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Determination of the pKa values of some selected aromatic amines and naturally occurring compounds in polar and non-polar solvents at 25°C

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Abstract

Ionisation constant is a measure of the strength of acids and bases and is expressed in terms of the pKa of conjugate acids and bases. The pKa of naturally occurring khivorin, 7-keto-khivorin and some aromatic amines were measured in chloroform, toluene, 50% ethanol-methanol, 50% ethanol-water and 75% ethanol-methanol mixture at 25°C by potentiometric titration. The pKa values obtained are 3.23 for khivorin in toluene and 1.20 for 7-ketokhivorin in chloroform which demonstrate their acidic nature. The aromatic amines: indole and 4-dimethylaminopyridine have a higher pKa values in 50% ethanol-water solvent compared to their values in ethanol-methanol solvents. 3-methylindole and para-toluidine have a higher pKa values in 50% and 75% ethanol-methanol solvents than in ethanol-water solvent. The higher pKa values of indole and 4-diemthylaminopyridine in 50% ethanol-water signifies the best medium at which the strength of these amines could be determined; whereas p-toluidine is best determined in 50% ethanol-methanol and 3-methylindole in 75% ethanol-methanol mixture.

Keywords: pKa; 7-ketokhivorin; conjugate bases; potentiometric titration; khivorin.

Introduction

Determination of pKa value is of great importance in chemistry, in Life and Material Sciences, pharmaceutical industry and other research and development oriented enterprises [1]. Knowledge of pKa values is useful in many ways. For instance, important drug properties such as lipophilicity, solubility and trans-membrane transfer are all pH dependent [1]. The preparation of buffer solutions which are used extensively in biochemical reactions depends on the knowledge of pKa values of their components. In chemistry, pKa values have been used as tools to predict direction of acid-base equilibrium reaction [2], determine the conductivity of organic solute in aqueous solution [3], assign members of pairs of geometrical isomers by comparison of their ionization constants [4] and determine the presence of covalently bound water in an heterocyclic amine by its anomalously high pKa values [5].

Ionisation constant pKa is an important physical constant for a Bronsted acid. It is a thermodynamic property that measures the strength of acids and bases. It is defined as –log Ka where Ka is the acid ionization constant for any acid species in water [6] as shown by the equilibrium reaction below:

$$HA_{(aq)} + H_2O \rightleftharpoons H_3O^+_{(aq)} + A^-_{(aq)}$$

$$Ka = \frac{[H_3O^+][A^-]}{[HA]}$$

$$pKa = -\log Ka$$

Different organic compounds with the exception of carboxylic acid can be classified as acids and thus have associated pKa values [7].

The presence of lone pair of electrons on nitrogen atoms of amines makes all amines to act as organic bases capable of accepting protons from Bronsted-Lowry acids [8]. The formation of amine cation requires the donation of the lone pair on the nitrogen atom to a proton, thus any factor which increases its proton affinity will increase the strength of the base whereas any factor which decreases this electron density has

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the reverse effect [9]. The basic strength of these amines is expressed in terms of the pKa of their conjugated acid. There is limited data on acidity of N-substituted pyrroles and indoles in the literature [10]. Indole (2, 3-benzopyrrole) and 3-methylindole (skatole) are formed by decomposition of the L-tryptophan [10].The pKa of indole and 3-methylindole was determined by Characteristics Vector Analysis (CVA) method in phosphoric acid hydrochloric acids solutions and was reported to be 3.1±0.6, 2.1±0.15 and 1.3±0.09, 1.5±0.08 respectively [10], protonated form of indole have a pKa of -3.6 [11, 12].

Similarly, pKa values of indole-3-acetic acid a plant auxins in methanol-water mixture was determined by reversed phase liquid chromatography and potentiometric method and was reported to be 4.86 (30% v/v), 5.11 (40% v/v)and 5.38 (50% v/v) respectively [13]. Little was available on pKa values of dimethylaminopyridrine (DMAP) and toluidine in literature. Although, IK-Hwan *et al* determined the pKa value of DMAP in DMSO at 25°C to be 9.12 [14] and the pKa of p-toluidine determined to be 5.10 [15]. On the other hand, for the natural products khivorin and 7-ketokhivorin the presence of lone pair on oxygen of the furan ring of khivorin and 7-ketokhivorin gives them the ability to display basic character and act as a Lewis-base as well.

