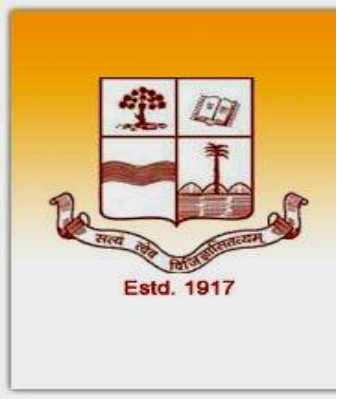
STRUCTURE OF PROTEINS



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Objectives

Learning the Levels of Molecular Organization in Protein Molecules

- Primary Structure
- Secondary Structure
- Tertiary Structure
- Quarternary Structure

Primary Structure of Proteins

- A description of all covalent bonds (mainly peptide bonds and disulfide bonds) linking amino acid residues in a polypeptide chain is its primary structure.

- The most important element of primary structure is the *sequence* of amino acid residues.

Features of Primary Structure

- Each protein has a distinctive number and sequence of amino acid residues.

- The primary structure of a protein determines how it folds up into a unique three-dimensional structure, and this in turn determines the function of the protein.

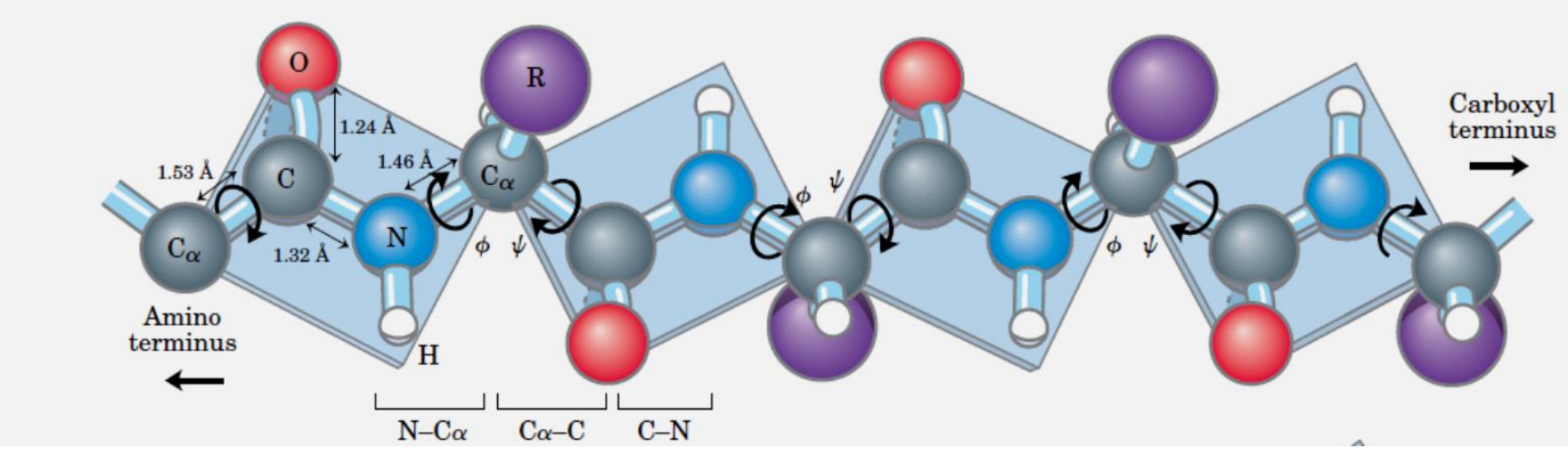
The Peptide Bond

- Pauling and Corey concluded that the peptide C-N bonds are unable to rotate freely because of their partial double-bond character.

- Rotation is permitted about the N-Cα and the Cα-C bonds.

- The backbone of a polypeptide chain can thus be pictured as a series of rigid planes with consecutive planes sharing a common point of rotation at Cα.

Folding of Polypeptide chain



By convention, the bond angles resulting from rotations at Cα are labeled ϕ (phi) for the N-Cα bond and ψ (psi) for the Cα-C bond.

Significance of Primary Structure

- The primary structure of a protein determines the other levels of structure.
- A single amino acid substitution can give rise to a malfunctioning protein, as is the case with sickle-cell anemia.
- Using molecular-biology techniques, such as site-directed mutagenesis, it is possible to replace any chosen amino acid residue in a protein.

