Forty Years of Progress in the Study of the Hydrogen Bond

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Abstract

The author looks back at developments over the last few decades concerning the H-bond. The list of atoms involved as proton donor and acceptor has broadened dramatically, including most electronegative atoms and even metals. The factors that control the transfer of the proton across the H-bond have been elucidated and show the importance of even minor changes in its geometry. Small stretches can shut down the transfer entirely and certain bends can force a proton to transfer against a pK gradient. Along with recognition that a CH··O interaction can represent a true H-bond, and one with strength comparable to more traditional H-bonds, has come an understanding of its contributions to protein structure and function. The replacement of the bridging H by any of a litany of electronegative atoms leads to similarly strong interactions, with many features virtually indistinguishable from a true H-bond. These noncovalent interactions are typically referred to as halogen, chalcogen, pnicogen, and tetrel bonds, depending upon the identity of the substitute bridging atom.

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This account serves as a flash summary of the areas that were of interest over the career of the author. The reader will hopefully glean the state of knowledge of each area at certain points in time, and how research by this group and others contributed to our current state of knowledge about each. As discussed below, the field under study here is the H-bond (HB), broadly defined. In addition to the structural, energetic, and spectroscopic aspects of this interaction, we have acquired quite a few new insights about the sorts of proton donor and acceptor atoms that can participate in a HB, the factors that control the proton transfer across the HB, the nature and applications of weak HBs, and the extension of the HB concept to very similar interactions that replace the H by some other element.

In the mid 1970s, when the author began his first research project as a graduate student, the concept of the HB had undergone some refinement [1-4] since its first inception earlier in that century. Experimental evidence for this interaction was derived from a number of directions. Crystal structures and microwave geometries were concerned with structural features, primarily short AH··D contacts and roughly linear arrangements. Vibrational spectroscopy sought out red shifts of the ν(A-H) stretching frequency, coupled with band intensification. NMR signals of the bridging proton were shifted downfield. And it was generally considered that the magnitudes of these effects were closely correlated with the strength of any such HB. The sources of stability of the HB were attributed first to an $A^{\delta-}-H^{\delta+}\cdots^{\delta-}D$ electrostatic attraction arising from the polarization of the A-H bond and the presentation of a lone pair of the D atom toward the approaching proton. A second contribution arose from a certain degree of charge transfer from the D lone pair into the σ^*(AH) antibonding orbital, which in turn was largely responsible for the weakening and lengthening of the A-H covalent bond, coupled to the ν_{AH} red shift. In terms of the nature of the A and D atoms in the AH··D HB, it was traditionally held that they must be electronegative atoms of the first row of the periodic table, i.e. N, O, F. With respect to the possibility that a proton could be transferred between the A and D atoms, it was widely held that transfer within a neutral system, that would generate a $A^-\cdots^+HD$ ion pair would be energetically disfavored. But there was little information concerning the transfer within an ionic system, e.g. $AH^+\cdots D \rightarrow A\cdots H^+D$, that would not generate a high-energy ion pair, and could in fact be an exothermic process.

In the mid 1970s, the status of computers was such that ab initio quantum chemical methods were hard pressed to be applied to systems much larger than benzene at a level that could be

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considered quantitatively reliable. Indeed, the majority of studies at that time were limited to the Hartree-Fock level, unable to include electron correlation in any meaningful way. To make matters worse, such calculations were forced to employ basis sets that are appallingly small and inflexible by current standards. For this reason, calculations of larger systems, with a size approaching biological applicability, were limited to semiempirical methods such as CNDO and MNDO. These approaches had the virtue of economy but were heavily based on empirical parameters, and their accuracy for processes for which they had not been parametrized could be dubious. Indeed, one of their earliest weaknesses had been their inability to handle HBs with even qualitative accuracy.

Early Study of Enzymatic Activity

For these reasons, there had been little in the way of quantum chemical calculations of a system that was large enough that it could be characterized as a model for a biological system up through the mid 1970s, at least with anything approaching quantitative accuracy. Fortuitously, the research group that I had just joined had recently developed a new method, with the acronym PRDDO, which approximated ab initio calculations but accompanied by a lesser drain on computer resources. This new approach allowed us to examine the mechanism of the chymotrypsin family of enzymes, which were able to break peptide bonds in substrate proteins. It had been proposed earlier that a key component of this mechanism was what was called a charge relay mechanism, consisting of a triad of residues: an Asp residue, connected to a Ser group through the intermediacy of a His. It was thought [5] that the Ser-OH group could swing down and attack the substrate peptide C, a process which would be aided if the Ser could be deprotonated. The charge relay system would function as the His N atom would remove the Ser proton, while at some point donating its NH proton up to the Asp carboxylate group. But there were numerous questions as to the energetic feasibility of this set of proton transfers, as well as the timing.

It was to this process of proton transfers within the pre-existing HBs that the PRDDO calculations were applied. The heart of this process [6,7] is portrayed in Fig 1 which displays the residues schematically in part a, and their actual geometrical disposition in part b which shows the two key inter-residue HBs. Fig 1c depicts the result of the two proton transfers, along with the attack of the Ser O atom to the C of the peptide, resulting in a tetrahedral intermediate. The PRDDO calculations provided evidence that a simultaneous double proton transfer is

energetically prohibitive; a stepwise process is preferred. Another essential ingredient of this process rests on the mobility of the central His residue. In order to pick up the proton from the Ser-OH, it must first swing down toward it, shortening the OH$\cdots$N HB. Once protonated the HisH$^+$ then swings up toward the aspartate, delivering a proton to its carboxylate group. But it was important to note that even with the stabilization that occurs by proton transfer from the HisH$^+\cdots^-$OOC-Asp ion pair to the more stable neutral His$\cdots$HOOC-Asp, this process cannot occur unless the two groups come close enough together. In other words, these calculations suggested the previously unappreciated importance of HB length to the ability of a proton to transfer within this bond.

Systematic Examination of Proton Transfers within HBs

It was natural to presume that this strong linkage between HB length and proton transfer (pT) is not limited to just the chymotrypsin family, but is a more general rule that applies to the numerous enzymatic processes that contain a proton transfer as an essential element. Moreover, the process of proton conduction in aqueous systems and in ice was thought [8,9] to begin with a long chain of HBs: $AH_a\cdots BH_b\cdots CH_c\cdots\cdots ZH_z$. The process begins with a single proton from A to B: $A\cdots H_aBH_b\cdots CH_c\cdots\cdots ZH_z$, followed by another from B to C: $A\cdots H_aB\cdots H_bCH_c\cdots\cdots ZH_z$, and so on to $A\cdots H_aB\cdots H_bCH_c\cdots\cdots H_cZH_z$, after which H_cZH_z can discharge its proton H_z. So the entire process conducts 1 net proton, but no individual proton moves very far, each one simply transferring between a pair of neighboring groups. This Grotthus or "bucket brigade" proton-shuttling mechanism, equated to a "proton wire" due to its analogy to an electron-carrying wire, would obviously be stunted were any of the single pT processes prevented, which again emphasizes the need for a more thorough understanding of the factors that influence pT.

