Organic Fluorine Hardly Ever Accepts Hydrogen Bonds

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Abstract: Statistical analysis of structural data and detailed inspection of individual crystal structures culled from the Cambridge Structural Database and the Brookhaven Protein Data Bank show that covalently bound fluorine (in contrast to anionic fluoride) hardly ever acts as a hydrogen-bond acceptor. The weakness of covalently bound fluorine as hydrogen-bond acceptor is backed by results of new molecular orbital calculations on model systems using ab initio intermolecular perturbation theory (IMPT), and is in accord with results of other physicochemical studies and with the physical properties of fluorinated organic compounds. Factors influencing the strength of hydrogen bonding in extended systems are discussed.

Keywords
ab initio calculations · Cambridge structural database · fluorine compounds · hydrogen bonds · protein data bank

Introduction

From a survey of intermolecular interactions in crystal structures, Murray-Rust et al.[1] concluded that "the C–F bond is capable of significant interactions with ... proton donors, although these are generally weaker than the corresponding ones involving C–O and C–N groups". In particular, OH groups were noted to be much better proton acceptors than C–F, so that the latter can be expected to hydrogen-bond to water or alcohols only in exceptional circumstances.[2] Nevertheless, H-bonding involving fluorine as proton acceptor has been postulated in inhibitor complexes of elastase,[3] even though, in such environments, water molecules must be present as alternative proton acceptors. The question has been taken up again by Shimoni and Glusker.[4] From a more extensive study of intermolecular interactions in fluorine-containing organic compounds they concluded that "*in spite of the high electronegativity of the fluorine atom* [our italics], a C–F group competes unfavorably with a $C-O^-$, C–OH, or C=O group to form a hydrogen bond to an O–H, N–H, or C–H group".

There is, of course, no question that fluoride ion (as distinct from covalently bound F) acts as a very strong proton acceptor; indeed, the H-bond energy of the bifluoride ion approaches 40 kcal mol^{-1},[5] making it by far the strongest known H bond. It was undoubtedly this special property of bifluoride ion that led to the emphasis on electronegativity in early accounts of H bonding. Pauling's statement in *The Nature of the Chemical Bond*[6a] has probably been very influential in this respect: "Only the most electronegative atoms should form hydrogen bonds, and the strength of the bond should increase with increase in the electronegativity of the two bonded atoms. Referring to the electronegativity scale, we might expect that fluorine, oxygen, nitrogen and chlorine would possess this ability, to an extent decreasing in that order. It is found empirically that fluorine forms very strong hydrogen bonds, oxygen weaker ones, and nitrogen still weaker ones." It is clear from the accompanying discussion that Pauling was thinking about the bifluoride anion, about HF, and about inorganic fluoride salts, but not about covalently bound fluorine. Indeed, twenty years later, in the 3rd edition of his book, he added the words: "It is interesting that in general fluorine atoms attached to carbon do not have significant power to act as proton acceptors in the formation of hydrogen bonds in the way that would be anticipated from the large difference in electronegativity of fluorine and carbon."[6b] Relatively few fluorine-containing organic crystal structures were known at that time, but it seems as if the few data available led Pauling to doubt the H-bond acceptor ability of covalently bonded fluorine, even though this appeared paradoxical because of the element's high electronegativity.

Since Pauling's work, the role of electronegativity has been emphasized over and over again by innumerable authors, although certainly not by all. In the case of the proton donor group (X–H in X–H $\cdots$ A), the relevance of electronegativity is clear. The greater the electronegativity of X in an X–H bond, the more the bonding electron pair is polarized towards X, the greater is the effective positive charge on the hydrogen atom, and hence the more easily the latter is removed, completely, as in acid dissociation, or partially, as in a H bond. Thus, HF is a stronger acid and a stronger H-bond donor than H_2O, which in

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turn is stronger than NH_3. However, the relevance of electronegativity to hydrogen bond *acceptor* ability is less clear. Electronegativity is a measure of the tendency to attract electrons, not protons. Thus, covalently bonded fluorine is an extremely weak base and, as such, may be expected to be an extremely weak proton acceptor. On the other hand, it is undeniable that the best H-bond acceptor atoms (oxygen and nitrogen) are electronegative.

In view of these problems, we have undertaken a new survey of hydrogen bonds involving covalently bound fluorine. We have focused on three issues. First, how commonly does carbon-bound fluorine accept hydrogen bonds, and under what circumstances? Secondly, what is the relevance (if any) of electronegativity to hydrogen-bond acceptor ability? Thirdly, what factors make a good hydrogen-bond acceptor? As our primary source of data, we have used the Cambridge Structural Database (CSD),[7] which contains the results of about 150000 small-molecule crystal structure determinations. In view of the suggested importance of fluorine as a hydrogen-bond acceptor in protein–ligand complexes (e.g. of elastase),[3] we have also examined crystal structures taken from the Brookhaven Protein Data Bank (PDB),[8] despite their much lower precision. In addition we have collated evidence from various published physicochemical studies. Finally, we have made molecular orbital calculations on model systems using ab initio intermolecular perturbation theory (IMPT).[9]

Methods

All calculations were performed on a Sun SPARCstation 5 or a Silicon Graphics Indigo [2].

Searches for H-Bonds in Small-Molecule Crystal Structures: Searches for H bonds were made with Version 5.09 of the CSD (April 1995), by using the nonbonded search capabilities of the program QUEST3D [10]. Only intermolecular contacts were considered. All searches were confined to error-free structures (according to the criteria of the CSD system) with crystallographic *R* factors of less than 10%. Contacts were only accepted as H bonds if the hydrogen-atom coordinates were in the CSD.

