5

POTENTIOMETRY

5.1 PRINCIPLES OF POTENTIOMETRIC MEASUREMENTS

In potentiometry, information on the composition of a sample is obtained through the potential appearing between two electrodes. Potentiometry is a classical analytical technique with roots before the twentieth century. However, the rapid development of new selective electrodes and more sensitive and stable electronic components since 1970 has tremendously expanded the range of analytical applications of potentiometric measurements. Selective potentiometric electrodes are currently widely used in many fields, including clinical diagnostics, industrial process control, environmental monitoring, and physiology. For example, such devices are used in nearly all hospitals around the globe for assessing several physiologically important blood electrolytes (K^+, Na^+, Ca^{2+}, Mg^{2+}, H^+, Cl^-) relevant to various health problems. The speed at which this field has developed is a measure of the degree to which potentiometric measurements meet the needs of the analytical chemist for rapid, low-cost, and accurate analysis. In this chapter, the principles of direct potentiometric measurements, based on ion-selective electrodes (ISEs), will be described. ISEs are chemical sensors with the longest history. The field of ISE bridges fundamental membrane science with fundamental host–guest chemistry. (The second major part of potentiometry, the so-called potentiometric titrations, will not be covered.) General books devoted exclusively to direct potentiometry can be found in Refs. 1–5.

The equipment required for direct potentiometric measurements includes an ion-selective electrode, a reference electrode, and a potential-measuring device (a pH/millivolt meter that can read 0.2 mV or better) (Fig. 5.1). Conventional voltmeters cannot be used because only very small currents can be drawn. The reference electrode should provide a highly stable potential for an extended period of time. The ion-selective electrode is an indicator electrode capable of selectively measuring the activity of a particular ionic species (known as the *primary* or *analyte ion*). Such electrodes exhibit a fast response and a wide linear range, are not affected by color or turbidity, are not destructive, and are very inexpensive. Ion-selective electrodes can be assembled conveniently in a variety of shapes and sizes. Specially designed cells allow flow or microliter analyses (see, e.g., Section 5-3).

Ion-selective electrodes are mainly membrane-based devices, consisting of permselective ion-conducting materials, which separate the sample from the inside of the electrode (Fig. 5.2). On the inside is a filling solution containing the ion of interest at a constant activity. The membrane is usually nonporous, water insoluble, and mechanically stable. The composition of the membrane is designed to yield a potential that is primarily due to the ion of interest (via selective binding processes, e.g., ion exchange, which occur at the membrane–solution interface). The trick is to find a membrane that will selectively bind the analyte ions, leaving co-ions behind. Membrane materials, possessing different ion recognition properties, have thus been developed to impart high
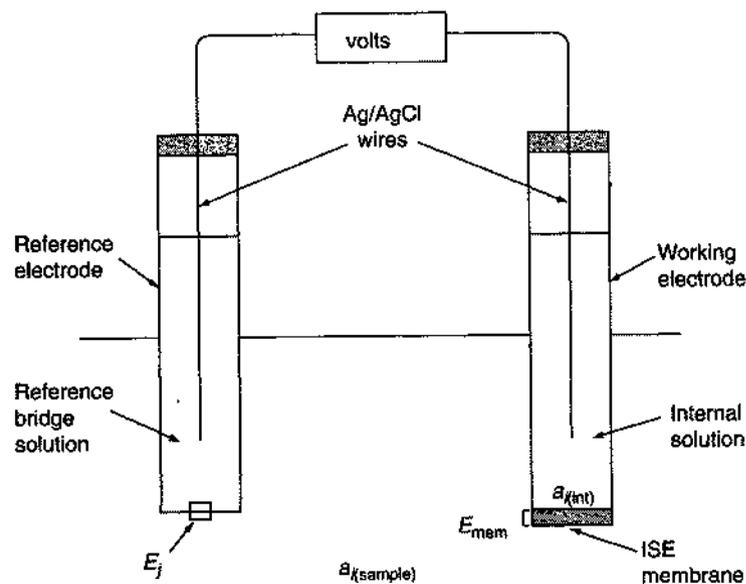

Figure 5.1 Schematic diagram of an electrochemical cell for potentiometric measurements.

$$E_M = RT/nF \ln (a_{i,\text{sample}} / a_{i,\text{inner solution}})$$
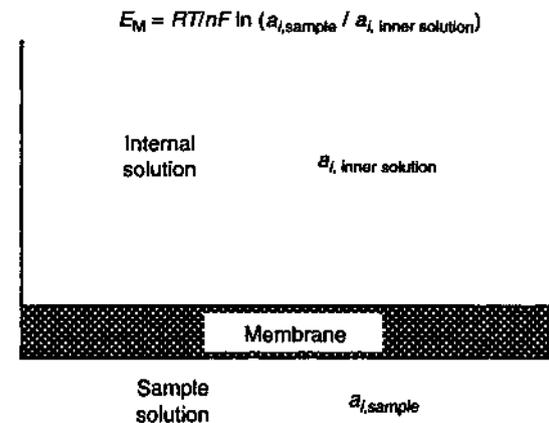
Figure 5.2 Membrane potential reflects the gradient of activity of the analyte ion in the inner and outer (sample) solutions.

selectivity (see Section 5.2). Detailed theory of the processes at the interface of these membranes, which generate the potential, is available elsewhere (6–8). The ion recognition (binding) event generates a phase boundary potential at the membrane–sample interface:

$$E_{PB} = \frac{RT}{z_i F} \ln k_i + \frac{RT}{z_i F} \ln \frac{a_i(\text{aq})}{a_i(\text{org})} \tag{5.1}$$

where R is the universal gas constant (8.134 J K^{-1} mol^{-1}), F is the Faraday constant, and T is the absolute temperature; $a_i(\text{aq})$ and $a_i(\text{org})$ are the activities of the primary ion (with charge z_i) in the aqueous sample and the contacting organic phase boundary, respectively, and k_i is a function of the relative free energies of solvation in both the sample and the membrane phase ($k_i = \exp(\{\mu_i^0$ (aq) $- \mu_i^0(\text{org})\})/RT$, where $\mu_i^0(\text{aq})$ and $\mu_i^0(\text{org})$ are the chemical standard potentials of the ion I^{z+} in the respective phase). The first term on the right-hand side of Eq. (5.1) is in fact the standard potential, which is constant for a given ion but varies from ion to ion. The phase boundary potential is a consequence the unequal distribution of the analyte ions across the boundary. From Eq. (5.1) it is apparent that a selective binding to a cation in the membrane decreases its activity in the membrane phase and thus increases the phase boundary potential.

Another phase boundary potential is developed at the inner surface of the membrane (at the membrane/filling solution interface). The membrane potential corresponds to the potential difference across the membrane:

$$E = \frac{RT}{nF} \ln(a_{i,\text{sample}} / a_{i,\text{int soln}}) \tag{5.2}$$

The potential of the ion-selective electrode is generally monitored relative to the potential of a reference electrode. Since the potential of the reference electrode is fixed, and the activity of the ion in the inner solution is constant, the measured cell potential reflects the potential of the ISE, and can thus be related to the activity of the target ion in the sample solution. Ideally, the response of the ISE should obey the following equation

$$E = K + (2.303\,RT/z_iF)\log a_i \qquad (5.3)$$

where E is the potential, and z_i and a_i are the ionic charge and activity, respectively, of the ion. The constant K includes all sample-independent potential contributions, which depends on various factors (influenced by the specific design of the ISE). Equation (5.3) predicts that the electrode potential is proportional to the logarithm of the activity of the ion monitored. For example, at room temperature a 59.1-mV change in the electrode potential should result from a 10-fold change in the activity of a monovalent ion ($z = 1$). Similar changes in the activity of a divalent ion should result in a 29.6-mV change of the potential. A 1-mV change in the potential corresponds to 4% and 8% changes in the activity of monovalent and divalent ions, respectively. The term "Nernstian behavior" is used to characterize such behavior. In contrast, when the slope of the electrode response is significantly smaller than $59.1/z_i$, the electrode is characterized by a sub-Nernstian behavior.

It should be noted again that ISEs sense the activity, rather than the concentration of ions in solution. The term "activity" is used to denote the effective (active) concentration of the ion. The difference between concentration and activity arises because of ionic interactions (with oppositely charged ions) that reduce the effective concentration of the ion. The activity of an ion i in solution is related to its concentration c_i by the following equation:

$$a_i = f_i c_i \qquad (5.4)$$

where f_i is the activity coefficient. The activity coefficient depends on the types of ions present and on the total ionic strength of the solution. The activity coefficient is given by the Debye–Hückel equation

$$\log f_i = \frac{-0.51 z_i^2 \sqrt{\mu}}{1 + \sqrt{\mu}} \qquad \text{(at 25°C)} \qquad (5.5)$$

where μ is the ionic strength. The ionic strength refers to the concentration of all ions in the solution and also takes into account their charge. The activity coefficient thus approaches unity (i.e., $a_i \cong C_i$) in very dilute solutions. The departure from unity increases as the charge of the ion increases.

Equation (5.3) has been written on the assumption that the electrode responds only to the ion of interest, i. In practice, no electrode responds exclusively to the ion specified. The actual response of the electrode in a binary

mixture of the primary and interfering ions (i and j, respectively) is given by the *Nikolskii–Eisenman equation* (9):

$$E = K + (2.303\,RT/z_iF)\log\!\left(a_i + k_{ij}a_j^{z_i/z_j}\right) \qquad (5.6)$$

where k_{ij} is the selectivity coefficient, a quantitative measure of the electrode ability to discriminate against the interfering ion (i.e., a measure of the relative affinity of ions i and j toward the ion-selective membrane). For example, if an electrode is 50 times more responsive to i than to j, k_{ij} has a value of 0.02. A k_{ij} value of 1.0 corresponds to a similar response for both ions. When $k_{ij} \gg 1$, then the ISE responds better to the interfering ion j than to the target ion i. Usually, k_{ij} is smaller than 1, which means that the ISE responds more selectively to the target ion. The lower the value of k_{ij}, the more selective is the electrode. Selectivity coefficients lower than 10^{-5} have been achieved for several electrodes. For an ideally selective electrode, the k_{ij} would equal zero (i.e., no interference). Obviously, the error in the activity a_i due to the interference of j would depend on their relative levels. The term z_i/z_j corrects for a possible charge difference between the target and interfering ions. Normally, the most serious interferences have the same charge as the primary ion so that $z_i/z_j = 1$. In practice, the contribution of all interfering ions present in the sample matrix ($\Sigma k_{ij}a^{z_i/z_j}$) should be included in the Nikolskii–Eisenman equation. For example, for a sodium electrode immersed in a mixture of sodium, potassium, and lithium, the response is given by

$$E = K + 2.303\,RT/F \log(a_{Na} + k_{Na,K}a_K + k_{Na,Li}a_{Li}) \qquad (5.7)$$

Accordingly, an ISE displays a selective response when the activity of the primary ion is much larger than the summation term of the interferents, specifically, $a_i \gg \Sigma k_{ij}a_j^{z_i/z_j}$. Under this condition, the effect of interfering ions is negligible, and changes in the measured potential can be related with confidence to variations in the activity of the target ion. The selectivity coefficients thus serve as guidelines as to how far a given ISE should be applicable for a particular analytical problem. Nonselective ISEs are rarely useful for real-life applications (with the exception of their combination with the operation of ISE arrays; see Section 6.4). In reality, equations with more than two components are rarely used. Deviations from the Nikolski–Eisenman equation have been reported for various situations (particularly for mixtures of ions of different charge, in the case of non-Nernstian behavior of interfering ions, and due to the concentration dependence of k_{ij}).

