Review Article

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Halogen bonding: a new territory for anion sensing

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Abstract: The field of anion sensing and recognition has grown significantly due to the need for selective identification, extraction, and transport of negatively charged species essential to chemical, biological, medical, and environmental processes. However, advancements in anion coordination chemistry have lagged behind cation chemistry due to the unique challenges posed by anions, including low charge-to-radius ratios, high solvation enthalpies, diverse geometries, and pH sensitivity. Traditional approaches employing hydrogen bonding and other non-covalent interactions have achieved some success, but designing effective synthetic receptors remains a challenge. Recently, halogen bonding (XB) has emerged as a powerful alternative, offering comparable directionality and binding strengths to hydrogen bonds. This review highlights significant advancements in the past decade, focusing on the development of solution-phase anion receptors utilizing XB. It explores their complementarity to hydrogen bonding, particularly in competitive solvent environments, and underscores XB's growing role in advancing anion recognition and supramolecular chemistry.

Keywords: halogen bonding; anion sensing; supramolecular chemistry; donor-acceptor; host-guest complex

1 Introduction

The realm of anion sensing and recognition has experienced significant growth in recent decades, driven by the necessity to selectively identify, extract, and transport negatively charged species.[1–3] These entities play pivotal roles in a wide array of chemical, biological, medical, and environmental processes.[4,5] Nonetheless, progress in this domain has lagged behind the advancement seen in cation coordination chemistry. Efforts to create synthetic receptor molecules that mimic the remarkable binding affinities and selectivities exhibited by natural anion binding proteins in water-based environments remain distant goals.[5,6] This delay is commonly attributed to the inherent difficulties associated with designing selective host systems for negatively charged species. Anions possess low charge-to-radius ratios, high solvation enthalpies, and less defined coordination preferences compared to cations. Additionally, they are pH-sensitive and exhibit diverse geometries. Countering these challenges often involves leveraging multiple non-covalent interactions simultaneously, adhering to established design principles such as complementarity, chelate cooperativity, preorganization, and the macrocyclic effect.[7,8] Traditionally, various non-covalent interactions including hydrogen bonding, electrostatic interactions, anion–π interactions, dispersion interactions, and solvatophobic effects have been employed for this purpose.[9,10] Hydrogen bonding interactions, in particular, have been extensively utilized in both natural and synthetic anion receptors. Recently, the halogen bond (XB) has emerged as a potent alternative non-covalent interaction in the realm of anion recognition, demonstrating significant promise.[11,12] Despite being likened to the hydrogen bond in terms of binding strengths and directionality, its significance in this field remains largely unexplored.[13]

While halogen bonding interactions have been extensively studied crystallographically[14] and theoretically,[15,16] and have long been employed in solid-state crystal engineering and materials design applications, their potential in solution-phase applications[17] has only recently begun to be explored. A surge in studies on halogen bonding interactions in anion coordination and supramolecular chemistry has revealed their complementarity to hydrogen bonding in terms of steric requirements, solvent dependencies, anion binding preferences, and tunability. Moreover, the ability of halogen-bond-based anion receptors to surpass hydrogen-bonding analogs in competitive protic solvent media is increasingly evident.[18]

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This review article showcases the advancements made in the past decade in the development of solution-based anion receptors that harness halogen bonding interactions.

2 The theory and definition of halogen bonding (XB)

Halogen atoms found in organohalo compounds are usually regarded as areas of elevated electron density due to their high electronegativity. Reflecting this well-established concept, it is widely acknowledged that halogen atoms can engage in attractive interactions by serving as electron donors, or nucleophiles. The capacity of halogen atoms to act as acceptors in hydrogen bonding was established by mid twentieth cenury,[19] and halogen atoms within halocarbons can also function as electron donors to various other elements, such as when coordinating alkali-metal or alkaline-earth-metal cations.[20] However, the electron density within halogen atoms is unevenly distributed when the atom is covalently bonded to one or more atoms. In cases where the halogen atom participates in the formation of a single covalent bond, which is the most common scenario, there exists a region of heightened electron density perpendicular to the covalent bond, where the electrostatic potential is typically negative. Conversely, there exists a region of reduced electron density (known as the σ-hole), where the potential is often positive, especially in heavier halogens, resulting in a region of diminished electron density along the extension of the covalent bond. This region can engage in attractive interactions with electron-rich sites. The general ability of halogen atoms to attractively interact with electron donor sites (nucleophiles) has only been fully acknowledged and comprehensively understood in recent times.[13,16,21]

In 1961, Zingaro and Hedges[22] were likely the first to coin the term "halogen bond" when describing the complexes formed in solution by halogens and interhalogens with phosphine oxides and sulfides. They used this term to depict interactions where halogens behave as electrophilic species, drawing an analogy to the behavior of hydrogen in hydrogen bonding. Later, in 1976, Martire and co-workers employed the term to describe adducts formed in the gas phase by haloforms with ethers and amines.[23] However, it wasn't until the 1983 review by Dumas, Gomel, and Guerin that results obtained through various experimental techniques in gas, liquid, and solid phases were systematically categorized under the term "halogen bond," distinct from other electron donor–acceptor interactions.[24]

The widespread adoption of the term began with the concept paper by Metrangolo and Resnati, which provided general heuristic principles correlating the structure of the halogen bond donor and acceptor sites with the strength of the resulting interaction.[25] Over the past two decades, there has been an exponential increase in interest from the scientific community in this field and both "halogen bond" and "halogen bonding" are used interchangeably, with "XB" serving as an acronym for both terms.

In 2006, Glaser[26] proposed adopting the term "halogen bond" to describe any interaction involving halogen atoms, regardless of whether they function as electrophiles or nucleophiles. In the absence of a clear and universally applicable criterion for determining whether an interaction qualifies as a halogen bond, confusion can arise. This is evident in situations where halogens interact with positively charged hydrogen atoms via the region of heightened electron density on their electrostatic potential surface. These interactions are unmistakably hydrogen bonds and should not be mistaken for halogen bonds. Doing so could lead to the dissemination of incorrect electronic and geometric information.

