College of Pharmacy

Third Stage

Biochemistry I

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Lecture 4

Structure of Protein

STRUCTURE OF PROTEIN

Overview

- The 20 amino acids commonly found in proteins are joined together by peptide bonds.
- The linear sequence of the linked amino acids contains the information necessary to generate a protein molecule with a unique three-dimensional shape.
- The complexity of protein structure is best analyzed by considering the molecule in terms of four organizational levels, namely: Primary, Secondary, Tertiary and Quaternary.

The Importance of Protein Structure

A protein's function depends on its specific conformation. In almost every case, the function depends on its ability to recognize and bind to some other molecule. For example, antibodies bind to particular foreign substances that fit their binding sites. Enzyme recognize and bind to specific substrates, facilitating a chemical reaction.

Note:

- A functional protein consists of one or more polypeptides that have been precisely twisted, folded, and coiled into a unique shape.
- It is the order of amino acids that determines what the three-dimensional conformation will be.

Levels of Protein Structure

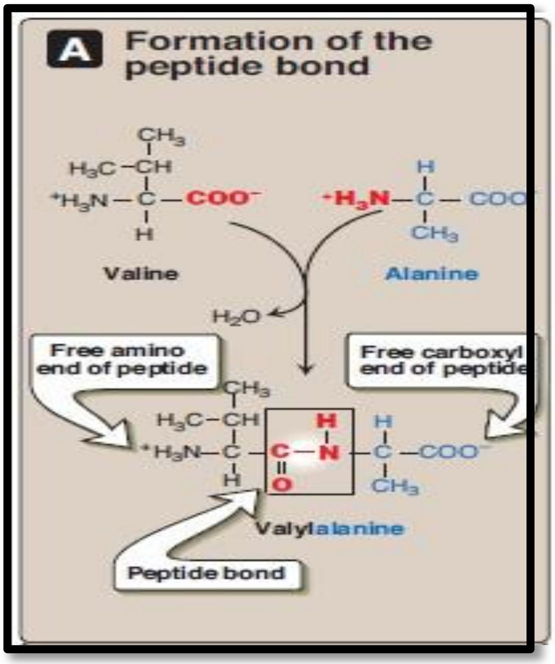
1. Primary Structure of Proteins

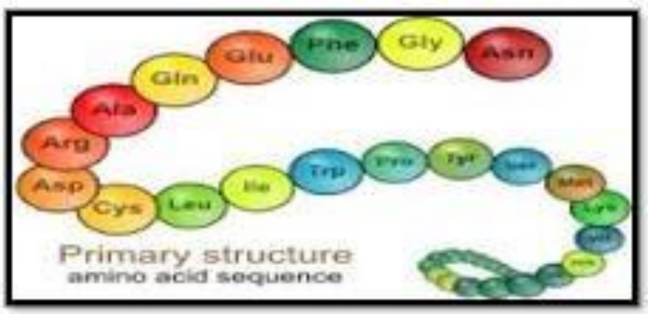
The primary structure of proteins involves the sequence of amino acids in a polypeptide chain.

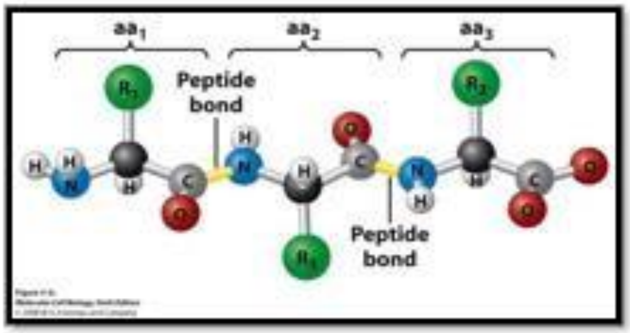
Understanding the primary structure of proteins is important because many genetic diseases result in proteins with abnormal amino acid sequences, which cause improper folding and loss or impairment of normal function.
Thus, studying the polypeptide chain means studying the primary structure of protein

A. Peptide bond

In proteins, amino acids are joined covalently by peptide bonds. Peptide bond are amide linkages between the α-carboxyl group of one amino acid and the α-amino group of another. For example, **valine** and **alanine** can form the dipeptide **valylalanine** through the formation of a peptide bond.

