CHAPTER

2 Molecular Interactions

Teaching Summary

This chapter reviews basic chemistry and biochemistry. There are many “Review” and “Essentials” boxes that provide a quick visual summary/review of chemical principles. Here are some ideas for teaching this chapter:

- For the material in this book, focus on *solutions* and *solutes* and *molecular interactions.* There are some worked examples on solutions that would make good classroom activities. *See* Fig. 2.7.
- Students need to be comfortable with the concept of ions in order to succeed in physiology.
- Review logarithms and pH.
- Discuss acids, bases, and buffers.
- Address the distinctions between the classes of biomolecules.

► Many students have a phobia about chemistry. Emphasize the relationship between chemistry and nutrition and digestion. Point out how the physical characteristics of water can be related to biology: surface tension of water in lungs; specific heat of water: captures and stores heat; important in temperature control of human body.

► Before you begin the chapter, have your students take the Chemistry Review Quiz found in the end-of-chapter materials. This will help you and your students understand their proficiencies and deficiencies with the material in this chapter.

Student Learning Outcomes

When students complete this chapter, they should be able to:

LO 2.1 Compare and contrast the composition, structure, and functions of the four major groups of biomolecules.

LO 2.2 Describe four important biological roles of electrons.

LO 2.3 Describe and compare the different types of covalent and noncovalent bonds.

LO 2.4 Contrast the structure and solubility of polar and nonpolar molecules.

LO 2.5 Describe the covalent and noncovalent interactions that contribute to molecular shape, and explain how molecular shape is related to molecular function.

LO 2.6 Define pH in words and mathematically, and explain the differences between acids, bases, and buffers.

LO 2.7 List seven important functions of soluble proteins in the body.

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LO 2.8 Explain the meanings of affinity, specificity, saturation, and competition in protein-ligand binding.

LO 2.9 Explain the different methods by which modulators alter protein binding or protein activity.

What's New?

- Changed "beta-pleated sheet" terminology to beta-strand
- Added phosphorylation/dephosphorylation
- Updated information on chromium supplements
- Expanded discussion of proteins

Teaching Outline

Molecules and Bonds

Most Biomolecules Contain Carbon, Hydrogen, and Oxygen

Figs. 2.1 (**Review: Lipids**), 2.2 (**Review: Carbohydrates**), 2.3 (**Review: Proteins**), 2.4 (**Review: Nucleic Acids**); Table 2.1

Key Words: organic molecules, biomolecules, conjugated proteins, lipoproteins, glycoproteins, glycolipids, polymers, functional groups

Electrons Have Four Important Biological Roles

Fig. 2.5 (**Review: Atoms and Molecules**); Table 2.2

Key Words: covalent bonds, ions, high-energy electrons, free radicals

Covalent Bonds between Atoms Create Molecules

Fig. 2.6 (**Review: Molecular Bonds**)

Key Words: covalent bonds, double bond

Polar and Nonpolar Molecules

Key Words: polar molecule, nonpolar molecule

Noncovalent Bonds Facilitate Reversible Interactions

Ionic Bonds

Fig. 2.6c

Key Words: anions, cations, ionic bonds

► Use the running problem to show students why they need to know about ions. Another example is that we take iron in vitamin pills but we don't eat rust. Can they think of other examples?

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- ► Use different colors of modeling clay to construct atoms. Draw circles on paper to represent the electron shells. Allow students to combine atoms into simple molecules to demonstrate how atoms gain, lose, or share electrons to form different types of bonds.

Hydrogen Bonds

Fig. 2.6d

Key Words: hydrogen bond, surface tension

- ► In describing surface tension, use the example of bugs that are able to walk on the surface of the water. On the surface of a fluid with surface tension, spherical objects distribute their force more evenly and are supported by the tension of the fluid surface. Consequently, the tips of water-walking insects' legs are shaped like spheres. A nice description of surface tension can be found in the textbook *Physics*, by Douglas C. Giancoli (Pearson).
- ► Challenge your students to float a steel needle on the surface of water. Then have them try to float the needle on water to which detergent (a surfactant) has been added.

