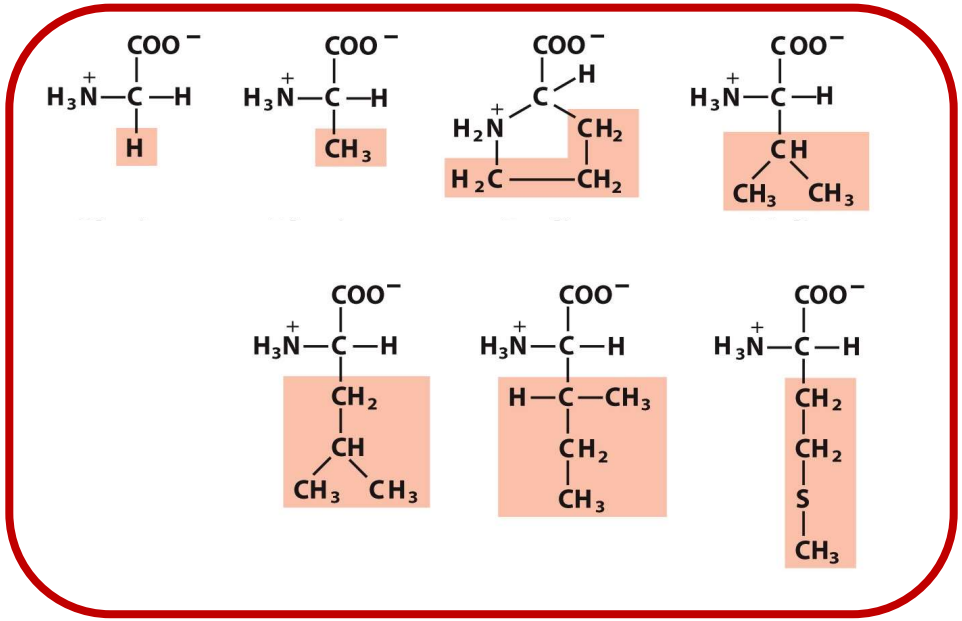
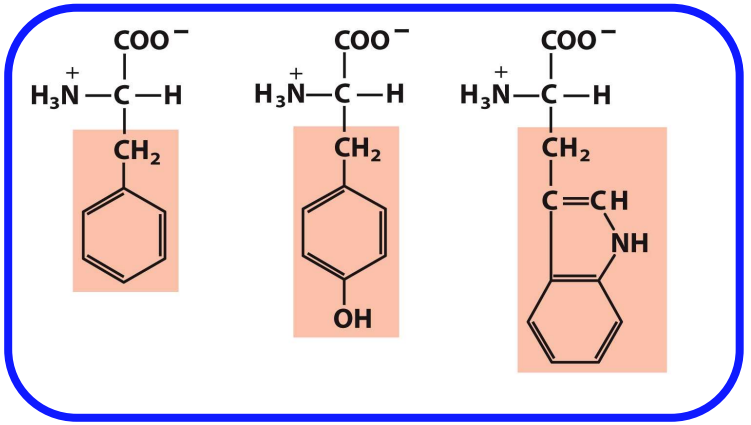
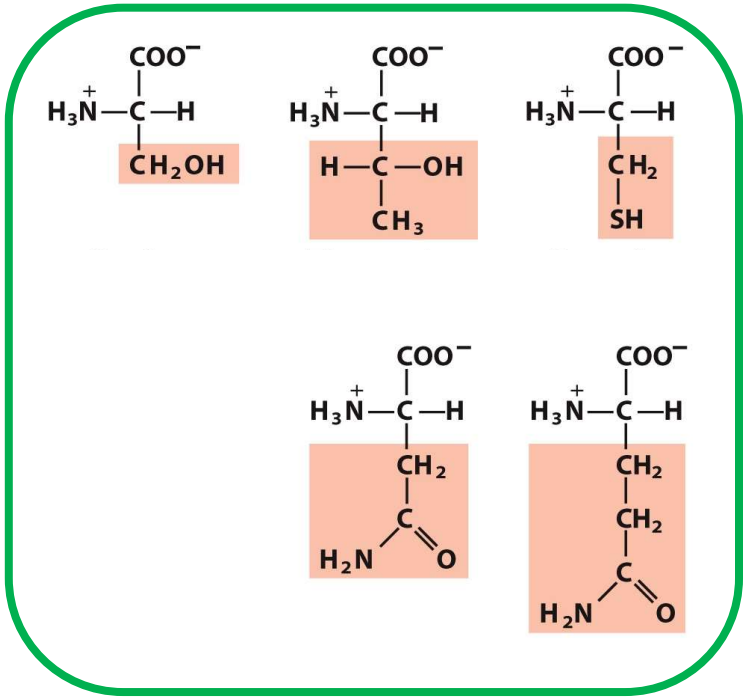
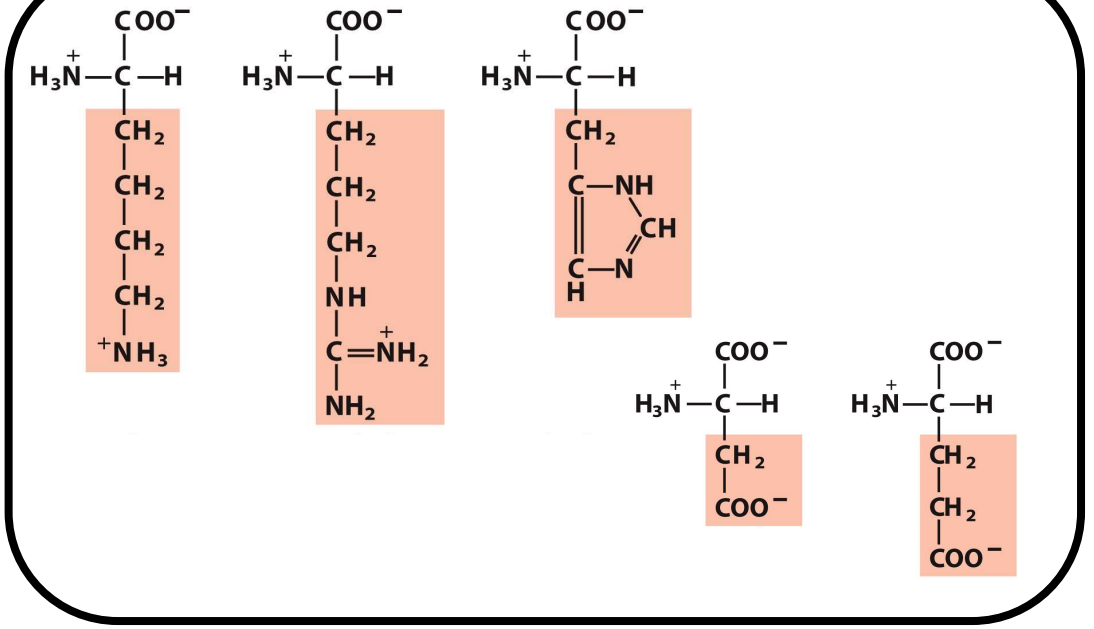


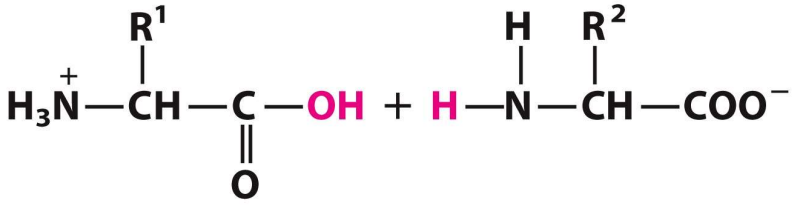


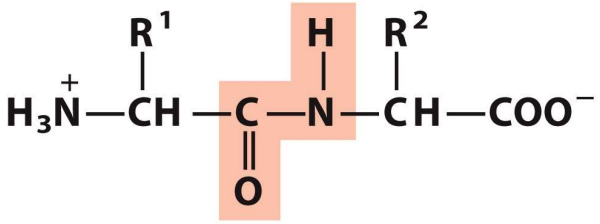




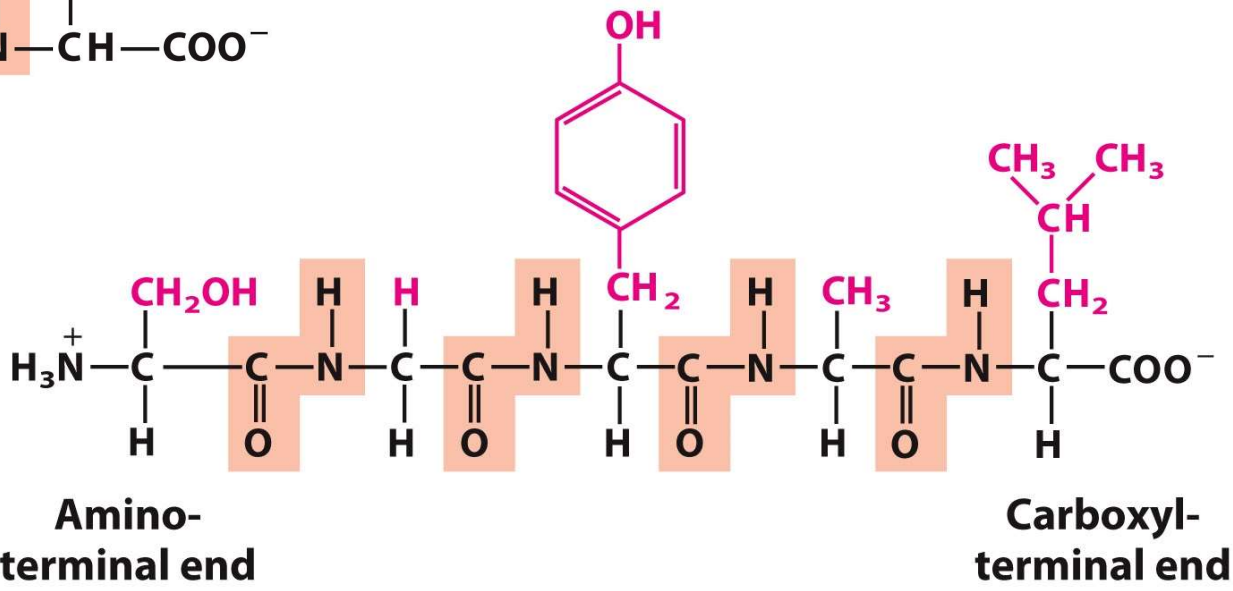
Amino Acids Polymerize to Form Peptides

Amino acids → peptides → proteins





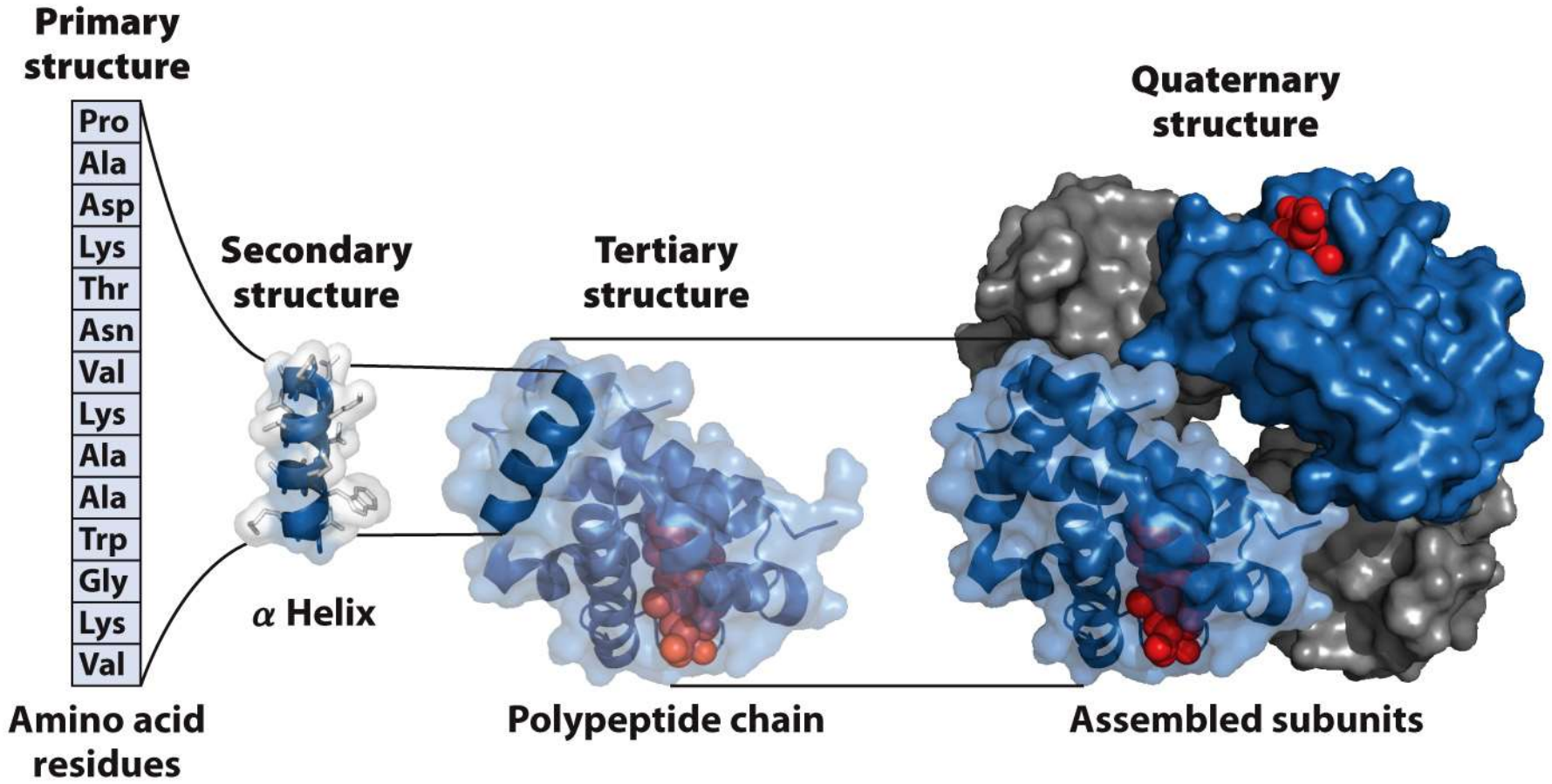
- serylglycyltyrosylalanylleucine
- Ser-Gly-Tyr-Ala-Leu
- SGYAL



Favorable Interactions in Proteins

- **Hydrophobic effect**
  - The release of water molecules from the structured solvation layer around the molecule as protein folds increases the net entropy.
- **Hydrogen bonds**
  - Interaction of N−H and C=O of the peptide bond leads to local regular structures such as α helices and β sheets.
- **Van der Waals force**
  - Attraction between all atoms contributes significantly to the stability in the interior of the protein.
- **Electrostatic interactions**
  - long-range strong interactions between permanently charged groups
  - Salt bridges, especially those buried in the hydrophobic environment, strongly stabilize the protein.

