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The halogen bond: Nature and applications

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Abstract:
The halogen bond, corresponding to an attractive interaction between an electrophilic region in a halogen (X) and a nucleophile (B) yielding a R−X···B contact, found applications in many fields such as supramolecular chemistry, crystal engineering, medicinal chemistry, and chemical biology. Their large range of applications also led to an increased interest in their study using computational methods aiming not only at understanding the phenomena at a fundamental level, but also to help in the interpretation of results and guide the experimental work. Herein, a succinct overview of the recent theoretical and experimental developments is given starting by discussing the nature of the halogen bond and the latest theoretical insights on this topic. Then, the effects of the surrounding environment on halogen bonds are presented followed by a presentation of the available method benchmarks. Finally, recent experimental applications where the contribution of computational chemistry was fundamental are discussed, thus highlighting the synergy between the lab and modeling techniques.

Keywords: *ab initio*calculations, charge-transfer, DFT calculations, electrostatic potential, halogen bond, σ-hole
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1 Introduction

In 1863 [1], Frederick Guthrie reported the purification and formulation of $NH_3{\cdot}I_2$, which he called "iodide of iodammonium", based on earlier observations of M. Colin in 1814 [2]. Still in the nineteenth century, similar adducts with Br_2 and Cl_2 were also prepared and described [3]. However, the odd interactions existing in those complexes remained essentially unexplored until the late twentieth century, in spite the continuous observation of related phenomena: the formation of adducts between iodoform and quinolone [4], the formation of halogen molecule bridges in chains of 1,4-dioxane and X_2 (X_2 = Cl_2, Br_2, I_2) [5], where Bent considered that "there is reason to believe that the O···Br−Br interaction is energetically comparable to a strong hydrogen bond" [6], and complexes formed by halogen molecules with oxygenated solvents [7], among other examples.

In his Nobel Lecture in 1970 [8], Hassel pointed out the importance of halogens in self-assembly but the phenomena at the time was not fully understood, falling in the generic classification of "donor–acceptor interaction" [6] or "charge–transfer bonding" [8]. In this interaction, which is now called halogen bond, the covalently-bound electronegative halogen atoms are able to establish attractive interactions with electron-rich entities (nucleophiles), i. e., a R−X···B interaction (X = Cl, Br, I; B = Lewis base/nucleophile).

The first systematic theoretical explanation for this apparently counterintuitive phenomena was put forward by Brinck, Murray and P. Politzer [9]. In that seminal paper the authors noticed that, in covalently-bonded halogens, their electrostatic potential is anisotropic, possessing positive regions at the tip of X (X = Cl, Br, I). This positive region was later coined as σ-hole [10], corresponding to a maxima of the electrostatic potential mapped on a surface ($V_{S,max}$). Therefore, halogen bonds were described as an electrostatically-driven noncovalent interaction between that positive σ-hole and a nucleophile (see Figure 1). The electrostatic potential characteristics elegantly explain the main features and directional preferences of the interactions with halogen atoms: side-on interactions are observed with electrophiles whereas head-on interactions, corresponding to halogen bonds with nucleophiles, possess R−X···B angles of ~180º (Figure 1). Indeed, halogen bonds and hydrogen bonds are considered orthogonal molecular interactions since they are geometrically perpendicular and energetically independent when sharing a common acceptor [11]. It must be pointed out that, since σ-holes originate from the polarization of the electronic charge toward the R−X covalent bond, if X is less polarizable and very electron-attracting, the σ-hole might be neutralized or even absent [10]. Therefore, typically, the halogen bond strength increases from chlorine to iodine, whereas fluorine is not usually considered a halogen bond donor.

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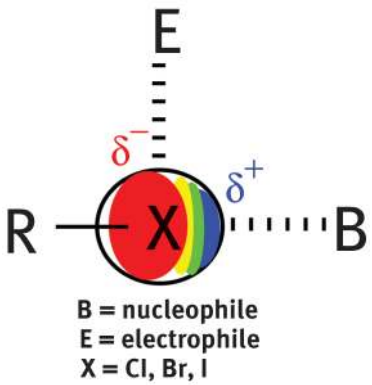

Figure 1: Schematic representation of an R–X···B halogen bond showing the anisotropic distribution of charge around the X atom. A possible orthogonal side-on interaction with an electrophile is also shown.

The theoretical explanation was accompanied by an explosive growth of research on halogen bonds, which found applications in diverse fields such as supramolecular chemistry [12], anion recognition [13], crystal engineering [14], and medicinal chemistry/chemical biology [15]. This is promptly seen by the increasing amount of research papers per year with the topic "halogen bonding" or "halogen bond" (Figure 2).

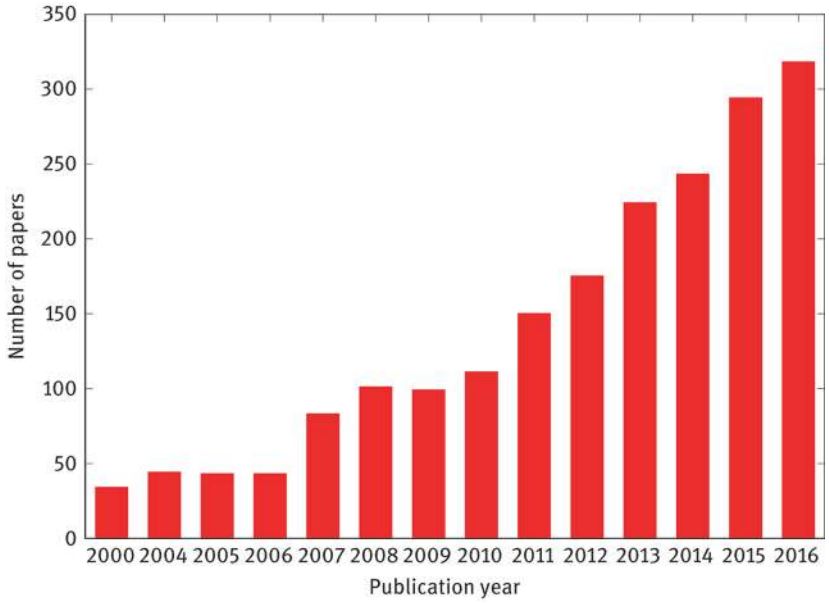

Figure 2: Number of publications containing the keywords "halogen bonding" or "halogen bond" (Source: Thomson Reuters Web of Science, 2017/03).

All theoretical and experimental results together with the increasing interest eventually led to a rationalization and unification process promoted by the International Union of Pure and Applied Chemistry (IUPAC), which started a project in 2009 aiming at a "comprehensive look at intermolecular interactions involving halogens as electrophilic species" and "give a modern definition of halogen bonding, which takes into account all current experimental and theoretical pieces of information" [16]. The final report issued in 2013 [17] states that "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."

This work intends to provide the reader with a succinct overview of the most recent theoretical and experimental developments, typically from 2015-onwards, in the field of halogen bonding and its applications. The most representative works and areas were selected. For a more systematic assessment, covering a broader range of research papers and also a larger period of time, the reader is directed to the recent reviews and perspectives on the topic [12–15, 18–25].

2 On the nature of the halogen bond: A longstanding debate

The nature of halogen bonds is a subject of a heated debate and in this point, theoretical calculations are of paramount importance. The halogen bonds are normally included in the realm of noncovalent interactions and their generic features are largely explained by the electrostatic interaction between a region of depleted electron density at the tip of a covalently bonded halogen, which is, as mentioned earlier, designated as σ-hole [10], and a negative site.

