An Updated Description of the Hydrogen Bond and Related Noncovalent Bonds

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ABSTRACT

The hydrogen bond is typically introduced briefly in General Chemistry as a simple electrostatic phenomenon involving a small and select group of atoms, a definition which is typically unchanged through higher levels in the curriculum. But this definition has undergone dramatic modernization of which students should be made aware. The original formulation in terms of only F, O, and N atoms has broadened very considerably, encompassing C as well as atoms from lower rows in the periodic table. The influence of hybridization, substituents, and overall charge cannot be overlooked. In addition to the Coulombic attraction, there are other "covalent" contributors such as charge transfer and polarization. Further broadening has occurred with the recognition that the bridging H can be replaced by a host of electronegative atoms in what have come to be denoted halogen, chalcogen, pnicogen, and tetrel bonds, with behavior very similar to H-bonds.

INTRODUCTION

A typical definition of a H-bond (HB) provided to freshmen, for example in Brown et al. [1], is "a special type of intermolecular attraction between the hydrogen atom in a polar bond (particularly an H-F, H-O, or H-N bond) and nonbonding electron pair on a nearby small electronegative ion or atom (usually an F, O, or N atom in another molecule)." This definition persists throughout higher levels of the chemistry curriculum, with only minor modifications, if any. For example, Levine [2] broadens the definition for higher-level physical chemistry students, but only slightly, allowing the idea that Cl and S can, "to a lesser extent" be included along with F, O, and N as electronegative atoms that might participate. It is at this level that a rationale is provided for the attraction, using the water dimer as an example. "In water, each OH bond is highly polar, and the small, positive H of one H_2O molecule is strongly attracted to the negative O of a nearby H_2O molecule". In other words, the attractive force is claimed to be Coulombic in nature, between the partial charges $H^{\delta+}$ and $O^{\delta-}$ of the two molecules. While the above concepts are inarguably correct, the vast body of research into the nature of the HB, which continues unabated to this day, has expanded the list of atoms that are involved, while also fleshing out the details of its fundamental nature. This report aims to update the reader as to our modern understanding of the HB, what are the contributing factors, which atoms and chemical groups can participate, and why is it that some HBs are stronger than others. It also expands the very definition of a HB to a set of very similar interactions, with atoms other than H acting as a bridge.

We begin with a definition and a caveat. A HB can be simply defined as AH··B wherein A is the proton donor atom (or group), and B is the proton acceptor. But it must be understood that the formation of this HB involves a transfer of a certain amount of electron density from B to A. In other words, A is both proton donor and electron acceptor, and vice versa for B. So the simple designation "acceptor", sometimes carelessly used in the literature, is an ambiguous one, and clarification is needed. The literature frequently refers to a HB energy. This term refers to the energy released when fully separated reactants AH and B come together to form the HB dimer, i.e. complex AH··B.

PROTON DONORS

The formulation of the H-bond which depends upon a polar A-H bond, with H as its positive end, would indeed mandate an electronegative A atom. But it must be remembered that the electronegativity of a given A atom in actual practice is not a single number, but depends upon a number of factors. Take the C atom for example. Its formal electronegativity is essentially equal to that of H. It is for this reason that the CH bond was historically not considered as polar enough to engage in a H-bond. But C takes on a variety of characteristics depending upon its covalent bonding environment.

