

Lehninger

SIXTH EDITION

Principles of Biochemistry

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- 1 | Foundations of Biochemistry
- 2 | Water and Aqueous Solutions

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Biochemistry is the Chemistry of Living Matter

- The basis of all life is the chemical reactions that take place within the cell.

Chemistry allows for:

- A high degree of complexity and organization
- Extraction, transformation, and systematic use of energy to create and maintain structures and to do work
- The interactions of individual components to be dynamic and coordinated.
- The ability to sense and respond to changes in surrounding
- A capacity for fairly precise self-replication while allowing enough change for evolution

The Molecular Logic of Life

We look at the chemistry that is behind:

- Accelerating reactions
- Organization of metabolism and signaling
- Storage and transfer of information

The ABCs of Life

Some of the amino acids of proteins

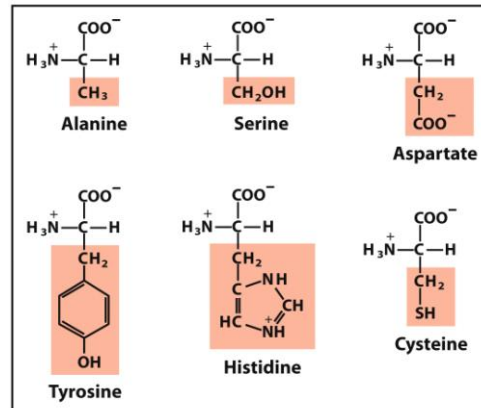
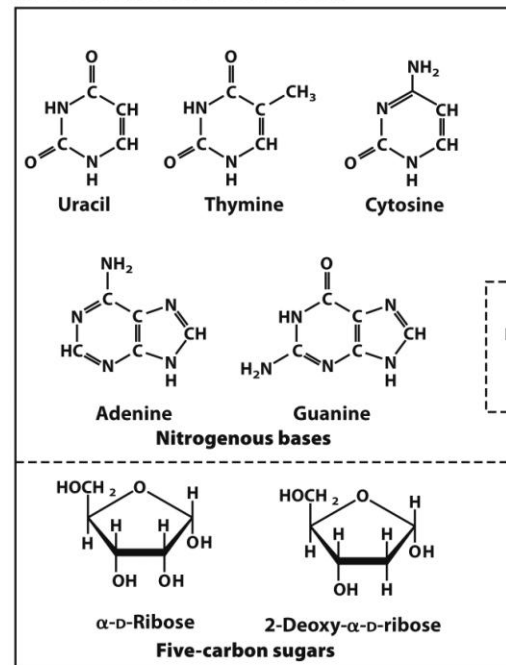
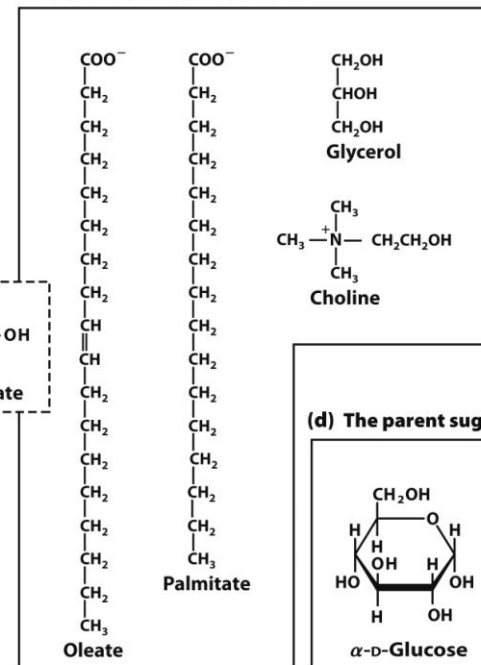


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(b) The components of nucleic acids



(c) Some components of lipids



(d) The parent sugar

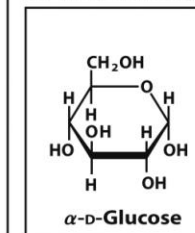


Figure 1-10bcd
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Cells build supramolecular structures

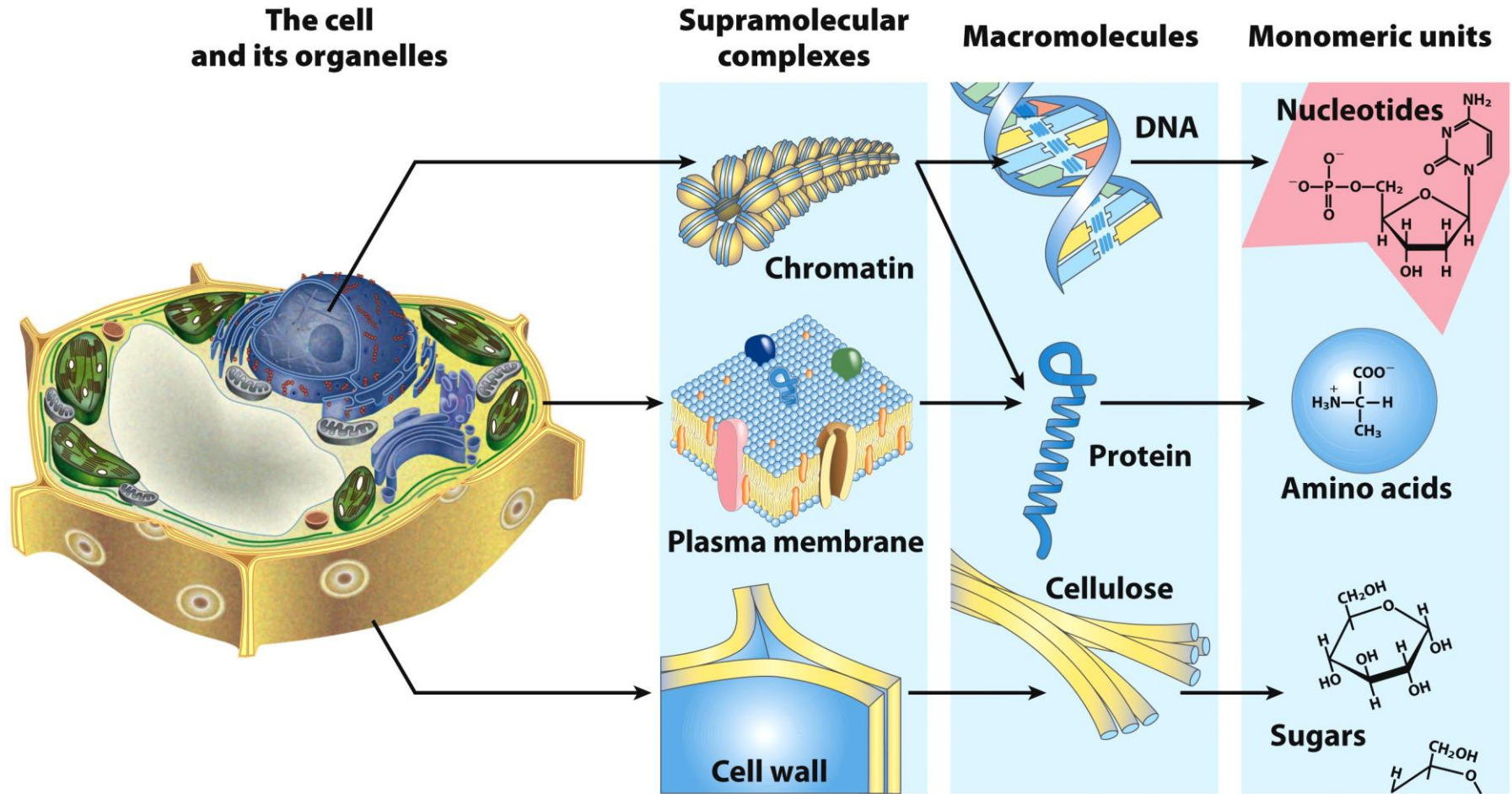


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Diameter, appx: Mito (1000 nm); ribosomes (20 nm); Hb (5.5 nm); Alanine (0.5 nm)

