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Analysis and Dissociation of Certain Acidic Pharmaceutical Compounds in n-Butanol

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Visual and potentiometric titrations of aspirin, benzoic acid, hydrochloric acid, nicotinic acid, perchloric acid , phenyl butazone, salicylic acid, chloropromazine hydrochloride, ephedrine hydrochloride, mepyramine maleate and procaine hydrochloride were carried out in n-butanol, using potassium butoxide as the titrant. For visual end points, thymol blue was used as indicator, while potentiometric measurements were assessed by a glass indicator electrode. The dissociation constants of the studied compounds were determined by the use of the electromotive force method and revealed the good applicability of n-butanol as a solvent for non-aqueous titration of acidic pharmaceutical compounds.

Many organic acids, basis and salts are sparingly soluble in water or possess such weak dissociation constants, that handicap their determination by ordinary acid-base titrations. Such shortcomings are oftenly overcomed by the use of non-aqueous titrations. Occasionally, the study of the solute-solvent equilibria is recommended for suggesting the probability of solving the handled problem. Many scientists

suggested to study such processes in mixed organic
...nts, mostly with water. This is because of the dif-
...ies mostly met with during measurements of the emf
...e cell used.Typical examples are : the long time nee-
...for the establishment of equilibrium between electro-
...nd investigated solutions, sensitivity of the examin-
...ations in pure organic solvents to atmospheric car-
...oxide and susceptibility of most organic solvents
...olatilization that may lead to change in concentration
...hese solutions.

Alcohol-water mixtures have particular interest bet-
...the investigations while studying the acidity pheno-
...(1).Most of these mixtures are ethanol-water (2-4),
...ethanol-water (5-7). In pure isopropanol and ethanol,
...tions of several inorganic acids and some dibasic acids
...ome (8-10). Roy et al (11-12)by careful emf measure-
...of hydrogen and silver chloride electrodes have stud-
...properties of hydrogen chloride in n-propanol as
...in isopropanol and in their aqueous mixtures.
...gh the hydrogen electrode is difficult to handle,
...frequently used in the determination of dissociation
...ants by the emf method. However, glass electrode have
...employed instead of hydrogen electrode for such measure-
...and was found to give reproducible measurements at
...opriate pH range, i.e. not so strong acidic or so strong

basic medium (13 - 15)

The present investigation presents the use of pure n-butanol as a good solvent that would surpass other lower alcohol homologs by virtue of its promising differentiating and solubilizing effects. For this purpose, potentiometric titrations of certain acids and acidic pharmaceutical salts and the determination of dissociation constants of the acids in n-butanol were carried out. The more stable and easy to handle glass electrode had been used for emf measurements.

E X P E R I M E N T A L

Reagents and Apparatus:

1-Chemicals- solvent.n-butanol reagent grade was further dried over anhydrous sodium sulfate then distilled and collected the medium fraction at 117.7°C. Aspirin, benzoic acid, hydrochloric acid, nicotonic acid, perchloric acid, phenyl butazone, salicylic acid, chloropromazine hydro chloride, mepyramine maleate, procaine hydrochloride and other chemicals as mettalic potassium and thymol blue were of the analytical grade. The accurate composition of the acids and salts were estimated by the E.P. and other standard methods.

2-Titrant-0.02 N potassium butoxide in n-butanol was prepared by dissolving the required amount of metallic potassium in cold n-butanol to obtain 0.02 N solution. The concentration of this titrant was determined by potentiometric titration against standard benzoic acid in n-butanol.

3-Solutions of Acidic Compounds-0.02 N solutions in n-butanol were accurately prepared from the investigated compounds.

4-Solutions of Hydrogen Chloride-Hydrogen chloride gas was generated by adding concentrated sulfuric acid dropwise to reagent grade hydrochloric acid. The gas was dried by passing through a series of U-tubes filled with P_2O_5, and fused $CaCl_2$ respectively. The gas was finally passed into pure n-butanol contained in a flask. The latter was kept in an ice bath to avoid any possible exothermic interactions. The molality of stock solution of hydrogen chloride in n-butanol was ca. 0.3 $mol.Kg^{-1}$ The series of cell solutions for emf measurements were made by serial dilution of the stock solution with n-butanol by weight. The final concentrations were known within $\pm$ 0.02 % when titrated with the standard potassium butoxide solution (potentiometric and thymol blue indicator).