The electrostatic potential that the electrons and nuclei produce at any point r is given by (eq. 1).

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r' - r|} \tag{1}$$

In this equation, Z_A is the charge of the nucleus A located at R_A and $\rho(r')$ is the electronic density of the molecule. It is common to evaluate $V(r)$ on the 0.001 electrons Bohr^{-3} contour of the density $\rho(r)$ [26] labeling it $V_s(r)$. In halogen bond donors, when the electrostatic potential surface extrema are evaluated, the covalently-bonded halogen atom possess a maxima, $V_{S,max}$, corresponding to the σ-hole [10]. This σ-hole is nicely illustrated in Figure 3(a) where the electrostatic potential of bromopentafluorobenzene (C_6F_5Br), mapped on the 0.001 au contour of the electronic density obtained at the B3LYP/6–311G** level of theory is depicted. As mentioned earlier, σ-holes arise from the polarization of the electronic charge toward the R−X covalent bond. In this case, the presence of the fluorine atoms enhance that polarization, depleting the electron density from the bromine atom, thus forming a positive tip at the halogen atom (blue region) with a $V_{S,max}$ value of 26.06 kcal mol^{-1} [27].

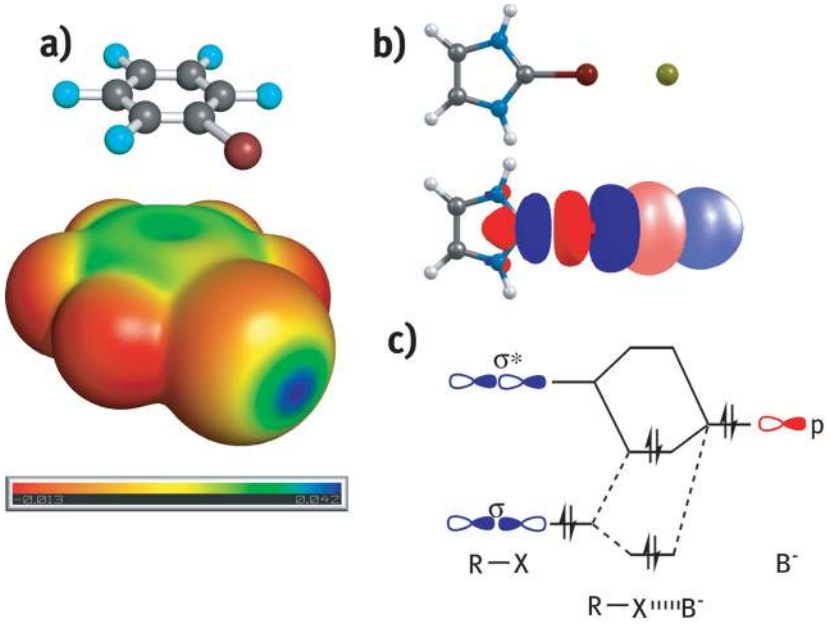

Figure 3: On the nature of halogen bonds: a) electrostatic potential of bromopentafluorobenzene (C_6F_5Br) mapped on the 0.001 au contour of the electronic density obtained at the B3LYP/6-311G** level of theory. Notice that the fluorines are negative whereas the bromine σ-hole is shown as a blue positive region, corresponding to a $V_{S,max}$ value of 26.06 kcal mol^{-1}; b) Natural Bond Orbital (NBO) donor-acceptor interaction corresponding to a donation from a chloride anion (light orbital) to a σ* C–Br orbital of 2-bromo-1*H*-imidazol-3-ium in a charge-assisted halogen bond (adapted from reference 36); c) simplified orbital interaction diagram for an R−X···B$^-$ halogen bond (R, X, B = F, Cl, Br, and I), adapted from reference 23.

A major supporting argument for the electrostatic nature of the halogen bond is the observed correlation of the calculated interaction energies with the $V_{S,max}$ values of the halogen bond donors [28, 29]. Moreover, polarization is also involved as it is an intrinsic part of the electrostatic interaction, i. e., the positive σ-hole and the negative B acceptor induce mutual electron density rearrangement, the rearrangement obviously depending on their polarizabilities [25]. This model based mainly on electrostatics and polarization, although dispersion can also play a role especially in week halogen bonds [30], accounts for the general features of halogen bonds such as the R−X···B bond angles of ~180º and the possibility of a side-on interaction with an electrophile (Figure 1).

The electrostatic nature of the halogen bond is not consensual and some authors have pointed out a dominant charge-transfer nature, i. e., a donor–acceptor interaction [23] to explain the characteristics of this interaction. This charge-transfer nature, sometimes called covalent character [23], is supported by several theoretical and experimental studies [31–34]. In this interpretation, there is a stabilization arising from HOMO–LUMO interactions between a lone pair of B and the σ* orbital of C–X [35]. This interaction is illustrated in Figure 3(b) which shows the donation from a chloride anion to a σ* C–Br orbital in a charge-assisted ion-pair halogen bond between 2-bromo-1H-imidazol-3-ium and Cl^- [36]. This system will be analyzed more thoroughly below. From a molecular orbital theory perspective, schematically represented in Figure 3(c), there is mixing between the antibonding σ* R–X orbital of the halogen bond donor and a lone pair of the halogen bond acceptor B. In the case of a low-lying σ* C–X orbital, acting as a Lewis acid, and a strong Lewis base, the interaction is enhanced.

Ab initio valence bond (VB) theory also endorses charge-transfer as a key player as Shaik and co-workers [37] reported in a study on 55 halogen-bonded complexes reaching a "clear cut" conclusion: "most of the X-bonds are held by charge transfer interactions as envisioned more than 60 years ago by Mulliken".

It must be mentioned that Politzer, Murray and Clark [38] pointed out that the electrostatic potential around a molecule is an observable, i. e., a real physical property which can be determined by diffraction techniques whereas orbitals are mathematical constructions used to obtain the system's wave function and its electronic density. In their interpretation, there is no actual physical distinction between charge-transfer and polarization [25, 38], and this discussion corresponds to a semantic problem; the overlap between the σ* C–X orbital with a donating one of B corresponds to the polarization of B toward the σ-hole of X. Polarization and donor–acceptor charge transfer are equivalent for weak interactions such as halogen bonds, but polarization is a physical observable whereas charge-transfer is a mathematical construct [39].

2.1 Latest theoretical insights

As the debate endures, this theme is still hot in the literature and in the last couple of years new reports emerged. Studies on anionic halogen-bonded systems $CX(F_nH_{3-n})\cdots X^-$ (with X = F, Cl, and n = 0–3), based on MP2/aug'-cc-pVTZ calculations [40], showed the existence of tetrel, hydrogen, and halogen bonds. For instance, the interaction energy for $CF_3Cl\cdots Cl^-$ was −43.1 kJ mol^{-1}, corresponding to a charge-transfer interaction of −33.1 kJ mol^{-1} from the Cl^- lone pair to the antibonding C–Cl orbital of the substituted methane. Indeed, charge-transfer values correlated with intermolecular distances and with the interaction energies of these complexes.

