HHS Public Access

Author manuscript

Acc Chem Res. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

Acc Chem Res. 2019 October 15; 52(10): 2870–2880. doi:10.1021/acs.accounts.9b00189.

Hydrogen bond enhanced halogen bonds: A synergistic interaction in chemistry and biochemistry

Asia Marie S. Riel[1], **Rhianon K. Rowe**[2], **Ethan N. Ho**[2], **A. K. Rappé**[3], **Orion B. Berryman**[1,*], **P. Shing Ho**[2,*]

[1]Department of Chemistry & Biochemistry, University of Montana, Missoula, MT

[2]Department of Biochemistry & Molecular Biology, Colorado State University, Fort Collins, CO

[3]Department of Chemistry, Colorado State University, Fort Collins, CO

Conspectus

The halogen bond (XB) has become an important tool for molecular design in all areas of chemistry, including crystal and materials engineering, and medicinal chemistry. Its similarity to the hydrogen bond (HB) makes the relationship between these interactions complex—at times competing against, other times orthogonal to each other. sRecently, our two laboratories have independently reported and characterized a new synergistic relationship, in which the XB is enhanced through direct intramolecular HBing to the electron-rich belt of the halogen. In one study, intramolecular HBing from an amine, polarized iodopyridinium XB donors in a bidentate anion receptor, resulting HB enhanced XB (or HBeXB) preorganized and further augmented the donors. Consequently, the affinity of the receptor for halogen anions was significantly increased. In a parallel study, a *meta*-chlorotyrosine was engineered into T4 lysozyme, resulting in an HBeXB that increased the thermal stability and activity of the enzyme at elevated temperatures. Computational studies on the two systems show that the HBeXB extends the range of interaction energies to being significantly greater than that of the XB alone. Additionally, surveys of structural databases indicate that the components for this interaction are already present in many existing molecular systems; however, the HBeXB has not been previously recognized. The confluence of the independent studies from our two laboratories demonstrates the reach of the HBeXB across both chemistry and biochemistry, and that intentional engineering of this enhanced interaction will extend the applications of XBs beyond these two initial examples.

Introduction

The Hydrogen Bond

The hydrogen bond (HB) has become a central topic in chemistry, since it was first described in water nearly a century ago.[1–4] In structural biochemistry HBs are the primary noncovalent interactions that define the functional conformations of nucleic acids and proteins.[5–7] More recently, the halogen bond (XB),[8] and its cousins (*e.g.,* the chalcogen,

*Corresponding Authors: Orion.Berryman@mso.umt.EDU, Shing.Ho@ColoState.EDU.

pnictogen, and tetrel bonds are becoming increasingly recognized as important contributors to molecular assembly and recognition across diverse fields of chemistry, chemical engineering, and biology.[9] The relationships between these various noncovalent interactions can be complex, particularly when two or more are present in the same system.[10–12] Here, we highlight a synergistic relationship, recently described separately in a chemical and a biochemical system, in which an HB greatly enhances the XB potential of a halogen substituent. The principle behind this HB enhanced XB (HBeXB for short) can potentially be applied to other pairs of noncovalent interactions, thereby extending their range of energies and, consequently, applications as design tools for molecular engineering.

HBs[13] share similar characteristics yet important differences with XBs.[8] The initial description of the HB as primarily an electrostatic interaction has its roots with Pauling,[2] who described the electropositive nature of a hydrogen of water as being attributed to the high electronegativity of the bonded oxygen. The result is that the positive region of the O–H dipole (as the HB donor) aligns with the electronegative lone pair of an adjacent electron-rich acceptor (typically an O, N, S or, importantly for this discussion, a halogen).

The Halogen Bond

The XB can similarly be described as primarily an electrostatic interaction, with a halogen substituent serving as the analogous donor to an electron-rich XB acceptor.[8] In this case, the electropositive potential of the donor can be attributed to depletion of the p_Z-molecular orbital of the halogen as its valence electron becomes subsumed in forming a σ-covalent bond—the σ-hole theory.[14] An important distinction is that the halogen maintains an electronegative belt around its equator, orthogonal to this electron-depleted σ-hole. Thus, the halogen can serve both as an XB donor in line with the covalent σ-bond and as an HB acceptor perpendicular to the bond (Figure 1b). This electronic representation also highlights the greater directionality observed for XBs, as well as the hierarchy of I > Br > Cl >> F as XB donors.[14]

This purely electrostatic σ-hole model is complemented by other considerations. In fact, the XB, previously referred to as a charge-transfer bond,[16,17] received early recognition in the context of crystal engineering,[18] and has since been exploited as a molecular design tool in chemistry (most prominently in the past two decades).[9] There are arguments to be made that support the steric repulsion, dispersion, polarization and the original concept of charge transfer as a significant contributor to this interaction. Indeed, high-level quantum mechanical (QM) analyses indicate that the strong directionality of the XB can be attributed primarily to dispersion rather than purely electrostatic forces.[19] It is likely that the richest understanding of this interaction comes from a description including electrostatic, charge-transfer and covalent principles. Additionally, the dominant characteristic will depend on the particular XB donor and acceptor being studied. We will, however, rely primarily on the σ-hole electrostatic model for this discussion, but with a recognition that it may not be complete in its description of the observed effects.

The Halogen Bond in Chemistry

The study of XBs in chemistry has become one of the fastest growing research areas in the past decade.[9] This noncovalent interaction was overlooked for the majority of the past two centuries despite early evidence that molecular halogens (I_2, Br_2 and Cl_2) can form complexes with ammonia.[20] Initial theoretical and solid-state studies focused primarily on inorganic XB donors. Building upon influential work of primarily inorganic XB donor complexes, the tunability and geometry of organic based XB donors has been elegantly detailed and employed in crystal engineering,[21,22] computational studies,[23,24] catalysis,[25,26] liquid crystals,[27] drug design,[28,29] self-assembly[30–33] and solution studies.[34,35]

The Halogen Bond in Biochemistry

XBs relevant in biology were first recognized from a survey of the Protein Data Bank (PDB[36]), which found the prevalence of short-range interactions involving halogens in the crystal structures of biomolecules.[37] This and subsequent surveys show that XB donors are predominantly found in halogenated inhibitors, while the dominant acceptors are carbonyl oxygens of peptide bonds in proteins (although various amino acid side chains also provide oxygen, nitrogen, and aromatic acceptors).[38] The structure-energy relationships of biological XBs have been characterized in both DNAs[39] and model proteins,[40,41] and reflect the general trend that I > Br > Cl as XB donors, with F considered primarily only as an occasional HB acceptor.[15]

Interplay Between HBing and XBing

The similarity between HBs and XBs makes the relationship and interplay between the two interactions interesting and important.[12] From the perspective of a common acceptor atom, the two interactions can be competitive[11] or energetically orthogonal[39] to each other (Figure 2 a and b). For example, Aakeröy et al. have evaluated competition between XBs and HBs in crystal engineering, that resulted in techniques to avoid HB and XB "synthon crossover."[11] In a series of studies on model DNA systems, the competition between these two interactions led to estimates for the energies of XBs in biological environments.[42] Voth, *et al.* highlighted a geometric and energetic orthogonality between the HB and XB when simultaneously interacting with a carbonyl oxygen in proteins.[39] This concept has inspired several small molecule mimics such as cocrystallization of N-methylacetamide and N-methylbenzamide with select iodinated XB donors in the solid state[43] and amino acid complexes in solution.[44]

The polarized halogens and its cousins are amphoteric[45,46] and thus can serve both as an XB donor (in the direction of the σ-hole) and/or an HB acceptor (perpendicular the σ-hole) (Figure 2c). In this review we introduce the HBeXB as a polarization enhanced noncovalent interaction—where the σ–hole of the XB donor is directly enhanced through polarization by an HB to the electronegative waist of the halogen (Figure 2c).