1. Hybridization

Consider ethane as a prototype. The very similar electronegativities of C and H would lead to a basically nonpolar CH bond in C_2H_6. And indeed, ethane does not engage in H-bonds, nor do other alkanes. But C is not limited to the sp^3 hybridization of ethane. Other common hybridizations are sp^2 and sp, which would correspond to C_2H_4 and C_2H_2, respectively. One might expect the differing proportions of s and p orbitals mixed into the C-H bonds might affect the polarity of the C-H bonds. To quantify this idea, one can examine the molecular electrostatic potential (MEP) that surrounds a given molecule, corresponding to what an external point charge might feel. This potential is plotted out for each of the different hybridized molecules in Fig 1 where the red areas indicate negative potential, and positive regions are indicated in blue. The H atoms in C_2H_6 are surrounded by a very light blue area, signifying a slight C^-H^+ polarity. But open changing the C hybridization to the sp^2 of ethylene, this same region is darkened, indicating a greater polarity. This same trend is further enhanced in the sp environment of acetylene. In other words the sp C is considerably more electronegative than sp^3 C. Consequently, the CH group of alkynes are capable of engaging in H-bonds [3], even if fairly weak ones. The H-bond energy of HCCH with water, for example, is roughly half that of the water dimer with its classic OH··O H-bond.
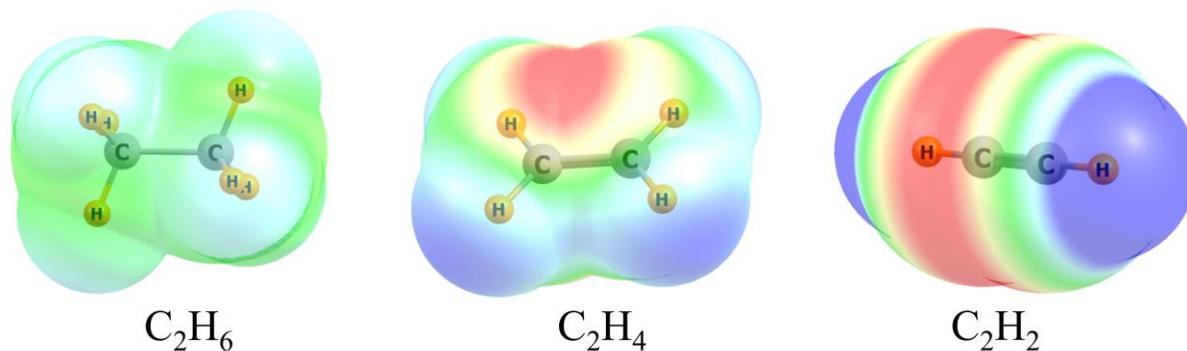
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C_2H_6 C_2H_4 C_2H_2

Fig 1. Molecular electrostatic potential surrounding hydrocarbons with different C
hybridization. Blue and red colors refer respectively to +0.025 and -0.025 au.

2. Substituents

As another very important factor, it must be recalled that the ability of C to pull electron density away from an adjoining H atom can be influenced by substituents. The strong ability of F atoms to shift electron density toward themselves would lead to a more positive H atom. This potential is plotted out for each of the fluorosubstituted derivatives of methane in Fig 2. As one, two, and then three F atoms are added to methane, the region around the H atom on the right progresses from a small very light blue area, to a larger region with a darker blue color, showing how the F atoms suck up electron density and make the H atom a more attractive target for an approaching electronegative atom such as the O of H_2O. And indeed, this fluorination process does allow the CH bond to act as a proton donor in a H-bond. Quantum calculations [4] show the interaction energy of each of the molecules in Fig 1 with a water molecule increases progressively from only 0.2 kcal/mol for CH_4, too weak to be considered a H-bond, to 1.3 and 2.5 kcal/mol for the mono and difluorinated species respectively, (weak H-bonds), and then to nearly 5 kcal/mol for CF_3H. The latter value is within 1 kcal/mol of the OH··O H-bond within the water dimer.
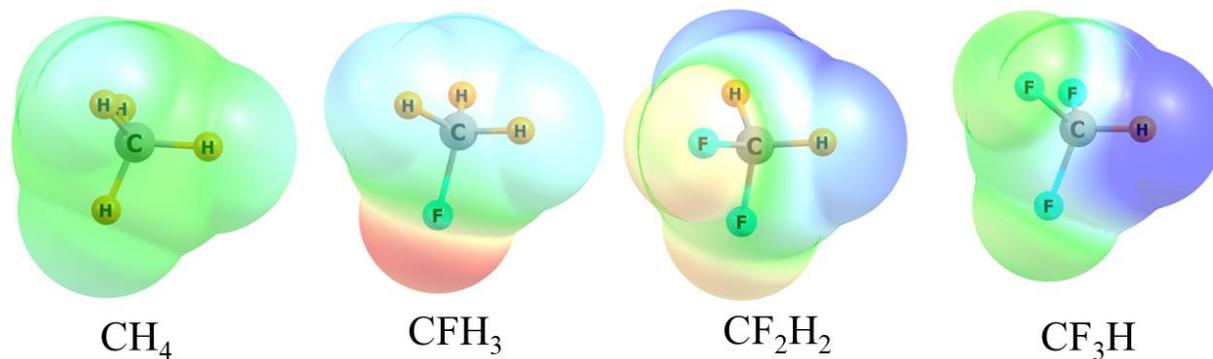
Fig 2. Molecular electrostatic potential surrounding indicated derivatives of methane. Blue and red colors refer respectively to +0.05 and -0.05 au.