Four Levels of Protein Structure



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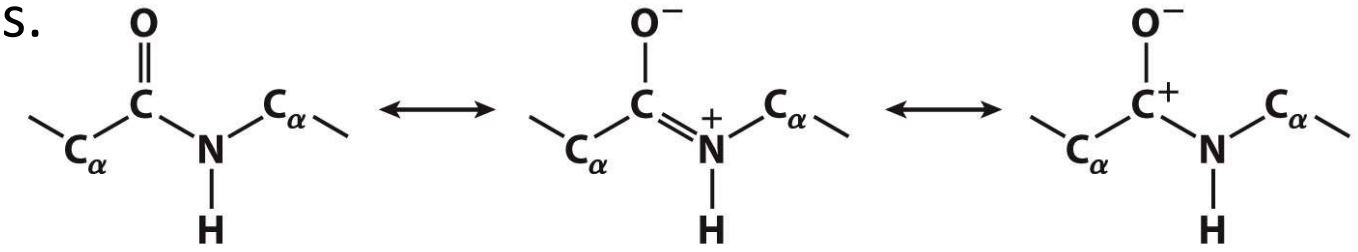
Primary Structure: The Peptide Bond

- The structure of the protein is partially dictated by the properties of the peptide bond.
- The peptide bond is a resonance hybrid of two canonical structures.



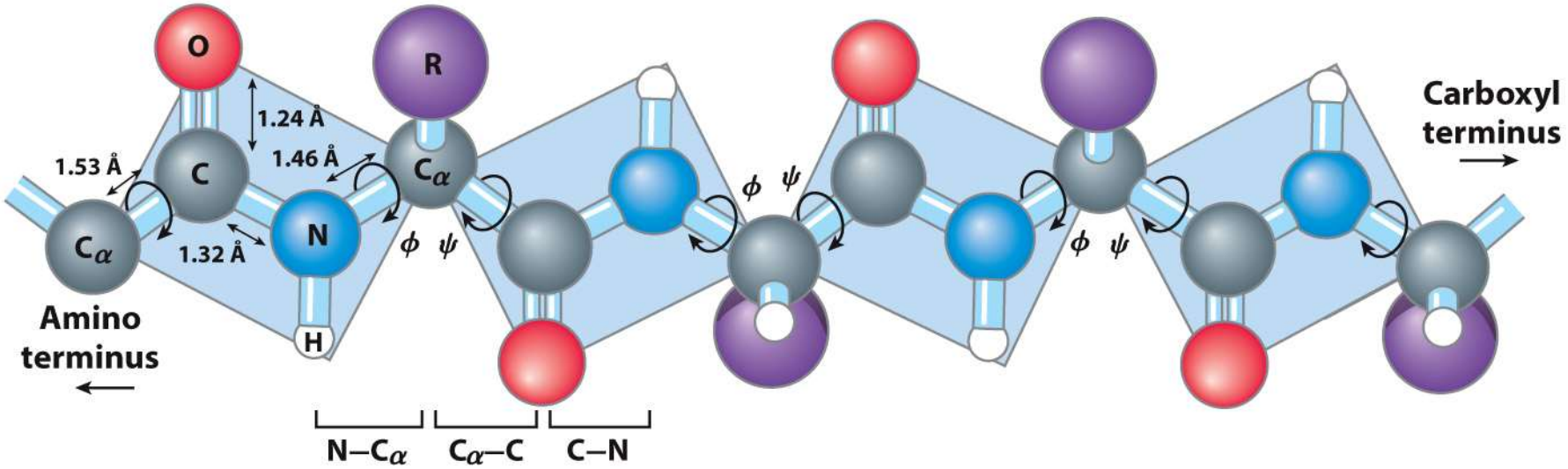
- The resonance causes the peptide bonds:
  - to be less reactive compared with esters, for example
  - to be quite **rigid** and nearly **planar**
  - to exhibit a large dipole moment in the favored trans configuration

The Rigid Peptide Plane and the Partially Free Rotations

- Rotation around the peptide bond is not permitted due to resonance structure.
- Rotation around bonds connected to the α carbon is permitted.
  - ϕ (phi): angle around the α carbon—amide nitrogen bond
  - ψ (psi): angle around the α carbon—carbonyl carbon bond
- In a fully extended polypeptide, both ψ and ϕ are 180° .

The organization around the peptide bond, paired with the identity of the R groups, determines the secondary structure of the protein.

The Polypeptide Is Made Up of a Series of Planes Linked at α Carbons



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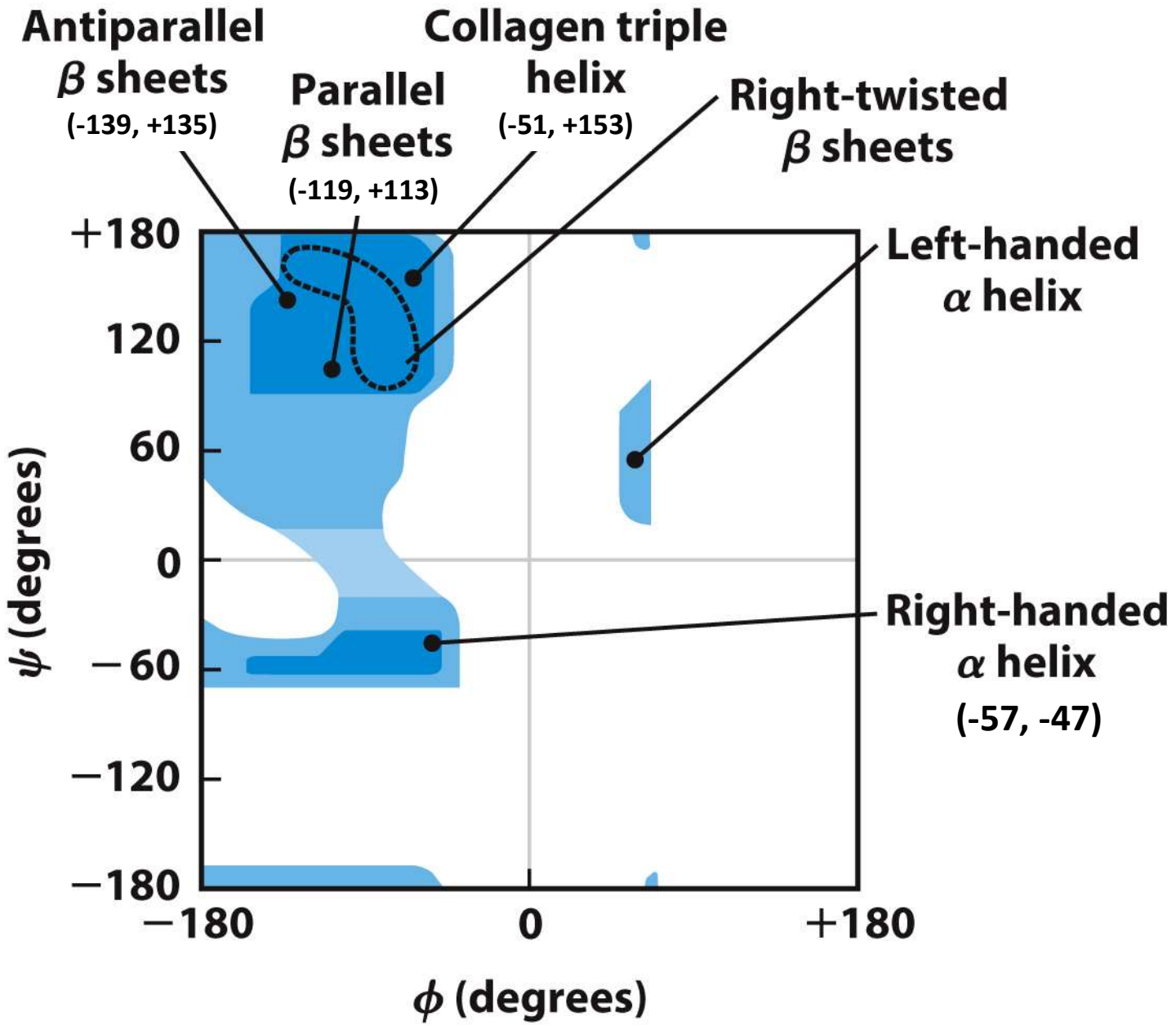

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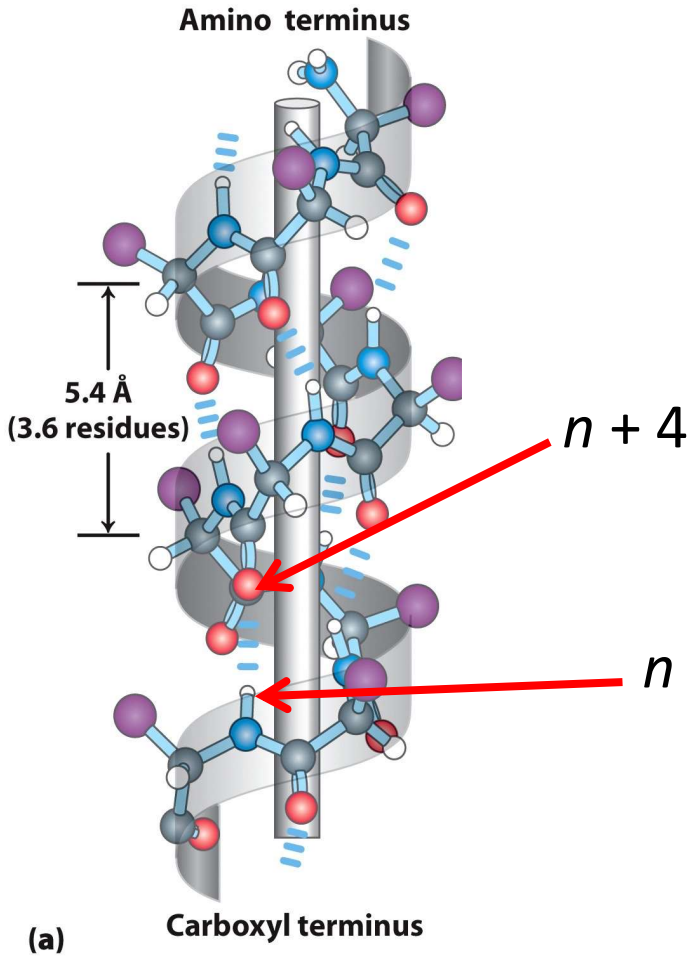
Secondary Structures

- Secondary structure refers to a local spatial arrangement of the polypeptide backbone.
- Two regular arrangements are common:
  - the **α helix**
    - stabilized by hydrogen bonds between nearby residues
  - the **β sheet**
    - stabilized by hydrogen bonds between adjacent segments that may not be nearby
- Irregular arrangement of the polypeptide chain is called the random coil.

The α Helix

- Helical backbone is held together by hydrogen bonds between the backbone amides of an *n* and *n* + 4 amino acids.
- It is a right-handed helix with 3.6 residues (5.4 Å) per turn.
- Peptide bonds are aligned roughly parallel with the helical axis.
- Side chains point out and are roughly perpendicular with the helical axis.



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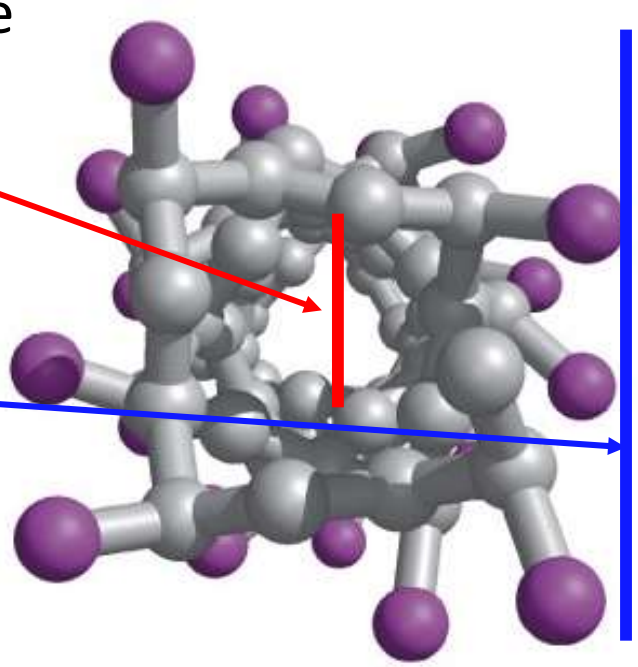
The α Helix: Top View

- The inner diameter of the helix (no side chains) is about 4–5 Å.
  - too small for anything to fit "inside"
- The outer diameter of the helix (with side chains) is 10–12 Å.
  - happens to fit well into the major groove of dsDNA
- Amino acids #1 and #8 align nicely on top of each other.



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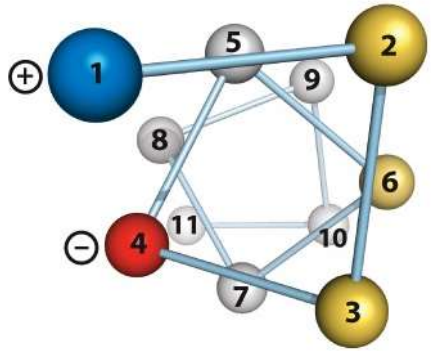

Sequence Affects Helix Stability

- Not all polypeptide sequences adopt α-helical structures.
- Small hydrophobic residues such as Ala and Leu are strong helix formers.
- Pro acts as a helix breaker because the rotation around the N-C_a (φ-angle) bond is impossible.
- Gly acts as a helix breaker because the tiny R group supports other conformations.
- Attractive or repulsive interactions between side chains 3 to 4 amino acids apart will affect formation.

