

Potentiometric Determination of Overlapping Dissociation Constants

PAUL J. NIEBERGALL[▲], ROGER L. SCHNAARE, and EDWIN T. SUGITA

Abstract □ The dissociation constants of polyprotic acids can be determined potentiometrically by defining a variable, P , as the average number of protons dissociated. The proton balance equation for the titration of these acids with base led to a general expression which could be solved graphically or through the use of linear regression or nonlinear regression analysis. Experimental data for a number of acids and for a series of simulated titration curves were analyzed using the three methods. The graphical solution was found to be applicable in all instances. As the ratio of K_1 to K_2 for diprotic acids increased from 50 to 1000, the value of K_2 estimated by the use of linear regression became progressively worse and finally could not be determined at all. In all instances, the value of K_1 was determined to within a relative error of 0.5%. In all instances in which nonlinear regression analysis was used, the values for K_1 were determined to within 0.3% and those for K_2 were determined to within 0.02%. This technique requires an initial estimate of each constant. These initial estimates are then refined in an iterative procedure until satisfactory convergence is obtained. The digital computer program used in this work is unique in that initial estimates are obtained within the computer program itself. The program also determines the total number of dissociable protons. This latter property can be extremely useful for compounds with an unknown number of acidic sites.

Keyphrases □ Polyprotic acids—potentiometric determination of overlapping dissociation constants, computer estimation of initial constants □ Dissociation constants, overlapping, of polyprotic acids—potentiometric determination, computer estimation of initial constants □ Potentiometry—determination of overlapping dissociation constants for polyprotic acids, computer estimation of initial constants □ Computer estimation of initial dissociation constants—used in potentiometric determination of overlapping dissociation constants for polyprotic acids

Determination of the thermodynamic dissociation constants for polyprotic acids is quite complicated, particularly if the ratio of the successive dissociation constants is less than 1000. One major difficulty is the estimation of individual ion activity coefficients; because of this, most of the data appearing in the literature have been obtained by extrapolating to infinite dilution the dissociation constants obtained in media of known ionic strength. This procedure, however, can lead to erroneous results for the second and successive dissociation constants (1).

Speakman (2) developed an equation which permitted a simple graphical solution for the thermodynamic dissociation constants of diprotic acids and which obviated the need for extrapolation to infinite dilution. It was suggested (2) that the equation would be useful for triprotic and higher order acids if conditions could be chosen such that only two successive dissociation constants would be operative at one time. In many instances, this is not possible. For example, the ratios of K_1/K_2 and K_2/K_3 for citric acid were both shown to be approximately 44 at 25° (3). Other investigators (3–5) developed a general procedure based upon electromotive force measurements in cells without liquid junc-

tions. This method yields results with a high degree of accuracy and precision, but it does require the preparation of a relatively large number of precisely made buffer solutions.

Litchinsky *et al.* (1) extended the method of Speakman to cover any polyprotic acid, regardless of whether successive dissociation constants overlap. This method, although it obviates the need for preparing a large number of precisely made buffer solutions, requires the use of a digital computer. It is apparent, however, that these methods (1, 3–5) are the methods of choice for determining the thermodynamic dissociation constants of polyprotic acids.

However, in many instances, thermodynamic dissociation constants must be corrected for both ionic strength and temperature before they can be utilized. Due to the uncertainties in these corrections, many investigators prefer to obtain either an apparent (K') or a concentration-based (K_c) dissociation constant for an acid under the exact conditions of their study. Numerous methods are available for the potentiometric determination of dissociation constants for monoprotic acids and for polyprotic acids whose dissociation constants do not overlap (6, 7). Perhaps the most widely used method for determining practical dissociation constants for polyprotic acids is that of Parke and Davis (8). This method, however, was subjected to a critical evaluation by Garrett (9), who found that it had little advantage over the half-neutralization method for acids whose pKa values ranged from 4 to 10. The purpose of this article is to report the authors' experiences with a general method for the determination of either K' or K_c values for polyprotic acids with overlapping dissociation constants.

EXPERIMENTAL

Reagents—The following were used: succinic acid¹, citric acid², glycine hydrochloride³ (m.p. 182°), potassium chloride (reagent grade), and carbonate-free potassium hydroxide (0.0997 *N*).

