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M.Sc. Zoology (Semester II)
CC7- Biochemistry

Unit: 3.2

Stabilising forces in protein structure

Dr Gajendra Kumar Azad
Assistant Professor
Post Graduate Department of Zoology
Patna University, Patna
Email: gajendraazad@outlook.com

Stabilizing the Shape of Proteins

Proteins are made of amino acid chains, or polypeptides. Amino acids have a basic backbone made of an amino group and a carboxyl group, and differ in their side-chains.

These polypeptide chains of amino acids can be shaped as helixes or sheets, which come together to form a 3-Dimensional structure. The 3-Dimensional structure of proteins is referred to as its “tertiary structure”.

The process of folding proteins into their tertiary structures is spontaneous and involves bonds and intermolecular forces to make the structure stable, are broadly categorized into two classes

1. Covalent interactions

2. Non-covalent interactions

Covalent interactions

Covalent bonds are the strongest chemical bonds contributing to protein structure. In addition to the covalent bonds that connect the atoms of a single amino acid and the covalent peptide bond that links amino acids in a protein chain, covalent bonds between cysteine side chains are important determinants of protein structure.

Cysteine is the sole amino acid whose side chain can form covalent bonds, yielding disulfide links or bridges.

Disulfide links

Disulfide bonds are formed between two sulfur (SH) atoms, which are found in the side-chain of the amino acid cysteine.

When two cysteines are brought into close proximity in the tertiary structure, covalent disulfide bond can be formed as a result of oxidation.

The two cysteine residues involved in the bond formation may be far apart in the primary structure but are brought close together as a result of protein folding

Disulfide links

Disulfide bonds within and between polypeptide chains form as a protein folds to its native conformation.

Some polypeptides whose Cys residues have been derivatized to prevent disulfide bond formation can still assume their fully active conformations, suggesting that disulfide bonds are not essential stabilizing forces.

They may, however, be important for “locking in” a particular backbone folding pattern as the protein proceeds from its fully extended state to its mature form.

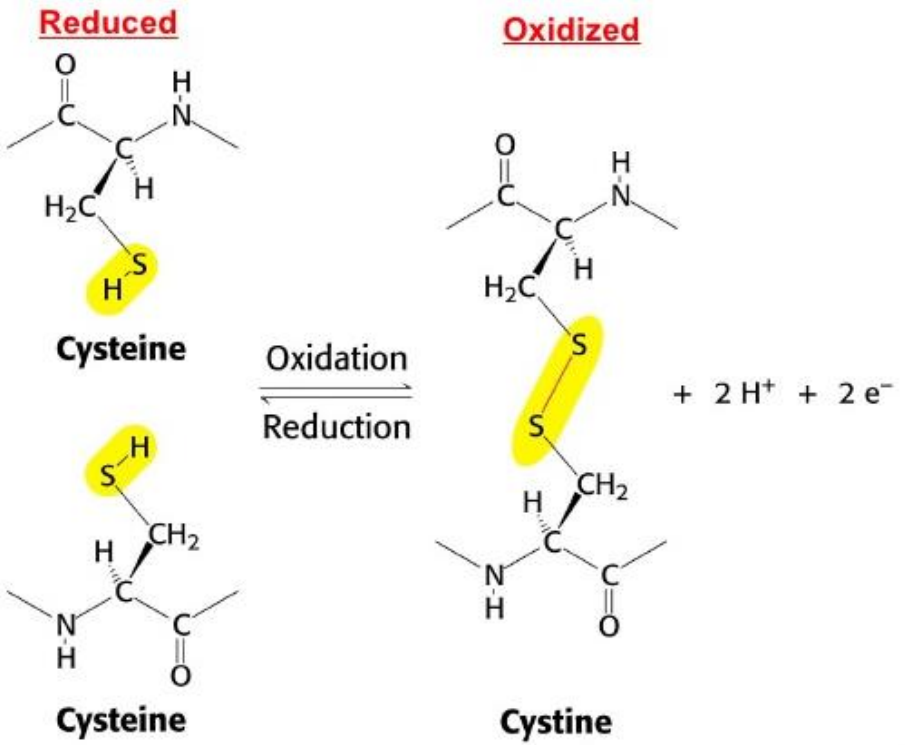


Figure 1: formation of disulfide bond

Non-covalent interactions

The 3-dimensional (3D) structure of proteins results from a delicate balance between various types of non-covalent interactions acting between the amino acid present the polypeptide chain and also with the surrounding environment.

