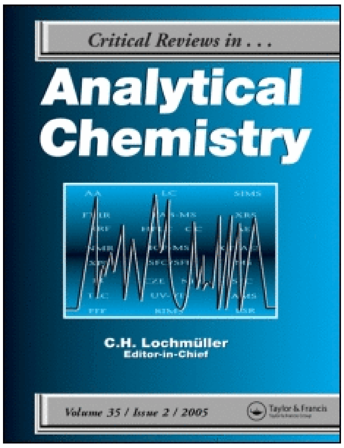

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Buffer Capacity of a Polyprotic Acid: First Derivative of the Buffer Capacity and *pK*<i>a</i> Values of Single and Overlapping Equilibria

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Buffer Capacity of a Polyprotic Acid: First Derivative of the Buffer Capacity and pK_a Values of Single and Overlapping Equilibria

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Buffer capacity appears in a variety of fields, and its approximate calculation is of practical importance for the design of new buffer solutions, being also a quantity related to titrations. The aims of this paper are (i) to devise simple expressions for the buffer capacity and its first derivative for a polyprotic acid, which may be easily extended to a mixture of acids, e.g., universal buffer solutions; (ii) to evaluate overlapping acidity constants ($pK_a's$) for diprotic acids, from the knowledge of the singular points in the buffer capacity curve; and (iii) at the same time to provide a critical overview of the topic, with some twist of novelty. Hyperbolic functions in analytical chemistry have been surveyed. Conditions for the appearance of singular points in the buffer capacity curve for monoprotic acids and diprotic acids with overlapping pK_a values have been established. Methods to evaluate strong and moderate overlapping $pK_a's$ are suggested and applied to literature data. To check the computed values, the acidity constants were also determined by the graphical method of Irving and Rossotti, taken as reference. Results obtained agree well for moderate overlapping $pK_a's$ values, whereas in the case of strong overlapping $pK_a's$ values the agreement is excellent. Limiting K_{a1}/K_{a2} ratio as well as the relation between the acidity constants ratio and the half-values of the formation function, and the problem of distinguishing polyprotic acids from monofunctional ones have been envisaged. An attempt has also been made to derive compact expressions suitable for computer usage for the $V = f(pH)$ derivative curves and buffer capacity curves, taken into account the dilution effects.

Keywords Buffer capacity, polyprotic acids, first and second derivatives, $pK_a's$, overlapping equilibria

INTRODUCTION

Acid-base equilibria and pH calculations (1–5) are very important topics in analytical chemistry and methods and applications based on pH titrations are used in a wide variety of fields (6). Buffer solutions, i.e., have been used since the beginning of the 20th century (7–9); they were termed “tampons”(10) by Fernbach in 1900 and translated to “buffer” for Sorensen who made a careful analysis of the buffering ranges of the borates, citrates, phosphates and glycine (7). The buffer value was introduced by Van Slyke, in 1922, as the amount of strong acid or base necessary to change the solution pH (8) a given quantity. Something later, Kolthoff (9, 10) introduced in 1937 the term of “buffer capacity or “buffer index” as a name for the differential ratio dC_B/dpH.

Buffer capacity appears in varied disciplines (14), including analytical, environmental (15), geo- and biochemistry (16), physiology, pharmacy, i.e., drug solubility (17), medicine, dentistry and agriculture (18). Anything that causes a pH change would affect the pH-sensitive attributes, quality and shelf life of a food (19), being on this way buffers of great worth in food technology (20). Buffer capacity profiles are used in the framework of automatic monitoring of water quality (21). A plot of buffer capacity can be used to find regions of maximal buffering when a mixture of species is present and to estimate the overall amount of acid or base that may be added without changing solution pH (22–24). Buffering power of e.g., amphoteric electrolytes in water solution chemistry of complex mixtures represents in laboratory practice a matter of great importance for many methods of bioorganic substance separations including electrophoresis and several types of chromatography (25–31).

By use of dissociation fractions and formation function (32) incorporated in the equations defining the charge and mass balances, expressions for evaluating the buffer capacity and its first

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derivative curve of a polyprotic acid$H_N R$, are readily derived, as shown in this paper. Attention is also given in this report to the conditions that must be fulfilled in order that the minima, maxima and inflexion points of the graph $\pi = f(pH)$for diprotic acids may be obtained. Though this topic has been thoroughly covered by Ricci (5), the notation employed and the equations derived were cumbersome (33) and difficult to understand and apply. For this reason a different approach is advocated in this article, which can also be regarded as providing a critical survey of the buffer capacity topic, which is closely related to titrations *via* the $\tilde{n}$ secondary concentration variable, known as the formation function.

The position of the central minimum and the two adjacent maxima in the graph of π against pH (inflexion points of the formation function) can be employed to calculate values of the moderate overlapping acidity constants for a diprotic acid. A hyperbolic relationship may be derived that expresses the acidity constants quotient as a function of the position of the singular points in the $\pi - pH$ curve. However, the method to be applied requires graphic differentiation. As a continuous function, π, can be subjected to linear approximation (14). The exactness obtained depends on how closely ΔpH approaches dpH. A number of points very closely spaced and preferably of high precision are needed in order the methods reported may be successively applied. Otherwise, the numerical difference calculation does not necessarily give sufficient accurate singular points. Strong overlapping acidity constants for diprotic acids may be evaluated instead from the maximum in the$\pi = f(pH)$ curve and the slope of the formation function.

Attention has also been paid to the half-points in the formation function in relation to the position of the inflexion points (extremes in the buffer capacity by neglecting dissociation of water). In addition, an attempt has been made to derive compact expressions suitable for computer usage for the $V = f\,(pH)$derivative curves and buffer capacity curves, taken into account the dilution effects.

The simple titration reaction, as stated by previous authors (34, 35) may be expressed in terms of inverse hyperbolic or trigonometric functions. Table 1 summarizes the application of hyperbolic functions in potentiometric titration procedures. Hyperbolic functions have found uses in separation, electrical, optical or kinetic methods (Table 2). This paper is enclosed in a systematic investigation on the use of hyperbolic functions in parameter estimation (81–83).

GENERAL EXPRESSION FOR THE BUFFER CAPACITY AND ITS FIRST DERIVATIVE

The molar fraction of the jth species (i.e., the partition of any given acid-base species among its different$N+1$ forms) and the function of formation (97–100) $\tilde{n}$ (i.e., the average number of bound protons per acid anion) of a polyprotic acid are given by

$$f_j = \frac{[H_jR]}{C_R} = \frac{\beta_j[H]^j}{\sum \beta_j[H]^j} = f_0\beta_j[H]^j \qquad [1]$$

and

$$\tilde{n} = \frac{1}{C_R}\sum j[H_jR] = \sum jf_j = \frac{\sum_0^N j\beta_j[H]^j}{\sum_0^N \beta_j[H]^j} \qquad [2]$$

respectively, where $\beta_j$is the overall stoicheiometric constant of the protonated complex H_jR, ($\beta_0 = 1$ by definition) $\beta_j = [H_jR]/([H]^j[R])$, C_R is the total concentration of polyprotic acid H_NR, $C_R = \sum[H_jR]$. The mathematical complexity of solution equilibria is considerably reduced working in a medium of fixed ionic strength. It has been shown (101) that stoichiometric rather than thermodynamic acidity constants can and should be used in the buffer capacity theory, because of the advantages gained in the definition of dimensionless parameters. A neutral salt is assumed to be present in sufficient amount to keep activity coefficients constant and the pH-meter is assumed to have been calibrated with solutions of known hydrogen ion concentrations (102, 103). The acidity constant K_{aj} is given by

$$K_{aj} = \frac{[H_{N-j}R][H]}{[H_{N+1-j}R]} = \frac{\beta_{N-j}}{\beta_{N+1-j}} \qquad [3]$$

If the buffer solution is regarded as composed of strong acid (HX), strong base (BOH) and the polyprotic acid, a charge balance gives

$$\begin{aligned}[H]+[B] &= [OH]+[X]+[H_{N-1}R] \\ &\quad +2[H_{N-2}R]+\cdots+N[R]\end{aligned} \qquad [4]$$

where for the sake of simplicity charges of the particles are omitted. That is taking into account Equations 1, 2 and 4 we get

$$\begin{aligned}C_a - C_b &= [H]-[OH]-\sum(N-j)[H_jR] \\ &= [H]-[OH]-NC_R+C_R\tilde{n}\end{aligned} \qquad [5]$$

where C_a and C_b are the concentration of strong acid and strong base, respectively, in the final mixture. The buffer capacity with respect to strong base will be given by

$$\begin{aligned}\pi = \frac{d(C_a - C_b)}{d(\log[H])} = \frac{dC_b}{dpH} = -C_R\frac{d\tilde{n}}{dpH} \\ + \ln 10([H]+[OH])\end{aligned} \qquad [6]$$

where $C_a$is taken constant for this differentiation (dilution effects are neglected) and $pH = -\log[H]$. The total buffer capacity is the sum of the buffer capacity of the individual systems H_NR, H and OH, and is closely related to the slope of the formation curve (104). However, the relationship between the buffer capacity and the formation function perhaps has not been enough yet underlined. In effect the slope of Equation 2, $-d\tilde{n}/dpH$, is a measure of the buffer capacity, and its reciprocal $-dpH/d\tilde{n}$, evaluated at the equivalence points, measures the sharpness index of the corresponding titration (37, 105). The terms $[H]$ and $[OH]$ in Equation 6 are independent of the buffer used and determine the increase in buffer capacity in a strongly acid and alkaline region, respectively, and confirm the buffering character of concentrated solutions of strong acids and bases (106).

TABLE 1
Hyperbolic functions in acid-base titration procedures

Ref.	Chemical Problem	Authors
(34)	Titration curves in terms of inverse hyperbolic or trigonometric functions	Morales, 2002
(36)	pH calculation of mixtures of monoprotic acids with independent acidity constants.	Herman et al., 1990
(37)	Hyperbolic sine expression for the titration error.	González et al., 1990
(38)	Hyperbolic tangent expression for the mathematical modeling of the region before and after the equivalence point.	Perosa et al., 1986
(39)	Arcsine hyperbolic expression for the chloride concentration in potentiometric titrations.	Michalowski and Stepak, 1985
(35)	Symmetrical sigmoidal curve represented by an inverse hyperbolic function	Smit and Smit
(40)	Hyperbolic and trigonometrical functions in complete exchange of a ligand titrations.	Winkler-Oswatitsch and Eigen, 1979
(41)	pH in a mixture of strong acids and bases and monoprotic weak acids and bases in terms of hyperbolic trigonometric functions.	Rang, 1976
(42)	Concentration of the species AL_2, AL, and A in terms of the concentration of free ligand	Dixon, 1975
(43)	Concentrations of non-ligated, uni-ligated and bi-ligated forms by means of hyperbolic functions.	Dixon, 1974
(44)	Inflexion point versus point of maximum slope on redox titration curves	Goldsman, 1967
(45)	Fraction titrated at a pH value equal to pK_a expressed as a quotient of to hyperbolic sine expressions	Goldsman and Meites, 1964
(46)	Inverse hyperbolic sine of a titration function for calculating titration errors	Goldman, 1963
(47)	Method for determining the end point and the acidity constant in a potentiometric titration	Fortuin, 1961
(48)	Hyperbolic expressions for sharpness index and feasibility of redox titrations	Nightingale, 1958
(5)	Logarithmic form of solution of quadratic equation (hyperbolic relationship). Hyperbolic expressions for half titration values	Ricci, 1952
(49)	Simplification of Roller's relationships for the determination of the errors in acid-base titrations.	Jakob, 1950
(50)	Titration error expressed as a hyperbolic sine equation.	Roller, 1932
(51)	Developing highly refined methods of titration with the use of$X = \sinh U$ equation.	Cavanach, 1930
(52)	$X = \sinh U$ where U and X represent distance from the equivalence point in terms of potential and of quantity of reagent, respectively.	Cavanach, 1928
(53)	Potential change due to the addition of reagent expressed as an hyperbolic cotangent expression.	Cavanach, 1928

By differentiating Equation 2 with respect to pH we obtain

$$\frac{d\tilde{n}}{dpH} = \sum j \frac{df_j}{dpH} = -\ln 10 \sum jf_j(j - \tilde{n}) \qquad [7]$$

and substituting this relation into Equation 6 we get finally for the buffer index

$$\pi = \ln 10\Big(C_R \sum jf_j(j - \tilde{n}) + [H] + [OH]\Big) \qquad [8]$$

Equation 8 can even be simplified somewhat when we define (107, 108) a buffer strength equal to $\pi/\ln 10$. The suggestion to delete the factor ln 10 from the definition stems from Henderson (109). If the solution also contains other polyprotic acid systems (e.g., n_i) then we must separate the first term inside the parentheses by the sum of such terms calculated for each of the system. Thus we obtain the general expression

$$\pi = \ln 10\left(\sum_{i=1}^{n_i}\left[C_{R_i}\sum_{j=0}^{N} j_i f_{ji}(j_i - \tilde{n}_i)\right] + [H] + [OH]\right) \qquad [9]$$

This makes it possible to obtain a simple, closed form mathematical expression for any mixtures of acids, regardless of the number of sample components and the number of dissociable protons of these components. Several buffers utilized in daily laboratory practice are polyprotic, e.g., succinate, phosphate or citrate (110, 111). Citric and phosphoric acid as well as their salts are commonly used in foods to control pH and modify tartness (19). On the other hand, pH control over a wide range can be achieved with universal buffer solutions. A universal buffer mixture contains acids chosen such that, over

