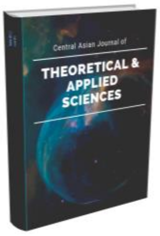

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Article

A Brief Overview of Hydrogen Bonds

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Abstract: This study aims to provide a comprehensive understanding of hydrogen bonds, which are the most significant directional molecular interactions in various chemical systems, ranging from inorganic to biological. The research examines the importance of hydrogen bonds in influencing molecular conformation, assembly, and function, as well as the evolution of related research, which saw a decline in the 1980s but rapidly resumed growth since the 1990s. The methodology employed in this study includes a theoretical and experimental review of various types of hydrogen bonds commonly found in condensed phases, as well as an analysis of interaction energy and covalent contributions in short, strong hydrogen bonds (SSHB). Additionally, the study adopts wave function analysis and the Quantum Theory of Atoms in Molecules (QTAIM) to evaluate hydrogen bond strength. The results indicate that hydrogen bonds exhibit diverse characteristics and are essential in various scientific disciplines, including supramolecular chemistry, biology, and inorganic chemistry. Hydrogen bonds play a critical role in stabilizing protein structures, proton transfer, and molecular self-assembly, and have significant implications in specific chemical reactions, such as the oxidative addition of bonds in complex molecules.

Keywords: Hydrogen Bond, Interactions, Energy, Resonance-Assisted, Electronegativity

1. Introduction

Hydrogen bonds are essential in different scientific fields, like chemistry, biology, and materials science. These bonds are crucial for the structure, function, and dynamics of biological molecules. (1) The strength of hydrogen bonds can vary significantly, ranging from weak interactions to nearly covalent in nature. (2) In biological systems, hydrogen bonds are continuously forming and breaking, impacting the stability and conformation of molecules. (3) The energy associated with hydrogen bonds can be stronger than the weakest covalent bonds or comparable to van der Waals interactions. (2) Hydrogen bonds' nature can differ depending on the context. Strong hydrogen bonds often exhibit more covalent character, while weak hydrogen bonds are typically driven by electrostatic interactions. (4) The formation energies of hydrogen bonds are notably more favorable in aprotic solvents compared to water, with water having a tendency to lengthen hydrogen bonds, affecting their potential energy. (5) In proteins, hydrogen bonds are vital for stabilizing structures, and the lack of sufficient hydrogen bonds can lead to a loss of folding stability. (6) Hydrogen bonds could involve a variety of additional types in addition to the classic donor-acceptor interactions, including hydrogen bonds with p acceptors, protein-water hydrogen bonds, and C-H-X hydrogen bonds. (7) Another class of hydrogen interactions that can be seen in various biological and chemical systems are known as short-strong hydrogen bonds (SSHB), which highlights the variety of such interactions. (7)

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The charged nature of certain residues in proteins enables the formation of charge-assisted hydrogen bonds, contributing to stability of protein structures. (8) In supramolecular chemistry, hydrogen bonds are crucial for processes like proton transfer and the self-assembly of molecules into specific structures. (9) Optimizing hydrogen-bond networks in protein structures can significantly influence the stability and function of proteins. (6) Additionally, hydrogen bonds play a critical role in various chemical systems, influencing phenomena like the solvatochromism and fluorescence. (10) The significance of hydrogen bonds extends beyond chemistry into fields like medicine, where these interactions are involved in drug-receptor binding. (11) In inorganic chemistry, hydrogen bonding can facilitate specific reactions, such as the oxidative addition of bonds in complex molecules. (12) Theoretical and experimental studies on hydrogen bonds have gained increasing attention due to their fundamental roles in chemistry, physics, and biology. (13) Overall, hydrogen bonds are versatile and fundamental interactions that underlie a wide range of phenomena across different scientific disciplines. Their strength, nature, and impact can vary depending on the specific context in which they occur, highlighting the complexity and significance of these interactions in the natural world.

2. Materials and Methods

The methodology of the research is not explicitly outlined in a dedicated section in the document. However, the research methodology can be inferred from the text that describes the approach used to analyze hydrogen bonds, which includes both theoretical and experimental aspects. Specifically, the study employs techniques such as wave function analysis and the Quantum Theory of Atoms in Molecules (QTAIM) to evaluate the characteristics and strength of hydrogen bonds. Additionally, various energy decomposition methods are utilized to break down and understand the interaction energies involved in hydrogen bonding. This methodological approach is discussed across several sections of the document, particularly where the study explains the use of supermolecular techniques, energy decomposition strategies, and wave function analysis to understand hydrogen bonds.

