Journal of Statistical Physics, Vol. 78, Nos. 1/2, 1995

An Alternative Approach to Electrochemistry

Katrine Seip Førland[1] and Tormod Førland[1]

Received October 13, 1993; final March 29, 1994

The concepts used conventionally in electrochemistry, single-ion chemical potential and electrostatic potential difference, are not obtainable from measurements in an inhomogeneous system. The use of nonoperational and mutually dependent forces in flux equations has impeded our understanding of electrochemical processes, and has led to wrong conclusions. The equation for entropy production is derived using only operationally defined quantities, chemical potentials of neutral components and the electric potential measured with reversible electrodes. The electric potential enters calculations as external electric work in the first law of thermodynamics. From entropy production, flux equations are obtained where the forces are operationally defined, measurable quantities. Three different problems from electrochemistry are discussed, the liquid junction potential, the Donnan potential, and energy coversion in mitochondria. The conventional method of calculations and the operational method are compared. The operational method permits more detailed calculations of emf, and an understanding of the process from a different approach.

KEY WORDS: Donnan potential; electric potential; electrochemical cell; external electric work; liquid junction potential; mitochondria; Onsager reciprocal relations; operational quantities; single-ion chemical potential; state function.

INTRODUCTION

Previously we have presented the operational approach to electrochemistry in various contexts.$^{(1-3)}$ This is an updated presentation offering improvements in the derivations and in the arguments for the operational approach.

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[1] Department of Physical Chemistry, NTH, University of Trondheim, N-7034 Trondheim, Norway.

0022-4715/95/0100-0513$07.50/0

1. ENTROPY PRODUCTION, FLUXES, AND FORCES EXPRESSED BY OPERATIONAL QUANTITIES

1.1. The Onsager Reciprocal Relations

Onsager based his treatment on the postulate of microscopic reversibility. His treatment is restricted to the linear range where there are *linear relations* between fluxes and forces,

$$J_i = \sum L_{ij} X_j \tag{1}$$

The Onsager reciprocal relations (ORR) were originally developed for a set of *independent variables* A_i. These may be the internal energy U, the volume V, or the amounts of the different components n_i. It is postulated that at equilibrium the values of these variables fluctuate independently. Their deviation from the equilibrium value is $\alpha_i = A_i - A_{i,\mathrm{eq}}$. The *postulate of microscopic reversibility* is formulated as

$$\overline{\alpha_i(t)\,\alpha_j(t+\Delta t)} = \overline{\alpha_j(t)\,\alpha_i(t+\Delta t)} \tag{2}$$

where t is time.

By means of statistical considerations the ORR for cross coefficients are derived from the above postulate$^{(4,5)}$:

$$L_{ij} = L_{ji} \tag{3}$$

1.2. Electrolyte Solutions and Electrochemical Cells

When dealing with electrolyte solutions frequently $\tilde{\mu}_{\mathrm{ion}}$, the electrochemical potential for single ions, is used as a force, and fluxes of ions as conjugate fluxes.$^{(6-8)}$ The electrochemical potential is defined by

$$\tilde{\mu}_{\mathrm{ion}} = \mu_{\mathrm{ion}} + Z_{\mathrm{ion}} F \psi \tag{4}$$

where μ_{ion} is the single-ion chemical potential, Z_{ion} is the charge of the ion, and ψ is the electrostatic potential. This equation has, according to Guggenheim,$^{(9)}$ "no physical significance as the value of ψ is quite arbitrary."

For an ionic compound $\mathrm{C_m A_n}$, we have

$$\mathrm{m}Z_{\mathrm{C}} + \mathrm{n}Z_{\mathrm{A}} = 0 \tag{5}$$

The single-ion chemical potentials are defined such that their sum is equal to the chemical potential of the compound:

$$\mathrm{m}\mu_{\mathrm{C}} + \mathrm{n}\mu_{\mathrm{A}} = \mu_{\mathrm{C_m A_n}} \tag{6}$$

The sum of the electrochemical potentials is

$$m\tilde{\mu}_C + n\tilde{\mu}_A = m\mu_C + n\mu_A + (mZ_C + nZ_A)F\psi = \mu_{C_mA_n} \tag{7}$$

The quantities μ_C, μ_A, and ψ are all unmeasurable. Since a solution of an electrolyte is essentially electrically neutral (see Section 2.1 about charge separation), μ_C and μ_A are *mutually dependent* and similary $\tilde{\mu}_C$ and $\tilde{\mu}_A$, except in an electrochemical cell with a closed circuit. With dependent forces there is no proof that the ORR are valid for flux equations. Onsager and Fuoss,(10) however, pointed out that the ORR "can be derived from the very reasonable assumption that molecular dynamical systems, like those known to our macroscopic experience, possess symmetry in past and future."

