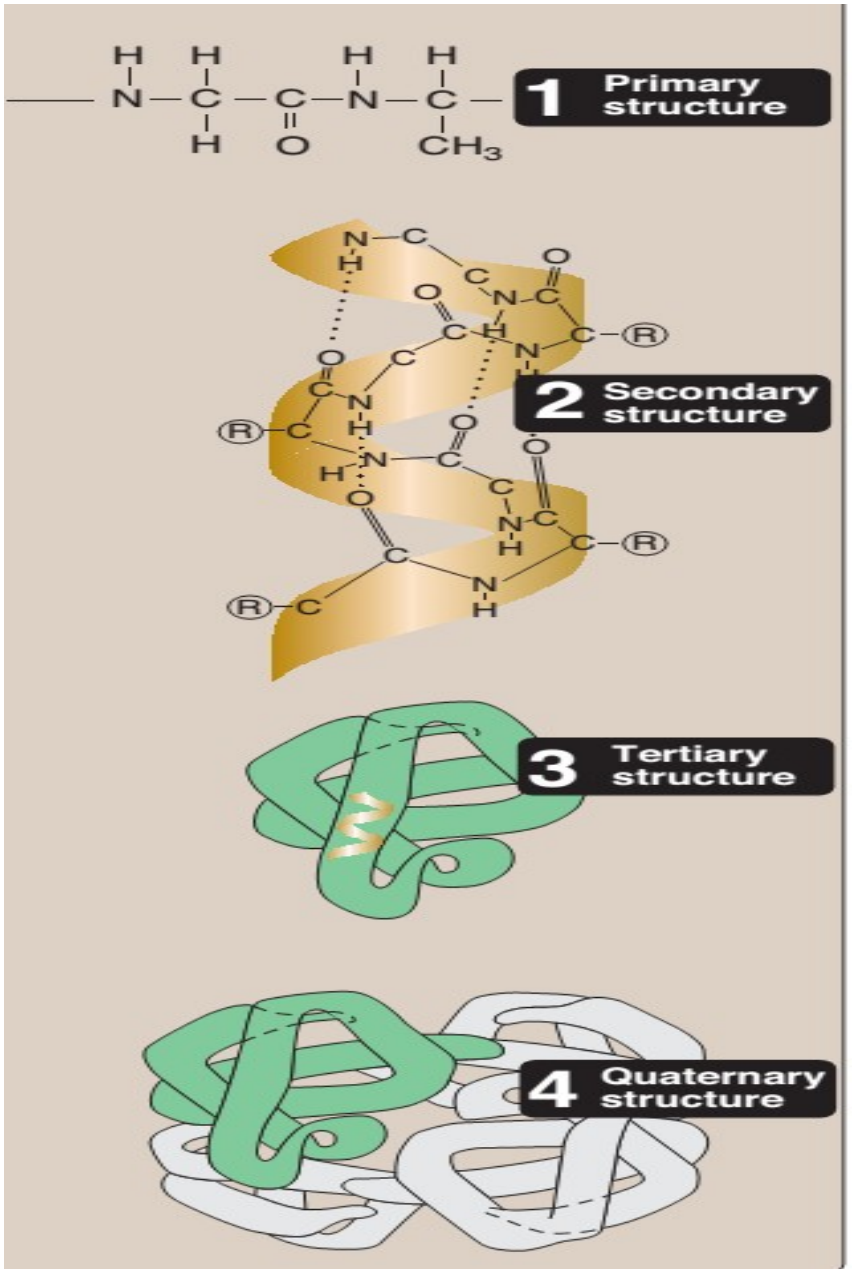
Structure of Proteins

Introduction

- ✓ The 20 amino acids are joined together by peptide bonds.
- ✓ The linear sequence of the linked amino acids generate a protein molecule with a unique three-dimensional shape.
- ✓ The complexity of protein structure is analyzed by considering the molecule in terms of four organizational levels,



