ions. Moreover, the entropies of bromides and iodides in 1 *M* solution, after correcting for the mass, are approximately 3 and 6 units, respectively, less than those of the chlorides, which is in agreement with the differences in the heats of solution.

It may also be pointed out that the results presented in this paper offer strong support to the Debye treatment of solutions of strong electrolytes, although the values which he calculates for the radii of influence of the ions are considerably larger.

## Summary

The energies of solution of fourteen ions have been calculated.

The radii of the ions calculated from the relation $\Delta E = (e^2/2r)(1-(1/D))$ are found to agree very closely with the values of Bragg and Bragg for ionic radii.

Approximate values for the entropies of ions in aqueous solution have been given.

Values for the electron affinities of chlorine, bromine and iodine have been calculated.

BERKELEY, CALIFORNIA

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

# DISSOCIATION OF POLYVALENT SUBSTANCES
# I. RELATION OF CONSTANTS TO TITRATION DATA

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**I. Notation.**—The notation used in this article is as follows.

**Constants.**—$K_1'$, $K_2'$, $K_3'$, etc. = "Dissociation constants" of a polyvalent acid base or ampholyte, not corrected for activity, and representing the "*steps*" in formation of more negative ions from less negative ions (or molecules). These constants do not refer to groups.

$G_1'$, $G_2'$, $G_3'$, etc. = "Titration constants" obtained by calculating the titration data as if the solution contained monovalent acids in equivalent quantities.

$K_1$, $K_2$, $K_3$, etc. = Dissociation constants corrected for activity.

$G_1$, $G_2$, $G_3$, etc. = Titration constants corrected for activity.

$K_0^{\rm I}$, $K_0^{\rm II}$, $K_0^{\rm III}$, etc. = "Intrinsic constants" of the individual *groups*.

**Concentrations** (lower case letters).—$\alpha_1$, $\alpha_2$, $\alpha_3$, = Probabilities of dissociation according to $G_1'$, $G_2'$ and $G_3'$, respectively.

$u$ = Fraction of a substance in un-ionized form.

$m$ = Fraction of a substance in mono-ionic form (mono-ion singly charged ion).

$d$ = Fraction of a substance in di-ionic form (di-ion doubly charged ion).

$t$ = Fraction of a substance in tri-ionic form (tri-ion triply charged ion).

n = Fraction of a substance in the more negative form (predominating at a lower $P_{\rm H}$ than $P_{\rm K}$).

p = Fraction of a substance in the more positive form (predominating at a higher $P_{\rm H}$ than $P_{\rm K}$).

$c$ = Molal concentration of substance.
$a$ = Molal concentration of strong acid.
$b$ = Molal concentration of strong base.
$b'$ = "Corrected equivalents of base" (see Equation 34).
$b''$ = $(b - a + h - oh)$ in Equation 41.
$\bar{b}''$ = $1 - (b - a + h - oh)$ in Equation 42.
$h$ = Hydrogen-ion concentration.
$oh$ = Hydroxyl-ion concentration.
**Activities** (capital letters).—H = Hydrogen-ion activity.
OH = Hydroxyl-ion activity.

**Miscellaneous.** $\left(\frac{f_0}{f_1}\right)$, $\left(\frac{f_0}{f_2}\right)$, $\left(\frac{f_0}{f_3}\right)$, etc. = Ratios of activity coefficients before and after dissociation of one, two, three, etc. groups.

$r$ = Activity coefficient ratio for a single step in ionization.
$z$ = Number between 1 and 2, in Equation 28.
$\nu$ = Valence.
$y$ = Number of groups which ionize as bases (amino groups).
$Q$ = Special factor for Equation 38.
$P_X$ = —log $X$ where $X$ is any constant or variable.
$E$ = Constant in Equation 28.
$L$ = Function of electrostatic work between groups.
$A$ and $B$ = Special functions in Equations 11 to 13.

"Dissociation" refers to the effect of ionization of the acid groups and hydrolysis of the salts of basic (amino) groups.

**II. Introduction.**—The ionization of a divalent acid may be represented by the classical equations in the following form (see table of notations),

$$K_1' = \text{H}\,\frac{\text{HA}^-}{\text{H}_2\text{A}} = \text{H}\,\frac{m}{1-m-d} \qquad (1)$$

$$K_2' = \text{H}\,\frac{\text{A}^=}{\text{HA}^-} = \text{H}\,\frac{d}{m} \qquad (2)$$

in which $K_1'$ and $K_2'$ are the classical dissociation constants. Similar equations apply to acids of higher valence.

The titration data of an acid consist of measurements of hydrogen-ion activity (H) when different concentrations of strong base ($b$) have been added to a concentration ($c$) of the acid. It is desirable to know the relationship between the titration data and the dissociation constants.

Various formulas have been derived by Larsson,[1] Harris,[2] Hammarsten[3] and by Auerbach and Smolczyk[4] for calculating dissociation constants from titration data. These formulas are cumbersome, limited in application, and sometimes incorrect.

