Understanding the effect of substitution on the formation of S...F chalcogen bond

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Abstract. In this study, we have investigated the effect of substitution on the formation of S...F non-covalent interactions in $XHS...FCH_3$ complexes (X = −H, −F, −Cl, −OH, −OCH_3, −NH_2, −NHCH_3, −NO_2, −CN) at MP2/aug-cc-pVDZ level of theory. The formation of S...F chalcogen bonds was observed in all the cases, except for X = −H. The binding energy of the S...F non-covalent interactions is strongly dependent on the nature of the substituent groups. The energy decomposition analysis revealed that electrostatic and exchange energy component are the dominant contributors towards the stability of these interactions. The topological analysis established the presence of the S...F chalcogen bond due to the presence of a bond critical point exclusively between sulphur and fluorine atoms representing a closed-shell interaction. The natural bond orbital analysis shows that the stability of the interaction comes from a charge transfer from F(lp) to σ^*(S-X) orbital transition.

Keywords. Non-covalent interactions; chalcogen bonds; binding energies; energy decomposition; topology; NBO.

1. Introduction

The understanding of non-covalent interactions is a very important aspect of supramolecular chemistry as well as in biology.[1-5] Non-covalent interactions such as hydrogen bonds[6-8] as well as interactions involving π systems[9-11] are now very well-understood and extensively documented in the literature. In addition to this, halogen bond[12-14] has also become one of the well-studied non-covalent interactions in the past few years. The current focus has now shifted towards the understanding of other kinds of non-covalent interactions such as chalcogen bonds, which is similar to halogen bond. It is defined as a class of non-covalent interactions in which chalcogen (O, S, Se, Te) atoms are attracted non-covalently to an electron donating atom such as O and N but not only limited to these two.[15] The role of chalcogens in the activation of thyroid hormones[16] determining the function of proteins,[17] in addition to having antioxidant properties,[18] make studying non-covalent interactions involving chalcogens very important. Another important aspect of chalcogens is that it can act as both acceptor and donor atom in the formation of non-covalent interactions[19,20] and can form strong intermolecular interactions similar to hydrogen bonds.[21]

Sulphur is an important element due to its role in chemistry and biology.[22-24] The involvement of sulphur in non-covalent interactions is also well-known[25-27] and have significant importance in protein stabilization[28] and molecular recognition.[29] Both SF_2 and SF_4 have been observed to form S...π chalcogen bonds.[30] Another study showed the involvement of sulphur in the formation of bifurcated chalcogen bonds.[31] It has been analyzed that S...O interaction in addition to S...π interaction significantly impacts the binding energies of the complexes.[32] S...O non-covalent bonds are one of the most investigated chalcogen bonds due to its role in biological systems.[33,34] Thomas *et al.*, recently analyzed the role of S...O chalcogen bonding in sulfa drugs from charge density analysis.[35] In another study, Nziko and Scheiner discussed the role of S...O chalcogen bond in molecular geometries of substituted phenyl-SF_3 molecules.[36] S...N contact has been also widely investigated both theoretically and experimentally. A recent study by Khan *et al.*, showed the importance of S...N interaction on the crystal packing of triazolothiadiazoles.[37] Various theoretical studies have shown that the S...N are well-stabilized contacts which in some cases can have strength comparable to hydrogen and halogen bonds.[38-40] While S...O

and S...N chalcogen bonds have been studied in detail both experimentally as well as theoretically, there are not enough studies on the nature of S...F non-covalent interactions[41,42] and hence require a detailed investigation to further enhance our understanding of non-covalent interactions involving sulphur.

The aim of this study was to understand the effect of substitution on the strength of the S...F chalcogen bond in XHS and using fluorine present in CH_3F as the electron donor. The substitutions used for this study were = −H, −F, −Cl, −OH, −OCH$_3$, −NH$_2$, −NHCH$_3$, −NO$_2$ and −CN. The magnitude of the σ-hole will differ depending on the nature of the substituent attached to sulphur and will alter the stability of the S...F contact. The reason we used CH_3F as an electron donor was due to the importance of organic fluorine in supramolecular chemistry[43−45] and its role in the pharmaceutical and medicinal industry.[46,47]

