Medicinal Chemistry: An Overview

Course Outline

Lecture	Date	Topic
1	2015/12/17	General Aspects of Medicinal Chemistry
2	2016/01/07	General Biochemistry
3	2016/01/21	Principles of Chemical Synthesis
4	2016/02/04	Chemical Synthesis of Small and Complex Molecules
5	2016/02/18	Chemical Synthesis of Peptides
6	2016/03/03	Strategies for Discovery of Lead Compounds
7	2016/03/17	Structure Activity Relationship
8	2016/03/31	Spatial Organization, Receptor Mapping and Molecular Modeling
9	2016/04/14	Pharmacokinetic Properties
10	2016/04/28	Legal and Economic Aspects of Drug Development

Biochemistry

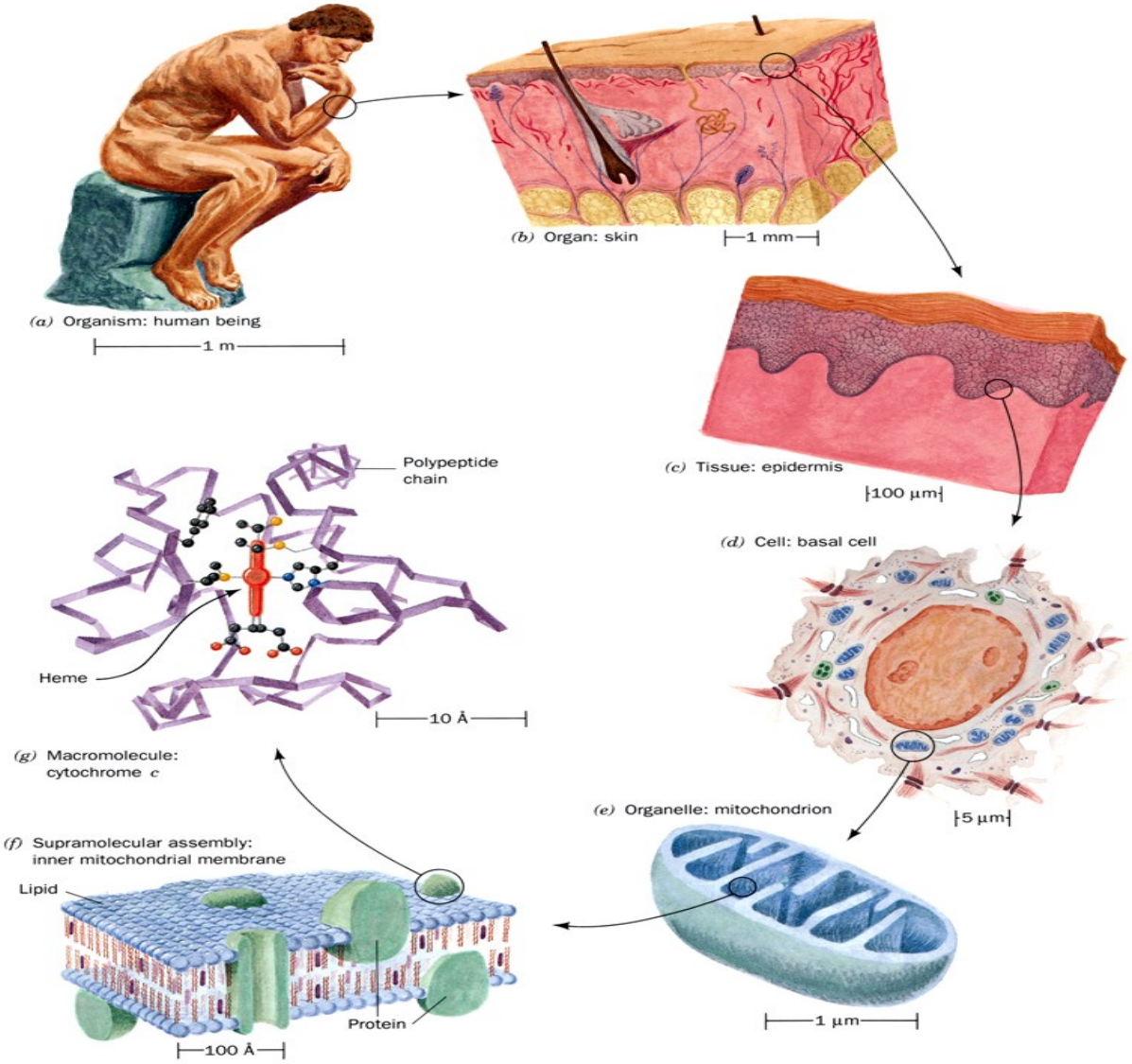


Figure 1-14

The chemical study of the various processes occurring in living things.

hierarchical organization of biological structures

Molecules of Life

Proteins: composed of amino acid building blocks.

Nucleic acids: composed of nucleotides.

Carbohydrates: composed of sugars.

Lipids: composed of organic compounds that are essentially insoluble in water due to mainly hydrophobic nature.

Vitamins: organic compounds required in small amounts by the body.

Hormones: intercellular chemical messengers.

Acid-Base Theory

$$HA + H_2O \rightleftharpoons H_3O^+ + A^- \equiv HA \rightleftharpoons H^+ + A^-$$

Brønsted acid | Brønsted base | conjugate acid | conjugate base | (proton)

dissociation constant (K)

$$K = \frac{[H^+]\,[A^-]}{[HA]}$$

for strong acids, $K > 1$
for weak acids, $K < 1$

pH for easy comparison of $[H^+]$

$$pH = -\log[H^+]$$

The relative concentrations of acids and bases determines the pH of a solution

$$pH = pK + \log\left(\frac{[A^-]}{[HA]}\right)$$

Henderson–Hasselbalch equation

The pH of a solution is stabilized by a buffer

Properties of an ideal buffer

1. Impermeability to biological membrane.
2. Biological stability and lack of interference with metabolic biological processes.
3. Lack of significant absorption of ultraviolet and visible light.
4. Lack of formation of insoluble complexes with cations.
5. Minimal effect of ionic composition or salt concentration.
6. Limited pH change in response to temperature.

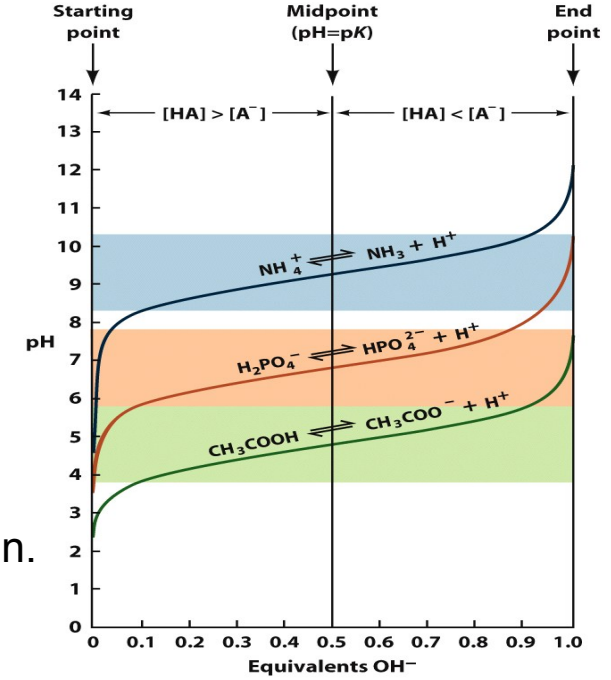


Figure 2-11

Laws of Thermodynamics

First Law: Energy is conserved.

$\Delta U = q - w$ where ΔU = net energy, q = heat, w = work

Second Law: The universe tends toward maximum disorder.

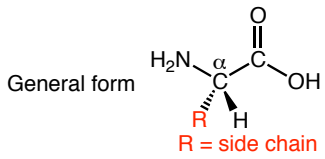
$S = k_B \ln W$ where S = entropy, k_B = Boltzmann constant, W = disorder

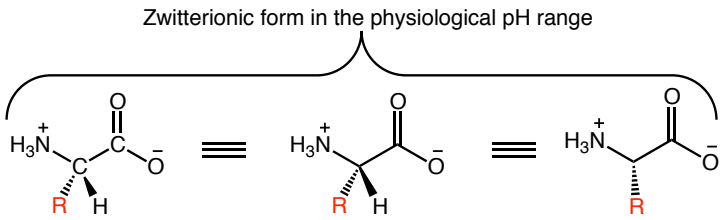
Gibbs Free Energy: An indicator of spontaneity of constant temperature (*T*) and pressure processes.

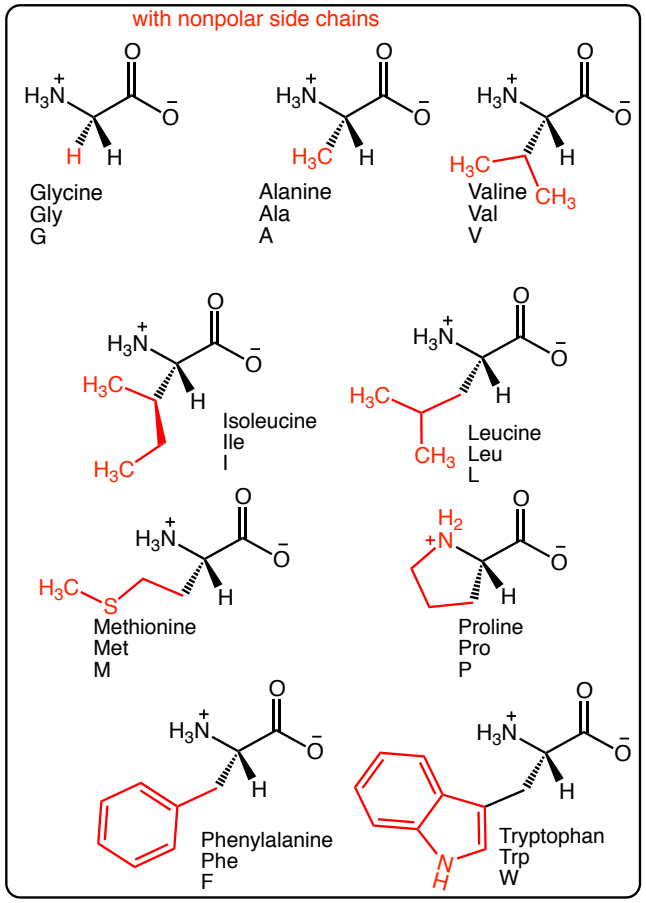
$G = H - TS$ where G = Gibbs free energy, H = Enthalpy

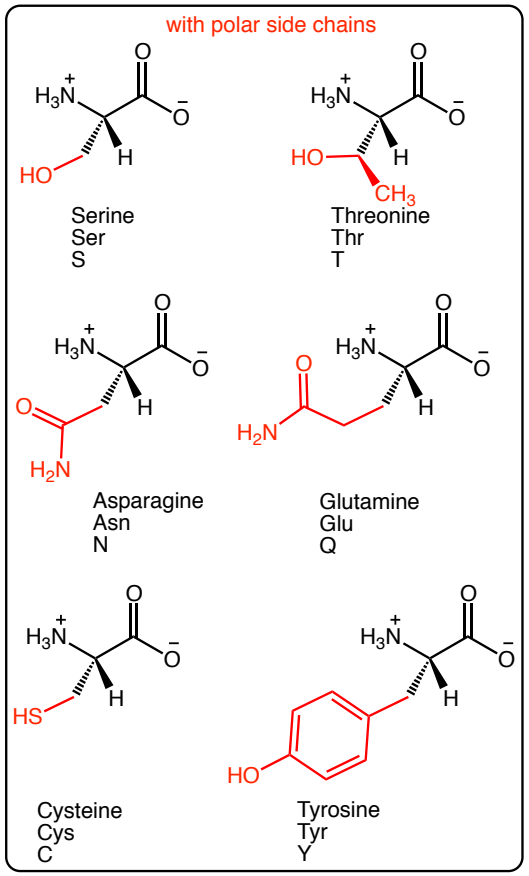
$\Delta G = \Delta H - T\,\Delta S$ when $\Delta G \leq 0$, process is spontaneous (**exergonic**).
when $\Delta G \geq 0$, process is not spontaneous (**endergonic**).

