Packing similarities in organic crystals with C–H/C–F exchange: a database analysis of CH_3/CF_3 pairs

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The prediction of packing motifs in organofluorine compounds is relevant to crystal engineering, drug design and materials chemistry. A Cambridge Structural database analysis of 50 CH_3/CF_3 organic crystal structures has been carried out, that is pairs of molecules in which a methyl group is replaced with trifluoromethyl. These 50 CH_3/CF_3 hits are classified into four categories: identical organisation in the crystals (24 hits), different packing modes (6 hits), perfluorination (6 hits) and a miscellaneous category with 14 hits. Identical packing may be expected in crystal structures stabilised by robust, cyclic supramolecular synthons (hydrogen bonding) or in molecules with a large, rigid, polycyclic carbon skeleton (van der Waals interactions).

The exchange of C–H with C–F groups in molecular crystals has been shown to result in two distinct situations: the CH/CF related pair of structures has different packing motifs, or the structures are similar because these groups play an isosteric role. Differences in the crystal packing of molecules involving CH/CF exchange have been variously explained in terms of C–H···F, C–F···π, F···F, O–H···π and π–π interactions.[1–6] A study of some fluorine-containing organic compounds has shown that C–H···F–C interactions are extremely weak and that C–F groups compete unfavourably compared to $C–O^-$, C=O or C–OH as acceptor groups. Yet, C–F···H–Y interactions (Y = C, N, O) should not be ignored in the analysis of molecular packing.[7] The role of fluorine in influencing crystal packing could be indecisive, as in γ-hydroquinone and its tetrahalogenated derivatives,[8] or deep-seated, as in the crystal structures of the fluorobenzenes.[9] All these studies suggest that while F often behaves like H, and at times even like OH, its behaviour is quite different from the higher halogens. Unlike Cl and Br, F mostly does not form polarisation-induced type II F···F contacts as revealed in a recent database study.[8]

The van der Waals radii of H and F atoms are smaller than all other atoms in a molecule (Bondi radius: H 1.20, F 1.47, O 1.52, N 1.55, C 1.70, Cl 1.75, S 1.80, Br 1.85, I 1.98 Å).[10] However, the electronegativity of H and F are widely differing when compared with other atoms (Pauling scale: H 2.1, C 2.5, Cl 3.0, F 4.0). Therefore, replacement of H with the nearly isosteric F can cause differences in the organofluorine crystal packing through attractive interactions of F with donor and acceptor groups. Specific interactions involving the F atom have been correlated with changes in photophysical,[1] thermal[2] and topochemical[3,6] properties. On the other hand, isomorphism in a solid solution mixed crystal of CH_3 and CF_3 components is known,[11] despite the 2–3 times larger volume of the CF_3 group (van der Waals hemisphere: CH_3 16.8, CF_3 42.6 $Å^3$).[12,13] In drug molecules and enzyme inhibitors,[12–17] F analogues function as isosteric mimics of H ligands because they bind to the receptor in the same way but the reactive F atom causes competitive or suicide inhibition of the enzyme.[14] Such a dual, chameleon-like behaviour exhibited by CH/CF compounds—that is, differences in structure and property in some pairs and mimicry effects in other instances—led to the present database study on the effect of C–H → C–F substitution on crystal packing and molecular recognition. The objective of carrying out a comparison of the archived CH_3/CF_3 crystals was three-fold: (1) to assess the chemical diversity of structures with such a substitution; (2) to understand the molecular and supramolecular features that promote isomorphism or isostructurality in these pairs; (3) to propose a model that predicts the modes of molecular aggregation in organofluorine crystals.

Results and discussion

The Cambridge Structural Database[18] (CSD, October 1998, Version 5.16, 190 307 entries) was searched for pairs of organic compounds that are identical except that a CH_3 group is replaced by CF_3. Such data cannot be retrieved routinely using the automated, built-in search protocols. A sub-database of CF_3-containing organic molecules (1042 hits) was created and the CSD searched with each CF_3 entry as input for the presence of its CH_3 counterpart. Fifty pairs of organic CH_3/CF_3 compounds were retrieved for which X-ray crystal structures are reported to good accuracy (screens 33, 35, 57, 88, 153).† Based on the similarities and differences in packing motifs, these structures were classified into four categories: (A) similar crystal packing with the same supramolecular synthon and/or identical lattice parameters (F atom plays only a space-filling role); (B) non-identical crystal structures with different packing motifs (electronegative F atom changes the conformation and/or intermolecular interactions); (C) C–H → C–F replacement is a big change in a small molecule (multiple substitution or perfluorination leading to a change in structure); (D) structures that are difficult to categorise as (A), (B) or (C) (no dominant packing features could be identified). The CSD refcodes of these 50 pairs of CH_3/CF_3 crystal structures, their space groups and their classification in one of these four categories are listed in Table 1. Fig. 1 and 2 show some examples of the chemical structures discussed in this paper.

