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A Theory of Chemical Separations: The Fundamental Equation for Ideal Partitioning Separation Systems

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Summary

The fundamental conservation-of-mass equation is derived for linear one-dimensional chemical systems in which no lateral diffusion or rate control exists. The theoretical results are applied to (a) a comparison of the fields of chemical separations, thermodynamics, and kinetics; (b) the derivation of a general equation for gradient elution and programmed temperature chromatography; and (c) the description of three new carrier chromatographic techniques, carrier magnetochromatography, solid phase carrier electrochromatography, and inverse carrier electrochromatography. The role of chemical equilibria in chromatographic systems is briefly discussed.

INTRODUCTION

In a keynote article in the first issue of *Separation Science*, Pfann stated (*1*): ". . . advances in the field of separation and purification have been retarded . . . because of the lack of a feeling of commonality on the part of the diverse disciplines involved. There is much common ground for a science of purification. Major goals of such a science, both in theory and in practice, can be: (1) to learn how to perform single-stage separations more effectively, (2) to seek new methods of producing concentration differences in a system, (3) to seek new methods of utilizing countercurrent flow and reflux, (4) to seek out and define the underlying unity of the various classes of materials and methods involved, and (5) to express this underlying unity in basic, elementary theoretical form, much as thermodynamics underlies the various sciences today. We need a Willard Gibbs for separation processes." These comments nicely summarize the current state of the field of chemical separations as well as the growing interest in the unifying aspects of all types of separation processes. Somewhat similar views have recently been advanced by Giddings and Latimer (2) in their brief introduction of this journal, Giddings and Keller (3), Pratt (*4*), and Miller (5) in a brochure to a recent NSF-sponsored short course on the theory of chromatography.

Although a single unifying theory of chemical separations does not appear to exist, there is sufficient evidence from the voluminous separation literature for one to be optimistic that the essential aspects of the field can be presented (especially to students) with a limited number of "simple unifying theories." In pursuing such theories, there is always the exciting possibility for the industrial chemist that new separation techniques or improvements to existing ones can be predicted solely on the basis of the improved theoretical approach to separation processes.

As a first step in the development of a unifying approach to the field of chemical separations, a "separation index" must be found that can, for any type of separation process, quantify the question: How well have a pair of chemical components been separated? One proposal for such an index has already been advanced (*6–8*). Since the majority of separation processes involve physical and chemical equilibria as the driving force for the separation of components, the development of a unifying theory which would allow one to discuss, characterize, and classify the simple chemical aspects of all such processes (called *partitioning* separation processes) would be an appropriate second step. This is the object of the present article. Finally, there are a variety of *nonpartitioning* separation processes [called *kinetic* processes by Pfann (*1*)], such as thermal diffusion, mass spectroscopy, ideal electrophoresis, and ultracentrifugation, that must be related theoretically to partitioning processes. This will be done by the author at a later date.

LINEAR MULTISTATE CHEMICAL SYSTEMS

A *linear multistate chemical system,* for present purposes, is assumed to be a one-dimensional chemical system in which u_1 is the orthogonal curvilinear coordinate of interest. The term *multistate* refers to the fact that a chosen chemical component i in the system equilibrates rapidly, in directions lateral to u_1, among a variety of different physical and chemical environments s. Superimposed upon these equilibria are the much slower rate processes of diffusion, convection, and pseudo-first-order reaction that occur in directions parallel to u_1. The term *linear* refers to the assumption that the concentrations of component i in the various lateral environments s, $c_{is}(u_1,t)$, are all related to each other at any point u_1 and time t by time-dependent linear partition coefficients, $\kappa_{is}(t)$. When a component is present in a specific environment, it is present either within a single phase or at only one type of interface (otherwise, one or more additional environments must be defined).

The present article in some respects parallels developments in physics many decades ago. For example, in the field of mechanics and acoustics, Newton's laws yielded lumped linear ordinary differential equations with mass, compliance, and frictional resistance as passive parameters and force, distance, and velocity as time-dependent variables. Similarly, in the field of electronics and electromagnetism, Maxwell's laws were first linearized to give linear partial differential equations and then lumped to give linear ordinary differential equations with capacitance, inductance, and resistance as passive parameters and voltage, charge, and current as time-dependent variables. Both of the above fields are elegantly treated by Harmon and Lytle (9).

The object of the present article is to derive the fundamental linear partial differential equations of chemistry and to correctly define the passive parameters—$D_{i\mathrm{eff}}$, the effective dispersion coefficient, $V_{i\mathrm{eff}}$, the effective molar velocity, and $k_{i\mathrm{eff}}$, the effective pseudo-first-order rate constant—that appear in them. These equations are idealized models and have, at best, only a limited range of applicability (the same is true with the linear equations of mechanics and electromagnetism mentioned above). Existing derivations of the linear conservation-of-mass equations (*10–12*), however, are considerably more restricted than the present one.

NOMENCLATURE AND DEFINITIONS

A *component* is defined as one of the ingredients of a mixture or one of the distinct atomic, molecular, ionic, or aggregative species composing a mixture. This term must be distinguished from a similar term, *constituent*, which already has a relatively precise thermodynamic definition [such as the one given by Findlay et al. (*13*)]. A component can be any chemical entity that participates in reversible reactions.

The term *environment* refers to the immediate physical or chemical environment of a specific component i and is denoted by the symbol s. Examples of physical environments are gas, liquid, or solid phases and interfaces between these phases. A chemical environment is the specific chemical compound or surface site s to or with which the component i is attached, bonded, complexed, or associated. Each component in a chemical system is generally found in a number of different environments, so it is convenient to define the term *partition state*, which represents the chemical state characterized by component i and environment s. In this paper a partition state will be symbolized by the notation $\boxed{i:s}$ and by the subscript is. An environment will be defined as long as a single component participates in it, so there will never be more than $i_{\max}\, s_{\max}$ different partition states in a chemical system.

The distinction between a chemical reaction and a physical reaction has been the subject of continuing controversy. We shall consider a *chemical reaction* in the Dalton sense of the term as an elementary reaction which can be represented by a stoichiometric equation (where the stoichiometric coefficients are usually integers whose magnitudes are less than 10). A *physical reaction* is a reaction which, when all of the constituents are included, generally cannot be represented by a stoichiometric equation. For example, the dissolution of a gas in a liquid usually does not proceed in a stoichiometric manner since 1 mole of gas does not dissolve for every m moles of solvent (where m is an integer).

A *chemical equilibrium* is a chemical reaction in which the chemical affinity is equal to zero. A *physical equilibrium* is a physical reaction in which the chemical affinity is equal to zero. Prigogine and Defay present a discussion of the term chemical affinity (*14*).

The terms distribution and partition are used interchangeably and defined as verbs instead of nouns: To *distribute* or *partition* a component is to divide it among two or more different environments or, alternatively, to divide it among two or more of its partition states. Rogers has given an excellent discussion of other partition terminology (*15*). Following his suggestions, the *dis-*

tribution coefficient, K_{is}, is defined as the ratio of the amounts of component i in environments s and $s$ref or, alternatively, as the ratio of the amounts of partition states $\boxed{i:s}$ and $\boxed{i:s\text{ref}}$:

$$K_{is} = \frac{n_{is}}{n_{is\text{ref}}} \tag{1}$$

where $s$ref is the index number of the reference environment, and the *partition coefficient,* κ_{is}, is defined as the ratio of the concentrations of partition states $\boxed{i:s}$ and $\boxed{i:s\text{ref}}$:

$$\kappa_{is} = \frac{c_{is}}{c_{is\text{ref}}} \tag{2}$$

The partition coefficient can also be defined with respect to the interface between two phases. Thus the partition coefficient, κ'_{is}, is defined as the ratio of the surface concentration of an interfacial partition state $\boxed{i:s}$ to the volume concentration of partition state $\boxed{i:s\text{ref}}$:

$$\kappa'_{is} = \frac{c'_{is}}{c_{is\text{ref}}} \tag{3}$$

The quantities c'_{is} and κ'_{is} refer to an interfacial partition state and thus have dimensions of moles/cm^2 and moles/cm^2:moles/cm^3, respectively.