Van der Waals Forces

Key Word: Van der Waals forces

Noncovalent Interactions

Hydrophilic Interactions Create Biological Solutions

Fig. 2.7 (**Review: Solutions**), Fig. 2.8 (**Review: Molecular Interactions**)

Key Words: solubility, hydrophilic, hydrophobic

- ► Give students chemical formulas and have them calculate molecular mass and gram molecular mass for common molecules such as water, CO_2, and glucose ($C_6H_{12}O_6$).
- ► *See* Fig. 2.7 **(Review: Solutions)**. Consider walking through the examples in the Review Figure as classroom activity to gauge and reinforce student proficiency with solutions.

Molecular Shape Is Related to Molecular Function

Figs. 2.3, 2.4, 2.5, 2.6b, 2.8c

Key Words: secondary structures, alpha-helix, beta-strands, fibrous proteins, globular proteins, tertiary structure, disulfide bonds

- ► Emphasize that loss of shape may lead to loss of function.

Hydrogen Ions in Solution Can Alter Molecular Shape

Fig. 2.9 (**Review: pH**)

Key Words: acids, bases, buffer

Protein Interactions

Key Words: enzymes, membrane transporters, signal molecules, receptors, binding proteins, immunoglobulins, regulatory proteins, binding site, ligand, substrates

- ► The Human Proteome Organization: www.hupo.org/about-hupo/

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- ► The Swiss Institute of Bioinformatics ExPASy Bioinformatics Resource Portal for proteomics: www.expasy.org/proteomics

Proteins Are Selective About the Molecules They Bind

Fig. 2.10

Key Words: specificity, induced-fit model, molecular complementarity

Protein-Binding Reactions Are Reversible

Key Words: affinity, equilibrium, equilibrium constant (K_{eq}), dissociation

Binding Reactions Obey the Law of Mass Action

Fig. 2.11

Key Word: law of mass action

- ► The Law of Mass Action is part of LeChâtelier's principle, which states that if a system at equilibrium is disturbed by a change in concentration of one of the components or in temperature or pressure, the system will shift until a new equilibrium is reached. All reactions have an equilibrium constant, K:

$$K = \frac{[A]^m \bullet [B]^n}{[C]^p \bullet [D]^q}$$

where m, n, p, and q represent the number of molecules of A, B, C, and D, respectively, in the balanced equation.

- ► The following enzymatic reaction is an important reversible reaction which takes place in the body:

$$\underset{\text{substrates}}{CO_2 + H_2O} \xrightarrow{\text{carbonic anhydrase}} \underset{\text{products}}{H^+ + HCO_3^-}$$

Assume the reaction is at equilibrium. The concentration of H^+ is decreased by some outside force. Once the equilibrium state has been restored according to the Law of Mass Action, what will have happened to the concentrations of the following? (You do not need to know the relative concentrations of the substrates and the products or the equilibrium constant K in order to answer this question.)

CO_2? Decreases.

HCO_3^-? Increases.

H_2O? Decreases; but in the body is present in such excess that this is not significant.

The Dissociation Constant Indicates Affinity

Key Words: dissociation constant (K_d), competitors, agonists

Multiple Factors Affect Protein Binding

Isoforms

Fig. 2.3

Key Word: isoforms

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Activation

Fig. 2.12 (**Essentials: Protein Activation and Inhibition**)

Key Word: cofactor

Modulation

Fig. 2.12; Table 2.3

Key Words: modulator, chemical modulators, antagonists, competitive inhibitors, allosteric modulators, covalent modulators

