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Ability of Peripheral H Bonds to Strengthen a Halogen Bond

Steve Scheiner*

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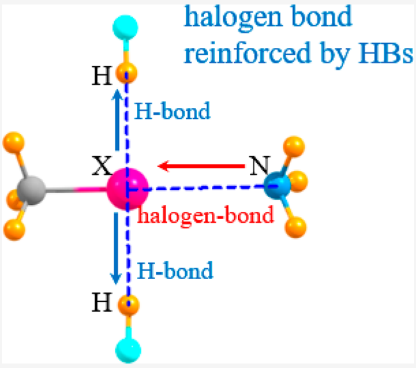
ABSTRACT: Quantum calculations study the manner in which the involvement of a halogen atom as a proton acceptor in one or more H bonds (HBs) affects the strength of the halogen bond (XB) it can form with a nucleophile aligned with the X σ-hole. A variety of Lewis acids wherein X = F, Cl, Br, and I are attached to a tetrel atom C or Ge engaged in a XB with nucleophile NH_3. One, two, and three HF molecules were positioned perpendicular to the XB axis so that they could form a HB to the X atom. Each such HB strengthened the XB by an increment of 1 kcal/mol or more that does not attenuate as each new HB is added, potentially increasing the interaction energy manyfold. Additionally, the presence of one or more HBs facilitates the formation of a XB by molecules which are reluctant to engage in such a bond in the absence of these auxiliary interactions. Even the F atom, which avoids such a XB, can be coaxed to participate in a XB of moderate strength by one or more of these external HBs.



■ INTRODUCTION

A century of study has provided a wealth of knowledge about the H bond (HB): the source of its stability, its spectroscopic signature, and its many important manifestations and implications throughout chemistry and biology.[1−8] The electrostatic portion of the interaction energy arises in large measure from an attraction between the bridging proton with its partial positive charge and the negative segment of the proton-accepting base, usually coincident with its lone pair. This attraction is augmented by a stabilizing transfer of charge from the base's lone pair into the AH σ* antibonding orbital of the proton donor unit. It is this population of an antibonding orbital which is primarily responsible for the stretch of the A−H covalent bond and the well-known red shift of its stretching frequency.

More recent work has delved into the properties of the closely related halogen bond (XB) characterized by the replacement of the bridging proton of a HB with any of a number of different X halogen atoms. The parallels with the HB are striking, including a very similar range of binding energy. Like the HB, the XB too is stabilized by a certain amount of charge transfer from the nucleophile into the σ*(AX) antibonding orbital. Although the X atom does not carry an overall positive charge as does the H, the strong anisotropy of its surrounding electron density nevertheless yields a small positive region which can attract the negative segment of the approaching base. This positive area lies directly along the projection of the A−X bond axis and is commonly termed a σ-hole.

Years of study have revealed a number of general features of the XB.[9−20] In the first place, this bond strengthens along with the size of the X atom, attributed to an associated rise in electropositivity and polarizability. Indeed, the highly compact and electronegative F atom is rarely observed to participate in a XB and then only under certain limited conditions. The addition of electron-withdrawing substituents on the Lewis acid intensifies the X σ-hole and thereby strengthens the XB. Much like the HB, the placement of a positive charge on the Lewis acid and/or negative charge on the base reinforces the XB in what is sometimes called charge assistance.

In parallel with the manner by which an electron-withdrawing substituent on the acid augments the σ-hole and strengthens the XB, the same sort of effect can be achieved by a third separate molecule interacting with the acid that tends to draw density toward itself. A cation would be one example of a unit that could fulfill this function. This sort of enhancement of the electron-accepting ability of a molecule by its interaction with another commonly falls into the category of cooperativity,[21−25] which is often discussed within the HB context but is equally valid in the framework of XBs.

And indeed there has been some study of cooperativity as it pertains to XBs. The overarching conclusion from this work[26−37] confirms the thesis that reinforcement of both bonds occurs when the central unit acts simultaneously as both electron donor and acceptor. Of some particular importance, this same concept applies also when the two noncovalent interactions involved are a XB and a HB.[38−47]

Most of the earlier work studied model systems wherein the third molecule draws density not directly from the X atom itself

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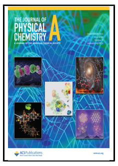

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but is noncovalently bonded instead to some other atom of the halogen-containing unit, separated from X by one or more covalent bonds. But it is reasonable to expect that a direct attachment to X would be a more effective vehicle to draw density from X and permit it to engage in a stronger XB with a nucleophile. Indeed, the anisotropy of the electron density and potential surrounding the X atom suggests just such an arrangement. Just as the positively charged σ-hole along the pole of the covalent A−X bond attracts a nucleophile, so would the negative charge around the X atom's equator draw in an electrophile.

