

9

Electromotive Force and Oxidation–Reduction

Electrochemical Cells

Electrometric Determination of pH, Specific Ions, and Redox Potentials

In Chapter 6, an electrolytic cell was described in which chemical reactions were produced by passing an electric current through an electrolyte solution. In this chapter, we consider the reverse process, in which an electric current is produced by allowing a chemical reaction to occur. Such an electrochemical reaction depends on the relative abilities of species in solution to be oxidized or reduced, and this in turn will be related to processes occurring at the electrodes, which connect the species in solution to any external circuit. The electrochemical reactions may be used to determine pH, activity coefficients, or the quantity of a specific ion in solution. These determinations involve *potentiometry*, in which there is no significant current flow through the system. The application of this technique to pharmacy will be discussed.

ELECTROCHEMICAL CELLS

Electromotive Force of a Cell. An electrochemical cell normally consists of two *electrodes* immersed in an electrolyte solution, or solutions, that are in contact with each other. The Daniell cell, shown in Figure 9–1, is a typical electrochemical cell. It consists of a zinc electrode in a solution of zinc sulfate in one compartment and a copper electrode in a solution of copper sulfate in the other compartment. The compartments are known as the *half-cells* of the electrochemical cell and are separated by a porous diaphragm that allows electric contact between the solutions but does not permit excessive mixing of the two solutions.

Zinc has a greater tendency to ionize, that is, to lose electrons, than does copper. Therefore, a spontaneous reaction can occur when the two half-cells are connected by an external wire; atoms of the zinc electrode go into solution as Zn^{2+} ions and leave electrons behind on the

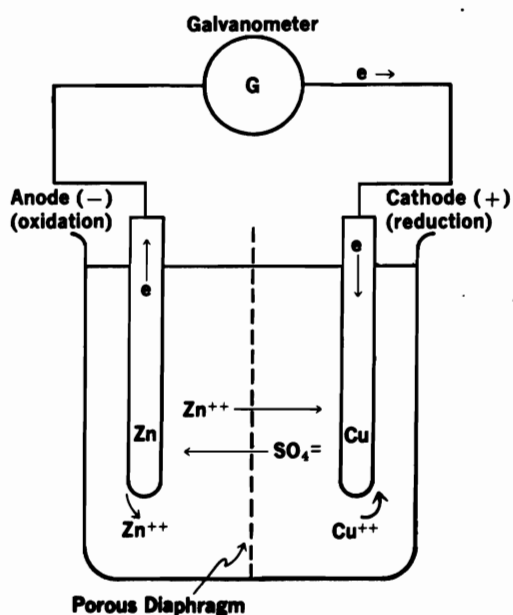


Fig. 9–1. Daniell cell showing oxidation at the anode, reduction at the cathode, and the flow of electrons (e^-) in the external circuit. The Zn^{2+} and SO_4^{2-} ions diffuse through the porous diaphragm in opposite directions to maintain electroneutrality in each half-cell as the reaction proceeds.

electrode. The electrons pass from this negatively charged electrode or *anode* through the external wire to the copper electrode. Here, at the *cathode*, copper ions from the solution take on electrons and deposit copper atoms on the electrode surface. The cathode thus loses electrons to the solution, so that it is considered to be positively charged. This spontaneous reaction corresponds to the oxidation of zinc metal at the zinc electrode while copper ions are being reduced at the copper electrode, which can be expressed in the following *half-reactions*:

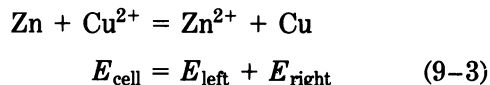
Anode reaction (oxidation)



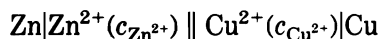
Cathode reaction (reduction)



Each half-reaction represents the change occurring at a single electrode, and the two half-reactions can be added together to express the overall cell reaction:



The individual *electrode potentials* (E_{left} and E_{right}) occur at the junction between each electrode and its surrounding solution. The sum of the two electrode potentials corresponds to E_{cell} , which is the *electromotive force* (emf) or *voltage* of the cell. Note that the term *emf* refers to the voltage of the complete cell, whereas *potential* refers to voltage from an electrode. In accordance with convention, the electrodes of the cell are always written so that *electrons are given up to the external circuit at the left electrode (anode) and accepted from the external circuit at the right electrode (cathode)*. A schematic depiction of the Daniell cell therefore is written as



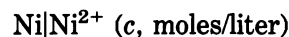
in which a single vertical line represents the junction between two different phases, and the double vertical line indicates a liquid junction, that is, an electric contact between two electrolyte solutions. The concentrations of the different ions in the half-cells (c_{ion}) are also given in the diagram.

The Daniell cell is *reversible*; that is, by applying an external current opposite to and infinitesimally greater than that of the cell, zinc will deposit at the zinc electrode, and copper will go into solution at the copper electrode. An irreversible cell, such as one in which an escape of hydrogen accompanies the chemical reaction, cannot be reversed completely by an infinitesimally greater applied potential. Irreversible cells are not ordinarily used in electrochemical studies, since their operation is not susceptible to thermodynamic treatment. An electrochemical cell, such as the Daniell cell, in which a spontaneous reaction occurs at the electrode surfaces and that can be used to provide electric energy from the chemical reaction occurring within it, is known as a *galvanic cell*.

Types of Electrodes. A number of electrodes of differing types can be constructed, and by combining any two of the electrodes, a variety of cells is obtained. Only a few of the possible types of electrodes that can be made are described here.

Metal–Metal Ion Electrodes. The Daniell cell consists of electrodes of this type. Each electrode is made simply by immersing a metal strip into a solution

containing ions of the metal. For example, a nickel electrode can be represented by



Amalgam Electrodes. A variation of the metal–metal ion electrode replaces the metal strip by a metal amalgam, and this is immersed in a solution containing the metal ion. An advantage of this type of electrode is that active metals such as sodium or potassium that otherwise would react with aqueous solutions can be used as electrodes. A sodium–amalgam electrode is represented by



Metal–Insoluble Salt Electrodes. The calomel (mercurous chloride) electrode and the silver–silver chloride electrode are the most frequently used reference electrodes. Reference electrodes produce an invariant potential that is not affected by changes in solution concentration. They are used with another electrode, usually called the *indicator electrode*, under an infinitesimally small amount of current flow, as described for reversible cells. The measurement of cell potential with a reference electrode will be discussed in a subsequent section.

The calomel electrode (Fig. 9–2) consists of mercury, a paste of mercurous chloride, and a solution of KCl, which provides chloride ions. The electrode is represented by

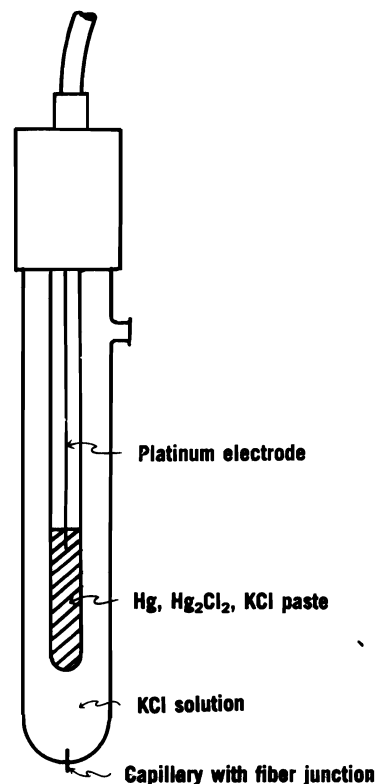
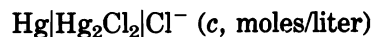
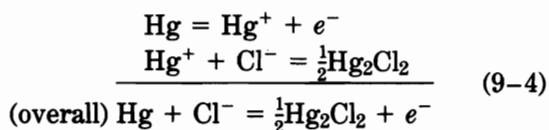
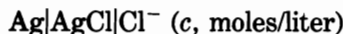


Fig. 9–2. Cross-section of a calomel reference electrode.

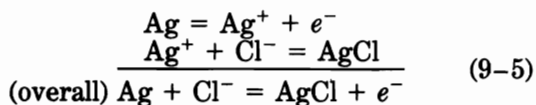
The electrode reaction is



A silver chloride electrode consists of a layer of silver chloride on a silver wire that is immersed in a solution containing chloride ions. This electrode is represented by

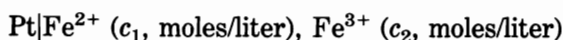


and the electrode process is

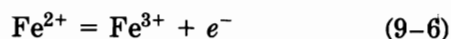


Oxidation-Reduction Electrodes. Although every electrochemical half-cell fundamentally involves an oxidation-reduction reaction, only half-cells containing an inert electrode immersed in a solution consisting of both the oxidized and reduced forms of a substance are called oxidation-reduction electrodes. An advantage of this type of electrode is its ability to function as either a cathode or an anode in a cell. The direction taken by the electrode reaction depends on the potential of the other electrode in the cell.

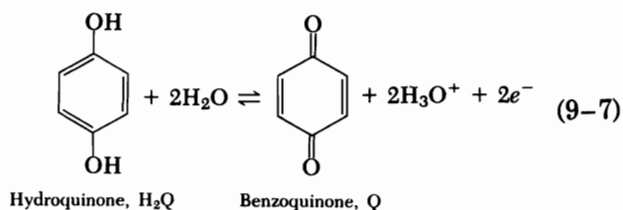
Platinum is the metal most frequently used for inert electrodes. Gold and silver have limited usefulness as inert electrodes since both are soft and since silver, in addition, is prone to oxidation. A platinum wire immersed in a solution containing ferrous and ferric ions is typical of an electrode in this category. The electrode may be abbreviated as



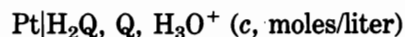
in which the comma designates that both chemical species are in the same solution. The electrode reaction for this half-cell is



Oxidation-reduction electrodes can also be made using organic substances that exist in two different oxidation states. Quinhydrone, an equimolar mixture of benzoquinone, Q, and hydroquinone, H₂Q, which is only slightly soluble in water, are involved in the reversible oxidation-reduction reaction,



Introducing an inert platinum wire produces an oxidation-reduction electrode. The electrode can be written as

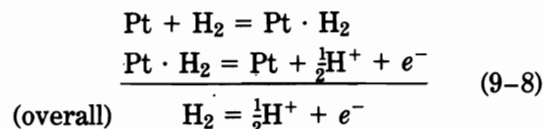


The potential of the quinhydrone electrode varies with the H₃O⁺ concentration according to the electrode reaction just given. Therefore, hydrogen ion activity (i.e., pH), can be monitored with this electrode.

Gas Electrodes. Bubbling a gas over an inert metal wire immersed in a solution containing ions that can be derived from the gas produces a gas electrode. A platinum electrode, normally coated with colloidal platinum black to increase the effective electric surface area and thereby to facilitate the electrode reaction, can be used. For example, the hydrogen electrode,



may have its electrode reaction represented by



Membrane Electrodes. The use of a thin, ion-sensitive glass membrane enclosing an electrolyte solution has produced electrodes that can detect potentials arising at the glass/solution interface. By carefully controlling the composition of the glass or crystalline membrane, the electrode can become particularly sensitive to certain ions in solution. These ion-selective electrodes are discussed more fully in a subsequent section of this chapter. The pH glass electrode is the most common type of membrane electrode. It consists of a platinum wire dipping into a solution of hydrochloric acid. The wire is in contact with an internal reference electrode, usually either a silver-silver chloride or a calomel electrode, which is sealed within the same high-resistance body, as shown in Figure 9-3. The glass membrane in this electrode is responsive to protons and other monovalent ions but relatively unresponsive to divalent cations. By carefully adjusting the three-dimensional arrangement of cations (including Na⁺, Ca²⁺, Li⁺, and Ba²⁺) located in the silicate structure of the glass membrane, the responsiveness of the electrode to monovalent cations other than hydrogen can be controlled. For example, the usual glass pH electrode produces a "sodium error" caused by the responsiveness of most glass membranes to sodium ions at high pH values. This error can be reduced by employing a glass membrane with a high concentration of lithium ions incorporated in the silicate matrix. The glass membrane pH electrode is represented as



In practice, the glass pH electrode must be attached to an external reference electrode to complete the cell. If two glass electrodes are immersed in the same solution and connected to a pH meter, a small potential

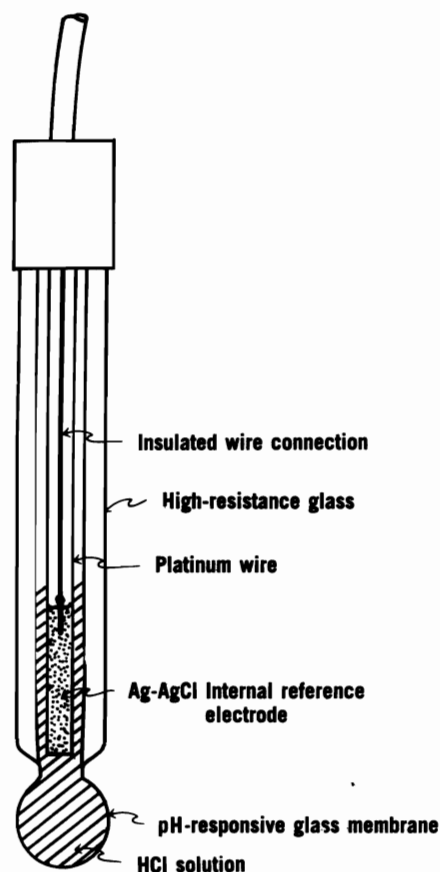


Fig. 9-3. Schematic representation of a typical glass pH electrode.

difference can be noticed between the two electrodes. This is due to slight differences in the properties of the individual glass membranes, and for pH measurement, this individual electrode variation requires standardization of each cell containing a glass electrode against a buffer of known pH.

Membrane electrodes may also be fabricated from cellulose, polyethylene, collodion, or liquid ion-exchange resins that are insoluble in water. Salt crystals may also be used in place of glass as ion-selective membrane electrodes.

Microelectrodes. Recent developments in manufacturing have provided electrodes that are small enough to contact a single cell or neural unit in an intact animal. These microelectrodes typically have metal or glass tips, shaped like tapered needles, with electrode diameters on the order of $1\ \mu\text{m}$ or less. The electrodes are composed of the same electrolyte solutions and materials as previously described in this section; however, the entire electrode is usually about the size of a small hypodermic needle or a micropipette, and normally it can be sterilized and implanted in an animal for pharmacologic studies. The use and properties of microelectrodes are described by Ferris.¹

Measuring the Electromotive Force of Cells. A *voltmeter* draws a measurable amount of current from a circuit; therefore, the voltage determined becomes dependent

on the resistance of the cell to current flow, according to Ohm's law (p. 126), in which $E = IR$. A *potentiometer* measures voltage by opposing the emf of a cell with an applied potential while no current is being drawn through the external circuit. This absence of current flow through the sample cell makes *potentiometry* a useful method for determining the emf of a reversible electrochemical cell. It simply balances one current flow against another without producing changes in potential due to cell resistance. A potentiometer circuit is shown schematically in Figure 9-4. When the key is pressed, an applied current is allowed to flow from the battery (B) through a variable resistor (R) to a galvanometer (G). The variable resistor (R), which is also called a voltage divider, can be adjusted so that the galvanometer, G , shows no current deflection. When this is done, the voltage read on the voltmeter, V , from the applied potential must be equal and exactly opposed to the potential of the cell whose emf is being determined. Thus the potential differences across the points $O-X$ on the resistor (R) must be equal but opposite in sign to the potential of the cell, E_x , when the galvanometer shows no deflection. As long as the galvanometer is balanced quickly by tapping the key (K), current does not flow for an appreciable time while there is a deflection of G , and the emf measured for the cell can be considered a true equilibrium value. This method is sometimes referred to as *null-point potentiometry*.

