

# Chapter 2

## Understanding of Noncovalent Interactions Involving Organic Fluorine

Piyush Panini and Deepak Chopra

**Abstract** Due to the unpredictable nature of organic fluorine in its participation in the formation of different supramolecular motifs which concomitantly influences the physicochemical properties of the compounds of interest, the study of noncovalent interactions involving organic fluorine will always be an expanding area of research amongst the scientific community. The participation of organic fluorine in the formation of intermolecular interactions has always been questioned. In this book chapter, we provide insights into new structural features, nature, and energetics associated with intermolecular interactions, namely C–H $\cdots$ F–C, C–F $\cdots$ F–C, C–F $\cdots$ X (N, O, S, halogen) from researchers across the world. The studies show that interactions involving fluorine are ubiquitous and play a central role in the existence of diversified solid state properties, namely polymorphism, crystal engineering, and cocrystallization.

### 2.1 Introduction

Noncovalent interactions play a pivotal role in the design of a new material with specific properties [1–6]. Their role has been very well recognized in different fields related to biological, pharmacological, chemical, physical, and materials sciences [7–10]. In this regard, the strong hydrogen bonds, e.g., O/N–H $\cdots$ O/N with their high directional characteristics is found to be very effective in the supramolecular assembly of molecules [11]. In view of their importance in many fields of science, the debate on the nature, properties, and importance of hydrogen bonds is increasing day by day. Recently, a task group formed by IUPAC has provided a modern definition of the hydrogen bond [12, 13]. It is as follows: “The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a

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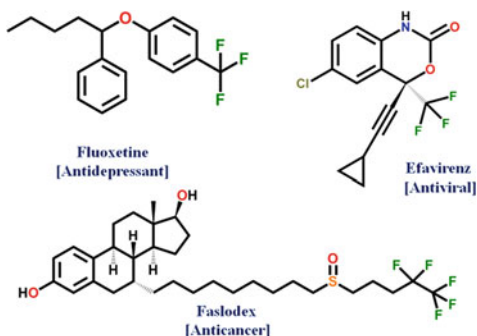
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molecular fragment H–X in which X is more electronegative than H, and an atom or group of atoms in the same or a different molecule, in which there is evidence of bond formation.” Keeping in mind the definition given by Pauling [14] as “Only the most electronegative atoms (such as N, O, F) should form hydrogen bonds (denoted as  $X-H\cdots Y$ ), and the strength of the bond should increase with increase in the electronegativity of the two bonded atoms,” the modern definition is now more general as it extends the list of possible donors and acceptors which participate in the formation of the hydrogen bond. This includes the possibility of hydrogen bond formation when either the donor or acceptor is weak or possesses moderate electronegativity. These aspects constitute the characteristics of the “weak hydrogen bond,” [15, 16]. The stabilization energy of a hydrogen bond lies approximately in the range of 170–2 kJ/mol (the higher range corresponds to ionic hydrogen bonds). Hence, the strongest hydrogen bond can provide energetic stabilization similar in magnitude to a covalent bond, while the weakest one can be close to being a van der Waals interaction. The criterion which differentiates an interaction being a hydrogen bond from a van der Waals interaction is related to the “directionality” as is emphasized by Professor Desiraju [15], and also recommended in the modern IUPAC definition of the hydrogen bond [12, 13]. The evidence of existence of weak hydrogen bonds like  $C-H\cdots O$ ,  $C-H\cdots N$ ,  $C-H\cdots \pi(C)$ ,  $O/N-H\cdots \pi(C)$  are now well established in modern supramolecular chemistry, and are being utilized in the systematic design of materials [17–20]. More over, apart from hydrogen bonds, the  $\pi$ – $\pi$  stacking [21], anion/ $p\cdots\pi$  [22–25], and halogen bonds [26–33] occupy a prominent position amongst noncovalent interactions and their importance in the area of chemistry and biology is very well recognized. The halogen bond is an attractive interaction which arises due to the anisotropy in the charge distribution over covalently bound halogen atoms. This generates a positive electrostatic potential (positive  $\sigma$ -holes) opposite to the C–X  $\sigma$ -bond and having negative electrostatic potential perpendicular to the bond, and hence the positive  $\sigma$ -holes site can now interact with the negative sites in an attractive manner. In addition, interactions involving halogens [ $O/N/C-H\cdots X$ ,  $X\cdots X$ ] have also received considerable attention in recent years and have been investigated in detail with inputs from crystallographic, computational, and spectroscopic studies [34–40]. Amongst these, the presence of intra- and intermolecular interactions involving fluorine has been a subject of study for over two decades [41, 42]. In spite of possessing the highest electronegativity amongst all the elements, noncovalent interactions involving fluorine have always been questioned and its existence is still a subject of debate amongst the scientific communities. Due to differences in electronegativity, the C–F bond (termed as “organic fluorine”) would be highly polar and one might expect the fluorine atom to act as a good H-bond acceptor and can also participate in other related noncovalent interactions, namely  $C-F\cdots F-C$ ,  $C-F\cdots \pi$ , and  $C-F\cdots O$ , respectively. In recent years, significant inputs from crystallography, spectroscopy, and computational studies have strongly contributed toward the understanding of the nature and energetics of interactions involving organic fluorine (in particular

### 2.1.1 Why Fluorine Is So Special?

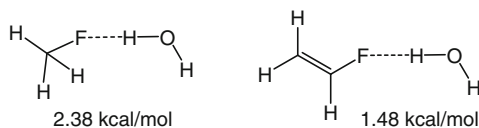
**Fig. 2.1** List of important fluorinated drugs available in market



## 2.2 Debate on Participation of Fluorine as a Hydrogen Bond Donor: Overview of the Weak $X-H\cdots F-C$ ; $X = N, O, C$ Hydrogen Bond

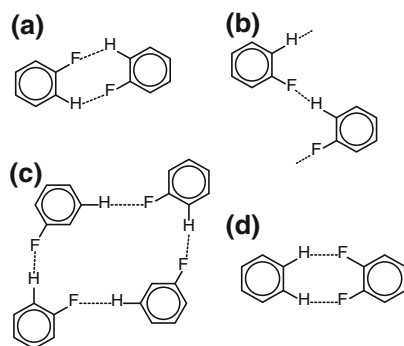
According to Pauling, only the most electronegative atoms should form hydrogen bonds and the strength of the bond should increase with increase in the electronegativity of the two bonded atoms [14]. Hence it might be expected that fluorine being an element with the highest electronegativity [4.0, Pauling scale] in the periodic table, it can form very strong hydrogen bonds. With respect to the hydrogen bond acceptor capability of the fluoride ion (the H-bond energy of the bifluoride ion in  $HF_2^-$  is approximately 40 kcal/mol which is similar to that of a covalent bond and this makes it the strongest known Hydrogen bond) the Pauling statement seems correct. However F-atom connected with C-atom, termed as “organic fluorine,” behaves as a very poor acceptor of hydrogen bond. This statement is supported by inputs from the work of Shimoni and Glusker [61]. Based on a CSD study, it was concluded that the C–F group fails to compete favorably with O and N atom as hydrogen bond acceptors when these atoms are present in the crystal structure, however in the absence of these acceptors, weak  $C-H\cdots F-C$  interactions can be observed. Furthermore, similar conclusions have been made by Dunitz and Taylor on the study of  $O/N-H\cdots F-C$  interactions in an article entitled “Organic Fluorine Hardly Ever Accepts Hydrogen Bonds” [62]. They stated that because of low proton affinity (low basicity, low-lying lone pair orbitals, tightness of its electron shell, i.e., low polarizability) of the covalently attached fluorine and its inability to modify this by intramolecular electron delocalization or intermolecular cooperative effects, organic fluorine possess very low capability of hydrogen bond formation except in “exceptional crystal and molecular environment.” Moreover, Howard et al. performed a CSD study for the existence of  $C-F\cdots H-X$  (where  $X = O, N, C$ ) interactions in different crystal structures and concluded that  $C(sp^3)-F$  is a better hydrogen bond acceptor than  $C(sp^2)-F$  [63]. The strength of a  $C(sp^3)-F\cdots H-O$  and  $C(sp^2)-F\cdots H-O$  H-bond was calculated to be 2.38–1.48 kcal/mol respectively (Fig. 2.2). They also stated “the predominant  $C-F\cdots H-C$  contacts in the Database appear to have very little significance in energy terms and are essentially van der Waals complexes.”

Furthermore, Desiraju and co-workers studied the existence and nature of  $C-H\cdots F-C$  interactions in crystalline fluorobenzenes [64]. These compounds were chosen because they have only C, H, and F and hence do not possess any other

