

Proteins 3: 2° & 3° Structure & Folding and Stability

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Applies Biosciences

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Outline

- Secondary Structure: Regular Ways to Fold the Polypeptide Chain
- Fibrous Proteins: Structural Materials of Cells and Tissues
- Globular Proteins: Tertiary Structure and Functional Diversity
- Factors Determining Secondary and Tertiary Structure
- Dynamics of Globular Protein Structure
- Prediction of Protein Secondary and Tertiary Structure
- Quaternary Structure of Proteins

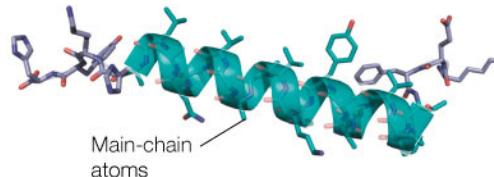
1° , 2° , 3° & 4° Structure: haemoglobin

...KEFTPPVQAAYQKVAGVANALAHKYH...

(a) Primary structure (amino acid sequence):

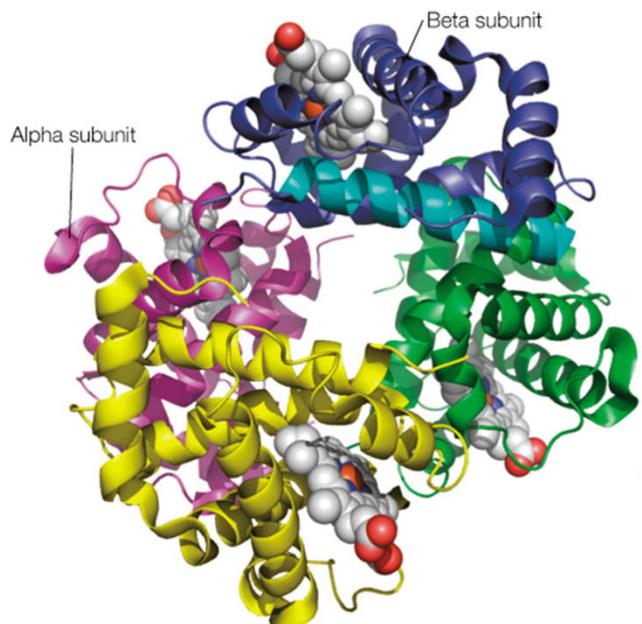
A portion of the amino acid sequence of human beta globin is shown. The sequence highlighted in cyan adopts a helical conformation, and is shown in the same orientation in parts (b-d).

Some parts of the primary sequence adopt a local regular repeating structure (" 2° structure")



(b) Secondary structure:

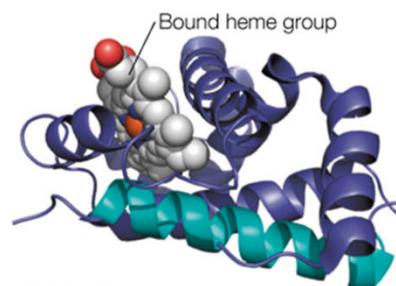
A stick representation of the amino acid sequence from part (a) is shown. Superimposed on the stick structure is a cartoon rendering of



(d) Quaternary structure:

Four separate protein subunits, two alpha subunits (magenta and green) and two beta subunits (yellow and blue/cyan) associate to form the fully assembled hemoglobin protein. The four subunits are shown in cartoon rendering with hemes in space-filling display (PDB ID: 2hhb).

Several 2° structure elements associate along their hydrophobic surfaces to give a stably folded structure (" 3° structure")



(c) Tertiary structure:

The entire beta globin chain is shown in its well-defined folded structure. As in myoglobin the helical regions interact to define the folded structure, which binds a heme (shown in space-filling display).

FIGURE 6.2 The four levels of structural organization in proteins.



Naturally occurring secondary structures in proteins

Figure 6.4

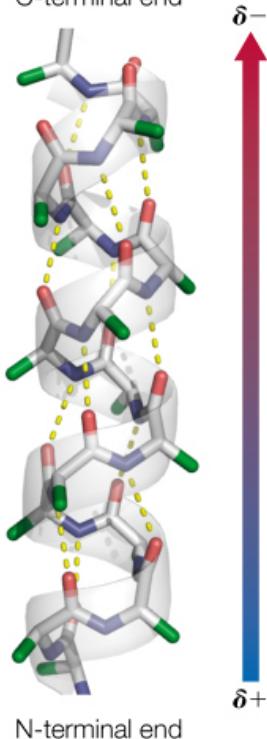
The right-handed α helix,

β sheet,

and

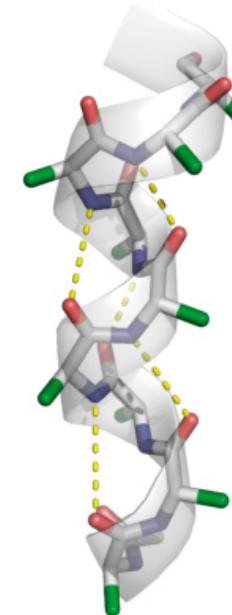
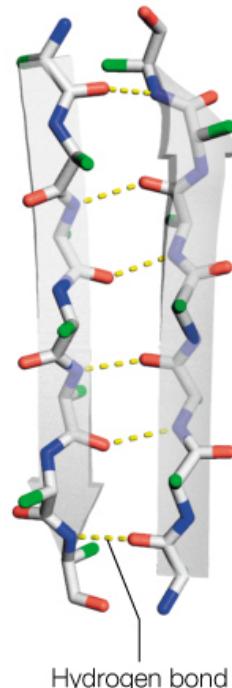
3_{10} helix.

C-terminal end



N-terminal end

- (a) In the α helix, the hydrogen bonds are within a contiguous stretch of amino acids and are almost parallel to the helix axis. This orientation of the amide bonds in the helix gives rise to a helical macrodipole moment shown by the arrow (see Figure 2.5). The N-terminal end of the helix has partial (+) charge character, and the C-terminal end has partial (−) charge character.
- (b) In the β sheet, the hydrogen bonds are between adjacent strands (only two strands are shown here), which are not necessarily contiguous in the primary sequence. In this structure, the hydrogen bonds are nearly perpendicular to the chains. Note that in the cartoon rendering a strand is shown by a flat arrow, where the head of the arrow points to the C-terminus of the strand.



- (c) The 3_{10} helix is found in proteins but is less common than the α helix. Note that, compared to the α helix, the 3_{10} helix forms a tighter spiral.



Common Secondary Structure Elements

Side chain positions in an α -helix

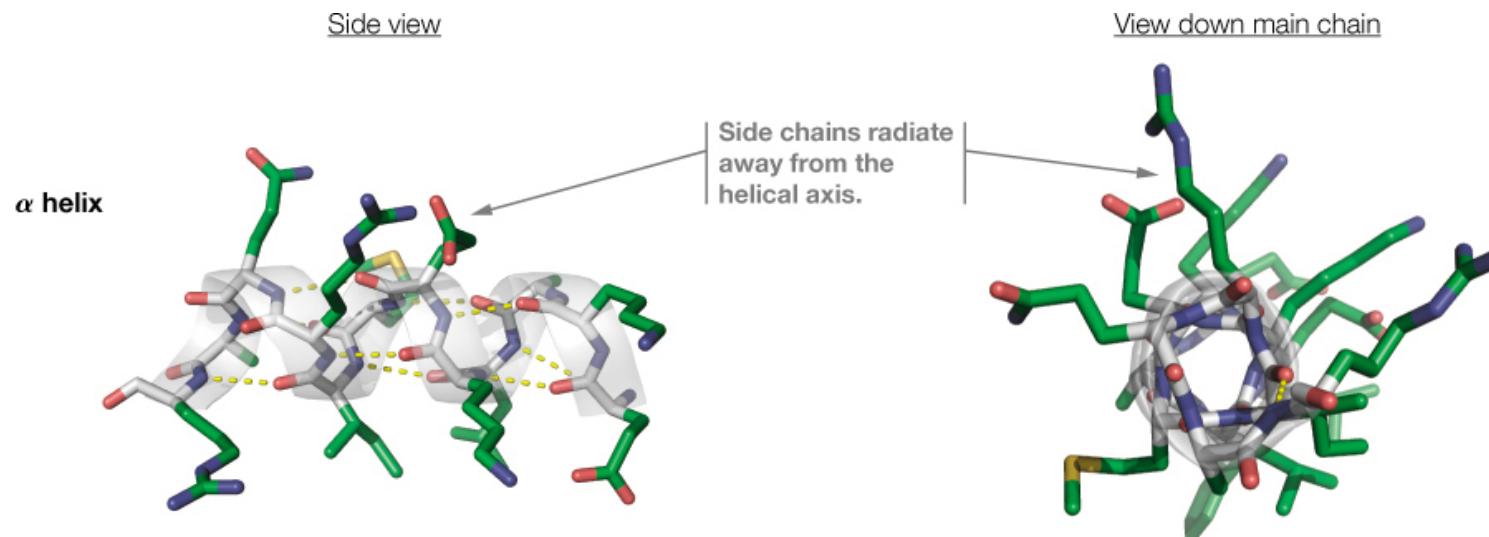


FIGURE 6.7 The positions of side chains in the α helix and β sheet.

In an α -helix, the side chains radiate away from the helical axis. Its center consists backbone atoms, closely packed. The hydrogen bonds that stabilize the helix are shown as yellow dashes.

Common Secondary Structure Elements

Side chain positions in a β -sheet

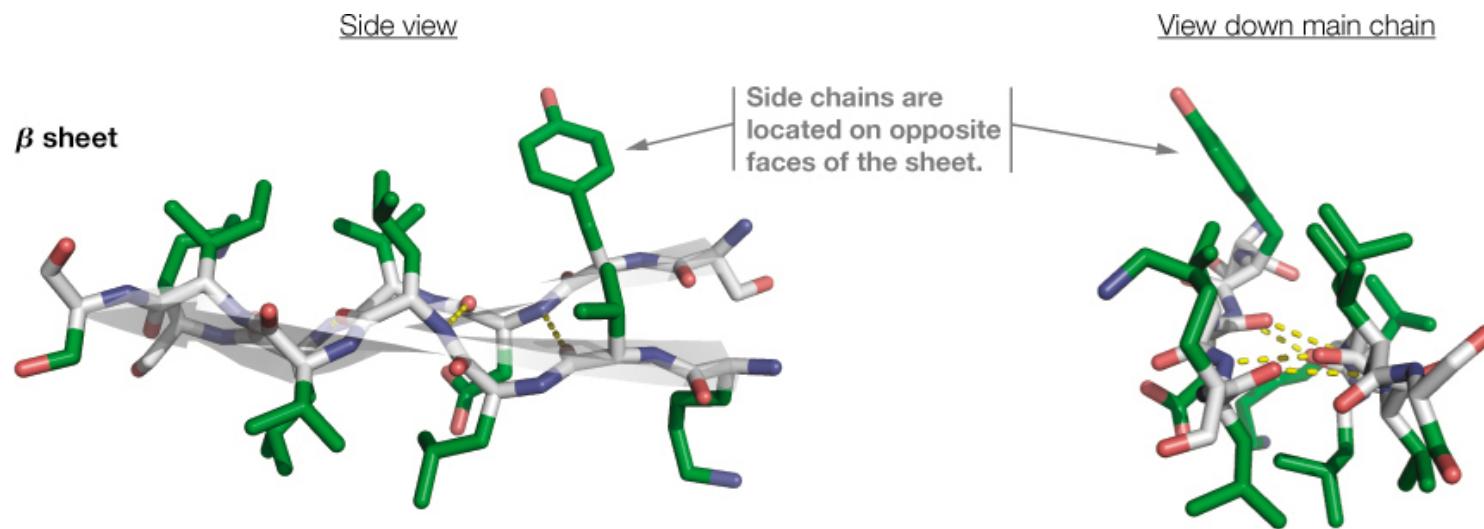


FIGURE 6.7 The positions of side chains in the α helix and β sheet.

In a β -sheet, neighboring side chains are located on opposite faces of the sheet, which is stabilized by main-chain hydrogen bonds between adjacent β -strands.

Rotations around the N-C_α and the C_α-C bonds of the protein backbone

- Free rotation is only allowed about the C_α carbons.
 - However, this rotation is restricted by steric interactions.
- Such rotation is described by two torsional angles termed ϕ (between N and C_α) and ψ (between C_α and the carbonyl C).
- Torsions refer to two different residues.
- Each residue maintains its peptide bond planarity of the atoms involved in the peptide bond.
- Steric interference of adjacent R groups leads to only some allowed Φ (phi) and Ψ (psi) values.

