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Studies of the Chemical Reactivity of a Series of Rhodanine Derivatives by Approaches to Quantum Chemistry

Wacothon Karime Coulibaly[1,2*], Jean Stéphane N'dri[3], Mamadou Guy-Richard Koné[3], Camille Déliko Dago[2], Christelle N'ta Ambeu[2], Jean-Pierre Bazureau[2], Nahossé Ziao[3]

[1]UFR des Sciences Biologiques, Université de Péléforo Gon Coulibaly, Korhogo, Cote d'Ivoire
[2]Université de Rennes 1, Institut des Sciences Chimiques de Rennes (ISCR), UMR CNRS 6226, Groupe ICMV, Bât. 10A, Campus de Beaulieu, Rennes Cedex, France
[3]Laboratoire de Thermodynamique et de Physico-Chimie du Milieu, UFR SFA, Université Nangui Abrogoua, Abidjan, Côte-d'Ivoire
Email: *wacothon@gmail.com

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Abstract

This theoretical chemical reactivity study was conducted using the Density Functional Theory (DFT) method, at computational level B3LYP/6-31G (d). It involved a series of six (06) 5-arylidene rhodanines and allowed to predict the chemical reactivity of these compounds. DFT global chemical reactivity descriptors (HOMO and LUMO energies, chemical hardness, softness, electronegativity) were examined to predict the relative stability and reactivity of rhodanin derivatives. Thus, the compound 6 which has an energy gap between the orbitals of ΔEgap = 3.004 eV is the most polarizable, the most reactive, the least stable, the best electron donor and the softest molecule. Calculation of the local indices of reactivity as well as dual descriptors revealed that the sulfur heteroatom of the Rhodanine ring is the privileged site of electrophilic attack in a state of sp3 hybridization and privileged site of nucleophilic attack in a state of sp2 hybridization.

Keywords

Rhodanine Derivatives, Global Descriptors, Local Descriptors, Dual Descriptors

1. Introduction

The tumor is an abnormal structure that appears in the body. It comes from multiplication of cells. It is insensitive to the controls of the body and more or

less resembles the tissue from which it derives. The tumor is recognizable because it is autonomous and no longer responds to the mechanisms of the body that limit the proliferation of cells. Treatment of the tumor is done either by surgical removal in the case of the benign tumor; or by radiotherapy and cancer chemotherapy if it is a malignant tumor. It is in this context that medicinal chemistry or therapeutic chemistry which is a scientific discipline at the intersection of chemistry and pharmacy including the design of new molecules and their development is on the lookout for new molecular entities with biological activity or therapeutic even more powerful with a broad spectrum of action. It is for this purpose that Rhodanine derivatives and heterocyclic compounds study as potential pharmacochemical precursors has been initiated [1]. These compounds are widely distributed in nature and are essential to life in various ways [2]. The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is also interesting for its theoretical implications, for the diversity of its synthetic processes, and for the physiological and industrial significance of heterocyclic compounds. Studies on heterocyclic compounds have long been an interesting area in medicinal chemistry. A number of heterocyclic derivatives containing a sulfur or nitrogen atom serve as unique and versatile scaffolds for the design of experimental drugs [3]. Rhodanine derivatives are attractive compounds because of their many biological activities. The various biological activities of rhodanines (2-thioxothiazolidin-4-ones) and their analogues have been known since the beginning of the 20th century. The five multi-heterocyclic rings, and in particular the synthon rhodanine, are currently the subject of controversial debate in the medicinal chemistry community [4]. Indeed, these compounds and their derivatives have a broad spectrum of biological effects [5]. They include anticonvulsants, antibacterial [6] antivirals [7], antidiabetic agents [8], antimalarial [9] anti-tuberculosis [10], pesticides [11], fungicides [12], anti-inflammatory [13] insecticides [14], antithyroid [15], anti-tumor [16]. To date, numerous molecules derived from rhodanine have been synthesized, characterized and tested for their properties, in particular 5-arylidene-2-thioxo-1,3-thiazolidinin-4-ones or 5-arylidene rhodanines, which are the object of several scientific studies. Studies on heterocyclic compounds have long been an interesting area in medicinal chemistry. A number of heterocyclic derivatives containing heteroatoms (nitrogen, sulfur, oxygen) serve as unique and versatile scaffolds for the design of experimental drugs [17]. The therapeutic properties are related to the conformation of the molecules and the interactions that they can establish with each other. The knowledge of the molecular conformation and the interactions goes through the determination of the physicochemical descriptors through the theoretical chemistry. With the development of computer techniques and computational chemistry, quantum chemistry gives insight into the electronic structures of molecules and strongly propels the development of traditionally experimental chemistry [18]. Currently, the method of Density Functional Theory (DFT) has been accepted as a popular