Equipment—The acids were titrated using a 1-ml. microburet⁴ calibrated to 0.0002 ml. The pH measurements were made with a digital readout pH meter⁵ standardized against 0.05 *M* potassium hydrogen phthalate (pH 4.01) and 0.1 *M* borate (pH 9.00).

Method—Dilute solutions of the acids to be titrated (about 1.00×10^{-3} *M*) were made in distilled, deionized water which had been degassed by boiling for 30 min. Sixty milliliters of the solutions, adjusted to an ionic strength of 0.1 with potassium chloride, was placed in a thermostated vessel ($30 \pm 0.05^\circ$), and nitrogen was bubbled through the solution. Small increments of base were added, and the pH was noted after each addition.

¹ Certified 99.9%, Fisher Scientific Co.

² Reagent grade, J. T. Baker Chemical Co.

³ Nutritional Biochemical Co.

⁴ Manostat Digi-Pet.

⁵ Orion model 801.

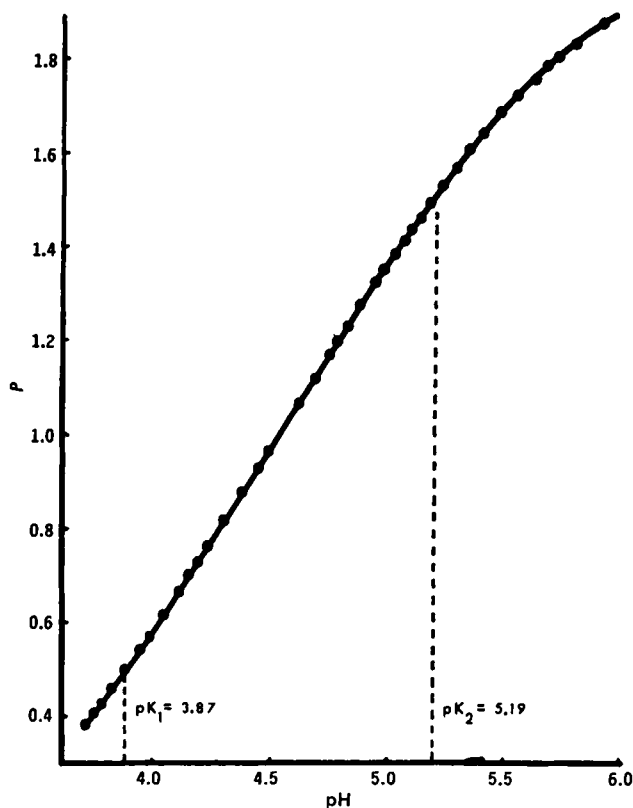


Figure 1—Plot of P versus pH for succinic acid.

THEORETICAL

The dissociation constants for a polyprotic acid, H_nA , in which n represents the total number of dissociable protons, can be determined potentiometrically by defining a variable P as the average number of protons dissociated or:

$$P = \frac{\sum_{j=1}^n j[H_{n-j}A^{-j}]}{C_a} \quad (\text{Eq. 1})$$

in which j is the number of protons dissociated and C_a is the stoichiometric concentration of acid.

The proton balance equation for the acid when titrated with base is:

$$B + [H_3O^+] = [OH^-] + \sum_{j=1}^n j[H_{n-j}A^{-j}] \quad (\text{Eq. 2})$$

or:

$$Z = \sum_{j=1}^n j[H_{n-j}A^{-j}] = B + [H_3O^+] - [OH^-] \quad (\text{Eq. 3})$$

in which B is the total concentration of base added. Inserting Eq. 3 into Eq. 1 gives:

$$P = Z/C_a \quad (\text{Eq. 4})$$

which enables the experimental value for P to be determined at each data point. The concentration of all species derived from the acid, H_nA , as given by Eq. 1, can be defined solely in terms of hydronium concentration and dissociation constants, using the method described by Niebergall (10), to give:

$$P = \frac{\sum_{j=1}^n j \left([H_3O^+]^{n-j} \prod_{m=1}^j K_m \right)}{[H_3O^+]^n + \sum_{j=1}^n \left([H_3O^+]^{n-j} \prod_{m=1}^j K_m \right)} \quad (\text{Eq. 5})$$

