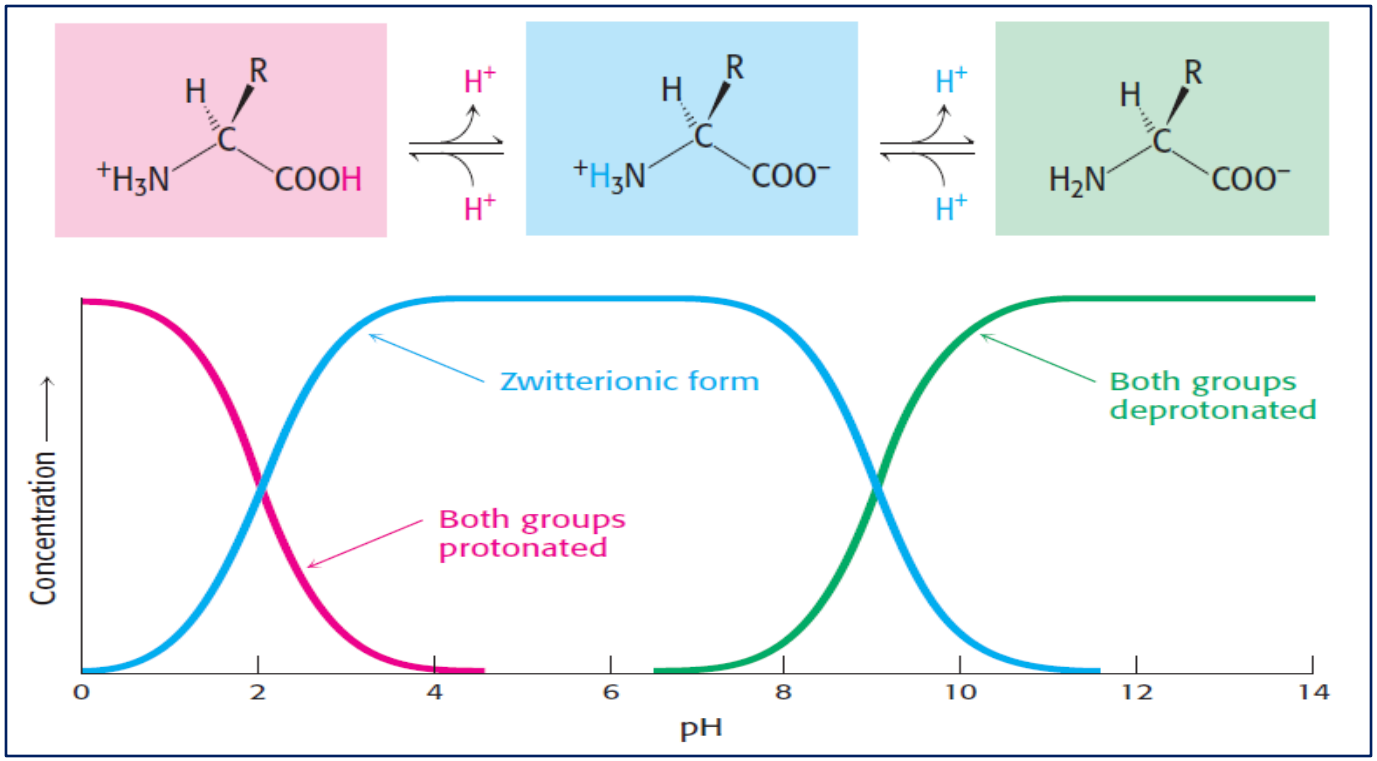
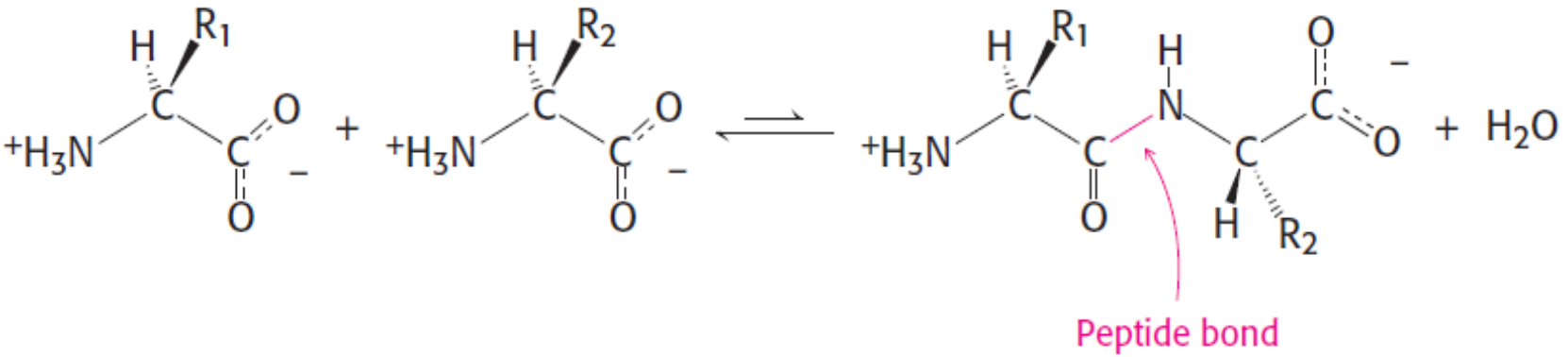
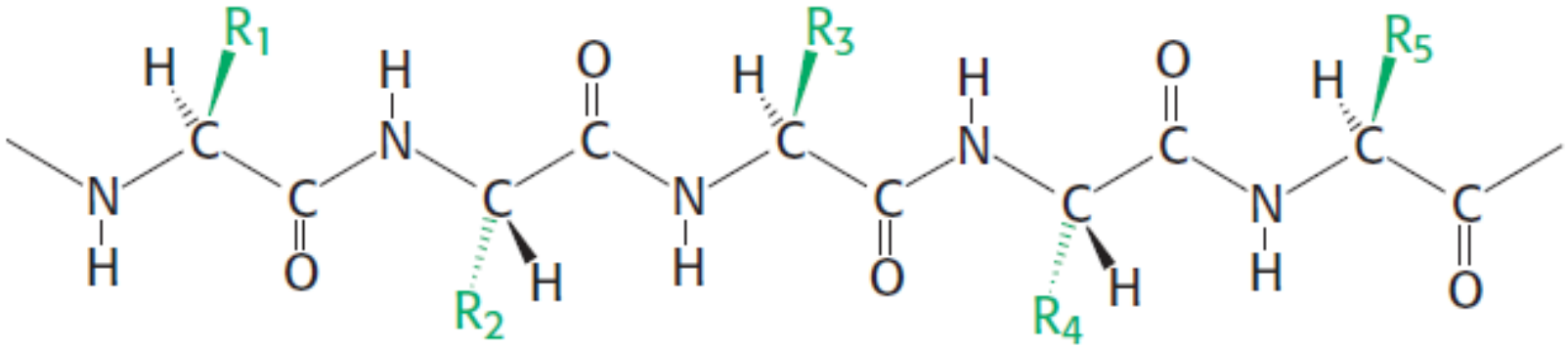
3D Structure of Protein

Amino acids in solution at neutral pH exist predominantly as *dipolar ions* (also called *zwitterions*). In the dipolar form, the amino group is protonated ($—NH_3^+$) and the carboxyl group is deprotonated ($—COO^-$). The ionization state of an amino acid varies with pH (Figure 2.6). In acid solution (e.g., pH 1), the amino group is protonated ($—NH_3^+$) and the carboxyl group is not dissociated (—COOH). As the pH is raised, the carboxylic acid is the first group to give up a proton, inasmuch as its pK_a is near 2. The dipolar form persists until the pH approaches 9, when the protonated amino group loses a proton.

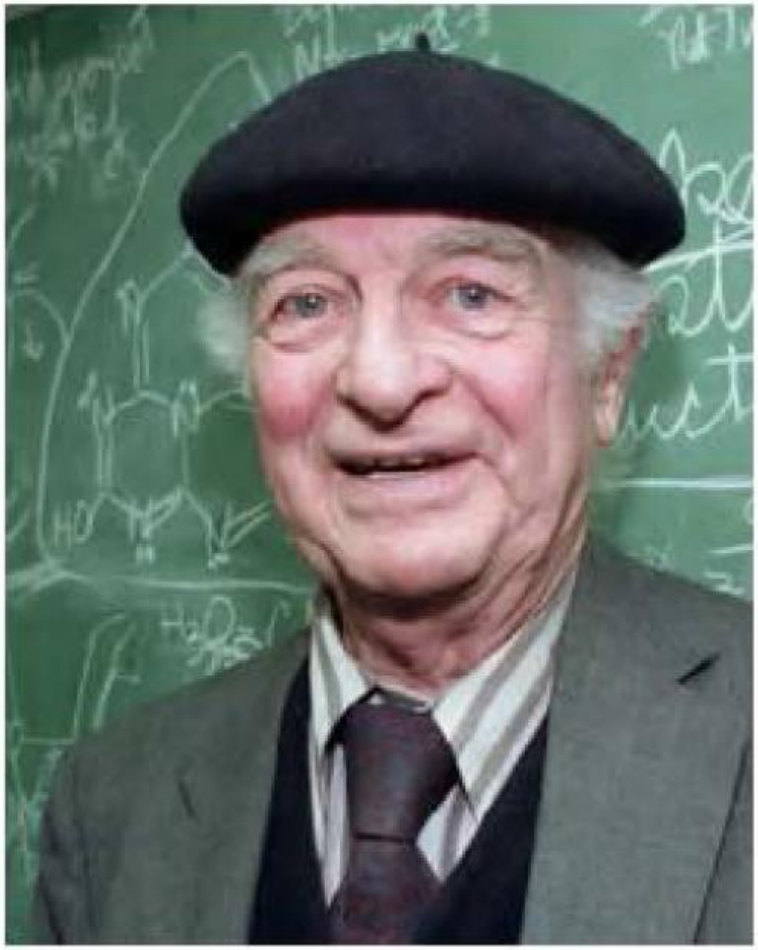




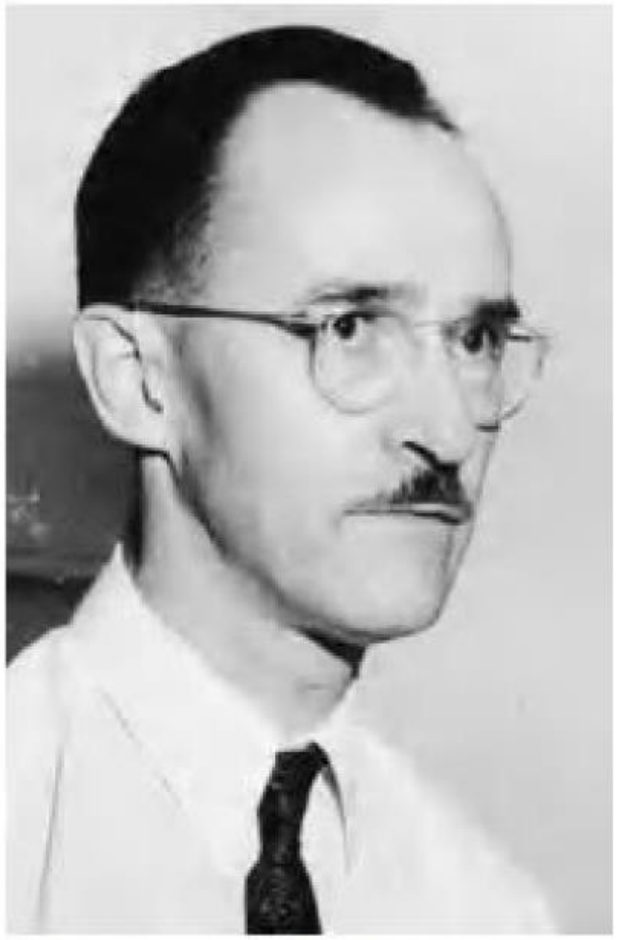
Peptide-bond formation. The linking of two amino acids is accompanied by the loss of a molecule of water.



Components of a polypeptide chain. A polypeptide chain consists of a constant backbone (shown in black) and variable side chains (shown in green).

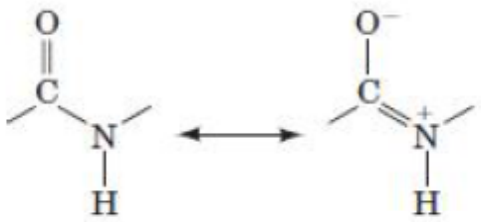


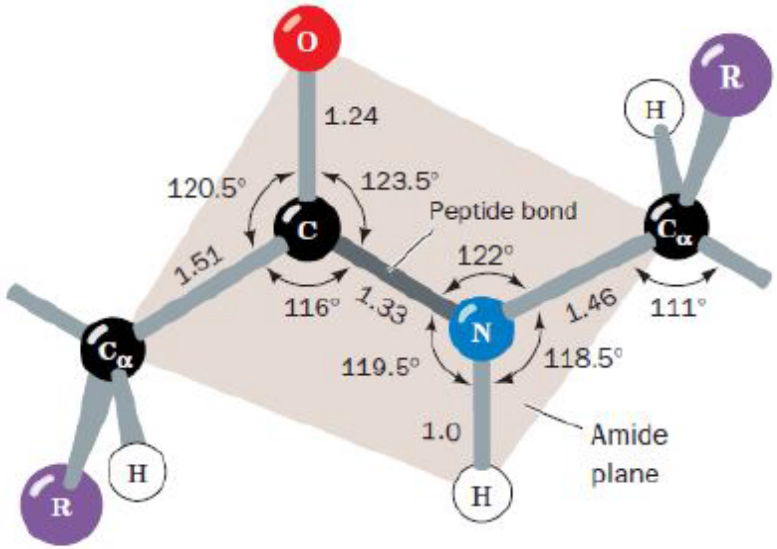
Linus Pauling, 1901–1994



Robert Corey, 1897–1971

- The properties of a protein are largely determined by its three-dimensional structure.
- A polymer's **secondary structure** (2 structure) is defined as the local conformation of its backbone. For proteins, this has come to mean the specification of regular polypeptide backbone folding patterns: helices, pleated sheets, and turns.
- In the 1930s and 1940s, Linus Pauling and Robert Corey determined the X-ray structures of several amino acids and dipeptides in an effort to elucidate the structural constraints on the conformations of a polypeptide chain.
- These studies indicated that *the peptide group has a rigid, planar structure, which, Pauling pointed out, is a consequence of resonance interactions that give the peptide bond an 40% double-bond character:*





The trans-peptide group. *The standard dimensions (in angstroms, Å, and degrees,) of this planar group were derived by averaging the corresponding quantities in the X-ray crystal structures of amino acids and peptides.*

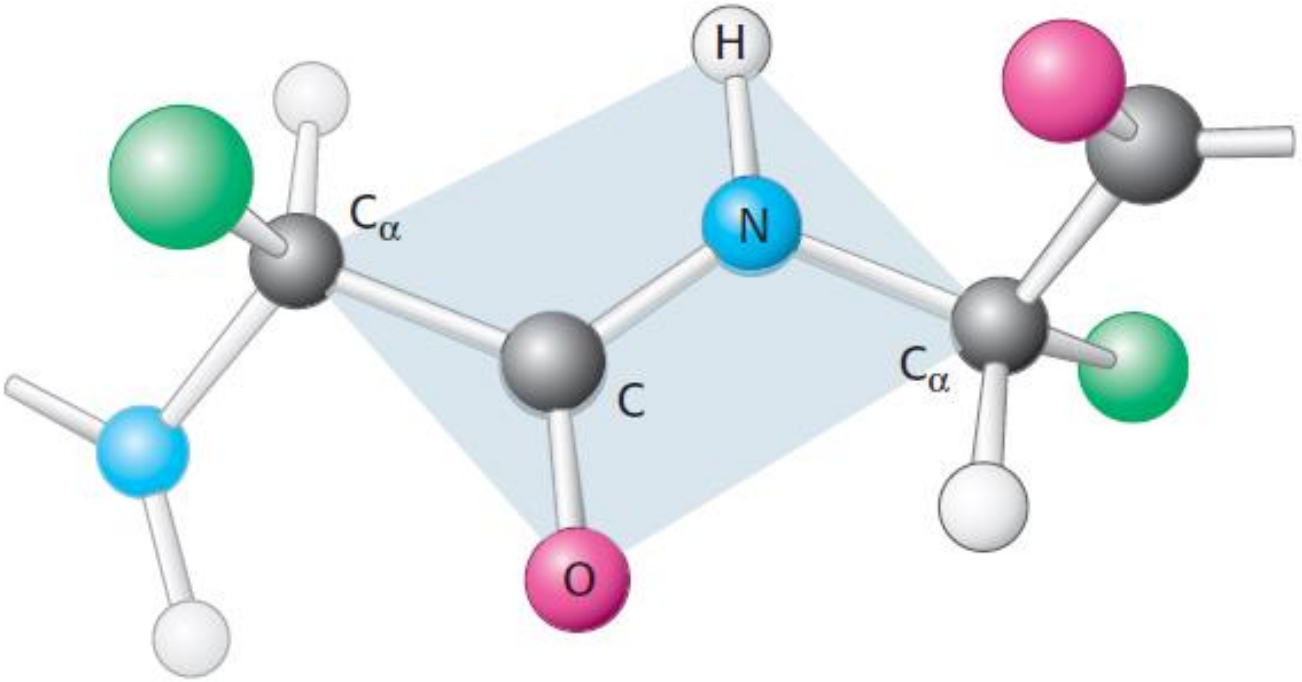
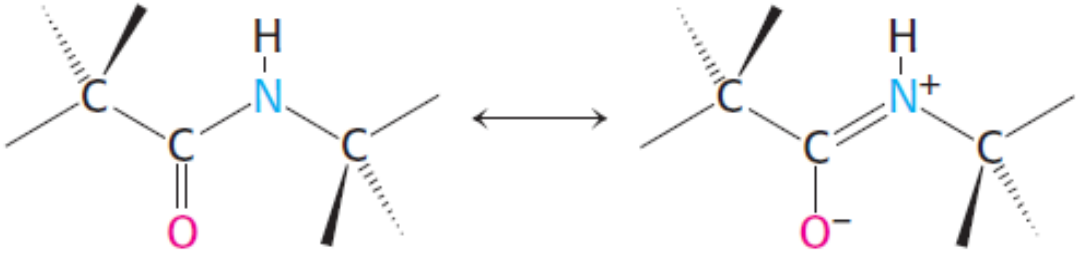


Figure 2.18 Peptide bonds are planar. In a pair of linked amino acids, six atoms (C_α, C, O, N, H, and C_α) lie in a plane. Side chains are shown as green balls.

Polypeptide chains are flexible yet conformationally restricted

Examination of the geometry of the protein backbone reveals several important features. First, *the peptide bond is essentially planar* (Figure 2.18). Thus, for a pair of amino acids linked by a peptide bond, six atoms lie in the same plane: the α-carbon atom and CO group of the first amino acid and the NH group and α-carbon atom of the second amino acid. The nature of the chemical bonding within a peptide accounts for the bond's planarity. The bond resonates between a single bond and a double bond. Because of this *double-bond character,* rotation about this bond is prevented and thus the conformation of the peptide backbone is constrained.



