

Theoretical Studies of the Chemical Reactivity of a Series of Coumarin Derivatives by the Density Functional Theory

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Abstract

The global descriptors of reactivity such as HOMO and LUMO energies, chemical hardness, electrophilicity, softness and dipole moment are theoretically determined for five coumarin derivatives in this paper. The analysis of the determined descriptors allows us to classify the studied molecules according to their reactivities. Thus, compound M3 is qualified to be the most reactive and the least stable with 3.933 eV as its gap energy ΔE_{gap} . It is at the same time the softest, the best electron donor, the most electrophilic and the most polar molecule. The study of thermodynamic parameters shows that all the reactions of formation of studied coumarin derivatives are exothermic and spontaneous with less disorder. Furthermore, Hirschfield population analysis was carried out in order to locate the reactive sites, that are assumed to be the electrophilic and nucleophilic sites of the molecules. It appears that all the reactive sites are located on carbon atoms except those of molecule M3 which are located on oxygen atoms. Compounds M1 and M2 have the same electrophilic site (C15) and the same nucleophilic site (C13) thereby showing that the methyl group does not have any influence on the reactive site. The electrophilic site of the molecule M3 is located on both the identical oxygen atoms O33 and O34 while its nucleophilic site is located on the oxygen atoms O12. The electrophilic sites of compound M4 and M5 are the same and it is located on carbon atom (C11) while the nucleophilic site is located on carbon atom C23 for molecule M4.

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Concerning the nucleophilic sites of molecule M5 it is located on carbon atom C20. The difference nucleophilic reactive site may be due to the conjugation of activity of both fluorine atom and methyl group on the M5.

Keywords: coumarin derivatives; global descriptors; DFT; reactivity.

1. Introduction

Coumarins are heterocyclic compounds which possess crucial importance in life because they play an essential role in the metabolism of all living cells[1]. Coumarins are substances coming from plants and they have considerable therapeutic importance. They can exhibit potent biological and pharmacodynamic properties such as photosensitizing, anti-solar, antibiotic, anticoagulant (antivitamin) and antihemorrhagic properties[2]. The study of heterocyclic chemistry is a widespread and growing field of chemistry with applications in medicine, agriculture, photodiodes [3], cosmetology [4] and many other fields. Several heterocyclic derivatives containing sulfur and/or nitrogen atoms serve as a unique and versatile scaffold for the design of new drugs [5]. Coumarins are well known for their multiple biological activities including anticancer, anti-HIV, antitumor and antioxidant [6]. According to their biological activities' usefulness, they have been considered as a subject of special attention. Regarding the harmful side effects of existing treatments for pathologies such as cancer and AIDS, access to new therapeutic molecules that are effective and free of adverse effects has become the backbone of chemists. Computational chemistry is therefore both an independent research area and a vital adjunct to experimental studies [7]. Density functional theory (DFT) is recognized as a popular approach for calculating the structural and energetic characteristics of molecules[8-10]. This popularity is due to the fact that it provides very precise information for the evaluation of molecular properties[10]. The general objective of this study is to determine theoretically the chemical reactivity sites of five coumarin derivatives by the DFT method.

2. Materials and Methods

2.1 Level of Calculation Theory

All calculations were performed by using the DFT method at B3LYP level and 6-31G(d, p) was used as basis set. The calculations were performed with Gaussian 09 software developed by Frisch and his colleagues [11]. It is important to note that Becke's three-parameters hybrid function known as B3LYP correlation function is one of the most robust functions of the hybrid family [12,13]. The output files were visualized using the GAUSS VIEW 05 graphical interface [14]. All the calculations were performed over the optimized molecules characterized by the minimum of energy. Besides, this state is indicated by the absence of imaginary frequencies. Figure 1 displays the structures of the studied molecules.