Although non-covalent interactions are typically orders of magnitude weaker than covalent bonds but they play important role in the formation and maintenance of 3D structural integrity of protein.

Individual amino acids are distinguished by the chemical nature of their side chains. They can be roughly grouped into categories as being hydrophobic , aromatic, hydrophilic, charged, etc. This diversity in the amino acids enables them of forming a wide range of non-covalent interactions.

Some of the common non-covalent interactions observed in Proteins are:

1. Hydrophobic bond or interactions
2. Van Der Waals interactions
3. Electrostatic or ionic bond or salt bond or salt bridge
4. Hydrogen Bond

1. Hydrophobic Interactions

Hydrophobic bonds are a major force driving proper protein folding. Some amino acids have side-chains which repel water, or are hydrophobic.

The hydrophobic nature of the amino acids enables them to interact with one another by what is called hydrophobic “interactions”.

The aggregation of nonpolar side chains in the interior of a protein is favored by the increase in entropy of the water molecules that would otherwise form ordered “cages” around the hydrophobic groups.

Hydrophobic interactions forms an interior, hydrophobic protein core, where most hydrophobic side chains can closely associate and are shielded from interactions with solvent H_2O's.

The combined hydrophobic and hydrophilic tendencies of individual amino acid residues in proteins can be expressed as hydropathies. The greater a side chain’s hydropathy, the more likely it is to occupy the interior of a protein and vice versa.

Hydropathies are good predictors of which portions of a polypeptide chain are inside a protein, out of contact with the aqueous solvent, and which portions are outside.

