Determination of Metal-Ligand Stability Constant of Transition Metal Complexes with Pharmacologically Active Ligand N-[(E)-(2-Nitrophenyl)methylen]isonicotinohydrazid

Zamzam Taher Omar (Al-Ahdal)1, Shivaji L. Jadhav2 and Megha J. Rai1* 
1Dr. Rafiq Zakaria College for Women, Aurangabad - 431001, MS, INDIA
2Tarai College Paithan, Aurangabad - 431001, MS, INDIA
*Correspondence: E-mail: drmeghat08@gmail.com & zamzamomar1984@gmail.com
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ABSTRACT: Proton–ligand association constants of organic ligand N-[(E)-(2-Nitrophenyl)methylene]isonicotinohydrazid with Mn (II), Co (II), Ni (II), Cu (II) and Zn (II) metal ions have been studied by pH-metric technique at 27±1C in 70% (v/v) ethanol – water medium at 1M (NaClO4) ionic strength. Organic ligand was synthesized by condensation of equimolar mixture of Anti-mycobacterial agent with aromatic aldehyde. The reaction progress and purity of organic ligands were confirmed by thin layer chromatography. Formation of organic ligands was confirmed with the help of MP, IR, 1H NMR, 13C NMR and elemental analysis. The stability constants of these binary complexes were evaluated and order of stability constant found as Zn (II) > Ni (II) > Cu (II) > Mn (II) > Co (II).

Keywords: pH-metric technique; Binary complexation; N-[(E)-(2-Nitrophenyl)methylen]isonicotinohydrazid and transition metals.

INTRODUCTION: In the field of coordination chemistry, metal ions carry out spirited roles in biological processes. Schiff bases are now well known for their importance in biological fields such as anticancer, antimicrobial anti-inflammatory, analgesic and pesticidal agents, so Schiff bases have a broad variety of applications in different region such as pharmacological activity, organic and inorganic chemistry.1 & 2 Schiff bases are assignment in coordination chemistry because they easily form stable complexes with most transitional metal ions.3 & 4 Schiff bases containing an amine group (–RC=N–) are usually formed by the condensation of an initial amine with an active carbonyl.5 & 6 Isoniazid is a starting point in the search for new vital derivatives and analogues such as hydrazones which have been informed as active antituberculosis drugs, also it is anti-mycobacterial drug and used also primarily as a tuberculostatic.7,9 The chemistry of Metal-drug coordination compounds is more spread now than before especially in the range of more biologically active drugs.10-12 The complexes have been studied with the basic Schiff links to be applied in the clinical, biological, analytical and pharmacological fields.13,16 The complexation of Schiff base with transition metals promote the biological activity.17-20 PH-metric study is one of the best vastly used technique because it has several distinction such as, it is easy to understand and work, cheap technique etc. A pH meter was used to find the stability constant which is advantageous for the formation of a complex in solution.21-32 Metal ions are known to affect the action of many drugs.33 The stability constant of complexes has been found to be greater than zero, if all the possible stability constants for a given system have been determined that means it is possible to calculate the equilibrium activity of complexes.34 The stability of metal complexes with medicinal drugs perform greater role in the biological and chemical activity.

Due to these valuable findings observed in literature review and very less work observed on complexation of 2-nitrobenzaldehyde. Present work was planned and well executed for the preparation of organic ligands through the condensation of 2-nitrobenzaldehyde with isoniazid Complexation of newly synthesized organic ligand was carried out with transition metals [Mn(II), Co(II),Ni(II),Cu(II) and Zn(II)] to determine the order of stability constants by using pH-metric technique.
MATERIALS AND METHODS:

Experimental:

**Synthesis of Schiff base:** Take equimolar mix of isoniazid and 2-nitrobenzaldehyde (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 : Di methyl sulfoxide (2:8) as solvents. Then reaction mixture was cooled at room temperature and poured on ice-cold water. The precipitate product was filtered and recrystallized by alcohol. The purity of these compounds was verified by TLC, and structures were confirmed by IR, NMR and melting points.

