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REVIEW ARTICLE

Unravelling the Importance of H bonds, σ–hole and π–hole-Directed Intermolecular Interactions in Nature

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Abstract | The field of intra- and intermolecular interactions has received a major boost in the past one decade. Significant advances in both instrumentation (for experimental purposes) and computational resources (development of theoretical models) have provided strong impetus to this area of research. The understanding of the nature, energetics and the topological characteristics of these interactions are the driving forces which govern intermolecular recognition. This is strongly dependent on the state of aggregation of the substance. The environment (solid, liquid and gas) plays an extremely crucial and subtle role in deciphering the mechanism via which molecules interact with each other. In the past two decades, there has been rigorous development in the understanding of strong hydrogen bonds. The focus has now shifted towards the quantitative assessment of weak intermolecular interactions, of the type C–H···X (X = F in particular), X···X, X(lp)···π along with σ–hole-directed intermolecular interactions involving tetrels, chalcogens, pnictogens, halogens and the aerogens. In addition, there is increasing evidence for the assessment of the relevance of π–hole-based interactions in tetrels, chalcogens, and pnictogens as well. The current perspective highlights the importance of the above-mentioned interactions and their associated electronic features. This has strong implications in the area of materials and related applied sciences with relevance towards the technological applications of these interactions in terms of understanding structure–property correlation in the mechanical, optical and electrical properties of matter.

1 Introduction to Intermolecular and Intramolecular Interactions

Intermolecular and intramolecular forces are the two ubiquitous forces that are responsible for the existence of individual molecules and bind the atoms together. *Intermolecular forces* are the forces which mediate an interaction between molecules, including forces of attraction between nucleus and electrons or repulsion between nuclei and electrons separately.[1–3] The resultant of all these forces act between the molecules and other types of neighbouring particles, e.g. atoms or ions and are responsible for the existence of the condensed phase. Intermolecular forces are weak relative to intramolecular forces—the forces which hold a molecule together. For example, the covalent bond, involving sharing of electron pairs between atoms, is much stronger than the forces present between neighbouring molecules. Both sets of forces are essential parts of the force fields that are frequently used in molecular mechanics. The dynamic nature of the molecules is controlled via a balance of all these forces and hence these

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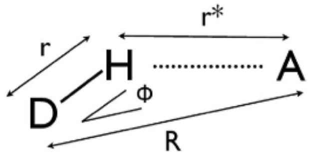


Scheme 1: Simple diagrammatic representation of the hydrogen bond.

determine the chemical and physical characteristics of all substances in nature.

2 Hydrogen Bond

This can be defined as a form of association between an electronegative atom (labelled **A**, Scheme 1) and a hydrogen atom attached to another electronegative atom (labelled **D**). The **D**–**H** bond is referred to as a *donor* and the atom **A** is referred to as the *acceptor* atom.

It is primarily considered as an electrostatic interaction, heightened by the small size of hydrogen, which permits proximity of the interacting dipoles or charges. The electronegative atoms are usually N, O, F, Cl, S, π, etc. Hydrogen prefers to form short [small magnitude of r* (H⋯A)] and directional (high magnitude of $\phi = \angle \text{D–H} \cdots \text{A}$) hydrogen bond.[4–7]. The occurrence of the ubiquitous hydrogen bond is a unique phenomenon in structural chemistry, materials science and biology. Its fundamental importance lies in its role in defining the nature and associated energetics of the molecular association. The magnitude of the hydrogen bond is extremely sensitive to the nature of the donor and acceptor atoms and the electronic environment within the molecules, i.e. the electronic/steric roles of the participating functional groups in molecules (organic, organometallics, inorganic complexes, viruses and proteins). Based on the interaction strength, the hydrogen bond can be categorized into very strong (15–40 kcal/mol), moderately strong (4–15 kcal/mol) and weak (4 kcal/mol).[1–3]. This system of division has been given by Jeffrey[8] who called hydrogen bonds moderate if they resemble those between water molecules or in carbohydrates.

2.1 Strong Hydrogen Bond

Hydrogen bonds are a key feature of chemical structure and reactivity. Recently, there has been much interest in a special class of hydrogen bonds called "strong" or "low-barrier" H bonds and are characterized by high magnitudes of strength, very short distances, a low or vanishing barrier to hydrogen transfer and distinctive features in the NMR spectrum. The strength of these hydrogen bonds ranges from 4 kcal/mol to 40 kcal/mol.[1–3] These bonds have strong directionality and bond angles with 170°–180°.[9] Some examples of strong hydrogen bonds are $\text{F–H}\cdots\text{F}^-$, $\text{S–H}\cdots\text{S}^-$ and $\text{P—O–H}\cdots\text{O}^-\text{P}$.

2.2 Weak Hydrogen Bond

These types of hydrogen bonds are characterized by reduced magnitude of stabilization energy, the energy being less than 4 kcal/mol. These bonds are "electrostatic" in nature, but this characteristic is modified via "dispersive" and "charge-transfer" components that depend primarily on the nature of donor and acceptor group. The strongest of these bonds such as O–H⋯Ph and C≡C–H⋯O are sufficiently electrostatic and comparable to a bond like O–H⋯O–H. These lie in the energy range of -2 to -4 kcal/mol. The weakest of these, of the type C–H⋯π, are formed by unactivated methyl groups (about -0.5 kcal/mol).[2] All kinds of hydrogen bonds are different, and likewise all kinds of weak hydrogen bonds are also different. These include the following combinations: weak donor/strong acceptor (for examples C–H⋯O/N and more recently M–H⋯O (M = TM); strong donor/weak acceptor (O–H/N–H⋯C=C/C≡C/M), weak donor/weak acceptor (C–H⋯π, S–H⋯π, C–H⋯M and C–H⋯F–C).