Primary Structure of Proteins

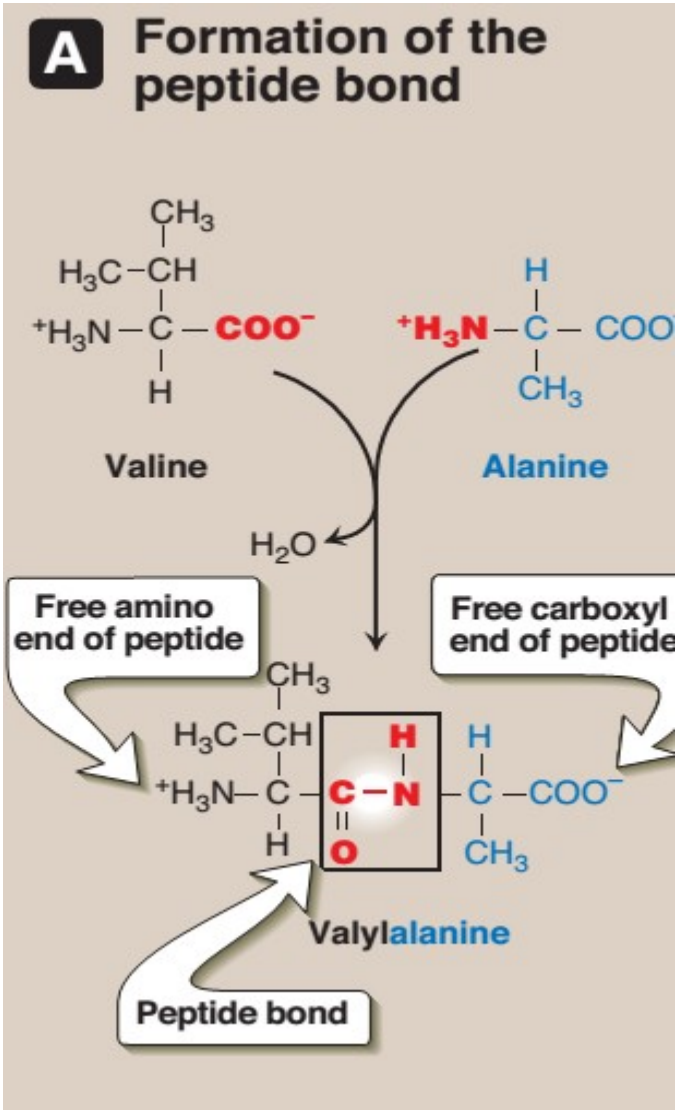
- The sequence of amino acids in a protein is called the primary structure of the protein.

- 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.

- If the primary structures of the normal and the mutated proteins are known, this information may be used to diagnose or study the disease.

Peptide Bond

- are amide linkages between the α-carboxyl group of one amino acid and the α-amino group of another.
- are not broken by conditions that denature proteins, such as heating or high concentrations of urea.
- Prolonged exposure to a strong acid or base at elevated temperatures hydrolyzes these bonds non-enzymically.



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.

- ✓ 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”.

- ✓ 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-

Characteristics of The Peptide Bond

- has a partial double-bond character, that is, it is shorter than a single bond, and is rigid and planar.
- This prevents free rotation around the carbonyl carbon and the nitrogen of the peptide bond.
- However, the bonds between the α-carbons and the α-amino or α-carboxyl groups can be freely rotated (limited by the size and character of the R-groups).
- This allows the polypeptide chain to assume a variety of possible configurations.

- is generally a trans bond (instead of cis), in large part because of steric interference of the

B Characteristics of the peptide bond



Peptide bonds in proteins

- Partial double-bond character
- Rigid and planar
- Trans configuration
- Uncharged but polar

Secondary Structure of Proteins

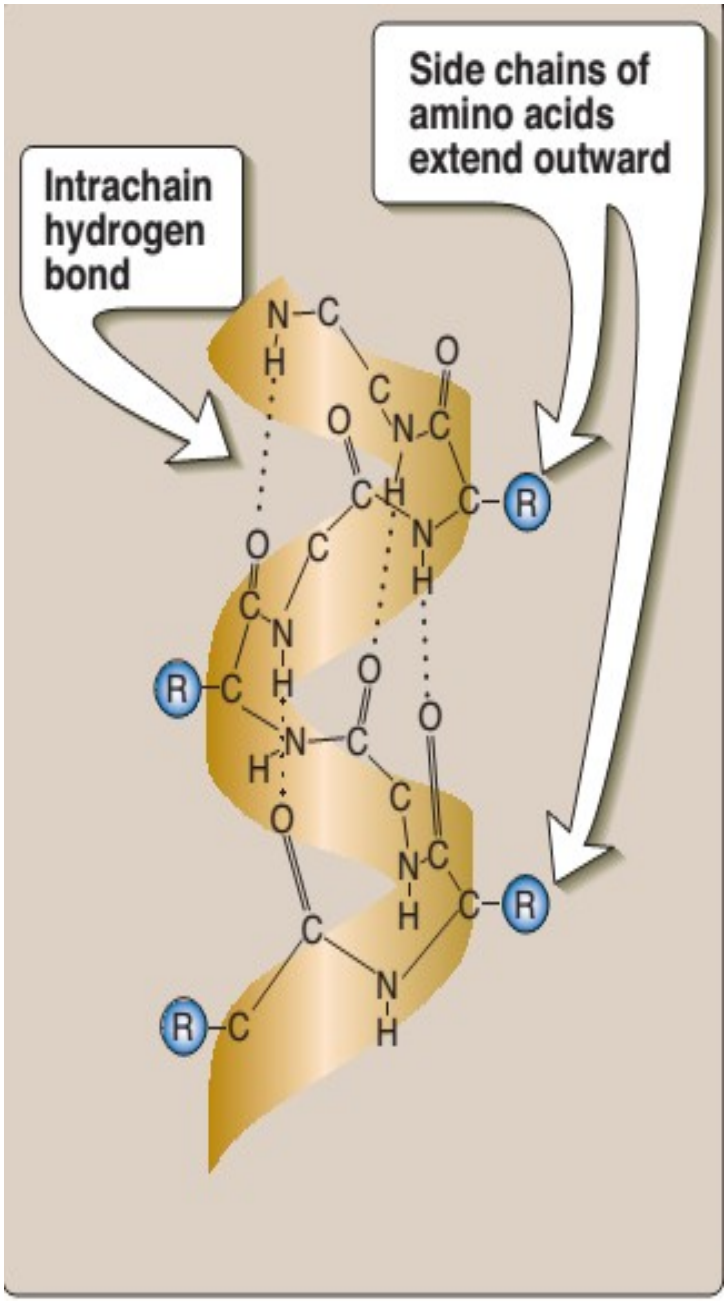
- The polypeptide backbone forms regular arrangements of amino acids that are located near to each other in the linear sequence.