Hydrophobic Interactions

Hydrobhobic amino acids

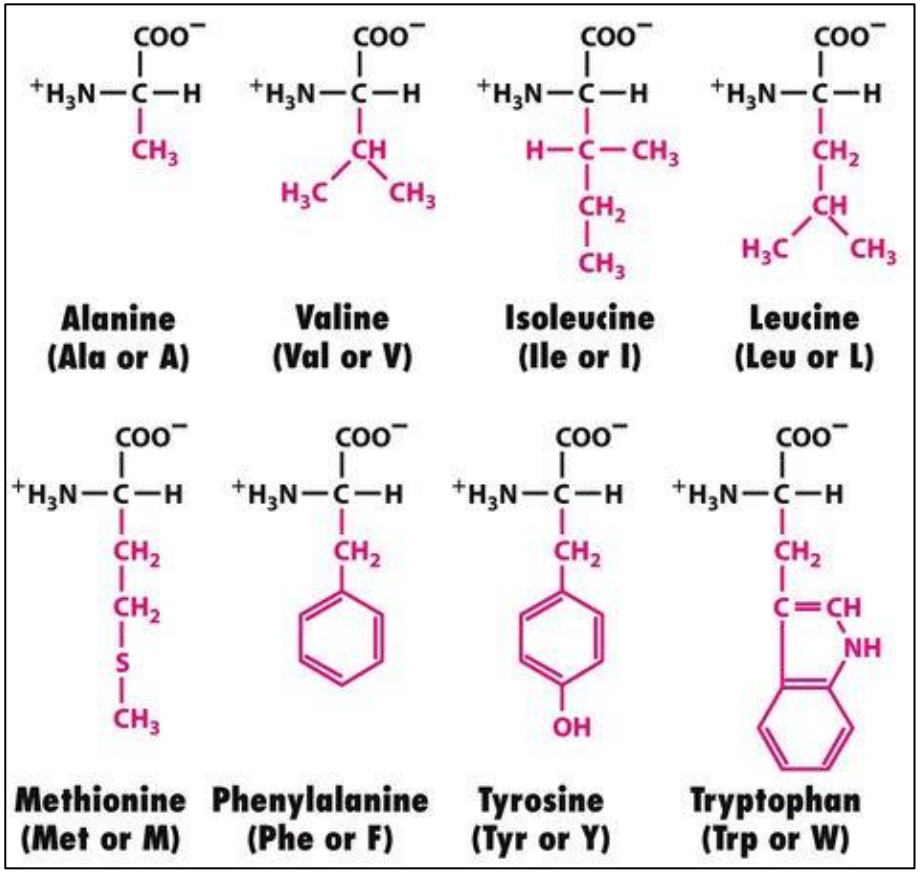


Figure 2: Most hydrophobic side chains can closely associate and are shielded from interactions with aqueous environment of cell. These amino acids tends to remain in the interior of the 3-dimensional protein tertiary structure.

Hydropathy index of amino acids

Side-chain	Hydropathy index
Isoleucine	4.5
Valine	4.2
Leucine	3.8
Phenylalanine	2.8
Cysteine/cystine	2.5
Methionine	1.9
Alanine	1.8
Glycine	−0.4
Threonine	−0.7
Tryptophan	−0.9
Serine	−0.8
Tyrosine	−1.3
Proline	−1.6
Histidine	−3.2
Glutamic acid	− 3.5
Glutamine	−3.5
Aspartic acid	−35
Asparagine	− 3.5
Lysine	−3.9
Arginine	− 4.5

Figure 3: The greater a side chain's hydropathy index, the more likely it is to occupy the interior of a protein and vice versa.

