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Validity of the Criterion pKa = pH at the Half Equivalence Point for the Potentiometric Evaluation of the Ionization Constant of a Monoprotic Acid

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Abstract: *The aim of this paper is to draw attention to the conditions under which the potentiometric evaluation of the acidity constant of a monoprotic acid, HA, can be performed from the single half point titration curve. We may usually adopt the pH corresponding to this point, $pH_{T=0.5}$, as the pKa value avoiding the need of using a rigorous method of calculation involving the entire V-pH titration data. The complete and approximate theoretical relationships that allow making effective that choice have been derived. A literature search have been carried out in order to gather a number of papers in which the criterion pKa= $pH_{0.5}$ has been used. In spite of the frequency with which this criterion is applied, it is only valid in favourable cases. A number of practical cases are included for study.*

Keywords: *Ionization constant; Half equivalence point; Potentiometric Measurements; Monoprotic acid*

1. INTRODUCTION

The location of inflection points in S-shaped titration curves is a recurrent topic in analytical chemistry, and some recent papers [1, 2] have been published on this respect. The basic papers concerning the location of inflexion points of weak acid-strong basic titrations date [3-5] from the 1960's. Meites et al. [3, 4] include the dilution in their treatment thus arriving at conclusions different from those previously stated by Roller [6-8]. The equivalence versus inflexion points has been the subject of a paper from Stokes [9]. On the other hand Fournaise and Petitfaux [10] have also studied the limits to the use of inflection points as points of equivalence in the treatment of acid-base titration data.

A number of papers (Table 1) adopt as criterion for the calculation of acidity constants that the pKa value coincides with the pH corresponding to the half point titration, T(fraction titrated)=0.5, the ionic strength being fixed. This practice is extended, but some limitations on its use are apparent. An approximation to this topic is made in this paper following the Meites et al guidelines [3, 4] with the purpose of bringing some light to the subject but fleeing from complex mathematical treatments. Some practical cases have been tackled.

Table1. *Selected papers in which the criterion pKa=pHT=1/2 (half titration) is applied*

Comment	Ref.
Study of the X-ray structure of an anion complexed by a HBD receptor at the half-equivalence point.	[13]
Study of the deprotonation at the half-equivalence point of (thio)amido-benzimidazoles in the presence of anions.	[14]
Book including 35 advanced chemistry experiments designed for use with Vernier data-collection technology.	[15]
Evaluation of thiol Raman activities and pKa values using internally referenced raman-based pH titration.	[16]
Investigation to identify and assess the factors causing systematic errors in the degree of deacetylation obtained from pH-potentiometric titrations.	[17]
A challenge to the readers in order to prove that the iconic pKa= $pH_{1/2}$ is just a simplification of a more complex equation	[18]

A demonstration of why the simple equation $pH_{1/2}$ = pKa still survives in all analytical chemistry textbooks despite its poor predicting power.	[19]
Method involving $EP_{1/2}$ is further investigated in order to obtain more accurate and precise results.	[20]
A method for the determination of acidity constants by feedback-based flow ratiometry and half equivalence point ($EP_{1/2}$) estimation.	[21]
High-performance liquid chromatography as a technique to determine pKa values of drug candidates that show poor solubility in water.	[22]
Determination of dissociation constants of weak acids by feedback-based flow ratiometry.	[23]
Study of the micro-volume flow titration and screening the dissociation constants (pKa) of weak acids.	[24]
Description of a simple method for calculating acidity parameters, as well as constants for the modified Henderson–Hasselbach equation.	[25]
Teaching students how to make a qualitative sketch of the expected titration curve helps to focus attention on the general principles.	[26]
Overview on theoretical works on potentiometric titration of ion exchangers.	[27]
Letter to editor about a simpler approach to “apparent” pKa´s based on a recent paper published by Cawley, 1995.	[28]
Titration and determination of "apparent" pKas. It challenges the students to do some critical about of the technique using pH at one-half titration over the whole pH scale.	[29]
Titration and determination of "apparent" pKas of very weak acids with some critical about using pH at one-half titration over the whole pH scale.	[30]
Potentiometric study of methanoic acid and glucuronic acid using a well-established experimental technique for suspensions of cellulosic fibers.	[31]
A laboratory experiment for the determination of pKa using the half-volume method.	[32]
Calculation of the end point position of the potentiometric titration curve for boric acid.	[5]
Evaluation of the locations of points at which pH= pKa on potenciometric acid-base titration curve.	[4]
Investigation of the locations of inflection points on acid-base and related titration curves.	[3]
Potenciometric titration of weak acids and bases in dilute aqueous solution.	[33]

