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DFT, Atoms in molecule and Non-Covalent Interactions Study of the Intramolecular Hydrogen Bonding in Dienaminones and Dienaminothiones

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Abstract

This study presents a detailed computational investigation of the tautomerism and intramolecular hydrogen bonding in selected dienaminones and dienaminothiones derived from β-diketones. Density Functional Theory (DFT) calculations employing the long-range corrected hybrid functional wB97XD with the cc-pVTZ basis set reveal that the most stable forms of these compounds are six-membered chelated tautomers stabilized by resonance-assisted intramolecular hydrogen bonding (RAHB) involving N–H···O or N–H···S interactions. Alternative tautomers, such as those with O–H or S–H groups, were found to be significantly less stable.Atoms in Molecules (AIM) topological analysis confirms that the energetically preferred tautomers adopt a **cis**-configuration around the ethylene (–CH_2–CH_2–) bridge. Non-Covalent Interaction (NCI) analysis, supported by Reduced Density Gradient (RDG) isosurfaces, provides further evidence for the presence and strength of intramolecular hydrogen bonds in the N–H containing tautomers, while indicating their absence or weakness in the corresponding O–H and S–H analogues.

Keywords: DFT, enaminones, enaminothiones, tautomerism, intramolecular hydrogen bonding, AIM, NCI, RDG.

دراسة التاصر الهيدروجيني الضمني في الاينامينونات الاينثايونات الثنائية بالاستناد الى حسابات نظرية دالية الكثافة والذرات في الجزيئات والتداخلات غير التكافؤية.

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الخلاصة

تم في هذه البحث دراسة التاصر الهيدروجيني الضمني والتوتومرية لبعض الاينامينونات و الثايواينامينونات المشتقة من البتادايكيتونات. لقد أظهرت الحسابات النظرية المستندة الى نظرية دالية الكثافة وباستخدام الدالية wB97XD والمعززة بالمجموعة الأساسية cc-pVTZ بان أكثر المركبات استقرارا تظهر على شكل توتومرات متميزة بالحلقة السداسية المخلبية ذات التاصر الهيدروجيني الضمني المعزز بالرنيين (RAHB) من خلال الاصرة N–H··O أو N–H··S. اما بقية التوتومرات التي تحتوي على مجموعات O–H أو S–H، أقل استقرارًا. وقد بينت حسابات الذرات في الجزيئات (Atoms In Molecules AIM) بان الجزيئات المدروسة تتخذ الشكل سيس حول المجموعة الجسرية الرابطة بين جزئي المركب وهي المجموعة CH2-CH2. بالإضافة الى ذلك بينت حسابات التداخلات غير التكافؤية (Non-Covalent Interactions (NCI وحسابات ميل الكثافة المختزلة (Reduced Density Gradient RDG) بان التوتومرات ثايوياناميون الذي يتميز بالاصرة N-H هو الذي يتميز بالاصرة الهيدروجينية الضمنية اما التوتومرات التي تتضمن الاواصر O-H و S-H فلا تتميز بذلك.

1. Introduction

Hydrogen bonding is among the most important interactions between molecules, playing a vital role in various phenomena of life and chemistry [1,2]. It is not merely a type of weak chemical interaction; it is a fundamental force that governs countless biological processes. Water, for example, which is essential for life, owes its unique properties-such as its high boiling point and exceptional solvation capability to an extensive network of O-HO hydrogen bonds that facilitate interactions between water molecules and other biomolecules [3].

Proteins, considered the backbone of living cells, are composed of complex chains of amino acids that fold into specific three-dimensional structures. These conformations are stabilized by intramolecular hydrogen bonds formed between amino acid residues [4]. Likewise, nucleic acids such as DNA and RNA rely heavily on hydrogen bonding between complementary nitrogenous bases to maintain the double-helical structure and ensure the accurate replication and transmission of genetic information [5].

According to the IUPAC (2011) definition, a hydrogen bond is an attractive interaction between a hydrogen atom from a group X–H, where X is more electronegative than hydrogen, and another group Y which may exist in the same molecule (intramolecular) or in a different one (intermolecular) [6]. This broad definition encompasses a variety of chemical environments and bonding scenarios. Intramolecular hydrogen bonding arises when both donor and acceptor atoms are present within the same molecule and spatially close enough to interact, forming a pseudo-cyclic structure that contributes to molecular stability [7,8].

