21.11 PROTEIN STRUCTURE

Protein molecules are described by several levels of structure. The **primary structure** of a protein is the sequence of amino acids in the chain and the location of all the disulfide bridges. The **secondary structure** describes the regular conformation assumed by segments of the protein's backbone. In other words, the secondary structure describes how local regions of the backbone fold. The **tertiary structure**

describes the three-dimensional structure of the entire polypeptide. If a protein has more than one polypeptide chain, it has quaternary structure. The **quaternary structure** of a protein is the way the individual protein chains are arranged with respect to each other.

Proteins can be divided roughly into two classes. **Fibrous proteins** contain long chains of polypeptides that occur in bundles. These proteins are insoluble in water. All the structural proteins described at the beginning of this chapter, such as keratin and collagen, are fibrous proteins. **Globular proteins** are soluble in water and tend to have roughly spherical shapes. Essentially all enzymes are globular proteins.

21.13 SECONDARY STRUCTURE OF PROTEINS

Secondary structure describes the conformation of segments of the backbone chain of a peptide or protein. In order to minimize energy, a polypeptide chain tends to fold in a repeating geometric structure. Three factors determine the choice of secondary structure:

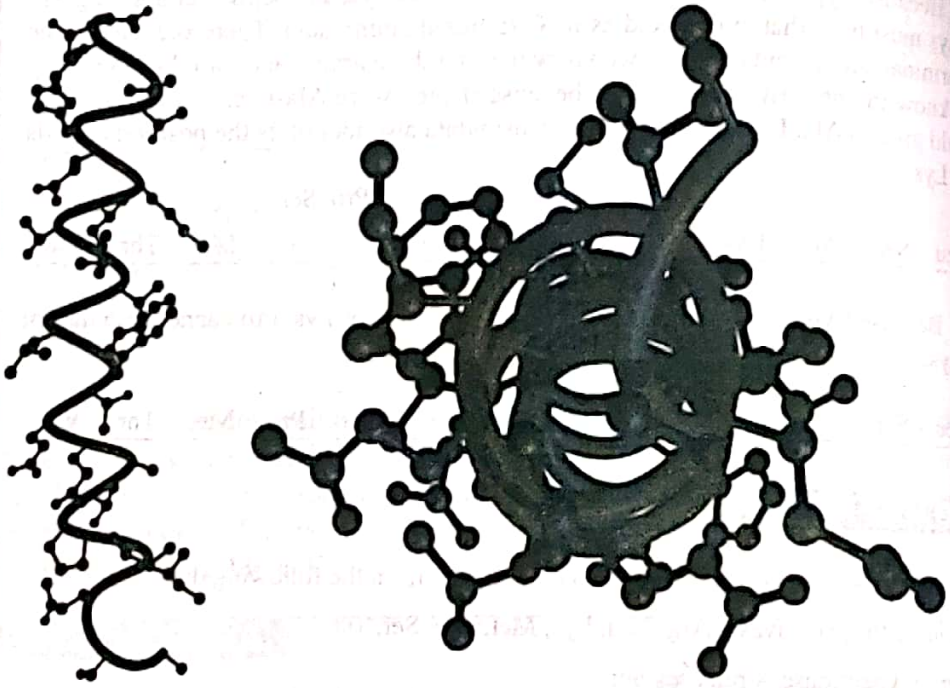
- the regional planarity about each peptide bond, which limits the possible conformations of the peptide chain (Section 21.7).
- maximizing the number of peptide groups that engage in hydrogen bonding (i.e., hydrogen bonding between the carbonyl oxygen of one amino acid residue and the amide hydrogen of another).
- adequate separation between nearby R groups to avoid steric hindrance and repulsion of like charges.

=O------H—N

α-Helix

One type of secondary structure is the **α-helix.** In an α-helix, the backbone of the polypeptide coils around the long axis of the protein molecule (Figure 21.8). The helix is stabilized by hydrogen bonds—each hydrogen attached to an amide nitrogen is hydrogen bonded to a carbonyl oxygen of an amino acid four residues away. The substituents on the α-carbons of the amino acids protrude outward from the helix, thereby minimizing steric hindrance. Because the amino acids have the L-configuration, the α-helix is a right-handed helix. A right-handed helix rotates in a clockwise direction as it spirals down. Each turn of the helix contains 3.6 amino acid residues, and the repeat distance of the helix is 5.4 Å.

re 21.8 ▶
segment of a protein in
-helix.
ooking up the longitudi-
xis of an α-helix.



