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# Potentiometric Determination of $pK_a$ Values of Benzoic Acid and Substituted Benzoic Acid Compounds in Acetonitrile-Water Mixtures

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The dissociation $pK_a$ values of benzoic acid and substitued benzoic acids have been determinated in water and acetonitrile-water media (10, 20 and 30 %) by potentiometric measurements. The results obtained shows that the solvents affect the acid equilibrium. The potentiometric data of benzoic compounds at various pH values (pH 2.0-11.0) were recorded. The calibration of the electrode system was done potentiometrically by Gran's method. Data were processed using the Hyperquad 2006 which calculate stability constants of the pure species by multi linear regression. The obtained results are in good concordance with literature values.

**Key Words: Benzoic acid and Substituted benzoic acids, Dissociation constants, Potentiometrically.**

## INTRODUCTION

The $pK_a$ value is a key parameter to predict the ionization state of a molecule with respect to pH. Knowledge of this parameter is essential in the estimation of ADME (adsorption, distribution, metabolism and excretion) properties since absorption and distribution are highly affected by the ionization of the compound. It is also necessary for the measurements of pH-dependent moleculer properties, for example solubility and lipophilicity[1]. A scheme of acid-base equilibria set up between acids (both molecular and cationic) and organic bases in non-aqueous media is very complicated and depends on properties of medium[2]. IUPAC has remarked on the importance of the knowledge of pH values of buffers in mixed solvents in order to achieve complete and effective pH standardization in these media.

The establishment of reference pH values of buffer in mixed solvents requires the determination of the acid-base pK values of the acids and bases that compose the buffer in the mixed solvent[3]. Solvent mixtures are interesting, because two solvents mixed together produce a solvent with quite different properties, both physically (electric permittivity, density, viscosity) and chemically (acid-base and acceptor-donor properties). As far as the acid-base properties are concerned, an important feature is that the nature of solvent is crucial for the strength of acids and bases. In particular, proton affinity or in the other words, the proton-donating and proton-accepting properties of solvent, as well as its polarity are important factors. Also the ionization degree of solute depends on the dielectric constant of solvent. Media of high dielectric constants are strongly ionizing, whereas those of low dielectic constants ionize to a lesser extent. Potentiometric measurement of the hydrogen ion activity based on the Nernst equation:

$$E = E° - s.pa_{H+} \quad (1)$$

where E is the e.m.f. for a particular hydrogen ion activity, E° the standard e.m.f of the cell and s the slope of the glass electrode characteristics. On the basis of the measured E values, the hydrogen ion activity can be determined in solution if the cell parameters s and E° are known. They are determined by a procedure of the calibration of the glass electrode, which means the measurement of the e.m.f of the cell in a series of buffer solutions (containing acid and conjugate salt) of different concentrations[4].

Acetonitrile (MeCN) is one of the most important dipolar aprotic solvent. It is used extensively as a reaction medium for mechanistic studies, in electrochemistry and in high performance liquid chromatography. It is also employed as a solvent for non-aqueous titrations[5]. MeCN behaves as a weaker base and as much weaker acid than water. It has a relatively high dielectric constant ($\varepsilon = 36$) and a small autoprotolysis constant ($pK_s = 33.6$). Accordingly, MeCN acts as a strongly differentiating solvent with a modest solvating power for many polar ionic solutes[6].

Potentiometric titration data are commonly used for determining the dissociation constants of polyprotic acids and bases. A variety of computational methods have been developed for this purpose in last decades[7]. A physical property of the analyte is measured as a function of the pH of the solution and the resulting data are used for the determination of the dissociation constants. The use of MeCN-water mixtures requires the correct measurement of pH in these media. Measurements are performed in a similar way to those performed in water using IUPAC standardization rules and the standard pH values assigned in MeCN-water mixtures for primary reference buffer solution of the NIST scale[8].

The calibration of glass electrodes in terms of hydrogen ion concentration may be performed following IUPAC recommendations which are based on the use of either one or two designated buffer solutions, or on the basis of a regression procedure performed with data from more than two buffer solutions. These procedures are not wholly satisfactory for potentiometric titrations using a backround medium of high ionic strength, as is usual in the determination of stability constants[9].