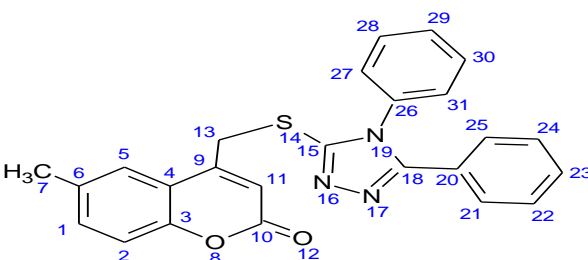
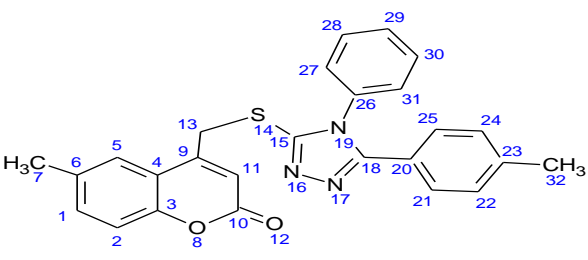
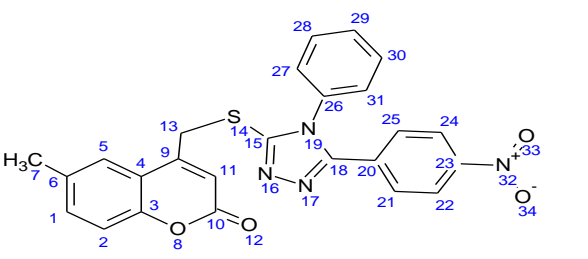
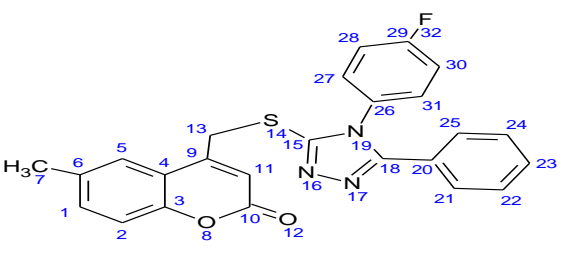
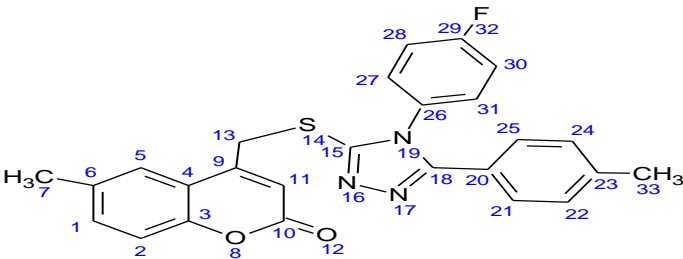
<p>M1</p> 	<p>M2</p> 
<p>4-((4,5-Diphenyl-4H-1,2,4-triazol-3-yl)sulfanyl)methyl)-6-methyl-2H-chromen-2-one</p>	<p>6-Methyl-4-((4-phenyl-5-(4-methylphenyl)-4H-1,2,4-triazol-3-yl)sulfanyl)methyl)-2H-chromen-2-one</p>
<p>M3</p> 	<p>M4</p> 
<p>6-Methyl-4-((5-(4-nitrophenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)sulfanyl)-2H-chromen-2-one</p>	<p>4-((4-(4-Fluorophenyl)-5-(phenyl)-4H-1,2,4-triazol-3-yl)sulfanyl)methyl)-6-methyl-2H-chromen-2-one</p>
<p>M5</p> 	
<p>4-((4-(4-Fluorophenyl)-5-(4-methylphenyl)-4H-1,2,4-triazol-3-yl)sulfanyl)methyl)-6-methyl-2H-chromen-2-one</p>	

Figure 1: Structures of studied coumarin molecules

2.2 Thermodynamic Parameters

The knowledge of a molecule's thermodynamic parameters is useful for understanding its behavior in terms of reactivity and disorder which can characterize a chemical component energetically. The thermodynamic parameters which have been considered in this study are enthalpy of formation ($\Delta_f H_{298}^0$), free enthalpy of formation ($\Delta_f G_{298}^0$) and entropy of formation ($\Delta_f S_{298}^0$). These parameters are calculated according to Ochtersky [15] by using the following relationships:

$$\Delta_f H_{298k}^0(M) = \Delta_f H_{0k}^0(M) + (H_{298k}^0(M) - H_{0k}^0(M)) - \sum_{atoms} x(H_{298k}^0(X) - H_{0k}^0(X)) \quad (1)$$

$(H_{298k}^0(M))$ corresponds to Hcorr (thermal correction to enthalpy) in Gaussian's output of the molecule,

$H_{0k}^0(M)$ corresponds to its ZPE (Zero Point Energy) and

$$\Delta_f H_{0k}^0(M) = \sum_{atoms} x \Delta_f H_{0k}^0(X) - \sum_{atoms} D_0(M) \quad (2)$$

$H_{298k}^0(X) - H_{0k}^0(X)$ and $\Delta_f H_{0k}^0(X)$ are given in JANAF table [16].