Several additional parameters that must be defined for the chemical system are V, the total volume; $A_\perp$, the total cross-sectional area lateral to the orthogonal coordinate u_1; V_{is}, $A_{\perp is}$, and S_{is}, the total volume, cross-sectional area, and surface area, respectively, of the phase or interface in which partition state $\boxed{i:s}$ is contained. It is more convenient, however, to employ fractional quantities such as the *volume fraction,* ϵ_{is},

$$\epsilon_{is} = \frac{A_{\perp is}}{A_\perp} \tag{4}$$

or

$$\epsilon_{is} = \frac{V_{is}}{V} \tag{5}$$

(in most situations these two definitions are equivalent), and the *surface fraction,* σ_{is},

$$\sigma_{is} = \frac{S_{is}}{V} \tag{6}$$

If $A_{\perp is}$, V_{is}, and S_{is} are independent of the component, the subscript i can be dropped:

$$\epsilon_s = \frac{A_{\perp s}}{A_\perp} \tag{7}$$

$$\epsilon_s = \frac{V_s}{V} \tag{8}$$

$$\sigma_s = \frac{S_s}{V} \tag{9}$$

THEORETICAL

The three-dimensional conservation-of-mass equation (at constant temperature and pressure) for component i in environment s, that is, the conservation-of-mass equation for partition state $\boxed{i:s}$, is given by

$$\frac{\partial c_{is}}{\partial t} - D'_{is}\,\nabla^2 c_{is} + v'_{is}\,\nabla c_{is} + k'_{is}c_{is} + \nabla_\perp \cdot \mathbf{N}_{\perp is} = 0 \tag{10}$$

where $c_{is}(u_1,t)$ = molar concentration of partition state $\boxed{i:s}$
$D'_{is}(u_2,u_3,t)$ = local diffusion coefficient of $\boxed{i:s}$
$k'_{is}(u_2,u_3,t)$ = local pseudo-first-order rate constant of $\boxed{i:s}$ (it is assumed here that the extent of reaction is sufficiently small that the products do not perturb the system)
$\mathbf{N}_{\perp is}(u_2,u_3,t)$ = molar flux of $\boxed{i:s}$ in direction lateral to u_1
t = time
u_1, u_2, u_3 = orthogonal curvilinear coordinates (u_2 and u_3 are the "lateral" coordinates)
$v'_{is}(u_2,u_3,t)$ = local molar velocity of $\boxed{i:s}$ due to convection, forced diffusion (electric, magnetic, and gravitational fields), pressure diffusion, and thermal diffusion combined
∇ = gradient operator with respect to orthogonal coordinate u_1
∇^2 = Laplacian operator with respect to orthogonal coordinate u_1

To solve Eq. (10), we first integrate over the cross-section area,

$A_{\perp}(u_2,u_3)$, lateral to the orthogonal coordinate u_1:

$$\iint_{A_{\perp is}} \frac{\partial c_{is}}{\partial t}\, dA_{\perp} - \iint_{A_{\perp is}} D'_{is}\, \nabla^2 c_{is}\, dA_{\perp} + \iint_{A_{\perp is}} v'_{is}\, \nabla c_{is}\, dA_{\perp} + \iint_{A_{\perp is}} k'_{is} c_{is}\, dA_{\perp} + \iint_{A_{\perp is}} \mathbf{\nabla}_{\perp} \cdot \mathbf{N}_{\perp is}\, dA_{\perp} = 0 \quad (11)$$

where it can be observed that integration over $A_{\perp}$ is equivalent to integration over the effective cross-sectional area, $A_{\perp is}$, of the single phase in which partition state $\boxed{i:s}$ is contained. For Cartesian coordinates ($u_1 = x$, y, or z), cylindrical coordinates ($u_1 = r$ or z), and spherical coordinates ($u_1 = r$), the following relationships hold (*16*):

$$\iint_{A_{\perp is}} \frac{\partial c_{is}}{\partial t}\, dA_{\perp} = A_{\perp is} \frac{\partial c_{is}}{\partial t} \quad (12)$$

$$\iint_{A_{\perp is}} k'_{is}\, dA_{\perp} \equiv A_{\perp is} k_{is}(t) \quad (13)$$

$$\iint_{A_{\perp is}} v'_{is}\, \nabla c_{is}\, dA_{\perp} = \nabla c_{is} \iint_{A_{\perp is}} v'_{is}\, dA_{\perp} \equiv A_{\perp is} v_{is}(t)\, \nabla c_{is} \quad (14)$$

$$\iint_{A_{\perp is}} D'_{is}\, \nabla^2 c_{is}\, dA_{\perp} = \nabla^2 c_{is} \iint_{A_{\perp is}} D'_{is}\, dA_{\perp} \equiv A_{\perp is} D_{is}(t)\, \nabla^2 c_{is} \quad (15)$$

where $k_{is}(t)$, $v_{is}(t)$, and $D_{is}(t)$, respectively, represent the local values $k'_{is}(u_2,u_3,t)$, $v'_{is}(u_2,u_3,t)$, and $D'_{is}(u_2,u_3,t)$ averaged over the cross-sectional area $A_{\perp is}(u_2,u_3)$. Equations (13) to (15) do not hold for $u_1 = \phi$ in cylindrical coordinates and $u_1 = \phi$ or θ in spherical coordinates, but somewhat similar relationships (in which the derivatives of c_{is} are separated from appropriately averaged values of k'_{is}, v'_{is}, and D'_{is}) can be derived.

We now sum Eq. (11) for component i over all environments $s = 1, 2, \ldots n$ and employ Eqs. (12) to (15) to obtain

$$\sum_{s=1}^{n} A_{\perp is} \frac{\partial c_{is}}{\partial t} - \sum_{s=1}^{n} A_{\perp is} D_{is}\, \nabla^2 c_{is} + \sum_{s=1}^{n} A_{\perp is} v_{is}\, \nabla c_{is} + \sum_{s=1}^{n} A_{\perp is} k_{is} c_{is} + \sum_{s=1}^{n} \iint_{A_{\perp is}} \mathbf{\nabla} \cdot \mathbf{N}_{\perp is}\, dA_{\perp} = 0 \quad (16)$$

If we have performed this summation correctly, the last term in the equation will be proportional to the total lateral molar flux, which will be assumed to have a value of zero:

$$\sum_{s=1}^{n} \iint_{A_{\perp is}} \nabla \cdot \mathbf{N}_{\perp is}\, dA_{\perp} = 0 \tag{17}$$

by Green's theorem (impermeable lateral boundaries) or by symmetry (such as for a thin circular disk, sphere, or infinite membrane).