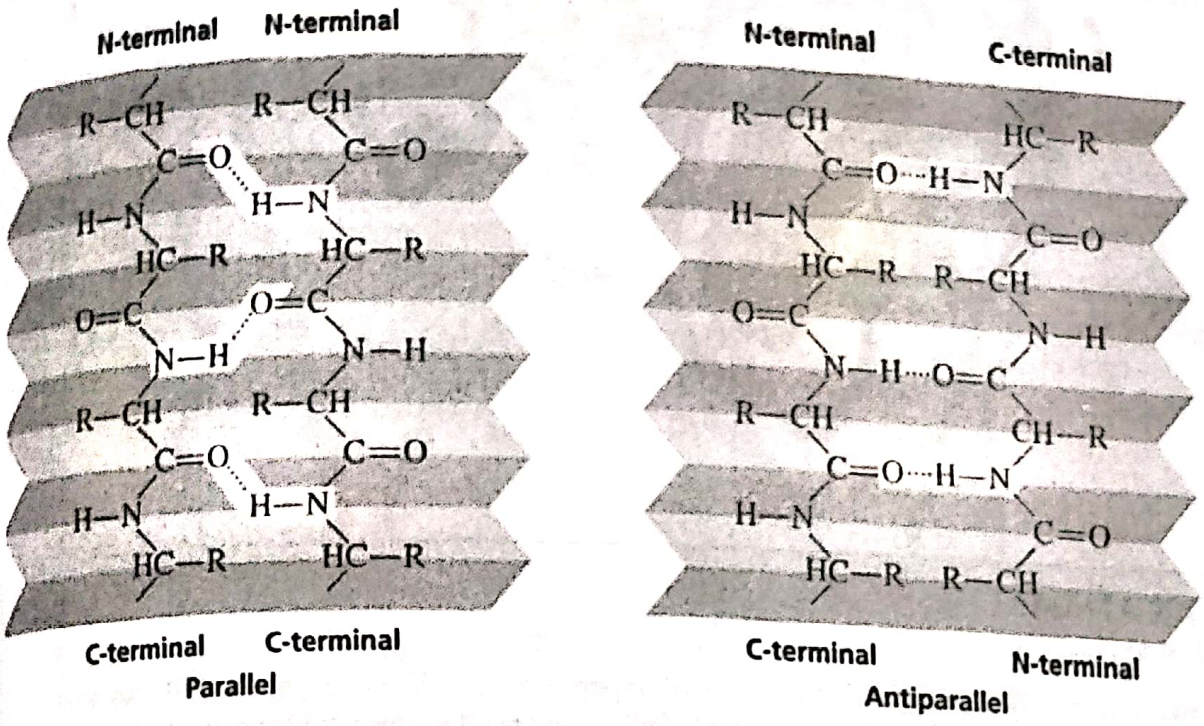
3-D Molecule: An α-helix

Not all amino acids are able to fit into an α-helix. A proline residue, for example, forces a bend in a helix because the bond between the proline nitrogen and the α-carbon cannot rotate to enable it to fit readily into a helix. Two adjacent amino acids that have more than one substituent on a β-carbon (valine, isoleucine, or threonine) cannot fit into a helix because of steric crowding between the R groups. Two adjacent amino acids with like-charged substituents cannot fit into a helix because of electrostatic repulsion between the R groups. The percentage of amino acid residues coiled into an α-helix varies from protein to protein, but on average about 25% of the residues in globular proteins are in α-helices.

β-Pleated Sheet

The second type of secondary structure is the **β-pleated sheet.** In a β-pleated sheet, the polypeptide backbone is extended in a zigzag structure resembling a series of pleats. A β-pleated sheet is almost fully extended—the average two-residue repeat

distance is 7.0 Å. The hydrogen bonding in a β-pleated sheet occurs between neighboring peptide chains. The adjacent hydrogen-bonded peptide chains can run in the same direction or in opposite directions. In a **parallel β-pleated sheet,** the adjacent chains run in the same direction. In an **antiparallel β-pleated sheet,** the adjacent chains run in opposite directions (Figure 21.9).



▲ **Figure 21.9**
Segment of a β-pleated sheet drawn to illustrate its pleated character.

Because the substituents (R) on the α-carbons of the amino acids on adjacent chains are close to each other, the chains can nestle closely together to maximize hydrogen-bonding interactions only if the substituents are small. Silk, for example, a protein with a large number of relatively small amino acids (glycine and alanine), has large segments of β-pleated sheets. The number of side-by-side strands in a β-pleated sheet ranges from 2 to 15 in a globular protein. The average strand in a β-pleated sheet section of a globular protein contains six amino acid residues.