And energy of atomization denoted D_0 which is the amount of energy changes when a compound's bonds are broken and the component atoms are reduced to individual atoms.

$$\sum D_0(M) = \sum_{atoms} x \varepsilon_0(X) - \varepsilon_0(M) - \varepsilon_{ZPE}(M) \quad (3)$$

To calculate these quantities, we need a few component pieces first. In the abovementioned descriptions, we use:

M to stand for the molecule,

X to represent each element that makes up M,

x is the number of X atoms in M.

ε_0 stands for total energy.

Regarding the enthalpies of formation, its calculation requires two steps processes. The first step is to calculate the enthalpies of formation ($\Delta_f H^\circ(0K)$) of the species at 0k involved in the reaction. The second step is to calculate the enthalpies of formation of the species at 298K.

The entropy of formation is calculated according to the following formula

$$\Delta S_f^0(M, 298K) = S_M - \sum_{atoms} x \Delta S(X, 298K) \quad (4)$$

$\Delta S_f^0(M, 298K)$ Corresponds to the entropy of the molecule M at 298K.

S_M corresponds to the value of entropy given by Gaussian output in thermochemistry section.

$\Delta S(X, 298K)$ Corresponds to the entropy of the atom X given in JANAF table.

The free enthalpy of Gibbs will be calculated by using the following relation

$$\Delta_f G_{228}^0(M) = \Delta_f H_{298}^0(M) - T \Delta S_f^0(M, 298K) \quad (5)$$

2.3 Global and Local Indices Derived from the Conceptual DFT

Frontier Molecular Orbital theory (FMO) is used to characterize the overall reactivity of a compound [17]. This theory predicts the excitation properties of a molecule. Therefore, it constitutes quantum parameters for the determination of molecular reactivity [18][19]. The lower the energetic gap between HOMO and LUMO orbitals, the more reactive the molecule is. The functions of Fukui are obtained by using the procedure based on the finite difference method [20][21][22]. They allow to highlight the electrophilic and nucleophilic sites through f values. The different values of the local descriptors are calculated from equations (6) and (7) below.

$$f_k^+ = q_k(N + 1) - q_k(N) \quad (6)$$

$$f_k^- = q_k(N) - q_k(N - 1) \quad (7)$$

$q_k(N)$: electron population of the atom k in the neutral molecule.

$q_k(N + 1)$: electron population of the atom k in the anionic molecule.

$q_k(N - 1)$: electron population of the atom k in the cationic molecule.

The function $f(r)$ reflects the ability for a molecular site to accept or to donate electrons. High values of $f(r)$ are related to high reactivity at that site [23]. Besides, Dual descriptors are good tool to predict reactivity because they give information about the ability for a site to give or to gain electron density. They also permit to understand the problem of regioselectivity. Indeed, a dual positive descriptor corresponds to a site which can receive electron density thereby becoming the most electrophilic. Conversely, dual negative descriptor corresponds to a site which is capable to yield electron density. Thus, it is the most nucleophilic site. A site with a value of the dual descriptor close to zero corresponds to a site whose capacity to receive and to liberate electron density are equal. The different values of the local descriptors are calculated from the following relationship [24]

$$\Delta f = f_k^+ - f_k^- \quad (8)$$

The chemical potential μ measures the tendency of electron cloud to escape from the molecule. This reactivity parameter can be expressed as a function of ionization potential PI and the electronic affinity AE. It corresponds to the opposite of the electronegativity χ as defined by Pauling and Mulliken[25,26].

$$PI = -E_{HOMO} \text{ et } AE = -E_{LUMO} \quad (9)$$

$$\mu = -\frac{PI+AE}{2} = -\chi \quad (10)$$

E_{HOMO} and E_{LUMO} are respectively the energies of the HOMO and LUMO frontier molecular orbitals.

The hardness η , the softness S and the electrophile index ω can be expressed as a function of the ionization

potentials (PI) and the electron affinity (AE) [27][28].

$$\eta = \frac{1}{s} = (PI - AE)/2 \quad (11)$$

$$\omega = \frac{\mu^2}{2\eta} = \frac{\chi^2}{2\eta} \quad (12)$$

3. Results and Discussion

3.1 Thermodynamic descriptors

The thermodynamic parameters that were determined in this study are standard enthalpy of formation, standard free enthalpy of formation and standard entropy of formation. All values are summarized in Table 1.

Table 1: The standard thermodynamic parameters of formation of studied compounds.

