IRREVERSIBLE THERMODYNAMICS AND RATE THEORY*  
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Introduction.—The “classical theory of irreversible thermodynamics”¹ may be
said to have its origin in the formulation of the “reciprocity relations” by Onsager.²
The basis of this theory may be summarized briefly as follows (for a complete dis-
cussion see works cited in ref. 1 and 2): in the limit of small excursions from ther-
mosdynamic equilibrium, changes in the properties of any system are described by
certain formalized forces and fluxes. In general, the flux of any property (e.g.,
matter, heat, electricity, etc.) may be taken as linearly dependent upon all the
forces (concentration or temperature gradients, potential differences, etc.). If, in
this set of linear equations—called the “phenomenological equations”—the forces
and fluxes are properly defined, the coefficient \( L_{ij} \) of the \( j \)th force in the equation for
the \( i \)th flux must, according to the “reciprocity relations,” equal the coefficient
\( L_{ji} \), defined in the same manner. The correct choice of these forces and fluxes is
determined by the condition that the time rate of change of the entropy of the
system be given by the sum over the products of each force by its corresponding
flux.

The application of this treatment to processes involving simultaneous gradients
of temperature, concentration, chemical potential, or electrical potential has been
uniformly successful, provided only that the gradients are sufficiently small, i.e.,
the system is nearly at equilibrium. Exactly how near the equilibrium state the
system must be, however, in order that the postulated linearity will suffice as an
adequate approximation is not always made clear; for most purely physical phe-
nomena of this type, as, for example, Thompson and Peltier heats, it appears that
the formulation is adequate under nearly all experimental conditions. In diffusion
and chemical reaction, on the other hand, the several approximations described
above are almost never satisfactory in cases of practical interest, and the deductions
of this type of theory become, to a large extent, only academically interesting. It
would appear that in these cases, at least, a higher degree of approximation in relati-
ng the forces and fluxes of a given system is required. Unfortunately, any attempt
in this direction requires that the linear relation between forces and fluxes, and hence
the symmetry properties of the matrix of phenomenological coefficients (the Onsager
conditions), be given up, and the whole approach becomes impractically cumber-
some.

An additional problem arises from the fact that, strictly speaking, thermody-
namic variables such as entropy which appear in the algebraic formulation are not
well defined except at thermodynamic equilibrium, and their precise meaning be-
comes less clear the further the system deviates from this state. Any attempt to
describe a nonequilibrium system in terms of purely thermodynamic variables must
suffer from this logical difficulty, and it is not immediately apparent that there
exists any way in which this conflict can be resolved within the framework of the
classical theory of continuum thermohydrodynamics.

On the other hand, there is quite general treatment of irreversible processes based
upon the idea that in any transport process, or chemical reaction, the molecules occupy successive equilibrium states and pass from one to the next through a region of relatively high potential energy. The properties of the intermediate state of highest potential energy determine to a large extent the probability with which transition from one equilibrium position to the next will occur. It is thus not sufficient to specify the state of the system in terms of its equilibrium parameters and their expansion in terms of small departures from equilibrium values except in such special cases as occur when the activation energy for transport is comparable in magnitude to the extent of these energy fluctuations. This will almost never be true in chemical reactions, for example, where the activation energy will generally be some tens or hundreds of kilocalories.

It has been shown that a formulation of this type applies quite generally to irreversible processes and, in particular, to cases in which several forces are coupled to produce an equal number of fluxes. In all cases the properties of the activated state and the forces which provide the motive power for the rate process together determine the rate of transport of heat, matter, charge, etc. It is both convenient and appropriate that, in the limit of small activation free energies and small forces, this molecular formulation both reduces to the linear phenomenological equations of classical irreversible thermodynamics and provides the symmetric matrix of coefficients demanded by the Onsager reciprocity relations.

It seems quite clear that rate theory, the treatment of irreversible thermodynamics from the point of view of the activated complex, not only suffices to explain the behavior of systems considerably out of equilibrium, such as chemical reactions proceeding at quite rapid speeds, but in the limit of near-equilibrium conditions also contains all the information available from the classical theory. Since both treatments depend ultimately upon the principle of microscopic reversibility and derive from considerations of statistical fluctuations, it would seem a fair conclusion to say that the classical theory derived from the reciprocity conditions of Onsager is a special case of the more general rate theory, couched in the mathematical language of continuum physics. It is not clear that anything is gained by pursuing this special case further, since most examples of practical interest do not fall into the area of near-equilibrium conditions demanded by it. Equally important, the classical theory cannot be generalized to include transport processes further from equilibrium, since it deals only with the properties of the system in the several equilibrium positions, the minima of the potential-energy surface. The activated states, intermediate between these minima, do not appear in the formulation; since the rate of progressing from one minimum to the next depends upon the height of this barrier the treatment is necessarily severely restricted.

