

Titration of Acids and Acid Mixtures in Benzene–Acetonitrile Binary Solvent System

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Abstract □ In this investigation, the half-neutralization potential of a series of acids of varying pKa was determined in the benzene–acetonitrile solvent system. The half-neutralization potential value of the acids was related to the pKa in a series of benzene–acetonitrile mixtures covering a range of dielectric constants ($D_m = 5-35$). The slopes of these straight-line relationships were then related to the dielectric constants of the solvent mixtures. The solvent mixture showing the maximum slope ($D_m = 30$) was used as a differentiating solvent for titrating binary and ternary sulfonamide mixtures.

Keyphrases □ Solvent systems, binary—benzene–acetonitrile system used for determination of half-neutralization potential of acids, effect of dielectric constant □ Benzene–acetonitrile binary solvent system—used for determination of half-neutralization potential of acids, effect of dielectric constant □ Acetonitrile–benzene binary solvent system—used for determination of half-neutralization potential of acids, effect of dielectric constant □ Dielectric constant—series of benzene–acetonitrile mixtures used to determine half-neutralization potential of acids □ Titrimetry—benzene–acetonitrile mixtures of varying dielectric constant used to determine half-neutralization potential of acids

Fritz (1) titrated certain amines potentiometrically in acetonitrile and observed that the millivoltage reading at the half-neutralization point could be correlated with the base strength of the amine. For the alkylamines titrated in certain nonaqueous media, the observed order of base strength was similar to that in alcohol or water (2). Consequently, when data obtained for the nonaqueous solvents were plotted against the equivalent data obtained for water, straight-line relationships were obtained.

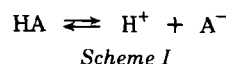
The potentiometric titration method was used in studying the relationship between the half-neutralization potential and the pKb (3). When basic amines and phenothiazines were studied in five organic solvents, a linear relationship existed between the pKb in water and the half-neutralization potential values determined in the organic solvents.

A linear relationship between the Δh_{np} (difference in half-neutralization potential from a standard acid) and the pKa on one hand and between the Δh_{np} and Hammett's σ value on the other was reported (4). The comparative strengths of some acids in benzene were studied and linear relationships were observed (5). A similar study was reported (6) in which the relative acidity strengths of *meta*- and *para*-substituted benzoic acids and aliphatic monocarboxylic acids in pyridine and water were investigated. Linear relationships were again observed. Organic bases in nitromethane have been studied and a linear relationship between the relative strength of these bases in nitromethane and water was found (7). The factors that may influence the half-neutralization potential of acids and bases in different solvents have been outlined (8). In all these investiga-

tions, a straight-line relationship was noted between the relative strengths of acids in water and in nonaqueous media. Thus, the literature indicates that when acids are transferred from water to a nonaqueous medium, the order of their relative strengths generally remains the same. Consequently, if the half-neutralization potential is plotted against the pKa, the relationship is best represented by a straight line. Deviations from linearity are usually explained on the basis of the structural differences among the acids.

THEORETICAL

The dissociation of an acid is represented by Scheme I:



The dissociation constant, K_a , is given by:

$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]} \quad (\text{Eq. 1})$$

This equation can be rewritten as:

$$-\log K_a = -\log[\text{H}^+] - \log \frac{[\text{A}^-]}{[\text{HA}]} \quad (\text{Eq. 2})$$

and thus:

$$\text{pH} = \text{pKa} + \log \frac{[\text{A}^-]}{[\text{HA}]} \quad (\text{Eq. 3})$$

When the acid HA is dissolved in water and titrated with a base, at the half-neutralization point the concentration of the base $[\text{A}^-]$ is equal to the concentration of the acid $[\text{HA}]$ and $\log [\text{A}^-]/[\text{HA}]$ is equal to zero. Therefore, $\text{pH} = \text{pKa}$ at the half-neutralization point. For a glass–calomel electrode system in an aqueous medium, Delahay (9) used the following equation:

$$V = b + 1.983 \times 10^{-4} T \text{pH} \quad (\text{Eq. 4})$$

where V is the corresponding voltage, b is a constant, and T is the temperature in absolute degrees (Kelvin). This equation indicates that there is an electrical potential (voltage) corresponding to the pH of the aqueous solution and it varies linearly with the pH. One can readily deduce that the pKa of an acid dissolved in an aqueous medium can also be expressed in terms of the electrical potential (millivolts) existing between the two electrodes of the calomel–glass electrode system.