φ (phi), ψ (psi)

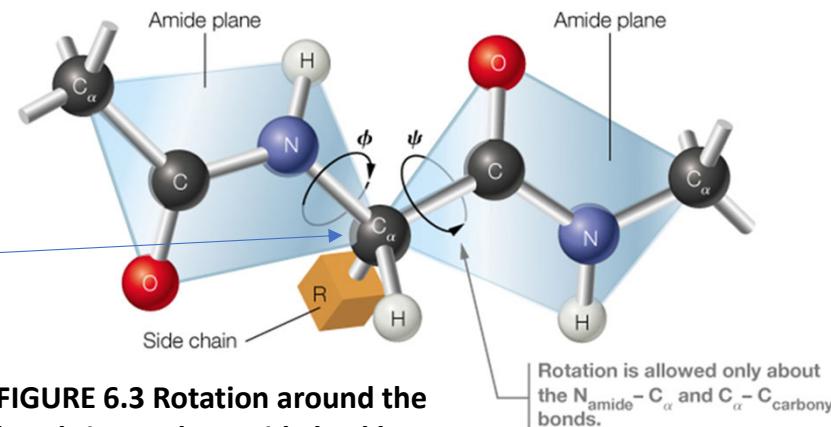
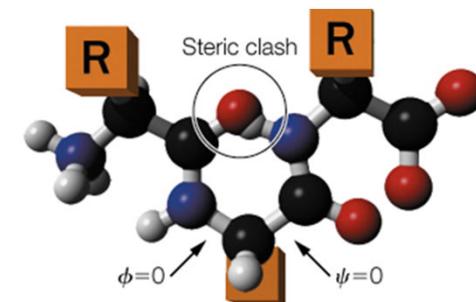


FIGURE 6.3 Rotation around the bonds in a polypeptide backbone.

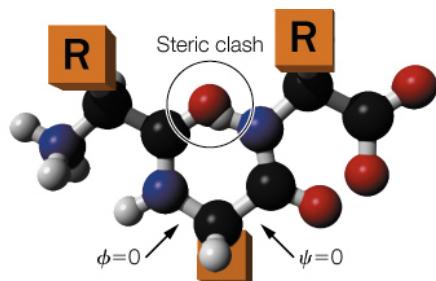


(a) A sterically nonallowed conformation. The conformation $\phi = 0^\circ$, $\psi = 0^\circ$ is not allowed in any polypeptide chain because of the steric crowding between main-chain atoms. A tripeptide is shown, where the central amino acid has $\phi = 0^\circ$ and $\psi = 0^\circ$. Notice that the carbonyl oxygen of residue #1 (on the left) would clash with the amide hydrogen of residue #3 (on the right).

Figure 6.8, Steric interactions determine peptide conformation.

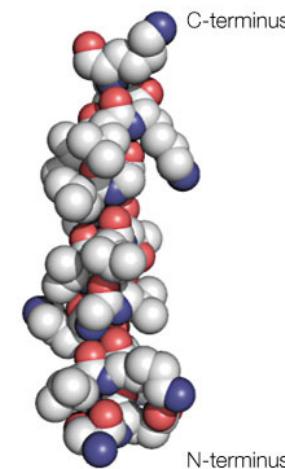
Common Secondary Structure Elements

Steric Interactions determine peptide conformation



(a) A sterically nonallowed conformation. The conformation $\phi = 0^\circ$, $\psi = 0^\circ$ is not allowed in any polypeptide chain because of the steric crowding between main-chain atoms. A tripeptide is shown, where the central amino acid has $\phi = 0^\circ$ and $\psi = 0^\circ$. Notice that the carbonyl oxygen of residue #1 (on the left) would clash with the amide hydrogen of residue #3 (on the right).

Certain ϕ and ψ angles result in steric clashes, where atoms are closer than their van der Waals radii. These angles and related conformations are not allowed.



(b) The atoms in a helix are closely packed but do not clash sterically. Here, a segment of an α helix in sperm whale myoglobin is shown as a space-filling model (this is the longer green helix in Figure 6.1; PDB ID: 1mbn).

The backbone of an α helix results in closely packed atoms that do not sterically clash.

FIGURE 6.8 Steric interactions determine peptide conformation.

Ramachandran Plots

Graphing sterically allowed ϕ and ψ angles

- poly-L-alanine

- white areas are from theoretical predictions
- Glycines can go anywhere

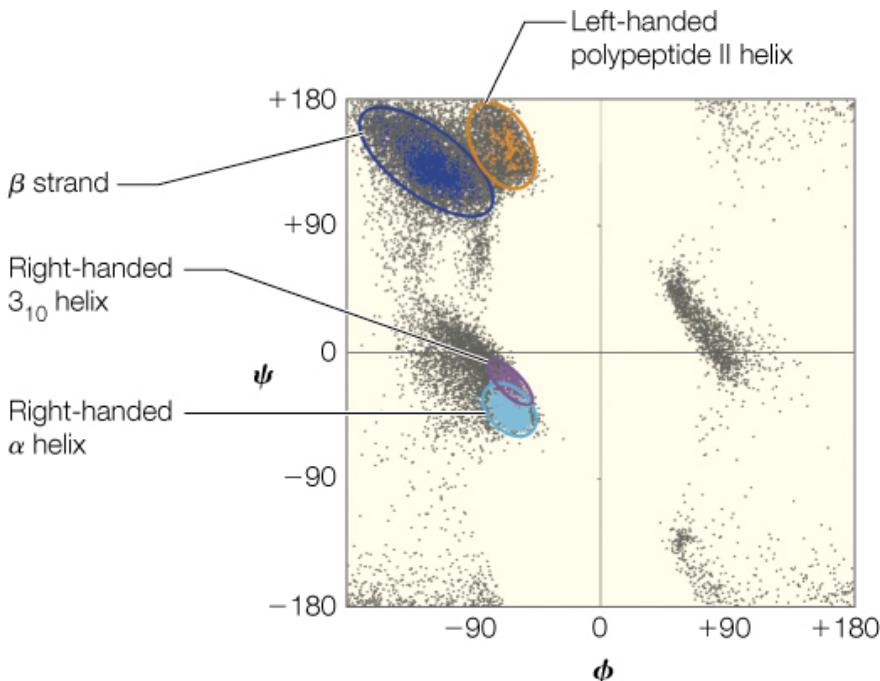


FIGURE 6.11 Observed values of ϕ and ψ from protein structural data.

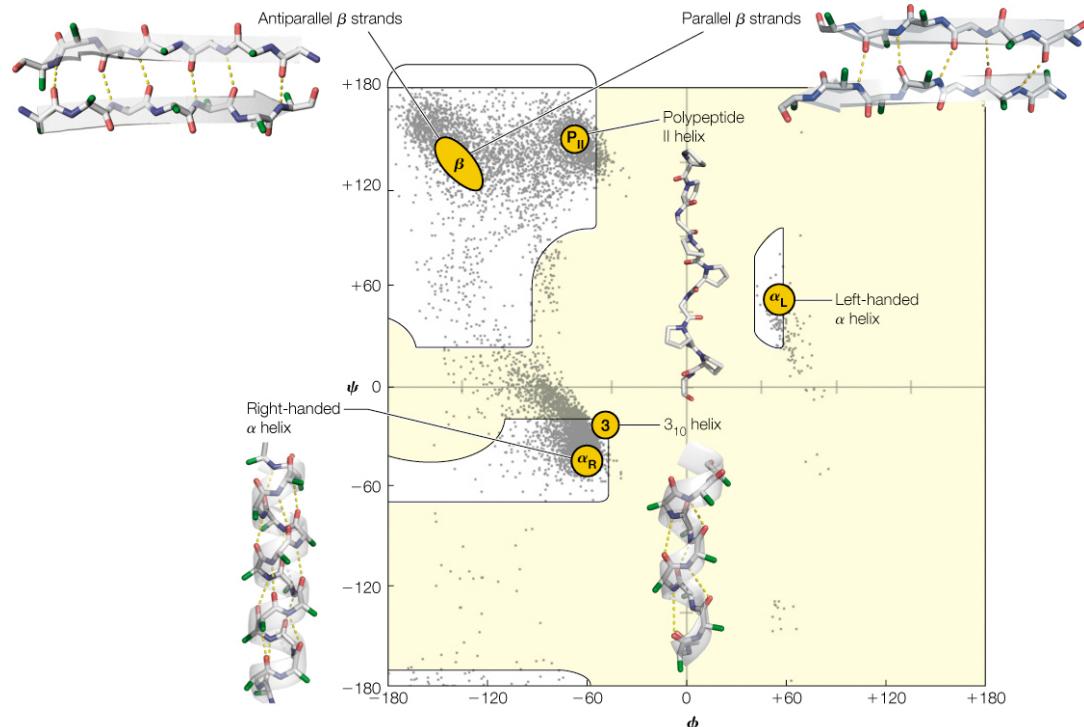


TABLE 6.2 Ranges of allowed ϕ and ψ angles for some polypeptide secondary structures

Structure Type	ϕ	ψ
β strand	-150° to -100°	$+120^\circ$ to $+160^\circ$
α helix	-70° to -60°	-50° to -40°
3_{10} helix	-70° to -60°	-30° to -10°
Polypeptide II helix	-80° to -60°	$+130^\circ$ to $+160^\circ$

Data from *Protein Science* 18:1321–1325 (2009), S. A. Hollingsworth, D. S. Berkholz, and P. A. Karplus, On the occurrence of linear groups in proteins.

FIGURE 6.9 A Ramachandran plot for poly-L-alanine.

Fibrous Proteins as Structural Materials

- Fibrous proteins are elongated molecules with well-defined secondary structures
- Examples include:
 - keratin—hair, fingernails, feathers, scales, or intermediate filaments (intracellular)
 - fibroin—silk cocoons
 - collagen—abundant connective tissue protein; matrix material in bone on which mineral components precipitate

- High abundance of certain amino acids in fibrous proteins

TABLE 6.3 Amino acid compositions of some fibrous proteins

Amino Acid	α -Keratin (wool)	Fibroin (silk)	Collagen (bovine tendon)	All Proteins ^c
Gly	8.1	44.6	32.7	7.9
Ala	5.0	29.4	12.0	8.7
Ser	10.2	12.2	3.4	5.8
Glu + Gln	12.1	1.0	7.7	6.6 (3.7)
Cys	11.2	0	0	1.3
Pro	7.5	0.3	22.1 ^a	4.7
Arg	7.2	0.5	5.0	5.0
Leu	6.9	0.5	2.1	8.9
Thr	6.5	0.9	1.6	5.6
Asp + Asn	6.0	1.3	4.5	5.9 (4.2)
Val	5.1	2.2	1.8	7.2
Tyr	4.2	5.2	0.4	3.5
Ile	2.8	0.7	0.9	5.5
Phe	2.5	0.5	1.2	4.0
Lys	2.3	0.3	3.7 ^b	5.5
Trp	1.2	0.2	0	1.5
His	0.7	0.2	0.3	2.4
Met	0.5	0	0.7	2.0

Note: The three most abundant amino acids in each protein are indicated in magenta. Values are given in mole percent.

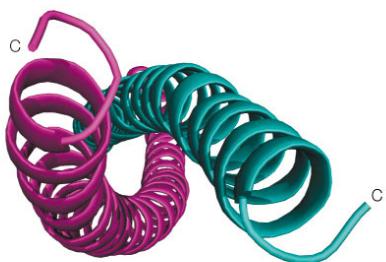
^aAbout 39% of this is hydroxyproline.

^bAbout 14% of this is hydroxylysine.

^cData from *Journal of Chemical Information and Modeling* (2010) 50:690–700, J. M. Otaki, M. Tsutsumi, T. Gotoh, and H. Yamamoto, Secondary structure characterization based on amino acid composition and availability in proteins.

Examples of fibrous proteins

In α -keratin, large hydrophobic residues repeat every four positions. The α -helix has 3.6 residues per turn, giving each helix a hydrophobic side, which defines the interface between two long helices in the coiled-coil structure typical of keratin.



(b) View looking down the axis of the coiled-coil from the C-terminal end of the two monomers (side chains removed for clarity).



(a) Side view of two monomers interacting via a parallel coiled-coil. N- and C-termini are indicated.