Molecules	$\Delta_f H_{298}^0$ (kcal/mol)	$\Delta_f G_{298}^0$ (kcal/mol)	$\Delta_f S_{298}^0$ (kcal/mol- K)
M1	-1375.949	-894.735	-1.614
M2	-1428.322	-950.388	-1.603
M3	-1575.789	-1099.047	-1.599
M4	-1423.329	-943.606	-1.609
M5	-1475.769	-999.623	-1.597

It is noted that any variation in enthalpy and free enthalpy reflects respectively the thermicity of a chemical reaction and the spontaneity with which a chemical reaction takes place. As far as entropy is concerned, it provides relative information on the level of disorder in each chemical system. All the calculated values of thermodynamic parameters in this study are negative. These negative values of enthalpy and free enthalpy mean respectively that the reactions are exothermic and spontaneous under the required conditions for the study. Furthermore, compound M3 is discovered as the most spontaneous and exothermic molecule during the synthesis. Regarding the entropy, its negative value is assumed to increase the order during the syntheses of coumarin molecules. Thus, the formation of all studied compounds is spontaneous, exothermic and reduces the order. According to overmentioned statement, it can be assumed that all these compounds exist and are thermodynamically stable.

3.2 Global Reactivity Descriptors

Global reactivity parameters are necessary for the classification of compounds according to their chemical reactivity. These descriptors are calculated from HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest unoccupied Molecular Orbital) energies and they are grouped in Table 2.

Table2: Global Reactivity Descriptors from Frontier Molecular Orbitals (FMOs)

Molecules	$E_{\text{HOMO}}(\text{eV})$	$E_{\text{LUMO}}(\text{eV})$	$\Delta E_{\text{gap}}(\text{eV})$	ω (eV)	η , (eV)	S (eV^{-1})	χ (eV)	$\mu(\text{D})$
M1	-6.214	-1.868	4.346	3.757	2.174	0.460	-4.041	6.600
M2	-6.162	-1.845	4.317	3.713	2.160	0.463	-4.003	6.563
M3	-6.371	-2.653	3.718	5.475	1.859	0.538	-4.512	9.363
M4	-6.254	-1.920	4.334	3.854	2.169	0.461	-4.087	5.200
M5	-6.233	-1.893	4.339	3.804	2.169	0.461	-4.063	5.233

Table 2 shows that the compound M3 has the smallest value of the gap energy ($\Delta E_{\text{gap}} = 3.718$ eV), which allows to qualify it as the most reactive and the least kinetically stable among all the studied molecules. Conversely, the compound M1 is the least reactive with the highest value of the gap energy ($\Delta E_{\text{gap}} = 4.346$ eV) thereby appearing as the most stable compound, i.e. the least reactive molecule. The analysis of the other global reactivity indices, such as global softness (S) reveals that compound M3 displays the highest value ($S = 0.538$ eV). It is therefore admitted as the softest studied molecule. Moreover, this compound M3 also has the lowest value of electronegativity ($\chi = -4.512$ eV) assuming it to be the best electron donor of the studied compounds. In addition, the electrophilic index value of compound M3 ($\omega = 5.475$ eV) indicates that it is the most electrophilic molecule. Other parameter such as the solubility which is studied by the mean of the dipole moment of the five studied compounds was also considered. It varies from 5.200 to 9.363 Debye and the highest value of the dipole moment belongs to the compound M3. Therefore, M3 is assumed to be the most polar compound. This can be explained by the presence of the nitro group ($-\text{NO}_2$) as a substituent. At the end of this analysis, we retain that M3 is the most reactive, the least stable, the softest, the best electron donor, the most electrophilic and the most polar compound.

3.3 Functions of Fukui

Thanks to Hirschfeld parameters that were calculated from the optimized structures. Fukui indices were determined to highlight the electrophilic and nucleophilic attack sites. The calculated Fukui indices are shown in Tables 3 and 4. The nucleus which is concerned by this study is the coumarin nucleus, the triazol ring and the two benzenic cycles which are connected to the triazol ring.

Table 3: Fukui Indices and dual descriptors of M1, M2 and M3 using Hirshfeld Population Analysis (HPA).

