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Halogen Bonding from the Bonding Perspective with Considerations for Mechanisms of Thyroid Hormone Activation and Inhibition

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Abstract

Halogen bonding interactions are often discussed in terms of an area of positive electrostatic potential on the halogen center along the bond axis called the σ -hole, yet various authors have noted a lack of completeness in this model. The nature of the XB interaction is explored from the perspective of bonding theories beginning from models that explain the electrostatic σ -hole and continuing to orbital-based donor-acceptor descriptions in which the donor lone pair MO mixes with the acceptor R-X and R-X* MOs to form a set of XB MOs related to three-center-four-electron bonding in hypervalent molecules. The strength of the XB interaction for a large series of RX...Cl⁻ and RX...SeMe₂ complexes correlate well with the energy of the acceptor R-X* MO and the contribution of the halide to the R-X and R-X* MOs, factors relevant to favourable overlap with the donor lone pair. An orbital-based focus accounts for the partial covalency of the XB interaction and can be extended to descriptions of enzymatic dehalogenation mechanisms. Applications of this MO perspective to the deiodination of thyroid hormones by the iodothyronine deiodinases and a possibly related mechanism of inhibition are discussed.

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Bonding models of halogen bonding help understand how thyroid hormones and xenobiotic inhibitors affect thyroid activity through iodothyronine deiodinase.

Introduction

Halogen bonding (XB) interactions, defined as close contacts between halogens and donor atoms, are important for their application to crystal engineering, protein-ligand recognition,

and drug design.^{1–10} XB is often described in terms of the interaction of a donor with an area of positive electrostatic potential on the halogen atom along the R-X bond axis opposite the R group.^{11–13} This “ σ -hole” has been illustrated in mappings of the electrostatic potential (ESP) on the isodensity surface.^{11,14,15} These images provide a popular and attractive visual representation, but close contacts of less than the sum of the van der Waals radii suggest a partially covalent contribution that is not recovered by a predominantly electrostatic model. Emphasis on electrostatics also tends to overlook other energetic contributions including dispersion and the partial covalency of the interaction.^{16–18} Computational analyses of XB including energy decomposition analysis, natural bond orbital (NBO) analysis, atoms-in-molecules and other methods have been reviewed by various authors.^{13,19–22,9}

Several groups have shown that XB interactions are determined by charge transfer.^{21–23} Huber et al explored the shortcomings of the σ -hole model and the assumption that RX Lewis acidic acceptors (often referred to as the XB donor) form stronger interactions with more electronegative R groups to show that the ESP of the σ -hole was not proportional to the interaction energy for XB complexes of CX₃I (X = F, Cl, Br, I) with Cl[–] and NMe₃.²⁴ The more electronegative lighter trihalomethyl groups enhanced the ESP of the σ -hole (F > Cl > Br > I), but this result did not translate into a stronger interaction with either donor.²⁴ Instead, the interaction correlated with an enhanced donor-acceptor interaction based on the stabilization of the ϕ_{R-X}^* LUMO across the series. Donation of electron density (i.e., charge transfer) into this MO is also assigned a contributing factor to XB.^{25–29} As a counterpoint to the electrostatic model, various groups,^{23,26,27,30–32} have explored orbital-based descriptions of XB interactions to include early contributions by Mulliken.³³

The origin of the σ -hole can be understood in terms of how the p-type halide AOs are used in bonding with the R fragment.¹¹ The R-X bond is assumed to be made up of the combination of the p X AO oriented along the σ -bond axis (p_{axial}) with orbitals of R. If X is less electronegative than R, it retains much of its p_{axial} character in the subsequent polar bond. As the electronegativity of R increases, electron density must be depleted from p_{axial} in order to form the bond. For a given R, varying X from F to I destabilizes the X AOs relative to the R fragment due to the trend in decreasing electronegativity (Fig. 1A). As a result, the R-X bonding MO becomes more ‘R’-like, or more polarized toward R, and the X contribution along the bond axis is reduced. These factors lead to the observed area of positive ESP and the depletion in the X density opposite the R group.¹¹ The surrounding ring of higher density (anisotropic density^{34,35}) is due to the p-type X lps orthogonal to the bond axis which are less affected by bond formation. Electronegative R groups lower the energy of the R fragment relative to the X AOs to further deplete the axial ESP for a more positive σ -hole.

