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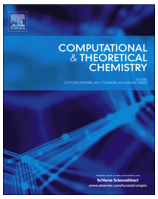

The role of intramolecular H-bonds predominant effects in myricetin higher antioxidant activity

Abolfazl Barzegar *

Research Institute for Fundamental Sciences (RIFS), University of Tabriz, Tabriz, Iran
Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Flavonoid antioxidants play essential roles in the prevention of damage caused by free radicals, which is concerned in many chemical and biological processes. The structural electronic properties of myricetin (Myc) and six respective radicals such as total electronic energies, bond dissociation enthalpy magnitudes (BDEs), intramolecular H–bonds strength and charges density distributions have been computed using density functional theory approach with B3P86 level. The important Myc molecular characteristics, the antioxidant activities, electronic structure–activity relationships, OH numbers and positions–activity relationships as well as radical scavenging mechanisms were discussed. The sequential active OH groups for H atom abstraction was predicted as 4′-OH > 3′-OH ≈ 5′-OH > 3-OH > 7-OH > 5-OH that concomitant with B-ring > pyrone C-ring > A-ring activity in Myc structure. The vital role of intramolecular H-bonds was comprehensively monitored for the stabilization of B-ring radicals (4′-O$^{\cdot}$, 3′-O$^{\cdot}$, 5′-O$^{\cdot}$), that lead to the highest activity of 4′-OH, 3′-OH, 5′-OH in B-ring. Also, the electrons delocalization among A, B and C-ring (increasing co-planarity) play second possible role for easy H atom donation. The number of three ortho-phenolic OH groups and radical stabilization by the strength of intramolecular H-bonds make B-ring to be very active and excellent to react with free radicals among three-rings in Myc structures. Our findings may be useful to elucidate the radical scavenging mechanism of other flavonoid antioxidants for the aim to design novel antioxidants.

1. Introduction

Flavonoids are the most important classes of compounds from the dietary phytochemicals, not only in terms of their great abundance in the diet, but also for the in vitro and/or in vivo antioxidant properties [1–4]. They have also received considerable interest in the food industry as food additives because of their antioxidant and anti carcinogenic properties [4,5,6]. The medical and nutritional aspects of antioxidants in general, are to prevent the oxidative damage that occurs in biomolecule by scavenging the reactive oxygen species (ROS) [1,3]. Myricetin (Myc) is one of the most important flavonoids in diet due to its abundance in foods and its bioavailability with the highest antioxidant activity [7–12]. The generic structure of flavonoids such as Myc consists of two benzenes A-ring and B-ring linked together by a heterocyclic pyrone C-ring as displayed in Fig. 1. Myc (3,5,7,3′,4′,5′-hexahydroxyflavone) is a stronger antioxidant, which has been attributed to the presence of the six hydroxyl groups (Fig. 1). The sequence of antioxidant activities of different flavoniods is: myricetin > quercetin > α-tocopherol > luteolin ≈ baiculein > morin ≈ kaempferol > apigenin > lysionotin [13,14,15]. Hence, because of the superb antioxidant activity of Myc among other flavoniods, Myc has been widely studied by different researchers for many years. Myc is highly effective with respect to scavenging ROS and exhibits a cytoprotective effect against oxidative stress [10,16,17]. Already compared many flavonoids with different OH groups in different sites of A-ring, B-ring and C-ring showed that the presence of OH groups on B-ring significantly increase their antioxidant activity [15]. Higher antioxidant activity of flavonoids directly correlates to low bond dissociation enthalpy (BDE) of O—H atom [18–20]. Comparing flavoniods (quercetin with kaempferol, or luteolin with apigentin) indicated that the presence of ortho-hydroxyl on B-ring decreases the O—H BDE by 8 kcal/mol. Also, the presence of 5′-OH in myricetin decreased the ortho O—H BDE by 6 kcal/mol [15]. However, the main parts of previous researches emphasized on the role of OH positions and the contribution of the B-ring in the antioxidant activity of Myc through comparative methods. Nevertheless, the main reason about the stronger antioxidant activity of Myc with low O—H BDE was not completely

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* Address: Research Institute for Fundamental Sciences (RIFS), University of Tabriz, Tabriz, Iran.

E-mail address: barzegar@tabrizu.ac.ir

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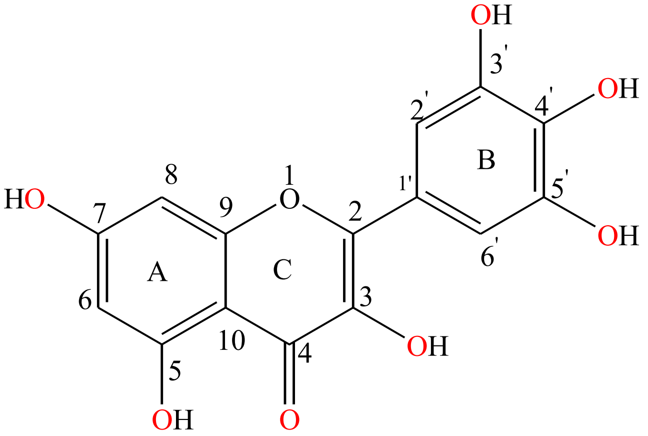

Fig. 1. The chemical structure of myricetin (Myc).

explained. Instead of previous comparative studies of Myc with other flavonoids, herein we have systematically focused on the Myc and Myc-radicals using computational density functional theory (DFT) method in order to find the main parameter(s) that affect the strong antioxidant activity of Myc. Data indicated that the intramolecular H-bonds have the most important effects on Myc radicals stabilizations accompanied by higher antioxidant activity.