Coupled cluster theory, in particular, CCSD(T)/aug-cc-pVTZ calculations were performed in order to study the nature and strength of a series of $YX\cdots BR_m$ dimers (where X = F, Cl, Br; Y = donor group; BR_m = acceptor group) comprising 36 neutral and anionic halogen bonded complexes together with eight complexes bearing hydrogen, pnicogen, or chalcogen bonds [41]. In this study, Natural Bond Orbital (NBO) charges, charge-transfer energies, electrostatic potentials, vibrational frequencies, local stretching and bending force constants, and relative bond strength orders, among other properties were analyzed. Bond strength orders (BSO), derived from local stretching force constants, differentiate between weak and predominantly electrostatic halogen bonds, normal halogen bonds and strong, predominantly covalent halogen bonds, indicating that the majority have both electrostatic and covalent nature. The covalent bond is due to a 3c-4e (three-center-four-electron) interaction, giving rise to the characteristic calculated charge-transfer values. The electrostatic term is dependent on the polarizing strength of B together with the polarity of the X–Y bond and the polarizability of X. The same authors expanded this study to 202 halogen-bonded complexes, using ωB97XD/aug-cc-pVTZ and CCSD(T)/aug-cc-pVTZ calculations [42], showing that most of the halogen bonded systems possess sizable covalent contributions and that they are more covalent than its counterparts, i. e., hydrogen bonds and pnicogen bonds. Nonetheless, electrostatic contribution arising from the interaction of the σ-hole with B is also important. However, the authors point out that the analysis of the σ-hole can provide some insight into the electrostatic terms but not the potentially covalent character of a halogen bond since the covalent contributions depend on both potential and kinetic energy.

Halogen bonded complexes involving phosphines, $H_3P\cdots ClF$, $H_3P\cdots BrF$, and $H_3P\cdots IF$, were studied at the CCSD(T)-F12c, M06-2X, and ωB97X-D levels of theory. All systems presented relatively short intermolecular P···X distances and strong interaction energies, as high as −19.61 kcal mol^{-1} for $H_3P\cdots ClF$, leading the authors to the designation "*Mulliken inner complex*". Indeed, NBO analysis portioned the complex $H_3P\cdots ClF$ as H_3PCl^+ and F^-. SAPT analysis indicates that, for instance, in the mentioned $H_3P\cdots ClF$ complex, induction (which includes charge-transfer) contributes almost with the same amount as electrostatics.

In bifurcated halogen bonds formed between dihalogen molecules (ClF, BrF, and BrCl) and the methoxy groups of several 4-substituted 1,2-dimethoxybenzenes [43], M06-2X/def2-TZVPPD calculations show that the asymmetric interaction is preferred whereas the symmetric arrangement is a first-order saddle point. This was ascribed to a polarization effect. A QTAIM analysis indicates closed-shell interactions and the interaction energies correlate linearly with the sum of the delocalization indices between the halogen and the two oxygen atoms

obtained by this type of calculations, displaying the contribution from exchange–correlation to the binding energy. Energy decomposition analysis corroborates this data; in weak halogen bonds the main stabilizing term is the exchange–correlation whereas in strong halogen bonds the electrostatic component becomes dominant. Nonetheless, it was evident that ''electron sharing'' contribution correlates with the halogen bond interaction energy. A second-order stabilization energy calculation from a NBO analysis indicated that the most important stabilization arises from a charge-transfer from the oxygen lone pairs toward the σ* orbital of the dihalogen. Again, it seems that covalency (as represented by the exchange–correlation) is extremely important in the description of halogen bonds.

The role of charge-transfer has been very recently studied by Řezáč and co-workers [44] using the novel constrained DFT method for noncovalent complexes [45]. In this scheme, a charge transfer-free reference state corresponding to the superimposition of the electron densities of the non-interacting fragments is used, thus avoiding the vanishing of the charge-transfer at the complete basis set limit. Using the X40 dataset [46] that covers a wide range halogen bonds and the B-LYP, B3-LYP, BH-LYP, PBE, and PBE0 functionals, the amount of charge-transfer was evaluated. For weak halogen bonds, charge-transfer contributes only with 3 % whereas for all halogen bonded complexes, the average contribution is 10 % of the interaction energy. It was however surprising that the charge-transfer energies correlated with the interaction energies (R^2 = 0.85) which was attributed to a synergy between this character, electrostatics (i. e., the magnitude of the σ-hole), and dispersion. Nonetheless, the nature of B is important and when B involves nitrogen, the halogen bonds are stronger than the ones involving oxygen or sulfur, possessing also the larger values of charge-transfer but this is accompanied by stronger electrostatic interactions. Overall, the authors concluded that charge-transfer is undeniably involved in halogen bonding but cannot be considered its driving force.

Thirman and Head-Gordon [47] developed an energy decomposition analysis (EDA) of intermolecular interactions based on absolutely localized molecular orbitals (ALMOs) which can be applied to MP2 calculations (MP2 ALMO EDA). In this scheme, the binding energy is decomposed into frozen interaction, polarization, charge-transfer, and dispersion. The method was tested on the $FCl\cdots OH_2$ system (in analogy with the water dimer) and in this particular halogen bond, the interaction is driven by charge-transfer and is not particularly directional; electrostatics favor a planar geometry but charge-transfer effects are able to overcome this geometry in line with a more favorable alignment with the oxygen lone pair.

As stated before, according to *ab initio* valence bond (VB) theory, halogen bonds are "held by charge-transfer interactions" [37]. Very recently [48], block-localized wave function calculations, which are based on VB theory, tried to offer a unified theory for blue- and red-shifts in the vibrational frequencies of hydrogen and halogen bonds. Typically, hydrogen and halogen bonds exhibit red-shifts upon the formation of the complexes; however, blue-shifts occur in certain systems. The red-shifts are explained by the n(B) → σ*(R−X) charge transfer that, by populating the antibonding orbital, stretches the R−X bond, with a concomitant decrease in the HOMO-LUMO gap due to the interaction with the electrostatic field of B. This also indicates a more effective orbital mixing within the acid, which corresponds to polarization and therefore, both charge-transfer and polarization stabilize halogen bonds. In other words, stretching of the R−X bond leads to a lower energy of the σ* R−X orbital which in turn allows a more efficient charge-transfer from B. The red-shifts are thus explained by the polarization and charge-transfer nature of these interactions. On the other hand, the shrinking of the R−X bond, leading to blue-shifts, occurs when the frozen energy term (composed of the electrostatic and Pauli repulsion energies) is dominant. Overall, the preference toward R−X bond elongation or shrinkage upon halogen bond formation is determined by a competition between this frozen energy term and charge-transfer/polarization. The same holds for the formation of a hydrogen bond.

Another unified picture of hydrogen bonds and halogen bonds was provided in a MP2(full)/aug-cc-pVDZ(-PP) study performed on 108 halogen and hydrogen bonded complexes of the R–X···NH_3 family (X = H, Cl, Br, and I) [49]. The interaction energies correlate linearly with the $V_{S,max}$ values but also with second-order perturbation stabilization energies and the amount of charge transferred (Q_{CT}), indicating that both factors (electrostatics *vs*. charge-transfer) are important. Indeed, $V_{S,max}$ and Q_{CT} are complementary in the description of the interaction energies and a two-parameter linear regression was proposed allowing a better prediction of the interaction energies of both hydrogen and halogen bonds. This type of two-parameter regression was also recently proposed for charge-assisted ion-pair halogen bonds between imidazolium derivatives and Cl^- [36] as will be discussed in more detail below.

