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Titration Error in Polyprotic Acid-Base Titrations: Applications to Titration of Vinegar, Cola Drinks and Antibiotic Batches

Julia Martín, Gloria Cañamares Marin, Agustin G. Asuero*

Department of Analytical Chemistry, The University of Seville, Spain

Corresponding Author:** ***Agustin G. Asuero, *Department of Analytical Chemistry, The University of Seville, Spain*

Abstract: *Though a number of excellent papers have been published dealing with titration error in acid-base chemical systems of the monoprotolytic kind, the estimation of titration error of polyprotic acid (or polyacid bases and ampholytes) have received a scarce attention. Nevertheless, using the dissociation and formation (ñ) functions the chemical complexity involved in such kind of calculations is reduced considerably. Simple general expressions, based on the inverse approach for titration curves, i.e., V=f(pH), are derived for titration error of polyprotic acid (H_NA), polyprotic bases (B or Na_NT) or ampholytes ($Na_{N-x}H_xT$), in the nth-equivalence point (1 to N for polyprotic acid or base, and 1 to x (or N-x) for ampholyte titrated with strong base (strong acid)). Among possible analytical applications the determination of acetic acid in vinegar, phosphoric acid in Coca-Cola, and vancomycin purity in batches of raw material were selected for study.*

Keywords: *Titration error; Polyprotic acids and bases;Potentiometric titration; Vinegar; Coca-Cola; Vancomycin*

1. INTRODUCTION

The speciation of polyprotic acids [1-3] is a common problem in analytical, pharmaceutical and food chemistry, covering applications from pH control in simple and complex experiments [4], to the evaluation of acidity constants [5] of polyprotic systems (polyprotic acids, polyacid bases, or ampholytes). Titration curves and titration error of such complex systems are readily derived by the incorporation of the molar fractions of the dissociated species and the formation function, ñ (Bjerrum index or average number of bound protons) into the equations defining the mass and charge balances. Working in a medium of ionic strength fixed considerably reduces the mathematical complexity.

Although a number of excellent studies corresponding to the titration error of single equilibria have been published [6], the estimation of the polyprotic acid titration error has received scarce attention. Various systems of analytical interest, including monoprotic and diprotic acids and bases, triprotic and tetraprotic acids, and ampholytes; i.e. acetic acid (vinegar), phosphoric acid (Coca Cola), and vancomycin (antibiotic, antibacterial), are subject of consideration in this paper.

2. EVALUATION CURVE OF A POLYPROTIC ACID

The calculation of pH as a function of the volume V of titrant generally requires the solution of a high degree equation [7-8]. The usual approach is to write a polynomial equation in terms of hydrogen ion concentration and then find a positive root, which is a complex task (unless approximations are introduced), requiring the use of a computer. The inverse approach [10-11] for the derivation of the titration curves involves calculating the volume of titrant V (dependent variable, extensive), added to a given volume of acid (or acids) as a function of pH (independent variable, intensive). It is very easy to obtain and it does not require any of the simplifications generally performed in textbooks.

In the potentiometric titration of a neutral polyprotic acid H_NA [10], to a volume V_0 of initial acid (which may contain the background electrolyte) at an initial concentration C_A, is added a volume V of strong titrant base (which may contain the background electrolyte at the same concentration as the acid solution), BOH, at a concentration C_B. Electroneutrality rule is satisfied at any moment in the course of the titration (charges are omitted in the following for simplicity).

$$[H]+[B]=[OH]+[H_{N-1}A]+2[H_{N-2}A]+...+(N-1)[HA]+N[A] \quad (1)$$

Given the increase in volume of the solution in the course of titration we get the mass balances

$$C_A \frac{V_0}{V_0+V} = [H_N A] + [H_{N-1} A] + [H_{N-2} A] + \ldots + [HA] + [A] = \sum_0^N [H_j A] \tag{2}$$

$$C_B \frac{V}{V_0+V} = [B] \tag{3}$$

Taking into account that $f_j$is the fraction molar of the species $H_jA^{(N-j)}$

$$f_j = \frac{[H_j A]}{\sum [H_j A]} \tag{4}$$

we have

$$[H_j A] = f_j \sum [H_j A] = f_j C_A \frac{V_0}{V_0+V} \tag{5}$$

$$\sum j [H_j A] = C_A \frac{V_0}{V_0+V} \sum j f_j = C_A \frac{V_0}{V_0+V} \tilde{n} \tag{6}$$

Where $\tilde{n}$ is the formation function [11] or Bjerrum index

$$\tilde{n} = \frac{C_H - [H]}{C_A \frac{V_0}{V_0+V}} = \frac{[HA] + 2[H_2 A] + \ldots + N[H_N A]}{[A] + [HA] + [H_2 A] + \ldots + [H_N A]} = \tag{7}$$

$$= \frac{j\beta_j [H]^j}{\sum_0^N \beta_j [H]^j} = \frac{\sum_0^N j[H_j A]}{\sum_0^N [H_j A]} = f_1 + 2f_2 + \ldots + Nf_N = \sum_0^N j f_j$$

Being β_j the global stability constant related with the formation constants K_j' s and the acidity constants K_a's by means of

$$\beta_j = \frac{[H_j A]}{[H]^j [A]} = K_1 K_2 \ldots K_j = \frac{1}{K_{aN}} \frac{1}{K_{a,N-1}} \ldots \frac{1}{K_{a,N+1-j}} \tag{8}$$

corresponding to the formation global equilibrium $A + jH = H_jA$, K_j is the formation constant corresponding to the equilibrium $A_{j-1}H + H = A_jH$, y K_{aj} the acidity constant corresponding to the equilibrium $H_{N+1-j}A = H_{N-j}A + H$

$$K_{aj} = \frac{\beta_{N-j}}{\beta_{N+1-j}} = \frac{1}{K_j} \tag{9}$$

$$f_j = \frac{\beta_j [H]^j}{\sum_0^N \beta_j [H]^j} \tag{10}$$

By combining Eqns. (2)-(6) we get

$$\Delta = [H] - [OH] =$$

$$= \left(f_{N-1} + 2f_{N-2} + \ldots + (N-1) f_1 + N f_0 \right) C_A \frac{V_0}{V_0+V} - C_B \frac{V}{V_0+V} \tag{11}$$

$$\Delta = \frac{(N - \tilde{n}) C_A V_0 - C_B V}{V_0 + V} \tag{12}$$

and on rearrangement

$$V = V_0 \frac{(N-\tilde{n})C_A - \Delta}{C_B + \Delta}$$

which allow to evaluate the secondary variable ñ as a function of titration parameters

$$\tilde{n} = N - \frac{C_B V}{C_A V_0} - \frac{\Delta}{C_A \frac{V_0}{V_0+V}} = N - T - \frac{\Delta}{C_A \frac{V_0}{V_0+V}} \tag{13}$$

where T is the titrated fraction.

