

Research Article

Computational Nutraceuticals: Chemical Reactivity Properties of the Flavonoid Naringin by Means of Conceptual DFT

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The M06 family of density functionals has been assessed for the calculation of the molecular structure and properties of the Naringin molecule. The chemical reactivity descriptors have been calculated through Conceptual DFT. The active sites for nucleophilic and electrophilic attacks have been chosen by relating them to the Fukui function indices and the dual descriptor $f^{(2)}(\mathbf{r})$. A comparison between the descriptors calculated through vertical energy values and those arising from the Koopmans' theorem approximation has been performed in order to check for the validity of the last procedure.

1. Introduction

The term nutraceutical is the result of a contraction between nutrition and pharmaceutical. In 1989, Dr. Stephen Defelice defined nutraceutical [1] as any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of diseases [2]. In this work, we are coining the term "Computational Nutraceuticals" for the practice of predicting the molecular structure, spectroscopy, and chemical reactivity of nutraceuticals by means of Computational Chemistry and Molecular Modeling.

The major active nutraceutical ingredients in plants are flavonoids. As is typical for phenolic compounds, they can act as potent antioxidants and metal chelators. They also have long been recognized to possess anti-inflammatory, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities [3]. Naringin (C₂₇H₃₂O₁₄; mol. wt. 581; IUPAC Name 7-[[2-O-(6-Deoxy- α -L-mannopyranosyl)- β -D-glucopyranosyl]oxy]-2,3-dihydro-5-hydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is a flavanone glycoside. It is a major flavonoid in grapefruit and gives the grapefruit juice its bitter taste. It is metabolized to

the flavanone naringenin in humans. The aim of this work is to do a comparative study of the performance of the M06 family of density functionals for the description of the chemical reactivity of Naringin as a part of a continuing Computational Nutraceuticals study of flavonoids.

The knowledge of reactivity on a molecule is an essential concept; it is of a crucial interest because it allows to understand interactions that are operating during a reaction mechanism. In particular electrostatic interactions have been successfully explained by the use of the molecular electrostatic potential [4, 5].

On the other hand, there is no a unique tool to quantify and rationalize covalent interactions; however, since 2005 a descriptor of local reactivity whose name is simply dual descriptor [6, 7] has allowed to rationalize reaction mechanisms in terms of overlapping nucleophilic regions with electrophilic regions in order to get a maximum stabilization thus leading to final products or intermediates; all those favorable nucleophilic-electrophilic interactions have been explained as a manifestation of the Principle of Maximum Hardness [8]; in addition, chemical reactions have been understood in terms of the Hard and Soft Acids and Bases

Principle [9–14], the principle that has been used even with the aim of replacing the use of the molecular orbital theory to understand the whole chemistry [15]. In fact the present work is a good chance to test the capability of the most recent reactivity descriptors coming from the Conceptual DFT [16–23]; therefore the framework of this conceptual theory will be presented in the next section.

2. Theory and Computational Details

At a local level, electronic density is the first local reactivity descriptor to be used when electrostatic interactions are predominant between molecules; within the framework of Conceptual DFT it is defined as follows:

$$\rho(\mathbf{r}) = \left[\frac{\delta E}{\delta v(\mathbf{r})} \right]_N. \quad (1)$$

But when chemical reactions are governed by interactions mainly of covalent nature, in such a case a second-order local reactivity descriptor or LRD called Fukui function [18] is used instead of electronic density. Fukui function is defined in terms of the derivative of $\rho(\mathbf{r})$ with respect to N ; through a Maxwell relation, the same descriptor is interpreted as the variation of μ with respect to $v(\mathbf{r})$ [18, 24–26] as follows:

$$f(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N} \right)_{v(\mathbf{r})} = \left[\frac{\delta \mu}{\delta v(\mathbf{r})} \right]_N. \quad (2)$$

The function $f(\mathbf{r})$ reflects the ability of a molecular site to accept or donate electrons. High values of $f(\mathbf{r})$ are related to a high reactivity at point \mathbf{r} [18].