In 2009, the International Union of Pure and Applied Chemistry (IUPAC) initiated a project (project no. 2009-032-1-100) with the objective of comprehensively examining intermolecular interactions involving halogens acting as electrophilic species and categorizing them.[27] The project concluded in 2013, with IUPAC issuing a definition for halogen bonds.[28] According to this definition, "A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity."

Therefore, a typical halogen bond (XB) is represented as

$$R - X \ldots Y$$

where the three dots symbolize the bond. R–X serves as the XB donor, with X being a halogen atom covalently linked to the R group and exhibiting an electrophilic region, or a potentially electrophilic region, on its electrostatic potential surface. Y acts as the XB acceptor (donor of electron density) and can be either an anion or a neutral species possessing at least one nucleophilic region, such as a lone-pair-containing atom or a π-system. This definition by IUPAC has been formulated to be straightforward and inclusive, encompassing all scenarios where there is evidence of bond formation involving a nucleophile and a positive region on a halogen atom X from a molecule or molecular fragment R–X.

The seeming contradiction of electronegative halogen atoms acting as electrophilic entities can be rationalized by considering the anisotropic distribution of electron density surrounding a covalently bonded halogen atom. Molecular electrostatic potential surfaces calculated for molecules containing halogen atoms reveal a localized region of diminished electron density along the R–X bond axis, termed an 'σ-hole'.[29] This electron-deficient area is immediately surrounded by an electrically neutral zone, followed by a lateral band of negative electrostatic potential. This characteristic enables halogen atoms to interact attractively with electrophiles approaching orthogonally to the covalent R–X bond, in addition to their electrophilic behaviour (Figure 1). The distinct localization of the σ-hole justifies the linear nature of halogen bond (XB) interactions. The strength of these interactions generally increases with decreasing electronegativity and increasing polarizability of the halogen atom (I > Br > Cl >> F), as well as with the enhancing electron-withdrawing capability of the substituent R.[30,31]

While the electrostatic σ-hole model explains most observed features of XB interactions, there are some anomalies that have led to proposed additional contributions from charge-transfer and dispersion components. Numerous theoretical and experimental studies have aimed to clarify the various factors influencing these interactions. However, there remains ongoing debate regarding the classification of XB interactions, with the relative significance of electrostatic/polarization, charge transfer, and dispersion contributions likely varying between different systems, depending on the local environment and the nature of the interacting molecules.

3 Anion sensing with halogen bonding

Due to their inherent electron-rich nature, anions are expected to engage in robust attractive interactions while serving as XB acceptors.[11] This anticipation has sparked considerable interest in recent years regarding the integration of XB donor groups into anion receptor molecules. The majority of developed receptors have incorporated polarized XB donor groups, such as haloimidazolium (**A**, Figure 2), haloperfluoroarene (**B**, Figure 2), halotriazole/halotriazolium (**C**/**D**, Figure 2), or interlocked rotaxane/catenane motifs (**E**/**F**, Figure 2). These groups are typically utilized in a multivalent manner, either independently or in conjunction with other noncovalent interactions like hydrogen bonding. The subsequent sections provide an overview of the application of each of these motifs in the design of anion receptors.

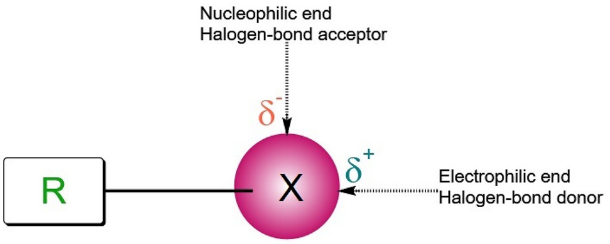


Figure 1: An anisotropic distribution of charge around the X atom is depicted in the schematic representation of a R-X···Y halogen bond, along with a potential orthogonal side-on interaction with an electrophile.

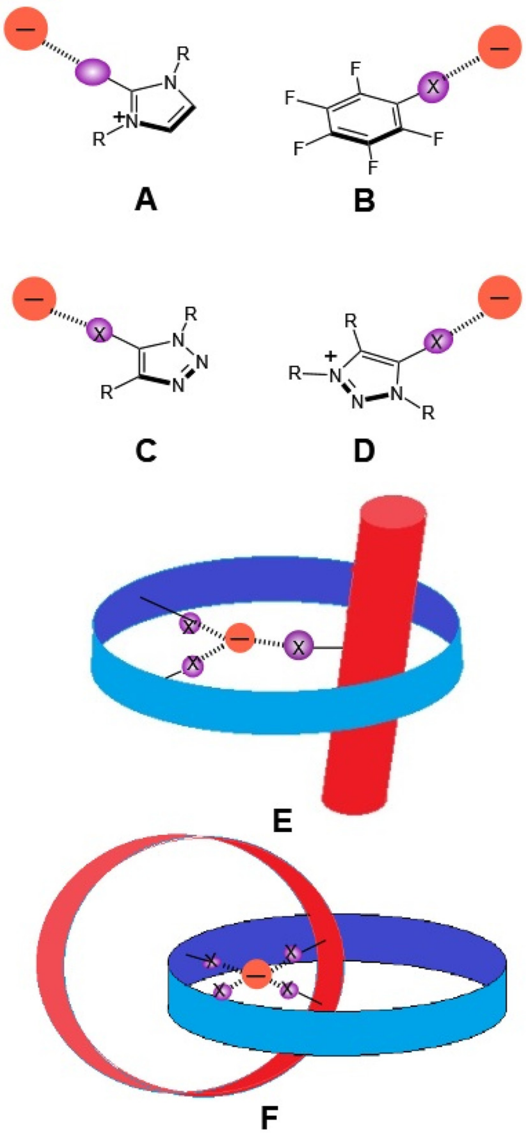


Figure 2: Schematic representation of major XB-donating motifs.

