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DFT Investigation on the Electronic Properties and Intramolecular Hydrogen Bond of *Trans-Cis* and *Cis-Trans* Methyl Substituted N-Benzoyl-N'-(2-pyridyl)thiourea

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Abstract: Five single molecule methyl substituted Benzoyl pyridinylthiourea compounds namely N-benzoyl-N'-(2-pyridyl)thiourea, N-benzoyl-N'-(6-methyl-2-pyridyl)thiourea, N-benzoyl-N'-(5-methyl-2-pyridyl)thiourea, N-benzoyl-N'-(4-methyl-2-pyridyl) thiourea and N-benzoyl-N'-(3-methyl-2-pyridyl)thiourea are investigate theoretically for *trans-cis* and *cis-trans* conformation at B3LYP 6-31G(d,p) level of theory. Electronic properties have been analyzed by Gaussian 09W package and AIMAll code. Methyl substituent and its position give noticeable effect to reactivity, stabilization, and hydrogen bond interaction strength. AIM prove that 6-methyl substituted on pyridyl ring has significant effect to preferent conformation.

Keywords: Benzoyl pyridinylthiourea, DFT, AIM, electronic properties, intramolecular hydrogen bond.

1. Introduction

Benzoyl pyridinylthiourea derivatives have wide range of chemical and biological activity i.e. metal extraction, anion detection, antitumor, antibacterial, antifungal, antitubercular, antithyroid, antihelmintic, insecticidal, herbicidal and plant growth regulator properties. The different functionalities of the compound are cause by vary in electronic property and conformation [1-3]. The compounds show diverse conformational and stabilized by intramolecular hydrogen bond (HB) [4]. The strength of intramolecular HBs and electronic properties are depending on the nature, size and position of the substituent groups [5]. *N*-benzoyl-*N'*-phenylthiourea derivatives stabilized by intramolecular HB (O···H-N) that form pseudo-six membered ring. Thus, adopt *trans-cis* conformation across the thiourea moieties that have been experimentally and theoretically studied [6–10] but *N*-Benzoyl-*N'*-(2-pyridyl)thiourea derivatives can form O···H-N and N···H-N intramolecular HB leads to *trans-cis* [11-14] and *cis-trans* [15-18] conformation respectively and both producing pseudo-six membered ring. However, *cis-trans* conformations are very rare. All the *cis-trans* crystalized N-Benzoyl-*N'*-(2-pyridyl)thiourea derivatives have a methyl substituted group adjacent to the pyridyl nitrogen heteroatom (6-methyl). We have chosen five compounds namely *N*-benzoyl-*N'*-(2-pyridyl)thiourea (**I**), *N*-benzoyl-*N'*-(6-methyl-2-pyridyl)thiourea (**II**), *N*-benzoyl-*N'*-(5-methyl-2-pyridyl)thiourea (**III**), *N*-benzoyl-*N'*-(4-methyl-2-pyridyl) thiourea (**IV**) and *N*-benzoyl-*N'*-(3-methyl-2-pyridyl)thiourea (**V**) to clarify whether the methyl substituent and its position affect the electronic properties and intramolecular HB (Fig. 1**)**.

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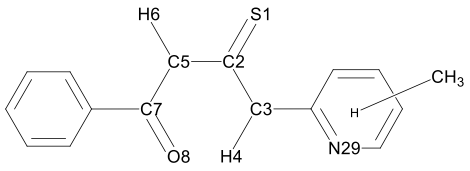
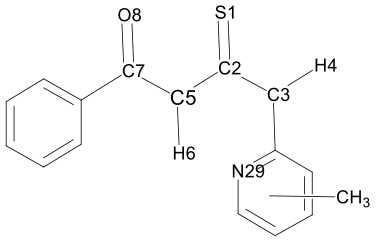
2. Computational Method

Input preparations in the calculations on single molecules of **I – V** were constructed using GaussView 5.0 [19]. The quantum calculations of the electronic properties of compound **I - V** were performed with Gaussian 09W [20] software package. Single molecule optimization and all the electronic properties calculation were carried out with Density Functional Theory (DFT) method. The hybrid functional B3LYP based on Becke's three-parameter exchange potential functional and Lee's correlation functional [21] with 6-311G(d.p) basis set is used.