2. Computational Methodology

All the calculations in this study were performed using second order Møller−Plesset theory (MP2)[48] using aug-cc-pVDZ level basis set.[49] Several studies on non-covalent interactions have employed this method and reliable results have been obtained.[38−40,50,51] Results obtained from this method has been found to be comparable with the results obtained by using computationally more expensive CCSD(T) level of theory using higher basis set.[50,52] Optimization of initial geometry was performed using Gaussian 09[53] package and all the optimized structures were verified to be the true minima with no imaginary frequencies. All further calculations were performed by utilizing the coordinates of the optimized structures. G09 was further utilized to plot molecular electrostatic potential maps for the monomers participating in non-covalent interactions. Counterpoise-corrected binding energy for all the complexes was evaluated by taking into account the basis set superposition error.[54] We have performed energy decomposition analysis (EDA) using the LMOEDA module present in GAMESS-US[55,56] to obtain the total binding energies of the complexes partitioned into the corresponding electrostatic, exchange, polarization, repulsion, and dispersion components, respectively. In the EDA methods, the difference between the energy of the super molecule and the difference between the energy of the monomers constitute the total binding energy. The electrostatic energy is generally an attractive interaction which originates because of the interaction between the static charge densities of each monomer within the super molecule. The stabilizing exchange energy is the consequence of the asymmetric

nature of the wave function which permits the exchange of electrons between monomers. The evaluation of the repulsion energy requires the energy to be expressed in terms of monomer orbitals that are orthonormal to each other. The polarization contribution is stabilizing and originates because of the relaxation of the supermolecular wave function. The dispersion energy is evaluated by computing the difference in the energy of the system calculated from MP2 approach and HF approach. The LMOEDA method has been applied extensively in the analysis of non-covalent interactions.[57−59] The basis set for EDA analysis was obtained from the EMSL basis set library.[60,61] The topological properties such as the electron densities (ρ), Laplacian ($\nabla^2\rho$), local potential energy (V_b), and kinetic potential energy (G_b) at the bond critical point were obtained for all the noncovalent contacts by using AIMALL[62] which is based on the Bader's Theory of Atoms in Molecules.[63] We also used G09 to evaluate the magnitude of second-order perturbation energy E(2) using Natural Bond Orbital (NBO) analysis at the DFT level with NBO6.[64−66]

3. Results and Discussion

The molecular electrostatic potential maps are a very useful tool to identify the electron depleted and electron-rich region in a molecule and have been employed extensively in different types of research.[11,37,50] Molecular electrostatic potential maps were plotted for all the XHS monomers to identify the effect of substitution on the strength of the positive electrostatic region (σ-hole) on the sulphur atom (Figure 1). Depending on the electron withdrawing or donating capability of the substituent, the strength of the σ-hole changed significantly. The strength of the σ-hole on sulphur was observed to be large for strong electron withdrawing substituents i.e., X = −F, -Cl, −NO$_2$, −CN. For X = −OH, −OCH$_3$, these also have a substantial magnitude of the electropositive region on sulphur. The effect of substitution on σ-hole was not observed to be prominent in the case of X = NH$_2$, NHCH$_3$. In all cases, σ-hole on sulphur was observed to be maximum opposite to the S-X bond and hence we have used this orientation only for our study.