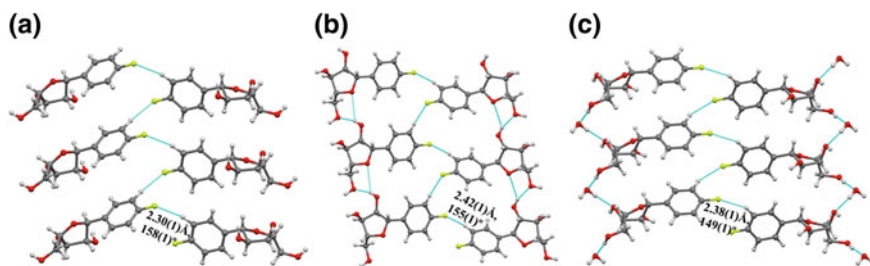


**Fig. 2.2**  $C(sp^3)-F\cdots H-O$  and  $C(sp^2)-F\cdots H-O$  H-bond strength

**Fig. 2.3** Four types of possible supramolecular synthons for C–H···F–C interactions



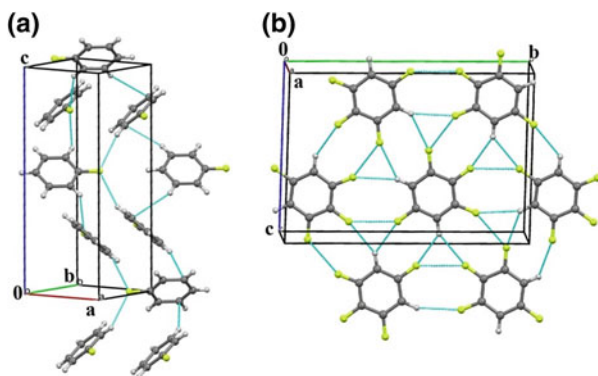
elements like N or O which can compete with fluorine and are also responsible for the increase in the acidity of hydrogen atoms in its vicinity. On the basis of distance-angle ( $d/\theta$ ) correlation plots for the presence of C–H···F–C interactions in these crystal structures, it was observed that these interactions have the characteristics of weak hydrogen bonds. The supramolecular synthons for C–H···F (Fig. 2.3) [64] were observed to be topologically similar to well-known C–H···O and C–H···N synthons and can be used in the design of novel and functional crystals. On the comparison of these crystal structures with their chloro, bromo and iodo analogues, it was observed that fluorine prefers C–H···F interactions rather than F···F contacts, whereas the heavier halogens prefer halogen···halogen interactions. Furthermore, the significance of C–H···F–C interactions were observed in a series of crystal structures of ribonucleic acids [65] and these were claimed as “hydrogen bonds.” The authors concluded that the C–H···F–C hydrogen bonds observed at distances shorter than sum of van der Waal radii of hydrogen and fluorine in their crystal structures, (for example, in the two polymorphs and a hemihydrate of 1'-deoxy-1'-(4-fluorophenyl)- $\beta$ -D-ribofuranose and the nature of the C–H···F–C chain is similar in the crystal packing of these three solid forms, Fig. 2.4) are responsible to provide further stabilization in modified RNA duplex containing fluorine atoms at Watson–Crick binding site.



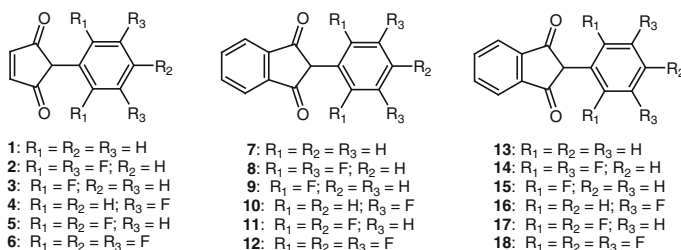
**Fig. 2.4** The nature of short and directional C–H···F–C hydrogen bonds forming chains in **a** Form I, **b** Form II and **c** hemihydrate of 1'-deoxy-1'-(4-fluorophenyl)- $\beta$ -D-ribofuranose are observed to be similar in the solid state [65]

A few years later, a review by Dunitz, entitled “Organic Fluorine: Odd Man Out” [66], raised further speculation about the nature of organic fluorine. Furthermore the interpretation presented by Desiraju from the crystal structure analysis of fluorobenzenes were quantified by inputs from Molecular-Pair analysis (from PIXEL [67] calculations) [68]. It was proposed that one of the hypothetical (computed) high pressure forms of benzene adopts the same tetragonal packing as fluorobenzene and hence  $\text{C-H}\cdots\text{F-C}$  interactions behave similar to  $\text{C-H}\cdots\text{H}$  interactions and have the same structure-directing ability. This conclusion was further supported in the crystal packing analysis of 1,2,3,4-tetrafluoronaphthalene, -anthracene, and -phenanthrene by Gavezzotti et al. [69]. It was observed that the  $\text{C-H}\cdots\text{F-C}$  interactions does not provide any significant stabilization to the crystal packing. Following this work, immediately, Ganguly, and Desiraju [70] observed that in the hypothetical (computed) high pressure forms of benzene, the  $\text{C-H}\cdots\text{H}$  interactions can be more accurately represented as  $\text{C-H}^{\delta+}\cdots\text{H}^{\delta-}$ . Further, on the basis of crystal structure analysis of 1,2,3,5-tetrafluorobenzene, by Boese and Desiraju, it was established that  $\text{C-H}\cdots\text{F-C}$  interactions have similar structure direction ability as a hydrogen bond [71]. It was observed that the title compound which has shape and size similar to many fluorobenzenes, does not adopt the tetragonal packing in the solid. Instead it preferred to crystallize in monoclinic  $P2_1/c$  space group, stabilized by the presence of  $\text{C-H}\cdots\text{F-C}$  hydrogen bonds (Fig. 2.5).

The role of intermolecular interactions involving organic fluorine has been analyzed by many researchers in the last two decades exploiting various experimental, theoretical, and database studies. These have been excellently compiled in recent reviews [41], highlight [72] and a perspective [73]. It was initially anticipated that such weak  $\text{C-H}\cdots\text{F}$  hydrogen bonds are only significant in the absence of any other strong intermolecular forces [74]. In the crystal structure analysis of fluorine



**Fig. 2.5** **a** Depiction of the tetragonal packing in fluorobenzene via  $\text{C-H}\cdots\text{F-C}$  and  $\text{C-H}\cdots\pi$  interactions (ref code: FACFAQ; crystallizes in  $P4_32_12$ ) [64]. **b** Formation of a molecular sheet down the  $bc$ -plane in 1,2,3,5-tetrafluorobenzene with utilization of  $\text{C-H}\cdots\text{F-C}$  and  $\text{C-F}\cdots\text{F-C}$  interactions (crystallizes in  $P2_1/c$ ) [71]

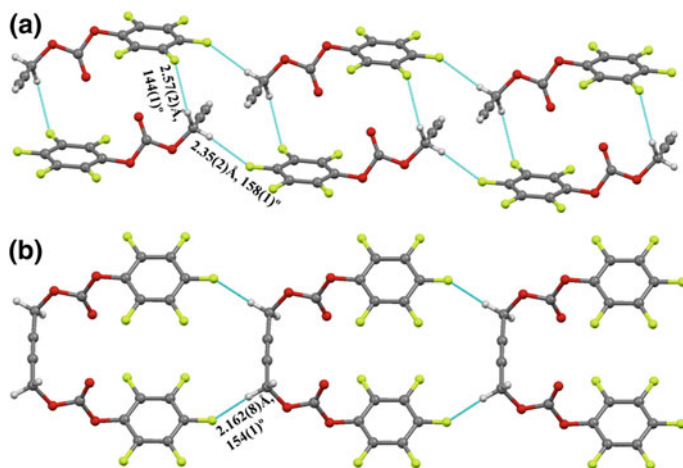


**Fig. 2.6** Fluorine substituted phenylmaleimides and corresponding phthalimides [78]

substituted isoquinolines [75, 76], trifluoroacetophenones [77] *N*-phenylmaleimides and corresponding phthalimides [78], benzonitriles [79], pyridines [80], *N*-benzylideneanilines [81], azobenzenes [82], etc., the importance of weak  $C-H\cdots F-C$  hydrogen bonds was observed in the absence of any strong hydrogen bond donor. Crystal packing analysis of a series of fluorine substituted isoquinolines was observed to be stabilized by mainly  $C-H\cdots F$  hydrogen bonds along with  $C-F\cdots F-C$  and  $C-F\cdots\pi$  in the absence of any other relatively stronger intermolecular forces such as hydrogen bonding,  $C-H\cdots\pi$  or  $\pi\cdots\pi$  interactions [75, 76]. The detailed analysis of eighteen crystal structures of fluorine substituted phenylmaleimides and corresponding phthalimides (Fig. 2.6) by Schwarzer and Weber revealed that although  $C-H\cdots O$  plays the dominant role in their crystal packing, the presence of  $C-H\cdots F$  hydrogen bonds along with other related weak interactions like  $C-F\cdots F-C$ ,  $C-F\cdots\pi$ ,  $\pi\cdots\pi_F$  interactions provide further stabilization in the molecular assemblies [78]. The major influence of these weak interactions was observed in case of polymorphs of 12 (labeled as 12A and 12B [78]). In case of 12A, the crystal packing was stabilized by the presence of two short  $C-H\cdots F$  hydrogen bonds (forming a chain), along with  $C-H\cdots O$  hydrogen bond and other weak  $C-F\cdots F-C$  and  $C-F\cdots\pi$  interactions. On the other hand, short  $C-H\cdots O$  hydrogen bonds (forming chain), along with one dimeric weak  $C-H\cdots F$  hydrogen bond and  $C-F\cdots F-C$  interactions were observed in the crystal packing of 12B.

Moreover, Choudhury and Guru Row noticed in the crystal packing of pentafluorophenylprop-2-ynylcarbonate that the  $C-H\cdots F$  hydrogen bond dominated over the  $C-H\cdots O$  hydrogen bond [83], which was considered to be highly structure directing and a preferred interaction (Fig. 2.7a). This observation promoted the debate regarding the significance of  $C-H\cdots F$  hydrogen bond. Further, it was observed (by the same research group) that the occurrence of  $C-H\cdots F$  hydrogen bond (utilizing acidic methylene protons in the formation of highly short and directional interaction) in the crystal packing of but-2-yne-1,4-diylbis(pentafluorophenylcarbonate) [84], stabilized the rare and unusual *cisoid* conformation of the molecule (Fig. 2.7b).