Although still sparse, the body of previous work suggests that participation of a halogen atom as electron donor within a HB can activate this atom as electron acceptor in an accompanying XB. Experimental and theoretical data[41,48−50] indicate just such a concept, albeit within the specialized framework of cation−anion interactions involved in halide binding. This HB/XB cooperativity has demonstrated implications for protein structure and function[51,52] and catalysis.[53,54]

There are a number of important questions whose answers carry potentially far-reaching implications. In the first place, just how much of a strengthening effect on a halogen bond can be expected from one or more HBs to the X atom? How quickly do these effects attenuate as more of these HBs are added to the system? How might these effects differ from one X atom to the next within the halogen series. Another question concerns implications of the presence of substituents on the atom to which the halogen is covalently attached as well as the hybridization of this atom. Is there a distinction between aliphatic and aromatic systems? How do the putative XB reinforcements by external HBs change with the identity of the atom to which X is bonded? As a corollary, can the presence of one or more HBs facilitate the formation of a F−halogen bond when the latter is normally highly unusual?

To address these questions in a systematic fashion, a number of carefully designed systems are constructed and studied by quantum chemical calculations. With regard to the Lewis acid, each halogen atom, F, Cl, Br, and I, is affixed first to a C atom. Within the context of sp^3 hybridization, the C atom is part of both the CH_3 and its CF_3 congener so as to examine how the strongly electron-withdrawing F atoms affect the situation. Also considered are the aromatic benzene and imidazole rings for the placement of the halogen atom to provide insights into both sp^2 hybridization and aromaticity. The point of attachment is enlarged from C to Ge which is both more electropositive and more polarizable than C and thus will add information concerning how the effects are affected by atom size. So as to ensure uniform treatment of all these Lewis acids, the NH_3 base was chosen to form the XB with the relevant halogen atom. This nucleophile is of moderate strength, comparable to what might be seen in a chemical or biological context, and is of small enough size so as to minimize complications that would arise from secondary interactions. One or more HF molecules are positioned around the X atom, perpendicular to the halogen bond, so as to study the primary issue as to how the ensuing FH··X HBs modulate the strength and other properties of the XB.

METHODS

Quantum chemical calculations were performed via the Gaussian 16[55] set of codes, applying density functional theory (DFT) in the framework of the M06-2X functional,[56] along with the polarized triple-ζ def2-TZVP basis set. The interaction energy E_{int} of each dyad was derived as the difference between the energy of the complex and the sum of the energies of the Lewis acid and NH_3 base, each in the context of the geometry they adopt within the dimer. After optimization of the larger complexes containing n HF molecules, the same formalism was applied where the two subunits consisted of NH_3 on one hand and the {Lewis acid·$(HF)_n$} assembly on the other. The basis set superposition error was corrected by the standard counterpoise prescription.[57] The Multiwfn program[58] located and quantified the relevant maxima of the molecular electrostatic potential (MEP) residing on the ρ = 0.001 au isodensity surface of each monomer.

The disposition of each $RX\cdot\cdot NH_3$ complex, and those wherein n HF molecules have been added, are illustrated in Figure 1 for the example of H_3CBr. The geometry of the halogen-bonded pair in Figure 1a was fully optimized, yielding a linear CBr··N arrangement. To avoid displacements of the molecules from their desired locations, e.g., formation of a $FH\cdot\cdot NH_3$ or FH··FH dyad, geometry restrictions were imposed upon addition of one or more FH units. Specifically, CBr··N was held to be linear, as was each FH··Br H bond. In addition, the FH units were all placed perpendicular to the XB axis, i.e., θ(CBr··H) = 90°. Multiple HF units were kept as far apart from one another as was possible, with the dihedral angle φ(HBrCH) = 180° in Figure 1c and ±120° in Figure 1d. All other features of each structure were fully optimized, including their distance from the central Br atom. These same restrictions were placed on all complexes, with H_3CBr serving as an example. Figure 2 depicts analogous arrangements for the $ImCl\cdot\cdot NH_3$ complexes, showing how the first HF was positioned above the Im plane, with the dihedral angle φ(NCCl··H) = 90°. As visible in Figure 2c, the second HF is located directly opposite the first, with φ(NCCl··H) = −90°. The three φ(NCCl··H) angles in Figure 2d are −90°, 30°, and 150° (coordinates of all complexes can be found in the Supporting Information).