- 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.

α-Helix

- ✓ is the most common polypeptide helix.
- ✓ It 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.
- ✓ Proteins which contains α-helices. For example, keratins, myoglobin



Hydrogen Bonds

- An α-helix is stabilized by extensive hydrogen bonding between the peptide-bond carbonyl **oxygens** and amide hydrogens that are part of the polypeptide backbone.

- The hydrogen bonds extend up and are parallel to the spiral from the carbonyl oxygen of one peptide bond to the -NH- group of a peptide linkage four residues ahead in the polypeptide.

- Hydrogen bonds are individually weak, but they collectively serve to stabilize the helix.

Amino Acids Per Turn

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

- ✓ Thus, amino acid residues spaced three or four residues apart in the primary sequence are spatially close together when folded in the α-helix.

Amino Acids that Disrupt an α-helix

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

✓ it inserts **a kink in the chain**, which **interferes** with the smooth, helical structure.

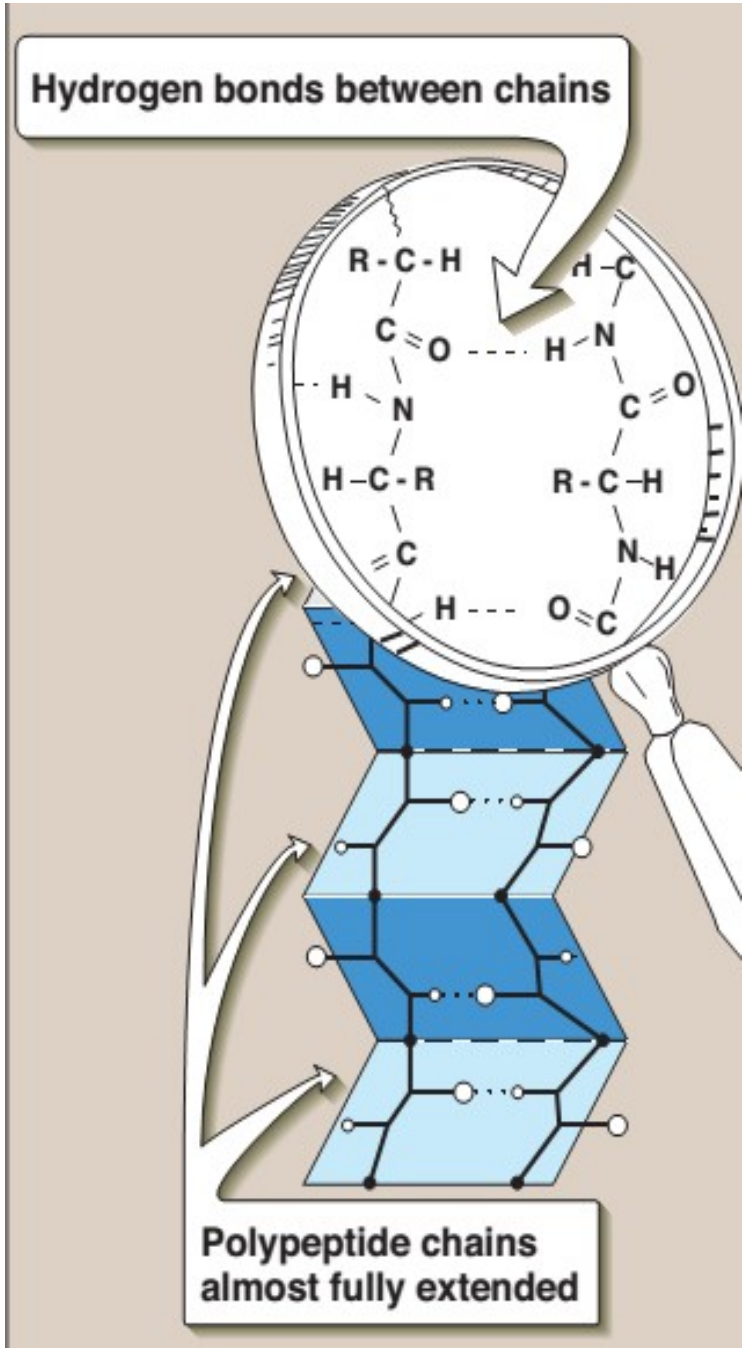
- Charged amino acids (**glutamate, aspartate, histidine, lysine, or arginine**) also disrupt the helix by forming ionic bonds, or by electrostatically repelling each other.