In vitro, in vivo, in silico

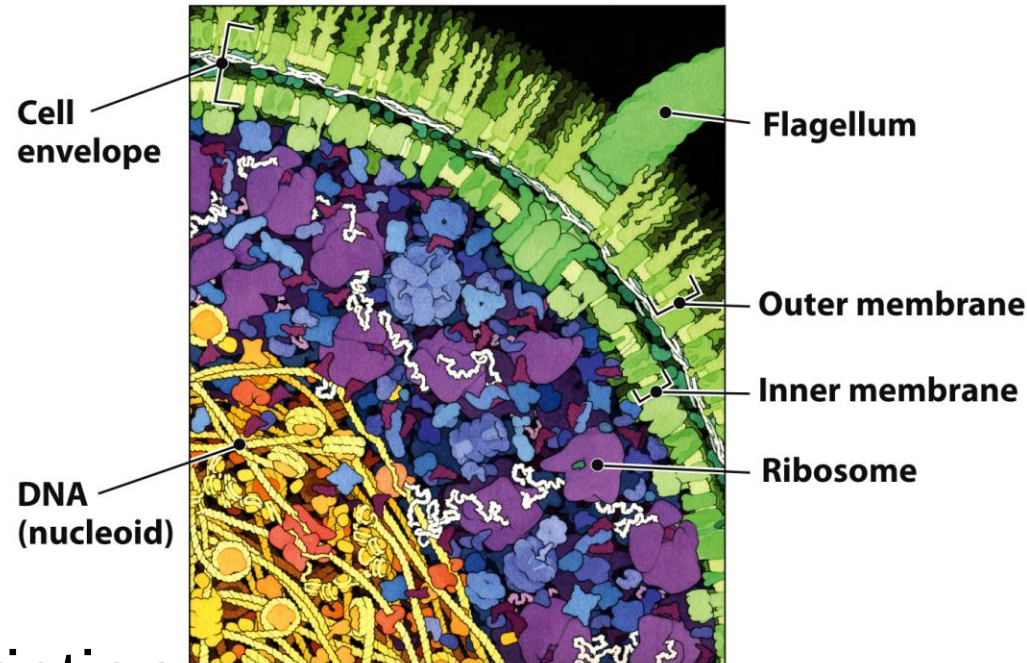
We can study biological processes either

- ***In vivo*** – in the living, study of molecules within cells
- ***In vitro*** – in glass, study of molecules without interference from other molecules
- ***In silico*** – simulations using computers
- Keeping in mind that the environment in the cell is much different from inside the test tube

The cytosol is very crowded

A certain molecule can behave differently in vitro than in vivo

- Crowding of cytosol → less diffusion of molecules and more friction
- An enzyme activity in vitro may be very different from that in vivo



Biochemistry: 30 Elements Essential for Life

- Other than carbon, elements H, O, N, P, S are also common
- Metal ions (e.g., K^+ , Na^+ , Ca^{++} , Mg^{++} , Zn^{++} , Fe^{++}) play important roles in metabolism

1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba		72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra																

Bulk elements

Trace elements

Lanthanides

Actinides

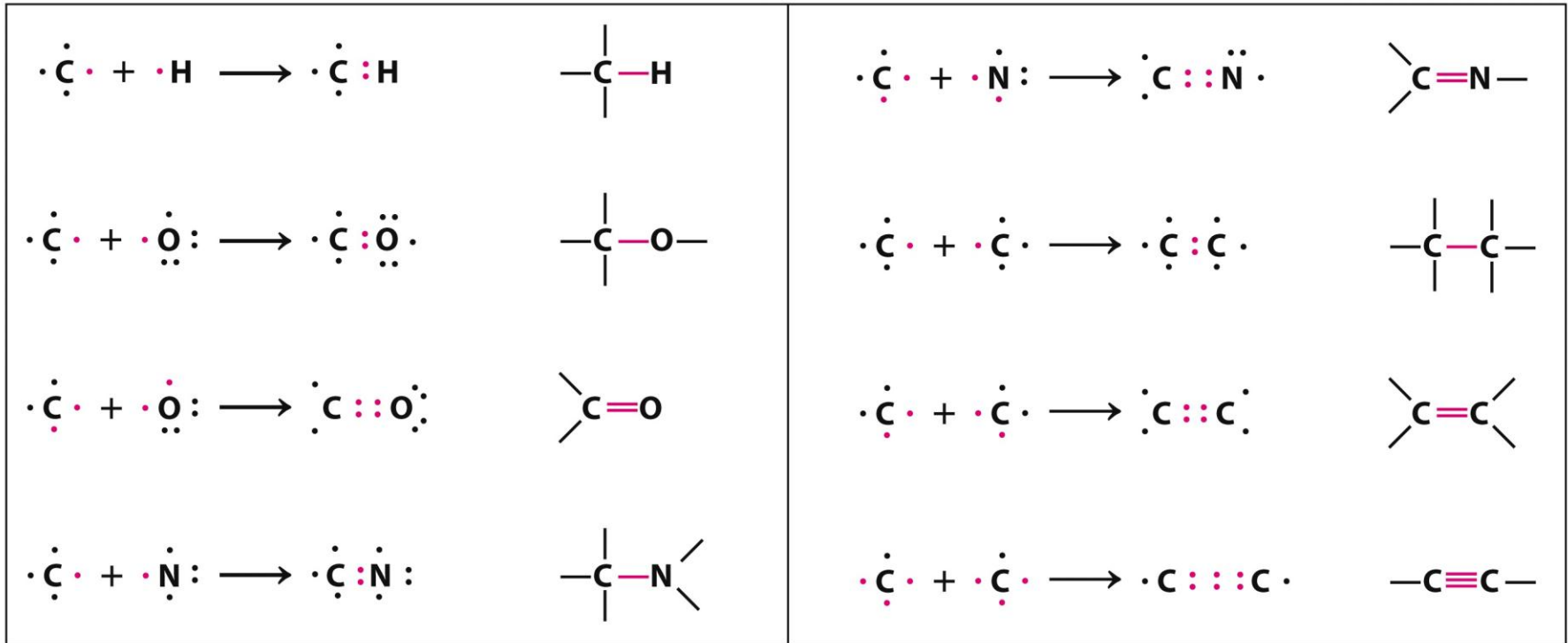
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Biochemistry: Unique Role of Carbon

- Ability of C to form very stable bond with up to 4 other C atoms



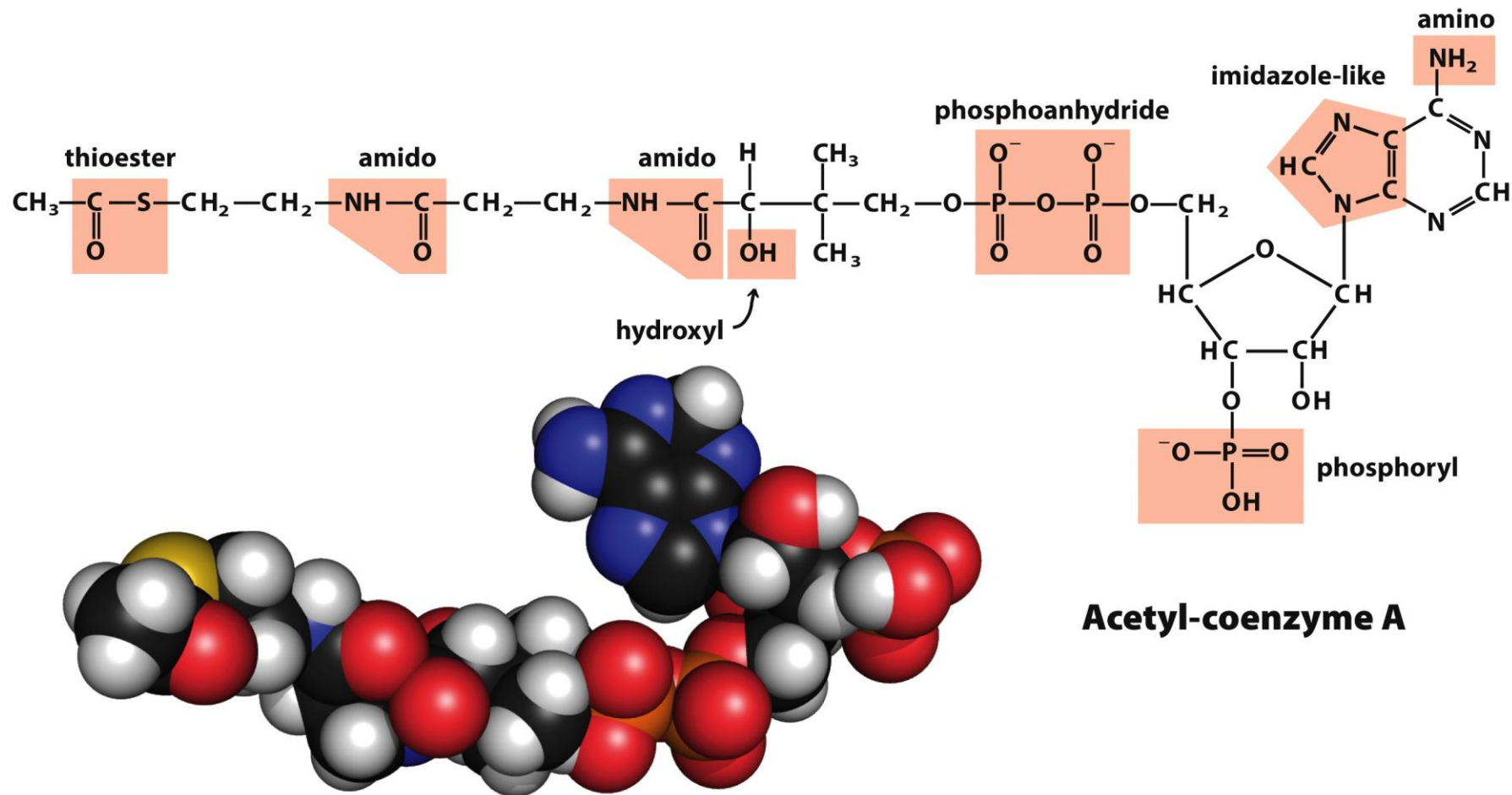
- Recall, single bonds are 0.154 nm, double bonds are 0.134 nm
- Bonding versatility of C was a major factor in selecting C for molecular machinery during evolution. *No other chemical element can form molecules of such widely different sizes, shapes and composition!*