Our first step was to define suitable geometric criteria for a H bond. For this, only organic structures were included (CSD bit screen 28 set to zero—meaning no metals present—and elements As, Se, Te also excluded). From data for H bonds of the types O–H···O=C, N–H···O=C, O–H···N(Ar), and N–H···N(Ar) (O=C = any carbonyl group, N(Ar) = any aromatic nitrogen acceptor), histograms of H···O and H···N H-bond distances were prepared with the VISTA package [10,11]. The results (Figure 1) show that nearly all of the H bonds have H···O or H···N distances less than 2.2 Å. Since fluorine has a smaller van der Waals radius than either oxygen or nitrogen [12], it might seem reasonable to exclude C–F···H–X contacts (X = O, N) as possible H bonds unless the F···H distance is also less than 2.2 Å. In fact, we used a less severe criterion, namely, F···H < 2.3 Å, with the additional constraint that the F···H–X angle must exceed 90°. We are aware that even this relaxed distance criterion is liable to criticism. The sum of the van der Waals radii of fluorine and hydrogen lies between 2.5–2.7 Å, depending on which literature values are chosen [12,13]. Some authors [14] consider that acceptor···hydrogen contacts much longer than the sum of van der Waals radii may still be regarded as H bonds. However, *any* distance criterion—indeed, any definition of hydrogen bonding—is to some extent arbitrary. In the present case, we wish to focus on cases in which covalently bonded fluorine *unequivocally* acts as a H-bond acceptor, hence our choice of a distance limit that is significantly shorter than the sum of van der Waals radii, as found in the typical H bonds involving O and N acceptors. With these geometric constraints, several CSD searches were made to determine the frequency with which H bonds to fluorine occur and to characterize individual examples. Short F···H–X contacts thus found were examined visually with the programs SYBYL [15] (Version 6.1) and PLUTO [10]. Visual inspection is always called for because a short contact is not, in itself, definitive evidence for H bonding. Any observed crystal structure results from an equilibrium between attractive and repulsive forces. It follows that some interatomic distances less than—but not too much less than—the sum of van der Waals radii may correspond to repulsive contacts, provided that compensatory attractive contacts are present. This means that short H···F contacts in structures where other strong H bonds are present are not *necessarily* to be interpreted as H bonds. Only where no other strong intermolecular attractions are present can such an interpretation be made with confidence.

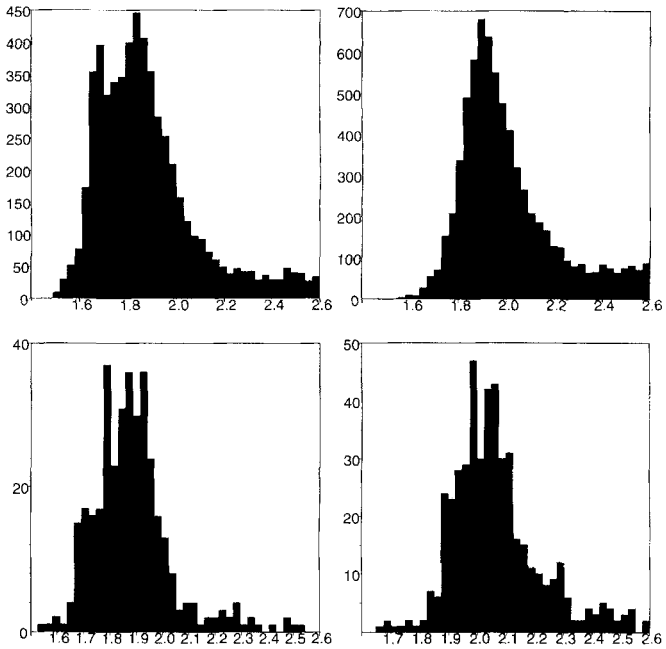

Fig. 1. Histograms of H···O(N) H-bond distances in CSD crystal structures. Top left: C=O···H–O; top right: C=O···H–N; bottom left: N(Ar)···H–O; bottom right: N(Ar)···H–N. Distances along horizontal axis in Å.

Searches for H Bonds in Protein–Ligand Crystal Structures: The protein-search capabilities of QUEST3D were used to find all protein–ligand complexes in the PDB (October 1994 release) containing the character string "fluor" in the compound-name field. Each hit was inspected visually with SYBYL to confirm that the ligand contained at least one C–F bond. If so, all F···X contacts of less than 3.5 Å (X = any protein, cofactor or solvate atom) were identified, by using the SYBYL program. These were regarded as possible H bonds and examined in more detail. Since hydrogen atoms are almost never located in protein crystal structure determinations, the analysis was necessarily based on X···F rather than H···F distances.

IMPT Calculations: IMPT calculations were used to calculate intermolecular interaction energies for various bimolecular model systems. The method of Hayes and Stone [9] was used, as implemented in Version 4.2 of the program CADPAC [16], with 6-31G* basis sets taken from the standard CADPAC library. Interaction energies from IMPT are calculated as the sum of five components, namely, electrostatic (classical Coulombic) energy (E_{es}), exchange repulsion (E_{er}), polarization (E_{pol}), charge transfer (E_{ct}), and dispersion (E_{disp}). The first two terms are first order, the others second order. An important feature of the CADPAC software is that E_{ct} is free of basis set superposition error [17].

Results

Overall Frequency Statistics: Initial CSD searches were aimed at determining the overall frequency with which fluorine acts as a hydrogen-bond acceptor. All crystallographically independent

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C–F bonds occurring in crystal structures with at least one potential H-bond donor group (i.e. X–H, where X = O or N) were found. Out of 5947 C–F bonds (in 1218 crystal structures), only 37 (i.e. 0.6%) are involved in possible C–F···H–X hydrogen bonds, according to our geometric criteria (see Methods). As discussed below, some of these are unlikely to be genuine hydrogen bonds. Thus, it is *extremely uncommon* for C–F groups to accept hydrogen bonds. For comparison, corresponding figures for C=O and N(Ar) groups are 42 and 32%, respectively (Table 1). While these simple statistics are affected by a multitude of factors apart from the intrinsic ability of C–F, C=O, and N(Ar) groups to accept hydrogen bonds (e.g., the donor:acceptor ratio in any given crystal structure), the differences in the percentages are so striking that there can be little room for doubt: C–F groups are very weak hydrogen bond acceptors compared with conventional acceptors such as carbonyl oxygen and aromatic nitrogen.

Table 1. Numbers of short C–F···H–X, C=O···H–X, and N(Ar)···H–X contacts (X = O, N) in the CSD.

Grouping, Y	Total no. of occurrences [a]	Total no. of short contacts to H–X [b]	Average no. of short contacts per grouping
C-bound F (C–F)	5947	37	0.01
carbonyl O (C=O)	42301	17718	0.42
N(Ar) [c]	3354	1060	0.32

[a] Total number of occurrences of grouping Y in CSD crystal structures (count confined to those structures in CSD containing at least one H–X group). [b] Total number of short contacts in CSD between Y and H–X (see text for definition of short contact). [c] For example, in pyridine; not quaternary.

Hydrogen Bonds to Fluorine in Small-Molecule Crystal Structures: Each of the 37 short F···H contacts found above (Table 2) was inspected visually. In several cases, the H atom involved in the short contact is closer to a conventional (oxygen or nitrogen) acceptor (e.g., AFSACO,[19] BUXGOQ,[1] PINCUK[43]).[50] In these structures, the F···H contacts may therefore be regarded as incidental, particularly if the O–H···F or N–H···F angle is far from linear (e.g., BUXGOQ[1]). Some of the short C–F···H–X contacts occur in organometallic structures (e.g., ABDARU,[18] BUXLOV[23]). Although these interactions may qualify as possible H bonds, the structures are complicated by additional factors and are not good models for the organic systems in which we are principally interested. We therefore omit them from further study. A discussion of the remaining contacts follows.

