CrystEngComm

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Journal:	*CrystEngComm*
Manuscript ID:	CE-ART-02-2014-000319.R2
Article Type:	Paper
Date Submitted by the Author:	21-Mar-2014
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Competition and Cooperation: Hydrogen and Halogen Bonding in Co-Crystals Involving 4-Iodotetrafluorobenzoic Acid, 4-Iodotetrafluorophenol and 4-Bromotetrafluorophenol

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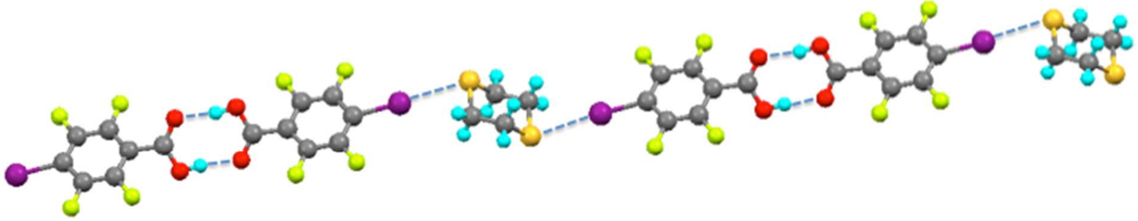
Abstract:

Co-crystallisation of 4-iodotetrafluorobenzoic acid with 1,4-dithiane leads to a polymer in which the benzoic acid dimer remains intact, forming halogen bonds with the dithiane, showing that considering both pK_b and the iodine basicity scale (pK_{BI2}) can direct the structure formed. Crystallisation of 4-halotetrafluorophenols with 1,4-dithiane or tetrahydrothiophene was always accompanied by oxidation to the *S*-oxide or *S,S'*-dioxide and in two cases the co-crystals formed involved hydrogen bonding (4-bromotetrafluorophenol) and both hydrogen and halogen bonding (4-iodotetrafluorophenol). Co-crystallisation of 4-iodotetrafluorophenol with 4,4'-bipyridine leads to a linear polymer with both hydrogen and halogen bonding.

Graphic Abstract:

Careful choice of components can lead to the favouring of halogen over hydrogen bonding.



Introduction

In the construction of supramolecular systems, it is beneficial to be able to predict the resulting structure and, in the case of building blocks with multiple donor and acceptor sites, it is necessary to consider a notional hierarchy of interactions. Halogen bonding[1] is now becoming a well-established interaction used in supramolecular chemistry that has binding energies ranging from as little as 5 kJ mol^{-1} to as much as 180 kJ mol^{-1} when interactions with ions are involved, at which level it is easily comparable to hydrogen bonding. It is therefore necessary to understand the possibilities for competition and cooperation in systems where both halogen and hydrogen bonding are possible.

Instinctively, it would be expected that where there is simple competition then hydrogen bond formation would be preferred over the generally weaker and more labile halogen bond. For example, in our own studies of 2 : 1 and 1 : 1 co-crystals formed between 4-alkoxystilbazoles and 4-iodotetrafluorophenol, the 1 : 1 co-crystals showed N···H hydrogen bonding, although the strongly electrophilic nature of the iodine led to formation of intramolecular I···O contacts with the oxygen of the alkoxy chain to give a polymeric arrangement.[2]

Examples exist of situations where halogen bonding is preferred over hydrogen bonding, as described by Corradi *et al*.[3], who showed in a competition experiment that using 1,2-di(4-pyridyl)ethane, co-crystals formed with the very strong halogen bond donor, 1,4-diiodotetrafluorobenzene rather than with 1,4-hydroquinone, which is perhaps not so strong a hydrogen bond donor. Indeed, some of the shortest pyridine···I halogen bonds have been found using 1,4-diiodotetrafluorobenzene.[4] However, turning the situation around, there are several examples where supramolecular structures have been formed using complementary and cooperative hydrogen and halogen bonding. For example, halogen and hydrogen bonding observed cooperatively in the crystal structures of 4-iodopyridine with 4-nitrobenzoic acid and 3,5-dinitrobenzoic acid with hydrogen bonding between the pyridyl nitrogen and the carboxylic acid being favoured leading to bifurcated halogen bonding between the iodine and nitro group.[5]

However, by far the most extensive study in this area has been conducted by Aakeröy and co-workers[6-10] and some highlights are now described (Fig. 1). Thus, halogen and hydrogen bonding have been combined in the formation of co-crystals between *iso*-nicotinamide and 1,4-diiodotetrafluorobenzene.[6] The *iso*-nicotinamide exists as a hydrogen-bonded dimer through the amide group and the pyridyl nitrogen forms a halogen bond with an iodine atom of the halogen bond donor. The amide group favours hydrogen bonding since it features a donor and an acceptor. Similarly, co-crystallisation of carboxylic acids with pyridine/aminopyrimidine synthons showed that the carboxylic acid binds preferentially to the aminopyrimidine site over the pyridyl site unless a sufficiently electrophilic halogen is present in which case a halogen bond is formed to the pyridyl nitrogen.[7] 2-Aminopyrazine also has two potential sites that can accept hydrogen and halogen bonds and when co-crystallised with 1,4-diiodotetrafluorobenzene, it is found to form a dimer with N···H–N hydrogen bonds leaving the single point pyrazine nitrogen to form a halogen bond with the iodine atom of the halogen bond donor.[8]

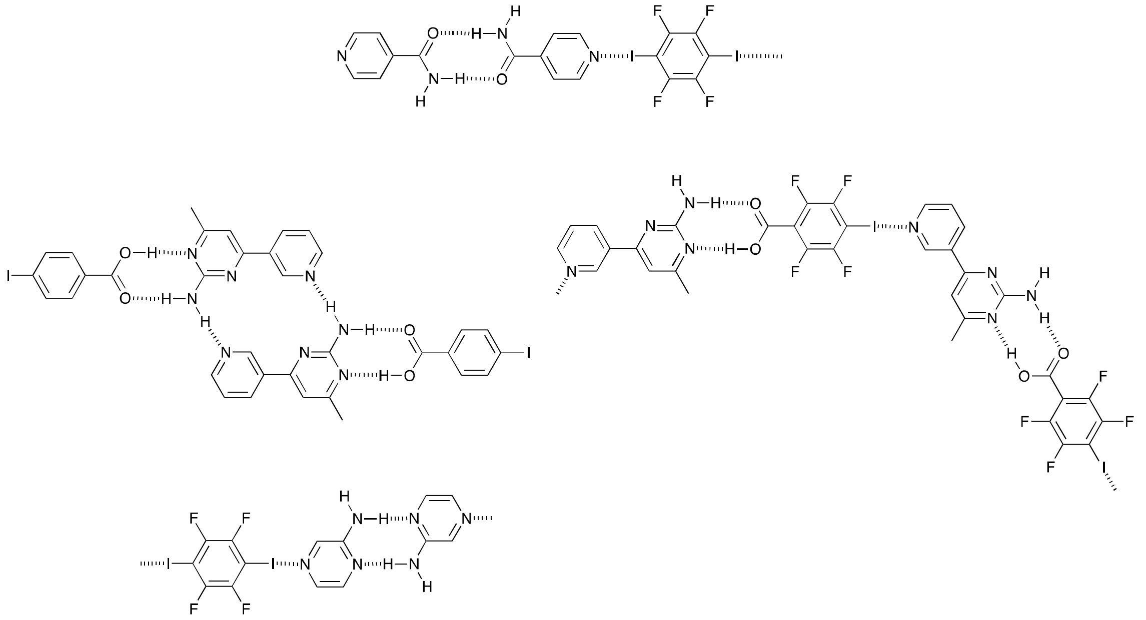


Figure 1 Hydrogen and halogen bonding motifs described by Aakeröy and co-workers.[6-10]

4-Halo-2,3,5,6-tetrafluorobenzoic acids are useful supramolecular building blocks since they feature both a halogen bond donor, a hydrogen bond donor and a halogen/hydrogen bond acceptor. Co-crystallisation of these benzoic acids with aminopyrazines leads to the formation of a 1-dimensional chain with two hydrogen bonds formed between the carboxyl group and the amino group and halogen bonds between the pyrazyl nitrogen and the halogen.[9] Bromination of the base can reduce the basicity of the nitrogen atoms and prevent deprotonation of the carboxylic acid, as observed in the crystal structure with 2-aminopyrazine.

