DFT Study of Molecular Stability and Reactivity on Some Hydroxamic Acids: An Approach by Hirshfeld Population Analysis.

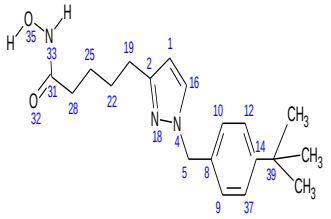
Doh Soro, Lynda Ekou, Mamadou Guy-Richard Koné, Tchirioua Ekou, and Nahossé Ziao

***Abstract*—Several studies have been carried out on the structure of hydroxamic acids as histone deacetylase inhibitors. Scientists discovered that the (-CONHOH) moiety of hydroxamic acids was responsible for the chelation of the zinc ion into the active site of histone deacetylases thereby inhibiting the activity of these. In this work, we conducted a study using the new dual descriptor from the conceptual DFT to determine the atoms responsible for zinc chelation in order to propose new, more active molecules. The calculations were performed to determine the local reactivity of the hydroxamic acids studied using Fukui functions by the Hirshfeld method. Global parameters were also determined to predict the relative stability and reactivity of hydroxamic acids. The work was conducted at computational level B3LYP / 6-311G (d, p). The most polarizable compound has an energy gap of 3.933 eV. The analysis of the local indices of reactivity as well as the dual descriptors revealed that an oxygen of these compound is the most favorable site vis-à-vis electrophilic attack.**

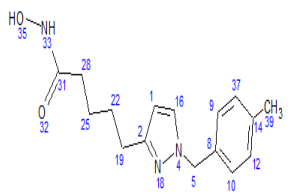
***Index Terms*—Hydroxamic Acid; Conceptual DFT; Dual Descriptor; Hirshfeld Charges.**

I. Introduction

Hydroxamic acids have strong abilities to form chelators [1] and H bonds, responsible for their many biomedical applications. They can act as a monodentate and bidentate ligand through their deprotonated hydroxamate group and oxygen carbonyl [2]. Hydroxamic acids are molecules bearing the -CONHOH functional group and have been specifically evaluated for their effectiveness against cancer [3], malaria [4] and other autoimmune diseases. In fact, histone deacetylases (HDACs) are aberrantly found in many types of cancer. HDACs are grouped into four classes [5] according to their catalytic domain. HDACs from class III are nicotinamide adenine dinucleotide-dependent (NAD +) and are not affected by trichostatin A (TSA) [6]. On the other hand, Classes I, II and IV histones belong to the classical HDAC family and are metalloproteins requiring zinc (Zn^{2+}) ions as a cofactor and whose activities are inhibited by trichostatin A and often suberoylanilide acid (SAHA) of the family of hydroxamic acids. Hydroxamic acids are effective and selective inhibitors of many enzymes, such as urease [7], matrix metalloproteinases [8], histone deacetylases [9], etc. The detailed role of hydroxamic acid derivatives as enzyme inhibitors has been well described by Muri et al. [10]. They have been developed as drugs against all these diseases that can arise by overactivation of these enzymes. In addition to acting as enzyme inhibitors, hydroxamic acids have also been described as acting against cancer [9], malaria, tuberculosis and fungi [11], HIV [12], disease Alzheimer's and cardiovascular disorders [13]. All these biological activities of hydroxamic acids are due to their core structure, which allows them to form multiple hydrogen bonds with the enzyme [14]. Thus, using the new dual descriptor, one of the methods of quantum chemistry, we are interested in the local reactivity of six hydroxamic acid compounds. The Density Functional Theory (DFT) method has been accepted as a popular approach for the calculation of the structural characteristics and energies of molecules by the community [15] and for the efficiency and accuracy of the evaluation of several molecular properties [16]. Parr and Yang followed the idea that well-known chemical properties such as electronegativity, chemical potentials, and affinities could be accurately described and calculated by manipulating the electron density as the fundamental quantity [17]. Moreover, based on the work of Fukui and his theory of frontier molecular orbitals (FMO) [18], the same authors generalized the concept and proposed the Fukui function as a tool for describing local reactivity in molecules [19]. In this work, the aim is to determine the most favorable atom for an electrophilic attack during a chemical reaction. By implementing quantum chemistry methods, we determined Fukui indices using the Hirshfeld population analysis and then calculating the numerical value of the dual descriptor. We also considered the relative stability of these compounds in this work. This study was conducted on six compounds from the hydroxamic acid family shown in Fig. 1 to determine the atom (s) able to form complexes with the zinc ion present in certain histone deacetylases [20]. Yao et al synthesized all the molecules used in this study [9], etc.



Compound1:5-(1-(4(tert-butyl)-1H-pyrazol-3-yl)-N-hydroxypentanamide.



