

sess a viscosity greater than that of water, irrespective of the viscosity of the solute.

The effect of depolymerization of water upon the property of viscosity was no more apparent at 10° than at 25°, except possibly in the case of the urea solutions.

The results were discussed from the point of view of compound formation and orientation of polar molecules.

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THE TITRATION CONSTANTS OF MULTIVALENT SUBSTANCES

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It has long been known that the titration curve of a multivalent acid resembles that of a mixture of monovalent acids. Based upon the apparent identity of these two classes of titration curves, as judged by experiment, H. S. Simms¹ has developed equations which correlate the apparent with the true dissociation constants of a multivalent acid. The equations are given for a divalent and trivalent acid, and the same considerations readily yield the equations for any number of valencies.

Apparently without knowledge of Simms' contribution, H. H. Weber² has recently treated this problem in a very similar manner. The equations which he obtains are more restricted and not as generally applicable as those developed by Simms, since he introduced the further assumption that the titration curve of the multivalent acid resembles that of a single monovalent acid. In discussing these two papers in our seminar, it became apparent that the assumption of resemblance is unnecessary, for the general equations of Simms may be obtained by a purely mathematical transformation of the classical dissociation equations given by the mass law.³ This mathematical transformation yields no equations other than those developed by Simms, but in that the same relations are obtained without any assumption, the behavior of multivalent substances as described by the classical equations is vested with a slightly altered interpretation which rendered it desirable to communicate the calculations.

The classical dissociation constants for the n steps of dissociation of a multivalent acid may be written

¹ H. S. Simms, *THIS JOURNAL*, **48**, 1239 (1926).

² H. H. Weber, *Biochem. Z.*, **189**, 381 (1927).

³ In a previous seminar Professor Scatchard was able to derive Weber's equations on the assumption that the probability of dissociation was the same for each group, and independent of the number of groups dissociated.

$$\begin{aligned}
 K'_1 &= \frac{[H][\cdot H_{n-1} A']}{[H_n A]} \\
 K'_1 K'_2 &= \frac{[H]^2 \cdot [H_{n-2} A'']}{[H_n A]} \\
 &\dots \\
 &\dots \\
 &\dots \\
 K'_1 K'_2 \dots K'_n &= \frac{[H]^n \cdot [A^{n-}]}{[H_n A]}
 \end{aligned}
 \tag{1}$$

The dissociation of a monovalent as well as of a multivalent acid can be described in terms of the following ratios

- (1) $\frac{\text{Concentration of dissociated hydrogen ions}}{\text{Concentration of undissociated hydrogen ions}} = \alpha$
- (2) $\frac{\text{Concentration of dissociated hydrogen ions}}{\text{Equivalent concentration}} = \beta$
- (3) $\frac{\text{Concentration of undissociated hydrogen ions}}{\text{Equivalent concentration}} = \rho$

In terms of the classical dissociation constants these ratios take the form

$$\alpha = \frac{\frac{K'_1}{[H]} + 2 \frac{K'_1 K'_2}{[H]^2} + \dots + (n-1) \frac{K'_1 K'_2 \dots K'_{n-1}}{[H]^{n-1}} + n \frac{K'_1 K'_2 \dots K'_n}{[H]^n}}{n + (n-1) \frac{K'_1}{[H]} + (n-2) \frac{K'_1 K'_2}{[H]^2} + \dots + \frac{K'_1 K'_2 \dots K'_{n-1}}{[H]^{n-1}}}
 \tag{2}$$

$$\beta = \frac{1 \frac{K'_1}{[H]} + 2 \frac{K'_1 K'_2}{[H]^2} + \dots + (n-1) \frac{K'_1 K'_2 \dots K'_{n-1}}{[H]^{n-1}} + n \frac{K'_1 K'_2 \dots K'_n}{[H]^n}}{n \left(1 + \frac{K'_1}{[H]} + \frac{K'_1 K'_2}{[H]^2} + \dots + \frac{K'_1 K'_2 \dots K'_{n-1}}{[H]^{n-1}} + \frac{K'_1 K'_2 \dots K'_n}{[H]^n} \right)}
 \tag{3}$$

