by the ionisation potential (IP) of phenol (Equation 2). In general, compound with low BDE or IP possesses high hydrogen atom transferring or electron donating ability. In this study, BDE was calculated at 298.15 K using the sum of electronic and thermal species as follows:

$$ArOH \rightarrow ArO^{.} + H^{.}$$
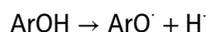
$$BDE = H_r + H_h - H_n \tag{1}$$

Figure 2. Potential energy scan profile for rotation around the C2–C1′ bond of Morin in gas phase.
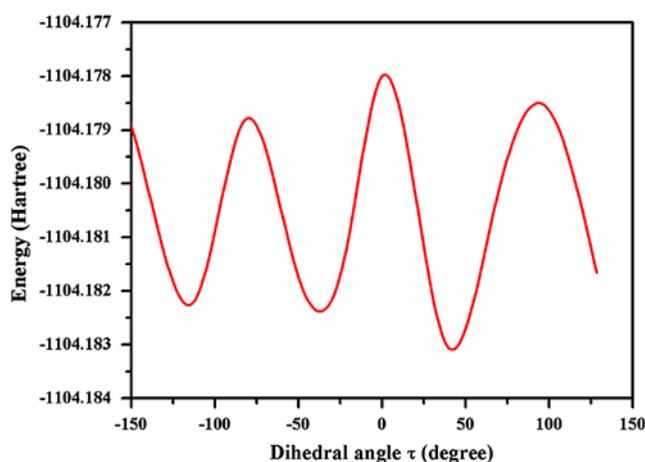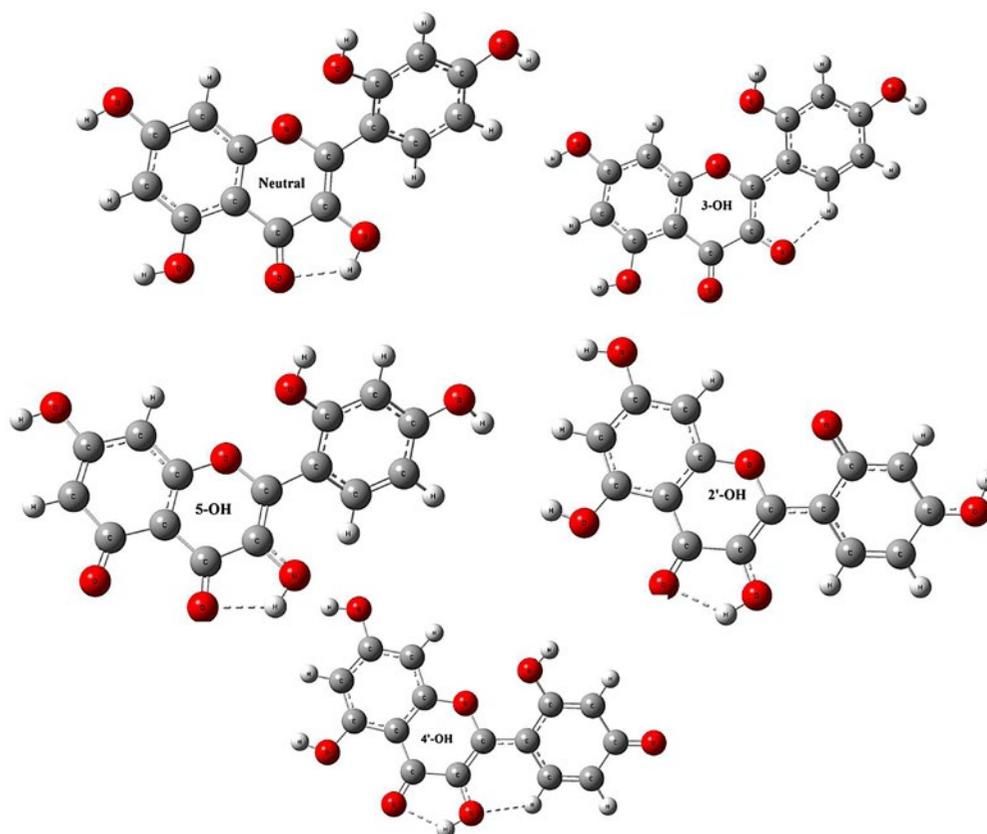
Figure 3. Optimised geometries of neutral and radical species of Morin.