Since the number of electrons N is a discrete variable [27–29], right and left derivatives of $\rho(\mathbf{r})$ with respect to N have emerged. Thus, two definitions of Fukui functions depending on total electronic densities are obtained as follows:

$$\begin{aligned} f^+(\mathbf{r}) &= \left(\frac{\partial \rho(\mathbf{r})}{\partial N} \right)_{v(\mathbf{r})}^+ = \rho_{N+1}(\mathbf{r}) - \rho_N(\mathbf{r}), \\ f^-(\mathbf{r}) &= \left(\frac{\partial \rho(\mathbf{r})}{\partial N} \right)_{v(\mathbf{r})}^- = \rho_N(\mathbf{r}) - \rho_{N-1}(\mathbf{r}), \end{aligned} \quad (3)$$

where $\rho_{N+1}(\mathbf{r})$, $\rho_N(\mathbf{r})$ and $\rho_{N-1}(\mathbf{r})$ are the electronic densities at point \mathbf{r} for the system with $N + 1$, N , and $N - 1$ electrons, respectively. The first one, $f^+(\mathbf{r})$, has been associated to reactivity for a nucleophilic attack, so that it measures the intramolecular reactivity at the site \mathbf{r} toward a nucleophilic reagent. The second one, $f^-(\mathbf{r})$, has been associated to reactivity for an electrophilic attack, so that this function measures the intramolecular reactivity at the site \mathbf{r} toward an electrophilic reagent [24].

The densities of frontier molecular orbitals (FMOs), $\rho_L(\mathbf{r})$ (LUMO density) and $\rho_H(\mathbf{r})$ (HOMO density), come to the picture since it has been shown [24, 30, 31] that when the frozen orbital approximation (FOA) is used there is a direct relation between $f^\pm(\mathbf{r})$ and the density of the appropriate

FMO thus avoiding calculations of the system with $N + 1$ and $N - 1$ electrons as follows:

$$\begin{aligned} f^+(\mathbf{r}) &\approx \rho_L(\mathbf{r}), \\ f^-(\mathbf{r}) &\approx \rho_H(\mathbf{r}). \end{aligned} \quad (4)$$

On the other hand, the use of (4) instead of (3) allows one to diminish the computational effort without losing the qualitative picture of the local reactivity, but this approach should be always checked by comparison of these two couples of working equations because the first level of approximation based on total electronic densities will always be more accurate than the second level of approximation based on densities of FMOs.

Condensation to atoms is achieved through integration within the k th-atomic domain Ω_k [32–37] as follows:

$$f_k^\pm = \int_{\Omega_k} f^\pm(\mathbf{r}) d\mathbf{r}, \quad (5)$$

where f_k^\pm is now an atomic index that is used to characterize the electrophilic/nucleophilic power of atom k .

Even much better, Morell et al. [7, 11, 15, 38–41] have proposed a local reactivity descriptor (LRD) which is called the dual descriptor (DD) $f^{(2)}(\mathbf{r}) \equiv \Delta f(\mathbf{r})$. In spite of having been discovered several years ago, a solid physical interpretation was not provided in such a moment [42]. They used the notation $\Delta f(\mathbf{r})$, but currently it has been replaced by the modern notation $f^{(2)}(\mathbf{r})$ in order to highlight that this is a Fukui function of second order. Its physical meaning is to reveal nucleophilic and electrophilic sites on a molecular system at the same time. Mathematically it is defined in terms of the derivative of the Fukui function, $f(\mathbf{r})$ [18], with respect to the number of electrons, N . Through a Maxwell relation, this LRD may be interpreted as the variation of η (the molecular hardness which measures the resistance to charge transfer [43–45]) with respect to $v(\mathbf{r})$, the external potential. The definition of $f^{(2)}(\mathbf{r})$ is shown as indicated by Morell et al. [7, 11] as follows:

$$f^{(2)}(\mathbf{r}) = \left(\frac{\partial f(\mathbf{r})}{\partial N} \right)_{v(\mathbf{r})} = \left[\frac{\delta \eta}{\delta v(\mathbf{r})} \right]_N. \quad (6)$$

As mentioned above, DD allows one to obtain simultaneously the preferably sites for nucleophilic attacks ($f^{(2)}(\mathbf{r}) > 0$) and the preferably sites for electrophilic attacks ($f^{(2)}(\mathbf{r}) < 0$) into the system at point \mathbf{r} . DD has demonstrated to be a robust tool to predict specific sites of nucleophilic and electrophilic attacks in a much more efficient way than the Fukui function by itself because dual descriptor is able to distinguish those sites of true nucleophilic and electrophilic behavior; in consequence some works have been published with the aim of remarking the powerfulness of $f^{(2)}(\mathbf{r})$ and all those LRDs depending on DD [7, 11, 15, 38–41].

