Halogen Bonding: A Paradigm in Supramolecular Chemistry**

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Dedicated to Professor Jean-Pierre Beguè on the occasion of his 60th birthday

Abstract: The term halogen bonding describes the tendency of halogen atoms to interact with lone pair possessing atoms. The binding features and structural properties of halogen bonding are discussed and applied to drive the intermolecular self-assembly of hydrocarbons and perfluorocarbons in chemo-, site-, and enantioselective supramolecular synthesis. The halogen bonding is thus an effective and reliable tool in crystal engineering at the disposal of the supramolecular chemist.

Keywords: donor–acceptor complexes · fluorine · hydrogen bonds · iodine · supramolecular chemistry

Introduction

Metal ion coordination[1] is frequently the key interaction in inorganic system self-organisation and hydrogen bonding[2] is by far the most frequently used tool to assemble organic molecules in the solid, liquid, or gas phase. In this paper we show how halogen bonding[3] is also an effective and reliable tool in crystal engineering and can be considered as a new item of the palette of non-covalent interactions on the disposal to the chemist as the cement to assemble molecules into supramolecular architectures.

It is well known that halogen molecules (frequently iodine and bromine, but also chlorine and even fluorine[4]) or alkyl and aryl halides form complexes with atoms containing lone pairs.[5] This tendency had already been recognised as early as two centuries ago[6] and more recently a large number of more or less stable intermolecular complexes obtained by using this non-covalent interaction have been described, as described in Table 1.

Table 1. Selected examples from the literature of complexes between halogens, interhalogens or halocarbons and various lone-pairs possessing heteroatom substituted hydrocarbons.

Electron acceptor	Electron donor	Interaction parameter
Br_2	trimethylamine[a]	–
	1,4-dioxane[b]	$d_{Br\cdots O}$ 2.71 Å
Cl_2		$d_{Cl\cdots O}$ 2.67 Å
CHI_3	quinoline[c]	$d_{I\cdots N}$ 3.05 Å
	1,4-dithiane[d]	$d_{I\cdots S}$ 3.32 Å
	1,4-dioxane[e]	$d_{I\cdots O}$ 3.04 Å
	1,4-diselenane	$d_{I\cdots Se}$ 3.51 Å
	hexamethylenetetramine	$d_{I\cdots N}$ 2.94 Å
	triethylamine[f]	K_{DP} 3.2
$CHBr_3$		K_{DP} 0.9
$CHCl_3$		K_{DP} 0.4
BrCl	ammonia[g]	$d_{Br\cdots N}$ 2.63 Å
	hydrogen sulfide	$d_{Br\cdots S}$ 3.01 Å
ClF	ammonia	$d_{Cl\cdots N}$ 2.38 Å
	hydrogen sulfide	$d_{Cl\cdots S}$ 2.86 Å
$I_2C_6H_4$	1,4-dinitrobenzene[h]	$d_{I\cdots O^-}$ 3.37 Å
	TCNQ	$d_{I\cdots N}$ 3.45 Å

[a] J. F. Norris, I. Remsen, *Am. Chem. J.* **1896**, *18*, 90; [b] O. Hassel, J. Hvoslef, *Acta Chem. Scand.* **1954**, *8*, 873; [c] T. Bjorvatten, O. Hassel, *Acta Chem. Scand.* **1962**, *16*, 249; [d] T. Bjorvatten, O. Hassel, *Acta Chem. Scand.* **1966**, *20*, 2601; [e] C. K. Prout, B. Kamenar, *Molecular Complexes, Vol. 1* (Ed.: R. Foster), Elek Science, London, **1973**, p. 151; [f] C. Geron, M. Gomel, *J. Chim. Phys. Phys.-Chim. Biol.* **1978**, *75*, 241; [g] A. C. Legon, *Angew. Chem.* **1999**, *111*, 2850; *Angew. Chem. Int. Ed.* **1999**, *38*, 2686; [h] F. H. Allen, B. S. Goud, V. J. Hoy, J. A. K. Howard, G. R. Desiraju, *J. Chem. Soc. Chem. Commun.* **1994**, 2729.

An electron density transfer occurs from the electron donor site (Lewis base) to the halogen atom (acceptor site, Lewis acid) resulting in an interpenetration of van der Waals volumes. Some characteristics of these non-covalent interactions depend on the nature of the interacting partners, for instance the relative role of the specific attractive forces between the involved atoms (e.g. electrostatic effects, polarisation, charge-transfer, dispersion contributions).[7] Some other aspects remain quite constant in a wide variety of interactions, for instance the angle (approximately planar in most cases) formed by the covalent and non-covalent bondings around the halogen atom. Numerous properties characterizing this interaction run parallel to those of the hydrogen bond and the term "halogen bond" has been proposed to stress the existing analogies.[3]

Halogen molecules (mainly I_2 and Br_2, but also Cl_2 and interhalogens such as ICl) have traditionally played a key role

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[**] Perfluorocarbon-Hydrocarbon Self-Assembly, Part 14; for Part 13 see: ref. [17d]

in the identification of the structural aspects of these intermolecular interactions. They nevertheless may not be the ideal modules to define the inherent characteristics of the halogen bonding. In fact, one or both the iodine atoms of I_2 work as electron acceptors as a function of the strength of the electron donor species, resulting in dramatic differences on the supramolecular architecture of the formed co-crystals.[8] In other cases I_2 can work as an amphoteric species, one iodine atom functioning as electron acceptor and the other as electron donor.[9]

The use of modules which are better defined and more robust in the pattern of the halogen bonding they inherently tend to form, allows a deeper and more subtle study of the characteristics of this intermolecular interaction. Polyhalogenated carbon derivatives possess these definition and robustness requirements and have already been employed with a wide variety of electron donors. For instance, triiodo- and tribromomethane as well as their tetrasubstituted analogues have been used since early sixties while, more recently, particular attention has been paid to diiodobenzene[10] and iodoacetylenene[11] derivatives. Being bound to a carbon framework, the different halogen atoms of these compounds do not directly interact each other from the electronic point of view and thus work as independent acceptor sites, the involvement of one of them in an halogen bonding causing no substantial changes in the binding ability of the other halogen atom(s) of the molecule.

In order to deepen the understanding of the properties of the halogen bonding and structural aspects of the supramolecular architectures in addition to the potential of this interaction in crystal engineering, we focussed our attention on haloperfluorocarbon compounds as they present some advantages with respect to their hydrocarbon parents.

