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Halogen Bonding

Halogen Bonding in Supramolecular Chemistry

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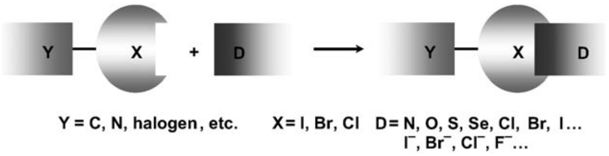
anion coordination · crystal engineering · fluorinated tectons · halogen bonding · supramolecular chemistry

Halogen bonding is the noncovalent interaction where halogen atoms function as electrophilic species. The energetic and geometrical features of the interaction are described along with the atomic characteristics that confer molecules with the specific ability to interact through this interaction. Halogen bonding has an impact on all research fields where the control of intermolecular recognition and self-assembly processes plays a key role. Some principles are presented for crystal engineering based on halogen-bonding interactions. The potential of the interaction is also shown by applications in liquid crystals, magnetic and conducting materials, and biological systems.

1. Introduction

Halogen atoms are typically located at the periphery of organic molecules and are thus ideally positioned to be involved in intermolecular interactions. These interactions can be remarkably different as far as their energetic and geometric features are concerned. This Minireview focuses on halogen bonds (XBs), namely the interactions in which halogen atoms function as electrophilic species. XBs can be described in general as D···X−Y, where X is the electrophilic halogen atom (Lewis acid, XB donor), D is a donor of electron density (Lewis base, XB acceptor), and Y is a carbon, nitrogen, or halogen atom (Scheme 1).

The ability of halogen atoms to attractively interact with electron donors was recognized in dihalogens and halocarbons as early as the 19th century.[1] More than 50 years later, the seminal paper by Benesi and Hildebrand reported the first cases of intermolecular donor–acceptor complexes formed from iodine and aromatic hydrocarbons.[2] However, it was Hassel who stressed in his Nobel lecture in 1970 the importance of halogen atoms for directing molecular self-assembly phenomena.[3]



Scheme 1. General scheme for the formation of halogen bonds.

The ability of halogen atoms to function as general, effective, and reliable sites for directing intermolecular recognition processes in the gas, liquid, and solid phases remained largely undervalued until the 1990s. In the last decade, a number of studies were reported that describe the supramolecular architectures formed by iodo- and bromoperfluorocarbons with neutral and anionic electron donors. These examples underscored the ability of these halocarbons to function as versatile building blocks in crystal engineering and established XBs in supramolecular chemistry.[4] The proof that XBs could induce useful functional properties followed shortly after. For example, XBs have been used to direct the self-assembly of nonmesomorphic components into supramolecular liquid crystals,[5] to control the structural and physical properties of conducting and magnetic molecular

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materials,[6] to separate mixtures of enantiomers and other isomers,[7] to afford and tune second-order nonlinear optical responses,[8] to exert supramolecular control on the reactivity in the solid state,[9] to optimize the binding of ligands in a receptor, molecular folding, and other biopharmacological properties,[10] as well as to bind anions in solution and in the solid state.[11]

At the beginning of this Minireview, some general geometric and energetic properties of XBs will be described. Furthermore, the characteristics a molecule must have to participate in halogen-bonding interactions are described. From this, it will be easy to predetermine the structure of the supramolecular architectures resulting from the self-assembly of building blocks tailored to form halogen bonds. Some characteristics of bulk materials are related to the non-covalent interaction(s) that direct their architecture and that are derived from their nano- and microscopic architectures. Since XBs control the structure of the self-assembled system, it has great potential in the development of useful materials.

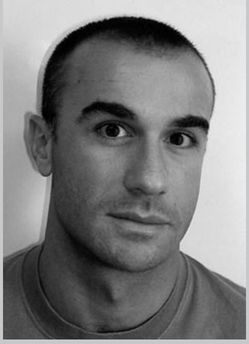
Molecular complexes of halogen and interhalogen compounds have provided fundamental contributions towards the understanding of XBs.[2,12] These complexes are still attracting great interest,[13] notably in regard to polyhalide anions and adducts involving sulfur, selenium, or arsenic XB acceptors. Halogen atoms bound to nitrogen and phosphorus atoms can also function as XB donor sites. Both n and π electrons can be involved in the formation of XBs; the latter usually form weaker interactions.[12,14] However, we will concentrate here on recognition and self-assembly processes involving carbon-bound halogen atoms and n-XB acceptors.

2. The Theory of Halogen Bonding

2.1. Energetic and Geometric Features

Theoretical studies predict, and experimental studies confirm, that electron density is anisotropically distributed around halogen atoms in organic halides. In covalently bonded halogen atoms, the effective atomic radius along the extended C–X bond axis is smaller than in the direction perpendicular to this axis, and a region of positive electrostatic potential is present along the covalent bond.[15] This "σ hole" disposes the lone pair closer towards the halogen atom, and accounts for the orientation of the halogen bonds.

In general, the positive potential along the C–X axis increases on moving from F to I, namely with the polarizability of the halogen atom. The electrostatic potential remains negative all around the F atom, whereas an area of positive charge emerges for Cl, Br, and I. This area is surrounded by an electroneutral ring and, further out, a negatively charged belt (Figure 1). The magnitude of the positive area increases as the electron-withdrawing effect of



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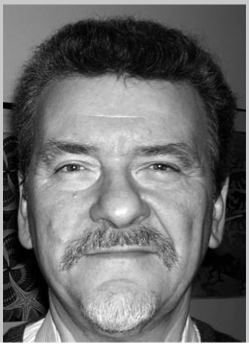
Franck Meyer obtained his PhD in Organic Chemistry in 2000 at the Pontoise University (France). After two years at a pharmaceutical company, in 2004 he joined Prof. Resnati as a postdoctoral researcher at the Politecnico di Milano, where since 2005 he has been temporary assistant professor. His research interests are the synthesis of fluorinated tectons for recognition processes.



Tullio Pilati obtained his "Laurea" in Chemistry (specialization in Physical chemistry) in 1971 at the University of Milan, where he is currently a Senior Researcher of the National Research Council. His research interests are in the crystallography of perfluorocarbon–hydrocarbon hybrid materials and bioactive compounds.

Giuseppe Resnati started his career at pharmaceutical companies and in 1982 moved to the Politecnico di Milano, where initially he was researcher of the National Research Council, then associate professor (1998), and full professor in 2001. He has spent sabbaticals at the University of Clemson (USA, 1990, NATO stipendium), at the Université Paris XI (France, 1993), and Nagoya University (Japan, 2001). Since 2001 he has been a member of the Editorial Board of the Journal of Fluorine Chemistry. His research interests are fluorine chemistry, synthetic methods, and self-assembly processes.

Giancarlo Terraneo obtained his PhD in organic chemistry in 2006 at the University of Milan. Before that he had been VLAG Fellow at the University of Wageningen (The Netherlands, 2003) and spent a research period at the University of Zurich (Switzerland, 2004). In 2007 he moved to the Politecnico di Milano for postdoctoral research with Prof. Resnati. In 2008 he was a visiting scientist at the University of York (UK). His research interests are in the fields of synthetic methods for materials chemistry.

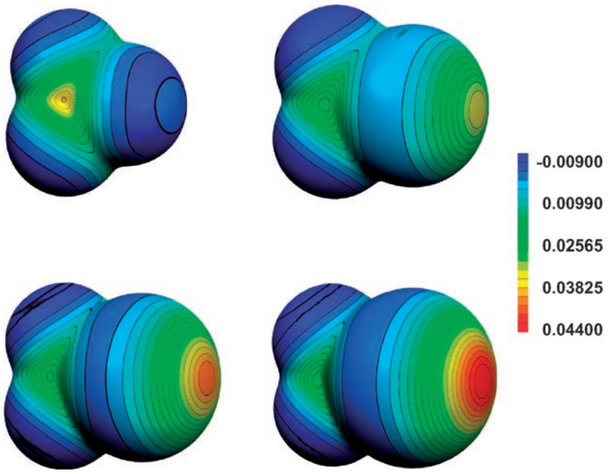


Figure 1. The molecular electrostatic potential (in Hartrees) at the isodensity surface with 0.001 electrons Bohr^{-3}: CF_4 (top left), CF_3Cl (top right), CF_3Br (bottom left), CF_3I (bottom right). Reproduced with permission from Ref. [15c].

the neighboring groups increases. Experimental results prove it is possible to carefully tune the strength of the halogen bond in a given halocarbon by modifying the substituents on the carbon skeleton.[16]

In keeping with the anisotropic electrostatic potential model described above, Cl, Br, and I show "amphiphilic" character. Halogen atoms, thus, function as electron-deficient sites when they form contacts at the pole (electrophilic end), but can also function as electron-rich sites on forming contacts at the equator (nucleophilic end).[17] The term "halogen bonding" addresses the former contacts exclusively.[18] The binding nature of XBs results in the D···X distances being shorter than the sum of the van der Waals radii of the involved atoms—the stronger the halogen bond, the shorter the D···X distance. Consistent with the rationalization of halogen bonding as being an electron donation from D to the antibonding X−Y orbital,[19] the formation of a halogen bond slightly lengthens the covalent X−Y bond.