The general working equation to obtain DD is given by the difference between nucleophilic and electrophilic Fukui function [15]. A well-known first level of approximation implies the use of finite difference method where the sum

of electronic densities of the system with one more electron and one less electron is subtracted by the double of the total electronic density of the original system. Since this level of approximation implies a time-demanding computing, a second level of approximation has been used for some years where the densities of FMOs provide an easier-to-compute working equation as follows:

$$f^{(2)}(\mathbf{r}) = f^+(\mathbf{r}) - f^-(\mathbf{r}) \approx \rho_L(\mathbf{r}) - \rho_H(\mathbf{r}), \quad (7)$$

where densities of LUMO and HOMO are represented by $\rho_L(\mathbf{r})$ and $\rho_H(\mathbf{r})$, respectively.

Molecular symmetry can influence upon the local reactivity and on the other hand has been demonstrated that the Fukui function must conserve the symmetry [46, 47]. In addition, as the degeneration that may arise in frontier molecular orbitals is related with the molecular symmetry, within the framework of the second level of approximation, this phenomenon has been taken into account thus providing a mathematical expression to be applied on closed-shell molecular systems [48].

Hence, when an interaction between two species is well described through the use of this LRD, it is said that the reaction is controlled by frontier molecular orbitals (or frontier controlled) under the assumption that remaining molecular orbitals do not participate during the reaction [49].

The dual descriptor can also be condensed through an appropriate integration within the k th-atomic domain Ω_k as follows:

$$\int_{\Omega_k} f^{(2)}(\mathbf{r}) d\mathbf{r} = f_k^{(2)}. \quad (8)$$

When $f_k^{(2)} > 0$ the process is driven by a nucleophilic attack on atom k , and then that atom acts as an electrophilic species; conversely, when $f_k^{(2)} < 0$ the process is driven by an electrophilic attack over atom k , therefore atom k acts as a nucleophilic species.

3. Settings and Computational Methods

All computational studies were performed with the Gaussian 09 [50] series of programs with density functional methods as implemented in the computational package. The equilibrium geometries of the molecules were determined by means of the gradient technique. The force constants and vibrational frequencies were determined by computing analytical frequencies on the stationary points obtained after the optimization to check if there were true minima. The basis set used in this work was MIDIY, which is the same basis set as MIDI with a polarization function added to the hydrogen atoms. The MIDI basis is a small double-zeta basis (DZ) with polarization functions on N-F, Si-Cl, Br, and I [51–56]. The MIDI basis set and its derivatives have not attracted the attention that they deserve. However, based on our experience, these basis sets, combined with the proper density functional, are as good for the prediction of molecular properties as the usual DZ basis sets of the Pople's type.

For the calculation of the molecular structure and properties of the studied system, we have chosen the hybrid

meta-GGA density functionals M06, M06L, M06-2X, and M06HF [57], which consistently provide satisfactory results for several structural and thermodynamic properties [57–59].

Within the conceptual framework of DFT [18, 43], the chemical potential μ , which measures the escaping tendency of electron from equilibrium, is defined as

$$\mu = \left(\frac{\partial E}{\partial N} \right)_{v(\vec{r})} = -\chi, \quad (9)$$

where χ is the electronegativity.

The global hardness η can be seen as the resistance to charge transfer as follows:

$$\eta = \frac{1}{2} \left(\frac{\partial^2 E}{\partial N^2} \right)_{v(\vec{r})}. \quad (10)$$

Using a finite difference approximation and Koopmans' theorem [53–56], the previous expressions can be written as

$$\begin{aligned} \mu &\approx -\frac{1}{2}(I + A) \approx \frac{1}{2}(\epsilon_L + \epsilon_H), \\ \eta &\approx \frac{1}{2}(I - A) \approx \frac{1}{2}(\epsilon_L - \epsilon_H), \end{aligned} \quad (11)$$

where ϵ_H and ϵ_L are the energies of the highest occupied and the lowest unoccupied molecular orbitals, HOMO and LUMO, respectively. However, within the context of density functional theory, the previous inequalities are justified in light of the work of Perdew et al. [60], where they commented on the significance of the highest occupied Kohn-Sham eigenvalue and proved the ionization potential theorems for the exact Kohn-Sham density functional theory of a many-electron system. In addition the use of the energies of frontier molecular orbitals as an approximation to obtain I and A is supported by the Janak's theorem [61]. In particular, the negative of Hartree-Fock and Kohn-Sham HOMO orbital has been found to define upper and lower limits, respectively, for the experimental values of the first ionization potential [62] thus validating the use of energies of Kohn-Sham frontier molecular orbital to calculate reactivity descriptors coming from Conceptual DFT [22, 37, 63].

