

Halogen Bonding Based Recognition Processes: A World Parallel to Hydrogen Bonding[†]

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Received October 28, 2004

ABSTRACT

Halogen bonding is the noncovalent interaction between halogen atoms (Lewis acids) and neutral or anionic Lewis bases. The main features of the interaction are given, and the close similarity with the hydrogen bonding will become apparent. Some heuristic principles are presented to develop a rational crystal engineering based on halogen bonding. The focus is on halogen-bonded supramolecular architectures given by halocarbons. The potential of the interaction is shown by useful applications in the field of synthetic chemistry, material science, and bioorganic chemistry.

Introduction

The electron density donation from rich to poor sites is probably the most general way intermolecular interactions take place.¹ The hydrogen atom is the most common electron acceptor site, and hydrogen bonding (HB) is by far the most frequently occurring noncovalent interaction in recognition processes. Other atoms equally work as acceptor sites, and in this paper, we will focus on halogen atoms and the interaction to which they give rise, halogen bonding (XB).² A general overview on XB will be given first

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to acquaint the nonexperts. This overview will show how XB is a strong, specific, and directional interaction that gives rise to well-defined supramolecular synthons. Then we will focus on interactions involving halocarbons and on the supramolecular architectures that they produce. Some heuristic principles will spring from this, enabling us to develop an XB based crystal engineering, which may complement the possibilities offered by HB. Applications and prospects will conclude the paper.

The first unequivocal report on the ability of halogen atoms to form well-defined adducts with electron donor species dates back to 1863 when Guthrie described the formation of the $\text{NH}_3 \cdots \text{I}_2$ complex.³ In 1896, Remsen and Norris proved the general tendency of amines to form adducts with bromine and chlorine.⁴ Sixty years later, the crystallographic studies of Hassel were a landmark in the understanding of the XB characteristics. In his Nobel lecture, Hassel stressed the similarities between interactions where halogen and hydrogen atoms work as electron acceptors.⁵ Particularly important reviews on XB have been published by Bent (solid adducts),⁶ Dumas et al.,⁷ and Legon (gaseous adducts).⁸

Generalities on XB

The term XB will be used here for defining any noncovalent interaction involving halogens as electron acceptors. The general scheme $\text{D} \cdots \text{X}-\text{Y}$ thus applies to XB, in which X is the halogen (Lewis acid, XB donor), D is any electron donor (Lewis base, XB acceptor), and Y is carbon, nitrogen, halogen, etc.

This definition greatly generalizes the term used by Dumas et al.⁷ and comprises, among others, anion \cdots halogen and halogen \cdots halogen interactions, which were not included in the early meaning of the term.

The XB interaction energy spans over a very wide range, from 5 to 180 kJ/mol, the weak $\text{Cl} \cdots \text{Cl}$ interaction between chlorocarbons and the very strong $\text{I}^- \cdots \text{I}_2$ interaction in I_3^- being the extremes. Thanks to its strength, XB can prevail over HB in selecting the modules to be involved in competitive recognition processes.⁹

The attractive nature of XB causes $\text{D} \cdots \text{X}$ distances shorter than the sum of van der Waals radii of involved atoms. The stronger the interaction is, the shorter the $\text{D} \cdots \text{X}$ distance is.

In many cases, XB adducts are prereactive complexes (or intermediates) formed prior to chemical reactions. Indeed, the stronger interactions easily evolve into different molecular species if concentration, temperature, solvent polarity, or other parameters are changed. The 1:1 complex that dihalogen molecules form with alkenes and aromatics is a particularly well-known example.¹⁰ It lays on the way to addition/substitution products' formation.

[†] Dedicated to Prof. Dick Chambers on occasion of his 70th birthday.

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Theoretical investigation on the trends in XB shows that the nature of the involved atoms determines the relative relevance of different attractive forces between them. Charge-transfer, electrostatic effects, polarization, and dispersion contributions all play an important role.¹¹

Theoretical and experimental data prove that all four halogens work as XB donors, and the tendency to form strong interactions is $I > Br > Cl > F$. Dihalogen molecules, and interhalogens form strong XBs. Fluorine has a unique behavior. F_2 is a strong XB donor,^{8,12} but fluorocarbons are definitively poor XB donors as they exceptionally form XB.

As to halocarbons, XB formation is routinely observed with aryl and heteroaryl halides. This is not the case with unfunctionalized monohaloalkanes, which typically afford nucleophilic substitution products. On the other hand polyhaloalkanes frequently form halogen-bonded adducts. The strength order $C-X(sp) > C(sp^2) > C-X(sp^3)$ is usually followed.

The more electron withdrawing the atom, or the moiety, bound to the halogen is, the stronger is the XB to which it gives rise.¹³ Indeed, iodoperfluoroalkanes are particularly tailored to XB based crystal engineering.

Both π and n electrons can be involved in XB formation, and usually the former give weaker interactions than the latter.⁸ Increased electron density on the donor site results in stronger interactions.¹⁴ Anions are usually better XB acceptors than neutral species. Among halide anions, the tendency to form strong interactions in the condensed phases is $I^- > Br^- > Cl^- > F^-$. Nitrogen gives stronger XB than oxygen and sulfur. The relative effectiveness of the last two elements in XB formation often depends on the nature of the XB donor, as pairings after HSAB theory are favored. Moreover, when subtle differences are compared, it may happen that different techniques give different scales.

Several analytical methods have been used to detect XB formation,¹⁵ to define its nature, to establish its energetic and geometric characteristics, and to reveal the striking similarities between XB and HB. Practically all the energetic and geometric features known for HB complexes are encountered in XB complexes as well. Expectedly, halogens being larger than hydrogen, XB is more sensitive to steric hindrance than HB.

