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Crystallographic and computational investigation of intermolecular interactions involving organic fluorine with relevance to the hybridization of the carbon atom.

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Abstract

The characteristics of the **C**(***sp,sp^2,sp^3***)-H…F-**C**(***sp,sp^2,sp^3***) intermolecular interactions present in molecular crystals on the basis of the hybridization of the carbon atom in the interaction has been analyzed. The Cambridge Structure Database has been extensively searched for the existence of such interactions as a function of the different combinations of hybridization possible for C-H…F-C interactions. The parameters in the search involve restriction with the following limits: 2.1 Å < H…F distance < 3.0 Å and 110° < C-H…F angle < 180°. PIXEL calculations performed on selected molecular pairs showed that C-H…F interactions is mainly of a dispersive nature. In molecules involving the presence of C-H donor atom wherein the carbon exists in *sp* hybridization, preferential electrostatic contribution was observed. A full topological analysis using the QTAIM approach confirms the presence of a BCP in all the extracted molecular pairs at the crystal geometry, thereby confirming the presence of the C-H…F interaction regardless of the hybridization of the participating atoms. Both the electron density (ρ) and the Laplacian ($\nabla^2\rho$) evaluated at the BCP showed exponential dependence on the bond path length for all the existing interactions.

1. Introduction

The study and investigation of intermolecular interactions in crystals has always been one of the main attractions in the field of crystal engineering [1]. A detailed understanding of these intermolecular interactions plays a pivotal role in determining the physical and chemical properties of molecular crystals [2]. Amongst the various interactions that are analyzed the most explored and well studied interaction is the formation of the hydrogen bond [3]. While strong hydrogen bonds are well characterized and established, the recent focus is on studying weak hydrogen bonds such as C-H…N/O[4] , C-H…π[5], C-H…X-C[6] (X= F, Cl, I, Br). Amongst these, weak interactions involving organic fluorine, namely C-H…F-C interactions, have attracted considerable attention and focus in the past two decades [6a-b, 7]. Previously it was believed that fluorine hardly accepts hydrogen bond [8] because of its high electronegativity and non polarizable nature. Desiraju and coworkers showed that fluorine can participate in the formation of weak C-H…F interactions [9]. Recent research depicts that the substitution of hydrogen with fluorine can affect the crystal packing due to existence of different intermolecular interactions involving organic fluorine [10]. Furthermore, organic fluorine also participates in the formation of various intermolecular interactions such as C-F...X (X= F, Cl, I, Br), C-F…π in presence and absence of other strong or weak intermolecular interactions [9-11]. Due to the weak nature of these C- H…F-C interactions, it is also very important to compute the energetics of stabilization associated with such weak interactions. In the last decade, computational studies have been carried out to understand the energetics of intermolecular interactions [12] including hydrogen bonds involving organic fluorine [13]. Cambridge Structural Database (CSD) has been explored extensively for analyzing the overall behavior of intermolecular interactions [14-15]. The nature of C-H…F-C interaction also depends on the availability of the *lp* of fluorine which in turn depends on the hybridization of the carbon atom to which it is attached. In this contribution we intend to evaluate the occurrence of **C-H…F-C** interactions in which the donor hydrogen atom and the acceptor fluorine atom are attached to a carbon atom of a given hybridization (sp, sp^2, sp^3) in the crystal packing. With this focus, we have systematically analyzed the relevant crystal structures present in the CSD Database and performed computational calculations on selected motifs to understand the nature, energetics and topological properties of C-H…F-C interaction on changing the hybridization of the carbon atom involved in a particular interaction of interest. Such studies indicate the global trends in the nature of such weak interactions, which albeit weak, can contribute significantly to crystal packing principles.

2. Methodological Details

All the searches in the CSD [16] were performed using version 5.35. Only those structures were involved in the study whose 3D structures were determined and R-factor < 0.10. All the disordered, polymer and ionic structures were excluded from the search in addition to those structures determined through powder diffraction.**Table S1** lists the bond precision obtained from the crystal structure determination for all the molecules of interest.

All the geometrical graphs were plotted using the Mercury software [17]. The cone corrected C-H…F angular distribution has been reported to present an unbiased distribution [Figure 1]. The necessity of performing the cone correction is a very well established procedure [18a] and is highly recommended by the scientific community [18b].

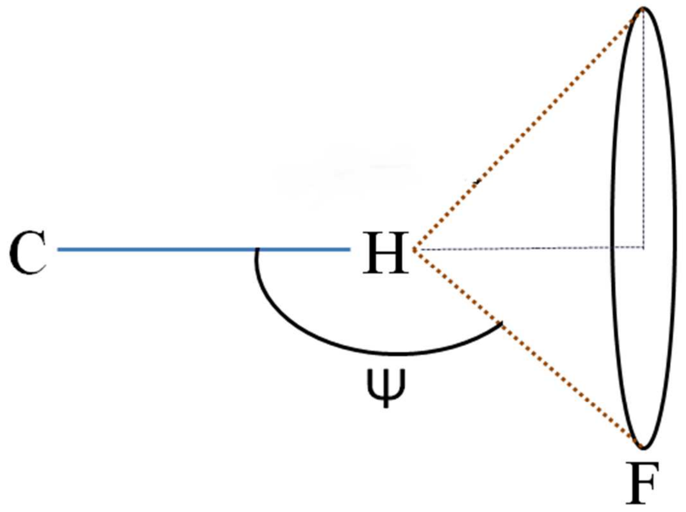

Figure 1: Schematic diagram for cone correction. Ψ denotes the C-H…F angle.

We divided our study into different sections based on the hybridization of the carbon atom attached to hydrogen and fluorine, resulting in three different sections i.e. C-H…F-C(*sp*){**Section-1**}, C-H…F-C(sp^2){**Section-2**} and C-H…F-C(sp^3){**Section-3**} [Figure 2]. For the case of sp^2 hybridized atom, in case of the donor and the acceptor {Section-2}, we have only considered the possibility of phenyl ring in our study. This is on account of the following two main reasons.

Firstly, for the donor atom, the probability of interaction arising from the phenyl ring is a maximum. Furthermore, from the viewpoint of the donor and the acceptor atom, the fluorine substituted phenyl ring accounts for more than 50% of *sp*^{2} hybridization and the second reason arises from certain limitations of the CSD. In CSD, the double bond in a heterocyclic molecule (REFCODE: BIKSIX) is shown as a part of the aromatic ring while in some other cases, such double bonds are constrained as alternating single and double bond respectively (REFCODE: ADEZAL02 which creates complications in the search procedures[Figure 3].

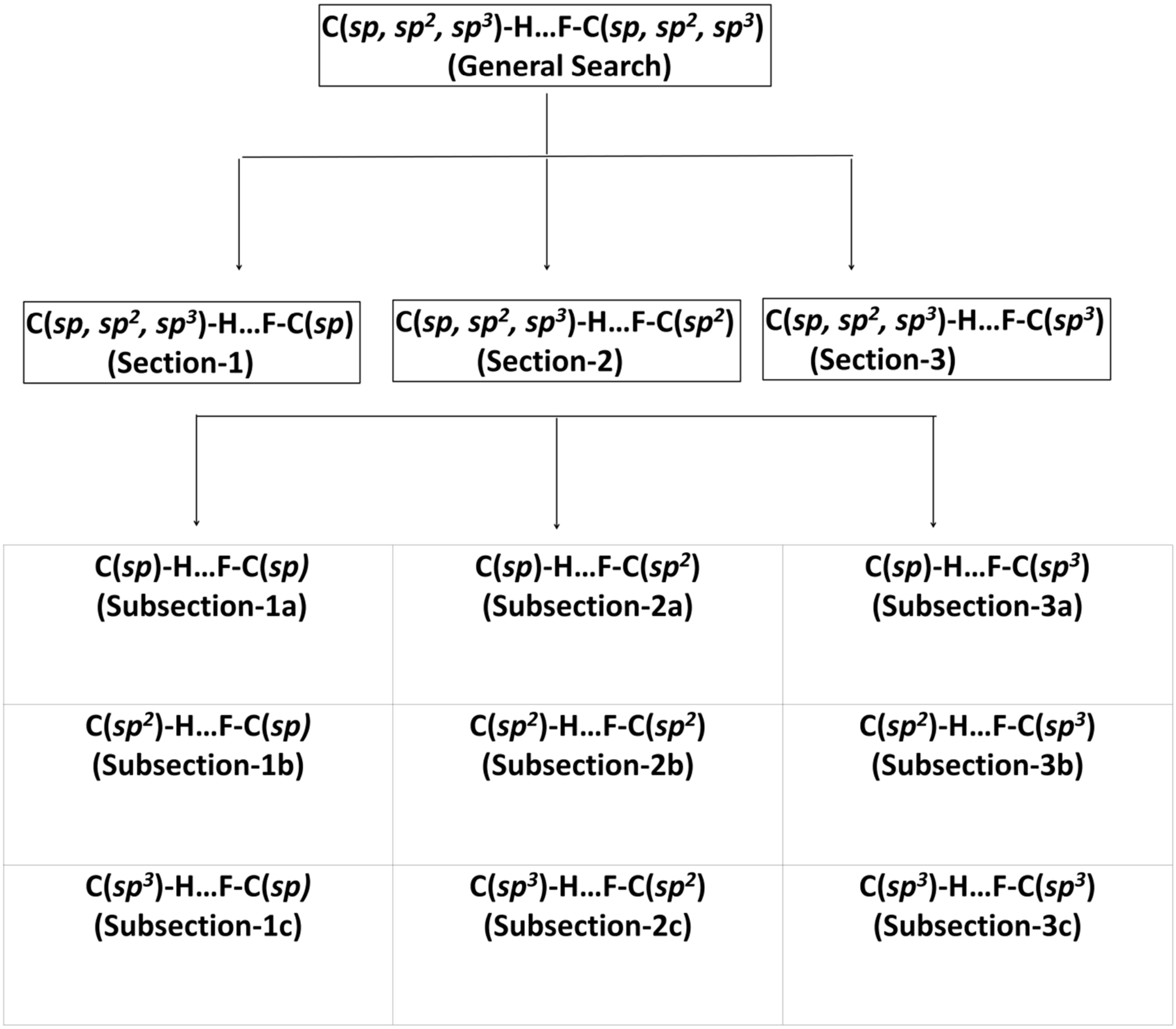

Figure 2: Schematic representation of the different searches performed in CSD.