Ionization constant varies with solvent, temperature and the nature of substance in focus. It was observed that dissociation in non-polar solvents is substantially less than in water as is expected with media of lower dielectric constant. Different methods can be employed in determination of pKa values these includes: conductimetry, phase equilibra, thermometric, electrophoresis and potentiometric titration. Potentiometric titration gives the most convenient method with accuracy.

Materials and methods

The aromatic amines, KHP, sodium hydroxide pellets and concentrated hydrochloric acid were of British Drug House and were used without further purification. Methanol and ethanol were purified by distillation prior to use. The naturally occurring compounds khivorin and 7-ketokhivorin have been isolated and purified and were used as such.

The titrant 0.1M NaOH was standardised using 0.1M KHP (potassium hydrogen phthalate). The pH meter electrode was calibrated with buffer solutions of pH 4.0 and pH 7.0 prior to use. Concentrations of the amine samples 0.01M were prepared in different solvent mixtures 50% ethanol-methanol, 50% ethanol-water and 75% ethanol-methanol solvents mixtures. 0.01M solution of khivorin and 7-ketokhivorin were also prepared in non-polar solvents toluene and chloroform, respectively.

Amine sample (40 mL) was pipette into a 100 mL beaker followed by the addition of two drops of 1M HCl solution. The solution was placed in a magnetic stirrer and stirred continuously with the pH electrode dipped in it. The pH of the solution was taken at volume zero of the titrant NaOH. This was followed by repeated addition of 0.2 cm^3 aliquots of 0.1M NaOH at each time and the corresponding pH values taken after each stirring. The equivalence point was soon observed and the titration continued until further addition of the titrant produced a constant pH value.

A plot of pH against volume of titrant was carried out. From the plotted graph, the experimental pKa value was deduced. The volume of NaOH required at the equivalence point was extrapolated from the graph and the pH at half this volume gave the experimental pKa value. Results were obtained in duplicates for all the samples studied.

Results and discussion

The experimental pKa values obtained for the aromatic amines indole, 3-methylindole, p-toluidine and 4-diemthylaminopyridine in distilled water and their solvents mixtures are presented in Table 1. The graphical plots are shown in Figures 1-4 respectively. For the naturally occurring compounds khivorin and 7-ketokhivorin, the results are presented in Table 2 and the graphical plots shown in Figures 5 and 6.

Table 1. Summary of pKa values of aromatic amines.

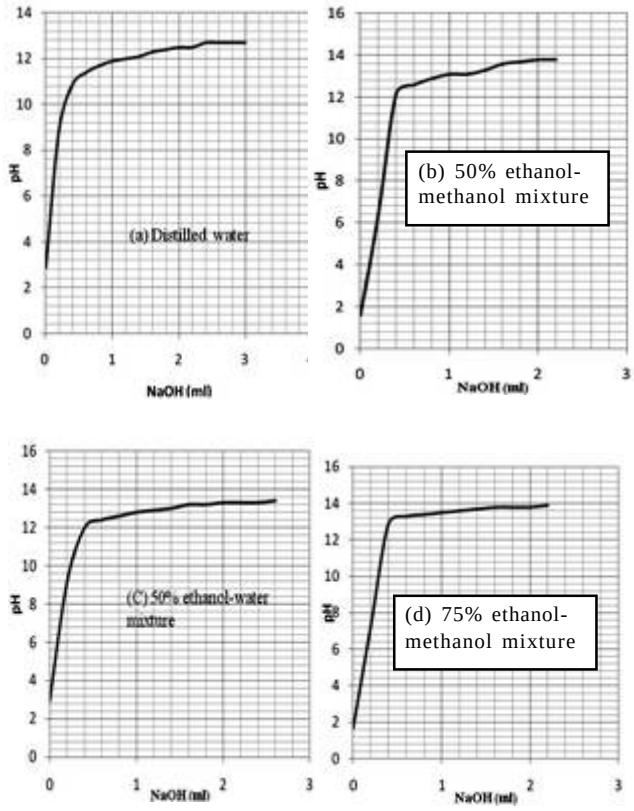
Samples	pKa values in distilled water	pKa in 50% ethanol-methanol	pKa in 50% ethanol-water	pKa in 75% ethanol-methanol
Indole	7.4	5.2	8.0	5.6
3-methylindole	7.2	7.6	5.6	7.9
p-toluidine	9.2	10.2	5.6	7.4
4-dime-thylaminopyridine	5.2	2.8	10.8	2.8

Table 2. Summary of pKa values of khivorin and 7-ketokhivorin in toluene and chloroform at 25°C.