approach for the calculation of structural features and energies of molecules by the scientific community [19] [20] [21] [22] and for the efficiency and accuracy of the evaluation of a number of molecular properties [23]. 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 [24] [25]. Moreover, from the work of Fukui and his theory of Frontier Molecular Orbitals (FMO) [26], the same authors generalized the concept and proposed Fukui's function as a tool for describing local reactivity in molecules [27] [28]. The present study focuses on six (06) Rhodanine derivatives shown **Figure 1**.

These Rhodanine derivatives studied in our work were synthesized and identified as potential inhibitors of several protein kinases by Wacothon Coulibaly *et al.* [3]. Indeed, these authors tested a series of 5-arylidene rhodanine derivatives on a panel of six representative 6 tumor cell lines, namely Huh7 D12 (differential hepatocellular carcinoma), Caco2 (differentiation of colorectal adenocarcinoma), HCT (colorectal carcinoma at active proliferation), PC3 (carcinoma of the prostate), NCI-H_2 (lung carcinoma), MDA-MB 231 (breast carcinoma) and diploid skin fibroblasts as normal cell lines for control. The purpose of this work is to theoretically determine the preferred sites of electrophilic and nucleophilic attack on the aromatic carbon atoms and heteroatoms contained in the rhodanine ring by different methods of quantum chemistry.

2. Material and Methods

2.1. Level of Calculation Theory

The theoretical study of chemical reactivity was conducted based on three theoretical approaches. The first concerns the analysis of molecular electrostatic potential surfaces. The second approach relates to boundary molecular orbitals.The last approach focuses on local indices of responsiveness as well as dual descriptors. The geometries of the molecules were optimized at the DFT calculation level with the functional B3LYP [29] [30] in the base 6-31 G (d) using the Gaussian 09 software [31]. This Hybrid functional gives better energies and is in line with the ab initio methods of high level [32] [33]. As for the split-valence and double-dzeta base (6-31G (d)), it is sufficiently extended and the taking into account of the polarization functions are important for the explanation of the free doublets of the heteroatoms. Geometries are kept constant for cationic and anionic systems. Global indices of reactivity were obtained from the conceptual DFT model [19]. The hierarchical ascending classification analysis was conducted using the XLSTAT software [34]. As for the indices of local chemical reactivity, they were determined using the electronic populations calculated with the Mulliken population analysis (MPA) [35].