This task was accomplished methodically, using small molecule models of the various functional groups that are present in proteins. The first sorts of molecules, used for illustrative purposes here are the hydroxyl groups, as contained in water molecules. Each transfer potential was evaluated [10] for a fixed interoxygen $R(O\cdots O)$ distance, as might occur for example if the two hydroxyl groups were held in place by a protein backbone. As illustrated in Fig 2, the barrier to pT is quite small for short separations, and even disappears for R<2.4 Å as the transfer potential takes on a symmetric single-well character. But the barrier grows quickly as the water separation elongates, climbing by 17 kcal/mol for a stretch of only 0.4 Å from 2.55 to 2.95 Å. Note also that the transfer properties are hardly influenced if the two central waters are flanked

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by two peripheral molecules. The earlier observation for the chymotrypsin model that a simultaneous transfer of two protons was energetically disfavored as compared to a stepwise process was confirmed here in the general case [10].

Continuation of these sorts of calculations for a number of other chemical groups, i.e. amine, sulfhydryl, carbonyl, imine, carboxyl, alkyne, $N\equiv CH$, alkene, amide [11-21] verified many of these trends, nor was there much perturbation when the groups were enlarged by adding alkyl groups [22,23], and the trends remain if the pT occurs between a pair of anions as opposed to two neutral entities [22,24-26]. The similarity in these trends is most evident in Fig 3 which characterizes the simpler hydrides of O, N and S. For example, the transfer between N atoms must overcome a slightly lower transfer barrier than does $OH\rightarrow O$ at a given HB length, and that between S atoms is even lower, but the rapid increase in barrier with R is quite similar. The data in Fig 3 also extend to asymmetric transfers between two different atoms. These barriers also show steep increase with R, but depend on the additional factor of the different proton affinities of the donor and acceptor groups [11,14,27-29].

It is of course understood that a higher barrier will slow down a chemical process, but it was deemed useful to have some quantitative assessment of just how much. An early analysis [30] focused on the quantum tunneling by way of the splitting between vibrational levels, placing the process in the ps time scale. But any factor which removed the perfect symmetry of the pT potential would drastically slow the transfer process. More sophisticated calculations [31] employed a variant of RRKM theory, with the inclusion of tunneling, so important for the transfer of the very light proton. Indeed, the latter accelerates the tunneling rate by a factor of 30 at 27 C, and even dominates the process for temperatures below 200 K. The bottom line was that the rate of pT is excruciatingly sensitive to the transfer barrier. For example, increasing the barrier from 12.1 to 15.4 kcal/mol drops the pT rate by 3 orders of magnitude at a temperature of 300 K.

The rapid rise of pT barrier with intermolecular separation, when coupled to the high sensitivity of pT rate to barrier, leads to an important principle guiding this process in enzymes and other sorts of systems. The HB distance can be thought of as a sort of spark plug gap. In order for a pT to occur between the two groups engaged in a HB, they must approach close enough for the "spark" to be able to jump across the gap, i.e. there is a critical HB length, beyond which the proton is unable to transfer. This idea offers a more general expression of the ideas

described above for chymotrypsin where the proton-shuttling His residue needed the mobility to move back and forth between the ultimate donor Ser and acceptor Asp residues.

Angular Aspects of the HB

Just as a protein may hold the two groups apart at some distance other than their preferred HB length, these same macromolecular restraints prevent them from achieving their optimal angular orientations, as shown by countless surveys of HBs in proteins. Many of the earlier studies mentioned above had in fact found that angular deformations of this type raise the proton transfer barrier, analogous to the stretches. An interesting aspect of this idea is that a misalignment of only one of the two groups can lead to an asymmetric pT potential even if the two groups are identical. Perhaps even more interesting, and with important implications, a suitable angular deformation can push a proton toward the less basic of the two groups. Or to put this into enzymatic language, a protein can push a proton in either direction along a HB, even against as pK gradient, simply by adjusting the angular aspects of this HB.

An illustrative example of the importance of this principle can be drawn from the case of bacteriorhodopsin (bR). This membrane protein enables certain halophilic bacteria to convert light energy into a transmembrane proton gradient. It was thought that the absorption of a photon caused a geometric isomerization that altered the orientation of a protonated Schiff base (imine) with respect to a neighboring amine group. In some way, this rearrangement led to a proton transfer from the imine to the amine, which was the key step.

The misalignment ideas arising from the calculations of pT in general were able to provide a possible answer as to the linkage between isomerization and proton transfer [32]. The imine and amine were modeled by the simple $H_2C=NH$ and NH_3, both competing for a proton between them. They were held apart by a fixed distance, but the orientation of the NH_3 with respect to the imine was varied so as to simulate the effect of the isomerization within bR. The pT potential on the left of Fig 4 shows proton association with the imine is more favorable by 2.5 kcal/mol when the two groups are perfectly aligned. However, the situation reverses if the amine is turned away from the imine, and the proton now prefers association with the imine by the same 2.5 kcal/mol. In other words, the misalignment of the HB, caused in this case by an isomerization, pushes the proton across from one group to the other.

Although this reversal might at first sight seem counterintuitive, it is easily explained based on simple principles involving Coulombic interactions between the charge distributions of the

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two species [17,33-36]. While this idea has direct application to bR, it is far more general and involves any groups, not just imine and amine, and within varying environments [37,38] and has much further reaching implications for enzymatic activity and for reaction mechanisms in general. In brief, this principle can be stated as follows: one can push a proton from one group to another within a HB simply by manipulation of the angular characteristics of the HB.

Other Aspects of Proton Transfer

Along with these fundamental aspects of pT that were examined systematically, there arose a number of interesting ideas in the literature that lent themselves to detailed verification or refutation. For example, one of the central ideas of electron transfer theory arose with Rudy Marcus's theory [39,40] relating the energy barrier of the process to the electron affinities of the two units competing for the electron, along with several other parameters. It seemed natural to wonder if this same set of ideas could apply equally well to proton transfers. Such a test [23] was successful for the transfer in an arbitrary AH··D system. The only parameters required for estimation of the proton transfer barrier in any generic system were i) the pT barrier that pertains to a fully symmetric transfer in AH··A and ii) the overall exothermicity of the AH··D system. The quantity estimated in this fashion was a dead-on mimic of the actual barrier calculated for the entire process. Not only was this approach found accurate for asymmetric AH··B systems, but was equally applicable when an asymmetry was introduced [41] by external agents such as ions and point dipoles. The accuracy of this approach opened the door to estimating pT barriers in any arbitrary system, however large.