Secondary Structure of Proteins

- The spatial arrangement of atoms in a protein is called its **conformation.**
- The possible conformations of a protein include any structural state that can be achieved without breaking covalent bonds.
- Of the numerous conformations that are theoretically possible in a protein containing hundreds of single bonds, one or (more commonly) a few generally predominate under biological conditions.

Control Over Folding Patterns

- Hydrophobic residues are largely buried in the protein interior, away from water.
- The number of hydrogen bonds within the protein is maximized.
- Insoluble proteins and proteins within membranes, follow somewhat different rules because of their function or their environment, but weak interactions are still critical structural elements.

Distribution of ϕ and ψ Dihedral Angles

- Other single bonds in the backbone may also be rotationally hindered, depending on the size and charge of the R groups.
- Some φ and Ψ combinations are very unfavorable because of steric crowding of backbone atoms with other atoms in the backbone or side chains.
- Some φ and Ψ combinations are more favorable because of chance to form favorable H-bonding interactions along the backbone.

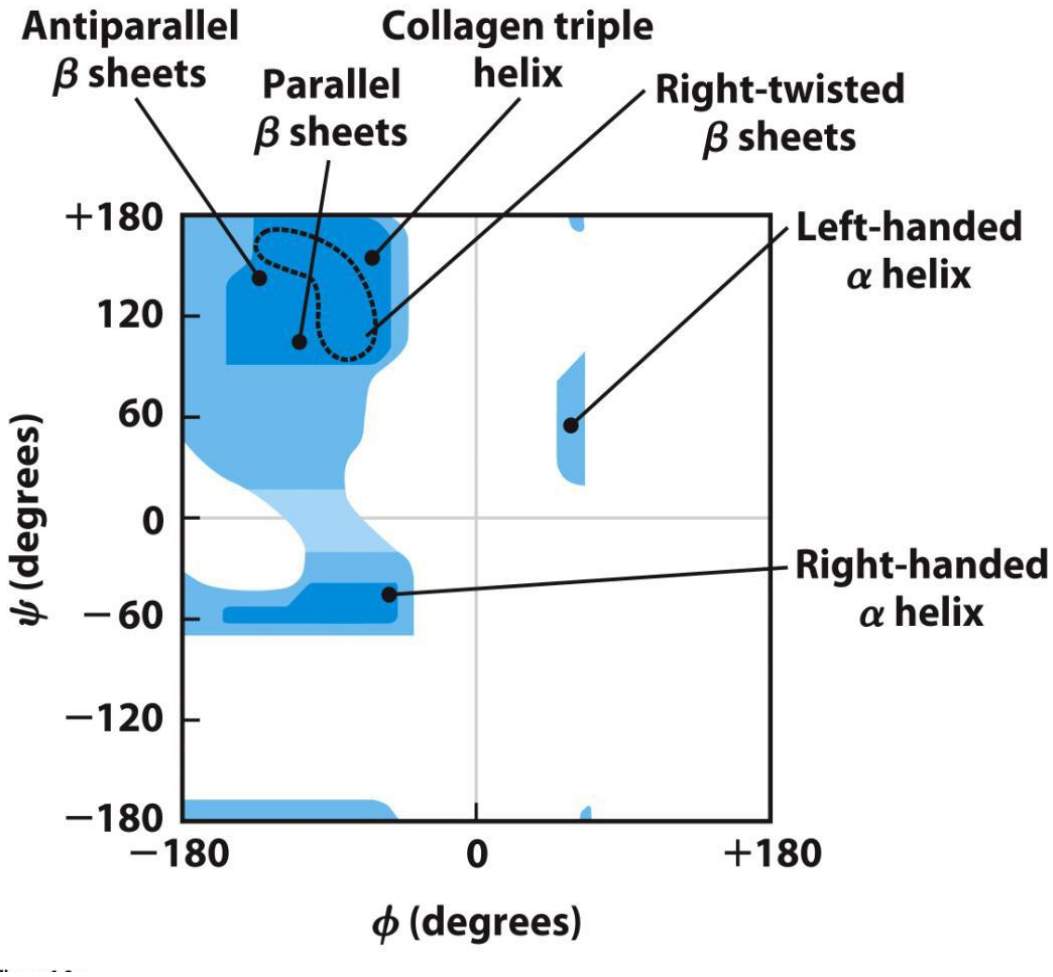
Ramachandran Plot

- A Ramachandran plot shows the distribution of φ and Ψ dihedral angles that are found in a protein.