3. Molecular Charge

In keeping with the idea that the proton acceptor molecule is drawn toward the partial positive charge acquired by a H atom, it is logical to suppose that this trend would be enhanced if the proton donor entity is a cation, with a full-fledged positive charge. And indeed such is found to be the case. Going by several names, such as ion-molecule, ionic HB, or charge-enhanced HB, these interactions are indeed quite strong [5]. The OH··O H-bond energy of the water dimer, for example, is magnified six-fold [6] in $(H_3O)^+$··OH_2. In its sp^3 hybridization, the CH_3 group of trimethylamine engages in only a weak H-bond with a poor proton acceptor, but this interaction is strengthened [7] by a factor between 4 and 7 when the proton donor acquires an overall positive charge.

4. Real World Applications

The ability of the CH group to engage in H-bonds is of more than passing or academic interest. CH··O and CH··N H-bonds have proven to be important in the structure of a number of different systems. Combined experimental and theoretical data illustrated its contribution to the conformational preferences of α-fluoroamides [8] and to the catalytic function of enzymes [9]. While NH··O H-bonds are certainly of proven importance to protein structure, it must be recalled that the peptide group, as well as numerous amino acid sidechains contain CH groups that are potential proton donors. A prime candidate is the C^{α}H of the peptide backbone which can participate in CH··O H-bonds with energies roughly half that of the OH··O HB of the water dimer [10], and even stronger if a cationic residue such as Lys$^+$. Although the interaction between adjacent strands of the β-sheet structure of proteins is attributed to interchain NH··O

HBs, there is evidence [11] that CH··O HBs make a contribution to the stability that is only slightly smaller. Sidechain groups are also competent proton donors, as for example [12] the imidazole CH groups of the His side chain. Interestingly, depending upon the precise conformation of the polypeptide backbone, CH··O HBs can even surpass [13,14] NH··O HBs in terms of strength

It is not only C whose electronegativity can be bumped up high enough to donate protons in H-bonds, but this same logic applies to a host of other atoms throughout the periodic table. Since C has proven it can donate protons, it is not surprising that the same can be said of its neighbors in the periodic table first row of the periodic table B [15] and N. Second row atoms P, S, and Cl fall into this category, as is also true of Se, Br, and I [16].