On the other hand, it is well known that the titration curve of a divalent acid (see Fig. 1) *resembles* that of a mixture of two monovalent acids. In fact, we may calculate the titration data as if there were actually two

[1] Larsson, *Z. anorg. allgem. Chem.*, **125**, 281 (1922).
[2] Harris, (a) *J. Chem. Soc.*, **123**, 3294 (1923); (b) *Proc. Roy. Soc.*, **95B**, 440 (1923).
[3] Hammarsten, *Biochem. Z.*, **144**, 383 (1924).
[4] Auerbach and Smolczyk, *Z. physik. Chem.*, **110**, 65 (1924).

monovalent acids present,[5] and we obtain ("titration") constant $G_1'$ and $G_2'$ which are the dissociation constants such acids would have.

$$G_1' = \text{H}\,\frac{\alpha_1}{1-\alpha_1} \qquad G_2' = \text{H}\,\frac{\alpha_2}{1-\alpha_2} \tag{3}$$

These constants are not identical with the dissociation ($K'$) constants of the divalent acid (owing to the fact that the first step of ionization may not be complete when the second begins). There has been no theoretical reason for considering these as true constants.

It is the purpose of this article to show that (under certain conditions of ionic strength) these titration ($G'$) constants are true constants, and are related to the classical dissociation constants ($K'$) by the equations

$$K_1'K_2' = G_1'G_2' \tag{4}$$

and

$$K_1' = G_1' + G_2' \tag{5}$$

from which it follows that

$$1/K_2' = 1/G_1' + 1/G_2' \tag{6}$$

and

$$\frac{K_1'}{K_2'} = \frac{G_1'}{G_2'} + \frac{G_2'}{G_1'} + 2 \tag{7}$$

and that similar formulas may be applied to *any* polyvalent acid base or ampholyte.

The calculation of the titration constants from titration data, is very simple (see section VIII). The above formulas then give us the dissociation constants.

**III. Proof.**—Suppose we have one solution containing a divalent acid with constants $K_1'$ and $K_2'$ and another solution containing the same concentration of each of two monovalent acids with constant $G_1'$ and $G_2'$. If we add $b'$ equivalents of alkali to both solutions, they will have the same $P_\text{H}$, providing

$$b' = m + 2\,d = \alpha_1 + \alpha_2 \tag{8}$$

where, according to the mass law (see Equations 3)

$$\alpha_1 = \frac{G_1'}{\text{H} + G_1'},\ \text{and}\ \alpha_2 = \frac{G_2'}{\text{H} + G_2'} \tag{9}$$

From Equations 1, 2, 8 and 9

$$b' = \frac{\text{H}K_1' + 2\,K_1'K_2'}{\text{H}^2 + \text{H}K_1' + K_1'K_2'} = \frac{\text{H}\,(G_1' + G_2') + 2\,G_1'G_2'}{\text{H}^2 + \text{H}\,(G_1' + G_2') + G_1'G_2'} \tag{10}$$

The two solutions can have the same titration data at all values of $b'$ only if Equation 10 holds at all values of H. Let us substitute

$$A = K_1';\ B = K_1'K_2';\ A' = G_1' + G_2'\ \text{and}\ B' = G_1'G_2' \tag{11}$$

Since $A$ must be independent of H we may solve for $A$ and place its partial differential with respect to H equal to zero.

$$\frac{\partial A}{\partial \text{H}} = \frac{(\text{H}^2 + \text{H}A' + B')\,(B - B')}{(\text{H}^2 - B')^2} = 0,\ \text{or}\ B = B' \tag{12}$$

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[5] This calculation is very simple, even for a complex substance. Either the "buffer valve" method of Van Slyke may be used, or the direct formulas presented in this article (section VIII).

Similarly

$$\frac{\partial B}{\partial \mathrm{H}} = \frac{(\mathrm{H}^2 + \mathrm{H}A' + B')\,(A' - A)}{(2\mathrm{H} + A')^2} = 0, \text{ or } A = A' \tag{13}$$

This gives us Equations 4 and 5, and proves that Equations 4 to 7 are correct.

**IV. Unsymmetrical Divalent Acids.**—E. Q. Adams[6] (using different notation) stated in 1916 that for an unsymmetrical acid

$$K_1 = K_0^{\mathrm{I}} + K_0^{\mathrm{II}} \quad \text{and} \quad K_2 \leqq \frac{K_0^{\mathrm{I}}\,K_0^{\mathrm{II}}}{K_0^{\mathrm{I}} + K_0^{\mathrm{II}}} \tag{14}$$

where $K_0^{\mathrm{I}}$ and $K_0^{\mathrm{II}}$ are intrinsic constants of the individual groups.

Multiple ionization involves electrostatic work and work in distortion of the molecules. If $L_1$ and $L_2$ are functions of this work in the first and second steps, respectively, we may show[7] that (disregarding activity correction)

$$K_1 = (K_0^{\mathrm{I}} + K_0^{\mathrm{II}})\,L_1 \quad \text{and} \quad K_2 = \left(\frac{K_0^{\mathrm{I}}\,K_0^{\mathrm{II}}}{K_0^{\mathrm{I}} + K_0^{\mathrm{II}}}\right) L_2 \tag{15}$$

Since these work functions are independent of $\mathrm{H}$, $K_1$ and $K_2$ are true constants as defined by Equations 1 and 2. Therefore, Equations 3, 4 and 5 apply also to unsymmetrical acids.