It is important for the analytical chemist to realize the selectivity coefficient of a particular electrode. Various methods have been suggested for determining the selectivity coefficient, including the fixed-interference method, separate solution method, and the fixed primary ion method (10,11). The most popular fixed interference method involves two solutions, one containing a

constant concentration of the interfering ion and the second, containing a zero concentration. Also popular is the separate solution method, which involves the preparation of calibration curves for each ion. As selectivity is a complex function of the membrane composition and the experimental design, the values of selectivity coefficients should be regarded as operationally defined (i.e., valid for the particular set of conditions used for their determination).

Usually, the analytical chemist needs to determine the concentration of the ion of interest rather than its activity. The obvious approach to converting potentiometric measurements from activity to concentration is to make use of an empirical calibration curve, such as the one shown in Figure 5.3. Electrodes potentials of standard solutions are thus measured and plotted (on a semilog paper) versus the concentration. Since the ionic strength of the sample is seldom known, it is often useful to add a high concentration of an electrolyte to the standards and the sample to maintain approximately the same ionic strength (i.e., the same activity coefficient). The ionic strength adjustor is usually a buffer (since pH control is also desired for most ISEs). The empirical calibration plot thus yields results in terms of concentration. Theoretically,
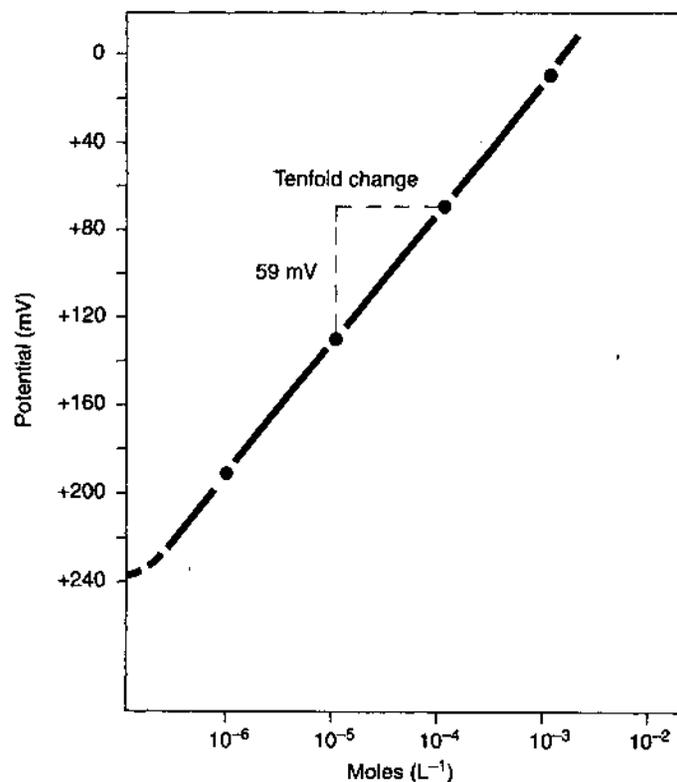

Figure 5.3 Typical calibration plot for a monovalent ion.

such a plot should yield a straight line, with a slope of approximately $59/z_i$ mV (Nernstian slope). Detection by means of ion-selective electrodes may be performed over an exceedingly broad concentration range, which, for certain electrodes, may embrace five orders of magnitude. In practice, the usable range depends on other ions in the solution. Departure from the linearity is commonly observed at low concentrations (about 10^{-6} M) due to the presence of coexisting ions [Eq. (5.6)]. The extent of such departure (and the minimum activity that can be accurately measured) depend on the selectivity coefficient as well as upon the level of the interfering ion (Fig. 5.4). The detection limit for the analyte ion is defined by

$$a_{i,min} = k_{ij} a_j^{z_i/z_j} \qquad (5.8)$$

and corresponds to the activity of i at the intersection of the asymptotes in the $E/\log a_i$ calibration plot, that is, where the extrapolated linear and zero-slope segments meet (see Ref. 12 and Fig 5.5). It is only when the plot becomes almost horizontal that the activity measurement becomes impossible. At high concentrations of the ions of interest, interference by species of opposite charge [not described by Eq. (5.6)] may lead to deviation from the linear electrode response.
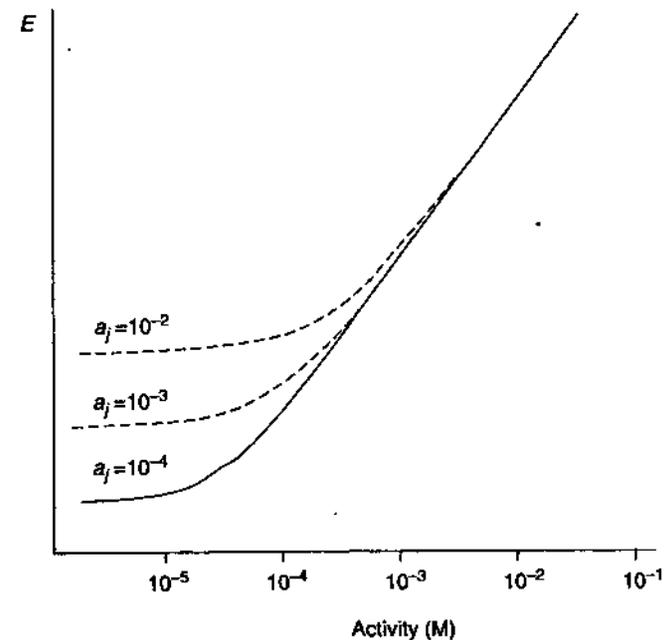

Figure 5.4 The potential response of an ion-selective electrode versus activity of ion i in the presence of different levels of an interfering ion j.
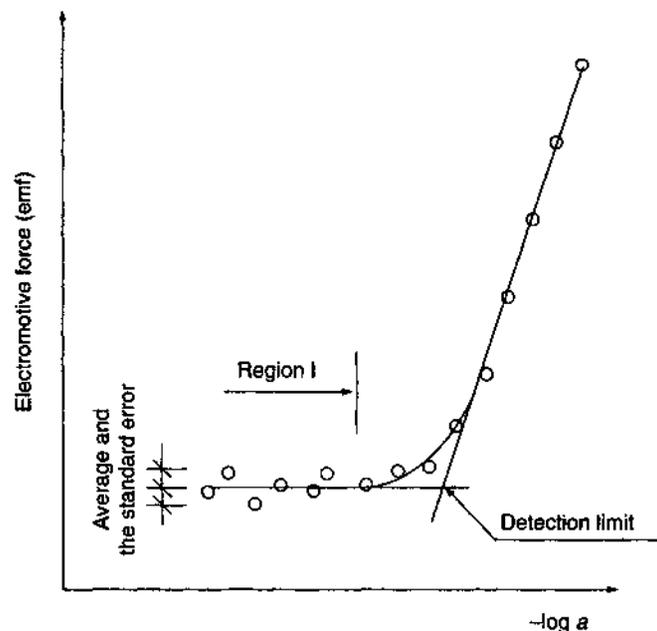
Figure 5.5 Determination of the detection limit of ion-selective electrodes. (Reproduced with permission from Ref. 12.)

The logarithmic response of ISEs can cause major accuracy problems. Very small uncertainties in the measured cell potential can thus cause large errors. (Recall that an uncertainty of ± 1 mV corresponds to a relative error of ~4% in the concentration of a monovalent ion.) Since potential measurements are seldom better than 0.1 mV uncertainty, best measurements of monovalent ions are limited to about 0.4% relative concentration error. In many practical situations, the error is significantly larger. The main source of error in potentiometric measurements is actually not the ISE, but rather changes in the reference electrode junction potential, namely, the potential difference generated between the reference electrolyte and sample solution. The junction potential is caused by an unequal distribution of anions and cations across the boundary between two dissimilar electrolyte solutions (which results in ion movement at different rates). When the two solutions differ only in the electrolyte concentration, such liquid junction potential is proportional to the difference in transference numbers of the positive and negative ions and to the log of the ratio of the ions on both sides of the junction:

$$E = \frac{RT}{F}(t_1 - t_2)\ln\frac{a_i(1)}{a_i(2)} \qquad (5.9)$$

Changes in the reference electrode junction potential result from differences in the composition of the sample and standard solutions (e.g., on switching from whole blood samples to aqueous calibrants). One approach to alleviate this problem is to use an intermediate salt bridge, with a solution (in the bridge) of ions of nearly equal mobility (e.g., concentrated KCl). Standard solutions with an electrolyte composition similar to the sample are also desirable. These precautions, however, will not eliminate the problem completely. Other approaches to address this and other changes in the cell constant have been reviewed (13).

5.2 ION-SELECTIVE ELECTRODES

The discussion in Section 5.1 clearly illustrates that the most important response characteristic of an ISE is selectivity. Depending on the nature of the membrane material used to impart the desired selectivity, ISEs can be divided into three groups: glass, liquid, or solid electrodes. More than three dozen ISEs are commercially available and are widely used (although many more have been reported in the literature). Such electrodes are produced by firms such as Thermo-Electron (Orion), Radiometer, Corning Glass, Beckman, Hitachi, or Sensorex. Recent research activity has led to exciting advances in the area of ISE, including dramatic lowering of their detection limits (to enable trace analysis), identification of new ionophore systems, or new membranes responding to important polyionic species (e.g., heparin) or to neutral species (such as surfactants) (14).

5.2.1 Glass Electrodes

Glass electrodes are responsive to univalent cations. The selectivity for these cations is achieved by varying the composition of a thin ion-sensitive glass membrane.

