

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

Halogen Bonding in Solution

Máté Erdélyi^{a,b}

Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

DOI: 10.1039/b000000x

Halogen bonding is the electron density donation based weak interaction of halogens with Lewis bases. Its applicability for molecular recognition processes long remained unappreciated and has so far mostly been studied *in silico* and in solid state. As most physiological processes and chemical reactions take place in solution, investigations in solutions are of highest relevance for its use in the pharmaceutical and material scientific tool boxes. Following a short discussion of the phenomenon of halogen bonding, this tutorial review presents an overview on the methods hitherto applied for gaining an improved understanding of its behaviour in solutions and summarizes the gained knowledge in order to indicate the scope of the techniques and to facilitate exciting future developments.

1. Introduction

Halogens are typically positioned on molecular surfaces and are thereby easily available for involvement in molecular recognition processes. Such interactions are exploited by Nature, for which illustrative examples are the iodine - carbonyl oxygen interaction mediated selective binding of the hormone thyroxine (T_4) to its transporter protein transthyretin,¹ and the interaction of triiodo-thyronine (T_3) with its hormone receptor involving an aromatic-iodine contact.² Halogenation of proteins and nucleic acids has been associated with human diseases.³ Although natural products are traditionally believed to lack halogens,⁴ thousands of halogenated substances have lately been isolated from natural sources⁵ and many of them have quickly entered medical usage (vancomycin, spongistatin, chloramphenicol, chlortetracycline, etc).⁶ Along with the recently recognized significance of such halogenated natural substances, a steady growth in the number of halogenated synthetic compounds in pharmaceutical use has been observed since the 19th century, with an explosive advance in their applications in all therapeutic classes following World War II.⁴ To date over 50% of the molecules selected for high throughput screening⁷ and approximately one third of all drugs in therapeutic use⁴ are halogenated, pointing towards a vast impact of their secondary interactions in molecular recognition events. Despite the extensive exploitation of halogens in the pharmaceutical industry, the fundamental understanding for their frequent utilization is scanty. The influence of metabolic pathways upon halogenation is being explored.⁸ The generally accepted, classical explanation for the often observed advantageous effect of halogen substitution on bioactivities relates to an increased lipophilicity upon halogenation, which in turn favours penetration through biomembranes and thereby improves bioavailability.⁴ Halocarbon anaesthetics are traditionally given as proof for this theory, although the early Meyer-Overton hypothesis proposing non-specific binding of volatile halocarbons has been found over-simplistic and refuted

decades ago as a consequence of, among others, the observation of a greatly different anaesthetic potency of the enantiomers of anaesthetic agents,⁹ and the negligible change in membrane fluidity upon anaesthetic treatment.¹⁰ The fact that polyhalogenated volatile anaesthetics act by selective protein binding has been recognized already decades ago,¹¹ yet the general role of halogens in molecular recognition processes has not been thoroughly revisited. The observation that halogen substitution in specific positions may profoundly influence bioactivity, often to an extent not reconcilable exclusively with their hydrophobic, inductive or steric effects, motivates a systematic reinvestigation of their non-covalent interactions.

The conventional text book description^{12, 13} of covalently bound halogens assigns a partial negative charge to the halogen, as shown in Fig. 1A. This satisfactorily explains the electrophilic behaviour of the halogenated carbon^{12, 13} and to a certain degree the hydrogen bonding ability of halogens,¹⁴ however, it is much too simplistic for a general interpretation of their secondary interactions. Resulting from the early crystallographic efforts of arthasrathy,^{15, 16} the extensive x-ray crystallographic work of Metrangolo, Resnati and co-workers¹⁷ and of the computational

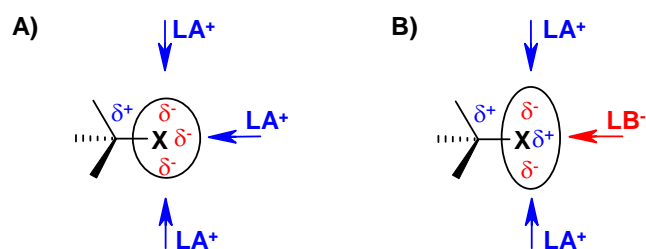


Fig. 1 Schematic description of the electron density distribution of covalently bound halogens and the expected intermolecular interactions. (A) Traditional text book description^{12, 13} and (B) the description based on calculated molecular electrostatic potentials.^{18, 19} In contrast to the conventional simplistic description based on electronegativities only, the predicted electron density-based depiction allows for orientation dependent interactions with both Lewis acids (LA^+) and bases (LB^-).

predictions of Price,¹⁹ Allen,²⁰ Murray and Politzer,²¹ this model has been recently revised and replaced by one that better reflects the anisotropic distribution of the electrons of halogens (Fig. 1B) and is thereby capable of satisfactory explanation of the interaction of halogens with electron donors as well as with electron acceptors. Accordingly, halogens act as Lewis bases by donating electrons from their non-bonding orbitals when interacting with Lewis acids with typical Z-X⁻LA⁺ angles of 90-120°, where Z stands for any type of atom, X for halogen and LA⁺ for Lewis acid. A typical example for such binding is hydrogen bonding (HB), with interaction energies up to 140 kJmol⁻¹ and the trend F > Cl > Br > I in strength.¹⁴ When acting as Lewis acids, the Z-X⁻LB⁻ angle, - where LB⁻ stands for a Lewis base - shows a tendency for linear directionality²² and enables interaction strengths commonly 5-30 kJmol⁻¹, but in exceptional cases up to 180 kJmol⁻¹, with the opposite trend in strength as compared to hydrogen bonding, namely I > Br > Cl > F.¹⁷ This latter type of interaction has received the name halogen bonding (XB) and has during the past decades been increasingly investigated by crystallographic^{17, 23} and computational^{21, 24} methods. Based on analysis of crystallographic data its possible role in the stabilization of small molecule-protein complexes has very recently been proposed.²⁵ Although XB is expected to play an essential role in biological processes, which overwhelmingly take place in solutions, and presumably to a significant extent lies behind the increasing production of halogenated drugs, our understanding of its solution behaviour is still limited. Following a short description of the concept of halogen bonding, this review presents a first synopsis of the techniques so far successfully utilized for solution studies of XB and discusses their scope to strengthen the basis for further methods development.

2. Halogen bonding (XB)

Halogen bonding was discovered one and a half centuries ago²⁶ and its crystallographic description was awarded by a Nobel prize in 1969.²⁷ Subsequently, it was largely forgotten for decades, and the exploration of its potential has just recently begun, to a large extent resulting from the efforts at the Politecnico di Milano, where careful studies have been revealing the immense potential of XB in supramolecular chemistry.²⁸

Halogen bonding is the collective term for electron density donation-based interactions of halogen atoms and neutral or anionic Lewis bases, such as N, O, S, P or halogen functionalities and π electron donors. A key feature for the interaction is the anisotropic electron density distribution around the interacting halogen atom (Fig. 1), which is the result of the halogen atom being covalently bonded to another atom. The concept is broad and hence XB has been classified in a variety of terms, for example as general charge-transfer or electrostatic electron donor-acceptor type. It has been interpreted as the interaction of the antibonding orbital of the Z-X covalent bond (where Z is any atom and X is halogen) with electron donors and in terms of electron transfer between the HOMO of the Lewis base and the LUMO localized on the participating halogen.¹⁵ It has also been categorized as a σ -hole interaction, in which the σ -hole represents the region of positive electrostatic potential on the outermost portion of a covalently bound halogen atom.²⁹

The electron density transfer resulting from XB results in an up to 20% shortening of the interatomic distance of the participating atoms (X⁻LA⁺) below the sum of their van der Waals radii,³⁰ whereas the Z-X bond to the halogen lengthens. The halogen involved in XB may either be covalently bound to any type of atom (i.e. I-Cl, I-I, CF₃-I, etc)¹⁷ or may be of partly ionic character.³¹ The bond angles are consistent with the proposed n \rightarrow σ^* -type non-covalent interaction,²⁰ and the directionality and the depth of the penetration increase from F towards I within the periodic group. As halogens act here as Lewis acids, analogies between XB and HB were often drawn.¹⁷ To emphasize this similarity, the participating partially positively charged halogen is called halogen bond donor, whereas the Lewis base is named halogen bond acceptor.³² It should be noted that this nomenclature contradicts the common convention of electron donor-acceptor interactions; however, traditionally for XB the electron donor is assigned to the halogen bond acceptor and the electron acceptor halogen to the halogen bond donor. Competition between HB and XB³³ in solution, was first studied by Di Paolo and Sándorfy and was suggested to play a role in the molecular mechanism of action of volatile anaesthetics.³⁴

Our present understanding of XB is primarily based on *ab initio* calculations, gaseous phase and X-ray investigations. Computational predictions³³ are not always in full agreement with the sparse experimental evidence from solution studies.³⁵ The fact that the utilization of XB in complex organic compounds in solution and in biopolymers has repeatedly been reported as unsuccessful³⁶⁻³⁸ indicates the need for development of novel, highly sensitive techniques for its detection and quantitative characterization in solutions rather than the lack of its applicability.

