Ilorin Journal of Science
Volume 4, Number 1, 2017, pp. 174 – 181 (Printed in Nigeria)
ISSN: 2408 – 4840 © 2017 Faculty of Physical Sciences, University of Ilorin
https://doi.org/10.54908/iljs.2017.04.01.013

ILORIN
JOURNAL OF SCEINCE

ILJS-17-029

Stability constant of some Anti-Tuberculosis metal drug complexes

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Abstract

The formation of Isonicotinic Acid Hydrazide and Pyrazine-2-carboxamide complexes were prepared and analyzed by determining the stoichiometry and stability constant (Spectrophotometric method). The ionic strength used was maintained constant at 0.1 M KNO_3. The stability constants were calculated to be log 61.21 - 254 in Isonicotinic Acid Hydrazide while in Pyrazine-2-carboxamide 55.5 - 274.29. The order of stability constant of the metal to ligand reaction follows this trend: Ni(II) > Cu(II) > Co(II) > Fe(II) > Mn(II) > Zn(II). The order of the stability constant is in agreement with the trend of Electronegativity.

Keywords: Isonicotinic Acid Hydrazide, Pyrazine-2-carboxamide, complexes, ionic strength, stability constant

1. Introduction

Isonicotinic Acid Hydrazide and Pyrazine-2-carboxamide are pro-drug with some therapeutic uses. They are known as a front-line drug for prophylaxis and treatment of tuberculosis. They are very potent chelating agent (Fredrickson *et al.*, 2004; Kolyva *et al.*, 2012). Their coordination to metal ions has significant biological implication (Crisponi *et al.*, 1995; Kozklowski *et al.*, 1992). According to Tella *et al* (2010), metal drug complexes are used as an antidote for the treatment of chronic metal intoxication. Transition metals were found to be at a very low concentration in the environment (Bukhari *et al.*, 2005; Wallace *et al.*, 2001). It has been discovered that the involvement of OH or NH groups in a particular position relative to the -C=N group give more opportunity for increased intramolecular and intermolecular interactions (Berkesi *et al.*, 2003). This is as a result of hydrazones being derived from isoniazid. This help to have more effective biological activities as a result of the interactions with the binding sites.

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From previous research, it has been observed that metal complexes of the hydrazones may behave as models for biological application (Rakesh *et al*., 2009). It has also been shown in the area of bioinorganic chemistry toward metal complexes of the hydrazones. Hydrazones are useful for drug design (Gupta *et al.,* 2008). Tuberculosis is one of the most common diseases causing death (Abdul-Fadl *et al.,* 2011; Da Costa *et al*., 2012).

The aim of this research work is to determine the relationship between the parent ligands and their metal ions: Zn(II), Cu(II), Fe(II), Ni(II), Co(II) and Mn(II) by determining their stability constant. This is to be able to examine their potential as antidotes metal poisoning.

2. Material and Methods

All the reagents used were of analytical grade without further purification. Isonicotinic Acid Hydrazide and Pyrazine-2-carboxamide were obtained from Sigma –Aldrich, United States of America and used without any further purification.

Stoichiometry and stability constant of the complexes

Preparation of ligands solution

Procedure followed by Tella *et al*. (2010) was used in this research work. Fresh stock solution of Isonicotinic Acid Hydrazide and Pyrazine-2-carboxamide were prepared. A known weight of the ligands: Isonicotinic Acid Hydrazide (0.14 g/L in 0.1 M,) and Pyrazine-2-carboxamide (0.12 g/L in 0.1 M) were measured by dissolving them in their appropriate solvents (20 ml of ethanol and 20 ml of mixed acetone-methanol) respectively in ratio in 1:1.

Preparation of metals solution

Solution of 0.05 M of Zn(II), Cu(II), Fe(II), Ni(II),Co(II) and Mn(II) metals (0.07g/L, 0.06 g/L, 0.06 g/L, 0.06 g/L, 0.06 g/L and 2.75 g/L) respectively were prepared by dissolving them in distilled water.

Determination of the Absorbance of the metals - ligands solution

Different solutions were prepared by adding different volumes of 0.05 M of each solution of the metals and the ligands. The ionic strength was maintained at 0.1 M KNO_3 at a pH of 7.4. The absorbance was determined using Ultraviolet spectroscopy (Tella *et al*., 2010).

Stoichiometry Determination

Solution of 0.05 M of the ligands and the metals were prepared. Different mixtures of the metal ions (Y ml) and (30-Y) ml of the ligands were top up to 30 ml of a volumetric flask. Absorbance was determined using Ultraviolet spectroscopy following Job method of continuous variation (Benesi *et al*., 1949; Hill *et al*., 1986). A graph of absorbance against concentration of metal ion divide by concentration of the metal ions and concentration of the ligands were plotted.

