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Research Article

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Potentiometric study of transition metal and rare earth metal complexes with Isoniazid drug in 20 % (V/V) ethanol-water mixture

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ABSTRACT

The interaction of transition metal ions and rare earth metal ions with Isoniazid drug has been investigated in 20% (V/V) ethanol-water mixture at 0.1 M ionic strength at temp 298 K by Potentiometric titration .The data obtained is used to calculate the values of proton- ligand stability constant (pK) and metal-ligand stability constant (logK). It is observed that transition metal ions and rare earth metal ions forms 1:1 and 1:2 complexes.

Keywords: Stability Constant, transition metal, rare earth metal (lanthanide) Isoniazid drug.

INTRODUCTION

The stability of metal complexes with medicinal drugs play a major role in the biological and chemical activity [1, 2] Metal Complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc.[3]Most of the d-block & f- block elements form complexes. There are different kinds of ligand used for complexation. For the present investigation, we selected antibacterial drug isoniazid. Isoniazid is antibacterial agent used primarily as a tuberculostatic. It remains the treatment of choice for tuberculosis. Isoniazid (Laniazid, Nydrazid), has IUPAC name pyridine-4-carbohydrazide also known as isonicotinyl hydrazine (INH), is an organic compound that is the first-line medication in prevention and treatment of tuberculosis. The compound was first synthesized in the early 20th century, but its activity against tuberculosis was first reported in the early 1950s, and three pharmaceutical companies attempted unsuccessfully to simultaneously patent the drug Isoniazid is a prodrug and must be activated by a bacterial catalase peroxidase enzyme that in M. tuberculosis is called KatG. KatG couples the isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex. This complex binds tightly to the enoyl-acyl carrier protein reductase known as InhA, thereby blocking the natural enoyl-AcpM substrate and the action of fatty acid synthese. This process inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall. A range of radicals are produced by KatG activation of isoniazid, including nitric oxide, which has also been shown to be important in the action of another antimycobacterial prodrug. Nlhjhjmmmopiuk Isoniazid is bactericidal to rapidly dividing mycobacteria, but is bacteriostatic if the mycobacteria are slow-growing. Isoniazid reaches therapeutic concentrations in serum, cerebrospinal fluid, and within caseous granulomas. It is metabolized in the liver via acetylation. Two forms of the enzyme are responsible for acetylation, so some patients metabolize the drug more quickly than others. The physical properties of medicinal drug Isoniazid is shown below[4,5]

Molecular weight = 137.13g/mol
Phase = solid (at STP)
M.P. = 171.4ºC
Refractivity = 37.46
Polarizability = 13.21
Solubility = Soluble in water 140mg/ ml or 3.49e+01gm/lit

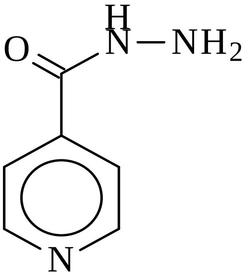

fig1: Structure of Isoniazid ($C_6H_7N_3O$)

Literature survey reveals that a very few researchers have done such type of work using medicinal drug as a ligand.[6-18] Therefore we decide to study stability constant of binary complexes of Isoniazid drug with transition metal ions Fe(III),Co(II),Ni(II),Cu(II),Zn(II),Cd(II) and rare earth metal ions La(III), Ce(III), Nd(III),Sm(III),Gd(III),Tb(III)&Dy(III) using pH metry.

EXPERIMENTAL SECTION

Materials and Solution: The ligand Isoniazid is soluble in double distilled water. NaOH ,$NaClO_4$,$HClO_4$ & metal salt were of AR grade .The solutions used in the potentiometric titration were prepared in double distilled water .The NaOH solution was standardized against oxalic acid solution (0.1M) and standard alkali solution was again used for standardization of $HClO_4$. The metal salt solutions were also standardized using EDTA titration.[19] All the measurements were made at 298 K in 20% (V/V) ethanol-water mixture at 0.1 M $NaClO_4$ strength The thermostat model SL-131 (Adar Dutt and co(India) pvt.ltd. Mumbai) was used to maintain the temperature constant. The pH measurement were made using a digital pH meter model Elico L1- 120 in Conjunction with a glass and reference calomel electrode (reading accuracy ±0.01 pH units) the instrument was calibrated at pH 4.00 ,7.00 and 9.18 using the standard buffer solutions .