In the following sections we propose to consider coupled chemical reactions, to present the derivation of a general equation for transport in molecular terms, and to show that, in cases in which the linearization referred to above is proper, these equations do reduce to the formalism of the classical theory. In order to demonstrate this, an example of diffusion of ions in the presence of an electrical field is described.

*Cyclic Chemical Reactions.*—In a recent publication Zwolinski and Marcus have shown that near equilibrium the rate of unimolecular reaction can be expressed in the linear form
For complex reactions, involving several individual chemical transformations, the velocity with which species \( i \) is transformed into species \( j \) is given in generalized form as

\[
v_{ij} = -\frac{\kappa C_{ij}^+ \Delta F_{ij}}{hN}
\]

Now imagine the simplest possible cyclic sequence of three unimolecular reactions:

\[A \rightleftharpoons B, B \rightleftharpoons C, C \rightleftharpoons A.\]

For such a cyclic system one may write, using subscripts 1, 2, and 3 to refer to substances \( A, B, \) and \( C \), respectively:

\[
\begin{align*}
dc_1 &= -v_{12} - v_{13}, \\
dc_2 &= -v_{11} - v_{23}, \\
dc_3 &= -v_{31} - v_{32}.
\end{align*}
\]

Here the \( v \)'s are net velocities (forward minus reverse), and the direction of the reactions is indicated by the order of the subscripts. If the system is sufficiently close to equilibrium, one can substitute expression (2) for each of equations (3) and obtain

\[
\begin{align*}
dc_1 &= \frac{\kappa C_{12}^+ \Delta F_{12}}{hN} + \frac{\kappa C_{13}^+ \Delta F_{13}}{hN}, \\
dc_2 &= \frac{\kappa C_{21}^+ \Delta F_{21}}{hN} + \frac{\kappa C_{23}^+ \Delta F_{23}}{hN}, \\
dc_3 &= \frac{\kappa C_{31}^+ \Delta F_{31}}{hN} + \frac{\kappa C_{32}^+ \Delta F_{32}}{hN}.
\end{align*}
\]

Thus one obtains a general equation for cyclic systems of this type:

\[
\frac{dc_i}{dt} = \sum_j \left\{ -\frac{\kappa C_{ij}^+ \Delta F_{ij}}{hN} \right\} \quad (i \neq j).
\]

The right-hand side of the set of equations (5) can be represented as a square array whose diagonal terms vanish, due to the definition of \( \Delta F_{ij} \), in terms of the chemical potential, \( \mu_i \), of the \( i \)th species:

\[
\Delta F_{ij} = \mu_j - \mu_i.
\]

The square matrix of the coefficients of the \( \Delta F \)'s can be written as

\[
\begin{pmatrix}
0 & \frac{\kappa C_{12}^+}{hN} & \frac{\kappa C_{13}^+}{hN} \\
\frac{\kappa C_{21}^+}{hN} & 0 & \frac{\kappa C_{23}^+}{hN} \\
\frac{\kappa C_{31}^+}{hN} & \frac{\kappa C_{32}^+}{hN} & 0
\end{pmatrix}.
\]
It is easily seen that when the transmission coefficient \( \kappa \) is unity (\( h \) and \( N \) being Planck's constant and Avogadro's number, respectively), the matrix is symmetrical, since \( c^\dagger \) is by definition equal for the forward and reverse reactions. If \( \kappa \) should differ from unity, it is still true that

\[
\kappa_{ij} = \kappa_{ji} \quad (i \neq j),
\]

since the transmission coefficient refers to the initial and final states only. This model can be extended to cyclic systems made up of any number of successive unimolecular reactions. In general, one has always

\[
\frac{dc_i}{dt} = \sum_j \left\{ -\kappa c_{ij}^\dagger \Delta F_{ij} \right\} / hN
\]

with the conditions \( i \neq j, \ j = i \pm 1 \).