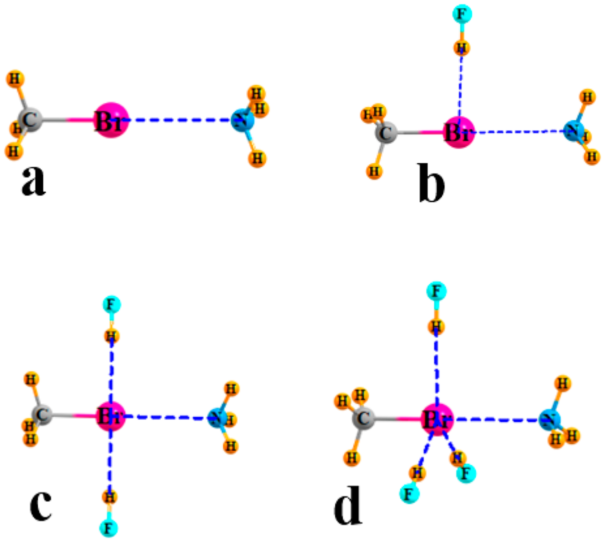

Figure 1. Representative arrangements of the halogen bond between H_3CBr and NH_3 in the presence of (a) 0, (b) 1, (c) 2, and (d) 3 molecules of HF.

RESULTS

Energetics. The interaction energy of the XB formed by each Lewis acid with NH_3 is listed in the first column of Table 1. The pattern is generally consistent with the idea that the XB weakens

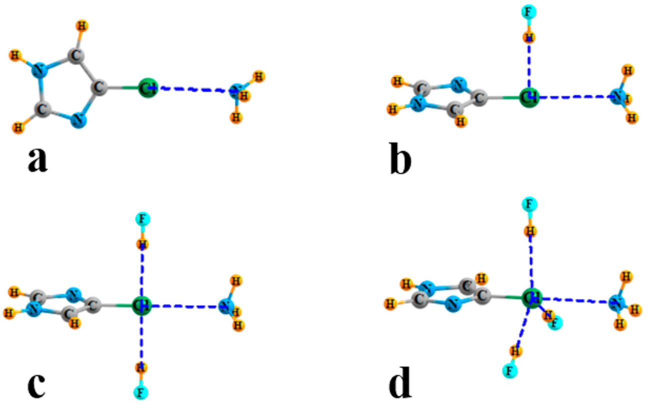

Figure 2. Optimized structures of the halogen bond between ImCl and NH_3 in the presence of (a) 0, (b) 1, (c) 2, and (d) 3 molecules of HF.

Table 1. Interaction Energy ($-E_{int}$, kcal/mol) of Complex between Listed Lewis Acid and NH_3 in the Presence of *n* HF Molecules

n =	0	1	2	3
H_3CI	3.03	4.48	5.82	7.27
H_3CBr	1.29	2.87	4.31	5.87
F_3CBr	4.07	5.61	7.01	8.42
H_3CCl	0.29[a]	1.97	3.50	5.12
H_3CF			1.14	2.93
F_3CF	0.13[a]	1.07	2.18	2.99
ImCl	0.94[a]	2.34	3.69	5.04
BzCl	0.89	2.32	3.62	5.00
BzF			1.23	2.29
H_3GeBr	0.42[a]	1.53	2.58	3.72
F_3GeBr	3.37	4.57	5.65	6.72
H_3GeCl	−0.32[a]	0.82	1.93	3.09

[a] Not true min.

as the X atom diminishes in size. The interaction energy of H_3CI and H_3CBr is respectively 3.0 and 1.3 kcal/mol. H_3CCl only engages in a XB with NH_3, and a very weak one at that if the N is held to the C−Cl axis; this linear arrangement is not a true minimum on the surface, as it displays imaginary frequencies. Even with such a linearity restriction, H_3CF and NH_3 do not engage in a stable complex, with the two separating from one another. Adding electron-withdrawing F substituents to the C center substantially strengthens the XB, tripling from 1.3 kcal/mol for H_3CBr to 4.1 kcal/mol for F_3CBr. Adding the same three F substituents to H_3CF allows F_3CF to engage with NH_3, but only if the CF··N arrangement is held linear, and even so the interaction energy is vanishingly small.