To remove the derivatives outside of the summations in Eq. (16), we employ a linear relationship between c_{is} and $c_{is\mathrm{ref}}$, the concentration of reference partition state $\boxed{i{:}s\mathrm{ref}}$:

$$c_{is} = \kappa_{is}(t)\, c_{is\mathrm{ref}} \tag{18}$$

where $\kappa_{is}(t)$ is a linear partition coefficient that can be a function of time. With this assumption, Eq. (16) simplifies to

$$\frac{\partial c_{is\mathrm{ref}}}{\partial t} + c_{is\mathrm{ref}} \frac{\sum_{s=1}^{n} A_{\perp is}\, (\partial \kappa_{is}/\partial t)}{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}} - \nabla^2 c_{is\mathrm{ref}} \frac{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}D_{is}}{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}}$$

$$+ \nabla c_{is\mathrm{ref}} \frac{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}v_{is}}{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}} + c_{is\mathrm{ref}} \frac{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}k_{is}}{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}} = 0 \tag{19}$$

An *adiabatic multistate system* (i.e., a system in which there are only "slow" time perturbations relative to the rates of equilibration, diffusion, convection, and reaction) will be defined as one in which the second term in Eq. (19) is small:

$$\frac{\sum_{s=1}^{n} A_{\perp is}\, (\partial \kappa_{is}/\partial t)}{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}} \approx 0 \tag{20}$$

If we drop the subscript ref (the choice of reference environment is arbitrary) and define the "effective" parameters $D_{i\mathrm{eff}}(t)$, $V_{i\mathrm{eff}}(t)$, and $k_{i\mathrm{eff}}(t)$ as

$$D_{i\mathrm{eff}}(t) \equiv \frac{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}D_{is}}{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}} \equiv \frac{\sum_{s=1}^{n} \epsilon_{is}\kappa_{is}D_{is}}{\sum_{s=1}^{n} \epsilon_{is}\kappa_{is}} \equiv \frac{\sum_{s=1}^{n} K_{is}D_{is}}{\sum_{s=1}^{n} K_{is}}$$

$$\equiv \sum_{s=1}^{n} Y_{is}D_{is} \tag{21}$$

$$V_{i\mathrm{eff}}(t) \equiv \frac{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}v_{is}}{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}} \equiv \sum_{s=1}^{n} Y_{is}v_{is} \tag{22}$$

$$k_{ieff}(t) \equiv \frac{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}k_{is}}{\sum_{s=1}^{n} A_{\perp is}\kappa_{is}} \equiv \sum_{s=1}^{n} Y_{is}k_{is} \tag{23}$$

Eq. (19) simplifies to

$$\frac{\partial c_{is}}{\partial t} - D_{ieff}(t)\ \nabla^2 c_{is} + V_{ieff}(t)\ \nabla c_{is} + k_{ieff}(t)c_{is} = 0 \tag{24}$$

which is the fundamental linear one-dimensional conservation-of-mass equation for component i in an adiabatic multistate chemical system containing n different physical or chemical environments. The *segregation fraction*, Y_{is}, in the definitions for D_{ieff}, V_{ieff} and k_{ieff} is the fraction of component i in environment s:

$$Y_{is} \equiv \frac{K_{is}}{\sum_{s=1}^{n} K_{is}} = \frac{n_{is}}{n_i^0} \tag{25}$$

The general linear multistate equations for the disciplines of chemical separations, kinetics, and thermodynamics can easily be obtained if the appropriate terms in Eq. (24) are neglected. These equations thus become:

1. Chemical separations:

$$\frac{\partial c_{is}}{\partial t} - D_{ieff}(t)\ \nabla^2 c_{is} + V_{ieff}(t)\ \nabla c_{is} = 0 \qquad \text{(transient)} \tag{26}$$

$$-D_{ieff}\ \nabla^2 c_{is} + V_{ieff}\ \nabla c_{is} = 0 \qquad \text{(steady state)} \tag{27}$$

2. Chemical kinetics and rate-controlled chemical separations:

$$\frac{\partial c_{is}}{\partial t} + k_{ieff}(t)c_{is} = 0 \qquad \text{(transient)} \tag{28}$$

$$c_{is} = \text{constant} \qquad \text{(steady state)} \tag{29}$$

3. Diffusion-controlled chemical separations:

$$\frac{\partial c_{is}}{\partial t} - D_{ieff}(t)\ \nabla^2 c_{is} = 0 \qquad \text{(transient)} \tag{30}$$

$$-D_{ieff}\ \nabla^2 c_{is} = 0 \qquad \text{(steady state)} \tag{31}$$

4. Convection-controlled chemical separation:

$$\frac{\partial c_{is}}{\partial t} + V_{i\text{eff}}(t)\ \nabla c_{is} = 0 \qquad \text{(transient)} \tag{32}$$

$$V_{i\text{eff}}\ \nabla c_{is} = 0 \qquad \text{(steady state)} \tag{33}$$

5. Diffusion-controlled chemical kinetics:

$$\frac{\partial c_{is}}{\partial t} - D_{i\text{eff}}(t)\ \nabla^2 c_{is} + k_{i\text{eff}}(t) c_{is} = 0 \qquad \text{(transient)} \tag{34}$$

$$-D_{i\text{eff}}\ \nabla^2 c_{is} + k_{i\text{eff}} c_{is} = 0 \qquad \text{(steady state)} \tag{35}$$

6. Convection-controlled chemical kinetics:

$$\frac{\partial c_{is}}{\partial t} + V_{i\text{eff}}(t)\ \nabla c_{is} + k_{i\text{eff}}(t) c_{is} = 0 \qquad \text{(transient)} \tag{36}$$

$$V_{i\text{eff}}\ \nabla c_{is} + k_{i\text{eff}} c_{is} = 0 \qquad \text{(steady state)} \tag{37}$$

7. Diffusion- and convection-controlled chemical kinetics:

$$\frac{\partial c_{is}}{\partial t} - D_{i\text{eff}}(t)\ \nabla^2 c_{is} + V_{i\text{eff}}(t)\ \nabla c_{is} + k_{i\text{eff}}(t) c_{is} = 0 \qquad \text{(transient)} \tag{38}$$

$$-D_{i\text{eff}}\ \nabla^2 c_{is} + V_{i\text{eff}}\ \nabla c_{is} + k_{i\text{eff}} c_{is} = 0 \qquad \text{(steady state)} \tag{39}$$

8. Chemical thermodynamics:

$$k_{i\text{eff}} = 0 \tag{40}$$

$$\kappa_{is} = \frac{c_{is}}{c_{is\text{ref}}} \tag{41}$$

Equations (26) through (41) demonstrate that there is a strong thread of mathematical continuity between multistate chemical kinetics, thermodynamics, and separations. As shown by Eq. (24), this continuity is a consequence of the fact that they all have a common mathematical origin—the conservation-of-mass equation for a multistate chemical system. Equation (24) has a further significance in that no assumptions regarding the chemical nature of either the component i or the environments $s = 1, 2, \ldots, n$ have been made.

Equation (26) is the fundamental equation for all linear multistate chromatographic systems. As long as $V_{1\text{eff}} \neq V_{2\text{eff}}$, a mixture of two chemical components injected as a single instantaneous pulse at the entrance of a chromatographic system will eventually yield two Gaussian elution peaks. It is not necessary to assume the existence of two phases (one stationary and the other mobile). In fact, chromatographic behavior can occur within a single phase, as will be discussed later.

REPRESENTATION OF PARTITION STATES

When there are many different environments in a chemical system, it usually is quite cumbersome to repeat the conservation-of-mass equation for each partition state $\boxed{i:s}$:

$$\epsilon_{is}\frac{\partial c_{is}}{\partial t} - \epsilon_{is}D_{is}\nabla^2 c_{is} + \epsilon_{is}v_{is}\nabla c_{is} + \epsilon_{is}k_{is}c_{is} + \frac{1}{A_\perp}\iint_{A_{\perp is}} \nabla_\perp \cdot \mathbf{N}_{\perp is}\, dA_\perp = 0 \quad (42)$$

where ϵ_{is} has been previously defined in Eqs. (4) and (5). A shorthand notation is desirable both to eliminate this inconvenience and also to highlight more efficiently the specific characteristics of the multistate system. Such a shorthand is now proposed.