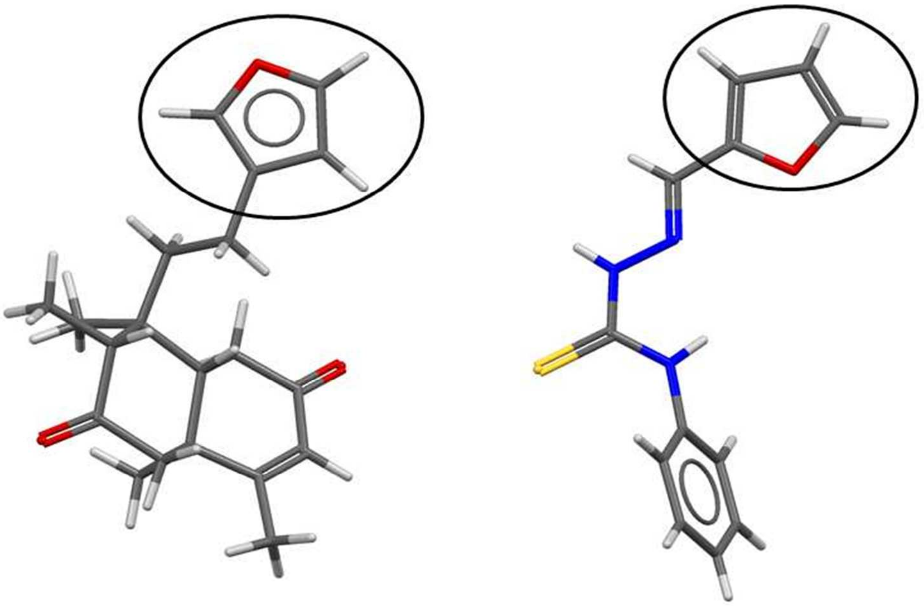

Figure 3: Discrepancy in the definition of bonding in similar ring systems in CSD.

The results of each section were further divided into three subsections each by putting restriction on the hybridization of the carbon atom attached to the hydrogen atom involved in C-H…F-C interaction (9 subsections, **Figure 2**). For each section and subsequent subsection, the search for H…F distance distribution and C-H…F angular distribution, the CSD search was divided in three different sets of individual searches. **Search-A** consisted of the search from the complete database. **Search-B** results consisted of only those molecules in which only C, H and F are present. **Search-C** is a difference search result of **A** and **B**. The aim of such an analysis was to see the variations in "distance and angle distribution" for the presence of C-H…F interactions in different molecular environments in the crystal.

3. Theoretical Methods

Molecular pairs exclusively containing C-H…F interactions were retrieved from the CSD and their intermolecular interaction energies were calculated using PIXEL [16-19] method present in the CLP module. PIXEL method has proved to be very efficient in determining the lattice energy [20] along with the strength and nature of different kinds of intermolecular interactions. The magnitudes observed are in accordance with values obtained from *ab initio* calculations [21]. The main advantage of using the PIXEL method is that it provides a partitioning of the interaction energy into its dispersion, coulombic, polarization and repulsive components.

The topological analysis was performed using AIMALL (version 13.05.06) [22] to generate selected topological parameters such as the electron densities (ρ), Laplacian ($\nabla^2\rho$), local potential energy (V_b), kinetic potential energy (G_b) at the bond critical point. For the AIMALL calculation, *ab initio* calculations for the selected dimers at the crystal geometry, with the hydrogen atoms moved to their neutron value, was performed at MP2/6-311G** level of theory (with "density =current" keyword) using Gaussian 09 [23]. Then the formatted checkpoint file (fchk) was considered for the input for AIMALL, which is then used to generate the wave function file (.wfx file) by the software itself and followed by the topological analysis.

Table 1: Distance distribution for C-H…F-C interactions in different hybridization environments.

	Hits	**Frequency**	**Min. H…F / Max. H…F Distance (Å)**	**Mean / Median Distance (Å)**
General				
Search-A	9349	40444	2.11/ 3.00	2.71/ 2.72
Search-B	329	1998	2.19/ 3.00	2.71/ 2.71
Search-C	9020	38446	2.11/ 3.00	2.71/ 2.72
1. C-H…F-C(*sp*)	**No hits were observed**			
2. C-H…F-C(*sp*^{2})				
Search-A	4618	18971	2.13/ 3.00	2.69/ 2.69
Search-B	213	1199	2.21/ 3.00	2.69/ 2.69
Search-C	4405	17772	2.13/ 3.00	2.69/ 2.69
2a)C(*sp*)-H…F-C(*sp*^{2})				
Search-A	19	25	2.25/ 2.93	2.57/ 2.59
Search-B	8	12	2.25/ 2.93	2.55/ 2.54
Search-C	11	13	2.33/ 2.74	2.59/ 2.59
2b)C(*sp*^{2})-H…F-C(*sp*^{2})				
Search-A	3407	11929	2.13/ 3.00	2.67/ 2.67
Search-B	182	1078	2.22/ 3.00	2.68/ 2.68
Search-C	3225	10851	2.13/ 3.00	2.67/ 2.67
2c)C(*sp*^{3})-H…F-C(*sp*^{2})				
Search-A	2904	13685	2.10/ 3.00	2.71/ 2.73
Search-B	72	296	2.29/ 3.00	2.73/ 2.74
Search-C	2832	13389	2.10/ 3.00	2.71/ 2.73
3. C-H…F-C(*sp*^{3})				
Search-A	4878	21988	2.11/ 3.00	2.73/ 2.74
Search-B	124	836	2.19/ 3.00	2.73/ 2.75
Search-C	4754	21152	2.11/ 3.00	2.73/ 2.74
3a)C(*sp*)-H…F-C(*sp*^{3})				
Search-A	3	5	2.38/ 2.67	2.52/ 2.57
Search-B	-	-	-	-
Search-C	3	5	2.38/ 2.67	2.52/ 2.57
3b)C(*sp*^{2})-H…F-C(*sp*^{3})				
Search-A	3042	12051	2.13/ 3.00	2.72/ 2.73
Search-B	88	575	2.19/ 3.00	2.73/ 2.75
Search-C	2954	11476	2.13/ 3.00	2.72/ 2.73
3c)C(*sp*^{3})-H…F-C(*sp*^{3})				

Search-A	3861	17021	2.11/ 3.00	2.74/ 2.75
Search-B	71	388	2.33/ 3.00	2.73/ 2.73
Search-C	3790	16633	2.11/ 3.00	2.74/ 2.75

Table 2: Angular distribution for C-H…F-C interactions in different hybridization environments.

	Hits	**Frequency**	**Min. C-H…F / Max. C-H...F angle (°)**	**Mean/ Median Angle (°)**
General				
Search-A	9349	40444	110/ 180	136/ 134
Search-B	329	1998	110/ 179	136/ 133
Search-C	9020	38446	110/ 180	136/ 134
1. C-H…F-C(*sp*)	**No hits were observed**			
2. C-H…F-C(sp^2)				
Search-A	4618	18971	110/ 180	136/ 134
Search-B	213	1199	110/ 178	136/ 133
Search-C	4405	17772	110/ 180	136/ 134
2a)C(*sp*)-H…F-C(sp^2)				
Search-A	19	25	112/ 161	131/ 127
Search-B	8	12	112/ 157	128/ 127
Search-C	11	13	112/ 161	133/ 127
2b)C(sp^2)-H…F-C(sp^2)				
Search-A	3407	11929	110/ 180	136/ 134
Search-B	182	1078	110/ 178	136/ 133
Search-C	3225	10851	110/ 180	136/ 134
2c)C(sp^3)-H…F-C(sp^2)				
Search-A	2904	13685	110/ 180	137/ 136
Search-B	72	296	110/ 177	138/ 137
Search-C	2832	13389	110/ 180	137/ 136
3. C-H…F-C(sp^3)				
Search-A	4878	21988	110/ 179	136/ 134
Search-B	124	836	110/ 179	136/ 133
Search-C	4754	21152	110/ 179	136/ 134
3a)C(*sp*)-H…F-C(sp^3)				
Search-A	3	5	128/ 152	141/ 145
Search-B	-	-	-	-
Search-C	3	5	128/ 152	141/ 145
3b)C(sp^2)H…F-C(sp^3)				
Search-A	3042	12051	110/ 179	135/ 133
Search-B	88	575	110/ 174	135/ 132
Search-C	2954	11476	110/ 179	135/ 133
3c)C(sp^3)-H…F-C(sp^3)				
Search-A	3861	17021	110/ 180	137/ 136
Search-B	71	388	111/ 179	136/ 136
Search-C	3790	16633	110/ 180	137/ 136

