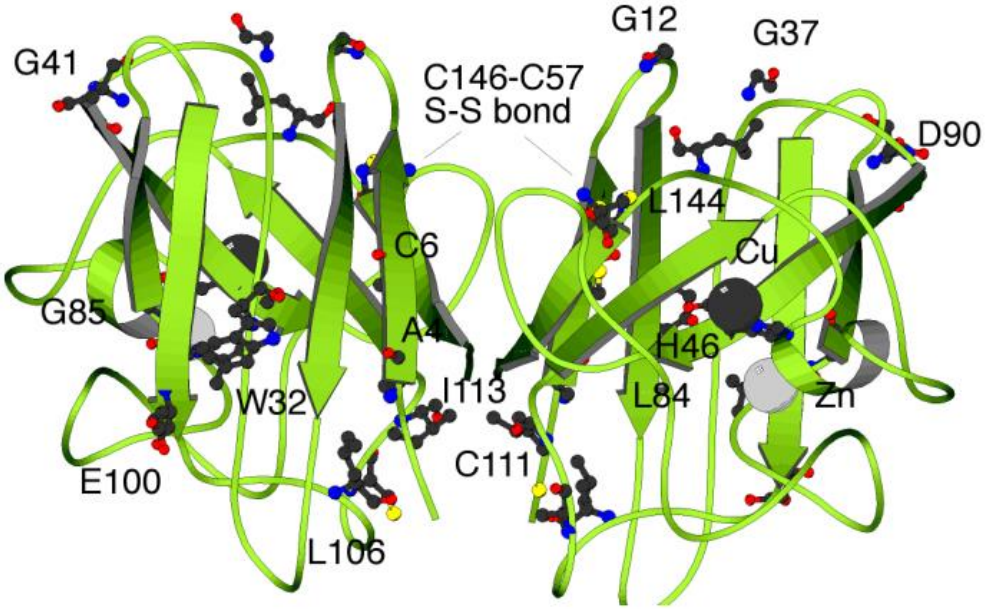
Chemistry of Amino acids, Peptides and Proteins (3 hr)



Model illustrating the formation of a misfolded species (M) from a folding intermediate (I). The region of the protein that misfolds is shown in red. The misfolded protein itself, or a self-assembled form, may be toxic to cells, leading to disease. The black arrows represent the relative rates of the various conformational events under native physiological conditions in the absence of mutation. The blue dash arrows represent the possible effects of mutation.

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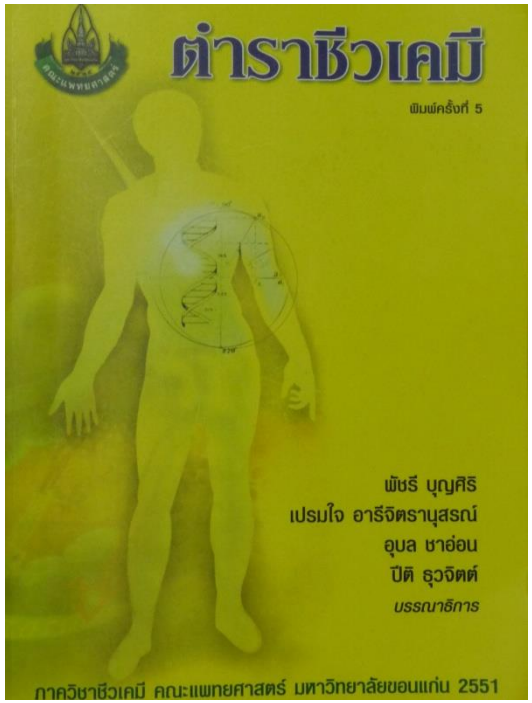
Objectives

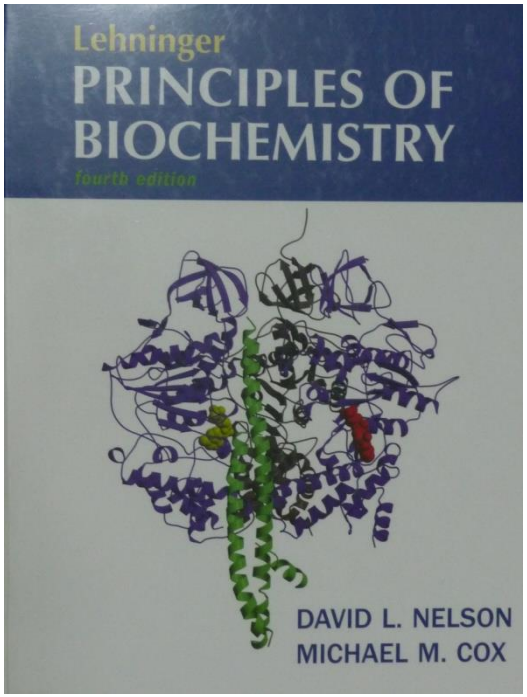
1. Amino acid
    - 1.1 Definition
    - 1.2 Structure of α amino acid
    - 1.3 Standard amino acids
    - 1.4 Essential amino acid
    - 1.5 Physical and chemical properties of amino acids
    - 1.6 Biological role of amino acid
2. Peptide
    - 2.1 Definition
    - 2.2 Peptide bond is covalent bond
    - 2.3 Buffer property
3. Protein
    - 3.1 Definition
    - 3.2 Protein structure
    - 3.3 protein denaturation/renaturation
    - 3.4 Functional roles of proteins

References:

1. ตำราชีวเคมี, พัชรี บุญศิริและคณะ (บรรณาธิการ) ภาควิชาชีวเคมี คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น พิมพ์ครั้งที่ 5 (2551)

2. Principles of Biochemistry (Lehninger), David L. Nelson & Michael M. Cox (editors), W.H. Freeman and Company, New York, Forth edition (2005)

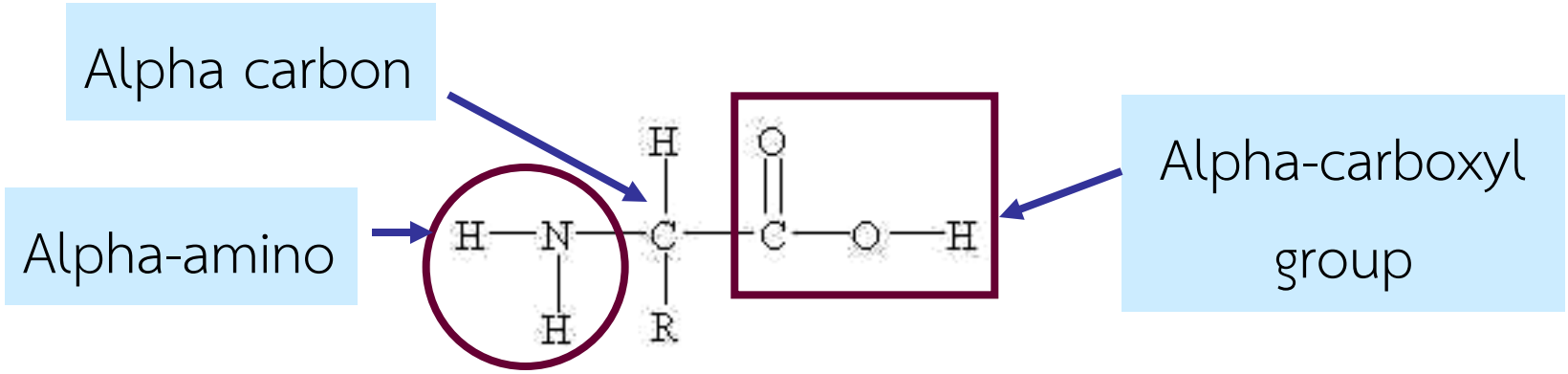




Amino acids

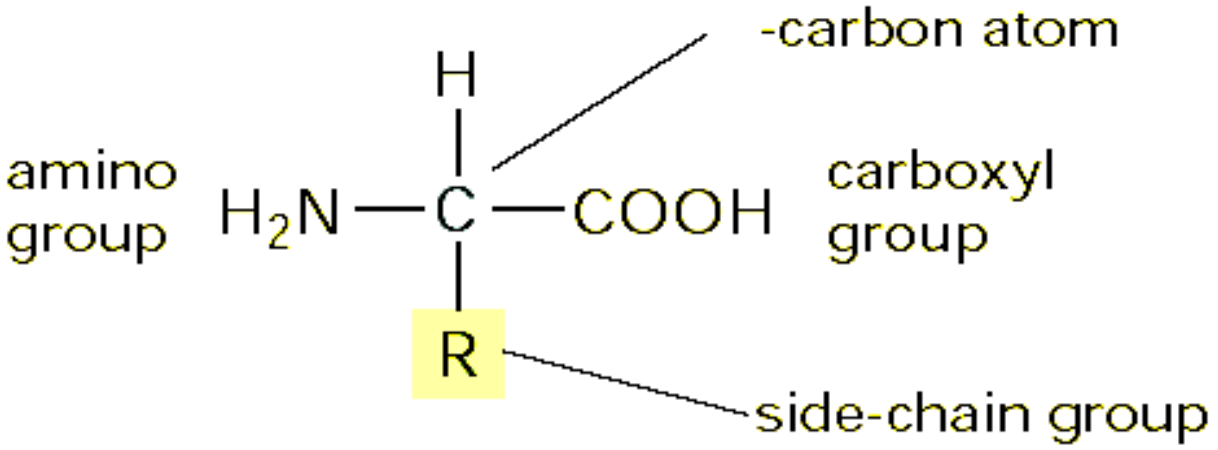
Amino acids are the monomer (building block) of proteins by which each amino acid residue joined to its neighbor by a specific type of covalent bond.

Structure of amino acid

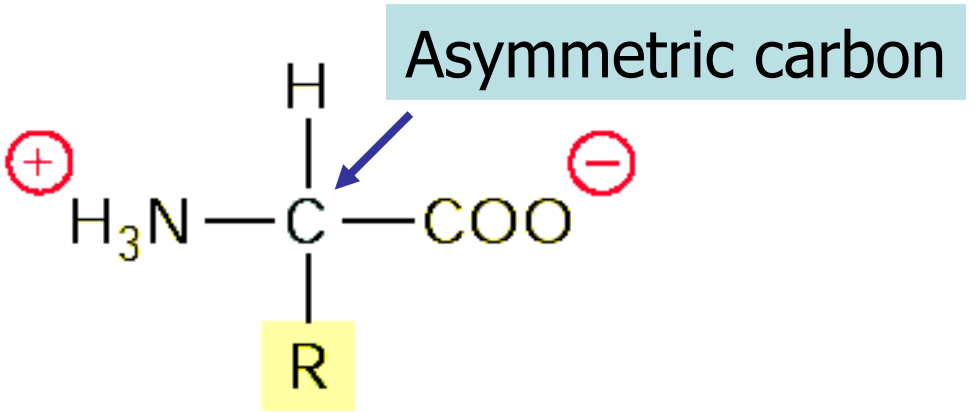


Functional groups of amino acids

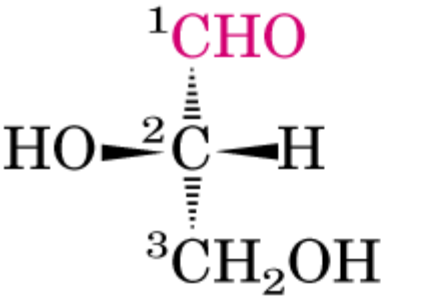
The general formula of an amino acid is



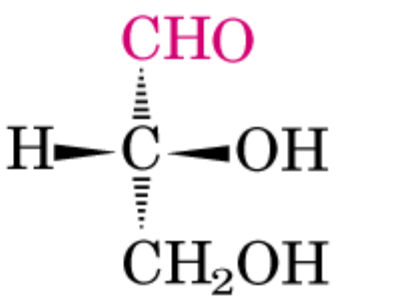
R is commonly one of 20 different side chains. At pH 7 both the amino and carboxyl groups are ionized.



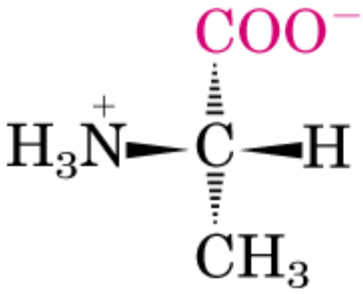
The Amino Acid Residues in Proteins Are L Sterioisomers



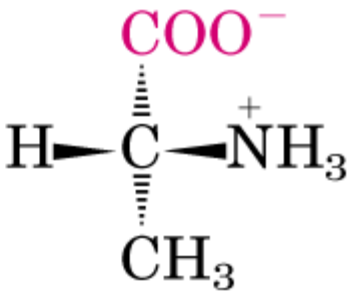
L-Glyceraldehyde



D-Glyceraldehyde



L-Alanine



D-Alanine

Standard amino acids

Asparagine (Asn) (1806)
Alanine (Ala)
Arginine (Arg)
Aspartic acid (Asp)
Cysteine (Cys)
Glutamic acid (Glu)
Glutamine (Gln)
Glycine (Gly)
Histidine (His)
Isoleucine (Ile)
Leucine (Leu)
Lysine (Lys)
Methionine (Met)
Phenylalanine (Phe)
Proline (Pro)
Serine (Ser)
Threonine (Thr) (1938)
Tryptophan (Trp)
Tyrosine (Tyr)
Valine (Val)

Essential amino acids

Amino acids that are no able to be synthesized so need to get from food.

Histidine
Isoleucine
Leucine
Lysine
Methionine
Phenylalanine
Threonine
Tryptophan
Valine
Arginine (small amount can be synthesized from urea cycle)

Amino Acids Can Be Classified by R Group

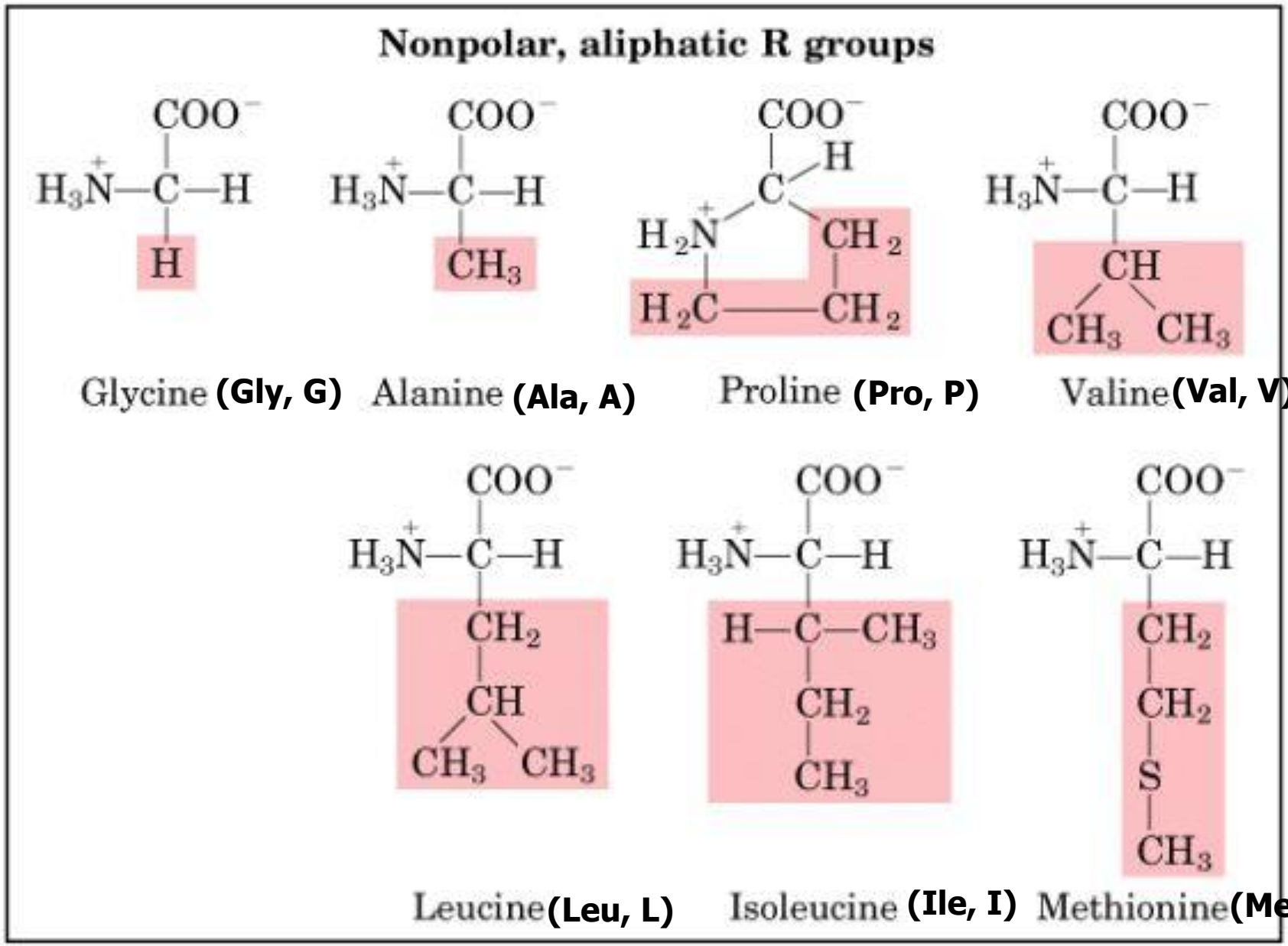
The common amino acids are grouped according to whether their side chains are

- **Nonpolar, aliphatic R groups**
- **Polar, uncharged R groups**
- **Aromatic R groups**
- **Positive charged R groups**
- **Negative charged R groups**

These 20 amino acids are given both three-letter and one-letter abbreviations.

