'Halogen Bonding' Interactions in Molecular Crystals: From Early Recognition to Recent Developments

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Abstract | 'Halogen Bonding', a non-covalent interaction between halogen atoms (as acceptors of electron density) and lone-pair-possessing atoms (mostly O and N) is reviewed from its early recognition till its utilization in recent years in the field of crystal engineering, molecular recognition and even in complex biological systems. This interaction, closely resembling hydrogen-bonding contact, has been investigated by several theoretical and experimental methods. The scope and potential of this interaction is discussed with the examples of crystal structures from literature and from our own laboratory.

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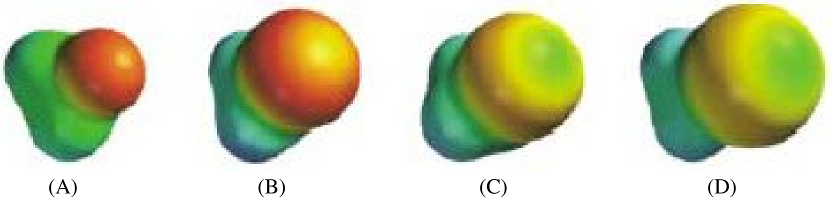
1. Introduction

Non-covalent interactions continue to be the subject of intensive research, as knowledge of these is the central problem in designing a wide range of materials. It is interesting to trace the literature on many of the intermolecular interactions as how they were first recognized and started getting widely accepted over the period. This review addresses one such interaction, where halogen atoms make short contacts with lone pair possessing atoms such as oxygen or nitrogen, which analogous to Hydrogen bonding is termed as 'Halogen bonding' contact. With its implications on all the fields where design and manipulation of aggregation phenomena play a key role, halogen bonding has become the subject of serious study only recently. It is now been recognized as a well-defined, strong, specific and directional interaction for assembling complex supramolecular architecture. We wish to highlight the significance of these intermolecular interactions that interface a wide range of applications in chemistry, keeping in mind that it is not possible to review exhaustively all that has appeared in the literature on halogen bonding.

1.1. *Intermolecular Interactions*

Before discussing the interactions involving halogen atoms, some of the (weak) intermolecular interactions central to practically every branch of research, ranging from metallurgy to molecular biology, and from material science to chemistry are worth the mention. Single crystal structure analysis by X-ray diffraction is one of the most suitable techniques that provide us accurate information on the process of molecular association that balances all possible intermolecular interactions in the solid state. It is rather intriguing that in spite of a large number of crystal structures (~360000, deposited in the Cambridge Crystallographic Data Centre), the blind tests given to predict the crystal structure of simple organic molecules posed a formidable challenge.[1] Several workers, Gavezzotti[2] and Dunitz,[3] have discussed the complexities involved in predicting a crystal structure. The non-covalent intermolecular interactions that lead to crystal formation can typically be divided into strong, moderate and weak interactions,[4] although the demarcations between them are not sharp.[5] 'Hydrogen bonding' is a classical

Figure 1: Molecular electrostatic potential surfaces of (A) methyl fluoride, (B) methyl chloride, (C) methyl bromide and (D) methyl iodide. The red regions represent negative electrostatic potential, the blue regions positive electrostatic potential and yellow is neutral.



example of a strong, specific and highly directional intermolecular interaction. This has emerged as the most important organizing principle not only for the crystal structures (or engineering) but also for assemblies of biologically larger molecules.

Weak interactions such as C–H$\cdots$O,[4] C–H$\cdots$N,[6] C–H$\cdots$F,[7] C–H$\cdots\pi$,[8] C–H$\cdots$X (X = Cl, Br, I),[4] $\pi\cdots\pi$,[9] X$\cdots$X[10] are of considerable importance (in the absence of classical hydrogen bonds) as they play an important role in molecular packing arrangement. The ability of carbon atoms to act as proton donors depends on the hybridization at the C-atom site (C(sp)–H > C(sp2)–H > C(sp3)–H). The presence of electron withdrawing groups on adjacent atoms also appears to play a role in the proton donating ability of a carbon atom. However, non-convential hydrogen bonds have been the subject of controversy for many years. D. J. Sutor[11] conducted a survey of crystal structures containing short C–H$\cdots$O contacts in 1963. She described, these short contacts that are generally attractive in nature, with roughly one third the energy of convential O–H$\cdots$O hydrogen bond as weak hydrogen bonds. However, if there are a large number of such interactions, their collective contribution to the stability of a system could be substantial. The importance of C–H$\cdots$O interactions in supramolecular chemistry,[12]crystal engineering,[13] biological systems,[14] nucleic acid and protein structures[15] has been well documented.

Other types of weak interaction such as $\pi\cdots\pi$ interaction,[16] which involves interaction between the π-electron systems (aromatic as well as aliphatic), are generally called π-complexes. The two molecules forming such a π-complex consist of a donor molecule with a low ionization potential so that an electron can be donated (a delocalized π-electron of the polycyclic aromatic hydrocarbon) to an acceptor molecule with a high affinity for electrons. As a result, stacks of alternating donor and acceptor molecules are found in the crystal structures. These interactions are characterized by short intermolecular distance perpendicular to the stacking direction. Hydrogen bonds formed with electrons in π bonds acting as the acceptor are attracting much interest currently, both in the fields of structural chemistry and structural biology. The most important amongst these are those with π cloud of the phenyl rings, Y–H$\cdots$Ph (aromatic hydrogen bonds), which occur in many chemical and biological systems.[17] C–H$\cdots\pi$ interactions come under the category of weak interactions where hydrogen atoms point towards electron rich aromatic ring and most of the interacting distances are shorter than sum of the van der Waals radii of the hydrogen atom and the sp^2 carbon atom. These interactions control the conformation and packing modes in organic solids mainly via charge transfer from the π system to the anti-bonding orbital of the C–H bond. Like other weak interactions, these also play a crucial role in the formation molecular assemblies,[8c] group transfer reactions,[18] stability of peptides,[19] proteins[20] and conformation of small organic molecules.[8]Other weak interactions, O–H$\cdots\pi$, (small molecules[21] and several proteins structures reported in PDB[22]) and N-H$\ldots\pi$,[23]are also observed in the crystal structures. The other weak intermolecular interactions include C=O$\cdots$C=O,[24] C–F$\cdots$C=O[25] and S=O$\cdots$C=O[26](dipole-dipole interactions). These dipolar contacts have also been suggested to play an important role in the molecular aggregation and the formation of stable host guest framework.

1.2. *Interactions Involving Halogen Atoms*

Intermolecular interactions involving halogens F, C1, Br and I continue to be the subject of investigation, as halogens can form short non-bonded contacts with electron acceptors as well as electron donors.[27] This behavior has been rationalized based on anisotropic (non-spherical) charge distribution in halogen atoms.[28] Thus, heavier halogens (except fluorine, due to extreme electronegativity and limited polarizability) exhibit electrophilic character along the axis of C–X bonds and nucleophilic character perpendicular to these bonds. Hence, electrophiles in general tend to approach halogens at angles of *ca* 100^o and nucleophiles at 165°.[29] Calculation of electrostatic potential surfaces of methyl halide by Hunter *et al.* using STO-3G basis set in Spartan (Figure 1) supports this view.[30] According to their calculations, the heavier halogens have more positive region on the surface opposite to the C–X bond and negative region perpendicular to this bond. The magnitude and area of the zone of positive potential increases with the size of the halogen, so that iodine, in particular makes relatively strong interactions with hydrogen-bond acceptors. Thus, halogens can act as hydrogen-bond donors or acceptors depending on the angle of approach.