TABLE 2
Hyperbolic functions in analytical chemistry

Ref.	Chemical Problem	Authors
Separation Methods		
(54)	Equation to predict the concentration profile of the least absorbed component in the partition section for an injection time t_o	Row, 1996
(55)	Dependence of distribution coefficient of a protein on salt concentration in the mobile phase is described by transition functions such as logistic dose response and hyperbolic tangent functions	Kaltenbrunner and Jungbauer, 1996
(56)	Reverse-flow gas chromatography employed to evaluate adsorption equilibrium constants	Yun et al., 1996
(57)	Charge density of the complex cation on the membrane side and that of the hydrophilic counteranions expressed as hyperbolic sine functions	Tohda et al., 1995
(58)	General equation for retention time expressed as a hyperbolic cotangent function.	Benincas and Giddings, 1992
(59)	Hyperbolic cosine expression for the capacitance of the electrostatic diffuse layer at the inner capillary/inner aqueous interface.	Lee et al., 1991
(60)	Bilogarithmic hyperbolic cosine method for determining acidity constants of amphoteric substances from solubility measurements.	Asuero, 1989
(61)	Evaluation of overlapping acidity constants of amphoteric substances from liquid-liquid distribution measurements	Asuero, 1988
(62)	Evaluation of overlapping acidity constants of amphoteric substances from solubility measurements	Asuero, 1988
(63)	Sine hyperbolic function for the charge density produced by the positive surface excess of co-ions	Cantwell and Puon, 1979
(64)	Equation for calculating the relative electrophoresis mobility of substances from their molecular weight and pK_a, and the pH of background solution.	Mori et al., 1972
(65)	Concentration in the phase mobile and stationary expressed by means of hyperbolic relationships	Grushka, 1972
(66)	Retention ratio at constant viscosity as a hyperbolic cotangent function of a dimensionless parameter related with the width of the flow channel.	Hovingh et al., 1970
(67)	Zone mobility of a compound with dissociable proton plotted against the pH value of the background solution expressed by a hyperbolic tangent function	Kiso et al., 1968
(68)	Percentage of metal extracted into the organic phase as a hyperbolic tangent expression of pH.	Irving and Williams, 1949
(69)	Percentage of extraction as a function of distribution constant and hyperbolic cotangent expression of pH	Irving et al., 1949
Electrical Methods		
(70)	Potentiometric evaluation of overlapping acidity constants	Asuero, 1992
(71)	Myland and Oldham expression for the steady-state diffusion to a spherical electrode.	Birke and Huang, 1992
(72)	Numerical solution of the integral equation for a simple charge transfer and diffusion to a micro-cylindral electrode: hyperbolic functions	Nendeck and Dittrich, 1991
(73)	Empirical shape dependent factor and short time current.	Myland and Oldham, 1990
(74)	Dependence of the semiintegral on time.	Oldham and Zoski, 1980
(75)	Simple hyperbolic function for the fundamental harmonic value for high values of the superimposed a.c. voltage in fast redox systems and a linear diffusion pattern.	Moring and Kies, 1977
(76)	Relationship between the integral and the total membrane potential difference	Morf et al., 1976
(77)	Term utilized to gradually merge the Gaussian leading edge and the exponential trailing edge.	Gutknecht and Perone, 1970

(Continued)

TABLE 2
Hyperbolic functions in analytical chemistry *(Continued)*

Ref.	Chemical Problem	Authors
(78)	Approximation for the error function	Delmastro and Booman, 1969
(79)	Component of the current amplitude function	McCord and Smith, 1969
(80)	Solution of Fick's second law, and formulation of the current expression in the potential-reverse methods.	Oldham and Topol, 1967
Optical Methods		
(81)	Stability constants of weak complexes from continuous variation data	Sayago and Asuero, 2006
(82)	Stability constants of weak complexes from mole ratio data	Boccio et al., 2006
(83)	Acidity constants of diprotic acid from spectrophotometric data	Fernández-Recamales et al., 2006
(84)	Bilogarithmic spectrophotometric method for the evaluation of overlapping acidity constants.	Asuero, 1993
(85)	Peak something in between a Gaussian and a Lorentzian peak shape	Swarte, 1992
(86)	N-order Taylor approximation in cases of linear dependence of absorbance on wavelength	Dose and Guiochon, 1989
(87)	Radiant cell transmitted by a cell.	Ramsey, 1980
(88)	Wedding errors in absorbance subtract spectrometry.	Hirschfeld, 1979
(89)	Transmittance and reflectance of the medium related to the coefficients of scatter and absorbance.	Huff, 1977
(90)	Transmittance of a layer of light-absorbing material in a scattering medium, coefficients of scatter and absorption and thickness of the layer.	Huff et al., 1976
(91)	Mathematical description of the extreme left-hand side of the total absorption peak in gamma-ray spectra.	Sterlinski, 1970
(89)	Modified hyperbolic secant for describing the photopeak, and complete function for the major regions of a monoenergetic gamma-ray spectrum.	Kowalski and Isenhour, 1968
Kinetic Methods		
(92)	Number of moles reacting per unit time.	Freeman and Seltz, 1978
(93)	Relaxation time for ionization.	Cornish-Bowden, 1976
(94)	Hyperbolic cosine relationship for the amount complexed in hydrogen-bonding interaction.	Wood, 1974
(93)	Steady state distribution of substrate and product concentrations and fluxed within the membrane	Blaedel et al., 1972

a considerable pH range, the pH is an approximately linear function of the volume of base added. On this context, universal buffer solutions (Table 3) have the advantage of affording a wide range of pH values (112–121).

The buffer capacity can be resolved into a series of terms, with one term for each active component

$$\pi = \left(\sum \pi_i\right) + \pi_H + \pi_{OH} \qquad [10]$$

Thus, in contrast to the pH of the titration curve the buffer capacity is additive in the concentration of the sample components.

However, if we suppose that the titrant is much more concentrated than the titrated solution, differentiation of Equation 8 against pH gives

$$\frac{d\pi}{dpH} = \ln 10\, C_R\left(-\sum j f_j \frac{d\tilde{n}}{dpH} + \sum (j-\tilde{n}) j \frac{df_j}{dpH} - \ln 10([H]-[OH])\right) \qquad [11]$$

From Equations 1, 7 and 11 we finally get

$$\frac{d\pi}{dpH} = \ln^2 10[C_R\left(\tilde{n}\sum j f_j (j-\tilde{n}) - \sum j f_j (j-\tilde{n})^2\right) - [H] + [OH]] \qquad [12]$$

Thus, general equations for the buffer capacity curve and its first derivative curve have been formulated, and the relationship with the formation function and the molar fractions of the distribution diagram adequately emphasized. Buffer capacity is of worth for calibration buffer solutions, but also it is very important for natural (122–125) and technical systems (126–131). The pH, e.g., in cells, body fluids, and reaction vessels can only be maintained constant if the buffer capacity is appropriate (132). Approximate calculation of a buffer value is of practical importance for the design of new buffer solutions (133). The reader is also referred to (134–136) for additional information on buffer solutions at fixed ionic strength.

TABLE 3
Universal buffer solutions

Authors	Components	Ref.
Prideaux	Acetic acid, phosphoric acid, boric acid	(112,113)
Prideaux and Ward	Phenylacetic acid, phosphoric acid, boric acid	(114)
Britton and Robinson	Citric acid, potassium dihydrogen phosphate, boric acid, and veronal	(115,116)
Ellis	Sodium carbonate, 2-amino-2-methyl propan-1:3 diol, sodium dihydrogen ortophosphate, and citric acid	(117)
Theorell and Steinhagen	Citric acid, phosphoric acid, and boric acid	(118,119)
Avdeef and Bucher	Potassium acetate, potassium dihydrogen phosphate, ethylendiammonium dichloride, and borax	(120)
de Levie	3-nitro-2,6-dimethylpyridine, 4-cyano-2,6-dimethylpyridine, 2,6-dimethylpyridine-3-sulfonic acid, 3-acetyl-2,4,6-trimethylpyridine, 2,6-dimethylpyridine, and 4-methoxy,2,6-dimethylpyridine	(121)

MONOPROTIC ACID

For a monoprotic acid neglecting the contribution of H and OH, Equation 8 leads to

$$\pi = \ln 10\, C_R(f_1(1-f_1)) = \ln 10\, C_R f_1 f_0 \qquad [13]$$

and the slope of the graph of π as a function of pH is given (Equation 12) by

$$\begin{aligned}\frac{d\pi}{dpH} &= \ln^2 10\, C_R(\tilde{n} f_1(1-\tilde{n}) - (1-\tilde{n})^2 f_1)\\ &= \ln^2 10\, C_R f_1 f_0 (f_1 - f_0) \qquad [14]\end{aligned}$$

Singular points are given by the condition $d\pi/d(pH) = 0$, which correspond to the solution $f_0 = f_1 = 0.5$, $pH = pK_{a1}$, in which case (137) the buffer capacity takes the maximum value $\pi = \ln 10 C_R/4$. Two asymptotes correspond to $f_0 = 0$ and $f_1 = 0$ at high and low pH values, respectively, due to the omission of $-[H] + [OH]$ in Equation 12.

On the other hand, for a monoprotic acid we have

$$\frac{d^2\pi}{d(pH)^2} = \ln^3 10\, C_R f_0 f_1 (f_0^2 + f_1^2 - 4 f_0 f_1) \qquad [15]$$

Values of $d^2\pi/d(pH)^2 = 0$ will locate inflexion points in the graph of π against pH. The non trivial roots of this equation can be evaluated by making the term between parentheses of Equation 15 equal to zero, and then once upon dividing by f_0^2 and taking into account Equation 1 we have

$$\beta_1^2[H'']^2 - 4\beta_1[H''] + 1 = 0 \qquad [16]$$

which leads to

$$[H''] = \frac{2 \pm \sqrt{3}}{\beta_1} = K_a(2 \pm \sqrt{3}) \qquad [17]$$

and

$$pH'' = pK_a \pm 0.5719 \qquad [18]$$

Kolthoff et al. (138–140) used first and second difference of dependent variable to locate the end point in potentiometric titrations. As a matter of fact, the derivative curve of the sigmoid produced during titrations with potentiometric monitoring offers an accurately way of determining the end point titrations (141).

The use of differential titrations in analysis is a familiar technique (142), which has been mainly applied to monoprotic or to diprotic acids with well-separated constants (143–145). Kilpi et al. (146) have obtained numerous acidity constants from the buffer value at the potentiometric end points. A computerizable derivative method may be used for a precise description of the end point and consequently the pK_a values (147). A method that belongs to the differential category for determining the end points from potentiometric titration curves has been presented recently (148). A survey of the applications of potentiometric and differential titration curves are listed in Table 4. Early contributions to the treatment of theoretical titration curves are found in Table 1 of the Anfalt and Jagner paper (183). The first titration to be monitored by potentiometric means was reported in 1893 (212–213) at Ostwald's Institute in Leipzig (mercurous nitrate solution with potassium halides).

DIPROTIC ACID

Several investigators have theoretically studied the relative position of the equivalence point and the inflexion points on the titration curve of diprotic acids (5, 23, 101, 129, 217). A different approach based on similar principles (104) is given in that follows. For a diprotic acid, Equation 8 leads to

$$\begin{aligned}\pi &= \ln 10[C_R(f_1(1-\tilde{n}) + 2 f_2(2-\tilde{n}))]\\ &= \ln 10[C_R(f_1 f_0 + 4 f_2 f_0 + f_2 f_1) + [H] + [OH]] \qquad [19]\end{aligned}$$

TABLE 4
Examples of applications of potentiometric and differential titration curves

Ref.	Chemical Problem	Authors
(149)	Value of the end point titration with software specifically designed for graphing (SigmaPlot)	Soli, 2004
(150)	Location of reliable inflexion points by means of a multiscale wavelet data treatment	Martins et al., 2003
(148)	New differential determination of the end point from potentiometric titration curve	Kholeif, 2001
(151)	Arc tangent curve fitting method of determination of the end point	Ma and Tsang, 1998
(152)	Buffer curve smoothing and differentiation of titration data	de Levie et al., 1998
(143)	Protonation constants from derivative analysis of potentiometric titration data	Chen et al., 1996
(141)	Titration end points from pseudoderivative curves	Marasinghe et al., 1996
(153)	Buffer capacities from titration data: second derivative curves and end-point determination	Clark et al., 1995
(154)	Potentiometric detection of end points in acid-base titrations	Pournaghi-Azar and Farhadi, 1995
(155)	Description capabilities of a modular microcomputer-controlled universal electrochemical meter	Radomski et al., 1995
(104)	Inflexion points in the formation function curve	Asuero, 1993
(156)	Graphical presentation of acid-base reactions with the aid of a computer interfaced autotitrator	Lake et al., 1992
(157)	MS-DOS microcomputer controlled titration system	Stangeland and Anjo, 1992
(158)	Lab-interface spreadsheet software to find the equivalence point by taken the derivative of the pH volume curve	Amend et al., 1991
(159)	Effect of the titrated concentration level on the shape of the titration curve.	Rossi et al., 1990
(160)	Development of the methods for finding the equivalence volume in potentiometric titrations	Gran, 1988
(161)	Localization of inflexion points in acid-base titrations and error associated assuming that they are identical with equivalence points	Fournaise and Petitfaux, 1987
(162)	Classical technique (maximum slope) for locating the end point of a potentiometric titration	Meites et al., 1987
(38)	Simplex method applied to sigmoidal and segmented acid-base titration curves	Perosa et al., 1986
(163)	Inflexion point of potentiometric titration curve by means of a rational spline function	Ren and Ren-Kurc, 1986
(164)	Derivative curves obtained with an automated equilibrium titrator	Arnold et al., 1985
(165)	RC filter for automatic differential potentiometry	Jaffar et al., 1985
(32)	Equivalence point in potentiometric titration	Michalowski and Stepak, 1985
(166)	Slope of redox titration curves	Perez Ruiz et al., 1984
(167)	Survey of automated potentiometric titration procedures	Stur et al., 1984
(168)	Second derivative of a sigmoidal titration curve by means of automated titration processes	Smit and Smit, 1982
(169)	First derivative of the titration curve of a weak base	Petho and Burger, 1981
(170)	Differential potentiometric method for the evaluation of the acidity constant of a very slightly soluble drug	Fleuren et al., 1979
(171)	End point determination by the second derivative curve	Carter and Huff, 1979
(172)	First derivative of titration of a mixture of strong base and a salt of a weak dibasic acid	Covington et al., 1978
(173)	Trouble in connection with the application of second derivative method	Choi and Kim, 1978
(174)	Relative position of the inflection point and equivalence point of a homogeneous redox reaction	Meretoja et al., 1978
(175)	Inflexion point versus equivalence point in potentiometric titration	Lund, 1976

(Continued on next page)

TABLE 4
Examples of applications of potentiometric and differential titration curves *(Continued)*