3. Results and Discussion

Definition of Hydrogen Bond

The chemical variety and complexity of observed phenomena, which encompass both the weakest and strongest species in the family and intra- and intermolecular interactions, could just be adequately captured by extremely broad and variable meanings of the term "hydrogen bond." Pimentel and McClellan's definition, which stated that "there is a hydrogen bond if i) there’s proof of a bond, ii) there’s evidence that this bond sterically includes hydrogen atom that is bonded to another one already," is an example of an early, forward-thinking definition. (14,15) The chemical makeup of participants, such as their polarities and net charges, has not been made clear by this idea. Other than the requirement that the hydrogen atom be "involved," there are no restrictions on the interaction geometry. The most fundamental prerequisite is the presence of a "bond," which might be difficult to describe in and of itself. There are limitations to the methods utilized to determine through experimentation if criteria I and II are met. Diffraction investigations make it easy to determine whether a H atom is present in crystalline compounds, but they cannot guarantee that a particular contact is truly "bonding". (16) According to Pauling's definition, X—HY H-bond requires that Y and X atoms be electronegative, HY distance to be less than total of respective van der Waals radii, and interaction to be primarily electrostatic. Pauling (17) added that covalent contribution may be taken into account within such interaction for extremely short and very strong H-bonds. (18) In addition to basic chemical definitions, there are other specific definitions of hydrogen bonding depending on properties which could be studied with the use of a particular method. For instance, specific characteristics of experimental electron density distributions (such as the presence of "bond critical point" between A and H, with numerical parameters within specific range values) or interaction geometries in crystal structures have all been used for defining hydrogen bonds. (16) All of these definitions are directly related to a particular method, and they could be quite helpful in the regime that it is applicable to. However, they are essentially meaningless outside of that range, and using such concepts outside of their relevance has led to many misunderstandings in the literature on hydrogen bonds. (16)

Different between hydrogen bonds and other Intermolecular Bonds

Depending on the type of interaction, all known intermolecular bonds fall into one of three basic categories: ionic bonds, van der Waals bonds, or hydrogen bonds. Their primary traits are:

- Hydrogen bonds are inter-molecular bonds that show A–HX topology. The majority of time, proton donor (A–H) group points to the area where the proton acceptor group (X) has accumulated electronic density, such as the position of bonding p-electrons or lone-pair electrons. It suggests that there is a critical point for HX bond between the atoms of X and H. O-HO bond seen in water dimers is prototypical example. It is important to note that aggregates with 1 or 2 molecules that are involved in the interaction having net charge might also have this topology and bond characteristics (thus, stable ion-solvent interactions displaying A–HX topology must be included here). Dipole–dipole term often dominates the interaction energy in a case when the bond contains neutral dimers; however, this isn’t necessarily the case where fragments are charged. (19)
- The intermolecular bonds known as ionic bonds occur when a species that is involved has a net charge, which is an ion by definition. Although Na+ Cl- interaction is the prototypical example, such class includes ion - solvent interactions. For such bonds to form, the two ions involved must have opposite charges to one another; otherwise, the interaction would be repulsive and would not meet the necessary energy stability requirements to qualify as a bond. (19)
- Van der Waals bonds represent intermolecular bonds made by an AB bond critical point connecting two atoms, B and A, which exhibit strong electronic localization (lone pairs, p-orbitals). Those bonds are typically the weakest of all potential bonds, originating from the dispersion terms. The bond in Ar2 dimer or the one between aromatic molecules arranged in p-stacks, which is frequently observed in numerous molecular crystals, is a prototypical instance. The topology regarding bond critical points estimated through AIM analyses could be used to determine whether a van der Waals bond or a hydrogen bond is formed in complex geometrical groupings. (20)

Those three groups include all known intermolecular interactions. In the case when more than one option is available, we recommend using dominant interaction energy component to identify the type of molecule (e.g., Ar ···Ar interaction represents a van der Waals interaction and is therefore a bond because it has energetical stability, whereas the isoelectronic K+ ··· K+ is an ionic interaction and isn’t a bond because it is destabilizing energetically). (19)

Hydrogen bonding interactions

Of the numerous weak, reversible, mostly non-covalent interactions, hydrogen bonding (HB) interactions are amongst the strongest, most direct, and dynamic. Since terrestrial life would not survive without HB, such interactions are very significant. For instance, HB causes folding of proteins, increased density regarding frozen water, and self-complementarity of nucleic acids. A hydrogen acceptor bonded to donor (D), which is more electro-negative when compared to the hydrogen, and HB acceptor (A) with only one pair of electrons should exhibit both an attractive acceptor as well as evidence of bond format interaction. (21-23) HA (L1) and DA (L2) distances, as well as D–Ha (A1) and R–A–H (A2) bond angles, are parameters frequently studied in HB systems. Stronger HB interactions are typically correlated with shorter L1 distances and A2 angles that are close to 180° (Fig1).