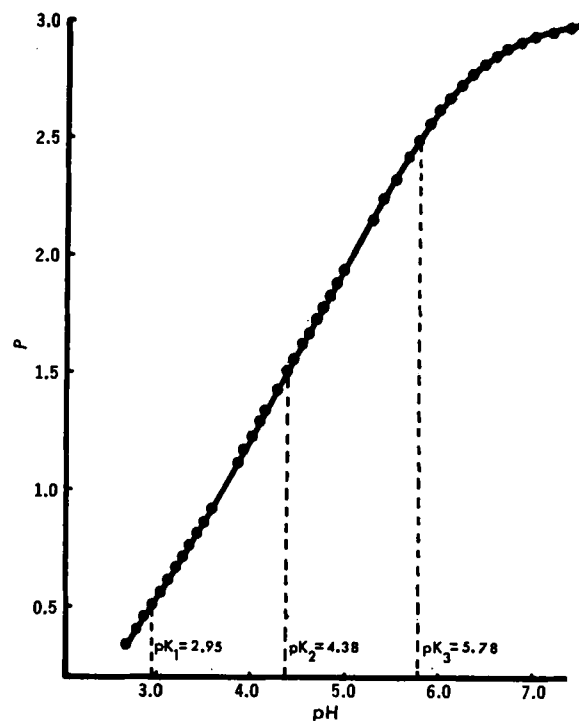


Figure 2—Plot of P versus pH for citric acid.

in which K_m represents the acid dissociation constants.

In the case of a diprotic acid, Eq. 5 becomes:

$$P = \frac{K_1[H_3O^+] + 2K_1K_2}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (\text{Eq. 6})$$

which can be rearranged to:

$$\frac{[H_3O^+]^2 P}{(2-P)} = K_1K_2 + \frac{K_1[H_3O^+](1-P)}{(2-P)} \quad (\text{Eq. 7})$$

which can be analyzed using the usual methods of linear regression analysis. Equation 7 is equivalent to the linear equation used by Speakman (2), with the ordinate and abscissa values being the same for both. One advantage of using the variable P rather than the variables given by Speakman is that rather good approximate values for the dissociation constants can be obtained from a plot of P versus pH , in a manner similar to the Bjerrum (11) half \bar{n} method for obtaining association constants. The value of pK_j is equal to the pH at which $P = j - 0.5$.

Equation 5 can be analyzed directly using the techniques of non-linear regression analysis. The general method and digital computer

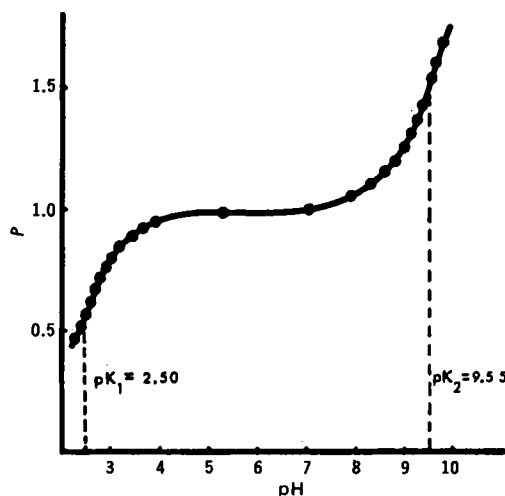


Figure 3—Plot of P versus pH for glycine hydrochloride.

Table I—pK Values Obtained at 30° and Ionic Strength 0.1

Constant	P Plots	Eq. 7	Eq. 5	Literature ^a
Citric Acid				
pK ₁	2.95	—	3.023	2.993
pK ₂	4.38	—	4.395	4.386
pK ₃	5.78	—	5.750	5.791
Succinic Acid				
pK ₁	3.87	3.952	3.956	3.953
pK ₂	5.19	5.116	5.117	5.151
Glycine Hydrochloride				
pK ₁	2.50	2.131	2.512	2.432
pK ₂	9.55	5.192 ^b	9.558	9.532

^a Corrected to ionic strength 0.1. L. G. Sillen and A. E. Martell, "Stability Constants," Metcalfe and Cooper, Ltd., London, England, 1964. ^b Deemed not significantly different from zero at the 95% confidence level using the *t* test.

program utilized to analyze the data presented in this report were given in detail by Niebergall *et al.* (12). Briefly, the method consists of taking the partial derivatives of Eq. 5 with respect to each dissociation constant and evaluating each derivative at each data point, using the experimental variables *P* and [H₃O⁺] and initial estimates for each constant. Summing these calculated values in the manner described (12) yields a set of normal equations which can be solved to give correction vectors for each constant. The initial estimates are corrected and the process is repeated until two sets of constants agree to within a specified degree.