The electrophilicity index ω represents the stabilization energy of the systems when it gets saturated by electrons coming from the surrounding

$$\omega = \frac{\mu^2}{2\eta} \approx \frac{(I + A)^2}{2(I - A)} \approx \frac{(\epsilon_L + \epsilon_H)^2}{2(\epsilon_L - \epsilon_H)}. \quad (12)$$

The electron donating (ω^-) and electron accepting (ω^+) powers have been defined as [64]

$$\begin{aligned} \omega^- &= \frac{(3I + A)^2}{16(I - A)}, \\ \omega^+ &= \frac{(I + 3A)^2}{16(I - A)}. \end{aligned} \quad (13)$$

It follows that a larger ω^+ value corresponds to a better capability of accepting charge, whereas a smaller value of ω^- value of a system makes it a better electron donor. In order to compare ω^+ with $-\omega^-$, the following definition of net electrophilicity has been proposed [65]:

$$\Delta\omega^\pm = \omega^+ - (-\omega^-) = \omega^+ + \omega^- \quad (14)$$

that is the electron accepting power relative to the electron donating power.

4. Results and Discussion

The molecular structure of Naringin was preoptimized by starting with the readily available PDB structure and finding the most stable conformer by means of the conformers module of Materials Studio through a random sampling with molecular mechanics techniques and a consideration of all the torsional angles. The structure of the resulting conformer was then optimized with the M06, M06L, M06-2X, and M06-HF density functionals in conjunction with the MIDIY basis set. The optimized molecular structure of the Naringin molecule (with the M06 density functional) is shown in Figure 1.

The validity of the Koopmans' theorem within the DFT approximation is controversial. However, it has been shown [62] that although the KS orbitals may differ in shape and energy from the HF orbitals, the combination of them produces Conceptual DFT reactivity descriptors that correlate quite well with the reactivity descriptors obtained through Hartree-Fock calculations. Thus, it is worth to calculate the electronegativity, global hardness, and global electrophilicity for the studied systems using both approximations in order to verify the quality of the procedures.

The HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ , total hardness η , and global electrophilicity ω of the Naringin molecule calculated with the M06, M06L, M06-2X, and M06-HF density functionals and the MIDIY basis set are presented in Table 1. The upper part of the table shows the results derived assuming the validity of Koopmans' theorem, and the lower part shows the results derived from the calculated vertical I and A . As can be seen from Table 1, the Koopman's theorem holds approximately for the density functionals which include some percentages of HF exchange, but it fails completely for the M06L density functional (without inclusion of HF exchange).

The condensed Fukui functions can also be employed to determine the reactivity of each atom in the molecule. The corresponding condensed functions are given by $f_k^+ = q_k(N+1) - q_k(N)$ (for nucleophilic attack), $f_k^- = q_k(N) - q_k(N-1)$ (for electrophilic attack), and $f_k^0 = [q_k(N+1) - q_k(N-1)]/2$ (for radical attack), where q_k is the gross charge of atom k in the molecule.

It is possible to evaluate condensed Fukui functions from single-point calculations directly, without resorting to

TABLE 1: HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ , total hardness η , and global electrophilicity ω of Naringin calculated with the M06, M06L, M06-2X, and M06-HF density functionals and the MIDIY basis set. The upper part of the table shows the results derived assuming the validity of Koopmans' theorem, and the lower part shows the results derived from the calculated vertical I and A .

Property	M06	M06L	M06-2X	M06-HF
HOMO	-5.9078	-4.6497	-7.0972	-9.0262
LUMO	-0.6291	-1.3507	-1.6054	-1.4177
χ	3.2685	3.0002	4.3513	5.2220
η	2.6394	1.6495	2.7459	3.8043
ω	2.0238	5.8694	3.4477	3.5840
I	7.9980	8.2522	7.7756	8.3975
A	0.7513	0.7309	0.8358	0.8151
χ	4.3747	4.4916	4.3057	4.6063
η	3.6234	3.7607	3.4699	3.7912
ω	2.6409	2.6823	2.6714	2.7983

additional calculations involving the systems with $N-1$ and $N+1$ electrons as follows:

$$f_k^+ = \sum_{a \in k} \left[c_{ai}^2 + c_{ai} \sum_{b \neq a} c_{bi} S_{ab} \right] \quad (\text{where } i = \text{LUMO}), \quad (15)$$

$$f_k^- = \sum_{a \in k} \left[c_{ai}^2 + c_{ai} \sum_{b \neq a} c_{bi} S_{ab} \right] \quad (\text{where } i = \text{HOMO})$$

with c_{ai} being the LCAO coefficients and S_{ab} being the overlap matrix. The condensed Fukui functions are normalized, thus $\sum_k f_k = 1$ and $f_k^0 = [f_k^+ + f_k^-]/2$.

