A Quantitative and Qualitative Investigation of Conformational Analysis, Tautomeric Preference and Intramolecular Hydrogen Bonding on N-nitroso N-thionitrosamine (NTA)

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Abstract Various aspects of NTA were performed using B3LYP and MP2 methods with 6-311++G (d,p) basis set. First, the conformational analysis and characterization of equilibrium conformations, especially global minima, were carried out. On the basis of relative energies, we found that the N-nitroso N-thionitroso amine (TN) tautomer is more stable than the others, which is followed by1-hydroxy 2-thionitroso diazene (HT) and 2-mercpto diazene (NM) tautomers. This preference is well interpreted in terms of tautomerization process, thionitrosamine resonance and charge transfer energies. Furthermore, the nature of S-H···O and O-H…S intramolecular hydrogen bond (IMHB), in chelated forms of HT-11, NM-11, HT-13 and NM-13 were comprehensively studied to evaluate the effect of hetero atoms N and S on the characteristic of intramolecular hydrogen bond systems. The results of isodesmic method clearly show that this approach is unsuitable for estimation the IMHB energy. Whereas, both of the energy–geometry correlation and the electron density analysis Espinosa emphasize on HT-11 as a chelated form with the strongest hydrogen bond, that is followed by MA, NM-11, HT-13 and NM-13. Additionally, the geometrical, atoms in molecules (AIM) and natural bond orbital's (NBO) parameters also are in line with this conclusion.

Keywords N-Nitroso compounds, Intramolecular hydrogen bond, Conformational Analysis, AIM and NBO

1. Introduction

N-Nitroso compounds, which include nitrosamines and its derivatives, have been known for more than 100 years, but nothing was known of their toxicological properties until 1937, when Freund [1] described a laboratory poisoning by nitrosodimethylamine. Then Barnes and Magee [2] in 1954 described a thorough toxicological examination of the compound in several species, in which liver and lung injury caused death. This culminated in a chronic toxicity test in rats, which resulted in a high incidence of animals with liver tumors within a year [3].The parent nitrosamine, NH_2-NO, is of special interest in atmospheric chemistry and it has been studied in very much detail [4]. Several theoretical works have been carried out in nitrosamine and its derivatives including ab initio calculations relevant to the mechanism of chemical carcinogenesis by N-nitrosamines [5], investigation of the interaction of the nitrosamines with the

active site of cytochrome P450 [6, 7], study of the electronic properties of the low-lying spin states of dimethylnitrosamine coordinated to Fe(Ш) heme models [8], studies of the origin of rotational barrier in nitrosamine, study of the kinetics parameters associated with the rotation of nitroso group about the N–N bond in five and six-membered cyclic nitrosamine compounds and analysis of rotational energy barrier in six-membered cyclic nitrosamine compounds [9-11]. Also, recently a theoretical work was carried out by our research group in dinitrosoamine [12].

By replacement of a thionitroso functional group in dinitrosamine instead nitroso group, N-nitroso N-thionitros amine (NTA) is formed. This compound can participate in the N-nitroso N-thionitroso amine (TN) ↔ 1-hydroxy 2-thionitroso diazene (HT) ↔1-nitroso 2-mercpto diazene (NM) tautomeric equilibriums (Fig.1). Therefore, NTA can have three different tautomers which are converted to each other by tautomeric equilibrium. In HT and NM tautomers, the appropriate arrangement of functional groups can forms S-H…O and O-H…S intramolecular hydrogen bonds (IMHB) which are assisted by π-electrons delocalization. This kind of hydrogen bond is represented by RAHB symbol

that links the strength of the hydrogen bond to the resonance in chelated rings [13]. The chelated enol forms of β-dicarbonyl compounds, especially malonaldehyde (MA) and its derivatives, are the simplest members of RAHB systems which have been extensively studied [14-17]. Similar to MA and dinitrosamine [12], NTA shows several interesting features, such as equilibriums tautomerism, nitrosamine and thionitrosamine resonance and S-H…O and O-H…S intramolecular hydrogen bonds. Moreover, the presence of three hetero atoms (N) and one hetero atom (S) have an important role in determining the molecular structure of equilibrium conformations, tautomeric preference, intramolecular interactions and π-electron delocalization. In spite of these attractive properties, as far as we know, no extensive theoretical study about the NTA was published. Consequently, we think that it is necessary to carry out a comprehensive theoretical study about various aspects of NTA.

The aims of present study are as follows: 1) identification of the equilibrium conformations, especially global minimum, 2) investigation of the conformational and tautomeric preferences, 3) estimation of the IMHB energies and significance of π-electron delocalization in chelated forms of HT and NM tautomers, 4) exploration of the heteroatom effects especially hetero atom (S).
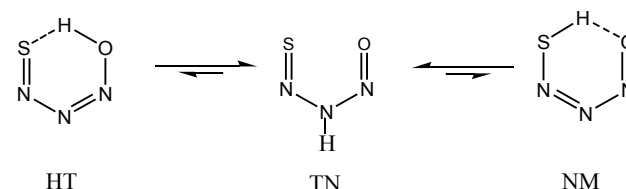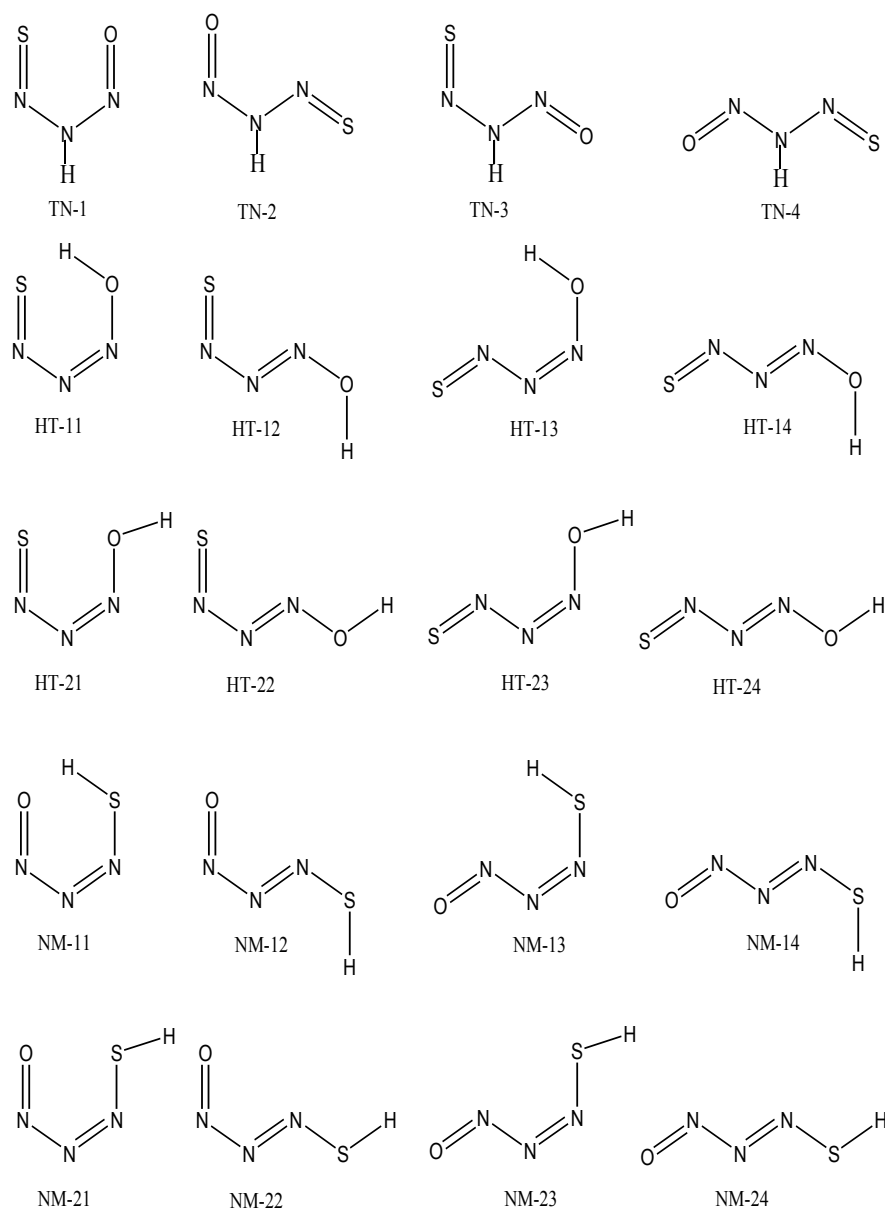

