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Mixed ligand complexes of Calcium (II) and Magnese (II) with pyrazinecarboxamide and isonicotinic acid hydrazide

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ABSTRACT

Mixed Ligand Metal Complexes of Pyrazinecarboxamide and Isonicotinic Acid Hydrazide prepared by using salts of Ca(II), Mg (II). Stoichiometry of Mixed Ligand Metal Complexes was determined by conductometric titration, which was found in 1:1:1 ratio. These complexes were characterized on the basis of I.R., NMR, Spectroscopy and screened for biological activities.

Key words: Infrared spectroscopy, nuclear magnetic resonance spectroscopy.

INTRODUCTION

Coordination chemistry of Magnese and Calcium has received consideration interest in recent years, mainly due to the realization of the involvement of these elements in many biological process[1,2].

Coordination of organic molecule to metal ions significantly alters the effectiveness of biomolecule. The use of PZA as antitubercular drug was suggested by Kushner & Coworker[3], which is important antitubercular drug effective against slow multiplying bacilli formed in macrophages. The drug shows antitubercular activity in "vitro" at an acidic pH. INH is another antitubercular drug effective as bacteriocidal agent against replicating bacilli and also as bacteriostatic agent against non replicating bacilli, both the drug have tremendous tendency of chelation and due to suitable geometrical arrangement they have property to form protonated species.

With reference to multidrug chemotherapy in 1984 MDR TB (Multidrug resistant) tuberculosis concept was proposed.

EXPERIMENTAL

Synthesis of mixed ligand complexes

The Mixed Ligand Metal Complexes were prepared by mixing aqueous solution of metal salt, pyrazinamide and Isoniazid in 1:1:1 molar ratio and keeping the reaction mixture in hot water bath for about 6 hours. The complexes were filtered, washed with distilled water, dried in vacuum and stored in air tight bottles. All the complexes are soluble in water, ethyl alcohol and acetone but insoluble in Benzene and Carbon Tetrachloride. Analytical data of the complexes are given in Table No. 1.

The stoichiometry of the complex in solution was ascertained by conductometric titration using 20 ml of each ligand (PZA/INH) solution (0.01m) with 0.1 m metal solution. Metal – Ligand – Ligand (M + L + L') constants of various species have been evaluated potentiometrically at 30^0C and 0.1 m ionic concentration by adopting the pH titration technique of Calvin – Bjerrum Titration Method modified by Irrving – Rossoti Method.[4,5]

Metal–Ligand–Ligand (M + L + L') stability constants were calculated with Job's method by

Table 1: Analytical data of mixed-ligand complexes

Complexes	C	H	N	Metal	O
PZA	49.48	3.86	34.00	-	15.03
INH	51.55	5.10	34.14	-	11.67
Mixed Ligand complexes of Ca	41.52	4.52	34.10	12.25	9.98
Mixed Ligand complexes of Mn	34.29	4.30	33.89	16.58	11.19

Table 2: Proton- Ligand stability constant of PZA & INH

Temp. 30^0C μ = 0.1 M

Method	PZA		INH	
	Log K,H	Log K_2H	Log pH	Log K, H
Half ò A method	7.70	6.7	14.37	6.40
point wise	7.65	6.6	14.35	6.84
calculation Linear	7.7	6.7	14.37	6.67
plot method	(7.68)	(6.6)	(14.33)	(6.63)

spectro-photometrically, which is quite adequate with the value obtained by Irriving Rossoti Method.

Metal Ligand stability constant was determined by formation curves by plotting η & p^{L-} ion by using various computational method presented in Table No. 2.

RESULT AND DISCUSSION

I.R. data reveals that the bonding between pyrazinamide and metal ions involves tertiary nitrogen and – NH_2 group to form five membered chelate ring. In case of isoniazid bonding involves – CO and –NH_2 group forming the five membered ring.

Table 3: Stability constants of metal complexes of PZA - INH

Temp. 30^0C μ = 0.1(KNO_3)

Metals	Log K	DG kcal / mole
Ca complex	7.35	- 5.1
Mn complex	7.70	- 5.3

Table 4: Proton nucler, magnetic resonance spectroscopy

Complexes	Solvent	Chemical Shift
PZA (Pure)	DMSO-D6	7.85δ
		8.22δ
		8.72δ
		8.77δ
		9.11δ
PZA (Pure)	D20-DCl	8.44δ
		8.62δ
		8.77δ
PZA-INH+ Ca^{2+}	DMSO-D6	7.85δ
		8.22δ
		8.70δ
		8.88δ
		9.14δ
PZA-INH+Ca^{2+}	D20+DCl	8.48δ
		8.62δ
		8.81δ
PZA-INH-Mn^{2+}	DMSO-D6	7.81δ
		8.82δ
		8.66δ
		9.18δ

Table 5: Effect of Mixed –Ligand Complex of PZA-INH on mycobacterium tuberculosis

Temp.37^{0}C
Time-21 days

Concentration-0.01mg
MIC of PZA-0.10mg
MIC of INH-0.10 mg

S.No.	Compound	CFU Obtained
1.	Pure pyrazinamide (PZA) Control	30 colonies
2.	Pure Isoniazide (INH) Control	40 colonies
3.	INH – PZA – Ca^{2+}	06 colonies
4.	INH – PZA – Mn^{2+}	04 colonies

NMR spectra data also supports that the deprotonation takes places from –$CONH_2$ moiety.

The antitubercular study revealed an effective increase in potency of isoniazid and pyrazinamide when chelated with Mn^{2+},Ca^{2+}. In these cases pronounced decrease in the number of colonies as compared to pure isoniazid and pyrazinamide. The values of log K is also supported for these activity. This is due to low dissociation constant (High stability constant) and shows a strong metal-ligand-ligand bond.

IR spectra of the isolated complexes were recorded on Perkin-Elmer FR spectrophotometer model 337 by the KBR disc techniques. NMR spectra were recorded at Lupin Laboratory,Bhopal.

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