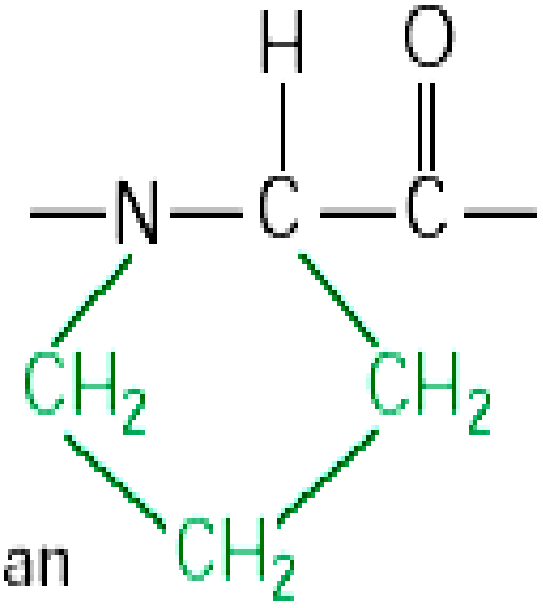
Thus: alanine = Ala = A

Nonpolar, aliphatic R groups



proline

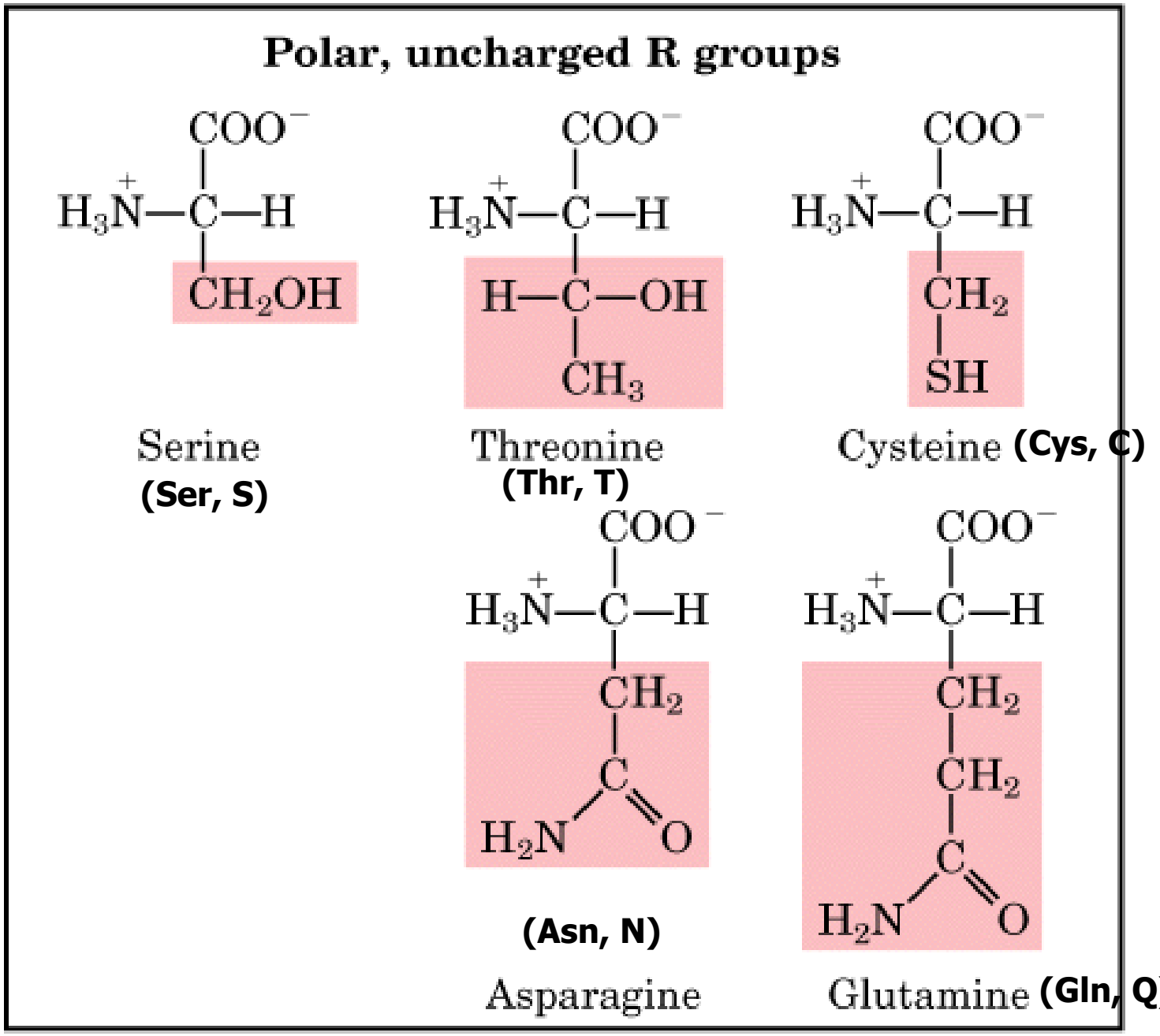
(Pro, or P)

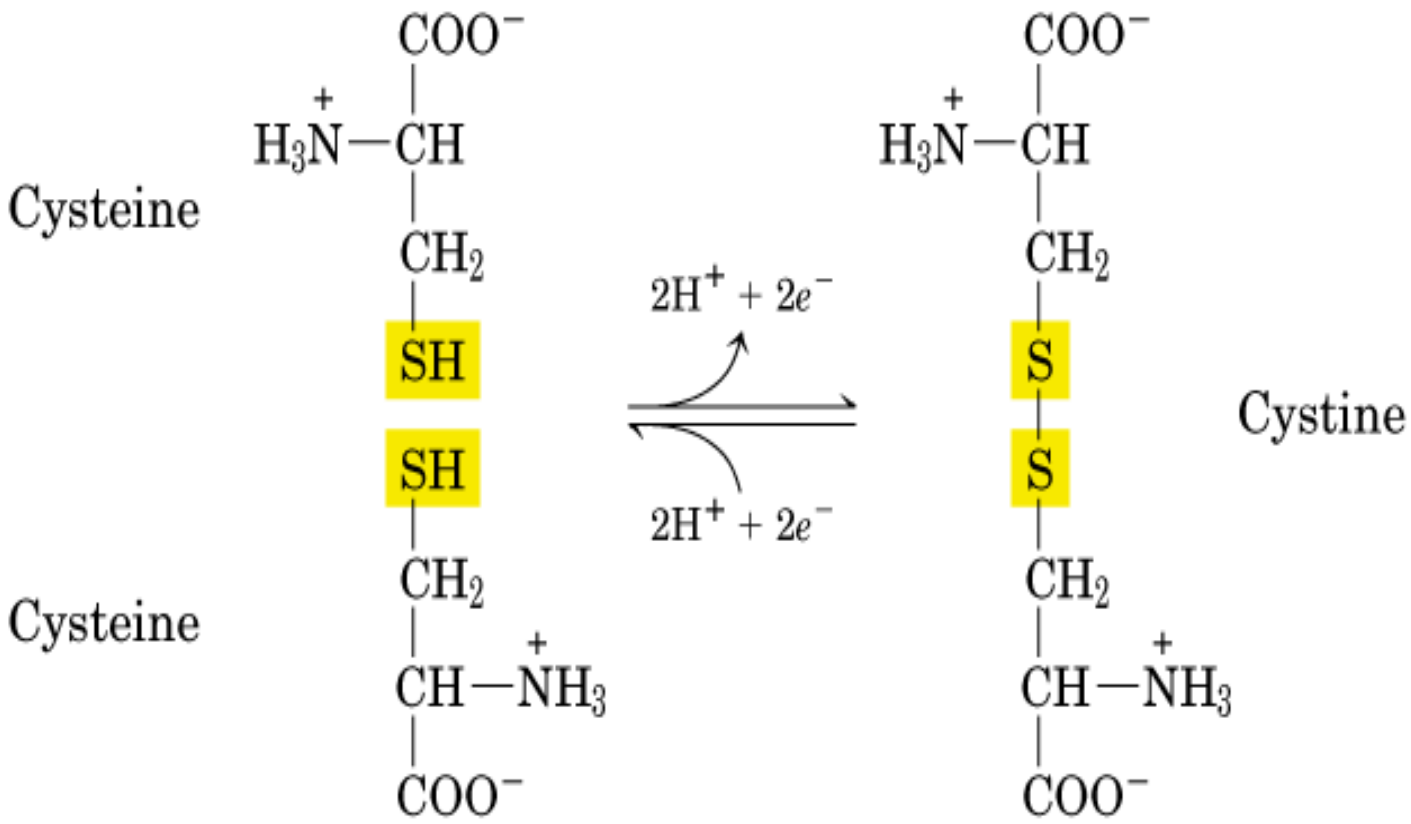


(actually an imino acid)

Proline has an aliphatic side chain with a distinctive cyclic structure which held in a rigid conformation that reduces the structural flexibility of polypeptide regions containing proline.

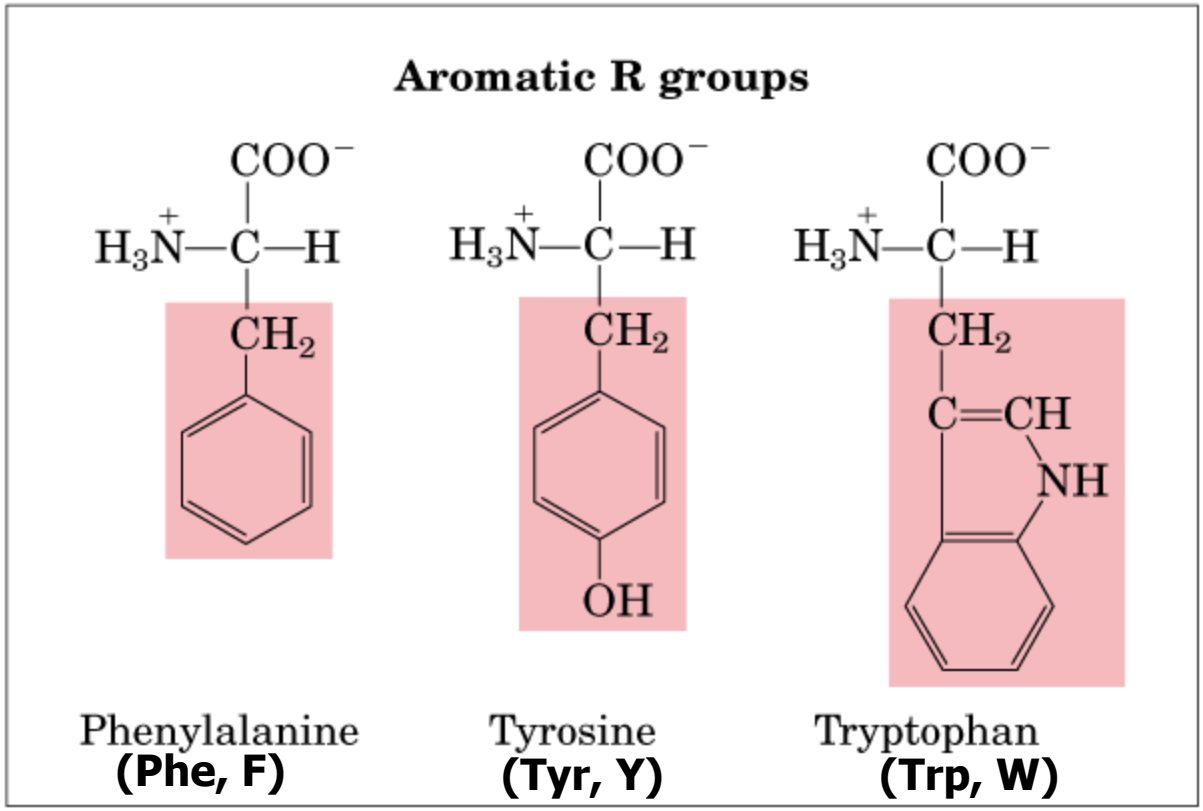
Polar, uncharged R groups



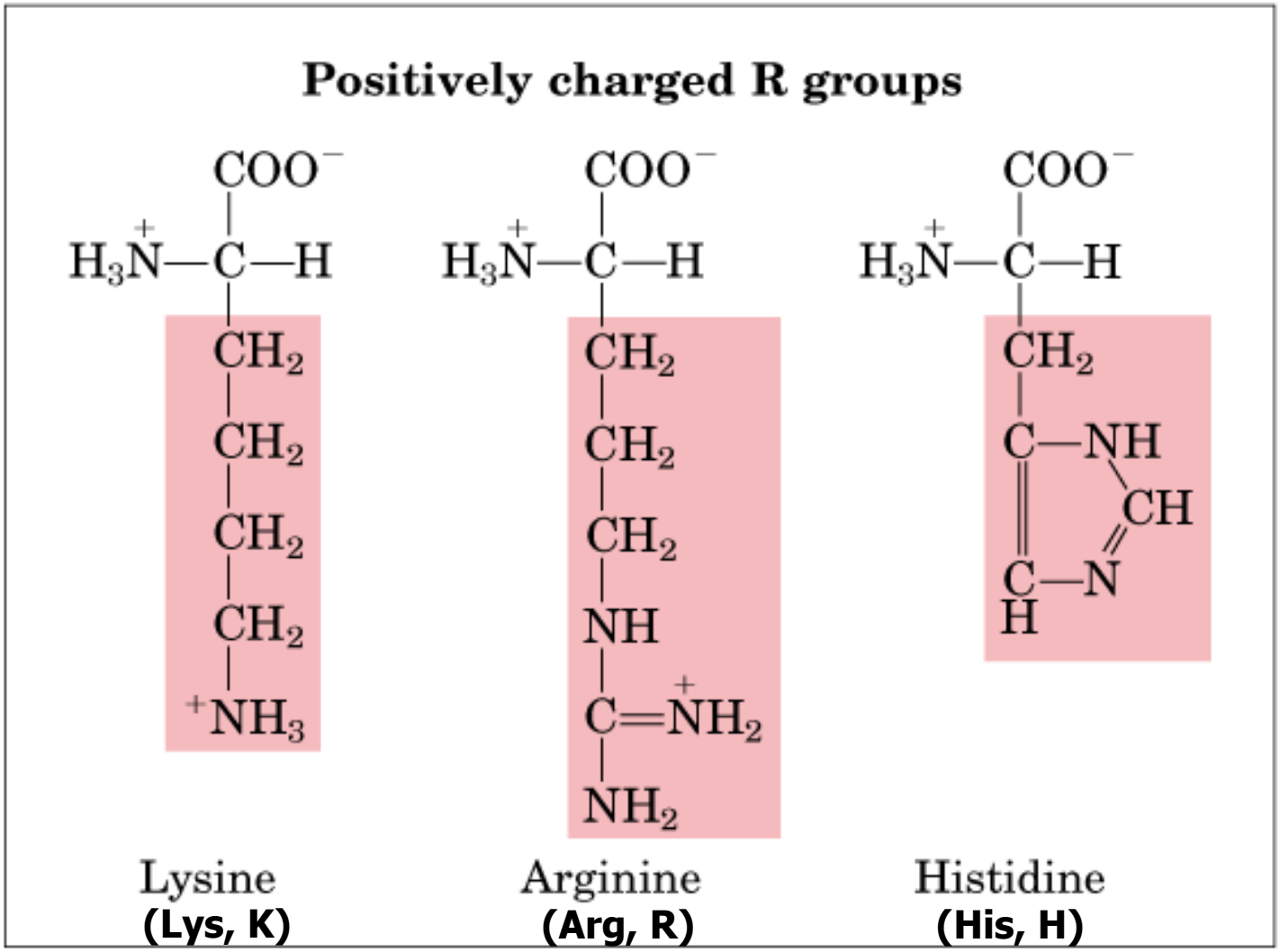


Reversible formation of a disulfide bond by the oxidation of two molecules of cysteine which stabilize the structures of many proteins

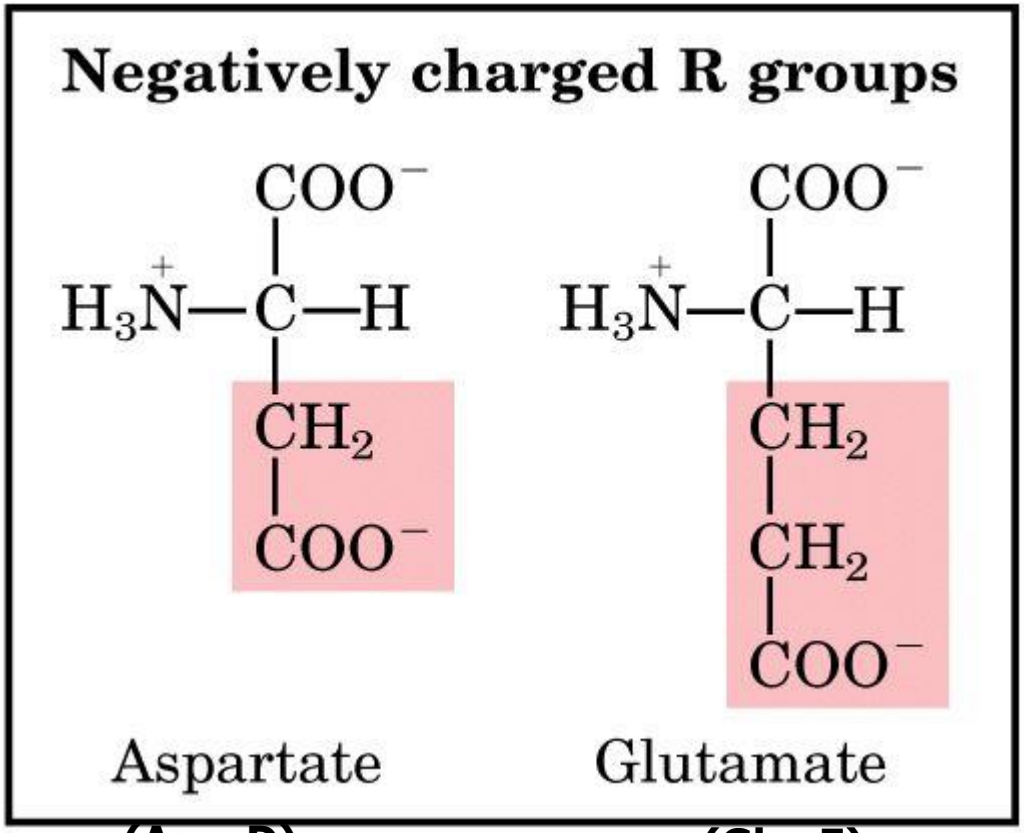
Aromatic R groups



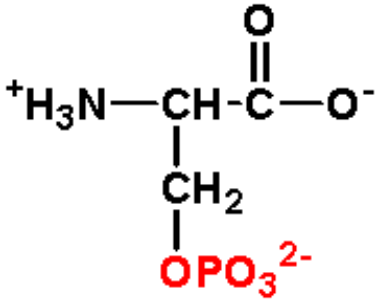
Positively charged R groups



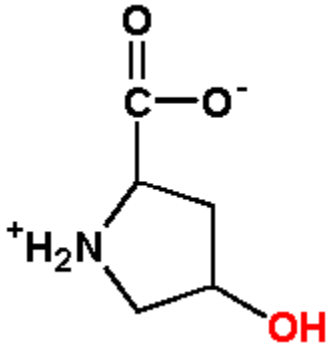
Negatively charged R groups



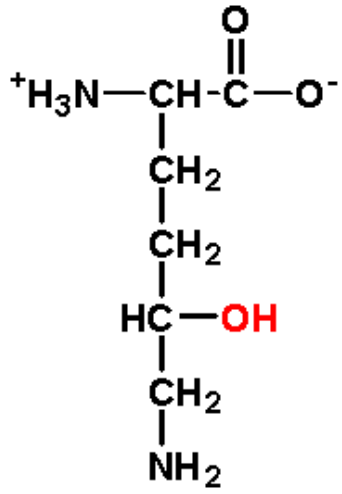
Uncommon amino acids



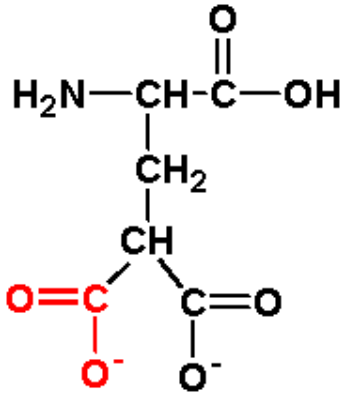
Phosphoserine



4-Hydroxyproline



5-Hydroxylysine



γ-carboxyglutamate

1) reversible phosphorylation and dephosphorylation of Ser, Thr, and Tyr residues very important in covalent regulation of activity of some enzymes and many biosignalling proteins, including some hormone receptors and transcription factors

2) 4-hydroxyproline & 5-hydroxylysine important in structure of collagen (fibrous protein in connective tissue)

3) γ-carboxyglutamate important in a number of proteins whose function involves Ca2+ binding, including several proteins involved in blood clotting

