ISSN: 2455-1848
INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH & GROWTH
VOLUME-I ISSUE-III JANUARY-2016
WWW.IJIRG.COM

SPECTRAL STUDIES OF ISONIAZID (ANTI TB. DRUG) WITH TRANSITION METALS

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Abstract
Stepwise formation constant and corresponding values of free energy change of complexes of Isoniazid (Inz) an important anti-tubercular drug with transition metal ions {V(II), Zr(IV), Cd(II), La(III), Tl(I)} have been determined at 26°C and 36°C and 0.1M ($NaNO_3$) ionic strength. Probable structures of isolated chelates have been assigned on the basis of IR, and spectral data.

Keywords: *Isoniazid (Inz), Mycobacterium, Tuberculosis (Tb)*

Introduction

Structural modification of organic molecule has considerable biological relevance. Metal complexes play an important role in biological activity of drugs. In many cases metal complexes of drugs are more potent than the parent drug. Some physico-chemical property helpful in biological activity. The present paper report the thermodynamic stability constants and free energy change for the interaction of Isoniazid (Inz) with transition metals {V(II), Zr(IV), Cd(II), La(III), Tl(I)} determined by Bjerrum Calvin pH titration technique as adopted by Irving Rosotti at 26°C and 36°C and 0.1M ($NaNO_3$) ionic strength. Probable structures of isolated chelates have been assigned on the basis of IR, and spectral data.

Material and Methods

All the chemicals were used of A.R. and S.M. Grade, solution of metal salts were prepared in millipore water. The metal salt solutions were standardized by appropriate standard methods. Complete study has been carried out by using millipore water.

Isoniazid (Inz) metal complexes were prepared by mixing of Isoniazid (Inz) and metal salt in 1:1 molar ratio and refluxing the mixture for 5-6 hours over water bath. The solution on concentration gave insoluble complex, which was filtered washed and dried (after re-crystallization) in vacuum. The complexes were stored in airtight bottles.

The stoichiometry of the metal chelates have been established by conductometric and potentiometric (pH) titrations, utilizing the monovariation method. Molar conductance was measured on a Systronics digital (model type 306) conductivity bridge. The general experimental procedures employed were carried out with a Systronic type 362 digital pH meter a pH meter with combined glass calomel electrode was used. I.R. spectra (KBr) were recorded on JASCO, FT/IR-470 PLUS, and spectrometer.

The formation constant was determined by Bjerrum Calvin pH titration technique as adopted by Irving and Rossotti. The Bjerrum Calvin pH titration technique was used to determine proton ligand constant of Isoniazid (Inz). The following mixtures (total volume 50ml) were titrated with a carbonate free 0.1 M NaOH solution: (a) 5ml of 0.01M HNO_3. (b)Mixture (a) + 10 ml 0.002 M Inz (c) Mixture (b) + 5ml 0.01 M metal.

The ionic strength of above solutions were maintained to 0.1M by adding required

quantity of 1.0 M $NaNO_3$ solution and the total volume of solution to be titrated was made 50ml by the addition of required volume of Millipore water. The proton legend formation constant and the value of stability constants are recorded in table.

TABLE-1

Proton - lagan stability constant

At 26°C & 36°C and at μ=0.1M ($NaNO_3$)

Ligand	Method	log K^H_1	
		26°C	36°C
INZ	(a)	5.75	5.64
	(b)	5.73	5.62
	(c)	5.71	5.65

(a) Half Integral method (b) Point-wise calculation method

(c) Least Square Method

TABLE-2

Stability constant

INZ-COMPLEXES at 26°C & 36°C and at μ=0.1M ($NaNO_3$)

Metal	Temp	log K_1	log $ß_2$
V (II)	26°C	5.55	5.55
	36°C	4.59	4.59
Zr (IV)	26°C	5.14	5.14
	36°C	4.75	4.75
Cd(II)	26°C	5.74	5.74
	36°C	4.99	4.99
La(III)	26°C	5.44	5.44
	36°C	5.11	5.11
Tl (I)	26°C	5.77	5.77
	36°C	5.38	5.38

TABLE-3

Ligation free energy, enthalpy and Entropy change of inz-complexes

At 26°C & 36°C and at μ=0.1M ($NaNO_3$)

Metal	-ΔG (K.Cal/mole)		ΔH (K.Cal/mole)		-ΔS (K.Cal/mole)	
	26°C	36°C	26°C	36°C	26°C	36°C
V (II)	6.70	5.95	234.22	199.12	21.51	23.55
Zr (IV)	5.37	7.39	212.90	459.31	23.82	49.57
Cd (II)	6.55	8.55	257.47	230.41	22.59	24.99
La (III)	6.55	8.55	272.27	258.31	30.26	26.75
Tl (I)	6.88	7.89	235.78	223.93	23.40	22.89

TABLE-4
Characteristic i.r. frequency of isoniazid (inz)

Sample	N-H Primary		-NH Sec. Bending	Tert. N-Aromatic	vC=O	vC-O	Coord. H2O
	Stretching	Bending					
INZ	3565	1667	1557	1337	1748	1337	846
Vo(II)	3566	1541	1541	1541	1716	1338	964
Zr (IV)	3580	1600	1549	1421	1753	1223	847
Cd (II)	3565	1601	1550	1386	1716	1386	886
La (III)	3556	1691	1548	1367	1725	1419	869
Tl (I)	3565	1683	1540	1374	1732	1396	847

Results and discussion

Metal- Isoniazid (Inz) Interaction

Conduct metric studies of the metal - Isoniazid (Inz) (Drug) equilibrium in solution (binary system) utilizing Nair and Pande's mono variation method indicated formation of two complexes in these systems with metal- Isoniazid (Inz) molar ratio method.