EXPERIMENTAL

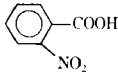
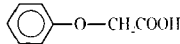
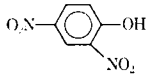
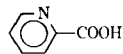
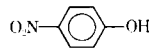
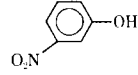
Titrimeter—The titrimeter¹ used for the potentiometric titrations was equipped with a microtitration assembly² using a saturated calomel and glass electrode system. The titrimeter has an "input range" of ± 1400 mv and a "zero stability" of 2 mv/hr after a warmup of no longer than 10 min. The sensitivity is 2 mv and the scale readability is ± 2 mv. The accuracy is $\pm 0.5\%$.

Materials—Tenth normal sodium methoxide in benzene–methanol was prepared and standardized as described previously (10).

¹ Fisher model 35.

² Fisher, catalog No. 9-313-280.

Table I—Seven Randomly Selected Acids Used

Acid	Structure	Molecular Weight	pKa at 25°	Reference
<i>o</i> -Nitrobenzoic acid		167.12	2.22	13
Phenoxyacetic acid		152.14	3.12	12
2,4-Dinitrophenol		184.11	4.09	13
Picolinic acid		123.11	5.30	14
4-Nitrophenol		139.11	7.16	13
<i>m</i> -Nitrophenol		139.11	8.34 ^a	12
γ -Aminobutyric acid	NH ₂ —CH ₂ CH ₂ CH ₂ COOH	103.12	10.43	12

^a The only pKa value available to the authors for this acid was 8.34 at 18°.

All other reagents and solvents including benzene, acetonitrile, the different acids, and the sulfonamides were of the highest purity grades available and were used without further purification.

Selection and Preparation of Solvent System—Acetonitrile was selected as the polar component of the binary solvent system to be investigated and benzene was selected as the nonpolar component. Solvent mixtures having dielectric constants of 5, 10, 15, 20, 25, 30, and 35 were prepared according to the procedures described previously (11).

Determination of Half-Neutralization Potentials of Acids—Acids were selected on the basis of their acidic strength in water (pKa) and their physical properties, such as solubility and lack of hygroscopicity, but without regard to their structure; thus the structure effect was randomly distributed. Three hundred potential acids were screened (12–16) and only 25 were found to fulfill these criteria. When these acids were arranged in the order of increasing pKa, seven pKa groups were formed, each containing one or more acids. From these groups, the seven acids listed in Table I were selected for this study.

Exactly 0.15 mEq of acid was weighed into a 20-ml beaker. Fifteen milliliters of the solvent mixture was pipeted into the beaker, and the beaker was immediately covered. The mixture was stirred from 15 to 45 min with the aid of a magnetic stirrer. Usually only 15 min of stirring was required for complete solution. The solution was then titrated potentiometrically with 0.1 *N* sodium methoxide. The titrant was delivered in 0.1-ml increments at a rate of approximately 1 ml/25 min. The beaker remained covered throughout the titration. The titration curve was constructed, and the millivolt reading corresponding to the half-neutralization point was determined and reported as the half-neutralization potential value.

The $\Delta\text{hnp}/\Delta\text{pKa}$ (the slope of the straight-line graphs obtained by plotting half-neutralization potential of the acids *versus* pKa) was plotted against the dielectric constants of various mixtures of the benzene-acetonitrile solvent system in which the half-neutralization potential's were determined. This curve showed a maximum value for $\Delta\text{hnp}/\Delta\text{pKa}$ at a dielectric constant, D_m , equal to 30. A large volume of the benzene-acetonitrile mixture having a $D_m = 30$ was prepared according to the procedure described earlier (11). This was used as the solvent for the differentiating titrations of synthetic powder mixtures of sulfonamides.

Titration of Sulfonamides—Various sulfonamides were selected for study based on their use in medicine and their availability in pure powder form (Table II).