3. TITRATION ERROR IN POLYPROTIC ACID-BASE TITRATIONS: THEORY

From the mass and charge balances, it may easily be shown [7-8] that the fraction of acid titrated in the titration of a volume V_0 of a neutral polyprotic acid, H_NA, of concentration C_A with a volume V of strong base e.g. BOH, of concentration C_B is related to the formation function ñ by means of (ionic strength is assumed to be constant)

$$T = \frac{C_B V}{C_A V_0} = \frac{[OH]-[H]}{C_A \frac{V_0}{V_0+V}} + N - \tilde{n} \tag{14}$$

Then the (fractional) titration error at the*n*-th end point will be given by

$$\Delta T = \left[\frac{T-n}{n}\right]_{end} = \frac{1}{n}\left[\frac{[OH]-[H]}{C_A} + N - \tilde{n} - n\right]_{end} \tag{15}$$

The volume (dilution) factor near the *n*-th equivalence point, can be approximated by using T=n to be

$$C_{A,end} = C_A \frac{V_0}{V_0+V_{end}} = \frac{C_A}{1+rT_{end}} = \frac{C_A}{1+rn} \tag{16}$$

where dilution coefficient *r* is given by

$$r = \frac{C_A}{C_B} \tag{17}$$

It is to be noted that it is not necessary to know the values of pH at equivalence points in order to calculate the error.

Note in Eqn. (15) the sum of two terms; one that manifests itself at low or high pH values, which is dependent on the concentration C_A, and another, *N-ñ-n*, which is independent of the concentration (N-ñ is the degree of deprotonation of the acid).

3.1. Application to Diprotic Acid

In the case of a diprotic acid, N=2, $\tilde{n}=f_1+2f_2$ and when n=1 the Eqn. (15) becomes

$$\Delta T = \frac{[OH]-[H]}{C_{A,end}} + 2 - (f_1 + 2f_2) - 1 = \frac{[OH]-[H]}{C_{A,end}} + 1 - f_1 - 2f_2 = \frac{[OH]-[H]}{C_{A,end}} + (f_0 + f_1 + f_2) - f_1 - 2f_2 = \frac{[OH]-[H]}{C_{A,end}} + f_0 - f_2 \tag{18}$$

since the sum of the molar fractions of the different species of diprotic acid is equal to unity, $f_0+f_1+f_2=1$. The Eqn. (18) corresponds to Eqn. (16) of the paper of Butcher and Fernando [12], since for the diprotic acid

$$f_0 = \frac{1}{1+\beta_1[H]+\beta_2[H]^2} = \frac{1}{1+\frac{[H]}{K_{a2}}+\frac{[H]^2}{K_{a2}K_{a1}}} = \frac{K_{a1}K_{a2}}{[H]^2 + K_{a1}[H] + K_{a1}K_{a2}} \tag{19}$$

$$f_2 = \frac{\beta_2 [H]^2}{1+\beta_1[H]+\beta_2[H]^2} = \frac{\frac{[H]^2}{K_{a1}K_{a2}}}{1+\frac{[H]}{K_{a2}}+\frac{[H]^2}{K_{a2}K_{a1}}} = \frac{[H]^2}{[H]^2+K_{a1}[H]+K_{a1}K_{a2}} \quad (20)$$

where the global stability constants, successive formation constants and acid dissociation constants of the diprotic acid are related through the expressions

$$\beta_1 = K_1 = \frac{1}{K_{a2}} \quad (21)$$

$$\beta_2 = K_1 K_2 = \frac{1}{K_{a2}} \cdot \frac{1}{K_{a1}} \quad (22)$$

When we titrate to the second equivalence point, n=2, the Eqn. (15) leads to

$$\Delta T = \frac{1}{2}\left[\frac{[OH]-[H]}{C_{A,end}} + 2 - (f_1 + 2f_2) - 2\right] = \frac{1}{2}\left[\frac{[OH]-[H]}{C_{A,end}} - f_1 - 2f_2\right] = \frac{[OH]-[H]}{2C_{A,end}} - \frac{f_1}{2} - f_2 \quad (23)$$

with

$$f_1 = \frac{\beta_1[H]}{1+\beta_1[H]+\beta_2[H]^2} = \frac{\frac{[H]}{K_{a2}}}{1+\frac{[H]}{K_{a2}}+\frac{[H]^2}{K_{a2}K_{a1}}} = \frac{K_{a1}[H]}{[H]^2+K_{a1}[H]+K_{a1}K_{a2}} \quad (24)$$

The Eqn. (23) corresponds to Eqn. (18) of the paper of Butcher and Fernando [12].

3.2. Application to Monoprotic Acid

For a weak monoprotic acid, N=1, ñ=f_1, and Eqn. (15) becomes

$$\Delta T = \frac{[OH]-[H]}{C_{A,end}} + 1 - f_1 - 1 = \frac{[OH]-[H]}{C_{A,end}} - f_1 \quad (25)$$

being f_1 in this case equal to

$$f_1 = \frac{\beta_1[H]}{1+\beta_1[H]} = \frac{\frac{[H]}{K_a}}{1+\frac{[H]}{K_a}} = \frac{[H]}{[H]+K_a} = \frac{1}{1+\frac{K_a}{[H]}} \quad (26)$$

The Eqn. (25) corresponds to Eqn. (7) of the paper of Butcher y Fernando [12] already quoted. For a strong acid, f_1=0, and the titration error is given by the first part of the second member of Eqn. (25): $\Delta T=([OH^-]-[H^+])/C_{A,end}$.

3.3. Hyperbolic Sine Expression for Titration Error: Polyprotic Acid

The Eqn. (15) can be transformed into a hyperbolic sine relationship, as we will see in the following. The difference [OH]-[H] can be expressed as

$$[OH]-[H] = \frac{K_w^c}{[H]} - [H] = \sqrt{K_w^c}\left(\frac{\sqrt{K_w^c}}{[H]} - \frac{[H]}{\sqrt{K_w^c}}\right) \quad (27)$$

and taking into account the definition of hyperbolic sine

$$\sinh x = \frac{e^{x} - e^{-x}}{2} \tag{28}$$

we get

$$\Delta T = \frac{1}{n}\left[\frac{2\sqrt{K_w^c}}{C_A}\sinh\left(1n10\left(p[H] - \frac{pK_w^c}{2}\right)\right) + N - \tilde{n} - n\right] \tag{29}$$

4. TITRATION CURVE OF POLYACID BASES AND AMPHOLYTES

A volume V_0 mL of a polyacid base Na_NA of concentration C_B, may be titrated with a volume V of strong monobasic acid HX of concentration C_A, to give HA, $H_2A\ldots H_NA$. We also may titrate a neutral polyacid base B which undergoes, when titrated with the strong acid, N successive protonations to give BH^+, BH_2^{2+},...BH_N^{N+}.

