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Theoretical Investigation for ^{1}H NMR chemical shift of the N-H…S proton due to intramolecular hydrogen bonding formation in di thiocarboxamides using Post Hartree-Fock and density functional theory.

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Abstract

A three hypothetical derivatives are derived from β-diketones were studied in this work. The molecules were substituted with different arbitrary selected substituents of wide range of Hammett constants that span the negative through the positive sigma para values range. To determine the tautomeric form of the molecules the non-substituted molecule was freely geometry optimized in the gas phase at the MP2/6-311++G(d,p) and the ωB97XD /6-311++G(d,p) levels of theory. The substituted molecules were then subjected to geometry optimization at and the ωB97XD /6-311++G(d,p) level of theory. The optimized structures used to calculate the 1H NMR chemical shifts at the MPW1PW91/6-311+(2d,p) level of theory.2

Our calculations show that the enolic form enaminothione is the most stable tautomer than others derivatives of these molecules. The cis isomer of the di enaminothione is most stable than the trans isomer. A fair correlation between the energy of the intra molecular hydrogen bond (R^2= 0.756) expressed by the N…S distance and the ^{1}H chemical shift of the N-H…S proton.

Keywords: Intramolecular hydrogen bonding, enaminothione, binding energy, chemical shift, DFT.

Introduction

Hydrogen bonding is an important phenomenon that occurs in a large body of chemical and biological systems [1-3]. A special case of hydrogen bonding is intramolecular hydrogen bonding which is govern the structural and chemical properties of several molecular systems such as β-diketones, beta thioxoketones and enaminones [4-7]. The presence of such hydrogen bond in these and their analogs systems leads to the formation of the intramolecular hydrogen bonded chelated ring system which in general shifts the stability of the molecular structure from the diketo form to the enol form. This shift accompanied by several chemical and spectral properties changes like the large downfield shift of the ^{1}H NMR chemical shift of the

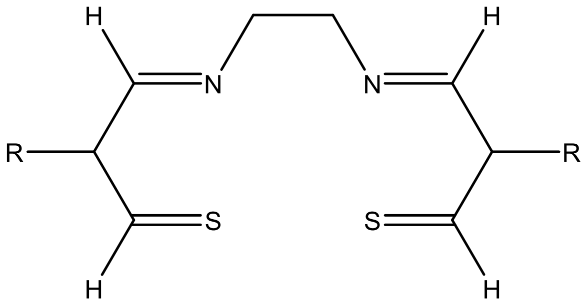
O-H and N-H chelated protons and the red shift of frequency of the O-H, N-H and C=O stretching vibrations in the infrared spectra. These changes are due to the engagement of these groups in the intra- molecular hydrogen bonded system which is stabilized by both conjugation and resonance [8-10]. The hydrogen bonding in these systems is called Resonance Assisted Hydrogen Bonding (RAHB) and it is responsible for the relative energy stability. Increasing works were devoted to study the interamolecular hydrogen bonding in beta diketones and their analogs with the aim to find correlation between the hydrogen bond energy and the structural properties. The general conclusion is there is such a correlation between the hydrogen bond energy and some of the structural properties in the substituted molecules like the O-H, N-H, O...H, and N...H bond as well as the O...O and O...N distances and the O-H...O and N-H...O angles [14-15]. Theoretical calculations found that the intramolecular hydrogen bond energy is increased with increasing O-H and N-H bond lengths and X-H...Y angle while decreased with decreasing O...H and N...H bond lengths and decreasing O...O and N...O distances. In our opinion, since these properties affect the stability of these molecules they may be used as descriptors for their biological activities, since intramolecular hydrogen bonding affects their biological properties [16]. Vinylogous thiocarboxamides are intermediates for the synthesis of a variety of heterocyclic compounds [17,18]. A study based on their NMR spectra showed that their analogs, namely thiophenoxyketenimines exist primarily as a zwitterionic form [19]. The aim of this work is to investigate the relationship between the ^{1}H NMR chemical shift of the intra molecularly hydrogen bonded proton in the N-H…S bridge and the energy of the hydrogen bond.

