



Study of Reactivity and Molecular Stability by the Density Functional Theory Method on 2,3-Dihydro - 1H-Perimidine: Comparative Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. Author TNT designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SD and KB managed the analyses of the study. Authors KC, YOB and ZN managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Numerous studies have been carried out on the structure of 2,3-dihydro-1H-perimidine substituted as compounds with various biological activities. Researchers have found that these compounds exhibit characteristics potentially useful in medicinal chemistry research and have many therapeutic applications. In this work, we carried out a study using descriptors of the conceptual DFT in order to determine the atoms responsible for the chelation of certain metals (zinc, copper, iron ...) in order to propose new stable molecules complexed with these metals. Calculations were performed to determine the local reactivity of substituted 2,3-dihydro-1H-perimidine using Fukui functions by the Natural Population Analysis method. Overall parameters were also determined to predict the relative stability and reactivity of substituted 2,3-dihydro-1H-perimidine. This work was carried out at the calculation level B3LYP / 6-311G (d, p). Compound 2 with an energy difference from the frontier

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orbitals of $\Delta E_{\text{gap}} = 4.031$ eV is the most polarizable. Also, the study of frontier orbitals locates HOMO on the function of substituted 2,3-dihydro-1H-perimidine. Analysis of local reactivity indices as well as of the dual descriptor revealed that nitrogen N17 and N19 are the most favorable sites for electrophilic attack.

Keywords: Substituted 2,3-dihydro- 1H- perimidine ; DFT ; dual descriptor ; NPA charges.

1. INTRODUCTION

Perimidins are showing increasing interest as an important class of natural and synthetic products, most of which exhibit essential biological activity [1]. Several synthetic routes have been reported for the preparation of perimidins. Interest in perimidin derivatives stems from the appearance of these heterocyclic systems in many biologically active compounds [2]. Indeed, there is continued interest in the synthesis of perimidin ring structures. However, acid catalyzed reaction methods are not very efficient. Therefore, there is a need for a novel catalyst effective for this organic transformation. Hence the interest of 1-H perimidins.

Among other things, 1-H perimidins are perinaphtho-fused pyrimidines [3]. They were first discovered by Aguiar in 1874 [4]. As for substituted 2,3-dihydro-1H-perimidine, these are six-membered heterocyclic compounds bearing two nitrogen atoms and have been extensively studied [5-9]. They are characterized by either a deficit of binding or an excess of π binding [10]. They are of great interest to researchers thanks to their biological activities [11] and their ability to act as antimicrobial, antiulcer, antifungal and antitumor agents [12-13]. These molecules exhibit characteristics potentially useful in medicinal chemistry research and many therapeutic applications. We decided to study their reactivities using quantum chemistry methods in order to predict their interaction with certain chemical compounds.

Indeed, DFT (Density Functional Theory) has been accepted as a popular approach for calculating the structural characteristics and energies of molecules by the scientific community [14]. DFT has been distinguished by its efficiency and precision in the evaluation of several molecular properties [15]. Parr and Yang followed the idea that well-known chemical properties such as electronegativity, chemical potentials and affinities could be described and calculated with precision by manipulating electron density as a fundamental quantity [16].

Moreover, based on the work of Fukui and his theory of frontier molecular orbitals (FMO) [17], these same researchers generalized this concept and proposed Fukui's function as a tool for describing the local reactivity of molecules [18]. In this work, the objective is to determine the atom most favorable to a nucleophilic attack during a chemical reaction. Based on quantum chemistry methods, we determined the Fukui indices using natural population analysis and then calculating the numerical value of the dual descriptor. We have also considered the relative stability of these compounds in this work.

This study was carried out on five compounds of the 2,3-Dihydro -1H-perimidine family represented in Fig.1 to determine the atom or atoms capable of fixing cations. These molecules have been synthesized in our laboratory.

Gaussian 05 software allowed us to represent 3D structures using its graphical interface. Then, we optimized the structures using Gaussian 09 software in order to find the information useful for this work.

