Conformational and Topology Analysis of Diphenylthiourea and Diarylhalidethiourea Compounds Using DFT

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Abstract: *The disubstituted thiourea compounds have shown its reliability on their usages in various industries compared to the thiourea compounds. However, they also show capability to exist in different configurations, which would render them to possess different properties and hence affect their usability by unsuspected users. In this study, investigation was carried out on the polymorphism of five disubstituted thiourea compounds in which the phenyl rings and arylhalide acted as substituents. Using the B3LYP/DEF2–TZVP model chemistry with D3–BJ and gCP correctional schemes, the energetic analysis on the possible structural arrangements of the compounds was performed. The topology analysis of non-covalent interaction and electrostatic potential surfaces was used for understanding the interaction and reactivity of the constitute molecules of the compounds. Energetic results show that for all interested compounds, CT and TT configurations may coexist. Between the two types of substituents, phenyl substituted molecules are more flexible with better capability to be nucleophilic compounds. On the other hand, the arylhalide substituted molecules form better electrophilic compounds. The reactive sites of the molecules rotated to the stable new configurations are similar to the molecules in their original configurations observed from experiments.*

Keywords: *conformational analysis; topology analysis; thiourea substituent compounds; density functional theory*

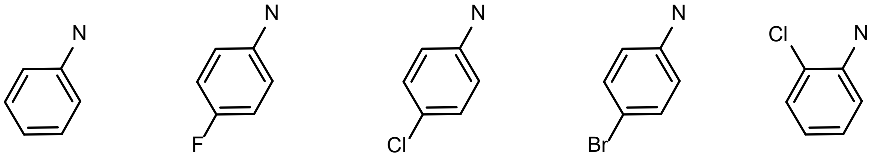
■ INTRODUCTION

Thiourea molecules have three potential coordination sites: the sulphur of thiourea moiety (S_T) and the two nitrogen atoms of the NH group. One of the thiourea derivatives, the symmetrically disubstituted thioureas, which have the form RHN–(C=S)–NHR' where R=R', have received much interest due to their diverse applications in medicine, agriculture, and chemical industries [1-5]. In addition, disubstituted thioureas are known to form stable, neutral coordination compounds with various transition metal ions [6].

This study focusses on five disubstituted thiourea compounds, as listed in Table 1. Two types of substituents were considered, namely phenyl rings and arylhalides. The phenyl substituted (Ph) compounds are labelled as Ph-1, 2, 3 and 4 to indicate compounds from different works. For arylhalide substituted (Ah) compounds, Ph-F, Ph-Cl and Ph-Br were considered, indicating attachment of fluorine, chlorine and bromine atoms to the phenyl ring. The attachment of the halogens at the ortho- and the para- site to the phenyl ring (as shown in Fig. 1) is appended with o- and p-, respectively. Experimentally, for these compounds, the structural arrangements of the molecules are shown to have preference towards the trans-trans (TT) and cis-trans (CT) configurations. As shown in Table 1, there is no connection between the crystal system and occurrence of TT or CT configurations. Thus, all these compounds show unrelated relationship of the configuration, crystal system and type of substituent. It has to be mentioned that

Table 1. List of the phenyl and arylhalide substituted compounds considered in this study

No.	Compound	Original configuration of the molecules	Crystal system	Substituent
1	1,3-diphenylthiourea ($C_{13}H_{12}N_2S_1$) [7-8] (*)	TT	orthorhombic	Ph–1
		CT	monoclinic	Ph–2
		TT	orthorhombic	Ph–3
		TT	orthorhombic	Ph–4
2	1,3-bis(4-fluorophenyl)thiourea ($C_{13}H_{10}F_2N_2S_1$) [9]	TT	orthorhombic	Ph–F–p
3	1,3-bis(4-chlorophenyl)thiourea ($C_{13}H_{10}N_2S_1$) [10-11]	TT	orthorhombic	Ph–Cl–p–1
		TT	monoclinic	Ph–Cl–p–2
4	1,3-bis(4-bromophenyl)thiourea ($C_{13}H_{10}Br_2N_2S_1$) [12]	TT	monoclinic	Ph–Br–p
5	1,3-bis(2-chlorophenyl)thiourea ($C_{13}H_{10}Cl_2N_2S_1$) [13-14]	CT	orthorhombic	Ph–Cl–o–1
		TT	monoclinic	Ph–Cl–o–2



Ph Ph–F–p Ph–Cl–p Ph–Br–p Ph–Cl–o

Fig 1. The molecular structure of the arylhalide substituent compounds

cis-cis (CC) configuration is conspicuously missing in Table 1 as it is not found to be favorable for these thiourea derivatives.

The existence of the same compounds with different stable configurations (CT and TT, shown in Table 1) as found from the experiments rendered the compounds conformationally polymorphic. In general, polymorphic compounds with different structural arrangements, would lead to different properties of the compounds due to the different intra– and intermolecular interaction. For the compounds considered in this study, those in TT configuration always have the molecules stack in head-to-tail to form zigzag tapes. It involves twin $NH\cdots S_T$ contacts of 2.50 to 2.70 Bohr [7-12,14]. The $NH\cdots S_T$ contact can be interpreted as hydrogen-bonding interactions to a bifurcated sulphur acceptor. It is similar in the TT configuration of the arylhalide compounds as the $NH\cdots S_T$ hydrogen bonds are known as a characteristic part of the solid-state assembly of thiourea molecules [15]. The head-to-tail orientation is common for TT configuration as dimer aromatic rings are favored to be in T-shaped (90° angle between dimer) or slipped parallel [16]. However, for CT configuration compounds, centrosymmetric orientation is shown with one $NH\cdots S_T$ interaction with opposite substituents away from the thiourea moiety.

