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STUDIES ON THE "DIFFUSION EFFECT" UPON IONIC DISTRIBUTION

I. SOME THEORETICAL CONSIDERATIONS

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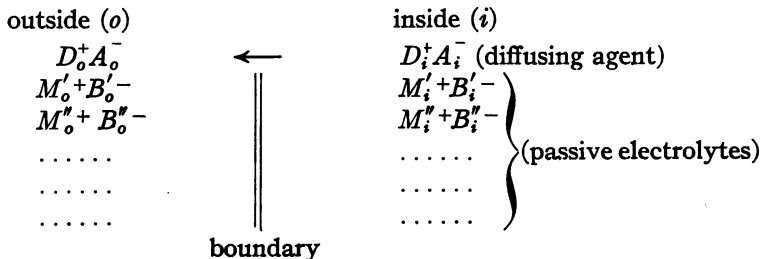
I. These studies are intended to throw some light upon certain possibilities of producing ionic distribution of the type which can occur in biological systems, i.e., great concentration differences across a boundary *permeable* to the ions under consideration.

It will be shown theoretically and in experiments that such ionic distributions can be produced in aqueous systems with at least one electrolyte *diffusing* across a boundary. It is noticeable that the theory for such systems predicts a distribution of ions of the same kind as is generally regarded as characteristic for the well-known Gibbs-Donnan equilibrium, which applies to cases where indiffusible ions are present.

Under certain conditions great "accumulations" or the contrary may be expected as a consequence of the theory given. Such conditions might well occur in biology.

II. *Assumptions.*—It seems necessary to state these in some detail.

(a) We consider a system of ideally dilute solutions in water of binary univalent strong electrolytes, at the same temperature.



(The arrow indicates a steady outward diffusion of DA which is kept constant.)

The boundary is in general something supporting concentration gradients. Here it may be assumed to be a membrane of a type in which water is present (the electrolytes in the membrane being strong). We will, below, refer to the boundary as the diffusion layer or the membrane (cf. footnote 11). Further it is assumed that the solutions are kept homogeneous on both sides up to the boundary by some form of convection.

(b) The membrane is permeable for *all* ions, but the movement of water is prevented in some way.¹³ The ionic mobilities *within the membrane* (assumed constant) may be denoted by u_D , u_M , etc., for the cations and v_A , v_B , etc., for the anions.

(c) The ionic concentrations D_o , M'_o , M''_o , etc., and A_o , B'_o , B''_o , etc., outside are kept constant either by assuming that the volume of (*o*) is ∞ or in some other manner. The volume of (*i*) is finite.

(d) Also D_i^+ is *maintained constant* and the ratio $D_i^+/D_o^+ > 1$, for instance by a continuous addition of DA inside. Accordingly, DA is a *steadily diffusing electrolyte*. The following discussions are limited to the presence of only one such species. The electrolytes MB are called *passive* and may be present in any number.

(e) No chemical reaction takes place.¹³

(f) No other electric field is present besides that due to diffusion potential.

(g) Heat effects are ignored as well as special membrane effects.

III. *The Development of a Steady State*.—Assume that in the initial state the concentrations are $(MB)_i = (MB)_o$ and $(DA)_i > (DA)_o$ (Fig. 1). If the mobilities u_D and v_A are unequal an electrical diffusion potential, π , will arise across the membrane. Assume here that u_D is $> v_A$, then the positive current will tend to pass through the membrane from (*i*) to (*o*) and the sign of (*o*) in a fictitious external circuit will be positive. As will be shown under IV below each ion in the membrane is caused to migrate by the influence of two forces, (a) one due to the *concentration gradient*, and (b) one being an *electrical potential gradient*.

As the concentration gradients for M and B in the initial state are zero, the only force acting is the electrical one. This will move the positive M ions in the pos. \rightarrow neg. direction, i.e., from (*o*) to (*i*), and the negative B ions the opposite way. This flux for any passive ion will continue as long as the force due to the concentration gradient is less than the electrical force. Finally, however, these forces must balance each other and a steady state will be approached. The electroneutrality which would be disturbed by the separation of the ions of MB , is maintained by a compensating separation of the ions of DA . The steady state will thus be characterized by (cf. Fig. 1)

$$\left. \begin{array}{l} M_i > M_o \\ B_i < B_o \\ \text{(if } u_D > v_A) \end{array} \right\} \quad \text{or} \quad \left\{ \begin{array}{l} M_i < M_o \\ B_i > B_o \\ \text{(if } u_D < v_A) \end{array} \right.$$

Accordingly a diffusion of one electrolyte may produce an accumulation or impoverishment inside of other cations or anions depending upon the mobilities of the ions of the diffusing agent. This effect upon the ionic distribution arising from diffusion may be called the *diffusion effect* (cf. Teorell^{1,2}).