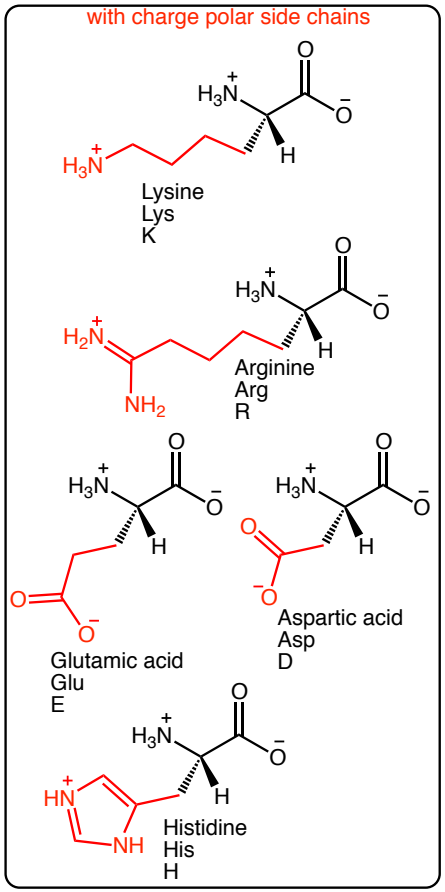
Standard Amino Acids



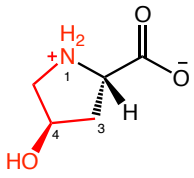


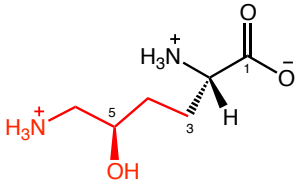






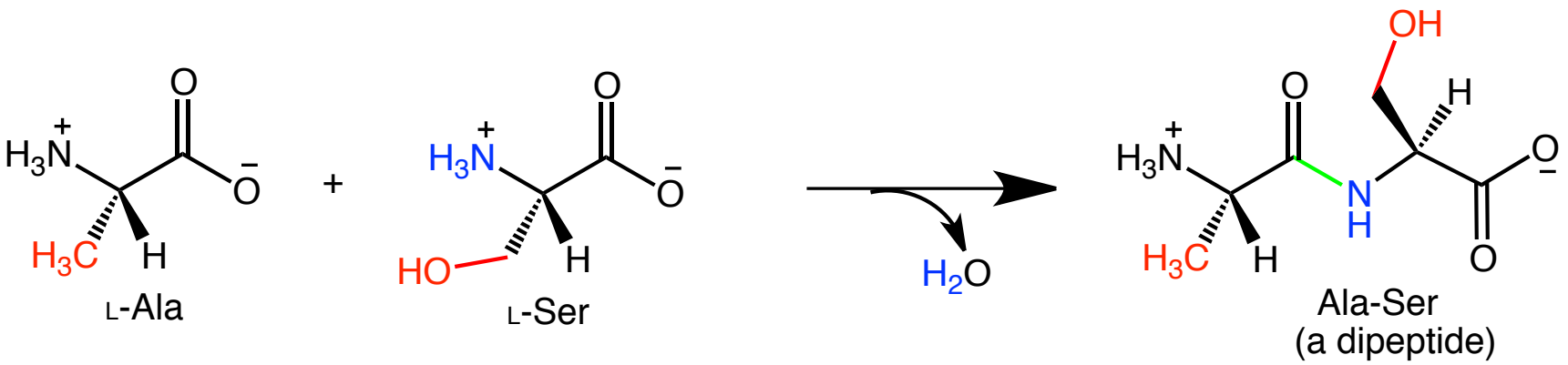
Nonstandard amino acids also exist

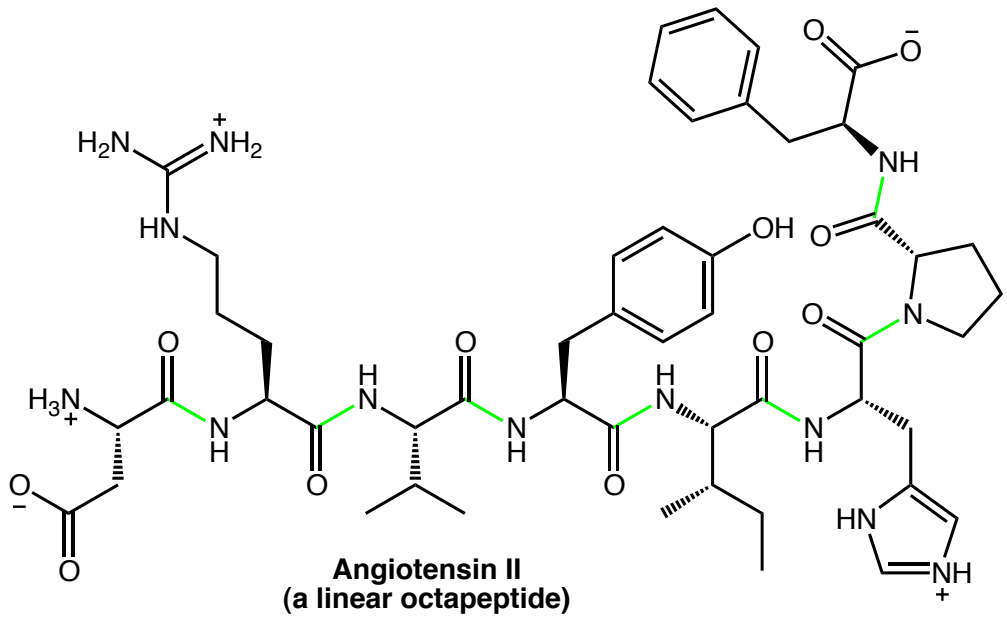


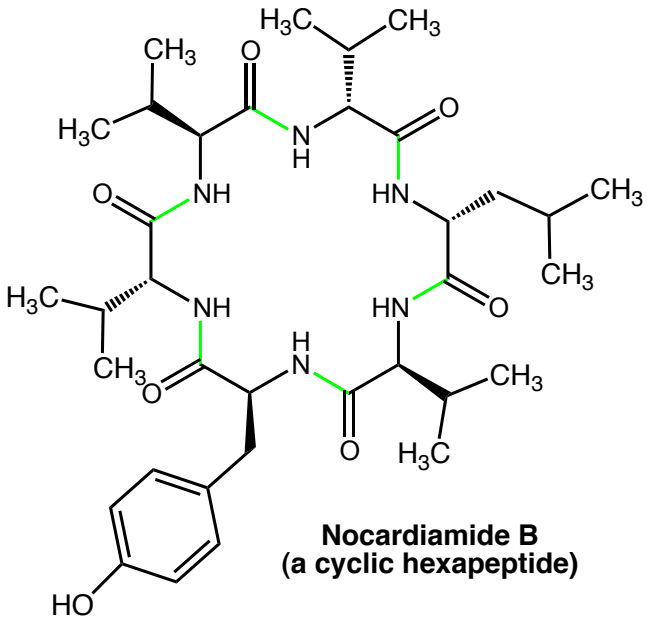


Peptide (Amide) Bond

peptide bond indicated by green line







Wu et al. *Journal of Natural Products* **2013**, *76*, 694–701

Protein Structure

Primary structure
amino acid sequence of its polypeptide chain.

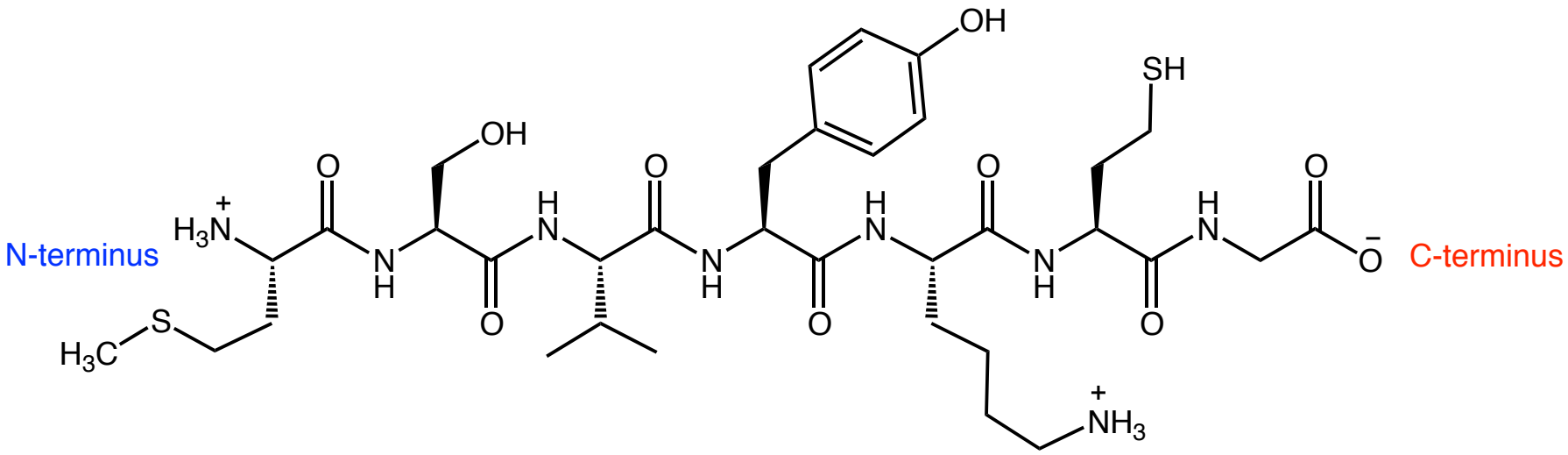
Secondary structure
local spatial arrangement of polypeptide backbone
(α helices and β sheets).

Tertiary structure
3-D structure of polypeptide chain.

Quaternary structure
spatial arrangement of its subunits.

Protein structures are determined by X-ray crystallography and nuclear magnetic resonance (NMR).

Primary Structure



3-letter code: Met-Ser-Val-Tyr-Lys-Cys-Gly

1-letter code: M-S-V-Y-L-C-G = MSVYLCG

Secondary Structure (α-Helix)

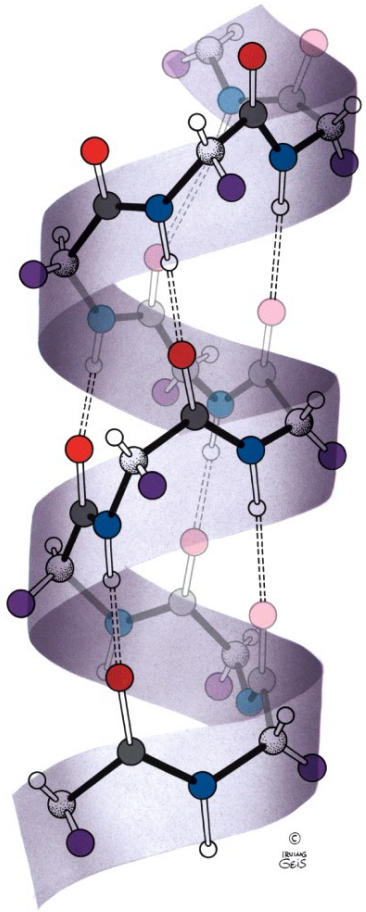


Figure 8-11
Illustration, Irving Geis. Image from the Irving Geis Collection, Howard Hughes Medical Institute. Reprinted with permission.

Stereo, space-filling representation of an α-helical segment of sperm whale myoglobin (E-helix) PDB 1A6M

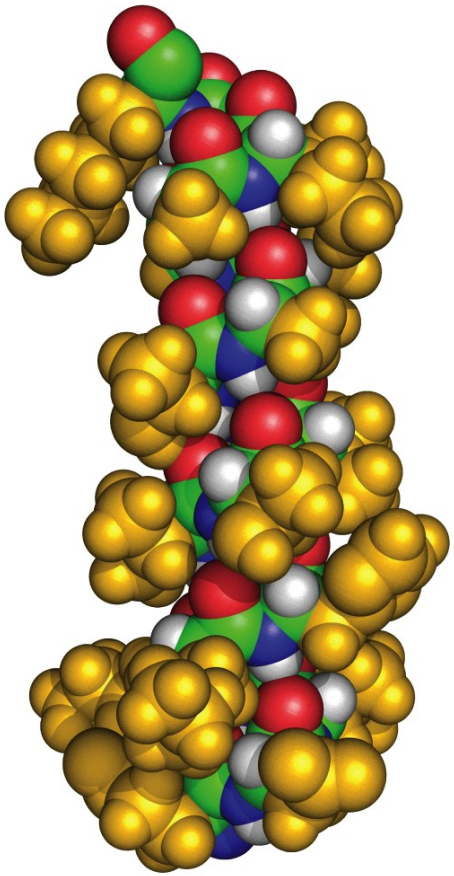
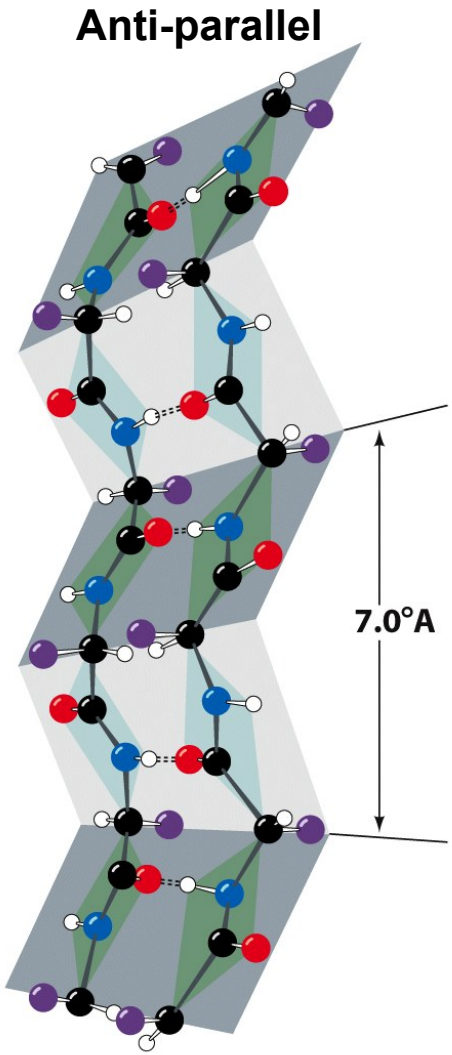


Figure 8-12

Secondary Structure (β-Sheets)