CONTRIBUTING FACTORS

Before proceeding to a discussion of proton acceptors it would be useful to update the earlier ideas about the underlying forces that contribute to H-bonding. The Coulombic attraction between the positive potential around the bridging H, and the negative region of the approaching base is undoubtedly a strong factor, and in most cases accounts for more than half of the total. But it must be understood that the approach of the base toward the proton donor induces rearrangements of its electron density, and vice versa. The energetic manifestations of these shifts can be categorized as polarization if internal to each molecule, and charge transfer if they involve motion of density from one molecule to the other. In the case of H-bonds, there is a characteristic shift from the lone pair of the nucleophile into the A-H σ^* antibonding orbital, sometimes referred to as n→σ^*. It is this shift that is responsible for the well known elongation of the A-H bond, and the red shift of its A-H stretching vibrational frequency. Sometimes no attempt is made to separate intermolecular charge transfer from internal polarization, and their total is called induction. These inductive forces are categorized by some as "partial covalency". Yet another contributing factor is termed London dispersion in General or Physical Chemistry texts, due to instantaneous charge fluctuations in the two monomers, but would not ordinarily be connected with covalency.

A great deal of data amassed over recent decades can be generalized as follows, with the caveat that there are numerous exceptions to these rules. Coulombic attraction is typically the largest contributor accounting for perhaps 50-65% of the total bond energy. Induction makes a smaller, but by no means negligible, contribution, as well as accounting for structural and

spectroscopic effects of H-bonding. Induction is usually smaller, but grows if the participating atoms are drawn from lower rows of the periodic table, e.g. S or Cl. In summary, H-bonding cannot fairly be termed a purely electrostatic phenomenon, as it involves a modicum of covalent factors.

PROTON ACCEPTORS

One of the prime factors allowing an atom to accept a H-bonding proton is the presence of a negative electrostatic potential. It is partly for this reason that the lone pairs of atoms such as O and N are the primary proton acceptors in most H-bonds. But there are other atoms that retain at least one lone pair within their typical bonding environment, such as P [17,18], S [19], Se [20], Cl [21,22], Br [15,23], and I [24], all of which are demonstrated proton acceptors, even if perhaps not as strong as O and N. Even metal atoms can serve as proton acceptors in certain circumstances [25,26]. It should be stressed that while electronegativity offers an advantage in a proton donor, the reverse is true for the acceptors. The less electronegative atom holds on to its lone pair less tightly, thus making it more available to the proton, so as a general rule $N > O > F$ as proton acceptors. And it should be emphasized as well that just as hybridization affects proton donating ability, the same can be said of acceptor potency. The sp^3 N lone pair of amines is a better proton acceptor than the sp^2 N lone pair in an amide. It is for this reason that the backbone peptide N atom is a rare partner in HBs within proteins, despite the prevalence of this atom in every single residue. Note that again the proton accepting trend: $sp^3 > sp^2 > sp$, is the reverse of the donation pattern.

It may be recalled from the above section that a second component for H-bonding is the transfer of electron density from the proton acceptor to the donor. Lone pairs are not the only possible source of charge. The loosely held π electrons within a double or triple bond can serve the same function, as can the π electrons of an aromatic system [27]. There is evidence that even the more tightly held electrons of a σ-bond, as in H_2 for example, are amenable to H-bond formation [28]..

Returning again to the electrostatic attraction common to most H-bonds, there is a tendency for the A-H donor to be drawn toward any negative region. There are certain bonding situations wherein a H atom can bear a partial negative charge, for example when bonded to a metal atom M. When a common $A^{\delta-}$-$H^{\delta+}$ group approaches such a $M^{\delta+}$-$H^{\delta-}$ bond, there is a tendency for the two H atoms to attract one another, in what has been christened a dihydrogen bond [28].

COUSINS OF H-BONDS

As indicated above, one of the prime factors that enables the formation of a HB is the positive potential surrounding the proton. This aspect is highlighted by the blue area near the H in the molecular electrostatic potential (MEP) of HCl in Fig 3a. Now suppose we replace the H atom by a CF_3 group. The MEP of the CF_3Cl molecule in Fig 3b has displaced the blue region to the Cl atom. Doesn't this violate the central idea of General Chemistry that halogen atoms acquire partial negative charges? Yes and no. In the first place, the CF_3 is an electron-withdrawing group, so a partial positive charge on the Cl is not entirely unreasonable. But note also that although there is a blue area along the extension of the C-Cl bond, there is an equatorial belt of much less positive, even negative potential perpendicular to this bond. In other words, the potential around the Cl atom is highly anisotropic so its overall charge is largely irrelevant. This positive region along the bond extension is commonly referred to as a σ-hole [29]. If the CF_3 is replaced by a simple F atom, this σ-hole is intensified as in Fig 3c.