FIGURE 6.12 The coiled-coil structure of α -keratin intermediate filaments.

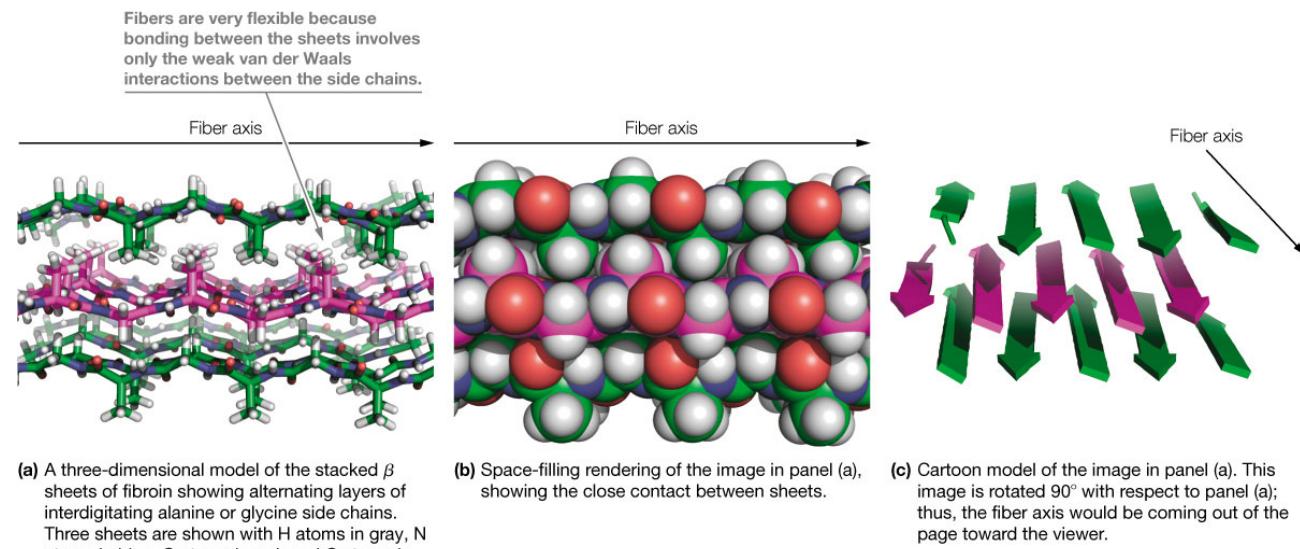
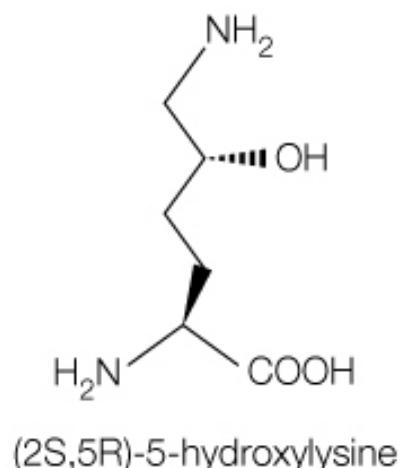
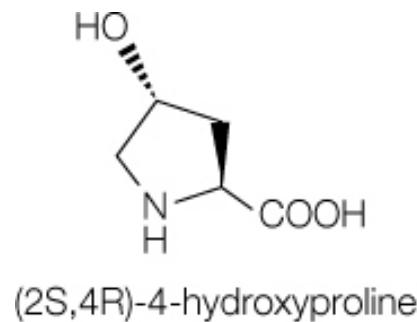


FIGURE 6.13 Theoretical model for the structure of silk fibroin.

The extensive close-packed β sheet of fibroin is interrupted by compact folded regions which provide some elasticity.

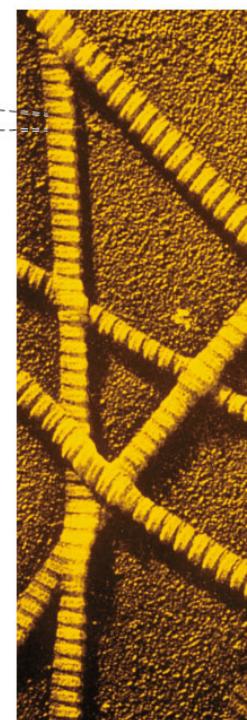
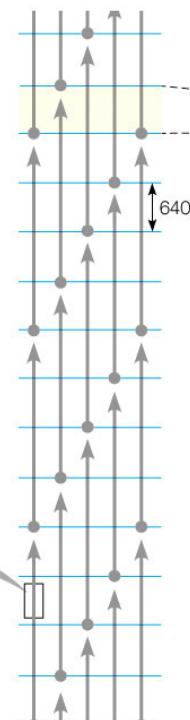
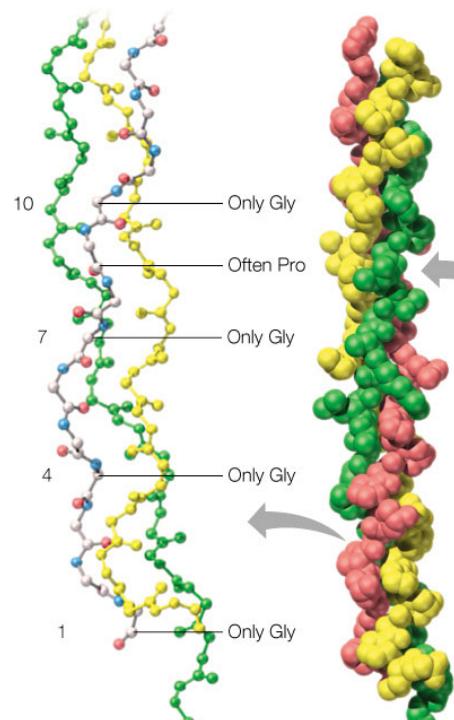
Collagen



- It is an abundant connective tissue protein; matrix material in bone, on which mineral components precipitate; triple-strand left-handed helix
- It contains hydroxyproline (Hyp) and hydroxylysine
- G-X-Y tripeptide motif, where X is Pro and Y is Pro or Hyp, lends itself to triple-strand structure
- Polypeptide chains are crosslinked and glycosylated
- Vitamin C (ascorbic acid) is a cofactor required for proline hydroxylation; vitamin C deficiency (scurvy) leads to collagen degeneration



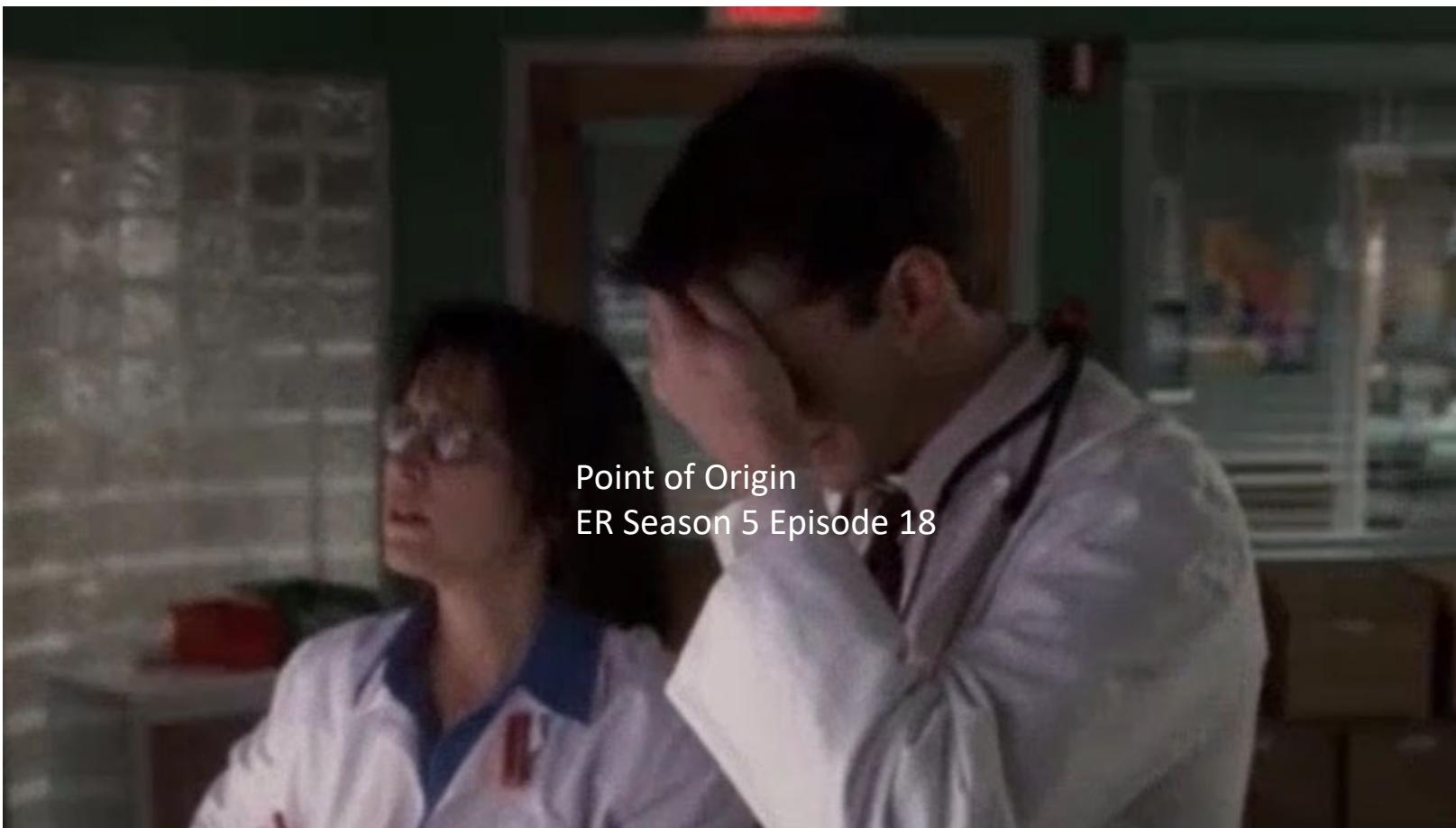
Collagen



Collagen diseases

Collagen disease	COL1:	Osteogenesis imperfecta · Ehlers–Danlos syndrome, types 1, 2, 7
	COL2:	Hypochondrogenesis · Achondrogenesis type 2 · Stickler syndrome · Marshall syndrome · Spondyloepiphyseal dysplasia congenita · Spondyloepimetaphyseal dysplasia, Strudwick type · Kniest dysplasia (see also C2/11)
	COL3:	Ehlers–Danlos syndrome, types 3 & 4 (Sack–Barabas syndrome)
	COL4:	Alport syndrome
	COL5:	Ehlers–Danlos syndrome, types 1 & 2
	COL6:	Bethlem myopathy · Ullrich congenital muscular dystrophy
	COL7:	Epidermolysis bullosa dystrophica · Recessive dystrophic epidermolysis bullosa · Bart syndrome · Transient bullous dermolysis of the newborn
	COL8:	Fuchs' dystrophy 1
	COL9:	Multiple epiphyseal dysplasia 2, 3, 6
	COL10:	Schmid metaphyseal chondrodysplasia
	COL11:	Weissenbacher–Zweymüller syndrome · Otospondylomegaepiphyseal dysplasia (see also C2/11)
	COL17:	Bullous pemphigoid
	COL18:	Knobloch syndrome





Point of Origin
ER Season 5 Episode 18

Osteogenesis imperfecta:

<https://www.metacritic.com/tv/er/season-5/episode-18-point-of-origin>

Hydrogen bonds in an α -helix: from residue i to residue $i+4$: 1-5, 2-6, etc.