Common Functional Groups of Biological Molecules

- Biomolecules** are derivatives of hydrocarbons
- H-atom is replaced by functional groups
- Recall the naming of groups, and groups without H from organic chemistry*

Methyl		Ether		Guanidinium	
Ethyl		Ester		Imidazole	
Phenyl		Acetyl		Sulfhydryl	
Carbonyl (aldehyde)		Anhydride (two carboxylic acids)		Disulfide	
Carbonyl (ketone)		Amino (protonated)		Thioester	
Carboxylate		Amido		Phosphoryl	
Hydroxyl (alcohol)		Imine		Phosphoanhydride	
Enol		N-Substituted imine (Schiff base)		Mixed anhydride (carboxylic acid and phosphoric acid; also called acyl phosphate)	

Biological molecules typically have several functional groups (polyfunctional)



Acetyl-coenzyme A

Figure 1-17

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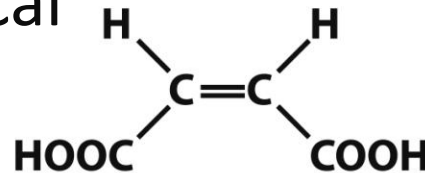
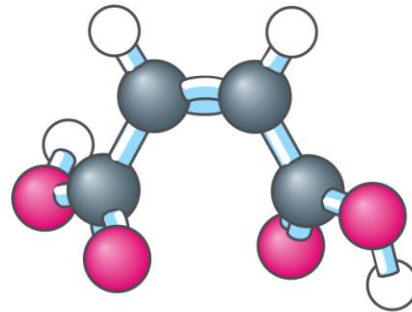
The function of molecules strongly depends on three-dimensional structure

- Stereoisomers
 - have **different** physical properties
 - have same chemical bonds, different **configuration** around the bonds
 - Cannot be interconverted without temporarily breaking one or more covalent bonds
 - Configuration is due to:
 - (1) double bonds
 - (2) chiral centers
 - Interactions between biomolecules are **stereospecific**

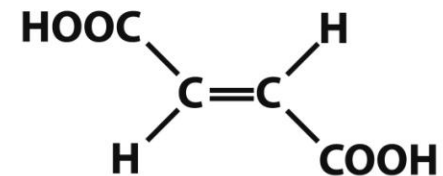
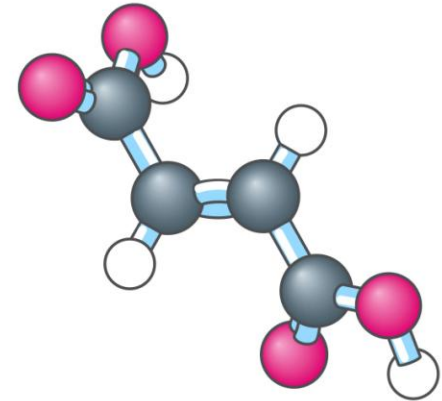
Cis-Trans isomers (geometrical isomers)

- Geometric Isomers

- have **different** physical and chemical properties
- differ in the arrangement about a double bond
- An enzyme binding site that fits maleic acid will not fit fumaric acid and vice versa



Maleic acid (cis)



Fumaric acid (trans)

Why we see is because of a cis-trans configurational change

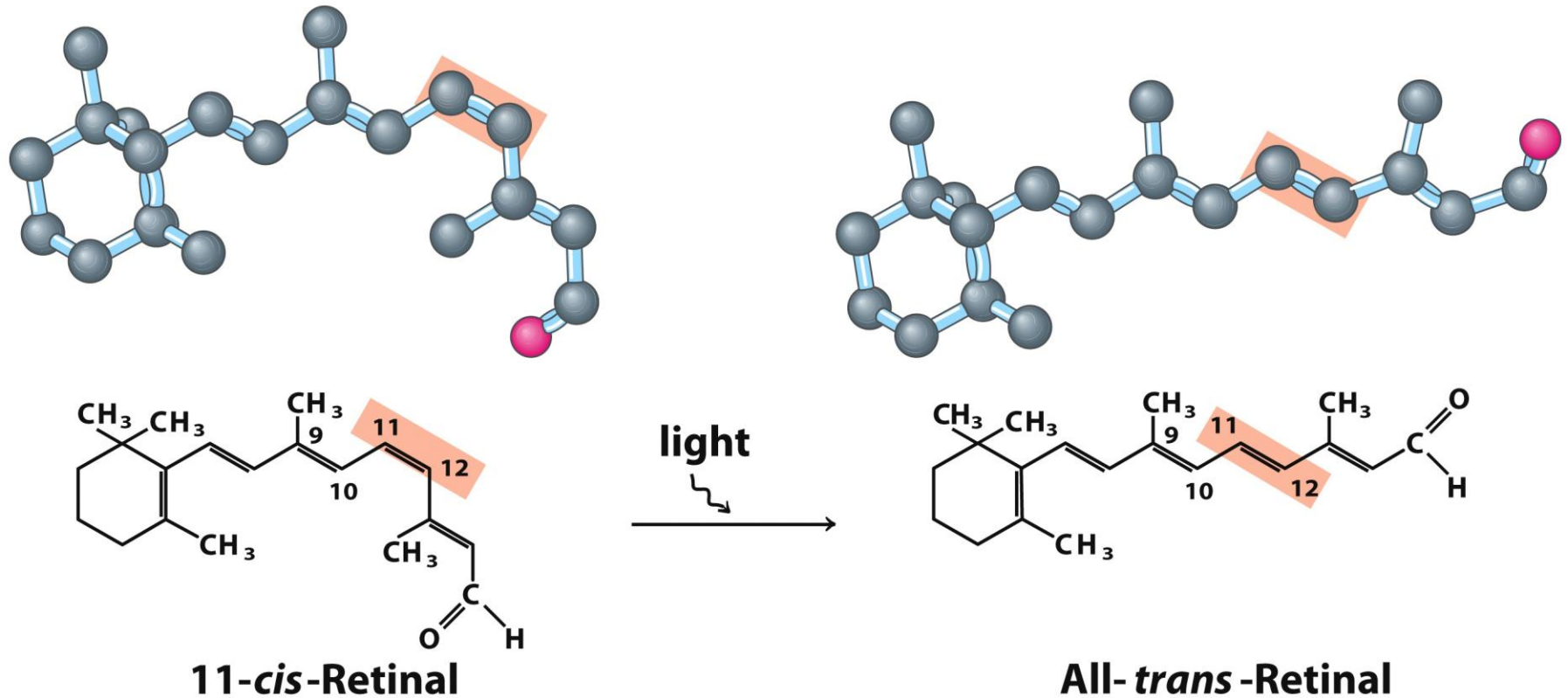


Figure 1-19b

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Enantiomers and Diastereomers

- Enantiomers (mirror images)

- have

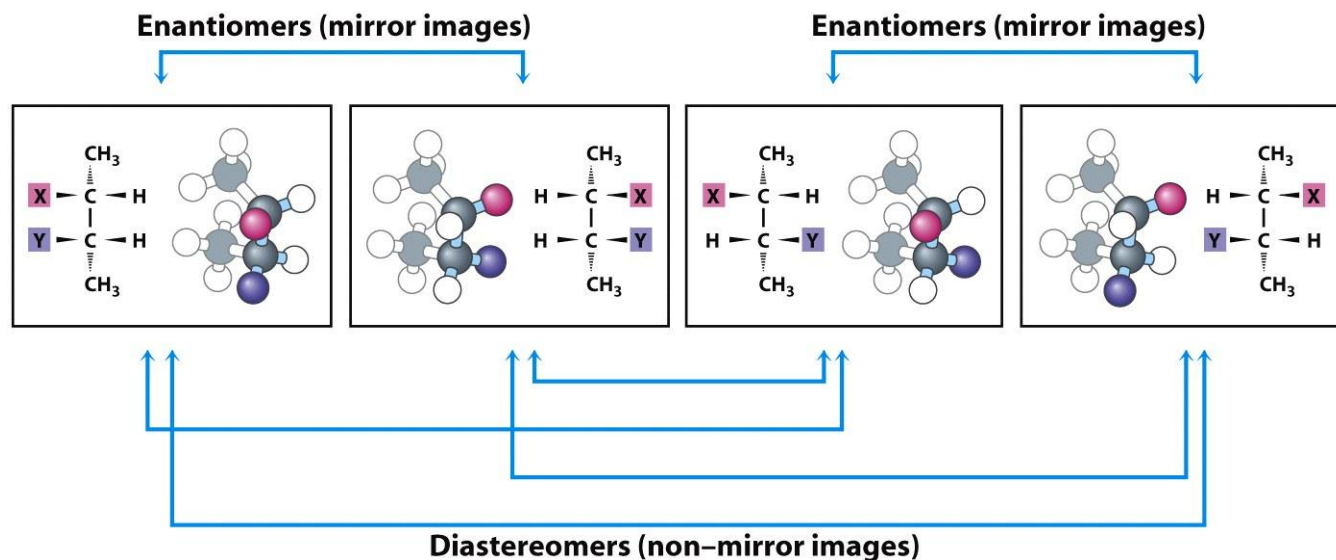
identical

physical properties

(except with regard to polarized light) and react identically with achiral reagents