Peptide-bond resonance structures

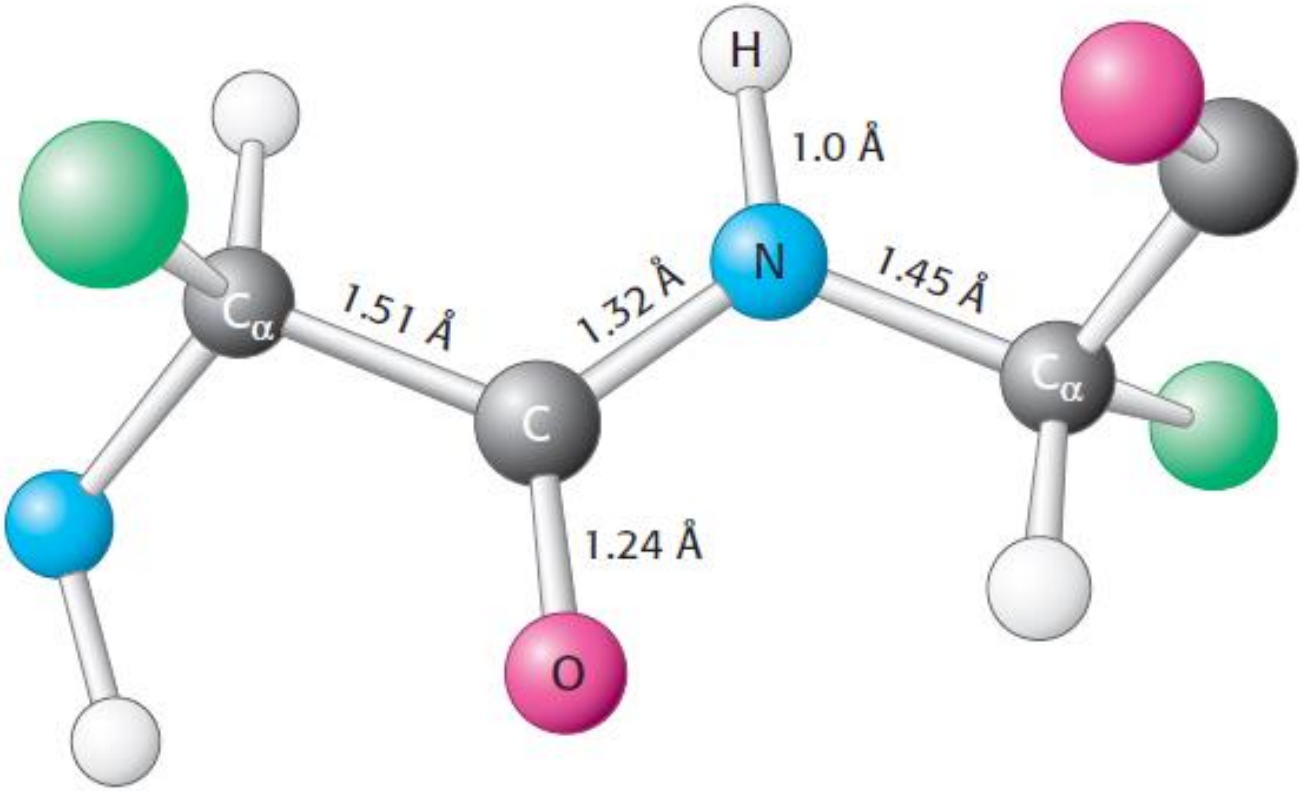
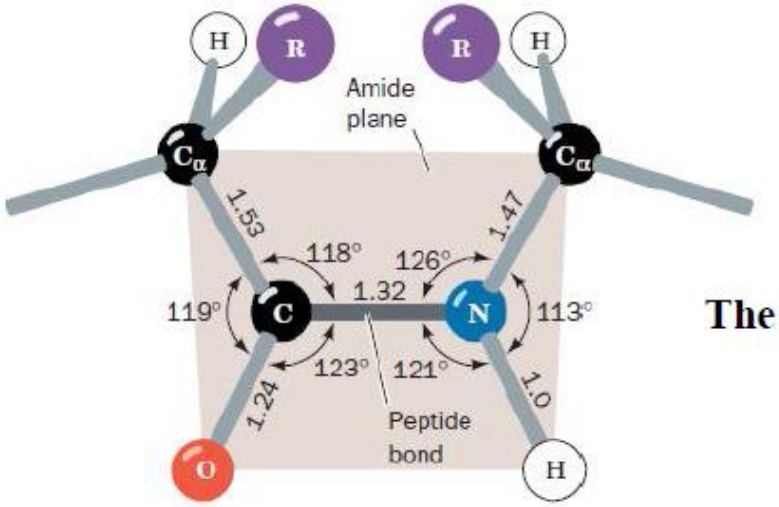


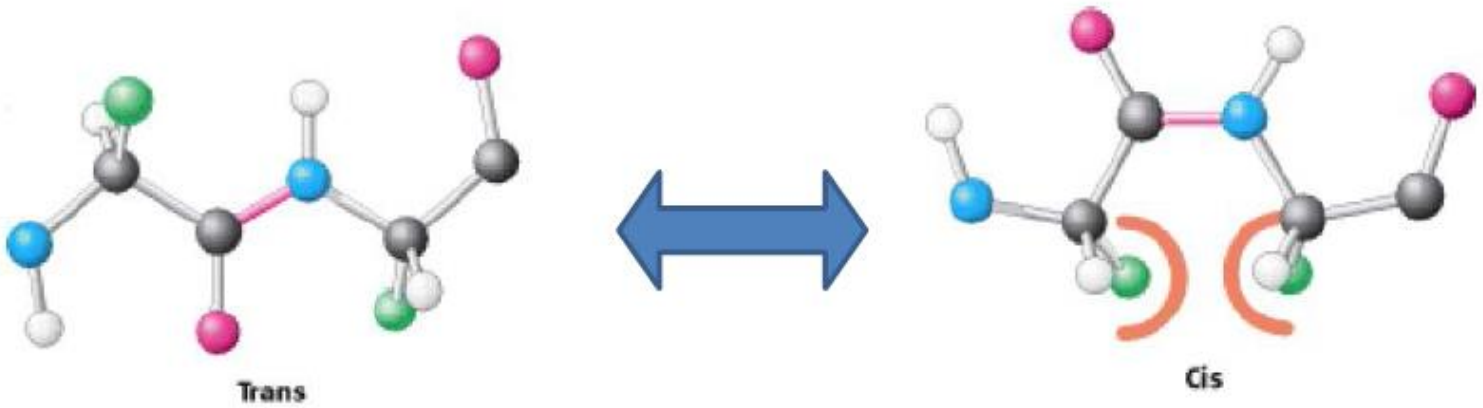
Figure 2.19 Typical bond lengths within a peptide unit.
The peptide unit is shown in the trans configuration.

The double-bond character is also expressed in the length of the bond between the CO and the NH groups. The C-N distance in a peptide bond is typically 1.32 Å, which is between the values expected for a C-N single bond (1.49 Å) and a C=N double bond (1.27 Å).

Peptide groups, with few exceptions, assume the trans conformation: that in which successive Cα atoms are on opposite sides of the peptide bond joining them.
This is partly a result of steric interference, which causes the cis conformation to be ~8kJ. Mol^{-1} less stable than the trans conformation.



The cis-peptide group



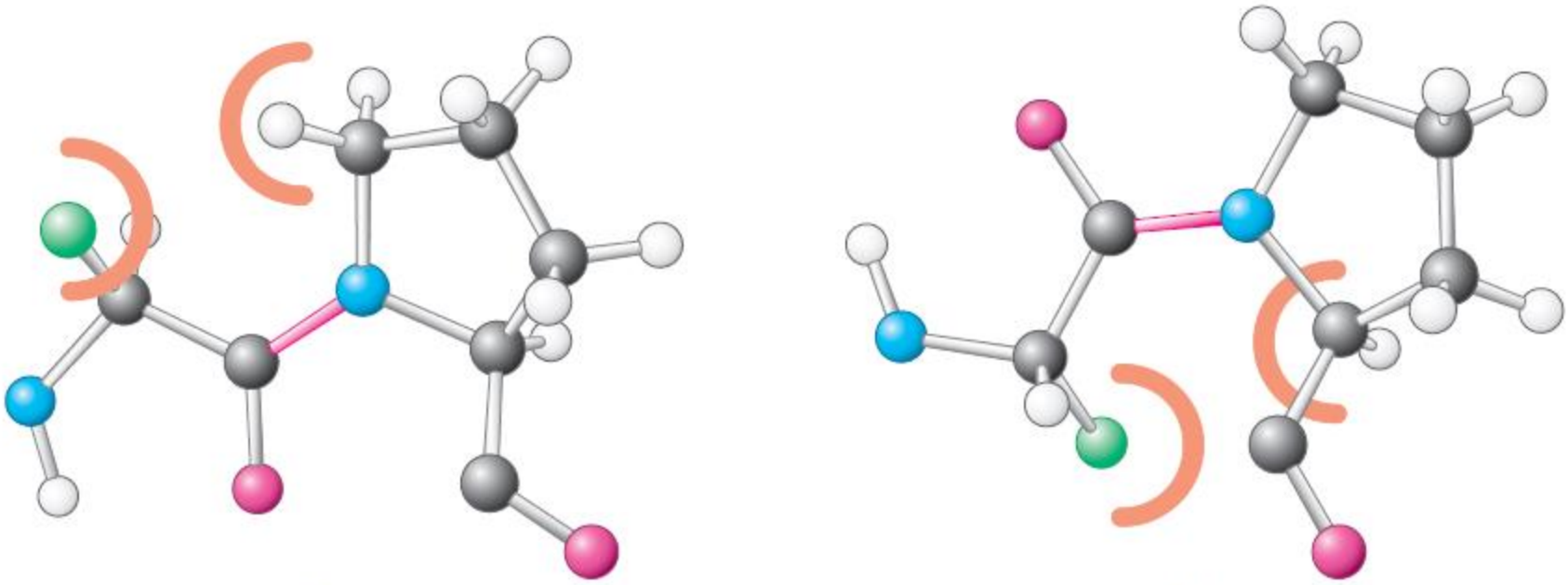


Figure 2.21 Trans and cis X–Pro bonds. The energies of these forms are similar to one another because steric clashes arise in both forms.

- 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.
- A change in conformation could occur, by rotation about single bonds. Of the numerous conformations that are theoretically possible in a protein containing hundreds of single bonds, one or a few generally predominate under biological conditions.
- The conformations existing under a given set of conditions are usually the ones that are thermodynamically the most stable, having the lowest **Gibbs free energy (*G*)**. Proteins in any of their functional, folded conformations are called **native proteins**.
- Native proteins are only marginally stable; the ΔG separating the folded and unfolded states in typical proteins under physiological conditions is in the range of only 20 to 65 kJ/mol.
- A given polypeptide chain can theoretically assume countless different conformations, and as a result the unfolded state of a protein is characterized by a high degree of conformational entropy.
- This entropy, and the hydrogen-bonding interactions of many groups in the polypeptide chain with solvent (water), tend to maintain the unfolded state. The chemical interactions that counteract these effects and stabilize the native conformation include disulfide bonds and the weak (noncovalent) interactions : hydrogen bonds, and hydrophobic and ionic interactions.

- The stability of a protein is not simply the sum of the free energies of formation of the many weak interactions within it.
- Every hydrogen-bonding group in a folded polypeptide chain was hydrogen-bonded to water prior to folding, and for every hydrogen bond formed in a protein, a hydrogen bond (of similar strength) between the same group and water was broken.
- The net stability contributed by a given weak interaction, or the *difference in free energies of the folded and unfolded* states, may be close to zero.
- When water surrounds a hydrophobic molecule, the optimal arrangement of hydrogen bonds results in a highly structured shell, or **solvation layer,** of water in the immediate vicinity.
- The increased order of the water molecules in the solvation layer correlates with an unfavorable decrease in the entropy of the water. However, when nonpolar groups are clustered together, there is a decrease in the extent of the solvation layer because each group no longer presents its entire surface to the solution.
- The result is a favorable increase in entropy. This entropy term is the major thermodynamic driving force for the association of hydrophobic groups in aqueous solution. Hydrophobic amino acid side chains therefore tend to be clustered in a protein's interior, away from water.

- ☑ Hydrophobic interactions are clearly important in stabilizing a protein conformation; the interior of a protein is generally a densely packed core of hydrophobic amino acid side chains.
- ☑ It is also important that any polar or charged groups in the protein interior have suitable partners for hydrogen bonding or ionic interactions.
- ☑ One hydrogen bond seems to contribute little to the stability of a native structure, but the presence of hydrogen-bonding or charged groups without partners in the hydrophobic core of a protein can be so *destabilizing* that conformations containing these groups are often thermodynamically untenable.
- ☑ In addition, hydrogen bonds between groups in proteins form cooperatively. Formation of one hydrogen bond facilitates the formation of additional hydrogen bonds.
- ☑ The interaction of oppositely charged groups that form an ion pair (salt bridge) may also have a stabilizing effect on one or more native conformations of some proteins.

Most of the structural patterns reflect two simple rules:

(1) hydrophobic residues are largely buried in the protein interior, away from water;

(2) 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.

In contrast with the peptide bond, the bonds between the amino group and the α-carbon atom and between the α-carbon atom and the carbonyl group are pure single bonds. The two adjacent rigid peptide units can rotate about these bonds, taking on various orientations. *This freedom of rotation about two bonds of each amino acid allows proteins to fold in many different ways*. The rotations about these bonds can be specified by *torsion angles*

The angle of rotation about the bond between the nitrogen and the α-carbon atoms is called phi (ϕ). The angle of rotation about the bond between the α-carbon and the carbonyl carbon atoms is called psi (ψ). A clockwise rotation about either bond as viewed from the nitrogen atom toward the α-carbon atom or from the carbonyl group toward the α-carbon atom corresponds to a positive value. The ϕ and ψ angles determine the path of the polypeptide chain.

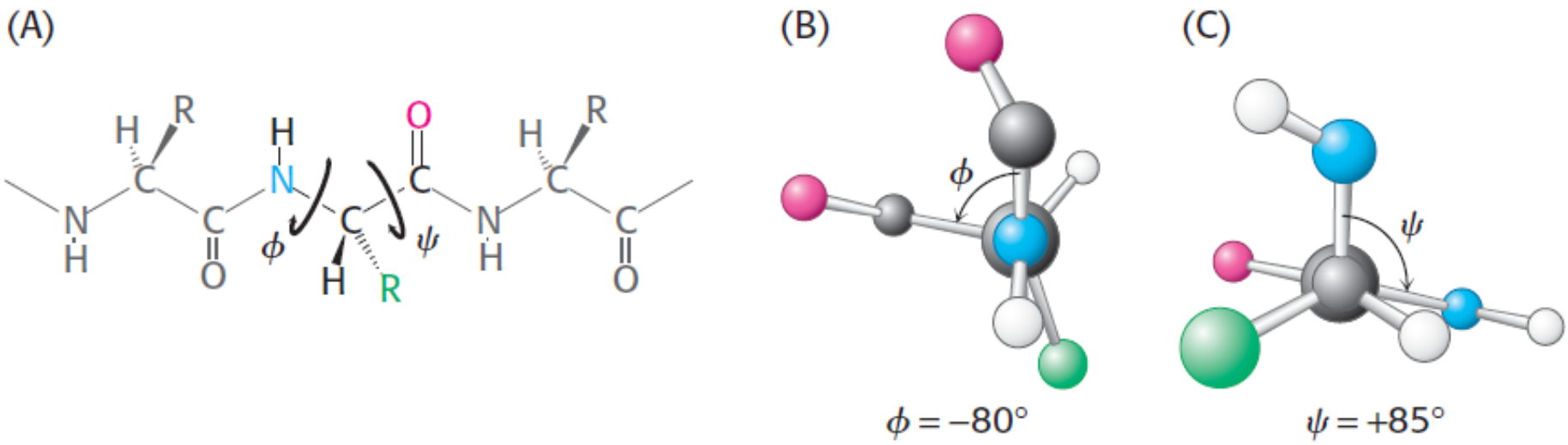
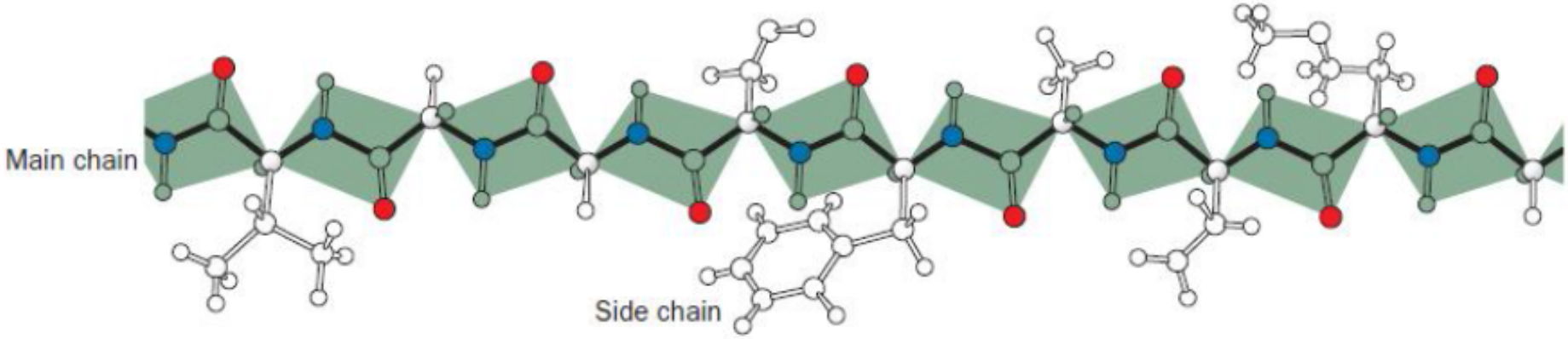
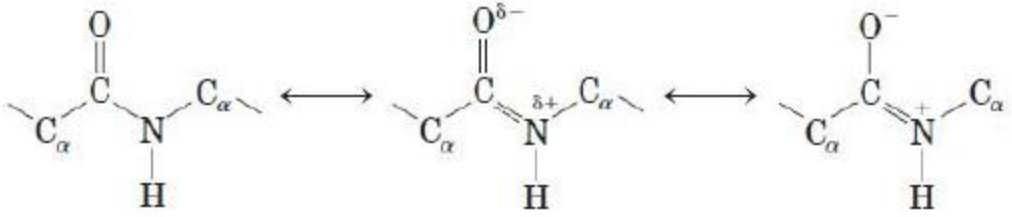


Figure 2.22 Rotation about bonds in a polypeptide. The structure of each amino acid in a polypeptide can be adjusted by rotation about two single bonds. (A) Phi (ϕ) is the angle of rotation about the bond between the nitrogen and the α-carbon atoms, whereas psi (ψ) is the angle of rotation about the bond between the α-carbon and the carbonyl carbon atoms. (B) A view down the bond between the nitrogen and the α-carbon atoms, showing how ϕ is measured. (C) A view down the bond between the α-carbon and the carbonyl carbon atoms, showing how ψ is measured.

- Polypeptide Backbone Conformations May Be Described by Their Torsion Angles.
- It is important because they indicate that *the backbone of a protein is a linked sequence of rigid planar peptide groups.*
- *We can therefore* specify a polypeptide's backbone conformation by the torsion angles (rotation angles or dihedral angles) about C_α –N bond (ϕ) and C_α – C bond (Ψ) of each of its amino acid residues.
- These angles, and , are both defined as 180° when the polypeptide chain is in its planar, fully extended (all-trans) conformation and increase for a clockwise rotation when viewed from C_α.

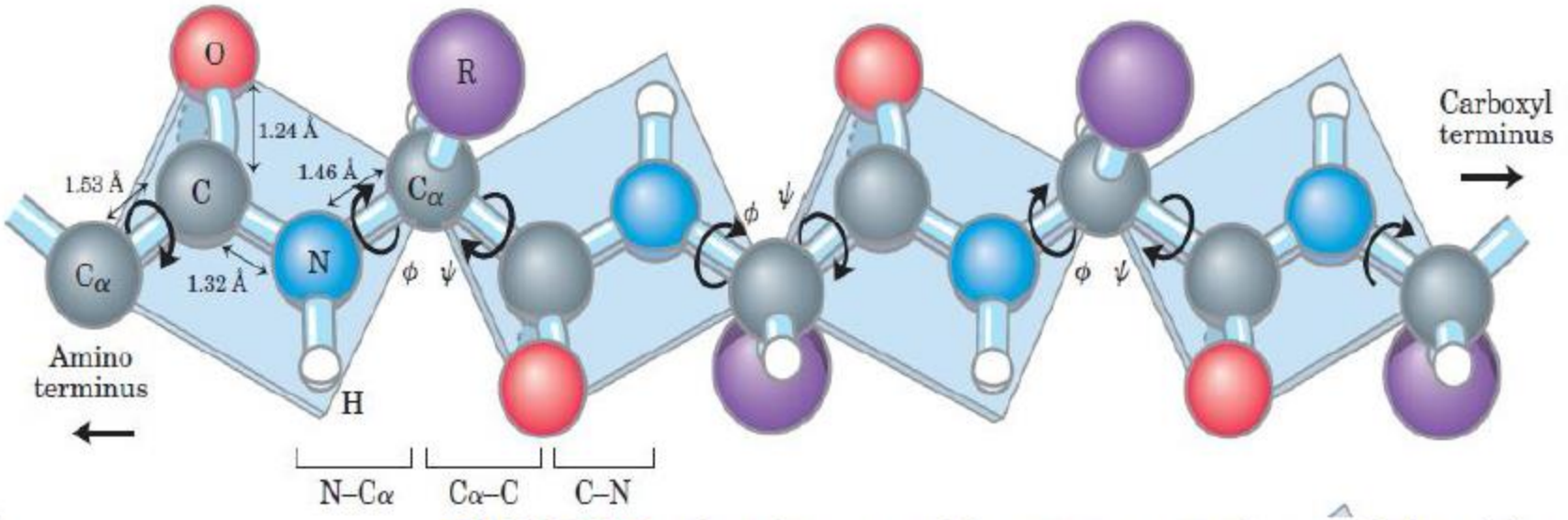


A polypeptide chain in its fully extended conformation showing the planarity of each of its peptide groups.



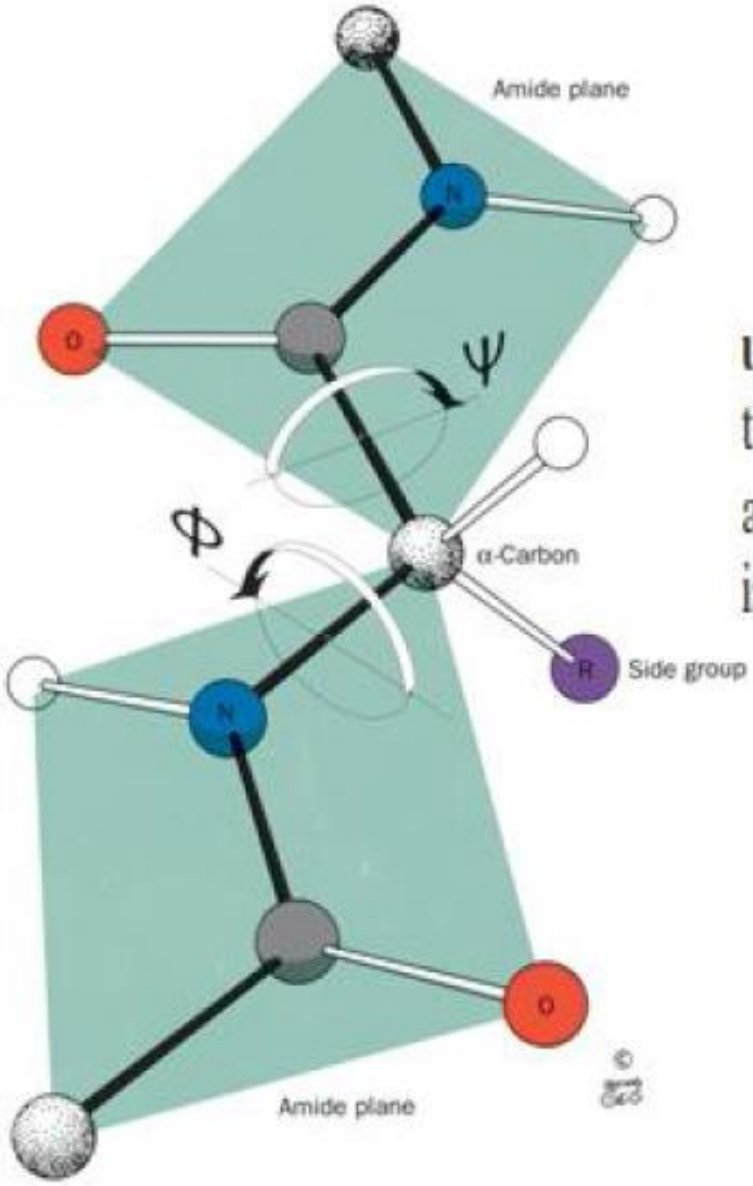
The carbonyl oxygen has a partial negative charge and the amide nitrogen a partial positive charge, setting up a small electric dipole. Virtually all peptide bonds in proteins occur in this trans configuration; an exception is noted in Figure 4–8b.

