

STUDY OF METAL-LIGAND STABILITY CONSTANT OF CEFADROXIL WITH Cu^{2+} METAL ION pH METRICALLY AT 0.1M IONIC STRENGTH

Dinkar B Kamkhede

Department of Chemistry, Vidyabharti Mahavidyalaya, C. K Naidu Road, Camp, Amravati – 444602, Maharashtra, India.

ABSTRACT

pH metry is one of the most convenient and successful technique for metal-ligand complex equilibrium measurements. In the present work we investigate the Metal - Ligand Stability Constant of Cefadroxil with Metal ion pH metrically at 0.1 M ionic strength. As carried out in this process against standard sodium hydroxide solution (0.12) were carried out in 60%, 70%, 75%, 80% and 85% Dioxane-water mixtures. Ionic strength of the solution was maintained constant at (2 = 0.1 M) by adding an appropriate amount of 1 M HNO_3 solution. The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine metal-ligand stability constant ($\log K$) values. It is observed that a lanthanide metal ion forms 1:1 and 1:2 complexes. The trend in the formation constants for lanthanide metal ions follows the order: $\text{La}^{3+} < \text{Ce}^{3+} < \text{Nd}^{3+} < \text{Sm}^{3+} > \text{Gd}^{3+} < \text{Tb}^{3+} < \text{Dy}^{3+}$ and shows a break at gadolinium. The thermodynamic parameters such as, Gibb's free energy change (ΔG), entropy change (ΔS) and enthalpy change (ΔH) associated with the complexation reactions were calculated. The formations of metal complexes were found to be spontaneous and exothermic in nature. The metal Ligand stability constant is the association or formation constant. For the conversion of any Calvin-Bjerrum titrations data into stability constants.

Keywords: pH metry, Stability Constant, Cefadroxil metal Ligand Thermodynamic parameter.

INTRODUCTION

The coordination chemistry of metal ion in aqueous solution is the vast field of investigation²⁵. A complex is a cluster of ions and molecules, which can exist independently but prefers to join together in a structurally well defined manner. A metal complex consists of a metal ion, often structurally well-defined manner. A metal complex consists of a metal ion, often referred to as the central metal atom or ion, which binds a number of ions and or molecules, called ligand.

The stability constants can be of significance in order to predict different chemical processes such as isolation, extraction, or preconcentration methods^{6,7}. The accurate determination of acidity and stability constants values are fundamental to understanding the behavior of ligands and their interaction with

metal ions in aqueous solution. Potentiometric titration is accepted as a powerful and simple electro analytical technique for determination of stability constants. The determination of stability constants is an important process for many branches of chemistry⁸. Drugs have various functional groups present in its structure. They can bind to metal ions present in human body². Metal complexes of drugs are found to be more potent than parent drugs. It has been found that numbers of drugs are known to inhibit protein synthesis in bacteria by causing misreading of the genetic code³. Chemistry of drugs attracts many researchers because of its application in medicinal study. The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity¹⁰. Metal complexes are widely used in various fields, such as biological processes,

pharmaceuticals, separation techniques, analytical processes etc. Recently, there is great interest in The interaction of transition metal ions with biological molecules provides one of the fascinating areas of coordination chemistry¹⁴. The application has been grown readily due to their wide range in household, industry, medicine, chemical and biological system. Plants need various nutrients for healthy growth. Essential nutrients include number of metal such as iron, copper and zinc etc. Iron in the +3 state the soil is mostly hydrolyzed to form insoluble iron hydroxide, which cannot be taken up by plants. Deficient in iron are likely to develop a disorder known as iron chlorosis, evidenced by yellowing leaves. Iron chlorosis particularly affects the yield of fruit from citrus trees. The standard treatment, frequently used in citrus trees with Fe (III)- EDTA complex. This water – soluble complex readily enters the roots of trees. Where it is eventually converted into a utilized form. Therapeutic chelating agents in which coordination complex of platinum effectively inhibit the growth of cancerous cells. It has long been suspected that chelation processes are associated both with the development of cancer and with antitumor activity. The cleaning action of soap in hard water is hampered by the reaction of Ca^{2+} ions in the water with the soap molecule to form insoluble salt. The detergent industry introduced a builder usually sodium tripolyphosphate, to circumvent this problem. The tripolyphosphate is an effective chelating agent that forms stable, soluble complexes with Ca^{2+} ions. Cefadroxil is a broad – spectrum antibiotic of the cephalic sporum HPE Effective in gram positive and gram negative bacterial infection. It is a antibiotic. Cefadroxil is a first generation cephalosporin antibacterial active of cefadroxil .it has been affection of the skin and urinary tract. In Pharmacokinetics cefadroxil is almost completely absorbed from gastrointestinal tract after dose of 500 mg and 19 by mouth, peak plasma concentration of about 16 and 30 micrograms/ ml are reached after 1.5 to 2 hours. It is widely distributed to body tissue and fluid it crosses the placenta and appears in breast milk. Dental use as antibiotic prophylaxis dental procedure for patients allergic to penicillin. Veterinary use for treating interrelated wounds on animals usually in powder form mixed with water has a colorant smell similar amount dependent on their severity of interacting. Literature survey reveals that a very few researchers have done such type of work using medicinal drug as a ligand⁹⁻¹⁵. The detail study of complex under