**Potentiometric determination of Stability constant:** In the present study Calvin-Bjerrum titration technique has been used for the determination of stability constants. The experimental procedure involved pH-metric titration of solutions. The solution of the ligand (0.01 M) was prepared 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 prepared by dissolving the requisite amount of the metal ions in (mix of 70% of ethanol and 30% of double distilled water). The pH-metric titration was carried out at 27±1°C using Elico digital pH-meter model L-120 with combined glass-calomel electrode. The pH-meter was standardized against buffer solution pH 9.2 and pH 4. The solution of complex titration was prepared by three systems:

i) **Free HClO₄ (A).**
0.2N HClO₄ (5ml) + 1M NaClO₄ (5ml)

ii) **Free HClO₄ + Ligand (A+L).**
0.2N HClO₄ (5ml) + 1M NaClO₄ (5ml) + 0.01N ligand (10ml)

iii) **Free HClO₄ + Ligand + Metal ion (A+L+M).**
0.2N HClO₄ (5ml) + 1M NaClO₄ (5ml) + 0.01N ligand (10ml) + 0.01N transition metal solution (10ml).

RESULTS AND DISCUSSION: Organic ligands of the present investigation are prepared as per scheme 1:

N-[(E)-(2-Nitrophenyl)methylene]isonicotinohydrazid was successfully synthesized through condensation between isoniazid with 2-nitrobenzaldehyde. Formation of Schiff base was confirmed with TLC, single spot observed confirms the formation of product. MP was carried out in open capillary tube and elemental analysis was done which is mention in Table-1. Confirmation of structure was carried out with the help of spectral analysis such as IR, ¹H NMR and ¹³C NMR data mentioned below.

N-[(E)-(2-Nitrophenyl)methylene]isonicotinohydrazid, Nature: solid, yellow color, M.P= 235°C

**IR** (cm⁻¹): 3446 (N-H), 1698 (C=O), 1674 (allic C=O), 1362 (Ar. C=N), 1350 (C-NO₂), 1575 (Ar. C=C).

¹H NMR (400MHz, DMSO-d₆): 12.323 δ N-H, 8.732 δ aliphatic-H, (8.941-9.390) δ [d, 2H, J= 4.4Hz, Pry-H], (8.723-8.713) δ [d, 2H, J=4Hz, Ar-H], (8.186-8.175) δ [d, 2H, J=4.4Hz, Pry-H], (8.167-8.157) δ [T,2H, J= 4 Hz, Ar-H].

¹³C NMR (100MHz, DMSO-d₆): 121.88, (pry-carbon), 124.87, 128.63, 129, 131.04, 133.87 (Benzene C), 140.34 Carbon next to carbonyl carbon, 144.73 (aliphatic N=CH), 148.56 (Carbon next to NO₂), 150.50 (Pry-Carbon next to N), 162.35 (carbonyl carbon).

The pH was 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 determined in 70% ethanol-30% water mixture at 27±1°C. The dissociation of OH⁻ clearly indicated by the titrations (acid +ligand) curves deviated from acid curves at pH 2 and continued up to pH 11.55. The proton-ligand formation number ¹H was determined from the titration curves of acid and (acid + ligand). ¹H defined as hydrogen ions bound to one ligand molecule. This is given by:

\[ n_A = \gamma - \frac{(\epsilon^0 + N) \times (V_2 - V_1)}{(V_0 - V_1) \times T_L^0} \]  (1)

Where γ denote the replaceable H⁺ ion, \( \epsilon^0 \) is concentration of acid, \( T_L^0 \) is concentration of ligand, N is normality of alkali, \( V_1 \) and \( V_2 \) are the volumes of alkali required during the acid and ligand titrations at the given pH and \( V_0 \) is the total volume of the mixture. 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 3.11, metal ion Co(II) at pH 4, metal ion Ni(II) at pH 3.74, metal ion Cu(II) at pH 3.96, and metal ion Zn(II) at pH 4.53 and devia-
tion increased continuously up to pH 10.49, pH 11.55, pH 11.17, pH 10.72 and pH 11.55 respectively. The average number of metal ions associated with the ligand at different pH values was calculated from the metal ions and ligand titration curves using equation as follows:

\[ \bar{n} = \left( \frac{(e^0 + N) \times (V_3 - V_2)}{V_2 + V_3 - \bar{T}_m^0} \right) \]  

Where N, \( e^0 \), V_0 and V_3 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 and \( \bar{T}_m^0 \) is the concentration of the metal ion in the reaction mixture. Metal complexes titration curve was observed 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 the graph 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.