The electrostatic nature of the C–H⋯O/N hydrogen bond determines its role in influencing the crystal packing. The coulombic interactions between point charges (separated by a distance r) are relatively long range, falling off as r^{-1}. For comparison, the short-range van der Waals interaction falls off as r^{-6}. It may be thus inferred that even incipient C–H⋯O bonds have an orienting effect on the crystalizing molecules, and before the effects are felt of the van der Waals interactions that will ultimately determine the close-packing characteristics of molecules in the solid state. The hydrogen bond determines general connectivity patterns of molecules, while the dispersive interactions which are of an isotropic nature determine both the "intramolecular conformation" and "intermolecular close packing" within the basic scaffolding established by the hydrogen bonds. Weak C–H⋯O hydrogen bonds play a supportive and intrusive role, wherein their directional preferences are satisfied within the geometrical constraints of the stronger O–H⋯O and N–H⋯O hydrogen bonds, which can significantly disturb the effects of close-packing interactions. C–H⋯O hydrogen bonds are able to discriminate between alternative O–H···O or N–H···O networks, which though geometrically reasonable are structurally quite distinct. In such cases, weak hydrogen bonds may be termed steering or tugboat interactions, which though small in energy are sufficient to select a particular pathway from amongst different possibilities. The energy of individual C–H···O/N hydrogen bond may be small, but if their number crosses a critical threshold, the structure may direct itself into an unconventional packing.

In recent years, several studies have addressed the relevance of the criteria as proposed by IUPAC.[4]. In particular, the following factors are deemed significant:

1. the electronegativity of the participating donor and acceptor atoms which is very sensitive to the chemical environment of the molecule;
2. the sum of the van der Waals radii of the donor and the acceptor atoms as indicators of hydrogen bonding;
3. the role of directionality of H bonds in crystal packing.

Studies via quantitative insights, from experimental and theoretical electron density analysis, have looked at the above-mentioned characteristics in systems containing organic fluorine in molecular crystals, wherein C–H···F H bonds have been observed and organic fluorine has been established to be indeed polarizable.[5] In addition, a “region of overlap” has been identified, in terms of electron and energy densities, which distinguishes between C–H···O interactions (H bond) and C–H···π interactions (van der Waals interaction) in molecular crystals.[6] Furthermore, a similar region has also been identified by a topological investigation of C–H···X (X=–Cl, –Br, –I) interactions in molecular crystals of halogen containing benzamides.[7]

The understanding of the electronic features of weak hydrogen-bonded interactions, and their role in structure–property correlation, has undergone a major renaissance in the last one decade.

3 σ–hole and Its Interactions

The σ–hole is a positive electrostatic surface on a molecular entity along the extension of the Y–Ge/P/Se/X covalent σ bond (Y = electron-rich group; Ge/P/Se/X = Groups IV–VII). Depending upon the electronic environment along the σ bond, the electron cloud gets redistributed anisotropically along the bond and results in the formation of a region with positive electrostatic region and low electron density. For a molecule, the molecular electrostatic potential (MESP) produced by the electron and the nuclei is given by the following expression,

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')\mathrm{d}r'}{|r' - r|} \tag{1}$$

where Z_A is the charge of nucleus A; $\rho(r')$ is the electron density of the molecule; R_A is the location of the nucleus.

In this equation, the first part represents the positive electropositive potential on atomic nuclei. The second negative term is for the electron cloud.[10, 11]

The formation of a σ–hole can be explained by general chemical concepts. This σ–hole is generally formed at the more electropositive atom along the outer extension of a σ covalent bond. The explanation for the existence of a σ–hole in Group 14 to Group 18 can be obtained from the accumulation of the electron density in the bond region and consequently its depletion in the elongation of this bond at the centre considered.[9] During the formation of a σ covalent bond, an electron density is produced between the nuclei and the potential energy is decreased on account of the same. This leads to a decrease in the electron density beyond the bond and hence the name termed as σ–hole.[9]

The σ–hole can act as an electrophile and can interact attractively with an electron-rich region of a same molecule or a different molecule resulting in the formation of a σ–*hole bond* (Fig. 2).[12, 13]

The σ–hole bond is a noncovalent interaction between a covalently bonded atom of group 14–17 and a negative site of the molecule (intramolecular) or with a different molecule (intermolecular), e.g. a lone pair of a Lewis base or an anion. It involves the presence of a σ–hole on the extension of the σ covalent bond.[14] On the basis of the group of the element on which the σ–hole is present, there are four types of σ–hole interactions: halogen bonds[15] (Gr 17); chalcogen bonds[16] (Gr 16); pnictogen bonds (Gr 15)[17] and tetrel bonds (Gr 14).[18] Figure 1 represents the MESP of the molecule centres from Group 14–17 (plotted on an electron density isosurface of 0.001 au). Here, the positive electrostatic potential on Br, Se, As and Ge centres (Z-centres) ranges from 0.07 to 0.08 au along the F–Z bond. It is interesting to note that, Br, Se and As centres, and other halogens, chalcogens and pnictogens