RESULTS AND DISCUSSION

Plots of *P* versus pH are shown in Figs. 1, 2, and 3 for succinic acid, citric acid, and glycine hydrochloride, respectively. A plot of Eq. 7 using the data for succinic acid is shown in Fig. 4. The dissociation constants obtained using the *P* plots, Eq. 7, and nonlinear regression analysis of Eq. 5 are given in Table I. In general, there was good agreement between the methods, and the experimentally determined constants were in good agreement with literature values. The value for *K*₂ of glycine hydrochloride obtained using Eq. 7, however, was not significantly different from zero at the 95% confidence level when analyzed using the *t* test, and it was markedly different from the literature value.

To determine whether the problem was with the data or with the analysis of the data and to give a further test for the applicability of Eqs. 5 and 7, the authors decided to simulate titration curves for a number of hypothetical diprotic acids in which *K*₁ was equal to 3.00 × 10⁻³ and *K*₂ was varied to give *K*₁/*K*₂ ratios ranging from 50 to 1000. This was done by combining Eqs. 3, 4, and 6 to give:

$$B + [H_3O^+] - (K_w/[H_3O^+]) = \frac{(K_1[H_3O^+] + 2K_1K_2)C_a}{[H_3O^+]^2 + K_1[H_3O^+] + 2K_1K_2} \quad (\text{Eq. 8})$$

in which *K_w* is the ion product of water. The Newton-Raphson method of successive approximations and the digital computer program described by Niebergall (13) were used to solve for [H₃O⁺] after each hypothetical addition of a small quantity of base. The

Table II—Effect of the Ratio of *K*₁/*K*₂ upon the Suitability of Eq. 7 for Determining *K*₁ and *K*₂

Ratio of <i>K</i> ₁ / <i>K</i> ₂	Percentage Difference between Theoretical and Calculated	
	<i>K</i> ₁	<i>K</i> ₂
50	0.37	3.17
100	0.30	6.07
180	0.20	8.80
250	0.37	14.25
300	0.23	15.68
500	0.27	27.95
1000	0.40	61.73 ^a

^a The value for *K*₂ was found to be not significantly different from zero at the 95% confidence level using the *t* test.

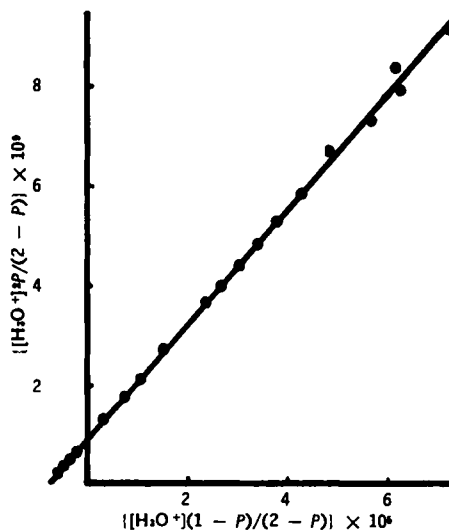


Figure 4—Plot of Eq. 7, using data obtained for succinic acid.

actual concentration of base after each increment was obtained from:

$$B = \frac{(\text{milliliters base})(\text{normality})}{\text{Vol} + (\text{milliliters base})} \quad (\text{Eq. 9})$$

in which Vol represents the initial volume of the solution before any base had been added. The term *C_a* was corrected for volume changes during titration (although these were less than 2%) by:

$$C_a = \frac{(\text{initial concentration of acid})(\text{Vol})}{\text{Vol} + (\text{milliliters base})} \quad (\text{Eq. 10})$$