5-Half-neutralized solutions of Phenyl butazone- the accurately weighed amount of phenyl butazone was dissolved in n-butanol to obtain ca. 0.1 $mol.Kg^{-1}$ of phenyl butazone solution. The accurate concentration was determined potentiometrically by titration with potassium butoxide, and the calculated amount, by weight, of the titrant needed to half-neutralize the phenyl butazone in this stock solution was added. The series of solutions of half-neutralized phenyl butazone in n-butanol, required for emf

measurements were made by dilution, by weight, of the stock solution with n-butanol. The final concentrations were calculated accurately.

6-Half-neutralized Solutions of Acids-Solutions of the investigated acids were accurately prepared in n-butanol, then half-neutralized with potassium butoxide.Concentrations of the acids and their salts in n-butanol were the same in all cases (0.0025 $mol.Kg^{-1}$).

Apparatus: The emf values were measured using a pH meter[1] in conjunction with a glass electrode and a sealed calomel electrode filled with saturated solution of potassium chloride in n-butanol. The emf readings were taken after appropriate times of equilibration, when emf values remained constant within ± 0.02 mV, for ca. 20 min. All measurements were carried at 25°C(±0.05) under a stream of nitrogen. The glass electrode was soaked or preserved in dil. aqueous hydrochloric acid solution in the time between measurements.

Procedure:1-Quantitative Assay of Acids and Salts- 10.0 ml of the acid or salt solutions in n-butanol were titrated against the standard titrant till the change of the green color to blue color (thymol blue).Paralell to the visual end point a potentiometric determination was carried out.

2-Determination of the Standard Potential ,E_o - The cell E_o was determined from measurements of the emf of hydrogen chloride solutions in n-butanol, using the cell

[1]OP 401,Radelkis,Budapest,Hungary.

type (I) :

(I) :	Glass electrode	HCl (m), BuOH		Hg_2Cl_2,Hg KCl sat.BuOH

A sample of hydrogen chloride solution in n-butanol was placed in the cell (I) and the emf was recorded after complete equilibration (15-20 min.).

Determination of pK_a of Phenyl butazone Standard Solution- was achieved through measurements of the emf of half-neutralized solutions of phenyl butazone in n-butanol, when placed in the cell type (II) :

(II):	Glass electrode	phenyl butazone (m). phenyl butazone potassium salt (m) BuOH		Hg_2Cl_2,Hg KCl sat. BuOH

Determination of pK_a of other Acids -was similarly assessed from the emf measurements using a cell of the type (III):

(III) :	Glass electrode	Phenyl butazone (m) Phenyl butazone potassium salt (m) BuOH	Ax (m) Ax potassium salt (m) BuOH	Glass electrode

where (m) = 0.0025 $mol.Kg^{-1}$ and Ax stands for the investigated acidic pharmaceutical compounds.The glass elctrodes were of the same glass and had the same potential.

ANALYSIS & DISSOCIATION

Dry hydrogen chloride was chosen as a strong proton donating in n-butanol medium. The use of perchloric acid, the most powerful proton donor in general, would have affected the solvating ability of n-butanol due to the introduction of small amount of water with it. The more concentrated perchloric acid is ca. 72 % and it could not be prepared in dry form. However, the evaluation of the effect of this perchloric acid on the E_o of the cell type (I) is in progress. The dissociation constant of the standard acid, phenyl butazone, in n-butanol equals 7.55 units pK, figure 3. The determination was conducted by the extrapolation method (I5-I7). The extrapolated pK'_a values were calculated from the relationship:

$$pK'_a = \frac{E - Eo}{0.059} + \log \frac{C_{acid}}{C_{salt}}$$

where E is the emf for the cell type II.

The calculated pK'_a values and the measured emf readings for the series of half-neutralized phenyl butazone in n-butanol are given in Table III.

Using the pK_a of phenyl butazone (pK_A St) and the measured emf values of the half-neutralized solutions of the investigated acids in n-butanol, the pK_a of these acids were computed, Table IV.