This work is carried out to study the polymorphic phenomenon of the Ph- and Ah-substituted thiourea compounds. It is aimed to find the effect of different configurations to the properties of the molecules without changing the intermolecular hydrogen bonding and geometry of the molecules. Changing the entire geometry of the molecule to the minimum forces would exchange the real crystal structure of the molecules and lose the effect of the configuration changes. The addition of the halogens to the phenyl ring at different sites may alter the intra- and intermolecular interactions significantly, resulting in configurations that are stable but yet-to-be-found from experiments. Furthermore, the electronic properties of the compounds in the gaseous state of monomer and dimer systems would also be investigated, as to provide insights to alterations in the properties between the original and predicted configurations.

■ COMPUTATIONAL METHODS

The geometries of interested compounds, taken from Cambridge Structural Database (CSD), were all fixed with rotation only along the C–N bond between the thiourea moiety and its substituents. Avoiding the geometry changes will preserve the interaction for the parts not affected by the rotation (as obtained from experimental studies). The cis- (C) and trans- (T) orientations referred in the following sections are based on the relative orientation of the hydrogen to the sulphur in each conformer as depicted in Fig. 2. For the calculations of the dimer systems, the same sides of each molecule were rotated simultaneously.

The calculations were carried out using the Gaussian 09 suite of programs [17]. Previous electronic properties study on the other thiourea derivative molecules was proved reliable using B3LYP [18]. Thus, the single point calculations were performed at B3LYP level of theory with the DEF2-TZVP as the basis set. Previous study had suggested that DEF2-TZVP offers a good balance between accuracy and performance for molecules [19-20]. At DFT level, DEF2-TZVP basis is proved to be able to achieve results that are almost similar to the DEF2-QZVP [21]. It is also performed well when combined with DFT method [22-23]. However, due to the lack in describing the dispersion, D3-BJ [24] correctional scheme is included in this study. To verify the stability of the method, calculations were performed on the S66 dataset using Cuby4 [25] interfaced with Gaussian 09 [17]. The RMSE obtained is 0.71 kcal/mol. Comparing to the previous study reported by Jan Rezac [26], other methods, i.e. methods MP2/TZ and CCSD/CBS also have similar RMSE energy. Thus, method used in this study is sufficient to be used for the interested compound. For dimers, gCP scheme is included to reduce the basis set superposition error [27]. The total energy is then given as:

$$E_T = E_{SCF} + E_{D3-BJ} + E_{gCP} \quad (1)$$

where E_T is the total energy of the cluster, which is the sum of self-consistent field energy E_{SCF}, corrective energies of dispersion E_{D3-BJ} and counterpoise correction of gCP, E_{gCP}. The relative energy is then used to compare the stability between two different configurations.

Another energy analysis used to study the stability of compounds is by using the interaction energy of the dimers. Interaction energy is caused by interaction of both monomers to form the compound [28]. The positive energy shows the repulsive interaction while the negative shows the attractive interactions.

Topology analysis were performed to complement the energetic results. The non-covalent interaction (NCI) using the reduced density gradient (RDG) was performed using the Multiwfn software [29]. The results are shown through the visual molecular dynamics program (VMD) [30]. The 3D NCI isosurface of a compound is colored according to the corresponding values of sign(λ_2)ρ (shown in Fig. 3). It is an indicator of the types of interactions. For this study, the Blue-Green-Red (BGR) scheme was used where blue indicates bonding interaction, green is of vdW and red indicates non-bonding interactions. 0.3 au isosurface cutoff and color scale of $-0.04 < \rho < 0.02$ were used for this study. These quantities were proved to encapsulate the noncovalent interaction region of interest [31].

The further studies on the reactivity of the compounds were performed using the electrostatic potential (ESP) surfaces. For this study, the color range of red-green-blue (RGB) was used. Red and blue indicate

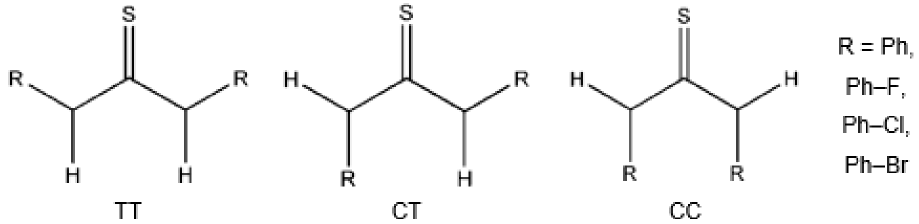


Fig 2. The conformers of the diphenylthiourea and arylhalide thiourea compounds

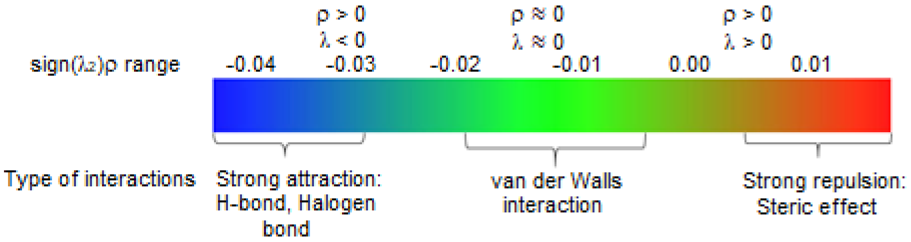


Fig 3. The range of color for the NCI isosurfaces

electron abundance (most negative sites) and depletion (most positive sites) respectively while green color indicates uniform electron distribution. Preferable isosurface of 0.001 au is used in this study as it shows the surface lies beyond the van der Waals radii [32]. The ESP surfaces was post-processed using the Gauss View program [33].

