Chapter 2

Water

1. Water is the medium for life

- Life evolved in water
- Organisms typically contain 70-90% water
- Chemical reactions occur in aqueous environment
- Water is both a solvent and a reactant
- Water is a critical determinant of the structure and function of proteins, nucleic acids, and cell membranes.

Structure of the water molecule

- **Each H atom of a H_2O molecule shares a pair of electrons with the central O atom**

- **Unequal electron sharing results in two electric dipoles along each of the H-O bonds in H_2O molecule**

- **There is electrostatic（静电） attraction between the O atom of one H_2O molecule and the H atom of another H_2O molecule --- hydrogen bond（氢键）**

There is a nearly tetrahedral arrangement of the outer-shell electron pairs around the oxygen atom; the two hydrogen atoms have localized partial positive charges and the oxygen atom has a partial negative charge.
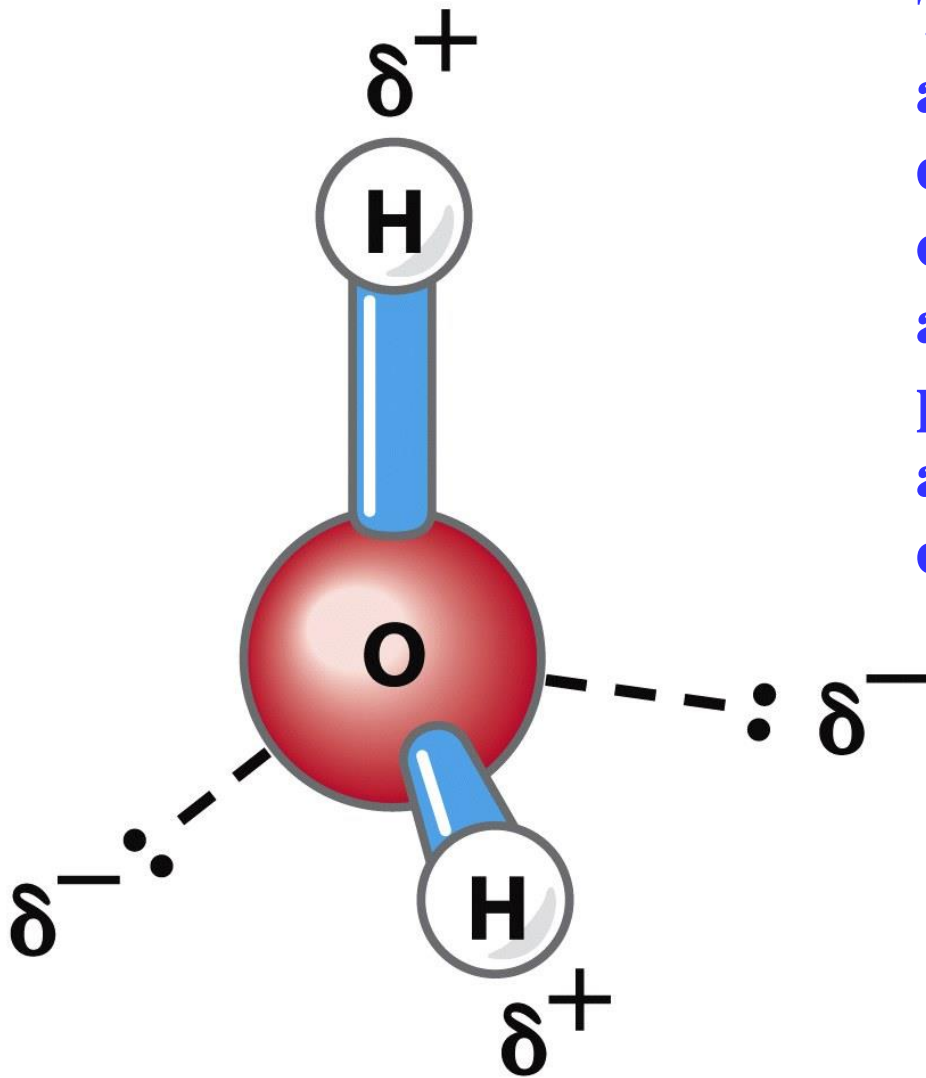
Figure 2-1a
Lehninger Principles of Biochemistry, Fifth Edition
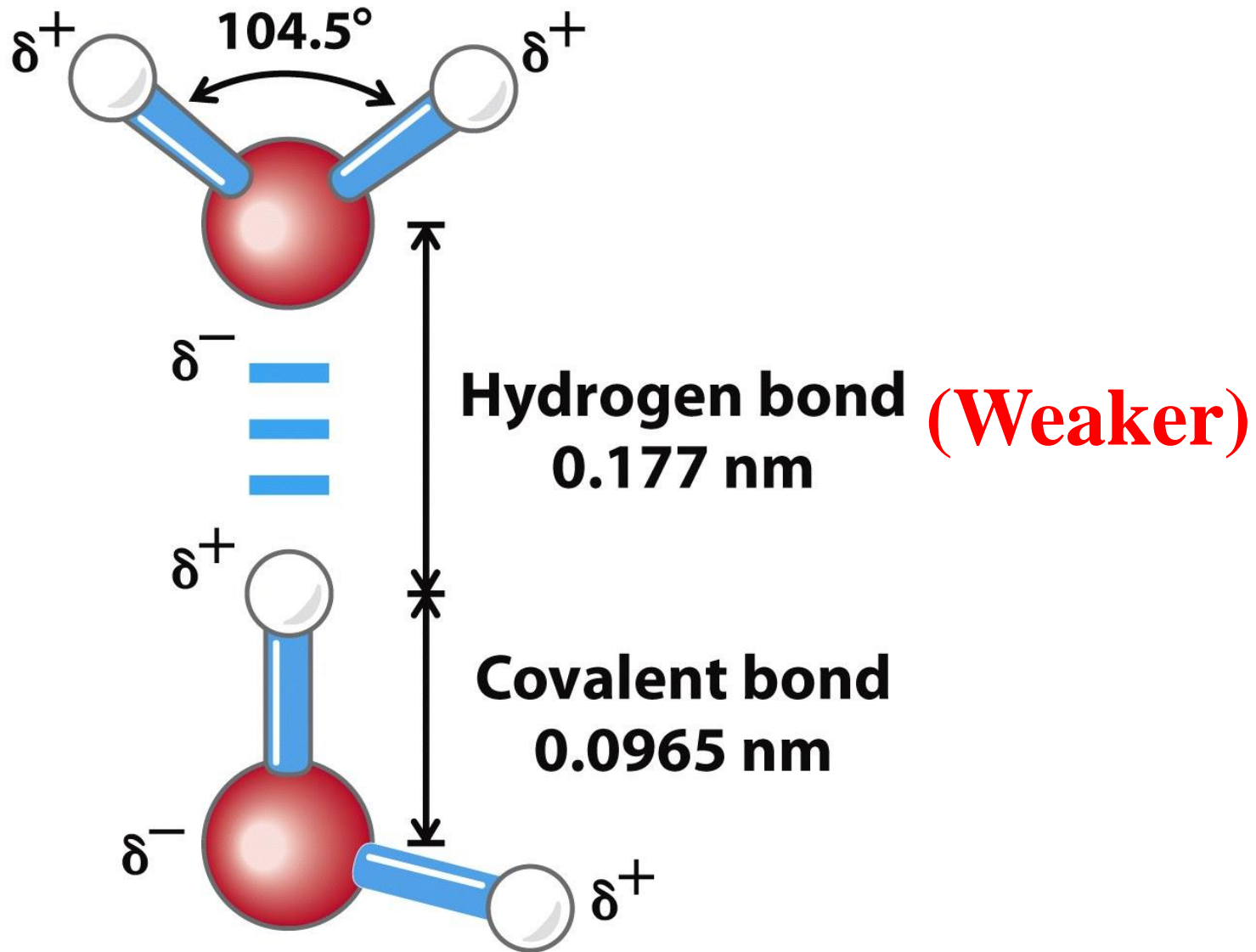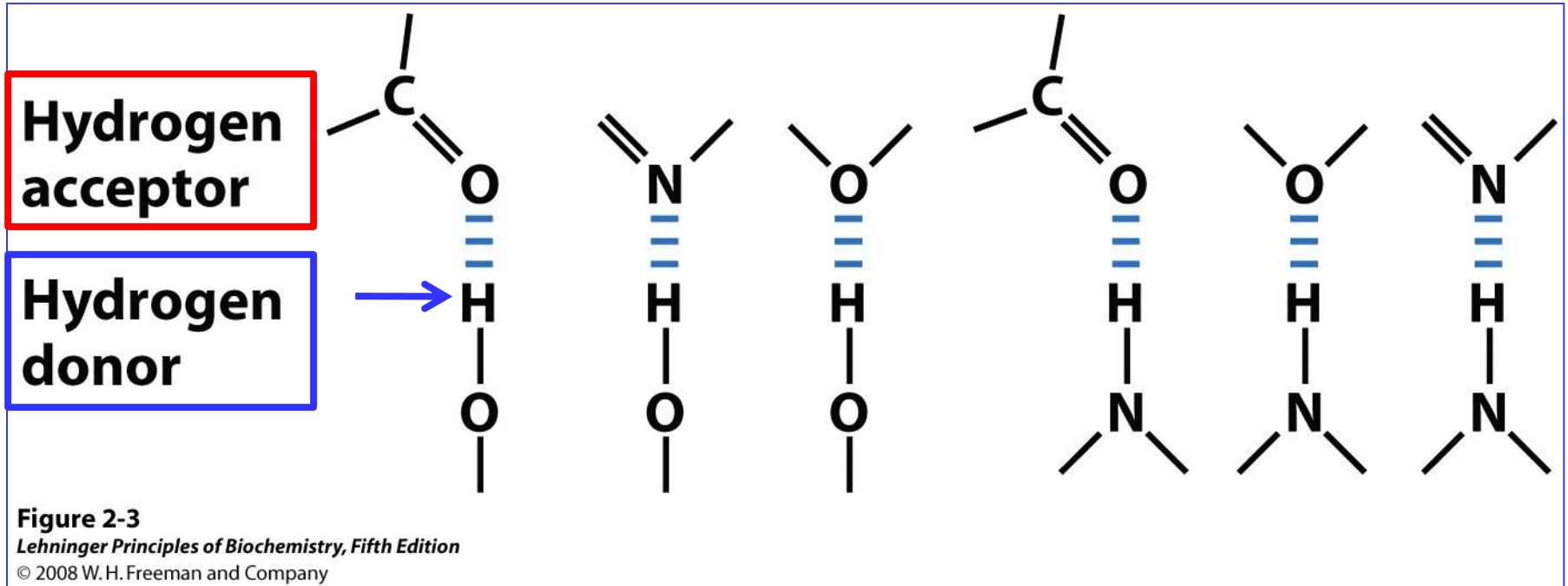© 2008 W. H. Freeman and Company

Structure of the water molecule

δ+ 104.5° δ+

δ⁻

Hydrogen bond **(Weaker)**
0.177 nm

δ+

Covalent bond
0.0965 nm

δ⁻ δ+

Figure 2-1b
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Two H₂O molecules joined by a hydrogen bond

2. Hydrogen bonds

- **Strong dipole-dipole or charge-dipole interaction between an electronegative atom (the H acceptor, frequently N and O) and a H atom covalently bonded to another electronegative atom (the H donor) in the same or another molecule**

- **Typically 4-6 kJ/mol for bonds with neutral atoms, and 6-10 kJ/mol for bonds with one charged atom**

- **Hydrogen bonds are strongest when the bonded molecules are oriented to maximize electrostatic interaction. Ideally, the three atoms involved lie in a straight line.**