The dissociation constant of the investigated acid(pK_{AX}) was calculated from the formula:

$$pK_{Ax} = pK_A \text{ St} \pm \frac{E}{0.059}$$, where E is the emf for the cell of the type III.

The equimol concentration of every acid and its salt, in cells of the type III, was chosen to approximate 0.0025 mol. Kg^{-I}, so as to insure the possibility of the total dissociation of all electrolytes in solution, with the least error obtained during preparation of solutions. In this case, reality of the presented pK_a values could be assured.

From the comparison of the pK_a values in n-butanol with those obtained in water, inhibition of the dissociation of the investigated acids in n-butanol can be remarked. The great differentiating effect of this solvent towards strong acids is also evident, especially when the cases of perchloric and hydrochloric acids are taken into consideration.

ANALYSIS & DISSOCIATION

These acids are considered as strong electrolytes, with total dissociation in water, whereas their ΔpK_a in n-butanol was found : 6.53-1.79 = 4.74 units. Moreover, the pH scale of n-butanol can be suggeseted to be more than 20 units, that is much greater than the pH scale for water. This suggestion bases on the fact, that the well titrated in n-butanol benzoic acid has got a pK_a value of 8.99, Table IV, while the weakly and very weakly dissociated acids should have higher pK_a values in n-butanol. Hence, the half acidic scale of the latter would be ca. 10 or more. Occaisonally, the higher the pH scale, the more is the differentiating power of the solvent used.
Although theoretically less differentiating than its tertiary isomer (18), n-butanol offers no experimental difficulties for its manipulation ; tertiary butanol solidifies at 25°C, the conventional temperature for pK_a determinations. Application of n-butanol for the determination of the investigated acids in mixtures, as well as other pharmaceutical compounds with functional acidic or basic properties is in progress.

C O N C L U S I O N S

1-Estimation of aspirin, benzoic acid, hydrochloric acid, nicotinic acid, perchloric acid, salicylic acid , phenylbutazone, ephedrine hydrochloride, chloropromazine hydrochloride, mepyramine maleate and procaine hydrochloride

in pure n-butanol was achieved with an accuracy of ca. ±1.0 %, using potassium butoxide solution in n-butanol.

2-To study the influence of n-butanol on the dissociation of acids, the pK_a of several acids were determined by application of the emf method and using phenyl butazone as the standard acid.

3-Comparison between the pK_a values of the investigated acids obtained in n-butanol and those reported in water revealed the great differentiating power of n-butanol towards strong acids, and correspondingly towards strong and weak acids, that recommends the use of n-butanol to solve mixtures of such acids.

4-Although theoretically less differentiating than its tertiary isomer, n-butanol offers no experimental difficulties during its manipulation, while the tertiary isomer is usually solidifying at room temperature.

Table I-Analysis of Acids and Salts in n-Butanol

Compound	Added, mg/10 ml	Found, %	SD, ±	Potential rise at end point, mV/ml
Aspirin	25.2	99.70	0.08	800
Benzoic acid	24.4	99,34	0.14	600
Hydrochloric acid	30.0	100.01	0.09	5300
Nicotinic acid	24.8	99.12	0.17	1400
Perchloric acid	25,1	99.30	0.13	7600
Salicylic acid	27.5	98.93	0.11	1900
Phenylbutazone	31.7	99.50	0.25	1600
Ephedrine hydrochlor.	30.3	100.9	0.21	600
Chloropromazine hydrochloride	35.5	99.91	0.19	1400
Mepyramine maleate	34.0	98.99	0.17	840
Procaine hydrochlor.	20.7	100.62	0.23	800

Table II- Determination of the E_o of cells of the type (I)

m, HCl	$m,^{1/2}$ HCl	E, -V	E_o', -V
0.00115	0.03391	0.197	0.370
0.00167	0.04095	0.213	0.377
0.00202	0.04493	0.221	0.380
0.00218	0.04668	0.226	0.383
0.00259	0.05091	0.233	0.386
0.00306	0.05532	0.242	0.390
0.00344	0.05864	0.218	0.393

Table III-Determination of pK_a St of Phenyl butazone

m, St	μ^*	E, V	pK_aSt
0.00128	0.00256	0.110	7.63
0.00183	0.00366	0.111	7.65
0.00294	0.00588	0.114	7.70
0.00364	0.00729	0.117	7.74
0.00445	0.00891	0.119	7.78
0.00497	0.00995	0.120	7.80

μ^* = ionic power = 1/2 the concentration of the total ions in solution.