Parallel and Antiparallel β Sheets

- Multi β-strand interactions are called sheets.
- Sheets are held together by the hydrogen bonding of amide and carbonyl groups of the peptide bond from opposite strands.
- Two major orientations of β sheets are determined by the directionality of the strands within:
  - Parallel sheets have strands that are oriented in the same direction.
  - Antiparallel sheets have strands that are oriented in opposite directions.

In parallel β sheets, the H-bonded strands run in the same direction.

- Hydrogen bonds between strands are bent (weaker).

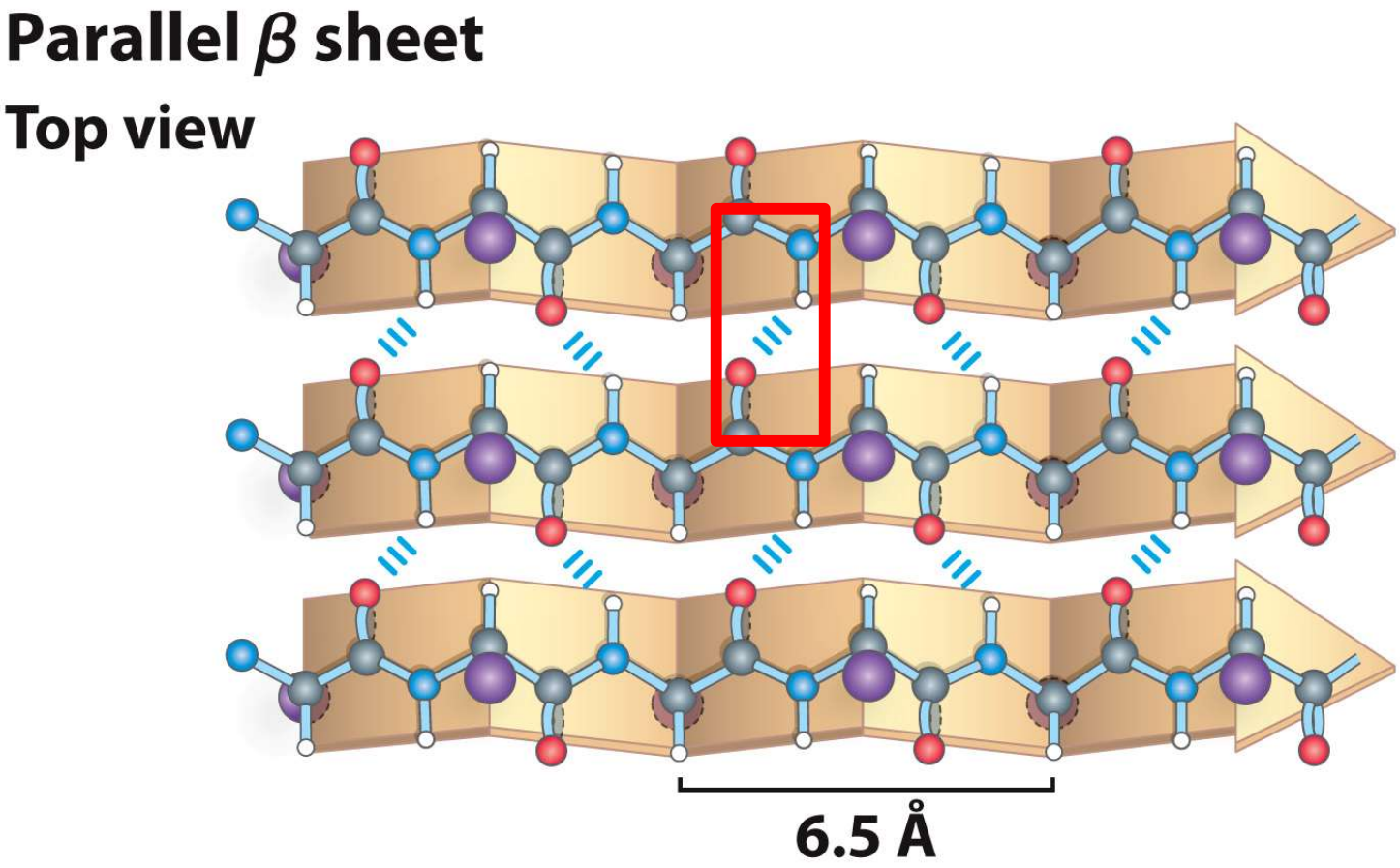

Figure 4-6c
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In antiparallel β sheets, the H-bonded strands run in opposite directions.

- Hydrogen bonds between strands are linear (stronger).

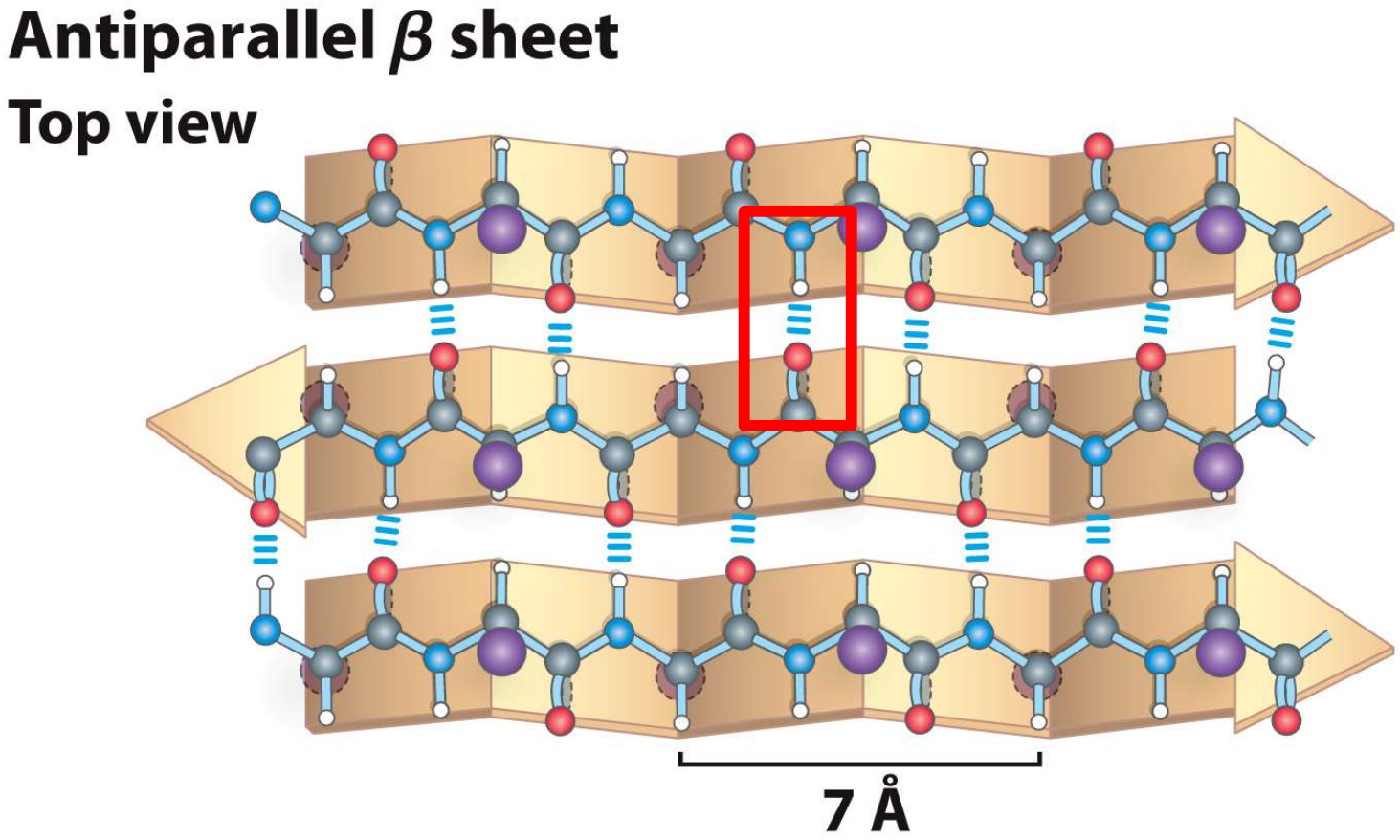

Figure 4-6b
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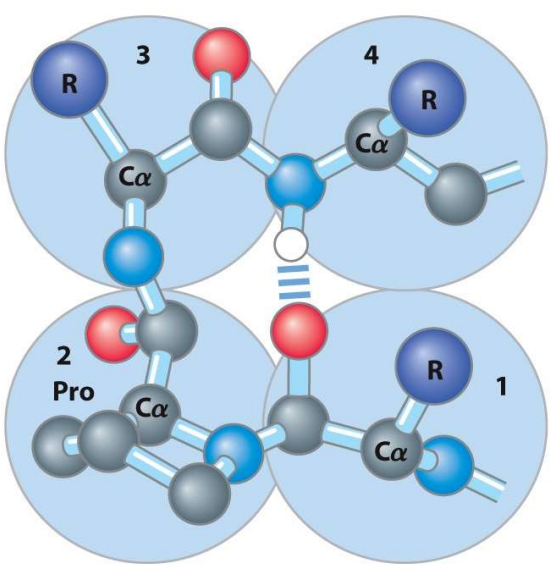
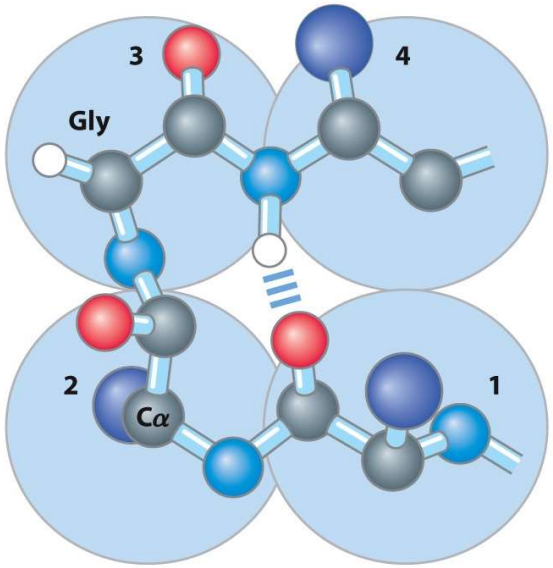
β Turns

- β turns occur frequently whenever strands in β sheets change the direction.
- The 180° turn is accomplished over four amino acids.
- The turn is stabilized by a hydrogen bond from a carbonyl oxygen to amide proton three residues down the sequence.
- Proline in position 2 or glycine in position 3 are common in β turns.



Type I β turn



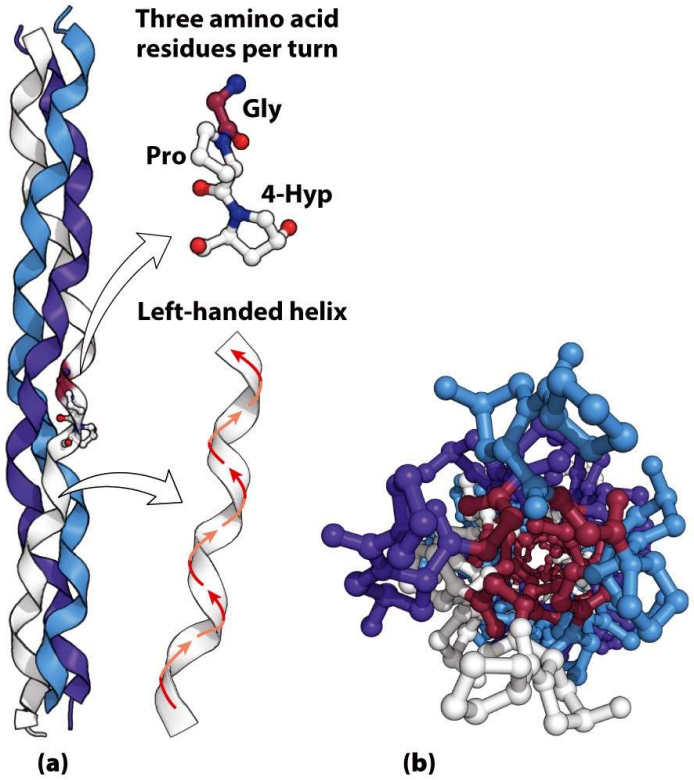
Type II β turn

Protein Tertiary Structure

- Tertiary structure refers to the overall spatial arrangement of atoms in a protein.
- Stabilized by numerous weak interactions between amino acid side chains
  - largely hydrophobic and polar interactions
  - can be stabilized by disulfide bonds
- Interacting amino acids are not necessarily next to each other in the primary sequence.
- Two major classes:
  - fibrous:
  - globular:

Fibrous Proteins

TABLE 4-3	Secondary Structures and Properties of Some Fibrous Proteins	
Structure	**Characteristics**	**Examples of occurrence**
α Helix, cross-linked by disulfide bonds	Tough, insoluble protective structures of varying hardness and flexibility	*α*-Keratin of hair, feathers, nails
β Conformation	Soft, flexible filaments	Silk fibroin
Collagen triple helix	High tensile strength, without stretch	Collagen of tendons, bone matrix



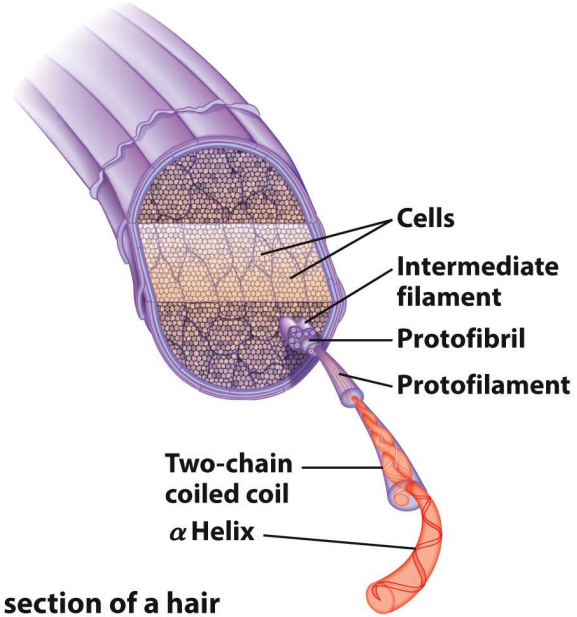


Figure 4-11b
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Structure of α-Keratin in Hair