(a)

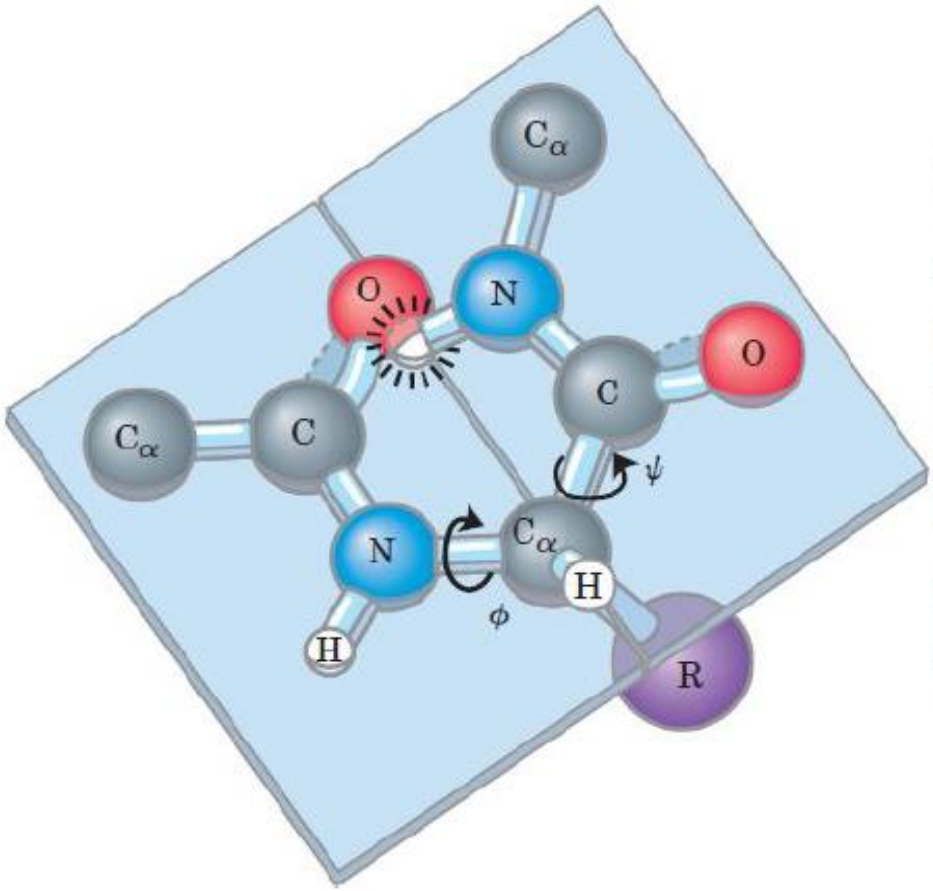


(b)

FIGURE 4–2 The planar peptide group. (a) Each peptide bond has some double-bond character due to resonance and cannot rotate. (b) Three bonds separate sequential α carbons in a polypeptide chain. The N—C_α and C_α—C bonds can rotate, with bond angles designated ϕ and ψ, respectively. The peptide C—N bond is not free to rotate. Other single bonds in the backbone may also be rotationally hindered, depending on the size and charge of the R groups. In the conformation shown, ϕ and ψ are 180° (or −180°). As one looks out from the α carbon, the ψ and ϕ angles increase as the carbonyl or amide nitrogens (respectively) rotate clockwise.

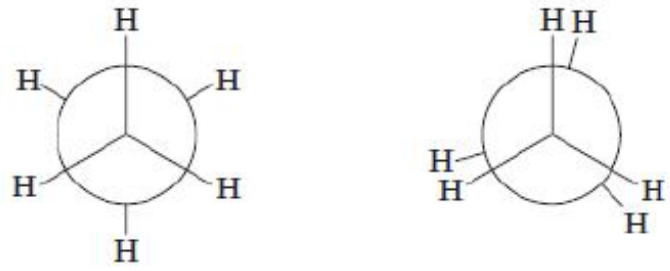


The torsional degrees of freedom in a peptide unit. The only reasonably free movements are rotations about the C_α—N bond (ϕ) and the C_α—C bond (ψ). The torsion angles are both 180° in the conformation shown and increase, as is indicated, in a clockwise manner when viewed from C_α.



(c) By convention, both ϕ and ψ are defined as 0° when the two peptide bonds flanking that α carbon are in the same plane and positioned as shown. In a protein, this conformation is prohibited by steric overlap between an α-carbonyl oxygen and an α-amino hydrogen atom. To illustrate the bonds between atoms, the balls representing each atom are smaller than the van der Waals radii for this scale. 1 Å = 0.1 nm.

- There are several steric constraints on the torsion angles, ϕ and Ψ, of a polypeptide backbone that limit its conformational range. The electronic structure of a single (σ) bond, such as a C¬C bond, is cylindrically symmetrical about its bond axis, so that we might expect such a bond to exhibit free rotation.
- If this were the case, then in ethane, for example, all torsion angles about the C¬C bond would be equally likely. Yet certain conformations in ethane are favored due to quantum mechanical effects arising from the interactions of its molecular orbitals.
- The **staggered conformation** (torsion angle = 180°) is ethane's most stable arrangement, whereas the **eclipsed conformation** (torsion angle = 0°) is least stable.
- The energy difference between the staggered and eclipsed conformations in ethane is ~12kJ mol^{-1} , a quantity that represents an **energy barrier** to free rotation about the C– C single bond.



(a) **Staggered** *(b)* **Eclipsed**

Conformations of ethane. Newman projections indicating the (*a*) staggered conformation and (*b*) eclipsed conformation of ethane.

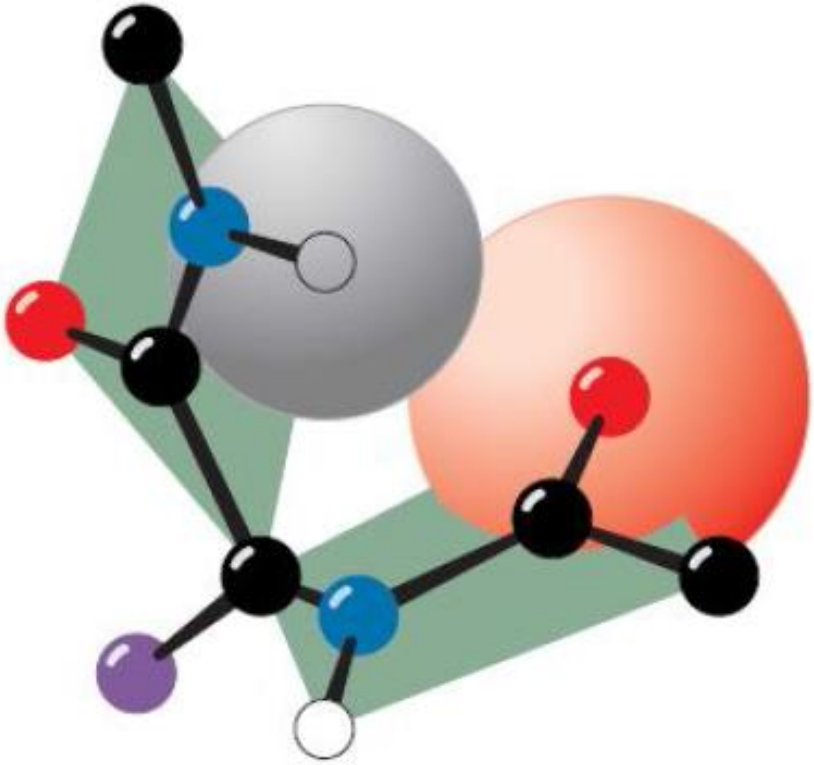
- Substituents other than hydrogen exhibit greater steric interference; that is, they increase the size of this energy barrier due to their greater bulk. Indeed, with large substituents, some conformations may be sterically forbidden.

Are all combinations of ϕ and ψ possible? Gopalasamudram Ramachandran recognized that many combinations are forbidden because of steric collisions between atoms. The allowed values can be visualized on a two-dimensional plot called a *Ramachandran diagram* (Figure 2.23). Three-quarters of the possible (ϕ, ψ) combinations are excluded simply by local steric clashes. *Steric exclusion, the fact that two atoms cannot be in the same place at the same time, can be a powerful organizing principle.*

Allowed Conformations of Polypeptides Are Indicated by the Ramachandran Diagram

The sterically allowed values of ϕ and Ψ can be determined by calculating the distances between the atoms of a tripeptide at all values of ϕ and Ψ for the central peptide unit.

Sterically forbidden conformations, such as that shown in Fig, are those in which any nonbonding interatomic distance is less than its corresponding van der Waals distance. Such information is summarized in a **conformation map or Ramachandran diagram,** which was invented by G. N. Ramachandran.



Steric interference between adjacent residues.
The collision between a carbonyl oxygen and the following amide hydrogen prevents the conformation $\phi = -60°, \psi = 30°$.

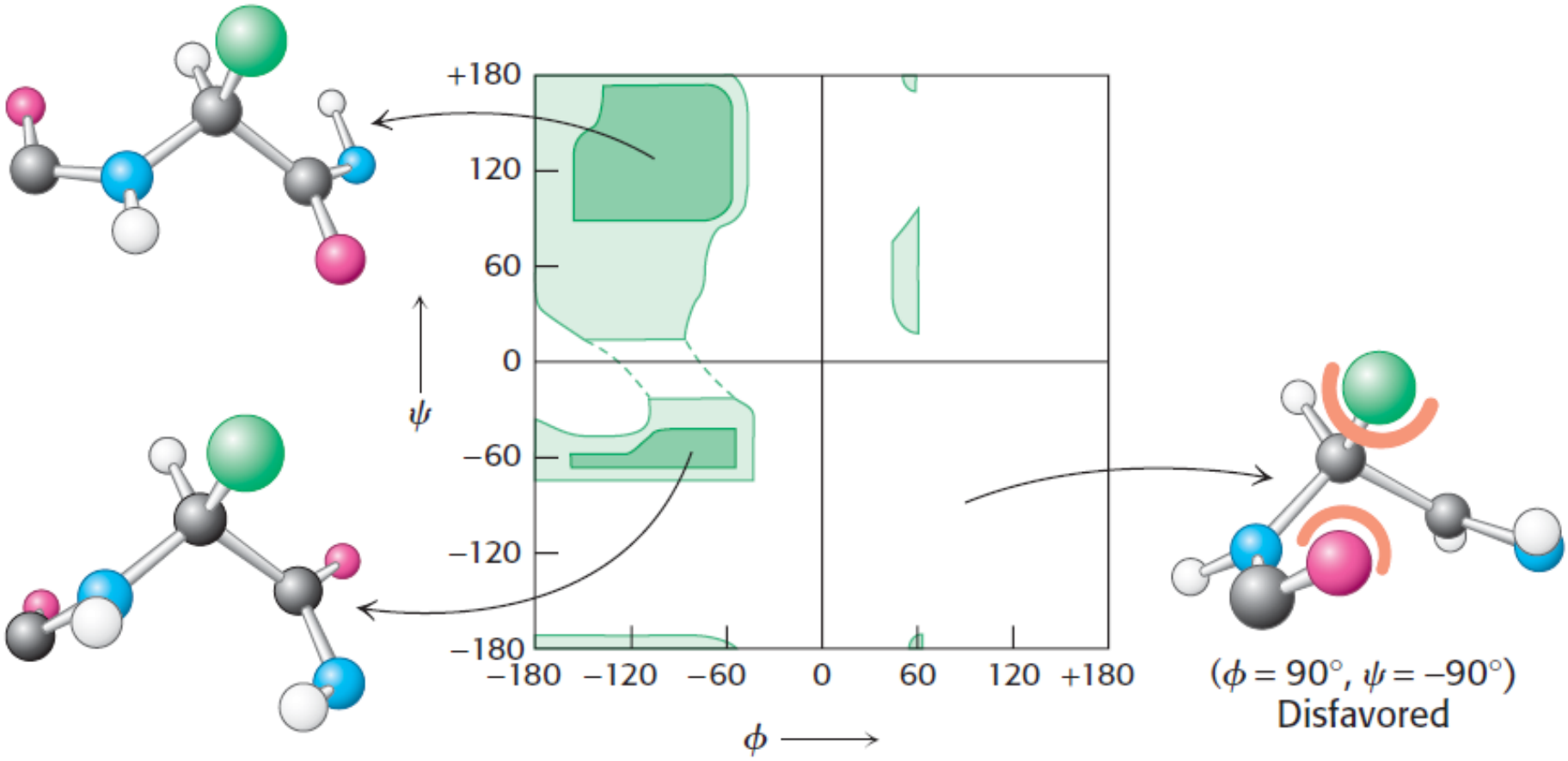


Figure 2.23 A Ramachandran diagram showing the values of ϕ and ψ. Not all ϕ and ψ values are possible without collisions between atoms. The most favorable regions are shown in dark green; borderline regions are shown in light green. The structure on the right is disfavored because of steric clashes.

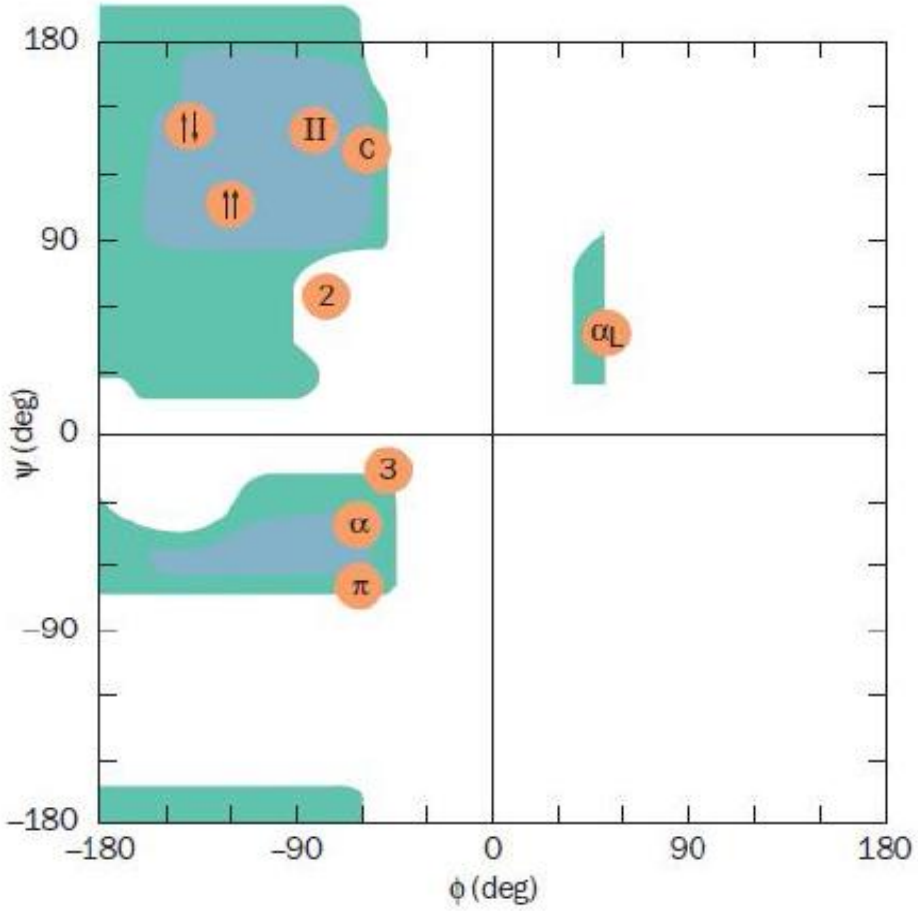
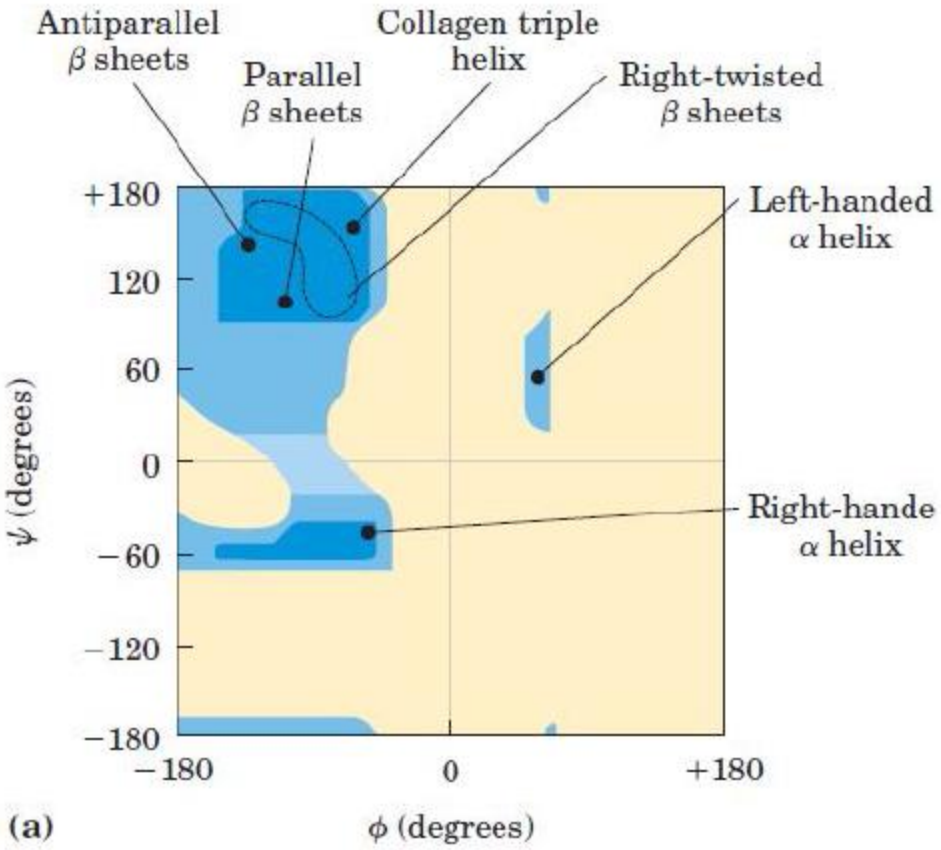
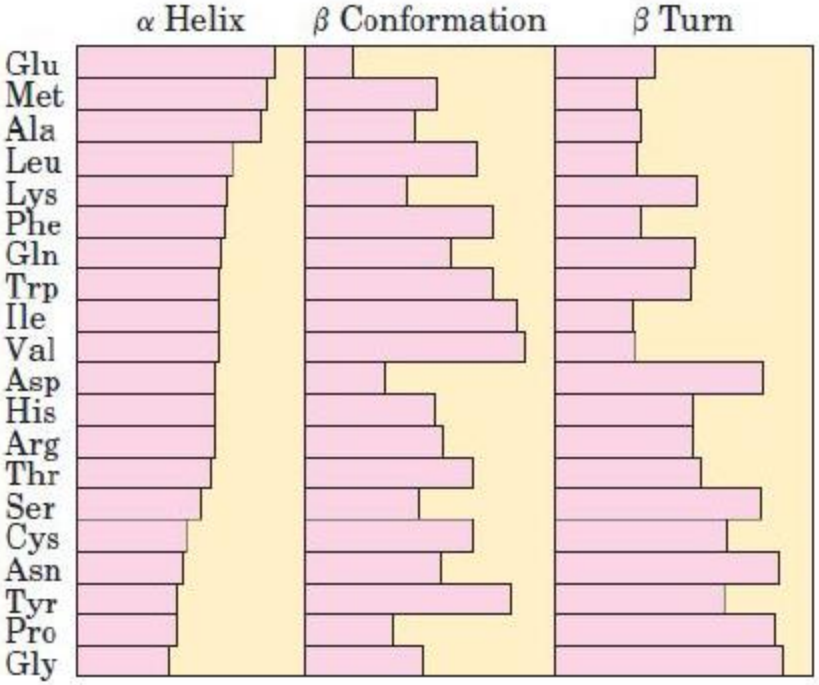


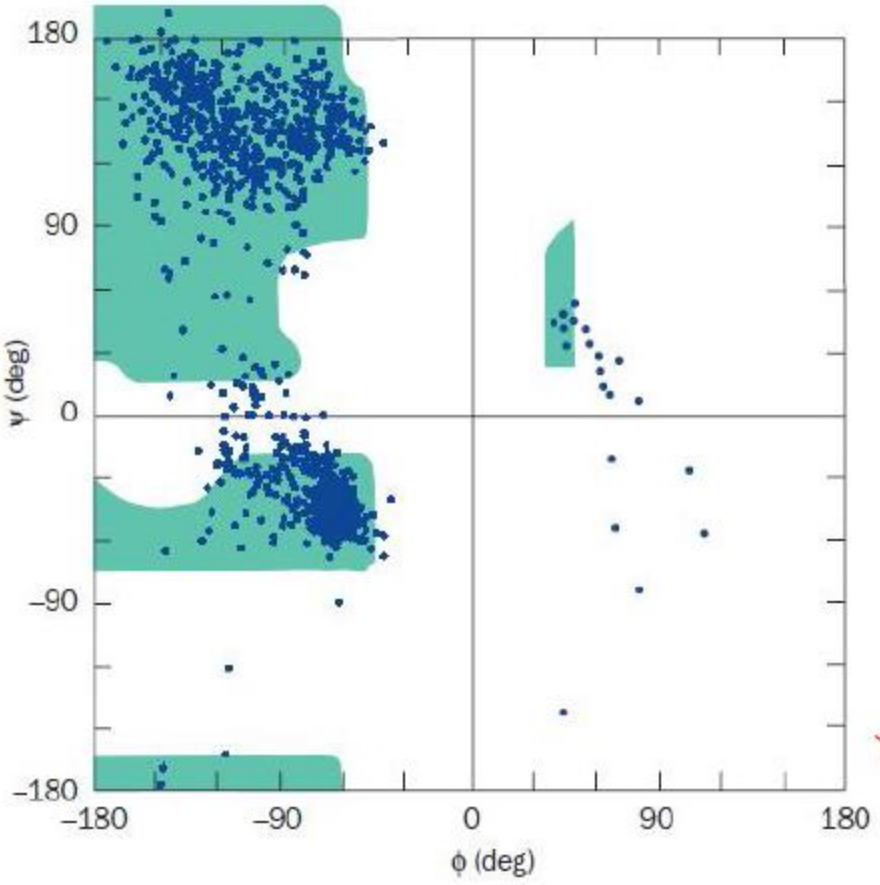
FIGURE 8-7 The Ramachandran diagram. It shows the sterically allowed ϕ and ψ angles for poly-L-alanine and was calculated using the van der Waals distances in Table 8-1. Regions of "normally allowed" ϕ and ψ angles are shaded in blue, whereas green-shaded regions correspond to conformations having "outer limit" van der Waals distances. The conformation angles, ϕ and ψ, of several secondary structures are indicated below:

Secondary Structure	ϕ (deg)	ψ (deg)
Right-handed α helix (α)	−57	−47
Parallel β pleated sheet (↑↑)	−119	113
Antiparallel β pleated sheet (↑↓)	−139	135
Right-handed 3_{10} helix (3)	−49	−26
Right-handed π helix (π)	−57	−70
2.2_7 ribbon (2)	−78	59
Left-handed polyglycine II and poly-L-proline II helices (II)	−79	150
Collagen (C)	−51	153
Left-handed α helix (α_L)	57	47

- It indicates that ~70% of the Ramachandran diagram (most combinations of ϕ and Ψ) is conformationally inaccessible to a polypeptide chain.