Physical properties of amino acids

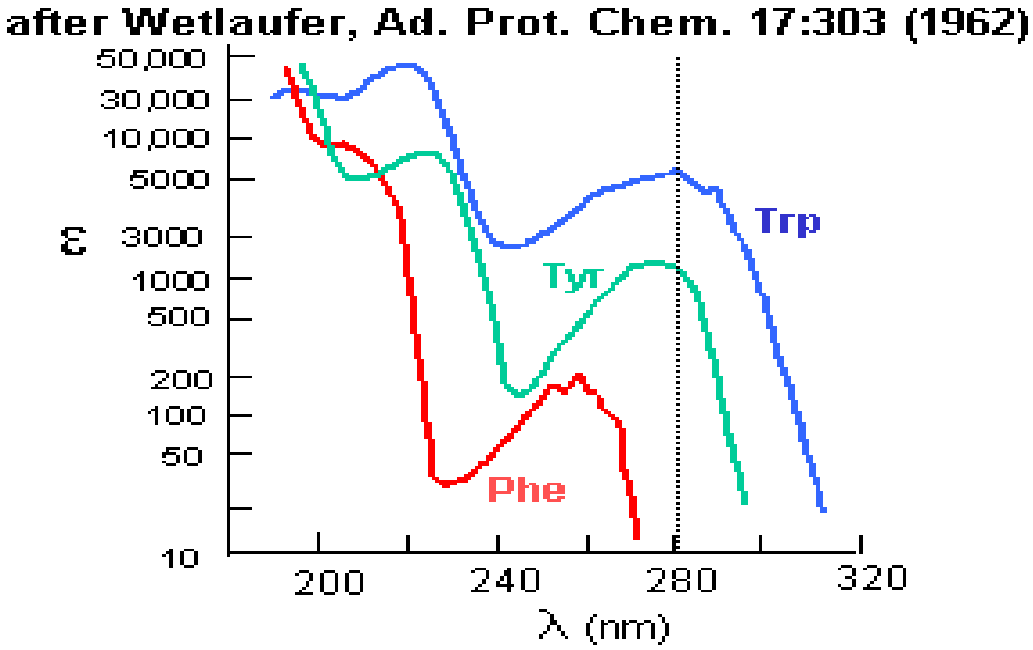
1. **Water solubility**

   Hydrophilic amino acids: Asn, Gln, Cys, Ser, Thr, Tyr, Asp, Glu, Lys, Arg, His

   Hydrophobic amino acids: Gly, Ala, Val, Leu, Ile, Met, Pro, Phe

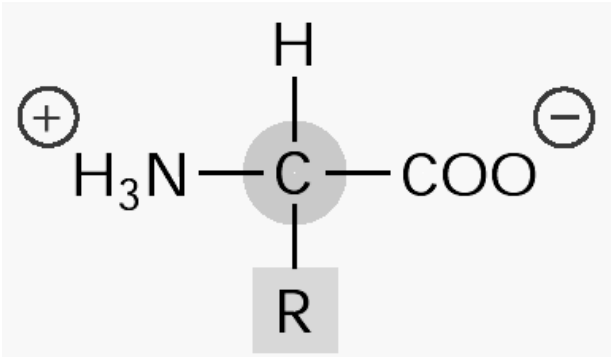
2. **Absorption spectrum of aromatic amino acids**

Trp and Tyr can absorb UV light at 280 nm (maximum wavelength)



3. Amino Acids Can Act as Acid, Bases and Buffer

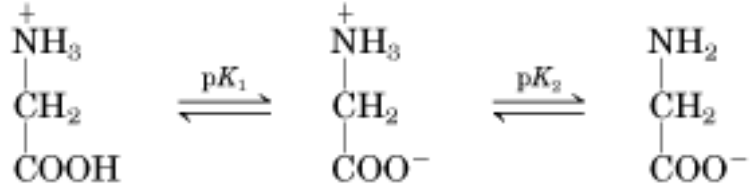
When an amino acid is dissolved in water, it exists in solution as the dipolar ion, or zwitterion (hybrid ion).

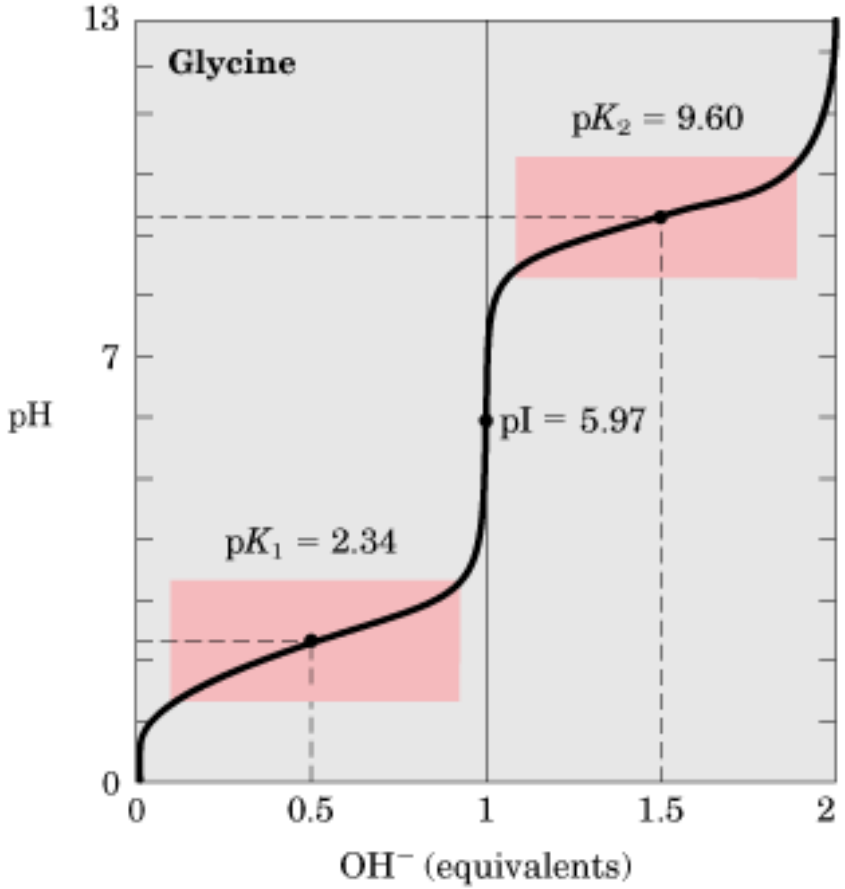


Substances having this dual nature are amphoteric and are often call ampholytes (amphoteric electrolytes).

Amino acid is a buffer

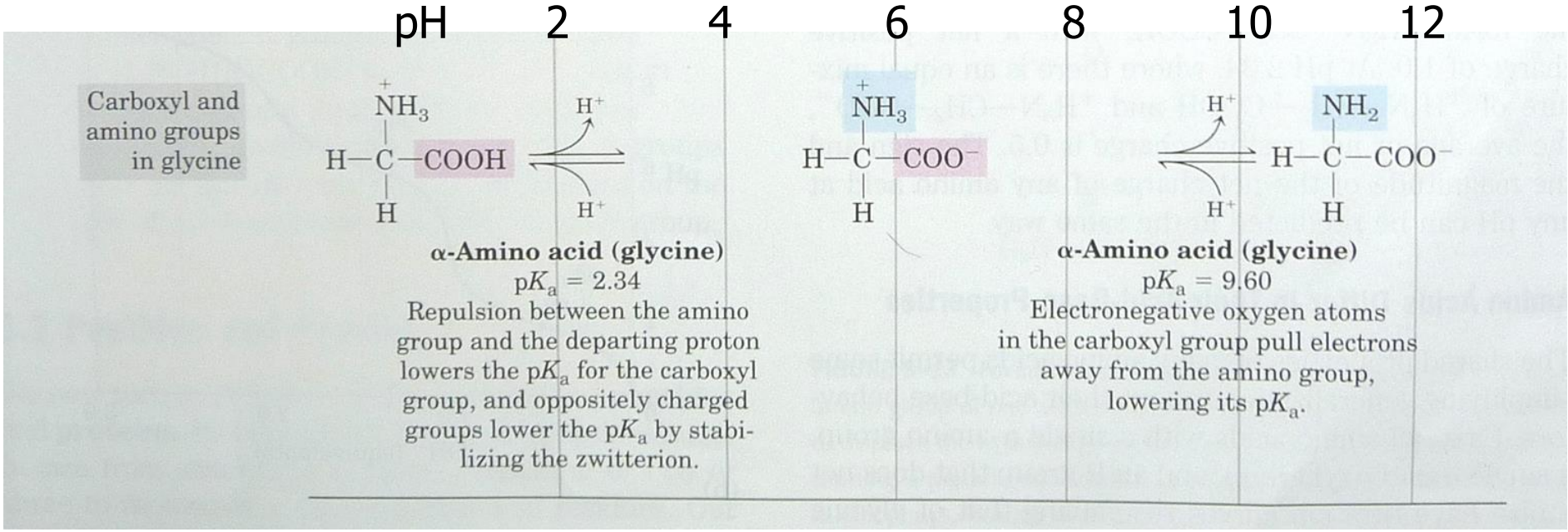
Amino acids have characteristic Titration curve





Titration curve of Glycine

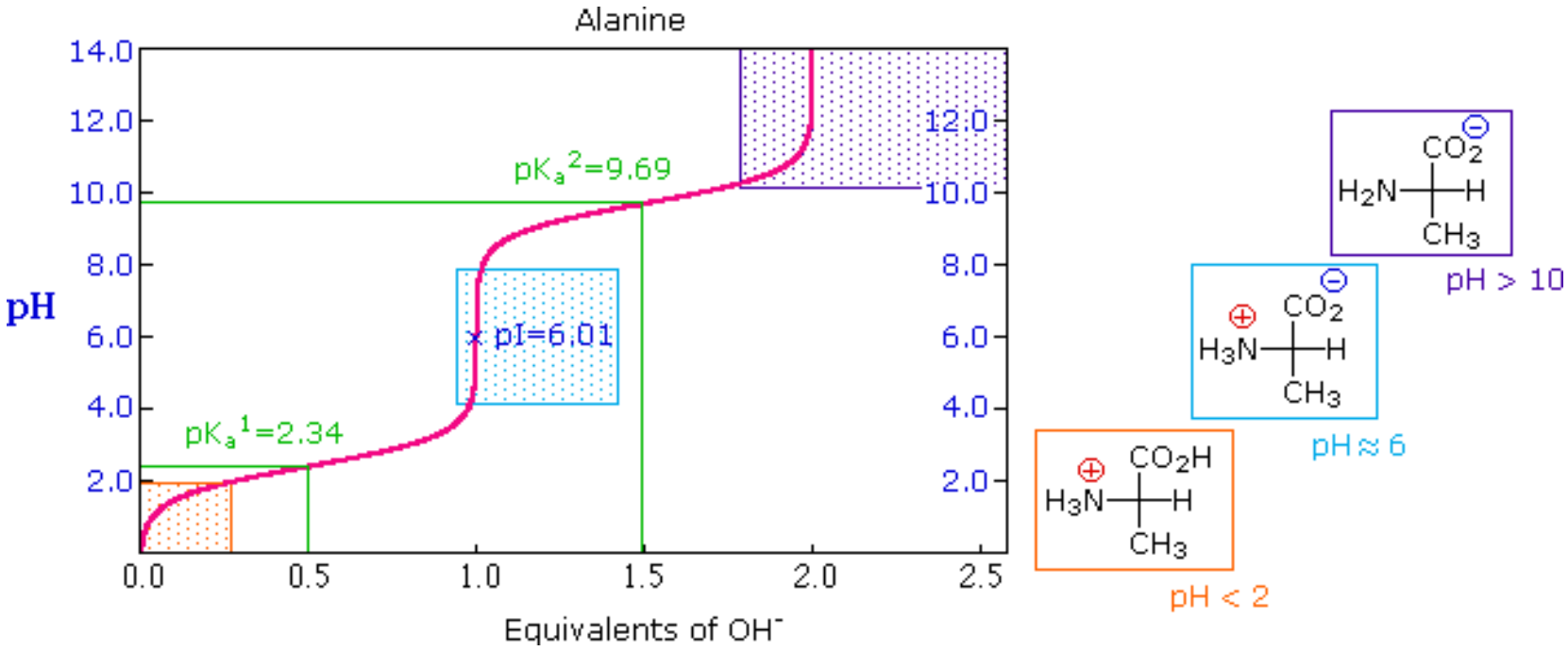
Titration Curves Predict the Electric Charge of Amino Acids



pH < pKa Protonation (NH_2 -> NH_3^+ or COO^- -> COOH)

pH > pKa Ionization (COOH -> COO^- or NH_3^+ -> NH_2)

The characteristic pH at which the net electric charge is zero is called the **isoelectric point** or **isoelectric pH**, designated **pI**.

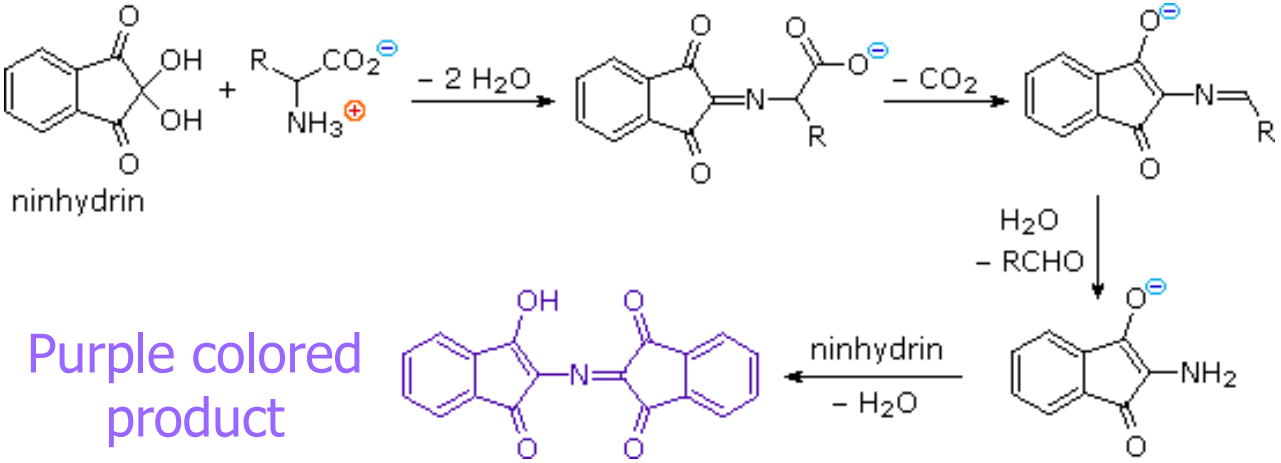


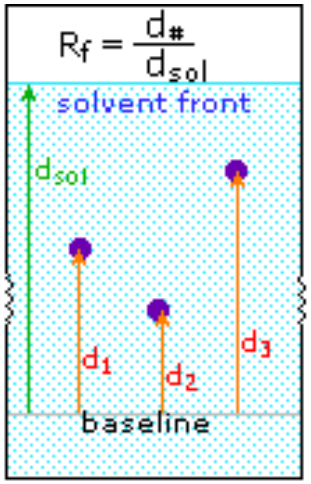
Chemical properties of amino acids

Chemical reactions of amino acids depend on the reaction of amino, carboxylic and R group.

Chemical reactions of amino group

Ninhydrin reaction



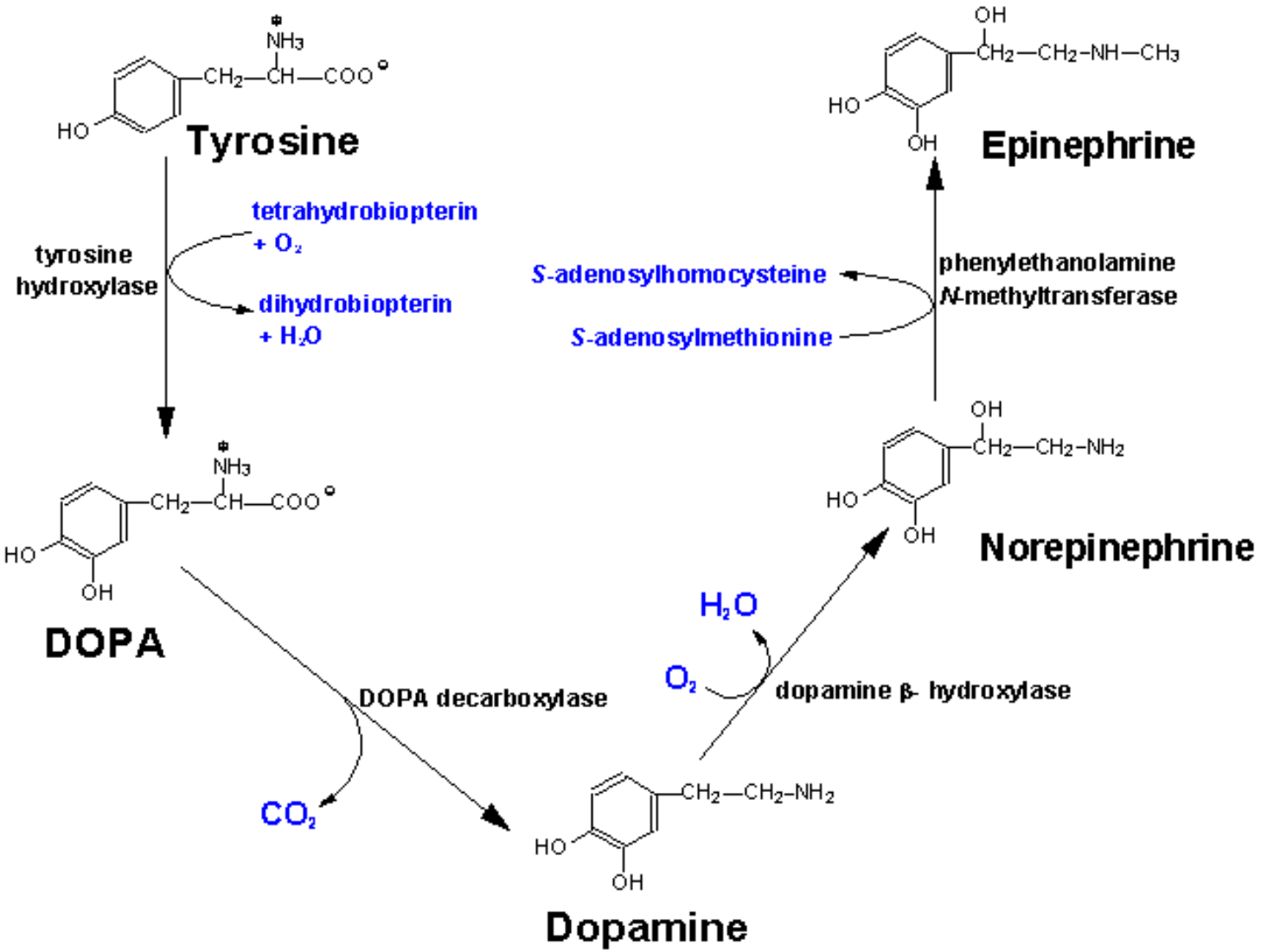


Paper Chromatography

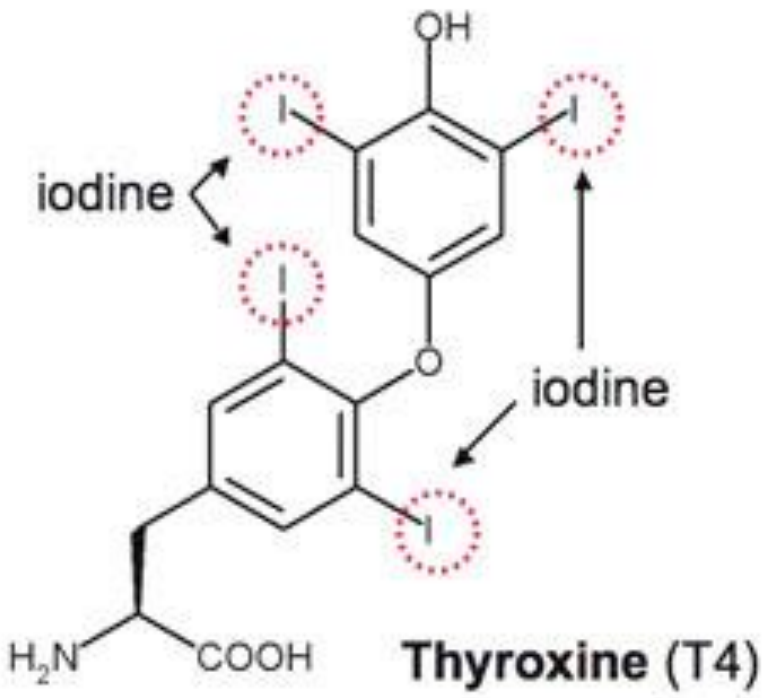
Biological function of amino acids

- **Building block of proteins**
- Spared energy source
- Substrates for the synthesis of biomolecules