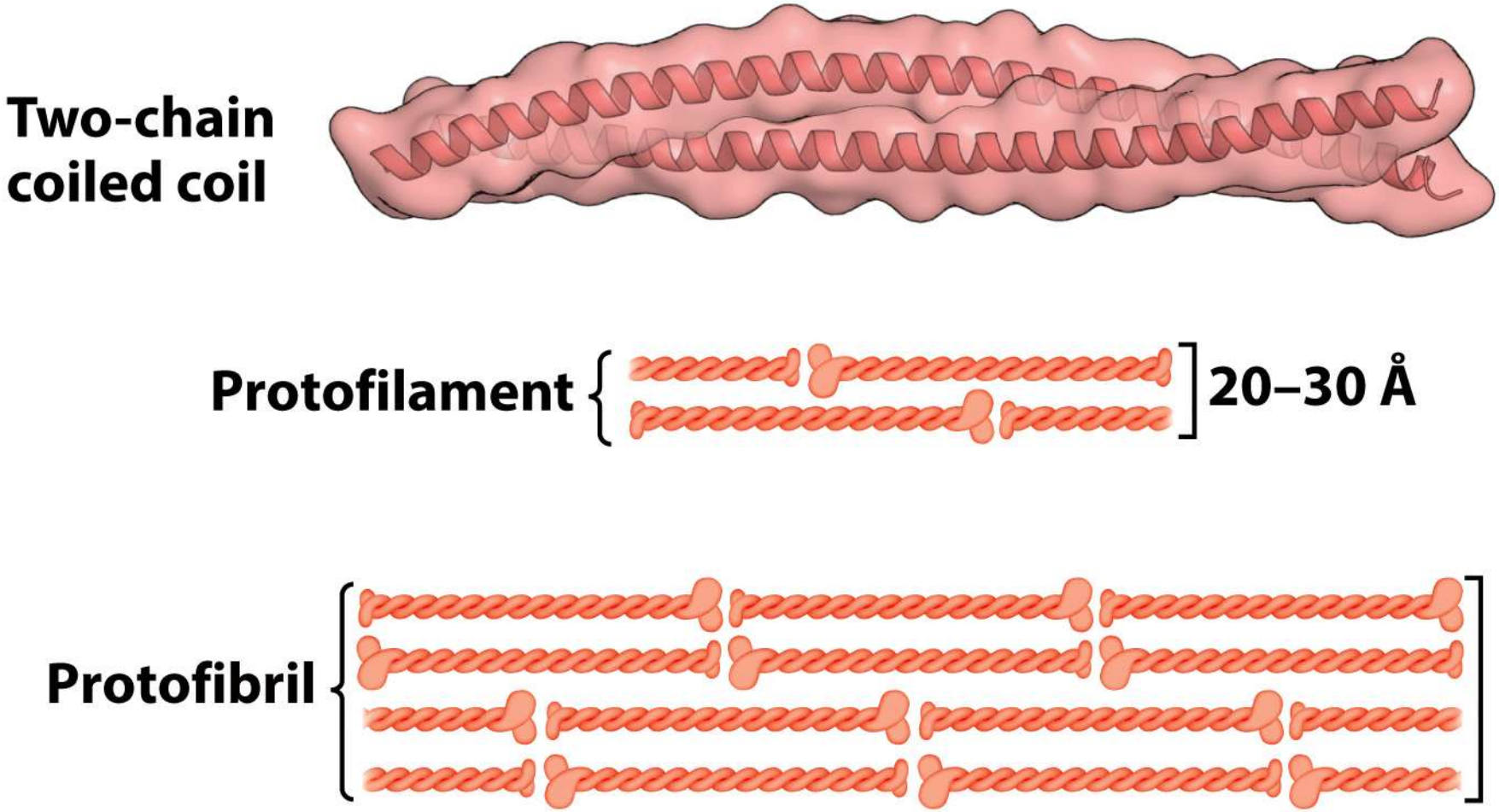

Figure 4-11a
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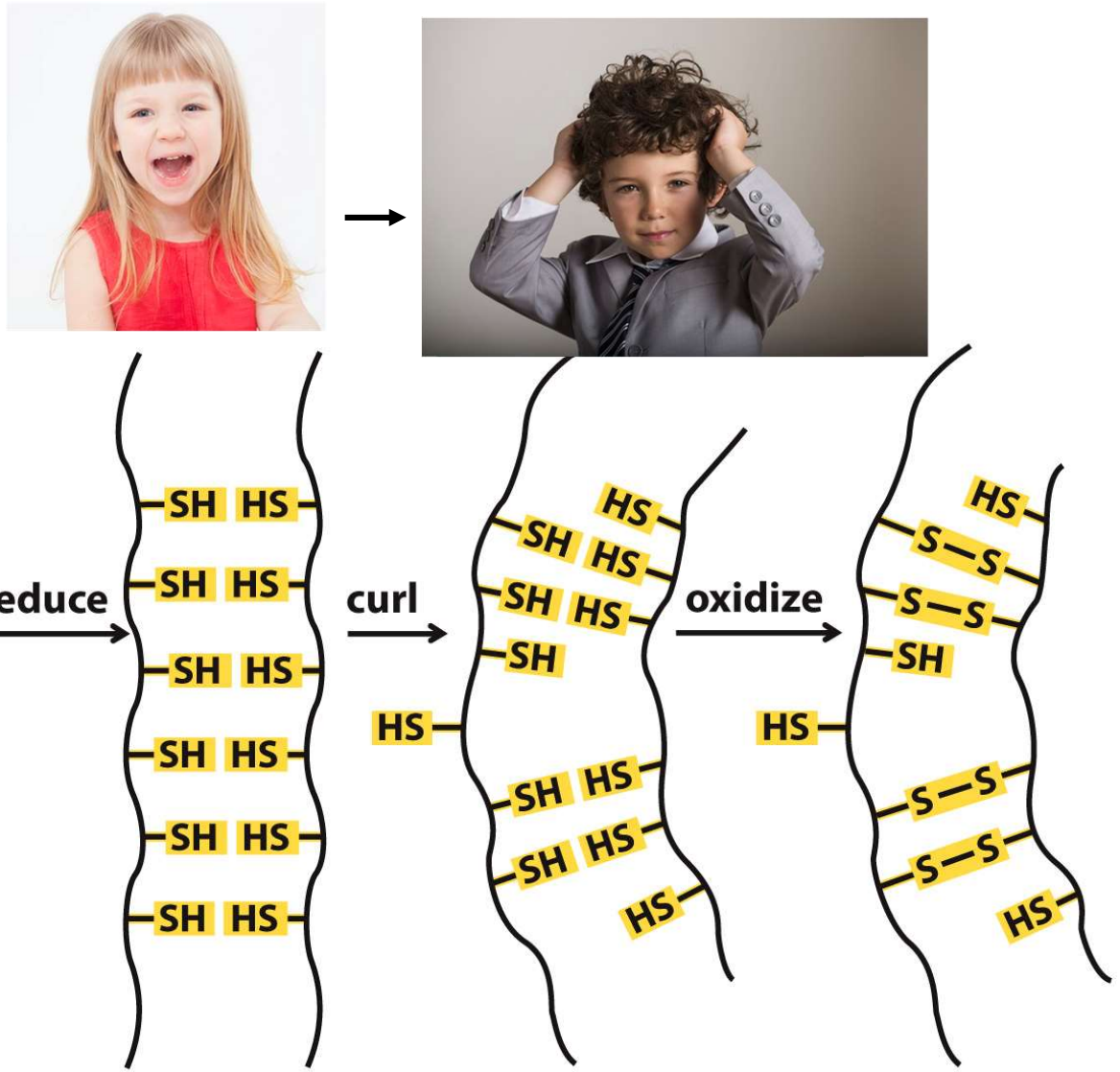
Chemistry of Permanent Waving



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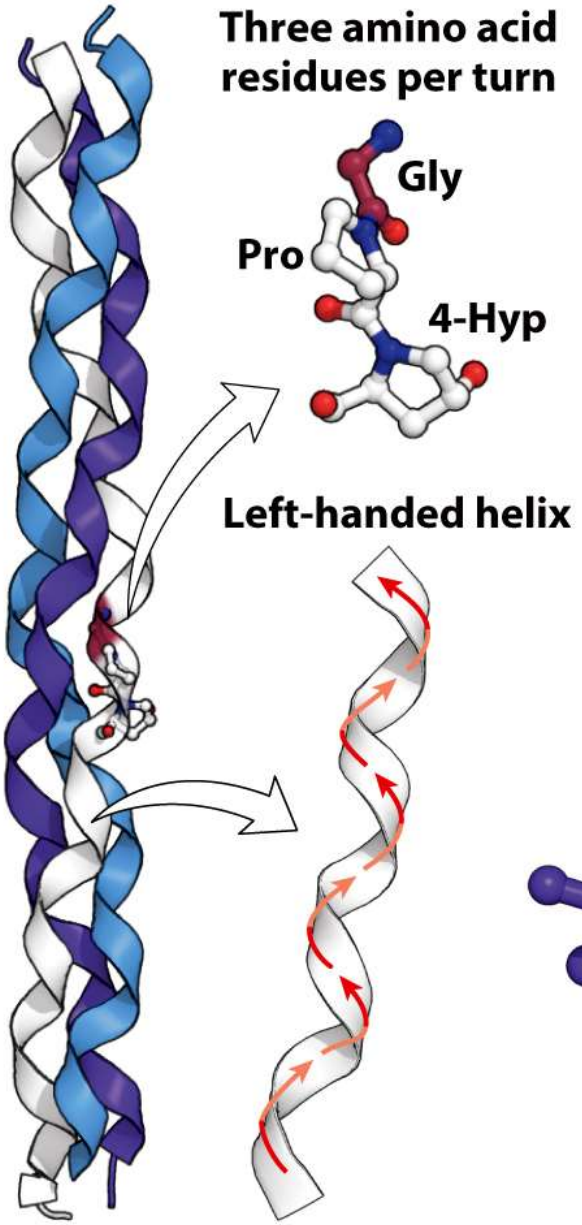
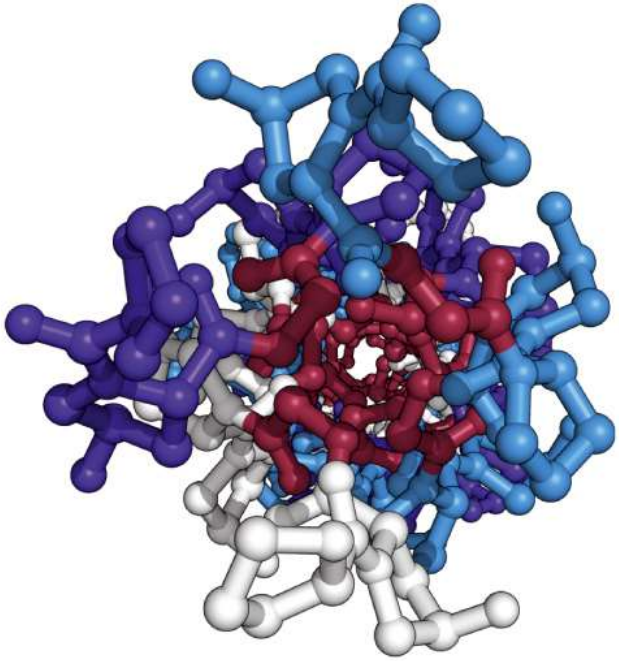
Structure of Collagen

- Collagen is an important constituent of connective tissue: tendons, cartilage, bones, cornea of the eye.
- Each collagen chain is a long Gly- and Pro-rich left-handed helix.
- Three collagen chains intertwine into a right-handed superhelical triple helix.
- The triple helix has higher tensile strength than a steel wire of equal cross section.
- Many triple-helices assemble into a collagen fibril.





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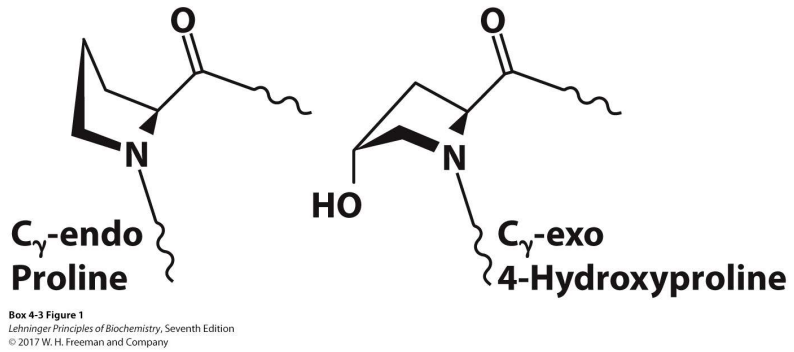

Box 4-3 Figure 1
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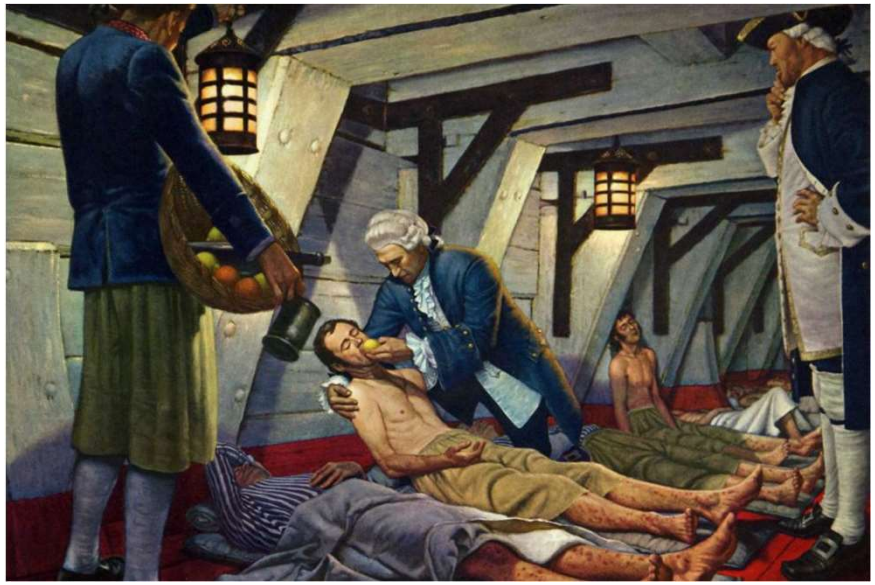
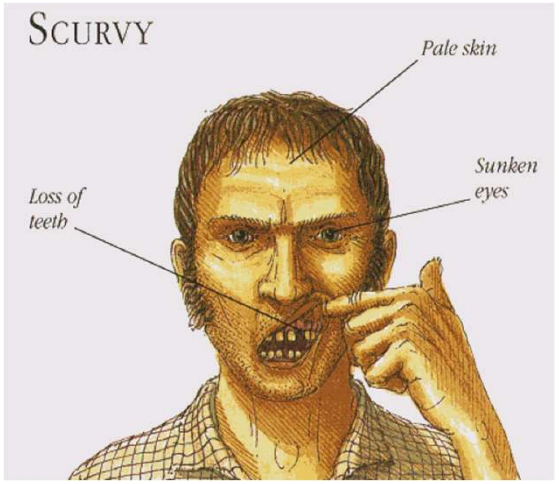
4-Hydroxyproline in Collagen

- Forces the proline ring to be a structure favorable to fold.
- Offers more hydrogen bonds between the three strands of collagen.
- The posttranslational processing is catalyzed by prolyl hydroxylase and requires α-ketoglutarate, molecular oxygen, and ascorbate (vitamin C).