4. Results and Discussion

Firstly, we performed three different types of searches, as mentioned above, with no restriction on the hybridization of the carbon atom involved in the interaction. **Figure 4(a) – (l)** reveals the general trends in the distance and angular distribution for the different C-H…F-C intermolecular interactions observed in different packing motifs in molecular solids present in the CSD. The statistical results of the different searches performed have been shown in **Table 1** and **Table 2** respectively. **Search-A** gave 9349 hits resulting in 40444 interactions in contrast to 433 interactions that was observed in comparison to the CSD search performed on C-H…F in 1998 [9]. This substantial increase in the number of C-H…F interactions demonstrates the remarkable efforts made by researchers to analyze such interactions in the past one and a half decades. For **Search-B** we observed a total of 329 hits consisting of 1998 unique C-H…F-C intermolecular interactions. **Search-C** resulted in 9020 hits resulting in 38446 interactions. The contribution of **Search-B** is only ~ 4.9% of the total number arising from all the interactions. On the contrary, the average number of interactions, defined as the ratio of number of interactions divided by the number of hits is 6.07 for **Search-B**. In comparison, this ratio is 4.26 for **Search-C** and 4.32 for **Search-A** suggesting that the propensity of formation of a C-H…F-C interaction is higher in molecules containing C, H and F only. **Figure 4[(a)-(c)]** represents the H…F intermolecular distance distribution and it is reflects the fact that the maximum frequency in all cases occurs in the range of 2.6-2.8 Å which is expected to be in the range of the sum of the vdW radius of hydrogen and fluorine [24], the sum being 2.67 Å.. **Figure 4[(d)-(f)]** represents the C-H…F angle distribution and in all the three types of searches there is a increase in frequency with increase in angularity followed by a gradual decrease in the frequency as we move towards higher angularity. In all the searches, the maximum frequency occurs below 130°. The cone-corrected angle distribution for **Search-B** shows a clear tendency toward linearity while the **Search-C** shows a gradual increase in frequency with angle and then there is a sudden rise in the frequency. The scatter plot for **Search-B** show a maximum density of points in the low angle region; suggesting the presence of relatively long C-H…F-C interactions at very short angles. **Search-C** shows the presence of shortest C-H…F-C interactions in the region of high angularity.

Figure 4[(g)-(i)] represents the cone corrected C-H…F angular distribution which shows preference towards linearity for the C-H…F-C interactions and **Figure 4[(j)-(l)]** represents the scatter plot distribution for all types of search. **Search-A** reveals the absence of a very short C-H…F-C interaction at low angularity and the presence of a very short C-H…F-C interaction at high angularity. It is clear from **Search-B** that interactions with short distance and high angularity are not present in molecules where only C, H and F are present suggesting that presence of other heteroatoms can govern the nature of C-H…F-C interactions in crystal packing. Also **Search-C** closely resembles the overall distribution in each respect to **Search-A** because of a high number of fragments that lies in this category.

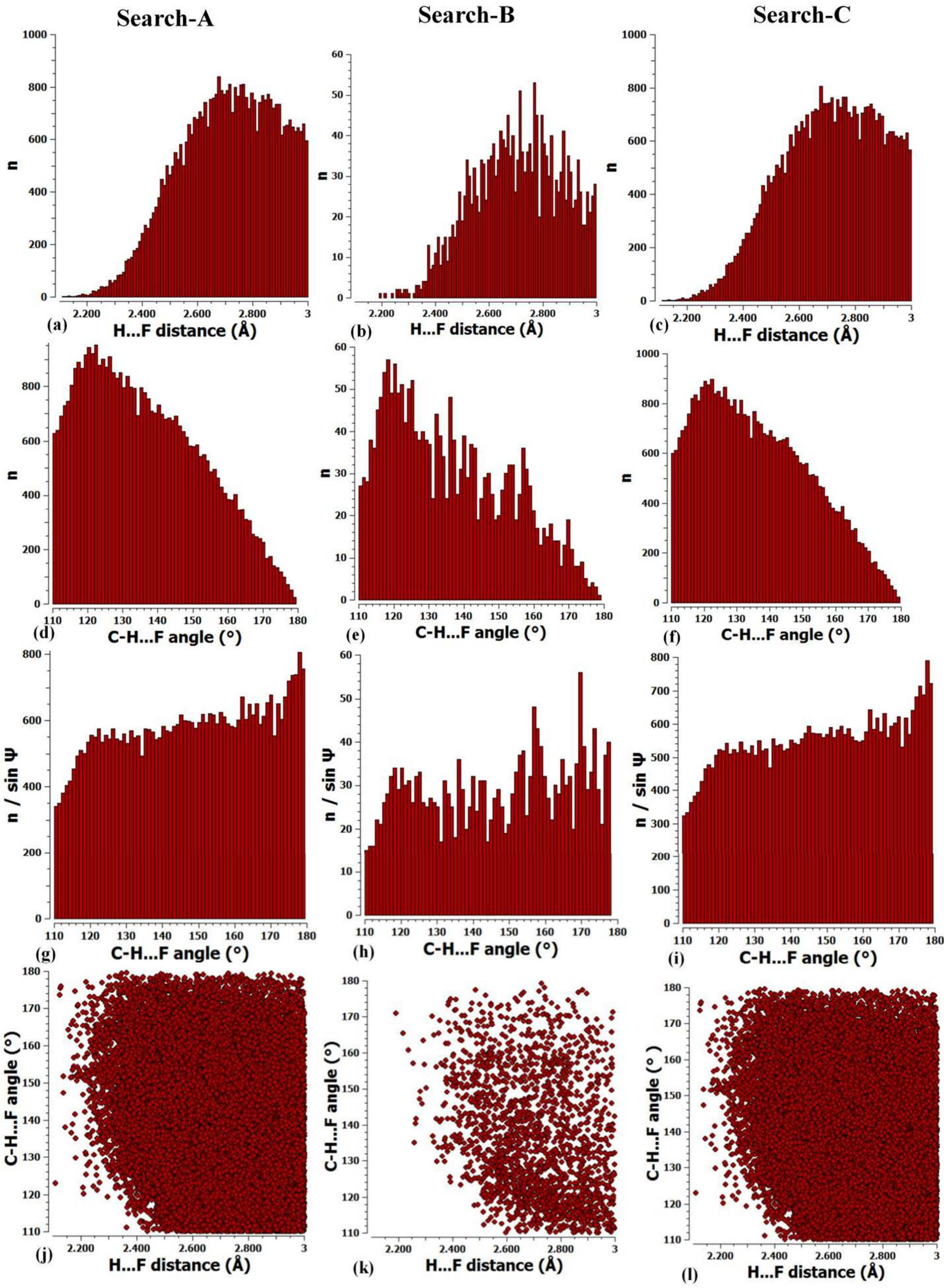

Figure 4: (a)-(c) H…F intermolecular distance distribution for the general search performed (n denotes the frequency). (d)-(f) C-H…F angular distribution for general search performed. (g)-(i) Cone corrected angle distribution was performed for the general search. n / sin *Ψ* denotes the angular distribution to be corrected for the difference in solid angle sweep of the donor hydrogen as a function of *Ψ* with the weighting factor 1/sin *Ψ*, the so-called cone correction. (j)-(l) Scatter plots between H…F distance and C-H…F angle for general search performed.

Section-1: C-H…F-C (*sp*) interaction.

No hits were observed for any possible C-H…F-C (*sp*) interaction in **Search-A**. There was no structure containing a fluorine atom connected to a *sp* hybridized carbon atom depicting that the formation of a C-F bond requires more *p* character on the carbon atom directed towards more highly electronegative groups.

Section-2: C-H…F-C(sp^2) interaction.

In this section, we first screened the CSD database for C-H…F-C interactions in which fluorine is attached to a sp^2 carbon while putting no restrictions on the hybridization of the carbon atom in the C-H bond. **Search-A** reveals that there were overall 4618 hits containing 18971 interactions. This shows that the molecules in which fluorine is attached to sp^2 hybridized carbon is the most extensively studied as more than 40% of the total hits and interactions were present in this section [Table 1]. Whilst the **Search-A** and **Search-C** shows a maximum frequency between the regions of distance 2.6-2.8 Å, **Search-B** does not exhibit a well defined distribution [**Figure 5(a)-(c)].** While maximum fragments have directionality in the region of 110-140°, **Search-B** reveals that the region around 150-160° is also very prevalent [**Figure 5(d)-(f)].** As expected C-H…F-C interactions have very high preference for linearity [**Figure 5(g)-(i)].** Here also the scatter plot reveals that short distance-high angularity interactions are present in molecules present in the results obtained from **Search-C [Figure 5(j)-(l)].**