identical set of experimental condition is still lacking²⁵. Therefore we decide to study the effect of temperature on thermodynamic parameters ΔG , ΔH and ΔS of complexes of drug like Cefadroxil with Metal ion at 0.1 M ionic strength .Against standard sodium hydroxide solution (0.12) were carried out in 60%, 70%, 75%, 80% and 85% Dioxane-water mixtures. by adding an appropriate amount of 1 M HNO_3 solution by using pH metric titration technique.

Experimental Sections

Materials and Solutions

All the chemicals used were of high grade of purity. The pure drug Cefadroxil obtained as a gift sample from a reputed pharmaceutical industry is soluble in hot water. The solutions used in the pH metric titration were carried out in 60%, 70%, 75%, 80% and 85% Dioxane-water mixtures. Ionic strength of the solution was maintained constant at ($\mu = 0.1 \text{ M}$) by adding an appropriate amount of 1 M HNO_3 solution. Against standard sodium hydroxide solution (0.12) double distilled water. The pH measurement were made using a digital pH meter model Elico L1-120 in conjunction with a glass and reference calomel electrode (reading accuracy ± 0.01 pH units) the instrument was calibrated at pH 4.00, 7.00 and 9.18 using the standard buffer solutions. It is necessary to calibrate pH meter scale over the entire range as the p1-1 of the solution in the titration vessel can vary continuously between 2.00 and 11.00 during titration. A calibration check was made at p1-14.01 and 9.15 only. The titration are carried out in the present investigation is calculated from the following formula supplied by manufacturers.

$$\text{pH } t^{0c} = \{\text{pH } 15^0_c - 0.0085 (t - 15)\} \text{ for buffer solution of pH } 9.15$$

$$\text{pH } t^{0c} = \left\{ \text{pH } 15^0_c = \left\{ \frac{0.5(t-15)^2}{100} \right\} \right\} \text{ for buffer solution of pH } 4.01$$

pH-Metric Measurements

pH Metric titrations

Nitric acid ($1 \times 10^{-2} \text{ M}$), Nitric acid ($1 \times 10^{-2} \text{ M}$) and ligand ($20 \times 10^{-4} \text{ M}$)

Nitric acid ($1 \times 10^{-2} \text{ M}$), the ligand ($20 \times 10^{-4} \text{ M}$) and metal salt ($4 \times 10^{-4} \text{ M}$) Following constants were determined in the present work [1] pk values of substituted pyrazole ligands in dioxane medium [2] log K values of rare transition metals (Cu II) chelates with ligands mentioned in Chapter-I. The results are discussed accordingly. The pH-metric

titrations data for same systems are presented in Tables No1. The graphs are plotted between pH of the solution and volume of NaOH in ml. The representative graphs for some of the systems are shown in Fig No 1.

The curves are designed as

- 1) Acid titration curve A.
- 2) Acid + ligand titration curve (A 4)
- 3) Acid + ligand + metal titration curve (A + L + M).

Calculation of Proton-Ligand Stability Constants (pk Values)

The proton-ligand stability constants or dissociation constants of substituted pyrazole were determined pH-metrically in dioxane medium. The ligands used in present investigation are as given below substituted pyrazoles [Cefadroxil (Li)].