There is a very small stabilizing effect if the C atom is part of an aromatic ring. The XB energies of ImCl and BzCl with NH_3 are about 1 kcal/mol. Again, however, F resists any such XB when placed on a phenyl ring, even if linearity is enforced. Switching out the C atom to which X is bonded to a larger tetrel atom such as Ge can be expected to weaken the XB because Ge is less electronegative than C, so ought to reduce the depth of any σ-hole that might occur on X. Indeed, this guess is confirmed as seen in the last three rows of Table 1. Although H_3CBr engages in a legitimate XB with NH_3, its heavier H_3GeBr congener only does so if held linear, and even then the interaction energy is well smaller than 1 kcal/mol. This pattern is clear also in the comparison of fluoro-substituted F_3CBr with F_3GeBr where the latter is involved in a somewhat weaker XB, 3.4 vs 4.1 kcal/mol. H_3GeCl does not engage in a viable XB: even if held linear, the counterpoise-corrected interaction energy is slightly repulsive.

The next three columns of Table 1 document the manner in which the addition of 1, 2, or 3 HF molecules acts to strengthen each and every XB, which becomes progressively stronger with each new HF addition. Taking H_3CI in the first row as an example, the XB strength grows from 3.0 to 4.5 kcal/mol in the presence of a single HF and then proceeds to increase to 5.8 and then 7.3 kcal/mol with each additional peripheral acid. In quantitative terms, these 3 HF molecules more than double the XB energy. Of particular note, there are several cases where it is only in the presence of one or more HF units that a XB will form at all. H_3CF is a case in point: It will only engage attractively with NH_3 in the presence of 2 or 3 HF units. This same pattern characterizes BzF as well. Closely related to this effect, there are several Lewis acids, viz. H_3CCl, F_3CF, ImCl, H_3GeBr, and H_3GeCl, where only 1 HF is required to permit the appearance of a XB complex as a true minimum.

It is particularly interesting to consider the increments added to each XB energy by each new HF molecule. One might have anticipated that the effects ought to become progressively less dramatic as *n* grows larger. But in fact, the increments are nearly constant. Taking ImCl as an example, each additional HF molecule added to the system results in a 1.4 kcal/mol increment to E_{int}. As another interesting aspect, the magnitudes of these increments are surprisingly uniform from one system to the next. These increments amount to roughly 1.4 kcal/mol for all the systems containing a C−X bond (with the exception of F_3CF) and are slightly smaller at 1.1 kcal/mol for Ge−X Lewis acids. The closely linear rise of XB energy with number of HF units can be seen graphically in Figure 3. The R^2 correlation coefficients of E_{int} with *n* all exceed 0.999. Although there is of course some difference from one Lewis acid to the next, the slopes of these lines are surprisingly similar.

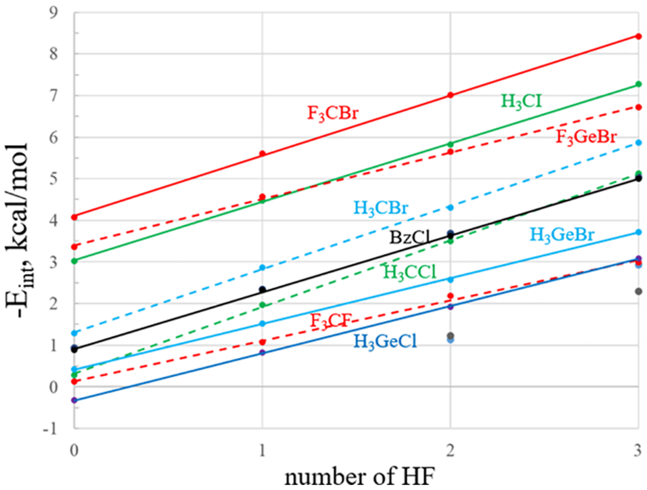

Figure 3. Growth of XB energy as *n* molecules of HF are added to the complex of NH_3 with each of the indicated Lewis acids. ImCl is not included as it is virtually indistinguishable from the BzCl energies. Points without connecting lines refer to H_3CF and BzF which do not engage in a XB for $n < 2$.