In an electrochemical cell with a closed circuit, the electrochemical potentials of single ions can be defined operationally (ref. 1, pp. 53–54; ref. 2, pp. 349–350) instead of by Eq. (4). We shall illustrate this for a simple example, an electrochemical cell with Ag/AgCl electrodes and an aqueous solution of HCl as the electrolyte. Here we have $\Delta\tilde{\mu}_{H^+} + \Delta\tilde{\mu}_{Cl^-} = \Delta\mu_{HCl}$ and $\Delta\tilde{\mu}_{Cl^-} = -\Delta\varphi$, where $\Delta\varphi$ is the measurable outer electric potential of the cell. The $\Delta\mu_{HCl}$ and $\Delta\varphi$ can be varied independently, and thus $\Delta\tilde{\mu}_{H^+}$ and $\Delta\tilde{\mu}_{Cl^-}$ are independent. Similarly J_{H^+} and J_{Cl^-} are independent in a cell with a closed circuit. (If the Ag/AgCl electrodes are replaced by H^+/H_2 electrodes, the electric potential is $\Delta\varphi'$ and $\Delta\tilde{\mu}_{H^+} = \Delta\varphi'$.)

1.3. The Use of Operational Quantities in Flux Equations

In order to avoid the problem of unmeasurable and dependent quantities as forces, one may use only *operational quantities*, fluxes of neutral components. The conjugate forces will be gradients in chemical potential of the neutral components. In an electrochemical cell we have an additional variable, the electric work supplied, with force $\nabla\varphi$, the gradient in the outer electric potential of the cell (which can be obtained by introducing local test electrodes; see Fig. 2). The chemical potentials of the components are interdependent by the Gibbs–Duhem relation. When using one of the components as the frame of reference, the forces are independent.

1.4. Transfer of Matter and Electric Charge in an Electrochemical Cell

We shall consider an adiabatic system of uniform temperature consisting of two open subsystems in contact with each other. The two subsystems have the same temperature, but may have different pressures and different

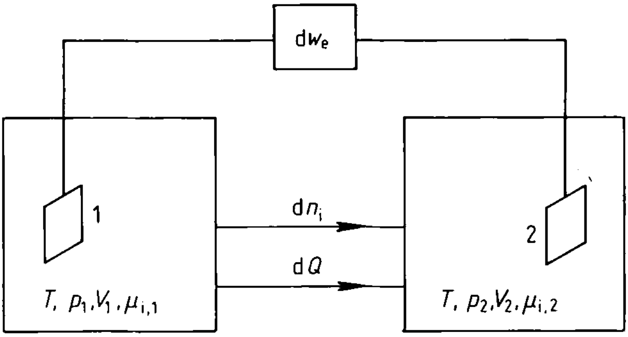

Fig. 1. An adiabatic system consisting of two open subsystems at the temperature T. Transfer of matter, dn_i, and charge, dQ, from subsystem 1 to subsystem 2. Electric work dw_e is added to the system.

chemical potentials for the components. An electric potential difference $\Delta\varphi$ can be observed when connecting the two subsystems with electrodes and metallic leads through a potentiometer. Differential quantities of neutral components dn_i and charge dQ are transferred between the subsystems, while a differential outer electric work dw_e is added to the system via the electrodes; see Fig. 1.

We assume no significant accumulation of charge in the system, and thus no significant change in electrostatic energy by the transport process (see Section 2.1).

The changes in internal energy are expressed by *internal variables*:

$$\begin{aligned} &\text{subsystem 1:} \quad dU_1 = T\,dS_1 - p_1\,dV_1 + \sum_i \mu_{i,1}\,dn_{i,1} \\ &\text{subsystem 2:} \quad dU_2 = T\,dS_2 - p_2\,dV_2 + \sum_i \mu_{i,2}\,dn_{i,2} \end{aligned} \tag{8}$$

The differential changes in μ_i, p, and T caused by the transfer do not give any contribution to dU, since we have from the Gibbs–Duhem equation

$$\sum_i n_i\,d\mu_i - V\,dp + S\,dT = 0$$

Equations (8) solved with respect to entropy changes give

$$\begin{aligned} dS_1 &= \frac{dU_1}{T} + \frac{p_1}{T}\,dV_1 - \frac{1}{T}\sum_i \mu_{i,1}\,dn_{i,1} \\ dS_2 &= \frac{dU_2}{T} + \frac{p_2}{T}\,dV_2 - \frac{1}{T}\sum_i \mu_{i,2}\,dn_{i,2} \end{aligned} \tag{9}$$