The Pattern of Titration Curves -The acid + ligand titration curves (A + L) deviated from acid titration curves (A) for all the systems at pH 2.70 and deviation increased continuously upto pH 12.06. Which shows the dissociation of — OH group of ligands. The ligands used in present investigation may be considered as monobasic acid containing only one dissociable H^+ ion from -OH groups.



Calculation of Proton- Ligand Formation Number (\bar{n}_A) –

Proton-ligand formation number shows the replacement of H^+ ion from functional groups of ligand with respect to pH- value.

The \bar{n}_A values were calculated by Irving Rossetti's expression –

$$\bar{n}_A = y - \left[\frac{(V_2 - V_1)(E_0 + N)}{(V_0 + V_1)TLO} \right]$$

Where V^0 is the initial volume of solution, E^0 and T^0_L are initial concentrations of mineral acid and ligand respectively, V_1, V_2 volumes of alkali of normality N during acid and ligand titration of given pH, y is the replaceable protons from the ligand. The difference (V_1 and V_2) was estimated from the plot between volume of NaOH and pH of solution. The values of \bar{n}_A calculated along with values of $(V_2 - V_1)$ at various pH are presented in Tables No 01.

Formation Curves

The formation curves were constructed by plotting the values of \bar{n}_A against pH of solution and are presented in Fig.No 01. The dissociation constant pK of ligands are calculated from formation curves. The values of pK obtained are represented in Table No 01. The dissociation constants (pK values) for substituted ligands are found to be above pH 10.00 for all the systems.

Methods for Calculation of Proton-Ligand Stability Constants

Half Integral Method

The proton- ligand stability constants are initially calculated from the formation curves. The values of pH where $\bar{n}_A = 0.5$ corresponds to value of pH for only one dissociable group. Kabadi et al²⁸ Nat-wade et al²⁹ have determined pH value of salicylaldehyde, salicylic acid, sulphonic acid respectively by similar procedure. Sondawale³⁰ Meshram³¹ have determined the pK -values of ligands pH metrically by similar method.

Method of Point wise Calculations

The accurate values of pK are determined pointwise calculation. For the values of $\bar{n}_A < 1.0$, the formation function (number) of 1:1 complex can be given by the expression. $\text{Log} \frac{\bar{n}_A}{1 - \bar{n}_A} = pK - pH$. The values of \bar{n}_A are selected in the range of 0.9 to 0.1. The average of values obtained by solving the linear equation for different values of \bar{n}_A and pH, is taken as the correct value of pK . The values of pK calculated by pointwise calculations method are in good agreement with those obtained by the half integral method.

Meta I-Ligand Stability Constants

The metal Ligand stability constant is the association or formation constant. For the conversion of any Calvin-Bjerrum titrations data into stability constants, following conditions should hold good for the system under investigation.

1. Formation of complex or chelate under the experimental conditions employed.
2. Absence of metal ion hydrolysis, polynuclear hydrogen and hydroxyl complexes and anion of complexing metal ions.
3. Absence of complexes of very high and very low stability.

Metal-Ligand stability constant

System	$\log K_1$	$\log K_2$
Cu (II) ligand	1.29	0.386

EXPERIMENTAL RESULT AND DISCUSSION

pK – Values

It could be seen the pK value for L1 arc found to be slightly, greater. ThreentparerFttroth. This may be due to the effect of electron releasing substituent in higher percentages of water mixture.

Log K- Values

Determination of metal-ligand stability constants requires the accurate values of proton-ligand stability constants. Higher values or log K₁ and log K₂ showed that ligands are stronger chelating agents and vice versa. Metal-ligand stability constants of complexes have played important tool in thermochemistry for determining thermodynamic parameters (ΔH , ΔG and ΔS). Narwade et al²⁹ have determined metal-ligand stability constant of cefadroxil Cu(II) transition metal ions with substituted cefadroxil 0.1 M ionic strength potentiometrically, pH metrics and spectrophotometrically. Mahajan D. T19. have investigated metal-ligand stability constants of transition metal ions with sulphonic acid. Log K₁ and log K₂ values of substituted cefadroxil with metal ion complexes in the present investigation are presented in Tables. The difference between log K₁ and log K₂ values is found to be smaller that indicated the simultaneously complex formation.