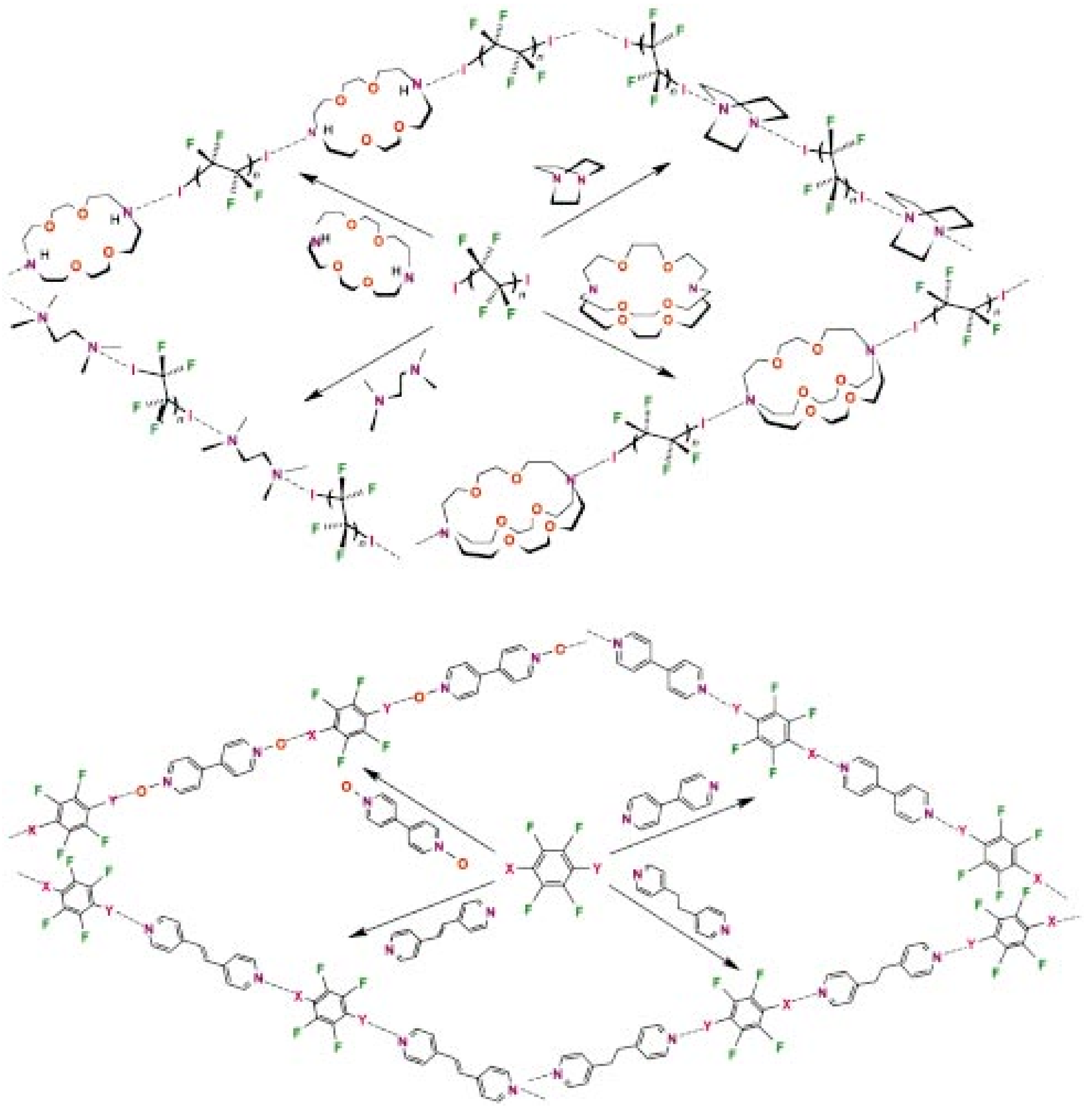
Fluorine atoms and perfluorinated residues are strongly electronegative[12] so that the electron accepting ability of halogen atoms in perfluorocarbon (PFC) halides is definitely higher than in corresponding hydrocarbon (HC) halides. Emblematically, the reaction of trimethylamine with iodomethane begins with the nitrogen lone pair entering the carbon atom from the opposite side to the iodine atom in an S_N2-type reaction. In contrast, trimethylamine reacts with iodotrifluoromethane through either a halogenophilic mechanism (i.e., S_N2 attack on the partially positively charged halogen) or an $S_{RN}1$ sequence;[13] in both cases the start of the reaction is marked by the entrance of the nitrogen lone pair on the iodine atom from the side opposite to the carbon atom. Moreover, C−H groups in the HC halides can be involved in weak attractive interactions with electron donor sites[14] and their formation may prevent or alter the formation of other interactions of comparable strength, as may sometimes be the case of the halogen bonding. Differently, the C−F groups of PFC derivatives have a very weak tendency to give rise to any attractive interaction, as made apparent by the non-miscibility of many perfluorinated hydrocarbons, ethers, and tertiary amines with both water and common organic solvents.[15] As a consequence, the use of PFC halides minimises possible interferences in a pattern of intermolecular interactions controlled by the halogen bonding. Finally, one of the reasons of the recent revival of interest in the use of iodine for the formation of halogen bonded co-crystals, is that I_2 allows polymorphs to be isolated and interconverted[8] as it easily works as a removable structural template. Also PFC derivatives can behave similarly as they are notoriously more volatile than parent HCs.

Discussion

Few reports can be found in the literature describing the attractive intermolecular interaction existing between PFC halides and nucleophilic species, low temperatures being frequently used when solid complexes were studied.[16] The employment of dihalo PFCs and dinitrogen HCs allowed us to obtain adducts which are routinely solid and stable in the air at room temperature. Indeed, when bifunctional electron acceptors and bifunctional donors are used, the interaction is doubled at either ends of the modules and the one-dimensional infinite chains formed are solid at room temperature, while analogous dimers, formed by monofunctional modules, are usually liquid under the same conditions. The effectiveness of the protocol is proven by the fact that a wide diversity of highly crystalline supramolecular architectures have been obtained starting from diiodoperfluoroalkanes or -arenes as acid modules and from pyridine derivatives or dialkyl- or trialkyl amines as basic modules[17] as in Scheme 1.

Extensive studies of these halogen-bonded architectures by X-ray analyses showed how the attractive $N\cdots I\text{-}R_f$ interaction (R_f = perfluoroalkyl or perfluoroaryl residue) is specific, directional and strong enough to overcome the low affinity existing between PFC and HC modules and to drive their self-assembly into one-dimensional infinite networks. The similarity between perfluoroalkyliodides and iodine in halogen bonded co-crystal formation holds not only for the $N\cdots I$ bond length, which is around 2.80 Å in the $N\cdots I\text{-}R_f$ adducts (approximately 0.8 times the sum of the van der Waals radii for nitrogen and iodine[18]), but also for the $N\cdots I\text{-}X$ angle width (X = C or I, respectively); the latter spans from 177 to 165° (see Schemes 1, 2) in a nearly linear geometry of the $N\cdots I\text{-}X$ system, which is consistent with the $n \rightarrow \sigma^*$ character of the interaction.[19] An extented C−X (X = Br, I) bond length was observed in the co-crystals with respect to the pure halo PFC, so generally the stronger the halogen bonding, the greater the lengthening turns out to be, consistent with an electron donation from nitrogen to iodine.[20]

A covalent bond can be characterised by its length and dissociation energy, or alternatively by the selective reactions; the selectivity then is merely a result of the peculiarities of the bond and its surrounding. Similarly, a non-covalent interaction can be characterised by its geometric and energetic properties or by the selective supramolecular synthesis. After establishing some structural features of the halogen bonding (e.g. bond angles and lengths) as briefly summarised above, some dynamic features (e.g. recognition preferences, ability to prevail over other interactions in driving self-assembly processes, and ability to be exchanged from one network to another without losing its structural properties) will be addressed by considering conveniently tailored experiments of selective non-covalent synthesis where the components



Scheme 1. Diagrams showing co-crystals given by aliphatic dinitrogen HCs with α,ω-diiodoperfluoroalkanes (top) and aromatic dinitrogen HCs with α,ω-dihaloperfluoroarenes (bottom).

