Research Article

General Analytical Procedure for Determination of Acidity Parameters of Weak Acids and Bases

Bogusław Pilarski,¹ Roman Kaliszan,² Dariusz Wyrzykowski,³ Janusz Młodzianowski,¹ and Agata Balińska¹,²

¹Cerko Sp. z o.o. Sp.K, Al. Zwycięstwa 96/98, 81-451 Gdynia, Poland
²Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdańsk, Gen. J. Hallera 107, 80-416 Gdańsk, Poland
³Faculty of Chemistry, University of Gdańsk, Wita Stwosza 63, 80-308 Gdańsk, Poland

Correspondence should be addressed to Bogusław Pilarski; bpilarski@cerko.pl

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The paper presents a new convenient, inexpensive, and reagent-saving general methodology for the determination of $pK_a$ values for components of the mixture of diverse chemical classes weak organic acids and bases in water solution, without the need to separate individual analytes. The data obtained from simple pH-metric microtitrations are numerically processed into reliable $pK_a$ values for each component of the mixture. Excellent agreement has been obtained between the determined $pK_a$ values and the reference literature data for compounds studied.

1. Introduction

Prediction or determination of $pK_a$ value is of great importance in chemistry, in particular in life and material sciences, pharmaceutical industry, and other R&D oriented enterprises. Important drug properties, such as lipophilicity, solubility, and transmembrane transfer, are all pH dependent. Also, rational drug formulation requires the knowledge of $pK_a$. The proportion of drugs with an ionizable group has been estimated at 95% [1], but only 62.9% of drugs under analysis were ionizable at pH 2–12 [2]. According to Wells data 75% of drugs are weak bases and 20% weak acids and the remaining contain nonionics, ampholytes, and alcohols [1].

Recently, some theoretical approaches were employed to predict the $pK_a$ value, for example, ab initio quantum mechanical calculations [3, 4] or QSAR (quantitative structure-property relationship) modeling [5, 6] as well as QSAR models which employ partial atomic charges as descriptors [7, 8]. The theoretical models take into account electronic effects (induction, resonance), solvation of compounds of type HA, BH and their ionic forms, that is, $A^-$ and $BH^+$, hydrogen bonding, and various stereochemical effects.

This report presents an application of pH-metric microtitration to determine standard $pK_a$ parameters of components of mixtures of various weak acids and bases by employing a technologically advanced potentiometer device and a software based on an algorithm straightforwardly accounting for complex acid-base equilibria (see below). A composition of the mixtures under study can be expressed as follows:

\[
\begin{align*}
H_3A_1 + H_2A_2 + HA_3 + B_1 + B_2 + (R_1R_2)CH_2 + (R_1R_2)N=H + Ar-OH
\end{align*}
\]  

(1)

where $H_3A_1 + H_2A_2 + HA_3$ represents 3-H, 2-H, and 1-H protic carboxylic acids, $B_1 + B_2$ represents organic bases, $(R_1R_2)CH_2$ represents the so-called C–H acids, $R_1R_2N–H$ represents the N–H acids, and ArOH denotes phenolic/enolic moiety (O–H acids). The C–H, N–H, and O–H acids are often reported as tautomeric forms of heterocyclic compounds with pharmacological activity and are identified.
within different groups of natural compounds (flavonoids, quinines, etc.).

**Numerical Modelling.** Numerical procedures are based on an original algorithm elaborated by Kostrowicki and Liwo [9] as well as the CVEQUID program, which was adopted in the Cerko Lab software within the Cerko Lab System microtitrator unit (Cerko, Gdynia, Poland). All details concerning Kostrowicki and Liwo algorithm were described previously [10]. The CVEQUID program is based on a least-square method for the determination of all parameters and takes into account all the sources of experimental errors considered in potentiometry, that is,

(a) electrode calibration parameters \( E^0 \), the standard potential (cell constant) and \( S \), the standard Nernstian slope parameter;
(b) composition of titrand \( D \), its concentration \( C_0 \) (mol/L), and volume \( V_0 \) (mL);
(c) composition of titrant \( T \), its concentration (mol/L), and added volume (mL);
(d) measured EMF (the electromotive force) in mV.

