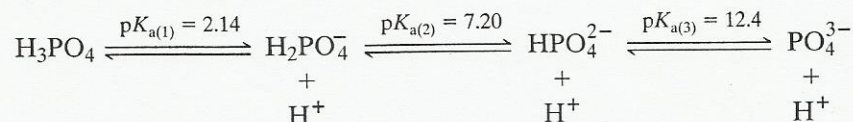


the solution. Acetic acid is relatively weak (there is only slight dissociation), so most acetic acid molecules just prior to titration are in the form of CH_3COOH . The curve changes direction (inflects) at the midpoint. At the inflection point, 0.5 mol of base has been added for each mole of acid present. Here, exactly one-half of the original acid has undergone dissociation so equal amounts of two forms of acetic acid are present: the undissociated form CH_3COOH (50%) and the conjugate base form CH_3COO^- (50%). The pH at this inflection point is equal to the pK_a of acetic acid. (We will show mathematical proof for this statement in the next section.) At the end point (or equivalence point, where 1 mol of base has been added for each mole of acid), equal amounts of acetic acid and sodium hydroxide have reacted, so essentially all molecules of acetic acid are dissociated to the conjugate base $\text{CH}_3\text{COO}^- \text{Na}^+$. The titration experiment is valuable because it reveals the pK_a value as well as the ionic forms of acetic acid present at various pH values.

Polyprotic Acids Our discussion to this point has concentrated on a monoprotic acid, which is an acid molecule with only a single hydrogen atom that can dissociate. Many acids of biochemical importance have two or more acidic protons; that is, they are **polyprotic**. Some of these, listed in Table 2.4, include malic acid, citric acid, carbonic acid, and phosphoric acid. All of the acidic protons on a polyprotic acid do not dissociate at the same pK_a , but are released in sequence at different pK_a values. For example, phosphoric acid has three dissociable protons and, therefore, three pK_a values listed in Table 2.4, one value for each proton. The three-step ionization for phosphoric acid proceeds accordingly:



Note that the conjugate base for the first ionization reaction (H_2PO_4^-) becomes the proton donor (acid) for the second reaction, and so on. Titration curves for polyprotic acids become more complex than those for monoprotic acids, but they are obtained in the same manner and they provide the same useful structural and quantitative information.

Before You Go On . . .

1. Draw the titration curve for each of the following acids. See Table 2.4 for structures and pK_a values. Assume they are titrated with NaOH as in Figure 2.10.
 - a. Malic acid
 - b. Phosphoric acid

The Henderson–Hasselbalch Equation

In the previous section, we were able to use titration data to define the ionic forms of acetic acid present at three pH values: the beginning, midpoint, and the end of the titration. In addition, it was possible to estimate the concentration of each species at the three pH values. With the use of the **Henderson–Hasselbalch equation**, it is possible to calculate the concentration of acid and conjugate base at *all* points of the titration curve. The equation can be derived from the definition for dissociation constant:

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

where HA is the dissociating acid and A^- is the conjugate base of the acid. If one thinks of this equation as containing four unknown but measurable quantities (pH, pK_a , $[\text{A}^-]$, and $[\text{HA}]$), then, if three are determined, the fourth can be calculated.

The Henderson–Hasselbalch equation may be used for many purposes—for calculating $[A^-]$ and $[HA]$ separately, or as a ratio $[A^-]/[HA]$, and for use in preparing laboratory buffer solutions. Note that when $[A^-] = [HA]$ (at the inflection point of the titration curve), the equation becomes

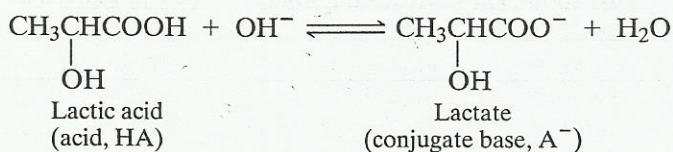
$$\begin{aligned} \text{pH} &= \text{p}K_a + \log 1 \\ \log 1 &= 0 \\ \text{pH} &= \text{p}K_a \end{aligned}$$

When a solution contains equal concentrations of HA and A^- , the pH of that solution is equal to the $\text{p}K_a$ for the acid.

Before You Go On...

1. Lactic acid is present in our muscles after strenuous exercise. What is the value of the ratio $[A^-]/[HA]$ in a solution of lactic acid at a pH of 7.2?

Solution: The titration of lactic acid proceeds as follows:



We need to calculate the ratio $[\text{lactate}]/[\text{lactic acid}]$. From Table 2.4, the $\text{p}K_a$ for lactic acid is 3.86. The Henderson–Hasselbalch equation for lactic acid is

$$\text{pH} = \text{p}K_a + \log([\text{lactate}]/[\text{lactic acid}])$$

Inserting known quantities gives

$$\begin{aligned} 7.2 &= 3.86 + \log([\text{lactate}]/[\text{lactic acid}]) \\ \log([\text{lactate}]/[\text{lactic acid}]) &= 7.2 - 3.86 = 3.34 \\ [\text{lactate}]/[\text{lactic acid}] &= 10^{3.34} = \frac{2188}{1} \end{aligned}$$

In a solution of lactic acid at pH 7.2, there are about 2200 molecules (or moles) of the conjugate base lactate for each molecule (or mole) of lactic acid. Therefore, the solution at pH 7.2 consists of 99.9% lactate and 0.1% lactic acid.