The role of polarizability in halogen bonds was studied recently [50] using the model complexes F–Br···X–R (X = F, Cl, Br, I and R = H, F) and the calculation of molecular electrostatic potential (MEP), atoms in molecules (AIM) analysis, energy decomposition analysis (EDA), and molecular polarizability based on MP2/aug-cc-pVTZ optimizations. The topological analysis of the electron density and the analysis of the atomic quadrupole moments reveal that the Br···X interactions are electrostatic in nature, however, the analysis of the MEPs indicate that considering only the static electrostatic interactions is insufficient to explain all features of the interactions.

The calculated molecular polarizabilities show a deformation of the electron density of X and this deformation capability plays an important role in the stability of these complexes.

A distinction in the character of halogen bonds formed with n-type (e. g. pyridine) and p-type (e. g. benzene) halogen bond acceptors was found in C_6F_5X, C_6H_5X, and CF_3X model systems using CCSD(T) calculations [51]. For halogen-π interactions (p-type), dispersion interactions are quite significant whereas for in n-type acceptors, strong halogen bonds are formed with a larger contribution from electrostatic interactions.

A coordinative nature was attributed to a strong $I^+\cdots S$ interaction in the S–I^+–S iodonium complex [52] as depicted in Figure 4. The authors assigned this interaction to a halogen bond between an iodonium cation (halogen bond donor) and the sulfur atom in a thione group (halogen bond acceptor) based on a QTAIM analysis complemented with NMR spectroscopy and mass spectrometry studies. They concluded that the interaction is quite strong (-60 kJ mol^{-1}) and even though a considerable electrostatic nature exists, the $I^+\cdots S$ interaction is not purely electrostatic as a considerable amount of electron sharing between the iodine and the two sulfur atoms was observed and therefore, according to the authors, this interaction has a dual nature with considerable coordinative character. There is however a question whether if this interaction falls in the halogen bond category given the current IUPAC definition that mentions a halogen in a molecular entity.

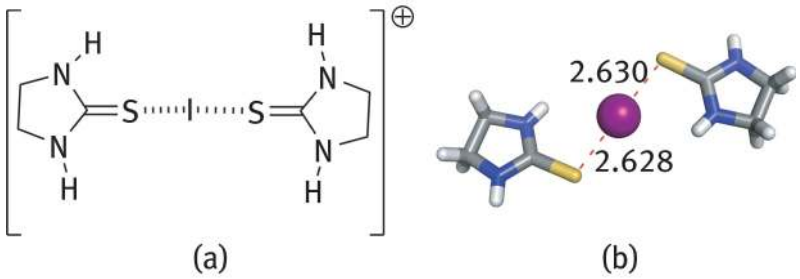

Figure 4: Schematic representation of the $[I(2\text{-imidazolidinethione})_2]^+$ complex (left) together with the X-ray structure [52] (right) with the $I^+\cdots S$ interaction highlighted in red.

Overall, the latest developments afford contradictory information given the multitude of calculations, analysis schemes, and their interpretation. It is not unlikely that the relative importance of the electrostatic, charge-transfer and dispersion contributions are dependent on the system, interacting partners and surrounding environment [13], as will be seen next. However, the controversy on the nature of the halogen bond will surely endure and a very recent paper on NBO and hydrogen bonds [53] might fuel new discussions. In that paper, AJ Stone argues that the charge-transfer component of the interaction energy of a hydrogen bond is contaminated by the basis set superposition error and therefore, NBO analysis of the interaction energies "*are meaningless in the context of intermolecular interactions*". Additionally, the values obtained for the charge-transfer energy were described as "*worthless*" whereas symmetry-adapted perturbation theory (SAPT) methods provide a better description of the interaction. Although the studied system was the hydrogen-bonded hydrogen fluoride dimer, the same conclusions might also hold if this methodology is applied to halogen-bonded dimers.

2.2 Surrounding environment effects on the nature and strength of halogen bonds

Halogen bonds are influenced by the surrounding media and the solvent indeed plays a role, opening the door for a multitude of applications [19] including for instance, the design of macromolecular hosts capable of recognizing and binding anions. In this scope, halogen bonds can be superior when compared to hydrogen bonds in the binding of anions in water as demonstrated by the experimental binding studies, complemented with molecular dynamics simulations, on a simple acyclic mono-charged receptor [54]. Therefore, a theoretical understanding of how the external media modulates the halogen bond is of paramount importance.

Halogen bonds are present in dimers of charged molecules with the same sign, i. e., cation–cation and anion–anion complexes [55], however, DFT calculations (M06-2X/aug-cc-pVTZ) indicate that the complexes are thermodynamically unstable although kinetically stable since the calculated dissociation barriers prevent dissociation of the complexes. The external media plays an important role as the inclusion of solvent in the calculations reduces the electrostatic repulsion, stabilizing the dimers. The SAPT method together with NBO and QTAIM analysis provided some indications on the mechanism of bonding. The critical point obtained from the QTAIM analysis show a partial covalent nature corroborated by the NBO analysis which yielded large charge-transfer stabilizing energies in both cation–cation and anion–anion systems. From the SAPT analysis, induction contributions are important.

Calculations on a series of I···O halogen bonds in complexes of iodobenzene derivatives with formaldehyde [56] showed that the solvent, in this case diethylether ($\varepsilon = 4.2400$) or water ($\varepsilon = 78.3553$), modeled using

the conductor-like polarizable continuum model, had a destabilizing effect on the interaction. Moreover, in $C_2F_3I\cdots B$ and $C_6F_5I\cdots B$ halogen bonded complexes (B = Cl^-, Br^-, I^-, NH_3, OH_2) calculated in chloroform (ε = 4.7113), acetone (ε = 20.493) and water [57], the solvent had a larger impact on the charged systems whereas for the neutral systems the interaction energies are changed to a lesser extent, although they are also weakened. This is illustrated by the drop of the interaction energy calculated at the B3LYP/aug-cc-pVDZ level of theory in the gas-phase (−19.71 kcal mol^{-1}) and in water (−0.55 kcal mol^{-1}) in the charged system $C_6F_5I\cdots Cl^-$.

The solvent is not the only surrounding factor playing a role in modulating the strength of halogen bonds. For instance, it was soon recognized that halogen bonds are present in biological molecules, stabilizing inter- and intramolecular interactions, ligand bonding, and folding [58]. A putative example of the importance of these type of interactions is the structure of phospho-CDK2/cyclin A in complex with the inhibitor 4,5,6,7-tetrabromobenzotriazole (Figure 5).

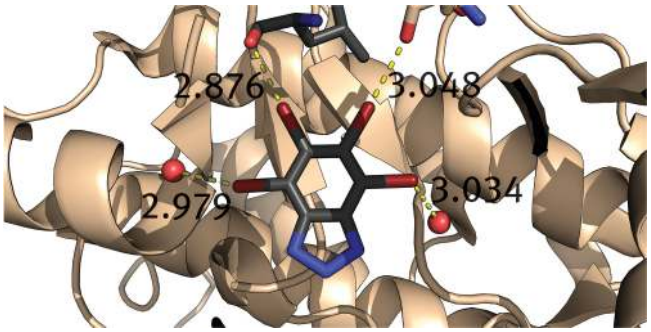

Figure 5: Example of a protein-ligand complex highlighting the presence of halogen bonds: the X-ray structure of phospho-CDK2/cyclin A in complex with the inhibitor 4,5,6,7-tetrabromobenzotriazole (PDB ID code 1P5E) showing four Br···O halogen bonds (dashed yellow lines) [59].