■ RESULTS AND DISCUSSION

Stability Analysis

For the energetic analysis, as tabulated in Table 2, it can be seen that CT configuration is the most preferable configuration, followed by TT configuration. Both of these configurations are the low-energy conformation with relative energy range from 0.1 to 0.2 eV. The CC configuration is the least preferable configuration with high relative energy (between 3.4 to 7.2 eV). This observation can be related to the results from the experiments where only polymorphs in TT and CT configurations were obtained. CT configuration is preferable as it had delocalization between the substituent with the thiourea moiety. The TT configuration are less preferable from the steric repulsive of the nitrogen lone pair and CC configuration had steric repulsion of the substituents [2,34]. Results also show that comparing between Ph- and Ah-substituents, Ph-substituent is more flexible to be in CT, TT and CC configuration while CC only exists for Ph-Cl-p-1 of Ah-substituent.

Even though both the CT and TT configurations are shown to be possible in the monomer systems, rotation of the dimer systems shows that the substituents are too close or overlapping (as shown in Fig. 4 for the dimer of Ph-Cl-p). Thus, those dimers are unable to exist with new configuration in a similar crystal system. However, the possibility for them to exist in different configuration of different crystal systems cannot be discarded.

Table 2. Summaries of the possible configuration for monomer of the Ph- and Ah-substituted molecules. For each set, the minimum energy conformation is used as the reference

Substituent	Most Stable Configuration	Other possible configuration with its relative energy (eV)			
Ph–1	CT	TT	0.1377	CC	6.6177
Ph–2	CT	TT	0.2045		
Ph–3	CT	TT	0.1761	CC	6.5187
Ph–4	CT	TT	0.1731	CC	7.2727
Ph–F	CT	TT	0.1569	CC	3.3776
Ph–Cl–p–1	CT	TT	0.1537	CC	6.4029
Ph–Cl–p–2	CT	TT	0.1031		
Ph–Br	CT	TT	0.1464		
Ph–Cl–o–1 (a)	CT	TT	0.1237		
Ph–Cl–o–1 (b)	CT	TT	0.1860		
Ph–Cl–o–2	CT	TT	0.1779		

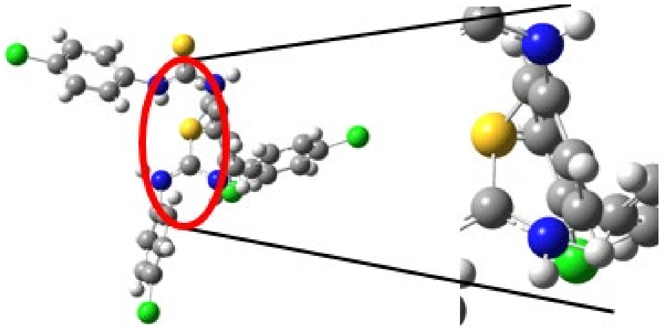


Fig 4. The overlapped structure of the rotated substituent

Interaction Energy

The interaction energy between molecules in the dimeric systems is shown in Table 3. It can be seen that, for all the compounds considered in this study, as the interaction energy is negative, the dimeric molecules are attracting each other. For the magnitude of interaction, molecule with Ph-Br substituent has the highest interaction energy (most negative at –1.0573 eV) while Ph-2 substituent has the lowest (–0.5477 eV).

Between TT and CT configurations, TT has higher interaction than the CT configuration, as evidenced by the molecules with Ph- and Ph-Cl-o substituents. The Ph-2 substituent, as the only polymorph in the CT configuration among the molecules with Ph-substituent, has the smallest value of interaction energy. As for the case of Ph-Cl-o-2 and Ph-Cl-o-1, the CT configuration also has interaction energy that is of lower magnitude compared to the polymorph in TT configuration. However, no significant changes to the interaction energy can be found with or without halogen atom in the systems considered.

As for the effect of the halogens on the phenyl ring, molecules are more cohesive as the halogens in the substituents change from fluorine, chlorine, and bromine in the rank F < Cl < Br. This effect is due to the polarizability of the halogens. Thus, the molecules where the substituents contain fluorine had lower attraction compared to the compound with bromine.

The interaction energies are not affected much by the different attachment sites of the halogen to the phenyl rings. This can be seen from the chlorophenyl substituent Ph-Cl, where the chlorine is either attached to para- or ortho- positions. With this substituent, the interaction energies range in between –0.731 to – 1.006 eV, where the higher value is from the attachment to the para-position. In the para-position, the molecules are taking the head-to-tail orientation, with the molecule stack parallel to the thiourea backbone for the case of Ph-Cl-p-2 substituent. However, with higher angle of the zigzag between molecules (Ph-Cl-p-1), the interaction between molecules becomes less. Molecules with Ph-Cl-o-2 substituents have the similar head-to-tail orientation but the molecule is rotated to the substituent of the compound. This orientation has less interaction between the substituent of the molecules. While Ph-Cl-o-2 has dual NH···S_T interaction with close substituents of the molecules, Ph-Cl-o-1 have single NH···S_T interaction with substituents that are away from each other, producing dimer with the weakest interaction energy.