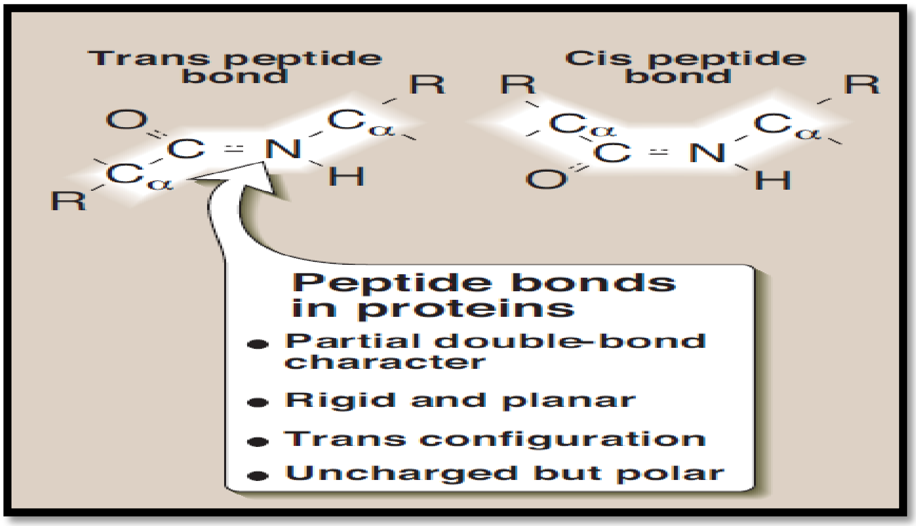






B. Characteristics of the peptide bond:

- The peptide bond has a partial double-bond character, that is, it is shorter than a single bond, and is rigid and planar.
- The peptide bond is generally a trans bond (instead of cis) in large part because of steric interference of the R-groups when in the cis position.
- Peptide bonds are not broken by conditions that denature proteins, such as heating & high concentrations of urea.
- Prolonged exposure to a strong acid or base at elevated temperatures is required to hydrolyze these bonds non-enzymatically.



Characteristics of the peptide bond

C. Naming the peptide:

- By convention, the free amino end (N-terminal) of the peptide chain is written to the left and the free carboxyl end (C-terminal) to the right. Therefore, all amino acid sequences are read from the N- to the C-terminal end of the peptide. For example, in the previous figure the order of the amino acids is "valine, **alanine**."

- Linkage of many amino acids through peptide bonds results in an unbranched chain called a polypeptide.

- Each component amino acid in a polypeptide is called a "residue" because it is the portion of the amino acid remaining after the atoms of water are lost in the formation of the peptide bond.

- When a polypeptide is named, all amino acid residues have their suffixes (-ine, -an, -ic, or -ate) changed to -yl, with the exception of the C-terminal amino acid. For example, a tripeptide composed of an N-terminal **valine**, a **glycine**, and a C-terminal **leucine** is called **valyl glycyl leucine**.

2. Secondary Structure of Proteins

Secondary structure is defined as the local three-dimensional conformation of the polypeptide backbone excluding the side chains. These arrangements are termed the secondary structure of the polypeptide. The α-helix, β-sheet, and β-bend (β-turn) are examples of secondary structures frequently encountered in proteins.

- It results from hydrogen bond formation between hydrogen of -NH group of peptide bond and the carbonyl oxygen -C=O of another peptide bond.

- According to H-bonding the following are forms of secondary structure:

1. α-helix:

- α-helix is a spiral structure, consisting of a tightly packed, coiled polypeptide backbone core, with the side chains of the component amino acids extending outward from the central axis to avoid interfering sterically with each other.