Ref.	Chemical Problem	Authors
(176)	Disordering effects of boric acid and carbon-dioxide in mass analysis of ammonia	Maly, 1976
(177)	End point in high precision coulometry	Koch et al., 1975
(178)	End points of potentiometric titrations from the difference of electrode potentials at equal steps of titrant volumes	Ebel and Kalb, 1972
(179)	Survey of potentiometric end-point determination	Anfalt and Jagner, 1971
(180)	Derivative titration curves and comparison with potentiometric titration curves and segmented titration curves	Meites and Meites, 1970
(181)	Difference between inflexion and equivalence point in coulometric titrations	Marinenko and Champion, 1969
(182)	Methods for calculating the end point in potentiometric analysis from potential versus concentration curve as function of the reagent added	Hahn, 1969
(183)	Rigorous calculation of titration curves by means of the computer program HALTAFALL	Anfalt and Jagner, 1969
(184)	Inflexion points on homogeneous redox titration curves	Goldman, 1968
(185)	Maximum slope and equivalence point of potentiometric chelatometric titration curves	Meites and Meites, 1967
(186)	Inflection points and symmetrical redox titration curves	Goldman, 1967
(187)	Equation for the entire titration curve obtained in homogeneous and symmetrical redox titrations	Goldman, 1966
(188)	Divided differences method in the interpolation theory to calculate the end point with unequal volume increments	Yan, 1965
(189)	Boric acid-mannitol titration end point	Duigou and Lauer, 1965
(190)	Inflection points in strong acid-strong base and precipitation titration curves	Meites and Goldman, 1964
(191)	Inflection points in potentiometric asymmetrical titration curves	Meites and Goldsman, 1964
(192)	Dilution effect and location of the inflection points in acid-base and related curves	Meites and Goldsman, 1963
(193)	Rapid method to estimate the end point in a redox or precipitation reaction from a few preliminary potentiometric measurements	Herringshaw, 1962
(194)		Hahn, 1961
(195)		Hahn, 1960
(196)	Evaluation of acidity constants by the half equivalence point procedure	Almond, 1959
(197–199)	Method of calculation the end point through difference quotient parameters	Hahn, 1958
(200)	The increment of volume by increment of pH versus volume graphs in the vicinity of the equivalent point are very nearly straight lines	Gran, 1950
(139)	Arithmetic method for obtaining the point of maximum slope	Kolthoff and Laitinen, 1944
(201)	Titration curves for homogeneous redox reactions	Murgulescu and Dragulescu, 1940
(202)	Differential titrations: acidity constants from the buffer value	Kilpi and Meretoja, 1937
(203)	Differential titrations: acidity constants from the buffer value	Kilpi, 1935
(204)	Differential titrations: acidity constants from the buffer value	Kilpi, 1935
(205)	Location of the inflection point in a potentiometric titration curve by means of a cubic polynomial	Fenwick, 1932
(138)	Arithmetic method for obtaining the point of maximum slope	Kolthoff and Furman, 1931

(Continued)

TABLE 4
Examples of applications of potentiometric and differential titration curves *(Continued)*

Ref.	Chemical Problem	Authors
(206)	End point versus inflection point in electrometric titrations	Roller, 1928
(207)	End point determination in potentiometric titrations	Hahn and Frommer, 1927
(208)	The measured potentials reach a sharp maximum at the end of the titration	MacInnes and Jones, 1926
(209)	Differential titration is simpler and more accurate than electro-titration as usually practiced.	Cox, 1925
(210)	Position of inflection points in hydrogen-electrode titration curves	Eastman, 1925
(211)	First application of the derivative method to located the end point in the titration of ferrous iron with dichromate in hydrochloric acid medium	Hostetter and Roberts, 1919

and from Equation 12, after lengthy but straightforward algebra we get

$$\begin{aligned}\frac{d\pi}{dpH} &= \ln^2 10[C_R((1-\tilde{n})(f_1(2\tilde{n}-1)+4f_2(\tilde{n}-2))\\ &\quad -[H]+[OH]] = \ln^2 10[C_R(f_0-f_2)\\ &\quad \times\left(f_1^2 - f_1 f_2 - f_0 f_1 - 8 f_2 f_0\right) - [H] + [OH]]\end{aligned} \qquad [20]$$

By making use of the dimensionless quantities defined by

$$y = [H]\sqrt{\beta_2} = \frac{[H]}{\sqrt{K_{a1}K_{a2}}} \qquad [21]$$

and

$$R = \frac{\beta_1}{\sqrt{\beta_2}} = \sqrt{\frac{K_{a1}}{K_{a2}}} \qquad [22]$$

Equations 19 and 20 are transformed in

$$\begin{aligned}\pi &= \ln 10\left[\frac{C_R y}{(1+Ry+y^2)^2}(R+4y+Ry^2)+[H]+[OH]\right]\\ &= \ln 10\left[\frac{C_R\left(R\left(\frac{1}{y}+y\right)+4\right)}{\left(\left(\frac{1}{y}+y\right)+R\right)^2}+[H]+[OH]\right]\end{aligned} \qquad [23]$$

and

$$\begin{aligned}\frac{d\pi}{dpH} &= \ln^2 10\left[\frac{C_R y(1-y^2)}{(1+Ry+y^2)^3}(-R+(R^2-8)y-Ry^2)\right.\\ &\quad \left. -[H]-[OH]\right]\\ &= \ln^2 10\left[\frac{C_R\left(\frac{1}{y}-y\right)}{\left(\left(\frac{1}{y}+y\right)+R\right)^3}\left(-R\left(\frac{1}{y}+y\right)+R^2-8\right)\right.\\ &\quad \left. -[H]-[OH]\right]\end{aligned} \qquad [24]$$

respectively. Figures 1a and 1b show π and $d\pi/d(pH)$ against $\log y = 0.5\ (pK_{a1} + pK_{a2}) - pH$, for varying values of R assuming $[H]$ and $[OH]$ to be negligible. The shape of the $\pi = f(pH)$ curve is then depending only of the parameter R, whereas its position on the pH axis depends only on $(pK_{a1} + pK_{a2})/2$. Note that, $dpH = -d\log y$, and $d^2pH = d^2\log y$. The parameter $R = \sqrt{K_{a1}/K_{a2}}$ is arbitrarily chosen in Figure 1 to illustrate the factors which determine the shape of the curves. When $\log R = 2$ ($\Delta pK_a = 4$), the whole curve can be considered to consist of two separate systems. As K_{a1} approaches K_{a2} the curve $\pi = f(pH)$ cannot be viewed as a composite of two sigmoidal curves and if the acidity constants of the acid lie close to each other, then the curve $\pi = f(pH)$ tends to fuse into a single break (5, 23), approaching a pH equal to $(pK_{a1} + pK_{a2})/2$ at a K_{a1}/K_{a2} ratio equal to 16, as we will shown later.

From Equation 24, $d\pi/dpH = 0$ implies either $1/y' - y' = 0$; $y' = 1$; $f_0 - f_2 = 0$, or the term between brackets be zero. The first condition gives for the central minima $[H']_{(1)}$

$$[H']_{(1)} = \frac{1}{\sqrt{\beta_2}} = \sqrt{K_{a1}K_{a2}} \qquad [25]$$

K_{a1} and K_{a2} are the acidity constants of the diprotic acid. The average acidity constant (geometric mean of the two constants) is the hydrogen ion concentration at the central minima point, and from Equation 21

$$\log y_1' = \frac{1}{2}(pK_{a1} + pK_{a2}) - pH_{(1)}' = 0 \qquad [26]$$

The second condition in Equation 24

$$-R\left(\frac{1}{y'} + y'\right) + R^2 + 8 = 0 \qquad [27]$$

must therefore give the two maxima $pH_{(2)}'$ and $pH_{(3)}'$ at the left and right, respectively, of the central minimum. Two additional minima, one on the acid side and another in the alkaline side may occur (5), however, if we take into account $-[H] + [OH]$

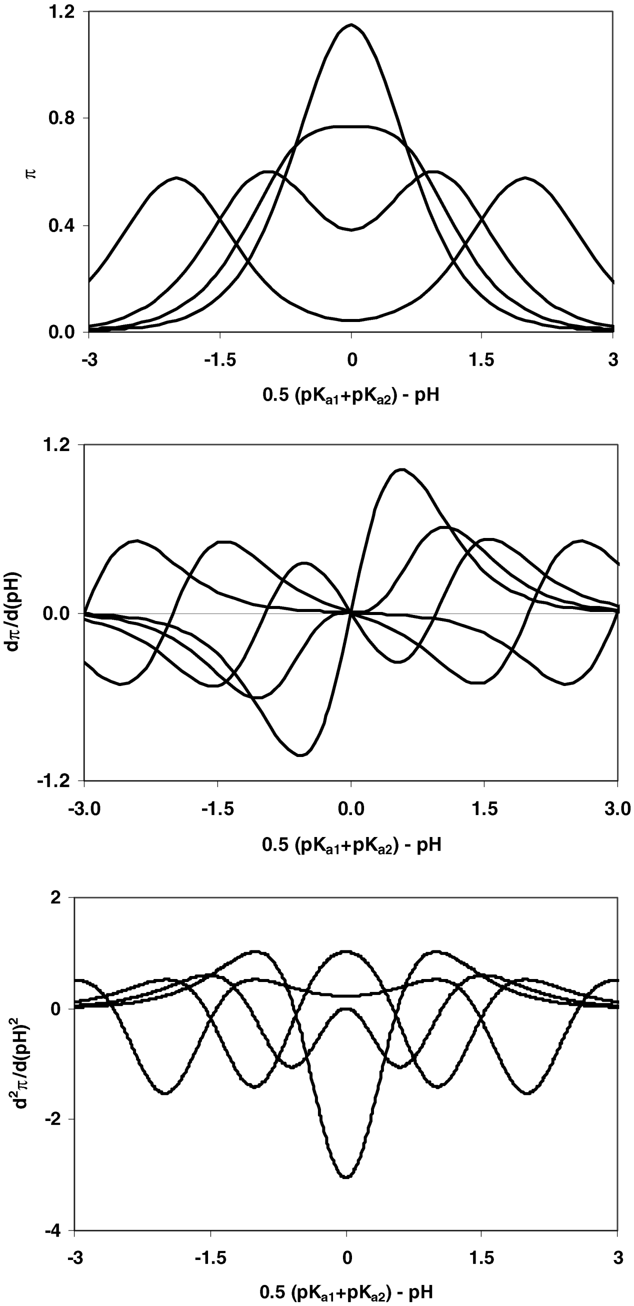

FIG. 1. Top: Buffer index against $0.5(pK_{a1} + pK_{a2}) - pH$ curves for a diprotic acid. Middle: Derivative $d\pi/d(pH)$ against $0.5(pK_{a1} + pK_{a2}) - pH$. Down: Derivative $d^2\pi/d(pH)^2$ against $0.5(pK_{a1} + pK_{a2}) - pH$ curves. R values of 2, 4, 10 and 100 in all cases; C_R is taking as unity and $|H|$ and $|OH|$ being negligible. Note that $\log y = 0.5(pK_{a1} + pK_{a2}) - pH$.

in Equation 24. From Equation 27 we get

$$R - \frac{8}{R} = \frac{1}{y'} + y' \qquad [28]$$

By multiplying and dividing the left hand of Equation 28 by $2\sqrt{2}$ we have

$$2\sqrt{2}\left(\frac{R}{2\sqrt{2}} - \frac{2\sqrt{2}}{R}\right) = 10^{\Delta pH'} + \frac{1}{10^{\Delta pH'}} \qquad [29]$$

where

$$\Delta pH' = pH'_{(1)} - pH'_{(2)} \qquad [30]$$

$$-\Delta pH' = pH'_{(1)} - pH'_{(3)} \qquad [31]$$

given the property of symmetry of the $\pi = f(pH)$ curves when $[H]$ and $[OH]$ are negligible.

Taking into account the definition of hyperbolic sine and cosine functions, $\sinh(x) = (e^x - e^{-x})/2$ and $\cosh(x) = (e^x + e^{-x})/2$, we obtain

$$2\sqrt{2}\sinh\left(\ln\left(\frac{R}{2\sqrt{2}}\right)\right) = \cosh(\ln 10\Delta pH') \qquad [32]$$

From Equation 32 we may evaluate the square root of the ratio of successive acidity constants

$$R = \sqrt{\frac{K_{a1}}{K_{a2}}} = 2\sqrt{2}\exp a\sinh\left(\frac{1}{2\sqrt{2}}\cosh\left(\ln 10\Delta pH'\right)\right) \qquad [33]$$

where $a\sin x$ is the inverse hyperbolic sine of x.

Thus, the $\sqrt{K_{a1}/K_{a2}}$ value is inserted in the equations that follow in order to yield

$$pK_{a2} = pH'_{(1)} + \log R \qquad [34]$$

$$pK_{a1} = pH'_{(1)} - \log R \qquad [35]$$

Many organic compounds behave as diprotic weak acids with moderately overlapping pK_a values, thus the method devised is useful. Thus, by neglecting the autodissociation of water, and by focusing on appropriate pH intervals of the titration curve, Equations 34 and 35 work quite well.

Conversely, from Equation 33 we get

$$\Delta pH' = \frac{1}{\ln 10}a\cosh\left(2\sqrt{2}\sinh\left(\ln\left(\frac{1}{2\sqrt{2}}\sqrt{\frac{K_{a1}}{K_{a2}}}\right)\right)\right) \qquad [36]$$

where $a\cosh x$ is the inverse hyperbolic cosine of x. The main difficulty of the method is to locate accurately the maximum and minimum in the $\pi = f(pH)$ graph. Experimental values of the formation function $\tilde{n}$ are obtained at various pH values; as many points as possible are obtained. Note that for a diprotic acid, from Equations 2, 21 and 22 we have

$$\tilde{n} = \frac{Ry + 2y^2}{1 + Ry + y^2} \qquad [37]$$

and

$$\frac{d\tilde{n}}{d(-\log y)} = -\ln 10y\frac{R + 4y + Ry^2}{(1 + yR + y^2)^2}$$

$$= -\ln 10y\frac{R\left(\frac{1}{y} + y\right) + 4}{\left(\left(\frac{1}{y} + y\right) + R\right)^2} = -\frac{\pi}{C_R} \qquad [38]$$

Equation 38 demonstrates that the slopes at any distance in both directions from the mid-point are the same; i.e., the function is symmetric. In order to increase the precision in the evaluation of the maximum (or minimum), in the $\pi = f(pH)$ curve, the ratio

$$-\frac{\Delta\tilde{n}}{\Delta pH} = -\frac{\tilde{n}_{n+1} - \tilde{n}_n}{pH_{n+1} - pH_n} \qquad [39]$$

can be plotted against $(pH_{n+1} + pH_n)/2$, where $pH_n$and $\tilde{n}_n$denote the $pH$and $\tilde{n}$ value, respectively, for the $\tilde{n}$th point. Values of $-\Delta\tilde{n}/\Delta pH$may also be derived from Lagrangian polynomials (143). Methods based on differentiating with interpolation spline function or with smoothing spline function may also be used (214).

In practice, because of the ineludible contribution of either H or OH,$\Delta pH'$ is evaluated from experimental data as

$$\log y_2' = pH_{(1)}' - pH_{(2)}' \quad \left(\text{if } pH_{(1)}' > pK_w/2\right) \qquad [40]$$

or

$$\log y_3' = pH_{(1)}' - pH_{(3)}' \quad \left(\text{if } pH_{(1)}' < pK_w/2\right) \qquad [41]$$

With $[H]$ and $[OH]$assumed to be negligible, and for very large R values (the two pK_a values being far apart), the buffer capacity must be expected to have maxima at $pH_{(2)}' = pK_{a1}$ and $pH_{(3)}' = pK_{a2}$. As R decreases (K_{a2} approachesK_{a1}), the two dissociation steps interfere with each other, the maxima increase andπchanges shape so that the two maxima moves toward $(pK_{a1} + pK_{a2})/2$, i.e., their location on the pH axis are displayed towards each other, and its follows that $pH_{(2)}' < pK_{a1}$ and $pK_{a2} < pH_{(3)}'$.