Hence, interactions of halogens with nucleophiles (e.g. O, N) display roughly linear geometry with respect to the halogens, whereas interaction with electrophiles occur in side-on fashion.[31] Some of the (now) recognized weak intermolecular interactions involving halogen atoms are mentioned below, before going into a discussion on halogen bonding interactions.

1.3. *C–H···Halogen Interactions*

C–H···X (X = F, Cl, Br and I) type interactions were observed to occur when halogen atom acts as hydrogen atom acceptor. However, the existence of C–H···Cl hydrogen bonds has been questioned.[32] Gibb *et al.*[33] carried out a systematic survey of Cambridge Crystal Structure Database, which established the extensive occurrence of C–H···Cl hydrogen bonds. Furthermore, they showed that C–H···X interactions are real and they do play an important role in molecular aggregation and are useful for the prediction of crystal structure. It was observed that chloride anions are better hydrogen-bond acceptor systems than neutral chloride-containing molecules and a similar situation pertains for the other halides. The number of occurrence of C–H···halogen bonding with F and Cl are more compared to that of bromine and Iodine, probably because as the size of the halogen atom increases (decrease in electronegativity) it becomes electron pair acceptor rather than donor.[33] In C–H···F type interactions, the C–F bond acts as proton acceptor and it is one of the predominant interactions in fluorine containing compounds and hence it is considered as a tool for crystal engineering.[34] However, the ability of other halogen atoms to function as H-bond acceptors is still under debate.

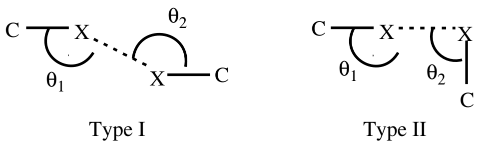
1.4. *C–Halogen···π Interactions*

The involvement of halogen atom is also found in C-halogen···π type interactions. The nature of this interaction depends on the halogen atom and electron withdrawing or electron donating substituents on the aromatic ring. The existence of such interactions was first noted by Dastidar *et al.*[35] while analyzing the structure of Zinc–tetra(4–bromophenyl) porphyrins. They noted the close approach of C–Br···π as a possible specific interaction to result in well-defined packing. Guru Row *et al.* carried out a systematic Cambridge Crystallographic Database[36] and Protein Data Bank study[37] on the intra and intermolecular geometries of C-halogen···π contacts. The intramolecular contacts involving fluorine were relatively abundant as compared to other halogens. Their study showed that C–X···π interactions are highly directional. The fluorinated hydrocarbons showed greater propensity for the formation of such interactions as compared with other halogens. The C–F···π intramolecular interactions appeared to spread across the histogram, while the other halogen atoms showed a tendency to cluster near D_{max} (cut-off values of distance). The intermolecular C–X···π interactions for all the halogen atoms clustered around D_{max}. C–X···π appears to play an important role in the stability of host guest complex.[38] The directional nature of the halogen···π contacts makes these relatively weak interactions capable of influencing the packing of organic molecular crystals decisively, thus providing a new tool for crystal engineering of both homomolecular and supramolecular organic solids.[37,39]

1.5. *Halogen···Halogen Interactions*

As a consequence of the spatially segregated regions of complementary electrostatic potential, interhalogen bonding is also observed with halogen groups acting as both nucelophiles and electrophiles. Desiraju *et al.*[40] carried out systematic CSD search on the geometries of these contacts and deduced that the short X···X intermolecular distances arise from the specific attractive forces between the two halogen atoms in crystals and the non-spherical shape (polar flattening) of the halogen atoms was the consequence of this interaction. Price *et al.*[41] showed that for X···X short distances especially chlorine–chlorine interactions could originate from anisotropic effects (non-spherical atomic charge distribution) between elliptically shaped chlorine atoms. Murray-Rust and coworkers classified X···X interactions based on the two C–X···X angles θ_1 and θ_2 with the classes being denoted as type I (θ_1 or $\theta_2 = 90$), type II (θ_1

Figure 2: Schematic representation of halogen···halogen interactions.



or $\theta_2 = 180$) and type III ($\theta_1 = \theta_2$ and the two halogen atoms being related by crystallographic center of inversion).[42] The nomenclature for these X···X interactions was subsequently simplified by Desiraju and cowokers;[40] type I interactions ($\theta_1 = \theta_2$) and type II interactions ($\theta_1 \cong 180°$ and $\theta_2 \cong 90°$, Figure 2). The type II contact is consistent with the polarization of adjacent X atoms as $\delta(+)$ and $\delta(-)$ while type I contact is a consequence of crystallographic symmetry, the X atoms being located across a centre of inversion.

The role of X···X contacts, appears to be important (irrespective of their cause) in determining supramolecular structures and it may be possible to exploit them directly in crystal engineering and for the design of supramolecular aggregates.[43]

1.6. *Halogen...NO2 contacts*

Desiraju and coworkers[44] first successfully reported the importance of new supramolecular cement in crystal engineering. They designed the supramolecular assemblies via NO_2···halogen contacts in several co-crystals of halo and nitro derivatives of aromatic compounds and concluded that the halogen–oxygen linked assemblies are useful supramolecular synthons in developing strategies for systematic and general crystal engineering.[44] However, a single oxygen atom making short contacts with organic halogen has been recognized and exploited in recent years for designing functional solids.[45]

1.7. *Halogen Bonding (C-halogen... O) Contacts*

There has been growing interest in this rediscovered weak interaction between halogen and oxygen atoms. This contact was earlier categorized as charge transfer or electron–donor–acceptor bond, but now it is generally termed as 'halogen bonding' interaction. The term "Halogen bonding" was introduced by Dumas *et al.* in 1983[46] and latter used by several others[47] to stress its similarity with hydrogen bonding.[48]

Halogen bonding is the attractive donor acceptor interaction[49] involving an atom possessing one or more lone pair of electrons (such as O, N or S, which donates electrons, Lewis base) and a halogen atom (Cl, Br or I functioning as Lewis acids accepting the lone pair of electrons).[50] The strength of the interaction increases in the order Cl < Br < I. Like hydrogen bond, in which H-atom covalently bonded to an electronegative atom approaches another electronegative atom,[13] in halogen bond, the halogen atom bonded to an atom approaches a more electronegative atom (Figure 3). The stronger the electron-withdrawing environment around the halogen atoms, higher is their ability to be engaged in halogen bonding interactions. The resulting complexes were considered by Prout and Kamenar as belonging to the $n\sigma^*$ type.[51] The halogen bond seems to be mainly electrostatic in origin with some contribution from dihalogen polarization upon complex formation.[52]

1.8. *Early Observations*

The first unequivocal report on the ability of halogen atoms to form well-defined adducts with electron donor species dates back to 1863 when Guthrie described the formation of the $H_3N \cdots I_2$ complex.[53] Remsen and Norris[54] in 1896 proved the general tendency of amines to form adducts with bromine and chlorine; pale yellow crystals of composition $(CH_3)_3N \cdot Br_2$ were obtained by direct addition of trimethylamine to bromine. The crystallographic analysis of Hassel is a landmark in the study of the halogen bond phenomenon. He first demonstrated that halogen bonding is a powerful tool in driving the self-assembly of endless chains of alternating donor and acceptor modules.[55] He studied the X-ray structure of molecular addition compound containing dihalogens and electron pair donor molecule 1,4 dioxane. The crystal structure investigation of bromine—1,4 dioxane complex revealed the presence of endless chains consisting of alternating dioxane and bromine molecules (Figure 4). The oxygen–bromine–bromine–oxygen arrangement is linear. The most striking feature of the structure was the short contact between an oxygen atom of the dioxane and a bromine atom. The O···Br distance in the crystal is 2.71 Å, which is very much less than the sum of the van der Waals radii (3.35 Å) and the angle at the bromine atom making short contact is almost linear. Each bromine atom is involved in short O···Br interactions, off each end of the Br–Br bond and each dioxane molecule is involved in two O···Br interactions.