Halogen atoms are much larger and polarizable than hydrogen atoms; thus XBs are more sensitive to steric hindrance than are hydrogen bonds (HBs).[20] With the exception of this difference, most of the energetic and geometric trends found in HBs, as well as other features known from spectroscopic and theoretical investigations, are also found with XBs.[21]

According to the definition given above, the term halogen bonding comprehensively covers a vast class of noncovalent interactions whose strength can vary in the range 10–200 kJ mol^{-1}.[15d,e] The remarkable strength of some halogen bonds allows them to prevail over analogous hydrogen-bonding recognition processes. For example, the formation of intermolecular hydrogen bonds between dissolved species are considerably suppressed if a strong XB donor is added as cosolute, and in experiments on competitive cocrystal formation, various hydrocarbon derivatives containing two nitrogen atoms prefer to cocrystallize with XB donors rather than with HB donors.[22] This ability of XBs to substitute for HBs allows water-free samples of hygroscopic compounds to be easily prepared.

The formation of the halogen-bonded adduct frequently leads to significant charge transfer or even eventually to a chemical reaction.[12c,13a,b] Stronger XBs easily evolve into molecular species different from the starting materials if an appropriate concentration, temperature, and solvent polarity are used.[23] The 1:1 complexes formed from dihalogen molecules with alkenes is a particularly well-known example. Depending on the reaction conditions, halogen-bonded adducts or perfluoroalkylation products are obtained from iodoperfluoroalkanes and aniline derivatives.

2.2. Halogen-Bond Donors and Acceptors

Experimental data from the solid, liquid, and gas phases confirm the theoretical predictions that the strength of the halogen-bond donor increases in the order Cl < Br < I. This tendency was confirmed for the self-complementary 3-halocyanoacetylene function, where the N···X distances serve as a measure of the strength of the halogen bonds in the adducts.[24]

The strength of the halogen bonds increase as the electron-withdrawing nature of the atom, or moiety, bound to a given halogen increases. The order $C(sp)\text{-}X > C(sp^2)\text{-}X > C(sp^3)\text{-}X$ is generally followed, and haloalkynes are particularly good XB donors.[9c,25]

Haloarenes are usually good halogen-bond donors; the same is true for haloheteroarenes, where the halogen atom becomes an even better donor when the heteroaromatic ring is positively charged.[26] This effect has been exploited with particular success to control the packing of bromo- and iodo-substituted tetrathiafulvalene derivatives, which are interesting molecular conductors (see Section 4.2).

Unfunctionalized monohaloalkanes usually form S_N2-type products rather than halogen-bonded adducts on reaction with n-electron donors. This arises because the formation of products resulting from the nucleophilic back-side attack at the carbon atom of the covalent C−X bond is favored over nucleophilic attack at the halogen atom. However, the presence of strong electron-withdrawing residues geminal to the halogen atom in monohaloalkanes boosts the Lewis acidity of the halogen atom and allows for the formation of strong halogen bonds. This is the case, for example, for various halomethyl onium salts.[27]

In polyhaloalkanes, both steric and electronic reasons favor the attack of n-electron donors from the front-side of the C−X covalent bond over the back-side attack; thus, these compounds frequently form halogen bonds. Tribromo, triiodo, and tetrabromomethane have been used extensively to form halogen-bonded adducts,[28] while iodoperfluoroalkanes are very effective building blocks for crystal engineering based on halogen bonds.[29] Iodine(III) derivatives can also function as XB donors; for example, iodopentafluorobenzene difluoride affords adducts with various pyridine derivatives.[30]

Typical organic compounds containing nitrogen atoms (for example, amine and pyridine derivatives) form stronger XBs than do standard oxygen and sulfur compounds (for example, ethers, alcohols, and thioethers).[24c,d] The relative effectiveness of the oxygen and sulfur atoms as XB acceptor sites typically depends on the nature of the XB donor. The pairings predicted by the HSAB theory are favored, but a general ordering of XB acceptors or donors according to their strength cannot be made.

Sterically hindered XB acceptors are less efficient, since a close approach of the halogen atom is disfavored. On the other hand, an increased electron density on the electron-pair donor increases its Lewis basicity and favors XB formation. For example, neither the oxygen nor the nitrogen atoms of ω-iodoperfluoroalkylsulfonamides form XBs, while ω-iodoperfluoroalkylsulfonic salts show intermolecular O···I halogen bonds in the solid state.[31] Moreover, the XB acceptor ability of sp^2-hybridized oxygen atoms increases in solution from acetone, to dimethylsulfoxide, to hexamethylphosphortriamide.[24c,d] Nitrogen atoms are usually better XB acceptors than oxygen atoms, but the reverse is true when pyridine derivatives and the corresponding *N*-oxides are compared, and is consistent with the electron densities on the respective donor sites.[32]

Anions are usually better XB acceptors than neutral species,[33] thus demonstrating the great potential of XBs in anion coordination chemistry. The more dissociated an ion pair is, the stronger is the XB formed with the anion. Most of the known halogen-bonded adducts are formed from halide anions, with iodide and fluoride anions being the most and the least frequently recurring XB acceptors, respectively. Polyhalide anions, such as $[I_3]^-$, $[Br_3]^-$, and $[ICl_2]^-$,[34,27b,d] as well as $[CN]^-$ and $[SCN]^-$ [35] can function as XB acceptors. The solvation energies of the starting anions and their adducts as well as the strength of the formed XB both greatly affect association processes. The relative relevance of the two parameters is different in solution and in the solid state.

Halogen bonding is a highly directional interaction—more directional than hydrogen bonding—and short interactions are more directional then long ones.[13a] The consequence of the anisotropic distribution of electron density around the halogen atom is that the angle between the covalent and noncovalent bonds around the halogen atom in D···X−Y is approximately 180°. When n-electron donors such as ethers and amines function as XB acceptors the interaction preferentially develops along the axis of the donated lone pair of electrons.[4,12,36] In halogen bonds involving pyridine derivatives, the C−X bond is roughly coplanar with the pyridine ring, and the two C−N···X angles are approximately 120°.[37] Carbonyl groups, with a trigonal planar geometry around the O atom, can act as acceptors for one or two XBs. Similarly, sulfoxides and imines form XBs along the axis of the lone pair of electrons.[38]

3. XBs in Crystal Engineering

Wuest and co-workers defined a tecton as a molecular building block that possesses the structure and molecular recognition features to predictably self-assemble into crystalline networks.[39] Halogen atoms in which the σ hole is augmented by electron-withdrawing neighboring groups can effectively function as the "sticky sites" that direct molecular association. This is the case for polyhalocarbons, which frequently behave as reliable tectons. In the following section we discuss how the directionality of XBs allows the supramolecular architecture to be anticipated from the structure of the starting molecules.