In the special case of a divalent acid having very distant groups, $L_1$ and $L_2$ would each equal unity; then $K_0^{\mathrm{I}}$ would equal $G_1$ and $K_0^{\mathrm{II}}$ would equal $G_2$. Otherwise there is no simple relation.

**V. Polyvalent Acids.**—The reasoning in Sections III and IV may be used to show that if the titration data of a trivalent acid be calculated as if there were three monovalent acids present in equivalent quantities, we will obtain three titration constants $G_1,'$ $G_2'$ and $G_3'$ which are related to the dissociation constants as follows,

$$K_1' = G_1' + G_2' + G_3' = \Sigma\, G' \tag{16}$$

$$K_1'K_2' = G_1'G_2' + G_1'G_3' + G_2'G_3' = \Sigma\, G'G' \tag{17}$$

$$K_1'K_2'K_3' = G_1'G_2'G_3' = \Sigma\, G'G'G' \tag{18}$$

where $K_2'$ = Equation 17 divided by 16
and $K_3'$ = Equation 18 divided by 17, or

$$\frac{1}{K_3'} = \frac{1}{G_1'} + \frac{1}{G_2'} + \frac{1}{G_3'} = \Sigma\,\frac{1}{G'}, \tag{19}$$

Similarly, for higher polyvalent acids.

When the constants are very different in value (for example, when $K_1' > 1000\,K_2'$; when $K_2' > 1000\,K_3'$; etc.) these equations become

$$K_1' = G_1';\; K_2' = G_2';\; K_3' = G_3';\; \text{etc.} \tag{20}$$

or, in general, "isolated" titration constants are equal to the corresponding dissociation constants.

**VI. Bases and Ampholytes.**—On the addition of alkali, a weak acid

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[6] Adams, This Journal, 38, 1503 (1916).

[7] These equations, and also Equations 24 to 26 are simplified from some which will be derived in the second paper.

ionizes, while the salt of a base hydrolyzes. There is nothing in the titration data to distinguish one from the other[8] (aside from the effect of altering the ionic strength or the dielectric constant). Hence, *the above formulas for polyvalent acids apply also to bases and ampholytes.* For the ionization of a monovalent acid, or an acid group in a polyvalent substance we may write

$$K_0L = \mathrm{H}^+\frac{\mathrm{A}^-}{\mathrm{HA}}\left(\frac{f_1}{f_0}\right) \tag{21}$$

and for the hydrolysis of the salt of a monovalent base or an amino group in a polyvalent substance

$$K_0L = \mathrm{H}^+\frac{\mathrm{R{\cdot}NH_2}}{\mathrm{R{\cdot}NH_3^+}}\left(\frac{f_1}{f_0}\right) \tag{22}$$

We may define "dissociation" as referring to either process, since a hydrogen ion is removed in passing from a low $P_\mathrm{H}$ value to a high $P_\mathrm{H}$ value, in either case, or

$$K_0L\left(\frac{f_0}{f_1}\right) = \mathrm{H}^+\,\frac{\mathrm{n}}{\mathrm{p}} \tag{23}$$

where $K_0$ is the intrinsic constant of the group, $L$ is a function of electrostatic work between groups (see subsequent article), $(f_0/f_1)$ is the ratio of activity coefficients of the more *positive* ionic form $p$ (predominating at a lower $P_\mathrm{H}$ value) and of the more *negative* form $n$ (predominating at a higher $P_\mathrm{H}$ value).

The dissociation (and titration) constants of a polyvalent substance *do not* correspond to individual chemical groups (except when widely different numerically) although some one group predominates in determining the value of each constant and the number of these constants equals the number of groups. We may write for a trivalent acid, base, or ampholyte (compare with Equations 16, 17 and 18

$$K_1' = K_0^{\mathrm{I}}\,L^{\mathrm{I}}\left(\frac{f_0}{f_1}\right)^{\mathrm{I}} + K_0^{\mathrm{II}}\,L^{\mathrm{II}}\left(\frac{f_0}{f_1}\right)^{\mathrm{II}} + K_0^{\mathrm{III}}\,L^{\mathrm{III}}\left(\frac{f_0}{f_1}\right)^{\mathrm{III}} \tag{24}$$

$$K_1'K_2' = K_0^{\mathrm{I}}K_0^{\mathrm{II}}L^{\mathrm{I\,II}}\left(\frac{f_0}{f_2}\right)^{\mathrm{I\,II}} + K_0^{\mathrm{I}}K_0^{\mathrm{III}}L^{\mathrm{I\,III}}\left(\frac{f_0}{f_2}\right)^{\mathrm{I\,III}} + K_0^{\mathrm{II}}K_0^{\mathrm{III}}L^{\mathrm{II\,III}}\left(\frac{f_0}{f_2}\right)^{\mathrm{II\,III}} \tag{25}$$

$$K_1'K_2'K_3' = K_0^{\mathrm{I}}\,K_0^{\mathrm{II}}\,K_0^{\mathrm{III}}\,L^{\mathrm{I\,II\,III}}\left(\frac{f_0}{f_3}\right)^{\mathrm{I\,II\,III}} \tag{26}$$

where $K_2'$ equals Equation 25 divided by Equation 24 and $K_3'$ equals Equation 26 divided by 25; $\left(\frac{f_0}{f_1}\right)$, $\left(\frac{f_0}{f_2}\right)$ and $\left(\frac{f_0}{f_3}\right)$ are the activity coefficient ratios between initial and final states when one, two or three groups have "dissociated." The groups are indicated by Roman numerals. The values of $L$ involve electrostatic work between groups.