It is interesting to note that two fundamental postulates, common to all kinetic formulations, are implied by the statement

\[
c_{ij}^\dagger = c_{ji}^\dagger,
\]

viz., for a given reaction, the identically same critical complex is involved irrespective to the direction of the reaction, and the concentration of this complex is independent of the direction being considered. Furthermore, the well-defined linear approximation (eq. [2], arrived at by expansion of the generally occurring exponential relationship) makes it possible to calculate the limit to which the theory is applicable. For instance, \( \Delta F \) must be less than \( 1/kT \), or 200 cal. at room temperature, in order that the error introduced by neglecting the square term in the expansion shall be no greater than 10 per cent. This conclusion again emphasizes that the Onsager treatment, while undoubtedly correct in its domain, is rather ineffectual as a tool for studying coupled chemical reactions.

**General Equations for Transport.**—It is not difficult to write the equations of transport in terms of the flux of a particular species across the several individual barriers in the form discussed by Zwolinski, Eyring, and Reese⁶ and by Eyring, Lumry, and Woodbury.⁷ In the usual way one derives for the flux of a species across the \( i \)th barrier in the forward direction the expression

\[
Q_i = c_i \lambda_i k_i - c_{i+1} \lambda_{i+1} k'_{i+1},
\]

where \( c_i \) is the concentration at the \( i \)th potential minimum, \( \lambda_i \) is the width of the potential barrier between the \( i \)th and the \((i + 1)\)st minima, and \( k_i \) and \( k'_{i} \) are the specific reaction rate constants for traversing the barriers to the right and left of the \( i \)th minimum, respectively.

The set of equations which is obtained by writing equation (11) for all \( i \) from zero to \((n - 1)\) may be represented by the matrix equation

\[
\begin{pmatrix}
Q_0 - c_0 \lambda_0 k_0 \\
Q_1 \\
\vdots \\
Q_n
\end{pmatrix}
= 
\begin{pmatrix}
-\lambda_1 k'_1 & \ldots & 0 & 0 \\
\lambda_1 k'_1 & -\lambda_2 k'_2 & \ldots & 0 & 0 \\
\vdots & \vdots & \ddots & \vdots & \vdots 
\end{pmatrix}
\begin{pmatrix}
c_1 \\
c_2 \\
\vdots \\
c_n
\end{pmatrix}.
\]

\[(12)\]

In the steady state, where all \( Q_i \) are equal to the macroscopic flux \( Q \), equation (12) may be solved for any particular concentration \( c_i \) by applying Cramer's rule:
\[ c_i = \frac{QA^{t_1} + QA^{t_2} + \ldots + QA^{t_n}}{|A|} \]  

where \( |A| \) is the determinant of the square matrix of equation (12), and \( A^{t_1}, A^{t_2}, \ldots, \) are its cofactors for column and row indicated \( (A^{*} = \partial |A|/\partial A_{ij}) \). In practice, the concentrations in which one is mainly interested are those corresponding to the first and to the last minimum, respectively; solving for the flux across the macroscopic diffusion barrier in terms of these concentrations, one obtains

\[ Q = \frac{c_0 \lambda_0 k_0 - (k_1'k_2'\ldots k_{n-1}')/(k_1 k_2\ldots k_{n-1})k_0'c_n \lambda_n}{1 + (k_1'/k_1) + (k_1'k_2'/k_1 k_2) + \ldots + (k_1'k_2'\ldots k_{n-1}')/(k_1 k_2\ldots k_{n-1})}. \]  

This expression is not generally useful, since in the absence of some relation between the various rate constants it remains simply a formalism. The various terms in the denominator of equation (14) can be written as

\[ \frac{k_1'k_2'\ldots k_i'}{k_1 k_2\ldots k_i} = \exp \left( \delta F^i \right), \]  

where \( \delta F^i \) is the difference between the free energy at the top of the barrier to the right of the zeroth minimum and that at the right of the \( j \)th minimum. In many cases it appears that this difference can be taken as a linear function of the distance in the direction of transport. Under such conditions one has

\[ \delta F^i = \frac{i}{n} \Delta F_n \quad (i = 1, 2, \ldots, n - 1), \]  

where \( \Delta F_n \) is the total free-energy change through which the particle falls in crossing the set of \( (n - 1) \) barriers. With this assumption the denominator of equation (14) becomes a simple power series, and the steady-state equation for the flux of any species is

\[ Q = \frac{\lambda_0 k_0 \left[ c_0 - (\lambda_n/\lambda_0)c_0 \exp (\Delta F_n/RT) \right]}{1 + x + x^2 + \ldots + x^{n-1}}, \]  

where

\[ x = \exp \left( \frac{\Delta F_n}{nRT} \right). \]  