Studies concerning the hydrogen bond concept span a wide range of the periodic table atoms that contribute to bonding, the strength and directionality of the hydrogen bond are influenced by the electronegativity of the atom bonded to hydrogen, with more electronegative atoms e.g., fluorine, oxygen, nitrogen forming stronger and more linear hydrogen bonds, while less electronegative atoms e.g., sulfur, chlorine form weaker and more flexible interactions [9–14]. it was found that less electronegative atoms like sulfur, chlorine, phosphorus, and carbon can act as donating atoms [13–16]. Moreover, instead of lone pairs of electrons, both sigma and pi bonds can act as acceptors to the hydrogen bond [17–19]. Among those atoms, the hydrogen bond associated with sulfur gained attention due to its role

in maintaining the structure and function of proteins, peptides, nucleic acids, organic compounds, and organic complexes [20].

Intramolecular hydrogen bonding occurs when the donor and the acceptor atoms are close and on the same molecule. When the system including the intramolecular hydrogen bond is closed and associated by conjugated single and double bonds, the hydrogen bond is said to be resonance-assisted in this case, there is delocalization for the pi electrons and polarization of the donor atom. This leads to the transfer of the H atom to the middle of the distance between the donor and the acceptor atoms, leading to an increase in the bond strength [21,22].

Intramolecular hydrogen bonding is closely connected with tautomerism [23] where the proton transfer within the molecule leads to more than one isomeric form which is known as tautomerism [24], where tautomerization can change the hydrogen donor atom to hydrogen acceptor [25]. Many techniques were used to study the intramolecular hydrogen bond including IR spectra, NMR spectra, electronic spectra, and computational chemistry. Computational chemistry provides means that cannot accessed by other methods. Among these the calculation of the interaction energy between the donors and the acceptors of the hydrogen bonds which is about 2 kcal mol^{-1} as the lowest limit. These methods include the natural bond orbital, atoms in molecules, and non-covalent interactions [26,27]. The Hydrogen bond is still an unknown realm of science and thus needs more investigation [28]. Enaminones and enaminothiones may offer good resources for studying hydrogen bonding because they include the O-H, N-H, and S-H hydrogen bonds.

Aim of the study

The present study aims to conduct a computational investigation of tautomerism and resonance-assisted intramolecular hydrogen bonding in enaminones and enaminothiones as model compounds. This will be achieved through the use of DFT-based calculations, AIM and NCI analyses, and complementary spectral techniques. The work focuses on understanding the role of N–H···O and N–H···S hydrogen bonding in stabilizing molecular conformations and the influence of proton transfer.

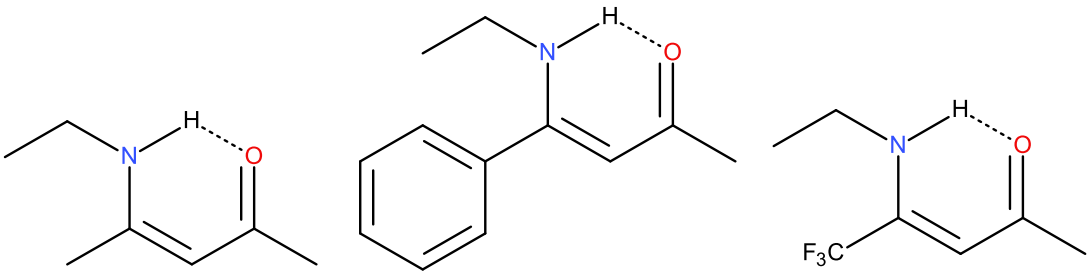
2. Computational methods

All computational calculations were done with the g16 system of programs [29]. The functional wB97XD assisted with Dunning basis set cc-pVTZ and Pople basis set 6-311++G(d,p) were used throughout the calculations. The structures were freely relaxed

without any restrictions. Calculations were done in solution using the Integral Equation Formalism Polarizable Continuum Model IEFPCM with chloroform as a solvent [30]. Vibrational frequency calculations were also done to the optimized structures at the same level of theory to ensure that the obtained structures are real minima on the potential energy surface. Atoms in molecules (AIM) calculations were done with the AIMAll program [31] and NCI calculations were done with the NCIPOLT program [32]. Gaussview program was used as an interface as an input script and for viewing the obtained outputs.