A definitive piece of information is given by X-ray structural analysis. It proves that the angle between the covalent and noncovalent bonds around the halogen in $D \cdots X-Y$ is approximately 180° .^{2,5} This is consistent with theoretical calculations according to which the electron density is anisotropically distributed around the halogen nucleus and the effective atomic radius along the extended $C-X$ bond axis is smaller than that in the direction perpendicular to this axis. When n electron donors are involved, XB is preferentially along the axis of the orbital containing the lone pair of D .¹⁶ Figure 1 shows the Crystal Structure Database (CSD) scatterplots of intermolecular $N \cdots I-C$ and $O \cdots I-C$ interactions versus $N \cdots I$ and $O \cdots I$ distances, respectively. Figure 2 shows the analogous scatterplot for the $I \cdots I-C$ interaction. The shorter the

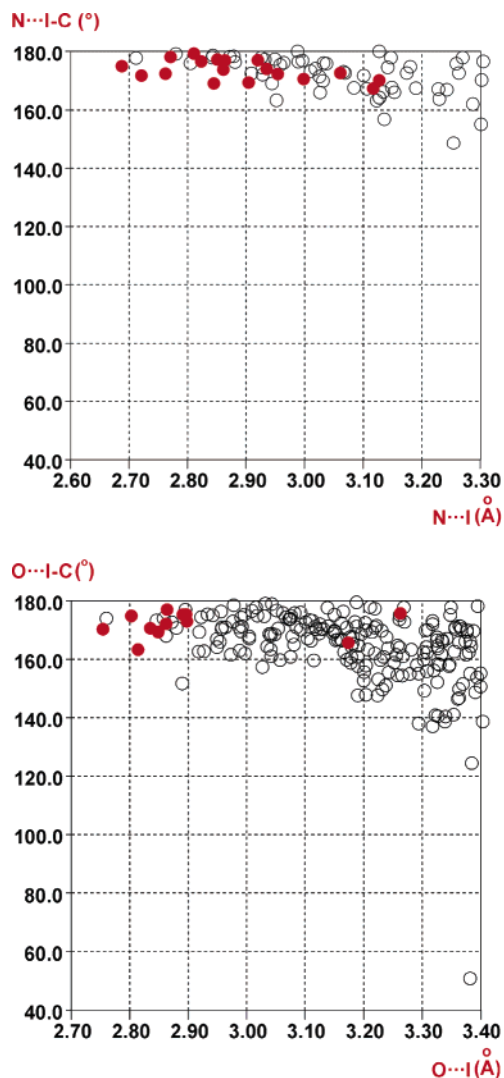


FIGURE 1. Scatterplots derived from the CSD (298,097 crystal structures; only error-free and nonpolymeric structures containing single-bonded iodine atoms and showing no disorder with $R < 0.06$ are considered) reporting $N \cdots I-C$ angle (deg) vs $N \cdots I$ distance (Å) (top) and $O \cdots I-C$ angle (deg) vs $O \cdots I$ distance (Å) (bottom) data for crystal structures containing intermolecular $N \cdots I$ and $O \cdots I$ contacts, respectively. Red circles correspond to crystals of iodofluorocarbons.

interactions, the more directional they are. Similar trends are shown by brominated and chlorinated XB donors, but observed directionalities decrease in the order.¹⁷

Halocarbon Based Crystal Engineering

Dihalogens have given a fundamental contribution in the understanding of the properties of XB.^{8,12} However, when used in XB based crystal engineering, they present disadvantages. For instance, I_2 and Br_2 are mono or bidentate ligands or amphoteric species as a function of the partner's nature.¹⁸ Dramatic differences on the formed supramolecular architectures result, and it is hard to anticipate their structures.

The pattern of XB given by dihalocarbons shows a better definition and greater robustness. When separated by a carbon framework, two halogen atoms work as

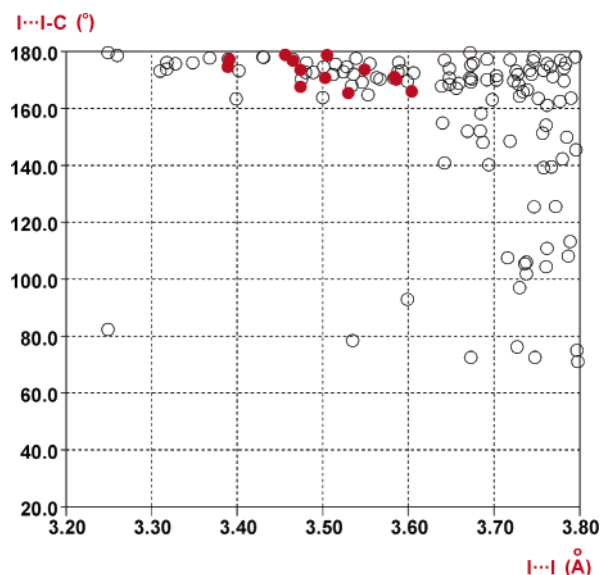


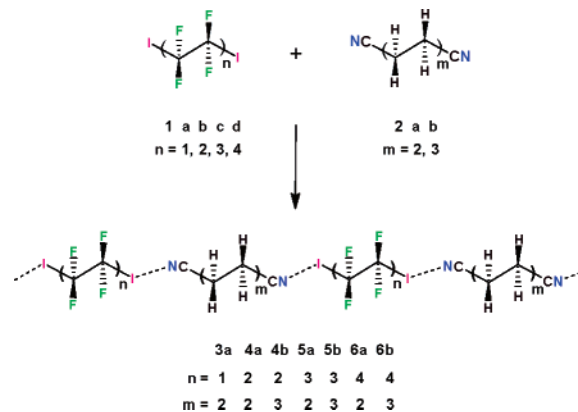
FIGURE 2. Scatterplot derived from the CSD reporting $I\cdots I-C$ angle (deg) vs $I\cdots I$ distance (Å) data for crystal structures containing intermolecular $I\cdots I$ contacts. Red circles correspond to crystals of iodo-fluorocarbons.

independent XB donors and their involvement in XB formation is highly independent of the partner. The strength of the resulting XB can be carefully tuned by simply controlling the nature of the carbon framework and its substituents. For instance, the $N\cdots I$ interaction energy in the infinite chain 4,4'-dipyridyl/1,4-diiodobenzene is 13.19 kJ/mol and the $N\cdots I-C$ interaction length is 3.032 Å (sum of van der Waals radii is 3.53 Å).¹⁹ The same parameters become 24.32 kJ/mol and 2.851 Å when 1,4-diiodotetrafluorobenzene is used.²⁰ The $I\cdots I-C$ interaction lengths are 3.535, 3.431, and 3.328 Å in the adducts that a cyclopropenium iodide forms with mono-, di-, and tri-nitro-iodobenzenes, respectively.¹³