Until now, the direct interplay between XBs and HBs has been primarily studied by gas phase calculations. Computational studies by Li *et al.* on the cooperativity between the XB and the HB in $NH_3\cdots XX\cdots HF$ (X = F, Cl, Br) complexes showed that XBs in a triad were strengthened by HB interactions with HF.[47] This is an example of an indirect polarization

enhanced XB, however it would not be considered an HBeXB because the polarization does not occur through direct interaction with the donor atom. In another computational example, Lin, *et al.* evaluated intermolecular HBs on XB donors in ligand-protein binding.[48] Their quantum mechanical (QM) calculations and survey of the PDB found a significant contribution in protein-ligand binding when a XB accepted HBs. Finally, early studies were published by Laurence *et al.* showing how a "hydrogen-bond-assisted iodine bond" (a theoretical HBeXB) between thioamides and thioureas and iodine increased the Lewis basicity of the iodine. They concluded that molecular iodine is electronically amphoteric, allowing it to form augmented XBs when also accepting HBs.[49] Although there are computational studies to suggest enhancement of XBs with HBs, experimental examples are rare.[50,51] Our two labs were the first to experimentally examine the nature and limitations of HBing to a XB donor in chemical and biochemical systems. Nevertheless, systematic studies to understand and quantify the effect of the HB on the XB are critically lacking resulting in few applications taking advantage of the amphoteric nature of the XB.

Experimental Characterization of the HBeXB

We present here the experimental descriptions of a previously unquantified relationship, in which an HB to a halogen substituent increases the XB donating potential. This HBeXB was recognized in a bidentate halide receptor[52] and, independently, with a *meta*-halotyrosine modified enzyme.[53] The manifestation of HBeXBs in both small molecules and a protein suggests this synergistic interaction will be widely relevant across the fields of chemistry. In this account, we summarize the studies characterizing the HBeXBs in these two experimental systems. In addition, we present results from surveys of structural data bases indicating that HBeXBs are highly prevalent across a broad range of chemical compounds and complexes.

HBeXB Increases Anion Binding

The Berryman laboratory recently developed bisethynyl pyridinium XBing receptors that bind anions and neutral Lewis bases in a bidentate fashion.[54,55] The alkynes promote rigidity and directionality; however, their low rotational barrier allowed the scaffolds to adopt three planar binding conformations. After considering ways to preorganize the structure, we determined that macrocyclization and external intramolecular HBs (away from the binding site) were not synthetically tractable. Instead, we introduced an electron-deficient aniline to HB to the electron-rich belt of the XB donors. This internal intramolecular HB was a unique departure from traditional preorganization techniques in that it also enhanced XB donor strength.

First generation 1,3-bisethynyl iodopyridinium **G1XB** (no intramolecular HB donor) and second generation **G2XB** (intramolecular HB and fluorine) receptors were recently synthesized (Figure 3). The HB's role in preorganization and enhanced XBing (in **G2XB**) as compared to our first-generation receptor (**G1XB**) was quantified by ^{1}H NMR titrations with chloride, bromide and iodide. Intramolecular HBeXBing increased halide binding by nearly 9-fold over **G1XB** (in 40 % $CDCl_3$/60% CD_3NO_2), which lacked the HBeXB. The halide K_{11} values for **G2XB** are 23,700 M^{-1} for Cl^-, 32,900 M^{-1} for Br^- and 36,900 M^{-1} for I^-. However, **G1XB** binds halides much more weakly with association constants of 2,630 M^{-1}

for Cl^-, 4,690 M^{-1} for Br^- and 4,380 M^{-1} for I^-. The second binding event (K_{12}) for all receptors is quite weak and presumably represents nonspecific ion pairing to balance charge. To further assess the HBeXB and verify that the amine is not the primary reason for the increase in binding strength, we compared **G2XB** to **G2HB**, which lacks the XB donors. We observed nearly an order of magnitude stronger binding for **G2XB** compared to **G2HB**—concluding that the amine does not significantly HB to the anions in this system. These first solution studies of HBeXBing demonstrate that intramolecular preorganization and enhanced XBing is operable and contributes to the improved halide recognition.

Simultaneous preorganization and enhancement of the XB was further confirmed by gas-phase computations (B3LYP, 6–31+G(d,p), aug-cc-pVTZ and LANDL2DZdp ECP). DFT single point energy calculations demonstrate that the bidentate conformation—with intramolecular HBs—is more stable than the conformation without HBs by 1.29 kcal/mol. Additionally, electrostatic potential (ESP) maps illustrate that **G2XB**, with the intramolecular HBeXBs contains a larger, more electrophilic σ-hole (Figure 4b) compared to **G1XB**, which lacks the HBeXBs (Figure 4a). Additional ESP maps of **G2XB** with no amine (Figure 4c) and **G2XB** with no fluorine (Figure 4d) verify that the enhanced polarization is caused by the intramolecular HBs from the amine. The magnitude by which HBing enhances bidentate XBing was calculated through interaction energies of **G2XB** and **G2XB-no NH_2** (with no amine therefore no intramolecular HBs) with Br^-. These energies with bromide highlight that the bidentate intramolecular HBeXBs in **G2XB** are over 3.2 kcal/mol stronger than solely the XBs in **G2XB-no NH_2**, which lacks the HBeXBs. These calculations suggest that a single HBeXB interaction in this system provides approximately 1.6 kcal/mol of stabilization. Together, these calculations corroborate the solution data and dual role of the intramolecular HBeXB to enhance the σ-hole and promote preorganization.

Crystallographic data with halide counteranions provided detailed structural evidence of HBeXBing (Figure 5). When the intramolecular HB is present, we observed a 5% contraction of the XB distances between methyl derivatives of **G2XB (G2XBme)** and both Br^- and I^- compared to **G1XB (G1XBme)**. Additionally, the intramolecular HBeXB preorganizes the complexes of **G2XB** and **G2XBme** with Br^- and I^- which promotes planarity in the receptor backbone. The pyridinium rings of **G1XBme** twist out of planarity up to 15°, however the addition of the HBing amine decreases ring twist by over half, with the smallest angle at 2.4°. The crystals of **G2XB** and **G2XBme** confirm that the intramolecular HBeXB can preorganize a receptor while simultaneously improving XB strength.

Solvatochromism and Fluorescence Response

During these initial studies, it became apparent that the fluoroaniline core–engendering HBeXBs–elicited unique photophysical effects compared to our first-generation receptors. **G2XB** and **G2HB** (both as neutral and charged species) exhibit solvatochromatic effects as well as anion induced fluorescence quenching.[56] Considering the directionality of the XB, we viewed this as an additional opportunity to evaluate possible selectivity of these systems for solvents or anions. In comparison to their neutral counterparts, the charged derivatives

exhibited opposite solvatochromism, which we attribute to their charged states and differences in binding ability.

Qualitative evaluation of anion sensing showed that anion-induced fluorescence quenching of **G2XB** was less efficient than **G2HB** with most anions. We hypothesized that loose bolt effect was occurring, which states that flexible groups or substituents absorb energy and induce nonradiative decay pathways to the ground state thus quenching fluorescence. The HBeXBs in **G2XB** preorganize the adjacent pyridinium rings, thus reducing their flexibility, and subsequent ability to induce nonradiative decay pathways. Through these studies it was discovered that **G2XB** can selectively sense I^- over other anions by a significant fluorescence quenching after the addition of one equivalent of tetra-*n*-butylammonium iodide. In contrast, the neutral and charged **G1XB** lacked these unique photophysical effects.