Computational Methods

In order to predict the most stable tautomer within the tautomeric mixture of the studied molecules the non-substituted structures were geometry optimized using both the MP2/6-311++G(d,p) and ωB97XD/6-311++G(d,p) levels of theory in the gas phase. The MP2 [20] method takes into account the electron correlation effect while the wb97xd [21] is one of the range-separated (R-S) functionals that are parameterized to accurately predicting electronic transitions of conjugated systems as well. After that, all the studied substituted molecules were geometry optimized at the ωB97XD/6-311++G(d,p) level of theory. Shielding constants for the studied molecules, as well as, TMS were calculated with the standard MPW1PW91/6-311+(2d,p) level of theory [22] using the GIAO method [23] in the gas phase. Chemical shifts were then calculated with respect to the shielding constant of TMS. All calculations were done with the Gaussian 16 suite of programs [24].

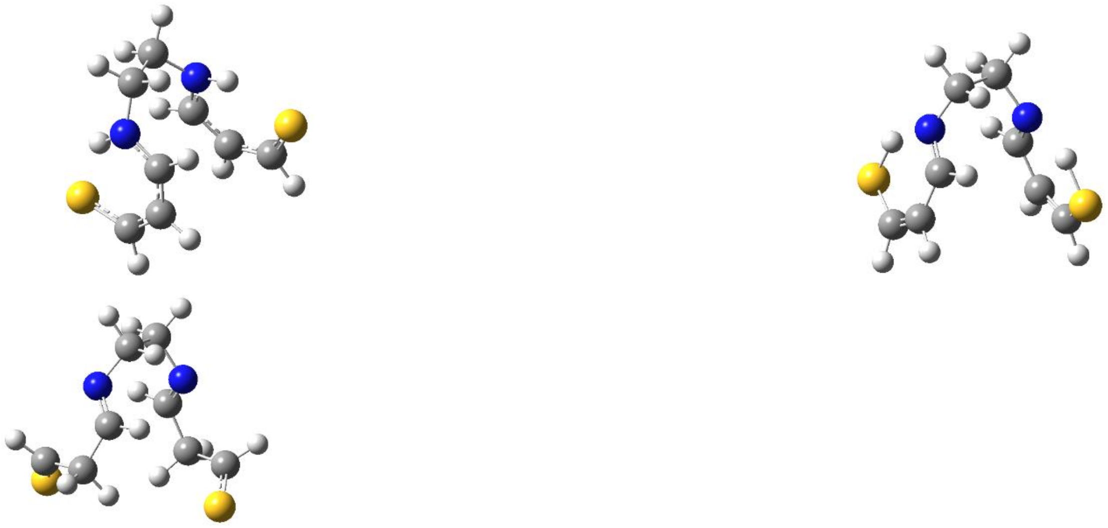
Results and Discussion

The studied compounds have the general formula I.



I

As with the case of their analogs, β-diketones, these molecules could exist as a tautomeric mixture of three tautomers, namely, enaminothione, eniminothiol which represent the enolic tautomer, and the eneiminethione tautomer’s which represents the diketo tautomer’s as in Fig. 1.



enaminothione (enol) eneiminothiol (enol) eneiminethione (diketo)

Fig. 1. The molecular structures of the three tautomers of the non-substituted enaminothione calculated at the MP2/6-311++G(d,p) level of theory.