† CSD screens: 33 (error-free), 35 (no disorder), 57 (organic only), 88 ($R \leqslant 0.10$), 153 (atom coordinates present).

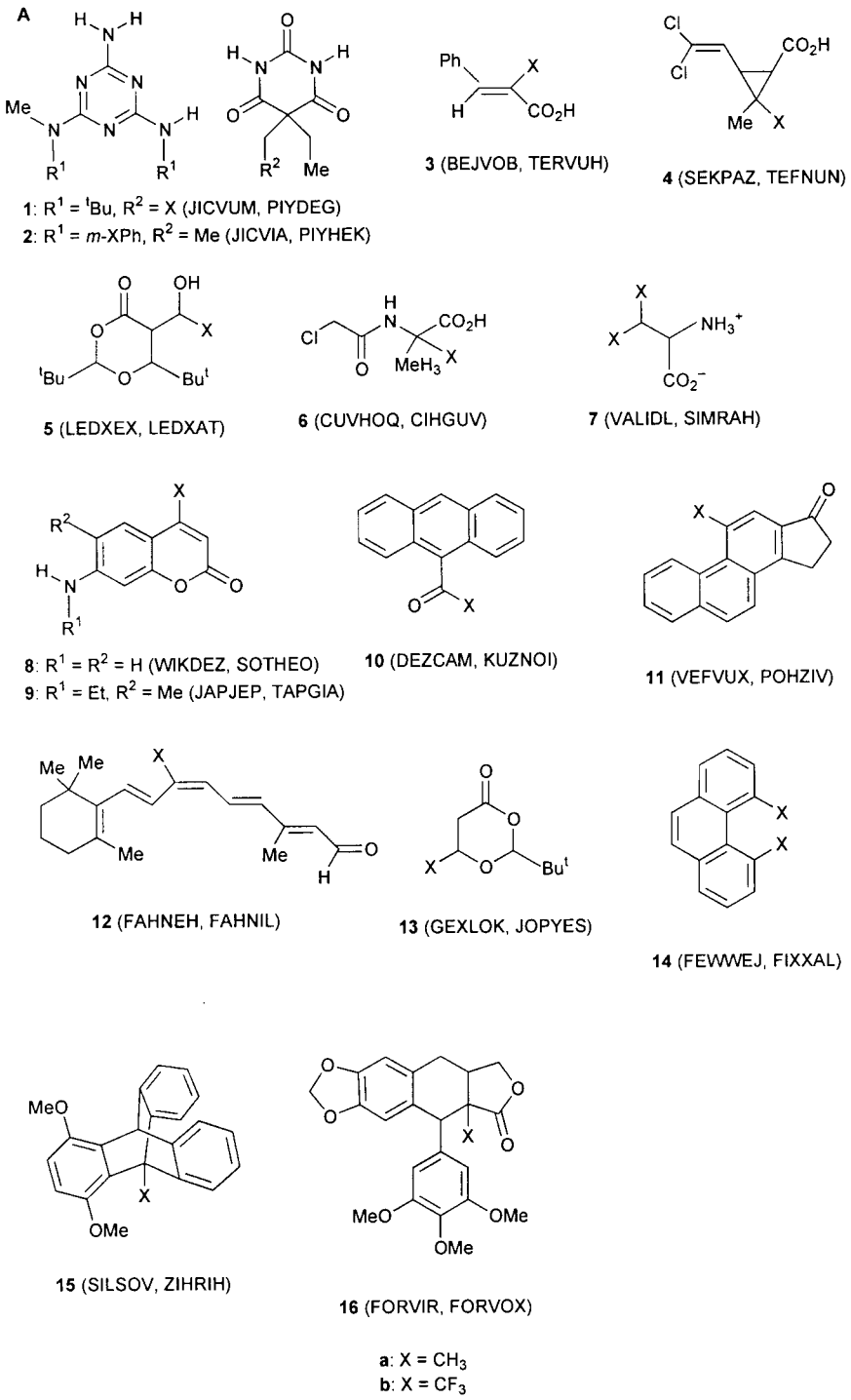


Fig. 1 Some examples of CH_3/CF_3 crystal structures retrieved from the CSD falling into category A. See text for an explanation of the classification.