Table 2. Short C–F···H–O and C–F···H–N contacts in the CSD.

CSD refcode	F [a]	H [a]	F···H [b]	F···H–X [b]	Ref.
ABDARU	F3′	H3–N	2.17	154	[18]
AFSACO	F2	H14–O	2.13	150	[19]
AMMFAC	F1	H4–N	2.29	141	[20]
BARZUP	F31	H5–N	2.23	176	[21]
BUSSIR	F9	H12–N	2.21	167	[22]
BUXGOQ	F1	H210–N	2.21	121	[1]
BUXLOV	F5	H302–O	2.26	157	[23]
CEVGUF	F1	H1–O	2.02	170	[24]
CIJLOW	F1	H3–O	1.75	95	[25]
DOLSEC	F1	H42–N	2.19	130	[26]
FLCTRT	F1	H7–O	2.27	118	[27]
FLESDL10	F2	H25–O	2.09	151	[28]
FOHSOK	F3	H1–O	2.25	139	[29]
FPBXZL	F2	H1–N	2.24	154	[30]
HAJLAF	F6	H4–O	2.27	141	[31]
HAJWUK	F8	H16–O	2.28	138	[32]
HEBZOD	F4	H4–N	2.28	127	[33]
KETXAI	F1	H9–O	2.06	165	[34]
KEYXOB	F1	H26–N	2.10	143	[35]
KEYXUH	F1	H26–N	2.28	158	[35]
KIKJAP	F2	H1–N	2.29	139	[36]
KINWIN	F1	H5–N	2.23	120	[37]
KOVCAZ	F1	H1–O	2.02	152	[38]
KUMTER	F1	H5–N	2.29	166	[39]
KUNGIJ	F1	H1–N	2.12	164	[40]
LEPWOS	F8	H3–O	2.29	122	[41]
PIBXUT	F4	H1–O	2.24	158	[42]
PINCUK	F5	H16–N	2.29	121	[43]
PINCUK	F23	H9–N	2.30	126	[43]
SETMAF	F22	H6–N	2.17	123	[44]
SETMAF	F24	H2–N	2.22	176	[44]
SEZTIA	F2	H2–N	2.09	146	[45]
SUBXOC	F1	H7–N	2.26	156	[46]
VELXUF	F1	H6–N	2.30	172	[47]
VELYAM	F1	H1–N	2.27	170	[47]
VOYWIP	F1	H2–N	2.21	147	[48]
YAMSAG	F4	H2–N	2.25	155	[49]

[a] Atoms numbered as in CSD. [b] Distances (Å) and angles (°) computed from normalized H-atom positions [11]; X = O, N.

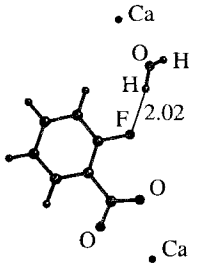

Fig. 2. C–F···H-O interaction in CEVGUF (calcium bis[2-fluorobenzoate] dihydrate).

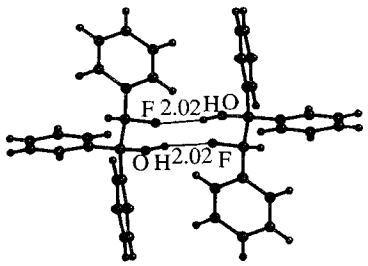

Fig. 3. C–F···H–O interaction in KOVCAZ (2-fluoro-1,1,2-triphenylethanol).

C–F···H–O Hydrogen Bonds: There are only two structures in our set where the existence of an O–H···F hydrogen bond seems beyond question. These are CEVGUF and KOVCAZ. In CEVGUF (calcium bis[2-fluorobenzoate] dihydrate, space group $C2/c$, $Z = 4$),[24] each water molecule is bonded to a Ca^{2+} ion and makes two H bonds, one to a carboxylate O (O–H···O, 1.77 Å, angle 173°), the other to the *ortho*-F atom (O–H···F, 2.02 Å, angle 170°; Figure 2). The F atom is part of an anion and must therefore be unusually electron rich. Moreover, because the H_2O molecule is coordinated to Ca^{2+}, it should be a stronger proton donor (acid) than a normal water molecule. Thus, the conditions for H bonding to covalently bound F are about as favorable as possible.

In KOVCAZ (2-fluoro-1,1,2-triphenylethanol, $P2_1/n$, $Z = 4$),[38] the molecules are linked into pairs across inversion centers by H bonds (O–H···F, 2.02 Å, 152°; Figure 3). Brock and Duncan[51] have pointed out that, for steric reasons, monoalcohols cannot easily pack in extended periodic structures by O–H···O interactions involving the usual symmetry operations such as translations, glides, and twofold screw rotations. Moreover, dimer formation through O–H···O interaction leads to one dangling H atom and one free O acceptor. The dimeric

structure of KOVCAZ avoids this by forming two O–H···F bonds instead of a single O–H···O one.

O–H···F interactions that may qualify as possible H bonds occur in three other structures—PIBXUT, FLESDL10, and FOHSOK. In PIBXUT (*trans*-3,3,4,4-tetrafluoro-2,5-dihydroxy-2,5-bis[trifluoromethyl]tetrahydrofuran, $I\bar{4}2d$, $Z = 8$),[42] the molecules sit on dyad axes. Given the difficulty of attaining good H-bonding arrangements for alcohols and the high ratio of F to O in this molecule, it is not surprising that the closest contacts made by the alcoholic H atoms are to fluorine (O–H···F, 2.24 Å, 158°). We have here what one might describe as a bona fide but forced O–H···F hydrogen bond.

FLESDL10 (4-fluoro-estra-1,3,5[10]-triene-3,17β-diol hemimethanolate, $P1$, $Z = 2$)[28] is a complicated structure with two independent sets of molecules, each arranged in head-to-tail chains and interconnected by H bonds through the methanol OH groups. The authors state that in one set, the H atom attached to O(17) is disordered over two possible positions. In the minor site it makes a H bond to O(17) of the other set, in the major one it makes a H bond to the F atom of the following molecule in its own chain; "although the O–H···F distance between O(17′) and F′ ... (2.989 Å) seems to be rather large for this type of hydrogen bond, the difference synthesis clearly reveals the existence of the hydrogen bond." We are not convinced that all the H atoms in this crystal structure have been correctly placed. For example, the published H positions lead to several intermolecular H···H distances of less than 2.10 Å, which seems unlikely. In summary, this is a possible, but not very probable O–H···F hydrogen bond.