Co-crystallisations between 4-halotetrafluorobenzoic acids, 4-halotetrafluorophenols and 4-halotetrafluoroaldoximes, which all have hydrogen and halogen bond donors, and 3,3'-azobipyridine and 4,4'-azobipyridine were set up to investigate the competition between hydrogen and halogen bonding to the pyridyl nitrogen atoms.[10] In crystal structures with 4,4'-azopyridine, where the pyridyl nitrogen atoms are in a co-linear arrangement, halogen and hydrogen bonding were found to be equally favoured with one interaction at each nitrogen. The exception to this was the structure with 4-bromotetrafluoroaldoximes, where hydrogen bonding was preferential. With the exception of 4-iodotetrafluoroaldoximes, crystal structures with 3,3'-azopyridine, where the pyridyl nitrogen atoms are antiparallel, hydrogen bonding was favoured over halogen bonding.

In order to further explore the cooperativity between halogen and hydrogen bonding, the crystal structures of 4-iodo-2,3,5,6-tetrafluorobenzoic acid, 4-iodotetrafluorophenol or 4-bromotetrafluorophenol with a range of Lewis bases, including weak sulfur bases, have been solved.

Crystal Structure Determinations

Co-crystals/salts were obtained (Fig. 2) as described in the experimental section and the key structural parameters are collected in Table 1.

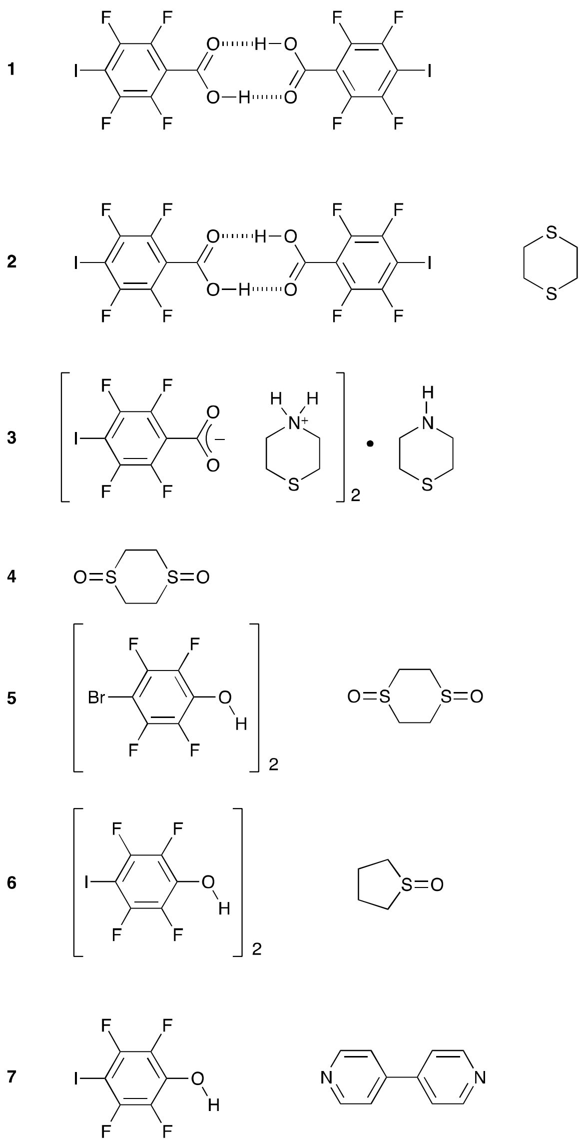


Figure 2 Co-crystals discussed in this paper.

*4-Iodotetrafluorobenzoic Acid (**1**)*

4-Iodobenzoic acid crystallised as expected as a hydrogen-bonded dimer (Fig. 3a), with two dimers in the unit cell. The two phenyl rings in each dimer are close to co-planar (inter-plane angles of 0.7° and 1.13°) while the carboxylate groups make angles to the phenyl rings of 12.3(8)° and –34.8(8)°, as seen clearly in an end-on view (Fig. 3b); this twist is likely due to the steric effect of the fluorines *ortho* to the carboxylate function (Fig. 3c). The oxygen···oxygen separation in the dimer is about 2.65 Å.

Table 1 Crystallographic parameters for the new structures

	1	**2**	**3**	**4**
CCDC Reference No.	985842	985843	985844	985845
Empirical formula	$C_7HF_4IO_2$	$C_9H_5F_4IO_2S$	$C_{11}H_{10}F_4INOS$	$C_4H_8O_2S_2$
Formula weight / g mol^{-1}	319.98	380.09	949.50	152.22
T / K	110.00(10)	110.00(10)	110.00(10)	110.00(10)
Crystal system	monoclinic	Triclinic	Triclinic	monoclinic
Space group	$P2_1$	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
Unit cell dimensions /Å	a = 6.7596(2)	a = 6.2546(4)	a = 5.7209(7)	a = 6.2950(3)
	b = 31.6474(8)	b = 7.8761(4)	b = 10.3273(13)	b = 6.3948(5)
	c = 7.9922(3)	c = 11.5781(6)	c = 14.4539(17)	c = 8.090(3)
α / °	90	78.743(5)	107.044(11)	90.00
β / °	108.548(3)	75.347(5)	99.741(10)	104.161(13)
γ / °	90	83.455(5)	92.149(10)	90.00
Volume / $Å^3$	1620.92(9)	539.94(5)	801.23(17)	315.78(11)
Z	8	2	1	2
ρ_{calc} / Mg m^{-3}	2.6222	2.338	1.968	1.601
Absorption coefficient / mm^{-1}	3.989	3.200	2.243	0.747
F(000)	1181.7	360	464	160.0
Crystal size / mm^3	0.266 × 0.1624 × 0.0939	0.22 × 0.17 × 0.11	0.20 × 0.06 × 0.02	0.294 × 0.2065 × 0.1504
θ range for data collection	3.98 to 30.08°	2.94 to 30.01°	3.00 to 29.77°	3.69 to 31.88°
Index ranges	$-8 \le h \le 9$, $-44 \le k \le 44$, $-11 \le l \le 10$	$-8 \le h \le 8$, $-11 \le k \le 11$, $-16 \le l \le 16$	$-6 \le h \le 7$, $-12 \le k \le 13$, $-19 \le l \le 10$	$-8 \le h \le 9$, $-9 \le k \le 8$, $-9 \le l \le 11$
Reflections collected	15874	6552	6397	1632
Independent reflections	8789 [R(int) = 0.0206]	6552 [$R_{(int)}$ = 0.000]	4026 [$R_{(int)}$ = 0.0311]	973 [R(int) = 0.0181]
Completeness (%) to (θ)	99.10 (30.01)	?	99.01% (27.50°)	97.52 (30.01)
Data / restraints / parameters	8789/144/517	6552 / 0 / 159	4026 / 14 / 211	973/0/37
Goodness-of-fit on F^2	1.046	1.097	1.066	1.139
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0341, wR_2 = 0.0808	R_1 = 0.0346, wR_2 = 0.1000	R_1 = 0.0494, wR_2 = 0.1024	R_1 = 0.0292, wR_2 = 0.0759
R indices (all data)	R_1 = 0.0359, wR_2 = 0.0848	R_1 = 0.0383, wR_2 = 0.1025	R_1 = 0.0695, wR_2 = 0.1123	R_1 = 0.0337, wR_2 = 0.0827
Largest diff. peak and hole	0.98/–1.50	1.066/–0.679	3.307/–1.378	0.35/–0.37