2. MATERIALS AND METHODS

2.1 Descriptors of Reactivity

In the qualitative interpretation of chemical reactivity, frontier orbitals play a fundamental role. The highest occupied molecular orbital (HOMO) is the outer orbital containing electrons that tends to donate these electrons in a chemical reaction. However, the lowest vacant molecular orbital (LUMO) is perceived to be the lowest orbital containing free places that can accept electrons. These frontier orbitals therefore play an important role in the qualitative interpretation of chemical reactivity [19]. While the energy of HOMO is directly related to ionization potential, that of LUMO is directly related to electron affinity. The energy difference between HOMO and LUMO, called the energy gap, is an important stability factor for structures. The energy difference (EHOMO-ELUMO) makes it possible to characterize the chemical reactivity and the kinetic stability of the molecule [19]. A

molecule with a high energy difference (ΔE) is less polarizable and is generally associated with low chemical reactivity and high kinetic stability [20].

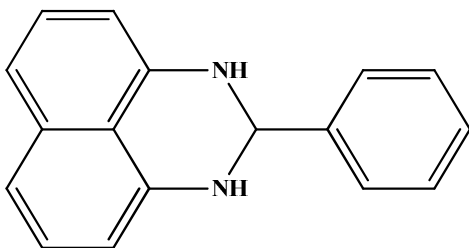
2.1.1 Global descriptors

Theoretical descriptors related to DFT such as lowest unoccupied molecular orbital energy (ELUMO), electronegativity (χ), highest occupied molecular orbital energy (EHOMO), smoothness (s), hardness (η) and electrophilicity are predisposed to predict chemical reactivity. (ω) [21]. They are all obtained from optimized molecules. The energy of LUMO shows sensitivity to the molecule's nucleophilic attack, and while that of HOMO, characterizes its sensitivity to electrophilic attack. The electronegativity (χ) is the parameter which results in the capacity of a molecule not to let out its electrons. These parameters are calculated from equations (1):

$$\begin{aligned} PI &= -E_{HOMO} \\ AE &= -E_{LUMO} \\ \chi &= -\mu = -1/2(E_{LUMO} + E_{HOMO}) \\ \eta &= (E_{LUMO} - E_{HOMO}) / 2 \\ \omega &= \chi^2 / 2\eta \\ s &= 1/\eta \end{aligned} \quad (1)$$

2.1.2 Dual descriptor

This descriptor is new among the responsiveness descriptors, but has a huge advantage over the Fukui indices. Over time other local descriptors have shown their effectiveness in predicting the most reactive electrophilic or nucleophilic attack sites of molecules. The Fukui functions f^+ and f^- show that the molecular site which the greatest value of one of these functions should be the most likely to react with electrophiles or nucleophiles. However, these Fukui functions have limitations because they can show that one is both nucleophilic and electrophilic. The descriptor



Compound 1: 2-phenyl-2,3-dihydro-1H-

Dual has a meaning of selectivity. The Fukui functions demonstrate between the values of the Dual descriptor and the nucleophilic or electrophilic character of a molecular site. The approximate expression [22] to calculate the double selectivity descriptor (Δf) is obtained from equations (2) and (3):

$$\Delta f(r) = [f(r)^+ - f(r)^-] \quad (2)$$

$$\Delta f(r) = [f(r)^{BV} - f(r)^{HO}] \quad (3)$$

According to equation (3) the Dual descriptor is defined as the difference between the density of border orbitals at a point r .

If $\Delta f(r) > 0$ at point r , then the Fukui electrophilic function increases with respect to the average at this point and the site is said to be electrophilic.

If $\Delta f(r) < 0$ at point r , then the Fukui nucleophilic function increases relative to the average at this point and the site shows nucleophilic character.

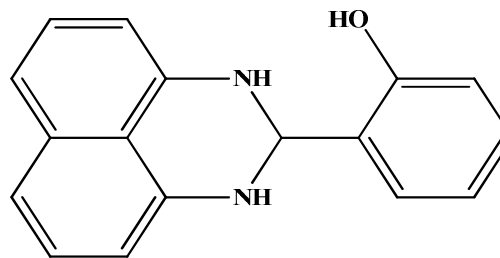
3. RESULTS AND DISCUSSION

The Gaussian 09 optimized structures of the compounds are given in Fig. 2 below.

3.1 Analysis of frontier Molecular Orbitals

Fig. 3 below shows the patterns of the HOMO and LUMO boundary molecular orbitals of 2,3-dihydro-1H-perimidines obtained using the B3LYP / 6-311 G (d, p) method. This diagram was represented using the Chemissian software.