Table 3. Interaction energy of the compounds

Substituent	Interaction Energy (eV)	Configuration
Ph–1	-0.9292	TT
Ph–2	-0.5477	CT
Ph–3	-0.8630	TT
Ph–4	-0.8629	TT
Ph–F	-0.7809	TT
Ph–Cl–p–1	-0.8699	TT
Ph–Cl–p–2	-1.0056	TT
Ph–Br	-1.0573	TT
Ph–Cl–o–1	-0.7306	CT
Ph–Cl–o–2	-0.8806	TT

Non-covalent Interaction (NCI)

The noncovalent interaction is shown through the NCI isosurfaces using the RDG plot in Fig. 5. For each monomer, the dual green-red NCI isosurfaces in the region between S_T and the phenyl ring indicate that there are attractive and repulsive interactions. In the TT configuration, the S···π interactions act as the attractive interactions (the green surfaces), while the interaction in the region of S_T-C-N-C_P constitute the repulsive interactions (the red surface). On closer inspection, the wider the divergence between the S_T and carbon of the phenyl ring (C_P) from region of S_T-C-N-C_P, the lesser red isosurface will be shown. These two interactions are typical for the molecules with TT configuration for Ph or

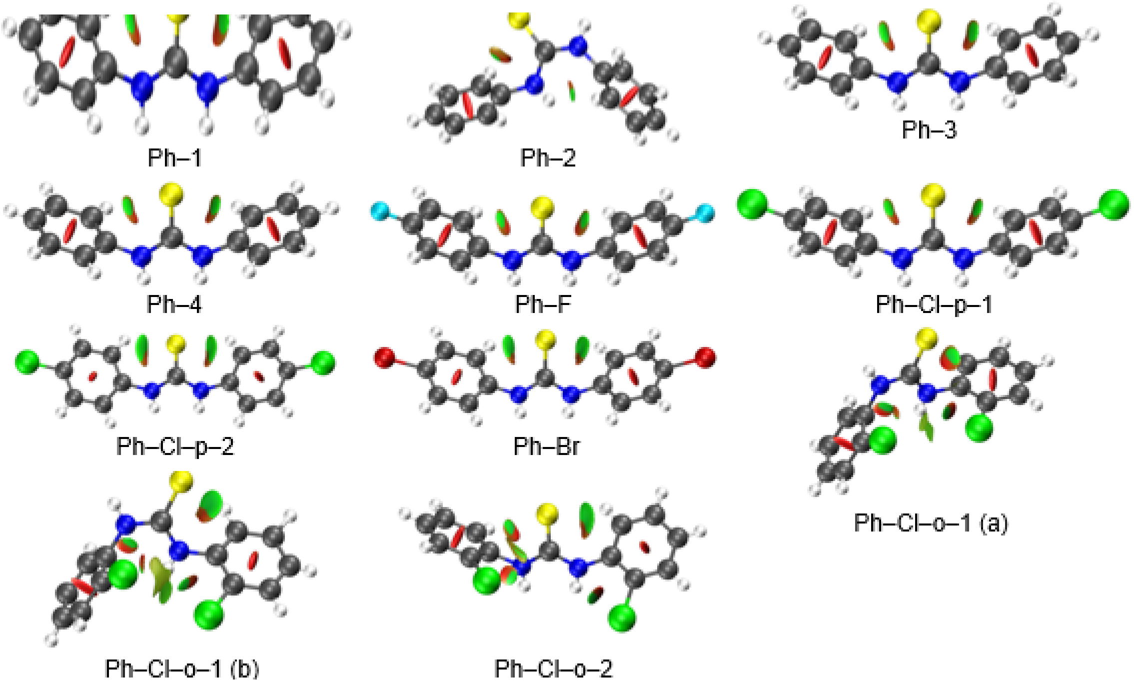


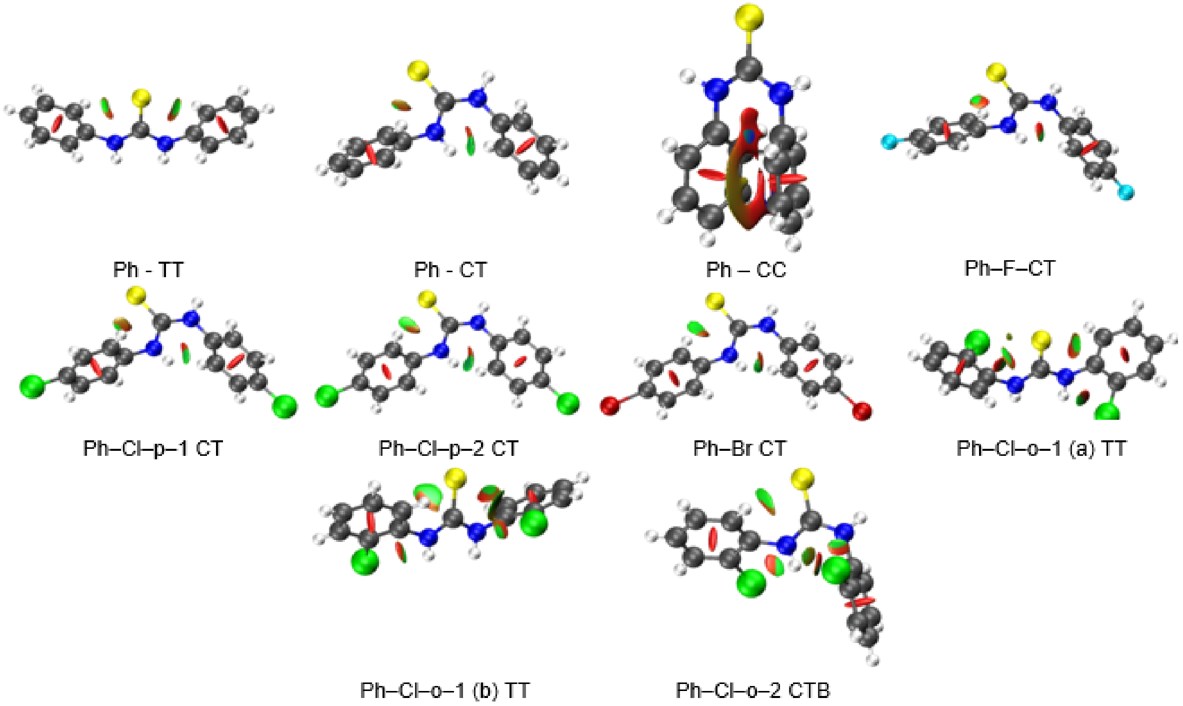
Fig 5. The NCI isosurfaces for the monomers original configuration

Ah-substituents with halogen atom attached at the para-position. The Ph-Cl-o-2 had an extra Cl···N and Cl···S interaction from the ortho-position of the chlorine atoms.

For the molecule with the CT configuration (Ph-2 and Ph-Cl-o-1), the NCI dual green-red isosurfaces in the region between nitrogen of thiourea (N_T) and the phenyl ring for the cis-orientation side comes from the NH···π interaction (for attractive interaction), while the repulsive