- Amino acids with bulky side chains

β-Sheet

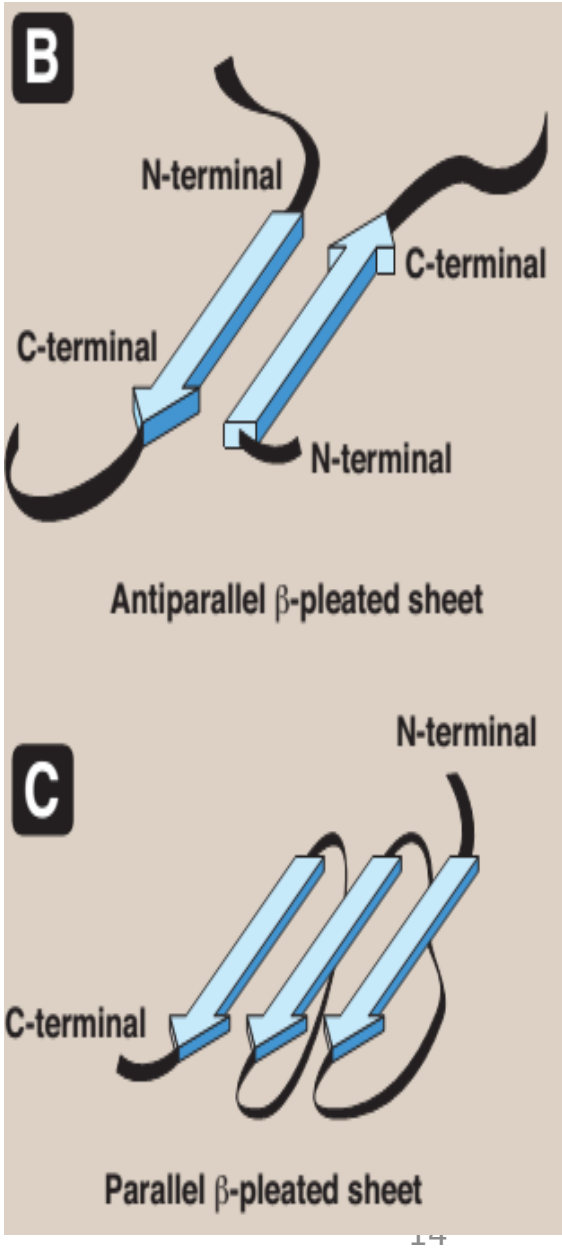
- All of the peptide bond components are involved in hydrogen bonding.
- The surfaces of **β-sheets** appear "pleated," and these structures are, therefore, often called " β-pleated sheets."
- Unlike the α-helix β-sheet:

1. are composed of two or more peptide chains (β-strands), or segments of polypeptide chains, which are almost fully extended.
2. The hydrogen bonds are perpendicular to the **polypeptide backbone.**



Parallel And Antiparallel Sheets:

- β-sheet are arranged either antiparallel to each other (with the **N-terminal** and **C-terminal ends** of the β-strands in opposite direction).
- Parallel to each other (N-termini & C-terminal ends of the β-strands are in the same direction).
- When the hydrogen bonds are formed between separate polypeptide chains, they are termed interchain bonds.
- A β-sheet can also be formed by a single polypeptide chain folding back on itself in this case, the hydrogen bonds are intrachain bonds.



- **β-Bends** reverse the **direction of a polypeptide chain**, helping it form a compact, globular shape.

- usually found on the surface of protein molecules, and often include charged amino acids.

- β-Bends were given this name because they **often connect** successive strands of antiparallel β-sheets.

- are generally composed of some amino acids (**proline, Glycine**).

