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INTRODUCTION

There is a tendency in many fields of contemporary physical and chemical science to seek impulses from biology for solving problems. This tendency shows promise, not only because it leads to new artificial tools, materials or processes, but also because it forms models permitting deeper understanding, at least in certain areas, of the actual processes occurring in nature. Efforts to imitate nature thus facilitate its deeper understanding.

Ion-selective electrodes are a remarkable product of this approach. Their development can be followed in several circular pathways from natural bioelectric phenomena to artificial membrane systems and back again, to attempts to explain processes at a cellular level.

The relationship between electric and physiological processes was discovered in 1791 by L. Galvani [27] in his classic experiments with frog muscles and nerves. In spite of these exciting results, the study of electrophysiological phenomena did not progress for several decades. M. Faraday [99] studied the electricity produced by the torpedo, but only in order to prove that this 'animal' electricity is the same as other kinds of electricity, for example 'voltaic' electricity from an electric machine or 'galvanic' electricity from a galvanic cell.

In 1848 du Bois-Reymond [21] suggested that the surfaces of biological formations have a property similar to the electrode of a galvanic cell and that this is the source of bioelectric phenomena observed in damaged tissues. The properties of biological membranes could not, however, be explained before at least the basic electrochemistry of simple models was formulated. The thermodynamic relationships for membrane equilibria were derived by Gibbs in 1875 [29], but because the theory of electrolyte solutions was formulated first by Arrhenius as late as 1887, Gibbs does not mention either ions or electric potentials.

A further important step forward was the work of Nernst [73, 74] and Planck [81, 82] on transport in electrolyte solutions. Here the concept of the diffusion potential was defined; diffusion potential arises when the mobilities of the electrically-charged components of the electrolyte are different and is important both for description of conditions within membranes as well as for quantitative determination of the liquid-junction potential.

A basic property of the membrane surface, the potential at the membrane/solution boundary, was defined and determined by Nernst and Riesenfeld [75, 85, 86] for the phase boundary between two immiscible liquids.

Membrane electrochemistry proper began in 1890 with the work of W. Ostwald [79], who formulated the concept of a semipermeable membrane that selectively affects the membrane transport of ions. According to Ostwald, 'not only electric currents in muscles and nerves, but also the mysterious phenomenon of electric fishes will finally find an explanation in the properties of semipermeable membranes'.

At the same time (1902), a membrane theory was proposed for the electrical properties of cells and tissues by Overton [80] and Bernstein [8], whose principles remain valid to the present day.

At the turn of the century, considerable attempts were being made to find suitable membrane models. These models fall into two groups: compact, usually liquid ('oil') and solid membranes [10, 33, 62, 75]; and porous membranes [9]. At the very beginning of the study of compact membranes, the glass electrode was discovered [18, 34], whose membrane represented the first observation of marked selectivity for a particular type of ion, here the hydrogen ion. It is interesting that this first ion-selective electrode remains the best and most widely used of all such electrodes.

Although the problem of the liquid membrane potential was solved in principle by Nernst, a discussion developed in the ensuing two decades between Bauer [6], who developed the adsorption theory of membrane potentials, and Beutner [10, 11, 12], who based his theories on Nernst's work. This problem was finally solved by Bonhoeffer, Kahlweit and Strehlow [13], and by Karpfen and Randles [49]. The latter authors also introduced the concept of the distribution potential.

The search for models of biological membranes among porous membranes continued in the twenties and thirties. Here, Michaelis [67] and Sollner (for a summary of his work, see [90]; for development in the field, [89]) should be mentioned. The existence and characteristics of Donnan membrane equilibria could be confirmed using this type of membrane [20]. The theory of porous membranes with fixed charges of a certain sign was developed by Teorell [93], and Meyer and Sievers [65].

On the basis of the older results of Gorter and Grendel [31], Danielli and Davson [19] developed a theory in 1935 according to which the membranes of cells and cellular organelles are very thin formations composed of a bimolecular phospholipid layer covered on both sides by adsorbed protein. Further progress was made with the theory of membrane potentials at excitable (especially nerve) cells, developed by Goldman [30] and Hodgkin, Huxley and Katz [35, 36, 50]. Bilayer lipid membranes obtained first by Mueller and coworkers [72] are important models of biological membranes.

Research on thicker membranes has progressed in two directions since the thirties. It was apparent that the theory of the glass electrode based on the concept of the concentration cell or membrane potential with a diffusible hydrogen ion cannot explain certain of its properties, notably its marked selectivity for sodium ions, which is very strong for glasses of certain composition [60]. This fact led Nikolsky and Tolmacheva [77] to develop the ion-exchange theory of the glass electrode. The formation of a diffusion potential within the glass membrane was included in a perfected theory of the glass electrode by Eisenman and coworkers [22]. The new construction principle is included in gas probes with a hydrophobic membrane permeable for gases and with a glass internal electrode [88].