Potentiometric procedure: For evaluating the protonation constant of the ligand and the formation constant of the complexes in 20 % (V/V) ethanol-water mixture with different metal ions. We prepare the following sets of solutions.

(A) $HClO_4$ (A)
(B) $HClO_4$+ Isoniazid drug (A+ L)
(C) $HClO_4$+ Isoniazid drug+ Metal (A+ L+ M)

The above mentioned sets prepared by keeping M: L ratio, the concentration of perchloric acid and sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was made up to 50ml with double distilled water and the reaction solution were potentiometerically titrated against the standard alkali at temp 298K.

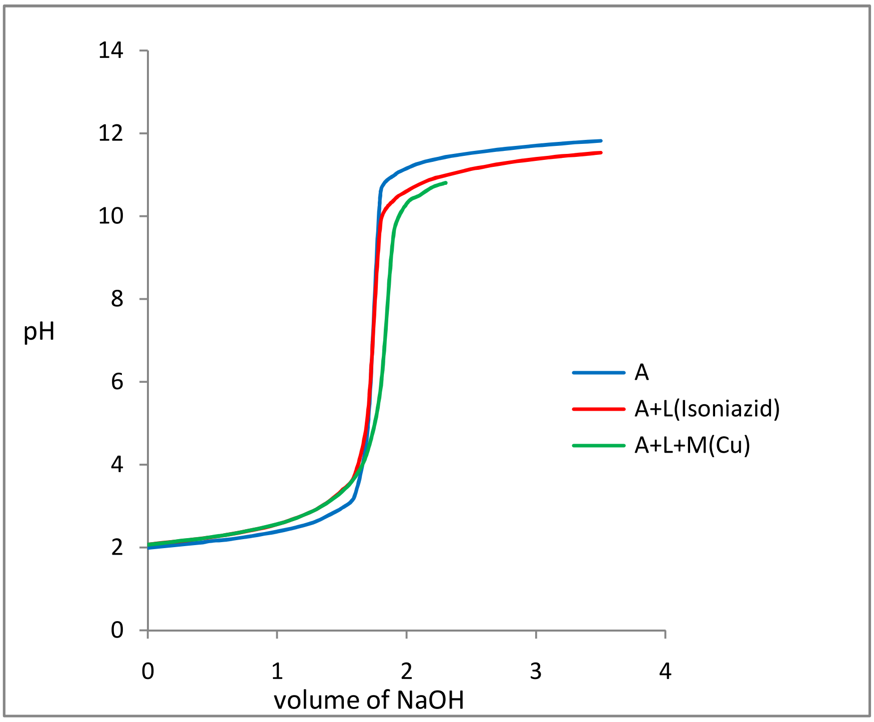

fig2: Variation of pH with volume of NaOH for Cu metal

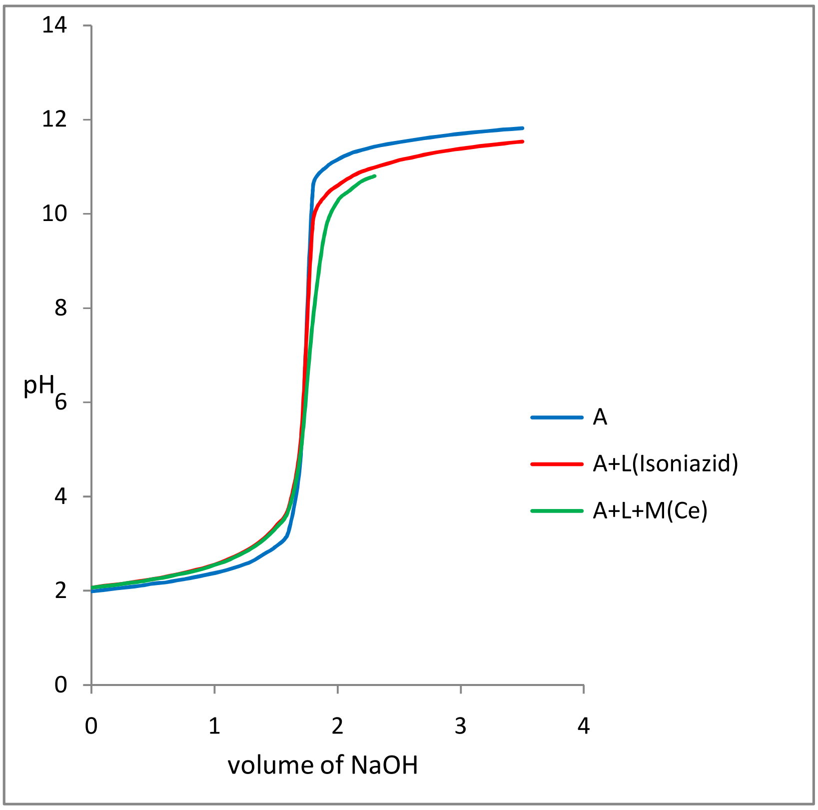

Fig3: Variation of pH with volume of NaOH for Ce metal

Table-1 Proton-ligand stability constant and Metal-ligand stability constant of transition metal ions with Isoniazid drug at 0.1M ionic strength in 20 % (V/V) ethanol-water mixture.

Metal ion	Proton-ligand stability constant	Metal-ligand stability constant			$LogK_1/LogK_2$
		$LogK_1$	$LogK_2$	$Log\beta$	
Fe(III)	$pK_1=3.192$ $pK_2=10.65$	12.14	10.50	22.64	1.156
Co(II)		5.415	4.370	9.785	1.239
Ni(II)		5.595	4.710	10.30	1.187
Cu(II)		9.011	7.521	16.53	1.198
Zn(II)		5.891	4.954	10.84	1.189
Cd(II)		5.273	4.229	9.502	1.246

Table-2 Proton-ligand stability constant and Metal-ligand stability constant of rare earth metal ions with Isoniazid drug at 0.1M ionic strength in 20 % (V/V) ethanol-water mixture.

Metal ion	Proton-ligand stability constant	Metal-ligand stability constant			$LogK_1/LogK_2$
		$LogK_1$	$LogK_2$	$Log\beta$	
La(III)	$pK_1=3.192$ $pK_2=10.65$	6.388	4.952	11.340	1.289
Ce(III)		6.477	5.249	11.726	1.233
Nd(III)		7.181	5.643	12.824	1.272
Sm(III)		7.624	6.745	14.369	1.130
Gd(III)		7.007	5.622	12.629	1.246
Tb(III)		7.410	6.597	14.007	1.123