HBeXB Increases Enzyme Stability and Function

The growth in the development of polypeptide-based therapeutics spurred the Ho laboratory to determine whether XBs can be engineered to stabilize protein structures, using the enzyme T4 lysozyme (T4L) as the model system (Figure 6).[40] Within the active site of T4L, tyrosine residue (Y18) forms an HB to the carbonyl oxygen of a neighboring glutamate (E11) that is essential for the enzyme's structure and function. In order to determine whether an XB can replace this critical HB, we made T4L constructs in which Y18 was replaced by a halogenated phenylalanine (^{X}F18, where X = Cl, Br, or I).[40] As a control, we made analogous ^{X}F replacements at position Y88, a solvent exposed residue that cannot form XBs, and found these constructs to be destabilizing to the protein. The ^{X}F18-T4L constructs, however, formed XBs that replaced the essential HB of Y18, thus rescuing the stability of the protein (with Cl < Br < I) relative to the Y88 controls. The rescue, however, was incomplete, in that the engineered XB could not entirely compensate for the loss of stability and function afforded by the essential HB from the hydroxyl of Y18.

We next attempted to augment, rather than replace the critical hydroxyl HB of Y18 by introducing a halogen that can form an XB to a different, nearby carbonyl oxygen acceptor (at G28). {Carlsson, 2018 #24} This T4L variant was constructed by replacing Y18 with a *meta*-halotyrosine (^{mX}Y18). The engineered $^{m\mathrm{Cl}}$Y18-T4L indeed showed that the chlorine formed an XB to the peptide G28 backbone, resulting in a protein that was more thermally stable than the wildtype. The melting temperature (T_m) and melting enthalpy (ΔH_m) were both elevated (1° C and ~3 kcal/mol, respectively), as determined by differential scanning calorimetry (DSC). In addition, this chlorinated construct showed 15% greater enzymatic activity over the wildtype at 40° C.

The surprising aspect of these results was that the increased stabilization and elevated activity came from adding a single chlorinated substituent, while the brominated and iodinated variants (both expected to have larger σ-holes and therefore stronger XBs) had no effect or was destabilizing. The iodine of the $^{\mathrm{I}}$Y18 was too large to fit into the tight and rigid loop into which the halogen must sit and, thus, sat exposed to solvent, thereby destabilizing the protein. The $^{\mathrm{Br}}$Y18 placed the intermediate sized halogen partially exposed and partially XBed within the protein loop, with the stabilizing/destabilizing effects essentially neutralizing each other. Only the small chlorine fits into this loop to form a stabilizing XB.

The question, however, is why the Cl-XB of the ^{Cl}Y18 construct has such a significant stabilizing influence on this protein. We had previously shown that a Cl-XB to a very strong anionic oxygen acceptor could provide 0 to 0.5 kcal/mol of stabilizing potential in a DNA system, while Br- and I-XBs contributed 2 to >6 kcal/mol of enthalpic stability. Furthermore, quantum mechanical (QM) calculations suggest that a hydroxyl group should be electron donating to *ortho*-substituents (Figure 7) and, therefore, the chlorine of the ^{Cl}Y18 should be a weaker XB donor even compared to a ^{Cl}F. The solution to this conundrum came from considering not simply the standard substituent effects of the hydroxyl group, but also its ability to serve as an HB acceptor to the OH of the Y18 side chain. QM analyses on chlorophenol models indicate that the OH can rotate to form an intramolecular HB to the electronegative annulus of the chlorine; thus the σ-hole becomes enhanced, resulting in an XB-donor that is comparable to that of bromo- or iodobenzene in stabilizing potential. The significantly stronger XB interaction observed in ^{Cl}Y18-T4L can thus be attributed to this HBeXB. Such an intramolecular O–H···X HB is supported by calculations and experiments on halophenols in non-aqueous environments.[57] In addition to its enhanced stabilizing potential, the QM calculations also indicate that the σ-hole encompasses a larger area of the atomic surface and, therefore, the HBeXB also should show a broader range of angles (θ_1) for the approach of acceptors to the halogen XB donor.[53] The resulting enhanced XB in the ^{Cl}Y18 T4 lysozyme is thus the first recognition that an HBeXB can increase the stability and function of a biomolecule.

HBeXB in the Cambridge Structure Database and Protein Data Base

Interest in the XB has dramatically increased since the turn of the century, with the number of annual publications on the topic growing from <10 prior to 2000 to >450 in 2017. This dramatic increase parallels the application of XBs as a molecular design element in nearly all fields of chemistry. The XB is very similar to the HB in terms of their competing acceptors and interaction energies, but the more directional nature of the XB has been seen as a limitation, particularly in biomolecular engineering. However, the HBeXB has the potential to extend the application of XBs by not only increasing the strength of the interaction to be comparable to a traditional HB, but also expand the atomic surface encompassed by the electropositive σ-hole and, consequently, extending the angles at approach by the acceptor.

The experimental observations of HBeXBs in a small molecule anion receptor and in an engineered protein, involving various XB donors and HB donors suggest that this interaction is applicable across a wide range of chemical systems. We thus addressed the question of whether HBeXBs could be present in other chemical systems by surveying the Cambridge Structural Database (CSD[59]) for structures in which the basic elements of this interaction are present. Our initial survey searched for aromatic compounds with Cl, Br, or I that are *ortho*- to OH, or NH_2 substituents, and within short distance (≤105% of the sum of the van der Waals radii, $\sum R_{vdW}$) of an XB acceptor (O or N) of an interacting compound. This analysis identified 772 complexes, indicating that the potential for HBeXBs is very high, even with these very limited criteria.

A radial distribution plot of the XB donor approach to the acceptor (the θ_1-angle) showed that these interactions cluster around the σ-hole of the halogen ($\theta_1 \approx 180°$, Figure 8), as expected for XBs, but extending to the electronegative annulus ($\theta_1 \approx 90°$). It is interesting that at $\theta_1 \approx 180°$, the normalized XB distance ($R_{X\cdots(O/N)}$) does not extend beyond 100% of $\sum R_{vdW}$. However, detailed analysis of the distance from the acceptor to the halogen ($R_{X\text{-}A}$) and to the HB donor atoms ($R_{X\text{-}A}$) shows a significant number of these contacts are primarily HBs to the *ortho*–OH or –NH substituents, instead of HBs to the XB donors (Figure 8b). With these HBs removed from the dataset, the resulting radial analysis is even more highly clustered around the σ-hole, but more broadly distributed across θ_1-angles (with $R_{X\cdots(O/N)} \leq 1.0$ to < 135°) than seen in previous surveys of XBs (Figure 8c). An initial survey of the Protein Data Bank with these same limiting criteria identified over 1,000 structures with the components required to form HBeXBs, consistent with the previous survey by Lin, *et al.*[48] The difference, however, is that the results from our CSD survey now allows us to distinguish between HBs and potential HBeXBs in biomolecular structures. Thus, the two examples of HBeXBs found in the halide receptor and the model protein, as described here, are most likely not singular exceptions, but simply the first experimental recognition of a potentially prevalent molecular interaction.

Conclusion and Perspective

This review highlights the concept that an HB directly to the electron-rich region of a halogen augments its potential as an XB donor. The resulting HBeXB extends the stability and the geometry of an XB interaction, rendering it comparable and potentially stronger than a classical HB. While the concept of the HBeXB had previously been suggested, our studies are highlighted as the first experimental characterization of this synergistic relationship. Our initial surveys of the CSD and PDB highlight the strong likelihood that HBeXBs are common in both chemical and biochemical molecular systems.