Figure 1. Tautomeric equilibriums in NTA

Figure 2. The theoretical structure of possible conformations of the NTA
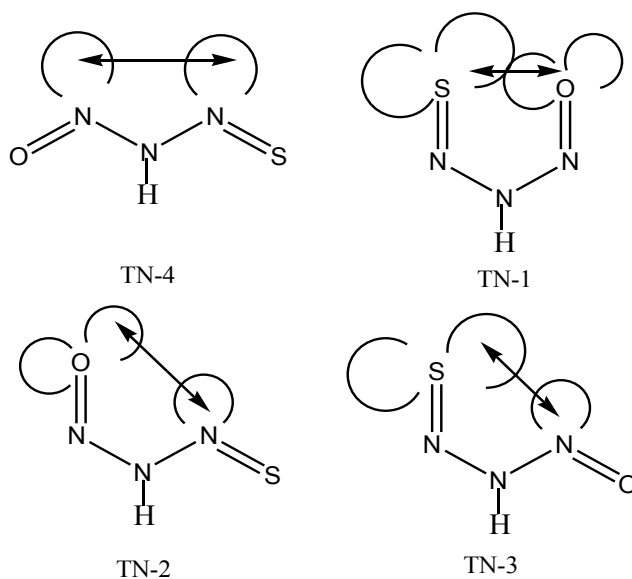
Figure 3. Electrostatic repulsion between nitroso and thionitroso groups in TN conformers
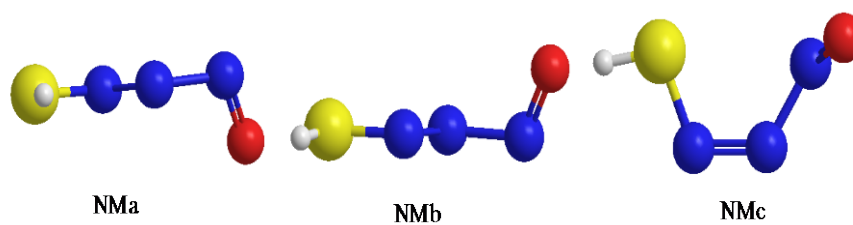

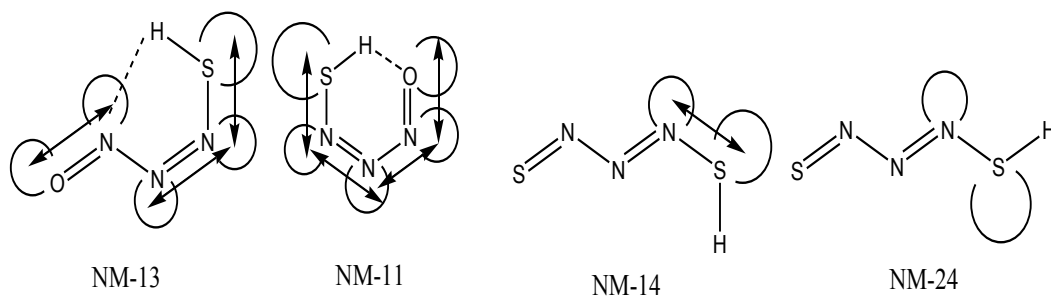**Figure 4.** The optimized structures of NMa, NMb and NMc conformers

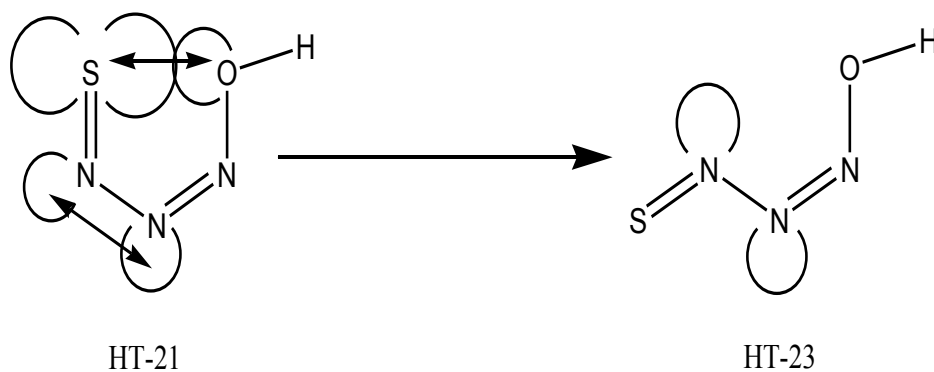**Figure 5.** The eclipsed and staggered orientation of lone pairs in some of NM conformers