Molecule M1				Molecule M2				Molecule M3			
atom	F+	F-	Δf	atom	F+	F-	Δf	atom	F+	F-	Δf
C1	0.042	0.047	-0.005	C1	0.042	0.046	-0.004	C1	0.045	0.072	-0.027
C2	0.040	0.043	-0.003	C2	0.040	0.042	-0.002	C2	0.030	0.051	-0.020
C3	0.004	0.004	0.000	C3	0.005	0.004	0.001	C3	0.009	0.046	-0.037
C4	-0.004	-0.007	0.003	C4	-0.004	-0.007	0.003	C4	0.002	0.037	-0.035
C5	0.015	0.014	0.002	C5	0.015	0.013	0.002	C5	0.021	0.034	-0.013
C6	0.014	0.016	-0.002	C6	0.015	0.016	-0.001	C6	0.014	0.051	-0.037
C7	0.031	0.034	-0.004	C7	0.031	0.034	-0.003	C7	0.029	0.073	-0.043
O8	0.023	0.025	-0.003	O8	0.023	0.025	-0.002	O8	0.017	0.038	-0.02
C9	0.039	0.022	0.017	C9	0.04	0.022	0.018	C9	0.031	0.013	0.018
C10	0.032	0.028	0.004	C10	0.032	0.027	0.005	C10	0.019	0.021	-0.002
C11	0.063	0.103	-0.04	C11	0.064	0.102	-0.038	C11	0.041	0.049	-0.008
O12	0.059	0.070	-0.011	O12	0.059	0.069	-0.010	O12	0.034	0.077	-0.043
C13	0.111	0.218	-0.107	C13	0.113	0.216	-0.103	C13	0.036	0.03	0.006
S14	0.150	0.154	-0.005	S14	0.151	0.152	-0.001	S14	0.054	0.060	-0.006
C15	0.024	-0.008	0.032	C15	0.023	-0.008	0.031	C15	0.017	0.018	0.000
N16	0.048	0.026	0.022	N16	0.046	0.026	0.020	N16	0.018	0.020	-0.002
N17	0.026	0.025	0.001	N17	0.023	0.024	-0.001	N17	0.024	0.033	-0.009
C18	0.040	0.023	0.017	C18	0.039	0.022	0.017	C18	0.012	0.024	-0.012
N19	0.017	0.007	0.010	N19	0.018	0.007	0.011	N19	0.013	0.007	0.006
C20	0.001	-0.001	0.002	C20	-0.001	0.000	-0.001	C20	0.039	0.010	0.028
C21	0.014	0.010	0.004	C21	0.032	0.023	0.009	C21	0.042	0.022	0.020
C22	0.033	0.026	0.007	C22	0.008	-0.006	0.014	C22	0.050	0.025	0.025
C23	0.046	0.036	0.010	C23	0.026	0.022	0.004	C23	0.027	0.029	-0.003
C24	0.026	0.020	0.006	C24	0.023	0.019	0.004	C24	0.049	0.028	0.021
C25	0.027	0.016	0.011	C25	0.027	0.023	0.004	C25	0.041	0.023	0.018
C26	-0.008	-0.009	0.001	C26	0.006	0.003	0.003	C26	-0.009	-0.009	0.000
C27	0.008	-0.006	0.014	C27	-0.007	-0.009	0.002	C27	0.008	0.006	0.003
C28	0.021	0.012	0.009	C28	0.001	0.001	0.000	C28	0.024	0.024	0.000
C29	0.030	0.025	0.005	C29	0.027	0.023	0.004	C29	0.028	0.027	0.001
C30	0.027	0.023	0.004	C30	0.030	0.025	0.005	C30	0.016	0.016	-0.001
C31	0.000	0.002	-0.001	C31	0.020	0.012	0.008	C31	-0.007	-0.006	-0.001
				C32	0.034	0.030	0.004	N32	0.051	0.005	0.046
								O33	0.088	0.024	0.064
								O34	0.088	0.024	0.064

The analysis of these data shows that the smallest and the highest values of Δf are obtained for C13 and C15 carbon atoms, respectively. These atoms represent respectively the nucleophilic and electrophilic sites. These

reactive sites are the same for compounds M1 and M2 however their structures are different from a methyl group on M2 specially localized on carbon C23.

Table 4: Fukui Indices and dual descriptors of M4 et M5 using Hirshfeld Population Analysis (HPA).