Table IV- Dissociation Constants of Some Pharmaceutical Acids in n-Butanol

Compound	E, V,	pK_{Ax}	pK_{water}
Perchloric acid	-0.340	1.79	----
Hydrochloric acid	-0.060	6.53	-----
Salicylic acid	-0.009	7.40	2.97
Phenyl butazone	-----	7.55	-----
Nicotinic acid	+ 0.015	7.80	-----
Aspirin	+ 0.052	8.42	3.49
Benzoic acid	+ 0.085	8.99	4.21

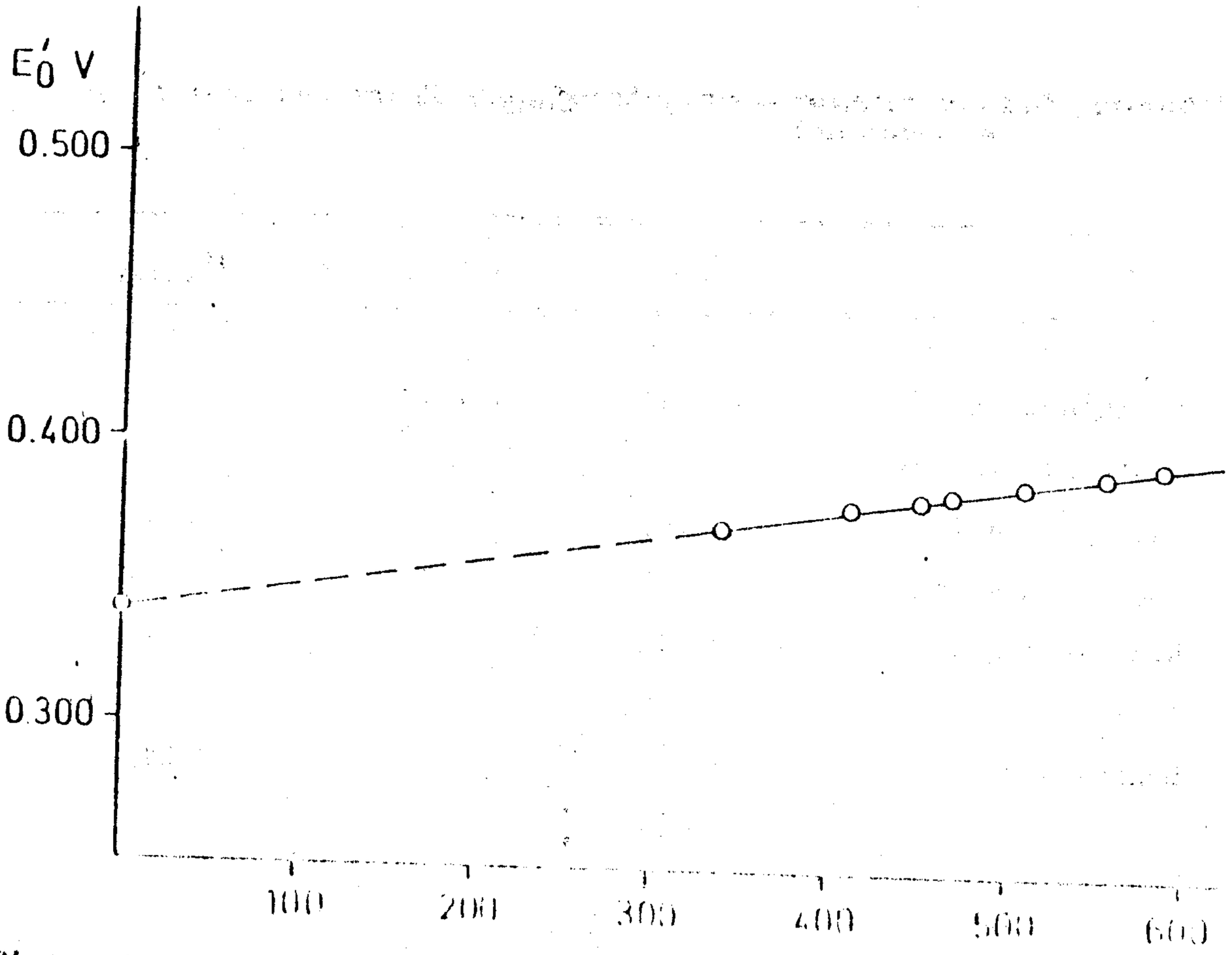

Figure 2- Determination of E_o by the Extrapolation Method.

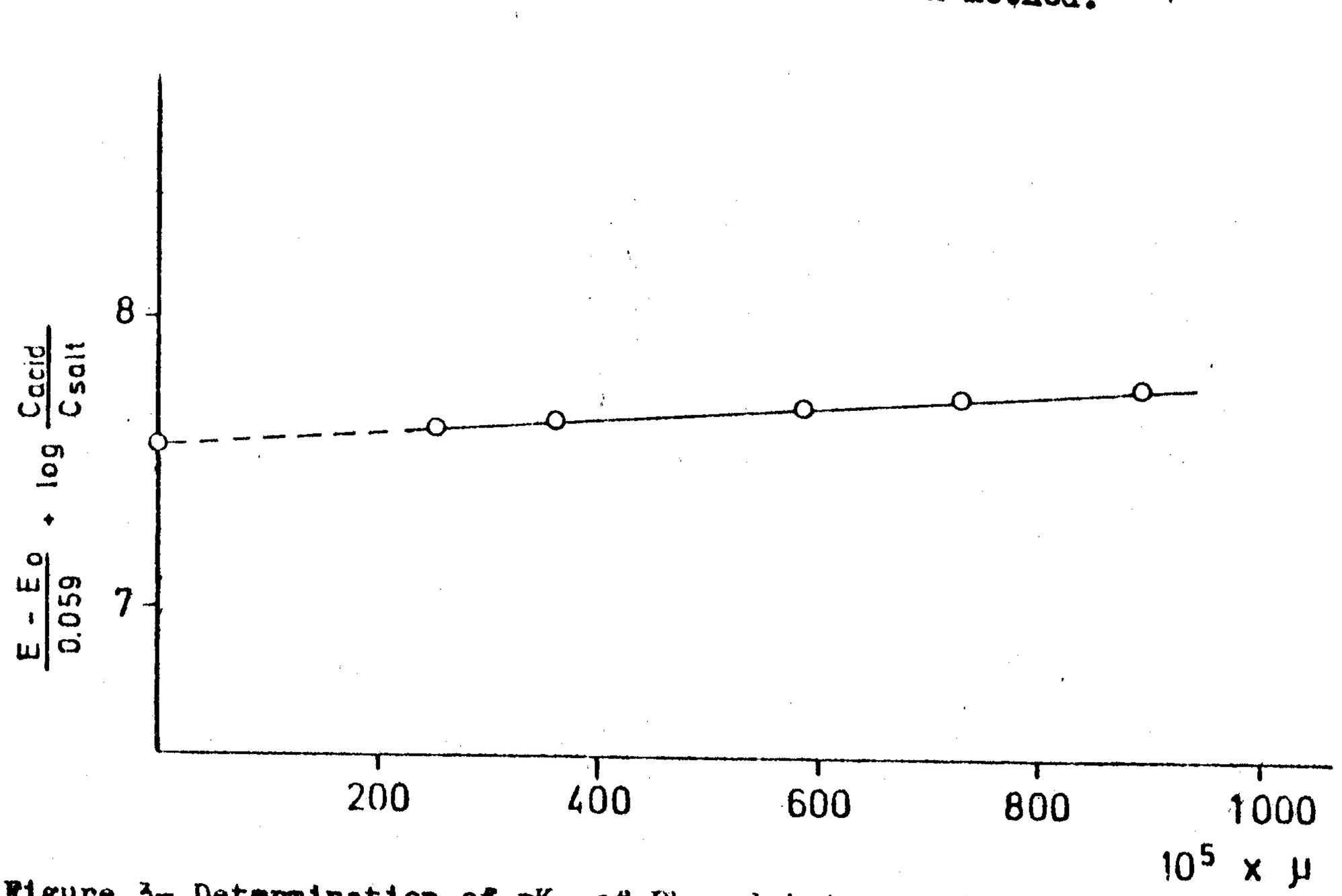

Figure 3- Determination of pK_a of Phenyl butazone in n-Butanol.