Recently, it was demonstrated by means of DFT calculations (M06-2X) that the protein environment is not an innocent factor in stabilizing halogen bonds, even the oddest ones involving negatively charged halogen bond donors with acceptors in proteins (B = O, N, S) as depicted in Figure 6(a) [60]. Calculations on model systems consisting of $^-OOC-(C{=}C)_n-C_6H_5-X\cdots NH_3$ dimers (n = 0−5; X = Br, I) were performed in different dielectric media in order to predict the variation of the binding energies. Indeed, proteins possess an anisotropic dielectric environment (ε = 4–80) and to mimic that variation, a PCM model was applied to the calculations using chlorobenzene (ε = 5.6), dichlorobenzene (ε = 10.4), acetone (ε = 20.5), dimethyl sulfoxide (ε = 46.8), and water (ε = 78.4) as solvents. The distance between the negative COO^- group and the C-X moiety (halogen bond donor) is important and the interaction is strengthened as that distance is increased. More interestingly is the fact that the solvent enhances the halogen bond strength at short distances ($n \leq 2$) more significantly that at large distances ($n > 2$) when compared with vacuum calculations. An ETS-NOCV approach, which is a combination of the extended transition state (ETS) method with the natural orbitals for chemical valence (NOCV) scheme [61], showed that the electrostatic interaction has the major role, however, orbital interactions account for 42−36 % of the halogen bond, which is quite significant. The NBO analysis indicates that the main intermolecular interaction is a charge-transfer between the lone pair of NH_3 and the empty σ* C–X orbital. Overall, the halogen bond strength can be tuned *via* the distance between the negative center and halogen atom and the environment (dielectric), which is indeed relevant for drug design.

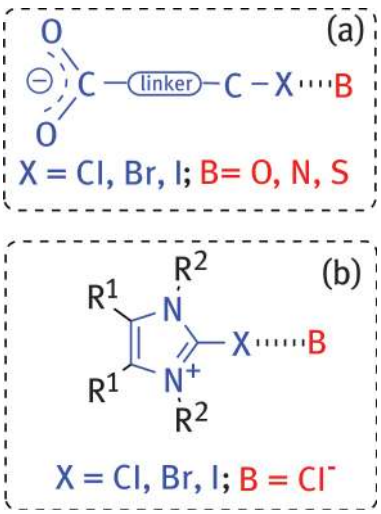

Figure 6: (a) Scheme of halogen bonds involving negatively charged donor systems as reported in reference 60. (b) Interaction of a series of 2-halo-functionalized imidazolium derivatives with chloride as reported in reference 36.

Above, some examples were discussed on how solvent or surrounding environment, e. g., a protein, can modulate the strength of the halogen bond. More surprising is when the solvent is able to modulate not only the strength, but also the electrostatic *vs*. charge transfer nature (or at least their relative weights). A series of 2-halo-functionalized imidazolium derivatives, bearing different R^1 and R^2 groups (Figure 6(b)) were studied computationally (DFT and *ab initio*) [36] for their capability of binding anions, in particular chloride, *via* charge-assisted halogen bonds. These haloimidazolium motifs are particularly suitable for anion binding [62] and supramolecular assembly, e. g., anion-templated assembly of pseudorotaxanes [63] and catenanes [64]. For this special kind of halogen bonds, MP2/aug-cc-pVDZ calculations gave the best agreement when compared with the state-of-the-art CCSD(T) results. Amongst the tested DFT functionals (B3LYP, B97-1, M06, and the variation M06-2X), the M06-2X gave the best performance. In the gas-phase, unrealistically large interaction energies were calculated owing to the ion-pair nature of the interaction. One might anticipate an enormous contribution from electrostatics given the opposite charge of the imidazolium cation and the chloride anion, however, very large bond orders (Mayer or Wiberg) and high contributions from $n_{Cl^-} \rightarrow \sigma^*$ C–X charge-transfer, were obtained by a second-order perturbation stabilization energy of donor–acceptor interactions E(2). These values are more consistent with a dative/covalent nature of the halogen bond. In these systems, the solvent effect on the interaction energies is dramatic. Indeed, calculations in both chloroform ($\varepsilon = 4.7$) and water ($\varepsilon = 78.4$) showed that the interaction energies and the charge-transfer are highly reduced. However, the variation of the interaction energy for the tested series can be predicted by a two-parameter linear regression which optimizes the weights of charge-transfer and electrostatic interactions *via* the values of the computed E(2) and $V_{S,max}$ values, respectively. Surprisingly, the media modulates not only the strength but also the weight of these contributions; in the gas-phase, the weight of the electrostatic interactions is dominant whereas in water, charge-transfer has the greater coefficient. In chloroform both contributions are more balanced showing the importance of the solvent polarity in the rational design of new chloride receptors based on halogen bonds.

The solvent effects in halogen bond strengths and character are not straightforward. For instance, Brammer, Hunter, and co-workers [65] studied by UV/vis absorption and ^{1}H NMR titration experiments the influence of the solvent polarity on the stability of both hydrogen and halogen bonds using as model systems 4-(phenylazo)phenol (hydrogen bond donor), I_2 (halogen bond donor), and tetramethylurea/tetramethylthiourea (acceptors). Surprisingly, the halogen bonded complex $I_2\cdots$tetramethylthiourea is stable even in polar alcohol solvents contrasting with the hydrogen bonded complexes which were sensitive to the solvent polarity. This, according to the authors, indicates that simple electrostatic arguments are not sufficient to explain the behavior and stability of the halogen bond and therefore, charge-transfer is an important factor to account for the remarkable stability of these interactions.

3 Method benchmarks

In spite the existence of several computer modeling techniques for the description of halogen bonds [66] herein the focus will be on the latest studies concerning quantum mechanical methods. Normally, the CCSD(T) method is the "gold standard" to evaluate the quality of the computational methods and in the particular case of halogen bonds, the X40 data set [46] was developed, being extremely useful as it provides a non-biased molecular set containing both halogen a non-halogen bonded complexes. Other data sets containing solely halogen bonded complexes such as the XB18 and XB51 [67] are also useful. An analysis of the root-mean-square errors (RMSEs) of different post-HF methods results when compared with the CCSD(T)/CBS reference values applied to the X40 data set indicates that MP2/aug-cc-pVDZ yields an error of 0.55 kcal mol^{-1} for the binding energies whereas the best performance was achieved for SCS-MI-CCSD/CBS (0.06 kcal mol^{-1}). BLYP-D3/def2-QZVP calculations outperform MP2 (0.39 kcal mol^{-1}) thus providing a reliable tool for the description of noncovalent interactions [66]. Concerning the XB18 and XB51 sets [67], M06-2X and ωB97XD provided the best performance among the tested hybrid DFT methodologies while for DFT GGAs, only M06-L gave reasonable accuracies. The authors did not recommended MP2 as it overestimates binding. Additionally, they recognized the difficulty of calculating accurate halogen bond energies since the chosen method has to account for electrostatic, dispersion, polarization, and charge transfer, in what the authors defined has a mixture of bonding "unicorns".