	5	**6**	**7**
CCDC Reference No.	985846	985847	985848
Empirical formula	$C_{16}H_{10}Br_2F_8O_4S_2$	$C_{10}H_9F_4OIS$	$C_{16}H_9F_4IN_2O$
Formula weight / g mol^{-1}	642.18	688.10	448.15
T / K	110.05(10)	110.00(10)	110.00(10)
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$
Unit cell dimensions /Å	a = 5.89886(16)	a = 9.1682(14)	a = 16.0299(11)
	b = 21.0112(5)	b = 9.4618(16)	b = 4.0059(2)
	c = 16.1143(4)	c = 12.3168(16)	c = 25.154(3)
α / °	90.00	75.183(14)	90.00
β / °	95.557(3)	74.084(13)	106.546(9)
γ / °	90.00	79.202(14)	90.00
Volume / Å^3	1987.85(9)	985.6(3)	1548.4(2)
Z	4	2	4
ρ_{calc} / Mg m^{-3}	2.146	2.319	1.922
Absorption coefficient / mm^{-1}	4.386	3.387	2.118
F(000)	1248.0	648	864.0
Crystal size / mm^3	0.3096 × 0.0734 × 0.0333	0.14 × 0.09 × 0.06	0.2442 × 0.0622 × 0.0253
θ range for data collection	3.17 to 27.95°	2.93 to 32.08°	3.26 to 25.09°
Index ranges	$-7 \le h \le 6$, $-27 \le k \le 25$, $-21 \le l \le 21$	$-12 \le h \le 12$, $-14 \le k \le 14$, $-12 \le l \le 18$	$-19 \le h \le 16$, $-4 \le k \le 4$, $-25 \le l \le 30$
Reflections collected	11592	10138	4832
Independent reflections	4103 [R_{int} = 0.0290]	6120 [$R_{(int)}$ = 0.0239]	2738[R(int) = 0.0391]
Completeness (%) to (θ)	99.56% (25.01°)	99.20% (30.01°)	99.28 (25.04)
Data / restraints / parameters	4103 / 0 / 297	6120 / 0 / 279	2738/12/221
Goodness-of-fit on F^2	1.032	1.044	1.325
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0292, wR_2 = 0.0612	R_1 = 0.0254, wR_2 = 0.0517	R_1 = 0.0651, wR_2 = 0.1239
R indices (all data)	R_1 = 0.0395, wR_2 = 0.0651	R_1 = 0.0317, wR_2 = 0.0556	R_1 = 0.0724, wR_2 = 0.1267
Largest diff. peak / hole	0.53/ –0.39	0.871/ –0.733	1.65/–1.95

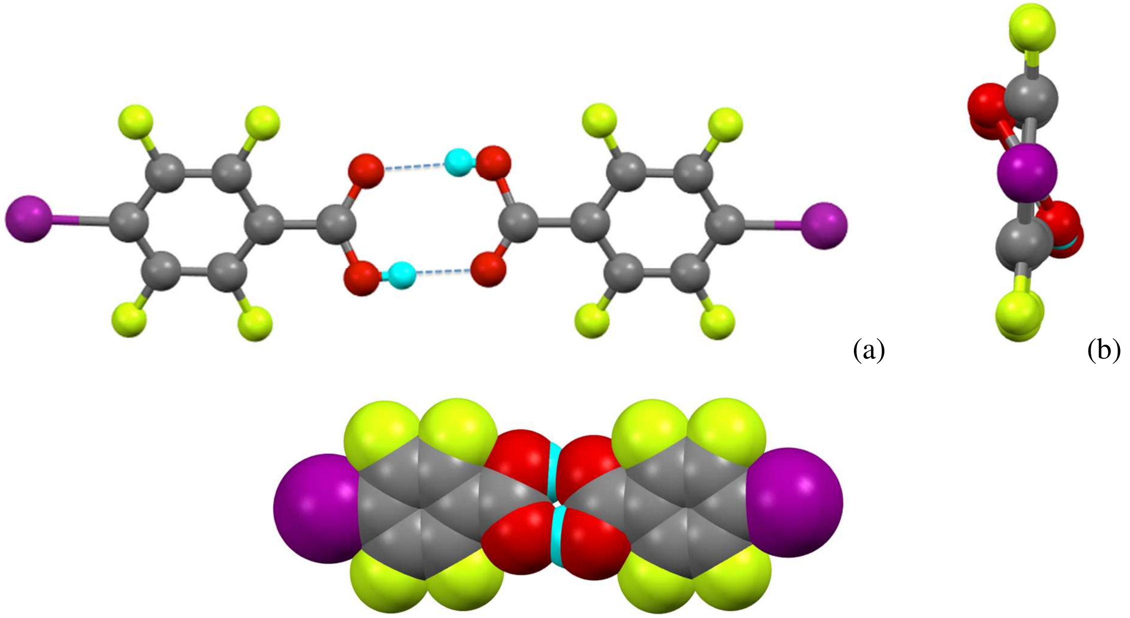


Figure 3 Molecular structure of the dimer of 4-iodotetrafluorobenzoic acid (a) seen from above and (b) in an end-on view, (c) space-filling representation of the 4-iodotetrafluorobenzoic acid dimer.

The dimers propagate through the structure in a slipped-stacking (staircase) arrangement (Fig. 4a) and the terminal iodines alternate their positions slightly through the plane as shown in Fig. 4a. The iodines are then close to the iodines of dimers in another such arrangement (Fig. 4b) with I···I separations of 3.9502(5) Å (black lines, less than the sum of the van der Waals radii) and 4.1349(5) Å (red lines, greater than the sum of the van der Waals radii) depending on the position of alternation. With C–I···I angles at 166.5 and 97.4° for those where there is some formal interaction (black lines), these interactions are geometrically Type II but are too long to be attractive in nature.

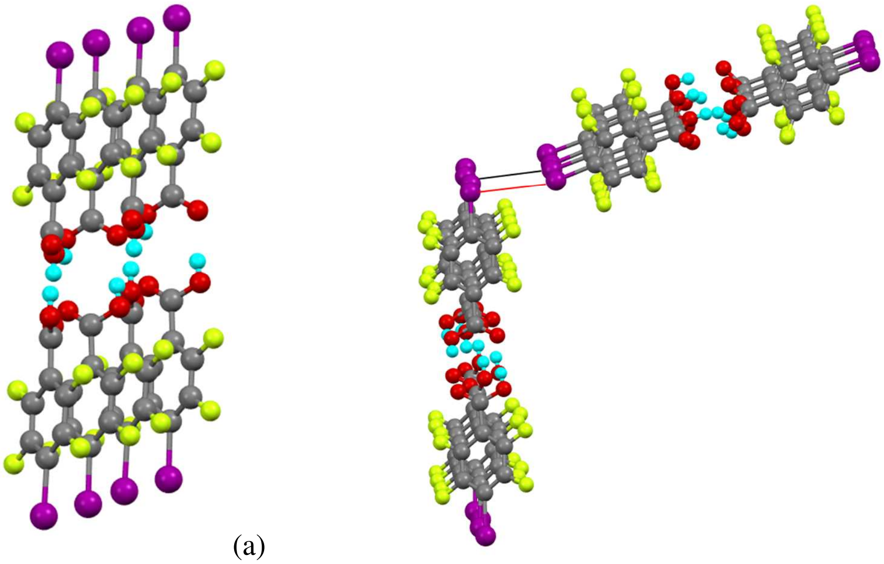


Figure 4 Packing of **1** in the solid state (a) showing the slipped-stack (staircase) and (b) showing the shorter (black line) and longer (red line) I···I separations as two staircase arrangements meet. Hydrogen bonds omitted for clarity.