5.2.1.1 pH Electrodes
The most common potentiometric device is the pH electrode. This electrode has been widely used for pH measurements for several decades. Besides direct pH measurements, the pH glass electrode is commonly employed as the transducer in various gas and biocatalytic sensors, involving proton-generating/consuming reactions (see Chapter 6). Its remarkable success is attributed to its outstanding analytical performance, in particular its extremely high selectivity for hydrogen ions, its remarkably broad response range, and its fast and stable response. The phenomenon of glass selectivity was reported by Cremer in 1906 (15). Glass pH electrodes of different configurations and dimensions have been in routine use since the early 1940s following their commercial introduction by A. Beckman. A schematic of a commonly used configuration is shown in Figure 5.6. This consists of a
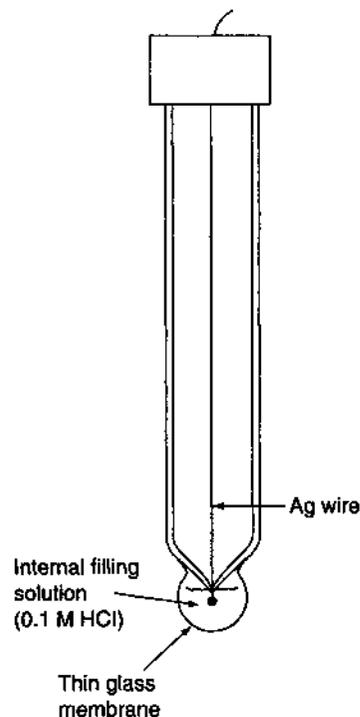
Figure 5.6   A glass pH electrode.

thin, pH-sensitive glass membrane sealed to the bottom of an ordinary glass tube. The composition of the glass membrane is carefully controlled. Usually, it consists of a three-dimensional silicate network, with negatively charged oxygen atoms, available for coordinating cations of suitable size. Some of the more popular glasses have three-component compositions of 72% SiO_2–22% Na_2O–6% CaO or 80% SiO_2–10% Li_2O–10% CaO. Inside the glass bulb are a dilute hydrochloric acid solution and a silver wire coated with a layer of silver chloride. The electrode is immersed in the solution whose pH is to be measured, and connected to an external reference electrode. (In the so-called combination electrode, the external reference electrode is combined with the ion-selective electrode into one body.) The rapid equilibrium established across the glass membrane, with respect to the hydrogen ions in the inner and outer solutions, produces a potential:

$$E = K + (RT/F)\ln(H^+)_{inner}/(H^+)_{outer} \tag{5.10}$$

The potential of the electrode is registered with respect to the external reference electrode. Hence, the cell potential (at 25°C and after introducing the definition of pH) follows the relation

$$E_{cell} = K' + 0.059 \text{ pH} \tag{5.11}$$

The measured potential is thus a linear function of pH; an extremely wide (10–14 decades) linear range is obtained, with calibration plots yielding a slope of 59 mV/pH unit. The overall mechanism of the response is complex. The selective response is attributed to the ion exchange properties of the glass surface, in particular replacement of sodium ions associated with the silicate groups in the glass by protons:

$$Na^+_{glass} + H_3O^+_{soln} = H_3O^+_{glass} + Na^+_{soln} \tag{5.12}$$
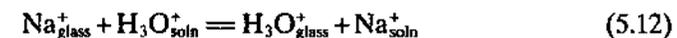
The theory of the response mechanism has been thoroughly discussed (16).

The user must be alert to some shortcomings of the glass pH electrode. For example, in solutions of pH ≥ 11, the electrode shows a so-called alkaline error in which it also responds to changes in the level of alkali metal ions (particularly sodium):

$$E_{cell} = K + 0.059 \log([H_3O^+] + k_{H,Na}[Na^+]) \tag{5.13}$$

As a result, the pH is lower than the true value (Fig. 5.7). This error is greatly reduced if the sodium oxide in the glass is replaced by lithium oxide. Still, even
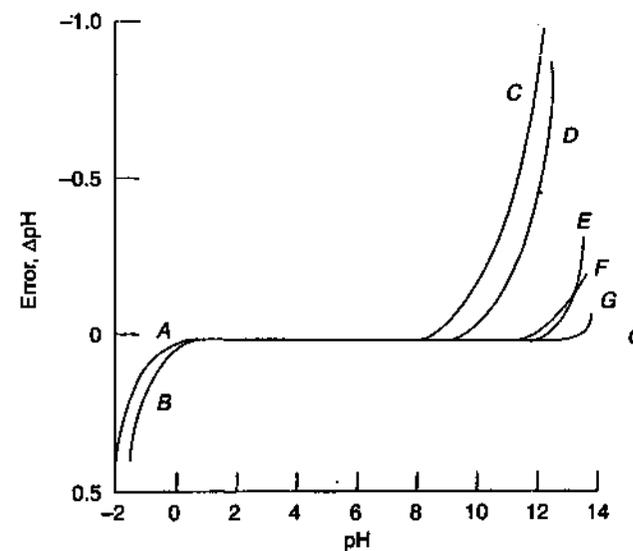

Figure 5.7   The alkaline and acid errors of several glass pH electrodes: A, Corning 015/H_2SO_4; B, Corning 015/HCl; C, Corning 015/1 M Na^+; D, Beckman-GP/1 M Na^+; E, L&N BlackDot/1 M Na^+; F, Beckman E/1 M Na^+; G, Ross electrode. (Reproduced with permission from Ref. 17.)

with new glass formulations (with $k_{H,Na} < 10^{-10}$), errors can be appreciable when measurements are carried out in highly basic solutions (e.g., NaOH). Many glass electrodes also exhibit erroneous results in highly acidic solutions (pH < 0.5); the so-called acid error yields higher pH readings than the true value (Fig. 5.7).

Before using the pH electrode, it should be calibrated using two (or more) buffers of known pH. Many standard buffers are commercially available, with an accuracy of ±0.01 pH unit. Calibration must be performed at the same temperature at which the measurement will be made; care must be taken to match the temperature of samples and standards. The exact procedure depends on the model of pH meter used. Modern pH meters, such as the one shown in Figure 5.8, are microcomputer-controlled, and allow double-point calibration, slope calculation, temperature adjustment, and accuracy to ±0.001 pH unit, all with few basic steps. The electrode must be stored in an aqueous solution when not in use, so that the hydrated gel layer of the glass does not dry out. A highly stable response can thus be obtained over long time periods. As with other ion-selective electrodes, the operator should consult the manufacturer's instructions for proper use. Commercial glass electrodes are remarkably

Figure 5.8 A modern microprocessor-controlled pH meter.

robust and, with proper care, will last for more than a year. Proper maintenance of the reference electrode is also essential to minimize errors.

Measurements of pH can also be performed using other types of potentiometric sensors. Nonglass electrodes offer various advantages for certain pH measurements (particularly intravascular and intraluminal clinical applications, food assays, and operation in fluoride media), including ease of preparation, low electrical resistance, and safety in handling. The most common examples are the quinhydrone electrode in which the response is due to a proton transfer redox reaction (of the quinone–hydroquinone couple) and the antimony electrode (based on the redox reaction between antimony and antimony oxide involving protons). Other metal—metal oxide couples, such as palladium—palladium oxide, have been applied for pH measurements. Membrane electrodes based on various neutral hydrogen ion carriers (e.g., tridodecylamine) can also be employed (18). The resulting electrodes exhibit excellent selectivity, reproducibility, and accuracy, but their dynamic range is inferior compared with glass electrodes. (Such a range appears to depend on the acidity constant of the incorporated ionophore.) New pH sensors based on new glass compositions or nonglass formulations are currently (as of 2005) being developed in various laboratories. While such electrodes may be useful for specific applications, glass electrodes are likely to remain the choice for routine analytical applications.

5.2.1.2 Glass Electrodes for Other Cations

From the early days of glass pH electrodes, alkaline solutions were noted to display some interference on the pH response. Deliberate changes in the chemical composition of the glass membrane (along with replacements of the internal filling solution) have thus led to electrodes responsive to monovalent cations other than hydrogen, including sodium, ammonium, and potassium (16). This usually involves the addition of B_2O_3 or Al_2O_3 to sodium silicate glasses, to produce anionic sites of appropriate charge and geometry on the outer layer of the glass surface. For example, the sodium- and ammonium-selective glasses have the compositions $11\% Na_2O$ –$18\% Al_2O_3$ –$71\% SiO_2$ and $27\% Na_2O$ –$4\% Al_2O_3$ –$69\% SiO_2$, respectively. Unlike sodium silicate glasses (used for pH measurements), these sodium aluminosilicate glasses possess what may be termed $AlOSiO^-$ sites with a weaker electrostatic field strength and a marked preference for cations other than protons. The overall mechanism of the electrode response is complex but involves a combination of surface ion exchange and ion diffusion steps. To further minimize interference from hydrogen ions, it is desirable to use solutions with pH values higher than 5. Improved mechanical and electrical properties can be achieved using more complex glasses containing various additives.

5.2.2 Liquid Membrane Electrodes

Liquid-membrane-type ISEs, based on water-immiscible liquid substances impregnated in a polymeric membrane, are widely used for direct potentio-

metric measurements (18–20). Such ISEs are particularly important because they permit direct measurements of several polyvalent cations as well as certain anions. The polymeric membrane [commonly made of plasticized poly(vinyl chloride) (PVC)] separates the test solution from the inner compartment, containing a standard solution of the target ion (into which a silver–silver chloride wire is dipped). The filling solution usually contains a chloride salt of the primary ion, as desired for establishing the potential of the internal silver–silver chloride wire electrode. The membrane-active (recognition) component can be an ion exchanger or a neutral macrocyclic compound. The selective extraction of the target ion at the sample–membrane interface creates the electrochemical phase boundary potential. The membranes are commonly prepared by dissolving the recognition element, a plasticizer (e.g., o-nitrophenyl ether, which provides the properties of liquid phase), and the PVC in a solvent such as tetrahydrofuran. (The recognition element is usually present in 1–3% amount.) Slow (overnight) evaporation of the solvent leaves a flexible membrane of 50–200 μm thickness, which can be cut (with a cork borer) and mounted on the end of plastic tube. The ion-discriminating ability (and hence the selectivity coefficient) depends not only on the nature of the recognition element but also on the exact membrane composition, including the membrane solvent and the nature and content of the plasticizer. The extraction properties of the membrane can be further improved by adding ion-pairing agents to the plasticizer. The PVC matrix provides mechanical strength and permits diffusion of analytes to the recognition sites. The hydrophobic nature of the membrane prevents leaching of the sensing element and the plasticizer into the aqueous sample solution, and thus extends the operational lifetime. Different methacrylic–acrylic copolymers were suggested as alternative to PVC (21). Such polymers require no plasticizer and facilitate the covalent attachment of crown-ether recognition elements.