Another interesting hypothesis had arisen with the introduction of the idea that a HB formed between two units A and D with very similar pKs, i.e. proton affinities, would have an outsized HB energy. The A and D units would, according to this speculation, be drawn in to a very close approach which would in turn result in the proton occupying a position midway between the A and D units. This idea was proposed [42-44] in conjunction with the unusual characteristics of certain enzymes; it came with several labels, including very-strong HB (VSHB) or low-barrier HB (LBHB). The topic seemed ripe for a rigorous quantum mechanical test, since some of the requisite features could be included in the systems under study, and the effects of slight variations therefrom determined accurately. The calculations [45] refuted the suggestion in a number of ways. For electrically neutral HBs, there is simply not enough energy available. No matter what the bond length, even shorter than its equilibrium value, one simply cannot stabilize

the system by the 10-20 kcal/mol proposed. Ionic HBs, pairing a cation AH^+ with a neutral D, are typically quite a bit stronger, and usually significantly stronger. But this strength is not drastically affected by pK difference. As one introduces asymmetry into the system, and a small pK difference, the interaction energy does not change in a precipitous manner as the theory would predict, but rather changes much more gradually. These principles emanating from the quantum calculations found experimental support as well [46-48].

Nominally Weak HBs

As we watched the broadening of the list of atoms that might be involved in HBs, the C atom grew in importance. The C-H group is so pervasive in chemistry and biochemistry, that its ability to participate in a HB is of utmost importance. While a simple alkane does not provide a sufficiently polar CH group to act in this fashion, it is well documented that a HB is formed if the C changes its hybridization from sp^3 to sp, as in $HC{\equiv}CH$ or $N{\equiv}CH$. Another means to amplify the CH polarity is the placement of electron-withdrawing substituents on the C, as would naturally occur in a protein where each $C^\alpha H$ is flanked by a pair of peptide groups. There was some early opposition to referring to a CH··O interaction as a true HB which rested on a quirk in their behavior. Specifically, instead of shifting the A-H stretching frequency to the red as had been taken as a necessary condition of a AH··D HB, a certain subset of CH··O interactions shifted the C-H stretch to the blue. Although all other aspects of the interaction were fully consistent with traditional HB behavior, this one anomaly led some to rule it out as a true HB, referring to it instead as a "blue-shifting", "unconventional", or even "anti" HB. However calculations from our lab and from others [49-53] quickly countered this idea, and established its bona fides as a member of the HB class.

As they had inspected their protein structures over the years, it was the rare structural biochemist to even consider the possibility of a CH··O HB, even when the two groups were perfectly aligned. But as the landscape changed and CH··O HBs were documented in so many chemical systems that one lost count, it was time for the world of proteins to accept this new reality. Alongside the experimental track, quantum chemistry was evaluating the criteria for accepting the presence of such a HB, as well as its energetic consequence. Our own lab showed [54] that the $C^\alpha H$ group of nearly any amino acid could participate in such a bond and established its strength as just below that of a standard NH··O interaction. With respect to

sidechains containing an aromatic group, e.g. Tyr or Im, the CH of the aromatic ring was also a viable proton donor [55].

In terms of some of the most common secondary structures within proteins, it had been part of conventional wisdom that it is the NH··O HBs between strands that hold the β-sheet together. But a glance at the actual structure in Fig 5 shows that CH groups might also serve this same function, a possibility which had heretofore been completely ignored. Quantum calculations addressed this issue specifically [56] and found quite the opposite: The interstrand CH··O HBs were competitive in strength with NH··O, and serve as an integral component in the stability of the β-sheet, a finding that has since been confirmed by others [57-62].

More detailed and thorough examination showed something perhaps even more surprising. It had been long presumed that a HB between two given groups depends only upon their relative geometry, i.e. HB length and angles. But quantum calculations showed this not to be the case. Even when a pair of peptide groups is locked into a given configuration [63], the interaction energy is highly sensitive to the overall structure of the polypeptide chain on which they occur. In particular, extended conformations of a polypeptide are capable of only weak NH··O HBs, and the interstrand NH···O H-bonds in parallel and antiparallel β-sheets are weaker than those found in other conformations, such as helices, ribbons, and *β*-bends, even if the specific HB geometries are similar. In a similar vein, the CH··O HB is even stronger than NH··O within the context of a simple dipeptide [53] when in a C_5 geometry, a small model roughly approximating the β-sheet. These trends, so important to protein structure, are not restricted only to *in vacuo* settings, but retain their integrity within the context of a dielectric continuum model of a protein interior [64].

The importance of the CH··O HB is not limited to structural aspects per se. As the prevalence of this interaction was increasingly recognized, it was invoked in various enzymatic mechanisms. Our group tested out one of these ideas within the context of the serine proteinase family of enzymes [65]. Earlier workers had suggested what they called a "ring-flip" hypothesis involving a 180° rotation of a key His residue as a vital step in the catalysis. This mechanism relied on the presence of a CH··O HB in order to stabilize one of the intermediates in the formation of the tetrahedral intermediate. The calculations were generally supportive of this idea but raised some important discrepancies that required resolution before its acceptance. This sort of HB has implications in other enzymatic mechanisms as well [66]. There are also contributions of this weak HB as a determining factor [67-69] in the conformation of certain

organic systems. Needless to say, even normally weak HBs can be strengthened by the acquisition of charge on either the proton donor or acceptor group [70-72].

As experimentalists continue to examine systems for the presence of CH··O HBs, they require certain trademark or fingerprint characteristics for which to search. In addition to geometric aspects which are already fairly well understood, it is common to apply spectroscopic methods to these biological systems. Quantum calculations have provided some such characteristics for which to search [73-75]. It was noted earlier that CH stretching frequencies can shift in either direction; nonetheless a blue shift would be a valuable indicator as it would not occur in the absence of such a bond. A downfield shift of the bridging proton's NMR signal would reinforce this supposition. With respect to the proton acceptor, a large upfield shift of the O chemical shift, by as much as 16 ppm, can serve as another indicator.

