

# Investigations Regarding the Antioxidant Character of Some Flavonols

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**Abstract:** The antioxidant character of three flavonols (azaleatin, kaempferide and isorhamnetin) has been evaluated at HF/6-31+G level of theory. Thermodynamic parameters like BDE (bond dissociation enthalpy) have been computed, as well as frontier charge density indices. Based on these results, a hierarchy of the antioxidant capacity of OH groups within the three investigated flavonols has been proposed. Also, the atomic charges were computed by using three different approaches.

**Keywords:** flavonols, atomic charge, bond dissociation enthalpy, *ab initio*.

## 1. Introduction

During the last years, researches on compounds with antioxidant activity have gained an increased importance. There is a large number of studies regarding the applications of natural compounds with antioxidant activity in medicine, as adjuvants in treatment of diabetes, cardiovascular diseases or cancer [1,2]. Flavonols are a class of compounds frequently encountered in various plant extracts, with pronounced antioxidant properties [3]. They found applications in adjuvant treatment of cancer, diabetes or cardiovascular disease [4].

A special class of natural antioxidants is represented by the flavonols; their structure is depicted in Figure below:

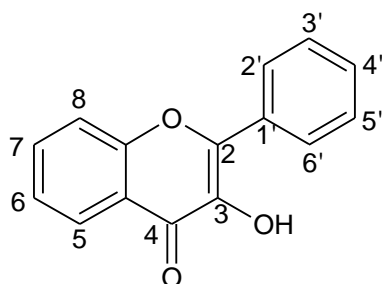


Figure 1. The flavonol skeleton (3-hydroxy-2-phenylchromen-4-one)

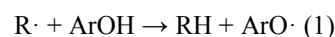
Flavonols	3	5	7	3'	4'	5'
Azaleatin	OH	OCH <sub>3</sub>	OH	H	OH	OH
Kaempferide	OH	OH	OH	H	OCH <sub>3</sub>	H
Isorhamnetin	OH	OH	OH	OCH <sub>3</sub>	OH	H

The flavonol skeleton is based on the 3-hydroxy-2-phenylchromen-4-one structure; the flavonols are differentiated by the position and the number of OH and OCH<sub>3</sub> groups, respectively.

The antioxidant activity of these polyphenolic compounds is due to the radical-scavenging ability of the OH groups. In this regard, parameters like BDE (Bond

Dissociation Enthalpy) which represents the change in enthalpy associated to the reaction are useful tools for the estimation of the antioxidant activity of each OH group [5-7].

The BDE index is computed for the general reaction 1:



$$BDE = \Delta H_{ArO\cdot} + \Delta H_{H\cdot} - \Delta H_{ArOH} \quad (2)$$

Another parameter that has been successfully used for the estimation of antioxidant capacity is the frontier charge density [8,9], which represents a measure of the antioxidant activity of a phenolic compound towards oxygen and the oxygen dianion.

The frontier charge density is computed by means of Equation (3):

$$Q_f = 2\sum c_i^2 \quad (3)$$

where  $c_i$  – orbital coefficients of the atom  $i$  in the HOMO orbital.

A literature survey reports a number of computational studies regarding the antioxidant capacity of flavonoids [10,11], as well as regarding the evaluation of the antioxidant capacity of azaleatin and isorhamnetin (at B3LYP/6-311++G(d,p) level of theory) [12].

Also, our previous studies dealt with the theoretical evaluation of the antioxidant character of anthocyanidins [13], when different mechanisms of the radical scavenging capacity have been discussed.

The present paper aims to investigate the antioxidant character of three of the most wide-spread flavonols, namely azaleatin, kaempferide and isorhamnetin. In this regard, parameters like BDE, frontier charge density and atomic charges have been computed for each OH groups of the investigated flavonols.

## 2. Computational Details

All the computations were performed with G09W suite of programs [14]. BDE index computations were carried out at ROHF/6-31+G level of theory, in order to avoid the issues regarding the spin contamination. NBO (Natural bond orbital analysis) was performed, in order to compute the natural charges of the O atoms. Also, population analysis has been performed, in order to determine the Mulliken and Merz-Singh-Kollman charges.

## 3. Results and Discussion

According to the Equation (2), the BDE index is highly related to the stability of both the radical and the parent structure. If the obtained radical has an increased stability, the BDE value is lower, leading thus to an enhanced antioxidant character. The results presented in Table 1 outline the specific behavior of the 3-OH groups. According to the structure depicted in Figure 1, the 3-OH groups and the C2-C3 bond can be involved in a keto-enol tautomerism. Also, there is a possible intramolecular hydrogen bond between the 4-O and 3-OH group.