The dissociation constant of benzoic acids are important physico-chemical parameters for a thorough understanding of certain chemical phenomena such as activity and reacting rates, biological uptake and receptor binding of substances at the molecular level. Dissociation constants of substances can be determined by several different methods. The potentiometric, chromatographic, electrophoretic methods have also been used widely. But a method based on spectrophotometry has been still used widely by the help of improving computer programs[10-12]. In most of these methods a physical property of the analyte is measured as a function of the pH of the solution and the resulting data are used for the determination of dissociation constant. The use of MeCN-H$_2$O mixtures requires the correct measurement of pH in these media. Measurements are performed in a similar way to those performed in water using IUPAC standardization rules[13-15].

In this work, the pKa values of selected benzoic acid substances in water and 10, 20 and 30 % (v/v) acetonitrile-water mixture using potentiometric measurements have been determined. We have proposed models that relate the pK values with the solvent composition. The results are thought as necessary for the separation of compounds at the methods of chromatographic and electrophoretic. We studied at the media of 10, 20 and 30 % MeCN-H$_2$O mixtures since some of benzoic acids have not been determined as potentiometric in this media so far.

## EXPERIMENTAL

Analytical reagent grade chemicals were used, unless otherwise indicated. The structure of substituted benzoic acids are shown in Fig. 1. These compoumds were purchased from Merck (Darmstadt, Germany), Aldrich (Milwaukee, WS, USA )and Fluka (Milwaukee, WS, USA).

Water, with conductivity lower than 0.05 _S cm1, was obtained with a Milli-Q water purification system (Millipore Corp.). MeCN (HPLC grade), was supplied by Merck. Potassium hydroxide (Merck), potassium chloride (Merck), hydrochloric acid (Merck) was used. While potentiometric measurements were done, solutions of individual benzoic phenolic compounds were prepared at a concentration of *ca.* $5 \times 10^{-4}$ mol L$^{-1}$. All the solutions were prepared in 0.1 mol L$^{-1}$ KCl to adjust the ionic strength. The calibration of the electrode system was done potentiometrically by Gran's method[16,17].

The cell was thermostated externally at 25 ± 0.1 ºC with a cooler system water bath (Heto CBN 8-30 and temperature control unit Heto HMT 200) and the test solution was stirred magnetically under a continuous stream of purified nitrogen. The e.m.f measurements to evaluate the pH of the solution were performed with a model ORION 5 STAR pH/ion analyzer with Ag/AgCl combined pH electrode system (± 0.1 mv).

**Potentiometric measurements:** The pK$_a$ values of the different substances were determined by means of the data obtained from potentiometric titrations in in water and 10, 20 and 30 % (v/v) MeCN-H$_2$O mixture at 25 ± 0.1 ºC and in 0.1 mol L$^{-1}$ ionic strength (KCl). For each benzoic acid compound various series of measurements were performed in studied media. In the first step, the electrodic system was calibrated by Gran's method as in the case of potentiometric measurements in order to obtain E$^o$ value. Previously, a suitable amount of a solution containing the compound to be analyzed at the required conditions of temperature, ionic strength and solvent

