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Stability Analysis on the Polymorphic Compound of Thiourea Derivatives: 1,3-Bis(1-(4-Methylphenyl)Ethyl)Thiourea

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ABSTRACT: *Polymorphism is the ability of a compound to form more than one crystalline form in the solid state. Compounds having this ability would display different stabilities for different forms, hence affecting its applicability. Symmetrically substituted thiourea derivatives have been shown to be polymorphic due to the flexibility of the C–N bond. One of this type of compounds, known as 1,3-bis(1-(4-methylphenyl)ethyl)thiourea, is studied on its stabilities and ability to exist in different forms. Since the molecule of this compound was experimentally found to exist in trans-trans configuration, the stability of the cis-trans and cis-cis configurations are assessed using theoretical calculations. Rotations along the C–N bonds are performed using Gaussian 09 suite program. Level of method B3LYP, complemented by basis set DEF2-TZVP, is used. The stability of the molecules in different configurations is then studied in terms of its interactions using reduced density gradient. Apart from the original trans-trans configuration, with the difference of 0.024 eV, cis-trans configuration are also possible to exist. Next possible configuration is cis-cis with relative energy 1.8412 eV. Both the non-covalent CH···HN and CH···S interactions are found to provide stabilising effect in the cis-trans and trans-trans configurations.*

Keywords: Polymorphism, thiourea derivatives, density functional theory, topology analysis, non-covalent interactions.

1. INTRODUCTION

Polymorphism is a phenomenon where a compound can exist in different configurations. Its unexpected and unavoided occurrences gained interest from various industries.[1] Since different forms lead to different properties, the different forms would affect their roles in industries.[2] In this report, the focus is on 1,3-bis(1-(4-methylphenyl)ethyl)thiourea, $C_{19}H_{24}N_2S_1$ which is a thiourea derivatives compound known as HAMFIL with ((methylphenyl)ethyl) group attached at the terminal two N atoms.[3] The HAMFIL is like other thiourea derivatives, exhibiting potent inhibiting characteristics that will prevent a particular chemical reaction, or reduce the activity of a particular reactant or catalyst. HAMFIL exists with total symmetry with respect to its substituents where the bond, angle and torsion angle are the same for both sides of the molecule, as shown in Figure 1. The stabilities and ability to exist in different forms of groups are studied. The stability of the *cis-trans* and *cis-cis* configuration are assessed using theoretical calculations.

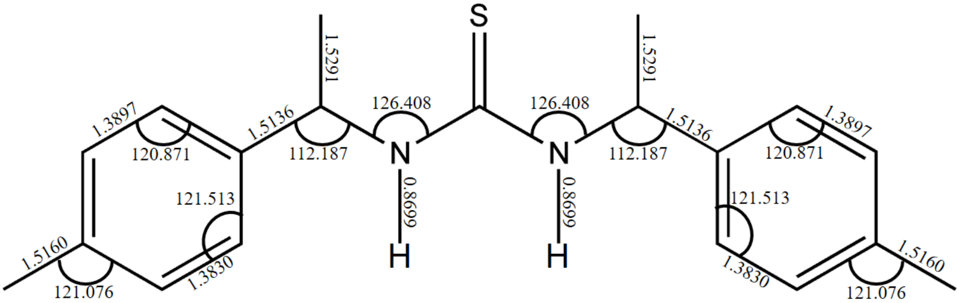

Figure 1: Molecular structure of HAMFIL and its bond lengths and angles. Only certain parameter included to indicate the total symmetry of both substituents of HAMFIL. Bond lengths are in Å and angles in °.

The reduced density gradient (RDG) is used in this study to show the non-covalent interactions (NCI) in compound. NCI was used to study the stability of the polymorph and interaction in complexes.[4,5] The RDG, s is defined as:

$$s = \frac{1}{2(3\pi^2)^{\frac{1}{3}}} \frac{|\nabla\rho|}{\rho^{\frac{4}{3}}} \tag{1}$$

where ∇ρ is the gradient of the electron density. Since s is dependent on $|\nabla\rho|/\rho^{4/3}$, a plot of s vs $|\nabla\rho|/\rho^{4/3}$ enables the identification of weak interaction in the molecular system. The $\rho(\mathrm{r})^{4/3}$ term approaches zero with higher decay rate compared to ∇ρ. s will be high when further from the nuclei and approaches small value when closer to the nuclei.