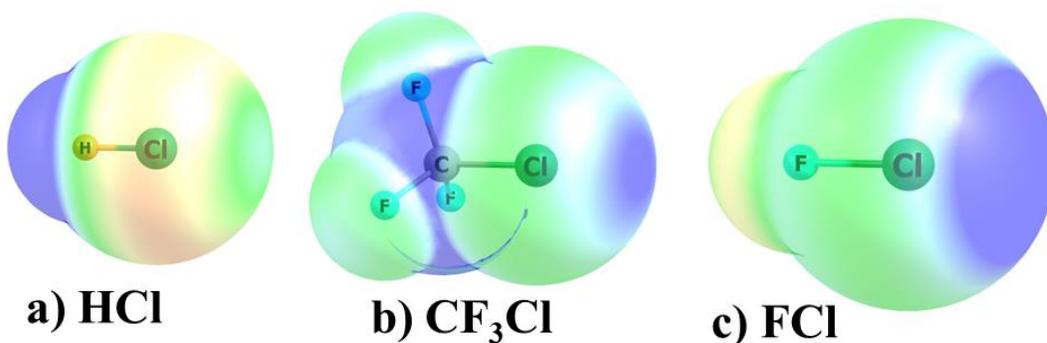a) HCl   b) CF$_3$Cl   c) FCl

Fig 3. Molecular electrostatic potentials of HCl, CF_3Cl, and FCl. Blue and red colors refer respectively to +0.03 and -0.03 au.

Could this positive MEP attract a nucleophile in the same way as the proton of HCl? Well, why not? Not only would one have the correct electrostatic attraction, but the charge transfer component of the H-bond could be preserved. Instead of transferring into a σ*(ClH) antibond, the charge would simply accumulate in the equivalent σ*(C-Cl) (Fig 3b) or σ*(F-Cl) antibond of Fig 3c. Even the dispersion attraction of a H-bond could be duplicated. In other words, the bridging H atom has simply been replaced by a Cl atom in what has been come to be known as a "halogen bond", or simply XB.

There are several factors that play into the strength of the XB. In the first place, the lower the electronegativity of the X atom, the more positive can be its potential. The MEP surrounding the FX molecules, wherein X is one of the halogen atoms, is portrayed in Fig 4. It may be seen that the blue area to the right of X, i.e. the σ-hole, becomes bluer and more intense as X becomes larger. This larger size also makes for a more polarizable X atom, which also contributes to the strength of the XB. Indeed, the very electronegative nature of the small F atom makes it a reluctant participant in halogen bonding. Just like in H-bonding, the placement of electron-withdrawing substituents on the halogen-donor molecule adds to the strength of any XB.
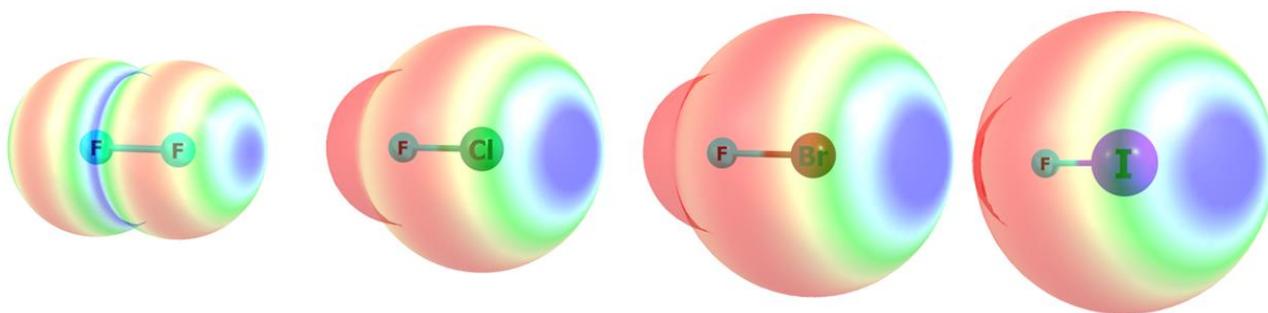