The calculated energies for the three tautomers at the levels Mp2/6-311++G(d,p) and ωB97XD/6-311++G(d,p) are shown in Table 1. The calculated total energies for the three possible tautomers of the thiocarboxamide molecule with the two levels of theory (Mp2/6-311++G(d,p) and ωB97XD/6-311++G(d,p)) are in the order:

Eneiminethione > Eneiminothiol > Enaminothione

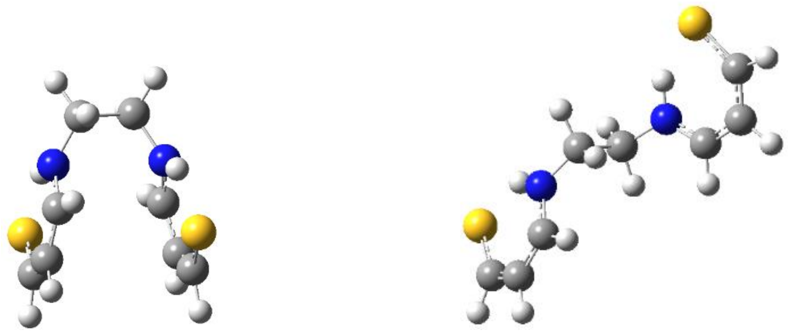
Accordingly, the enaminothione tautomer is the most stable tautomer with total energy of -1215.715410 hartree at the MP2 level and -1217.908372 hartree at the ωB97XD level since the eneiminothiol and the eneiminethione tautomers have relatively higher energies of -1215.691169 and -1215.677016 hartree respectively calculated at the MP2 level. The large relative difference in energies which are 16.0 and 33.2 kcal/mol for the eneiminothiol and the eneiminethione tautomers respectively is an indication of the diminished possibility for the existence of these tautomers in the equilibrium. From these results the enaminothione tautomer should be the only one tautomer that represents the electronic structure of the studied molecules.

Table 1. Calculated energies (hartree) and relative energies (kCal/mol) of the three tautomers.

No.	Level of theory / Molecule	MP2/6-311+G(d,p)		ωB97XD /6-311+G(d,p)	
		Total Energy, hartree	Relative energy, kCal/mol	Total Energy, hartree	Relative energy, kCal/mol
1	Enaminothione	-1215.715410	0	-1217.908372	0
2	Eneiminothiol	-1215.691169	16.2	-1217.872792	22.3
3	Eneiminethione	-1215.677016	33.2	-1217.856025	32.0

The larger energy difference with respect to the diketo tautomer reflects the stabilization energy gained by the intramolecular hydrogen bond that characterized the enaminothione enolic tautomer. The higher stability in the enaminothione compared to the eneiminothiol means that the hydrogen bond system N-H…S is stronger than the N…H-S system. This is in agreement with other studies undertaken on analog molecules such as β-diketones [4], β-thioxoketones [5] and enaminones [6,7].

The enaminothione tautomer could on the other hand exits as a trans and cis isomer, as shown in Fig. 2.



The cis isomer The trans isomer

Fig 2. The cis and the trans isomers of the enaminothione tautomer.

The energies calculated for the two isomers at the Mp2/6-311++G(d,p) level of theory are

-1215.715410 and -1215.711326 Hartree for the cis and the trans isomers respectively indicating the cis isomer as the more stable one. A scan of total energy of dihedral angle about the CH_2-CH_2 bond of the ethylene bridge of the molecule at the PM6 semi empirical Hamiltonian illustrates the foregoing finding (Fig. 3).