3. Techniques for solution studies of XB

A variety of spectroscopic techniques have so far been utilized for investigation of weak molecular forces in solutions. Optical spectroscopy was the first, whereas NMR spectroscopy has been by far the most widely used technique for solution studies of XB. Although it offers exceptionally detailed structural information and a high versatility, NMR spectroscopy suffers from comparably poor sensitivity with a typical limit of detection in the nanomole range for the most commonly detected ¹H and ¹⁹F nuclei, when using standard equipment. Conversely optical methods, such as UV-VIS spectroscopy provides sensitivity in the femtomole range, yet they offer limited structural information. The main advantages of Raman and IR spectroscopies are their low sample volume requirement and their ability to provide direct information on chemical bonds. The applicability of Electron Spin Resonance spectroscopy is limited by its dependence on the presence of an unpaired electron close to the interaction site. The so far scarcely utilized calorimetry allows for straightforward thermodynamic characterization of equilibrium processes; however, in similarity to optical spectroscopy it is inherently insufficient in directly yielding atomic level information. A discussion of the use, advantages and disadvantages of these techniques for the detection and characterization of XB is given below.

3.1 UV-VIS spectroscopy

One of the initial proposals on the interaction of halogens with electron-pair donors originated from the observation that free iodine dissolved in electron donating solvents, such as water or alcohol, gives brown solutions, whereas red-violet solutions are obtained when dissolving it in solvents of low basicity, such as carbon tetrachloride or benzene.³⁹ The cause of the brownish solution colour was interpreted by Lachman as the formation of “molecule-solvent+I₂” complexes, in good agreement with the crystallographically proven I₂⋯NH₃ complex.²⁶ A dark red colour, instead of the expected violet (indicating no interaction with the solvent) was also observed when dissolving I₂ in ethyl bromide, and was at that time explained with the probable presence of impurities. The observation of solvent dependent reactivity of iodine⁴⁰ was interpreted in terms of the strength of a solvent-iodine – XB – interaction. A further evidence for donor-acceptor complexes, in which halogens act as Lewis base, is the significantly increased solubility of molecular halogens in water upon addition of halide ions, owing to the formation of X₃⁻.⁴¹ Diiodine provides an outstanding opportunity for the straightforward study of XB with various Lewis bases from three different regions of the electronic spectrum, in which the absorption is directly related either to the concentration of the halogen bonded complex (charge-transfer band at 240-350 nm and a blue-shifted band at 400-510 nm) or the concentration of the free I₂ (520 nm in n-heptane).⁴² Correlating the solvent electron donation ability to the frequency of absorption maximum of the complex (Fig. 2)^{39, 43} may provide a semiquantitative scaling of the strength of halogen bonding in solution, similar to the currently more commonly applied ¹⁹F NMR chemical shift alteration-based quantification.⁴⁴ Thus, upon addition of a Lewis base to an iodine solution, two pronounced changes occur in its UV spectrum: the visible transition undergoes a blue, hypsochromic shift, and a new band due to a charge transfer transition arises in the UV region.⁴⁵ In medium and weak complexes, the band of free iodine overlaps with the visible band of the complex, but computational spectral treatment methods still allow the accurate measurement of the blue shift.^{46, 47} By collecting a large number of Δν data for pyridines, nitriles, ethers, carbonyls, sulfur and π-bases, good correlation between the hypsochromic shifts of the diiodine visible band and the diiodine basicity scale (pK_{BI2}) was discovered.⁴⁵ This scale is analogous to the pK_B scale commonly used to describe basicity towards protons and is based on the use of I₂ as a reference Lewis acid at standard conditions (25 °C, alkane solution) and the detection of the formation of 1:1 iodine:Lewis base complexes by spectroscopic methods. By collection of literature data, an extensive scale entirely based on the detection of the interaction of diiodine with various Lewis bases has been constructed that reflects well the Lewis base electron density based dependence of XB interaction strengths.⁴⁵ Quantitative UV titrations in organic solvents were performed by Rebek *et al* for studying nitrogen-halogen interactions,⁴⁸ and for the investigation of the Cl⁻ binding of an artificial anion receptor by Taylor and co-workers.⁴⁹ Although inexpensive and straightforward, originating from its limited ability to provide in depth structural information, UV-VIS spectroscopy has lately not been extensively utilized in the assessment of XB.

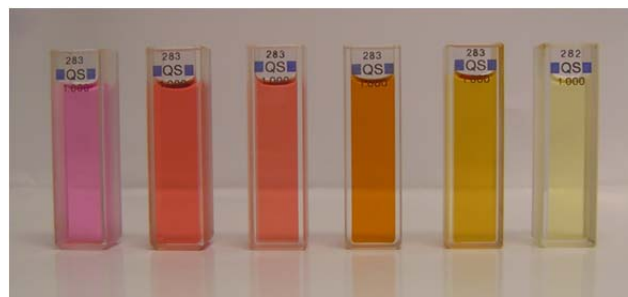


Fig. 2 The colour of iodine solutions reflects the electron donating ability of the employed solvents. From left to the right the characteristic colours of I₂ dissolved in hexane, toluene, dichloroethane, acetonitrile, methanol and pyridine are shown, with corresponding λ_{max} = 520, 513, 500, 460, 447 and 374 nm. A stronger XB results in lowered absorption frequency.

3.2 Infrared spectroscopy

Upon interaction of iodine with Lewis bases the frequency of I-I stretching motions is lowered, which is observable using infrared spectroscopy. This frequency shift is greater for stronger bases, such as amines, than for weaker Lewis bases.⁵⁰ Other halogen molecules and interhalogens experience similar perturbations in their stretching motions. Hence, these frequency shifts are indicative of the XB interaction strength. A spectroscopic scale of soft basicity was proposed based on the correlation of Δν(I-CN) frequency shift and the diiodine affinity to 41 Lewis bases,⁵¹ for which the number of bases has later been further extended.⁴² The frequency shift of iodine cyanide, as compared to its free form in dichloromethane (485 cm⁻¹), spans over 100 cm⁻¹ upon complexation. As its coupling to the vibration ν(I⁻Lewis base) of the complex at ca 100 cm⁻¹ is negligible, the observed shift can be interpreted in terms of relative halogen bonding strength. A similar, general iodine scale could not be developed as the iodine frequency shift upon complexation does not simply relate to the change in force constant of the I-I bond, but also depends on the coupling between the ν(I-I) and ν(LB⁻I) bands, which are generally close in frequency. Establishment of a general IR spectroscopic scale using I-Cl was attempted as well, however, its high chemical reactivity, low solubility in non-polar solvents and easy ionization limited its use to nitriles, oxygen and aromatic π-bases. For strong complexes the frequency shifts must again be interpreted with care as coupling between the ν(I-Cl) and ν(LB⁻I) bands may become significant. All in all, the IR frequency changes of I-CN, and to a certain degree of I-Cl and of I-I reflect the logK_a values of halogen bonded complexes for families of bases encompassing similar XB acceptor sites. Even though observation of such frequency shifts provides valuable theoretical information on XB, overlap of absorption bands prohibit the use of IR spectroscopy for more complex molecules.