Tyrosine-derived neurotransmitters

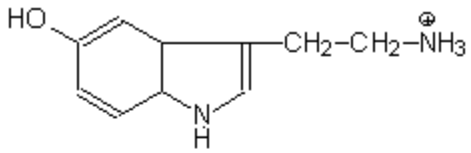


Thyroxine, the tyrosine derived thyroid hormone



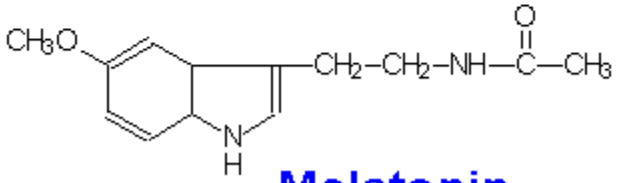
Thyroxine (T4)

Tryptophan-derived neurotransmitters



Serotonin

(5-hydroxytryptamine)

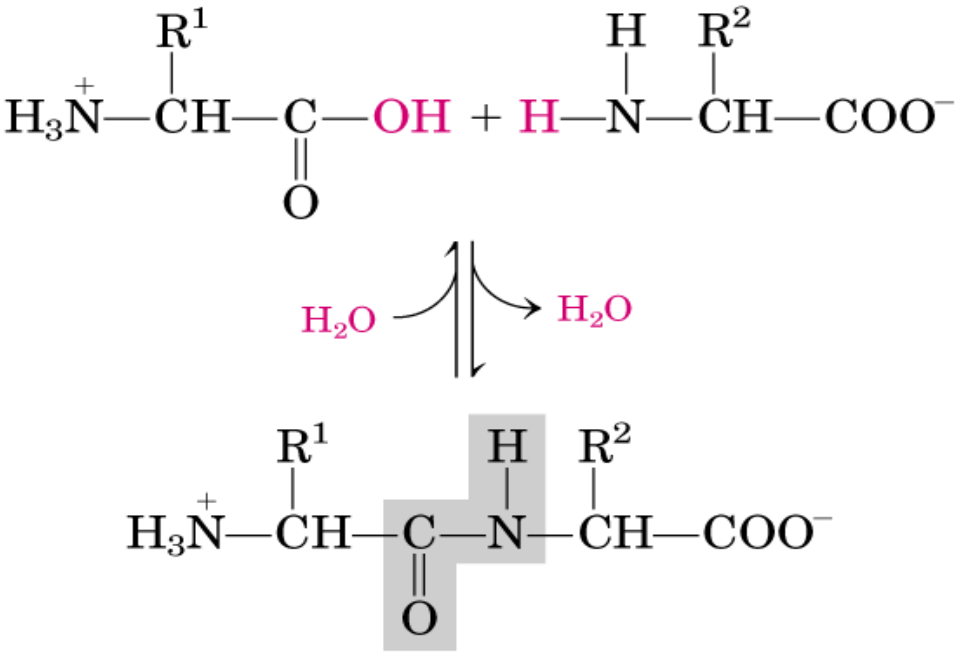


Melatonin

PEPTIDES

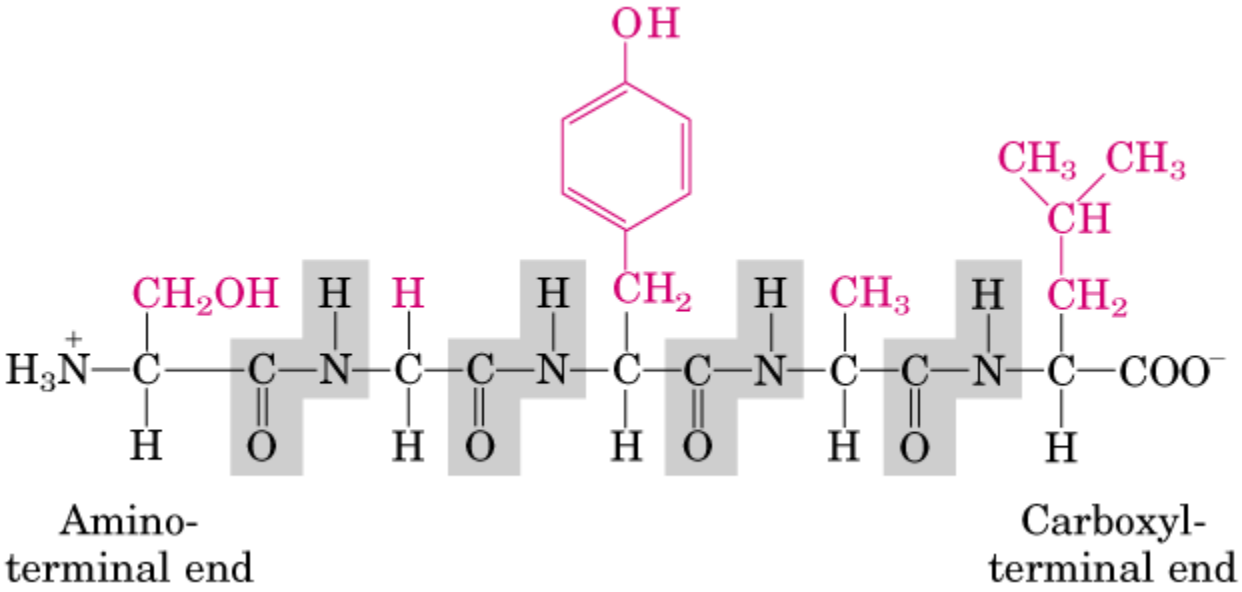
The Peptide Bond

- Peptides and proteins:polymers of amino acids joined by peptide bonds.
- **Amide** linkages from condensation of **α-carboxyl group** of one amino acid with **α -amino group** of another amino acid.
- Covalent bond (amide bond)



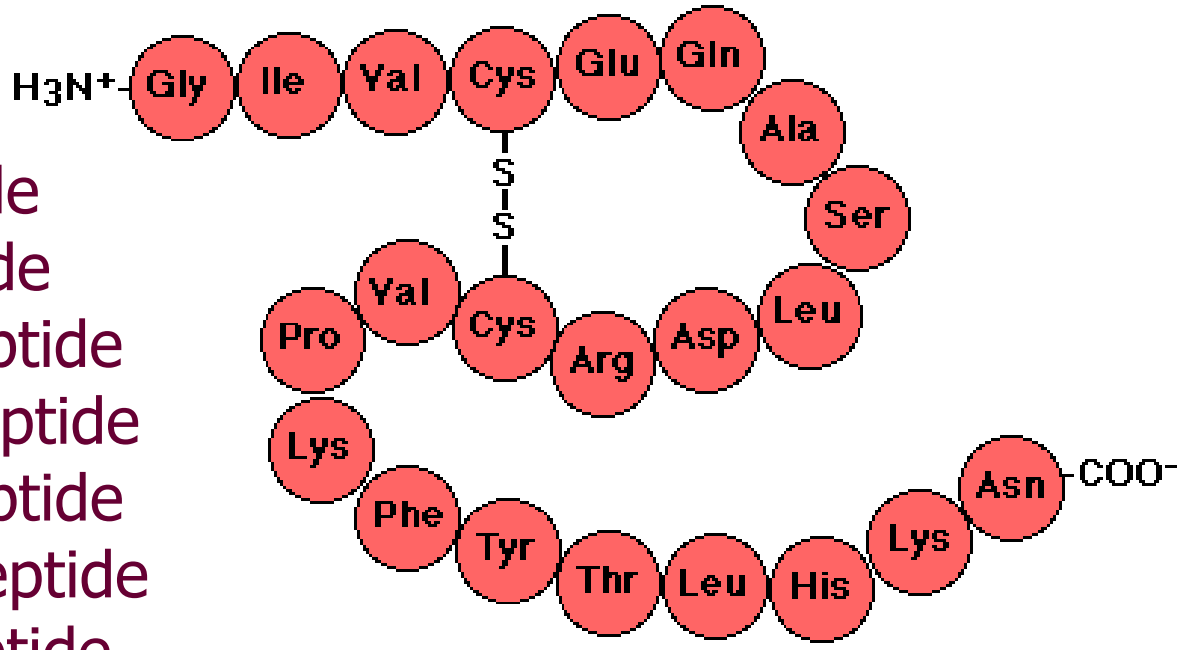
PEPTIDE

- process repeated many times --> linear chain of amino acids, a **polypeptide chain**
- convention: sequence written from left to right starting with **residue** with free a-amino group (the **N-terminal** or amino terminal amino acid residue) and ending with the residue containing the free a-carboxyl group (the **C-terminal** or carboxyl t



- small peptides (a "few" amino acid residues) = ***oligo****peptides*

PEPTIDE

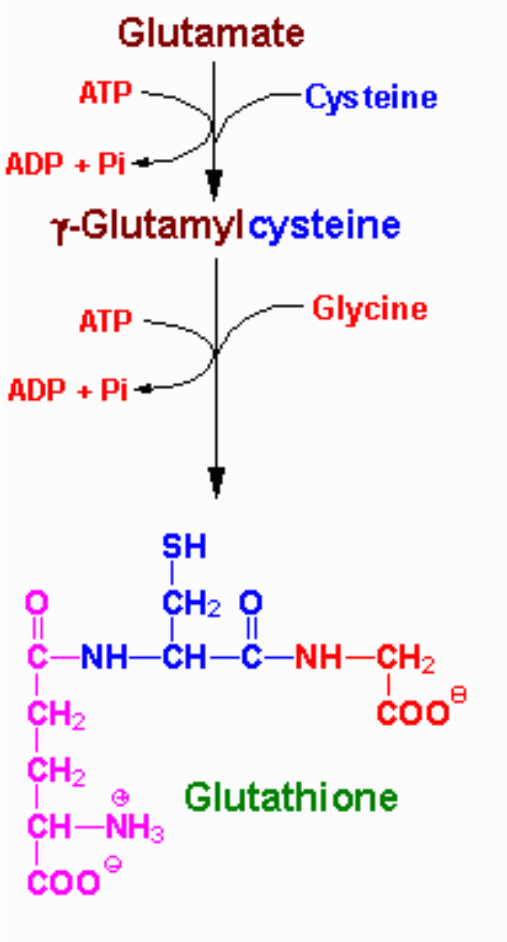


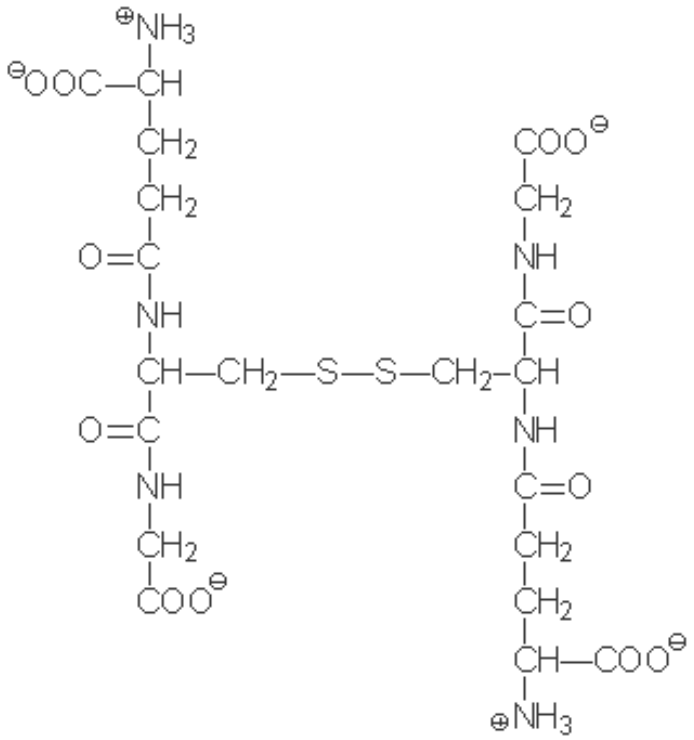
Dipeptide
Tripeptide
Tetrapeptide
Pentapeptide
Hexapeptide
Heptapeptide
Octapeptide
Nonapeptide
Decapeptide

Peptide: < 40 amino acids residues
Protein: > 50 amino acids residues

Peptides in biological system

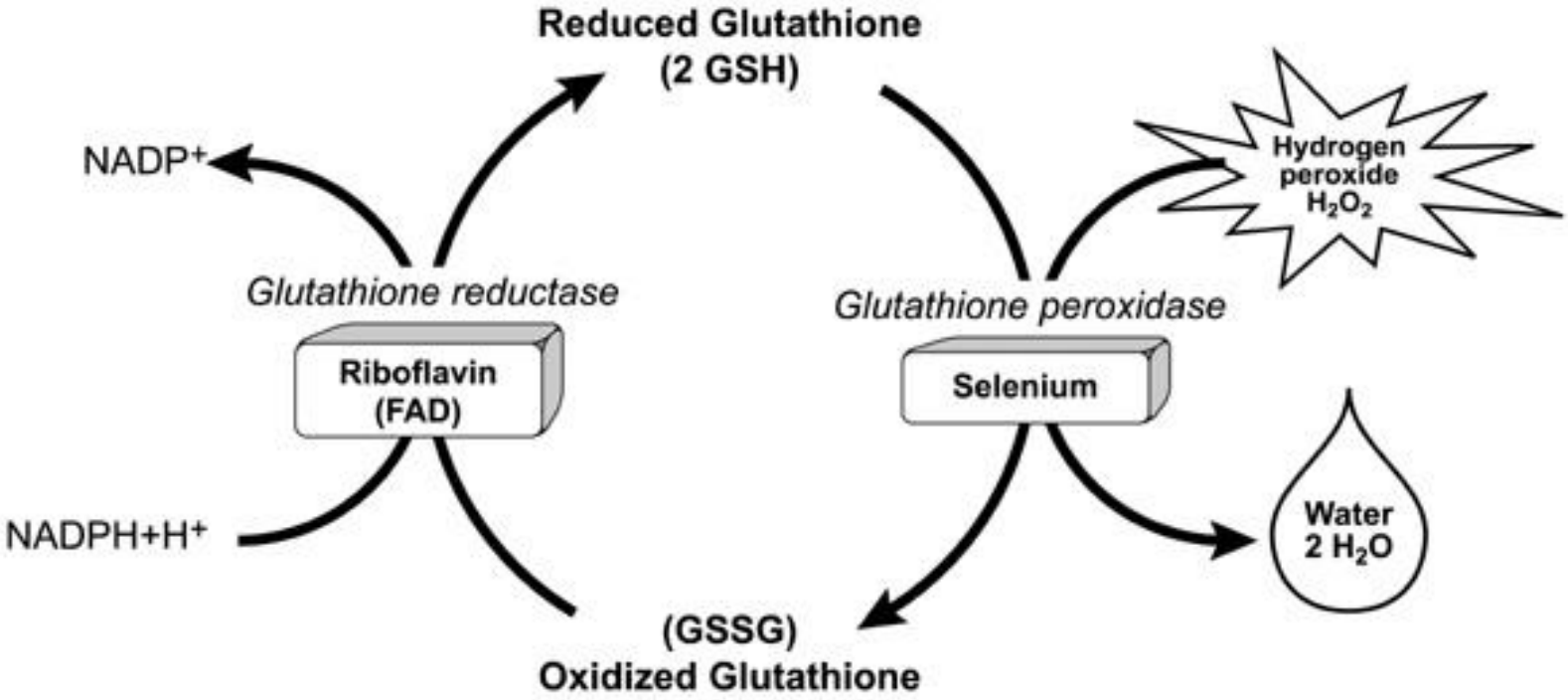
Glutathione : Anti-oxidant for Red Blood Cell
Gamma glutamyl cysteineyl glycine



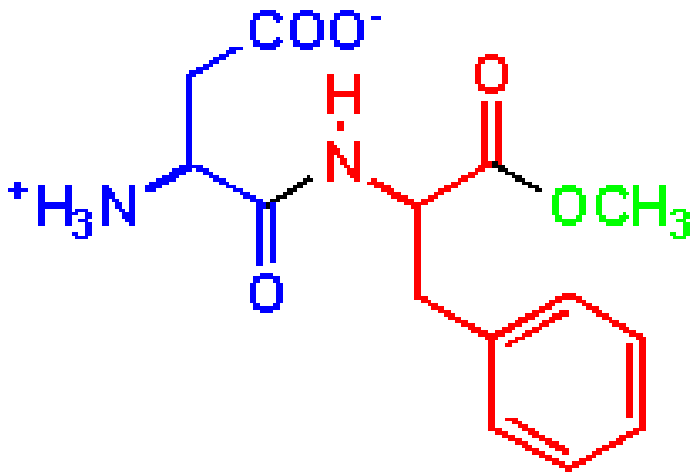


Glutathione disulfide (GSSG)

Glutathione is an antioxidant in red blood cells



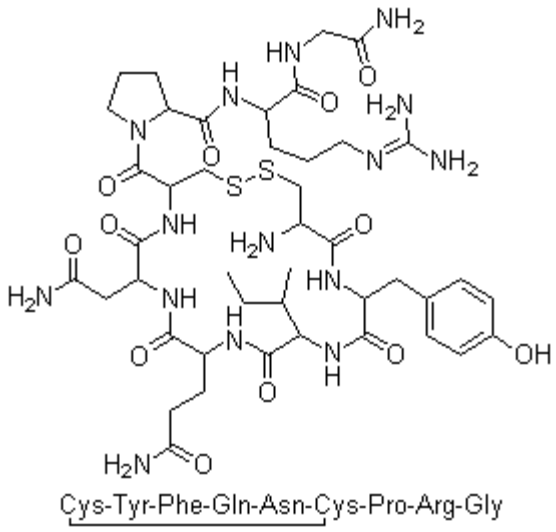
Aspartame sweet-tasting dipeptide



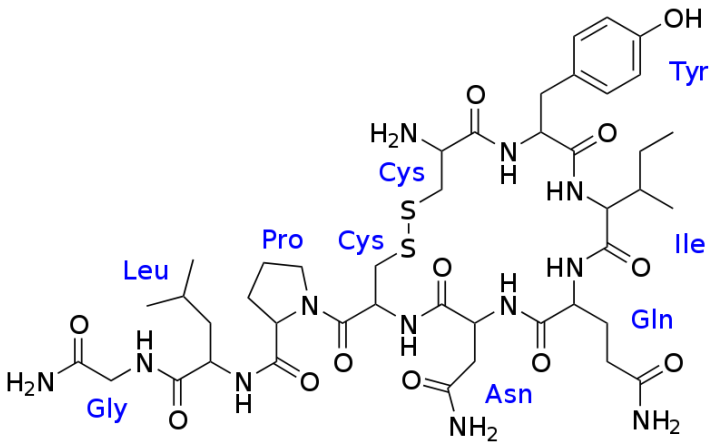
Aspartyl-phenylalanine methyl ester

PEPTIDE HORMONE

Nonapeptides: single intramolecular disulfide; cyclic peptide		
Hormone	Target	Major physical roles
Antidiuretic hormone Vasopressin Oxytocin	Kidney Myoepithelial cells Uterine smooth muscle	Promote water retention Milk Promotes contraction