The deviation of (metal+ ligand) titration curves from ligand curve. 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 2.

The protonation constant of ligand and Metal-ligand stability constant are shown in Table 3.

The order of stability constants of complexes with respect to the N-[E](2- Nitrophenyl) methylen] isonicotinohydrazid was found to be Zn(II) > Ni(II) > Cu(II) > Mn(II) > Co(II).

Table 1: Characterization data of organic ligand.

| Ligand structure / mol. Formula | Mol. Wt | M. P. | Elemental analysis |
|--------------------------------|---------|-------|-------------------|
|                                  |         |       | C     | H     | N      |
| [C_{13}H_{10}N_2O_3]            | 270     | 235°C | 57.80 | 3.72  | 20.76  |
|                                 |         |       | 57.78 | 3.70  | 20.74  |

Table 2: The pH titration reading of Acid, Acid + Ligand, Acid + Ligand + Metal at T = 27±1°C, solvent Ethanol-Water (70:30).

| Volume of NaOH (ml) | A     | A+L   | A+L+Mn^{2+} | A+L+Co^{2+} | A+L+Ni^{2+} | A+L+Cu^{2+} | A+L+Zn^{2+} |
|--------------------|-------|-------|-------------|-------------|-------------|-------------|-------------|
| 0.6                | 2.15  | 2.18  | 2.06        | 2.05        | 2.04        | 2.05        | 2.07        |
| 1.2                | 2.27  | 2.24  | 2.1         | 2.09        | 2.08        | 2.09        | 2.11        |
| 1.8                | 2.41  | 2.4   | 2.14        | 2.15        | 2.13        | 2.13        | 2.19        |
| 2.4                | 2.63  | 2.52  | 2.23        | 2.19        | 2.19        | 2.27        | 2.27        |
| 3                  | 3.07  | 2.82  | 2.32        | 2.29        | 2.29        | 2.36        | 2.41        |
| 3.6                | 10.62 | 3.97  | 2.46        | 2.41        | 2.39        | 2.47        | 2.5         |
| 4.2                | 11.14 | 7.97  | 2.86        | 2.65        | 2.86        | 2.95        | 2.8         |
| 4.8                | 11.32 | 9.87  | 6.87        | 3.1         | 3.74        | 3.77        | 3.5         |
| 5.4                | 11.42 | 10.16 | 8.29        | 6.75        | 7.42        | 7.25        | 7.73        |
| 6                  | 11.51 | 10.68 | 9.07        | 7.25        | 8.29        | 7.69        | 8.31        |
| 6.6                | 11.59 | 10.85 | 9.18        | 7.93        | 9.11        | 8.67        | 9.41        |
| 7.4                | 11.66 | 11.1  | 9.38        | 9.18        | 9.34        | 9.22        | 10.23       |
| 8                  | 11.71 | 11.24 | 9.57        | 9.48        | 9.45        | 9.52        | 10.37       |

Table 3: Protonation constant of ligand and Metal-Ligand Stability.

| Metal   | pK   | Stability Constant (logK) |
|---------|------|---------------------------|
| Zn(II)  | 3.95 | 5.49                      |
| Ni(II)  | 3.95 | 4.49                      |
| Cu(II)  | 3.95 | 3.91                      |
| Mn(II)  | 3.95 | 3.66                      |
| Co(II)  | 3.95 | 3.57                      |

CONCLUSION: N-[E](2-Nitrophenyl)methylen] isonicotinohydrazid 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-[E](2-Nitrophenyl)methylen]isonicotinohydrazid follows the
order of stability constants is Zn(II) > Ni (II) > Cu(II) > Mn (II) > Co (II).

Figure 1: The pH titration reading of acid, acid + Ligand, acid + Ligand + Metal at T =27±1°C, solvent Ethanol-water (70:30).

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