Thermodynamics of Electrochemical Cells. The work done by an electrochemical cell operating reversibly, $-\Delta G$, equals the electromotive force E multiplied by

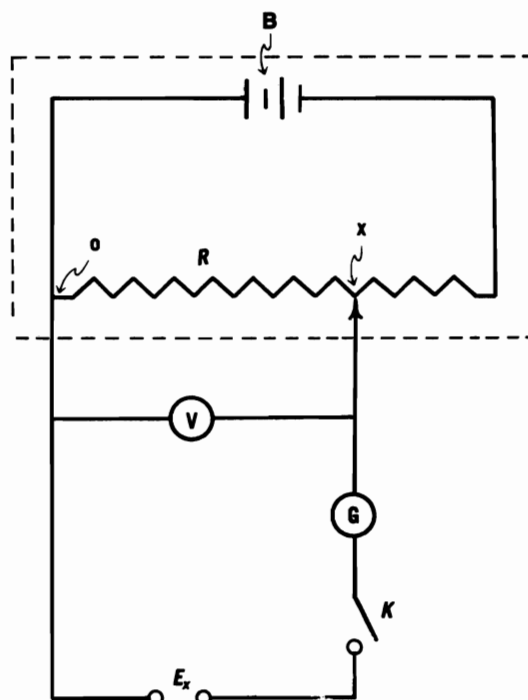


Fig. 9-4. Schematic diagram of a potentiometer. (From R. N. Adams, *J. Pharm. Sci.* 58 (10), 1172, 1969, reproduced with permission of the copyright owner.)

the number of faradays, nF coulombs, of electricity that pass through the cell

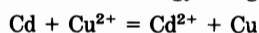
$$-\Delta G = nFE \quad (9-9)$$

When the electromotive force is positive, the process is spontaneous, which accounts for the negative sign. For the reactants and products under standard conditions, one writes

$$\Delta G^\circ = -nFE^\circ \quad (9-10)$$

The faraday, F , is approximately 96,500 coulomb/Eq of ions, and n is the number of equivalents of ions reacting or the number of electrons transferred. E° is the cell emf determined by potentiometry under reversible electrochemical conditions at a fixed temperature and pressure.

Example 9-1. What is the free energy change for the cell reaction



in which $E_{\text{cell}} = +0.750$ volt?

$$\Delta G = -nFE = -2\text{Eq/mole} \times 96,500 \text{ coulomb/Eq} \times 0.750 \text{ volt}$$

$$\Delta G = -144,750 \text{ joule/mole}$$

Equilibrium constants, K , can be obtained from the standard potential using equation (9-10) together with equation (3-115) on page 70.

$$RT \ln K = nFE^\circ$$

or

$$\log K = \frac{nFE^\circ}{2.303RT} \quad (9-11)$$

Example 9-2. The Daniell cell has a standard potential E° of 1.100 volts. What is the value of K at 25° C for the reaction, $\text{Zn} + \text{Cu}^{2+} = \text{Zn}^{2+} + \text{Cu}$, in which the activities of the solid phases, Zn and Cu, are taken as unity?

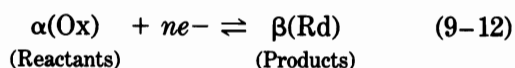
$$\log K = \frac{2 \times 96,500 \text{ coulombs/Eq} \times 1.100 \text{ volt}}{2.303 \times 8.314\text{JK}^{-1} \text{ mole}^{-1} \times 298^\circ \text{K}}$$

$$\log K = 37.2$$

$$K = \frac{a_{\text{Zn}^{2+}}}{a_{\text{Cu}^{2+}}} = 1.6 \times 10^{37}$$

This large value for the equilibrium constant signifies that the chemical reaction in the Daniell cell proceeds essentially to completion.

The Nernst Equation. By convention, any half-cell reaction is written as a reduction, that is, an acceptance of electrons by the reactants to form the products:



in which α moles of the oxidized species (Ox) in the half-cell is reduced by a reaction involving n electrons to β moles of the reduced species (Rd) in the half-cell. The change in free energy for such a half-cell reduction can be expressed, according to equation (3-116) (p. 70), as

$$\Delta G = \Delta G^\circ + RT \ln \frac{a(\text{Rd})^\beta}{a(\text{Ox})^\alpha} \quad (9-13)$$

in which $a(\text{Rd})$ signifies some arbitrary activity of the products and $a(\text{Ox})$ some arbitrary activity of the reactants. Following the law of mass action (p. 144), each term is raised to a power equal to the number of moles β of products or α of reactants. Now, $-nFE$ and $-nFE^\circ$ can be substituted into equation (9-13) for ΔG and ΔG° giving

$$-nFE = -nFE^\circ + RT \ln \frac{a(\text{Rd})^\beta}{a(\text{Ox})^\alpha}$$

and

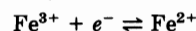
$$E = E^\circ - \frac{RT}{nF} \ln \frac{a(\text{Rd})^\beta}{a(\text{Ox})^\alpha} \quad (9-14)$$

Equation (9-14) is known as the *Nernst equation*. E° is the standard potential, that is, the emf when the activities of all reactants and products are unity, and is normally expressed for reductions, as in Table 9-1. The Nernst equation is used to compute either an individual electrode potential or a cell emf from a known E° at a specified temperature, T , for a reaction involving n electrons at specified activities of the reactants and products. At 25° C, equation (9-14) becomes

$$E = E^\circ - \frac{0.0592}{n} \log \frac{a_{\text{products}}}{a_{\text{reactants}}} \quad (9-15)$$

The individual *electrode potentials* are calculated from the Nernst equation as shown in *Example 9-3*. The emf of the entire cell obtained using the Nernst equation is discussed in the next section.

Example 9-3. What is the reduction potential at 25° C of platinum wire electrodes immersed in an acidic solution of ferrous ions, at a concentration of 0.50 molal (m), and of ferric ions, at a concentration of 0.25 m ? The activity coefficient, γ , for the ferrous ion is 0.435 and that for the ferric ion is 0.390 under the experimental conditions. $E^\circ_{\text{Fe}^{3+} \rightarrow \text{Fe}^{2+}} = 0.771$ volts from Table 9-1. The electrode reaction, at the inert platinum electrode, is



The activity of each ion in the electrode reaction is given by $a = \gamma(m)$, so $a = 0.435 \times 0.50 = 0.218$ for the ferrous ion, and $a = 0.390 \times 0.25 = 0.0975$ for the ferric ion. From equation (9-15), with $n = 1$,

$$E_{\text{electrode}} = E^\circ_{\text{Fe}^{3+} \rightarrow \text{Fe}^{2+}} - \frac{0.0592}{1} \log \frac{a_{\text{Fe}^{2+}}}{a_{\text{Fe}^{3+}}}$$

$$E_{\text{electrode}} = 0.771 - 0.0592 \log \frac{0.218}{0.0975}$$

$$= 0.771 - 0.021$$

$$E_{\text{electrode}} = 0.750 \text{ volt}$$

In the example just given, the electrode is acting as the cathode, and a reduction is observed. If an electrode reaction is expressed as an oxidation rather than a reduction, that is, the electrode is acting as the anode, then the sign of E° as given in Table 9-1 must be changed, since by convention it is a reduction potential, and equation (9-15) becomes

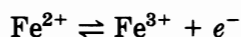
TABLE 9-1. Standard Half-cell Reduction Potentials at 25° C

| Reduction Reaction | Reduction Electrode* | E° (volts) |
|--|--|----------------------|
| $\frac{1}{2}\text{Cl}_2 + e^- = \text{Cl}^-$ | $\text{Cl}^- \text{Cl}_2, \text{Pt}$ | +1.360 |
| $\frac{1}{4}\text{O}_2 + \text{H}^+ + e^- = \frac{1}{2}\text{H}_2\text{O}$ | $\text{H}^+ \text{O}_2, \text{Pt}$ | +1.229 |
| $\text{Hg}^{2+} + e^- = \frac{1}{2}\text{Hg}_2^{2+}$ | $\text{Hg}^{2+}, \text{Hg}_2^{2+} \text{Pt}$ | +0.907 |
| $\text{Ag}^+ + e^- = \text{Ag}$ | $\text{Ag}^+ \text{Ag}$ | +0.799 |
| $\frac{1}{2}\text{Hg}_2^{2+} + e^- = \text{Hg}$ | $\text{Hg}_2^{2+} \text{Hg}$ | +0.854 |
| $\text{Fe}^{3+} + e^- = \text{Fe}^{2+}$ | $\text{Fe}^{3+}, \text{Fe}^{2+} \text{Pt}$ | +0.771 |
| $\frac{1}{2}\text{I}_2 + e^- = \text{I}^-$ | $\text{I}^- \text{I}_2$ | +0.536 |
| $\text{Fe}(\text{CN})_6^{3-} + e^- = \text{Fe}(\text{CN})_6^{4-}$ | $\text{Fe}(\text{CN})_6^{3-}, \text{Fe}(\text{CN})_6^{4-} \text{Pt}$ | +0.356 |
| $\frac{1}{2}\text{Cu}^{2+} + e^- = \frac{1}{2}\text{Cu}$ | $\text{Cu}^{2+} \text{Cu}$ | +0.337 |
| $\frac{1}{2}\text{Hg}_2\text{Cl}_2 + e^- = \text{Hg} + \text{Cl}^-$ | $\text{Cl}^- \text{Hg}_2\text{Cl}_2, \text{Hg}$ | +0.268 |
| $\text{AgCl} + e^- = \text{Ag} + \text{Cl}^-$ | $\text{Cl}^- \text{AgCl}, \text{Ag}$ | +0.223 |
| $\text{AgBr} + e^- = \text{Ag} + \text{Br}^-$ | $\text{Br}^- \text{AgBr}, \text{Ag}$ | +0.071 |
| $\text{H}^+ + e^- = \frac{1}{2}\text{H}_2$ | $\text{H}^+ \text{H}_2, \text{Pt}$ | 0.000 |
| $\frac{1}{2}\text{Pb}^{2+} + e^- = \frac{1}{2}\text{Pb}$ | $\text{Pb}^{2+} \text{Pb}$ | -0.126 |
| $\text{AgI} + e^- = \text{Ag} + \text{I}^-$ | $\text{I}^- \text{AgI}, \text{Ag}$ | -0.156 |
| $\frac{1}{2}\text{Ni}^{2+} + e^- = \frac{1}{2}\text{Ni}$ | $\text{Ni}^{2+} \text{Ni}$ | -0.250 |
| $\frac{1}{2}\text{Cd}^{2+} + e^- = \frac{1}{2}\text{Cd}$ | $\text{Cd}^{2+} \text{Cd}$ | -0.403 |
| $\frac{1}{2}\text{Fe}^{2+} + e^- = \frac{1}{2}\text{Fe}$ | $\text{Fe}^{2+} \text{Fe}$ | -0.440 |
| $\frac{1}{2}\text{Zn}^{2+} + e^- = \frac{1}{2}\text{Zn}$ | $\text{Zn}^{2+} \text{Zn}$ | -0.763 |
| $\text{Na} + e^- = \text{Na}$ | $\text{Na}^+ \text{Na}$ | -2.714 |
| $\text{K}^+ + e^- = \text{K}$ | $\text{K}^+ \text{K}$ | -2.925 |
| $\text{Li}^+ + e^- = \text{Li}$ | $\text{Li}^+ \text{Li}$ | -3.045 |

*A single line represents the boundary between an electrode and its solution. A comma is used to separate two species that are present together in the same phase.

$$E = -E^\circ - \frac{0.0592}{n} \log \frac{a_{\text{products}}}{a_{\text{reactants}}} \quad (9-16)$$

The reaction in *Example 9-3* expressed as an oxidation becomes



and the oxidation potential at the anode is

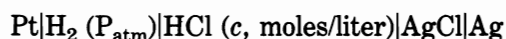
$$E_{\text{electrode}} = E_{\text{Fe}^{3+} \rightarrow \text{Fe}^{2+}} - \frac{0.0592}{1} \log \frac{a_{\text{Fe}^{3+}}}{a_{\text{Fe}^{2+}}}$$

$$E_{\text{electrode}} = -0.771 - 0.0592 \log \frac{0.0975}{0.218}$$

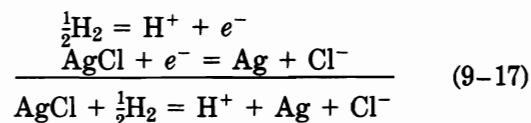
$$E_{\text{electrode}} = -0.771 + 0.021 = -0.750 \text{ volt}$$

Standard EMF of Cells. The term E° in the Nernst expression, equation (9-14), is defined as the measured emf of a cell, E , when all the reactants and products have unit activity. In the following example, an experimental method to measure E° will be described. This method uses the Debye-Hückel limiting law (Chapter 6) to describe the reactants and products with unit activity.