The condensed Fukui functions have been calculated using the AOMix molecular analysis program [66, 67] starting from single-point energy calculations. We have presented, discussed, and successfully applied the described procedure in our previous studies on different molecular systems [68–71].

The condensed dual descriptor has been defined as $f^{(2)}(\mathbf{r})_k = f_k^+ - f_k^-$ [7, 11]. From the interpretation given to the Fukui function, one can note that the sign of the dual descriptor is very important to characterize the reactivity of a site within a molecule toward a nucleophilic or an electrophilic attack. That is, if $f^{(2)}(\mathbf{r})_k > 0$, then the site is favored for a nucleophilic attack, whereas if $f^{(2)}(\mathbf{r})_k < 0$, then the site may be favored for an electrophilic attack [7, 11, 72].

The electrophilic f^+ and nucleophilic f^- condensed Fukui functions and $f^{(2)}(\mathbf{r})$ over the atoms of the Naringin molecule calculated with the M06, M06L, M06-2X, and M06-HF density functionals and the MIDIY basis set are shown in Table 2. The actual values have been multiplied by 100 for an easier comparison.

In Table 2, those atoms with a value for $f^{(2)}(\mathbf{r})$ close to zero are not shown. All four density functionals predict the same behavior. It can be concluded from the analysis of the results on Table 2 that C8 will be the preferred site for

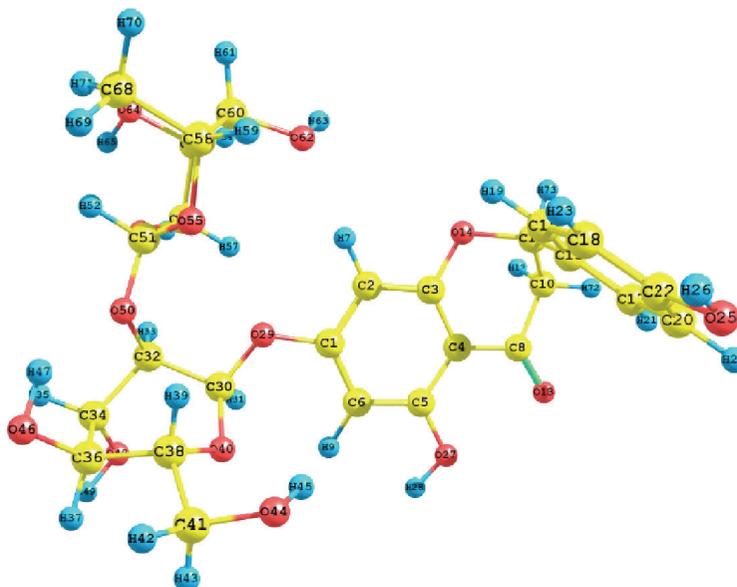


FIGURE 1: Optimized Molecular Structure of the Naringin Molecule.

TABLE 2: Electrophilic f^+ and nucleophilic f^- condensed Fukui functions and $f^{(2)}(\mathbf{r})$ over the atoms of the Naringin molecule calculated with the M06, M06L, M06-2X, and M06-HF density functionals and the MIDIY basis set. The actual values have been multiplied by 100 for an easier comparison. H atoms are not shown.