2. EXPERIMENTAL

HAMFIL originally existed in *trans-trans* configuration as shown in Figure 2. *Trans* is configuration when hydrogen is opposite to the sulphur in the thiourea moiety. Rotation at one side of thiourea is labelled as side A while another one as side B. For dimer calculations, side of each molecules are labelled as in Figure 2. For this research, all combinations are considered and labelled as combination of AC, AD, BC and BD. For *cis-cis* configuration, both substituents of both molecules are rotated to *cis* configuration.

Single point calculations are carried out on the different configurations of the systems of interest, either single molecule or dimer. The dimer system, together with the rotations on the substituents, is shown in Figure 2.

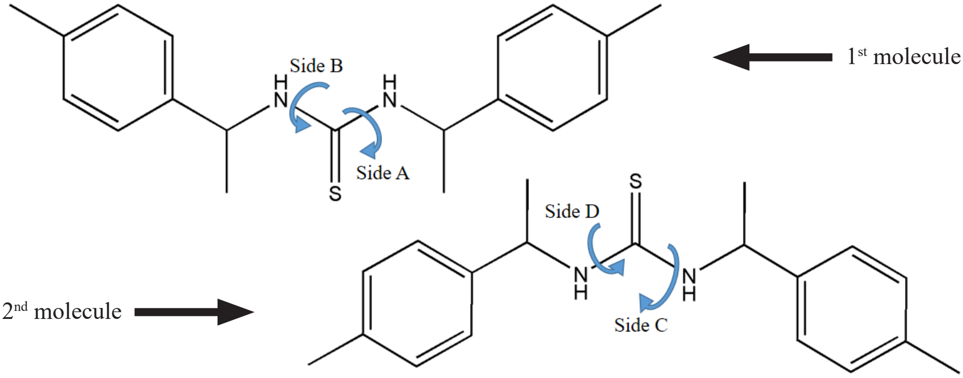

Figure 2: The structure of the dimer of HAMFIL with sides labelled as A, B, C and D.

The calculations are performed using the Gaussian 09 software at the B3LYP with the DEF2-TZVP basis set. The correctional scheme of D3-BJ and gCP are included in this study. The total energy is then given as:

$$E_{\text{total}} = E_{\text{SCF}} + E_{\text{D3–BJ}} + E_{\text{gCP}} \tag{2}$$

where E_{SCF} is self-consistent field energy, $E_{\text{D3-BJ}}$ is dispersion correction and E_{gCP} is counterpoise correction. The total energy of different configurations are compared to the one from the *trans-trans* configuration.

The NCI of different configuration are performed using the Multiwfn. The results are shown through the visual molecular dynamics (VMD). NCI-RDG isosurface of a compound is coloured according to the corresponding values of sign(λ_2)ρ (shown in Figure 3). It is an indicator of the strength of interactions. For this study, we are using the Blue-Green-Red (BGR) scheme where blue indicates bonding interaction, green of vdW and red indicates non-bonding interactions. The cutoff used for the RDG, $s(r)$, is 0.3 au and the colour scale is $-0.04 < \rho < 0.01$.

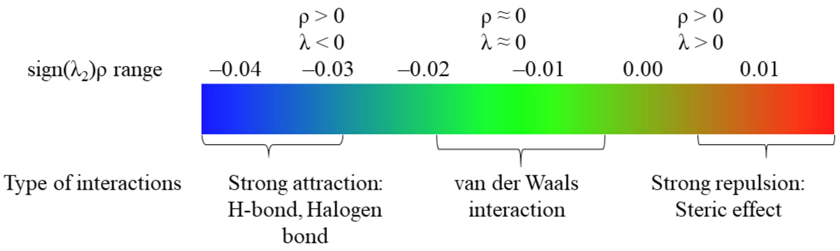

Figure 3: Colour range ($-0.04 < \text{sign}(\lambda_2)\rho < 0.02$ au) of the non-covalent interactions.