4 Receptors incorporating haloimidazolium as halogen bond donor groups

Beer and co-workers invested the anion recognition capabilities driven by halogen bonding (XB) of 2-haloimidazolium derivatives. X-ray structural analysis of the hexyl- and benzyl-substituted haloimidazolium salts **1**–**3** (Figure 3) provided an initial indication of the ability of these motifs to form strong, linear halogen bonds with halide counteranions.[32,33] These studies were triggered by previously utilized imidazolium derivatives as charge-assisted C–H hydrogen bond donors in anion recognition processes.[34,35]

Resnati, Metrangolo, and colleagues conducted an analysis on the solid-state complexes of Cl^-, Br^-, and I^- ions with a 2-iodoimidazolium receptor **4**, that features an anthracenyl substituent (Figure 3). They noted robust, linear halogen bonding (XB) interactions in all three halide complexes. Notably, the crystal structure of the $H_2PO_4^-$ complex of this receptor revealed an exceptionally short I–O XB interaction. 1H NMR studies in solution demonstrated that compound **4** exhibits selective binding towards $H_2PO_4^-$ over AcO^-, Cl^-, Br^-, and I^- anions in DMSO solution. This makes it a rare example of XB-driven anion recognition with preference for oxoanions. In DMSO, halide anions are bound in the order of increasing charge density ($Cl^- > Br^- > I^-$), with a slight preference for AcO^- over Cl^-.[36] A theoretical investigation by Lu and co-workers offers further understanding of the electrostatic, dispersion, and covalent contributions to XB interactions in haloimidazolium-based anion receptors.[37]

Beer and co-workers devised a range of macrocyclic bis-haloimidazoliophane receptors with the aim to improve the binding affinities and selectivities towards anions observed in the previously described acyclic monodentate haloimidazolium receptors. These receptors exhibit the ability to recognize halide anions exclusively through charge-assisted bidentate halogen bonding interactions in a competitive solvent mixture of aqueous methanol.[38–40] The macrocyclic receptors, namely **5**, **6**, and **7** (Figure 3), exhibit significantly improved halide binding affinities in comparison to their protoimidazolium-functionalized hydrogen-bonding analogs.[38] Attributed to a complex interplay between steric and geometric factors, the *meta*-xylylbromoimidazoliophane macrocycle **5** demonstrated a notably heightened selectivity for Br^- among the halide anions. Substituting the xylyl spacer with an elongated naphthalene spacer in **6** led to notably increased affinities for heavier halides, causing a reversal in the selectivity towards Br-over I- observed in receptor **5**.[39] Conversely, the naphthyl-containing bis-iodoimidazoliophane macrocycle 7 exhibited selective complexation with Br^- over I^-. Both **6** and 7 displayed minimal affinities for smaller halide and oxoanions, exclusively sensing Br- and I- which is demonstrated through enhancements in their fluorescence emission spectra. X-ray crystallography,[40] in conjunction with computational density functional theory and molecular dynamics simulations, supported the formation of stable receptor-halide complexes in solution via cooperative bidentate halogen bonding donation from the receptors' haloimidazolium groups to the guest anions. Although dimeric 2:2 receptor:anion complexes were observed in the solid-state, 1H NMR Job plot and DOSY NMR experiments indicated a preference for monomeric 1:1 receptor:halide complexes in solution.[39]

The group of Ghosh have integrated iodoimidazolium halogen bond donor patterns into preorganized bipodal host compound **8** (Figure 3). These compounds were demonstrated to effectively recognize halide anions in deuterated acetonitrile/water mixtures. The distinct trends in halide selectivity observed in the bipodal ($Cl^- > Br^- > I^-$) system are likely influenced by geometric and size-complementary considerations.[41] Similar studies were also reported by Berryman's group with a tripodal version (**9**) (Figure 3). **9** demonstrated a halide selectivity ($Br^- > Cl^- > I^-$) in acetonitrile solution.[42] The X-ray structural analysis of the halide or mixed halide/hexafluorophosphate salts for each of these receptors verified the existence of robust C–I…X^- halogen bonding interactions in their solid forms. Additionally, it was shown that the bromide salt of the tripodal receptor **9**.$2PF_6$ can be specifically isolated through crystallization from a DCM/DMF solution despite the presence of various competing guest anions.

Huber harnessed the strong XB-donor capability of the 2-iodoimidazolium motif for organocatalysis purposes. Through calorimetric titration experiments and DFT calculations, it was shown that compound **10**. 2OTf effectively binds Cl^- anions with a high affinity in CH_3CN, facilitated by the formation of cooperative bidentate C–I…Cl^- halogen bonds. This mechanism was suggested to underlie its notably high organocatalytic effectiveness.[43]

5 Receptors incorporating haloperfluoroarene as halogen bond donor groups

The groundbreaking 2005 study by Metrangolo, Resnati, and colleagues showcased the capability of XB interactions to steer anion recognition processes in solution. They illustrated this using a heteroditopic receptor (**11**, Figure 4) containing