interaction is from the interaction of N_T-C-N-C_P. However, this dual color region is seen to be smaller than the one from the trans-orientation, and can be attributed from the smaller size of hydrogen as compared to the S_T. The interaction from the trans-orientation side of this CT configuration is the same as in the case of TT orientation. Nevertheless, in the CT configuration, for Ph-Cl-o-1, extra interaction exists in the form of Cl···Cl interaction. This can be seen from the proximity between the chlorine atoms, which is in the ortho-position of the phenyl ring, and the nitrogen of the thiourea moiety. This explains the higher interaction energy of Ph-Cl-o-1 than that of Ph-2 (as discussed in the NCI results for dimer).

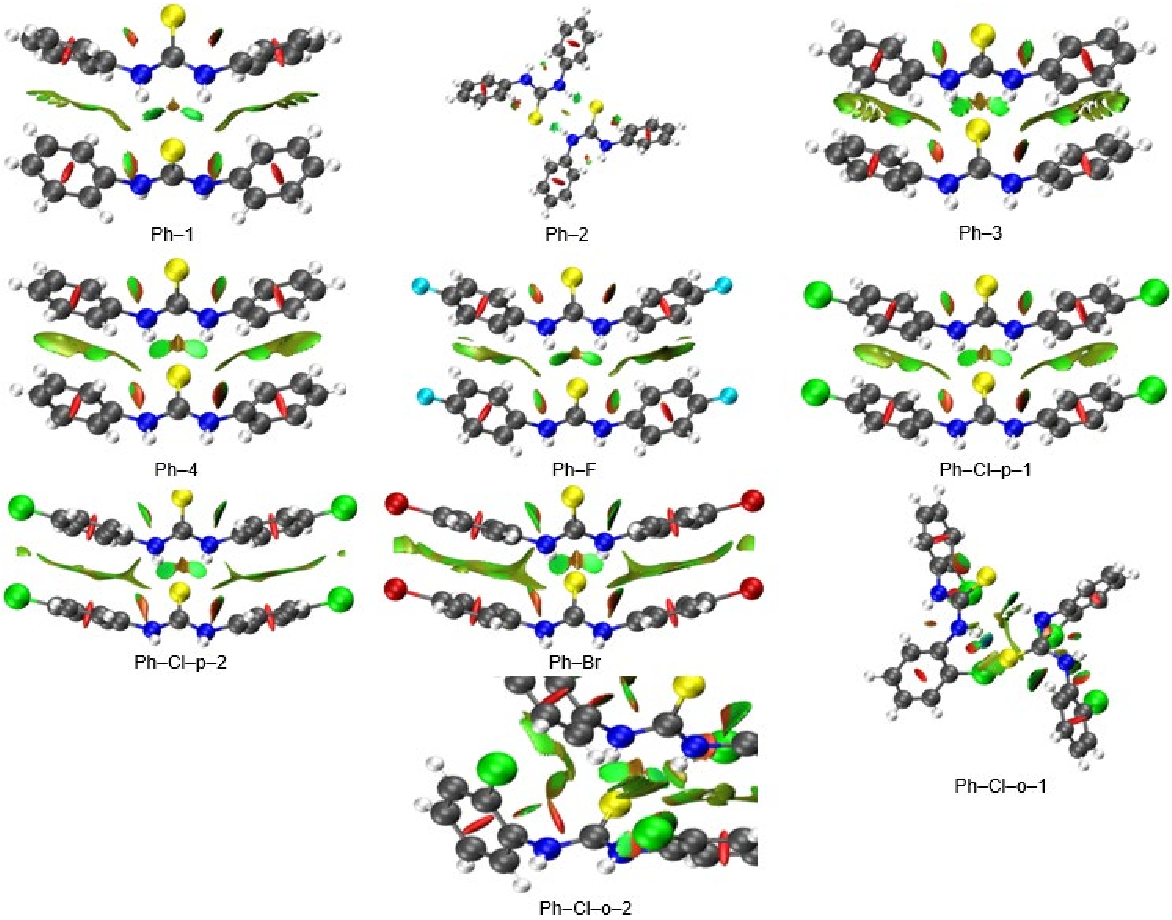
For the new configurations of the molecules shown in Fig. 6 (where the substituents are rotated), the NCI isosurfaces are similar as those in the original CT and TT configurations. This indicates that the new configurations are possible as they have similar type of interactions as those that generally appear in the original configurations. CT configuration shows the combination of S···π (for *trans*) and NH···π (for *cis*), while TT configuration show S···π interaction for both sides. The CC configuration shows the large red isosurfaces, indicating large repulsive interaction between substituents. This explains the less preferable CC configuration compared to CT and TT configuration from the energetic aspect. The CC configuration in Fig. 6 is represented using only the molecule with Ph-substituent, as other compounds also have similar patterns.