2. What is the pH of a lactic acid solution that contains 60% lactate form and 40% lactic acid undissociated form?

Solution: The ionization of lactic acid proceeds as shown in question 1. The Henderson–Hasselbalch equation becomes

$$\text{pH} = \text{p}K_a + \log(0.60/0.40)$$

The $\text{p}K_a$ for lactic acid is 3.86.

$$\begin{aligned} \text{pH} &= 3.86 + \log(0.60/0.40) \\ \text{pH} &= 3.86 + \log 1.5 \\ \text{pH} &= 3.86 + 0.18 \\ \text{pH} &= 4.04 \end{aligned}$$

Notice from these two examples how the concentration ratio of conjugate base (lactate) to acid (lactic acid) varies with pH.

These examples illustrate two of many applications for the Henderson–Hasselbalch equation. In the next section, we discover yet another practical use of the equation.

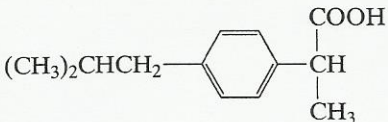
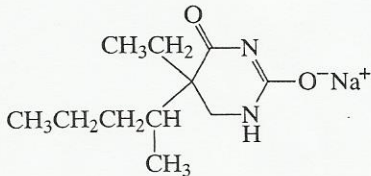
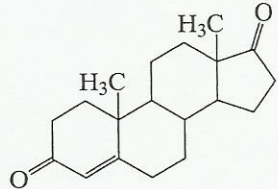
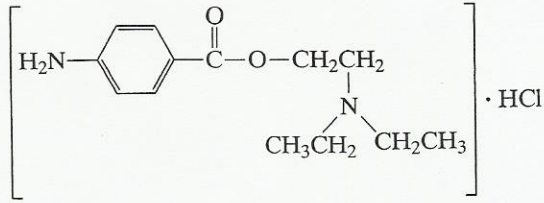
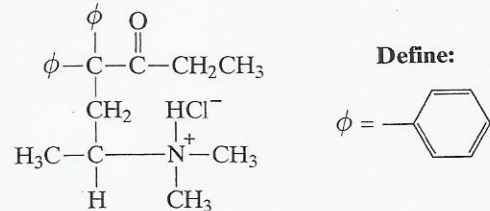
Before You Go On...

1. Write out all of the proton dissociation reactions for carbonic acid, H_2CO_3 . Use Table 2.4 for $\text{p}K_a$ values.
2. What is the ratio of acetate to acetic acid in a solution at a pH of 5.0?

Drug Efficacy Depends on Water Solubility

The study of water solvation, ionization, pH, and equilibrium constants may seem to be theoretical and not of great significance in practical biochemistry. However, it must be recognized that before we can use ingested energy molecules (carbohydrates, proteins, and fatty acids), nutrients, and vitamins, they must be dissolved in the most abundant physiological solvent, water, and distributed throughout the body for metabolism. As we study these important biomolecules throughout this book, we will note that most are water soluble because they contain functional groups that can

Table 2.5
Structures and Actions of Common Drugs

Structure ^a	Name	Use/Action
	Ibuprofen (Advil)	Analgesic, anti-inflammatory agent, relief of pain
	Sodium pentobarbital (Nembutal)	Sedative, induces sleep
	4-Androstene-3,17-dione ("andro")	Anabolic steroid, enhances physical performance
	Procaine-HCl (Novocain)	Local anesthetic
	Methadone-HCl	Narcotic analgesic, treatment of opiate addiction

^aNote the number of charged groups and polar functional groups in the molecules. These groups enhance solubility in body fluids. Three of the drugs are marketed and administered as the salts shown here.

ionize (carboxyl and amino) to form highly soluble, charged salts and/or they have functional groups that are polar and can be hydrated. Polar functional groups include hydroxyl, carbonyl, amino, and amide groups.

The same kinds of chemical characteristics must be present in pharmaceutical compounds that are used to treat abnormal medical conditions. In order for an administered drug to be effective, it must dissolve in aqueous body fluids and be transported to its target organs or cells. Therefore, not only must drugs be designed with chemical functional groups that treat the malady, but they must also have chemical structures that lead to water solubility and the ability to be transported across cell membranes.

The chemical structures of several widely used drugs (legal and illicit) are shown in Table 2.5. Although the structures are complex, it is still possible to identify functional groups that enhance water solubility. Note that some have polar functional groups that can hydrogen bond and be solvated with water.

Some compounds have functional groups that can ionize to form charged salts. Many drugs have basic amino groups that react with HCl and other acids. This leads to a positively charged salt that can easily dissolve in body fluids such as blood plasma or cerebrospinal fluid. The pK_a of these amino groups is about 10, so they would be protonated and positively charged in blood plasma (pH about 7.4) and in the stomach (pH about 1–2). Carboxyl groups in drugs may be converted to soluble, negatively charged groups by reaction with NaOH and other bases. The pK_a of these carboxyl groups is about 4, so they would be ionized in blood plasma but not in the stomach. Some of the drugs shown in Table 2.5 are sold and administered as water-soluble salts. These include sodium pentobarbital, procaine hydrochloride, and methadone hydrochloride. The presence of hydrophobic groups (carbon skeletons and phenyl rings) assists in transport of the molecules across cell membranes (Chapter 9).