- Diastereomers

- have different physical and chemical properties



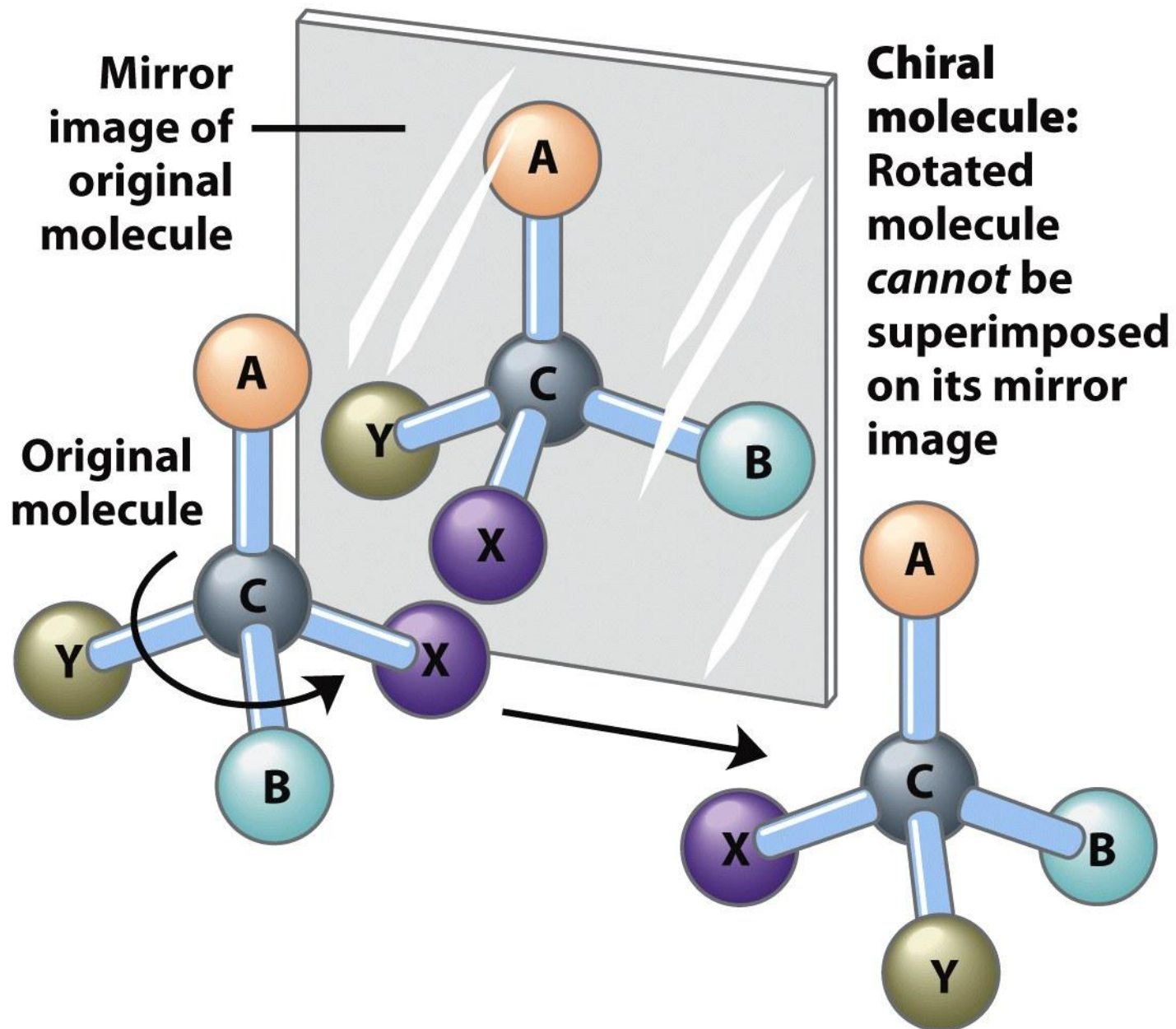


Figure 1-19a

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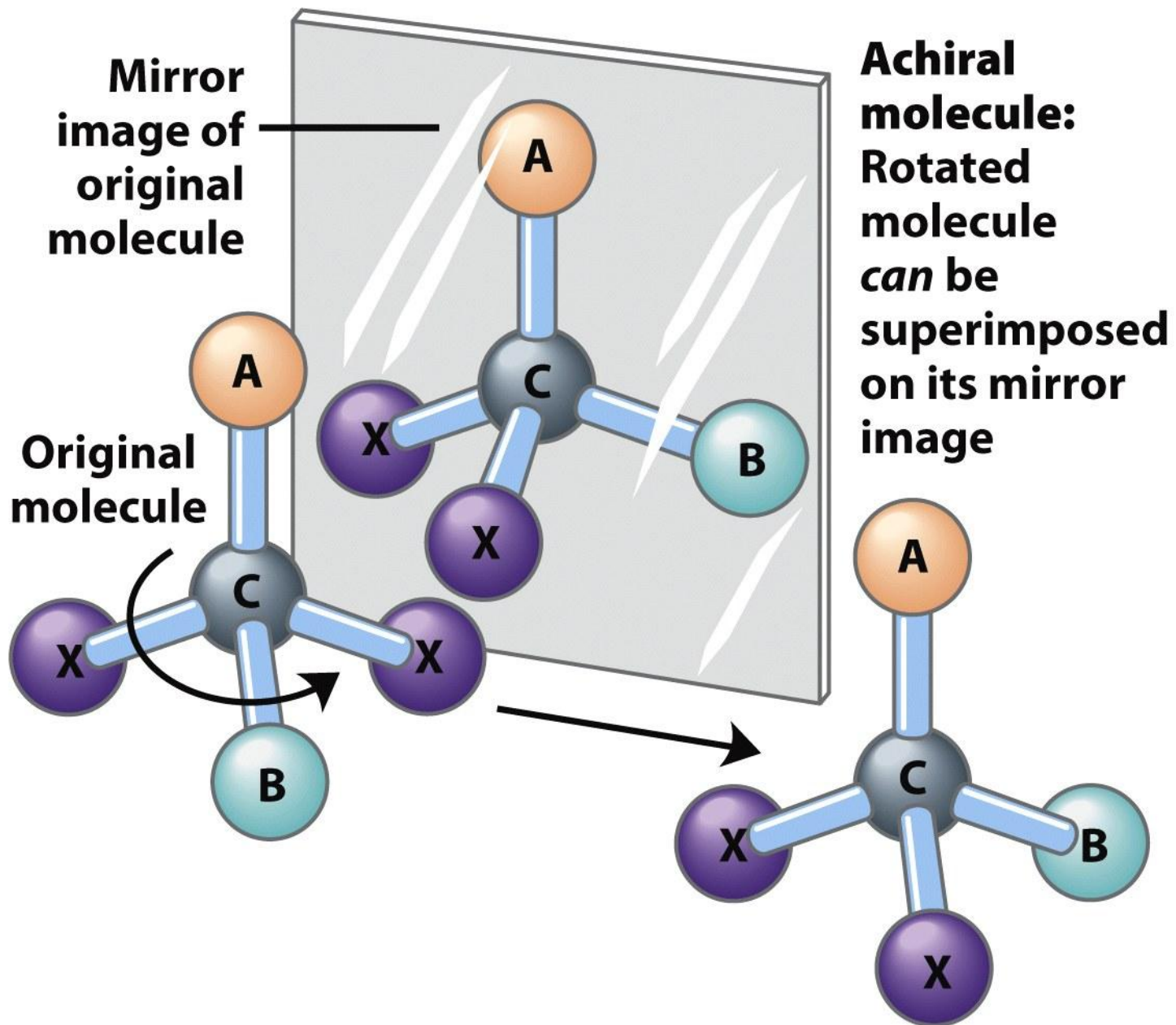
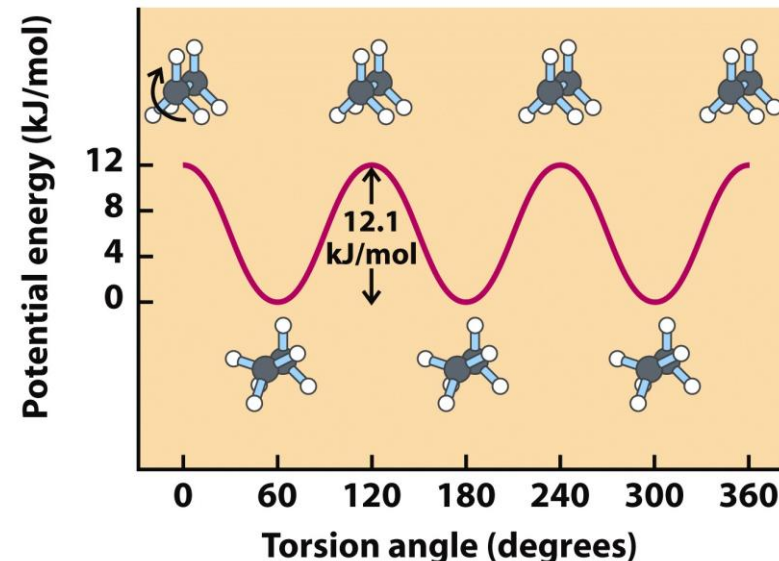