(a)



(b)

Fig. 1-*Trans-cis* (A) and *cis-trans* (B) schematic diagram for compound **II** (6-methyl), compound **III** (5-m4thyl), compound **IV** (4-methyl) and compound **V** (3-methyl)

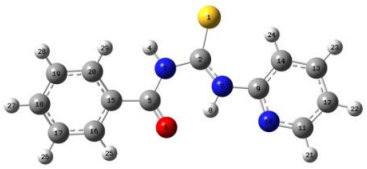
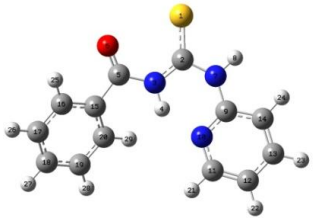
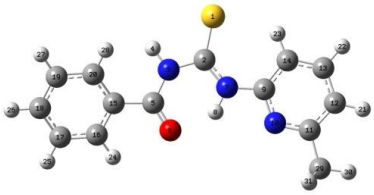
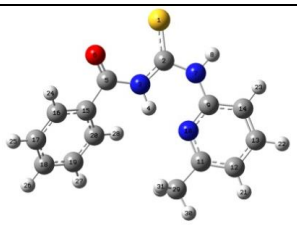
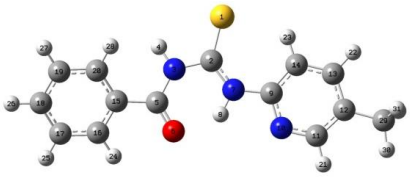
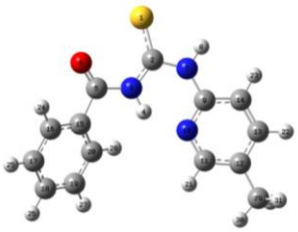
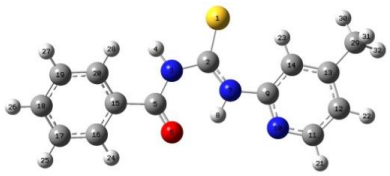
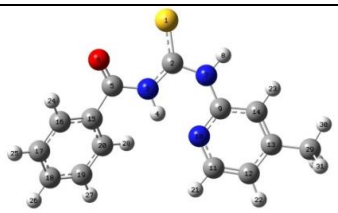
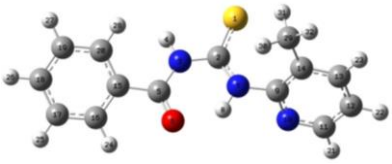
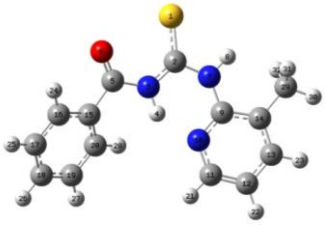
The intramolecular HB in two conformers of optimized methyl substituted *N*-Benzoyl-*N'*-(2-pyridinyl)thiourea is analyzed by Atom In Molecule theory (AIM) [22]. It's the powerful toll for prediction of inter and intramolecular HBs and comparison of their strength. In this work, we use AIMAll code [23].

3. Result and Discussion

3.1 Structural Optimization

Compounds **I-V** can adopt several conformational isomers by rotating the two thioamidic bond (C2-N3 and C2-N5). In this present work, optimization of compounds **I-V** has been employed for the conformation of *trans-cis* and *cis-trans* without symmetry constraint. Those conformers were found to be at minimum energy state. This was confirmed by frequency calculation at the same level of theory and has no imaginary frequency. *Trans-cis* conformer form C2-N5-C7-O8···H4-N3 pseudo-six membered ring stabilized by O8···H4-N3 intramolecular HB and *cis-trans* conformer form C2-N3-C9-N29···H6-N5 pseudo-six membered ring through N29···H6-N5 intramolecular HB. Table 1 shows the optimized structure with its energy. *Trans-cis* conformer is more stable compared to *cis-trans* conformer in a single molecule. On top of that, compound **II** is the most stable in both conformations. This indicates that the combination of appropriate positioning of a pyridyl heteroatom (N29) and its substituted methyl group increases the stability of the molecule **II**. Where, the methyl group position is adjacent to the N(29).