1.1. Theory

Basic Relationships

The equilibrium of acid dissociation of a weak monoprotic acid is given by

$$HA \rightleftharpoons H^+ + A^-$$

being the corresponding mixed (apparent) acidity constant at an ionic strength (I) fixed

$$K_a = \frac{\left(H^+\right)\left[A^-\right]}{\left[HA\right]} \tag{1}$$

where parenthesis indicate activities and brackets concentrations. In titrating an initial volume V_0 of a solution of HA of concentration C_A with a volume of a solution of strong monoprotic base, BOH, of concentration C_B we have

$$C_A \frac{V_0}{V_0 + V} = \left[HA\right] + \left[A^-\right] \tag{2}$$

$$\left[A^-\right] + \left[OH^-\right] = \left[B^+\right] + \left[H^+\right] = C_B \frac{V}{V_0 + V} + \left[H^+\right] \tag{3}$$

for the mass balance and the electroneutrality rule, respectively. Then

$$\left[A^-\right] = C_B \frac{V}{V_0 + V} + \Delta \tag{4}$$

where

$$\Delta = \left[H^+\right] - \left[OH^-\right] = \frac{\left(H^+\right)}{\gamma_{H^+}} - \frac{\left(OH^-\right)}{\gamma_{OH^-}} = \frac{\left(H^+\right)}{\gamma_{H^+}} - \frac{K_w^T}{\left(H^+\right)\gamma_{OH^-}} \tag{5}$$

where γ_H and γ_{OH} are the activity factors of hydrogen and hydroxide ion, respectively, which may be evaluated [11] from Debye and Hückel.

By combining Eqns. (1), (2) and (4) we get

$$K_a = \left(H^+\right)\frac{T + \frac{\Delta}{C_A \frac{V_0}{V_0 + V}}}{1 - T - \frac{\Delta}{C_A \frac{V_0}{V_0 + V}}} \tag{6}$$

where T is the titrated fraction

$$T = \frac{C_B V}{C_A V_0} \tag{7}$$

In those cases in which the second term of the numerator of the right hand of Eqn. (6) can be despised against *T* and (1-*T*), we obtain

$$K_a \simeq \left(H^+\right)\frac{T}{1-T} \tag{8}$$

and then at the half titration, when *T*=0.5 we get

$$pK_a \simeq pH_{T=0.5} \tag{9}$$

Note that [12]

$$\tilde{n} = \frac{C_H - \left[H^+\right]}{C_A \frac{V_0}{V_0 + V}} = \frac{\left[HA\right]}{C_A \frac{V_0}{V_0 + V}} = f = 1 - T - \frac{\Delta}{C_A \frac{V_0}{V_0 + V}} \tag{10}$$

and then

$$K_a = \left(H^+\right)\frac{1-\tilde{n}}{\tilde{n}} \tag{11}$$

and thus it is always true that

$$pK_a = pH_{\tilde{n}=0.5} \tag{12}$$

Derivation of the Relationship Between the Titrated Fraction When Ph=Pka as a Function of the Concentration and the Acidity Constant

From Eqn. (6) by simple algebra we get

$$-\left[H^+\right]^3 - \left(K_a + T\,C_A \frac{V_0}{V_0 + V}\right)\left[H^+\right]^2 + \left(\left(1-T\right)C_A K_a \frac{V_0}{V_0 + V} + K_w\right)\left[H^+\right] + K_a K_w = 0 \tag{13}$$

and taking into account that

$$y = \frac{\left[H^+\right]}{K_a} \tag{14}$$

$$r = \frac{C_A}{C_B} \tag{15}$$

$$\frac{V_0}{V_0+V} = \frac{1}{1+\frac{V}{V_0}} = \frac{1}{1+T\frac{C_A}{C_B}} = \frac{1}{1+T\,r} \tag{16}$$

we get

$$y^3 + \left(1+\frac{C_A}{K_a}\left(\frac{T}{1+rT}\right)\right)y^2 - \left(\left(\frac{1-T}{1+rT}\right)\frac{C_A}{K_a} + \frac{K_w}{K_a^2}\right)y - \frac{K_w}{K_a^2} = 0 \tag{17}$$