Figure 2 (left) shows the representation of the

$$\Delta pK_a = pK_{a2} - pK_{a1} = 2\log R \qquad [42]$$

as a function of

$$\Delta pH'^{*} = pH_{(3)}' - pH_{(2)}' = 2\Delta pH' \qquad [43]$$

Note that the inflection points and the half values of the titration curve (maxima in the buffer capacity curves) coincide with pK_a values of polyprotic acids only under special circumstances (215). The curve line tends to a limiting value of $\Delta pH' = 0$ (which implies$pH_{(1)}' = pH_{(2)}' = pH_{(3)}'$) and then

$$R_{\lim} = 2\sqrt{2}\exp\left(a\sinh\left(\frac{1}{2\sqrt{2}}\right)\right) = 4 \qquad [44]$$

That is, when $K_{a1}/K_{a2} = R^2 = 16\,(\Delta pK_a = 4\log 2 = 1.204)$, the three points fuse at $pH' = (pK_{a1} + pK_{a2})/2$. As can be seen in Figure 2 (right) when $\log R \quad (\Delta pK_a)$ decreases, the difference between the maximum value and the pK_a increases reaching the limiting value of $2\log 2$. The difference between pK_{a2} and $pH_{(1)}'$ (or between $pH_{(1)}'$ and pK_{a1}) is always $\Delta pK_a/2$. On the other hand it is well known (216–219) that the limiting ratio $K_{a1}/K_{a2} = 4$.

For the strong overlapping case, the method above devised is not applicable. In those cases, we may evaluate $R$from the slope (98) of the mid-point $\tilde{n} = f(pH)$. From Equation 7 we get

$$\begin{aligned} D &= \left(\frac{d\tilde{n}}{dpH}\right)_{\tilde{n}=1.0} \\ &= -\ln 10\left[\frac{Ry(1-\tilde{n}) + 2y^2(2-\tilde{n})}{1 + Ry + y^2}\right]_{\tilde{n}=1.0=y} \\ &= -\ln 10\frac{2}{2+R} \end{aligned} \qquad [45]$$

which is related to R by the expression

$$\begin{aligned} R &= \sqrt{\frac{K_{a1}}{K_{a2}}} = -\left[\frac{D(1+y^2) + 2\ln 10 y^2(2-\tilde{n})}{Dy + \ln 10(1-\tilde{n})}\right]_{\tilde{n}=1.0=y} \\ &= -2\left[1 + \frac{\ln 10}{D}\right] \end{aligned} \qquad [46]$$

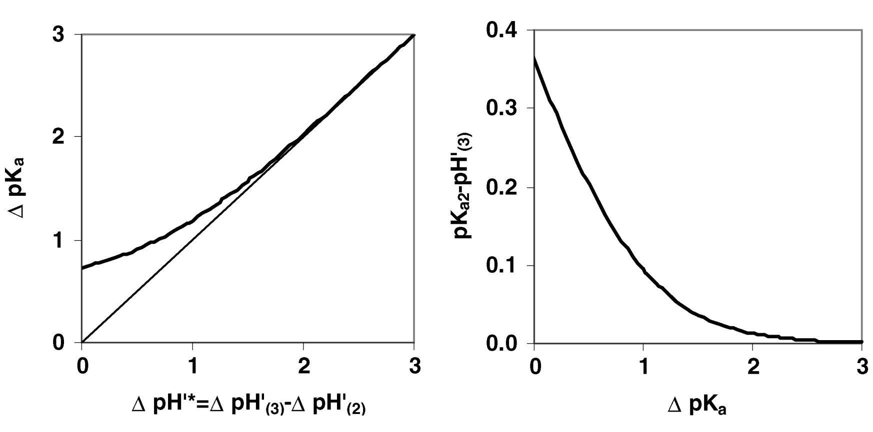

FIG. 2. Left: Representation of ΔpK_a as a function of $\Delta pH'^{*}$: curve line a straight line $y = x$ is included with comparative purposes. Right: Representation of $pK_{a2} - pH_{(3)}'$ as a function of ΔpK_a.

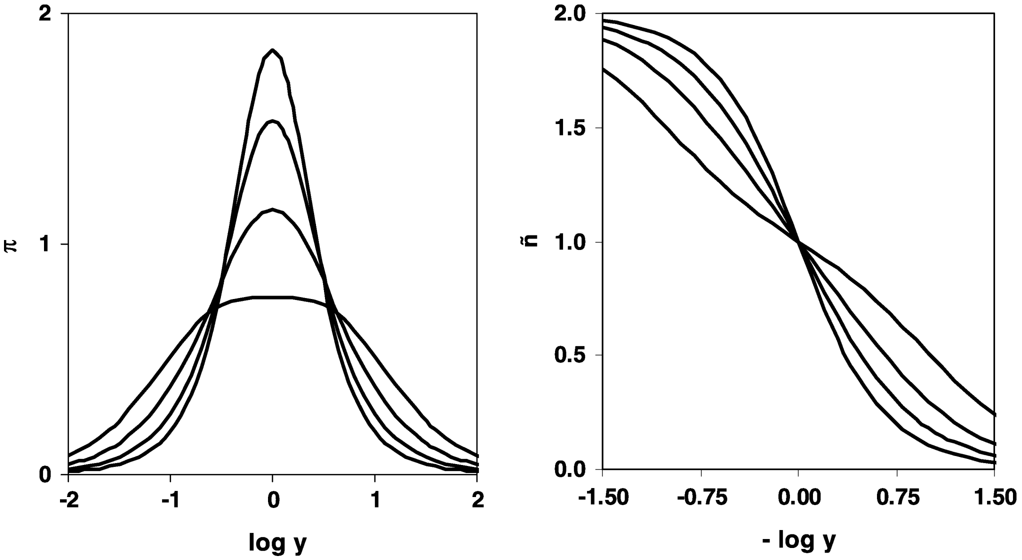

FIG. 3. Left: Buffer index against log y curves for a diprotic acid with R values of 1, 2, 4 and 10. Right: Function of formation curve versus – log y for$R$ values of 1, 2, 4 and 10 (ΔpK_a values of 0, 0.602, 1.204 and 2, respectively). Note that $\log y = 0.5\,(pK_{a1} + pK_{a2}) - pH$.

It is interesting to note that the rate of change of $\tilde{n}$ with pH at the $\tilde{n} = 1.0$ point is a function only of the variable R (Fig. 3). The $(\tilde{n}, pH)$ data pairs in the neighborhood of the $pH_{\tilde{n}=1.0}$ follows (in those cases) a straight line, which makes the location of the maximum in the $\pi = f(pH)$ curve easy. Figure 4 shows the variation of $-D_{\tilde{n}=1.0}$ as a function of the ΔpK_a values. However, note that when $\tilde{n} = 1$, the buffer capacity (Equations 8 and 10) is given by

$$[\pi_i]_{\tilde{n}=1} = \ln 10 \left(2\frac{C_R}{2+R} \right) \qquad [47]$$

In the limiting case, $R = 2$, and the buffer capacity of such diprotic acid is twice of a monoprotic acid at the same concentration.

As suggested by Equation 23 and seen in Figures 1a and 3, the shape of the curve is largely determined by the difference between the K_a values, and a noticeable feature of the graph is the sharp maximum at K_{a1}/K_{a2} ratio values lower than 16. Acids of such low R values could be used to prepare buffers of much higher buffer capacity than those that can be made from monofunctional ones or the familiar polyfunctional ones (216). A different mathematical account of the buffer capacity of bivalent ampholytes by using dimensionlees parameters has been given by Rilbe (217).

Limiting K_{a1}/K_{a2} ratio

As a general rule, successive acidity constants decreases regularly in the sense$K_{a1} > K_{a2}$, and it has been shown that if a diprotic acid has two equivalent (symmetrical molecule) and independent ionization processes, the minimum value of K_{a1}/K_{a1} is 4 (216, 218–220). Then, it follows that in any real situation

$$\frac{K_{a1}}{K_{a2}} \geq 4 \qquad [48]$$

In general, for any polyprotic acid if we assume that the ratio of the successive acidity constants is determined statistically alone, then (221, 222)

$$\frac{K_{aj}}{K_{a,j+1}} = \frac{(j+1)(N-j+1)}{j\,(N-j)} \qquad [49]$$

as we will show later. In Table 5 are shown the statistical ratios of successive acidity constants calculated from Equation 49. It can

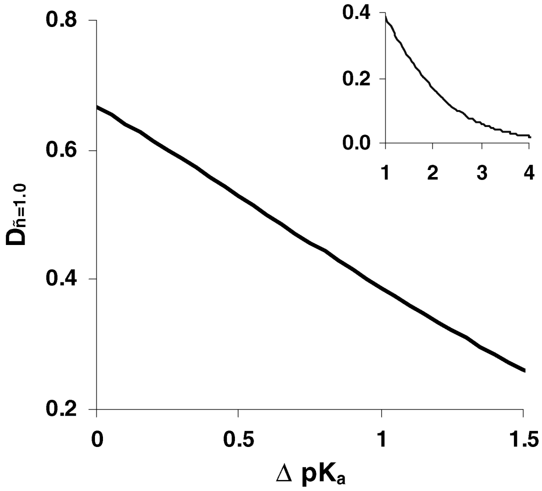

FIG. 4. Variation of the slope of the formation function at $\tilde{n} = 1.0$ against ΔpK_a.

TABLE 5
Values of the statistical ratios of the successive acidity constants

N	K_{a1}/K_{a2}	K_{a2}/K_{a3}	K_{a3}/K_{a4}	K_{a4}/K_{a5}	K_{a5}/K_{a6}	K_{a1}/K_{aN}
2	4	—			—	4
3	3	3	—		—	9
4	2.67	2.25	2.67	—	—	16
5	2.50	2	2	2.50	—	25
6	2.40	1.88	1.78	1.88	2.40	36

be seen that the statistical values of $K_{aj}/K_{a,j+1}$ vary regularly, in an interval with almost the same order of magnitude. It is interesting to observe that the value of K_{a1}/K_{aN} calculated on a statistical basis coincides with N^2.

The basis of this discussion has been a protonation reaction but the same principles apply for a metal complexation reaction $M + L \rightleftharpoons ML$: $pK_{a1} = \log K_2$; $pK_{a2} = \log K_1$; $K_i = [ML_i]/([ML_{i-1}][L])$. Both phenomena, protonation and complexation, are chemically basically different, but formally identical; the only differences are that L takes the place of H and R takes the place of M. However, the absolute values and the ratio of stability constants of the successive complexes are determined by a number of factors, some of which are still unknowns (223). Several authors have pointed out that the real conditions cannot be expressed as simply as these statistical quotients. Other factors, besides the statistical effects, have to be taken into consideration. This implies that it may be possible that $K_j < K_{j-1}$, but the number of systems in which $K_j < K_{j-1}$ is rather limited (224–226). A constant ratio smaller than the statistical value means, that the filling of some coordination site of the metal ion increases the possibility of incorporation of the next ligand. This phenomenon is observed with complexes of silver(I), e.g., silver(I)-ammine complexes (98), and mercury(II). It should be noted that if the value of K_1/K_2 is small, the complex ML is formed only in low concentration and consequently the stepwise constants K_1 and K_2 can generally be determined only with appreciable inaccuracy (227), the value of $\beta_2 = K_1 K_2$ can only be calculated accurately. It has been pointed that for the correct evaluation of the stability constants of the complexes it is necessary to know the number and the type of the complexes (228).

LIMIT OF APPLICABILITY OF THE METHOD

A limit obviously exists in the ability to apply the methods devised. This will be imposed, on the one hand by characteristics of the solution, and on the other, by imprecision in the measurements. From the condition $d\pi/d(pH) = 0$ with $[OH] \ll [H]$ we get an equation that may be solved for given values of $C_R\sqrt{\beta_2}$ and R, by the Newton-Raphson method (229, 230)

$$\begin{aligned} &- y'^6 - 3Ry'^5 + (C_R\sqrt{\beta_2}R - 3(R^2+1))y'^4 \\ &+ (C_R\sqrt{\beta_2}(8 - R^2) - R(R^2+6))y'^3 \\ &- 3(R^2+1)y'^2 + (C_R\sqrt{\beta_2}(R^2-8) - 3R)y' \\ &- C_R\sqrt{\beta_2}R - 1 = 0 \end{aligned} \qquad [50]$$

As $C_R\sqrt{\beta_2}$ decreases, the central minimum moves to the right ($\log y'_1 = (pK_{a1} + pK_{a2})/2 - pH'_{(1)} < 0$) and both maxima moves to the left in the pH scale, the effect being more noticeable on the acid maximum (Table 6), which disappears for a critical value of the $C_R\sqrt{\beta_2}$. Though this cause a negligible effect on the evaluation of pK_{a2}, the error in $pK_{a1} \approx 0.02$ when $C_R\sqrt{\beta_2} = 500$.

TABLE 6
Location of the central minimum and the two adjacent maxima in the buffer index curves for a diprotic acid

	$\Delta pK_a = 2$			$\Delta pK_a = 1.5$		
$C_R\sqrt{\beta_2}$	$\log y'_2$	$\log y'_1$	$\log y'_3$	$\log y'_2$	$\log y'_1$	$\log y'_3$
10^6	0.9586	0	– 0.9586	0.5963	0	−0.5963
10^5	0.9589	– 0.0001	– 0.9586	0.5965	0	−0.5963
10^4	0.9621	– 0.0005	– 0.9585	0.5984	−0.0008	−0.5962
10^3	0.9960	– 0.0052	– 0.9581	0.6180	−0.0076	−0.5950
500	1.0415	– 0.0102	– 0.9577	0.6408	−0.0150	−0.5936
250	1.2907	– 0.0199	– 0.9569	0.6918	−0.0292	−0.5908
100	—	– 0.0469	– 0.9543	—	−0.0676	−0.5820

Figure 5 shows theoretical $\pi = f(pH)$ curves and the corresponding derivative curves calculated with complete Equations 8 and 12, respectively, and its decomposition after subtracting the contribution of H into two individual peaks. The curve (buffer solution) is compared to the corresponding curve of a solution (no buffering) that contains only water and strong acids.

It is well known that if the titration $V = f(pH)$ curve is very step and if many readings are taken in the region of highest slope, the equivalence volume may be estimates with satisfactory accuracy, from the minima in the derivative dV/dpH (maximum dpH/dV slope). Nevertheless, the existence of multiple peaks (231) in the immediate vicinity of the equivalence point of the differential titration curves sometimes introduce an uncertainty in the choice of the exact volume of the equivalence volume.