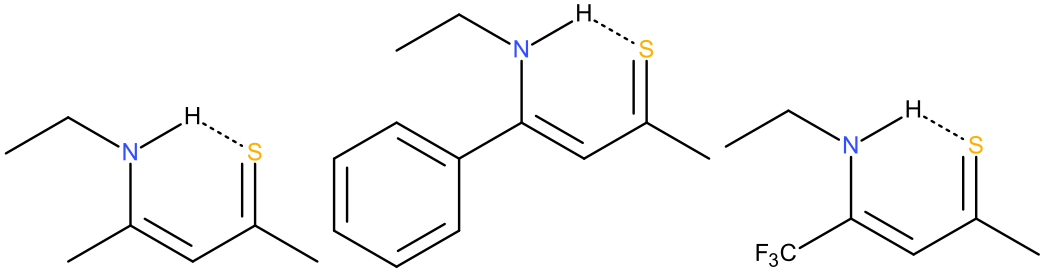
3. Results

The studied molecules have the following structures (truncated at the ethylene bridge CH2-CH2).



1 **2** **3**

A. The studied enaminones.



4 **5** **6**

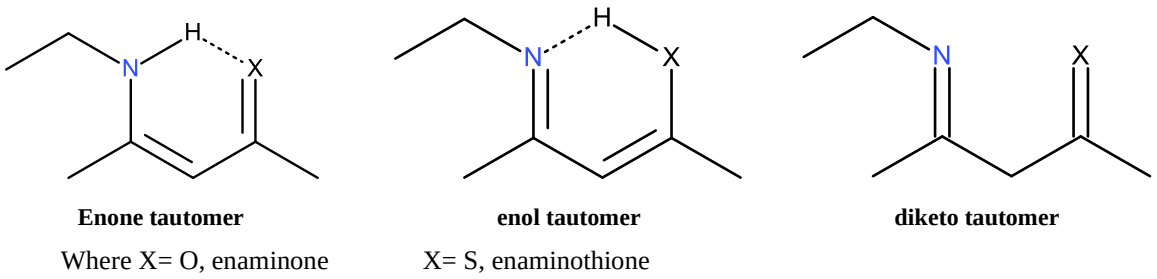
B. The studied enaminothiones.

Fig- 1 The truncated structures of the studied compounds.

3.1 The tautomeric stability

The studied molecules were analyzed to determine the stability of their possible tautomeric forms: enone, enol, and diketo (Figure 2). These tautomers differ in the positions

of protons and double bonds, influencing the formation of intramolecular hydrogen bonds and the extent of electron delocalization.



Enone tautomer **enol tautomer** **diketo tautomer**

Where X= O, enaminone X= S, enaminothione

Fig- 2 The expected tautomers of the studied compounds.

DFT calculations at the wB97XD/cc-pVTZ level provided total energies for each tautomer, and the corresponding Boltzmann distributions are shown in Table 1. It was observed that tautomer 1 (the enaminone/enaminothione form with a chelated six-membered ring) is the most stable for all compounds.

In enaminones (compounds 1–3), total energies ranged from –729.316792 to –1324.835794 hartree for tautomer 1 and from –729.291115 to –1324.805335 hartree for tautomer 2. A similar trend was observed for enaminothiones (compounds 4–6), with tautomer 1 energies between –1375.248403 and –1970.767872 hartree, compared to higher energies for tautomer 2. The Boltzmann distribution showed that tautomer 1 dominates in all cases, with populations exceeding 51% (Table 1).

Table 1- Total energies and Boltzmann distribution of the studied compounds (hartree).

	Total energy		**Boltzmann distribution%**	
Tautomer	**1**	**2**	**1**	**2**
Aminones				
1	-729.316792	-729.291115	51.083	48.917
2	-1112.775196	-1112.748420	51.130	48.870
3	-1324.835794	-1324.805335	51.285	48.715
Thiones				
1	-1375.248403	-1375.207058	51.744	48.256
2	-1758.706656	-1758.664252	51.789	48.211
3	-1970.767872	-1970.726175	51.759	48.241

These findings are supported by the optimized geometries (Figure 3), where the six-membered chelated ring with N–H...O or N–H...S hydrogen bonding contributes significantly to the molecular stability.