Cousins of HBs

In terms of broadening the definition of a HB, what could be more of a drastic change than removal of the H itself. Over earlier decades, there had been development of the idea, and substantial discussion [76-78] of halogen bonds, a A-X···D connection, where X=Cl, Br or any other halogen atom, and D again represents a nucleophilic electron donor. What made this proposal seem counterintuitive is the partial negative charge that should arise on the electronegative X atom that ought to repel, rather than attract, a nucleophile. The resolution of this apparent paradox was an analysis of the electron density surrounding the X atom. There is indeed an overall accumulation of electron density around this atom which imparts to it a partial negative charge. But this density is not uniformly distributed. There is a deficit along the extension of the A-X bond, which has been termed a "polar flattening", which in turn causes a region of positive electrostatic potential in this region, commonly referred to as a σ-hole [79-83]. It is this localized positive region which can attract a nucleophile, in much the same way as does the H in a AH··D HB. This σ-hole is illustrated for the CF_3Br molecule in Fig 6a, along with the negatively charged belt.

Nor is this idea limited to halogen atoms. Fig 6b shows the potential around the chalcogen Se atom also contains a σ-hole opposite the CF_3 group. Its attractive interaction with a nucleophile would thus be termed a chalcogen bond. Note that the H atom bonded to the Se is also positive, allowing the possibility of a SeH··D HB which might compete with a chalcogen bond. The equatorial belt surrounding the halogen atom, is replaced by a negative region along a

Se lone pair direction (actually two of them, one not shown). A very similar potential is present for the As atom in Fig 6c, which can engage in what is commonly called a pnicogen bond. The absence of a lone pair on Ge in Fig 6d eliminates a negative region near this atom, but retains both the σ-hole and positive H areas, so this molecule might engage in either a tetrel or H bond.

   This idea resonated with the author in the context of a 2011 joint study of weak HBs [84] with an Iranian group. When a phosphine was paired with HSN, it was expected that a PH··N HB ought to form, even if not necessarily strong. But instead the phosphine rotated so as to present not its proton to the N, but rather to move this proton *away from* the P···N axis. More focused attention to this interaction [85] showed this to be no anomaly but rather a general feature. When PH_3 is paired with NH_3, the two molecules are oriented such that the P and N atoms face one another directly, without the intermediacy of a H atom. This interaction is a prototype of a P··N pnicogen bond, with N acting as the nucleophile. Part of the interaction arises from the donation of charge from the N lone pair into the σ*(PH) antibonding orbital. This transfer is identical to that in a PH··B HB, except that it is the P-end of this orbital which points toward the N, rather than the H-end.

   This σ* orbital becomes a more effective recipient of charge when the H is replaced by an electron-withdrawing agent such as F [86]. In fact, this substitution is even capable of making first-row N capable of accepting charge in a N··N pnicogen bond [87]. And the pnicogen bond is strengthened as the P atom is replaced by its heavier congeners such as As. Indeed, there is a general rule [88,89] that the pnicogen bond is strengthened by the electron-withdrawing power of the substituent which the Lewis base/nucleophile is placed directly opposite [90]. This trend is parallel to that for HBs, as the more electronegative substituent will draw density toward itself, making the H more positive. A second factor has to do with the electronegativity and polarizability of the pnicogen atom: Larger atoms yield stronger pnicogen bonds [91] in the order P < As < Sb. This trend has no parallel to HBs as it is always the proton that acts as bridge. (It might be added that first-row atoms, due to their high electronegativity and low polarizability, seldom participate in these bonds but can be persuaded to do so in certain circumstances.)

   As one might anticipate, since halogen and pnicogen atoms can replace the proton in HBs, the same idea can be extended to chalcogen (S, Se, etc) atoms as well. Work by our group [92-96] as well as numerous others [97-103] elaborated on these ideas. The extension to tetrel atoms (the Si family) occurred soon thereafter, showing many of the same controlling factors that are

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present for halogen, chalcogen, and pnicogen atoms [104-107]. The normally tetravalent tetrel atoms introduced a new factor which had been less prominent in the other sorts of bonds. In order for a base to approach the central tetrel atom along a face of the tetrahedron, the three proximate substituents must "peel back" away from this base, changing the originally tetrahedral structure into something akin to a trigonal bipyramid. There is thus a good deal of deformation energy that must be surmounted [108-110] if this tetrel bond is to form. This deformation energy makes the tetrel bond formation less exothermic than it would otherwise be, and can even control the particular site at which the base can attack.

The idea of tetrel bonds brought up an interesting issue. It had typically been considered that a nucleophile lying along the R-C extension of a R-CH_3 group constituted a trifurcated HB, i.e. interaction with three H atoms. And there are certainly many such geometrical dispositions of this sort, in both chemical and biological systems [111]. But how can one distinguish this idea of a trifurcated HB from the newer concept of a R-C···D tetrel bond? Indeed there are spectroscopic markers that are different for the two sorts of interactions [112,113], and it is hoped that the future will witness attempts to distinguish these two types of interactions.

As work has progressed in this area, it has become recognized that the positive regions are not limited only to σ-holes lying along the extension of a particular covalent bond. There are π-holes as well, wherein the positive potential sits above the plane of a molecule, as in H_2SiO for example, in the vicinity of the electronic π-cloud. This broadening of the idea has been probed extensively and shown that while the π-hole interactions are usually weaker than their σ parallels, this trend is sometimes reversed [105,114-116]. Of course, such π-hole interactions do not have a H-bonding parallel.

These relatives of the HB are hardly exotic academic novelties, but have a wide range of applications, such as serving as synthons in self-assembling networks [117], biological catalysis [118], oxidative addition [119], self-assembled monolayers [120], S_N2 reaction catalysis [121], design of functional mesomorphic materials [122], and even directed construction of supramolecular quadruple and double helices [123]. One of the more interesting uses concerns selective binding of anions [124-131].   It was realized that the replacement of the H atom of certain multidentate anion receptors with a halogen atom allowed them to engage in halogen bonds with an anion, which in turn strengthened the interaction, and enhanced the selectivity for certain anions over others.

Calculations were applied to this idea, and were able to suggest certain options that ought to enhance these abilities. Optimal choices of particular halogen atoms were proposed, along with identification of chemical groups to which they ought to be bonded, spacer groups between the halogen bonding groups, and overall charge [132-134]. Subsequent work broadened this idea beyond simply halogen bonds, but considered their chalcogen, pnicogen, and tetrel counterparts [135-138]. It was concluded that tetrel bonds offered a particularly tempting choice for their interactions with a halide, offering both very strong interactions, and a marked preference for F^- over other halides.

In retrospect, the discovery of each new facet of H-bonding has gone hand-in-glove with developments in methods in quantum chemistry and computational technology. Given the fact that even after a century, research continues to uncover new and previously unsuspected properties of H-bonds, it would seem unlikely that this area of discovery has reached its conclusion. And just as surely, as the future unfolds, the ability of quantum chemists to look at larger and larger systems in increasingly greater detail, will play an integral role as each step is taken toward greater understanding of this phenomenon and all of its offshoots and applications.