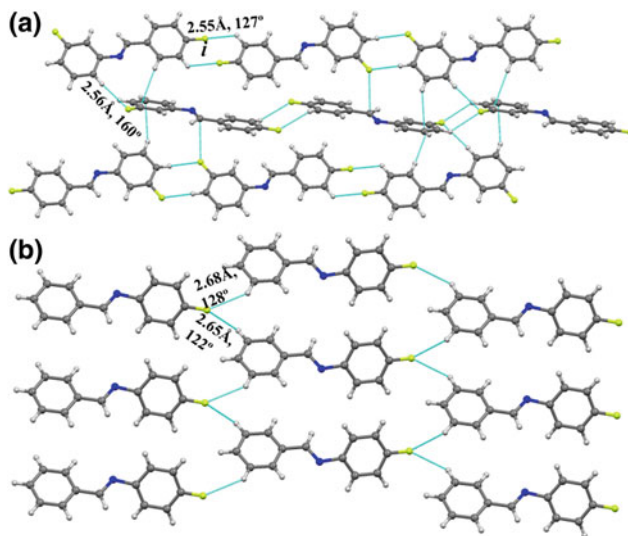
Fluorobenzonitriles [79] and fluorinated pyridines [80] were crystallized by in situ crystallization, and the significance of interactions involving “organic fluorine” was studied by Merz et al. The weak  $C-H\cdots F$  along with  $C-H\cdots N$



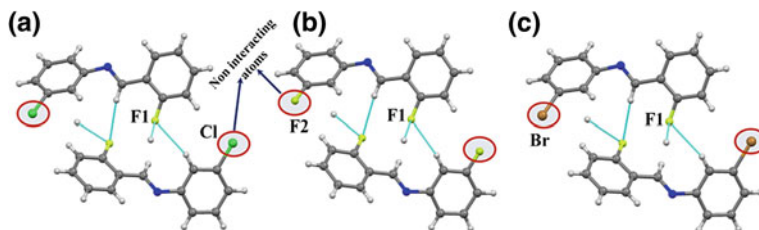
**Fig. 2.7** **a** Part of crystal packing in pentafluorophenyl prop-2-ynyl carbonate, displaying short C–H···F–C hydrogen bond [83]. **b** *cisoid*-conformation of but-2-yne-1,4-diylbis(pentafluorophenylcarbonate) stabilized by the presence of short C–H···F–C hydrogen bonds in the crystal packing [84]

hydrogen bond were observed in the molecular assembly of fluoro substituted benzonitriles and subsequent increase in the melting point with the sequential change in the position of fluorine (*ortho*-, to *meta*-, to *para*-) over the phenyl ring relative to cyano group were noticed. In case of fluorine substituted pyridines with the increase in fluorine substitution, noticeable changes in their crystal packing were discovered. It was observed that the crystal packing changes stepwise from a herringbone packing in monofluorinated pyridine to parallel arrangement of the molecules in the trifluorinated pyridine and then to the edge-to-face molecular arrangement in case of perfluorinated pyridine. In crystal structure analysis of a series of 15 newly synthesized fluorine substituted (*mono*- and *di*-) isomeric *N*-benzylideneanilines [81], it was observed that C–H···F acts as a significant contributor in the construction of various supramolecular synthons in their crystal packing (Fig. 2.8a, b). Furthermore, Kaur and Choudhury, have investigated the capability of organic fluorine to participate in the formation of interactions involving fluorine in the presence of other halogens in *N*-benzylideneanilines (Figs. 2.9 and 2.10) [85]. It was observed that the replacement of noninteracting fluorine atoms by either Cl or Br does not alter the packing motifs in comparison to the corresponding difluorinated analogues while modification in the crystal packing was detected when the interacting fluorine atom was replaced (Figs. 2.9 and 2.10). Recently, Merz et al. examined changes in crystal packing behavior of toluene ( $\alpha$ -polymorph) with systematic replacement of the H-atom with the fluorine atom on the methyl group [86]. The authors concluded that increase in fluorination due to replacement of  $-\text{CH}_3$  by  $-\text{CHF}_2$  and  $-\text{CF}_3$  leads to the changes in molecular assembly, from corrugated layers to parallel arrangement in their crystal packing.



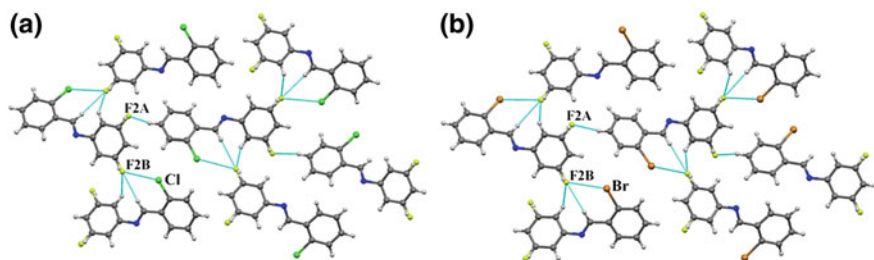


**Fig. 2.8** **a** Packing of molecules in 3-fluoro-*N*-(4-fluorobenzylidene)aniline via C-H...F-C and C-H... $\pi$  hydrogen bonds. **b** Formation of a molecular chain in *N*-Benzylidene-4-fluoroaniline with utilization of bifurcated C-H...F-C hydrogen bonds [81]

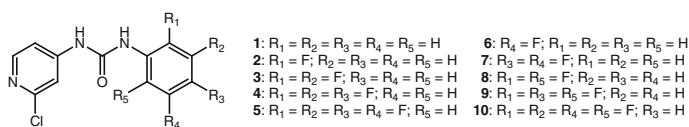


**Fig. 2.9** Conservation of supramolecular motifs on replacement of noninteracting fluorine atom (F2) in case of **a** 3-chloro-*N*-(2-fluorobenzylidene)aniline **b** 3-fluoro-*N*-(2-fluorobenzylidene)aniline and **c** 3-bromo-*N*-(2-fluorobenzylidene)aniline [85]

Further, the capability of organic fluorine as H-bond acceptor was also studied extensively in the presence of strong hydrogen bond donor [87–93]. The importance of such C-H...F interactions being weak and cooperative in nature has been realized in the crystal structure analysis of fluorinated *N*-(2-Chloropyridin-4-yl)-*N'*-phenylureas (Fig. 2.11) [87], halogenated benzanilides (fluorinated [88] and hetero halogenated with at least one side of the phenyl ring contains fluorine [88–90]), trifluoromethyl (–CF<sub>3</sub>) substituted benzanilides [91], fluoro-*N*-(pyridyl)benzamides [92], fluorine-substituted benzimidazoles [93]. In the crystal packing of a series of fluorinated *N*-(2-Chloropyridin-4-yl)-*N'*-phenylureas (Fig. 2.11), short and highly directional C-H...F-C interactions were observed in the solid state [87]. The authors concluded that the influence in the crystal packing by fluorine substitution



**Fig. 2.10** Replacement of interacting F-atom (F1, Fig. 2.9b) with Cl or Br leads to alteration in crystal packing in case of **a** 3-fluoro-*N*-(2-chlorobenzylidene)-aniline and **b** 3-fluoro-*N*-(2-bromobenzylidene)-aniline



**Fig. 2.11** Series of fluorinated *N*-(2-Chloropyridin-4-yl)-*N'*-phenylureas synthesized for the analysis of interactions involving “organic fluorine”

appeared mainly due to the (i) polarity of the C–F bond and the associated electrostatic changes and (ii) increase in C–H acidity neighboring to the F-atoms.

An important breakthrough on the importance and capability of organic fluorine in the formation of intermolecular interactions was realized by Desiraju and co-workers. This involved the study of the structural landscape of benzoic acid [94]. In this analysis, different structural landscapes (a total of 100 structures were predicted, corresponds to different rank) of benzoic acid was obtained using COMPASS26 and DREIDING force field using Material Studio (with restriction of space group to  $P2_1/c$  and  $P-1$  only, these being the most common in case of organic compounds). This study was based on crystal structure prediction (CSP) [95, 96].

This study involves the computational prediction of a series of crystal structures of a given compound having different lattice energy (called the crystal energy landscape). This may result in different hypothetical structures of the compound of interest (some of these may correspond to polymorphs as well, a fundamental application of this computational exercise). The crystal structure corresponds to the global minimum and this may be similar to the experimentally observed crystal structure. In the investigation by Prof. Desiraju and co-workers, it was observed that the experimental crystal structure of fluorinated (mono or poly) benzoic acid was similar to the “high energy” crystal structure of benzoic acid, predicted computationally (Table 2.1). In other words, it may be concluded that substitution of fluorine on benzoic acid actually stabilized its high energy form by introducing the possibilities of different intermolecular interactions like  $C-H \cdots F-C$  and  $C-F \cdots F-C$  (these are present in the experimental crystal structure of fluorinated benzoic acid [94]) in the crystal packing. Moreover, in the same work, this behavior was

**Table 2.1** Structural landscape of benzoic acid [94]

Compound	Structure type <sup>a</sup>	Rank
Benzoic acid	(5-5-22)	5th and 23rd
3,4-difluorobenzoic acid		
2,3,4-trifluorobenzoic acid		
3,4,5-trifluorobenzoic acid		
2-fluorobenzoic acid	(6-4-25)	99th
3-fluorobenzoic acid	(4-6-26)	55th
4-fluorobenzoic acid		
2,3-difluorobenzoic acid		
2,4-difluorobenzoic acid		
2,5-difluorobenzoic acid	(4-14-12)	56th
3,5-difluorobenzoic acid		
2,3,5-trifluorobenzoic acid		

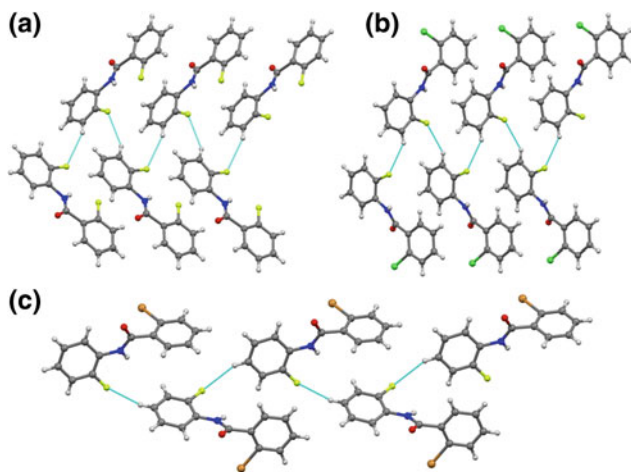
<sup>a</sup> Corresponds to nearest integer of unit cell parameters  $a$ ,  $b$ ,  $c$ ; For example, for benzoic acid:  $a = 5.510$  Å,  $b = 5.157$  Å,  $c = 21.973$  Å, Structure type: 5-5-22

observed to be more consistent with fluorine than with chloro or bromo substituted benzoic acid. This concept has been further extended to a two component system (cocrystal). It was observed that the experimental crystal structure of 1:1 cocrystal of fluorobenzoic acids with isonicotinamide corresponds to a high energy computed structure of 1:1 benzoic acids and the isonicotinamide cocrystal [97]. Intermolecular interactions like  $\text{C-H}\cdots\text{F-C}$ ,  $\text{C-F}\cdots\text{F-C}$ ,  $\text{C-F}\cdots\text{O}$  were observed in the crystal packing of a different fluorinated analogue (the 1:1 cocrystal of benzoic acids and isonicotinamide) along with other related strong and weak interactions.