- Competitive inhibitors may be molecules that bind to the active site without being acted on by the enzyme. In other cases, the competing molecule is a substrate that can be acted on by the enzyme. For example, ethylene glycol, better known as antifreeze, is a poison that kills about 50 people and untold numbers of pets each year. In the body, ethylene glycol is converted to a toxic compound called oxalic acid by the enzyme alcohol dehydrogenase. The treatment for ethylene glycol poisoning is administration of ethanol. Ethanol is also a substrate for alcohol dehydrogenase, so it competes with ethylene glycol for the alcohol dehydrogenase binding site. When ethanol is administered after ingestion of ethylene glycol, it binds to alcohol dehydrogenase in place of ethylene glycol. This blocks the production of oxalic acid and decreases the toxic effects of ethylene glycol ingestion.
- Noncompetitive inhibitors bind to the enzyme at some site other than the active site. They do not affect enzyme-substrate binding but in some other manner inhibit the enzyme from catalyzing the reaction. Some noncompetitive inhibitors act by binding to the inorganic ion cofactors of enzymes.
- Ask the class to brainstorm about what they would do to design a synthetic compound that could mimic the effects of penicillin. *Scientists analyzed the amino acid sequence of the active site of the bacterial enzyme. They also found and sequenced the region of the penicillin molecule that binds to the active site. Using this information, they were able to synthesize chemical analogs (*ana-, *according to* + logos, *proportion), molecules that have the antibiotic activity of penicillin but otherwise are not identical. The development of synthetic penicillin-type antibiotics made the drugs widely available for the treatment of bacterial infections.*

  Another interesting aspect is the development of similar drugs that have differing side effects. Two examples are the antihistamines that do not cross the blood-brain barrier and therefore do not cause drowsiness, and the erythromycin-like drugs that lack the gastrointestinal side effects of erythromycin.
- Calcium ions are another important covalent modulator. Changes in free intracellular calcium concentrations often act as signals by binding to enzymes such as protein kinase C or control proteins such as calmodulin. (*See* Chapter 6.)

Physical Factors

Fig. 2.13a (**Essentials: Factors that Influence Protein Activity**)

Key Word: denature

The Body Regulates the Amount of Protein in Cells

Fig. 2.13b

Key Words: up-regulation, down-regulation

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Reaction Rate Can Reach a Maximum

Fig. 2.13c

Key Word: saturation

Talk the Talk

acetylcholine
acid
acidic
adenine
adenosine diphosphate (ADP)
adenosine triphosphate (ATP)
affinity
agonists
alkaline
allosteric activators
allosteric inhibitors
allosteric modulators
alpha-helix
amino acids
anion
antioxidants
antagonists
aqueous
atomic mass
atomic mass units (amu)
atomic number
atoms
bases
basic
beta-strand
binding proteins
binding site
biomolecules
bonds
buffer
carbohydrates
cations
cellulose
chemical modulators
cofactor
competitive inhibitors
competitors
compounds
concentration
conjugated proteins
covalent bonds
covalent modulators
creatine
cyclic adenosine monophosphate (cyclic AMP, or cAMP)
cytosine
dalton (Da)
deciliter
degrade
denature
deoxyribonucleic acid (DNA)
deoxyribose
dephosphorylation
dextrose
disaccharides
dissociation
dissociation constant (K_d)
disulfide bond
double bond
down-regulation
eicosanoids
electrons
element
enzymes
equilibrium
equilibrium constant (K_{eq})
equivalent
essential amino acids
fatty acids
fibrous proteins
flavin adenine dinucleotide (FAD)
functional groups
gamma-amino butyric acid (GABA)
globular proteins
glucose
glycerol
glycogen
glycolipids
glycoprotein
glycosylated
gram molecular mass
guanine
high-energy electrons
hydrogen
hydrogenated
hydrophilic
hydrophobic
immunoglobulin
induced-fit model
inhibitors
ion
ionic bonds
irreversible antagonists
isoforms
isotopes
ligand
lipids
lipoproteins
membrane transporters
milliequivalent (mEq)
millimoles (mmol)
modulator
molarity
molecular complementarity
molecules
monosaccharides
monounsaturated
neutrons
nicotinamide adenine dinucleotide (NAD)
nitrogenous base
noncovalent interactions
nonpolar molecule
nucleic acids
nucleotide
nucleus
oligopeptide
organic molecules

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peptide
peptide bond
percent solutions
periodic table of the elements
pH
phosphorylation
polar molecules
polymers
polypeptide
polysaccharides
polyunsaturated
primary structure
proteins
proteolytic activation
protons
purines
pyrimidines
quaternary structure
receptors
ribose
ribonucleic acid (RNA)
ring structure
saturation
secondary structure
solubility
solutes
solution
solvents
specificity
starch
steroids
substrates
sulfhydryl group
surface tension
tertiary structure
tetramer
thymine
double helix
transcription factors
triacylglycerols
triglycerides
up-regulation
uracil
van der Waals forces

Running Problem: Chromium Supplements

Here's a brief summary of the research into the clinical relevance of chromium supplementation.