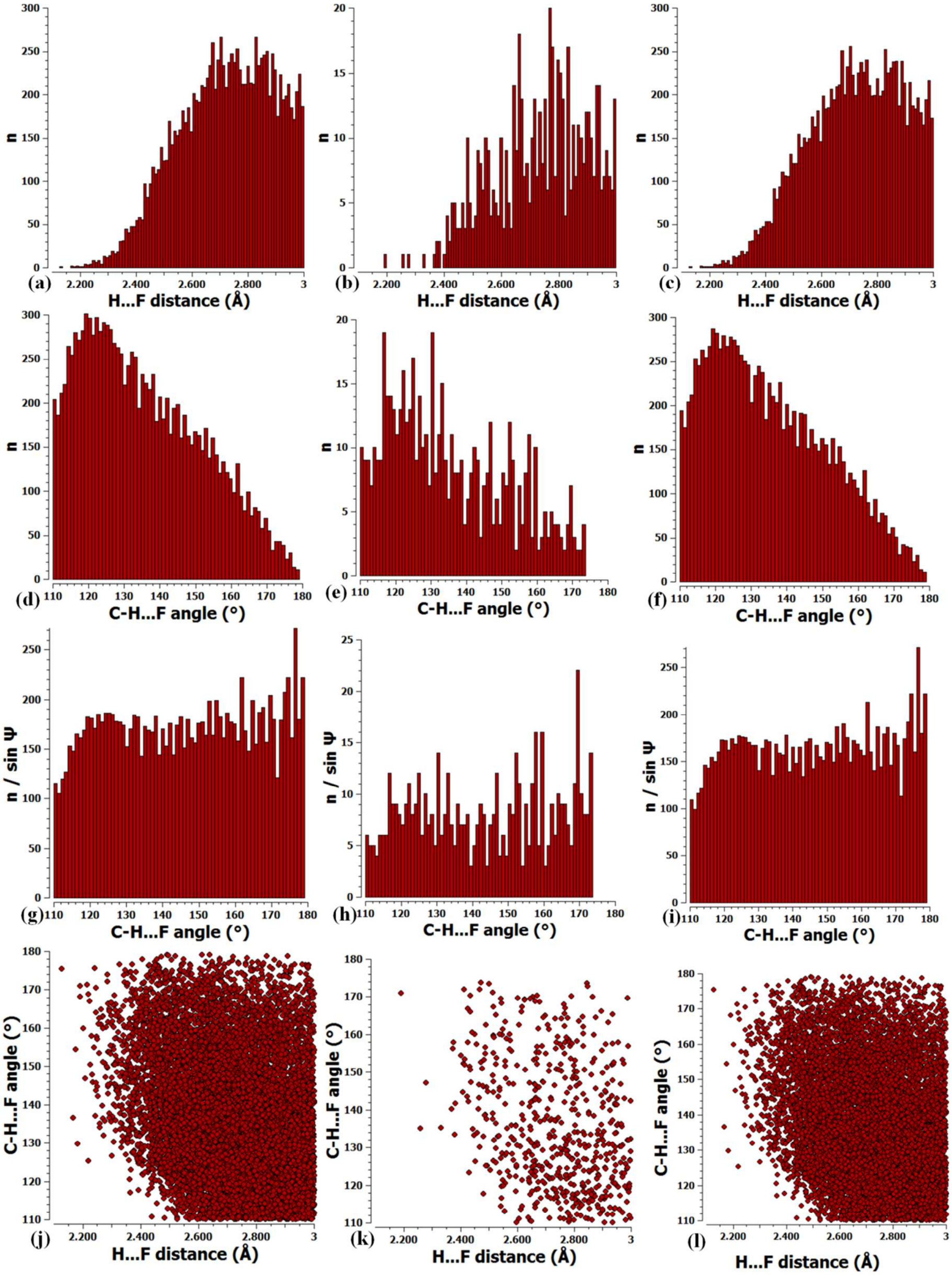
(a)
(b)
(c)
n
H...F distance (Å)
2.200
2.400
2.600
2.800
3
0
50
100
150
200
250
300
5
10
15
20
(d)
(e)
(f)
C-H...F angle (°)
110
120
130
140
150
160
170
180
(g)
(h)
(i)
n / sin Ψ
25
(j)
(k)
(l)
C-H...F angle (°)
H...F distance (Å)

Figure 5: (a)-(c) H…F intermolecular distance distribution for **Section 2**; (d)-(f) C-H…F angle distribution; (g)-(i) Cone corrected angle distribution; n / sin *Ψ* denotes the angular distribution to be corrected for the difference in solid angle sweep of the donor hydrogen as a function of *Ψ* with the weighting factor 1/sin *Ψ*, the so-called cone correction.(j)-(l) Scatter plot between H…F distance and C-H…F angle for **Section 2**.

We further analyzed the results of this section by putting the restriction on hybridization of the carbon atom of the C-H bond involved in C-H…F-C(sp^2) interaction. Furthermore, for each possible combination of hybridization we have performed **Search-A**, **Search-B** and **Search-C** respectively. The number of hits increases in the order: $sp<sp^3<sp^2$ [with respect to the donor atom] in all the three types of searches possible for each combination of hybridization. However, the number of C-H…F-C(sp^2) interactions follows the trend $sp<sp^2<sp^3$, except in case of **Search-B** wherein the trends follow the order $sp<sp^3<sp^2$ [Table 1]. This is because the presence of a sp^3 hybridized carbon atom increases the number of possible hydrogen bond donors which can participate in a C-H…F interaction. It is also of interest to note that for **Search-B** the number of C(sp^2)-H…F-C(sp^2) contacts is much higher than C(sp^3)-H…F-C(sp^2) interactions. The mean distances increases in the order $sp<sp^2<sp^3$ which is coincidentally similar to the overall order for the number of interactions. The number of unique interactions observed for C(sp^2)-H…F-C(sp^2) was 11929 as compared to just 155 observations made in 1998 [9]. It is worthy to note that the mean value for C(sp^2)-H…F-C(sp^2) interaction is 2.67Å which is exactly equal to the sum of the vdW radii of hydrogen and fluorine [Table 1]**.** One interesting point to note is that the maximum frequency of the interactions in case of the sp^2 hybridized C-H bond lies below the H…F distance of 2.6Å **[Figure S2(a)-(c)],** this magnitude is higher in case of sp^3 hybridized C-H bond (the distance range is 2.65 - 2.80 Å] **[Figure S3(a)-(c)]**. The C-H…F angle distribution also reveals some interesting results. For all the possible hybridization combinations, it reveals the presence of C-H…F-C interactions at a minimum possible angle i.e. 110°, except for the *sp* hybridized carbon of the C-H bond. On the contrary, the maximum angle varies for each search of the respective subsection [**Table 2, Figure S1(d)-(f), Figure S2(d)-(f), Figure S3(d)-(f)**]. The mean C-H…F angle of each subsection increases in the order $sp<sp^2<sp^3$ [Table 2] . The cone corrected angular distribution shows a strong preference for high C-H…F angularity. The preference for linearity is less for molecules present exclusively in **Search-B** as compared to those

present in **Search-C** for each subsection **[Figure S1(h)-(i), Figure S2(h)-(i), Figure S3(h)-(i)]**. The scatter plot distribution in each subsection reveals the absence of interactions having a short H…F distance and small C-H…F angle. But there is a large number of interactions present at short H…F distance and large C-H…F angle in case of **Search-C** as compared to **Search-B** of each subsection **[Figure S1(k)-(l), Figure S2(k)-(l), Figure S3(k)-(l)] .**

Section-3: C-H…F-C(sp^3) interaction.

In this section we looked for structures in which the fluorine is attached to a sp^3 hybridized carbon atom. A total of 4878 hits (21988 interactions) were observed in **Search-A** out of which 124 hits (836 interactions) belong to **Search-B** category and 4754 hits (21152 interactions) belonged to **Search-C** category [Table 1]**.** Comparing the result of **Search-A** of this Section with the results of **Search-A** in **Section-2**, we observed that the number of hits as well as the number of C-H…F-C interactions in this section were larger than that of **Section-2**. This is because there are a greater number of C-F bonds which can function as hydrogen bond acceptors in **Section-3** as compared to **Section-2.** The mean H…F distance was calculated to be 2.72Å for all the three searches **(A, B and C)** [Table 1] and the mean C-H…F angle was calculated to be 136.6° for **Search-A** and **Search-C** while it was close to ~136° for **Search-B** [Table 2]**.** The cone corrected angular distribution shows a strong preference towards linearity **[Figure 6(g)-(i)]**. The scatterplot distribution shows that most of the C-H…F-C interactions present in this section are present at long distance and low angularity **[Figure 6(j)-(l)]**. We further analyzed the result of this section by putting restriction on the hybridization on the carbon atom attached to hydrogen atom in the participating C-H…F-C(sp^3) interactions. For **Subsection-3(a)** involving C(sp)-H…F-C(sp^3) interaction, we observed only 3 hits consisting of only five interactions and hence we will be excluding this subsection from further discussion. The discussion shall focus on sp^2 and sp^3 donor C-H bonds only. In the remaining two subsections, the number of hits was in the order $sp^2 < sp^3$ for each of the **Search-A** and **Search-C** of each subsection and follows the order $sp^3 < sp^2$ for **Search-B** [Table 1]. The number of unique C-H…F-C(sp^3) interactions follows the same order as observed for the number of hits for **Search-A, B and C** respectively. The mean C-H…F-C(sp^3) interaction distance lies in the range of 2.69-2.73Å [Table 1] while the mean angle range is from

135- 141°[Table 2] for different subsections. The distance distribution for both subsections i.e. **Subsection- 3b** and **Subsection-3c** shows that the distance at which maximum interaction frequency lies is greater than 2.8Å in case of **Search-A** and **C [Figure S5(a), Figure S5(c) ,Figure S6(a),Figure S6(c)]** while it lies around 2.7Å for **Section-B[Figure S5(b), Figure S6(b)]**. The cone-corrected angle distribution in each subsection shows a high preference towards linearity and in accordance with previous cases the scatter plots shows the presence of a majority of the interactions at large distance and high angularity.