An ampholyte$Na_{N-x}H_xT$ may be titrated either with a monoprotic strong base or a strong acid, respectively. Note that the charge which supports T is - N, and that for x = N coincides with the neutral polyprotic acid H_NT, and for x = 0 we get the N-charged polyacid base situation, Na_NT. A volume V_0 mL of the $Na_{N-x}H_x$Tampholyte of concentration C_A, may be titrated by adding V mL of a strong base, i.e. KOH, of concentration C_B. For the reverse titration, V_0 mL of $Na_{N-x}H_x$Tampholyte of concentration C_B, is titrated with a volume V of strong monoprotic acid, i.e., hydrochloric acid. From the mass and charge balances (as for the case of polyprotic acid) we get the results compiled in Table 1, where the expression for the titration curve, the titration error formula as well as an alternative titrated fraction expression are shown. Expressions of the titration errors for particular cases are easily deduced from the general expression contained in Table 1, as we have previously seen for the polyprotic acid case.

Table 1. *Titration curve, titration error and titration fraction expressions.*

Titration of	Titration curve	Titration error formula	Titrated fraction (alternative)
Neutral polyprotic acid titrated with a strong base (H_NA type acid)	$V = V_0\dfrac{(N-\tilde{n})C_A - \Delta}{C_B + \Delta}$	$\Delta T = \dfrac{1}{n}\left[\dfrac{[OH]-[H]}{C_A\dfrac{V_0}{V_0+V}} + N - \tilde{n} - n\right]$	$T = \dfrac{N - \tilde{n} - \dfrac{\Delta}{C_A}}{1 + \dfrac{\Delta}{C_B}}$
Neutral polyacid base B titrated with a strong acid (N-charged base of the type A^{N-})	$V = V_0\dfrac{\tilde{n}C_B + \Delta}{C_A - \Delta}$	$\Delta T = \dfrac{1}{n}\left[\dfrac{[H]-[OH]}{C_B\dfrac{V_0}{V_0+V}} + \tilde{n} - n\right]$	$T = \dfrac{\tilde{n} + \dfrac{\Delta}{C_B}}{1 - \dfrac{\Delta}{C_A}}$
$Na_{N-x}H_xT$ ampholite titrated with a strong base	$V = V_0\dfrac{(x-\tilde{n})C_A - \Delta}{C_B + \Delta}$	$\Delta T = \dfrac{1}{n}\left[\dfrac{[OH]-[H]}{C_A\dfrac{V_0}{V_0+V}} + x - \tilde{n} - n\right]$	$T = \dfrac{x - \tilde{n} - \dfrac{\Delta}{C_A}}{1 + \dfrac{\Delta}{C_B}}$
$Na_{N-x}H_xT$ ampholite titrated with a strong acid	$V = V_0\dfrac{(\tilde{n}-x)C_B + \Delta}{C_A - \Delta}$	$\Delta T = \dfrac{1}{n}\left[\dfrac{[H]-[OH]}{C_B\dfrac{V_0}{V_0+V}} + \tilde{n} - x - n\right]$	$T = \dfrac{\tilde{n} - x + \dfrac{\Delta}{C_B}}{1 - \dfrac{\Delta}{C_A}}$

5. TITRATION ERROR OF ACETIC ACID AND IST DETERMINATION IN VINEGAR

The data corresponding to a titration of HCH_3COO (plus HCl) using a Metrohm 702 Titrino automatic titrator [13] coupled with a combined pH electrode with NaOH are shown in Table 2, and Figure 1 with the derivative curve obtained incrementally.

Table 2. *Titration with NaOH 0.4905 M, of 3.96 mmol of acetic acid plus 0.484 mmol de HCl dissolved in 200 mL of KCl 0.10 M.*

V(mL)	pH	V(mL)	pH	V(mL)	pH	V(mL)	pH	V(mL)	pH	V(mL)	pH
0.00	2.79	1.80	3.87	3.60	4.50	5.40	4.92	7.20	5.38	9.00	7.23
0.30	2.89	2.10	4.01	3.90	4.58	5.70	4.98	7.50	5.49	9.30	10.14
0.60	3.06	2.40	4.15	4.20	4.67	6.00	5.05	7.80	5.61	9.60	10.85
0.90	3.26	2.70	4.25	4.50	4.72	6.30	5.12	8.10	5.76	9.90	11.20
1.20	3.48	3.00	4.35	4.80	4.78	6.60	5.21	8.40	5.97	10.20	11.39
1.50	3.72	3.30	4.42	5.10	4.85	6.90	5.29	8.70	6.28	10.50	11.54

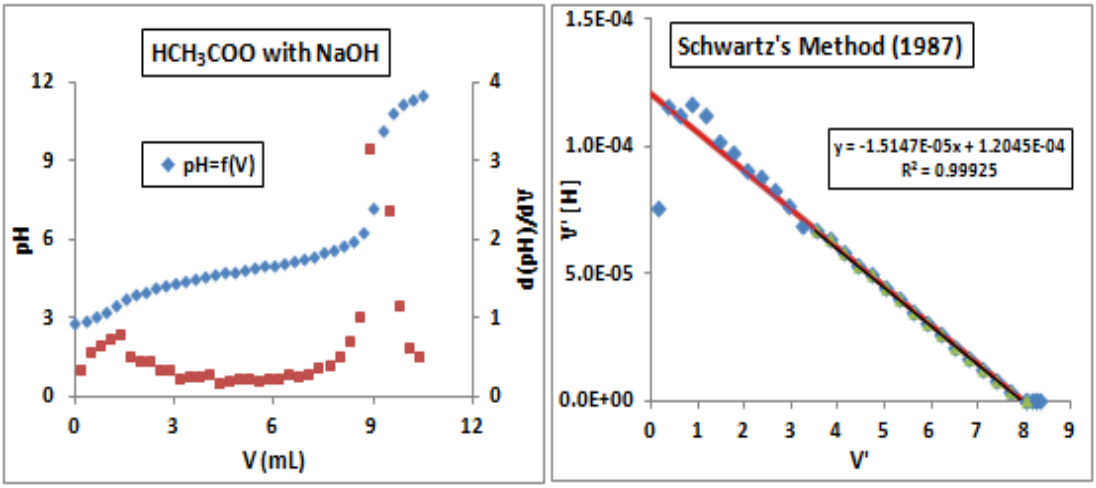


Figure 1. Left: *Titration of NaOH 0.4905 M of 200 mL de HCH_3COO 0.0198 M +HCl 0.00242 M and derivative curve*. **Right:** *Schwartz' method. pH-meter calibrated with buffers of pH 4.00, 7.00 and 9.00.*

The theoretical volume required reaching the 2[nd]equivalence point is 0.987 + 8.073 = 9.060 mL. The derivative curve shows a maximum at 8.85 mL (minimum at 9.15 on the dV/dpH curve versus V), so the valuation error will be

$$E = T - 1 = \frac{C_B V - C_H V_0}{C_A V_0} - 1 = \frac{C_B V_{pf\,2}}{C_B V_{pe2}} - 1 = \frac{V_{pf\,2}}{V_{pe2}} - 1 = \frac{8.85 - 0.987}{8.073} - 1 = -0.026 \tag{30}$$