Although we have now sampled HBeXBs at the two extremes of chemical complexity and with different pairs of XB and HB donors, there remain many aspects of polarization effects that are yet to be explored. For example, we expect that stronger a HB donor in these coordinated systems, will strengthen the XB donor potential of the halogen. Similarly, the geometry of the HB···X (the distance and angle of approach of the HB interaction) would affect the XB acceptor to donor geometry. A shorter HB, for example, would be expected to have a stronger polarizing effect on the σ-hole and, thus produce a stronger attractive force with the acceptor. Alternatively, the angle of approach of the HB to the halogen could affect the position of the σ-hole at the halogen surface, thereby affecting the approach θ_1-angle of the acceptor. Quantum calculations on simple model systems show that when the HB deviates from being perpendicular to the C–X bond (near the optimum 90° of the electronegative center), the most electropositive point of the σ-hole deviates from the ideal 180° along the C–X bond. Our research groups are studying these and other physical properties and effects on the HBeXB to better understand how we can rationally design the interaction for molecular and biomolecular engineering.

Finally, we highlight that the HBeXB is a type of polarization enhanced noncovalent cooperativity (Figure 9, green box, σ-bond cooperativity). As a subclass of noncovalent

cooperativity,[60] polarization enhanced XBs are unique—they can be polarized either directly through noncovalent interaction with the donor (e.g. HBeXB) or indirectly by noncovalent interaction with an adjacent atom that shares a σ-bond with the donor (Figure 9, red box). The generality of this approach is foreshadowed by a recent computational study showing that intramolecular HBs also can enhance tetrel bonds (HBeTeB) in fluorosilyl and fluorogermanium complexes.[61] The HBeXB and HBeTeB can be considered as two related subcategories of polarization enhanced noncovalent interactions (Figure 9, pink and orange boxes), where HBs and other noncovalent interactions can cooperatively strengthen or weaken the noncovalent bonding of polarizable atoms (such as halogen or tetrel substituents). While this strategy is only now being explored, it has the potential to extend the utility of these interactions in chemistry and biochemistry, providing powerful alternatives to the classic HB in molecular engineering.

References

(1). Latimer WM; Rodebush WH Polarity and Ionization from the Standpoint of the Lewis Theory of Valence. J. Am. Chem. Soc. 1920, 42, 1419–1433.

(2). Pauling LCN-QP 1960. The Nature of the Chemical Bond and the Structure of Molecules and Crystals; an Introduction to Modern Structural Chemistry, 3d ed.; Cornell University Press: Ithaca, N.Y., 1960.

(3). Smith DA A Brief History of the Hydrogen Bond In Modeling th Hydrogen Bond (ACS Symposium Series); Smith DA, Ed.; American Chemical Society: Washington DC, 1994; pp 1–4.

(4). Pimentel GC; McClellan AL The Hydrogen Bond; W. H. Freeman and Co.: San Francisco, 1960.

(5). Baker EN Hydrogen Bonding in Biological Macromolecules In International Tables for Crystallography Volume F: Crystallography of biological macromolecules; Rossmann MG, Arnold E, Eds.; Springer Netherlands: Dordrecht, 2001; pp 546–552.

(6). Saenger W Principles of Nucleic Acid Structure; Cantor CR, Ed.; Springer-Verlag: New York, 1984.

(7). Kuriyan J; Konforti B; Wemmer DE The Molecules of Life; Garland Science, Taylor & Francis Group: New York, NY, 2013.

(8). Desiraju GR; Ho PS; Kloo L; Legon AC; Marquardt R; Metrangolo P; Politzer P; Resnati G; Rissanen K Definition of the Halogen Bond (IUPAC Recommendations 2013). Pure Appl. Chem. 2013, 85, 1711–1713.

(9). Cavallo G; Metrangolo P; Milani R; Pilati T; Priimagi A; Resnati G; Terraneo G The Halogen Bond. Chem. Rev. 2016, 116, 2478–2601. [PubMed: 26812185]

(10). Metrangolo P; Resnati G Chemistry: Halogen versus Hydrogen. Science 2008, 321, 918–919. [PubMed: 18703728]

(11). Aakeröy CB; Panikkattu S; Chopade PD; Desper J Competing Hydrogen-Bond and Halogen-Bond Donors in Crystal Engineering. Cryst. Eng. Comm. 2013, 15, 3125–3136.

(12). Rowe RK; Ho PS Relationships between Hydrogen Bonds and Halogen Bonds in Biological Systems. Acta Crystallogr. B 2017, 73, 255–264.

(13). Arunan E; Desiraju GR; Klein RA; Sadlej J; Scheiner S; Alkorta I; Clary DC; Crabtree RH; Dannenberg JJ; Hobza P; Kjaergaard HG; Legon AC; Mennucci B; Nesbitt DJ Definition of the Hydrogen Bond (IUPAC Recommendations 2011). Pure Appl. Chem. 2011, 83, 1637–1641.

(14). Clark T; Hennemann M; Murray JS; Politzer P Halogen Bonding: The σ-Hole. J. Mol. Model. 2007, 13, 291–296. [PubMed: 16927107]

(15). Scholfield MR; Zanden CM; Carter M; Ho PS Halogen Bonding (X-Bonding): A Biological Perspective. Protein Sci. 2013, 22, 139–152. [PubMed: 23225628]

(16). Mulliken RS Molecular Compounds and Their Spectra III. The Interaction of Electron Donors and Acceptors. J. Phys. Chem. 1952, 56, 801–822.

(17). Hassel O Structural Aspects of Interatomic Charge-Transfer Bonding In Nobel lectures, Chemistry 1963–1970.; Elsevier publishing company: Amsterdam, 1972.

(18). Metrangolo P; Resnati G Halogen Bonding: A Paradigm in Supramolecular Chemistry. Chem. - Eur. J. 2001, 7, 2511–2519. [PubMed: 11465442]

(19). Riley KE; Vazquez M; Umemura C; Miller C; Tran KA Exploring the (Very Flat) Potential Energy Landscape of R-Br···π Interactions with Accurate CCSD(T) and SAPT Techniques. Chem. - Eur. J. 2016, 22, 17690–17695. [PubMed: 27786398]

(20). Guthrie F XXVIII.—On the Iodide of Iodammonium. J. Chem. Soc. 1863, 16, 239–244.

(21). Fourmigué M; Batail P Activation of Hydrogen- and Halogen-Bonding Interactions in Tetrathiafulvalene-Based Crystalline Molecular Conductors. Chem. Rev. 2004, 5379–5418. [PubMed: 15535654]

(22). Mukherjee A; Tothadi S; Desiraju GR Halogen Bonds in Crystal Engineering: Like Hydrogen Bonds yet Different. Acc. Chem. Res. 2014, 47, 2514–2524. [PubMed: 25134974]

(23). Legon AC The Halogen Bond: An Interim Perspective. Phys. Chem. Chem. Phys. 2010, 12, 7736–7747. [PubMed: 20495729]

(24). Karpfen A Theoretical Characterization of the Trends in Halogen Bonding. In Structure and Bonding; Springer Berlin Heidelberg, 2008; pp 1–15.

(25). Schubert US; Tepper R Halogen Bonding in Solution: From Anion Recognition through Templated Self-Assembly to Organocatalysis. Angew. Chem. Int. Ed. 2018, 10, 6004–6016.

(26). Bulfield D; Huber SM Halogen Bonding in Organic Synthesis and Organocatalysis. Chem. - Eur. J 2016, 22, 14434–14450. [PubMed: 27465662]

(27). Bruce DW Halogen-Bonded Liquid Crystals. In Structure and Bonding; 2008; pp 161–180.

(28). Lu Y; Shi T; Wang H; Yan X; Luo X; Jiang H; Zhu W Halogen BondingsA Novel Interaction for Rational Drug Design? J. Med. Chem. 2009, 52, 2854–2862. [PubMed: 19358610]

(29). Hardegger LA; Kuhn B; Spinnler B; Anselm L; Ecabert R; Stihle M; Gsell B; Thoma R; Diez J; Benz J Systematic Investigation of Halogen Bonding in Protein–Ligand Interactions. Angew. Chem. Int. Ed. 2011, 50, 314–318.