Figure 1-19b
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The function of molecules strongly depends on three-dimensional structure

- All molecules can assume different **conformations**
 - Spatial arrangement of groups that are free to take different positions without breaking any bonds
 - Because of freedom of rotation about single bonds
 - Some conformations are more favorable than others (e.g. staggered versus eclipsed in ethane)

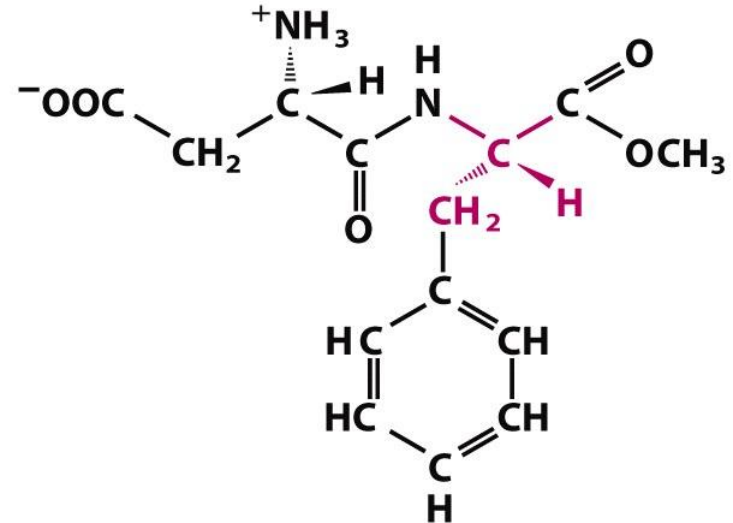
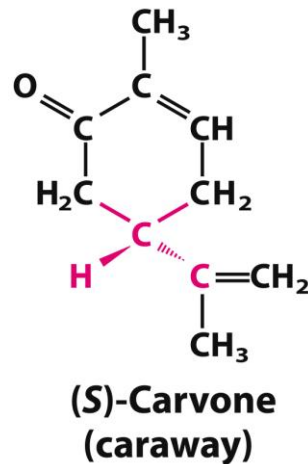
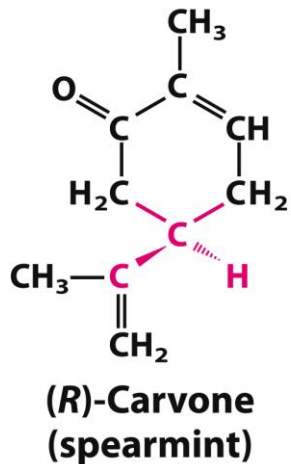


Interactions between biomolecules are specific

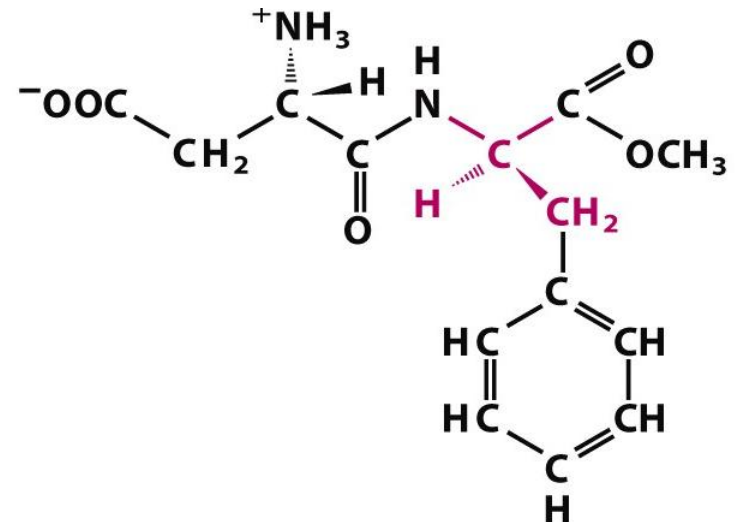
- Macromolecules have unique binding pockets
- Only certain molecules fit in well and can bind
- Binding of chiral biomolecules is stereospecific (if a binding site on a protein is complementary to the L stereoisomer, it will not fit the D stereoisomer)

Interactions between biomolecules are stereospecific

Stereoisomers have different effects in humans



L-Aspartyl-L-phenylalanine methyl ester
(aspartame) (sweet)



L-Aspartyl-D-phenylalanine methyl ester
(bitter)

Water is the medium for life

- Organisms typically contain 70–90% water
- Chemical reactions occur in aqueous milieu (water environment)
- Water is a critical determinant of the structure and function of proteins, nucleic acids, and membranes

Physics of Noncovalent Interactions

Noncovalent interactions do not involve sharing a pair of electrons. Based on their physical origin, one can distinguish between:

- **Ionic (Coulombic) Interactions**

- Electrostatic interactions between permanently charged species, or between the ion and a permanent dipole

- **Dipole Interactions**

- Electrostatic interactions between uncharged, but polar molecules

- **van der Waals Interactions**

- Weak interactions between all atoms, regardless of polarity
- Attractive (dispersion) and repulsive (steric) components

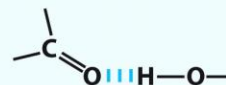
- **Hydrophobic Effect**

- Complex phenomenon associated with the ordering of water

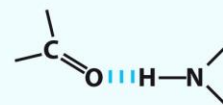
Examples of Noncovalent Interactions

TABLE 2-5 Four Types of Noncovalent ("Weak") Interactions among Biomolecules in Aqueous Solvent

Hydrogen bonds
Between neutral groups



Between peptide bonds



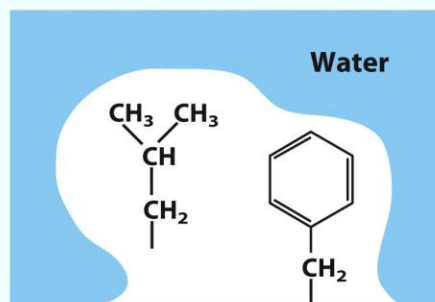
Ionic interactions
Attraction



Repulsion



Hydrophobic interactions



van der Waals interactions

Any two atoms in close proximity

van der Waals Interactions

- van der Waals interactions have two components:
 - Attractive force (London dispersion) depends on the interaction of electron clouds together
 - Repulsive force (Steric repulsion) depends on the size of atoms
- Attraction dominates at longer distances (typically 0.4–0.7 nm)
- Repulsion dominates at very short distances
- There is a minimum energy distance for every atom (**van der Waals radius**)

TABLE 2-4**van der Waals Radii and Covalent (Single-Bond) Radii of Some Elements**

Element	van der Waals radius (nm)	Covalent radius for single bond (nm)
H	0.11	0.030
O	0.15	0.066
N	0.15	0.070
C	0.17	0.077
S	0.18	0.104
P	0.19	0.110
I	0.21	0.133

Sources: For van der Waals radii, Chauvin, R. (1992) Explicit periodic trend of van der Waals radii. *J. Phys. Chem.* 96, 9194–9197. For covalent radii, Pauling, L. (1960) *Nature of the Chemical Bond*, 3rd edn, Cornell University Press, Ithaca, NY.

Note: van der Waals radii describe the space-filling dimensions of atoms. When two atoms are joined covalently, the atomic radii at the point of bonding are less than the van der Waals radii, because the joined atoms are pulled together by the shared electron pair. The distance between nuclei in a van der Waals interaction or a covalent bond is about equal to the sum of the van der Waals or covalent radii, respectively, for the two atoms. Thus the length of a carbon–carbon single bond is about $0.077 \text{ nm} + 0.077 \text{ nm} = 0.154 \text{ nm}$.