Synthetic powder mixtures of two sulfonamide components were prepared by weighing exactly 0.1 mEq of one and mixing it

with exactly 0.15 mEq of the other. The mixture was dissolved in 15 ml of solvent contained in a 20-ml beaker with the aid of a magnetic stirrer. The dissolution process required from 15 to 45 min. The beaker was covered at all times. The solution was then titrated using the same apparatus and method as described previously. The titration curve was obtained by plotting millivolt readings *versus* milliliters of titrant added. The exact end-points were determined from the inflections in the titration curve. Synthetic powder mixtures of three sulfonamide components were also prepared by mixing exactly 0.1, 0.15, and 0.2 mEq, respectively, of the sulfonamides, and the mixtures were titrated in the same manner as described earlier. All titrations were run in duplicate.

RESULTS AND DISCUSSION

Titration System—Tenth normal sodium methoxide in benzene-methanol was selected as the titrant, and the glass-saturated calomel couple was used as the electrode system. The results of this study are specific to the particular titrant and electrode combination employed. The selected solvents were inert, did not present any leveling effects, and provided a range of dielectric constants while remaining constant in terms of chemical structure. According to Kucharsky and Safarik (18), a wide range of potential measurements is also possible in these types of solvents. The mixture of benzene and acetonitrile acted, in effect, more as a nonreactive medium in which the acid molecules were dispersed and suspended as monomer, dimer, trimer, or higher polymolecular aggregates. The effect and extent of polarity and intermolecular attractions among the solvent molecules themselves are incorporated in the dielectric constant. This is an important parameter in considering a particular solvent mixture to be employed in half-neutralization potential determinations.

Selecting a binary solvent system of a polar and nonpolar component provided a range of available dielectric constants (limited by those of the pure components) out of which it was possible to select mixtures with definite compositions and specific dielectric constants. This approach was more satisfactory than using pure solvents of different dielectric constants, since in the latter case the solvent molecular structure varies with each dielectric constant. In the former case, the molecular species of the solvent system are the same and only their ratio varies with the dielectric constant. Furthermore, it is virtually impossible to find an array of solvents that will provide a range of dielectric constants with a fixed increment in dielectric constant as those of the benzene-acetonitrile solvent system used in this study. It is possible, how-

Table II—Sulfonamides Used in the Differentiating Titrations

Sulfonamide	R	Molecular Weight	pKa at 25°	Reference
Sulfacetamide	—COCH ₃	214.24	—	—
Sulfadiazine		250.28	6.48	17
Sulfadimethoxine		310.33	—	—
Sulfaethidole		284.36	—	—
Sulfamerazine		264.30	7.06	17
Sulfamethoxypyridazine		280.32	6.7	12
Sulfanilamide	H	172.21	10.43	12
N-Sulfanilylbenzamide		276.31	4.57	12
Sulfapyridine		249.29	8.44	17
Sulfathiazole		255.32	7.12	17
Sulfisomidine		278.34	—	—
Sulfisoxazole		267.30	—	—

ever, that the dielectric constant of the environment immediately surrounding the acid molecule may not necessarily be the same as that measured for the bulk of the binary solvent system. However, any differences should not be significant since the acid molecule will interact with the components of the binary solvent system essentially in the same manner in every case.

Half-Neutralization Potential Determinations—Titration curves for a series of acids in a binary solvent system having variable dielectric constants were obtained by plotting millivolt readings *versus* titrant volume. End-points were readily determined from the inflection in the titration curve. The millivolt reading corresponding to a titrant volume of one-half that represented by the titration end-point was determined and reported as the hnp₁ (first half-neutralization potential value) for the particular acid. This procedure was repeated with the same solvent system and the same acid, and the second half-neutralization potential reading was designated as hnp₂. This process required: (a) making the solvent mixture of the desired dielectric constant, (b) weighing the exact amount of the acid, and (c) titrating the acid in that solvent using 0.1 N sodium methoxide. Seven solvent mixtures were employed ($D_m = 5, 10, 15, 20, 25, 30,$ and 35). Seven acids were studied with two replications of the half-neutralization potential measurements for each acid. The order of operations in Steps a, b, and c was determined prior to experimentation by randomizing each step in itself. The two half-neutralization potential determinations on the same acid were not performed immediately. Instead, an entire set of hnp₁ determinations in the

same solvent and on all seven acids was performed first; later, a second determination of hnp₂ in the same solvent and for all seven acids was performed.