3.3 Raman spectroscopy

Raman spectroscopy is well-fitted for the study of XB as the halogen-stretching frequency is Raman active in the complexed as well as in the uncomplexed molecule, and is detectable using rubidium or helium sources. The spectrum of the electron donor species is expected to experience perturbations upon complexation to halogens that may be manifested as new bands, or as intensity or frequency variations of existing bands. As a consequence of the electron donation into a nonbonding orbital of the halogen or interhalogen, its covalent bond weakens and

thus the Z-X stretching frequency is expected to decrease upon XB. Halogen charge-transfer complexes have been studied using Raman spectroscopy first by Stammreich and co-workers⁵² and later by Klaboe.⁵³ These included the investigation of I₂, Br₂ and ICl in interaction with a variety of solvents. The I-I stretching modes were observed at 210-140 cm⁻¹, with the frequency decreasing with higher electron donating ability of the interaction partner (i.e. benzene - 205 cm⁻¹, ethanol - 202 cm⁻¹, pyridine - 317-276 cm⁻¹, and for I-Cl a frequency range of 251-384 cm⁻¹ were observed; for both molecules the data were consistent with the relative basicities of the donors and hence the expected interaction strengths. In addition, a solvent polarity dependence of the Raman bands was observed, indicating a stronger interaction (lower frequency bands) in more polar solvents. This observation is in agreement with the charge-transfer interpretation of the interaction; however, it is in contradiction with the observations of others, who found stronger XB in non-competitive non-polar solvents than in polar ones.^{35, 44}

XB between iodoperfluoroalkanes and pyridine was studied using coherent anti-Stokes Raman spectroscopy (CARS), a variant of Raman spectroscopy providing higher sensitivity.⁵⁴ The interaction energy, indicated by the magnitude of the blue frequency shift (7-10 cm⁻¹) was found comparable to that observed for the HB interaction of water and pyridine (8 cm⁻¹). Although variable temperature studies in principle permit determination of the thermodynamic parameters of an equilibrium process from Raman spectra, here only qualitative indications could be given. The association constant of the 2-iodo-perfluoropropane – pyridine interaction was observed to be a magnitude larger than that of the interaction of 1-iodo-perfluoroalkanes, which is in agreement with the observations using other spectroscopic techniques.^{35, 44} In addition, a larger degree of self-halogen bonding (I...F) was observed for the branched iodo-perfluorocarbon analogue than for the linear one that affected the observable enthalpy and entropy changes of the system. Discussion of the effect of self-halogen bonding of polyhalogenated halogen bond donors on the thermodynamic data appears here for the very first time. Since most NMR studies have so far been performed using perfluorinated halogen bond donors, this aspect is expected to gain further attention.

Recently, Raman and IR spectroscopy were applied for the study of the interaction of small model compounds ((CH₃)₂S and CF₃X, where X= Cl, Br, I) in liquid argon or liquid krypton. Although these mixtures are formally solutions at temperatures below 83 and 120 K, respectively, these studies^{55, 56} provide better support for the improvement of the predictive ability of computational techniques than novel information on the solution behaviour of XB for e.g. drug development. Hence, even if mentioned as a curiosity to cover the entire spectrum of investigations, these studies are not discussed in detail here.

Raman spectroscopy provides analogous information to infrared spectroscopy, yet a frequency range that appears especially advantageous for the investigations of XB, because it provides information on the alteration of bond strengths of all species involved in the interaction process: the XB donor, the XB acceptor as well as the formed Z-X...LB' complex.

3.4 NMR spectroscopy

To date, NMR spectroscopy is doubtlessly the most powerful technique for spectroscopic studies of solutions. It provides a variety of methods for observation of intermolecular interactions, the most common being chemical shift titration experiments. Comparative monitoring of ¹H NMR chemical shift changes was utilized for the detection of halogen bond formation first by Bertrán and Rodríguez⁵⁷⁻⁶⁰ and later by Metrangolo and Resnati⁴⁴ for quantification of the interaction strength. Common features of these studies are the use of the Lewis base as solvent to shift the equilibrium process towards complex formation and the application of the difference in chemical shift of the substrate when dissolved in interacting and in non-interacting solvents as a semi-quantitative measure.

3.4.1. Semi-quantitative NMR shift correlation studies

Bertrán and Rodríguez⁵⁷ have measured the haloformic proton shifts in solvents of varying electron donor abilities, using cyclohexane as a non-interacting reference, and interpreted the shift alterations in terms of HB and XB characteristics. The ¹H NMR chemical shifts of CHBr₃ and CHI₃ were correlated to those observed for CHCl₃ solutions (Fig 3.), presuming a negligible extent of XB interactions for chloroform. Whereas HB is indicated by a chemical shift (δ) increase of the acidic proton in basic solvents, resulting from a decreased electron density of the CHX₃ carbon, XB yields a decreased δ_{H} originating from an electron density increase due to electron donation to the halogens from the Lewis bases. The relative extent of these opposing effects is estimatable from correlation plots of the 'solvent shifts', representing here the ¹H NMR shifts of the investigated compounds in different solvents. Presuming limiting solvent shifts corresponding to the fully hydrogen bonded and fully halogen bonded states, Δ_{HB} (high) and Δ_{XB} (low), respectively, the relative extent of HB and XB were estimated for CHBr₃ and CHI₃ when dissolved in three major solvent types. For bromoform only a negligible extent of XB (<10%) was observed in ether, ester, keton and amine solutions. In contrast, the iodoform chemical shifts revealed 60-95% XB in solvents encompassing aminic

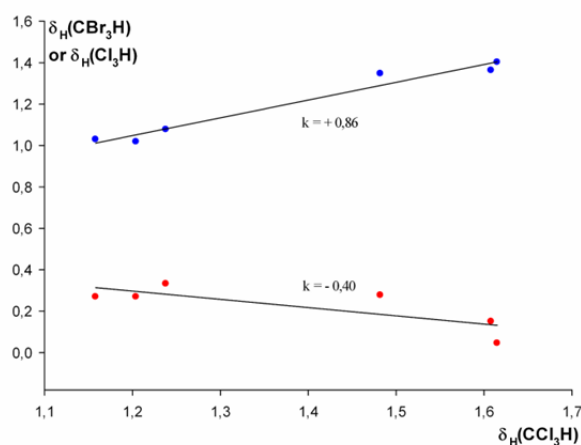


Fig. 3 The ¹H NMR chemical shifts of CBr₃H (blue) and CI₃H (red) plotted against those of CCl₃H for a series of amine solutions (from left to the right: triethylamine, morpholine, dicyclohexylamine, n-hexylamine, piperidine, and pyrrolidine) as reported by Bertrán and Rodríguez.⁵⁷ A positive correlation indicates the dominance of HB, whereas a negative correlation is observed for the predominance of XB over HB interaction.

electron donors (Fig. 3), whereas 10-30% XB in ethers and up to 15% XB was seen in esters and ketones. Even if the unknown shifts of the completely hydrogen and halogen bonded states make the approximations somewhat inaccurate, the conclusions are in good agreement with the currently generally accepted trend of XB interaction strengths of $\text{Cl} < \text{Br} < \text{I}$ and $\text{O} \leq \text{S} < \text{N}$. Follow-up studies did not detect XB-type interactions of haloformic halogens with the π electrons of aromatic solvents, but revealed dipole-induced dipole interactions.^{59, 60} Similar to most solution studies of XB, Bertrán and Rodríguez allowed the haloformic XB donors to interact with a large excess of Lewis base and thereby forced the weak equilibrium process of binding towards completion (~50-90%) and was therefore able to detect comparably large (0.1-1.6 ppm) chemical shift changes. It should be noted that techniques capable of precisely estimating the limiting chemical shifts of an equilibrium process that follows a two-state behaviour are available⁶¹ and would allow improvements of the semi-quantitative estimation of this technique.

Two decades later the above approach was further developed by Metrangolo and Resnati,⁴⁴ who by detection of chemical shift alterations of polyfluorinated XB donors upon interaction with solvents of varying electron donating properties proposed a quantitative scale for the strength of XB in solution. Initially, the N···I interaction of quinuclidine and 1-iodo-perfluoropropane was evidenced by the observation of a 16 ppm ¹⁹F and a 7 ppm ¹⁴N NMR shift alteration along with a 960 Hz to 2160 Hz line broadening of the ¹⁴N NMR signal, using pentane solutions of the substrates as shift references.⁶² The association constant of the complex was determined by ¹⁹F NMR titration to be 10.7 ± 0.4 M.⁴⁴ Subsequently, the magnitude of the ¹⁹F NMR chemical shift difference of the CF₂-group closest to I or Br of a chosen diiodo- or dibromoperfluoroalkane XB-donor⁴⁴ when dissolved in a N-, S- or O-donor solvent (Fig. 4) as compared to that in a non-interacting, n-pentane or cyclohexane, solution ($\Delta\delta_{\text{CF}_2\text{-solvent}} = \delta_{\text{CF}_2, \text{ non-interacting solvent}} - \delta_{\text{CF}_2, \text{ interacting solvent}}$) was established as a general, quantitative measure of the relative strength of XB. As the result of the halogen bond mediated electron density transfer, using this scale a larger $\Delta\delta_{\text{CF}_2\text{-solvent}}$ of the reporter nucleus is indicative of a stronger XB interaction. The previously computationally and crystallographically established XB-donor strength order of $\text{I} > \text{Br}$ and XB-acceptor strength of $\text{N} > \text{S} \geq \text{O}$ was confirmed in solution. In agreement with the expectations for a charge-transfer interaction, steric hindrance and electron withdrawing substituents on the Lewis base were shown to decrease the interaction strength. Decreasing the electron density of the halogen bond donor by increasing the substitution grade in the order of primary < secondary < tertiary perfluoroalkyl chains of comparable mass increased the interaction strength. Here, it should be noted that investigation of polyfluorinated halogen bond donors is beneficial for the solution study of XB in several ways. Hence, originating from its large inductive effect, fluorine substitution exceptionally efficiently magnifies the σ -hole of close-by I, Br and Cl and thereby increases the strength of the weak interaction. Simultaneously, the presence of fluorine atoms close to the interaction site allows for NMR detection with high intrinsic sensitivity (85% of ¹H) and with an exceptionally broad ~800 ppm chemical shift scale. The XB interaction induced slight