The simplest polyhalocarbons, tribromo- and triiodomethane as well as their tetrahalogenated analogues, effectively arrange electron donors after a tetrahedral geometry.^{5,6,21,22} By designing and using specific polyhalocarbons, one can effectively pursue particular structural and functional targets. The simplest function of the polyhalocarbon is to distance adjacent electron donors. Thanks to the robustness of the $X\cdots I-C(sp)$ supramolecular synthon,²³ the XB driven self-assembly of α,ω -diiodopolyynes (from acetylene to tetrayne) with dinitrogen-, dioxygen-, disulfur-, and diselenium-substituted derivatives^{5,6} easily and invariably affords infinite chains where the donor and acceptor modules alternate. Moving from shorter to longer diiodopolyynes, the electron donor groups' distance increases.

Haloperfluoroalkanes are particularly robust tectons,^{24,25} and they are nicely tailored to XB based supramolecular chemistry (Figures 1 and 2).²⁶ The XB interactions that they form are particularly short and directional, thus allowing structural control of forming supramolecular aggregates. A rigorously metric crystal engineering was realized when α,ω -diiodoperfluoroalkanes **1a-d** were self-assembled with 1,4-dicyanobutane (**2a**) and 1,6-dicyano-hexane (**2b**) to give cocrystals **3-6** (Scheme 1).

Scheme 1. XB Driven Self-Assembly of 1,4-Dicyanobutane (**2a**) and 1,6-Dicyanohexane (**2b**) with the Range of α,ω -Diiodoperfluoroalkanes **1**



All the cocrystals show highly consistent geometric characteristics. The donor and acceptor modules alternate in infinite chains the pitch of which shows a very good linear correlation with the number of the methylene groups in **2** and the number of the difluoromethylene groups in **1**.²⁷ The low affinity between hydrocarbons (HCs) and perfluorocarbons (PFCs) induces remarkable segregation, and the infinite chains produce alternating layers of PFCs and HCs with impressively similar overall structures. Tectons **1d** and **2b**, which form **6b**, are bis-homologues of **1c** and **3a**, which give **5a**. The layers in **6b** are thus thicker than those in **5a** (Figure 3). The high directionality of the XB, along with the mesogenic character of the perfluorocarbon and hydrocarbon chains, allow the metrics of both chains and layers to be anticipated from the metrics of tectons.

Segregation of modules and formation of hybrid materials with defined and separated domains is a constant in self-assembly processes involving perfluoroalkyl halides.²⁸ This behavior is highly independent of the donor and acceptors modules. The behavior of dibromoperfluorocarbons²⁹ is very similar to their iodo analogues, as shown by the architecture 1,8-dibromoperfluorooctane/ N,N,N',N' -tetramethylphenylenediamine (Figure 4).

Layered materials are also obtained when anionic XB acceptors are used.³⁰ The ternary system **8b** formed by Kryptofix 222 c KI **7** and 1,4-diiodoperfluorobutane (**1b**) (Scheme 2, Figure 5, top) is an example. Once again, the overall crystal packing is largely invariant with respect to the size of the iodoperfluoroalkane chains. In fact, when 1,8-diiodoperfluorooctane (**1d**) is used, the formed ternary system **8d** has overall crystal packing quite close to that of **8b** (Figure 5, bottom). In both cases, iodoperfluoroalkyl modules work as bidentate ligands and are halogen-bonded to iodide anions that work as tridentate ligands. (6,3)-Nets form where iodide anions are the nodes and iodoperfluoroalkanes the bridges. Compound **1b** being smaller than **1d**, **8b** shows smaller meshes and narrower fluorinated layers than **8d**.

The synthesis of dihaloperfluoroalkanes is not trivial and the structural diversity of commercially available compounds is inherently limited. Haloperfluoroarenes

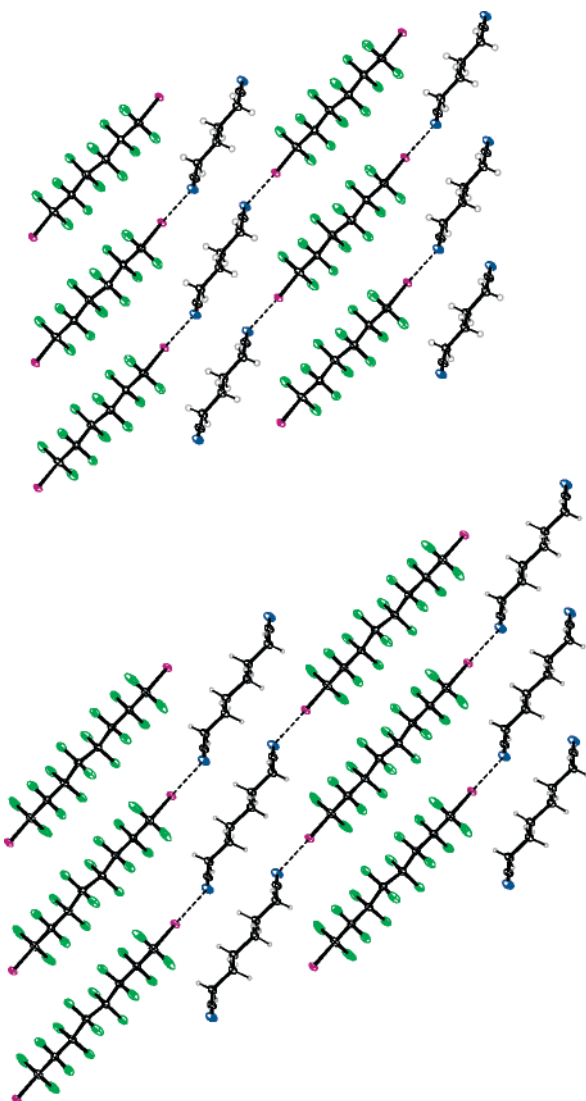


FIGURE 3. Ortep III crystal packing of **5a** (top) and **6b** (bottom) viewed down the *a* crystallographic axis. Colors are as follows: carbon, black; hydrogen, gray; nitrogen, blue; fluorine, green; iodine, purple. Halogen bonds are dashed lines.

show a supramolecular behavior quite close to their aliphatic analogues,³¹ and they can be easily appended to a wide diversity of organic compounds. In fact, the nucleophilic aromatic substitution (S_NAr) of oxygen or nitrogen sites for fluorine in perfluorobenzene derivatives **9** occurs in good yields under mild conditions. When bromo- and iodopentafluorobenzene (**9c,d**, respectively) are used, reactions occur with very high selectivity on the fluorine atom in the para position (Scheme 3).³² Figure 6 lists a selection of the halotetrafluorophenyl-substituted tectons thus prepared.