Molecule M4				Molecule M5			
Atom	F ⁺	F ⁻	Δf	Atom	F ⁺	F ⁻	Δf
C1	0.076	0.063	0.013	C1	0.076	0.057	0.019
C2	0.051	0.045	0.006	C2	0.052	0.041	0.010
C3	0.017	0.039	-0.021	C3	0.017	0.034	-0.017
C4	0.007	0.029	-0.022	C4	0.008	0.025	-0.017
C5	0.042	0.028	0.014	C5	0.042	0.025	0.018
C6	0.023	0.045	-0.022	C6	0.023	0.040	-0.017
C7	0.046	0.064	-0.017	C7	0.046	0.058	-0.011
O8	0.031	0.033	-0.002	O8	0.031	0.030	0.001
C9	0.063	0.010	0.053	C9	0.063	0.008	0.055
C10	0.039	0.017	0.022	C10	0.039	0.015	0.024
C11	0.091	0.038	0.053	C11	0.091	0.032	0.06
O12	0.066	0.064	0.002	12	0.066	0.056	0.010
C13	0.050	0.030	0.020	C13	0.049	0.029	0.020
S14	0.075	0.054	0.021	C14	0.074	0.051	0.023
C15	0.007	0.026	-0.019	C15	0.006	0.028	-0.022
N16	0.016	0.027	-0.010	N16	0.016	0.028	-0.012
N17	0.019	0.039	-0.019	N17	0.019	0.039	-0.021
C18	0.022	0.023	-0.001	C18	0.022	0.021	0.001
N19	0.011	0.009	0.002	N19	0.011	0.009	0.002
C20	0.006	0.027	-0.021	C20	0.004	0.034	-0.030
C21	0.017	0.034	-0.018	C21	0.015	0.037	-0.022
C22	0.031	0.041	-0.010	C22	0.027	0.044	-0.017
C23	0.049	0.073	-0.024	C23	0.025	0.047	-0.022
C24	0.029	0.046	-0.017	C24	0.025	0.049	-0.023
C25	0.020	0.035	-0.015	C25	0.019	0.039	-0.020
C26	-0.004	-0.010	0.006	C26	-0.003	-0.010	0.007
C27	0.011	0.006	0.005	C27	0.011	0.006	0.004
C28	0.030	0.025	0.005	C28	0.030	0.024	0.006
C29	0.018	0.014	0.005	C29	0.018	0.013	0.005
C30	0.02	0.017	0.003	C30	0.02	0.017	0.003
C31	0.002	-0.006	0.008	C31	0.003	-0.006	0.009
F32	0.018	0.016	0.002	C32	0.018	0.016	0.002
				C33	0.037	0.064	-0.027

Through this difference regarding the structures and yet the reactive sites are the same, we can assume that the

methyl donor group has no influence on the coumarine molecules. Regarding the molecule M3, a nitro group has substituted the methyl group. Here, the lowest value of Δf is found on oxygen atoms O12 and the highest value is attributed to both oxygen atoms O33 and O34 which are in the same environment. This finding allows to understand that O33 and O34 is the electrophilic sites where it will happen nucleophilic attack. This molecule must be bidentate during the electrophilic attacks as both O33 and O34 and the same. Besides O12 is the nucleophilic site where it will happen electrophilic attack. The presence of nitro group at carbon C23 influences seriously the sites of reactivity because they are no longer carried by carbon atoms but by oxygen ones.

Hirshfeld population study of molecule M4 shows that C11 atom is the electrophilic site where it will happen nucleophilic attack due to the fact it displays the highest value of Δf . On the other hand, the carbon atom C23 has the lowest value of the same parameter, which makes it the nucleophilic site. Thus, we can assume that the presence of electronegative atom favors the displacement of reactivity sites. Concerning molecule M5, plus the fluorine atom on C29, the methyl group has been maintained on C23 comparatively to M4. It appears that the electrophilic site remains C11. However, the nucleophilic site has shifted from C23 to C20 regarding Δf values. The fact that the nucleophilic site moves from C23 to C20 can be explained by the conjugation of activity of both the electro-donnor ($-\text{CH}_3$) and the electro-attractor (F) groups. It can be underlined that the fact of adding methyl group to carbon C23 of the molecule containing fluorine atom influences only the nucleophilic site.

4. Conclusion

At the end of our study carried out by the DFT method at B3LYP/6-31G (d, p) level, we determined the most reactive molecule from the values of the global descriptors of chemical reactivity. The analysis of the results showed, on one hand that compound M3 is the most polar because, it has the highest chemical reactivity and has both the lowest kinetic stability and the smallest energy gap of the studied molecules. On the other hand, compound M1 is discovered as the least polar, with the lowest chemical reactivity and the highest kinetic stability. Besides, Hirshfeld's population analysis method allowed to highlight the sites of reactivity that are the sites of electrophilic and nucleophilic attacks. These sites are all located on carbon atoms except for molecule M3 in which they are located on oxygen atoms. This displacement is explained by the presence of nitro group. This work can help to understand the reactivity of coumarin derivatives and may be useful in the synthesis of new coumarin precursors.

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