Consider a cell that consists of a hydrogen gas electrode as the anode and a silver-silver chloride electrode as the cathode immersed in an aqueous solution of hydrochloric acid:



The overall cell reaction is determined by summing the half-reactions at each electrode:



At 25° C, the emf of this cell is given by equation (9-15):

$$E = E^\circ - \frac{0.0592}{1} \log \frac{a_{\text{H}^+} a_{\text{Ag}} a_{\text{Cl}^-}}{a_{\text{AgCl}} a_{\text{H}_2}^{1/2}} \quad (9-18)$$

Since the solid phases are assigned an activity of 1, as mentioned on p. 134, and the pressure of hydrogen gas can be adjusted to 1 atm, at which it behaves ideally and has an activity of 1, equation (9-18) can be simplified to

$$E = E^\circ - 0.0592 \log a_{\text{H}^+} a_{\text{Cl}^-} \quad (9-19)$$

The individual ionic activities can be expressed in terms of *mean ionic* activities, as described on p. 132 of Chapter 6. This substitution leads to

$$E = E^\circ - 0.0592 \log \gamma_{\pm}^2 c_{\text{H}^+} c_{\text{Cl}^-} \quad (9-20)$$

in which γ_{\pm} is the mean ionic activity coefficient for a solution of hydrochloric acid whose ion concentrations (molality, that is, moles per kilogram of solvent) are c_{H^+} and c_{Cl^-} , respectively. According to the overall reaction for the cell, the concentrations of H^+ and Cl^- must be equal, so equation (9-20) can be expressed as

$$E = E^\circ - 0.0592 \log \gamma_{\pm}^2 c^2 \quad (9-21)$$

in which c is the molar concentration of HCl in the solution. Equation (9-21) can be rearranged to obtain

$$E + 0.0592 \log c^2 = E^\circ - 0.0592 \log \gamma_{\pm}^2$$

or

$$E + 0.1184 \log c = E^\circ - 0.1184 \log \gamma_{\pm} \quad (9-22)$$

Using the Debye-Hückel limiting law (p. 135), the $\log \gamma_{\pm}$ term in equation (9-22) can be replaced by $-Az^2\sqrt{\mu}$, in which A is a constant for a particular medium (0.509 for water at 25° C), z is the valence of the ions (1 in this example), and μ is the ionic strength of the solution. This gives the equation

$$E + 0.1184 \log c = E^\circ + 0.1184(0.509)\sqrt{\mu}$$

or

$$E + 0.1184 \log c = E^\circ + 0.0603\sqrt{\mu} \quad (9-23)$$

Since $\mu = \frac{1}{2}\sum c_i z_i^2$, for i ionic species in solution, according to equation (6-56), then for the cell with only HCl in solution,

$$E + 0.1184 \log c = E^\circ + 0.0603\sqrt{c} \quad (9-24)$$

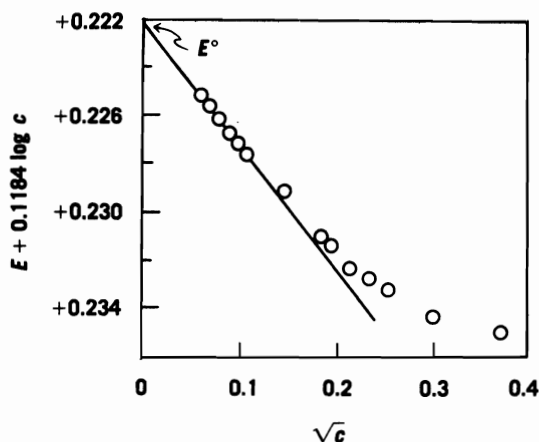
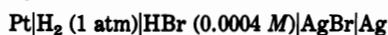


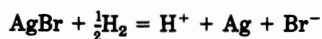
Fig. 9-5. Determination of E° for the cell, $\text{Pt}|\text{H}_2|\text{HCl}(c)|\text{AgCl}|\text{Ag}$. Notice that the values on the vertical axis decrease in the upward direction, so the negative slope of the line corresponds to a positive value, $+0.0603$, in equation (9-24).

The Debye-Hückel limiting law is satisfactory only for dilute solutions. Therefore, when we apply equation (9-24) to the actual determination of the standard emf of the cell, we find that a linear relationship between the left-hand side of the equation and the square root of the concentration of HCl, that is, $c^{1/2}$, is obtained only for small values of c . This is shown in Figure 9-5. Extrapolating the line so that it intersects the vertical axis yields a value for E° that corresponds to the emf of the cell at infinite dilution. This is the desired standard emf for the cell in the example, namely, $+0.222$ volt.

Example 9-4. What is the standard potential, E° , for a cell consisting of a hydrogen gas electrode ($P = 1$ atm) as the anode and a silver-silver bromide electrode as the cathode immersed in a solution of 0.0004 *m* hydrobromic acid? The cell emf, E , is determined by potentiometry to be 0.4745 volts. The cell can be depicted as



The overall cell reaction is



The equations used for the AgCl cell in our previous example hold also for this cell, so equation (9-24) can be applied:

$$E + 0.1184 \log c = E^\circ + 0.0603\sqrt{c}$$

Therefore,

$$E^\circ = E + 0.1184 \log c - 0.0603\sqrt{c}$$

$$E^\circ = 0.4745 - 0.4023 - 0.0012 = 0.071 \text{ volt}$$

Reference Electrodes and Standard Potentials. The absolute potential of a single electrode cannot be measured but as a relative potential can be assigned by combining the electrode with a *reference electrode* to form a cell and then measuring the cell emf. The potential of the reference electrode is known, so the potential of the unknown electrode can be obtained as a difference. To compare a series of emf's determined in this way for a variety of electrodes, it is necessary to specify whether oxidation or reduction is occurring at

the electrode. According to the Gibbs-Stockholm agreement or convention,* the measured emf should be designated as a *reduction potential*. That is, the unknown electrode is the cathode in the cell, and the relative ability of the electrode to accept electrons is measured against a reference electrode. The cell may thus be written as

$$E_{\text{cell}} = E_{\text{reference}} + E_{\text{unknown electrode}} \quad (9-25)$$

in which the unknown electrode is the right electrode in the cell schematic (i.e., the cathode). If the potentials are determined under standard conditions, that is, 25°C , 1 atm pressure, and unit activity of all species, then, for the standard reduction potential,

$$E_{\text{cell}}^\circ = E_{\text{reference}}^\circ + E_{\text{unknown electrode}}^\circ \quad (9-26)$$

If the electrodes were switched so that the reference electrode became the cathode and the unknown electrode became the anode, an *oxidation potential* would be determined for the unknown electrode. Oxidation potentials are not normally used for comparing cell potentials, according to convention. It is important to note that oxidation potentials differ from reduction potentials only by having the reverse sign, as demonstrated in *Example 9-3*. Thus, if the standard reduction potential for the silver-silver chloride electrode is $+0.223$ volt, its oxidation potential must be -0.223 volt.

Consider a cell that consists of a reference hydrogen electrode and a second electrode whose potential is being determined. The cell, according to convention, is represented as

$$E_{\text{cell}} = E_{\text{H}_2(\text{anode})}^\circ + E^\circ_{\text{unknown electrode}(\text{cathode})} \quad (9-27)$$

Under unit hydrogen ion activity and standard conditions, the reference hydrogen electrode, which is a primary reference electrode, is arbitrarily assigned a potential of 0.000 volt,

$$E_{\text{H}_2}^\circ = 0 \quad (9-28)$$

Thus, according to this definition, the measured standard cell emf corresponds to a standard electrode reduction potential:

$$E_{\text{cell}}^\circ = E^\circ_{\text{unknown electrode}(\text{cathode})} \quad (9-29)$$

In addition to the hydrogen electrode, secondary reference electrodes, with which other electrodes can be combined, include the 0.1 -*N* calomel electrode, the 1 -*N* calomel electrode, the saturated calomel electrode (in which the concentration terms refer to the chloride ion concentration), and the silver-silver chloride electrode. These electrodes can be standardized by combining them with the hydrogen electrode, as

*This convention was adopted in 1953 at the 17th Conference of the International Union of Pure and Applied Chemistry in Stockholm.

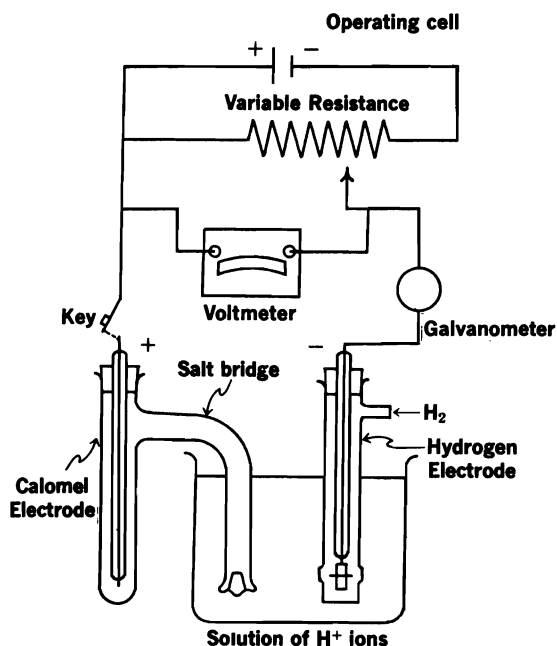


Fig. 9-6. Hydrogen electrode in combination with a calomel electrode. (After F. Daniels and R. A. Alberty, *Physical Chemistry*, Wiley, New York, 1955, p. 418.)

shown in Figure 9-6. These secondary reference electrodes are most often used for laboratory measurement since they are rugged and require practically no adjustment before use. In contrast, a hydrogen electrode, in which the hydrogen gas pressure must be carefully controlled, requires careful handling and frequent adjustment.

A KCl solution acts as the electrolyte solution in all of the mentioned secondary reference electrodes. It also acts as a *salt bridge* to make electric contact between the electrode and the rest of the cell. The salt bridge (represented by double lines, ||, in cell schematic diagrams) minimizes the potential difference that occurs across the liquid boundary between two solutions. The KCl solution in the salt bridge is prevented from mixing to any significant extent with the external solution by introducing a porous ceramic plug or permeable membrane at the boundary between the solutions. The potential difference at this boundary is known as the *liquid junction potential*. In cells that contain such a liquid junction potential, which comes about owing to unequal diffusion of ions across the barrier between the solutions, it is correct to write the overall cell emf as

$$E_{\text{cell}} = E_{\text{anode}} + E_{\text{junction}} + E_{\text{cathode}} \quad (9-30)$$

It is possible to design electrodes with liquid junctions that have minimum junction potential, as described by Durst² and by Connors.²

Standard and Formal Reduction Potentials. Copper ions accept electrons and are reduced more easily to the corresponding metal than lead ions, and lead ions in

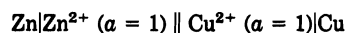
turn are more easily reduced than zinc ions. Therefore, the elements and their respective ions may be arranged in an electromotive series with those ions that accept electrons most readily, that is, those that are reduced most easily under standard conditions at the top of the list in Table 9-1. The standard reduction potentials, E° , are the potentials of the reduction reaction, occurring at the cathode, at *unit activity* of reactants and products.

By comparison, the *formal potential* of an electrode is obtained using specified concentrations of all species with equal concentrations of the oxidized and reduced species in the half-cell reaction. The formal potential is an experimentally observable value that takes into account liquid junction potentials, ionic strength, complexation, and other cell variations that will affect the cell emf. For example, the standard reduction potential E° of the calomel electrode, at unit activity of all species, is +0.268 volt, whereas the formal reduction potential of the 0.1-N calomel electrode is +0.334 volt; of the 1-N calomel electrode, +0.280 volt; and of the saturated calomel electrode, +0.242 volt at 25° C. In some cases, the standard reduction potential, E° , of an electrode cannot be measured since limited solubility of a species involved in the half-cell reaction prevents obtaining a solution with unit activity. In these cases, only formal potentials can be obtained.

In Table 9-1, the potentials are all standard reduction potentials using the standard hydrogen electrode, with an assigned E° of 0.000 volt as a reference. For an *oxidation* reaction, the sign of the potential in Table 9-1 is reversed. In oxidations, the electrode with a larger positive potential would be oxidized more easily than that with a smaller potential. For example, the $\text{Li}|\text{Li}^+$ electrode would be oxidized more easily than the $\text{Zn}|\text{Zn}^{2+}$ electrode.

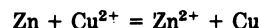
Example 9-5. Calculate E°_{cell} for an electrochemical cell consisting of a zinc electrode and a copper electrode, each immersed in a solution of its ions at an activity of 1.00.

The cell is written as



in which oxidation takes place at the left electrode and reduction at the right electrode, and electrons flow through the external circuit from left to right. How do we know that oxidation will occur at the zinc electrode and not at the copper electrode?

The standard reduction potentials for the zinc and copper electrodes are -0.763 volt and +0.337 volt, respectively, from Table 9-1. These E° values indicate that copper is reduced more easily than zinc, because of the larger positive E° potential of the copper electrode. It follows, from what has been said previously about oxidation potentials, that zinc must be oxidized more easily, that is, it has a greater standard *oxidation* potential. Therefore, in this particular cell, oxidation must occur at the zinc electrode and reduction at the copper electrode. The overall cell reaction is



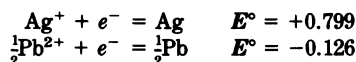
The emf of the cell is the sum of the *oxidation* potential of the left electrode and the *reduction* potential of the right electrode. The standard oxidation potential for the zinc half-cell is +0.763, that is,

the E° value listed in Table 9-1, but with the *opposite sign*. Equation (9-3), under standard conditions is written as

$$\begin{aligned} E_{\text{cell}}^\circ &= E_{\text{left}}^\circ + E_{\text{right}}^\circ \\ &= E_{\text{Zn} \rightarrow \text{Zn}^{2+}}^\circ + E_{\text{Cu}^{2+} \rightarrow \text{Cu}}^\circ \\ &= -E_{\text{Zn}^{2+} \rightarrow \text{Zn}}^\circ + E_{\text{Cu}^{2+} \rightarrow \text{Cu}}^\circ \\ E_{\text{cell}}^\circ &= +0.763 + (+0.337) = 1.100 \text{ volts} \end{aligned}$$

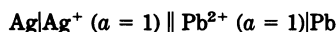
Example 9-6. Will a silver electrode reduce a lead electrode at 25° C when both half-cells are at unit activity?

The two reduction reactions and their corresponding standard potentials from Table 9-1 are

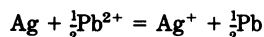


The silver potential is more positive than that for lead; therefore, silver is reduced more easily than lead. A silver electrode cannot reduce a lead electrode, and if the cell is written with the mistaken belief that silver is the oxidation electrode and lead is the reduction electrode, the cell emf, when calculated, will be found to have a negative value. The emf of any cell must be positive to provide a flow of electrons in the external circuit from the anode to the cathode, and this can be used as a guide to indicate whether the cell has been written properly. It is useful to remember that *the cell emf must always be positive, whereas the potentials of the individual electrodes can be either positive or negative.*

Suppose the cell is written as

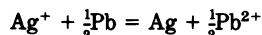
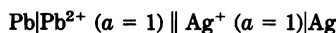


and the overall reaction as



$$E_{\text{cell}}^\circ = E_{\text{Ag} \rightarrow \text{Ag}^+}^\circ + E_{\text{Pb}^{2+} \rightarrow \text{Pb}}^\circ = -0.799 + (-0.126) = -0.925 \text{ volt}$$

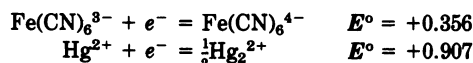
This result is wrong since E_{cell}° is negative; the mistake can be corrected by reversing the electrodes:



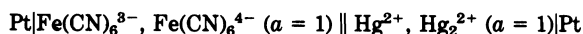
$$E_{\text{cell}}^\circ = E_{\text{Pb} \rightarrow \text{Pb}^{2+}}^\circ + E_{\text{Ag}^+ \rightarrow \text{Ag}}^\circ = +0.126 + (+0.799) = +0.925 \text{ volt}$$

Example 9-7. What is the correct configuration for a cell composed of a ferrocyanide-ferrocyanide electrode and a mercurous-mercuric electrode when both half-cells are at unit activity at 25° C? This type of cell is known as an oxidation-reduction system.