3.1. 1D Architectures

XBs tend to be linear, formed along the C−X bond axis of the XB donor and along the axis of the lone pair of electrons of the heteroatom in the XB acceptor. As a consequence, pyramidal aggregates with four building blocks are formed when a pyramidal tridentate XB donor interacts with a monodentate XB acceptor (for example, in the CHI_3/isoquinoline system), while linear aggregates with three building blocks are formed when a linear bidentate XB donor (or acceptor) interacts with a monodentate XB acceptor (or donor).[40]

One-dimensional (1D) chains are formed when both the donor and the acceptor are bidentate (Figure 2). Linear polymers are formed when the axes of the donor and acceptor sites are parallel and coaxial,[8b,c,24a,25c,37a,41] while stepped infinite chains are formed when the binding sites are parallel, but no longer collinear.[23f,24a,34,37a,42]

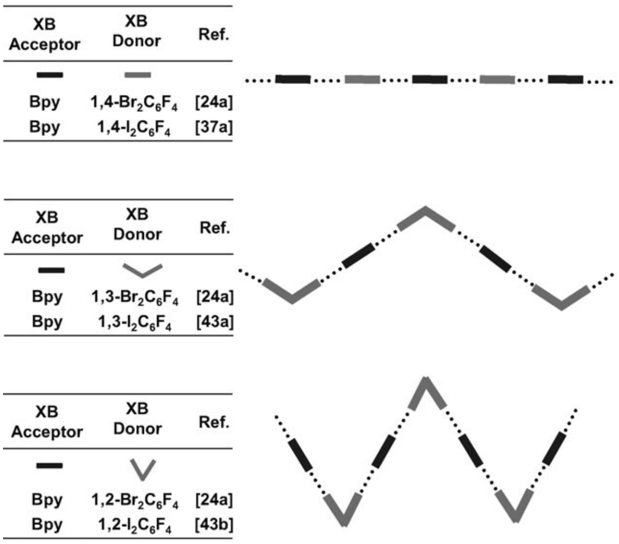
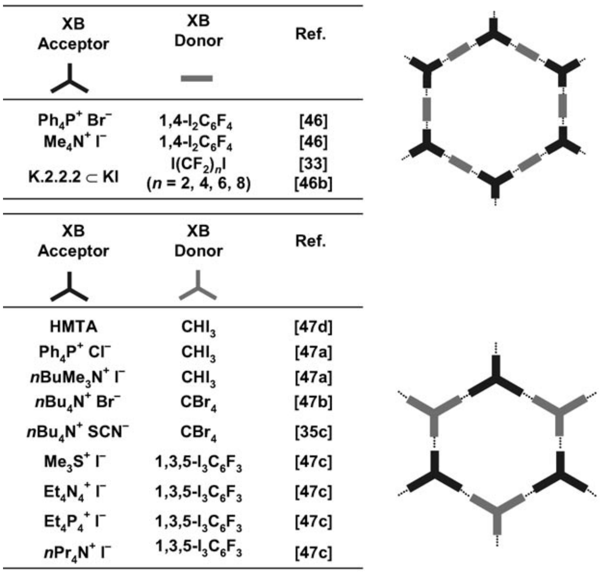


Figure 2. Linear (top) and herringbone (middle and bottom) infinite chains formed by the self-assembly of bidentate XB donors and acceptors. Bpy = 4,4′-bipyridine.

The self-assembled chains assume a herringbone arrangement when the axes of the binding sites in the components are not parallel; the angles along the chain strictly correspond to the angles of the binding sites axes in the components. For example, 4,4′-bipyridine, and its ethylene analogue 4,4′-ethane-1,2-diyldipyridine, afford linear chains with 1,4-diiodotetrafluorobenzene, but zigzag chains on interaction with the 1,3- and 1,2- analogues (Figure 2).[43] Many cases have been described where the XB donor,[24c,43c] the XB acceptor,[9a,25b,36,38,44] or both sites[23f,35c] present an angled geometry. The linear and/or angled modules can be both neutral and anionic species, and halide anions frequently function as bidentate XB acceptors and assume linear or angled geometries[17b,26b,45] as a function of the overall crystal-packing requirements.

3.2. 2D Architectures

When one or both of the interactive modules form three or more halogen bonds, two-dimensional (2D) architectures are formed. A frequently recurring pattern is the (6,3) network (honeycomb structure), which is formed when halide anions self-assemble with dihalocarbons (Figure 3, top).[33,46] Halides function as tridentate XB acceptors that occupy the nodes while the dihalocarbon molecules function as bidentate XB donors that connect the nodes. Since the trigonal arrangement around the nodes is not planar, a corrugated 2D honeycomb structure is formed.



XB Acceptor	XB Donor	Ref.
Ph_4P^+ Br^-	1,4-$I_2C_6F_4$	[46]
Me_4N^+ I^-	1,4-$I_2C_6F_4$	[46]
K.2.2.2 ⊂ KI	$I(CF_2)_nI$ (n = 2, 4, 6, 8)	[33] [46b]

XB Acceptor	XB Donor	Ref.
HMTA	CHI_3	[47d]
Ph_4P^+ Cl^-	CHI_3	[47a]
nBuMe_3N^+ I^-	CHI_3	[47a]
nBu$_4N^+$ Br^-	CBr_4	[47b]
nBu$_4N^+$ SCN^-	CBr_4	[35c]
Me_3S^+ I^-	1,3,5-$I_3C_6F_3$	[47c]
$Et_4N_4^+$ I^-	1,3,5-$I_3C_6F_3$	[47c]
$Et_4P_4^+$ I^-	1,3,5-$I_3C_6F_3$	[47c]
nPr$_4N^+$ I^-	1,3,5-$I_3C_6F_3$	[47c]

Figure 3. Honeycomb networks formed by the self-assembly of bidentate XB donors and tridentate acceptors (top), and by the self-assembly of tridentate XB donors and tridentate acceptors (bottom). HMTA = hexamethylenetetramine.

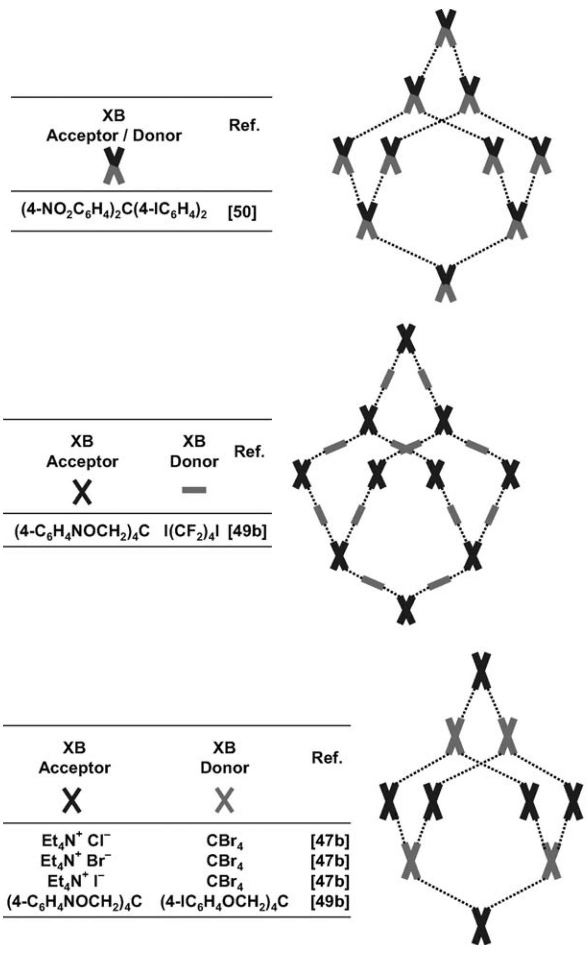
Alternatively, the (6,3) topology can be formed by the self-assembly of tridentate XB donors with tridentate XB acceptors. In this case, the complementary partners alternate at the nodes of the 2D architecture. This is the case when CHI_3, CBr_4, or 1,3,5-$C_6F_3I_3$ self-assemble with some onium halides (Figure 3, bottom).[35c,47] In these cases too, the linear XBs connect the pyramidal halomethane and halide building blocks at the nodes of the network into the corrugated honeycomb structure.

Other architectures can be formed by the self-assembly of tridentate components with bi- or tridentate partners. Ribbons are formed,[9b,46a,48] for example, when halide anions function as tridentate or T-shaped nodes connected by bidentate dihalocarbons.