Common hydrogen bonds in biological systems

Figure 2-3
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The hydrogen acceptor is usually oxygen or nitrogen; the hydrogen donor is another electronegative atom.
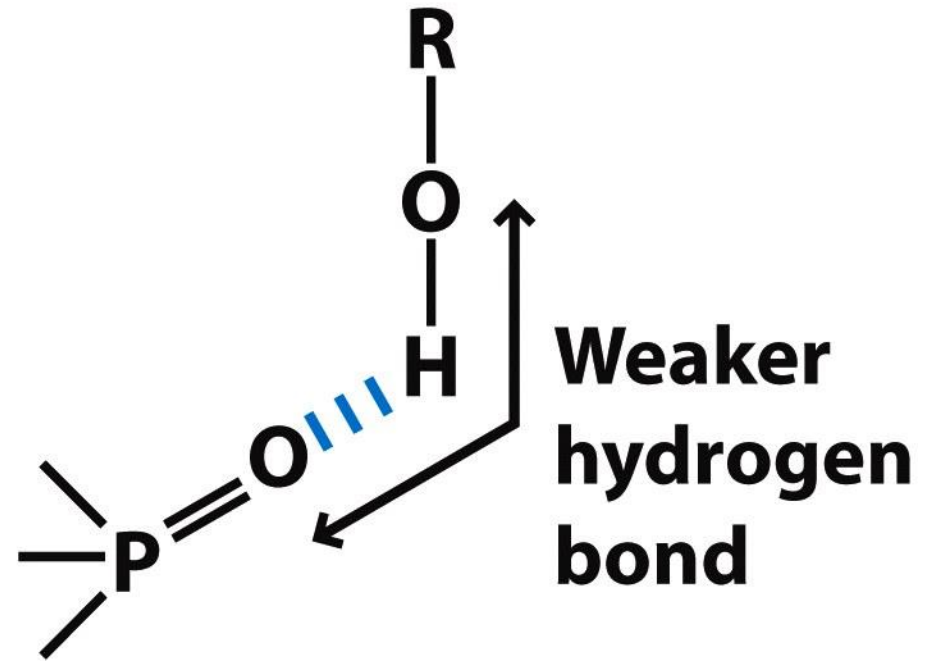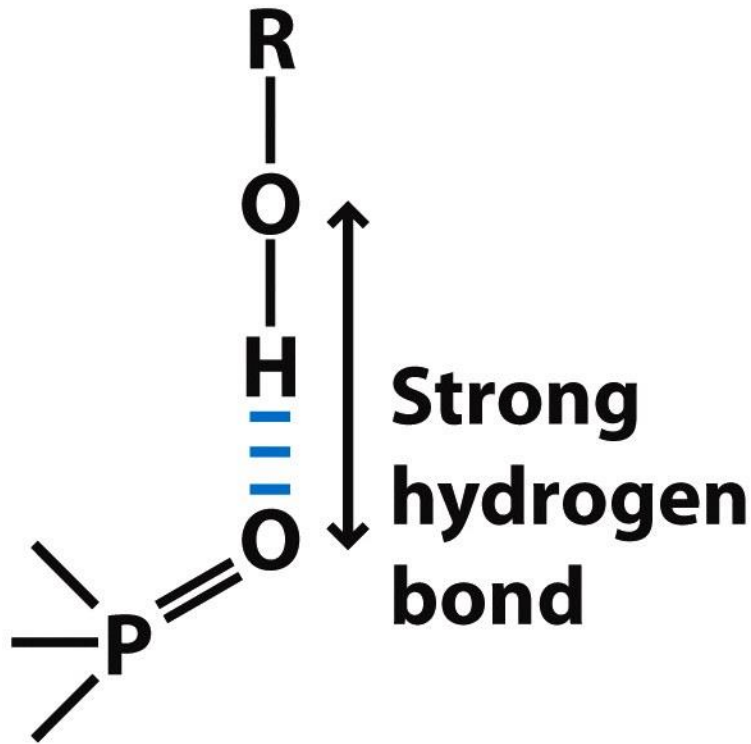
Figure 2-5
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# Directionality of the hydrogen bond

Importance of hydrogen bonds

- Source of unique properties of water
- Structure and function of proteins
- Structure and function of DNA
- Structure and function of polysaccharides
- Binding of substrates to enzymes
- Binding of hormones to receptors
- Matching of mRNA and tRNA

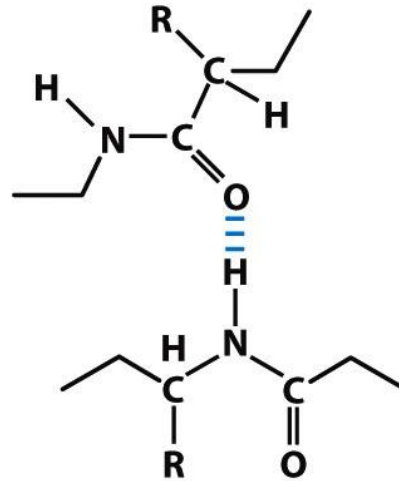**Between the hydroxyl group of an alcohol and water**

Between the carbonyl group of a ketone and water
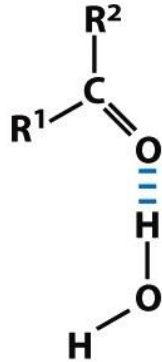
Between peptide groups in polypeptides

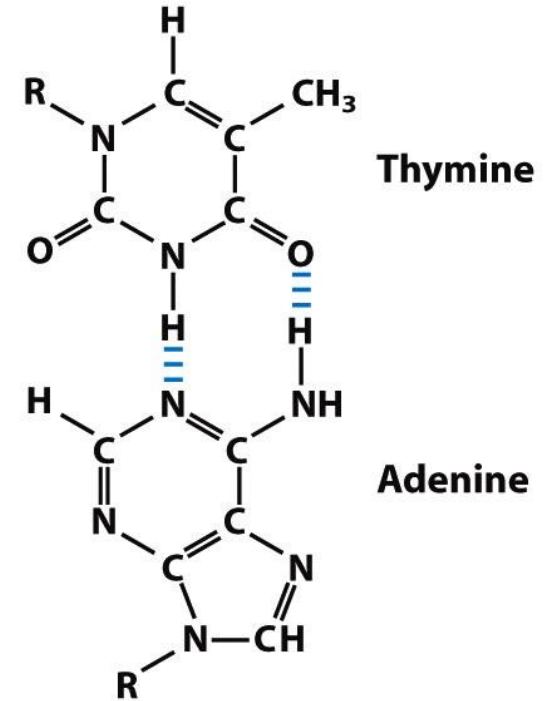**Between complementary bases of DNA**

Thymine

Adenine

Figure 2-4
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Some biologically important hydrogen bonds

Hydrogen bonds in water

- H_2O can serve as both an H donor and an H acceptor
- H_2O is a polar molecule, capable of forming hydrogen bands with itself or with other molecules
- Hydrogen bonds between H_2O molecules provide the cohesive forces that make H_2O a liquid at room temperature and a solid (ice) at cold temperature
- Up to four hydrogen bonds per H_2O molecule gives H_2O
  – anomalously high boiling point
  – anomalously high melting point
  – unusually large surface tension
- Hydrogen bonding in H_2O is cooperative

TABLE 2–1	Melting Point, Boiling Point, and Heat of Vaporization of Some Common Solvents		
	Melting point (°C)	Boiling point (°C)	Heat of vaporization (J/g)*
→ Water	0	100	2,260
Methanol (CH_3OH)	−98	65	1,100
Ethanol (CH_3CH_2OH)	−117	78	854
Propanol ($CH_3CH_2CH_2OH$)	−127	97	687
→ Butanol ($CH_3(CH_2)_2CH_2OH$)	−90	117	590
Acetone (CH_3COCH_3)	−95	56	523
Hexane ($CH_3(CH_2)_4CH_3$)	−98	69	423
Benzene (C_6H_6)	6	80	394
→ Butane ($CH_3(CH_2)_2CH_3$)	−135	−0.5	381
Chloroform ($CHCl_3$)	−63	61	247

*The heat energy required to convert 1.0 g of a liquid at its boiling point and at atmospheric pressure into its gaseous state at the same temperature. It is a direct measure of the energy required to overcome attractive forces between molecules in the liquid phase.

Table 2-1
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Ice: water in a solid state

- **Water has many different crystal forms; the hexagonal ice is the most common**

- **In ice, each water molecule forms hydrogen bonds with 4 other water molecules to yield a regular lattice structure (3.4 in liquid water)**

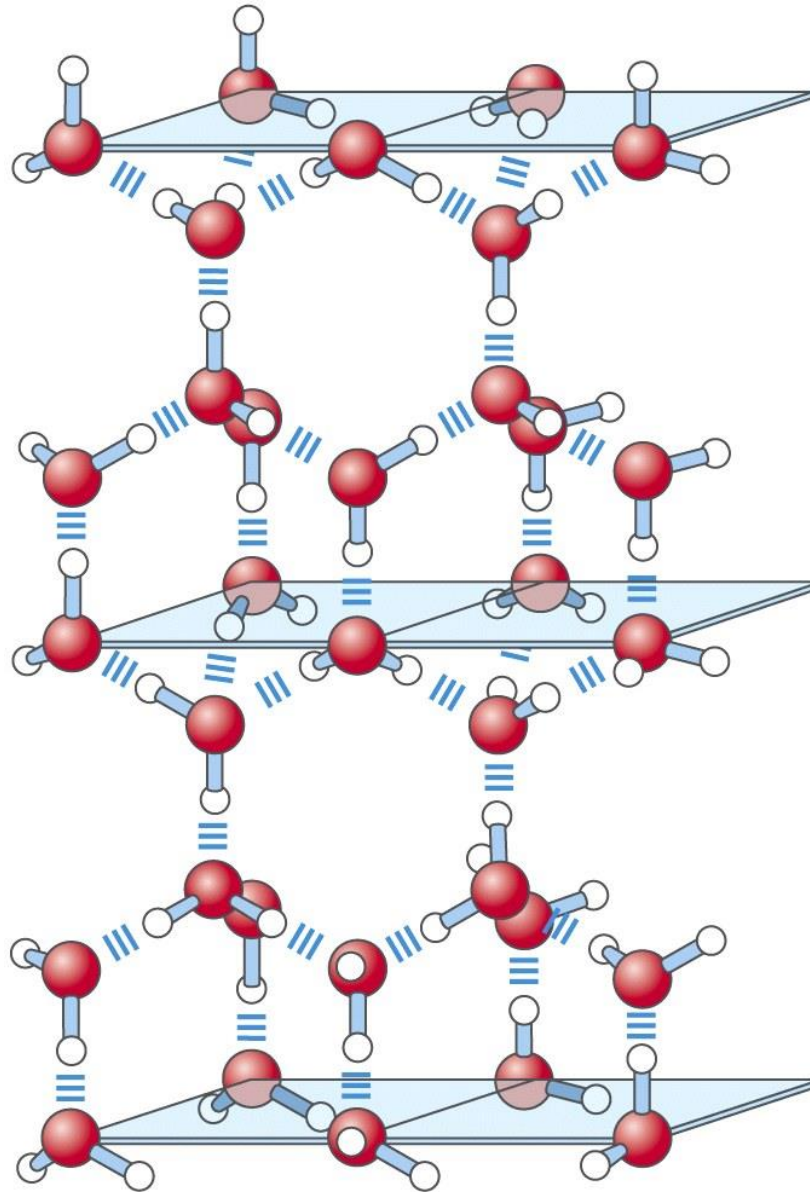- **Ice has lower density than liquid water, thus ice floats on liquid water**

Figure 2-2
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Hydrogen bonding in ice

Water as a solvent

- **The polarity and hydrogen-bonding capability of water make it an excellent solvent for polar molecules.**

- **Water greatly weakens electrostatic forces and hydrogen bonding between polar molecules by competing for their attractions.**
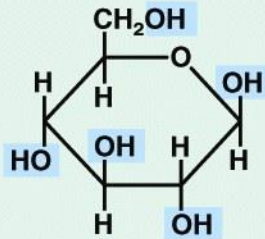
Water as a solvent

- **Water is a good solvent for charged and polar (hydrophilic) compounds**
  - **amino acids and peptides**
  - **small alcohols**
  - **carbohydrates**

- **Water is a poor solvent for nonpolar (hydrophobic) compounds**
  - **nonpolar gases**
  - **aromatic moieties**
  - **aliphatic chains**

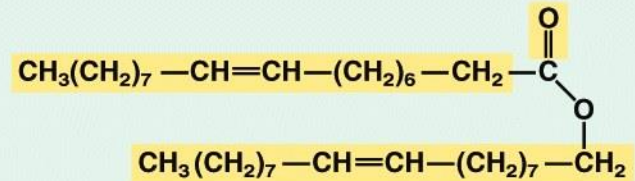**TABLE 2–2** Some Examples of Polar, Nonpolar, and Amphipathic Biomolecules (Shown as Ionic Forms at pH 7)
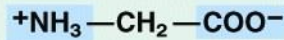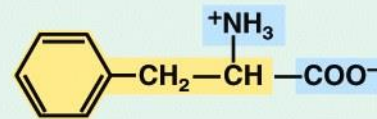
Polar

Glucose

Nonpolar

Typical wax

$CH_3(CH_2)_7$ —CH=CH—$(CH_2)_6$—CH_2—C

$CH_3(CH_2)_7$ —CH=CH—$(CH_2)_7$ —CH_2

Amphipatic

Phenylalanine

Glycine

$^+NH_3$—CH_2—COO^-

Aspartate

^-OOC—CH_2—$\overset{+NH_3}{\underset{|}{CH}}$—$COO^-$

Lactate

CH_3—$\overset{|}{\underset{OH}{CH}}$—$COO^-$

$\overset{+NH_3}{\underset{|}{CH}}$

—CH_2—CH —COO^-

Phosphatidylcholine

$CH_3(CH_2)_{15}CH_2$—C—O—CH_2

$CH_3(CH_2)_{15}CH_2$—C—O—CH

CH_2—O—P—O—CH_2—CH_2—$\overset{+}{N}(CH_3)_3$

O^-

Glycerol

$HOCH_2$ —$\overset{|}{\underset{OH}{CH}}$—$CH_2OH$
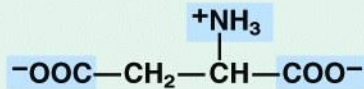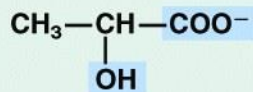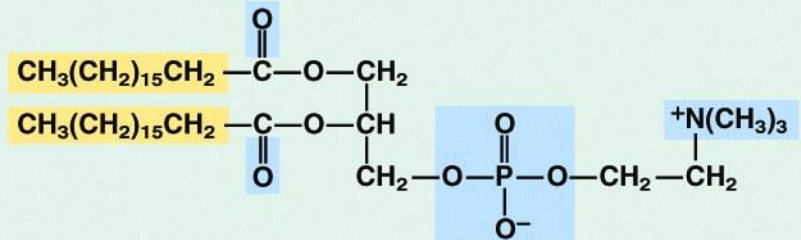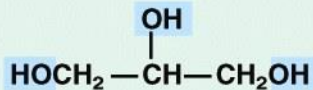
☐ Polar groups ☐ Nonpolar groups

Table 2-2
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TABLE 2–3 **Solubilities of Some Gases in Water**

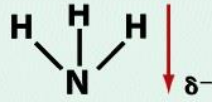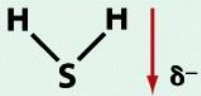| Gas	Structure*	Polarity	Solubility in water (g/L)[†]
Nitrogen (N_2)	$N\equiv N$	Nonpolar	0.018 (40 °C)
Oxygen (O_2)	$O=O$	Nonpolar	0.035 (50 °C)
Carbon dioxide (CO_2)	δ^- δ^- $O=C=O$	Nonpolar	0.97 (45 °C)
Ammonia (NH_3)	H H H N δ^-	Polar	900 (10 °C)
Hydrogen sulfide (H_2S)	H H S δ^-	Polar	1,860 (40 °C)

*The arrows represent electric dipoles; there is a partial negative charge (δ^-) at the head of the arrow, a partial positive charge (δ^+; not shown here) at the tail.