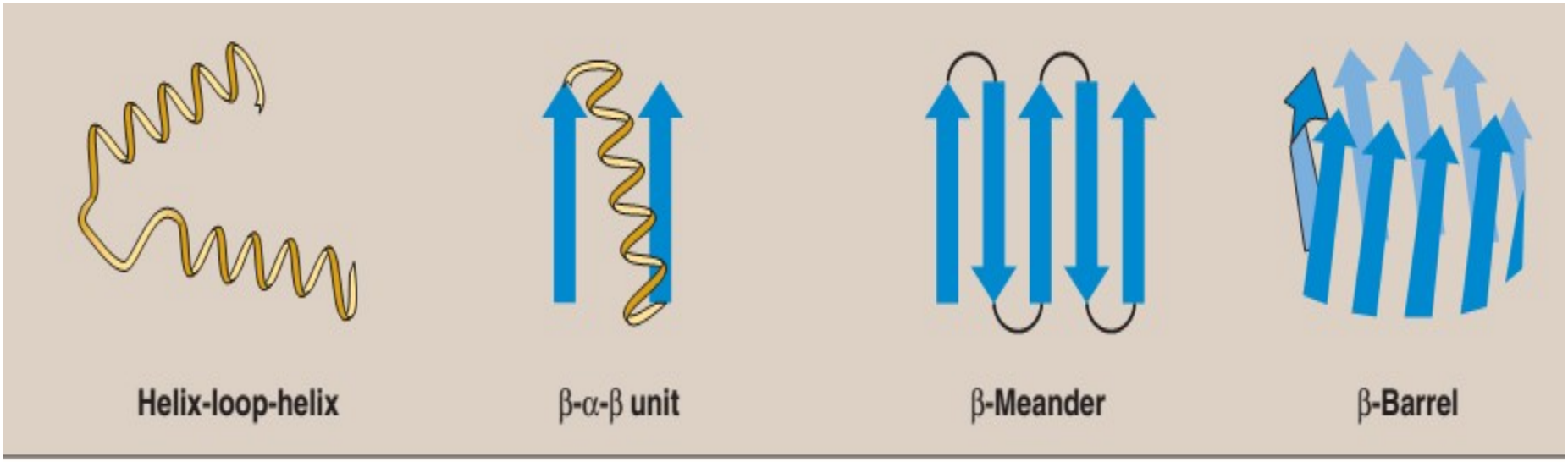
- Approximately one half of an average globular protein is organized into repetitive structures, such as the α-helix and/or β-sheet.

- The remainder of the polypeptide chain is described as having a loop or coil conformation.

- These nonrepetitive secondary structures are not "random," but rather simply have a **less regular structure**.

- Note: The term "random coil" refers to the disordered structure obtained when proteins are denatured.

- **Globular proteins** are constructed by combining secondary structural elements (α-helices, β-sheets, nonrepetitive sequences).
- ✓ These form primarily the core region-that is, **the interior of the molecule.** They are connected by loop regions (for example, β-bends) at the surface of the protein.
- Super secondary structures are usually produced by packing side chains from adjacent secondary structural elements w/c are close to each other.



Tertiary Structure of Globular Proteins

- The primary structure of a polypeptide chain **determines** its **tertiary structure**.
- **"Tertiary"** refers both to the folding of domains (the basic units of **structure** and **function**) and to the final arrangement of domains in the polypeptide.

- **Polypeptide chains** that are greater than **200 amino acids** in **length** generally consist of **two or more domains**.

- ✓ The **core of a domain** is **built** from **combinations** of super secondary structural elements (motifs).

- Therefore, **each domain** has the characteristics of a small, compact globular protein that is **structurally independent** of the other domains in the polypeptide chain.

Interactions Stabilizing Tertiary Structure

- The unique three-dimensional structure of each polypeptide is determined **by its amino acid sequence**.

- Interactions between the **amino acid side chains** **guide** the **folding of the polypeptide** to form **a compact structure**.

- The following **four types of interactions cooperate** in **stabilizing** the **tertiary structures** of globular proteins.