Figure 6. Electrostatic repulsion between nitrogen-nitrogen lone pairs in HT-21 and HT-23
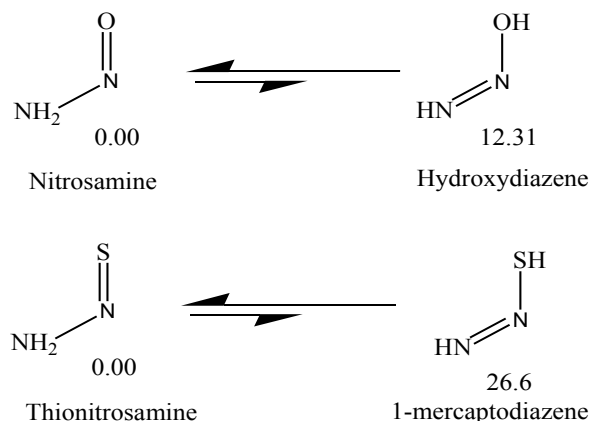
Figure 7.   The energy of tautomerism process in NTA

2. Computational Methods

All of calculations in this study were performed by GAMESS software ab initio package [18]. The geometry optimizations were carried out by B3LYP and MP2 methods with the standard, 6-311++G (d,p), basis set. Harmonic vibrational frequencies were evaluated at the same levels in order to identify the nature of the stationary points and employing the zero point vibrational energy (ZPVE) corrections. The optimized structures at B3LYP/6-311++G (d,p**)** level of theory were used to obtain the appropriate wave functions files for AIM and NBO analyses. The nature of the IMHB in the chelated forms has been studied using the AIM theory with AIM2000 software [19].

The natural bond orbital analysis was carried out using the version 5.0 of NBO package [20] included in GAMESS program. NBO analysis stresses the role of orbital's interactions in studded molecule, particularly charge transfers. This is carried out by considering all the possible interactions between filled donor and empty acceptor NBOs and estimating their energetic importance by second-order perturbation theory. For each donor NBO (i) and acceptor NBO (j), the stabilization energy $E^{(2)}$ associated with electron delocalization between donor and acceptor is estimated as eq. (1):

$$\Delta E_{i \to j}^{(2)} = q_i \frac{(F_{ij})^2}{\epsilon_i - \epsilon_j} \qquad (1)$$

Where q_i is the orbital occupancy, ϵ_i, ϵ_j are diagonal elements and F_{ij} is the off-diagonal NBO Fock matrix element.

Moreover, we estimated the IMHB energy of NM-11, NM-13, HT-11, HT-13 and MA according to the following methods:

1. Electron density analysis of Espinosa. In this method, the IMHB energy is equal to half of the local potential energy density at critical point of hydrogen bond [21].
2. Energy-geometry correlation of Musin and Mariam. In this method, the IMHB energy is determined based on the following eq. (2) [22].

$$E_{IHB}(kcal.mol^{-1} = (-5.554 * 10^5)exp(-4.12 * R_{O \ldots O}) \quad (2)$$

3. Isodesmic reactions method. In this method, the IMHB energy is obtained from the energy difference between the products and reactants of a suitable isodesmic reaction (see Fig.9) [23].

3. Results and Discussion

3.1. Conformational Analysis

Theoretically, NTA has about 20 plausible conformers which systematically arranged in three tautomeric classes, N-nitroso N-thionitroso amine (TN), 1-hydroxy 2-thionitroso diazene (HT) and 1-nitroso 2-mercpto diazene (NM) with 4, 8 and 8 members, respectively.

Table 1.   The relative energies of the equilibrium conformations of TN at various levels of theory (kJ mol⁻¹)

Possible Conformer	MP2	B3LYP
TN-1	22.85(21.83)	30.67(33.81)
TN-2	9.450(11.17)	8.500(8.290)
TN-3	17.37(16.07)	19.76(18.65)
TN-4	0.000(0.000)	0.000(0.000)
NM-11	96.80(94.65)	104.5(102.7)
NMa	19.62(17.56)	37.04(38.76)
NM-13	29.12(27.65)	44.62(43.65)
NM-14	19.64(17.34)	34.19(33.76)
NMb	19.00(18.34)	33.75(32.11)
NMc	17.42(18.65)	32.61(30.26)
NM-24	18.20(19.87)	34.97(34.02)
HT-11	66.65(63.22)	81.21(82.30)
HT-12	9.070(10.34)	9.460(10.11)
HT-13	--	52.84(56.89)
HT-14	6.450(8.560)	9.450(10.05)
HT-23	--	34.86(34.31)
HT-22	9.040(10.070)	9.440(9.890)
HT-24	6.401(8.120)	8.85(7.670)

Table 2. The selected charge transfer energies of TN forms at B3LYP/6-311G (d,p) level(kcal mol^{-1})

Charge Transfer Energy	TN-1	TN-2	TN-3	TN-4
LP(N)→π*N=S	24.13	59.13	48.70	57.11
LP(N)→π*N=O	22.62	44.72	46.12	47.51
Total	46.75	103.85	94.82	104.62

Theoretical structures of these conformers and their relative energies are shown in Fig. 2 and Table 1. Based on relative energies, at all of the computational levels, it can be concluded that the energy of TN tautomer is slightly higher than the HT and NM tautomers. The investigation of conformational preference is the main goal of this section.

3.1.1. TN Tautomer

From theoretical point of view, we considered four planar conformers for TN tautomer (TN-1, TN-2, TN-3 and TN-4), which are different in orientation of nitroso and thionitorso functional groups (Fig. 2). Full optimization and frequency calculation of TN forms, at different computational levels, shows four local minimum on the potential energy surface. Moreover, from the relative energies (Table 1), it can be concluded that the TN-4 is not only the most stable form among the TN conformers, which is followed by TN-2 , TN-3 and TN-1, but also is global minima amongst the known local minimums. It seems that the energy gap between the consecutive forms can be related to electrostatic repulsion amongst the nitrogen, oxygen and sulfur electron lone pair's in nitroso and thionitroso functional groups and donor-acceptor stabilization charge transfers. In order to investigation of the electrostatic repulsion effects on the stability of TN forms, orientations of nitroso and thionitroso functional groups have been considered. In more stable form TN-4, the trans orientation of groups with respect to each other decrease the electrostatic repulsion while in more unstable form TN-1 the groups are in axial situation, which

this configuration considerably increase the electrostatic repulsion. That's shown in Fig.3. In the other forms, TN-2 and TN-3 nitroso and thionitorso functional groups are in axial situation, respectively (Fig.3). It can conclude from Fig.3 which probably more polarizability of sulfur heteroatom in the thionitroso group increase overlap between electrons lone pairs sulfur and nitrogen atoms and unstable T-3 with respect to TN-2. These results are in good agreement with the energy order of TN conformers. The selected donor–acceptor charge transfer energy of TN forms, at B3LYP/6-311G (d,p) level of theory, are gathered in Table 2. The total values of charge transfer energies between the nitrogen lone pair and anti-bonding orbital of nitroso group ($\pi*_{N=O}$) (nitrosamine resonance) and thionitorso group ($\pi*_{N=S}$) (thionitosamine resonance) of TN-1, TN-2, TN-3 and TN-4 are about the 46.75, 103.85, 94.82 and 104.62kcalmol^{-1}, respectively. These results are in good agreement with the energy order of TN conformers. Furthermore, the data in Table 2 clearly show that charge transfer energy between the central nitrogen lone pair and $\pi*_{N=S}$ is more in compare with $\pi*_{N=O}$. This result refers to significant role of the high polarizability of sulfur heteroatom in electron delocalization. The nitrosamine and thionitosamine resonance significantly strengthened the N-N bonds of TN forms. As evident from Table 3, the N-N bonds lengths of TN-1, TN-2, TN-3 and TN-4, are about 1.330, 1.315, 1.323 and1.310 Å, respectively, which is in line with the previous conclusion.