[†]Note that polar molecules dissolve far better even at low temperatures than do nonpolar molecules at relatively high temperatures.
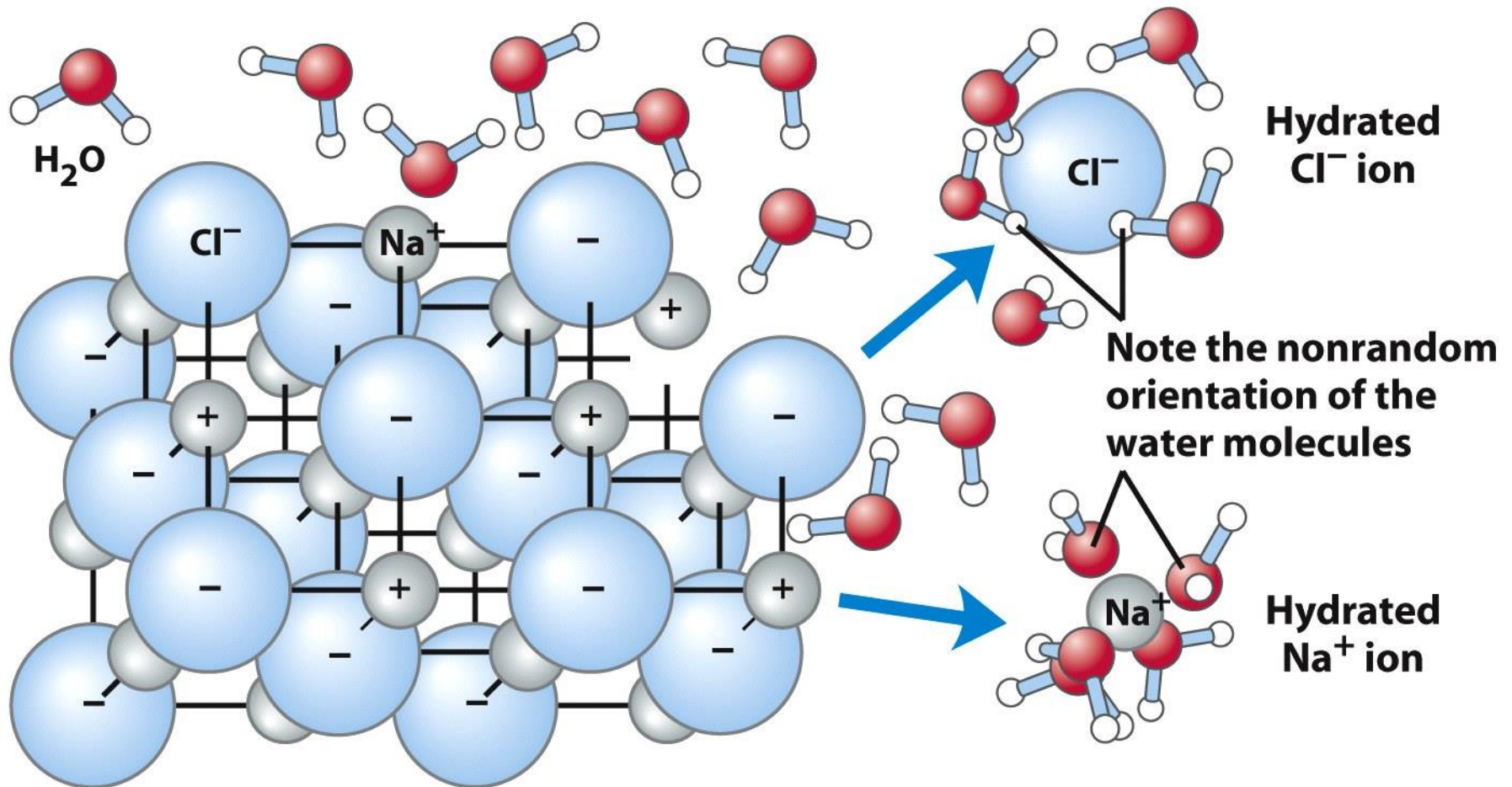
Figure 2-6
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Water dissolves many crystalline salts by hydrating their component ions

3. The hydrophobic effect

- **Refers to the association or interaction of nonpolar molecules or components of molecules in the aqueous solution**

- **Does not arise because of some attractive direct force between two nonpolar molecules**

- **Is one of the main factors behind:**
  - **Protein folding**
  - **Protein-protein association**
  - **Formation of lipid micelles**
  - **Binding of steroid hormones to their receptors**

Hydrophilic "head group"

Hydrophobic alkyl group

"Flickering clusters" of H_2O molecules in bulk phase

Highly ordered H_2O molecules form "cages" around the hydrophobic alkyl chains
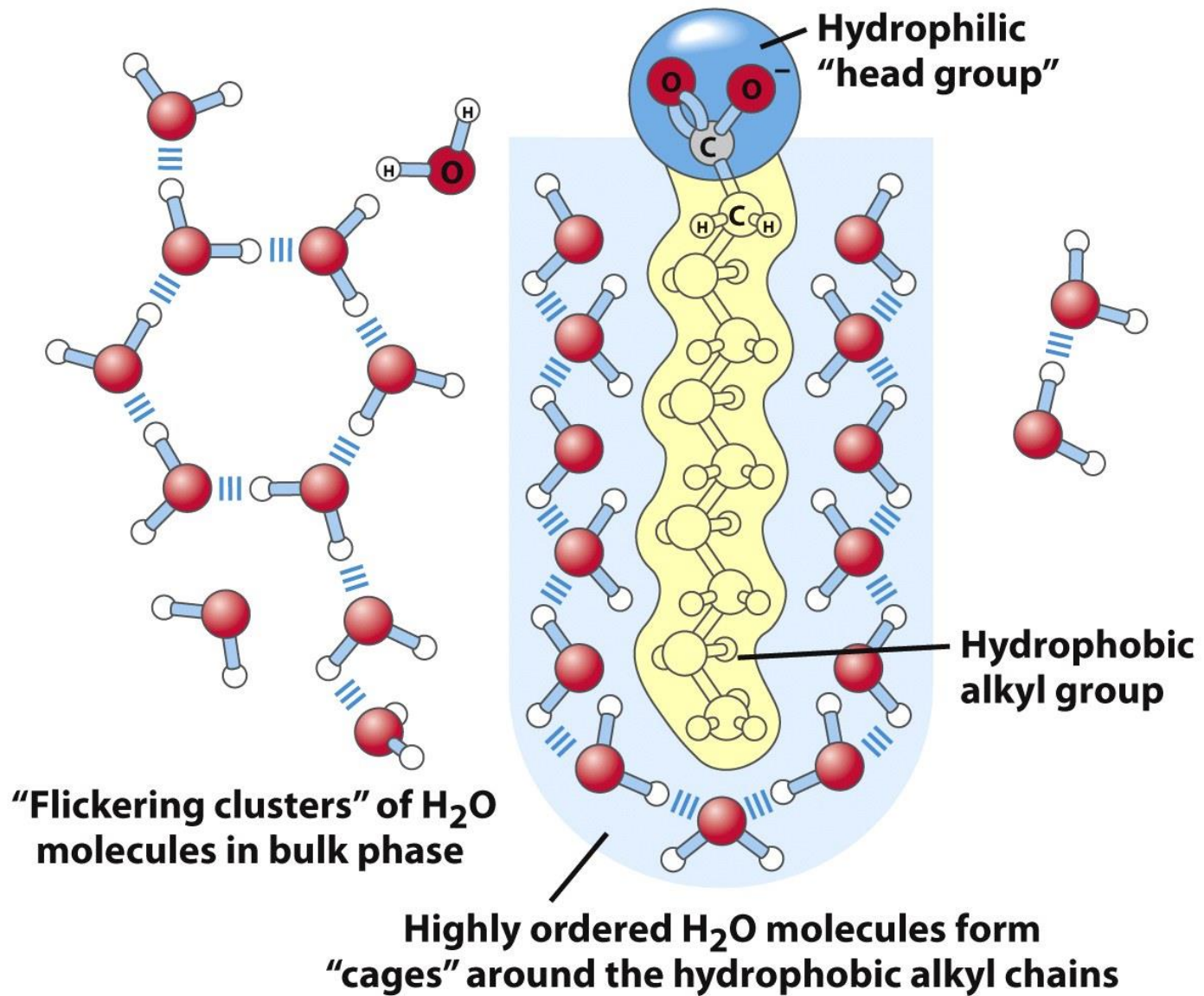
Figure 2-7a
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Long-chain fatty acid in aqueous solution
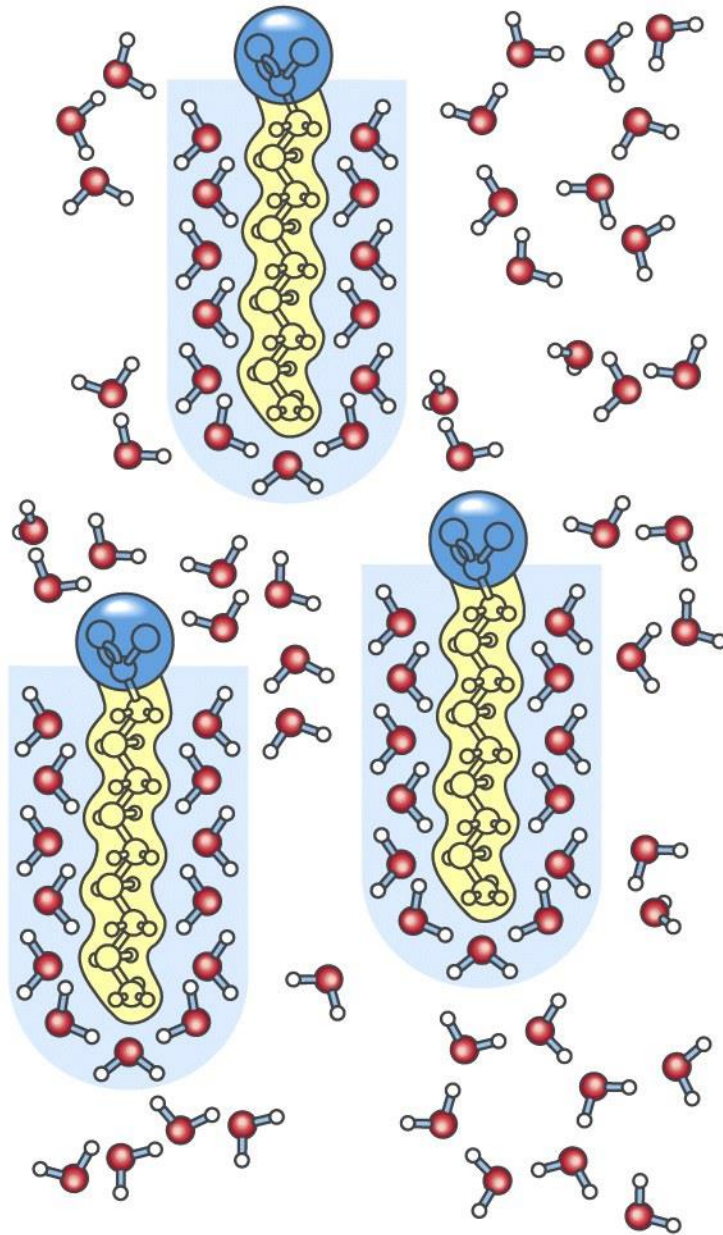
Dispersion of lipids in H_2O

Each lipid molecule forces surrounding H_2O molecules to become highly ordered.
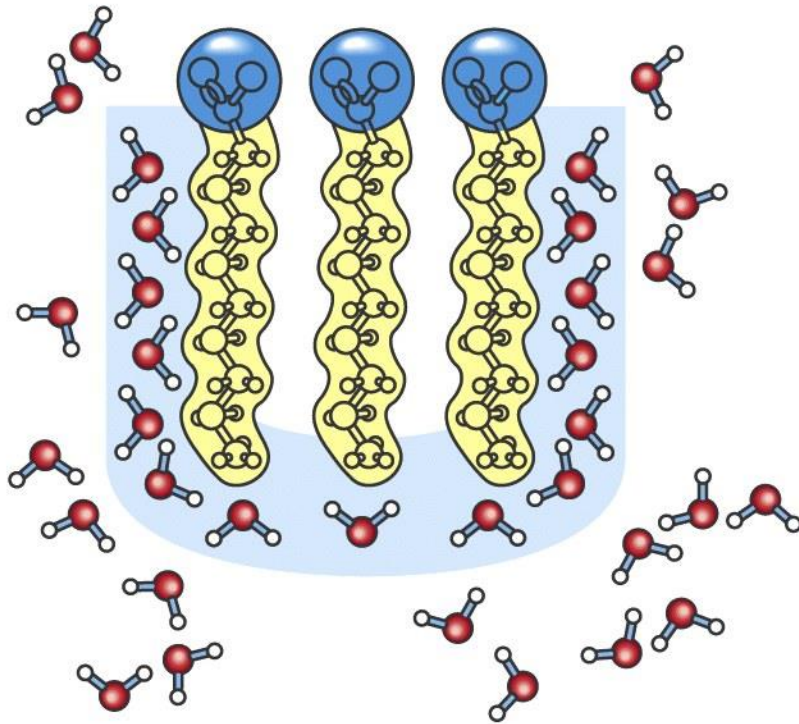
Clusters of lipid molecules

Only lipid portions at the edge of the cluster force the ordering of water. Fewer H_2O molecules are ordered, and entropy is increased.