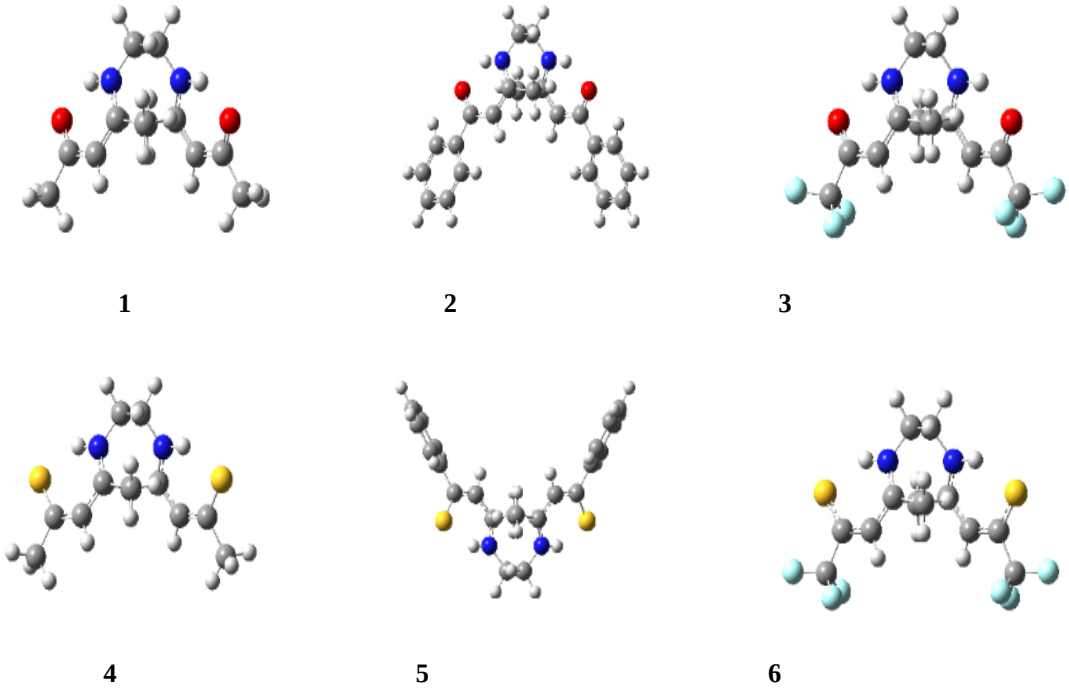
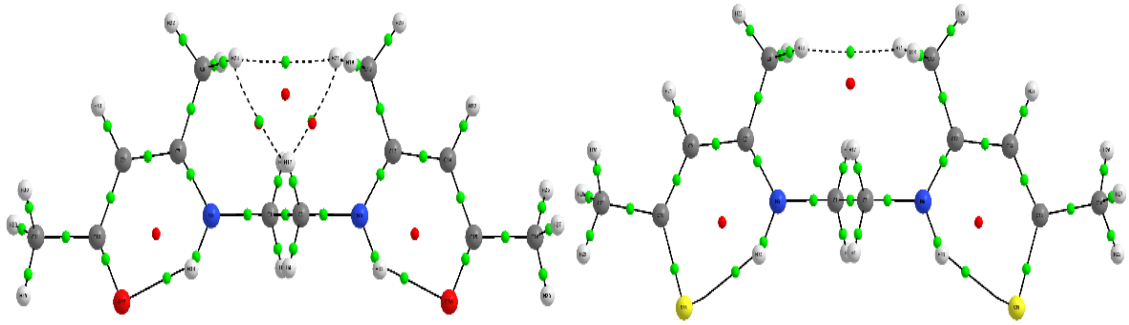


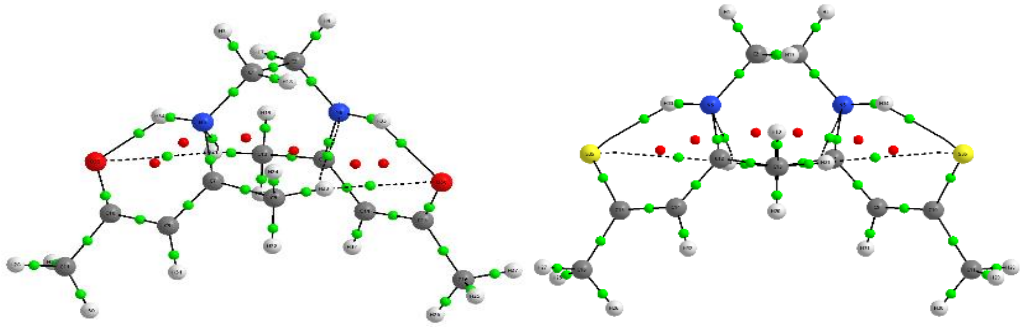
Fig- 3 The optimized structures of the studied compounds at the wB97XD/cc-pVTZ level.

3.2 Atoms in molecules (AIM) calculation

Atoms in Molecules (AIM) analysis was performed to explore the influence of cis and trans configurations across the CH2–CH2 ethylenic bridge [33]. The calculated energies for compounds 1 and 4 showed that the cis configuration is more stable than the trans, as supported by the AIM topological maps (Figure 4).