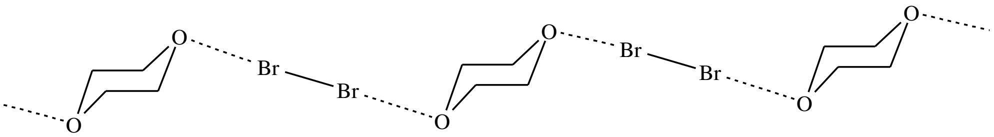
Hassel and coworkers[55] concluded that charge transfer from the donor atom (O) to the acceptor atom (Br) takes place since the molecular complex possesses appreciable dipole moment while Br_2 and dioxane lack dipole moment. They studied

Figure 3: Analogy of halogen bond with hydrogen bond

D − H ··· A   D − X··· A (X = Cl, Br, I; A = O, N, S, Se and D = donor atom)

Hydrogen Bond   Halogen Bond

Figure 4: Formation of O···Br-Br···O bridge in molecular complex of dioxane and bromine.



crystal structures of several addition compounds involving dihalogens and ether as well as carbonyl oxygens; in all the complexes the halogen···oxygen distance was much less than the sum of van der Waals radii and the halogen bond between oxygen and halogen was stronger with heavier halogen atoms. Like halogen bonding between dihalogen and ether oxygen, the bonding between dihalogen and carbonyl oxygen is linear. They concluded that the complex formation was due to the charge transfer interactions between electron pair donor atoms and halogen atom of dihalogen molecules. In Hassel's Nobel lecture,[56] he stressed the similarities between the interactions where halogen and hydrogen work as electron acceptors. Thus, his solid-phase structural studies (using X-ray crystallography) unequivocally established the existence of a D···X (D = electron-pair donor, X = halogen, electron-pair acceptor) interaction with a defined linear geometry. Bent *et al.*[48a] reviewed halogen-bonding interactions, establishing the analogy between halogen bonding and conventional hydrogen bonding. Bent pointed out many organic halides can also form such complexes via halogen bonding.

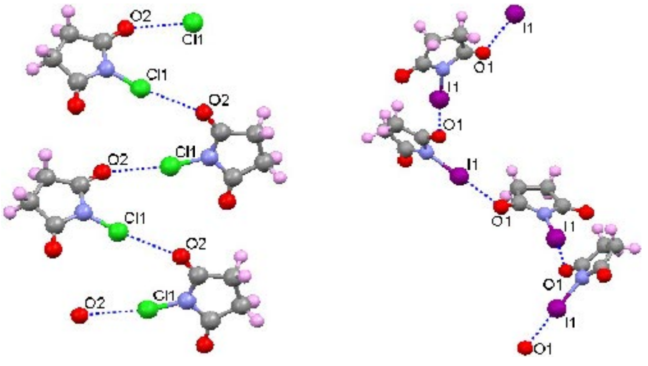
Although, CSD shows several short halogen…oxygen contacts in organic crystals, only a few researchers recognized them to make a specific mention in their publications. For example, Brown et. al. [57] in 1963 first observed halogen bonding contact in a single component system. In crystals structure of N-chloro-succinimide, the chlorine atom bound to nitrogen makes short contact (2.88 Å) with carbonyl oxygen atom forming zig-zag chains (Figure 5A). Latter on Pritzkow *et al.*[58] and Padmanabhan *et al.*[59] also reported short Br···O (2.80 Å) and I···O (2.580 Å) in N-bromo-succinimide and N-iodo-succinimide respectively (Figure 5B).

Sabesan and Venkatesan[60] also observed short Br···O contact in 3-*p*-bromophenyl-1-nitroso-2-pyrazoline and assumed it was a charge transfer type weak interaction. Pascal *et al.*[61] also noticed, nitrogen–chlorine donor–acceptor interactions in the crystal structure of cyanuric chloride (2,4,6-triochloro-1,3,5-trizine) which dominate the complete crystal packing.

1.9. *Cambridge Crystallographic Database Survey for Halogen Bonding Interactions*

Murray-Rust and Motherwell[62] found 219 crystal structures containing O atom and C–I bonds in the Cambridge Crystal Structure Database. They analyzed these structures for I···O contacts (<5 Å) along with the C–I···O angle. They found over 500 contacts in this range and the sharp variation of I···O distance with the C–I···O angle. At 90° the minimum I···O distance was 3.6–3.7 Å, whereas at 180° it was as low as 2.8 Å. They pointed out that when the halogen to oxygen approach was linear the halogen···oxygen distances were much less than the sum of van der Waals radii. Similar results were found for C–Br···O and C-Cl···O contacts with over 3000 examples of each, although the minimum X···O distance did not approach that of I···O. Further, they did not find any difference in the distribution when the analysis was carried out with different chemical nature of oxygen (ether, ester and carbonyl). Hence, they concluded that the distribution is independent of the nature of oxygen atom. They also analyzed the environment around halogen centers in hundreds of crystal structures[63] and found the angular preferences of intermolecular forces around halogen centres; nucleophiles approach X of C–X along the back side of the bond whereas the electrophile approach of X nearly perpendicular to C–X (Figure 6). Thus,

Figure 5: (A) Endless chain of N-chloro-succinimide molecules formed via C-Cl···O contacts (N-bromo-succinimide also has similar crystal structure) and (B) polymeric layer formed in N-iodo-succinimide crystals via C–I···O short contact.



(A) (B)

the contacts of O or N with X are nearly "head on" with O, N approaching X along backside of C–X and the angle of approach is about 165°. Molecular orbital study of the dimer $H_3N\cdots F_2$[29] was used to qualitatively explain the directionality of charge-transfer between the highest occupied molecular orbital (HOMO) of the electronegative atom (O or N) and the lowest unoccupied molecular orbital (LUMO) of the halogen.

A decade latter, Allen *et al.*[28] carried out systematic analysis on the nature and geometry of intermolecular interactions between carbon bonded halogens (C–X, X = F, Cl, Br or I) and electronegative atoms (El = N, O and S).They found that the electronegative atoms in various hybridization states clearly prefer to form contacts with Cl, Br and I (but not F) in the direction of the extended C–X bond axis, at interatomic distances less than the sum of the van der Waals radii. The scattergram of C-Cl···O geometry (Figure 7) represents a hemisphere around the nucleus of the chlorine atom at the terminal side of the covalent C-Cl bond, up to a maximum Cl···O distance of $d = 4.12$ Å. Allen *et al.* also performed *ab initio* intermolecular perturbation theory (IMPT) calculations, which showed that the attractive nature of the X···El interaction is mainly due to electrostatic effects, but polarization, charge-transfer and dispersion contributions all play an important role. They calculated the interaction energy for the chloro-cyanoacetylene dimer and found it to be about 2–3 Kcal/mol, which is about half the magnitude of an average hydrogen bond, highlighting the potential importance of these kinds of non-bonded interactions. The directionality of the interaction was explained by the anisotropic electron distribution around the halogen atom (Figure 6), causing a decreased repulsive wall and increased electrostatic attraction for electronegative atoms in the observed preferred position. Amongst the different halogens, tendency to form short X···El interactions (I > Br > Cl > F) parallels the order of their polarizabilities. This suggests that polarization and/or charge-transfer energies related to the halogen atom play a significant role in the interaction. They ruled out the concept of 'polar flattening' (short contact merely due to consequences of close packing of anisotropic X atom, as observed by Price *et al.*[41]) in Cl···Cl intermolecular contact, in case of C–X···El (El = N, O and S) bond and also demonstrated that it is not a consequence of close packing by closely analyzing the structure of 2,5-disubstituted-1,4-benzoquinones.[28] In 2,5-dichloro-1,4-benzoquinone crystal structure, all chlorine and oxygen atoms are involved in 1:1 contacts (Figure 8A). Similarly, in 2,5-dibromo-1,4-benzoquinone, all bromine atoms form 1:1 contacts with oxygen atoms (Figure 8B). Thus, despite the much larger volume of bromine atoms, the crystal is isostructural with the dichloro analog and shows X···El to be an essential driving force in the formation of the crystal structure. This was supported by the structure of 2,5-dimethyl-1,4-benzoquinone, although the volume of methyl groups is comparable to that of chlorine atoms, it has completely different crystal packing (Figure 8C). Furthermore, the electrostatic nature of the halogen bond was confirmed due to the fact that the order in which interaction becomes stronger (S < N < O) corresponds to the increase in electro-negativities of the atoms. Also the hybridization state of the

Figure 6: Schematic view of approach of electrophile and nucleophile towards halogen atom.