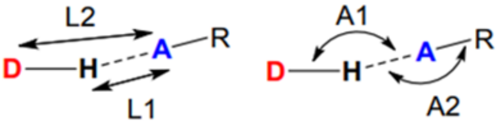


Fig.1 Bond lengths and bond angles usually measured in the HB systems. (24)

Polarization, electrostatics, dispersion, charge transfer, and exchange repulsion represent some of the attracting and repulsive factors that give rise to hydrogen bonding interactions. (23) The main contributing force in an HB is usually electrostatic forces, which are directional and determined by the electro-static potential of D–H and A atoms. Functionalization is an easy way to modify electrostatic interactions, which are improved by raising partial charges on acceptor and donor atoms. The strength regarding electrostatic interactions decreases the least with increasing H···A distances of all attractive forces because they're least dependent on inter-atomic distances. The capacity of HB acceptor to rearrange electron density in order to enhance its participation in hydrogen bonding is related to polarization. The overlap of empty D-H anti-bonding orbital and a filled lone pair orbital on an HB Acceptor results in charge transfer forces. Those forces are very linearly conditioned and decrease sharply with increasing distance and with a departure from the ideal HB geometry. Lastly, Lennard-Jones potential could be used for approximating van der Waals forces, which are dispersion and exchange repulsion forces combined. (25) Because of their isotropic nature and general weakness, such forces are frequently the main causes of non-linear hydrogen bonds.(24)

Weak, medium and strong bonds of hydrogen

Hydrogen bonds are important in many chemical interactions, and their strength can be divided into three categories: weak, moderate, and strong. The categorization is based on the energy of the hydrogen bonds. Shi et al. (26) describe weak hydrogen bonds as those with energies that range from 4kJ/mol to 15 kJ/mol, moderate hydrogen bonds as the ones with energy levels between 15 and 60kJ/mol, and strong hydrogen bonds as the ones with energy levels of 60 to 170 kJ/mol. This classification aids in understanding the nature and characteristics of various hydrogen bond interactions. Chen et al. (27) also draw a distinction between weak or common hydrogen bonds and strong or very strong hydrogen bonds. They underline that hydrogen bonding can be broadly classified into two kinds based on their strength. Furthermore, Panigrahi and Desiraju (28) state that both strong (O-H···O, N-H···O) and weak (C-H···O) hydrogen bonds are required to complete out hydrogen bond potential of an acceptor or donor, with weak bonds complementing stronger ones. Furthermore, Cassidy et al. (29) define low-barrier hydrogen bonds (LBHBs) as short, strong bonds of hydrogen that are particularly strong under certain conditions. These LBHBs are distinguished by their exceptional strength and formation under specific conditions. The occurrence of LBHBs, as well as conventional weak and strong hydrogen bonds, adds to the wide variety of hydrogen bond interactions seen in various chemical systems.

In addition for that Barich et al. (30) suggest that hydrogen bonds in p-aminosalicylic acid fall between moderate and strong categories, indicating the effectiveness of the Electrostatic Interaction Model (EIM) for bonds primarily arising from electrostatic interactions. Parthasarathi et al. (31) Show that electron density at hydrogen bond critical point grows linearly with stabilization energy, progressing from weak to moderate to strong bonds of hydrogen. According to Özen et al. (32), weak and moderate hydrogen bonds can be explained using a simple electrostatic model. However, strong hydrogen bonds require a more thorough theory due to covalent interactions. Kawasaki et al. (33) emphasize the significance of geometrical features in dividing hydrogen bonding into strong, moderate, and weak categories. Deshmukh et al. (34) and Afonin & Vashchenko (35) give energy ranges for each group, with weak hydrogen bonds ranging from about 1.0

– 4.0 kcal/mol, moderate hydrogen bonds from 4.0 – 15.0 kcal/mol, and strong hydrogen bonds from 15.0 – 40.0 kcal/mol. Liu et al. (36) divide hydrogen bonds into weak, moderately strong, and strong categories based on their interactions. Widelicka et al. (37) offer a classification of hydrogen bonds based on topological factors to distinguish weak, moderate, strong, and very strong interactions. In the context of molecular systems, Sarkhel and Desiraju (38) explore the occurrence of strong and weak bonds of hydrogen at protein ligand interfaces, emphasizing their significance in molecular recognition processes. This systematic approach helps us comprehend the various roles of hydrogen bonding in different molecular environments. Table 1 lists some of the general characteristics of these groupings.