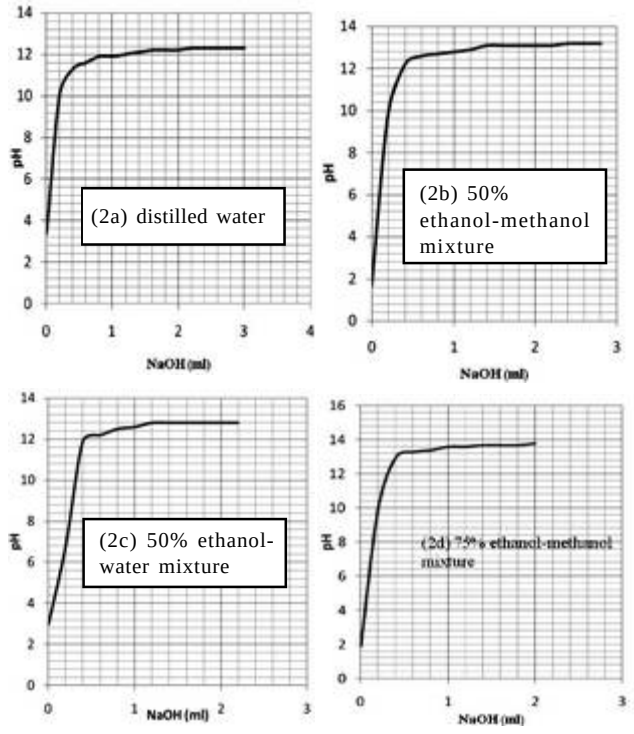
Sample	Toluene	Chloroform
Khivorin	3.23	–
7-ketokhivorin	–	1.20

The data shown in Table 1 allows the effect of solvent mixture on the basicity of amines to be compared. The two samples indole and 4-dime-thylaminopyridine have a higher pKa values in 50% ethanol-water solvent compared to their values in

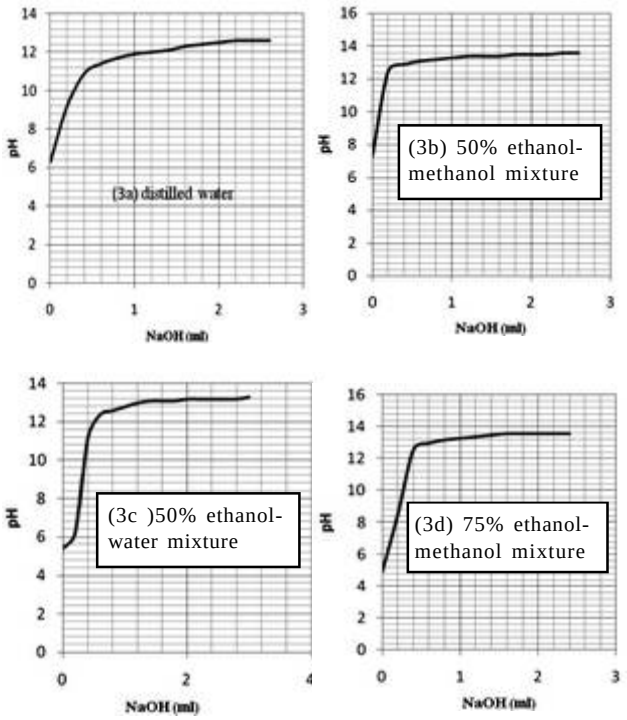
mixtures of ethanol-methanol solvents, whereas 3-methylindole and p-toluidine have a higher pKa values in a mixture of ethanol-methanol solvents at both 50% and 75% concentration than their values in ethanol-water mixture.