(30). Massena CJ; Wageling NB; Decato DA; Rodriguez EM; Rose AM; Berryman OB A Halogen-Bond-Induced Triple Helicate Encapsulates Iodide. Angew. Chem. Int. Ed. 2016, 12398–12402.

(31). Dumele O; Trapp N; Diederich F Halogen Bonding Molecular Capsules. Angew. Chem. Int. Ed. 2015, 54, 12339–12344.

(32). Corradi E; Meille SV; Messina MT; Metrangolo P; Resnati G Halogen Bonding versus Hydrogen Bonding in Driving Self-Assembly Processes. Angew. Chem. Int. Ed. 2000, 39, 1782–1786.

(33). Vanderkooy A; Taylor MS Solution-Phase Self-Assembly of Complementary Halogen Bonding Polymers. J. Am. Chem. Soc. 2015, 137, 5080–5086. [PubMed: 25867188]

(34). Erdelyi M Halogen Bonding in Solution. Chem. Soc. Rev. 2012, 41, 3547–3557. [PubMed: 22334193]

(35). Beale TM; Chudzinski MG; Sarwar MG; Taylor MS Halogen Bonding in Solution: Thermodynamics and Applications. Chem. Soc. Rev. 2013, 42, 1667–1680. [PubMed: 22858664]

(36). Berman HM; Westbrook J; Feng Z; Gilliland G; Bhat TN; Weissig H; Shindyalov IN; Bourne PE The Protein Data Bank. Nucleic Acids Res. 2000, 28, 235–242. [PubMed: 10592235]

(37). Auffinger P; Hays FA; Westhof E; Ho PS Halogen Bonds in Biological Molecules. Proc. Natl. Acad. Sci. U. S. A. 2004, 101, 16789–16794. [PubMed: 15557000]

(38). Sirimulla S; Bailey JB; Vegesna R; Narayan M Halogen Interactions in Protein-Ligand Complexes: Implications of Halogen Bonding for Rational Drug Design. J. Chem. Inf. Model. 2013, 53, 2781–2791. [PubMed: 24134121]

(39). Voth AR; Hays FA; Ho PS Directing Macromolecular Conformation by Halogen Bonds. Proc. Natl. Acad. Sci, 2007, 104, 6188–6193. [PubMed: 17379665]

(40). Scholfield MR; Ford MC; Carlsson AC; Butta H; Mehl RA; Ho PS Structure-Energy Relationships of Halogen Bonds in Proteins. Biochemistry 2017, 56, 2794–2802. [PubMed: 28345933]

(41). Danelius E; Andersson H; Jarvoll P; Lood K; Grafenstein J; Erdelyi M Halogen Bonding: A Powerful Tool for Modulation of Peptide Conformation. Biochemistry 2017, 56, 3265–3272. [PubMed: 28581720]

(42). Carter M; Voth AR; Scholfield MR; Rummel B; Sowers LC; Ho PS Enthalpy-Entropy Compensation in Biomolecular Halogen Bonds Measured in DNA Junctions. Biochemistry 2013, 52, 4891–4903. [PubMed: 23789744]

(43). Takemura A; McAllister LJ; Hart S; Pridmore NE; Karadakov PB; Whitwood AC; Bruce DW Halogen- and Hydrogen-Bonded Salts and Co-Crystals Formed from 4-Halo-2,3,5,6-Tetrafluorophenol and Cyclic Secondary and Tertiary Amines: Orthogonal and Non-Orthogonal Halogen and Hydrogen Bonding, and Synthetic Analogues of Halogen-Bonded Biological Syst. Chem. - Eur. J. 2014, 20, 6721–6732. [PubMed: 24796890]

(44). Vasylyeva V; Nayak SK; Terraneo G; Cavallo G; Metrangolo P; Resnati G Orthogonal Halogen and Hydrogen Bonds Involving a Peptide Bond Model. Cryst. Eng. Comm. 2014, 16, 8102–8105.

(45). Nelyubina YV; Antipin MY; Dunin DS; Kotov VY; Lyssenko KA Unexpected "Amphoteric" Character of the Halogen Bond: The Charge Density Study of the Co-Crystal of N-Methylpyrazine Iodide with I_2. Chem. Commun. 2010, 46, 5325–5327.

(46). Bui TT; Dahaoui S; Lecomte C; Desiraju GR; Espinosa E The Nature of Halogen···Halogen Interactions: A Model Derived from Experimental Charge-Density Analysis. Angew. Chem. Int. Ed. Engl. 2009, 48, 3838–3841. [PubMed: 19373823]

(47). Li Q; Lin Q; Li W; Cheng J; Gong B; Sun J Cooperativity between the Halogen Bond and the Hydrogen Bond in H3N···XY···HF Complexes (X, Y=F, Cl, Br). Chem. Phys. Chem. 2008, 9, 2265–2269. [PubMed: 18814160]

(48). Lin FY; MacKerell AD Jr. Do Halogen-Hydrogen Bond Donor Interactions Dominate the Favorable Contribution of Halogens to Ligand-Protein Binding? J. Phys. Chem. B 2017, 121, 6813–6821. [PubMed: 28657759]

(49). Laurence C; Graton J; Berthelot M; El Ghomari MJ The Diiodine Basicity Scale: Toward a General Halogen-Bond Basicity Scale. Chem. - Eur. J. 2011, 17, 10431–10444. [PubMed: 21834107]

(50). Laurence C; El Ghomari MJ; Le Questel J-Y; Berthelot M; Mokhlisse R Structure and Molecular Interactions of Anti-Thyroid Drugs. Part 3. Methimazole: A Diiodine Sponge. J. Chem. Soc. Perkins Trans. 2 1998, 1545–1551.

(51). Cristiani F; Devillanova FA; Garau A; Isaia F; Lippolis V; Verani G Charge-transfer Complexes between Some S-methylated Derivatives of 5, 5-dimethyl-2, 4-dithiohydantoin and Molecular Diiodine. A UV-Visible, IR, FT-Raman, and ^{13}C NMR Study. Heteroat. Chem. 1994, 5, 421–428.

(52). Riel AM; Decato DA; Sun J; Massena CJ; Jessop MJ; Berryman OB The Intramolecular Hydrogen Bonded–Halogen Bond: A New Strategy for Preorganization and Enhanced Binding. Chem. Sci. 2018, 9, 5828–5836. [PubMed: 30079195]

(53). Carlsson AC; Scholfield MR; Rowe RK; Ford MC; Alexander AT; Mehl RA; Ho PS Increasing Enzyme Stability and Activity through Hydrogen Bond-Enhanced Halogen Bonds. Biochemistry 2018, 57, 4135–4147. [PubMed: 29921126]

(54). Massena CJ; Riel AMS; Neuhaus GF; Decato DA; Berryman OB Solution and Solid-Phase Halogen and C–H Hydrogen Bonding to Perrhenate. Chem. Commun. 2015, 51, 1417–1420.

(55). Riel AMS; Jessop MJ; Decato DA; Massena CJ; Nascimento VR; Berryman OB; Experimental Investigation of Halogen-Bond Hard–Soft Acid–Base Complementarity. Acta Crystallogr. B 2017, 73, 203–209.

(56). Sun J; Riel AMS; Berryman OB Solvatochromism and Fluorescence Response of a Halogen Bonding Anion Receptor. New J. Chem. 2018, 42, 10489–10492.

(57). Abraham MH; Abraham RJ; Aliev AE; Tormena CF Is There an Intramolecular Hydrogen Bond in 2-Halophenols? A Theoretical and Spectroscopic Investigation. Phys. Chem. Chem. Phys. 2015, 17, 25151–25159. [PubMed: 26352197]

(58). Hammett LP The Effect of Structure upon the Reactions of Organic Compounds. Benzene Derivatives. J. Am. Chem. Soc. 1937, 59, 96–103.