It is advisable to designate the constants of a polyvalent substance in order of numerical value, regardless of the group which predominates in

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[8] Bjerrum, *Z. physik. Chem.*, **104**, 147 (1923).

determining each value; thus, $G_1' > G_2' > G_3'$, etc. and $K_1' > K_2' > K_3'$, etc.

**VII. Correction for Inter-ionic Attraction.**—For a monovalent acid, or an acid *group*, we may write

$$\left(\frac{f_0}{f_1}\right) = \tau \tag{27a}$$

and for a monovalent base or a basic *group*,

$$\left(\frac{f_0}{f_1}\right) = \frac{1}{\tau} \tag{27b}$$

where $\tau$ represents the activity-coefficient ratio for a single step in *ionization* and may be estimated by the approximate equation,[9]

$$\log \tau = E\sqrt{\Sigma i\nu^z} = 0.30\sqrt{\Sigma i\nu^z} \tag{28a}$$

where $E$ is a constant (equal to about 0.30 at 25° and dielectric constant of 80) and $\Sigma i\nu^z$ is the sum of all the ion concentrations, each multiplied by the $z$ power of its valence.[10]

For the hydrogen ion, $E$ is more nearly equal to 0.20:

$$\log \tau_{\mathrm{H}} = \log \frac{h}{\mathrm{H}} = 0.20\sqrt{\Sigma i\nu^z} \tag{28b}$$

If we consider a polyvalent acid (or a polyvalent base), we may assume that the activity coefficient ratios $(f_0/f_1)$ are all equal to each other and equal to $\tau$ (or to $1/\tau$) in Equation 24. Then, if we assume $(f_0/f_2) = \tau^2$ (or $1/\tau^2$) and $(f_0/f_3) = \tau^3$ (or $1/\tau^3$), we may write for a given dissociation constant and titration constant

$$K' = K\tau \text{ and } G' = G\tau \text{ for a polyvalent acid} \tag{29a}$$

$$K' = K/\tau \text{ and } G' = G/\tau \text{ for a polyvalent base} \tag{29b}$$

where $K$ is the corrected constant and $G$ is defined by these equations. If we substitute Equation 29 in Equations 24 to 26 or in 5 and 6 and 16 to 19 we find that the $\tau$ values cancel out. Hence in these equations $G$ may be substituted for $G'$ and $K$ for $K'$, for polyvalent acids or bases—*but not for ampholytes*. Equations 4 and 18 are the only ones which apply to the corrected constants in ampholytes.

The logarithmic form of the mass-action equation for a titration constant is

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[9] Brönsted and LaMer, THIS JOURNAL, **46**, 555 (1924). Debye and Hückel, *Physik. Z.*, **24**, 185 (1923). Noyes, THIS JOURNAL, **46**, 1080, 1098 (1924).

[10] When the charged groups in a polyvalent ion are very close together in space, we may multiply its concentration by the *square* of its valence (thus: $i\nu^2$) but when the groups are very far apart the concentration should be multiplied by the *first power* of its valence (thus: $i\nu$). The true value of $\log \tau$ for a solution containing a polyvalent ion, may be obtained by using for that ion, a value equal to $i\nu^z$ where $z$ is a value between 1 and 2 and is dependent upon the concentration and the distance between the groups. There is no direct mathematical relation between the value of $z$ and the concentration and distance, although an empirical relation might be found. In Table I, $z = 1$.

$\Sigma i\nu^2$ equals *twice* the "ionic strength" as defined by Lewis.

$$P_{G'} = P_{\mathrm{H}} - \log \frac{\alpha}{1-\alpha} \tag{30}$$

Hence, from Equation 29:

$$P_G = P_{\mathrm{H}} - \log \frac{\alpha}{1-\alpha} \pm \log \tau = P_{G'} \pm \log \tau \tag{31}$$

where the ± sign is positive for an acid and negative for a base. Log $\tau$ has the value given in Equation 28a. This equation may be applied to polyvalent acids and polyvalent bases, but only to those ampholytes which have constants widely different in value. An ampholyte is considered as an acid above the iso-electric point and as a base below, regardless of the intrinsic constants of the individual groups.