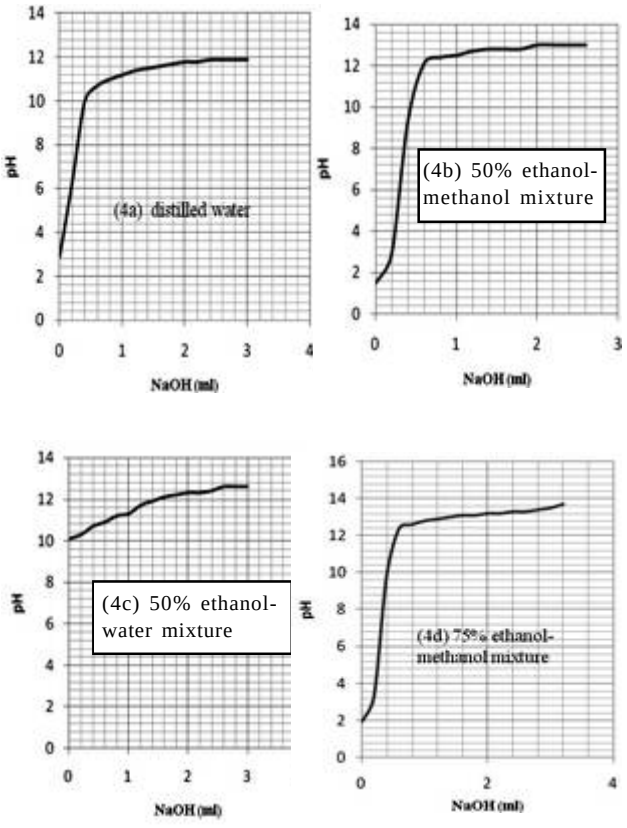
Figures 1. Titration curves of indole in different solvent mixtures at 25°C.



Figures 2. Titration curve of 3-methylindole in different solvent mixtures at 25°C.



Figures 3. Titration curve of P-toluidine in different solvent mixtures at 25°C.



Figures 4. Titration curves of 4-dimethylaminopyridine in different solvent mixtures at 25°C.

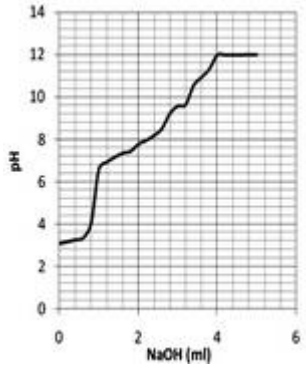


Figure 5. Khivorin in toluene at 25°C.

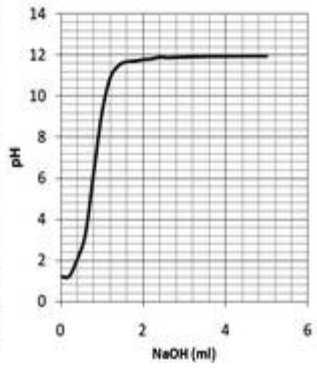


Figure 6. 7-ketokhivorin in chloroform at 25°C.

Values of each sample in water correlate to the total of the induction constant of the substituents on the aromatic ring. P-toluidine with a high pKa value of 9.2 demonstrated high basicity which is attributed to the relief of strain upon protonation and strong internal hydrogen bonding [9], this is higher than the value obtained using semi-micro HPLC method [15]. The high pka value of 7.2 of 3-methylindole in water is due to increase electron density on nitrogen atom of the amineand the 7.4 value for indole in water is due to NH substituent conjugation with the aromatic ring which increases the stability of the deprotonated form.These values are not in agreement with the reported value of 2.1±0.15 and 3.1±0.6 in phosphoric acid using the CVA method [10].

From Table 1, it was also observed that the pKa values of indole and 4-dimethylaminopyridine in 50% ethanol-methanol solvents decreases to 5.2 and 2.8 respectively compare to their values in distilled-water. This is due to the decrease in basic character of the solvents compare to water which makes the amino group more acidic. However, the increased pKa values demonstrated by some samples in some solvent mixtures other than water signify the best medium at which their strength can be determined.

Furthermore, the pKa values of khivorin and 7-ketokhivorin could not be determine in distilled water due to their insolubility. pKa determination for khivorin was done in toluene giving average value of 3.23 while that of 7-ketokhivorin was done in chloroform which gives a pKa value of 1.20. The values showed low basicity. It should be noted that these values may vary with solvents employed and temperature. No data is available in literature on the pKa values of these naturally occurring compounds.

Conclusion

It can be concluded from this studies that aromatic amines indole, 3-methylindole, p-toluidine and 4-dimethylaminopyridine are very good organic bases due to their pKa values in distilled water which is the medium present in biological system. Their pKa values depend on the solvent employed. Aside from water another good solvent for indole and 4-dimethylamino-pyridine is 50% ethanol-water solvent while for 3-methylindole and p-toluidine we have 50% ethanol-methanol solvent mixture. Thus, in these medium they will function at their best as bases. The naturally occurring compounds are not so basic in character although their pKa can be conducted in other solvents.

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