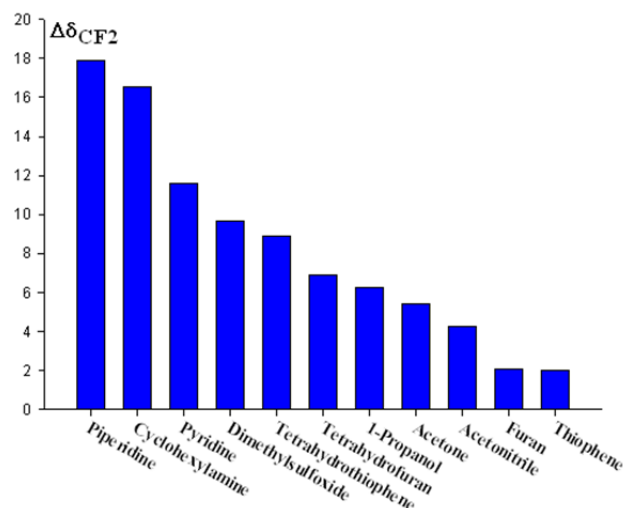


Fig. 4 The ¹⁹F NMR chemical shift differences ($\Delta\delta_{\text{CF}_2\text{-solvent}}$) of 1,8-diiodoperfluoroctane in cyclohexane and the given solvent.⁴⁴ A stronger Lewis basic solvent causes a larger ¹⁹F shift alteration, compatible with the formation of a charge transfer complex, revealing the effectiveness of the $\Delta\delta_{\text{CF}_2\text{-solvent}}$ parameter to reflect the strength of the formed XB interactions and thereby be used for ranking XB donors and acceptors.

electronic changes are greatly magnified in ¹⁹F as compared to ¹H NMR, which in turn has a narrow chemical shift scale of ~12-15 ppm. In addition, polyfluorination provides compounds having high solubility in non-polar solvents, which are optimal for observation of XB as they do not compete with the weak interaction by means of e.g. HB. All in all, a careful substrate and method selection made this chemical shift scaling study exceptionally impactful, although its applicability for compounds of general interest, lacking polyfluorination, may be questionable. Here, it should be noted that XB could not be detected by Kaupp and co-workers using the sample principle (comparison of chemical shift for inert and electron donor solutions of XB donors), but using non-fluorinated molecules and ¹³C NMR detection.⁶³ A weakness of the method is that the $\Delta\delta_{\text{CF}_2\text{-solvent}}$ of chemically different halogen bond donors, such as alkanes and arenes, are not comparable as the alteration of the ¹⁹F chemical shift depends on the distance of the reporter nucleus from the interaction site (i.e. the C-N bond length is 1.47 Å in quinuclidine, whereas it is 1.37 Å in pyridine). Therefore, the scale is applicable for comparison of the properties of halogen bond acceptor species, but only to a limited extent for that of donors. This fact reveals the need for establishment of a spectroscopic technique that is insensitive to variations in intramolecular distances of atoms not participating in the XB interaction, but is capable of quantitatively reflecting the interaction strength.

3.4.2. Thermodynamics of XB by solution NMR

To further develop a quantitative scale of XB, the Taylor group has determined the association constants for the interaction of tri-n-butylphosphine oxide (Bu₃PO) with a series of substituted iodoperfluoroarenes and iodoperfluoroalkanes by ¹⁹F NMR titrations.³⁵ Systematic variation of the para-substituent of the haloarene R-C₆F₄-I indicated that electron donating groups lower the logK_a of the interaction, whereas an electron withdrawing R substituent increases the halogen bond donor ability of iodine. The established linear free energy relationships revealed a better correlation of the logK_a of the complexes to the Hammett

substituent constants σ_{meta} than to σ_{ortho} or σ_{para} . As σ_{meta} reflects inductive effects, this fact indicates the predominantly electrostatic origin of the studied XB, for which the observation is in excellent agreement with related previous studies.^{51, 64, 65} As further evidence, the measured $\log K_a$ values have been shown to correlate excellently with the surface electrostatic potential at the iodine when predicted on the density functional theory (DFT) level. Further analysis revealed that DFT methods with the B3LYP hybrid functional are capable of reasonable prediction of the interaction strength for most XB complexes with the exception of the strongest bonds, such as the $\text{C}_8\text{F}_{19}\text{I}$ - quinuclidine halogen bond, which may also involve charge-transfer, dispersion, or covalent contributions. The first systematic investigation of the influence of solvents on XB was performed by acquisition of the association constants for the iodoperfluorooctane – triethylamine interaction in ten solvents. The strongest XB was observed in the least polar, non-hydrogen bonding solvents cyclohexane and benzene with K_a values of 2.8 and 2.6 M^{-1} , respectively. Although the bond strength decreased in Lewis basic solvents, only a minor response to increased solvent polarity (K_a in acetonitrile 1.9, in acetone 1.3, in dioxane 1.2) was observed, which - importantly - was significantly lower than expected based on predictions by an electrostatic model. In contrast, hydrogen bond donor solvents, such as alcohols or chloroform, efficiently competed with the halogen bond resulting in negative $\log K_a$'s having large experimental errors. The above observations are expected to be of significance for the applications of XB in drug development and also reveal the need for development of further methods of improved sensitivity and accuracy, capable of the precise characterization of such exceedingly weak complexes even in polar solvents. A major advance of the investigation of the Taylor group was transferring the determination of XB strength in solutions from semi-quantitative scales to one based on spectroscopically determined association constants. The findings of this study are in agreement with those of the work presented by Hunter, which, however, was limited to non-polar solutions (C_6H_6 , CCl_4 , and CHCl_3).⁶⁶

The significance of $\text{C-X}\cdots\pi$ interactions is well exemplified by the structure of the thyroid hormone triiodothyroxine (T_3) bound to its receptor.⁶⁷ The molecular recognition is mediated by e.g. the close contact of the T_3 -5'-iodo substituent with Phe-455 of the protein. This favourable interaction of a halogen with an aromatic π -system was first studied in solution by Waters⁶⁸ utilizing a well-designed, peptidomimetic model system (Fig. 5). Making use of the fact that the cooperative folding of a β -hairpins is to a significant extent driven by side chain – side chain interactions, the thermal denaturation NMR studies of a series of β -hairpins permitting interstrand halo-phenylalanine – phenylalanine edge-to-face ($\text{x}\cdots\pi$) interactions were performed. Maximum stabilization of the folded conformer was observed for iodine-mediated XB-interaction, providing $\Delta\Delta G^0 = -2.26 \text{ kJmol}^{-1}$ stabilization of the folded conformation of the I-substituted as compared to the non-substituted analogue. Quantifiable stabilization was observed also for the bromo-, chloro- and fluoro-analogues (-1.97, -1.42 and -0.50 kJmol^{-1} , respectively) demonstrating an exceptional sensitivity of the applied technique. The thermodynamic analysis indicated an enthalpy driven interaction having dispersion as the primary driving force.

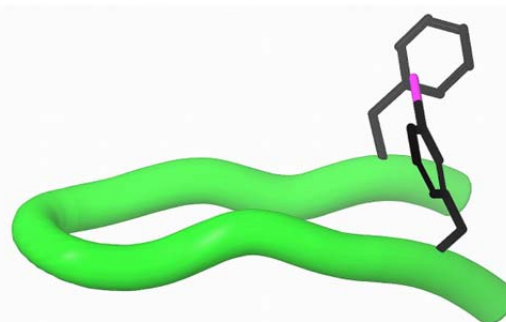


Fig. 5 The 3-iodophenylalanine derivative (Phe-2) of the β -hairpin mimetic $\text{Ac-RF(X)VOVNGKEIFQ-NH}_2$ used by Waters to probe $\text{C-X}\cdots\pi$ interactions.⁶⁵ For clarity, the aromatic rings involved in the interstrand edge-face interaction are shown in green, the peptide backbone is visualized as a blue ribbon and non-polar hydrogens are omitted.