- Shows the common secondary structure elements and reveals regions with unusual backbone structure.

A Ramachandran Plot

The values of Φ and Ψ for various allowed secondary structures are overlaid on the plot from Figure(RHS). Although left-handed α helices extending over several amino acid residues are theoretically possible, they have not been observed in proteins.

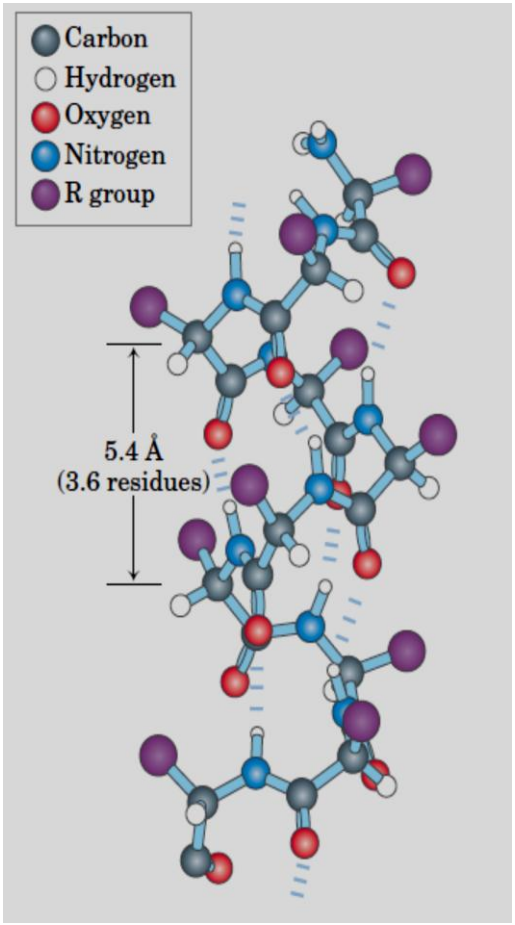


Common Types of Secondary Structures

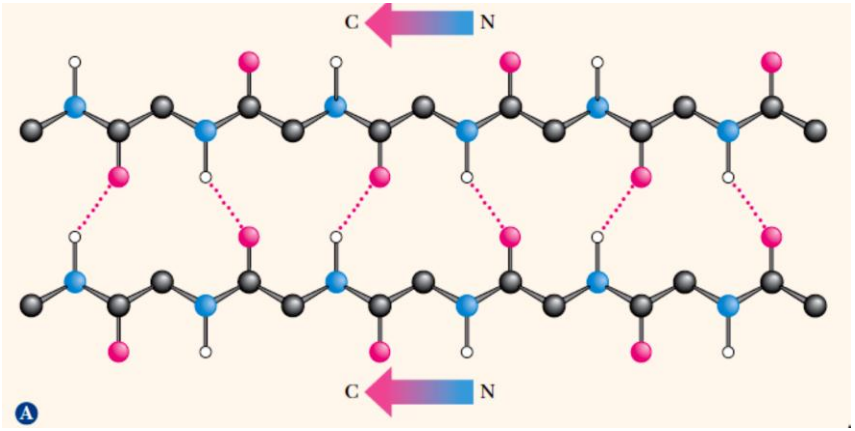
- The most prominent are the **α-helix** and **β-sheet conformations.**
- **α-Helix** (Pauling and Corey) has a regular structure that repeats every 5.15 to 5.2 Å.
- The repeating unit is a single turn of the helix, which extends about 5.4 Å along the long axis.
- Irregular arrangement of the polypeptide chain is called the **random coil** or extended chain.

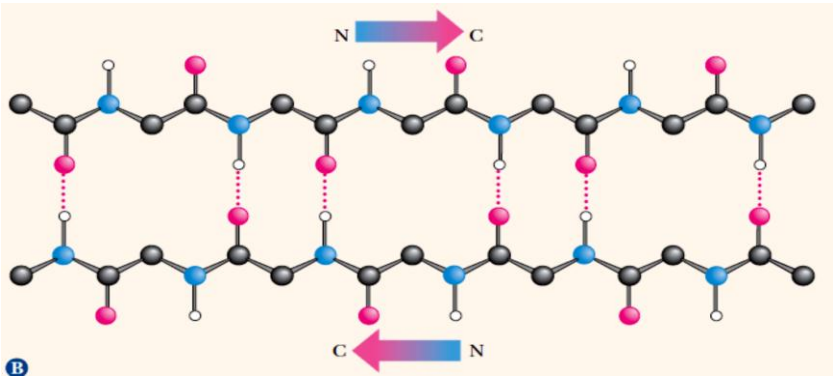
The α-Helix and The β-Sheets

α-Helix



β-Sheet : Parallel (UPPER) and Antiparallel (LOWER)





Parallel and Antiparallel β-Sheets

- In **parallel β sheets** the H-bonded strands run in the same direction resulting in bent H-bonds (weaker).