Table 3. The selected geometrical parameters of TN formers at B3LYP/6-311G (d,p) level (A°)

Possible Conformers	TN-1	TN-2	TN-3	TN-4
R(N=S)(A°)	1.601	1.603	1.602	1.604
R(N-N)(A°)	1.330	1.315	1.323	1.310
R(N=O)(A°)	1.183	1.184	1.197	1.198
R(N-N)(A°)	1.448	1.433	1.438	1.392

Table 4. The total charge transfer energies of NM forms at B3LYP/6-311G (d,p) level (kcal mol^{-1})

Charge Transfer Energy	NM11	NMa	NM13	NM14	NMb	NMc	NM24
π*N=S→σ*N=N	20.68	0.78	19.63	10.96	0.98	0.91	9.52
LP(S)→π*N=N	16.02	11.93	15.15	11.04	--	11.67	11.06
LP(S)→π*N=N	8.42	--	11.17	1.58	11.43	--	1.54
LP(N)→π*N=N	24.90	5.40	21.66	0.77	18.23	5.74	0.59
LP(N)→π*N=S	17.93	10.91	7.51	1.39	--	12.90	1.59
LP(N)→π*N=O	22.26	3.38	17.35	3.07	--	3.45	2.84
π*N=N→σ*N=N	--	37.25	--	--	55.15	48.74	--
LP(O)→π*N=N	63.45	16.97	47.63	35.63	11.40	13.87	31.45
Total	173.7	86.62	140.1	64.44	97.19	97.8	58.59

Table 5. The forward and backward potential energies barriers of proton transfer in some of tautomeric equilibriums (kJ mol^{-1})

Plausible Equilibrium	E_af	E_ab
NM-11 ⇌ TN-1	149.4	75.6
NM-12 ⇌ TN-3	159.6	112.3
NM-22 ⇌ TN-3	159.6	108.3
NM-14 ⇌ TN-4	151.9	117.7
Avarage potential energy	155.1	103.4
HT-11 ⇌ TN-1	196.3	184.1
HT-12 ⇌ TN-3	201.7	196.3
HT-22 ⇌ TN-3	201.6	199.0
HT-14 ⇌ TN-4	198.8	176.3
Avarage potential energy	199.6	188.9

3.1.2. NM Tautomer

Due to the presence of π-electron delocalization, eight planar NM conformers were proposed (Fig. 2). All of these theoretical forms were fully optimized by MP2 and B3LYP methods with standard basis set, 6-311++G (d,p). The absence of imaginary frequency reveals that all of these planar forms, except NM-12, NM-21, NM-22 and NM-23, have a particular local minimum on the potential energy surface of molecule. After full optimization, NM-12 changes to NMa and NM-22 changes to NMb while NM-21 and NM-23 convert to NMc. The optimized structures of NMa, NMb and NMc are presented in Fig. 4. During the optimization, the nitroso groups of NM-12, NM-22 and (NM-21, NM-23) pair have been rotated around the N-N bond by 72.89°, 95.50°, and 66.10°, respectively. These rotations may be assigned to the electrostatic repulsion between the oxygen, nitrogen and sulfur electrons lone pairs. The eclipsed orientation of lone pairs in the theoretical planar structures increases the electrostatic repulsion. But, the orientation of lone pairs in the optimized structures is staggered, which considerably reduce the electrostatic repulsion. The energy gaps between the initial and final structures reveal the difference of electrostatic repulsion between the eclipsed and staggered orientations of lone pairs. The corresponding values of NM-12, NM-22, and NM-21 and NM-23 pair are about 31.76, 36.86, 73.50 and 40.12 kJmol[-1], respectively. Surprisingly, NM-11 with S-H···O intramolecular hydrogen bond is the least stable form. Also, there are significant energy difference between the least stable NM-11 form and other conformers. This instability is mainly due to the eclipsed orientation of five NM-11 lone pairs, which are maximized the repulsions. Furthermore, all of the computational levels emphasize on NMc as the most stable form whereas the relative energies of NMa, NMb and NM-24 are close or nearly degenerate (Table 2).

It seems that the energy order of NM conformers, similarly TN forms, is related to electrostatic repulsions and electron delocalization factors. The eclipsed and staggered orientation of lone pairs in the theoretical planar structures of NM conformers and their total values of charge transfer

energies are shown in Fig.5 and Table.4. Results in Table 4 and Fig.5, Clearly show that the energy order of NM conformers is related to outcome influence of mentioned factors. For example the total values of charge transfer energies of the most unstable form NM-11and the most stable form NMc are about 173.7 and 97.8 kcalmol[-1], respectively. As well as in the NM-14 and NM-24, which differ only in $\omega_{N=N-S-H}$ dihedral, reveals the repulsion between the sulfur-nitrogen lone-pairs. This repulsion energy at B3LYP/6-311++G (d,p) level is about 1.44 kJ mol^{-1}. (Fig.5) While the total values of charge transfer energies of NM-14 and NM-24 are about 64.44 and 58.59 kcal mol^{-1}, respectively. These results clearly show that the electrostatic repulsion is a superior factor in the relative stability of these conformers .But in the other conformers such as NMa, NMb and NMc, as shown in the table.4, charge transfer energies plays an important role in their energy order.

3.1.3. HT Tautomer

Similarly of NM conformers, eight planar HT conformers were proposed (Fig. 2). All of these theoretical forms were fully optimized by MP2 and B3LYP methods with standard basis set, 6-311++G (d,p). The absence of imaginary frequency reveals that all of these planar forms have a particular local minimum on the potential energy surface of molecule. After full optimization, HT-21 converts to HT-23. During the optimization, the thionitroso group of HT-21 has been rotated around the N-N bond by 118.7°. This rotation may be assigned to the electrostatic repulsion between the nitrogen-nitrogen electron lone pairs that shown in Fig.6. The energy gaps between the HT-21 and HT-23 structures reveal the difference of electrostatic repulsion between the nitrogen-nitrogen electron lone pairs. The corresponding value is about 11.23 kJmol[-1].