**VIII. Calculation of Constants from Titration Data.**—For electrical neutrality in a solution of a polyvalent acid, base or ampholyte

$$h + b + yc = a + oh + \alpha_1 c + \alpha_2 c + \alpha_3 c + \text{etc.} \tag{32}$$

Hence,

$$b' + y = \alpha_1 + \alpha_2 + \alpha_3 + \text{etc.} = \Sigma\,\alpha \tag{33}$$

where

$$b' = \frac{b - a + h - oh}{c} \tag{34}$$

is the "corrected equivalents of base." In the last equation the activities of the hydrogen and hydroxyl ions may be used in place of their concentration, with a small error.

$$b' = \frac{b-a}{c} + \frac{\mathrm{H} - \mathrm{OH}}{c}\ \text{(approx.)} \tag{35}$$

By means of Equations 9, 33, 34, 30, 31 and 28 we may calculate the titration constants of any polyvalent acid base or ampholyte; and these may be converted into the dissociation constants by Equations 5 and 6 or 16 to 20. The complete procedure is as follows.

*First.*—Plot the experimental values of $P_{\mathrm{H}}$ against $b_1'$ (Equation 34) and estimate graphically (with a paper mold cut the shape of a typical monovalent dissociation curve; Equation 9) the approximate $P_{G'}$ values.

*Second.*—At each $P_{\mathrm{H}}$ within the buffer range of a given $P_{G'}$, calculate (with Equation 9), the $\alpha$ values corresponding to all the other (approximate) $P_{G'}$ values.

*Third.*—By subtracting these from $b' + y$ (Equation 33) find the $\alpha$ value of the $P_{G'}$ in question.

*Fourth.*—Equation 30 gives the $P_{G'}$ value.

*Fifth.*—To correct for activity use Equations 31 and 28a.

*Sixth.*—To find the dissociation constants, use Equations 5 and 6 or 16 to 20, or better still (for a divalent acid), by the following logarithmic forms of Equations 5 and 6:

$$P_{K'_1} = P_{G_1'} - \log\left(1 + \frac{G_2'}{G_1'}\right) \tag{36}$$

$$P_{K_2'} = P_{G_2'} + \log\left(1 + \frac{G_2'}{G_1'}\right) \tag{37}$$

In Fig. 2 the values of log $[1 + (G_2'/G_1')]$ may be found for known values of log $K_1'/K_2'$ or log $G_1'/G_2'$. Remember that these equations apply also to the corrected constants ($K$ and $G$) of acids and of bases—but not of ampholytes.

*Seventh.*—Correct for activity Equations 31 and 28a, if the correction was not made on the titration constant (fifth step).

In the second and fourth steps the relation between a $P_G$ value and an $\alpha$ value (at a given $P$H value) can be most readily found by a chart in which $P\text{H} - P_{G'}$ is plotted against $\alpha$ (Equation 30).

This method of calculation of titration constants is illustrated in the case of malonic acid. See Table I and Fig. 1. The concentration was constant throughout and the $P$H measurements were made in a water-jacketed hydrogen electrode.[11] This method has been used by the author on various other substances.[12]

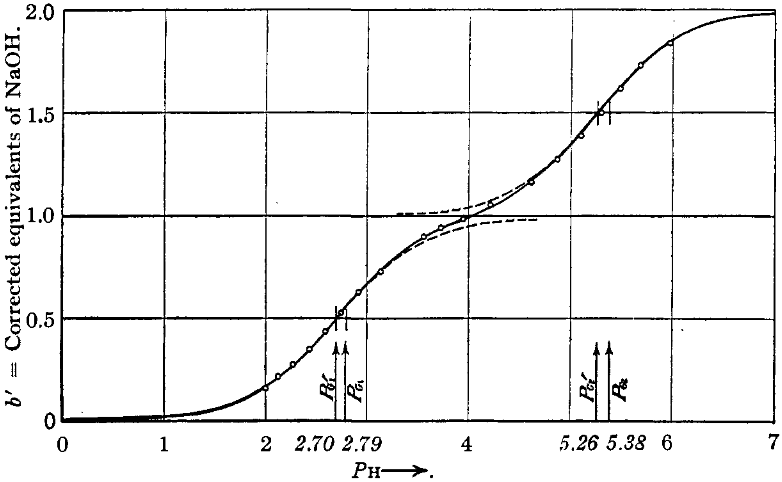

Fig. 1.—Titration curve of malonic acid at 25°.

See Table II and Fig. 2 for relative values of dissociation constants and titration constants.

**IX. Other Formulas.**—The following formulas are presented for convenience.

*The hydrogen-ion activity* of a solution of any divalent acid is (from Equations 9 and 32);[13]

$$\text{H} = Q\left(\sqrt{1 + G_1\frac{c + \alpha_2 c - (b - a)}{Q^2}} - 1\right) \qquad (38)$$

$$\text{where } Q = \frac{G_1}{2} + \frac{b - a - \alpha_2 c}{2\tau_{\text{H}}} = \text{(approximately) } \frac{G_1 + b - a - \alpha_2 c}{2}$$

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[11] Simms, This Journal, **45,** 2503 (1923).

[12] (a) Levene, Simms and Pfaltz, *J. Biol. Chem.*, **61**, 445 (1924). (b) Levene and Simms, *ibid.*, **63,** 351 (1925); **65**, (c) 31, (d) 519 (1925).

[13] The value of *oh* in Equation 32 is neglected here.