Compound 1 trans **compound 4 trans**



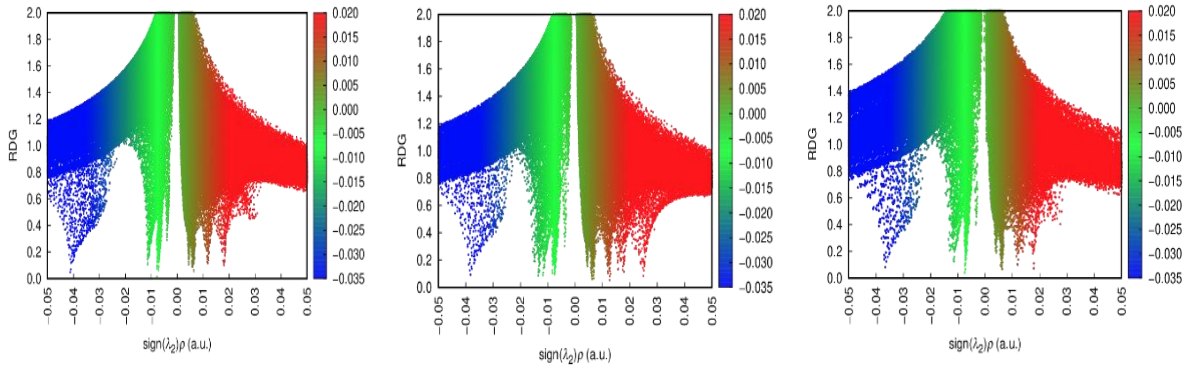
Compound 1 cis **compound 4 cis**

Fig- 4 Cis and trans configurations of compounds 1 and 4 about the CH2-CH2 bridge.

In the cis configuration, favorable intramolecular hydrogen bonds were observed between methyl group hydrogens and electronegative atoms (O or S) on the opposite side of the molecule. This caged structure enhances stability compared to the trans arrangement, where such interactions are less favorable.

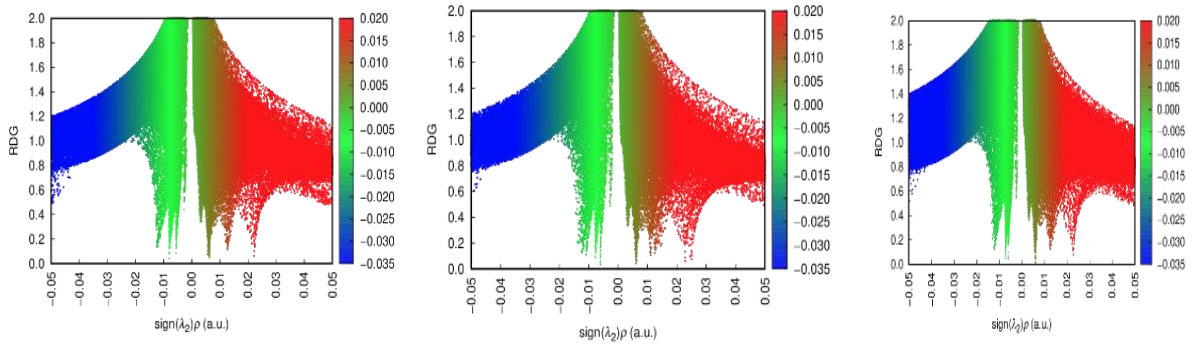
3.3 Non-Covalent interactions (NCI)

Non-Covalent Interaction (NCI) plots and RDG-based surfaces (Figures 5 and 6) provide strong visual evidence of intramolecular hydrogen bonding [34] in tautomer 1. The ρ vs. RDG plots show prominent blue spikes near –0.04 a.u., indicative of hydrogen bonding. In contrast, these features are absent in the 2nd tautomer, suggesting the loss or significant weakening of hydrogen bonds.