FOHSOK (dimethylaminebis[trifluoromethyl]boronic acid, $P2_1/n$, $Z = 4$)[29] is a borammine derivative containing a very polar N–B bond (several other borammines are mentioned in the following discussion). The principal intermolecular interaction is a N–H···O bond (H···O 1.93 Å, N–H···O 172°) to the boronic acid hydroxyl O, while the "acid" H makes a contact with one of the six trifluoromethyl F atoms (O–H···F, 2.25 Å, 139°) of another molecule—a possible, but not easily classifiable hydrogen bond.

During our analysis we detected an error in the CSD. The initial survey pointed to CIJLOW ([1*S*,2*S*-α-*S*]-1-α-carboxyethyl-3,3-bis[trifluoromethyl]diaziridine, $P3_1$, $Z = 3$)[25] as a structure with a close O–H···F interaction (1.75 Å, 95°!), by far the shortest in our collection. On the other hand, the carboxylic acid groups were not, apparently, engaged in H bonding. These two unusual features raised the suspicion that the published description of the structure might be incorrect. The molecules are arranged in spirals around the threefold screw axis, and alteration of the chiral space group from $P3_1$ to enantiomorphic $P3_2$ led to a far more plausible packing arrangement, with infinite O=C–OH···O=C–OH···O=C–OH··· spirals along the threefold screw axis and with no short H···F distances. The space group had been incorrectly reported in the original publication, and the error was not detected in the standard checks when the structural data were introduced into the CSD.

C–F···H–N Hydrogen Bonds: Twelve structures in our set contain interactions that may qualify as possible N–H···F hydrogen bonds. Of these, the most convincing example is in SUBXOC ([*RS,SR*]-ethyl α-3-phthalimidopropyl-α-chlorfluoromethyl-*N*-methoxycarbonylglycinate, $P\bar{1}$, $Z = 2$; Figure 4).[46] Here, the molecules are linked into pairs across inversion centers by contacts between the amide H of one partner and the F of the chlorofluoromethyl group of another, to form a 10-membered ring (graph symbol[52] $R_2^2(10)$; N–H···F, 2.26 Å, 156°). It is of interest that none of the potential O acceptors are involved; a rare case where the N–H···F interaction is preferred to N–H···O.

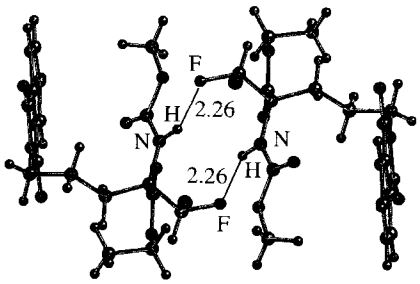

Fig. 4. C–F···H–N interaction in SUBXOC ([*RS,SR*]-ethyl α-3-phthalimidopropyl-α-chlorfluoromethyl-*N*-methoxycarbonylglycinate).

Three tris(trifluoromethyl)borammine complexes form an interesting series (Figure 5). In YAMSAG (tris[trifluoromethyl]-borammine, *Pnma*, $Z = 4$, mirror-symmetric molecules),[49] the

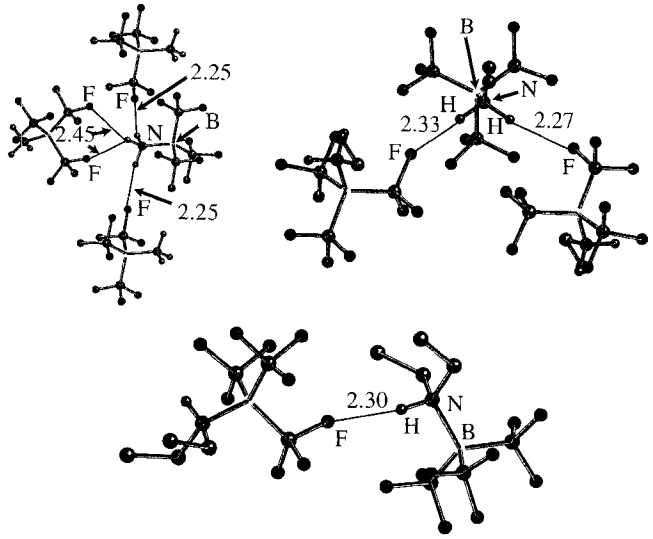

Fig. 5. C F···H–N interactions in YAMSAG (tris[trifluoromethyl]-borammine; top left), VELYAM (tris[trifluoromethyl]borethylammine; top right), and VELXUF (tris[trifluoromethyl]bordiethylamine; bottom).

two symmetry-related H atoms of the ammine moiety make intermolecular N–H···F contacts of 2.25 Å, 155°. The third H (lying on the mirror plane) makes two such contacts (2.45 Å, 136°). In VELYAM (tris[trifluoromethyl]borethylammine, $P2_1/c$, $Z = 4$),[47] both H atoms of the ammine moiety make intermolecular N–H···F contacts (2.27 Å, 170°; 2.33 Å, 166°). These distances are markedly less than the C–H···F distances (>2.70 Å). Finally, in VELXUF (tris[trifluoromethyl]bordiethylamine, *Pnma*, $Z = 4$, mirror-symmetric molecules),[47] the shortest intermolecular N–H···F contact made by the single ammine H atom is 2.30 Å , 172°, compared with the shortest C–H···F distance of 2.72 Å. While uncomplexed

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amines are poor H-bond donors, one might expect from the usual Lewis formulation of the borane complexes that the ammine H atoms would acquire enhanced acidity and the F atoms of the trifluoromethyl groups enhanced basicity. Nevertheless, the N–H···F contacts found in these three complexes, although shorter than the C–H···F distances, barely qualify as hydrogen bonds according to our distance criterion, certainly not as strong ones.

Related to these borammine examples is the more complex FPBXZL (*B*,*B*-bis[4-fluorophenyl]boroxazolidine, $P2_12_12_1$, $Z = 4$).[30] Of the two protons of the disubstituted ammonium group in the boroxazolidine ring, one is engaged in a clear-cut intermolecular H bond to the ring O (N–H···O, 1.93 Å, 176°) while the other makes contact with a fluorine (N–H···F, 2.24 Å, 154°).