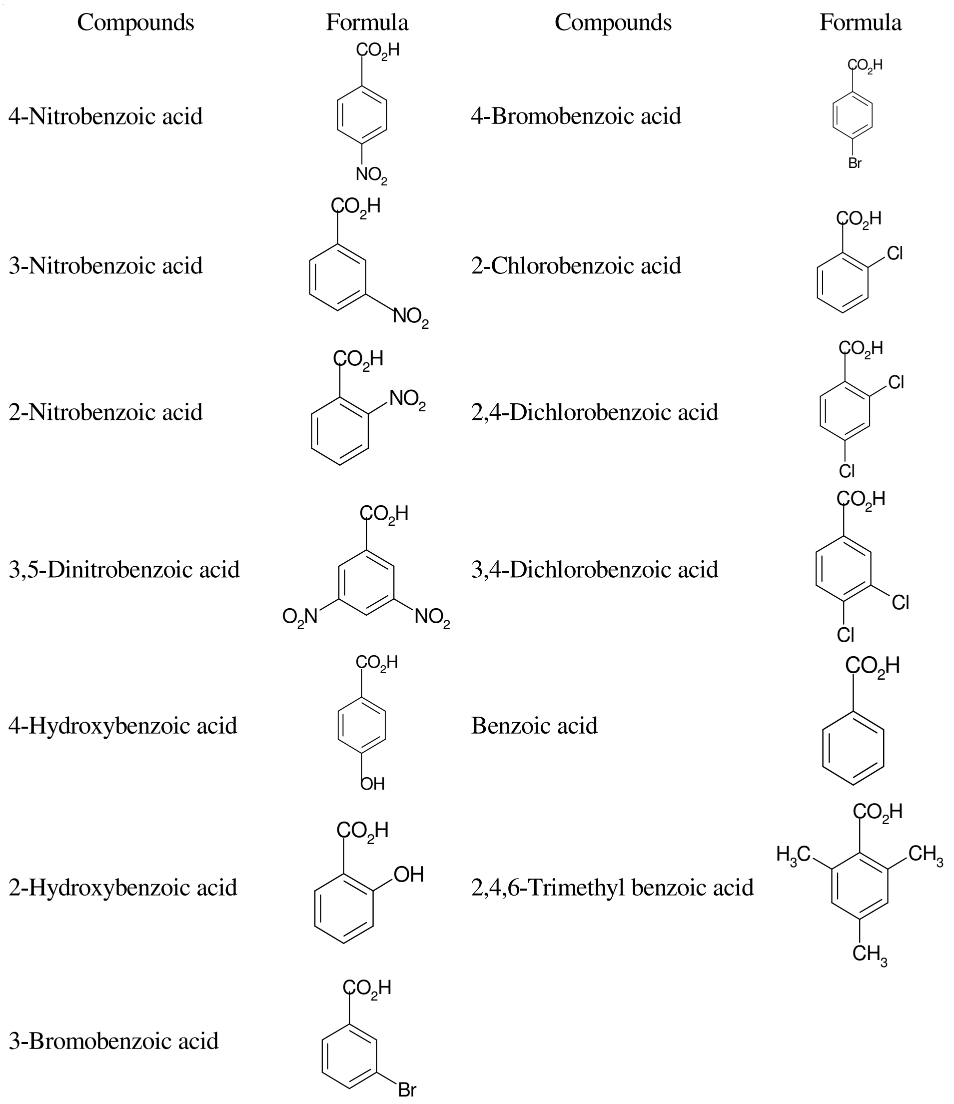


Fig. 1. Structural formulae of substituted benzoic acids

composition was added to the pre-titrated background solution and small amounts of hydrochloric acid solutions were then added. After each addition, the potential was allowed to stabilize and the potential value was used to calculate the pH of the solution using the value of E° calculated in the calibration step.

$$E = E^\circ - 0.059 \log a_{H+} \qquad (2)$$

$$E = E^\circ - 0.059\ pH$$

$$pH = E - E^\circ / 0.059$$

Data were processed using the program Hyperquad 2006 can be used to derive stability constants from potentiometric titration data, spectrophotometric titration data or batch measurements of either kind. It can handle both potentiometric and spectrophotometric data obtained on the same solutions. The stability constant refinement is performed by means of a compiled FORTRAN program. The program takes its data from files and outputs its results to a file. Once the calculation is finished the results appear in the output viewer. The package includes 15 sets of sample data, each one illustrating a different type of calculation such as ligand protonation (both by potentiometry and by spectrophotometry), metal complex formation (likewise), ternary complex formation, competition method, oxygen complexes, systems including redox reactions, *etc*. There is also a detailed Help file which has descriptions of all the program's functions[18].

## RESULTS AND DISCUSSION

The calibration and titration curves of benzoic acid compounds in water and 10, 20 and 30 % (v/v) acetonitrile-water mixture at various pH values were recorded. Sample calibration curves of 3,4-dichlorobenzoic acid and benzoic acid in different media are shown in Fig. 2. Gran Function is used to sketch in this calibration curves.

**Gran function:**

$\phi = (V_0 + V_{HCl}).\ 10^{-pH}$ (Acid region)
$\phi = (V_0 + V_{HCl}).\ 10^{+pH}$ (Basic region)
$V_0$ = Beginning volume
$V_{HCl}$ = Added 0.1 M HCl volume