Category A

Let us consider crystal structures of the 1 : 1 barbiturate–melamine complexes (**1a**,**b** and **2a**,**b**; **a**: X = CH_3 and **b**: X = CF_3 in Fig. 1; refcodes JICVUM, PIYDEG, JICVIA, PIYHEK in Table 1). These structures have a crinkled- or linear-tape architecture mediated by supramolecular synthon[19] **I** (Fig. 3) with repeat distances of *ca.* 15.7 (**1a**,**b**) and *ca.* 9.8 Å (**2a**,**b**). There are no F-rich regions and no F···F contacts below the van der Waals radius sum (3.0 Å) in the CF_3CH_2 complex **1b**. In the *m*-CH_3/CF_3 phenyl pair (**2a**,**b**), the structures are identical despite the inclusion of CH_3CN solvent in the *m*-CF_3 adduct, suggesting that the tape substructural unit **I** is robust enough to tolerate a substitution change together with guest inclusion.

Similarly, carboxy dimer synthon **II** is the common recognition motif in CH_3 and CF_3-substituted cinnamic acid **3a**,**b** (BEJVOB, TERVUH) and *cis*-permithrinic acid **4a**,**b** (SEKPAZ, TEFNUN). The dominant synthon in the identical crystal structures of 1,3-dioxan-4-ones **5a**,**b** (LEDXEX, LEDXAT) is the O–H···O=C hydrogen bond. Interestingly, **5a**,**b** not only have the same space group (both $P2_12_12_1$) and crystal packing (O···O 2.76, 2.80 Å) but also have nearly equal lattice parameters (*a* 9.46, 9.71; *b* 10.60, 10.52; *c* 15.22, 15.64 Å)—they are isostructural with a unit cell similarity index,[20] Π, of 0.017. In trichloroaminoisobutyric acid and its CF_3 derivative **6a**,**b** (CUVHOQ, CIHGUV), O–H···O and N–H···O hydrogen bonds between screw axis-related molecules stabilise the crystal structures. Molecules in the centro-

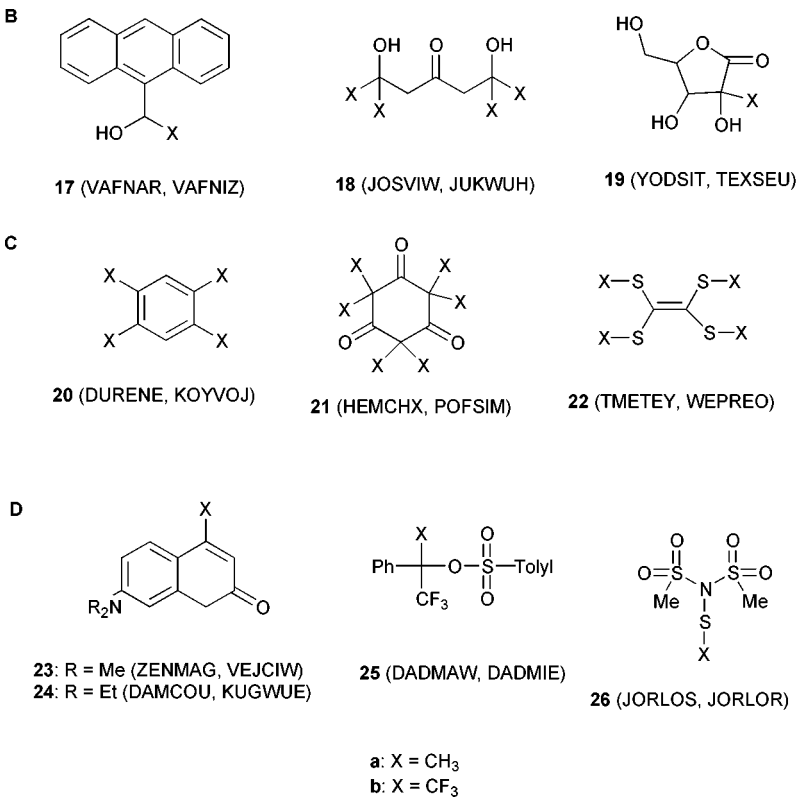


Fig. 2 Some examples of CH_3/CF_3 crystal structures retrieved from the CSD falling into categories B, C and D. See text for an explanation of the classification.

symmetric crystals of *rac*-valine and its bis(trifluoromethyl) derivative **7a**,**b** (VALIDL, SIMRAH) are arranged around columns of hydrogen-bonded ammonium and carboxylate ions, the $NH_3^+\cdots CO_2^-$ synthon,[21] such that the *c* axis (10.10 Å) in the monoclinic cell of **7b** is about twice the repeat distances (*a* 5.22, *b* 5.40 Å) in the triclinic cell of **7a**.