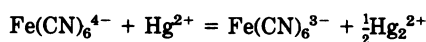
The two electrode reactions, when written as reductions, along with their E° values from Table 9-1, are



The mercurous-mercuric electrode has a larger reduction potential and therefore will oxidize the ferrocyanide to ferricyanide. The cell is correctly written as



and the overall reaction is



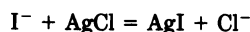
The calculated E_{cell}° is

$$\begin{aligned} E_{\text{cell}}^\circ &= E_{\text{Fe}(\text{CN})_6^{4-} \rightarrow \text{Fe}(\text{CN})_6^{3-}}^\circ + E_{\text{Hg}_2^{2+} \rightarrow \frac{1}{2}\text{Hg}_2^{2+}}^\circ \\ &= -0.356 + (+0.907) = +0.551 \text{ volt} \end{aligned}$$

Example 9-8. Compute the emf of the following cell at 25° C:



The cell reaction is



Applying equation (9-15) in which $n = 1$ for this reaction,

$$E_{\text{cell}} = E_{\text{cell}}^\circ - \frac{0.0592}{1} \log \frac{a_{\text{AgI}} a_{\text{Cl}^-}}{a_{\text{I}^-} a_{\text{AgCl}}}$$

The activities of the two solids, AgI and AgCl, are 1 and may be eliminated from the last term of the equation. The standard potential of the cell is the sum of the two standard half-cell potentials:

$$\begin{aligned} E_{\text{cell}}^\circ &= E_{\text{I}^- \rightarrow \text{AgI}}^\circ + E_{\text{AgCl} \rightarrow \text{Cl}^-}^\circ \\ &= +0.156 + (+0.223) = +0.379 \text{ volt} \end{aligned}$$

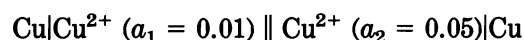
and the emf of the cell is

$$E_{\text{cell}} = 0.379 - 0.0592 \log \frac{0.8}{0.4}$$

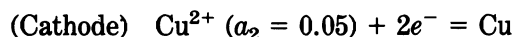
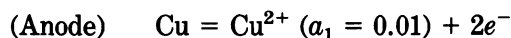
$$E_{\text{cell}} = 0.379 - 0.018 = +0.361 \text{ volt}$$

Concentration Cells. Thus, far, this chapter has discussed *chemical cells* in which an emf is produced by an oxidation-reduction reaction occurring with two different electrodes. In a concentration cell, the emf results from the differences in *activities* of solutions of the same material constituting the two half-cells.

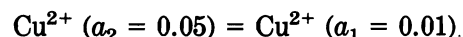
Suppose that a cell consists of two copper electrodes immersed in copper sulfate solutions at 25° C having activities of 0.01 and 0.05. The cell is represented by



The reactions at the anode and the cathode are



and the overall reaction is



The corresponding Nernst equations for the individual electrodes are

$$E_{\text{left}} = E_{\text{Cu} \rightarrow \text{Cu}^{2+}}^\circ - \frac{0.0592}{2} \log a_1$$

$$E_{\text{right}} = E_{\text{Cu}^{2+} \rightarrow \text{Cu}}^\circ - \frac{0.0592}{2} \log \frac{1}{a_2}$$

The equation for the cell emf is

$$\begin{aligned} E_{\text{cell}} &= E_{\text{left}} + E_{\text{right}} \\ &= \left(E_{\text{Cu} \rightarrow \text{Cu}^{2+}}^\circ - \frac{0.0592}{2} \log a_1 \right) \\ &\quad + \left(E_{\text{Cu}^{2+} \rightarrow \text{Cu}}^\circ - \frac{0.0592}{2} \log \frac{1}{a_2} \right) \\ &= (E_{\text{Cu} \rightarrow \text{Cu}^{2+}}^\circ + E_{\text{Cu}^{2+} \rightarrow \text{Cu}}^\circ) - \frac{0.0592}{2} \log \frac{a_1}{a_2} \end{aligned}$$

Since $E_{\text{Cu} \rightarrow \text{Cu}^{2+}}^\circ = -0.337$ and $E_{\text{Cu}^{2+} \rightarrow \text{Cu}}^\circ = +0.337$, $E_{\text{cell}}^\circ = 0$, and the general equation for a concentration cell at 25° C is

$$E_{\text{cell}} = -\frac{0.0592}{n} \log \frac{a_1}{a_2} \quad (9-31)$$

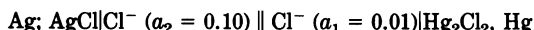
The electrolyte at the higher activity a_2 tends to diffuse spontaneously into the solution of lower activity

a_1 , and the cell emf arises from this difference in effective concentrations.

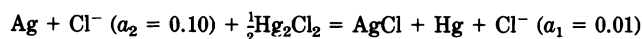
Example 9-9. Calculate the cell emf of the concentration cell just discussed.

$$E_{\text{cell}} = -\frac{0.0592}{2} \log \frac{0.01}{0.05} = 0.021 \text{ volt}$$

Example 9-10. Calculate the emf at 25° C arising from the cell



In this case, we have two different electrodes but a common ion in the electrolyte solutions, so that the cell acts as a chemical cell with some cell emf arising out of the difference in electrolyte activities. The overall reaction is



The corresponding Nernst equations for the individual electrodes are:

$$E_{\text{left}} = E_{\text{Cl}^- \rightarrow \text{AgCl}}^{\circ} - \frac{0.0592}{1} \log \frac{a_{\text{AgCl}}}{a_{\text{Ag}} a_{\text{Cl}^- (a_2)}}$$

$$E_{\text{right}} = E_{\frac{1}{2}\text{Hg}_2\text{Cl}_2 \rightarrow \text{Cl}^-}^{\circ} - \frac{0.0592}{1} \log \frac{a_{\text{Hg}} a_{\text{Cl}^- (a_1)}}{a_{\text{Hg}_2\text{Cl}_2}}$$

The equation for the cell emf is

$$E_{\text{cell}} = E_{\text{left}} + E_{\text{right}}$$

and since the activity of all solids in the overall reaction is unity, the cell emf becomes

$$E_{\text{cell}} = E_{\text{Cl}^- \rightarrow \text{AgCl}}^{\circ} - 0.0592 \log \frac{1}{a_2} + E_{\frac{1}{2}\text{Hg}_2\text{Cl}_2 \rightarrow \text{Cl}^-}^{\circ} - 0.0592 \log a_1$$

With values from Table 9-1, this becomes

$$E_{\text{cell}} = \left(-0.223 - 0.0592 \log \frac{1}{0.10} \right) + \left(+0.268 - 0.0592 \log 0.01 \right) \\ = -0.282 + 0.386 = +0.104 \text{ volt}$$

It is interesting to note that this cell would be represented incorrectly if the concentrations of chloride in the half-cells were reversed, that is, if $a_2 = 0.01$ and $a_1 = 0.10$. In that case, a negative E_{cell} of -0.014 volt would be calculated, and it would be necessary to represent the calomel as the oxidation electrode on the left and the silver-silver chloride electrode as the reduction electrode on the right to achieve a positive E_{cell} .

ELECTROMETRIC DETERMINATION OF pH, SPECIFIC IONS, AND REDOX POTENTIALS

The determination of pH can be made by means of any electrode whose potential depends on the hydrogen ion activity.³ The hydrogen and glass electrodes are discussed here as typical pH electrodes. Two hydrogen electrodes may be combined to measure pH, one serving as the indicating electrode and the other as the reference electrode, although this arrangement is not generally used in practice. The calomel and the silver chloride electrode are more convenient as reference electrodes and are typically used with commercial pH meters. The National Bureau of Standards (NBS) determines the pH of its standard buffers in a cell composed of a hydrogen-indicating electrode and a silver-silver chloride reference electrode. Some of the

NBS buffers available to laboratories for standardizing pH meters are listed in Table 9-2.

The Hydrogen Electrode. The chemical cell using a hydrogen and a saturated calomel electrode is shown in Figure 9-6. The half-cell reactions together with the overall cell reactions are

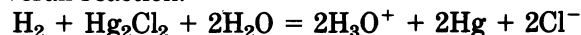
Left (oxidation):



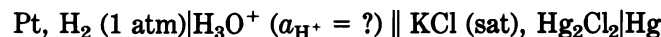
Right (reduction):



Overall reaction:



and the cell is represented as



in which ($a_{\text{H}^+} = ?$) stands for the hydrogen ion activity of the test solution, the pH of which is being determined.

The emf of the cell is

$$E_{\text{cell}} = E_{\text{H}_2 \rightarrow 2\text{H}_3\text{O}^+} + E_{\text{Hg}_2\text{Cl}_2 \rightarrow 2\text{Hg}} \quad (9-33)$$

The potential of the hydrogen electrode at 25° C and at a partial pressure of the hydrogen gas of 1 atm is written

$$E_{\text{H}_2} = E_{\text{H}_2 \rightarrow \text{H}_3\text{O}^+}^{\circ} - 0.0592 \log \frac{a_{\text{H}_3\text{O}^+}}{1 \text{ atm}}$$

Under these conditions, $E^{\circ} = 0$, from Table 9-1, and the equation becomes

$$E_{\text{H}_2} = -0.0592 \log a_{\text{H}_3\text{O}^+}$$

and since $\text{pH} = -\log a_{\text{H}_3\text{O}^+}$

$$E_{\text{H}_2} = 0.0592 \text{ pH}$$

The potential of the saturated KCl calomel electrode in the reduction reaction of equation (9-32) is $+0.242$ volt at 25° C. Hence, from equation (9-33),

$$E_{\text{cell}} = 0.0592 \text{ pH} + 0.242$$

TABLE 9-2. National Bureau of Standards Reference Buffer Solutions at 25° C

| Composition | pH | Dilution Value (change in pH on dilution with an equal volume of water) | Buffer Capacity, β |
|--|------|---|-----------------------------|
| Potassium tetraoxalate, 0.05 M | 1.68 | +0.19 | 0.070 |
| Potassium hydrogen phthalate, 0.05 M | 4.01 | +0.05 | 0.016 |
| Potassium dihydrogen phosphate and disodium hydrogen phosphate, anhydrous, each 0.025 M | 6.86 | +0.08 | 0.029 |
| Borax (sodium tetraborate, decahydrate), 0.01 M | 9.18 | +0.01 | 0.020 |

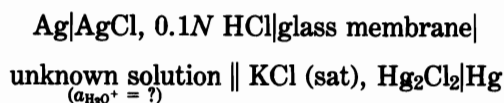
and

$$\text{pH} = \frac{E_{\text{cell}} - 0.242}{0.0592} \quad (9-34)$$

Example 9-11. A solution is placed between the hydrogen electrode and the calomel electrode in Figure 9-6. The emf of the cell is +0.963 volt at 25° C. What is the pH of the solution?

$$\text{pH} = \frac{0.963 - 0.242}{0.0592} = 12.2$$

The Glass Electrode. The glass membrane electrode is typical of the membrane-type electrodes described on p. 192. It is now the most widely used pH-indicating electrode. The conventional electrode includes an acidic electrolyte solution of 0.1 *N* HCl, and an internal silver-silver chloride reference electrode, as depicted in Figure 9-3. The complete cell, using a saturated calomel reference electrode (abbreviated SCE), can be represented as



The pH of the unknown solution is obtained from the cell emf if the pH of the internal solution, 0.1 *N* HCl, is constant. The emf of this cell at 25° C results from the sum of four separate potentials, arising at separate interfaces:

$$E_{\text{cell}} = E_{\text{SCE}} + E_{\text{ASYM}} - E_{\text{AgCl,Ag}} \\ + 0.059 (\text{pH}_{\text{unknown}} - \text{pH}_{\text{HCl solution}}) \quad (9-35)$$

where E_{SCE} arises at the boundary, $\text{Hg}_2\text{Cl}_2|\text{Hg}$; E_{ASYM} , known as the asymmetry potential, comes from the two boundaries of the glass membrane and is equivalent to differences in resistance that arise owing to variations in manufacture; and $E_{\text{AgCl,Ag}}$ arises at the boundary $\text{Ag}|\text{AgCl}$. The $\text{pH}_{\text{HCl solution}}$ term comes from the 0.1-*N* HCl solution, while the $\text{pH}_{\text{unknown}}$ is the pH of the solution being determined. The asymmetry potential may be associated with the mechanical properties of the glass membrane, which can effect unequal mobility or absorption of ions on the two sides of the membrane. Although the E_{ASYM} potential varies from one glass membrane to another, it can be considered constant for a particular cell arrangement using one glass electrode, and equation (9-35) can be simplified at 25° C to

$$E_{\text{cell}} = E_{\text{constant}} + 0.0592 \text{ pH(unknown)} \quad (9-36)$$

or

$$\text{pH} = \frac{E_{\text{cell}} - E_{\text{constant}}}{0.0592} \quad (9-37)$$

E_{constant} is the sum of all the boundary potentials in the cell plus the constant potential arising from the 0.1-*N* HCl solution.

The value of E_{constant} cannot normally be determined accurately because of the variation in E_{ASYM} from one glass electrode to another; however, this is not neces-

sary inasmuch as the pH meter can be standardized using a reference buffer solution, as listed in Table 9-2. The pH of a reference buffer, measured with the glass electrode and cell just described, is

$$\text{pH}_s = \frac{E_s - E_{\text{constant}}}{0.0592} \quad (9-38)$$

in which pH_s is the pH and E_s is the emf of the NBS reference buffer solution. Subtracting (9-38) from (9-37) to eliminate the undetermined E_{constant} results in the expression

$$\text{pH} - \text{pH}_s = \frac{E_{\text{cell}} - E_s}{0.0592}$$

or

$$\text{pH} = \text{pH}_s + \frac{E_{\text{cell}} - E_s}{0.0592} \quad (9-39)$$

Equation (9-39) is the *operational* or practical definition of pH now accepted by the NBS and the British Standards Institute.

In the actual measurement of pH, a *standardization dial* on the pH meter is adjusted manually until the needle on the scale reads the pH of a reference buffer solution. For accurate determinations, it is best to use two reference buffers, one with a pH below and the other with a pH above that for the unknown solution. The pH meter is similar in operation to the potentiometer discussed previously, except that it functions with a high input resistance, associated with the glass electrode. A diagram of a representative instrument is shown in Figure 9-7.

The chemical composition of the membrane of the glass electrode is critical for a correct potential response to the pH of a solution. At high pH values, a negative deviation from the theoretic potential is often found with glass membranes containing a high proportion of sodium ions, as shown in Figure 9-8. This "sodium error" is due to the fact that, at a high pH, the electrode potential can be partially determined by sodium ions in solution. In strongly acid solutions, a

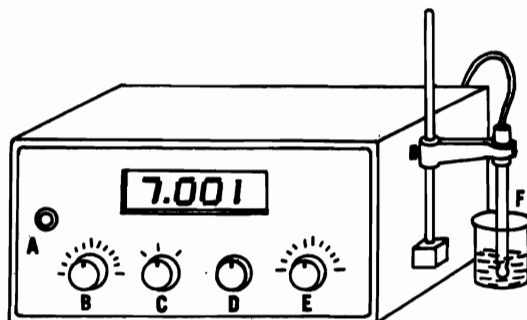


Fig. 9-7. Schematic diagram of a pH meter. A, On-off stand-by switch; B, temperature compensation; C, pH-millivolt switch; D, standardization dial; E, asymmetry or % slope dial; F, combination electrode.