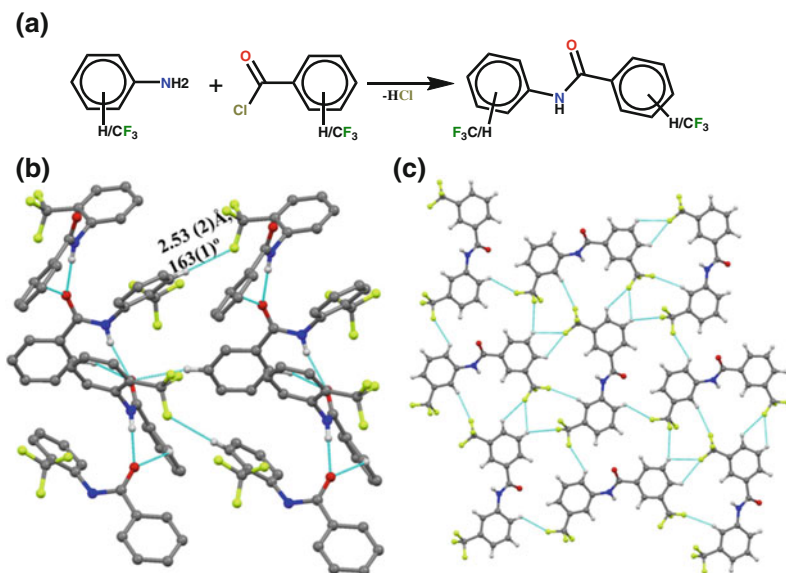
The detailed exhaustive investigation of nature and  $\text{C-H}\cdots\text{F-C}$  interactions were carried out by Novoa, by a combination of CSD search and ab initio theoretical calculations [98]. It was observed that in case of the neutral molecular fragment, the  $\text{C-H}\cdots\text{F-C}$  interaction behaves as a weak hydrogen bond with stabilization energy being  $\sim -0.40$  kcal/mol. The interaction energy were divided into the sum of the following five components (i) the exchange-repulsion component,  $E_{\text{er}}$ , (ii) electrostatic component,  $E_{\text{el}}$ , (iii) polarization component,  $E_{\text{p}}$ , (iv) charge-transfer components,  $E_{\text{ct}}$  and (v) dispersion component,  $E_{\text{disp}}$  by IMPT method [99]. The results suggested that in case of  $\text{C-H}\cdots\text{F}$ , the interaction energy is mainly dominated by the electrostatic and dispersion component with the latter being more prevalent. The relevance and nature of hydrogen bond with fluorine was further reviewed in detail in solution, gas phase, and in solid state with inputs from computational and spectroscopic studies on this interaction [100]. The free energy for  $\text{C-H}\cdots\text{F}$  hydrogen bond in  $\text{CCl}_4$  was computed to be 6 kJ/mol which was higher than other halogens and the value increases with the change in hybridization of C-atom connected to the fluorine atom (from  $sp^3$  to  $sp^2$  to  $sp$ ).

Furthermore, the relevance of  $\text{C-H}\cdots\text{F-C}$  interactions were observed in the formation of different motifs such as dimer, chain, chains of dimers, etc., in the presence of strong  $\text{N-H}\cdots\text{O=C}$  hydrogen bond and other related weak interactions like  $\text{C-H}\cdots\text{O}$ ,  $\text{C-H}\cdots\pi$ ,  $\pi\cdots\pi$ , halogen-halogen interactions in the crystal packing studies of halogenated benzanilides [88–92]. The significance of these studies was to acquire the systematic analysis of interactions involving organic fluorine when the molecular skeleton was fixed and the position of fluorine atoms were varied, thus an isomeric series was obtained. In these series of compounds, the introduction of a F-atom and its systematic variation in position over phenyl ring leads to a concomitant variation in the crystal system and space group (from centrosymmetric to noncentrosymmetric). The cooperative and robust nature (an important condition for considering an interaction as a “hydrogen bond”) of  $\text{C-H}\cdots\text{F-C}$  interactions were observed and found to contribute significantly toward the crystal packing in these series of compounds. In one such example, the molecular chain generated with the utilization of  $\text{C-H}\cdots\text{F-C}$  H-bonds in 2-fluoro-*N*-(2-fluorophenyl)benzamide remain invariant when the fluorine not participating in this interaction is replaced by chlorine atom in case of 2-fluoro-*N*-(2-chlorophenyl)benzamide (Fig. 2.12a, b) [88, 89]. Moreover, on replacement of the Cl-atom with Br-atom in 2-fluoro-*N*-(2-bromophenyl)benzamide leads to change in the crystal packing but a similar molecular chain via  $\text{C-H}\cdots\text{F-C}$  H-bonds were still present in the crystal packing (Fig. 2.12c) [89].

Furthermore, the focus is now shifted to analyze the changes in molecular conformation and crystal packing on replacement of a  $-\text{F}$  by a  $-\text{CF}_3$  moiety at the *o*-, *m*- and *p*- positions on either or both of the phenyl rings in this class of compounds. For this purpose, 15 compounds were synthesized [10 crystal structures [91]



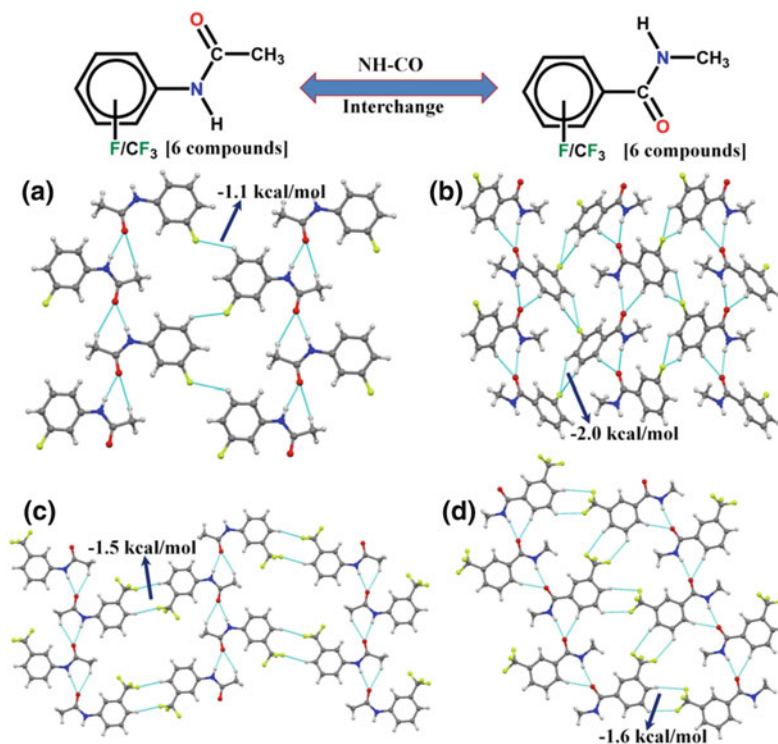
**Fig. 2.12** Identical molecular chain formed via  $\text{C-H}\cdots\text{F-C}$  H-bonds in case of **a** 2-fluoro-*N*-(2-fluorophenyl)benzamide **b** 2-fluoro-*N*-(2-chlorophenyl)benzamide. **c** Part of crystal packing in 2-fluoro-*N*-(2-bromophenyl)benzamide showing presence of  $\text{C-H}\cdots\text{F-C}$  H-bonds [88, 89]



**Fig. 2.13** **a** Chemical scheme for the fifteen trifluoromethyl substituted benzanilides. **b** Packing of the molecule in *N*-[2-(trifluoromethyl)phenyl]benzamide via strong  $\text{N-H}\cdots\text{O}=\text{C}$ , weak  $\text{C-H}\cdots\text{O}=\text{C}$  and short  $\text{C}(\text{sp}^2)\text{-H}\cdots\text{F-C}(\text{sp}^3)$  H-bonds. **c** Formation of a herringbone arrangement in the crystal packing of 3-(Trifluoromethyl)-*N*-[3-(trifluoromethyl)phenyl]benzamide with the utilization of a network of  $\text{C}(\text{sp}^2)\text{-H}\cdots\text{F-C}(\text{sp}^3)$  H-bonds [91]

were determined] (Fig. 2.13a). The salient purpose was to introduce the following electronic characteristics and see the changes in structure disposition: (i) The  $-\text{CF}_3$  group being strongly electron-withdrawing in nature affects the behavior of hydrogen atoms present in its vicinity which participates in H-bond formation. (ii) Well documented, better H-bond acceptor abilities of  $\text{C}(\text{sp}^3)\text{-F}$  could be utilized (iii) In addition to  $\text{C-H}\cdots\text{F-C}$  H-bonds, the possibilities of formation of other interactions like  $\text{C-F}\cdots\text{F-C}$  and  $\text{C-F}\cdots\pi$  was now increased. In this systematic and complete analysis of crystal packing of this series of compounds, the weak but directional  $\text{C}(\text{sp}^2)\text{-H}\cdots\text{F-C}(\text{sp}^3)$  H-bonds were observed acting cooperatively to generate unique packing motifs. The acidic hydrogens (adjacent to  $-\text{CF}_3$  group) appeared in the participation of the H-bonds utilizing the key symmetry elements of the corresponding space groups in which they crystallized. For examples, in case of *N*-[2-(trifluoromethyl)phenyl]benzamide (crystallizes in the rare tetragonal non-centrosymmetric space group  $P4_1$ ), a relatively short and directional  $\text{C}(\text{sp}^2)\text{-H}\cdots\text{F-C}(\text{sp}^3)$  H-bonds (symmetry code:  $-\gamma + 1, x, z + 1/4$ ) were observed to connect the molecular chain formed by strong  $\text{N-H}\cdots\text{O}$  hydrogen bond along  $4_1$ -screw parallel to  $z$ -axis (Fig. 2.13b). In another example, networks of  $\text{C}(\text{sp}^2)\text{-H}\cdots\text{F-C}(\text{sp}^3)$  H-bonds appeared to stabilize the formation of herringbone packing in case of 3-(Trifluoromethyl)-*N*-[3-(trifluoromethyl)phenyl]benzamide (Fig. 2.13c).