Hence, the increased stability of the folded, halogen bonded conformation was detected to be associated with a favourably more negative enthalpic term, a concomitant entropic cost and a slightly decreased change in heat capacity. Such alteration of ΔH^0 and ΔS^0 simultaneous to a small change in ΔC_p^0 is unexpected for hairpin folding classically primarily driven by hydrophobic effect.^{69, 70} Increased folding with an increasing enthalpic drive and decreasing change in heat capacity upon halogenation was interpreted as a sign of the increased impact of dispersion forces by the authors.⁶⁸ In addition to having provided one of the very first quantitative methods for solution characterization of XB, this study showed several hitherto exceptional features: (a) thermodynamic analysis was performed using ^1H NMR spectroscopic detection, which is a less sensitive tool as it has a narrow chemical shift scale as compared to ^{13}C and ^{19}F NMR; (b) the model system of Waters did not apply polyfluorination to increase the σ -hole of the XB donor, but measured the interaction in a compound resembling halogen-aromatic interactions of biological relevance; (c) the applied peptidomimetic realistically mimicked a complex protein-like environment and thereby provided a superior system for evaluation of the scope of XB for pharmaceutical development; (d) XB strength was here quantified for the very first time in aqueous solution, revealing the potential of the method for successful application for the study of the competition of XB and HB; and (e) fluorine centered XB, whose existence has been a matter of debate from the early beginning²³ and only recently was confirmed crystallographically and computationally,⁷¹ was detected here as an attractive interaction force. The success of the investigation may have depended on the ease of studying weak forces in an intramolecular system stabilized by cooperative forces. The weak point of this study is that the possibility of an $\text{Ar-H}\cdots\text{X}$ interaction could not be excluded even if a substantial enhancement in the preference for edge-face interaction was observed upon halogen substitution, implying a $\pi\cdots\text{X}$ interaction, and the effect of halogen substitution on the stability of the folded hairpin conformation was convincingly presented.

The existence of a $\pi\cdots\text{I}$ XB interaction was confirmed six years later by Hansen and Herrebout⁷² on a perfluoriodopropane-toluene model system using variable temperature studies, to a certain degree resembling the investigations of Metrangolo and Resnati,⁴⁴ and of Taylor.³⁵ Recording the temperature dependence of the ^{19}F NMR shifts of the iodine-based XB donor, equilibrium

constants ($K = 0.32\text{--}0.43 \text{ M}^{-1}$ at 299 K) were determined by Erb-Bluhm-type non-linear least squares analysis of binding isotherms, whereas complexation enthalpy ($-2.7 - -2.9 \text{ kJmol}^{-1}$) and entropy ($-16.0 - -19.1 \text{ JK}^{-1}\text{mol}^{-1}$) were derived by Van't Hoff analysis of the variable temperature data. While perfluorination of the XB donor and the non-protic and non-polar environment increases the XB interaction strength, detecting the interaction intermolecularly instead of intramolecularly weakens it by an increased entropic factor, as compared to the above model system of Waters.⁶⁸

3.4.3. Solution NMR spectroscopic investigations of the XB interaction of halide anion receptors

Utilizing well-designed artificial receptors, the XB of halide anions to covalently bound halogens has first been investigated in non-polar solution by Resnati *et al.*,⁷³ and has recently been systematically studied in polar aprotic solvents by the Taylor group.^{49, 74, 75} The previously established ¹⁹F NMR titration and variable temperature NMR methods³⁵ were utilized for determination of the association constants for the interaction of a variety of anions with perfluorinated, multidentate XB donors. Formation of 1:1 complexes was shown by acquisition of NMR binding isotherms and further confirmed by electrospray ionization mass spectrometry. The multidentate anion receptors in this study showed the order of affinity $\text{Cl}^- > \text{Br}^- > \text{I}^-$ correlating to the charge density of the halogen bond acceptor and a considerably higher preference of the receptors to halide anions over oxoanions. This fact may be indicative of a greater contribution of charge-transfer or dispersion forces in XB as compared to HB. The estimated incremental free energy per halogen bond was observed to be $< 1.5 \text{ kJmol}^{-1}$ for oxianions whereas $\sim 4 \text{ kJmol}^{-1}$ for halide anions. Here, it should be noted that XB-based anion receptors showing opposite selectivity ($\text{I}^- > \text{Br}^- > \text{Cl}^-$; oxoanion $>$ halide⁷⁵) as compared to that observed in the above study⁷⁴ have also been reported. As expected, lower electron density, achieved by increased degree of fluorination, resulted in stronger binding. By simultaneous incorporation of XB and HB sites, the tuning of anion selectivity has been accomplished and the relative strength of the corresponding interactions became estimatable. Similar to the above β -hairpin model system,⁶⁸ a main strength of the applied method is the utilization of (chelate) cooperativity, which allows for the measurement of very weak interactions in an intermolecular model system that would hardly have been possible using the attractive force of a single XB site.

3.4.4. NMR spectroscopic symmetry investigation of XB

The impact of bond symmetry has been discussed in its relation to bond length and strength.⁷⁷ Symmetric species showing a single-well potential were traditionally presumed to be especially short and strong, and were proposed to contribute to the stabilization of intermediates and transition states, for example in enzyme catalysis.⁷⁸ In a recent study, the symmetry of XB was investigated by application of the method of isotopic perturbation of equilibrium processes.³¹ This technique⁷⁹ has a unique capability of distinguishing between truly symmetric, static molecular systems that are described by a single-well energy potential and rapidly equilibrating non-symmetric tautomers characterized by a double-well potential (Fig. 6). It makes use of the fact that desymmetrizing isotopic substitution perturbs equilibrium processes, here the equilibrium between two

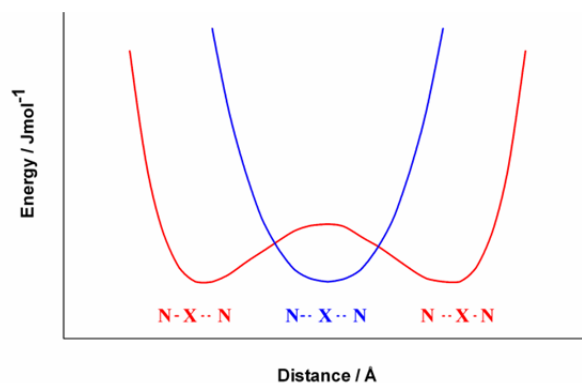


Fig. 6 Schematic potential energy curves for a static, symmetric halogen bond (single-well blue) and that of a rapidly tautomerizing asymmetric one (isoenergetic double-well, red). Differentiation between the two types of halogen bonded systems has been performed using the NMR technique isotopic perturbation of equilibrium on the model substances bis(pyridine)halonium triflates in dichloromethane solution.³¹

tautomeric structures, whereas it does not have an analogous effect on a single symmetrical structure in the absence of any equilibrium processes. For assessment of the symmetry of XB in systems encompassing nitrogen-based XB acceptors and iodous or bromous XB donors, the model system bis(pyridine)halonium triflates was investigated using isotopic perturbation of the halogen bond through selective incorporation of deuterium at the C2 of pyridine.³¹ By evaluation of the temperature dependence of the secondary isotope effects, measured by ¹³C{¹H,²H}6 NMR, the interactions of Br and I to the two coordinating pyridine nitrogens were found equivalent, interpretable as two identical N··X halogen bonds (Fig. 6, blue), instead of one of the N-X bonds being shorter and thus stronger than the second, which would have yielded an asymmetric complex with one classical covalent and one classical halogen bond (Fig. 6, red). In contrast to the analogous N-H-N hydrogen bond, which was reported to be symmetric in the solid state yet asymmetric in solution, the studied N-I-N halogen bond appears symmetric both in the crystal and in solution, whereas the N-Br-N analogue is asymmetric in the crystal (x-ray), but symmetric in solution. The recognition of this difference between HB and XB, besides their wide similarities, is expected to support the application of XB as a complementary tool to HB in molecular recognition processes. Additional, in the field new features of this study are the investigation of a less conventional type of XB and the use of very weak isotope effects observable through the utilization of a “built-in, internal chemical shift reference” ($\Delta\delta = \delta_{\text{C(D)}} - \delta_{\text{C(H)}}$).

Main advantages of NMR spectroscopy for the examination of XB are its versatility, its ability to provide nucleus specific information and its sensitivity to detecting small electron density changes.