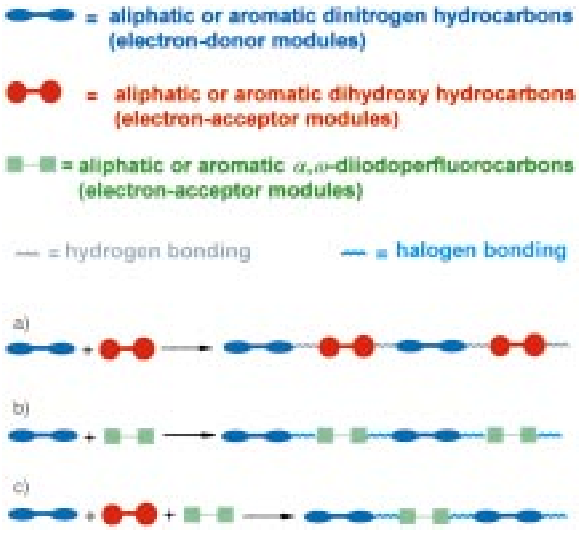
(sites) involved in self-assembly phenomena are identified out of a multi-component (multi-site) system.

Selectivity between hydrogen bonding and halogen bonding: A first indication of the relative strength of the hydrogen and halogen bonding came from solution calorimetry which is a simple and convenient tool to study weak intermolecular interactions. A complex formation enthalpy (ΔH_f) of 31.4 kJ mol^{-1} was measured for the dimer between 1-iodoperfluorohexane and 2,2,6,6-tetramethylpiperidine[21] and a prototype hydrogen-bonded complex (triethylamine/*n*-butanol) gave $\Delta H_f = 23$ kJ mol^{-1}.[22] The difference between halogen and hydrogen bonding for other couple sets can be even larger than we report here as tetramethylpyperidine is a medium strength electron donor.[23]

Experimental results consistent with this relative strength of the halogen and hydrogen bondings were obtained by directly contrasting the two interactions in competitive experiments.

A solid halogen bonded network is obtained by co-crystallising 1,2-bis(4-pyridyl)ethane and 1,4-diiodotetrafluorobenzene; when the same Lewis base is treated with hydroquinone an hydrogen bonded one-dimensional infinite chain is formed. The thermal characterisation by differential scanning calorimetry (DSC) of co-crystals thus obtained gave some useful qualitative information about the species formed. The melting endotherms of the pure components were missing in corresponding co-crystals. The difference between the melting point of the halogen bonded complex and the melting points of starting modules was definitely higher than shown by the hydrogen bonded co-crystal and corresponding starting modules. These results, along with the measurement of fusion enthalpies, clearly indicate that halogen bonded assemblies are more effectively stabilised than solids held together by hydrogen bondings.

To test the ability of the halogen bonding to control the selection of the interacting partners, equimolar amounts of the above-mentioned three components (1,2-bis(4-pyridyl)-ethane, 1,4-diiodotetrafluorobenzene, and hydroquinone) were dissolved in excess acetone. After a few days at room temperature, only the pure co-crystal compounded by the dinitrogen heteroaromatic and the diiodoperfluoroarene separated, while hydroquinone remained in solution (Scheme 2). In this system halogen bonding proved more effective than hydrogen bonding in controlling the construction of supramolecular architectures.



Scheme 2. Schematic diagram representing the formation of hydrogen bonded a) and halogen-bonded b) networks. When the two non-covalent interactions are competing at the same time in the solution c), the latter prevails over the former in identifying the modules to be involved in the self-assembly process.

Other competitive experiments performed with aliphatic rather than aromatic molecular units further proved the general ability of halogen bonding to prevail over hydrogen bonding in identifying the complementary motifs involved in the supramolecular self-assembly process.

Hydrogen bonding plays an important role in stabilising supramolecular aggregates even in water. In aqueous solution the nitrogen lone pairs of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) are hydrogen bonded to the solvent; when a stochiometric amount of 1,2-diodotetrafluoroethane, which is completely insoluble in water, was added to an aqueous solution of TMEDA, a rapid precipitation of the pure halogen bonded co-crystal occurred. *N*,*N*,*N*′,*N*′-Tetramethyl-1,4-butanediamine and its -1,6-hexane- analogue as well as 4,4′-dipyridyl gave similar behaviour. In all these cases, halogen bonding is strong enough to drive the phasing out of the different dinitrogen compounds from the aqueous solution.[2]

Interestingly from a preparative point of view, no crystallisation water is ever found in the formed PFC-HC complexes, when starting from the hydrated form of the hydrocarbon electron donor; this is largely independent from the solvent used for the crystallisation. This peculiar property of halogen bonded PFC iodides to substitute water in the crystal packing of the lone-pair donors, coupled with the easy removal of these iodoperfluoro compounds from the formed PFC-HC co-crystals through vacuum pumping, could be developed as a general, low cost, and large scale way to obtain dinitrogen electron donors (or their derivatives) in anhydrous form. Indeed, polyamines and their *N*-oxides are usually highly hygroscopic and their dehydration is often troublesome. This is the case for instance of 1,4-diazabicyclooctane (DABCO) and 4,4′-bipyridine-*N*,*N*′-dioxide; these chemicals are marketed in polyhydrated form and were easily obtained in anhydrous form by co-crystallisation with 1,2-diiodotetrafluoroethane and 1,4-diiodotetrafluorobenzene, respectively, and successive sublimation of the iodoperfluoro module.

Selectivity amongst different electron acceptors: Numerous analytical techniques consistently show how in the solid, liquid and gas phases the halogen bonding formed by chlorine, bromine and iodine atoms have different strengths.[3a,b, 5] Quantum chemical calculations at the DFT and MP2 level on the $CF_3X \cdots NH_3$ intermolecular interactions,[24] predict that the non-covalent binding energies in the complexes increase moving from chlorine to bromine to iodine, thus following the order of halogen atom polarisabilities, consistent with a key role of halogen polarisation (and/or charge-transfer energies) in the interaction. A non-covalent binding energy as high as 27 $kJ\,mol^{-1}$ is calculated for the $CF_3I \cdots NH_3$ interaction.