Within the Cerko Lab System software, the equilibrium is denoted as model. The model consists of a set of equations. Each equation is related to a particular pK value and to pK\(_w\). The model includes also information about the composition of the titrant \( T \) and titrand \( D \). The stoichiometric matrix, required for the numerical procedures, is generated from the model automatically. The representative models and the corresponding stoichiometric matrix for \( H_2A \) (model 1) as well as \( H_3A + H_2A_1 + HA_2 \) (model 2) systems are given below.

**Model 1.** Reagents include titrand \( D = H_2A \) and titrant \( T = OH \). Individual equilibria that contribute to the overall equilibrium of the system are as follows:

1. \( H_2A = H^+ + HA^- \), \( K_1A = [H^+][HA^-]/[H_2A] \),
2. \( HA^- = H^+ + A^- \), \( K_2A = [H^+][A^-]/[HA^-] \),
3. \( 0 = H^+ + OH^- \), \( K_w = K[H_2O] = [H^+][OH^-] \).

The stoichiometric matrix for the above model is presented in Table 1.

The concentration of titrand, \( D (C_0 = C_{01} + C_{02} + C_{03} + \cdots) \), and titrand volume \( (V_0 = V_{01} + V_{02} + V_{03} + \cdots) \), used in the potentiometric titration, result from mixing of various types of acid-base solutions.

**Model 2.** Reagents include titrand \( D = H_3A + H_2A_1 + HA_2 \) and titrant \( T = OH \) (Table 2). The model consists of a water solution of different types of acids. The equilibrium constants and stoichiometric matrix are as follows:

(1) \( H_3A = H^+ + H_2A^- \), \( K_{1A} = [H^+][H_2A^-]/[H_3A] \),
(2) \( H_2A^- = H^+ + HA^- \), \( K_{2A} = [H^+][HA^-]/[H_2A^-] \),
(3) \( HA^- = H^+ + A^- \), \( K_{3A} = [H^+][A^-]/[HA^-] \),
(4) \( H_2A_1 = H^+ + HA_1^- \), \( K_{1A_1} = [H^+][HA_1^-]/[H_2A_1] \),
(5) \( HA_1^- = H^+ + A_2^- \), \( K_{2A_1} = [H^+][A_2^-]/[HA_2] \),
(6) \( HA_2 = H^+ + A_2^- \), \( K_{1A_2} = [H^+][A_2^-]/[HA_2] \),
(7) \( 0 = H^+ + OH^- \), \( K_w = K[H_2O] = [H^+][OH^-] \).

**Scheme 1**

**2. Experimental**

**2.1. Apparatus and Reagents.** The pH-meter titrations were performed in a 30 mL thermostatted (25.0 ± 0.2°C) cell, using a Cerko Lab microtitration unit, fitted with a pH electrode (Hydromet ERH-13-6). The temperature was controlled using...
Table 2: Stoichiometric matrix for model 2.

|   | H\(^+\) | H\(_2\)A | H\(_3\)A \(^-\) | H\(_2\)A \(^-\) | H\(_3\)A \(^-\) | A \(^-\) | A \(^-\) | A \(^-\) | OH \(^-\) |
|---|---|---|---|---|---|---|---|---|---|
| pK\(_{1A}\) | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| pK\(_{2A}\) | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| pK\(_{3A}\) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| pK\(_{1A}\) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| pK\(_{2A}\) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| pK\(_{3A}\) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

Table 3: The experimental pK\(_a\) data obtained for the mixture of PhA, Py4CA, and MA at various compositions of titrand D.