Wool and the fibrous protein of muscle are examples of proteins with secondary structures that are almost all α-helices. Consequently, these proteins can be stretched. In contrast, the secondary structures of silk and spider webs are predominantly β-pleated sheets. Because the β-pleated sheet is a fully extended structure, these proteins cannot be stretched.

Coil Conformation

Generally less than half of a globular protein is in an α-helix or β-pleated sheet (Figure 21.10). Most of the rest of the protein is still highly ordered but is difficult to describe. These polypeptide fragments are said to be in a **coil conformation** or a **loop conformation.**

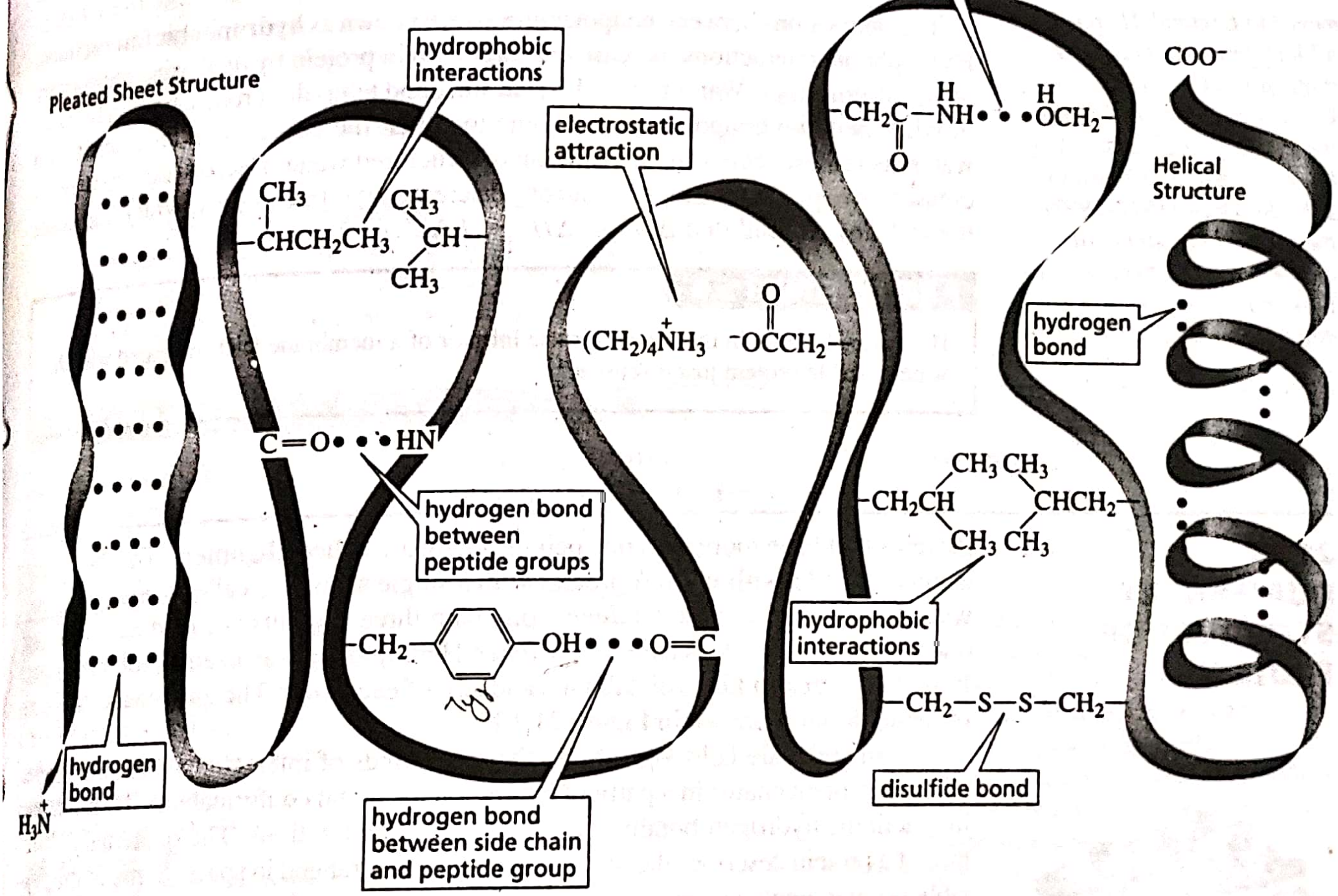
21.14 TERTIARY STRUCTURE OF PROTEINS

Max Ferdinand Perutz *and* ***John Cowdery Kendrew*** *were the first to determine the tertiary structure of a protein. Using X-ray diffraction, they determined the tertiary structure of myoglobin (1957) and hemoglobin (1959). For this work they shared the 1962 Nobel Prize in chemistry.*

The *tertiary structure* of a protein is the three-dimensional arrangement of all the atoms in the protein. Proteins fold spontaneously in solution in order to maximize their stability. Every time there is a stabilizing interaction between two atoms, free energy is released. The more free energy released (the more negative the $\Delta G°$), the more stable the protein. So a protein tends to fold in a way that maximizes the number of stabilizing interactions (Figure 21.11).