where H_r is enthalpy of radical generated through H-atom abstraction, H_h is the enthalpy of hydrogen atom [−0.49765 hartree] and H_n is the enthalpy of neutral compound. The adiabatic IP is calculated as the energy difference between neutral compound and the corresponding cation as follows:

$$ArOH \rightarrow ArOH^{\cdot+} + e^-$$

$$IP = E_{cation} - E_{neutral} \tag{2}$$

From the BDE values (Table 1), the most stable radical is found to be 3-OH obtained from removal of the hydrogen atom from the hydroxyl group attached adjacent to carbonyl group at ring C. Morin exhibits the following BDE sequence for the OH groups existing on its molecular framework: 3-OH < 2′-OH < 4′-OH < 5-OH < 7-OH. This clearly confirms that H-atom abstraction from the cinnamoyl system is easier as compared to benzoyl system. The reason being the frequent generation of semiquinone on account H-atom abstraction from 3-OH, 4′-OH, 2′-OH. So based on this observation, B-ring has the capacity to pass on significant activity by moving as a hydrogen atom donor and enabling the formation of a relatively stable flavonoid radical through electron delocalisation. The adiabatic IP value of studied system obtained in this study is 189 kcal/mol, which is close to quertcein and mearnsetin flavonoids. The implementation of solvent system properties on the model compounds reveals that the polarity of the solvent increases the radical scavenger activity of the studied flavonoid (Table 1).

The reactivity and instability of the studied system were viewed in terms of global and local descriptors that have been defined within the context of DFT. The global electrophilicity index(ω) measures the capability of a system to acquire electronic charge from the environment, however, the chemical hardness(η) is a measure of resistance to charge transfer cmget the electronegativity(χ) is a measure of the tendency to attract electrons in a chemical bond and are calculated as follows:

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Table 1. Calculated IP and BDE (kJ/mol) at 298.15 K in gas and solvent phases for Morin and radical species at DFT level of theory

	Gas		Water		Acetonitrile	
	B3PW91 6-31G (d,p)	B3PW91 6-311G (d,p)	B3PW91 6-31G (d,p)	B3PW91 6-311G (d,p)	B3PW91 6-31G (d,p)	B3PW91 6-311G (d,p)
IP	798	784	773	761	763	746
BDE: 3-OH	371	363	359	361	353	348
BDE: 5-OH	418	401	415	411	411	392
BDE: 7-OH	398	391	389	387	393	386
BDE: 2`-OH	379	376	376	373	374	361
BDE: 4`-OH	383	379	371	378	363	357

Electronegativity (χ): $\mu = -\chi = -\dfrac{IP + EA}{2}$ (3)

Hardness $(\eta) \approx \dfrac{IP - EA}{2}$ (4)

Softness $(S) = \dfrac{1}{2\eta}$ (5)

Electrophilicity $(\omega) = \dfrac{\mu^2}{2\eta}$ (6)

The values of the molecular descriptors that are displayed in Table 2 reveal that the hardness of hydroxy groups present on benzol ring are lower than hydroxy groups on cinymol. It is interesting that the 3-OH and 2′-OH, 4′-OH are closer in reactivity values (ω) but lower than 5-OH and 7-OH. Therefore, the stability analysis based on these descriptors suggests the frequent rate of radicals generation obtained by abstraction of hydrogen from 3-OH and 2′-OH, 4′-OH as compared to 5-OH and 7-OH on account of radical stability of former compared to later.

3.3. Frontier molecular orbital's

The frontier molecular orbitals (FMOs) studies (HOMO, LUMO and HOMO–LUMO energy gap) can be used as a tool to understand the ability of charge transfer interactions and the way the molecules interact with other species. The contours of HOMO and LUMO (Figure 4) displayed difference in charge distribution in the neutral and radical species. As an electron donor, the HOMO represents its efficiency to donate electron and the LUMO to accept electron. In case of neutral species, it is found that electron density is more concentrated in B and C rings as compared A. However, in LUMO, the

Table 2. DFT calculated HOMO, LUMO energies, IPs, electron affinity (EA) using Koopmans' theorem for Morin and radical species

	E_{HOMO}	E_{LUMO}	ΔE	IP (eV)	EA (eV)	χ (eV)	η (eV)	S (eV)	ω (eV)
Neutral	−5.230	−1.267	3.962	5.230	1.267	3.248	1.981	0.252	2.663
3-OH	−5.212	−1.690	3.523	5.212	1.690	3.451	1.761	0.284	3.381
5-OH	−5.871	−1.689	4.183	5.871	1.689	3.780	2.091	0.239	3.416
7-OH	−5.985	−1.875	4.110	5.985	1.875	3.930	2.055	0.243	3.758
2′-OH	−5.726	−1.827	3.899	5.726	1.827	3.777	1.950	0.256	3.658
4′-OH	−5.761	−1.930	3.831	5.761	1.930	3.845	1.916	0.261	3.859

Figure 4. The FMOs of Morin and its radical derivatives at DFT/ B3PW91/6-311++ G (d,p) level of theory.