Later the X40 data set, together with other data sets for noncovalent interactions, was used to evaluate the accuracy of popular QM methods [68]. Besides the popular DFT functionals B3LYP, B97-D, M06-2X, and ωB97X-D, semiempirical PMx methods were also tested. M06-2X and B97-D3 achieve high accuracy whereas PMx methods were generally inaccurate for halogenated and ionic molecules. The capability of semiempirical methods in describing halogen bonds is important since they could be used in large systems such as the ones

involving proteins. In this scope, a review on the applicability of semiempirical quantum mechanical (SQM) methods for noncovalent interactions was recently published [69]. Controversies apart, *i. e.*, whether the interaction is purely electrostatic, the σ-hole is only described by QM methods with reasonable sized basis sets whereas SQM methods use minimal basis sets, and therefore, are not able to correctly account for that positive region at the tip of the halogen. Curiously, the PM6 method affords good interaction energies when compared with QM calculations but their potential energy surface is completely inaccurate; an empirical correction was therefore proposed [70] and the latest version of this method is called PM6-D3H4X [71]

Another assessment of the accuracy of DFT functionals in the description of halogen bonds was performed for the specific case of R–X···π interactions involving benzene as halogen bond acceptor [72]. In this case, T-shaped R–X···benzene dimers (R = H, F, and HCC; X = Cl, Br) were calculated at the CCSD(T)/CBS level and compared with 34 DFT functionals along with ab initio MP2 and MP2.X methods. Again, MP2 appears to overestimate the binding and double hybrid functionals B2PLYPD and mPW2PLYPD, which account for dispersion contributions, provide the best results concerning energies and equilibrium geometry although M06-2X also performs very well.

The fact that some of the above-mentioned studies refer that MP2 overestimate binding is in contrast with the calculations performed on charge-assisted halogen bonds present in 2-bromo-1*H*-imidazol-3-ium with chloride [36]. Here, MP2/aug-cc-pVDZ gave the best agreement when compared with CCSD(T)/aug-cc-pVDZ calculations. However, it must be mentioned that this was not extended to other systems and therefore, cannot be generalized.

The use of expensive methods with large basis sets to study halogen bonds might not be feasible for large systems such as biochemical or supramolecular entities. Recently, a benchmark of DFT methods with small basis sets was performed [73] using the XB18 data set together with a larger data set comprising 33 complexes from the X40 dataset with iodobenzene derivatives and pyridine (termed iodobenzene data set). Diverse combinations of DFT functionals and basis sets were evaluated, yielding a total of 46 methods (15 functionals and 16 basis sets). For the XB18 data set, the M06-2X/DGDZVP combination had the best performance although PBE0 also gave quite good results. Concerning the larger iodobenzene data set, PBE0 outperforms M06-2X. Nonetheless, the small to moderate sized DGDZVP basis set is a good choice to study halogen bonds in medium to large size systems were the computational cost of more expensive methods could be prohibitive, such as supramolecular and biochemical systems.

Indeed, large supramolecular systems offer particular challenges for the theoretical study of halogen bonds. Although one could in principle apply force field methods [62–64], it is also important to test the applicability of QM methods to these systems. In this scope, and using the first supramolecular capsule based solely on halogen bonds reported by Diederich [74, 75] (Figure 7) as test case, Grimme and co-workers [76] reported on the applicability of DFT to predict supramolecular thermochemical parameters. Unquestionably, the existence of experimental thermochemical data allows an alternative approach to test the accuracy of the theoretical methods. In this case, the experimental binding free energies were −4.83 kcal mol^{-1} and −3.60 kcal mol^{-1} for the iodine and bromine analogues, respectively [74]. Calculations were performed with dispersion corrected density functional theory using the TPSS-D3/TZ level of theory for geometry optimization and the PW6B95-D3/QZ for single-point energies. The statistical corrections to the free energy in the gas phase were calculated with the HF-3c method, which is a fast-minimal basis set Hartree–Fock based method whereas the solvent effects were included *via* the COSMO-RS model. For iodine, PBEh-3c//PBEh-3c (−2.6 kcal mol^{-1}) and PW6B95-D3//TPSS-D3/TZ (−5.7 kcal mol^{-1}) produced the best results. The authors also tested the capability of the methods in predicting the binding affinities for two guest molecules inside the iodine capsule (1,4-dioxane and 1,4-dithiane) and both the less expensive PBEh-3c//PBEh-3c and PW6B95-D3/QZ//TPSS-D3/TZ provided good accuracy.

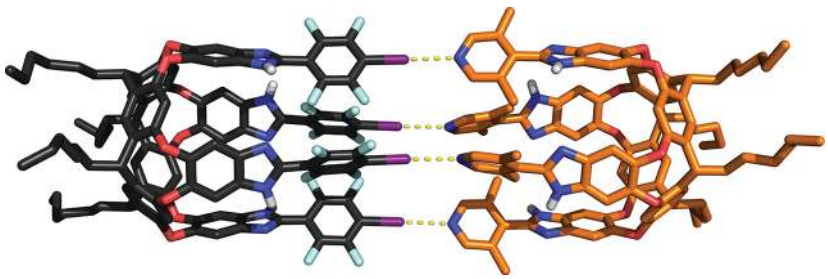

Figure 7: X-ray structure of an halogen bond capsule reported in reference 75 assembled *via* two resorcin[4]arene cavitands. Encapsulated benzene molecules, solvent, and non-polar hydrogen atoms were omitted for clarity. The halogen bond donor is represented in dark grey whereas the halogen bond acceptor is depicted in orange.

4 Applications

The continuous interest in the theoretical understanding of halogen bonding is accompanied by new developments in the experimental field. Indeed, theoretical calculations are often used to guide experiments or interpret experimental data. Even the simplest calculations such as the evaluation of the $V_{S,max}$ in a series of small halogen bond donors (Figure 8 (a)), combined with structural chemistry experiments and vibrational spectroscopy studies, can provide useful insights for crystal engineering applications [77]. This study used as premise the fact that more pronounced σ-holes, i. e., higher $V_{S,max}$ values, yield a more effective halogen bond donor and therefore, will be more efficient at forming co-crystals with a complementary halogen bond acceptor, B. Indeed, the results from the co-crystallization experiments showed the influence of the halogen bond capability as determined by the QM calculations. A similar rationale was later used [78] to guide the selectivity of halogen bond interactions in the co-crystallization of 9 perfluorinated halogen bond donors and 12 ditopic acceptors (Figure 8(b)). They were able to achieve co-crystallization (monitored by IR spectroscopy) of 89 compounds and obtained 35 new crystal structures. From the calculated values, the halogen bond acceptors can be categorized according to their ΔE values. Here, ΔE is defined as the difference between the two halogen bond acceptor's electrostatic potential minima, $V_{S,min}$. Only when ΔE > 167 kJ mol^{-1}, the halogen bond donor favors the best acceptors site for all co-crystals. The calculated values, together with the experimental data, allowed the proposal of some guidelines: if ΔE >; 75 kJ mol^{-1} (between two accessible halogen bond acceptors), one can expect intermolecular selectivity as the preference of the halogen bond donor toward the best acceptor is a sufficient driving force. A parallel rationale based on the differences in the electrostatic potential between the competing sites of halogen bond acceptors, namely [1,2,3]triazalo-[3,5-α]quinoline and [1,2,3]triazalo-[3,5-α]pyridine, was also reported [79]. In this case, electrostatic potential differences > 75 kJ mol^{-1} lead to a preference toward the best acceptor whereas no selectivity was observed when ΔE is smaller.