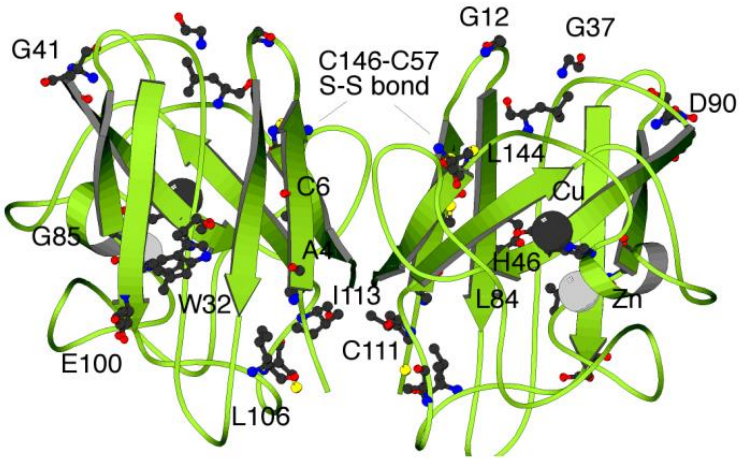
Vasopressin



Oxytocin

Protein

Proteins (also known as **polypeptides**) are organic compounds made of amino acids arranged in a linear chain polymer and joined together by peptide bonds between the carboxyl and amino groups of adjacent amino acid residues.
It consists of 20 types of L-alpha amino acids.
It contains buffer properties.
Maximum absorption at 280 nm



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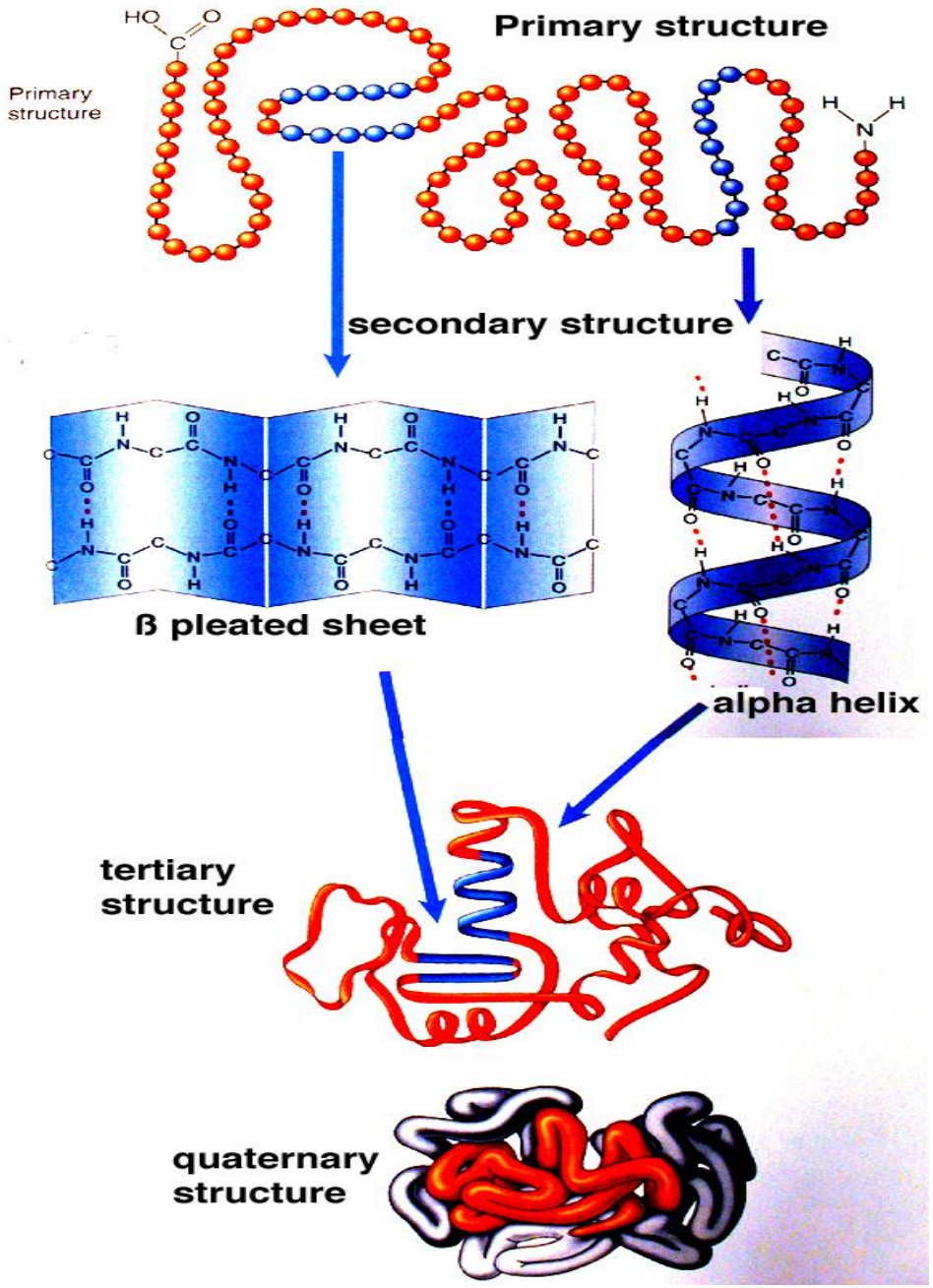
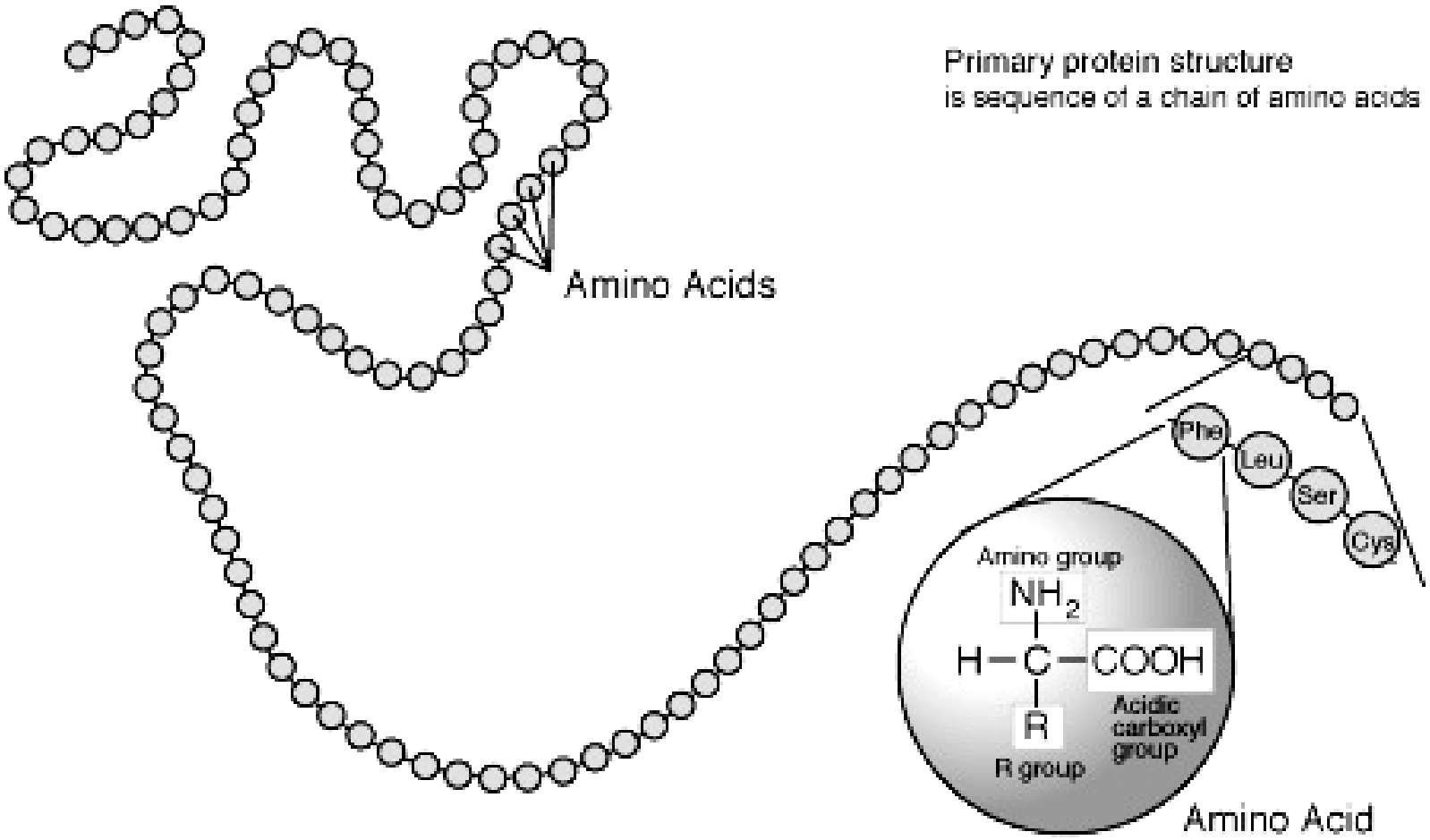
Protein structure)

There are 4 levels of protein structure:

1. Primary structure
2. Secondary structure
3. Tertiary structure
4. Quaternary structure



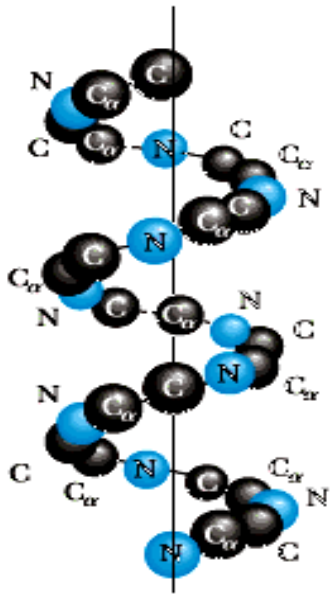
Primary structure



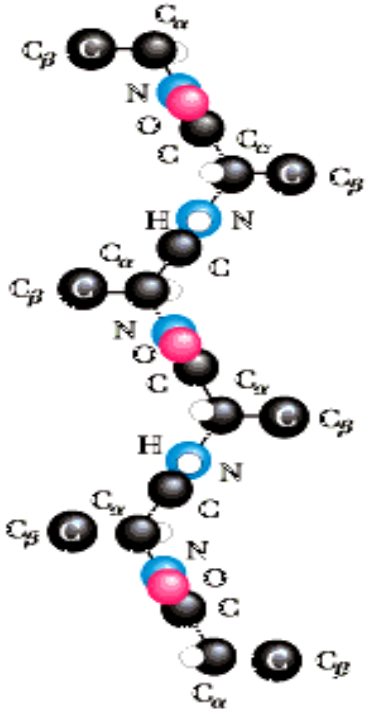
Amino acid sequence - no protein folding

Secondary structure

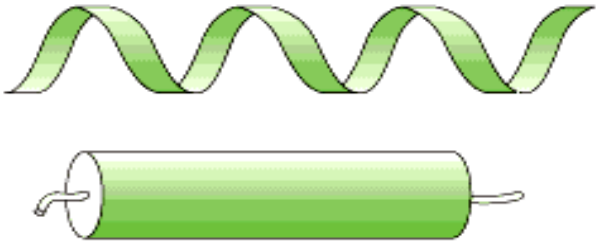
α - Helix
Only the N—C_α—C backbone is represented. The vertical line is the helix axis.



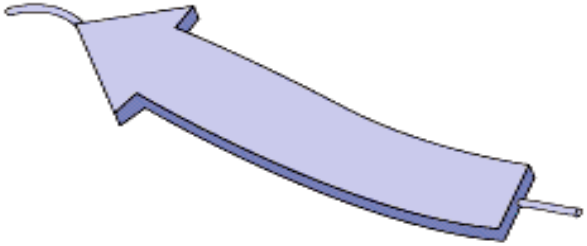
β - Strand
The N—C_α—C backbone as well as the C_β of R groups are represented here. Note that the amide planes are perpendicular to the image.



"Shorthand" α-helix



"Shorthand" β-strand



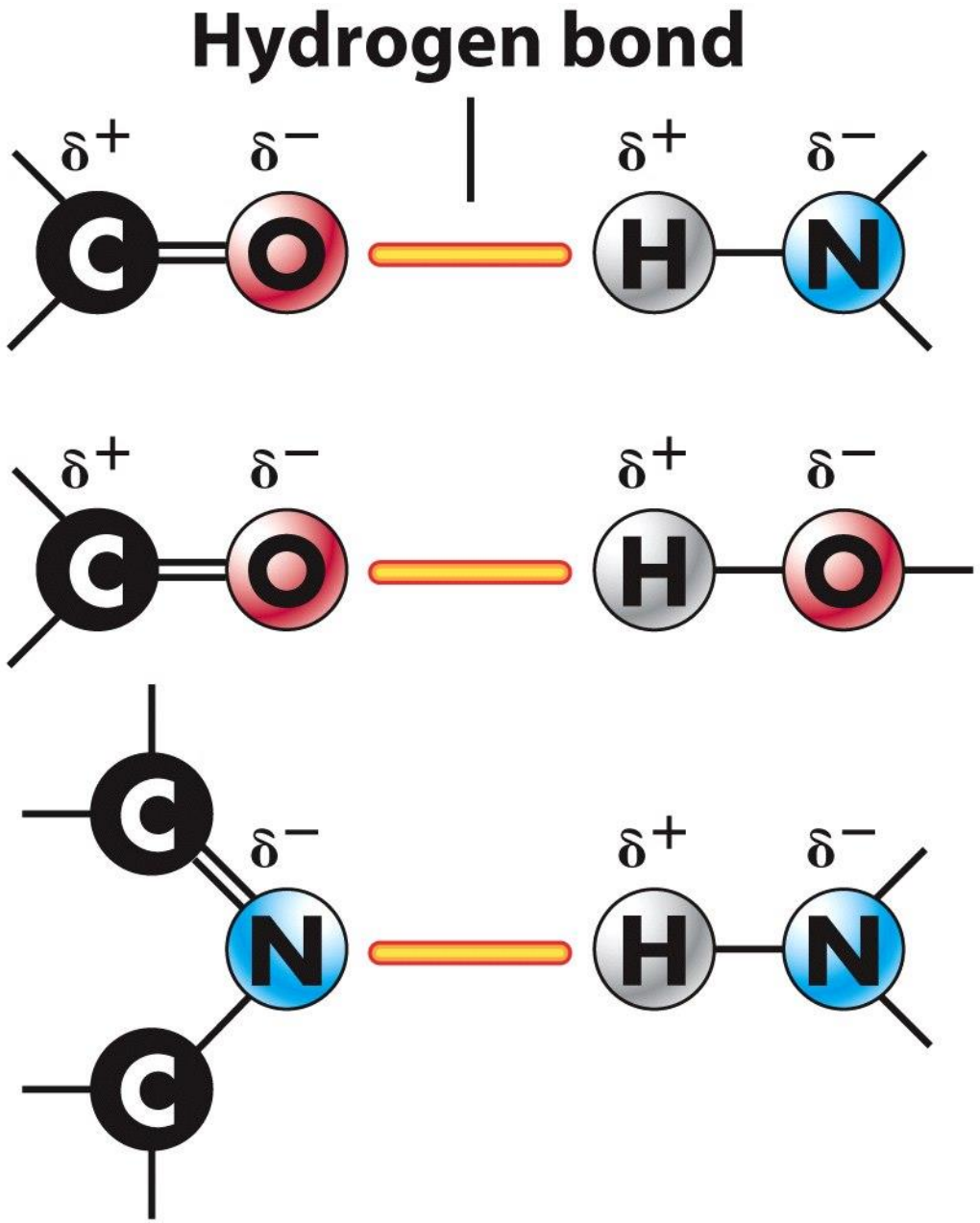


Figure 2-4 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Secondary structure

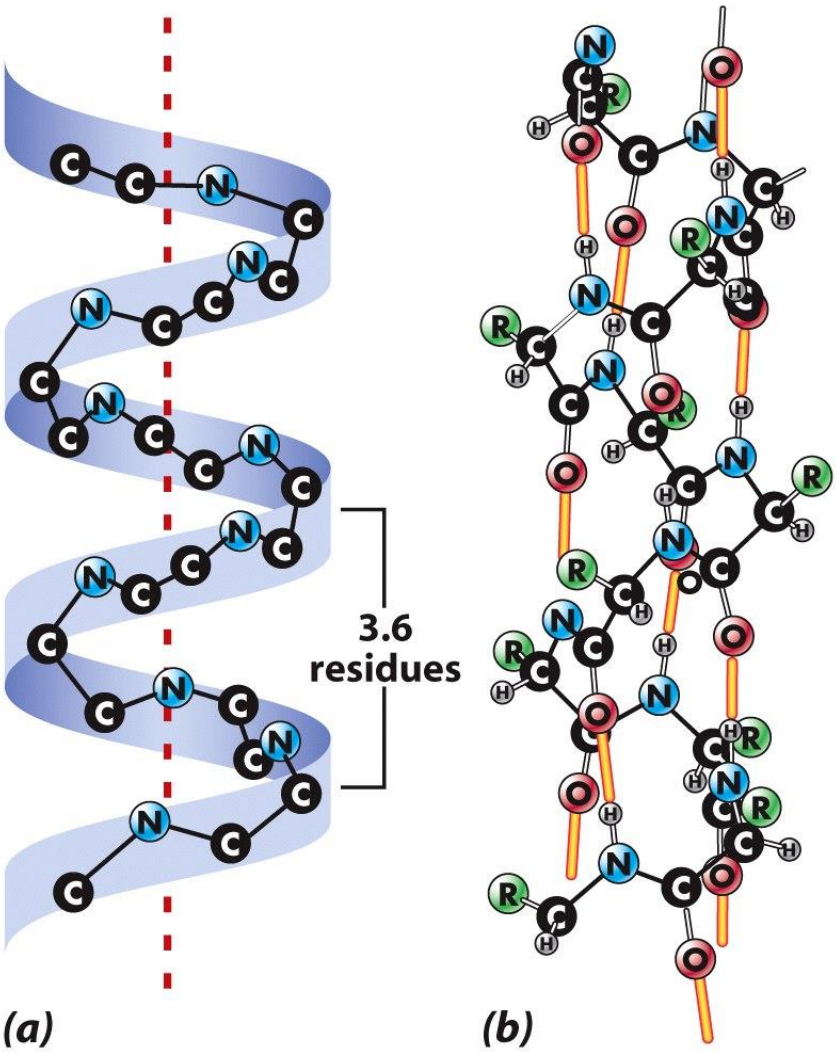
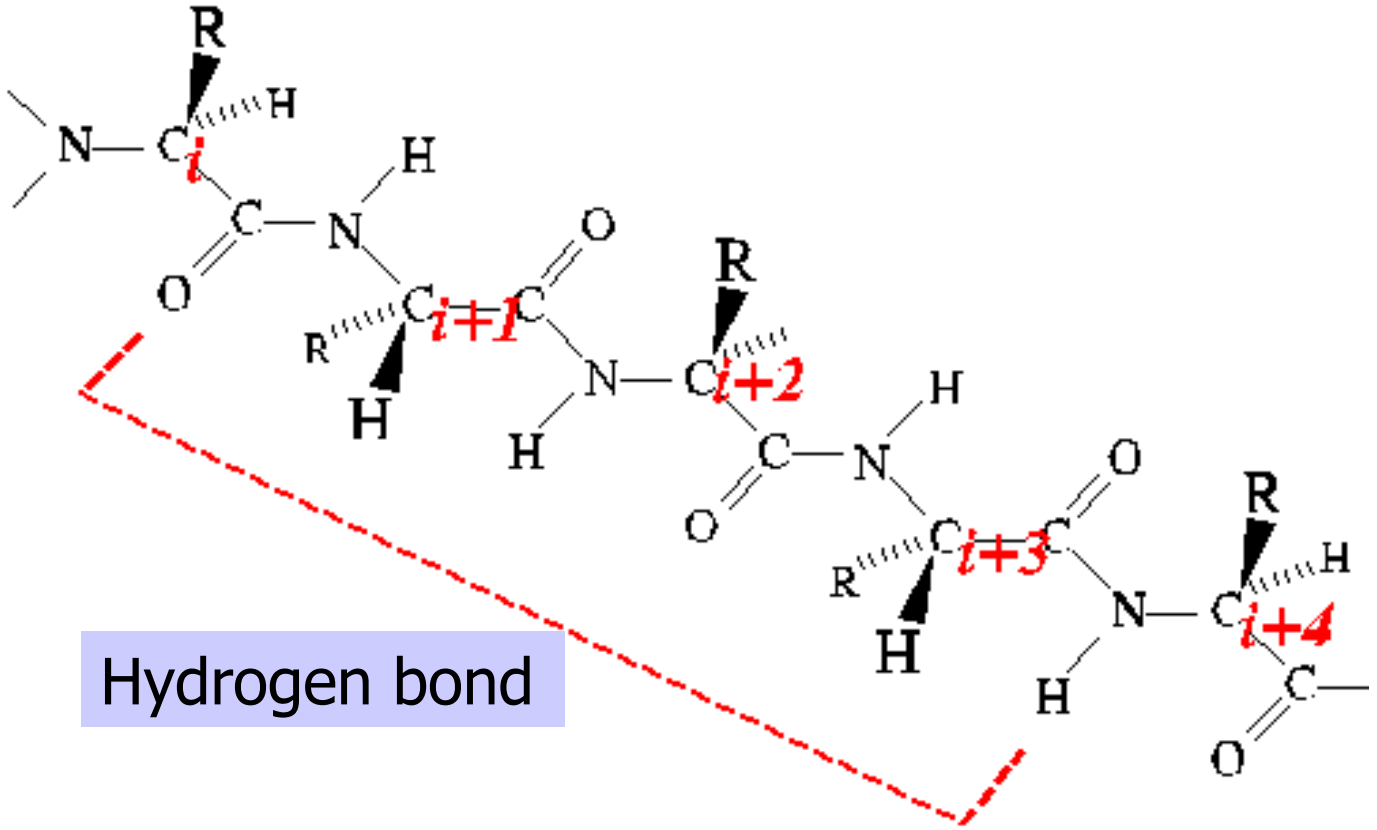