Similarly NM-11 form, HT-11 with O-H···S intramolecular hydrogen bond is the least stable form that after full optimization converts to HT-13. Also, HT-13 with O-H···N hydrogen bond, in a five membered ring, is not among the most stable forms. There are significant energy difference between the least stable (HT-11, HT-13) pair and other conformers. This instability is mainly due to the eclipsed orientation of five (HT-11) and four (HT-13) lone pairs, which are maximized the repulsions. Furthermore, all of the computational levels emphasizes on HT-24 as the most stable form whereas the relative energies of HT-14 and HT-24 are close or nearly degenerate. It seems that the greater stability of HT-14 and HT-24, with respect to other HT forms, is related to the minimization of electrostatic repulsions, owing to the staggered direction of lone pairs.

The energy gap between HT-11 and HT-13, which differ only in $\omega_{N=N-N=S}$ dihedral, reveals the repulsion between the nitrogen-nitrogen lone-pairs. This repulsion energy at B3LYP/6-311++G (d,p) level is about 28.37kJ mol^{-1} while these repulsion energy is lower than the corresponding value of dinitrosoamine(NH-11 and NH-13), 36.42kJ mol^{-1} [12]. Finally, the total values of charge transfer energies of HT-14,

HT-24, HT-11and HT-13, are about 76.92, 84.46, 143.23 and 114.79 kcalmol^{-1}, respectively. These results clearly show that the electrostatic repulsion is a superior factor in the relative stability of the HT forms.

3.2. Tautomeric Preference

Up to this point, we only identified the equilibrium conformations of tautomers and examined their preferences. These tautomers (TN, NM and HT) can be converted to each other by tautomeric equilibrium (Fig. 1). As previous mentioned, TN tautomer is slightly stable than the others, which is followed by HT and NM tautomers. This energy gaps can be related to the various factors such as tautomerization process, nitrosamine and thionitrosamine resonance of TN tautomer and π-electron delocalization of NM and HT tautomers.

Enolization of keto functional group destabilize the molecule, because C=O, C-C and C-H bonds are broken and C-O, C=C and O-H bonds are formed. Based on bond average energies, the energy difference between the keto and enol forms of acetaldehyde is about 56 kJ mol^{-1}, which is near to the computational energy gap [24]. By quantum chemical calculation at MP2/6-311++G (d,p) level we approximately obtained the same value [25]. In the same manner, it can be estimated the energy difference between the (nitrosamine, hydroxy-diazene) and (thionitrosamine, 1-mercaptodiazene) tautomers of the parent nitrosamine and thionitrosamine molecules (Fig. 7). From the average bond energies, this energy gaps between two tautomeric processes were estimated to be about 73 and 78kJ mol^{-1}, respectively. These values show the energy gaps among of the TN, NM, and HT tautomers. Our computational results, at B3LYP/6-311++G (d,p) level, are in agreement with these conclusions. However, the theoretical energy gap between these tautomers is about 12.3 and 26.6 kJ mol^{-1}, which is considerably lower than the previous values, 73 and 78 kJ mol^{-1}. Probably, these differences are mainly due to the especial donor-acceptor charge transfers, which is usually, entitle as nitrosamine and thionitrosamine resonance. Similar to amide resonance, the nitrosamine and thionitrosamine resonance are ones of the most important stabilizing factors in TN tautomer with respect to NM and HT tautomers. In TN forms, the central nitrogen heteroatom can delocalize the electrons of its lone pair into the π* antibonding orbital's of nitroso and thionitroso functional groups. The most obvious feature of this phenomenon is lengthening of the N=O and N=S bonds, shortening of the N-N bonds, coplanarity of attached atoms, restricted rotation around the N-N bond and red shift nitroso and thionitroso stretching frequency. For instance, the (N=O, N=S) bond length of TN-1, TN-2, TN-3 and TN-4 are about (1.183, 1.601), (1.184, 1.603), (1.197, 1.602) and (1.198, 1.604) Å, respectively (see Table 3). It is apparent that these values are different from the corresponding N=O bond length of dinitrosamine with $R_{N=O}$=1.208 Å and refer to significant role of sulfur heteroatom in more delocalize the central nitrogen electrons

lone pair. [12] Hence, these results show that thionitrosamine resonance is higher than of nitrosamine resonance and can be considered as superior factor in the stability of TN forms.

Although, the nitrosamine and thionitrosamine resonance can be evaluated by various methods such as geometrical parameters, rotational barrier of N-N and AIM analyses, the significant of charge transfer associated with these resonance can be carefully calculated by the second order perturbation theory in NBO analyses [26-29]. The NBO population analyses of TN conformers also reveals that the (LP (N) → π*$_{N=O}$, LP (N) → π*$_{N=S}$) charge transfers of TN1, TN2, TN3 and TN-4 are about (22.62, 24.13), (44.72, 59.13), (46.12, 48.70) and (47.51, 57.11) kJ mol^{-1}, respectively. These values are in good agreement with the results of geometrical parameters and can be comparing with N-formylformamide and dinitrosamine [30, 12].

Also, in order to investigation of energy gap between NM and HT tautomers the total donor–acceptor charge transfer energies of NM and HT forms, at B3LYP/6-311G(d,p) level of theory, were calculated. Results of calculations show that the total values of charge transfer energies of NM and HT tautomers are about the 87.25 and 104.06 kcal mol^{-1}, respectively. Furthermore, the geometrical parameters of NM and HT tautomers were extracted from outputs files. The average R (N-N) and R (N=N) for all of the plausible conformers of NM and HT are about 1.366, 1.248, 1.341 and 1.253 Å, respectively. These results are in good agreement with the energy gap of NM and HT forms. Finally, we found that these three factors, tautomerism, thionitrosamnie resonance and charge transfer energy can be rationalized the energy gaps of TN, NM and HT tautomers. In the present study, we also investigated the proton transfer in TN↔NM and TN↔ HT tautomerism. Some of the plausible equilibriums with their forward and backward potential energy barrier height (E_a) are given in Table 5. It is evident that, in all of the equilibriums, the backward energy barrier is lower than the corresponding forward energy barrier (Fig. 8). Also, it can be concluded from Fig.8 that the average difference backward and forward energies of NM→TN and HT→TN are about 51.7 and 10.07 kJ mol^{-1}, respectively. These results clearly show that the NM→TN and HT→TN are more favorable than the reverse process and emphasize on the more stability of HT with respect to NM tautomer. Consequently, we found that the kinetically and thermodynamically tendencies are collinear and consistent with the tautomeric preference results.

