2

AN OVERVIEW OF HYDROGEN BONDING

2.1 HYDROGEN BONDING

The hydrogen bond in organic compounds was introduced by Huggins in 1919 [7]. He described semi-qualitatively the nature of these interactions referring to them as hydrogen bridges. Later, in 1920 Latimer and Rodebush defined the hydrogen bond as “the hydrogen nucleus held by two octets constitutes a weak bond” [44]. But it was in 1939 with Linus Pauling that the hydrogen bond (H-bond) was introduced into a broader chemical scope. In his paper entitled “The Nature of the Chemical Bond” the hydrogen bond was defined as a strong attraction of hydrogen to two atoms simultaneously [45]. Nowadays IUPAC recommendations define hydrogen bonding as an interaction between an electronegative atom (N, O, F) and a hydrogen attached to another electronegative atom, see Figure 2.1 [46–48].

![Figure 2.1](image)

**Figure 2.1:** (a) Hydrogen bonded dimer. (b) Hydrogen donor and acceptor. (c) Molecular orbitals of a N-methylacetamide hydrogen bonded dimer.

The doubly occupied nonbonding orbital (lonepair) of the electronegative atom (N, O, F) points towards the hydrogen atom of the polar group, forming an interaction that typically is stronger than a Van der Waals interaction and
weaker than a covalent bond. The group that contains the hydrogen atom (O-H, N-H) is defined as the donor group, whereas the polar group is the accepting one. These hydrogen bonds are defined as intramolecular H-bonds, when they occur between atoms inside the same molecule, or intermolecular H-bonds when formed between two different molecules. *Ab initio* [49,50] methods have been used to study the chemical nature of the hydrogen bond and they suggest four contributing mechanisms: polarization, quantum forces, Pauli exchange and London dispersion forces. Resulting from the combination of these effects, the strength of H-bonds may vary between weak (8 kJ mol$^{-1}$) and strong (160 kJ mol$^{-1}$) [51–53]. The nonbonding orbital of the electronegative atom of the acceptor is deformed due to the polarization arising from the strong dipole moment of the donor group [5]. Such effect is present in all hydrogen bonds and it is the main contributor. Quantum forces are caused by the overlap between the orbitals of the involved groups, resulting in the electron transfer from the nonbonding orbital of the acceptor to the antibonding orbital of the donor. This causes a weakening of the covalent bond of the donating group and consequently an increase in the variation of the electric dipole moment of the donor/acceptor [5]. Furthermore, this phenomenon is also accompanied by a $s$-$p$ rehybridization of the orbitals of the acceptor group. The last two effects arise from the Pauli exclusion principle and the London dispersion forces and are typical for strong hydrogen bonds. One example of weak H-bonding is in the water-benzene complex, which results from the polarization of the benzene $\pi$ orbitals by the oxygen of water. Medium strength hydrogen bonds are formed between carboxylic acids, whereas the strong ones occur either in acid salts or fluorine compounds [5].

The geometrical properties of hydrogen bonds have been measured by X-ray diffraction methods and have been related to thermodynamic properties. The equilibrium distance distribution typically ranges between 2.5 to 3.6 Å for strong and weak H-bonds, respectively. The equilibrium angle distribution is centered around 0° with a width of 15°, showing the high directionality of the hydrogen bond, which makes them distinct from the more isotropic Van der Waals interactions. This means that the H-bonds are on an almost straight line in their equilibrium position, allowing them to dictate the assembly of supramolecular structures. Their low formation energy at room temperature associated with the directionality make them unique: they constitute the only type of interaction that has both stability and flexibility [5]. Hydrogen bonding is present in various condensed matter systems ranging from crystals to liquids,
and complex matter such as proteins, and is responsible for their structure and dynamics.