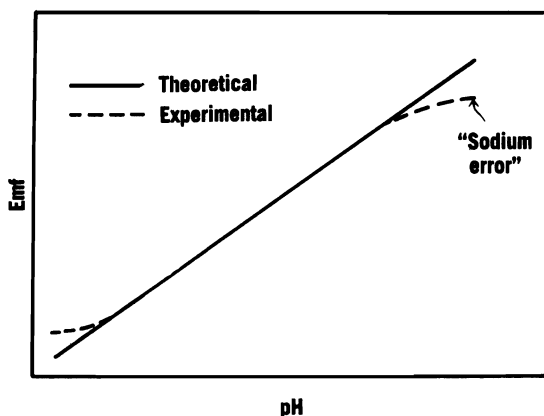


Fig. 9-8. The relationship between the cell emf and the pH for a glass electrode. (From W. C. Purdy, *Electroanalytical Methods in Biochemistry*, McGraw-Hill, New York, 1965, p. 44, used with the permission of McGraw-Hill Book Company.)

positive deviation from the theoretic emf also may be encountered. This error is believed to be due to a decrease in the activity of water, which may be associated with a decrease in the ability of the solution to hydrate the membrane surface and the ions in solution.

Electrodes currently available reduce the "sodium error" by incorporating a high proportion of lithium ions into the glass lattice. The glass electrode has an advantage over other electrodes in that it is not affected by oxidation-reduction systems since there is no exchange of electrons across the membrane, although it can be affected by cation exchange between the glass and the solution. The lithium ions incorporated in the glass do not exchange with other cations in the glass, unlike the sodium ion. This decrease in the ion-exchange property produces a more stable glass lattice with a decreased sodium ion exchange at high pH values and, therefore, a reduction in the alkaline error. A typical structure of a glass used in glass electrodes, as visualized by Perley,⁴ is sketched in Figure 9-9. The composition of glass membranes for potentiometry is discussed by Purdy.⁵

A modern innovation in pH electrodes is the *combination electrode*. This incorporates a reference electrode junction next to a glass membrane so that both electrodes are within a single body. This provides a

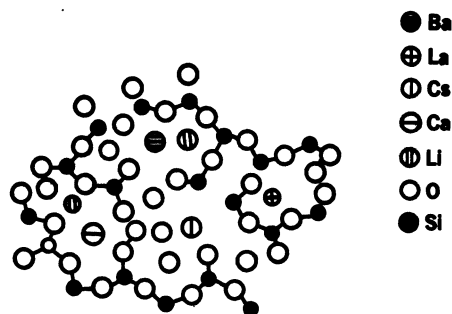


Fig. 9-9. The structure of glass used in glass electrodes. (After G. E. Perley, *Anal. Chem.* 21, 392, 1949).

compact electrochemical system that can be used with small or poorly accessible samples. A recent development involves the use of a fiber-optics sensor that allows the measurement of pH within a single living cell (*Chem. Eng. News*, Nov. 2, 1992).

Instructions for the determination of pH using the glass electrode are given in some detail by Bates.⁶ Useful information on the determination of pH and the use of buffer solutions for the standardization of pH meters are given in the U.S. Pharmacopeia, XXII, pp. 1598, 1599.

A Summary of pH Definitions. The reader should be reminded that pH has been defined in three distinctly different ways in this book.

1. It was first introduced on pages 149, 150, according to Sørensen's definition of $\text{pH} = -\log [\text{H}_3\text{O}^+]$.

2. It was then shown on page 150 that the *activity*, rather than the concentration, of hydrogen ions should be used, and the definition became $\text{pH} = -\log a_{\text{H}_3\text{O}^+}$.

3. Unfortunately, however, it is not possible by experimental means to measure the activity of a single ion. For this reason, the pH scale in the United States and Great Britain is now defined in terms of a reference standard buffer that has been assigned an arbitrary pH value so as to conform as closely as possible to the thermodynamic definition $\text{pH} = -\log a_{\text{H}_3\text{O}^+}$.

This last definition, known as the *operational* or *experimental pH*, does not correspond exactly to the pH on the activity scale since the junction potentials of the cells used cannot be eliminated. Consequently, pH is not a true physical constant but rather a practical scale of acidity and alkalinity measured in an appropriate cell that is calibrated by use of a reference standard buffer.

Finally, it should be observed that the pH numbers obtained by measuring solutions containing colloids and nonaqueous solvents have little correspondence with pH on the activity scale, and they should be specified as *arbitrary pH numbers*. These arbitrary values may be useful for control purposes to ensure uniformity of acidity or alkalinity of marketed products as long as the conditions are specified and it is recognized that the pH values do not correspond to the operational definition.

Ion-Selective Electrodes.² Electrodes that exhibit a selective and sensitive response to certain ions in solution are known as ion-selective electrodes. In this sense, the glass electrode just discussed is an ion-selective electrode since it is particularly sensitive to H_3O^+ ions. By carefully controlling the glass composition, it was discovered that electrodes could be constructed that showed enhanced sensitivity to certain monovalent cations, for example, K^+ or Na^+ , compared with hydrogen ions. The glass surface can act as an ion exchanger, and certain ions can be held strongly at surface-binding sites depending on the glass composition. In addition, ion mobility through the glass can be controlled by modifications in the glass lattice structure. Through glass composition and structure, a

membrane can be made selective for certain ions. With these membrane electrodes, complete selectivity cannot be achieved, since the glass response cannot be made completely independent of hydrogen or other ions in solution. Nonetheless, the selectivity is usually adequate for many applications.

The sensing barrier of the ion-selective electrode operates through the selective exchange of ions between two solutions on either side of the barrier. Potentials arise owing to concentration differences between the solutions as well as from the resistance of the barrier. Salt crystals, liquids, and enzymes, as well as glass membranes, have been used either by themselves or incorporated into some structural matrix, such as a plastic, to form a sensing barrier.

An example of the salt-type of barrier is the fluoride-sensitive electrode, which uses a fluoride salt of one of the lanthanum elements (see periodic table, inside front cover) as an insoluble membrane. For example, a crystal containing LaF_3 , praseodymium or europium fluoride (PrF_3 or EuF_3), can be sealed into the end of an electrode. An inner filling solution of a known activity, a , of NaF is used with an internal reference electrode, such as silver-silver chloride. The entire electrode can be represented as

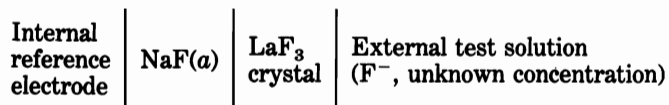


Figure 9–10 shows the construction of a typical fluoride

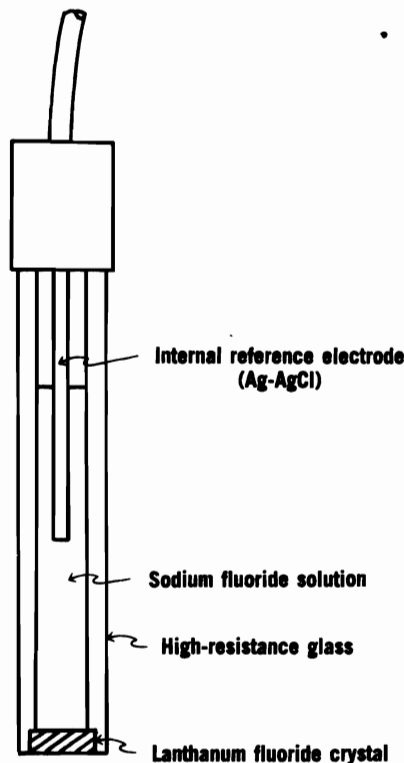
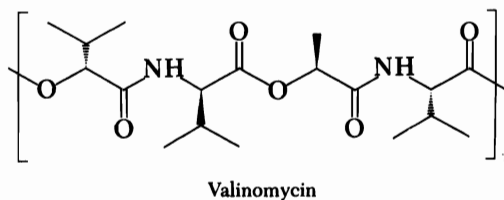


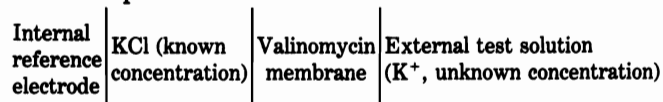
Fig. 9–10. Schematic representation of a fluoride-selective electrode.

electrode. The potential difference across the LaF_3 crystal is due exclusively to the conductance of F^- ions, unless lanthanum ions are present in appreciable concentration in the test solution. The electrode is practically free of interferences and can be considered selective for fluoride ion. For biologic samples, fluoride concentrations as low as $10^{-6} M$ can be determined quickly, usually with only a dilution or solubilization step, after calibration. Accuracy of the method is usually within $\pm 10\%$ for solution pH values between 4 and 8. Interferences are limited to hydroxide ions present at higher pH values, fluoride complexes, and hydrofluoric acid formation at lower pH values.

Membrane barriers can also be constructed from electrically neutral, and water-insoluble, sensors. The compound is incorporated into a plastic matrix such as a polyvinyl chloride (PVC) membrane. This is accomplished simply by mixing the sensor with a suitable solvent, adding the PVC, mixing, and then removing the solvent. The membrane produced can be incorporated directly as a barrier. One of the most selective sensors being used is the antibiotic valinomycin.



This antibiotic has a 36-membered ring structure and acts as a selective complexing agent for potassium ions. The electrode mechanism involves cation exchange across the antibiotic membrane to produce a potential between solutions on either side. The valinomycin electrode shows a selectivity of 4000:1 for K^+ over Na^+ ions and selectivity of 20,000:1 for K^+ over H^+ ions. It has a linear potential response over the region from about 10^{-5} to $10^{-1} M$ for potassium ions. The electrode can be represented as:



Charged ion exchangers, such as phosphate diesters, may also be used as sensors. In this case, the compound can be dissolved in an appropriate solution that is in contact with a porous membrane that acts as a barrier and a junction to the test solution.

An enzyme may be incorporated into a polyacrylonitrile plastic film to act as part of a sensing barrier. For example, urease, which converts urea to ammonium ions by the reaction



can be used. The immobilized enzyme in the plastic matrix is attached to a glass membrane electrode. The glass membrane in this case is sensitive to ammonium

TABLE 9-3. Some Ions Detectable with Commercially Available Ion-Selective Electrodes*

| | Minimum Detectable Concentration (M) | Possible Interfering Ions |
|----------------|--------------------------------------|---|
| Cations | | |
| Cadmium | 10^{-7} | Silver, mercuric, or cupric |
| Calcium | 10^{-5} | Zinc, ferrous |
| Copper | 10^{-7} | Silver, mercuric, cadmium, ferric or high levels of chloride or bromide |
| Lead | 10^{-7} | Silver, mercuric, cupric, high levels of cadmium or ferric |
| Potassium | 10^{-5} | Cesium, ammonium, hydrogen, silver |
| Silver | 10^{-7} | Mercuric |
| Sodium | 10^{-6} | Cesium, lithium, hydrogen, silver, rubidium, thallium |
| Anions | | |
| Bromide | 5×10^{-6} | Sulfide, iodide |
| Chloride | 5×10^{-5} | Perchlorate, sulfide, bromide, iodide, cyanide |
| Cyanide | 10^{-6} | Sulfide, chloride, iodide |
| Fluoride | 10^{-6} | Hydroxide |
| Fluoroborate | 10^{-5} | — |
| Iodide | 2×10^{-7} | Sulfide |
| Nitrate | 10^{-5} | Bromide, iodide, nitrite |
| Perchlorate | 10^{-5} | — |
| Sulfide | 10^{-7} | — |
| Thiocyanate | 10^{-6} | Hydroxide, iodide, sulfide |

*Adapted from the *Guide to Electrodes and Instrumentation*, Orion Research, Cambridge, Mass.

ions. The ammonium ions formed from the enzyme reaction migrate through the plastic membrane to the glass surface where they are detected through a change in potential. This electrode can detect urea in solution over a linear response range from approximately 10^{-4} to 10^{-2} M.

Typical ions detectable with ion-selective electrodes are listed in Table 9-3. Potential interferences from other ions in solution as well as minimum detectable concentrations are also listed.

All the ion-selective electrodes produce a response that is directly proportional to the logarithm of the activity of the ion. That is, from equation (9-36) at 25° C:

$$E_{\text{cell}} = E_{\text{constant}} + \frac{0.0592}{n} \log (a) \quad (9-41)$$

in which a is the activity of the ion being monitored. In practice, the concentration of the ion is determined from a calibration curve, which relates E_{cell} on the y axis to standard ionic concentrations on the x axis. A typical calibration curve for fluoride ion is shown in Figure 9-11. In this case, the ionic strength of the standards has been adjusted to that of the test solutions by treating each with an appropriate buffer of high molarity. This eliminates errors that might be produced when analyzing solutions of widely varying ionic strengths. The emf of a cell incorporating an ion-selective electrode is usually determined with an expanded-scale pH meter. Such a pH meter can be used with a high-resistance input and allows any 100-mV portion of the voltmeter's scale to be expanded to the full scale, thus increasing the accuracy of the emf reading. Of course, like the ordinary pH meter, the voltmeter draws an infinitesimally small current from the electrochemical cell. This current is so small that it produces no distortion in cell emf, and the reading can

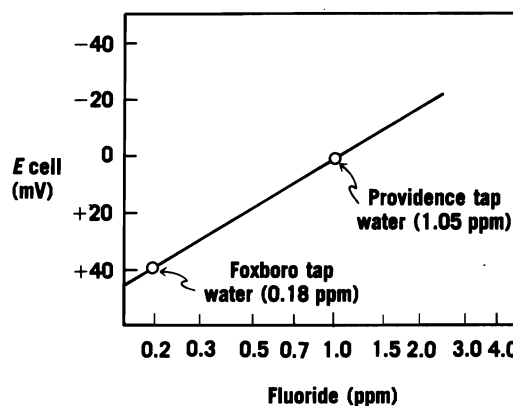


Fig. 9-11. Determination of fluoride in municipal water supplies using ionic-strength buffering. (Adapted from T. S. Light, in *Ion-Selective Electrodes*, R. A. Durst, Ed. N.B.S. Special Publication 314, Washington D.C., U.S. Government Printing Office, 1969.)

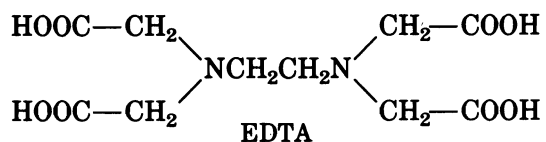
be considered essentially as a potentiometric determination.

