



Forty years of progress in the study of the hydrogen bond

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Received: 29 April 2019 / Accepted: 15 May 2019 / Published online: 3 June 2019
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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 the 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 of 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.

Keywords Proton transfer · CH...O H-bonds · Halogen bonds · Tetrel bonds

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 $\nu(\text{A-H})$ stretching frequency, coupled with band intensification. NMR signals of the bridging proton were shifted downfield. Also, 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 $\text{A}^{\delta-}\text{H}^{\delta+}\cdots\delta^-\text{D}$ 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 $\sigma^*(\text{AH})$ 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, and 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 $\text{A}^-\cdots^+\text{HD}$ ion pair would be energetically disfavored. But there was little information concerning the transfer within an ionic system, e.g., $\text{AH}^+\cdots\text{D} \rightarrow \text{A}\cdots\text{H}^+\text{D}$, 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 considered quantitatively reliable. Indeed, the

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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. Fortunately, the research group that I had just joined had recently developed a new method, with the acronym partial retention of diatomic differential overlap (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 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 interresidue HBs. Figure 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

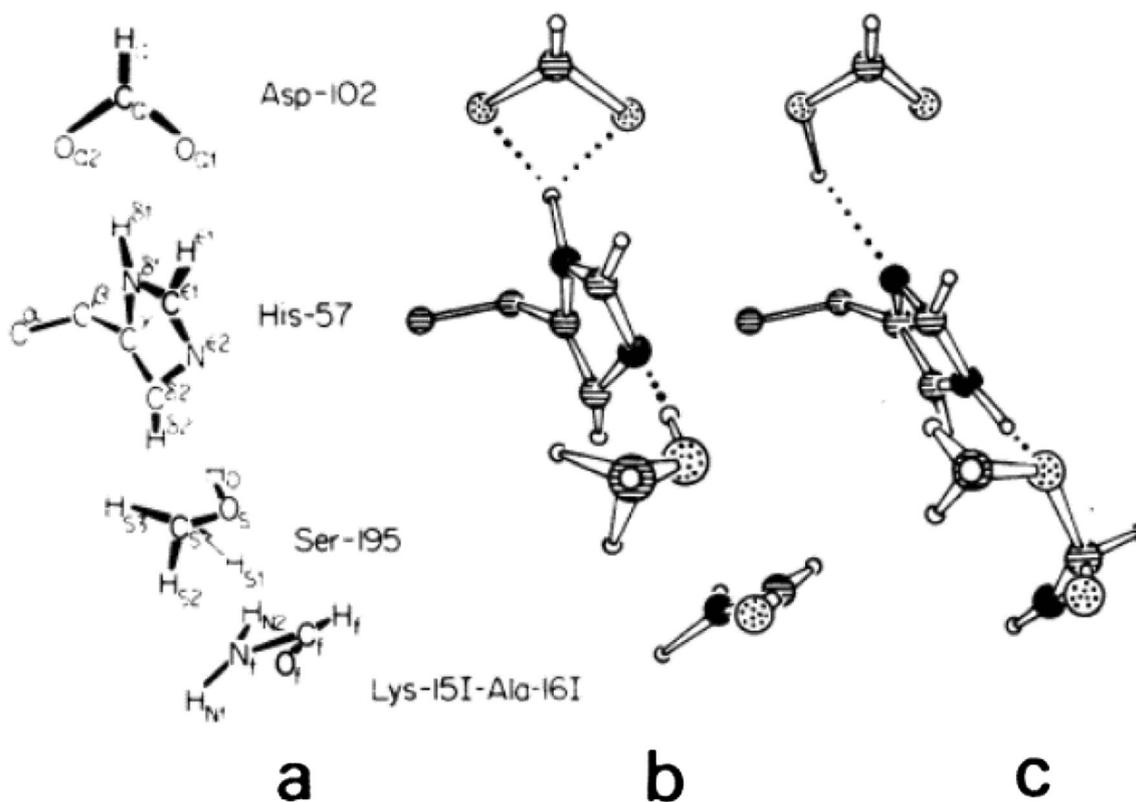


Fig. 1 Identities and dispositions of key catalytic residues in chymotrypsin [6]. Bound state of substrate is shown in part b, including HBs as broken lines. Part c illustrates geometry following proton transfers and formation of tetrahedral intermediate. N atoms are solid, C are striped, and O are speckled