| Composition of D | pK\(_a\) | pK\(_{\text{PhA}}\) ± s | pK\(_{\text{Py4CA}}\) ± s | pK\(_{\text{MA}}\) ± s |
|-----------------|---------|------------------|------------------|------------------|
| PhA + Py4CA + MA | pK\(_1\) | 2.97 ± 0.07 | — | 3.30 ± 0.03 |
| (1:1:1) | pK\(_2\) | 5.31 ± 0.04 | 4.69 ± 0.03 | — |
| PhA + Py4CA + MA | pK\(_1\) | 2.81 ± 0.06 | — | 3.12 ± 0.03 |
| (1:2:2) | pK\(_2\) | 5.45 ± 0.03 | 4.71 ± 0.01 | — |
| PhA + Py4CA + MA | pK\(_1\) | 2.78 ± 0.04 | 4.76 ± 0.02 | 3.4\(^*\) |
| (1:2:1) | pK\(_2\) | 5.53 ± 0.04 | — | — |

* pK\(_a\) value const. taken from the literature [see Table 1].

Table 4: The experimental pK\(_a\) data obtained for the mixture of A + MA + PhA + Py3CA and 2,6PyDCA + Py3CA.

| Composition of D | pK\(_a\) | pK\(_{\text{PhA}}\) ± s | pK\(_{\text{Py3CA}}\) ± s | pK\(_{\text{MA}}\) ± s | pK\(_{\text{A}}\) ± s |
|-----------------|---------|------------------|------------------|------------------|------------------|
| A + MA + PhA + Py3CA | pK\(_1\) | 3.11 ± 0.05 | — | 3.74 ± 0.03 | 4.68 ± 0.02 |
| pK\(_2\) | 5.62 ± 0.03 | 4.82\(^*\) | — | — |
| 2,6PyDCA + Py3CA | pK\(_1\) | 2.41 ± 0.04 | — | — | — |
| pK\(_2\) | 4.72 ± 0.02 | 5.19 ± 0.04 | — | — |
| PhA + Py3CA + CA | pK\(_1\) | 3.12 ± 0.03 | 4.82\(^*\) | 4.46 ± 0.05 | — |
| pK\(_2\) | 5.53 ± 0.03 | 6.05 ± 0.04 | — | — |

* pK\(_a\) value const. from the literature [see Table 1].

the Lauda E100 circulation thermostat. The electrode was calibrated with the use of buffer solutions: potassium hydrogen phthalate (pH 4.00), citric acid/Na\(_2\)HPO\(_4\) (pH 7.00), and boric acid/KCl/NaOH (pH 10.00).

Titrant T (0.1 mol/L NaOH) was standardized according to the general analytical procedure and protected from carbon dioxide. Double distilled water of conductivity approximately 0.18 \(\mu\)S/cm was used throughout for the preparation of aqueous solutions of organic acids and bases under study. It was freshly produced in order to avoid carbon dioxide absorption. Other reagents together with their abbreviations used in the text are listed in Abbreviations section.

2.2. Analytical Procedure. Volume \(V_0\) of 4.0 mL to 5.0 mL of titrand (D) was titrated with 0.1 mol/L\(^{-1}\) of titrant (T) using a Cerko Lab System, equipped with a syringe pump. Titrant (T) was added to titrand (D) in increments of 0.01 mL, with a pause of 7 s. The pK\(_a\) values were calculated from the experimental data points \((V_j, pH_j)\) \(j = 1, \ldots, N\) according to the Kostrowicki and Liwo algorithm [9, 10].

3. Results and Discussion

3.1. Carboxylic Acids Mixture. The representative pH titration curves for the mixture of carboxylic acids PhA : Py-4CA : MA are presented in Figures 1 and 2. Compositions of titrand D for the mixture (PhA : Py-4CA : MA) were as follows: 1:1:1, 1:2:1, 1:2:2, and 1:1:1 with 0.5 mole ratio of HCl. The titration and fitted curves pH = \(f(V_{NaOH})\) obtained for mixture with molar ratio of the components 1:2:2 (PhA : Py-4CA : MA) are shown in Figure 2. The pK\(_a\) data determined for the mixtures of carboxylic acids under study are listed in Tables 3 and 4.