Ion-selective electrodes have been used to determine the dissolution rate of tablets containing alkali metal ions,⁷ and the release of sodium phenobarbital through a dialysis membrane has been studied by monitoring the dialyzed solution with a sodium-selective electrode.⁸ Such applications can provide a rapid and continuous determination of the release rate of a drug from a formulation and may be particularly useful in monitoring slow-release preparations.⁹

Potentiometric Titration.¹⁰ A glass electrode and a suitable reference electrode, such as the calomel electrode, can be used with a pH or millivoltmeter to measure cell emf for potentiometric acid-base titrations. The change in potential of the glass electrode is measured as the volume of titrant of a known concentration is added. The titration curves obtained by

plotting E_{cell} , usually in millivolts, against the volume of titrant added are similar to those shown in Figure 8-1 (p. 175). When the endpoint is not marked by a sharp inflection in the curve, it is more desirable to plot the slope of the emf versus the volume of acid or base added, that is, $\Delta E/\Delta V$ against volume V . ΔE can be obtained directly from the pH meter for a set change in volume, ΔV . A differential titration curve is obtained, Figure 9-12, the maximum point of which represents the endpoint of the titration.

An ion-selective electrode also may be used with a suitable reference electrode for potentiometric titrations. For example, ethylenediaminetetraacetic acid (EDTA) can be determined in solution by titrating with a standard calcium ion solution.



The calcium-EDTA complex is formed during the titration until the endpoint is reached, whereupon free calcium ion in solution can be detected with a calcium-selective indicating electrode. This endpoint is observed as a sudden increase in the electrode signal, analogous to the inflection observed in the previous acid-base titration.

Potentiometric Determination of Dissociation Constants.¹⁰ The titration curve may be used to obtain a rough estimation of the dissociation constant of a weak acid by invoking the Henderson-Hasselbalch equation from Chapter 8:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}]}{[\text{acid}]} \quad (9-42)$$

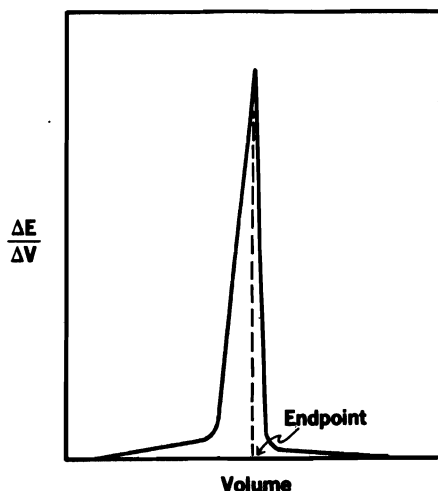


Fig. 9-12. Results of a potentiometric titration plotted as a differential curve of $\Delta E/\Delta V$ against the volume of titrant added.

This equation is useful over a limited range for relatively dilute buffers. In practice, at the equivalence point of the titration where $[\text{salt}] = [\text{acid}]$, the second term of the right-hand side of the equation becomes zero, and $\text{pH} = \text{p}K_a$. For a more exact determination of $\text{p}K_a$, the buffer equation should be used in its general form:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}]}{[\text{acid}]} + \log \gamma_A^- \quad (9-43)$$

in which γ_A^- is the activity coefficient of the anion (p. 132). Introducing the Debye-Hückel expression (pp. 135, 170), the formula becomes

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}]}{[\text{acid}]} - \frac{Az^2\sqrt{\mu}}{1 + a_iB\sqrt{\mu}} \quad (9-44)$$

in which A , a_i , and B are constants and μ is the ionic strength. One experimental procedure involves "half-neutralizing" the acidic drug by titrating with sodium hydroxide until $[\text{salt}] = [\text{acid}]$ and the $[\text{salt}]/[\text{acid}]$ ratio becomes unity, whereby the second term on the right-hand side of equation (9-44) becomes zero, and

$$\text{pH} = \text{p}K_a - \frac{Az^2\sqrt{\mu}}{1 + a_iB\sqrt{\mu}} \quad (9-45)$$

sodium chloride is added in varying amounts to produce solutions of different ionic strengths. The pH of each solution is determined, and the results are plotted against μ to yield a curve as shown in Figure 9-13. In this figure, phenobarbital is the weak acid, and sodium phenobarbital the salt. Extrapolating the line to the intercept of the vertical axis where $\mu = 0$ gives a close approximation to the thermodynamic dissociation con-

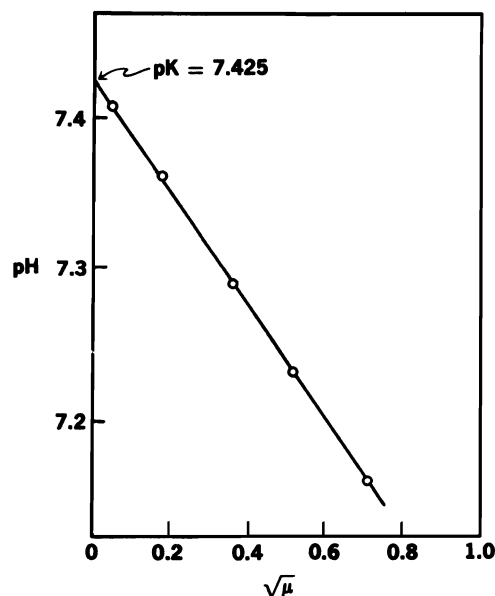
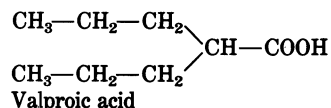


Fig. 9-13. Approximate determination of the thermodynamic dissociation constant of phenobarbital.

stant, pK_a , of the drug. An equation similar to (9-45) can be written for weak bases, and their pK_b values can be determined by an analogous procedure.

For the accurate pK_a or pK_b determination of an acid-base pair of unequal strength, correction should be made for the undissociated weak acid or base, as described by Benet and Goyan.¹¹

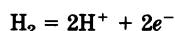
Example 9-12. Calculate the dissociation constant and pK_a of valproic acid,



for a cell

Pt|H₂ (P = 1 atm)|valproic acid (10⁻⁶ m), sodium valproate (10⁻⁸ m), H⁺ (?m) || H⁺ (α = 1)|H₂ (P = 1 atm)|Pt which develops an emf of +0.175 volt.

As shown, the cell has a standard hydrogen electrode as the cathode (i.e., $E_{\text{cathode}} = 0.000$ volt). The reaction occurring at the hydrogen anode depends on the hydrogen ion activity according to the oxidation,



so

$$E_{\text{anode}} = E^\circ - \frac{0.0592}{2} \log \frac{a_{\text{H}^+}{}^2}{P = 1 \text{ atm}} = 0.000 - 0.0296 \log \frac{a_{\text{H}^+}{}^2}{1}$$

Since

$$\begin{aligned} E_{\text{cell}} &= E_{\text{anode}} + E_{\text{cathode}} \\ E_{\text{cell}} &= 0.175 = 0.000 - 0.0296 \log a_{\text{H}^+}{}^2 - 0.000 \end{aligned}$$

Therefore, after rearrangement,

$$\begin{aligned} \log a_{\text{H}^+}{}^2 &= -\frac{0.175}{0.0296} \\ a_{\text{H}^+}{}^2 &= 1.22 \times 10^{-6} \end{aligned}$$

and, if the activity coefficient is considered to be nearly unity under relatively dilute conditions, then $[\text{H}^+] = 1.11 \times 10^{-3}$ m. Since the valproic acid is mostly undissociated under acidic conditions,

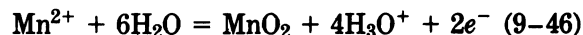
$$\begin{aligned} K_a &= \frac{[\text{H}^+][\text{valproate}^-]}{[\text{valproic acid}]} = \frac{(1.11 \times 10^{-3})(10^{-6})}{(10^{-6})} \\ &= 1.11 \times 10^{-5} \text{ approximately} \end{aligned}$$

and, therefore, the pK_a is about 4.96.

By using a method similar to the ionic strength method previously described in this section, Krahl¹² determined the dissociation constants of a number of substituted barbituric acids. Improved determinations have been introduced since 1940; a more recent listing of barbiturate pK_a values is provided by Pranker and others in Table 7-6. Spectrophotometric methods are also used for determining pK_a values, as described on pages 81, 82 in Chapter 4. The pK_a of estrogens has been determined using a pH meter and a spectrophotometric assay procedure developed by Hurwitz and Liu.¹³ A thorough description of potentiometric methods used for pK_a measurements is given by Albert and Serjeant,¹⁴ and the determination of pK_a by various methods is reviewed by Cookson.¹⁵

The exact determination of the thermodynamic dissociation constant of a weak electrolyte involves the use of cells without liquid junctions. Such cells are described by Buck,¹⁶ and methods using such cells are discussed by Harned and Owen.¹⁷

Hydrogen Ion Concentration in Oxidation-Reduction. Hydrogen ion concentrations must be considered in certain oxidation-reduction (redox) reactions, such as the oxidation

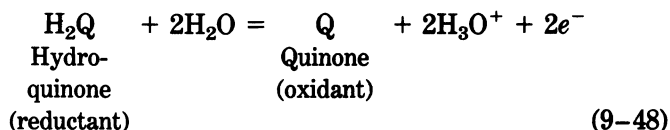


The oxidation-reduction potential is given the symbol E_D . For the oxidation of Mn^{2+} at 25° C the oxidation-reduction potential is

$$E_D = -E^\circ - \frac{0.0592}{2} \log \frac{a_{\text{H}_3\text{O}^+}^4}{a_{\text{Mn}^{2+}}} \quad (9-47)$$

which shows the influence of the hydrogen ion activity on E_D .

A number of reversible organic oxidation-reduction reactions of the quinone type involve acid-base equilibria and hence are influenced by hydrogen ions. As shown on page 192, the hydroquinone-quinone reaction is written as



The potential for the *oxidation* is therefore

$$E_D = -E^\circ - \frac{RT}{2F} \ln \frac{a_{\text{Q}} a_{\text{H}_3\text{O}^+}^2}{a_{\text{H}_2\text{Q}}} \quad (9-49)$$

or, in general,

$$E_D = -E^\circ - \frac{RT}{2F} \ln \frac{a_{\text{Ox}}}{a_{\text{Red}}} - \frac{RT}{F} \ln a_{\text{H}_3\text{O}^+} \quad (9-50)$$

from which it is seen that increasing the hydrogen ion activity, or decreasing the pH, reduces E_D . If the pH of the system is held constant, the last term of equation (9-50) may be combined with E° to yield a standard potential $E^{\circ'}$, characteristic of the system at a fixed hydrogen ion activity or pH, which for an oxidation yields

$$E_D = -E^{\circ'} - \frac{RT}{2F} \ln \frac{\text{Ox}}{\text{Rd}} \quad (9-51)$$

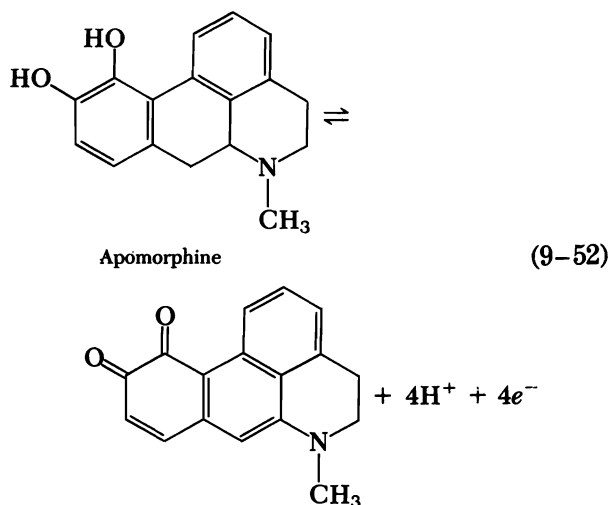
The standard potentials $E^{\circ'}$ for some organic oxidation-reduction systems of importance to pharmacy and the biologic sciences are listed in Table 9-4, together with the pH at which they were determined.

The decomposition processes of many drugs in formulations can be described as oxidation-reduction reactions. For example, the decomposition of apomorphine in tablets can occur via the following reaction:

TABLE 9-4. Standard Reduction Potentials at Specified pH Values for Some Oxidation-Reduction Systems*

| Redox System | E° (volt) | pH | Temperature (°C) |
|------------------------|-----------------------|--------------|---------------------|
| Homogentisic acid | +0.570 | 1.98 | 25 |
| Epinephrine | +0.380 | 7.0 | 30 |
| | +0.791 | 0.29 | 30 |
| Vitamin K ₁ | +0.363 | 0.2 N HCl | 20 |
| | | +95% alcohol | |
| Cytochrome C | +0.256 | 6.77 | 30 |
| Ascorbic acid | +0.115 | 5.2 | 30 |
| | +0.136 | 4.58 | 30 |
| Methylene blue | +0.011 | 7.0 | 30 |
| Riboflavin | -0.208 | 7.0 | 30 |
| | -0.117 | 5.0 | 30 |

*The algebraic sign of the E° values in this table and throughout this chapter correspond to the reduction potentials as defined in the text.



Because of the participation of hydrogen ions in this reaction, the decomposition is pH dependent. It has been found that apomorphine is more stable in acidic formulations and rapidly decomposes in basic or neutral solutions. In general, the stability of many drugs in aqueous solutions often depends on the pH of the solution. Usually, pH must be controlled in liquid formulations to inhibit redox reactions, and for most drugs this requires a low pH. Stability and oxidation will be discussed in more detail later in this chapter. Chapter 12 treats the kinetics of drug stability.

McCreery¹⁸ has shown that oxidation potentials of chlorpromazine metabolites at selected pH values can be associated with their pharmacologic features. Additionally, Marzullo and Hine¹⁹ have associated redox mechanisms with opiate receptor function. Such conclusions, which associate redox potentials with drug actions at particular pH values, are important for drugs acting as neurotransmitters and help to explain mechanisms of drug-receptor interaction.

Titration Curves of Oxidation-Reduction Systems. An inorganic or organic oxidation-reduction system may

be titrated by placing the solution in a cell containing a platinum and a suitable reference electrode, such as the calomel electrode. The potentiometric titration may be performed by adding measured quantities of either a powerful reducing agent, such as titanous chloride, to a buffered solution of the oxidized form of a compound, or an oxidizing agent, such as potassium dichromate, to the reduced form. If a 1N calomel electrode is used, the value 0.280 volt at 25° C is subtracted from E_{cell} to obtain E_D at any stage of the titration. Typical curves resulting from plotting the potential E_D of the inert electrode against the volume of reducing agent, or the percent reduction, are shown in Figure 9-14. When the system is 50% reduced, $\text{Ox/Red} = 1$ and $E_D = E^{\circ}$ at a definite hydrogen ion activity. The slopes of the curves depend on n , the number of electrons transferred, and the vertical position of each curve on the graph depends on the value of E° . Oxidation-reduction systems are said to be *poised* to the maximum extent at half-reduction, just as acid-base systems show maximum buffer capacity at half-neutralization. A system that resists changes in E_D on the addition of oxidizing or reducing agents exhibits good *poising action*.