2.4

Buffer Systems

Learning Objective

Be able to describe how buffers function to maintain a constant physiological pH.

Maintaining a Constant pH

The hydrogen ion concentration of intracellular and extracellular fluids must be maintained within very narrow limits. A pH change in blood plasma of ± 0.2 to ± 0.4 may result in serious damage to an organism or even death. A constant pH ensures that acidic and basic biomolecules are in the correct ionic state for proper functioning. This is especially critical for enzymes and other proteins (Section 5.2) that are sensitive to pH changes. Metabolic reactions generate high concentrations of organic acids that would change fluid pH values if buffering agents were not present. Consider the following experiment. If 1.0 mL of 10 M HCl is added to 1.0 L of 0.15 M NaCl solution at pH 7.0, the pH would tumble to pH 2.0. If 1.0 mL of 10 M HCl is added to 1 L of blood plasma, the pH would fall only from pH 7.4 to pH 7.2. There is nothing magical about blood. Its ability to maintain a constant pH is due to a heterogeneous mixture of biomolecules that can act to neutralize added acids and bases. Blood and other biological fluids contain **buffer systems**: reagents that resist changes in pH when H^+ or OH^- are added. Chemically, buffer systems contain acid–base conjugate pairs. (See Window on Biochemistry 2-1.)

Effective Buffering Range

The titration curve for acetic acid (see Figure 2.10) displays a region in which the pH changes little with addition of OH^- . The center of this region is an inflection point that coincides with the pK_a of the titrated acid. The acetic acid solution at that

point (0.5 mol OH⁻ per mol of acetic acid; pH = 4.76) shows the smallest change in pH and represents the most effective buffering range for the acetic acid–acetate conjugate pair. Remember that at this point there is an equal concentration of acetic acid (50%) and acetate (50%). The solution has a large amount of acetic acid to react with and neutralize added base *and* a large amount of acetate (base) to react with and neutralize added acid. Therefore, the solution is buffered or protected against pH changes caused by added acids or bases. In general, an acid–base conjugate pair is most effective as a buffer system at a pH equal to its pK_a. The **effective buffering range** for an acid–base conjugate pair can be estimated:

$$\text{effective buffering range (pH)} = \text{pK}_a \pm 1$$

Acetic acid–acetate is an effective buffer in the pH range of 3.76–5.76. Phosphoric acid is an effective buffer in three pH ranges: (1) pH = 1.14–3.14, (2) pH = 6.20–8.20, and (3) pH = 11.40–13.40.

Laboratory Buffers

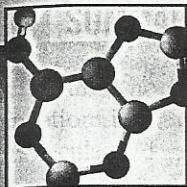
Biochemical processes that occur in cells and tissues depend on the strict regulation of the hydrogen ion concentration provided by natural buffers. When *in vitro* studies are done in the laboratory, artificial, buffered media are used to mimic the cell's natural environment. When cell components are isolated by using cell homogenates (see Window on Biochemistry 1-2), the constituent biomolecules are most stable when maintained in the natural pH range, which is usually 6–8. Sodium and potassium salts of phosphoric acid are among the most widely used buffers in biochemical research. The phosphate acid–base conjugate pair, H₃PO₄–HPO₄²⁻, has a pK of about 7.2, which provides a useful pH range of 6.2–8.2 (see Table 2.4). Because phosphate is a normal constituent of the cell, its presence provides a natural environment. Other natural buffering agents that may be used in the laboratory include the acid–base conjugate pairs of acetic acid, citric acid, carbonic acid, and others listed in Table 2.4.

Sometimes natural buffers like phosphate and citrate interfere with laboratory *in vitro* studies and it is necessary to use synthetic buffers. N. E. Good at Michigan State University synthesized and tested several acid salts that are now widely used as buffering agents (Table 2.6). The use of the synthetic buffer tris(hydroxymethyl)aminomethane (TRIS) is now probably greater than that of phosphate salts.

Table 2.6
Some synthetic buffers

Name (Abbreviation)	pK _a	Useful pH Range	Ionization Reaction ^a
<i>N</i> -(2-Acetamido)-2-aminoethanesulfonic acid (ACES)	6.9	6.4–7.4	$\text{H}_2\text{NCOCH}_2\text{NH}_2\text{CH}_2\text{CH}_2\text{SO}_3^- \rightleftharpoons \text{H}_2\text{NCOCH}_2\text{NHCH}_2\text{CH}_2\text{SO}_3^- + \text{H}^+$
3-(Cyclohexylamino)propanesulfonic acid (CHAPS)	10.5	10.0–11.0	$\text{Cyclohexyl-NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_3^- \rightleftharpoons \text{Cyclohexyl-NHCH}_2\text{CH}_2\text{CH}_2\text{SO}_3^- + \text{H}^+$
<i>N</i> -(2-Hydroxyethyl)piperazine- <i>N'</i> -2-ethanesulfonic acid (HEPES)	7.5	7.0–8.0	$\text{HOCH}_2\text{CH}_2\text{N}^+\text{H}(\text{C}_4\text{H}_8\text{N})\text{NCH}_2\text{CH}_2\text{SO}_3^- \rightleftharpoons \text{HOCH}_2\text{CH}_2\text{N}(\text{C}_4\text{H}_8\text{N})\text{NCH}_2\text{CH}_2\text{SO}_3^- + \text{H}^+$
Tris(hydroxymethyl)aminomethane (TRIS)	8.3	7.5–9.0	$(\text{HOCH}_2)_3\text{CNH}_3^+ \rightleftharpoons (\text{HOCH}_2)_3\text{CNH}_2 + \text{H}^+$

^a Each reaction shows the two predominant forms (acid and base) present in the useful pH range.