Antiparallel β sheets
Parallel β sheets
Collagen triple helix
Right-twisted β sheets
Left-handed α helix
Right-hande α helix
+180
120
60
0
−60
−120
−180
−180
0
+180
ψ (degrees)
ϕ (degrees)
(a)


α Helix
β Conformation
β Turn
Glu
Met
Ala
Leu
Lys
Phe
Gln
Trp
Ile
Val
Asp
His
Arg
Thr
Ser
Cys
Asn
Tyr
Pro
Gly

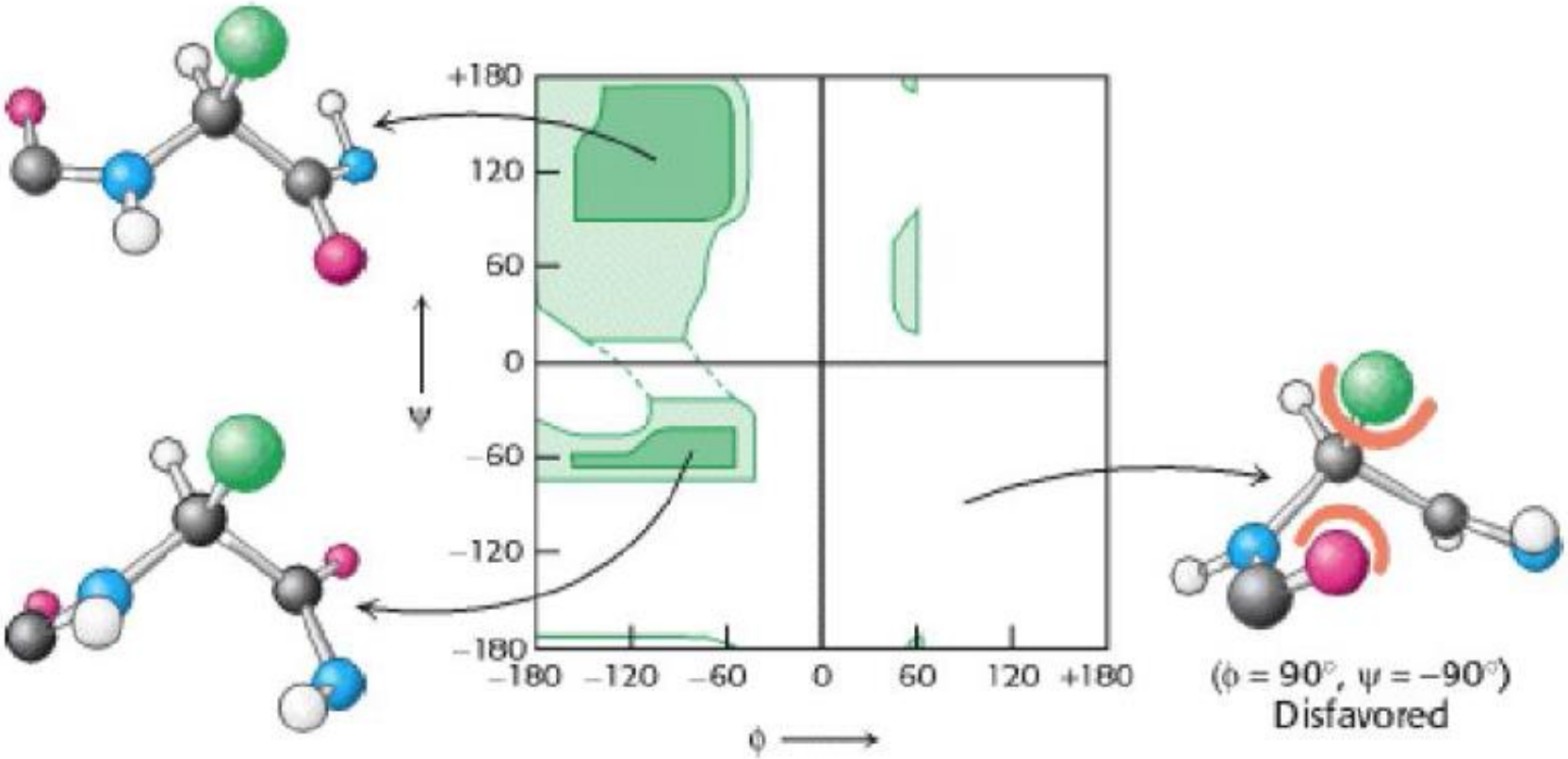


Conformation angles in proteins. *The conformation angle distribution of all residues but Gly and Pro in 12 precisely determined high-resolution X-ray structures is superimposed on the Ramachandran diagram.*

TABLE 8-1 van der Waals Distances for Interatomic Contacts

Contact Type	Normally Allowed (Å)	Outer Limit (Å)
H···H	2.0	1.9
H···O	2.4	2.2
H···N	2.4	2.2
H···C	2.4	2.2
O···O	2.7	2.6
O···N	2.7	2.6
O···C	2.8	2.7
N···N	2.7	2.6
N···C	2.9	2.8
C···C	3.0	2.9
C···CH_2	3.2	3.0
CH_2···CH_2	3.2	3.0

- The particular regions of the Ramachandran diagram that represent allowed conformations depend on the van der Waals radii chosen to calculate it. But with any realistic set of values, such as that in Table 8-1, *only three small regions of the conformational map are physically accessible to a polypeptide chain.*
- Nevertheless, as we shall see, all of the common types of regular secondary structures found in proteins fall within allowed regions of the Ramachandran diagram.



A Ramachandran Diagram Showing the Values of ϕ and ψ. Not all ϕ and ψ values are possible without collisions between atoms. The most favorable regions are shown in dark green; borderline regions are shown in light green. The structure on the right is disfavored because of steric clashes.

The ability of biological polymers such as proteins to fold into well-defined structures is remarkable thermodynamically. An unfolded polymer exists as a random coil: each copy of an unfolded polymer will have a different conformation, yielding a mixture of many possible conformations. The favorable entropy associated with a mixture of many conformations opposes folding and must be overcome by interactions favoring the folded form. Thus, highly flexible polymers with a large number of possible conformations do not fold into unique structures. *The rigidity of the peptide unit and the restricted set of allowed* ϕ *and* ψ *angles limits the number of structures accessible to the unfolded form sufficiently to allow protein folding to take place.*

Helical Structures

In 1951, Linus Pauling and Robert Corey proposed two periodic structures called the α *helix (alpha helix)* and the *β –pleated sheet (beta pleated sheet)*. Subsequently, other structures such as the β *turn and omega (Ω) loop* were identified. Although not periodic, these common turn or loop structures are well defined and contribute with α helices and β sheets to form the final protein structure.

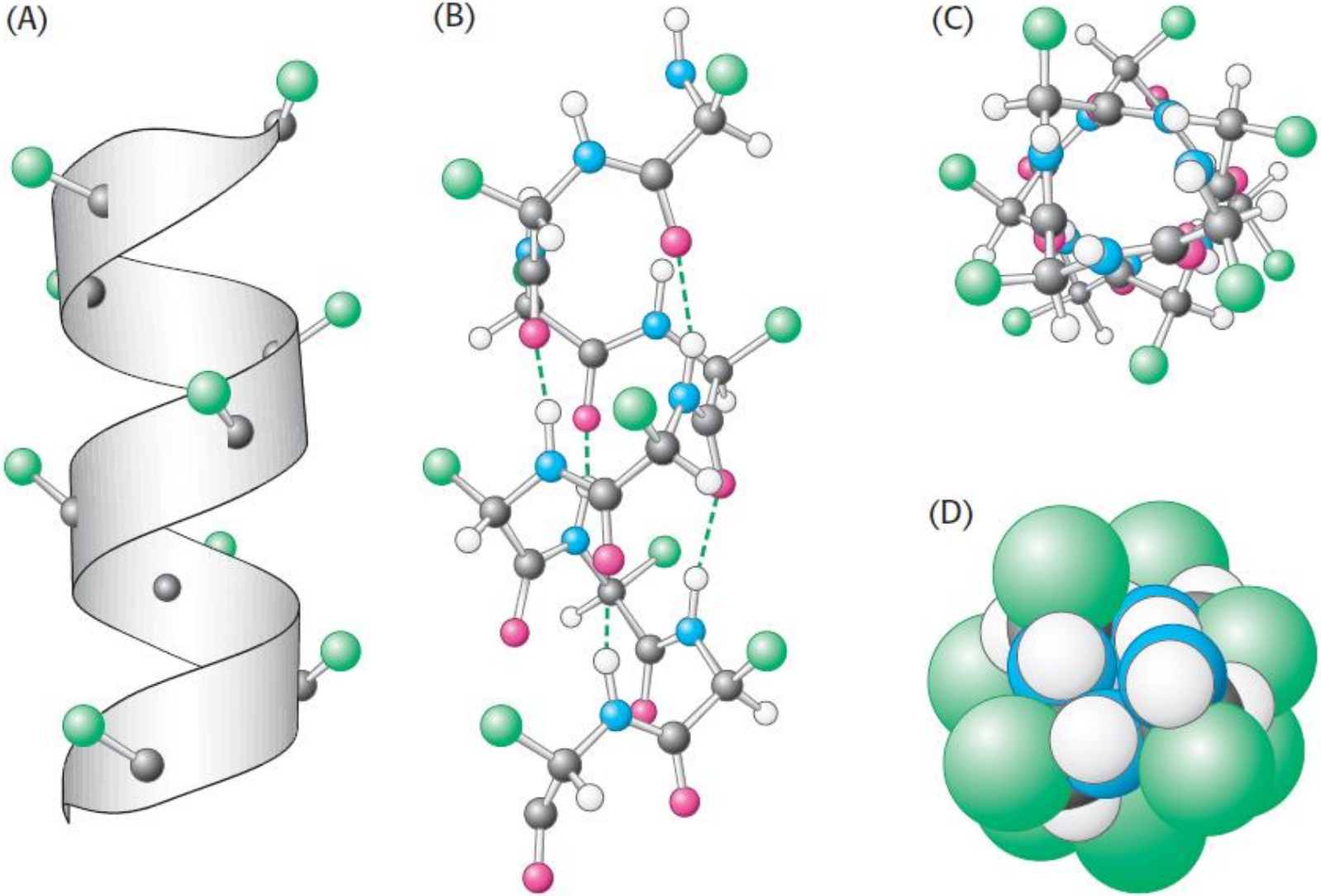
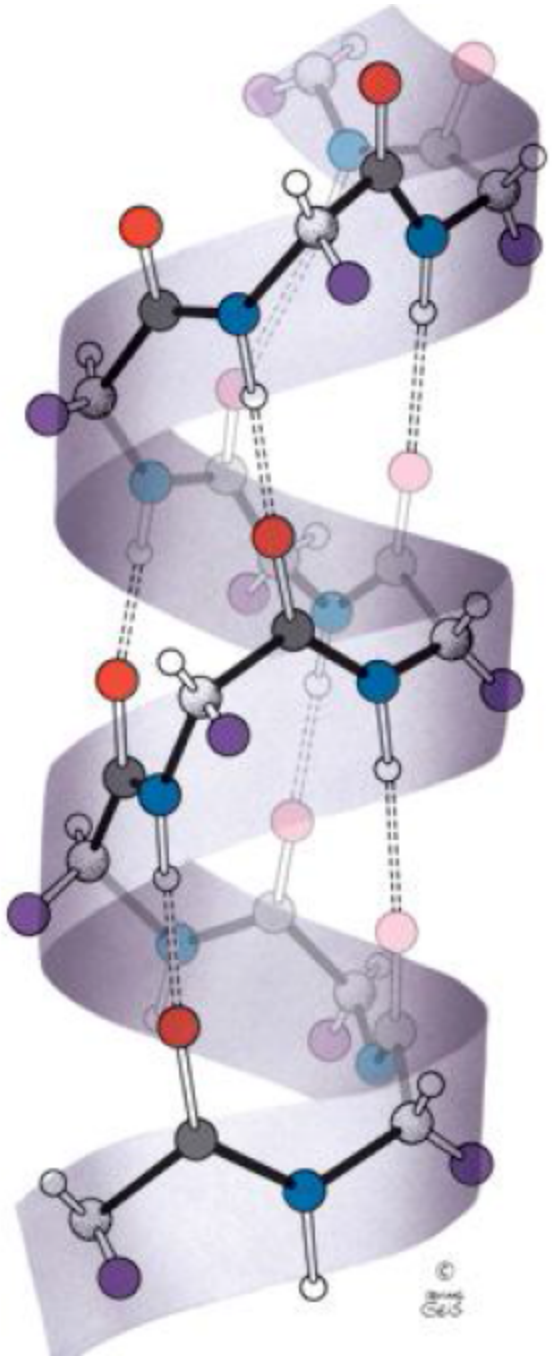


Figure 2.24 Structure of the α helix. (A) A ribbon depiction shows the α-carbon atoms and side chains (green). (B) A side view of a ball-and-stick version depicts the hydrogen bonds (dashed lines) between NH and CO groups. (C) An end view shows the coiled backbone as the inside of the helix and the side chains (green) projecting outward. (D) A space-filling view of part C shows the tightly packed interior core of the helix.

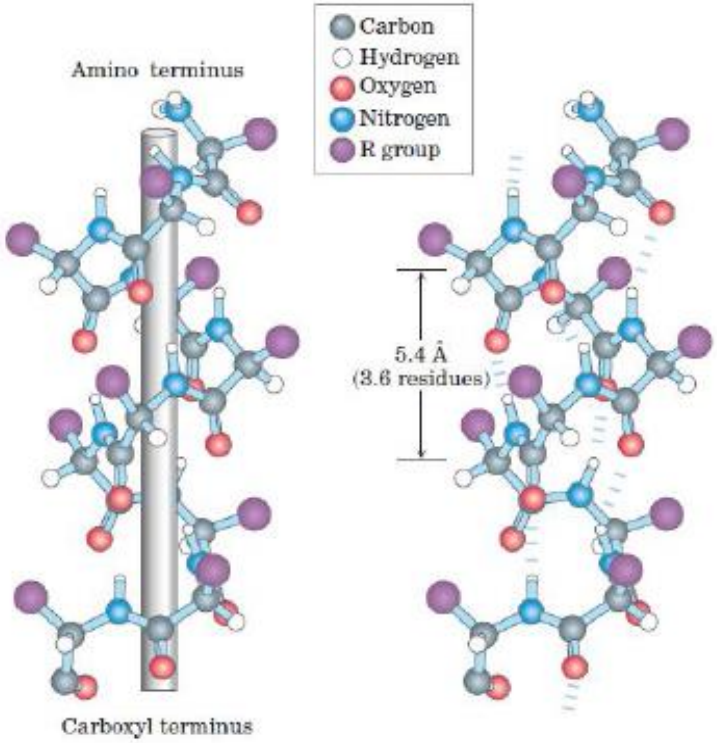


The Alpha Helix Is a Coiled Structure Stabilized by Intrachain Hydrogen Bonds

- The simplest arrangement the polypeptide chain could assume with its rigid peptide bonds is a helical structure, which Pauling and Corey called the ***helix.***
- In this structure the polypeptide backbone is tightly wound around an imaginary axis drawn longitudinally through the middle of the helix, and the R groups of the amino acid residues protrude outward from the helical backbone.
- The repeating unit is a single turn of the helix, which extends about 5.4 Å along the long axis, as observed on x-ray analysis of hair keratin. The amino acid residues in an α *helix* have conformations with Ψ = - *45° to* - *50° and* ϕ = -60°, and each helical turn includes 3.6 amino acid residues.
- The helical twist of the α–*helix* found in all proteins is right-handed. The α *helix* proved to be the predominant structure in α-keratins.
- More generally, about one-fourth of all amino acid residues in polypeptides are found in helices, the exact fraction varying greatly from one protein to the next.

- The helix is stabilized by hydrogen bonds between the NH and CO groups of the main chain. In particular, the CO group of each amino acid forms a hydrogen bond with the NH group of the amino acid that is situated four residues ahead in the sequence. Thus, except for amino acids near the ends of an α helix, all *the main-chain CO and NH groups are hydrogen bonded.*

- Within the *helix, every peptide bond* (except those close to each end of the helix) participates in such hydrogen bonding. Each successive turn of the *helix is held to adjacent turns by three to four* hydrogen bonds. All the hydrogen bonds combined give the entire helical structure considerable stability.



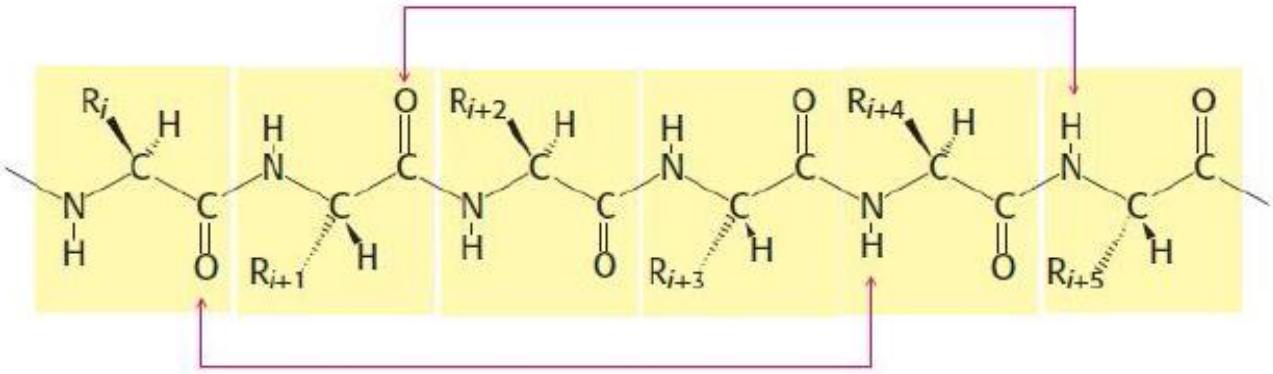
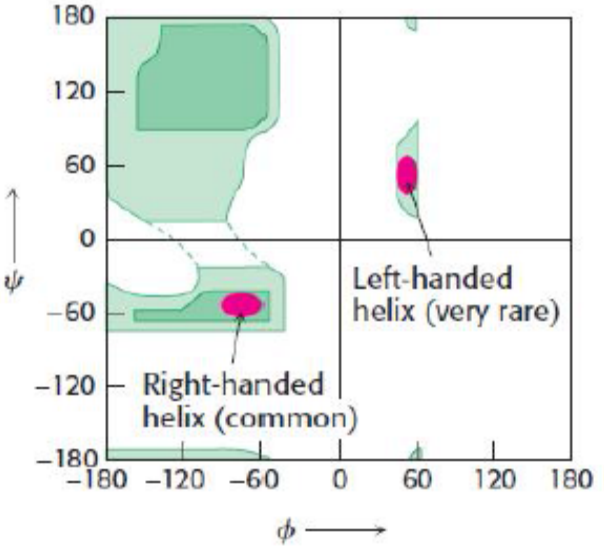
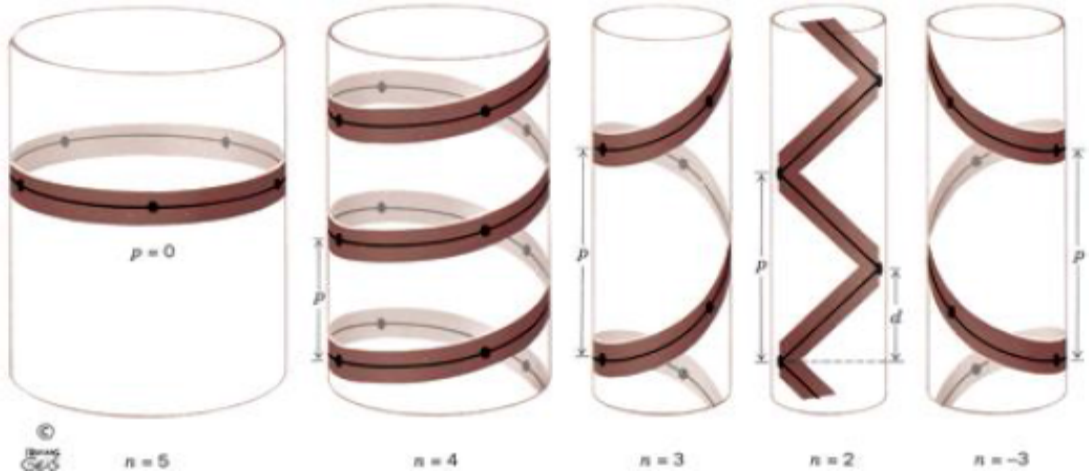


Figure 2.30 Hydrogen-bonding scheme for an α helix. In the α helix, the CO group of residue i forms a hydrogen bond with the NH group of residue $i + 4$.

- Each residue is related to the next one by a rise, also called *translation,* of 1.5 Å along the helix axis and a rotation of 100 degrees, which gives 3.6 amino acid residues per turn of helix.
- Thus, amino acids spaced three and four apart in the sequence are spatially quite close to one another in an helix. In contrast, amino acids spaced two apart in the sequence are situated on opposite sides of the helix and so are unlikely to make contact.
- The *pitch* of the helix, which is equal to the product of the translation *(1.5 Å)* and the number of residues per turn (3.6), is 5.4 Å.
- The *screw sense of a helix* can be right-handed (clockwise) or left-handed (counterclockwise). The Ramachandran diagram reveals that both the right-handed and the left handed helices are among allowed conformations.





Examples of helices. These provide definitions of the helical pitch, *p,* the number of repeating units per turn, *n,* and the helical rise per repeating unit, $d = p/n$. Right- and left-handed helices are defined, respectively, as having positive and negative values of *n. For n=2 the helix degenerates to a* nonchiral ribbon. For p = 0 the helix degenerates to a closed ring.

- Right-handed helices are energetically more favorable because there is less steric clash between the side chains and the backbone. Essentially all helices found in proteins are right-handed. In schematic representations of proteins, helices are depicted as twisted ribbons or rods.

- Pauling and Corey predicted the structure of the helix 6 years before it was actually seen in the x-ray reconstruction of the structure of myoglobin.