Taking 9.15 mL the error is 0.011. On the other hand, from Eqn. (12) taking into account the two acids, removing denominators and regrouping terms is reached to the expression

$$\frac{\Delta(V_0 + V)}{C_B} + V - V_{eq1} = V' = V_{eq2} f_{0.2} = V_{eq2} \frac{K_a}{K_a + [H^+]} \tag{31}$$

which is of the form (Schwartz, 1987)

$$V'[H^+] = K_a V_{eq2} - K_a V' \tag{32}$$

from which the values of 7.952, 4.82 (I = 0.1) and 0.0195 for V_{eq2}, pK_a and C_A, respectively, are obtained. Assuming the values of the starting parameters as absolute, the error is given by: E = (7.952 / 8.073) -1 = -0.015 or -1.5%. Kraft [13] obtains a pK_a of 4.83 for that data series, using a different method.

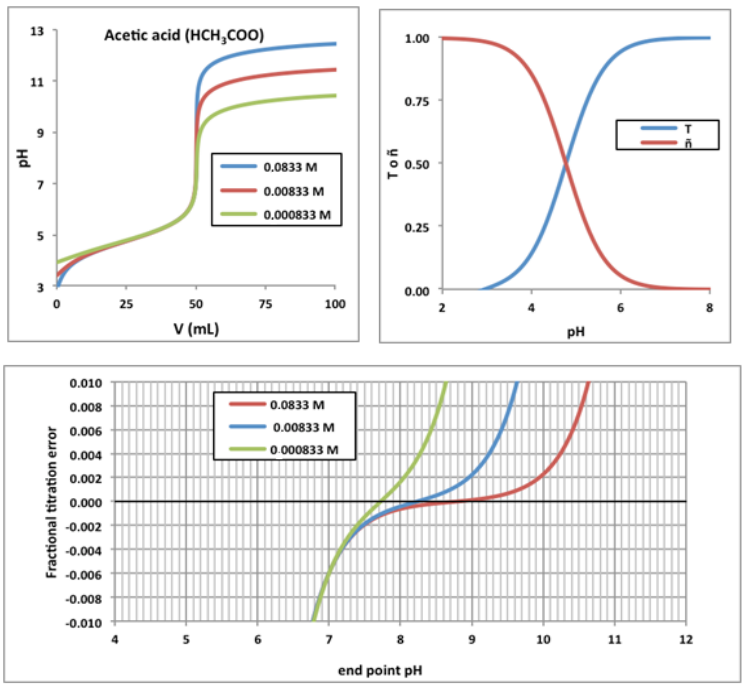
The calculation of the titration error is a common analytical problem. Given the acidity constants, the error associated with the pH range of colour change is estimated. The pH limits of these ranges are tabulated [14-15] and only need to calculate the corresponding titration volumes. The calculation is therefore simple: the extreme pH's of the indicator range are selected and T (= V/V_{eq}) is calculated for these limits (Table 3), determining the resulting error ΔT (= (V/V_{eq}) -1). Likewise, the titration error resulting from a preset value or from a pH reading can be obtained immediately.

Table 3. *Estimation of the titration error corresponding to the transition pH ranges of the indicator used in the titration of 50 mL of acetic acid (pK_a = 4.76) with sodium hydroxide at the indicated concentrations (pK_w = 14.00).*

HCH_3COO	C_A(M)	0.0833	0.00833	0.000833	0.000833	0.000833
NaOH	C_B(M)	0.0833	0.00833	0.000833	0.001666	0.004165
Indicator	pH Range	Error percentage of titration corresponding to the extreme values of the pH range of the tabulated indicators (% ΔT)				
Phenol Red	6.4–8.0	-2.24 –-0.06	-2.25 – -0.03	-2.33 – 0.18	-2.31 – 0.12	-2.29 – 0.09
Neutral Red	6.8– 8.0	-0.90 – -0.06	-0.91 – -0.03	-0.93 – 0.18	-0.92 – 0.12	-0.92 – 0.09
Cresol Red	7.2– 8.8	- 0.36 – 0.01	-0.36 – 0.14	-0.34 – 1.52	-0.34 – 1.13	-0.35 – 0.90
α-Naphtholphthalein	7.3 – 8.7	-0.29 – 0.00	-0.28 – 0.11	-0.25 – 1.20	-0.26 – 0.89	-0.27 – 0.71
Cresol Purple	7.4 – 9.0	-0.23 – 0.02	-0.22 – 0.23	-0.18 – 2.42	-0.19 – 1.81	-0.20 – 1.44
Thymol Blue	8.0 – 9.6	-0.06 – 0.09	-0.03 – 0.96	0.18 – 10.04	0.12 – 7.34	0.09 – 5.79
Phenolphthalein	8.2 – 10.0	-0.03 – 0.24	0.00– 2.43	0.34 – 27.28	0.25 – 19.16	0.19 – 14.76

Acetic acid is a component of vinegar, a water-miscible sour-tasting liquid, derived from the acetic fermentation of alcohol assisted by bacteria *Mycodermaaceti*. The concentration of vinegar in acetic acid is about 5%; ie, 0.833 M. Titration curves corresponding to 1:10, 1:100 and 1:1000 dilutions are shown in the top left-hand side of Fig. 2. Titration error (in the interval of -1% to 1%) for the different molar concentrations of acid is drawn in Fig. 2 middle. The pH at the equivalence point (Fig. 2 bottom) fluctuates between 7.699 and 7.806 when a 0.000833 M acid is titrated with a strong base solution 1, 2, 3, 4 and 5 times more concentrated. The calculations made allow us to verify (Table 3) that neutral red, cresol red and α-naphtholphthalein are satisfactory indicators for the titration of acetic acid in all cases. Thymol blue and phenolphthalein are not recommended except at high concentrations of acid. Natural vinegars also contain small amounts of tartaric acid and citric acid. Among the varieties of vinegar are wine, aceto-balsamic, Sherry, cider or apple, and Porto. The concentration of acetic acid in vinegar ranges from 3% to 5%.

It is also possible to titrate vinegar solution up to a fixed endpoint, in order to avoid the plotting of the entire potentiometric titration curve. This makes it necessary to know how the titration error varies with the acid concentration at given pH values (Fig. 3). For example, for a 1:250 dilution of vinegar, its pC_A will be of the order of 2.50, with titration errors lower than 1% if the titration is carried out to a pH of 7.2 to 9.2. If higher accuracy is desired, the above pH range should be limited, using the same diagram. Bottles of vinegar of different format are shown in Fig. 4. The experimental titration curve of a dark mahogany coloured Sherry vinegar (Fig. 5), shows that at pH 7.4–9.1 the error is minimal, according to the developed theory. The degree of acidity of the Sherry vinegar tested is 7.51%, higher than that of conventional vinegar, whose acidity degree was equal to 6.98%. In both cases we get higher values than those declared in label values (7 and 6%, respectively). The pH value at T=0.5 is 4.53.