The change in internal energy for the whole system, $dU = dU_1 + dU_2$, can be expressed by external variables. For an adiabatic system there is no exchange of heat or matter with the surroundings. The work consists of pressure–volume work $p\,dV$ and externally supplied electric work dw_e. Thus we have

$$dU_1 + dU_2 = -p_1\,dV_1 - p_2\,dV_2 + dw_e \tag{10}$$

In these equations we have

$$dn_i = -dn_{i,1} = dn_{i,2} \tag{11}$$

and

$$dw_e = -\Delta\varphi\,dQ \tag{12}$$

where dQ is the electric charge transferred and $\Delta\varphi$ is the electric potential.

From Eqs. (9)–(12) we obtain the entropy production in the adiabatic system:

$$dS = dS_1 + dS_2 = -\frac{1}{T}\sum_i \Delta\mu_i\,dn_i - \frac{1}{T}\Delta\varphi\,dQ \tag{13}$$

where $\Delta\mu_i = \mu_{i,2} - \mu_{i,1}$.

In this derivation of the entropy production the electric potential difference $\Delta\varphi$ enters the equation via external electric work as expressed in the first law, Eq. (10). It is an operational quantity different from $\Delta\psi$ in Eq. (4).

Many irreversible processes take place in a continuous system with gradual changes in properties.

Consider the entropy production by transfer of matter and charge across a membrane separating two mixtures, 1 and 2. The mixtures are of different pressure and composition; each mixture, however, is uniform in these variables. The membrane allows a gradual change in the variables from mixture 1 to mixture 2, giving fluxes of matter. With electrodes in the two mixtures and a closed electric circuit, there will also be a flux of charge, an electric current. It will be assumed that the process does not create macroscopic kinetic energy changes and that there is no transport of bulk solution through the membrane. A frame of reference for the transport is needed in order to describe the local changes in composition (or any other intensive property). Here it is convenient to choose the membrane matrix as the frame of reference.

For the calculation of local entropy production in the membrane, fluxes and changes in intensive variables will be described as taking place in small steps. Thus the membrane will be considered as composed of narrow sections or subsystems of uniform intensive variables. Test electrodes are placed in the subsystems; see Fig. 2. They are only used for measuring local electric potentials. The currents passing through these electrodes in a stepwise charge transfer will cancel. For simplicity in calculation, we shall consider forces and fluxes in the x direction only.

The entropy production by a one-step transfer from subsystem a to b can be expressed in a similar way to Eq. (13). If the length of each subsystem is dx, the entropy production per unit length in any region of the subsystem is given by

$$\frac{d}{dx}(dS) = -\frac{1}{T}\sum_i \left(\frac{d\mu_i}{dx}\right) dn_i - \frac{1}{T}\left(\frac{d\varphi}{dx}\right) dQ \tag{14}$$

If the quantities dn_i and dQ pass a cross section of unit area in the course of the time dt, the entropy production per unit volume and unit time θ is obtained:

$$\theta = -\frac{1}{T}\sum_i \left(\frac{d\mu_i}{dx}\right) J_i - \frac{1}{T}\left(\frac{d\varphi}{dx}\right) j \tag{15}$$

where j is the current density.

It is common to define fluxes and forces from the dissipation function $T\theta$ rather than from the entropy production, Eq. (15). We have

$$T\theta = -\sum_i (d\mu_i/dx)\, J_i - (d\varphi/dx)\, j \tag{16}$$

with the forces

$$-\frac{d\mu_i}{dx} = X_i, \qquad -\frac{d\varphi}{dx} = X_j \tag{17}$$

The conjugate fluxes are

$$dn_i/dt = J_i, \qquad dQ/dt = j \tag{18}$$

Both S_1 and S_2 in Eq. (13) and the entropy of each subsystem illustrated in Fig. 2 are *state functions*. Therefore dS_1, dS_2, and the entropy changes of the subsystems are independent of how the changes came about, by transfer of ions or transfer of neutral components. Thus Eqs. (13), (15), and (16) are also valid, independent of how the change came about. The contribution to entropy production by the externally supplied energy, $dw_e = -(d\varphi/dx)\, dQ$, can be varied independently of all the other contributions. Therefore $-d\varphi/dx = X_j$ is an *independent force*. This permits us to