This behavior could be attributed to two facts (232). First, the process of obtaining derivatives from experimental data usually results in a decrease in accuracy. Second, in the neighborhood of the equivalence point the response of the glass electrode couple was slower than that observed in the buffer regions of the same titration curve. Instrumental analysis techniques that employ measurements based on inflection points may have their accuracy compromised due to the need for signal differentiation, which is very sensitive to instrumental noise (150). However, note that the location of the maxima in the $-\Delta\tilde{n}/\Delta pH$ versus pH (symmetric) curve for a diprotic acid involves measurements of pH in buffered solutions, which are more precise that those carried out in unbuffered ones. Note also that for a diprotic acid, the central minimum in the $-\Delta\tilde{n}/\Delta pH$ versus pH (symmetric) curve coincides with the first equivalence point of the

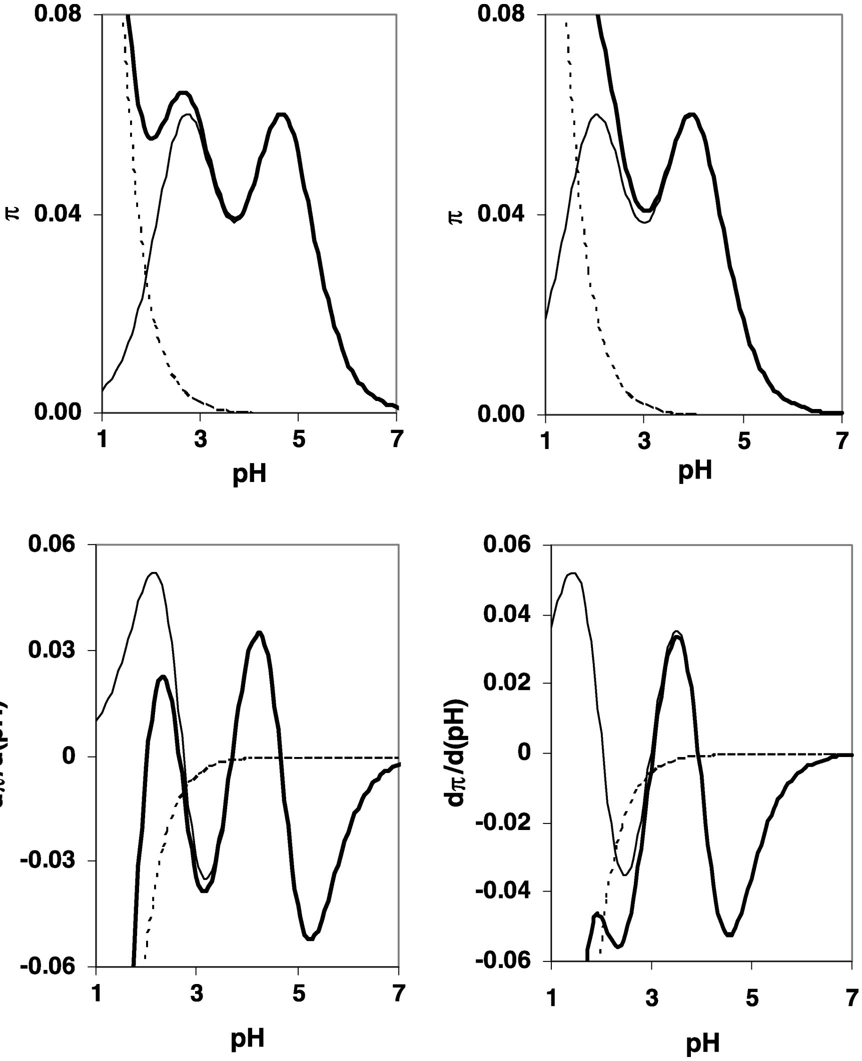

FIG. 5. Buffer index against pH (top) and derivative curve (dawn) for a diprotic acid with $R = 10$ and $C_R = 0.1$. Left side: $\log \beta_2 = 7.398$. Right side: $\log \beta_2 = 6.000$. The solid line is the overall function and the thin line is the approximation that neglects the contribution of $[H]$, which is also depicted as a dotted line, in both cases.

titration $V = f(pH)$ curve, being the slope at this later point less pronounced as pK_{a2} approaches pK_{a1}.

Automatic titration instruments produce a continuous record of potential versus milliliter of titrant added and also of the rate of change of cell emf with change in volume, which easily allows singular point detection with a relatively high degree of accuracy and precision (233–235).

INFLEXION POINTS

Differentiating Equation 24, we have

$$\frac{d^2\pi}{d(pH)^2} = - \ln^3 10\left[\frac{C_R y}{(1+Ry+y^2)^4}(-Ry^6 + 4(R^2-4)y^5 + R(-R^2+13)y^4 + 8(-R^2+8)y^3 + R(-R^2+13)y^2 + 4(R^2-4)y - R) - [H] + [OH]\right] \quad [51]$$

which is depicted in Figure 1c assuming $[H]$ and $[OH]$to be negligible.

By making

$$z = y + \frac{1}{y} \quad [52]$$

we easily get

$$\frac{d^2\pi}{d(pH)^2} = \ln^3 10\left(C_R\left(\frac{Rz^3 + (16-4R^2)z^2 + (R^3-16R)z + 16R^2 - 96}{(z+R)^4}\right) - [H] - [OH]\right) \quad [53]$$

TABLE 7
Inflexion points and maxima points in the buffer index curves for a diprotic acid

R	$\pm \log y''$		$\pm \log y'$
2	0.5719		0
3	0.8564		0
4	1.0653		0
5	1.2024	0.2670	0.4878
10	1.5553	0.5198	0.9586
25	1.9673	0.8490	1.3916
50	2.2703	1.1334	1.6974
100	2.5718	1.4297	1.9996
500	3.2709	2.1271	2.6990

In those cases $d^2\pi/d\,(pH)^2 = 0$ requires

$$z''^3 + \left(\frac{16}{R} - 4R\right)z''^2 + \left(R^2 - 16\right)z'' + 16R - \frac{96}{R} = 0 \quad [54]$$

and from the roots of Equation 54 we may obtain (Equation 52) the $\log y''$ values (Table 7)

$$\log y'' = \pm\frac{1}{\ln 10} ar\cosh\left(\frac{z''}{2}\right) \quad [55]$$

As the value of R rises, $pH'_{(2)} \to pK_{a1}$, $pH'_{(3)} \to pK_{a2}$, the difference between the maxima and the inflexion point reaches the limiting value of 0.5719, as in the monoprotic acid case.

The maxima and minimum for the case of a diprotic acid with R value equal to 10 are depicted in Figure 6 (left) whereas in Figure 6 (right) is shown the four inflexion points of the π curve. Calculation of the first and second derivative of a data set, however, tends to emphasize the noise in the data set; that is, small errors in the measurements become relatively much more important (236).

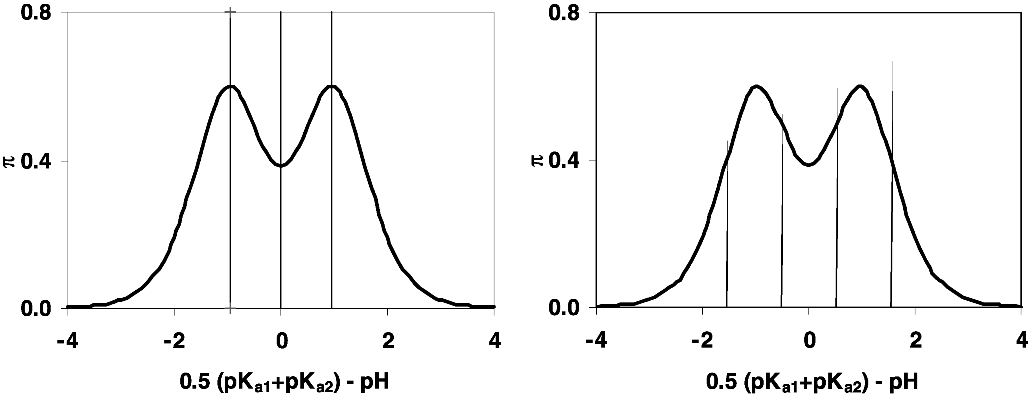

FIG. 6. Buffer index (capacity) curve against for a diprotic acid with $R = 10\,(\Delta pK_a = 2)$ and $C_R = 0.1$; $[H]$ and $[OH]$ being negligible. Left: Two maxima and one minimum. Right: Four inflexion points.

HALF-VALUES OF THE FORMATION FUNCTION

It is illuminating to analyze (237,238) the relationship between the ratio of the acidity constants at the half-values of the formation function $\tilde{n}$ (average number of protons bound per R). It is easily shown from Equation 37 that

$$(2-\tilde{n})\,y^2 + R\,(1-\tilde{n})\,y - \tilde{n} = 0 \qquad [56]$$

Expression 56 is a quadratic equation of y with the physically meaningful root

$$y = \frac{-R\,(1-\tilde{n}) + \sqrt{R^2\,(1-\tilde{n})^2 + 4\,(2-\tilde{n})\,\tilde{n}}}{2\,(2-\tilde{n})} \qquad [57]$$

This relationship is particularly simple for the half-values; Equation 57 can be written as

$$y_{0.5} = \frac{-\frac{R}{2} + \sqrt{\left(\frac{R}{2}\right)^2 + 3}}{3} \qquad [58]$$

$$y_{1.5} = \frac{R}{2} + \sqrt{\left(\frac{R}{2}\right)^2 + 3} \qquad [59]$$

By dividing Equation 59 by 58 and taking into account Equation 21 we get

$$\frac{y_{1.5}}{y_{0.5}} = \frac{[H]_{1.5}}{[H]_{0.5}} = \left[\frac{R}{2} + \sqrt{\left(\frac{R}{2}\right)^2 + 3}\right]^2 \qquad [60]$$

and then (97) we have

$$10^{2\Delta pH} - R \cdot 10^{\Delta pH} - 3 = 0 \qquad [61]$$

where

$$\Delta pH = pH_{1.0} - pH_{1.5} = pH_{0.5} - pH_{1.0} \qquad [62]$$

for which we obtain

$$R = 10^{\Delta pH} - \frac{3}{10^{\Delta pH}} = \sqrt{3}(10^{\Delta pH - \log 3} - 10^{-\Delta pH + \log 3}) \qquad [63]$$

and taking into account the properties of hyperbolic sine

$$R = 2\sqrt{3}\sinh(\ln 10(\Delta pH - \log\sqrt{3})) \qquad [64]$$

Conversely, Equation 64 yields

$$\begin{aligned}\Delta pH* &= pH_{0.5} - pH_{1.5} = 2\Delta pH \\ &= 2\log e\, a\sinh\left(\frac{R}{2\sqrt{3}}\right) + \log 3\end{aligned} \qquad [65]$$

Equation 65 allow us to evaluate the pH increment from the knowledge of the square root of the K_{a1} by K_{a2} ratio (Figure 7). When $R = 2$; $K_{a1}/K_{a2} = 4$; and

$$\Delta pH* = 2\log 3 = 0.9542 \qquad [66]$$

Note that for a diprotic acid, when $[OH]$ and $[H]$ are negligible, $\tilde{n} = 2 - T$, and (239) $\Delta pH* = pH_{0.5} - pH_{1.5} = T_{3/4} - T_{1/4}$, where T is the fraction titrated $T = C_B V/(C_R V_0)$.

For the titration of a weak monoprotic acid

$$\tilde{n} = \frac{\beta_1\,[H]}{1 + \beta_1\,[H]} = \frac{\frac{[H]}{K_a}}{1 + \frac{[H]}{K_a}} = \frac{p}{1+p} \qquad [67]$$

and

$$\frac{p_{0.75}}{p_{0.25}} = \frac{[H]_{0.75}}{[H]_{0.25}} = 9 \qquad [68]$$

and then

$$pH_{0.25} - pH_{0.75} = 2\log 3 = 0.9542 \qquad [69]$$

For a monoprotic acid with $[OH]$ and $[H]$ negligible, we get $\tilde{n} = 1 - T$, and $pH_{0.25} - pH_{0.75} = T_{3/4} - T_{1/4}$. Thus for a monoprotic acid the change in pH (239) between the one-fourth and three-fourths titrations is seen to be 0.954. The pH increment is usually greater than 1 for diprotic acids; so that the diprotic acid curve has a steeper slope (239, 240) thorough the buffer region. This criterion is attractive because of its simplicity, is also applicable in nonaqueous medium (241), and may be used to distinguish between weak monobasic acid and weak dibasic (or polybasic) acids under specific conditions (242–244).

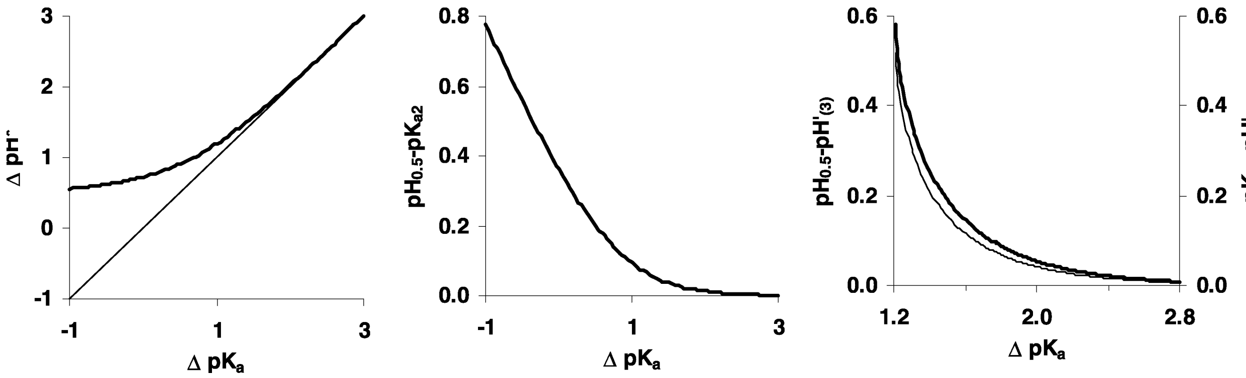

FIG. 7. Left: Representation of $\Delta pH* = pH_{0.5} - pH_{1.5}$ against ΔpK_a. Middle: Representation of $pH_{0.5} - pK_{a2}$ against ΔpK_a. Right: Representation of $pH_{0.5} - pH'_{(3)}$ against ΔpK_a (solid line) and$pK_{a2} - pH'_{(3)}$ against ΔpK_a (thin line).