There are a number of CH_3/CF_3 coumarins in the CSD. In 7-amino coumarin **8a**,**b** (both $P\bar{1}$; WIKDEZ, SOTHEO), the multi-point synthon **III**, mediated through N–H···O and C–H···O hydrogen bonds, controls self-assembly and aggregation of similar crystal structures. The *N*-ethyl coumarin molecules **9a**,**b** (JAPJEP, TAPGIA) are connected by N–H···O=C bonds and their structures show some local packing similarities. A reduction in synthon size from four-point in **8** (two N–H···O and two C–H···O) to a single hydrogen bond in **9** (N–H···O) leads to a lesser degree of similarity in the latter pair of CH_3/CF_3 structures. In effect, the strength of a supramolecular synthon, or its recurrence in crystal structures,‡[22] may be correlated with the extent of similarity in trifluoromethyl crystal packing with the methyl structure. Given the significance of robust synthons in CH_3/CF_3 isomorphism, it is not surprising that *N*,*N*-dimethyl and *N*,*N*-diethyl coumarins **23a**,**b** and **24a**,**b** (ZENMAG, VEJCIW and DAMCOU, KUGWUE), molecules devoid of strong hydrogen bond functionality, have diverse aggregation motifs in different crystal systems (entries 40 and 48 in Table 1). These molecules are accordingly classified in category D. In the absence of robust synthons, molecular size together with a degree of rigidity in the carbon skeleton could favour CH_3/CF_3 isostructurality. For example, 9-acetylanthracene and its CF_3 derivative **10a**,**b** (DEZCAM, KUZNOI), both have centrosymmetrically π-stacked aromatic rings (category A). This comparison shows that though neither anthracene **10** nor coumarins **23**, **24** have strong hydrogen bond functionality, the tricyclic aromatic template of anthracene is able to steer CH_3/CF_3 mimicry but the smaller bicyclic hetero-aromatic coumarin is unable to exhibit such a structural effect. The role of size and rigidity in category A molecules is discussed next.

The crystal structures of cyclopentaphenanthrene ketones **11a**,**b** (VEFVUX, POHZIV) and *cis*-retinals **12a**,**b**, (FAHNEH, FAHNIL) are similar because the molecule is large (C_{15}–C_{20})

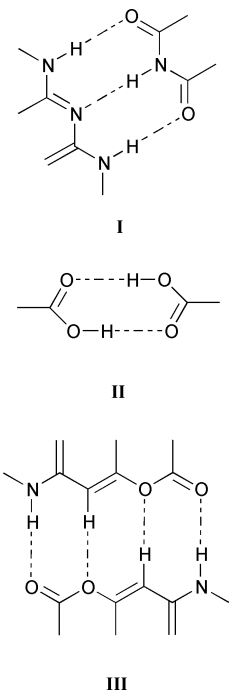


Fig. 3 Multi-point recognition supramolecular synthons in some crystal structures of category (A).

‡ Ref. 22 lists the frequencies of occurrences of 75 cyclic supramolecular synthons.

Table 1 List of 50 pairs of CH_3/CF_3 organic refcodes retrieved from the CSD. Some entries have more than two refcodes for stereoisomer, enantiomer, fluorinated isomer, solvate, polymorph or redetermination of structure. Duplicate refcodes archived as ABCDEF## are designated with letters only. In the case of polymorphs, the different space groups are mentioned. Entries are classified as A, B, C and D in alphabetical order of the CH_3 structure refcode within each category