Figure 2-7b part 2
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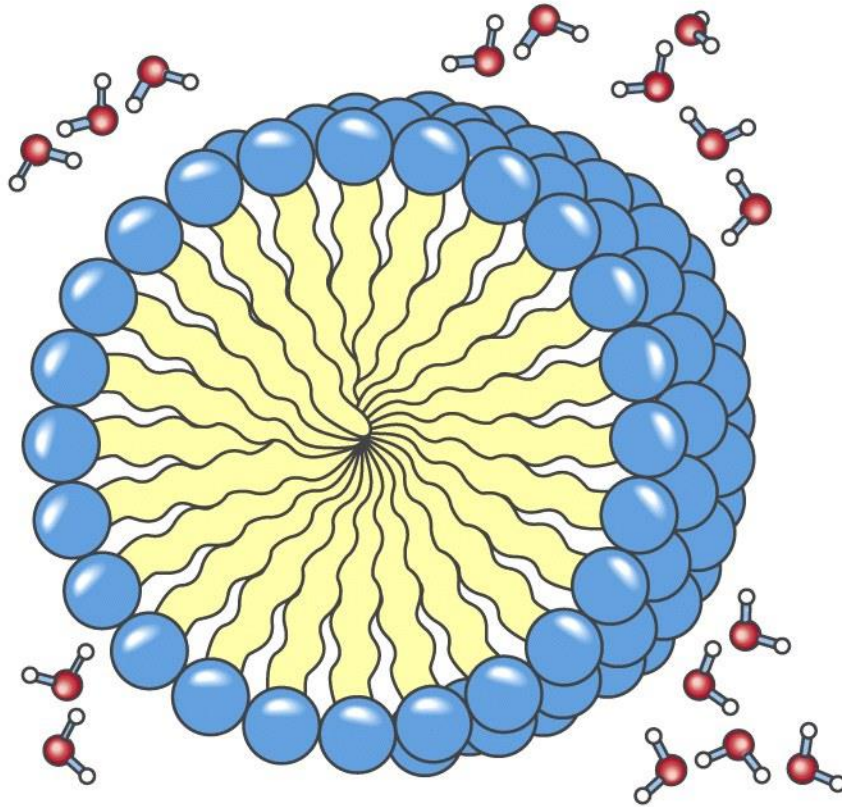
Micelles

All hydrophobic groups are sequestered from water; ordered shell of H_2O molecules is minimized, and entropy is further increased.

Figure 2-7b part 3
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By clustering together in micelles, the fatty acid molecules expose the smallest possible hydrophobic surface area to the water, and fewer water molecules are required in the shell of ordered water. The energy gained by freeing immobilized water molecules stabilizes the micelle.

Hydrophobic effect favors ligand binding

- **Binding sites in enzymes and receptors are often hydrophobic**

- **Such sites can bind hydrophobic substrates and ligands such as steroid hormones**

- **Many drugs are designed to take advantage of the hydrophobic effect**

Ordered water interacting with substrate and enzyme

Enzyme

Substrate

Disordered water displaced by enzyme-substrate interaction

Enzyme-substrate interaction stabilized by hydrogen-bonding, ionic, and hydrophobic interactions
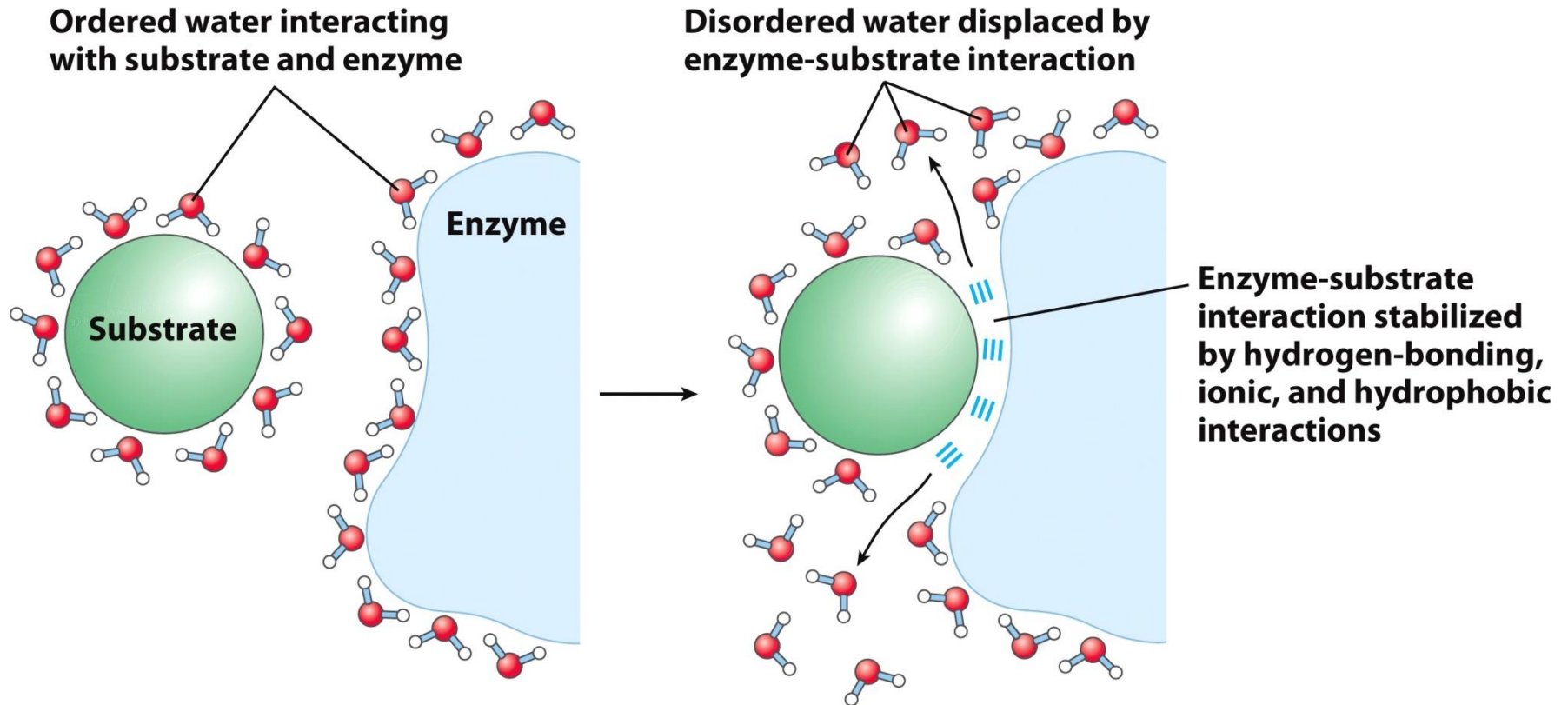
Figure 2-8
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Release of ordered water favors formation of an enzyme-substrate complex

4. Van der Waals interactions

- **Weak intermolecular forces between molecules as a result of each inducing polarization in the other**
- **Occur between any two atoms close to each other**
- **Van der Waals interactions have two components:**
  - **Attractive force: depends on the polarizability**
  - **Repulsive force: 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 (van der Waals radius or van der Waals contact distance)**

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 nm + 0.077 nm = 0.154 nm.

Table 2-4
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Biochemical significance of van der Waals interactions

- **Weak individually**
  - **Easily broken, reversible**
- **Universal**
  - **Occur between any two atoms that are near each other**
- **Importance**
  - **stabilizes biological macromolecules (stacking in DNA)**
  - **facilitates binding of polarizable ligands**

Chemical reactions: breaking & forming of covalent bonds
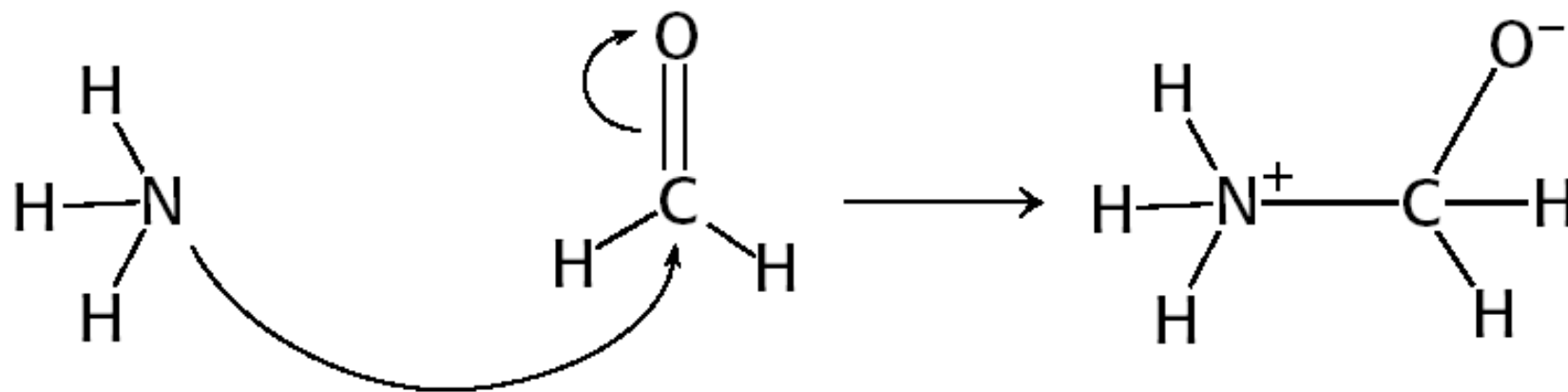
Covalent interactions

- **A covalent bond is formed by the sharing of a pair of electrons between adjacent atoms**

- **Covalent bonds are the strongest bonds present in biomolecules (100 kcal/mol)**

- **Noncovalent interactions do not involve sharing a pair of electrons**

Noncovalent interactions

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

- **Hydrogen bonds**
  - **Weak electrostatic interactions between one electronegative atom and a H atom covalently linked to a second electronegative atom**

- **Van der Waals interactions**
  - **Weak interactions between all atoms, regardless of polarity**
  - **Attractive and repulsive component**

- **Hydrophobic interactions**
  - **The association of nonpolar groups or compounds with each other in aqueous systems**
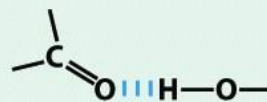
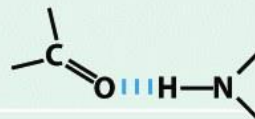| TABLE 2–5	Four Types of Noncovalent ("Weak") Interactions among Biomolecules in Aqueous Solvent

*****

Hydrogen bonds
   Between neutra groups

$$\overset{|}{\underset{|}{C}}\!=\!O \parallel\!\parallel\! H\!-\!O\!-$$

   Between peptide bonds

$$\overset{|}{\underset{|}{C}}\!=\!O \parallel\!\parallel\! H\!-\!N\!\overset{|}{\underset{|}{}}$$

Ionic interactions
   Attraction

$$-^+NH_3 \;\rightarrow\!\leftarrow\; ^-O\!-\!C\!=\!O$$

   Repulsion

$$-^+NH_3 \;\leftarrow\!\rightarrow\; H_3N^+-$$

Hydrophobic interactions

water

CH$_3$ CH$_3$
CH
CH$_2$

CH$_2$
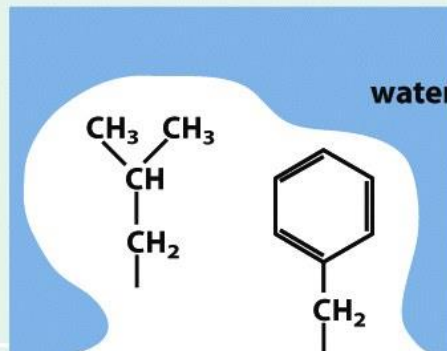
Van der Waals interactions | **Any two atoms in close proximity**

Table 2-5
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Noncovalent interactions

- **Much weaker than covalent bonds**

- **Reversible --- continually forming and breaking**

- **Weak individually, but strong cumulatively**

- **Weak interactions are crucial for structure and function of DNA, RNA and proteins**

- **The most stable macromolecular conformations are those in which hydrogen bonding is maximized within the molecule and between the molecule and the solvent, and in which hydrophobic moieties cluster in the interior of the molecule away from the aqueous solvent.**

5. Ionization of water

$$H_2O \rightleftharpoons H^+ + OH^-$$

- O-H bonds in H_2O are polar
- H_2O can dissociate into a proton (H^+, immediately hydrated to form hydronium ions H_3O^+) 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 MΩ•cm)
- The equilibrium $H_2O \rightleftharpoons H^+ + OH^-$ 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}

$$H_2O \rightleftarrows H^+ + OH^- \qquad K_{eq} = \frac{[H^+] \bullet [OH^-]}{[H_2O]}$$

K_{eq} can be determined experimentally, it is $1.8 \bullet 10^{-16}$ M at 25^oC.