Compound2: N-hydroxy-5-(4-methylbenzyl)-1H-pyrazol-3-yl)pentanamide.

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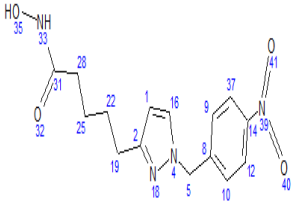
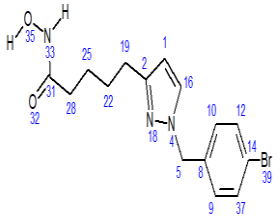
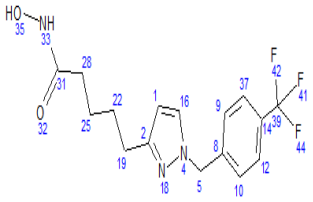


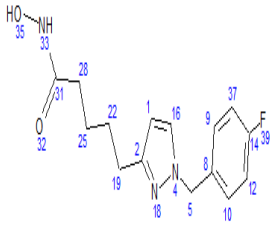
Compound4:5-(1-(4-(dihydroxyamino)benzyl)-1H-pyrazol-3-yl)-N-hydroxypentanamide.



Compound3 :5-(1-(4-bromobenzyl)-1H-pyrazol-3-yl)-N-hydroxypentanamide.



Compound5: N-hydroxy-5-(4-triguoromethylbenzyl)-1H-pyrazol-3-yl) pentanamide.



Compound6:5-(1-(4-fluorobenzyl)-1H-pyrazol-3-yl)-N-hydroxypentanamide.

Fig. 1. Numbered molecular structures of hydroxamic acids compounds 1-6

II. Material And Methods

A. *Descriptors of Reactivity*

1) *Global Descriptors*

Some theoretical descriptors related to DFT have been predisposed to predict chemical reactivity. The energy of the lowest unoccupied molecular orbital (**E**LUMO), electronegativity (**χ**), the energy of the highest occupied molecular orbital (**E**HOMO), the softness (**s**), the hardness (**η**), and the electrophilicity (***ω***) [21]. These descriptors are all determined from the optimized molecules. It should be noted that the descriptors related to frontier molecular orbitals were computed as part of Koopmans' approach [22]. The LUMO energy which characterizes the sensitivity of the molecule to a nucleophilic attack, and as for the HOMO energy, it characterizes the susceptibility to a molecule of an electrophilic attack. Electronegativity (**χ**) is the parameter that results in the ability of a molecule not to let out its electrons. Global softness (s) expresses resistance to a change of electron name. The overall electrophilicity index characterizes the electrophilic power of the molecule. These different parameters are calculated from (1):

$$\begin{gathered} PI = -E_{HOMO} \\ AE = -E_{LUMO} \\ \chi = -\mu = -1/2\,(E_{LUMO} + E_{HOMO}) \\ \eta = (E_{LUMO} - E_{HOMO})/2 \\ \omega = \frac{\chi^2}{2\eta} \\ s = 1/\eta \end{gathered} \tag{1}$$

2) *Duals Descriptors*

The introduction of the new dual reactivity descriptor [23] has several advantages over Fukui indices. Although advanced work has shown the effectiveness of local descriptors in predicting the most reactive molecular sites in the presence of electrophilic or nucleophilic attack. The Fukui's functions f^+ and f^- would indicate which molecular site with the greatest value one of these functions should be most likely to react with electrophiles or nucleophiles. However, these functions have limitations because they can at the same time designate a nucleophilic and electrophilic site. The dual descriptor has an indisputable physical meaning. Fukui's functions highlight between the dual descriptor values and the nucleophilic or electrophilic character of a molecular site.

The approximate expression [23] for calculating the dual descriptor of selectivity (Δf) is obtained from (2):

$$\Delta f(r) = \left[f^{+}_{(r)} - f^{-}_{(r)}\right] \tag{2}$$

The effect of the quantum model on the numerical results of the dual descriptor can be avoided by employing the finite difference approximation and the Koopmans theorem resulting in (3):

$$\Delta f(r) = \left[\rho(r)_{BV} - \rho(r)_{HO}\right] \tag{3}$$

This expression defines the descriptor as the difference between the density of the frontier orbitals at a point r.

If $\Delta f(r) > 0$ at the point r, then the electrophilic Fukui function increases with respect to the average at this point and the molecular site has an electrophilic character.