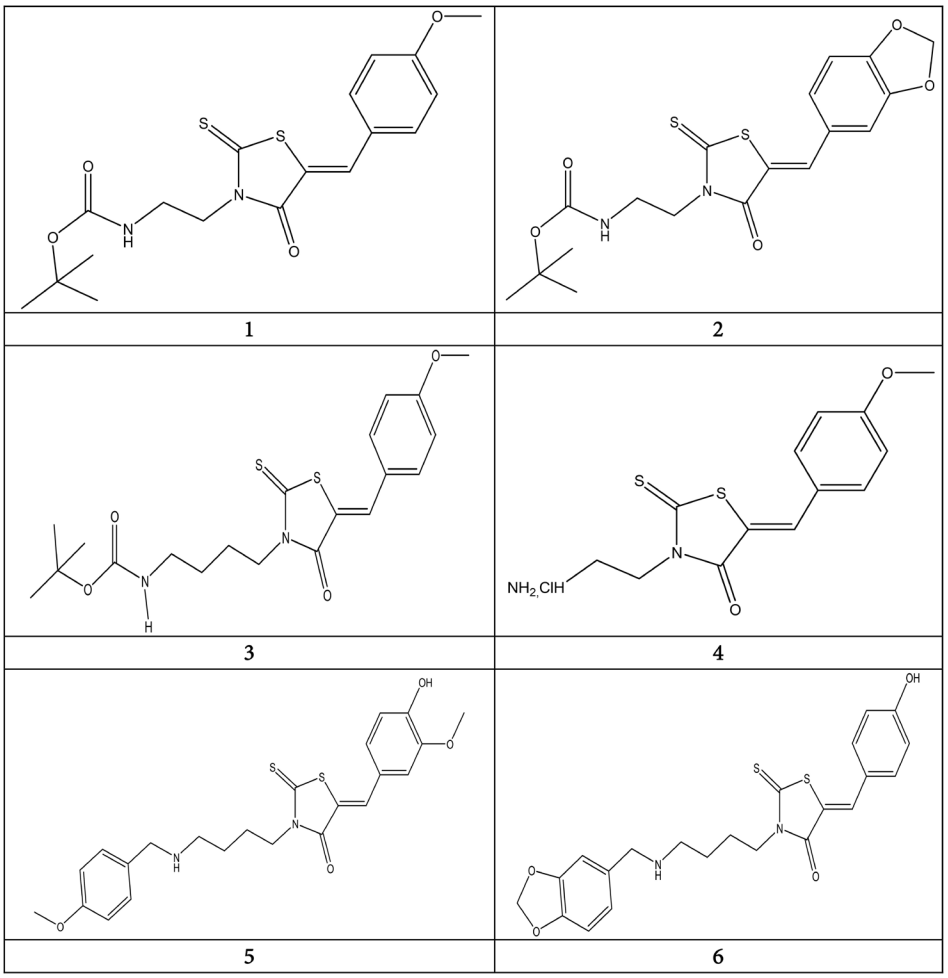


Figure 1. Molecular structures of the Rhodanines derivatives studied.

2.2. Reactivity Descriptors

2.2.1. Global Descriptors

To predict chemical reactivity, some theoretical descriptors related to conceptual DFT have been determined.In particular, the Lowest Unoccupied (vacant) Molecular Orbital (LUMO) energy (E_{LUMO}), the Highest Occupied Molecular Orbital (HOMO) energy (E_{HOMO}), the electronegativity ($\boldsymbol{\chi}$), the global softness (σ) and the overall electrophilicity index **($\boldsymbol{\omega}$)**. These descriptors are all determined from the optimized molecules. It should be noted that the descriptors related to frontier molecular orbitals have been calculated in a very simple way in the context of the Koopmans approximation [36]. LUMO energy characterizes the sensitivity of the molecule to a nucleophilic attack, and as for the HOMO energy, it characterizes the susceptibility of a molecule to an electrophilic attack. Electronegativity (χ) is the parameter that reflects the ability of a molecule not to let out its electrons. Global softness (σ) expresses the resistance of a system to the change in its number of electrons. The overall electrophilicity index characterizes the electrophilic power of the molecule. These different parameters are calculated from the Equations (1):

$$
\begin{aligned}
I &= -E_{\text{HOMO}} \\
A &= -E_{\text{LUMO}} \\
\chi &= -\mu = -1/2\left(E_{\text{LUMO}} + E_{\text{HOMO}}\right) \\
\eta &= \left(E_{\text{LUMO}} - E_{\text{HOMO}}\right)/2 \\
\omega &= \frac{\chi^2}{2\eta} \\
\sigma &= 1/\eta
\end{aligned} \tag{1}
$$