Table 2-4

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Biochemical Significance of Weak Interactions

- Weak individually
 - easily broken, reversible
 - much weaker than covalent bonds
 - much more in amount than covalent bonds; cumulative effects are very significant
- Universal
 - occur between any two atoms that are near each other (van der Waal)
 - occur between positive and negative ions (ionic)
 - occur between H-bond donor and acceptor (H-bond)
- Importance
 - stabilizes biological macromolecules
 - facilitates binding of ligands

Affects of Solutes on Properties of Water

- Colligative Properties

- Boiling point, melting point, and osmolarity
- *Do not depend on the nature of the solute, just the number of solute particles*
- The concentration of water is lower in solutions than in pure water

- Noncolligative Properties

- Viscosity, surface tension, taste, and color
- Depend on the chemical nature of the solute

- Cytoplasm of cells are highly concentrated solutions and have high osmotic pressure

Osmotic Pressure

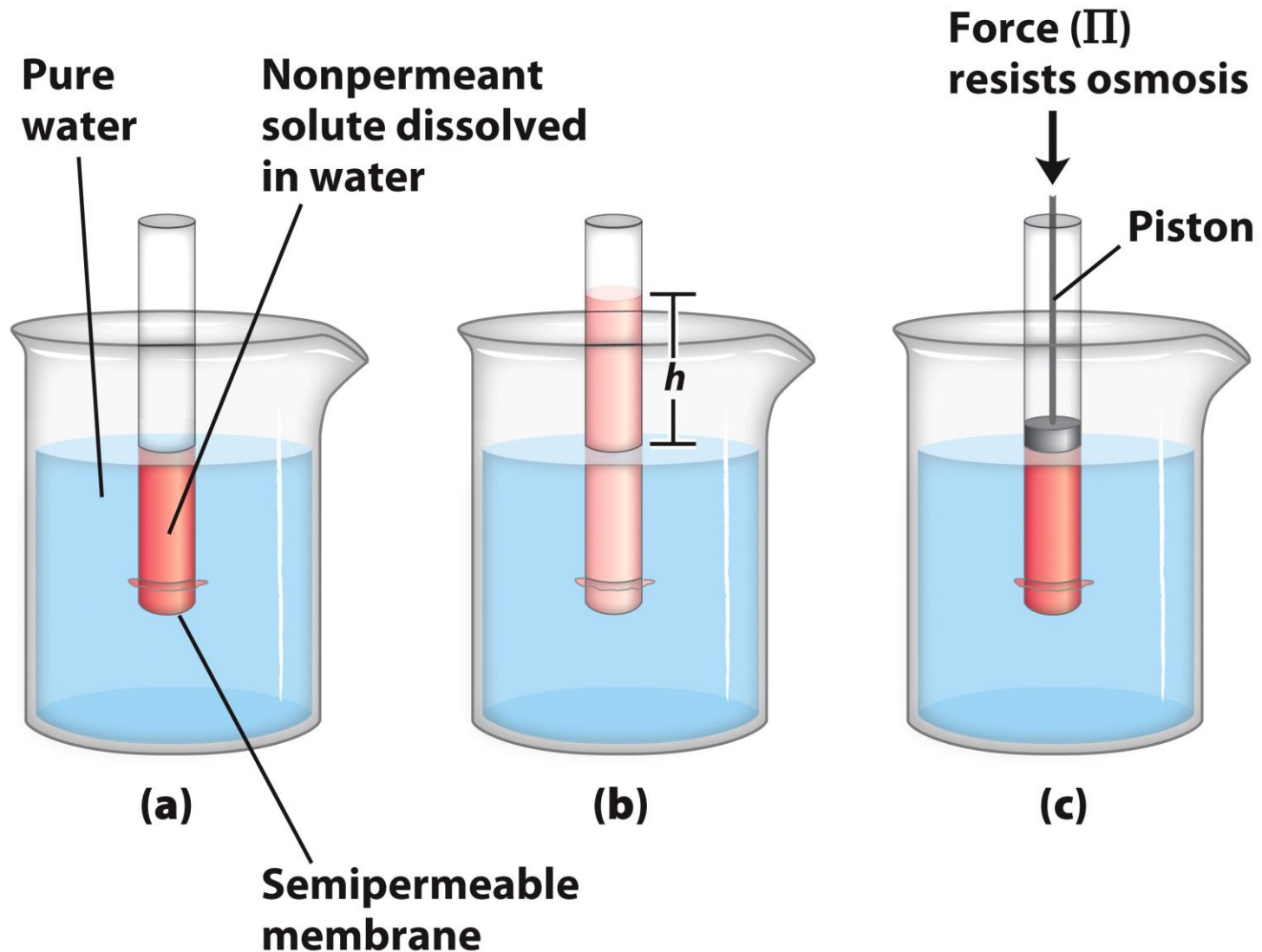


Figure 2-12

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Osmotic pressure

- Osmotic pressure, $\Pi = icRT$
 - $i = 1$ for all nonionizing solutes (e.g. glucose)
 - $i = 2$ for completely ionizing salts with 1:1 ratio (dilute NaCl solution)
 - ic is the **osmolarity** of the solution
- For solutions with several solutes, $\Pi = RT(i_1c_1 + \dots i_nc_n)$
- The effects of solutes on osmolarity depends on the **number** of particles, not their mass
 - macromolecules have much less effect on osmolarity than an equal mass of monomeric components
 - **1 g** of polysaccharide of 1000 glucose monomers has the **SAME** effect on osmolarity of **1 mg** of glucose!

Effect of Extracellular Osmolarity

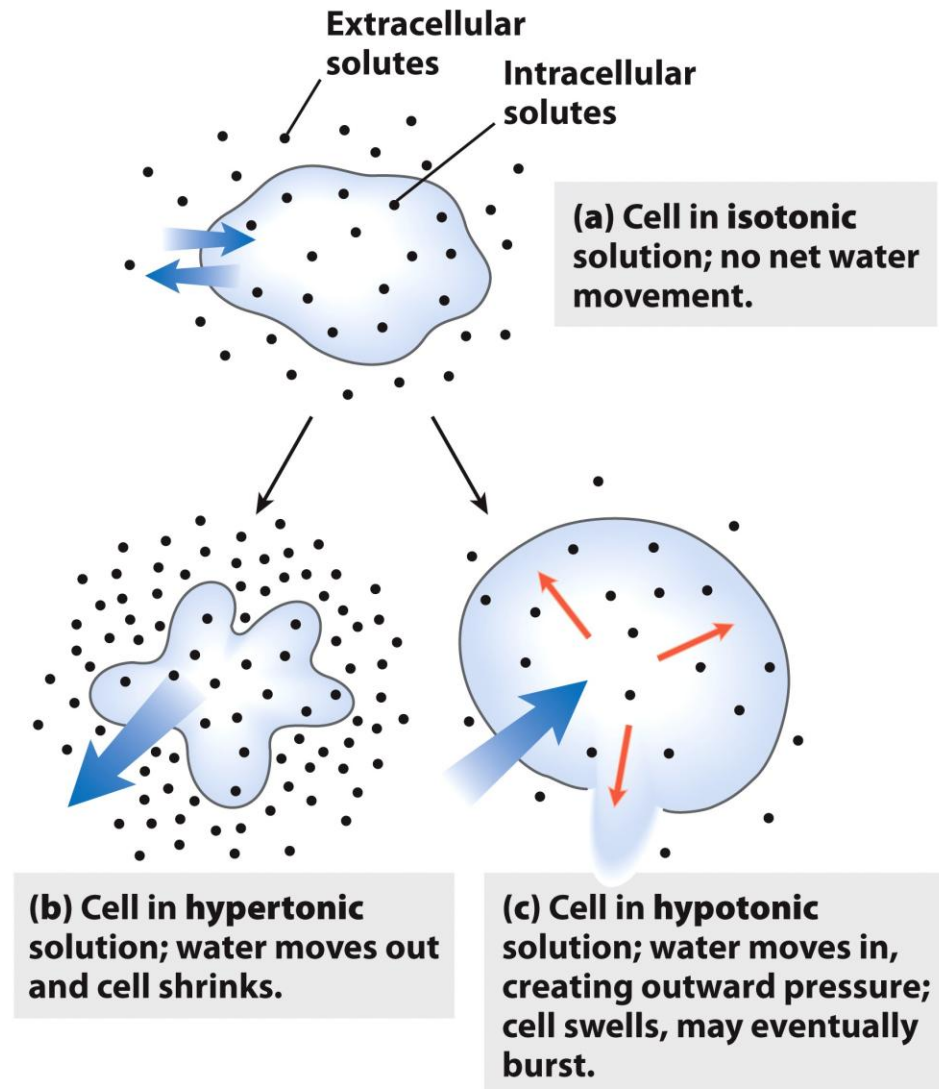


Figure 2-13
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Ionization of Water



- O-H bonds are polar and can dissociate
- Products are a **proton** (H^+) and a **hydroxide ion** (OH^-)
- Dissociation of water is a rapid reversible process
- Most water molecules remain un-ionized, thus pure water has very low electrical conductivity (resistance: $18 \text{ M}\Omega\cdot\text{cm}$)
- The equilibrium is strongly to the ***left***
- Extent of dissociation depends on the temperature

Ionization of Water:

Quantitative Treatment

Concentrations of participating species in an equilibrium process are not independent but are related via the **equilibrium constant**:



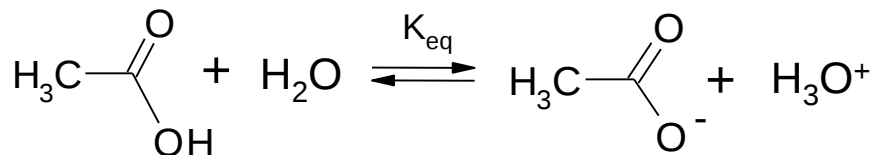
K_{eq} can be determined experimentally, it is $1.8 \cdot 10^{-16} \text{ M}$ at 25°C .
 $[\text{H}_2\text{O}]$ can be determined from water density, it is 55.5 M .