$$\rho = \frac{n + (n-1) \frac{K'_1}{[H]} + (n-2) \frac{K'_1 K'_2}{[H]^2} + \dots + \frac{K'_1 K'_2 \dots K'_{n-1}}{[H]^{n-1}}}{n \left(1 + \frac{K'_1}{[H]} + \frac{K'_1 K'_2}{[H]^2} + \dots + \frac{K'_1 K'_2 \dots K'_{n-1}}{[H]^{n-1}} + \frac{K'_1 K'_2 \dots K'_n}{[H]^n} \right)}
 \tag{4}$$

These rather complicated expressions⁴ can be simplified considerably by a mathematical transformation, known as *separation into partial fractions*. The rational algebraic expression $F(x)/\Phi(x)$ can be expressed as the sum of partial fractions, which have the several factors of $\Phi(x)$ as denominators and which have constants for numerators. In order to show how Equations 2, 3 and 4 can be separated into partial fractions, the detailed calculation for 3 is given here. With appropriate modifications the same method can be applied to (2) and (4).

⁴ The terms in the mass law equations have, for mathematical convenience, been written as stoichiometrical concentrations rather than as activities. Activity coefficients could, of course, be introduced into these series.

The first step which is taken is to render Equation 3 more convenient for further transformation by multiplying both numerator and denominator by $[H]^n$

$$\beta = \frac{1K'_1[H]^{n-1} + 2K'_1K'_2[H]^{n-2} + \dots + (n-1)K'_1K'_2 \dots K'_{n-1}[H] + nK'_1K'_2 \dots K'_n}{n([H]^n + K'_1[H]^{n-1} + K'_1K'_2[H]^{n-2} + \dots + K'_1K'_2 \dots K'_{n-1}[H] + K'_1K'_2 \dots K'_n)} \tag{3a}$$

In (3a) the denominator has the form of the expansion of the general polynomial

$$(k_1 + x)(k_2 + x)(k_3 + x) \dots (k_n + x) \tag{4a}$$

which in the expanded form can be written

$$x^n + \Sigma_{k_1} x^{n-1} + \Sigma_{k_1 k_2} x^{n-2} + \Sigma_{k_1 k_2 k_3} x^{n-3} + \dots + \Sigma_{k_1 k_2 k_3 \dots k_n} \tag{4b}$$

The symbol Σ_k represents the sum of the elements $k_1 + k_2 + k_3 + \dots k_n$, $\Sigma_{k_1 k_2}$ the sum of the combinations without repetition of the elements $k_1, k_2, \dots k_n$ taken two at a time, $\Sigma_{k_1 k_2 k_3}$ the sum of the combinations without repetition of the elements $k_1, k_2, \dots k_n$ taken three at a time, and so forth.

Comparison of Equation 4b with the denominator in (3a) shows that both are identical except for the factors of corresponding powers of $[H]$ and x . By equating the undetermined factors of corresponding powers of $[H]$ and x , n equations are obtained which define completely the new factors $k_1, k_2, \dots k_n$ in terms of the old factors $K'_1, K'_2, \dots K'_n$.

$$\begin{aligned} K'_1 &= \Sigma_{k_1} &= k_1 + k_2 + k_3 + \dots k_n \\ K'_1 K'_2 &= \Sigma_{k_1 k_2} &= k_1 k_2 + k_1 k_3 + \dots + k_1 k_n + \dots k_{n-1} k_n \\ K'_1 K'_2 K'_3 &= \Sigma_{k_1 k_2 k_3} &= k_1 k_2 k_3 + k_1 k_3 k_4 + \dots k_{n-2} k_{n-1} k_n \\ &\dots &\dots \\ &\dots &\dots \\ K'_1 K'_2 \dots K'_n &= \Sigma_{k_1 k_2 \dots k_n} &= k_1 k_2 k_3 \dots k_n \end{aligned} \tag{5}$$