Entry	CH_3 structure	CF_3 structure	CH_3 space group	CF_3 space group	Category
1	BEJVOB	TERVUH	$P2_1/c$	$P2_1/n$	A
2	BMCLMH	CXBEFH	$P2_1/n$	$P2_1/a$	A
3	CHOLET	ZIPZIH	$P2_12_12_1$	$P2_12_12_1$	A
4	CUVHOQ	CIHGUV	$P2_12_12_1$	$P2_1$	A
5	DEZCAM	KUZNOI	$P2_1/n$	$P2_1/c$	A
		YAKHIB		$P2_1/c$	
6	FAHNEH	FAHNIL	$P\bar{1}$	$P\bar{1}$	A
7	FEWWEJ	FIXXAL	$P2_1$	$F2dd$	A
8	FIXWAK	FIXWEO	$P\bar{1}$	$F2dd$	A
9	FORVIR	FORVOX	$A2/a$	$Pcab$	A
	DECGEX		$C2/c$		
10	GEXLOK	JOPYES	$Pna2_1$	$Pna2_1$	A
		JOPYOC		$Pbca$	
11	HEPDEL	HEPDIP	$Pbca$	$Pna2_1$	A
12	JAPJEP	TAPGIA	$P2_1/c$	$P\bar{1}$	A
13	JICVIA	PIYHEK	$P\bar{1}$	$P2_1/c$	A
14	JICVUM	PIYDEG	$Pna2_1$	$P2_12_12_1$	A
15	KUYFEP	SEGLIZ	$P2_1$	$P2_1$	A
		FILMIW		$P2_1/n$	
		FUSTIW		$P2_1/n$	
		SEGLEV		$P2_1/c$	
16	LEDXEX	LEDXAT	$P2_12_12_1$	$P2_12_12_1$	A
17	POMDAW	ZURWEO	$P2_1/c$	$Pccn$	A
18	SEKPAZ	TEFNUN	$P\bar{1}$	$P2_1/c$	A
	SEKNUR		$P2_1$		
19	SILSOV	ZIXRIH	$P2_1/a$	$C2/c$	A
20	TNAPHB	TNAPHA	$P2_1$	$P2_12_12_1$	A
	TNAPHC		$Pca2_1$		
21	VALIDL	SIMRAH	$P\bar{1}$	$P2_1/c$	A
	LVALIN		$P2_1$		
22	VEFVUX	POHZIV	$Pcab$	$C2/c$	A
23	WEGSAC	VOVVAD	$P2_12_12_1$	$Pca2_1$	A
24	WIKDEZ	SOTHEO	$P\bar{1}$	$P\bar{1}$	A
25	ACETAC	TFACET	$Pna2_1$	$P2_1/c$	B
26	ACTCBZ	SETLUY	$P\bar{1}$	$P2_1/c$	B
27	BUBZSB	OTMSIN	$P2_12_12_1$	$P2_1/c$	B
28	JOSVIW	JUKWUH	$C2/c$	$P2_1/c$	B
29	VAFNAR	VAFNIZ	$I4_1cd$	$Pbca$	B
		SOCLIF		$P2_1$	
30	YODSIT	TEXSEU	$P2_12_12_1$	Cc	B
31	CUCPIZ	CUCPOF	$C2/c$	$P2_1/c$	C
32	DOVVAL	LEBFED	$P2_1/n$	$P\bar{1}$	C
33	DURENE	KOYVOJ	$P2_1/a$	$Pbca$	C
34	HEMCHX	POFSIM	$P2_1/n$	$P2_1/n$	C
35	RIJHIB	YAMSAG	$Pna2_1$	$Pnma$	C
36	TMETEY	WEPREO	$P\bar{1}$	$P2_1/c$	C
37	ANISAZ	LACGUR	Cc	$P\bar{1}$	D
38	BIZHUN	KTFMFB	$Pbca$	$P2_1/c$	D
39	DADMAW	DADMIE	$P2_1/n$	$P2_1/c$	D
40	DAMCOU	KUGWUE	$P2_1$	$P\bar{1}$	D
41	DOFJUD	CUMVEL	$P2_1/c$	$Pna2_1$	D
42	EBYBUA	JIJWEE	$P2_1/c$	$P\bar{1}$	D
43	IBZDAC	CEZBEO	$Pnn2$	$P\bar{1}$	D
44	JENRAV	ZUDCOQ	$P2_1$	$Iba2$	D
		ZUDCIK		$P2_12_12_1$	
45	JORLOS	JORLOR	$P2_1/n$	$Pbca$	D
46	QQQCVG	SINGUR	$P4/nmm$	$P2_1/m$	D
47	VEMJUS	DEHWIW	$P2_1/c$	$P2_1/c$	D
48	ZENMAG	VEJCIW	$P\bar{1}$	$Pnma$, $P2_1/a$	D
49	ZUSYIV	ZUSYER	$P2_1/c$	$P\bar{1}$	D
50	ZZZMUC	SAWBIB	$P2_1ab$, $P2_1/b$	$P2_1/n$	D