Table 1 - Optimized structure of compound I-V for *trans-cis* and *cis-trans* conformation with energy calculated at B3LYP/6-311G(d,p) level of theory

Compound	*tran-cis*	*cis-trans*
I		
E (Hatree)	-1139.926	-1139.916
II		
E (Hatree)	-1179.257	-1179.247
III		
E (Hatree)	-1179.254	-1179.244
IV		
E (Hatree)	-1179.255	-1179.246
V		
E (Hatree)	-1179.248	-1179.244

3.2 The Global Chemical Indexes

Global Chemical Indexes is used to describe the electronic properties based on The Koopman's theorem. which are Highest Occupied Molecular Orbital, HOMO energy (E_{HOMO}) is related to the Ionization Potential (*IP)* and the Lowest Unoccupied Molecular Orbital, LUMO energy (E_{LUMO}) is used to estimate the Electron Affinity (*EA)*, Chemical Potential (μ), Chemical Hardness (η), Electronegativity (χ) . The theorem stated that in a system contain N number of electrons; the ground-state electronic energy is the function of the number of electrons, $E(N)$, the derivative of $E(N)$ at a constant external potential $V(\vec{r})$, is the chemical potential, μ or the negative of the absolute electronegativity, $-\chi$ (eq.1).

$$\mu \sim \left(\frac{\delta E}{\delta N}\right)_{V(\vec{r})} = -\chi \qquad (1)$$

The second derivative of $E(N)$ at a constant external potential $V(\vec{r})$ will give chemical hardness η (eq.2)

$$\eta = \frac{1}{2}\left(\frac{\delta^2 E}{\delta N^2}\right)_{V(\vec{r})} = \frac{1}{2}\left(\frac{\delta \mu}{\delta N}\right)_{V(\vec{r})} \quad (2)$$

Thus,

$$\chi = \frac{(E_{HOMO}+E_{LUMO})}{2} \quad (3)$$

And

$$\eta = \frac{(E_{HOMO}-E_{LUMO})}{2} \quad (4)$$

Chemical potential, μ is useful for describing physical phenomena and processes, such as phase transitions, nuclear reactions and chemical hardness η signifies the resistance towards the deformation of the electron cloud under small perturbation that encountered during a chemical reaction [24-28]. Another parameter is proposed by Parr [29] is the global electrophilicity, ω contains information about both electron transfer (chemical potential) and stability or hardness. It also encompasses both the ability of an electrophile to acquire an additional electronic charge and the resistance of the system to exchange electronic charge with the environment. Thus, defined as follows:

$$\omega = \frac{\mu^2}{2\eta} \quad (5)$$

Methyl is the inductive electron donating group. Its only increase the electron density to the existing conjugated system does not increase the conjugated system. By this reason methyl group has the capability to deactivate electrophilic character of a molecule. [30,31]. The global chemical indexes of conformer *trans-cis* for molecule **I**, **II**, **III**, **IV** and **V** are shown in Table 2. Methyl substituted compound **II**, **III, IV** and **V** decreases in chemical hardness and electrophilicity relatives to molecule **I**. This phenomenon gives an assumption that methyl substituted compounds increase their nucleophilic character and reactivity by two to four percent. The position methyl substituent in the pyridyl ring is based on IUPAC system relative thiourea moiety. *o*-methyl (compound **V**), *m*-methyl (compound **II** and **IV**) and *p*-methyl (compound **III**) relative to thiourea moiety. The decreasing order of electrophilicity is **II**, **IV**, **III** and **V**. Vary in electrophilicity values indicate that position of each methyl group contribute different percentage of its electron density form HOMO and LUMO.

The global chemical indexes of compound **I**, **II**, **III**, **IV** and **V** for *cis-trans* conformer were tabulated in Table 3. The μ values increases with the existence of methyl substituent group relative to molecule **I**. Meanwhile, compound **III**. has decreases. Thus, methyl substituent causes the molecule to become more stable except for compound **III**. Where compound **I** is the most stable. In contrast, methyl group decreases electrophilicity and the variation is less compared to *tans-cis* conformation. Meaning that in this conformation each position of methyl group contributes its electron density percentage in the formation of HOMO and LUMO more evenly.

Table 2 - HOMO and LUMO energy with a global chemical reactivity descriptor and percentage differences for molecule I-V calculated at B3LYP/6-311G(d,p) level of theory for *trans-cis* conformation.