From Eqn. (14), y=1, when

$$pH_{y=1} = pK_a \tag{18}$$

making thus possible to evaluate the value of *T* at this point

$$2 + \frac{C_A}{K_a\left(1+r\,T_{y=1}\right)}\left(2\,T_{y=1}-1\right) - 2\frac{K_w}{K_a^2} = 0 \tag{19}$$

which on rearrangement gives

$$T_{y=1} = \frac{0.5 + \frac{K_a}{C_A}\left(\frac{K_w}{K_a^2}-1\right)}{1+r\,\frac{K_a}{C_A}\left(1-\frac{K_w}{K_a^2}\right)} \tag{20}$$

Thus, the variation of the value of T when the pH = pKa (y=1) as a function of the concentration (pCA = - log CA), at different pKa values between 3 and 11 is shown in Fig. 1, for values of r = CA / CB = 1. The variation of the value of T (for y=1) as a function of concentration, for values of pKa = 9, 10.2 and 3.5, and different values of r (1, 0.1, 0.05 and 0) is shown in Fig. 2. In Fig. 3 the variation of the values of T (when y=1) as a function of pCA is observed for pKa values between 5.0 and 4.0. Finally, Fig. 4 shows the variation of the values of T (pH = pKa) as a function of pKa for pCA values between 1.0 and 5.0. A look at the figures reveals that the mistake made taken T as 0.5 is null when the pKa = pKw/2 and increases as the pKa distances from pKw/2 and decreases the concentration CA and increases the ratio r = CA / CB.

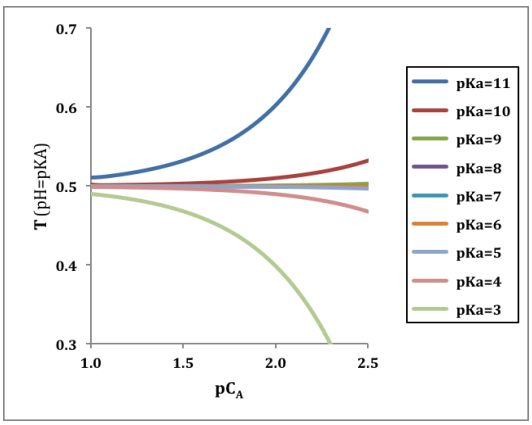

Figure1. *Variation of the value of T when the pH = pKa (y=1) as a function of the concentration (pCA = - log C_A), at different pKa values.*

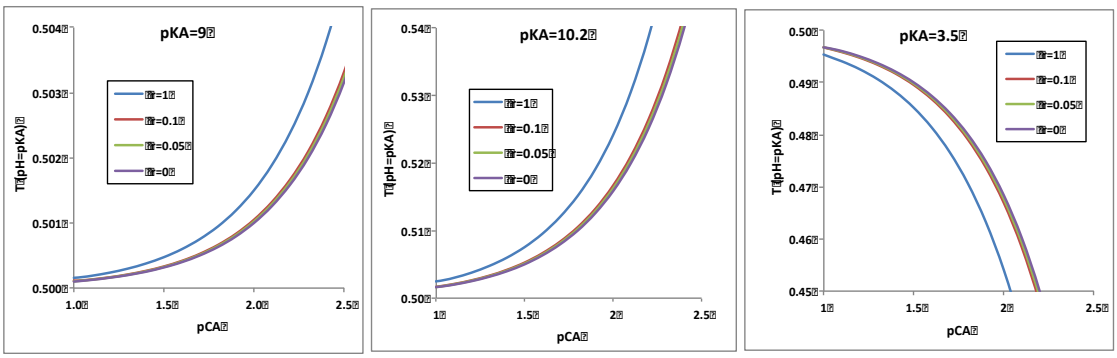

Figure2. *Variation of the value of T (for y=1) as a function of concentration and different values of r; pKa = 9 (left), 10.2 (middle) and 3.5 (right).*

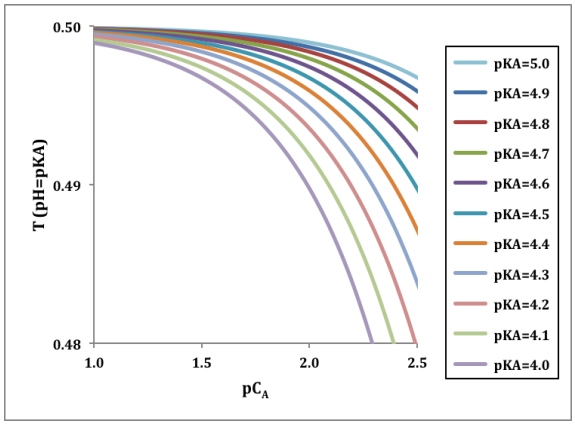

Figure3. *Variation of the values of T (when y=1) as a function of pC_A; pKa values between 5.0 and 4.0*