A 2003 meta-analysis found no evidence that chromium supplementation promotes increased lean muscle mass or strength (Nissen and Sharp 2003). However, if students Google chromium, they will still find it promoted on body-building sites.

Most of the clinical research focuses the role of chromium in glucose metabolism, but there is scant current evidence for determining whether clinically relevant chromium deficiency is a real concern for most people. Two meta-analyses done in 2002 and 2007 indicate that chromium has no effect in normal subjects but might improve glucose uptake by cells in diabetic patients (Althuis 2002, Balk *et al.* 2007). A 2006 review by the U.S. Food and Drug Administration reviewed a number of studies and concluded that there was no evidence supporting chromium intake and decreased risk of developing type 2 diabetes (Trumbo and Ellwood 2006).

More recent meta-analyses show a lack of consensus in the research data. For example, Suksomboon *et al*. (2014) found the available evidence suggests chromium supplementation improves glycemic control in patients with diabetes and that chromium monosupplementation might also improve triglycerides and HDL-C levels. However, Landman *et al*. (2014) found the evidence suggests there is no benefit to chromium supplementation (no improvement in glycemic control, no improvement of fasting glucose levels, no clinically relevant effect on body weight) and conclude that chromium should not be part of the treatment protocol for diabetic patients. Both studies suggest future research should focus on long-term effects and safety, and Landman *et al*. suggest more research to identify reliable ways to estimate chromium status in patients in order to identify those who might have a clinical risk of deficiency.

For another recent review article on chromium supplementation, *see*

- Vincent JB. Chromium: Is it essential, pharmacologically relevant, or toxic? *Met Ions Life Sci*. 13: 171–198, 2013. doi: 10.1007/978-94-007-7500-8_6.

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Additional activities you might do with your students:

The amount of chromium in dietary supplements varies. A bottle of chromium picolinate that says 500 µg has 500 µg of chromium and ignores the weight of the picolinate. On the other hand, a tablet of 500 µg chromium chloride has 500 µg of the compound, and therefore has less chromium.

- ► Calculate the weight of chromium in a 500 µg tablet of chromium chloride.
- ► Have students go to a drug store and read the labels on diet supplements (calcium supplements that come in different forms are particularly good). Do you get the same amount of calcium when the weight of the pill is equal?
- ► Another topic for discussion is bioavailability. Even though you may take equal amounts of an element, not all forms are absorbed equally well in the intestine. (Example of Ca^{2+}). In addition, certain foods ingested at the same time may complex with the element and reduce the body's ability to absorb it.

Chromium is only one of several elements that are being investigated for their role in human health. Zinc and selenium are two others that you might have students research.

Zinc is needed for proper functioning of more than 300 different enzymes. *Zinc finger proteins* are DNA-binding proteins in which zinc atoms bind to two amino acids and create loops or fingers. Thyroid and steroid hormone receptors are zinc finger proteins.

Zinc is also touted as improving immune function. Have students look up the use of zinc lozenges for colds. Zinc deficiency causes stunted growth in children, and by one estimate nearly half (about 48%) of the world's population may be zinc-deficient. For more information, see www.zinc.org/health.

Selenium is an element that comes mainly from plant foods. The amount of selenium in a plant depends on its soil uptake. It has been suggested that selenium supplementation may help prevent cancer, and several studies on this topic are underway, including one on prostate cancer being done in the United States. *See* http://ods.od.nih.gov/factsheets/list-all/Selenium.

Focus On: Physiology

1. Which of the molecules below is more likely to dissolve in water: glycerol, amino acid A, or amino acid B? Explain. (Hint: Which molecule(s) is/are polar and which molecule(s) is nonpolar?)