- In **antiparallel β sheets** the H-bonded strands run in opposite directions resulting in linear H-bonds (stronger).

Why the α-Helix Is More Common?

- An α–helix makes optimal use of internal hydrogen bonds.
- Every peptide bond (except those close to each end of the helix) participates in such hydrogen bonding.
- Each successive turn of the *α*- helix is held to adjacent turns by three to four hydrogen bonds.

Factors Controlling Twists in α-Helix

- The twist of an a helix ensures that critical interactions occur between an amino acid side chain and the side chain three (and sometimes four) residues away on either side of it.

- Positively charged amino acids are often found three residues away from negatively charged amino acids, permitting the formation of an ion pair.

The β-Sheet Secondary Structure

- More extended conformation of polypeptides.
- The zigzag polypeptide chains can be arranged side by side to form a structure resembling a series of pleats and thus named β-**sheet.**
- The R groups of adjacent amino acids protrude from the zigzag structure in opposite directions, creating the alternating pattern.

Supersecondary Structures : Domains and Motifs

- The combination of α- and β-strands produces various kinds of **supersecondary** structures in proteins.
- Polypeptides with more than a few hundred amino acid residues often fold into two or more stable, globular units called **domains.**
- The most common feature of this sort is the βαβ ***unit,*** in which two parallel strands of β-sheet are connected by a stretch of α-helix.

- A motif is regarded as Specific arrangement of several secondary structure elements

  (a) All alpha-helix

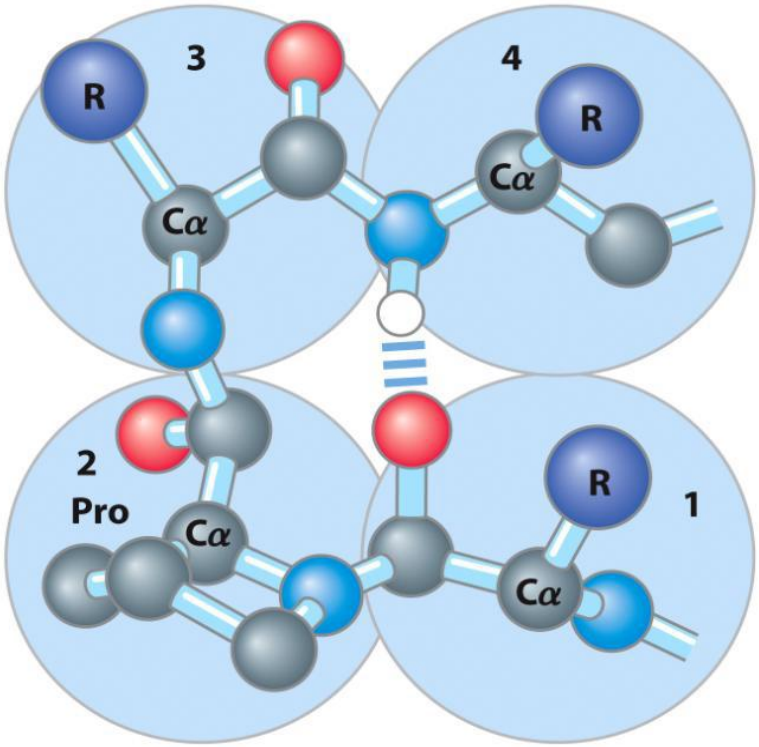
  (b) All beta-sheet

  (c) Both.
- Motifs can be found as reoccurring structures in numerous proteins.
- Proteins are made of different motifs folded together.