Fig 4. Molecular electrostatic potentials of FX, X=F,Cl,Br,I. Blue and red colors refer respectively to +0.05 and 0.00 au.

There is no reason that these ideas must be limited only to halogen atoms. Other electronegative atoms toward the right of the periodic table are subject to many of the same principles. Fig 5 illustrates the MEPs surrounding FSH, FPH_2, and $FSiH_3$, all of which display a blue positive region to the right of the central atom. Each of them contains a σ-hole opposite the electron-withdrawing F atom, in addition to any positive areas associated with the H atoms. The noncovalent bonds in which each of these molecules engage with a nucleophile are typically designated as chalcogen, pnicogen, and tetrel [30-34], corresponding to the particular family of the periodic table.
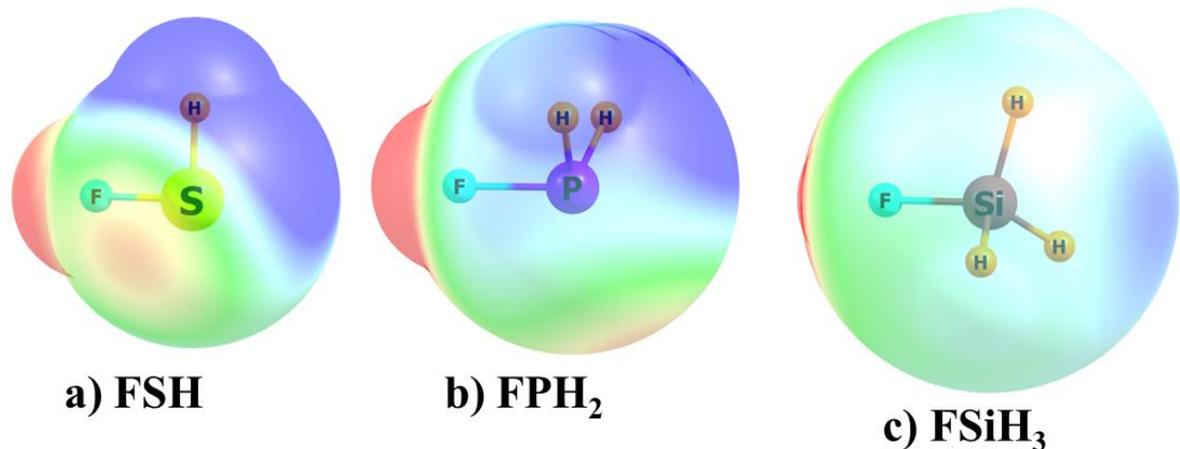
Fig 5. Molecular electrostatic potentials of FSH, FPH$_2$, and FSiH$_3$. Blue and red colors refer respectively to +0.03 and -0.03 au.