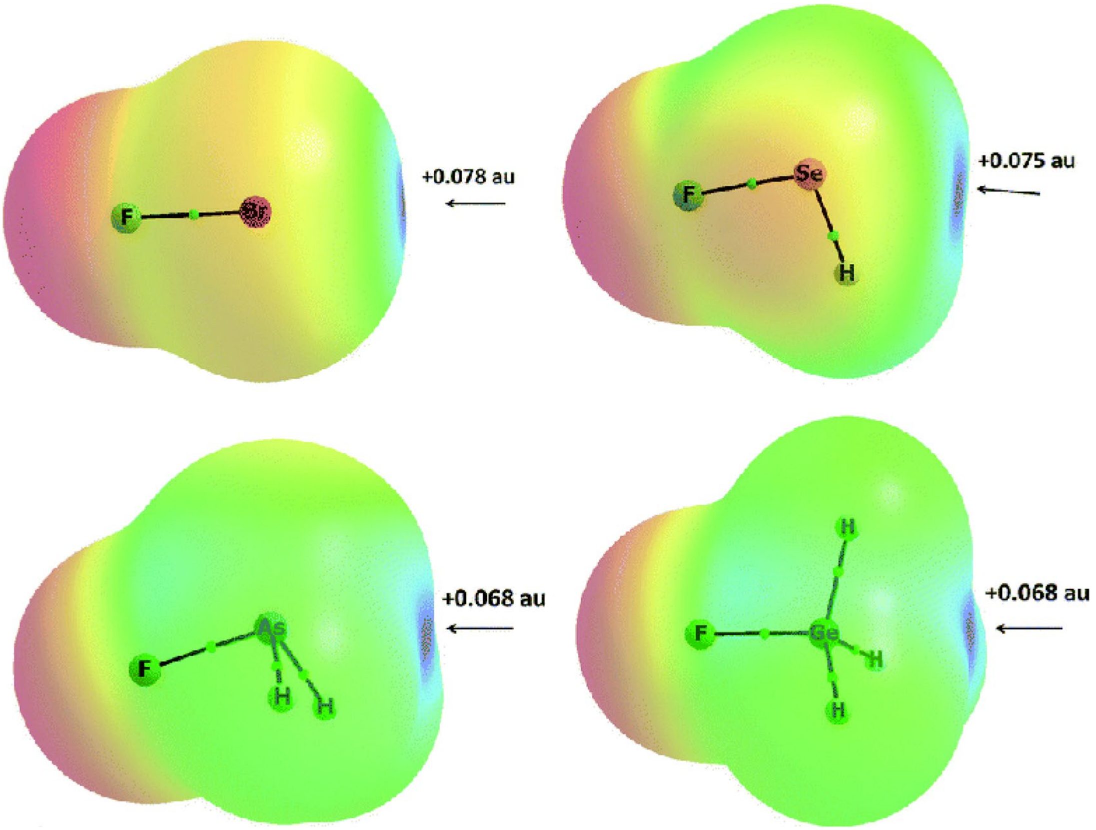


Figure 1: Electrostatic potential maps of BrF, SeFH, $AsFH_2$ and $GeFH_3$ for the surface characterized by an electron density of 0.001 au. The arrows show the maximum EP corresponding to the presence of the σ–hole (reproduced by permission of PCCP Owner Societies Copyright 2017, Grabowski[9]).

exhibit amphoteric character, as these may usually act as the Lewis acid and Lewis base at the same time, since these possess the regions of σ–hole (positive MESP) and the regions of lone pair with negative MESP. The tetrel sp^3 hybridized centres are an exception, because of not having a lone pair. The elongation of the bond to the tetrel centre is usually characterized by the σ–hole with positive molecular electrostatic potential.[9] There are some exceptions, such as:

- The σ–hole cannot be always characterized by the positive electrostatic potential, because in some cases the electron density depletion is not sufficient to obtain the advantage of the nuclear electrostatic potential over the electrostatic potential of the electrons.
- The elements of Group 14 possess regions attributed to lone pairs of electron and consequently of negative EP in carbenes and other tetrylenes: silylenes, germylenes, stannylenes and plumbylenes.
- There are many differences between elements of the same group such as –F atom generally does not have the areas with positive electrostatic potential, while heavier halogens possess a dual character.[9]
- For tetrel species, such as CH_4, the carbon atom often does not possess positive electrostatic potential region, but in the case of $CClH_3$, a positive electrostatic potential region has been observed along the elongation of the C–Cl bond, which may lead to the initiation of the SN_2 reactions.[19]
- For monovalent halogens, a positive electrostatic potential region accompanied by a negative electrostatic potential, corresponding to the presence of lone pairs, is often observed, but in the case of multivalent halogens (e.g.: BrF_3 and BrF_5) only a positive electrostatic region is observed.[20]

In Fig. 2, the presence of a σ–hole (positive electrostatic potential) on the atom (marked in bold) of the different groups along the extension

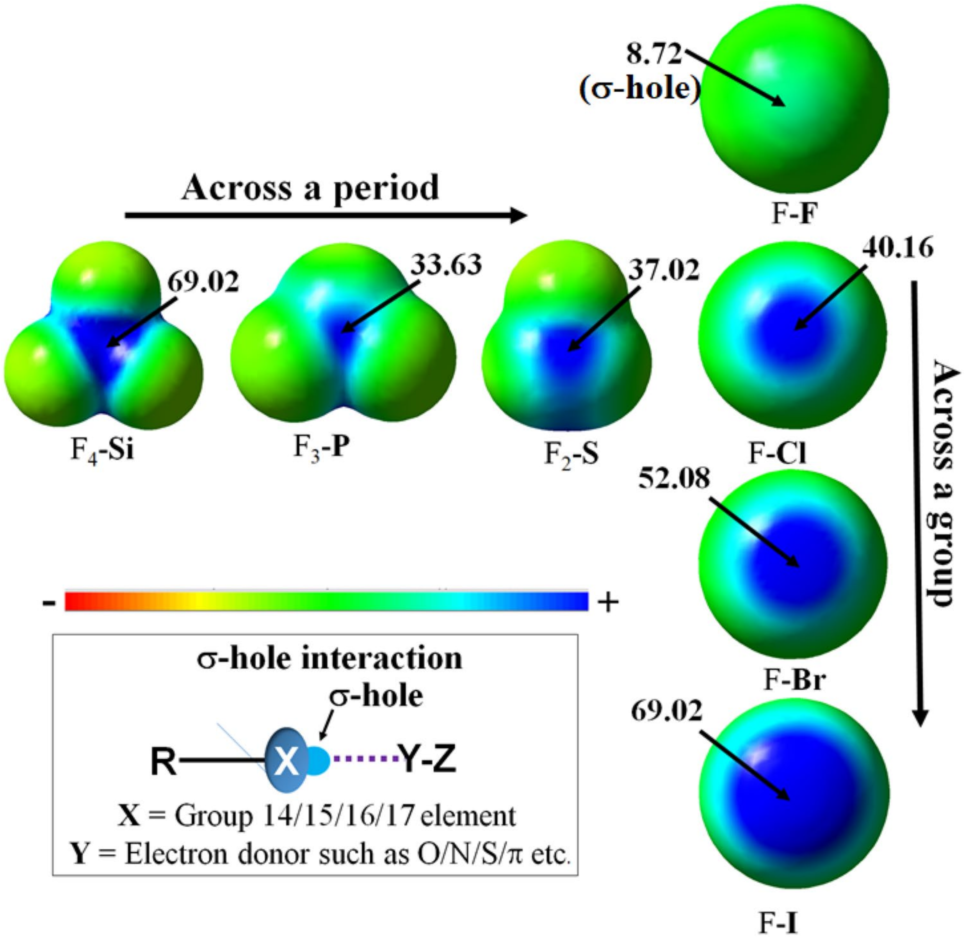


Figure 2: The molecular electrostatic potential and magnitude of the σ–hole (marked by arrow) on atoms across a period (F_4Si, F_3P, F_2S and FCl) and across a group (FF, FCl, FBr, and FI) on a 0.001 au electron density isosurface computed at MP2/aug-cc-pVDZ (MP2/LANL2DZ for FI). All values are in kcal/mol.