The diffusion effect may be *permanent* or *temporary* according as the diffusion is steady or temporary. If initially, for instance, the concentra-

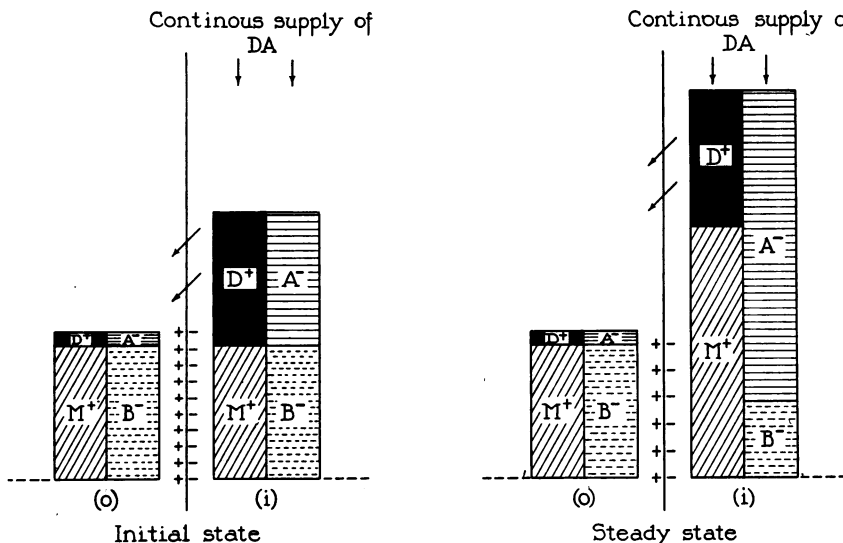


FIGURE 1

The effect of a steady diffusion of DA upon the ionic distribution when $u_D > v_A$. DA is by some means (by addition or production) steadily supplied "inside" (i). The concentrations of the electrolytes "outside" (o) are kept constant. An electrical potential arises across the boundary (membrane). This causes an inward migration of M^+ and an outward migration of B^- . Finally the concentration gradients have become sufficiently large to balance the electrical gradient and the system approaches a steady state. Thus the M ions became "accumulated" and the B ions diminished in amount inside.

tion $(DA)_i > (DA)_o$, but no additional supply of $(DA)_i$ is furnished, $(DA)_i$ will diffuse out and approach the value of $(DA)_o$. During this diffusion, however, a temporary diffusion effect will appear.⁴ This has been experimentally demonstrated by the author^{1,2} and by Norberg.³

A diffusion effect arising from a permanent diffusion has qualitatively been shown in some experiments by Straub,⁵ who spoke of a "Harmonie-Einstellung" of the ions.⁶ A series of experiments including potential

measurements performed by the author confirm the theory of the diffusion effect also from a quantitative point of view. These results will be dealt with in another paper.

IV. (a) A quantitative treatment of the influence of the diffusion effect on the distributions of interest, namely, M_i'/M_o' , M_i''/M_o'' , etc., and B_i'/B_o' , etc., valid for the steady state, can be performed in a classical way if we follow the kinetic treatment of electrolyte diffusion first given by Nernst⁷ and more rigorously developed by Planck.⁸

The migration of any ion species through a surface element in the membrane of the thickness dx , where its concentration is C , is caused by superposition of two forces:

(1) one due to a concentration gradient, this force is per gram ion equal to $RT \cdot \frac{1}{C} \frac{dC}{dx}$.

(2) one due to the electrical potential gradient, written $F \cdot \frac{d\varphi}{dx}$.