According to this plan, once the same procedure was performed for each of the seven solvent mixtures, each of the seven acids had been titrated twice and two independent half-neutralization potential values were obtained for it in each of the seven solvent mixtures. The two half-neutralization potential measurements (hnp₁ and hnp₂) for the benzene-acetonitrile solvent system are arranged in Table III. In this table, the pKa's of the seven acids are arranged in an increasing order vertically and the D_m values of the seven mixtures are arranged in an increasing order horizontally. The half-neutralization potentials are recorded in millivolts. It can be seen from this table that the acid with a pKa of 2.22 was titrated in solvent mixtures of $D_m = 5, 10, \dots, 35$. The two sets of values (hnp₁ and hnp₂) are similar determinations which were performed independently from each other, even with respect to time. All the half-neutralization potential values given vertically under $D_m = 5$ were determined in a set. This was done by first preparing the solvent mixture of $D_m = 5$, then weighing all of the acids according to the predetermined random order, and finally titrating them according to the predetermined random order. The process was then repeated to obtain the hnp₂ values given under $D_m = 5$. As a result of this arrangement, the variations due to temperature fluctuations in the room ($\pm 1^\circ$), fluctuations in the instrument performance from day to day, and environmental conditions due to time and consequent change in con-

Table III— hnp_1 and hnp_2 Values Determined in Benzene–Acetonitrile Binary Solvent System

pKa		D_m						
		5	10	15	20	25	30	35
2.22	hnp_1^a	42	-4	-2	2	15	20	20
	hnp_2	52	-12	-6	-5	19	11	18
3.12	hnp_1	47	42	46	52	57	50	48
	hnp_2	54	40	58	55	55	48	44
4.09	hnp_1	32	18	6	22	42	56	56
	hnp_2	30	10	12	28	38	51	58
5.30	hnp_1	-36	-73	-61	-29	-49	-55	-21
	hnp_2	-2	-76	-61	-41	-44	-38	-24
7.16	hnp_1	-58	-180	-200	-194	-227	-230	-225
	hnp_2	-132	-184	-189	-189	-217	-227	-213
8.34	hnp_1	-293	-300	-256	-294	-292	-294	-292
	hnp_2	-296	-311	-292	-314	-285	-298	-304
10.43	hnp_1	-396	-393	-419	-364	-425	-425	-390
	hnp_2	-280	-412	-433	-453	-412	-438	-408

^a The half-neutralization potential values are recorded in millivolts.

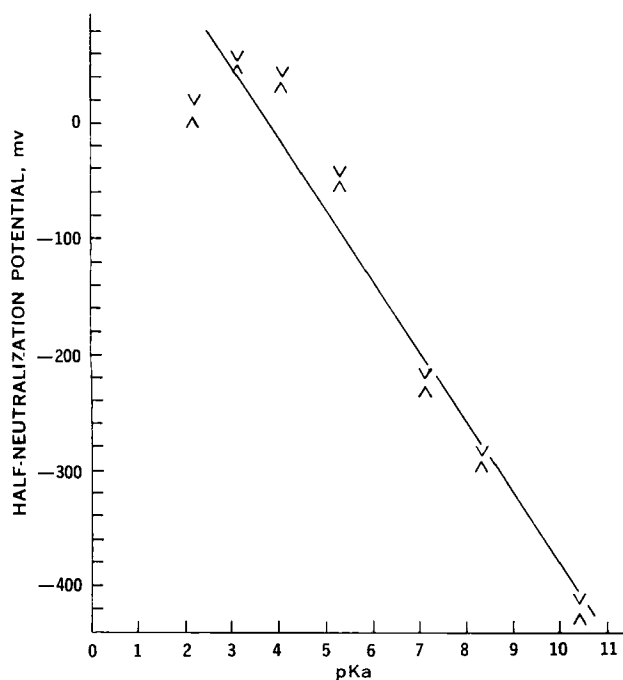


Figure 1—Half-neutralization potential values of the seven acids measured in a benzene–acetonitrile mixture ($D_m = 25$) and plotted against the corresponding pKa values.

ditions were randomly distributed among all measured half-neutralization potential values. The plotting of the necessary graphs was also randomized, since it followed the same order as the sequence of the titrations.