The XB interaction may also be described using bonding models based on either valence bond (VB) or molecular orbital (MO) theory. Using these descriptions, we have linked XB to the activity of the thyroid enzyme iodothyronine deiodinase (Dio) in a mechanism²⁶ that

has been supported by experimental studies^{36,37} and the recently solved crystal structure of Dio3.³⁸ In the VB picture, resonance structures for the XB interaction can be written in analogy to the three-center-four-electron (3c4e) bond in hypervalent molecules (eq 1).^{39,40} (Wang et al use a more complex VB description of XB.²²) The right-hand resonance structure mixes with the dominant R-X bond to an extent defined by the strengths of the donor and the R-X bond. Strong Lewis donors and weak R-X bonds increase the admixture of the right-hand resonance structure for a strong XB interaction. Equal weighting of both resonance structures leads to a true hypervalent 3c4e bond as found in the linear I_3^- ion.

From the MO perspective, XB interactions were discussed in early papers as a HOMO-LUMO donor-acceptor interaction^{33,41,42} involving the mixing of a filled lone-pair (lp) MO (ϕ_{lp}) on the donor with an empty R-X antibonding MO (ϕ_{R-X^*}) on the acceptor (scheme 1A). More recently, Mealli^{30,31} showed that the MOs for an XB interaction could be written as a combination of ϕ_{lp} with the acceptor R-X and R-X* MOs (scheme 1B). The bonding combination ϕ_A of ϕ_{R-X} and ϕ_{lp} contributes to the covalency of the XB interaction. The antibonding combination ϕ_B of the filled ϕ_{R-X} and ϕ_{lp} is stabilized through mixing with ϕ_{R-X^*} . The XB MOs that result from this stabilizing effect are similar to those of a 3c4e hypervalent bond such as found for the trihalide I_3^- .^{39,40,43} A similar phenomenon is observed in S_N2 pathways of silicon, which forms a hypervalent minimum where carbon has a transition state for substitution.⁴⁴ The XB interaction is enhanced by (a) destabilization of ϕ_{lp} in a strong Lewis base and (b) stabilization of the energy of ϕ_{R-X^*} through a weak acceptor R-X bond to allow better mixing with ϕ_B . Within this MO description, the directionality of the XB interaction is understood in terms of overlap.⁴¹ For an XB pair of the type D-Y...X-R, the R-X...Y angle is typically near 180° in order to maximize the overlap between the donor ϕ_{lp} and ϕ_{R-X^*} . The D-Y...X angle is variable and dependent upon the character of the donor MO and its ability to hybridize. Light donor atoms such as O or N form angles in accordance with the hybridization of their lp MOs. Heavier atoms with pure p lps will have D-Y...X angles closer to 90°. Each of these criteria are subject to competition from crystal packing forces and interactions within substrate binding sites of proteins.

In the context of this MO XB picture, the factors that govern the X contributions to the R-X bonding MO ϕ_{R-X} in Figure 1 also define ϕ_{R-X^*} . A decrease in the X p_{axial} character in ϕ_{R-X} conversely leads to an increase in the p_{axial} contribution to ϕ_{R-X^*} . As a result, these MOs are lower in energy for better overlap with the donor, more polarized toward X and composed of more p_{axial} character than R-X bonds of smaller halogens or those having less electronegative R groups (Fig 1B). A lower energy ϕ_{R-X^*} should better stabilize ϕ_B (scheme 1) to strengthen the XB interaction.

In this article, DFT calculations on a large series of organic halides paired with chloride ion and organochalcogen donors are used to explore how trends in the energies and composition of the R-X MOs affect their ability to act as Lewis acids in a XB interaction. The molecules included in this test were selected to provide a broader range of R-X bond types than is typically represented in common test sets of XB complexes such as XB18 and XB51.²⁰ These trends are also related to bonding perspectives on the relationship between XB and mechanisms of thyroid hormone activation and the inhibition of Dio proteins by halogenated aromatics such as polybrominated biphenyl ethers.