3. RESULTS AND DISCUSSION

Table 1 shows that for the 1-molecule system, the *cis*-*trans* configuration is more stable than the original configuration of *trans*-*trans*, as the relative energy is negative. Since it is a symmetric molecule, rotation for both side (side A and B) of the molecule produced the same relative energy of –0.0243 eV. The *cis*-*cis* configuration is less stable with a relative energy of 1.8412 eV. In this configuration, the small distance between the two hydrogens of CH(side A)···HC(side B) has a distance of 0.9548 Å, and creates a pseudo 7-membered ring. The ring produces repulsion at the centre of the ring, and lowered the stability of the whole system. Graphical explanation will be given later in the discussion of NCI plot.

In the case of dimer, Table 1 also shows that the *cis*-*trans* configuration is more stable with relative energy of –0.0298 eV for BC configuration. In the BC configuration, the first and second molecules have the B and C sides rotated to the *cis* configuration, while keeping A and D sides fixed. *Cis*-*trans* configurations of AC, AD and BD are less stable compared to the *trans*-*trans* configuration, since they have higher positive relative energy than the one in *trans*-*trans* configuration. Higher relative energy shows that compound have less favourable intermolecular interaction compare to the *trans*-*trans* configuration.[6] *Cis*-*cis* configuration also shows similar condition where the relative energy higher than *trans*-*trans* configuration with 5.8879 eV. Hence energetically, while *cis*-*trans* is shown to be able to exist, *cis*-*cis* is not a preferable configuration for HAMFIL.

Table 1: The relative energy from different configuration of HAMFIL. The capital letters for the *cis*-*trans* configuration of dimer are explained in the text.

	Relative energy (eV)					
System	*Trans-trans*	*Cis-trans*				*Cis-cis*
1-Molecule	0.000	–0.0243				1.8412
Dimer	0.000	0.1040 (AC)	0.2574 (AD)	–0.0298 (BC)	0.1413 (BD)	5.8879

The NCI plot of the *trans*-*trans* configuration shows similar isosurfaces on both of its substituents (Figure 4(a)) due to the compound having total symmetrical substituents. The dual colour isosurface of green-red at CH···HC and CH···HN interactions are from the combination of the van der Waals (vdW) and steric repulsion interactions of the atoms.[5,7] Less steric repulsion exists at the green-yellow isosurface of CH···S interaction is due to increment in their distance to 3.2546 Å, compare to the green-red isosurface (2.6513 Å). The red-bullet shapes, common in the ring compound, is due to high steric repulsion.[5]

The NCI surfaces for *cis*-*trans* configuration are similar either rotation of side A or B. Thus, only one rotation's side are shown in Figure 4(b). This can be attributed to the total symmetry of the side substituents. Comparing the NCI plots for *cis*-*trans* and *trans*-*trans* configurations, isosurfaces for both configurations are similar. However, the CH···S interaction in *trans* configuration is replaced with the CH···HN interaction in the *cis* configuration. The difference in NCI plot shows that the energy difference between these configurations are affected by the different interaction of CH···S and CH···HN. It also shows that the CH···HN has stronger interaction compared to the CH···S interaction. This is due to the shorter distance of the former (1.829 Å) than the latter (2.651 Å).

For *cis*-*cis* configuration (Figure 4 (c)), the red-bullet isosurface is visual at the H–C···C–H ring closure replacing the CH···S interaction in *trans*-*trans* configuration. Red-bullet isosurface appears in ring-like interactions due to density overlap in the central part of the ring closure.[5] This indicates that the lesser stability of *cis*-*cis* configuration is due to the existence of the repulsive interaction at this ring closure.

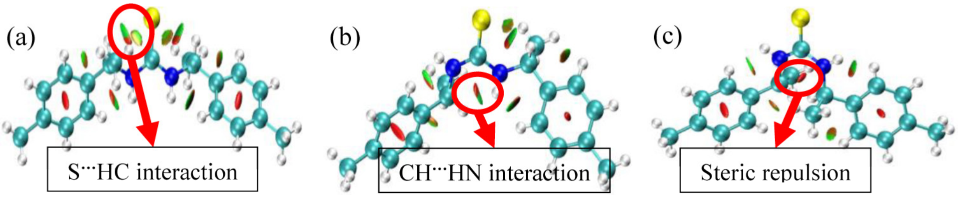

Figure 4: The NCI plot of the 1-molecule HAMFIL in (a) *trans*-*trans*, (b) *cis*-*trans* and (c) *cis*-*cis* configurations.