All the optimized structures along with the geometrical parameters have been shown in Figure 2. Table 1 shows all the parameters evaluated from the different analysis. All structures were observed to be having an S...F non-covalent interaction except for the case of X = −H where the complex was stabilized by hydrogen bonding [Figure 2(a), Table S2 in Supplementary Information]. The S...F bond distance ranged from 2.69 Å to 3.08 Å and was shorter than the sum of the vdW
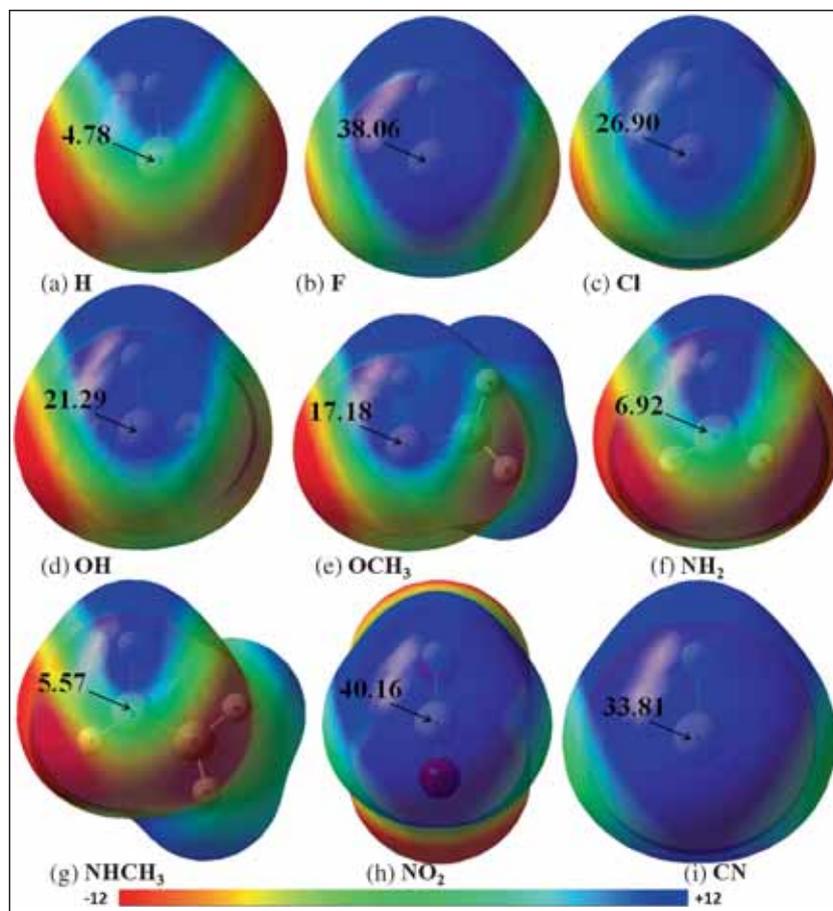
Figure 1. Electrostatic potential maps for the electrostatic positive regions of monomers with substitution X = (a) H, (b) F, (c) Cl, (d) OH (e) OCH$_3$, (f) NH$_2$, (g) NHCH$_3$, (h) NO$_2$, and (i) CN on the total density isosurface. Red and blue indicate electrostatic negative and electrostatic positive regions, respectively. All energy values are reported in kcal/mol. Black arrow indicates the maximum magnitude of positive electrostatic potential observed on Sulphur.

radius of sulphur and fluorine in all cases.[67] For all the complexes, the X-S bond was pointing towards the lone pair of fluorine resulting in the directionality at the X-S...F angles ranging from 158° to 167°.

The nature of the substituent directly influences the strength of the S...F interactions. The counterpoise corrected binding energy increased in the order NHCH$_3$ ~NH$_2$ < OCH$_3$ < OH < Cl < CN < NO$_2$ < F with the values ranging from −1.67 kcal/mol to −3.57 kcal/mol (Table 1). Interestingly, an increase in binding energy was accompanied by a decrease in the distance of the S...F contact. In comparison to similar studies on S...N contacts,[40] S...F contacts are relatively weak in strength. This is in accordance with previous studies, where N was observed to be a better electron donor than others.[68] To get a deep insight into the nature of S...F interaction, energy decomposition analysis was performed for all the complexes. Figure 3 shows the percentage contribution of the individual components