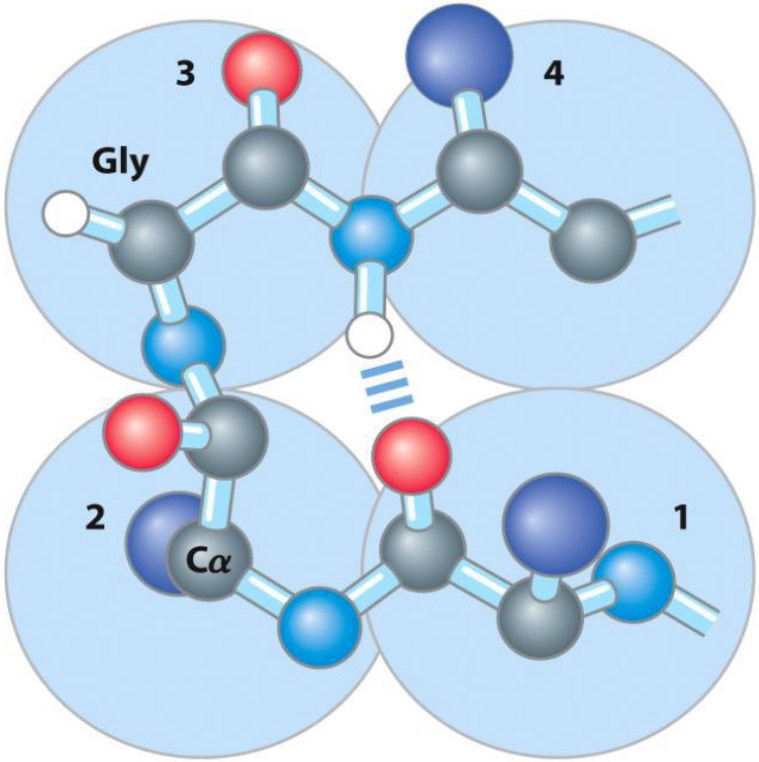
β- Turns

- β-turns occur frequently whenever strands in β-sheets change the direction.
- The 180° turn is accomplished over four amino acids.
- The turn is stabilized by a hydrogen bond from a carbonyl oxygen to amide proton three residues down the sequence.
- Proline in position-2 or glycine in position-3 are common in β-turns.

Understanding the β-Turns



Type I β turn



Type II β turn

Type I and Type II β-Turns

- Type I β-turns occur more than twice as frequently as type II. Type II β-turns usually have Gly as the third residue.

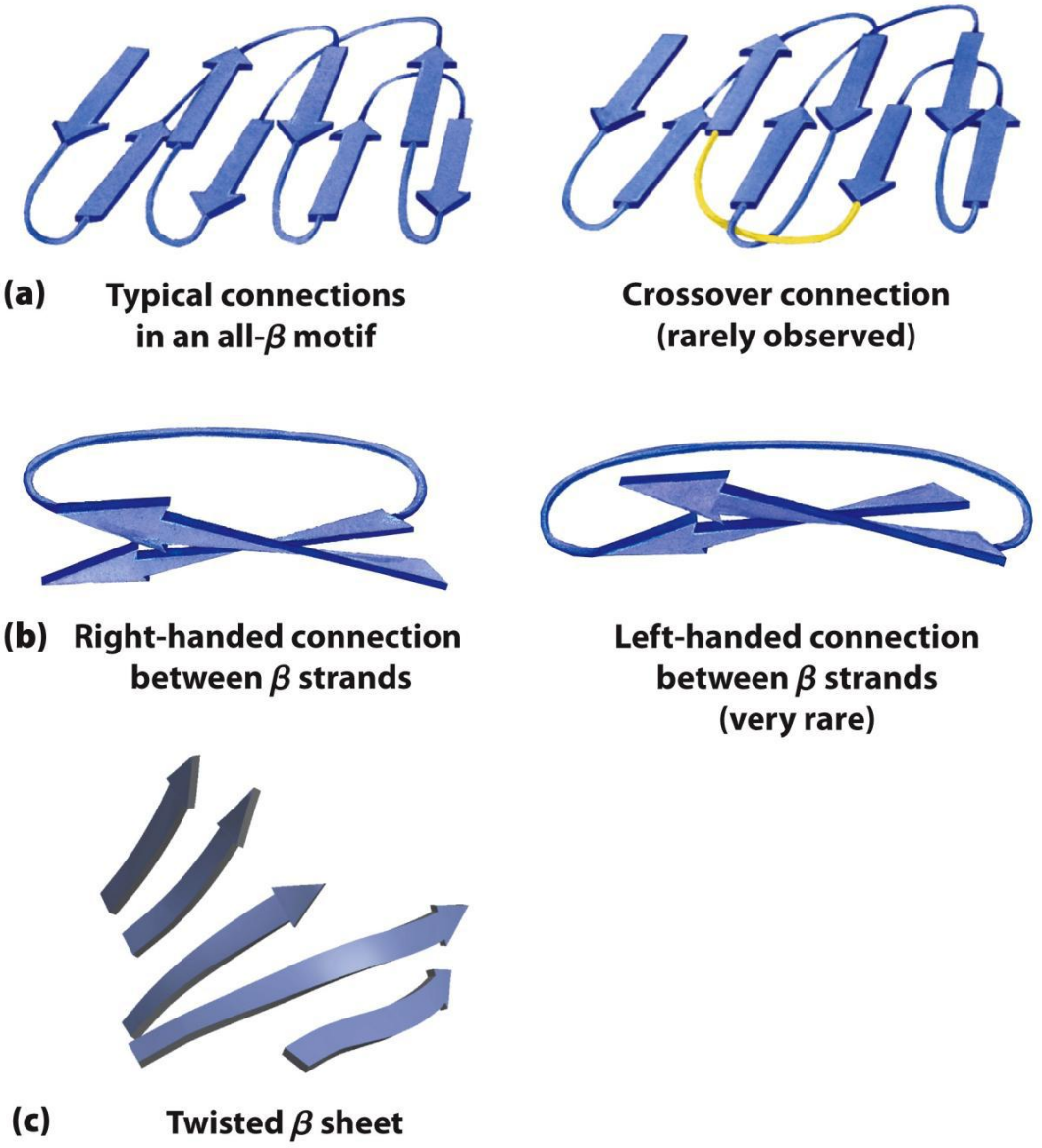
- Note the hydrogen bond between the peptide groups of the first and fourth residues of the bends. (Individual amino acid residues are framed by large blue.