3.5 Electron spin resonance spectroscopy

Electron spin resonance (ESR) spectroscopy is an old, yet rapidly developing technique that allows for studying species encompassing unpaired electrons, such as radicals and transition metal complexes, and applies the concepts of NMR spectroscopy, however, on electron spins. Its main advantage is its specificity resulting in clear spectra that originate from the fact that ordinary species having paired electrons do not give rise to ESR signal,

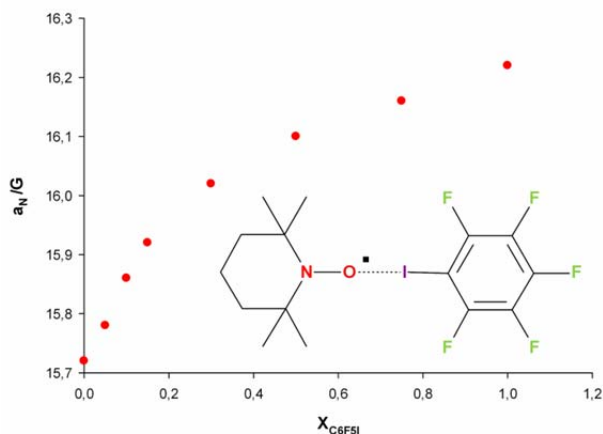


Fig. 7 The dependence of the nitrogen hyperfine splitting constant a_N on the C_6F_5I mole fraction at 298 K in hexafluorobenzene.⁸⁰ An increased a_N reflects increased spin density on the nitrogen upon XB; measurement of the concentration dependent alteration allows the determination of the equilibrium constant of the formed complex by ESR spectroscopy.

whereas radicals with unpaired electron(s) do.

ESR spectroscopy was first used by Lucarini and co-workers for characterization of halogen bonded complexes of perfluoroalkanes and perfluoroarenes with the electron donor nitroxide group of the 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO).⁸⁰ As the nitrogen hyperfine splitting constant, a_N , of nitroxides is proportional to the unpaired electron spin density on their nitrogens, environments favouring the dipolar structure N^+-O^- , in which the electron spin is delocalized on the nitrogen, over the $N-O\cdot$ form give rise to an increased nitrogen splitting. Hence, any charge transfer interactions in which the negative charge is stabilized on the oxygen is expected to be manifested in an increased a_N . Using this approach, XB was observed by determination of the concentration dependent increase of the hyperfine splitting, a_N , (Fig. 7) and of an increased broadening of the nitrogen ESR signal of the interacting nitroxide upon titration with C_6F_5I . Notably, titration with non-fluorinated iodoarenes did not yield any significant change in the ESR spectrum of the nitroxide and thereby indicated a negligible or non-measurable strength of interaction for these compounds. Similar to most spectroscopic methods, the observed ESR signal of the mixtures of TEMPO and haloperfluorocarbons is the molar fraction weighted average of the signals of the free and of the halogen bonded forms. With the presumption of fast exchange, the averaged signal can be deconvoluted by spectral simulation into the two limiting forms, which allows the determination of the equilibrium constant (K_a) of the process. Observation of the temperature dependence of K_a allows determination of its thermodynamic parameters. Iodoperfluoro-alkanes and arenes were shown to complex with TEMPO with association constants in the range of 0.1-15 M^{-1} , and steric hindrance was shown to weaken the interaction. The ESR findings on complexation of perfluorous halogen bond donors with paramagnetic TEMPO were confirmed by a combined ^{19}F NMR and computational DFT study.⁸¹ Contrary to the commonly observed NMR chemical shift decrease upon XB to diamagnetic halogen bond acceptors (Lewis bases), complexation to a paramagnetic electron donor resulted in a chemical shift increase of CF_2 functionalities nearby the halogen bond donor I or Br, in good agreement with the applied theory (MP2/aug-cc-pVTZ).

The N-O \cdots I XB interaction was further investigated using ESR by Micallef et al, who studied the 2:1 complex of the isoindoline nitroxide 1,1,3,3-tetramethylisoindolin-2-yloxy (TMIO) and 1,4-diodotetrafluorobenzene.⁸² Although nitroxide radicals are generally considered to be poor electron donors, in similarity to the study of Lucarini et al, strong complexes of perfluoroarenes were detected. Halogen bonding was demonstrated to induce an increased spin density at the nitroxide nitrogen simultaneous to an increase in the nitroxide rotational correlation time, which in turn results from the increased hydrodynamic radius of the halogen bonded complex as compared to its free constituents. The increased rotational correlation time causes line broadening. An increased a_N is consistent with an increased spin density at the nitrogen, explained as stabilization of the ionic resonance structure of TIMO by XB.

The main advantage of ESR is the absence of signal overlaps and hence comparably simple spectra. Its major disadvantage is the necessity of the presence of an unpaired electron close to the interaction site for detection, which may be difficult to achieve for types of Lewis bases other than nitroxides.

3.6 Calorimetry

Calorimetric studies involve the measurement of heat changes of a sample. Its most commonly used variant is differential scanning calorimetry (DSC) that allows for the direct measurement of the enthalpy of processes taking place in solutions and for derivation of the corresponding equilibrium constants and stoichiometries, entropies and Gibbs free energies. Its use for the determination of thermodynamic data in a variety of contexts has a long tradition, and it is superior for the analysis of stabilities of biological systems and investigations of ligand-protein binding in a native-like state. So far it has been sparsely applied in the context of XB,⁸³ most likely due to the fact that this interaction has hitherto almost only been examined in small, simplified model systems. However, the exceptional applicability of calorimetry for the analysis of XB is well-reflected by the vast information gained from its use in the following study.

Ho et al. applied DSC for solution investigation of the stabilizing effect of a bromous halogen bond on a four-stranded DNA junction.⁸⁴ The DNA construct studied was observed to undergo a concentration-dependent transition from a duplex geometry to a junction. Two analogous DNA sequences were synthesized differing only in a strategic H to Br substitution and permitting HB or XB to a phosphate oxygen. The energetic gain upon XB (ΔE_{XB-HB}) was assessed by estimation of the difference in the melting energies at high and low concentrations of the halogen and hydrogen bonded constructs with the presumption that the single-stranded H and Br forms are energetically equivalent. At low concentrations (15-20 μM), a duplex to single-strand transition, whereas at high concentrations simultaneously a four-stranded junction to single-strand transition was identified. DSC measurements were performed by concentration alteration of the construct and acquisition of the melting energies of the conformational transitions. The stabilizing effect of the bromous halogen bond relative to a comparable hydrogen bond on the studied DNA junction was determined to be ~ 20 $kJmol^{-1}$ and was attributed to electrostatic and dispersion forces. The enthalpic gain was associated with a negative entropy ($T\Delta S \sim -8$ $kJmol^{-1}$ at 298K) yielding an overall stabilization free energy of -

12 kJmol⁻¹. The hydrophobic and steric effects of the bromine substitution were assessed by investigation of a methyl analogue (bromouracil to methyluracil substitution) of the construct, presuming comparable hydrophobicity and size of a CH₃ group as compared to Br but lack of the electrostatic component. This comparison suggested a 2 kJmol⁻¹ destabilization of the halogenated DNA junction originating from steric effects. The authors suggest that the enthalpic differences between the stability of the hydrogen and halogen bonded adducts in solution provides a direct measure of halogen bonding in biomolecular systems. Besides the major advantage of smooth applicability to biomolecules, the main limitation of calorimetry is that it requires comparatively high concentrations for studies of weak binders, and in contrast to NMR spectroscopy it does not inherently provide detailed structural information. It allows straightforward detection and thermodynamic characterization of binding, but it does not permit direct elucidation of an unknown binding site. Upon comparison of closely related, rationally varied analogues, an atomic level interpretation is possible.

4. Conclusions and outlook

For the writing of this review, the critical evaluation of all the available literature data was not attempted, but light has been shed on a few outstanding examples of studies attempting methods development for the accurate detection and description of the behaviour of XB in solution. The examples indicate the present state of the art and the immense activity in the field. Optical spectroscopy was utilized early on, and the data collected over decades has provided the basis for the recently developed measurement of the halogen bond acceptor ability of solvents: the diiodine basicity scale.⁴⁵ Despite its inexpensiveness, use of UV-VIS spectroscopy has lately decreased as its applicability is limited to a narrow range of compounds having suitable absorption properties and as a consequence of the emergence of advanced spectroscopic techniques that provide detailed, atomic level information. The main advantage of vibrational spectroscopy (IR and Raman) is its rapid time scale whereas its major weakness is its limited applicability for complex molecules possibly giving overlapping bands and thereby spectra that may be difficult to interpret. Technical developments, such as the advance of 2D-IR, providing higher spectral resolution, and of reliable computational spectrum prediction methods are expected to significantly widen the use of vibrational spectroscopies. Although calorimetry is only capable of measuring the overall heat changes of equilibrium processes, and in that aspect shows similarities to optical spectroscopy, its use in a comparative manner was demonstrated to provide detailed thermodynamic information on a sub-molecular level. The abilities of NMR spectroscopy to follow tiny electron density alterations, to provide nucleus specific information and to give detailed thermodynamic data have arguably made NMR spectroscopy the most important tool for the investigation of XB. It has become a useful technique for investigation of a wide range of compounds, from small molecular model systems to complex proteins. ESR is capable of the determination of thermodynamic parameters of XB in solution; however, in its present form its scope is limited to complexes of radicals with small, chemically inert species.