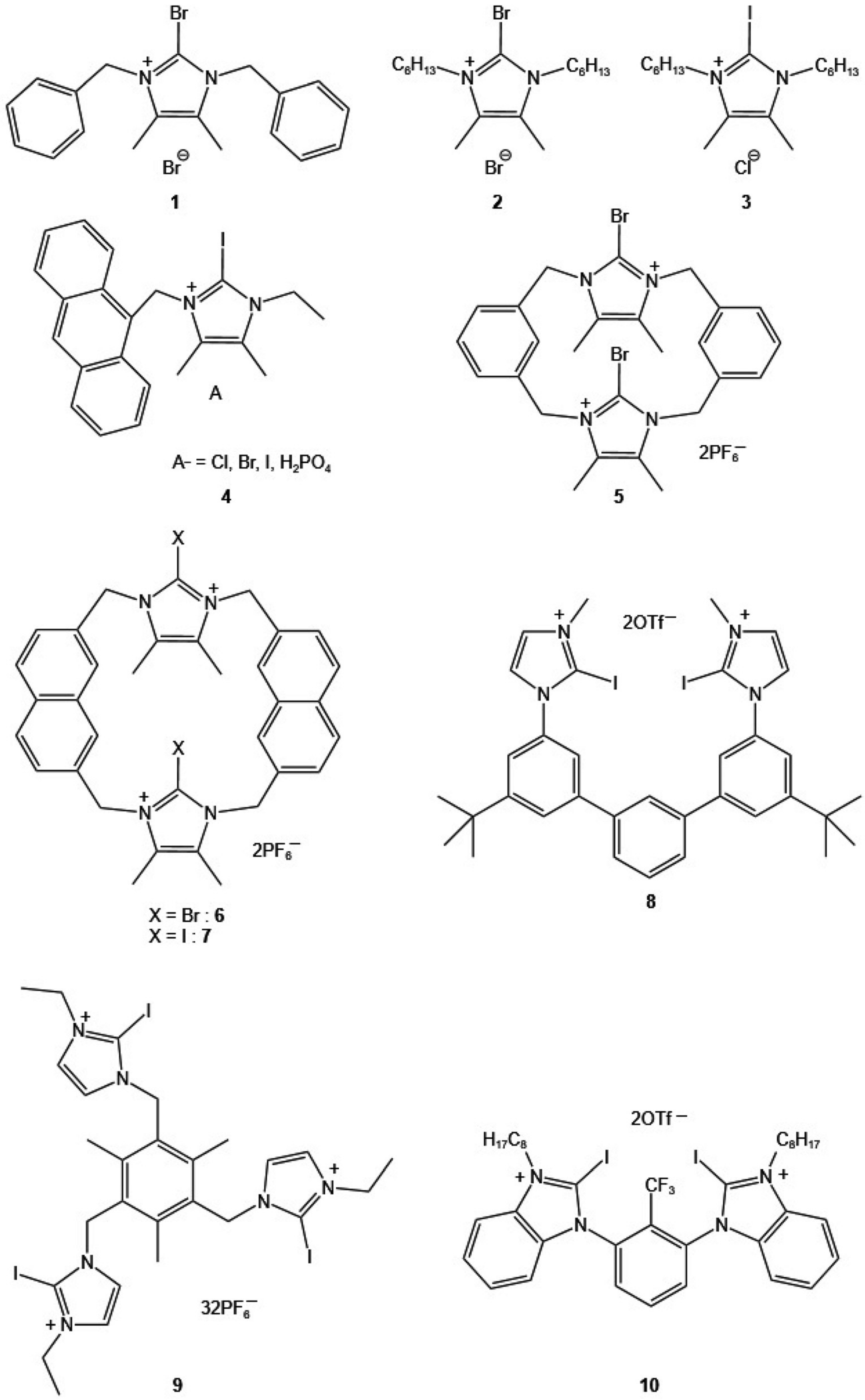


Figure 3: Anion receptors incorporating haloimidazolium as halogen bond donor groups.

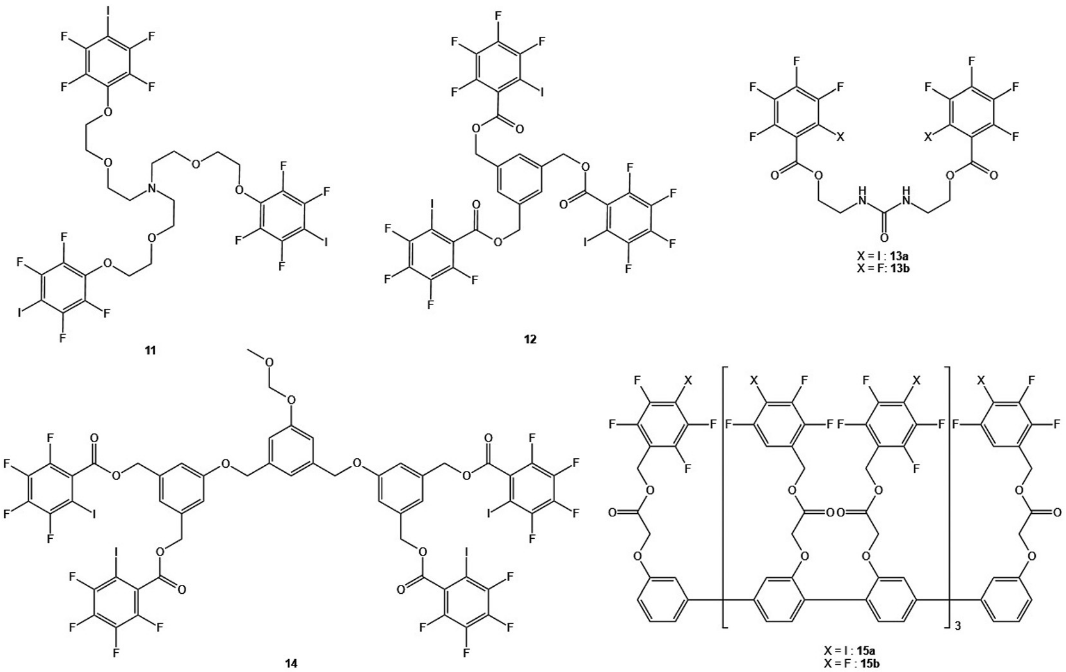


Figure 4: Anion receptors incorporating haloperfluoroarene as halogen bond donor groups.

tris(polyoxyethylene)amine and 4-iodotetrafluorophenyl recognition sites for a cation and counteranion, respectively.[44] Through 1H NMR competition experiments, they demonstrated that this receptor complexes a NaI ion-pair with notably higher affinity compared to the perfluorinated monotopic receptor in $CDCl_3$. Mass spectrometry competition experiments further revealed the XB receptor's selectivity in complexing I^- over Cl^- and Br^- anions. The solid-state characterization of the NaI complex of **11** confirmed the presence of C–I…I^- halogen bonds between the pendant iodoperfluoroaryl groups and the iodide anion. Due to the divergent arrangement of the halogen bond donor groups, the anion couldn't interact cooperatively with the receptor's three XB donor groups. Instead, a monodentate exo-binding mode was observed, with each iodide anion forming bridging XBs to adjacent molecules, forming an infinite linear chain.