If an organic substance has two forms of different colors corresponding to its reversible oxidation-reduction couple, it may be useful as an indicator of the endpoint for an oxidation-reduction titration. Such indicators should show a color change that corresponds to a change in potential of the system rather than a change in concentration of one of the reactants. Most of these indicator redox systems depend on hydrogen ion concentration. For example, the redox indicator methylene blue undergoes the following reaction under neutral conditions (pH = 7) with $E^{\circ} = +0.011$:

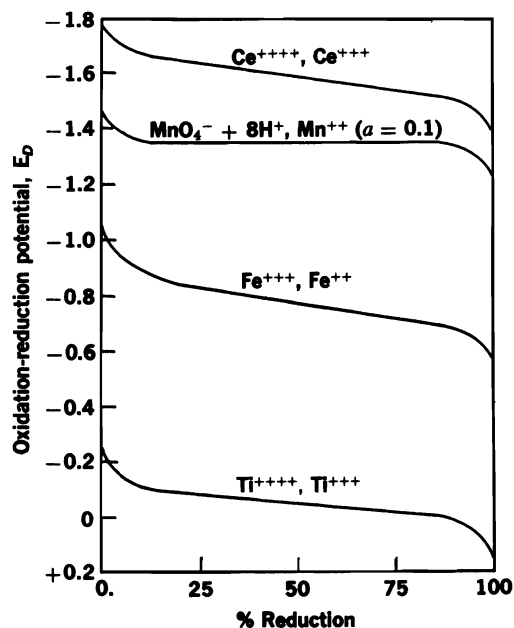
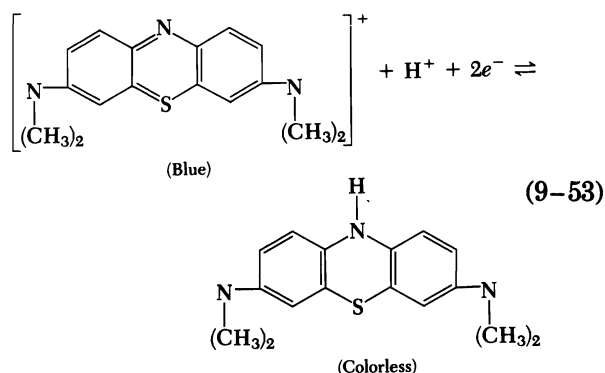


Fig. 9-14. Oxidation-reduction titration curves.



For changes in the hydrogen ion activity, the E_D range at which a color change of blue (oxidized form) to colorless (reduced form) occurs for this indicator at 25° C is given by

$$E_D = E^\circ \pm \frac{0.0592}{n} + 0.0592 \log a_{\text{H}^+} \quad (9-54)$$

This equation is derived from (9-50), in which a color change is defined as occurring for the ratio between

$$\frac{1}{10} \leq \frac{a_{\text{Ox}}}{a_{\text{Red}}} \leq 10 \quad (9-55)$$

which is equivalent to a range of $\pm \frac{0.0592}{n}$ at 25° C for the second term on the right side of equation (9-50). From equation (9-54), the E_D range for methylene blue at pH 7 is calculated as approximately +0.040 to -0.019 volt. An oxidation-reduction indicator is useful within the narrow range of $E^\circ \pm 0.059$ when n is unity. Some commonly used indicators are listed in Table 9-5.

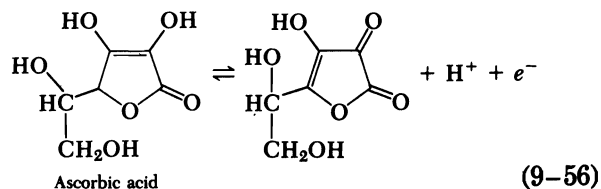
Oxidation-Reduction in Stages and the Use of Potential Mediators. Some oxidation-reduction reactions proceed in steps, particularly when n , the number of electrons between the oxidized and reduced states, is large. The oxidation-reduction reactions of many organic compounds involve a transfer of two electrons, which may be transported together or in consecutive steps. If two stages are involved, the oxidation titration curve shows two equivalence points, and the curve is similar to that

for a dibasic acid, such as H_2CO_3 , titrated with the strong base, NaOH.

When n is large, the oxidation-reduction reaction may be slow, and the measured emf will be in doubt, since a truly reversible system is not attained. Under these circumstances, an easily oxidized or reduced substance may be added to act as a *potential mediator*. Ti^{3+} and I_3^- react together sluggishly except in the presence of certain indicators, acting as mediators, which accept electrons one by one from Ti^{3+} and donate them in pairs to the triiodide ion.²⁰

Oxidation-Reduction in Pharmacy. Some pharmaceutical compounds are affected significantly by oxidation and reduction. These include ascorbic acid, riboflavin, vitamin K, epinephrine, vitamin E, morphine, and chlorpromazine. Additionally, fats and oils are susceptible to redox mechanisms. A limited number of examples are given here to show the kind of oxidation-reduction that can occur with medicinal compounds.

Ascorbic acid in aqueous solution oxidizes slowly in contact with air according to the following reversible reaction:



This reaction is somewhat faster under acid conditions owing to hydrogen ion catalysis. The dehydration product can undergo further irreversible hydrolysis in alkaline solution to form diketogulonic acid and, eventually, oxalic acid, $(\text{COOH})_2$, among other products. As the decomposition proceeds, the ascorbic acid solution turns from light yellow to a deep red color.

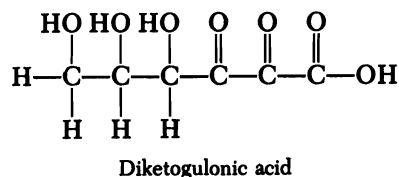
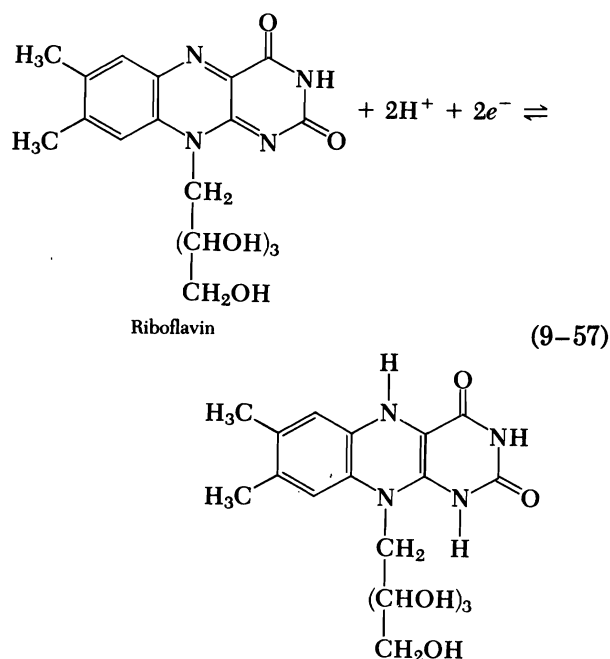


TABLE 9-5. Reduction Potentials of Some Oxidation-Reduction Indicators

| Substance | E° (reduction potential) (volt) | pH |
|-------------------------------------|---|----|
| <i>p</i> -Nitrodiphenylamine | +1.06 | 0 |
| <i>o</i> -Toluidine | +0.87 | 0 |
| Diphenylamine-4-sulfonate (Na salt) | +0.85 | 0 |
| 2,6-Dichloroindophenol (Na salt) | +0.217 | 7 |
| Methylene blue | +0.011 | 7 |
| Indigo trisulfonate (Na salt) | -0.081 | 7 |
| Cresyl violet | -0.173 | 7 |

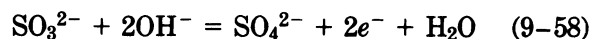
Ball²¹ found that adding a small amount of a potential mediator, such as methylene blue, which has an E° value similar to that of the ascorbic acid system, creates a thermodynamically reversible system. By using a suitable oxidizing agent and mediator and buffering the system well in the acid range, one obtains E° from the E_D value at the point where 50% of the compound is oxidized according to equation (9-51). At a pH of 4.58 and a temperature of 30° C, the value of E° for the ascorbic acid system is +0.1362 volt.

Riboflavin, vitamin B₂, is also subject to a redox mechanism according to the reversible reaction.



The activity of this vitamin depends on the relative amount of the dihydro product in a formulation. Dry preparations of riboflavin are quite stable; however, the redox reaction becomes significant when the vitamin is dissolved in aqueous solution, especially alkaline solutions that are exposed to sunlight. Both riboflavin and ascorbic acid have greatest stability, that is, the lowest rate of oxidation-reduction, when buffered on the acid side to pH 5 and 6, respectively.

In addition to pH control, oxidation or reduction can be controlled by the addition of compounds that are more easily oxidized or reduced, respectively, than the particular drug. In many instances, *antioxidants* are added to formulations to prevent the oxidation of a particular drug. Antioxidants must be oxidized more easily than the compound they are meant to protect. In a closed container, the antioxidant acts as a reducing agent to eventually consume the oxygen that is present. In many instances, combinations of antioxidants are used to increase their effectiveness. Typical water-soluble antioxidants include sodium bisulfate, ascorbic acid (used here *because* of its ability to oxidize), sodium sulfite, sodium metabisulfite, cysteine hydrochloride, thioglycolic acid, and sulfur dioxide. Oil-soluble antioxidants include ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, and α -tocopherol. The sulfite ion in aqueous solution undergoes oxidation according to the reaction



This reaction has a reduction potential, E° , of -0.93 volt, which is equivalent to a standard oxidation potential, in accord with the way the reaction is written, of $+0.93$ volt. Sulfite is a useful antioxidant for drugs that undergo redox reactions with smaller posi-

tive oxidation potentials, in other words, drugs that are less easily oxidized.

Example 9-13. Is a solution containing 10^{-2} *M* sulfite ion useful to prevent oxidation of 10^{-3} *M* ascorbic acid in a pH 7 aqueous solution at 25°C ? K_1 for ascorbic acid at 25°C is 8.5×10^{-5} . K_2 is insignificant and may be neglected.

For the sulfite reaction:

$$K = \frac{[\text{SO}_4^{2-}]}{[\text{SO}_3^{2-}][\text{OH}^-]^2}$$

At pH 7, the OH^- and H_3O^+ concentrations must be equal so,

$$K_{(\text{pH}=7)} = \frac{[\text{SO}_4^{2-}]}{[\text{SO}_3^{2-}][\text{H}_3\text{O}^+]^2}$$

If we assume that the differences between activities and concentrations for the various species are small, the sulfite oxidation potential and concentration can be substituted in a slightly modified version of equation (9-50) to give, at 25°C ,

$$E_D = -E^\circ - \frac{0.0592}{2} \log \frac{[\text{SO}_4^{2-}]}{[\text{SO}_3^{2-}]} + 0.0592 \log [\text{H}_3\text{O}^+]$$

At pH 7, $[\text{H}_3\text{O}^+] = 10^{-7}$ *M*, and if we assume that the $[\text{SO}_4^{2-}]$ term should not exceed 10^{-7} *M*, that is, the sulfate level is being governed only by the availability of hydroxide ion to drive reaction (9-57), then

$$E_D = -E^\circ - \frac{0.0592}{2} \log \frac{(10^{-7})}{(10^{-2})} + 0.0592 \log (10^{-7})$$

or

$$E_D = 0.93 + 0.15 - 0.41 = +0.67 \text{ volt}$$

It is of interest to note that if the $[\text{SO}_4^{2-}]$ term becomes somewhat larger, which would occur as oxidation proceeds, the second term on the right-hand side of the equation becomes smaller, which is consistent with a decrease in the oxidation potential.

For ascorbic acid, which is a dibasic acid, the E° reduction potential value at 25°C is approximately -0.383 volt. Since the oxidation of ascorbic acid is similar to the hydroquinone redox reaction discussed on page 205 equation (9-50) becomes

$$E_D = -E^\circ - \frac{0.0592}{2} \log \frac{[\text{Ox}]}{[\text{Ascorbic acid}]} - 0.0592 \log [\text{H}_3\text{O}^+]$$

For $[\text{Ox}]$, one obtains

$$[\text{Ox}] = K_a[\text{Red}]/[\text{H}_3\text{O}^+]$$

Thus

$$[\text{Ox}] = 8.5 \times 10^{-5}[10^{-3}]/10^{-7} = 0.85$$

at equilibrium and

$$\begin{aligned}
 E_D &= -E^\circ - \frac{0.0592}{2} \log \frac{(0.85)}{10^{-3}} - 0.0592 \log (10^{-7}) \\
 &= 0.383 - 0.087 + 0.414 = +0.710 \text{ volt}
 \end{aligned}$$

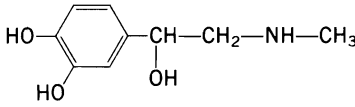
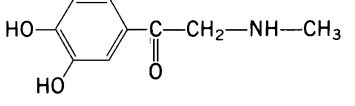
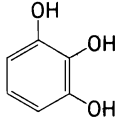
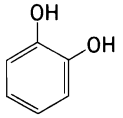
At the beginning of the oxidation, $[\text{Ox}]$ must be small compared with $[\text{Red}]$. If we assume that $[\text{Ox}]$ is 10^{-7} *M*, comparable to $[\text{H}_3\text{O}^+]$, then before significant oxidation has occurred,

$$E_D = -E^\circ - \frac{0.0592}{2} \log \frac{(10^{-7})}{(10^{-3})} - 0.0592 \log (10^{-7})$$

$$E_D = 0.383 + 0.118 + 0.414 = +0.915 \text{ volt}$$

Both the E_D value at the start of the oxidation and at equilibrium for ascorbic acid are greater than the E_D for sulfite. Therefore, the sulfite would not be effective as an antioxidant under the stated conditions. This implies that, at the concentrations specified at 25°C , ascorbic acid is a greater reducing agent than sulfite, and the oxidation of ascorbic acid would proceed *before* that of sulfite under the stated conditions. To prevent oxidation of ascorbic acid, some other compound should be chosen and the pH adjusted to a more acidic

TABLE 9-6. Standard Potentials of Some Compounds that Readily Undergo Oxidation—Reduction*

| | E° (reduction potential) (volt) | E° (Oxidation Potential) (volt) | Structure |
|-------------|--|--|--|
| Epinephrine | +0.808 | -0.808 |  |
| Adrenalone | +0.909 | -0.909 |  |
| Pyrogallol | +0.713 | -0.713 |  |
| Catechol | +0.792 | -0.792 |  |

*From E. G. Ball and T. T. Chen, *J. Biol. Chem.* **102**, 691, 1933.

value. For example, dimercaptopropanol and various metal chelating agents have been found to reduce the rate of ascorbic acid oxidation under acidic conditions.²² Such compounds are useful in pharmaceutical applications only if they are nontoxic.

Oxidation–reduction potentials are related to chemical structure, as shown in Table 9–6 for some hydroxyaromatic compounds. The more readily the reduced form loses electrons to yield the oxidized form, the better a reducing agent it is. Thus, pyrogallol, with its oxidation potential of –0.713 volt, is more easily oxidized, that is, it is a greater reducing agent, than catechol, with an oxidation potential of –0.792 volt. This greater ease of oxidation is related to the additional hydroxy group in the pyrogallol molecule.