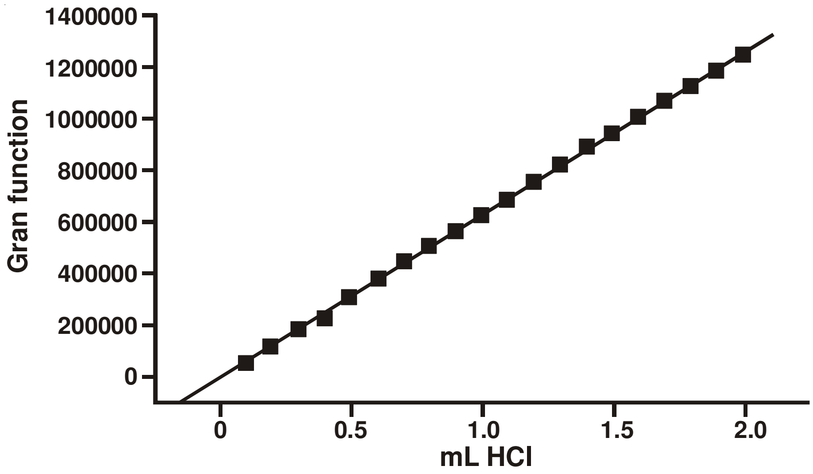


Fig. 2. Calibration values of 3,4-dichlorobenzoic acid in 20 % (v/v) MeCN-H$_2$O

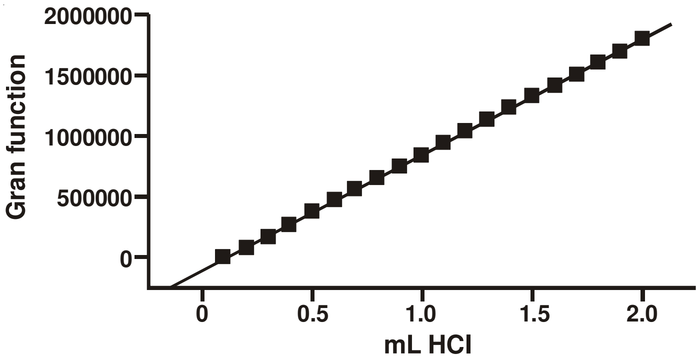


Fig. 3. Calibration values of benzoic acid in 20 % (v/v) MeCN-$H_2O$

Solvent mixtures are interesting, because two solvents mixed together produce a solvent with quite different properties, both physically (electric permittivity, density, viscosity) and chemically (acid-base and acceptor-donor properties). As far as the acid-base properties are concerned, an important feature is that the nature of the solvent is crucial for the strength of acids and bases. In particular, the proton affinity or in other words, the proton-donating and proton-accepting properties of solvent, as well as its polarity are important factors. Also the ionization degree of solute depends on the dielectric constant of solvent. Media of high dielectric constants are strongly ionizing, whereas those of low dielectric constants ionize to a lesser extent. By mixing solvents of different polarity in proper ratios, dielectric constant of the medium can be varied and, at the same time, the strength of dissolved acids and bases. It should also be emphasized that solvent mixtures can be more convenient than individual solvents owing to enhanced solubilising capacity and more manageable shape of acid-base titration curves.

The standards used for the determination of the $pK_a$ values have successfully been utilized in hydro organic media and employed in particular for potantiometry as an experimental technique. On the other hand, increasing interest in acid-base interactions taking place in solvent mixtures raised the need for the development of a method for the determination of the $pK_a$ values for standards in such media. For this reason, the primary objective of this contribution was to develop a potentiometric method for the determination of acid dissociation constants (commonly expressed as $pK_a$) of benzoic acid compounds in solvent mixtures.

From Tables 1 and 2, it is deduced that the variations of the $pK_a$ values with the percentage of MeCN were different for each substance. However, the pK values increased for all benzoic acids as the MeCN content increased as expected. This can be explained by structural features of MeCN-$H_2O$ mixtures because the dissociation of uncharged acids in MeCN-$H_2O$, as in other aqueous-organic mixtures, is ruled by electrostatic interactions as well as specific solute-solvent interactions (solvation effects)[14-21].