Later, Taylor and colleagues reported a series of monodentate, bidentate, and tridentate iodoperfluoroarene derivatives capable of recognizing anions exclusively through single or multiple convergent halogen-bonding interactions in acetone solution.[45,46] ^{19}F NMR titration experiments demonstrated that the tripodal receptor **12** (Figure 4) exhibits the highest affinity for binding halide anions in acetone-d6, with selective binding of Cl-over Br- and I-. Control experiments showed that the analogous receptors, where the iodine atom is replaced by bromine, fluorine, and hydrogen atoms respectively, exhibited significantly lower chloride binding affinities. van't Hoff analysis revealed that Cl^- recognition is driven by favorable enthalpic and entropic contributions in case of **12**. The Taylor group has also investigated the anion recognition properties of a series of mixed hydrogen- and halogen-bonding receptors, which feature a bidentate urea HB-donor group along with either one or two iodoperfluorobenzoate halogen-bond-donor groups. Comparing these receptors with control systems lacking the iodine XB donor substituent showed that the presence of the XB donor groups significantly enhances the receptors' affinities for halide anions.[47] The XB receptors demonstrated halide recognition in acetonitrile-d3 with a general selectivity trend of $Cl^- > Br^- > I^-$. The most notable XB enhancement effect was observed in the symmetric bis-iodoperfluorobenzoate-functionalized receptor **13a** (Figure 4), which exhibited halide association constants 16–30 times higher than those of the perfluorinated control receptor **13b**.

Feng and colleagues have reported on a dendritic organogelator molecule functionalized with peripheral iodoperfluorophenyl XB donor groups, which acts as a specific visual sensor for Cl^- anions. In the absence of Cl^- anions, the dendritic organogelator **14** (Figure 4) was observed to form stable gels in various organic solvents.[48] The addition of tetrabutylammonium chloride induced a sol–gel phase transition, leading to complete collapse of the gel within 10 min. This phenomenon was attributed to a perturbation in the conformation of the organogelator molecules due to XB interactions between the Cl^- anion and iodophenyl XB donor groups, thereby disrupting the aromatic stacking interactions responsible for the gelation process. In contrast, other anions such as Br^-, I^-, NO_3^-, HSO_4^-, and CN^- were found to induce only partial or negligible collapse of the gel, even in excess.

Matile and colleagues have explored the incorporation of iodoperfluorophenyl XB donor groups into synthetic anion transporter molecules, taking advantage of the strength, directionality, and hydrophobic nature of XB interactions.[49] The linear XB octameric derivative **15a** (Figure 4) was shown to facilitate Cl^-/OH^- antiport across a lipid bilayer membrane with an EC_{50} value of 0.11 ± 0.02 μM, marking the highest anion transport activity reported for an XB transporter to date.[50] In contrast, the non-halogenated control receptor **15b** (Figure 4) was found to be 26 times less active.

6 Receptors incorporating halotriazole and halotriazolium as halogen bond donor groups

Halotriazole and halotriazolium structures have garnered significant interest as halogen bond (XB) analogues to the well-studied and easily synthesized C–H hydrogen-bond-donating triazole and triazolium motifs. Several computational and experimental studies suggest that the XB donor capability of these halotriazole-based systems improves with the increasing size of the halogen substituent (I > Br > Cl). Theoretical and experimental evidence has demonstrated that the cationic halotriazolium motif is a more potent XB donor compared to the neutral halotriazole motif. This enhanced effectiveness is due to the combined effects of charge assistance and increased C–X bond polarization.[51,52] Incorporating multiple chelating iodotriazole motifs onto preorganized scaffolds has proven to be an effective strategy for designing anion receptors. Schubert and co-workers developed a bidentate receptor (**16,** Figure 5) where a carbazole scaffold is symmetrically functionalized with hydroxyl and iodotriazole units at the 2 and 3 positions, respectively.[53] X-ray crystal structures and solution NMR experiments revealed that intramolecular O–H…N hydrogen-bonding interactions between the hydroxyl and iodotriazole groups preorganize the triazole into a co-planar syn–syn conformation. This conformation promotes cooperative bidentate anion recognition and reduces the need for conformational reorganization of the host prior to anion complexation. The binding properties of Cl^- and Br^- to this receptor were investigated using isothermal titration calorimetry in THF. Both anions bind in a 2:1 receptor:anion ratio with similar association constants, and the binding is driven by favorable enthalpic and entropic contributions. The advantage of preorganization is clear when compared to receptor **17** (Figure 5), which shows significantly lower binding affinities for Cl^- and Br^-, mainly due to a greater entropic penalty in forming the receptor-halide complex.

In the bimetallic bis-iodotriazole pyrimidine derivative **18a** (Figure 5), the chelation of the two Re(I) centers preorganizes the iodotriazole groups and likely increases the polarization of the C–I bonds. This receptor exhibits distinct binding affinities and selectivities for various halide and oxoanions compared to the hydrogen-bonding bis-prototriazole analogue **18b** (Figure 5). In a $CDCl_3$:CD_3OD 1:1 solution, the halide, hydrogen carbonate, and acetate binding affinities of the XB receptor **18a** are significantly higher than those of the HB receptor **18b**. However, the HB receptor slightly outperforms in binding $H_2PO_4^-$, ClO_4^-, SO_4^{2-}, and NO_3^- anions. The HB receptor demonstrates minimal discrimination among monovalent anions ($92 \le Ka \le 548\ M^{-1}$), whereas the XB receptor shows a pronounced selectivity for I^- ($Ka > 10^4\ M^{-1}$).[54]

The introduction of four iodotriazole motifs onto a preorganized picket-fence-style Zn(II) metalloporphyrin scaffold (**19a,** Figure 5) facilitated anion recognition through multidentate C–I…X XB interactions and simultaneous ligation of the anionic guest to the Lewis acidic Zn(II) center.[55] The anion recognition properties of the XB receptor **19a** and its analogous HB receptor **19b** (Figure 5) were studied using UV-visible titration experiments in $CHCl_3$, acetone, and acetonitrile. Both receptors exhibited a general preference for oxoanions over halide anions, with halide binding affinities following the trend based on anion charge density ($Cl^- > Br^- > I^-$). Notably, the halide binding affinities of the XB receptor were consistently higher than those of the HB receptor in all three solvents, whereas this trend did not apply to oxoanions. Interestingly, the anion binding capabilities of both the XB and HB receptors showed a pronounced dependence on the solvent used (acetone > acetonitrile > chloroform).