- Ionic product of water:

$$K_w = K_{\text{eq}} \cdot [\text{H}_2\text{O}] = [\text{H}^+][\text{OH}^-] = 1 \cdot 10^{-14} \text{ M}^2$$

- In pure water $[\text{H}^+] = [\text{OH}^-] = 10^{-7} \text{ M}$

Dissociation of Weak Electrolytes: Principle



$$K_a = K_{\text{eq}} \cdot [\text{H}_2\text{O}]$$

$$K_a = \frac{[\text{H}^+][\text{CH}_3\text{COO}^-]}{[\text{CH}_3\text{COOH}]} = 1.74 \cdot 10^{-5} \text{ M}$$

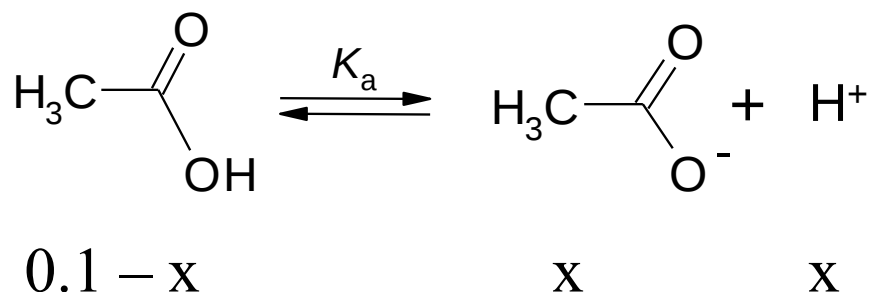
$$[\text{H}^+] = K_a \cdot \frac{[\text{CH}_3\text{COOH}]}{[\text{CH}_3\text{COO}^-]}$$

- Weak electrolytes dissociate only partially in water.
- Extent of dissociation is determined by the acid dissociation constant K_a .
- We can calculate the pH if the K_a is known. But some algebra is needed!

Dissociation of Weak Electrolytes:

Example

What is the final pH of a solution when 0.1 moles of acetic acid is added to water to a final volume of 1L?



$$K_a = \frac{[x][x]}{[0.1-x]} = 1.74 \cdot 10^{-5} \text{ M}$$

$$x^2 = 1.74 \cdot 10^{-6} - 1.74 \cdot 10^{-5} x$$

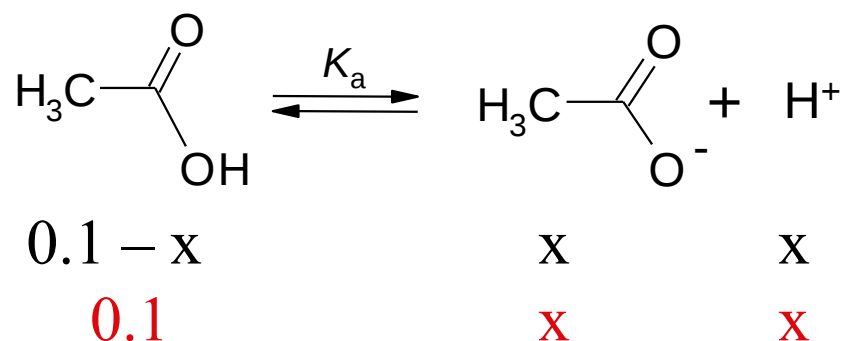
$$x^2 + 1.74 \cdot 10^{-5} x - 1.74 \cdot 10^{-6} = 0$$

$$x = 0.00131, \quad \text{pH} = -\log [\text{H}^+] = 2.88$$

- We assume that the only source of H^+ is the weak acid

- To find the $[\text{H}^+]$, a quadratic equation must be solved

Dissociation of Weak Electrolytes: Simplification



$$K_a = \frac{[x][x]}{[0.1]} = 1.74 \cdot 10^{-5} \text{ M}$$

$$x^2 = 1.74 \cdot 10^{-6}$$

$$x = 0.00132, \quad \text{pH} = 2.88$$

- The equation can be **simplified** if the amount of dissociated species is much less than the amount of undissociated acid
- Approximation works for sufficiently **weak** acids and bases
- Check that $x < [\text{total acid}]$

Buffers are mixtures of weak acids and their anions (conjugate base)

- Buffers resist change in pH
- At $\text{pH} = \text{p}K_a$, there is a 50:50 mixture of acid and anion forms of the compound
- Buffering capacity of acid/anion system is greatest at $\text{pH} = \text{p}K_a$
- Buffering capacity is lost when the pH differs from $\text{p}K_a$ **by more than 1 pH unit**

Acetic Acid-Acetate as a Buffer System

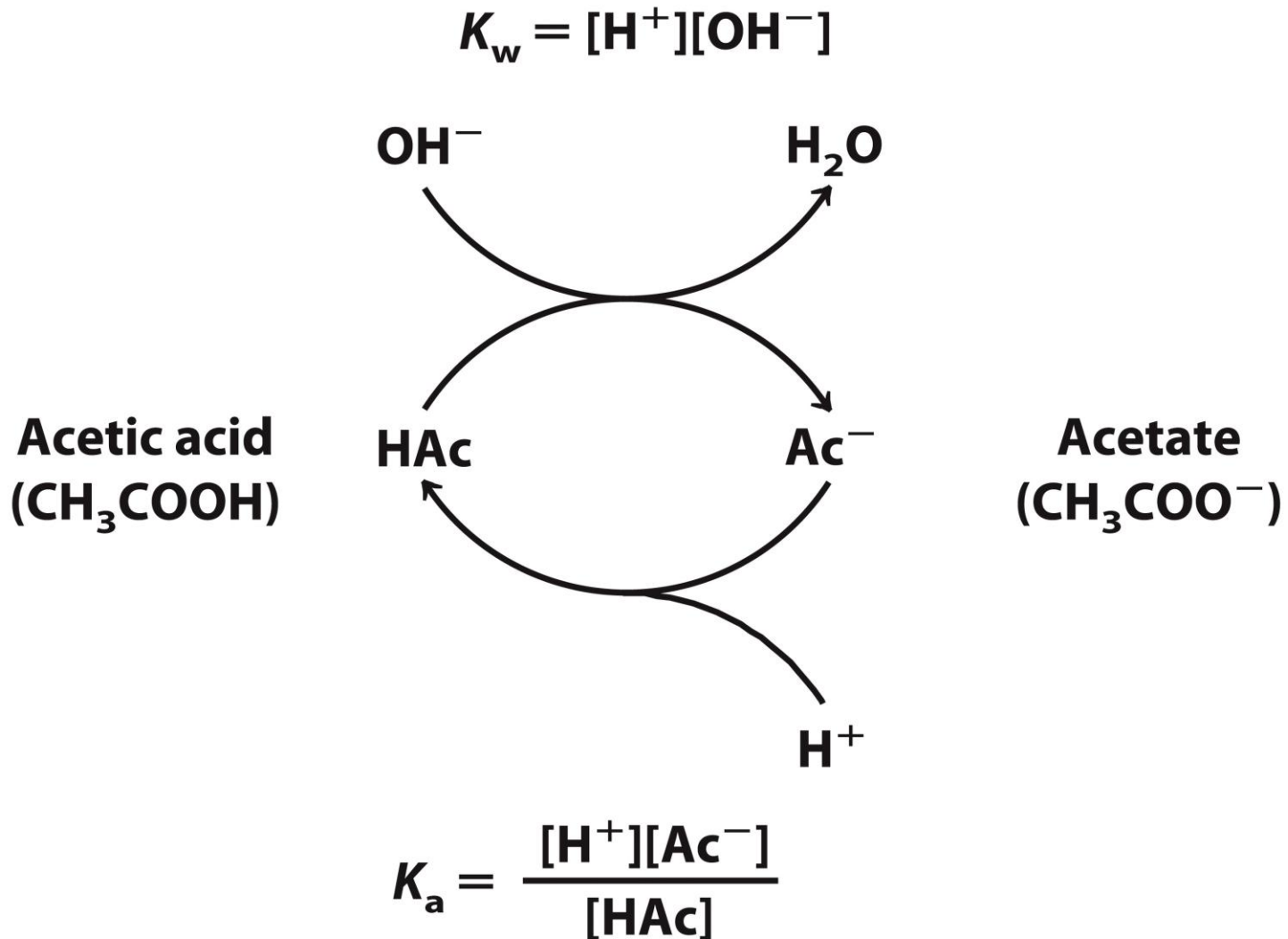


Figure 2-19

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The titration curve of acetic acid. After addition of each increment of NaOH to the acetic acid solution, the pH of the mixture is measured. This value is plotted against the amount of NaOH added.