Viewing Motifs

(a) Connections between β-strands in layered β-sheets.

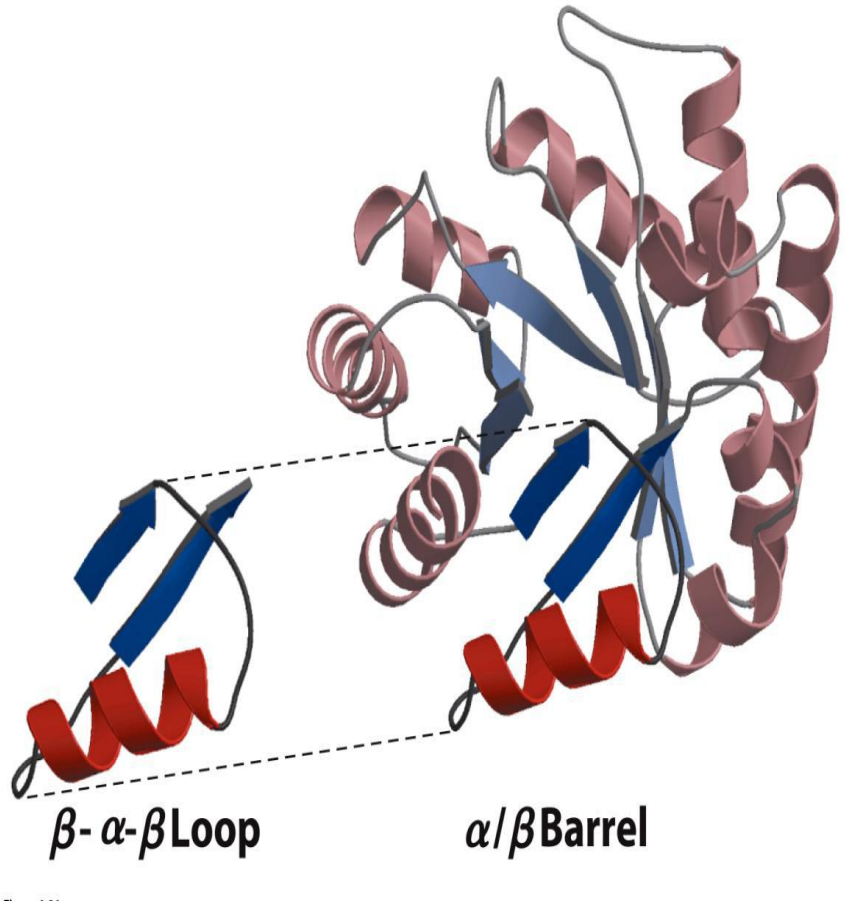
(b) Because of the right handed twist in β strands, connections between strands are generally right-handed.