towards the stabilization of the complex. The magnitude of each component has been reported in Table S3 (in Supplementary Information). The results showed that the major contribution towards the stability of the interactions comes from the exchange energy component followed by the electrostatic energy component. The percentage contribution towards stabilization was evaluated by adding the electrostatic, exchange, polarization and dispersion energy components and then dividing the magnitude of the individual terms with the total stabilization energy obtained. The percentage contribution of the exchange energy towards stabilization energy was more than 40% for all the complexes with the maximum being for X = −NHCH$_3$. The percentage contribution of the electrostatic energy was more than 25% in all the cases with maxima for X = −NO$_2$ (Figure 3). With the exception of NO$_2$ and CN-substituted complexes, the contribution of the exchange energy increases with increase in total binding
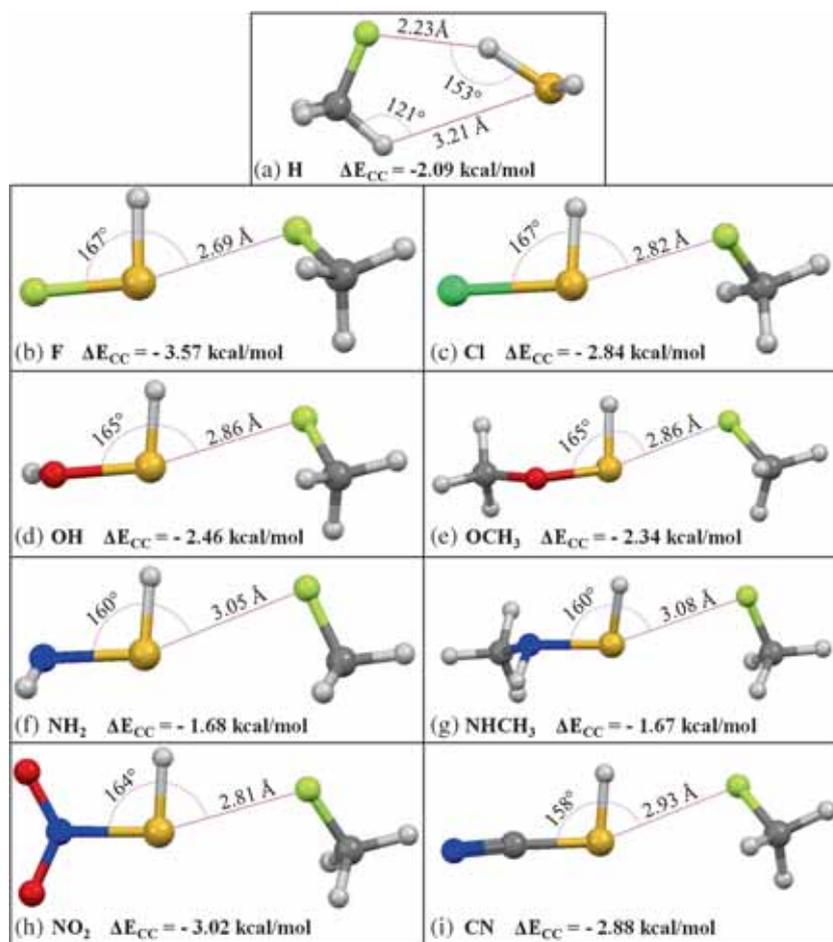
Figure 2. Optimized geometries of the XHS$\cdots$FCH$_3$ complex for X = (a) $-$H, (b) $-$F, (c) $-$Cl, (d) $-$OH, (e) $-$OCH$_3$, (f) $-$NH$_2$, (g) $-$NHCH$_3$, (h) $-$NO$_2$, (i) $-$CN.

Table 1. Geometrical Parameters, binding energies, topological parameters and charge transfer energies obtained for different XHS$\cdots$FCH$_3$ complexes.

X	F	NO$_2$	CN	Cl	OH	OCH$_3$	NH$_2$	NHCH$_3$
S$\ldots$F (Å)	2.69	2.81	2.93	2.82	2.86	2.88	3.05	3.08
$\angle$X-S$\ldots$F($^\circ$)	167	164	158	164	165	165	160	160
ΔE_{cc}^a(kcal/mol)	-3.57	-3.02	-2.88	-2.84	-2.46	-2.34	-1.68	-1.67
BPL(Å)	2.705	2.819	2.935	2.832	2.876	2.893	3.054	3.080
ρ(e/Å^3)	0.111	0.093	0.074	0.089	0.080	0.077	0.056	0.054
$\nabla^2\rho$(e/Å^5)	1.596	1.298	1.142	1.294	1.205	1.163	0.898	0.868
$|V_b|/G_b$	0.950	0.919	0.854	0.908	0.893	0.888	0.822	0.816
E(2)$_{F(lp)to\sigma*(S-X)}$(kcal/mol)	5.12	3.32	1.52	2.97	2.48	2.38	0.95	0.88

^{a}Counterpoise-corrected binding energies.