The S_NAr is so general that virtually any hydroxyl or amine group can be transformed into its *p*-halotetrafluorophenyl derivative. DAB dendrimers up to the third generation have been obtained.³³ Iodotetrafluorophenyl-ethers and -amines give XB with geometric and energetic characteristics identical to those of other iodoperfluorocarbons (Figure 7). It is thus possible to anticipate in the

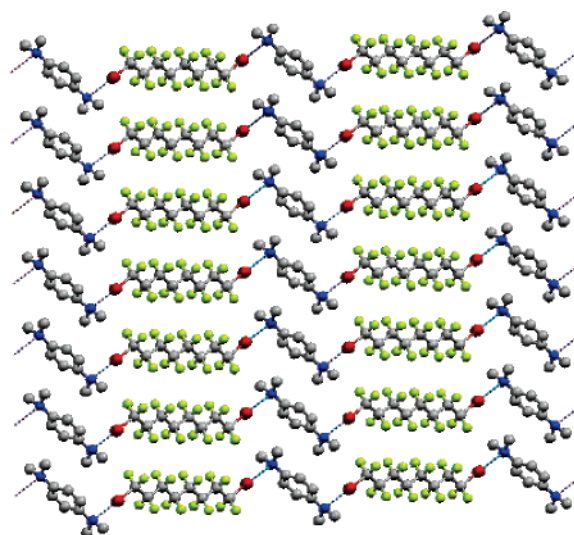
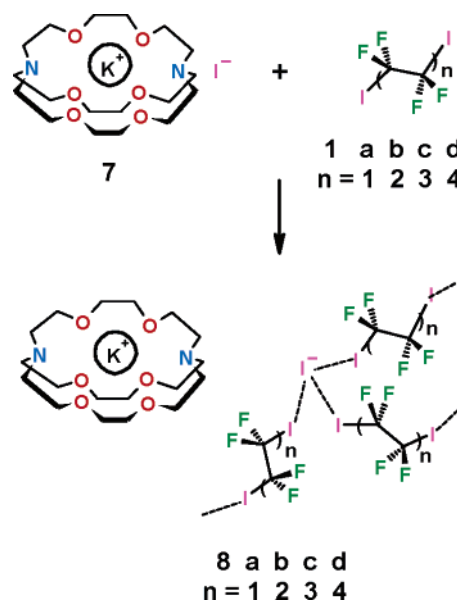


FIGURE 4. Mercury 1.3 diagram of perfluorocarbon–hydrocarbon segregated halogen-bonded layers given by the self-assembly of *N,N,N',N'*-tetramethyl-*p*-phenylenediamine and 1,8-dibromoperfluorooctane. Colors are as follows: carbon, gray; nitrogen, blue; fluorine, green; bromine, red. Hydrogen atoms have been omitted. Halogen bonds are dashed lines.

Scheme 2. Diagram Showing the Formation of Fluorous Polyiodide (6,3) Networks **8a-d Starting from Cryptate **7** and Differently Sized Telechelic Diiodoperfluoroalkanes **1****



details the self-assembly profile of any scaffold bearing *p*-iodotetrafluorophenyl pendants.

The power of the protocol lies on the fact that a simple, general, and high yield reaction (the S_NAr between hydroxy and amino groups and halopentafluorobenzenes) transforms typical HB recognition sites into effective XB recognition sites. The potential of this approach is very promising.

XB in Action

The full utilization of the so-called bottom-up approach to functional materials requires new and effective non-covalent interactions for assembling supramolecular ar-

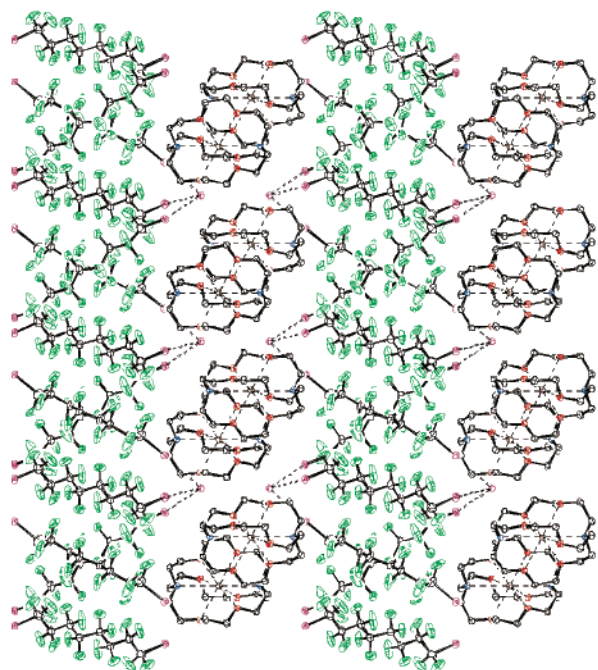
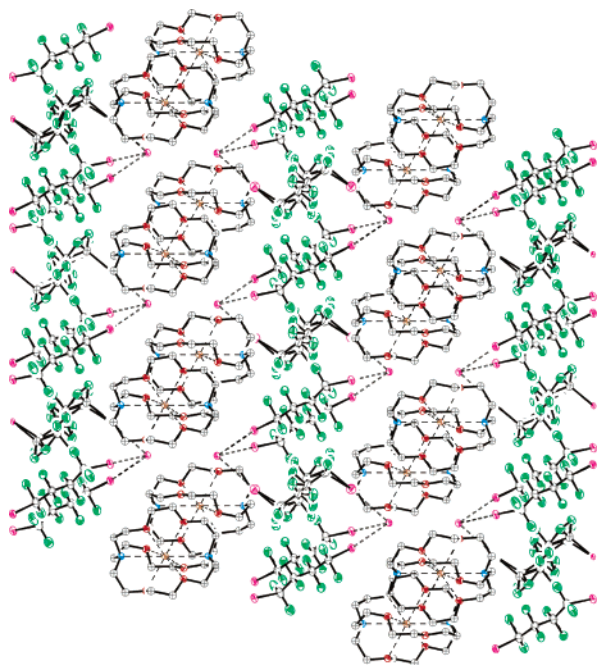
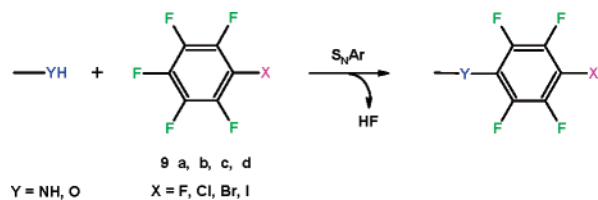