Geometries. There are two primary factors that play into the length of a typical XB. Strengthening this bond will naturally pull the two subunits toward one another. While a heavier X atom commonly leads to a stronger bond, it also has a larger radius which will tend to a longer intermolecular distance. Both of these

Table 2. Halogen Bond and Mean HB Length (Å) in Complex Pairing Listed Lewis Acid with NH_3 in the Presence of n HF Units

	R(X··N)				R(X··H)		
n =	0	1	2	3	1	2	3
H_3CI	3.152	3.108	3.070	3.033	2.547	2.594	2.621
H_3CBr	3.144	3.081	3.032	2.982	2.324	2.377	2.411
F_3CBr	2.984	2.939	2.911	2.880	2.480	2.520	2.571
H_3CCl	3.151	3.055	2.992	2.935	2.155	2.221	2.261
H_3CF			3.006	2.853		1.844	1.879
F_3CF	3.805	3.127	3.037	3.017	2.756	2.583	2.837
ImCl	3.110	3.024	2.976	2.939	2.224	2.289	2.352
BzCl	3.107	3.037	2.988	2.944	2.222	2.283	2.305
BzF			3.016	2.952		1.947	2.177
H_3GeBr	3.381	3.265	3.212	3.172	2.359	2.406	2.428
F_3GeBr	3.129	3.088	3.059	3.032	2.552	2.608	2.670
H_3GeCl	3.406	3.260	3.166	3.116	2.204	2.244	2.283

two trends are in evidence in the first column of Table 2. For example, even though H_3CI forms a stronger XB than does H_3CBr, the latter has a slightly shorter R(X··N) distance due to the smaller size of Br. The weakening of the XB when Br is replaced by Cl overwhelms the smaller Cl atom, and the XB elongates a small amount. The dominance of the weakened XB is clear in the much longer XB involving F_3CF, despite the small size of F. The attachment of the Cl to the aromatic ring of Im or Bz shortens the R(Cl··N) distance relative to H_3CCl, suggesting a slightly stronger XB. The XB weakening that accompanies the change from a CBr to a GeBr bond is mimicked by a longer XB for F_3GeBr as compared to F_3CBr.

Just as the addition of the peripheral H-bonding HF atoms raises the XB energies, so too does one observe reductions in R(X··N). The amount of this bond contraction is largest for the first HF, but the ensuing reduction upon adding the second or third HF is only slightly smaller. Taking the complexes involving H_3CBr as an example, the first HF shortens R(Br··F) by 0.06 Å, while the further contractions for second and third HF are each 0.05 Å.

The last three columns of Table 2 contain the HB lengths, i.e., R(H··X), separating the various HF molecules from the X center. These distances generally lie in the range between 2.2 and 2.8 Å, with a few exceptions as noted below. Just as the XBs, the lengths of these bonds are controlled both by X atom size and strength of the bond. But in this case, both trends are in the same direction, viz., smaller X atoms are also superior HB acceptors, so these bond lengths shrink steadily in the progression $H_3CI > H_3CBr > H_3CCl > H_3CF$. As additional HF units are added, they all depend upon electron donation from the same X atom, so there is a negative cooperativity that results in the progressive elongation of R(H··X) as n increases.

The change in the length of the R−X covalent bond arising from formation of a XB can provide insights into the strength and nature of the XB. The first column of Table 3 shows that this bond undergoes a small contraction in most, but not all, of the dyads. The exceptions are H_3CI and H_3CBr, both of which are elongated to a certain extent. In fact, this variability of the sign of Δr has been observed previously in various complexes and is the subject of active study. Perhaps of greater importance, all R−X bonds stretch when the XB is strengthened by the addition of one or more HF H bonds to the X atom. And like the energetics and intermolecular distance, each further addition of another HF adds another increment to Δr. And again, this increment does not die off quickly as n rises. Using H_3CBr as an example, r(CBr) stretches by another 0.006 Å for each additional HF molecule added to the complex. The individual step sizes are 0.008, 0.009, and 0.007 Å for H_3CCl and 0.003, 0.004, and 0.003 Å for H_3CI. In fact, there is also a trend that the sizes of these steps rise as X becomes smaller.