*Co-crystal between 4-Iodotetrafluorobenzoic Acid and 1,4-Dithiane (**2**)*

The complex is found as a polymer, which contains the dimer of 4-iodotetrafluorobenzoic acid with each iodine being bound to one sulfur of a dithiane; the polymer propagates as the other sulfur forms a halogen bond to the iodine of another benzoic acid dimer as illustrated in Fig. 5. The halogen bond length (all are symmetry equivalent) is 3.2644(7) Å representing 86.4% of the sum of the van der Waals radii of the two elements, while the C–I···S angle is 171.01(7)°.

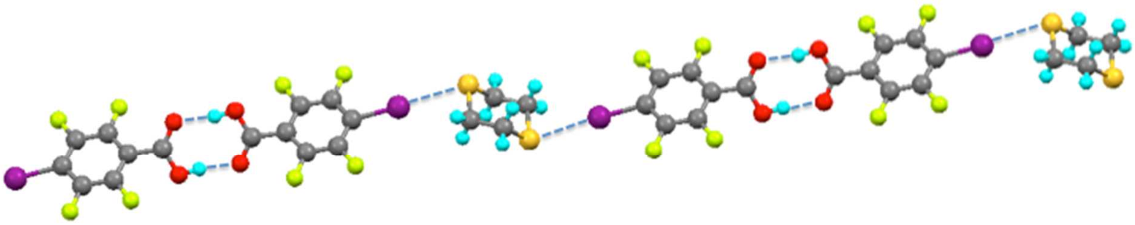


Figure 5 Structure of the polymeric unit of **2**.

The structure in a 'staircase' manner along the *a*-axis and an off-axis view is shown as Fig. 6a. The only intermolecular interactions found in this direction are between the carboxylate carbons and fluorines from neighbouring molecules, whose lengths are 3.011(3) and 3.046(3) Å representing 95% and 96%, respectively, of the sum of the van der Waals radii; the respective C–F···C angles are 117.5(1)° and 137.0(2)°. Thus, each carboxylate carbon has one of these fluorines above the plane and the other below (Fig. 6b) and strictly the fluorines are involved in an electrostatically attractive interaction between δ^- fluorine and δ^+ carbon, but the extent to which these interactions are truly structure-directing is perhaps open to debate.

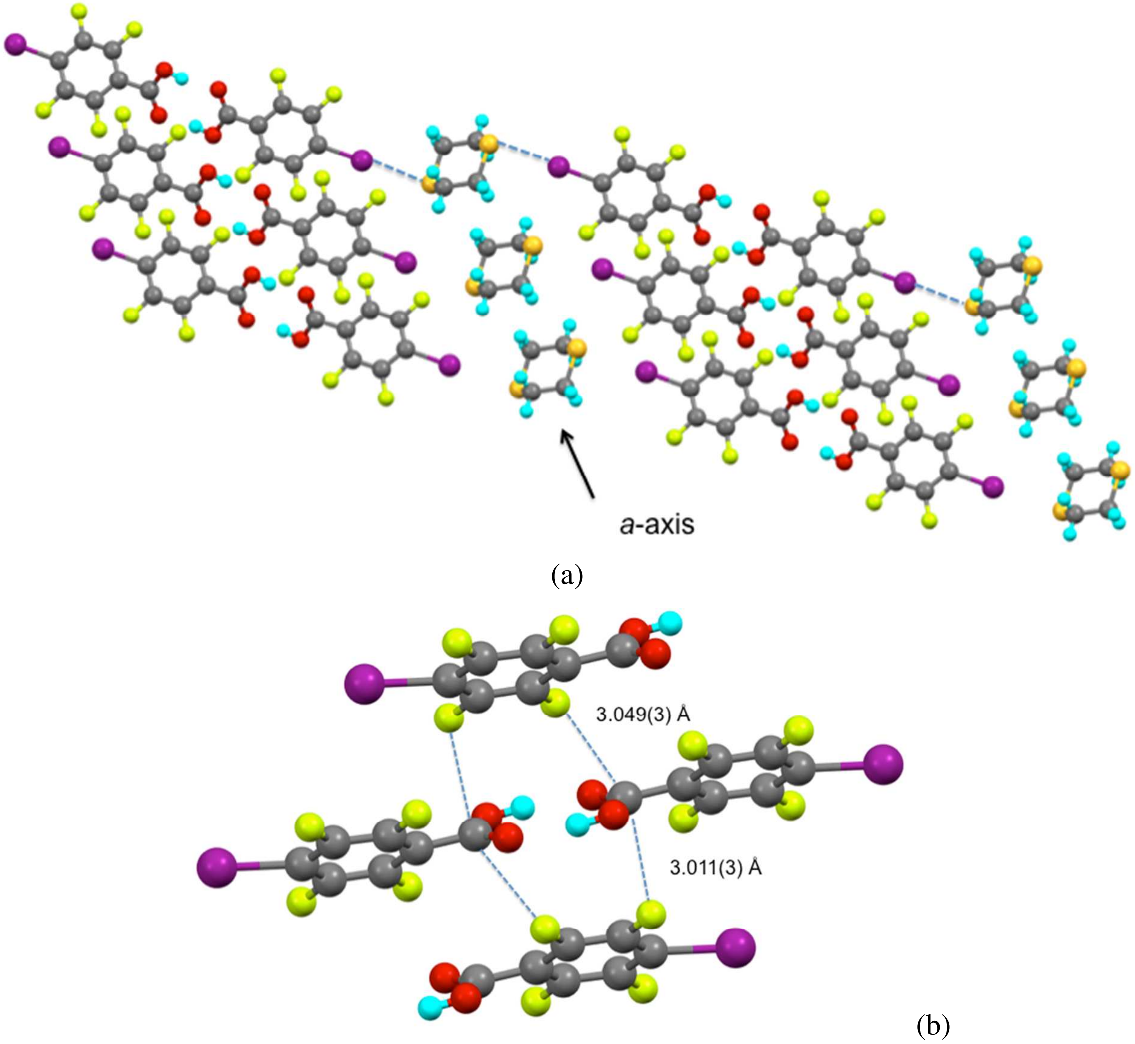


Figure 6 (a) Structure and packing of complex **2** with the direction of the *a*-axis shown (hydrogen-bonding interactions omitted), (b) **2** showing intermolecular interactions between the carboxylate carbon and neighbouring fluorine atoms.

The structure propagates in the *ab* plane as shown in Fig. 7 and the only contacts shorter than the sum of the respective van der Waals radii are the indicated F···F interactions at 2.809(2) Å and arise due to the close packing of the molecules.