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

B. *Hirshfeld Population Analysis*

The calculation of Hirshfeld's atomic charge plays an important role in the study of molecular systems in quantum chemistry [24]. For the quantitative description of a molecular charge distribution, the molecule is dissected into well-defined atomic fragments. A general and natural choice is to share the charge density at each point between the different atoms in proportion to their free atom densities at the corresponding distances of the nuclei [25]. In this work, the atomic charge values were obtained by the Hirshfeld population analysis. The geometry of the molecules was optimized by the DFT calculation method with the functional B3LYP [26] in the 6-311G base (d, p) using the Gaussian 09 software [27]. This Hybrid functional gives better energies and is in line with high-level ab initio methods [28].

III. Results and Discussion

A. *Analysis of Frontier Molecular Orbital*

The highest occupied molecular orbital (HOMO) is the electron-containing outer orbital that tends to give these electrons in a chemical reaction. However, the lowest vacant molecular orbital (LUMO) is perceived as 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 [29]. While the energy of the HOMO is directly related to the ionization

potential, that of the LUMO is directly related to the electronic affinity. The difference in energy between the HOMO and the LUMO, called the energy gap, is an important stability factor for structures. The HOMO-LUMO energy gap helps characterize the chemical reactivity and kinetic stability of the molecule [29]. A molecule with a high energy gap (ΔE) is less polarizable and is generally associated with low chemical reactivity and high kinetic stability [30]. Fig. 2 below shows the HOMO and LUMO frontier molecular orbital patterns of the hydroxamic acids obtained using the B3LYP / 6-311 G (d, p) method.

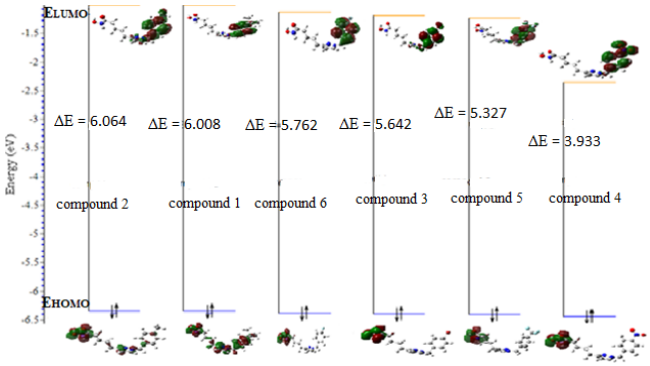


Fig. 2. Highest and Lowest Occupied Molecular Orbital of Compounds 1-6.

The analysis of the frontier orbitals indicates the HOMO covering the hydroxamic acid function in which the O35, N33 and O32 heteroatoms are located while the LUMO covers most of the carbon atoms. The energy parameters obtained from the energies of the frontier orbitals are grouped in Table I.

TABLE I: ENERGY PARAMETERS OF THE COMPOUNDS 1-6 STUDIED

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔEgap (eV)	PI (eV)
1	-6.568	-0.560	6.008	6.568
2	-6.569	-0.504	**6.065**	6.569
3	-6.612	-0.970	5.642	6.612
4	-6.657	-2.725	**3.933**	6.657
5	-6.632	-1.305	5.327	6.632
6	-6.603	-0.840	5.762	6.603

These results show that **compound 4** has the smallest energy difference (ΔEgap = 3.933 eV), so it is the most polarizable, has the highest chemical reactivity and the lowest kinetic stability with respect to all the molecules studied. The increasing order of the energy gap of the six compounds is as follows:

Compound4 <Compound5 <Compound3 <Compound6 <Compound1 <Compound2.

However, compound 2 has the largest value of the energy gap of 6.065 eV. It is therefore the least polarizable, with low chemical reactivity and high kinetic stability on all the molecules studied.

B. Descriptors of Reactivity

1) Global Reactivity Descriptors

The study of the global reactivity of molecules is based on the calculation of global indices deduced from electronic properties. The overall indices of the reactivity of the HDACi studied were calculated from (1) and recorded in Table II.

TABLE II: GLOBAL DESCRIPTORS OF CHEMICAL REACTIVITY OF HYDROXAMIC ACIDS 1-6.