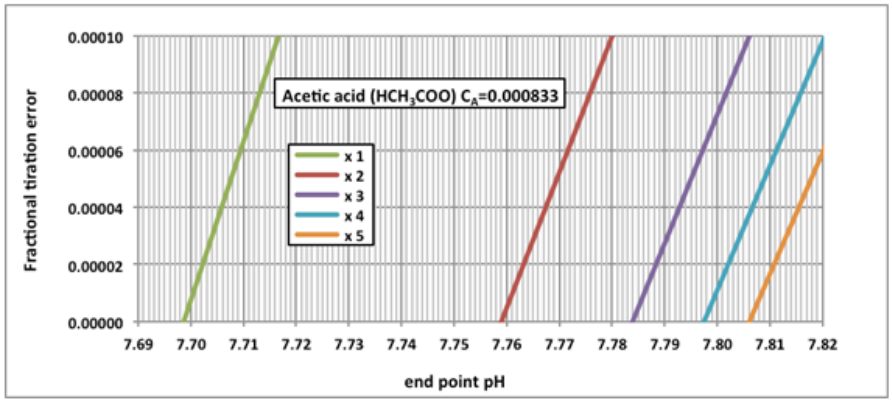


Figure 2. ***Top left:*** *titration curves of acetic acid with sodium hydroxide at the same concentration;* ***Top right:*** *titrated fraction and Bjerrum index as a function of pH.* ***Middle:*** *fractional titration error. Bottom: enhanced error scale allowing to get the end point pH value in the titration of 0.000833 M acetic acid with sodium hydroxide n more concentrated times (n = 1, 2, 3, 4 and 5).*

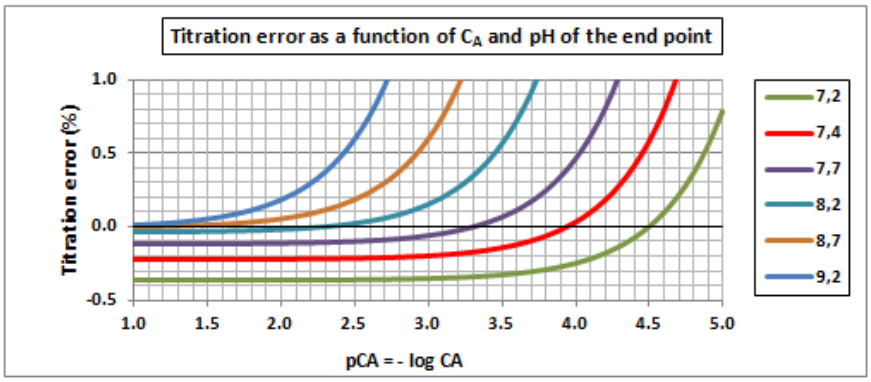


Figure 3. *Titration error for acetic acid as a function of C_A and pH of the end point.*

Figure 4. *Bottles of vinegar of different formats (wikipedia, n.d.).*

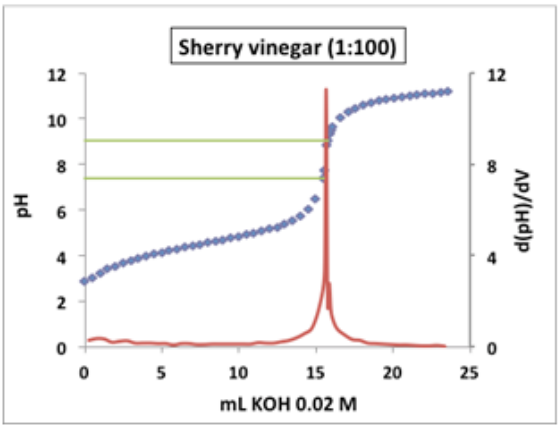


Figure 5. *Titration curve of diluted Sherry vinegar 1:100 (V_0=25 mL; end point = 15.65 mL).*

6. PHOSPHORIC ACID SYSTEM AND ITS DETERMINATION IN COLA DRINKS

Phosphoric acid is a triprotic acid with pK_{a1} = 2.15, pK_{a2} = 7.20 and pK_{a3} = 12.15, whose titration curve shows (Fig. 6, top) two jumps. The fraction titrated together with the degree of deprotonation are shown in Fig. 6 middle, whereas the curves corresponding to the fractional error for the equivalence points corresponding to both jumps (end point (e.p.) 1º and e.p. 2º) are depicted in Fig. 6 bottom.

The experimental data obtained in the titration of 25 mL of a 0.04389 M phosphoric acid solution with 0.09948 M NaOH [16], using a Orion Model 420 A pH meter(equipped with an Orion electrode Model 91-57 "Triode" immersed in 4 MKCl saturated with AgCl prior to use), are shown in Table 4together with the incremental curve (pH -meter is calibrated with pH 4.00, 7.00 and 9.00 buffers).

The theoretical volume required to reach the first and second equivalence points is equal to 11.03 and 22.06 mL, respectively. Since the derivative curve (Fig. 7) shows maximums at 10.90 and 22.15 mL, the titration error will be given by