Table 1. Jeffrey's classification includes strong, medium and weak hydrogen bonds. (39)

	strong	**medium**	**weak**
Type of Interaction	strongly covalent	mostly electrostatic	electrostat./ dispers.
X-H versus H···A	X-H ≈ H···A	X-H < H···A	X-H << H···A
Bond lengths[Å] H···A	1.20 - 1.50	1.50 - 2.20	> 2.20
lengthening of X-H [Å]	0.080 - 0.250	0.020 - 0.080	< 0.020
bond angles [°]	170.0 – 180.0	> 130.0	> 90.0
X···A [Å]	2.20 - 2.50	2.50 - 3.20	> 3.20
directionality	strong	medium	weak
bond energy [kcal mol^{-1}]	15.0 – 40.0	4.0 – 15.0	< 4.0
relat. IR shift $\Delta\bar{\upsilon}_{XH}$ [cm^{-1}]	25.0%	10.0 – 25.0%	< 10.0%
^{1}H downfield shift	14.0 – 22.0	< 14.0	

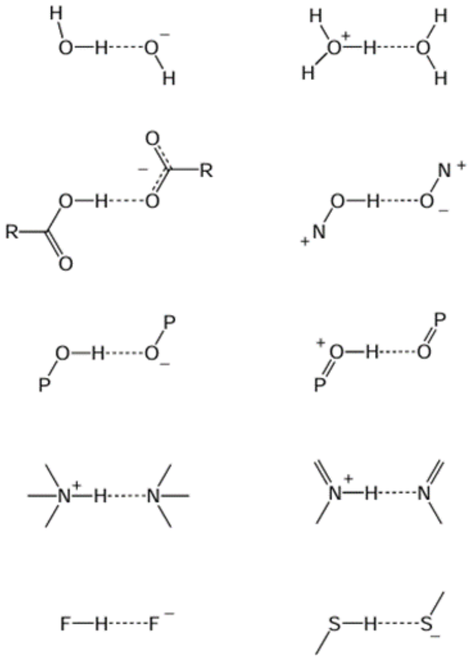


Fig.2 Examples of strong hydrogen bonding between the acids and the supportive bases.(40)

Hydrogen Bond Energy

To determine the hydrogen bond strength, a variety of methods were put forth. (41-33) It is standard procedure to specify interaction energy which is associated with hydrogen bond energy for quantitative description regarding hydrogen bond interactions. The complex containing hydrogen bonds has been treated as a single molecule in supermolecular technique, and the overall energy E_{AB} is ascertained. Using unrelaxed monomers E_A and E_B's total energies as a point of reference, intrinsic interaction energy E equals

$$E = E_{AB}\left(\vec{R}_A + \vec{R}_B\right) - E_A\left(\vec{R}_A\right) - E_B\left(\vec{R}_B\right) \ldots\ldots\ldots\ldots\ldots 1$$

In which $\vec{R}_B$ and $\vec{R}_A$ represent coordinates of atoms of B and A monomers in complex. Because of definition in eq1, the attractive interaction energy is negative. For simpler reading, term energy is an indication of absolute energy value $|E|$ in the following. This energy of the interaction captures other van der Waals interaction as a dispersion or induction and potential repulsive interactions, electro-static contributions and others. (54)

6.1. The disintegration of the interaction energy

The covalency regarding strong and short hydrogen bonds is a topic that is occasionally explored at the same time. Further research is thus necessary in order to gain a deeper comprehension of HB. Early research revealed that the interaction energy is made up of the following terms: polarization, dispersion, exchange (steric), charge transfer, and electrostatic (Coulombic).(55,56) With the supermolecule technique, each term is calculated concurrently, and the energy terms need to be separated out by a process. The breakdown of the interaction energy put forth by *Kitaura and Morokuma* was one of the early strategies.(56,57) Binding or H-bond energy can likewise be broken down in this manner. SCF interaction energy can be divided to aforementioned energy terms by using that approach.

$$\Delta E_{SCF} = ES + PL + EX + CT + MIX \ldots\ldots\ldots\ldots\ldots 2$$

The energy of the interaction between undistorted charge distributions of 2 interacting monomers has been known as electrostatic interaction energy (ES). (PL) can be described as energy of polarization interaction, or distortion energy of charge distributions of monomers; put differently, complex formation is responsible for charge distribution distortion inside the monomers. (CT) is the energy involved in the complexation-induced transfer of charge from 1 molecule to another. The exchange energy, or (EX), is produced when electron cloud repulsion occurs. Known as "coupling energy term," (MIX) represents energy difference between such four components and the (SCF) interaction energy.(56) It is important to remember that although PL, ES, and CT are frequently negative attractive energy expressions, EX is a repulsive energy word. The electron correlation energy phrase CORR's most significant attractive energy component is the dispersion energy, which was previously noted. CORR, on the other hand, is not part of the binding energy of SCF. For instance, one could write (eq. (3)) under the most often used MP2 method, which includes the electron correlation:

$$\Delta E_{MP2} = \Delta E_{SCF} + CORR \ldots\ldots\ldots\ldots\ldots 3$$

It is noteworthy that multiple decomposition regarding the interaction energy have been demonstrated. For instance, the most comprehensive, symmetry-adapted version of inter-molecular Moller Plesset perturbation theory (IMPPT) has been presented and designated. (58–61) Another variation-perturbation technique (62,63) yields the subsystems' beginning wave functions in dimer-centered basis set (DCBS). Base set superposition error (BSSE) is eliminated from total interaction energy and all of its constituent parts (64) as a consequence of the complete counterpoise correction. The next components of interaction energy are obtained by using this approach:

$$\Delta E = E_{EL}^{(1)} + E_{EX}^{(1)} + E_{DEL}^{(R)} + E_{CORR} \ldots\ldots\ldots\ldots\ldots 4$$

In which $E_{EL}^{(1)}$ represent the 1st order electro-static term that describes Coulomb interaction of the distributions of the static charge of the two molecules; $E_{EX}^{(1)}$ represent repulsive 1st order exchange component coming from the principle of Pauli exclusion; and $E_{DEL}^{(R)}$ and E_{CORR} represent higher order delocalization and correlation terms.

All of the classical induction, exchange-induction, and so on, from 2nd order to infinity is covered by the delocalization referrals. To draw attention to the differences between the two decomposition procedures, the designations of interaction energy components differ compared to those used in eq. (2). A charge transfer term that is heavily reliant on the basis set has been included in significantly less basis set sensitive delocalization contribution. (62,63) It is important to note that basis set superposition errors affect both overall energy and its constituent parts for the most often used *Kitaura Morokuma* technique (57, 56). In this method, charge transfer term is related to shifts of density from one molecule to another, whereas polarization interaction energy is roughly associated with internal re-distribution of electron charge. As the most well-known disintegration strategy represents the first *Morokuma and Kitaura* approach, the decompositions described by equations (2) and (4) are discussed here.

Resonance-assisted hydrogen bonds

Through the interaction of moieties in the same (intramolecular) or different (intermolecular) molecules, hydrogen bonds could be created. In the former scenario, the format ion of intra molecular hydrogen bonds may lead to significant alterations in molecular structure and characteristics with broad ramifications. In fact, intra molecular hydrogen bonds could (i) change the lipophilicity, water solubility, and membrane permeability of molecules in the area of medicinal chemistry (65) or (ii) result in significant changes in photochemical characteristics of molecules, like shifts in photo-absorption energy (66) or significant changes in their photoisomerization processes. The notion of "resonance-assisted hydrogen bonding" (RAHB), which links π-electron de-localization to hydrogen bonding in compounds, was introduced by Gilli et al. in the late 1980s. (69–72) The researchers observed that β-diketones exhibited increased π-electron delocalization when they formed either (i) intra-molecular hydrogen bonds or (ii) a linear array of inter-molecular hydrogen bonds (Fig. 3). (69)

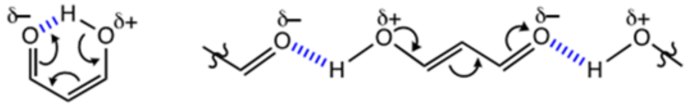


Fig.3 Intramolecular and intermolecular RAHB in β-diketone.(73)

The connection between proton group and acceptor group in RAHB is a highly energetic hydrogen bond. Since its introduction in Gill and colleagues' crystallographic work (69,74-76), the idea of RAHB was effectively embraced through chemical community for explaining phenomena in a variety of domains, including physical(77–79) as well as organic chemistry(80–82) and nuclear magnetic resonance (83,84).