Thom Robert Alan (1959) *James Lind-conqueror of scurvy* Parke, Davis & Company

collagen diseases!





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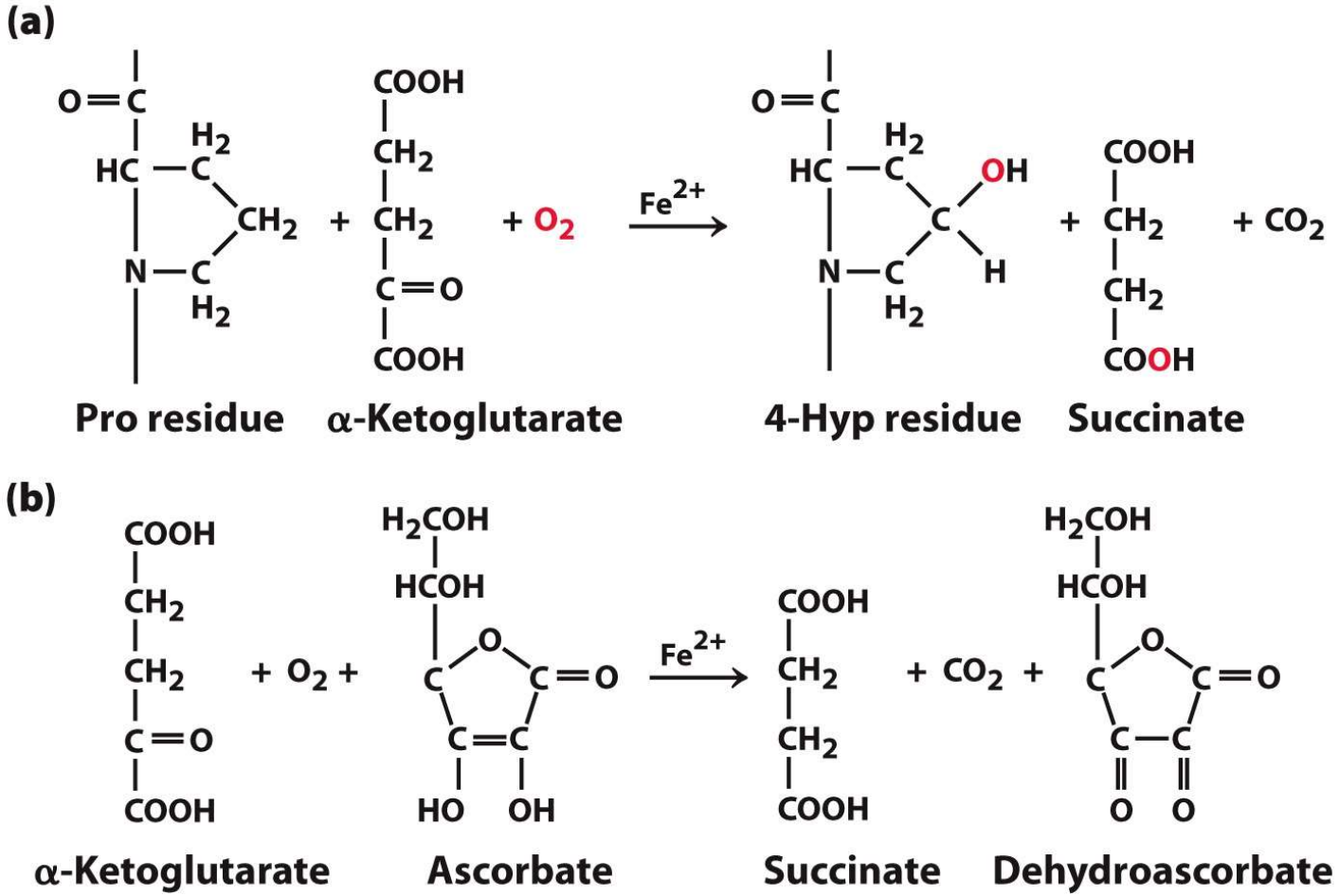
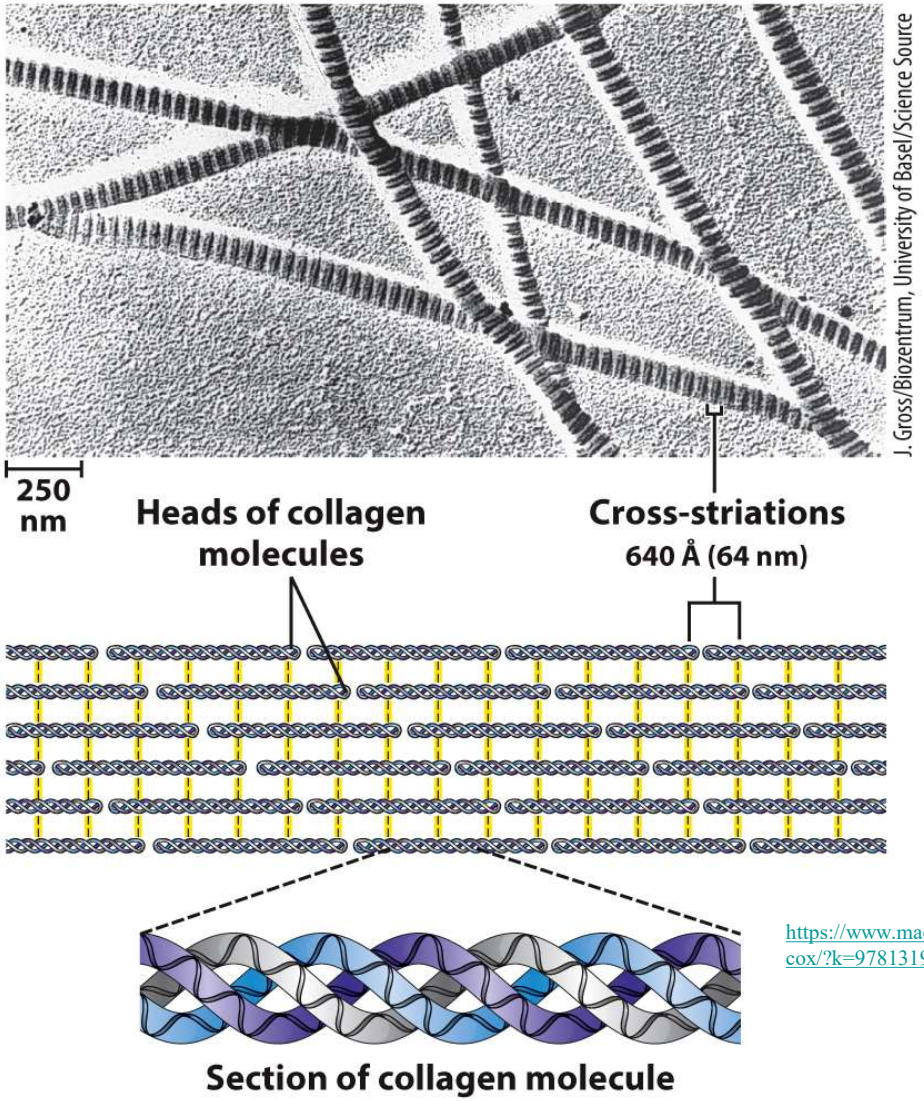
Vitamin C in Prolyl 4-Hydroxylase Restores Fe^{2+}

State: Homework*



Collagen Fibrils



- Collagen superstructures are formed by cross-linking of collagen triple-helices to form collagen fibrils.
- Crosslinks are covalent bonds between Lys or HyLys, or His amino acid residues.

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Figure 4-13
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Water-Soluble Globular Proteins:

X-ray diffraction of myoglobin by John Kendrew *et al*, 1950

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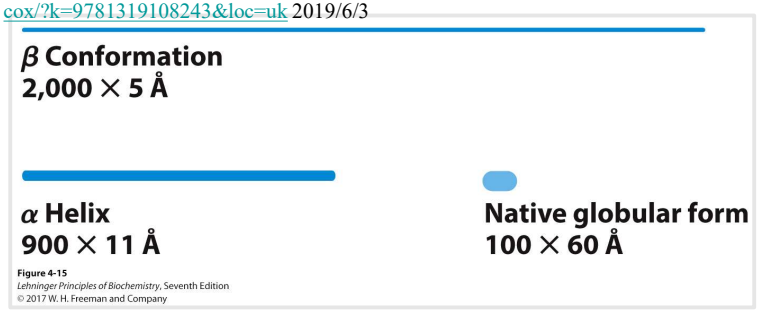
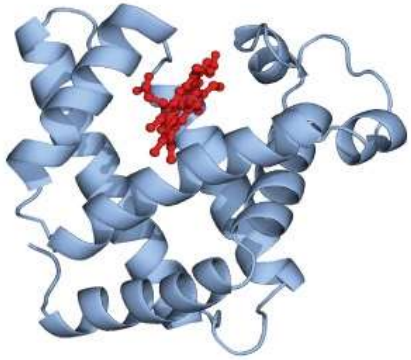
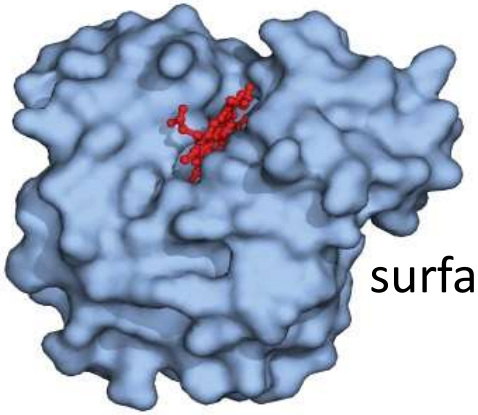


- store oxygen
- facilitate oxygen diffusion in muscle
- single polypeptide with 153 aa + 1 heme

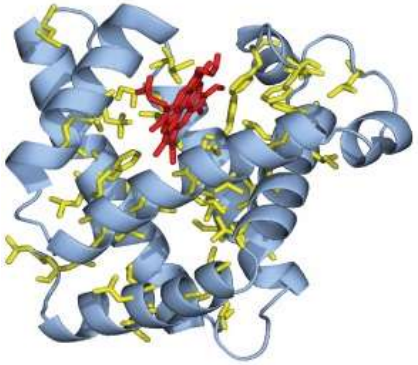
ribbon representation

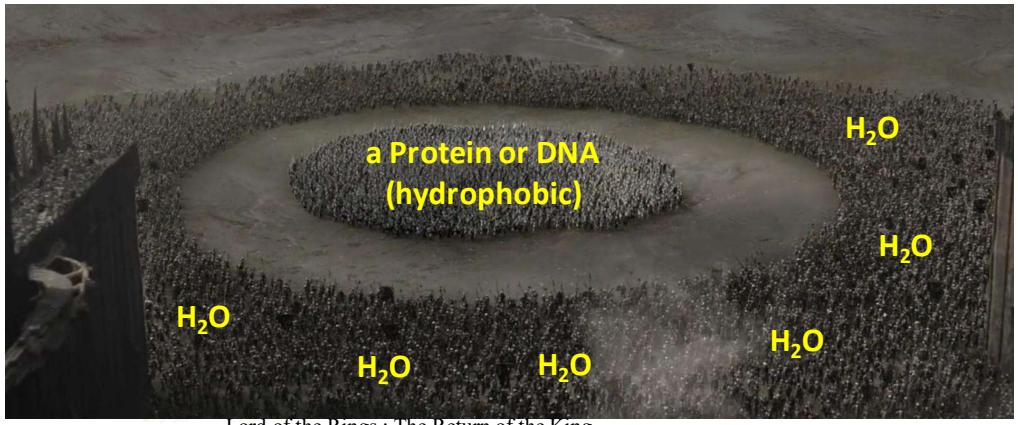




surface contour image

ribbon representation with s-c of LIVF





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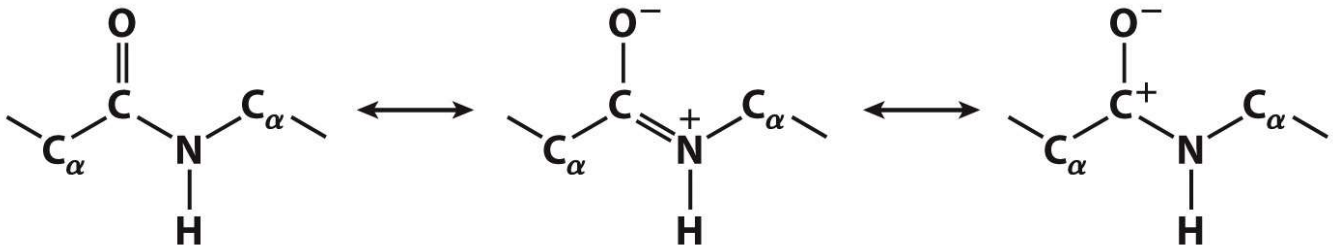
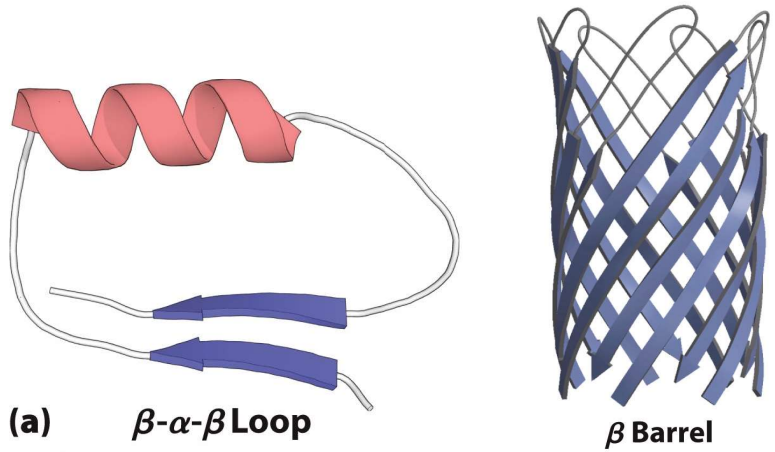
X-ray Diffraction of Myoglobin Confirms:

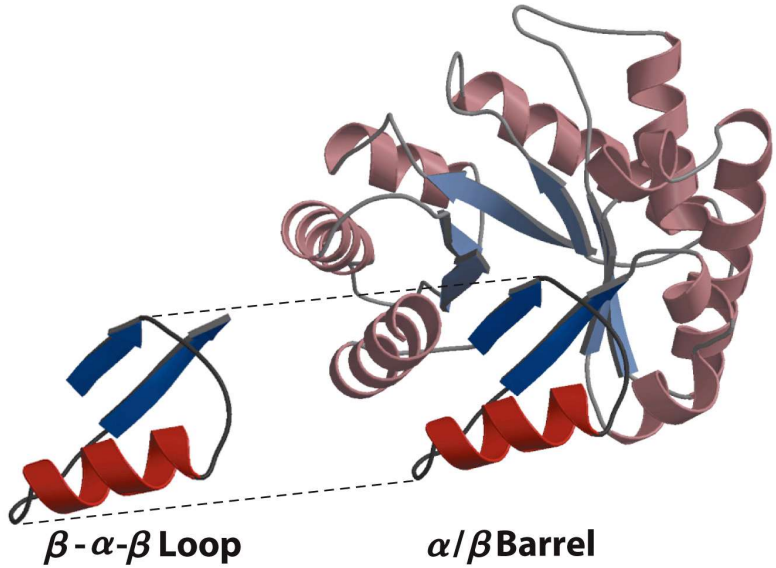


- All the peptide bonds are in the planar trans configuration – the first evidence of such structure!
- Three of the 4 Pro residues are found at bends.
- The fourth Pro residue occurs within an alpha helix, where it creates a kink necessary for tight helix packing.
- The Fe in the heme group binds to His 93.

Repeated Motifs Contribute to Final Fold

- Motifs: Specific arrangement of several secondary structure elements
  - all α helix
  - all β sheet
  - both
- Motifs can be found as recurring structures in numerous proteins.
- Globular proteins are composed of different motifs folded together.
- Domains: independent functionally and structurally.





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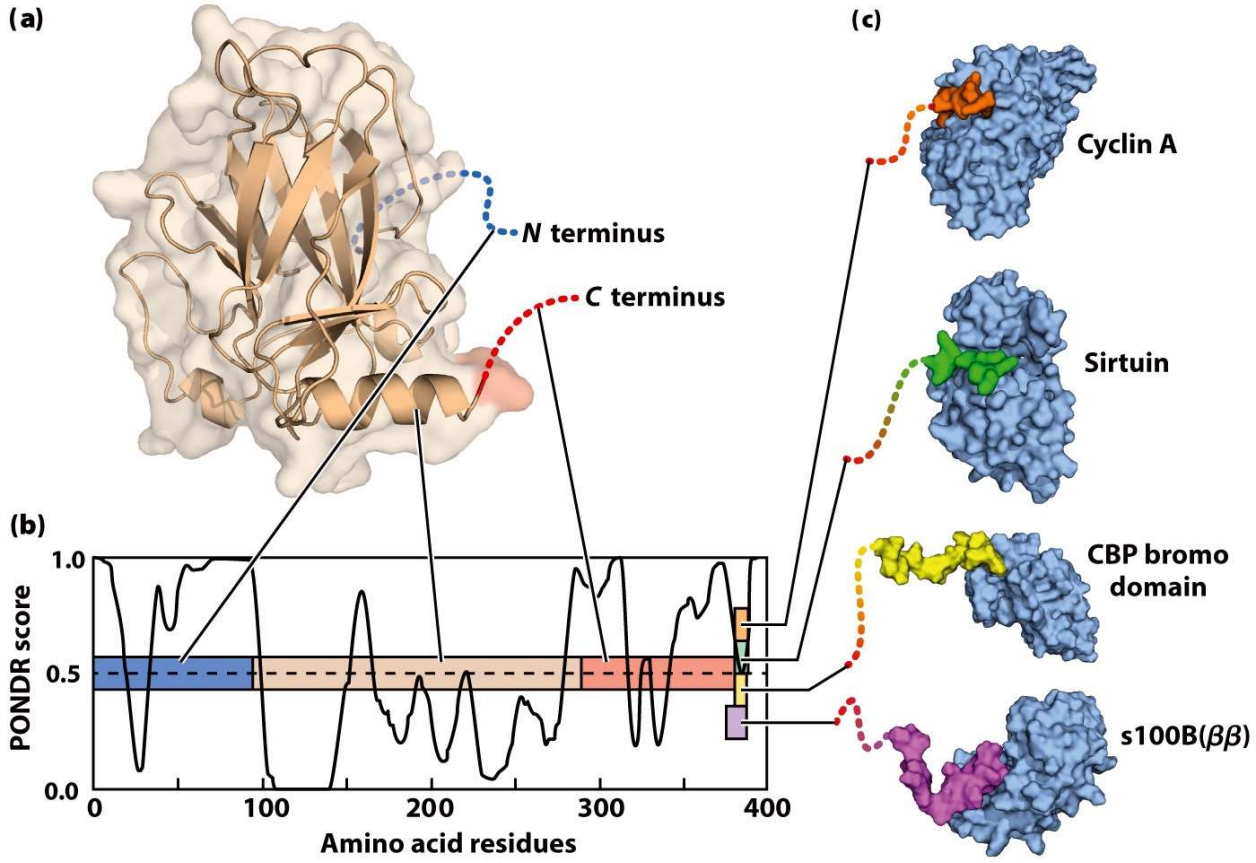
Intrinsically Disordered Proteins

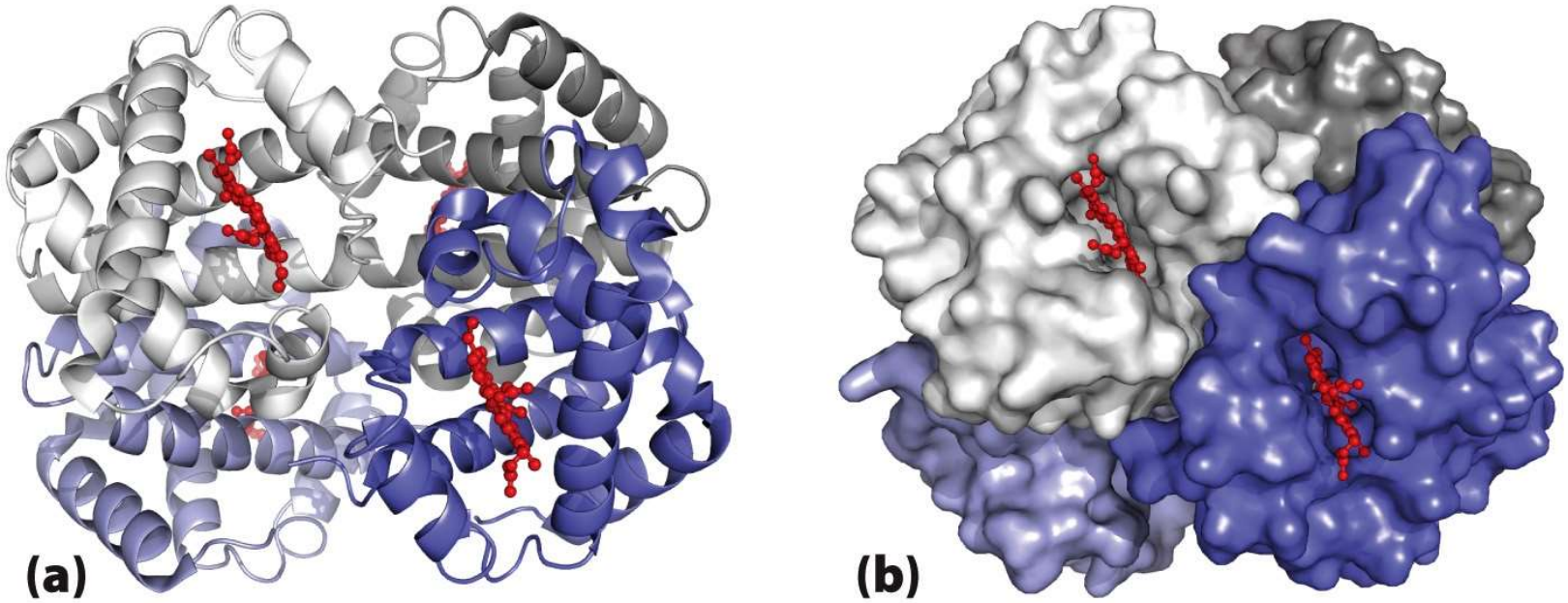
- Contain protein segments composed of amino acids whose higher concentration forces less-defined structure (K, R, E, P)
- Disordered regions can conform to many different proteins, facilitating interaction with numerous different partner proteins.

predictor of natural disordered regions



Quaternary Structure

A quaternary structure is formed by the assembly of individual polypeptides into a larger functional cluster: Subunits, why?



2α (141 aa) + 2β (146 aa)

Protein Structural Determination Methods: X-Ray Crystallography

Steps needed

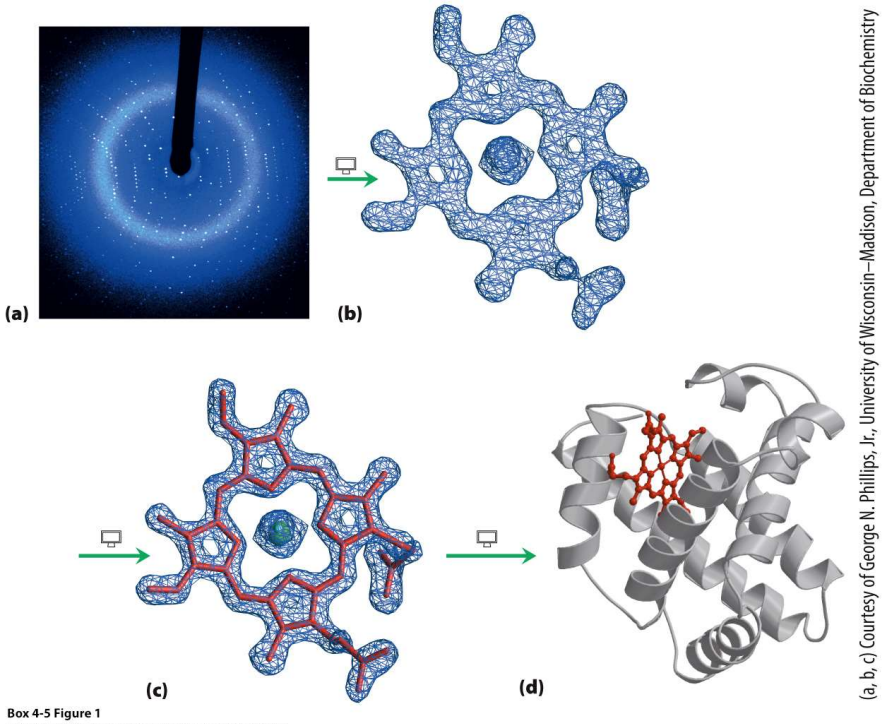
- purify the protein
- crystallize the protein
- collect diffraction data
- calculate electron density
- fit known amino acid residues into density

Pros

- no size limits
- well established

Cons

- difficult for membrane proteins
- cannot resolve (see) hydrogens



Box 4-5 Figure 1
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(a, b, c) Courtesy of George N. Phillips, Jr., University of Wisconsin–Madison, Department of Biochemistry

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Protein Structural Determination Methods: Biomolecular NMR

Steps needed

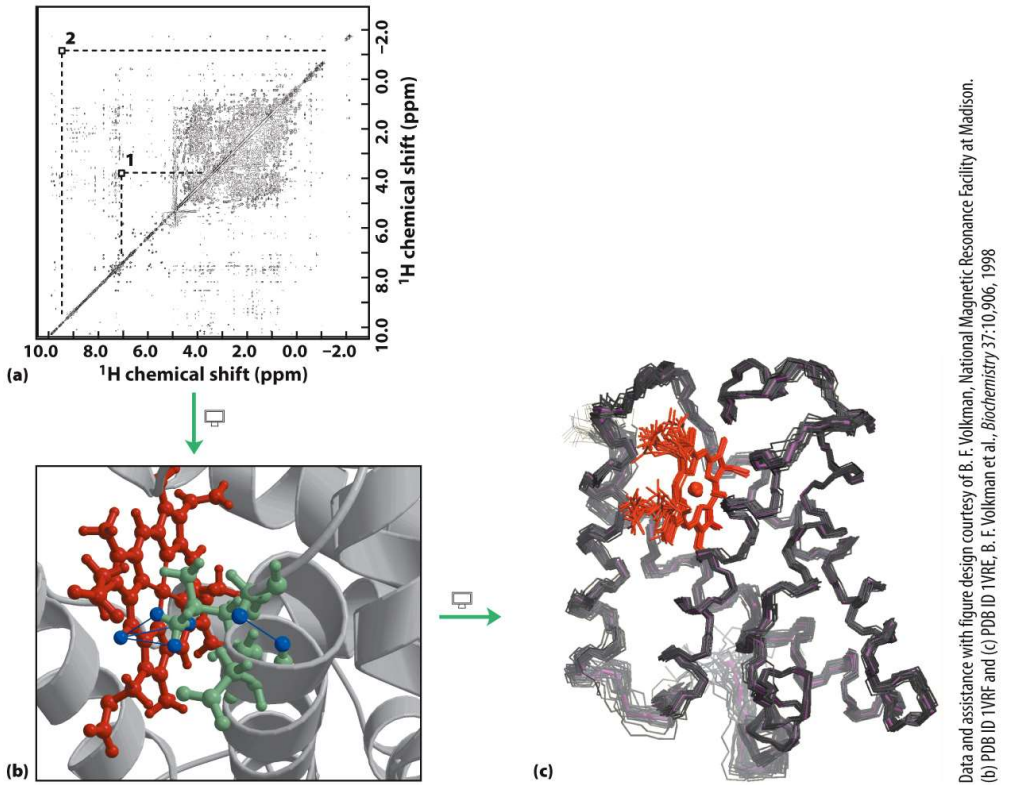
- purify the protein
- dissolve the protein
- collect NMR data
- assign NMR signals
- calculate the structure