The elucidation of the structure of the α helix is a landmark in biochemistry because it demonstrated that the conformation of a polypeptide chain could be predicted if the properties of its components are rigorously and precisely known.

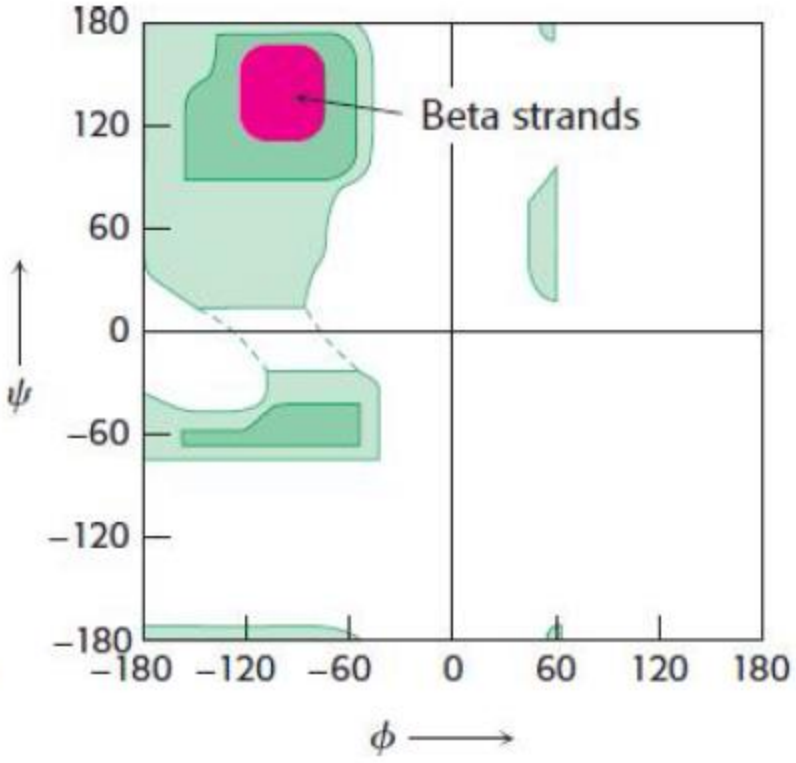
- The α-helical content of proteins ranges widely, from none to almost 100%. For example, about 75% of the residues in ferritin, a protein that helps store iron, are in helices. Indeed, about 25% of all soluble proteins are composed of helices connected by loops and turns of the polypeptide chain. Single α helices are usually less than 45 Å long. Many proteins that span biological membranes also contain helices.

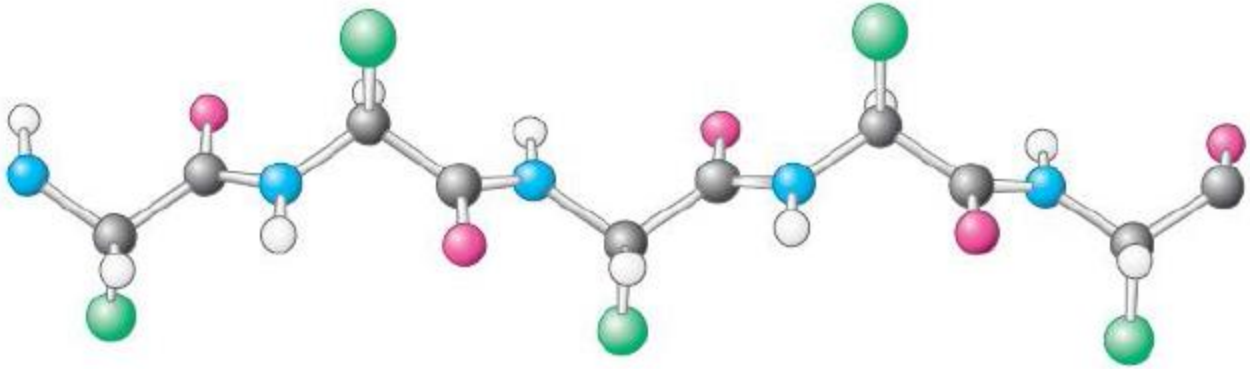
β pleated sheet

In 1951, the year that they proposed the α helix, Pauling and Corey also postulated the existence of a different polypeptide secondary structure, the **β pleated sheet.**

- As with the α helix, the β pleated sheet's conformation has repeating and angles that fall in the allowed region of the Ramachandran diagram and utilizes the full hydrogen bonding capacity of the polypeptide backbone.
- *In β pleated sheets, however, hydrogen bonding occurs between neighboring polypeptide chains rather than within one as in α helices.*

A β strand is almost fully extended rather than being tightly coiled as in the α helix. A range of extended structures are sterically allowed

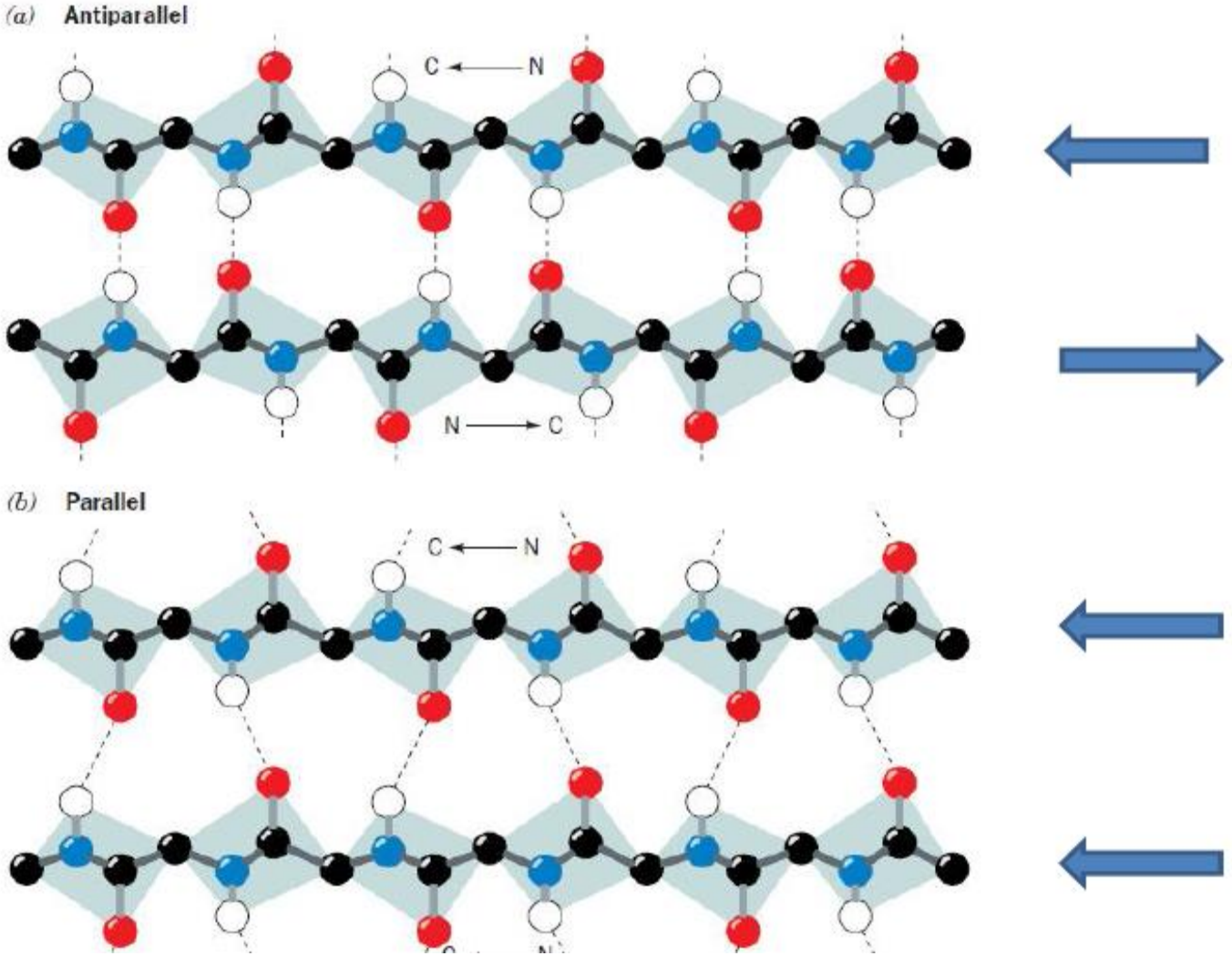




Structure of a β strand. *The side chains (green) are alternately above and below the plane of the strand.*

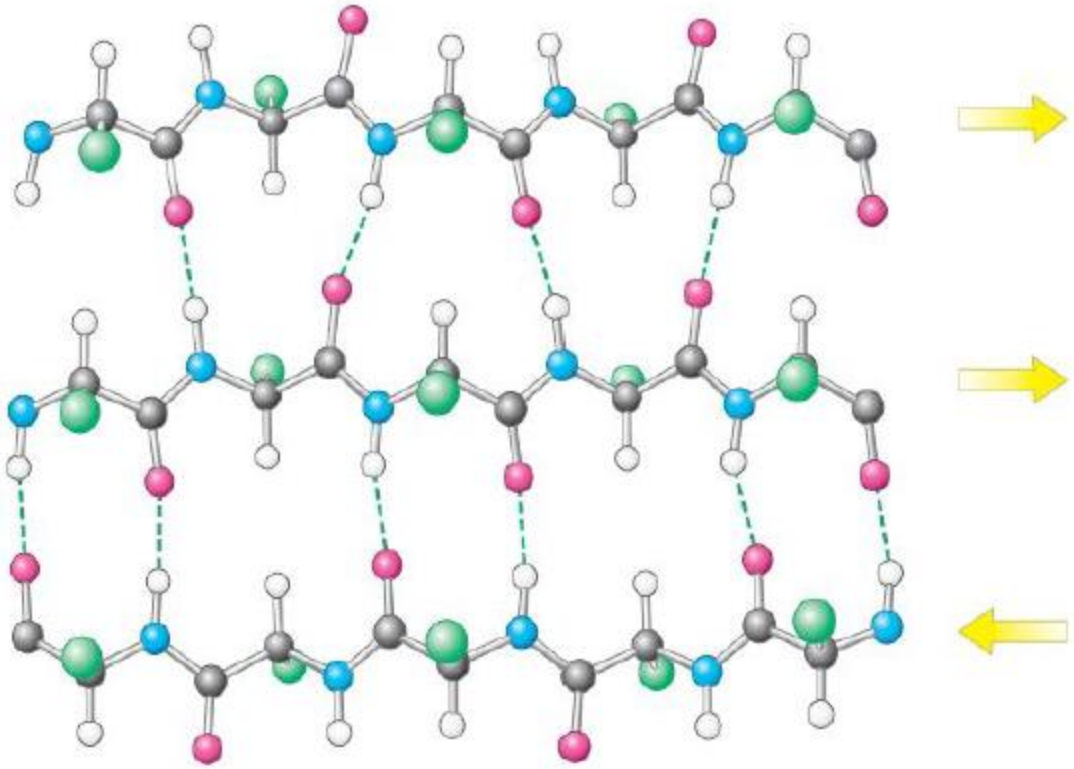
β Pleated sheets come in two varieties:

- ✓ **The antiparallel pleated sheet,** in which neighboring hydrogen bonded polypeptide chains run in opposite directions.
- ✓ **The parallel pleated sheet,** in which the hydrogen bonded chains extend in the same direction.

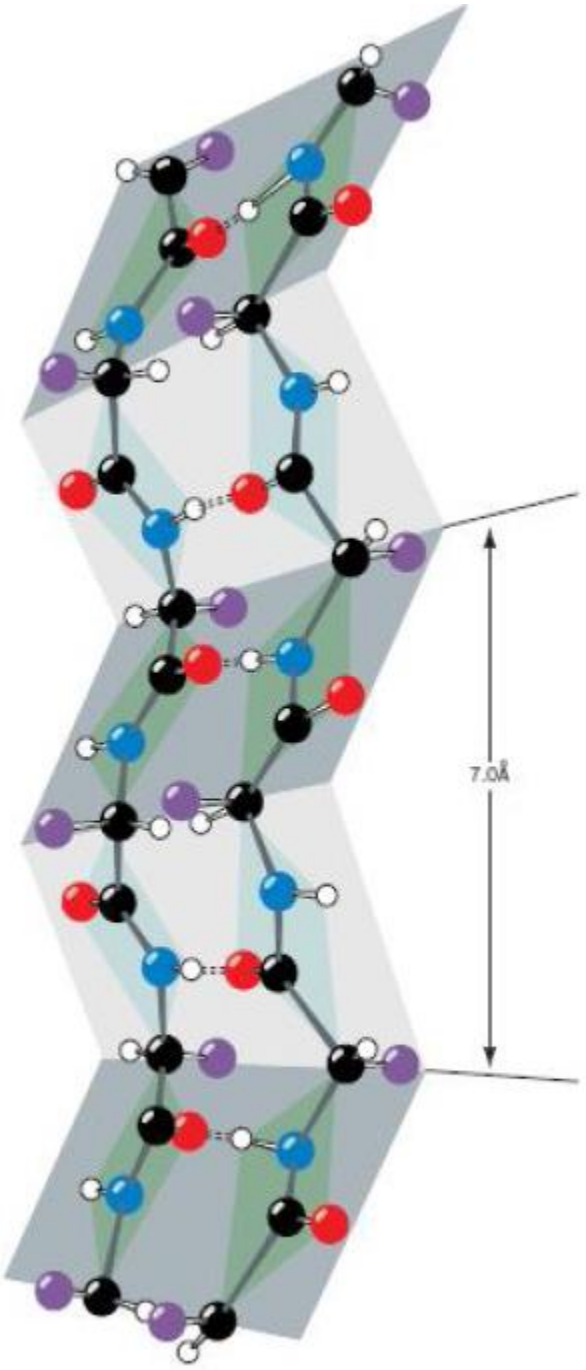


- The distance between adjacent amino acids along a β strand is approximately 3.5 Å, in contrast to a distance of 1.5 Å along an α helix.
- The side chains of adjacent amino acids point in opposite directions. A β sheet is formed by linking two or more β strands lying next to one another through hydrogen bonds. Adjacent chains in a β sheet can run in opposite directions (antiparallel sheet) or in the same direction (parallel sheet).
- In the antiparallel arrangement, the NH group and the CO group of each amino acid are respectively hydrogen bonded to the CO group and the NH group of a partner on the adjacent chain. In the parallel arrangement, the hydrogen-bonding scheme is slightly more complicated.

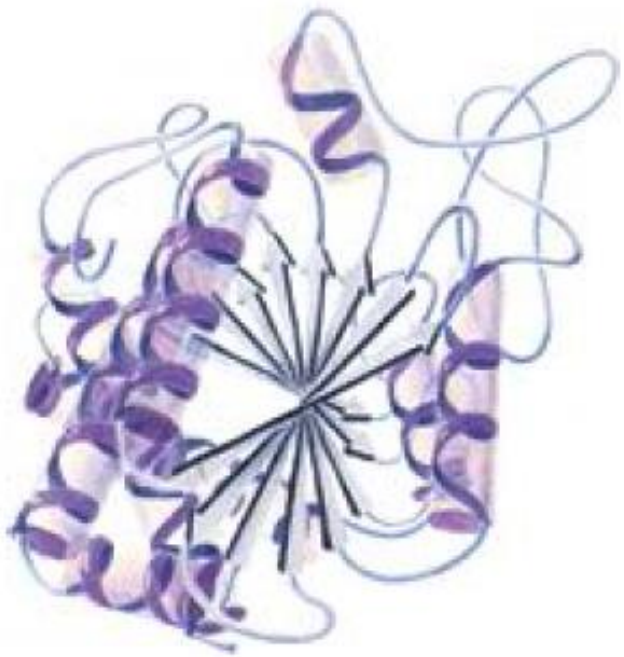
- For each amino acid, the NH group is hydrogen bonded to the CO group of one amino acid on the adjacent strand, whereas the CO group is hydrogen bonded to the NH group on the amino acid two residues farther along the chain.
- Many strands, typically 4 or 5 but as many as 10 or more, can come together in β sheets. Such sheets can be purely antiparallel, purely parallel, or mixed.



- The conformations in which these β structures are optimally hydrogen bonded vary somewhat from that of a fully extended polypeptide ($\phi = \Psi = \pm 180°$).
- They therefore have a rippled or pleated edge-on appearance (Fig.), which accounts for the designation "pleated sheet." In this conformation, successive side chains of a polypeptide chain extend to opposite sides of the pleated sheet with a two-residue repeat distance of 7.0 Å.
- β Sheets are common structural motifs in proteins. In globular proteins, they consist of from 2 to as many as 15 polypeptide strands, the average being 6 strands, which have an aggregate width of ~25Å.
- The polypeptide chains in a sheet are known to be up to 15 residues long, with the average being 6 residues that have a length of ~21Å.
- Parallel β sheets of less than five strands are rare. This observation suggests that parallel β sheets are less stable than antiparallel β sheets, possibly because the hydrogen bonds of parallel sheets are distorted in comparison to those of the antiparallel sheets.



- Mixed parallel– antiparallel β sheets are common but, nevertheless, only ~20% of the strands in β sheets have parallel bonding on one side and antiparallel bonding on the other (vs an expected 50% for the random mixing of strand directions).
- The β pleated sheets in globular proteins invariably exhibit a pronounced right-handed twist when viewed along their polypeptide strands. Such twisted β sheets are important architectural features of globular proteins since β sheets often form their central cores.



b. Other Polypeptide Helices

Figure 8-13 indicates how hydrogen bonded polypeptide helices may be constructed. The first two, the **2.2_7 ribbon** and the **3_{10} helix,** are described by the notation, n_m, where n, as before, is the number of residues per helical turn and m is the number of atoms, including H, in the ring that is closed by the hydrogen bond. With this notation, an α helix is a 3.6_{13} helix.

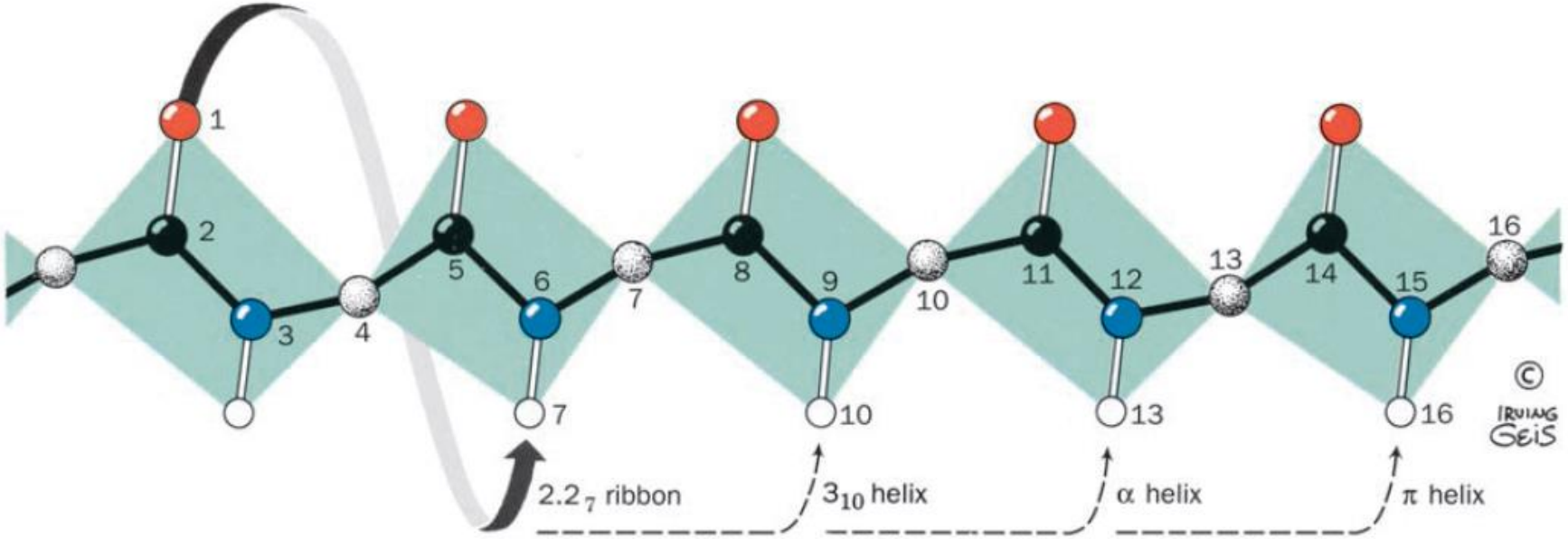


Figure 8-13 **The hydrogen bonding pattern of several polypeptide helices.** In the cases shown, the polypeptide chain is helically wound such that the N—H group on residue n forms a hydrogen bond with the C═O groups on residues $n - 2, n - 3, n - 4$, or $n - 5$. [Illustration, Irving Geis. Image from the Irving Geis Collection, Howard Hughes Medical Institute. Reprinted with permission.]

The right-handed 3_{10} helix (Fig. 8-14*a*), which has a pitch of 6.0 Å, is thinner and rises more steeply than does the α helix (Fig. 8-14*b*). Its torsion angles place it in a mildly forbidden zone of the Ramachandran diagram that is rather near the position of the α helix (Fig. 8-7), and its R groups experience some steric interference. This explains why the 3_{10} helix is only occasionally observed in proteins, and then mostly in short segments that are frequently distorted from the ideal 3_{10} conformation (the longest known 3_{10} helix in a protein has 15 residues). The 3_{10} helix most often occurs as a single-turn transition between one end of an α helix and the adjoining portion of a polypeptide chain.

The **π helix** (4.4_{16} helix), which also has a mildly forbidden conformation (Fig. 8-7), has only rarely been observed and then only as segments of longer helices. This is probably because its comparatively wide and flat conformation (Fig. 8-14*c*) results in an axial hole that is too small to admit water molecules but too wide to allow van der Waals associations across the helix axis; this greatly reduces its stability relative to more closely packed conformations. The 2.2_7 ribbon, which, as Fig. 8-7 indicates, has strongly forbidden conformation angles, has never been observed.