of the covalent bond in the electrostatic potential maps has been depicted. From this molecular electrostatic potential map of the representative compounds, it has been observed that the magnitude of the σ–hole across a period follows the trend $F_3\mathbf{P} < F_2\mathbf{S} < F\mathbf{Cl} < F_4\mathbf{Si}$. Here, the role of the steric environment is also of significance and dominates, as the presence of four covalent bonds inhibit the capability of σ–hole on Si to participate in the formation of an interaction as an electron acceptor. Generally, the σ–hole is more accessible for atoms with lower valence and follows the trend: $F\mathbf{Cl} > F_2\mathbf{S} > F_3\mathbf{P} > F_4\mathbf{Si}$. Also, the magnitude of the σ–hole increases down the group due to the high polarizability of the heavier atom.[21] In the representative compounds, involving halogens, the magnitude of the σ–hole on the halogen follows the trend $FF < F\mathbf{Cl} < F\mathbf{Br} < FI$. In the concept on σ–hole, the role of electrostatic potential is emphasized. The centre with maximum electrostatic potential in the Lewis acid units determines the directionality of interaction with Lewis bases; besides these, numerous relations have been found between those potential values and interaction energies which may confirm the electrostatic nature of the σ–hole bonds.[12, 22] The strength of the σ–hole interactions depends on the magnitudes of the positive and negative electrostatic potential on the σ–hole and the negative site, respectively. In some cases, the polarizability also plays a crucial role, as the polarization of the negative site can be viewed as a degree of dative sharing (coordinate covalence). The strengths of this bond also depend on dispersion[23, 24] as claimed by Politzer, Murray and Clark that "Their features and properties can be fully explained in terms of electrostatics and polarization plus dispersion".[12] The polarization can also be understood as the attractive interaction related to electron charge shifts resulting from complexation. Such shifts imply the "transfer" of electron charge from the Lewis base to the Lewis acids, which is common in case of all Lewis acid–Lewis base interactions.[23, 24]

3.1 Halogen Bond

In 1863, Dr. Frederick Guthe reported about the purification and formulation of NH_3:I_2,[25] but at that time the nature of the interaction and the reason behind its formation were unexplored. In 1954, for the first time, a crystallographic study was done on a 1:1 molecular complex of dioxane and bromine, the interaction between the molecules pointing to the possibility of a Br···O interaction in the solid state.[26, 27] In 1970, Prof Hassel discussed about the capability of halogen to act as a nucleophile and its importance in supramolecular chemistry.[28] After that, many related studies have been performed and the first major result has come in a breakthrough that happened in 1992, when it was observed that the ESP distribution in halogen is anisotropic[29] and there is a region with positive ESP (presently known as σ–hole) at the tip of the covalent-bonded halogen atom, corresponding to a maxima of the electrostatic potential mapped on a surface ($V_{S,max}$).[30] After several years, it was revealed that this σ–hole can also form an attractive bond with an electron-rich region (π electron cloud), a halogen bond.[21, 31, 32] In 2013, IUPAC proposed a definition of the halogen bond: "A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity".[30]

From the electrostatic potential distribution of the atoms involved in the formation of the halogen bond, and the directional preferences during the interactions, such as side on interactions with electrophile and head-on interactions with nucleophile, the geometrical requirement that satisfies these requirements results in the R-X-B angle nearly linear, the magnitude being close to 180° (Fig. 3).[33]

Halogen bonds and hydrogen bond are considered to have orthogonal molecular interactions, because while sharing a common acceptor they are energetically independent and geometrically perpendicular.[34] As the σ–hole originates from the polarization of the electronic charge towards the R–X covalent bond, if X is less polarizable and more electron withdrawing, then the σ–hole might be neutralized or may even be absent.[35] The σ–hole on the halogen is more positive, because the heavier halogen is more polarizable and has less electronegativity. The electron-withdrawing tendency decreases from fluorine to iodine. The fluorine atom withdraws sufficient electron density from other parts of the molecule to reduce the magnitude of the σ–hole, so the fluorine centres are not usually characterized by the Lewis acid properties.[9] So, the strength of the halogen bond increases from chlorine to iodine, and fluorine is not considered as a halogen bond donor. There exists a relationship between the calculated interaction energies and the observed $V_{S,\,max}$, which supports the electrostatic nature of the halogen bond.[36, 37] The positive σ–hole and the negative B acceptor (Fig. 3) induce mutual electron density rearrangement, which depends on the polarizabilities of the participating atoms.[38] It can be concluded that polarization is also an intrinsic part that contributes towards the overall nature of the interaction. Besides polarizability and electrostatics, dispersion also plays a significant role in the nature of the interaction, primarily in the case of weak halogen bond,[39] such as the R–X···B bond angle of ~ 180° and the polarizability of a side-on interaction with an electrophile (Fig. 3). Apart from acting as an electrophile due to the presence of σ–hole, the halogen can act also as an electron donor during the formation of an interaction due to the presence of lone pair of electrons. That is why in the case of halogen–halogen interaction, there are two types of contacts involving halogens, named Type 1 and Type 2, based on the orientation of the two interacting halogens with respect to each other (Fig. 4)[40] Only Type 2 is considered as a halogen bond[41], because in this case the electrophilic

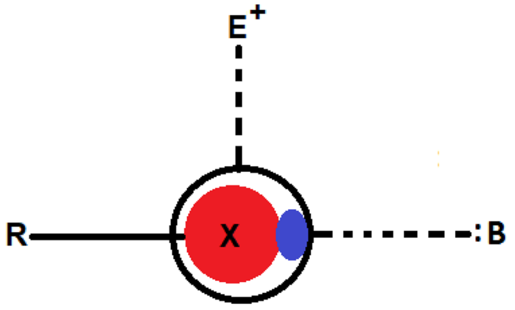
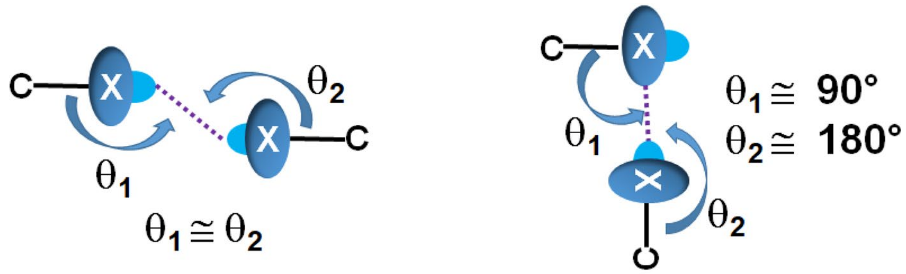


Figure 3: Schematic representation of an **R–X····:B** halogen bond with an anisotropic charge distribution around X. The blue and red regions represent the electrostatically positive and electrostatically negative regions, respectively. E^+ represents the electrophilic and :B represents the nucleophile with a lone pair of electrons.