3.3. 3D Architectures

Two- or three-dimensional (3D) architectures are formed when one or both of the interactive modules are tetradentate. Examples of 2D architectures are the (4,4) networks formed from the self-assembly of tetradentate XB acceptors at the nodes and bridging linear bidentate XB donors.[9a,49]

Adamantanoid networks are examples of 3D architectures that are formed by the self-assembly of different components. Such a network is present, for example, in the homocrystal of a self-complementary tetradentate building block that contains two XB donor sites and two XB acceptor sites (Figure 4, top).[50] The 3D architectures are also formed by the self-assembly of tetradentate XB acceptors, that sit at the nodes, with bidentate XB donors, that function as spacers (Figure 4, middle)[49b] and by the alternation of tetradentate XB donors and tetradentate XB acceptors at the nodes of the network (Figure 4, bottom).[47b,49b]



XB Acceptor / Donor	Ref.
$(4\text{-}NO_2C_6H_4)_2C(4\text{-}IC_6H_4)_2$	[50]

XB Acceptor	XB Donor	Ref.
$(4\text{-}C_6H_4NOCH_2)_4C$	$I(CF_2)_4I$	[49b]

XB Acceptor	XB Donor	Ref.
Et_4N^+ Cl^-	CBr_4	[47b]
Et_4N^+ Br^-	CBr_4	[47b]
Et_4N^+ I^-	CBr_4	[47b]
$(4\text{-}C_6H_4NOCH_2)_4C$	$(4\text{-}IC_6H_4OCH_2)_4C$	[49b]

Figure 4. Self-assembly of three-dimensional networks by the self-assembly of bi- or tetradentate XB donors and bi- or tetradentate acceptors.

The halogen-bonded 2D and 3D networks described above frequently contain large cavities, as is the case for similarly sized networks assembled through hydrogen bonding or other interactions.[51] The empty space present in the overall crystal packing is filled by solvent molecules or through interpenetration.[46b,49b] The formation of porous networks through halogen-bonding interactions is expected to become a field of great interest.

4. XBs in Materials Chemistry

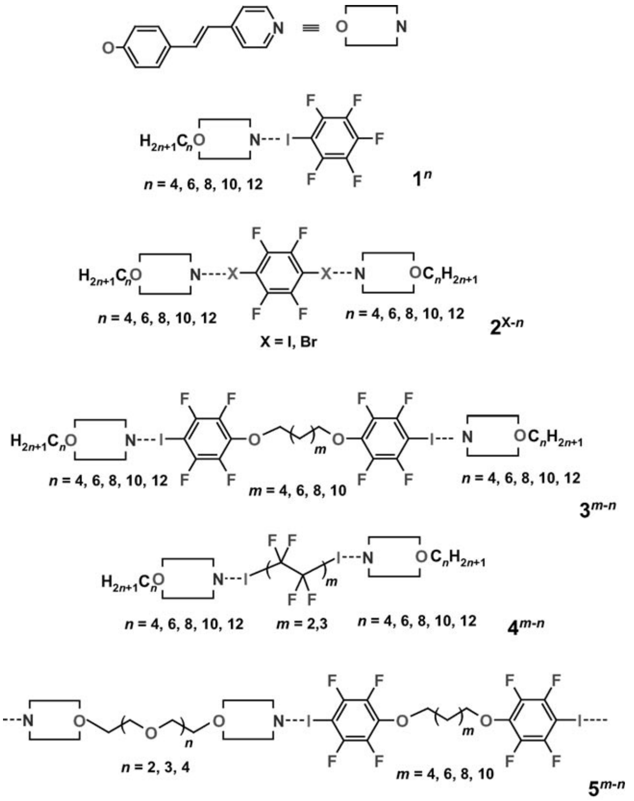
The great potential for the development of high-value functional materials based on the formation of XBs is already known. Herein we focus on several specific examples of halogen-bonded supramolecular architectures with applications in fields as diverse as liquid crystals, organic semiconductors, and paramagnetic materials. At the end, we consider developments in other research areas that exploit the remarkable possibilities offered by XBs for the design and development of new compounds and materials.

4.1. Liquid Crystals

The use of noncovalent interactions (for example, HBs as well as quadrupolar and charge-transfer interactions) led to the development of new families of supramolecular mesogens by self-assembly.

The incorporation of fluorinated groups into mesogens is an efficient strategy to improve the physical properties of liquid crystals (LCs) and to exert control over their supramolecular organization.[52] Haloperfluorocarbons are particularly effective tectons for the self-assembly of systems through the formation of XBs. It is thus not surprising that various research groups employed XBs for the preparation of supramolecular and fluorinated LCs. In all the cases reported to date, the self-assembly process is driven by the formation of N···I interactions. Thermotropic LCs with both low molar mass and high molar mass (polymeric) have been obtained which form smectic A (SmA) and/or nematic phases.

The evaporation of equimolar solutions of iodopentafluorobenzene and 4-alkoxystilbazoles ((*E*)-4-(4-alkoxystyryl)pyridines) afforded the halogen-bonded dimers $\mathbf{1}^n$ ($n=4$–12, Scheme 2), which were the first examples of thermotropic LCs obtained from a self-assembly driven by the formation of XBs in nonmesomorphic starting materials.[5a] Both starting modules are colorless solids, but adducts $\mathbf{1}^n$ are pale yellow crystals, consistent with a degree of charge transfer from the N to the I atom. The presence of strong N···I XBs, which are responsible for the formation of the cocrystals, was confirmed by single-crystal X-ray analysis of the dimer $\mathbf{1}^8$. Bromopentafluorobenzene or hexafluorobenzene afforded no corresponding adducts, thus indicating that the weak N···Br XBs and the arene–perfluoroarene quadrupolar interactions are unable to self-assemble these starting modules into mesomorphic supramolecular species. The behavior observed for the mesogens $\mathbf{1}^n$ was typical for simple, polar mesogens. Nematic mesophases are formed by $\mathbf{1}^n$ with shorter alkoxyl chains ($n=4$, 6), while smectic A mesophases are formed by $\mathbf{1}^n$ with longer alkoxyl chains ($n=6, 8, 10, 12$). Transitions of $\mathbf{1}^4$ and $\mathbf{1}^6$ were monotropic while those of other derivatives were enantiotropic.



Scheme 2. Supramolecular mesogens formed by self-assembly through XBs.

In a similar manner, adducts $\mathbf{2}^{X-n}$ ($X=I$, $n=4$–12) were the only adducts formed when 1,4-diiodotetrafluorobenzene and alkoxystilbazoles were mixed in 1:2 ratio or when other ratios were used.[5b] Interestingly, 1,4-dibromotetrafluorobenzene and 4-*n*-octyloxy-4′-stilbazole afforded the trimeric adduct $\mathbf{2}^{Br-8}$, but no adduct was formed with 1,4-diiodobenzene. The pale yellow color as well as the IR spectra and melting points of all adducts $\mathbf{2}^{X-n}$ are indicative of the presence of N···X halogen bonds; these were unequivocally proven by single-crystal X-ray analysis of $\mathbf{2}^{I-8}$ and $\mathbf{2}^{Br-8}$. The two structures are isomorphous, but their thermal and optical behaviors were noticeably different. On heating, all compounds $\mathbf{2}^{X-n}$ melted directly to the isotropic liquid. On cooling from the homogeneous isotropic state, $\mathbf{2}^{I-4}$, $\mathbf{2}^{I-12}$, and $\mathbf{2}^{Br-8}$ showed no mesophase, while a monotropic nematic phase was seen for $\mathbf{2}^{I-6}$, $\mathbf{2}^{I-8}$, and $\mathbf{2}^{I-10}$, with thermodynamic N-I phase transitions around 110 °C. Clearly, the stronger N···I interaction is able to survive in these systems at temperatures higher that 100 °C, and can induce mesomorphism in supramolecular species obtained from the isotropic state. In contrast, the weaker N···Br interaction either does not persist in the molten phase or, if surviving, is unable to induce mesomorphism. Mixtures are a common feature of LCs and are attractive, as they can lead to wide mesophase ranges. This was also the case for the systems under study, and the four-component mixture of butyloxystilbazole/octyloxystilbazole/dodecyloxystilbazole/diiodotetrafluorobenzene in a 1:2:1:2 ratio showed an enantiotropic nematic phase that was stable over a larger temperature range than that of adducts formed solely from the two building blocks.