Solution studies have confirmed most previous computational

predictions and crystallographic observations regarding the strength of XB, which in general parallels the trends in charge transfer capabilities (I > Br > Cl > F; N > S ≥ O). Yet, a charge transfer mechanism alone is unable to explain the results of solution studies of the Z-X...LB' interaction.^{44, 57} Electrostatic models have been shown to be successfully applicable for the interpretation of the differences between XB donors using small aromatic model systems.³⁵ Nevertheless, the limitations of a purely electrostatic interpretation of XB are apparent from studies of solvent effects. Strong XB interactions are more favourable in polar, competitive solvents than expected based on predictions of an entirely electrostatic model, which in turn points to the possible ability of XB to a certain degree to compete with other weak interactions in biologically relevant yet barely investigated environments.⁷⁵ Studies of more complex structures confirm the limits of a purely electrostatic explanation of XB as well as imply subtle differences between the mechanisms of HB and XB.^{31, 35} Besides the, to our present understanding, dominant electrostatic mechanism, the contributions of charge transfer,⁴⁴ polarisation and dispersion⁶⁸ are important, especially for the strongest XB interactions formed by I donors. For a unified description of the relative importance of the above forces, further studies are required.

Achievement of a detailed understanding of the behaviour of XB in polar environments will enable its wide-ranging use in the material science and pharmaceutical tool boxes as a complementary device to well-explored weak interaction forces. A further motivation for additional studies is the inaccessibility of computational tools for accurate prediction of the structure-energy relationships of halogens, which to date severely hinders the application of XB in rational drug design strategies.

A variety of approaches have been borrowed from closely related research fields for the description of XB in solutions. The applied models were commonly simplistic in structure and often perfluorinated to achieve the strongest possible interactions. Whereas such studies undoubtedly provide immense information for an improved theoretical understanding of the mechanisms of the formation of halogen-bonded complexes, most are inapplicable for the assessment of complex, real-life molecular systems of general interest. As organic halides used in pharmaceuticals and as synthetic intermediates as well as those isolated from plants lack perfluorination, their XB interactions are significantly weaker than those detectable by most available methods. Hence, the limitations in sensitivity and in accuracy make most techniques at hand inapplicable for investigations of polar solutions. The fact that molecules of general interest do not contain ¹⁹F NMR reporter nuclei causes further complications. Given the impact that halogenations can have on biological activity^{4, 85, 86} and chemical reactivity⁸⁷ there is an urgent need for the development of further, more sensitive techniques applicable to real-life systems. As most biological processes take place in solutions, future experimental solution studies utilizing techniques of improved sensitivities are expected to be of tremendous scientific impact.

Acknowledgements

The Swedish Research Council (2007:4407) is gratefully acknowledged for financial support. The research leading to these

results has received funding from the European Research Council under the European Community's Seventh Framework Programme (FP/2007-2013)-ERC grant agreement 259638.

Notes and references

^a Department of Chemistry and Molecular Biology, University of Gothenburg, Kemivägen 10, SE-41296 Gothenburg, Sweden. Fax: +46 31 772 1394; Tel: +46 31 786 9033; E-mail: mate@chem.gu.se

^b Swedish NMR Centre, Medicinareg. 5c, SE-41390 Gothenburg, Sweden.

‡ In similarity to conventional, covalently bonded halogens, the electron density distribution of partially ionic character in the cited study is anisotropic. In a strong ligand field, their electron configuration is $p_x^2 p_y^2 p_z^0$ providing an equator of large electron density and an electropositive axis (p_z^0) available for sp hybridization with the s orbital at the next higher energy level. The positive charge is partially distributed into the XB donor of the bonded ligand and the interaction is best described as covalent with an ionic character.^{88, 89}