In KUMTER (3-chloro-4-fluoroaniline at 120 K, *Pbca*, $Z = 8$),[39] each anilino H atom points towards a possible H-bond acceptor: N–H4···N, 2.29 Å, 168°; N–H5···F, 2.29 Å, 166°. The anilino N atom is markedly pyramidal, as expected when the atom acts as H-bond acceptor. If the N–H···N contact is taken as a weak hydrogen bond, then so also must the N–H···F one. Similar weak interactions occur in KEYXOB (cisapride monohydrate) and KEYXUH (demethoxycisapride ethanol solvate).[35] In both structures there is a contact between the N–H of the terminal 3-chloro-4-aminophenyl group of one molecule and the F of the 4-fluorophenyl group of its neighbor (N–H···F, 2.10 Å, 143°; 2.28 Å, 158°).

In BARZUP (1,5,8-trioxa-2,2-bis[trifluoromethyl]-3-imido-4-[1,1,1-trifluoro-2-[trifluoromethyl]ethoxy]-6,6,7,7-tetrakis[trifluoromethyl]-4-phosphaspiro[3.4]octane, $P\bar{1}$, $Z = 2$)[21] the molecular periphery consists of eight CF_3 groups. The single N–H group pointing outwards has almost no alternative but to interact with a fluorine atom. The result is a weak but reasonably convincing H bond (N–H···F, 2.23 Å, 176°). In a similar vein, the KUNGIJ (hexakis[2-fluorophenylamino]disiloxane, $P\bar{1}$, $Z = 1$)[40] molecule has six potential H-bond donors, but the only good acceptor is the O sandwiched between the two Si atoms. The only available acceptors are the F atoms. The molecules pair across inversion centers to give a 10-membered ring arrangement (graph symbol[52] $R_2^2(10)$; N–H···F 2.12 Å, 164°). It is interesting that three of the structures studied in this analysis share the $R_2^2(10)$ hydrogen-bonding pattern.

SETMAF (2-trifluoroacetylamino-5,5-bis[trifluoromethyl]-1,3,4-thiadiazolidine, $P2_1/c$, $Z = 12$)[44] has a complicated packing arrangement involving three independent sets of molecules. One set forms dimers linked by centrosymmetrically related N(amide)–H···N(ring) hydrogen bonds, the other two sets form similar, but not symmetry related, dimers. In addition, the closest contact made by the N–H group of each thiadiazolidine ring is with a F atom of the trifluoroacetyl group of another molecule (2.17 Å, 123°; 2.22 Å, 176°; 2.52 Å, 117°). Especially for this highly fluorinated molecule, these contacts can hardly be taken as convincing H bonds, but the regular pattern suggests that, even though the N–H···F interaction is weak, it is better than the other possible interactions.

The amino group of the cytidine moiety in DOLSEC (5-fluoroarabinocytosine, $P2_12_12_1$, $Z = 4$)[26] makes two intermolecular contacts through its two H atoms, one to O5′ of the sugar (N–H···O, 1.88 Å, 170°), the other to the fluoro substituent (N–H···F, 2.19 Å, 130°). However, the corresponding N···F distance, 2.94 Å, is only slightly less than the N···F distance involving N3 of the cytidine ring (3.06 Å).

Ammonium Fluoroacetates: Several of the most convincing examples of X–H···F bonding involve molecules where the F atom can be associated with some anionic character. However, X–H···F bonding is certainly not a general feature of such structures. If it were so, we would expect to find N–H···F bonding in the ammonium salts of mono-, di-, and trifluoroacetic acid;[20, 53] after all, the ammonium ion is a stronger acid than the water molecule in CEVGUF or the OH group in KOVCAZ, and electron withdrawal by halogen atoms (especially F) is commonly invoked to explain the acid-strengthening effect of α-halogen substituents in aliphatic carboxylic acids.[54] Nevertheless, the acid ammonium H-atoms in these three salts are H-bonded exclusively to carboxylate O atoms (Table 3). Only in the monofluoro salt is there a hint of a bifurcated H bond involving carboxylate O and the *syn*-planar F atom, but the latter is more than 0.25 Å more distant from the H atom (Figure 6). It is interesting that in the trifluoro salt, with an excess of putative F acceptors, there is no trace of H bonding to F. The ammonium H atoms clearly prefer to bond to O atoms rather than to F.[55]

Table 3. H bonds in crystal structures of ammonium fluoroacetates.

Structure [a]	NH [b]	H···X (Å) [c]	N–H···X (°) [c]	X	Ref.
$NH_4^+ CF_3COO^-$	H1	1.91	164	O2	[53]
(AMTFAC)	H2	1.86	173	O1	
	H3	1.92	166	O1	
	H4	1.92	170	O2	
$NH_4^+ CF_2HCOO^-$	H2	1.90	160	O2	[20]
(AMDFAC)	H3	1.80	174	O1	
	H4	1.85	159	O1	
	H5	1.83	172	O2	
$NH_4^+ CFH_2COO^-$	H3	1.79	168	O2	[20]
(AMMFAC)	H4	2.03	143	O2	
	H4	2.29	141	F1	
	H5	1.85	163	O1	
	H6	2.22	131	O1	

[a] CSD refcode in parentheses. [b] H atoms numbered as in CSD. [c] Distances and angles computed from normalized H-atom positions [11]; X = O,F.

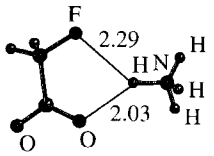

Fig. 6. C–F···H–N interaction in AMMFAC (ammonium monofluoroacetate).

Possible Hydrogen Bonds to Fluorine in Protein–Ligand Complexes: Fourteen protein–ligand complexes were found in which the ligand contains at least one crystallographically located carbon-bound fluorine atom (Table 4). Between them, they contain 49 C–F groupings. The environment of each F atom was characterized as described in the Methods section and assigned to one of six categories: 1) makes no intermolecular contacts (< 3.5 Å) to any atom (4 examples); 2) makes contacts only to carbon atoms (13 examples); 3) makes contacts only to carbon atoms, or to oxygen or nitrogen atoms that cannot be H-bond donors, such as carbonyl oxygen (3 examples);

Table 4. Protein–ligand complexes containing carbon–fluorine bonds, taken from the Protein Data Bank.