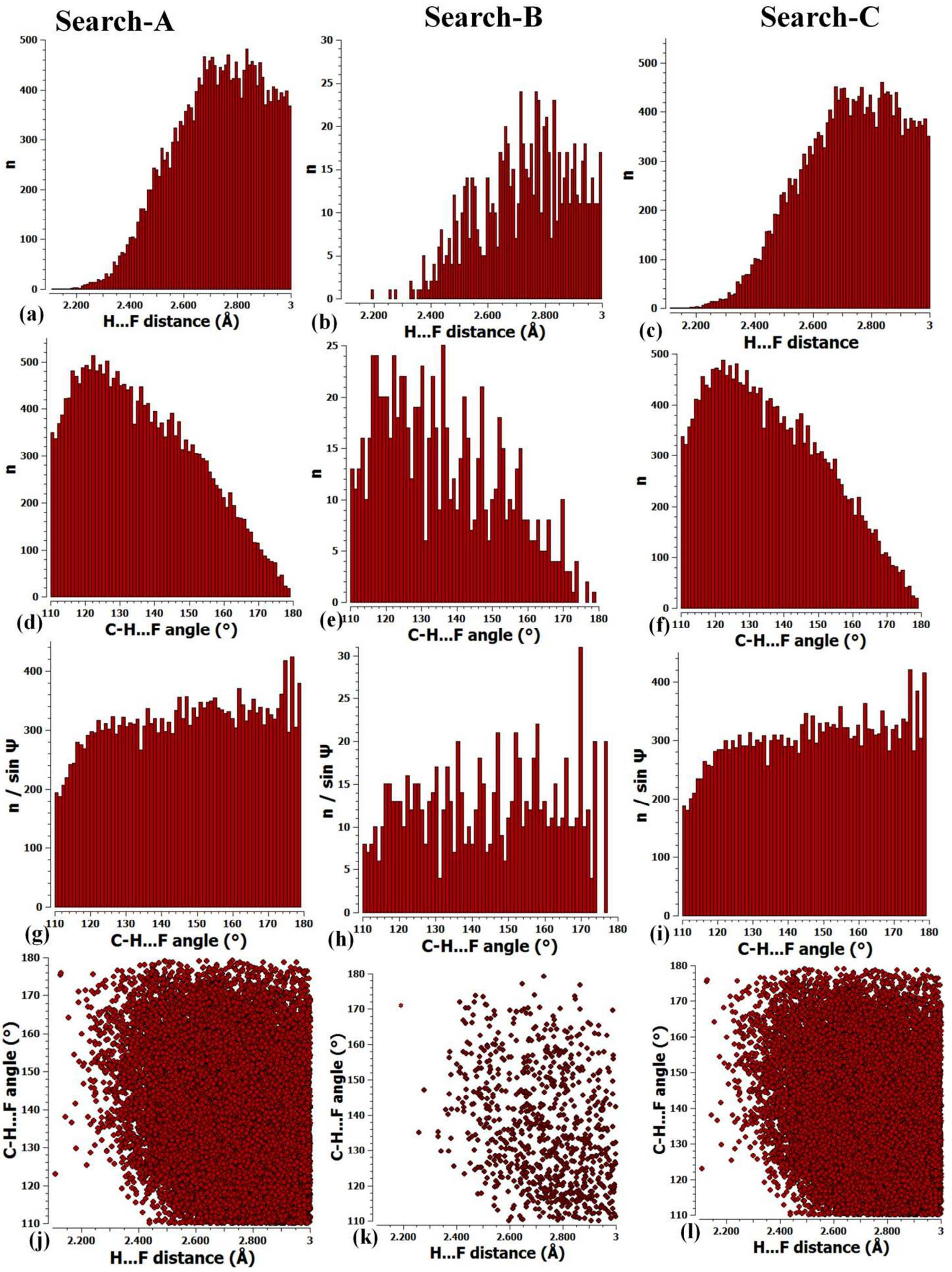
Search-A
Search-B
Search-C
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
(i)
(j)
(k)
(l)
n
n / sin Ψ
H...F distance (Å)
H...F distance
C-H...F angle (°)
0
5
10
15
20
25
30
100
200
300
400
500
110
120
130
140
150
160
170
180
2.200
2.400
2.600
2.800
3

Figure 6: (a)-(c) H…F intermolecular distance distribution for **Section 3**; (d)-(f) C-H…F angle distribution for **Section 3**; (g)-(i) Cone corrected angle distribution; (j)-(l) Scatter plot between H…F distance and C-H…F angle for **Section 3**.

In order to understand the stability of C-H…F-C interaction in different electronic and steric environment, we retrieved the selected molecules from the CSD database and calculated the intermolecular interaction energy using the program PIXEL. It is to be realized that any given molecular pair extracted from the crystal consists of multiple C-H…F-C interactions along with the presence of other strong and/or weak interactions. Hence it is of significance to consider only those molecular pairs for the evaluation of the energetics of the associated interaction connected by a single C-H…F interaction or by a dimeric C-H…F interaction only. It is of interest to realize that till date most of the studies on the intermolecular interaction energies have been performed on model hypothetical molecules which generally consists of a small number of atoms [25]. Although, this approach gives insight into the nature and energetics of the intermolecular interactions, it is of importance to study the presence of intermolecular interaction in an experimental crystal wherein a plethora of such interactions play a vital role in crystal packing. In the formation of crystalline solids, various factors, such as the shape and size of the molecule and the influence of the crystal packing forces affects the nature of the intermolecular interactions. We have calculated the energies of the interaction for forty four molecular pairs spanning the "general search" in our study. Out of these forty four pairs, twenty six belonged to **Section-2** and remaining eighteen belonged to **Section-3** of our CSD search. These energies depend on the donor/acceptor ability of the participating atom as well as the spatial extent of the molecules participating in the formation of the molecular pair. **Table 3** shows the REFCODE of the molecule on which calculations were performed along with the H…F distance, C-H…F angle and respective interaction energy. REFCODE* implies the molecule involved was a centrosymmetric dimeric C-H…F-C interaction. **Figure S8** lists the molecular schemes alongwith the molecular pairs depicting all the relevant bcp's (intermolecular) extracted from the crystal environment in different hybridization environment under different "general search" procedures.

Table 3: Intermolecular interactions energies of selected C-H…F interaction present in selected molecular pairs retrieved from CSD database along with the respective REFCODES.

REFCODE (H…F dist. (Å) / C-H…F angle (°))	R_{cc} (Å)	E_{col} (kcal/mol)	E_{pol} (kcal/mol)	E_{dis} (kcal/mol)	E_{rep} (kcal/mol)	E_{tot} (kcal/mol)
Section 2:						
Subsection-2a: C(sp)-H…F-C(sp^2[arm])						
Search-B						
LURNOB* (2.41/136)	9.052	-0.69	-0.22	-1.03	0.73	-1.21
Search-C						
ASUYOC (2.34/153)	9.884	-0.76	-0.19	-0.95	0.67	-1.24
Subsection-2b: C(sp^2[arm])-H…F-C(sp^2[arm])						
Search-B						
AXUCEC01 (2.39/153)	7.296	-0.74	-0.21	-1.12	0.95	-1.12
FACFAQ (2.47/140)	6.118	-0.54	-0.24	-1.70	0.97	-1.45
NECMUD* (2.58/132)	7.245	-0.56	-0.13	-0.84	0.53	-1.00
CUWYUP* (2.76/114)	6.283	-0.22	-0.07	-0.83	0.35	-0.77
AXUCEC01 (2.88/136)	6.792	-0.40	-0.14	-1.43	0.67	-1.33
ZELDOJ01* (2.96/124)	7.715	-0.31	-0.04	-0.53	0.22	-0.66
Search-C						
NIZVAU02 (2.11/174)	8.473	-0.86	-0.48	-1.55	2.60	-0.26
NIZVAU02 (2.15/151)	8.463	-0.74	-0.50	-1.53	2.53	-0.23
BAJREJ (2.28/154)	10.998	-0.95	-0.26	-1.19	1.33	-1.09
LEGMOB (2.38/164)	11.855	-0.64	-0.19	-1.17	0.86	-1.14
VAYBUU (2.44/136)	7.451	-0.76	-0.33	-2.41	1.50	-2.00
ABABUC (2.52/144)	18.556	-0.69	-0.16	-1.00	0.59	-1.26
ACEWUB* (2.65/143)	11.547	-0.22	-0.08	-0.71	0.30	-0.71
WESBEB* (2.98/178)	8.346	-0.28	-0.04	-0.45	0.06	-0.71
Subsection-2c: C(sp^3)-H…F-C(sp^2[arm])						
Search-B						
UJIXAN (2.69/138)	18.000	-0.21	-0.09	-0.88	0.38	-0.78
COZKAE (2.78/114)	19.338	-0.09	-0.07	-0.78	0.43	-0.52
WUMWAD* (2.87/148)	8.272	-0.46	-0.15	-2.16	0.76	-2.01
SOHVOB (2.99/121)	18.306	-0.16	-0.09	-1.14	0.38	-1.02
Search-C						
AWUZEY (2.36/132)	9.473	-0.69	-0.26	-1.09	1.31	-0.74
AMARUB (2.48/121)	11.984	-0.14	-0.16	-1.26	1.05	-0.52
PEWMAH (2.52/129)	16.828	-0.04	-0.31	-1.79	1.29	-0.86
ANOZOT (2.67/148)	9.020	-0.24	-0.38	-2.24	0.57	-1.79
PETLOR (2.76/145)	8.198	-0.07	-0.16	-0.83	0.19	-0.88
VAXQAO (2.91/157)	8.017	-0.54	-0.11	-0.88	0.11	-1.43

REFCODE (H…F dist. (Å) / C-H…F angle (°))	R_{cc} (Å)	E_{col} (kcal/mol)	E_{pol} (kcal/mol)	E_{dis} (kcal/mol)	E_{rep} (kcal/mol)	E_{tot} (kcal/mol)
Section 3:						
Subsection-3a: C(sp)-H…F-C(sp^3)						
Search-C						
AGAVOU (2.56/145)	12.282	-1.00	-0.21	-1.00	0.35	-1.86
Subsection-3b: C(sp^2[arm])-H…F-C(sp^3)						
Search-B						
FELLOY (2.45/140)	14.298	-0.45	-0.19	-1.26	0.76	-1.17
FOHMEU (2.54/164)	9.343	-0.35	-0.11	-1.07	0.45	-1.09
Search-C						
BERGAH (2.22/146)	12.79	-1.29	-0.40	-2.34	2.00	-2.05
IJUDAT06 (2.77/142)	13.970	-0.04	-0.04	-1.24	0.28	-1.05
CANNIQ (2.80/137)	12.677	-0.21	-0.28	-2.00	0.97	-1.53
AZOKOP (2.91/118)	8.314	-0.26	-0.19	-2.17	0.78	-1.84
Subsection-3c: C(sp^3)-H…F-C(sp^3)						
Search-B						
FOHMIY (2.49/149)	9.924	-0.26	-0.12	-1.38	0.54	-1.24
RIQBID (2.54/147)	9.629	-0.38	-0.14	-1.29	0.59	-1.21
ZIXRON (2.64/129)	10.130	-0.28	-0.07	-1.70	0.47	-1.53
UBEDAI (2.73/143)	10.846	-0.09	-0.07	-1.14	0.28	-1.02
TOFMFL (2.96/130)	11.872	-0.69	-0.09	-0.74	0.14	-1.38
Search-C						
BAPFAB (2.36/153)	7.164	-1.12	0.26	-0.93	0.93	-1.38
ACEJIC (2.46/169)	8.266	-1.09	-0.21	-1.09	0.54	-1.84
XEFREH (2.57/168)	10.120	-0.57	-0.14	-1.09	0.45	-1.36
GECLIL (2.63/121)	10.854	-0.40	-0.09	-1.21	0.48	-1.24
LEGJIS (2.70/153)	12.140	-0.62	-0.09	-0.64	0.21	-1.14
ABUDIM (2.83/116)	16.299	-0.02	-0.01	-0.02	0.01	-0.04
DEFMUX (2.92/129)	12.846	-0.09	-0.14	-1.62	0.54	-1.29

Note: * denotes molecular pair having a centrosymmetric dimeric interaction.