1. L. K. Steinrauf, J. A. Hamilton, B. C. Braden, J. R. Murrell and M. D. Benson, *J Biol Chem*, 1993, **268**, 2425-2430.
2. B. D. Darimont, R. L. Wagner, J. W. Apriletti, M. R. Stallcup, P. J. Kushner, J. D. Baxter, R. J. Fletterick and K. R. Yamamoto, *Genes Dev*, 1998, **12**, 3343-3356.
3. W. Wu, M. K. Samoszuk, S. A. Comhair, M. J. Thomassen, C. F. Farver, R. A. Dweik, M. S. Kavuru, S. C. Erzurum and S. L. Hazen, *J Clin Invest*, 2000, **105**, 1455-1463.
4. C. G. Wermuth, *The Practice of Medicinal Chemistry*, 3rd Edition edn., Elsevier Ltd, China, 2008.
5. G. W. Gribble, *Accounts Chem Res*, 1998, **31**, 141-152.
6. C. S. Neumann, D. G. Fujimori and C. T. Walsh, *Chem Biol*, 2008, **15**, 99-109.
7. P. Metrangolo and G. Resnati, *Science*, 2008, **321**, 918-919.
8. H. Sun, C. E. Keefer and D. O. Scott, *Drug Metab Lett*, 2011.
9. C. Nau and G. R. Strichartz, *Anesthesiology*, 2002, **97**, 497-502.
10. E. I. Eger, 2nd, D. D. Koblin, R. A. Harris, J. J. Kendig, A. Pohorille, M. J. Halsey and J. R. Trudell, *Anesth Analg*, 1997, **84**, 915-918.
11. N. P. Franks and W. R. Lieb, *Nature*, 1978, **274**, 339-342.
12. L. G. J. Wade, *Organic Chemistry*, 7 edn., Pearson Education Inc., Upper Saddle River, 2010.
13. J. McMurry, *Organic Chemistry*, 3 edn., Wadsworth Inc., Belmont, 1992.
14. A. Kovacs and Z. Varga, *Coordin Chem Rev*, 2006, **250**, 710-727.
15. N. Ramasubbu, R. Parthasarathy and P. Murrayrust, *J Am Chem Soc*, 1986, **108**, 4308-4314.
16. G. R. Desiraju and R. Parthasarathy, *J Am Chem Soc*, 1989, **111**, 8725-8726.
17. P. Metrangolo, H. Neukirch, T. Pilati and G. Resnati, *Acc Chem Res*, 2005, **38**, 386-395.
18. P. Metrangolo, G. Resnati, T. Pilati and S. Biella, *Struct Bond*, 2008, **126**, 105-136.
19. S. L. Price, A. J. Stone, J. Lucas, R. S. Rowland and A. E. Thornley, *J Am Chem Soc*, 1994, **116**, 4910-4918.
20. J. P. M. Lommerse, A. J. Stone, R. Taylor and F. H. Allen, *J Am Chem Soc*, 1996, **118**, 3108-3116.
21. P. Politzer, P. Lane, M. C. Concha, Y. G. Ma and J. S. Murray, *J Mol Model*, 2007, **13**, 305-311.
22. J. S. Murray, Z. P. Shields and P. Politzer, *Int J Quantum Chem*, 2010, **110**, 2823-2832.
23. D. M. P. Mingos, ed., *Halogen Bonding, Fundamentals and Applications*, Springer-Verlag, Berlin, 2008.
24. P. Politzer, J. S. Murray and T. Clark, *Phys Chem Chem Phys*, 2010, **12**, 7748-7757.
25. E. Parisini, P. Metrangolo, T. Pilati, G. Resnati and G. Terraneo, *Chem Soc Rev*, 2011, **40**, 2267-2278.
26. F. Guthrie, *Journal of Chemical Society*, 1863, **16**, 239-244.
27. O. Hassel, *Science*, 1970, **170**, 497-502.
28. G. Resnati and P. Metrangolo, *Chem-Eur J*, 2001, **7**, 2511-2519.
29. T. Clark, M. Hennemann, J. S. Murray and P. Politzer, *J Mol Model*, 2007, **13**, 291-296.
30. A. Bondi, *J Phys Chem-U.S.*, 1964, **68**, 441-&.
31. A. C. C. Carlsson, Gräfenstein, J.; Laurila, J. L.; Bergquist, J.; Erdelyi, M., *Chem Commun*, 2011, **48**, 1458-1460.
32. P. Metrangolo and G. Resnati, *Science*, 2008, **321**, 918-919.
33. Q. Z. Li, B. Jing, R. Li, Z. B. Liu, W. Z. Li, F. Luan, J. B. Cheng, B. A. Gong and J. Z. Sun, *Phys Chem Chem Phys*, 2011, **13**, 2266-2271.
34. T. Dipaolo and C. Sandorfy, *Nature*, 1974, **252**, 471-472.
35. M. G. Sarwar, B. Dragisic, L. J. Salsberg, C. Gouliaras and M. S. Taylor, *J Am Chem Soc*, 2010, **132**, 1646-1653.
36. A. R. Voth, P. Khuu, K. Oishi and P. S. Ho, *Nat Chem*, 2009, **1**, 74-79.
37. D. A. Kraut, M. J. Churchill, P. E. Dawson and D. Herschlag, *ACS Chem Biol*, 2009, **4**, 269-273.
38. M. Sekine, R. Tawarada and K. Seio, *J Org Chem*, 2008, **73**, 383-390.
39. A. Lachman, *J Am Chem Soc*, 1903, **25**, 50-55.
40. J. Kleinberg and A. W. Davidson, *Chem Rev*, 1948, **42**, 601-609.
41. E. E. Havinga and E. H. Wiebenga, *Recl Trav Chim Pay B*, 1959, **78**, 724-738.
42. C. G. Laurence, Jean-Francois, *Lewis basicity and affinity scales: Data and measurement*, John Wiley & Sons Ltd, Wiltshire, UK, 2010.
43. O. J. Walker, *Transactions of the Faraday Society*, 1935, **31**, 1432-1438.
44. P. Metrangolo, W. Panzeri, F. Recupero and G. Resnati, *J Fluor Chem*, 2002, **114**, 27-33.
45. C. Laurence and J.-F. Gal, *Lewis Basicity and Affinity Scales. Data and Measurement*, 1 edn., John Wiley & Sons Ltd, Chircester, UK, 2010.
46. M. Berthelot, M. Helbert and C. Laurence, *Cr Acad Sci Ii*, 1982, **295**, 1093-1096.
47. P. Nicolet and C. Laurence, *J Chim Phys Pcb*, 1983, **80**, 677-680.
48. P. L. Wash, S. Ma, U. Obst and J. Rebek Jr., *J Am Chem Soc*, 1999, **121**, 7973-7974.
49. M. G. Chudzinski, C. A. McClary and M. S. Taylor, *J Am Chem Soc*, 2011, **133**, 10559-10567.
50. J. Yarwood and W. B. Person, *J Am Chem Soc*, 1968, **90**, 594-.
51. C. Laurence, M. Queignecabaretos, T. Dziembowska, R. Queignec and B. Wojtkowiak, *J Am Chem Soc*, 1981, **103**, 2567-2573.
52. H. Stammreich, R. Forneris and Y. Tavares, *Spectrochim Acta*, 1961, **17**, 1173-1184.
53. P. Klabeo, *J Am Chem Soc*, 1967, **89**, 3667-3676.
54. H. Fan, J. K. Eliason, A. C. Moliva, J. L. Olson, S. M. Flancher, M. W. Gealy and D. J. Ulness, *J Phys Chem A*, 2009, **113**, 14052-14059.
55. D. Hauchecorne, A. Moiana, B. J. van der Veken and W. A. Herrebout, *Phys Chem Chem Phys*, 2011, **13**, 10204-10213.
56. D. Hauchecorne, R. Szostak, W. A. Herrebout and B. J. van der Veken, *Chemphyschem*, 2009, **10**, 2105-2115.
57. J. F. Bertran and M. Rodriguez, *Org Magn Reson* 1979, **12**, 92-94.
58. J. F. Bertran and M. Rodriguez, *Org Magn Reson*, 1980, **14**, 244-246.
59. J. F. Bertran and M. Rodriguez, *Org Magn Reson*, 1981, **16**, 79-81.
60. J. F. R. Bertran, Maria, *Revisita Ciencias Quimicas*, 1982, **13**, 1-8.
61. N. Kobayashi, S. Honda, H. Yoshii and E. Munekata, *Biochemistry*, 2000, **39**, 6564-6571.
62. G. Resnati, M. T. Messina, P. Metrangolo, W. Panzeri and E. Ragg, *Tetrahedron Lett*, 1998, **39**, 9069-9072.
63. R. Glaser, N. Chen, H. Wu, N. Knotts and M. Kaupp, *J Am Chem Soc*, 2004, **126**, 4412-4419.
64. C. Laurence, M. Queignecabaretos and B. Wojtkowiak, *J Chem Soc Perk T 2*, 1982, 1605-1610.
65. C. Laurence, M. Queignecabaretos and B. Wojtkowiak, *Can J Chem*, 1983, **61**, 135-138.
66. R. Cabot and C. A. Hunter, *Chem Commun*, 2009, 2005-2007.
67. K. R. Yamamoto, B. D. Darimont, R. L. Wagner, J. W. Apriletti, M. R. Stallcup, P. J. Kushner, J. D. Baxter and R. J. Fletterick, *Gene Dev*, 1998, **12**, 3343-3356.
68. C. D. Tatko and M. L. Waters, *Org Lett*, 2004, **6**, 3969-3972.
69. A. J. Maynard, G. J. Sharman and M. S. Searle, *J Am Chem Soc*, 1998, **120**, 1996-2007.
70. M. Varedian, M. Erdelyi, A. Persson and A. Gogoll, *J Pept Sci*, 2009, **15**, 107-113.

-
71. J. S. Murray, P. Metrangolo, T. Pilati, P. Politzer, G. Resnati and G. Terraneo, *Cryst Growth Des*, 2011, **11**, 4238-4246.
72. W. A. Herrebout, D. Hauchecorne, B. J. van der Veken and P. E. Hansen, *Chem Phys*, 2011, **381**, 5-10.
- 5 73. A. Mele, P. Metrangolo, H. Neukirch, T. Pilati and G. Resnati, *J Am Chem Soc*, 2005, **127**, 14972-14973.
74. M. S. Taylor, M. G. Sarwar, B. Dragisic and S. Sagoo, *Angew Chem Int Edit*, 2010, **49**, 1674-1677.
75. E. Dimitrijevic, O. Kvak and M. S. Taylor, *Chem Commun*, 2010, **46**,
10 9025-9027.
76. N. L. Kilah, M. D. Wise, C. J. Serpell, A. L. Thompson, N. G. White, K. E. Christensen and P. D. Beer, *J Am Chem Soc*, 2010, **132**, 11893-11895.
77. C. L. Perrin, *Accounts Chem Res*, 2010, **43**, 1550-1557.
- 15 78. J. Emsley, *Chem Soc Rev*, 1980, **9**, 91-124.
79. M. Saunders, L. Telkowski and M. R. Kates, *J Am Chem Soc*, 1977, **99**, 8070-8071.
80. V. Mugnaini, C. Punta, R. Liantonio, P. Metrangolo, F. Recupero, G. Resnati, G. F. Pedulli and M. Lucarini, *Tetrahedron Lett*, 2006, **47**,
20 3265-3269.
81. C. Cavallotti, P. Metrangolo, F. Meyer, F. Recupero and G. Resnati, *J Phys Chem A*, 2008, **112**, 9911-9918.
82. G. R. Hanson, P. Jensen, J. McMurtrie, L. Rintoul and A. S. Micallef, *Chem-Eur J*, 2009, **15**, 4156-4164.
- 25 83. E. Corradi, S. V. Meille, M. T. Messina, P. Metrangolo and G. Resnati, *Angew Chem Int Ed Engl*, 2000, **39**, 1782-1786.
84. M. Carter and P. S. Ho, *Cryst Growth Des*, 2011, **11**, 5087-5095.
85. J. Zhou, K. Gupta, S. Aggarwal, R. Aneja, R. Chandra, D. Panda and H. C. Joshi, *Molecular Pharmacology*, 2003, **63**, 799-807.
- 30 86. L. A. Hardegger, B. Kuhn, B. Spinnler, L. Anselm, R. Ecabert, M. Stihle, B. Gsell, R. Thoma, J. Diez, J. Benz, J. M. Plancher, G. Hartmann, D. W. Banner, W. Haap and F. Diederich, *Angew Chem Int Ed Engl*, 2011, **50**, 314-318.
87. S. M. Walter, F. Kniep, E. Herdtweck and S. M. Huber, *Angew Chem Int Ed Engl*, 2011.
35
88. G. H. Y. Lin and H. Hope, *Acta Crystall B-Stru*, 1972, **B 28**, 643-646.
89. N. W. Alcock and G. B. Robertson, *J Chem Soc Dalton*, 1975, 2483-2486.

40