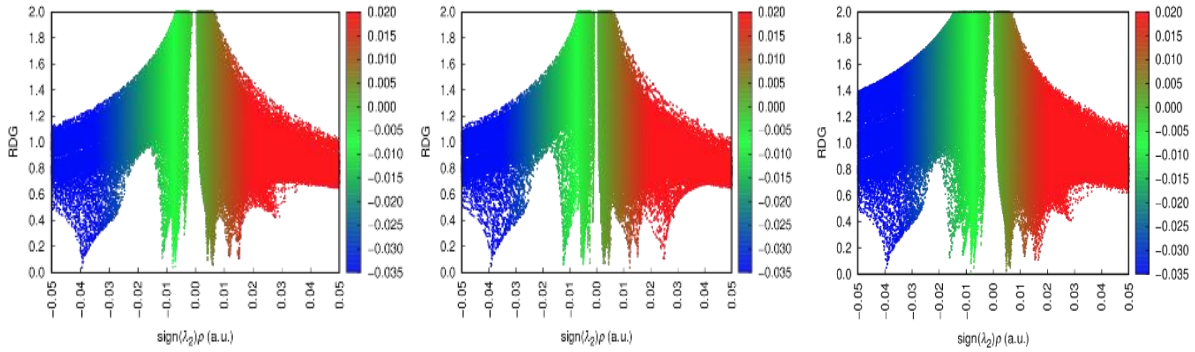


1 **2** **3**

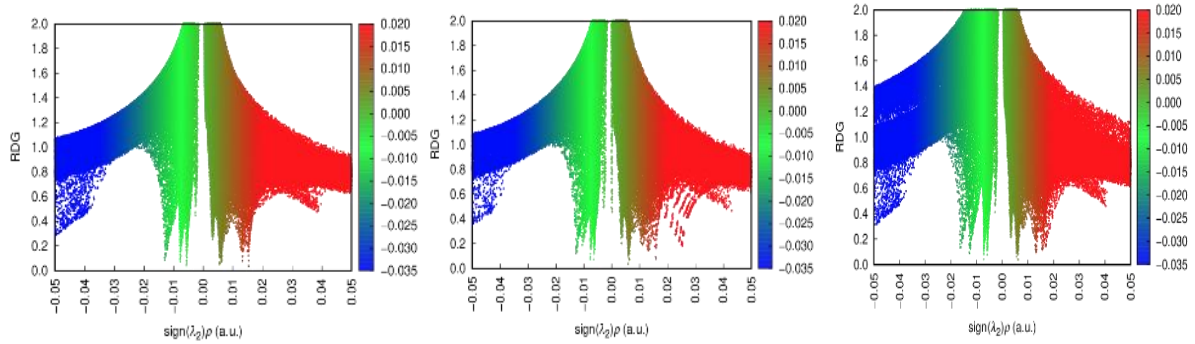
NCI results for compounds 1-3 in the enaminone tautomeric form.



NCI results for compounds 1-3 in the enaminone tautomeric form.



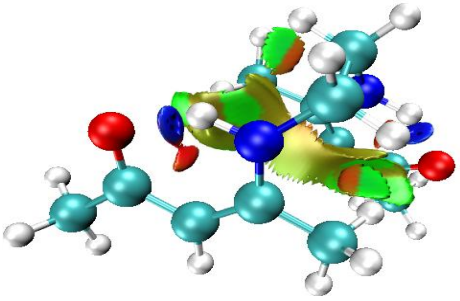
NCI results for compounds 4-6 in the enaminothione tautomeric form.



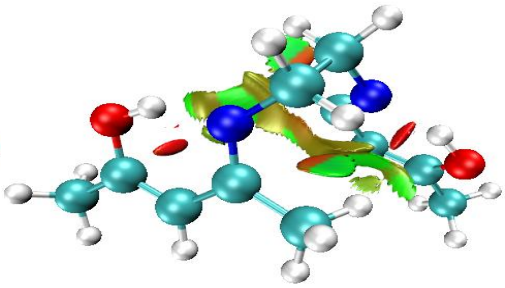
NCI results for compounds 4-6 in the thioenol tautomeric form.

Fig- 5 ρ vs RDG plots from non-covalent interactions calculation results of the studied compounds.

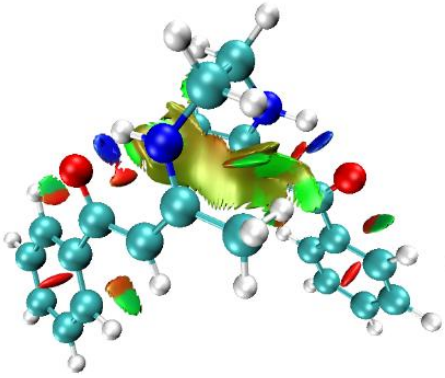
RDG isosurfaces further confirm this pattern. Tautomer 1 structures display distinct blue discs at hydrogen bonding regions, while tautomer 2 shows either no discs or only weak interactions (e.g., rings in thiol forms). Green and red areas in the figures correspond to van der Valls interactions and steric repulsion, respectively [35,36].