Consequently we may write

$$\begin{aligned} n([H]^n + K'_1[H]^{n-1} + K'_1K'_2[H]^{n-2} + \dots + K'_1K'_2 \dots K'_{n-1}[H] + K'_1K'_2 \dots K'_n) &\equiv \\ \equiv n([H]^n + \Sigma_{k_1}[H]^{n-1} + \Sigma_{k_1 k_2}[H]^{n-2} + \dots + \Sigma_{k_1 k_2 \dots k_{n-1}}[H] + \Sigma_{k_1 k_2 k_3 \dots k_n}) &\equiv \\ \equiv n((k_1 + [H])(k_2 + [H])(k_3 + [H]) \dots (k_n + [H])) &\tag{6a} \end{aligned}$$

The numerator can also be transformed by means of the same set of Equations (5), yielding the following identity

$$\begin{aligned} \frac{1K'_1[H]^{n-1} + 2K'_1K'_2[H]^{n-2} + \dots + (n-1)K'_1K'_2 \dots K'_{n-1}[H] + nK'_1K'_2 \dots K'_n}{n([H]^n + K'_1[H]^{n-1} + K'_1K'_2[H]^{n-2} + \dots + K'_1K'_2 \dots K'_{n-1}[H] + K'_1K'_2 \dots K'_n)} &\equiv \\ \equiv \frac{1 \Sigma_{k_1}[H]^{n-1} + 2 \Sigma_{k_1 k_2}[H]^{n-2} + \dots + (n-1) \Sigma_{k_1 k_2 \dots k_{n-1}}[H] + n \Sigma_{k_1 k_2 \dots k_n}}{n((k_1 + [H])(k_2 + [H])(k_3 + [H]) \dots (k_n + [H]))} &\tag{6b} \end{aligned}$$

This transformed expression of (3) may now be separated into partial fractions and we may write

$$\begin{aligned} \frac{\Sigma_{k_1}[H]^{n-1} + 2 \Sigma_{k_1 k_2}[H]^{n-2} + \dots + (n-1) \Sigma_{k_1 k_2 \dots k_{n-1}}[H] + n \Sigma_{k_1 k_2 k_3 \dots k_n}}{n((k_1 + [H])(k_2 + [H])(k_3 + [H]) \dots (k_n + [H]))} &\equiv \\ \equiv \frac{1}{n} \left(\frac{k_1}{k_1 + [H]} + \frac{k_2}{k_2 + [H]} + \frac{k_3}{k_3 + [H]} + \dots + \frac{k_n}{k_n + [H]} \right) &\tag{7} \end{aligned}$$

The proof that the separation into partial fractions (7) is correct may be obtained by clearing the left and the right side of fractions. Since this procedure is well known to those familiar with partial fractions, it has been omitted.

Applying the same transformation to Equations 2 and 4, corresponding identities are obtained, which are given without the calculation, as the procedure is very much the same as for Equation 3.

$$\alpha = \frac{\frac{\kappa_1}{\kappa_1 + [\text{H}]} + \frac{\kappa_2}{\kappa_2 + [\text{H}]} + \frac{\kappa_3}{\kappa_3 + [\text{H}]} + \dots + \frac{\kappa_n}{\kappa_n + [\text{H}]}}{[\text{H}] \left(\frac{1}{\kappa_1 + [\text{H}]} + \frac{1}{\kappa_2 + [\text{H}]} + \frac{1}{\kappa_3 + [\text{H}]} + \dots + \frac{1}{\kappa_n + [\text{H}]} \right)} \quad (2')$$

$$\beta = \frac{1}{n} \left(\frac{\kappa_1}{\kappa_1 + [\text{H}]} + \frac{\kappa_2}{\kappa_2 + [\text{H}]} + \frac{\kappa_3}{\kappa_3 + [\text{H}]} + \dots + \frac{\kappa_n}{\kappa_n + [\text{H}]} \right) \quad (3')$$

$$\rho = \frac{1}{n} \left(\frac{[\text{H}]}{\kappa_1 + [\text{H}]} + \frac{[\text{H}]}{\kappa_2 + [\text{H}]} + \frac{[\text{H}]}{\kappa_3 + [\text{H}]} + \dots + \frac{[\text{H}]}{\kappa_n + [\text{H}]} \right) \quad (4')$$