Certain synthetic homopolypeptides assume conformations that are models for helices in particular proteins. **Polyproline** is unable to assume any common secondary structure due to the conformational constraints imposed by its cyclic pyrrolidine side chains. Furthermore, the lack of a hydrogen substituent on its backbone nitrogen precludes any polyproline conformation from being knit together by hydrogen bonding. Nevertheless, under the proper conditions, polyproline precipitates from solution as a left-handed helix of all-trans peptides that has 3.0 residues per helical turn and a pitch of 9.4 Å (Fig. 8-15). This rather extended conformation, which is known as the **polyproline II helix,** permits the Pro side chains to avoid each other. Curiously, **polyglycine,** the least conformationally constrained polypeptide, precipitates from solution as a helix whose parameters are essentially identical to those of polyproline, the most conformationally constrained polypeptide (although the polyglycine helix may be either

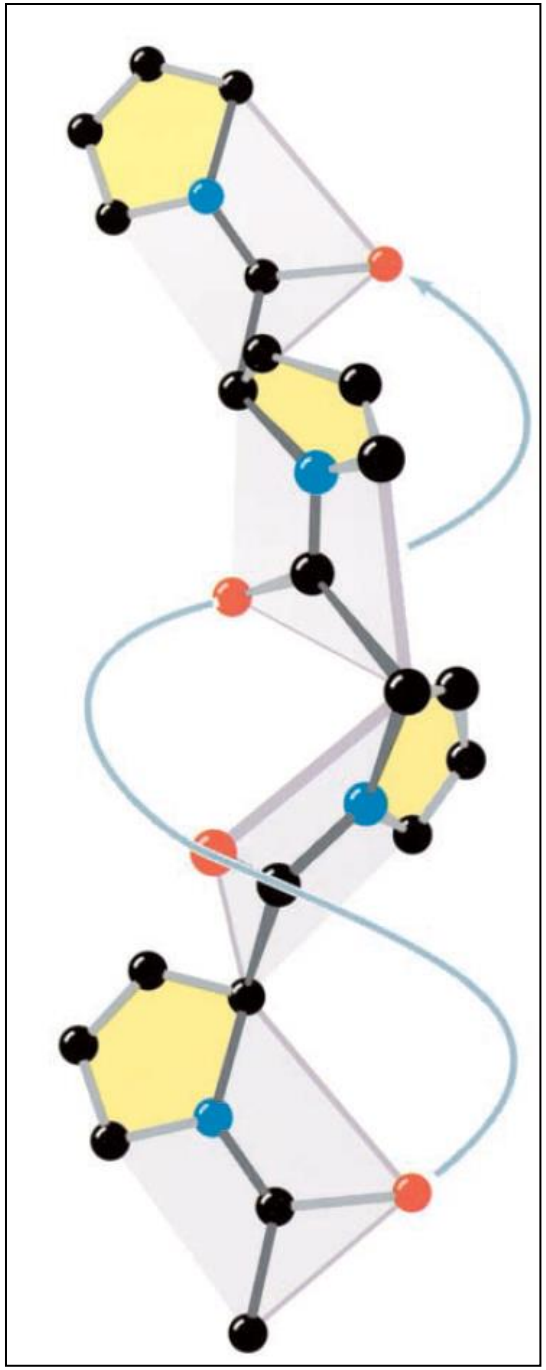


Figure 8-15 **The polyproline II helix.** Polyglycine forms a nearly identical helix **(polyglycine II)**. [Illustration, Irving Geis. Image from the Irving Geis Collection, Howard Hughes Medical Institute. Reprinted with permission.]

Nonrepetitive Structures

- *Regular secondary structures—helices and β sheets— comprise around half of the average globular protein.*
- The protein's remaining polypeptide segments are said to have a **coil or loop conformation.** That is not to say, however, that these nonrepetitive secondary structures are any less ordered than are helices or β sheets; they are simply irregular and hence more difficult to describe.
- Globular proteins consist largely of approximately straight runs of secondary structure joined by stretches of polypeptide that abruptly change direction. Such **reverse turns or β bends** (so named because they often connect successive strands of antiparallel β sheets) almost always occur at protein surfaces; indeed, they partially define these surfaces.
- Most reverse turns involve four successive amino acid residues more or less arranged in one of two ways, Type I and Type II, that differ by a flip of the peptide unit linking residues 2 and 3.
- Both types of β bends contain a hydrogen bond, although deviations from these ideal conformations often disrupt this hydrogen bond.
- Type I β bends may be considered to be distorted sections of 3_{10} helix. In Type II β bends, the oxygen atom of residue 2 crowds the C_β atom of residue 3, which is therefore usually Gly. Residue 2 of either type of β bend is often Pro since it can facilely assume the required conformation.

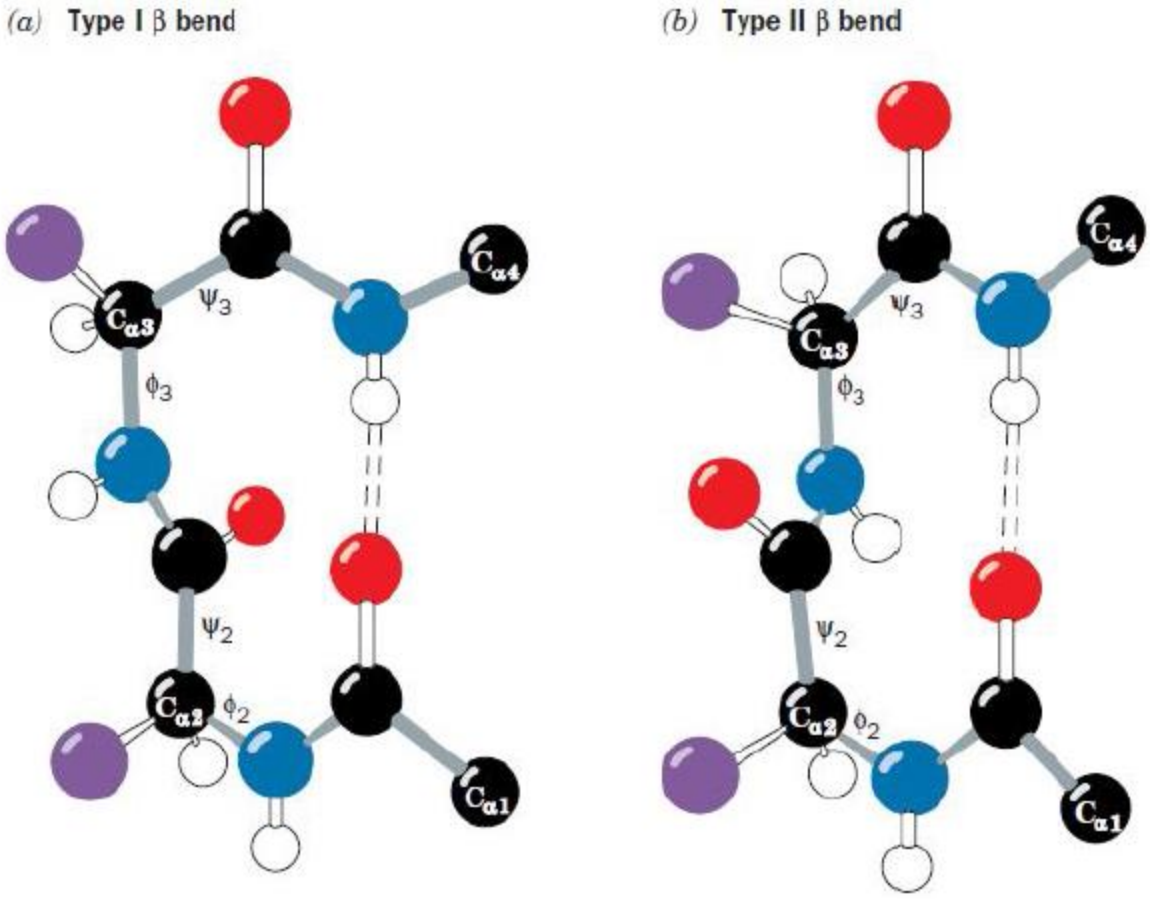


FIGURE 8-22 Reverse turns in polypeptide chains. (*a*) A Type I β bend, which has the following torsion angles:

$$\phi_2 = -60°, \quad \psi_2 = -30°,$$
$$\phi_3 = -90°, \quad \psi_2 = 0°.$$

(*b*) A Type II β bend, which has the following torsion angles:

$$\phi_2 = -60°, \quad \psi_2 = 120°,$$
$$\phi_3 = 90°, \quad \psi_3 = 0°.$$

Variations from these ideal conformation angles by as much as 30° are common. Hydrogen bonds are represented by dashed lines. [Illustration, Irving Geis/Geis Archives Trust. Copyright Howard Hughes Medical Institute. Reproduced with permission.] See Kinemage Exercise 3-4

- Almost all proteins >60 of residues contain one or more loops of 6 to 16 residues that are not components of helices or β sheets and whose end-to-end distances are <10Å.
- Such Ω **loops (so named because they have the necked-in** shape of the Greek uppercase letter omega), which may contain reverse turns, are compact globular entities because their side chains tend to fill in their internal cavities.
- Since Ω loops are almost invariably located on the protein surface, they may have important roles in biological recognition processes.

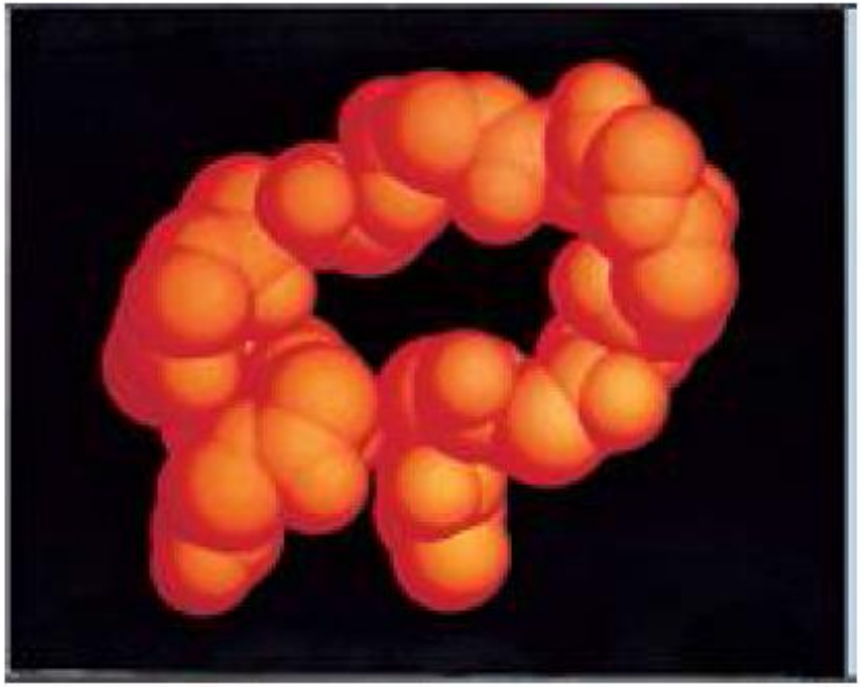
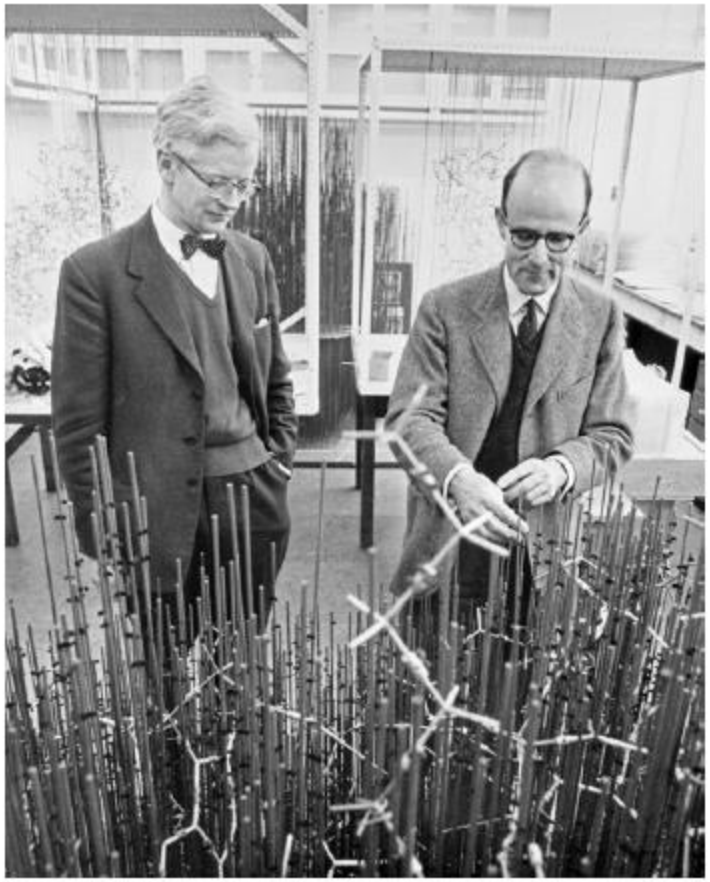


FIGURE 8-23 Space-filling representation of an Ω loop comprising residues 40 to 54 of cytochrome *c*. Only backbone atoms are shown; the addition of side chains would fill in the loop. [Courtesy of George Rose, Washington University School of Medicine.]

Protein Architecture
Tertiary Structure of Small Globular Proteins: Myoglobin

Max Perutz, 1914–2002 (left) John Kendrew, 1917–1997 (right)



John Kendrew and Max Perutz shared the 1962 Nobel Prize in Chemistry for determining the structure of myoglobin and other globular proteins.

- ✓ The first breakthrough in understanding the three-dimensional structure of a globular protein came from x-ray diffraction studies of myoglobin carried out by John Kendrew and his colleagues in the 1950s.

- ✓ Myoglobin is a relatively small (*Mr 16,700),* oxygen-binding protein of muscle cells. It functions both to store oxygen and to facilitate oxygen diffusion in rapidly contracting muscle tissue.

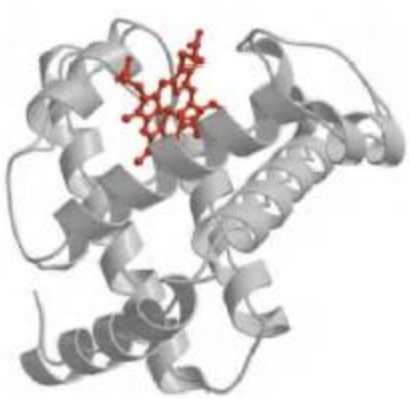
- ✓ Myoglobin contains a single polypeptide chain of 153 amino acid residues of known sequence and a single iron protoporphyrin, or heme, group.

- ✓ The same heme group that is found in myoglobin is found in hemoglobin, the oxygen-binding protein of erythrocytes, and is responsible for the deep red-brown color of both myoglobin and hemoglobin.

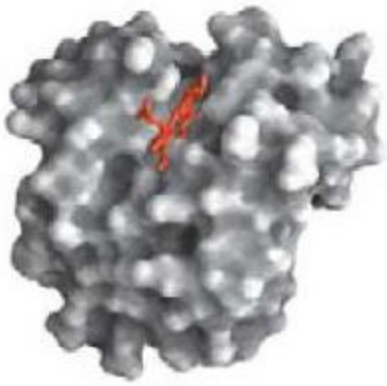
- ✓ Myoglobin is particularly abundant in the muscles of diving mammals such as the whale, seal, and porpoise - so abundant that the muscles of these animals are brown.

- ✓ Storage and distribution of oxygen by muscle myoglobin permits diving mammals to remain submerged for long periods.

Tertiary structure of sperm whale myoglobin

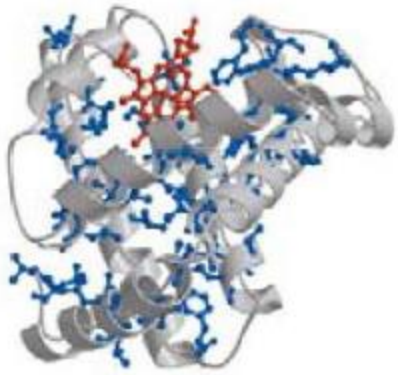


(a)

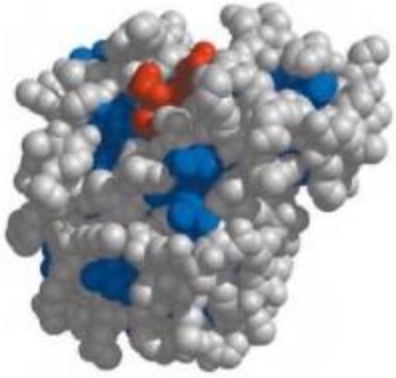


(b)

(PDB ID 1MBO)



(c)



(d)

The red group surrounded by protein is heme. The backbone of the myoglobin molecule consists of eight relatively straight segments of α helix interrupted by bends, some of which are β turns.

The longest α helix has 23 amino acid residues and the shortest only 7; all helices are right-handed. More than 70% of the residues in myoglobin are in these - α helical regions. X-ray analysis has revealed the precise position of each of the R groups, which occupy nearly all the space within the folded chain.

- ✓ The positioning of amino acid side chains reflects a structure that derives much of its stability from hydrophobic interactions. Most of the hydrophobic R groups are in the interior of the molecule, hidden from exposure to water.
- ✓ All but two of the polar R groups are located on the outer surface of the molecule, and all are hydrated. The myoglobin molecule is so compact that its interior has room for only four molecules of water.
- ✓ This dense hydrophobic core is typical of globular proteins. The fraction of space occupied by atoms in an organic liquid is 0.4 to 0.6. In a globular protein the fraction is about 0.75, comparable to that in a crystal (in a typical crystal the fraction is 0.70 to 0.78, near the theoretical maximum).
- ✓ In this packed environment, weak interactions strengthen and reinforce each other. For example, the nonpolar side chains in the core are so close together that short-range van der Waals interactions make a significant contribution to stabilizing hydrophobic interactions.

Three of the four Pro residues are found at bends. The fourth Pro residue occurs within an α helix, where it creates a kink necessary for tight helix packing.

The flat heme group rests in a crevice, or pocket, in the myoglobin molecule. The iron atom in the center of the heme group has two bonding (coordination) positions perpendicular to the plane of the heme.

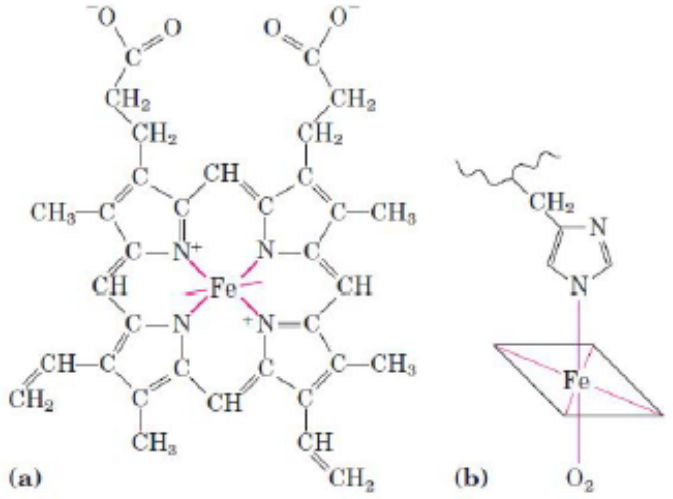


FIGURE 4–16 The heme group. This group is present in myoglobin, hemoglobin, cytochromes, and many other proteins (the heme proteins). (a) Heme consists of a complex organic ring structure, protoporphyrin, which binds an iron atom in its ferrous (Fe^{2+}) state. The iron atom has six coordination bonds, four in the plane of, and bonded to, the flat porphyrin molecule and two perpendicular to it. (b) In myoglobin and hemoglobin, one of the perpendicular coordination bonds is bound to a nitrogen atom of a His residue. The other is "open" and serves as the binding site for an O_2 molecule.

One of these is bound to the R group of the His residue at position 93; the other is the site at which an O_2 molecule binds. Within this pocket, the accessibility of the heme group to solvent is highly restricted.

This is important for function, because free heme groups in an oxygenated solution are rapidly oxidized from the ferrous (Fe^{2+}) form, which is active in the reversible binding of O_2, to the ferric (Fe^{3+}) form, which does not bind O_2.

We need to analyze its folding patterns

- **Motif**, also called **a supersecondary structure or fold.** A motif is simply a recognizable folding pattern involving two or more elements of secondary structure and the connection(s) between them.
- A motif can be very simple, such as two elements of secondary structure folded against each other, and represent only a small part of a protein for example a ***β–α–β loop.***
- A motif can also be a very elaborate structure involving scores of protein segments folded together, such as the β *barrel*. In some cases, a single large motif may comprise the entire protein. The term encompasses any advantageous folding pattern and is useful for describing such patterns. The segment defined as a motif may or may not be independently stable.
- Note that a motif is not a hierarchical structural element falling between secondary and tertiary structure.
- It is a folding pattern that can describe a small part of a protein or an entire polypeptide chain. The synonymous term "supersecondary structure" is thus somewhat misleading because it suggests hierarchy.

(a) β-α-β Loop

Motifs. (a) A simple motif, the β-α-β loop. (b) A more elaborate motif, the β barrel. This β barrel is a single domain of α-hemolysin (a toxin that kills a cell by creating a hole in its membrane) from the bacterium *Staphylococcus aureus* (derived from PDB ID 7AHL).

β Barrel

- The second term for describing structural patterns is **domain**. A domain, as defined by Jane Richardson in 1981, is a part of a polypeptide chain that is independently stable or could undergo movements as a single entity with respect to the entire protein.
- Polypeptides with more than a few hundred amino acid residues often fold into two or more domains, sometimes with different functions.
- In many cases, a domain from a large protein will retain its native three-dimensional structure even when separated (for example, by proteolytic cleavage) from the remainder of the polypeptide chain.
- In a protein with multiple domains, each domain may appear as a distinct globular lobe more commonly, extensive contacts between domains make individual domains hard to discern.
- Different domains often have distinct functions, such as the binding of small molecules or interaction with other proteins. Small proteins usually have only one domain (the domain is the protein).