The hnp_1 and hnp_2 values determined for all seven acids in one solvent mixture were plotted (on the Y-axis) against the pKa values (on the X-axis). The procedure recommended by Batson (19) for the least-squares regression line analysis of a univariate normal model completely randomized design was used to determine the formula of the straight line obtained. A representative curve is shown in Fig. 1. Seven such plots were obtained, one for each benzene–acetonitrile mixture. The deviations from the straight line may be due to any one or a combination of the following factors: steric effect, electric field effect, and hydrogen bonding. The formulas of the seven straight lines are reported in Table IV. The slope of these plots is $\Delta hnp/\Delta pKa$, i.e., the change in the observed half-neutralization potential of the acids per unit pKa. Seven such slopes were obtained and plotted against seven D_m values (5, 10, 15, 20, 25, 30, and 35), which represent the entire available dielectric constant range for the benzene–acetonitrile solvent system. The curve obtained (Fig. 2) shows how the change in half-neutralization potential per unit change in pKa

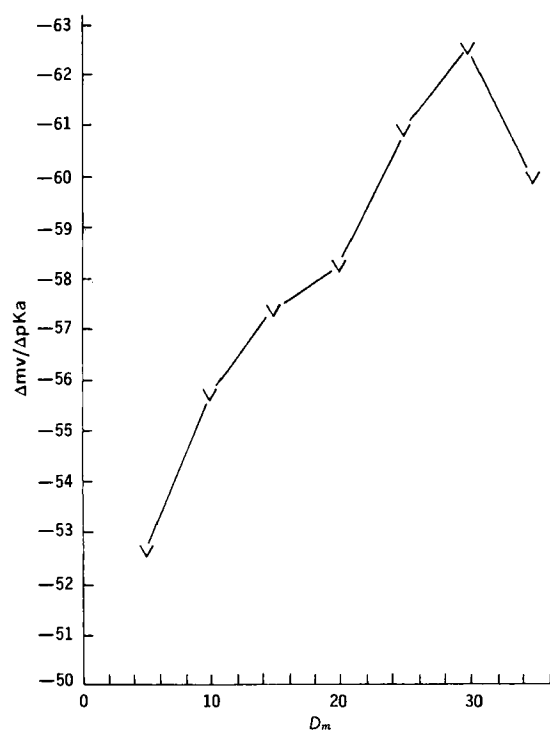


Figure 2—Slopes of the straight-line relationships obtained in a benzene–acetonitrile binary solvent system plotted against the dielectric constant of the solvent system.

varies with the dielectric constant of the solvent. The maximum in the curve indicates the D_m and the composition of the benzene–acetonitrile solvent mixture that may be most suitable for differentiating titrations of mixtures of acids. In differentiating titrations in nonaqueous media, it is desirable to maximize the difference in strength of the components of the mixture of acids to be titrated. This may be realized in differentiating titrations performed in a mixture of benzene–acetonitrile containing 79.50% (w/w) or 81.50% (v/v) of acetonitrile, the composition corresponding to the maximum in the curve depicted in Fig. 2.

The negative slopes of the straight lines (Table IV) indicate that the half-neutralization potential decreases as the pKa increases. In other words, as the acid strength decreases, the half-neutralization potential decreases too (approaching larger and larger negative values). The shape of the curve in Fig. 2 indicates that the acidity strength in the benzene–acetonitrile binary solvent system depends on the value of D_m . The dielectric constant of the mixture (D_m) is a physical constant that represents the total result of all intra- and intermolecular interactions in the binary solvent

Table IV—Formulas for Straight-Line Graphs of the Half-Neutralization Potentials (hnp) Plotted against pKa Values

D_m	Slope of Straight Line ^a	Formula of Straight Line
5	-52.62	hnp = -52.62 pKa + 217.3
10	-55.70	hnp = -55.70 pKa + 192.5
15	-57.36	hnp = -57.36 pKa + 204.8
20	-58.21	hnp = -58.21 pKa + 215.0
25	-60.88	hnp = -60.88 pKa + 230.4
30	-62.52	hnp = -62.52 pKa + 236.8
35	-59.96	hnp = -59.96 pKa + 231.7

^a The slope, $(\Delta\text{hnp})/(\Delta\text{pKa})$, is in millivolts per unit pKa.