Stability Constant Determination

Stability constant of the metal salts and the ligands were determined using Ultraviolet spectroscopy according to Benesi *et al*. (1949). Different solutions of the metals and the ligands were prepared with a constant concentration of metals and variable ligands concentration. The ionic strength was maintained at 0.1 M KNO_3 at pH 7.4. The solutions were stirred continuously and left to stand for 15 minutes according to Tella *et al.* (2010). Absorbance of each solution was determined using Ultraviolet spectroscopy. The equation for the Stability Constant is as shown below:

$M_o/A = 1/\beta\varepsilon_c[1/L_o] + 1/\varepsilon_c$ **.**

A graph of M_o/A against $[1/L_o]$ was plotted in order to determine the stability constant.

3. Results and Discussion

Table 1: Stability Constant data for Metals-Isonicotinic acid hydrzide in solution.

	METAL: LIGAND	**λ (nm)**	**Lo**	**Mo/A X 10^{-4}**	**1/Lo**	**STABILITY CONSTANT (log β)**
ISONICOTINIC ACID HYDRAZIDE	Zn(II)ISO	214	0.01	4.67	100	
		303	0.02	3.30	50	61.21
		377	0.03	2.65	33.3	
		512	0.05	1.95	20	

Fe(II)ISO	187	0.01	5.35	100	
	209	0.02	4.78	50	131.8
	255	0.03	3.92	33.3	
	276	0.05	3.62	20	
Cu(II)ISO	101	0.01	9.90	100	
	116	0.02	8.62	50	158
	123	0.03	8.13	33.3	
	178	0.05	5.62	20	
Ni(II)ISO	214	0.01	4.67	100	
	303	0.02	3.30	50	254
	377	0.03	2.65	33.3	
	512	0.05	1.95	20	
Co(II)ISO	187	0.01	5.35	100	
	209	0.02	4.78	50	135.9
	255	0.03	3.92	33.3	
	276	0.05	3.62	20	
Mn(II)ISO	279	0.01	3.58	100	102
	322	0.02	3.10	50	
	393	0.03	2.54	33.3	
	512	0.05	1.95	20	

M_o=0.01M Equation for determining stability constant of complexes: $M_o/A = 1/\beta\varepsilon_c[1/L_o] + 1/\varepsilon_c$, λ(nm) = Absorbance (A), L_o = Concentration of the ligand, M_o = Concentration of the metal ion, β = Stability constant.

A graph of M_o/A against $[1/L_o]$ was plotted in order to determine the stability constant.

Table 2: Stability constant determination of Metal-Pyrazine-2-Carboxamide in solution

	METAL: LIGAND	λ (nm)	Lo	Mo/A X 10^{-4}	1/Lo	STABILITY CONSTANT (log β)
PYRAZINE-2-CARBOXAMIDE	Zn(II)PY	153	0.01	3.27	100	55.50
		186	0.02	2.69	50	
		211	0.03	2.37	33.3	
		446	0.05	1.12	20	
	Ni(II) PY	186	0.01	2.67	100	
		211	0.02	2.37	50	274.29
		235	0.03	2.13	33.3	
		241	0.05	2.07	20	
	Fe(II) PY	146	0.01	3.42	100	
		154	0.02	3.25	50	194.08
		175	0.03	2.86	33.3	
		219	0.05	2.28	20	
	Cu(II) PY	193	0.01	2.59	100	
		205	0.02	2.44	50	227.00
		243	0.03	2.06	33.3	

	265	0.05	1.89	20	
Co(II) PY	171	0.01	2.92	100	
	189	0.02	2.65	50	197.50
	195	0.03	2.56	33.3	
	265	0.05	1.89	20	
Mn(II) PY	112	0.01	4.46	100	
	318	0.02	1.57	50	156
	323	0.03	1.55	33.3	
	439	0.05	1.14	20	

Mo= 0.05

From the result obtained in stability constants of the complexes in Table 2, it was observed that the order of stability constant of the metal to ligand reaction follows this trend: Ni(II) > Cu(II) > Co(II) > Fe(II) > Mn(II) > Zn(II). The order of the stability constant is in agreement with the trend of Electronegativity. Decrease in order of Electronegativity indicates that Irving-William rule is followed (Irving *et al*., 1953). Ni(II) complex is the most stable while Zn(II) complex is the least stable because the crystal field stabilization energy of zinc is equal to zero and the electronic configuration is d^{10}. The result is in good agreement with Saha *et al*. (1979).

According to the data obtained, the order of stability constant follows this trend: Ni >Cu > Co > Fe > Mn > Zn. The study shows that the stability constant for Pyrazine-2-carboxamide and the metal ions is dependent on the donor site (Nitrogen of pyrimidine group) to the metal ion. It is suggested to be the normal periodic trend in which the ionic radius become reduce from Mn(II) and Zn(II). There is an increase in CFSE starting from Manganese which is zero to Nickel. This enhances the complexes to be more stable. The extra stability of Cu(II) complexes are as a result to Jahn-Teller effect (Saha *et al*., 1979).

4. Conclusion

In conclusion, stability constant were carried out on Pyrazine-2-carboxamide and Isonicotinic acid hydrazide. The order of stability constants of Pyrazine-2-carboxamide follows the trend of electronegativity in which Irving–Williams rule was obeyed. For Isonicotinic acid hydrazide, increase in Crystal Field Splitting Energy was observed from Mn to Zn which helped the metal complexes to be more stable.

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