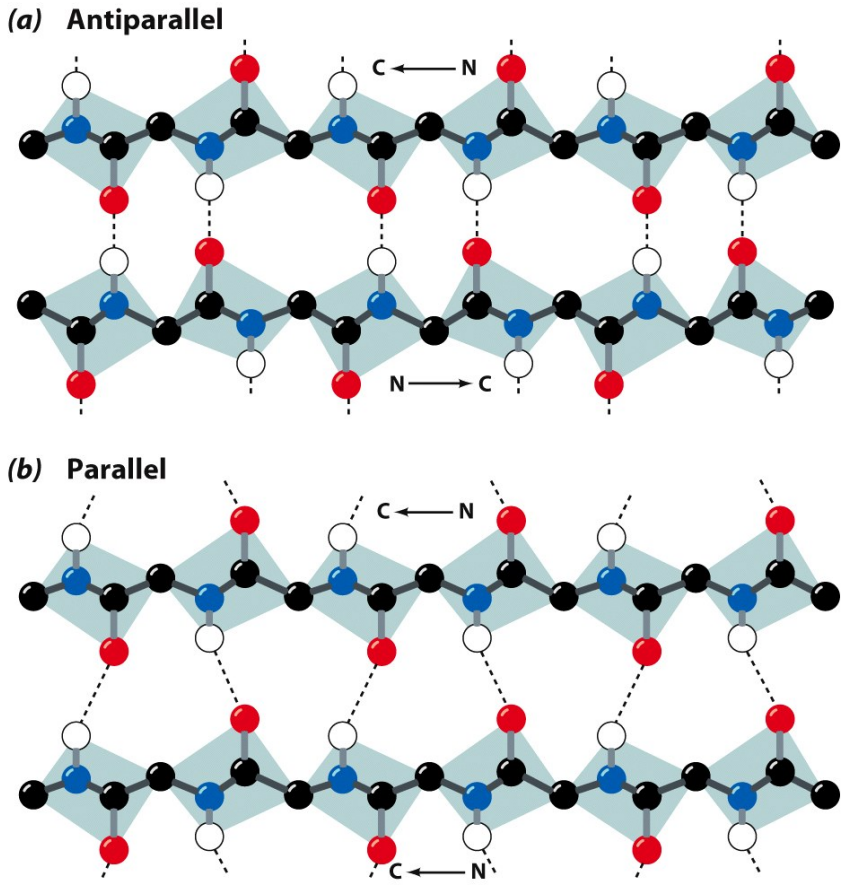


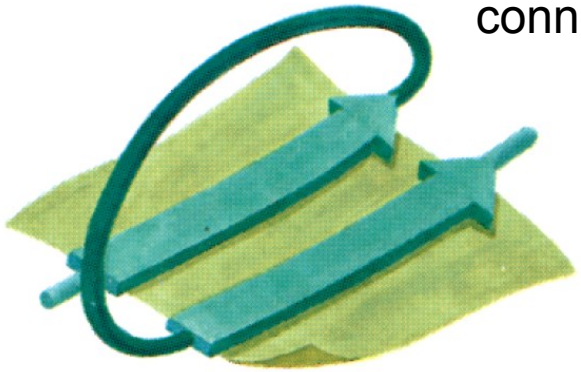
Figure 8-16
Illustration, Irving Geis. Image from the Irving Geis Collection, Howard Hughes Medical Institute. Reprinted with permission.

Figure 8-17
Illustration, Irving Geis. Image from the Irving Geis Collection, Howard Hughes Medical Institute. Reprinted with permission.

Topology of β-Sheets

(a) Hairpin connection

(b) Right-handed crossover connection



(c) Left-handed crossover connection

Figure 8-20

Tertiary Structure

The first protein X-ray structure was that of sperm whale myoglobin about 60 years ago.

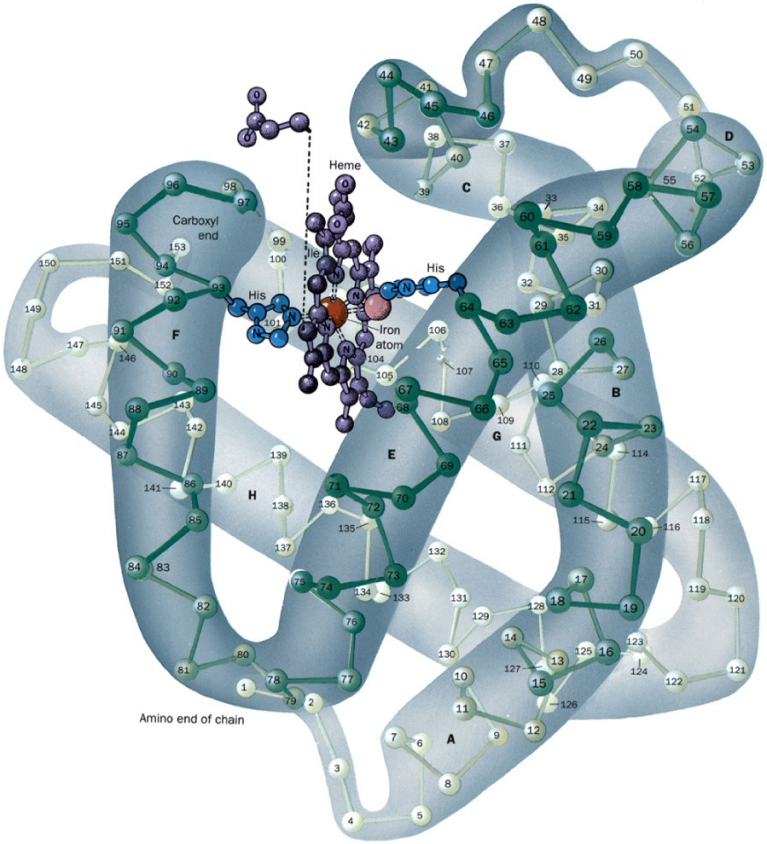


Figure 8-39b
Illustration, Irving Geis. Image from the Irving Geis Collection, Howard Hughes Medical Institute. Reprinted with permission.

PDB 1MBN

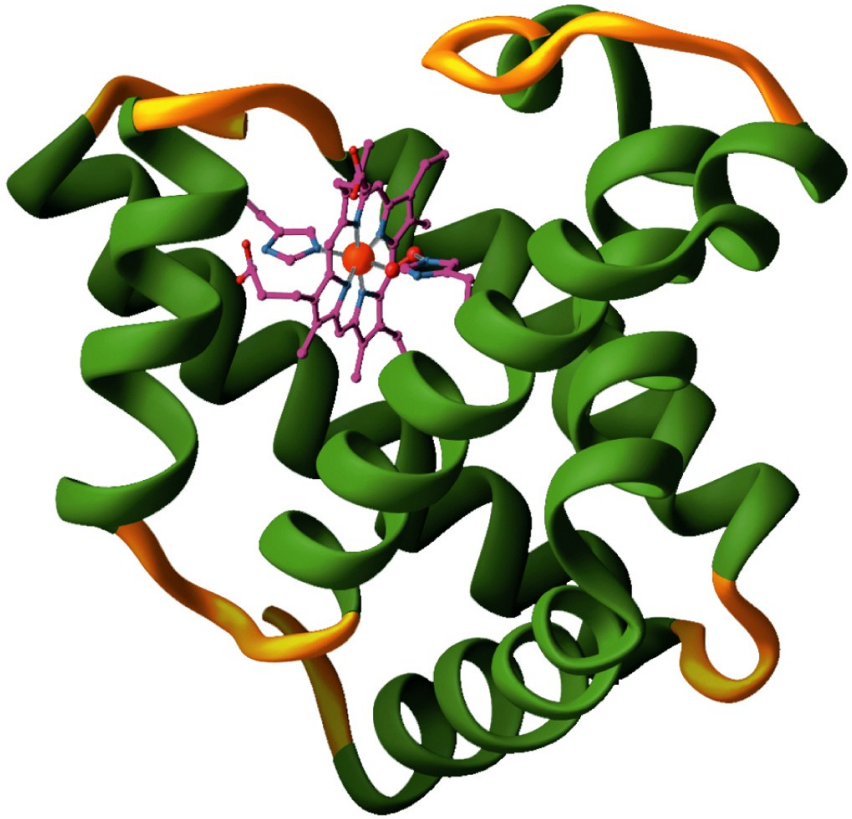
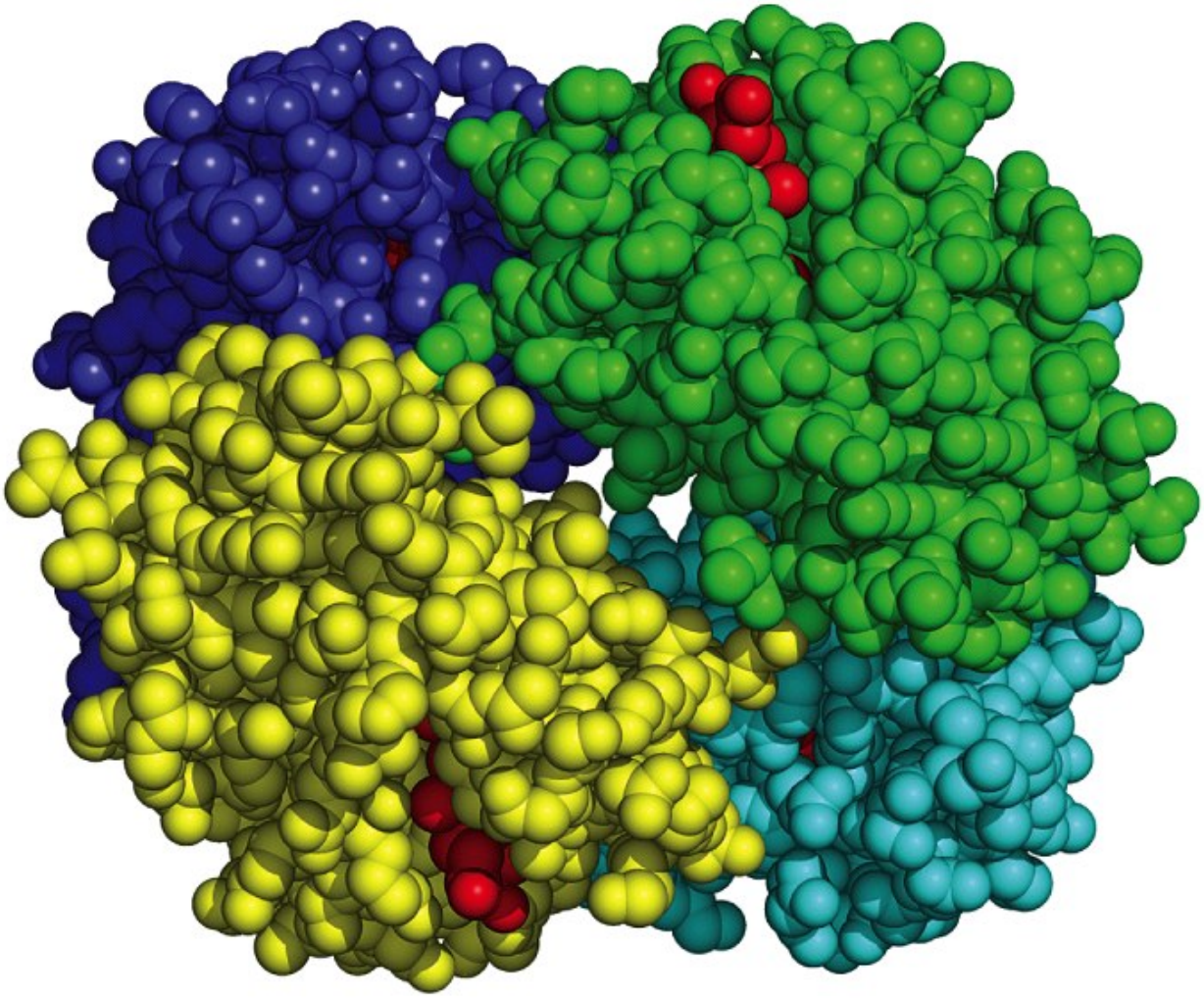


Figure 8-39c

PDB 1MBO

Quarternary Structure



Hemoglobin contains α_1 (yellow), α_2 (green), β_1 (blue), and β_2 (cyan).

The heme groups are in red.

PDB 2DHB

Figure 8-64

Solid Phase Peptide Synthesis

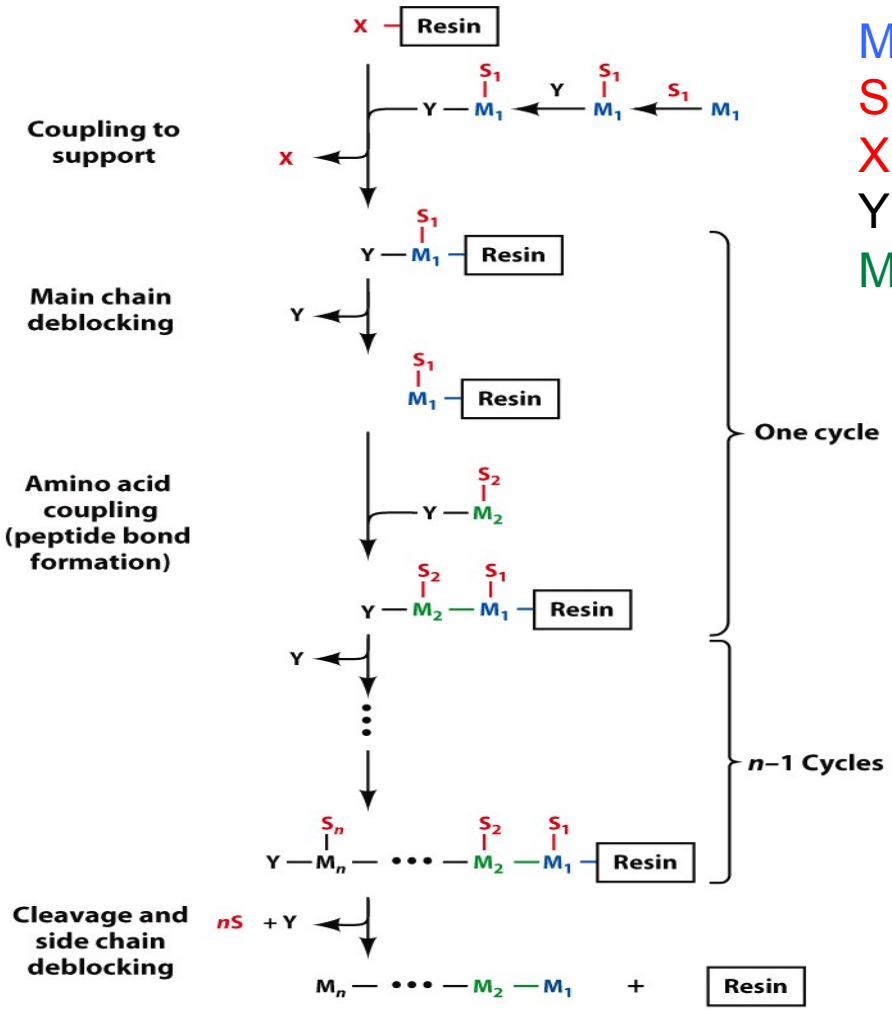
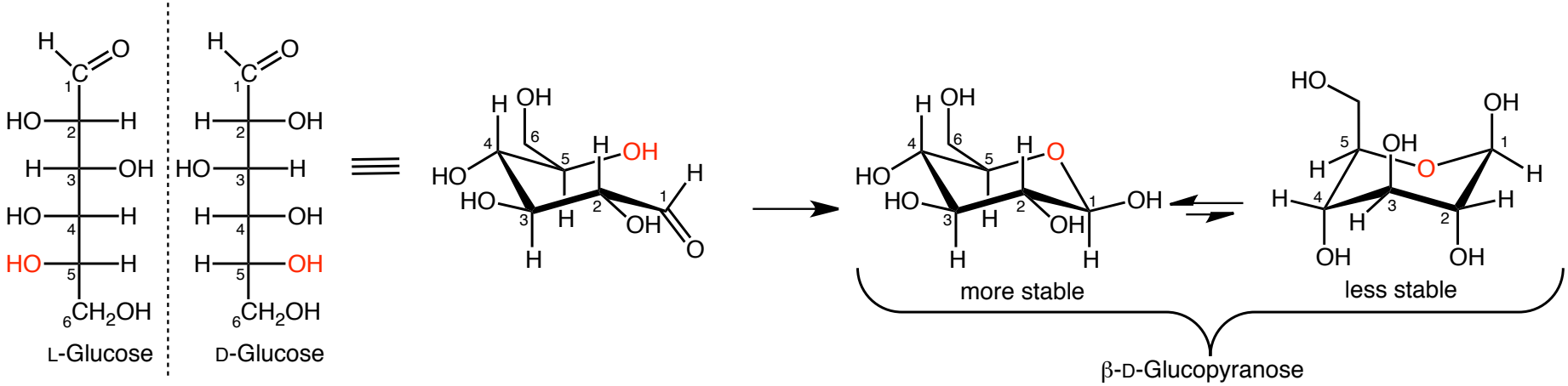