pick up the proton from Ser–OH, it must first swing down toward it, shortening the OH \cdots N HB. Once protonated, 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 ZH $_z$. The process begins with a single proton transfer from A to B: A \cdots H $_a$ BH $_b$ \cdots CH $_c$ \cdots ZH $_z$, followed by another from B to C: A \cdots H $_a$ B \cdots H $_b$ CH $_c$ \cdots ZH $_z$, and so on to A \cdots H $_a$ B \cdots H $_b$ C \cdots H $_c$ ZH $_z$, after which H $_c$ ZH $_z$ 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 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].

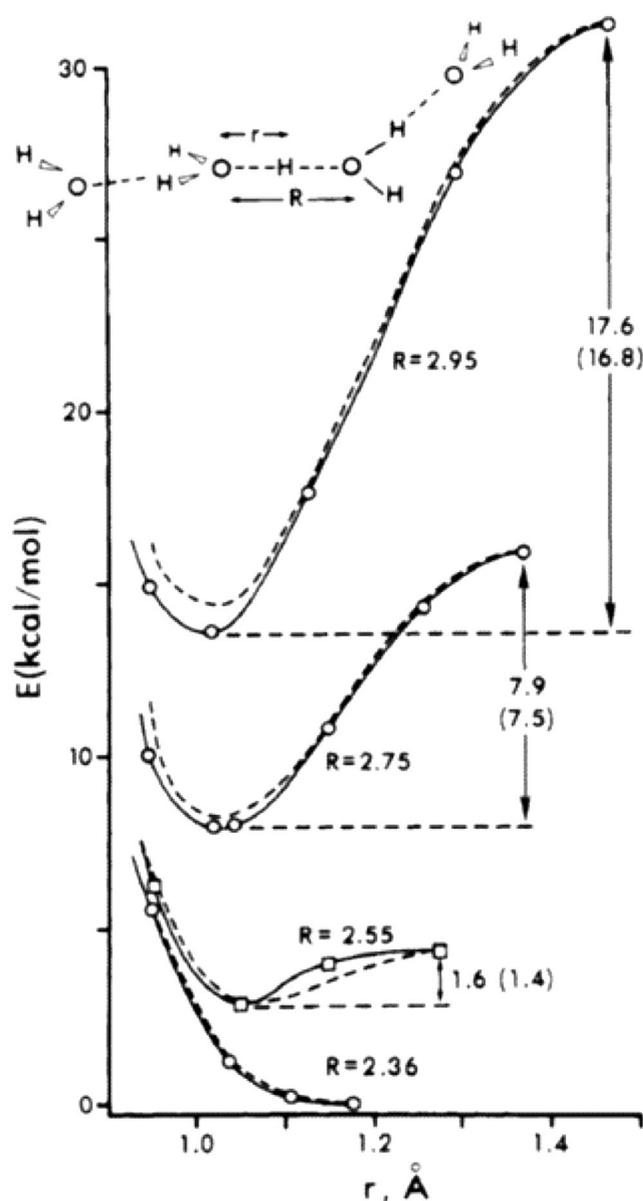


Fig. 2 Left half of proton transfer potentials [10] for (H $_5$ O $_2$) $^+$ (broken curves) and (H $_9$ O $_4$) $^+$ (solid curves). Energy barriers for dimers in parentheses

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, and 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