Equations 2', 3' and 4' were derived from (2), (3) and (4) by separation into partial fractions and by introducing a set of new constants $\kappa_1, \kappa_2, \dots, \kappa_n$ for mathematical convenience. If one formulates the fractions α, β, ρ for a mixture of monovalent acids, with dissociation constants G'_1, G'_2, \dots, G'_n (using Simms' notation), an identical set of equations is obtained, in which the G'_1, G'_2, \dots, G'_n replace the constants $\kappa_1, \kappa_2, \dots, \kappa_n$.

$$\kappa_1 = G'_1; \quad \kappa_2 = G'_2; \quad \dots \quad \kappa_n = G'_n$$

These constants which have so far been used as a mathematical convenience without any specific meaning attached to them, are therefore the titration constants, and in order not to complicate the nomenclature can be replaced by the titration constants of Simms. They are related to the classical constants by Equation 5, which is, of course, identical with the equation, previously developed by Simms, with the assumption of similarity. In our treatment we have assumed only validity of the classical mass law equations and the result has been derived by mere mathematical transformation of these equations. It follows, therefore, that between the titration curve of a multivalent acid and a mixture of monovalent acids there is no difference. In other words, if the classical dissociation constants of a multivalent acid are known, it is possible to make a mixture of monovalent acids which will give exactly the same titration curve, provided that the individual dissociation constants of the monovalent acids satisfy Equations 5.

Generally one deals with the opposite problem. From the titration curve the titration constants G'_1, G'_2, \dots, G'_n are experimentally obtained and the classical constants K'_1, K'_2, \dots, K'_n can be determined by using Equations 5. We wish again to emphasize that this is only valid in so far as the classical mass law formulation is an accurate description of the facts. Provided this is the case, there is no difference between the dissociation of a multivalent acid and a properly chosen mixture of monovalent acids, and

the titration constants are at the same time the "intrinsic" constants of the groups.⁵ This relation of course will hold only if the electrostatic work of ionization and the work which is involved in distortion of the molecule are disregarded.

The formulas given by Weber can also be obtained from Equations 5 by assuming that the G'_1, G'_2, \dots, G'_n are all equal, an assumption which Weber has introduced by stating that the titration curve of the multivalent acid resembles that of a single monovalent acid. On this assumption much simpler identities result. Instead of n titration constants, one alone is found, therefore

$$G'_1 = G'_2 = G'_3 = \dots = G'_n = G'$$

$$\alpha = \frac{G'}{[H]} \quad (2'') \quad \beta = \frac{G'}{G' + [H]} \quad (3'') \quad \rho = \frac{[H]}{G' + [H]} \quad (4'')$$

and the classical dissociation constants are defined by

$$K'_1 = n G'; \quad K'_2 = \frac{n-1}{2} G'; \quad K'_3 = \frac{n-2}{3} G'; \quad \dots; \quad K'_n = \frac{1}{n} G' \quad (5')$$

relations which are of course identical with those of Weber. It is obvious that the values of K'_1, K'_2, \dots, K'_n in Equations 5' are not independent of each other, since they are all related to definite fractions of one titration constant G' .

Similar conditions are obtained from the titration data of proteins. Instead of obtaining n independent values for the titration constants G' , these constants seem to fall into groups of m elements which are identical. Therefore only n/m independent values are obtained. This reduces the number of independent Equations 5, relating the titration constants with the classical constants, to n/m . The n classical constants K' fall, therefore, into n/m groups of related constants. The case which has been treated by Weber represents grouping of the titration constants G' into one group of identical constants ($n = m$). For the corresponding group of classical constants K' the following relation is obtained

$$\frac{K'_1}{n} = \frac{2K'_2}{n-1} = \frac{3K'_3}{n-2} = \dots = \frac{nK'_n}{1} \quad (5a'')$$