Table 4: Topological parameters for selected C-H…F interactions (in addition to related intermolecular interactions) present in different molecular pairs.

REFCODE	Rij (Å)	ρ (e/Å^3)	∇^{2}ρ (e/Å^5)	V$_b$ (a.u.)	G$_b$ (a.u.)	D.E.^{V} / D.E.^{G} (kcal/mol)
Section 2:						
Subsection-2a: C(sp)-H…F-C(sp^2[arm])						
Search-B						
LURNOB* **π…π**	**2.447** 4.03	**0.050** 0.014	**0.753** 0.132	**-0.005521** -0.000858	**0.006621** 0.001117	**1.73/1.78** 0.26/0.30
Search-C						
ASUYOC	2.396	0.051	0.736	-0.005508	0.006573	1.72/1.76
Subsection-2b: C(sp^2[arm])-H…F-C(sp^2[arm])						
Search-B						
AXUCEC01	2.404	0.058	0.786	-0.006233	0.007196	1.95/1.93
FACFAQ	2.491	0.052	0.710	-0.005553	0.006460	1.74/1.73
NECMUD*	2.625	0.040	0.573	-0.004200	0.005073	1.31/1.36
CUWYUP*	2.889	0.031	0.498	-0.003227	0.004197	1.01/1.12
AXUCEC01 **F…F** **C-H…F**	**2.915** 2.937 3.231	**0.016** 0.035 0.019	**0.311** 0.556 0.445	**-0.001863** -0.003664 -0.002562	**0.002545** 0.004719 0.003594	**0.58/0.68** 1.14/1.27 0.80/0.96
ZELDOJ01* **F…F**	**3.019** 2.945	**0.015** 0.038	**0.284** 0.721	**-0.001570** -0.005420	**0.002259** 0.006452	**0.49/0.60** 1.70/1.73
Search-C						
NIZVAU02	2.135	0.095	1.433	-0.011111	0.012993	3.48/3.49
NIZVAU02	2.174	0.088	1.345	-0.010342	0.012150	3.24/3.27
BAJREJ	2.305	0.064	0.936	-0.007195	0.008452	2.25/2.27
LEGMOB	2.404	0.055	0.748	-0.005812	0.006786	1.82/1.82

REFCODE	Rij (Å)	ρ(e/Å^3)	∇^{2}ρ (e/Å^5)	V$_b$ (a.u.)	G$_b$ (a.u.)	D.E.^{V} / D.E.^{G} (kcal/mol)
Section 3:						
Subsection-3a: C(sp)-H…F-C(sp^3)						
Search-C						
AGAVOU	2.588	0.036	0.535	-0.003775	0.004666	1.18/1.25
Subsection-3b: C(sp^2[arm])-H…F-C(sp^3)						
Search-B						
FELLOY	2.485	0.051	0.712	-0.005490	0.006438	1.72/1.73
FOHMEU	2.566	0.037	0.517	-0.003959	0.004664	1.24/1.25
Search-C						
BERGAH **C-H…F** **C-H…F**	**2.252** 3.382 3.238	**0.081** 0.012 0.010	**1.163** 0.228 0.178	**-0.009300** -0.001081 -0.00078	**0.010687** 0.001728 0.001320	**2.91/2.57** 0.34/0.4 0.44/0.3
IJUDAT06 **C-H…F** **C-H…F**	**2.797** 3.348 3.202	**0.026** 0.015 0.016	**0.398** 0.272 0.290	**-0.002704** -0.001380 -0.001497	**0.003416** 0.002103 0.002257	**0.84/0.9** 0.43/0.56 0.47/0.60
CANNIQ	2.829	0.027	0.402	-0.002695	0.003435	0.84/0.92
AZOKOP **C-H…F** **C-F…π**	**2.992** 3.185 3.802	**0.022** 0.033 0.015	**0.374** 0.520 0.241	**-0.002222** -0.003301 -0.001192	**0.003052** 0.004352 0.001848	**0.69/0.82** 1.03/1.1 0.37/0.49
Subsection-3c: C(sp^3)-H…F-C(sp^3)						
Search-B						
FOHMIY	2.520	0.048	0.648	-0.005082	0.005904	1.59/1.58
RIQBID **C-H…F**	**2.563** 3.047	**0.041** 0.016	**0.572** 0.290	**-0.004375** -0.001600	**0.005158** 0.002304	**1.37/1.3** 0.50/0.62
ZIXRON **C-H…F**	**2.684** 3.067	**0.032** 0.014	**0.501** 0.251	**-0.003582** -0.001351	**0.004393** 0.001978	**1.12/1.18** 0.42/0.53

VAYBUU	2.468	0.056	0.765	-0.006062	0.006998	1.90/1.88	**UBEDAI**	2.755	0.030	0.433	-0.003046	0.003772	0.95/1.01
ABABUC	2.532	0.043	0.612	-0.004709	0.005570	1.47/1.49	**TOFMFL**	3.114	0.020	0.333	-0.001893	0.002673	0.59/0.71
ACEWUB* **F…F**	**2.685** 3.293	**0.030** 0.016	**0.446** 0.389	**-0.003167** -0.002018	**0.003899** 0.003030	**0.99/1.04** 0.63/0.81	**Search-C**						
WESBEB*	2.998	0.014	0.239	-0.001324	0.001904	0.41/0.51	**BAPFAB**	2.388	0.058	0.796	-0.006327	0.007291	1.98/1.96
Subsection-2c: **C(sp^3)-H…F-C(sp^2[arm])**							**ACEJIC**	2.496	0.045	0.621	-0.004713	0.005580	1.47/1.50
Search-B							**XEFREH**	2.601	0.037	0.509	-0.003873	0.004577	1.21/1.2
UJIXAN	2.716	0.032	0.461	-0.003323	0.004054	1.04/1.09	**GECLIL**	2.671	0.038	0.559	-0.004100	0.004951	1.28/1.3
COZKAE	2.829	0.033	0.545	-0.003637	0.004645	1.14/1.25	**LEGJIS**	2.728	0.028	0.408	-0.002902	0.003566	0.91/0.96
WUMWAD*	2.904	0.021	0.335	-0.002113	0.002797	0.66/0.75	**ABUDIM**	**2.908**	**0.024**	**0.388**	**-0.002482**	**0.003255**	**0.77/0.87**
SOHVOB	3.033	0.020	0.320	-0.001873	0.002601	0.58/0.70	C-H… π	3.389	0.021	0.222	-0.001495	0.001904	0.46/0.51
Search-C							**DEFMUX**	2.969	0.017	0.298	-0.001764	0.002431	0.55/0.6
AWUZEY	2.387	0.062	0.894	-0.007035	0.008158	2.20/2.19							
AMARUB	2.540	0.053	0.760	-0.005833	0.006862	1.83/1.84							
PEWMAH	2.552	0.050	0.699	-0.005413	0.006341	1.69/1.70							
ANOZOT	2.698	0.034	0.467	-0.003389	0.004120	1.06/1.10							
PETLOR	2.782	0.025	0.383	-0.002545	0.003261	0.79/0.87							
VAXQAO	2.929	0.018	0.294	-0.001762	0.002406	0.55/0.64							