Consider a component i in environments $s = 1, 2, \ldots, n$ within a multistate chemical system. The two equations which characterize each partition state are the above conservation-of-mass equation and the linear partition-coefficient equation [Eq. (18)]. There are a total of five physical parameters in these two equations (κ_{is}, ϵ_{is}, D_{is}, v_{is}, and k_{is}). If the absolute magnitudes of these parameters are known as a function of time for all partition states $\boxed{i:s}$, the behavior of component i in the chemical system is completely determined (subject, of course, to the initial and axial boundary conditions). Therefore, rather than writing down the above equations for each partition state in the system, we need only to find a convenient method for representing the above class of five physical parameters. The following shorthand representation is suggested:

(Description of partition state $\boxed{i:s}$)
κ_{is}
ϵ_{is}
D_{is}
v_{is}
k_{is}

(at constant temperature and pressure)

Since the partition coefficient for the reference partition state, $\boxed{i{:}s\mathrm{ref}}$, is identically equal to 1 (by definition),

$$\kappa_{is\mathrm{ref}} \equiv 1 \tag{43}$$

the representation of the reference state is slightly different from the above:

(Description of reference
partition state $\boxed{i{:}s\mathrm{ref}}$)
1
$\epsilon_{is\mathrm{ref}}$
$D_{is\mathrm{ref}}$
$v_{is\mathrm{ref}}$
$k_{is\mathrm{ref}}$

(at constant temperature
and pressure)

In the application of this type of representation, one additional convention is employed: Whenever the value of any partition-state parameter is independent of the nature of the component, the subscript i is deleted [as was done in Eqs. (7) through (9)]. In most multistate chemical systems, the volume fraction, surface fraction, and molar velocity all possess this particular characteristic. The exceptions to this behavior usually occur in systems containing molecular sieves or heavily cross-linked polymeric resins.

APPLICATIONS

Equations (26) through (41) are extremely general; examples of their application to various chemical systems can be found throughout the chemical literature. Some particular applications which have recently been published include the mutarotation of tetramethyl-D-glucose in benzene [Eq. (28)] (*17*), supported liquid phase and multiphase catalysts [Eq. (35)] (*18*), and steady-state diffusion and flow tubes [Eqs. (35), (37), and (39)] (*19*). In the present article, however, we shall be concerned only with partitioning chromatographic systems.

GRADIENT ELUTION CHROMATOGRAPHY

Probably the most powerful chromatographic techniques known today are those which come under the general heading of gradient elution chromatography. In addition to gradient elution solid–liquid and liquid–liquid chromatography, where the chemical composition of the eluting solvent is changed as a function of time, there is the extremely versatile technique of programmed-temperature gas–liquid chromatography, where the temperature of the chromatographic column is slowly increased to accelerate the elution of the slower moving components. Horvath and Lipsky (*20*) have recently pointed out that one can obtain almost an order-of-magnitude improvement in peak capacity over regular elution chromatography by applying gradient elution techniques. We shall now derive a general solution for gradient elution chromatography in multistate chemical systems.

We start with the fundamental conservation-of-mass equation for a transient multistate separation system (in cylindrical coordinates, where $u_1 = z$):

$$\left(\frac{\partial c_{is}}{\partial t}\right)_z = D_{i\text{eff}}(t)\left(\frac{\partial^2 c_{is}}{\partial z^2}\right)_t - V_{i\text{eff}}(t)\left(\frac{\partial c_{is}}{\partial z}\right)_t \tag{44}$$

By defining a new parameter y_i,

$$dy_i = dz - V_{i\text{eff}}(t)\,dt \tag{45}$$

or

$$y_i = z - \int_0^t V_{i\text{eff}}(t)\,dt \tag{46}$$

we can successively employ the definition for the total differential

$$dc_{is} = \left(\frac{\partial c_{is}}{\partial y_i}\right)_t dy_i + \left(\frac{\partial c_{is}}{\partial t}\right)_{y_i} dt \tag{47}$$

to obtain

$$\left(\frac{\partial c_{is}}{\partial t}\right)_z = -V_{i\text{eff}}(t)\left(\frac{\partial c_{is}}{\partial y_i}\right)_t + \left(\frac{\partial c_{is}}{\partial t}\right)_{y_i} \tag{48}$$

$$\left(\frac{\partial c_{is}}{\partial z}\right)_t = \left(\frac{\partial c_{is}}{\partial y_i}\right)_t \tag{49}$$

$$\left(\frac{\partial^2 c_{is}}{\partial z^2}\right)_t = \left(\frac{\partial^2 c_{is}}{\partial y_i^2}\right)_t \tag{50}$$

Thus Eq. (44) can be converted to

$$\left(\frac{\partial c_{is}}{\partial t}\right)_{y_i} = D_{i\text{eff}}(t)\left(\frac{\partial^2 c_{is}}{\partial y_i^2}\right)_t \tag{51}$$

or simply

$$\frac{\partial c_{is}}{\partial t} = D_{i\text{eff}}(t)\,\frac{\partial^2 c_{is}}{\partial y_i^2} \tag{52}$$

For chromatographic systems, Eq. (52) can be solved for an instantaneous pulse, $\delta(y_i)$, at $y_i = 0$ to yield (*21*)

$$c_{is} = \frac{n_{is}^0}{\sigma_i A_{\perp is}\sqrt{2\pi}} \exp\left(-\frac{y_i^2}{2\sigma_i^2}\right) \tag{53}$$

where σ_i is the standard deviation of the elution peak

$$\sigma_i = \sqrt{2\int_0^t D_{i\text{eff}}(t)\,dt} \tag{54}$$

and the retention length and time are

$$z_{Ri} = \int_0^t V_{i\text{eff}}(t)\,dt \tag{55}$$

$$L = \int_0^{t_{Ri}} V_{i\text{eff}}(t)\,dt \tag{56}$$

respectively (22).

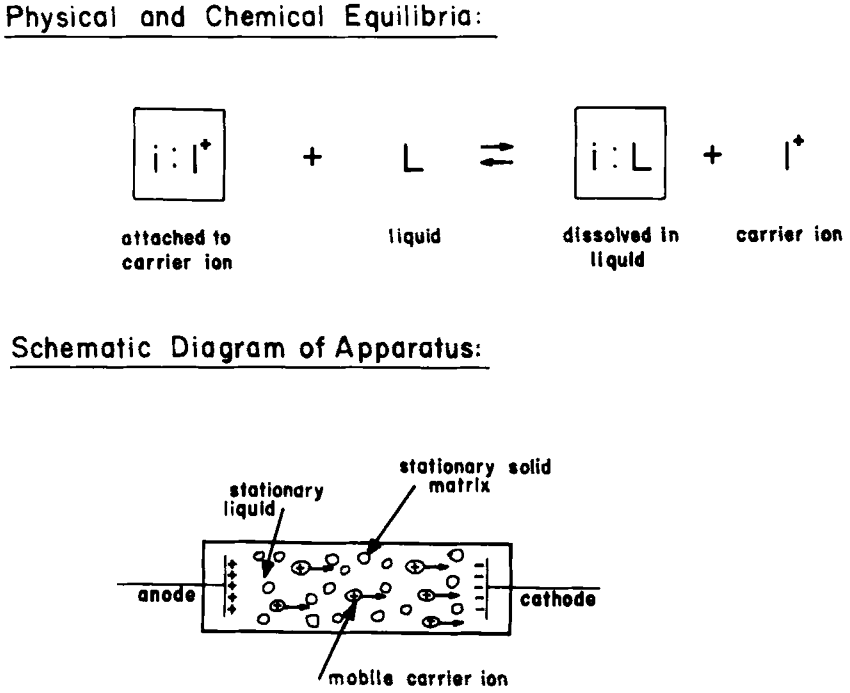
Equation (53) is the most general equation derived to date for an *ideal* chromatographic system. It is valid for any type of linear physical or chemical equilibrium and any adiabatic time-dependent change in $V_{i\text{eff}}$, such as a time-varying partition coefficient, $\kappa_{is}(t)$; molar velocity, $v_{is}(t)$; or volume fraction, $\epsilon_{is}(t)$ (the first two types of time-dependent parameter changes are well known, but apparently few, if any, attempts have been made to decrease the stationary-phase volume fraction as a function of time to isothermally accelerate the elution of the slower moving components).