4. Hydrogen Bond

Although, structures with the intramolecular hydrogen bond (IMHB) in five and six membered rings such as NM-11, NM-13, HT-11 and HT-13 are not present among the most stable forms, it is necessary to study the IMHB of them and evaluate the effect of hetero atoms N and S on the nature of hydrogen bond. Therefore, we estimated the IMHB energy of NM-11, NM-13, HT-11, HT-13 and MA by various

models, such as electron density analysis of Espinosa, energy-geometry correlation of Musin and Mariam and isodesmic reactions method of Alkorta. Also, these results were compared with the results from dinitosamine molecule [12]. The calculated IMHB energies, at various computational levels, are gathered in Table 6. According to the results of isodesmic reaction method, the IMHB energy of NM-11 is greater than the MA. Whereas, both of the energy–geometry correlation and the electron density analysis Espinosa emphasize on HT-11 as a chelated form with the strongest hydrogen bond, that is followed by MA, NM-11, HT-13 and NM-13. In the isodesmic reactions method, the energy of the hydrogen bond is equal to the energy difference between the reactants and products of a suitable isodesmic reaction (Fig.9). However in products, a five membered ring with IMHB can be formed, which is shown by a dashed line that connects the H atom and NH2 group. Due to this interaction, the isodesmic approach is unsuitable for estimation the IMHB energy. Hence, the results of electron density analysis and energy–geometry correlation are more reliable. Consequently, the presence of three nitrogen heteroatom's (N) decreased the IMHB strength of NM-11 with respect to the chelated form of

malonaldehyde, while the suitable position of sulfur atom in the HT-11 is a significant factor in its IMHB strength.

The geometrical parameters can be applied for qualitative description of IMHB strength. The selected geometrical parameters of chelated enol form of MA, NM-11, HT-11, NM-13 and HT-13 are gathered in Table 7. It is well known that with strengthening of the X–H···X(X=O, S) hydrogen bond, $R(X \cdots X)$ and $R(H \cdots X)$ decrease and $R(X–H)$ increases. For example, the values of $R(X \cdots X)$ and $R(H \cdots X)$ for chelated forms of (NM-11, HT-11, MA) are about (2.852, 2.523, 2.584) and (2.127, 1.618, 1.695,) Å, respectively. These values clearly show that the IMHB of HT-11 is stronger than the NM-11 and MA (Table 7). This conclusion is also in agreement with the results of electron density analysis and energy-geometry correlation methods. Recently, we found a linear correlation between the RRM energies and $R(X \cdots X)$; $E_{RRM} = 128.06\ R_{X \cdots X} - 379.12$, in malonaldehyde derivatives as a set of ideal RAHB systems [31]. According to this equation, the corresponding RRM energies of NM-11, HT-11 and MA are about 13.89, 56.02 and 48.08 kJ mol^{-1}, respectively. These results again support the previous conclusion.
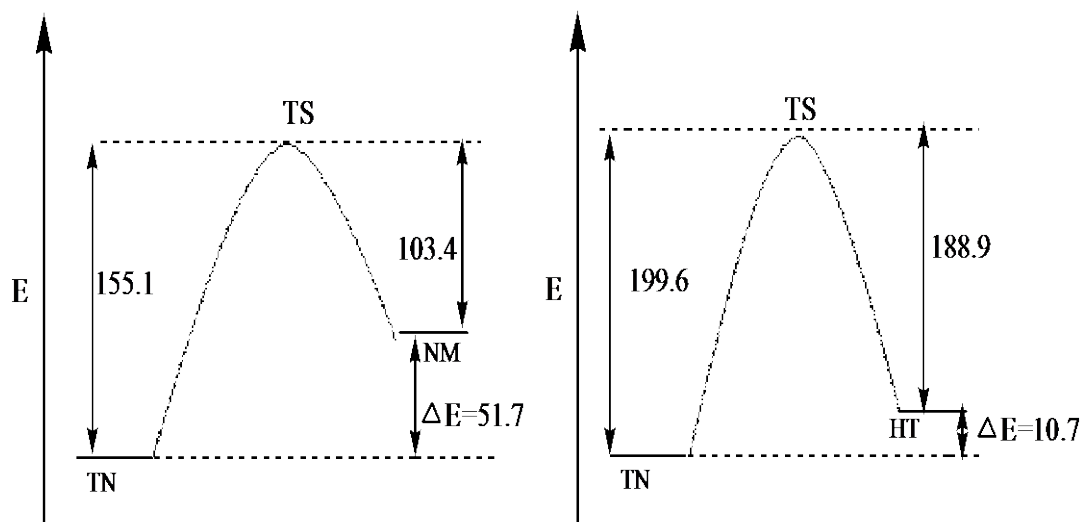

Figure 8.   The forward and backward potential energy of the barrier height of TN↔NM and TN↔ HT
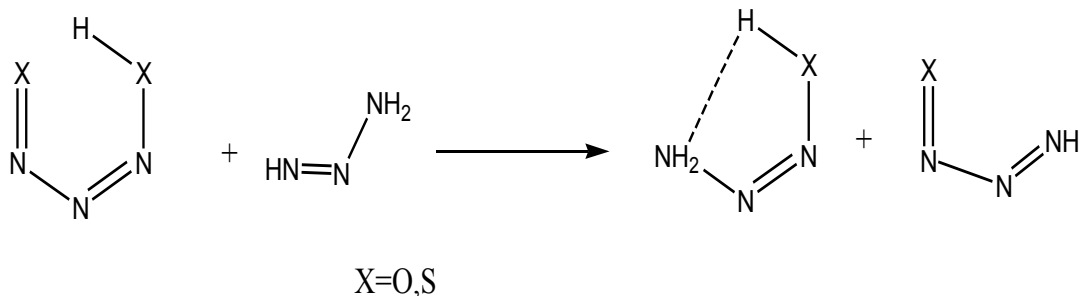

X=O,S

Figure 9.   Isodesmic reaction representation for estimate IMHB

The QTAIM is a powerful tool in characterization and qualitative description of IMHB. In order to get a deeper knowledge of the nature of possible hydrogen bonds, a topological analysis of electronic charge density, ρ_{BCP}, and its Laplacian, $\nabla^2\rho_{BCP}$ were performed. The topological parameters of chelated enol form of MA, NM-11, HT-11, NM-13 and HT-13 at the B3LYP/6-311++G (d,p) level, were evaluated and collected in Table 8. The electron densities and their Laplacian at BCPs evidently show that the IMHB in HT-11 is the strongest that follow by MA, NM-11, HT-13 and NM-13. Moreover, from the correlation between IMHB energy and electron density, we can easily evaluate the IMHB energy using the Grabowski and RRM equations. The obtained results strongly support the previous conclusion [31, 32].