2.2.2. Local Descriptors and Dual Descriptors

In order to differentiate the reactive behaviors of atoms forming a molecule, different indices have been used. These are precisely local indices and dual descriptors of responsiveness.Local responsivity descriptors, in this case Fukui function [37] $\left(f_k^+, f_k^-\right)$, local softness $\left(\sigma_k^+, \sigma_k^-\right)$, local electrophilic power $\left(\omega_k^+, \omega_k^-\right)$, and dual descriptors have been proposed to explain the electrophilic and nucleophilic selectivity of the molecule.It should be remembered that Fukui's function f_k^+ expresses reactivity when the molecule is attacked by a nucleophilic reagent, whereas Fukui's function f_k^- provides information on electrophilic attack on a given site. The value of the highest Fukui function is assigned to the most active site. The condensed indices σ_k^+ and ω_k^+ express the ability of a site to receive electron density by nucleophilic attack, whereas the indices σ_k^- and ω_k^- express the ability of a site to yield electron density by electrophilic attack. With regard to the dual descriptor, it is a good tool for predicting responsiveness and identifying the problem of regioselectivity. Indeed, a positive dual descriptor corresponds to a site likely to receive electron density, so more electrophilic. Conversely, a negative dual descriptor corresponds to a site capable of yielding electronic density, and therefore more nucleophilic. A site with a value of the dual descriptor near zero corresponds to a site whose capacity to receive and that to yield of the electronic density are equivalent. The different values of the local descriptors are calculated from the Equations (2) [38] [39] [40] [41]:

$$
\begin{aligned}
f_k^+ &= q_k\left(N+1\right) - q_k\left(N\right) \\
f_k^- &= q_k\left(N\right) - q_k\left(N-1\right) \\
\sigma_k^+ &= \sigma f_k^+ \\
\sigma_k^- &= \sigma f_k^- \\
\omega_k^+ &= \omega f_k^+ \\
\omega_k^- &= \omega f_k^-
\end{aligned} \tag{2}
$$

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

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

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

The values of the dual descriptors [42] [43] [44] are obtained from the Equations (3):

$$
\Delta f = f_k^+ - f_k^-
$$

$$\Delta\sigma = \sigma_k^+ - \sigma_k^- \quad (3)$$
$$\Delta\omega = \omega_k^+ - \omega_k^-$$

3. Results and Discussions

3.1. Molecular Electrostatic Potentials (MEP)

The different values of the electrostatic surface potential are represented by different colors. The potential increases in this order from red < orange < yellow < green < blue. The color code of these cards is between −8.026e−2 a.u. (bright red) and 8.026e−2 a.u. (dark blue) in compounds 1 to 6, where red indicates the most negative potentials and blue the most positive potentials [45] by successively passing through orange, yellow and green [46]. The surfaces of the electrostatic potentials of the studied molecules were represented after optimization at the B3LYP/6-31 G (d) level. They are shown in **Figure 2**.

These maps indicate that oxygen and sulfur heteroatoms in a hybridization state (sp3) of the rhodanine nucleus, have a negative neighborhood of negative potential with a high electronic concentration around the oxygen representing an electrophilic attack site on the rhodanine core. This zone is more concentrated for compounds 1 and 2. As for the other atoms of this nucleus, their light blue neighborhood indicates that they constitute electropositive weakening zones.

3.2. Analysis of Frontier Molecular Orbitals

The highest occupied (HOMO) and lowest vacant (LUMO) orbitals play a fundamental role in the qualitative interpretation of chemical reactivity [47]. The highest occupied molecular orbital (HOMO), which can be thought of as the outer electron-containing orbital, tends to give these electrons as an electron donor. On the other hand, the lowest vacant molecular orbital (LUMO) is perceived as the lowest orbital containing free places to accept electrons [48]. Therefore, 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 the structures [49]. The HOMO-LUMO energy gap helps characterize the chemical reactivity and kinetic stability of the molecule [50]. A molecule with a high energy gap (ΔE) is less polarizable and is generally associated with low chemical reactivity and high kinetic stability [51]. The energy parameters of the boundary orbitals are summarized in **Table 1**.

These results show that **compound 6** has the smallest energy gap (**ΔEgap = 3.004 eV**) so it is the most polarizable. It has the highest chemical reactivity and the lowest kinetic stability with respect to all the molecules studied. In contrast, **compound 3** has the largest value of the energy gap of 3.443 eV. Compound 3 is therefore the least polarizable, with low chemical reactivity and high kinetic stability on all six molecules studied.