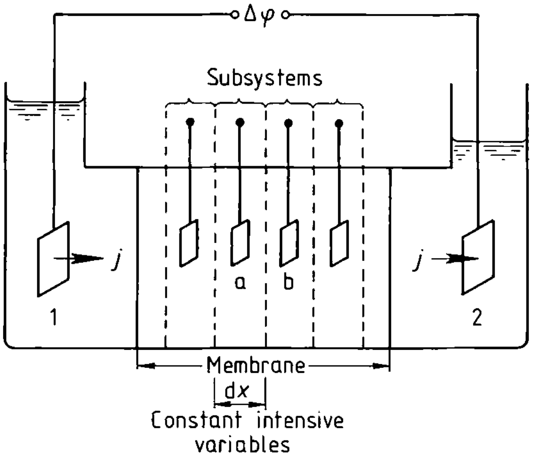

Fig. 2. Transfer of matter and charge in an adiabatic system composed of a series of subsystems.

describe the entropy production by the well-defined forces and fluxes of neutral components, the flux of charge j, and the measurable electric potential difference $\Delta\varphi$. See ref. 1, Chapter 2, and ref. 2, pp. 340–384 (particularly pp. 341–350), for a similar development including also temperature gradients.

2. COMPARISON OF THE CONVENTIONAL AND THE OPERATIONAL APPROACHES. EXAMPLES

We shall consider some problems in electrochemistry, the *liquid junction potential*, the *Donnan potential*, and the energy conversion in *mitochondria*, where both approaches have been applied.

2.1. The Liquid Junction Potential

The non-Nernstian behavior of electrodes is a problem in analytical chemistry. Covington(11) stated that such behavior can be caused by the liquid junction of the reference electrode, not only by the ion-selective electrode. So far a quantitative analysis of the problem is lacking.

In order to demonstrate the principal difference between the conventional approach and the operational approach, we shall consider a very simple system, the concentration cell (see Fig. 3):

$$\mathrm{Ag(s)\,|AgCl(s)\,|\,HCl(aq,\,c_1)_I|\ |HCl(aq,\,c_2)_{II}\,|\,AgCl(s)|\ Ag(s)}$$

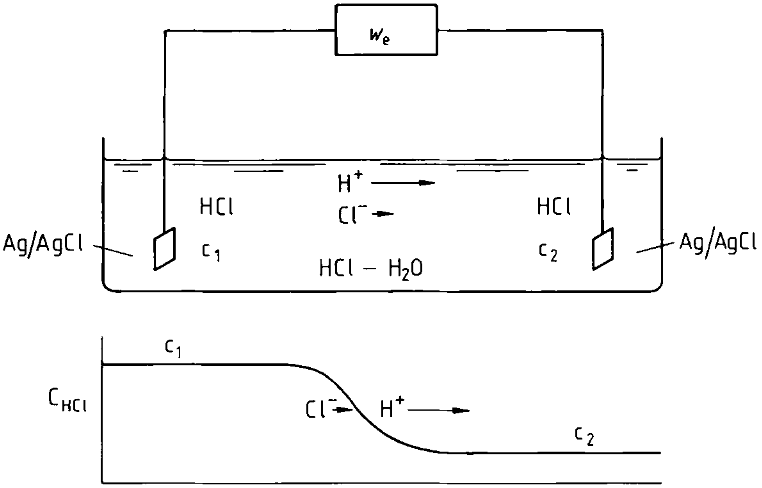

Fig. 3. A simple concentration cell with liquid junction.

The Conventional Approach. For the mathematical treatment, see, e.g., Adamson.$^{(12)}$ The potential changes at the electrodes and over the liquid junction are calculated separately and added to give the emf of the cell. The calculation involves the use of single-ion activities, which are not measurable, nor are the separate potentials. Usually the unmeasurable quantities sum up to give measurable quantities. It is a problem, however, if we want to introduce approximations when we deal with unmeasurable quantities, that the approximations cannot be checked by experiments.

The Operational Approach. By the emf measurements a small electric charge dQ is passed through the cell during a short time interval dt. In order to obtain the Gibbs energy change by transport, we need the flux equations. They are obtained from the equation for $T\theta$, Eq. (16).

We have

$$J_{HCl} = -L_{11}\nabla\mu_{HCl} - L_{12}\nabla\varphi \tag{19}$$

$$j = -L_{21}\nabla\mu_{HCl} - L_{22}\nabla\varphi \tag{20}$$

Water is chosen as the frame of reference for the transport.