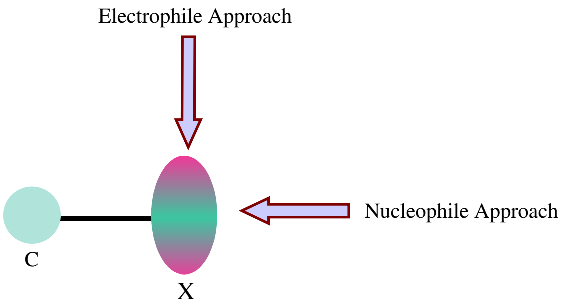
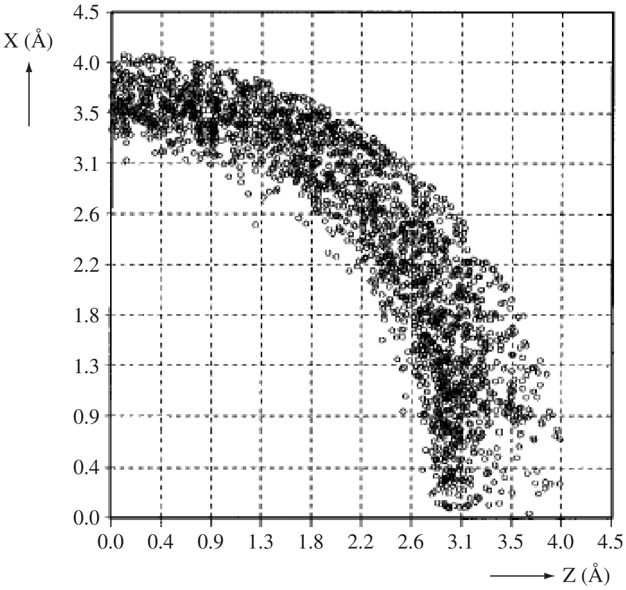


Figure 7: Distribution of sp2 hybridized oxygen atom around carbon-bonded chlorine atoms found in the crystal structures in the CSD. Each circle represents one unique contact of an oxygen atom to the chlorine atom, placed at the origin.



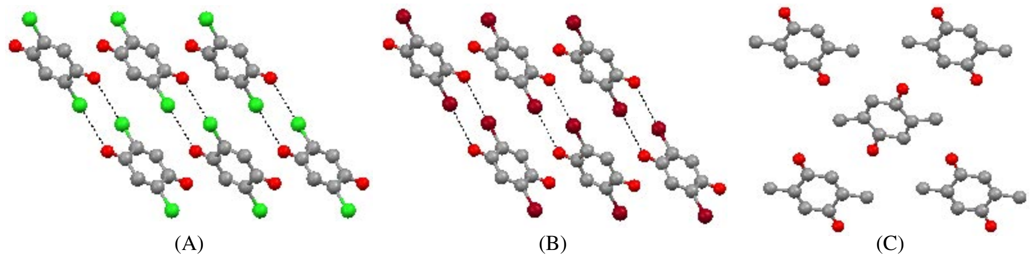
El atom has an effect on the nature of the halogen bond. El atoms in sp and sp2 hybridization states attract electrons by resonance. This is not possible in sp3-hybridized state because of steric crowding and hence El cannot approach halogen atoms at shorter distances.

Lourence *et al.*[64] also carried out the analysis of the halogen bonding geometry of dihalogen complexes Y–X···B using CSD. From the analysis they concluded that, in the solid state, the I–I···B halogen bond is more linear compared to O–H···B bond by 10–38° and the halogen bond appears to be stronger than hydrogen bond. The direction of the halogen bond (vector X···B) is very close to the axis of the non-bonding electron pair of B and shortening of X···B interactions lengthens the Y-X bond.

1.10. *Recent Developments in the Study of Halogen Bonding*

For the last 10 years, there has been substantial increase in the publications centered on 'halogen bonding' interactions. The strong, directional and selective nature of halogen bonding interactions makes it effective and reliable tool in crystal engineering and can be considered as a new type of glue to achieve supramolecular architecture for designing of functional solids.[65] These non-covalent interactions can be strong enough to control aggregation of organic molecules in solids,[66]

Figure 8: Packing of 2,5-disubstituted-1,4-benzoquinones in their crystals. The dotted lines show the contacts of oxygen and halogen atoms, (A) 2,5-dichloro-1,4- benzoquinone, (B) 2,5-dibromo-1,4-benzoquinone and (C) 2,5-dimethyl-1,4-benzoquinone.



liquid,[67] liquid crystals[68] and gas phase.[48(e,f),69] Resnati and coworkers have been the most prominent researchers who have successfully utilized halogen bonding contacts in supramolecular architecture,[70] molecular recognition[71] and solid state synthesis.[72] They experimentally proved the domination of halogen bond over hydrogen bond under appropriate conditions in molecular recognition controlling self-assembling process.[70e] A few representative examples dealing with various aspects of halogen bonding interactions are discussed below, which demonstrate the potential implications of this interaction.

1.11. *Crystal Engineering*

Resnati and coworkers[73] showed that the halogen atom in perfluorocarbons (PFC) halides has better electron accepting ability than corresponding hydrocarbon (HC) halides and therefore they form excellent halogen bonding contact. They successfully explored the self-assembly of PFC and HC derivatives via halogen bonding contacts and utilized them in crystal engineering. The effectiveness and the reliability of halogen bonding in forming one-dimensional infinite network from PFC-dihalides and initrogen substituted HC's was well demonstrated. These were claimed to be the first crystalline halogen-bonded complex involving bromoperfluoroalkanes. The N···Br halogen bonding effectively drives the intermolecular recognition between bromoperfluoroalkanes and nitrogen substituted hydrocarbons in the liquid and solid phases. The interaction is strong enough to control the self-assembly of *N*, *N*, *N*′, *N*′-tetramethyl-*p*-phenylenediamine and 1,8-dibromoperfluorooctane into a co-crystal that is solid and stable at room temperature in air (Figure 9). One-dimensional infinite chains are formed where the two modules alternate.[73] Bromoperfluoroalkanes are thus new tectons for the formation of hybrid perfluorocarbon-hydrocarbon crystalline materials.

Another example is from Pennington and coworkers, in which N. . . I halogen bonding has been exploited.[74] X-ray analysis revealed that 4,4'-bipyridine, 1,2-bis(4-pyridyl)ethylene, and hexamethylenetetramine form donor–acceptor complexes with 1,4-diiodobenzene, 1,4-diiodotetrafluorobenzene, and tetraiodoethylene respectively in which the N···I distance is longer than that for the corresponding I_2 complexes (Figure 10).[74] As opposed to the corresponding I_2 complexes that are molecular adducts, these complexes have extended structures and longer N. . . I distances. They concluded that the steric and electronic effects influenced the strength of the N. . . I interaction and subsequently the crystal packing.