It was shown that leaching of the primary ion (from the internal electrolyte solution) leads to its higher activity at the layer adjacent to the membrane (relative to the bulk sample), and hence to increased detection limits of carrier-based liquid membrane electrodes (22–26). These fluxes maintain a micromolar activity in the proximity of the membrane–solution interface, even if the sample contains virtually no primary ions. Such a localized accumulation of ions makes it impossible to measure dilute samples and restricts the detection limits to the micromolar range. In addition, this leak limits the selectivity coefficients to $\sim 10^{-4}$. By choosing an internal electrolyte with low activity of the primary ion and preventing it from leaking it is possible to greatly lower the detection limits by up to six orders of magnitude down to the picomolar (ppt) range (23–26). Several schemes have thus been suggested for minimizing biases due to ion fluxes through the membrane and improving the detection limits. One way to accomplish this is to add a hydrophilic complexing agent (such as EDTA) or ion exchanger to the inner solution of the membrane. Such adjustment of the inner solution can be combined with membranes that are less sensitive to concentration gradients. Another way to

avoid leaching of primary ions from the membrane into the sample is to apply a very small external current that generates a steady flux of cations toward the inner compartment of the ISE (27). This procedure is attractive because it is easier to change the required current (rather than adjusting the inner solution). Such current-induced galvanostatic elimination of undesired leaching is displayed in Figure 5.9. Inward fluxes (i.e., siphoning of the primary ion from the sample) may also result from significant ion exchange at the inner side of the membrane. This can lead to depletion of the primary ion from the sample side of the membrane and hence to a super-Nernstian response along with poor practical detection limits. Accordingly, fluxes in either direction should be avoided. Active research in various laboratories is currently elucidating these interfacial ion fluxes relative to the development of potentiometric sensors for trace analysis. Covalent bonding of the ionophore to a polymer backbone has also been shown useful for addressing the adverse effect of zero-current ion fluxes and for improving the detection limits (28). Such covalent attachment also extends the lifetime of the corresponding ISE.

5.2.2.1 Ion Exchanger Electrodes One of the most successful liquid membrane electrodes is selective toward calcium. Such an electrode relies on the ability of phosphate ions to form stable complexes with the calcium ion. It uses a liquid cation exchanger, consisting of an aliphatic diester of phosphoric acid
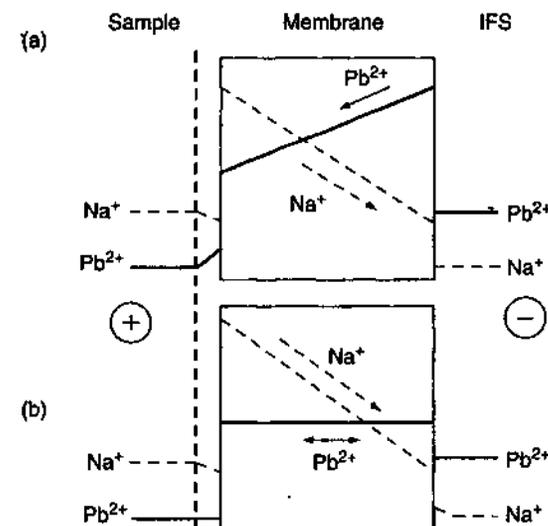

Figure 5.9 Elimination of primary ion leaching from the inner filling solution across the membrane, into the sample, by applying a negative current. Hypothetical concentration profiles in a lead-selective membrane before (a) and after (b) applied negative current. Arrows indicate the direction of the net ion fluxes. (Reproduced with permission from Ref. 25.)

$[(RO)_2PO_2^-$ with R groups in the C_8–C_{16} range], that possesses high affinity for calcium ions. The ion exchanger is held in a porous, plastic filter membrane that separates the test solution from the inner compartment, containing a standard calcium chloride solution (Fig. 5.10). The preferential uptake of calcium ions into the membrane can thus be represented as

$$Ca^{2+} + 2(RO)_2PO_2^- \rightleftharpoons [(RO)_2PO_2]_2 Ca \tag{5.14}$$
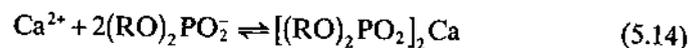
The resulting cell potential is given by

$$E_{cell} = K + \frac{0.059}{2} \log a_{Ca} \tag{5.15}$$

Calcium activities as low as $5 \times 10^{-7} M$ can be measured, with selectivity coefficients of $K_{Ca,Mg}$ and $K_{Ca,K}$ of 0.02 and 0.001, respectively. Such potential response is independent of the pH over the pH range 5.5–11.0. Above pH 11, $Ca(OH)^+$ is formed, while below 5.5, protons interfere. Because of its attractive response characteristics, the calcium ISE has proved to be a valuable tool for the determination of calcium ion activity in various biological fluids.

Anion exchangers, such as lipophilic quaternary ammonium salts (e.g., see Fig. 5.11) or phosphonium salts, have been employed for the preparation of
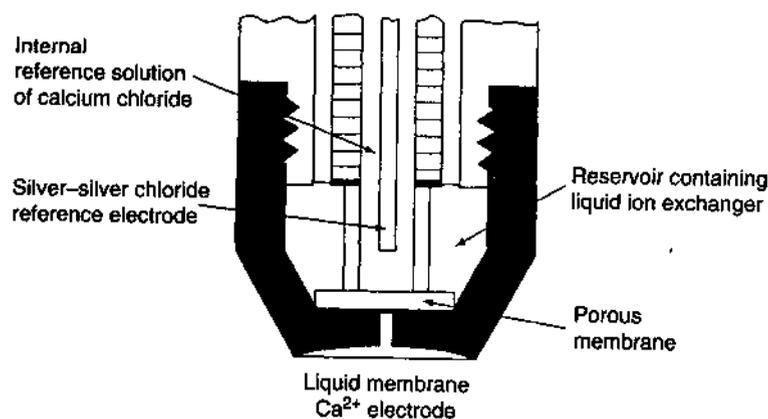

Internal
reference solution
of calcium chloride

Silver–silver chloride
reference electrode

Reservoir containing
liquid ion exchanger

Porous
membrane

Liquid membrane
Ca²⁺ electrode

Figure 5.10 Schematic diagram of a calcium-ion-selective electrode.
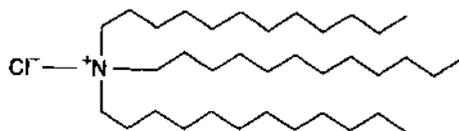

Cl⁻—⁺N

Figure 5.11 Quaternary alkyl ammonium chloride.

anion-selective sensors. The resulting ISEs usually lack an anion recognition function, and hence display anion selectivity corresponding to the anion partition into the supporting hydrophobic membrane. This gives rises to the following selectivity order, which is known as the *Hofmeister series*: large liphophilic anions > ClO_4^- > IO_4^- > SCN^- > I^- > NO_3^- > Br^- > Cl^- > HCO_3^- > $H_2PO_4^-$ (i.e., with maximum response to lipophilic anions) (29). Accordingly, several commercial sensors (e.g., NO_3^- "selective" electrodes), based on ion-exchange-type membranes, suffer an interference from liphohilic anions (e.g., ClO_4^-). Electrodes useful for nitrate (30), thiocyanate (31), and chloride (32) ions have thus been developed. Sensors responsive to anionic macromolecules have also been developed despite the greater difficulty in identifying appropriate membrane chemistry that yields a significant and selective response (33,34). A very successful example is the use of the quaternary ammonium salt tridodecyl-methylammonium chloride (TDMAC) for detecting the clinically important drug heparin (33). Apparently, the polyionic heparin is favorably extracted into the membrane through ion-pairing interaction with the positively charged nitrogen atoms (Fig. 5.12). Such an extraction process results in a steady-state change in the phase boundary potential at the membrane–sample interface. Analogous potentiometric measurements of other macromolecular polyanionic (e.g., polyphosphates, DNA) or polycationic (e.g., protamine, polyarginine) species, based on the use of various lipophilic ion exchangers, have been reported (34,35). Ion exchange electrodes sensitive to large organic cations have also been described. For example, PVC membranes containing dinonylnaphthalenesulfonic acid (DNNS) have been used for the detection of drugs of abuse (e.g., opiate alkaloids) (36). Such organic-responsive elec-
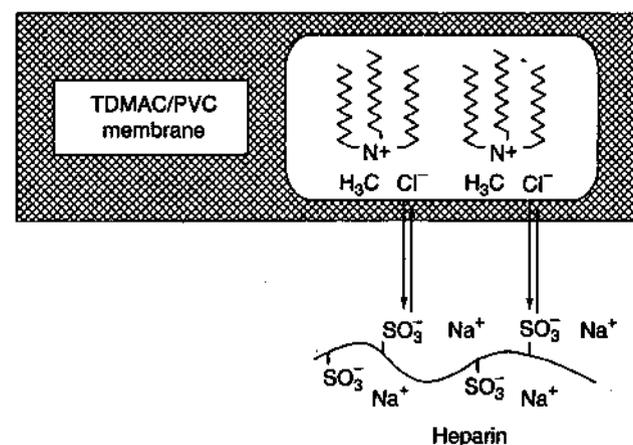

TDMAC/PVC
membrane

N+   N+
H₃C Cl⁻   H₃C Cl⁻

SO₃⁻ Na⁺   SO₃⁻ Na⁺
SO₃⁻ Na⁺   SO₃⁻ Na⁺

Heparin

Figure 5.12 The recognition process occurring at the TDMAC/PVC membrane-sample interface used for measurements of heparin. (Reproduced with permission from Ref. 34.)

trodes, however, lack sufficient selectivity and are limited to simple samples, such as pharmaceutical formulations.

5.2.2.2 Neutral Carrier Electrodes In addition to charged liquid ion exchangers, liquid membrane electrodes often rely on the use of complex-forming neutral-charged carriers. Since the early 1980s much effort has been devoted to the isolation or synthesis of compounds containing cavities of molecule-sized dimensions. Such use of chemical recognition principles has made an enormous impact on widespread acceptance of ISEs. For example, most blood electrolyte determinations are currently being performed with ionophore-based sensors, either with centralized clinical analyzers or with decentralized disposable units.