Hydrophobic Interactions

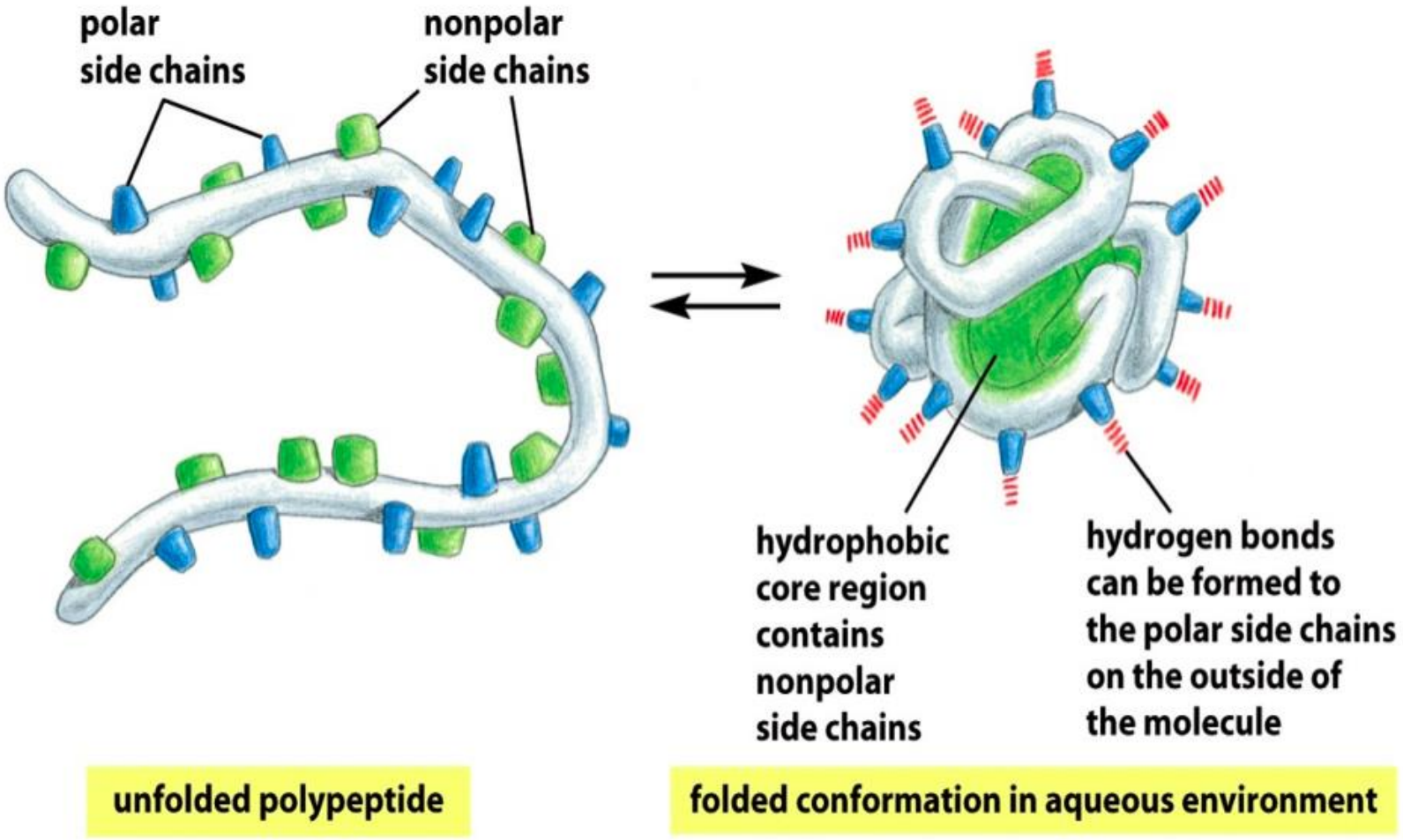


Figure 4: Hydrophobic interaction helps in the folding of protein in aqueous environment

2. Van Der Waals forces

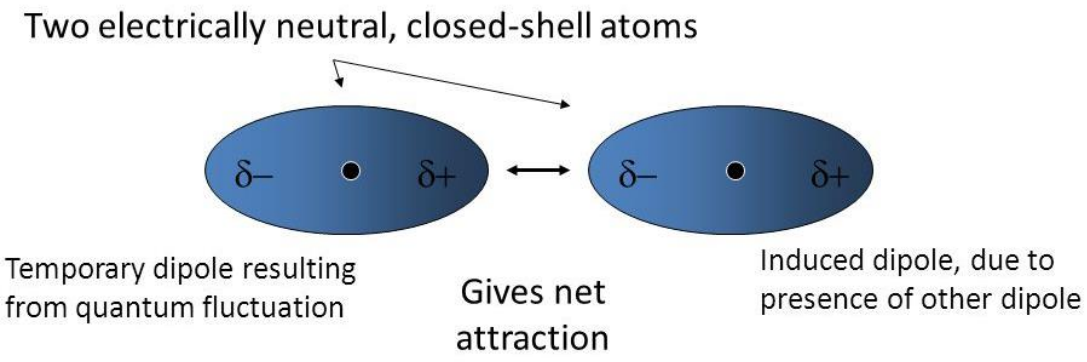
The Van der Waals force is a transient, weak electrical attraction of one atom for another.

Van der Waals attractions exist because every atom has an electron cloud that can fluctuate, yielding a temporary electric dipole.

The transient dipole in one atom can induce a complementary dipole in another atom, provided the two atoms are quite close.

These short-lived, complementary dipoles provide a weak electrostatic attraction known as the Van der Waals force.

The appropriate distance required for Van der Waals attractions depends on the size of each electron cloud of atoms and is referred to as the Van der Waals radius.



Van der Waals forces

In 3-dimensional structure of proteins , the formation of Van der Waals forces depends on the shape of the side-chain; if the atoms within the side-chains of neighboring amino acids fit well, then Van der Waals force is formed.

Well packed hydrophobic cores of proteins represent optimized van der Waals interactions between non-polar residues.

Although individually weak, numerous neighbor interactions in such central cores can contribute a significant stabilization to the native structure.

Van der Waals forces can play important roles in protein-protein recognition when complementary shapes are involved. This is the case in antibody-antigen recognition, where a "lock and key" fit of the two molecules yields extensive Van der Waals attractions.