Theoretical Methods

Geometries were optimized using Gaussian 09⁴⁵ and the M06–2x exchange-correlation (xc) functional.⁴⁶ This functional was found to be a superior hybrid functional for the XB18 and XB51 test sets.²⁰ All atoms except for I and Te were represented by the augmented correlation-consistent split-valence triple- ζ basis sets of Dunning (aug-cc-pVTZ).^{47–49} Iodine and tellurium were represented by the Peterson et al relativistic effective core potential (RECP) aug-cc-pVTZ basis set.⁵⁰ Large basis are not required for the following analysis of XB interactions and similar trends can be found with the TZVP, TZV2P+ and smaller basis sets as well as with functionals, such as mPW1PW91, that perform less-well for established test sets than M06–2X. Natural bond orbital (NBO) calculations⁵¹ on the optimized structures were used to examine the compositions of the R-X and R-X* orbitals, the donor-acceptor properties and the Wiberg bond indices.⁵²

Results and Discussion

Trends in R-X bonding

NBO calculations on a series of 90 saturated and unsaturated organic halide (RX) molecules (see ESI[†]) were performed to examine the relationship between the R-X bonding and antibonding NBOs, their p_{axial} contributions and energy of $\phi_{\text{R-X}^*}$. For MeX (X = F, Cl, Br, I), the fluoride has the highest contribution to the C-X bonding NBO (73.1% F) with heavier halides increasingly polarized away from X (Cl (56.0%) < Br (52.4%) < I (48.0%)). This trend is accompanied by an increase in the %p character of the X contribution to the NBO (73.1% (MeF) to 89.8% (MeI)). The trend in the ratio of the gross Mulliken populations of the p_{axial} and $p_{\perp}$ AOs (F < Cl < Br < I) supports the lower contribution of the p_{axial} X AOs relative to the p-type X lps consistent with the anisotropy in the halide density and the size of the σ -hole.⁵³

The change in the character of the C-X bonding NBO is mirrored in the shape of $\phi_{\text{R-X}^*}$ as the %X and %p contribution increases down the halogen group (Fig 1B). The low to non-existent Lewis acidity of MeF and MeCl is attributed to the high energy of their $\phi_{\text{R-X}^*}$ MOs and the polarization toward the Me group. In contrast, F₂ can act as an acceptor⁵⁴ because $\phi_{\text{R-X}^*}$ is stabilized relative to MeF and has a higher %X (50%, by definition). The polarization of $\phi_{\text{R-X}^*}$ also defines the most favourable approach of the donor. For example, the polarization of the $\phi_{\text{R-X}^*}$ of IF toward I is consistent with results reported by Wolters and Bickelhaupt²⁷ that XB complexes with IF favour interaction at the I end of the molecule. The $\phi_{\text{R-X}^*}$ of the heavier halides are stabilized, and approach and exceed 50% X character with significant contributions from the p AO, making MeBr and MeI better, albeit weak, acceptors. Replacing the Me group with the electron-withdrawing –CF₃ group further increases the contribution of X to $\phi_{\text{R-X}^*}$ and stabilizes it to reduce the gap between the bonding and antibonding MOs. In general, the energy of the R-X* MO also correlates well with the %X contribution to $\phi_{\text{R-X}^*}$ (Fig 2). Surprisingly, $\phi_{\text{R-X}^*}$ is further polarized toward X for –CX'₃ (X = Cl, Br, I) despite the lower electronegativity of these halides. Generally, the

[†]Electronic Supplementary Information (ESI) available: Table of bond distances, charges, NBO data and energies for the series of RX molecules and their complexes with SeMe₂ and Cl[–]. See DOI: 10.1039/b000000x/

%X contribution to the R-X* bond decreases with the s AO contribution from the carbon end of the bond ($sp > sp^2 > sp^3$), consistent with trends in XB interaction strengths.^{55,56}

In aryl halides, the composition of the R-X* bond is influenced by the inductive effect of the ring substituents. Generally, electron withdrawing groups pull electron density out of the ring to stabilize and increase the %X contribution to ϕ_{R-X^*} . For example, fluoro substitutions to iodobenzene polarize the C-I bond toward iodine to strengthen XB interactions ($\text{PhI} < p\text{-FC}_6\text{H}_4\text{I} < 3,5\text{-F}_2\text{C}_6\text{H}_3\text{I} < 2,6\text{-F}_2\text{C}_6\text{H}_3\text{I} < 2,4,6\text{-F}_3\text{C}_6\text{H}_2\text{I} < \text{C}_6\text{F}_5\text{I}$). Electron donating groups such Me destabilize the ϕ_{R-X^*} energy and decrease the %X contributions to ϕ_{R-X^*} ($2,4,6\text{-MePhI} < 4\text{-MePhI} < \text{PhI}$). Additionally, because these groups are not directly bonded to the carbon involved in C-X bond, the trends in strengths of XB interactions with aryl halides are expected to be less sensitive to the electronegativity of the ring substituents than in saturated halides. Whereas all RI molecules have ϕ_{R-I^*} as their LUMO, the stronger C-Cl and C-Br bonds in aryl halides shift ϕ_{R-X^*} to higher energies and the LUMO often has π^* rather than C-X* character.