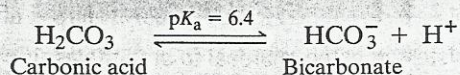


2 - 1

Window on Biochemistry

Buffers in Blood and Other Cellular Fluids

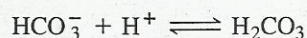
The major buffer system of blood and other extracellular fluids is the **carbonic acid–bicarbonate conjugate pair**:



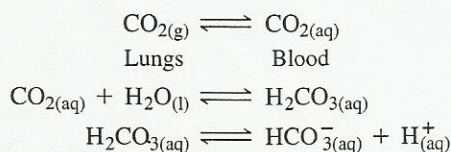
A base added to blood would be neutralized by the following reaction:



The addition of an acidic substance to blood also results in neutralization:



These reactions (see figure) illustrate how blood is protected against pH changes. The actual pH of blood (pH = 7.4) is at the upper limit of the buffering range of carbonic acid–bicarbonate ($6.4 \pm 1 = 5.4\text{--}7.4$) and may not seem as efficient as desired. This inefficiency is remedied by a reserve supply of gaseous CO_2 in the lungs, which can replenish H_2CO_3 in the blood by the following series of equilibrium reactions:



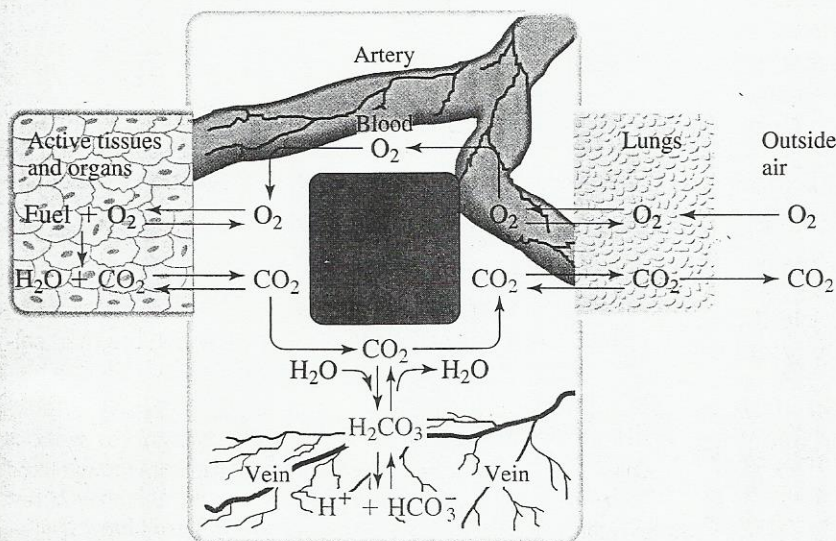
The reactions also work in reverse. A major product of metabolism, H^+ is removed from cells by the blood plasma.

It is neutralized by reaction with HCO_3^- and leads to eventual release of $\text{CO}_{2(g)}$, which is exhaled from the lungs.

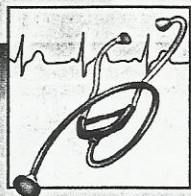
The carbonic acid–bicarbonate conjugate pair is the most important buffer system in biological fluids; however, it is not the only one. A diverse array of amino acids, peptides, and proteins with ionizable functional groups ($-\text{COOH}$ and $-\text{NH}_3^+$) assist in buffering. A major protein constituent of blood, hemoglobin also serves as a buffering agent. Details of the function of hemoglobin are discussed in Chapter 4.

Medical conditions caused by changes in blood pH are **acidosis** and **alkalosis**. An increase in the $[\text{H}^+]$ of blood (acidosis) may have causes that are of metabolic or respiratory origin. Metabolic acidosis occurs in individuals with untreated diabetes or in those on starvation diets or on high-protein, low-fat diets. All of these metabolic conditions lead to **ketosis**, the excessive generation of **ketone bodies**, which are acidic and increase the $[\text{H}^+]$ of blood. Respiratory acidosis is caused by a change in $[\text{CO}_2]$ that is often a symptom of pulmonary problems associated with emphysema or asthma. Untreated acidosis leads to coma and eventually death.

An increase in blood pH (alkalosis) also has metabolic or respiratory origins. Clinical administration of the salts of metabolic acids (sodium lactate or sodium bicarbonate) in excessive amounts or cases of severe vomiting cause metabolic alkalosis. Respiratory alkalosis is induced by hyperventilation (heavy breathing), which may result from hysteria, anxiety, or altitude sickness.



Control of blood pH by the carbonic acid–bicarbonate conjugate pair. There is some CO_2 in arterial blood and some O_2 in venous blood; not all of the CO_2 is exhaled as blood flows through the lungs. CO_2 in the lungs is in equilibrium with CO_2 in the blood. A high concentration of CO_2 in the lungs leads to respiratory acidosis while a low CO_2 concentration causes respiratory alkalosis.