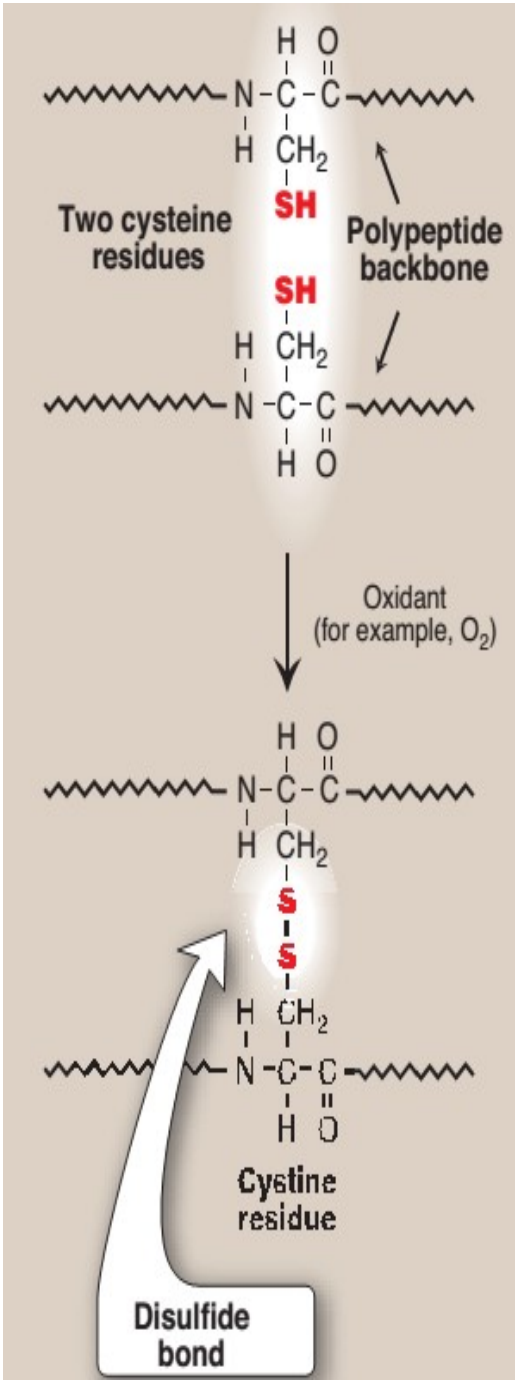
1 . Disulfide Bonds

- is a covalent linkage formed from the sulfhydryl group (–SH) of each of **two cysteine residues**.

- The folding of the polypeptide chain(s) brings the cysteine residues into proximity, and **permits covalent bonding** of their side chains.

- Contributes to the stability of the three-dimensional shape of the protein molecule, & **prevents it from becoming denatured** in the extracellular environment.

- For example, many disulfide bonds are found in proteins such as immunoglobulins that are secreted by cells.

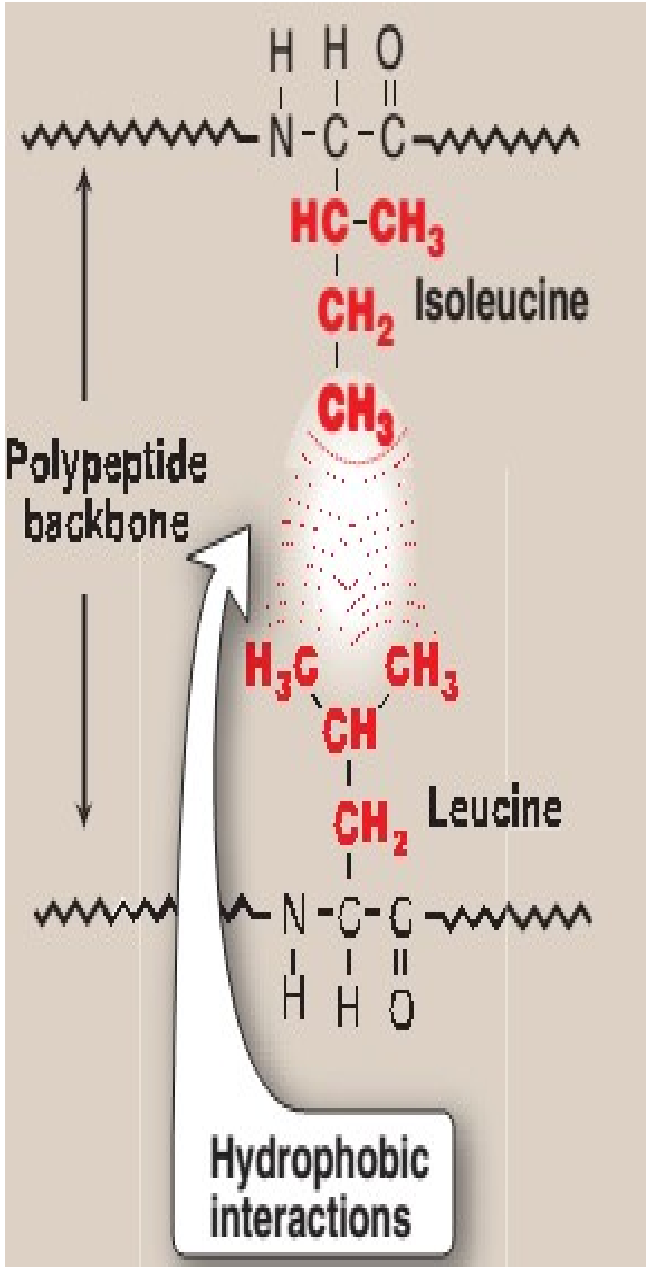


2. Hydrophobic Interactions

- Amino acids with nonpolar side chains tend to be located in the interior of the polypeptide molecule, where they associate with other hydrophobic amino acids .

- amino acids with polar or charged side chains tend to be located on the surface of the molecule in contact with the polar solvent.