Figure 2-30b,c Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

" **Alpha helix"**
Hydrogen bond

In alpha helices, the CO of residue *i* is hydrogen-bonded to the NH of residue *i+4*.



Hydrogen bond

Secondary structure

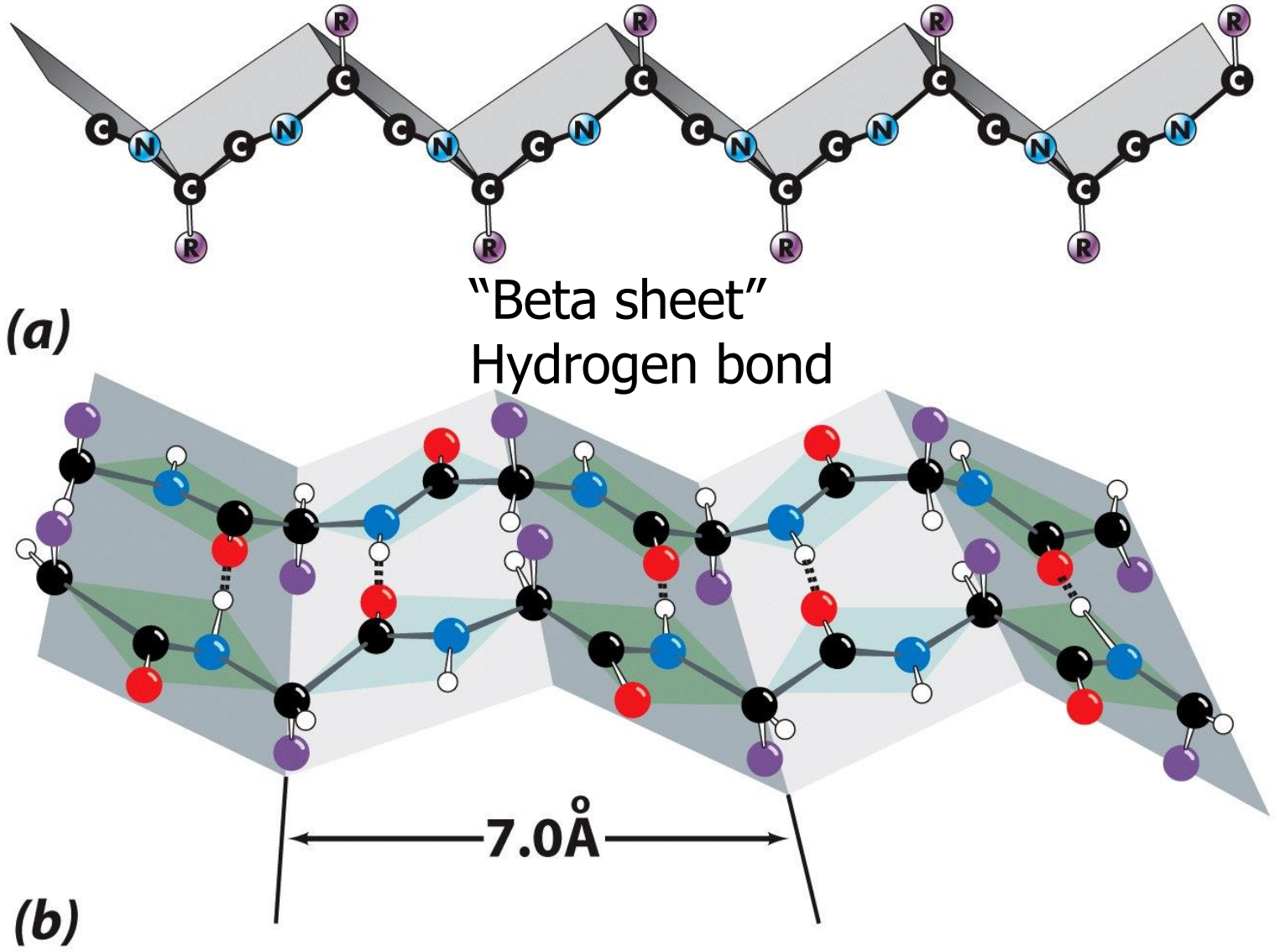
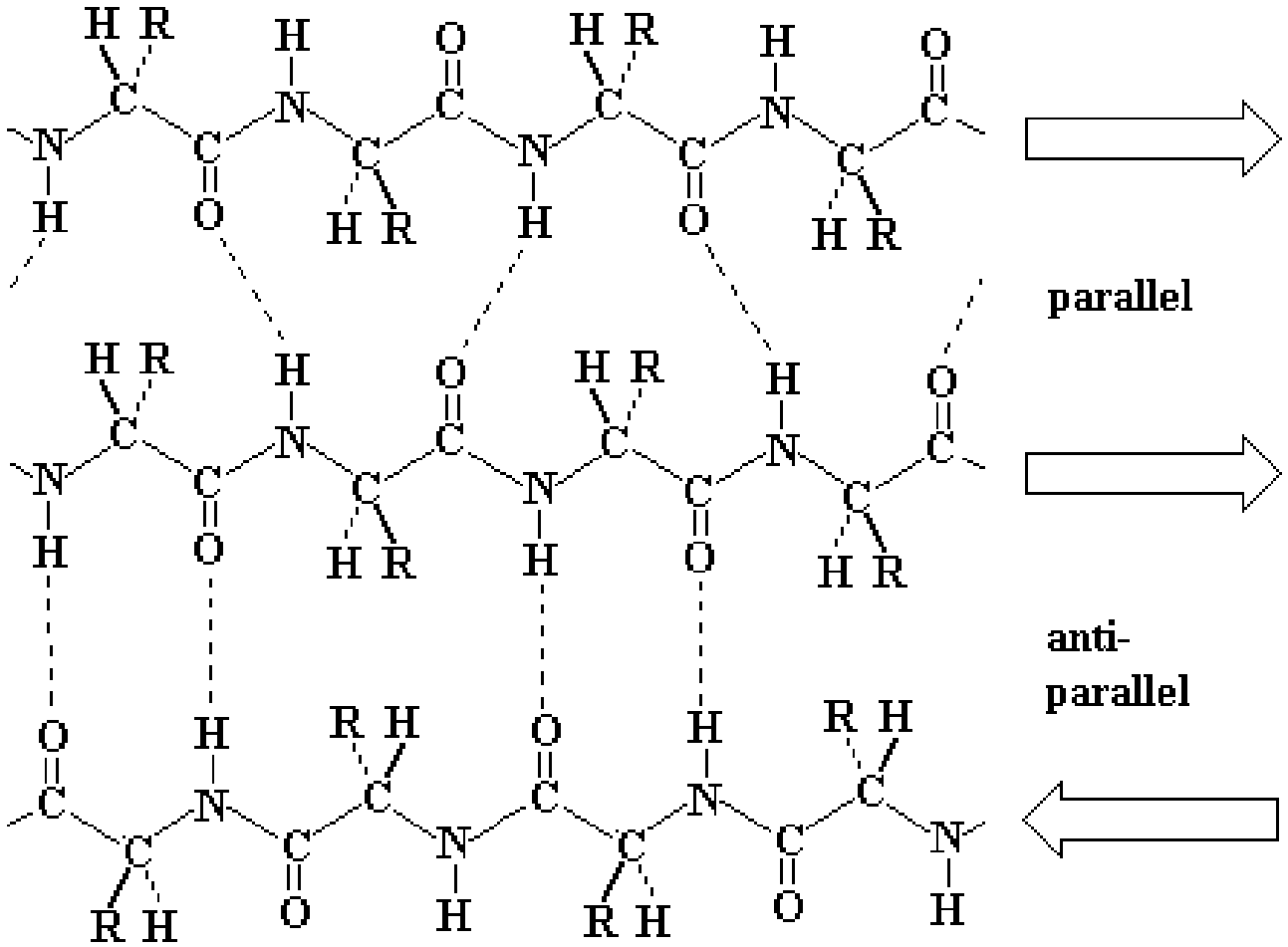
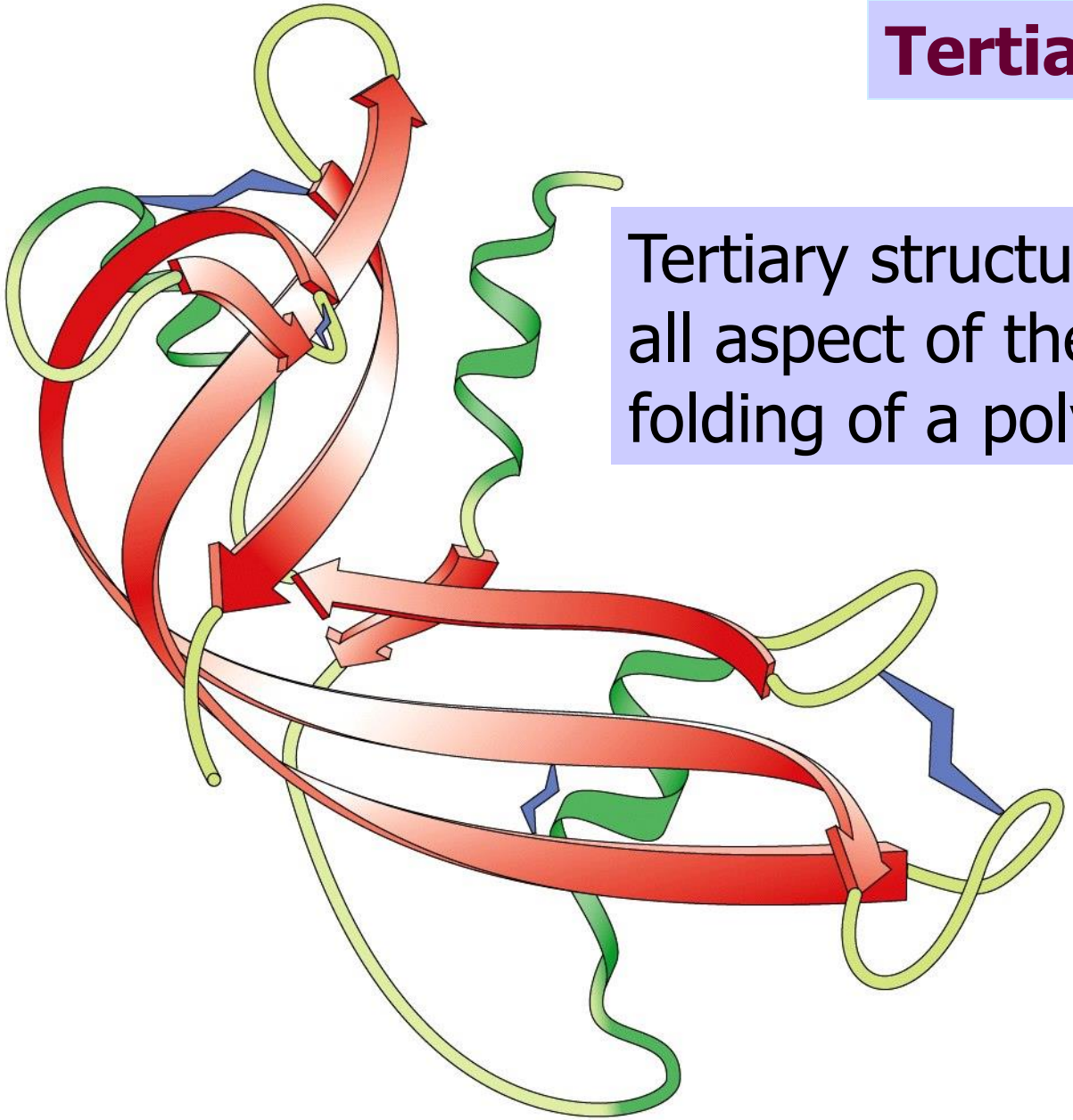


Figure 2-31 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Types of β-sheet



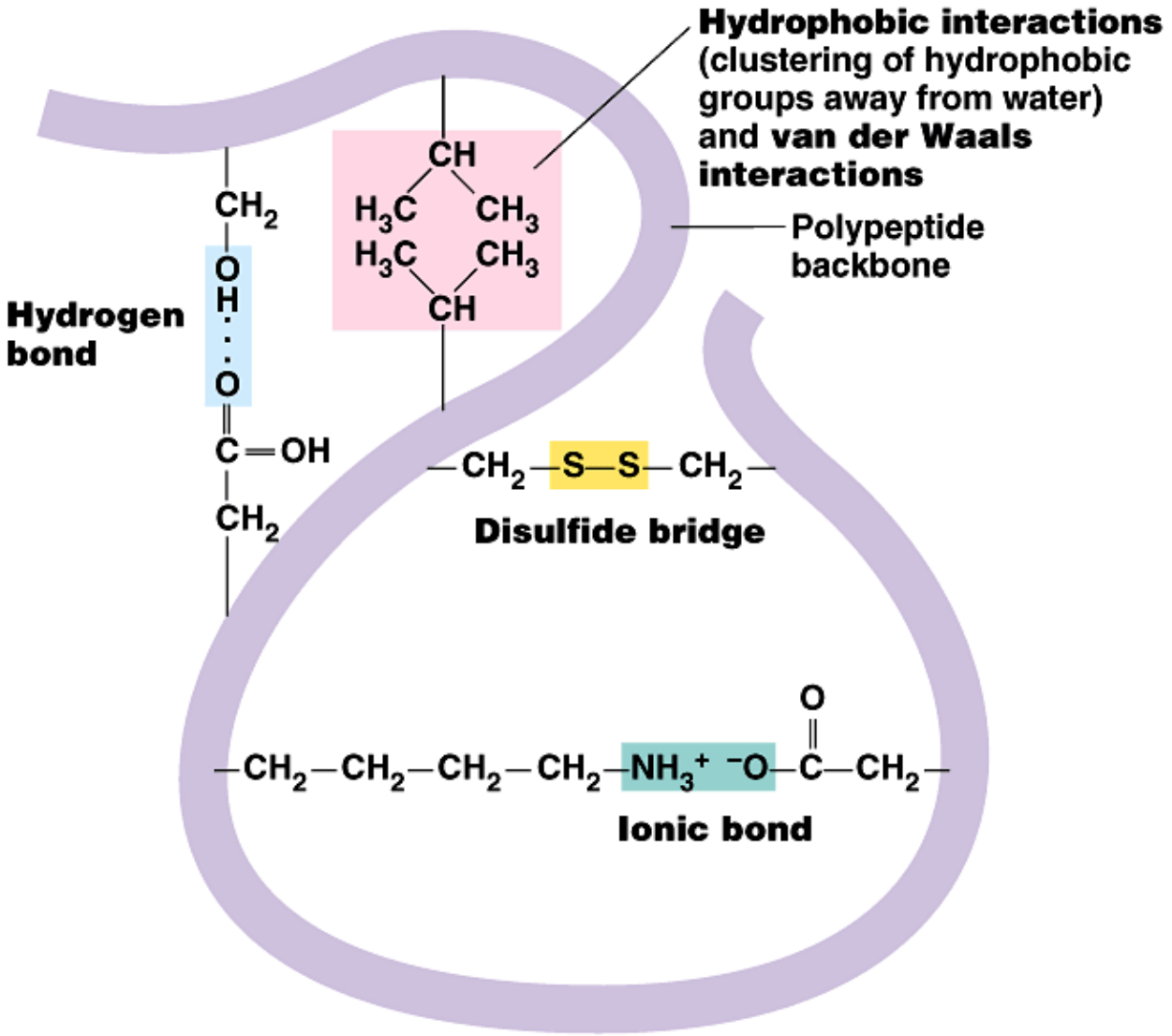
Tertiary structure



Tertiary structure describe all aspect of the three-dimensional folding of a polypeptide

Figure 2-32 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Hydrophobic interaction in tertiary structure