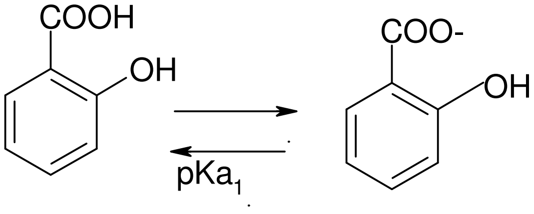
TABLE-1
THEORITICAL p$K_a$ VALUES OF BENZOIC ACID COMPOUNDS

| Compounds | $H_2O$ p$K_a$ | 10 % MeCN-$H_2O$ p$K_a$ | 20% MeCN-$H_2O$ p$K_a$ | 30% MeCN-$H_2O$ p$K_a$ |
|---|---|---|---|---|
| 4-Nitrobenzoic acid | 3.43[a] | 3.50[a] | 3.82[a] | 4.10[a] |
| | 3.44[b] | 3.48[e] | 3.82[e] | 4.11[e] |
| | 3.43[c] | | | |
| | 3.44[e] | | | |
| 3-Nitrobenzoic acid | 3.49[a] | 3.54[a] | 3.75[a] | 4.01[a] |
| | 3.49[b] | 3.52[e] | 3.72[e] | 4.04[e] |
| | 3.46[c] | | | |
| | 3.45[e] | | | |
| 2-Nitrobenzoic acid | 2.22[a] | 2.58[a] | 2.95[a] | 3.29[a] |
| | 2.17[b] | 2.43[e] | 2.93[e] | 3.29[e] |
| | 2.17[c] | | | |
| | 2.35[e] | | | |
| 3,5-Nitrobenzoic acid | 2.82[a] | 2.97[e] | 3.35[e] | 3.80[e] |
| | 2.82[b] | | | |
| | 2.81[e] | | | |
| 3-Bromobenzoic acid | 3.82[a] | 3.95[e] | 4.28[e] | 4.50[e] |
| | 3.81[b] | | | |
| | 3.81[c] | | | |
| 4-Bromobenzoic acid | 3.97[a] | 4.14[e] | 4.46[e] | 4.53[e] |
| | 4.00[b] | | | |
| | 3.96[c] | | | |
| | 3.97[e] | | | |
| 2-Chlorobenzoic acid | 2.94[a] | 3.14[e] | 3.53[e] | 3.80[e] |
| | 2.94[b] | | | |
| | 2.90[c] | | | |
| | 2.94[e] | | | |
| 2,4-Dichlorobenzoic acid | 2.72[a] | 3.01[e] | 3.11[e] | 3.48[e] |
| | 2.71[e] | | | |
| 3,4-Dichlorobenzoic acid | 3.60[a] | 3.78[e] | 4.19[e] | 4.48[e] |
| | 3.57[e] | | | |
| 4-Hydroxybenzoic acid | 4.58[a] | pka$_1$:4.85[e] | pka$_1$:5.00[e] | pka$_1$:5.28[e] |
| | 4.58[b] | pka$_2$:9.49[e] | pka$_2$:9.56[e] | pka$_2$:9.90[e] |
| | pka$_2$:9.23[b] | | | |
| | 4.57[c] | | | |
| | pka$_1$:4.53[e] | | | |
| | pka$_2$:9.21[e] | | | |
| 2-Hydroxybenzoic acid | 2.98[a] | | pka$_1$:3.63[e] | |
| | 3.00[b] | pka$_1$:3.22[e] | pka$_2$:12.7[e] | pka$_1$:3.80[e] |
| | pka$_2$:12.38[b] | pka$_2$:12.5[e] | | pka$_2$:13.2[e] |
| | 2.98[c] | | | |
| | pka$_1$:3.00[e] | | | |
| | pka$_2$:12.28[e] | | | |
| Benzoic acid | 4.21[a] | 4.49[a] | 4.77[a] | 5.05[a] |
| | 4.21[b] | 4.48[e] | 4.77[e] | 4.96[e] |
| | 4.204[c] | | | |
| | 4.231[d] | | | |
| | 4.20[e] | | | |
| 2,4,6-Trimethyl benzoic acid | 3.44[a] | 3.55[e] | 3.97[e] | 4.33[e] |
| | 3.44[b] | | | |
| | 3.40[e] | | | |

a: Ref. 19; b: Ref. 20; c: Ref. 21; d: Ref. 22; e: Ref. 23.