Compliance with ethical standards
Ethical statement
All ethical guidelines have been adhered.
Conflict of interest
The author declares that he has no conflict of interest.

REFERENCES

1.   Pimentel GC, McClellan AL. The Hydrogen Bond; Freeman: San Francisco, 1960.
2.   Vinogradov SN, Linnell RH. Hydrogen Bonding; Van Nostrand-Reinhold: New York, 1971.
3.   Joesten MD, Schaad LJ. Hydrogen Bonding; Marcel Dekker: New York, 1974.
4.   Schuster P, Zundel G, Sandorfy C, Eds. The Hydrogen Bond. Recent Developments in Theory and Experiments; North-Holland Publishing Co.: Amsterdam, 1976.
5.   Birktoft JJ, Blow DM (1972). J Mol Biol 68:187-240
6.   Scheiner S, Kleier DA, Lipscomb WN (1975). Proc Nat Acad Sci, USA 72:2606-2610
7.   Scheiner S, Lipscomb WN (1976). Proc Nat Acad Sci, USA 73:432-436
8.   Nagle JF, Mille M (1981). J Chem Phys 74:1367-1372
9.   Nagle JF, Morowitz HJ (1978). Proc Nat Acad Sci, USA 75:298-302
10.   Scheiner S (1981). J Am Chem Soc 103:315-320
11.   Scheiner S (1982). J Chem Phys 77:4039-4050
12.   Scheiner S, Harding LB (1981). J Am Chem Soc 103:2169-2173
13.   Scheiner S (1981). J Chem Phys 75:5791-5801
14.   Scheiner S (1984). J Chem Phys 80:1982-1987
15.   Bigham L, Scheiner S (1985). J Chem Phys 82:3316-3321
16.   Scheiner S, Hillenbrand EA (1985). J Phys Chem 89:3053-3060
17.   Hillenbrand EA, Scheiner S (1985). J Am Chem Soc 107:7690-7696
18.   Hillenbrand EA, Scheiner S (1986). J Am Chem Soc 108:7178-7186
19.   Cybulski S, Scheiner S (1987). J Am Chem Soc 109:4199-4206
20.   Scheiner S, Wang L (1992). J Am Chem Soc 114:3650-3655
21.   Scheiner S, Wang L (1993). J Am Chem Soc 115:1958-1963
22.   Hillenbrand EA, Scheiner S (1984). J Am Chem Soc 106:6266-6273
23.   Scheiner S, Redfern P (1986). J Phys Chem 90:2969-2974
24.   Szczesniak MM, Scheiner S (1982). J Chem Phys 77:4586-4593
25.   Cybulski SM, Scheiner S (1989). J Am Chem Soc 111:23-31
26.   Latajka Z, Scheiner S (1986). Int J Quantum Chem 29:285-292
27.   Scheiner S, Harding LB (1981). Chem Phys Lett 79:39-43
28.   Scheiner S (1983). Int J Quantum Chem 23:753-764
29.   Scheiner S, Harding LB (1983). J Phys Chem 87:1145-1153
30.   Szczesniak MM, Scheiner S (1985). J Phys Chem 89:1835-1840
31.   Scheiner S, Latajka Z (1987). J Phys Chem 91:724-730
32.   Scheiner S, Hillenbrand EA (1985). Proc Nat Acad Sci, USA 82:2741-2745
33.   Scheiner S (1985). Acc Chem Res 18:174-180
34.   Scheiner S, Redfern P, Hillenbrand EA (1986). Int J Quantum Chem 29:817-827
35.   Scheiner S (1988). J Mol Struct 177:79-91
36.   Cybulski SM, Scheiner S (1989). J Phys Chem 93:6565-6574
37.   Scheiner S, Duan X (1991). Phys Chem Chem Phys 60:874-883
38.   Duan X, Scheiner S (1992). J Am Chem Soc 114:5849-5856
39.   Kresge AJ (1975). Acc Chem Res 8:354-360
40.   Koch HF (1984). Acc Chem Res 17:137-144
41.   Scheiner S, Duan X (1993). J Mol Struct (Theochem) 285:27-32
42.   Gerlt JA, Gassman PG (1993). J Am Chem Soc 115:11552-11568
43.   Cleland WW, Kreevoy MM (1994). Science 264:1887-1890

44.   Frey PA, Whitt SA, Tobin JB (1994). Science 264:1927-1930
45.   Scheiner S, Kar T (1995). J Am Chem Soc 117:6970-6975
46.   Guthrie JP, Kluger R (1993). J Am Chem Soc 115:11569-11572
47.   Warshel A, Aqvist J (1991). Annual Revies in Biophysics and Biophysical Chemistry 20:267-298
48.   King G, Lee FS, Warshel A (1991). J Chem Phys 95:4366-4377
49.   Gu Y, Kar T, Scheiner S (1999). J Am Chem Soc 121:9411-9422
50.   Scheiner S, Gu Y, Kar T (2000). J Mol Struct (Theochem) 500:441-452
51.   Scheiner S, Grabowski SJ, Kar T (2001). J Phys Chem A 105:10607-10612
52.   Scheiner S, Kar T (2002). J Phys Chem A 106:1784-1789
53.   Gu Y, Kar T, Scheiner S (2000). J Mol Struct 552:17-31
54.   Scheiner S, Kar T, Gu Y (2001). J Biol Chem 276:9832-9837
55.   Scheiner S, Kar T, Pattanayak J (2002). J Am Chem Soc 124:13257-13264
56.   Scheiner S (2006). J Phys Chem B 110:18670-18679
57.   Pohl G, Plumley JA, Dannenberg JJ (2013). J Chem Phys 138:245102
58.   Wang C-S, Sun C-L (2010). J Comput Chem 31:1036-1044
59.   Guo H, Gorin A, Guo H (2009). Interdiscip Sci Comput Life Sci 1:12-20
60.   Vener MV, Egorova AN, Fomin DP, Tsirel'son VG (2009). Russ J Phys Chem B 3:541-547
61.   Vener MV, Egorova AN, Fomin DP, Tsirelson VG (2007). Chem Phys Lett 440:279-285
62.   Parthasarathi R, Raman SS, Subramanian V, Ramasami T (2007). J Phys Chem A 111:7141-7148
63.   Scheiner S (2007). J Phys Chem B 111:11312-11317
64.   Scheiner S, Kar T (2005). J Phys Chem B 109:3681-3689
65.   Scheiner S (2008). J Phys Chem B 112:6837-6846
66.   Horowitz S, Adhikari U, Dirk LMA, Del Rizzo PA, Mehl RA, Houtz RL, Al-Hashimi HM, Scheiner S, Trievel RC (2014). ACS Chem Biol 9:1692-1697
67.   Jones CR, Baruah PK, Thompson AL, Scheiner S, Smith MD (2012). J Am Chem Soc 134:12064-12071
68.   Scheiner S (2015). Cryst 5:327
69.   Driver RW, Claridge TDW, Scheiner S, Smith MD (2016). Chem Eur J 22:16513-16521
70.   Adhikari U, Scheiner S (2013). J Phys Chem A 117:10551-10562
71.   Nepal B, Scheiner S (2015). Chem Eur J 21:1474-1481
72.   Nepal B, Scheiner S (2015). Chem Phys 463:137-144
73.   Scheiner S, Kar T (2008). J Phys Chem A 112:11854-11860
74.   Scheiner S (2009). J Phys Chem B 113:10421-10427
75.   Scheiner S (2010). Int J Quantum Chem 110:2775-2783
76.   Hassel O (1970). Science 170:497-502
77.   Lommerse JPM, Stone AJ, Taylor R, Allen FH (1996). J Am Chem Soc 118:3108-3116
78.   Allen FH, Lommerse JPM, Hoy VJ, Howard JAK, Desiraju GR (1997). Acta Cryst B53:1006-1016
79.   Ikuta S (1990). J Mol Struct (Theochem) 205:191-201
80.   Hathwar VR, Row TNG (2010). J Phys Chem A 114:13434-13441
81.   Sedlak R, Kolář MH, Hobza P (2015). J Chem Theory Comput 11:4727-4732
82.   Politzer P, Lane P, Concha MC, Ma Y, Murray JS (2007). J Mol Model 13:305-311
83.   Clark T, Hennemann M, Murray JS, Politzer P (2007). J Mol Model 13:291-296