The stabilizing interactions that occur in folding are covalent bonds, hydrogen bonds, electrostatic attractions, and hydrophobic (van der Waals) interactions. The interactions can occur between peptide groups (atoms in the backbone of the protein), between side-chain groups (α-substituents), and between peptide and side-chain groups. Because the side-chain groups help determine how a protein folds, the tertiary structure of a protein is determined by its primary structure.

Disulfide bonds are the only covalent bonds that can form when a protein folds. The other bonding interactions that occur in folding are much weaker but, because there are so many of them (Figure 21.12), they are the most important interactions in determining how a protein folds.



▲ **Figure 21.11**
Stabilizing interactions responsible for the tertiary structure of a protein.

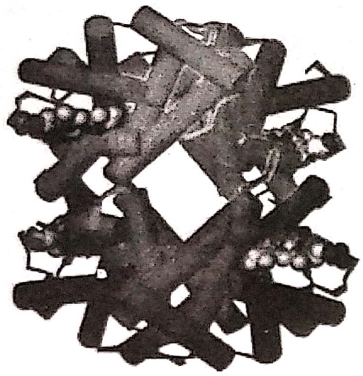
Most proteins exist in aqueous environments. Therefore, they tend to fold in a way that exposes the maximum number of polar groups to the aqueous environment and that buries the nonpolar groups in the interior of the protein, away from water.

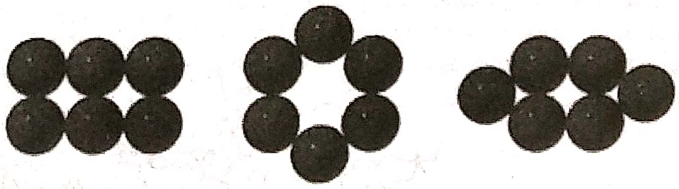
The interactions between nonpolar groups are known as **hydrophobic interactions.** Hydrophobic interactions increase the stability of a protein by increasing the entropy of water molecules. Water molecules that surround nonpolar groups are highly structured. When two nonpolar groups come together, the surface area in contact with water decreases, decreasing the amount of structured water. Decreasing structure increases entropy. Increasing the entropy decreases the free energy, which increases the stability. (Recall that $\Delta G° = \Delta H° - T\Delta S°$.)

21.15 QUATERNARY STRUCTURE OF PROTEINS

Proteins that have more than one peptide chain are called **oligomers.** The individual chains are called **subunits.** A protein with a single subunit is called a *monomer;* one with two subunits is called a *dimer;* one with three subunits is called a *trimer;* and one with four subunits is called a *tetramer.* Hemoglobin is an example of a tetramer. It has two different kinds of subunits and two of each kind. The quaternary structure of hemoglobin is shown in Figure 21.13.

The subunits are held together by the same kinds of interactions that hold the individual protein chains in a particular three-dimensional conformation—hydrophobic interactions, hydrogen bonding, and electrostatic attractions. The quaternary structure of a protein describes the way the subunits are arranged in space. Some of the possible arrangements of the six subunits of a hexamer are shown here.





21.16 PROTEIN DENATURATION

Destroying the highly organized tertiary structure of a protein is called **denaturation.** Anything that breaks the bonds responsible for maintaining the three-dimensional shape of the protein will cause the protein to denature (unfold). Because these bonds are weak, proteins are easily denatured. The totally random conformation of a denatured protein is called a **random coil.**

- Changing the pH denatures proteins because it changes the charges on many of the side chains. This disrupts electrostatic attractions and hydrogen bonds.
- Certain reagents such as urea and guanidine hydrochloride denature proteins by forming hydrogen bonds to the protein groups that are stronger than the hydrogen bonds formed between the groups.
- Detergents such as sodium dodecyl sulfate denature proteins by associating with the nonpolar groups of the protein, thus interfering with the normal hydrophobic interactions.
- Organic solvents denature proteins by disrupting hydrophobic interactions.
- Proteins can also be denatured by heat or by agitation. Both increase molecular motion, which can disrupt the attractive forces. A well-known example is the change that occurs to the white of an egg when it is heated or whipped.