Neutral carriers can be natural macrocyclic molecules or synthetic crown compounds (e.g, cyclic polyethers) capable of enveloping various target ions in their pocket. Electron-donor atoms, present in the polar host cavity, further facilitate and influence the interaction with the target ion. For example, while oxygen-containing crown ethers form stable complexes with alkali or alkali earth metals, sulfur-containing ones are best suited for binding heavy metals. The extent of this interaction is determined by the "best fit" mechanism, with larger ions that cannot fit in the molecular cavity, and smaller ones that are weakly coordinated. Often, a subunit group is added to the crown compound to impart higher selectivity (through a steric/blockage effect) and improved lipophilicity. Overall, these ionophores serve as reversible and reusable binding reagents that selectively extract the target analyte into the membrane. Such binding event creates the phase boundary potential at the membrane–sample interface. To ensure reversible binding, it is essential to keep the free energy of activation of the analyte–ionophore reaction sufficiently small (37). Molecular modeling techniques are being used to guide the design of ionophores toward target analytes. The specific design takes into consideration the selectivity demands imposed by clinical or environmental samples.

A host of carriers, with a wide variety of ion selectivities, have been proposed for this task. Most of them have been used for the recognition of alkali and alkaline metal cations (e.g., clinically relevant electrolytes). A classical example is the cyclic depsipeptide valinomycin (Fig. 5.13), used as the basis for the widely used ISE for potassium ion (38). This doughnut-shaped molecule has an electron-rich pocket in the center into which potassium ions are selectively extracted. For example, the electrode exhibits a selectivity for K^+ over Na^+ of approximately 30,000. The basis for the selectivity seems to be the fit between the size of the potassium ion (radius 1.33 Å) and the volume of the internal cavity of the macrocyclic molecule. The hydrophobic sidechains of valinomycin stretch into the lipophilic part of the membrane. In addition to its excellent selectivity, such an electrode is well behaved and has a wide working pH range. Strongly acidic media can be employed because the electrode is 18,000 times more responsive to K^+ than to H^+. A Nernstian response to potassium ion activities, with a slope of 59 mV/pK$^+$, is commonly observed
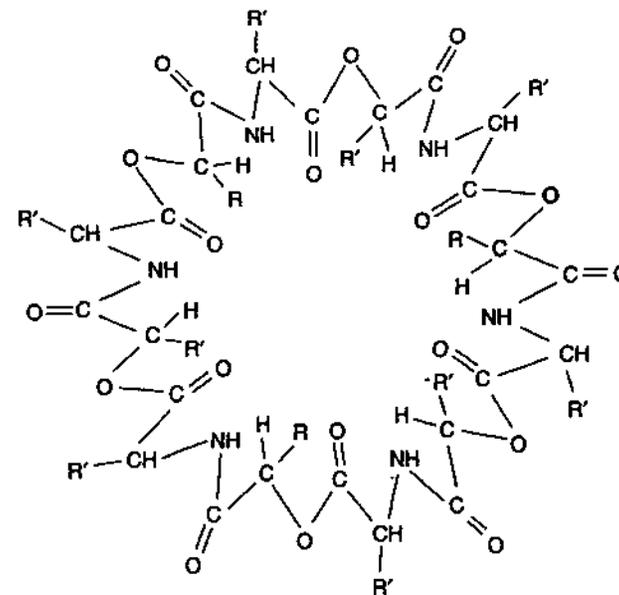
Figure 5.13 Valinomycin.

from 10^{-6} to 0.1 M. Such attractive performance characteristics have made the valinomycin ISE extremely popular for clinical analysis (with 200 million assays of blood potassium carried out annually in the United States using this device).

Many other cyclic and noncyclic organic carriers with remarkable ion selectivities have been used successfully as active hosts of various liquid membrane electrodes. These include the 14-crown-4-ether for lithium (39); 16-crown-5 derivatives for sodium; bis (benzo-18-crown-6 ether) for cesium; the ionophore ETH 1001[(R,R)-N,N'-bis(11-ethoxycarbonyl)undecyl-N,N'-4,5-tetramethyl-3,6-dioxaoctanediamide] for calcium; the natural macrocyclics nonaction and monensin for ammonia and sodium (40); respectively; the ionophore ETH 1117 for magnesium, calixarene derivatives for sodium (41) and lead (42); and macrocyclic thioethers for mercury and silver (43). Some common ionophores used for sensing different cations are displayed in Figure 5.14. The development of highly selective lithium electrodes for clinical monitoring of psychiatric patients (receiving lithium-based drugs) has been particularly challenging considering the large sodium interference. Similarly, highly selective ionophores for sodium are needed to address the large excess of potassium in the intracellular fluid. Neutral carrier ISEs have been successfully applied for environmental samples, including trace (subnanomolar) measurements of lead and lead speciation in various natural waters (42). For example, adjusting a lead-containing sample to various pH values has allowed reliable measurement of the fractions of uncomplexed lead (with a good correlation to the the-
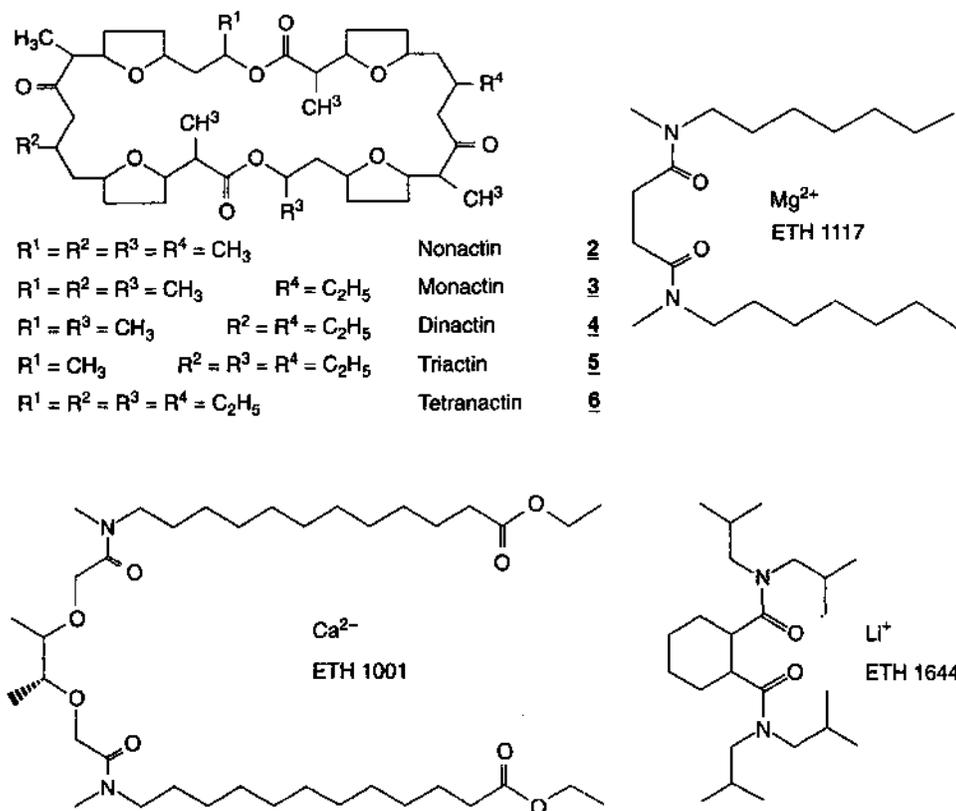
R¹ = R² = R³ = R⁴ = CH₃		Nonactin	**2**
R¹ = R² = R³ = CH₃	R⁴ = C₂H₅	Monactin	**3**
R¹ = R³ = CH₃	R² = R⁴ = C₂H₅	Dinactin	**4**
R¹ = CH₃	R² = R³ = R⁴ = C₂H₅	Triactin	**5**
R¹ = R² = R³ = R⁴ = C₂H₅		Tetranactin	**6**

Figure 5.14 Structure of neutral carriers used in liquid membrane ion-selective electrodes.

Figure 5.15 Direct potentiometic speciation of lead ion in Zurich tapwater as a function of pH. Dotted lines: expected from the known anions in the water sample and their complex equilibria with lead ion for two different carbonate concentrations. (Reproduced with permission from Ref. 42.)

oretical expectations; Fig. 5.15). The values obtained with various drinking-water samples were validated by inductively coupled plasma–mass spectrometry measurements.

Anion-selective liquid membrane electrodes have also been developed, based on the coordination of the anionic guest to host materials, such as metallophorphyrin or hydrophobic vitamin B_{12} derivatives, alkyltin compounds or macrocyclic polyamines (see Refs. 44–48 and Fig. 5.16). Such biomimetrically designed ionophores offer effective sensing of inorganic and organic anions, such as thiocyanate, carbonate, salicylate, phosphate, or adenosine nucleotides. Unlike anion exchanger electrodes, these anion sensors display selectivity patterns greatly different from the Hofmeister sequence (due to the direct interaction of the host with the specific anion). Often, this interaction involves an exchange of the coordinated anion at the metal center of the organometallic ionophore with the target anion in the sample solution. A review in 1998 describes in detail individual carrier-based ISEs, according to the analyte for
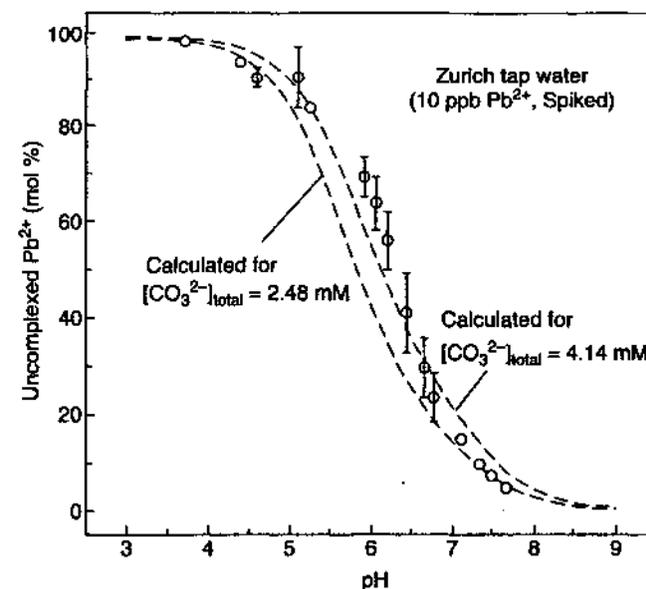
which they have been developed (49). Many exciting developments based on novel host–guest chemistry (e.g., recognition by steric shapes) are anticipated in the near future.

5.2.3 Solid-State Electrodes

Considerable work has been devoted to the development of solid membranes that are selective primarily to anions. The solid-state membrane can be made of single crystals, polycrystalline pellets, or mixed crystals. The resulting solid-state membrane electrodes have found use in a great number of analytical applications.