The creation of anion host molecules that can detect and interact with anions that are important to biology and the environment has been made easier by the application of the extremely powerful cationic iodotriazolium halogen bond (XB) motif. For use in environmental research and health, it is essential to design receptors with remarkable selectivity for certain anionic targets in aqueous settings. However, because of the high solvation energies of anions in water, this is still difficult to accomplish. Halogen bond (XB)-driven anion recognition in aqueous solution was investigated using the bis-iodotriazolium receptor **20a** (Figure 6), which was rendered water-soluble by the addition of six peripheral tetraethylene glycol groups. The halide binding affinities of this receptor and its hydrogen bond (HB) analog **20b** (Figure 6) in D_2O show the predicted Hofmeister series

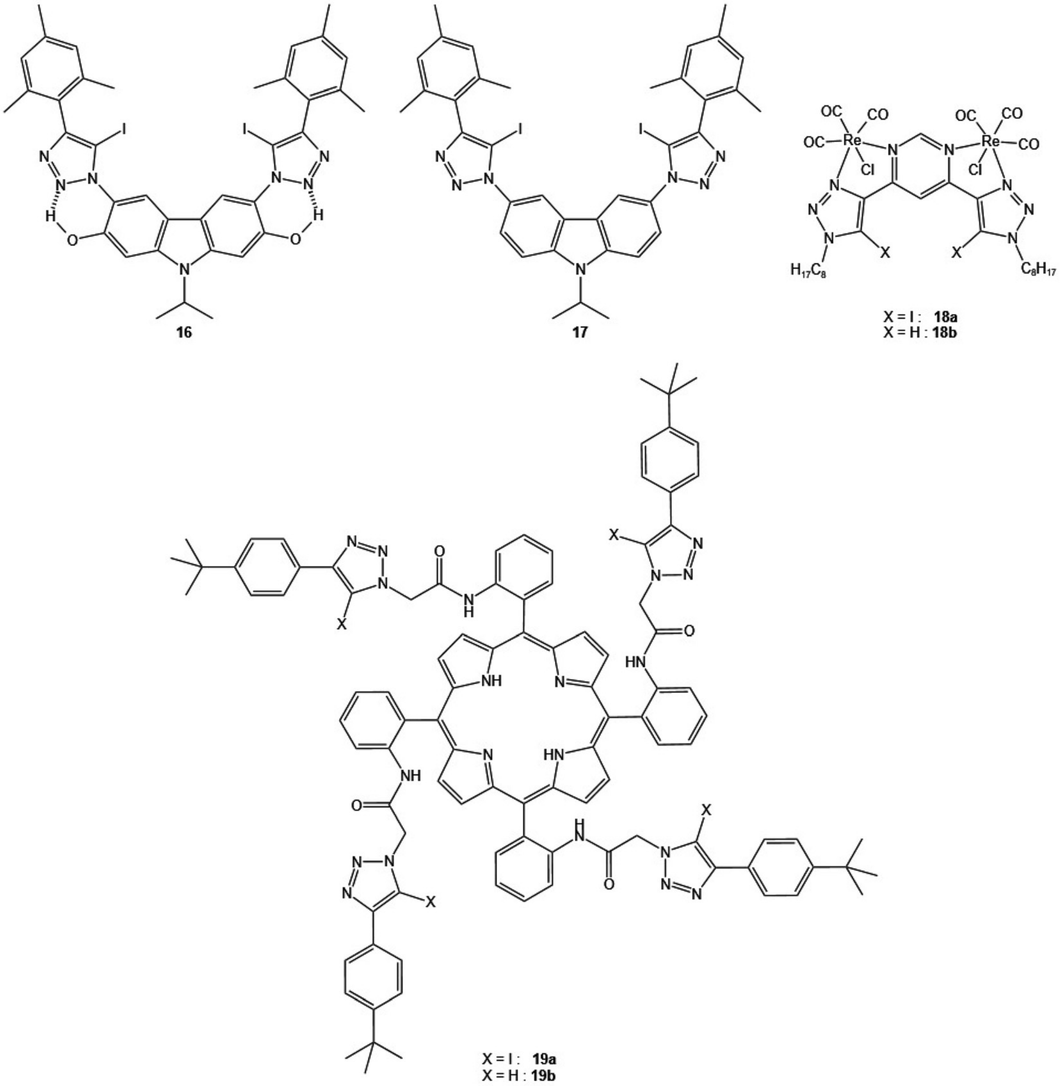
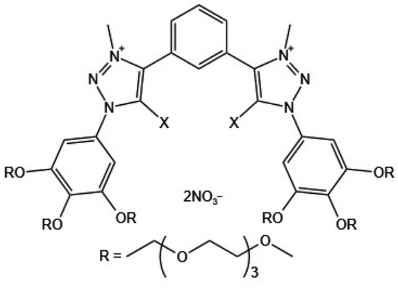


Figure 5: Anion receptors incorporating halotriazoles as halogen bond donor groups.