- Formed by a H-bond between every 4th peptide bond - C=O to N-H

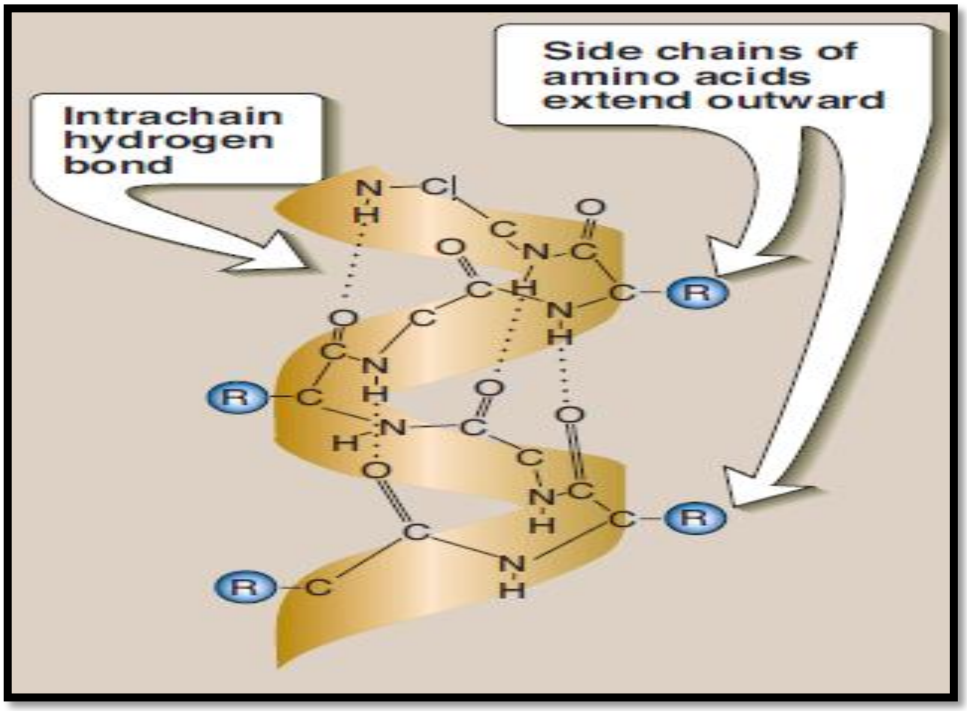
- Usually found in proteins that span a membrane.

- The helix can either coil to the right or the left.

- Each turn of an α-helix contains 3.6 amino acids.

- Proline disrupts an α-helix because its secondary amino group is not geometrically compatible with the right-handed spiral of the α-helix.

- Example of proteins contains α-helices: keratins are a fibrous protein. They are a major component of tissues such as hair and skin. Myoglobin, a globular, flexible protein molecule.



α-Helix showing peptide backbone

2. β-sheets:

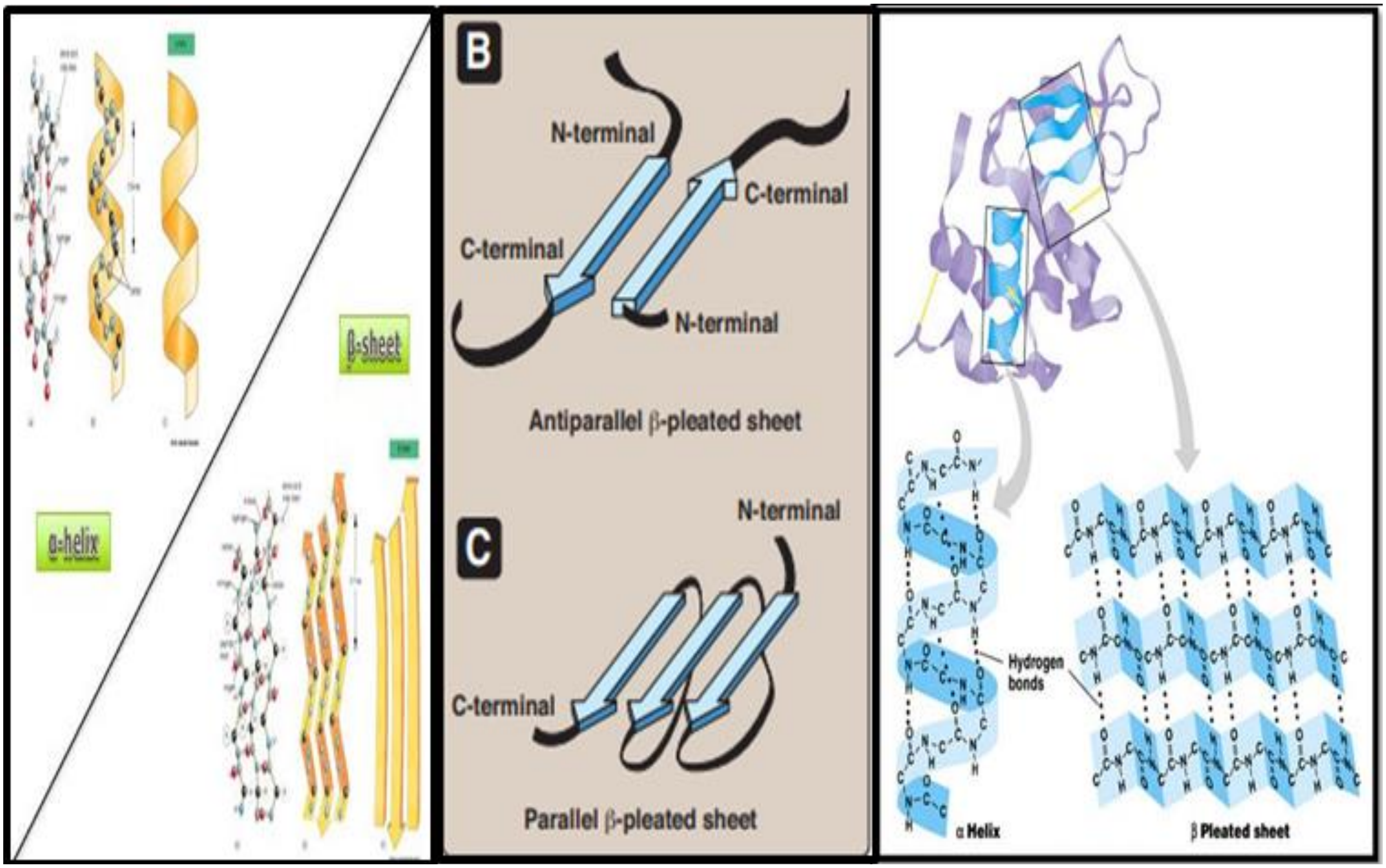
- It is another form of secondary structure in which two or more polypeptides (or segments of the same peptide chain) are linked together by hydrogen bond between H- of NH- of one chain and carbonyl oxygen of adjacent chain (or segment).