Relation Between log K and pK-

The proton-ligand stability constants (pK) and metal-ligand stability constants of complexes (log K) are used to verify the validity of $\log K = a.pK + b$ relation. This relation was verified for vanadyl ion complexes of sulphonic acids¹¹⁴ and uranyl complexes of chalcones¹¹⁵ at 0.1 M ionic strength. The validity of relationship can be tested only for metal complexes of similarly substituted ligands. In our present investigation, linear relation between $\log K_1 / \log K_2$ and pK is observed for Cu II. The values of slopes or the straight lines are given as

Cu II

Narwade et al²⁹ have studied the linear relation for substituted sulphonic acids. Many workers have investigated linear relationship between log K and log pK. According to Ernst and Menash³¹, the effect of substitution in the ligand on stability of metal ligand complexes as compared to that of proton ligand complexes will be

1. to some extent if slope = 1
2. to lesser extent if slope < 1
3. to greater extent if slopes > 1.

The values or slopes of Cu(II), Ni(II) and Co(II) complexes in present work are not in good agreement with the values Jones et al regarding the behaviour of $\pi\bar{e}$ donors like Cu(II) and Ni(II). The disagreement may be attributed to the fact that π electrons donating and accepting properties of cations may not be the only factor which influences slope values. Other factors, such as ionization potential of metal ion, nuclear repulsion between metal ion, and donor atoms. Tendency of metal ions to form π bonds. Ligand field stabilization may influence slope values.

Effect of Metal Ion

Metal ion and size of metal ions are very important factors because the chelation properties can be related to the properties of metal ion. Mellor and Melley have obtained the following order of relative stabilities of bivalent metal ions. Irving and Rossotti have observed that irrespective of the nature of ligand, stability of metal complexes always follow the following order whether the scenic hindrance occurs or not. Pfeiffer et al have obtained the order of relative stabilities as

$Cu > Ni > Fe > 7.12 > Mg$

In the plots of log K_n against atomic number. Irving Williams showed that the stabilities increases with increase in atomic number upto the end of transition series. Calvin and Melchoir from the study of 5-SSA sulphonic complexes of Cu(II), Ni(II) and Cu(II) discovered a correlation between stability constants of complexes and second ionisation potentials of gaseous atoms. They concluded that d-orbitals are somehow involved in the binding of ligands of this type with these metal. The stability of metal complexes in the present investigation follows the order for 1:1 complexes.

Cu II

The order of the stability constants given above follow the Irving Williams order. Irving Williams order will ideally hold for transition metal complex if the various factors such as metal-ligand bond energy, Polarization energy of ligands, hydration energy etc. contributing to standard enthalpy change vary uniformly except the difference in the ligand field stabilization energy of spin free ions in octahedral field.

The difference between log K₁ and log K₂ values is smaller in all systems. It seems therefore that both 1:1 and 1:2 complexes are formed simultaneously and not in a stepwise process. Deshpande and Devrankar¹³¹ have studied lanthanide complexes with aryl-furyl and aryl-thionyl-P- diketones. Showed the formation of 1:1 and 1:2 complexes. The

difference between $\log K_1$ and $\log K_2$ complexes were less than 2-5, indicating simultaneous formation of 1:1 and 1:2 complexes. They showed linear relationship between $\log K$ and pK values of ligands suggesting identical binding sites in all ligands. Jones et al¹⁻¹⁶ suggested on the basis of purely electrostatic model that the slopes will increase with increasing cationic charge and decreasing distance of separation.

Formation of 1:2 Complexes

The complex formation of 1:1 complex ($n = 1$) are always before the pH of hydrolysis of the metal ion. As regards 1:2 complexes, some values of n above 1.5 were in the hydrolysis region. Formation curves were constructed from the values of the pH and n calculated using values of $\log K_1$ and $\log K_2$ from the equation.

$$\frac{\bar{n}}{(\bar{n} - 1) [L]} = \frac{(2 - \bar{n}) [L]}{(n - 1)} K_1 K_2 - K_1$$

by least square method. The values of \bar{n} between 0.95 and 1.05 were not used for calculations, because values of $\bar{n} / (\bar{n} - 1)$ and $(2 - \bar{n}) / (\bar{n} - 1)$ become very large and therefore sensitive to experimental errors in \bar{n} . The

calculated \bar{n} were compared with values of \bar{n} obtained experimentally. The agreement between two sets of values in each system is in good agreement.