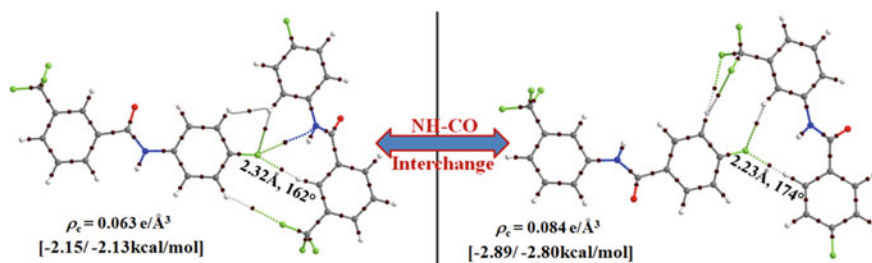
Furthermore, to investigate the geometrical and energetic features associated with weak  $C(sp^3/sp^2)-H\cdots F-C(sp^3/sp^2)$  intermolecular interactions, in addition to the well-recognized  $N-H\cdots O=C$  and  $C-H\cdots O=C$  hydrogen bonds, a library of 12 compounds (derivatives of acetamide and benzamide, Fig. 2.14) were synthesized and their crystal structures were determined [101]. The  $C(sp^3/sp^2)-H\cdots F-C(sp^3/sp^2)$  intermolecular interactions formed different chains (for example, Fig. 2.14a), molecular chains utilizing bifurcated  $C-H\cdots F$  (for example, Fig. 2.14b), dimeric (two kinds, first, where two acceptors are from different molecules (for example, Fig. 2.14c) and second, where the two acceptors are from the same molecule (for example, Fig. 2.14d)) were observed in the crystal packing of these series of compounds. The interaction energies for different molecular motifs extracted from the crystal packing was determined by PIXEL calculation [102, 103]. The molecular motifs comprising  $C-H\cdots F-C$  hydrogen bonds were observed to provide stabilization of 1.0–2.0 kcal/mol towards the crystal packing. From, the detailed investigation of all these crystal structures, it is also observed that  $C(sp^3/sp^2)-H\cdots F-C(sp^3)$  provides more stabilization than  $C(sp^3/sp^2)-H\cdots F-C(sp^2)$ , hence supporting



**Fig. 2.14** Different molecular motifs formed via  $C-H\cdots F-C$  hydrogen bonds in the presence of strong  $N-H\cdots O=C$  and weak  $C-H\cdots O=C$  hydrogen bonds in **a**  $N-(3\text{-fluorophenyl})\text{acetamide}$ , **b**  $3\text{-fluoro-}N\text{-methylbenzamide}$ , **c**  $N-(3\text{-(trifluoromethyl)phenyl})\text{acetamide}$ , and **d**  $N\text{-methyl-3-(trifluoromethyl)benzamide}$  [101]



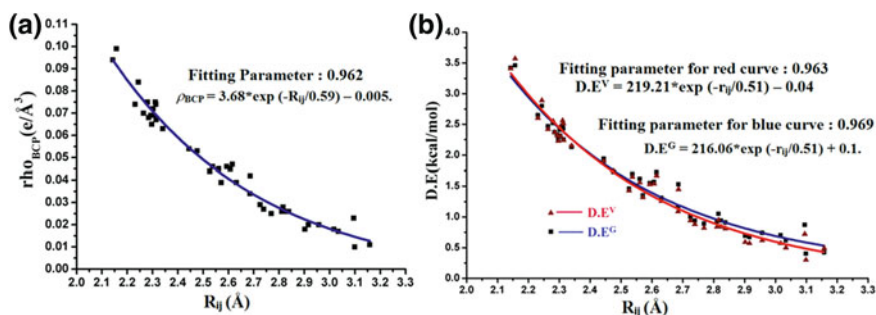
the fact that fluorine connected to  $sp^3$  hybridized carbon has a greater propensity of forming H-bonds. In order to further extend the systematic investigation of interactions involving organic fluorine, 18 benzanilides containing  $-F$  or  $-CF_3$  group on either side of the phenyl ring were synthesized and the preliminary analysis of their crystal structures revealed significant geometrical observations regarding interactions related to organic fluorine [104]. It was observed that one compound, *N*-(4-fluorophenyl)-3-(trifluoromethyl) benzamide exhibits dimorphism wherein two forms crystallize in a rare combination of noncentrosymmetric space groups (orthorhombic  $Pna2_1$  and monoclinic  $Cc$ , respectively). In another related compound, 4-fluoro-*N*-[3-(trifluoromethyl)phenyl] benzamide (can be viewed as NH-CO interchange from the previous one) exists in a centrosymmetric form (monoclinic  $P2_1/c$ ). The primary recognition motif consisting of  $N-H\cdots O=C$  and  $\pi\cdots\pi$  interaction was observed to be similar in all the three structures and the major difference appeared in the nature of the weaker interactions. In the orthorhombic form of *N*-(4-fluorophenyl)-3-(trifluoromethyl) benzamide, the crystal packing was stabilized by mainly the weak  $C-H\cdots\pi$  interactions along with only one  $C-H\cdots F$  interaction [ $2.61\text{ \AA}/137^\circ$  (neutron normalized)], the distance being less than the sum of the van der Waals radii ( $2.67\text{ \AA}$ ) of hydrogen and fluorine. In case of the monoclinic form, out of the 8 fluorine atoms in the asymmetric unit, six are involved in the formation of short  $C-H\cdots F$  interactions, including the one with the  $H\cdots F$  distance being  $2.32\text{ \AA}$  and a directionality of  $162^\circ$  (neutron normalized). Further, in the crystal packing of a related isomer, 4-fluoro-*N*-[3-(trifluoromethyl)phenyl] benzamide, a short and highly directional  $C-H\cdots F$  [ $2.23\text{ \AA}/173^\circ$  (neutron normalized)] was observed. It is to be noticed that such short contacts were observed in the presence of strong  $N-H\cdots O=C$  hydrogen bonds (involving acidic hydrogens) were observed to participate in the formation of short  $C-H\cdots F\cdots C$  contacts (Fig. 2.15). In the work, a molecular pair consisting of  $C-H\cdots F$  interactions were extracted from the crystal packing and analyzed by the PIXEL method [102, 103] and Atoms in Molecule (AIM) [105, 106] theory. From the PIXEL energy calculations, it was obtained that the interaction energy of a molecular pair containing short  $C-H\cdots F\cdots C$



**Fig. 2.15** Similar molecular motif in monoclinic form of *N*-(4-fluorophenyl)-3-(trifluoromethyl) benzamide and 4-fluoro-*N*-[3-(trifluoromethyl)phenyl] benzamide displaying short  $C-H\cdots F$  hydrogen bonds (marked with arrows) with other interactions. Bond critical points are shown with brown spheres. Reprinted with the permission from Ref. [104]. Copyright 2014 American Chemical Society

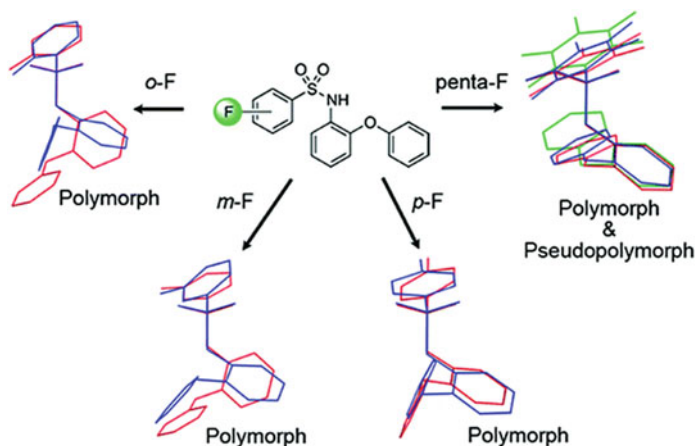
contacts have a substantial Coulombic contribution (approx. 35 %) in comparison to the other weak interactions which are primarily of a dispersive character. The topological analysis were performed on the molecular pair consisting of C–H $\cdots$ F interactions, by program AIMALL and the results showed the presence of (3, –1) bond critical point (BCP) for C–H $\cdots$ F interactions in the molecular pairs. Topological parameters like electron density ( $\rho$ ), Laplacian of the electron density ( $\nabla^2\rho$ ), local potential ( $V_b$ ), and kinetic energy density ( $G_b$ ) were obtained. Local stabilization energy were obtained from equations: (i)  $D.E^V(\text{int}) = -0.5V_b$  (in atomic units) [107] (ii)  $D.E^G(\text{int}) = 0.429 G_b$  (in atomic units) [108, 109]; where  $D.E(\text{int})$  is the dissociation energy of the interaction. Interaction energy ( $I.E$ ) =  $-D.E$   $V_b$  and  $G_b$  are local potential and kinetic energy density at the bond critical points (BCP) respectively. Exponential decrease in electron density at BCP and D.E with increase in bond path distance was observed (Fig. 2.16). The magnitude of the stabilizing interaction energy were calculated to be –2.15 and –2.89 kcal/mol, for the short C–H $\cdots$ F interaction in the case of the monoclinic form of *N*-(4-fluorophenyl)-3-(trifluoromethyl) benzamide and 4-fluoro-*N*-[3-(trifluoromethyl)phenyl] benzamide respectively. The observed strength was found to be 30–40 % of the strength of a strong traditional H-bond in amides, N–H $\cdots$ O=C, whose interaction energy was calculated to be 6–8 kcal/mol. Furthermore, the value of the Laplacian of electron density was observed to be positive for all the C–H $\cdots$ F's which showed that these exhibit closed shell character and for the contacts below 2.7 Å, such values were observed to lie above 0.578 e/Å<sup>5</sup> (which is the criterion for considering an interaction as a hydrogen bond [105, 106]). Moreover, the value of  $|V_b|/G_b < 1$  for all the ranges in  $R_{ij}$  for H $\cdots$ F interactions was observed, which is an important criterion for H-bond, as suggested by Espinosa [110]. Finally with respect to the criteria constituted by IUPAC it was concluded that C–H $\cdots$ F interactions at short distances are a true “hydrogen bond”.