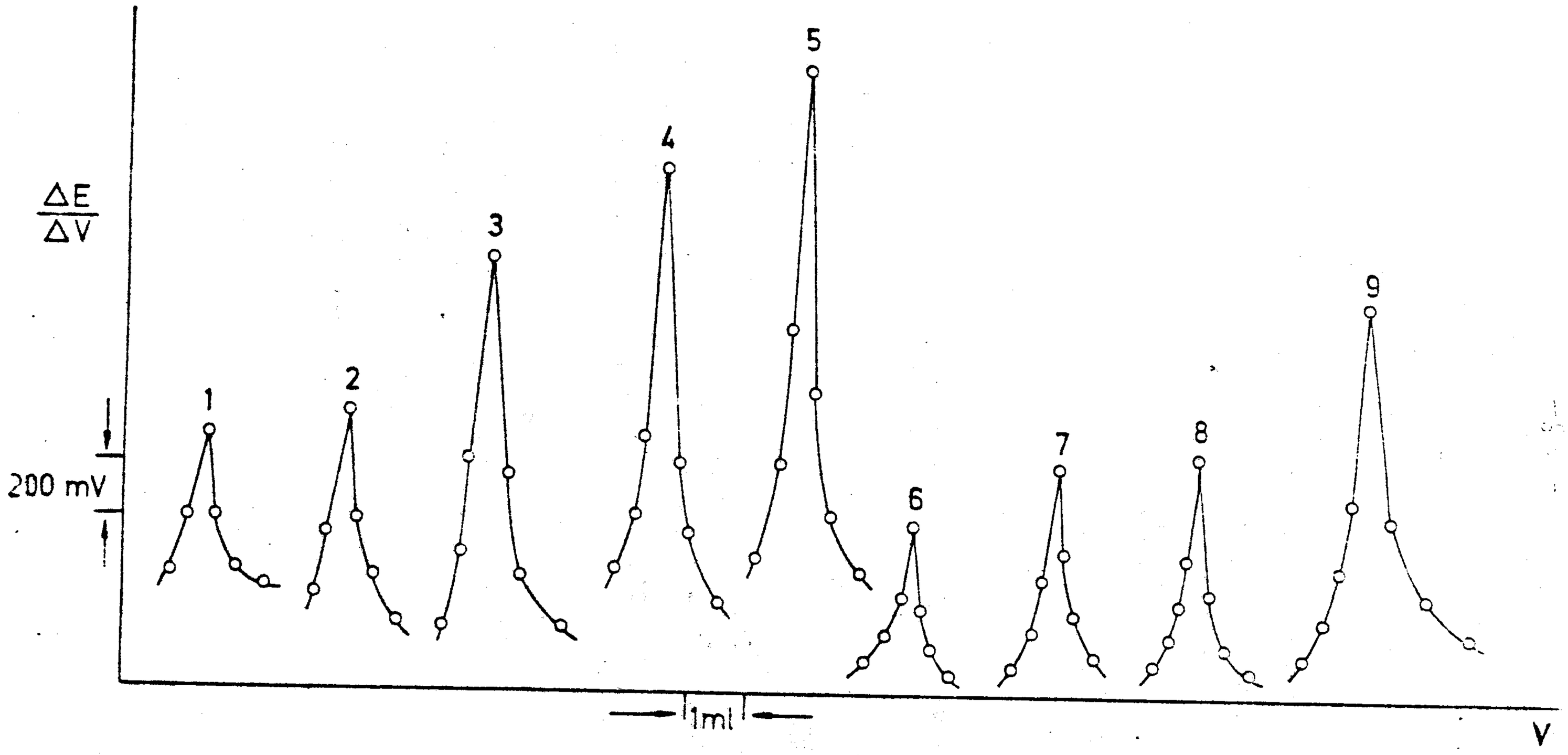

Figure 1- Potentiometric Titration Curves of :1-benzoic acid,2-aspirin,3-nicotinic acid,4-phenyl butazone,5-salicylic acid,6-ephedrine HCl,7-procaine HCl,8-mepyramine maleate and 9-chloropromazine HCl in n-Butanol.