2 - 1

Biochemistry in the Clinic

Aspirin Overdose and Salicylate Poisoning



(© Felicia Martinez/
Photo Edit.)

The first day on your new job as a physician in the emergency department at Riverside County Hospital has been calm—an ankle sprain, a cut finger, and a broken rib—nothing life threatening. Your morning coffee break is interrupted by an ambulance bringing in a mother with her 4-year-old, semiconscious son, Sam. The mother reported what had happened: two hours earlier, Sam had complained of stomachache, had vomited, was hyperactive, began breathing heavily and fast, developed a fever, became drowsy, and finally collapsed. Sam's mother also brought in what she thought had caused the accident, an empty bottle that once contained about 30 orange-flavored, children's aspirin tablets. Careful examination of the patient showed classic aspirin-overdose symptoms—a fever, rapid heart rate, disorientation, and hyperventilation. You know that ingestion of aspirin, acetylsalicylic acid (or any acid), disturbs acid-base balance (see Window on Biochemistry 2-1), so you order measurements of Sam's blood gases, pH, bicarbonate, and salicylate:

	Sam (after 2 hrs)	Normal
Partial pressure of CO ₂	20 mm Hg	35–45 mm Hg
Partial pressure of O ₂	115 mm Hg	75–100 mm Hg
pH	7.45	7.35–7.45
HCO ₃ ⁻	18 mM	24–28 mM
Salicylate	75 mg/100 mL	0 mg/100 mL

While you are awaiting the test results, your medical school lectures on aspirin overdose flash through your mind. Aspirin in the stomach is hydrolyzed by acid and enzymes to salicylate, another acid as strong as aspirin. Salicylate is an uncoupling agent that increases respiration—it enhances oxygen uptake and thus increases the rate of aerobic metabolism (see Section 17.3). The energy from metabolism is not stored and used in the normal way (to make ATP), but is channeled to the production of heat (fever). The hyperventilation initially induces respiratory alkalosis, a rise in blood pH and decline in carbon dioxide. With the increased production of metabolic acids (lactate, pyruvate), the respiratory alkalosis is quickly changed to metabolic acidosis (lower blood pH). The presence of salicylate in Sam's blood confirms your suspicions about aspirin overdose and you begin treatment:

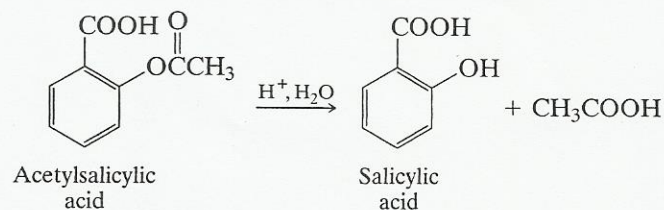
1. Perform a gastric lavage (stomach pumping) with a sodium bicarbonate solution. The basic solution speeds elimination of the acid salicylate in the urine and helps neutralize the metabolic acidosis condition.

2. Administer activated charcoal to bind the aspirin and salicylate and to enhance their elimination before they are absorbed into cells.
3. Use bicarbonate infusion to maintain urine pH above 7.5 to hasten the elimination of the acids.
4. Let Sam rest, but administer fluids (juices, milk, etc.) and assess response to treatment by monitoring changes in metabolic indices (see table). Concentrations of CO₂, O₂, and HCO₃⁻ and pH should move to normal values in about 24 hours.
5. If symptoms do not improve after several hours, use a kidney machine to perform hemodialysis to clear the blood of aspirin and salicylate.

The prognosis (probable outcome) for a patient like Sam is usually very good unless the level of aspirin is very high (above 150–300 mg/kg). For levels below this range, the mortality rates are less than 2%. For levels above the range, the mortality rates can be as high as 25%.

Study Questions

1. Aspirin in the stomach is hydrolyzed under the acidic conditions (pH about 2) to salicylic acid:



- a. Write the reaction for the proton ionization of the carboxyl group in salicylic acid.
- b. Use the Henderson-Hasselbalch equation to calculate the ratio of salicylate to salicylic acid in Sam's stomach (pH about 2.0) and in gastric lavage sodium bicarbonate solution (pH about 8.5). The pK_a for the carboxyl group is about 3.0.
- c. Explain why salicylate is more water soluble than salicylic acid.

References

Cornely, K., 1999. Acute aspirin overdose: Relationship to the blood buffering system. In *Cases in Biochemistry*, pp. 1–2. New Jersey: John Wiley & Sons.

SUMMARY

- Water, a nonlinear, polar molecule, serves at least three functions in the cell: It is an effective solvent, it is a reactive molecule, and it is a temperature buffer. As a solvent, water is able to dissolve biomolecules that are ionic and polar.
- The most important reaction of water is its reversible ionization to generate the hydronium ion (H_3O^+ or the proton, H^+) and the hydroxide ion (OH^-). The extent of ionization is quantified by the pH scale ($\text{pH} = -\log[\text{H}^+]$).
- The strength of an acid is defined by its pK_a , the negative log of its dissociation constant. The pK_a for an acid is equivalent to the pH at which there is an equal concentration of an acid and its conjugate base.
- Blood and other cellular fluids are maintained at a constant pH by natural buffer systems including the carbonic acid–bicarbonate conjugate pair and the hydroxyphosphate–dihydroxyphosphate conjugate pair.