Analysis of the titration curve was carried out according to the procedure of Irving and Rossotti. The pH titration curves in case of Isoniazid (Inz) Ligand before the acid curve indicating that in acidic solutions each molecule of the ligand is in association with one equivalent of proton. This proton should be attached with the lone pair of electrons present on the nitrogen of the ring in the case of Isoniazid (Inz). Isoniazid (Inz) shows one step of acid dissociation due to deprotonation of one secondary amine group.

Representative set of experimental titration curves, obtained according to the sequence for different Metal- Isoniazid (Inz) reveals that below pH 6.7 formations of different M-Inz binary complexes takes place. This is clear from the appeared divergence of each of the 1:1 binary M-Inz titration curve from that of the corresponding free drug curve. Binary complexes are stable up to pH 5-8 in case of different metal ions. Hydrolysis of the complexes leads to the formation of hydroxocomplex species. The nature of the pH titration curves indicates that stepwise complex formation takes place through deprotonation of secondary amine group.

Stability constants

The proton ligand stability constants of the drug (Inz) have been calculated at 26^{o}C and 36^{o}C at 0.1M ($NaNO_3$) ionic concentration utilizing the Irving Rossotti pH titration technique. The value of proton ligand formation constant log K^{H}_{1} are given in (table-1) with increasing temperature ligand (Inz) show dissociation of the species. The metal ligand formation constants are given in (table-2). The values were directly obtained from the formation curve.

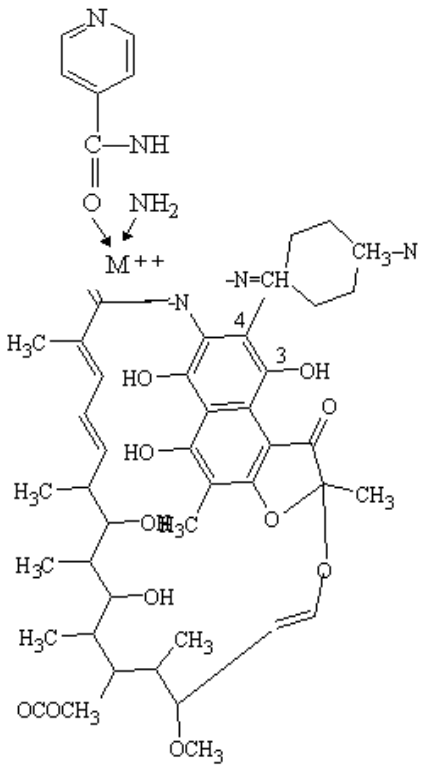
The thermodynamic parameters (ΔG ΔH and ΔS) are calculated at 26^{o}C and 36^{o}C at 0.1M ($NaNO_3$) ionic strength indicate the interaction enthalpy characterized (table-3). The reaction is exothermic in nature as supported by the negative value of free energy change.

In the mixed ligand complex formation when ligands coordinated to the metal ion, the metal atom is introduced into the ligands vibrating system and the infrared spectrum of the coordinated ligand will, thus be different from that of the free ligands. It should therefore, be possible to correlate the change in the spectra with the geometry. The structure of the complex may be determined. The spectra of the complex may differ from that of ligands in (1) bond position. (II) Bond intensity and of appearance of new often weak bonds

and (III) splitting of some of the bonds of free ligands, therefore compare the spectrum of a complex with that of the free ligands and the change interpreted in the light of the structure of the mixed ligand complexes.

The IR date of the isolated binary complex of Inz (table-4) shows that N-H Stretching at 3565^{cm-1} and N-H bending at 1667^{cm-1} vC-O frequency at 1337^{cm-1}. In Binary complex N-H frequency changes 3565^{cm-1} to 3556^{cm-1} and 1667^{cm-1} to 1660^{cm-1}.

The proposed structure of the metal complex is as follows;



Mixed legend complex of Isoniazid + Rifampicin

Acknowledgement

Authors thanks to Department of Chemistry, Govt. MVM, Bhopal for providing all laboratory facilities. Authors are extremely grateful to Lupin Pharmaceutical, Mandideep (Raisen) and HOD Pharmaceutical Lab. Ltd, Ratlam for providing pure samples of drugs, and to RSIC IIT Powai for conducting spectroscopic measurements.

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