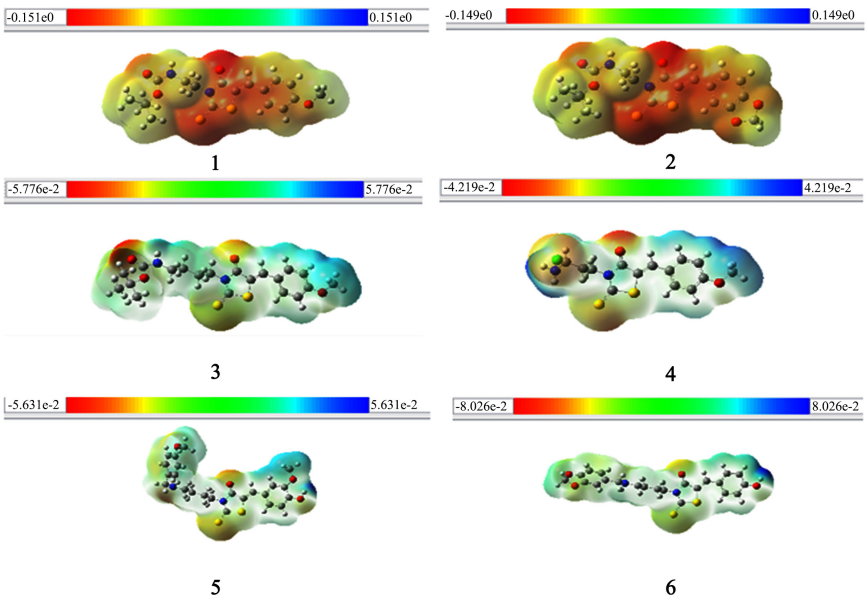


Figure 2. Molecular electrostatic potential surfaces of rhodanines derivatives studied.

Table 1. Energy descriptors of the compounds studied.

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE_{gap} (eV)	I (eV)	A (eV)
1	−5.923	−2.493	3.431	5.923	2.493
2	−5.867	−2.564	3.303	5.867	2.564
3	−5.897	−2.454	**3.443**	5.897	2.454
4	−5.909	−2.471	3.438	5.909	2.471
5	−5.667	−2.361	3.306	5.667	2.361
6	−5.432	−2.428	**3.004**	5.432	2.428

3.3. Hierarchical Cluster Analysis (HCA)

Figure 3 shows the hierarchical ascending classification analysis of the studied molecules. The horizontal lines represent the compounds. The vertical lines represent the similarity values between the pairs of compounds, a compound and a group of compounds and among the groups of compounds.

We can note from the results of this analysis that the compounds studied were grouped into three categories: the most active which are compounds 2 and 6. Compound 5 is moderately active and compounds 1, 3 and 4 are the least active.

3.4. Reactivity Descriptors

3.4.1. Global Reactivity Descriptors

The study of the global reactivity of molecules is based on the calculation of global indices deduced from electronic properties. The global indices of the reactivity of the studied molecules were calculated from the Equation (1) and recorded in Table 2.

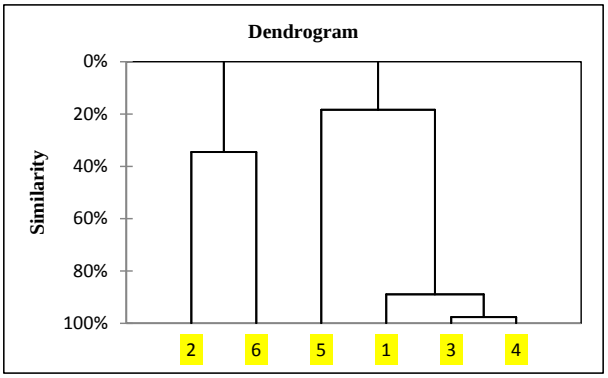


Figure 3. Dendrogram obtained from the studied compounds.