- In β-sheet all of the peptide bond components are involved in hydrogen bonding.

- Unlike the α-helix, β-sheets are composed of two or more peptide chains (β-strands), or segments of polypeptide chains, which are almost fully extended.

- The surfaces of β-sheets appear "pleated," and these structures are, therefore, often called "β-pleated sheets."

- A β-sheet can be formed from two or more separate polypeptide chains or segments of polypeptide chains that are arranged either antiparallel to each other (with the N-terminal and C-terminal ends of the β-strands alternating), or parallel to each other (with all the N-termini of the β-strands together).



3. β-Bends (reverse turns)

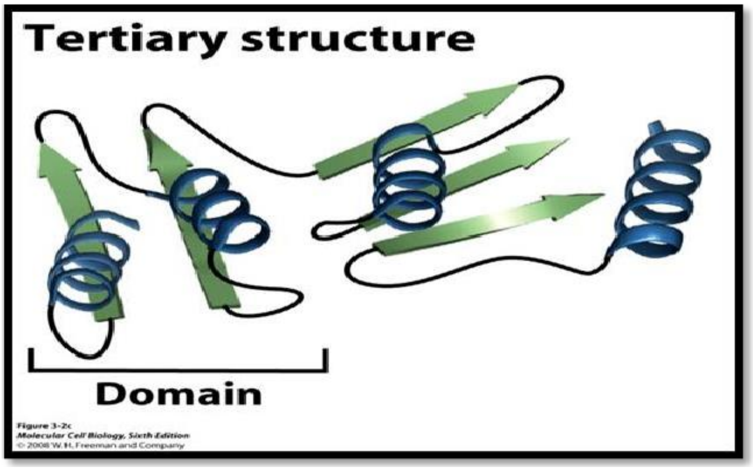
β-Bends reverse the direction of a polypeptide chain, helping it form a compact, globular shape. They are usually found on the surface of protein molecules. β Bends were given this name because they often connect successive strands of antiparallel β-sheets. β-Bends are composed of many amino acids, one of which may be proline (the amino acid that causes a "kink" in the polypeptide chain). Glycine, the amino acid with the smallest R-group, is also frequently found in β-bends. β-Bends are stabilized by the formation of hydrogen and ionic bonds.