CARRIER CHROMATOGRAPHY

As stated in any textbook or review article (23) on the subject of chromatography, there are only four different types of chromatographic systems: gas–liquid (GLC), gas–solid (GSC), liquid–liquid (LLC), and solid–liquid (SLC). Each of these systems is distinguished by the fact that the migrating components distribute between two phases. Almost any type of migrating component is amenable to separation by at least one of these techniques: small, volatile, and nonionic molecules by GLC and GSC and large, nonvolatile, and ionic molecules by LLC and SLC. Giddings, however, makes the interesting point that, in the separation of macromolecules, "in all but exceptional circumstances, $\Delta\mu^0$ [the change in chemical potential for the transfer of a mole of solute between a mobile and a stationary phase] is a very large positive or negative quantity compared to RT" (*24*). Consequently, κ_{is}, the partition coefficient for the macromolecule,

$$\kappa_{is} \propto exp\ (-\Delta\mu^0/RT) \tag{57}$$

is a very small or very large number and "separation fails to occur at a measurable rate" or "resolution is destroyed" (*24*). To circumvent this problem, Giddings has proposed a new type of chromatography, called field flow fractionation, which is a single-phase technique that is dependent upon lateral thermal, electric or gravi-


Physical and Chemical Equilibria:

Schematic Diagram of Apparatus:

FIG. 1. Schematic representation of the equilibria and the apparatus in carrier electrochromatography.

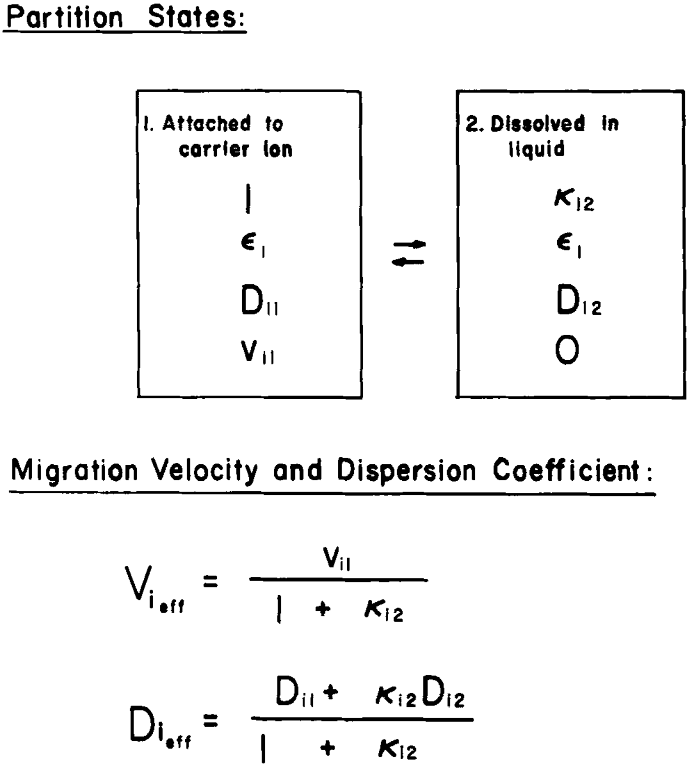


FIG. 2. Schematic representation of the partition states and formulas for $V_{i\mathrm{eff}}$ and $D_{i\mathrm{eff}}$ in carrier electrochromatography.

tational fields for the separation of macromolecules (25,26). We would like to offer an alternative solution to the problem of separating macromolecules by describing a fifth type of chromatography—*carrier electromatography*—that is, a single-phase partitioning chromatographic technique.

As shown in Figs. 1 and 2, the migrating component *i* distributes between stationary and mobile environments (the former being the liquid phase and the latter being a mobile *carrier ion*) that are present within a single phase. The difference between ideal (no partitioning on solid surfaces) electrophoresis and carrier electrochromatography can be demonstrated with the aid of Fig. 2. In electrophoresis, there is no partitioning between the migrating component *i* and the carrier ion; component *i* is either itself an ion and can migrate uncomplexed in the electric field (a trivial case) or else it is so tightly complexed to the carrier ion ($\kappa_{i2} = 0$) that there is essentially no uncomplexed component present. In the latter case, there is only one partition state and the migration velocity of the component is simply given by

$$V_{i\text{eff}} = v_{i1} \tag{58}$$

where v_{i1} is the mobility (in cm/sec) of the complex. In carrier electrochromatography, the migration velocity of the distributing component is given by

$$V_{i\text{eff}} = \frac{v_{i1}}{1 + \kappa_{i2}} \tag{59}$$

and the separation is determined not only by the value of v_{i1} but also by the value of the partition coefficient κ_{i2}.

Carrier electrochromatography is not a new chromatographic technique. While we do not wish to engage in a discussion of priorities, one of the earliest examples appears to be the work of Consden and Stanier (27), who separated monosaccharides in an aqueous borate medium:

$$\underset{\substack{\text{(migrating}\\ \text{component)}}}{\begin{matrix}\text{dissolved}\\ \text{monosaccharide}\end{matrix}} + \underset{\substack{\text{(carrier}\\ \text{ion)}}}{\begin{matrix}\text{borate}\\ \text{ion}\end{matrix}} \xrightleftharpoons{1/\kappa_{i2}} \underset{\text{(complex)}}{\begin{matrix}\text{monosaccharide–borate}\\ \text{ionic complex}\end{matrix}}$$

It should be observed that the monosaccharides (sugar molecules) are neutral molecules and are thus unaffected, when dissolved in water, by an electric field. However, if the partition coefficient is finite and has a value ranging between about 0.1 and 10, a carrier electrochromatographic separation can be achieved. The importance of the formation of the complex can be demonstrated if a similar separation is attempted in an aqueous chloride medium:

$$\begin{matrix}\text{dissolved}\\ \text{monosaccharide}\end{matrix} + \begin{matrix}\text{chloride}\\ \text{ion}\end{matrix} \xrightleftharpoons{1/\kappa_{i2}} \begin{matrix}\text{monosaccharide–chloride}\\ \text{complex}\end{matrix}$$

In this case, κ_{i2} is infinite and no separation is observed. This type of behavior can be and has been extended to a variety of molecules, such as amino acids

$$\underset{\substack{\text{(migrating}\\ \text{component)}}}{\text{amino acid}} + \underset{\substack{\text{(``carrier}\\ \text{ion'')}}}{\text{H}^+} \rightleftharpoons \underset{\text{(``complex'')}}{\text{amino acid H}^+}$$

and alkaloids

$$\underset{\text{(migrating component)}}{\text{alkaloid}} + \underset{\text{("carrier ion")}}{\text{H}^+} \rightleftharpoons \underset{\text{("complex")}}{\text{alkaloid H}^+}$$

The technique is extremely general.