R E F E R E N C E S

1- Bates,R.G .,in "Determination of pH",Interscience,New York 1973, p.211.

2- [illegible]s,R.G. and Schwarzenbach,G .,Helv.Chim.Acta,38,699, (1955) .

3- Schwache,K.,Chimia,13,358 (1959).

4- Schwarzenbach,G . and Stensby, P.,Helv.Chim.Acta,42,234, (1959).

5- Ender, F., Teltschik,F. and Schäfer,K.Z.,Elektrochem.,61, 775 (1957).

6- deLigny, C.L., Loriaux,H. and Ruiter,A.,Rec.Trav.Chim., 80,725 (1961).

7- Percampus,H.H. and Köhler,H.Z.,Elektrochem.,61,836 (1957).

8- Kreshkov,A.P.,Milaev,S.M.,Khanturgaev,G.A.,Zavod.Lab.,39, 922 (1973) and 40,926 (1974).

9- Trzmielewska,H.,Chem.Anal.(Warsaw),19,649 (1974).

10-Milaev,S.M. and Khartυrgaev,G.A.,Zh.Anal.Khim.,29,472(1974)

11-Roy,R.N.,Vernon,W. and Bathwell,A.L.M.,J.Chem.Soc.,Faraday, 1,68,2047 (1972).

12-Roy,R.N., Vernon,W.,Gibbons,J.J. and Bathwell,A.L.M., J.Chem.Thermodynam.,3,883 and 769 (1971).

13-Cookson,R.F.,Chem.Rev.,74,5 (1974).

14-Samolova,N.T. and Burmistrova,T.I.,Zh.Fiz.Khim.,50,989 (1976).

15-Evestratova,K.I. and EL-Rabbat,N.A.,Zh.Fiz.Khim.,48,1751 (1974)

16-Evestratova,K.I and EL-Rabbat,N.A.,Zh.Fiz.Khim,45,2320

17-Evestratova,K.I. and EL-Rabbat,N.A.,Zh.Farmacia,2,38 (1975)

18-Kreshkov,A.P.,Smolova,N.T.,Aldarova,N.S. and Gabidulina, N.A.,Zh.Anal.Khim.,26,2456 (1971).

(بسم الله الرحمن الرحيم)

تحليل وتعيين ثوابت التأين لبعض المركبات الصيدلية ذات التأثير الحمضي في وسط الكحول البيوتيلي

نوال على الرباط ـ محمود عبدالفتاح الجندى ـ كاملة محمود عمارة

امتدادا للابحاث الخاصة بالمذيبات اللامائية وتأثيرها على تأين موصلات التيار الكهربائي ـ أهتم البحث الحالي بدراسة تأثير الكحول البيوتيلي على تأين بعض المركبات الصيدلية بالاضافة الى امكانية تعيين هذه المركبات وتقييمها كميا في وسط هذا الكحول

باستخدام طريقة قياس فرق الجهد للمحاليل النصف متعادلة للمواد المطلوب تعيين ثوابت تأينها ـ ثم بالفعل تعيين ثوابت تأين سبع مواد صيدلية في محيط الكحول البيوتيلي ووجد أن تدرج حمضيتها على الوجه الاتي :

حمض البيركلوريك < حمض الهيدروكلوريك < حمض السلفسلفيك < فينيل البيوتازون < حمض النيكوتينيك < الاسبرين < حمض البنزويك

ومن نتائج تعيين هذه الاحماض وبعض الاملاح ذات التأثير الطبي بالمعايرة امام المحلول المعاري القلوي " بيوتيلات البيوتاسيوم " في الكحول البيوتيلي اثبت امكانية استخدام الكحول البيوتيلي كمذيب لتقييم هذه المركبات مفردة وفي مركباتها الصيدلية .