$[H_2O]$ can be determined from water density, it is 55.5 M.

- **Ionic product of water:**

$$K_w = K_{eq} \cdot [H_2O] = [H^+][OH^-] = 1 \cdot 10^{-14} M^2$$

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

What is pH?

$$\text{pH} = \text{-log[H}^+\text{]}$$

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

$$-\log[\text{H}^+] - \log[\text{OH}^-] = +14$$

$$\text{pH} + \text{pOH} = 14$$

- **pH is defined as the negative logarithm of the hydrogen ion ([H$^+$]) concentration.**
- **The pH and pOH must always add to 14**
- **pH can be negative ([H$^+$] = 6 M)**
- **In neutral solution, [H$^+$] = [OH$^-$] and the pH is 7**

TABLE 2–6	The pH Scale ✳✳✳✳✳		
$[H^+]$ (M)	pH	$[OH^-]$ (M)	pOH*
10^0 (1)	0	10^{-14}	14
10^{-1}	1	10^{-13}	13
10^{-2}	2	10^{-12}	12
10^{-3}	3	10^{-11}	11
10^{-4}	4	10^{-10}	10
10^{-5}	5	10^{-9}	9
10^{-6}	6	10^{-8}	8
10^{-7}	7	10^{-7}	7
10^{-8}	8	10^{-6}	6
10^{-9}	9	10^{-5}	5
10^{-10}	10	10^{-4}	4
10^{-11}	11	10^{-3}	3
10^{-12}	12	10^{-2}	2
10^{-13}	13	10^{-1}	1
10^{-14}	14	10^0 (1)	0

*The expression pOH is sometimes used to describe the basicity, or OH^- concentration, of a solution; pOH is defined by the expression pOH = $-\log [OH^-]$, which is analogous to the expression for pH. Note that in all cases, pH + pOH = 14.

Table 2-6
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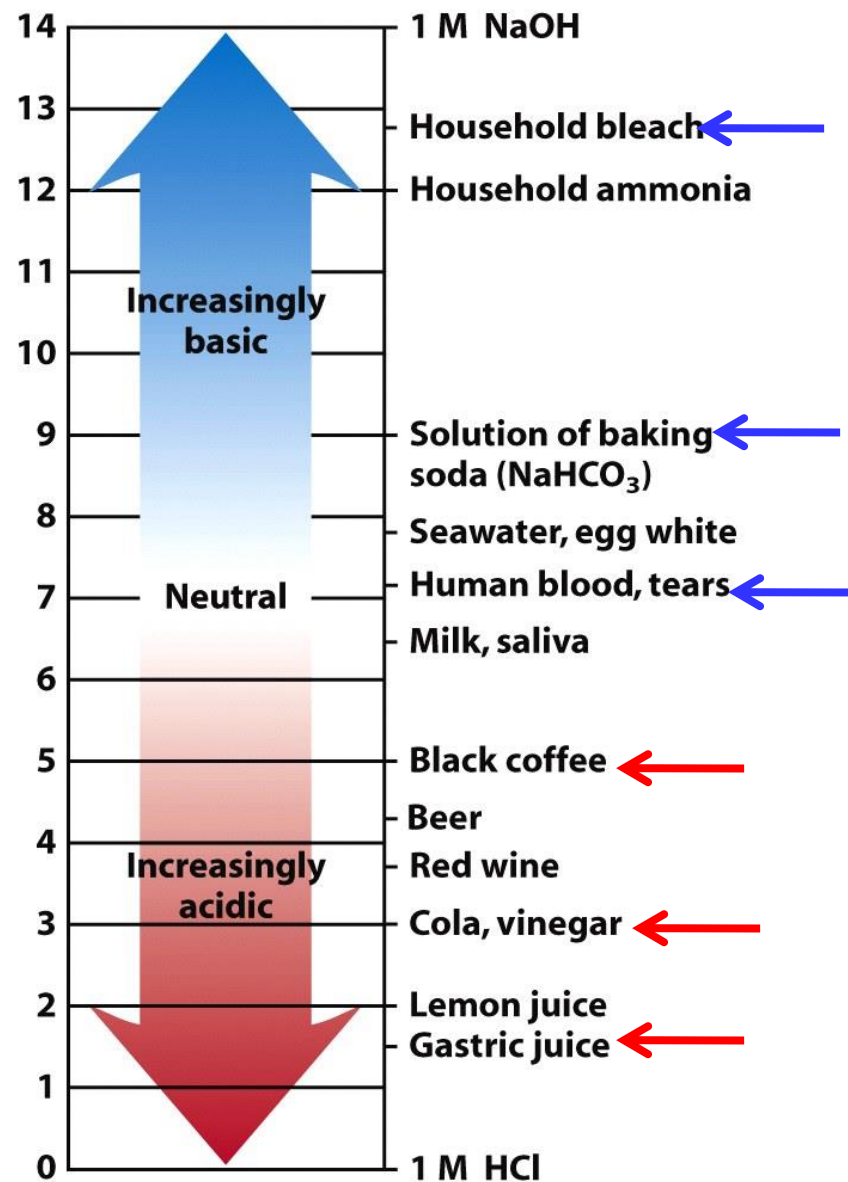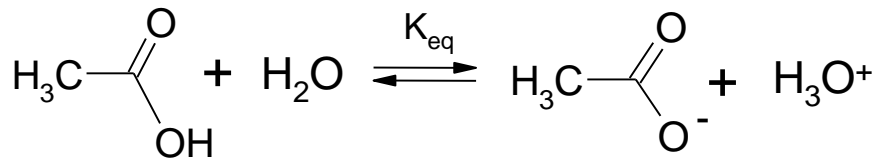© 2008 W. H. Freeman and Company

pH scale: 1 unit = 10-fold

Figure 2-14
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The pH of some aqueous fluids

6. Dissociation of weak acids and bases: principle

$$K_a = K_{eq} \cdot [H_2O]$$

$$K_a = \frac{[H^+][CH_3COO^-]}{[CH_3COOH]} = 1.74 \cdot 10^{-5}\,M$$

$$[H^+] = K_a \cdot \frac{[CH_3COOH]}{[CH_3COO^-]}$$

$$\mathbf{p}K_a = \mathbf{-log}\,K_a$$

- **Weak acids and bases dissociate partially in water**

- **The extent of dissociation is determined by the acid dissociation constant K_a**

- **pK_a indicates the relative strength of a weak acid or base**

pK_a = -log K_a (strong acid → large K_a → small pK_a)

Monoprotic acids
Acetic acid
($K_a = 1.74 \times 10^{-5}$ M)

Ammonium ion
($K_a = 5.62 \times 10^{-10}$ M)

Diprotic acids
Carbonic acid
($K_a = 1.70 \times 10^{-4}$ M);
Bicarbonate
($K_a = 6.31 \times 10^{-11}$ M)

Glycine, carboxyl
($K_a = 4.57 \times 10^{-3}$ M);
Glycine, amino
($K_a = 2.51 \times 10^{-10}$ M)

Triprotic acids
Phosphoric acid
($K_a = 7.25 \times 10^{-3}$ M);
Dihydrogen phosphate
($K_a = 1.38 \times 10^{-7}$ M);
Monohydrogen phosphate
($K_a = 3.98 \times 10^{-13}$ M)

$CH_3C(=O)OH \rightleftharpoons CH_3C(=O)O^- + H^+$
$pK_a = 4.76$

$NH_4^+ \rightleftharpoons NH_3 + H^+$
$pK_a = 9.25$

$H_2CO_3 \rightleftharpoons HCO_3^- + H^+$
$pK_a = 3.77^*$

$HCO_3^- \rightleftharpoons CO_3^{2-} + H^+$
$pK_a = 10.2$

$NH_3^+-CH_2C(=O)OH \rightleftharpoons NH_3^+-CH_2C(=O)O^- + H^+$
$pK_a = 2.34$

$NH_3^+-CH_2C(=O)O^- \rightleftharpoons NH_2-CH_2C(=O)O^- + H^+$
$pK_a = 9.60$

$H_3PO_4 \rightleftharpoons H_2PO_4^- + H^+$
$pK_a = 2.14$

$H_2PO_4^- \rightleftharpoons HPO_4^{2-} + H^+$
$pK_a = 6.86$

$HPO_4^{2-} \rightleftharpoons PO_4^{3-} + H^+$
$pK_a = 12.4$

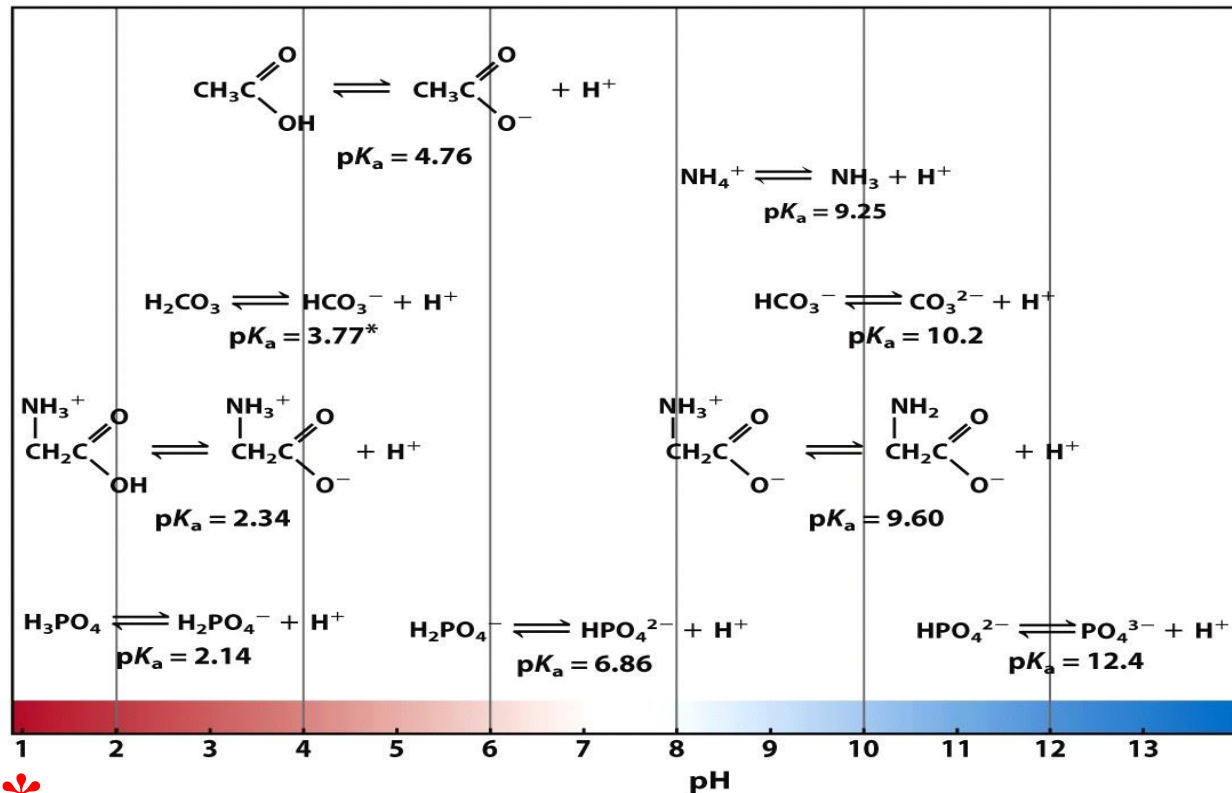pH: 1 2 3 4 5 6 7 8 9 10 11 12 13

Figure 2-15 *****
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Conjugate acid-base pairs consist of a proton donor and a proton acceptor

Dissociation of weak acids and bases: example

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

$0.1 - x$ x x

- **We assume that the only source of H^+ is the weak acid**
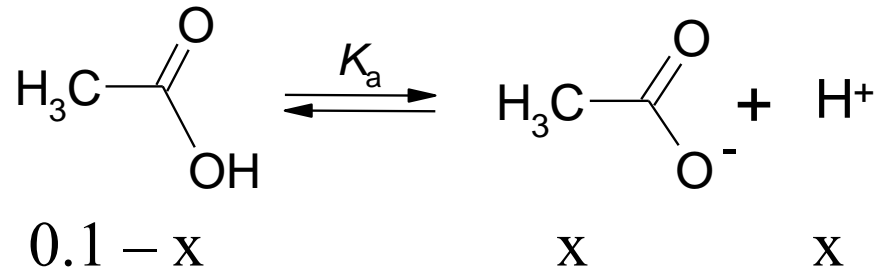
$$K_a = \frac{[x][x]}{[0.1 - x]} = 1.74 \cdot 10^{-5} \, M$$