3.2. Organic Bases in Protonated Form (Cationic Acids). The amino group is one of the most fundamental functional groups considered in organic and pharmaceutical chemistry
Table 5: The $pK_a$'s values of compounds determined in the multicomponent mixture of amines, heterocyclic moiety, and weak (Mes) and strong (HCl) acids at 25°C.

| Composition of D | $pK_A \pm s$ | $pK_{4NH_2Py} \pm s$ | $pK_{2NH_2Py} \pm s$ | $pK_{FA} \pm s$ |
|-----------------|--------------|---------------------|---------------------|---------------|
| A + HCl         | 4.650 ± 0.02 | —                   | —                   | —             |
| A + 4NH$_2$Py + HCl | 4.53 ± 0.04 | 9.27 ± 0.18         | —                   | —             |
| A + 4NH$_2$Py + 2NH$_2$Py + HCl | 5.13 ± 0.07 | 9.59 ± 0.07         | 7.18 ± 0.07         | —             |
| A + 2NH$_2$Py + FA | 4.7*        | —                   | 6.7*                | 3.05 ± 0.04   |

| Composition of D | $pK_{Mes} \pm s$ | $pK_{2NH_2Py} \pm s$ | $pK_{Py}_3CA \pm s$ | $pK_{Py}_4CA \pm s$ | $pK_{Bi} \pm s$ | $pK_{ImH} \pm s$ |
|-----------------|------------------|---------------------|---------------------|---------------------|----------------|----------------|
| Mes + Bt        | 6.24 ± 0.05      | —                   | 8.75 ± 0.59         | —                   |
| Mes + 2NH$_2$Py + Bi + HCl | 6.28 ± 0.05 | 7.22 ± 0.05         | —                   | 5.36 ± 0.04         |
| Mes + 2NH$_2$Py + Py$_3$CA | 6.29 ± 0.03 | 7.22 ± 0.03         | 4.78 ± 0.03         | —                   |
| Mes + 2NH$_2$Py + Py$_4$CA | 6.29 ± 0.34 | 6.39 ± 0.34         | 4.76 ± 0.30         | —                   |

| Composition of D | $pK_{ASA} \pm s$ | $pK_{2NH_2Py} \pm s$ | $pK_{Py}_3CA \pm s$ | $pK_{Py}_4CA \pm s$ | $pK_{AA} \pm s$ | $pK_{3MePy} \pm s$ |
|-----------------|------------------|---------------------|---------------------|---------------------|----------------|----------------|
| ASA + Py$_3$CA + AA | 3.66 ± 0.05      | —                   | 5.02 ± 0.04         | 4.15 ± 0.05         |
| ASA + 2NH$_2$Py + 3MePy | 3.61 ± 0.03 | 7.02 ± 0.03         | —                   | 5.82 ± 0.03         |

* $pK_a$ value const. from the literature [see Table 11].

Table 6: The $pK_a$'s values of compounds determined in the mixture containing four weak electrolytes (acids and bases) and a strong acid (HCl) at 25°C.

| Composition of D | $pK_n$ | $pK_{PhA} \pm s$ | $pK_{MA} \pm s$ | $pK_{Py}_3CA \pm s$ | $pK_{AA} \pm s$ | $pK_{Bi} \pm s$ | $pK_{ImH} \pm s$ | $pK_{Bt} \pm s$ | $pK_{HCl} \pm s$ |
|-----------------|----------|------------------|------------------|-------------------|-------------------|-----------------|-----------------|-----------------|-----------------|
| PhA + MA + Py$_3$CA + A + HCl | $pK_1$ | 3.11 ± 0.05      | 3.74 ± 0.03      | 4.8*              | 4.68 ± 0.02       |
|                  | $pK_2$ | 5.62 ± 0.03      | —                | —                | —                |
| Composition of D | $pK_n$ | $pK_{AA} \pm s$ | $pK_{Bi} \pm s$ | $pK_{ImH} \pm s$ | $pK_{Bt} \pm s$ | $pK_{HCl} \pm s$ |
| AA + Bi + ImH + BtH + HCl | $pK_1$ | 4.29 ± 0.13      | 5.98 ± 0.14      | 7.55 ± 0.14       | 9.19 ± 0.14       |