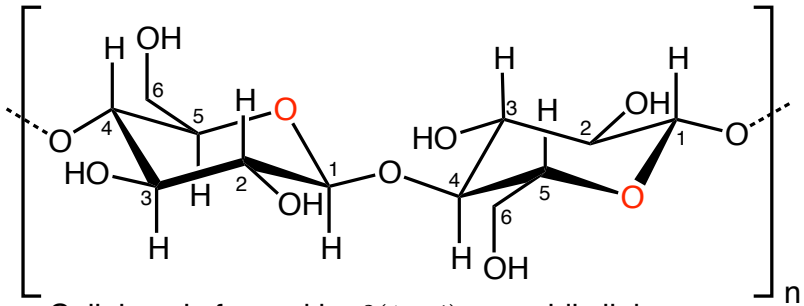
Figure 7-35

M_1 = first amino acid from the C-terminus
S_1 = protecting group for the side chain of M_1
X = leaving group
Y = main chain protecting group
M_2 = second amino acid from the C-terminus

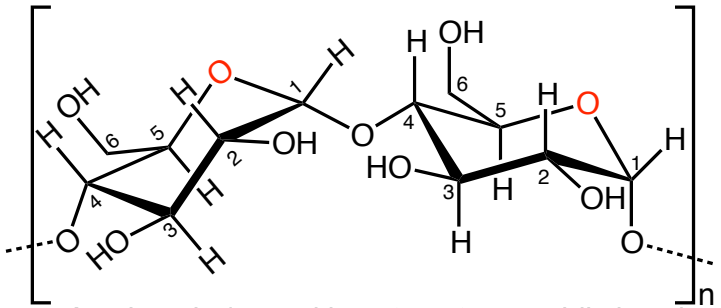
Liberty Blue SPPS machine from CEM

Polysaccharides



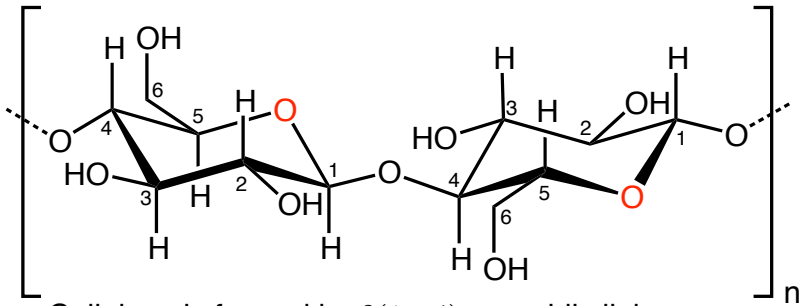


Cellulose is formed by β(1→4) gycosidic linkages between D-glucose residues.



α-Amylose is formed by α(1→4)-gycosidic bonds between D-glucose residues.

Polysaccharides



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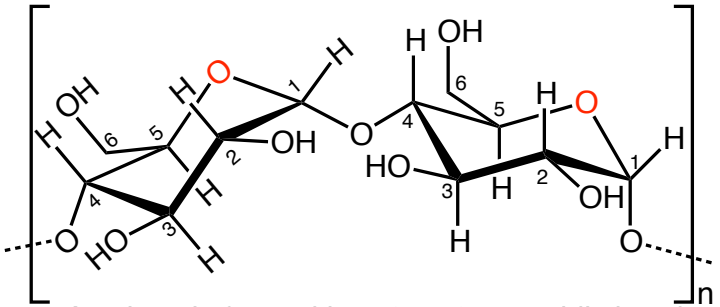

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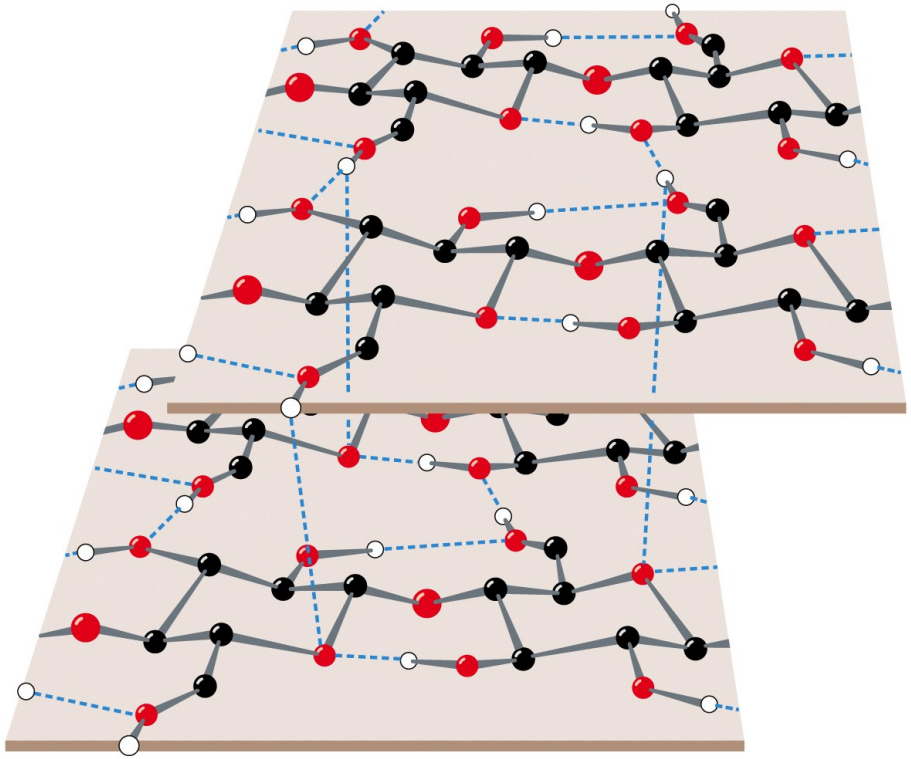

Figure 11-16
Illustration, Irving Geis. Image from the Irving Geis Collection, Howard Hughes Medical Institute. Reprinted with permission.

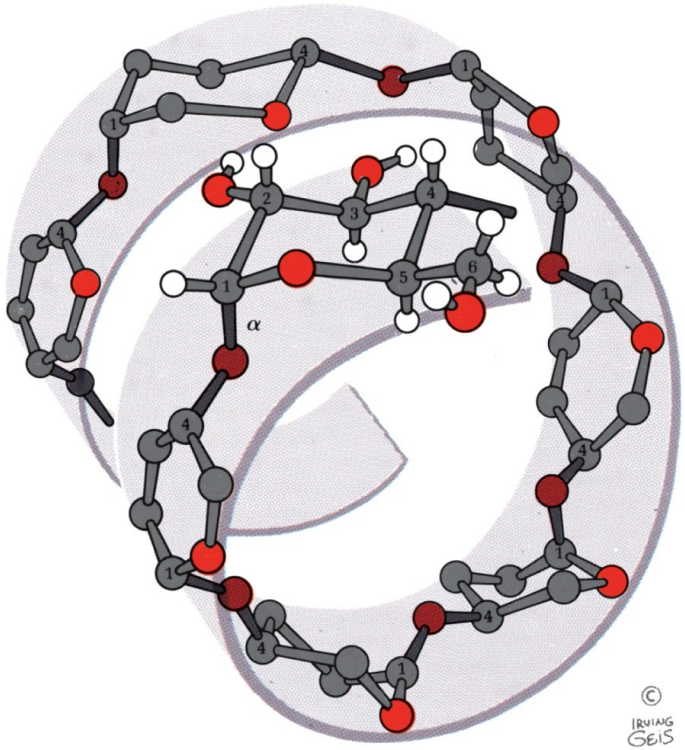

Figure 11-18b
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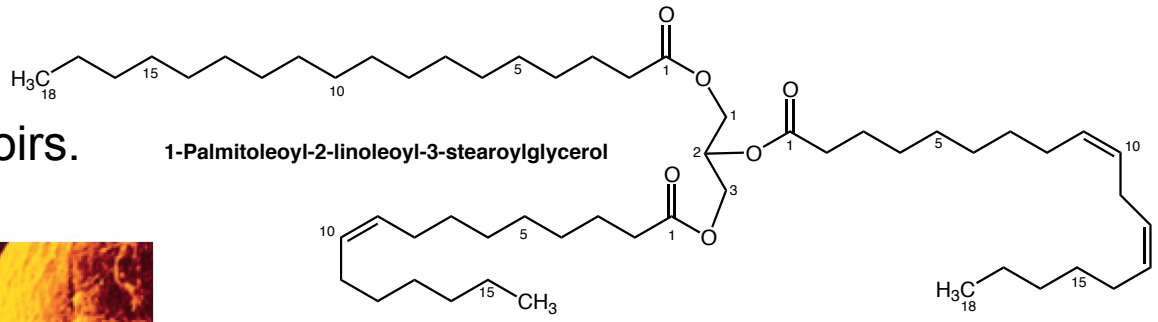
Lipids

Triacylglycerols: nonpolar, water-insoluble, energy reservoirs.



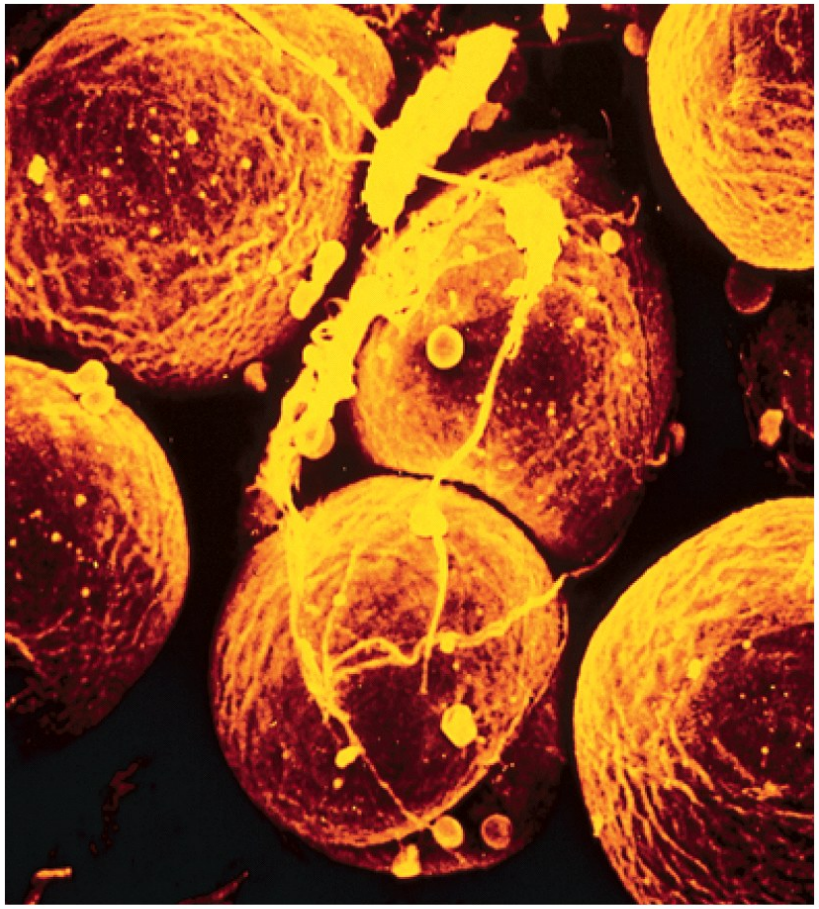
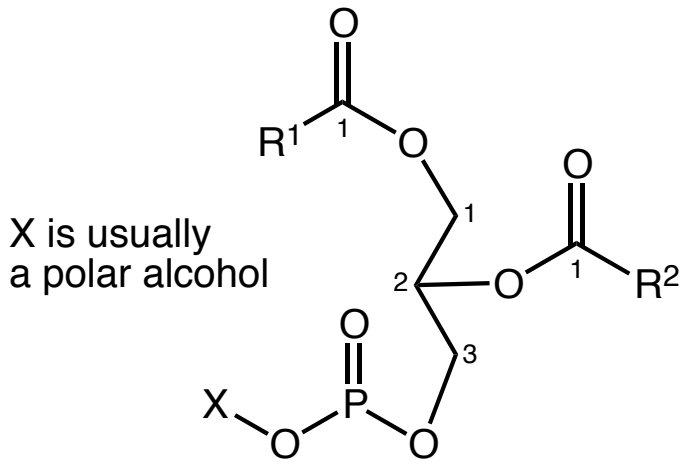