The same scale of electron acceptor effectiveness (R_f-Cl < R_f-Br < R_f-I) was established by using ^{19}F NMR spectroscopy.[23, 25] The -CF_2X signals show large high-field shifts ($\Delta\delta_{\text{-CF}_2\text{X}} = \delta_{\text{-CF}_2\text{X in } n\text{-pentane}} - \delta_{\text{-CF}_2\text{X solution with electron donor}} \gg 0$) upon halogen bonding formation and the stronger the interaction, the larger the shift. The ^{19}F NMR spectra of 1,2-diiodo- and 1,2-dibromotetrafluoroethane as well as of various 1-iodo- and corresponding 1-bromoperfluoroalkanes have been recorded by using a wide set of structurally different electron donor compounds, the upfield shifts given by the iodine substituted Lewis acids being invariably larger than those given by the bromine substituted acids (Table 2).

The acidity scale (Cl < Br < I) we observed in PFC halides is the same reported for HC halides,[7, 26] fluorine for hydrogen substitution simply resulting in definitively stronger interactions as predicted theoretically[24] and proven experimentally.[27] The neighbouring group effect on the electron accepting properties of a given halogen atom has been widely recognised, where the introduction of electron withdrawing residues results in stronger interactions.[7, 27] The chemical shift changes in ^{19}F NMR spectra of perfluoroalkyl halides, induced by a given electron donor, increase moving from primary to secondary to tertiary halides;[16d] the halogen bonding (pre-reactive state)[3c,d] evolves into a chemical reaction under

Table 2. ^{19}F NMR chemical shift differences of 1,2-dihalotetrafluoroethanes in different solvents.

Solvent	$I(CF_2)_2I$ $\Delta\delta_{CF_2I}$[a]	$Br(CF_2)_2Br$ $\Delta\delta_{CF_2Br}$[a]
cyclohexylamine	11.10	2.37
piperidine (PPR)	11.23	2.40
2,2,6,6-tetramethyl-PPR	6.92	1.48
N-methyl-PPE	8.89	2.07
1,2,2,6,6-pentamethyl-PPR	2.64	0.56
tetrahydrofuran	4.13	0.95
tetrahydrothiophene	5.38	0.76
pyridine	7.32	1.12
2,6-dimethylpyridine	5.86	0.90
4-isopropylpyridine	7.71	1.18
4-acetylpyridine	5.87	0.90
furan	1.11	0.13
thiophene	1.41	0.26
acetonitrile	2.74	0.45

[a] $\Delta\delta = \delta_{n\text{-pentane}} - \delta_{\text{solvent}}$; $\delta_{ICF_2CF_2I\text{ in }n\text{-pentane}} = -52.42$; $\delta_{BrCF_2CF_2Br\text{ in }n\text{-pentane}} = -63.32$.

milder conditions when starting from a tertiary than from a secondary or even a primary perfluoroalkyliodide.

In the solid phase, the acidity scale I > Br > Cl has been firmly recognised through Cambridge Structure Database searches.[7] As a result, it is not surprising that when diiodoperfluoroalkanes interact with dinitrogen substituted hydrocarbon donors (e.g. amine and pyridyl derivatives) halogen bonded adducts, which are solid at room temperature, are routinely formed, while dibromo- or dichloroperfluoroalkanes form adducts which are liquid; the higher volatility of these latter acids possibly play a role in this difference. Moreover, while both dibromo- and diiodoperfluoroarenes form solid 1:1 co-crystals with dinitrogen substituted HC donors (e.g. 1,4-dibromo- and 1,4-diiodotetrafluorobenzene with 1,2-bis-(4-pyridyl)ethane) (Scheme 3), melting points of bromine containing co-crystals are definitively lower than those of corresponding iodine containing co-crystals.

Scheme 3. Comparison of the structural parameters of two co-crystals given by 1,2-bis(4-pyridyl)ethane and 1,4-diiodotetrafluorobenzene (top) and 1,4-dibromotetrafluorobenzene (bottom). Colours are as follows: blue, nitrogen; orange, fluorine; red, iodine; violet, bromine; grey, carbon.

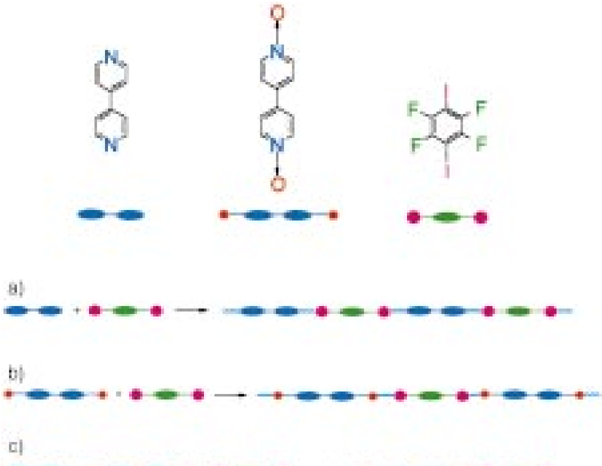
While only qualitative correlation can be established among the intermolecular interaction strength and the melting point, we adopted the melting point differences among co-crystals, containing structurally related modules, as an heuristic principle to predict the co-crystal precipitating preferentially from multi-component solutions. Indeed, co-crystals formed by 1,4-diiodotetrafluorobenzene with either 1,2-bis-(4-pyridyl)ethane or a 2,2′:6′,2″-terpyridine[28] precipitates in pure form from a clear acetone solution also containing equimolar amounts of 1,2-dibromotetrafluorobenzene; this is despite the fact that this latter acid also gives rise to solid and high melting adducts with the above-mentioned donors. While dibromoperfluoroalkanes do not form solid co-crystals with diamino or dipyridyl-substituted hydrocarbons, they can be incorporated into solid supramolecular architectures if particularly strong electron donors are used, namely if anionic rather than neutral bases are employed. For instance, preliminary experiments show how 2,3-dibromohexafluoropropane forms infinite networks which are solid at room temperature when bromide anions work as electron donor motifs and the self-assembly process is effective and selective enough to allow the resolution of the racemic fluorocarbon into single enantiomers when the hydrobromide of an enantiopure amine is used as donor species.[20]

Selectivity amongst different heteroatoms as electron donors: While different heteroatoms with free lone pairs (e.g. O, S, N, P) can work as electron donors to PFC as well as HC halides, up till now heteroatom NMR spectroscopy has been used to detect the direct involvement of the heteroatom in the halogen bonding only for nitrogen substituted electron donors. For instance, on dimer formation between quinuclidine and 1-iodoheptafluoropropane, the ^{14}N NMR signal shifts to lower fields and undergoes a significant line broadening (up to 7 ppm and up to 2.25 times, respectively, under conditions of maximum complexation), consistent with an increase in the quadrupolar relaxation of the ^{14}N nucleus due to a specific I···N intermolecular association.[23]