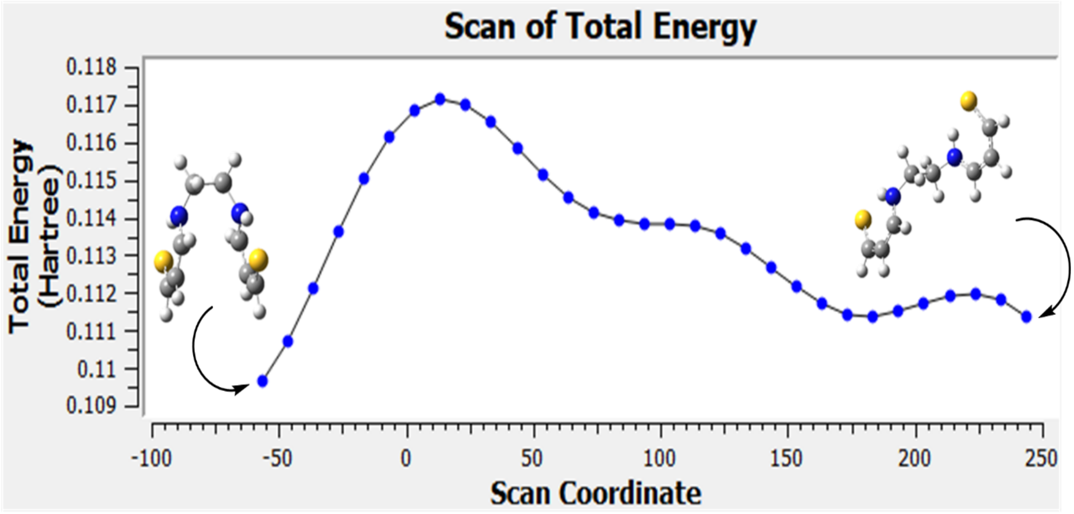


Fig 3. PM6 scan of total energy about the CH_2-CH_2 bond of the ethylene bridge of the enaminothione tautomer.

According to these results the cis enaminothione tautomer will be used for the calculation of the shielding constants of the substituted vinylogous thiocarboxamides. The calculated chemical shifts and the N...S distances as well as to Hammett sigma constants are shown in Table 2 while the relationship between the calculated chemical shift and the N…S distance is graphed in Fig 4. The calculated chemical shifts vs

Hammett constants are also shown in Fig 5 and 6. Table 2 shows the substituents used in the study as well as Hammett σ_p and σ_m constant belong to these substituents. In addition, the interatomic distance between the heteroatoms of the intramolecular hydrogen bonded bridge (N…S) is tabulated in Table 2. The calculated chemical shift with respect to the calculated chemical shift of TMS at the MPW1PW91/6-311+G(2d,p) level of theory are also shown n Table 2. It is well known that the intramolecular hydrogen bond energy is increased with the increase of the N-H bond length [26]. From table 2 it could be shown that there is a general increase of the calculated chemical shifts with the increasing N-H bond length, which reflects a direct relation with the hydrogen bond energy.

Table 2. Hammett σ_p and σ_m constants, the calculated N…S distance (Å) and the calculated chemical shifts of the N-H…S proton (ppm).

No.	R	σ_p	σ_m	N…S distance, Å	N-H chemical shift, ppm
1	H	0	0	3.0531	12.72
2	Cl	0.23	0.37	3.0599	12.55
3	NO	0.91	0.62	3.0367	12.96
4	NO2	0.78	0.71	3.0584	12.99
5	SH	0.15	0.25	3.0501	12.73
6	$N(Me)_2$	-0.83	-0.16	3.0489	12.65
7	CN	0.66	0.56	3.0626	12.67
8	CHO	0.42	0.35	3.0758	12.23
9	NH_2	-0.66	-0.16	3.0459	12.75
10	OH	-0.37	0.12	3.0638	12.16
11	SO_2Cl	1.11	1.2	3.0381	13.00
12	Me	-0.17	-0.07	3.0391	12.81
13	OMe	-0.27	0.12	3.0711	12.22
14	NHMe	-0.7	-0.21	3.0615	12.23
15	Cyclopropyl	-0.7	-0.07	3.0513	12.81