(59). Groom CR; Bruno IJ; Lightfoot MP; Ward SC The Cambridge Structural Database. Acta Crystallogr. B 2016, 72, 171–179.

(60). Jeffrey GA Hydrogen-Bonding: An Update. Crystallogr. Rev. 1995, 4, 213–254.

(61). Trujillo C; Alkorta I; Elguero J; Sanchez-Sanz G Cooperative Effects in Weak Interactions: Enhancement of Tetrel Bonds by Intramolecular Hydrogen Bonds. Molecules 2019, 24, 308.

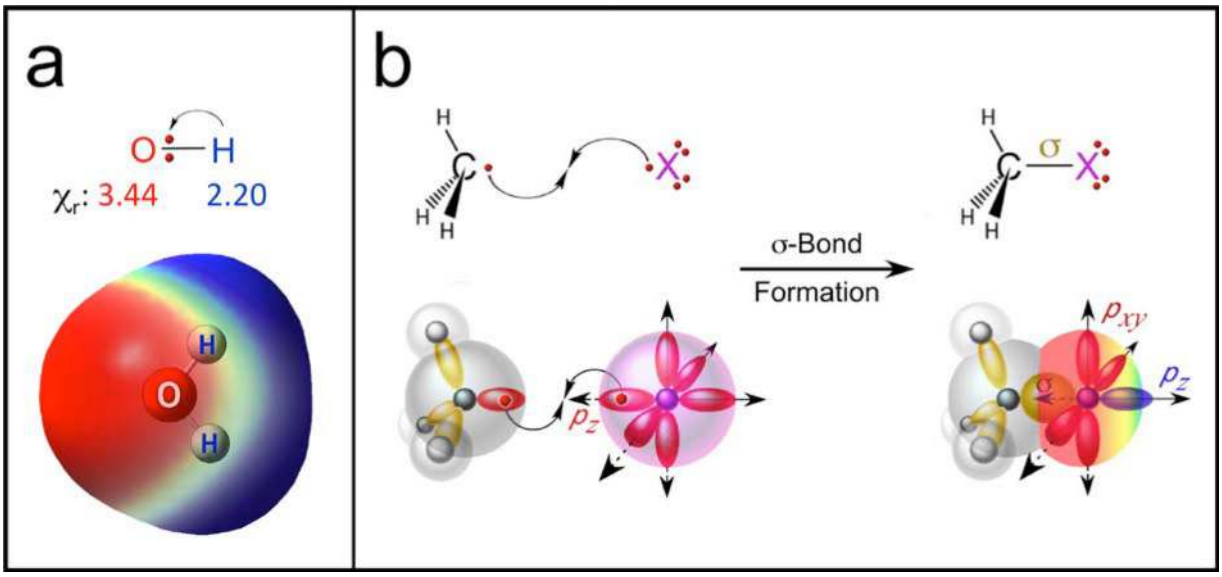

Figure 1.

Electrostatic models for the hydrogen bond (HB) and halogen bond (XB). **a.** In an OH bond, the more electronegative oxygen (reflected in the Pauling electronegativity scale, χ_r) draws more of the electron pair towards the oxygen, leaving an electropositive hydrogen to serve as the HB donor. This anisotropic distribution of charges is reflected in the electrostatic potential map calculated for water. **b.** The σ-hole model for an XB posits that in forming a covalent σ-molecular orbital, the pz orbital of the halogen (X) is depleted, resulting in an electropositive crown and slight flattening of the atom at the tip.[15]

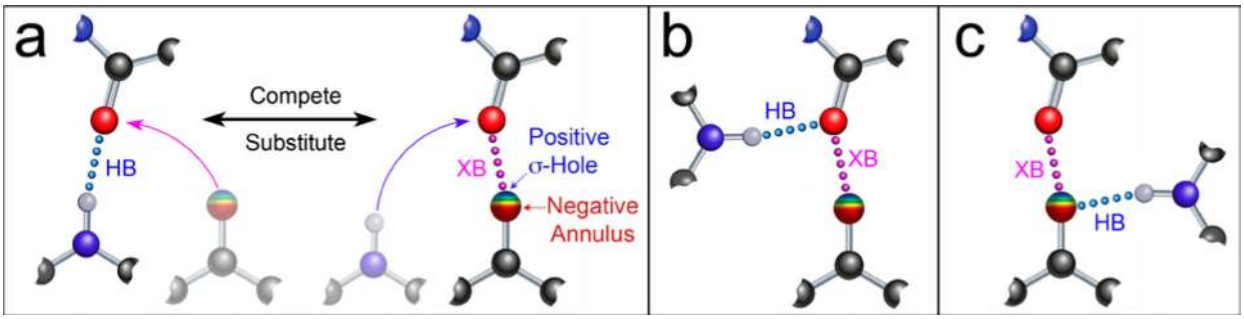

Figure 2.

Relationships between HB and XB donors and acceptors. **a.** Competitive XB and HB for an acceptor atom. **b.** Simultaneous HB and XB to an acceptor. **c.** HB to an amphoteric halogen that serves simultaneously as an XB donor. (Adapted from Rowe et al.[12])

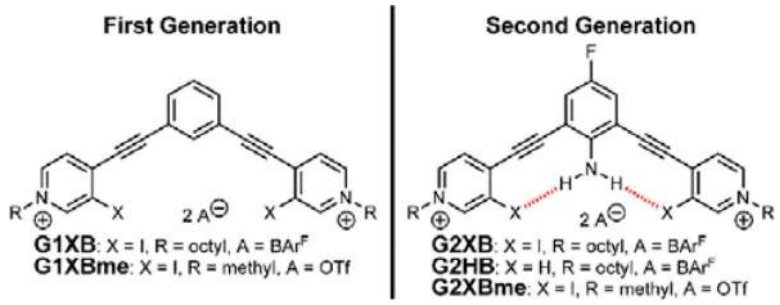

Figure 3:

Schematics of first generation XB receptor (**G1XB**) and second generation XB and HB receptors (**G2XB**). Syntheses can be found in the original publications.[52,54]

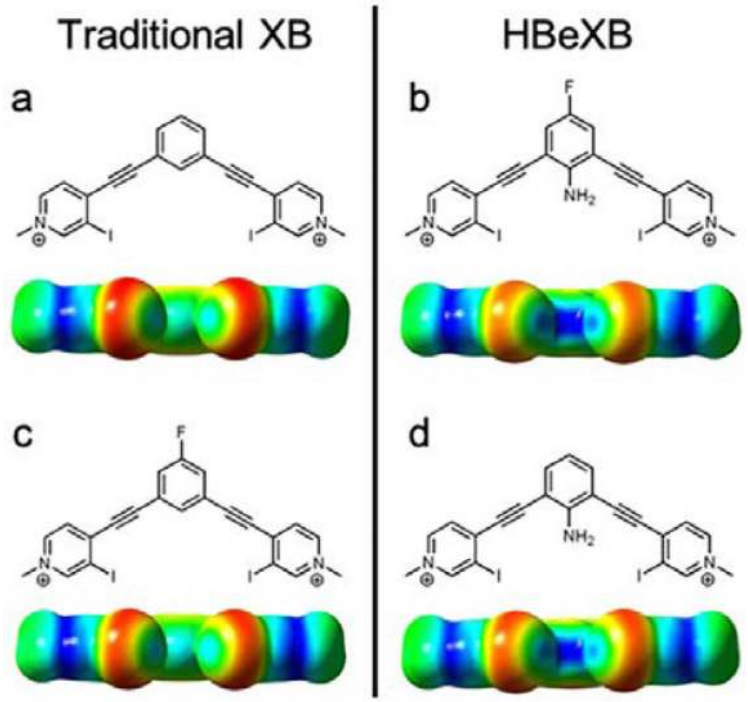

Figure 4:
Schematics and associated electrostatic potential (ESP) maps of **G1XB** (a), **G2XB** (b), **G2XB** no amine (c) and **G2XB** no fluorine (d) showing HBeXB enhancement of the electropositive σ-holes. ESP maps drawn at a 0.004 au isodensity.