Here R , the gas constant, is expressed in joules. C is the concentration in gram ion/liter. T is the absolute temperature. F is the charge of 1 gram equivalent in coulombs and φ the electrical potential in volts. The number of moles of any ion species which passes through the surface element in the unit time, $\frac{dC}{dt}$, or the flux, ϕC , is equal to mobility \times concentration \times force per gram ion or in general (u denotes mobility),

$$\phi C = u \cdot C \cdot \left(\frac{RT}{C} \frac{dC}{dx} \mp F \frac{d\varphi}{dx} \right). \quad (1)$$

The sign before the electrical term is taken negative when cations are concerned and positive for anions. " ϕC " means "the flux of C " (not a product).

In the steady state developed by a permanent diffusion⁹ there is no flux of the passive ion species M^+ and B^- :

$$\phi M' = \phi M'' \text{ etc.} = \phi B' = \phi B'' = 0 \quad (2)$$

and

$$\phi(\Sigma M) = \phi(\Sigma B) = 0. \quad (3)$$

Using equation (1) for the conditions (2) gives for any passive cation species the flux, ϕM , as

$$u_M \cdot M \left(\frac{RT}{M} \frac{dM}{dx} - F \frac{d\varphi}{dx} \right) = 0 \quad (4)$$

and for any passive anion species the flux, ϕB , as

$$v_B \cdot B \left(\frac{RT}{B} \frac{dB}{dx} + F \frac{d\varphi}{dx} \right) = 0 \quad (5)$$

which leads to

$$\frac{d\varphi}{dx} = \frac{RT}{F} \cdot \frac{1}{M} \frac{dM}{dx} = - \frac{RT}{F} \frac{1}{B} \frac{dB}{dx}. \quad (6.1 \text{ and } 6.2)$$

Integration between the limits (o) and (i) gives the diffusion potential π :

$$\pi = \varphi_o - \varphi_i = \frac{RT}{F} \int_i^o \frac{1}{M} \frac{dM}{dx} dx \quad (7)$$

or

$$\pi = \frac{RT}{F} \ln \frac{M_i}{M_o} = \frac{RT}{F} \ln \frac{B_o}{B_i}. \quad (8.1 \text{ and } 8.2)$$

It now becomes obvious that *the steady state* of a system of this nature with a steady diffusion *is characterized by a constant ratio series*

$$\frac{M_i'}{M_o'} = \frac{M_i''}{M_o''} = \dots = \frac{\Sigma M_i}{\Sigma M_o} = \frac{\Sigma B_o}{\Sigma B_i} = \dots = \frac{B_o''}{B_i''} = \frac{B_o'}{B_i'} = \xi. \quad (9)$$

A distribution of this type (9) has been hitherto generally regarded as typical for the so-called Donnan equilibrium. As a matter of fact it will be shown below (VII) that the genuine Donnan equilibrium appears to be a limiting case of the more general case discussed here, where we are dealing with *differences* in permeability instead of with *impermeability*.

(b) The formula (8.1 and 8.2) may be written

$$\pi F = RT \ln \frac{M_i}{M_o} = RT \ln \frac{B_o}{B_i}. \quad (10)$$

The work relation (10) may be interpreted as follows: *the unequal ionic distribution is produced and maintained by the presence of a diffusion membrane potential.* This arises from a diffusion of what may be called an "active" or "diffusing agent."

(c) As the diffusion potential π is equal to the expression for the electrode potential for any passive ion, a concentration chain consisting of reversible electrodes for such an ion species placed in the solution (o) and (i) should give no current, i.e., the energy obtained = 0. This conclusion may be expressed thus: when the system as a whole is in a steady state *the passive ionic constituents are in a true state of equilibrium*, just as in the Donnan equilibrium. "Equilibrium" is here interpreted as a state of matter from which no free energy can be obtained.

V. *The magnitude of the distribution ratio, in the steady state, $\frac{M_i'}{M_o'} = \frac{M_i''}{M_o''} = \dots = \frac{B_o'}{B_i'} = \frac{B_o''}{B_i''} = \dots = \xi$ (9), can be calculated in several somewhat different ways.*

(a) If the diffusion potential π is regarded as known then equation (8) could be used directly. (b) π can, however, be computed from a knowledge of the ionic composition and ionic mobilities. Planck⁸ and Henderson¹⁰ have proposed somewhat different formulas. As the values of M_o and B_o are assumed to be fixed, the unknown M_i or B_i must be computed so they satisfy simultaneously in equation (8) and in either of the formulas just referred to.¹¹ Planck suggests for the calculation of π the equation $\pi = \frac{RT}{F}$