Table 3. Change in Internal T−X Bond Length (Å) Caused by Complexation with NH_3 When H-Bonded to n HF Units

n =	0	1	2	3
H_3CI	0.0048	0.0075	0.0112	0.0143
H_3CBr	0.0015	0.0076	0.0140	0.0197
F_3CBr	−0.0029	0.0097	0.0194	0.0309
H_3CCl	−0.0006	0.0078	0.0167	0.0235
H_3CF			0.0338	0.0483
F_3CF	−0.0044	−0.0021	0.0064	0.0039
ImCl	−0.0007	0.0073	0.0136	0.0174
BzCl	−0.0021	0.0087	0.0167	0.0301
BzF			0.0278	0.0394
H_3GeBr	−0.0062	0.0141	0.0329	0.0512
F_3GeBr	−0.0011	0.0130	0.0255	0.0356
H_3GeCl	−0.0068	0.0166	0.0373	0.0604

Electrostatic Considerations. A good deal of previous work has tied the strength of a XB to the depth of the σ-hole on the X atom.[16,59−63] This depth is typically assessed as the maximum of the molecular electrostatic potential (MEP) on a ρ = 0.001 au isodensity surface. These quantities are displayed as V_{max} in the first column of Table 4 for each of the Lewis acid monomers. The patterns are consistent with chemical principles

Table 4. Maximum of Molecular Electrostatic Potential (V_{max}, kcal/mol) along the T−X Projection on the 0.001 au Isodensity Surface

n =	0	1	2	3
H_3CI	14.0	22.7	30.7	38.2
H_3CBr	5.5	15.5	24.5	33.0
F_3CBr	25.6	33.7	41.2	48.2
H_3CCl	−1.1	10.1	19.7	29.0
H_3CF	−22.9			
F_3CF	0.9			
ImCl	1.9	11.4	19.6	27.6
BzCl	4.4	12.9	20.8	28.3
BzF	−15.3			
H_3GeBr	0.2	7.8	14.7	21.4
F_3GeBr	25.1	32.0	38.5	44.3
H_3GeCl	−6.5	2.0	9.4	16.5

based on atomic electronegativity and polarizability. V_{max} declines along with rising electronegativity of X for the H_3CX series and drops below zero for both Cl and F. It is in part for this reason that both H_3CCl and H_3CF have difficulty in developing a XB with NH_3. The replacement of the three H atoms on the H_3CX series by the electron-withdrawing F very markedly deepens each σ-hole. Placing the Cl of F halogen atoms on an aromatic ring raises V_{max}, but not enough to yield a positive value for BzF. On the other hand, replacing the C−X bond by GeX has only a moderate effect on V_{max}.

The next three columns of Table 4 describe how the placement of H-bonding HF molecules assists the XB formation with NH_3 by deepening the σ-hole on X. This change is sensible in light of the loss of a certain amount of electron density from X to the HF units by virtue of each HB. The amount of this deepening is quite substantial; an increment of some 6−10 kcal/mol is associated with the addition of each new HF unit. These steps diminish as n rises, but only slowly. In the example of H_3CBr, the enhancement of 10.0 kcal/mol arising from the first HB is supplemented by another 9.0 kcal/mol for the second and 8.5 kcal/mol for the third. The HBs are also capable of changing the sign of V_{max} from negative to positive, for example H_3CCl or H_3GeCl. On the other hand, F is resilient to presenting a σ-hole, even in the presence of 3 HF molecules.

Vibrational Spectra. The A−H stretching frequency of the proton donor is well-known to shift to the red in the vast majority of H bonds.[64−67] The shifts in frequency occurring in the T−X stretch of the Lewis acid are collected in Table 5.

Table 5. Change in T−X Stretching Frequency (cm^{-1}) Caused by Complexation with NH_3 When H-Bonded to n HF Units

n =	0	1	2	3
H_3CI	−2.7	−6.0	−11.7	−17.1
H_3CBr	−0.6	−10.5	−20.8	−31.1
F_3CBr	−4.6	−10.0	−14.5	−20.2
H_3CCl	1.9	−8.6	−27.7	−42.1
H_3CF			−91.2	−126.5
F_3CF	14.3	10.8	−18.2	−10.0
ImCl	−0.2	−0.8	−1.1	−1.8
BzCl	3.9	−2.1	−6.9	−11.4
BzF			−45.7	−64.1
H_3GeBr	4.5	−6.8	−16.2	−26.2
F_3GeBr	2.1	−4.1	−10.6	−14.9
H_3GeCl	8.3	−13.4	−40.0	−67.1

Focusing first on the dyads in the first column, these shifts occur in both directions, both positive changes to the blue and red shifts with negative values. In most, but not all cases, red frequency shifts are associated with elongation of the T−X bond. There is some consistency among several of the subsets of Lewis acids. For example, all Ge−X bonds contract and undergo a blue frequency shift. The same is true when the halogen is attached to an aromatic ring, with the exception of ImCl where the shift is negligible. The largest variability occurs in connection with the C−X acids, where most undergo a red shift, with the exceptions of H_3CCl and F_3CF, whose blue shifts coincide with a C−X bond contraction.