In terms of RAHB energetics, some researchers consider the formation energy difference in the level of energy between associated closed and open conformers to be a gauge of RAHB strength. Never-the-less, a problem with this method to researching such interaction types—and, indeed, any other intramolecular contact is that YH···X bond rupture can't take place without resulting in a change to the molecule's structure. The aforementioned approach does, in fact, have the drawback of incorporating the energy of both the HB itself and the modifications occurring elsewhere in the molecule. Various methods for calculating RAHB interaction energy and other intra-molecular non-covalent interactions have been developed in this context. (86,87) A few of the most popular techniques, including interacting quantum atoms (IQA) approach of wave function analysis, are based on theoretical framework of Quantum Theory of Atoms in Molecules (QTAIM). (88,89) An energy partition scheme that divides an electronic system's total energy into intra- and interatomic components is used in the IQA approach. (90,91) Crucially, unlike conventional Energy Decomposition Analysis (EDA) techniques, IQA enables the unambiguous determination of intra-molecular interaction energy levels without necessitating the definition of non-interacting fragments. (92) IQA was utilized to investigate a variety of intramolecular interactions in general (93–97), with RAHBs serving as a case of particular significance for this study.(98–101)

Quantum Theory of Atoms in Molecules

The electronic density's structure determines how the QTAIM partitions space. Significant chemical concepts, like the atoms, atomic charges, functional groups, and bond ordering, can be recovered from electronic structure simulations or X-ray data using this wave function analysis method.(102) Consequently, a variety of physical and chemical problems were investigated using QTAIM, including the analysis of various bonds (103,104), adsorption (105–107), electrical conductivity (108–110), and catalysis (111–113). In order to partition total energy of an electronic system to the summation of the self-energies of every one of the atoms and the interaction energy values between atoms in the system, the usual IQA energy partition implementation begins with QTAIM atoms (90,91),

$$E = \sum_{A} E_{self}^{A} + \sum_{A>B} E_{int}^{AB} \dots\dots\dots\dots\dots 5$$

E_{self}^{A} in eq.(5) represent atom A energy, including its kinetic energy, electron–nucleus attraction and inter-electronic repulsion inside atom A.

E_{int}^{AB} represent total energy interacting between atoms B and A and it includes all potential combination cases of the terms of interaction between A’s nucleus and electrons on one hand, with B’s nucleus and electrons on the other.

By rearranges the terms in E_{int}^{AB}, we can gain further insight into the interaction between A and B,

$$E_{int}^{AB} = V_{cl}^{AB} + V_{xc}^{AB} \dots\dots\dots\dots\dots 6$$

V_{cl}^{AB} represents the ionic part of interaction energy, whereas V_{xc}^{AB} refers to the bond's covalency. (73,114)

Factor effecting Hydrogen Bond strength

The strength of hydrogen bonds in molecules is an important element in many chemical processes, including the design of UV absorbers and the dynamics of intrinsically disordered proteins. Research has demonstrated that the kind of substituent and its position in the molecule have a substantial impact on the strength of intramolecular hydrogen bonding. (115) Electron-absorbing groups such as halogens and -CN strengthen bonds, whereas electron-donating groups weaken them. Furthermore, the distribution of charges within the molecule influences the creation and stability of the bonds. When analyzing kinetics of hydrogen bonding between proteins and water molecules, excluding volume effects, hydrogen bond strength, and concentration of charged groups close hydrogen-bonding sites all contribute to determining the lifetimes of these interactions. (116) Overall, understanding these factors is essential for tailoring the properties of materials and proteins based on hydrogen bond interactions.

Electronegativity effects

Even though the substantial influence of electro-negativity on strengths of hydrogen bonds was well recognized, debates on hydrogen bonding nature persisted for the rest of the 20th century. An illustrated comparison of N–H···N and O–H···N hydrogen bonds has been shown in Fig4. O–H···N is thought to be a stronger hydrogen bond compared to the N–H···N based on electronegativity values of O (3.50) and N (3.00), and this tendency could be explained by orbital interaction as well as dipole-dipole interaction theories of hydrogen bonding: (i) The anti-bonding orbital of O–H will have stronger influence on electro-positive H because O is more electro-negative when compared to N, enhancing donor-acceptor orbital interaction (Fig. 4A). (ii) An H atom attached to O will have a higher positive charge than a N atom because O has been found more electronegative compared to N, which will strengthen the dipole-dipole interaction (Fig. 4B).(117)

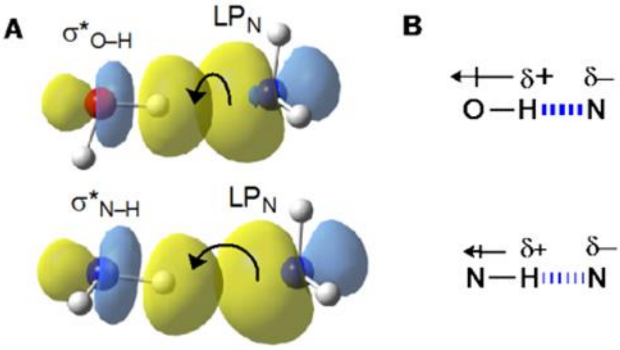
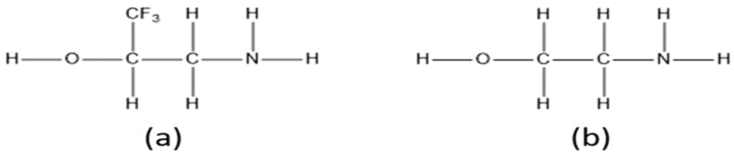