Trends in XB interactions

Having shown that the energy and X contribution to ϕ_{R-X^*} can be related to its ability to accept electron density from a donor, we to examine the effect of these contributions on the XB interaction for a series of donor-acceptor complexes between 85 organic halides (identical to the test set above excluding the fluorides) with Cl^- and SeMe_2 as reference donor species. The trends in the strengths of the XB interaction for the $\text{Me}_2\text{Se}\cdots\text{XR}$ and $\text{Cl}^-\cdots\text{XR}$ complexes ($X = \text{Cl}, \text{Br}, \text{I}$) are in general agreement with trends expected from the composition and energies of the acceptors' R-X bonds and ϕ_{R-X^*} MOs. The $\text{Cl}\cdots\text{X}$ and $\text{Se}\cdots\text{X}$ distances decrease with stronger interactions to a limit of 2.64 and 3.25 Å (Fig. 3), respectively, much less than the sum of the van der Waals radii consistent with the partial covalent character of these interactions. Cl^- is generally a stronger donor than SeMe_2 due to electrostatic contributions to the XB interaction. The transfer of electron density to ϕ_{R-X^*} generally increases the R-X bond distance, as previously noted.²⁵ The energies of formation (E) and the NBO donor-acceptor energies ($E_{d\rightarrow a}$) increase with heavier halogen acceptors ($\text{I} > \text{Br} > \text{Cl}$) consistent with the lower ϕ_{R-X^*} energies and greater contribution of X to ϕ_{R-X^*} (Fig 4A-D). Similarly, the IP of donor molecules was shown to correlate to the interaction energy in a series of XB complexes examined by VB.²² The trends in $d(\text{Se}(\text{Cl})\cdots\text{X})$, the increase in the $d(\text{C-X})$ distance and the $\text{Se}(\text{Cl})\cdots\text{X}$ Wiberg bond index, all measures of the strength of the interaction and the donation of electron density into ϕ_{R-X^*} also correlate well with ϵ_{R-X^*} and the % contribution of X to ϕ_{R-X^*} (Fig 4E-H, S1). The effect of perhalogenation on XB interactions with saturated RX is generally stronger than for aryl RX due to the direct effect of the adjacent substituents on carbon involved in the XB interaction. Values are more clustered for the $\text{Cl}^-\cdots\text{XR}$ interactions due to reduced steric interactions. Outliers in correlation plots are often either highly symmetric molecules in which ϕ_{R-X^*} is highly delocalized (e.g., CX_4 and HCCX).

A selected subset of XB complexes with SMe_2 and TeMe_2 (Table 1) was calculated to compare trends in $\otimes$ 7lp for completeness in 20 regards to strength of the donor in the MO model (scheme 1). The HOMO (p-type Y $\otimes$ lp) energy increases as $\text{S} (-0.275 \text{ a.u.}) < \text{Se}$

(-0.264 a.u.) $<$ Te (-0.250 a.u.) with the Lewis basicity of these donors leading to stronger XB interactions down the chalcogen group. This effect cannot be purely electrostatic as Natural 25 Population Analysis (NPA) atomic charges indicate that the partial positive charge of Y increases as S ($0.177e$) $<$ Se ($0.273e$) $<$ Te ($0.450e$) because these elements become more electropositive down the chalcogen group. Therefore, the destabilization of the p-type lp HOMO and the increase in its radial extent enhance the ability of the donor to participate in 35 halogen bonding.

The partial covalency of the XB interaction is reflected in the shortening of the Se(Cl)⋯X distance and the increase in the Se(Cl)⋯X Wiberg bond indices (WBI)⁵² with increasingly stabilized ϕ_{R-X}^* MOs (Fig 4D,H, S1). For the series CF₃X (X = Cl, Br, I), the redistribution of the charge density from the C-X bond to the XB interaction roughly doubles with each larger halide (WBI for CF₃X⋯SeMe₂ (Cl[−]): Cl = 0.022 (0.053); Br = 0.038 (0.116); I = 0.071 (0.225)). Similarly, destabilizing the donor MO of the Lewis base also enhances the covalency of the Y⋯X interaction (WBI for CF₃I⋯YMe₂: S = 0.064; Se = 0.071; Te = 0.081). For the strong CCl₃Cl₂I⋯SeMe₂ interaction ($E_{d\rightarrow a} = 15.3$ kcal/mol), the WBI of the C-I bond decreases from 0.920 in CCl₃Cl₂I to 0.825 in the XB complex. The weaker interactions of RCl are less covalent as a result of their high-energy, low %Cl ϕ_{R-Cl}^* MOs, but may not be predominately electrostatic because a σ -hole would be very shallow in these cases.