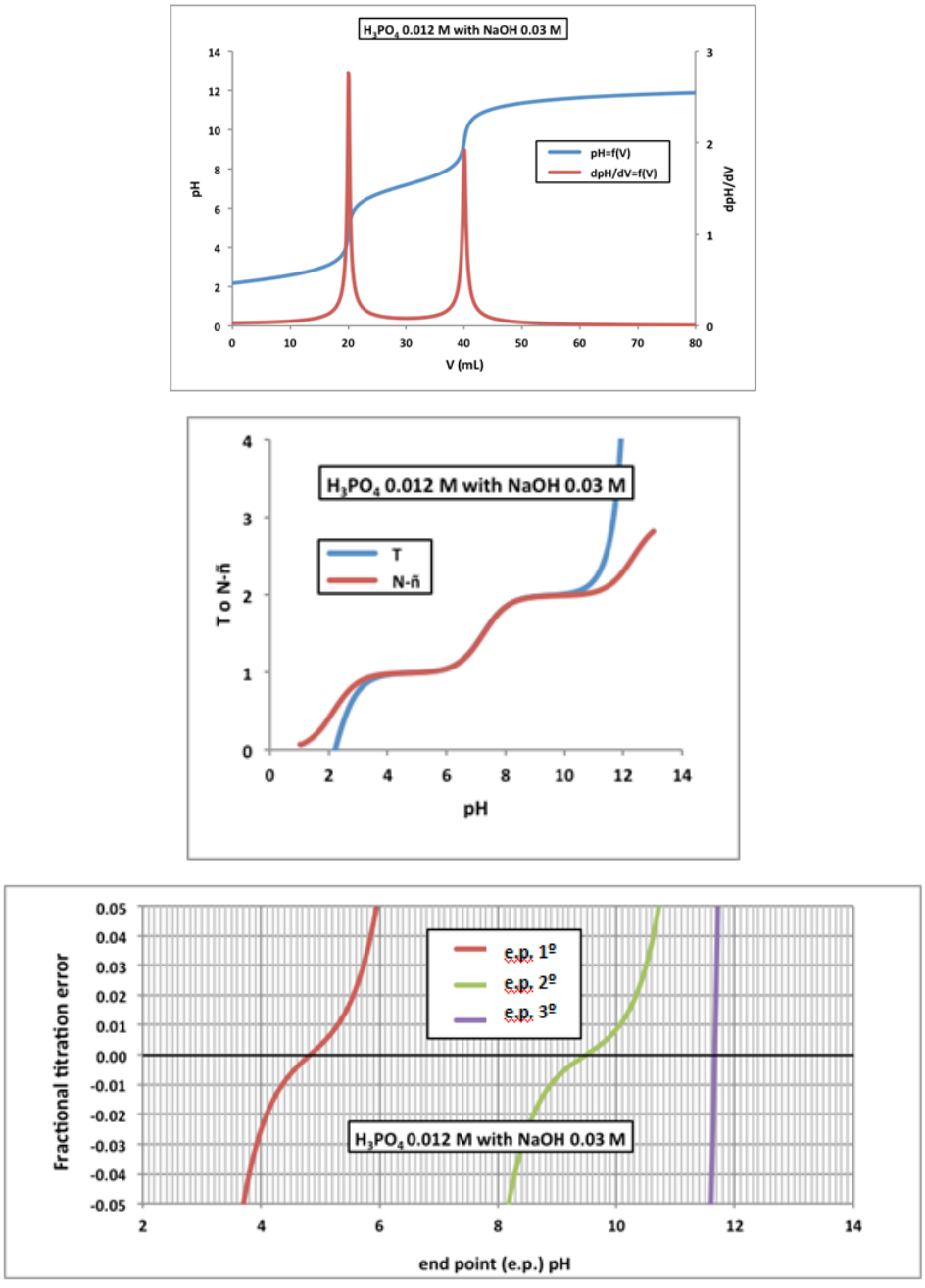


Figure 6. ***Top:*** *Titration curve of phosphoric acid with sodium hydroxide.* ***Middle:*** *Titrated fraction (T) and degree of deprotonation (n-ñ) as a function of pH.* ***Bottom:*** *Titration error at the different end points (e.p.) (1º y 2º; and 3º no detectable).*

$$\Delta T_{pf1} = \frac{V_{pf1}}{V_{eq1}} - 1 = \frac{10.9}{11.3} - 1 = -0.0118 \approx -1.2\% \tag{33}$$

$$\Delta T_{e.p.2} = \frac{V_{e.p.1}}{2V_{eq1}} - 1 = \frac{22.15}{2 \cdot 11.03} - 1 = -0.004 \approx 0.4\% \tag{34}$$

The titration curves in the concentration range of 1.2 10^{-1} to 6 10^{-4} M are shown in Fig. 8 (top). In the intermediate range ($H_2PO_4^-$ / HPO_4^{2-}), the pH is independent of the concentration. The titration error, T, at pH values close to the end points is also shown in Fig. 8 (middle and bottom). For the determination of H_3PO_4 in decarbonated (degassed) cola drinks [17, 18] potentiometric titration has to be applied, given its intense colour. The undiluted drink pH is 2.5 with

$$K_{a1} = \frac{\left[H^+\right]^2}{C_A - \left[H^+\right]} \rightarrow C_A = \frac{\left[H^+\right]^2}{K_{a1}} + \left[H^+\right] = \frac{\left(10^{-2.48}\right)^2}{10^{-2.15}} + 10^{-2.48} \approx 4.8 \cdot 10^{-3} M \tag{35}$$

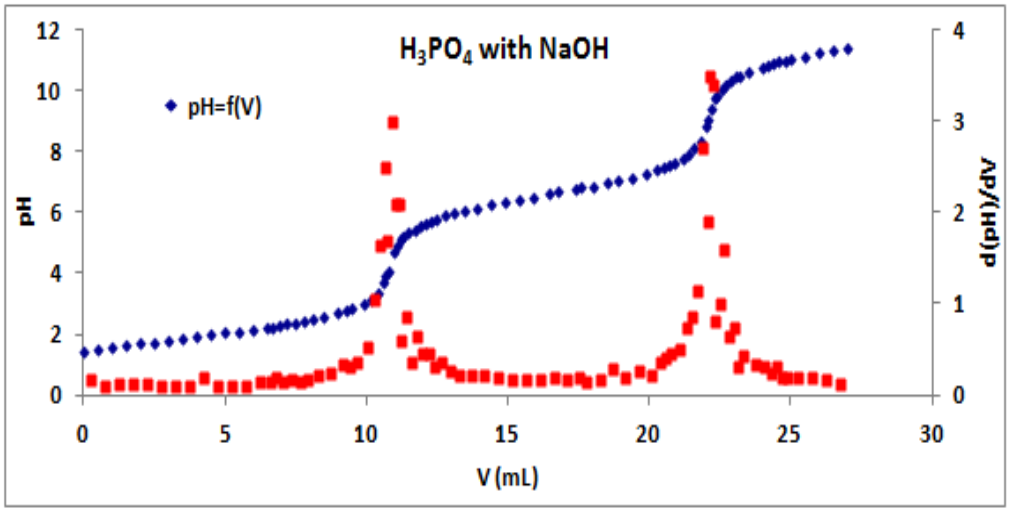


Figure 7. *Titration curve and derivative curve corresponding to the titration of 25 mL of 0.04389 M of phosphoric acid with NaOH 0.09948 M (without ionic strength adjustment).*

Table 4. *Titration of 25 mLof H_3PO_4 0.04389 M with NaOH 0.09948 M (V_{eq1}=11.03 mL; V_{eq2}=22.06 mL).*