Fig.4 Effects of electro-negativity on O–H···N and N–H···N hydrogen bonds strength. Explanations based upon: a) donor-acceptor orbital interactions, b) dipole-dipole interactions.(117)

The most fundamental explanation for hydrogen bond strengths is a variation in electronegativity, and in early crystallography days, hydrogen bonding patterns were interpreted using these effects. Donohue had found that all of the acidic hydrogens that are available in a molecule will be utilized in hydrogen bonding in that material's crystal depending on investigations of hydrogen bonding patterns in organic crystals.(118) This concept has been significantly advanced in Etter's research in the 1980s and 1990s, when she used graph sets for examining organic crystals and developed a group of the rules, taking under consideration that: (i) All of the good proton bonds and acceptors function in hydrogen bonding, and (ii) optimal donor and acceptor of hydrogen will preferentially form bonds of hydrogen with each other. (119, 120) The pKa match is a related hydrogen bond design approach that considers proton donors and acceptors' basicity and acidity. (121–124) It was proposed that a matching pKa value can result in short, strong, low-barrier hydrogen bonds, where a proton could quickly exchange between 2 atoms, when an acid and its conjugate base, for instance, HF···F– (in other words, [F···H···F]–)(125). Low-barrier hydrogen bond theory, which was first proposed for explaining how charged centers could be maintained by enzymes throughout catalytic events, is still up for debate. (126–128)

Distance between hydrogen bond donor and acceptor

The role of inductive effects on bonds of hydrogen, as demonstrated in a study that has been conducted by Kaili Yap et al. (129), highlights the significance of the distance between hydrogen bond donor and acceptor in determining bond strength. By comparing intra-molecular hydrogen bond characteristics in 2-amino-1-trifluoromethylethanol (2ATFME) with those in 2-aminoethanol (2AE), it becomes apparent that electron-withdrawing groups, such as the trifluoromethyl CF3 group, can influence this distance (Fig.5). The findings reveal a 4% decrease in the donor-acceptor distance, a 6% increase in the angle towards linearity, and a 23% decrease in the torsional angle towards planarity in 2ATFME relative to 2AE, indicating a strengthening of the hydrogen bond. Moreover, the approach outlined in Xuhai Zhu et al. (130) combines variable-temperature 1H NMR analysis with density functional theory to classify intramolecular and intermolecular H-bonds, shedding light on the intricate relationship between bond distance and stereochemistry. By considering these insights, a comprehensive understanding of the distance between hydrogen bond donor and acceptor emerges, underpinning its crucial role in bond stability and structural recognition in biochemical systems. (see Fig. 6 and 7 for examples of intramolecular and intermolecular HBs).



(a) (b)

Fig.5 Adding an electron-withdrawing CF3 group on the carbon nearest to the alcohol donor of the OH···N intramolecular hydrogen bond in (b) 2AE, (a) 2ATFME.(129)

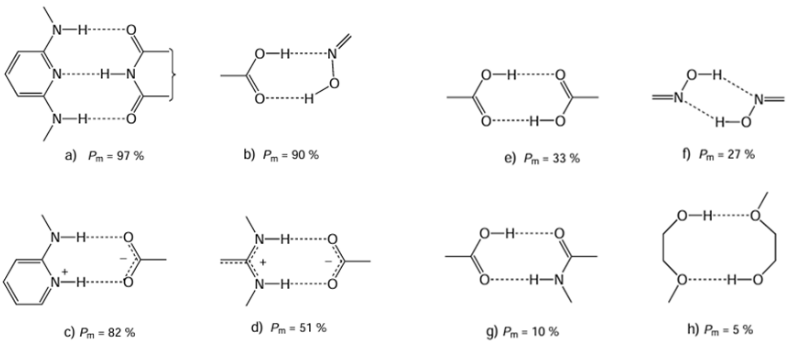


Fig.6 Eight cases of inter-molecular hydrogen bond motifs and their likelihood of production (Pm) in crystals

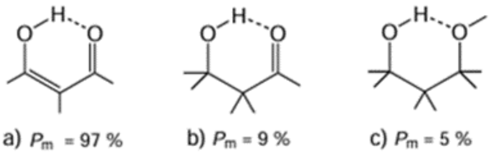


Fig.7 Three types of intramolecular OH---O hydrogen bonds and their production probability (Pm).(132)