STUDY EXERCISES

Understanding Terms

2.1 Define each of the following terms and give a specific example, if appropriate.

- a. An acid
- b. A base
- c. pH
- d. pK
- e. Henderson–Hasselbalch equation
- f. Noncovalent interactions
- g. A hydrophobic molecule
- h. A hydrogen bond
- i. Hydrophobic interactions
- j. Buffer system
- k. Acid–base conjugate pair
- l. Metabolic acidosis
- m. Micelle
- n. Good buffer
- o. Amphiphilic molecules
- p. Ionization of acids
- q. Molecular recognition

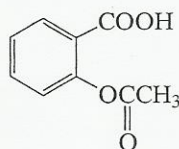
Reviewing Concepts

2.2 Calculate the hydrogen ion concentration $[H^+]$ in each of the following solutions.

- a. Gastric juice, pH = 1.80 d. Tomato juice, pH = 4.3
b. Blood plasma, pH = 7.40 e. Urine, pH = 5.0
c. Cow's milk, pH = 6.6 f. Maple tree sap, pH = 7.1

2.3 The amino acid glycine, $\text{H}_3\text{N}^+\text{CH}_2\text{COO}^-$, has pK_a values of 2.4 and 9.8. Estimate the effective buffer range(s) for glycine.

2.4 Aspirin (acetylsalicylic acid) has the following structure:



- Draw the ionic structure for the predominant form of aspirin as it would exist in blood plasma.
- Draw the ionic structure for the predominant form of aspirin as it would exist in gastric juice.

Hint: The pK_a for aspirin is 3.5.

2.5 Write acid dissociation reactions for each of the following biochemically important molecules. Show the ionization of all acidic protons.

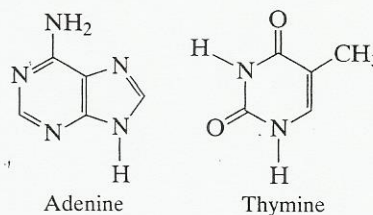
- HCl
- CH_3COOH (acetic acid)
- NH_4^+ (ammonium ion)
- $\text{CH}_3(\text{CH}_2)_{13}\text{CH}_2\text{COOH}$ (palmitic acid)
- $\text{H}_3\text{N}^+-\underset{\text{R}}{\text{CH}}\text{COOH}$ (an amino acid)
- H_3PO_4 (phosphoric acid)
- H_2O
- H_2CO_3 (carbonic acid)

2.6 Arrange the following natural solutions in decreasing order of acidity.

Gastric juice
Blood
Acid rain
Cola
Coffee

Hint: See Figure 2.9.

2.7 The nucleotide bases shown here form hydrogen bonds between the two strands of the double helix of DNA. Circle those atoms that may become involved in hydrogen bonding. Distinguish between acceptor atoms and donor atoms.



2.8 Determine whether each of the statements about noncovalent interactions is true or false. If false, change the statement so it is true.

- Ionic bonds are the result of electrostatic attraction between two ionized functional groups of opposite charge.
- Hydrogen bonds result from interaction of an anion with a hydrogen atom.
- Hydrophobic interactions are electrostatic attractions between nonpolar functional groups and water.
- H^+ and OH^- interact together by ionic bonding to form water.
- Hydrophobic interactions are important in the formation of micelles when the detergent sodium dodecanoate, $\text{CH}_3(\text{CH}_2)_{10}\text{COO}^-\text{Na}^+$, is added to water.

2.9 Identify the type of interaction that holds each of the following atoms or groups of atoms together. Choose from dipole–dipole, ion–ion, or dipole–ion.

- a. NaCl
b. $\text{Na}^+(\text{H}_2\text{O})_n$
c. $\text{CH}_3\text{COO}^-\text{Na}^+$
d. $\text{R}-\text{O}-\text{H}\cdots\underset{\text{H}}{\underset{|}{\text{O}}}-\text{R}$
e. $\text{RNH}_3^+\text{Cl}^-$

2.10 For each pair of molecules listed below, determine which one is more polar than the other.

- a. H_2O , CH_3OH
 b. H_2O , CH_3COOH
 c. $\text{CH}_3(\text{CH}_2)_3\text{CH}_3$, $\text{CH}_3\text{CH}_2\text{OH}$
 d. CH_2CH_2 , $\text{CH}_3\text{CH}_2\text{OH}$
 HO OH
 e. CH_3CNH_2 , $\text{CH}_3\text{C}(=\text{O})\text{NH}_2$
 f. CH_2CH_3 , CH_3CH_3
 NH_2
 g. $\text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}_2$, $\text{CH}_3-\text{C}(=\text{O})-\text{NH}_2$

2.11 What is the molar concentration of the HOH species in pure water?

2.12 Write the molecular formula for the conjugate acid of each of the following bases.

- a. OH^-
 b. HCO_3^-
 c. $\text{H}_3^+\text{NCH}_2\text{COO}^-$
 d. CH_3COO^-
 e. H_2PO_4^-

2.13 For each pair of molecules listed below, determine which one is the less polar (more nonpolar).

- a. CH_3CH_3 , CH_2CH_3
 OH
 b. CH_2CH_3 , H_2O
 OH
 c. $\text{H}_3^+\text{NCHCOO}^-$, $\text{H}_3^+\text{NCHCOO}^-$
 CH_3 CH
 CH_3 CH_3
 d. $\text{CH}_3\text{CH}_2\text{COOH}$, CH_3CHCOOH
 OH
 e. $\text{HOOCCH}_2\text{CH}_2\text{COOH}$, $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$

2.14 Write structures for the conjugate base of each of the following acids.

- a. H_2O
 b. $\text{H}_3^+\text{NCH}_2\text{COOH}$
 c. $\text{CH}_3(\text{CH}_2)_{10}\text{COOH}$
 d. HCO_3^-
 e. $\text{CH}_2(\text{CH}_2)_{10}\text{CH}_2$
 $^+\text{NH}_3$ $^+\text{NH}_3$

Solving Problems

2.15 Identify the type of bonding between each pair of atoms and molecules. In examples with more than one type, name the type of bonding indicated by the arrow.