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

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

- **To find the $[H^+]$, a quadratic equation must be solved.**

x = 0.001310,   pH = 2.883

Dissociation of weak acids and bases: simplification

$$0.1 - x \qquad\qquad x \qquad\qquad x$$

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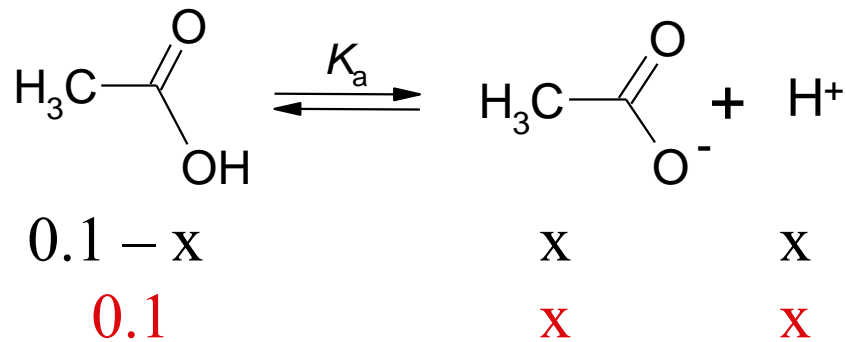
$$K_a = \frac{[x][x]}{[0.1]} = 1.74 \cdot 10^{-5}\,M$$

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

x = 0.00132, pH = 2.880

(<<0.1)

- **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 << [Total Acid]**

$$HA + NaOH \rightarrow Na^+A^- + H_2O$$
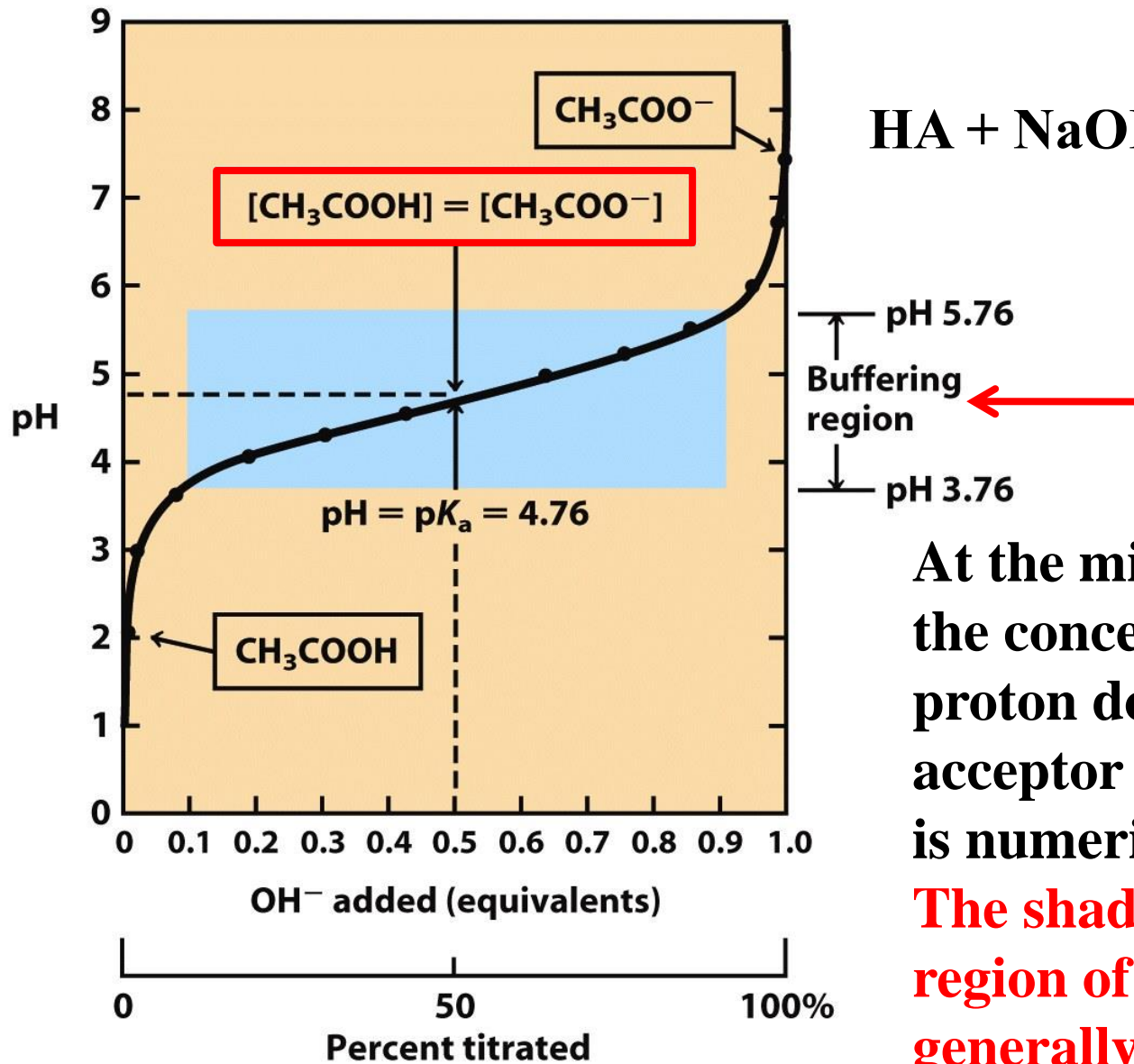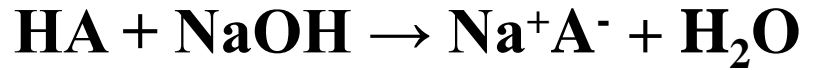
At the midpoint of the titration, the concentrations of the proton donor and proton acceptor are equal, and the pH is numerically equal to the pK_a. The shaded zone is the useful region of buffering power, generally between 10% and 90% titration of the weak acid.
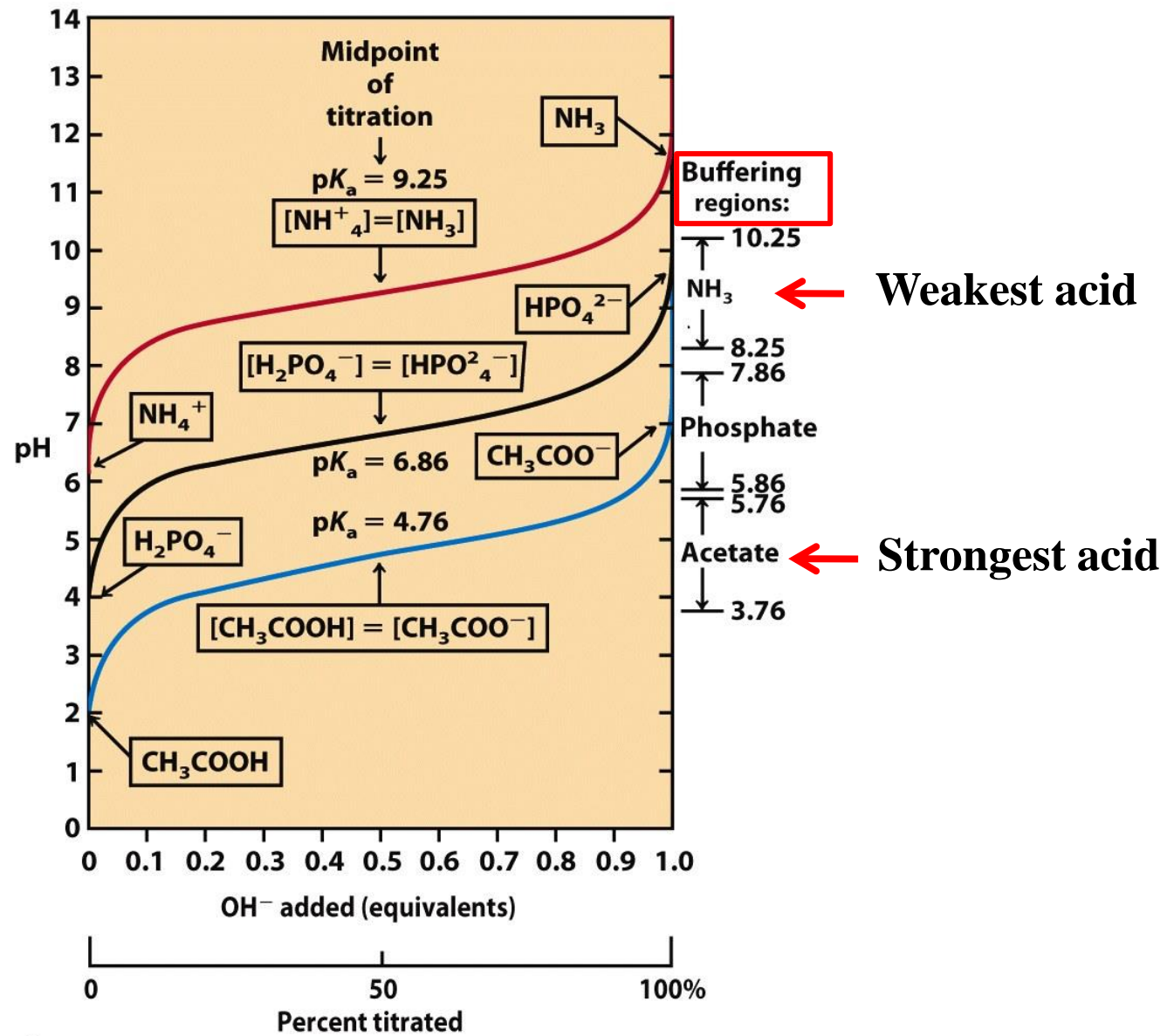
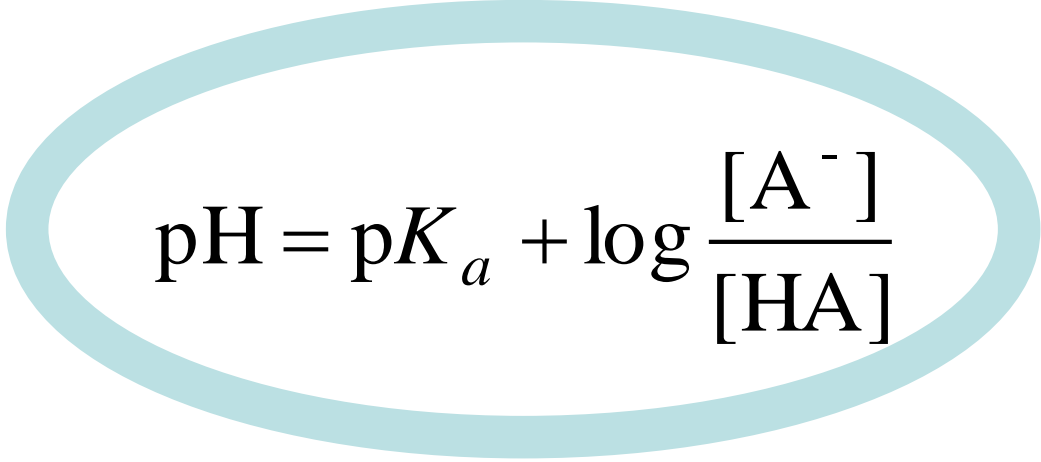The titration curve of acetic acid

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Comparison of the titration curves of three weak acids

Henderson–Hasselbalch Equation

$$HA \rightleftharpoons H^+ + A^-$$

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

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

The equation relates the pH of a solution of a weak acid and its salt to the relative concentrations of the acid and its salt

Relationship between pH and p*K*a

Consider the case of acetic acid ($pK_a = 4.76$).
Substitute this value for pK_a into the equation,
and calculate the pH when the salt (sodium
acetate) and the free acid are combined
in the ratios of 1/100, 1/10, 1/1, 10/1, and 100/1.
When the salt and acid concentrations differ
by an order of magnitude, what is the relationship
between the pH and the pK_a ? When they differ
two orders of magnitude? When the ratio is 1:1?