84.   Solimannejad M, Gharabaghi M, Scheiner S (2011). J Chem Phys 134:024312
85.   Scheiner S (2011). J Chem Phys 134:094315
86.   Scheiner S (2011). Chem Phys 387:79-84
87.   Scheiner S (2011). Chem Phys Lett 514:32-35
88.   Scheiner S (2013). Acc Chem Res 46:280-288
89.   Scheiner S (2013). Int J Quantum Chem 113:1609-1620
90.   Scheiner S (2011). J Phys Chem A 115:11202-11209
91.   Scheiner S (2011). J Chem Phys 134:164313
92.   Adhikari U, Scheiner S (2014). J Phys Chem A 118:3183-3192
93.   Nziko VdPN, Scheiner S (2014). J Phys Chem A 118:10849-10856
94.   Azofra LM, Alkorta I, Scheiner S (2015). J Phys Chem A 119:535-541
95.   Nziko VdPN, Scheiner S (2015). J Org Chem 80:2356-2363
96.   Nziko VdPN, Scheiner S (2015). J Phys Chem A 119:5889-5897
97.   Rosenfield RE, Parthasarathy R, Dunitz JD (1977). J Am Chem Soc 99:4860-4862
98.   Burling FT, Goldstein BM (1992). J Am Chem Soc 114:2313-2320
99.   Iwaoka M, Tomoda S (1994). J Am Chem Soc 116:2557-2561
100.   Del Bene JE, Alkorta I, Elguero J (2019). Chem Phys Lett 721:86-90
101.   Esrafili MD, Mousavian P, Mohammadian-Sabet F (2019). Mol Phys 117:726-733
102.   Alkorta I, Legon A (2018). Molecules 23:2250
103.   Gleiter R, Haberhauer G, Werz DB, Rominger F, Bleiholder C (2018). Chem Rev 118:2010-2041
104.   Scheiner S (2015). J Phys Chem A 119:9189-9199
105.   Nziko VdPN, Scheiner S (2016). Phys Chem Chem Phys 18:3581-3590
106.   Liu M, Li Q, Scheiner S (2017). Phys Chem Chem Phys 19:5550-5559
107.   Scheiner S (2017). J Phys Chem A 121:5561-5568
108.   Scheiner S (2018). J Phys Chem A 122:2550-2562
109.   Zierkiewicz W, Michalczyk M, Scheiner S (2018). Phys Chem Chem Phys 20:8832-8841
110.   Zierkiewicz W, Michalczyk M, Wysokiński R, Scheiner S (2019). Molecules 24:376
111.   Trievel RC, Scheiner S (2018). Molecules 23:2965-2981
112.   Scheiner S (2018). J Phys Chem A 122:7852-7862
113.   Scheiner S (2019). Chem Phys Lett 714:61-64
114.   Zhang J, Hu Q, Li Q, Scheiner S, Liu S (2019). Int J Quantum Chem 119:e25910
115.   Zierkiewicz W, Michalczyk M, Scheiner S (2018). Molecules 23:1416
116.   Wei Y, Li Q, Scheiner S (2018). ChemPhysChem 19:736-743
117.   Mukherjee A, Sanz-Matias A, Velpula G, Waghray D, Ivasenko O, Bilbao N, Harvey Jeremy N, Mali KS, De Feyter S (2019). Chem Sci 10:3881-3891
118.   Xu C, Loh CCJ (2019). J Am Chem Soc 141:5381-5391
119.   Carreras L, Benet-Buchholz J, Franconetti A, Frontera A, van Leeuwen PWNM, Vidal-Ferran A (2019). Chem Commun 55:2380-2383
120.   Hijazi H, Vacher A, Groni S, Lorcy D, Levillain E, Fave C, Schöllhorn B (2019). Chem Commun 55:1983-1986
121.   Zhang X, Ren J, Tan SM, Tan D, Lee R, Tan C-H (2019). Science 363:400-404
122.   Wang H, Bisoyi HK, Urbas AM, Bunning TJ, Li Q (2019). Chem Eur J 25:1369-1378
123.   Liu C-Z, Koppireddi S, Wang H, Zhang D-W, Li Z-T (2019). Angew Chem Int Ed 58:226-230