Sickle-cell anemia is caused by the substitution of valine for glutamic acid. One of the amino acids below is valine and the other is glutamic acid. Glutamic acid is hydrophilic and valine is hydrophobic. The change in one amino acid significantly alters the functional property of hemoglobin. Which amino acid is glutamic acid and which is valine?

HO–CH_2–CH–CH_2–OH Glycerol
|
OH

–O H
\ |
C – CH – C – CH_3 Amino acid A
// | |
O +H_3N CH_3

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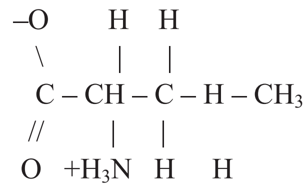

Amino acid B

Glycerol is the most nonpolar and least likely to dissolve. Amino acid A is valine, which has one polar region but nonpolar side chains (–CH_3). This nonpolar region makes valine more hydrophobic than glutamic acid (amino acid B), shown in its ionized form (glutamate).

2. Water striders are insects that literally walk on water. These insects are frequently found living on ponds. If hydrogen bonds did not exist, how would this affect the life of water striders? *The surface tension of water allows the water striders to walk on the surface of ponds. If there were no hydrogen bonds between water molecules, there would be no surface tension and the water striders would sink.*

3. If 100 mL of solution contains 5 grams of NaCl, what is the molarity of the solution in moles/L and in mmoles/L? What percent is this solution? *This solution contains 5 g/100 mL, therefore it is a 5% solution. The molecular mass of NaCl is 58.5 g/mole. One liter of the 5% solution contains 50 g NaCl. 50 g NaCl/L × 1 mole/58.5 g = 0.855 moles/L = 0.855 M or 855 mM.*

4. In an acid-base reaction, $H_2SO_4^{2-}$ ionizes to create two H^+ and one SO_4^{2-}. How many equivalents will one mole of $H_2SO_4^{2-}$ equal? *One mole = 3 equivalents.*

5. Convert 500 mg/dL of glucose to moles per liter. *500 mg = 0.5 g. 0.5 g/100 mL = 5 g/L. 5 g/L × 1 mole/58.5 g = 0.085 mol/L (= 85 mM).*

6. One mole of potassium chloride weighs approximately how many grams?

a. 39 **c.** 74.5
b. 36 **d.** 72

Answer: C

7. One mole of sodium contains the same number of ions as one mole of

a. chloride
b. carbon
c. uranium
d. all of the above
e. none of the above

Answer: D

8. How much does one mole of water weigh? Indicate the proper units. *One mole of water = 18 grams.*

9. What is the weight of 0.5 mole of glucose ($C_6H_{12}O_6$)? *Mol. wt. of glucose = 180 daltons. One mole weighs 180 g, so one-half mole weighs 90 g.*

10. Look at the following molecules. Which molecule is an amino acid? Write the equation (i.e., H_2O) for the molecule represented in b. Which molecule is a carbohydrate?

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a.

```
              NH2
               |
HOCH2 – C – COOH
               |
               H
```

Answer: This is the amino acid

b.

```
                    H   OH
HOOC – CH2 – C – C – COOH
                    |     |
                    C    H
                  /  \\
               HO    O
```

Answer: $C_8H_8O_1$

c.

```
O     H    H   H    H
 \\    |     |     |     |
  C – C – C – C – C – OH
 /     |     |     |     |
H     OH OH OH H
```

Answer: This is a carbohydrate $C_5H_{10}O_5$

Additional Resources

Althuis MD, *et al.* Glucose and insulin responses to dietary chromium supplements: A meta-analysis. *American Journal of Clinical Nutrition* 76(1): 148–155, 2002.

Balk EM, *et al.* Effect of chromium supplementation on glucose metabolism and lipids: A systematic review of randomized controlled trials. *Diabetes Care* 30(8): 2154–2163, 2007 Aug. doi: 10.2337/dc06-0996. This is a meta-analysis that provides an opportunity to discuss the quality of clinical studies.

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