Table 2. Global descriptors of chemical reactivity of rhodanine derivatives 1-6.

Compounds	μ (eV)	χ (eV)	η (eV)	σ (eV)	ω (eV)
1	−4.208	4.208	1.715	0.583	5.162
2	−4.216	4.216	1.652	0.605	5.380
3	−4.175	4.175	1.722	0.581	5.064
4	−4.190	4.190	1.719	0.582	5.107
5	−4.014	4.014	1.653	0.605	4.873
6	−3.930	**3.930**	**1.502**	**0.666**	5.140

Chemical reactivity varies with the structure of the molecules. Chemical hardness (η) and global softness (σ) express the resistance of a system to the change in its number of electrons. In a given series of molecules, when η is weak, the molecule is called soft and when it is high, the molecule is called hard. This is quite the opposite of softness that evolves in the opposite direction of hardness [52]. The value of the chemical hardness of **compound 6** is the lowest (η = 1.502 eV) among all the molecules. Also, we note that **compound 6** has a lower electronegativity value (χ = 3.930 eV) than other compounds; he is therefore the best electron donor and the softest molecule.

3.4.2. Local Descriptors and Dual Reactivity

Local indices and dual descriptors of reactivity were also determined for molecules 2, 6 and 5 according to Equations (2). The sites concerned are the atoms of the rhodanine ring of each molecule Figure 4.

These various indices and descriptors of the reactivity are grouped together in Tables 3-5.

The values of the local descriptors and dual descriptors of compound 2 calculated at the B3LYP/6-31G(d) level, show that the sulfur atom S1 in a sp3 hybridization state with the value $\Delta\omega$ = −0.172, is the preferred site of electrophile attack. According to this same level of calculation, a nucleophilic attack will have preferentially take place on the C4 atom with the value $\Delta\omega$ = 0.229.

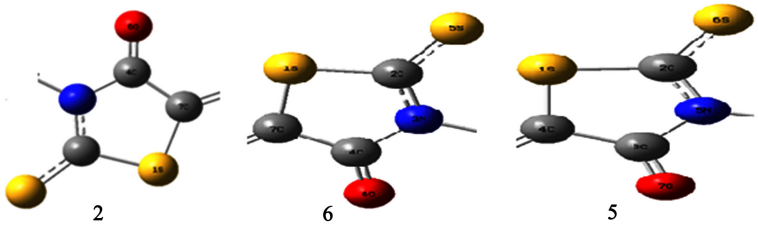


Figure 4. Numbering of the atoms of the rhodanine ring of molecules 2, 6 and 5.

Table 3. Compound 2 reactivity descriptors calculated using Mulliken population analysis (MPA).

Sites	Local descriptors								Dual descriptors		
	f−	f+	σ−	σ+	η−	η+	ω−	ω+	Δf	Δσ	Δω
S1	**0.107**	**0.075**	**0.065**	**0.045**	**0.177**	**0.124**	**0.575**	**0.403**	**−0.032**	**−0.019**	**−0.172**
N2	0.008	−0.011	0.005	−0.007	0.014	−0.018	0.045	−0.058	−0.019	−0.012	−0.103
C3	−0.024	0.007	−0.015	0.004	−0.040	0.012	−0.131	0.039	0.032	0.019	0.170
C4	**0.018**	**0.060**	**0.011**	**0.036**	**0.029**	**0.099**	**0.095**	**0.323**	**0.043**	**0.026**	**0.229**
S5	0.182	0.209	0.110	0.127	0.301	0.345	0.981	1.125	0.027	0.016	0.143
O6	0.050	0.105	0.030	0.064	0.083	0.174	0.270	0.566	0.055	0.033	0.296
C7	0.016	0.016	0.010	0.010	0.027	0.026	0.088	0.086	0.000	0.000	−0.002

Table 4. Compound 6 reactivity descriptors calculated using Mulliken population analysis (MPA).