V (mL)	pH	V (mL)	pH	V (mL)	pH	V (mL)	pH	V (mL)	pH	V (mL)	pH
0.0	1.44	6.9	2.29	11.0	4.70	14.9	6.36	20.9	7.63	23.5	10.63
0.5	1.52	7.2	2.33	11.1	4.91	15.4	6.44	21.2	7.78	24.0	10.80
1.0	1.57	7.5	2.38	11.2	5.12	15.9	6.52	21.4	7.93	24.2	10.86
1.5	1.63	7.8	2.42	11.3	5.18	16.5	6.61	21.6	8.10	24.4	10.91
2.0	1.69	8.1	2.47	11.5	5.35	16.8	6.68	21.8	8.33	24.6	10.97
2.5	1.75	8.5	2.56	11.7	5.42	17.4	6.78	22.0	8.87	24.8	11.01
3.0	1.80	9.0	2.68	11.9	5.55	17.6	6.82	22.1	9.06	25.0	11.05
3.5	1.85	9.3	2.78	12.1	5.64	18.0	6.88	22.2	9.41	25.5	11.15
4.0	1.90	9.5	2.84	12.3	5.73	18.5	6.96	22.3	9.75	26.0	11.24
4.5	2.00	9.9	2.98	12.5	5.79	18.9	7.07	22.4	9.83	26.5	11.32
5.0	2.05	10.2	3.14	12.8	5.90	19.4	7.17	22.6	10.03	27.0	11.38
5.5	2.10	10.4	3.35	13.1	5.98	19.9	7.30	22.7	10.19		
6.0	2.15	10.6	3.68	13.5	6.07	20.3	7.39	22.9	10.32		
6.5	2.22	10.7	3.93	13.9	6.16	20.5	7.46	23.1	10.47		
6.7	2.25	10.8	4.10	14.4	6.27	20.7	7.54	23.2	10.50		

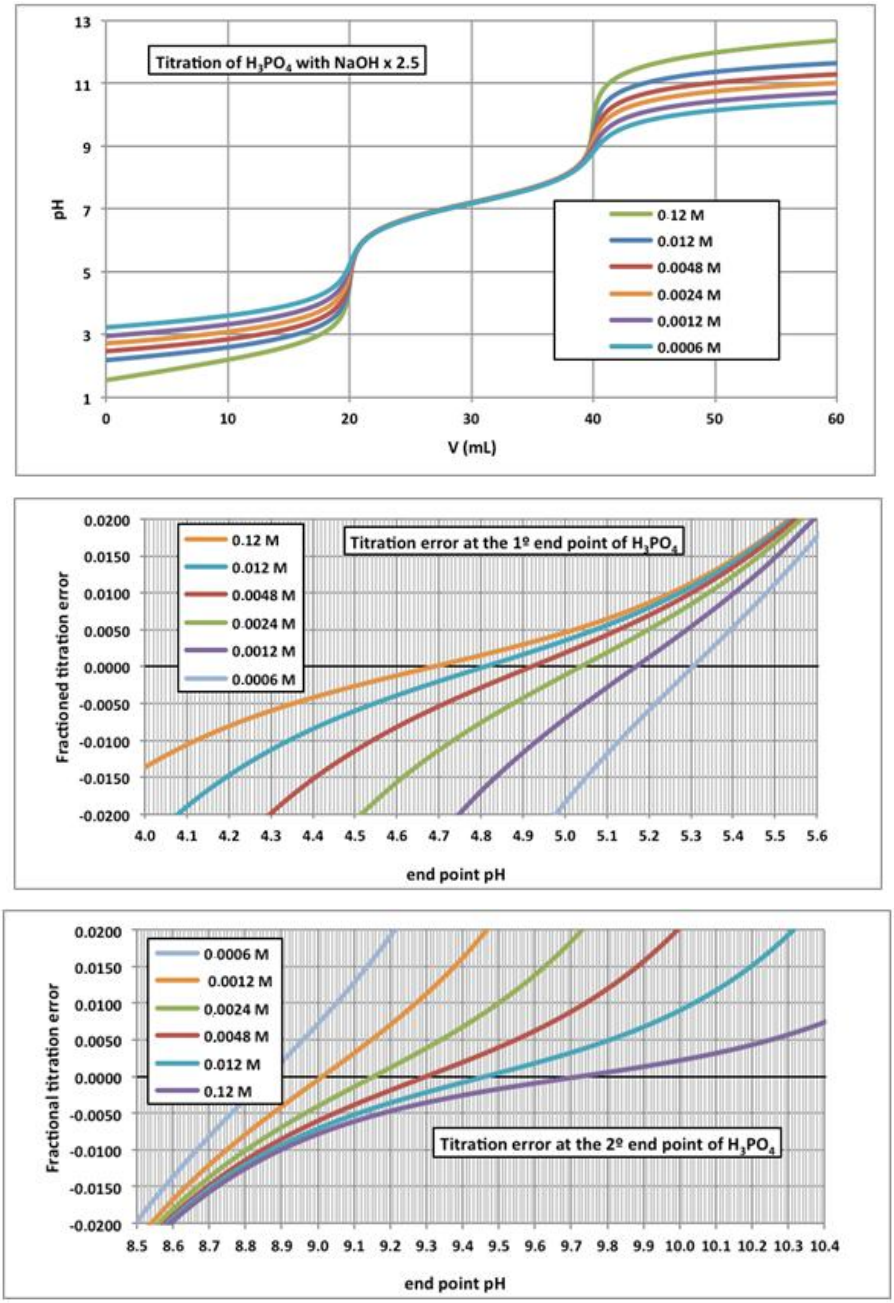


Figure 8. ***Top:*** *Titration curves of phosphoric acid with sodium hydroxide concentrations 2.5 times more concentrated.* ***Middle:*** *Titration error at varying concentrations of acid for the 1º end point.* ***Bottom:*** *Titration error at varying concentrations of acid for the 2º end point.*

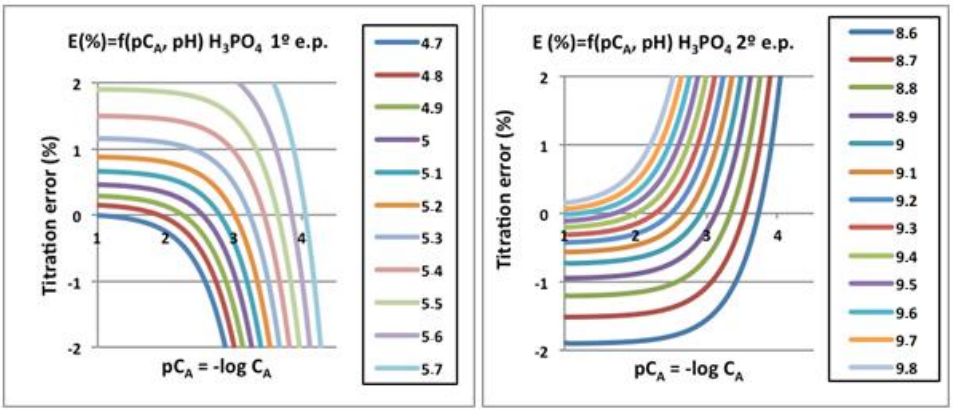


Figure 9. *Titration error as a function of concentration of H_3PO_4 and pH of the end point*