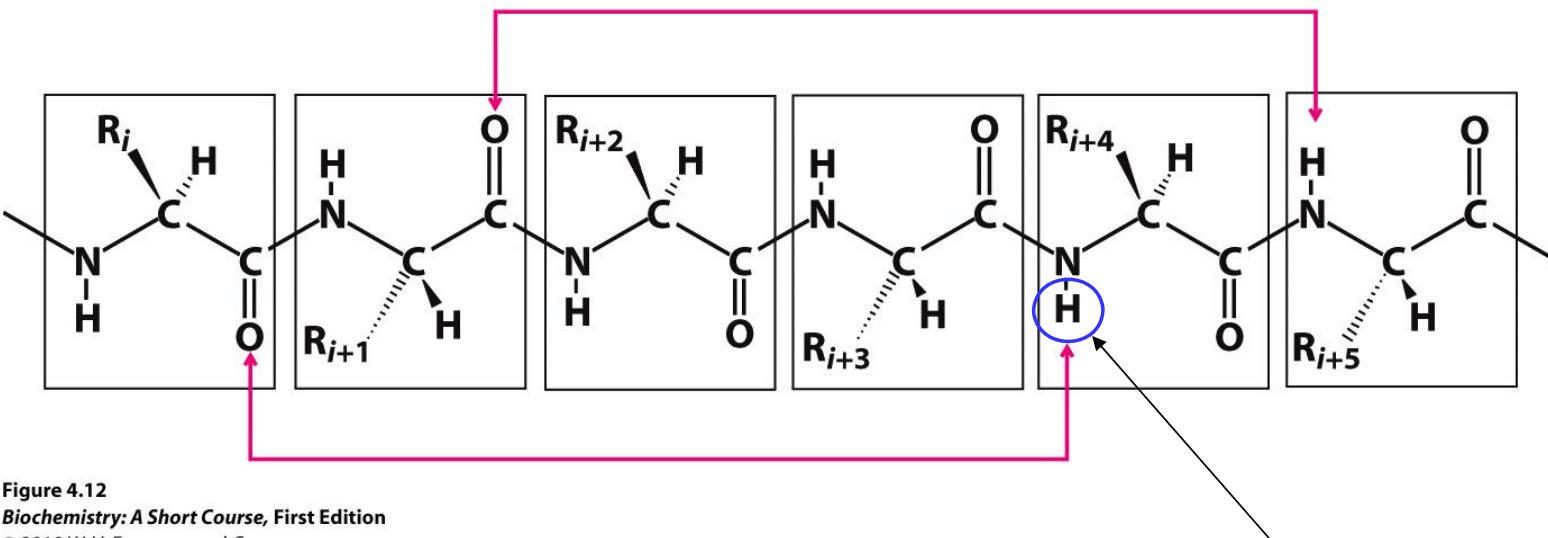


Figure 4.12
Biochemistry: A Short Course, First Edition
© 2010 W.H. Freeman and Company

Proline residues do not have this free H atom, because of the ring structure of its side chain bonding back to the α -N – they therefore break α -helices!

Hydrogen bond patterns in anti-parallel and parallel β -sheets

- ❖ β -strands:
 - opposite direction – **anti-parallel** or
 - same direction – **parallel**
- Look at protein chain direction: N- to C- for each amino acid

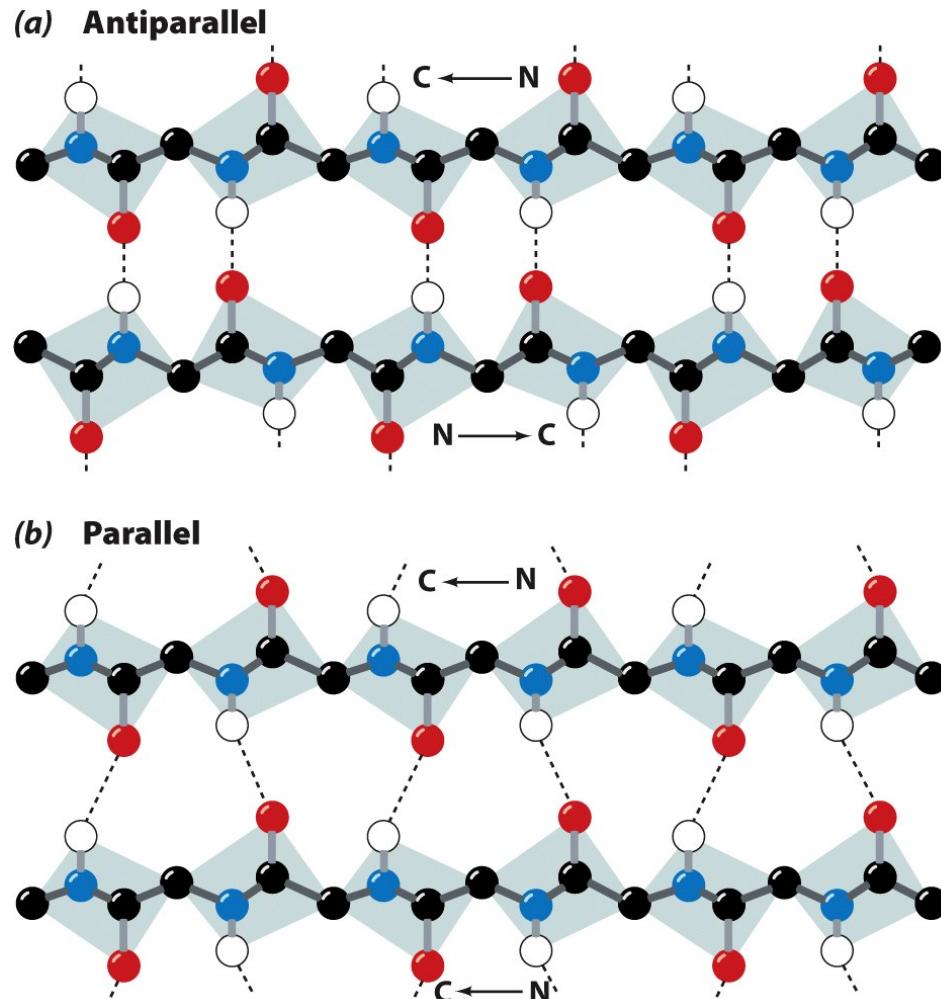


Figure 6-9
Illustration, Irving Geis. Image from the Irving Geis Collection/Howard Hughes Medical Institute. Rights owned by HHMI. Reproduction by permission only.

Connecting Adjacent β Strands by loops or turns

(a)



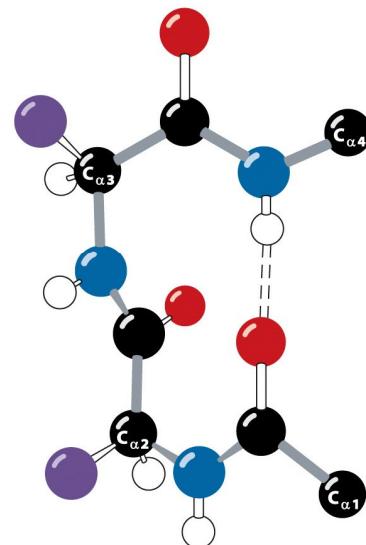
(b)



Figure 6-13
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- Turns are short hydrogen bonded segments
- Loops and turns for links between:
 - helices;
 - strands; and
 - helices and strands.

(a) Type I



(b) Type II

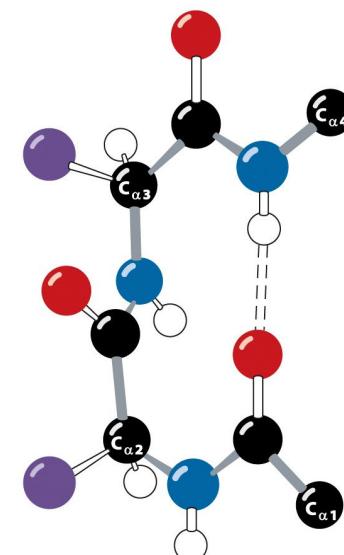


TABLE 6-1 Propensities of Amino Acid Residues for α Helical and β Sheet Conformations

Residue	P_α	P_β
Ala	1.42	0.83
Arg	0.98	0.93
Asn	0.67	0.89
Asp	1.01	0.54
Cys	0.70	1.19
Gln	1.11	1.10
Glu	1.51	0.37
Gly	0.57	0.75
His	1.00	0.87
Ile	1.08	1.60
Leu	1.21	1.30
Lys	1.16	0.74
Met	1.45	1.05
Phe	1.13	1.38
Pro	0.57	0.55
Ser	0.77	0.75
Thr	0.83	1.19
Trp	1.08	1.37
Tyr	0.69	1.47
Val	1.06	1.70

Source: Chou, P.Y. and Fasman, G.D., *Annu. Rev. Biochem.* 47, 258 (1978).

Sequence Affects 2° Structure

Unhappy in α -helix:
Pro, Gly, Asn, Tyr, Ser, Cys

Unhappy in β -sheet:
Glu, Asp, Pro

Gly prefers loops or turns

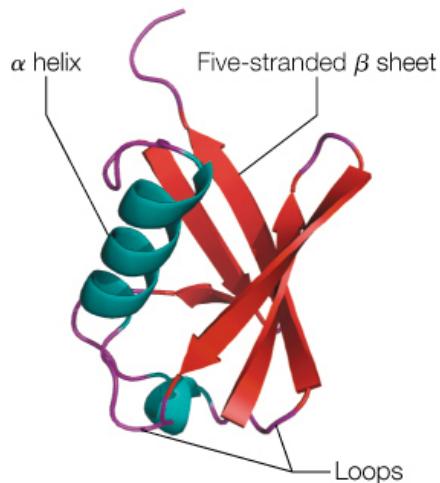
Thus, the aa composition and primary structure of a protein determine its secondary structure.

Protein Secondary Structure - summary

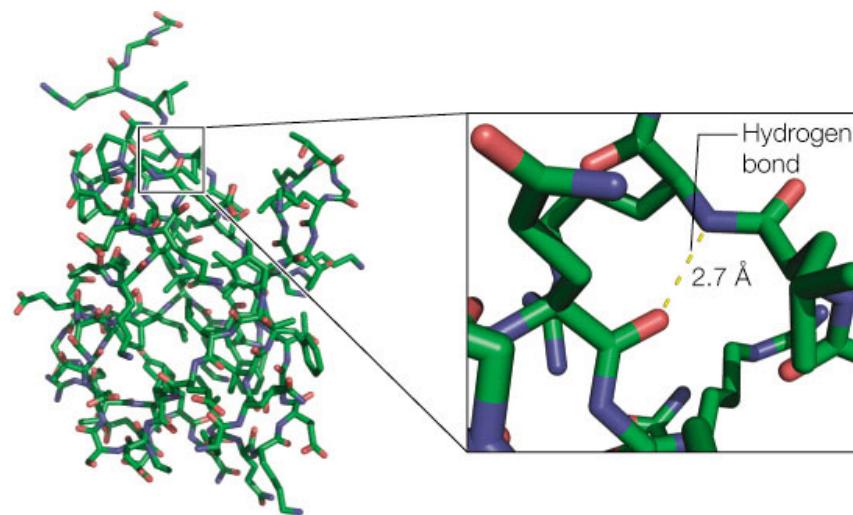
- The planar nature of the peptide group limits the conformational flexibility of the polypeptide chain.
- The α -helix and the β -sheet allow the polypeptide chain to adopt favorable ϕ and ψ angles and to form hydrogen bonds.
- Fibrous proteins contain long stretches of regular secondary structure, such as the “coiled coils” (α -helices twisted together) in α -keratin and the polyproline triple helix in collagen.
- Not all polypeptide segments form regular secondary structure such as α helices or β sheets.

Tertiary structure of globular proteins

Representations of 3D Structures



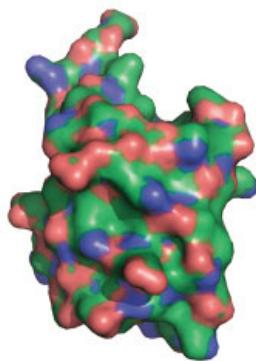
(a) A cartoon model of the protein backbone. An α helix (cyan) is packed against a five-stranded β sheet (red) composed of parallel and antiparallel strands. Loops are shown in magenta.



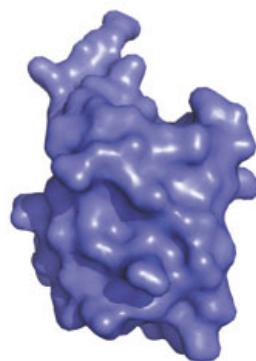
(b) A stick model showing the locations of all atoms (excluding H atoms). C atoms are green, N atoms are blue, and O atoms are red. The inset shows a hydrogen bond of 2.7 Å between main-chain atoms.

FIGURE 6.15 The structure of human ubiquitin.

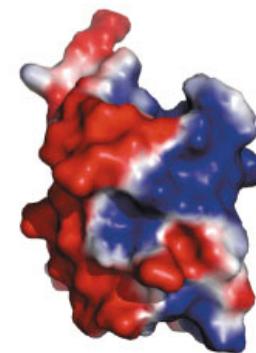
Representations of 3D Structures (2 of 2)



Atom coloring is the same as in panel (b).