An example of a very successful solid-state sensor is the fluoride-ion-selective electrode. Such a single-crystal device is by far the most successful anion-selective electrode. It consists of a LaF_3 crystal and an internal electrolyte solution (consisting of $0.1\,M$ NaF and $0.1\,M$ KCl, and containing the Ag/AgCl wire). The LaF_3 crystal is doped with some EuF_2 to provide vacancies ("holes") at anionic sites (Fig. 5.17). Such a solid-state membrane derives its selectivity from restriction of the movement of all ions, except the fluoride of interest. The latter moves by migration through the crystal lattice
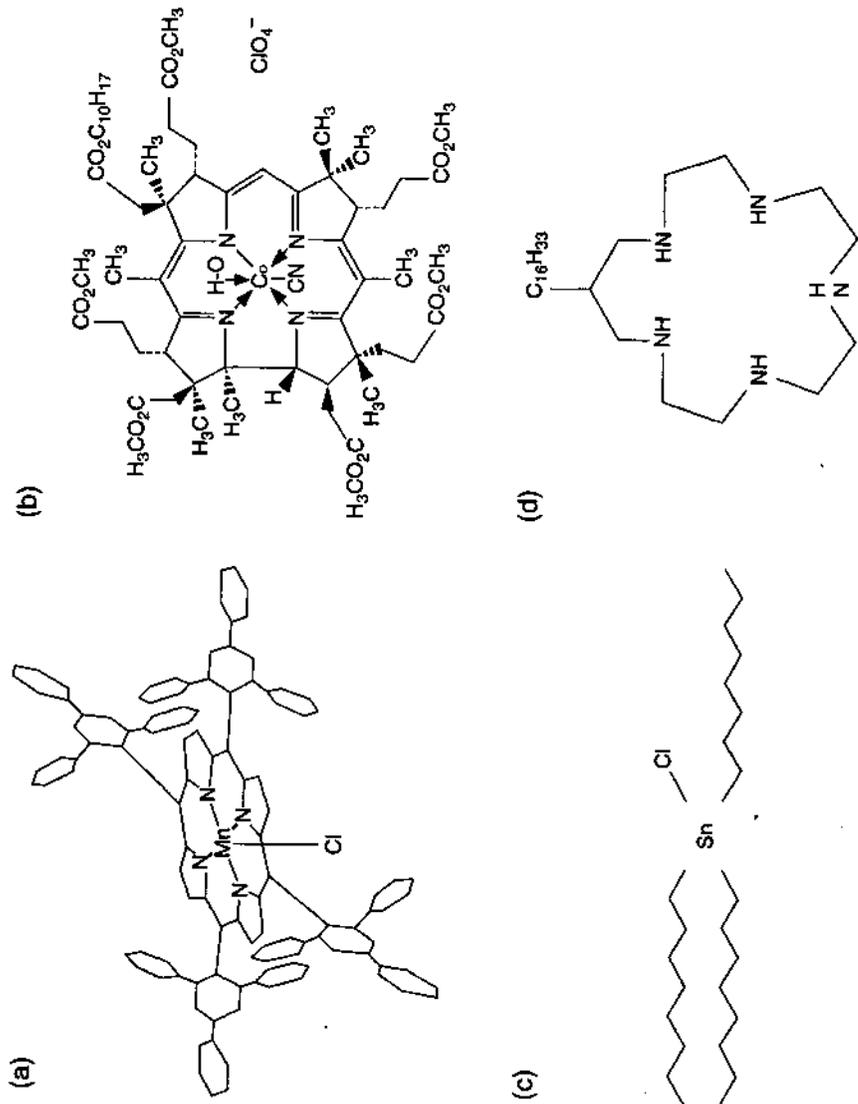
Figure 5.16 Structures of some chemical species useful for devising anion-selective electrodes: (a) Mn(III) porhyrin; (b) vitamin B₁₂ derivative; (c) tri-n-octyltin chloride; (d) lipophilic polyamine macrocyclic compound.
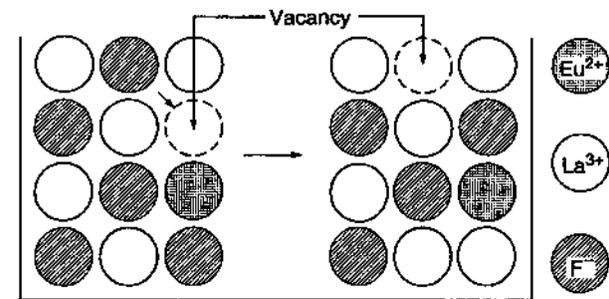
Figure 5.17 Migration of the fluoride ion through the LaF₃ lattice (doped with EuF₂). The vacancies created within the crystal cause jumping of neighboring F⁻ into the vacancy.

(by jumping from one vacancy defect to another), thus establishing the desired potential difference. A Nernstian response

$$E = K - 0.059 \log a_{F^-} \qquad (5.16)$$

is obtained down to ~10^{-6}M. The only interfering ion (due to similarity in size and charge) is OH⁻, for which the selectivity coefficient (K_{F^-/OH^-}) is 0.1. Hence, the electrode is limited to use over the pH range of 0–8.5. The electrode exhibits at least a 1000:1 preference for fluoride over chloride or bromide ions.

Other useful solid-state electrodes are based on silver compounds (particularly silver sulfide). Silver sulfide is an ionic conductor, in which silver ions are the mobile ions. Mixed pellets containing Ag_2S–AgX (where X = Cl, Br, I, SCN) have been successfully used for the determination of one of these particular anions. The behavior of these electrodes is basically determined by the solubility products involved. The relative solubility products of various ions with Ag⁺ thus dictate the selectivity [i.e., $k_{ij} = K_{SP(AgI)}/K_{SP(AgJ)}$]. Consequently, the iodide electrode (membrane of Ag_2S/AgI) displays high selectivity over Br⁻ and Cl⁻. In contrast, the chloride electrode suffers from severe interference from Br⁻ and I⁻. Similarly, mixtures of silver sulfide with CdS, CuS, or PbS provide membranes that are responsive to Cd^{2+}, Cu^{2+}, or Pb^{2+}, respectively. A limitation of these mixed-salt electrodes is that the solubility of the second salt must be much greater than that of silver sulfide. A silver sulfide membrane by itself responds to either S^{-2} or Ag⁺ ions, down to the 10^{-8}M level.

Sensors for various halide ions can also be prepared by suspending the corresponding silver halide in an inert support material, such as silicone rubber (50). Such support material provides a flexible, heterogeneous membrane with resistance to cracking and swelling. The resulting membrane is called a heterogeneous or precipitate-impregnated membrane. For example, a chloride-selective electrode is based on a heterogeneous membrane prepared by polymerizing monomeric silicone rubber in the presence of an equal weight

of silver chloride particles. A 0.5-mm-thick disk of this heterogeneous membrane is sealed to the bottom of a glass tube; potassium chloride and a silver wire are then placed in the tube. The sensitivity of such an electrode is limited by the solubility of silver chloride. Chloride concentrations from 5×10^{-5} to 1.0 M can be measured. Such an electrode operates over the pH range 2–12, and at temperatures between 5 and 5000°C. Ion-selective electrodes for thiocyanate (SCN⁻) or cyanide (CN⁻) can be prepared in a similar fashion. Such electrodes rely on a "corrosion" reaction between the silver halide (AgX) and the target ion, for example

$$AgX + 2CN^- \rightarrow Ag(CN)_2^- + X^- \tag{5.17}$$
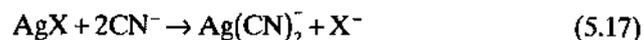
(Safety considerations dictate that cyanide measurements be carried out in strongly basic media.) The interference mechanism with silver-based solid-state ISEs differs from that of ISEs described earlier. Depending on the K_{SP} value, an excess of the interfering ion may result in its deposit as silver salt on the membrane surface. Removal of the interfering film (by scrubbing) is thus required for restoring the electrode activity. Table 5.1 lists some solid-state electrodes from a commercial source, along with their dynamic range and major interferences.

5.2.4 Coated-Wire Electrodes and Solid-State Electrodes Without an Internal Filling Solution

Coated-wire electrodes (CWEs), introduced by Freiser in the mid-1970s, are prepared by coating an appropriate polymeric film directly onto a conductor (Fig. 5.18). The ion-responsive membrane is commonly based on poly(vinyl

TABLE 5.1 Characteristics of Solid-State Crystalline Electrodes

Analyte Ion	Concentration Range (M)	Major Interferences
Br⁻	$10^0–5 \times 10^{-6}$	CN⁻, I⁻, S²⁻
Cd²⁺	$10^{-1}–1 \times 10^{-7}$	Fe²⁺, Pb²⁺, Hg²⁺, Ag⁺
Cl⁻	$10^0–5 \times 10^{-5}$	CN⁻, I⁻, Br⁻, S²⁻
Cu²⁺	$10^{-1}–1 \times 10^{-8}$	Hg²⁺, Ag⁺, Cd²⁺
CN⁻	$10^{-2}–1 \times 10^{-6}$	S²⁻
F⁻	Saturated to 1×10^{-6}	OH⁻
I⁻	$10^0–5 \times 10^{-8}$	
Pb²⁺	$10^{-1}–1 \times 10^{-6}$	Hg²⁺, Ag⁺, Cu²⁺
Ag⁺/S²⁻	Ag⁺: $10^0–1 \times 10^{-7}$	Hg²⁺
	S²⁻: $10^0–1 \times 10^{-7}$	
SCN	$10^0–1 \times 10^{-6}$	I⁻, Br⁻, CN⁻, S²⁻

Source: From *Orion Guide to Ion Analysis*, Orion Research, Cambridge, MA. 1983. With permission.
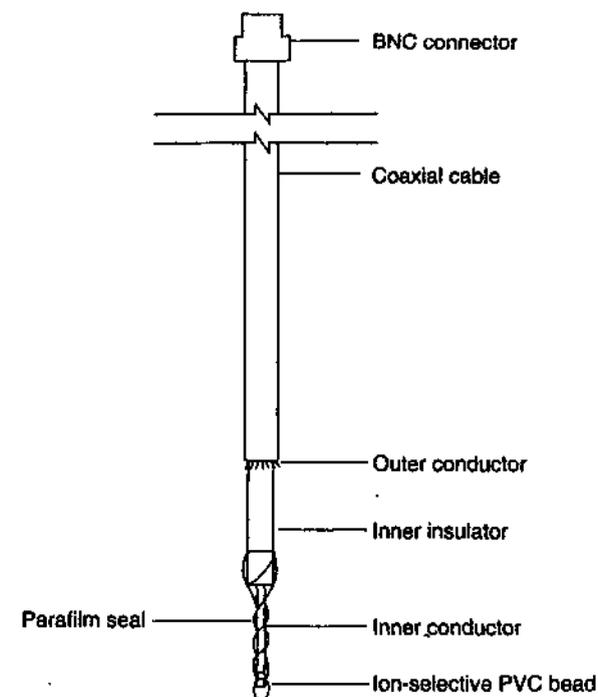
Figure 5.18 Coated-wire ion-selective electrode. (Reproduced with permission from Ref. 51.)