* $pK_a$ value const. from the literature [see Table 11].

Table 7: The $pK_a$'s values of compounds determined in the multicomponent mixture of amino acid, heterocyclic moiety, and weak (Mes) and strong (HCl) acids at 25°C.

| Composition of D | $pK_n$ | $pK_{His} \pm s$ | $pK_{Py}_3CA$ | $pK_{Mes}$ | $pK_{ImH}$ |
|-----------------|--------|-----------------|---------------|------------|------------|
| L-His           | $pK_1$ | 9.67 ± 0.01     | —             | —          | —          |
| L-His + HCl (1:1) | $pK_2$ | 6.28 ± 0.01     | —             | —          | —          |
| L-His + HCl (1:2) | $pK_3$ | 9.97 ± 0.01     | —             | —          | —          |
| L-His + HCl (1:2) | $pK_4$ | 1.54 ± 0.04     | —             | —          | —          |
| L-His + Py$_3$CA + + Mes + ImH | $pK_2$ | 6.28*           | 4.68 ± 0.24   | —          | —          |
| L-His + Py$_3$CA + + Mes + ImH + HCl | $pK_3$ | 10.06 ± 0.55    | —             | —          | —          |

| Composition of D | $pK_n$ | $pK_{Ala} \pm s$ | $pK_{His} \pm s$ | $pK_{Py}_3CA$ | $pK_{Mes}$ | $pK_{ImH}$ |
|-----------------|--------|-----------------|---------------|---------------|------------|------------|
| L-Ala           | $pK_1$ | 10.30 ± 0.01    | —             | —             | —          | —          |
| L-Ala + HCl (1:1) | $pK_2$ | 2.25 ± 0.01     | —             | —             | —          | —          |

* $pK_a$ value const. from the literature [see Table 11].
Table 8: The $p_K_a$ values of compounds determined in the multicomponent mixture of phenol and enol OH–acids together with other weak electrolytes at 25°C.

| Composition of D | $pK_A \pm s$ | $pK_{FA} \pm s$ | $pK_{4NO_2PhOH} \pm s$ | — |
|-----------------|-------------|-----------------|------------------------|---|
| A + FA + 4NO$_2$PhOH | 4.87 ± 0.02 | 3.05 ± 0.03 | 7.42 ± 0.04 | — |

| Composition of D | $pK_{MAL} \pm s$ | $pK_{FA} \pm s$ | $pK_{4NO_2PhOH} \pm s$ | — |
|-----------------|-----------------|-----------------|------------------------|---|
| FA + MAL + 4NO$_2$PhOH | 3.59 ± 0.04 | 2.50 ± 0.04 | 7.4 ± 0.03 | — |

| Composition of D | $pK_{AA} \pm s$ | $pK_{Mes} \pm s$ | $pK_{Pcm} \pm s$ | — |
|-----------------|-----------------|-----------------|-----------------|---|
| AA + Mes + Pcm | 4.14 ± 0.03 | 6.24 ± 0.04 | 9.95 ± 0.05 | — |

| Composition of D | $pK_{ASA} \pm s$ | $pK_{FA} \pm s$ | $pK_{4NO_2PhOH} \pm s$ | $pK_{Kpf} \pm s$ |
|-----------------|-----------------|-----------------|------------------------|---------------- |
| ASA + FA + 4NO$_2$PhOH + Kpf | 3.77 ± 0.05 | 2.91 ± 0.06 | 7.52 ± 0.05 | 4.68 ± 0.36 |