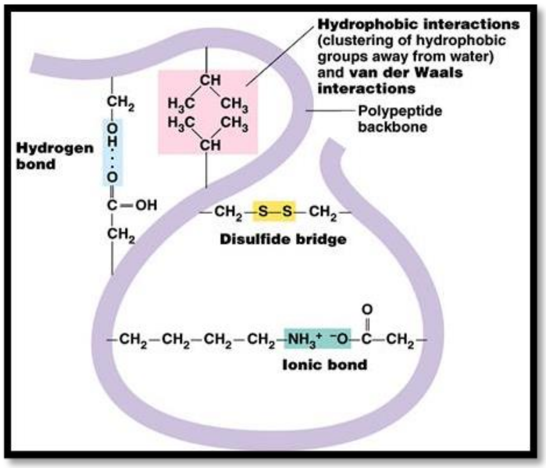
3. Tertiary Structure of Globular Proteins

- The three-dimensional arrangement of protein structure is referred to as tertiary structure. It is a compact structure with hydrophobic side chains held interior while the hydrophilic groups are on the surface of the protein molecule. This type of arrangement ensures stability of the molecule.

- Bonds of tertiary structure: Besides the hydrogen bonds, disulfide bonds (-S-S-), ionic interactions (electrostatic bonds), hydrophobic interactions and van der Waals forces also contribute to the tertiary structure of proteins.

- **Domain**: a compact and self-folding component of the protein that usually represents a discreet structural and functional unit. Polypeptide chains that are greater than 200 amino acids in length generally consist of two or more domains.





4. Quaternary Structure of Proteins

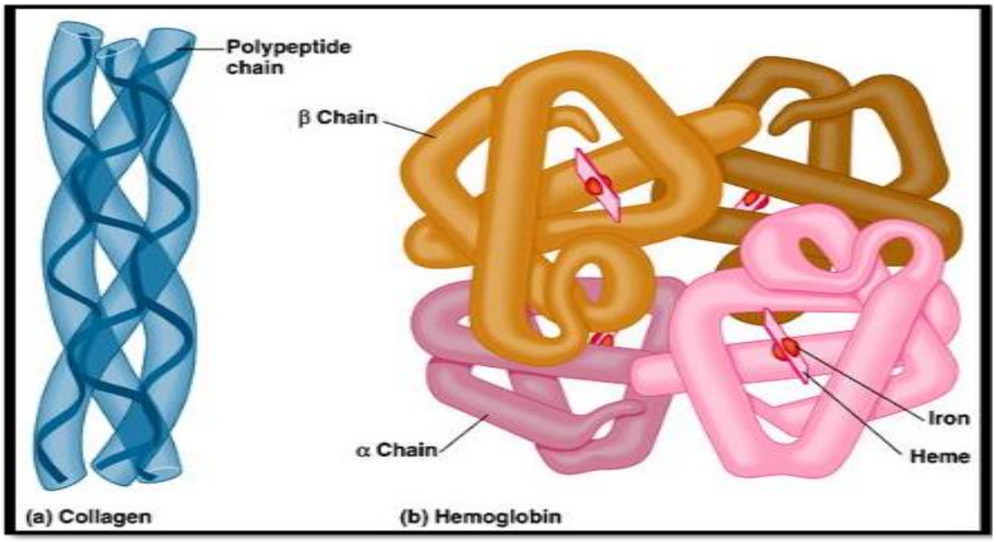
- Many proteins consist of a single polypeptide chain, and are defined as monomeric proteins. However, others may consist of two or more polypeptide chains that may be structurally identical or totally unrelated.

- The arrangement of these polypeptide subunits is called the quaternary structure of the protein. Subunits are held together by noncovalent interactions (for example, hydrogen bonds, ionic bonds, and hydrophobic interactions).

- Collagen is a fibrous protein of three polypeptides that are supercoiled like a rope.