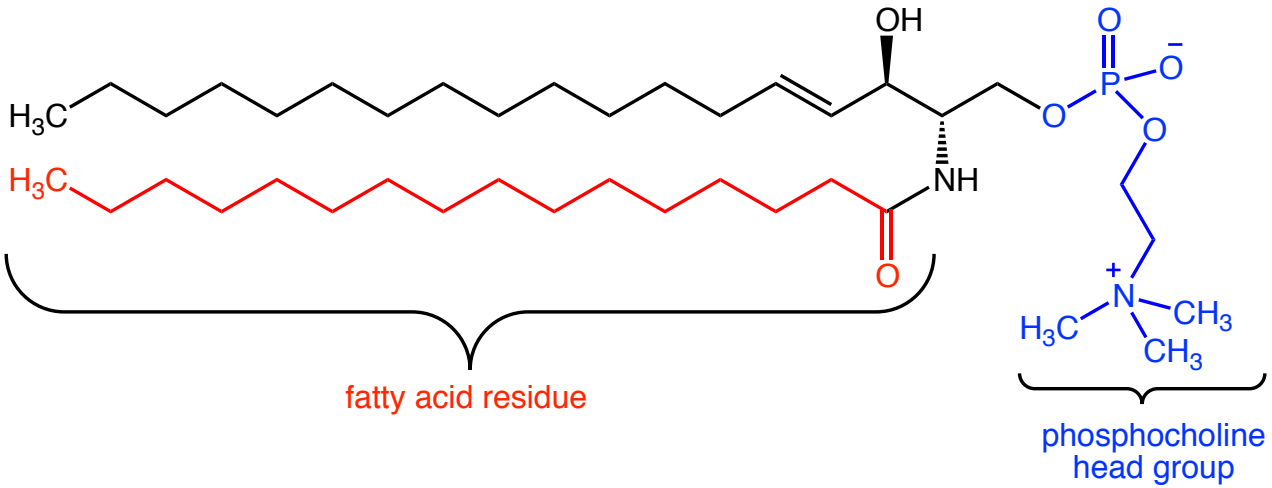
Figure 12-2
Fred E. Hossler/Visuals Unlimited

Glycerophospholipids: nonpolar hydrocarbon "tail" and polar phosphoryl-X "head"-amphiphilic molecules that are found in biological membranes.

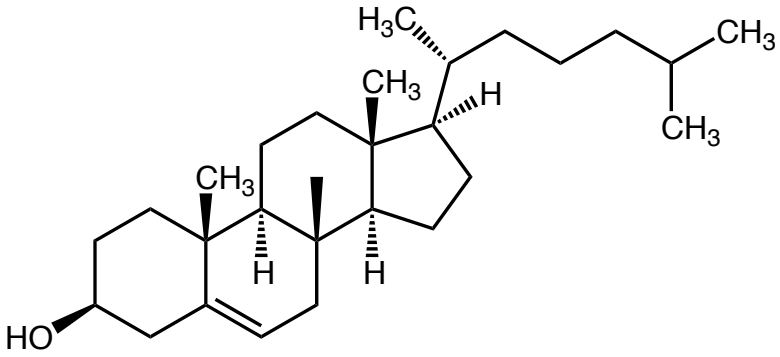


Lipids

A sphingomyelin: found in myelin sheath that surround nerve cell axons.



Cholesterol: 1) constitutes between 30 to 40% of the animal plasma membrane.
2) greater rigidity than other membrane lipids due to fused ring system.



Plasma Membrane

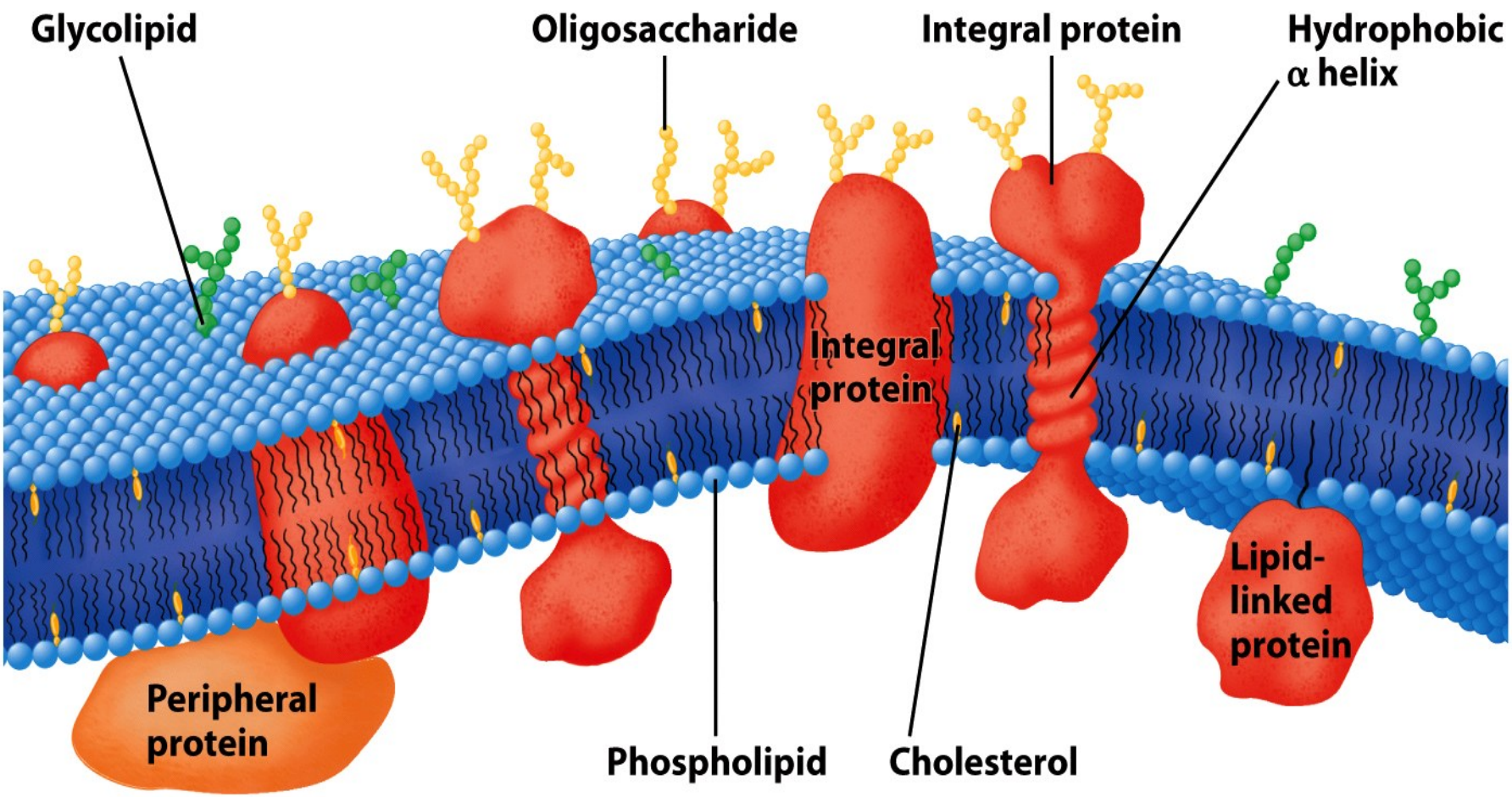


Figure 12-20

Fluid Mosaic Model

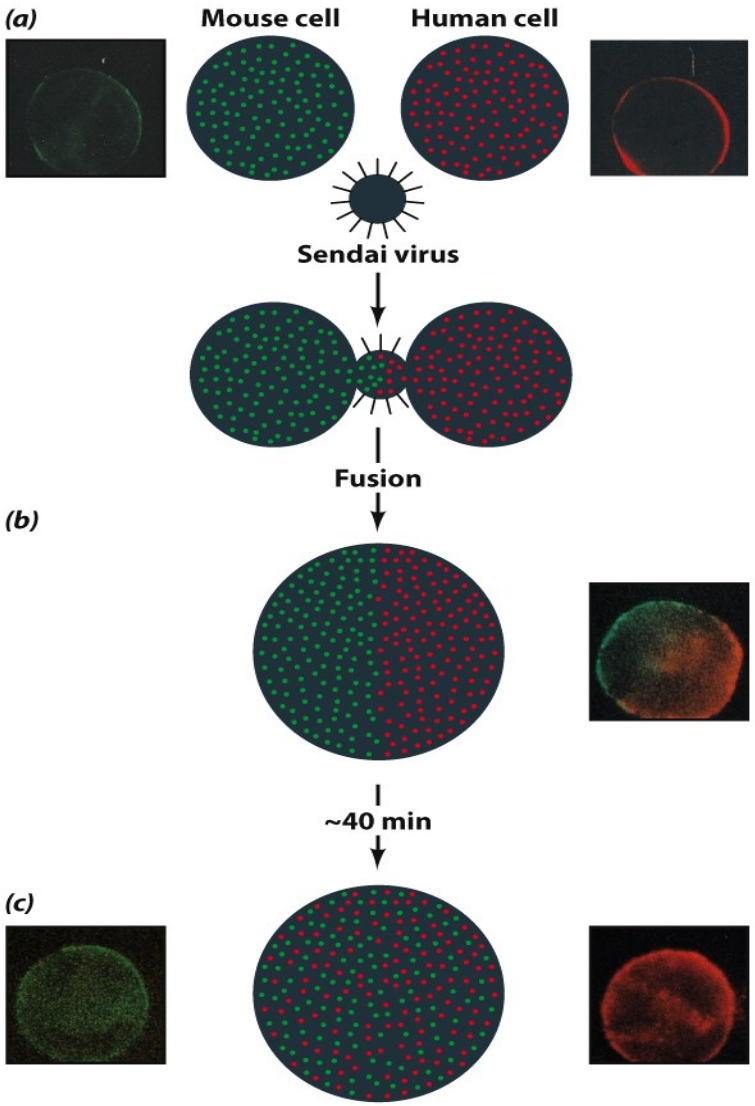
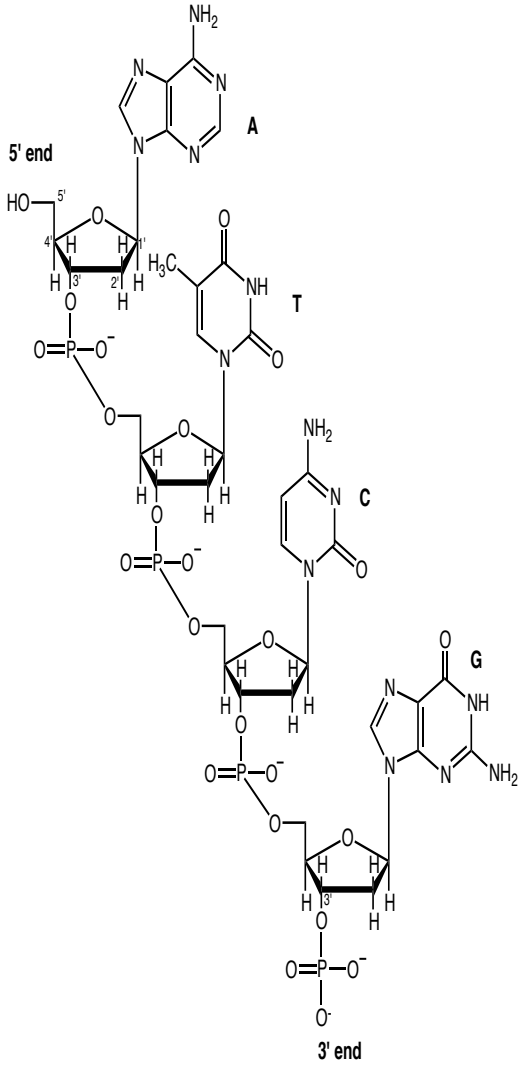


Figure 12-31

Model was proposed by
S. J. Singer and G. Nicolson.
Science **1972**, *175*, 720−731.

Experimental proof by M. Edidin.
Journal of Cell Science **1970**, *7*, 319−335.