Moore²³ has described a photooxidation system that can determine the relative efficiency of an antioxidant. The system measures the rate of a photochemically induced model oxidation reaction, the oxidation of benzaldehyde, after a known amount of an antioxidant is added. This method has been used to determine the efficiencies of a number of phenolic compounds with results that differ somewhat from the results in Table 9–6. For example, catechol is reported to be a more efficient antioxidant than pyrogallol. This implies that the relative efficiency of an antioxidant depends upon the specific mechanism of oxidation. Further work with other model systems may help to establish the relative dependency of antioxidation efficiency on oxidation conditions.

A number of new electrochemical methods and apparatus have been introduced into pharmaceutical analysis, and some of these are useful for the study of

oxidation–reduction systems. Electron transfer in redox reactions may be measured today by *voltammetry* (current plotted against voltage), *chronoamperometry* (current plotted against time), *rotating electrode* techniques, and others. Studies^{24–27} of antitumor activity, carcinogenesis, and antiviral and herbicidal activities provide examples of some applications of oxidation–reduction and voltammetry in analytic pharmaceutical chemistry. For a discussion of these rapidly advancing methods, refer to the literature^{28,29} and the references given there to modern electroanalytic instrumentation.

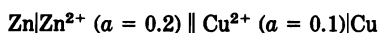
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Problems

9-1. Calculate the emf of the following cell at 25° C.



Answer: 1.091 volt

9-2. For a cell consisting of one half-cell with a nickel electrode dipping into a solution of Ni^{2+} ions ($a = 0.1$) and the other half-cell a cadmium electrode dipping into a solution of Cd^{2+} ions ($a = 0.5$) at 25° C, which electrode must be the cathode and which the anode?

Answer: The cadmium electrode is the anode.

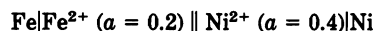
9-3. Calculate the oxidation potential of a finely divided iron electrode in an acidic solution of ferrous ion. The ferrous ion concentration is 0.50 M and the activity coefficient is 0.40. $E_{\text{Fe} \rightarrow \text{Fe}^{2+}} = 0.440$ (for oxidation) as seen in Table 9-1. The activity of the ferrous ion is obtained from the molar concentration and the activity coefficient. The electrons transported, n , is 2. The activity for solid iron, Fe, is unity.

Answer: $E_{\text{electrode}} = 0.461$ volt

9-4. Compute the emf of an iron-nickel cell:



in which the activity of ferrous is 0.2 and that of ionic nickel is 0.4. The two half-cells may be combined as



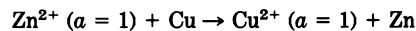
The electron transfer n is equal to 2.

Answer: $E_{\text{cell}} = 0.210$ volt; $E_{\text{cell}} = 0.219$ volt

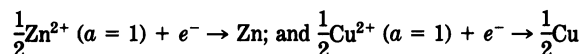
9-5. Calculate E_{cell}° for an electrochemical cell consisting of a lithium electrode and a lead electrode each immersed in a solution of its ions at an activity of 1.00 at 25° C. (a) Represent the electrodes of the cell and write the cell reaction. (b) Calculate E_{cell}° . (c) Oxidation is to take place at the left electrode. Reverse the electrodes so that the oxidation cell now becomes reduction and vice versa. Calculate E_{cell}° under these conditions. It is possible for this reaction to occur? Is it easier for lead to be oxidized than lithium?

Answers: (a) $\text{Li}|\text{Li}^+ (a = 1) \parallel \text{Pb}^{2+} (a = 1)|\text{Pb}$; (b) $E_{\text{cell}}^{\circ} = 2.919$ volt; (c) this part is left for the student to answer.

9-6. Calculate the E_{cell}° for the reaction



in which the half-cell reactions are



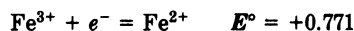
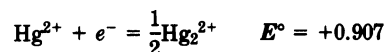
Will copper reduce zinc in such a cell?

Answer: $E_{\text{cell}}^{\circ} = -1.100$ volts. The copper reduction potential in Table 9-1 is more positive than the zinc reduction potential. Therefore copper is more easily reduced than zinc, and a copper electrode cannot reduce a zinc electrode.

9-7. The standard emf E° of a cell consisting of a hydrogen gas electrode as the anode and a silver-silver chloride electrode as the cathode in an aqueous solution of HCl is 0.223 volt at 25° C. When the electrodes are immersed in a 0.50-M solution of HCl the mean ionic activity coefficient γ_{\pm} is 0.77. (a) Write the overall cell reaction and the two half-cell representations. (b) Calculate the emf E of the cell at 25° C.

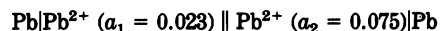
Answers: (a) see equations under Standard EMF of Cells, page 195; (b) $E = 0.272$ volt

9-8. Will mercurous mercury reduce ferric to ferrous iron at 25° C when both half-cells are at unit activity? This case is known as an oxidation-reduction system because it consists of mercurous, mercuric, ferrous, and ferric ions in solution. The two reduction reactions and their corresponding standard potentials at 25° C are found in Table 9-1:



Answer: The half cell potential E° for the mercury electrode is more positive than that of the iron electrode. Mercury is reduced more easily than iron and therefore cannot reduce the iron.

9-9. Consider a concentration cell consisting of two lead electrodes immersed in lead sulfate solutions at 25° C with activities of 0.023 and 0.075:



Calculate (a) the E_{cell}° and (b) the cell emf, E_{cell} .

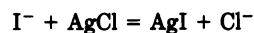
Answers: (a) $E_{\text{cell}}^{\circ} = 0$, as for all concentration cells; (b) $E_{\text{cell}} = 0.015$ volt

9-10. As observed in Table 3-1, electrical energy consists of an intensity factor (electromotive force in volts) multiplied by a capacity factor (the quantity of electrical charge in coulombs). In terms of free energy change, the amount of work $-\Delta G$ done by an electrochemical cell operating reversibly is equal to the electromotive force E_{cell} multiplied by the charge transferred, i.e., n moles or gram equivalents, Eq, times the Faraday constant F in coulombs per mole:

$$-\Delta G = E_{\text{cell}} (\text{volt}) \times (n \text{ Eq of charge transferred}) \times F (96,500 \text{ coulombs/Eq})$$

The resulting units on the free energy change are therefore volts \times coulombs or joules.

(a) What is the free energy change ΔG for the cell reaction

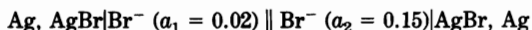


in which the standard emf is $E_{\text{cell}}^{\circ} = +0.361$ volt? This is not the standard potential, E_{cell}° (pp. 195, 196).

(b) The standard potential E° for the cell is +0.379 volt at 25° C. What is the value of the equilibrium constant, K (p. 194, equation (9-11)) and what is the value of ΔG° ?

Answers: (a) $\Delta G = -34,837$ J/mole or -8326 cal/mole; (b) $K = 2.55 \times 10^6$, $\Delta G^{\circ} = -8740$ cal/mole or $-36,568$ J/mole

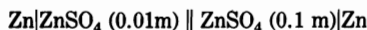
9-11. A concentration cell at 25° C is represented as



What is the emf of this cell?

Answer: 0.052 volt

9-12. Calculate the electromotive force of the concentration cell



Hint: It will be necessary to change molalities to activities by reference to Table 6-1, p. 133.

Answer: $E_{\text{cell}} = 0.017$ volt

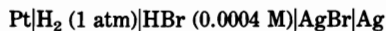
9-13. The pH of a solution containing benzylpenicillin and the potassium salt of this drug, both in a concentration of 0.02 mole/liter, was found to be 2.71 at 25° C. Compute the dissociation constant at this ionic strength, assuming that the average α_i value is 3×10^{-8} , B is 0.33×10^8 , and A is 0.509 (equation 9-45, p. 204 and Table 6-4, p. 136).

Answer: $K_a = 1.69 \times 10^{-8}$

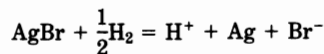
9-14. Instead of using the "half-neutralization" method for the determination of dissociation constants, equation (9-44) can be used directly if the concentration of acid and salt are known. The pH of a mixture containing 0.005 M of a new barbituric acid derivative and 0.01 M of its sodium salt was found to be 7.66 at 25° C. Compute the dissociation constant of the barbiturate at 25° C. The average α_i value is 2×10^{-8} and B is 0.33×10^8 . A at 25° C is 0.509. (See Tables 6-3 and 6-4, p. 136).

Answer: $K_a = 3.92 \times 10^{-8}$

9-15. In Example 9-4 we have a cell consisting of a hydrogen gas electrode as anode and a silver-silver bromide electrode as cathode in a solution of hydrobromic acid:



with an overall cell reaction of



The cell emf, E , is found to be 0.4745 volt and the E° value is 0.071 volt. Since the solid phases are assigned an activity of unity and the pressure of hydrogen gas is 1 atm, the emf of the cell can be written

$$E = E^\circ - 0.0592 \log a_{\text{H}^+} a_{\text{Br}^-}$$

Calculate the mean ionic activity coefficient, γ_{\pm} , for the solution of HBr in this reaction.

Answer: $\gamma_{\pm} = 0.977$

9-16. Ball and Chen³⁰ oxidized a 0.002 M solution of epinephrine with a 0.002 normal ceric sulfate solution in the presence of 0.5 M sulfuric acid. The pH of the solution was 0.29 and the temperature 30° C.

(a) When 39.86% epinephrine was oxidized, i.e., $[\text{Ox}] = 39.86\%$, and the remaining 60.14% was in the reduced form, i.e., $[\text{Rd}] = 60.14\%$, the observed E_D was -0.7850 volt.

(b) When $[\text{Ox}] = 71.5\%$ and $[\text{Rd}] = 28.5\%$, the observed E_D was -0.8030 at 30° C.

Compute $E^{\circ'}$ for each case at 30° C.

Answers: (a) $E^{\circ'} = -0.790$ volt; (b) $E^{\circ'} = -0.791$ volt

9-17. A solution contains Fe^{3+} and Fe^{2+} in the ratio $a_{\text{Fe}^{2+}}:a_{\text{Fe}^{3+}}$ of 10:1. Compute E_D , the redox potential, at 25° C. Hint: See Example 9-3.

Answer: 0.712 volt

9-18. What is the useful E_D range at 25° C for the oxidation-reduction indicator diphenylamine-4-sulfonate (Na salt) in a solution at pH 8, assuming the hydrogen ion activity is the same as its concentration? Note: We find $E^{\circ'}$ is equal to $+0.85$ at a pH of 0; we must calculate $E^{\circ'}$ for pH 8. Then add and subtract the quantity 0.0592 to obtain the useful range. See equations (9-54) and (9-55).

Answer: $+0.436$ to $+0.317$ volt

9-19. (a) In the oxidation of ascorbic acid with potassium ferricyanide at 30° C, the E_D value observed when ascorbic acid was oxidized 35.43% was -0.1284 volt. What is the $E^{\circ'}$ value?

(b) The E_D value observed when ascorbic acid was oxidized 90.79% was -0.1670 volt. Compute $E^{\circ'}$ for this case.

(c) Using the average $E^{\circ'}$ thus obtained, calculate E° for a solution buffered at pH 4.58.

Answers: (a) $E^{\circ'} = -0.1362$; (b) $E^{\circ'} = -0.1371$; (c) $E_{\text{av}}^{\circ'} = -0.1367$; $E^\circ = E_{\text{av}}^{\circ'} + 0.06016 \text{ pH} = -0.1289 + (0.06016)(4.58) = 0.1388$ volt

9-20. In the assay of ascorbic acid in orange juice, Ball and Chen³⁰ titrated 10 mL of orange juice with 0.1 N potassium ferricyanide in 40 mL of an acetate buffer containing 0.001 M thionine as a potential mediator. The ferricyanide solution was standardized against a reference standard ascorbic acid, and each milliliter of the ferricyanide solution was found to be equivalent to 0.87 mg of ascorbic acid in orange juice. If 6.8 mL of ferricyanide was required to reach the endpoint, what is the concentration of ascorbic acid in a 100-mL sample of orange juice?

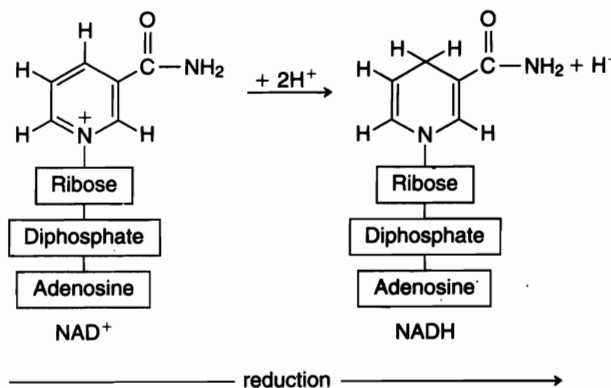
Answer: 59.2 mg

9-21. From Problem 9-16 it is observed that the $E^{\circ'}$ value of epinephrine at 30° C and pH 0.29 is -0.791 . The oxidation potential of the system may be represented by the equation

$$E^\circ = E^{\circ'} + 0.06 \text{ pH}$$

Compute E° for epinephrine using this data, and compare your answer with the oxidation potential in Table 9-6.

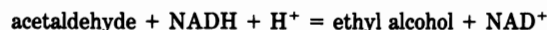
Answer: $E^\circ = -0.774$ volt



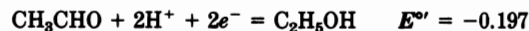
9-22.^{31,32} In the oxidation of metabolites in the mitochondria of aerobic cells, nicotinamide adenine dinucleotide (NAD^+) serves as an oxidizing agent and is reduced to NADH , as shown in the above reaction. The $E^{\circ'}$ value for the reaction at 25° C is -0.320 volt, with both NAD^+ and NADH at 1 M concentration ($a \approx 1$). A modification of the Nernst equation, viz. equation (9-51), is required to calculate E_D , the oxidation-reduction potential. Obtain the value of E_D when the reaction is conducted at a pH 1.0 (i.e., $[\text{H}^+] = 0.1$).

Answer: $E_D = -0.350$ volt

9-23. Calculate the equilibrium constant K and the standard free energy change $\Delta G^{\circ'}$ for the biologic reduction of acetaldehyde to ethyl alcohol in which NADH serves as the electron donor or reducing agent for the reaction³¹



at 25° C. The standard potentials $E^{\circ'}$ are



Hint: Subtraction of these two half-cell $E^{\circ'}$ values gives the overall cell $E^{\circ'}$. $E^{\circ'} = E^{\circ'}_{\text{left}} - E^{\circ'}_{\text{right}} = 0.123$ volt. Also $\ln K = \frac{nFE^{\circ'}}{RT}$, $n = 2$.

Answer: $K = 1.44 \times 10^4$; at 298.15° K, $\Delta G^{\circ'} = -23,739$ J/mole = -5674 cal/mole