Eliminating $\nabla\varphi$ from Eqs. (19) and (20), we obtain

$$J_{HCl} = -l_{11}\nabla\mu_{HCl} - t_{HCl}j \tag{21}$$

where $l_{11} = L_{11} - L_{12}L_{21}/L_{22}$ is a *diffusion coefficient* and $t_{\mathrm{HCl}} = (J_{\mathrm{HCl}}/j)_{\nabla\mu_{\mathrm{HCl}}=0} = L_{12}/L_{22}$ is a *transference coefficient for the neutral component*. It can be obtained from a Hittorf experiment. The transference coefficient is electrode dependent, as is the result of a Hittorf experiment. With AgCl electrodes, as in our example, HCl is transferred from left to right, and $t_{\mathrm{HCl}} = t_{\mathrm{H^+}}$. With $\mathrm{H^+/H_2}$ electrodes HCl is transferred from right to left, and $t_{\mathrm{HCl}} = -1 + t_{\mathrm{H^+}} = -t_{\mathrm{Cl^-}}$.

We shall consider transport only in the x direction, and a unit cross section. The current density j is constant throughout the cell. The transference coefficient t_{HCl}, however, varies with composition. This means that the local content of HCl will change when the charge dQ is transferred during the time interval dt. In addition, diffusion causes changes in the local content of HCl.

The change in c_{HCl} in a volume element of thickness dx is given by the difference between the flux into and out from the volume element:

$$dc_{\mathrm{HCl}}/dt = \frac{J_{\mathrm{HCl}(x)} - J_{\mathrm{HCl}(x+dx)}}{dx} = -\frac{dJ_{\mathrm{HCl}}}{dx} \tag{22}$$

Thus the change in the content of HCl is obtained by differentiating Eq. (21) with respect to x.

Products of local changes in HCl content and local chemical potentials of HCl are summed up to give the total Gibbs energy change dG over the liquid junction and at the two electrodes. The change dG consists of two separable terms, a time-dependent term $dG(t)$ proportional to t, and a charge-dependent term $dG(Q)$ proportional to Q:

$$dG = dG(t) + dG(Q) \tag{23}$$

where $dG(Q) = -\Delta\varphi\, dQ$; see ref. 1, Chapter 4.2, and ref. 2, p. 350, for more details.

We may consider the change in Gibbs energy per faraday electric charge transferred, and find $\Delta\varphi$. We may consider the cell as made up of sections. Then we find ΔG per faraday transferred for each section and add up these. For our simple cell we have the following:

Section I, the left-hand-side electrode compartment:

$$\Delta G_{\mathrm{I}} = \mu_{\mathrm{AgCl}} - \mu_{\mathrm{Ag}} - t_{\mathrm{HCl(I)}}\mu_{\mathrm{HCl(I)}}$$

The liquid junction:

$$\Delta G_{\mathrm{l.j.}} = -\int_{(\mathrm{I})}^{(\mathrm{II})} \mu_{\mathrm{HCl}}\, dt_{\mathrm{HCl}}$$

Section II, the right-hand-side electrode compartment:

$$\Delta G_2 = \mu_{\mathrm{Ag}} - \mu_{\mathrm{AgCl}} + t_{\mathrm{HCl(II)}} \mu_{\mathrm{HCl(II)}}$$

Adding up, we obtain

$$\Delta G(Q) = \Delta G_1 + \Delta G_{\mathrm{l.j.}} + \Delta G_2 = \Big|_{(\mathrm{I})}^{(\mathrm{II})} t_{\mathrm{HCl}} \mu_{\mathrm{HCl}} - \int_{(\mathrm{I})}^{(\mathrm{II})} \mu_{\mathrm{HCl}} \, dt_{\mathrm{HCl}}$$

$$= \int_{(\mathrm{I})}^{(\mathrm{II})} t_{\mathrm{HCl}} \, d\mu_{\mathrm{HCl}} = -\Delta\varphi \tag{24}$$

Only the charge-dependent term in Eq. (23) is connected to the emf E of the cell. This is seen from Eq. (20) for $j = 0$. Then

$$d\varphi = -(L_{21}/L_{22}) \, d\mu_{\mathrm{HCl}} \tag{25}$$

and by integration over the whole cell we obtain

$$EF = -\int_{(\mathrm{I})}^{(\mathrm{II})} (L_{21}/L_{22}) \, d\mu_{\mathrm{HCl}} \tag{26}$$

Introducing the ORR $L_{21} = L_{12}$ and $L_{12}/L_{22} = t_{\mathrm{HCl}}$, we obtain

$$EF = -\int_{(\mathrm{I})}^{(\mathrm{II})} t_{\mathrm{HCl}} \, d\mu_{\mathrm{HCl}} \tag{27}$$