- a. Na^+Cl^-
 b. $\text{H}-\text{O}-\text{H}$
 c. $\text{H}-\text{O}\cdots\text{H}-\text{O}$
 H H
 d. $\text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}-\text{H}\cdots\text{O}-\text{H}$
 (i) (ii)

Hint: Select from covalent, hydrogen, and ionic bonding.

2.16 Determine whether each of the statements is true or false. If false, rewrite it so it is true.

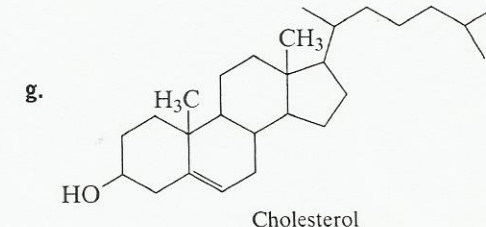
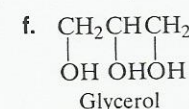
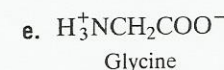
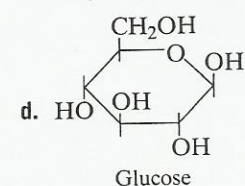
- a. Noncovalent bonds are usually more easily broken than covalent bonds.
 b. The strength of a typical noncovalent bond is usually at least 300 kJ/mol.
 c. Noncovalent interactions often occur between only certain molecules.
 d. Noncovalent bonds reversibly break and re-form at room temperature.

2.17 Define and contrast four types of noncovalent bonds that pair biomolecules for molecular recognition.

2.18 Describe the differences between hydrogen bonds and ionic bonds.

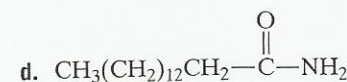
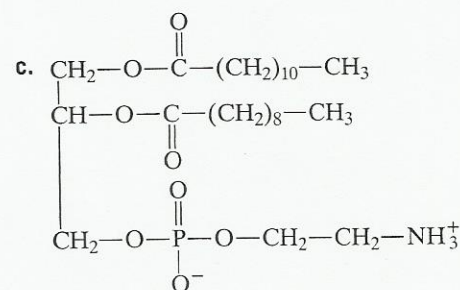
2.19 Predict which of the following compounds are soluble in water.

- a. $\text{CH}_3\text{CH}_2-\text{OH}$
 b. $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2-\text{OH}$
 c. $\text{CH}_3\text{CH}_2\text{COOH}$



2.20 Which of the following molecules will form micelles in water?

- a. $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{NH}_3^+\text{Cl}^-$
 b. $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{COO}^-\text{Na}^+$



Hint: Look for polar head and nonpolar tail.

2.21 You need to prepare a buffer for use at pH 4.0. Which substance would be most effective?

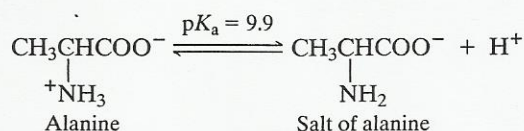
- a. Lactic acid b. Acetic acid c. Phosphoric acid

Hint: Check Table 2.4 for pK_a values.

2.22 The acid-base conjugate pair $H_2CO_3-HCO_3^-$ maintains the pH of blood plasma at 7.4. What is the ratio of bicarbonate to carbonic acid in blood?

2.23 Can you think of a possible emergency room treatment for a patient in a state of acidosis?

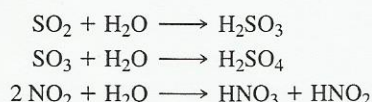
2.24 A buffer solution was prepared by mixing 0.05 mol of the sodium salt of the amino acid alanine with 0.1 mol of free alanine in water. The final volume is 1 L. The equilibrium reaction is



What is the pH of the final solution?

Hint: Use the Henderson-Hasselbalch equation.

2.25 The pH of normal rainwater is approximately 5.6. The slight acidity compared to pure water is caused by dissolved CO_2 . In some regions of the world, the acidity of rain has increased to a pH of approximately 3.5. This is caused by the presence of polluted air containing SO_2 , SO_3 , and NO_2 . These oxides react with rainwater to form acids:



Calculate the ratio of bicarbonate to carbonic acid in normal rainwater and in acid rain (pH = 3.5).

2.26 Excess "stomach acid," a result of our hectic, fast-paced lifestyles, is often treated with antacids. From your knowledge of acid-base chemistry, predict which of the following compounds would be an ingredient in over-the-counter antacids.