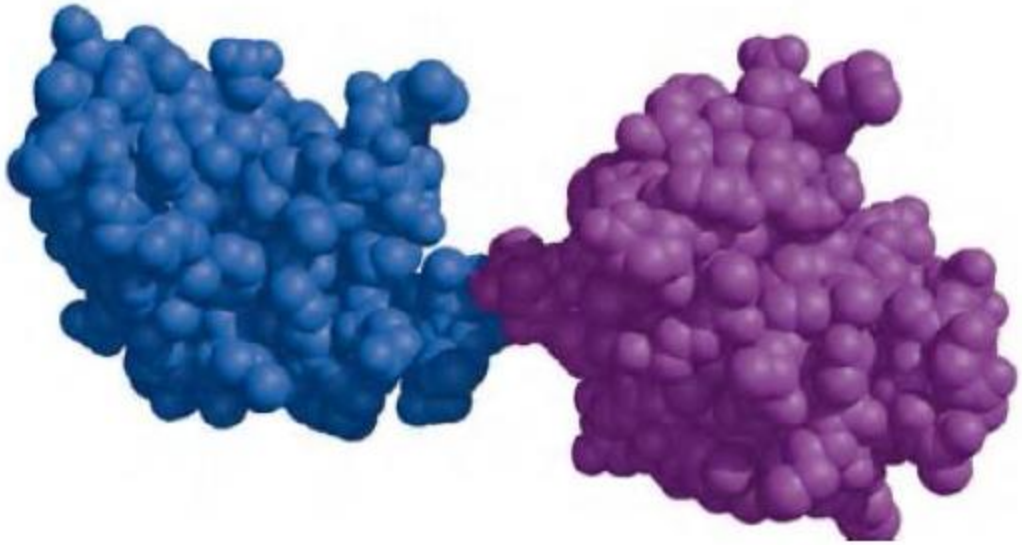


FIGURE 4–18 Structural domains in the polypeptide troponin C. (PDB ID 4TNC) This calcium-binding protein associated with muscle has two separate calcium-binding domains, indicated in blue and purple.

Folding of polypeptides is subject to an array of physical and chemical constraints, and several rules have emerged from studies of common protein folding patterns.

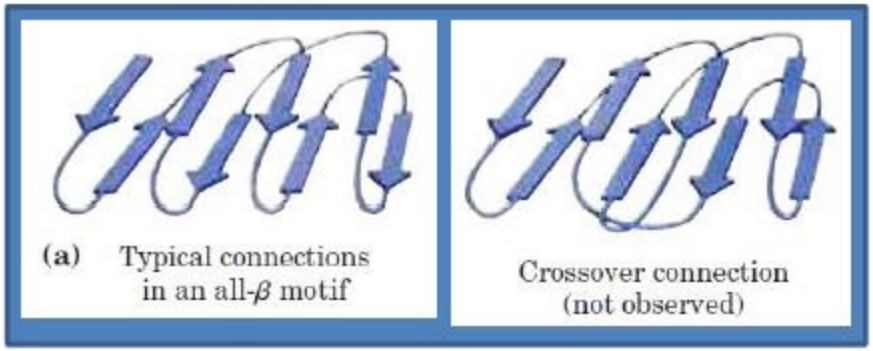
1. Hydrophobic interactions make a large contribution to the stability of protein structures. Burial of hydrophobic amino acid R groups so as to exclude water requires at least two layers of secondary structure. Simple motifs, such as the β–α–β *loop*, create two such layers.

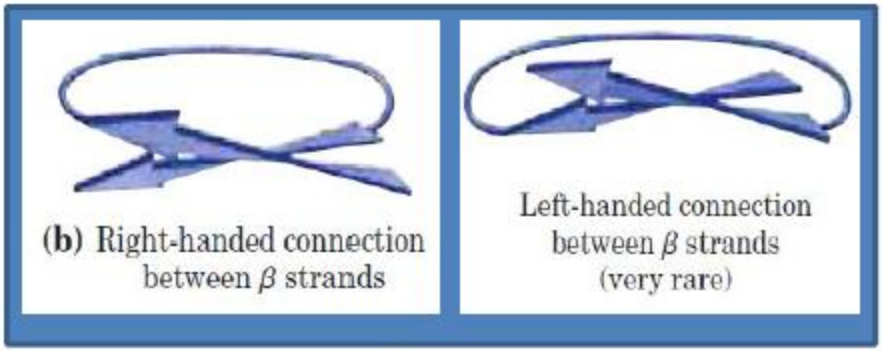
2. Where they occur together in a protein, α *helices* and β *sheets* generally are found in different structural layers. This is because the backbone of a polypeptide segment in the β *conformation* cannot readily hydrogen-bond to an α *helix* aligned with it.

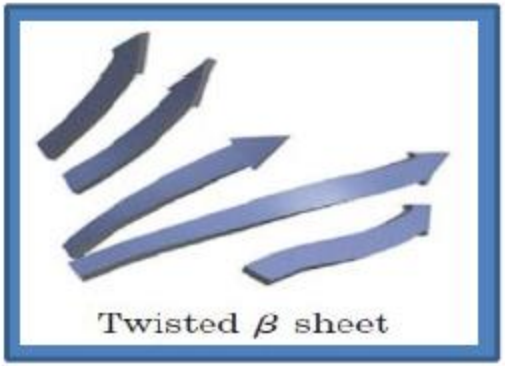
3. Segments adjacent to each other in the amino acid sequence are usually stacked adjacent to each other in the folded structure. Distant segments of a polypeptide may come together in the tertiary structure, but this is not the norm.

4. Connections between common elements of secondary structure cannot cross or form knots (**Fig. a**).

5. The β *conformation* is most stable when the individual segments are twisted slightly in a right handed sense. This influences both the arrangement of β *sheets* relative to one another and the path of the polypeptide connections between them.







Two parallel β *strands,* for example, must be connected by a crossover strand (Fig. b).

In principle, this crossover could have a right- or left-handed conformation, but in proteins it is almost always right-handed. Right-handed connections tend to be shorter than left-handed connections and tend to bend through smaller angles, making them easier to form. The twisting of β *sheets* also leads to a characteristic twisting of the structure formed by many such segments together, as seen in the β *barrel* and twisted β *sheet,* which form the core of many larger structures.

FIGURE 4–19 Stable folding patterns in proteins. (a) Connections between β strands in layered β sheets. The strands here are viewed from one end, with no twisting. Thick lines represent connections at the ends nearest the viewer; thin lines are connections at the far ends of the β strands. The connections at a given end (e.g., near the viewer) do not cross one other. (b) Because of the right-handed twist in β strands, connections between strands are generally right-handed. Left-handed connections must traverse sharper angles and are harder to form. (c) This twisted β sheet is from a domain of photolyase (a protein that repairs certain types of DNA damage) from *E. coli* (derived from PDB ID 1DNP). Connecting loops have been removed so as to focus on the folding of the β sheet.

- ✓ Following these rules, complex motifs can be built up from simple ones. For example, a series of ***β–α–β loops*** arranged so that the ***β strands*** form a barrel creates a particularly stable and common motif, the ***α/β barrel.***

- ✓ In this structure, each parallel ***β segment*** is attached to its neighbor by an ***α-helical*** segment. All connections are right-handed. The ***α/β barrel*** is found in many enzymes, often with a binding site (for a cofactor or substrate) in the form of a pocket near one end of the barrel. Note that domains with similar folding patterns are said to have the same motif even though their constituent ***α helices*** and ***β sheets*** may differ in length.

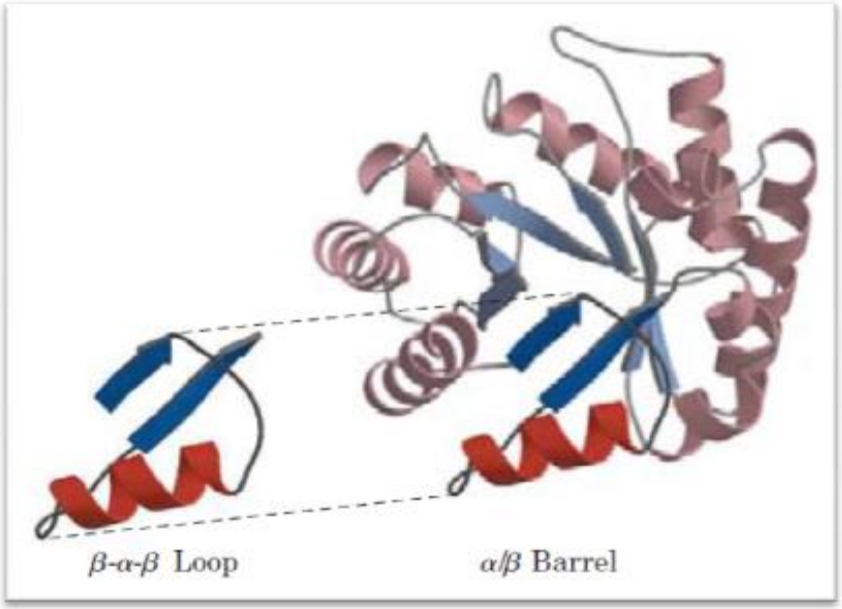


FIGURE 4–20 Constructing large motifs from smaller ones. The α/β barrel is a commonly occurring motif constructed from repetitions of the β-α-β loop motif. This α/β barrel is a domain of pyruvate kinase (a glycolytic enzyme) from rabbit (derived from PDB ID 1PKN).

Fibrous proteins provide structural support for cells and tissues

- Special types of helices are present in the two proteins a-keratin and collagen. These proteins form long fibers that serve a structural role.
- α-Keratin, which is the primary component of wool, hair, and skin, consists of two right-handed a helices intertwined to form a type of left-handed superhelix called an *α-helical coiled coil*.
- α-Keratin is a member of a superfamily of proteins referred to as coiled-coil proteins. In these proteins, two or more a helices can entwine to form a very stable structure, which can have a length of 1000 Å (100 nm, or 0.1 mm) or more.
- There are approximately 60 members of this family in humans, including intermediate filaments, proteins that contribute to the cell cytoskeleton (internal scaffolding in a cell), and the muscle proteins myosin and tropomyosin.
- Members of this family are characterized by a central region of 300 amino acids that contains imperfect repeats of a sequence of seven amino acids called a heptad repeat.

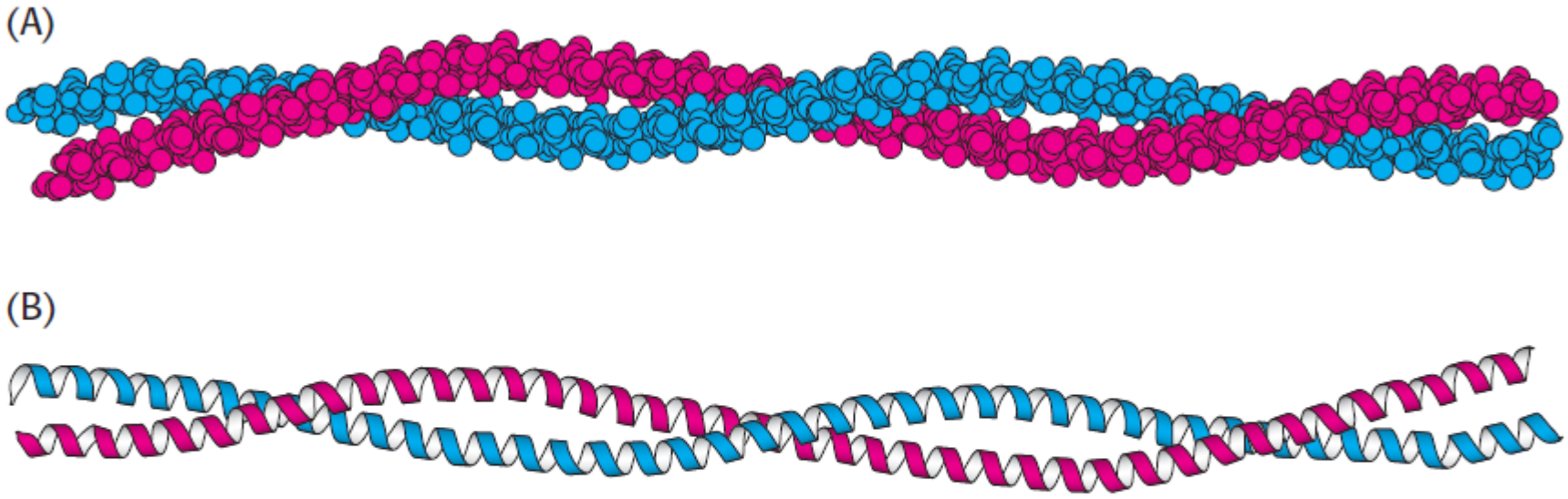


Figure 2.38 An α-helical coiled coil. (A) Space-filling model. (B) Ribbon diagram. The two helices wind around one another to form a superhelix. Such structures are found in many proteins, including keratin in hair, quills, claws, and horns. [Drawn from 1CIG.pdb.]

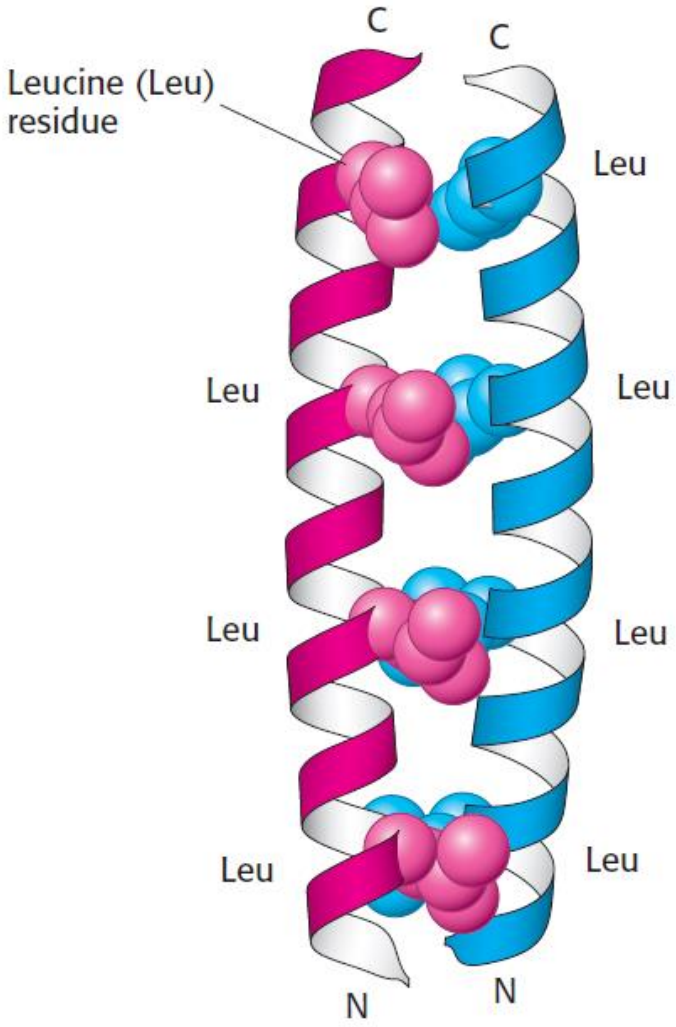
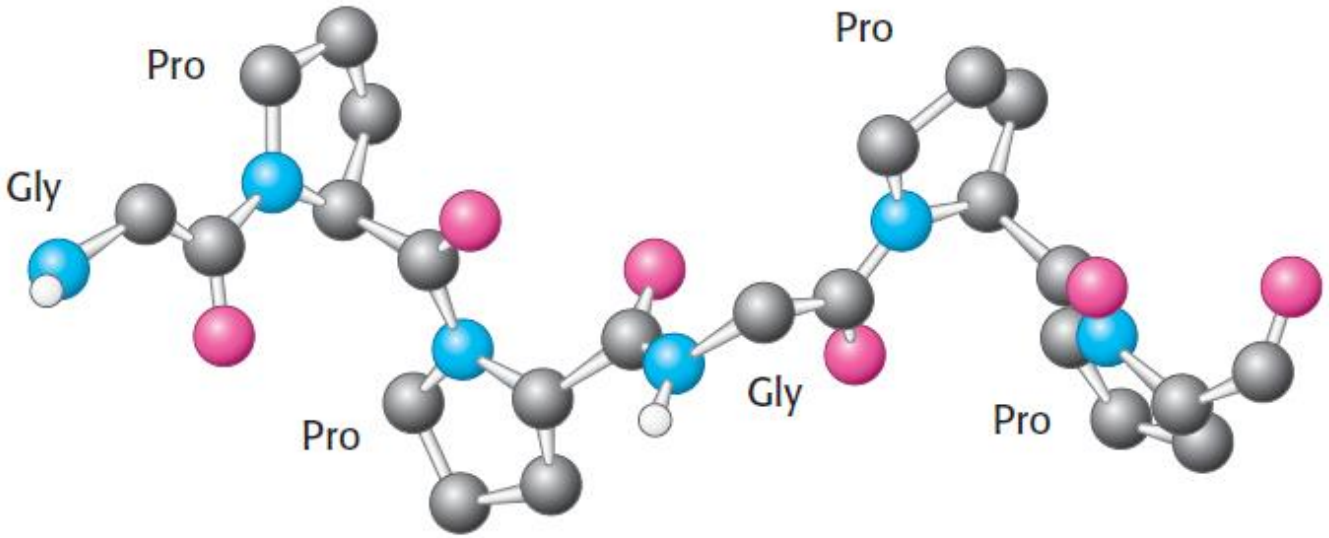


Figure 2.39 Heptad repeats in a coiled-coil protein. Every seventh residue in each helix is leucine. The two helices are held together by van der Waals interactions primarily between the leucine residues. [Drawn from 2ZTA.pdb.]

- The two helices in α-keratin are cross-linked by weak interactions such as van der Waals forces and ionic interactions. These interactions are facilitated by the fact that the left-handed supercoil alters the two right-handed a helices such that there are 3.5 residues per turn instead of 3.6.
- Thus, the pattern of side-chain interactions can be repeated every seven residues, forming the heptad repeats.
- Two helices with such repeats are able to interact with one another if the repeats are complementary.

For example, the repeating residues may be hydrophobic, allowing van der Waals interactions, or have opposite charge, allowing ionic interactions. In addition, the two helices may be linked by disulfide bonds formed by neighboring cysteine residues. The bonding of the helices accounts for the physical properties of wool, an example of an α-keratin. Wool is extensible and can be stretched to nearly twice its length because the α helices stretch, breaking the weak interactions between neighboring helices. However, the covalent disulfide bonds resist breakage and return the fiber to its original state once the stretching force is released. The number of disulfide bond cross-links further defines the fiber's properties. Hair and wool, having fewer cross-links, are flexible. Horns, claws, and hooves, having more cross-links, are much harder.

- A different type of helix is present in collagen, the most abundant protein of mammals. Collagen is the main fibrous component of skin, bone, tendon, cartilage, and teeth. This extracellular protein is a rod-shaped molecule, about 3000 Å long and only 15 Å in diameter.
- It contains three helical polypeptide chains, each nearly 1000 residues long. Glycine appears at every third residue in the amino acid sequence, and the sequence glycineproline- hydroxyproline recurs frequently. Hydroxyproline is a derivative of proline that has a hydroxyl group in place of one of the hydrogen atoms on the pyrrolidine rings.
- The collagen helix has properties different from those of the a helix. Hydrogen bonds within a strand are absent. Instead, the helix is stabilized by steric repulsion of the pyrrolidine rings of the proline and hydroxyproline residues.



13
-Gly-Pro-Met-Gly-Pro-Ser-Gly-Pro-Arg-
22
-Gly-Leu-Hyp-Gly-Pro-Hyp-Gly-Ala-Hyp-
31
-Gly-Pro-Gln-Gly-Phe-Gln-Gly-Pro-Hyp-
40
-Gly-Glu-Hyp-Gly-Glu-Hyp-Gly-Ala-Ser-
49
-Gly-Pro-Met-Gly-Pro-Arg-Gly-Pro-Hyp-
58
-Gly-Pro-Hyp-Gly-Lys-Asn-Gly-Asp-Asp-

Amino acid sequence of a part of a collagen chain. Every third residue is a glycine. Proline and hydroxyproline also are abundant.

The pyrrolidine rings keep out of each other's way when the polypeptide chain assumes its helical form, which has about three residues per turn. Three strands wind around one another to form a *superhelical cable* that is stabilized by hydrogen bonds between strands.

The hydrogen bonds form between the peptide NH groups of glycine residues and the CO groups of residues on the other chains. The hydroxyl groups of hydroxyproline residues also participate in hydrogen bonding, and the absence of the hydroxyl groups results in the disease scurvy.

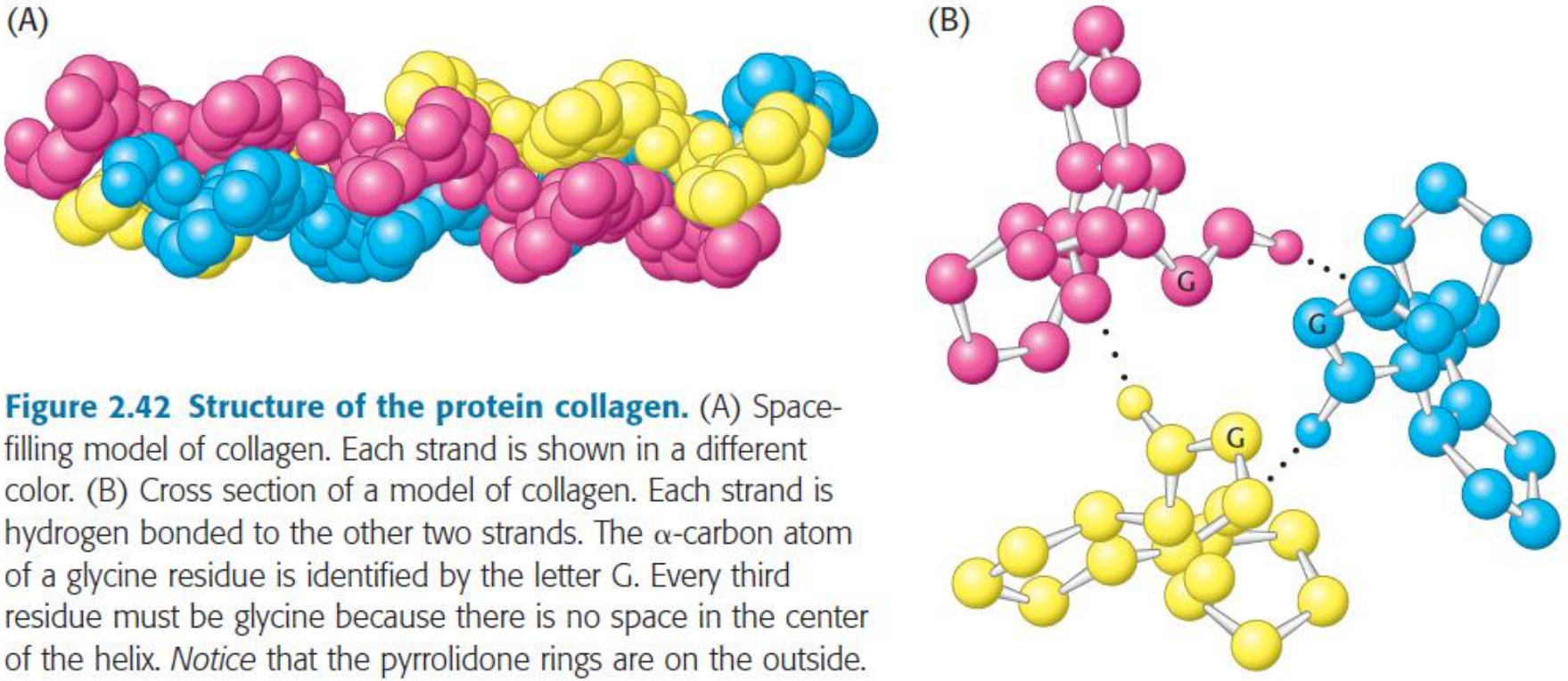


Figure 2.42 Structure of the protein collagen. (A) Space-filling model of collagen. Each strand is shown in a different color. (B) Cross section of a model of collagen. Each strand is hydrogen bonded to the other two strands. The α-carbon atom of a glycine residue is identified by the letter G. Every third residue must be glycine because there is no space in the center of the helix. *Notice* that the pyrrolidone rings are on the outside.