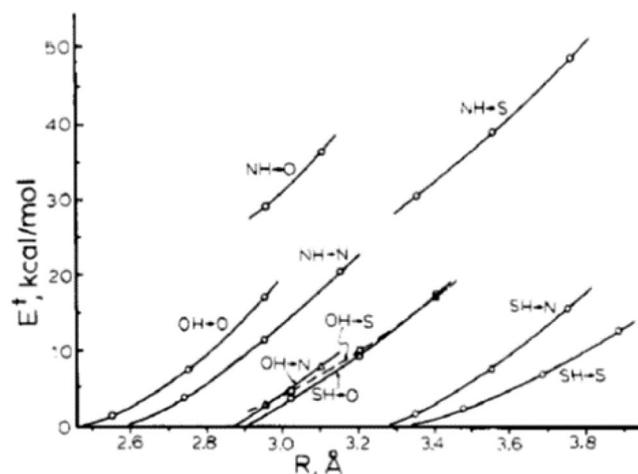


Fig. 3 Proton transfer energy barriers and their relation to H-bond length R [27]. The label on each curve represents the atoms directly involved in the transfer. Systems illustrated are $(H_nX-H-YH_m)^+$ where H_nX and $YH_m = OH_2, NH_3,$ and SH_2

asymmetric transfers between two different atoms. These barriers also show a steep increase with R , but depend on the additional factor of the different proton affinities of the donor and acceptor groups [11, 14, 28–30].

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 [31] 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 [32] employed a variant of the 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 the pT barrier with intermolecular separation, when coupled to the high sensitivity of the pT rate to the 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, is that 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 a 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 [33]. 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 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 that

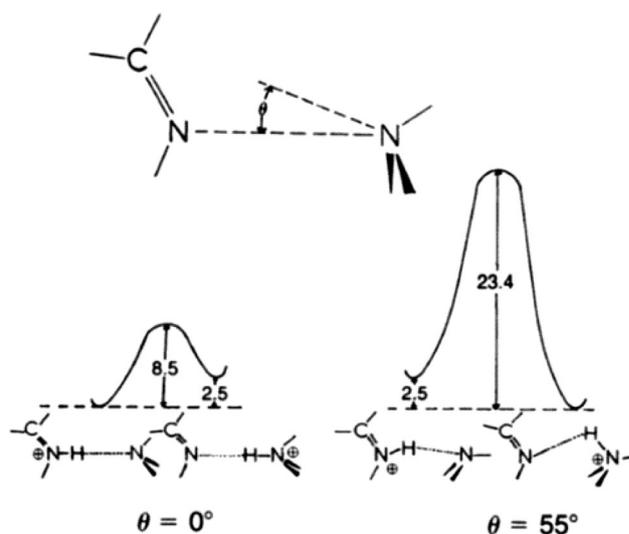


Fig. 4 Proton transfer potentials (kcal/mol) for $H_2C=NH$ and NH_3 . Intermolecular $R(N..N) = 2.75$ Å and $\theta(CN..N) = 129^\circ$

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 two species [17, 27, 34–36]. 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·D 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 into 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 shorter. 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 $CH\cdots O$ 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 $CH\cdots O$ 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 $CH\cdots O$ HB, even when the two groups were perfectly aligned. But as the landscape changed and $CH\cdots O$ 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 $NH\cdots O$ interaction. With

respect to side chains 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].

A 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].

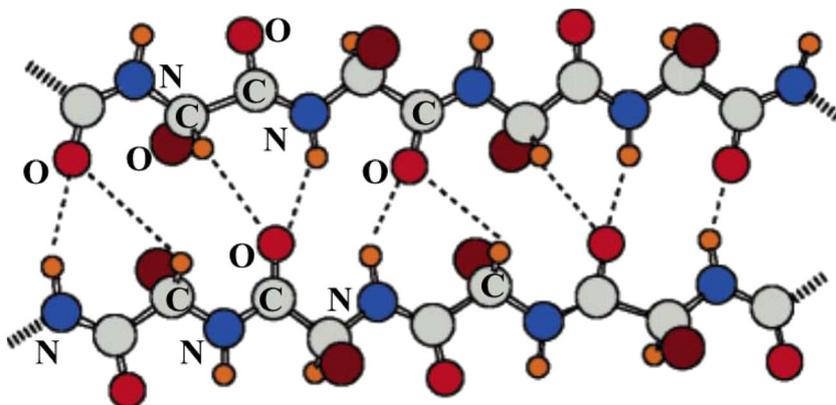
Earlier workers had suggested what they called a “ring-flip” hypothesis involving a 180° rotation of a key His residue as a vital step in the catalysis. This mechanism relied on the presence of a CH··O HB in order to stabilize one of the intermediates in the formation of the tetrahedral intermediate. 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 $A-X\cdots D$ 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

