International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.11 No.11, pp 211-216, 2018

Stability constant study of transition metal complexes with pharmacologically active ligand(N-[-(4-chlorophenyl)methylene] nicotinohydrazide) by pH metric Technique

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Abstract : Pharmacologically active organic ligands (N-[-(4-chlorophenyl)methylene] nicotinohydrazide) synthesized through the condensation of equimolar mixture of Anti-mycobacterial agent(nicotinohydrazide)with aromatic aldehyde. The reaction progress and purity of organic ligands were verifying by thin layer chromatography. Formation of organic ligands was confirming with the help of MP, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.Further formation of complexes of transition elements like Mn(II), CO(II), Ni(II), Cu(II) and Zn(II) with organic ligand (Schiff base) N-[-(4-chlorophenyl)methylene] nicotinohydrazide, were studying by the pH-metric technique at 27±1^{0}C in 70%(v/v) ethanol - water medium at 1M ($NaClO_4$) ionic strength. The stability constants of these binary complexes were evaluating and order of stability constant found as Zn (II) > Cu (II) >Ni (II) >Mn(II) > Co (II).

Key word : Binary complexation,N-[-(4-chlorophenyl)methylene]nicotinohydrazide, transition metals, pH metric technique.

Introduction

In the field of coordination chemistry, metal ions perform vital roles in biological processes. The mineral complexes have been studied with the basic Schiff links to be utilized in the biological, clinical, analytical and pharmacological fields[1].Schiff bases perform an important function in coordination chemistry because they easily form stable complexes with most transitional metal ions[2].Schiff bases have a broad assortment of applications in different regions such as biological chemistry, organic and inorganic chemistry[3].Schiff bases are now attracting the attention of medicinal chemist. Schiff base containing an amine group (–RC=N–) are commonly formed by the intensification of an initial amine with an active carbonyl[4]. Schiff bases and their complexes have a variety of applications in biological clinical and analytical fields[5].The complexation of Schiff base with transition metals increasethebiologicalactivity[6]. Isoniazid is anti-mycobacterial drug and used.

DOI= http://dx.doi.org/10.20902/IJCTR.2018.111121

also primarily as a tuberculostatic[7].Itbecomes a starting point in the search for new vital derivatives and analogues such as hydrazones which have been informed as active anti-tuberculosis drugs [8].For the investigation of stability constant various techniques are utilizing such as potentiometry etc. pH-metric study is one of the best widely used technique because it has several superiority such as, it is easy to understand and work, cheap technique etc.A pH meter is using to find the stability constant which is useful for the formation of a complex in solution[9-16].The stability of metal complexes with medicinal drugs perform greater role in the biological and chemical activity[17].

Due to these valuable findings observed in literature review, present work was planning and well executed for the preparation of organic ligands through the condensation of 4-chlorobenzaldehyde with isoniazid. Complexation of newly synthesized organic ligand was carrying out with transition metals to determine the order of stability constants by using pH-metric technique.

Material and Methods:

Experimental*:*

(A) Synthesis of Schiff base:

Take equimol a rmix of isoniazid and 4-chlorobenzaldehyde (as aromatic aldehyde)in appropriate volume of ethanol, charged 2-3 drops of glacial acetic acid at room temperature. Then raised temperature of reaction mass up to reflux, reaction mass reflux for 3-4 hrs under continuous stirring and progress of reaction check on TLC using Ethyl acetate : Hexane (5:5) as solvents. After completion of reaction, reaction mixture was cooling at room temperature and poured on ice-cold water. The precipitate product was filtering and recrystallizing by alcohol. The purity of these compounds were verifying by TLC, and structures were confirmed by IR, NMR and melting points.

B) Potentiometric determination of Stability constant:

In the present study Calvin-Bjerrum titration technique as been used for the determination of stability constants. The experimental procedure involved pH-metrictitration of solutions of:

i) Free $HClO_4$ (A).
ii) Free $HClO_4$ + Ligand (A+L).
iii) Free $HClO_4$ + Ligand + Metal ion (A+L+M).