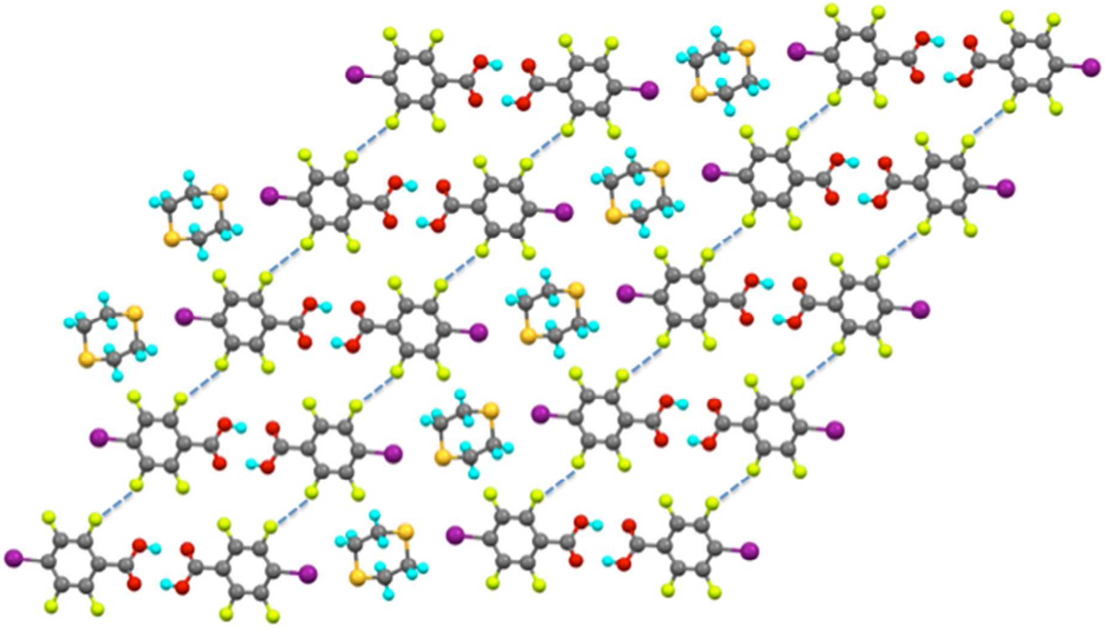


Figure 7 Structure and packing of co-crystal **2** in the *ab*-plane showing intermolecular F···F interactions (hydrogen- and halogen-bonding interactions omitted).

*Salt/Co-Crystal between 4-Iodotetrafluorobenzoic Acid and Thiomorpholine (**3**)*

The complex crystallises as $([C_4H_{10}NS][IC_6F_4COO])_2 \bullet C_4H_9NS$ – that is to say the molecular formula contains two equivalents of thiomorpholinium iodotetrafluorobenzoate, which co-crystallise with one equivalent of a neutral thiomorpholine. Within the structure, which is represented in Fig. 8a, the thiomorpholinium cations are not disordered, but the neutral thiomorpholine is because it sits on an inversion centre, so that while the carbons of the ring do not appear disordered, the S and N–H are indistinguishable (there is some disorder of the ring hydrogens). The iodotetrafluorobenzoic acid dimer breaks up on account of deprotonation by the thiomorpholinium nitrogen and the two carbonyl oxygens form hydrogen bonds – one to an N–H hydrogen that terminates the unit shown in Fig. 8b ($d_{(O\cdots H)}$ = 1.933(4) Å) and the other to a neighbouring N–H hydrogen ($d_{(O\cdots H)}$ = 1.800(4) Å), which acts to propagate the structure in the *a*-direction. The iodine at the other end of the ring forms a halogen bond to the neutral thiomorpholine and the formula unit is shown in Fig. 8a, while the propagation is shown in Fig. 8b, which shows both the hydrogen and halogen bonds ($d_{(\mathrm{I}\cdots\mathrm{S})}$ = 3.064(5) Å and $d_{(\mathrm{I}\cdots\mathrm{N})}$ = 3.37(2) Å, with the C–I···S angle = 170.3(2)° and the C–I···N angle = 172.5(3)°). The halogen bonds are found at 81% (I···S) and 95% (I···N) of the sum of the respective van der Waals distances. Note that there are no short contacts to the two sulfur atoms at the end of each formula unit.

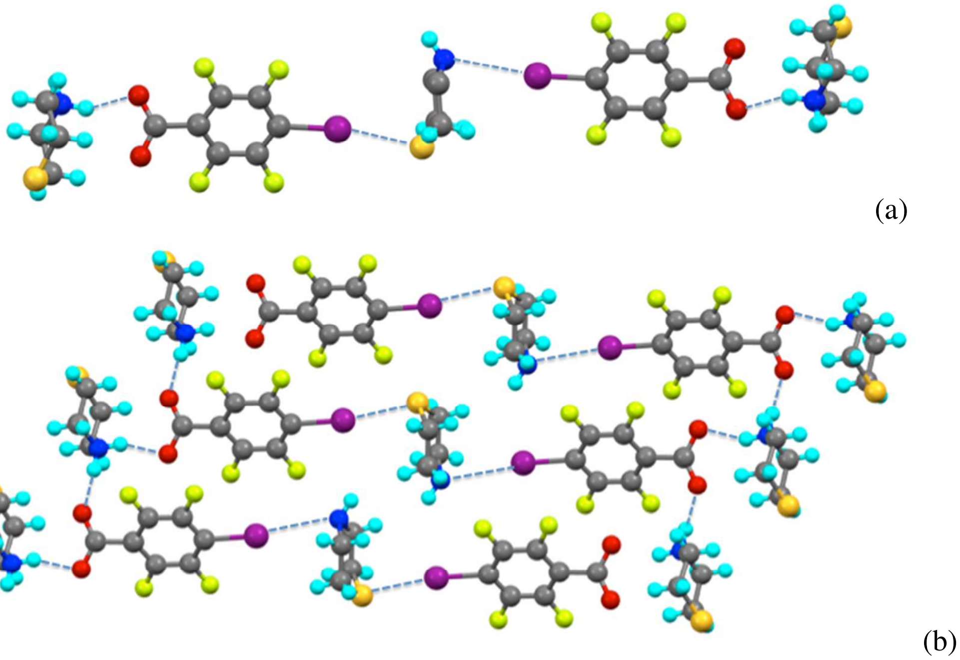


Figure 8 The structure of **3** showing (a) the formula unit and (b) propagation of the formula unit. Note that in (b), the distinction between S and N–H in the neutral thiomorpholine is an artefact of the program (Mercury[†]) used to create the figure.

*1,4-Dithiane-*S,S'*-dioxide (**4**)*

Using the much weaker acid, 4-iodotetrafluorophenol, in an attempt to form co-crystals with sulfur donors, colourless crystals were obtained that turned out to be of 1,4-dithiane-*S,S'*-dioxide. The six-membered ring formed a perfect chair conformation with an *anti* arrangement of the S=O bonds; the S=O bond length was 1.505(1) Å. The molecular structure

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[†] Mercury is available free of charge from: http://www.ccdc.cam.ac.uk/Solutions/CSDSystem/Pages/Mercury.aspx

is shown as Fig. 9. While the Cambridge database shows seven structural determinations of **4**, only one[11] reports the same space group and in this earlier determination, the S=O bond length is reported as 1.4764 Å.

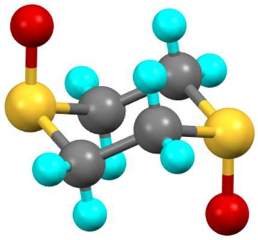

Figure 9 Molecular structure of **4**.

*Co-crystal between 4-Bromotetrafluorophenol and 1,4-Dithiane-*S,S'*-dioxide (**5**)*

Co-crystallisation of 4-bromotetrafluorophenol and 1,4-dithiane also led to the formation of the *S,S'*-dioxide, but this time two molar equivalents of 4-bromotetrafluorophenol were also found in the structure with the one phenolic hydrogen forming a hydrogen bond to an oxide oxygen at each end of the 1,4-dithiane with $d_{(\mathrm{H-O})}$ = 1.88(4) Å. The structure then extends into a sort of linear polymer by virtue of an intermolecular Br···F contact at 3.171(2) Å with a C–Br···F angle of 155.98(8)°, representing a shortening of *ca* 4% over the sum of the van der Waals radii (Fig. 10).