Type I halogen-halogen interaction

Type II halogen-halogen interaction ("Halogen Bond")

Figure 4: Geometrical features of Type **I** and **II** halogen–halogen interaction.

region of one halogen points to the nucleophilic region of another halogen.

The electrostatic nature of the halogen bond is still not consensual, and some researchers point towards the presence of a dominant charge-transfer nature, namely a donor–acceptor interaction.[42] This charge-transfer nature also constitutes the covalent character in the bond,[42] and its existence is supported by many theoretical and experimental studies.[43–45] According to this theory, the stabilization arises from HOMO–LUMO interactions between a lone pair of B and the σ^* orbital of C–X.[46]

The debate on the nature of this interaction continues and this is reflected in the fact that the number of research articles in this subject has been steadily increasing. In recent times, investigations on the nature of the halogen bond in solution are of active interest.[47] Coupled cluster theory, in particular with CCSD(T)/aug-cc-pVTZ calculations, has been used to study the nature and strength of a series of dimers of the type $YX\cdots BR_m$, where X = F, Cl, Br; Y is the donor group and BR_m is the acceptor group. These dimers comprise 36 neutral and anionic halogen-bonded complexes and eight complexes with hydrogen, pnictogen and chalcogen bond.[48] In this study, many quantitative estimates, based on natural bond orbital (NBO) charges, charge-transfer energies, molecular electrostatic potential, local stretching and bending force constants, relative bond strength orders and vibrational frequencies, have been obtained. Bond strength order (BSO) is derived from the local stretching force constants and this BSO differentiates the halogen bond into three categories, that is: (1) weak and predominantly electrostatic halogen bond (< 10 kcal/mol),[49] (2) normal halogen bond (10–45 kcal/mol)[49] and (3) strong and predominantly covalent halogen bond (~ 45 kcal/mol).[49] The covalent bond is due to a *3c–4e* (three-centre–four-electron) interaction, and from the characteristics of this covalent bond, the charge-transfer values are calculated. The electrostatic value of this interaction is mainly dependent on the polarizing strength of B, polarity of X–Y bond and the polarizability of X.[33] A similar analysis was done over 202 halogen-bonded complexes, using ωB97XD/aug-cc-pVTZ and CCSD(T)/aug-cc-pVTZ calculations.[49] The researchers have successfully shown that the halogen-bonded system possesses sizable covalent contributions and these have more covalent character than their counterparts, i.e. the corresponding hydrogen bonds and pnictogen bonds. It was also observed that the analysis of the σ–hole can explain the electrostatic origin of the halogen bond, but it cannot explain the covalent character of the halogen bond, because its covalency depends on both its potential and kinetic energy.[49] Recently, another study was done using a complex $F{-}Br\cdots X{-}R$ (X = F, Cl, Br, I and R = H, F) by the analysis of MEP (molecular electrostatic potential), atoms in molecules (AIM) analysis, energy decomposition analysis (EDA) and molecular polarizability based on MP2/aug-cc-pVTZ optimizations. This study was done to understand the role of polarizability of the electron pair donor in the formation of halogen bonds.[50] From the topological analysis of the electron density and the analysis of the atomic quadrupole moments, it was concluded that the $Br\cdots X$ interactions are electrostatic in nature. The controversy surrounding the nature of the halogen bond has increased, as indicated from the recently published literature[51], which says that the charge-transfer component of the interaction energy of a hydrogen bond is contaminated by the basis set superposition error and, therefore, NBO analysis of the interaction energies "are meaningless in the context of intermolecular interactions".[51] Various crystallographic studies have explored the importance of halogen bonding in the context of crystal packing,[52], polymorphism,[53, 54], co-crystal formation,[55], isostructurality[56, 57] and in biological systems[58] as well.

3.2 Chalcogen Bond

In 1977, for the first time, the concept of "chalcogen bond" was proposed, with the exploration of sulphur containing nonbonded interaction.[59] Row et al. explored the geometry of S···S interactions in molecular crystals through a crystallographic database study.[60] This interaction has also been investigated in a recent study via ab initio calculations.[61] The first detailed quantitative investigation of the chalcogen bond was done on S···O and Se···O interaction present in thiazole and selenazole nucleosides.[61] Nagoa et al. explored the importance of intermolecular S···O interaction in the crystal structure of (acylimino) thiadiazoline derivatives.[62] After that, many theoretical and experimental studies have been performed to explain the electrophilic character of chalcogen in the chalcogen bond. In 2007, after accounting for the presence of a σ–hole on the halogen bond,[30] Murray et al. extended the concept to chalcogens as well[63] and explored the existence of σ–hole-directed chalcogen bonds, even in case of gas phase molecular complexes.[64] A recent study, with combined inputs from the Cambridge Structural Database and ab initio calculations, was performed to investigate the S···S interactions and indicated that these were dispersive in nature.[65]

The term "Chalcogen Bond" was coined by Wang et al. in 2009.[66] In the last decade, it garnered tremendous significant attention across the scientific community with consistent efforts towards the understanding of the nature of this interaction. Generally, the formation of this bond can be explained by the formation of a σ–hole, the positive electrostatic region on the outermost position of the surface of chalcogen, opposite to the R–Ch bond (Fig. 5). This σ–hole refers to an electron-deficient outer lobe of a *p* orbital which is involved in the covalent bond.[67] The size of the σ–hole increases from the lighter to the heavier chalcogen atoms as the polarizability increases and electronegativity decreases (O < S < Se < Te). In the case of multivalent chalcogens, the respective σ–holes are localized on the axes of the covalent bonds (e.g. opposite to R^1 and R^2 in Fig. 5)[68], while the R–Ch covalent bond elongates along the direction of formation of chalcogen bonds. The importance of chalcogen bonds has also been realized in proteins.[69, 70] Due to the presence of lone pairs of chalcogen atoms, the σ–hole is surrounded by a region of negative potential, which determines the directionality of the chalcogen bonds. The linear geometry of the R–Ch···D fragment provides a maximal electrostatic attraction between the σ–hole and the area of negative molecular electrostatic potential around the lone pairs of Ch, resulting in a minimal repulsion between the areas of negative electrostatic potential.[71] These noncovalent contacts find applications in anion transport as well.[72] Similar to hydrogen bond, chalcogen bonds are also classified into several types: (1) negative charge-assisted chalcogen bonds ($Ch\cdots D^-$), (2) positive charge-assisted chalcogen bonds ($Ch\cdots D^+$), (3) conventional (or "neutral") chalcogen bonds (Ch···D) and (4) resonance-assisted chalcogen bonds (RACB).[73–78] In the case of RACB, the Ch interactions are assisted by a conjugate π system. There are some specific features[79–82] of chalcogen bonds such as:

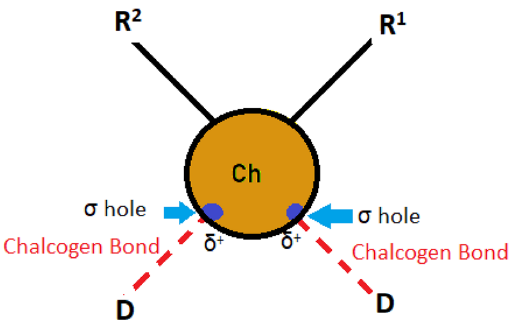


Figure 5: Schematic representation of chalcogen bonds (Ch denotes the chalcogen atom; R1 and R2 are electron-withdrawing groups). The blue spheres represent the electrostatically positive region.

- *Directionality* The localization of the region of positive electrostatic potential on the outermost region, opposite to R, results in the elongation of the R–Ch bond, linearly approaching D. Therefore, a typical R–Ch···D angle of 180° is formed. The stronger the chalcogen bond, the shorter is the Ch···D distance. The highly directional interaction between sulphur atom and the aromatic rings in the side chain of amino acids[83, 84] is crucial for the formation, stability and unique properties of α-helices in proteins.
- *Tunability* The strength of the chalcogen bonds can be tuned by the variation of R or D and by the replacement of the Ch atom by another (O, S, Se, Te).

- *Hydrophobicity* Chalcogen bond donors are more hydrophobic than the donors of the hydrogen bond, so on certain occasions the positive ESP region gets hindered by the presence of the remaining covalent bonds in the molecule.[71] The attached groups on the chalcogen atom prevent the solubility of organochalcogens in aqueous or polar solvents.[85]
- *Donor atom size* The van der Waals radius[86] of hydrogen atom (1.20 Å) is shorter than that of the chalcogen atoms (1.52, 1.80, 1.90 and 2.06 Å for O, S, Se and Te, respectively)[87], which results in the hydrogen bond being less sensitive to the steric hindrance than the chalcogen bonds.
- *Multiplicity* Chalcogen may have variable valency and can form multiple chalcogen bonds. This allows to make new type of molecules with unique properties during the process of synthetic transformation, catalysis, and in crystal engineering.

In comparison with the hydrogen bond and halogen bond, this chalcogen bond is less explored as a family member of σ–hole interaction. The first four properties mentioned here (directionality, tunability, hydrophobicity and donor atom size) can be exploited in synthetic operations like those of halogen bonding, but the multiple bond-forming capability is an additional aspect that is explored in synthesis and design. Multiple chalcogen bonds between S, Se and Te centres favour the formation of nanotube-like structures in the solid state, which are able to host other molecules.[88] Furthermore, the chalcogen bond can direct asymmetric organic reactions,[89] and stabilize organic radicals.[90, 91] This interaction can support the formation of thermodynamic isomers.[92] In catalysis, five-membered chalcogen bond cyclic intermediate can determine the path of the reaction.[93–97] In materials chemistry and crystal engineering, all types of chalcogen bond (positive, negative, neutral, RASP) have been employed successfully.[98–101] Chalcogen bonds have been also used in the recognition of neutral molecules and anions,[102–104] as well as in anion transport.[105] The role of chalcogen bond in biological systems is undeniable with special roles in the case of strategic inclusion of chalcogen bonds in artificial drug design and in the development of synthetic transmembrane.[106]

3.3 Pnictogen Bond

The pnictogen (pnicogen) bond is formed by a Lewis acid–Lewis base interaction in which a pnictogen atom, such as P, acts as the electron pair acceptor. This interaction was first observed in an ortho-carbaborane derivative.[107] The possibility of the presence of P···P interactions was known by NMR studies.[108] These P···P interactions were also reported in a series of halogenophosphane-functionalized naphthalene derivatives.[109] Apart from the P···P interactions,[110] there are reports of P···N,[111] N···N[112–114] and As···As[115] interactions as well, establishing the dual donor–acceptor character of the pnictogen atom, similar to that observed in halogens and chalcogens. Murray et al. analysed the MESP of different pnictogen-containing molecules to establish the σ–hole characteristics of these atoms.[116] Initially, there were questions on nitrogen acting as an electron acceptor during the formation of σ–hole interaction,[114] but it was proved experimentally that nitrogen can indeed act as an electrophile under appropriate electronic environment during the formation of the pnictogen bond.[111] The characteristics of the pnictogen bonds are explored using a variety of quantum chemical techniques.[117] The binding energy of pnictogen bond between PH_3 and NH_3 is 1.4 kcal/mol.[118] The energy of the P···P bond is a little weaker, i.e. 1.1 kcal/mol in PH_3 homodimer.[117] This bond can be strengthened by replacing one H atom of PH_3 by a more electronegative substituent.[119] A OH group, for example, can increase the binding energy to 3.6 kcal/mol, Cl can increase the magnitude to 5.4 kcal/mol and in the case of F the increase will be up to 6.2 kcal/mol. From these evidences, it can be said that the binding energy of a single substituted pnictogen bond can become comparable to that of an H bond, and can even exceed the magnitude of the H bond in favourable electronic environments.[117] As an extension of this idea, when both the molecules act as electron donor and acceptor in a symmetric FP···PF system, the most favourable geometry will be the presence of both the F atoms opposite to P of the partner molecule.[120] In an asymmetric system, with a well-defined donor and acceptor, an electronegative substituent on the electron donor will tend to weaken the interaction,[121] although the effect is smaller than when located on the acceptor. In case of the geometry of the pnictogen bond, the study has not been done on a sufficiently large enough number of compounds. However, the covalent contribution of the interaction, as determined by the Wiberg bond order[122], is very small and does not correlate with the bond strength, which makes this interaction more complex. H bonds typically have a high tendency to make a linear AH···D arrangement