2. Methods

2.1. Initial pdb structure of myricetin

The initial pdb structure of myricetin (Myc) was achieved from X-ray data deposited in RCSB web browser (http://www.rcsb.org/), pdb code; 4GQR with the high resolution of 1.20 Å. The pdb was used for semiempirical AM1 conformational analysis and followed by additional quantum DFT based computational studies.

2.2. Computations

Quantum chemical calculations were carried out to optimize the Myc and different respective radical structures in order to compute; the total electronic properties of the compounds [21,22,23], intramolecular hydrogen bond strength, and bond dissociation enthalpy (BDE) of O-H atoms. BDE is the key parameter involved in the radical-scavenging properties of phenolic antioxidants [18–20]. It is possible to achieve BDE by the help of quantum chemical geometry optimization. Density functional theory approach (DFT) is the most effective method for the BDE estimation of phenolic compounds related with the experimental data [18–20]. DFT method with B3P86 functional level [24] was used to calculate such properties. The B3P86 functional process with a large basis set leads to excellent results for the BDE estimation of phenol [25]. Therefore, the geometry of the Myc and the respective radicals were optimized using B3P86 functional level of DFT method with different basis sets of 6-31G (d), 6-311+G (d,p) and 6-311+G (2d,2p). The correspondence of the stationary points to minima on the potential energy landscape has been checked by the absence of imaginary frequency in the vibrational spectra. All optimized structures showed only positive harmonic vibrations (local energy minima). Single point energies' calculations were performed using respective optimized basis sets of 6-31G (d), 6-311+G (d,p) and 6-311+G (2d,2p). Geometry optimization of each radical was performed starting from the optimized structure of the parent Myc molecule, following the removal of H atom from 3′, 4′ or 5′, 3, 5, 7-OH positions. DFT computations for the parent Myc with paired electrons in doubly-occupied molecular orbitals called "restricted closed-shell" or "spin unpolarised". In this case, pairs of α and β spin orbitals are restricted to have the same three-dimensional part that each shell (spatial orbital) is closed, i.e. doubly occupied. Nevertheless, the molecules that contain unpaired electrons known open-shell species. Therefore, the ground-state geometries of Myc and the corresponding radicals were optimized at restricted closed-shell and restricted open-shell (half-filled orbital) levels, respectively. Specification of a restricted open-shell wavefunction for the B3P86 hybrid functional requires the ROB3P86 keyword, while the restricted closed-shell is specified using (R)B3P86. In restricted open-shell calculations (ROB3P86), all spatial shells mainly inner shells that in the reality contain two electrons are forced to stay together, as in restricted calculation, while those containing only one electron are computed as they are. This method should give more reasonable results, but requires more computational costs. Also, using restricted open-shell wave functions is a more effective way to decrease the impact of excessive spin contamination in acting on the radicals [26].

The geometry optimizations at the ground state and at the radical state were achieved through three different basis sets. Therefore, the BDE values calculated with zero-point energy (ZPE) correction, using a scale factor of 0.985 [27,28].

Table 1

The total electronic energy (*E*, hartree) and BDEs (kcal/mol) at 298 K for Myc and respective radicals using three different basis sets in B3P86 functional DFT level. G1, G2 and G3 denote the computations via basis sets of 6-31 G(d), 6-311+G(d,p) and 6-311+G(2d,2p), respectively. Six phenoxyl radicals were generated by H atom elimination and optimization from 3′,4′,5′,3,5 and 7-OH sites in gas and water phase. 4′-O· radical is the most stable among the others with lowest *E* and BDE (highlighted in bold).

	E			*BDE*		
	G1	*G2*	*G3*	*G1*^{a}	*G2*^{b}	*G3*^{b}
Myc (*gas*)	−1182.3264	−1182.6784	−1182.7210	–	–	–
3′-O· (*gas*)	−1181.6841	−1182.0278	−1182.0697	72.32	76.24	76.84
4′-O· (*gas*)	−**1181.6996**	−**1182.0425**	−**1182.0848**	**63.00**	**67.37**	**67.71**
5′-O· (*gas*)	−1181.6836	−1182.0273	−1182.0692	72.57	76.56	77.16
3-O· (*gas*)	−1181.6673	−1182.0110	−1182.0529	82.51	86.45	86.88
5-O· (*gas*)	−1181.6241	−1181.9881	−1182.0299	107.73	100.58	100.98
7-O· (*gas*)	−1181.6586	−1182.0034	−1182.0454	87.56	91.01	91.46
Myc (water)	−1182.346614	−1182.699248	−1182.740398	–	–	–
3′-O· (water)	−1181.699354	−1182.042673	−1182.083253	75.49	80.27	80.62
4′-O· (water)	−**1181.713718**	−**1182.055981**	−**1182.096885**	**66.80**	**72.23**	**72.38**
5′-O· (water)	−1181.699329	−1182.042667	−1182.083238	75.51	80.27	80.63
3-O· (water)	−1181.693309	−1182.037155	−1182.07762	79.21	83.65	84.07
5-O· (water)	−1181.671311	−1181.989947	−1182.03083	92.61	112.87	112.82
7-O· (water)	−1181.678835	−1182.025519	−1182.053143	87.78	90.44	98.93