## TABLE I

### TITRATION OF MALONIC ACID AT 25°

**Each solution was 0.0440 *M* with respect to malonic acid, and contained an amount of sodium hydroxide indicated in Col. 2.**
**Standard: 0.100 *M* HCl equals $P_H$ 1.090; saturated potassium chloride junction assumed constant.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Step |  |  |  |  |  |  |  | II | III | IV | V | II | III | IV | V |
| Equations |  | 29b | 29a | 29b |  |  | 31 | 9 | 31 | 27 | 28–9 | 9 | 31 | 27 | 28–9 |
| $P_H$ | $\frac{b}{c}$ | $\log \tau_H = 0.20\sqrt{\Sigma i v^z}$ | $\log \tau = 0.30\sqrt{\Sigma i v^z}$ | $P_H$ | $h \times 10^5$ | $\frac{h}{c}$ | $b' = \frac{b}{c} + \frac{h}{c}$ | $(\alpha_2) = \frac{(G_2')}{H + (G_2')}$ | $\alpha_1 = b' - (\alpha_2)$ | $P_{G_1}'$ | $P_{G_1}$ | $\alpha_1 = \frac{G_1'}{H + G_1'}$ | $\alpha_2 = b' - \alpha_1$ | $P_{G_2}'$ | $P_{G_2}$ |
| 2.01 | −0.076 | 0.06 | 0.09 | 1.98 | 1050 | 0.240 | 0.164 | 0.001 | 0.163 | 2.72 | 2.81 |  |  |  |  |
| 2.13 | +0.038 | .06 | .09 | 2.10 | 794 | .180 | .218 | .001 | .217 | 2.68 | 2.77 |  |  |  |  |
| 2.28 | .150 | .06 | .09 | 2.25 | 563 | .128 | .278 | .001 | .277 | 2.70 | 2.79 |  |  |  |  |
| 2.44 | .264 | .06 | .09 | 2.41 | 390 | .088 | .352 | .001 | .351 | 2.71 | 2.80 |  |  |  |  |
| 2.59 | .377 | .06 | .09 | 2.56 | 275 | .062 | .439 | .002 | .437 | 2.70 | 2.79 |  |  |  |  |
| 2.75 | .490 | .06 | .09 | 2.72 | 191 | .043 | .533 | .003 | .530 | 2.70 | 2.79 |  |  |  |  |
| 2.92 | .604 | .06 | .09 | 2.89 | 129 | .029 | .633 | .004 | .629 | 2.69 | 2.78 |  |  |  |  |
| 3.14 | .716 | .06 | .09 | 3.11 | 78 | .018 | .734 | .009 | .725 | 2.72 | 2.81 |  |  |  |  |
| 3.56 | .898 | .06 | .09 | 3.53 | 30 | .007 | .905 | .018 | .887 | 2.67 | 2.76 |  |  |  |  |
| 3.73 | .943 | .06 | .09 | 3.70 | 20 | .005 | .948 | .026 | .922 | (2.66) | (2.75) |  |  |  |  |
| 3.95 | .988 | .06 | .09 | 3.92 | 12 | .003 | .991 | .042 | .949 | (2.67) | (2.76) |  |  |  |  |
| 4.21 | 1.056 | .06 | .10 | 4.18 | 7 | .002 | 1.058 |  |  |  |  | 0.970 | 0.088 | (5.22) |  |
| 4.61 | 1.169 | .06 | .10 | 5.58 | 3 | .001 | 1.170 |  |  |  |  | .987 | .183 | 5.26 | 5.36 |
| 4.87 | 1.282 | .07 | .11 |  |  |  | 1.282 |  |  |  |  | .993 | .289 | 5.26 | 5.37 |
| 5.10 | 1.395 |  | .12 |  |  |  | 1.395 |  |  |  |  | .995 | .400 | 5.28 | 5.40 |
| 5.30 | 1.508 |  | .12 |  |  |  | 1.508 |  |  |  |  | .997 | .511 | 5.28 | 5.40 |
| 5.49 | 1.623 |  | .12 |  |  |  | 1.623 |  |  |  |  | .998 | .625 | 5.27 | 5.39 |
| 5.69 | 1.735 |  | .14 |  |  |  | 1.735 |  |  |  |  | .999 | .736 | 5.25 | 5.37 |
| 5.98 | 1.843 |  | .13 |  |  |  | 1.843 |  |  |  |  | .999 | .844 | 5.25 | 5.38 |
|  |  |  |  |  | Average $P_G$ values |  |  |  |  | 2.70 | 2.79 |  |  | 5.26 | 5.38 |
|  |  |  |  |  | $G \times 10^5$ |  |  |  |  |  | 162 |  |  |  | 0.42 |
|  |  |  |  |  | Corresponding $P_K$ values |  |  |  |  |  | 2.79 |  |  |  | 5.38 |

In this case the $K$ constants are equal to the $G$ constants, within experimental error (Equations 34–35).

The approximate value of $P_{G_2}'$ (found graphically in Step II) and used in Col. 9 was 5.30. The value (2.70) of $P_{G_1}'$, found in Col. 11 was used in Col. 13.

In Cols. 3 and 4, we have taken $z = 1$. See Ref. 10.

The value of $\alpha_2$ is obtained from approximate values of $\mathrm{H}$ (Equation 3).