chloride), while the conductor can be metallic (Pt, Ag, Cu) or graphite-based of any conventional shape, such as wire or disk. The conductor is usually dipped in a solution of PVC and the active substance, and the resulting film is allowed to air-dry. Other polymers and modified polymers, including poly(acrylic acid) and modified poly(vinylbenzyl chloride), can also be useful for various applications. In addition to the miniaturization capability, CWEs are extremely simple, inexpensive, and easy to prepare and function well over the 10^{-5}–0.1 M concentration range. The exact mechanism of the CWE behavior continues to be a mystery, in view of the lack of internal reference components. Coated-wire electrodes may suffer from reproducibility and long-term stability (drifting potential) problems, resulting from the poorly defined contact and mechanism of charge transfer between the membrane coating and the conducting transducer. Nevertheless, such devices have been found useful for various important applications, provided that the electrodes are calibrated periodically. The determination of basic drugs, such as cocaine, methodane (52), amino acids (53), potassium, and sodium (54), represents some of the useful applications of CWE. The principles and applications of CWEs have been reviewed (4). New concepts for preparing CWEs appear to improve their analytical performance, particularly with respect to stability and

reproducibility (through the achievement of thermodynamically defined interfaces). Such ability to eliminate the internal filling solution is currently receiving considerable interest in connection to mass production of potentiometric sensors and sensor arrays (see Section 6.3.2). Such ability offers great promise for eliminating steady-state ion fluxes (that lead to higher activity at the layer adjacent to the membrane) and hence to lower the detection limits compared to traditional ISE (25). Microfabricated (planar) ISE can also be designed with thin hydrogel layers, replacing the large-volume inner filling solution and addressing the stability and reproducibility limitations of CWEs. Such solid-state planar electrodes hold great promise for developing disposable ion sensors for decentralized applications ranging from home blood testing to on-site environmental monitoring.

Another route to address the potential stability of CWE and for mass-producing miniaturized ISE is to use an intermediate conducting polymer membrane between the conducting surface and the ion-selective membrane (55–57). This route gives solid-state ISE where the selectivity is determined by the ion-selective membrane, while the conducting polymer acts as the ion-to-electron transducer. Conducting polymers such as polypyrrole, polythiophene, or polyaniline have thus been shown useful for replacing the inner solution and preparing solid-state ISE. Such conducting-polymer-based sensors demonstrate high stability similar to that of conventional ISE (with an internal filling solution) (56). Doping the conducting polymer layer with an appropriate complexing agent can be used to lower the detection limits down to the nanomolar range (57). In certain cases, it is possible to incorporate the ion recognition sites directly into the conducting polymer matrix and hence eliminate the external ion-selective membrane (55).

5.3 ON-LINE, ON-SITE, AND IN VIVO POTENTIOMETRIC MEASUREMENTS

Various on-line monitoring systems can benefit from the inherent specificity, wide scope, dynamic behavior, and simplicity of ISEs. In particular, ISEs have been widely used as detectors in high-speed automated flow analyzers, such as air-segmented or flow injection systems (58,59). For example, Figure 5.19 shows the flow injection determination of physiologically important potassium in serum, using a tubular potassium selective electrode, at a rate of 100 samples per hour. Even higher throughputs, reaching 360 samples per hour, have been employed in connection with air-segmented flow systems (61). Such analyzers are now being routinely employed in most hospitals for the high-speed determination of physiologically important cationic electrolytes (e.g., K^+, Na^+, Ca^{2+}, Mg^{2+}, and H^+) or anions (e.g., Cl^-) in body fluids. The corresponding ISEs are usually placed in series, along a zigzag-shaped flow channel. Additional advantages accrue from the coupling of arrays of potentiometric detectors with chemometric (statistical) procedures (see Section 6.4).
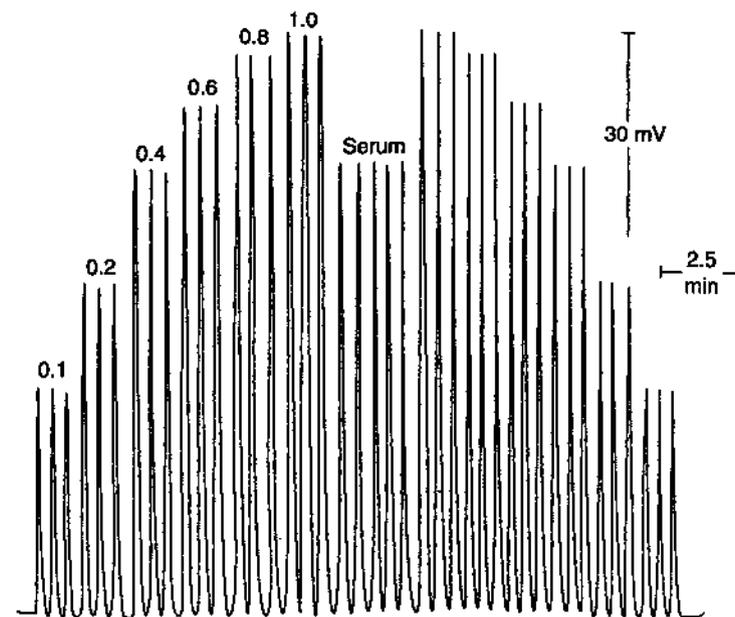
Figure 5.19 Flow injection potentiometric determination of potassium in serum. (Reproduced with permission from Ref. 60.)

The transient nature of flow injection potentiometric measurements (e.g., see Fig. 5.19) nicely addresses the potential drift problem common to analogous batch measurements. Such peak profiles are very reproducible, with any point on the peak easily related to the analyte activity. It can also be exploited for enhancing the selectivity by operating under kinetic (rather than equilibrium) control. Such kinetic selectivity reflects the faster rate of exchange of the primary ion (compared to interferents). Several designs of low-volume potentiometric flow detectors have been reported (60–64). The simplest design consists of an ISE fitted tightly with a plastic cap, with an inlet and outlet for the flowing stream (Fig. 5.20). The reference electrode is usually placed downstream from the ISE. It can also be immersed in a parallel (potassium chloride) flowing stream. Other common detector designs include the flow-through tubular ISE (used in Fig. 5.19), and tangential or wall-jet ISEs. Multi-ion detectors, based on ion-sensitive field effect transistors (discussed in Section 6.3) have been combined with miniaturized micromachined flow injection systems (63). Such coupling offers improved response times and reduced consumption of samples and reagents. Miniaturized arrays of multiple polymer membrane and solid-state ISE (for K^+, Na^{2+}, Ca^{2+}, Mg^{2+}, NH_4^+, Ba^{2+}, NO_3^-, Cl^-, and Li^+) have been developed for measuring terrestrial soil samples obtained in NASA missions to Mars (65).
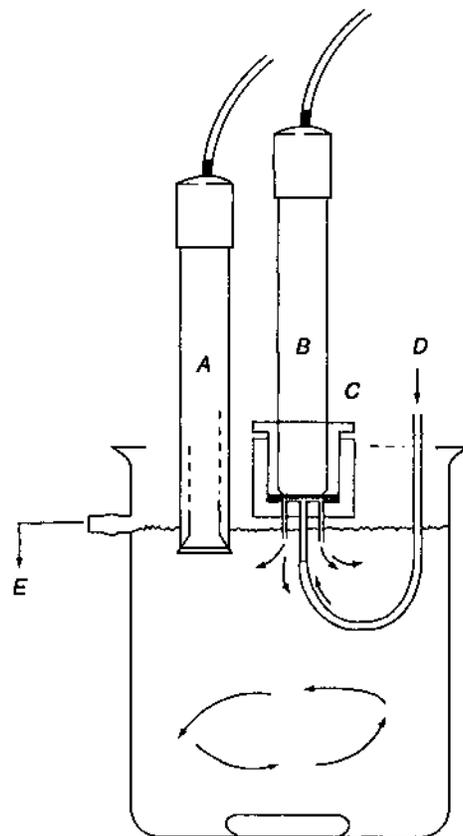
Figure 5.20 Flow-through potentiometric cell cap design: A, reference electrode; B, iodide electrode; C, flow-through cap; D, inlet; E, outlet. (Reproduced with permission from Ref. 62.)

In addition to automated analysis, ISEs can be used to detect ionic species in chromatographic effluents. Particularly powerful is the coupling of modern ion chromatography with potentiometric detection (66). Similarly, liquid membrane microelectrodes have been used as a small dead-volume detector in open tubular column liquid chromatography (67). Miniaturization has also permitted the adaptation of ISEs as on-column detectors for capillary-zone electrophoresis in connection with femtoliter detection volumes (68,69). The small dimensions in capillary electrophoresis require proper attention to the positioning of the ISE detector. Both micropipette and coated-wire ISEs have been useful for this task, with the latter offering a simplified electrode alignment (69). Micropipette ISEs have also been used as tips in scanning electrochemical microscopy (see Ref. 70; also Section 2.3, below).