- a. $NaHCO_3$ e. $NaAl(OH)_2CO_3$
b. Ascorbic acid (vitamin C) f. Aspirin
c. $Mg(OH)_2$ g. Lemon juice
d. CH_3COOH (acetic acid) h. $CaCO_3$

2.27 The aspirin product Bufferin contains magnesium carbonate, $MgCO_3$. What is the purpose of this ingredient?

2.28 Predict which of the compounds below can form hydrogen bonds with water. Show examples of hydrogen bonding for each one you select.

- a. CH_3CH_2OH d. $H_3N^+-CHCOO^-$
Ethanol |
CH₂
SH
Cysteine
b. $CH_3CH_2CH_3$
Propane
c. $H_2N-C(=O)-NH_2$
O
Urea

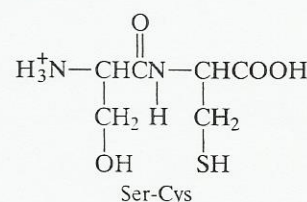
2.29 We will discover in the next chapter that amino acids are di- or triprotic acids. Classify each of the amino acids shown below as a diprotic or a triprotic acid and write all dissociation reactions showing removal of all acidic protons.

- a. $H_3N^+-CHCOOH$ c. $H_3N^+-CHCOOH$
| |
CH₃ (CH₂)₄
Alanine |
NH₃⁺
Lysine
b. $H_3N^+-CHCOOH$ d. $H_3N^+-CHCOOH$
| |
CH₂ CH₂
COOH C=O
Aspartic acid |
NH₂
Asparagine

2.30 Which of the compounds shown below would function as soaps or detergents?

- a. $CH_3(CH_2)_{12}CH_3$
b. $CH_3(CH_2)_9CH_2COO^-K^+$
c. $CH_3(CH_2)_{10}CH_2OH$
d. $CH_3(CH_2)_{10}CH_2OSO_3^-Na^+$

2.31 Shown below is the structure of a dipeptide formed with the amino acids serine and cysteine. Circle all atoms that may become involved in hydrogen bonding with H_2O . Distinguish between those atoms that are hydrogen bond donors and hydrogen bond acceptors.



2.32 What is the numerical value of the ratio $[lactate]/[lactic\ acid]$ in a solution of lactic acid at a pH of 5.0?

Hint: Use the Henderson-Hasselbalch equation: $pH = pK_a + \log([lactate]/[lactic\ acid])$.

2.33 What is the pH of a lactic acid solution that contains 75% lactate form and 25% lactic acid?

2.34 Phosphate buffers are often used in biochemical research because they can be prepared in the physiological pH range of 7 and because phosphates are naturally occurring biomolecules. How many moles of monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$) and dibasic sodium phosphate ($Na_2HPO_4 \cdot 7H_2O$) must be added to a liter of water to prepare a 0.5 M phosphate buffer of pH 7.0?

2.35 When compared to the hydrides of other nonmetallic elements (N, C, S), water has:

- a. The lowest boiling point
b. The lowest freezing point
c. The highest boiling point and the lowest freezing point
d. The highest viscosity

2.36 Which of the following statements about water as a solvent is not true?

- a. Ions in water are solvated by formation of hydration shells.
- b. Uncharged but polar compounds form favorable dipole-dipole interactions with water.
- c. Nonpolar compounds like decane are soluble because water can form a hydration cage around the decane molecules.

2.37 Compare the $[H^+]$ of gastric juice (assume $pH = 1.4$) to that of blood plasma (assume $pH = 7.4$).

- a. The $[H^+]$ of gastric juice is 6 times higher ($7.4 - 1.4$).
- b. The $[H^+]$ of gastric juice is 10^6 times higher.
- c. The $[H^+]$ of blood plasma is 6 times higher than gastric juice.
- d. The $[H^+]$ of blood plasma is 10^6 times higher.

2.38 You prepare a sodium phosphate buffer by mixing 100 mL of 0.1 M Na_2HPO_4 with 100 mL of 0.1 M NaH_2PO_4 . The pH of the final solution is 7.20. What is the pK_a ?

2.39 Which of the following acids would make the most effective buffer at $pH = 6$? See Tables 2.4 and 2.6 for pK_a values and structures.

- a. Acetic acid
- b. Lactic acid
- c. Histidine ($K_a = 9.12 \times 10^{-7} M$)
- d. TRIS ($K_a = 8.08 \times 10^{-9} M$)

2.40 Why are the carboxyl groups in drugs and other compounds ionized in blood plasma but not ionized in the stomach?

Writing Biochemistry

2.41 Your roommate does not have time to read this chapter before the next class exam. She has offered to pay you a handsome reward for writing a brief summary for her to review. Write a 100-word summary of Chapter 2 that contains a review of the most important concepts. Use the chapter summary as a guide, but be creative in your approach and style.

2.42 The Sixty-Second Paper. Your instructor will probably spend about one lecture on this chapter. Immediately after the lecture, use 1–2 minutes to write a paper answering the

following questions: (1) What were the central points outlined in the lecture? (2) What concepts were confusing?

2.43 Although methane and water have similar molecular masses (16 and 18 daltons, respectively), they have quite different properties. Explain why methane is unable to form hydrogen bonds with itself or with other molecules.

2.44 Your roommate, an English major, makes heavy use of antacid tablets especially just before her creative writing papers are due in class. She has asked you to explain how the tablets work to neutralize stomach acid. Write the explanation in a 100-word paragraph.



FURTHER READING

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