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



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 CF₃Br molecule in Fig. 6a, along with the negatively charged belt.

Nor is this idea limited to halogen atoms. Figure 6b shows the potential around the chalcogen Se atom also contains a σ -hole opposite the CF₃ group. Its attractive interaction with a nucleophile would thus be termed a chalcogen bond. Note that the H atom bonded to 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 pnictogen 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.

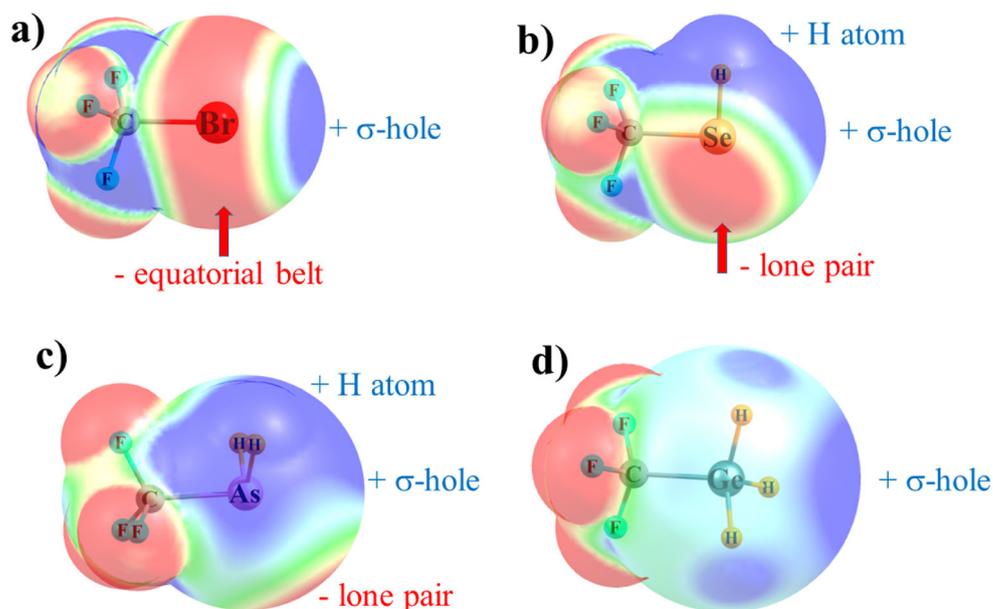
This idea resonated with the author in the context of a 2011 joint study of weak HBs [84] with an Iranian group. When phosphine was paired with HSN, it was expected that a PH··N HB ought to form, even if not necessarily strong. But instead, the phosphine rotated so as to present not its proton to the 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 PH₃ is paired with NH₃, 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 pnictogen 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 pnictogen bond [87]. Also, the pnictogen 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 pnictogen 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 pnictogen atom: larger atoms yield stronger pnictogen 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 pnictogen 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)

Fig. 6 Molecular electrostatic potentials surrounding **a** CF₃Br, **b** CF₃SeH, **c** CF₃AsH₂, and **d** CF₃GeH₃. Blue and red regions indicate positive and negative potential, respectively



occurred soon thereafter, showing many of the same controlling factors that are present for halogen, chalcogen, and pnictogen 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–CH₃ 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 H₂SiO 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, pnictogen, 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

Conflict of interest The author declares that he has no conflict of interest.

Ethical statement All ethical guidelines have been adhered to.

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