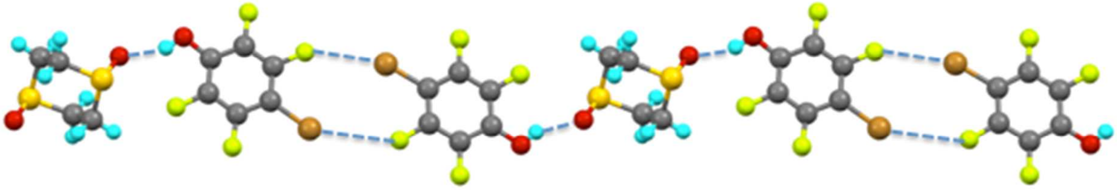

Figure 10 Polymeric arrangement in **5** showing the linking hydrogen bonds and Br···F interactions.

*Co-crystal between 4-Iodotetrafluorophenol and Thiophene-*S*-oxide (**6**)*

A similar co-crystallisation of 4-iodotetrafluorophenol with thiophene also led to oxidation to thiophene-*S*-oxide, but in this case the oxide co-crystallised with 4-iodotetrafluorophenol to give a crystal with a 2 : 1 ratio of phenol to oxide. The 2 : 1 ratio gives rise to a basic structural motif in which the oxygen of the thiophene-*S*-oxide forms hydrogen bonds to two phenol molecules in an unsymmetric fashion (Fig. 11). Thus, $d_{(\mathrm{H1–O3})}$ is 1.81(4) Å, while $d_{(\mathrm{H2–O3})}$ is 1.97(3) Å, with the two making an angle at O3 of 137(2)°. However, examination of other close contacts in the structure shows that both phenolic oxygen atoms (O1 and O2) are also halogen bonded, each to an iodine of another iodotetrafluorophenol (Fig. 11), with I···O separations of 3.079(2) Å (I2···O1) and 3.156(2) Å (I1···O2), halogen bond angles (C–I···O) of 172(4)° (I2) and 159(4)° (I1) and with H–O···I angles of 112(3)° at O1 and 104(3)° at O2.

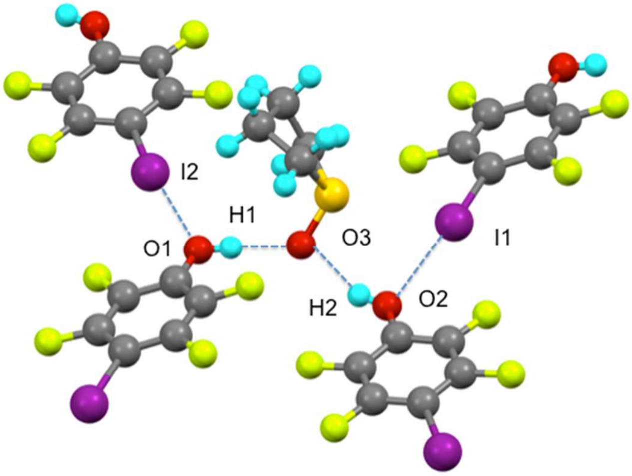

Figure 11 Molecular structure of **6** showing the two hydrogen bonds to the oxygen of the thiophene oxide. Atom numbering as in the cif file.

*Co-crystal Between 4-Iodotetrafluorophenol and 4,4'-Bipyridine (**7**)*

The crystal showed evidence of non-merohedral twinning but use of the diffraction software to resolve this as a two-component system gave a lower quality final structure (R_1 = 6.51%) than using a non-twinned model due to the predominance of overlapping reflections. The OH hydrogen was located by difference map and was allowed to refine.

A 1 : 1 co-crystal exists between the two species with the bipyridine forming a hydrogen bond at one end and a halogen bond at the other, leading to the formation of a linear polymer. Because in each polymeric chain, each bipyridine forms both hydrogen and halogen bonds, then the individual chains are formally polar (*i.e.* all hydrogen bonds in the same direction), but examination of the packing shows that alternate chains are arranged in the opposite fashion consistent with the centrosymmetric space group. Within the chains, the I···N halogen bond is 2.945(7) Å long (83.4% of the sum of the van der Waals radii), while the C–I···N angle is 168.1(3)°; the N···H distance is found at 1.8(1) Å with an O–H···N angle of 157(12)° (Fig. 12). Noteworthy also is a bowing of the iodophenol ring so that the C_{ipso}–C_{ipso}'–I and C_{ipso}'–C_{ipso}–OH angles are found at 174.75° and 176.64°, respectively. There is no apparent driving force for these distortions. A almost identical arrangement was reported recently by Aakeröy *et al.*[10] where the nitrogen base was 4,4'-diazobipyridine with *d*(I···N) = 2.960(3) Å and the C–I···N angle = 166.0(1)°. Curiously, the same study reported that when 4-iodotetrafluorophenol was co-crystallised with 3,3'-diazobipyridine, the phenolic oxygen was bound covalently to its hydrogen while forming an I···O halogen bond with a neighbouring iodine as found also in **6**.

Interestingly, there is a significant dissymmetry in the approach of the bipyridine to the iodophenol through both the halogen and the hydrogen bond. Thus, for example, an intramolecular F···H contact (2.556(5) Å) leads to the formation of a hydrogen-bonded ring-like structure analogous to those reported in the crystal structures of 4-alkoxystilbazoles with fluorophenols that have a fluorine *ortho* to the OH function.[12] Similarly, the distances between the iodine the two carbons *ortho* to the pyridine nitrogen are 3.505(8) Å and 4.05(1) Å mirroring the dissymmetry in halogen bonding noted by Ho[13] and by Präsang *et al.*[14]

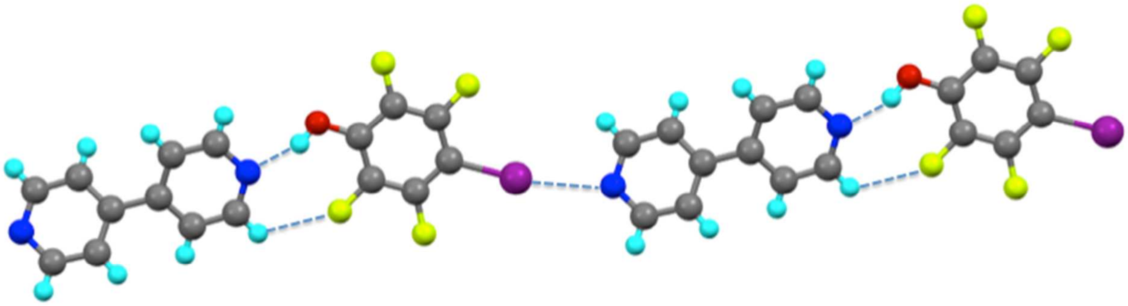

Figure 12 Polymeric arrangement of the 4-iodotetrafluorophenol : 4,4'-bipyridine co-crystal showing hydrogen and halogen bonds and the intermolecular H···F contact.

There are no short inter-chain interactions and viewed down the *c*-axis (Fig. 13a), the packing shows two series of polymer chains whose main axes (estimated from the planes of the aromatic phenol ring) make an angle of 61.13°; Fig. 13b is the same shot viewed down the *b*-axis.