Monochrome to emphasize the irregularities of the protein surface.



Distribution of positive (blue) and negative (red) charge density on the protein surface at pH = 7.

(c) Three surface models, showing the solvent-accessible surface of the molecule.

FIGURE 6.15 The structure of human ubiquitin.

Methods used to determine protein structure

- Electron microscopy (see collagen image – slide 18) – for large assemblies and membrane-embedded proteins
- X-ray diffraction of protein crystals (aka X-ray crystallography) – for globular proteins
- Nuclear magnetic resonance (NMR) spectroscopy – for small proteins
- Experimentally solved structures are in the Protein Data Bank (PDB)
- www.rcsb.org

X-Ray Diffraction

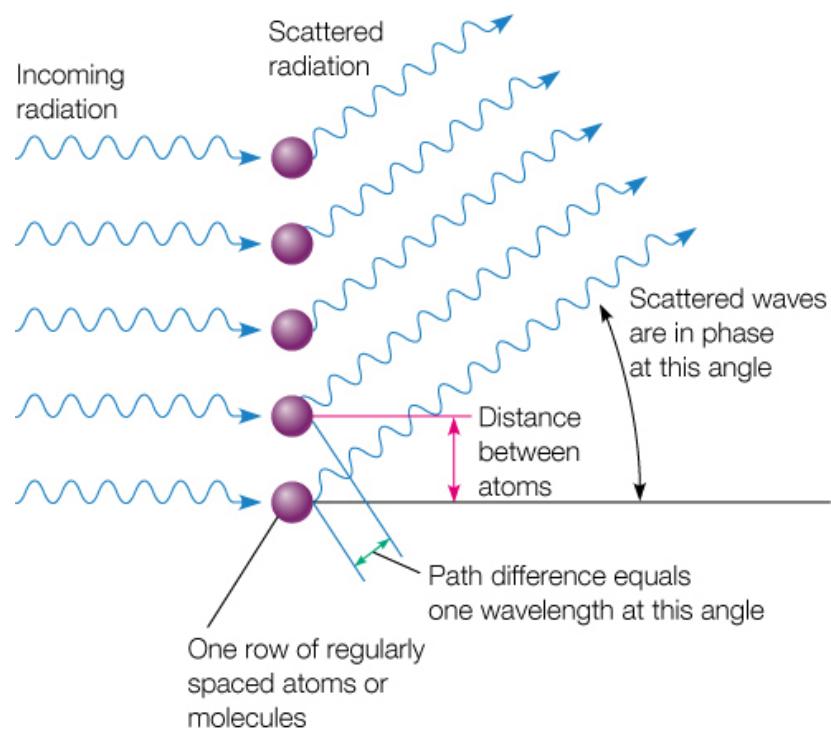


FIGURE 4B.1 Diffraction from a very simple structure—a row of atoms or molecules.

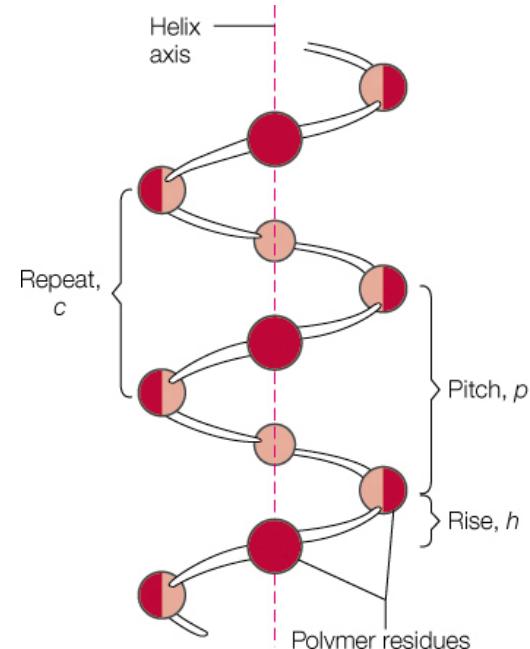


FIGURE 4B.2 A simple helical molecule.

X-ray Diffraction pattern

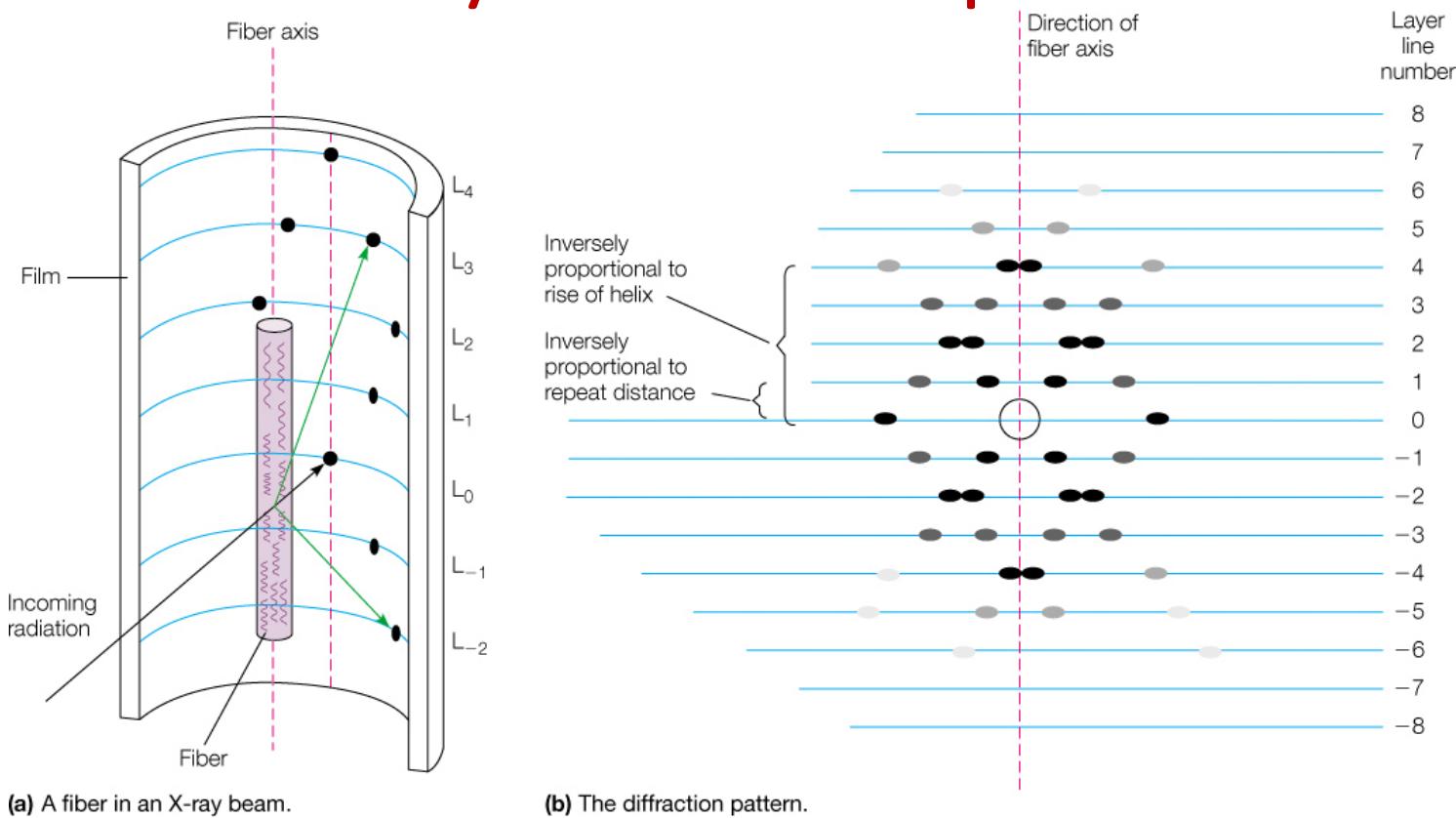
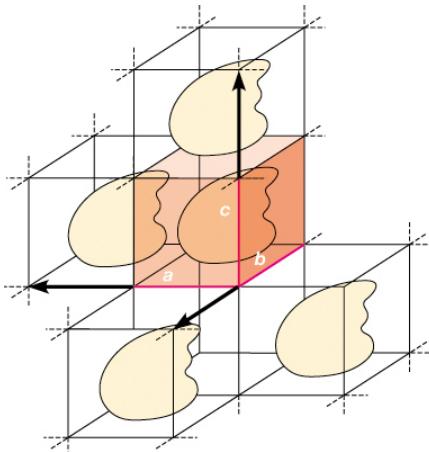
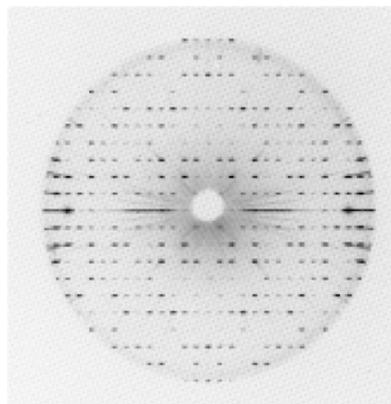


FIGURE 4B.3 Diffraction from fibers.

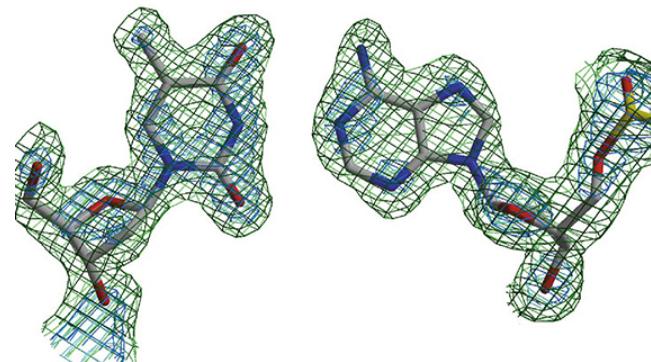
Crystal Diffraction



Molecules in a unit cell



Diffraction pattern of a small DNA crystal



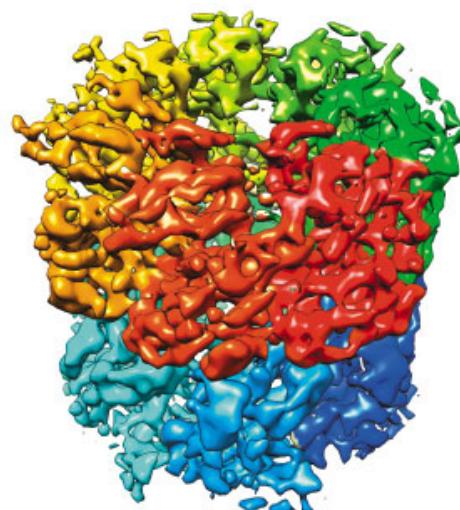
Partial electron density map derived from the diffraction pattern

Crystal Diffraction

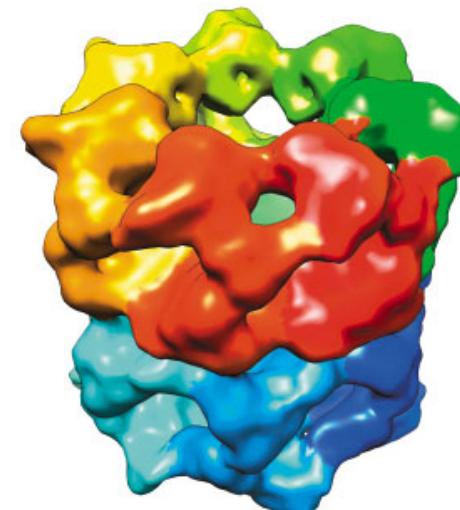
A model structure (GroEL) at different resolutions