Potentiometric microelectrodes are very suitable for in vivo real-time clinical monitoring of blood electrolytes, intracellular studies, in situ environmental surveillance, or industrial process control. For example, Simon's group

described the utility of a system for on-line measurements of blood potassium ion concentration during an open-heart surgery (71); Buck and coworkers (72) reported on the use of flexible planar electrode arrays for the simultaneous in vivo monitoring of the pH and potassium ion in the porcine beating heart during acute ischemia (Fig. 5.21). Miniaturized catheter-type ISE sensors, such

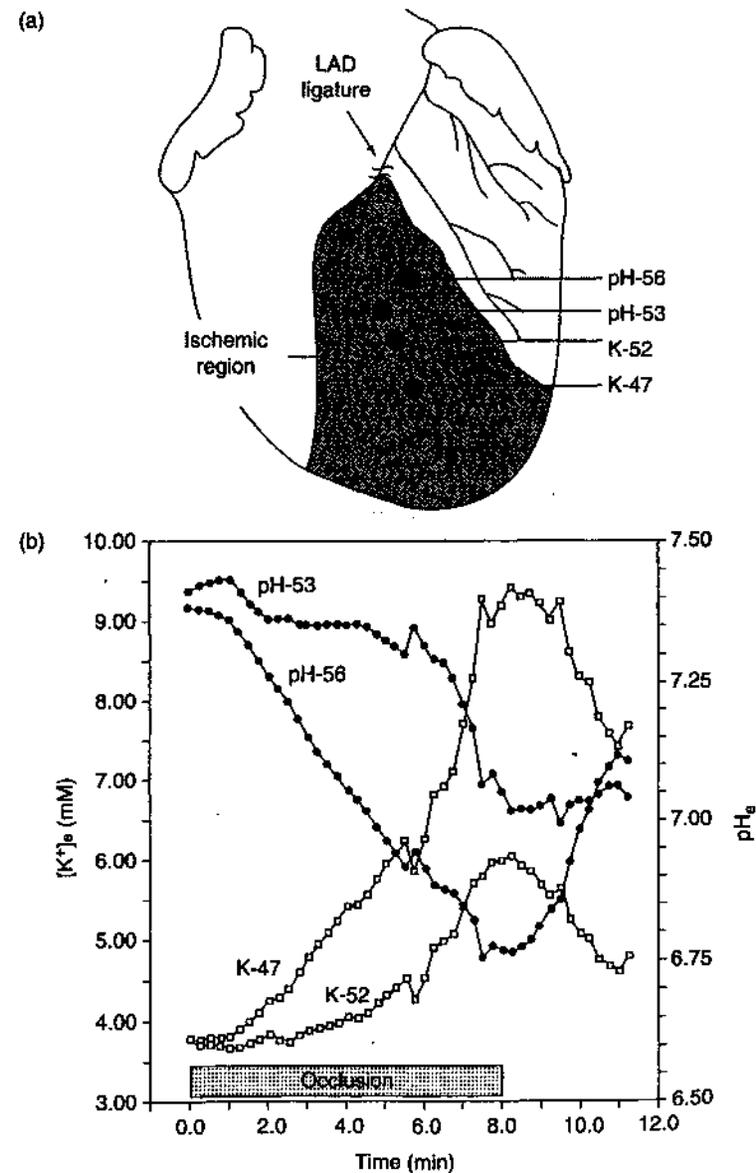

Figure 5.21 (a) Placement of the two pH and two potassium sensors (0.5 mm diameter) in the porcine heart; (b) recorded fall in the pH and increased potassium activity. (Reproduced with permission from Ref. 72.)
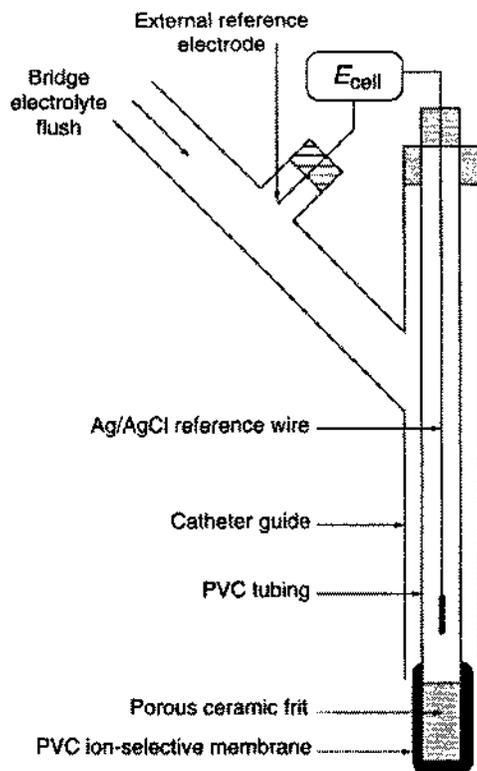
Figure 5.22 Miniaturized ISE catheter sensor for continuous monitoring of blood electrolytes. (Reproduced with permission from Ref. 73.)

as the implantable probe shown in Figure 5.22, represent the preferred approach for routine clinical in vivo monitoring of blood electrolytes. For these intravascular measurements the reference electrode is placed outside the artery (in the external arm of the catheter), thus obviating biocompatability and drift problems associated with its direct contact with the blood. Diamond's group developed an array of miniaturized chloride, sodium, and potassium ISEs for point-of-care analysis of sweat in connection to non-invasive diagnosis of cystic fibrosis (74). Note that shrinking ISE has a minimal effect on ISE behavior, since ISE response is size-independent. Yet, further miniaturization of ISEs to the nanometer domain is limited by the electrical resistance of the bulk liquid membrane.

EXAMPLES

Example 5.1 Calculate the relative error (in proton concentration) that would occur if the pH of a 1×10^{-2} M NaOH solution were measured with a pH glass electrode ($k_{H,Na} = 10^{-10}$, assuming an activity coefficient of 1.0).

Solution The concentration of the interfering sodium ion is 1×10^{-2} M, while that of the target proton is

$$[H^+] = K_w/[OH^-] = 10^{-14}/10^{-2} = 1 \times 10^{-12} \text{ M}$$

From Eq. (5.6), we thus obtain

$$E_{cell} = K + 0.059 \log[1 \times 10^{-12} + 10^{-10} \times (1 \times 10^{-2})]$$

The relative error in concentration is thus

$$[10^{-10} \times (1 \times 10^{-2})/10^{-12}] \times 100 = 100\%$$

Example 5.2 The following potentials were observed for a calcium electrode immersed in standard calcium solutions:

$[Ca^{2+}]$ (M)	E (mV)
1×10^{-5}	100
1×10^{-4}	129
1×10^{-3}	158

What potential is expected for a calcium concentration of 5×10^{-4}M? (Assume an activity coefficient of 1.0.)

Solution Plotting E against $\log[Ca^{2+}]$ gives a straight line with a slope of 29 mV/decade and an intercept of 245 mV. A calcium concentration of 5×10^{-4} M thus yields

$$E = K + 29 \log[5 \times 10^{-4}] = 245 - 95.7 = 149.3 \text{ mV}$$

Example 5.3 Calculate the error in millivolts that would occur if a solution containing 5×10^{-5} M F$^-$ (pH 10) were measured with a fluoride ISE ($k_{FOH} = 0.1$).

Solution The concentration of the interfering hydroxyl ion at pH = 10 can be obtained as follows:

$$[OH^-] = K_w/[H^+] = 10^{-14}/10^{-10} = 10^{-4} \text{ M}$$

From Eq. (5.4) we obtain

$$E_{cell} = K - 0.059 \log(5 \times 10^{-5} + 0.1 \times 10^{-4}) = K + 0.249$$

In the absence of hydroxyl ion, we would obtain

$$E_{cell} = K - 0.059 \log(5 \times 10^{-5}) = K + 0.254$$

Therefore the error (in mV) would be

$$\text{Error} = K + 249 - (K + 254) = -5 \, \text{mV}$$

Example 5.4 A student calibrated a Mg^{2+} ion-selective electrode using two standard solutions at 25°C and constant ionic strength and obtained the following results:

$[Mg^{2+}]$ (M)	E (mV)
1×10^{-3}	142
1×10^{-4}	113

What is the concentration of the test solution that gave a potential reading of 125 mV under the same conditions?

Solution Plotting E versus $\log[Mg^{2+}]$ gives a straight line; the magnesium concentration $(2.6 \times 10^{-4} M)$ corresponding to the 125-mV reading can be read directly from the axis.

Example 5.5 Calculate the error caused by sodium ion, $a_{Na} = 0.01$, in the measurement of lithium, $a_{Li} = 0.001$, using a lithium-ion-selective electrode $(k_{Li,Na} = 0.06)$.

Solution From Eq. (5.6), we thus obtain

$$E = K + 0.059 \log[0.001 + 0.06(0.01)] = K - 0.165 \, \text{V}$$

Without sodium, the potential is

$$E = K + 0.059 \log(0.001) = K - 0.177 \, \text{V}$$

The error is $(0.012/0.177) \times 100 = 6.8\%$.

PROBLEMS

5.1 Discuss the structural requirements for designing selective ionophores for ISE work. Give examples of such structures.

5.2 Explain (using one or multiple equations) why a highly selective ISE is not always sufficient for accurate potentiometric measurements.

5.3 Explain (using one or multiple equations) why the sodium ISE is more sensitive than the calcium one.

5.4 Describe the source of error in pH measurements using the glass pH electrode.

5.5 Describe the response mechanism of the fluoride-ion-selective electrode. Explain why the OH^- is the major interfering ion in F^- ISE measurements.

5.6 Give an example of a successful ISE for measuring a macromolecular polyanionic compound.

5.7 A major advance in ionophore-based ISEs is the finding that their detection limits can be lowered from the micromolar range to the nanomolar or picomolar level. Discuss recent developments and the new understanding that led to such dramatic improvements in the detectability.

5.8 Discuss the significance of the selectivity coefficient of an ISE. How would you determine its value?

5.9 Give an example of a successful ISE for measuring a macromolecular polyanionic compound.

5.10 Use the Nikolski–Eisenman equation to explain why lowering the detection limit requires careful attention to the selectivity of the resulting ISE.

5.11 Explain how the presence of magnesium ion can influence the response of a calcium ISE.

5.12 By how many millivolts will the potential of a calcium ISE change on transferring the electrode from a 1×10^{-3} M $CaCl_2$ solution to a 1×10^{-2} M $CaCl_2$ one?

5.13 Explain why small uncertainties in the measured cell potential can cause large error in the response of ISEs.

5.14 Discuss the major sources of error in potentiometric measurements.

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6

ELECTROCHEMICAL SENSORS

A chemical sensor is a small device that can be used for direct measurement of the analyte in the sample matrix. Ideally, such a device is capable of responding continuously and reversibly and does not perturb the sample. By combining the sample handling and measurement steps, sensors eliminate the need for sample collection and preparation. Chemical sensors consist of a transduction element covered by a chemical or biological recognition layer. This layer interacts with the target analyte, and the chemical changes resulting from this interaction are translated by the transduction element into electrical signals.

The development of chemical sensors is currently (as of 2005) one of the most active areas of analytical research. Electrochemical sensors represent an important subclass of chemical sensors in which an electrode is used as the transduction element. Such devices hold a leading position among sensors presently available, have reached the commercial stage, and have found a vast range of important applications in the fields of clinical, industrial, environmental, and agricultural analyses. The field of sensors is interdisciplinary, and future advances are likely to occur from progress in several disciplines. Research into electrochemical sensors is proceeding in a number of directions, as described in the following sections. The first group of electrochemical sensors, the potentiometric ion-selective electrodes (based on "ionic receptors"), has been described in Chapter 5.