$\ln \xi$, where ξ is defined by a transcendental expression (loc. cit. or text books). A comparison of Planck's $\pi = \frac{RT}{F} \ln \xi$, with equation (8.1) $\pi =$

$\frac{RT}{F} \ln \frac{M_i}{M_o}$ shows that Planck's ξ is identical with our desired ratio M_i/M_o ,

etc. Planck's formulas could accordingly be used and as a matter of fact a combination of Planck's transcendental expression for ξ with equation (8) gives the same result as will be obtained below (equation 18). The Henderson formula gives formally a different result but numerically values in close agreement with the results obtained here.

(c) We will, however, show that an expression for these distribution ratios, now called ξ , can be derived in consistency with the treatment already used under IV.

The *steady state* must, besides the zero flux condition (equations 2, 3) of the passive ions, in regard to the diffusing agent be characterized by

$$\phi D^+ = \phi A^- \quad (11)$$

Proceeding as under IV and substituting in (11) we get

$$u_D \cdot D \left(\frac{RT}{D} \frac{dD}{dx} - F \frac{d\phi}{dx} \right) = v_A \cdot A \left(\frac{RT}{A} \frac{dA}{dx} + F \frac{d\phi}{dx} \right) \quad (12)$$

which solved for $\frac{d\phi}{dx}$ gives

$$\frac{d\phi}{dx} = \frac{RT}{F} \cdot \frac{u_D \cdot dD - v_A \cdot dA}{u_D \cdot D + v_A \cdot A} \cdot \frac{1}{dx} \quad (13)$$

We now sum the equations of type (6) for all M (or B) species and write $\frac{d\phi}{dx} = \frac{RT}{F} \cdot \frac{1}{(\Sigma M)} \frac{d(\Sigma M)}{dx}$ and combine this with (13). Further we substitute the A terms, making use of the electroneutrality condition $D + \Sigma M = A + \Sigma B$ and obtain for (13)

$$\frac{RT}{F} \cdot \frac{1}{(\Sigma M)} \frac{d(\Sigma M)}{dx} = \frac{RT}{F} \cdot \frac{u_D \cdot dD - v_A [dD + d(\Sigma M) - d(\Sigma B)]}{u_D \cdot D + v_A [D + (\Sigma M) - (\Sigma B)]} \cdot \frac{1}{dx} \quad (14)$$

$d(\Sigma B)$ is substituted by $-\left(\frac{(\Sigma B)}{(\Sigma M)}\right) d(\Sigma M)$, a relation directly obtained from equations of type (6). Equation (14) is then solved for $\frac{dD}{d(\Sigma M)}$ when the (ΣB) terms will cancel out. The result is

$$\frac{dD}{d(\Sigma M)} = a \frac{D}{(\Sigma M)} + b \quad (15)$$

where the constants a and b denote $\frac{u_D + v_A}{u_D - v_A}$ and $\frac{2v_A}{u_D - v_A}$, respectively. The differential equation (15) gives a solution

$$D - \frac{b}{1-a} (\Sigma M) - I \cdot (\Sigma M)^a = 0 \quad (16.1)$$

or

$$D + (\Sigma M) - I \cdot (\Sigma M)^a = 0 \quad (16.2)$$

the I being an integration constant. This is eliminated by dividing two equations (16) applied to the limits (i) and (o) :

$$\frac{D_i + \Sigma M_i}{D_o + \Sigma M_o} = \frac{I \cdot (\Sigma M_i)^a}{I \cdot (\Sigma M_o)^a} \quad (17)$$

Finally taking the logarithms, substituting a , and considering the relations of equation (9) we obtain

$$\log \xi = \log \frac{\mathbf{M}_i'}{\mathbf{M}_o'} = \dots = \log \frac{B_o'}{B_i'} = \dots = \log \frac{(\Sigma \mathbf{M}_i)}{(\Sigma \mathbf{M}_o)} = \frac{u_D - v_A}{u_D + v_A} \log \frac{D_i + (\Sigma \mathbf{M}_i)}{D_o + (\Sigma \mathbf{M}_o)} \quad (18.1)$$

It should be noticed that the terms $D + (\Sigma M)$ are equal to the "total" concentration C . For a single ion species, for instance M' , we may write

$$\log \frac{\mathbf{M}_i'}{\mathbf{M}_o'} = \frac{u_D - v_A}{u_D + v_A} \log \frac{D_i + \frac{(\Sigma M_o)}{M_o'} \mathbf{M}_i'}{D_o + (\Sigma M_o)} \quad (18.2)$$

The transcendental expression (18.1.2) contains the desired quantitative description of the diffusion effect *valid for the steady state*. The terms which according to the assumption made under II are considered as known are printed in common type, those which are variables in heavy type.