Construction of Graphs

The graphs between $1/D$ versus $pK/\log K$ are constructed but nature of graphs was found to be linear at lower values of $1/D$ and non-linearship of the graphs was found at higher values of $1/D$. Similarly mole fraction versus $pK/\log K$ graphs have constructed and found good linear ionship. The same is observed by N.fig No 02&03.

CONCLUSION

The departure between acid curve and ligand curve indicated the dissociation of phenolic -OH group. The departure between ligand curve and metal curve indicated the commencement of complex formation. The change in colour during pH-metric titration also indicated the formation of complexes between ligands and metal ions. The values of pK and $\log K$ are increased with increasing the mixture of water which is attributed due to the effect of bulky solvent. The non-linear relationship for the graphs $1/D$ versus $pK/\log K$ but linear relationship for the graphs between mole fraction versus $pK/\log K$ is observed.

Table 1: pH – Metric Titration Data
System: - Cu II L1 complex
Medium: - Distilled water
V0 50ml N = 0.2N
Temp = 27 ± 0.10 M
E0 = 1 x 10⁻²

Volume of Alkali added	Titration free acid	Titration of free acid + Ligand	Titration of free acid +ligand + Metal Cu II
0.00	1.5	1.5	1.5
0.5	1.7	1.7	1.7
1.0	1.9	1.9	1.9
1.5	2.1	2.1	2.1
2	2.1	2.1	2.1
2.5	2.3	2.3	2.3
3	2.5	2.5	2.5
3.5	3	3	3
4	3.5	4	3.7
4.5	4.6	4.7	4.3
5	5.4	5.5	4.7
5.5	6.3	6.4	5.3
6	7.5	7.3	5.8
6.5	8.7	8.2	6.7
7	9.7	9.2	7.6
7.5	10.4	10	8.3
8	10.7	10.2	8.4
8.5	11.3	10.4	8.5
9	11.7	10.7	8.7
9.5	11.9	11.1	9
10	12.00	11.8	10.1