The calculation is easily extended to a system containing an electrolyte with several components:

$$EF = -\int_{(\mathrm{I})}^{(\mathrm{II})} \sum_i t_i \, d\mu_i \tag{28}$$

The method has been applied to electrochemical cells with a liquid junction between the two electrolytes, HCl(dilute)–KCl(high concentration) (ref. 2, pp. 351–354; refs. 3, 13, 14). The emf was calculated from Eq. (28) for well-defined concentration profiles, taking into account changes in mobilities and activity coefficients. Theoretical values were compared with experimental values, and a very good agreement was found.(14)

For a more complex system containing several liquid junctions and membranes, it is reasonable to divide the cell into several compartments. From the change in Gibbs energy by the transfer of one faraday electric charge one may find the electric work supplied and hence the change in electric potential for each part of the cell (ref. 1, Chapter 8.3; ref. 2, pp. 351–354, ref. 3).

The Contribution to the emf from Changes in Charge Separation in the Liquid Junction. In the liquid junction of the cell pictured in Fig. 3, diffusion of HCl takes place. Because H^+ ions have a higher mobility than Cl^- ions, an electrostatic potential gradient is created giving an electrostatic energy U_{el} in the liquid junction.

In the derivation of Eqs. (13) and (16) we assumed only insignificant changes in U_{el} by the transport process, and there was no contribution to dU in Eqs. (8) nor to the emf.

We shall estimate the order of magnitude of the contribution from $\partial U_{el}/\partial Q$. We assume the dilute electrolyte an ideal solution. The electrostatic energy in the liquid junction is given by the equation from electrostatics (see, e.g., Alonso *et al.*$^{(15)}$):

$$U_{el} = \tfrac{1}{2}\int_V \varepsilon(\nabla\varphi)^2\,dV \tag{29}$$

The integration is over the volume of the liquid junction. Here ε is the dielectric constant and $\nabla\varphi$ is measured using a large set of test electrodes (comp. Fig. 2). The contribution from $\partial U_{el}/\partial Q$ was calculated assuming a sharp gradient in c_{HCl} (from 0.01 M to 0.1 M over 1 mm).$^{(16,17)}$ The contribution to the emf was found to be of the order of magnitude 10^{-15} V. For a less sharp gradient it would be even smaller. Thus the contribution to the emf from a change in electrostatic energy by charge transfer is insignificant, as was assumed in the first section of this paper.

2.2. The Donnan Potential

In a cell, two electrolytes of, e.g., KCl are separated by a membrane. The cell is illustrated in Fig. 4. In compartment II a small amount of a second electrolyte, KR, has been added. The membrane is permeable to both K^+ and Cl^- ions, but impermeable to the R^- ions. Equilibrium is established over the membrane for KCl. The concentration of K^+ is higher in solution II than in solution I. (A small amount of a nonelectrolyte, e.g., sucrose, is added to solution I to compensate for the small difference in water activity.) The potential of this cell is called the *Donnan potential.*

The Conventional Approach. The electrochemical potential difference for K^+, $\Delta\tilde{\mu}_{K^+}$, is assumed to be equal to zero over the membrane:

$$\Delta\tilde{\mu}_{K^+} = \Delta\mu_{K^+} + F\,\Delta\psi = 0 \tag{30}$$

where $\Delta\psi$ is the electrostatic potential difference over the membrane. There is assumed no contribution to the emf from the salt bridges of the two

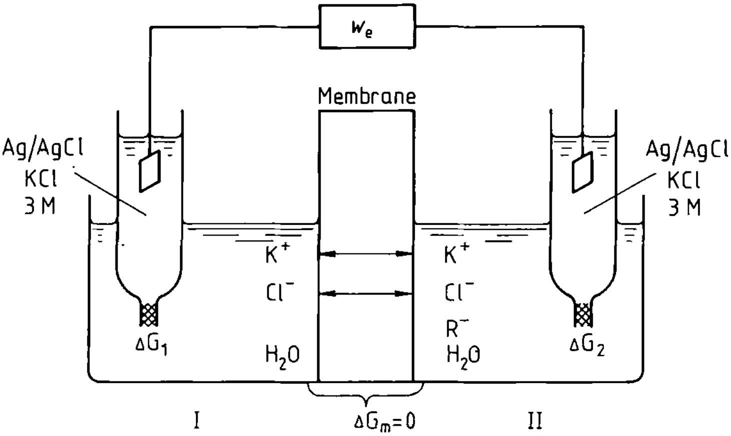

Fig. 4. Electrochemical cell for the measurement of the Donnan potential.

reference electrodes. The whole cell potential is created over the membrane. Furthermore, as an approximation, the activity of K^+, a_{K^+}, is replaced by the concentration c_{K^+}.