Sites	Local descriptors								Dual descriptors		
	f−	f+	σ−	σ+	η−	η+	ω−	ω+	Δf	Δσ	Δω
S1	0.070	0.081	0.046	0.054	0.105	0.122	0.358	0.418	0.012	0.008	0.060
C2	−0.015	0.009	−0.010	0.006	−0.023	0.013	−0.078	0.044	0.024	0.016	0.122
N4	**0.003**	**−0.010**	**0.002**	**−0.007**	**0.004**	**−0.016**	**0.014**	**−0.054**	**−0.013**	**−0.009**	**−0.068**
C5	0.008	0.063	0.006	0.042	0.013	0.095	0.043	0.323	0.055	0.036	0.281
S6	**0.090**	**0.217**	**0.060**	**0.145**	**0.135**	**0.327**	**0.462**	**1.117**	**0.128**	**0.085**	**0.656**
O7	0.021	0.107	0.014	0.071	0.032	0.161	0.110	0.552	0.086	0.057	0.442
C8	0.003	0.015	0.002	0.010	0.004	0.023	0.014	0.078	0.012	0.008	0.064

Table 5. Compound 5 reactivity descriptors calculated using Mulliken population analysis (MPA).

Sites	Local descriptors								Dual descriptors		
	f−	f+	σ−	σ+	η−	η+	ω−	ω+	Δf	Δσ	Δω
S1	0.070	0.081	0.046	0.054	0.105	0.122	0.358	0.418	0.012	0.008	0.060
C2	−0.015	0.009	−0.010	0.006	−0.023	0.013	−0.078	0.044	0.024	0.016	0.122
N3	**0.003**	**−0.010**	**0.002**	**−0.007**	**0.004**	**−0.016**	**0.014**	**−0.054**	**−0.013**	**−0.009**	**−0.068**
C4	0.008	0.063	0.006	0.042	0.013	0.095	0.043	0.323	0.055	0.036	0.281
S6	**0.090**	**0.217**	**0.060**	**0.145**	**0.135**	**0.327**	**0.462**	**1.117**	**0.128**	**0.085**	**0.656**
O6	0.021	0.107	0.014	0.071	0.032	0.161	0.110	0.552	0.086	0.057	0.442
C7	0.003	0.015	0.002	0.010	0.004	0.023	0.014	0.078	0.012	0.008	0.064

Table 4 summarizes the results of local index calculations and dual reactivity descriptors, using the MPA population analysis at computational level B3LYP/6-31G (d). It follows that an electrophilic attack probably occurs on the N14 heteroatom. However, the sulfur heteroatom in an sp2 (S6) hybridization state is the most favorable site for nucleophilic attack.

The results in Table 4 predict that the N3 site is the most favored against electrophilic attacks. As regards the nucleophilic attack, it occurs preferentially on the sulfur heteroatom in a sp2 (S6) hybridization state.

4. Conclusion

In conclusion, based on the B3LYP/6-31G (d) functional density method, global and local descriptors were used to study the reactivity of different nucleophilic, electrophilic and radical sites and the influence of these on molecular interaction qualitatively and quantitatively. The descriptors obtained could also provide more information and contribute to a better understanding of the electronic structure of rhodanine derivatives. Electrostatic potential maps have shown that areas of high electron density are located around oxygen and sulfur heteroatoms in a hybridization (sp3) state of the rhodanine ring. In particular, the oxygen atom represents an electrophilic attack site on the rhodanine nucleus. Of all these compounds, compound 6 has the highest chemical reactivity and the lowest kinetic stability with respect to the other molecules studied. In addition, this compound 6 is the softest molecule of all and the best electron donor. In addition, the local descriptors of reactivity of the rhodanine derivatives obtained by the Mulliken population analysis method indicate that the sulfur heteroatom of the rhodanine ring is the preferred site of electrophilic attack in a hybridization state sp3 and also the privileged site of nucleophilic attack in a sp2 hybridization state. Therefore, the sulfur heteroatoms contained in the rhodanine ring can be used as precursors for the synthesis of new rhodanine derivatives. Finally, we hope that these results will be useful in the search for experimental and theoretical proofs of new rhodanine compounds across molecular bonds.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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