For a monovalent acid, $\alpha_2 = 0$. For a trivalent acid, substitute $(\alpha_2 + \alpha_3)$ for $\alpha_2$. For a pure solution of acid, $b - a = 0$. When $b - a > 1$, interchange Subscripts 1 and 2.

For a base or ampholyte, substitute $(yc + b - a)$ for $(b - a)$.

*The concentration of base* required to bring a polyvalent substance to a given $P_{\mathrm{H}}$ value is

$$b - a = c\,(\alpha_1 + \alpha_2 + \alpha_3 + \text{etc.}) - h + oh - yc \qquad (39)$$

If we have an impure substance or a solution of unknown concentration it is necessary to calculate the value of $c$. *The concentration of* a polyvalent *substance* is

$$c = \frac{b - a + h - oh}{\alpha_1 + \alpha_2 + \alpha_3 + \text{etc.} - y} \qquad (40)$$

If the $G'$ values are unknown we cannot calculate the $\alpha$ values. However, for a *monobasic acid* (or a group sufficiently isolated to act like a monobasic acid), we may take values of $\mathrm{H}$ and of $b$ at two points.

$$c = \frac{b_1''b_2''\,(\mathrm{H}_1 - \mathrm{H}_2)}{\mathrm{H}_1 b_1'' - \mathrm{H}_2 b_2''} \qquad \text{where } b'' = (b - a + h - oh) \qquad (41)$$

or if $\bar{b}_1''$ and $\bar{b}_2''$ are moles of alkali (determined volumetrically) required to complete the titration at two points,

$$c = \frac{\bar{b}_1''\,\bar{b}_2''\,(\mathrm{H}_1 - \mathrm{H}_2)}{\mathrm{H}_1\bar{b}_2'' - \mathrm{H}_2\bar{b}_1''} \qquad \text{where } \bar{b}'' = 1 - (b - a + h - oh) \qquad (42)$$

*The iso-electric point* of a simple (mono-monovalent) ampholyte (if we define it as the point of equal concentrations of the ionized acidic and basic groups) is

$$\mathrm{H} = I = \sqrt{G_1'G_2'} = \sqrt{K_1'K_2'} \qquad (43)$$

For a polyvalent ampholyte having $y$ amino groups,

$$\mathrm{H} = I = \sqrt{K_y \cdot K_{y+1}} \text{ (approximately)} \qquad (44)$$

The exact expression in an ampholyte with two acid groups and two amino groups is

$$\mathrm{H} = I = \sqrt{K_2'K_3' + \frac{2K_2'K_3'K_4'}{\mathrm{H}} - \frac{2\mathrm{H}^3}{K_1'}} \qquad (45)$$

where the second term on the right-hand side is negligible when $K_4'$ is very small, and the last term is negligible when $K_1'$ is very large. For the values of $\mathrm{H}$ on the right-hand side we may substitute, approximately, $\sqrt{K_2'K_3'}$.

$$\mathrm{H} = I = \sqrt{K_2'K_3' + 2\sqrt{K_2'K_3'}\left(K_4' - \frac{K_2'K_3'}{K_1'}\right)} \qquad (46)$$

The expressions involving the titration constants are more complicated.[14]

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[14] See Levene and Simms [*J. Biol. Chem.*, **55**, 801 (1923)], Equation 15a. Since the notation in that article is different, we must substitute: $G_1' = k_{b_1}$; $G_2' = k_{b_2}$; $G_3' = Ka_1$; and $G_4' = Ka_2$.

The "*Buffer Value*" *method* of Van Slyke, for determining titration constants is advantageous for certain complex substances. By using Equations 32 and 9, and differentiating, we get for the "buffer value" of any substance at any $P_{\text{H}}$ value:

$$\beta = \frac{db}{dP_{\text{H}}} = 2.3\ \text{H}c\left[\frac{G_1'}{(\text{H} + G_1')^2} + \frac{G_2'}{(\text{H} + G_2')^2} + \text{etc.}\right] + 2.3\ (h + oh) \qquad (47)$$

when $P_{\text{H}} = P_{G_1}'$, we get

$$\frac{2.3\ \text{H}c_{G_1}'}{(\text{H} + G_1')^2} = \frac{2.3\,c}{4} = 0.575\,c \qquad (48)$$

This method is described by van Slyke[15] and by Hastings and van Slyke.[16] $\beta$ is the slope of the curve when $b$ is plotted against $P_{\text{H}}$.

As a modification, we may define the "corrected equivalent buffer value" as the slope of the curve when $b'$ (instead of $b$) is plotted against $P_{\text{H}}$:

$$\frac{db'}{dP_{\text{H}}} = \Sigma\beta' = \beta_1' + \beta_2' + \beta_3' + \text{etc.} = \text{(approximately)}\ \frac{b_2' - b_1'}{P_{\text{H}_2} - P_{\text{H}_1}} \qquad (49)$$

where

$$\beta_1' = \frac{2.3\ \text{H}G_1'}{(\text{H} + G_1')^2} = 2.3\ \alpha_1\ (1 - \alpha_1)$$

$$\beta_2' = \frac{2.3\ \text{H}G_2'}{(\text{H} + G_2')} = 2.3\ \alpha_2\ (1 - \alpha_2) \qquad (50)$$

and $b_1'$, $P_{\text{H}_1}$, $b_2'$ and $P_{\text{H}_2}$ are values at two points near each other.