Pros

- no need to crystallize the protein
- can see many hydrogens

Cons

- difficult for insoluble proteins
- works best with small proteins



Box 4-5 Figure 3
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Data and assistance with figure design courtesy of B. F. Volkman, National Magnetic Resonance Facility at Madison. (b) PDB ID 1VRF and (c) PDB ID 1VRE, B. F. Volkman et al., *Biochemistry* 37:10,906, 1998

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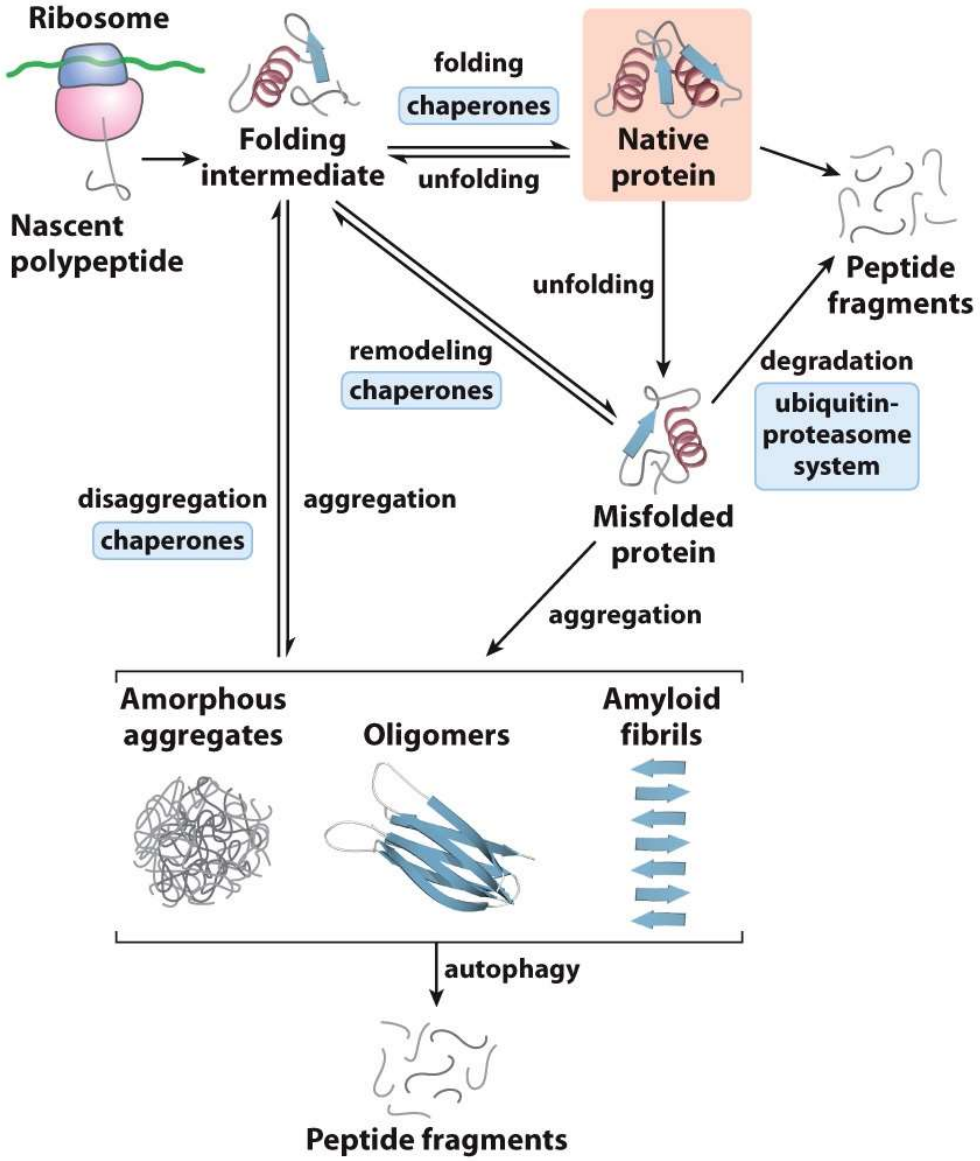
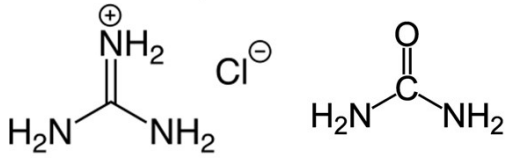
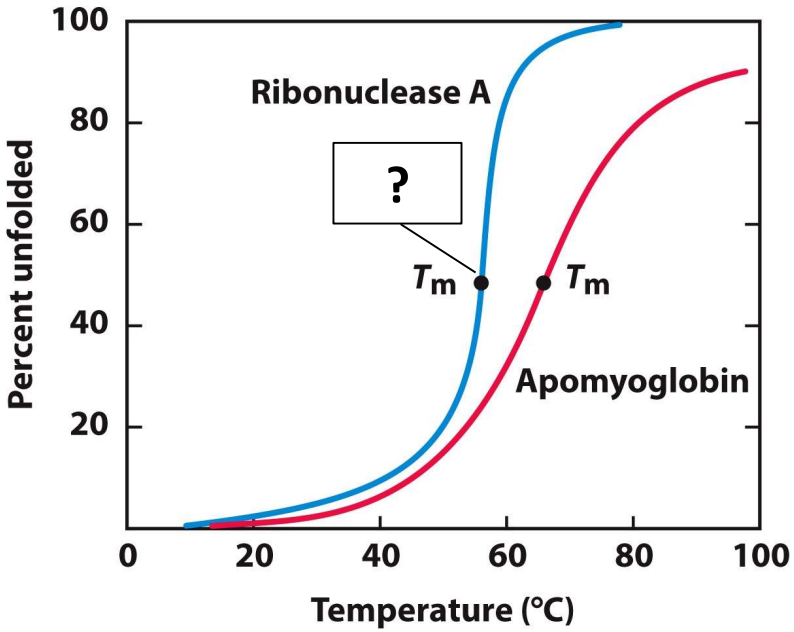
Proteostasis: The life of a protein

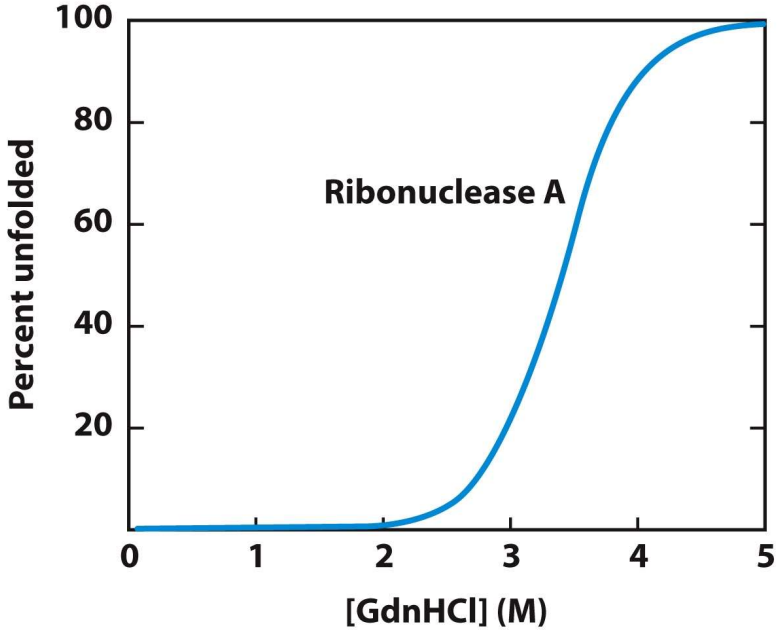


Protein Stability and Folding

- Loss of structural integrity with accompanying loss of activity is called denaturation.
- Proteins can be denatured by: temp, pH, organic solvents, chaotropic agents (urea, guanidine hydrochloride)

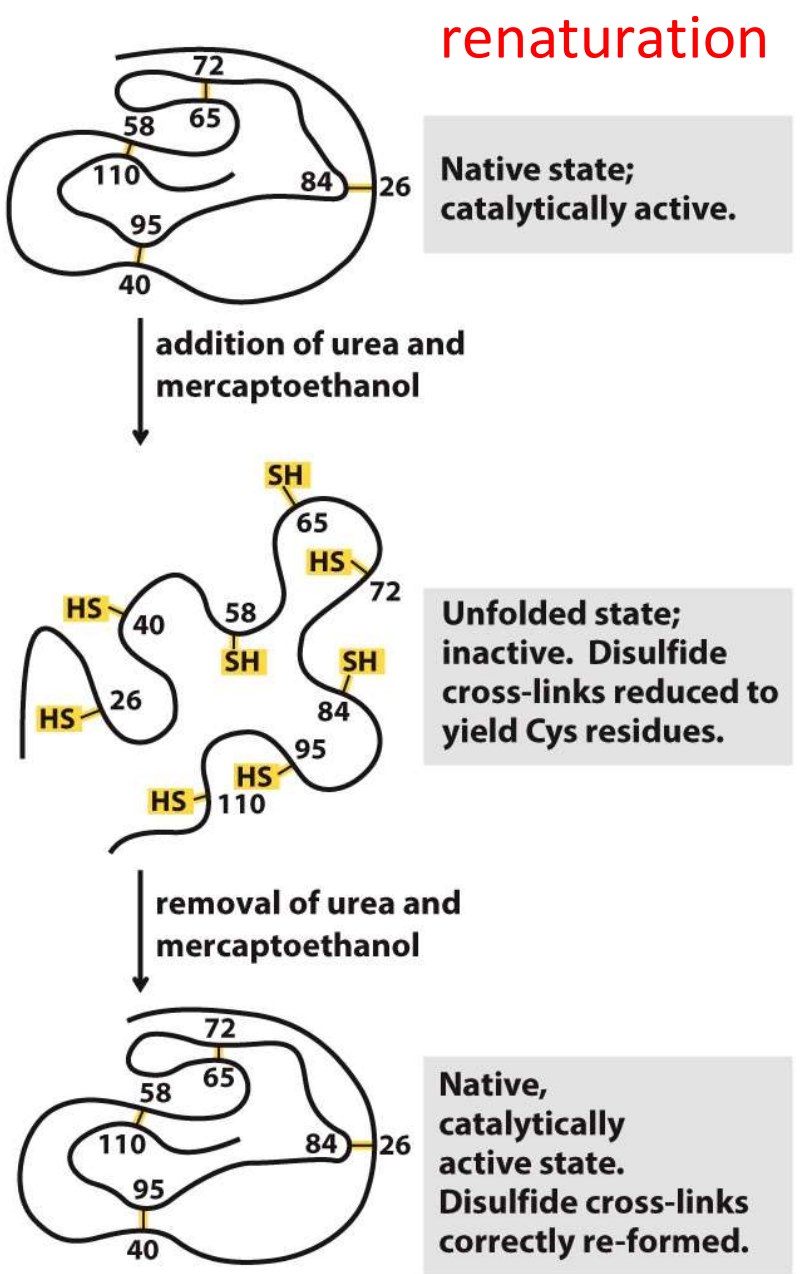






Ribonuclease Refolding

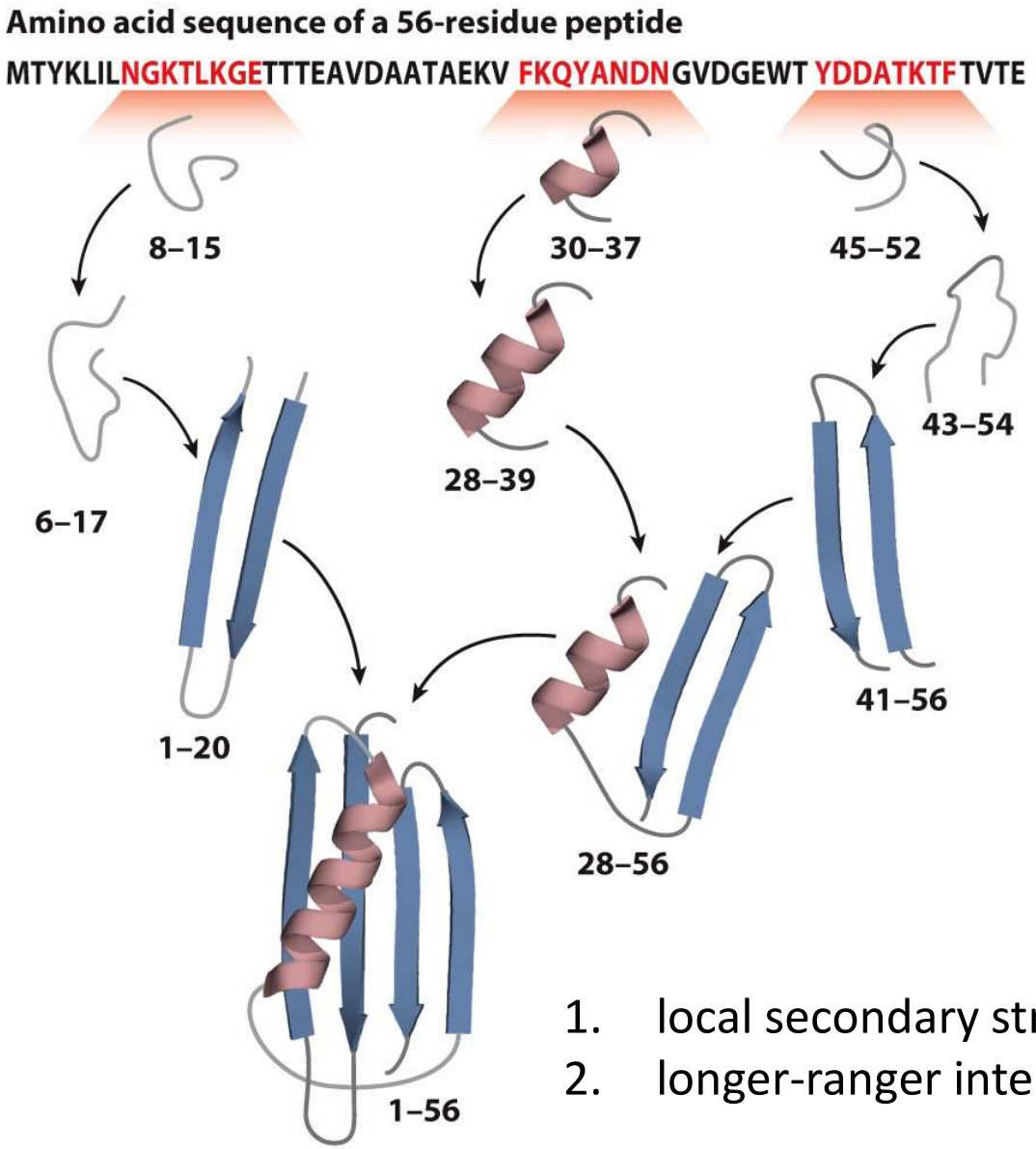
- Ribonuclease is a small protein that contains eight cysteines linked via four disulfide bonds.
- Urea in the presence of 2-mercaptoethanol fully denatures ribonuclease.
- When urea and 2-mercaptoethanol are removed, the protein spontaneously refolds, and the correct disulfide bonds are reformed.
- **The sequence alone determines the native conformation.**
- 1972 Chemistry Nobel Prize (Christian B. Anfinsen)



How Can Proteins Fold So Fast?