Recently, Azumaya et al. studied the role of fluorine substitution in the polymorphism of aromatic sulfonamides [111]. The existence of polymorphism was only observed in case of the fluorinated analogue of the sulfonamides (Fig. 2.17).



**Fig. 2.16** **a** Variation of the electron density ( $\rho_{\text{BCP}}$ ) at BCP versus H $\cdots$ F-bond path distance ( $R_{ij}$ ). **b** Variation of the dissociation energies (D.E) versus  $R_{ij}$ . Reprinted with the permission from Ref. [104]. Copyright 2014 American Chemical Society





**Fig. 2.17** Existence of polymorphism in fluorine-substituted *N*-(2-phenoxyphenyl)-benzene sulfonamides. Reprinted with the permission from Ref. [111]. Copyright 2012 American Chemical Society

The role of interactions involving organic fluorine like  $C-H\cdots F-C$ ,  $C$ ,  $C-F\cdots F-C$  (resulted in the formation of different molecular motifs) were observed to be crucial in the crystal packing of these polymorphs in presence of other stronger interactions like  $N-H\cdots O=S$ ,  $C-H\cdots O=S$ ,  $C-H\cdots \pi$ .

## 2.3 Inputs from Other Interactions Involving Organic Fluorine

### 2.3.1 Insight into Halogen–Halogen Interactions Involving Fluorine

Halogen–halogen interactions are routinely divided into two categories: type I and type II (Fig. 2.18). Both type I and type II contacts appear frequently in the literature and CSD search wherein the heavier halogen tends to form type II more frequently while the lighter one (fluorine) appears to form mainly type I contacts. The type I contacts are often considered to arise from the consequence of dense crystal packing and “does not” or provides very low stabilization to the crystal packing. It was considered to be a van der Waal interaction and arise when two halogen atoms minimize repulsion by interfacing the neutral regions of their electrostatic potential surfaces. The type II contact involves an approach of the electrophilic region of one halogen atom with the nucleophilic region of the other halogen leading to its *L*-shaped geometry. Further, due to the very low polarizability of the fluorine atom, its participation in  $F\cdots F$  interaction was questioned.

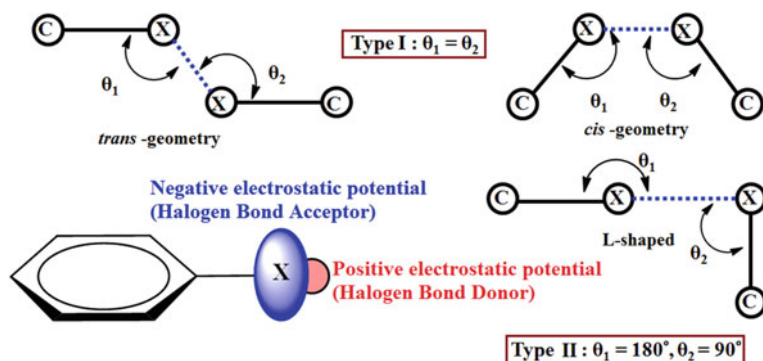


Fig. 2.18 Geometrical representation of halogen-halogen interactions

It was observed that it preferred to form weak C–H $\cdots$ F hydrogen bond rather than F $\cdots$ F interaction. However there are examples where F $\cdots$ F interactions have played a crucial role in the crystal packing. For example, in case of a uracil derivative, the F $\cdots$ F interactions were observed to be important in crystal packing [112]. In the crystal packing of (*N'*-(3-hydroxypropyl)-5-fluorouracil, a tetramer assembly of molecules held together by the presence of four type II F $\cdots$ F interactions was observed (Fig. 2.19a). In the crystal packing of *N'*-(4-hydroxycarbonylbutyl)-5-fluorouracil monohydrate, two molecules was observed to connect via a short (2.624 Å) type I F $\cdots$ F interaction in a molecular chain (Fig. 2.19b). These F $\cdots$ F interactions were studied by ab initio calculation using MP2/6-31+G\* method. The results suggested that the tetrameric motif having four type II F $\cdots$ F interactions provides 4 kcal/mol stabilization to the crystal packing (hence each contributed approximately 1 kcal/mol stabilization energy). Atoms in molecule (AIM) approach for this tetrameric motif confirmed the presence of (3, –1) BCPs and the value of

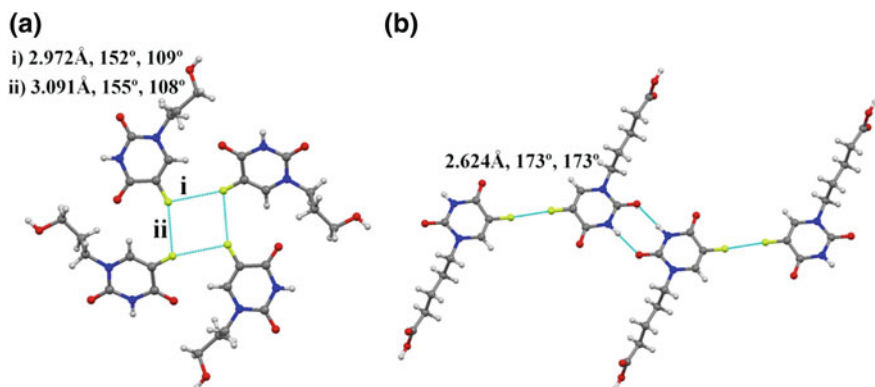
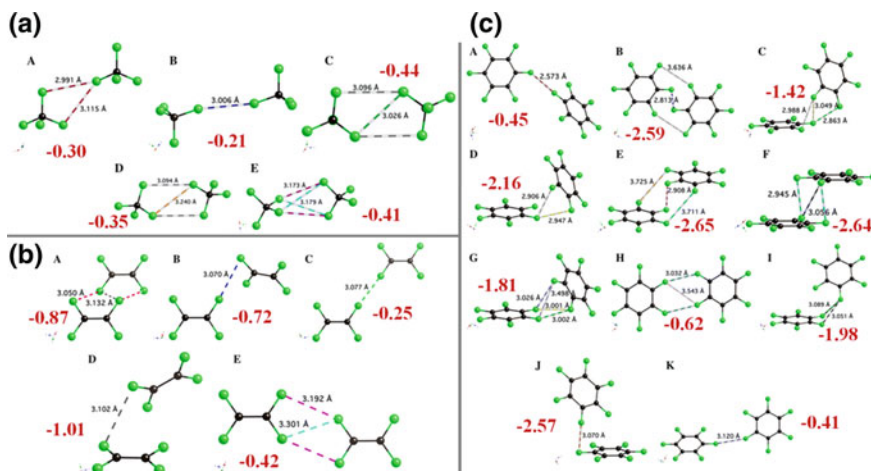


Fig. 2.19 Part of crystal packing in **a** (*N*<sup>1</sup>-(3-hydroxypropyl)-5-fluorouracil and **b** *N*<sup>1</sup>-(4-hydroxycarbonylbutyl)-5-fluorouracil monohydrate displaying F $\cdots$ F interactions [112]

the Laplacian was observed to be positive, suggesting that these were closed shell interactions. Similar results have been obtained from related experimental charge density studies [113–115]. Further, theoretical calculations at the same level for the short type I  $F\cdots F$  interaction were performed on the parent dimer and another wherein the long alkyl chain was replaced with the methyl group on the parent dimer. The interaction energies obtained were  $-1.7$  and  $-1.5$  kcal/mol for the two cases respectively. From AIM analysis, the value of the electron density ( $\rho$ ) at the BCP for this contact was more than that of type II  $F\cdots F$  contacts in the previous case. Therefore, these results suggested that the type I  $F\cdots F$  interaction can be as crucial as type II  $F\cdots F$  in the stabilization of crystal structure.