For the *trans*-*trans* configuration of dimer system (Figure 5(a)), NCI isosurfaces of the individual molecules are similar to the 1-molecule system. The CH···S, CH···HN and CH···HC interactions of the first and second molecules have similar NCI isosurfaces at the specific places. Based on this observation, the difference in energies can be said to have been resulted from the interaction between the molecules in the case of dimer. The vdW interaction is shown exist between the substituents.

For *cis*-*trans* configuration, similar NCI isosurfaces appear intramolecularly (Figure 5(b), (c) and (d)). However, the vdW interaction between molecules exists in different strengths can be ranked as BC > AC > BD > AD. The strengths are similar compared to the relative energy results. AD is not shown here due to having only slight vdW isosurfaces. Thus, the interaction between molecules affects the stability of dimer compound. For most energetically stable configuration which is *cis*-*trans* BC, the rotation of the substituent does not affect the vdW interactions from *trans*-*trans* configuration. However, from the changes of CH···S to CH···HN interaction, *cis*-*trans* became more stable than *trans*-*trans* configuration. The *cis*-*cis* configuration had been discussed previously to have highest relative energy. Red-bullet isosurfaces existed in the *cis*-*cis* configuration of 1-molecule system, still appeared at the CH···HC pseudo-ring for the dimer, and indicates that the repulsion is due to the ring closure repulsive interactions. As discussed previously, the vdW interaction had shown to affect the stability of the compound. However, only slight vdW interaction is visual due to less interaction between molecules.

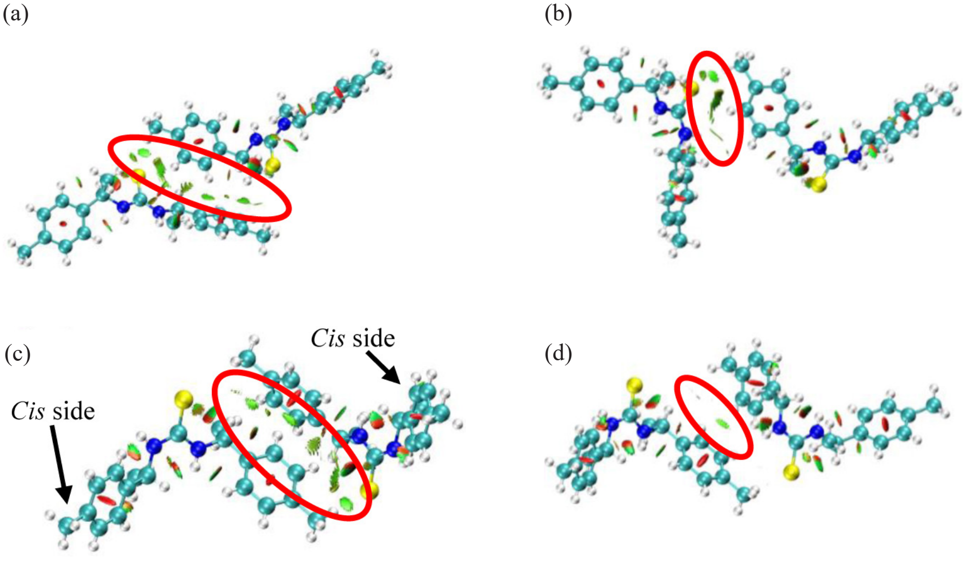

Figure 5: The NCI plot for (a) *trans*-*trans* and *cis*-*trans* configurations of different substituent couple (b) AC, (c) BC and (d) BD. The red circle on green isosurfaces indicate the van der Waals interaction between molecules.

4. CONCLUSION

The probability of HAMFIL to be a polymorphic compound is studied in this work. The molecules of HAMFIL are rotated along C–N bond from *trans-trans* configuration to *cis-trans* and *cis-cis* configurations. The energy analysis results show that the molecules are capable to exist in the *cis-trans* configuration. Calculations are repeated for a dimer system which results with the same conclusion. NCI isosurface also shows that *cis-trans* more stable with CH···HN interactions compared to CH···S interaction in *trans-trans*.

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