After many attempts to obtain a membrane electrode based on various kinds of crystalline materials, Pungor and Hallós-Rokosinyi [83] were finally successful in preparing the first practical ion-selective electrode with a heterogeneous membrane containing silver halide precipitate (Mirnik and Težak [68] made important earlier discoveries in this area). A real success in this field was the development of the first ion-exchange membrane from a single crystal by Frant and Ross [25]. Except for the glass electrode, their lanthanum trifluoride ion-selective electrode for determining fluoride is the most important sensor in this field.

Liquid membranes with dissolved ion-exchangers were used first by Sollner and Shean [91], but the first actual ion-selective electrode was constructed on this principle much later by Ross [87].

A different direction in ion-selective electrode research is based on experiments with antibiotics that uncouple oxidative phosphorylation in mitochondria [59]. These substances act as ion carriers (ionophores) and produce ion-specific potentials at bilayer lipid membranes [72]. This function led Štefanac and Simon to obtain a new type of ion-selective electrode for alkali metal ions [92] and is also important in supporting the chemi-osmotic theory of oxidative phosphorylation [69]. The range of ionophores, in view of their selectivity for other ions, was broadened by new synthetic substances [1, 61].

The ion-selective field-effect transistor (ISFET) represents a remarkable new construction principle [7, 63]. 'Inverse potentiometry' with ion-selective electrodes is the electrolysis at the interface between two immiscible electrolyte solutions (ITIES) [28, 55].

Biological principles are also used in enzyme electrodes, where the sensor (usually an ion-selective electrode) is covered by a polymeric carrier containing an enzyme [32]. The determinand reacts in the enzyme layer yielding a product that causes a signal in the sensor. The bacterium electrode is based on a similar principle [84], as are electrodes using tissue in place of the enzyme layer [2].

Research on ion-selective electrodes is progressing very rapidly and the literature contains more than four thousand publications (a practically complete survey of the literature up to the spring of 1982 can be found in four reviews in *Analytica Chimica Acta* [51-54]). Regular surveys of ion-selective electrode research are also given in *Analytical Chemistry* [13a-d, 25a, 96]. A number of books have been written on ion-selective electrodes [3-5, 14-17, 26, 38-40, 45, 46, 56, 57, 58, 64, 66, 70, 71, 76, 95, 97, 98]. A number of specialized symposia have been devoted to ion-selective electrodes and proceedings from them are often available in book form [17a, 23, 24, 37, 41-4, 47, 48, 94].

In the years from 1969 to 1972, Orion Research published a magazine devoted to developments in ion-selective electrodes [78], and, later, a guide to their products [34a]. Since 1979, the journal *Ion-Selective Electrode Reviews* has been published semi-annually [39a].

A great number of companies throughout the world manufacture ion-selective electrodes. In view of the rapid development of the field no survey of these companies will be presented in the present book.

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2

THE THEORY OF MEMBRANE POTENTIALS

In physics, an elastic two-dimensional plate is termed a membrane (Latin *membrana* = parchment) but in chemistry the term denotes a body, usually thin, which serves as a phase separating two other bulk phases. If this body is permeable to the same degree for all components of the adjacent phases and does not affect their mobility, then its only function is to prevent rapid mixing of the two phases. This is then termed a diaphragm. A real membrane must exhibit a certain selectivity, based on different permeability for the components of the two phases, and is then termed a semipermeable membrane. Membranes separating two electrolytes that are not permeable to the same degree for all ions are called electrochemical membranes. It is with these that we are concerned here.

Ion-selective electrodes are systems containing a membrane consisting basically either of a layer of solid electrolyte or of an electrolyte solution whose solvent is immiscible with water. The membrane is in contact with an aqueous electrolyte solution on both sides (or sometimes only on one). The ion-selective electrode frequently contains an internal reference electrode, sometimes only a metallic contact, or, for an ion-selective field-effect transistor (ISFET), an insulating and a semiconducting layer. In order to understand what takes place at the boundary between the membrane and the other phases with which it is in contact, various types of electric potential or of potential difference formed in these membrane systems must first be defined.