The MOs derived from the mixing of the donor Se(Cl) p-type lp and acceptor ϕ_{R-X} and ϕ_{R-X}^* MOs into ϕ_B for Me₂Se⋯XR (R = Me, CF₃, Ph, C₆F₅) and Cl[−]⋯XR (RX = CF₃Cl, CF₃I, C₆F₅I) are comparable to the relevant MOs of I₃[−] (Fig 5)^{31,43} and show a shift toward a more hypervalent electronic structure with stronger XB interactions. Similar ϕ_B -type MOs have been reported for other XB systems.^{26,57–59} Thus, although the XB has been described as a HOMO-LUMO interaction, strong interactions also involve the R-X bond, especially when a destabilized R-X bond can mix with ϕ_{lp} as in scheme 1. A comparison of the MOs shows that there appears to be more R-X* character in ϕ_B for donor-acceptor pairs with stabilized ϕ_{R-X}^* MOs (c.f., MeI and CF₃I in Fig 5). This qualitative observation is consistent with the trends in $E_{d\rightarrow a}$ values for the donation from the Se lp to ϕ_{R-X}^* and the relative increase in the C-X bond distance (Fig 4E). Given this dependence upon ϕ_{R-X}^* , the strength of the XB interaction, as measured by several energetic and structural parameters, correlates well with the R-X* MO energy (Fig 4). Because ϕ_{lp} mixing with ϕ_{R-X}^* is critical to the formation of the XB interaction, these MOs must be properly oriented to maximize their overlap (180° for the RX⋯SeMe₂ and RX⋯Cl[−]). The $E_{d\rightarrow a}$ value for the donation of the lp of Cl[−] into the ϕ_{R-X}^* of CF₃I rapidly decreases as $\angle Cl\cdots I-C$ varies from the angle of ideal overlap of these MOs (Fig 6).

Note that RCl acceptors form the weakest XB interactions, if they form at all. For example, the low contribution of Cl to the C-Cl* LUMO of MeCl leads to weak interactions with SeMe₂ and Cl[−] ($E_{d\rightarrow a} = 2.0$ and 2.9 kcal/mol, respectively). CF₃Cl and CCl₄ are also predicted to interact weakly with SeMe₂, consistent with the low percentage of Cl character and the high energy of ϕ_{R-Cl}^* . Generally, Me₂Se⋯XR XB interactions are very weak (> -2.5 kcal/mol) if ϕ_{R-X}^* is positive and/or the contribution of X to ϕ_{R-X}^* is less than 46%, as is the case for most RCl molecules. The high energy of ϕ_{R-X}^* in such cases prevents it from