Halogen bonding has been used for topochemical polymerization of olefins. In this case, halogen bonding and $\pi \ldots \pi s$ tacking both control reactivity in the solid state.[75] Halogen bonding drives the assembly of a template with an olefins carrier, orienting double bonds for photocyclization in the crystal.

The intramolecular face-to-face $\pi \ldots \pi$ interactions pre-organize the template and the intermolecular halogen bonding (N. . . I contact) assembles template and olefin carrier in ribbons. As a result of the remarkable strength and directionality of the halogen bonding, the alignment of the arms of the template is translated into alignment of olefins at the distance needed for the photoreaction (Figure 11A). On irradiation the co-crystal formed between trans-1,2 –bis(4-pyridyl) ethylene (substrate) and pentaerythritol ether (template), a stereo controlled photocyclization reaction occurs (Figure 11B), yielding tetrakis(4-pyridyl)cyclobutane in quantitative yield.

1.12. *Molecular selectivity*

We reported one of the remarkable examples of a highly selective host–guest system formed and stabilized due to concerted halogen. . . oxygen and C–H. . . O non-bonded interactions.[76] In racemic

Figure 9: Packing of co-crystal of 1,8-Dibromoperfluorooctane and N, N, N', N'-Tetramethyl-1,4-phenylenediamine viewed down $a$axis.

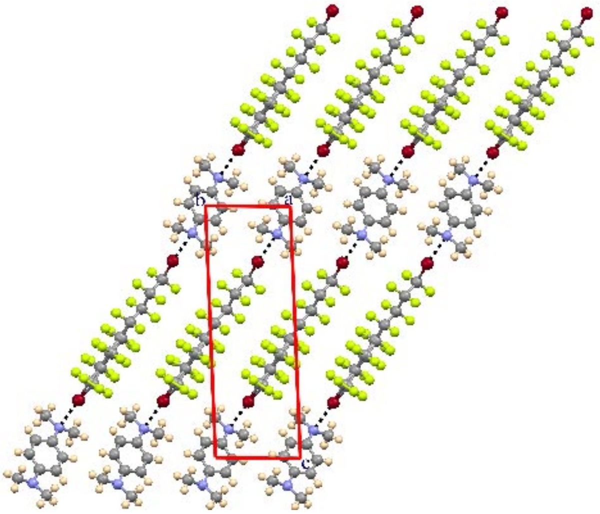
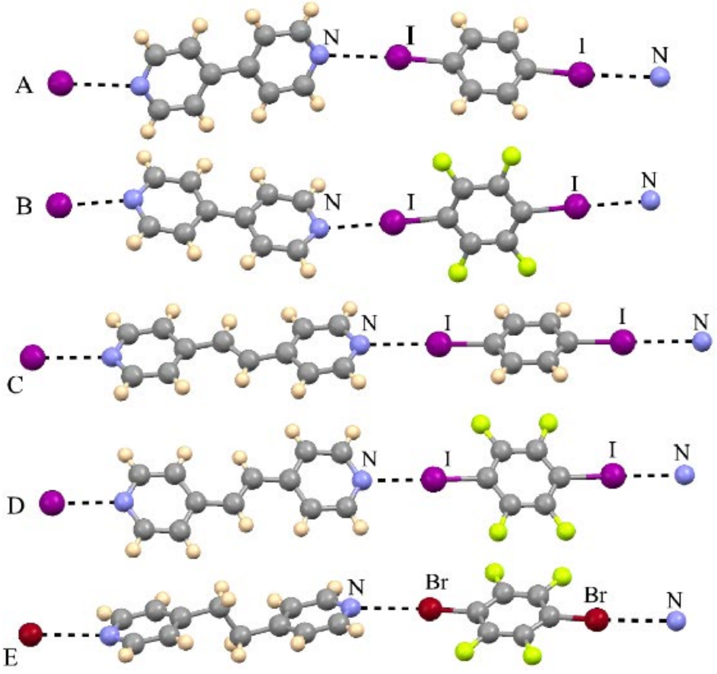


Figure 10: Thermal ellipsoid plots of (A) 4,4'-Bipyridine·diiodobenzene, (B) 4,4'-Bipyridine·1,4-diiodotetrafluorobenzene, (C) 1,2-bis(4-pyridyl)ethylene·diiodobenzene, (D) 1,2-bis(4-pyridyl)ethylene·1,4-diiodotetrafluorobenzene and (E) 1,2-bis(4-pyridyl)ethane·1,4-dibromotetrafluorobenzene co-crystals.



1,2,3,4,5-penta-*O*-benzoyl-6-*O*-tosyl *myo*-inositol–dihalomethane (CH_2X_2, X = Cl and Br) inclusion complexes, *myo*-inositol derivative (host) assembles around crystallographic 2-fold axis selectively accommodating dihalomethanes as guests having $C2$ symmetry (Figure 12).

Figure 11: (A) Infinite 1D halogen-bonded ribbons formed by self-assembling modules, pentaerythritol ether and *trans*-1, 2-bis (4-pyridyl) ethylene and (B) Sceheme of synthesis of tetrakis(4-pyridyl)cyclobutane isomer via templated photoreaction in the solid state.

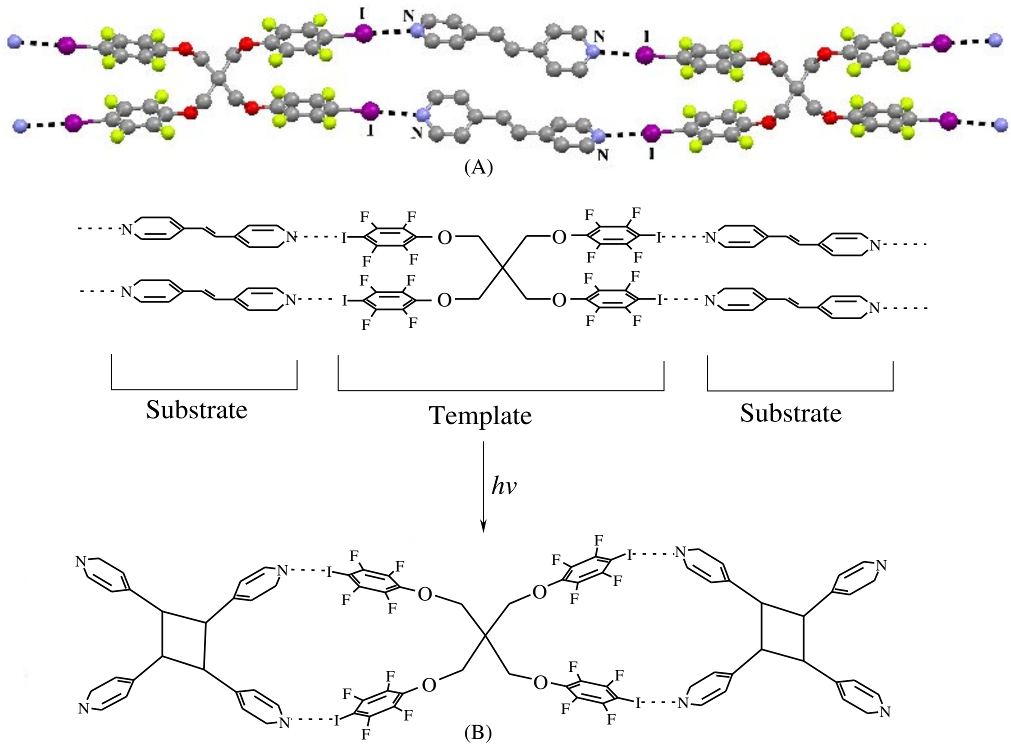
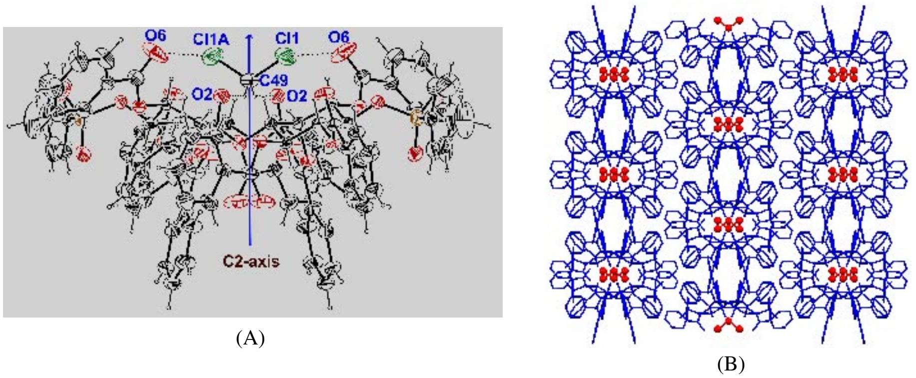