- Note: proteins located in **nonpolar (lipid) environments**, such as a membrane, exhibit the **reverse arrangement.**



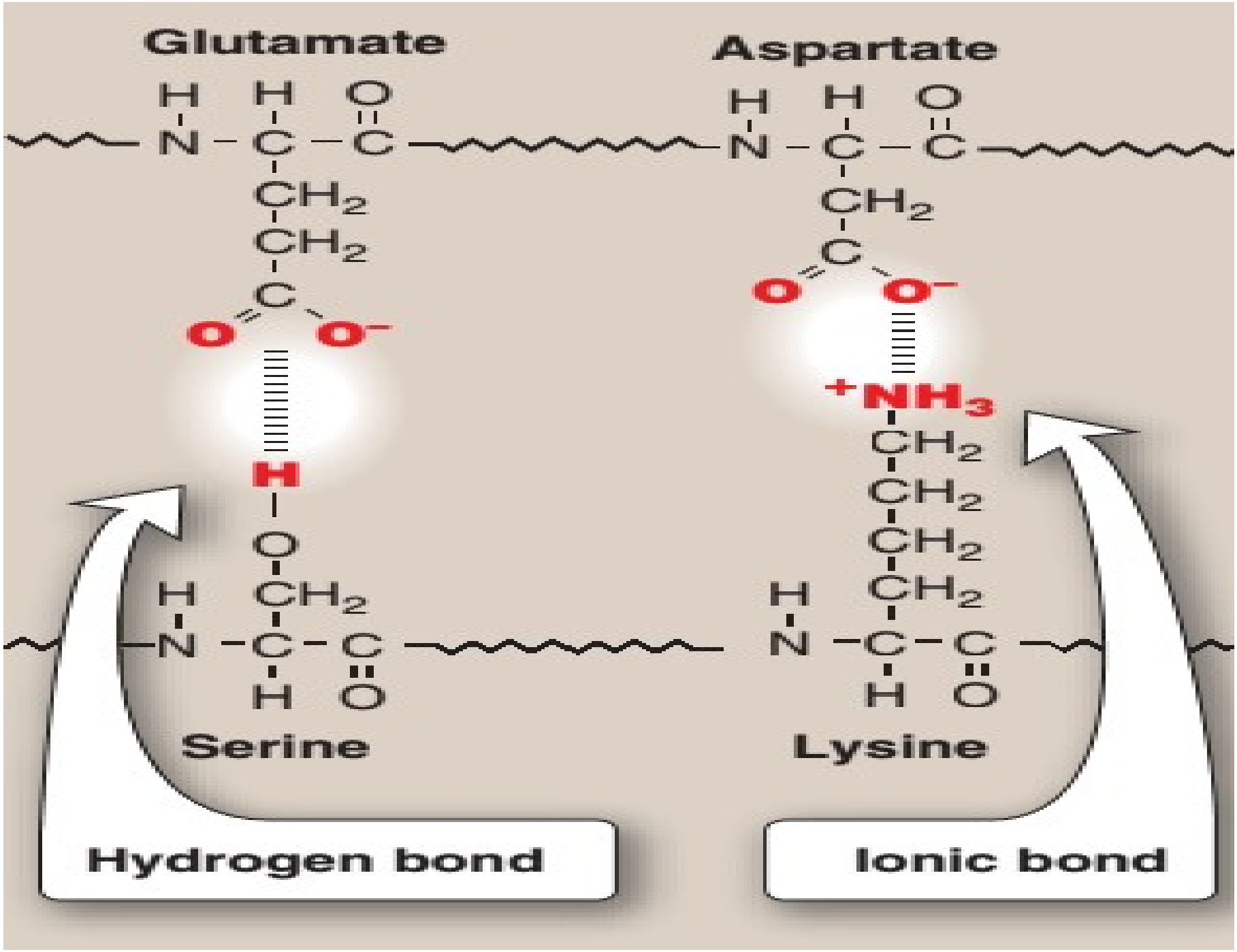
3. Hydrogen Bonds

- Amino acid side chains containing oxygen- or nitrogen-bound **hydrogen** (serine and threonine), can form hydrogen bonds with **electron-rich atom** (the oxygen of a carboxyl group or carbonyl group of a peptide bond).

- Formation of **hydrogen bonds** between polar groups on the surface of proteins and the aqueous solvent enhances the **solubility** of the protein.

4. Ionic Interactions

- ✓ Negatively charged groups, such as the **carboxylate group (– COO–)** in the **side chain** of aspartate or glutamate, can interact with positively charged groups, such as the amino group (– NH3+) in the **side chain** of lysine.