The geometric series in the denominator of equation (17) may be summed to give, as the equation for the steady-state flux, the expression

\[ Q = \frac{1 - x}{1 - x^n} \left\{ \lambda_0 k_0 \left( c_0 - \frac{\lambda_n}{\lambda_0} c_0 \exp (\Delta F_n/RT) \right) \right\}, \]  

or, upon rearranging,

\[ Q = \lambda_0 k_0^\circ \frac{x^{-1/2} - x^{1/2}}{x^{-n/2} - x^{n/2}} \left\{ x^{-n/2} - c_0 - \frac{\lambda_n}{\lambda_0} x^n c_n \right\}. \]  

In equation (20), \( k_0^\circ = k_0 \exp (\Delta F_n/2nRT) \) is the rate constant for crossing the first barrier in the absence of any applied force. The factor


\[
\frac{x^{-1/2} - x^{1/2}}{x^{-n/2} - x^{1/2}} \equiv \frac{g}{n}
\]

(21)

can usually be replaced by its approximate value, \(1/n\), unless \(\Delta F_n\) is large compared with \(RT\). The barrier widths \(\lambda\) may in most cases be taken to be approximately equal. With these definitions and approximations, one may write for the flux of a particular species the expression

\[
Q = \frac{\lambda_0 k_0^c g}{n} \{x^{1/2}c_n - x^{1/2}c_n\}.
\]

(22)

A similar equation may, of course, be written for the flux of each species present in the system at the steady state. The quantity \(x\), defined in equation (18), expresses the dependence of the flux of a species upon the force which drives the system toward equilibrium. Its precise formulation in specific cases will be illustrated later.

**Membrane Diffusion.**—We consider as an example the case discussed from a somewhat different point of view in a previous paper. Suppose two aqueous solutions of sodium and potassium chloride to be separated by a biological membrane, as is approximately the case in most living cells. In addition, assume that some neutral molecule, which we designate as \(P\), is produced on one side of the membrane and is destroyed or otherwise removed on the other. This unspecified metabolite, \(P\), is capable of complexing with the sodium ion preferentially, and the complex ion, \(NaP^+\), diffuses through the membrane more rapidly than the ion \(Na^+\). Under these conditions, it can be shown that in the steady state, when the metabolite is being produced and destroyed at equal, constant rates, a potential will be set up across the membrane which may be of the order of 100 mv. Designating the species \(Na^+, K^+, NaP^+, Cl^-\), and \(P\) by the subscripts 1 through 5, respectively, one obtains for the fluxes the equations

\[
Q_i = P_i \{x_i^{-n/2}c_{oi} - x_i^{n/2}c_{oi}\} \quad \text{(}i = 1, 2, 3, 4\text{)},
\]

(23)

\[
Q_5 = P_5 \{c_{o5} - c_{5}\},
\]

(24)

where we have written \(P_i = \lambda_0 k_0^c g/n\) (eq. [22]), and \(\Delta F_n = z_i\beta F\) (eq. [18]). Also, \(z_i\) is the charge on the \(i\)th ion, with sign; \(\beta\) is the faraday; and \(F\) is the potential across the membrane. For the total current, \(I = Q_5\), we write simply the sum of the fluxes of the charged ions, each multiplied by its charge:

\[
Q_5 = \sum_{i=1}^{4} Q_i z_i\beta F.
\]

(25)

The subscripts zero and \(n\) refer to the inside and the outside of the cell or membrane, respectively.

We have here a situation typical of those discussed in classical irreversible thermodynamics, viz., a diffusion of ions and molecules arising from the force of a concentration gradient opposed by the electrostatic force on the charged ions due to the membrane potential. Because of these opposing forces, the system is able to achieve a steady state, supported by the metabolic production of the carrier, \(P\). Since the equations have not been linearized, there are no restrictions on their validity, such as requiring the gradients and potentials to be small. On the other
hand, since the relation between the forces and fluxes is not linear, the symmetry conditions of Onsager obviously cannot be applied. In order to do this, it will be necessary to reduce the equations to the limiting form appropriate to near-equilibrium conditions.

If we write for the chemical potential on the two sides of the barrier the approximate equations

\[ \mu_{0i} = \mu_{0i}^\circ(T) + RT \ln c_{0i}, \quad \mu_{ai} = \mu_{ai}^\circ(T) + RT \ln c_{ai}, \] (26)

then the concentration gradient becomes, with \( \Delta \mu_i = \mu_{0i} - \mu_{ai} \),

\[ c_{0i} - c_{ai} = (c_0 + c_n) \frac{1 - (c_a/c_0)}{1 + (c_n/c_0)} = (c_0 + c_n) \cdot \tanh \frac{\Delta \mu_i}{2RT}. \] (27)

(Here it is assumed that the standard state is the same in each solution, whence \( \mu_{0i}^\circ = \mu_{ai}^\circ \).)