The utilization of Eqs. 8-10 would give unambiguous data for the titration curves, since no assumptions were made (except for the use of concentrations in the place of activities) and all possible equilibria in solution were considered. Thus, any discrepancy between the constants used to build the simulated titration curves and those obtained by analyzing the data using Eq. 5 or 7 would have to be due to the method of analysis. A small amount of scatter, representing an accuracy of ±0.005 pH unit, was built into the data through the use of a random numbers table. This scatter should result in the dissociation constants being determined to within 0.5% of their true values. Data were generated for 60 ml. of a 0.01 *M* solution of acid being titrated with 0.1-ml. increments of 0.205 *N* base at 30°. The data were analyzed using Eq. 7 (Table II). The values for *K*₁ were determined and agreed well with the theoretical values. The values for *K*₂, however, became progressively worse as the ratio of *K*₁/*K*₂ increased, which was rather surprising. When the ratio reached 1000, the value for *K*₂ was determined to be not significantly different from zero at the 95% confidence level, using the *t* test. Thus, the failure to determine *K*₂ for glycine hydrochloride, in which the ratio of *K*₁/*K*₂ is approximately 10⁷, using the linear plotting technique was due to the technique itself and not to any lack of reliability within the data.

The fact that the estimates of *K*₂ became progressively worse as the ratio of *K*₁/*K*₂ increased appears to be due to the fact that the

Table III—Effect of the Ratio of *K*₁/*K*₂ upon the Suitability of Eq. 6 for Determining *K*₁ and *K*₂

Ratio of <i>K</i> ₁ / <i>K</i> ₂	Percentage Difference between Theoretical and Calculated	
	<i>K</i> ₁	<i>K</i> ₂
50	0.20	0.02
100	0.27	0.03
180	0.21	0.05
250	0.20	0.04
300	0.19	0.03
500	0.27	0.08
1000	0.24	0.07

intercepts, as defined by Eq. 7, became progressively smaller as compared to the ordinate values as this ratio increased. Since excellent linearity was observed in all instances when the data were plotted according to Eq. 7, the experimenter has little basis for deciding whether the values of K_2 obtained in this manner are valid. He can be sure of this only when the ratio of K_1/K_2 approaches 50 or less, and he can be certain that the results are not valid only when K_1/K_2 approaches 1000 and the t test shows K_2 to be not significantly different from zero. Thus it would appear, based on this study, that the use of linear equations equivalent to Eq. 7 should be avoided if reliable estimates of the value of K_2 for diprotic acids are to be obtained.

The same data were analyzed using Eq. 6 and the techniques of nonlinear regression analysis (Table III). In all instances, the agreement between the actual and calculated values for the dissociation constants was excellent. Although the emphasis in this report is directed toward the determination of overlapping dissociation constants for di- and triprotic acids, Eq. 5 is perfectly general and can be used for monoprotic acids as well⁶, and n is not limited to a maximum of three.

Since plots of P versus pH also gave reasonable results for all of the systems studied, including the simulated titration data, it would appear that either these P plots or nonlinear regression analysis should be used for obtaining overlapping dissociation constants for polyprotic acids.

DIGITAL COMPUTER PROGRAM⁷

The utilization of nonlinear regression analysis requires an initial estimate for each dissociation constant which, in this instance, would ordinarily be obtained from plots of P versus pH. However, this

⁶ The dissociation constants for a large number of monoprotic acids were evaluated using the Benet and Goyan (6) linear equation:

$$Z = C_a - \frac{Z[\text{H}_3\text{O}^+]}{K}$$

in which the symbols have the meanings as given in this paper, and the following version of Eq. 5:

$$P = \frac{[\text{H}_3\text{O}^+]}{[\text{H}_3\text{O}^+] + K}$$

In all instances, the sum of squares of residuals (SS) between the experimental and calculated values of P were reduced by at least 95% when the nonlinear regression analysis was used. For example, the SS for sulfisomidine decreased from 3.21×10^{-9} to 0.17×10^{-9} , and the SS for sulfacetamide decreased from 46.0×10^{-9} to 0.04×10^{-9} .

⁷ A copy of the program, along with its documentation, can be obtained by writing the authors.

program is written in such a manner that if care is taken to obtain a number of data points around the addition of 0.5, 1.5, and 2.5 moles of base/mole of acid, good initial estimates will be obtained automatically from the input data as the program is run. The only necessary input data are the stoichiometric concentration and volume of acid, the ion product of water, the normality of the titrant, and the experimental values of pH and volume of base added. In the process of obtaining its own initial estimates from the raw input data, the program also determines the total number of dissociable protons for the acid. Thus, it would be extremely valuable for obtaining dissociation constants for an acid with an unknown number of dissociable protons.

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▲ To whom inquiries should be directed.