In its application to macromolecular separations, we envision a number of interesting possibilities: (a) the use of carrier macromolecules such as polypeptides, proteins, synthetic polymers, and the like; (b) the use of carrier micelles and colloids; and (c) the use of proteins fixed to a stationary surface and carrier proteins of similar chemical constitution. In each of these cases, advantage is taken of multiple adsorption sites on the carrier ion to selectively

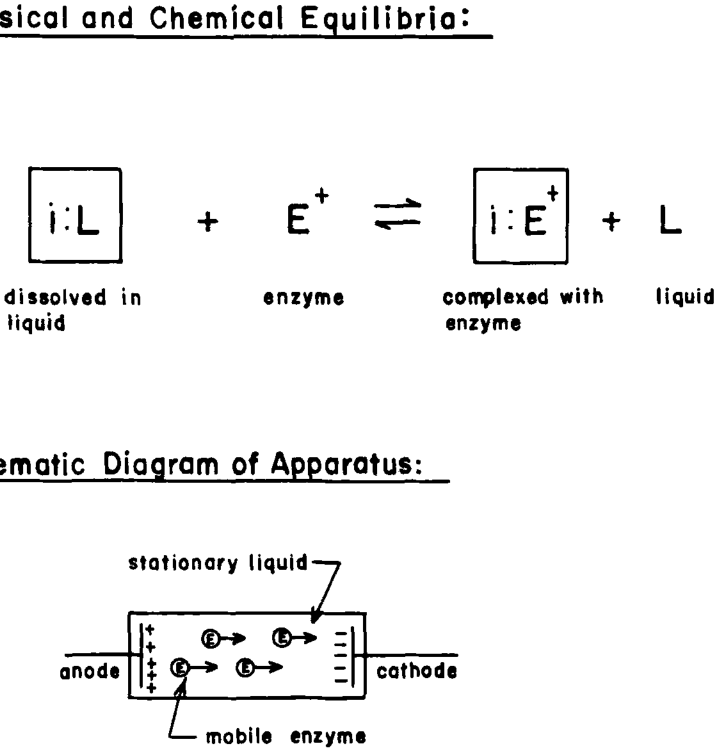


FIG. 3. Schematic representation of the equilibria and the apparatus in inverse carrier electrochromatography (with enzyme as carrier).

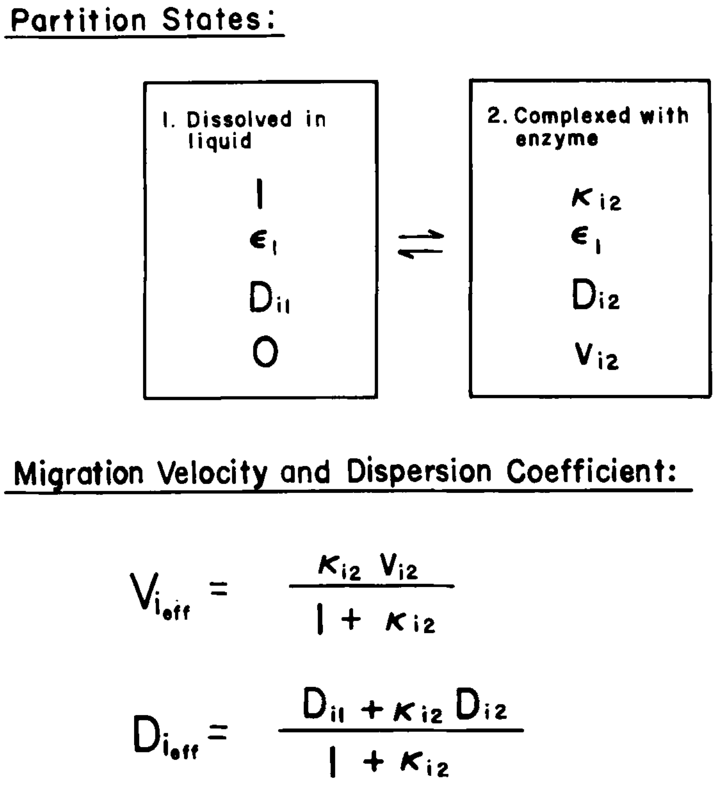


FIG. 4. Schematic representation of the partition states and formulas for V_{ieff} and D_{ieff} in inverse carrier electrochromatography (with enzyme as carrier).

partition macromolecules of different chemical constitution. With the recently developed Merrifield solid phase synthetic peptide technique (*28–30*), it is quite feasible to prepare quantities of polypeptide oligomers (of specified chemical constitution) that can ben employed as carrier ions.

In a related carrier technique, *inverse carrier electrochromatography*, a group of neutral migrating components are employed to characterize the chemical nature of the mobile ionic carrier. This technique is illustrated in Figs. 3 and 4, where the carrier ion is an enzyme. Since the neutral components are separated on the basis of their binding constants with the enzyme, a carefully chosen group of weakly complexing molecules can aid in the characterization of the carrier by forming a distinct elution "enzyme fingerprint." This technique can be extended to colloidal particles, charged micelles, biological cells, viruses, and any type of highly dispersed ionic substance that is difficult to characterize by other techniques.

Solid phase carrier chromatography, or simply solid phase chromatography, is apparently a new type of carrier chromatographic technique. As shown in Fig. 5, the chromatographic "column" is a thin polymeric or biological membrane placed between the closely spaced electrodes of, essentially, an electrophoresis apparatus. Migrating components are injected into the liquid space on one side of the membrane and migrate through it as solid-soluble complexes with a mobile ionic carrier, which is usually a low molecular weight ion. Inside the membrane, distribution of the migrating components occurs between the mobile carrier and the station-

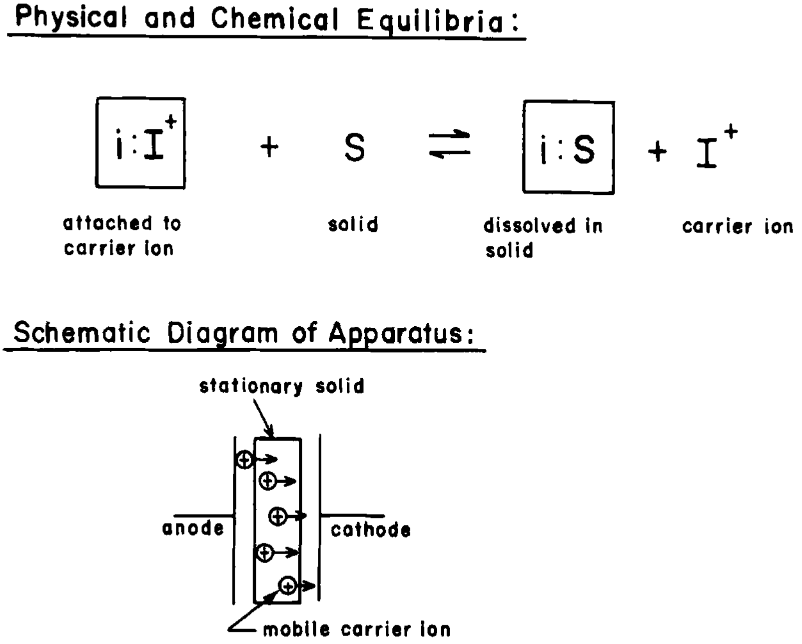


FIG. 5. Schematic representation of the equilibria and the apparatus in solid phase carrier electrochromatography.

