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Potentiometric Study of Hydroxamic Acids in Non-Aqueous Media

Piyush Kumar Thakur[1], Sandhya Patre[2]

[1]AVS Presidency International College, Mana Raipur (C.G.), India

[2]Govt. College Surgaon, Mungeli (C.G.), India

Abstract: ***Hydroxamic acids have been recognized as compounds of pharmacological, toxicological and pathological importance. The hydroxamic acid functionality -NOH.C=O, is the outstanding chemical feature of these molecules and is responsible for their biological and medicinal properties. The distribution, transport behavior, bonding to receptors and contribution to metabolic behavior of the molecules depend on the protonation constants. However its value depends on the structure of the molecules. The protonation behavior of two hydroxamic acids was determined in methanol and dimethylsulfoxide using glass and platinum electrode and calomel as reference electrodes. Tertbutylammonium hydroxides were used as the titrant in non-aqueous medium. Based on these data, pKa values of hydroxamic acids are then computed.***

Keywords: Hydroxamic acid, pKa, Potentiometric titration

1. Introduction

Hydroxamic acids are widely involved in pharmacological applications. These are used as antibiotics (1), anti-inflammatory (2), anti-virus (3), anti-tumor (4) and anti-cancer (5-10) agents. Some hydroxamic acids are reported as histone deacetylase (11-15), metalloprotinases (16-21), TNF-α converting enzyme (22-26), and peptide deformalize (27,28) inhibitors. Hydroxamic acid moieties are widespread in microbial and plant kingdom as key functional group of siderophore with remarkably high affinities scavenging of Fe(III) from its environment (29). Desferioxamine, a chelator of iron, aluminum and other metals is used for the treatment of iron overloaded patient (30,31). The ability of hydroxamic acid functionality to form a bidentate chelate with zinc and nickel in the enzymes active site is an important functional feature of this molecule (32-35). A very little knowledge is available (36) regarding the acid-base behavior of N-arylhydroxamic acids although they are recognized as drug like molecules for anti-tumor/ anti-cancer activity by this laboratory (37).

A knowledge of their pKa values is useful to predict the extent of ionization of functional groups with respect to pH. This information is important in drug discovery and development. Present investigation deals with the determination of their acid dissociation constants (pKa) in non-aqueous solvents. pKa is useful physico-chemical parameter describing the extent of ionization state of a particular functional group so as to understand the pharmacokinetic and pharmacodynamic properties of new drug substances. At the same time the distribution, transport behavior and bonding to the receptor depends upon the ionization constant (38). When a drug is ionized it will not be able to get through the lipid membrane, it will only be able to do so when it is non-ionized and therefore has higher lipid solubility.

2. Experimental Section

There are numerous advantages offered by acid – base titrations in non-aqueous solvent as compared to aqueous media. The most important advantage is that a much larger number of acids and bases can be titrated in non- aqueous solvents then may be titrated in aqueous solution. The solvent should provide a media in which there is a large change in the solvated proton concentration near the equivalence point for the titration. The substance to be titrated must be soluble in the solvent similarly, the product of the titration must be either soluble or, if it takes form of a precipitate, it must be compact and crystalline and not gelatinous.

3. Material and Methods

A. Preparation of Hydroxamic Acids Solution: 0.001mol/litre of each hydroxamic acid was prepared in methanol and dimethysulfoxide by direct weighing.

B. Preparation Of Tetra Butyl Ammonium Hydroxide Solution:- 0.001 mol/litre of Tetra Butyl Ammonium Hydroxide solution was prepared in methanol.

The titrations were carried out using a Digital Potentiometer with glass and calomel electrodes and micro burette with divisions of 0.01 ml. The cyber scan 510 model glass, platinum and calomel electrodes were used for pH measurement.

C. Proceduer

The titrations were carried out using a Digital Potentiometer with glass and calomel electrodes and micro burette with accuracy of 0.01 ml. The cyber scan 510 model glass, platinum and calomel electrodes were used for pH measurement. Before potentiometric titration the pH meter was calibrated according to the instruction supplied by the manufactures of the pH meter. During titration, the titrant was added in 0.2ml after beach stable recording of pH and millvolts. From the half – neutralization potential (HNP) of

S- shaped titration curves, the pKa value were determined. Each pKa value obtained was the average of three measurements.

4. Results and Discussion

A typical titration curve of N-Phenylbenzohydroxamic acid and P-Tolylbenzohydroxamic acid in methanol and dimethylsulfoxide using glass and platinum electrode and calomel as reference electrodes and tertbutylammonium hydroxide were used as the titrant in non-aqueous medium is shown in figure 1 & 2. As seen from the figures all titration curves are S-shaped.From this curve pKa value of both hydroxamic acids is found to be very low. The acidity of hydroxamic acids may be attributed essentially to the –OH group. The suppression of acidic character may be attributed to intramolecular hydrogen bonding present in the molecule.