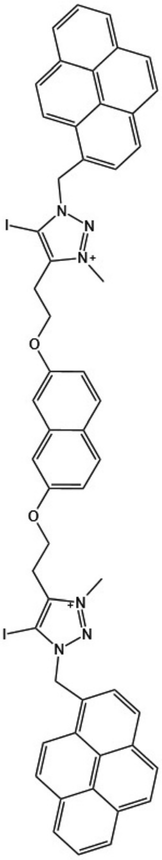
preference ($I^- > Br^- > Cl^-$), which corresponds to the heavier halides' decreasing desolvation energy.[56] For physiologically important pyrophosphate anions, the pyrene-functionalized bisiodotriazolium compound **21** (Figure 6) functions as a selective fluorescent chemosensor. In acetone, these anions increase the pyrene excimer band's emission intensity. Halogen bonding (XB) during complexation with hydrogen pyrophosphate promoted a conformational rearrangement, which was the cause of this event, according to computational modeling.[57] The first reported use of halogen bonding (XB) interactions for enantioselective anion recognition was by Beer and colleagues. They functionalized a chiral, enantiopure (S)-BINOL core with two convergent iodotriazolium motifs. Compared to the bis-prototriazolium hydrogen-bonding (HB) analogue **22b** (Figure 6) in $CD_3CN:D_2O$ (99:1), the resulting dicationic XB receptor **22a** (Figure 6) demonstrated higher affinities and enhanced enantioselectivity for recognizing various chiral amino acid carboxylate or BINOL-phosphate anions.[58]

7 Receptors incorporating interlocked halogen bond donor groups

For several reasons, using interlocked host molecules presents a viable strategy for overcoming the difficulties associated with anion complexation. With the help of this technique, complex, three-dimensional binding cavities with ideal size and form complementarity to a particular target guest can be created. Furthermore, because of the high



X = I : **20a**
X = H : **20b**



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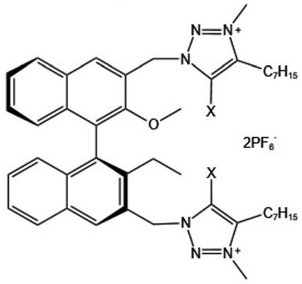


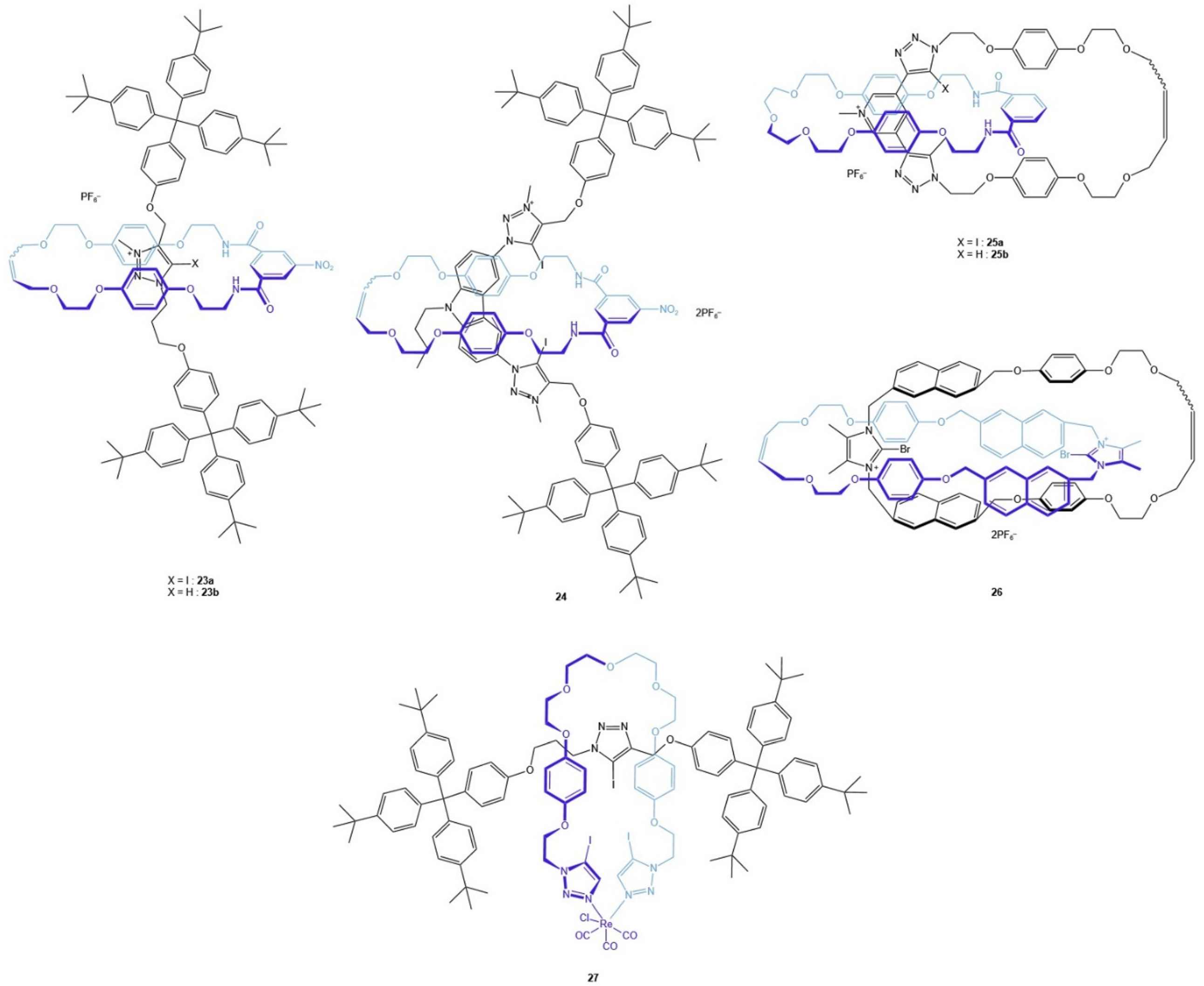
X = I : **22a**
X = H : **22b**

Figure 6: Anion receptors incorporating halotriazoliums as halogen bond donor groups.