16	$NHNH_2$	-0.55	-0.02	3.0667	12.35
17	COOH	0.45	0.37	3.0530	13.18
18	Pyridil	0.44	0.27	3.0446	12.88
19	$OCH=CH_2$	-0.09	0.21	3.0743	12.12
20	$SCH=CH_2$	0.2	0.26	3.0562	12.67
21	NHOH	-0.34	-0.04	3.0698	12.20
22	COMe	0.5	0.38	3.0440	13.10
23	NEt_2	-0.72	-0.23	3.0366	13.00
24	SO_2F	0.91	0.8	3.0749	12.49
25	SiH3	0.1	0.05	3.0381	13.05
26	Et	-0.15	-0.07	3.0455	12.78
27	OEt_2	-0.24	0.1	3.0723	12.24
28	SOF	0.83	0.74	3.0320	13.15
29	F	0.06	0.34	3.0897	11.92

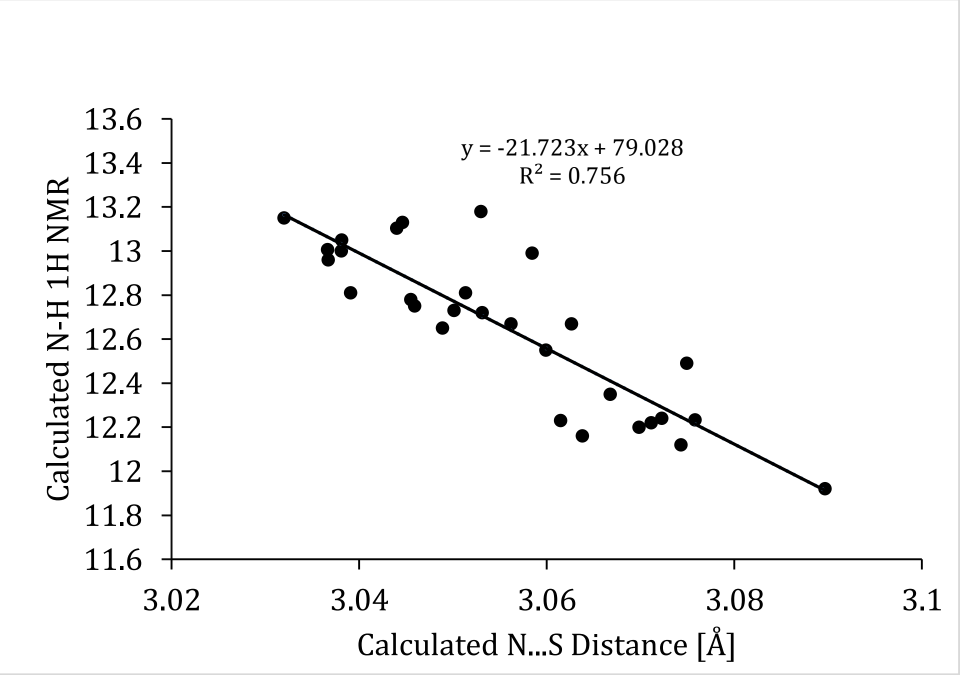


Fig 4. The calculated binding energy by docking with MOE software against the calculated chemical shifts of the N-H hydrogen.

It could be seen from Fig 8 that the calculated chemical shifts are within the range 11.92-13.10 ppm which is in good agreement with the chemical shift of the intramolecular hydrogen bonded proton in the aliphatic mono vinylogous thiocarboxamide which is 12.88 ppm [17]. As well there is a general trend of the N-H proton chemical shift to increase with decreasing value of the N…S distance. This trend is reflected by a linear correlation with a correlation constant R^2 of 0.756. The fair value of R^2 refers to that the chemical shift of the N-H…S proton is sensitive to the distance N…S of the heteroatoms that share intramolecular hydrogen bonded chelated ring. The calculated chemical shift increases with decreasing N…S distance. It is known that the O…O distance in related intramolecularly hydrogen bonded molecules correlates with the energy of the hydrogen bond and generally the shorter the O…O distance is the higher hydrogen bond energy [26]. Accordingly, it could be concluded that the chemical shift of the N-H…S proton could be a descriptor for the hydrogen bond energy in the studied molecules. This could be rationalized as follows; the small N…S distance means that the hydrogen bond is strong to the degree that it brings the N and S atoms closer and the hydrogen atom becomes highly bonded with them leading to a higher degree of deshielding at the hydrogen atom which reflects in turn in a downfield NMR chemical shift.