POLYPROTIC WEAK ACIDS INDISTINGUISHABLE FROM MONOPROTIC BY TITRIMETRY

The problem of discerning the conditions under which a solution of a monoprotic acid gives a titration curve indistinguishable from that for a polyprotic one has been envisaged by Meites (216, 222, 245). In that follows, this problem is approached (246) from a different standpoint. For a polyprotic acid $H_N R$ having successive acidity constants $K_{a1}, K_{a2}, \ldots K_{aN}$, from the mass balance $C_R V_0/(V_0+V) = \sum [H_j R]$ and the electroneutrality rule, Equation 4 with $[B] = C_B V/(V_0+V)$, we obtain the average number of protons bound as

$$\tilde{n} = \frac{C_H - [H]}{C_R} = N - \frac{C_B V}{C_A V_0} - \frac{[H] - \frac{K_w^c}{[H]}}{C_R \frac{V_0}{V_0+V}} \qquad [70]$$

where V_0 is the initial volume of acid of concentration C_R, V is the volume of titrant added of concentration C_B, and $K_w^c = [H][OH]$ is measured if necessary in the same electrolyte medium used to maintain ionic strength during the acid-base titration (247); $\tilde{n}$ is the average number of protons bound per species R, $\tilde{n} = \sum j f_j$ (Equation 2). In some cases it may be necessary to add a known quantity of strong acid to the solution of weak acid prior to titration. On rearranging Equation 70 we get

$$V = V_0 \frac{[OH] - [H] + (N - \tilde{n}) C_R}{C_B + [H] - [OH]} \qquad [71]$$

f_j (Equation 1) denotes the degree of formation of the species $H_j R$

$$f_j = \frac{[H]^j \prod_{i=1}^{i=N-j} K_{ai}}{[H]^N + K_{a1}[H]^{N-1} + \cdots + K_{a1} \cdots K_{aj}[H]^{N-j} + K_{a1} K_2 \cdots K_{aN}} \qquad [72]$$

Equation 71 may also be applied to a monoprotic acid ($N = 1$) having acidity constant K_a^*, and thus, the titration curves for a monoprotic acid (m) and a polyprotic (p) acid will be identical if and only if

$$[(N - \tilde{n}) C_R]_p = [(N - \tilde{n}) C_R]_m \qquad [73]$$

Taking into account the definition of $\tilde{n}$, Equation 73 is easily converted into

$$[f_{N-1} + 2 f_{N-2} + \ldots + N f_0]_p C_{R,p} = f_{0,m} C_{R,m} \qquad [74]$$

By substituting the corresponding f_j values given by Equation (72) and making

$$r = \frac{C_{R,m}}{C_{R,p}} \qquad [75]$$

we have

$$\begin{aligned} &[K_{a1}[H]^{N-1} + 2K_{a1}K_{a2}[H]^{N-2} + \cdots + N K_{a1} K_{a2} \ldots K_{aN}] \\ &(K_a^* + [H]) = K_a^* r [[H]^N + K_{a1}[H]^{N-1} + K_{a1}K_{a2}[H]^{N-2} \\ &\quad + \cdots + K_{a1}K_{a2} \ldots K_{aN}] \end{aligned} \qquad [76]$$

After some algebraic manipulation we get

$$\begin{aligned} &[K_a^*(-r) + K_{a1}][H]^N + \cdots + [K_a^*(j-1-r) + jK_{aj}] \\ &\quad K_{a1}K_{a2} \ldots K_{a,j-1}[H]^{N-(j-1)} \\ &\quad + \cdots + (N-r)K_a^* K_{a1} K_{a2} \ldots K_{aN} = 0 \end{aligned} \qquad [77]$$

For each of the successive powers of $[H]$ the requirements for Equation 77 to be zero is

$$C_{R,m} = N C_{R,p} \qquad [78]$$

(from the constant term and Equation 75) and

$$\begin{aligned} K_{aN} &= \frac{K_a^*}{N} \cdots \\ K_{aj} &= K_a^* \frac{N-(j-1)}{j} \cdots \\ K_{a1} &= K_a^* N \end{aligned} \qquad [79\ \text{a,b,c}]$$

The condition given by Equation 78 is introduced "a priori" by Meites (Equation 11 of reference 222). In fact, Equations 10 and 12 of Meites's paper are also a consequence of the identity 78 being true, as we will show in the following. In effect, by dividing Equation 78 by C_B we get the relationship between the dilution parameters for the monoprotic (r_m) and polyprotic (r_p) acids

$$r_m = N r_p \qquad [80]$$

On the other hand, by multiplying Equation 78 though by $V_0/(V_B C_B)$ on rearrangement we get instead

$$T_m = \frac{T_p}{N} \qquad [81]$$

being T_m and T_p the corresponding titration parameters for the monoprotic (T_m) and polyprotic (T_p) acids.

From Equations 79a, 79b and 79c, we have that the successive acidity constants of the polyprotic acid must be related by means of the Equation 49, which has been derived now. From Equations 79a, 79b and 79c, we also found that the acidity constants of the polyprotic acid and that of the monoprotic one are related by means of

$$K_{a1}K_{aN} = K_{a2}K_{a,N-1} = \cdots = K_{aj}K_{a,N-j+1} = K_a^{*2} \qquad [82]$$

from which

$$K_a^* = \sqrt{K_{aj} K_{a,N-j+1}} \qquad [83]$$

By making in Equation 83 $j = N/2 - k$, we obtain the Equation 19 of Meites's paper (222). Meites also gives a table that lists the ratios computed from Equation 49 for values of N ranging 2 to 6, indicating that for values of N equal to 2 and 3 the ratios were in agreement with previous values deduced by others, whereas for higher values of N, no data had been found in the literature. However, values of the statistical ratios of successive constants varying N from 2 to 6 were given previously by Beck (221) and Sen (223).

Kankare derived the same equations to distinguish polyprotic acids from monofunctional ones by using a different and rigorously algebraic approach (248). The same problem is treated with numerical computer methods. The characteristic deviation pattern obtained by fitting the titration curve of a monoprotic acid to that of the unknown acid reveals the number of removable protons in the acid. The titration curve of a diprotic acid resembles that of a mixture of (249–251) two monoprotic acids. As early as 1928, Simms postulated that polyvalent acids may be considered (249, 250) in a certain sense as a mixture of monoprotic ones, and proves that an n-protic acid can be replaced by n monoprotic acids. Simms titration constants can be expressed as the intrinsic constants of the individual groups (also called microscopic constants). Then, when titration results are evaluated mathematically, the calculations can be simplified and generalized by regarding (219) complexes of type A_nB as n complexes of type AB. Klas used (252) the Simms formula in order to facilitate the calculation of the hydrogen-ion concentration of aqueous solution of several polyprotic acids and to calculate stability constants of complexes (253).

TRIPROTIC AND TETRAPROTIC ACIDS

For a triprotic acid, from Equation 8, with H and OH neglected we have

$$\pi = \ln 10 C_R \left(f_1 (1 - \tilde{n}) + 2 f_2 (2 - \tilde{n}) + 3 f_3 (3 - \tilde{n})\right) \quad [84]$$

By substituting $j - \tilde{n} \quad (j = 0, 1, 2)$ as a function of molar fractions, after rearrangement we get

$$\pi = \ln 10 C_R \left(f_0 (f_1 + 4 f_2 + 9 f_3) + f_1 (f_2 + 4 f_3)\right) \quad [85]$$

as indicated by Perrin and Dempsey (254).

For a tetraprotic acid, from Equation 8 we get

$$\begin{aligned}\pi = {} & \ln 10 C_R (f_0 (f_1 + 4 f_2 + 9 f_3 + 16 f_4) \\ & + f_1 (f_2 + 4 f_3 + 9 f_4) + f_2 (f_3 + 4 f_4) + f_3 f_4) \quad [86]\end{aligned}$$

A search to Equations 12, 14, 28 and 29 reveals that they have the general form (255-257)

$$\pi = \ln 10 C_R \left(\sum_{j=0}^{N-1} f_j \left(\sum_{n=j+1}^{N} (n - j)^2 f_n\right)\right) \quad [87]$$

A BASIC program based on Equations 1, 2, 9 and 11 was written to perform the necessary calculations. The generated data was stored in ASCII format disk files that can be loaded into the spreadsheet for publication quality graphs. A printout of the program is available from the authors. In Figure 8 the formation curve for a triprotic acid such as citric acid and the $\pi = f(pH)$ and $d\pi/dpH$ curves, respectively, are depicted. The $\pi = f(pH)$ is characterized by a slope considerably smaller in the region where the weak acid undergoes multiple ionization steps. The efficient buffer capacity of citric acid extends over an approximate range of $pK_{a2} \pm 1.8$. Citric acid is of considerable importance because its ability to form stable complexes with metallic and non-metallic ions. Citric acid represents the major portion of the total organic acid content of grapefruit, lemon and orange juices (258–260). Citric acid is a well-known masking agent, the stability constants of the various chelates being a measure of its masking effectiveness. Citric acid is a protolyte with symmetrically spaced pK_a values; this symmetry implies a mathematical simplification that makes it possible to deduce the locations and magnitudes of the maxima and minima (261).

The formation curve corresponding to a tetraprotic acid such as N, N'-bis(3-aminopropyl)ethylendiamine (236, 262) is reproduced in Figure 9, together with the $-\Delta\tilde{n}/\Delta pH$ and $-\Delta^2\tilde{n}/\Delta pH^2$, obtained by successive graphic differentiation of the $\tilde{n} = f(pH)$ curve.

APPLICATIONS

Titrations are useful analytical tools for determining chemical amounts, important in routine practice in many laboratories (167, 263–264), but they also provide a major route to the determination of equilibrium constants (219, 221, 265). The above

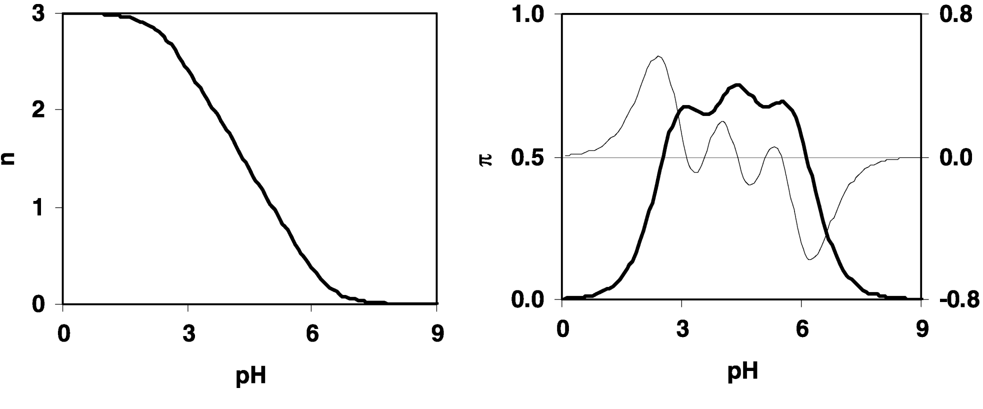

FIG. 8. Citric acid system: $C_R = 0.1$, $pK_{a1} = 2.93$, $pK_{a2} = 4.36$, $pK_{a3} = 5.74$. Left side: formation function $\tilde{n} = f(pH)$. Right side: buffer index $\pi = f(pH)$ curve (gross line) and its derivative $d\pi/d\,pH$ curve (thin line).

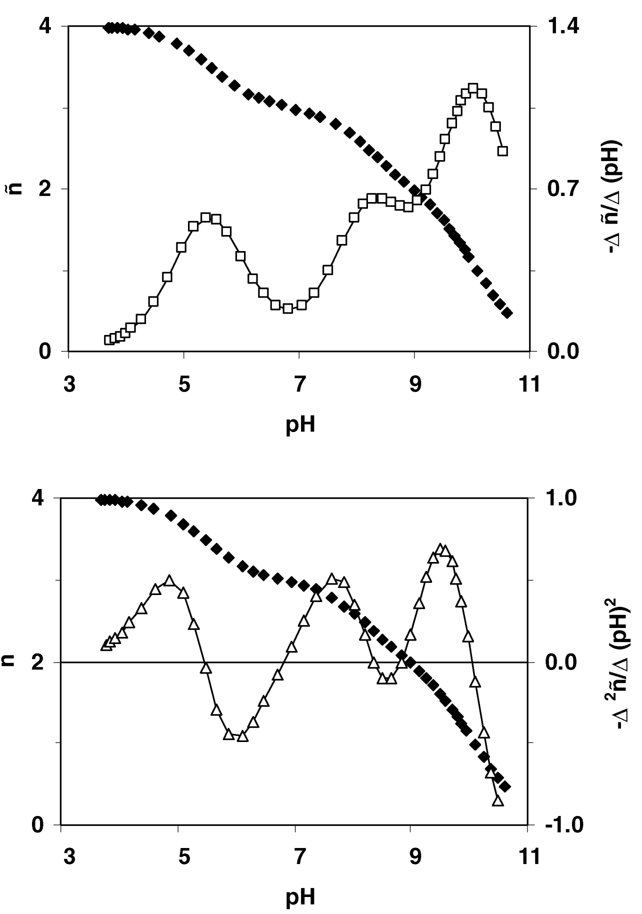

FIG. 9. N,N-bis(3-aminopropyl)ethylenediamine: $pK_{a1} = 5.44$, $pK_{a2} = 8.21$, $pK_{a3} = 9.74$, $pK_{a4} = 10.42$. Top: formation function (♦) and its graphical derivative (□) curve (buffer index curve for $C_R = 1$). Bottom: formation function curve (♦) and its second derivative (△) curve obtained by graphic differentiation.

methods explained, based on the use of Equations 33–35 and 46, 34 and 35, have been applied to literature data (266–270). Experimental details and volume versus pH data employed for two typical examples are given in here:

o-Methoxyphenyliminodiacetic Acid (269). $C_R = 1.173$ E-03 M; $V_0 = 100$ ml; $C_B = 0.11$ M KOH (carbonate-free). Ionic strength I=0.10-potassium nitrate. T = 20°C. Data pairs $\{V, pH\}$: 0, 3.135, 0.1, 3.189; 0.2, 3.240; 0.3, 3.298; 0.4, 3.361; 0.5, 3.440; 0.6, 3.531; 0.7, 3.642; 0.8, 3.787; 0.9, 3.989; 1.0, 4.263; 1.1, 4.600; 1.2, 4.880; 1.3, 5.095; 1.4, 5.277; 1.5, 5.446; 1.6, 5.607; 1.7, 5.775; 1.8, 5.961; 1.9, 6.190; 2, 6.531; 2.1, 7.620; 2.2, 9.519; 2.3, 9.917. A Radiometer pH-meter type $PHM4$ with a glass electrode and a saturated calomel reference electrode was used for the measurement of hydrogen-ion concentration. The glass electrode was calibrated by titrating a solution of perchloric acid in 0.1M-potassium nitrate.

Ethylmalonic Acid. (266):$C_R = 0.05905$ M; $V_0 = 150$ ml; $C_B = 1.596$. Data pairs $\{V, pH\}$: 0, 2.132, 0.25, 2.205, 0.48, 2.269; 0.88, 2.389; 1.32, 2.52; 1.78, 2.652; 2.27, 2.789; 2.88, 2.956; 3.35, 3.092; 3.75, 3.221; 4.2, 3.392; 4.62; 3.571; 4.98, 3.773; 5.18, 3.911; 5.5 4.181; 5.9, 4.553; 6.21, 4.762; 6.61; 4.965; 7.01, 5.12; 7.42, 5.272; 7.78; 5.388; 8.29, 5.536; 8.7, 5.66; 9.15, 5.807; 9.56, 5.956; 9.98, 6.136. Additional experimental details may be consulted in the original reference (266) i.e., all hydrogen potential measurements were made with accurately calibrated apparatus (hydrogen electrode) at 25°C. The alkali used was carbonate-free sodium hydroxide, and the solutions of the acids were made up with air-free distilled water immediately before use.