energy while the contribution of electrostatic energy decreased with increase in the binding energies. The anomalies with regard to NO$_2$ and CN-substituted complexes can be attributed to the electronic environment of the substituents. In the case of NO$_2$, three electronegative atoms are present as compared to other complexes where sulphur atom is attached to only one electronegative atom. The anomaly with regard to CN can be attributed to the fact that in this case sulphur is not directly attached to the electronegative atom. An anomaly with regard to some substitutions has been discussed in the previous studies.[38] While NO$_2$ and CN substitution results in highly stabilized complex, the nature of the substituent has more direct effect on the
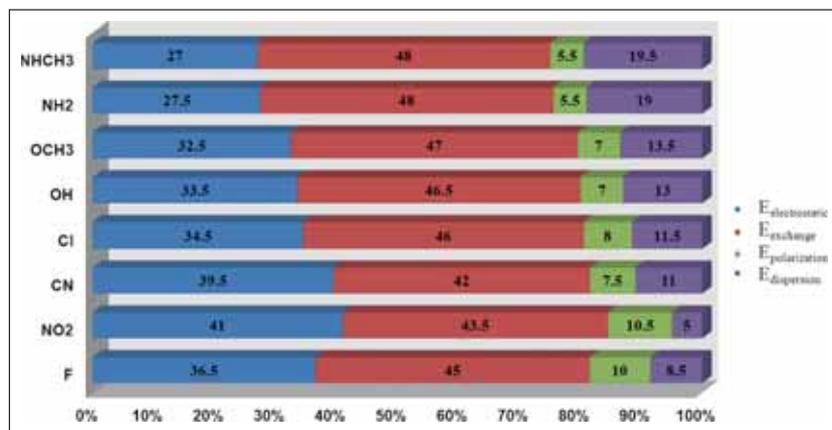
Figure 3. Percentage contribution of different energy components (obtained from energy decomposition analysis) contributing towards stabilization of different $XHS \cdots FCH_3$ non-covalent bond.

individual energy component. The percentage contribution of the polarization term was more than dispersion component for the F and NO_2 substituted complexes while the contribution of the dispersion component was higher for the rest of the complexes. Again, with the exception of NO_2 and CN, the contribution of polarization

decreased with decreasing binding energy while the contribution from dispersion component increased with decreasing binding energy.

The topological analysis was performed for all the complexes; in the case of X = −H, a Bond Critical Point (BCP) was observed between the hydrogen
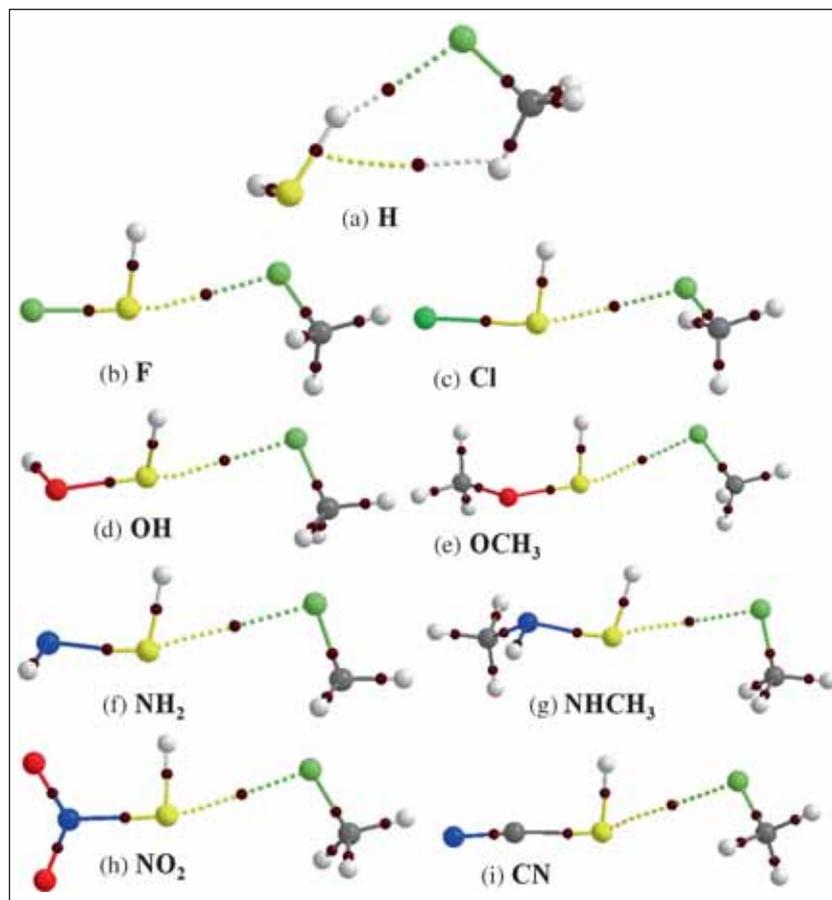