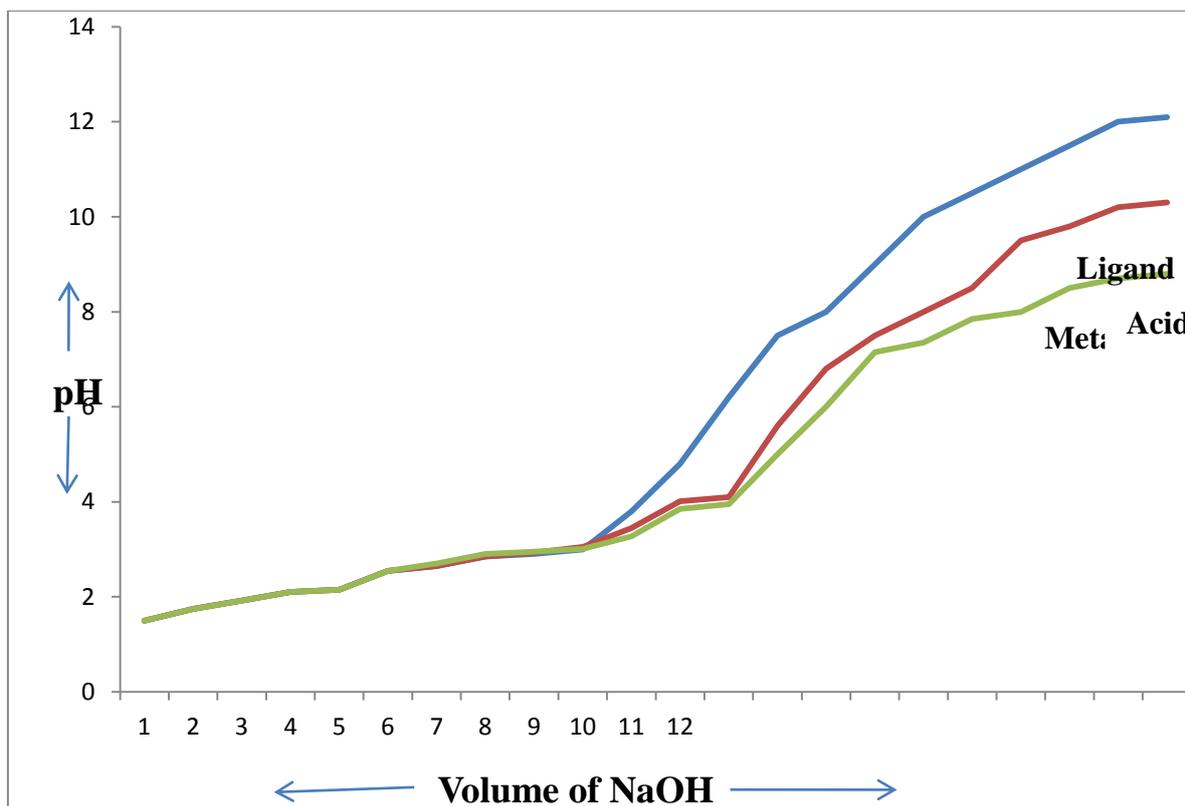


Fig. 1:

Table 2: Determination of \bar{n}_A Values
System: - Ligand L1
Medium: - Distilled water
V0 50ml N = 0.2N
Temp = 27 ± 0.10 M
E0 = 1 x 10⁻² M

pH	V1(ml)	V2(ml)	V2-(ml)	\bar{n}_A
4	4.8	4.90	0.10	0.8087
4.5	4.9	5.00	0.10	0.8087
5	5.10	5.20	0.10	0.8094
5.5	5.5	5.70	0.20	0.6216
6	5.80	6.00	0.20	0.6236
6.5	6.00	6.20	0.20	0.625
7	6.20	6.45	0.25	0.477
7.5	6.19	7.20	0.25	0.539
8	7.45	7.70	0.25	0.542
8.5	7.45	7.75	0.30	0.451
9	7.65	8.30	0.30	0.099
9.5				
10				

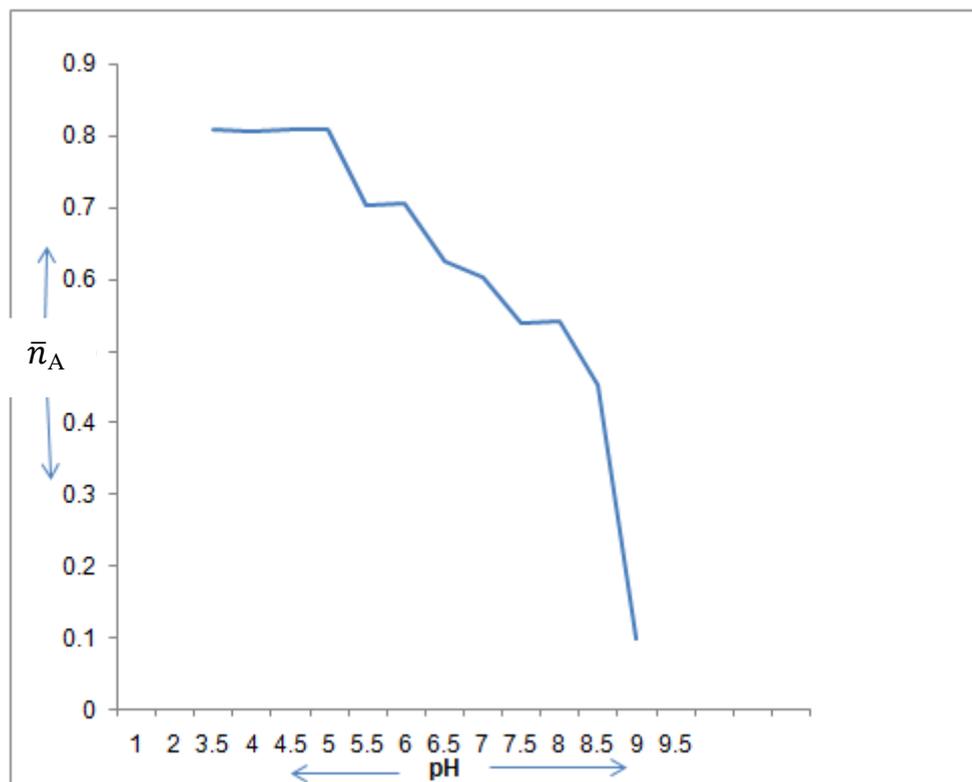


Fig. 2:

Table 3: Determination of \bar{n} Values

System: - Ligand L1

Medium: - Distilled water

V0 50ml

N = 0.2N

Temp = 27 ± 0.10 ME0 = 1×10^{-2} M

pH	V2(ml)	V3 (ml)	V3 - V2 (ml)	\bar{n}
4	4	3.7	0.3	2.91
4.5	4.7	4.3	0.4	8.83
5	5.5	4.7	0.8	7.56
5.5	6.4	5.3	1.1	10.2
6	7.3	5.8	1.5	13.74
6.5	8.2	6.7	1.6	14.52
7	9.2	7.6	1.6	14.98
7.5	10	8.3	1.7	17.60
8	10.2	8.4	1.8	16.83
8.5	10.4	8.5	1.9	16.68
9	10.7	8.7	2.0	17.90
9.5	11.1	9.00	2.1	18.04
10	11.8	10.1		

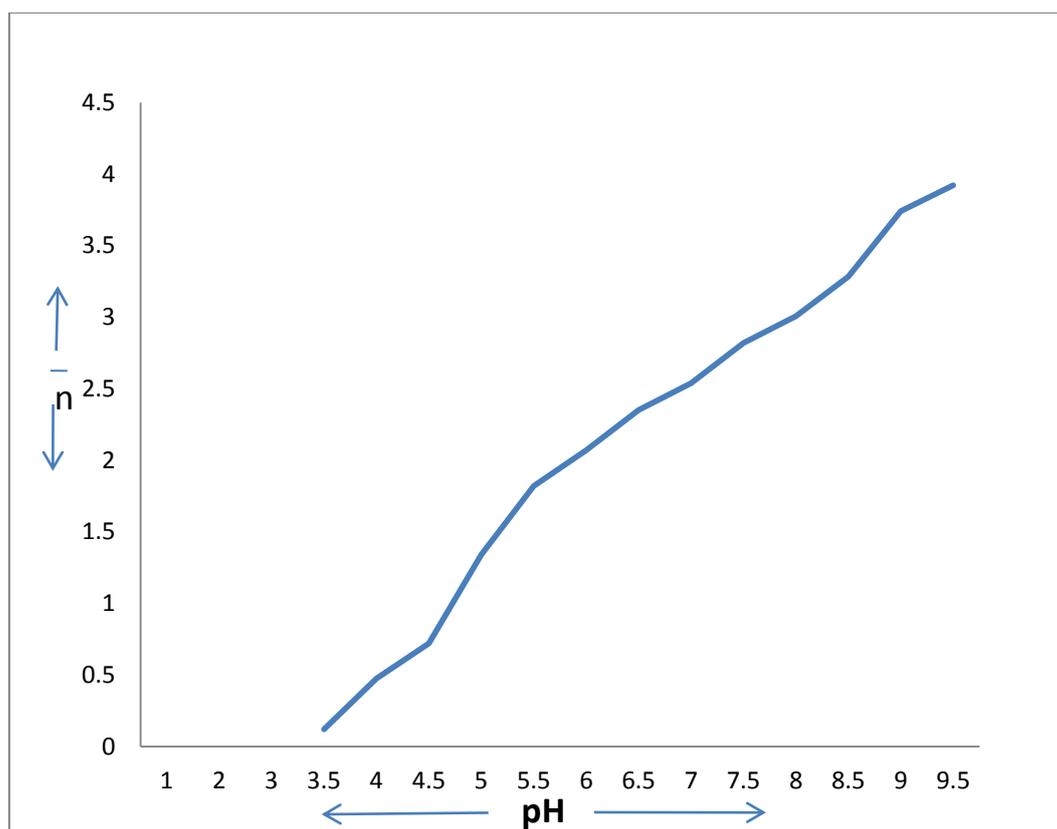


Fig. 3:

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