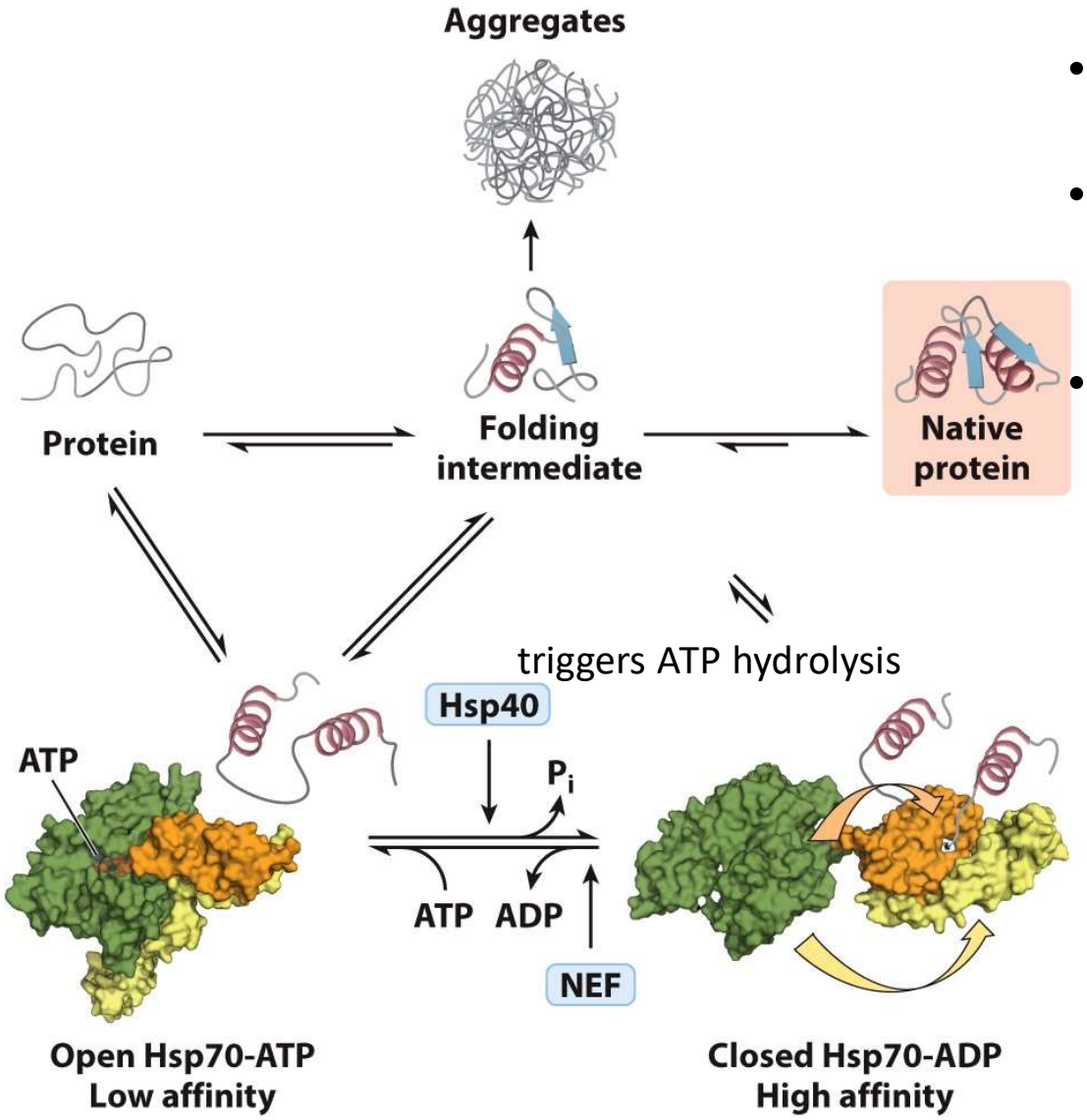
- Proteins fold to the lowest-energy fold in the microsecond to second time scales. How can they find the right fold so fast?
- It is mathematically impossible for protein folding to occur by randomly trying every conformation until the lowest-energy one is found (Levinthal's paradox).
- Search for the minimum is not random because the direction toward the native structure is **thermodynamically most favorable**.

Proteins Folding Follow a Distinct Path



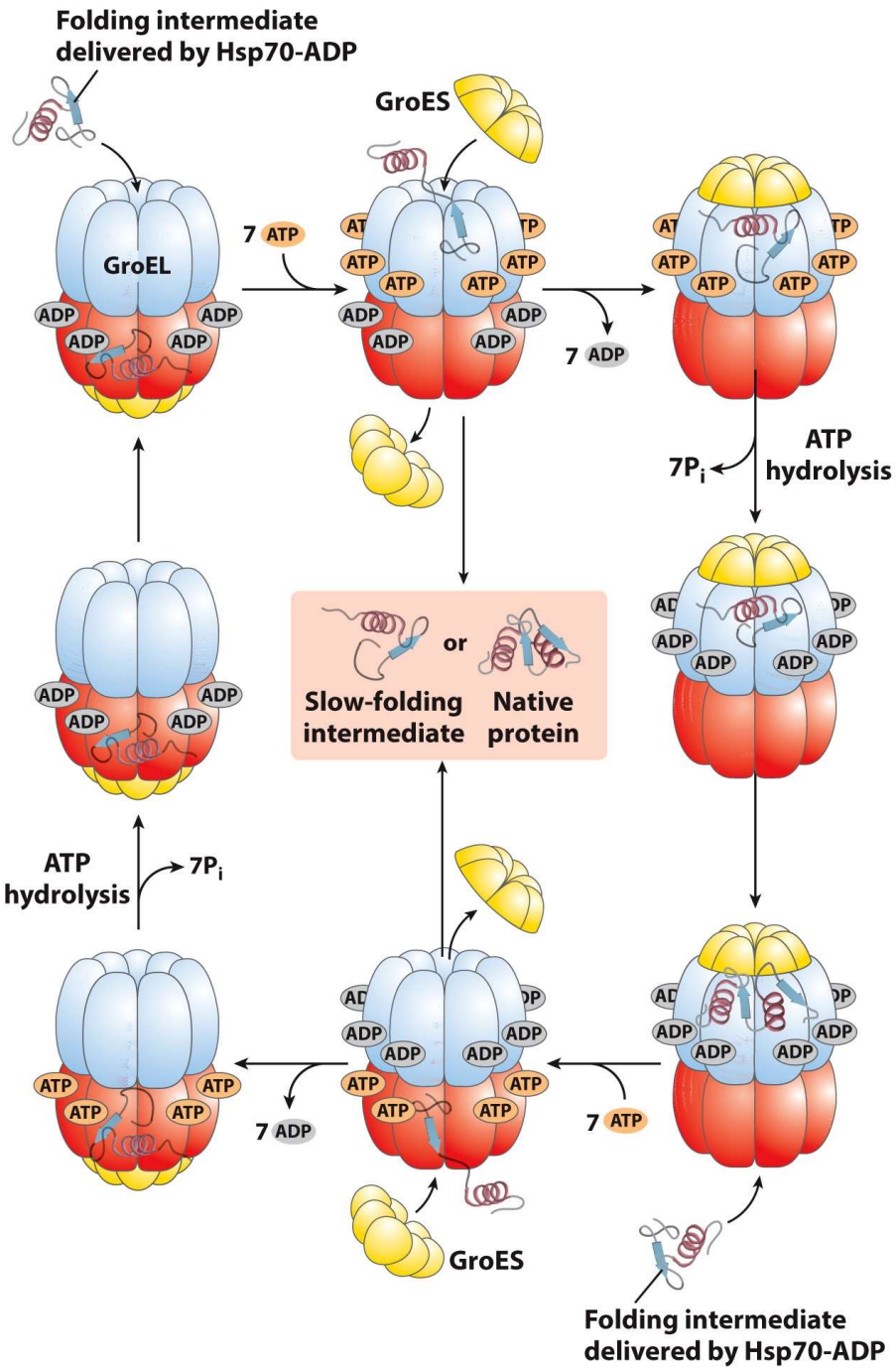
1. local secondary structures form
2. longer-ranger interaction

Chaperones Prevent Misfolding and Aggregation of Unfolded Peptides



- interact with partially- or mis-folded protein
- facilitate folding pathways or provide the microenvironments
- prevent aggregation

Chaperonins



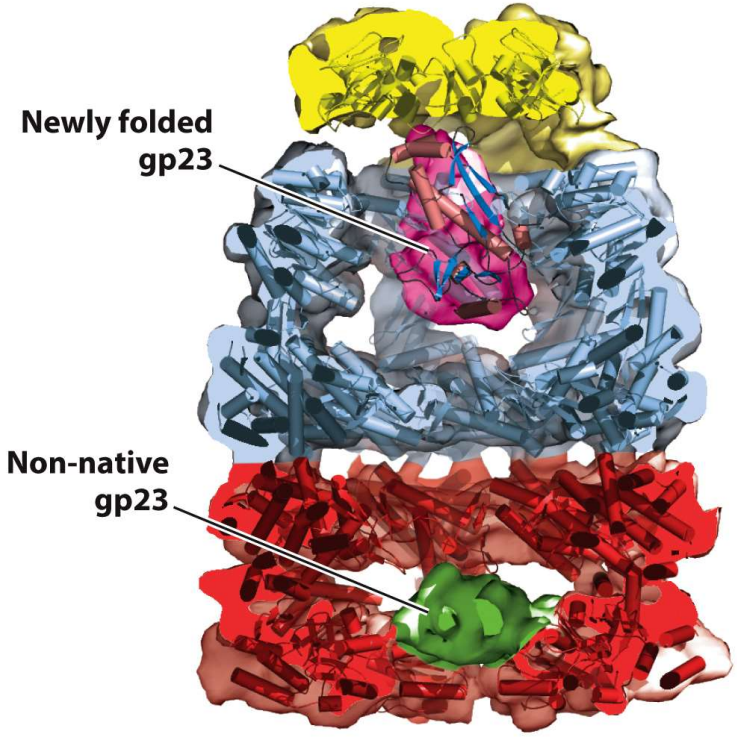


Figure 4-31b
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Protein Misfolding Is the Basis of Numerous Human Diseases

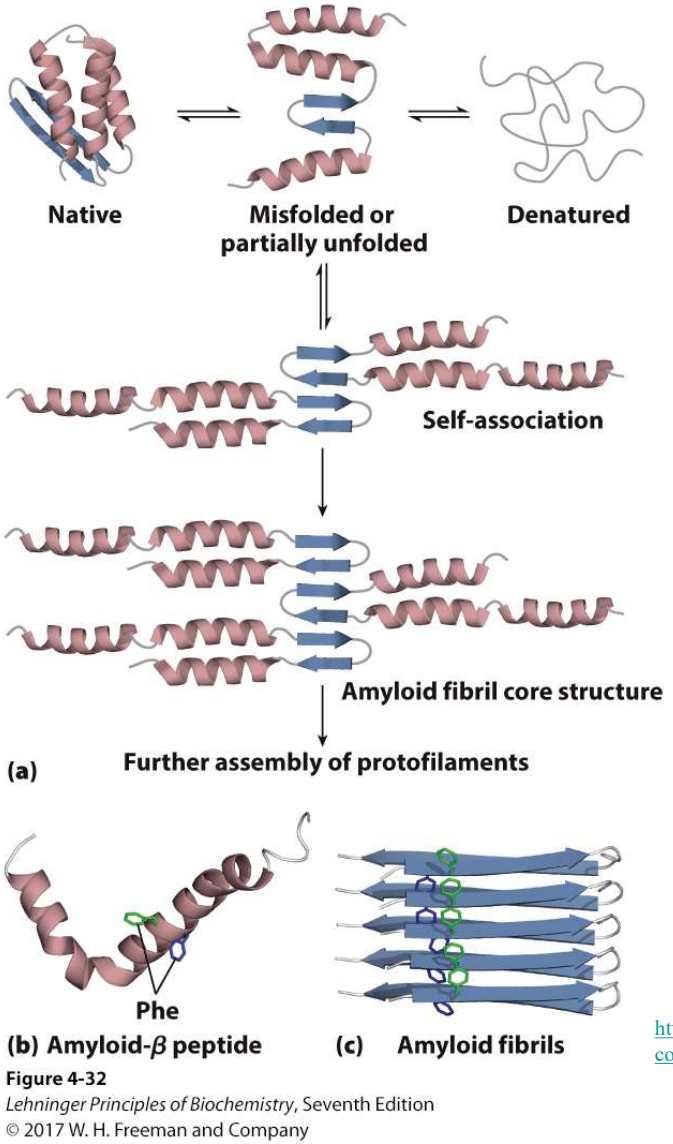

Figure 4-32
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- Native (correctly folded) β amyloid is a soluble globular protein,
- Misfolded β amyloid promotes aggregation at newly exposed protein-protein interface.
- Correctly folded helices are lost and peptides form β strands, β helices, and β sheets.

Homework!

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Summary

- the two most important secondary structures
  - α helices
  - β sheets
- Properties and function of fibrous proteins are related by their structures.
- Three-dimensional structures of proteins: protein folding and denaturation – one of the largest unsolved questions in biochemistry