4 Å



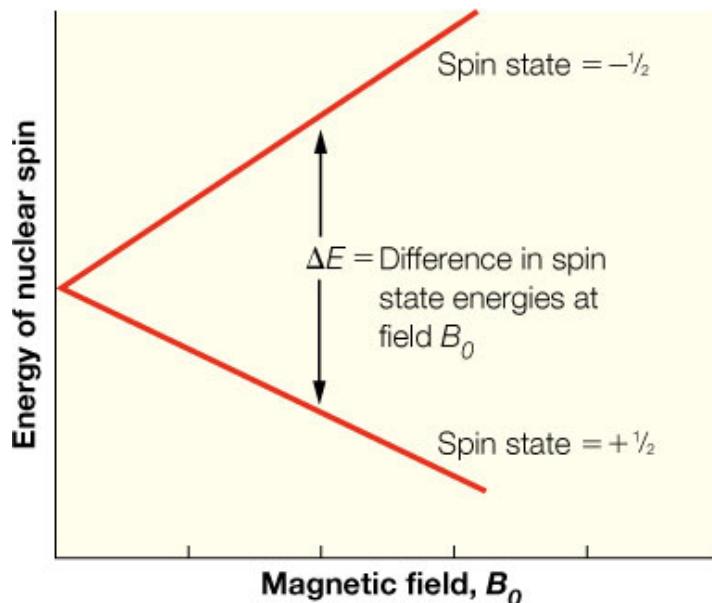
8 Å



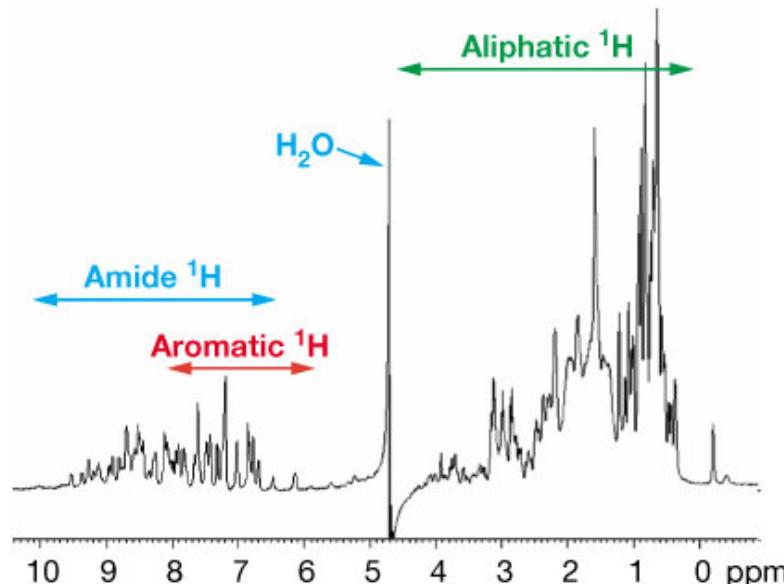
16 Å



NMR Spectroscopy



(a) The effect of magnetic field strength on the energies of nuclear spin states (e.g., ^1H , ^{13}C).



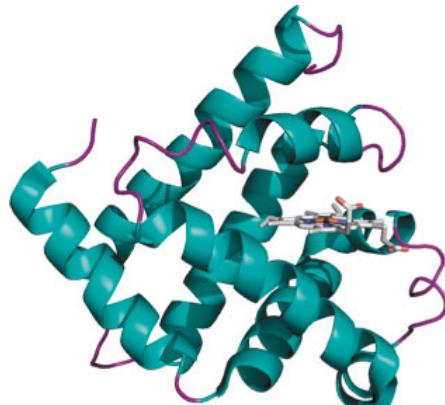
(b) A 500 MHz ^1H NMR spectrum of human ubiquitin (1 mM ubiquitin in 25 mM sodium phosphate, 150 mM NaCl, pH 7.0). This protein has 76 residues, which give rise to ~600 peaks in the ^1H NMR spectrum. The x-axis is the chemical shift, δ in parts per million (ppm).

Figure 6A.9, Nuclear magnetic resonance spectroscopy.

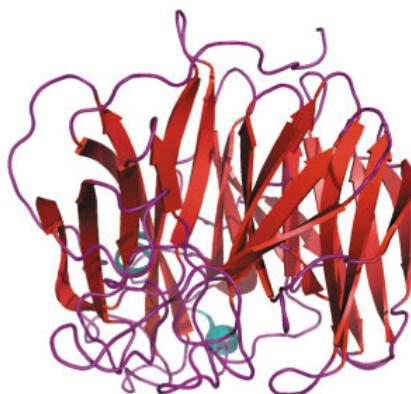
Folding into Defined Structures with Diverse Functions

- Proteins have diverse structures, with varying amounts of helix, sheet, and loop regions
- Larger proteins often contain two or more distinct “domains” of compact folded structure
- A typical protein “domain” is ~200 amino acids and will fold independently
- A domain frequently possesses some defined function (e.g., DNA recognition, oligomerization, cofactor binding, etc.)

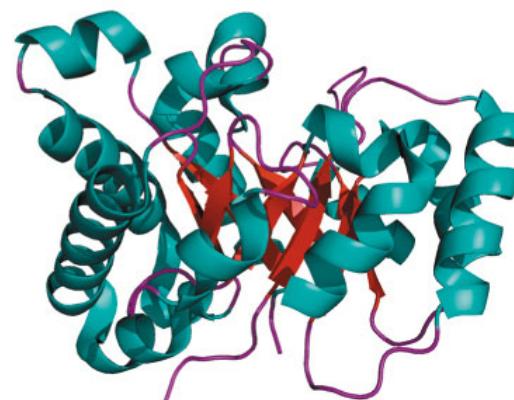
Folding into Defined Structures with Diverse Functions



Myoglobin



Neuraminidase



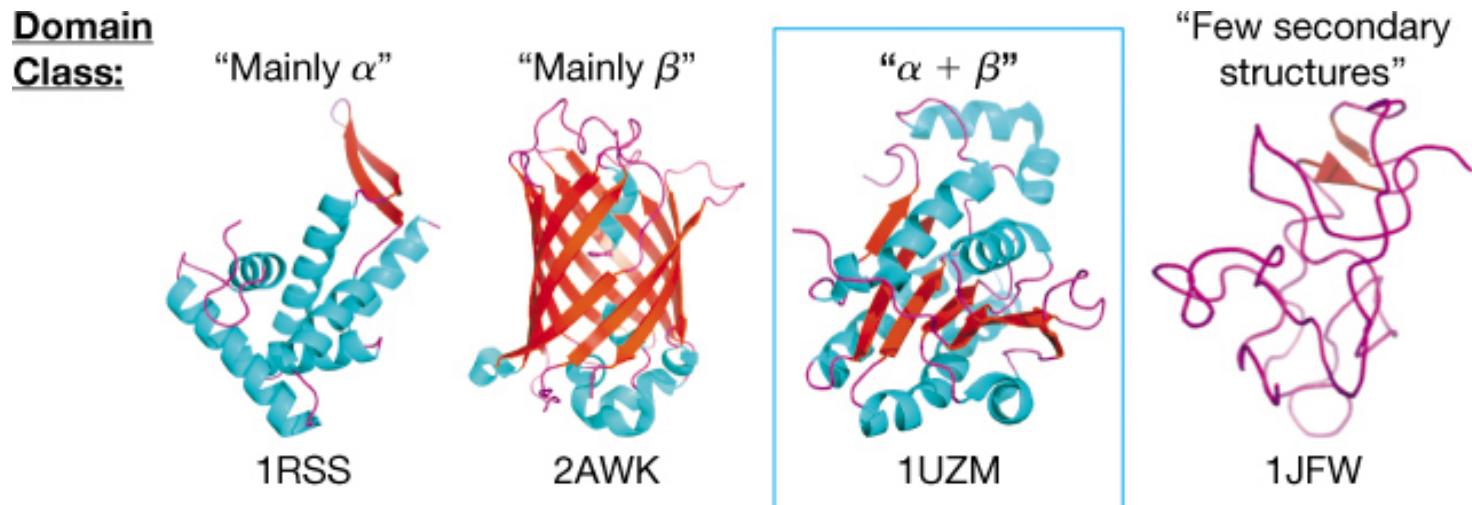
Triosephosphate isomerase (TIM)



Classification of Protein Structure

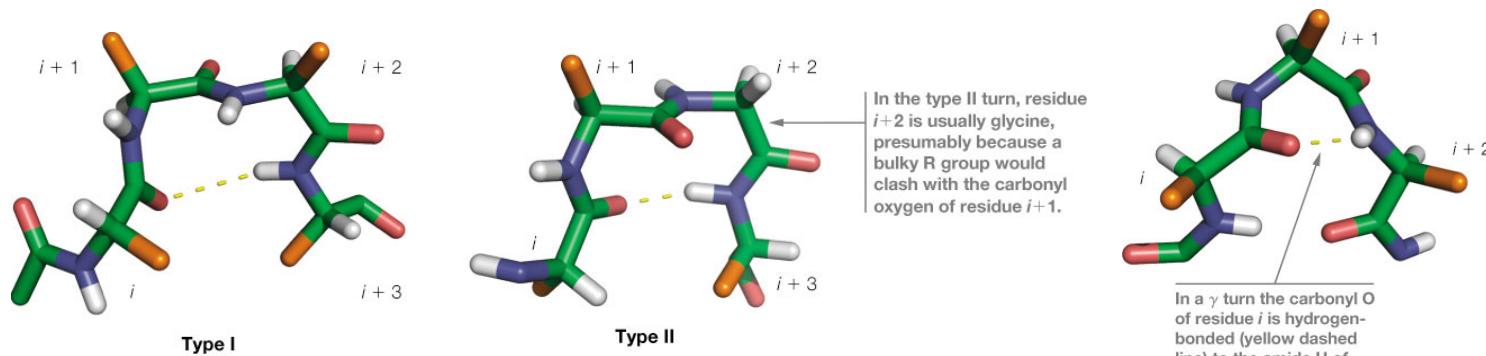
- Protein tertiary structure is characterized by the content of helix and sheet secondary structures, and by defined turns that link these secondary structures
- Some proteins are predominantly helix or sheet, others possess a mixture of helix and sheet, or very little defined secondary structure
- Not all parts of a globular protein structure can be categorized as helix, sheet, or turn. Such regions are often called “random coil” or, more properly, “irregularly structured regions.”

Classification of Protein Structure by Domains



Common Features of Folded Globular Proteins

- Globular proteins have a nonpolar (hydrophobic) interior and a more hydrophilic exterior
- β -sheets are usually twisted or wrapped into barrel structures
- The polypeptide chain can turn corners, for example, β -turns (type I and II left) or γ -turns (right)



Common Features of Folded Globular Proteins

Distribution of hydrophobic and hydrophilic residues in myoglobin

VLSEGEWQLV LHWWAKVEAD VAGHGQDILR LFLKSHPTEL EKFDRFKHLK
TEAEMKASED LKKHGVTVLT ALGAILKKKG HHEAEALKPLA QSHATKHKIP
IKYLEFISEA IIHVVLHSRHP GDFGADAGQA MNKALELFRK DIAAKYKELG
YQG

Hydrophobic residues are green,
hydrophilic ones are magenta, and
ambivalent ones are black

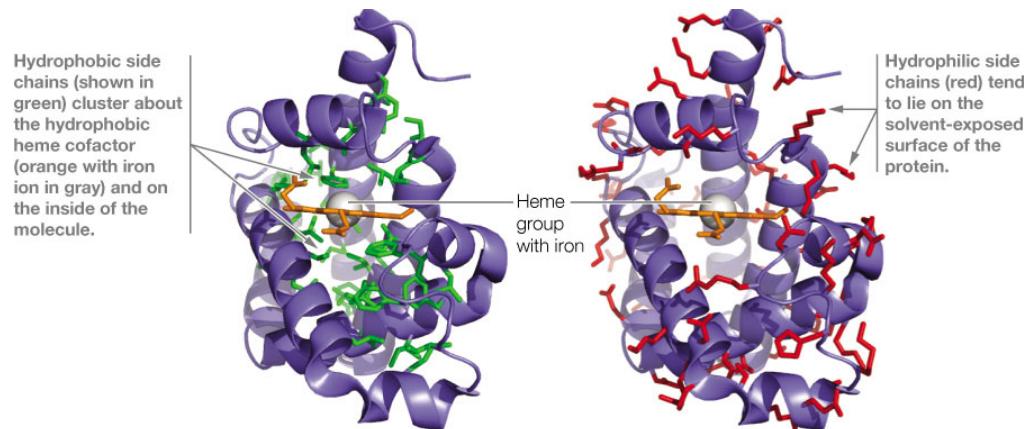


FIGURE 6.19 The distribution of hydrophilic and hydrophobic residues in globular proteins.

Where do the side chains go?