As the XBs are reinforced by the presence of the peripheral HBs to HF, there is a strong tendency for all frequencies to shift to the red. These decrements in ν are quite variable, less than 1 cm^{-1} for ImCl, but approaching 30 cm^{-1} for others, H_3GeCl especially. As was the case for many of the preceding parameters, these HB-induced red shifts do not fall off as n rises. H_3CBr provides a good example, where ν(CBr) decreases by 10 cm^{-1} for each additional HF unit added to the complex. As an added observation, just as in the case of Δr, the changes in ν caused by each new HF unit varies in the order $H_3CI < H_3CBr < H_3CCl$.

DISCUSSION

There is a certain amount of both experimental and computational support for the central idea that activity of a halogen atom as a proton acceptor in one or more HBs will accentuate its XB potency.[41,54] The replacement of Tyr within a protein by m-chlorotyrosine[51] raised its stability as well as its enzymatic activity as the newly introduced Cl atom engaged in a XB with the carbonyl O of a neighboring Gly. This XB was facilitated by the HB formed by this Cl to the OH on the tyrosine ring, even if the geometry of this internal bond was not in its optimal geometry. A molecule was constructed in which internal NH··I HBs occurred to I atoms on an aromatic pyridine ring,[48] which resulted in a 9-fold enhancement in the ability of I to bind to a halide nucleophile via a charge-assisted XB. The same sort of functional change occurred for an intramolecular NH··I wherein NH was part of an amide group[49] which bears direct applicability to protein function. Even a relatively weak HB such as that involving a CH group can provoke a stronger XB,[50] again within the context of an overall positive charge on the Lewis acid. Additional support arises from the study of enantioselective Michael addition[53] where an internal NH··X halogen bond activates a series of vinyl phosphonates. In these cases, the X atom was attached to a phenyl ring containing various electron-withdrawing substituents such as F and NO_2.

Calculations of neutral complexes have suggested that a CX··N XB to a substituted pyridine[68] can be strengthened by peripheral NH··X HBs, although the latter are highly bent. A joint spectroscopic/computational examination[69] pairing dihalogens with an aromatic ring containing both NH and C═O groups identified positive cooperativity between the X··O XB in the dimer and the NH··X HB to the same X atom. Certain dimers connecting DMSO with HOX[44] place the X atom so as to engage in both a XB and a HB, in which case the AIM parameters of the former are accentuated. There was also computational evidence provided[70] of HB/XB cooperativity in the (CH_3X)-(HNC)(HCN) trimer.

The calculations outlined above have demonstrated the ability of HBs to a halogen atom to greatly accentuate its ability to function as electron acceptor in a XB. This XB amplification grows continuously as each new HB is added and in a linear fashion which shows no sign of attenuating as the number of HBs increases. The strength of each XB is increased by severalfold as these HBs are added. The interaction energy of the CH_3I molecule, for example, more than doubles when the I is involved in 3 HBs. This continued growth is of particular import because a recent survey of protein−ligand crystal structures[52] has shown that multiple HBs to halogen atoms are not unusual: 3 is the most common number of such bonds which can range all the way up to 6. The introduction of these HBs is capable of allowing the formation of a XB where none is present in their absence. Although the XB involving ImCl is vanishingly weak, it will form a bond with strength greater than 2 kcal/mol when a single HB is present, growing to 5 kcal/mol if there are 3 such bonds.

In this same context, it is known that the F atom is particularly resistant to participation in a XB as Lewis acid. Crystal structures placing F in proximity to a potential electron donor are difficult to interpret as necessarily being due to any sort of attractive force.[71−74] There is some thought that such a bond might be induced in an intramolecular framework if the structure of the molecule is locked into a favorable but unusual configuration.[75] Recent computations[76] that addressed this particular question suggested a F−halogen bond, even a weak one, would require the F being attached to a very strong electron-withdrawing agent, as for example in NCF or F_2. The calculations presented here relax the requirement of this sort of extremely electronegative substituent. Even when covalently bonded to a simple and unsubstituted methyl or phenyl group, the F atom can be coaxed to form a XB amounting to 2−3 kcal/mol in the presence of two or more external HBs. This finding ought to have particular relevance to the activity of synthesized pharmaceutical agents which commonly contain a number of F atoms. In addition to any proton donors that might be present within the molecule itself, water molecules present in the aqueous milieu can serve a similar function.