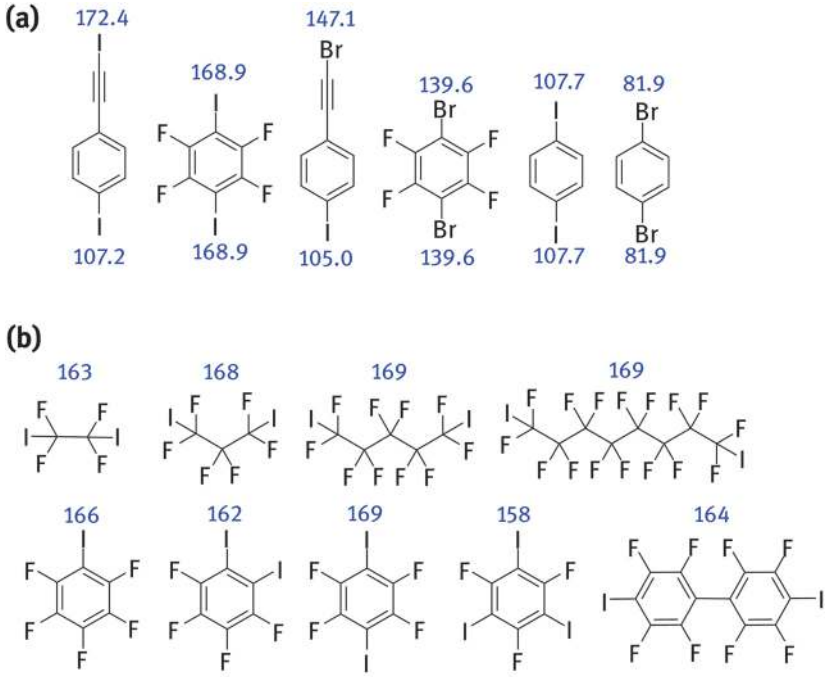

Figure 8: Small library of halogen donors together with their respective $V_{S,max}$ values (blue, kJ mol^{-1}) calculated at the B3LYP/6-311+ G** level of theory as reported in reference 77 (a) and reference 78 (b).

Halogen bonds are also responsible for interesting reactivity. For instance, molecular iodine (I_2) acts as a catalyst for many organic reactions but the origin of this phenomena is not completely clear. DFT calculations were performed [80], complemented with experimental work, trying to shed some light into this question. For that purpose, four model reactions involving α,β-unsaturated carbonyls or nitrostyrenes were studied. The catalytic effects of I_2 are ascribed to the possibility of molecular iodine to form halogen bonds, activating the electrophiles, substantially lowering the activation free energies. Halogen σ-holes are also responsible for the reactivity of chlorine in the reduction of a trichloromethyl group by sulfur nucleophiles [81]. In this case, the negative sulfur atom, acting as the halogen bond acceptor, interacts with the chlorine σ-hole, eventually leading to the abstraction of the halogen and the formation of a carbanion. This hypothesis was studied using a model reaction involving the reduction of a trichloromethyl pyrimidine derivative with thiophenol and sodium thiophenolate by means of DFT calculations (BMK/6-31G**). The electrostatic potential was calculated at the

MP2/cc-pVQZ level of theory. This was complemented by the experimental study of the reaction at −78 ºC, quenched at different reaction times (1, 5, 10, 30 and 90 minutes). The nucleophilic attack occurs at the chlorine atom in the trichloromethyl group. This is potentiated by the existence of a σ-hole at the chlorine atom as shown by the MP2 calculations.

Other example of the synergy between experiment and theoretical work is nicely illustrated by a proposed method based on NOE NMR/DFT methodology [82]. This method is able to discriminate between halogen bonds and other types of noncovalent interactions by the determination of the relative orientation of the halogen bond donors and the halogen bond acceptors represented by perfluorohexyl iodide, iodopentafluorobenzene, bromopentafluorobenzene (donors), 1,4-diazabicyclo[2.2.2]octane, and 2,4,6-trimethylpyridine (acceptors). Halogen bonds are generally stronger than the alternative noncovalent interactions, such as lone pair/π and π/π. The identification of halogen bonds was also made possible by the use of 2,3,5,6-tetrafluoro-4-iodobenzyl *tert*-butyl nitroxide (Figure 9) which could be used as a spin probe for the detection of halogen bonds in solution by EPR [83]. In this case the formation of a halogen bond complex with quinuclidine was accompanied by EPR spectroscopy, allowing the determination of thermodynamic parameters.

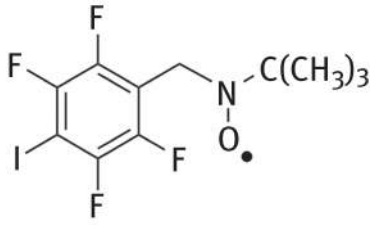

Figure 9: Structure of 2,3,5,6-tetrafluoro-4-iodobenzyl *tert*-butyl nitroxide.

The optimization of halogen bonds by manipulating the substituents is also of interest. Substituent effects were studied on the $[N{-}I{-}N]^+$ halogen bond on a series of [bis(pyridine)iodine]$^+$ and [1,2-bis((pyridine-2-ylethynyl)benzene)-iodine]$^+$ complexes by spectroscopic and computational methods [84]. The *para*-position was modified with -NO_2, -CF_3, -H, -F, -Me, -OMe, -NMe_2 and the ^{15}N NMR showed that the chemical shifts are governed by the π population on the ring instead of the electron population at the nitrogen atoms, *i. e.*, its magnitude does not reflect the strength of the halogen bond. Both NMR and DFT studies (B3LYP) indicate the existence of static and symmetric $[N{-}I{-}N]^+$ halogen bonds. It is also possible to play with the substituents in 2-halo-functionalized imidazolium derivatives (Figure 6(b)) in order to enhance their binding capability toward chloride [36]. When electron-withdrawing groups,*e. g.*, -NO_2, -F, are placed in the 4,5-positions, the halogen bond strength increases both the gas phase and solvent, including water. Bis(triazole)pyridinium receptors were also optimized toward the binding of halide anions [85]. Chirality is an important issue and halogen bond receptors can be designed for the enantiodiscrimination of acceptor molecules in solution as the ones based on the halotriazole and halotriazolium core bearing chiral substituents [86]. In particular, the mentioned chiral triazolium receptor was able to discriminate between enantiomeric thioureas *via* halogen bonds. Chiral (*S*)-BINOL-based receptors bearing halotriazolium units capable of halogen bonding enhance the enantioselective recognition of chiral anions (*N*-Boc-alanine, *N*-Boc-leucine, *N*-Boc-tryptophan, and BINOL-PO_4) [87]. The use of halogen bonds was superior to the hydrogen bonding analogues and MD simulations indicate that the intrinsic linearity of halogen bonds together with host–guest steric interactions play a dominant role in the recognition process. Neutral iodotriazoles, in particular 1,4-diaryl-5-iodo-1,2,3-triazole derivatives can also be used as scaffolds for halogen bond receptors [88].

The versatility of halogens bonds is outstanding and this type of interaction is able to potentiate even the oddest structures like supramolecular helixes [89]. Using *N*-amidothioureas bearing iodophenyl groups, β-turns are identified in the crystal structure. Moreover, C−I···π halogen bonds between adjacent molecules are also observed and help to propagate the helicity of the fragments as depicted in Figure 10, left. The supramolecular assembly exhibits enhanced CD signals, being the first example of chiral amplification in a supramolecular helix triggered by halogen bonds. The first triple helicate able to encapsulate iodine in organic and aqueous media as well as in the solid state by means of halogen bonds was also reported [90]. This triple helicate is shown in Figure 10 right, and is assembled from three tricationic arylethynyl strands around two iodine anions, being stabilized by multiple linear halogen bonds and π-stacking interactions.