The adducts $\mathbf{3}^{m-n}$ ($m = 4$–10, $n = 6$-12) formed from three building blocks by the self-assembly of 4-alkoxystilbazoles with bis(4-iodotetrafluorophenyl)ethers of α,ω-diols also formed thermotropic LCs, even though the starting components were not.[5e] X-ray photoelectron spectroscopy (XPS) and infrared (IR) analysis indicated the effective formation of the complex under XB control, even though the alkoxyl residues might decrease the electron-acceptor ability of the iodine atoms. All the mesogens formed from three building blocks except $\mathbf{3}^{8-4}$ and $\mathbf{3}^{10-6}$ gave a monotropic SmA phase. Surprisingly, the length of the spacers in the XB donors and the terminal groups in the XBs have little effect on the mesophase transition temperatures and temperature ranges.

Not only diiodoperfluoroarenes but also α,ω-diiodoperfluoroalkanes can connect two stilbazole molecules through halogen bonds. The adducts $\mathbf{4}^{m-n}$ ($m = 2, 3$; $n = 8$–12) were, in fact, formed on evaporation of 1:2 mixtures of starting materials.[5c] Single-crystal X-ray diffraction analysis of $\mathbf{4}^{3-8}$ proved the presence of short N···I interactions, and showed a strong phase segregation between the perfluoroalkyl and stilbazole groups. Thus, SmA mesophases could be expected, as is often the case when long perfluoroalkyl chains are present. In contrast, all complexes except $\mathbf{4}^{3-10}$ displayed a monotropic nematic phase with melting points in the range 95–108 °C and clearing points between 90 and 104 °C.

Finally, halogen-bonded polymers $\mathbf{5}^{m-n}$ ($m = 2$–8, $n = 2$–4) were obtained when the bis(4-iodotetrafluorophenyl) ethers of α,ω-diols present in adducts $\mathbf{3}^{m-n}$ were combined with bis(stilbazolyl) ethers of glycols.[5d] The flexible polyether chain between the XB acceptor groups plays a key role in the formation of the mesophase. No LC phases were observed for any of the polymers $\mathbf{5}^{m-2}$ with the shortest spacer ($n = 2$); unidentified, monotropic, highly ordered smectic phases were observed for $\mathbf{5}^{4-3}$, $\mathbf{5}^{6-3}$, and $\mathbf{5}^{8-3}$ with the midlength chain ($n = 3$); while monotropic nematic phases were observed for all $\mathbf{5}^{m-4}$ mesogens with the longest chain ($n = 4$). Consistent with this rationalization, the halogen-bonded polymers obtained by the self-assembly of the same bis(4-iodotetrafluorophenyl) ethers and less-flexible dipyridyl derivatives (for example, 4,4′-dipyridyl, 4,4′-dipyridylethane and -ethylene) formed no liquid-crystalline phases.

4.2. Magnetic and Conducting Materials

A precise distribution and topology of the spin-density interactions between radical molecules is needed for magnetic molecular solids. Similarly, the partially filled conduction bands of molecular conductors typically depend on the one-, two-, or three-dimensional architectures resulting from the intermolecular interactions between the molecules. Magnetic interactions, like the electronic bands are extremely sensitive to minute structural modifications. Thus, structural changes through the formation of XBs can improve the magnetic and conductive properties of molecular materials.

Nitroxide free radicals are used extensively as building blocks for molecular magnetic materials, and it has been described how their oxygen atoms function as XB acceptor sites. ESR spectroscopic measurements on TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) radicals in solution revealed an amplification of the hyperfine splitting of the nitrogen atom on addition of halocarbons, thus proving the formation of halogen-bonded complexes.[53] As expected, the effect was greater for iodoperfluorocarbons than for bromoperfluorocarbons and iodocarbons. A ΔH^0 value of $-7\,\text{kcal mol}^{-1}$ was measured for the formation of the TEMPO/n-$C_8F_{17}I$ complex. On formation of the XB, the unpaired spin density is in part transferred from the nitroxide moiety to the iodine atom, and at the same time its delocalization on the nitrogen atom increases. The involvement of nitroxide radicals in the formation of XBs in the solid phase was demonstrated in the single-crystal X-ray structure of the 1:1 adduct formed between 4-amino-TEMPO and 1,4-diiodotetrafluorobenzene.[54] The crystal packing was characterized by the presence of one-dimensional chains, in which the two components are linked through N···I and O···I halogen bonds involving the amino nitrogen atom and the nitroxyl oxygen atom, respectively. The short O···I distance (2.827 Å) confirms that nitroxyl radicals are strong XB acceptors. 4-(4-Iodobenzylideneamino)-TEMPO crystallizes as two polymorphs, with one of them exhibiting O···I contacts (Figure 5). Interestingly, the polymorph without halogen bonds shows a ferromagnetic transition, while the halogen-bonded polymorph is antiferromagnetic.[55] Analogous bromo- and iodo-substituted nitronyl nitroxides also exhibit short O···Br and O···I contacts (2.970 and 2.928 Å, respectively). Although the molecules have similar molecular packing, they show different magnetic properties (antiferromagnetic and ferromagnetic, respectively).[56]

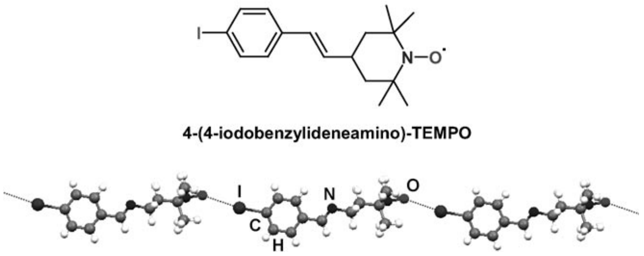


Figure 5. One-dimensional chain fragment of 4-(4-iodobenzylidene-amino)-TEMPO. ••••••: halogen bonds.

To the best of our knowledge, the first example of XBs in conducting molecular materials was reported by Imakubo et al. in 1995—this was the radical cation salt of an iodine-substituted tetrathiafulvalene (TTF) and $[Ag(CN)_2]^-$ as the XB acceptor.[57] The remarkably short XBs found in this compound demonstrate the general concept that oxidation of the TTF moiety to the radical cation boosts the positive charge in the polar region of the halogen atom and favors the formation of particularly strong halogen–anion interactions.

This innovative study prompted the preparation of numerous complexes based on halogenated TTFs. A recent review of this topic shows that XBs are effective in controlling the packing structure and might even contribute to increasing the conductivity through its involvement in broadening the conduction band.[6] Whether XBs occur with neutral TTFs, depends on the substitution pattern of the compounds. Monohalo TTFs rarely exhibit strong directional XBs, but dihalo TTFs, such as 2,6-diiodo-TTF exhibit intermolecular I···I XBs.[58]

As to the radical cation salts, adducts formed by iodinated or brominated TTFs—or their tetraselena or dithiadiselena analogues—with halide, polyhalide, or polyhalometalate anions have been obtained and studied. A wide diversity of XB patterns was observed, thereby proving that the interaction can adapt to the overall (supra)molecular requirements of the system.[59] Trihalides, where the anion negative charge is delocalized over three halogen atoms, usually form longer halogen bonds than halides with localized charge.[60] The negative charge is even more delocalized in polyhalometalates, and the resulting halogen bonds can be even longer than with the trihalides.[61] $[I_3]^-$ salts are semiconductors, with conductivities of 0.5 $\mathrm{S\,cm^{-1}}$ at room temperature. Conducting materials based on halogenated TTFs and (poly)halometalates have recently become a hot topic, since polyhalometalates often exist in a paramagnetic state and thus allow the investigation of possible π–d interactions. XBs could control the interaction between the π conducting electrons on the donor molecules and the localized d spins of the magnetic counterions. The use of paramagnetic anions, such as $[FeCl_4]^-$ and $[FeBr_4]^-$, and their diamagnetic analogues, such as $[GaCl_4]^-$ and $[GaBr_4]^-$, results in materials with magnetic properties that vary as a function of the π–d interactions.