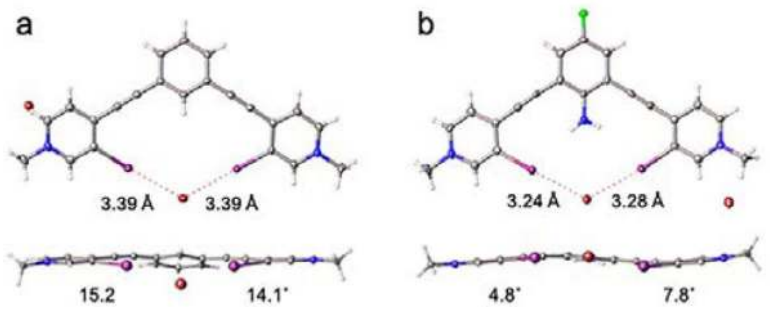

Figure 5:

Crystal structures of **G1XBme** with bromide top view (a, top) and planar view (a, bottom) comparing distances with **G2XBme** and bromide (b). The planar views include the degrees that the pyridnium rings twist out of coplanarity with the benzene (a, bottom) or fluoroaniline (b, bottom) core.

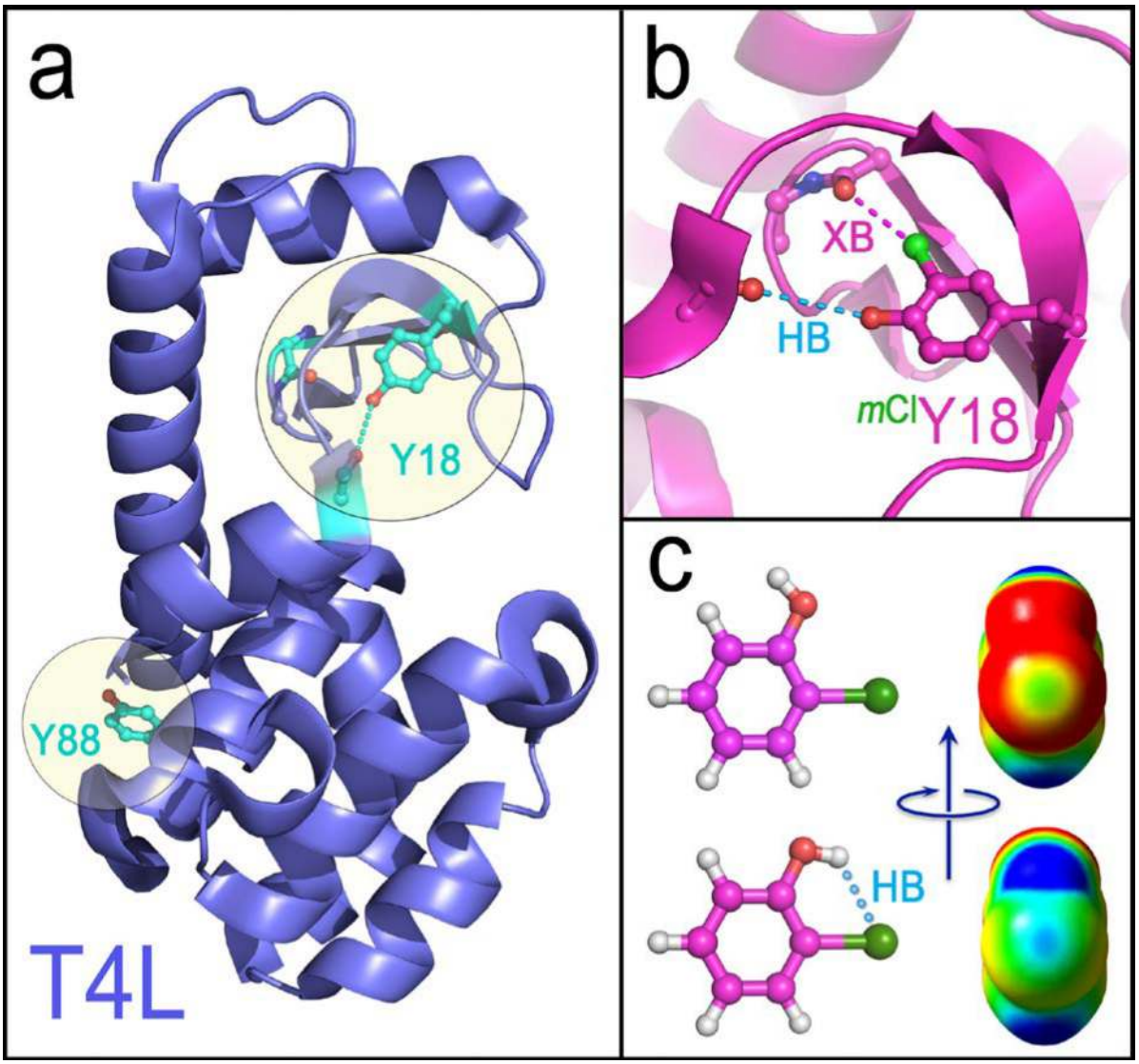

Figure 6.

The T4 lysozyme (T4L) model system for XB studies. **a.** The hydroxyl of the tyrosine amino acid at position 18 (Y18) forms an HB to the polypeptide backbone of glutamate E11 (dashes). The side chain of tyrosine at Y88, however, is solvent exposed and does not interact with the remainder of the protein. **b.** Replacing Y18 with a *meta*chlorotyrosine ($^{m\text{Cl}}$Y18) maintains the essential HB to E11, with the addition of an XB from the Cl to the peptide oxygen of glycine G28. **c.** Electrostatic potentials of a chlorophenol model of the $^{m\text{Cl}}$Y18 side chain. The Cl substituent shows a weak σ-hole when the hydrogen of the OH is rotated away from the halogen (top) but becomes significantly enhanced when rotated to form an HB.

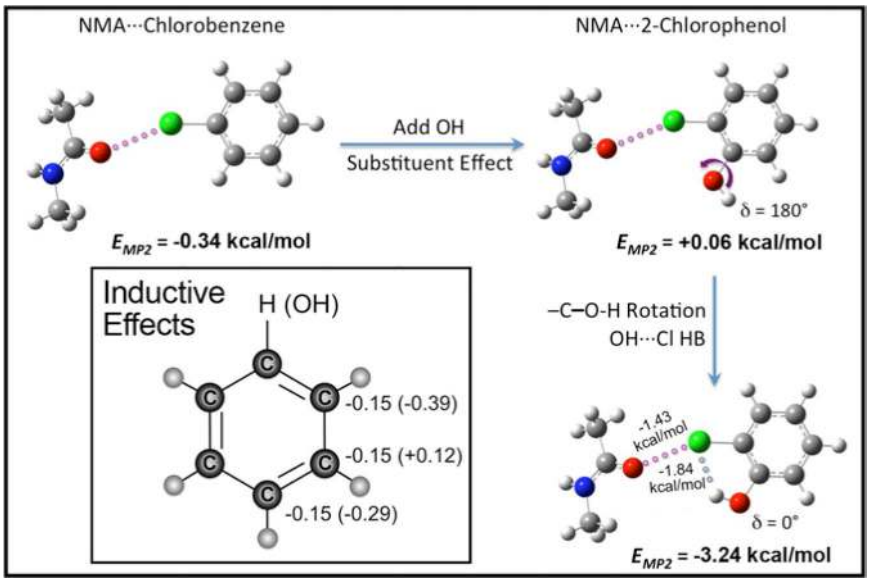

Figure 7.