Cooperative effects

Strong hydrogen bonding interactions can result from Networked hydrogen bonds. Water clusters can be formed by hydrogen bonds networks. Enzymes can use several interactions of hydrogen bonding for the purpose of stabilizing charges and enhancing catalysis (Fig.8A).(133,134)

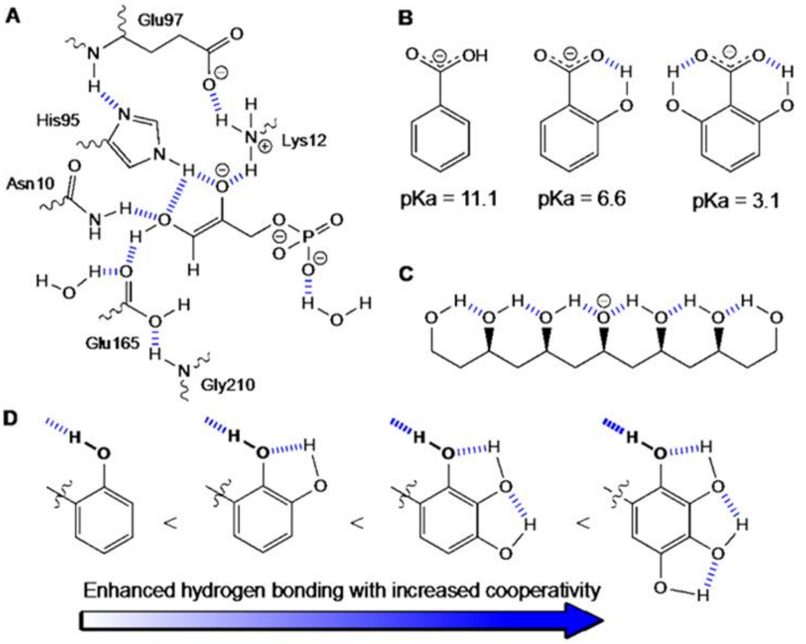


Fig.8 A) Networks of hydrogen bonding in triosephosphate isomerase active site. B) Cooperative hydrogen bonds can stabilize OH substituted benzoic acid's conjugate base. C) Illustration of covalent polyol system. D) Improved hydrogen bonding due to the neutral, short-range networks.(117)

The pKa of benzoic acid is decreased by four units in the case where one hydrogen bonding OH group is placed ortho to carboxylic acid group and through enormous 8 units in the case where 2 groups of OH are placed ortho to carboxylic acid group, as Herschlag and Shan demonstrated. These intra-molecular hydrogen bond networks have a potential of significantly increasing benzoic acid acidity in DMSO (Fig. 8B).(135) Wang, Kass and colleagues have shown that the hydrogen bonding networks could stabilize charged centers and that compounding effects of having several bonds of hydrogen might explain the way that the charges in enzyme active sites affect catalysis and conformational variations depending upon a series of the covalent polyol models (Fig. 8C).(136–137) These researchers proposed the theory that several hydrogen bonds stabilize charged centers in enzymes as opposed to the conventional theory that charges in enzymes are sustained by the presence of a single short, strong "low-barrier" hydrogen bond. It is possible for neutral systems to exhibit strong, close-range cooperation. A set of artificial molecular balances was used by Cockroft et al. to demonstrate how more cooperative intramolecular hydrogen bonding interactions could potentially strengthen neutral hydrogen bonds (Fig. 8D).(138) Inhibitors, catalysts, and molecular receptors have all been constructed using networks of hydrogen bonds.(139–142)

4. Conclusion

In the liquid, solid, and gas phases, hydrogen bonds (HBs) are the most prevalent interactions. An attractive interaction between two molecular moieties, where at least one of them has a hydrogen atom that serves a significant function, is known as the hydrogen bond (HB). Although two heteroatoms and a hydrogen atom make up classical HBs, more functional groups have been found to behave as hydrogen bond donors or acceptors in recent studies. The function, structure, and dynamics of biological molecules are all impacted by hydrogen bonds, making them essential in biology, chemistry, and materials science.

Based on the situation, their nature might change and their strength can range from weak to almost covalent. They could entail a variety of forms, including protein-water hydrogen bonds, p acceptor, and C-H-X bonds, and are crucial for maintaining protein structures. In some biological and chemical systems, there exist also Short Strong Hydrogen Bonds (SSHB). Hydrogen bonds are necessary for proton transfer and self-assembly in supra molecular chemistry. They are essential to chemical systems, affecting fluorescence and solvatochromism, among other phenomena. Their importance goes beyond chemistry to include inorganic chemistry and medicine, where they aid in particular reactions.

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