Relationship between pH and pK_a

Ratio	pH
1/100	2.76
1/10	3.76
1/1	4.76
10/1	5.76
100/1	6.76

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

$pK_a = 4.76$

7. Buffers are mixtures of weak acids and their conjugate bases

- **Buffer is a solution of a weak acid and its conjugate base that resists changes in pH upon addition of either strong acid or strong base**

- **Buffering capacity of acid/base system is maximal at pH = pK_a**

- **Buffering capacity is lost when the pH differs from pK_a by more than 1 pH unit**

- **Buffering action is the consequence of two reversible reactions taking place simultaneously and reaching their points of equilibrium as governed by their equilibrium constants, K_w and K_a**
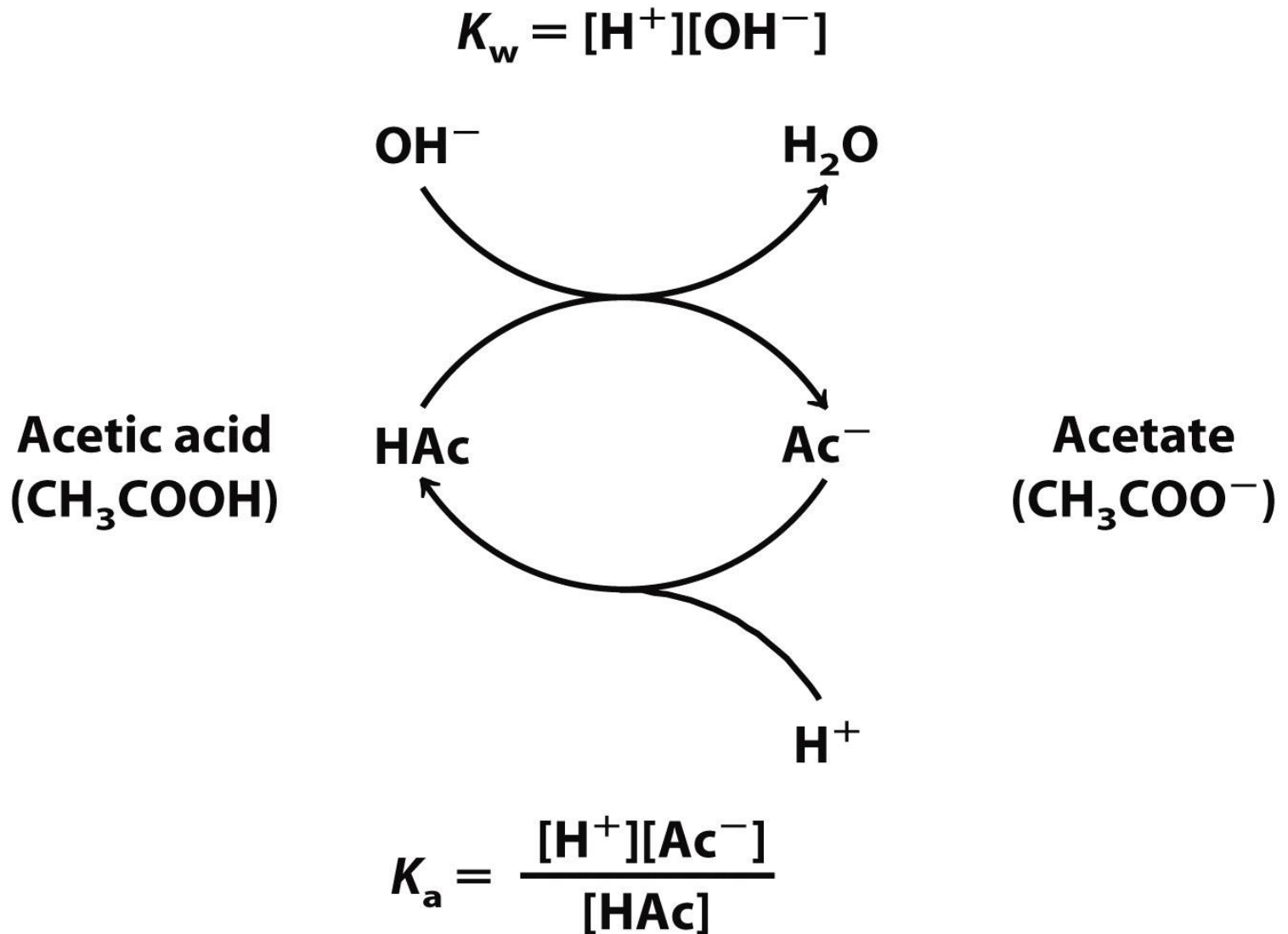
$$K_w = [H^+][OH^-]$$

$$OH^- \qquad H_2O$$

Acetic acid   HAc   Ac$^-$ **Acetate**
(CH$_3$COOH)   **(CH$_3$COO$^-$)**

$$H^+$$

$$K_a = \frac{[H^+][Ac^-]}{[HAc]}$$

Figure 2-18
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The acetic acid–acetate pair as a buffer system

Biological buffer systems

- **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 ($H_2PO_4^-$ / HPO_4^{2-}), acts in the cytoplasm**
  - **Bicarbonate (H_2CO_3 /HCO_3^-), important for blood plasma (pH 7.35-7.45)**
  - **histidine, efficient buffer at neutral pH**

- **Buffer systems *in vitro* are often based on sulfonic acids of cyclic amines**
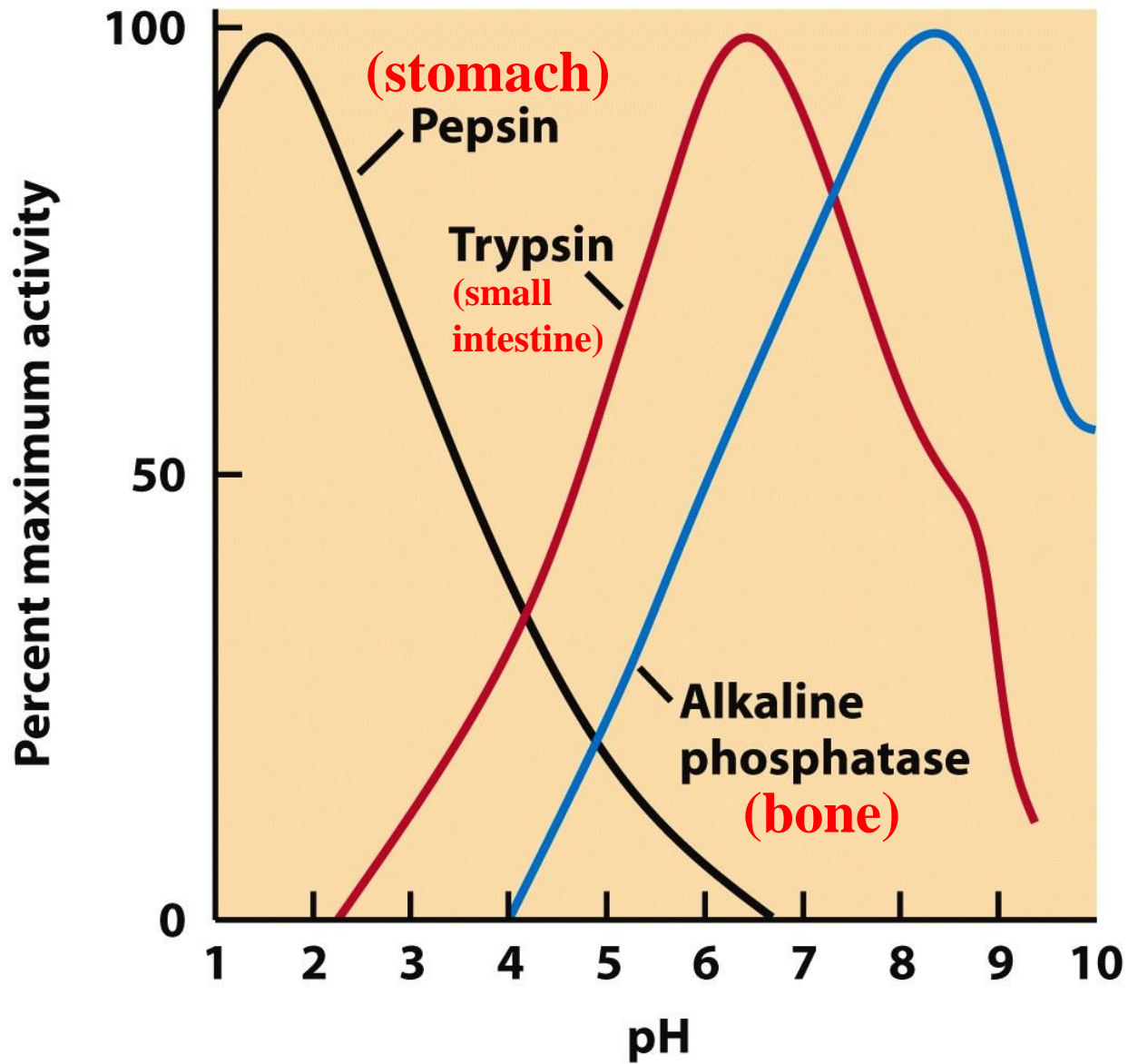 - **HEPES**
  - **PIPES**
  - **CHES**
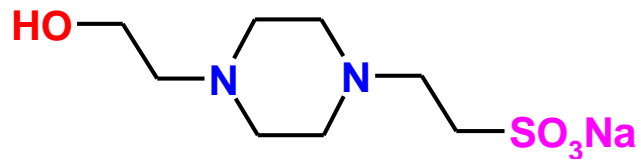
Figure 2-21
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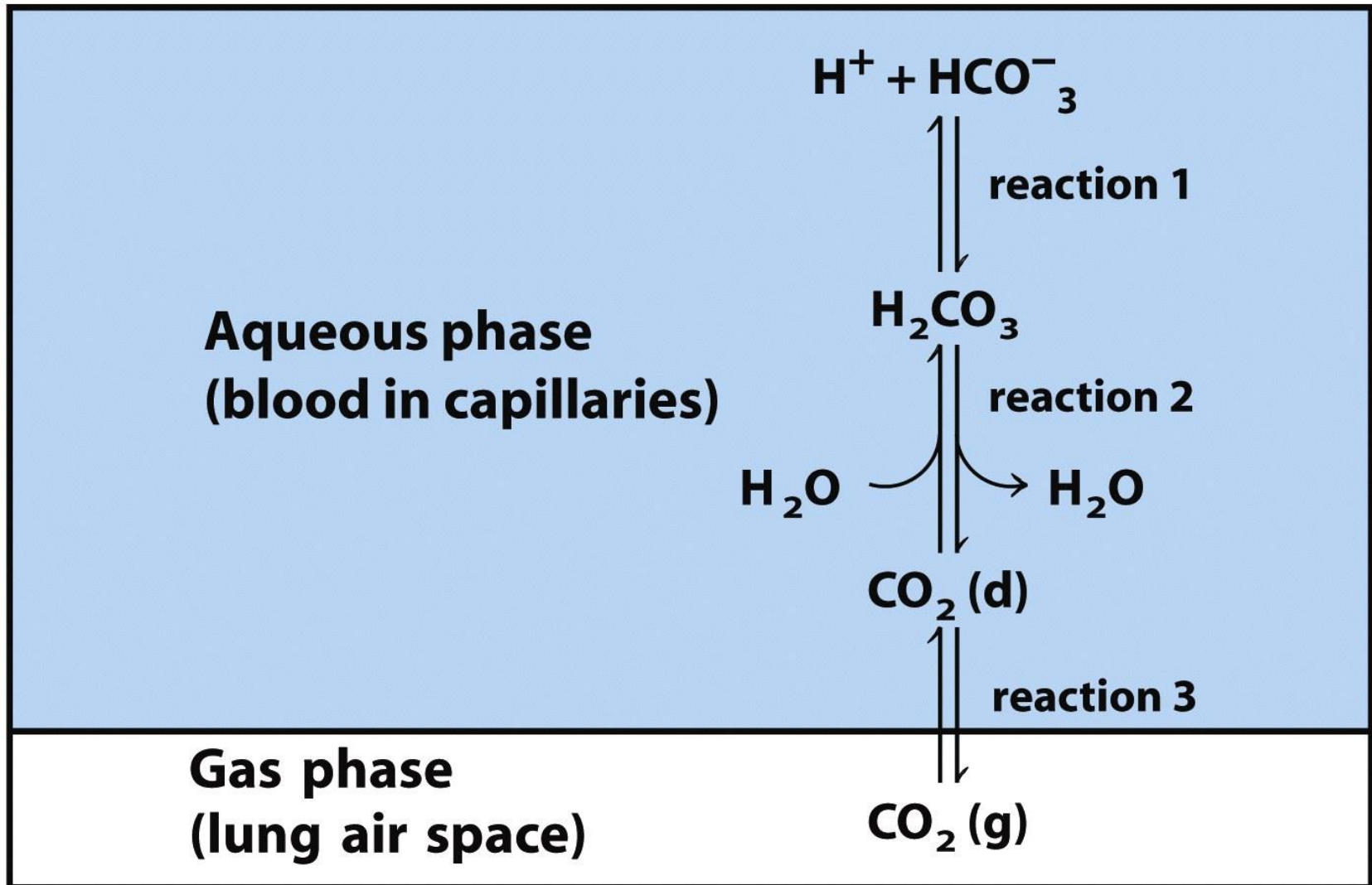
The pH optima of some enzymes