The existence of hydrogen bond implies that a certain amount of electronic charge is transferred from the proton acceptor to the proton donor and a rearrangement of electron density within each part of molecule occurred. The NBO occupation numbers for the proton donor antibond, lone pairs and their respective orbital energies (ε) at the B3LYP/6-311++G (d,p) level were evaluated and gathered in Table 9.

Table 6. The hydrogen band energy of conformers with IMHB at various level of theory (kJ mol^{-1})

Computational level	MP2	B3LYP
Espinoza HB energy		
HT-11	64.8	64.6
NM-11	33.1	33.9
MA	60.6	63.0
HT-13	23.0	22.2
NM-13	17.9	17.5
Mariam-HB		
HT-11	56.0	57.0
NM-11	19.7	18.3
MA	54.1	55.2
Isodesmic-HB		
HT-11	70.6	73.9
NM-11	57.2	59.1
MA	50.4	56.5
HT-13	23.8	24.9
NM-13	20.1	22.5

Table 7. The selected geometrical parameters of hydrogen bonded forms

Conformer	R(X…Y)^C	R(X-H)^C	R(X…H)^C	R(X…Y)^O	R(X-H)^O
HT-11	2.623	1.007	1.618	2.746	0.967
NM-11	2.852	1.327	2.127	2.934	1.321
MA-11	2.584	0.992	1.695	2.856	0.961
	R(N…X)^C	R(X-H)^C	R(N…H)^C	R(N…X)^O	R(X-H)^O
HT-13	2.634	0.986	2.017	2.643	0.967
NM-13	2.948	1.330	2.376	2.954	1.234

C: Close   O:Open

Table 8. The selected topological parameters of IMHB and ring critical points of hydrogen bonded forms

Conformer	ρ_{BCP}	$\nabla^2\rho_{BCP}$	H_{BCP}	ρ_{RCP}	$\nabla^2\rho_{RCP}$	H_{RCP}
HT-11	0.0568	-0.0413	0.0169	0.0375	-0.0377	-0.0071
NM-11	0.0236	-0.0230	0.0027	0.0204	-0.0213	-0.0043
MA-11	0.0521	-0.0382	0.0074	0.0213	-0.0349	-0.0055
HT-13	0.0222	-0.0207	0.0018	0.0195	-0.0196	-0.0035
NM-13	0.0172	-0.0139	-0.0010	0.0150	-0.0112	-0.0023

Table 9. The selected charge transfer energies of hydrogen bonded forms (kcal mol^{-1})

Conformer	LP(X)→σ* XH	ON$_{(LP)}$	ON$_{(\sigma^*)}$	E$_{(LP)}$ (a.u.)	E$_{(\sigma^*)}$ (a.u.)
HT-11	30.08	1.835(1.852)	0.158(0.004)	-0.327(-0.311)	0.292(0.378)
NM-11	10.60	1.871(1.875)	0.036(0.029)	-0.470 (-0.468)	0.156(0.163)
MA-11	28.67	1.870(1.887)	0.063(0.004)	-0.490(-0.423)	0.643(0.645)
HT-13	6.10	1.961(1.972)	0.041(0.004)	-0.535(-0.529)	0.330(0.368)
NM-13	0.58	1.955(1.960)	0.023(0.021)	-0.577(-0.574)	0.152(0.166)

The results in parentheses refer to the open forms.

In NBO analysis, charge transfer between the lone pairs of proton acceptor and proton donor antibond (σ^*) is the most significant descriptor of hydrogen bond.As we know, this charge transfer greatly changes the occupation number of the molecular orbital's which involved in IMHB. The occupation number of proton donor antibond (σ^*_{OH}) in non-hydrogen bonded forms is very small and near zero, while the corresponding value for proton acceptor lone pairs is near to the standard value of 2. The corresponding values in chelated enol forms with IMHB show a great change. These results can qualitatively predict the IMHB strength, which is consistent with the AIM analysis conclusion. The results of NBO analysis also show that in chelated forms, one or two lone pairs of proton acceptor and the proton donor antibond are involved and the corresponding stabilization energies of MA, NM-11, HT-11, NM-13 and HT-13 are about 21.93, 10.60, 30.08, 2.58 and 6.10 kcalmol^{-1}, respectively. These results re-emphasize on the previous conclusion that obtained from the geometrical and topological parameters.

5. Conclusions

Quantum chemical calculations, based on B3LYP and MP2 methods, are applied to study various aspects of potential energy surface of NTA. The results of ab-initio calculations were employed to evaluate the origin of conformational and tautomeric preferences. Additionally, the results of NBO and AIM analyses were used in order to estimate the IMHB strength. Following conclusions may be drawn from these theoretical calculations:

1. According to vibrational frequencies calculations, NTA has about eighteen equilibrium conformers.
2. At all of the theoretical levels, the TN forms have slight stability with respect to the other conformers. In addition, TN-4 form has greater stability with respect to the other forms and is global minima among the known local minimums.
3. A detailed investigation of equilibrium conformations clearly show that the energy order of conformers is related to outcome influence of two superior factors, the electrostatic repulsion and charge transfer energies.
4. A detailed investigation of tautomeric equilibrium clearly shows that three factors, tautomerism, thionitrosamine resonance and charge transfer energy can be rationalized the energy gaps of TN, NM and HT tautomers.
5. According to the results of isodesmic method, it can be concluded that this approach is unsuitable for estimation the IMHB energy. For instance, based on the isodesmic method the IMHB energy of NM-11 is greater than the MA. Whereas, the energy-geometry correlation method, the electron density analysis, geometrical, topological and molecular orbital descriptors suggest that the HT-11 has the strongest IMHB, which is followed by MA, NM-11, HT-13 and NM-13.

REFERENCES

[1] A.R. Tricker, R. Preussmann, 1991, Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential, Mutat. Res., 259, 277–289.

[2] A. R. Tricker, 1997, N-nitroso compounds and man: sources of exposure, endogenous formation and occurrence in body fluids, Eur .J. Cancer. Prev., 6, 226–68.

[3] P. Jakszyn, C. A. Gonzalez, 2006, Nitrosamine and related food intake and gastric and oesophageal cancer risk: a systematic review of the epidemiological evidence, World J. Gastroenterol. , 12, 4296–4303.

[4] L.A. Baker, S.Su, 1998, An ab initio molecular orbital study of the reaction NH2+NO → H2+N2O, Chem. Phys. 228(3), 9-16.

[5] S. A. do Monte, E. Ventura, T. F. da Costa S. R. de Santana, 2011, Ab initio and DFT conformational study on nitrosamine (H2 N–N=O) and N -Nitrosodimethylamine [(CH3)2 N–N=O], Struct. Chem., 22(3) 497-507.