- Based on polarity
 - **Nonpolar** (Val, Leu, Ile, Met, Phe) prefer the **hydrophobic interior**
 - **Charged** polar residues (Asp, Glu, His, Lys, Arg) are usually in contact with aqueous solvent and thus on the **surface**.
 - Uncharged polar groups (Ser, Thr, Asn, Gln, Tyr) are usually on the surface but when buried, form hydrogen bonds.
 - Amino acid mutations may disturb this distribution, and hence affect the stability and the 3D structure.
- **Hydrophobicity** is the **main driving force** for protein tertiary structure.

Thermodynamics, Folding and Stability of Proteins

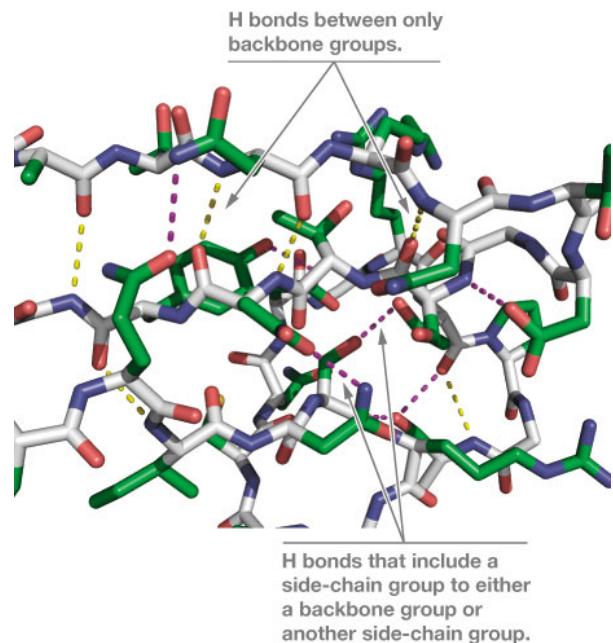


FIGURE 6.23 Details of hydrogen bonding in a typical protein.

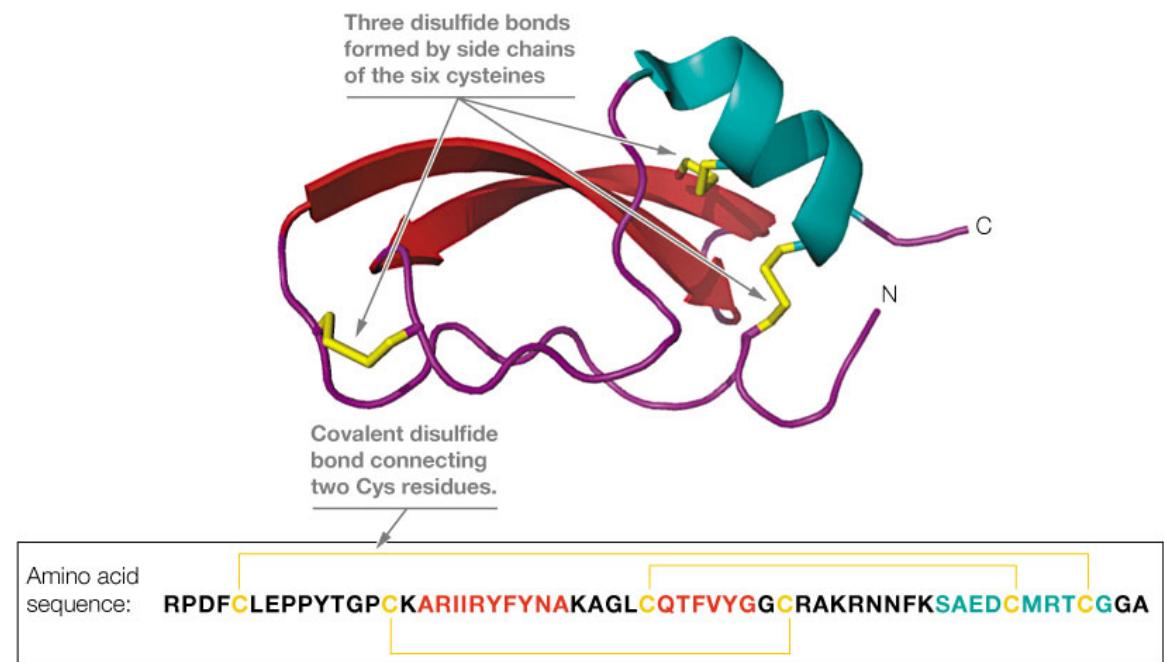
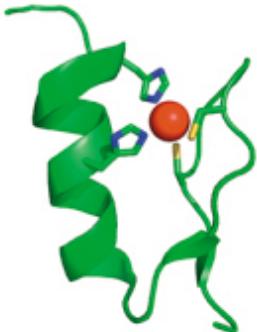


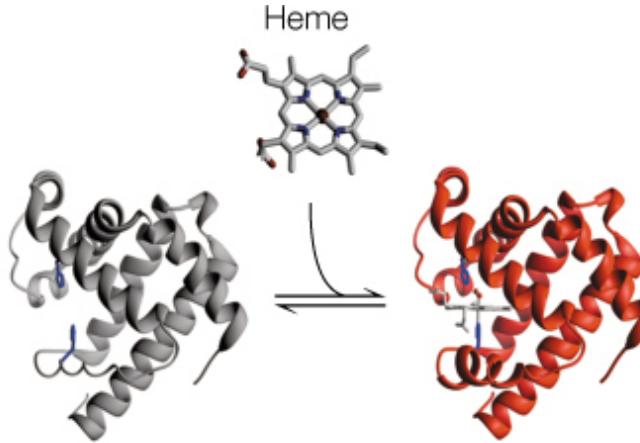
FIGURE 6.25 Disulfide bonds in bovine pancreatic trypsin inhibitor (BPTI).

Thermodynamics, Folding and Stability of Proteins



A “zinc finger” domain bound to a Zn^{2+} ion

(a) The side chains from two histidines and two cysteines bind specifically to a Zn^{2+} ion (red sphere) in a zinc finger domain. The Zn finger domain is a common structure among certain DNA-binding proteins (PDB ID: 1tf6).



Apomyoglobin
(no heme bound)

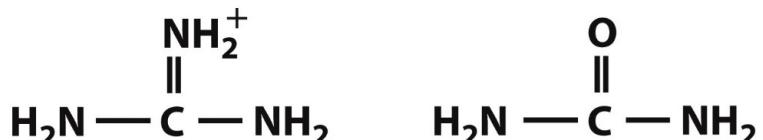
Holomyoglobin
(heme bound)

(b) Heme binding to apomyoglobin stabilizes the folded structure of myoglobin and gives the holoprotein its red color. Holomyoglobin includes both the myoglobin protein and the heme prosthetic group.

FIGURE 6.27 Ion or prosthetic group binding increases protein stability.

Proteins can undergo denaturation and renaturation

- Denaturation leads to **loss of function**.
- Proteins can be denatured by:
 - **Heating**: the entire polypeptide unfolds or “melts”.
Most proteins melt below 100°C.
 - **pH**: changes charge distributions and hydrogen bonding patterns
 - **Detergents**: stabilize hydrophobic side chains and can invert a folded protein.
 - **Chaotropic agents**



Guanidinium ion

Urea

Unnumbered 6 p159
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Denatured (unfolded) proteins can be renatured (folded): Anfinsen 1957

- Ribonuclease A (RNase A), a 124-residue single-chain protein, was **denatured by urea**.
- When the urea was removed, the protein **spontaneously renatured** (i.e. **refolded**)!
- The four disulphide bonds re-formed correctly, giving a functional protein.
- Proteins fold spontaneously into their native confirmations under physiological conditions
- Implies the protein's primary structure determines its 3D structure!

Information for Protein Folding

Denaturation and disulphide bond cleavage by β -mercaptoethanol (BME)

- Oxidation and urea removal: scrambled disulphide bonds
- Urea removal followed by oxidation: functional protein recovered!

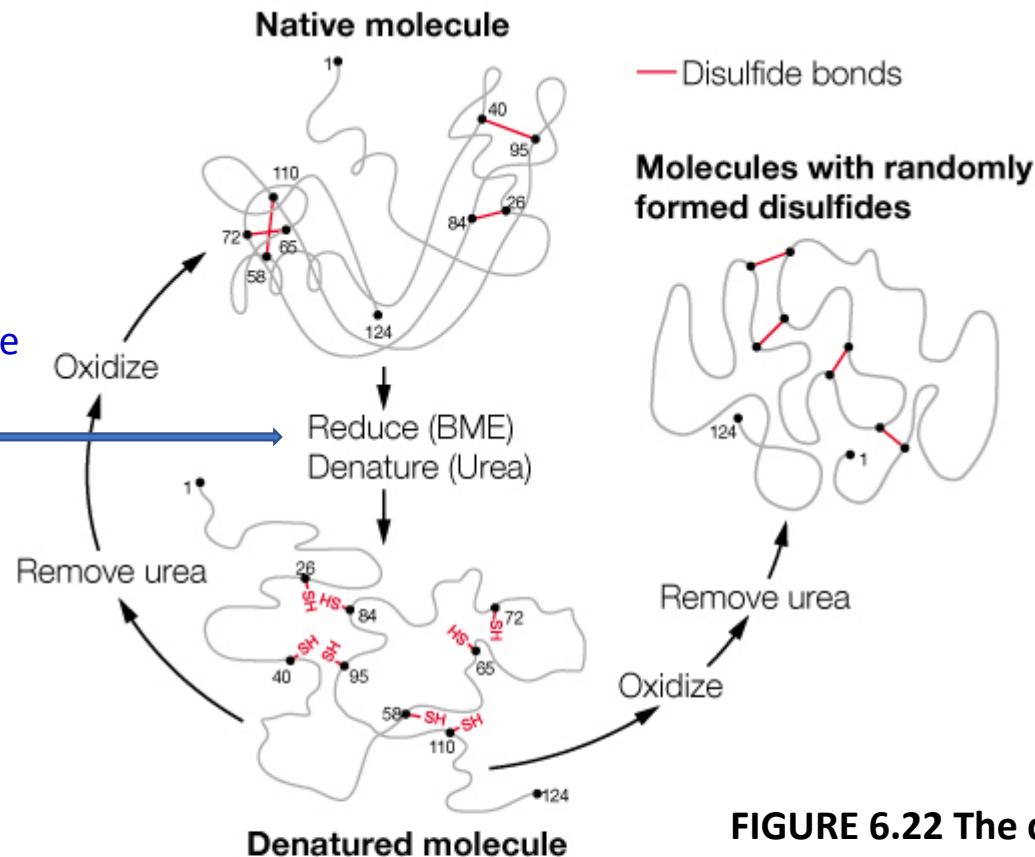
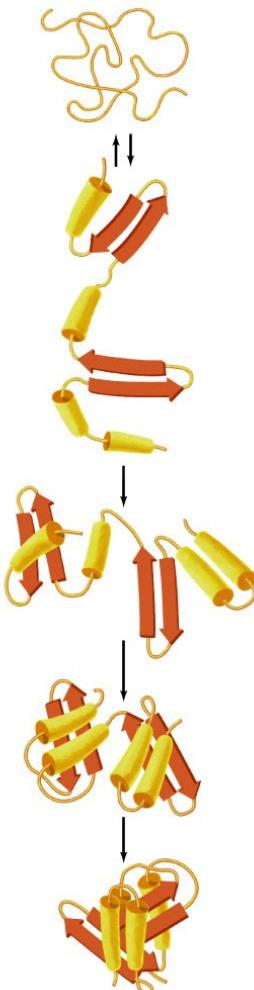


FIGURE 6.22 The denaturation and refolding of ribonuclease A.

(a) In the classic RNase A refolding experiment of Anfinsen, renaturation before disulfide bond formation yields the active, native conformation, but disulfide bond formation before renaturation yields multiple conformations with little recovery of enzymatic activity.



Hypothetical Protein Folding Pathway



- A protein folds from high energy and high entropy to low energy and low entropy.
- Proteins need to be properly folded for biological activity
- Misfolded proteins are shredded by proteases.
- Proper folding of misfolded proteins is possible with help from large proteins (chaperonins).
- Misfolding can lead to diseases.