PDB code	Description	Ref.
1APV	acid proteinase (penicillopepsin) (E. C.3.4.23.20) complexed with isovaleryl-Val-Val-hydrated difluorostatone-*N*-methylamide	[56]
1APW	acid proteinase (penicillopepsin) (E. C.3.4.23.20) complexed with isovaleryl-Val-Val difluorostatine-*N*-methylamide	[56]
1BCD	carbonic anhydrase II (E. C.4.2.1.1) complexed with trifluoromethane sulphonamide	[57]
1ELA	elastase (E. C.3.4.21.36) complexed with trifluoroacetyl-Lys-Pro-*p*-isopropylanilide	[58]
1ELB	elastase (E. C.3.4.21.36) complexed with trifluoroacetyl-Lys-Leu-*p*-isopropylanilide	[58]
1ELC	elastase (E. C.3.4.21.36) complexed with trifluoroacetyl-Phe-*p*-isopropylanilide	[58]
2EST	elastase (E. C.3.4.21.11) complexed with trifluoroacetyl-Lys-Ala-*p*-trifluoromethylphenylanilide	[59]
4EST	elastase (E. C.3.4.21.11) complexed with acetyl-Ala-Pro-Val-Val-difluoro-*N*-phenylethylacetamide	[60]
7EST	elastase (E. C.3.4.21.11) complexed with trifluoroacetyl-Leu-Ala-*p*-trifluoromethylphenylanilide	[61]
6GCH	gamma chymotrypsin (E. C.3.4.21.1) complexed with *N*-acetyl-Phe-trifluoromethyl ketone	[62]
7GCH	gamma chymotrypsin (E. C.3.4.21.1) complexed with *N*-acetyl-Leu-Phe-trifluoromethyl ketone	[62]
4GPB	glycogen phosphorylase B (E. C.2.4.1.1) (T state) complexed with 2-fluoro-2-deoxy-α-D-glucose-1-phosphate	[63]
1HLD	alcohol dehydrogenase (E. C.1.1.1.1) (EE isozyme) complexed with nicotinamide adenine dinucleotide, 2,3,4,5,6-pentafluorobenzyl alcohol, *p*-bromobenzyl alcohol and zinc	[64]
1RDS	ribonuclease Ms (E. C.3.1.27.3) complexed with 2′-deoxy-2′-fluoroguanylyl-(3′,5′)-cytidine	[65]

Table 5. Short contacts between fluorine atoms and possible H-bond donor atoms in protein–ligand complexes.

PDB code	F [a]	Possible donor atom, X	F···X (Å) [b]	Remarks
1APV	F2	OD2(Asp213)	2.9	uncertain whether OD2-(Asp213) protonated
1APW	F2	OD2(Asp213)	3.0	uncertain whether OD2-(Asp213) protonated
1ELA	F2	OG(Ser203)	3.0	
	F3	OG(Ser203)	2.9	
		N(Ser203)	3.1	
1ELB	F1	OG(Ser203)	3.2	
		NE2(His60)	3.3	
	F3	OG(Ser203)	3.0	
		N(Gly201)	3.4	
1ELC	F1	OG(Ser203)	3.3	
	F3	OG(Ser203)	2.8	
		N(Gly201)	3.5	
2EST	F2	OG(Ser195)	3.3	
	F3	OG(Ser195)	3.3	
4EST	F1	NE2(His57)	2.8	
7EST	F3	N(Ser195)	3.1	
6GCH	F11	NE2(His57)	2.8	
7GCH	F11	NE2(His57)	3.3	
	F13	N(Gly193)	3.3	
4GPB	F2 [c]	OH(Tyr573)	3.0	O–H···F angle very small (ca. 88°)
		OE1(Glu672)	3.3	uncertain whether OE1-(Glu672) protonated
		ND2(Asn284)	3.3	

[a] Atom numbering as in PDB. [b] X = O, N. [c] Inhibitor molecule GFP900.

4) makes contacts to crystallographically observed water, but to no other potential H-bond donors (7 examples); 5) makes a contact to a potential H-bond donor on the protein, but geometry of contact is unfavorable (acute F···H–X angle), and the protein H-bond donor is clearly hydrogen-bonded to something else (6 examples); 6) makes a possible H bond to a protein XH group (16 examples).

Given that water positions in protein structures are generally ill-determined, only the sixteen F atoms in category 6 (Table 5) need be considered further. For none of these is there *unequivocal* evidence of H bonding. This is hardly surprising because the lack of experimental H-atom positions makes it difficult to arrive at unambiguous interpretations of H-bonding patterns. However, in two cases (4EST, 6GCH) there is a good *possibility* of X–H···F hydrogen bonding.

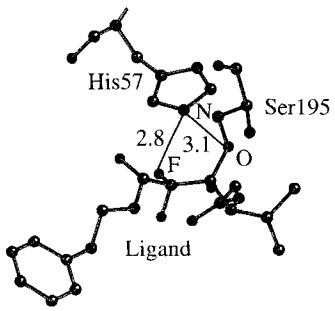

Fig. 7. H bonds in active-site region of 4EST, the complex between elastase and acetyl-Ala-Pro-Val-Val-difluoro-*N*-phenylethylacetamide.

In 4EST[60] (Figure 7), the inhibitor has reacted with the catalytic serine of the enzyme and is therefore anionic. One of the inhibitor F atoms (F1) forms a short (2.8 Å) contact to NE2(His57) (estimated F···H–N angle 129°). This N atom also forms a 3.1 Å contact to OG(Ser195) (O···H–N approximately 136°). The N–H···F contact may therefore be the stronger component of a bifurcated H bond. A very similar situation is found in 6GCH.[62]

The remaining F atoms in category 6 (Table 5) are either not H-bonded at all or are, at most, involved in H bonds with very poor geometries or in weak components of bifurcated or trifurcated H bonds. This list includes several elastase complexes, where the possibility of X–H···F hydrogen bonding has received some attention in the literature.[3] A typical example is represented by 1ELA[58] (Figure 8). Here, two F atoms (F2, F3) of the inhibitor trifluoroacetyl group form short contacts (3.0, 2.9 Å) to OG(Ser203). However, this O atom forms a much shorter (2.8 Å) contact to NE2(His60), which is undoubtedly a H bond, and, additionally, is in close contact with an acetate ion. F3 also forms a short (3.1 Å) contact to the backbone NH of Ser203, but there is an even closer contact (2.9 Å) with the backbone carbonyl oxygen of Cys199. The latter contact cannot possibly be a H bond. This shows that, even in macromolecular structures of nominal 1.8 Å resolution, contact

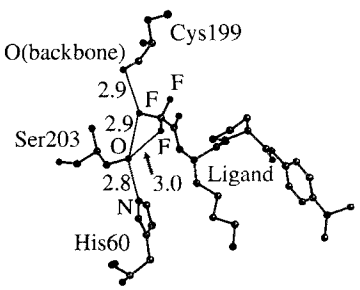

Fig. 8. H bonds in active-site region of 1ELA, the complex between elastase and trifluoroacetyl-Lys-Pro-*p*-isopropylanilide.

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distances of 2.9 Å or above are not conclusive evidence of H-bond formation.