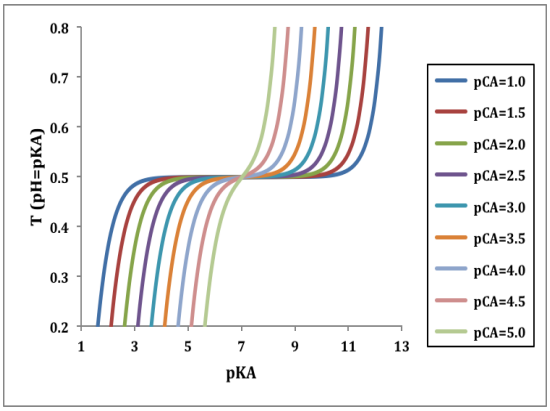

Figure4. *Variation of the values of T (pH = pKa) as a function of pKa for pC_A values between 1.0 and 5.0.*

Bilogaritmic Method for the Evaluation of the Acidity Constants

From Eqn. (11) we have

$$\log\left(\frac{\tilde{n}}{1-\tilde{n}}\right) = pK_a - pH \tag{21}$$

where the value of $\tilde{n}$ may be calculated at any point of titration by applying Eqn. (10).

Plotting the left hand of Eqn. (21) against pH a straight line ($y = a_0 + a_1 x$) of slope minus unity and intercept equal to pKa is obtained, from [34, 35] the least squares method. The pKa value is obtained at the point which cut the abscissa (pH) axis (because the experimental slope differs from the theoretical slope of minus unity), and then

$$pK_a = -\frac{a_0}{a_1} \tag{22}$$

Error Analysis

Note from Eqn. (22) that

$$pK_a = f\left(a_0, a_1\right) \tag{23}$$

and then by applying the random error propagation law [36, 37]

$$s^2_{pK_a} = \left(\frac{\partial pK_a}{\partial a_0}\right) s_0^2 + \left(\frac{\partial pK_a}{\partial a_1}\right) s_1^2 + 2\left(\frac{\partial pK_a}{\partial a_0}\right)\left(\frac{\partial pK_a}{\partial a_1}\right)\mathrm{cov}\left(a_0, a_1\right) \tag{24}$$

and then taking into account Eqns. (22) and (24) by simple algebra we obtain

$$s_{pK_a} = \sqrt{\frac{1}{a_0^2} s^2_{a_0} + \frac{a_0^2}{a_1^4} s^2_{a_1} - 2\frac{a_0}{a_1^3}\mathrm{cov}\left(a_0, a_1\right)} \tag{25}$$

The Excel function LINNEST [38] gives the parameters of the straight line (a_0 and a_1) and their corresponding standard deviations, and the standard deviation of the regression line, $s_{y/x}$. The covariance function may then easily estimated from

$$\mathrm{cov}\left(a_0, a_1\right) = -\bar{x}\frac{s^2_{y/x}}{S_{xx}} = -\bar{x}\, s^2_{a_1} \tag{26}$$

Mixed (Apparent) Acidity Constant and Thermodynamic Acidity Constant

The relationships between the thermodynamic pK_a^T and the mixed or apparent pK_a is given by

$$K_a^T = \frac{\left(H^+\right)\left(A^-\right)}{\left(HA\right)} = K_a\frac{\gamma_0}{\gamma_1} \tag{27}$$

$$pK_a^T = pK_a - \log\frac{\gamma_0}{\gamma_1} \simeq pK_a - \log\gamma_0 \tag{28}$$

where γ_0 and γ_1 are the activity factors of the species A and HA, respectively $(H_jA) = \gamma_j[HA]$; the value of the γ_1 of the neutral species is assumed to be the unity.