The titration data of an acid consists of measurement of the hydrogen ion concentration when different volumes V of the strong base of concentration C_B have been added to a initial volume V_0 of the acid at concentration C_R. The titration curve can be transformed into a formation function profile $\tilde{n} = f(pH)$ with an appropriate mathematical algorithm, in which a measure of the buffer capacity in each point is calculated as the minus derivative $-d\tilde{n}/dpH$. Note that strictly speaking, the ability of a solution to resist attempts to change its pH, called buffer capacity is volume dependent (271–273)

$$\pi = \frac{d\left(\frac{C_B V}{C_R V_0}\right)}{dpH} = \frac{C_B V}{(V_0 + V)^2}\frac{dV}{dpH} \qquad [88]$$

and is related to the formation function by means of a complex formula (which we will derive later), which in the middle of the pH scale is reduced to

$$\pi = -\left(\frac{V_0}{V_0 + V}\right)^2 C_R \frac{d\tilde{n}}{dpH} \qquad [89]$$

and then the buffer capacity is the minus C_R times the derivative of the formation function when the sample is titrated with infinitely concentrated strong base.

However, the graphic procedure referred to here is based on the relation that, on the one hand, the $\tilde{n}$ versus pH curves for diprotic acids are symmetric for $\tilde{n} = 1$, whereas the shape of the formation curve is determined by the K_{a1}/K_{a2} ratio (274). The evaluation of acidity constants proceeds as follows:

(i) Experimental data pairs (V, pH) are converted into $(\tilde{n}, pH)$ by means of Equation 70.
(ii) Then, the $-\Delta\tilde{n}/\Delta pH$ versus pH curve ($\tilde{n} \propto \pi$) is obtained by graphic differentiation with the use of very small increments in pH; a number of (V, pH) data closely spaced is required.
(iii) Approximate the $-\Delta\tilde{n}/\Delta pH$ curve in the neighborhood of the minimum and maximum by a third-order polynomial and setting its derivative equal to zero.

In fact, titration curves in the vicinity of half-neutralization (namely between 32% and 64% of the neutralization), can be fitted by a least-squares technique (275–279) to a polynomial equation (167–168). Alternatively, locate the $pH_{\tilde{n}=1.0}$ in the $\tilde{n} - pH$ curve as the minimum in the derivative curve, which is not always easy to locate.

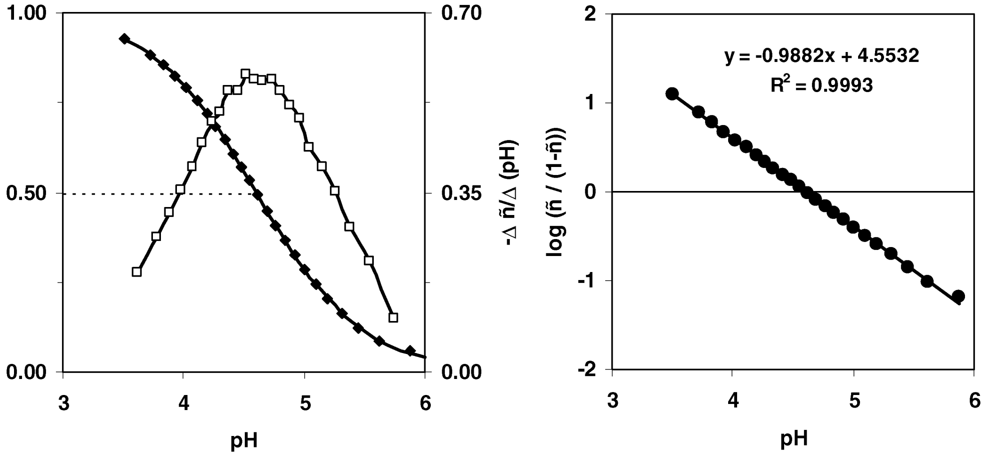

FIG. 10. 3-(3(Trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-one system. Left side: formation $\tilde{n} = f(pH)$ curve (♦) and $-\Delta\tilde{n}/\Delta pH$ curve (□), obtained by graphic differentiation. The solid lines are calculated with the pK_a value given in the text. Right side: graphical evaluation of $\log \beta_1 = pK_a$.

The values of the difference quotient in the flat parts of a titration curve are extremely sensitive to instrumental noise.

(iv) Calculate $\Delta pH'$either from the two maxima or from one of the maxima and the mid-point minima.

(v) Calculate the R value either from Equation 33 or 46 in cases of moderate or strong overlapping equilibria, respectively.

(vi) Finally apply Equations 34 and 35 to obtain the $pK_{a1}$and pK_{a2} values.

The calculated pK_a values evaluated in this study are shown in Table 8 for moderate overlapping equilibria and in Table 9 for strong overlapping equilibria. The numerical method of Auerbach and Smolcyk (280) was applied in the original studies of Gane and Ingold (266–267), in which the effect of ionic strength upon acid-base equilibria was neglected, the pK_a values being reported with two significant numbers. The dilution is such that the activity coefficient at intermediate pH values may be taken as unity. We reported values with three digits in all cases instead, even if they are not all significant. To check the computed values the acidity constants were also determined by the graphical method of Irving and Rossotti (281–283). The basic equation for calculating β_j as defined by Equation 2 is given by

$$\sum_{0}^{N} (\bar{n} - \tilde{n})\beta_n\,[H]^{\bar{n}} = 0 \qquad [90]$$

For systems in which $N = 1$

$$\frac{\tilde{n}}{(1-\tilde{n})} = \beta_1\,[H] \qquad [91]$$

A plot of the logarithm of the left side againstpH yields a straight line of -1 slope which at $\log \beta_1 = pK_a$. For systems in which $N = 2$, we may write Equation 90 in a linear form to give

$$\frac{\tilde{n}}{(1-\tilde{n})\,[H]} = \beta_1 + \frac{(2-\tilde{n})}{(1-\tilde{n})}\,[H]\,\beta_2 \qquad [92]$$

An xy plot where $\tilde{n}/((1-\tilde{n})\,[H])$ is y and $((2-\tilde{n})/(1-\tilde{n}))\,[H]$ is x should yield a straight line, calculated by the least squares method, whose slope is $\beta_2 = 1/(K_{a1}K_{a2})$ and intercept is $\beta_1 = 1/K_{a2}$. The calculations are done with the spreadsheet Microsoft Excel (version 2003). Points in the region of integral values of $\tilde{n}$ lead to leverage values and must be discarded. Only points in the region $0.05 \leq \tilde{n} \leq 0.95$ and $1.05 \leq \tilde{n} \leq 1.95$ were used (284–288).

The $\tilde{n} = f(pH)$ data for the 3-(3-(Trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-one monoprotic acid system (Figure 10) leads to a pK_a value of 4.605, obtained from the $\tilde{n} = 0.5$ point and to a value of 4.608 from the logarithmic form of Equation 91. Non linear regression analysis based on Solver Excel and Billo's SOLVSTAT (99) leads to a value of4.60 ± 0.01.

The buffer value is a quantity related to titrations. The traditional acid-base titration curve provides the pH as a function of the volume V of the titrant added, or of the titration degree Tdefined as the quotient $C_B V/(C_R V_0)$. Formation curves for diprotic acid systems, as the plots $\tilde{n} = f(pH)$ are called are shown in Figures 11 to 14. The central part of the plot may be a single sigmoid curve that rises linearly between about $\tilde{n} = 0.5$ and $\tilde{n} = 1.5$ as in Figures 13 and 14. Some formation curves are composed of the two distinct sigmoid steps (Figures 11 and 12). A long plateau at $\tilde{n} = 1$ is obtained when $\Delta pK_a > 4$.

Results obtained for moderate overlapping pK_a values with the hyperbolic method based on the use of Equation 33, 34 and 35, as shown in Table 8, agree well, within the limits of experimental error, with those obtained by Gane and Ingold (266–268) and by the graphical Irving and Rossotti method. In the case of

TABLE 8
Evaluation of acidity constanst of diprotic acids with moderate overlapping pKa values

Titration pairs data	System	$pH_{1.0}$or (pH at minimum)	pH at right maximum	$pK_{a1}$and pK_{a2} Eq. (34), (35) and (36)	pK_aIrving and Rossotti (this paper)	Data pairs $\tilde{n}$*	pK_aGane and Ingold, (30–32)
32	Ethylmalonic acid	4.237	5.532	2.932	2.891	29	2.90
				5.542	5.568		5.55
32	Isopropylmalonic acid	4.406	5.799	3.007	2.924	18	2.93
				5.805	5.814		5.80
32	Malonic acid	4.064	5.271	2.843	2.752	21	2.75
				5.285	5.367		5.36
20	Methylmalonic acid	4.238.	5.459	3.003	2.978	17	2.97
				5.473	5.469		5.46
28	$\tilde{n}$-Propylmalonic acid	(4.315)	5.630	2.991	2.972	20	2.97
				5.639	5.714		5.68
30	Diethylglutaric acid	(5.265)	7.113	3.416	3.464	18	3.46
				7.114	7.108		7.11
36	Dimethylglutaric acid	4.959	6.254	3.654	3.695	30	3.69
				6.264	6.260		6.26
30	Cicloheptane-1,1-diacetic acid	5.281	7.026	3.535	3.558	20	3.56
				7.027	7.001		6.96
27	Ciclopentane-1,1-diacetic acid	5.239	6.596	3.875	3.815	20	3.77
				6.603	6.603		6.58
24	o-methoxyphenyl-iminodiacetic acid	(4.198)	5.534	2.854	2.916	18	—
				5.542	5.597		

*used in the Irving and Rossotti method (this paper).

TABLE 9
Evaluation of acidity constanst of diprotic acids with strong overlapping pKa values

Titration pairs data	System	$pH_{1.0}$	$D_{1.0}$	pK_a Eq. (42), (35) and (36)	pK_a Irving and Rossotti (this paper)	Data pairs $\tilde{n}$*	pK_a Gane and Ingold, (30–32)
19	As,As-Di(2-carboxyethyl)p-chlorophenylarsine acid	4.264	−1.0227	4.231 5.027	4.235 5.030	17	—
23	As,As-Di(carboxymethyl)-phenylarsine acid	4.330	−0.6408	3.615 5.045	3.598 5.060	20	—
29	β−Methylglutaric acid	4.722	−0.8991	4.228 5.216	4.241 5.201	25	4.24 5.20
24	β−$\tilde{n}$-Propylglutaric acid	4.834.	−0.8508	4.301 5.367	4.305 5.363	22	4.30 5.36
19	Succinic acid	4.739	−0.7772	4.145 5.333	4.118 5.355	13	4.13 5.35
37	Glutaric acid	4.809	−0.9140	4.326 5.292	4.330 5.286	28	4.34 5.27
38	Adipic acid	4.848	−0.9854	4.421 5.275	4.418 5.275	29	4.41 5.28
27	Pimelic acid	4.989	−1.0081	4.488 5.308	4.484 5.307	21	4.48 5.31
23	Suberic acid	4.930	−0.9966	4.512 5.348	4.532 5.327	18	4.51 5.33
31	Azelaic acid	4.973	−1.0412	4.589 5.357	4.608 5.340	24	4.55 5.33

*Used in the Irving and Rossotti method (this paper).

ethylmalonic acid the theoretical curve obtained with the values reported by us does not fit well with the experimental $\tilde{n}$ versus pH data in the acid side of the pH range; this is due presumably to the fact that constant ionic strength has been assumed in order to apply our calculation method.

Table 9 summarizes the results obtained for compounds whose acidity constants were similar in magnitude so that the buffer regions overlapping considerably (see Figure 1a); the agreement obtained among the method based on the use of Equations 46, 34 and 35 and the Irving and Rossotti method and the values reported by Gane and Ingold was excellent.

BUFFER CAPACITY WITH DILUTION EFFECTS: THE UNIVERSAL BUFFER SOLUTIONS CASE

The change of volume on addition of titrant is usually neglected in buffer calculations. It can be easily taken into account in the present approach. Rigorous relationship may be derived for the buffer index of polyprotic acids by making use of molar fraction, titration fraction and formation function; compact expressions very appropriate for computer usage are thus obtained. For simplicity, however, ionic strength is considered to be fixed.

From Equation 71

$$(C_B + [H] - [OH])\frac{dV}{dpH} + V\frac{d}{dpH}([H] - [OH]) = V_0\left(\frac{d}{dpH}([OH] - [H]) - C_R\frac{d\tilde{n}}{dpH}\right) \quad [93]$$

and taking into account that

$$\frac{d}{dpH}([H] \mp [OH]) = -\ln 10\,([H] \pm [OH]) \quad [94]$$

by simple algebra, it is easily be shown that the slope of the graph $V = f(pH)$ is given by

$$\frac{dV}{dpH} = V_0\frac{\ln 10\left(\frac{V_0+V}{V_0}\right)([H] + [OH]) - C_R\frac{d\tilde{n}}{dpH}}{C_B + [H] - [OH]} \quad [95]$$

By substituting dV/dpHgiven by Equation 95 into Equation 89

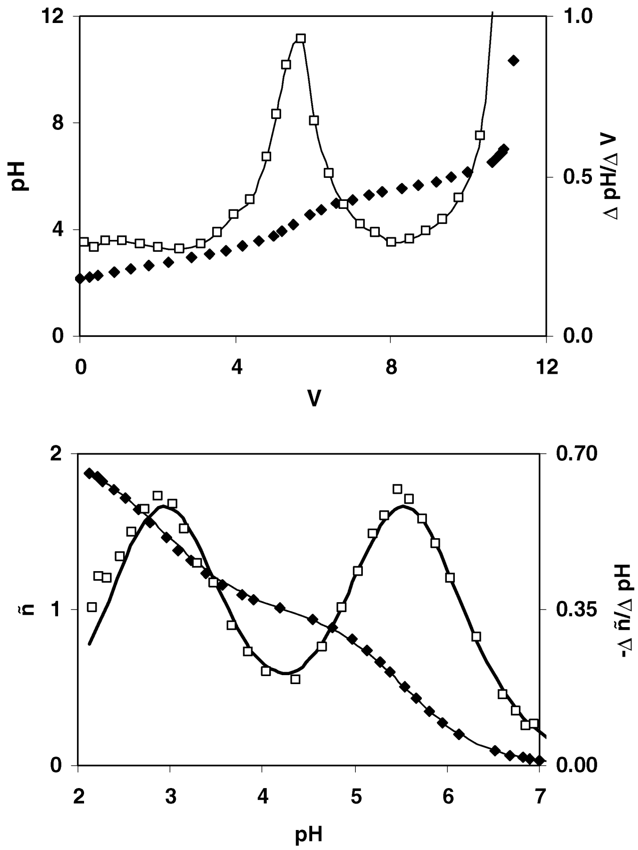

FIG. 11. Ethylmalonic acid system. Left side: Titration $V = f(pH)$ (♦) curve and its graphical derivative (□) curve. Right side: formation function $\tilde{n} = f(pH)$ curve (♦) and$-\Delta\tilde{n}/\Delta pH$ curve (□), obtained by graphic differentiation. The solid lines are calculated with the pK_a values given in the text.

we obtain

$$\pi = \frac{V_0^2}{(V+V_0)^2}\left[\frac{\ln 10\left(\frac{V_0+V}{V}\right)([H]+[OH]) - C_R\frac{d\tilde{n}}{dpH}}{1+\frac{[H]-[OH]}{C_B}}\right] \qquad [96]$$

The significance of Equation 96 is that it creates a link between the formation function and the buffer capacity. Thus, in the knowledge of the data on the formation function, the data in the buffer capacity can readily be calculated. The equation 96 is general and it may be extended to include any number of polyprotic acids, and forms a convenient basis for an algorithm for computer calculation of buffer capacity of mixtures of acids. Thus, for the titration of a mixture of k polyprotic acids$H_{N_i}R$ of concentration C_{R_i}, from Equations 96 and 97, we get

$$\pi = \ln 10\left[\left(\frac{V_0}{V_0+V}\right)([H]+[OH]) + \left(\frac{V_0}{V_0+V}\right)^2 \sum_{i=1}^{k}\left(C_{R_i}\sum_{j=1}^{N_i} j_i f_{ji}(j_i - \tilde{n}_i)\right)\right] \qquad [97]$$

The pK_a values of the components of universal buffer mixtures often lie quite close together, a situation that causes great difficulties in the traditional mathematical description of the resulting titration curves. The formalism given here does not suffer from such complications and is well suited for such calculation, which can readily be performed on, e.g., a simple spreadsheet.