In summary, the evidence from the PDB is consistent with that from the CSD: only rarely is fluorine seen to act as a hydrogen bond acceptor and, when it does, it is usually in an electron-rich environment.

Evidence from Physical Organic Chemistry: Water–octanol partition coefficients[66] (Table 6) indicate that fluoro and fluoroalkyl substituents are hydrophobic, not hydrophilic like typical H-bond acceptors.[67]

Table 6. Some water–octanol π constants [a].

Substituent	π	Substituent	π
CF_3	0.88	OMe	−0.02
Me	0.56	NO_2	−0.28
F	0.14	CHO	−0.65
H	0.00	SO_2Me	−1.63

[a] Ref. [66].

Abraham et al.[68] have developed spectroscopic methods for measuring the equilibrium constant of association (through hydrogen bonding) of an acid and a base in carbon tetrachloride solution. They measured the association constants of a variety of bases with a few standard acids. The measured constants were then transformed into an index, β_2^H, which they regard as a measure of hydrogen-bond acceptor ability—the bigger β_2^H, the better the base as an acceptor. Some representative β_2^H values are given in Table 7. They suggest that fluorobenzene is an extremely weak hydrogen-bond acceptor, weaker, in fact, than benzene itself. In agreement with this, and although gas-phase proton affinities cannot be translated directly into molecular properties in condensed phases, it is noteworthy that gas-phase protonation of fluorobenzene yields predominantly the ring-protonated isomer, the experimental proton affinity of the F atom being 40 to 50 kcal mol^{-1} less than that of the C atoms.[69]

Table 7. Some measured values of the H-bond acceptor index β_2^H [a].

Molecule	β_2^H	Molecule	β_2^H
alkanes	0.00	acetone	0.50
chlorobenzene	0.09	tetrahydrofuran	0.51
fluorobenzene	0.10	pyridine	0.62
benzene	0.14	diphenylsulfoxide	0.67
nitrobenzene	0.34		

[a] Ref. [68].

IMPT Calculations:

Fluorobenzene···H_2O, benzene···H_2O, and benzoquinone···H_2O: One of the few examples of convincing H bonding to fluorine occurs in the structure CEVGUF[24] (see above), where a water molecule is H-bonded to the fluorine substituent of an *ortho*-fluorobenzoate ion. IMPT calculations on *ortho*-fluorobenzoate···H_2O would be difficult to interpret because the effects of the proximal carboxylate and fluoro substituents could not be separated. Calculations were therefore done on the bimolecular complex fluorobenzene···H_2O. The geometry was taken from CEVGUF, the only change being the replacement of the *o*-carboxylate group by a hydrogen atom in a standard position (C–H = 1.08 Å). In particular, the dimensions of the C–F···H_2O system were kept at the values observed in CEVGUF, namely, F···H = 2.04 Å, F···O = 2.99 Å, F···H–O = 170°, C–F···H = 122°, C–F···H–O torsion = −36°, F···H–O–H torsion = −75°.

For comparison, calculations were also done on the bimolecular complexes benzene···H_2O and benzoquinone···H_2O. The geometry of the first system was generated by replacing the F atom of the fluorobenzene···H_2O system by H, leaving all other parameters unchanged. The geometry of benzoquinone was taken from the low-temperature X-ray determination of this compound.[70] The benzoquinone molecule was placed in the same orientation with respect to the water molecule as in the fluorobenzene···H_2O calculations. This was achieved by least-squares superposition of the ring atoms of benzoquinone onto those of the fluorobenzene, subject to the constraint that one of the benzoquinone oxygens was coincident with the fluorine atom of fluorobenzene.

Results are summarized in Table 8, which gives total interaction energies and the individual perturbation terms from which they are derived. The total energy of fluorobenzene···H_2O is attractive (−2.8 kcal mol^{-1}), whereas that of benzene···H_2O is slightly repulsive (0.1 kcal mol^{-1}).[71] The difference is mainly due to the first-order electrostatic term; the C–F grouping of fluorobenzene has a favorable Coulombic interaction with H_2O. However, the total energy of fluorobenzene···H_2O is only about half as attractive as that of benzoquinone···H_2O (−5.2 kcal mol^{-1}), showing that the carbonyl O atom is a much stronger hydrogen-bond acceptor. The difference is again mainly due to the first-order electrostatic term, but polarization, charge transfer, and dispersion all contribute too. Therefore, the weakness of F as a H-bond acceptor, relative to a conventional acceptor such as carbonyl O, seems to be due to a combination of effects. The calculated partial charge on F in a normal C–F bond is typically less than that on carbonyl O,[72] presumably because both the σ and the π components contribute to the latter. As expected from the hard nature of fluorine, the polarization contribution to a C–F···H–X hydrogen bond is also relatively small. Finally, charge transfer makes only a small contribution to the stability of C–F···H–X interactions, presumably because fluorine lone pair orbitals are low in energy.

Table 8. Calculated interaction energies of fluorobenzene···H_2O, benzene···H_2O, and benzoquinone···H_2O

System	ES	ER	PO	CT	DI	Total [a]
fluorobenzene···H_2O	−3.67	2.59	−0.35	−0.35	−1.03	−2.80
benzene···H_2O	0.11	0.76	−0.14	−0.09	−0.58	0.06
benzoquinone···H_2O	−6.67	4.18	−0.64	−0.63	−1.41	−5.16

[a] ES = first-order electrostatic interaction, ER = exchange repulsion, PO = polarization, CT = charge transfer, DI = dispersion; total energy and all energy components in kcal mol^{-1}.

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Effects of electron donating substituents: IMPT calculations were done on the complexes $H_2O\cdots$4-fluorophenol and $H_2O\cdots$4-fluoroaniline. Standard geometries were used for the OH and NH_2 substituents. All other parameters (H-bond geometries, etc.) were unchanged from those used above. Results are summarized in Table 9, which also gives the Hammett σ_p values of H, OH, and NH_2.[66] As expected, *para* substitution increases the stability of the C–F···H–O "hydrogen bond" by 0.2 (OH) and 0.5 kcal mol^{-1} (NH_2), the effect being at least qualitatively dependent on the substituent σ_p value and almost entirely due to the first-order electrostatic term. The results are thus consistent with our empirical observation that C–F groupings are more likely to accept H bonds when in an electron rich environment.

Table 9. Calculated interaction energies of *para*-substituted fluorobenzenes with H_2O.