Neutral-HOMO

Neutral -LUMO

3-OH HOMO

3-OH LUMO

2`-OH HOMO

2`-OH LUMO

4`-OH HOMO

4`-OH LUMO
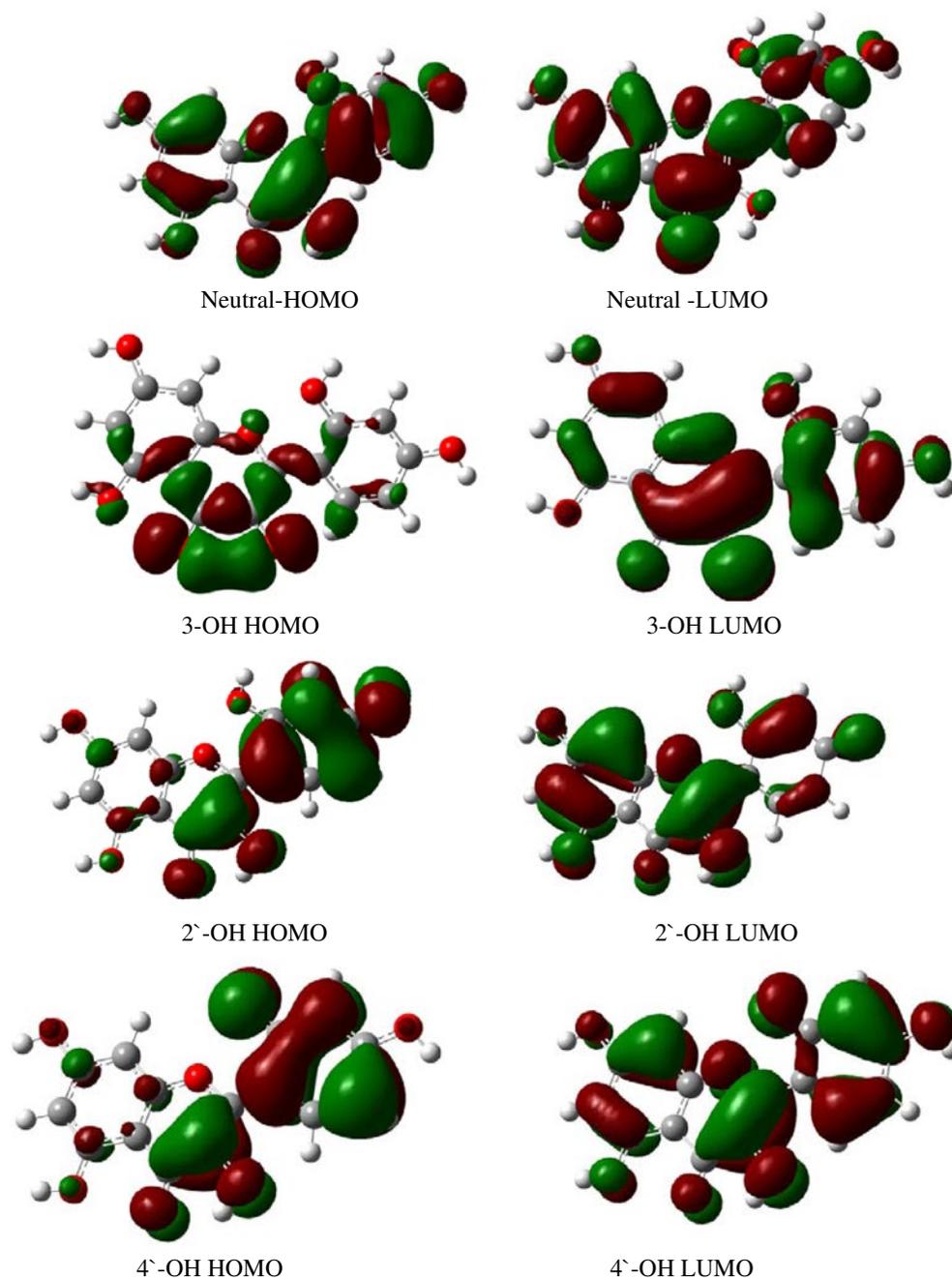
electron density is homogeneous over the three rings in neutral Morin species. In case of radical species of Morin, hydrogen abstraction centre has predominant contribution to HOMO and this gives the pictorial representation of lower bond dissociation energy for C ring hydroxyl groups compared to A ring. In other words, the FMO study reveals lesser reactivity of A-ring proton as compared to B- and C-ring protons present in the formed hydroxyl groups.

4. Conclusion

This work includes the conformational analysis, as well as the phenolic OH bond dissociations enthalpies, molecular descriptor, IP, FMO studies of Morin. The calculations were carried out using B3PW91/6-31G (d,p) and B3PW91/6-311G (d,p) levels of theory. From conformational analysis, the

most stable rotamer shows non-planarity with a dihedral angle of 38.39° stabilised by the formation of intramolecular hydrogen bond. The BDE and IP calculations reveal that 3-OH is most feasible position for hydrogen abstraction. It is important to remark that the global hardness values are in good agreement with the reactivity trends of all OH-sites present on the Morin. In light of the results obtained from molecular descriptor and frontier molecular studies, the conclusion favours the sufficient stability of B and C rings to remain in the environment long enough to react than A ring of the studied flavonoid.

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