Table 9: The $p_K_a$ values of compounds determined in the multicomponent mixture which comprises barbituric acid, 2(1H)-pyrazylideneacetonitrile, and phthalic acid at 25°C.

| Composition of D | $pK_{2(1H)PyAN} \pm s$ | $pK_{BA} \pm s$ | $pK_{PhA} \pm s$ | — |
|-----------------|--------------------------|-----------------|-----------------|---|
| 2(1H)PyAN + BA + PhA | 7.10 ± 0.09 | 4.01 ± 0.04 | 2.39 ± 0.08 | 5.76 ± 0.05 |

Figure 1: Titration curves $pH = f(V_{NaOH})$ obtained for the mixture of PhA, Py-4CA, and MA with different mole ratio of acids and with excess of HCl.

and its $pK_a$ is an important and extensively studied property. The $pK_a$ value of the amino group can vary over several orders of magnitude (ammonia, $pK_a = 9.26$; aniline, $pK_a = 4.63$ [11]), depending on its chemical environment. In our study the $pK_a$ refers to the conjugate acid $B + H^+ = BH^+$ and dissociation according to the scheme: $BH^+ = B + H^+$. We have tested a mixture of organic bases exemplified by aniline and pyridine derivatives (2- and 4-substituted aminopyridines and methylpyridine) at the presence of equimolar ratio of HCl. Organic bases exist in the system in the protonated form (cationic acids, $BH^+$) and dissociate according to the scheme: $BH^+ = B + H^+$, $K_{BH^+} = [B][H^+] / [BH^+]$. Based on the titration curve of mixture of amines (presented in the form of cationic acids), the $pK_a$ values were determined for aniline (B) and for 2- and 4-aminopyridine (2-NH$_2$Py, 4-NH$_2$Py). The heterocyclic five-membered ring systems of imidazole (Im), benztetrazole (Bt), and benzimidazole (Bi) were also investigated. We have applied a general procedure for the titration of mixtures of different types (and concentration) of organic acids and bases. The elaborated procedure was also tested in the presence of biological buffers exemplified by 2-(N-morpholino) ethane-sulfonic acid (Mes) [12].
Table 10: The p$K_a$ values of compounds with pharmaceutical importance determined in the mixture containing other weak electrolytes 25°C.

| Composition of D | p$K_{AA}$ ± s | p$K_{Mes}$ ± s | p$K_{Pcm}$ ± s | p$K_{ASA}$ | p$K_{CA}$ |
|------------------|---------------|---------------|----------------|------------|-----------|
| AA + Mes + Pcm   | 4.14 ± 0.03   | 6.24 ± 0.04   | 9.95 ± 0.05    | —          | —         |
| Composition of D | p$K_{ASA}$ ± s | p$K_{ImH}$ ± s | p$K_{ASA}$ ± s | —          | —         |
| ASA + ImH + Eph * HCl | 3.49 ± 0.03 | 6.21 ± 0.06 | 9.94 ± 0.05 | —         | —         |
| Composition of D | p$K_{Mes}$ ± s | p$K_{ImH}$ ± s | p$K_{Mes}$ ± s | —          | —         |
| Met + ImH + Mes  | 2.28 ± 0.04   | 7.35 ± 0.02   | 10.19 ± 0.01   | —          | —         |
| Composition of D | p$K_{ASA}$ ± s | p$K_{Mes}$ ± s | p$K_{L-His}$ ± s | —       | —         |
| ASA + Mes + L-His| 3.57 ± 0.03   | 6.29 ± 0.03   | 9.86 ± 0.05    | —          | —         |
| Composition of D | p$K_{ASA}$ ± s | p$K_{Mes}$ ± s | p$K_{Mes}$ ± s | —          | —         |
| ASA + Mes + L-His| 3.57 ± 0.03   | 6.29 ± 0.03   | 9.86 ± 0.05    | —          | —         |

*p$K_a$ value const. from the literature [see Table 11].