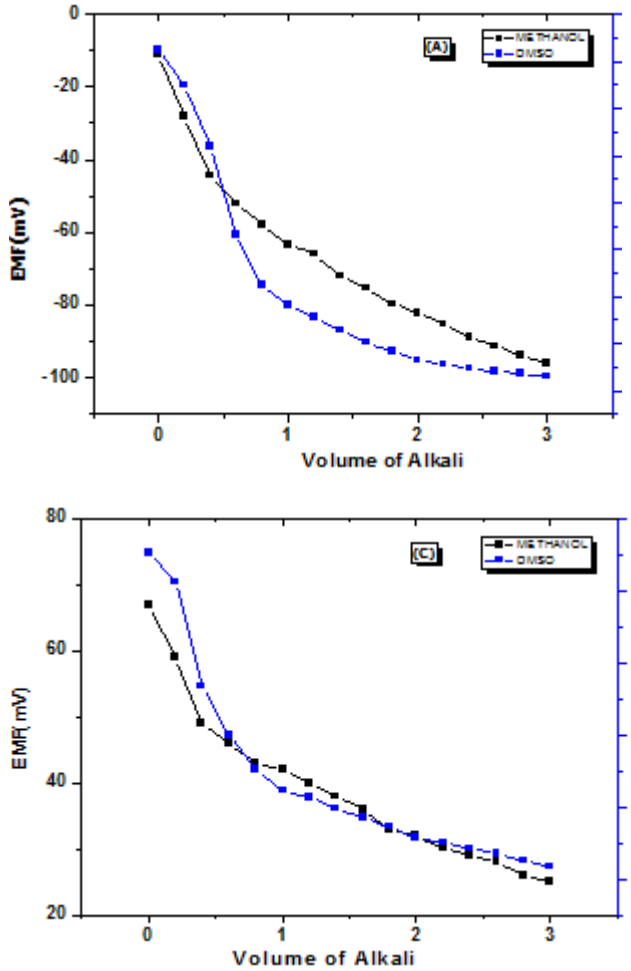

Figure 1: Potentiometric Titration Curve of N- Phenylbenzo And N-P-Tolylbenzo- Hydroxamic Acid In Methanol And Dmso Using Glass And Calomel Electrodes

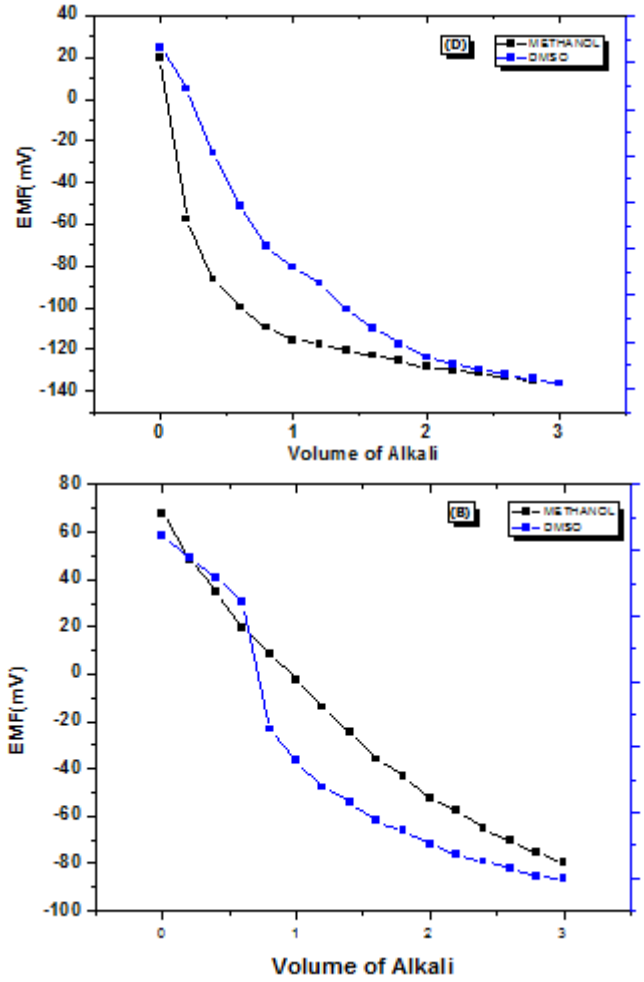

Figure 2: Potentiometric Titration Curve of N-Phenylbenzo And N-P-Tolylbenzo- Hydroxamic Acid In Methanol And Dmso Using Glass And Calomel Electrodes

pKa values obtained for PBHA in methanol and dimethylsulfoxide using glass and calomel electrode are 6.44 and 9.44 and for p-TBHA are 6.76 and 9.14, pKa values obtained for PBHA in methanol and dimethylsulfoxide using platinum and calomel electrode are 6.64 and 5.93 and for p-TBHA are 8.72 and 7.23, respectively

5. Conclusion

As it is well known that the acidity of compound depends on some factors. The two most important factors are the solvent effect and molecular structure. Table 4.9 and 4.10, shows that their HNP values and corresponding pKa values obtained from potentiometric titration depends on the non-aqueous solvent and electrode used.

Table 1: HNP, PKA Values and Amount of Base Required for Equivalence POINT/ML of Hydroxamic Acids Using Glass And Calomel Electrodes\

Hydroxamic Acids	Solvent	HNP (mV)	Amount of base required for equivalence point/ml	pKa
PBHA	Methanol	-38	0.29	6.64
	DMSO	183	0.30	9.44
N-o-Tolyl-4-	Methanol	49	0.20	6.76

methylbenzo -	DMSO	-166	0.35	9.14

Table 2: HNP, pKa Values and Amount of Base Required for Equivalence Point/ml of Hydroxamic Acids Using Platinum and Calomel Electrodes

Hydroxamic Acids	Solvent	HNP (mV)	Amount of base required for equivalence point/ml	pKa
PBHA	Methanol	62	0.15	6.64
	DMSO	104	0.21	5.93
N-o-Tolyl-4-methylbenzo-	Methanol	61	0.30	8.72
	DMSO	27	0.20	7.23

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