124. Serpell CJ, Kilah NL, Costa PJ, Félix V, Beer PD (2010). Angew Chem Int Ed 49:5322-5326
125. Caballero A, White NG, Beer PD (2011). Angew Chem, Int Ed Engl 50:1845-1848
126. Walter SM, Kniep F, Rout L, Schmidtchen FP, Herdtweck E, Huber SM (2012). J Am Chem Soc 134:8507-8512
127. Gilday LC, White NG, Beer PD (2013). Dalton Trans 42:15766-15773
128. Borissov A, Marques I, Lim JYC, Félix V, Smith MD, Beer PD (2019). J Am Chem Soc 141:4119-4129
129. Klein HA, Beer PD (2019). Chem Eur J 25:3125-3130
130. Hein R, Borissov A, Smith MD, Beer PD, Davis JJ (2019). Chem Commun 55:4849-4852
131. Chakraborty S, Maji S, Ghosh R, Jana R, Datta A, Ghosh P (2019). Chem Commun 55:1506-1509
132. Nepal B, Scheiner S (2015). Chem Eur J 21:13330-13335
133. Nepal B, Scheiner S (2015). J Phys Chem A 119:13064-13073
134. Nepal B, Scheiner S (2016). ChemPhysChem 17:836-844
135. Scheiner S (2017). J Phys Chem A 121:3606-3615
136. Scheiner S (2017). Faraday Disc 203:213-226
137. Scheiner S (2018). Molecules 23:1147-1155
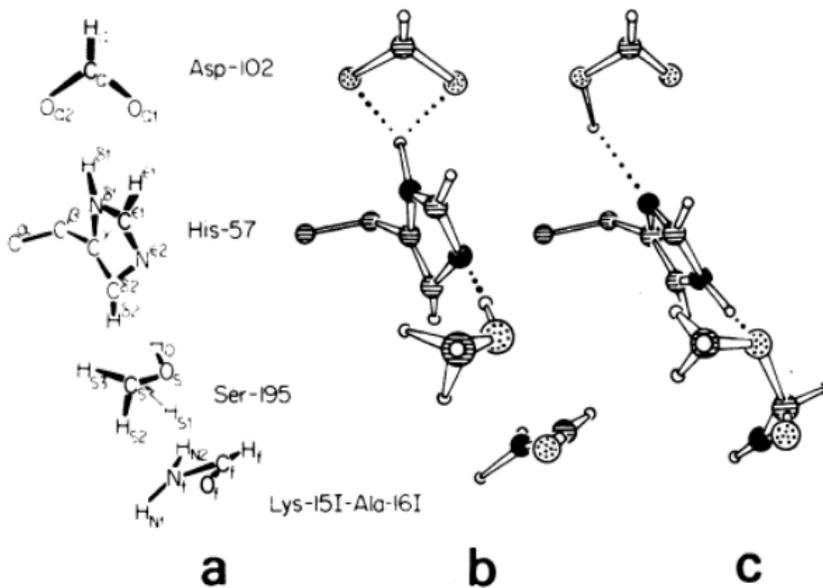138. Scheiner S (2019). Molecules 24:227

Fig 1. Identities and dispositions of key catalytic residues in chymotrypsin. Bound state of substrate is shown in part b, including HBs as broken lines. Part c illustrates geometry following proton transfers and formation of tetrahedral intermediate. N atoms are solid, C are striped, and O are speckled.
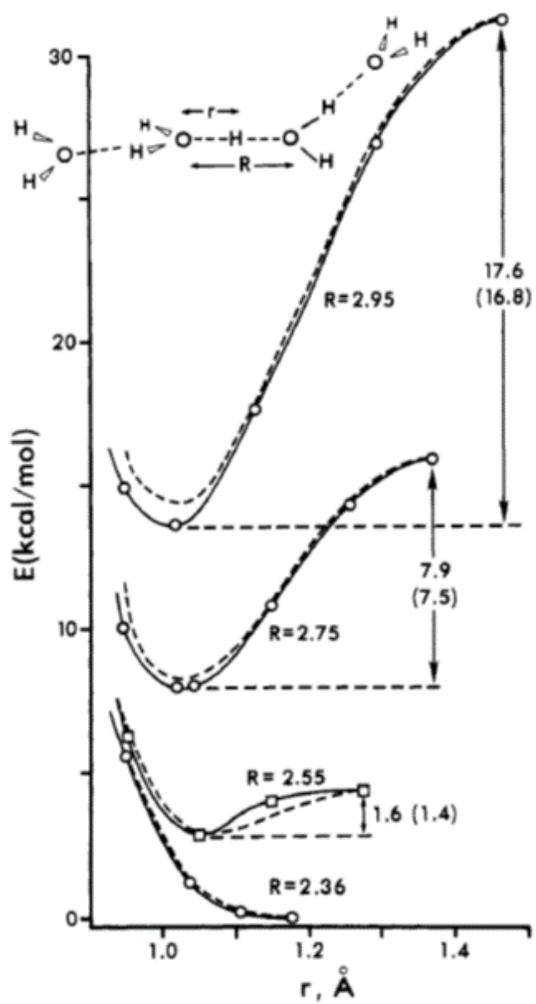
Fig 2. Left half of proton transfer potentials [10] for $(H_5O_2)^+$ (broken curves) and $(H_9O_4)^+$ (solid curves). Energy barriers for dimers in parentheses.
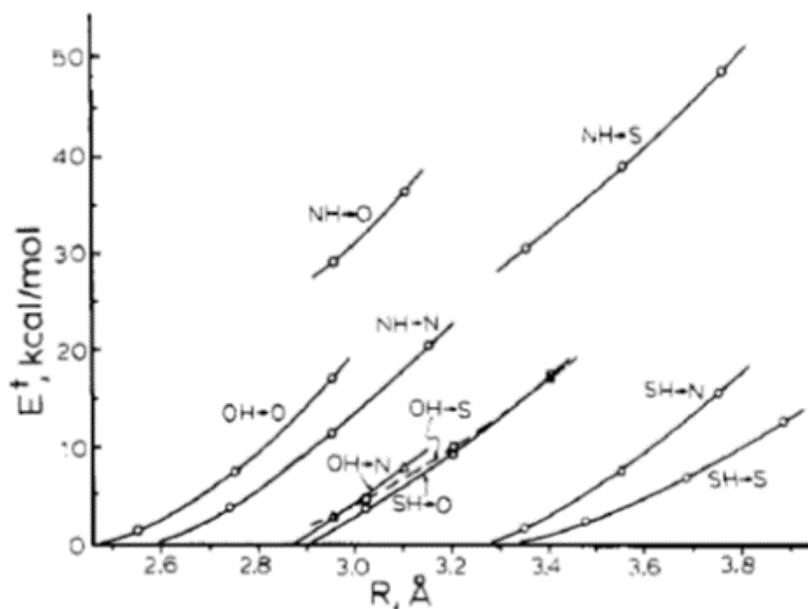
Fig 3   Proton transfer energy barriers and their relation to H-bond length R [33]. Label on each curve represents the atoms directly involved in the transfer. Systems illustrated are $(H_nX-H-YH_m)^+$ where H_nX and YH_m = OH_2, NH_3, and SH_2.
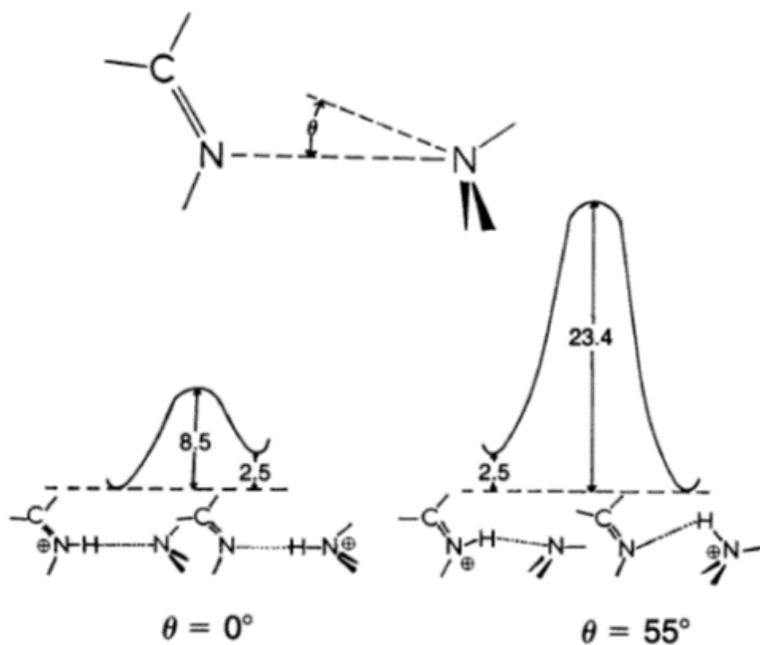