The analysis of the frontier orbitals indicates the HOMO covers the 2,3-dihydro-1H-perimidines function in which the heteroatoms N₁₇ and N₁₉ are found, while the LUMO covers most of the atoms of the different compounds. The energy parameters obtained from the energies of the frontier orbitals are grouped together in Table 1.



Compound 2: 2- (2,3-dihydro-1H-perimidin-

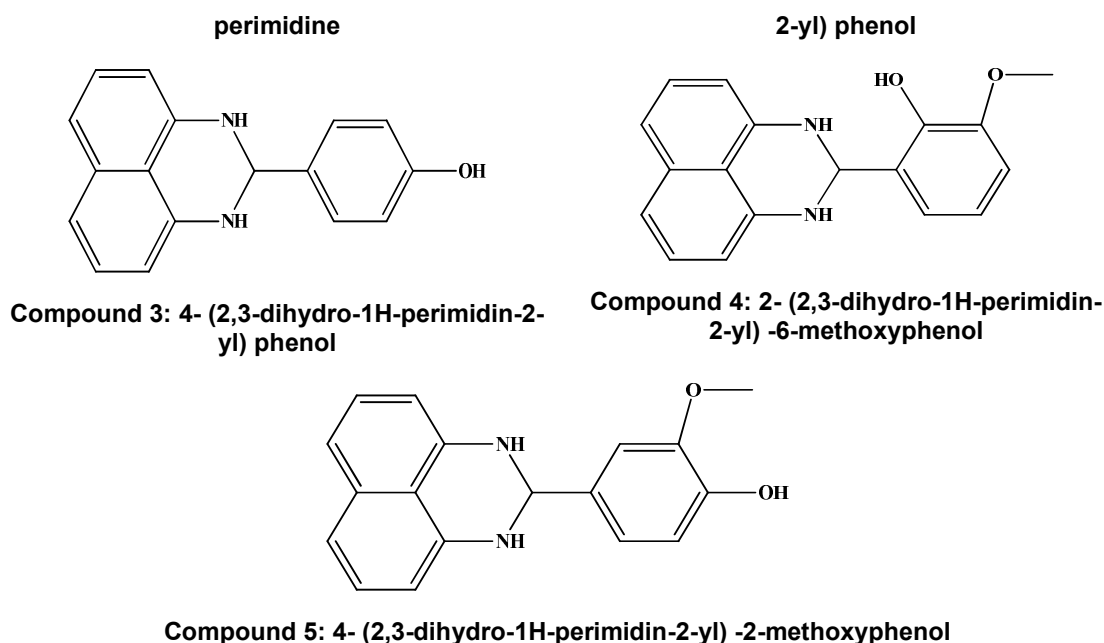


Fig. 1. Molecular structures of perimidin compounds 1- 5

Table 1. Energy parameters of the compounds 1-5

Compounds	HOMO(eV)	LUMO(eV)	ΔE_{gap} (eV)	EI(eV)
1	-5.009	-0.890	4.118	5.009
2	-4.914	-0.882	4.031	4.914
3	-4.972	-0.815	4.156	4.972
4	-4.846	-0.692	4.153	4.846
5	-4.990	-0.785	4.204	4.990

The results of the table show that the Compound 2 molecule, having the smallest energy difference ($\Delta E_{gap} = 4.031$ eV) is the most reactive while the Compound 5 molecule with the largest energy difference value (4.204 eV) is the most stable out of all five (05) molecules studied. The increasing order of the energy gap of the five molecules is as follows:

Compound 2 <Compound 1 <Compound 4 <Compound 3 <Compound 5

3.2 Descriptors of Reactivity

3.2.1 Descriptors of global reactivity

The overall reactivity indices vary depending on the structure of the molecules. Compound 2 has the lowest overall hardness value ($\eta = 2.015$ eV). It appears to be more reactive than all of the compounds studied. We thus note that

compound 1 has a higher electronegativity value ($\chi = 2.950$ eV) than those of the other compounds; it is therefore the best electron acceptor. Compound 1 has the highest electrophilic index ($\omega = 2.113$ eV) which makes it the most electrophilic.