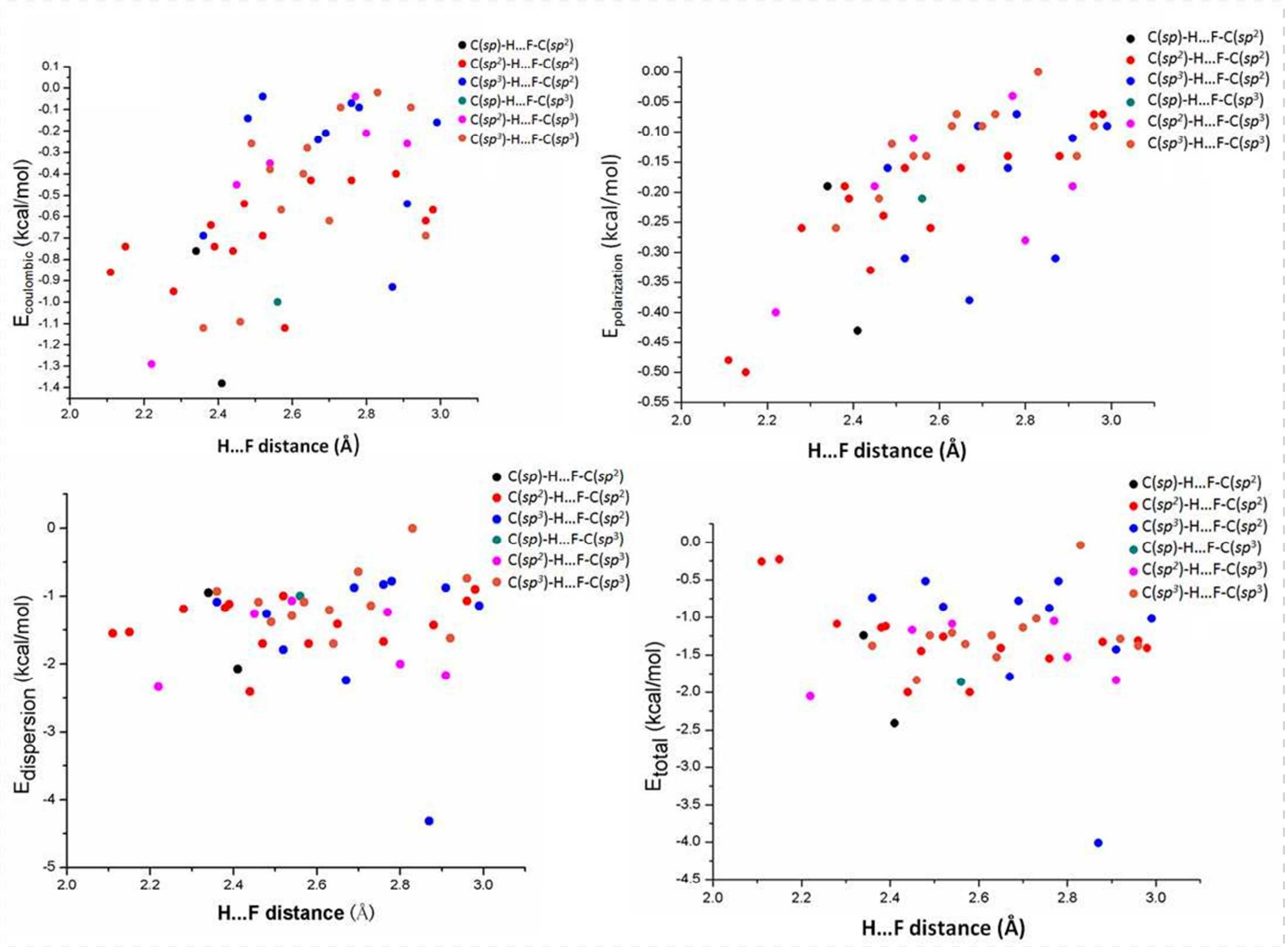

Figure 7: The energy plots highlighting the a) coulombic contribution b) polarization contribution c) dispersion contribution d) total stabilization; for all the C-H…F intermolecular interactions in the selected REFCODES with the relevant hybridization.

The trends in intermolecular interaction energies evaluated for the different molecular pairs depict interesting features [Table 3, Figure 7]. There exists possible C-H…F interactions in different hybridization environment with the coulombic contribution in the range of -0.02 to -1.29 kcal/mol (only for dimers there may be contribution from other interactions at the given distance; the maximum magnitude for the coulombic component is -0.46 kcal/mol in **WUMWAD**). The polarization contribution for the intermolecular interactions lies between -0.01 to -0.50 kcal/mol. The dispersion contribution lies in the range of -0.45 to -2.41 kcal/mol over the entire H…F distance range except in ABUDIM. The total energy has a distribution of points similar to that of the dispersion contribution [Figure 7]. It is to be noted that the shortest H…F distance (2.11-2.15Å) does not necessarily correspond to the maximum coulombic stabilization (for example in case of the molecule NIZVAU02, **Search-C**) wherein the contribution is in the range of 0.74-0.86 kcal/mol. The salient energetic features associated with different molecules are noteworthy. In case of LURNOB (B; H…F distance is 2.41Å), it forms a centrosymmetric dimer, the coulombic contribution being -0.69kcal/mol. This involves a C-H donor having *sp* hybridization, being strongly acidic, interacting with the fluorine connected to a sp^2 hybridized carbon atom. A similar situation is observed in the molecule AGAVOU [Search C], involving a C-H donor with *sp* hybridization but interacting with fluorine connected to a sp^3 hybridized fluorine atom (H…F distance is 2.56 Å), it is observed that the coulombic stabilization is -1.00 kcal/mol. This again indicates the significant role of the C-H donor on account of its higher acidity. An interesting case is observed from Search-C corresponding to the molecule BERGAH wherein the coulombic stabilization is high, the magnitude being -1.29kcal/mol, involving the commonly occurring C-H donor connected to sp^2 hybridized carbon interacting with a fluorine connected to a sp^2 hybridized carbon atom (commonly occurring aryl rings). For a given distance, it is noteworthy that more than one intermolecular interaction exists corresponding to a different hybridization environment for the participating atoms. For the C(sp^2)-H…F-C(sp^2) case, it has been observed that the crystal packing consists of dimeric C-H…F intermolecular interactions, a key supramolecular motif involving organic fluorine formed preferably in the absence of strong H- bonds [9].

In section **2**, we observed that the interaction energy is in the range of -0.23 kcal/mol (observed in NIZVAU02) to -2.01 kcal/mol (in WUMWAD) [Table 3]. Although, in a majority of molecules in this section, and in previous studies involving fluorine attached to aromatic carbon, the results indicate that the dispersion component is mostly the dominant contributor in such weak C-H…F interactions. Comparing ZELDOJ01 and WESBEB, which have similar intermolecular H…F distance but differ significantly in their angularity and have similar total stabilization energy (-0.66 and -0.71 kcal/mol respectively). A closer look at the contribution from the individual energy component, it was observed that the difference is mainly originating from the repulsion contribution. Even though it has been observed that the hydrogen bond is highly stabilized at shorter distances, calculations performed on NIZVAU02 showed that at very short distances the contribution from the repulsive component can overcome the dispersion component and lead to destabilization [Table 3]. In **Search-C**, of subsection-2b we observed that there is a decrease in the contribution from the dispersion component with increase in H…F distance (excluding VAYBUU). Similar trends were observed for the polarization energy and also for the repulsive energy. Such trends were not observed for any subsection in **Search-2**. Comparing between Subsection-2b and Subsection- 2c it was interesting to note that twelve out of the fourteen molecular pairs had a coulombic contribution greater than 0.25 kcal/mol while that number was reduced to three out of ten for the subsection-2c [Table 3].

In **section-3**, the stabilization energy range is from a value of -1.02 to -2.05 kcal/mol, except in the case of ABUDIM where the stabilization energy was only -0.04 kcal/mol [Table 3]. ABUDIN, is a special case, because although it satisfies the topological criteria for a hydrogen bond [26], it is less stabilized. This shows that the overall structure of the molecule in the crystal geometry plays an important role in determining the stability of the intermolecular interactions present in the molecule. Because of its negligible interaction energy we will be excluding ABUDIM from our PIXEL discussion. One important feature of molecules in section-3 is that the minimum total energy observed was -1.02 kcal/mol [Table 3]. This observation was important considering the fact that nearly 46% of the molecular pairs in **Section-2** had total stabilization energy of less than 1 kcal/mol. In this section also we observed that at very short distance the contribution coming from the repulsive component becomes significant (BERGAH). No trends in energies in any subsection were observed. One possible reason is due to the presence of multiple donors and acceptor atoms, depending on hybridization, affect the environment around the interacting atom and this in turn depends on the structure of the molecule.

Table 4 represents the parameters obtained through AIMALL calculations for the different dimeric motifs which have been considered for the analysis of intermolecular interactions having organic fluorine. A bond critical point (BCP) was observed for all the molecular pairs retrieved from CSD where we expected the presence of a C-H…F interaction [Figure S8]. In some of the molecular pairs we observed additional BCP also. The AIMALL analysis shows that the electron density (ρ) at the bond critical point (BCP) is small; the range being $0.095 > \rho > 0.014$ e/Å^3. This result is in accordance with the observed value of ρ calculated for C-H…F interactions in our previous studies [27]. The value of the Laplacian at the BCP is in the range $1.433 > \nabla^2\rho > 0.239$ e/Å^5. Accoring to Koch and Popelier criteria, the Laplacian value ranges from $3.350 > \nabla^2\rho > 0.578$ e/Å^5 for presence of an "H-bond" [26] and hence in our study all the interactions which satisfy the criteria can be regarded as a true hydrogen bond. These topological characteristics indicate the presence of a hydrogen bond between the interacting atoms for a given molecular motif of the molecule in the crystal. The conditions for closed-shell interactions are confirmed by having a small positive value of the electron density and positive value of the Laplacian at the BCP. This also confirms the presence of a hydrogen bond at a longer H…F distance and/or lower angularity for a C-H…F interaction. Both ρ and $\nabla^2\rho$ follows an exponential decrease with increase in bond path length (R_{ij}) [Figure 8(a)-(b)]. **Figure 8(c)** shows the polynomial behavior of the plot between $| V_b | / G_b$ and R_{ij}. The value of $| V_b | / G_b$ were observed to be less than one for all the C-H…F interactions in our study. This is in accordance with the results in similar studies performed recently on fluorinated benzanilides [10(a)]. **Figure 8(d)** shows the relationship between the dissociation energy and R_{ij}. D.E.^{V} denotes the dissociation energy evaluated using the local potential energy by utilizing the formula D.E.^{V} = $-0.5V_b$ and D.E.^{G} denotes the dissociation energy evaluated using the kinetic electron density by utilizing the formula D.E.^{G} = $0.429G_b$. Both D.E.^{V} and D.E.^{G} shows exponential decay with respect to R_{ij}, the fitting parameter being 0.95 for both types of dissociation energies. Both D.E.^{V} and D.E.^{G} have similar values up to ~ 2.5Å and after that it is observed that the exponential decrease of D.E.^{V} is faster than D.E.^{G}.