FIGURE 5. Ortep III views down the crystallographic *b* axis of the crystal packing of **8b** (top) and **8d** (bottom). Colors are as follows: carbon, black; nitrogen, blue; oxygen, red; fluorine, green; potassium, brown; iodine, purple. Hydrogen atoms have been omitted. Halogen bonds are dashed lines.

chitectures associated with preestablished functions. In previous paragraphs, it has been shown how XB is a new item of the palette of noncovalent interactions at the disposal of the chemist as the cement to assemble molecules. The great XB potential in the design of new and high-value functional materials is now emerging. For instance, $N\cdots I$ interactions have been used in a supramolecular route to fluorinated coating.³⁴ Both $O\cdots I$ ³⁵ and $O\cdots Br$ ³⁶ interactions have been employed for the obtainment of microcrystalline materials with NLO properties.

Scheme 3. General Scheme of the S_NAr Reaction between Oxygen or Nitrogen Sites and Haloperfluorobenzenes **9a-d**



Some other applications of XB for driving the construction of smart materials will be discussed in greater detail.

In 1995, Imakubo and Kato introduced the successful use of XB to control the solid-state organization of radical cation salts of iodotetrathiafulvalenes, such as EDT-TTF-I **10** (EDT = ethylenedithio, TTF = tetrathiafulvalene), with counterions possessing electron donor character (Br^- , $\text{Ag}(\text{CN})_2^-$) (Scheme 4).³⁷

Since then, XB has been fully investigated as a first choice noncovalent interaction to control the solid-state structures of molecular conductors and hence to influence their electronic properties.³⁸ HB also has been examined for the same targets, but the intrinsic flexibility of HB was found to hinder a reliable control of the crystal matrix

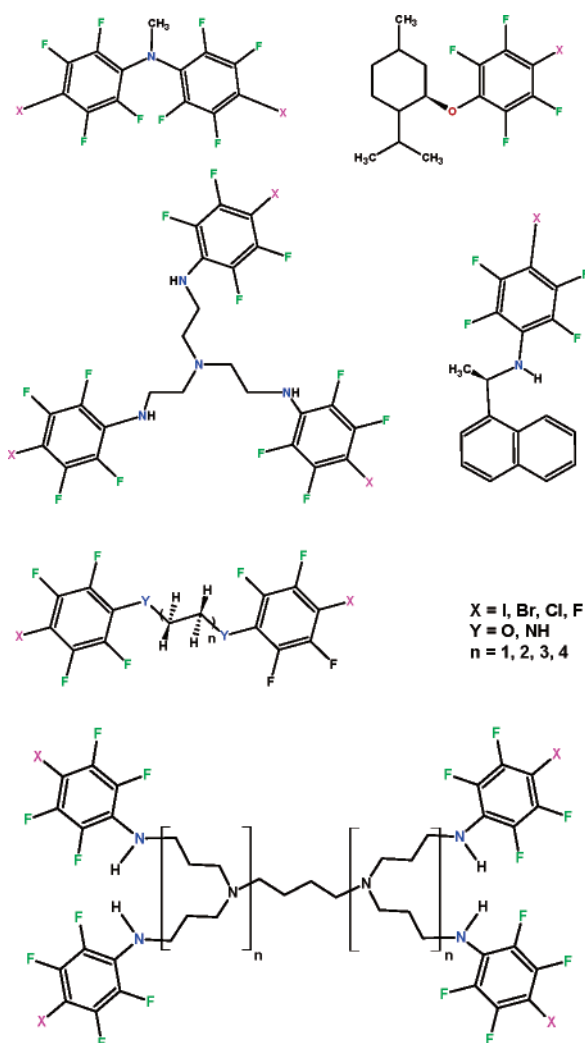


FIGURE 6. Selection of *p*-halotetrafluorophenyl substituted XB donors prepared through S_NAr reactions.

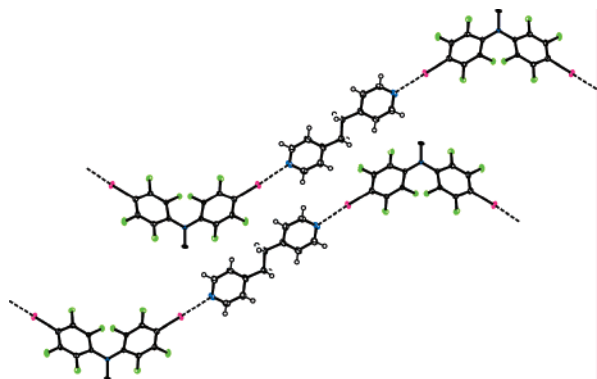
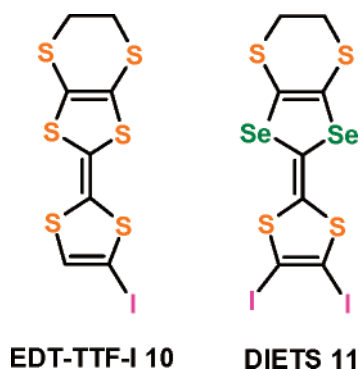


FIGURE 7. 1D infinite chains given by XB driven self-assembly of 1,2-bis(4-pyridyl)-ethane and *N*-methyl-*N,N*-bis(2,3,5,6-tetrafluoro-4-iodophenyl)amine. This latter ditopic XB donor has been obtained via S_NAr exhaustive reaction of methylamine with iodopentafluorobenzene.