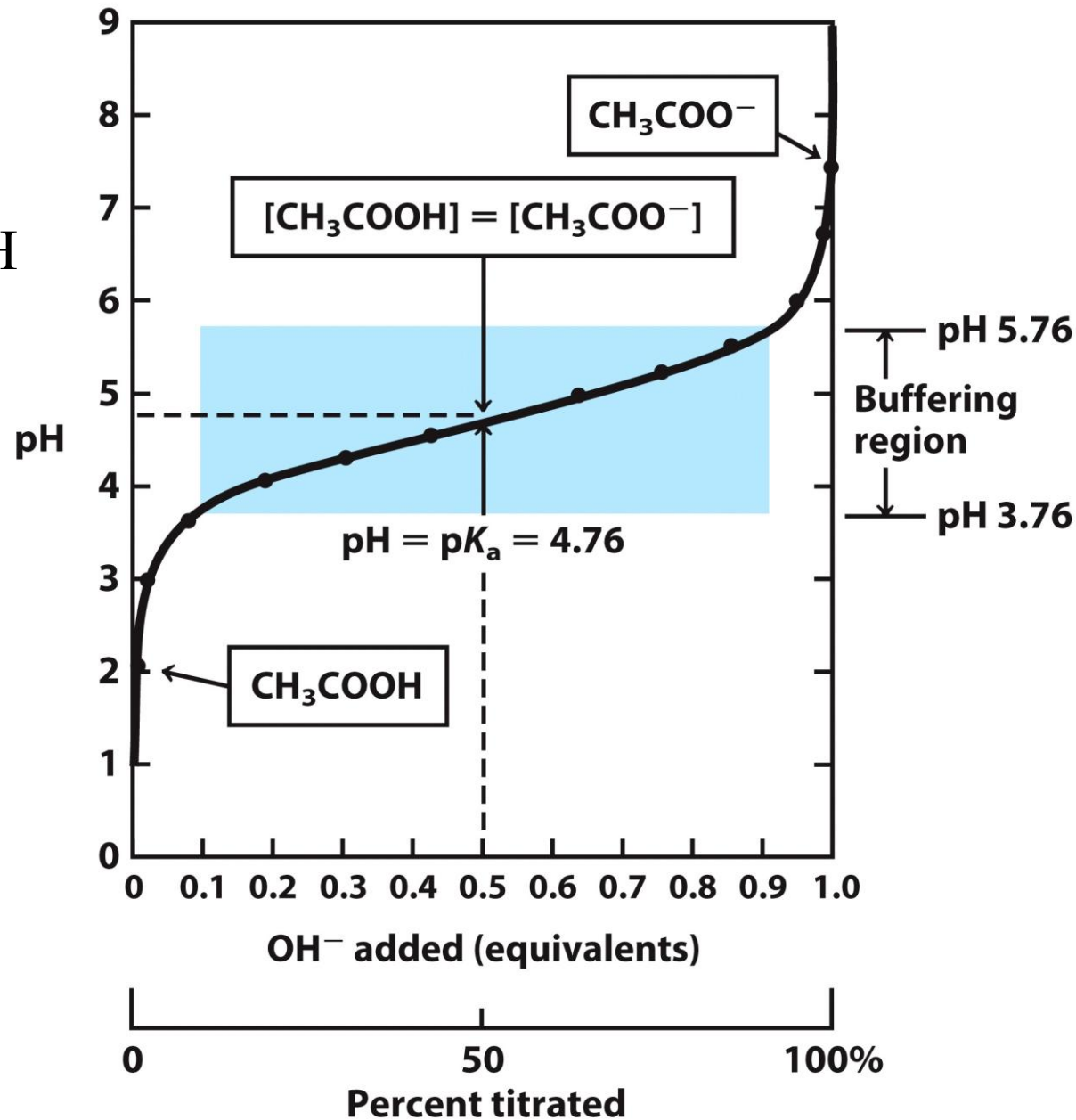


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Weak acids have different pK_a s

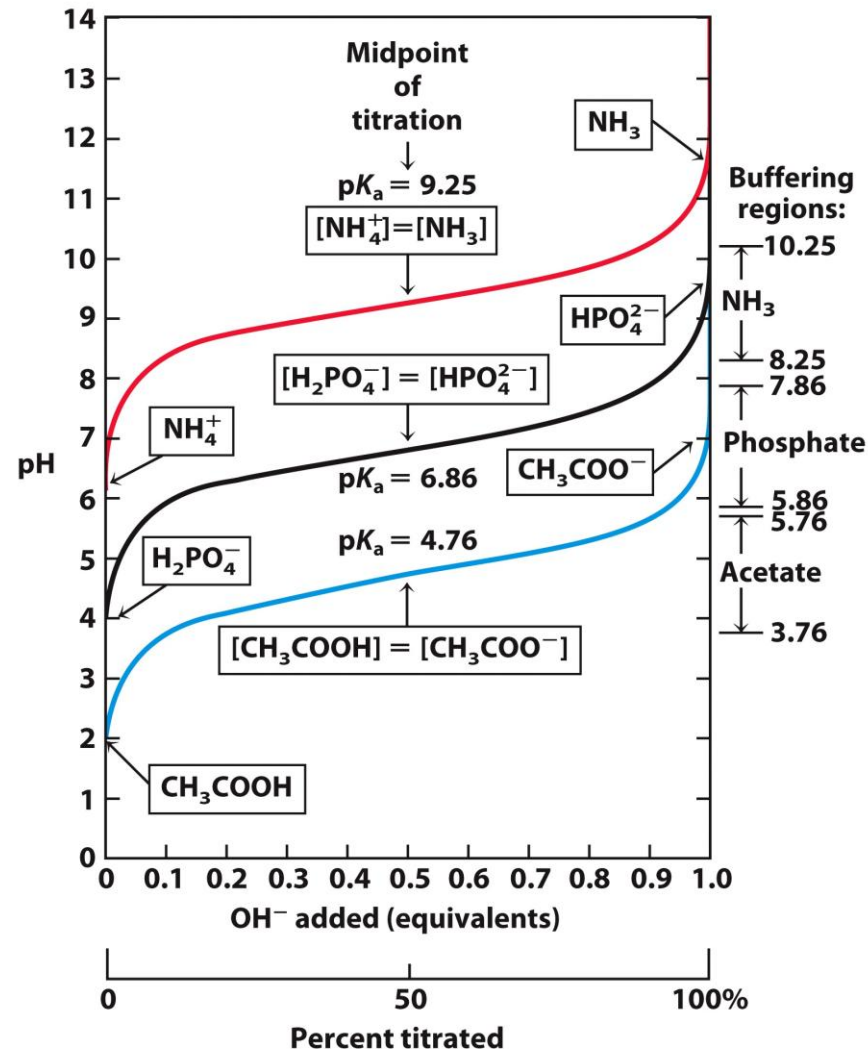
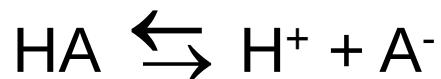


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Henderson–Hasselbalch Equation: Derivation

- The equation fits the titration curves
- Explains why the pKa of a weak acid is equal to the pH of the solution at the midpoint of the titration (you can do it!)



$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]} \rightarrow [\text{H}^+] = K_a \frac{[\text{HA}]}{[\text{A}^-]}$$



$$\text{pH} = \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

Untreated diabetes produces life threatening acidosis

- Maintenance of intracellular pH is vital to all cells
 - Enzyme-catalyzed reactions have **optimal pH**
 - Solubility of polar molecules depends on H-bond donors and acceptors
 - Equilibrium between CO_2 gas and dissolved HCO_3^- depends on pH
- Buffer systems *in vivo* are mainly based on
 - phosphate, concentration in millimolar range
 - bicarbonate, important for blood plasma
 - histidine, efficient buffer at neutral pH

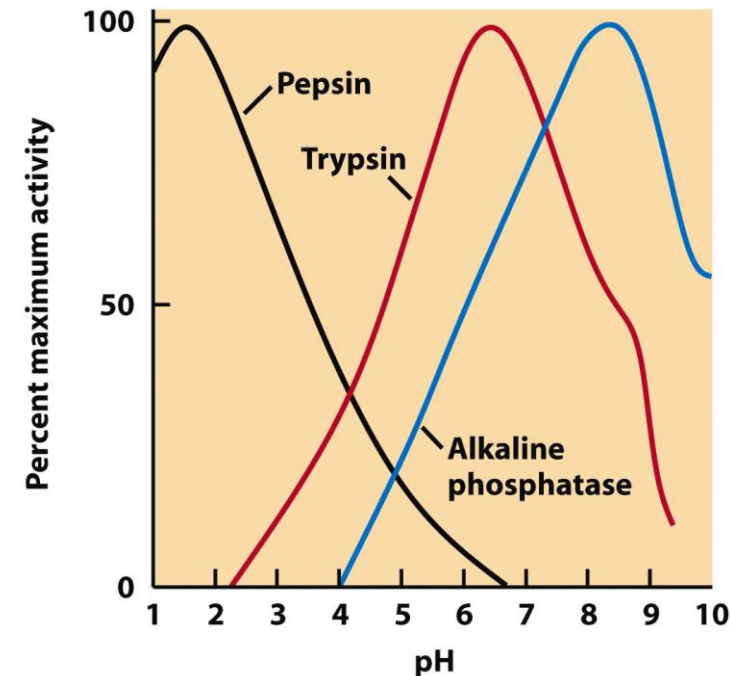


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