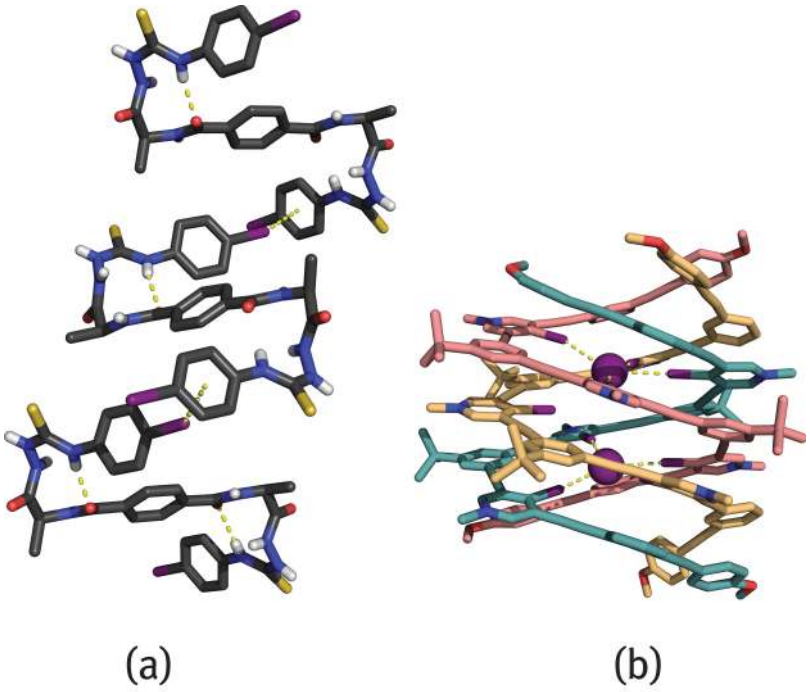

Figure 10: Left: X-ray structure of a supramolecular helix of bilateral *N*-amidothioureas bearing β-turns and intermolecular C−I···π interactions as reported in reference 89. Right: X-ray structure of triple helicate assembled from three tricationic arylethynyl as reported in reference 90.

In supramolecular arrangements, the halogen bond can be surprisingly short as the one present in a bridged triarylphoshine oxide and an aryl iodide in the solid state [91]. Here the *ortho*-bridged triarylphosphine oxide bearing sterically demanding fluorenyl bridging moieties interacts with 1,4-diiodotetrafluorobenzene establishing a very short P=O···I halogen bond (2.683 Å) in the solid state. Experimental and computational methods were used to study this unusual structure. The PBEh-3c and HSE-3c methods (mentioned earlier) were used for the dimer and the crystal structure, respectively. The halogen bond is not significantly stronger in the crystal when compared to the dimer and therefore, the stacking interactions of the fluorenyl flanks are the main factor governing co-crystal formation, being responsible for the short P=O···I distance.

Molecular machines gained special recognition with the award of the Nobel Prize to Jean-Pierre Sauvage, J. Fraser Stoddart and Bernard L. Feringa [92]. In this scope, halogen bonds are among the interactions that can be exploited for the design of new devices. A two-station rotaxane was designed [93] based on a isophthalamide-containing macrocycle and an axle, represented in Figure 11 in pale orange and dark grey, respectively. The axle comprises two stations, a naphthalene diimide group and a iodotriazolium group. These are able to interact with the hydroquinone moiety of the macrocycle and anions, respectively. In $CDCl_3$ solution, the macrocycle translocates from the naphthalene diimide station toward the iodotriazolium station by the addition of halide anions. Indeed, the iodotriazolium station recognizes the anion *via* halogen (C−I···Cl^-) and hydrogen (N−H···Cl^-) bonds, as shown in Figure 11. This shuttling behavior is accompanied by a color change in the solution, enabling naked-eye detection. Another example of halogen bonding supramolecular assembly driven by an external stimulus is the pH controlled assembly of halogen-bonded dimers [94]. This system takes advantage of the different orders of magnitude of the halogen binding acceptor capability of phenoxide (good) versus phenol (poor). In this system, an iodotriazole triazole derivative bearing also a phenoxide anion moiety is able to self-assemble via C−I···I^- halogen bonds, forming a stable dimer. Upon protonation, no assembly is observed in solution or solid state, therefore, self-assembly can be controlled by a change in the protonation state of the system. The system was also investigated computationally using DFT calculations (PSSh/def2-TZVP); the protonated dimer yielded an entropy of interaction of −4.26 kJ mol^{-1} (in an acetonitrile PCM model) whereas deprotonated phenoxide dimer afforded an enthalpy of dimerization of −50.4 kJ mol^{-1}.

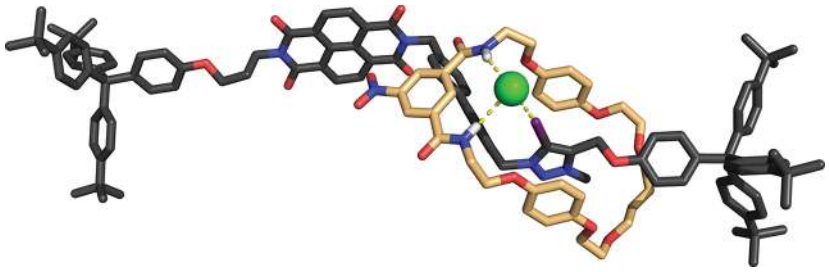

Figure 11: X-ray crystal structure of a two-station rotaxane as reported in reference 93. The macrocycle depicted in pale orange is located at the iodotriazolium station on the axle (depicted in dark grey). This structure is assembled by halogen (C−I···Cl^-) and hydrogen (N−H···Cl^-) bonds.

As mentioned earlier, halogen bonds are important in biological molecules [58] and can certainly be further explored. Indeed, their structural features might be overlooked as it was recently showed [95]. Earlier surveys of the PDB database indicate that halogen bonds were preferentially formed with the protein backbone (~65 %), and the majority of drug design applications focus on the backbone [96]. In this new study [95], the authors showed that the proportion of halogen bonds formed between halogenated molecules and the protein backbone or the protein side-chains changes with the structure resolution and as the resolution becomes worse, the side-chain halogen bonds percentage decreases. It is important to note that since the classic force fields, generally used to refine these structures, do not account for halogen bonding, these lower resolution areas (side-chains) loose the halogen bonds upon refinement. This was also supported by the fact that the effect of the resolution (main chain vs. side-chain interaction) is not observed for hydrogen bonds which the classical force fields can handle. These conclusions should not be ignored when designing new protein inhibitors exploiting halogen bonds. Curiously, the versatility of halogen bonds also enables the modulation of peptide−receptor interactions as shown by the halogenation of two native opioid peptides that bind opioid receptors [97]. If in one hand the replacement of a hydrogen of the peptide by a bulkier halogen atom can produce steric clashes reducing the binding, especially in small cavities, it can also increase the binding if the halogen (chlorine, bromine, or iodine) interacts with negatively charged atoms of the protein *via* halogen bonds. Modifications on the amino acids of a protein to observe the halogenation effect can also be performed. The replacement of the hydroxyl of the tyrosine by an iodine in a model T4 lysozyme [98] caused the displacement of the aromatic side chain toward an oxygen acceptor, showing that halogen bonds can circumvent destabilizing effects that other substitutions cause.

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