(c) This twisted β sheet is from a domain of photolyase



Larger Motifs

- The α/β barrel is a commonly occurring motif constructed from repetitions of the β-α-β loop motif. This α/β barrel is a domain of pyruvate kinase (a glycolytic enzyme) from rabbit (derived from PDB ID 1PKN).

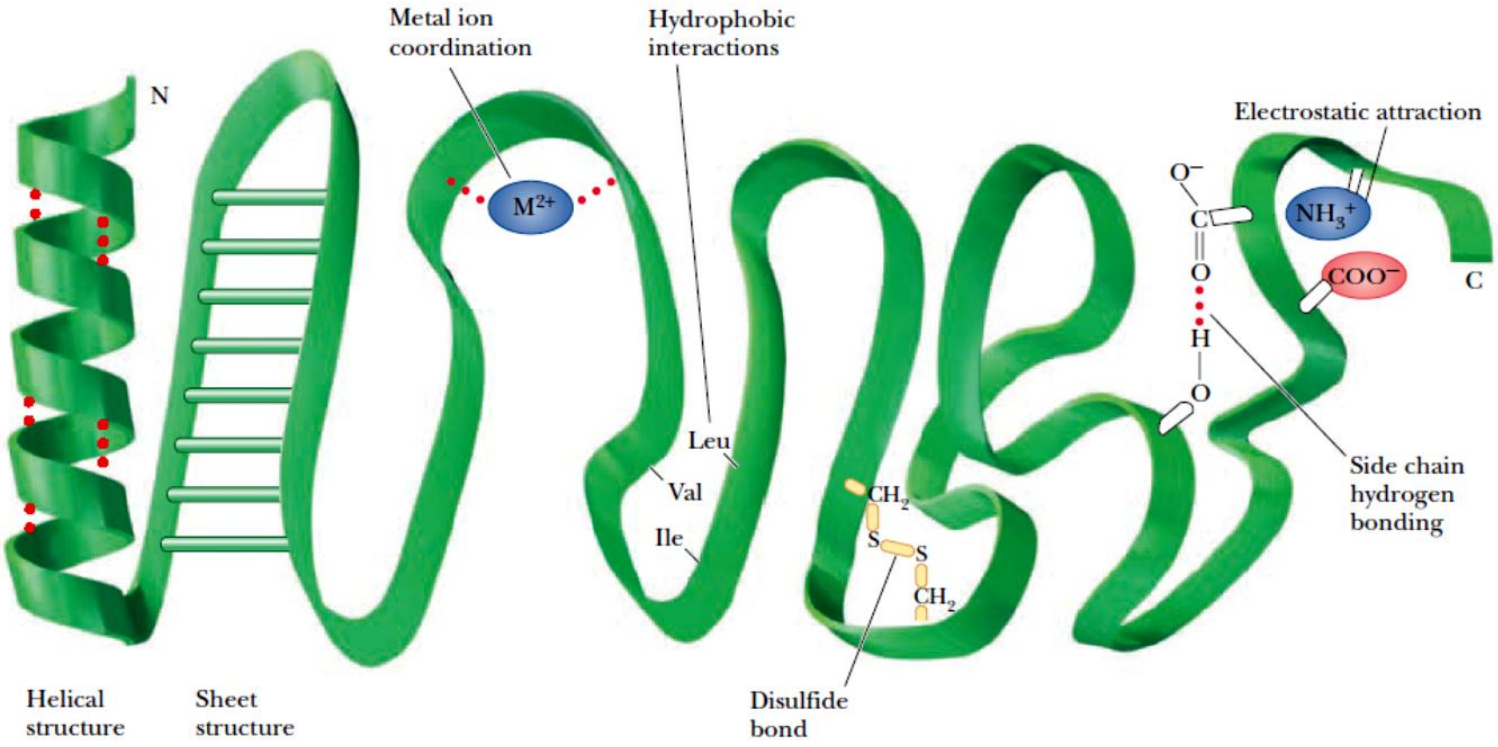


Tertiary Structure of Proteins

- The tertiary structure of a protein is the three-dimensional arrangement of all the atoms in the molecule.

- It essentially depends upon the way in which the helical and pleated-sheet sections fold back on each other.