2.1 General relationships

Electric potential differences are formed at the boundary between two phases, at least one of which contains electrically-charged species (ions, electrons, or even dipoles). These differences are of two basic types. The inner potential of a given phase α , $\phi(\alpha)$, is the electrical work required for transfer of a unit

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positive charge (the charge of one mole of electrons multiplied by -1 or the charge of a mole of protons) from a point in a vacuum infinitely distant from the given phase into the given phase. The difference in the inner potentials of two phases α and β ,

$$\Delta_{\beta}^{\alpha}\phi = \phi(\alpha) - \phi(\beta),$$

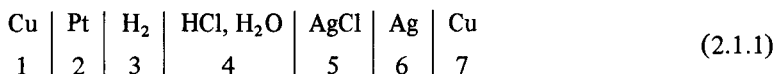
is termed the Galvani potential difference. Strictly, this quantity can be measured only when both phases have the same chemical composition, for example two wires of the same metal or two electrolyte solutions in the same solvent and with the same composition; however, extrathermodynamic procedures can sometimes be found to measure the Galvani potential between two chemically different phases.

The electrostatic or outer potential of a given phase $\psi(\alpha)$ is the electrical work required for transfer of a unit charge from a point in a vacuum infinitely distant from the given phase into the vicinity of that phase. The difference between the outer potentials of two phases α and β ,

$$\Delta_{\beta}^{\alpha}\psi = \psi(\alpha) - \psi(\beta),$$

is termed the Volta potential difference. This quantity can usually be measured directly.

Galvani potential differences are usually the basis of potentiometric measurements. A simple example of a Galvani potential difference is the electromotive force (EMF) of a galvanic cell. This quantity is given by the Galvani potential difference between chemically identical metallic leads to the two electrodes of the cell. An example of a reversible galvanic cell is the system consisting of a hydrogen electrode and a silver chloride electrode in an aqueous solution of hydrochloric acid.



According to the IUPAC convention, the individual phase boundaries are designated in the scheme by vertical lines. The EMF is given by the difference between the internal electrical potential of the right-hand metallic lead and the internal electrical potential of the left-hand metallic lead in the scheme (2.1.1), i.e.

$$E = \phi(7) - \phi(1). \quad (2.1.2)$$

The EMF, E , of a reversible galvanic cell is related to the change in the Gibbs energy ΔG in the cell reaction

$$E = -zF\Delta G, \quad (2.1.3)$$

where F is the Faraday constant and z is the charge number of the cell reaction.

This number gives the number of charges corresponding to a Faraday constant, i.e. the charge of 1 mole of protons that must pass through the cell in order for the cell reaction (the chemical reaction occurring in the cell on passage of an electric current) to occur to unit degree. The cell reaction corresponding to cell (2.1.1),



thus has a charge number of $z = 2$.

The electrode potential is the EMF of a cell in which the electrode on the right-hand side in the scheme is the test electrode, while the electrode placed on the left-hand side is a standard hydrogen electrode (i.e. a hydrogen electrode saturated with hydrogen under standard pressure $p_0 = 1.013 \times 10^5$ Pa and placed in a solution with an activity of hydronium ions equal to one).

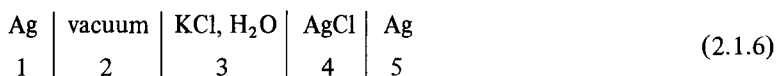
In the field of ion-selective electrodes the potentials of electrodes of the second kind, acting as reference electrodes, are especially important. The electrode potentials of the most important reference electrodes, the silver chloride and calomel electrodes, are

$$E_{\text{MCl}, \text{M}} = E_{\text{MCl}, \text{M}}^0 + (RT/F) \ln a_{\text{Cl}^-}, \quad (2.1.5)$$

where $E_{\text{MCl}, \text{M}}^0$ is the standard potential of the particular electrode of the second kind and a_{Cl^-} is the chloride ion activity.

So far we have considered electrodes whose potentials are determined through the cell reaction of the ions with which they are in contact. Such a potential cannot be formed on an ideally polarized electrode, for example a mercury electrode in a KCl solution within a certain potential region. In this case the electrode potential is determined by the electrode charge.

A cell whose equilibrium potential difference is affected by outer potentials is depicted in the scheme



Apparently no cell reaction can occur in this cell as the vacuum prevents movement of species between phases 1 and 3. The measured difference in the inner electric potentials of phases 5 and 1 is equal to the difference in outer electric potentials between phases 5 and 3,

$$U = \phi(5) - \phi(1) = \psi(5) - \psi(3). \quad (2.1.7)$$

Detailed consideration of similar cases will be given in section 4.3 on ISFETs.

The electrochemical systems described so far are equilibrium systems. However, many membrane systems are not in equilibrium. Irreversible processes connected with charge transfer take part in the formation of electrical potential differences. If this charge transfer occurs in a homogeneous phase (for example,