TABLE 1. BDE parameter, computed at HF/6-31+G level of theory

BDE(kcal/mol)	3	5	7	4'	5'
Azaleatin	67.81	-	71.31	69.10	93.94
Kaempferide	64.38	86.67	93.92	-	-
Isorhamnetin	67.78	89.68	74.72	76.28	-

Another group with pronounced antioxidant activity is 4'-OH, result that is in good agreement with other theoretical and experimental studies that underlines the higher antioxidant capacity of the hydroxyl groups of the phenyl ring [15,16].

The atomic charges of the O atoms of each hydroxyl group have been computed by means of three different computational approaches. The MSK (Merz-Singh-Kollman) charges are calculated by taking into account the electrostatic potential, while the natural atomic charges are computed as the difference between the dinuclear charge and the summed natural populations of natural atomic orbitals on the atom.

The results are summarized in Tables 2-4 and "more negative" values have been obtained for the OH groups within the phenyl ring (4'-OH and 5'-OH), as well as for the 7-OH groups.

TABLE 2. Atomic charges of the O atoms of hydroxyl groups (HF/6-31+G)

Atomic charges	3	5	7	4'	5'
Azaleatin	-0.658	-	-0.719	-0.800	-0.710
Kaempferide	-0.629	-0.484	-0.710	-	-
Isorhamnetin	-0.634	-0.756	-0.710	-0.704	-

TABLE 3. Merz-Singh-Kollman charges of the O atoms of hydroxyl groups (HF/6-31+G)

MSK charges	3	5	7	4'	5'
Azaleatin	-0.677	-	-0.834	-0.774	-0.765
Kaempferide	-0.682	-0.531	-0.822	-	-
Isorhamnetin	-0.680	-0.875	-0.816	-0.698	-

TABLE 4. Natural atomic charges (computed by means of NBO analysis) (HF/6-31+G)

Natural charges	3	5	7	4'	5'
Azaleatin	-0.745	-	-0.762	-0.787	-0.771
Kaempferide	-0.567	-0.757	-0.793	-	-
Isorhamnetin	-0.746	-0.775	-0.756	-0.770	-

The frontier charge density indices (Table 5) show that the hierarchy of the most reactive OH groups is 3-OH>5-OH>4'-OH. The reactivity of 3-OH and 4'-OH groups have been also proved by the results of the BDE index, but in the case of 5-OH the frontier charge density index is the only one that predicts an enhanced reactivity.

TABLE 5. Frontier charge density indices (HF/6-31+G)

Frontier charge density	3	5	7	4'	5'
Azaleatin	0.119	-	0.009	0.071	0.035
Kaempferide	0.104	0.100	0.009	-	-
Isorhamnetin	0.106	0.058	0.008	0.096	0.038

The electronic descriptors like electronegativity ( $\mu$ ), chemical hardness ( $\eta$ ) and electrophilicity ( $\omega$ ) have been also computed. The results are presented in Table 6:

TABLE 6. Electronic descriptors of the three flavonols (HF/6-31+G)

	Electronegativity (eV) $\mu = \frac{E_{HOMO} + E_{LUMO}}{2}$	Chemical hardness (eV) $\eta = E_{LUMO} - E_{HOMO}$	Electrophilicity (eV) $\omega = \frac{\mu^2}{2\eta}$
Azaleatin	-3.60	4.88	0.66
Kaempferide	-3.71	5.00	0.69
Isorhamnetin	-3.65	5.04	0.66

It results that there are no significant differences among the global electronic properties of the three investigated flavonols. The electrophilic index  $\omega$  is a good parameter for the characterization of the affinity of a system for electrons. The electrophilicity index ( $\omega$ ) is a measure of the affinity for electrons [13]. The low values that have been obtained suggest that the three flavonols tend to give electrons more easily than attracting them, proving thus their antioxidant character.

#### 4. Conclusions

A theoretical study regarding the evaluation of the antioxidant character of three flavonols has been performed. The results suggest an increase antioxidant activity for the 3-OH groups, followed by the 4'-OH groups within the phenyl ring. The frontier charge density index confirms the antioxidant capacity of the 3-OH and 4'-OH groups, but also predicts an enhanced reactivity of the 5-OH group of kaempferide (unlike the other descriptors). Global electronic properties show no significant differences among the three investigated compounds.

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Received: 17 October 2013

Accepted: 21 November 2013