^1H and ^{13}C NMR spectra of the donor modules also can show major changes on halogen bonded complex formation, but the most effective and simple tool to detect the formation of the halogen bonding in the liquid phase is ^{19}F NMR spectroscopy of PFC halides. In fact, the $\Delta\delta_{\text{-}CF_2X}$ values revealed to be a sensitive probe to rank not only the acceptor, as discussed above, but also the donor motifs according to the strength of the halogen bonding they form (Table 2). $\Delta\delta_{\text{-}CF_2X}$ Values, obtained by using several mono- or dihaloperfluoroalkanes as electron acceptor motifs, allowed a wide series of heteroatom substituted HC derivatives to be ranked as a function of their electron donor ability. In general, n-donors work better than π-donors and, for a given heteroatom, stronger interaction is observed in higher hybridisation states. Both steric and electronic effects in the donor module affect the strength of the halogen bonding formed by a given heteroatom. The more crowded the environment around the donor site is, the weaker the resulting interaction. An electron withdrawing or releasing environment around the donor heteroatom diminishes or increases, respectively, its donor ability. Interestingly while amongst the different halogens the tendency to form short C-X···El interactions (El = electron donor) is the same in HC and PFC halides (I > Br > Cl), as far as different heteroatom donors are concerned the order in which the interactions become stronger is $S < N < O$[7] and $S, O < N$ when HC and PFC halides are employed, respectively.

Raman and IR spectroscopies are also powerful tools to detect the formation of halogen bonded adducts because they allow the ranking of electron donors as a function of their strength both in the liquid and in the solid phases.[29] The scales obtained by using vibrational spectrosopies are strictly parallel to those filed by ^{19}F NMR spectroscopy. Compared with the stretching modes of the pure starting modules, halogen bonded complexes involving PFC halides show blue and red shifts for the C–H and the C–F stretching modes, respectively. However, the more diagnostic signals are the C–I stretching modes and the -CF$_2$I deformation modes in Raman spectra (occurring in the 270 and 670 cm^{-1} region, respectively); both bands undergo a red shift in the R_f-I···El adduct. Better donors result in larger shifts; for instance, ethers and thioethers cause smaller red shifts than amines and the larger the steric hindrance around the donor heteroatom, the smaller the observed red shift.

Our search for heteroatom sites which can work as better electron donors than amine and pyridine moieties moved from the observation that for oxygen donors, the higher the electron density on the oxygen, the stronger its electron donor ability. For instance, the $\Delta\delta_{\text{-CF}_2\text{X}}$ shown by 1,2-diiodotetrafluoroethane with acetone, DMSO, and HMPA are 3.63, 7.22, and 8.23, respectively.[23] It is thus not surprising that heteroaromatic *N*-oxides give particularly large high field shifts in ^{19}F NMR spectra of PFC halides. These shifts are even larger than those given by the nitrogen atoms of corresponding non-oxidized heteroaromatic parent compounds[30] as if the oxygen atoms of *N*-oxides are stronger donors than the nitrogen atoms of corresponding parent heteroaromatic compounds. Indeed, 1,4-diiodotetrafluorobenzene easily gives solid one-dimensional infinite networks with both 4,4′-bipyridine and its *N*,*N*-dioxide, Raman and IR analyses of the two co-crystals confirming that the I···O interaction is, in these cases, stronger than the I···N interaction. Consistent with these results only the oxygen donor is present in the solid supramolecular architecture which forms preferentially, while the nitrogen donor remains in solution (Scheme 4), when a mixture of 4,4′-bipyridine, its *N*,*N*′-dioxide, and 1,4-diiodotetrafluorobenzene is crystallized.



Scheme 4. Schematic diagram representing the formation of halogen-bonded networks involving 1,4-diiodotetrafluorobenzene and 4,4′-bipyridine a) and its *N*,*N*′-oxide derivative b). When the three components are present at the same time in the solution c), the crystal containing the *N*,*N*′-dioxide forms preferentially as the O···I interaction prevails over the N···I interaction in identifying the modules to be involved in the co-crystal.

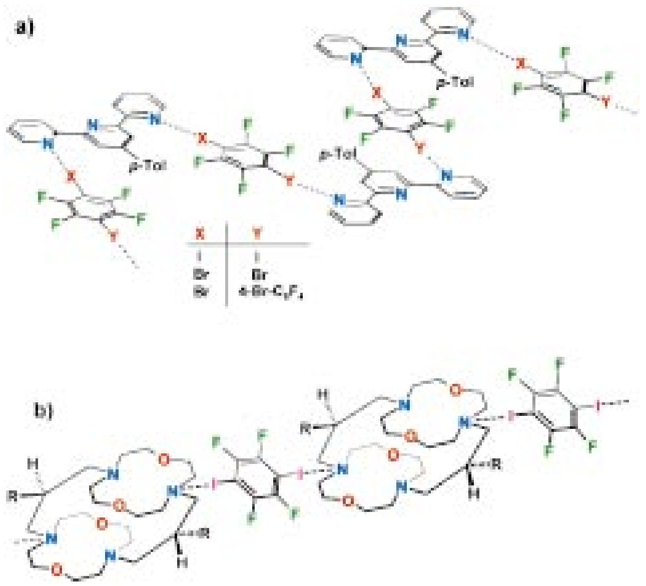
The R_fI···O-N halogen bond formed by pyridine *N*-oxide being particularly strong, prevails not only over other halogen bondings formed by different heteroatoms but also over the OH···O-N hydrogen bond. X-ray single-crystal analysis shows how crystallisation of the polyhydrated form of 4,4′-dipyridyl-*N*,*N*′-dioxide and 1,4-diiodotetrafluorobenzene from methanol generates a solid supramolecular network in which the *N*,*N*′-dioxide and the diiodofluorobenzene are exclusively present and alternate in a one-dimensional linear fashion. Clearly, the halogen bonding induces the precipitation of the *N*,*N*′-dioxide out of a methanol solution where it is heavily involved in hydrogen bonding networks; the *N*,*N*′-dioxide can be obtained in pure and anhydrous form after the iodofluoroarene is sublimed from the co-crystal. The halogen bonding stores the information for selection and instructs both the electron acceptor (competitive crystallisation of 4,4′-bipyridine, its *N*,*N*-dioxide, and 1,4-iiodotetrafluorobenzene mixture) and the electron donor (crystallisation of 4,4′-bipyridyl-*N*,*N*-dioxide polyhydrate and 1,4-iiodotetrafluorobenzene from methanol) to choose the partner with which it show preferential interaction.