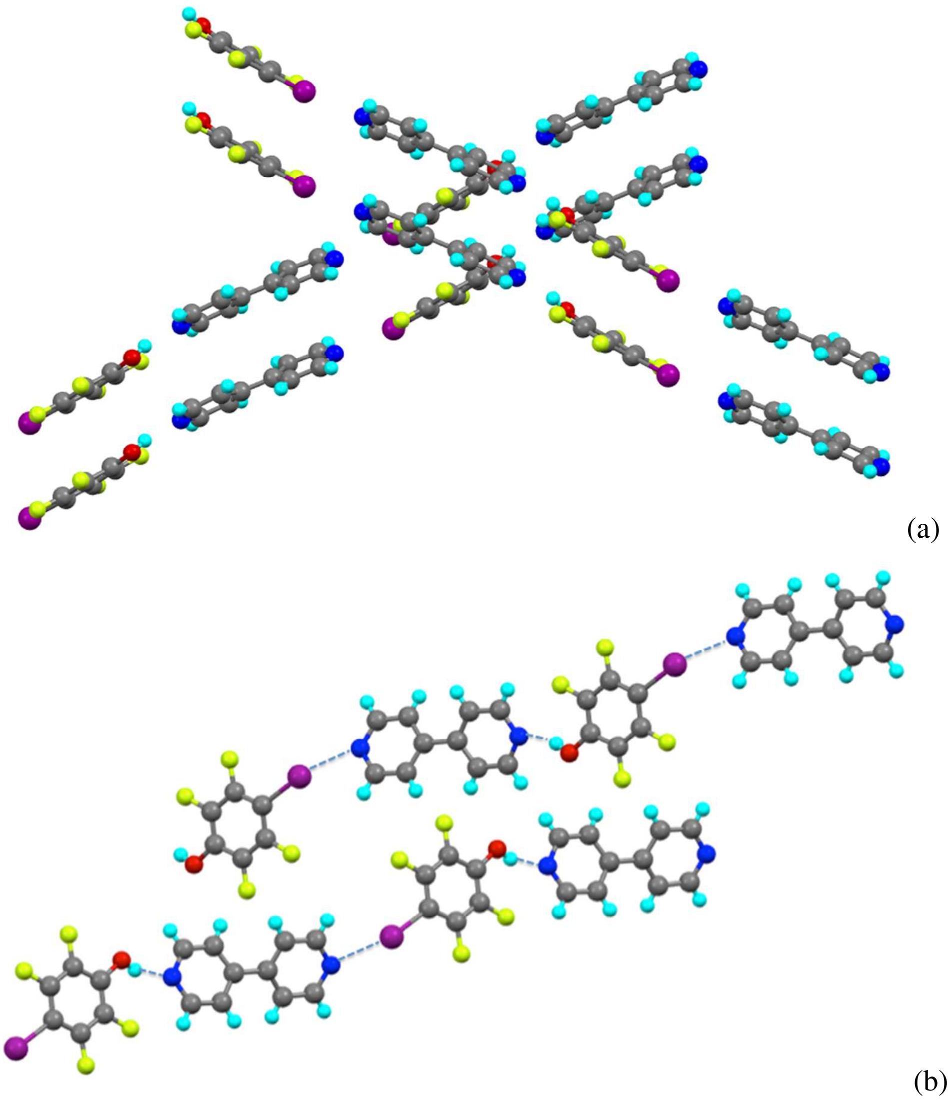

Figure 13 View of the packing in the structure of **7** (a) down the *c*-axis and (b) down the *b*-axis.

Discussion

As noted in the introduction, there has been interest both in the competition between hydrogen and halogen bonding and their cooperative co-existence, which extends from work on small-molecule co-crystals and salts, through to the proposals of orthogonality of hydrogen and halogen bonding made by Voth *et al.* following their analysis of non-bonded contacts to amide oxygens in peptide chains.[15]

In this regard, Aakeröy has shown consistently that where there is a good hydrogen bond acceptor, then the dimeric nature of 4-iodotetrafluorobenzoic acid will be disrupted to allow the carboxylate function to participate in hydrogen bonding; the iodine may then go on to form a halogen bond.[6-10] In this work, 4-iodotetrafluorobenzoic acid was mixed with a rather weak hydrogen-bond acceptor in 1,4-dithiane, which has allowed the acid to maintain its dimeric arrangement while the iodine forms halogen bonds to the sulfur atoms of the heterocycle leading to a polymeric structure. Iodine···sulfur halogen bonds are well documented in the literature and indeed there are examples from Blake *et al.* of co-crystals formed between I_2 or IBr and various thioether crowns,[16,17] although these were not labelled halogen bonds at that time. In these co-crystals with molecular iodine, S···I distances vary from the rather short (*e.g.* 2.747 Å – 75% of the sum of the van der Waals radii – in 18[ane]S_6 • 2 I_2) to the appreciably longer (3.22 Å – 85% of the sum of the van der Waals radii in 12[ane]S_4).[16] However, in co-crystals with, for example, dioodoacetylene or 1,4-diiodotetrafluorobenzene with 1,4-dithiane, I···S distances are typically at the longer end of this range at 3.268 Å[18] and 3.384 Å,[19] respectively. At 3.06 Å and 81% of the sum of the van der Waals radii, the I···S separation in **3** is slightly shorter than some of these examples, whereas in **2** ($d_{(I\cdots S)}$ = 3.26 Å) the distance is consistent with these other data.

Then, consistent with Aakeröy's work, replacing 1,4-dithiane with thiomorpholine, which contains a good hydrogen bond acceptor (secondary N–H), breaks up the benzoic acid dimer depronating the acid and forming a thiomorpholinium salt of the iodobenzoate, with the electrophilic iodine of two such salts forming a halogen bond to both the sulfur and the nitrogen of a neutral (disordered) thiomorpholine that also co-crystallises in the lattice. Thus, it seems that under most circumstances, hydrogen bonding will prevail where it can, but if the odds are stacked a little, for example in our use of 1,4-dithiane (**2**) or in the work of Corradi *et al.*,[3] then halogen bonding can be seen in preference.

Considering now the weaker hydrogen bond donors 4-iodotetrafluorophenol and 4-bromotetrafluorophenol, a slightly surprising observation was that co-crystallisation with 1,4-

dithiane or with thiophene led to the related *S,S'*-dioxide (**4**, **5**) or *S*-oxide (**6**), respectively. Further investigation of this oxidation is beyond the scope of this study and the driving force is not evident as conditions for crystallisation were no different to those employed in the rest of this work. However, of interest here was that thiophene-*S*-oxide co-crystallised with two molar equivalents of 4-iodotetrafluorophenol (**6**). Here, the phenolic oxygen bound covalently to a hydrogen and, in addition, formed a hydrogen bond to the oxide oxygen *and* a halogen bond to the iodine of a neighbouring iodotetrafluorophenol. This can be thought of as an example of the orthogonal halogen and hydrogen bonding proposed by Voth *et al.*[15] on the basis of an exploration of the PDB and exemplified in small-molecule salts and co-crystals by Takemura *et al.*[20]

It is then of interest to interpret these results in terms of the iodine basicity scale reported by Laurence *et al.*[21] The pK_{BI2} and pK_{BHX} scales they report are defined in such a way that larger values correspond to stronger halogen and hydrogen bond acceptors, respectively.[21,22] Some pK_{BI2} and pK_{BHX} values of *S*- and *N*-containing bases are shown in Table 2, where it can be seen that while nitrogen analogues are indeed stronger halogen- and hydrogen-bond acceptors, they can, at the same time, be strong bases that will lead to deprotonation, promoting the formation of salts. On the other hand, although sulfur analogues are much weaker halogen and hydrogen bond acceptors, they are less likely to be strong bases, thus promoting formation of co-crystals instead of salts. In fact, the negative pK_{BHX} values for the sulfur analogues mean that, for the formation of hydrogen-bonded complexes of these acceptors, the equilibrium lies towards the uncomplexed components. Thus, given the choice, these sulfur-containing acceptors are more likely to be involved in halogen bonding than hydrogen bonding, which was the case in **2**. The nitrogen atom in one of the thiomorpholinium cations in **3**, however, behaved as suggested above, which led to deprotonation and crystallisation of the salt.