and/or the carbon skeleton is rigid/polycyclic. In **11a**,**b** the molecules stack with a repeat distance of *ca.* 7.5 Å because of the dominance of aromatic–aromatic interactions while in **12a**,**b** the two triclinic cells have nearly the same dimensions and angles (both $P\bar{1}$ with $Z = 1$, a 5.72, 5.74; b 7.27, 7.23; c 23.25, 23.89 Å, α 89.7; 90.5; β 92.6, 93.9; γ 108.6, 106.9°). In *cis*-1,3-dioxan-4-ones **13a**,**b** (GEXLOK, JOPYES), the six-membered ring is conformationally locked because of the bulky *tert*-butyl group. The rigid template and a moderately strong C–H···O bond from the acetal CH to the ketone O acceptor (*ca.* 2.5 Å) suffice to produce isomorphous crystals of **13a**,**b** (both $Pna2_1$). In bis-CH_3/CF_3 phenanthrene **14a**,**b** (FEWWEJ, FIXXAL) and the dihydro analogues (FIXWAK, FIXWEO), the helical shape of the aromatic tricyclic core dictates self-assembly in the non-centrosymmetric space groups $P2_1$ and $F2dd$ in three out of four cases. The dimethyl and nominally isosteric bis(trifluoromethyl) groups in these structures play a bystander space-filling role. Support from the

weak (Me)C–H···π[23] and (Ph)C–H···F[7] interactions to favour polar stacking of molecular columns is possible in **14a** and **14b**, respectively. Continuing further to a three-dimensional rigid carbon skeleton, the roof-shaped triptycenes **15a**,**b** (SILSOV, ZIHRIH) with CH_3 and CF_3 groups at the bridgehead position have identical centrosymmetric packing of molecules in $P2_1/a$ and $C2/c$ space groups. Lastly, the anti-cancer agents, picrophyllotoxin **16a**,**b** (FORVIR, FORVOX), are noteworthy in category A. While methyl isodeoxy-picrophyllotoxin **16a** crystallises as a diethyl ether solvate, the CF_3 analogue **16b** is a single-component crystal. In both structures, however, the Y-shaped molecules pack in a similar manner, with disordered solvent molecules filling the interstitial voids in FORVIR. Thus, the phenomenon of CH_3/CF_3 structural mimicry can even extend to a comparison of a single-component crystal with a two-component crystal in exceptional cases. A solvent-included complex may be isostructural with its unsolvated analogue not only because of robust synthons, as in JICVIA and PIYHEK, but also through the concerted stabilisation from shape, hydrophobic packing and weak interactions.

Crystal packing in the CF_3 analogue is not altered significantly compared to the CH_3 structure in the aforementioned cases in spite of the fact that intermolecular interactions in these structures are of the weak type (C–H···O, C–H···F, C–H···π, π–π).[24] This is because the substitution is a relatively small change in volume compared to the volume of the molecule. Most organic crystals have packing coefficients in the range 0.65–0.77. The 30% void space can accommodate groups of variable size over a narrow range,[25] such as H *vs.* F, without perturbing the overall organisation in the lattice. Notwithstanding this rationale, and despite the small size of H and F atoms, CH/CF isostructurality would not have been possible but for the fact that F does not have a strong tendency to form any type of C–F···H–Y interaction (Y = O, N, C).[26] Naturally, this model is easily applicable when the molecule is large, say >15 carbon atoms, has a polycyclic carbon skeleton that confers to it a degree of rigidity, and has one or at most two methyl groups replaced by trifluoromethyl. If numerous CH_3 groups in a small molecule are exchanged with CF_3, then their crystal structures are quite different Category C.

Category B

In this category, the differences in crystal packing between a CH_3 and CF_3 pair of structures can be understood in terms of a change in hydrogen bonding. In racemic anthrylethanol **17a** (VAFNAR), the hydroxyl groups form a tetrameric helix with O–H···O bonds ($I4_1cd$) while in CF_3 carbinol **17b** (VAFNIZ) the centrosymmetric structure (*Pbca*) is stabilised by a O–H···π hydrogen bond[5] and not the erroneously postulated O–H···F–C interaction.[27] The reason for the incorrect interpretation (VAFNIZ)[27] was that the intermolecular interactions were analysed based on the hydroxy O atom position. Subsequently, the X-ray crystal structure of racemic **17b** was redetermined (VAFNIZ01)[5] with the hydroxyl protons located from ΔF maps. Based on the refined H atom positions, it is clear that the interaction changes from O–H···O in **17a** to O–H···π (2.3 Å) in **17b**. A possible reason for the change in hydrogen bonding motif could be that the adjacent electron-withdrawing CF_3 group reduces the basicity of the O atom so drastically that the benzo ring π-cloud is able to compete favourably as the O–H acceptor.