Figure 12: A) Association of the host molecule with the guest (dichloromethane) molecule around the C2-axis via short C-Cl. . . O (2.968 (9) Å) and C–H. . . O (2.524 Å) contacts and B) molecular packing viewed down c-axis showing thorough open channels formed by the host molecule accommodating the dihalomethane guest molecules.



(A)

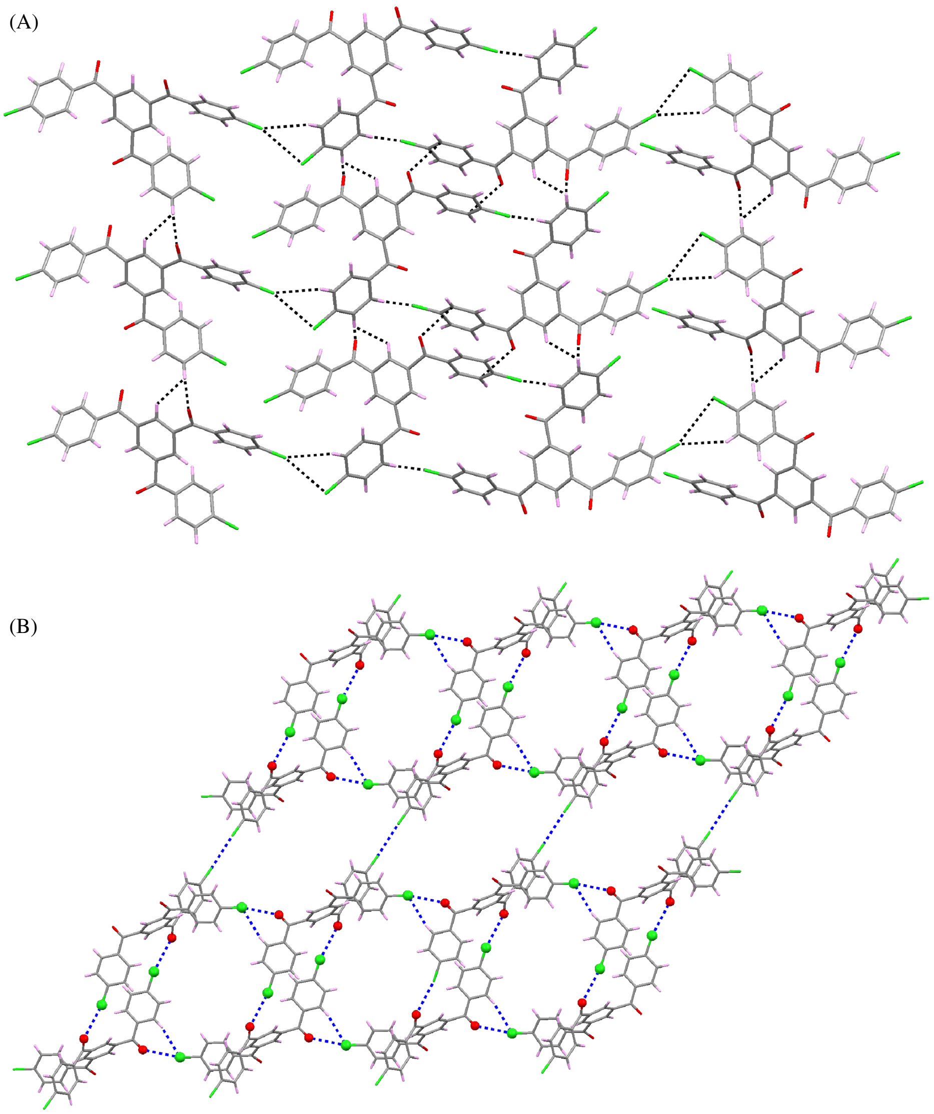
(B)

1.13. *Polymorphism*

Compared to the amount of literature on hydrogen bonding, instances of halogen bonding interactions are much less since these contacts are being analyzed only recently; therefore, it is not surprising that reports on polymorphism involving these contacts are less.[77]

A recent example from Pigge and coworkers[78] on two concomitant conformational polymorphs of 1,3,5-tris(4-chlorobenzoyl)benzene is shown

Figure 13: Association of molecules in dimorphs of 1,3,5-tris(4-chlorobenzoyl)benzene A) via C–H…O, C–H…Cl and Cl…Cl interactions in one form and B) through C=O…Cl and Cl…Cl interactions in another form.



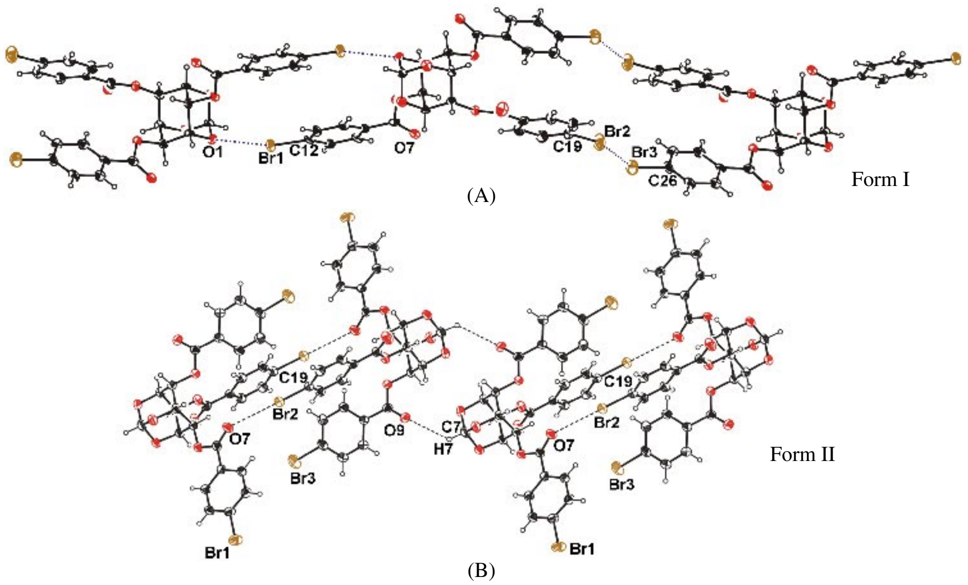
in figure 13. Both polymorphs self-assemble into discrete network architectures; in one case it is mediated by weak C–H…O, C–H…Cl and Cl…Cl interactions and in other case by multiple C=O…Cl and Cl…Cl interactions.