One obtains

$$EF = -\Delta\mu_{K^+} = -RT\ln(c_{K^+(II)}/c_{K^+(I)}) \tag{31}$$

where E is the emf of the cell.

The Operational Approach. In the operational approach we calculate the Gibbs energy change for the whole system by charge transfer $\Delta G(Q)$. The content of KCl on the two sides of the membrane changes by charge transfer. The contribution to $\Delta G(Q)$ in this region, however, is equal to zero, $\Delta G_m = 0$, because the chemical potential of KCl is the same on both sides of the membrane. All the charge-dependent Gibbs energy changes are created in the salt bridges, ΔG_1 and ΔG_2 (see Fig. 4).(18) We have

$$EF = -(\Delta G_1 + \Delta G_2) \tag{32}$$

The calculation of $\Delta G_1 + \Delta G_2$ is done using Eq. (28).

Assuming ideal solutions and for $c_{R^-} \ll c_{Cl^-}$ in the salt bridge of the right-hand side electrode, we obtain

$$EF = -RT\ln(c_{K^+(II)}/c_{K^+(I)}) \tag{33}$$

The two approaches to the emf calculation, Eqs. (30) and (32), give the same result when approximations are introduced. The two approaches, however, are fundamentally different. In the *conventional approach* one assumes that the emf is created over the membrane, and that the contribution to the emf from the salt bridges is equal to zero. The membrane potential is the electrostatic potential difference between two points, one on each side of the membrane. The system is inhomogeneous, and the electrostatic potential is not defined operationally. When two reference electrodes are inserted as shown in Fig. 4, the outer electric potential of the cell (the emf) is measured, not the electrostatic potential. A small electric charge is passed through the cell by the measurement, and a corresponding electric work $dw_e = -\Delta\varphi \, dQ$ is supplied to the system. The electric work $-\Delta\varphi \, dQ$ causes a change in Gibbs energy $dG(Q)$, where $dw_e + dG(Q) = 0$. This gives exact information about the origin of the electric work, and thus the origin of the emf. In the *operational approach* the sections of the cell responsible for the emf are found to be the salt bridges.

Although the conventional method permits a calculation of the emf, it gives the wrong information about the origin of the emf.

2.3. Energy Conversion in Mitochondria

The concept of membrane potential is widely used in biochemistry. One of the most important processes in biology is the energy conversion taking place in the membrane of an organelle called the mitochondrion. In the discussion of this process the membrane potential has played a central role.

The two important processes in the mitochondrial membrane are the oxidation of the molecule NADH by O_2 in the respiratory chain, and the formation of an energy carrier, ATP, which is the source of energy, e.g., in a muscle that carries out work. The oxidation takes place over three steps in the respiratory chain, and in each step about $4\,H^+$ are transported across the membrane. The H^+ are transported back through the membrane by means of an enzyme, the ATPase, whereby ATP is produced from ADP and inorganic phosphate, P_i:

$$\mathrm{ADP} + \mathrm{P_i} = \mathrm{ATP} \tag{34}$$

In his chemiosmotic theory, Mitchell(19) suggested, based on evidence, that the two processes, the oxidation and the ATP formation, are coupled. This opened a much better understanding of the oxidative phosphorylation, but still there were unexplained observations on mitochondria.

The Conventional Approach. Mitchell used the conventional concepts of electrochemistry, such as single-ion chemical potentials and an electrostatic potential, in his explanation. Problems arise when experimental observations are to be explained by a theory based on nonoperational quantities, $\Delta\mu_{H^+}$ and $\Delta\psi$. There is still no theory capable of a full explanation of the mechanism of the total process.

The Operational Approach. The total process can be analyzed using only operationally defined quantities, avoiding the quantities $\Delta\mu_{H^+}$ and $\Delta\psi$.(20)

Before we analyze the process, we refer to experiments by Rottenberg *et al.*(21) In their experiments the redox potential and the concentrations of ADP, ATP, and P_i could be varied. Their observations showed that (i) the process could be reversed, (ii) it could be balanced, and (iii) three H^+ passed through the ATPase for each ATP formed.