Figure 4. Molecular pairs representing bond critical point between S and F in $XHS \cdots FCH_3$ complexes (except for X = −H).

of SH_2 and fluorine atom present in CH_3F. In addition to this, an additional BCP was observed between the hydrogen of CH_3F and sulphur atom (Figure 4). In rest of the complexes, a BCP was observed to be exclusive between sulphur and the fluorine atom. The magnitude of S...F Bond Path Length (BPL) was observed similar to the corresponding S...F bond lengths (Table 1). Although the magnitude of bond path length and bond length were observed to be almost same, the origin of these values is different.[69] The magnitude of ρ ranged from 0.054 e/Å^3 for X = −$NHCH_3$ to 0.111 e/Å^3 for X = −F with the order being $NHCH_3$ < NH_2 < −CN < −OCH_3 < OH < Cl < NO_2 < F. Figure 5 shows that the magnitude of ρ decreases with increasing S...F BPL. The values of $\nabla^2\rho$ followed the same trend as observed for ρ with values ranging for 0.868 e/Å^5 to 1.596 e/Å^5 (Figure 6). Since the magnitude of ρ for the S...F interactions in all complexes is positive and has positive magnitudes of $\nabla^2\rho$, it confirms the S...F interactions in

all complexes is closed-shell in nature. The $|V_b|/G_b$ ratio for the entire S...F contacts was close to one, similar to those observed for other chalcogen bonds.[50]

The magnitude of second order perturbation energy obtained for F(lp) to σ*(S-X) charge transfer ranges from 0.88 kcal/mol to 5.12 kcal/mol (Table 1) but followed a different trend in comparison to the values obtained from counterpoise-correct binding energy. This difference in trend between ΔE_{CC} and E(2) can be attributed to the different ways in which these two sets of values are computed. The binding energies are evaluated by considering the basis sets of the entire molecule participating in the interaction, while the E(2) energies only show the contribution coming from a specific set of interacting orbitals. Here also anomalies with regard to the magnitude of F(lp) to S transition were observed for X = −NO_2 and X = −CN (Figure 7a). With the exception of these two complexes, the remaining analysis shows that E(2) extensively mimics the trends observed
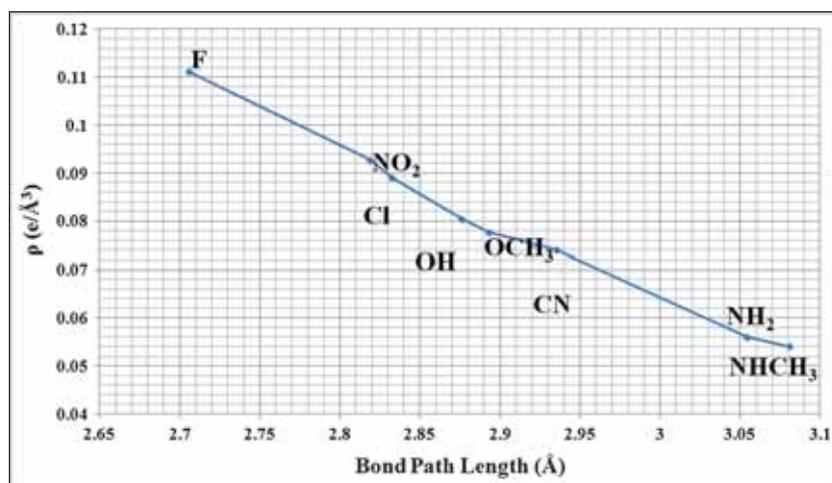

Figure 5. Plot showing variation of ρ with increasing bond path lengths for XHS···FCH_3 complexes.