The calculations have offered supplementary concepts concerning XB reinforcement by peripheral HBs. A primary vehicle by which this bond strengthening occurs is the electron transfer from X to the HF unit, which in turn deepens the X σ-hole. This hole augmentation continues to rise steadily with each new HB that is added to the system. The XB strengthening has geometric and spectroscopic implications as well. The $R(X{\cdot\cdot}N)$ halogen bond length diminishes steadily as n rises, shrinking by some 3−8% for $n = 3$. Whereas some of the covalent $r(T-X)$ bonds contract a small amount upon formation of the initial XB with NH_3, and their stretching frequency shifts to the blue, these bonds all stretch and red shift if there are external HBs present.

The calculations described above have considered NH_3 as the universal electron donor. This molecule was chosen as it is of moderate strength as a base, and its small size precludes the presence of complicating secondary interactions. It can be presumed that the XBs formed by the various Lewis acids would be enhanced if NH_3 were replaced by a stronger nucleophile, as would the increments added to each XB by external HBs. Incorporating the more basic NMe_3, for example, raises the dyad XB energy with H_3CCl from negligible for NH_3 to 1.52 kcal/mol. The XB energies in the presence of 1, 2, and 3 HF units are similarly increased to 2.94, 4.58, and 6.35 kcal/mol for $n = 1, 2$, and 3, respectively. These values represent increments to E_{int} of 1.4, 1.6, and 1.8 kcal/mol, actually rising as more HBs are added.

As a related issue, allowing the HF molecules to approach to their optimal distances from the halogen atom permits them to exert their maximal effect on the XB. Were the HBs to arise from intramolecular contacts, they would likely be held to longer distances from X by the geometrical constraints of the entire molecule. To assess how longer HBs might mitigate their effect, the H bond $R(Cl{\cdot\cdot}H)$ distances were all held constant at 2.5 Å from CH_3Cl, somewhat longer than their optimal bond lengths of about 2.2 Å. Making this change reduced the XB energies to 1.64, 2.97, and 4.40 kcal/mol for $n = 1, 2$, and 3, respectively, drops of 0.33, 0.53, and 1.10 kcal/mol relative to optimal HF positioning. As such, the lengthening of these HBs reduces the increment of XB energy caused by each additional HF unit from 1.6 to 1.4 kcal/mol. Note that the latter is only a bit smaller than the former, indicating that these HBs can have a substantial impact even at a distance.

Given the persistence of the XB reinforcing effect to increasing values of n, it would be reasonable to assert that the energetic reinforcement of a given XB will be roughly proportional to the number of peripheral HBs, as well as to the acidity of the surrounding proton donors, and their distance from X. It is hoped that these ideas will inform attempts to understand the underlying forces present in related chemical and biological systems.

It should finally be stressed that the systems examined here position the X atom in a central location where it can accept electron density from a nucleophile in a XB while simultaneously donating electron density to a proton donor in a HB. This situation should not be confused with some of those studied earlier within proteins[77] wherein it is a carbonyl group that is centrally located, serving as electron donor in both a HB and a XB simultaneously.

■ CONCLUSIONS

Adding external molecules that form n HB to the halogen atom of a molecule drastically enhances its ability to engage in a XB with a nucleophile. Each such HB raises the XB energy by an increment of more than 1 kcal/mol. This increment shows no sign of abating as H-bonding molecules are added, even for as many as three such HBs. Consequently, the presence of three HBs can magnify the strength of a given XB manyfold. Additionally, the presence of one or more HBs facilitates the formation of a XB by molecules that are reluctant to engage in such a bond in the absence of these auxiliary interactions. Even the F atom, which avoids such a XB, can be coaxed to participate in a XB of moderate strength by one or more of these external HBs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpca.2c07611.

Coordinates of complexes (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Steve Scheiner − *Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300, United States;* orcid.org/0000-0003-0793-0369;
Email: steve.scheiner@usu.edu

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.jpca.2c07611

Notes

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