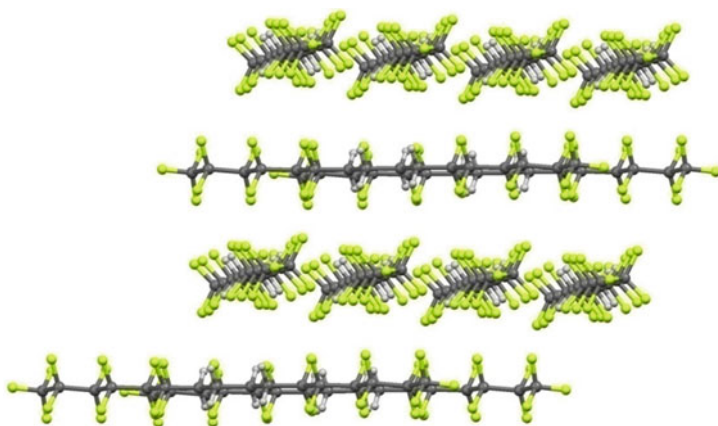
Further detailed analysis of  $F\cdots F$  interactions with input from ab initio calculations at MP2/aug-cc-pVDZ level, topological analysis (AIM) and SAPT calculations were performed over all nonsymmetry equivalent dimers present in  $CF_4$ ,  $C_2F_4$ , and  $C_6F_6$  crystals [116]. It was observed that all dimers are energetically stable with the stabilization energy ranging from  $-0.21$  to  $-2.65$  kcal/mol (Fig. 2.20). From AIM analysis the strength of a single  $C-F\cdots F$  was obtained as  $-0.21$  kcal/mol for  $F-C(sp^3)$ ,  $-0.25$  kcal/mol for  $F-C(sp^2)$ , nonaromatic) and  $-0.41$  kcal/mol for  $F-C(sp^2)$ , aromatic). The value of the Laplacian was observed to be positive for all interactions and hence these are classified as closed shell interactions. From the SAPT calculations, it was observed that the dispersion component is dominant for collinear contacts where as in many cases, particularly in most stabilized dimers, the electrostatic component was as significant as the dispersive component. Moreover, through the calculations of the stabilization energy for the  $C-F\cdots F$  interaction (interact collinearly) in model dimers of  $CHF_3$ ,  $CH_2F_2$ , and



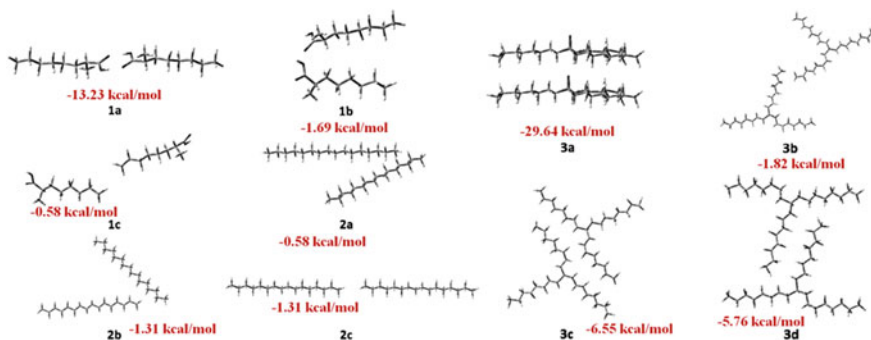
**Fig. 2.20** Extracted symmetry nonequivalent dimers from the crystal packing of **a**  $CF_4$  **b**  $C_2F_4$  and **c**  $C_6F_6$ . Numbers in brown colors represent BSSE corrected interaction energy (in kcal/mol) at MP2/aug-cc-pVDZ level. Reprinted with the permission from Ref. [116]. Copyright 2010 Springer-Verlag

$\text{CH}_3\text{F}$ , it was observed that with increase in H-atoms, the strength of  $\text{C-F}\cdots\text{F}$  interaction is reduced.

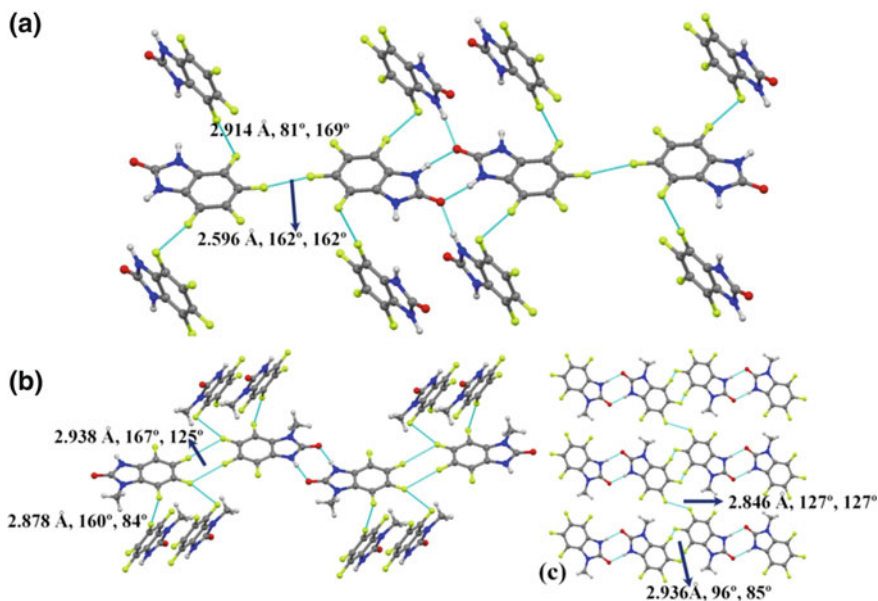
A recent experimental (crystal structure) and theoretical study (ab initio quantum calculation and AIM theory) for fluorine–fluorine interactions was performed on compounds containing a perfluorinated chain: **(1)**  $\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$ , **(2)**  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_4(\text{CF}_2)_5\text{CF}_3$  and **(3)**  $\{\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\}_3\text{P}=\text{O}$  and many short type I and type II  $\text{C-F}\cdots\text{F-C}$  interactions along with  $\text{C-H}\cdots\text{F-C}$  were observed in the crystal packing (Figs. 2.21 and 2.22) [117]. Selected dimers consisting of these interactions were extracted from the crystal packing and the interaction energy were calculated at DFT/B97-D using aug-cc-pVnZ, where  $n = \text{D, T, or Q}$ . basis set and stabilization energy ranging from 0.26 to 29.64 kcal/mol were



**Fig. 2.21** Packing of molecules in **2**



**Fig. 2.22** Molecular dimers extracted from the crystal packing of **1**, **2** and **3** along with their interaction energy. Reprinted with the permission from Ref. [117]. Copyright 2012 American Chemical Society



**Fig. 2.23** **a** The crystal structure packing in 4,5,6,7-tetrafluoro-1H-benzimidazole-2(3H)-one displaying short C-F...F-C contact. Crystal packing in **b** Form I and **c** Form II of 4,5,6,7-tetrafluoro-1-methyl-1H-benzimidazole-2(3H)-one, displaying differences in nature of C-F...F-C interactions in these [93]

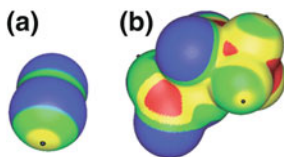
observed. The presence of these interactions in the different dimers was also confirmed by the presence of (3, -1) BCPs by Atoms in Molecule approach.

Recently, shortest F...F distances were reported (2.596(3) Å, type I, Fig. 2.23a) in the crystal packing of 4,5,6,7-tetrafluoro-1H-benzimidazole-2(3H)-one along with related type II F...F contacts by Pérez-Torralba et al. [93]. In the same work, it was also observed that the F...F contacts have implications in the generation of polymorphs in case of 4,5,6,7-tetrafluoro-1-methyl-1H-benzimidazole-2(3H)-one wherein the two forms have differences in molecular motifs containing F...F contacts (Fig. 2.23b, c). In case of one form, a centrosymmetric type II F...F contact along with two other short type II F...F contacts were observed to stabilize the crystal packing (Fig. 2.23b) while in the case of the second form, mainly type I F...F contacts were observed.

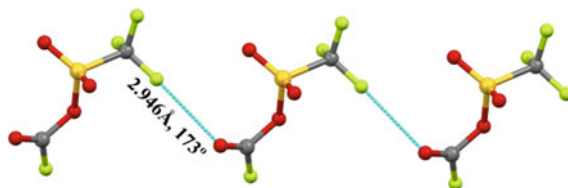
### 2.3.2 Insights into Halogen Bond Formation Involving Fluorine (C-F...X; X = Halogen, N, O, S)

After the well documented hydrogen bond, the halogen bonds constitute an important core of supramolecular chemistry [26–33]. This is an electrostatic

interaction and arises due to anisotropic distribution of the electron density over the covalently bonded halogen atom. There is presence of an electrophilic  $\delta^+$  character along the axis of the  $\sigma$ -bonded (C–X) halogen atom, which is termed as “the positive  $\sigma$ -hole”. Subsequently, perpendicular to the C–X bond, the halogen atoms exhibits nucleophilic  $\delta^-$  character. The strength of the halogen bond decreases in the order  $I > Br > Cl > F$  which is in accordance with the decrease in polarizability and increase in electronegativity. The IUPAC definition of halogen bond is given as follows: “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” [118]. In accordance with the IUPAC definition of the halogen bond, the type II halogen $\cdots$ halogen interactions can also be considered as halogen bond [119, 120]. The participation of fluorine as a halogen bond donor was questioned because it is the least polarizable and the most electronegative element. However, in recent years, experimental and theoretical studies support the possible role of organic fluorine as a halogen bond donor. Charge density studies on organic fluorine by Hathwar et al. [121] provides evidence for the presence of polarizability associated with a fluorine atom bonded to carbon. From recent works by Metrangolo and co-workers, it was established that fluorine can display a positive  $\sigma$ -hole, when connected to an electron withdrawing atom or a group [122, 123]. For example, in case of  $CF_3SO_2OCOF$ , the presence of a positive cap (can be considered as the positive  $\sigma$ -hole) on the fluorine attached to carbonyl group was observed on the computed electrostatic potential (0.001 au electron density molecular surface) while the  $-CF_3$  group has a positive ESP on its entire surface (Fig. 2.24) [122, 123]. The computed electrostatic maxima ( $V_s, \text{max}$ , in kcal/mol) on the 0.001 au isosurface of the molecule at the B3PW91/6-31G(d,p) level was observed to be +4.2 for  $O=C-F$  and +9.6, +9.6, +10.1 for  $CF_3$  [123]. In the crystal packing, participation of this fluorine as a halogen bond donor and oxygen atom, containing lone pair, as halogen bond acceptor was observed in the formation of a molecular chain (Fig. 2.25). The interaction energy for the  $F_2C-F\cdots O=C$  contact was computed at M06-2X/6-311G (3df,2p) level to be 1.13 kcal/mol [122]. Similarly, there are many related examples where fluorine atom can act as a halogen bond donor when attached to an atom or electron withdrawing groups [122, 123].