Prototype of Tertiary Structure



Regulating Folding Patters

- In a **fibrous protein** , the helical backbone of the protein does not fold back on itself.

- For a **globular protein**, considerably more information is needed. In fact, the Tertiary structure includes ***longer-range*** aspects of amino acid sequence.

Forces Involved in Tertiary Structures

- Higher-order levels of structure, such as the conformation of the backbone (secondary structure) and the positions of all the atoms in the protein (tertiary structure), depend mostly on non-covalent interactions.
- Non-covalent stabilizing forces contribute to the most stable structure for a given protein, the one with the lowest energy.

Types of Binding Interactions

- **Covalent interactions** : Contribute a little.
- **Hydrogen bonding :** Several types of hydrogen bonding occur in proteins. *Backbone* hydrogen bonding is a major determinant of secondary structure.
- **Hydrophobic interactions :** Nonpolar residues tend to cluster together in the interior of protein molecules as a result of *hydrophobic* interactions.

Prothestic groups and Disulfide interactions

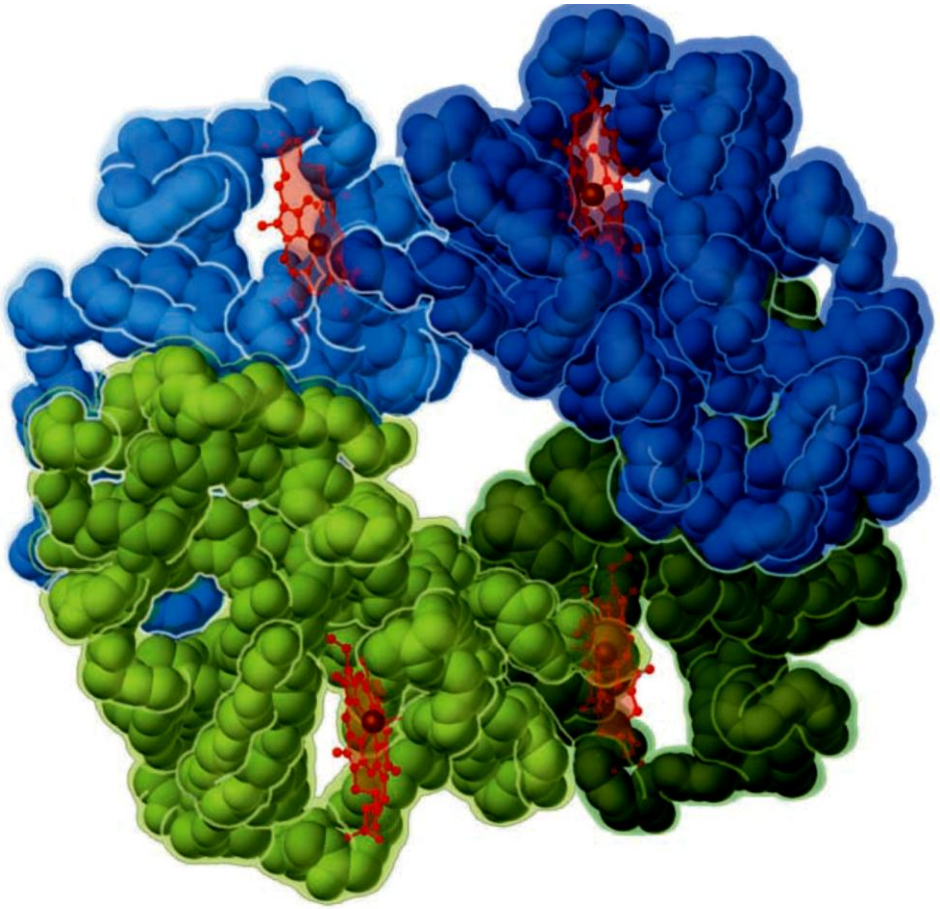
- Several side chains can be *complexed* to a single metal ion (metal ions also occur in some prosthetic groups.) In addition to these noncovalent interactions, *disulfide bonds* form covalent links between the side chains of cysteines.
- Not every protein necessarily exhibits all possible structural features.

Quarternary Structure of Proteins

- Quaternary structure is the final level of protein structure and pertains to proteins that consist of more than one polypeptide chain. Each chain is called a ***subunit***.

- The chains interact with one another noncovalently via electrostatic attractions, hydrogen bonds, and hydrophobic interactions.

Structure of Deoxyhemoglobin



Thank You