The radical cation salts of diiodo(pyrazino)diselenadithiafulvalene (DIPS) and its tetraselena analogue (DIPSe) are particularly elegant examples of the presence of XBs in fulvalene-based supramolecular conductors.[62] The octahedral counterions $[AF_6]^-$ (A = P, As, Sb) do not function as XB acceptors, but the pyrazino nitrogen atoms form quite short C-I···N contacts (2.84–2.88 Å in DIPS salts and 2.85–2.87 Å in DIPSe salts), which mediate the formation of systems with threefold symmetry and variable stoichiometry (for example, $(DIPS)_3(PF_6)(PhCl)_{1.15}$ or $(DIPSe)_3(PF_6)_{1.33}(CH_2Cl_2)_{1.2}$). The XB network affords lacunary crystal structures with two types of channels, in which the counterion and solvent molecules are dispersed (Figure 6). These porous supramolecular organic materials exhibit high conductivities: $\sigma_{RT} = 10\ \mathrm{S\,cm^{-1}}$ with $E_{act} = 50$ meV for the DIPS salts, and $\sigma_{RT} = 100\ \mathrm{S\,cm^{-1}}$ and a metallic behavior for the DIPSe salts.

A few examples have been reported where oxygen and sulfur atoms are used as electron-pair donors to TTF derivatives. Both anionic (for example, $[ClO_4]^-$, $[HSO_4]^-$, $[M(dmit)_2]^-$; dmit = 2-thioxo-1,3-dithiole-4,5-dithiolato, M = Ni, Pt, Pd)[63] and neutral (p-$C_6H_4(NO_2)_2$, ethylenedioxo compounds)[63a,64] chalcogen centers were employed.

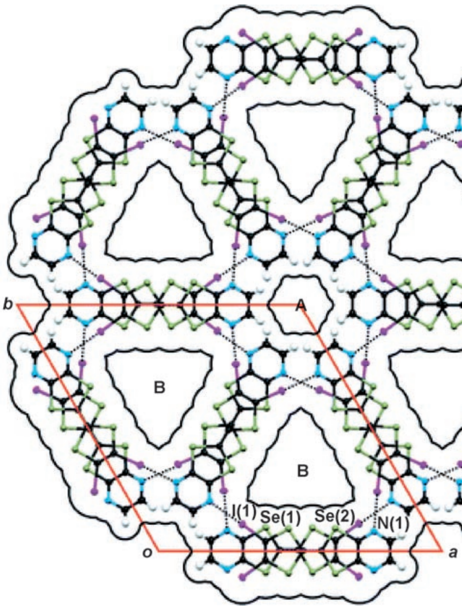


Figure 6. Crystal structure of $(DIPSe)_3(PF6)_{1.33}(CH_2Cl_2)_{1.2}$: viewed with the van der Waals outlines along the *c*-axis. •••••: I···N iodine bonds (2.852(9) Å). The PF_6^- counterions and enclosed solvent CH_2Cl_2 are omitted for clarity. "A" and "B" indicate the supramolecular channels running along the *c*-axis. C black, N blue, Se green, I purple, H light gray. Reproduced with permission from Ref. [15c].

In contrast, there are many examples where the nitrogen atoms or nitrile groups are the electron donors. A variety of inorganic cyanometalates were employed, such as the linear $[Ag(CN)_2]^-$[57] mentioned above, the square-planar $[Pt(CN)_4]^{2-}$ or $[Au(CN)_4]^-$, and the octahedral $[Cr(CN)_6]^{3-}$ or $[Fe(CN)_5NO]^{2-}$.[65] Larger cluster anions such as $[Re_6Se_8(CN)_6]^{4-}$, low-spin complex anions such as $[Fe(bpca)(CN)_3]^-$ (bpca = bis-(2-pyridylcarbonyl)amide), and thiocyanate anions such as $[Cr(isoq)_2(SCN)_4]^-$ (isoq = isoquinoline) were also used with success.[66] Particularly short and linear I···N contacts were observed in the obtained halogen-bonded architectures. Strong I···N XBs were also obtained with anions of organic nitriles such as the square-planar metal dithiolene complexes $[M(mnt)_2]^-$ (mnt = 1,2-dicyanoethylene dithiolate; M = Ni, Pt, Pd).[63b,67]

Finally, organometallic systems were obtained through galvanostatic oxidation of iodinated TTF derivatives in the presence of onium halides and diiodoacetylene, tetraiodoethylene, or other iodoorganic derivatives.[40c,68] Systems where halide anions are halogen-bonded to two, three, or even more iodine atoms of the neutral iodinated molecules are thus formed. The larger the coordination number of the halide, the longer is the XB formed.

4.3. Miscellaneous

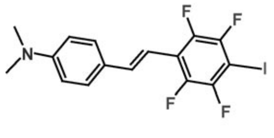
The synthesis of polar molecular materials is a fundamental target of contemporary materials research, especially in the context of designing efficient nonlinear optical (NLO) materials capable of second harmonic generation (SHG). The control that XBs can exert on structure has also been used to induce polar order in molecular materials.[44d] 4-Iodo-4′-nitrobiphenyl, for example, crystallizes into polar and parallel 1D infinite chains as a result of the formation of I···nitro XBs.

As a consequence, the structure is noncentrosymmetric and shows measurable SHG activity.[8b,c]

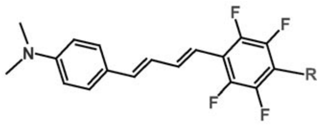
Another interesting compound is 1,3-dibromo-2,4,6-trinitrobenzene. Here, Br···nitro XBs result in a highly ordered polar material with a high SHG.[8d] Similarly, structure-directing CN···X interactions (X = Cl, Br, I) and fluorination were used as a way to reduce interchain interactions and control the formation of noncentrosymmetric structures of p-XC_6F_4CN compounds, which were shown to be SHG active.[69]

The formation of XBs between an NLO chromophore working as the XB donor and the solvent working as the XB acceptor can change both the value and the sign of the second-order NLO responses in solution.[8a] Compound **6a** and its vinylogue **6b** were synthesized and their second-order NLO properties were established at a molecular level (by the solution-phase electric field induced second-harmonic (EFISH) generation method). The ability of the solvent to behave as an XB acceptor leads to the aforementioned NLO chromophores giving rise to $\mu\beta_\lambda$ values that vary from $+192\times10^{-48}$ (in $CHCl_3$) to -465×10^{-48} esu (in DMF). In contrast, $\mu\beta_\lambda$ values of **7**, which cannot form any XBs, remain positive in any solvent (Table 1).

Table 1: $\mu\beta_\lambda$ values (10^{-48} esu) for solutions of NLO chromophores **6a**,**b** and **7** in $CHCl_3$ and DMF.



6a

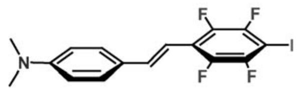


6b (R = I)
7 (R = H)

Compd	μ	CHCl$_3$		DMF	
		$\mu\beta_\lambda$	λ_{max}	$\mu\beta_\lambda$	λ_{max}
6a	6.31	+124	382	−380	387
6b	7.25 (6.8)[a]	+192	406	−465	410
7	6.10	+173	392	+70	396

[a] Experimental value in $CHCl_3$.