System	σ_p [a]	ES	ER	PO	CT	DI	Total [b]
fluorobenzene···H_2O	0.00	−3.67	2.59	−0.35	−0.35	−1.03	−2.80
4-fluorophenol···H_2O	−0.37	−3.80	2.59	−0.35	−0.36	−1.03	−2.96
4-fluoroaniline···H_2O	−0.66	−4.09	2.59	−0.38	−0.39	−1.03	−3.29

[a] Hammett σ_p constant of atom or group *para* to fluorine. [b] ES = first-order electrostatic interaction, ER = exchange repulsion, PO = polarization, CT = charge transfer, DI = dispersion; total energy and all energy components in kcal mol^{-1}.

Effects of donor···acceptor distance: We investigated how the energies of fluorobenzene···H_2O and benzoquinone···H_2O vary with donor···acceptor distance (i.e., F···H and O···H, respectively). All other geometrical parameters (bond distances and angles, C–F···H–O and C=O···H–O torsions, etc.) were unchanged from those used in the earlier calculations. Results are summarized in Table 10. The benzoquinone···H_2O interaction energy becomes slightly more favorable when the donor···acceptor distance is decreased by 0.1 Å, but that of fluorobenzene···H_2O remains practically unchanged. Thus, not only is benzoquinone a much stronger acceptor than fluorobenzene, it also forms shorter hydrogen bonds, despite the fact that the van der Waals radius of O is larger than that of F.[12]

Table 10. Variation with distance of interaction energies of fluorobenzene···H_2O and benzoquinone···H_2O.

System	r (Å) [a]	ES	ER	PO	CT	DI	Total [b]
fluorobenzene···H_2O	1.94	−4.39	3.89	−0.46	−0.49	−1.27	−2.73
fluorobenzene···H_2O	2.04	−3.67	2.59	−0.35	−0.35	−1.03	−2.80
fluorobenzene···H_2O	2.14	−3.11	1.72	−0.27	−0.25	−0.84	−2.75
benzoquinone···H_2O	1.94	−7.98	6.17	−0.83	−0.86	−1.78	−5.28
benzoquinone···H_2O	2.04	−6.67	4.18	−0.64	−0.63	−1.41	−5.16
benzoquinone···H_2O	2.14	−5.64	2.83	−0.50	−0.46	−1.14	−4.91

[a] H-bond distance, i.e., distance between water H atom and acceptor atom [F···H for fluorobenzene···H_2O complexes, (C=)O···H for benzoquinone···H_2O complexes]. [b] ES = first-order electrostatic interaction, ER = exchange repulsion, PO = polarization, CT = charge transfer, DI = dispersion; total energy and all energy components in kcal mol^{-1}.

Conclusions

Statistical analyses of appropriate intermolecular contact distances in small-molecule crystal structures harvested from the Cambridge Structural Database (CSD) show that C–F···H–X distances less than 2.3 Å are extremely uncommon (37 out of 5947 C–F bonds). Scrutiny of the few individual structures with short O–H···F and N–H···F contact distances shows that only two examples can be regarded as unequivocal hydrogen bonds, one involving an F atom with considerable anionic character. A few other examples in this group can be regarded as "possible" but very weak hydrogen bonds. Thus, the experimental evidence leaves no doubt that covalently bonded F hardly ever acts as a H-bond acceptor and then only in exceptional molecular and crystal environments.

This result is confirmed by analysis of X···F contacts in protein–ligand crystal structures from the Protein Data Bank (PDB). In these structures, the H-atom positions are almost never determined experimentally and must therefore be inferred. Because of this limitation, unambiguous interpretations of hydrogen-bonding patterns are impossible. Nevertheless, a few examples of "possible" hydrogen bonding involving covalently bound fluorine can be postulated. It is striking that, in all of them, the F atom in question is part of a bound inhibitor molecule with a formal negative charge.

The results of the structural data are largely confirmed by quantum mechanical (IMPT) calculations on simple model systems and by physicochemical evidence. Although gas-phase basicities cannot be correlated directly with H-bonding acceptor abilities in condensed phases, it is noteworthy that fluorobenzene is protonated in the gas phase at a C atom and not on the F.[69] (And one should not forget that fluorocarbons are even more hydrophobic than hydrocarbons; a reason why frying pans are coated with Teflon.)

These conclusions confirm and extend the results of earlier, more limited surveys.[1, 4] Nevertheless, they seem to be at variance with what one might call the present canonical view of hydrogen bonding. Thus, in a recent authoritative review, Bernstein et al.[73] wrote that: "The notion of the physical basis of the hydrogen bond has not changed since Pauling's description over half a century ago. It is an essentially electrostatic interaction resulting in an attractive force between a hydrogen atom H covalently bonded to a donor atom X and an electrongative atom A. Also in concert with Pauling's ideas, the strength of the hydrogen bond depends on the relative electronegativity of the X and A moieties." This statement leads us to expect that when A is fluorine, we should get strong hydrogen bonding with good donor atoms X; after all, F is the most electronegative element. Our survey has shown, however, that this expectation is not fulfilled. Hydrogen bonds to F as acceptor are few and weak, compared with the innumerable strong H bonds formed with O as acceptor. What is wrong?

At least two factors seem important. If we take hydrogen bonding as an intermediate stage in proton transfer, it is clear that the proton affinities (base strengths) of the donor and acceptor atoms must be closely matched. In molecular orbital terms, this means that the energies of the two orbitals that compete for the proton (in a simplified three-center, four-electron MO model) must not be too different. The binding energy of a

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2p electron of F is some 3 eV greater than than of O(2p) and some 6 eV greater than that of N(2p).[74]

The second factor is that the energies of the relevant orbitals can be modified by the effect of electron delocalization within molecules and of cooperativity in extended systems. With regard to the former, fluorine only forms single bonds, so it cannot attract electrons through the π system in the same way as, for example, carbonyl oxygen or imine nitrogen. Thus, although F is more electronegative than O or N, it is normally the latter atoms that are assigned the larger, negative partial atomic charges in quantum-mechanical calculations on organic molecules.[72] With regard to cooperativity effects, there are practically no examples where H_2O acts only as H donor or only as H acceptor. The H-donor and H-acceptor properties of H_2O act synergistically, and the same can be said for almost all good H-bonding systems (carboxylic acids and amides, nucleic acid bases, etc.).

In the lack of a better model and in spite of the negative partial charge on covalently bound F, its extremely weak H-bonding capability can be attributed to a combination of two factors: its low proton affinity (low basicity, low-lying lone pair orbitals, tightness of its electron shell) and its inability to modify this by intramolecular electron delocalization or intermolecular cooperative effects. At the same time, it has to be admitted that, in spite of the vast amount of work on hydrogen bonding over the years, the chemical factors influencing the strength of hydrogen bonds (especially factors influencing H-bonding acceptor ability) are still not completely understood.[75]

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