The solution of the ligand (0.01 M) was preparing by dissolving the requisite quantity of the ligand in (mix of 70% of ethanol and 30% of double distilled water). Transition metal solutions (0.01M) was preparing and standardizing by the EDTA. The pH-metric titration was carrying out at 27 ± 1^0C and was carrying out by using Elico digital pH-meter model L-120 with combined glass-calomel electrode. The pH-meter was standardizing against by buffer solution pH 9.2 and pH 4.The solution of complex titration was preparing by three systems:

First titration(A):5ml of 0.2N $HClO_4$ solution into a 50 ml standard flask, 5 ml of 1M $NaClO_4$solution and dilute up to the mark with double distilled water and titrated against 0.2N NaOH solution by using pH-meter and record the readings until constant of pH is obtained .

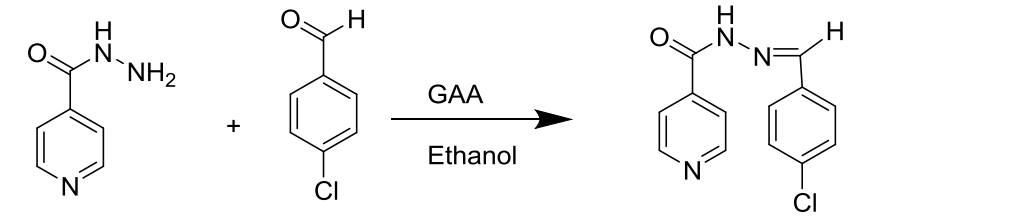
Second titration(A +L):5ml of 0.2N $HClO_4$solution into a 50 ml standard flask,5 ml of 1M $NaClO_4$ solution,10ml of0.01N ligand and dilute up to the mark with double distilled water and titrated against 0.2N NaOH solution by using pH-meter mode and record the readings until constant of pH is obtained.

Third titration(A+L+M):5ml of 0.2N $HClO_4$ solution into a 50 ml standard flask ,5 ml of 1M $NaClO_4$solution,10 ml of 0.01N ligand, 10 ml of 0.01Ntransition metal solution and dilute up to the mark with double distilled water and titrated against 0.2NNaOH solution by using pH-meter mode and record the readings until constant of pH is obtained .

Results and Discussion:

Organic ligands of the present investigation are prepared as per **scheme1:**

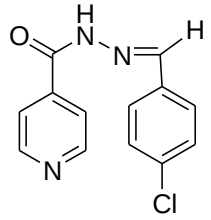
SCHEME I:



Nicotinohydrazide p-Chlorobenzaldehyde N-[-(4-chlorophenyl)methylene] nicotinohydrazide

Above organic ligand was successfully synthesized through condensation between isoniazid with aromatic aldehyde. Formation of organic ligand was confirmed with TLC, single spot observed confirms the formation of product. MP was carried out in open capillary tube and mention following **table-1**. Confirmation of structure was carried out with the help of spectral analysis such as IR and NMR data mentioned below.

Table.1: Characterization data of Organic ligand

ligand structure / mol. Formula	Mol.Wt	M.P.	Elemental analysis		
 [$C_{13}H_{10}N_3ClO$]	259.05	214^oC	Element	found	Calculated
			C	60.19	60.23
			H	3.83	3.86
			N	16.17	16.21

(N-[-(4-chlorophenyl)methylene] nicotinohydrazide), White color, M.P= 214^oC,

IR, N-H: 3443 cm^{-1}, C=O:1664 cm^{-1}, aliC=N: 1608 cm^{-1},Ar. C=N: 1486 cm^{-1}.

^{1}H NMR (400MHz, $DMSOd_6$) Spectrum recorded at δ 11.977 N-H,δ 8.407 aliphatic-H, δ 7.929Pry-CH, δ (8.705-8.691)[d,2H, J=5.6Hz, Pry-H], δ(7.777-7.763)[d,2H, J=5.6Hz,Ar-H], δ(7.702-7.681)[d,2H, J=8.4Hz, Pry-H], δ (7.369-7.348) [d,2H,J=8.4Hz,Ar-H next to Cl.