hydration energies of anions in water, the protected, hydrophobic structure of these interlocking domains encourages guest desolvation, which is a crucial prerequisite for efficient anion recognition in aqueous settings. Additionally, the interlocked components' secondary stabilizing interactions aid in favorably preorganizing the host system while maintaining some flexibility. Finally, when appropriate reporter groups are included, the dynamic characteristics of these systems can be used to generate sensory readouts upon guest binding. Beer's group presented the first XB interlocked host system in 2010: a [2]rotaxane where an iodotriazolium XB donor group from the axle and a bidentate isophthalamide HB donor motif from the macrocycle converge to form a central binding cavity (**23a**, Figure 7). The rotaxane-bromide complex's X-ray crystal structure verified that three complimentary hydrogen- and halogen-bonding contacts enclose the halide guest inside the interlocking cavity. Studies on solution-phase anion binding showed that this system had noticeably higher halide binding affinities than **23b** (Figure 7), its HB counterpart. Furthermore, in a $CDCl_3$:CD_3OD:D_2O (45:45:10) solvent mixture, the XB rotaxane exhibited a preference for I^-, whereas the HB rotaxane reversed this trend in a $CDCl_3$:CD_3OD (1:1) mixture.[59]

In order to improve anion binding affinities and fine-tune selectivities, Beer and colleagues investigated the incorporation of many convergent XB donor groups into interlocked frameworks, building on this groundbreaking work. They created a rotaxane with an axle component that has two XB iodotriazolium groups separated by a stiff carbazole spacer and a macrocycle functionalized with HB isophthalamide (**24**, Figure 7). In a $CDCl_3$:CD_3OD:D_2O (45:45:10) solvent mixture, this system showed significant selectivity for halides over AcO^- and $H_2PO_4^-$ anions, with Br^- exhibiting a particularly high affinity ($Ka \approx 4 \times 10^4\ M^{-1}$).[60] A chloride-anion templated ring-closing metathesis 'clipping' process was used to incorporate the bidentate 3,5-bis-(iodotriazole)-pyridinium motif into a mixed hydrogen- and halogen-bonding [2]catenane host structure (**25a**, Figure 7). In a competitive aqueous-organic $CDCl_3$/CD_3OD/D_2O solvent mixture, this receptor showed a substantial preference for I^- and Br^- over the smaller Cl^- anion and significantly higher halide binding affinities than the solely hydrogen-bonding catenane **25b** (Figure 7).[61]

As a logical progression of their research, the Beer's group have also examined interlocked host systems that can identify guest anions only through cooperative XB interactions. They synthesized the symmetrical 2-bromoimidazolium homo[2] catenane **26** (Figure 7) using a bromide anion-templated double-clipping process. This compound selectively detects and senses Cl^- and Br^- anions among different halides and



X = I : **23a**
X = H : **23b**

24

X = I : **25a**
X = H : **25b**

26

27

Figure 7: Anion receptors with interlocked halogen bond donor groups.

oxoanions in CH_3CN. The development of two convergent, charge-assisted C–Br…A^- XB interactions is the cause of this selectivity. The monomer and excimer emission bands of the fluorescent naphthalene reporter group showed distinctive alterations upon the addition of Cl^- or Br^- to CH_3CN solutions of the [2]catenane. Association constants for Cl^- and Br^- were determined by quantitative fluorescence titration studies to be Ka = 3.71×10^6 M^{-1} and 1.48×10^5 M^{-1}, respectively. However, when F^-, I^-, AcO^-, $H_2PO_4{}^-$, $NO_3{}^-$, or $HCO_3{}^-$ were added, no spectrum alterations were seen. This suggests that the exact placement of XB donor groups in the highly preorganized binding cavity of [2]catenane is incompatible with the radii and geometries of these other anions.[62] A neutral, all-halogen-bonding [2]rotaxane host system (**27**, Figure 7) with three convergent iodotriazole XB-donor groups was created using an active metal templation technique mediated by Cu(I). This host outperformed an acyclic Re(I)-complexed bis-iodotriazole model system in terms of halide anion selectivity over AcO^- in $CHCl_3$. The halide selectivity trend ($Cl^- > Br^- > I^-$) is noteworthy because it differs from the majority of cationic interlocked XB host systems previously discussed. This suggests that the Cl^- anion and the rotaxane's interlocked binding cavity have an ideal size match, as well as possible variations in competitive solvation effects brought on by the use of the aprotic solvent $CHCl_3$. Furthermore, no binding interactions between the metal-free counterpart of rotaxane **27** and halide anions were detected, highlighting the critical function of the Re(I) center in polarizing and preorganizing the axle bis-iodotriazole XB donor groups.[63]

8 Conclusions and future outlook

Over the course of the past decade, halogen bonding (XB) has demonstrated its potential in a variety of scientific applications, quickly gaining reputation as a revolutionary and adaptable technique in the field of anion detection. Its special qualities, which were initially overlooked, have shown significant benefits over more well-known non-covalent interactions, such hydrogen bonding (HB). Selective anion recognition, catalysis, enantioselective processes, transmembrane anion transport, and even intricate molecular mechanisms like nanoscale motion in rotaxane shuttles are just a few of the many applications where XB has been effectively employed. XB-based systems have frequently performed on par with or better than HB equivalents, particularly when it comes to identifying halide anions.

The demonstrated effectiveness of XB in competitive aquatic conditions is among the most encouraging advancements in XB research. Applications in the real world, like the selective identification, elimination, and movement of anions in intricate biological or environmental systems, are made possible by this finding. Additionally, theoretical and experimental research has improved our knowledge of this little-known solution-phase chemistry interaction by offering insightful information about XB's properties.

Despite these successes, there are still many obstacles to overcome. Analogous σ-hole interactions involving other p-block elements have not yet been thoroughly investigated, and the number and range of XB donor motifs studied to date are restricted. Furthermore, in order to develop a thorough set of design guidelines for anion coordination chemistry and gain a deeper understanding of XB-mediated reactions, thorough thermodynamic investigations are required. Closing these gaps will be essential to maximizing XB's promise in a variety of applications.

Looking ahead, it appears that halogen bonding will continue to advance quickly given the advancements made thus far and the unrealized potential in this area. XB-based systems have the potential to transform anion recognition as research advances, combining theoretical knowledge with real-world breakthroughs to tackle urgent issues in domains such as biomedical engineering and environmental science.

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