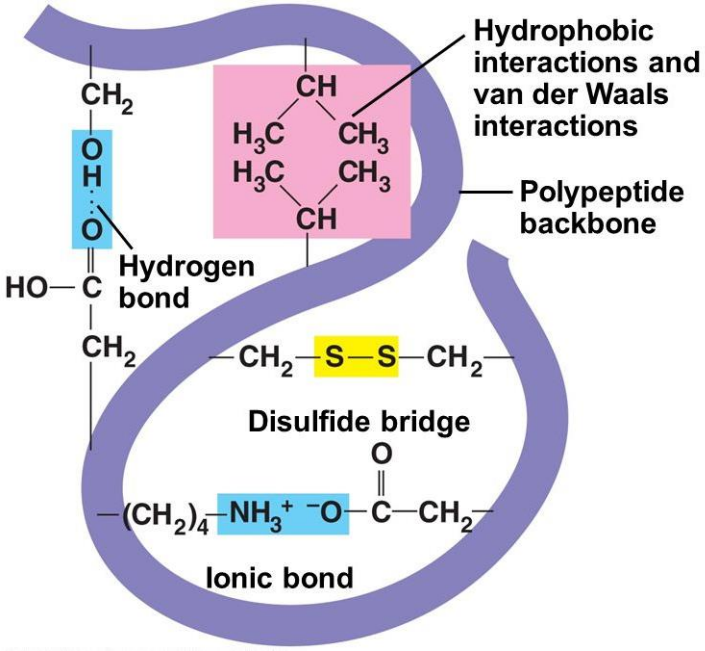


Figure 5: Van der Waals interaction between side chains of amino acids

3. Ionic Bonds- Salt Bridges

Salt bridges in proteins are bonds between oppositely charged residues that are sufficiently close to each other to experience electrostatic attraction.

Ionic bonds are formed as amino acids bearing opposite electrical charges are juxtaposed in the hydrophobic core of proteins.

Ionic bonding in the interior is rare because most charged amino acids lie on the protein surface.

Although rare, ionic bonds can be important to protein structure because they are potent electrostatic attractions that can approach the strength of covalent bonds.

An ionic or salt bridge can be formed between the carboxylate ion of an acidic residues such as aspartic acid or glutamic acid and an ammonium ion of the basic residue such as lysine, arginine or histidine

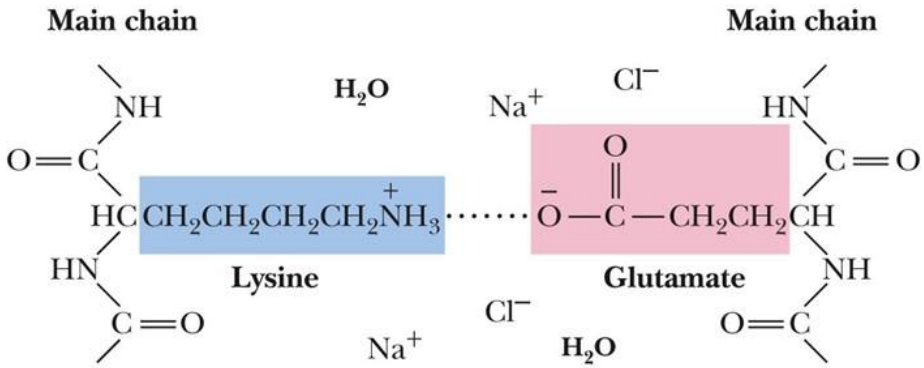
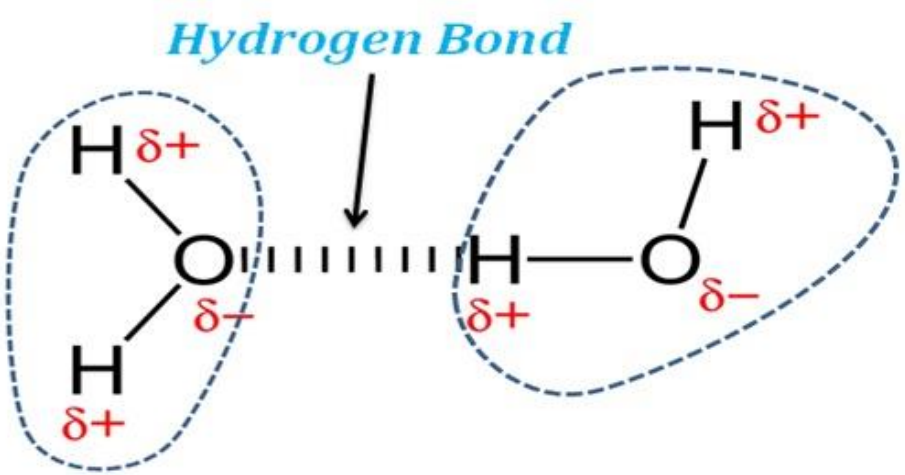


Figure 6: Salt bridge between side chains of amino acids

4. Hydrogen bonds

When two atoms bearing partial negative charges share a partially positively charged hydrogen, the atoms are engaged in a hydrogen bond (H-bond).