3.4. Phenol and Enol OH-Acids as Components of Titrand D. The acidity of the phenol group (OH-acid) depends on the substituent of the aromatic ring and its p$K_a$ ranges from 4 to 11 [8]. We have performed the titration and relevant calculations for several mixtures of phenolic compounds, exemplified by 4-NO$_2$ phenol and a drug N-(4-hydroxyphenyl)acetamide (paracetamol) with different type of organic acids and bases as titrands D. The results are summarised in Table 8.

3.5. Heterocyclic N–H-Acids as Components of Titrand D. The barbituric acid (BA) and a new class of 2(1H)-pyrazylidene acetonitrile derivatives (2(1H)PyAN), with marked pharmaceutical importance [13, 14], were tested at the presence of phthalic acid. Barbituric acid was also tested at the presence of different drugs (Table 9).

3.6. Determination of p$K_a$ Values for Different Drugs as a Components of Titrand D. For all tested compounds with pharmaceutical importance we confirmed that the elaborated method could be recommended as a general approach to the determination of p$K_a$ values for weak acids and bases in mixtures of any degree of complexity. The composition of titrand D and the p$K_a$ values determined for drugs under study are listed in Table 10.
Table I: Experimental and literature pKₐ’s values of the compounds under study.

| No. | Compounds | pK₁ₑₛᵖ | pKₐliterature | Reference |
|-----|-----------|---------|---------------|-----------|
| 1   | A         | 4.81    | 4.55–4.78     | [11]      |
| 2   | AA        | 4.17    | 4.10          | [15]      |
| 3   | ASA       | 3.67    | 3.30–3.74     | [16]      |
| 4   | BA        | 4.01    | 4.02          | [17]      |
| 5   | Bi        | 5.98    | 5.66          | [18]      |
| 6   | CA        | 5.03    | 4.76          | [19]      |
| 7   | Eph       | 9.94    | 9.56          | [20]      |
| 8   | FA        | 2.88    | 3.02          | [21]      |
| 9   | Im        | 7.43    | 6.95          | [22]      |
| 10  | KTL       | 3.09    | 2.90–3.29     | [16]      |
| 11  | Ktp       | 4.68    | 4.6           | [23]      |
| 12  | L-ala     | 1.67    | 1.54          | [18]      |
| 13  | L-his     | 6.22    | 6.07          | [22]      |
| 14  | MA        | 3.48    | 3.18–3.41     | [18]      |
| 15  | 3-MePy    | 5.82    | 5.61–6.02     | [18]      |
| 16  | MAL       | 3.59    | 3.11–3.30     | [18]      |
| 17  | Mes       | 6.27    | 6.27          | [22]      |
| 18  | Met       | 2.28    | 2.38          | [16]      |
| 19  | 2-NH₂Py   | 7.04    | 6.72–6.76     | [16]      |
| 20  | 4-NH₂Py   | 9.43    | 9.02–9.29     | [16]      |
| 21  | 4-NO₂PhOH | 7.44    | 7.02–7.15     | [11]      |
| 22  | PhA       | 2.86    | 2.95          | [22]      |
| 23  | Ppv       | 6.02    | 6.21–6.49     | [16]      |
| 24  | 2(1H)PyAN | 7.10    | —             | —         |
| 25  | Py-3CA    | 4.85    | 4.82          | [24]      |
| 26  | Py-4CA    | 4.72    | 4.84          | [24]      |
| 27  | 2,6-PyDCA | 2.41    | 2.00–3.45     | [18]      |

*pK₁ₑₛᵖ calculated as ∑pKᵢ/n.