Selectivity between different nitrogen atoms as electron donors: Whenever dinitrogen HCs having a linear shape interact with α,ω-dihalo-PFCs which have a rod-like structure (Figures 1 and 2) one-dimensional infinite chains invariably form in which the halogen bonding reiterates at either ends of each module and all the donor and acceptor sites interact each other.[31] When more complex modules are used, the reliability of the rational design diminishes as others factors (halogen bonding induced conformational changes in the modules, steric hindrance prevention against the halogen atom approach to the donor site, etc.), can influence the binding pattern and the lattice organisation in the co-crystals.

This is the case, for example, for 4′-(4-methylphenyl)-2,2′:6′-2″-terpyridine, which works as a bidentate donor when it forms co-crystals with 1,4-diiodotetrafluorobenzene, its dibromo analogue, and 4,4′-dibromooctafluorobiphenyl.[28] In the supramolecular architectures obtained, the HC and PFC modules are ordered in a herringbone fashion by the halogen bonding between the 1,1″-nitrogen atoms of each terpyridine (TPY) unit and two iodine atoms of two distinct perfluoroarene units (Scheme 5).

When TPY derivatives self-assemble with metal cations they adopt a partner induced conformation and reshape from the ground state 2,2′-*s-trans*,6′,2″-*s-trans* conformation[32] to the less stable 2,2′-*s-cis*,6′,2″-*s-cis* arrangement[28] in order to work as tridentate donors to a single cation. Differently, it preserved in the halogen-bonded co-crystal the ground state *s-trans-s-trans* arrangement, when we used TPY with haloperfluoroarenes, so that the approach of an iodine atom to the 1′-nitrogen was hampered by the two *ortho* pyridyl appendages and only the two 1,1″-nitrogens were halogen bonded. A site-selective supramolecular synthesis is realised as a consequence of steric hindrance.

Other cases have been observed where HC electron donors maintain their ground state conformation when involved in halogen bonded networks while they adopt a partner induced conformation when binding a metal cation. This difference

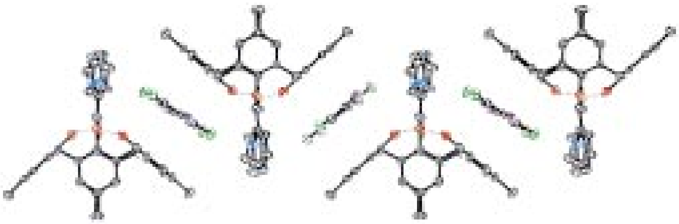


Scheme 5. a) View of the ribbon given by 4′-(4-methylphenyl)-2,2′:6′-2″-terpyridine with various dihaloperfluoroarenes. b) Infinite network formed by the reported macrotricyclic cylindrical cryptand and 1,4-diiodotetrafluorobenzene. In the HC–PFC supramolecular architecture only two of the four nitrogens of the electron donor motif are halogen-bonded to iodine atoms of the acceptor motif.

between halogen bonding and metal binding is not surprising if we consider that the strength of the latter interaction is intermediate between the covalent and the non-covalent domain. For instance, when the macrotricyclic cylindrical cryptand reported in Scheme 5 chelates metal cations it completely reshapes its structure,[33] directs all the four lone pairs inside the cavity and works, as far as nitrogen sites are concerned, as a tetradentate donor to a single metal ion. Conversely, when the cryptand interacts with 1,4-diiodotetrafluorobenzene it maintains its ground state conformation where only two out of the four nitrogen lone pairs are oriented inside the cavity so that it involves in halogen bonds only the two nitrogen lone pairs which are outwardly oriented thus behaving as a bidentate donor to two different iodines.[34]

Both K.2.2. (K = krypto fix) and K.2.2.2. afford one-dimensional infinite chains with α,ω-diiodoperfluoroalkanes.[31, 35] The competitive co-crystallisation, in which all three components are present in the solution, gives preferentially the infinite chain containing K.2.2. and the PFC diiodides. This is due to the fact that K.2.2. is pre-organised for divergent *exo*-intermolecular recognition processes[36] as the nitrogen lone pairs are directed outside the cavity defined by the polyoxomethylene chains[37] in the ground state conformation while K.2.2.2. directs its lone pairs inside the cavity and has thus to undergo nitrogen inversion before giving the PFC–HC co-crystal. The relevance of the ground state conformation of the donor module in divergent self-assembly processes becomes apparent.

In all the supramolecular architectures described above, the pattern of the crystal lattice is mainly controlled by the halogen bonding, as often occurs when the formation of a co-crystal is obtained resorting to a strong intermolecular interaction. But cases may also exist where the halogen bonding collaborates with another interaction to determine the packing of the module in the crystal lattice. For instance, in the co-crystal obtained starting from a 1,3-bis-(pyridylmethyl)calix[4]arene derivative and 1,4-diiodotetrafluorobenzene,[38] the two modules are held in a sandwich arrangement by the attractive π,π-interactions[39] occurring between the electron rich phenol ring faces directed outside the calixarene cavity and the two electron poor faces of 1,4-diiodotetrafluorobenzene, see Scheme 6.



Scheme 6. ORTEP III view of the crystal packing of the two-dimensional supramolecular network given by 1,3-bis-(pyridylmethoxy)calix[4]arene and 1,4-diiodotetrafluorobenzene. Colours are as follows: black, carbon; sky blue, nitrogen; red, oxygen; violet, iodine; green, fluorine. Hydrogen atoms and methyl groups of calixarene module are omitted for clarity. Dotted lines represent the intramolecular hydrogen bonds.

Infinite one-dimensional non-covalent ribbons are formed in which the two modules alternate and different ribbons are cross-linked in a two-dimensional supramolecular network by the halogen bonding between the picolyl nitrogen atoms of calixarene modules in one chain and iodine atoms of the perfluoroarene module in another chain. In this crystal lattice, only a half of the halogen bondings which can potentially be formed are present as a result of the requirements associated with the presence of π,π-interactions and with the space filling by the packing of large molecules.

Conclusion

It has been proven that the halogen bonding can be considered as a first choice intermolecular interaction both reliable and effective to understand and rationally design self-assembly processes. The use of halogens and HC iodo-, bromo-, and chloroorganic derivatives as electron acceptor modules is well documented in the literature[3, 5] and in this paper PFC iodides and bromides have been used as acceptor modules because of the fact that their unequivocally targeted features allow the halogen bonding to be studied free from dramatic interference by other intermolecular interactions. The profile of the halogen bonding has been sketched by establishing its geometric and energetic characteristics and by identifying its pairing preferences through experiments of chemo-, site- and enantiospecific supramolecular synthesis.

A new intermolecular interaction is therefore accessible, and new aggregation processes can be realised with the novelty coming from either the identity of single modules that are assembled or from the way the modules are assembled.

For instance, effective and general self-assembly of PFC and HC modules has been realised for the first time just resorting to the halogen bonding and anions acting as particularly strong electron donors to carbon bound halogens,[20, 40] the halogen bonding becomes particularly well tailored to anion centered supramolecular chemistry, a field which still has to be conveniently developed.