	HOMO (kJ/mol)	LUMO (kJ/mol)	η	%Δ η	χ	%Δ χ	μ	ω	%Δ ω
I	-605.26	-211.20	197.03	-	408.23	-	-408.23	422.90	-
II	-600.71	-207.99	196.36	-0.34	404.35	-0.95	-404.35	416.33	-1.55
III	-599.72	-206.26	196.73	-0.15	402.99	-1.28	-402.99	412.75	-2.40
IV	-600.85	-207.41	196.72	-0.16	404.13	-1.00	-404.13	415.12	-1.84
V	-589.84	-201.09	194.38	-1.35	395.47	-12.8	-395.47	402.29	-4.87

Table 3 - HOMO and LUMO energy with a global chemical reactivity descriptor and percentage differences or molecules I-V calculated at B3LYP/6-311G(d,p) level of theory for *cis-trans* conformation.

	HOMO (kJ/mol)	LUMO (kJ/nol)	η	%Δ η	χ	%Δ χ	μ	ω	%Δ ω
I	-554.16	-190.56	181.80	-	372.36	-	-372.36	381.33	-
II	-551.67	-186.10	182.79	0.54	368.88	-0.94	-368.88	372.22	-2.39
III	-548.20	-185.49	181.36	-0.24	366.85	-1.50	-366.85	371.03	-2.70
IV	-548.94	-184.44	182.25	0.25	366.69	-1.52	-366.69	368.90	-3.26
V	-551.43	-186.57	182.43	0.35	369.00	-0.90	-369.00	373.18	-2.14

3.3 AIM Analysis of Intramolecular Hydrogen Bond

The quantum theory of atoms in molecules has been useful in the characterization of bonds through a topological analysis of the electronic charge density and their Laplacian at the bond critical point (BCP). In the AIM theory the nature of the bonding interaction can be determined through an analysis of the properties of the charge density, ρ, and it's Laplacian $\nabla^2(\rho)$ at the BCP, and through the properties of the atoms, which are obtained by integrating the charge density over the atom orbitals [32]. The Laplacian gives information about the tendency of electron density to accumulate or deplete between the nuclei. Analyzing the sign of the Laplacian, one can define the regions where the charge density is concentrated ($\nabla^2(\rho) < 0$) indicates a shared interaction such as lone pairs and covalent bonds or depleted ($\nabla^2(\rho) > 0$) shows where the electron density is declining as in ionic, HBs and van der Waals interaction. Typical ranges of ρ and $\nabla^2(\rho)$ for HB in BCP are about 0.002–0.040 a.u. and 0.024–0.139 a.u., respectively [33]. According to Rozas *et al*. [34] energy density at the BCP (H_{BCP}) has proved to be a more sensible and appropriate index than $\nabla^2(\rho)$ to characterize the nature of HBs [35]. Thus, HBs have been classified as follows: Weak HB interactions show both $\nabla^2(\rho)_{BCP}$ and $H_{BCP} > 0$, and medium HB interactions show $\nabla^2(\rho)_{BCP} > 0$ and $H_{BCP} < 0$, while strong HB interactions show both $\nabla^2(\rho)_{BCP}$ and $H_{BCP} < 0$. Energy density can be determine by equation 8.

$$H_{BCP} = G_{BCP} + V_{BCP} \qquad (6)$$

Where, G_{BCP} is electron kinetic energy density, V_{BCP} electron potential energy density and H_{BCP} total electron energy density at the BCPs [36]. HB energies for all the conformers under investigation were evaluated by the Espinosa–Molins–Lecomte [37] formula based on the electron density distribution at the BCPs:

$$E_{HB} = \frac{1}{2}V_{BCP} \qquad (7)$$

Table 4 - Electron density (ρ_{BCP}), Laplacian ($\nabla^2(\rho)_{BCP}$), electron kinetic energy density (G_{BCP}), electron potential energy density (V_{BCP}) total electron energy density (H_{BCP}), ellipticity (ε) and HB energy ($E_{inta\ HB}$) at the bond critical point (BCP) calculated by AIM analysis at B3LYP/6-311G(d,p) level.