TABLE-2
pKa VALUES OF BENZOIC ACID COMPOUNDS OBTAINED BY POTENTIOMETRIC METHOD IN WATER AND ACETONITRILE-WATER MEDIA (10, 20 and 30 %)

| Compounds | $H_2O$ $pK_a$ | 10% MeCN-$H_2O$ $pK_a$ | 20% MeCN-$H_2O$ $pK_a$ | 30% MeCN-$H_2O$ $pK_a$ |
|---|---|---|---|---|
| 4-Nitrobenzoic acid | 3.6713±0.0195 | 3.4912±0.0474 | 3.9394±0.0328 | 4.2438±0.0934 |
| 3-Nitrobenzoic acid | 3.6832±0.0155 | 3.5267±0.1212 | 3.8454±0.0489 | 4.1769±0.0202 |
| 2-Nitrobenzoic acid | 2.5812±0.0262 | 2.4454±0.0138 | 3.0509±0.0110 | 3.4175±0.0205 |
| 3,5-Dinitrobenzoic acid | 3.0423±0.0182 | 2.9827±0.0270 | 3.47±0.0740 | 3.9312±0.0256 |
| 3-Bromobenzoic acid | 4.0456±0.0235 | 3.9687±0.0302 | 4.4032±0.0173 | 4.6367±0.0373 |
| 4-Bromobenzoic acid | 4.2780±0.0851 | 4.1554±0.0558 | 4.582±0.0723 | 4.66±0.0118 |
| 2-Chlorobenzoic acid | 3.1754±0.0150 | 3.1512±0.0952 | 3.6533±0.0815 | 3.93±0.0739 |
| 2,4-Dichlorobenzoic acid | 2.9440±0.1238 | 3.0213±0.1285 | 3.2342±0.0615 | 3.6111±0.0486 |
| 3,4-Dichlorobenzoic acid | 3.8760±0.0525 | 3.7919±0.0785 | 4.3164±0.0087 | 4.6148±0.0607 |
| 4-Hydroxybenzoic acid | 4.7640±0.0317 | 4.8645±0.0130 | 5.1227±0.0480 | 5.4106±0.0147 |
|  | 9.4430±0.0046 | 9.5890±0.0128 | 9.6869±0.0001 | 10.0374±0.0142 |
| 2-Hydroxybenzoic acid | 3.2367±0.0555 | 3.3485±0.0307 | 3.7538±0.0335 | 3.93±0.0544 |
|  | 12.514±0.0540 | 12.563±0.0149 | 12.882±0.0781 | 13.376±0.0558 |
| Benzoic acid | 4.43±0.0765 | 4.4942±0.0438 | 4.8971±0.0379 | 5.0997±0.030 |
| 2,4,6-Trimethyl benzoic acid | 3.63±0.0798 | 3.5671±0.0876 | 4.0916±0.0407 | 4.462±0.0397 |



If it is compared the strengths of a series of substitued benzoic acids with the strength of benzoic acid itself. It is saw that there are significant variations according to the nature of the substituent and its ring position, *ortho*, *meta* or *para*.Thus, all three nitro benzoic acids are appreciably stronger than benzoic acid in the order *para* (4-nitrobenzoic acid) > *ortho* (2-nitrobenzoic acid). A nitro substituent increases the rate.

The analysis methods commonly used to derive $pK_a$'s from titration curves include first-derivative ($\Delta^2$ mV/$\Delta V^2$), second-derivative ($\Delta^2$ mV/$\Delta V^2$). Sample spectra of some benzoic acids at different pH values in studied media are shown in Figs. 4-8. These benzoic acids are randomly chosen.

This can be explained by structural features of MeCN-$H_2O$ mixtures because the dissociation of uncharged acids in MeCN-$H_2O$, as in other aqueous-organic mixtures, is ruled by electrostatic interactions as well as specific solute-solvent interactions (solvation effects)[24-26].

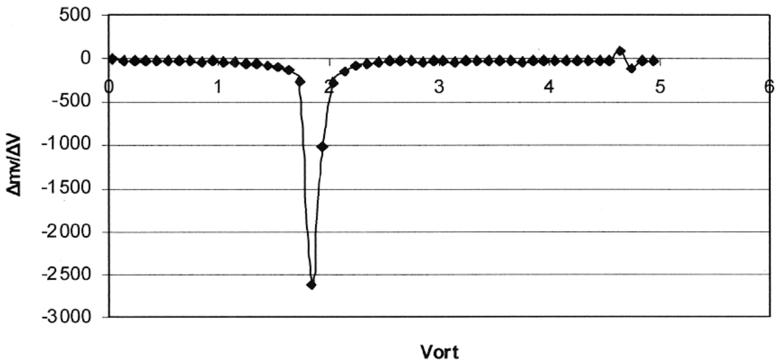


Fig. 4. Potentiometric first derivative titration curves of benzoic acid in water