The non-covalent interactions of the dimer, as can be seen in Fig. 7, show that the intramolecular interaction of the dimer is similar as the monomers (Fig. 5). In between the molecules, the green NCI isosurfaces are found between N-H and S_T, indicating the existence of the N-H···S_T interaction in all the compounds considered in this study. This result agrees with the findings from the experiments in which NH···S_T interaction is important



Ph - TT
Ph - CT
Ph – CC
Ph–F–CT
Ph–Cl–p–1 CT
Ph–Cl–p–2 CT
Ph–Br CT
Ph–Cl–o–1 (a) TT
Ph–Cl–o–1 (b) TT
Ph–Cl–o–2 CTB

Fig 6. The NCI isosurfaces for the new configuration of the molecules



Ph–1
Ph–2
Ph–3
Ph–4
Ph–F
Ph–Cl–p–1
Ph–Cl–p–2
Ph–Br
Ph–Cl–o–1
Ph–Cl–o–2

Fig 7. The NCI isosurfaces for the dimer compounds in holding the molecules in the crystal structure [7-14]. Hence, not only can the NH···S_T hydrogen bonds hold the thiourea molecules in the solid state [15], it is also responsible for the stability of the thiourea derivatives.

The higher interaction energy for dimers in the stacked TT configuration can be related to the NCI isosurfaces which show the dual NH···S_T interaction and wide green region between substituents of the compound. For both Ph- and Ah-substituent, strength of the vdW interaction is shown to depend on the angle and distance between two molecules. Lower angle and distance will have wider vdW interaction resulting to higher interaction energy. For Ah-substituent, Ph-F and Ph-Cl-p-1 show no NCI isosurface exist between halogen atoms, while for Ph-Cl-p-2 and Ph-Br, NCI isosurface appear between halogens. This agrees with the results from interaction energy fi, where Ah-substituent has higher interaction energy range compared to Ph-substituent. The amount of the vdW interaction changes according to Ph-F < Ph-Cl < Ph-Br, which is similar to the interaction energy results. Ph-F had the lowest interaction energy due to the highest angle of 96.82° between molecules.

For the CT configuration in chain arrangement, as exemplified by the Ph-2 and Ph-Cl-o-1 substituents, no enhancements of stability is observed in the dimer as the substituents are diverging from each other. However, as explained in monomer results, since Ph-Cl-o-1 has extra interaction compared to Ph-2, it reflects the higher interaction energy as shown in Table 3. The results from vdW isosurface agree with the observation that the molecules with Ph-Br substituent have the strongest interaction energy, and that the dimers in the CT configuration have the lowest interaction energy compared to the TT configuration.

Electrostatic Potential (ESP)

The reactivity of the monomers and dimers are shown in Fig. 8, 9 and 10. For all the compounds considered, the NH bond of the thiourea moiety always show blue ESP surfaces, indicating positive potentials at the region while the red ESP surfaces at the S_T indicate the negative potentials. However, there are differences in the magnitude of the interactions between the Ph- and Ah-substituted molecules, as tabulated in Table 4. Ph-substituted molecules have lower minimum range of the red and blue surfaces compared to the Ah-substituted molecules due to the inclusion of the halogen atoms. Thus, the Ph-substituted molecules have higher ability to donate its electrons while the Ah-substituted molecules have higher ability to attract electrons.

Quantitative study of different configurations also shows differences to the potentials at the NH bonds of different configurations. In the CT configuration, the potentials of the blue ESPs, with energy that range from 1.50 to 1.60 eV, are smaller than those in the TT configuration which is in between 2.44 and 2.90 eV. Further differences in the electronic properties of the CT and TT configurations occurred in the ESP of the S_T. In the CT configuration (Ph-Cl-o), the ESP of the S_T is in orange-ish color, compared to yellow-ish in the TT configuration. Numerically, the potential at the S_T for Ph-Cl-o is −1.51 and −1.46 eV, while that in TT configurations has values between −1.47 and −1.21 eV. Hence, while the TT configuration has enhancement in the positive potential of the NH sites, it also possesses slightly weaker negative potential for the S_T, compared to those in the CT configuration. The green ESP surfaces at the Ah-substituted molecules indicate that these sites have average potential and that the possibility of involvement in reaction is low. Thus, the change in the structural configuration does affect the electronic properties of the compounds considered.