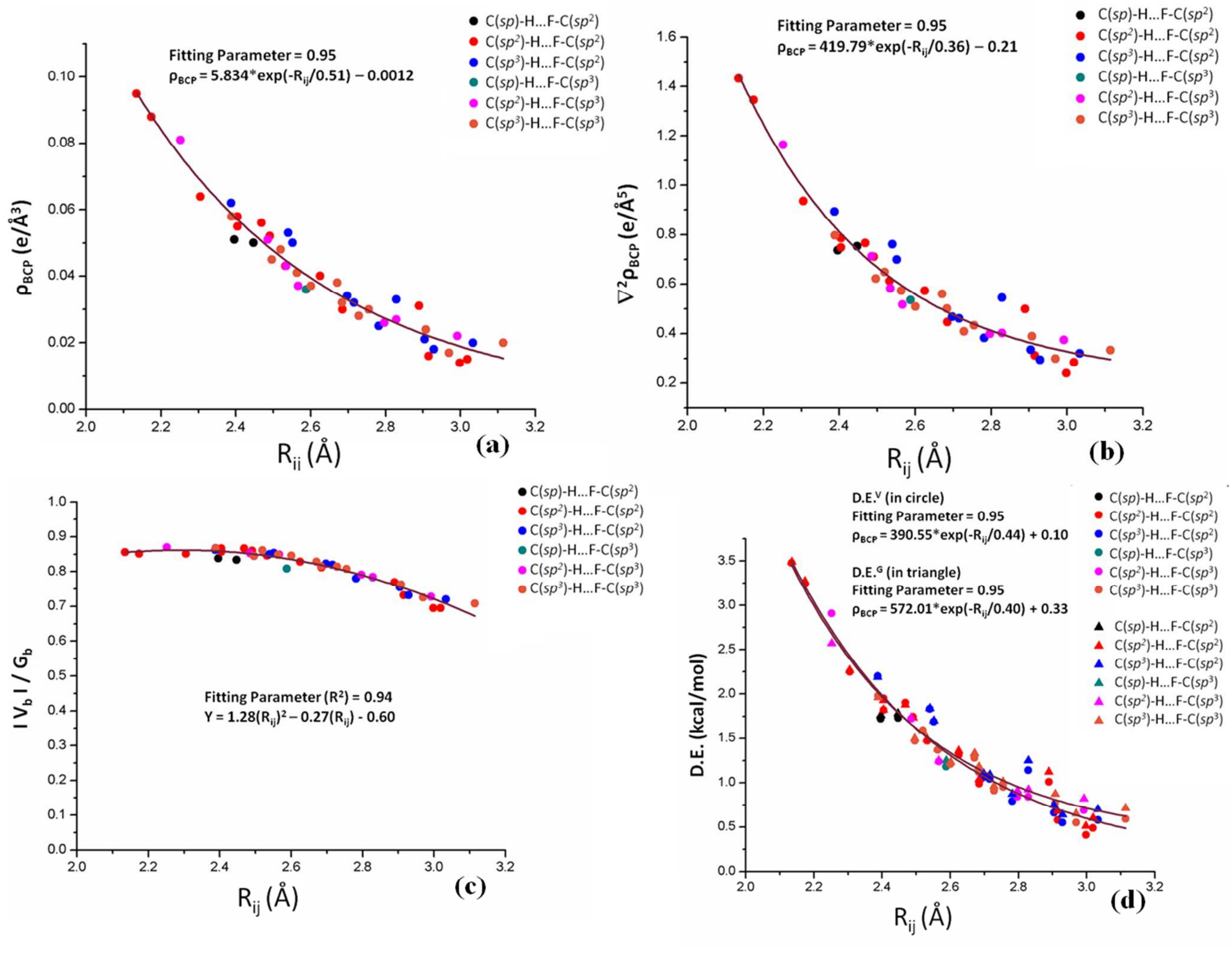

Figure 8: (a) Variation of the electron density (ρ) at BCP *vs* H…F bond path (R_{ij}). (b) Variation of Laplacian ($\nabla^2\rho$) with R_{ij}. (c) Variation of |Vb|/Gb with R_{ij}. (d) Variation of the dissociation energies (D.E.) vs R_{ij}.

Conclusions

A complete CSD analysis for the assessment of the formation of C-H…F intermolecular contacts in molecular crystals as a function of the hybridization of the donor and acceptor atom has been performed comprehensively. The C(sp^2)-H…F-C(sp^2) intermolecular interaction is the one (in terms of hybridization) which has been investigated in detail (both experimentally and computationally). The mean H…F distance is experimentally observed at 2.67 Å, which also is the sum of the van der Waals radius of hydrogen and fluorine atom. Furthermore, this particular intermolecular interaction exhibits, upon cone correction, a clear preference towards linearity. PIXEL calculations performed on selected molecular pairs further establish the fact that C-H…F-C interaction is mainly of a dispersive nature. It is of interest to note that the coulombic contribution is important when the donor atom involved in attached to a *sp* hybridized C, hence signifying the enhanced acidity of the donor atom. However it was also observed that at very short H…F distance, contribution from the repulsive term is significant. A topological analysis for all the interactions were performed which confirmed the presence of a (3,-1) BCP. The methodology described in this article can be extended to investigate intermolecular interactions involving organic fluorine in various organic molecules wherein both the donor and acceptor atom is attached to a sp^3 hybridized carbon. This is expected to reflect deeper insights into the nature of such intermolecular contacts involving organic fluorine

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Dedication

This article is dedicated towards the memory of Professor F. A. Allen for his pioneering contributions towards the development of CSD.

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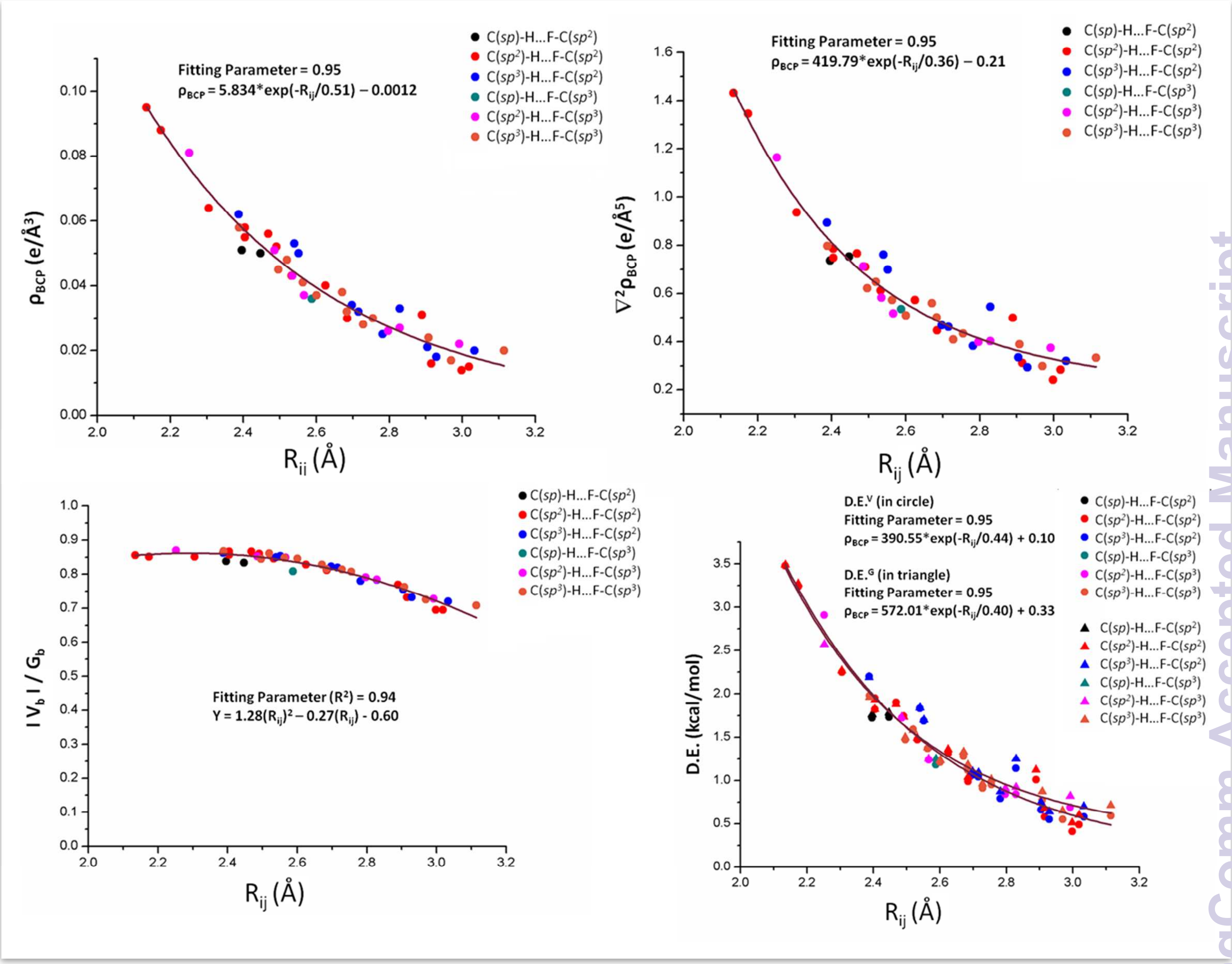

Analysis of C-H…F-C interaction on the basis of hybridization of the carbon atom participating in the interaction has been analyzed by performing statistical studies using CSD, evaluating the energetics using PIXEL and a topological analysis using AIMALL.