The order of evolution of the overall hardness of molecules is as follows:

$\eta(\text{Compound 2}) < \eta(\text{Compound 1}) < \eta(\text{Compound 4}) < \eta(\text{Compound 3}) < \eta(\text{Compound 5})$.

3.2.2 Dual descriptors of reactivity

The numerical values of the dual reactivity descriptor were also determined for each molecule at the B3LYP / 6-311G (d, p) level. All the atoms constituting the various compounds are concerned in this study with the exception of the hydrogen atoms. These different local indices and descriptors of reactivity are grouped together in Figs. 4a-e.

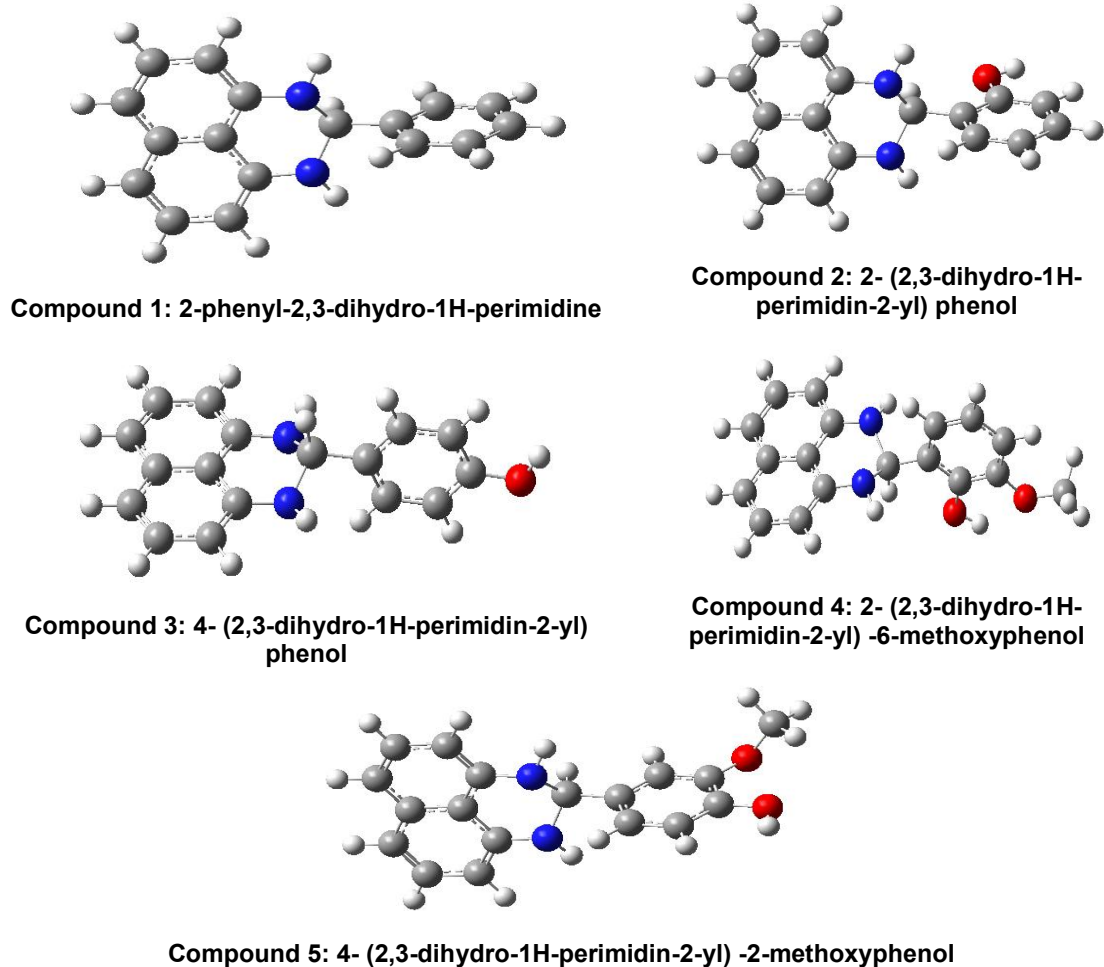


Fig. 2. Optimized molecular structures of perimidin compounds 1 to 5

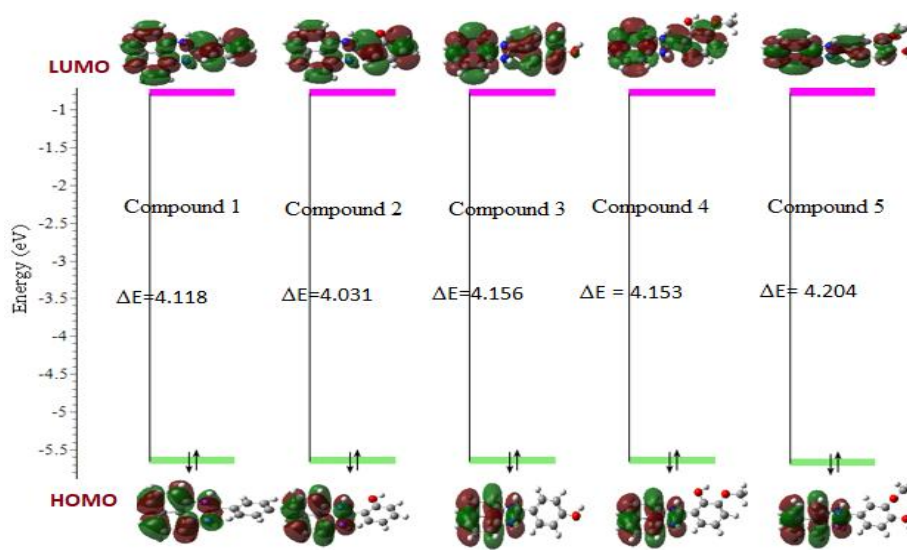


Fig. 3. Highest occupied and lowest vacant molecular orbitals of compounds 1-5

Table 2. Global descriptors of chemical reactivity of the compounds 1-5

Composés	$\mu(\text{eV})$	$\eta(\text{eV})$	$\omega(\text{eV})$	$\chi(\text{eV})$	$s(\text{eV}^{-1})$
1	-2.950	2.059	2.113	2.950	0.485
2	-2.898	2.015	2.083	2.898	0.496
3	-2.894	2.078	2.015	2.894	0.481
4	-2.769	2.076	1.846	2.769	0.481
5	-2.887	2.102	1.983	2.887	0.475