4. Conclusions

A new approach for studying equilibrium constants for the dissociation of different types of weak electrolytes present in a mixture of any degree of complexity has been proposed. Potentiometric titration technique and numerical procedure based on an original algorithm elaborated by Kostrowicki and Liwo and adopted in the Cerko Lab software have successfully been applied to obtain the pKₐ values of a variety of classes of compounds comprising of common organic acids and bases, amino acids, phenols and enols OH-acids, and heterocyclic N–H-acids as well as compounds of pharmaceutical importance. It was shown that the pKₐ values of the compound present in the mixture can be determined directly without the need to separate individual analytes. The obtained pKₐ values of the electrolytes under study are in a good agreement with those reported in the literature (Table I, Figure 3). Thus, the presented methodology can be considered as a fast, simple, inexpensive, and reagents-saving way for studying equilibria in the mixture of electrolytes. Moreover, it does not require a highly trained personnel. The methodology described in this paper can be routinely used in a regular analytical practice.

Abbreviations

C₀: Concentration [mol/L] of weak electrolyte
D: Titrand (solution titrated)
T: Titrant (titrating solution)
K: Dissociation constant for a weak electrolyte
pK = −log K: Acidity parameter
V: Volume [mL] of T
V₀: Volume [mL] of D
A: Aniline, aminobenzene (Sigma Aldrich > 99.5%)
AA: Ascorbic acid L(+-), (5R)-[1(5S)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5H)-one (Chempur, p.a.)
ASA: Acetylsalicylic acid, 2-acetoxybenzoic acid (Sigma Aldrich, >99.5%)
BA: Barbituric acid, pyrimidine-2,4,6(1H,3H,5H)-trione (Fluka, p.a.)
Bi: 1H-Benzimidazole (Sigma Aldrich)
Bt: 1,2,3-Benzo triazole (Sigma Aldrich)
CA: Citric acid monohydrate, 2-hydroxypropane-1,2,3-tricarboxylic acid (P.P.H. Standard S. z o. o., p.a.)
Eph: Ephedrine hydrochloride, (R,S)-2-(methylamino)-1-phenylprop-1-ol (RBI)
FA: Fumaric acid, (E)-butenedioic acid (Sigma Aldrich, >99%)
Im: 1H-Imidazole (Sigma Aldrich)
Kp: Ketoprofen, (RS)-2-(3-benzoylphenyl)propanoic acid
KTL: Ketoconazole, 1-[4-(4-[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl)piperazin-1-yl]ethan-1-one
L-ala: L-Alanine, 2-aminopropanoic acid (Fluka)
L-his: L-Histidine, 2-amino-3-(1H-imidazol-4-yl)propanoic acid (Sigma Aldrich)
MA: Mandelic acid, 2-hydroxy-2-phenylacetic acid (Alfa Aesar GmbH & Co, >99%)
MAL: Malic acid (hydroxybutanedioic acid)
Met: Metronidazole
(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol)
3-MePy: 3-Methylpyridine (Sigma Aldrich)
Mes: 2-(N-Morpholino)ethanesulfonic acid hydrate (Sigma Aldrich, ≥99%)
2-NH₄Py: 2-Aminopyridine (Sigma Aldrich)
4-NH₄Py: 4-Aminopyridine (Sigma Aldrich)
4-NO₂PhOH: 4-Nitrophenol (POCH S.A.)
Ppv: Papaverine
(1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline)
Pcm: Paracetamol
(N-(4-hydroxyphenyl)acetamide)
PhA: Phthalic acid, benzene-1,2-dicarboxylic acid (POCH S.A.)
2(1H)PyAN: α-2(1H)pyrazidilene
α-2-cyanoethylacetate
Py-3CA: Pyridine-3-carboxylic acid (Sigma Aldrich, p.a.)
Py-4CA: Pyridine-4-carboxylic acid (Sigma Aldrich, p.a.)
2,6-PyDCA: Pyridine-2,6-dicarboxylic acid (Sigma Aldrich, p.a.)

Conflict of Interests

The authors declare that there is no conflict of interests.

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