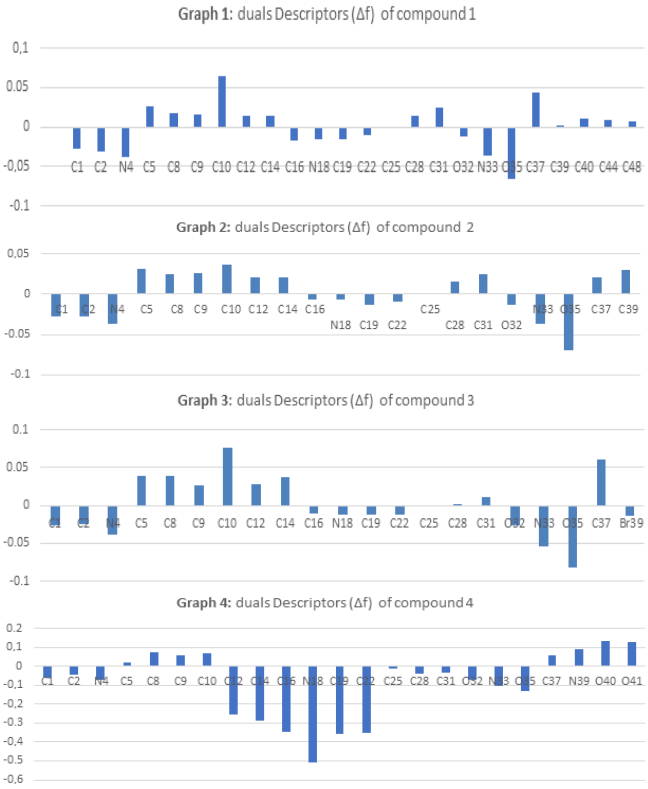
	χ(ev)	μ(ev)	η(ev)	ω(ev)	s(ev^{-1})
1	3.564	-3.564	3.004	2.114	0.333
2	3.537	-3.537	3.032	2.062	0.330
3	3.791	-3.791	2.821	2.548	0.355
4	4.691	-4.691	1.966	5.595	0.509
5	3.969	-3.969	2.664	2.957	0.375
6	3.721	-3.721	2.881	2.403	0.347

Global indices of reactivity vary according to the structure of the molecules. The value of the overall hardness of compound 4 (η = 1.966 eV) is the lowest of all molecules. Thus, it appears that the compound 2 is more reactive than all the compounds studied. Also, we note that compound 4 has a significantly higher electronegativity value (χ = 4.691 eV) than other compounds; he is therefore the best acceptor of electrons. In addition, the value of the electrophile index of compound 4 (ω = 5.595 eV) indicates that it is the most electrophilic.

2) Dual Descriptors of Reactivity

The numerical values of the dual descriptor of reactivity were also determined for each molecule according to (2). All the constituent atoms the different compounds are concerned in this study except the hydrogen atoms. These different local indices and descriptors of the reactivity are grouped in the graphs 1 to 6 (Fig. 3).

The numerical values of the dual descriptor of the compounds have been calculated at the B3LYP / 6-311G (d, p) level, show that the O_{35} oxygen atom is generally the preferred site of electrophilic attack.



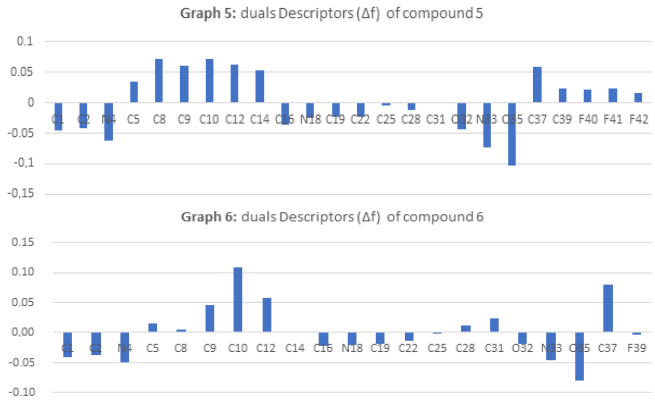


Fig. 3. Duals descriptors graphs from 1-6.

On all these graphs, oxygen O_{35} appears clearly as the molecular site having the most probable nucleophilic character. The numerical value of the C_{10} carbon dual descriptor shows, relative to the mean, that it is the most likely molecular site for nucleophilic attack. However, during the interactions of these different compounds in class I and II HDACs, this oxygen O_{35} would be the most likely site to bind Zinc (Zn^{2+}) ion to inhibit the effect of enzymes present in an aberrant in different types of cancer.

IV. Conclusion

In this work, the study of the frontier molecular orbitals has shown high electron densities around the hydroxamic acid function (-CONHOH). Compound 4 is relatively the most polarizable, having the highest chemical reactivity and the lowest kinetic stability with respect to all the molecules studied. Moreover, this compound is therefore the best electron acceptor and the most electrophilic of the compounds studied. The numerical values of the dual descriptor predict a high value on O_{35} oxygen which makes it the molecular site with the dominant nucleophilic character. In addition, analysis of the dual values also shows the N_{33} nitrogen of the hydroxamic acid function as the second nucleophilic site of these compounds after oxygen O_{35}. Thus, these O_{35} and nitrogen N_{33} oxygens should be the most favorable sites in the formation of chelates with the Zn^{2+} ion present in the active sites of HDACs of classes 1, 2 and 4. These results direct us to new complexes of hydroxamic acids that can prove their effectiveness in the fight against cancer by new theoretical calculations or even new experimental tests.

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