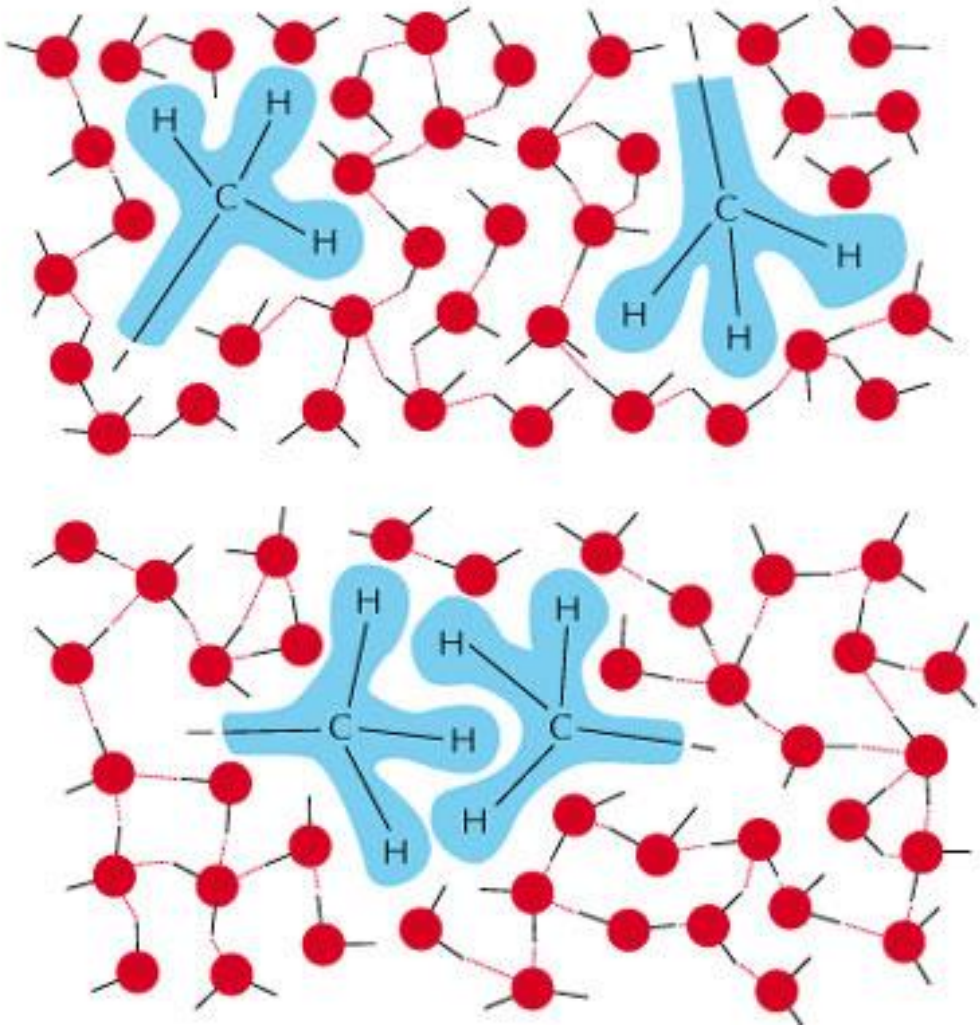
Hydrophobic interaction in tertiary structure

Hydrophobic interactions involve the side chains of Non-Polar amino acids:

Hydrocarbon -- Ala Val Leu Ile Pro Met

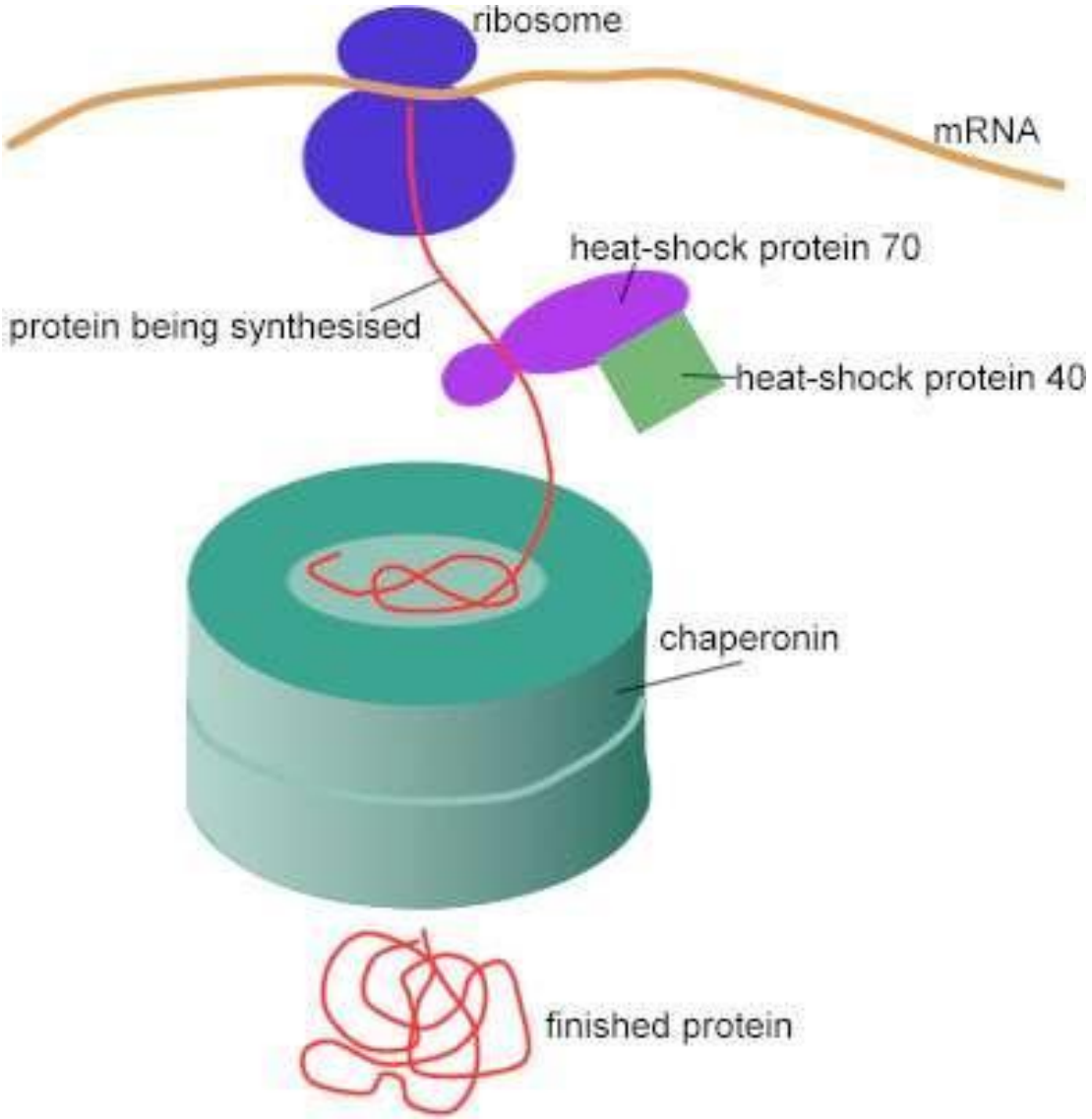
Aromatics ----- Phe Trp (Tyr)

Hydrophobic interaction



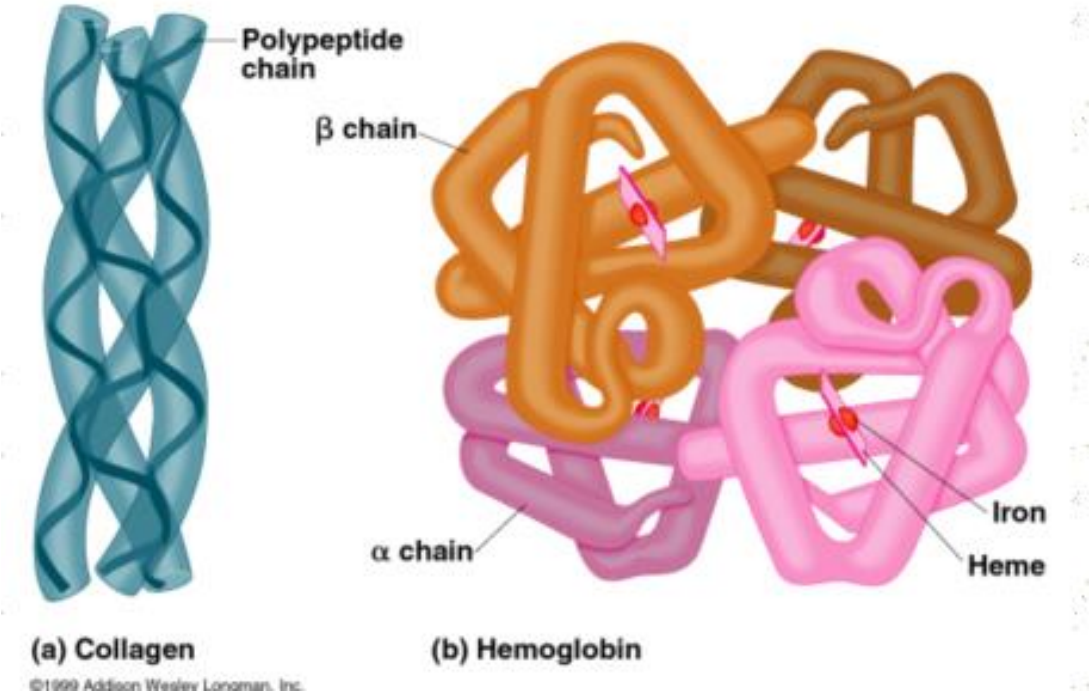
Water forces hydrophobic groups together in order to minimize their disruptive effects on the hydrogen-bonded water network. Hydrophobic groups held together in this way are sometimes said to be held together by "hydrophobic bonds," even though the attraction is actually caused by a repulsion from the water.

Protein Folding is not a random process



Quaternary structure

Collagens & elastins of connective tissue, keratins (hair, skin, fingernails), silk