[6] F. P. Guengerich, 2005, Human Cytochrome P450 Enzymes, 3rd, ed Kluwer Academic/Plenum New York.

[7] N. Xu, L. E.Goodrich, N.Lehnert, D. R.Powell, G. B. Richter-Addo, 2010, Five- and six-coordinate adducts of nitrosamines with ferric porphyrins: structural models for the Type II interactions of nitrosamines with ferric cytochrome P450, Inorg. Chem., 49, 4405-4419.

[8] F. V. Ezequiel, L.E. Ventura, O. Avio L, D. Santana, S. A. D. Monte, 2014, Electronic properties of the low-lying spin states of dimethylnitrosamine coordinated to Fe(III) heme models: An ab initio study, Int. J. Quant.Chem. 114, 508-520.

[9] H. Roohi, A. Ebrahimi, F.Alirezapoor, M. Hajealirezahi, 2005, AIM and NBO analyses of N–N rotational barrier in monocyclic nitrosamine compounds, Chem. Phys. Lett., 409, 212-218.

[10] H. Roohi, F. Deyhimi, A. Ebrahimi, 2001, Restricted rotation in five-membered cyclic nitrosamine compounds: DFT investigation of structural, energetic and kinetics properties, J. Mol. Struct. 543, 299-308.

[11] H. Roohi, F. Deyhimi, A. Ebrahimi, A. Khanmohammady, 2005, Restricted rotation in six-membered cyclic Nitrosamine compounds: an ab initio and DFT study and NBO analysis, J Mol. Struct. 718 , 123-132.

[12] P. Mohammadzadeh Jahani, A. Nowroozi, 2013, Conformational analysis, tautomeric preference, intramolecular hydrogen bonding, and solvent effect on dinitrosamine: A quantum chemical study, Int. J. Quant. Chem., 113, 1026-1033.

[13] G. Gilli, P. Gilli, 2009, the nature of the hydrogen bond: Outline of a comprehensive hydrogen bond theory, Oxford

University Press.

[14] A. Nowroozi, S. F. Tayyari, H. Rahemi, 2003, Fourier transforms infrared spectra and structure of triformylmethane. A density functional theoretical study, Spectrochim Acta A, 59(8) 1757-1772.

[15] A. Nowroozi, H. Raissi, 2006, Strong intramolecular hydrogen bond in triformylmethane ab-initio, AIM and NBO study J. Mol. Struct., 759 , 93-100.

[16] A. Nowroozi, H. Roohi, M. S. Sadeghi, M. Sheibaninia, 2011, the competition between the intramolecular hydrogen bond and π-electron delocalization in trifluoroacetylacetone—A theoretical study, Int. J. Quantum Chem., 111, 578-585.

[17] A. Nowroozi, A. F. Jalbout, H. Roohi, M. S. Sadeghi, H. Raissi, 2009, Hydrogen Bonding in Acetylacetaldehyde: Theoretical Insights from the Theory of Atoms in Molecules Int. J. Quantum. Chem., 109, 1505-1515.

[18] M. S.Gordon, M. W.Schmidt, C. E. Dykstra, G. Frenking,; K. S. Kim, G. E. Scuseria, 2005, Theory and Applications of Computational Chemistry: the first forty years and Advances in electronic structure theory: GAMESS a decade later, 1167-1189.

[19] F. Biegler-König, J. Schönbohm, D. A. Bayles, Aim 2000: Program To Analyze And Visualize Atoms In Molecules, University Of Applied Science, Bielefeld Germany.

[20] E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, F. Weinhold, 2001, Theoretical Chemistry Institute, University of Wisconsin, Madison, WI.

[21] E. Espinosa, E. Molins, 2000, Retrieving interaction potentialsfrom the topology of electron density distribution: The case of hydrogen bonds, J. Chem. Phys., 113(14) 5686-5694.

[22] R. N. Musin, Y. H. Mariam, 2006, An integrated approach to the study of intramolecular hydrogen bonds in malonaldehyde enol derivatives and naphthazarin: trend in energetic versus geometrical consequences, J. Phys. Org. Chem., 19, 425-444.

[23] I. Rozas, I. Alkorta, J. Elguero, 2001, Intramolecular

Hydrogen Bonds in ortho-Substituted Hydroxybenzenes and in 8-Susbtituted 1-Hydroxynaphthalenes: Can a Methyl Group Be an Acceptor of Hydrogen Bonds, J. Phys. Chem. A, 105(45), 10462-10467.

[24] L. Pauling, 1931, The Nature of the Chemical Bond, J. Am. Chem. Soc., 53(4) 1367-1400.

[25] A. Nowroozi, H. Roohi, M. S. Sadeghi, M. Sheibaninia, 2011, Conformational and tautomeric preferences in 3-aminoacrylaldehyde: A theoretical study, Int J. Quantum Chem., 111, 586-595.

[26] L. Xiao-Hong, T. Zheng-Xin, Z. Xian-Zhou, 2009, PCM study of bond dissociation energies in N-nitroso compounds, J. Mol. Struct., 899, 42- 45.

[27] K. Anandan, P. Kolandaivel, R. Kumaresan, B.G. Gowenlock, 2004, Quantum chemical studies on structure, conformation and isomerization of nitroso, nitro substituted benzene and 1,3-cyclopentadiene, J. Mol. Struct., 680, 149-157.

[28] A. Nowroozi, H. Raissi, 2006, Strong intramolecular hydrogen bond in triformylmethane ab-initio, AIM and NBO study, J. Mol. Struct., 759, 93-100.

[29] D. Nori-Shargh, H. Yahyaei, J. E. Boggs, 2010, Stereoelectronic interaction effects on the conformational properties of hydrogen peroxide and its analogues containing S and Se atoms: An ab initio, hybrid-DFT study and NBO analysis, J. Mol. Graphics. Modell. 28(8), 807-813.

[30] A. Nowroozi, P. Mohammadzadeh Jahani, N. Asli, H. Hajiabadi, S. Dahmardeh, H. Raissi, 2012, Evaluation of the origin of conformational and tautomeric preferences in N-formylformamide – A quantum chemical study, Int. J. Quantum. Chem., 112(2) 489-597.

[31] S. J. Grabowski, 2001, an estimation of strength of intramolecular hydrogen bonds — ab initio and AIM studies, J. Mol. Struct., 562, 137-143.

[32] A. Nowroozi, H. Raissi, H. Hajiabadi, P. Mohammadzadeh Jahani, 2011, Reinvestigation of intramolecular hydrogen bond in malonaldehyde derivatives: An ab initio, AIM and NBO study Int. J. Quantum. Chem., 111(12), 3040-3047.