Solid-state synthesis is a fascinating and rapidly emerging field of organic chemistry. It has been demonstrated that steering groups, such as chloro-, bromo-, fluoro-, trifluoro, methoxy, and acetoxy substituents, can force molecules to pack in the desired crystalline order to undergo [2+2] photoaddition in the solid state. On the other hand, the use of noncovalent interactions to dictate the self-assembly of unsaturated molecules around templates provides a very reliable and efficient tool to force unsaturated molecules to meet the requirements for cycloaddition. We described the first case where XBs drive the self-assembly of a template, namely a tetratopic XB donor, with an olefin, in which the double bonds were oriented for photocyclization in the crystal.[9b] A solid-state photoreaction under supramolecular control has also been used for the synthesis of the 2D heterotetratopic self-complementary XB tecton **9**. The 1D heteroditopic self-complementary XB tecton **8** with a central double bond was designed to also form heteropolar arene–perfluoroarene π–π stacking interactions (Figure 7, top). Schmidt's requirements are fulfilled, and on UV irradiation dimerization of the crystalline **8** occurs and forms **9** as a single steroisomer (Figure 7, bottom). The strength and directionality of the N···I XBs in this self-complementary cyclobutane derivative prevent the formation of π–π stacking interactions between the heteropolar arene groups, so that a close packing of the pendant arms, as in **8**, is prevented. Large voids are



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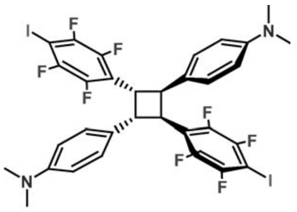

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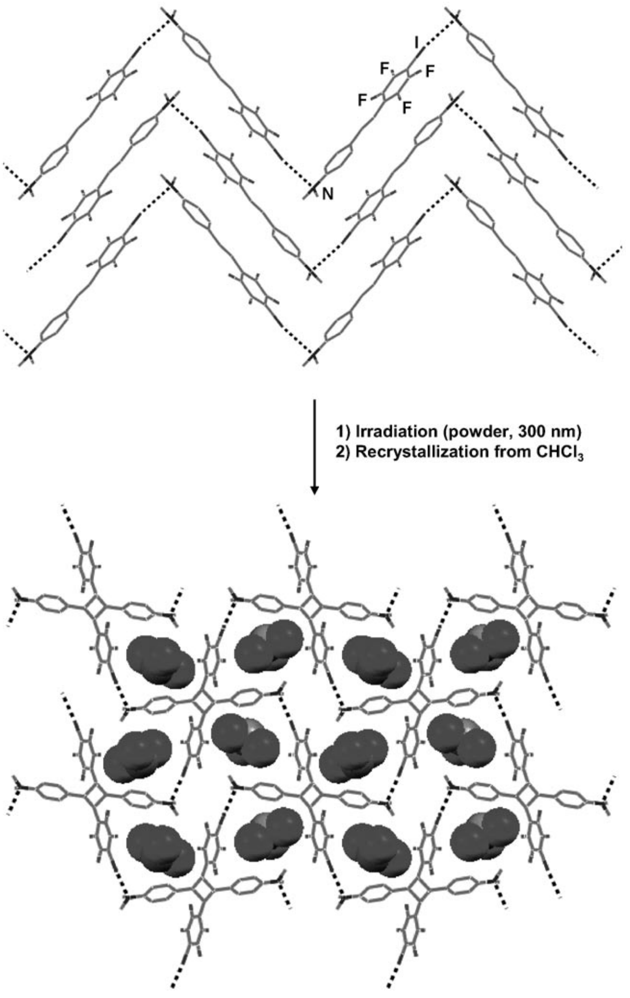
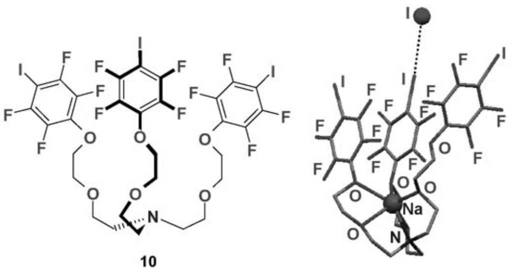


Figure 7. A view down the crystallographic c-axis of the crystal packing of the self-complementary tecton **8** (top) and **9** (bottom). ••••••: halogen bonds. Included $CHCl_3$ molecules are shown by space-filling models. H atoms are omitted for clarity.

present in the crystal matrix, which are filled by $CHCl_3$ molecules.[9a]

In a similar way, crystal engineering based on anions may be developed if their ability to function as electron-donor sites is fully exploited.

Metal cations play a key role in crystal engineering because of their effectiveness in driving self-assembly processes—mainly as a result of their strong tendency to function as electron-pair acceptors in the presence of a variety of Lewis bases. Conversely, the ability of anions to function as electron-pair donors forms the basis of crystal engineering in the solid state and the corresponding coordination chemistry in solution. The tripodal receptor **10** (Figure 8), comprised of a well-established motif for cation binding and a motif for anion recognition through the formation of an XB, showed its effectiveness for the full separation of the ion pair on coordination with alkali-metal halides.[11a] The structure of the complex formed between **10** and sodium iodide demonstrated the cooperativity of metal coordination and the $I^-\cdots I$ XB. The enhancing effect of the binding of the anion, through the formation of XBs, on the coordination of the cation has also been proved in solution by NMR experiments.



10

Figure 8. Tripodal receptor **10** (left) and single-crystal X-ray structure of the asymmetric unit cell of its complex with NaI (right). •••••: halogen bonds. H atoms are omitted for clarity.

We already mentioned in Section 3 that when halide anions are involved in the formation of XBs they can function as mono-,[70] bi-,[45a] tri-,[33,46b] and even tetradentate electron donors[35c] to give discrete adducts or 1D, 2D, or 3D networks. The degree of specificity that is possible with these systems is unusual for crystal engineering, and thus demonstrates that XBs can be considered a first-choice tool in anion coordination chemistry. For example, it was expected that 1,3,5-trifluoro-2,4,6-triiodobenzene, a module with threefold symmetry, would elicit a tridentate bonding of the I^- ion. Different sources of iodide anions self-assemble with trifluorotriiodobenzene to yield a series of anionic honeycomb-like networks (Figure 3).[47c]

A comprehensive review of all the functional materials based on XBs is beyond the scope of this article, but we wish to highlight some other applications that show the significance of this interaction. For example, the noncovalent fluorous coating of polymers,[71] the imprinting of polymers at the molecular level,[7b] and layer-by-layer fabrication of a polymer film [72] have exploited XBs as a new design concept. Other fields where halogen-bonded materials have found applications are the resolution of racemates,[7a] the stabilization of the outer sphere of metal–ligand complexes,[73] and for the reversible uptake of gaseous HCl.[11b]

5. XBs in Biological Systems

There are only a few high-resolution X-ray crystal structures of complexes of biomolecules with halogenated molecules. In fact, only 48 hits appear in the PDB (Protein Data Bank)[74] for high-resolution structures (<1 Å) of C-bound halogenated ligands with proteins and DNA sequences, and only 8 of these 48 structures involve bromine and iodine. For this reason, the possible role of XBs in the binding of biological molecules has been largely ignored. Nevertheless, a full understanding of how halogenated molecules bind to biological substrates could open the door to new and more effective approaches to drug development, as well as to the rationalization of the adverse effects of some chemicals to which humans are commonly exposed (for example, polyhalogenated molecules). Interestingly, the halogenation of proteins and nucleic acids is seen to be associated with a number of related diseases. For example, levels of chlorotyrosines have been correlated with chronic respiratory diseases in infants, while bromotyrosines are associated with allergen-induced asthma; these effects might be related to the formation of XBs.

In 2004, Auffinger et al. reported a comprehensive survey of protein and nucleic acid structures, which revealed that halogen bonds are potentially stabilizing inter- and intramolecular interactions that can affect ligand binding and molecular folding.[10c] The trigger for such a survey was prompted by the discovery of a four-stranded DNA Holliday junction in 2003, and an ultra-high-resolution structure of the complex of the enzyme aldose reductase with a halogenated inhibitor reported in 2004.[75] Both systems revealed unusually short Br···O contacts (12 % shorter than the sum of the van der Waals radii for Br and O). This survey targeted a data set of protein and nucleic acid structures with short halogen–oxygen distances. Quantum mechanical calculations were used to generate electrostatic potential maps to compare the polarizability of the halogen atoms in biological molecules. From this comprehensive study, the geometries of XBs in biological systems were proven to conform generally to the geometries seen in small molecules; a few exceptions were seen because of the more complex environment found in biomolecular systems.