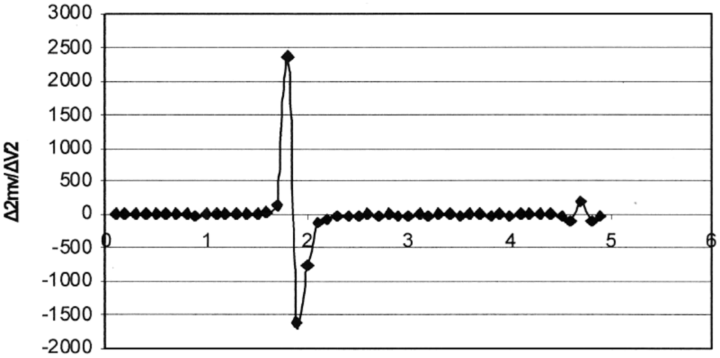


Fig. 5. Potentiometric second derivative titration curves of benzoic acid in water

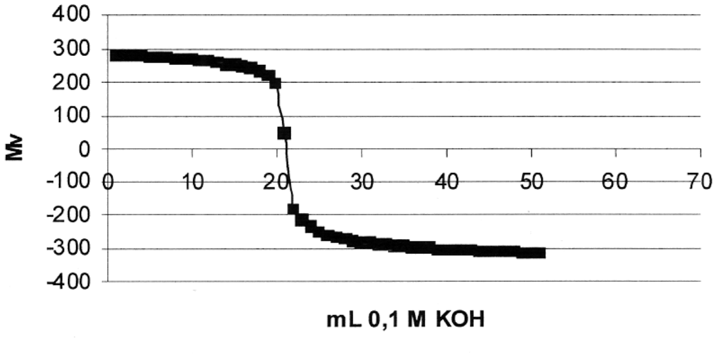


Fig. 6. Potentiometric titration curves of 3-bromobenzoic acid in 30 % MeCN-H$_2$O media

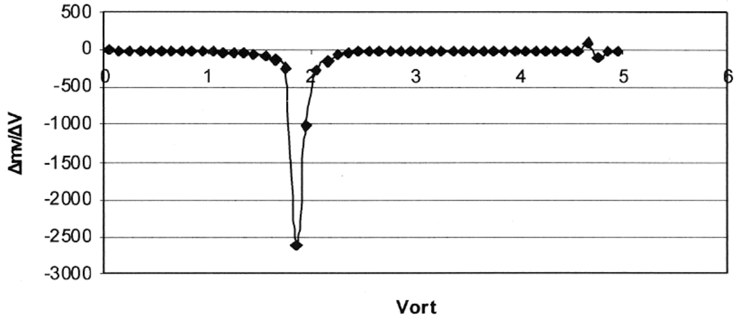


Fig. 7. Potentiometric first derivative titration curves of 3-bromobenzoic acid in 30 % MeCN-$H_2O$ media

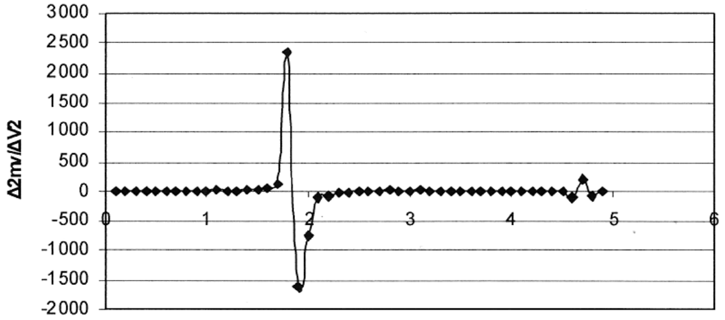


Fig. 8. Potentiometric second derivative titration curves of 3-bromobenzoic acid in 30 % MeCN-$H_2O$ media

## Conclusion

In this investigation, the determination of dissociation constants of benzoic acid and 13 substituted benzoic acids by potentiometric method has been performed. Although potentiometric method requires a relatively high pure substance, at least one of species (acid or basic) must contain an ionic group and the time and effort to calibrate the electrodic system. It provides excellent precision in the measurements. The true dissociation constants can be measured directly without inter ionic effects have been considered, the optical properties of the ions are virtually constant up to relatively high concentrations.

## ACKNOWLEDGEMENT

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