We have reported[77] a examples in which halogen bonding competed with other weak intermolecular interactions in the nucleation process that led to polymorphic behavior. Tri-*O*-[*p*-halobenzoyl]-*myo*-inositol 1,3,5-orthoformate produced concomitant dimorphs upon crystallization with ethyl acetate-petroleum ether mixture. Single Crystal X-ray studies of bromo-derivative revealed that both the forms utilized different 'halogen bonding' contacts; C–Br…O–C (ether oxygen) and C–Br…O=C (carbonyl oxygen) (Figure 14) in molecular association. The form (less yield), which has halogen bonding contact with ether oxygen underwent thermally induced crystal-to-crystal phase transformations to the form (more yield) containing halogen-bonding interactions with carbonyl oxygen atom.

1.14. ***Liquid crystalline materials***

Alkoxystilbazoles have been shown to be versatile materials for the construction of molecular materials including optically nonlinear systems, pyroelectric Langmuir–Blodgett fabrications, and

Figure 14: ORTEP views depicting differences in the halogen bonding contacts. (A) Dimers making C12-Br1. . . O1(–C) contacts linked by Br2. . . Br3 interactions and (B) centrosymmetric association linked via C19–Br2. . . O7(=C) bridged by C7–H7. . . O9 bonds.



metallomesogens. A liquid-crystalline material resulted on forming a halogen bond between an alkoxystilbazole and halo benzene where neither component was liquid crystalline. Thus, halogen bonding represents an example of a noncovalent, intermolecular interaction capable of inducing mesomorphism (liquid-crystallinity) from nonmesomorphic species. (Figure 15).[79] The strength of the liquid crystalline phases of the halogen bonded systems are similar to those of hydrogen-bonded systems.[80]

1.15. *Drug binding, a PDB survey*

A survey of single crystal structures of proteins and nucleic acids in PDB for halogen bonds, resulted in many hits which clearly demonstrate the potential significance of these interactions in ligand binding and recognition.[81] Figure 16 shows an example of the diversity of short X···O interactions that are involved in protein–ligand recognition; there are four short Br···O contacts between the inhibitor 4,5,6,7-tetra-bromobenzotriazole and the ATP binding site of phospho-CDK2-cyclin A

Figure 15: Molecular complex of 4-alkoxystilbazoles and iodopentafluorobenzene via N. . . I halogen bond (N. . . I = 2.811 Å); (A) schematic representation and (B) ball and stick model representation.

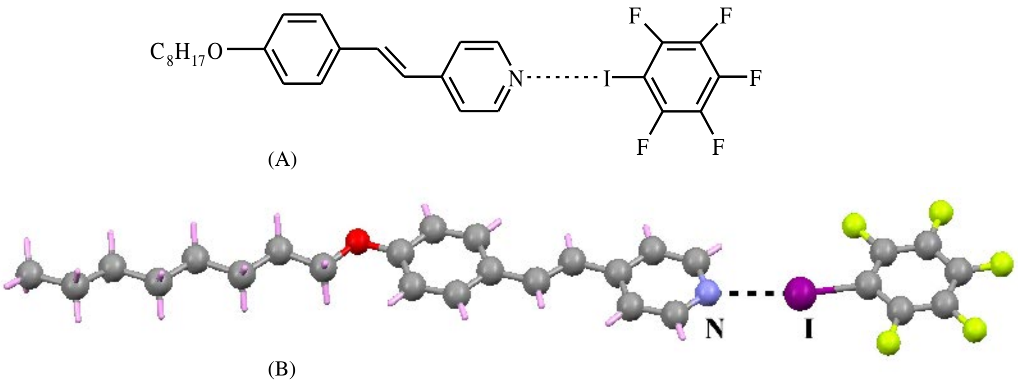


Figure 16: The 2.2 Å structure of phospho-CDK2/cyclin A in complex with the inhibitor 4,5,6,7-tetrabromobenzotriazole. The inhibitor is shown with three bromine halogen bonds to peptide carbonyl oxygens of the protein. Two interactions (middle) involve the lone pairs of the oxygen atom and one (right) involves the π system of the C=O group. In addition, one halogen bond to a water molecule (w) is seen (left).

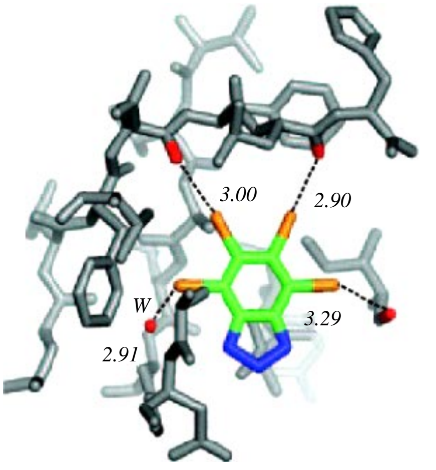
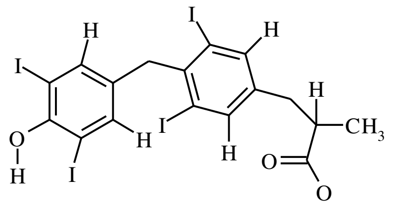


Figure 17: A structure of 3,5,3′,5′-tetraiodo-L-Thyronine (T4).



(2.2 Å structure, PDB ID code 1P5E).[81] Two $C\text{–}Br\cdots O{=}C$ interactions (middle) involve the lone pair of electrons of oxygen atom and one (right) involves the π electrons of a peptide O=C group. In addition, one halogen bond to a water molecule ($C\text{–}Br\cdots O_W$, left, Figure 16) also exists. In this case, the halogenated inhibitor very efficiently displaces the charged ATP ligand, mainly through halogen bonding interactions. This observation stresses the potential role of halogen bond in the design of new drugs and inhibitors.

Halogen substitution is known to enhance the activity of some drugs[82]; the mode of interaction of these molecules with the receptor is now considered via halogen bonding interactions. The X-ray crystal structures of complexes between halogen substituted drugs and their specific proteinaceous receptors proved the existence of halogen bonding interactions that optimized the receptorial fitting.[83] Thyroid hormones form a special class of molecules because they are the only naturally occurring biologically active iodine containing compounds which bind with the macromolecules. The iodine atoms in thyroid hormone thyroxin (T4) bind via short $I\cdots O$ contact with the carbonyl oxygen of the amino acid residue in the pocket of transthyretin (TTR), the major transporter of T4 (Figure 17) in human body.[84] Structure-function studies have been carried out on several thyroid hormone analogues in order to determine those features that are required for binding and activity.[85] These data showed that successive removal of the four iodines dramatically reduces their serum transport protein-binding affinity as well as affect their nuclear binding and biological activity.

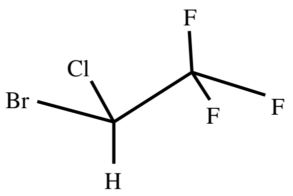
Another example is short $O\cdots Cl$ and $S\cdots Cl$ contacts that have been detected in the crystals structure of the complex between the factor *Xa* of the human blood coagulation cascade and a trichloro substituted inhibitor, which is used in the treatment of thrombotic diseases.[86]

Polyhalogenated organic compounds are used as general anesthetic. Halothane (Figure 18) is a common volatile anesthetic used in therapy in the racemic form; the two enantiomers have different pharmacological activities.[87] The enantioselective recognition of the drug in *vivo* by the formation of halogen-bonded complexes with electron-pair donors present in the receptor pockets is speculated.