Physical and chemical properties of bulk materials are not simply the sum of molecular properties of the constituting compound(s); this is particularly true when multicomponent materials are considered. A very few systems (e.g. PFC–HC emulsions or diblock and triblock compounds R_F-R_H and $R_F-R_H-R_F$, respectively) can be considered in the attempt to anticipate the properties of mixed PFC–HC supramolecular architectures. Nevertheless, also remembering that the unique and useful properties of PFC materials (e.g. Nafion, Teflon) are of high technological relevance, the few precedents cited above allow us to state that the properties of mixed PFC–HC supramolecular architectures, while hardly recognised, are expected to be of high interest.

The relevance of halogen bonding in the self-assembly of structurally different molecules extends to rather different fields. In biopharmacology for example, the interaction of iodine atoms of thyroid hormones with donor sites in the target protein has been suggested.[41] The C-X···El interactions can give explanation for the eudismic ratio observed for some anaesthetic agents commonly used in human therapy.[42] In synthetic chemistry, the halogen bonding can drag hydrocarbon reagents/catalysts into fluorous solvents, thus offering an alternative to the "perfluorinated ponytail" approach in fluorous based technology.[43] Moreover, this intermolecular interaction can lead to the development of a new generation of phase transfer catalysts useful in fluorous/aqueous, fluorous/organic biphasic systems,[44] where the anion is responsible for driving the transfer process and the cation turns into the naked, namely activated, species. As far as purification processes is concerned, the halogen bonding can be useful to purify both the donor and the acceptor modules. Specifically, it can allow hygroscopic bases to be obtained in anhydrous form, as discussed above, but it can also be used as a low cost and large scale approach for the separation of mixtures of PFC halides, a class of compounds of high technological relevance.[13] The halogen bonding may be also useful to obtain bromofluorocarbons in enantiopure form, for instance the anestethic halothane which is presently used in racemic form despite one enantiomer being more pharmacologically active than the other. The halogen bonding can also offer new entries in materials science. For instance, molecular conductors with a crystal structure determined by C-I···X (X = CN, Br, S) type cation···anion interaction have been described.[45] In addition, efficient non-linear optical (NLO) materials with a relatively rare packing, in which all β_{zzz} axes of the molecular hyperpolarisability β are aligned in a co-parallel fashion, have been obtained when halogen bonded architectures were formed starting from 1,4-diiodobenzene, 1,4-dinitrobenzene, 4-iodo-4′nitrobiphenyl or related species.[46]

In conclusion, the implications of the halogen bonding are far reaching and extend to all the fields where design and manipulation of aggregation processes play a key role.

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[1] *Transition Metals in Supramolecolar Chemistry* (Ed.: J.-P. Sauvage), Wiley, Chichester, **1999**.

[2] a) G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, Oxford, **1997**; b) C. B. Aacheröy, K. R. Seddon, *Chem. Soc. Rev.* **1993**, *22*, 397–407.

[3] a) J. M. Dumas, L. Gomel, M. Guerin, *The Chemistry of Functional Groups, Supplement D* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1983**, pp. 985–1020; b) H. A. Bent, *Chem. Rev.* **1968**, *68*, 587–648; c) A. C. Legon, *Chem. Eur. J.* **1998**, *4*, 1890–1897; d) A. C. Legon, *Angew. Chem.* **1999**, *111*, 2850–2880; *Angew. Chem. Int. Ed.* **1999**, *38*, 2687–2714; e) G. R. Desiraju, R. L. Harlow, *J. Am. Chem. Soc.* **1989**, *111*, 6757–6764.

[4] a) J. Burdeniuc, M. Sanford, R. H. Crabtree, *J. Fluor. Chem.* **1998**, *91*, 49–54; b) J. Burdeniuc, R. H. Crabtree, *Organometallics* **1998**, *17*, 1582–1586.

[5] O. Hassel, *Science* **1970**, *170*, 497–502.

[6] F. Guthrie, *J. Chem. Soc.* **1863**, *16*, 239; I. Remses, J. F. Norris, *Am. Chem. J.* **1896**, *18*, 90.

[7] J. P. M. Lommerse, A. J. Stone, R. Taylor, F. H. Allen, *J. Am. Chem. Soc.* **1996**, *118*, 3108–3116.

[8] a) R. D. Bailey, M. Grabarczyk, T. W. Hanks, W. T. Pennington, *J. Chem. Soc. Perkin Trans. 2* **1997**, 2781–2786; b) R. D. Bailey, G. W. Drake, M. Grabarczyk, T. W. Hanks, L. L. Hook, W. T. Pennington, *J. Chem. Soc. Perkin Trans. 2* **1997**, 2773–2779.

[9] E. L. Rimmer, R. D. Bailey, W. T. Pennington, T. W. Hanks, *J. Chem. Soc. Perkin Trans. 2* **1998**, *11*, 2557–2562.

[10] a) F. H. Allen, K. Biradha, G. R. Desiraju, V. J. Hoy, J. A. K. Howard, J. A. R. P. Sarma, R. Thaimattam, *Chem. Commun.* **1997**, 101–102; b) V. R. Pedireddi, A. Ranganathan, *Tetrahedron Lett.* **1998**, *39*, 1803–1806.

[11] a) R. Weiss, M. Rechinger, F. Hampel, A. Wolski, *Angew. Chem.* **1995**, *107*, 483–485; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 441–443; b) R. Weiss, O. Schwab, F. Hampel, *Chem. Eur. J.* **1999**, *5*, 968–974.

[12] S. G. Bratsch, *J. Chem. Ed.* **1985**, *62*, 101–103.

[13] C. Wakselman, A. Lanz in *Organofluorine Chemistry*: *Principles and Commercial Applications* (Eds.: R. E. Banks, B. E. Smart, J. C. F. Tatlow), Plenum Press, New York, **1994**.

[14] a) K. N. Houk, S. Menzer, S. P. Newton, F. M.Raymo, J. F. Stoddart, D. J. Williams, *J. Am. Chem. Soc.* **1999**, *121*, 1479–1487; b) M. Nishio, Y. Umezawa, M. Hirota, *The CH-Pi Interaction. Evidence, Nature and Consequences*, Wiley, New York, **1998**.

[15] a) J. Hildebrand, D. R. F. Cochran, *J. Am. Chem. Soc.* **1949**, *71*, 22–25; b) D. L. Dorset, *Macromolecules* **1990**, *23*, 894–901.

[16] a) I. J. McNaught, A. D. E. Pullin, *Aust. J. Chem.* **1974**, *27*, 1009–1015; b) A. C. Legon, D. J. Millen, S. C. Rogers, *Chem. Commun.* **1975**, 580–581; c) dimeric instead of polymeric structures have erroneously been attributed to some aggregates Q.-Y.Chen, Z.-T. Li, C.-M. Zhou, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2457–2462; d) Q.-Y. Chen, *Israel J. Chem.* **1999**, *39*, 179–192; e) G. K. Semin, T. A. Babushkina, S. P. Khrlakyan, E. Ya. Pervova, V. V. Shokina, I. L. Knunyants, *Teor. Eksp. Khim.* **1968**, *4*, 275–277 [*Chem. Abstr.* **1968**, *69*, 72685z].