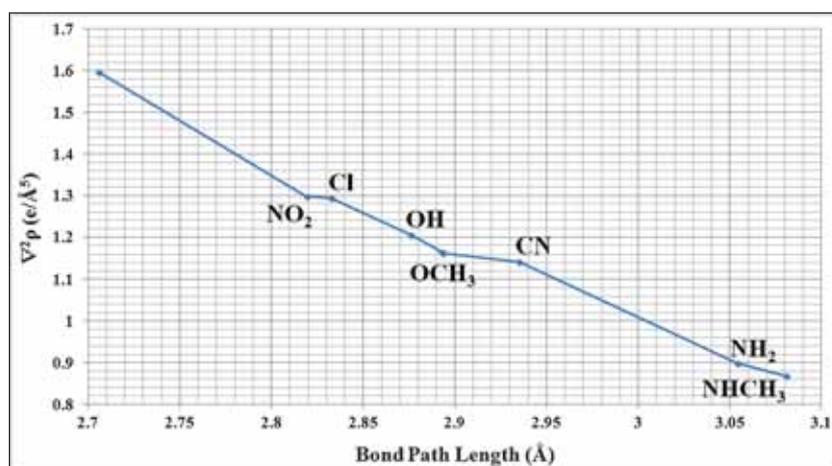**Figure 6.** Plot showing a variation of $\nabla^2\rho$ with increasing bond path length for XHS···FCH_3 complexes.
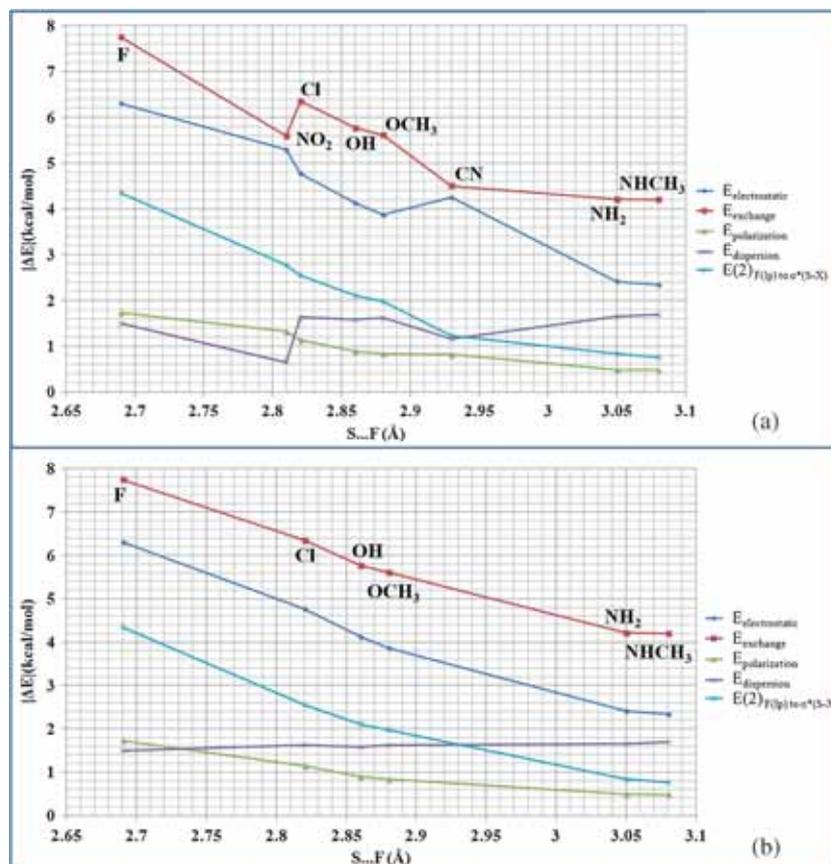
Figure 7. Variation of different energy decomposition terms with that of E(2) energy of XHS···FCH$_3$ complexes. (a) for all the substituents; (b) excluding X = −NO$_2$, −CN.

for electrostatic and exchange energy component and the origin of E(2) can be largely attributed to these two energy components (Figure 7b).

4. Conclusions

A theoretical investigation on XHS...FCH$_3$ model system was performed to study the effect of substitution on F...S non-covalent bonds. The results showed that the stability of the S...F contact is directly affected by the electron withdrawing ability of the substituent group. Electrostatic energy and exchange energy are the major contributors towards the stability of these contacts. The closed shell nature of the S...F contact was confirmed by the topological analysis of the electron densities. Hence, similar to other chalcogens and pnicogen atom which participate in the formation of chalcogen bonds, halogen atom can also form highly stabilized chalcogen bonds.

Supplementary Information (SI)

Coordinates of the optimized geometries for all the complexes, geometrical and topological parameters for X = −H complex and result of energy decomposition analysis (Tables S1–S3) are available at www.ias.ac.in/chemsci.

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