Numerical solution of equation (18) can be performed either (a) by a

graphical computation, the intersection of the curves for the left, respectively right-hand member obtained by inserting different values of the variables will be the solution, or (b) by a method of successive approximation.

VI. *The factors influencing the magnitude of the distribution ratio ξ (in the steady state) can be read off from equation (18). They are the ratios u_D/v_A , $D_i/\Sigma M_o$ and D_i/D_o . The larger any of these ratios are the greater the "accumulation" of M^+ ions "inside" (and correspondingly the decrease of B^- ions), provided $u_D > v_A$. If $u_D < v_A$ it is the B^- ions which will accumulate, etc.*

To get an impression of the very marked concentration differences which theoretically can be expected under certain conditions the tables 1 and 2 should be consulted.

TABLE 1

THE VALUE OF THE DISTRIBUTION RATIO $\xi \left(= \frac{M_i'}{M_o'} \text{ ETC.} \right)$

(u_D/v_A is assumed to be 5)

$D_i/\Sigma M_o$	D_i/D_o					
	1	10	100	1000	10,000	$(D_o = \infty)$
0.01	1	1.02	1.02	1.02	1.02	1.02
0.1	1	1.12	1.17	1.18	1.18	1.18
1	1	1.86	2.12	2.14	2.15	2.15
10	1	3.58	6.0	6.4	6.4	6.49
100	1	4.49	15.0	23.5	25.0	25.2
1000	1	4.64	20.5	56	101	107
10000	1	4.65	21.4	94	298	479
∞	1	4.65	21.5	100	465	∞

TABLE 2

THE DISTRIBUTION RATIO $\xi \left(= \frac{M_i'}{M_o'} \text{ ETC.} \right)$ AT DIFFERENT MOBILITY RELATIONS

(It is assumed that $D_i = \Sigma M_o$)

D_i/D_o	MOBILITY RATIO u_D/v_A						DONNAN EQUILIBRIUM ($v_A = 0$)
	2	5	10	100	1000	∞	
∞	1	1.33	2.15	3.31	16.9	>100	∞
100	1	1.32	2.12	3.13	15.0	85	100
10	1	1.27	1.86	2.70	6.9	9.9	10
1	1	1	1	1	1	1	1

VII. *The Donnan equilibrium can, as pointed out above, be regarded as a limiting case of the case discussed in this paper. If one of the ions of DA is prevented from diffusing, i.e., making either v_A or u_D equal to zero and the addition or production of DA is stopped, the equation (18.1) is transformed into*

$$\text{i. } (v_A = 0) \quad \log \frac{\Sigma M_i}{\Sigma M_o} = \log \frac{D_i + \Sigma M_i}{D_o + \Sigma M_o} \quad (15.1)$$

which means (remembering equation (9)) that

$$\frac{M_i'}{M_o'} = \frac{M_i''}{M_o''} = \dots = \frac{D_i}{D_o} = \dots = \frac{B_o''}{B_i''} = \frac{B_o'}{B_i'} \quad (15.2)$$

$$\text{ii. } (u_D = 0) \quad \log \frac{\Sigma M_i}{\Sigma M_o} = -\log \frac{D_i + \Sigma M_i}{D_o + \Sigma M_o} = \log \frac{C_o}{C_i} = \log \frac{A_o + \Sigma B_o}{A_i + \Sigma B_i} \quad (16.1)$$

which must be interpreted

$$\frac{M_i'}{M_o'} = \frac{M_i''}{M_o''} = \dots = \frac{A_o}{A_i} = \dots = \frac{B_o''}{B_i''} = \frac{B_o'}{B_i'} \quad (16.2)$$

Equations (15.2) and (16.2) are the equilibrium conditions requested by Donnan. The approach of the diffusion effect to the Donnan effect with increasing u_D/v_A (v_A tends to 0) is evident from table 2.