^{13}CNMR (100MHz, DMSO d_6) 121.84, 129.07, 129.10, 133.09, 135.64.140.70(Benzene C-Cl), 148.25(Pry-Carbone next to N), 150.43(aliphatic N=CH), 162.24 (carbonyl carbon).

The plots of volume of alkali (NaOH) against pH were using to estimate the proton-ligand stability constants of ligand and acid. The proton-ligand stability constant and metal-ligand stability constants and their complexes with Mn(II), Co(II),Ni(II),Cu(II) and Zn(II) metal ions were determining in 70% ethanol-30% water mixture at 27±1^{0}C. The dissociation of OH- clearly indicated by the titrations (acid +ligand) curves deviated from acid curves at pH 2.2 and continued up to pH 11.8. The proton-ligand formation number $\bar{\mathbf{n}}_\mathbf{A}$ was determined from the titration curves of acid and (acid+ligand).$\bar{\mathbf{n}}_\mathbf{A}$defined as hydrogen ions bound to one ligand molecule.This is given by:

$$\bar{n}_A = \gamma - \left[\frac{(E^0+N)\times(V_2-V_1)}{(V^0-V_1)\times T_L^0}\right]\text{-----1}$$

Where γ denote the replaceable H^+ ion, E^0 is concentration of acid, T_L^0 is concentration of ligand,N is normality ofalkali,V_1 and V_2 are the volumes of alkali required during the acid and ligand titrations at the given pH andV^0 is the total volume of the mixture. The data of $\bar{n}_A$ obtained at several of pH values along with difference (V_2-V_1)

for representative systems, which are represented in **Table-2.**The (acid + ligand + metal) titration curves (A+L+M) deviated from (acid + ligand) titration curves (A+L) in case of metal ion Mn(II) at pH 4.56, metal ion Co(II) at pH 5.42, metal ion Ni(II) at pH 4.43, metal ion Cu(II) at pH 6.63, and metal ion Zn(II) at pH 4.02 and deviation increased continuously up to pH 11.28, pH 11.60, pH 11.39, pH 10.54, and pH 11.41 respectively.

Table 2: Proton-ligand stability constants at 27±1˚C

pH	V_1	V_2	$\Delta V = V_2 - V_1$	$\bar{n}_A$
2.2	0.85	1	0.15	0.676
2.4	1.76	2	0.24	0.490
2.6	2.32	2.725	0.41	0.149
2.8	2.68	3.006	0.33	0.319
3	2.92	3.125	0.21	0.574
3.2	3.07	3.224	0.15	0.689
3.4	3.18	3.284	0.095	0.802
3.6	3.21	3.344	0.14	0.714
3.8	3.21	3.424	0.21	0.561
4	3.22	3.603	0.39	0.202
4.2	3.22	3.617	0.39	0.186
4.4	3.23	3.632	0.40	0.169
4.6	3.24	3.656	0.41	0.153

The average number of metal ions associated with the ligand at different of pH values was calculating from the metal ions and ligand titration curves using equation as follows:

$$\bar{n} = \left[\frac{(E^0+N)\times(V_3-V_2)}{(V^0+V_2)\times T_m^0}\right]\text{------2}$$

Where N, E^0, V_0 and V_2 have the same significance as in Eq. (1), V_3 is the volume of alkali added in the metal titration to attain the given pH reading, andT^0mis the concentration of the metal ion in the reaction mixture. At the time of completion, metal complexes titration curve was spotting always at lowest pH values of hydrolysis of metal ion.

The potentiometric titration curve obtained for acid, acid+ligand and acid+ligand+metal in following graph, from thegraph stability constant for proton ligand and metal ligand equilibria has been evaluated.Metal-ligand formation curves and acid-ligand formation curve represented In **Figure-1**