DNA



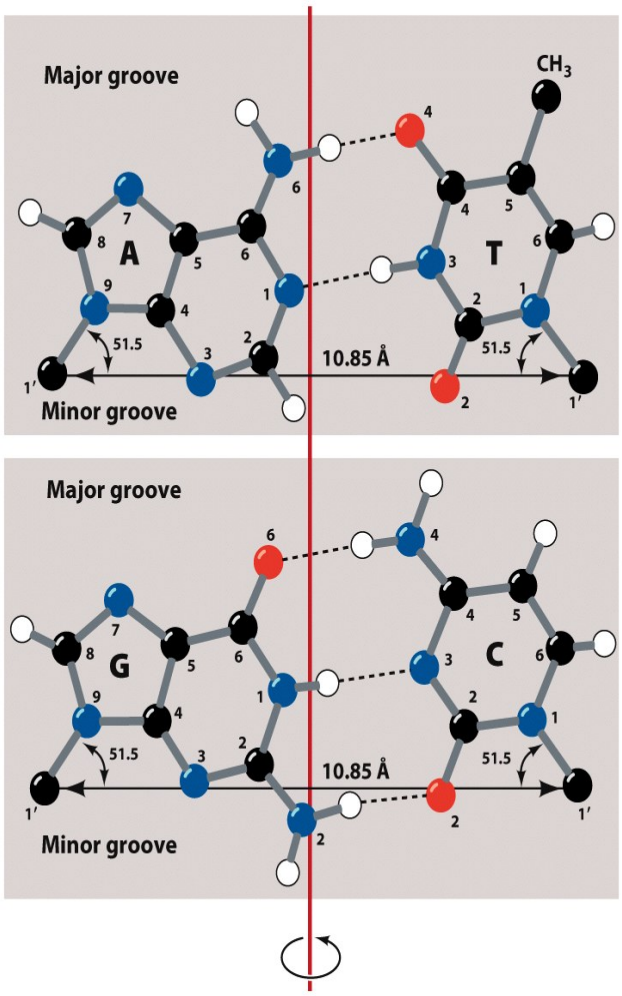


Figure 5-12

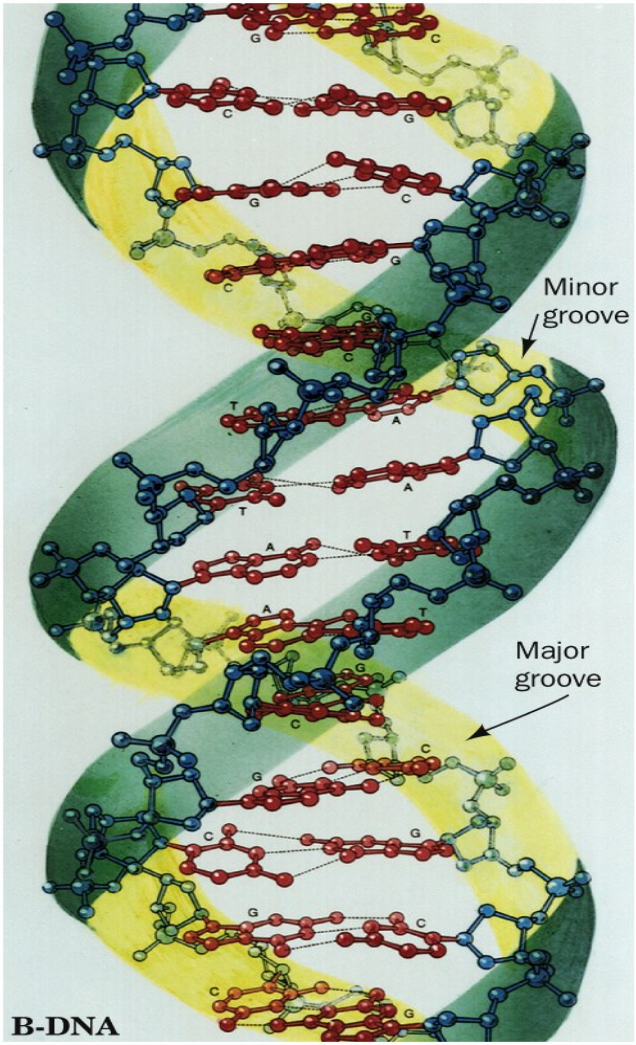


Figure 5-11
Illustration, Irving Geis. Image from the Irving Geis Collection, Howard Hughes Medical Institute. Reprinted with permission.

DNA Synthesis

Phosphoramidite method

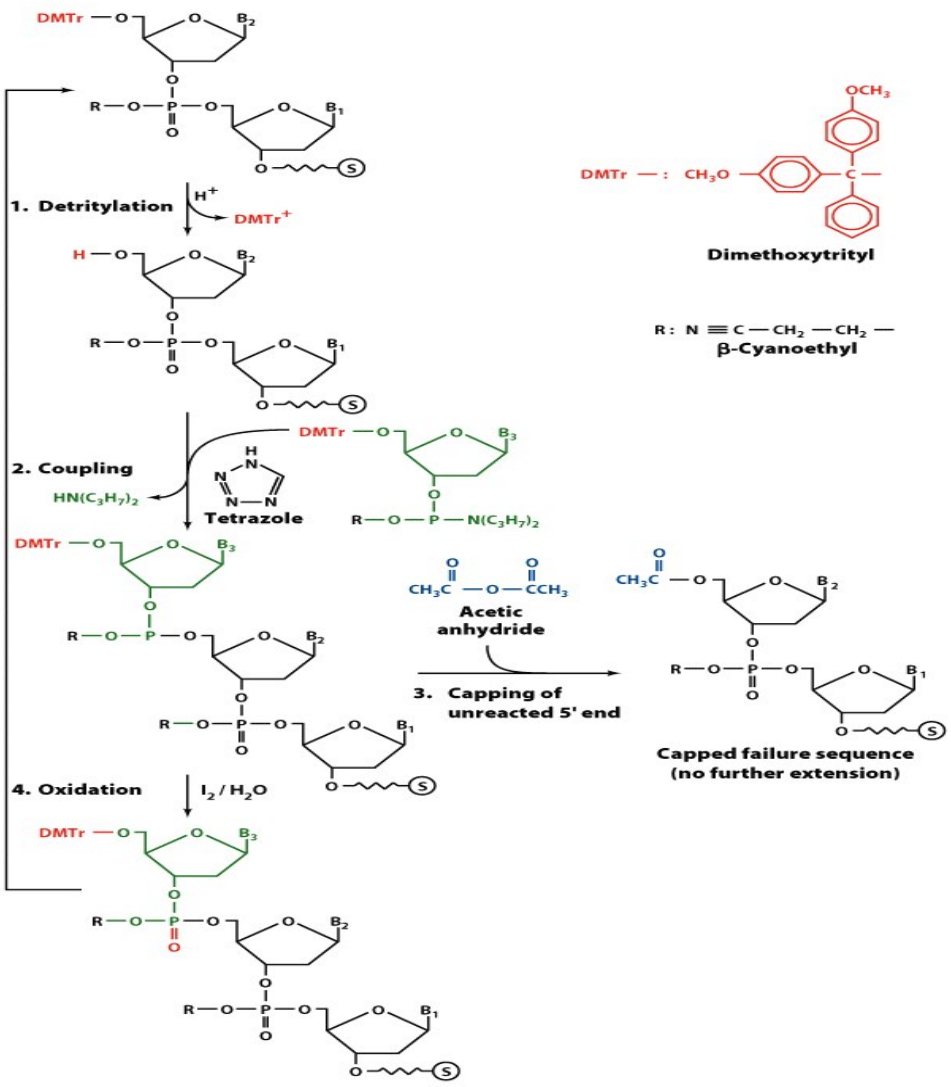


Figure 7-38

Photolithographic method

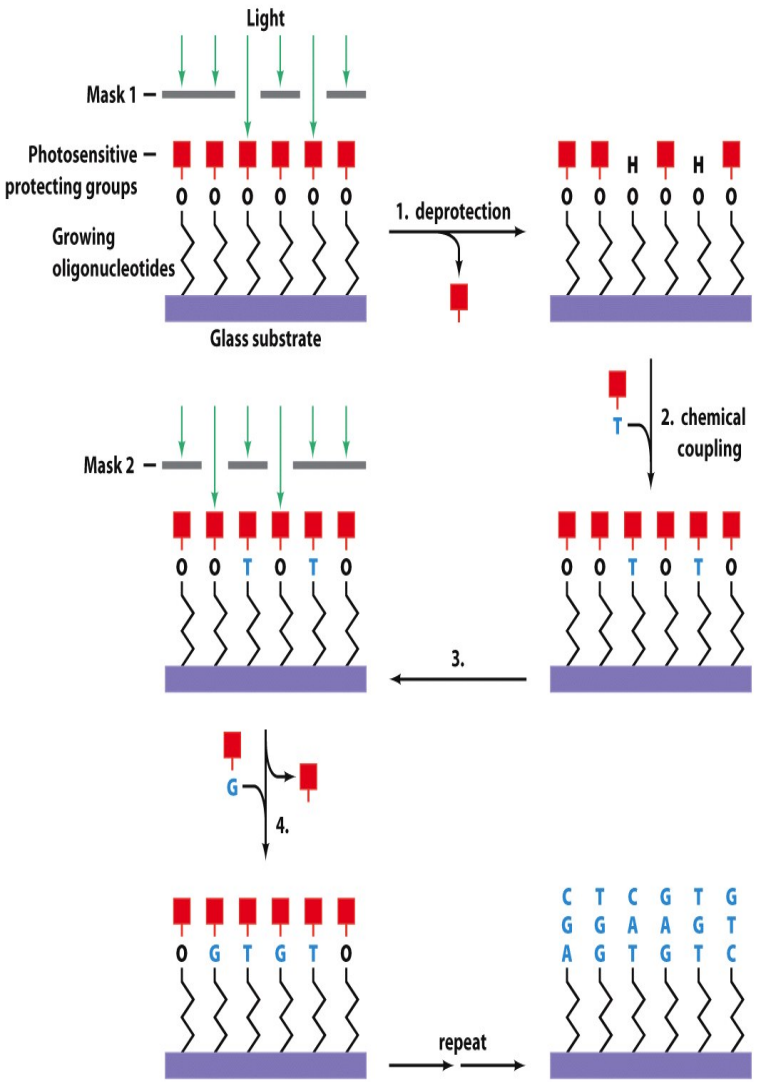


Figure 7-40

DNA Microarrays

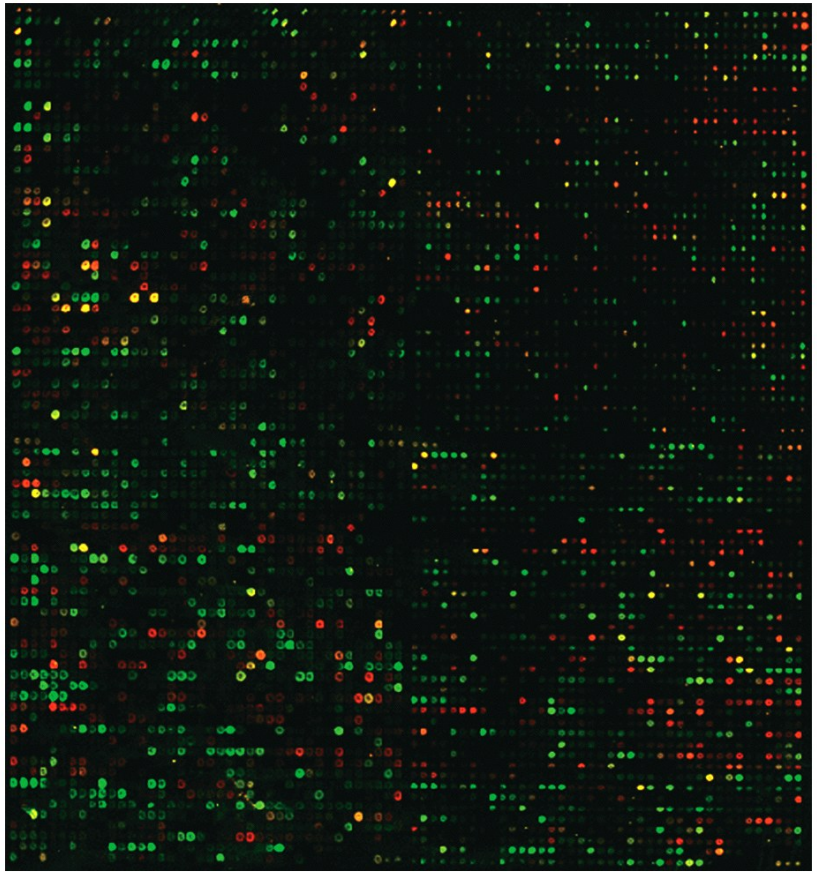


Figure 7-39
Courtesy of Patrick Brown, Stanford University School of Medicine

Figure 7-41
Courtesy of Affymetrix, Inc., Santa Clara, California

Protein Folding

The primary structure of a protein determines its three-dimensional structure.

Helices and sheets fill space efficiently hence they form about 60% of the average protein.

Internal residues mainly dictate protein folding.

Some proteins are natively unfolded but fold on binding to their target protein.

Proteins fold rapidly in an organized manner.

Accessory proteins such as protein disulfide isomerases (PDI), peptidyl propyl cis-trans isomerases and molecular chaperones aid protein folding.

Protein Dynamics

Atomic fluctuations
bond vibrations between 0.001 and 0.1 nanometers that range from 10^{-15} and 10^{-11} seconds.

Collective motions
movement of side chains and entire domains between 0.001 and more than 0.5 nanometers that range from 10^{-12} and 10^{-3} seconds.

Triggered conformational changes
external stimulus induced movement of individual side chains and subdomains between 0.05 and greater than 1 nanometers that range from 10^{-9} and 10^{3} seconds.