Table 2 pK_{BI2} and pK_{BHX} values of selected bases.[22]

Base	Atomic site	solvent	pK_{BI2}	pK_{BHX}	pK_b

1,4-Dithiane	S	CCl_4	1.64	–0.14	n/a
Piperazine	N–sp^3	heptane	3.74	2.11	4.17
Ethanethiol	S	hexane	1.37	–0.16	n/a
Ethylamine	N–sp^3	heptane	2.75	2.17	3.30

The results are also consistent with Pearson's classification of Hard and Soft Acids and Bases (HSAB),[23] which predicts successfully the preference for I···S over I···O interactions in **2** and **3** and the fact that, expressed as the sum of the van der Waals radii, the I···S interaction is shorter than the I···N interaction in **3** (*vide infra*).

The crystallographic disorder observed in **3** then provides interesting insights into the geometries of halogen-bonding interactions. The structures of 1,4-diiodotetrafluorobenzene and 1,4-dibromotetrafluorobenzene co-crystallised with thiomorpholine, thioxane, 1,4-dithiane, piperazine, morpholine and 1,4-dioxane have been reported in an extensive study by Cinčić *et al.*[24] where the isostructurality of several of the halogen bond acceptors was investigated. Although a direct analogy is inappropriate as the number of structures reported here is insufficient to identify structural equivalence, Cinčić *et al*. noted that the disorder of thio with imino or oxo groups suggests that all three groups may exhibit structural equivalence.[24,25] In **3**, however, only one of the thiomorpholine molecules was found to be disordered, and the other two were involved only in hydrogen bonding. Here, therefore, two of the thiomorpholines acted as a base deprotonating the acid, while the third acted only to form halogen bonds and so the thio and imino groups could indeed be considered equivalent from the point of view of halogen bonding. That the halogen-bonded iodine atom is found on the axial positions (Fig. 14) infers that the covalently bonded imine hydrogen atom is sterically more demanding as a substituent as suggested by Cinčić *et al*. The halogen contact distances in these two structures are given in Table 3.

A further, interesting comparison can then be made in considering the non-covalent interactions found in **5** and **6**, in which the potential sulfur donor has been oxidised to the *S*-

oxide. Here, the axial position at sulfur is now taken by the oxide oxygen, which acts as a pretty effective hydrogen-bond acceptor and now prevents the formation of a halogen bond at this position This result is of interest as it shows clearly how the introduction of a good hydrogen bond acceptor can generate alternative molecular arrangements and so provides a nice example of competition between halogen and hydrogen bonds.[‡]

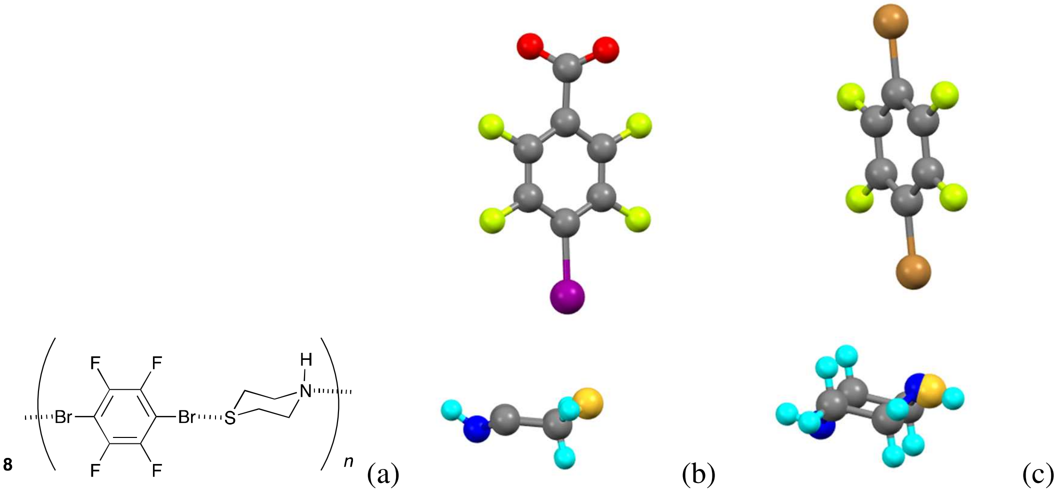

Figure 14 (a) Dibromodotetrafluorobenzene • thiomorpholine co-crystal (b) Axial arrangement of the halogen bond in **3** (disorder removed); (c) axial arrangement of the halogen bond in **8** reported by Cinčić *et al.*[24]

Table 3 List of short halogen contacts in **3** and **8**.

Structure	Space group	Contacts		
		Halogen contacts	Length / Å	% of ΣvdW radii
3	*P*-1	I···S	3.064(5)	81%
		I···N	3.37(2)	95%
8[23]	*P*-1	I···S	3.171(3)	84%
		I···N	2.989(9)	85%

It is clear from Table 3 that, while in **8** the I···S and I···N interactions show comparable degrees of contraction (16% and 15%), in **3** the contraction in I···S (19%) is much more

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[‡] We thank one of the referees for suggesting this interesting comparison.

significant than that in I···N (5%). It is also interesting to observe that the I···S halogen bonding in **3** is shorter than these in **2** and in the co-crystal between 1,4-diiodotetrafluorobenzene and thiomorpholine, however it is difficult to state conclusively that the I···S halogen bond in **2** is stronger just by comparing the intermolecular distances. Based on the melting points of the co-crystals measured by differential scanning calorimetry, Cinčić *et al.* suggested that the I···O and I···S interactions are of similar strengths, while the I···N bond is considerably stronger, although it is noted that the proposed equivalence of O and S would not necessarily agree with the iodine basicity scale.[21] That only one of the thiomorpholine molecules in **3** was involved in either of, but not simultaneously, hydrogen bonding and halogen bonding represents an example of an interesting balance between these two interactions. However, the crystallographic disorder observed in **3** prevents a definitive classification of the I···N and I···S interactions in the hierarchy of intermolecular interactions.

Conclusions

This study contributes to the body of work on co-existence of and possible competition between hydrogen and halogen bonding in co-crystals where one component has the possibility to participate in both binding modes. It is demonstrated that by choosing units carefully, halogen bonding between unlike components can be favoured over hydrogen bonding and that such results are consistent with both the iodine basicity scale and the long-established HSAB concept. Furthermore, the results also show some consistency with the proposal for the structural equivalence thio with imino or oxo functions.

Experimental

4-Iodotetrafluorobenzoic acid[9] and 4-iodotetrafluorophenol[26] were prepared according to the literature method, while all other compounds were commercial and were used as received. Single-crystal X-ray structures were determined as described elsewhere.[12]

In a typical co-crystallisation experiment, vapour diffusion techniques were used. The components were dissolved in a small volume of common solvent, and placed inside a tablet tube inside a vial and the tablet tube was then covered with aluminium foil which was punctured using a needle. The anti-solvent (*ca* 2 cm^3) was added to the vial, which was then sealed with a cap and covered in parafilm to prevent evaporation of the solvents. Solvents and anti-solvents are tabulated below.

Table 4 Solvents and anti-solvent used in crystallisation experiments

	Solvent	Anti-solvent
1	Chloroform	Cyclohexane
2	Diiosopropylether	Cyclohexane
3	THF	Cyclohexane
4	Diisopropylether	Cyclohexane
5	THF	None
6	Hexane	None
7	chloroform	cyclohexane

Acknowledgements

We thank EPSRC (LJM) and the Department of Chemistry, University of York (NEP) for funding. Access to the CCDB *via* the EPSRC-sponsored National Chemical Database Service access is acknowledged gratefully.

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