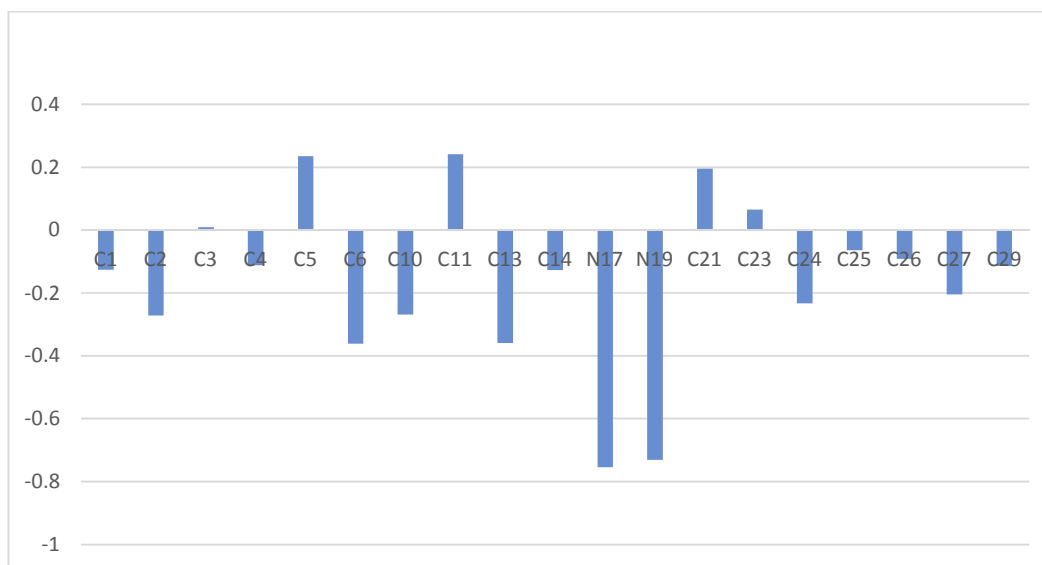


Fig. 4a. Dual descriptors (Δf) of compound 1

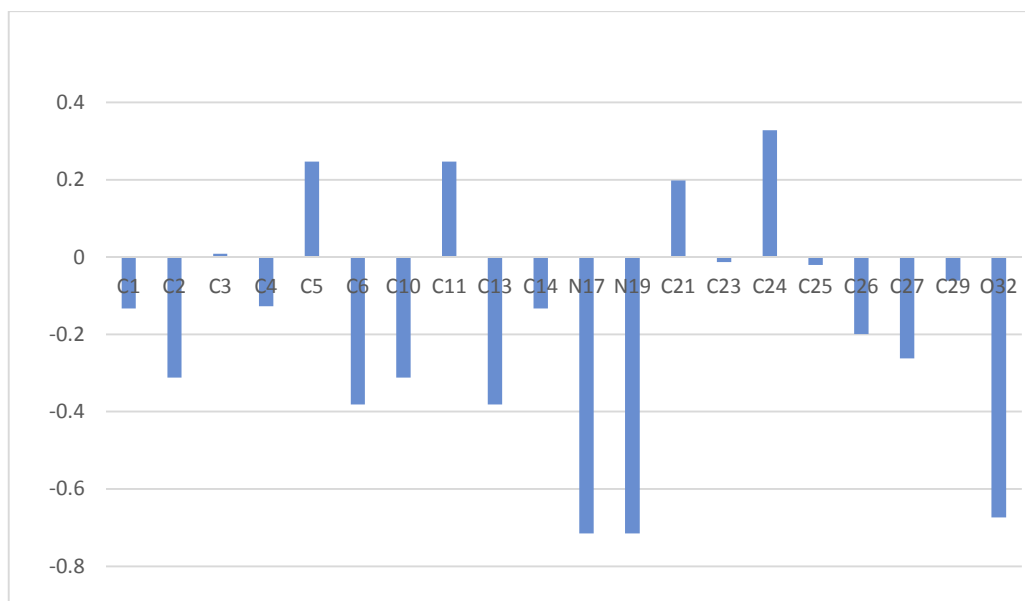


Fig. 4b. Dual descriptors (Δf) of compound 2

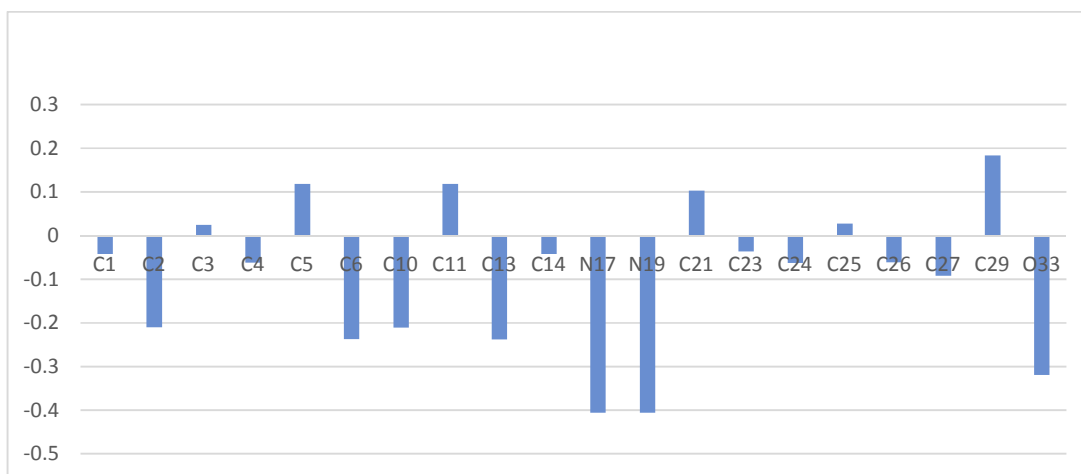


Fig. 4c. Dual descriptors (Δf) of compound 3

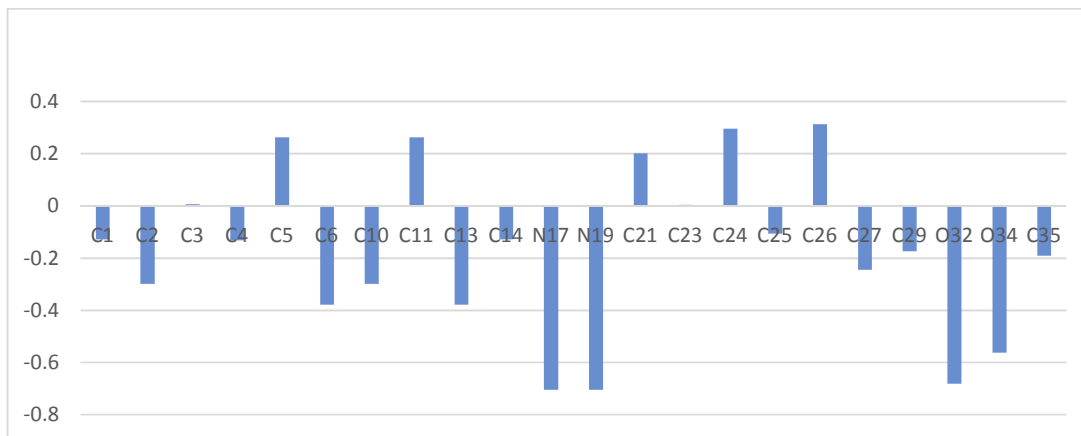


Fig. 4d. Dual descriptors (Δf) of compound 4

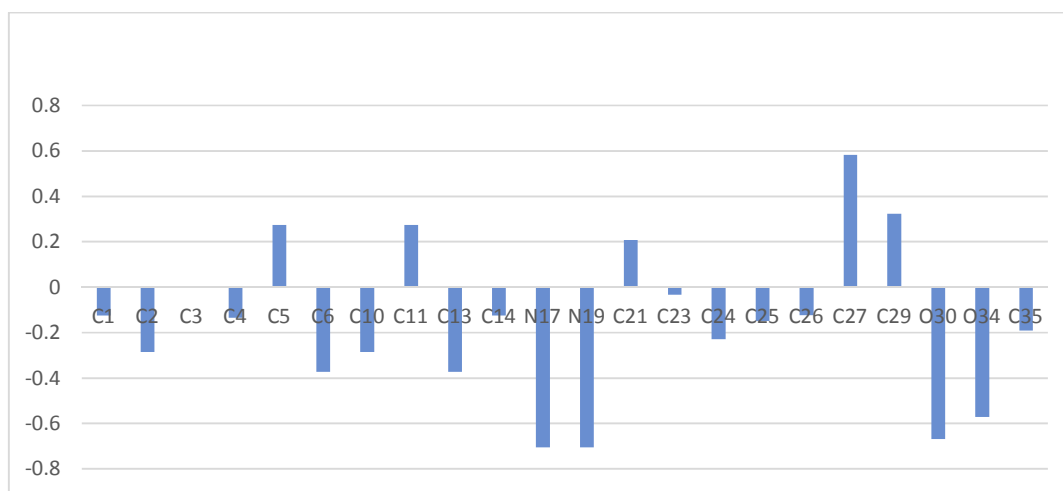


Fig. 4e. Dual descriptors (Δf) of compound 5

Fig. 4. Values of the dual descriptor for the heavy atoms of the five (05) compounds

Based on the analysis of the dual descriptor, nitrogen atoms N₁₇ and N₁₉ are clearly identified as the potential nucleophilic sites for all compounds. Nitrogen N₁₇ and N₁₉ will be the most likely to bind cations (Fe²⁺, Cu²⁺, Zn²⁺...) for these compounds.

4. CONCLUSION

In this work, the study of the global reactivity of frontier orbitals showed high electron densities around the substituted 2,3-dihydro-1H-perimidine function. Compound 2 is relatively the most polarizable, exhibiting the highest chemical reactivity and lower kinetic stability compared to all of the molecules studied. In addition, compound 1 appears to be the best electron acceptor and the most electrophilic of the compounds studied. The numerical values of the dual descriptor predict a strong value on N₁₇ and N₁₉ nitrogen which makes them the molecular sites with the dominant nucleophilic character. Thus, these nitrogen atoms N₁₇ and N₁₉ are the most favorable sites in the formation of chelates with cations (Fe²⁺, Cu²⁺, Zn²⁺...). These results direct us towards new 2,3-dihydro-1H-perimidine complexes which will thus be able to prove their effectiveness in the search for new biologically active compounds.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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