Enzyme-Substrate Complex

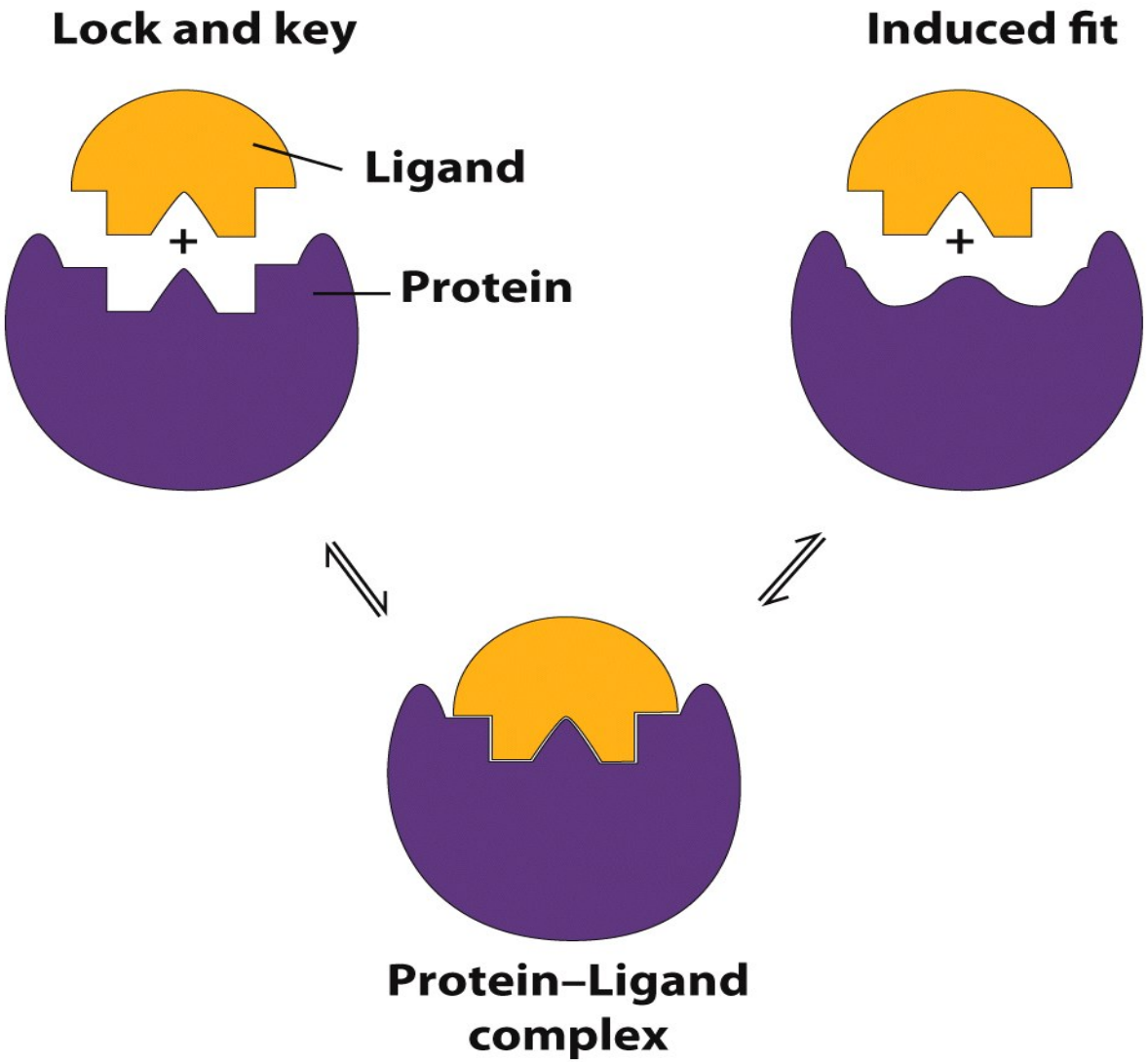
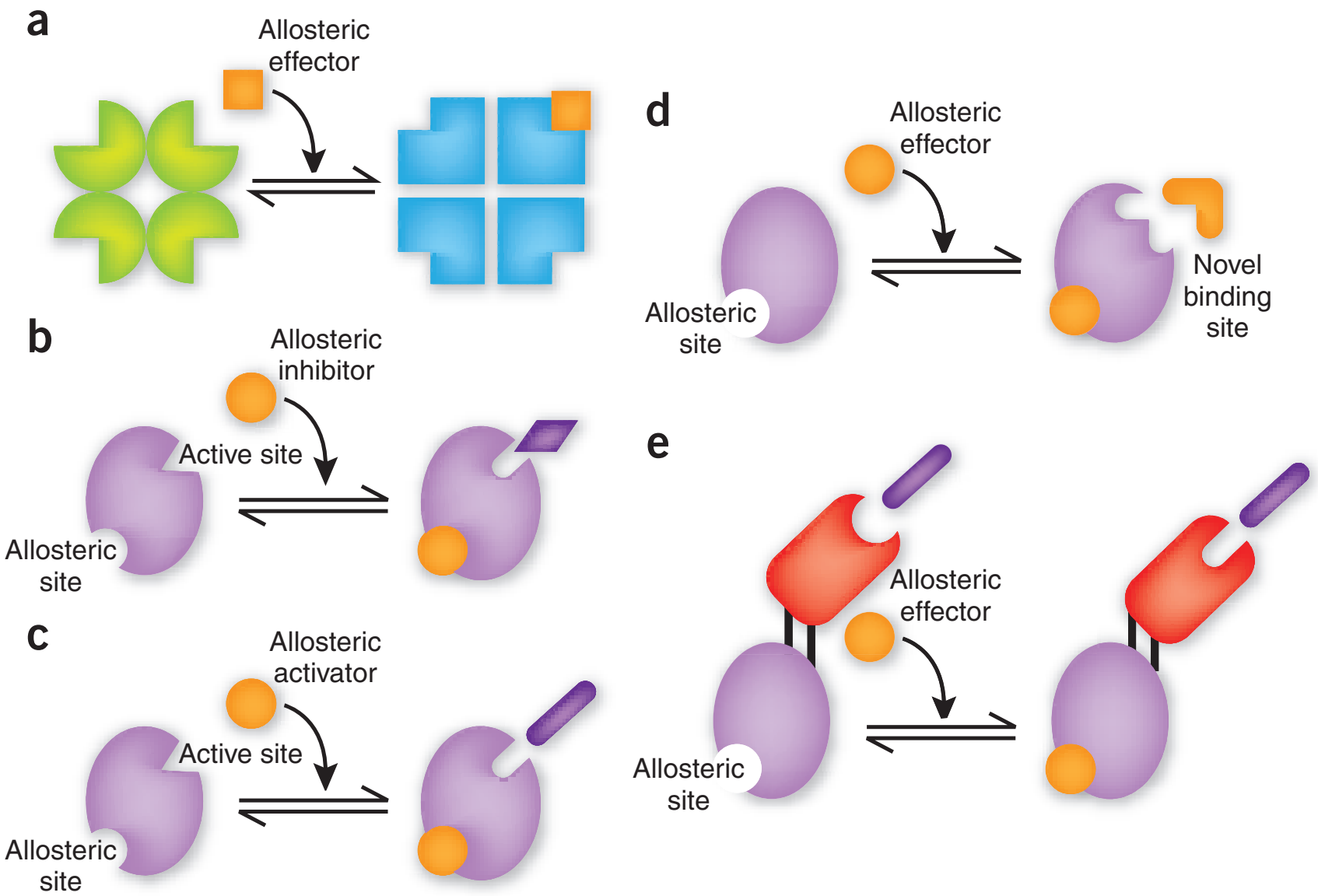


Figure 10-32

Allosteric Regulation



Goodey & Benkovic *Nature Chemical Biology* **2008**, *13*, 474−482.

Enzyme Kinetics

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} P + E$$

E (enzyme), S (substrate), ES (enzyme-substrate),
P (product), k_1 (forward rate constant), k_{-1} (reverse rate constant)

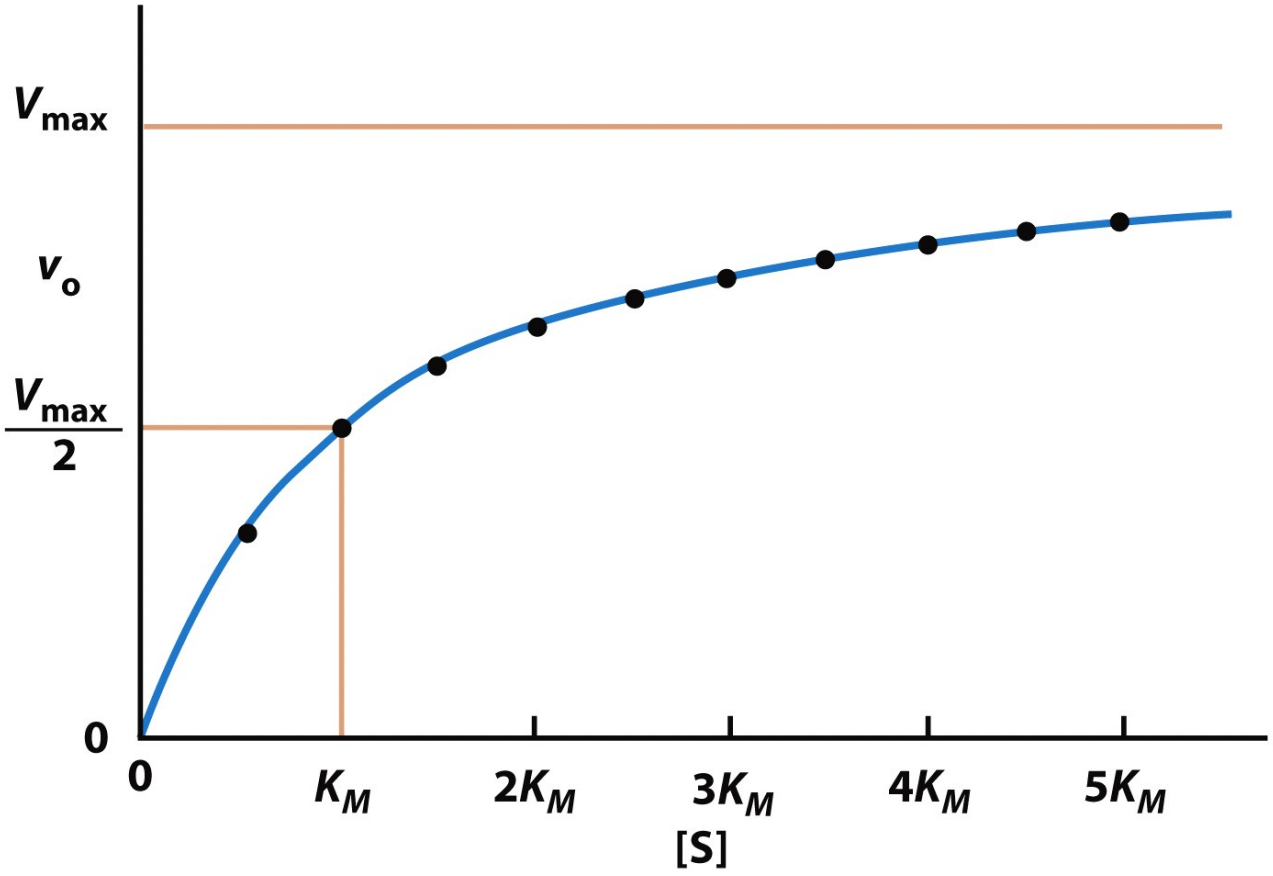


Figure 14-8

Michaelis-Menten equation

$$v_o = \frac{V_{max}[S]}{K_M + [S]}$$

v_o (initial velocity)
V_{max} (maximum velocity)
[S] (substrate concentration)
K_M (Michaelis constant)