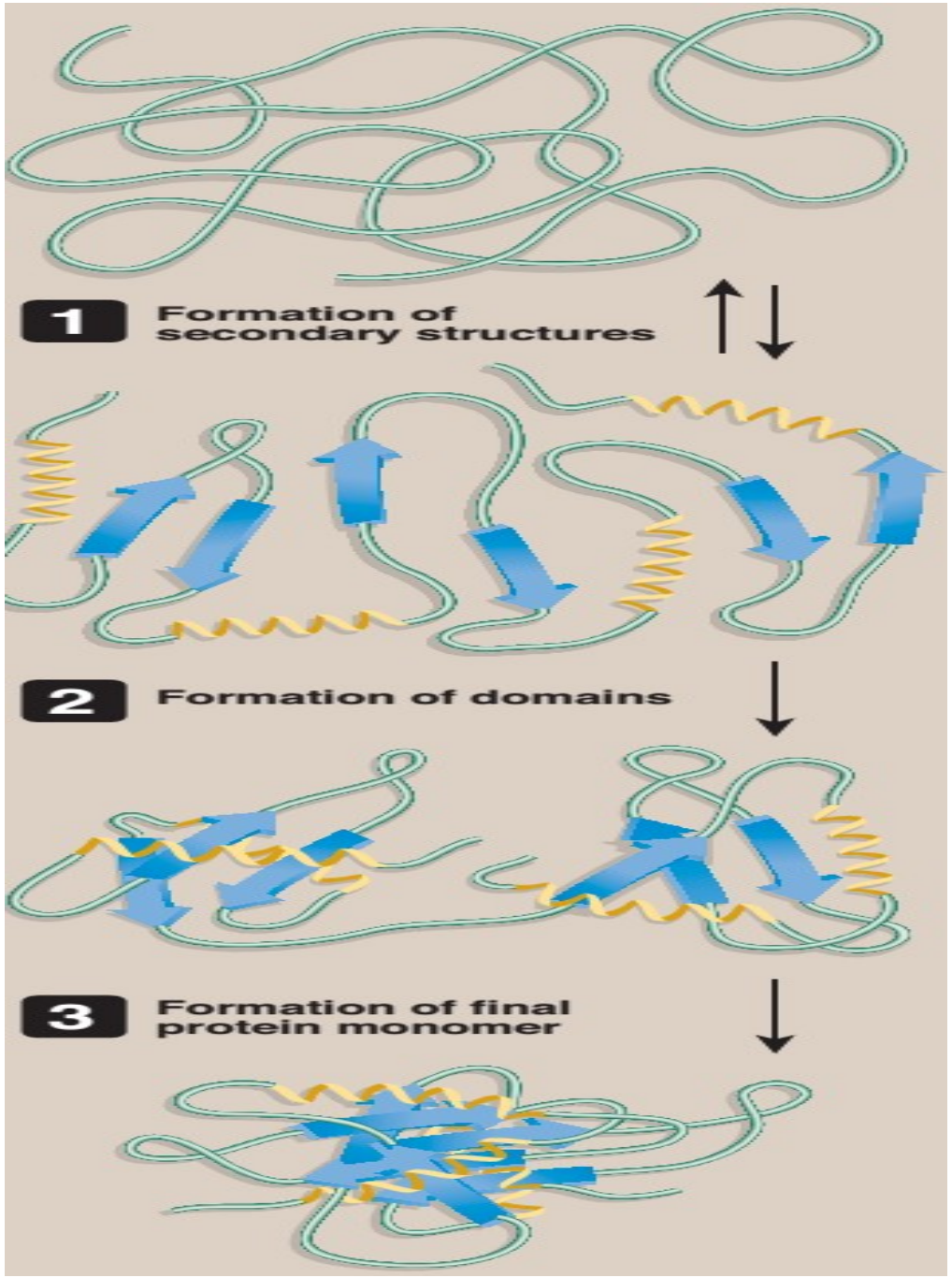

Glutamate
Aspartate
Serine
Lysine
Hydrogen bond
Ionic bond

- Interactions between the side chains of amino acids determine how a long polypeptide chain folds into the intricate three-dimensional shape of the **functional protein**.

- Protein folding occurs within the cell in seconds to minutes.

- As a peptide folds, its amino acid side chains are attracted and repulsed according to their **chemical properties**.

- In addition, interactions involving hydrogen bonds, hydrophobic interactions, and disulfide bonds all **exert an influence on the folding process.**


1
Formation of
secondary structures
2
Formation of domains
3
Formation of final
protein monomer

- 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, However, **most proteins, once denatured**, remain permanently disordered.

- Denatured proteins are often **insoluble** and, therefore, precipitate from solution.

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 two or more polypeptide subunits is called the quaternary structure of the protein.

- Subunits are held together by **noncovalent interactions** (hydrogen bonds, ionic bonds, and hydrophobic interaction).

Cont…

- **Isoforms** are proteins that **perform the same function** but have **different primary structures.**

- ✓ They can arise from different genes or from tissue-specific processing of the product of a single gene.

- If the proteins function as **enzymes**, they are referred to as **isozymes**.

Hierarchy of protein structure