2.1.1 Hydrogen bonding in liquids

Water is crucial to the existence of life and it is a strong hydrogen bonded liquid with tetrahedral H-bond arrangements [54–59]. The understanding of water opened doors to study the dynamics and structure of other liquids, such as alcohols and amides [33,34,60–63]. Alcohols have a hydroxyl group covalently bonded to an alkyl chain (R-OH) and with thermodynamic properties that vary according to the size of the adjacent groups. Containing one H-bond donor per molecule the characteristic three-dimensional H-bond network encountered in water is disrupted. With their amphiphilic nature alcohols carry the ability to form hydrogen bonds with their neighboring molecules, which is conditioned by the steric hindrance of the alkyl chain, see Figure 2.2 (a). The latter also changes their dynamical properties, which makes them a very interesting object of study [64,65].

![Figure 2.2: Hydrogen bonds (a) in bulk methanol, (b) and in bulk N-methylacetamide.](image)

N-Methylacetamide is a small molecule that contains a single carboxyl group covalently connected to an amide group, by a peptide bond. This molecule contains a donor group (N-H) and an acceptor group (C=O), which enables the formation of hydrogen bonds with the neighboring molecules, see Figure 2.2 (b). Even though their H-bonds are restricted by the steric hindrance of the methyl groups, they can assemble in different structures giving rise to long
hydrogen bonded chains of molecules in a bulk liquid. These interactions are very similar to those encountered between the protein backbones, which makes this molecule suitable to mimic properties of proteins.

2.1.2 Hydrogen bonding in proteins

Proteins are the engines of living systems and responsible for essentially all vital functions. They assemble in different levels of complexity from primary to quaternary structures, which arise from different types of interactions. Here the hydrogen bond plays a significant role in stabilization of well-defined arrangements, such as the secondary structure, see Figure 2.3. Because of the interchain H-bonds the degrees of freedom are restricted allowing the formation of well-defined and stable structures [5].

![Figure 2.3: Different secondary structure domains of proteins of DNA polymerase (PDB code:1AXC [66]). The α-helices are highlighted in purple, the β-sheets in yellow, the β-turns in light blue, the random coils in light grey, and the π-helices in dark blue.](image-url)
These hydrogen bonds are formed between the amino acids of the protein backbone, more precisely between the oxygen of the carbonyl group of one amino acid with the hydrogen of the amide group of another amino acid. The different types of secondary structure conformations are pleated β-sheets, α-helices, β-turns, and random coils [5].

![Figure 2.4: Ramachandran illustrations of the different protein motifs.](image)

To indicate which conformations are energetically accessible, the energy is plotted as a function of the dihedral angles φ and ψ indicated in Figure 2.4(a), in a so-called Ramachandran plot (Figure 2.4(b)). These dihedral angles are also known as Ramachandran angles. With Ramachandran angles of φ = -110° and ψ = +120° pleated β-sheets are divided in two types: parallel and antiparallel, in which two amino acids participate in two H-bonds, Figure 2.5 (c).

The α-helix secondary structures are more flexible than the other assemblies, but mechanically less resistant, see Figure 2.5 (a). With systematically separated H-bonds parallel to the helix axis, and composed by left handed amino acids, the right handed helices are favored. The most typical type is the α-helix, with Ramachandran angles of φ = -60° and ψ = -45°. In parallel β-sheets the polypeptide chain is connected by a large sequence of amino acids, called a β-turn, see Figure 2.5 (c). In the antiparallel β-sheet, however, the β-turn connecting both chains is smaller. The H-bonds of these assemblies also change, being paired and less constrained for the case of antiparallel β-sheets, thus, being more stable and easier to form than its parallel counterpart [5]. The β-turns are sequences of amino acids that connect the β-sheets together which are stabilized by hydrogen bonds, however, these are typically weaker and confer to the overall protein more flexibility. The random coils are protein domains
that do not have a defined secondary structure, and are present between α-helix and β-sheet domains, see Figure 2.5 (e). These motifs are very flexible, being responsible for fluctuations of the overall protein structure. The π-helix, Figure 2.5 (d), domains rarely appear on proteins, and the residue i from the backbone forms a hydrogen bond with residue i+5.

Even though important, hydrogen bonding is not only interaction dictating secondary structure. Interactions such as salt bridges, charge, and hydrophobicity are as well of extreme importance [5]. However, they have not been mentioned in this chapter since the overall goal is to provide an overview of hydrogen bonding in different systems.