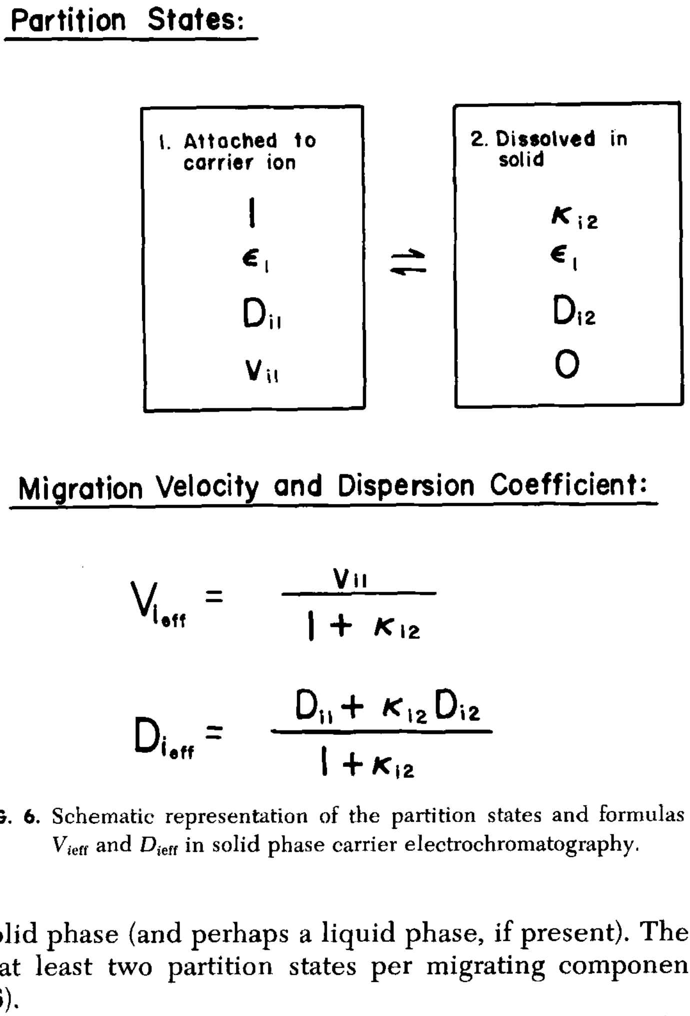


FIG. 6. Schematic representation of the partition states and formulas for V_{ieff} and D_{ieff} in solid phase carrier electrochromatography.

ary solid phase (and perhaps a liquid phase, if present). There are thus at least two partition states per migrating component (see Fig. 6).

Solid phase chromatography is based upon the concept of "active transport," which was proposed for biological systems as early as 1890 by Pfeffer (*31*). Freundlich and Gann performed a vivid experiment fifty years ago which clearly demonstrated the principle of carrier transport (*32*). The concepts of active transport, carriers, and carrier processes are still frequently postulated to account for unusual membrane transport behavior in biological systems. Shean and Sollner have recently illustrated the carrier principle in their experiments with liquid ion-exchangers (*33*).

In addition to organic and biological membranes, other solid materials such as glass can be employed as the solid matrix. This technique should facilitate the study of biological carrier systems and might eventually lead to small component-specific analytical probes similar to the ion-specific glass electrodes.

Carrier magnetochromatography, another new carrier technique (Figs. 7 and 8), may represent the first use of a magnetic field for the chromatographic separation of chemical components. Like carrier electrochromatography, the migrating component distributes between a stationary liquid phase and a mobile carrier particle. In this technique, however, a magnetic field is employed instead of an electric field and the carrier particle is magnetic rather than ionic. The chromatographic column can be a glass tube packed with a porous adsorbent, a piece of filter paper impregnated with a liquid, or a thin layer of a porous solid deposited on an impermeable

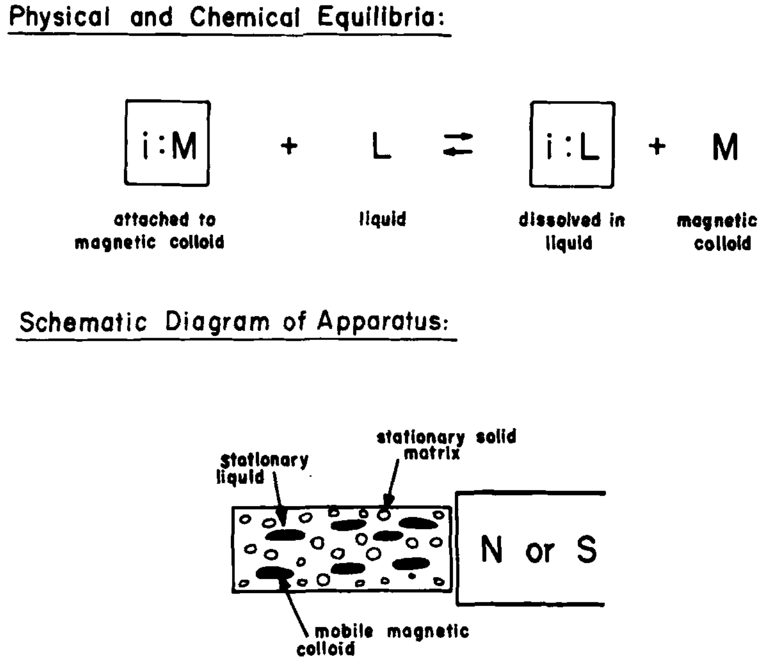


FIG. 7. Schematic representation of the equilibria and the apparatus in carrier magnetochromatography.

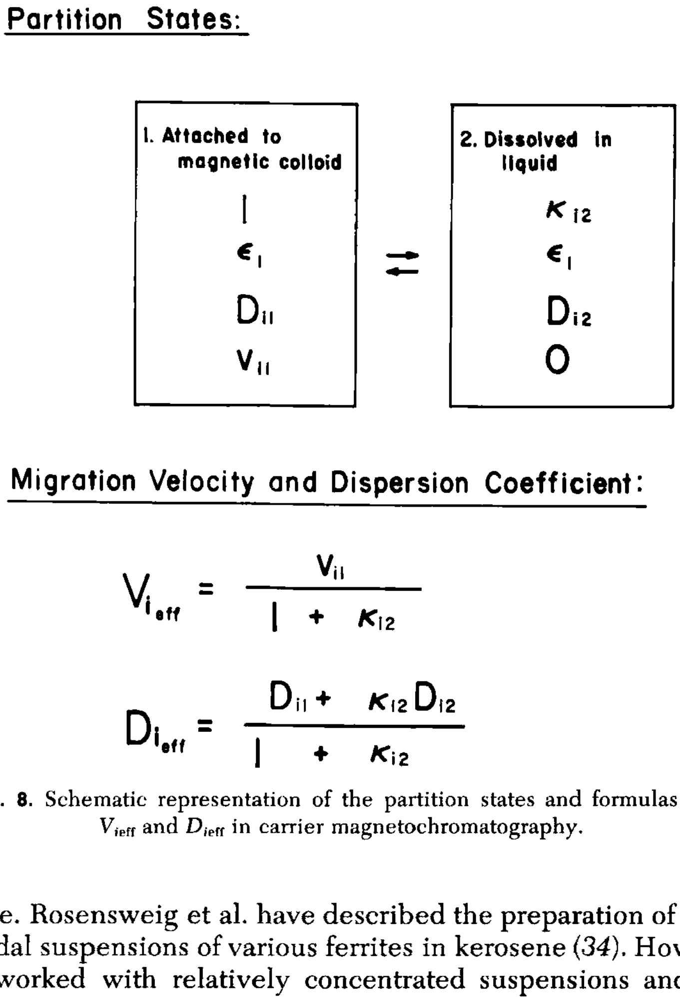


FIG. 8. Schematic representation of the partition states and formulas for V_{ieff} and D_{ieff} in carrier magnetochromatography.