On the other hand, from Equation 71 we may derive

$$1 + \frac{[H]-[OH]}{C_B} = \left(\frac{V_0}{V_0+V}\right)(1 + r\,(N - \tilde{n})) \qquad [98]$$

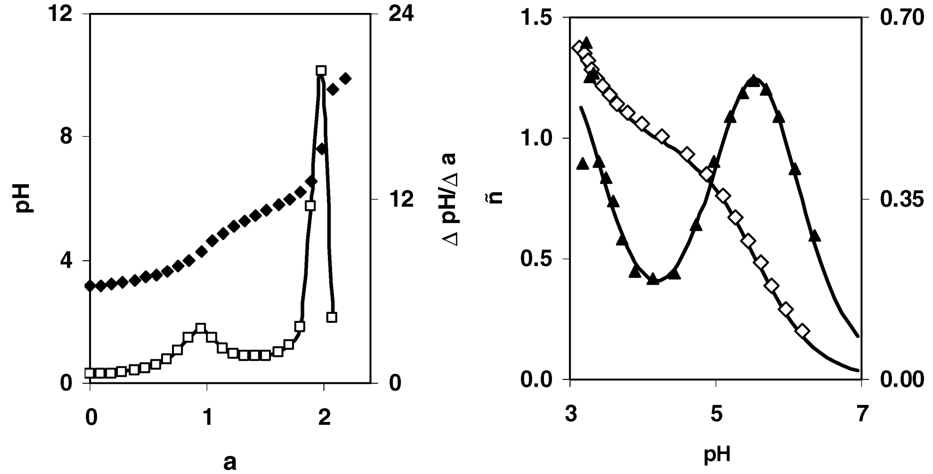

FIG. 12. o-methoxyphenyliminodiacetic acid system at 20°C and ionic strength of 0.1 (KNO_3). Left side: titration $a = f(pH)$ curve where a is the fraction titrated (dotted line) and its derivative (□) curve. Right side: formation $\tilde{n} = f(pH)$ curve (◇) and$-\Delta\tilde{n}/\Delta pH$ curve (▲), obtained by graphic differentiation. The solid lines are calculated with the pK_a values given in the text.

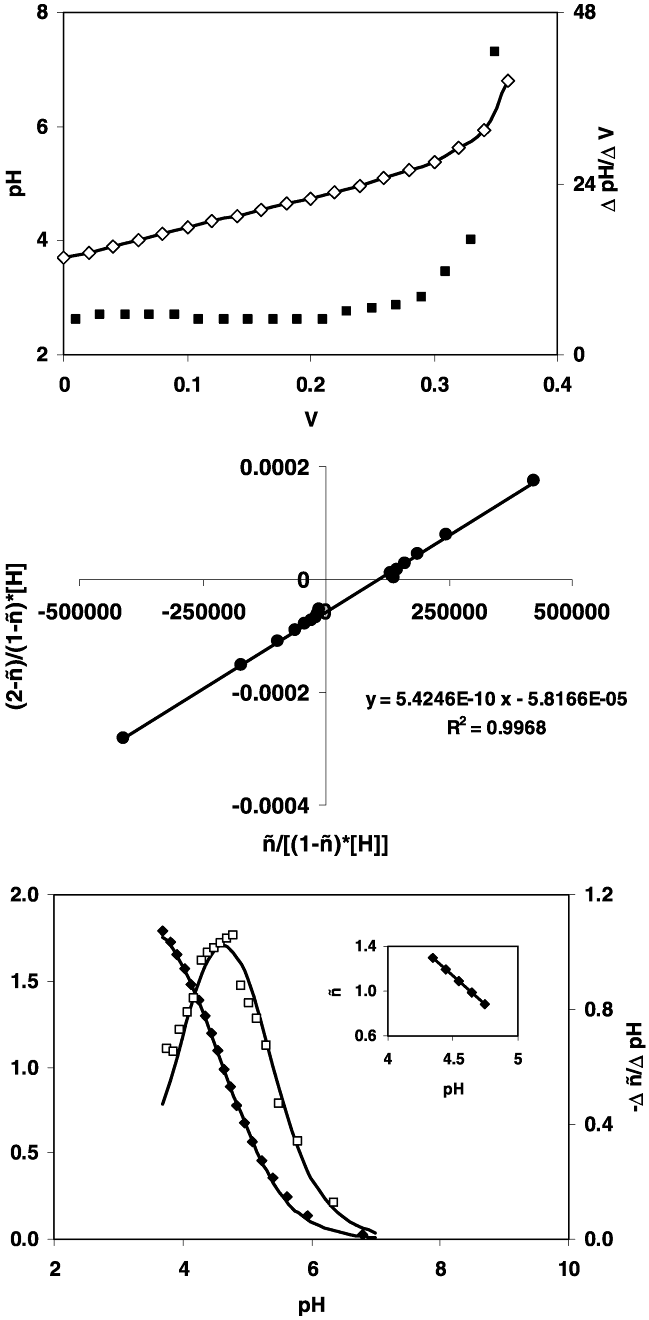

FIG. 13. As,As-di(2-carboxyethyl)p-chlorophenylarsine system. Top: titration $V = f(pH)$ curve (solid line) and its graphical derivative (■) curve. Middle: Irving-Rossotti graphical method for the evaluation of overlapping pK_{a1} and pK_{a2} values. Down: formation function$\tilde{n} = f(pH)$ curve (♦) and$-\Delta\tilde{n}/\Delta pH$ curve (□), obtained by graphic differentiation. The solid lines are calculated with the pK_a values given in the text. Inset: $\tilde{n} = f(pH)$ straight line function in the neighborhood of $\tilde{n} = 1$ ($y = -1.0227x + 5.7339$; R2 = 0.9999).

fi

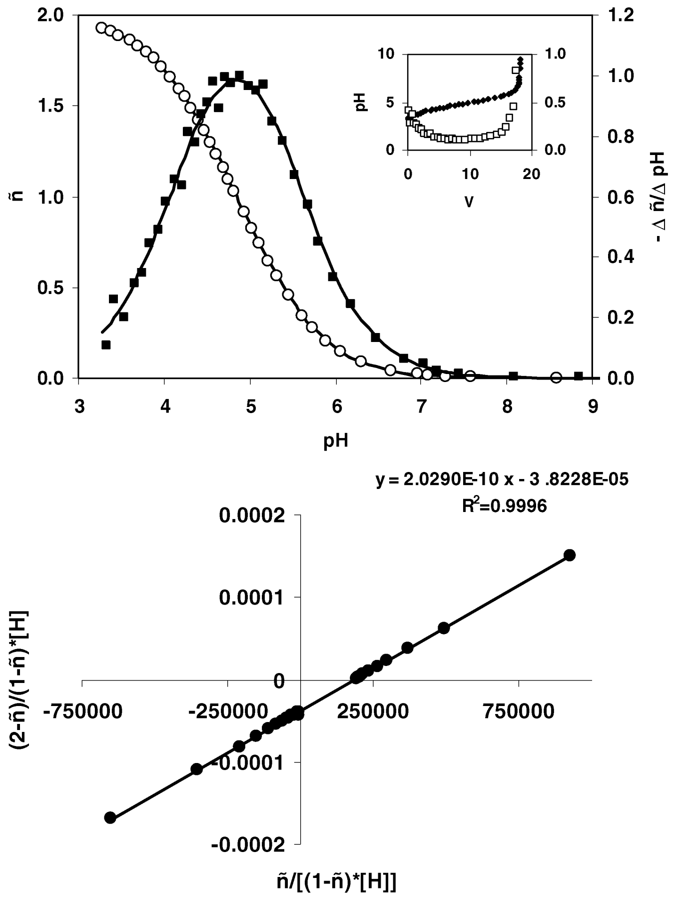

FIG. 14. Adipic acid system. Top: formation $\tilde{n} = f(pH)$ curve (○) and $-\Delta\tilde{n}/\Delta pH$ curve (■), obtained by graphic differentiation. The solid lines are calculated with the pK_a values given in the text. Inside: titration $V = f(pH)$ curve (♦) and its graphical derivative (□) curve. Bottom: Irving-Rossotti graphical method for the evaluation of overlapping pK_{a1} and pK_{a2} values.

where

$$r = \frac{C_R}{C_B} \qquad [99]$$

is the dilution parameter, and then the following relationship may be derived

$$\frac{V_0}{V_0 + V} = \frac{1}{1 + \frac{V}{V_0}} = \frac{1}{1 + Tr} \qquad [100]$$

where T is the degree of titration, $T = (C_B V)/C_R V_0$, or fraction titrated, as previously indicated twice.

Then, by combining Equations 7, 96, 98 and 100 we get finally for the buffer index of a polyprotic acid

$$\pi = \frac{\ln 10}{1 + r\,(N - \tilde{n})}\left([H] + [OH] + \frac{C_R \sum j f_j\,(j - \tilde{n})}{1 + Tr}\right) \qquad [101]$$

Note that if $Na_{N-x}H_xR$ is an ampholyte to be titrated with the strong base, Equations 98 and 101 go on being valid if we substitute N by x.

The sharpness index (37, 105, 289–291) can be easily related to the buffer index. Assuming that no strong acid was added before the beginning of the titration, the slope of the titration curve will be given by

$$\eta = \frac{dpH}{dT} = \frac{dpH}{d\left(\frac{C_B V}{C_R V_0}\right)} = \frac{C_R V_0}{C_B}\left(\frac{dpH}{dV}\right) \qquad [102]$$

Taking into account Equations 88 and 100

$$\eta = \left(\frac{V_0}{V_0 + V}\right)^2 \frac{C_R}{\pi} = \frac{C_R}{(1 + Tr)^2}\frac{1}{\pi} \qquad [103]$$

It is convenient to consider T as consisting of two parts, one solely as a function of concentration C_R and the pH of the point under consideration

$$\frac{dT}{dpH} = \frac{d}{dpH}\left(\frac{[OH] - [H]}{C_R \frac{V_0}{V_0 + V}}\right) - \frac{d\tilde{n}}{dpH} \qquad [104]$$

and when $[H]$ and $[OH]$ are negligible compared to the other acidic or basic species, a simple relationship between the sharpness index and the slope of the formation function is found

$$\eta = -\frac{1}{\left(\frac{d\tilde{n}}{dpH}\right)} \qquad [105]$$

and combining Equations 103 and 105 we obtain in those circumstances for the buffer capacity π the reduced expression

$$\pi = \frac{-C_R\left(\frac{d\tilde{n}}{dpH}\right)}{(1 + Tr)^2} \qquad [106]$$

CONCLUDING REMARKS

Buffer capacity, a continuous and nonlinear function, is a topic of great interest (4, 22–24, 125, 129, 292–294). Approximate calculation of a buffer value is of practical importance for the design of new buffer solutions. The existence of a simple expression for the buffer capacity, π, of a solution containing a polyprotic acid H_NR, has been subject of consideration (217, 295–297). This topic, in spite of its importance is widely scattered through the literature (5, 23, 129, 298) and for this reason it seems that a comprehensive theory should be developed to embody this conception.

The speciation of polyprotic acids (299, 300), on the other hand, is a common problem in analytical and pharmaceutical chemistry, the applications ranging from pH control in simple and complex experiments (301, 302) to the evaluation of acidity constants of natural or synthetic principle active having therapeutical interest (303, 304). The equations derived in this paper can be incorporated into a simple computer program to calculate as a function of pH, the degree of protolysis of each acid species, the formation function, the slope of the titration curve, the buffer index and its first derivative curve.

The methodology proposed here for the evaluation of strong and moderate overlapping $pK_a's$ values of diprotic acids, based on the location of the singular points in the buffer index (or titration curve) versus pH curve, proves to be useful and essentially agrees well with the Irving and Rossotti graphical method, taken as a reference. The measurements of only single-points may be dangerous, but by making a judicious choice of the singular points we obtain values in reasonable agreement with those calculated by making the fullest use of all the experimental points (274).

Although the number of direct instrumental methods of chemical analysis is continuously increased, titrations are still important in routine practice in many laboratories (167, 263). Automatic titrators enable to record automatically the change with pH in titre during an acid-base titration (155–158, 164, 214, 233–235, 305). Applying an on-line microcomputer for the control and data acquisition in the titration process the accuracy of the measurement increases (306). Data collection and data processing allows the possibility for curve-smoothing and differentiation (306, 307), thus increasing the potential of the method in practice.

The authors feel with Rilbe (261) and Kankare (248) that "classical mathematics will always hold its place beside modern computer methods." There are instances where methods and programs dedicated to the solution of special types of equilibria can be used to advantage (308, 309); the acid-base titration curve and related formation function and buffer capacity curves being a characteristic example. In general, very little attention has been paid to developing the mathematical properties of the systems of equations that govern a particular equilibrium system (310).

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