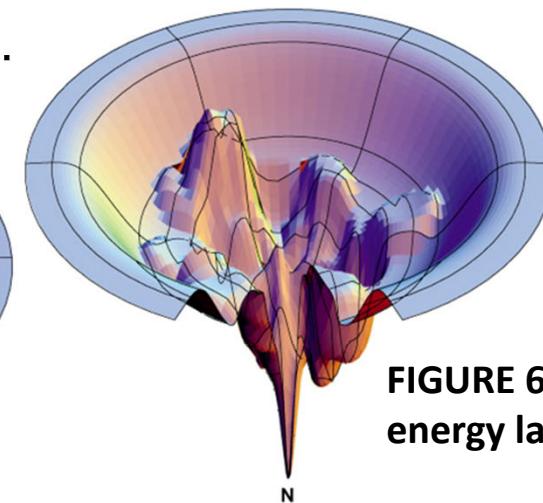
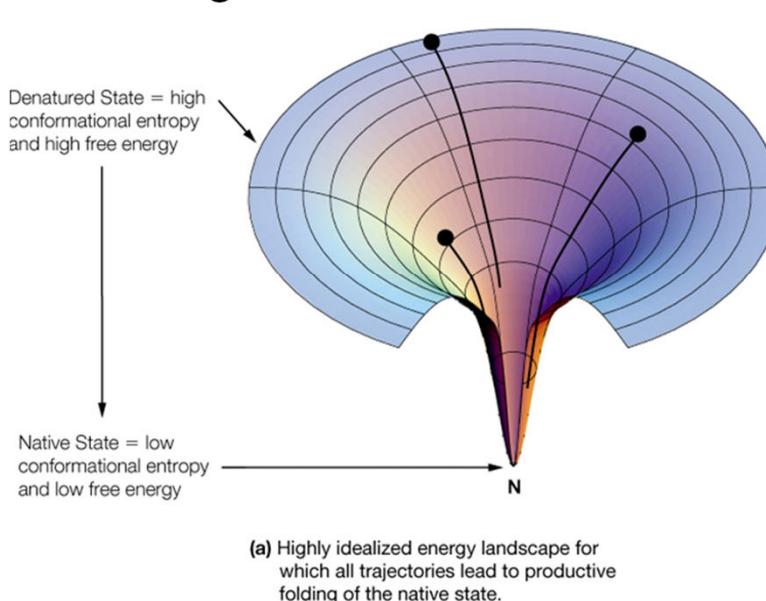


FIGURE 6.29 Protein folding energy landscapes.

(b) A more "rugged" energy landscape. Here, many different paths are possible, some of which lead "downhill" with no local energy minima and give rapid folding. Others may lead to conformations corresponding to local energy minima (i.e., stable intermediate states), which may slow folding (see Figure 6.30).

Models of Protein Folding and Aggregation

Amyloid fibrils and related diseases

Highly ordered amyloids form from non-native folding intermediates or disordered aggregate states

Prions: Infectious agents that cause disease by inducing amyloid formation on contact

TABLE 6.5 Examples of amyloid-related human diseases

Disease	Associated Protein
Alzheimer's disease	Amyloid β or "A β " peptide
Parkinson's disease	α -Synuclein
Spongiform encephalopathies (such as Creutzfeldt-Jakob disease and kuru)	Prion protein
Amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease)	Superoxide dismutase I
Huntington's disease	Huntingtin with polyQ tracts
Cataracts	γ -Crystallin
Type II diabetes	Islet amyloid polypeptide (IAPP)
Injection-localized amyloidosis	Insulin



Predicting Secondary Structures from Amino Acid Sequences

- Empirical methods are about 80% accurate
- Based on observed distributions of amino acids in helix vs. sheet conformations (e.g., Ala prefers helix, Val prefers sheet, etc.)
- Amphiphilic α -helix shows repeating patterns of side chain polarity every 3–4 residues
- Amphiphilic β strand shows repeating patterns of side chain polarity every other residue

Predicting Tertiary Structures from Amino Acid Sequences

- Critical need for accurate prediction from sequence, since structures are known for only about 1% of all known sequences
- Prediction of tertiary structure is difficult due to the need to correctly predict interactions between residues that are far apart in the primary structure
- Current computational methods are about 60% accurate

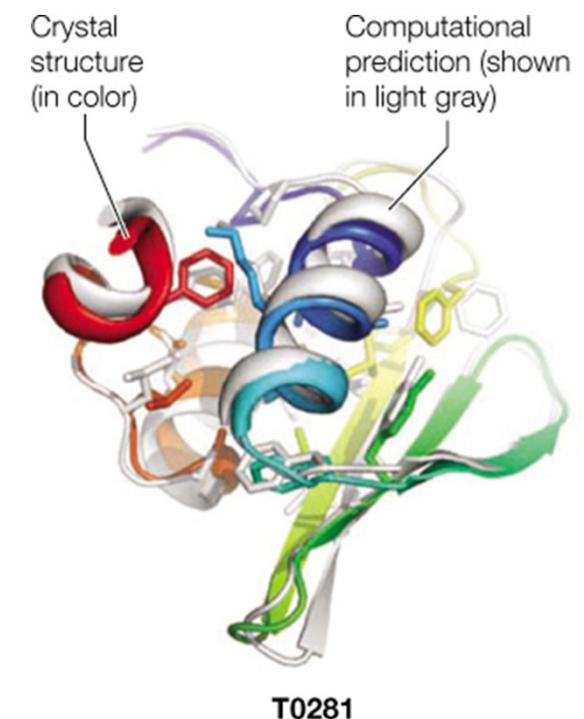
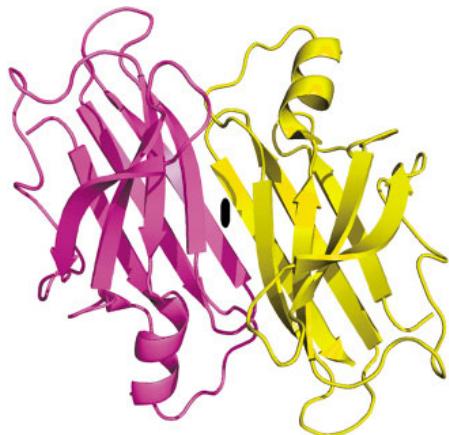
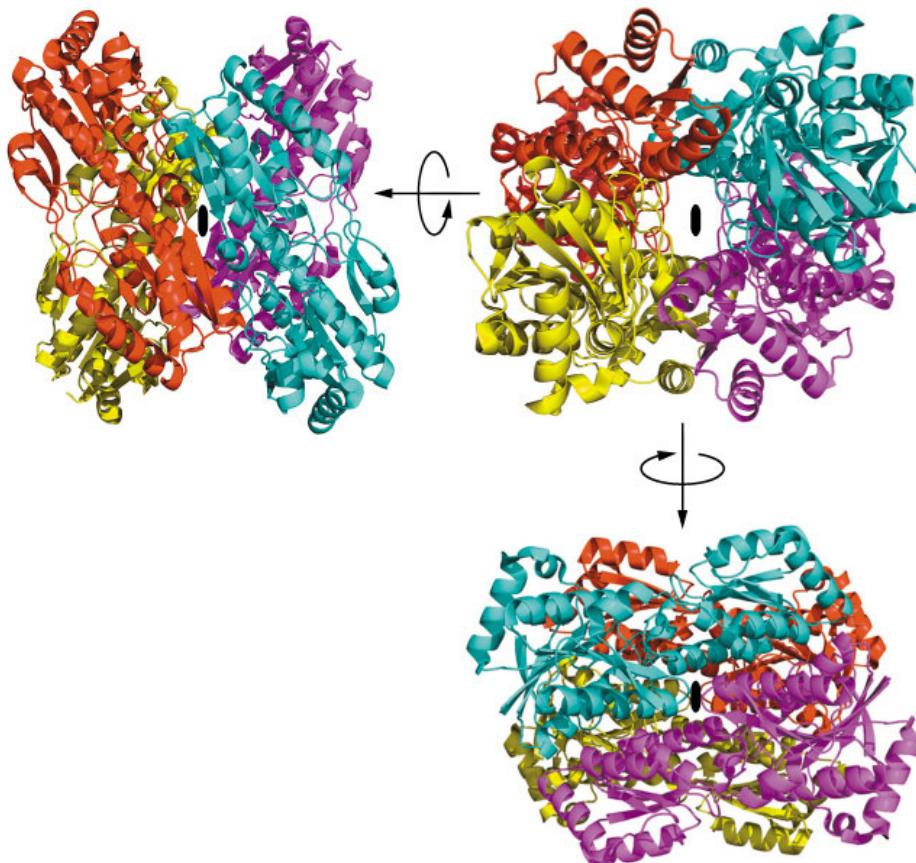


FIGURE 6.33 Comparison of *de novo* prediction to X-ray crystal structures.

Quaternary Structures



(a) In the transthyretin dimer, the two monomers combine to form a complete β sandwich, or flattened β barrel. The dimer has 2-fold symmetry about the C_2 axis perpendicular to the paper (black oval). The isologous interactions are mostly hydrogen bonds between specific β sheet strands.



(b) Three views of the tetrameric enzyme phosphofructokinase. Each view is down one of the three mutually perpendicular C_2 axes.

FIGURE 6.36 Examples of multisubunit proteins.

Quaternary Structures

Interaction between trypsin and the bovine pancreatic trypsin inhibitor (BPTI)

- This is an example of a heterotypic protein–protein interactions (between entirely different proteins)
- Complementary surfaces determine specific interactions

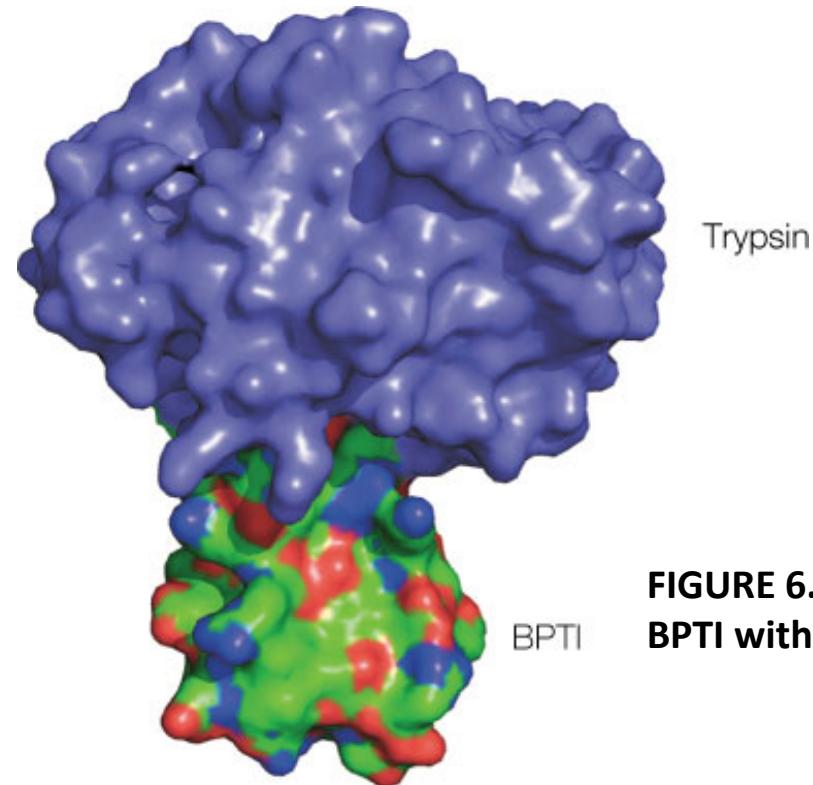


FIGURE 6.37 Interaction of BPTI with trypsin.

Four Levels of Protein Structure

- Primary (1°) structure refers to the amino acid sequence that makes up the protein
- Secondary (2°) structure refers to local areas of repeating main chain structure
- Tertiary (3°) structure refers to the spatial arrangement of the secondary structural elements in the polypeptide chain
- Quaternary (4°) structure refers to the spatial arrangement of multiple polypeptide chains to form multisubunit complexes

Summary

- All proteins have at least three levels of organization
 - Genes dictate the primary level, the amino acid sequences, which then dictates the other levels:
 - secondary,
 - tertiary and, in some cases,
 - quaternary structures.
 - The peptide bond limits the secondary structures that can be formed
 - Ramachandran plots visualize clusters of these sterically allowed secondary structures (α -helix, β -sheet, β_{10} -helix, β -turn, γ -turn, etc.)

Summary

- Proteins can be broadly distinguished into fibrous and globular
- Fibrous proteins are often elongated, performing structural roles in cells, while globular proteins have more complex tertiary structures and fold into compact shapes
- The folding of globular proteins occurs rapidly and spontaneously under standard biochemical conditions
- Many proteins form functional multisubunit assemblies (quaternary structures), for example exhibiting helical symmetry or point-group symmetry