The second case discussed in this section is a dihydroxy-ketone with four methyl groups replaced with tetrakis(trifluoromethyl), **18a,b** (JOSVIW, JUKWUH). Since **18a** is a tertiary alcohol, the possibility of O–H···O–H hydrogen bonding is diminished because of steric crowding. In general, O–H···O–H bonds are weaker with tertiary hydroxyl groups than in primary alcohols.[28,29] Surprisingly, **18a** does not form an intramolecular O–H···O=C bond with the ketone O atom, that is the strong donor approaching the strong acceptor, as one might have expected.[30] Diol **18a** is an example of a molecule that, although possessing excellent donor and acceptor functionalities, does not utilise them in hydrogen bonding. Instead, the structure has long intermolecular O–H···O–H bonds (2.26 Å, 168°) and an intramolecular C–H···O interaction (2.53 Å) between the CH_3 group and the ketone O atom. On the whole, the crystal is largely stabilised by close-packing. By lying on the 2-fold axis special position, the conformationally flexible molecules are able to assume a more symmetrical shape ($C2/c$, $Z = 4$). Crystal packing in the CF_3 derivative **18b** is expected to be different because the (Me)C–H···O bond that supports the closed conformation in **18a** is now replaced with CF_3. **18b** shows a more normal packing in that the hydroxyl and ketone groups are fully utilised in hydrogen bonding. While the electron-withdrawing bis(trifluoromethyl) group activates the OH as a donor, the basicity of the O atom is simultaneously reduced so much that it is no longer a viable acceptor. As a result, an unsymmetrical motif of intramolecular O–H···O=C hydrogen bonds with a bifurcated acceptor is formed, and this extends into a network through intermolecular O–H···O bonds with inversion-related molecules. However, none of the O–H···O bonds are particularly strong (>1.9 Å). Some stabilisation could accrue from C–H···F interactions (<2.7 Å). Incidentally, the absence of short O–H···F–C contacts in **17b**, **18b** and **19b**, molecules with OH and CF_3 groups, is not surprising because organic fluorine does not generally accept hydrogen bonds.[31]

A comparison of **5** (category A) with **17** and **18** (category B) suggests that while the presence of an OH functionality is a necessary requirement for CH_3/CF_3 isomorphism, it is by no means a sufficient condition. The important requisite for CH_3/CF_3 isostructurality is not the mere presence of strong hydrogen bonding groups but, more significantly, the recurrence of robust supramolecular synthons,[22] such as **I**–**III** (Fig. 3). The classification of ribonolactone **19a**, a polyhydroxy carbohydrate, and its trifluoromethyl derivative **19b** (YODSIT, TEXSEU) in category B confirms this hypothesis.

Categories C and D

Molecules in category C, such as **20**–**22**, are not very relevant from a drug design viewpoint because a large number of C–H groups are replaced by C–F. So the packing is naturally expected to change but for reasons that could be different in each case. These include the lack of opportunity for herring-bone packing or C–H···O interactions, or a change in molecular conformation due to perfluorination. Whilst exhaustive fluorination is not within the scope of the present discussion, it should be mentioned that phenyl–perfluorophenyl stacking involving donor–acceptor π–π interactions has been recently identified as a new supramolecular synthon in crystal design.[3]

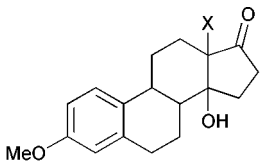
Compound pairs in category D show very different crystal packing. The case of *N*,*N*-dimethyl and *N*,*N*-diethyl coumarins **23** and **24** has been contrasted with anthracene **10** (category A) earlier in this paper. It is difficult to ascribe specific chemical/geometric effects to explain packing differences in these molecules (**23**–**26**) because no common pattern of intermolecular interactions could be gleaned after an examination of their crystal structures. One or more of the factors—a change in the conformation of the CF_3 derivative, concerted effect of numerous weak interactions (C–H···O, C–H···F, π–π), molecular conformation and supramolecular recognition acting jointly—could be responsible for differences in category D structures. Thus, when a molecule has neither strong hydrogen bond donor–acceptor groups nor a large/rigid carbon skeleton, then such pairs of CH_3/CF_3 crystals adopt divergent aggregation motifs.