Quantum mechanics (MP2) calculated energies (E_{MP2}) of XBs from chlorobenzene to the carbonyl oxygen of *N*-acetylamide (NMA, a model for a peptide bond), and effects from adjacent hydroxyl groups. The Cl-XB is fairly weak, and addition of a hydroxyl to an adjacent (*ortho*) carbon weakens the interaction further. Rotation of the OH to form an HB to the Cl, however, significantly increases the stabilizing potential of the Cl-XB (with E_{MP2} becoming more negative by ~1.5 kcal/mol). The inset shows the MP2 calculated inductive effects of a hydroxyl (OH) substituent on charges at the carbons of benzene (phenol). The carbons of benzene carry a charge of −0.15*e*, determined through an MP2 calculation. The charge at the *ortho*- and *para*-carbons become more negative, reflecting the electron donating effect, while that of the *meta*-carbon becomes more positive, indicative of the electron withdrawing effect of the hydroxyl group to these positions. The Hammett constants[58] for hydroxyl substituents are −0.37 for the *para*- and +0.12 for the *meta*-positions, consistent with the quantum calculated effects on the carbon charges.

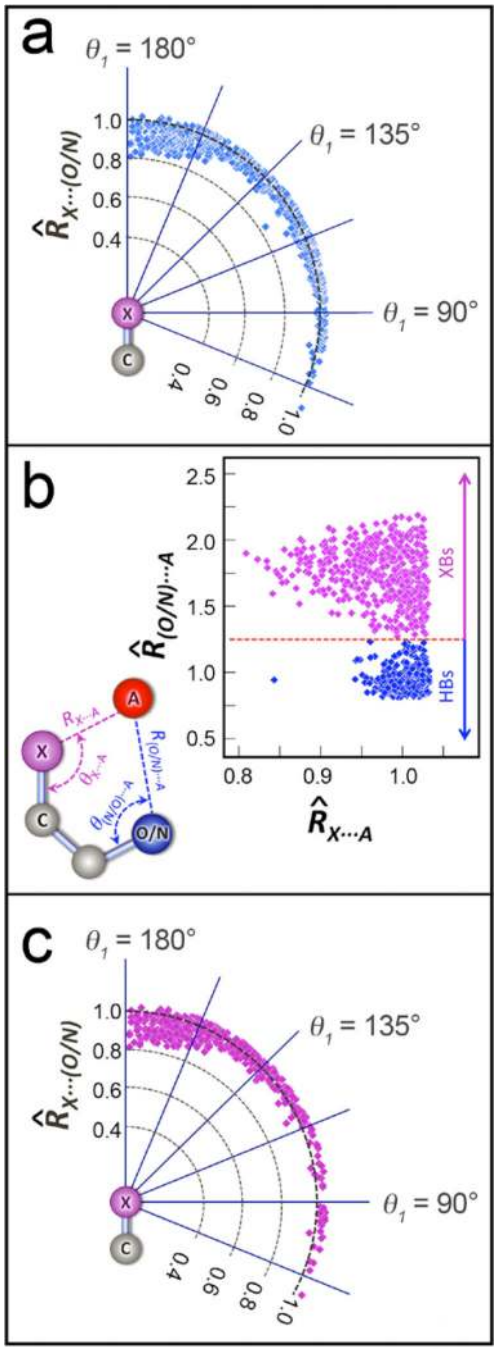

Figure 8.

Results from survey of structures from the Cambridge Structural Database (CSD) for potential HBeXBs. **a.** Radial distribution of potential HBeXBs. The CSD was surveyed for structures of halogenated aromatic compounds (Cl, Br, or I), with HB donors (OH or NH_2) at the *ortho*-position, that form complexes with an XB/HB acceptor (O or N). The distance from the halogen to the acceptor atom, normalized to the sum of the respective van der Waals radii ($R_{X\cdots(O/N)}$ ≤1.05) are plotted radially relative to the angle of approach of the acceptor to the C–X bond (θ_1). **b.** Plot of normalized distances from the acceptor (A) to the

halogen ($R_{X\cdots A}$) *versus* the distance to the HB donor ($R_{(O/N)\cdots A}$). HB interactions are distinguished from XBs by $R_{(O/N)\cdots A}$ ≤1.25. **c.** Radial plot of XBs from **a**, with HBs removed according to the criteria in **b**.

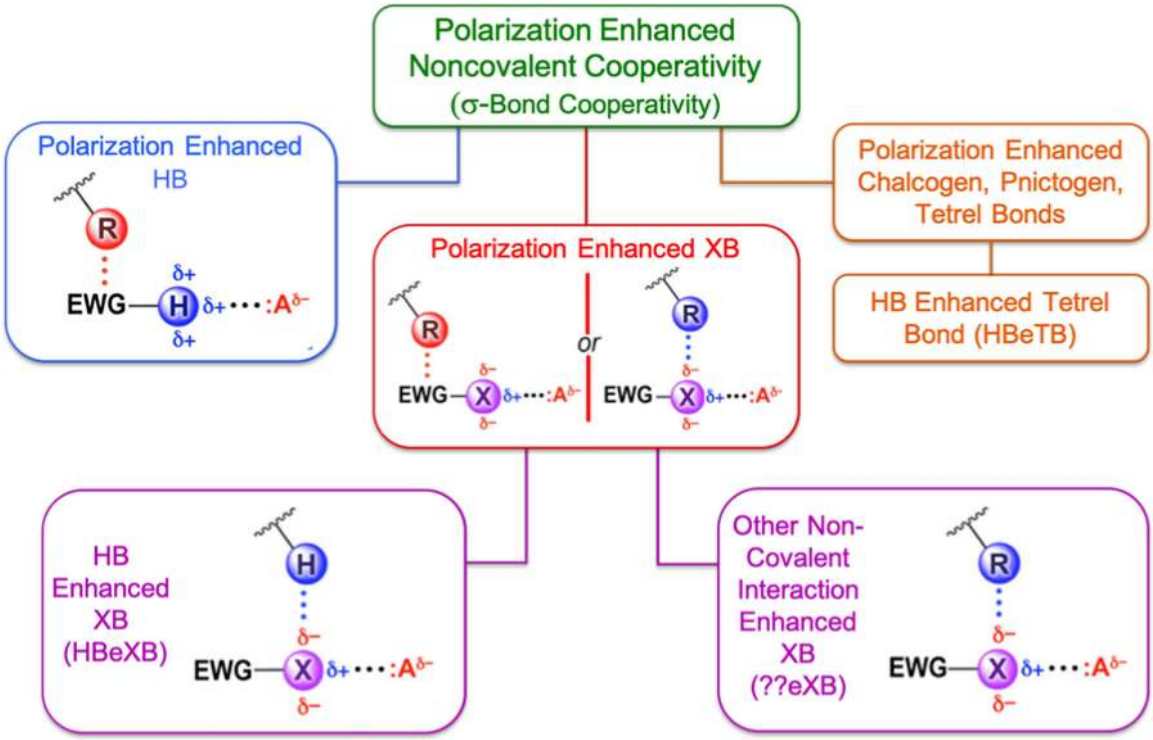

Figure 9.

Different types of polarization enhanced noncovalent cooperativity. The HBeXB is a subclass of polarization enhanced XBs where HBing directly to the XB donor enhances the XB interaction. EWG is an electron withdrawing group adjacent to a HB or XB donor, while A refers to electron-rich acceptors of HBs or XBs.