(A being the electron acceptor and D the electron donor), but the pnictogen bond shows an even greater degree of anisotropy.[17] A possible model of P–P nonbonding pnictogen bond may be a negative hyperconjugation of the lone pair of electrons at phosphorus LP_P with the antibonding orbital $\sigma^*_{P'X'}$ at the adjacent phosphorus and the substituent X′ along the P⋯P axis.[110] The strength of the pnictogen bond involving N, P and As was also investigated via ab initio calculations in 36 pnictogen homo- and heterodimers of the type $R_3E\cdots ER_3$ and $R_3E\cdots E'R'_3$, where E = N, P, As and it was observed to be a highly stabilizing interaction.[123]

In a recent study, ab initio MP2/aug′-cc-pVTZ calculation to investigate the pnictogen-bonded complexes involving $H_2YP{:}X^-$, for X, Y = Cl, NC, F, CCH and CH_3 were performed to understand which substituent was covalently bonded to P as Y and which substituent formed the P⋯X pnictogen bonds.[124] A computational study[125] via ab initio calculations was performed, wherein the activation of the pnictogen bond (involving phosphorus) in electrophiles significantly reduced the activation energy for the (aza)-Diels–Alder reaction or the addition to α,β unsaturated ketones. For this reason, pnictogen-bond donors are preferable for this conversion in comparison to the halogen-bond donor or hydrogen-bond donor. Catalytic processes should be feasible if the formed product is not a stronger pnictogen bond acceptor compared to the reactants. In the same article, it was mentioned that such a computational study may not be supported at the experimental level. For that purpose, detailed experimental studies and additional investigations are required to identify and isolate stable compounds of phosphorus that can be employed in such transformations. This pnictogen bond is a newly discovered interaction and it has attracted a lot of attention from the science community with steady progress observed, and this is reflected in the increase in the number of publications every year. In accordance with the literature,[110] the P–P nonbonding interaction can be characterized, as the pnictogen lone pair of e^-s avoid each other and interact with the electrostatically positive belt (known as σ–hole). In this case, there is repulsion also between the lone pairs, but it can be reduced by a better leaving group along the P⋯P bond axis. This allows an enhanced negative hyperconjugation of the lone pair of electrons into a σ* anti-bonding orbital. There have been many works reporting this interaction, and the utility of this interaction as a design element finds applications in organic synthesis, catalysis,[125] crystal engineering, drug design and many related fields of chemistry and biology.

3.4 Tetrel Bond

The interaction between σ–hole on Group 14 element and an electron-rich area is called tetrel bond. This type of interaction is relatively new, such that many significant features of this interaction are still not clear. The term "tetrel bond" was coined by Frontera and co-workers in 2013.[126] In 2001, Alkorta et al. investigated via ab initio calculations in silicon derivatives[127] where Group 14 elements act as a Lewis acid.[128, 129] In another study, the importance of Si⋯N in ring-chain tautomerism of selenide derivatives was explored extensively.[130, 131] Tetrel bonding with sp^3 tetrel atoms can be seen as a complex, which has been formed between a nucleophile (Lewis base) and a σ–hole on tetrel atoms (Lewis acid). In this type, consisting of R_4Tr molecules, there are four σ–holes and these are deeper and more exposed when the Tr atom is larger.[129] For this reason, the heavier Tr atoms such as Ge, Sn and Pb form hypervalent structures and on the other side the lighter Tr, such as Si and C, seems more prone to form noncovalent tetrel complexes. From these observations, it can be said that there exists the possibility of a carbon atom to act as an electrophilic centre under suitable electronic environments. Indeed, a 'carbon bond' was predicted even before the 'tetrel bond' was introduced in the literature and confirmed by NMR and X-ray diffraction and its importance shown in biological systems in the last few years.[132–137] For having four σ–holes, the steric hindrance is also a crucial factor for the stability of tetrel bonds. Such bonds are also required for the encapsulation of fluoride ion in several structures.[138] In some recent studies, it has been observed that the anionic tetrel bonds are highly directional and stabilized and that these can function as very good molecular linkers.[139, 140] Similar to other noncovalent σ–hole interactions, this interaction is also very cooperative in nature,[138] and hence has been observed to play an important role in molecular packing of several crystals.[139–141] The occurrence of the tetrel bond is a relatively new discovery and many features of this interaction are still unknown and need further investigation. Even carbon is the most common Tr atom in the biological world and understanding of the nature of interactions involving carbon-oriented noncovalent bond has created a vast field of research. This interaction is of importance and further in-depth investigations

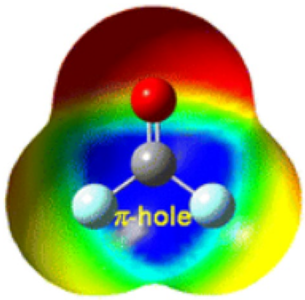


Figure 6: Surface electrostatic potential of F_2CO ($V_{s,max} = 185.3$ kJ mol^{-1}) calculated at the M06-2X/aug-cc-pVTZ(-pp) level of theory: (blue) positive region; (red) negative region; (green) transition region (reproduced with permission from Wang et al.[14] Copyright 2016 American Chemical Society).

are required to understand the role of this interaction, with implications in crystal engineering, drug design, biochemistry and supramolecular chemistry in the nearby future.

4 π–Hole Interaction

The π–hole is the region of low electron density, which is present perpendicular to the σ framework of the molecule and above the π region,[142] due to the induction effect of EWG groups or more electronegative groups bound to the π system.[143] It is also a region with positive electrostatic potential (Fig. 6).[14]

The π–holes are characterized by the presence of a partially empty π* orbital. Generally, the π–hole exists in π-conjugated (nonaromatic or aromatic) or π-nonconjugated inorganic molecules with or without covalent π bonds. So, this generally involves the π molecular orbital or the *p* orbital of the central atom.[14] The magnitude of the π–hole in a specific molecule depends on the order of Hammett substituent constants of its substitutents (σ_m^x where m and x refer to *meta* position and electron-withdrawing substituents, respectively). The greater the magnitude of the ESP for π–holes, higher will be the magnitude of the Hammett substituent constant.[14] For this reason, the capability of forming a π–hole bond depends on the Hammett constants. The interaction of this π–hole with the electron-rich species is called "π–hole interactions".[142] The term "π–hole interactions" is very new in science and this bond is supposed to be an alternative description of the interaction between anion/[144]lone pair of electrons[145] with the π-system[146] and the former is more extensive in comparison to the other. The π–hole contains not only the organic π–hole system with π bond or conjugated π bond, but also the inorganic π–hole system with or without π bond.[147, 148]