Formation of hydrogen bond between two water molecules

Hydrogen bonding is a form of weak attractive force between molecules that contain an electric charge. It is caused by electrostatic attraction and can alter the chemical properties of the molecules.

The Hydrogen bond attractive force is weaker than full ionic bonding.

Hydrogen bonds in proteins

The correct 3-dimensional structure of a protein is often dependent on an intricate network of H-bonds. These can occur between a variety of atoms, involving:

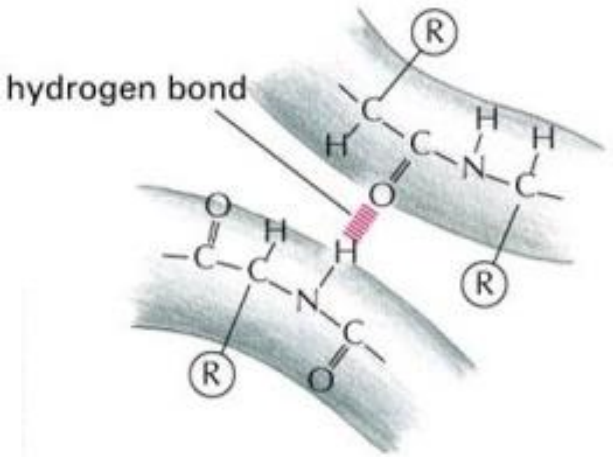
- atoms on two different amino acid sidechains
- atoms on amino acid sidechains and water molecules at the protein surface
- atoms on amino acid sidechains and protein backbone atoms
- backbone atoms and water molecules at the protein surface
- backbone atoms on two different amino acids

Polar groups exposed on the surface of proteins often have water as their hydrogen bonding partner. Polar groups within the core region usually form hydrogen bonds with other groups within the protein.

H bond can formed between large number of amino acid residues: serine, threonine, aspartic acid, glutamic acid, glutamine, lysine, arginine, histidine, tryptophan, tyrosine and asparagine.

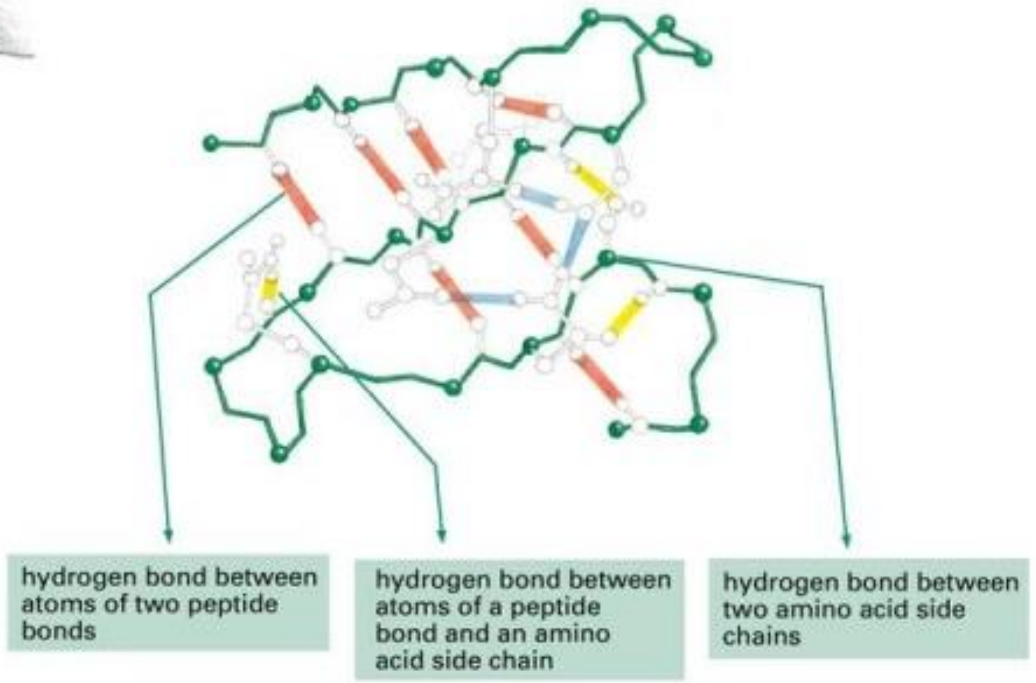
Hydrogen bonds are important determinants of native protein structures, because if a protein folded in a way that prevented a hydrogen bond from forming, the stabilizing energy of that hydrogen bond would be lost.