To summarise, of the 50 CH_3/CF_3 crystal pairs examined, the number of hits in categories A, B, C and D are 24, 6, 6 and 14. Some of the hits in the miscellaneous category D are what one would not normally classify as 'organic' molecules: $[X–BF_3^-]$ $[K^+]$, $[Me_3N^+–X]$ $[I^-]$, $[X–S^+Cl_2]$ $[AsF_6^-]$ ($X = CH_3$, CF_3).§ The existence of polymorphs in some structures (EBYBUA, VEJCIW and ZZZMUC; entries 42, 48, 50 in Table 1) does not detract from the main theme of this paper.¶

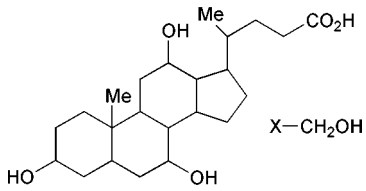
CH_3/CF_3 exchange mimicry

A survey of the CSD shows that the replacement of CH_3 with CF_3 will lead to similar/identical crystal packing if one of the following two conditions is fulfilled. (1) The CH_3 structure is stabilised by strong hydrogen bond, multi-point recognition supramolecular synthons, such as **I**–**III**. A robust synthon is able to tolerate changes in the substitution of small groups without disturbing the overall packing in the CF_3 crystal because of the predominance of the enthalpic factor. (2) The molecule is large ($>C_{15}$) with a fused aromatic or polycyclic carbon skeleton. The contribution from van der Waals interactions and/or shape-induced close-packing arguments during the self-assembly of hydrophobic molecules leads to identical arrays in such CH_3/CF_3 crystals, such as **11**, **12**, **14**. In conclusion, CH_3/CF_3 isostructurality may be expected when either robust synthons are present (dominance of chemical recognition) or for large, rigid molecules (dominance of geometric recognition). Multiple $CH_3 \rightarrow CF_3$ replacement is not within the scope of this model.

The relevance of CH_3/CF_3 structural mimicry to medicinal chemistry is illustrated by two examples from category A. Isostructurality of estrone **27a**, a cardiovascular agent, and its CF_3 analogue **27b** (WEGSAC, VOVVAD; $P2_12_12_1$, $Pca2_1$) could have been anticipated because the molecule is large, rigid and polycyclic with O–H···O=C hydrogen bonding in the crystal. Clathrate crystals with CH_3/CF_3 exchange in the solvent component could be used as models to study substrate–receptor and fluoro-inhibitor–receptor binding. Crystal structures of the ethanol and trifluoroethanol solvates of cholic acid, **28a,b** have been solved accurately by X-ray diffraction (CHOLET, ZIPZIH).[32] Both guest alcohols are accommodated inside the cavity of cholic acid in a similar manner. The intricate O–H···O hydrogen bond networks between the host–host (receptor–receptor) and host–guest (receptor–ligand) molecules are identical in these inclusion complexes. These clathrate crystals are isostructural (both $P2_12_12_1$, $\Pi = 0.007$).[20] Observations such as these validate the use structural mimicry through H/F exchange as a viable strategy in the design of flustrates (*flu*orine-containing sub*strates*).[13]



27 (WEGSAC, VOVVAD)



28 (CHOLET, ZIPZIH)

a: X = CH_3
b: X = CF_3

§ However, these are classified as 'organic' in the CSD: BIZHUN, KTFMFB; QQQCVG, SINGUR; VEMJUS, DEHWIW.
¶ One referee is thanked for suggesting this point.

Conclusions

The effect of CH_3 to CF_3 substitution on crystal packing has been systematically studied using the database approach. While there have been isolated cases of both CH_3 and CF_3 crystals being analysed by the same authors,[33–35] this exhaustive study covers the 50 such pairs documented in the CSD. Of these 50 cases, about half (24) belong to category A wherein replacement of CH_3 with CF_3 does not change the crystal structure. This is remarkable given that the retrieved hits are a random collection of 100 or so X-ray crystal structures that were studied with considerations other than crystal engineering in mind. A model is proposed that predicts whether the trifluoromethyl crystal packing is expected to be similar or different compared to the methyl compound, based on an examination of the molecular structure and the constituent supramolecular synthons. Given that fluorinated analogues are more difficult to synthesise than the parent molecules, an idea of the F-packing by an analysis of the H-structure will cut down unnecessary time spent on laborious synthesis. This predictive model has obvious applications in crystal engineering, drug design and materials chemistry research.

Exchanges of $CH \rightarrow CF$ and $CH_2 \rightarrow CF_2$ are far more ubiquitous when compared with $CH_3 \rightarrow CF_3$ substitution. However, a proper and complete comparison of such crystal pairs is not a trivial issue. The exchange of CH with CF on a methylene or methyl group reduces the symmetry of the molecule while substitution on a phenyl ring will lead to positional isomers. In turn, both these effects could result in further crystal structure changes. In summary, crystal packing changes are more difficult to dissect and understand even though the size perturbations in $CH \rightarrow CF$ and $CH_2 \rightarrow CF_2$ are not as severe as $CH_3 \rightarrow CF_3$. Studies are currently ongoing on these and related issues.

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