Scheme 4. Molecular Structures of EDT-TTF-I (10) and DIETS (11)



organization of molecular conductors. The much more directional $N\cdots I$ interaction is particularly suitable for this purpose, and several crystal systems of supramolecular organic conductors based on halogen-bonded TTFs have been reported. In particular, the organic conductor θ -(DIETS) $_2$ [Au(CN) $_4$] **11** (DIETS = diiodo(ethylenedithio)diselenadithiafulvalene) is a new superconductor with $T_c = 8.6$ K (onset, 10 kbar), which is the highest value among the known superconductors based on unsymmetrical organic π -donors.³⁹ In the crystal structure of this superconductor (Figure 8), cations and anions stack separately into different layers joined by $N\cdots I$ XB.

XB between the layers of DIETSs and counterions is stronger than the side-by-side chalcogen \cdots chalcogen contacts in conductors based on TTFs, thus increasing superconductivity in this kind of materials.

Solid-state synthesis is a rapidly emerging field of supramolecular chemistry. The XB has been recently used to pin olefin carriers to linear templates forming supramolecules meeting Schmidt's requirements for UV-induced [2+2] cycloaddition reactions in the solid state (Figure 9).⁴⁰

The pentaerythritol derivative **12** was synthesized via selective S_NAr reaction of the tetrol on iodopentafluorobenzene. Derivative **12** typically behaves as a tetratopic XB donor when interacting with telechelic and linear bases in the solid. Derivative **12** adopts a conformation where couples of tetrafluorophenyl rings lie on the same side

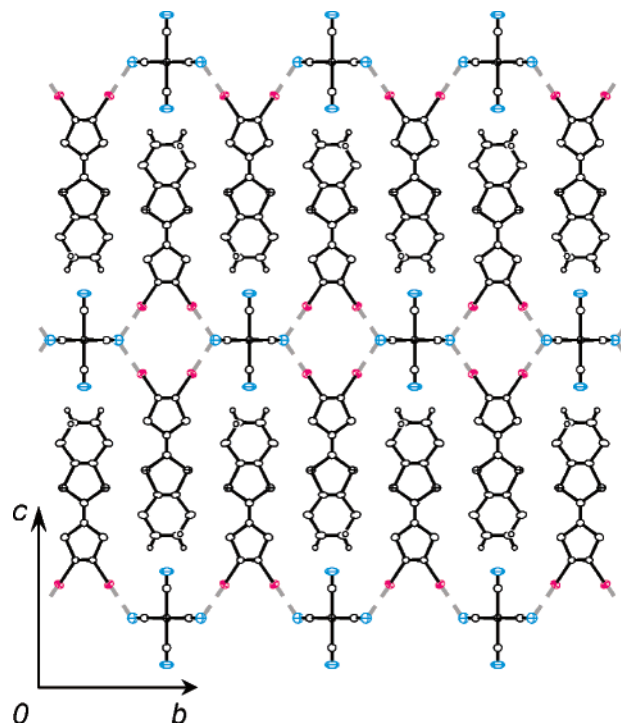


FIGURE 8. Crystal structure of DIETS **11**·Au(CN) $_4$ viewed along the *a* crystallographic axis. Colors are as follows: carbon and hydrogen, black; nitrogen, sky blue; iodine, purple. Halogen bonds are gray dashed lines.

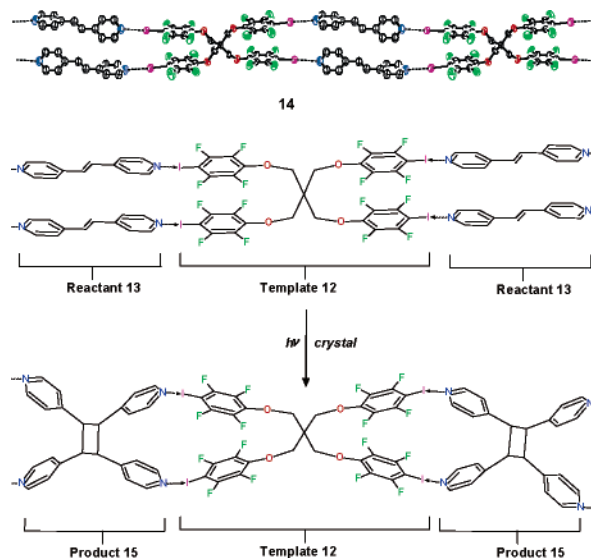
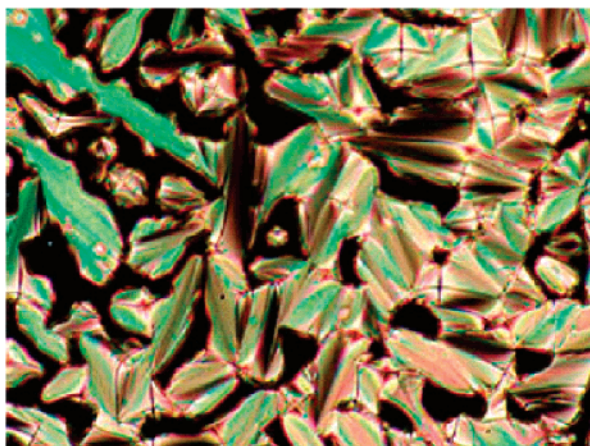
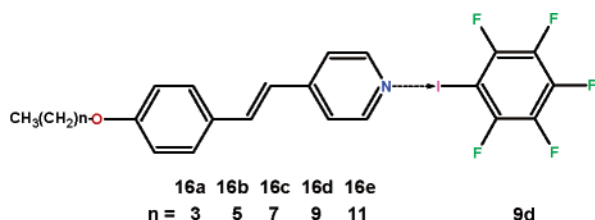