The same transformation is applicable in the case of the formula defining the stepwise dissociation of hemoglobin.⁶ The equation for the four steps of dissociation is given as

$$\text{Percentage saturation} = \frac{100\gamma' [\text{Hb}_4] (K'_1[\text{O}_2] + 2K'_1K'_2[\text{O}_2]^2 + 3K'_1K'_2K'_3[\text{O}_2]^3 + 4K'_1K'_2K'_3K'_4[\text{O}_2]^4)}{4\gamma' [\text{Hb}_4] (1 + K'_1[\text{O}_2] + K'_1K'_2[\text{O}_2]^2 + K'_1K'_2K'_3[\text{O}_2]^3 + K'_1K'_2K'_3K'_4[\text{O}_2]^4)} \quad (9)$$

Separation into partial fractions gives the simpler identity

⁵ E. Q. Adams, *THIS JOURNAL*, **38**, 1503 (1916).

⁶ G. S. Adair, *J. Biol. Chem.*, **63**, 529 (1925); *Proc. Roy. Soc.*, (London), **109A**, 299 (1925); R. M. Ferry and A. A. Green, *J. Biol. Chem.*, **81**, 177 (1929).

Percentage saturation =

$$\frac{100\gamma'}{4\gamma'} \left(4 - \left(\frac{G'_1}{G'_1 + [\text{O}_2]} + \frac{G'_2}{G'_2 + [\text{O}_2]} + \frac{G'_3}{G'_3 + [\text{O}_2]} + \frac{G'_4}{G'_4 + [\text{O}_2]} \right) \right) \quad (9a)$$

and the new constants are related to the old constants by the four equations

$$\frac{1}{K'_4} = \Sigma G'_i = G'_1 + G'_2 + G'_3 + G'_4 \quad (9b)$$

$$\frac{1}{K'_4 K'_3} = \Sigma G'_1 G'_2 = G'_1 G'_2 + G'_1 G'_3 + G'_1 G'_4 + G'_2 G'_3 + G'_2 G'_4 + G'_3 G'_4$$

$$\frac{1}{K'_4 K'_3 K'_2} = \Sigma G'_1 G'_2 G'_3 = G'_1 G'_2 G'_3 + G'_1 G'_2 G'_4 + G'_2 G'_3 G'_4 + G'_1 G'_3 G'_4$$

$$\frac{1}{K'_4 K'_3 K'_2 K'_1} = \Sigma G'_1 G'_2 G'_3 G'_4 = G'_1 G'_2 G'_3 G'_4$$

Expressing results in terms of classical constants necessitates the use of Equation 5, which is rather complicated. No substantial advantage is gained in doing this. It therefore appears advisable to express results directly in terms of titration constants and to abolish the classical constants altogether.

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THE ETHERATES OF MAGNESIUM BROMIDE

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The fact that the halides of magnesium are capable of uniting with ether to form compounds similar to hydrates has been known since the beginning of this century. Menschutkin² was the first to study them and gave them the name "etherates." He investigated their solubility in ether at various temperatures and found that as the solution became more concentrated, a heavy, oily, immiscible layer separated. He discovered that this heavy layer could be greatly supercooled and that when it did crystallize the magnesium halide was obtained in the form of the di-etherate. Later, Meisenheimer³ and his co-workers discussed some of the properties of this oily liquid and of the crystalline magnesium halide etherates.

From a review of the literature, it is apparent that very little is known concerning the formulas of these etherates. Some claim that they contain one molecule of ether;⁴ others, that they contain two molecules,⁵ while some

¹ University Fellow, 1927-1928.

² Menschutkin, *J. Russ. Phys.-Chem. Soc.*, **35**, 610 (1903).

³ Jakob Meisenheimer and Johannes Casper, *Ber.*, **54B**, 1655 (1921); Jakob Meisenheimer, Erich Piper and Hans Lange, *Z. anorg. allgem. Chem.*, **147**, 331 (1925).

⁴ Tissier and Grignard, *Compt. rend.*, **132**, 835 (1901); Grignard, *ibid.*, **136**, 1262 (1903).

⁵ (a) N. Zelinsky, *Chem. Zentr.*, II, 277 (1903); (b) W. Tschelinzeff, *Ber.*, **39**, 773 (1906).