mixing with the stabilized ϕ_{IP} of SeMe_2 to form ϕ_{B} and stabilize the interaction. The weakening of the R-X bond with heavier halogens significantly strengthens the donor-acceptor interaction ($E_{\text{d} \rightarrow \text{a}}$ (w SeMe_2) = 2.3 (Br), 4.5 (I)). Stronger interactions are found for the $\text{Cl}^- \cdots \text{Cl-R}$ complexes due to the greater Lewis basicity and electrostatics of the chloride donor ($E_{\text{d} \rightarrow \text{a}}$ (w Cl^-) = 2.9 (Cl), 7.5 (Br), 15.5 (I)). However, $\text{Cl}^- \cdots \text{ClR}$ complexes tend to have $d(\text{C-Cl})$ distances which are less than for free RCl (i.e., MeCl ($-0.004 \text{ \AA}$) and CF_3Cl ($-0.021 \text{ \AA}$)). In each of these cases, $\phi_{\text{R-Cl}}^*$ is polarized toward R in the isolated RCl molecule and the Cl^- donor lp lies below $\phi_{\text{R-X}}^*$ as indicated by its predominance in ϕ_{B} (i.e., $\text{Cl}^- \cdots \text{ClCH}_3$ in Fig 5). The low energy of the $\phi_{\text{R-X}}$ leads to very little mixing with ϕ_{IP} (ϕ_{A} for $\text{Cl}^- \cdots \text{ClCH}_3$ in Fig 5), so the XB interaction results from the weak interaction of ϕ_{IP} with $\phi_{\text{R-X}}^*$. Formation of this weak XB interaction requires a reorganization of $\phi_{\text{R-X}}^*$ to increase the %X contribution which, in turn, decreases the contribution of X to $\phi_{\text{R-X}}$ to shift the polarization of $\phi_{\text{R-X}}$ toward R.⁶⁰ This re-polarization of $\phi_{\text{R-X}}$ leads to a shortening of the R-X bond and is a consequence of the strength of the R-Cl bond. For example, in CF_3Cl , the carbon contributes 46% to the $\phi_{\text{R-X}}$ NBO, but its greater contribution in $\text{Cl}^- \cdots \text{ClCF}_3$ (50%) results in the shortening of the C-Cl bond by $-0.021 \text{ \AA}$. Generally, RX with greater than 52% contribution of X to $\phi_{\text{R-X}}$ (or less than 48% to $\phi_{\text{R-X}}^*$) show an overall shortening of the R-X distance when interacting with Cl^- . Strong XB interactions with heavy mixing between the donor and acceptor MOs do not reverse the composition of $\phi_{\text{R-X}}$ and do not show a decrease in the R-X distance. The decrease in $d(\text{C-Cl})$ for some XB complexes could also be attributed to repulsive effects between Cl p_⊥ lps on either end of these weak interactions. This type of XB interaction may be more consistent with favourable packing with the anisotropic densities of the organochlorides than a true XB interaction.^{35,61}

XB interactions applied to thyroid hormone activation

The activation of thyroid hormones (THs) by the iodothyronine deiodinases is a unique example where selenium and iodine come together to regulate a critical biochemical process.^{62–65} Early mechanisms for TH deiodination assumed that the phenolic ring must tautomerize to weaken the C-I bond (Scheme 2A).^{66,67} However, Dio proteins are also capable of deiodination at the inner ring where tautomerization is less likely. Given that Se and I readily form strong XB interactions, we considered the possibility that Dio could form an initial XB interaction with the TH based upon models used in work⁶⁸ on similar donor-acceptor interactions to selenium that are now referred to as chalcogen bonding.⁶⁹ From an initial XB intermediate which would be analogous to the prereactive complexes discussed by Hill and Legon,^{70,71} stabilization of the right-hand resonance structure in eq (1) by a proton donor within in the active site would convert the XB interaction into a nucleophilic substitution (scheme 2B). DFT calculations using a 2,6-diiodohydroquinone as model TH, methylselenol as the nucleophile and imidazole as proton donors and acceptors found the barrier for deiodination through the XB intermediate within the range expected for a biochemical process.²⁶ Replacement of Se with S gave a barrier consistent with the relative rate of a Cys Dio mutant. The selection of Se and I over S and Br for this process was attributed to the nucleophilicity of Se and the electrophilicity of I in spite of their significantly lower natural abundance. Further, as shown in the analysis above, the stabilization of and the greater polarization toward I of $\phi_{\text{R-I}}^*$ (Fig 2) makes iodinated biomolecules more susceptible to strong XB interactions that localize more charge on the

carbanion fragment with the enhanced contribution of the right-hand side of eq (1). In contrast, light halogens start from a weaker interaction with less activation, but various studies have shown that chlorinated and brominated xenobiotics, such as polychlorinated biphenyls⁷² and polybrominated diphenyl ethers (PBDEs)^{73–75} can disrupt Dio activity by mechanisms that are still under investigation.

As expected from the MO description of XB, interaction strengths of the full series of THs (Fig 7A) with MeSe^- correlate with the energy of $\phi_{\text{R-X}}^*$ which is most stable for the highly iodinated prohormone thyroxine (T_4), and decrease with decreasing iodination with a preference for XB to the outer ring (inner mono < outer mono < inner di < outer di, Fig 7B).⁷⁶ Interactions with the hydroxyl group on the outer ring tend to have an additional stabilizing effect. The XB interaction energy is more favourable as the %I contribution to R-I^* increases (Fig 7C).