More recently, Ho et al. used XBs to manipulate a conformational switch in a four-stranded DNA Holliday junction.[76] A short and directional XB (Br···O1P distance 2.87 Å; C5-Br···O1P angle 163.2°, Figure 9) formed between brominated uracil and phosphate oxygen atoms of the DNA backbone competes against the conventional hydrogen bond of cytosine in a similar position. Calculations show the halogen bond to be be nearly 5 kcal mol^{-1} more thermodynamic stability than the corresponding hydrogen bond. Preliminary results indicate that iodine can substitute for bromine at the junction center.[77]

With the aim of estimating the contribution of XBs to the stabilization of oligodeoxynucleotide duplexes, a series of

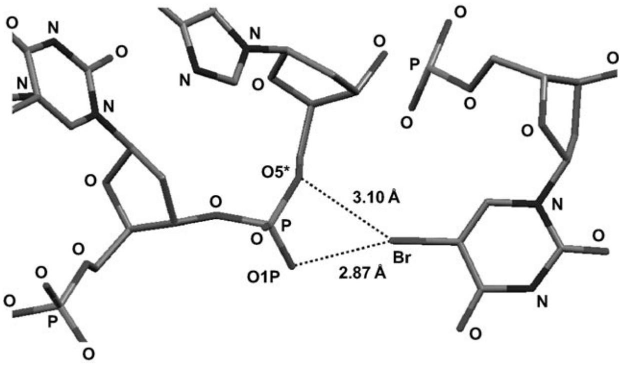
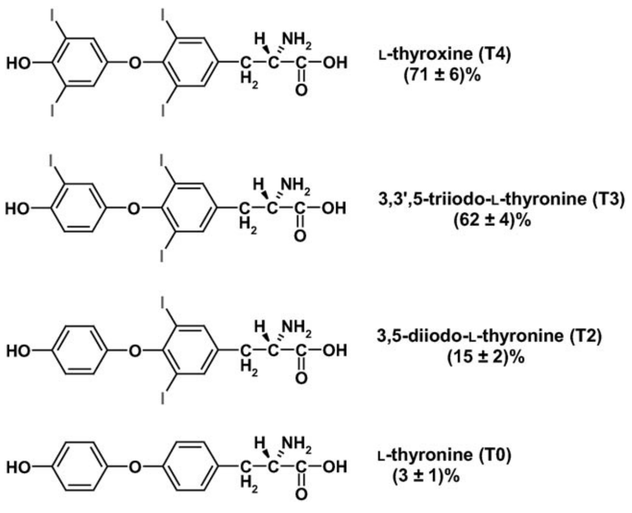


Figure 9. The unusually short XB between the bromine atom of a brominated uracil residue and the phosphate oxygen atoms in a four-stranded DNA junction.

artificial base pairs were designed that can form XBs. Ab initio calculations showed that the optimized structures of the artificial base pairs were almost consistent with those of the canonical base pairs, with interaction energies ranging from 5 to 11 $\mathrm{kcal\,mol^{-1}}$. However, the artificial base pairs studied had a stability lower than, for example, the A-T base pair.[78]

Halogen bonds undoubtedly appear to play a key role in the recognition of thyroid hormones. Thyroxine, a naturally occurring iodinated molecule, forms short I···O contacts with its transport protein transthyretin.[79] Thyroxine, was also the first compound to be bound to RNA sequences through halogen bonds.[80] Moreover, this type of binding is specific for thyroxine (T4) and triiodothyronine (T3), the active forms of the hormone (binding activities: $(71\pm6)\%$ and $(62\pm4)\%$, respectively), whereas other inactive derivatives, including thyronine (T0), do not form complexes (binding activities: $(15\pm2)\%$ for T2 and $(3\pm1)\%$ for T0; Scheme 3). These results suggest that this RNA aptamer specifically binds to the iodine moieties of the thyroxine.

The role played by high-resolution X-ray protein crystallography in drug design is broadly recognized. The strength of the method lies in its ability to locate critical enzyme/drug interactions that can be exploited to simultaneously increase the potency and specificity.[81] For this reason, we expect that as more structures of halogenated ligands bound to biological molecules are reported, the better the role of XBs in intermolecular recognition will be elucidated. Important contributions in the field are, for example, the X-ray crystallography of some tubulin-bound brominated taxanes, in which XBs to the protein are evident.[10e] The potential role of halogen atoms in taxane–tubulin binding suggests novel possibilities for the design of other microtubule-stabilizing compounds. Short O···Cl and S···Cl contacts have also been detected in the crystal structure of the complex formed between the factor Xa of the human blood coagulation cascade and a trichloro-substituted inhibitor, which is used in the treatment of thrombotic diseases.[10b] Furthermore, the iodine atom of iododiflunisal, a potent inhibitor of amyloid formation, is found to be tightly anchored into a pocket of the binding site of human transthyretin through a series of contacts with the residues Thr106, Ala108, Thr119, and Val121.[82]



Scheme 3. Structures of thyroxine derivatives and the binding activities of the RNA aptamer.

The possible binding of halogenated molecules to biological substrates through the formation of XBs has made a significant contribution to the long-lasting debate on the mechanism of action of inhaled halogenated anaesthetics. For example, halothane (1-bromo-1-chloro-2,2,2-trifluoroethane) is a potent anaesthetic still used clinically for inducing anaesthesia in children and maintaining anaesthesia in adults. Its activity can be explained in terms of specific binding rather than by unspecific hydrophobic interactions. In particular, the high-resolution crystal structure of the complex formed between halothane and human serum albumin (HAS) showed evidence that the bromine atom is involved in significant polar interactions with charged or polar amino acids, for example, through interaction with the sulfur atom of Cys438.[83] The enantioselective recognition of halothane in vivo mediated by the formation of halogen bonds with electron-pair donors present in the receptor pocket can thus be postulated as the cause of the different pharmacological activities of the two enantiomers.

Finally, it has been suggested that the formation of XBs is responsible for the unexpected solubilization and miscibility of perfluorooctyl bromide (n-$C_8F_{17}Br$), which is used for liquid ventilation in lung diseases. For example, 1-octanol is completely miscible with perfluorooctyl bromide, and simple nicotinic acid alkyl esters also show significant solublity. Although further investigation is needed, it could be envisaged that a solution of a drug in perfluorooctyl bromide could be directly administered to the lung during conventional mechanical ventilation. The use of anaesthetics and/or drugs in combination with liquid ventilation may be the first application of this drug delivery system in humans.[84]

6. Conclusions and Outlook

After the seminal papers by Benesi and Hildebrand,[2] and Hassel,[3] halogen bonds entered a dormant period in the 1970s and 1980s. This period ended in the 1990s with the gas-phase studies by Legon[13a,b] and solid-phase studies by Metrangolo, Resnati et al.[4]

The effectiveness of the interaction in the crystal engineering of 1D networks has been widely documented. Halogen-bonded 2D and 3D networks have been much less investigated, and it can be expected that the design and use of tridentate and polydentate tectons will receive increased attention. This will allow the study of interpenetration in halogen-bonded systems[46b,49b] and—more importantly—the preparation of halogen-bonded porous systems. Very promising examples have been reported of halogen-bonded architectures with an anionic electron-pair donor.[35c,46b,47b,c] The use of anions in self-assembly processes controlled by the formation of XBs will surely develop in the near future. It can be anticipated that anion coordination through the formation of strong XBs will evolve as a particularly “hot topic”.

The ability of XBs to control recognition, self-assembly, and aggregation processes in the solid and gas phases is well documented, and the relevance of the interaction in liquid crystals is also receiving increased attention.[5] While many analytical techniques consistently also prove the existence and the relevance of XBs in solution, supramolecular chemistry based on the formation of XBs in the liquid phase still remains to be fully developed.[24b]

The formation of halogen-bonded adducts can be considered as prereactive complexes (or intermediates) formed prior to significant charge transfer or a chemical reaction.[12c,13b,23d] The XB concept may thus be used as the general basis for the rationalization of some reaction mechanisms involving electrophilic halogens (for example, haloimides).

Halogen bonds play a role in all fields where the design and manipulation of aggregation phenomena are important. The use of XBs in the “bottom-up” approach towards functional systems is only in its infancy. The structural and electronic role played by XBs in magnetic and conducting organic systems is another topical research area. The formation of halogen-bonded adducts starting from nitroxide radicals[53–55] offers new perspectives for the preparation of interesting paramagnetic structures, particularly in view of the large number of such free radicals known.

The role of XBs in biological systems and its potential in drug design will also evolve into an important topic. In fact, it can be expected that as more structures of halogenated ligands bound to biological molecules are reported, the better will the role of XBs in biomolecular recognition be elucidated, thereby leading to a more powerful drug-design strategy.

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