The complexes formed by each of these molecules with NH$_3$ as the common base are illustrated in Fig 6. In keeping with the shape of the MEPs in Fig 5, the halogen and tetrel bonds are both linear, whereas the N is situated above the F-S/P axis for the chalcogen and pnicogen bonded structures. There is a general trend of diminishing binding energy: halogen > chalcogen > pnicogen > tetrel. But it is important to stress that these are quite strong bonds. They are all stronger than the paradigmatic HB energy in the water dimer which is only 5 kcal/mol. So these sorts of noncovalent bonds are far from negligible, and can play important roles in the structure and reactivity of a host of molecules.
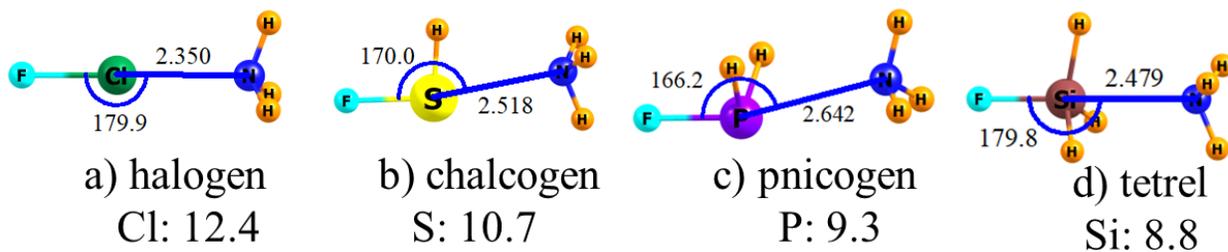

Fig 6. Geometries (Å and degs) and binding energies (kcal/mol) of various types of noncovalent bonds, with NH$_3$ as base.

As these sorts of interactions have gained traction in the literature, there has developed a need for some definition. After first tackling the recent broadening definition of the HB [35], IUPAC has gone on to commission a report on the XB [36], and there is another group currently developing a definition of the chalcogen bond, with others dealing with pnicogen and tetrel bonds sure to follow in short order.

Other features which these σ-hole interactions share with HBs are

1) the distance between the two closest atoms of the two molecules is shorter than the sum of their vdW radii.

2) a stretch of the A-E distance (where E represents the bridging atom)

3) the θ(A-E⋯B) angle tends toward linearity (B represents the electron donor or basic atom).

SUMMARY AND PERSPECTIVE

It should be clear then that the original concept of a H-bond has undergone extensive broadening over the years since its earliest inception. While the original highly electronegative F, O, and N atoms are of course still prime participants, there are many more atoms that can become involved as well. It is important to add in to this equation the hybridization of the atoms that can affect the HB strength, and at times determine if a HB possible is even possible. Another important factor is the set of substituents that surround the proton-donating and accepting atoms, or the presence of a full-fledged charge on either molecule. It is not only a lone pair on the basic atom that can be "shared" with the proton donor, but also the π-systems of the nucleophilic molecule. While simple Coulombic attraction between a polar A-H bond and a nucleophile is undoubtedly a very important element in the constitution of a HB, it is complemented by other essential ingredients. The latter include London dispersion and forces that can be considered as partially "covalent"; viz. charge transfer, polarization, induction, as well as other labels.

Although technically not HBs, the replacement of the bridging H by any of a large set of electronegative atoms leads to interactions that are different from HBs in only minor details. These so-called halogen, chalcogen, pnicogen, and tetrel bonds have very similar characteristics as HBs, shared dependence on substituents, a similar propensity for a linear atomic arrangement, depend upon the same physical phenomena for their binding, and have strengths that are easily

the equal of the classical HBs. They have been the focus of a great deal of scrutiny in recent years, and this examination is likely to continue for years to come.

 As they are becoming more widely recognized, whether weak HBs or their related cousins, researchers are beginning to look for their presence in systems where they were not previously noticed. One example comes from protein chemistry where the possibility of a CH··O HB was barely even considered for many years. But along with recent work that has documented their existence has come a continuing string of re-examinations of protein structures that see solid evidence of their presence, and their possible roles in structure and function. The same phenomenon is in evidence in the literature for halogen and related bonds which are rapidly becoming a handy tool in crystal engineering. There is every reason to believe that work will continue in these avenues and we will learn about new aspects of these and other sorts of noncovalent bonds.

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