XB interactions with different TH derivatives and at different iodination sites cannot distinguish the selectivity for inner- or outer-ring deiodination. The LUMO of T_4 is distributed over both diiodophenyl rings, but the lobes for the inner ring are somewhat larger, consistent with the slight favouring of inner-ring XB.⁷⁶ On the surface, this result would agree with the ability of Dio1 to deiodinate at either site (Fig 7A). However, the specificity of Dio2 for outer ring and Dio3 for inner ring indicates that XB interactions alone do not determine protein selectivity. Instead, additional interactions between the TH and the active site must control substrate binding in a way that has not yet been fully explored.

Recently, we have examined the possibility that polybrominated diphenylethers (PBDEs) and their hydroxylated metabolites (OH-BDEs) inhibit Dio activation through XB interactions.⁷⁶ In general, $\text{Se}\cdots\text{Br}$ interactions are weaker than $\text{Se}\cdots\text{I}$ because $\phi_{\text{R-Br}}^*$ are higher in energy with a smaller contribution from the halogen than $\phi_{\text{R-I}}^*$. The %Br contribution to R-Br^* is less, in agreement with the less-favourable interaction energies relative to the THs (Fig 7C). However, increased bromination places the XB interaction in

the same range as THs due to the inductive effect on the strength of the R-Br bonds and lowers the ϕ_{R-X}^* energies consistent with the overlap of regions of LUMO energies in Fig 4A,C. In asymmetric PBDEs like BDE-99, the most stable ϕ_{R-X}^* is localized on the more brominated phenyl group. For example, ϕ_{R-Br}^* (LUMO+1) for the trisubstituted ring of BDE-99 is 0.3 eV lower than the lowest ϕ_{R-Br}^* (LUMO+4) of the disubstituted ring. XB to bromines *ortho* and *meta* to the ether linkage tend to have stronger interactions than at *para* positions. In BDE-47, the donor-acceptor interaction at the *ortho* bromine is stabilized by 8 kcal/mol ($E_{d \rightarrow a}$) over the *para* position consistent with the greater polarization of the *ortho* ϕ_{R-Br}^* NBO toward Br (i.e., for BDE-47, %X = 51.2% (*ortho*), 50.5% (*para*)). The positional preference for XB in biphenyl ethers may be relevant to understanding substitution patterns in THs which are *ortho* and *meta* to the ether on the inner and outer rings, respectively. Because active site interactions are important to selectivity in TH activation, PBDEs/OH-BDEs that are similar in substitution would be expected to be strong inhibitors. For example, 3-OH-BDE-47 is structurally similar to rT₃ and was the most effective inhibitor of Dio2 in a study by Roberts et al.⁷⁵

Some PBDE/OH-BDEs appear to undergo a series of dehalogenation reactions,^{73,74} not necessarily by Dio, where others may simply bind to the active site Sec through an XB interaction to block TH binding. The bonding model for XB may help understand whether some PBDE/OH-BDEs are subject to dehalogenation or will reversibly bind to the active site selenocysteine. Increasing substitution with electron-withdrawing substituents lowers the ϕ_{R-X}^* for a stronger XB interaction that includes both an activation of the R-X bond and an increase in negative charge at the R fragment. Features within Dio that stabilize/protonate the carbanion may require a certain negative charge to accumulate in order for the XB interaction to convert to a nucleophilic attack. This possibility points to a threshold for XB interaction strength that must be exceeded for dehalogenation to occur. Thus, consideration of XB from a bonding model provides more insight than purely electrostatic models and may be important to identifying inhibitors of Dio that have high affinity, but do not react with the protein. However, when considering the XB interactions of TH with transthyretin (TTR) in the transport process,⁷ because weaker interactions of THs with the backbone amino acids in which electrostatics could be more dominant, the σ -hole model is probably sufficient. In these terms, an additional aspect of iodine in the thyroid pathway may be due to the unique nature of its XB interaction. Other halogens could interfere with either Dio or TTR,⁷⁷ but the strength of the XB iodine interactions would be preferred. Nonetheless, xenobiotics with other halogens could disrupt thyroid signalling through either pathway.