VIII. *The validity of the conclusions* above depends on the validity of the assumptions given under II. In experimental work with solutions which are not ideal one might expect deviations due to differences in activity, water migration, special influence of the membrane and several other complicating factors.¹² Experiments by the author show that this is the case. In dilute solutions, however, the agreement between theory and experiments can be considered good. These results and the discussion of the bearings of these theories on certain biological ionic distributions will be published in subsequent papers.

I wish to express my acknowledgment to Drs. W. J. V. Osterhout and L. G. Longworth for valuable criticism.

Summary.—1. The behavior of an aqueous system of strong electrolytes is studied, where a steady diffusion across an ion-permeable boundary (membrane) takes place.

2. Theoretical considerations predict, for the assumptions given, (a) the possibility of the development of concentration differences in respect to "passive" ions ("diffusion effect" upon ionic distribution); (b) an approach to a steady state of the system as a whole, where the "passive" ions are in a true state of equilibrium characterized by the relations

$$\frac{(\text{conc. of cation}) \text{ inside}}{(\text{conc. of cation}) \text{ outside}} = \frac{(\text{conc. of anion}) \text{ outside}}{(\text{conc. of anion}) \text{ inside}} = \xi.$$

3. The genuine Donnan equilibrium appears as a limiting case of the more general case treated here. The "diffusion effect" appears when a concentration gradient is present and is due to *differences* in ionic mobility

("relative impermeability"), whereas the "Donnan effect" is caused by "absolute impermeability" of one or several ion species.

4. A formula for the distribution ratio in the steady state has been derived and the factors which have influence upon it are pointed out. Some tables are given showing the calculated distribution ratio for various assumptions.

5. Theoretically very marked concentration differences across a boundary (membrane) are possible. It is emphasized, however, that deviations from the theory might occur, because the validity of the assumptions may be limited and factors not involved in the theory might play a rôle.

6. Diffusion effects of the type presented in this paper may be of biological importance.

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¹ Teorell, T., *J. Physiol.*, **78**, 11P (1933).

² Teorell, T., *Skand. Arch. Physiol.*, **66**, 225 (1933).

³ Norberg, B., *Pflüger's Arch.*, **234**, 200 (1933).

⁴ The possibility of a temporary migration of one ion species, initially uniformly distributed, in a system with one electrolyte diffusing was mentioned shortly by Abegg and Bose (Abegg, R., and Bose, E., *Z. physik. Chem.*, **30**, 545 (1899)) in a footnote (p. 549). Cf. recent theory of interdiffusion by Taylor (Taylor, P. B., *J. Phys. Chem.*, **31**, 1478 (1927)).

⁵ Straub, J., *Kolloid-Z.*, **62**, 13 (1933). Straub (*Ibid.*, **64**, 72 (1933)) connects his results in an interesting way with certain conceptions introduced by Schreinemakers.

⁶ Some related effects during dialysis are recently reported by Brintzinger and Wallach (Brintzinger, H., and Wallach, J., *Kolloid-Z.*, **68**, 36 (1934)).

⁷ Nernst, W., *Z. physik. Chem.*, **2**, 617 (1888); **4**, 154 (1889).

⁸ Planck, M., *Wied. Ann.*, **40**, 561 (1890).

⁹ A treatment similar to this given here can easily be applied to a temporary diffusion effect at the maximum condition.

¹⁰ Henderson, P., *Z. physik. Chem.*, **59**, 118 (1907).

¹¹ Planck and Henderson (loc. cit.) have different assumptions concerning the conditions in the diffusion layer. They do not enter into our discussion. Our treatment, however, is in principle that of Planck and experiments (unpublished) on the ionic distribution *within* the diffusion layer confirm Planck's assumptions rather than those of Henderson.

¹² McBain and Liu (McBain, J. W., and Liu, T. H., *J. Am. Chem. Soc.*, **53**, 59 (1931)) and McBain and Dawson (McBain, J. W., and Dawson, C. R., *Ibid.*, **56**, 52 (1934)) assume a "collision effect" in more concentrated solutions (loc. cit.).

¹³ Extensions of the theory given here, involving the influence of water migration and of chemical reactions, will be presented in subsequent communications.