Working at varying ionic strength we get

$$\log\left(\frac{\tilde{n}}{1-\tilde{n}}\right) - \log\gamma_0 = pK_a^T - pH \tag{29}$$

Note that in those cases in which Eqn. (10) may be simplified to give $\tilde{n}$=1-T then at the half titration (T=0.5) follows

$$pK_a \simeq pK_a^T + \log\gamma_{0(T=0.5)} \simeq pH_{T=0.5} \tag{30}$$

The activity coefficient of an ion of z charge is given by

$$-\log\gamma_i = \frac{A z^2\sqrt{I}}{1 + B\, a_i\sqrt{I}} \tag{31}$$

where A and B are constants [11] depending of the dielectric constant and temperature of solvent and a_i is the average distance of approximation of ions

The activity factor is depending of the ionic strength of the medium

$$I = \frac{1}{2}\sum C_i z_i^2 = \frac{1}{2}\left(\left[B^+\right] + \left[H^+\right] + \left[A^-\right] + \left[OH^-\right]\right) \tag{32}$$

where C_i are the concentration of the ions involved and z_i its charge. By combining Eqns. (3) and (32) we get

$$I = \left[B^+\right] + \left[H^+\right] = \frac{C_B V}{V_0 + V} + \frac{\left(H^+\right)}{\gamma_{H^+}} \tag{33}$$

Note that for either a cationic acid of the type HA^+ (i.e. ammonium ion, NH_4^+) or a neutral monoacid base B (i.e. TRIS which on protonation fives the species HB^+), the relationship between the thermodynamic and apparent constant is given by

$$pK_a^T = pK_a + \log\gamma_1 \tag{34}$$

being now γ_1 the activity coefficient of the species positively charged (i.e HA^+). The expression applicable now for the potentiometric evaluation of the acidity constants is

$$\log\left(\frac{\tilde{n}}{1-\tilde{n}}\right) - \log\gamma_1 = pH - pK_a^T \tag{35}$$

and we get then

$$pK_a = pK_a^T - \log\gamma_{1(T=0.5)} = pH_{T=0.5} \tag{36}$$

2. Material and Methods

2.1. Reagents

Acetic acid (CH_3COOH) M=60 g/mol (Merck> 99.5%, 1.049 g/mL); Alanine ($NH_2CH_2CH_2COOH$) M=89.09 g/mol (Merck, analytical grade); Chloroacetic acid ($ClCH_2COOH$) M=94.5 g/mol (Merck> 99.5%); Tris(hydroxymethyl)-aminomethane (TRIS) $(HOCH_2)_3CNH_2$ M=121.14 g/mol (Merck> 99.5%); Sodium chloride (NaCl) M=58.44 g/mol (Merck, analytical grade); 1M hydrochloric acid (HCl) (Merck, analytical grade); Potassium hydroxide (KOH) 1M (Merck, analytical grade); Water for ACS analysis (Panreac).

2.2. Instruments

Analytical balance (Metler AE200) (4 decimals), pH-meter Crison GPL 21 Model (3 decimals), burette of 5 mL (Brand) (± 0.01 at 20 ºC), burette of 2 mL (Brand) (± 0.01 at 20 ºC).

2.3. Titrations

Potentiometric Titration of Acid with Potassium Hydroxide (0.1 M) or Base with Hydrochloric Acid (0.1 M)

Fifty mL of 0.01 M or 0.001 M acid (chloroacetic acid, acetic acid, alanine) solution (see Table 2) is pipetted into a 100 mL beaker. Then the acid solution was titrated potentiometrically with potassium hydroxide solution 0.1 M (or 0.01 M) using the glass pH electrode and a burette of 5 mL (or 2 mL). At fixed I=0.1 (NaCl) ionic strength, 100 mL 0.005 M of acid solutions (and 0.1 M in NaCl) were titrated with potassium hydroxide 0.1 (and 0.1 M in NaCl). TRIS 0.01 M was also titrated with 0.1 M hydrochloric acid solution at varying ionic strength.

Table2. *Evaluation of acidity constants of acidic compounds (bilogarithmic method)*

Compound	V_0	C_A	C_B	I	a_1	a_0	pKa^T	pKa
$ClCH_2COOH$	50	0.0103	0.1	var	-1.008	2.766	2.744± 0.006	
	100	0.00515	0.1	0.1	-1.010	2.623		2.600±0.010
	50	0.00098	0.01	var	-1.003	2.756	2.746 ±0.030	
CH_3COOH	50	0.01	0.1	var	-1.023	4.841	4.729 ±0.004	
	100	0.005	0.1	0.1	-0.998	4.517		4.525±0.004
$NH_2CH_2CH_2COOH$	50	0.01	0.1	var	-0.891	9.086	10.202±0.003	
	100	0.005	0.1	0.1	-0.916	9.163		10.007±0.005
Compound	V_0	C_B	C_A	I	a_1	a_0	pKa^T	pKa
$(HOCH_2)_3CNH_2$	50	0.010013	0.1	var	0.982	-8.039	8.190±0.005	