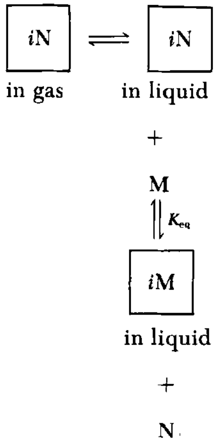
surface. Rosensweig et al. have described the preparation of stable colloidal suspensions of various ferrites in kerosene (*34*). However, they worked with relatively concentrated suspensions and took steps to minimize particle sedimentation by a magnetic field, conditions exactly opposite to those required for carrier magnetochromatography.

CHEMICAL EQUILIBRIA IN CHROMATOGRAPHY

Most chromatographic separation techniques (excluding those based upon ion exchange and complexation or hydrogen bonding) employ physical reactions, such as adsorption on a surface or dissolution in a liquid, to achieve the separation of chemical components. In Eqs. (21) through (24), no distinction is made between physical or chemical equilibria, so it is clear that a variety of chemical reactions can, in principle, be used as the basis of subtle, selective, and sophisticated chromatographic separations. Bradford et al. (35) were the first to use a complexation equilibrium—the reaction of silver ion with an olefin to form a silver–olefin π complex—as the basis of a separation in gas–liquid chromatography. Karger (36) has summarized the work in this area and Purnell (37) has provided a theoretical treatment for such complexing reaction systems.

There are only two main requirements for the use of chemical reactions in chromatographic systems: (1) They must be rapid and reversible (conditions which frequently exist or can be achieved with the aid of catalysts) and (2) the equilibrium constant for the reaction must have an appropriate magnitude. Since chemical reactions are far more sensitive to chemical constitution than physical reactions, the exciting possibility exists (provided the above requirements are met) that the use of chemical reactions may quickly and easily solve some of the more difficult separation problems that are currently encountered.

We can obtain a rough estimate of the magnitude of the equilibrium constant required according to the following arguments. Let us, for simplicity, consider a gas–liquid chromatographic system in which the migrating component i distributes between three different partition states:



where M and N are exchangeable segments of the component and K_{eq} is an equilibrium constant for the exchange reaction (we shall assume that the activity coefficients are all equal to 1):

$$K_{eq} = \frac{c_{iM}c_N}{c_{iN}c_M} \tag{60}$$

The migration velocity of the component i is

$$V_{ieff} = \frac{v_1}{1 + K_i[1 + (K_{eq}c_M/c_N)]} \tag{61}$$

where v_1 is the velocity of the mobile gas phase and K_i is a gas-liquid distribution coefficient (dimensions of moles/moles). According to Giddings (*24*), the optimum range for the migration ratio, V_{ieff}/v_1, is between 0.1 and 0.9. This range corresponds to the inequality

$$0.1 < K_i < 9 \tag{62}$$

when $K_{eq}c_M = 0$ and to

$$0.1 < K_i \left(1 + \frac{K_{eq}c_M}{c_N}\right) < 9 \tag{63}$$

when $K_{eq}c_M \neq 0$. This latter inequality can be rearranged to give

$$\left(\frac{0.1}{K_i} - 1\right)\frac{c_N}{c_M} < K_{eq} < \left(\frac{9}{K_i} - 1\right)\frac{c_N}{c_M} \qquad (K_i < 0.1) \tag{64}$$

and

$$0 < K_{eq} < \left(\frac{9}{K_i} - 1\right)\frac{c_N}{c_M} \qquad (0.1 \leqq K_i \leqq 9) \tag{65}$$

Clearly, a wide range of K_{eq} values can be employed in chromatographic systems, provided only that we do not saturate any of the partition states and that we carefully choose the values of c_M, c_N, and perhaps K_i. The chemical reactions which appear to be the most interesting candidates for chromatographic systems include oxidation–reduction reactions (*38*), proton–exchange reactions (39), and protonation–deprotonation reactions (*40,41*). Proton-exchange GLC may provide a rapid method for measuring the equilibrium acidities of a wide variety of organic molecules. A potentially feasible GLC separation process for the three xylene isomers is one in which a low molecular weight polymethylstyrene carbanion is dissolved in a nonvolatile nonacidic liquid.

SUMMARY AND CONCLUSIONS

While the Van Deemter equation is widely considered to be the fundamental equation for the *physical* aspects of practical chromatographic systems, Eq. (26) is the fundamental equation for the *chemical* aspects of ideal linear chromatographic systems. The principles described in this article have been applied elsewhere (38) to the description of at least 33 different chromatographic systems (or variations thereof), including the standard techniques as well as a number of potentially novel techniques, such as carrier chromatography, aerosol chromatography, fiber chromatography, and membrane chromatography. These principles can also be applied to other linear partitioning separation processes such as a single equilibrium stage, a multistage column, the Craig countercurrent apparatus, coupled one-dimensional linear systems, and two-dimensional linear systems. In the extension of these ideas to more complicated systems, it is not the concepts that are limiting, but rather our ability to solve more complicated multistate conservation-of-mass equations.

Acknowledgments

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List of Symbols

$A_\perp$	total lateral cross-sectional area (cm^2)
c	volume concentration (moles/cm^3)
c'	surface concentration (moles/cm^2)
D	diffusion coefficient (cm^2/sec)
$D_{i\text{eff}}$	effective dispersion coefficient (cm^2/sec)
$\boxed{i:s}$	partition state consisting of component i in environment s
k	pseudo-first-order rate constant (sec^{-1})
$k_{i\text{eff}}$	effective pseudo-first-order rate constant (sec^{-1})
K	distribution coefficient (moles/moles)
K_{eq}	equilibrium constant

L	total axial length (cm)
n	number of moles (moles)
$\mathbf{N}_{\perp}$	molar flux in lateral direction (moles/cm^2 sec)
r	orthogonal coordinate in cylindrical or spherical systems
S	total surface area (cm^2)
t	time (sec)
t_R	retention time (sec)
u_1	principle orthogonal coordinate of linear multistate system
u_2, u_3	orthogonal coordinates lateral to u_1
v	molar velocity (cm/sec)
V	total volume (cm^3)
$V_{i\text{eff}}$	effective molar velocity (cm/sec)
x	orthogonal Cartesian coordinate
y	orthogonal Cartesian coordinate
y_i	quantity defined by Eq. (42)
Y	segregation fraction
z	orthogonal Cartesian or cylindrical coordinate
z_R	retention length

Greek letters

ϵ	volume fraction (cm^3/cm^3 or cm^2/cm^2)
θ	orthogonal spherical coordinate
κ	partition coefficient (moles/cm^3:moles/cm^3)
κ'	partition coefficient defined with respect to a surface (moles/cm^2:moles/cm^3)
σ	surface-to-volume fraction (cm^2:cm^3)
σ_i	standard deviation of a Gaussian peak (cm)
ϕ	orthogonal spherical or cylindrical coordinate

Superscripts

^{0}	initial value
$'$	local value

Subscripts

i	component i
is	component i in environment s (i.e., partition state $\boxed{i:s}$)

*is*ref	component *i* in reference environment *s*ref
s	environment *s*
*s*ref	reference environment
*i*1, *i*2, *i*3, etc.	specific partition states
1, 2, 3	specific phases

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