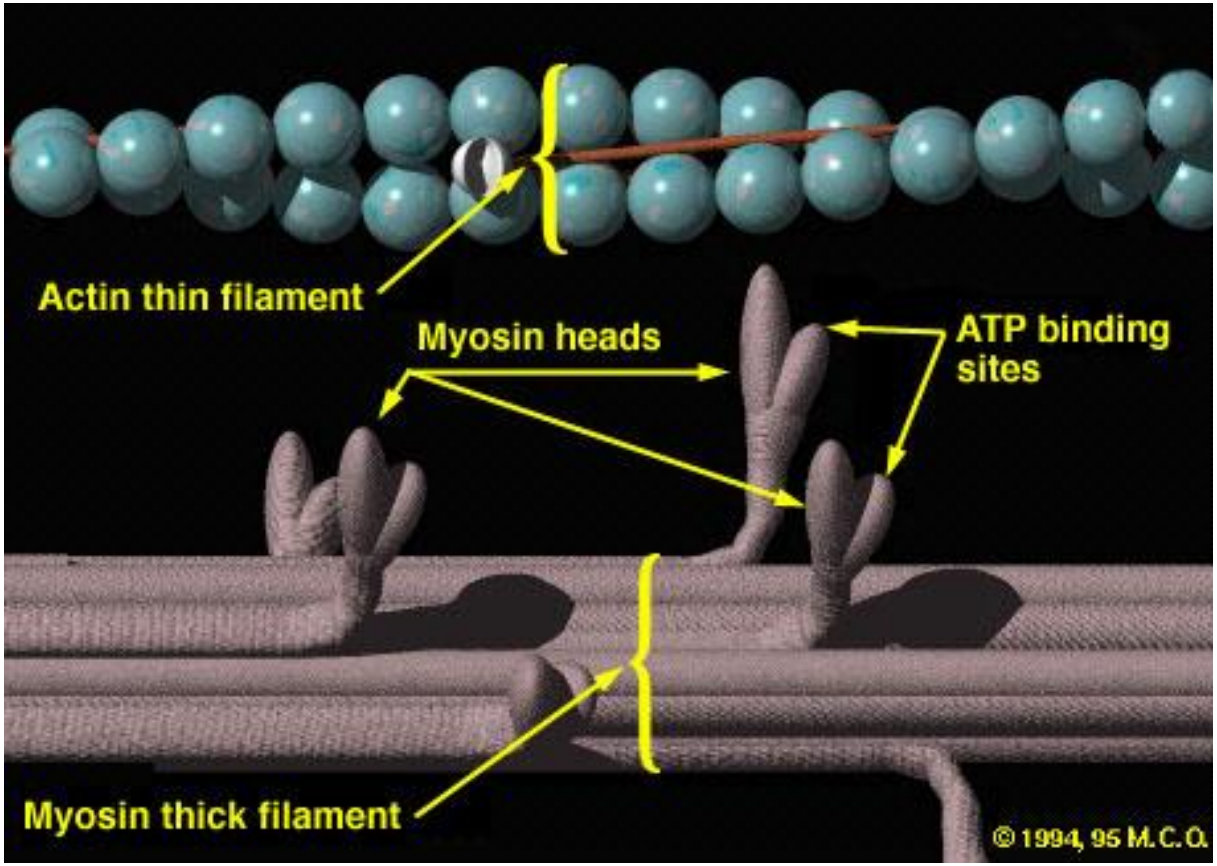
Hemoglobin

Fibrous protein

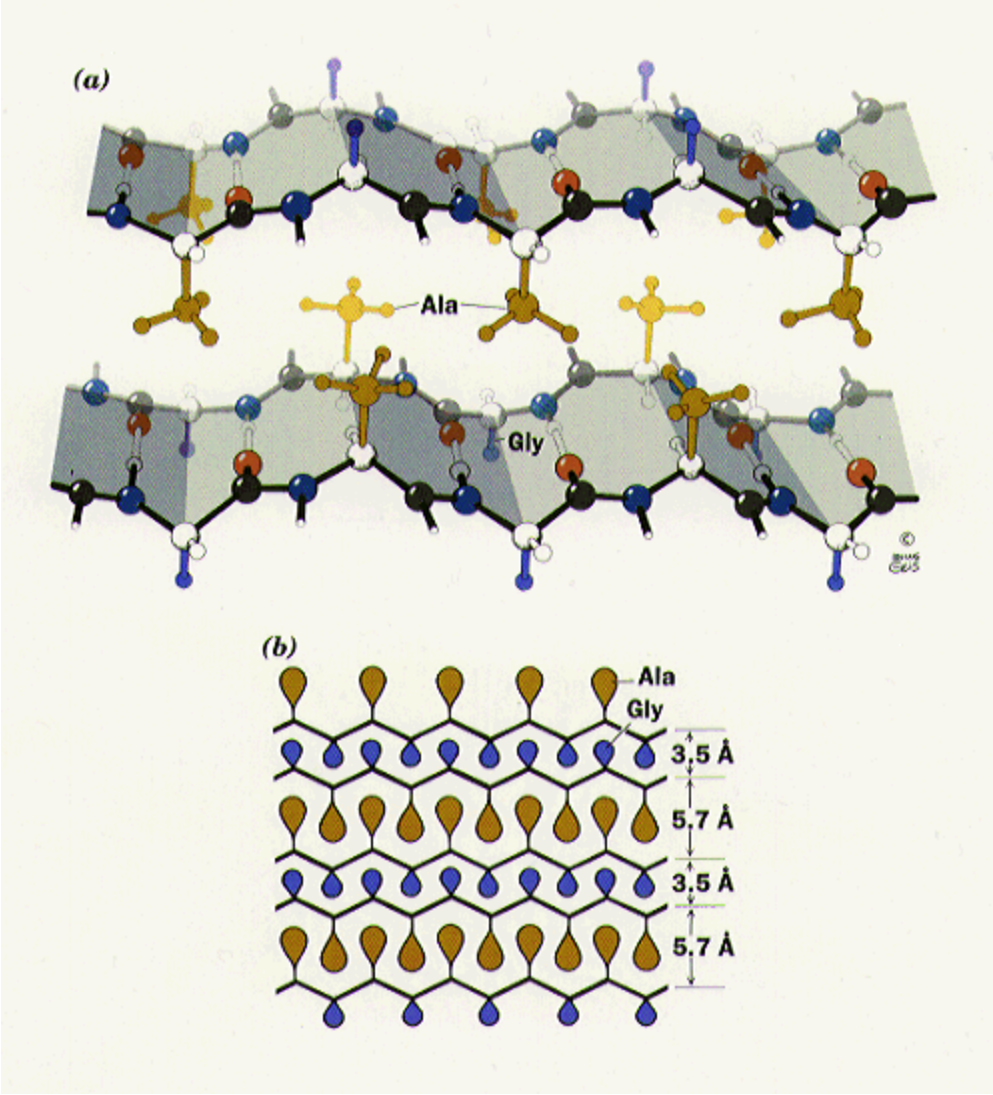
Globular protein

Contains more than 1 polypeptides

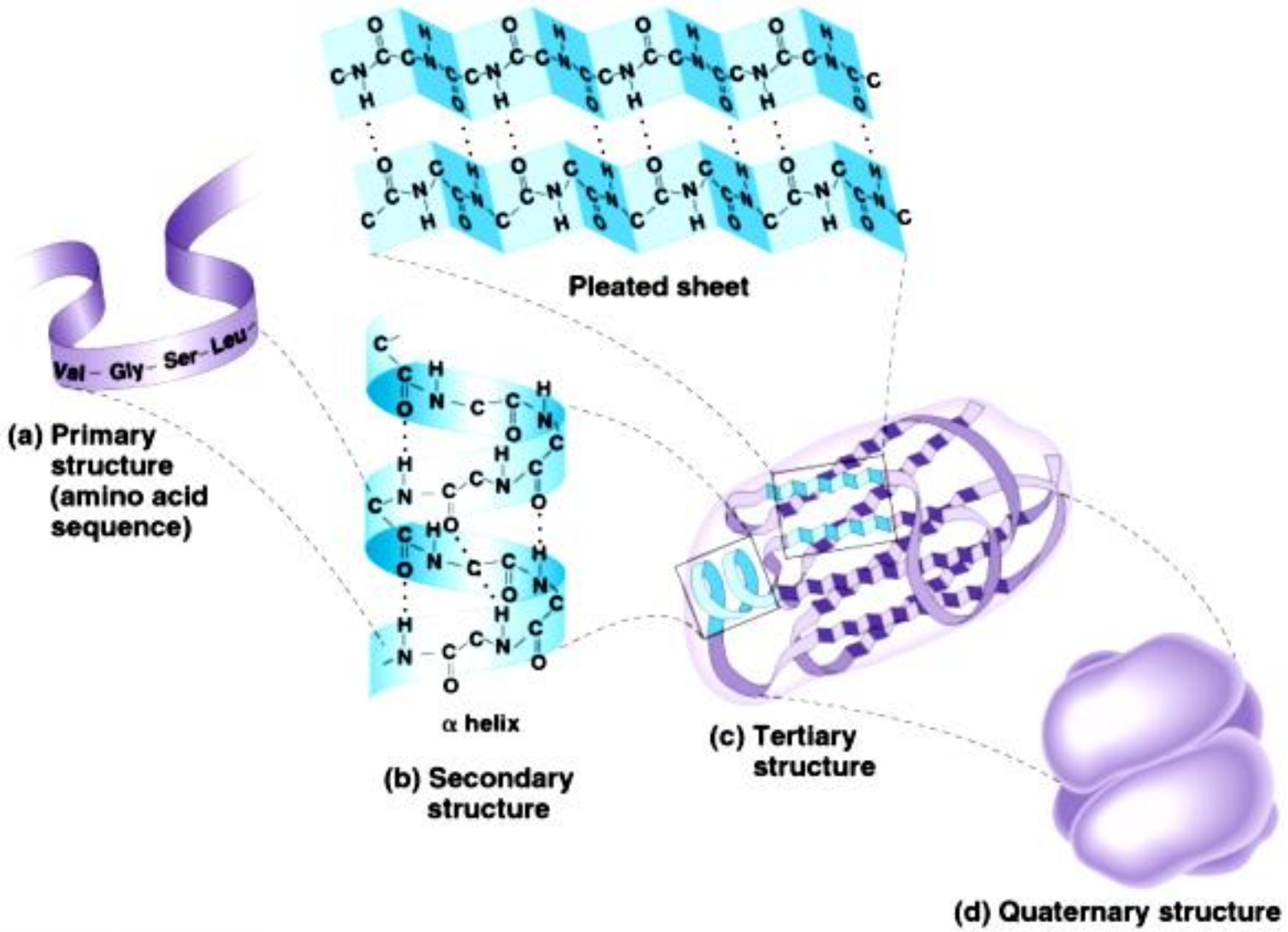
Fibrous protein
Actin, Myosin: Movement



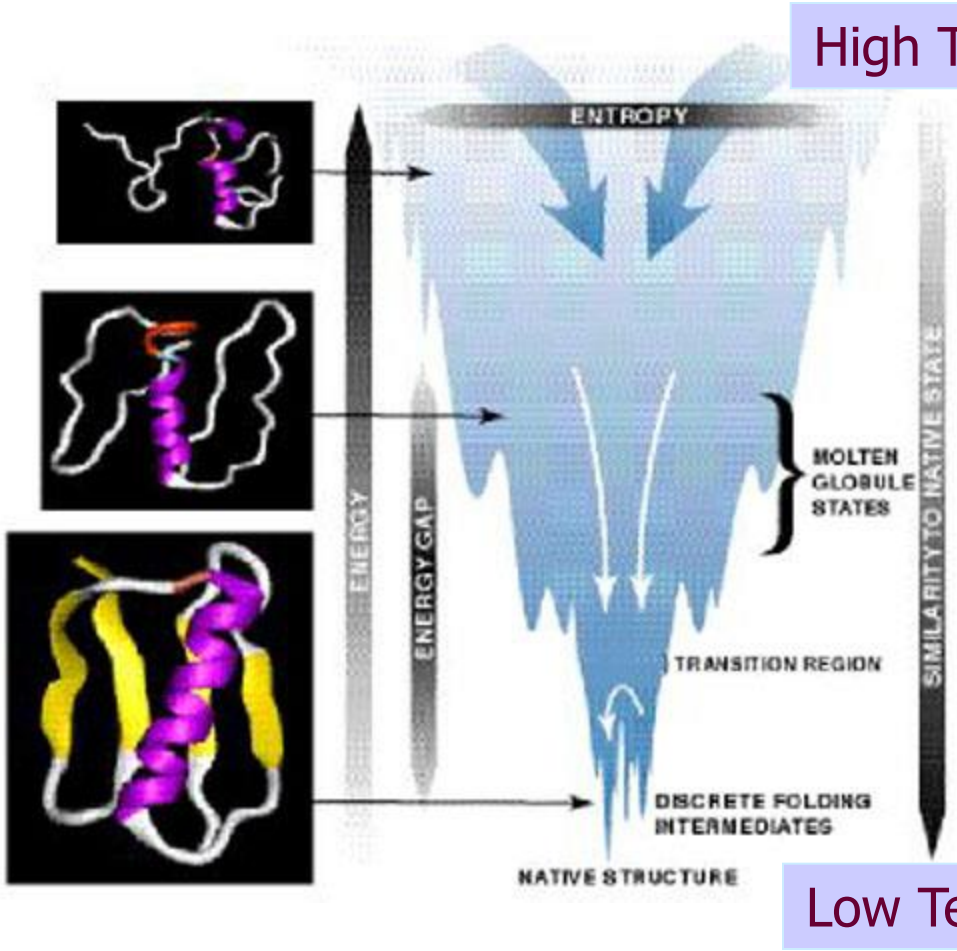
Quaternary structure of silk fibroin (beta-sheet)



Review of protein structure



Thermodynamic stability



Strong

Peptide bond

Hydrogen bond

Electrostatic interaction

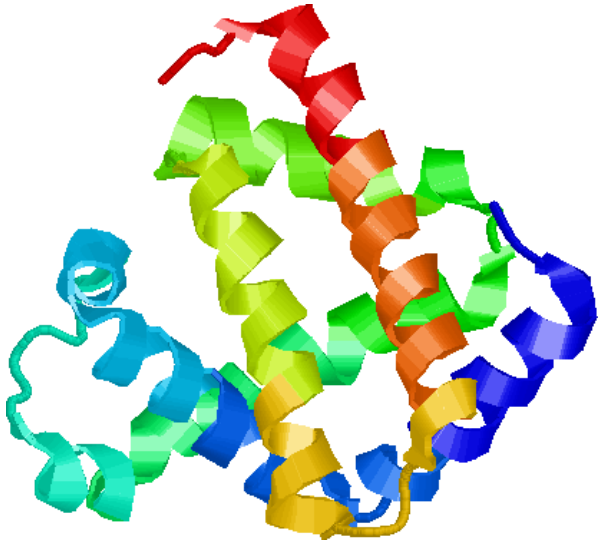
Hydrophobic interaction

van der Waals forces

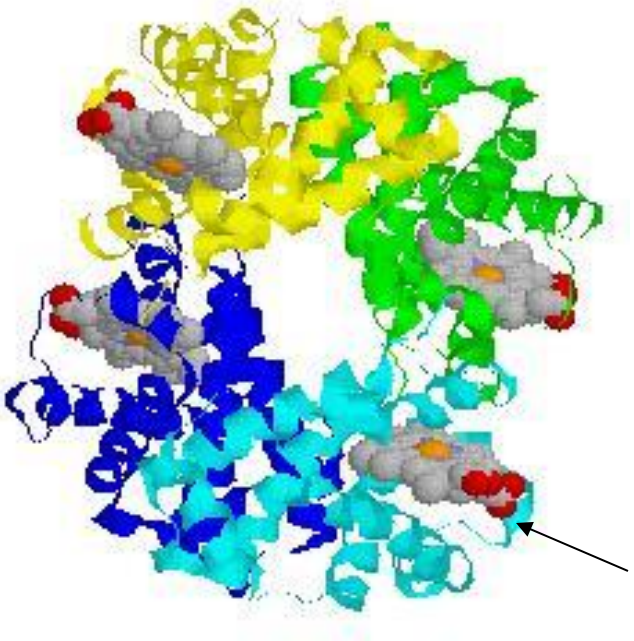
Weak

Types of protein

Simple protein

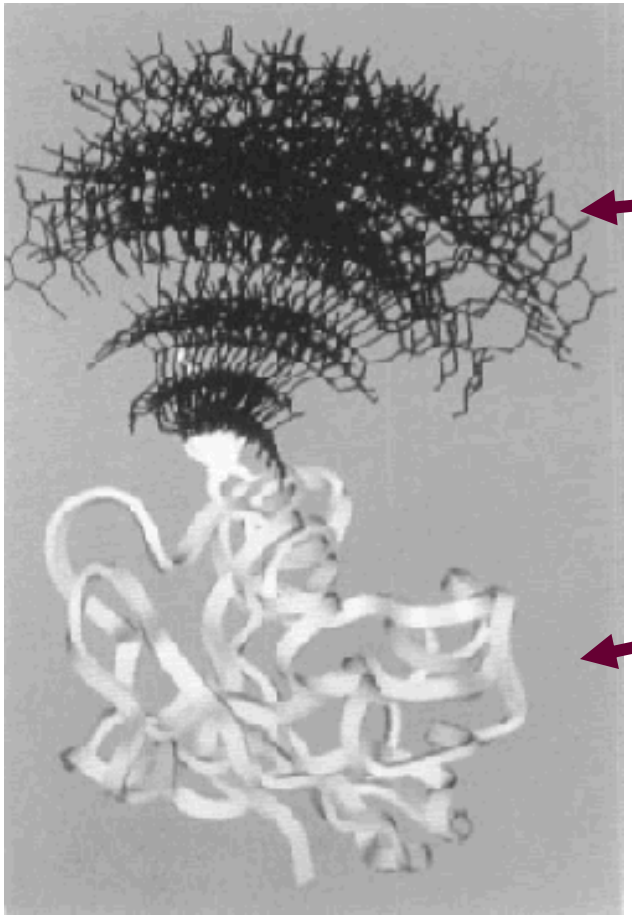


Conjugated protein



Hemoglobin

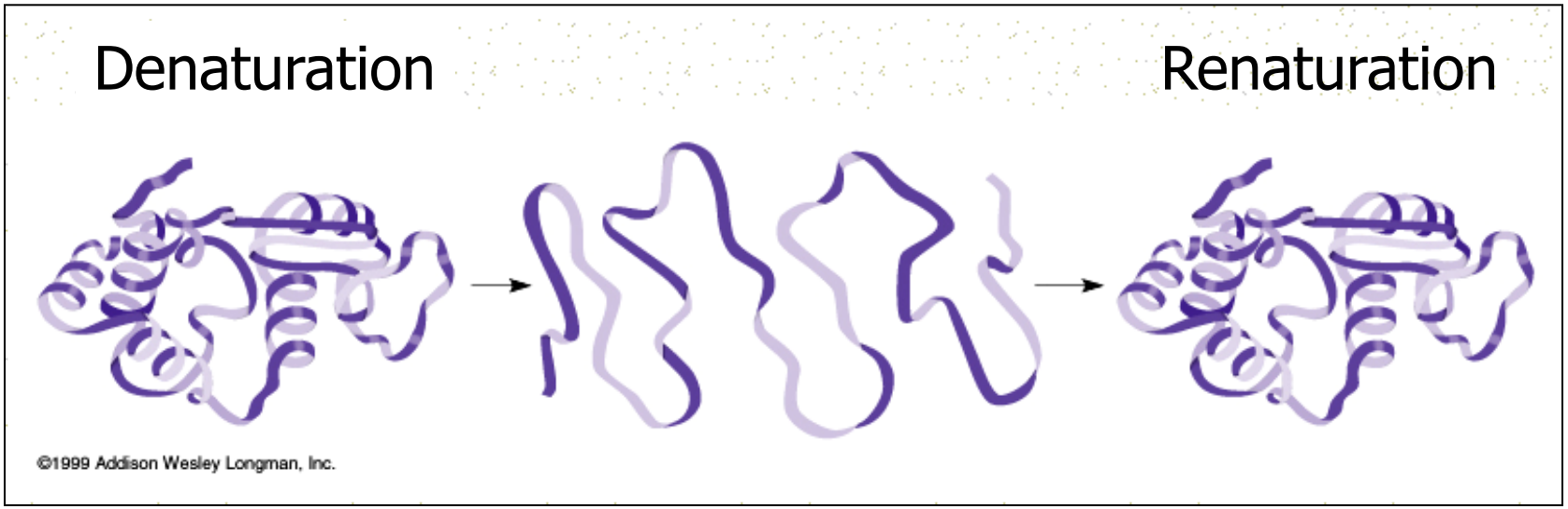
Glycoprotein



Carbohydrate

Polypeptide

Protein denaturation



Factors involved:

Heat : increase molecular vibration, disrupt structure

Freeze-thaw: denature structure

Detergents: disrupt hydrophobic interaction, electrostatic (SDS)

High salts: urea, guanidine: disrupt hydrogen bonding

pH: change net charge : disrupt structure

Mercaptoethanol, hair perm: disrupt disulfide bond

The effect of Detergents on denaturation

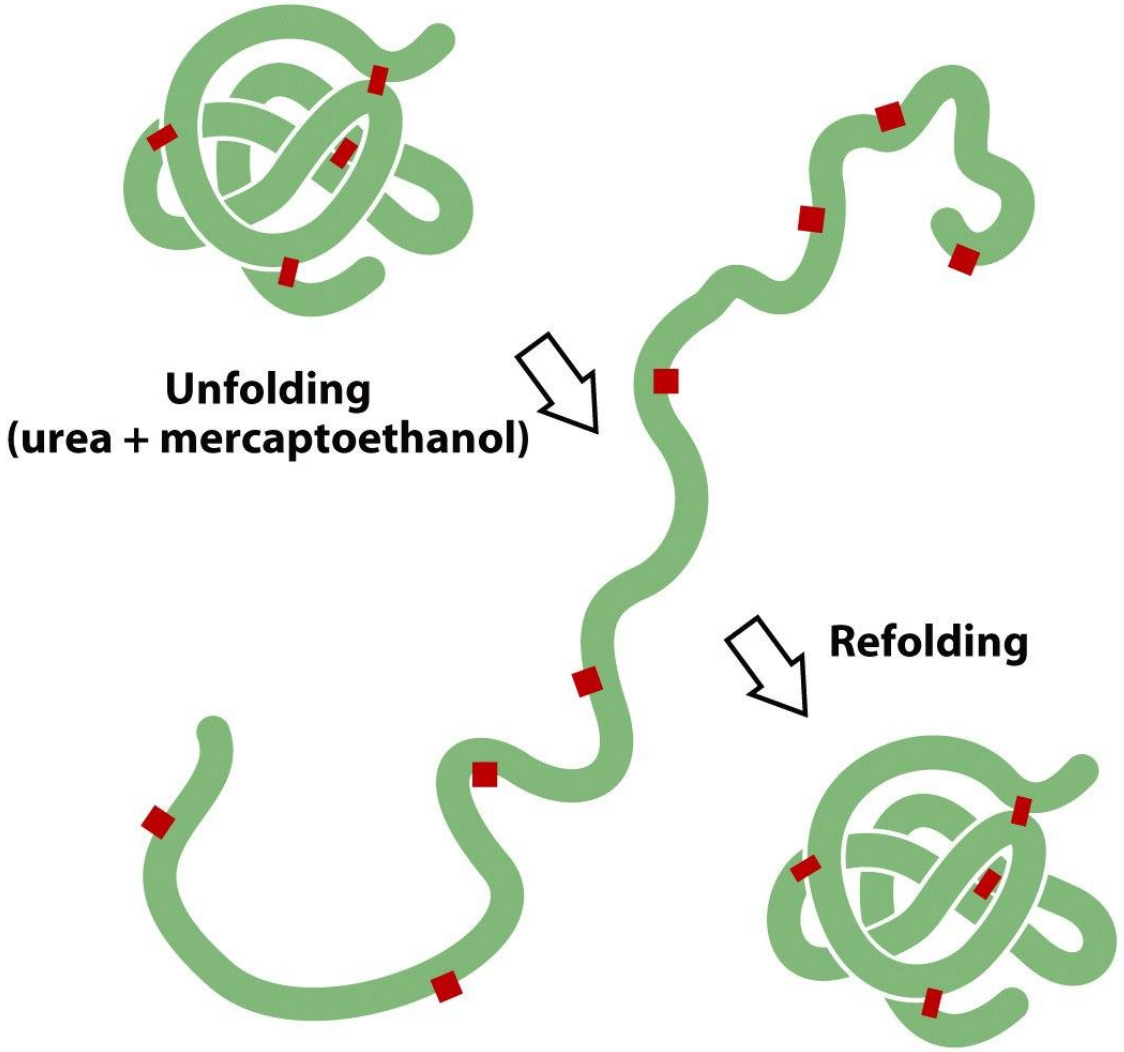


Figure 2-42 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

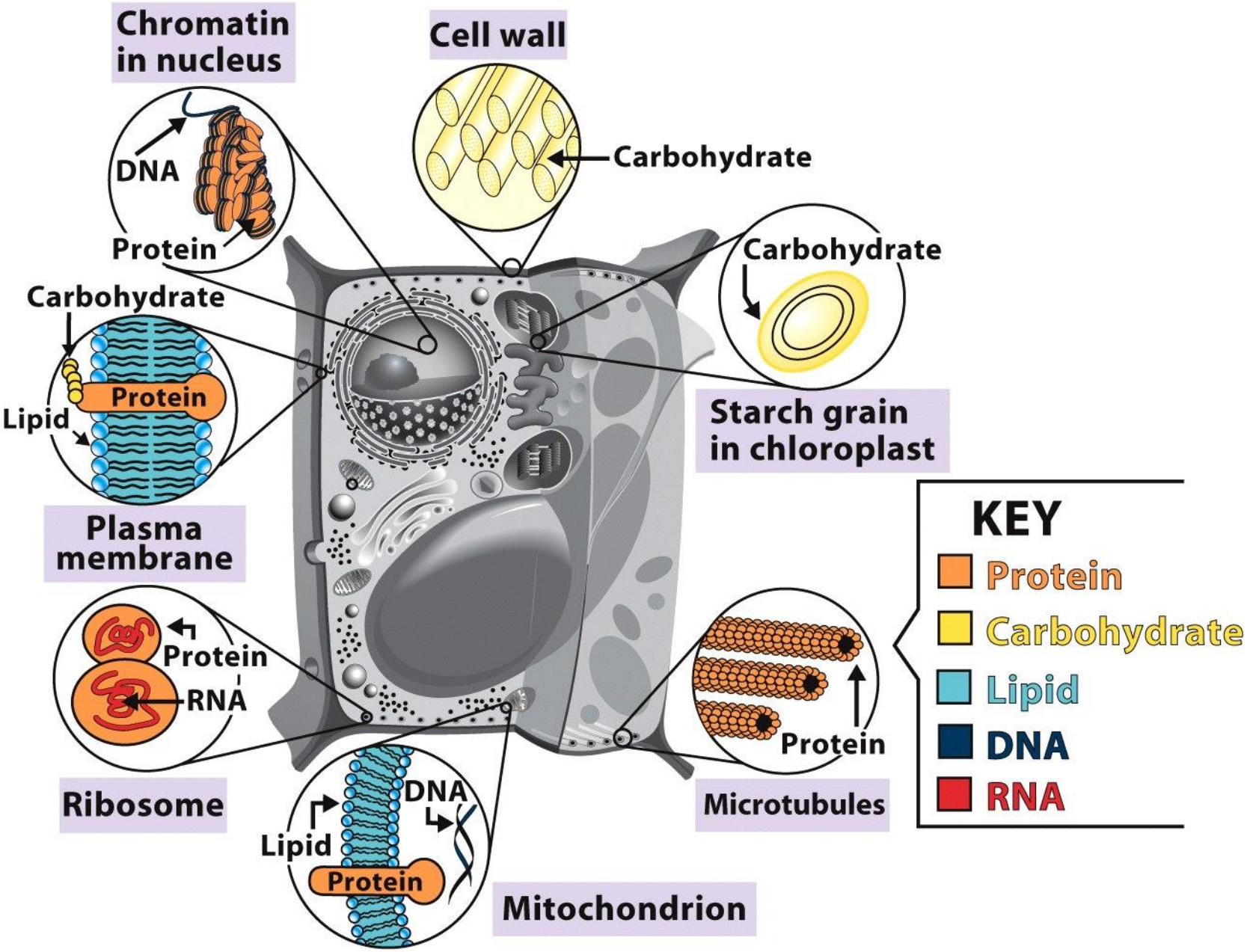


Figure 2-11 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Biological functions of protein in body system

1. **Enzyme**: Apart from a few catalytically active RNA molecules, all enzymes are proteins.
2. **Signaling**: Receptor protein in cell membrane can bind ligands (e.g. hormones) cause the responses of cell to that ligands.
   Some hormones are themselves small proteins, such as insulin and growth hormon
3. **Transport and storage**:
   - Hemoglobin transports oxygen in the RBC
   - Transferrin transports iron to the liver
   - Ferritin bounds with iron and stores in the liver
   - Dietary fats are carried in the blood by lipoproteins

Biological functions of protein in body system

4. **Structure and movement:**
   - Collagen is the major protein in skin, bone and connective tissues
   - Keratin is a major component of hair
   - Actin and myosin are the basis of muscle contraction
5. **Nutrition:** Casein and ovalbumin are the major proteins of milk and eggs, respectively
6. **Immunity:** Antibodies, which recognize and bind to bacteria, viruses and other foreign materials (the antigen) are proteins.
7. **Regulation:** Transcriptional factors bind to and modulate the function of DNA.