Fig. 9 shows the ESP surfaces for the rotated molecules. Results show that the reactive sites of all the new configurations are similar to those shown in the original configurations. The electrophilic site (blue surface) of the molecules are at the NH bonds region while nucleophilic site (yellow-red surface) are at the S_T. Comparing ESP surfaces between the original and new configurations, energy of new configurations show unclear changes in energy pattern. However, Ph-substituent had lower minimum energy range around −1.68 to −1.69 eV for both TT and CT configurations compared to Ah-substituent, ranging from −1.52 to −1.20 eV. This indicates that Ph-substituent had higher capability to act as a nucleophilic site compared to

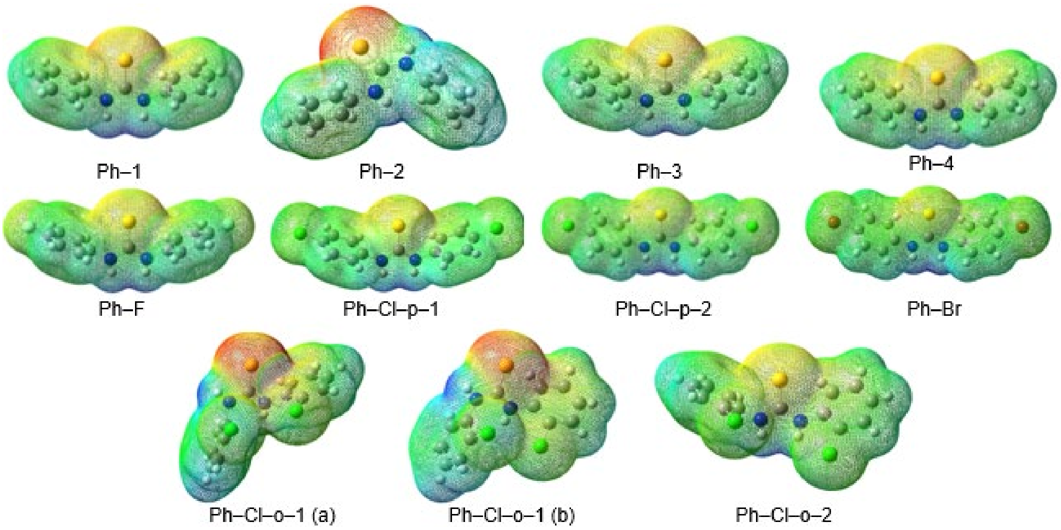


Fig 8. The ESP isosurfaces for the monomers original configuration

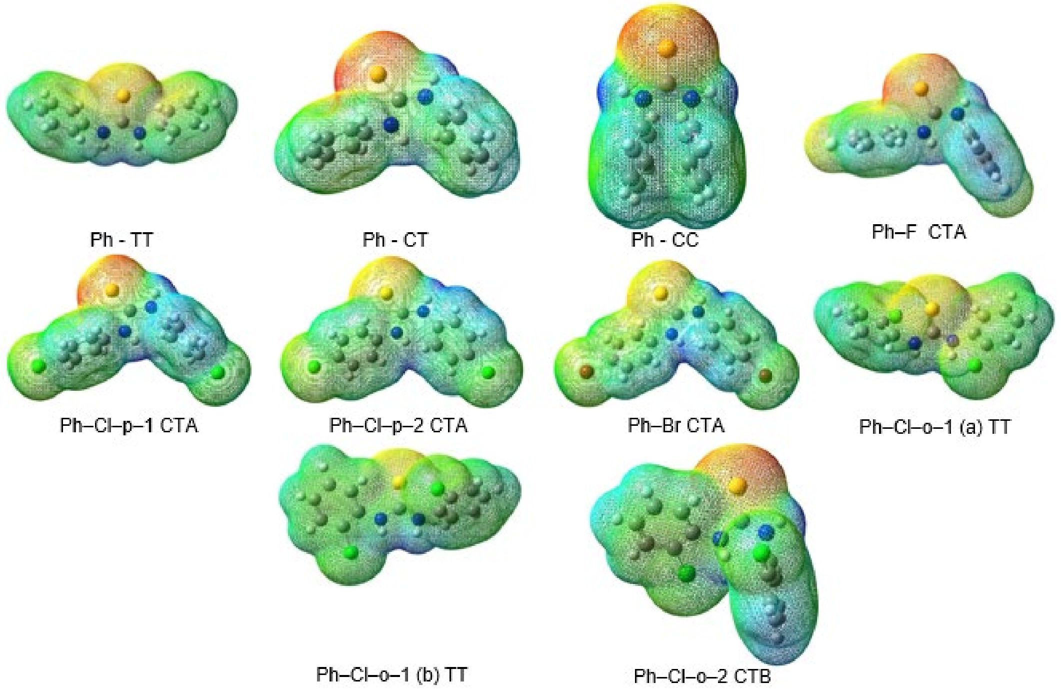


Fig 9. The ESP isosurfaces for the monomers new configuration

Ah-substituent. Hence, the results have similar electronic properties as the original configuration. For potential of blue ESP surfaces, rotation from TT to CT configuration shows a decrease in energy to the range of 1.55 to 1.90 eV, while rotation from CT to TT configuration increase the energy range to 2.31 to 2.41 eV. This shows that the compound of interest had higher capability to act as an electrophilic site in TT configuration. Both Ph- and Ah-substituent had similar energy range indicating that halogen did not have an effect on the potential of NH.