system (hydrogen bonding, induced dipole-induced dipole, permanent dipole-induced dipole, and permanent dipole-permanent dipole interactions). Figure 2 then represents the behavior of the acid molecule in the benzene-acetonitrile solvent system as the proportion of the acetonitrile molecules in the system is increased. The D_m was expressed earlier (11) as a function of X_1 and X_2 for the benzene-acetonitrile solvent system by:

$$D_m = (4.5840 \times 10^{-3}X_1 + 3.7530 \times 10^{-2}X_2^2) / (2.1153 \times 10^{-3}X_1 + 1.0000 \times 10^{-3}X_2^2) \quad (\text{Eq. 5})$$

By using $X_1 = 1 - X_2$, the equation can be solved for X_2 :

$$X_2 = (a - D_m c) / (D_m d - b + a) \quad (\text{Eq. 6})$$

In this equation the constants a , b , c , and d correspond to the coefficients in the previous equation, respectively. When D_m is 30 (maximum of the curve), the mole fraction of acetonitrile in the binary mixture (X_2) is 0.8866. Considering the fact that $X_1 = (n_1)/(n_1 + n_2)$ and $X_2 = (n_2)/(n_1 + n_2)$, where n_1 and n_2 are the number of moles of the nonpolar and polar components, respectively, one can write $(X_2)/(X_1) = (n_2)/(n_1)$. This means that the maximum in the curve occurs when, in every 10,000 molecules of the mixture, 8866 molecules are acetonitrile and 1134 are benzene.

Differentiating Titration of Synthetic Mixtures of Sulfonamides—The principle of differentiating titrations of acids in nonaqueous solvents is to determine quantitatively each component of a mixture of acids in a single titration. The success of such a titration depends on the combination of titrant, the electrode system, and the solvent used. The usual procedure is to vary each factor and to employ all possible combinations in titrating the same mixture. The millivolt readings are plotted against the milliliters of titrant added, and the end-points are determined from the inflection of the curve. A successful differentiating titration is one in which the number of end-points is equal to the number of acid components in the mixture and each end-point accurately reflects the amount of the corresponding acid present in the mixture. This is based on the assumption that acidic impurities in the solvent or the acid mixture, as well as any other external or internal factors that would cause abnormalities resulting in the appearance of false end-points, are absent.

The most common problem in differentiating nonaqueous titrations is the proximity of the strengths of the several acids in the mixture. In other words, if the pKa's of two or more acids in the mixture are too close to each other, the mixture will produce one end-point corresponding to the total acid present in the mixture. This difficulty is especially common when the components of the acid mixture are related structurally. It becomes necessary to test different electrode-titrant-solvent combinations to find a suitable system for differentiating the acids in the mixture.

Assuming that the behavior of an acid molecule in an inert binary solvent system is, among other factors, dependent on the polarity of the solvent system and the totality of the interactions in the solvent system as represented by its dielectric constant, then a solvent mixture of the binary solvent system possessing a D_m value for which the apparent acidity strength of the acid molecule is increased will be a desirable solvent mixture for differentiating nonaqueous titrations. Such a mixture in the benzene-acetonitrile binary solvent system possessed a D_m value of 30. This mixture was represented by a maximum in Fig. 2. Several two-component

Table V—Differentiating Titrations of Synthetic Binary Sulfonamide Mixtures in the Benzene-Acetonitrile Solvent System Containing 81.50% (v/v) or 79.50% (w/w) of Acetonitrile^a

B	Recovery of A , %	Recovery of B , %
Sulfacetamide	100.11	96.78
Sulfadimethoxine	96.61	97.11
Sulfaethidole	100.10	95.45
Sulfamerazine	100.11	95.11
Sulfapyridine	100.11	96.32
Sulfathiazole	97.61	102.66
Sulfisoxazole	102.62	98.32

^a $A = N$ -sulfanilylbenzamide, and $B =$ second sulfa drug.

(Table V) synthetic mixtures of the sulfonamides listed in Table II were titrated in the binary solvent system indicated above. Each two-component mixture contained 0.10 mEq of acid A (N -sulfanilylbenzamide) and 0.15 mEq of another acid, B , which was different in each mixture. A three-component mixture containing 0.10 mEq of N -sulfanilylbenzamide, 0.15 mEq of sulfamethoxy-pyridazine, and 0.20 mEq of sulfanilamide was also titrated in the same solvent mixture. The differentiation of the weak acid components of the mixtures was possible in all cases. The recoveries (average of duplicate samples) for the three-component mixture were 100.11, 96.78, and 102.59%, respectively.

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