Taking, in this limit, the average concentration, \( \bar{c}_i = \frac{1}{2}(c_0 + c_n) \), as approximately constant, and substituting equations (26) and (27) into equation (23), one obtains

\[ Q_i = 2P_i \bar{c}_i \left\{ \cosh \frac{z_i \delta\varepsilon}{2RT} \cdot \tanh \frac{\Delta \mu_i}{2RT} + \sinh \frac{z_i \delta\varepsilon}{2RT} \right\}. \] (28)

When \( \varepsilon \) is small compared to \( RT \), equation (28) may be expanded, retaining only terms to the first power in \( \Delta \mu_i \) and \( \varepsilon \), to give

\[ Q_i = \frac{P_i \bar{c}_i}{RT} \left\{ \Delta \mu_i + z_i \delta\varepsilon \right\}. \] (29)

To the same approximation, the flux of the neutral species is derived, in a similar manner, as

\[ Q_e = \frac{P_5 \bar{c}_5}{RT} \Delta \mu_5. \] (30)

These fluxes are now given as linear equations in the six forces \( \Delta \mu \), through \( \Delta \mu_5 \) and \( \varepsilon \), and the set of equations can be written in the matrix form

\[
\begin{bmatrix}
Q_1 \\
Q_2 \\
Q_3 \\
Q_4 \\
Q_5 \\
Q_6
\end{bmatrix}
= 
\begin{bmatrix}
P_1 \bar{c}_1 & 0 & 0 & 0 & 0 & P_1 \bar{c}_5 \\
0 & P_2 \bar{c}_2 & 0 & 0 & 0 & P_2 \bar{c}_5 \\
0 & 0 & P_3 \bar{c}_3 & 0 & 0 & P_3 \bar{c}_5 \\
0 & 0 & 0 & P_4 \bar{c}_4 & 0 & -P_4 \bar{c}_5 \\
0 & 0 & 0 & 0 & P_5 \bar{c}_5 & 0 \\
P_6 \bar{c}_6 & P_6 \bar{c}_5 & P_6 \bar{c}_5 & -P_6 \bar{c}_5 & 0 & \sum \frac{z_i P_i \bar{c}_5}{RT}
\end{bmatrix}
\begin{bmatrix}
\Delta \mu_1 \\
\Delta \mu_2 \\
\Delta \mu_3 \\
\Delta \mu_4 \\
\Delta \mu_5 \\
\varepsilon
\end{bmatrix}.
\] (31)
We note that in the square matrix of the coefficient one does obtain the reciprocity relations, i.e., the matrix is symmetrical about the diagonal. It is also interesting to note that in the process of linearization of equations (23)–(25), the flux of an ion becomes expressible in terms of two additive terms, one arising from the gradient in chemical potential and the other from the electrostatic force on the charge. That this separation is artificial is seen from the fact that in equation (28), a somewhat more general case, no such division of the force into "chemical potential" and "electrochemical potential" exists.

Conclusion.—It appears that rate processes can quite generally be treated by what is sometimes described as "relaxation theory," namely, by consideration of the statistical rate at which a molecule or an ion crosses an energy barrier from one equilibrium position to another. In such a treatment the properties of the system at the top of the barrier—the activated state—become of paramount importance in determining the net rate of transport of charge, matter, momentum, etc., and in cases of macroscopic transport it becomes completely impossible to describe the process without them. An alternative method of treating such changes in state, which we have here called the "classical treatment" of irreversible thermodynamics, is not only severely limited in application by the requirement that the changes be small, and that the system as a whole remain near equilibrium, but cannot be generalized to include systems far from equilibrium, since these properties of the activated state are never introduced.

Both methods of attack satisfy the same fundamental theorem: the principle of microscopic reversibility. It is thus not surprising that both reduce to the same formalism near equilibrium, as has been shown in the example given above. However, since the rate-theory approach not only yields the reciprocity relations in the extreme of linear dependence of fluxes on forces but also appears to suffice in the nonlinear range, it appears much more useful to employ this approach throughout the entire field of irreversible processes, leaving the classical theory as a special case.

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5 For complete generality, * should carry the subscript of the Ï† associated with it.