1.16. *Theoretical (energy estimation) and Spectroscopic Studies*

Theoretical investigations into charge transfer and electron donor–acceptor interactions of halogen-bonded complexes were performed earlier by Mulliken and Parson.[49], Price *et al.*[41] and Allen and co-workers.[28] They used intermolecular perturbation theory calculations on the complexes formed between chlorine containing molecules and electronegative atoms (N and O). Resnati and coworkers[88] conducted theoretical calculations (DFT and MP2) on the halogen-bonded complexes formed between fluoroallyl halides and ammonia and examined the effect of increasing the fluorine substitutions on halogen bonding. They found that equilibrium $C\text{–}X\cdots N$ geometries were linear and the $X\cdots N$ distances are shorter than the sum of the van der Waals radii (Figure 19). The binding energies of $CF_3X\cdots NH_3$ increased from 2 to 6 Kcal/mol on following the sequence X = Cl, Br, I. Also,

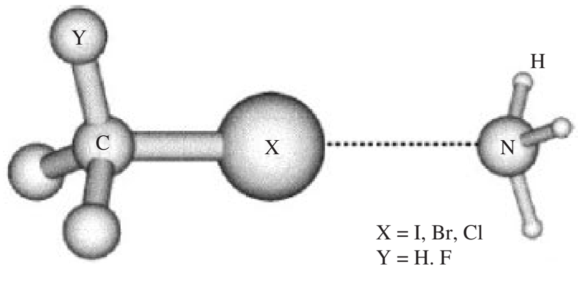
Figure 18: Structure of Halothane.



progressive introduction of fluorine atoms in methyliodides raised the interaction energy from 2 Kcal/mol for CH_3I to 6 Kcal/mol for CF_3I.

Chu *et al.*[89] carried out the theoretical calculations on fluorine containing donor–acceptor complexes. Their investigation revealed that the electron density is anisotropically distributed around the halogen nucleus and the effective atomic radius of X-atom along the C–X bond axis is smaller than that in the perpendicular direction. When electron donors are involved in the halogen bonding is preferentially along the axis of orbital containing the lone pair of donor. Romaniello and Lelj[90] analyzed the halogen bond between CF_3I adducts and several electron donors (N or O). These theoretical calculations revealed that the most important contribution to the intermolecular interactions of halogen atom is electrostatic, whereas the contribution from charge-transfer type interactions is minor and even negligible in some cases. The electron-accepting nature of the carbon-bound halogen atoms was further strengthened by the molecular surface electrostatic potential (ESP) calculations of some halogen containing molecules.[47b,91] Results clearly reveal that there is positive cap at the end regions of the halogen atoms along the C–X (X = Cl, Br and I) bond vectors.

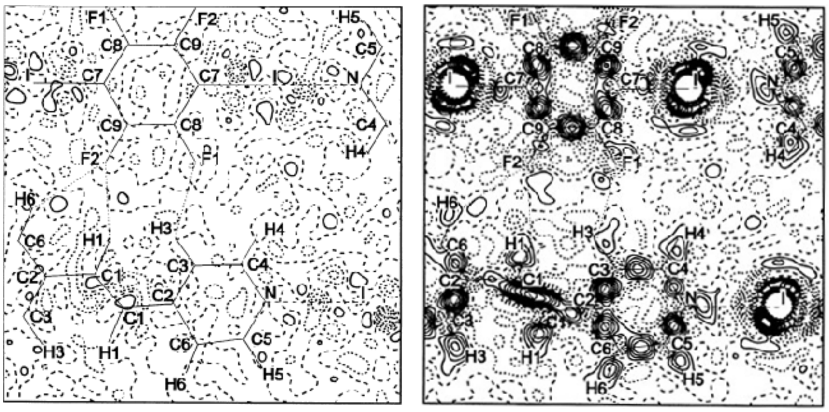
Figure 19: Schematic representation of the halogen-bonded complexes



Recently Zou and coworkers[92] performed *ab initio* study of a series of complexes formed between halogen-containing molecules and ammonia to gain a deeper insight into the nature of halogen bonding and the electron-accepting propensities of covalently bonded halogen atoms. They found that the dihalogen molecules form the strongest halogen bonding complexes with ammonia; followed by HOX and that charge-transfer-type contribution is predominant in halogen bonding. However, for carbon bound halogens (RX), the interaction energy mainly stems from electrostatic interactions. They also explored the influence of the hybridization state of the carbon atom bonded to the halogen and substitution upon the electron-accepting ability of the halogen atom. It has been disclosed that, sp-hybridized carbon-bound halogen atoms form the strongest halogen bond, followed by sp2- and then sp3-hybridized carbon-bound halogen atoms, which very much resembles the behavior of the corresponding hydrocarbons as hydrogen-bond donors. The halogen-bond strength is significantly enhanced by progressive fluorine substitution; the substitution of a hydrogen atom by a methyl group in the CH_3X weakens the halogen bonding in the $CH_3X \cdots NH_3$ complex.

Infrared and Raman spectroscopic analyses of the halogen-bonded adducts formed by α,α'-diiodoperfluoroalkanes with diazabicyclooctane and other electron donors was done by Resnati and co workers.[93] They used IR and Raman technique for the identification and characterization of adducts namely non-covalent co-polymers with 1,2-diiodotetra-fluoroethane and diazabicyclooctane and amines with 1,2-diiodoperfluoroalkanes. The changes of the vibrational modes of both single components on formation of adducts provide useful insights into the occurrence and the nature of the intermolecular interaction driving the self-assembly. In the latter adduct, a high frequency shift and an intensity decrease of the C–H stretching in the 3000–2800 cm^{-1} region are observed both in IR and Raman spectra when the "halogen bonding" is formed between the HC amines and the PFC iodides. These changes indicate a higher positive charge on hydrogen atoms consistent with the nitrogen atoms working as electron donors (Lewis bases) in the co-polymers. The development of the "halogen bonding" can be traced also through the absorption shifts of the diiodoperfluoroalkanes. The stretching motions due to the fluorinated component (1200–1050 cm^{-1} region) in IR spectra shift to lower frequency in the co-polymers and the extent of the shift is proportional to the electron donor ability of the amine.

Figure 20: (A) Residual density and B) deformation density maps in the leastsquares plane defined by the heavy atoms of F4DIB and bpe molecules. The contour interval is 0.10 e Å^{-3}. Solid lines: positive contours; short dashed lines: negative contours; wide dashed lines: zero contours.



(A)

(B)

1.17. *Charge Density Analysis*

Pilati *et al.*[94] has carried out the experimental electron density studies of the donor–acceptor complex of (E)-1,2-bis(4-pyridyl)ethylene (bpe) with 1,4-diiodotetrafluorobenzene (F4DIB) at 90 K with the aspherical atom formalism and analyzed by means of the topological theory of molecular structure. The residual electron density and deformation density maps are shown in Figure 20. The bpe and F4DIB molecules are connected by intermolecular I ...N bonds into infinite 1D chains. F...H bonds link these chains together to form the crystal assembly. The topological analysis reveals that the C–I bond is of the "closed shell" type. Its bond-critical properties run parallel to those found in metal–metal and metal–ligand bonds of organometallic compounds. The integrated net charges show that the I...N halogen bond has an essentially electrostatic nature. F...F, F...C, and C...C intermolecular interactions, for which a bond path was found, contribute to reinforce the crystal structure.

1.18. *Concluding Remarks*

We believe that the above examples of halogen bonding selected from different areas of chemistry illustrate the potential application value of these interactions in crystal engineering, crystal growth and polymorphism, topochemical polymerizations and biological systems to name a few. The halogens with their charge anisotropies create multitudes of environments exhibiting short contacts as electron acceptors, as electron donors or a fine balance between the two. However, the interactions analogous to Hydrogen bonding that can exist between halo carbons and atoms like oxygen, nitrogen and sulphur need further theoretical and experimental studies (planned in our laboratory) for their better understanding.

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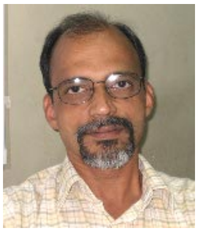

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