Dy(III)		7.528	6.711	14.239	1.121

RESULTS AND DISCUSSION

Proton ligand stability constant (pK) of Isoniazid drug was determined by point wise calculation method as suggested by Irving & Rossotti. Metal- ligand stability constant (logk) of transition metal ions and rare earth metal ions with Isoniazid drug were calculated by point wise and half integral method as suggested by Irving & Rossotti[20]. For the present investigation we have studied the stability constants of divalent transition metal ions except Fe which is in trivalent state. Since we got $n^{-}A$ between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 Complex formation .It will be interesting to study the solid state formation of such complex and to study its biological activity ,which is included in our future plan.

Till now very less or almost no work is observed on the complexation behavior of lanthanide with medicinal drug such as Isoniazid. As Lanthanides are having less capacity to form complexes still there stability constant values (log β) are comparable with that of transition metal ions. This might be due to the presence of diffused f-orbital, the trivalent charge present and effective nuclear charge .etc. Observed trend in the order of stability constant of **transition metal ions** was **$Fe^{3+ >}$ $Cu^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Cd^{2+}$**

which are accordance with the William -Irving series [21] and the order of stability constant of **rare earth(lanthanide) metal ions** was **$La^{3+} < Ce^{3+} < Nd^{3+} < Sm^{3+} > Gd^{3+} < Tb^{3+} < Dy^{3+}$** The graphs of logk vs. atomic number, atomic radii, were plotted & found in good agreement with earlier studies. The ratio of $logk_1/ logk_2$ is positive & greater than one in all cases .This implies that there is little or no steric hindrance to the addition of secondary ligand molecule.

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