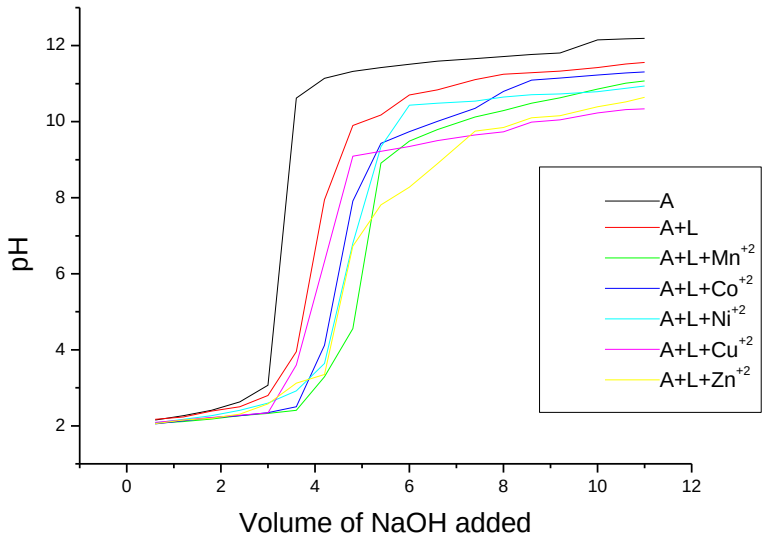


Fig1: The pH titration reading of acid, acid + Ligand, acid + Ligand + Metal at T =27±1^{0}C, solvent Ethanol-water (70:30)

The deviation of (metal+ ligand) titration curves from ligand curve were finding from 4.02 and continued up to11.6 This shows the formation of complexes with respect to change in color and readings related to estimate the value of pH and volume of alkali added presented in **Table-3.**

Table 3: The pH titration reading of acid, acid + Ligand, Acid + Ligand + Metal at T = 27±1^{0}C, solvent Ethanol-water (70:30).

Vol. of NaOH(ml)	A	A+R	A+R+Cu^{+2}	A+R+Ni^{+2}	A+R+Zn^{+2}	A+R+Co^{+2}	A+R+Mn^{+2}
0.6	2.15	2.17	2.09	2.08	2.06	2.05	2.07
1.2	2.27	2.23	2.15	2.17	2.15	2.13	2.11
1.8	2.41	2.39	2.22	2.27	2.2	2.21	2.18
2.4	2.63	2.50	2.28	2.41	2.31	2.27	2.27
3	3.07	2.8	2.34	2.60	2.58	2.35	2.33
3.6	10.62	3.95	3.6	2.92	3.12	2.5	2.41
4.2	11.14	7.95	6.32	3.64	3.35	4.12	3.29
4.8	11.32	9.9	9.09	6.80	6.73	7.91	4.56
5.4	11.42	10.18	9.22	9.34	7.81	9.43	8.91
6	11.51	10.7	9.35	10.43	8.28	9.74	9.49
6.6	11.59	10.84	9.5	10.49	8.9	10.01	9.79
7.4	11.66	11.11	9.65	10.54	9.75	10.35	10.12
8	11.71	11.25	9.73	10.65	9.85	10.8	10.29

Table 4: Protonation constant of ligand and Metal-Ligand Stability Constant

Metal	pK	Stability Constant (logK)
Cu(II)	5.24	4.0805
Ni(II)	5.24	3.9389
Zn(II)	5.24	4.2020
Co (II)	5.24	3.3415
Mn(II)	5.24	3.5132

The protonation constant of ligand and Metal-ligand stability constant are shown **in Table-4**.

The order of stability constants of complexes with respect to the N-[-(4- chlorophenyl)methylene] nicotinohydrazide was found to be Zn (II) > Cu (II) >Ni (II) >Mn(II) > Co (II).

Conclusion:

N-[-(4-chlorophenyl)methylene]nicotinohydrazide has been successfully and conveniently synthesized, which play the role of organic ligand in the complex formation with transition elements such as Mn (II), CO(II), Ni(II), Cu(II) and Zn(II) The present work describes the effect of organic ligands (Schiff base) on the stability of the complexes.Transition metal complexes of N-[-(4-chlorophenyl)methylene] follows the order of stability constants is Zn (II) > Cu (II) >Ni (II) >Mn(II) > Co (II).

Acknowledgement :

We are Thank full to Dr.Mazahar Farooqui, Principal Dr.RafiqZakaria College for Women, and Dean Dr BAMU, Aurangabad (M.S),India providing laboratory and library facilities to carry out this research work.

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