				O8···H4 intra HB			
molecule	ρ	$\nabla^2(\rho)$	ε	G_{BCP}	V_{BCP}	H_{BCP}	$E_{intraHB}$(kJ/mol)
I	0.0348	0.1238	0.0045	0.0300	-0.0291	0.0009	-38.32
II	0.0347	0.1236	0.0046	0.0300	-0.0290	0.0009	-38.17
III	0.0347	0.1237	0.0044	0.0300	-0.0291	0.0009	-38.26
IV	0.0346	0.1232	0.0050	0.0298	-0.0289	0.0010	-37.98
V	0.0339	0.1216	0.0179	0.0292	-0.0280	0.0012	-36.86
				N29...H6 intra HB			
I	0.0397	0.1139	0.0347	0.0309	-0.0333	-0.0024	-43.81
II	0.0388	0.1115	0.0369	0.0300	-0.0321	-0.0021	-42.23
III	0.0397	0.1138	0.0347	0.0009	-0.0334	-0.0325	-43.87
IV	0.0401	0.1145	0.0355	0.0312	-0.0339	-0.0026	-44.53
V	0.0409	0.1153	0.0353	0.0318	-0.0348	-0.0030	-45.73

Column 2 and 3 in Table 4 shows the value of ρ and $\nabla^2(\rho)$ for Intramolecular HB, O(8)···H(4) and N(29)···H(6) of *trans-cis* and *cis-trans* conformer respectively. The ρ and $\nabla^2(\rho)$ values lie within the above-mentioned AIM range for both conformers and the positive sign of $\nabla^2(\rho)$ shows electron density has been depleted that true for HB. In *trans-cis* conformation methyl substituent reduces the value of $\nabla^2(\rho)$. It mean that the electron density increases at BCP but very

small increment. Only compound **V** (*o*-methyl) has the value of $\nabla^2(\rho)$ less than compound **I** which is does not has the methyl substituent. This could be due to the obstructing of electron delocalization by the absent of planarity of pyridyl ring because of the repulsive nature between S(1) and methyl group.

By comparison, $\nabla^2(\rho)$ value for *cis-trans* conformer is lower compare to *trans-cis* conformer indicate that electron density increases at BCP. Noticeably, compound **II** (*m*-methyl) has the lowest $\nabla^2(\rho)$ value and has the highest electron density at BCP. This mean methyl at 6th position on the pyridyl ring gives significant effect to BCP electron density. Where, the inductive electron donating property of methyl group more effective at this position because it's the nearest to the intramolecular BH acceptor N(29). In column 7 of Table 4 shows BCP total energies density for the studied compounds and noteworthy intramolecular HB for *trans-cis* are classified as weak HBs but for *cis-trans* classified medium HBs. The formation of O(8)···H(4)N(3) and N(29)···H(6)C(5) intramolecular HB arise from different type of hydrogen bond acceptor. O(8) is the ordinary hydrogen bond acceptor but N(29) is included in the π acceptor system of pyridyl ring that makes it more electronegative [38]. Thus, increases the stability of N(29)···H(6)C(5) intramolecular HB. The last column in Table 4 shows the HB energy that support the intramolecular HB of *cis-trans* is more stable.

The ellipticity (ε) at the BCP is a sensitive index to monitor the π-character of bond. The lower values of ellipticity index confirm that there is electron delocalization through the corresponding atoms. However, the higher ellipticity values indicate that the electrons of these bonds are not delocalized [39]. O(8)···H(4)N(3) HBs have high electron delocalization but N(29)···H(6)C(5) HBs have high electron localization and compound **II** in *cis-trans* conformation is the highest ellipticity, therefore the strongest HB in this study.

4. Conclusion

In this work, the electronic properties of *trans-cis* and *cis-trans* methyl substituted *N*-Benzoyl-*N'*-(2-pyridyl)thiourea compounds were investigated using B3LYP method and 6-311G(d,p) level of theory. The total energy of optimized structure indicates *trans-cis* conformation is more stable than *cis-trans* conformation and both conformers are stabilized by intramolecular HB. Compound **II** is the most stable in both conformations. Generally, methyl substituent group increases and decreases the molecule reactivity in *trans-cis* and *cis-trans* conformation respectively. In addition, the electron density percentage donation of methyl group depends on its position in both conformers. AIM approach shows the involvement of π system increases the hydrogen bond interaction in *cis-trans* conformation. Especially compound **II** where it has the lowest value of Laplacian and highest ellipticity indicate high electron density at bond critical point, thus making the strongest intramolecular HB in both conformations. The position of methyl substituent adjacent to nitrogen heteroatom strengthens hydrogen bond interaction.

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