The redox process causing the transfer of H^+ across the membrane is equivalent to a transfer of H^+ by the use of two hydrogen electrodes, one on each side of the membrane, and a voltage source located in the membrane, the respiratory chain. The H^+ returning through the ATPase takes part in the phosphorylation process. This cell model is shown in Fig. 5. All steps in the cell reaction are reversible, no energy is lost in the process. Three electric charges are transferred for each ATP produced. From stoichiometry and charge balance we postulate that the negative ions entering the ATPase from the right-hand side are $ADPMg^-$ and HPO_4^{2-}.

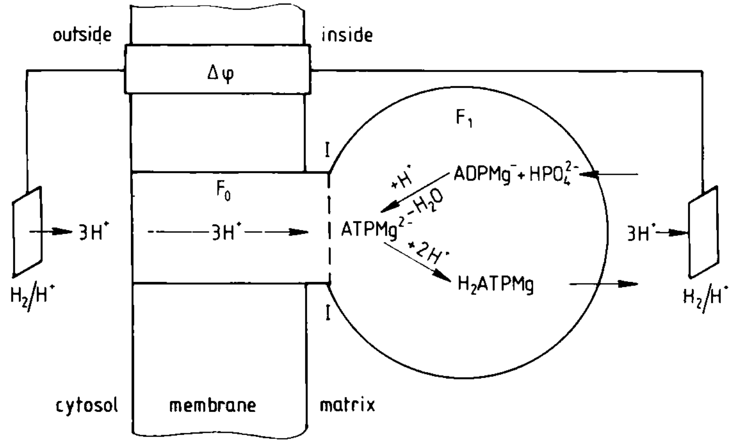

Fig. 5. An electrochemical cell model describing the synthesis of ATP. Reprinted, with permission, from ref. 20.

Experiments on detached F_1 particles show that ADP and P_i enter F_1 and form ATP strongly bound to F_1[22]. We assume the reaction

$$ADPMg^- + HPO_4^{2-} + H^+(F_1) = ATPMg^{2-}(F_1) + H_2O \qquad (35)$$

Only a very small supply of energy is needed for this reaction.

To discharge and release $ATPMg^{2-}$ a strong acid is needed. We postulate that this acid is produced in F_0. The unit F_0 is an H^+-conducting channel. We assume that the H^+–F_0^- bond is stronger on the left-hand side than on the right-hand side of the channel (Fig. 5). The H^+ ions are forced from left to right in the channel by the electric potential $\Delta\varphi$. This means that electric work is supplied to give an increase in Gibbs energy, representing a gradual weakening of the H^+–F_0^- bond from left to right. Hence the strength of the acid $H^+F_0^-$ is highest at the F_0–F_1 interface. The energy conversion from electric work to Gibbs energy in the H^+-conducting channel can take place in steps over some distance, and therefore $\Delta\varphi$ for each step is sufficiently low to prevent electric breakdown in the channel.

At the F_0–F_1 interface the neutral molecule H_2ATPMg is formed. It diffuses to the right and dissociates into $ATPMg^{2-}$ and $2H^+$ in the electrolyte.

The main point of the present discussion of the energy conversion is that the thermodynamics of each step in the process can be described by the chemical potentials of electrically neutral molecules, e.g., K_2ATPMg, KADPMg, K_2HPO_4, electrically neutral complexes, e.g., $H^+F_0^-$, and electric work, all well-defined operational quantities.(20) This analysis has given a new insight into the mechanism of the ATP synthesis in ATPase, and we can now explain some observations that could not be explained earlier.

3. CONCLUSIONS

Flux equations for electrolytes were derived using well-defined measurable forces, which are independent of one another. The forces are gradients in chemical potential of neutral components and gradients in electric potential as can be measured using reversible electrodes. The electric potential is introduced into the equation for entropy production by external electric work and the first law of thermodynamics. The fluxes are expressed as transfer of neutral components and of electric charge. Thus all forces and fluxes are operational quantities.

The flux equations are based on the equation for entropy production. This is shown to be independent of the transport mechanism, whether we consider migration of ions or transfer of neutral components.

The operational method leads to an insight into the mechanism from a different angle, and in some cases we obtain more information than by the conventional method.

For electrochemical cells with liquid junctions and membranes the operational method enables us to find where in the cell electric work is supplied, and the corresponding change in electric potential.

The analysis of the Donnan potential shows that the source of the potential is in the liquid junctions of the reference electrodes, not in the membrane. Hence the conventional approach to the Donnan potential misleads about where energy conversion takes place in a biological system.

The operational approach to the energy conversion in mitochondria has revealed new details in the mechanism of the ATP synthesis in the ATPase, which where not found by the conventional approach.

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