The anion–π interaction gives an impression of a negative–negative interaction, which is not correct, so the nomenclature "π–hole interactions" is more correct in accordance with the scientific literature and is more easily understandable.[144]. Figure 7 lists the molecular structures of many common molecules that consist of one or more π–holes.[14] The directionality of the π–hole bond refers to the angle between the plane of the σ framework and the vector direction from the centre of the π–hole (or interacting atoms) to the bond acceptor.[14] Many attempts have been made to know the physical nature and stability of the π–hole interaction, but those attempts were mainly based on the molecular electrostatic potentials. The π–hole bonds also can be categorized as chalcogen bond,[149] pnictogen bond or [150] tetrel bond[151] depending on the group of the atom on which the π–hole is present. In a recent study, a π–hole could possibly be anticipated to be present on the central halogen atom, in hypervalent $FClO_2$, but it has been shown that intermolecular interaction involving these hypervalent halogenated molecules is primarily mediated via σ–hole rather than by π–hole interaction.[152]

4.1 π–Hole Chalcogen Bond

The concept of π–hole is a very recent development, and studies on π–hole chalcogen bonds are sparse in the literature. Most of the observed features of this π–hole chalcogen bond were performed on gas phase molecular complexes. For the first time, Azofra et al., observed π–hole S···C chalcogen bond formation in the 1:2 and 2:1 complex of SO_3:CO.[153] In another similar recent study on $(SO_3)_{n=1,2}$:H_2CO complexes, it was observed that the global minima is these complexes were stabilized primarily by the S···O chalcogen bond.[154] In another study, nitrogen bases were observed to be better electron donors than phosphorus bases for the formation of π–hole chalcogen bonds.[149]

4.2 π–Hole Pnictogen Bond

Bauza et al. showed that the π–hole present on the nitro derivatives are energetically viable for the formation of the π–hole pnictogen bonds and can be used as a directional force in the solid state.[155] In another study, it was observed that the π–hole pnictogen bonds played an important

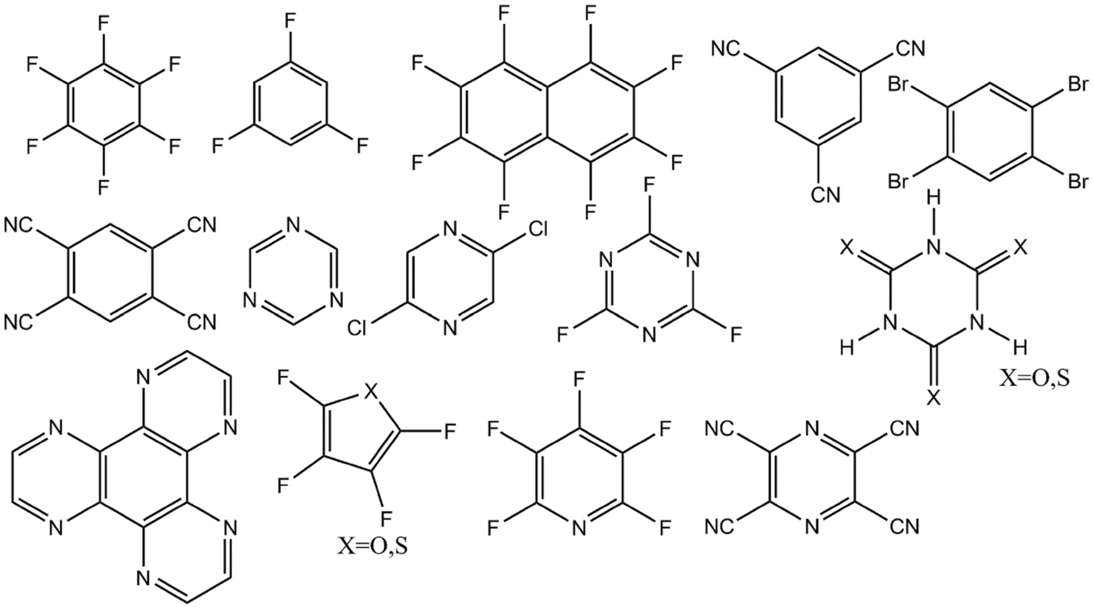


Figure 7: The molecules with one or more π–holes.

role in the self-assembly of thioxothiazolidinone derivatives.[156] In an ab initio study on complexes of $POCl_2$ and XCN/C_6C_6 (X = F, Cl, Br), it was observed that the π–hole pnictogen bond was stronger than the σ–hole halogen bond[157] with both interactions having a direct influence on each other. In another computational study, on a ternary complex of XO_2F:NCH:NCY and XO_2F:CNH:CNY (X = P, As; Y = H, Li), it was observed that the π–hole pnictogen bond exhibited higher cooperativity with hydrogen bond in comparison to σ–hole pnictogen bond.[157]

4.3 π–Hole Tetrel Bond

The π–hole tetrel bond is a type of interaction where the π–hole is situated on an atom of Group 14. This bond has been investigated thoroughly in several studies. The first case is the classical carbonyl–carbonyl interaction in which the *lp* of oxygen in the carbonyl group interacts with the π* of another carbonyl group.[158] This has a special geometry in which a nucleophile prefers to attack an electrophilic carbonyl centre. This is now well known as the Burgi–Dunitz angle.[159] Recently, Shen et al.[160] investigated the strength of π–hole tetrel bond in complexes of F_2ZO (Z = C, Si, Ge) with unsaturated molecules (for example, acetylene and ethylene) and observed that Si⋯π and Ge⋯π interaction was stronger than the C⋯π noncovalent interaction.[151]

5 Summary

The latest studies in the field of intermolecular interactions are directed towards the understanding of σ and π–hole-directed self-assembly processes either in solution or in the solid state. In this regard, both experimental (diffraction and spectroscopic) and computational techniques (solid state and gas phase) are expected to render new physical insights into the nature and energetics of such interactions. In addition, a complete topological analysis based on the electron density distribution (experimental and theoretical) shall provide quantitative inputs into the role of the structure and the associated reactivity in molecules wherein these interactions play a crucial role.

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