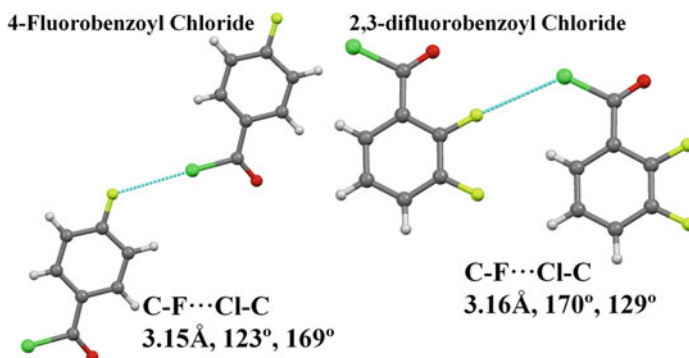
**Fig. 2.24** a Computed electrostatic potentials (on 0.001 au molecular surfaces) of  $F_2$  (A) and  $CF_3SO_2OCOF$  (B, the  $CF_3$  group is at the right). Color ranges, in kcal/mol, are: red, greater than 20; yellow, between 20 and 9; green, between 9 and 0; blue, negative. Black hemispheres denote the positions of the most positive potentials associated with the fluorine atoms. (Reprinted with the permission from Ref. [122]. Copyright 2011 Royal Society of Chemistry)



**Fig. 25** Molecular chain formation via  $\text{C-F}\cdots\text{O}=\text{C}$  halogen bond in  $\text{CF}_3\text{SO}_2\text{OCOF}$

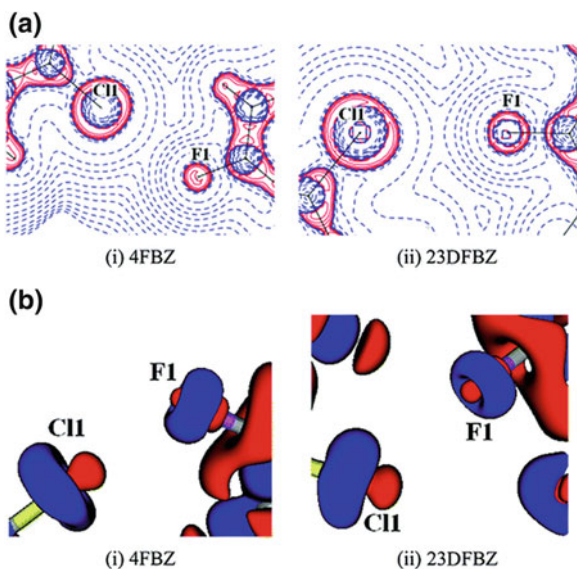
Recent charge density studies on 4-fluorobenzoyl chloride and 2,3-difluorobenzoyl chloride by Dikundwar and Guru Row [124] established that the fluorine atom can act as both a donor and acceptor for halogen bond formation (depicting “amphoteric” nature of fluorine, Figs. 2.26 and 2.27). Here it should be noted that the fluorine atom in the vicinity of two electron withdrawing groups (the other fluorine atom and the  $\text{-C=O}$  group) in case of 2,3-difluorobenzoyl chloride acting as halogen bond donor. The bond path ( $R_{ij}$ ) for  $\text{Cl}\cdots\text{F}$  interaction [characterized by the presence of a (3, -1) BCP’s] in both the compounds was observed to be shorter than the sum of the van der Waals radii of the participating atoms (the van der Waals radii of Cl and F are 1.75 and 1.47 Å [125], respectively). In the Laplacian maps and static 3D deformation density maps, attractive nature of the  $\text{Cl}\cdots\text{F}$  interactions was clearly visible. It was observed that the charge concentration (CC) regions were attracted towards the charge depleted (CD) regions (Fig. 2.27).

A recent charge density study on pentafluorophenyl 2,2'-bisthiazole by Pavan and Guru Row [126] has established type II  $\text{C-F}\cdots\text{F-C}$  and  $\text{C-F}\cdots\text{S-C}$  interactions (Fig. 2.28). The geometry of the type II  $\text{C-F}\cdots\text{F-C}$  observed as  $d_{\text{F}\cdots\text{F}} = 2.663$  Å,  $\theta_1 = 173.61^\circ$ ;  $\theta_2 = 88.91^\circ$  and for  $\text{C-F}\cdots\text{S}$  interaction as  $d_{\text{F}\cdots\text{S}} = 3.286$  Å,  $\theta = 162.82^\circ$ . The authors claimed it as the first experimental visualization of an  $\sigma$ -hole on organic fluorine. The presence of both the interactions was confirmed by the presence of (3, -1) BCP and a bond path. Laplacian maps and static 3D deformation density maps displayed the attractive nature of these interactions. The calculation of the

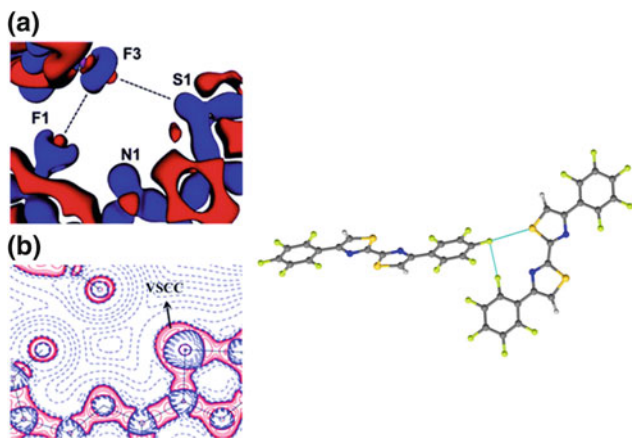


**Fig. 2.26** “Amphoteric” nature of fluorine in halogen bonds [124]



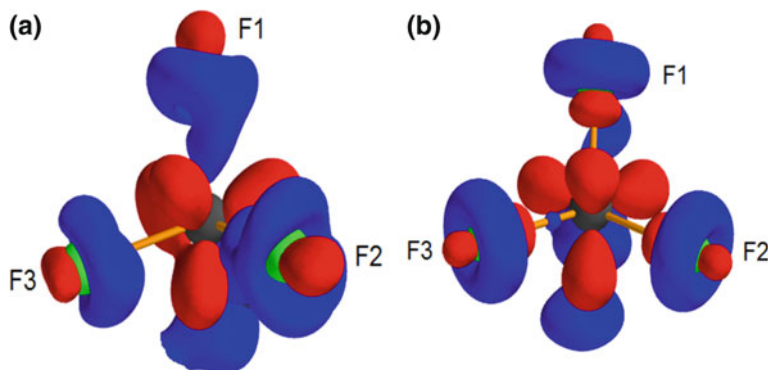


**Fig. 2.27** **a** Laplacian maps and **b** 3D static deformation density maps for Cl $\cdots$ F intermolecular interactions in (i) 4-fluorobenzoyl chloride and (ii) 2,3-difluorobenzoyl chloride. Contours are drawn at logarithmic intervals in  $\nabla^2\rho(r)$ ,  $\text{e}\text{\AA}^{-5}$ . Blue lines indicate positive contours, and red lines indicate negative contours.  $\Delta\rho(r)$  isosurfaces are drawn at  $\pm 0.1 \text{ e}\text{\AA}^{-3}$ . Reprinted with the permission from Ref. [124]. Copyright 2012 American Chemical Society



**Fig. 2.28** Experimental **a**  $\Delta\rho(r)$  and **b**  $\nabla^2\rho(r)$  maps drawn on the logarithmic scale in the F $\cdots$ F and S $\cdots$ F interaction region, +ve and -ve values represented by blue and red colors.  $\Delta\rho(r)$  isosurfaces are drawn at  $\pm 0.05 \text{ e}\text{\AA}^{-3}$ . Reprinted with the permission from Ref. [126]. Copyright 2014 American Chemical Society





**Fig. 2.29** 3D-deformation density map showing the presence of CD regions ( $\sigma$ -holes in red) and CC regions on the fluorine atoms of the trifluoromethyl group in *N*-(2-(trifluoromethyl)phenyl)benzamide obtained from **a** experiment **b** theory. The isosurfaces are drawn at  $0.15 \text{ e } \text{\AA}^{-3}$ . Reprinted with the permission from Ref. [128]. Copyright 2014 American Chemical Society

electrostatic interaction energies (from the multipole model) was performed by using the INTERN module in XD2006 [127] and it was observed that for the type II  $\text{F} \cdots \text{F}$  and  $\text{C}-\text{F} \cdots \text{S}$  interactions, the major contribution arises from the electrostatic energy rather than dispersion which suggests that both are of  $\delta^+ \cdots \delta^-$  type.

Furthermore, the unequivocal observation of the  $\sigma$ -hole on the fluorine atom of the trifluoromethyl group in the crystal has been revealed from both experimental and theoretical charge density analysis on *N*-(2-(trifluoromethyl)phenyl)benzamide (Fig. 2.29) [128]. Hence this study breaks the long accepted lore that “organic fluorine is not polarizable”.

## 2.4 Conclusions

From the above discussions, it is of interest and significance to realize that the contribution of organic fluorine in the formation of intermolecular interactions is noteworthy and does provide stability to the crystal structure. Due to the cooperative, flexible nature associated with these soft and weak interactions, their inevitable role in crystal packing cannot be predicted, given the knowledge of the chemical structure or conformation of the molecules. The existence of disorder, problems associated with multiple molecules in the asymmetric unit, and polymorphism further complicate the prediction of the crystal structure of a given compound. In the future, we propose to investigate interactions involving organic fluorine in different electronic and steric environments (in terms of changes in the nature of the donor C-H and the acceptor C-F of varying hybridizations) in the solid state.

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