Atom	M06			M06L			M06-2X			M06-HF		
	f^+	f^-	$f^{(2)}(\mathbf{r})$	f^+	f^-	$f^{(2)}(\mathbf{r})$	f^+	f^-	$f^{(2)}(\mathbf{r})$	f^+	f^-	$f^{(2)}(\mathbf{r})$
1C	16.48	0.65	15.83	15.04	-0.01	15.05	17.17	3.06	14.11	18.49	2.81	15.68
2C	0.74	5.61	-4.87	0.56	0.59	-0.03	0.80	9.57	-8.77	1.34	1.18	0.26
3C	10.11	0.49	9.62	9.68	0.34	9.34	10.37	0.24	10.13	9.76	1.08	8.68
4C	6.17	6.03	0.14	8.58	4.66	3.92	7.71	7.45	0.26	10.56	6.45	4.13
5C	8.59	1.86	6.73	8.86	0.26	8.60	7.98	4.27	5.71	7.91	1.09	6.82
6C	1.54	1.54	0.00	0.94	0.51	0.43	2.04	0.46	1.58	2.76	1.00	1.76
8C	19.52	0.83	18.69	21.16	1.04	20.12	17.99	0.15	17.84	14.63	0.14	14.49
10C	0.25	6.13	-5.88	0.23	10.45	-10.22	0.27	0.52	-0.25	0.28	0.31	-0.03
11C	1.60	1.10	0.50	1.51	1.35	0.16	1.58	0.34	1.24	1.74	0.46	1.28
13O	17.18	32.39	-15.21	18.96	69.06	-50.10	2.07	16.45	-14.38	1.04	14.47	-13.43
14O	1.85	1.81	0.04	2.12	0.37	1.75	1.40	1.19	0.21	0.83	0.17	0.76
15C	0.41	8.88	-8.47	0.24	0.73	-0.49	0.50	17.02	-16.52	0.69	24.01	-23.32
16C	3.04	2.28	0.76	2.92	0.32	2.60	3.59	3.75	-0.16	4.38	6.45	-2.07
17C	0.26	1.29	-1.03	0.31	0.19	0.12	0.37	2.57	-2.20	0.53	3.23	-2.70
18C	1.34	3.56	-2.22	1.49	0.17	1.32	1.65	7.21	-5.56	1.90	7.03	-5.13
20C	2.09	5.11	-3.02	2.09	0.48	1.61	2.66	8.28	-5.62	3.34	11.58	-8.24
22C	0.54	5.73	-5.19	0.50	0.54	-0.04	0.58	11.83	-10.25	0.66	18.17	-17.51
25O	0.14	8.16	-8.02	0.15	0.72	-0.57	0.11	11.92	-11.81	0.08	10.56	-10.48
27O	2.23	3.09	-0.86	2.56	1.22	1.34	1.66	4.28	-2.62	1.17	0.65	0.52
29O	2.62	0.74	1.88	2.94	0.05	2.89	2.22	2.31	-0.09	1.58	1.14	0.34

nucleophilic attack, while O13 will be the preferred site for electrophilic attack.

The electrodonating (ω^-) and electroaccepting (ω^+) powers and net electrophilicity $\Delta\omega^\pm$ of the Naringin molecule calculated with the M06, M06L, M06-2X, and M06-HF density functionals and the MIDIY basis set are presented in

Table 3. The upper part of the table shows the results derived assuming the validity of Koopmans' theorem, and the lower part shows the results derived from the calculated vertical I and A .

The results from Table 3 clearly indicate that Naringin is an electrodonating molecule, with the same result predicted

TABLE 3: Electrodonating (ω^-) and electroaccepting (ω^+) powers and net electrophilicity $\Delta\omega^\pm$ of Naringin calculated with the M06, M06L, M06-2X, and M06-HF density functionals and the MIDIY basis set. The upper part of the table shows the results derived assuming the validity of Koopmans' theorem, and the lower part shows the results derived from the calculated vertical I and A .

Property	M06	M06L	M06-2X	M06-HF
ω^-	3.9878	4.4348	5.9666	6.6704
ω^+	0.7194	1.4346	1.6152	1.4485
$\Delta\omega^\pm$	4.7072	5.8694	7.5818	8.1189
ω^-	5.2810	5.3980	5.2580	5.5754
ω^+	0.9064	0.9065	0.9527	0.9691
$\Delta\omega^\pm$	6.1874	6.3045	6.2107	6.5445

by all the four density functionals considered in this study. However, only the results obtained through the calculations with the M06, M06-2X, and M06-HF density functionals are in fairly agreement between those from vertical calculations of I and A and those coming from the assumption of the validity of the Koopmans' theorem in DFT.

5. Conclusions

From the whole results presented in this contribution it has been clearly demonstrated that the sites of interaction of the Naringin molecule can be predicted by using DFT-based reactivity descriptors such as the hardness, softness, and electrophilicity, as well as Fukui function calculations. These descriptors were used in the characterization and successful description of the preferred reactive sites and provide a firm explanation for the reactivity of the Naringin molecule.

The M06 family of density functionals (M06, M06L, M06-2X, and M06-HF) used in the present work leads to the same qualitatively and quantitatively similar description of the chemistry and reactivity of the Naringin molecule, yielding reasonable results. However, for the case of the M06L functional, which does not include HF exchange, the agreement between the results obtained through energy calculations and those that assume the validity of the Koopmans' theorem is definitively not true.

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