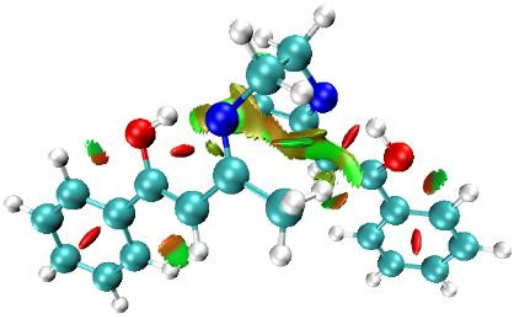
Enone-1



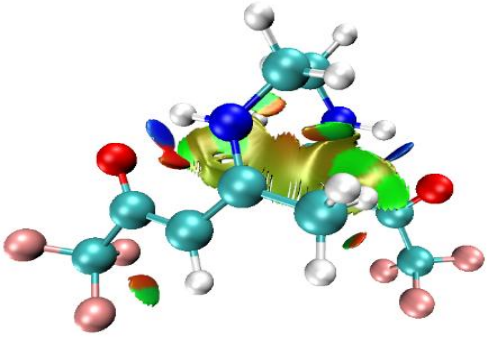
Enol-1



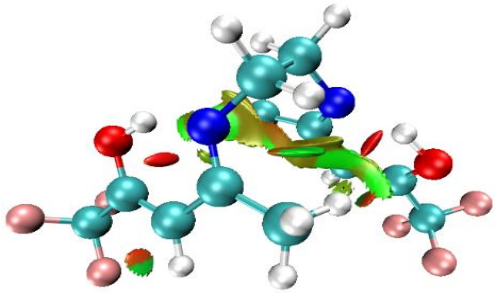
Enone-2



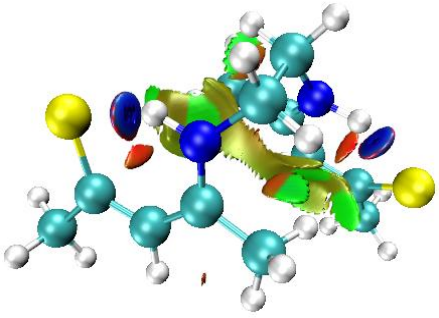
Enol-2



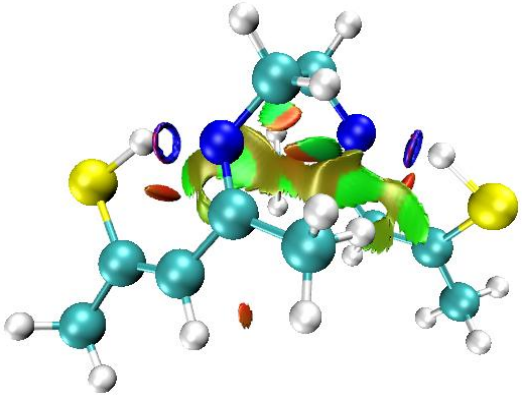
Enone-3



Enole-3



Thione-4



Thiol-4

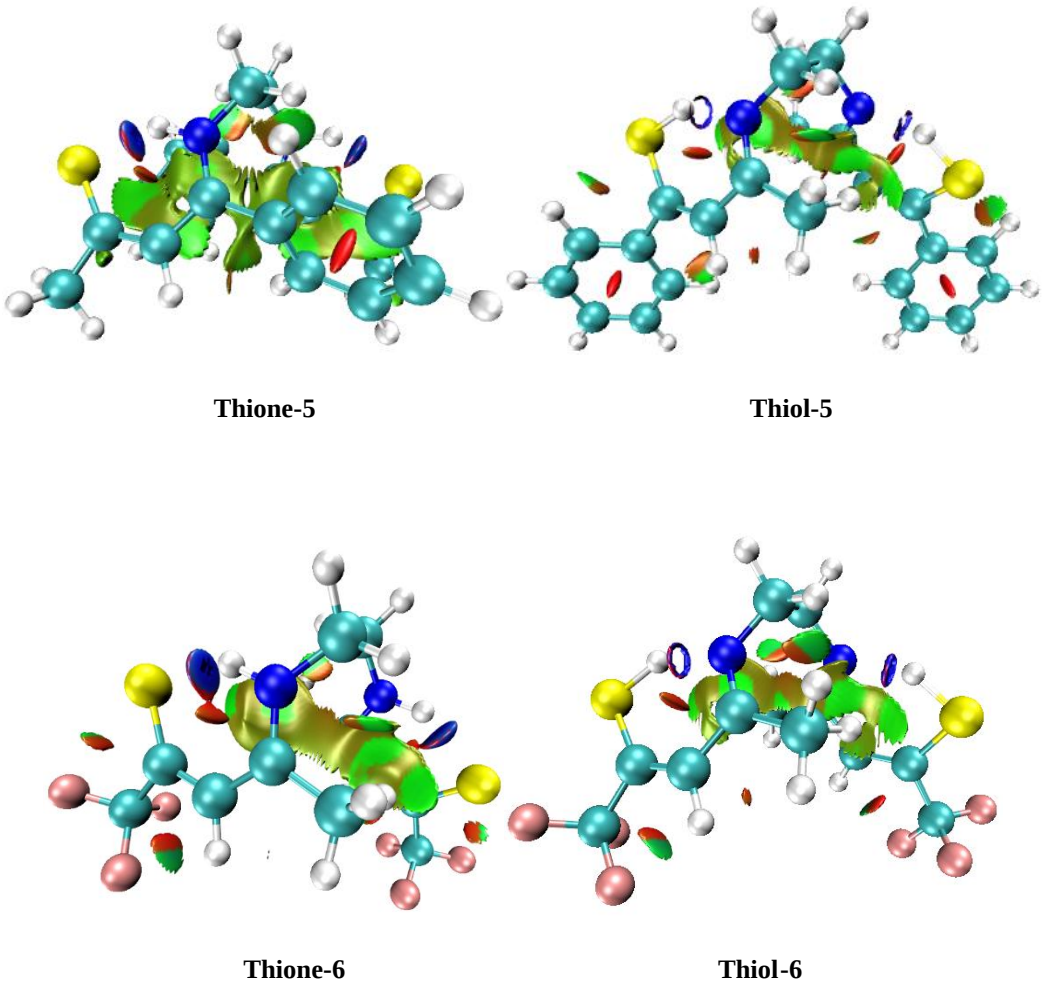


Fig- 6 RDG-based NCI surfaces for the studied compounds.

4. Discussion

The computational data presented in Table 1 and Figures 3 to 6 offer clear insight into the structural and energetic preferences of the studied enaminones and enaminothiones. The enone-like tautomer (tautomer 1) consistently exhibited the lowest total energies and highest Boltzmann distribution percentages across all compounds, indicating that this form is the thermodynamically favored structure. This trend is especially evident in Table 1, where tautomer 1 maintains an energetic advantage of several millihartrees over tautomer 2, which, while structurally viable, is less stable.

This energetic preference is attributed to the presence of a six-membered chelated ring stabilized by resonance-assisted intramolecular hydrogen bonding (RAHB), a well-documented phenomenon in conjugated systems. The optimized geometries in Figure 3 reveal the presence of such hydrogen bonds in tautomer 1, in which the N–H donor forms a

strong interaction with an electronegative O or S acceptor. This stabilizing interaction is absent or significantly weakened in tautomer 2, where the proton resides on a different atom, leading to less favorable electronic delocalization.

Further structural analysis using AIM (Figure 4) demonstrates that the cis configuration is favored over the trans configuration in both compounds 1 and 4. In the cis form, additional stabilizing hydrogen bonds are possible due to the spatial proximity of functional groups across the ethylenic bridge [37]. These caged geometries provide not only thermodynamic stability but also restrict conformational flexibility, which may be desirable in molecular design. The AIM results visually confirm that the electron density critical points between hydrogen and electronegative atoms exist more prominently in the cis structures [38].

The NCI plots (Figure 5) and RDG isosurfaces (Figure 6) strongly support these conclusions. Blue spikes in ρ vs. RDG plots for tautomer 1 indicate strong intramolecular hydrogen bonding, while the absence of such features in tautomer 2 further confirms its instability. RDG surfaces reveal blue discs in tautomer 1, corresponding to the same hydrogen bonds predicted by AIM [39] and DFT, while tautomer 2 surfaces lack these features. The presence of red regions (steric repulsion) and green/yellow areas (van der Valls forces) also provide insights into the intramolecular environment [40-42].

Notably, enaminothiones (compounds 4–6) show slightly weaker hydrogen bonding features compared to their enaminone analogues (1–3). This can be explained by the lower electronegativity and larger atomic radius of sulfur compared to oxygen, which leads to longer and weaker N–H...S interactions. These differences are reflected in the RDG isosurfaces, where the hydrogen bonding regions in thiones are less defined.

5. Conclusion

In this work the tautomeric structures and the intramolecular hydrogen bonding was studied by means of theoretically calculated total energies, atoms in molecules, and non-covalent interactions calculations. It could be concluded that the studied compounds are present mainly in the tautomer that has the N-H bond. The results showed that the enone is the only tautomer which possess hydrogen bond. Also, the molecules have the cis configuration about the CH2-CH2 linkage.

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