Transition State Theory

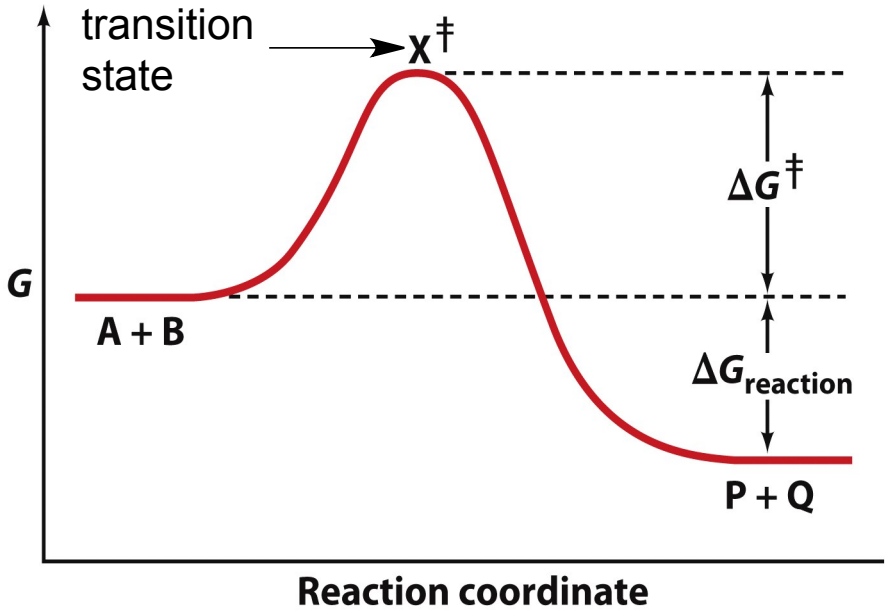


Figure 14-4b

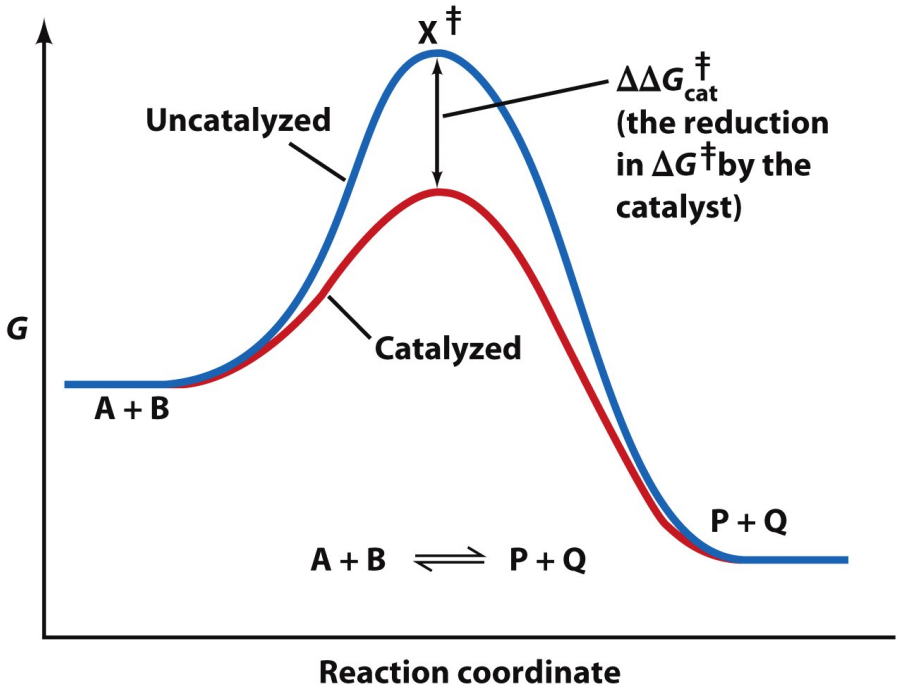
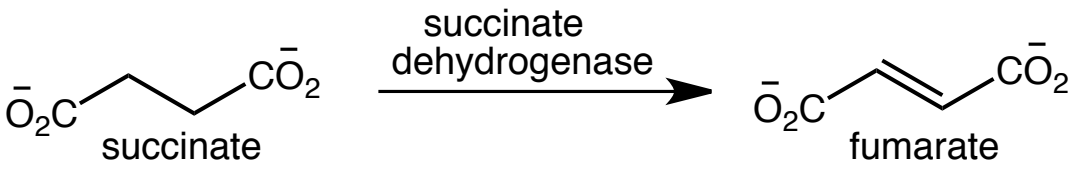
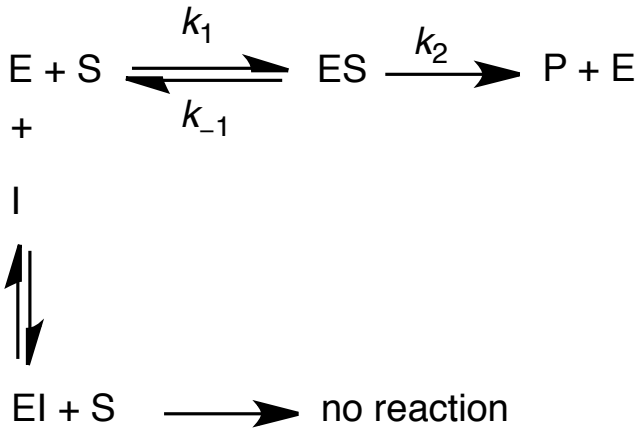


Figure 14-6

Enzyme Inhibition

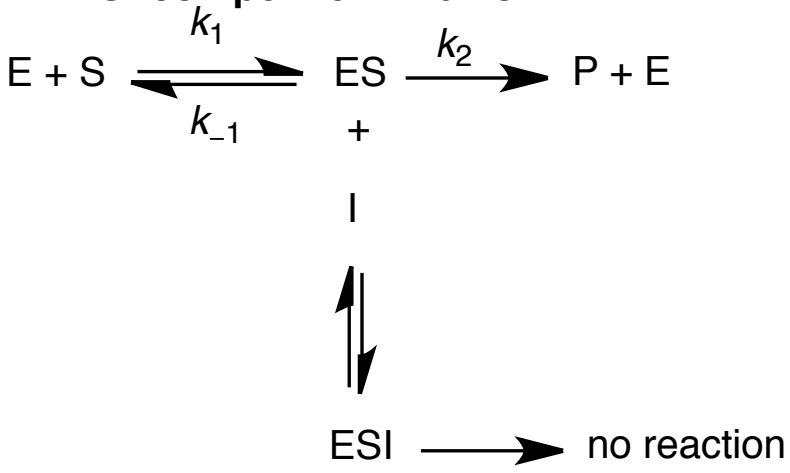
Competive Inhibition



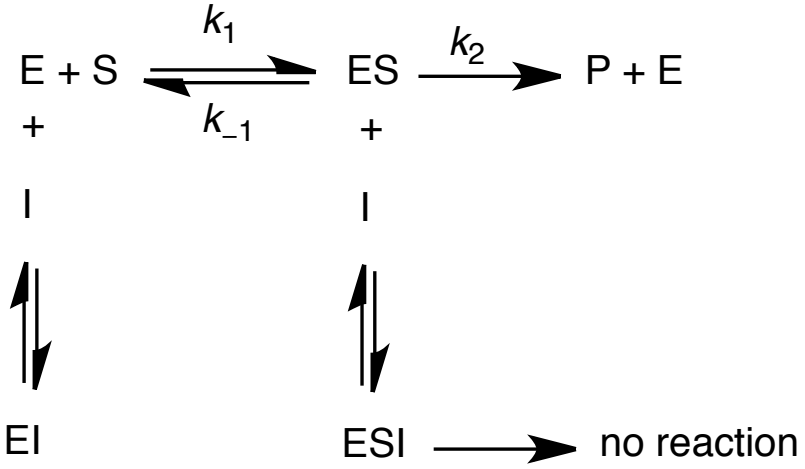


E (enzyme), S (substrate), I (inhibitor), ES (enzyme-substrate), P (product), k_1 and k_2 (forward rate constants) k_{-1} (reverse rate constant), EI (enzyme-inhibitor), ESI (enzyme-substrate-inhibitor),

Uncompetive Inhibition

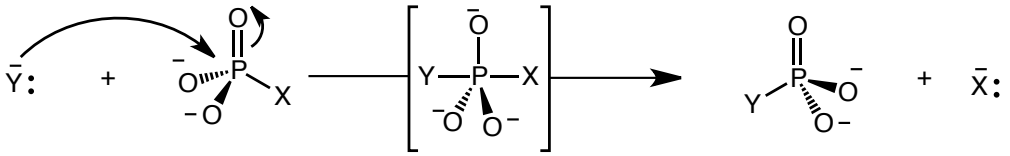


Mixed or Noncompetive Inhibition

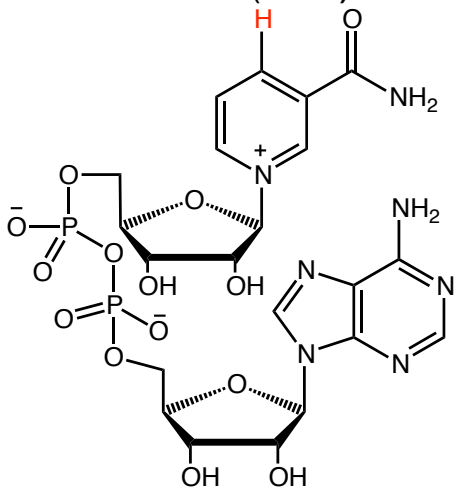


Biochemical Reactions

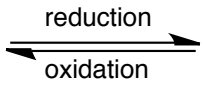
Group-Transfer Reactions
(transfer of phosphoryl, acyl and glycosyl groups)

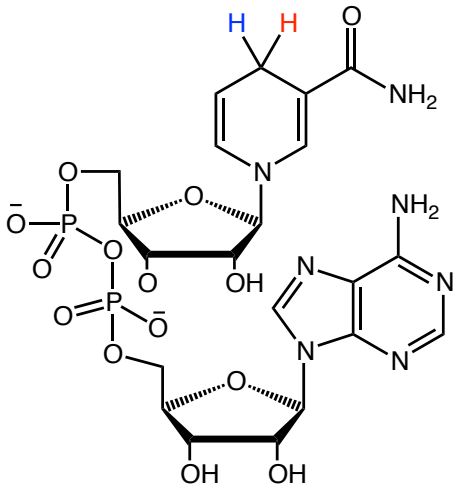


Reduction-oxidation (Redox) Reactions



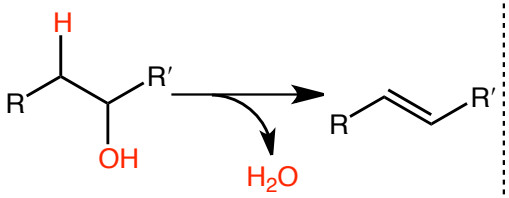
Nicotinamide adenine dinucleotide
(oxidized form) (NAD^+)



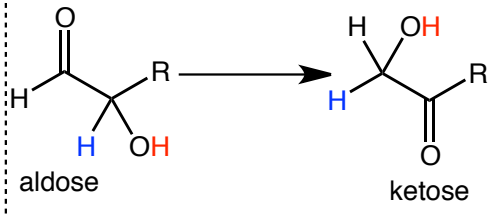


Nicotinamide adenine dinucleotide
(reduced form) (NADH)

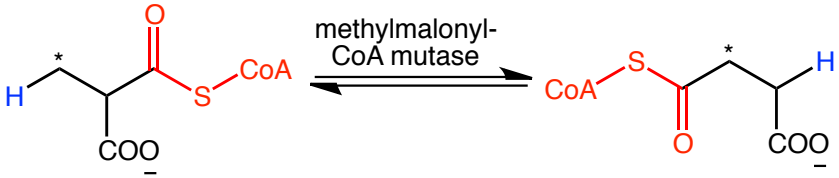
Elimination Reactions



Isomerization Reactions

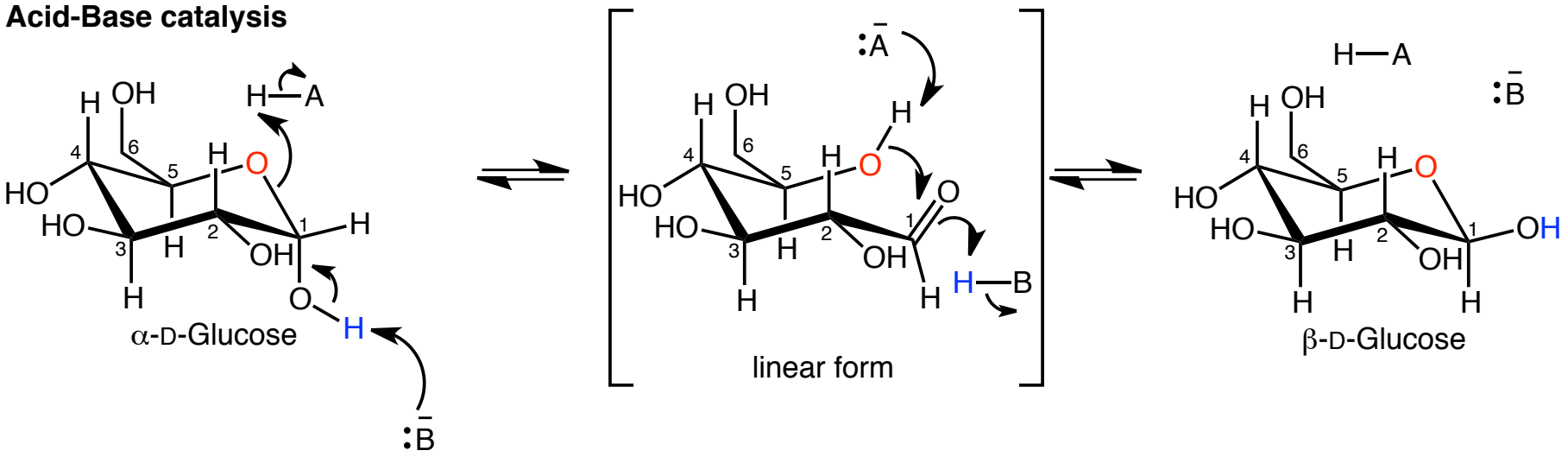


Rearrangement Reactions

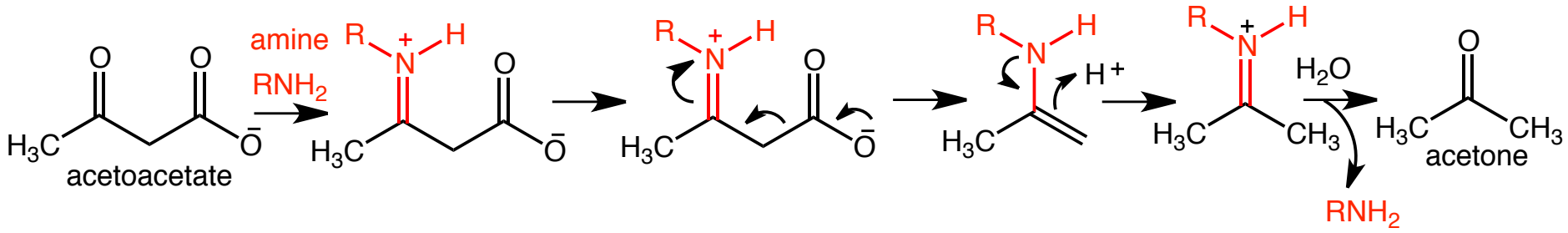


Catalytic Mechanisms of Enzymes

Acid-Base catalysis



Covalent catalysis



Catalytic Mechanisms of Enzymes

Metal Ion catalysis

Metalloenzymes
contain tightly bound metal ions such as Fe^{2+}, Fe^{3+}, Cu^{2+}, Zn^{2+}, Mn^{2+}, or Co^{2+}.

Metal-activated enzymes
loosely bind metal ions such as Na^{+}, K^{+} Mg^{2+}, or Ca^{2+}.

1. Proper orientation of substrates for reaction.
2. Mediate oxidation-redox reactions through reversible changes in oxidation states of the metal ion.
3. Stabilize or shield negative charge.

Electrostatic catalysis
supportive evidence indicate that charge distributions about active sites of enzymes stabilize transition states of the catalyzed reactions.

Orientation and proximity effects catalysis
closeness of reacting centers has little effect on catalysis, they have to be properly oriented.

Catalysis by selective transition state binding
binding of the transition state of an enzyme-catalyzed reaction in preference to the substrate is an important rate enhancement mechanism.

Summary

Life processes are regulated by biomolecules whose chemical structures determine their functions.

A comprehensive understanding of the structures of these biomolecules is vital to clarifying various biomedical processes.

Next Lecture, 2016/01/21

Principles of chemical synthesis: the logic behind the magic of how molecules are assembly by organic chemists.