FIGURE 9. Ortep III view (top) of the infinite 1D halogen-bonded ribbons **14** formed by self-assembly of modules **12** (template) and **13** (reactant). Hydrogen and disordered atoms are omitted for clarity. The bottom panel shows a scheme of the synthesis of the *rctt* isomer **15** via templated photoreaction in the solid state.

and are paired in a quasi-parallel fashion thanks to remarkable face-to-face $\pi\cdots\pi$ intramolecular interactions. Pairs of iodine atoms in the periphery of **12** are thus locked at a distance of about 4 Å. The remarkable strength and directionality of $N\cdots I$ interactions translate the alignment of the arms of the template into the alignment of the interacting modules. If olefin double bonds are present in the nitrogenated modules, olefins are pinned at the



16b-9d Cr-SmA (77 °C) SmA-I (80 °C)

FIGURE 10. Halogen-bonded dimeric complexes (top) between alkoxytilbazoles **16a–e** and iodopentafluorobenzene **9d** and optical texture (bottom) of the SmA phase of **16b/9d** adduct at 69 °C on cooling from the nematic phase.

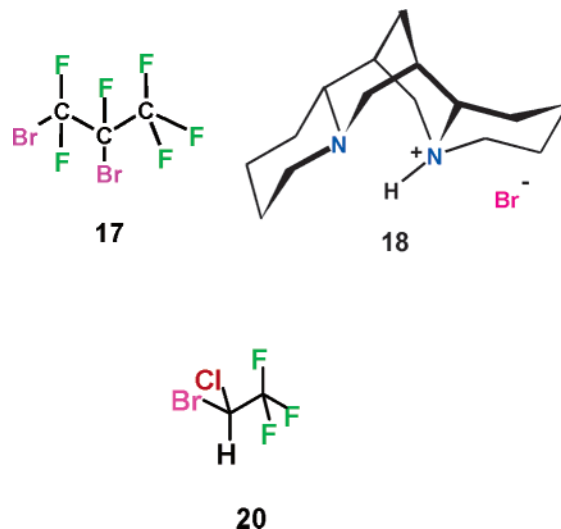
distance needed for photoreaction. Indeed, on irradiation of the cocrystal **14** between tecton **12** and *trans*-1,2-bis-(4-pyridyl)ethylene (**13**), a stereocontrolled photocyclization reaction occurs, yielding the *rc*tt isomer of tetrakis(4-pyridyl)cyclobutane (**15**) in quantitative yields.

Recently XB has also proven to be able to form liquid crystals from nonmesomorphic components. This is the case of the complexes between 4-alkoxystilbazoles **16** and iodopentafluorobenzene **9d** (Figure 10).⁴¹

The general ability of 4-alkoxystilbazoles to form XB interactions with **9d** was demonstrated undoubtedly by the single-crystal X-ray analysis of the complex **16c/9d**. Despite the nonmesomorphic nature of the 4-alkoxystilbazoles used, their halogen-bonded complexes with **9d** were all liquid-crystalline with thermotropic properties. Bruce et al. studied the mesomorphic properties of these complexes in comparison with their hydrogen-bonded analogues. The strengths of the liquid crystalline phases of the halogen-bonded systems are similar to those of hydrogen-bonded systems.

The formation of a diastereoisomeric salt with an enantiopure base is the standard technique for optical resolution of racemic compounds containing acidic groups. In most cases, the interaction responsible for salt formation is HB. If XB can also be used to drive the salt formation, the palette of salts forming resolving agents is enriched and the number of racemic compounds that can be resolved is enlarged. A case proving the viability of this approach was described. Racemic 1,2-dibromohexafluoropropane (**17**) crystallizes with (–)-sparteine hydro-

Scheme 5. Chemical Structures of Racemic 1,2-Dibromohexafluoropropane (**17**), (–)-Sparteine Hydrobromide (**18**), and Halothane (2-Bromo-2-chloro-1,1,1-trifluoroethane, **20**)



bromide (**18**) to give the diastereoisomeric salt **19** where (*S*)-**17** is exclusively present (Scheme 5).⁴² The driving force toward the cocrystal formation is Br[–]⋯Br–C XB between the bromide anions and carbon-bound bromine atoms.

Each bromide ion bridges the primary and secondary bromine of two distinct modules **17**, each of which is bound to two adjacent bromide ions yielding enantiopure infinite 2-fold helices (Figure 11). Haloperfluorocarbons are important for their technological relevance, but in enantiopure form they were a virtually unknown class of compounds. The process described above may be general and useful in resolving other halofluorocarbons, such as general anesthetics like halothane (2-bromo-2-chloro-1,1,1-trifluoroethane **20**, Scheme 5).

The X-ray crystal structures of complexes between halogen substituted drugs and their specific proteinaceous receptors unequivocally proved the existence of XB interactions that optimize the receptorial fitting. For example, short O⋯I contacts have been found between the iodine atoms of thyroid hormone thyroxine (T4) and the carbonyl oxygens of the amino acid residues in the pocket

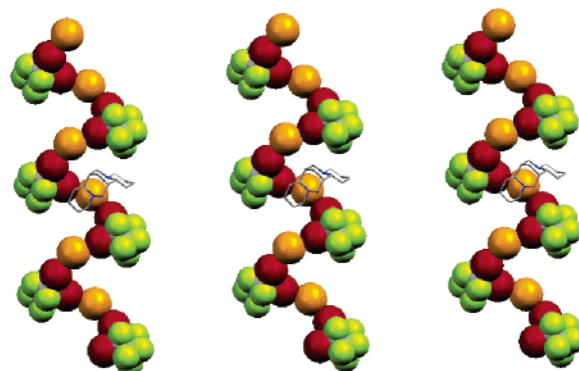


FIGURE 11. Space-filling representation of the enantiopure halogen-bonded helices, viewed down the crystallographic *a* axis, in the chiral cocrystal **19**. All the sparteine molecules but one have been removed for clarity. Colors are as follows: carbon, gray; fluorine, green; bromine atoms, red; bromide ions, orange; nitrogen, sky blue.