On the other hand, this shift could be due to the electron donating or electron withdrawing effects of the substituents expressed by Hammett σp or σm constants. In this contest, a correlation between the calculated chemical shifts and Hammett constants was tried as shown in Figs 5 and 6. The low correlation constants obtained in these relationships which are 0.237 and 0.111 for the σp and σm respectively rule out this possibility. Accordingly, the chemical shift of the proton in the N-H…S bridge could serve as a potent indicator for the energy of the intramolecular hydrogen bond in vinylogous thiocarboxamides.

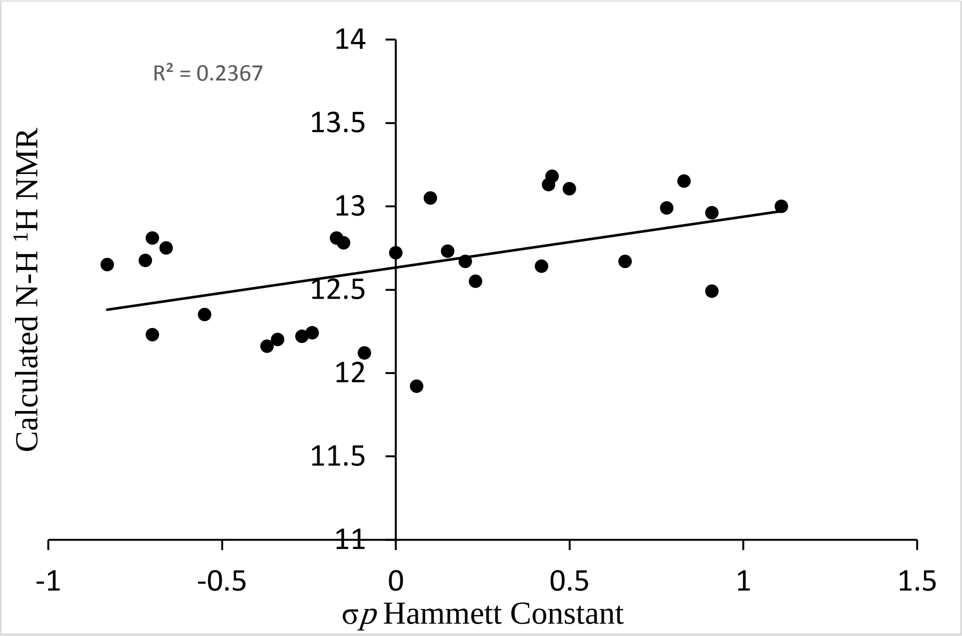


Fig 5. The calculated chemical shifts of the N-H…S proton vs σ*p* Hammett constants of the substituents.