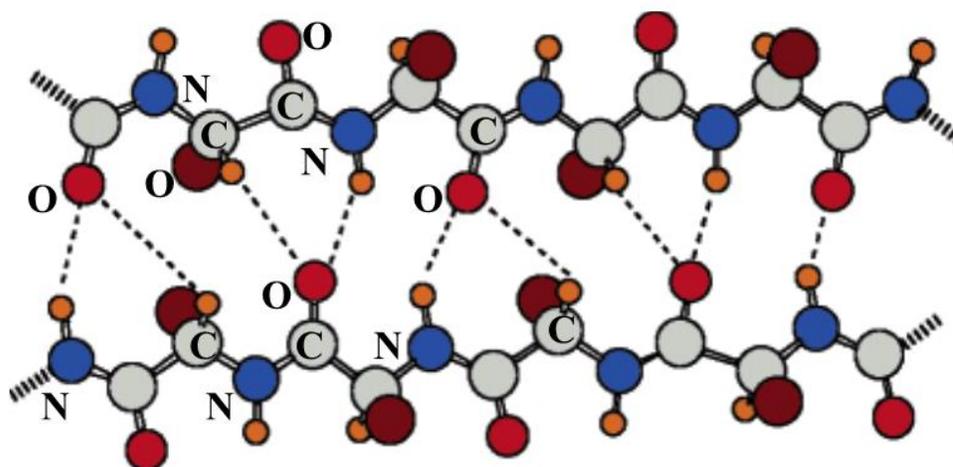Fig 4   Proton transfer potentials (kcal/mol) for $H_2C=NH$ and NH_3. Intermolecular $R(N··N)=2.75$ Å and $\theta(CN··N)=129°$.

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Fig 5   Schematic diagram of two strands of an anti-parallel β-sheet of a protein. Broken lines indicate putative HBs, of both NH··O and CH··O type.
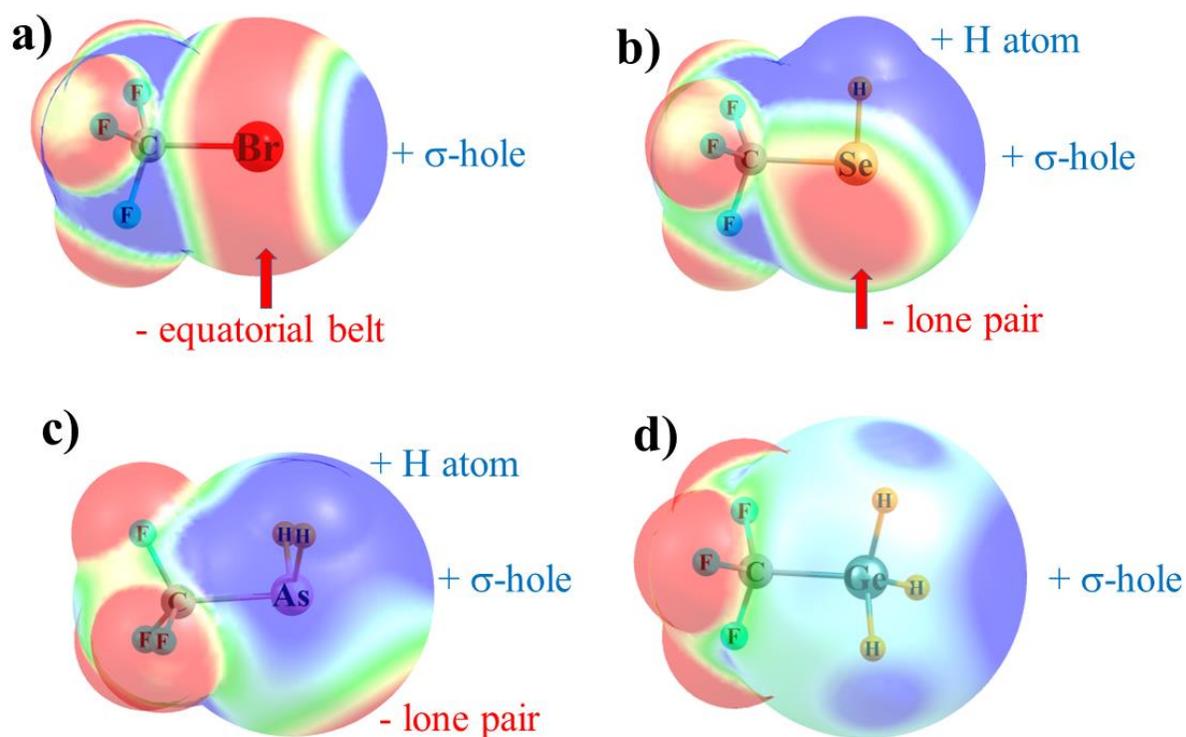

Fig 6   Molecular electrostatic potentials surrounding a) CF_3Br, b) CF_3SeH, c) CF_3AsH_2, and d) CF_3GeH_3. Blue and red regions indicate positive and negative potential, respectively.