These equations may be used in a manner similar to that described for 33 and 30. The easiest way to find a $G'$ value, when the corresponding $\beta'$ value has been calculated, is from a chart in which $\beta'$ is plotted against $P_{\text{H}} - P_{G'}$ (from arbitrary values of $\alpha$, equation (30) gives $P_{\text{H}} - P_{G'}$, and (50) gives $\beta'$). Equations 28 and 31 may be used to correct for activity of acids or bases, but not of ampholytes. The buffer-value method requires more data and greater accuracy than the direct method (28 to 35) of calculating titration constants.

TABLE II

VALUES OF DISSOCIATION CONSTANTS COMPARED WITH TITRATION CONSTANTS

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| Acid | $P_{K_1}$ | $P_{K_2}$ | $\log K_1/K_2$ | $\log\left(1 + \frac{G_2}{G_1}\right)$ | $P_{G_1}$ | $P_{G_2}$ | $\log G_1/G_2$ |
| Carbonic | 6.36 | 10.22 | 3.86 | 0 | 6.36 | 10.22 | 3.86 |
| Oxalic | 1,42 | 4.35 | 2.93 | 0 | 1.42 | 4.45 | 2.93 |
| Malonic | 2.79 | 5.38 | 2.59 | 0 | 2.79 | 5.38 | 2.59 |
| Succinic | 4.20 | 5.62 | 1.42 | 0.02 | 4.22 | 5.60 | 1.38 |
| Glutaric | 4.32 | 5.50 | 1.18 | .03 | 4.35 | 5.47 | 1.12 |
| Adipic | 4.43 | 5.62 | 1.19 | .03 | 4.46 | 5.59 | 1.13 |
| Pimelic | 4.49 | 5.59 | 1.10 | .04 | 4.53 | 5.55 | 1.03 |
| Suberic | 4.52 | 5.55 | 1.03 | .05 | 4.57 | 5.50 | 0.93 |
| Azelaic | 4.60 | 5.56 | 0.96 | .05 | 4.65 | 5.51 | .86 |
| Sebacic | 4.62 | 5.60 | .98 | .05 | 4.67 | 5.55 | .88 |

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[15] van Slyke, *J. Biol. Chem.*, **52**, 525 (1922).

[16] Hastings, A. B., and van Slyke, *ibid.*, **53**, 269 (1922).

## X. Summary

The electrometric titration data of *any* polyvalent acid, base or ampholyte (whether "symmetrical" or not) may be calculated (by Equations 28 to 35 or 47 to 50) as if it were an equivalent mixture of monovalent acids. (See Table I and Fig. 1 for malonic acid.)

The "titration" constants ($G'$), thus obtained, are nearly (but not exactly) equal to the classical "dissociation" constants ($K'$) to which they are related by simple formulas 4 to 7, 16 to 20 and 36 and 37. (See Table II and Fig. 2.) The corresponding ($G$ and $K$) constants (corrected for activity of the ions) are related to each other by the same formulas—for polyvalent acids and bases—but not for ampholytes (except in very dilute ion concentration).

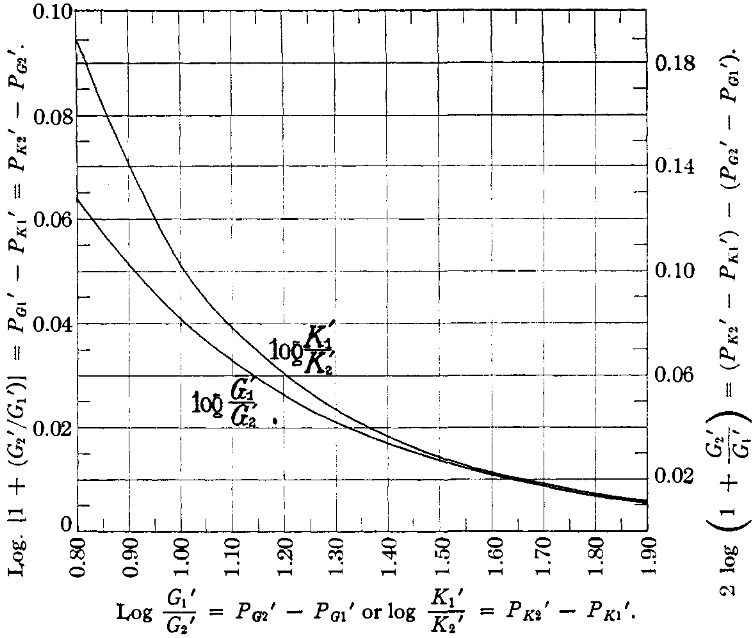

Fig. 2.—Plot for finding $\log \left(1 + \frac{G_2'}{G_1'}\right)$.

This gives a method of calculating dissociation constants which is easy, accurate and general in application.

Formulas are also given for calculating the concentration of base (39) or of substance (40–42); the hydrogen-ion activity (38); and iso-electric points (43–46).

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