[17] a) P. Cardillo, E. Corradi, A. Lunghi, S. V. Meille, M. T. Messina, P. Metrangolo, G. Resnati *Tetrahedron* **2000**, *56*, 5535–5550; b) M. T. Messina, P. Metrangolo, G. Resnati, *Asymmetric Fluoroorganic Chemistry*: *Synthesis*, *Applications and Future Directions*, ACS Symposium Series no. 746 (Ed. P. V. Ramachandran), American Chemical Society, Washington DC, **1999**, Chapter 17; c) E. Corradi, S. V. Meille, M. T. Messina, P. Metrangolo, G. Resnati, *Tetrahedron Lett.* **1999**, *40*, 7519–7523; d) P. Metrangolo, W. Panzeri, G. Resnati, A. Forni, T. Pilati, F. Fontana, *Supramol. Chem.* in press.

[18] A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441–451.

[19] R. Foster, *Organic Charge-Transfer Complexes*, Academic Press, London, **1969**, pp. 100.

[20] A. Farina, S. V. Meille, M. T. Messina, P. Metrangolo, G. Resnati, G. Vecchio, *Angew. Chem.* **1999**, *111*, 2585–2588; *Angew. Chem. Int. Ed.* **1999**, *38*, 2433–2436.

[21] E. Corradi, S. V. Meille, M. T. Messina, P. Metrangolo, G. Resnati, *Angew. Chem.* **2000**, *112*, 1852–1856; *Angew. Chem. Int. Ed.* **2000**, *39*, 1782–1786.

[22] E. M. Arnett, L. Joris, E. Mitchell, T. S. S. R. Murty, T. M. Gorrie, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1970**, *92*, 2365–2377.

[23] M. T. Messina, P. Metrangolo, W. Panzeri, E. Ragg, G. Resnati, *Tetrahedron Lett.* **1998**, *39*, 9069–9072.

[24] G. Valerio, G. Raos, S. V. Meille, P. Metrangolo, G. Resnati, *J. Phys. Chem. A* **2000**, *104*, 1617–1620.

[25] A. Lunghi, P. Cardillo, M. T. Messina, P. Metrangolo, W. Panzeri, G. Resnati, *J. Fluorine Chem.* **1998**, *91*, 191–194.

[26] P. L. Wash, S. Ma, U. Obst, J. Rebek Jr., *J. Am. Chem. Soc.* **1999**, *121*, 7973–7974.

[27] R. N. Haszeldine, *J. Chem. Soc.* **1953**, 2622–2626.

[28] A. Manfredi, M. T. Messina, P. Metrangolo, T. Pilati, S. Quici, G. Resnati, *Supramolecul. Chem.* **2000**, *12*, 405.

[29] M. T. Messina, P. Metrangolo, W. Navarrini, S. Radice, G. Resnati, G. Zerbi, *J. Mol. Struct.* **2000**, *534*, 87–94.

[30] P. Metrangolo, T. Pilati, G. Resnati, unpublished results.

[31] V. Amico, S. V. Meille, E. Corradi, M. T. Messina, G. Resnati, *J. Am. Chem. Soc.* **1998**, *120*, 8261–8262.

[32] a) C. A. Bessel, R. F. See, D. L. Jameson, M. R. Churchill, K. J. Takeuchi, *J. Chem. Soc. Dalton Trans.* **1992**, 3223–3328; b) D. Armspach, E. C. Constable, C. E. Housecroft, M. Neuburger, M. Zehnder, *New J. Chem.* **1996**, *20*, 331.

[33] P. L. Anelli, G. Ciani, F. Montanari, S. Quici, A. Sironi, *J. Org. Chem.* **1988**, *53*, 5292–5298.

[34] S. V. Meille, P. Metrangolo, G. Resnati, unpublished results.

[35] W. Navarrini; P. Metrangolo, T. Pilati, G. Resnati, *New J. Chem.* **2000**, *24*, 777–780.

[36] O. Félix, M. W. Hosseini, A. De Cian, J. Fischer, *Tetrahedron Lett.* **1997**, *38*, 1755–1758.

[37] L. R. MacGillivray, J. L. Atwood, *Chem. Commun.* **1997**, 477–478.

[38] M. T. Messina, P. Metrangolo, S. Pappalardo, M. F. Parisi, T. Pilati, G. Resnati, *Chem. Eur. J.* **2000**, *6*, 3495–3460.

[39] G. W. Coates, A. R. Dunn, L. M. Henling, J. W. Ziller, E. B. Lobkovsky, R. H. Grubbs, *J. Am. Chem. Soc.* **1998**, *120*, 3641–3649; S. M. Ngola, D. A. Dougherty, *J. Org. Chem.* **1998**, *63*, 4566–4567; G. W. Coates, A. R. Dunn, L. M. Henling, D. A. Dougherty, R. H. Grubbs, *Angew. Chem.* **1997**, *109*, 290–293; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 248–251.

[40] J. Grebe, G. Geiseler, K. Harms, B. Neumüller, K. Dehnicke, *Angew. Chem.* **1999**, *111*, 183–186; *Angew. Chem. Int. Ed.* **1999**, *38*, 222–225.

[41] L. K. Steinrauf, J. A. Hamilton, B. C. Braden, J. R. Murrel, M. D. Benson, *J. Biol. Chem.* **1993**, *268*, 2425.

[42] a) N. P. Franks, W. R. Lieb, *Nature* **1994**, *367*, 607–614; b) R. G. Eckenhoff, S. Johansson, *Pharmacol. Rev.* **1997**, *49*, 343–367.

[43] a) A. Studer, S. Hadida, R. Ferritto, S.-Y. Kim, P. Jeger, P. Wipf, D. P. Curran, *Science* **1997**, *275*, 823; b) I. T. Horwáth, J. Rabái, *Science* **1994**, *266*, 72.

[44] D. P. Curran, *Angew. Chem.* **1998**, *110*, 1230–1255; *Angew. Chem. Int. Ed.* **1998**, *37*, 1175–1196.

[45] T. Imakubo, T. Maruyama, H. Sawa, K. Kobayashi, *Chem. Commun.* **1998**, 2021; T. Imakubo, H. Sawa, R. Kato, *Chem. Commun.* **1995**, 1667–1668.

[46] J. Hulliger, P. J. Langley, *Chem. Commun.* **1998**, 2557–2558; N. Masciocchi, M. Bergamo, A. Sironi, *Chem. Commun.* **1998**, 1347–1348; J. A. R. P. Sarma, F. H. Allen, V. J. Hoy, J. A. K. Howard, R. Thaimattam, K. Biradha, G. R. Desiraju, *Chem. Commun.* **1997**, 101–102.