Figure 2-20
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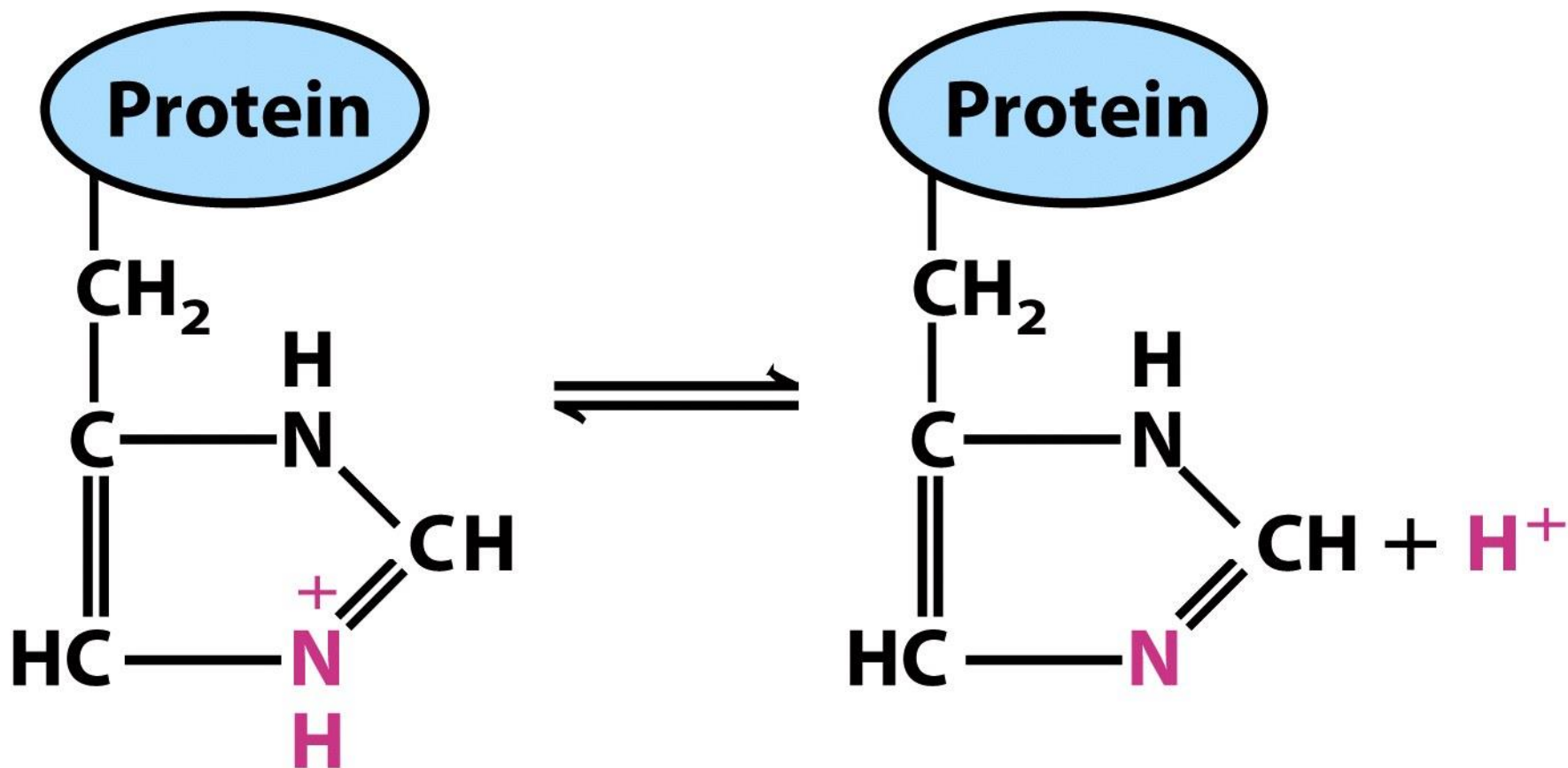© 2008 W. H. Freeman and Company

The bicarbonate buffer system

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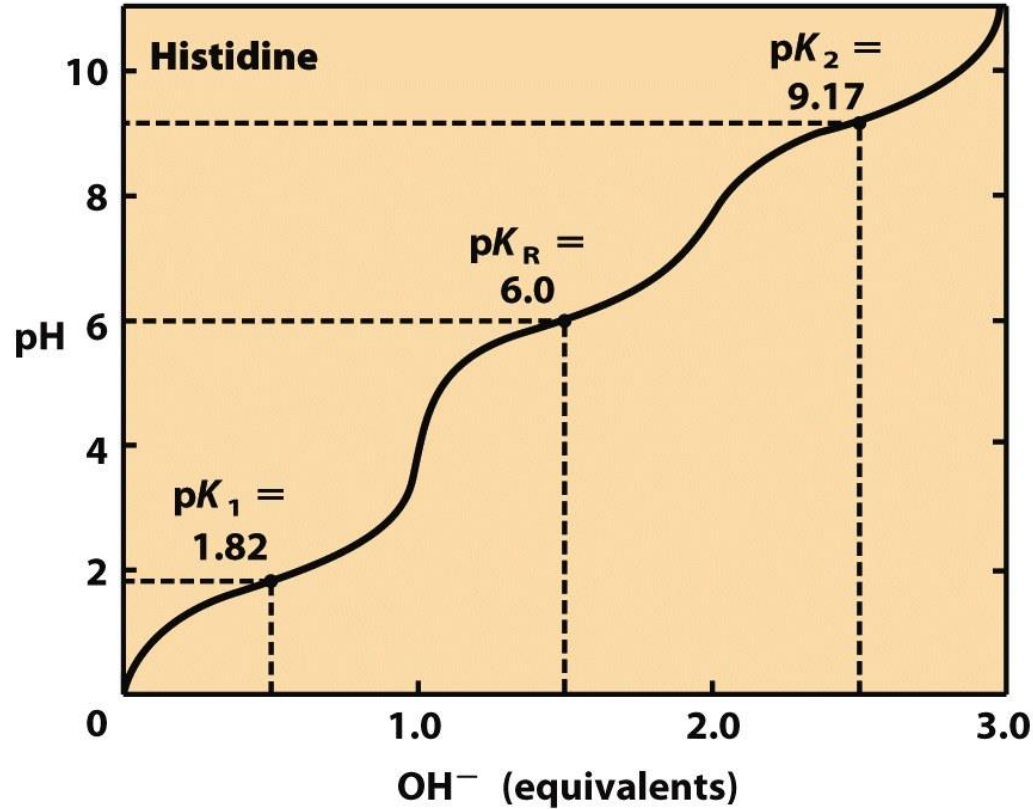The pK_a of the protonated nitrogen of the side chain of histidine is 6.0
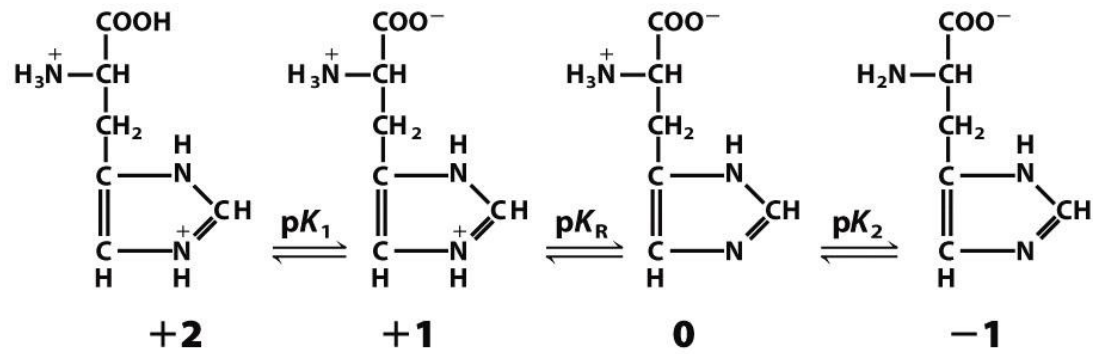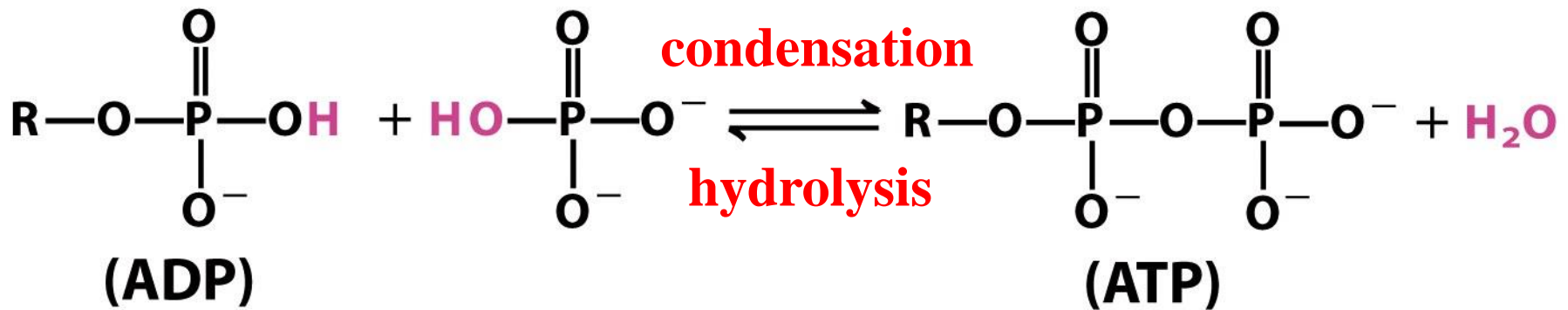
Figure 3-12b
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Titration curve for histidine

condensation

hydrolysis

(ADP)

(ATP)

Phosphoanhydride

Figure 2-22
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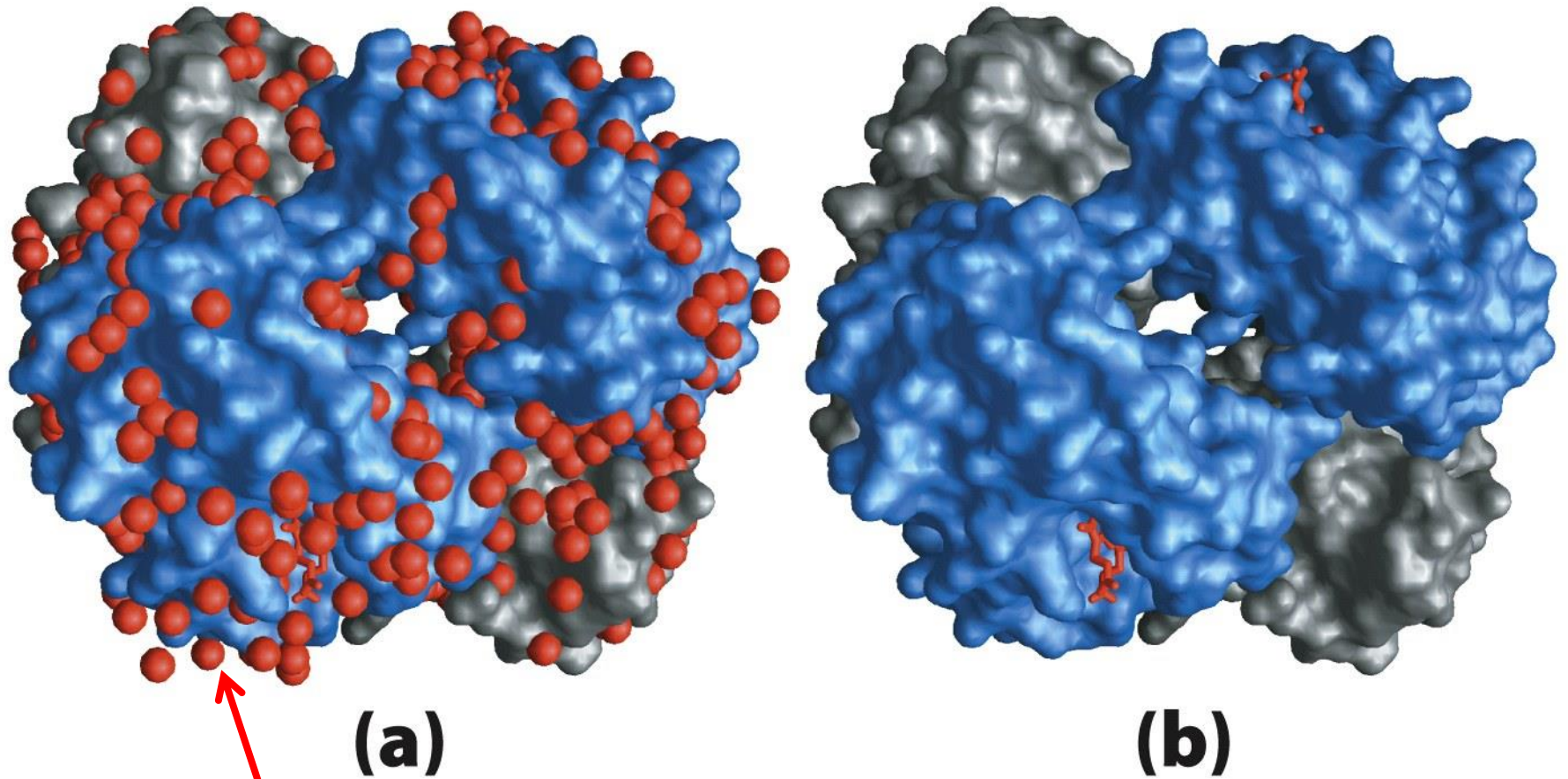**Participation of water as a reactant in biological reactions**

Figure 2-9
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These water molecules are so firmly bound to hemoglobin
that they affect the x-ray diffraction pattern
as though they were fixed parts of the crystal.
Water bound to proteins is essential for their function.

Keywords

- **Hydrogen bond**
- **Hydrophobic interaction**
- **pH**
- **pK_a**

Words of the week

- **hydrophobic vs. hydrophilic**
- **acid vs. base**
- **donor vs. acceptor**
- **solute, solvent, solution**

(A solute is dissolved in a solvent, resulting in a solution.)

Summary

- Water is the medium for life.

- Weak, noncovalent interactions are crucial for the structure and function of DNA, RNA and proteins.

- pH = -log[H^+]. It provides a standard way to measure the H^+ concentration in an aqueous solution.

- pK_a is an integral property of an ionizable group. It is the extent of ionization of an ionizable group that varies with the pH of the solution.

- The Henderson–Hasselbalch Equation relates the pH of a solution of a weak acid and its salt to the relative concentrations of the acid and the salt.

- Buffer is a solution of a weak acid and its conjugate base that resists pH changes in biological systems.