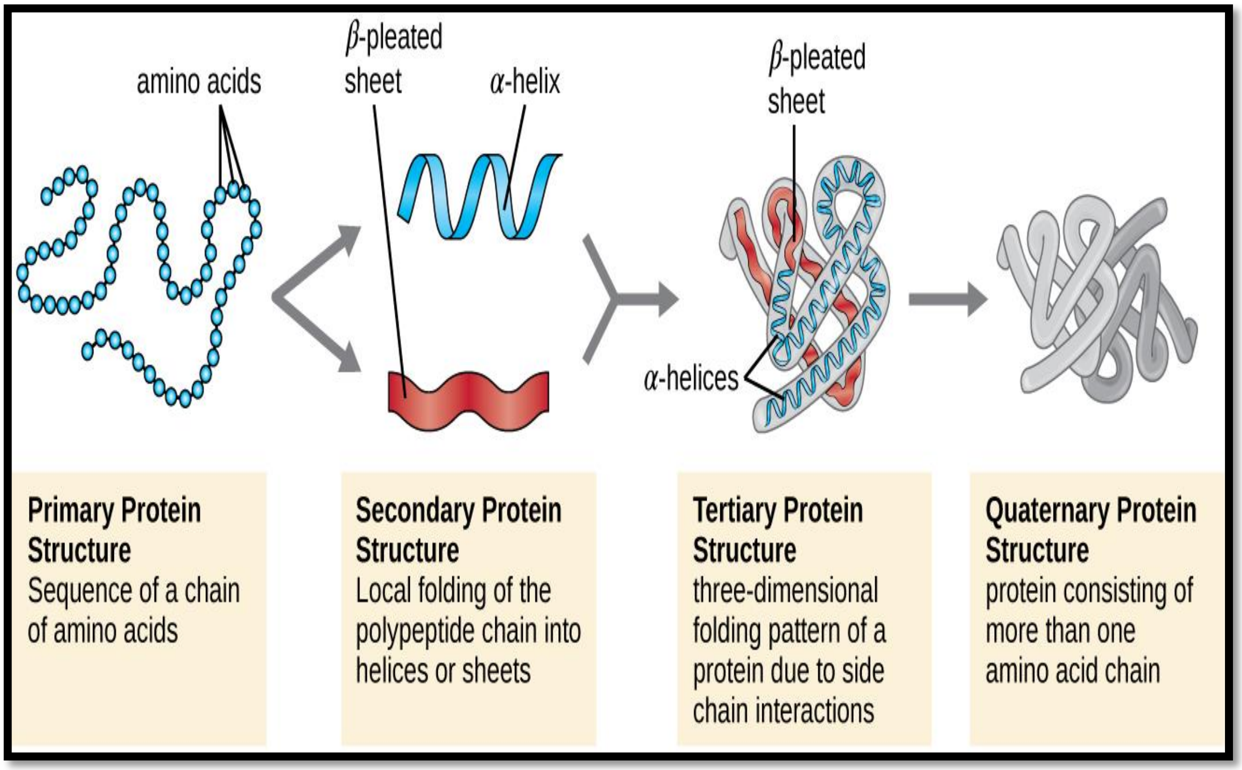
- Hemoglobin is a globular protein with two copies of two kinds of polypeptides.

- Subunits may either function independently of each other, or may work cooperatively, as in hemoglobin, in which the binding of oxygen to one subunit of the tetramer increases the affinity of the other subunits for oxygen.



Note:

- Any protein consisting of a single polypeptide chain is **not** in the quaternary structure and, is defined as monomeric protein.
- If there are two subunits, the protein is quaternary and is called "dimeric", if three subunits "trimeric", and, if several subunits, "multimeric."



Denaturation and Misfolding of Proteins

- Protein denaturation results in the unfolding and disorganization of the protein's secondary and tertiary structures, which are not accompanied by hydrolysis of peptide bonds.
- Denaturing agents include heat, organic solvents, mechanical mixing, strong acids or bases, detergents, and ions of heavy metals such as lead and mercury.
- Denaturation may, under ideal conditions, be reversible, in which case the protein refolds into its original native structure when the denaturing agent is removed. However, most proteins, once denatured, remain permanently disordered.
- Denatured proteins are often insoluble and, therefore, precipitate from solution.

Protein Classification

1. Fibrous Protein

- Polypeptides arranged in long strands or sheets.
- Water insoluble (lots of hydrophobic amino acids).
- Strong but flexible.
- Structural protein or contractile proteins (keratin, collagen, muscle, microtubules, cytoskeleton, mitotic spindle, cilia, flagella).

2. Globular Protein

- Polypeptide chains folded into spherical or globular form.
- Water soluble.
- Contain several types of secondary structure.
- Diverse functions (enzymes, hemoglobin, immunoglobulins, membrane receptor sites regulatory proteins).