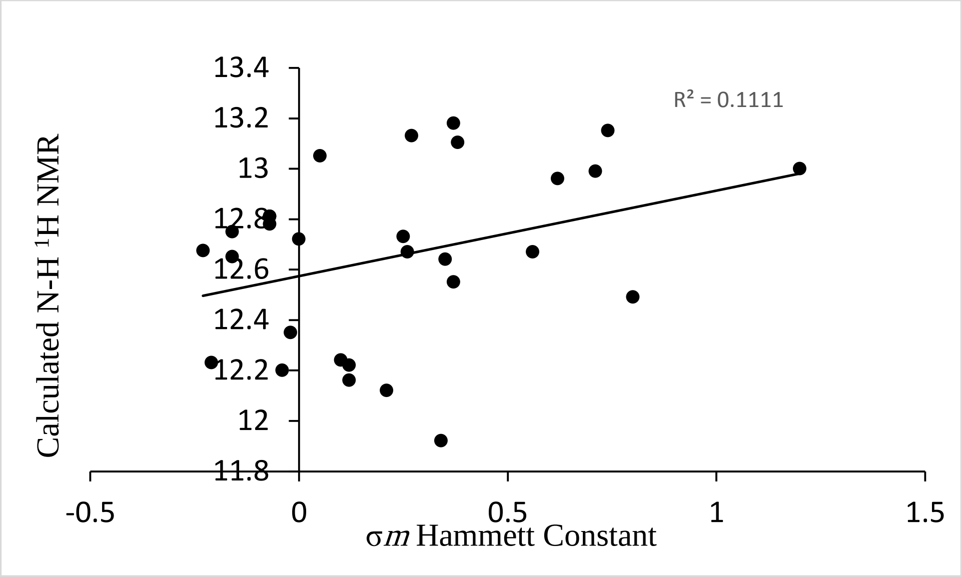


Fig 6. The calculated chemical shifts of the N-H…S proton vs σ*m* Hammett constants of the substituents.

Conclusion

- A three suggested derivatives of di vinylogous thiocarboxamides substituted at the α-position have been investigated for their tautomerism and 1H NMR chemical shifts.
- The enolic cis enaminothione is the most stable tautomer than other three proposed tautomers for these molecules.
- A fair correlation between the chemical shift of the N-H…S bridge proton and the hydrogen bond energy as expressed by the N…S distance in this bridge, where chemical shift increases as he N…S distance decreases.

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تأثير التاصر الهايدروجيني الضمني في الثايوكاربوكساميدات الثنائية على الازاحة الكيميائية لبروتون المجموعة N-H…S. دراسة بما بعد هارتري فوك و نظرية دالية الكثافة.

مريم عبدالكريم و بهجت علي سعيد

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المستخلص

تمت في هذا العمل دراسة مجموعة من الثايوكاربوكساميدات الثنائية الافتراضية المشتقة من الاينامينونات الثنائية. لقد تم تعويض الجزيئات بواسطة مدى من المعوضات الدافعة و الساحبة للالكترون و التي اختيرت بشكل عشوائي لتمتد بين اقصى قيم ثوابت هامت الموجبة و السالبة. في البداية اجريت عملية استمثال هندسي للجزيئة غير المعوضة و في الحالة الغازية عند كل من المستووين النظريين (MP2/6-311++G(d,p) و (ωB97XD /6-311++G(d,p) لتحديد الشكل التوتومري الاكثر استقرار الذي تظهر به الجزيئات. و قد بينت كلتا الطريقتين ان الشكل الاينولي اينامينوثايون هو الشكل الاكثر استقرارا. كما بينت الدراسة ايضا بان الايزومر سيس اينامينوثايون هو اكثر استقرارا من الايزور ترانس اينامينوثايون. ثم اجريت عملية الاستمثال الهندسي للجزيئات المعوضة و هي بصيغة السيس اينامينوثايون بالطريقة (ωB97XD /6-311++G(d,p). و قد حسبت ايضا ثوابت الحجب لاطياف لرنين النووي المغناطيسي البروتوني للجزيئات المعوضة اضافة الى جزيئة تراي مثيل سيلان بطريقة GIAO عند المستوى النظري (MPW1PW91/6-311+(2d,p) و في الحالة الغازية. حسبت بعد ذلك الازاحات الكيميائية لبروتون المجموعة N-H…S نسبة الى ثابت حجب التراي مثيل سيلان. لقد بينت النتائج ان هناك علاقة ترابطية بين هذه الازاحة الكيميائية و طاقة الاصرة الهايدروجينية معبرا عنها بالمسافة N…S و بثابت ارتباط بقيمة معتدلة هي 0.756. ان هذا يدل على ان الازاحة الكيميايئة للبروتون المشترك بالتاصر الهايدروجيني الضمني في هذه الجزيئات يمكن ان يمثل مقياسا و لو تقريبيا لطاقة الاصرة الهايدروجينية.