The ESP of the interactions between the components of dimeric systems is shown in Fig. 10. Generally, the electrophilic and nucleophilic sites between the monomers are interacting with each other, where the NH sites attract the electron-rich S_T site. The NCI isosurfaces also exist between the S_T and NH of the two

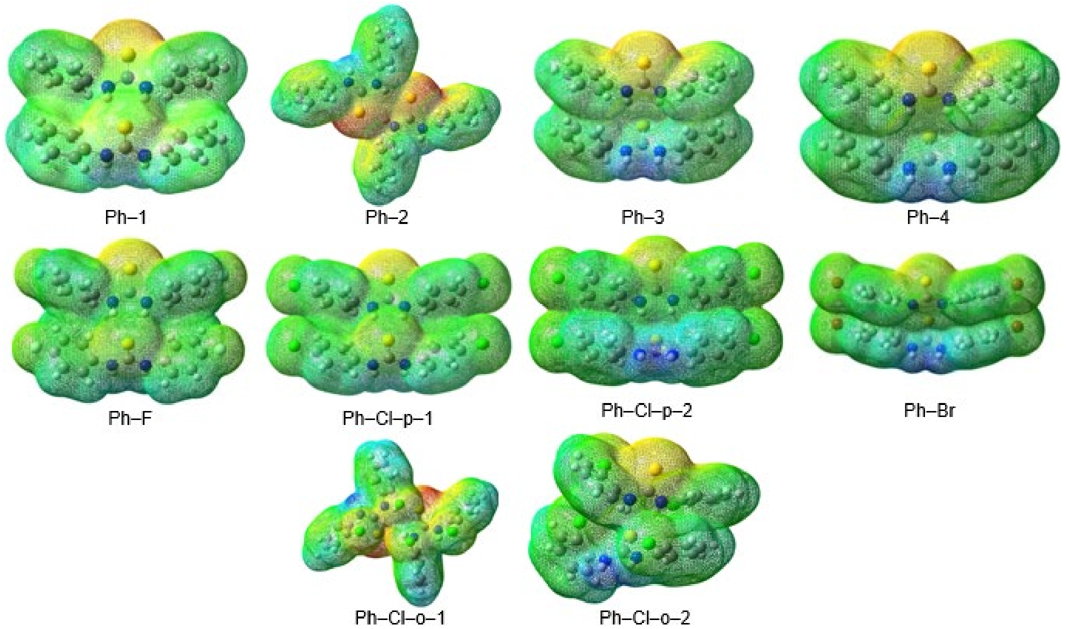


Fig 10. The ESP isosurfaces for the dimer compounds

Table 4. The ESP energy between original and rotated configurations

Substituent	Configuration		Minimum		Maximum	
	Original	Rotated	Original conf.	Rotated conf.	Original conf.	Rotated conf.
Ph–1	TT	CT	-1.6434	-1.6846	2.2682	1.6874
Ph–1	TT	CC	-1.6434	-1.4233	2.2682	1.7218
Ph–2	CT	TT	-1.6740	-1.6899	1.4984	2.3426
Ph–3	TT		-1.6806		2.3903	
Ph–4	TT		-1.6748		2.3878	
Ph–F	TT	CT	-1.4653	-1.4750	2.5707	1.6882
Ph–Cl–p–1	TT	CT	-1.4748	-1.4881	2.6248	1.6798
Ph–Cl–p–2	TT	CT	-1.2288	-1.2206	2.8203	1.8932
Ph–Br	TT	CT	-1.2073	-1.1922	2.8928	1.8705
Ph–Cl–o–1 (a)	CT	TT	-1.5099	-1.5150	1.6005	2.3104
Ph–Cl–o–1 (b)	CT	TT	-1.4594	-1.4288	1.5653	2.4115
Ph–Cl–o–2	TT	CT	-1.4560	-1.4592	2.4424	1.5515

monomers, indicating their importance in the interaction of molecules in crystal systems [7-14]. For the dimers, other than the sites where the monomers interact, the individual monomers also show similar reactive sites as in the case of the monomer, as shown in Fig. 9.

■ CONCLUSION

In this work, we studied the conformational stability of the polymorphic diphenylthiourea and diarylhalidethiourea substituted compounds. Without changing intermolecular hydrogen bonding and geometry of the molecules, energetic study concludes that compounds are more stable in CT configuration as monomers. However, the interaction energy for the molecules in TT configuration is higher. This shows that these compounds are flexible to coexist between CT and TT configurations. From these energetic results, supported by NCI and ESP topology isosurface, molecules rotated to new configurations show similar sites of reactivity as the original configurations.

Ph- and Ah-substituted molecules have similar reactive sites where the sulphur of thiourea moiety acts as the nucleophilic site, while the NH of thiourea moiety acts as the electrophilic sites. However, quantitative studies of the ESP shows that the Ph-substituted molecules are better electron donors and Ah-substituted molecules are better electron acceptors.

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