The inside of the triple-stranded helical cable is very crowded and accounts for the requirement that glycine be present at every third position on each strand. *The only residue that can fit in an interior position is glycine. The amino acid residue on either side of glycine is located* on the outside of the cable, where there is room for the bulky rings of proline and hydroxyproline residues.

The importance of the positioning of glycine inside the triple helix is illustrated in the disorder osteogenesis imperfecta, also known as brittle bone disease. In this condition, which can vary from mild to very severe, other amino acids replace the internal glycine residue. This replacement leads to a delayed and improper folding of collagen, and the accumulation of defective collagen results in cell death. The most serious symptom is severe bone fragility. Defective collagen in the eyes causes the whites of the eyes to have a blue tint (blue sclera).

Tertiary Structure: Water-Soluble Proteins Fold into Compact Structures with Nonpolar Cores

Myoglobin, the oxygen carrier in muscle, is a single polypeptide chain of 153 amino acids (see Chapter 7). The capacity of myoglobin to bind oxygen depends on the presence of *heme,* a nonpolypeptide *prosthetic (helper) group* consisting of protoporphyrin IX and a central iron atom. *Myoglobin is an extremely compact molecule*. Its overall dimensions are $45 \times 35 \times 25$ Å, an order of magnitude less than if it were fully stretched out (Figure 2.43). About 70% of the main chain is folded into eight α helices, and much of the rest of the chain forms turns and loops between helices.

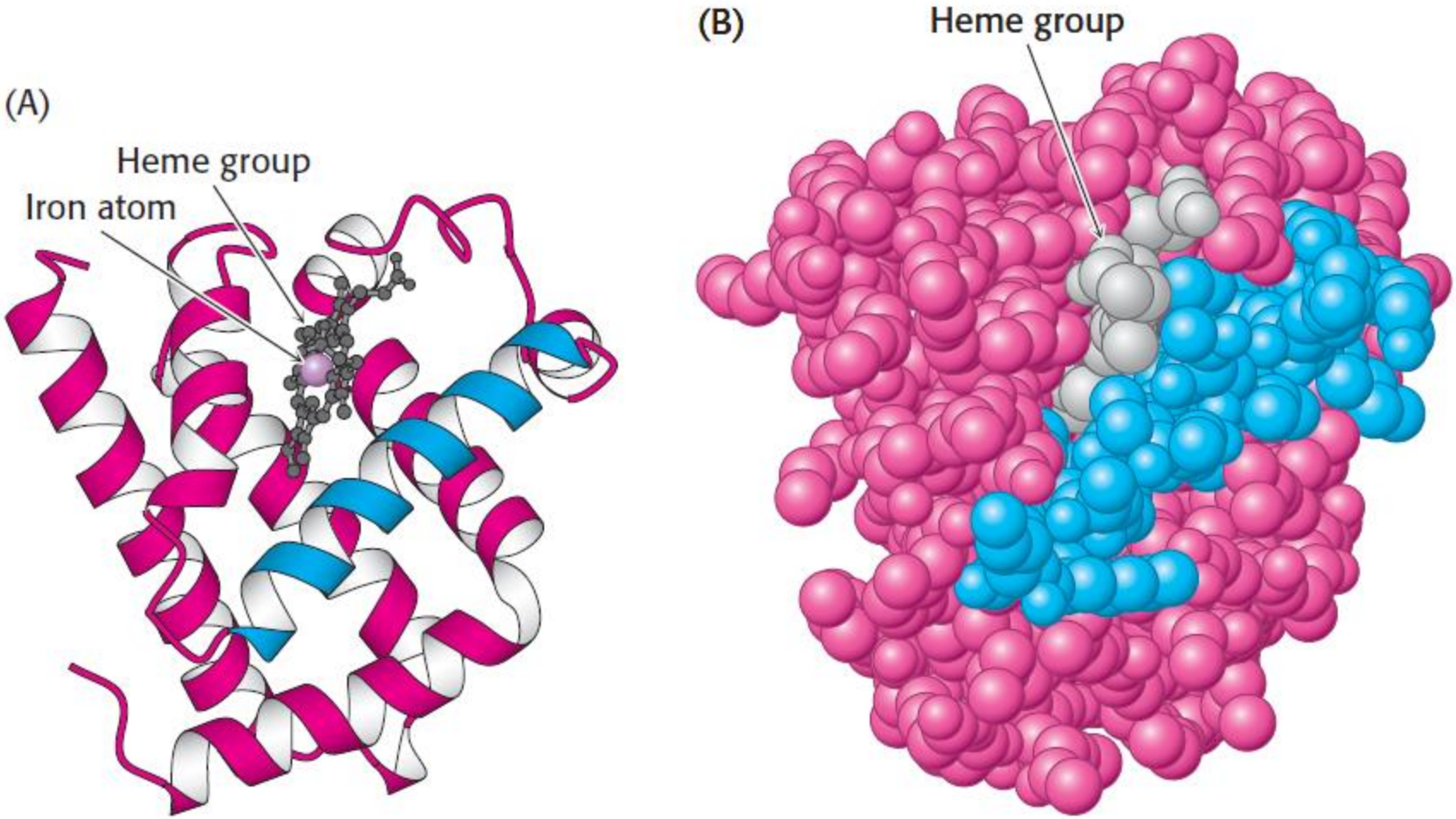


Figure 2.43 Three-dimensional structure of myoglobin. (A) A ribbon diagram shows that the protein consists largely of α helices. (B) A space-filling model in the same orientation shows how tightly packed the folded protein is. *Notice* that the heme group is nestled into a crevice in the compact protein with only an edge exposed. One helix is blue to allow comparison of the two structural depictions. [Drawn from 1A6N.pdb.]

The folding of the main chain of myoglobin, like that of most other proteins, is complex and devoid of symmetry. The overall course of the polypeptide chain of a protein is referred to as its *tertiary structure*. A unifying principle emerges from the distribution of side chains. The striking fact is that *the interior consists almost entirely of nonpolar residues* such as leucine, valine, methionine, and phenylalanine (Figure 2.44). Charged residues such as aspartate, glutamate, lysine, and arginine are absent from the inside of myoglobin. The only polar residues inside are two histidine residues, which play critical roles in binding iron and oxygen. The outside of myoglobin, on the other hand, consists of both polar and nonpolar residues. The space-filling model shows that there is very little empty space inside.

This contrasting distribution of polar and nonpolar residues reveals a key facet of protein architecture. In an aqueous environment, protein folding is driven by the strong tendency of hydrophobic residues to be excluded from water.

A system is more thermodynamically stable when hydrophobic groups are clustered rather than extended into the aqueous surroundings. The polypeptide chain therefore folds so that its hydrophobic side chains are buried and its polar, charged chains are on the surface.

Many α helices and β strands are amphipathic; that is, the α helix or β strand has a hydrophobic face, which points into the protein interior, and a more polar face, which points into solution.

The fate of the main chain accompanying the hydrophobic side chains is important, too. An unpaired peptide NH or CO group markedly prefers water to a nonpolar milieu.

The secret of burying a segment of main chain in a hydrophobic environment is to pair all the NH and CO groups by hydrogen bonding.

This pairing is neatly accomplished in an α helix or β sheet. Van der Waals interactions between tightly packed hydrocarbon side chains also contribute to the stability of proteins.

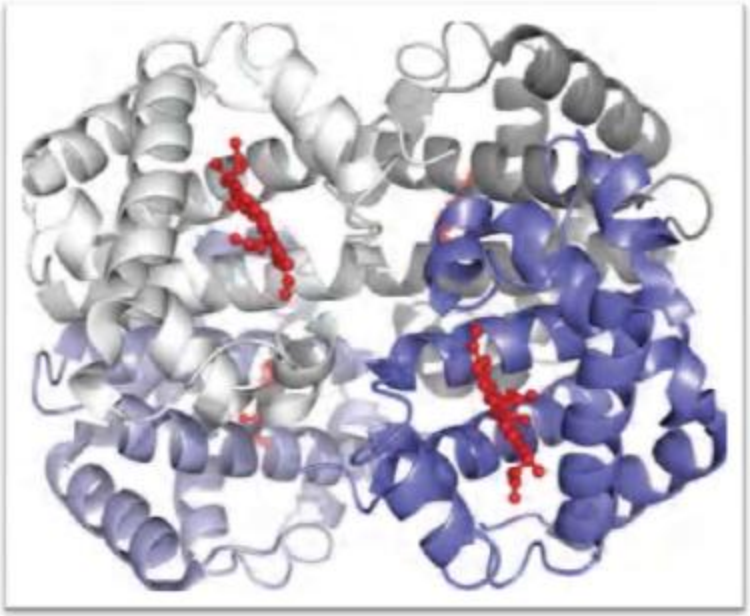
We can now understand why the set of 20 amino acids contains several that differ subtly in size and shape. They provide a palette from which to choose to fill the interior of a protein neatly and thereby maximize van der Waals interactions, which require intimate contact.

Some proteins that span biological membranes are "the exceptions that prove the rule" because they have the reverse distribution of hydrophobic and hydrophilic amino acids. For example, consider porins, proteins found in the outer membranes of many bacteria (Figure 2.45). Membranes are built largely of hydrophobic alkane chains (Section 12.2). Thus, porins are covered on the outside largely with hydrophobic residues that interact with the neighboring alkane chains. In contrast, the center of the protein contains many charged and polar amino acids that surround a water-filled channel running through the middle of the protein. Thus, because porins function in hydrophobic environments, they are "inside out" relative to proteins that function in aqueous solution.

Protein Quaternary Structures

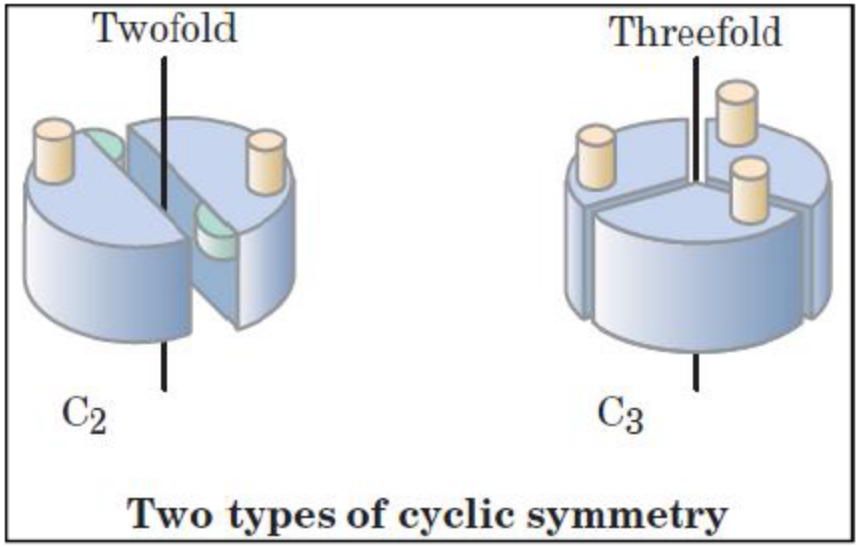
- ✓ The first oligomeric protein to have its three dimensional structure determined was hemoglobin (*Mr 64,500),* which contains four polypeptide chains and four heme prosthetic groups, in which the iron atoms are in the ferrous (Fe^{2+}) state.
- ✓ The protein portion, the globin, consists of two ***α chains*** (141 residues each) and two ***β chains*** (146 residues each).

Because hemoglobin is four times as large as myoglobin, much more time and effort were required to solve its three-dimensional structure by x-ray analysis, finally achieved by Max Perutz, John Kendrew, and their colleagues in 1959.



- ✓ The subunits of hemoglobin are arranged in symmetric pairs, each pair having one ***α*** and one ***β subunit***. Hemoglobin can therefore be described either as a tetramer or as a dimer of ***αβ protomers***.

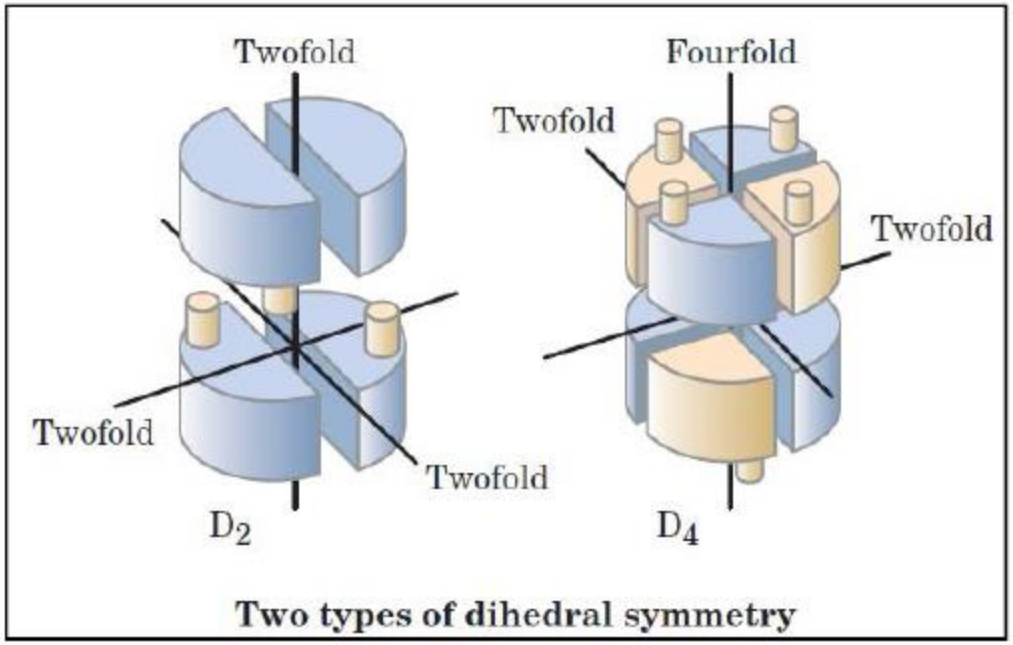
1. Identical subunits of multimeric proteins are generally arranged in one or a limited set of symmetric patterns. Oligomers can have either **rotational symmetry or helical symmetry;** that is, individual subunits can be superimposed on others by rotation about one or more rotational axes or by a helical rotation.



Two types of cyclic symmetry

2. There are several forms of rotational symmetry. The simplest is **cyclic symmetry**, involving rotation about a single axis. If subunits can be superimposed by rotation about a single axis, the protein has a symmetry defined as C_n *(C for cyclic, n for the number of subunits related by the axis*). The axis itself is described as an *n fold* rotational axis. The ***αβ protomers*** of hemoglobin are related by C_2 symmetry.

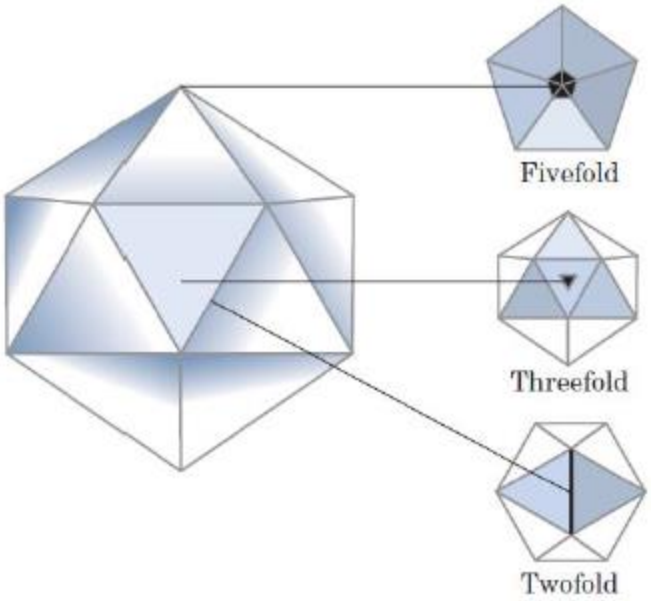
A somewhat more complicated rotational symmetry is **dihedral symmetry**, in which a twofold rotational axis intersects an *n-fold axis* at right angles; this symmetry is defined as D_n. A protein with dihedral symmetry has $2n$ *protomers*.



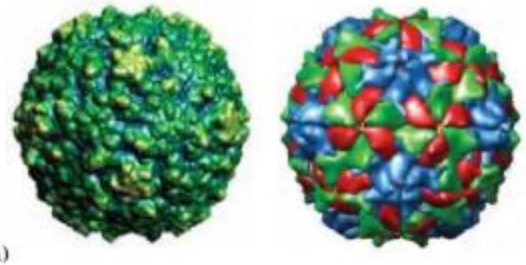
Two types of dihedral symmetry

Proteins with cyclic or dihedral symmetry are particularly common. More complex rotational symmetries are possible, but only a few are regularly encountered in proteins. One example is **icosahedral symmetry**.

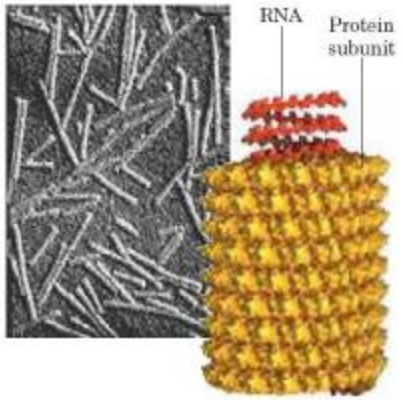
An icosahedron is a regular 12-cornered polyhedron with 20 equilateral triangular faces. Each face can be brought to coincidence with another face by rotation about one or more of three axes. This is a common structure in virus coats, or capsids. The human poliovirus has an icosahedral capsid



Icosahedral symmetry



(a)



(b)

Protein Denaturation and Folding

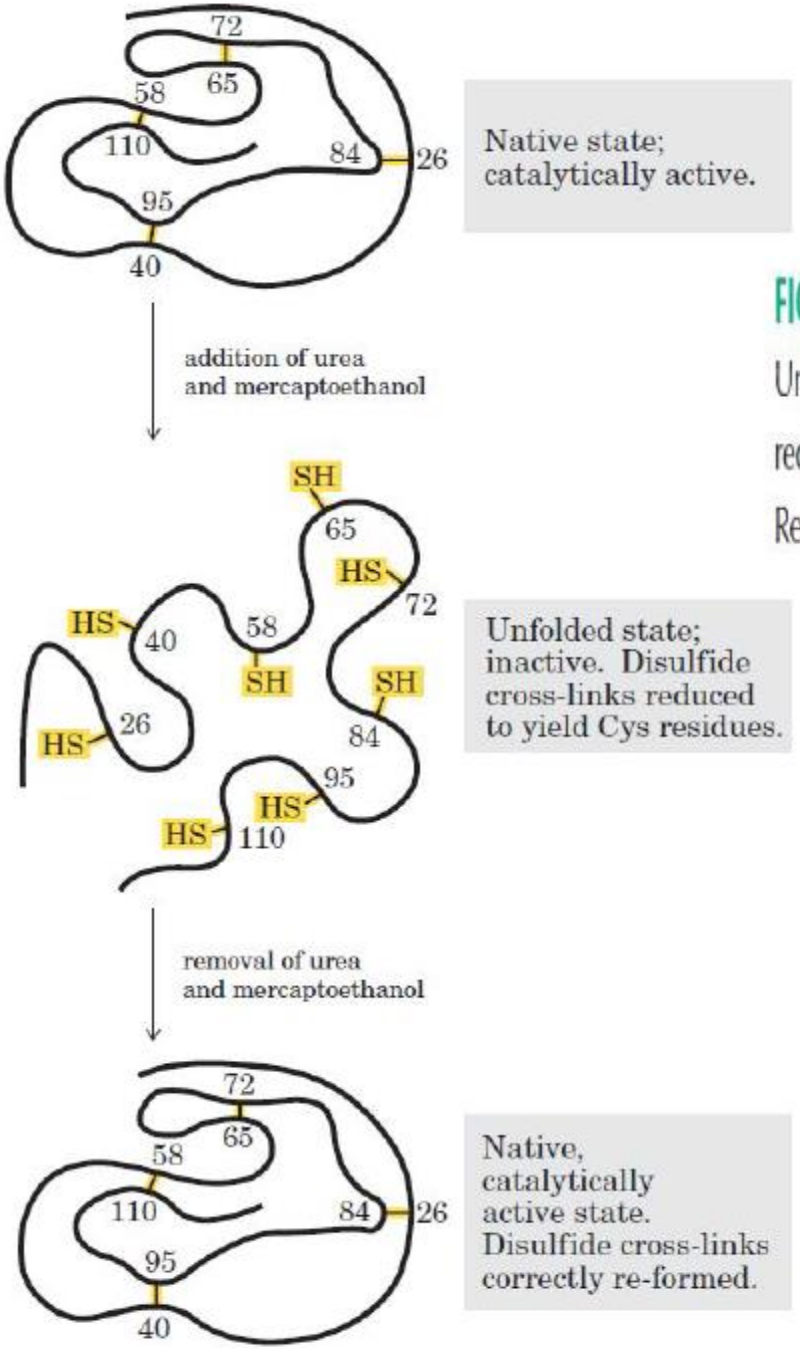


FIGURE 4–26 Renaturation of unfolded, denatured ribonuclease. Urea denatures the ribonuclease, and mercaptoethanol ($HOCH_2CH_2SH$) reduces and thus cleaves the disulfide bonds to yield eight Cys residues. Renaturation involves reestablishing the correct disulfide cross-links.