Conclusions

The σ -hole model is a popular visual tool that provides insight into XB and related phenomena like chalcogen and pnictogen bonding. However, we believe that it oversimplifies the underlying factors in XB by addressing only the acceptor (aka, the XB donor) and focusing on electrostatic and repulsive contributions while downplaying the significant bonding contribution to the interaction. From a bonding perspective, XB is more complex than the donor-acceptor HOMO-LUMO interaction as the mixing of the donor MO and the acceptor ϕ_{R-X} and ϕ_{R-X}^* MOs to form XB MOs analogous to 3c4e bonding in hypervalent molecules. Therefore, the partial covalency of XB interactions requires consideration of the

bonding contributions which originate in the nature of X and its contribution to the character and energy of ϕ_{R-X} and ϕ_{R-X}^* . The series of DFT calculations on a large set of organohalide molecules with SeMe_2 and Cl^- show that the strengths of XB interactions as measured by either geometric parameter or energetics correlate well with the energy and contribution of X to the ϕ_{R-X}^* MO of the isolated RX acceptor. Substitutions that stabilize the ϕ_{R-X}^* energy, increase the %X character of ϕ_{R-X}^* or pull electron density away from the XB donor group will increase covalency of the donor-acceptor interaction to strengthen XB. In this sense, models that go beyond the σ -hole viewpoint provide more flexibility because bonding contributions can be viewed as being along a continuum and allow a simple donor-acceptor interaction to morph into a nucleophilic attack without changing the underlying model. This viewpoint has contributed to interpretations of the mechanisms of thyroid hormone activation and inhibition and, coupled with an understanding of active site topology, may lead to the design of non-reactive inhibitors of Dio.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. The effect of electronegativity on the R-X MOs of simple alkyl halides. The contribution of X and p_{axial} AO to (A) $\phi_{\text{R-X}}$ and (B) $\phi_{\text{R-X}^*}$.

Fig. 2.
Comparison between the energy and the % contribution of X to the R-X* MO

Fig. 3.
Plot of the NBO donor-acceptor energies ($\Delta E_{d \rightarrow a}$) of the $\text{Me}_2\text{Se} \cdots \text{XR}$ complexes versus the (A) Se...X and (B) Cl...X distances (Å)

Fig. 4.

Correlation of the energy of the R-X* MO ($\epsilon \phi_{R-X^*}$, a.u.) or the % contribution of X to ϕ_{R-X^*} (%X) with several descriptors of the strength of the Me₂Se...XR (A, B, E, F) and Cl...XR (C, D, G, H) XB interactions: (A, B) $\epsilon \phi_{R-X^*}$ versus the energy of formation of the XB complex (ΔE , kcal/mol); (B, D) %X versus ΔE ; (E, G) %X versus the increase in d(C-X) in the XB complex ($\Delta d(C-X)$); (F, H) %X versus the Se...X Wiberg bond index (WBI).

Fig. 5. Relevant MOs for the XB interaction of SeMe_2 and Cl^- with several organohalides and the hypervalent I_3^- anion.

Fig. 6.
Dependence of the $E_{d \rightarrow a}$ on the orientation of the Cl^- donor to the C-I bond of CF_3I

Fig. 7.

A. Pathways for TH deiodination by the Dio family of selenoproteins B. Comparison of XB interaction strengths of THs with LUMO energies. Images from ref ⁷⁶. C. Comparison of XB interaction strengths and %X contribution to the R-X* NBO for THs and selected PBDEs (unreported data from ref ⁷⁶).

Scheme 1.

A. MO diagram for a donor-acceptor HOMO-LUMO model of XB B. MO diagram for a general XB interaction (adapted from reference ³¹). Note that to form the XB interaction, the lone pair of the donor must be aligned along the R-X bond axis in order to overlap with ϕ_{R-X^*} .

Scheme 2.

A. Deiodination through tautomerization. B. XB-based deiodination mechanism.²⁶

Table 1

Donor-acceptor energies ($E_{d\rightarrow a}$, kcal/mol), Y...X bond distances ($\text{\AA}$) and the elongation of the C-X bond distance in the $\text{Me}_2\text{Y}\cdots\text{XR}$ XB complexes

RX	Y	$E_{d\rightarrow a}$	$d(\text{Y}\cdots\text{X})$	$d(\text{C-X})$
CF_3I	S	9.60	3.291	0.008
	Se	10.14	3.413	0.010
	Te	11.17	3.589	0.012
PhI	S	3.86	3.492	0.002
	Se	4.08	3.606	0.005
	Te	4.35	3.775	0.006
<i>p</i>-$\text{FC}_6\text{H}_4\text{I}$	S	4.20	3.470	0.003
	Se	4.27	3.592	0.004
	Te	4.79	3.748	0.007