Hydrogen bonds in proteins



Proteins maximise hydrogen bonding.

Most bonds are between residues that are close in sequence.



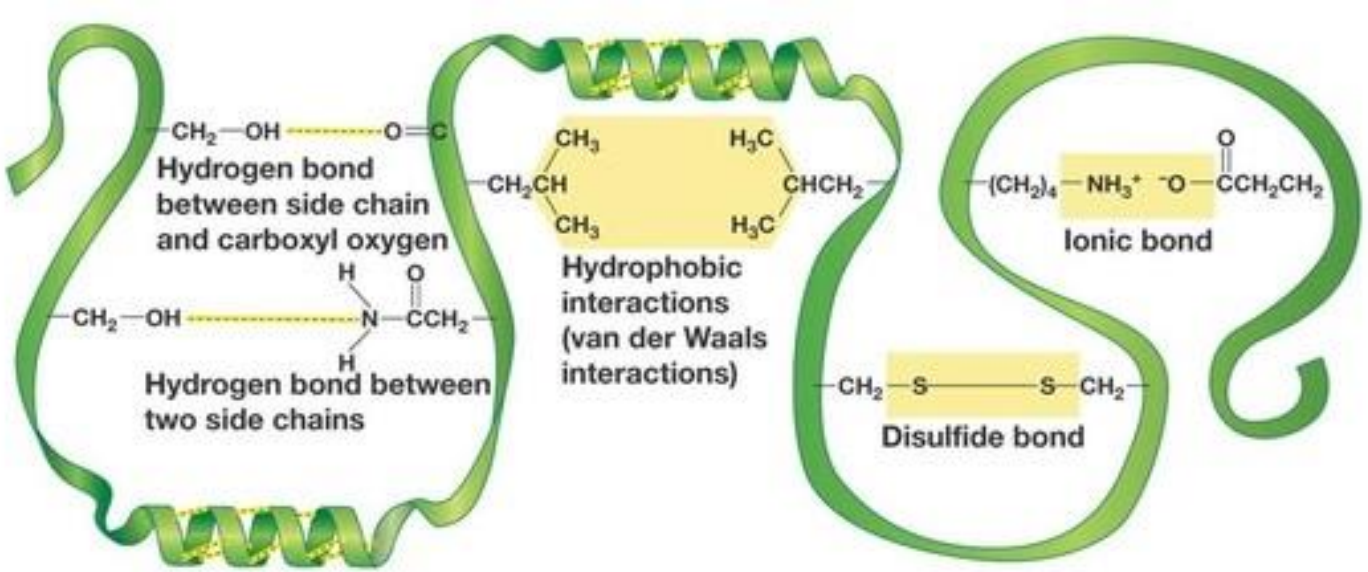
- H-bonds form between 1) atoms involved in the peptide bond; 2) peptide bond atoms and R groups; 3) R groups

Figure 7: Different kinds of Hydrogen bonds observed in protein molecule

Approximate strength of interactions between atoms in protein structure

Interaction type	**Strength (kJ/mol)**
Covalent bond (Disulfide)	167
Ionic bond	10-40
Hydrogen bond	8-40
van der Waals	4.0 (4-17 in protein interior) depending upon the size of the group
Hydrophobic interactions	4-12

Summary: Stabilising forces in protein structure



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