3. Results and Discussion

The experimental results obtained are summarized in Table 2. The thermodynamic acidity constants obtained for chloroacetic and acetic acid are similar to the values compiled by Shiels and Seybold [39] (pKa equals to 2.70 and 2.74, respectively). A good agreement is also observed between the value given by Albert and Serjeant [11] for TRIS, pKa=8.18, by the value obtained by us. On the other hand a pKa value of the order of 10.2 has been reported for β-alanine [40]. Figures 5 and 6 show the pKa graphical bilogaritmic method for chloroacetic acid 0.001 M and alanine 0.01 M, respectively, with the residual analysis [41] included. In Table 3 are compiled together with the pKa values obtained, the value of pH at the half titration (T=0.5), and both the experimental value of T when pH=pKa and the (approximate) theoretical value predicted. It can be seen that [3, 4, 42] the pH value a T (pH=pKa) is < 0.5 when pKa << 7, and T(pH=pKa) is >0.5 for pKa >> 7. That is, pH(T=0.5)> pKa in the range of acid pKa values, and pH(T=0.5)< pKa in the alkaline pKa range side.

Table3. *Comparison values among pKa, pH at T=0.5 and T at a pH=pKa*

Compound	C	I	pKa^T	pKa	pH (T=0.5)	T (exp.) (pH=pKa)	T (theory) (pH=pKa)
$ClCH_2COOH$	0.01	var	2.744		2.946	0.324	0.269
	0.005	0.1		2.600	2.975	< 0	-0.001
	0.001	var	2.746		3.500	< 0	-0.460
CH_3COOH	0.01	var	4.729		4.712	0.510	0.500
	0.005	0.1		4.525	4.540	0.492	0.500
$NH_2CH_2CH_2COOH$	0.01	var	10.202		10.146	0.530	0.524
	0.005	0.1		10.007	9.979	0.517	0.530
$(HOCH_2)_3CNH_2$	0.01	var	8.190		8.207	0.510	0.500

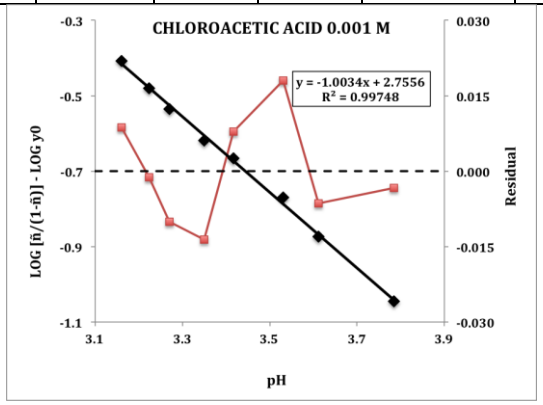

Figure5. *Bilogarithmic method for the potentiometric evaluation of pKa of chloroacetic acid*

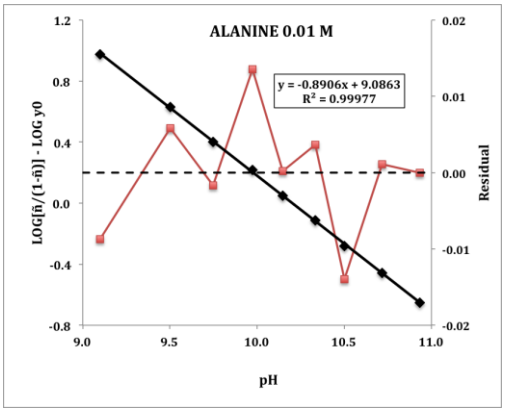

Figure6. *Bilogarithmic method for the potentiometric evaluation of acidity constants of alanine*

4. Conclusion

Therefore, the usual criterion of pKa = pH should be adopted with caution, since it is not applicable to very weak and highly diluted acids, or to medium strength and diluted acids. A look at Table 1 shows that this criterion is used with a certain frequency, having been applied to Raman, potentiometric, ion exchange, flow ratiometry, and liquid chromatographic among other measurements, although under

favourable conditions. Meija and Biseniek [18, 19] have also deal with this topic. However it is convenient to make as complete a use as possible [43] of the experimental data obtained. On this respect the use of the bilogarithmic method (Fig. 5 and 6) should be advocated.

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