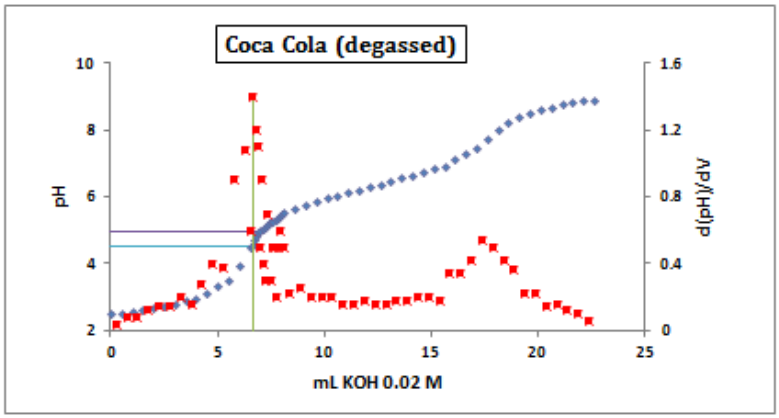


Figure 10. *Titration curve of 25 mL of degassed Coca Cola (1º end point at 6.65 mL)*

Other acids present (citric acid) exert a negligible influence [17], if titration is carried out to the first end point, since $V_{eq2} > 2\ V_{eq1}$. In order to evaluate for routine purposes up to a fixed pH range, we study how the titration error varies as a function of the concentration at given values of pH (Fig. 9). It is noted that a pH value of 5.2 covers the range of pC_A values from 2.0 to 3.3 with an error lower than 1%. Likewise, a pH value of 8.8– 9.0 (2nd end point) also covers that same range of pC_A.

The degassed (using an ultrasound bath) Coca Cola titration curve(Figure 10) shows that the error is minimal at the 1º end point when the pH is between 4.5 and 5.0, values some lower than expected, being logical the difference taking into account the complexity of the medium. The phosphoric acid concentration is $\approx 5.32\ 10^{-3}$ M.

7. TITRATION CURVES OF CIPROFLOXACIN AND VANCOMYCIN

Antibiotics are important antimicrobial agents whose behaviour in vivo is significantly influenced by their physicochemical properties, such as degree the of ionization and the ability to chelate metal ions. The transport of the active principle through the cells and the biological membranes is a function of their physical and chemical properties and pK_a values, which play a vital role in the development of new drugs. The acid-base character [19] is a key factor in the behaviour at the molecular level, since it governs solubility, absorption, distribution, metabolism and elimination. Antibiotics, belonging to various therapeutic families, i.e., macrolides, penicillins, sulphonamides, tetracyclines, cephalosporins, glycopeptides, carbapenem, are polyprotic acids or bases. The ciprofloxacin hydrochloride (pK_{a1}=3.01; pK_{a2}=6.14; pK_{a3}=8.70; pK_{a4}=10.58) and the vancomycinglycopeptide (pK_{a1}=2.18; pK_{a2}=7.75; pK_{a3}=8.89; pK_{a4}=9.59; pK_{a5}=10.40; pK_{a6}=12) titration curves are shown in Fig. 11 left and right, respectively.

It is possible to use visual indicators in the case of vancomycinglycopeptide, as shown in Table 5, after applying the formalism described in the first application. Of the indicators tabulated the one that is better is the red of methyl, although the ideal would be to have one that turns between pH 4.4 and 5.8. The case of ciprofloxacin requires further study in the direction applied to the case of phosphoric acid, since in practice the derived titration curves obtained from the experimental data are far from the ideal behaviour shown in Fig. 11 left.

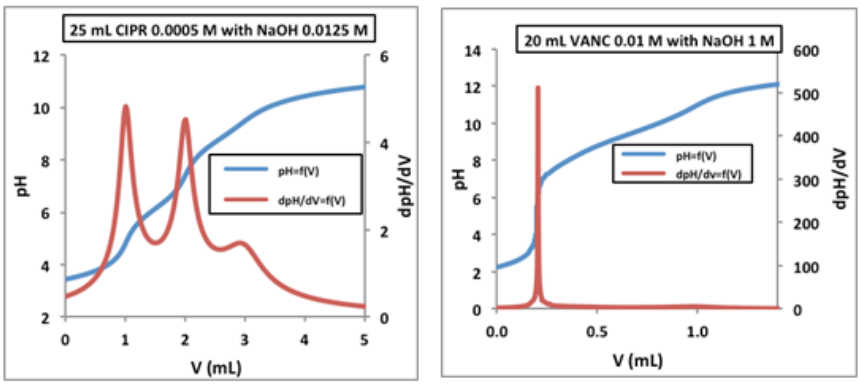


Figure 11. *Titration curves of ciprofloxacin (left) and vancomycin (right).*

Table 5. *Estimation of titration error corresponding to 0.01 M vancomycin.*

Indicator	pH Range	Color change	% Error
Ethyl Orange	3.4 – 4.8	Red to Yellow	-9.7 % – -0.3 %
Bromocresol Green	3.8 – 5.4	Yellow to Blue	-3.9 % – 0.03 %
HIn	4.4 – 5.8		-1.0 % – 1.1 %
Methyl Red	4.8 – 6.0	Red to Yellow	-0.3 % – 1.7 %
Chlorophenol Red	4.8 – 6.4	Yellow to Red	-0.3 % – 4.3 %

8. CONCLUSIONS

The traditional mathematical description of the titration curves described in terms of isolated points, fails for complex systems, such as polyprotic acid or bases and their salts. Nevertheless, from the charge and mass balances, the volume of titrant added (the extensive property) may be written as a explicit function of the pH (the intensive property); i.e., the titrant volume is calculated as a function of pH; V=f(pH).

Using the dissociation and formation (ñ) functions incorporated in the equations defining the charge and mass balances expressions considerably reduces the chemical complexity involvedfor tracing a titration curve or evaluate the titration error. The equations derived can be incorporated into a spreadsheet to calculate as a function of pH, the degree of protolysis of each acid species, the formation function, the titration curve (the titration fraction) and the titration error, $\Delta T=(1/n)[(T-n)/n]$ (n=0,1,…,N), for the H_NA case). Note that the approximation T=N-ñ (where T is the titration fraction and ñ the formation function), applies except at very high or low pH values, i.e., the dissociation curve is the mirror image of the formation curve. Ionic strength is assumed to be constant through the titration. This condition is normally fulfilled by addition of a neutral salt in a sufficient amount.

Given the acidity constants, the error associated with indicator pH ranges may be easily estimated. As the indicator pH ranges are tabulated in monographs and textbooks, only the corresponding titration volume has to be calculated from the inverse titration V=f(pH) curve. The titration error resulting from a preset final pH value may be immediately obtained in a similar way.

This paper provides first examples of optimizing a priori. On the basis of the relevant curves V=f(pH) or T=f(pH) one may select the appropriate $T=T_{eq}$ values where abrupt changes in the pH occur. This allows a better understanding of chemical reactions under given or required conditions as illustrated with the case of the acetic acid and phosphoric acid systems. Applications of the paper include the determination of acetic acid in vinegar, the determination of phosphoric acid in cola drinks, and the evaluation of purity in vancomycin batches.

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