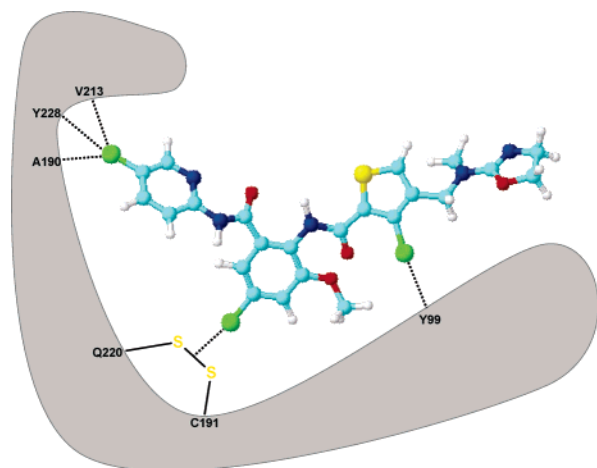


FIGURE 12. Artwork representing the binding of a trichloro substituted inhibitor of the human Xa factor of the human blood coagulation cascade and the receptorial pocket of the Xa factor. The reported contacts between its amino acid residues and the inhibitor (observed by X-ray) can be rationalized as $O\cdots Cl$ and $S\cdots Cl$ halogen bonds.

of transthyretin (TTR), the major transporter of T4 in human body.⁴³ Short $O\cdots Cl$ and $S\cdots Cl$ contacts have been detected in the crystal structure (Figure 12) of the complex between the factor Xa of the human blood coagulation cascade and a trichloro substituted inhibitor, which is used in the treatment of thrombotic diseases.⁴⁴ A survey of protein and nucleic acid structures clearly demonstrates the potential significance of XB in ligand binding and recognition, as well as in molecular folding.⁴⁵

Polyhalogenated organic compounds are used as general anesthetics. Halothane **20** (Scheme 5) is a common volatile anesthetic used in therapy in the racemic form. The two enantiomers have different pharmacological activities, and the measured eudismic ratio has been attributed to the specific binding with proteinaceous receptor sites.⁴⁶ The enantioselective recognition of the drug in vivo may be mediated by the formation of halogen-bonded complexes with electron-pair donors present in the receptor pockets. This hypothesis is supported by studies aiming at defining the structural features of volatile general anesthetic binding sites in protein targets. It was demonstrated that the binding affinity of halothane increased dramatically when a leucine residue was replaced with a methionine in the vicinity of the proposed anesthetic binding pocket. Polar interactions are therefore predicted to enhance anesthetic binding energetics.⁴⁷

Concluding Remarks

The effectiveness of a scientific concept often comes from the balance between its generality, resulting in a wide applicability, and its specificity, enabling it to predict specific phenomena. This holds also for the terminology used to enunciate the concept. A masterly example is the HB concept, which includes an extraordinary vast class of noncovalent interactions characterized by quite different natures and spread over a very wide range of energies

and geometries. In our opinion, the same is true for the XB concept. The terms chlorine bonding⁴⁸ and iodine bonding³⁹ have been proposed. They describe specific and homogeneous subclasses of interactions that are comprehensively encompassed by the term XB. General concepts in the area of intermolecular interactions allow new phenomena and ideas to be readily communicated among chemists working in different fields.

XB impacts all the fields wherein design and manipulation of aggregation phenomena play a key role. In the previous paragraph, XB relevance in fields as diverse as superconductors, liquid crystals, and substrate–receptor bindings have been highlighted. A full understanding of this noncovalent interaction is thus crucial in the development of numerous and different fields.

If it is neglected how frequently XB occurs, serious misinterpretations in several fields may result. The case of the simple halocarbons commonly used as solvents will be discussed. Bromotrifluoromethane is frequently employed in NMR studies at low temperature. Among others, it has been used to determine the activation barrier for inversion/rotation of amines. A barrier of 29.89 kJ/mol has been attributed to *N*-ethyl-*N*-methyl-*N*-isopropylamine.⁴⁹ However, this value refers to the amine–solvent complex because, under the adopted conditions, the amine is quantitatively complexed by the solvent as the interaction enthalpy of $N\cdots Br$ XB is close to 19.65 kJ/mol ($CF_3Br\cdots NH_3$ interaction).⁵⁰ Similar data misinterpretations occurred for other stereodynamic phenomena.⁵¹ The ability of chloroform to give HB is routinely considered, but the ability to be involved in XB formation is rarely taken into account despite the XB interaction enthalpy being more than a half the HB interaction enthalpy.⁵² Carbon tetrachloride is commonly considered an inert solvent. However enthalpies of complex formation with ethers, thioethers, amines, and amides span the range 6–16 kJ/mol. Spectra of nitrogen, oxygen, and sulfur containing compounds are of specifically solvated molecules with all the resulting conformational consequences.

As a consequence of their ability to form XB interactions, halocarbons are also effective in breaking typical HB interactions (e.g., $O\cdots H-O$, $N\cdots H-N$, $C=O\cdots H-N$). This aspect has far reaching consequences in the biological activity of halogenated xenobiotics. Interestingly, halofluorocarbons show a striking parallelism between the hydrogen bond breaking potency and the anesthetic potency.⁵³ Halofluorocarbon anesthetics, which contain an acidic hydrogen (halothane, methoxyflurane, enflurane), can give rise to both HB and XB, and the relative importance of the two phenomena vary from one anesthetic to another. Surprisingly, these conclusions have been neglected by some recent studies on these drugs.⁵⁴

An effective design of intermolecular recognition processes requires a thorough understanding of *all* the interaction forces and mechanisms that may be used. HB, metal coordination, and $\pi\cdots\pi$ interactions are well-known to any chemist. In this paper, we have shown how ubiquitous the occurrence of XB is. Despite this fact, XB has received limited attention and recognition. The XB

concept is still in its infancy. Theoretical and experimental studies on the interaction are thus highly desirable. They will allow the development of heuristic principles more detailed and powerful than those described above. A better understanding of XB based recognition processes could thus develop, and applications more effective than those already described will appear.

We are grateful to all colleagues, graduate students, and postdoctoral associates who worked with us on XB. Some of them are mentioned in the references.

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AR0400995