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Interaction of some anti tuberculosis drugs with transition metal ions

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ABSTRACT

Stability constant of some transition metals like Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes with pyrazinamide, isoniazid and ethambutol-HCl (22'-(1,2-Ethane dihydiimino)-bis-1-butanol) etb ,an antibacterial drugs have been evaluated at 30 °C & fixed 0.1 M ($NaClO_4$) ionic strength in aqueous medium pH metrically . Proton ligand stability constants & metal ligand stability constants were determined by using Calvin Bjerrum titration technique as modified by Irving & Rossoti. Stability constants were discussed in terms of order of stability, basicity of ligands & correlated with atomic number, ionization potential, electronegativity and reciprocal of ionic radii.

Key word: Stability constant, ligands, ionic strength , basicity, antibacterial drugs etc.

INTRODUCTION

The stability of metal complexes with medicinal drugs play a major role in the biological & chemical activity[1,2] .Metal exhibit a preference for particular ligand during interaction like ligands. This has important medicinal implication when one considers that most drugs contains group that can acts asa ligands. Attempts to measure metal ligand selectivity in terms of relative strengths of metal ligand bonds are based on stability constants. Generally metal complexes play a very important role in biological process such as metalloproteins, metalloenzymes, storage, transport, detoxification etc.[3] Literature survey reveals that a very few researchers have done such type of work[4].

The present paper describes interaction of pyrazinamide(pyrazine carboxamide) pyr, isoniazid (isonicotinic acid hydrazide) iso & ethambutol-HCl (22'-(1,2-Ethane dihydiimino)-bis-1-butanol) etb ,an antibacterial drugs (anti tuberculosis drugs**)** with some transition metal like Mn (II), Co(II), Ni(II), Cu(II) & Zn(II) ions in aqueous solution at fixed ionic strength (I= 0.1M $NaClO_4$) at 30°C through pH metric study.

EXPERIMENTAL

All the chemicals were A. R. grade. Pure drugs are obtained as a gift samples. All these solutions were prepared in double distilled, CO_2 free water having pH in between 6.70 to 6.90. The solutions of metal nitrates, free acid ($HClO_4$), NaOH were standardized before use by known methods[5] & used as afresh.

pH measurement were made with Elico pH meter(model. LI-120,Elico pvt. Ltd, Hyderabad, Acurracy 0.01) with combined glass electrode. All the solutions were allowed to attain equilibrium at

30 ^{0}C & titrated with 0.1 M carbonate free NaOH solution. Required amount of $NaClO_4$ (1 M) is added to maintain 0.1 M ionic strength.

The following three sets of solutions were titrated separately with NaOH(0.1M) . Initial Volume of each set was kept 50 ml.

- Free acid ($4x10^{-2}$) + $NaClO_4$ (1 M)
- Free acid ($4x10^{-2}$) + Ligand($4x\ 10^{-3}$) + $NaClO_4$ (1 M)
- Free acid($4x10^{-2}$) + Ligand ($4x\ 10^{-3}$) +Metal ($2x10^{-3}$) + $NaClO_4$ (1 M)

The data obtained for each titration is plotted as a volume of NaOH added vs pH .

Proton ligand stability constant (pK^H), metal ligand stability constants(LogK) were calculated by pointwise calculation method & half integral method.

RESULTS AND DISCUSSION

Proton Ligand Stability Constant (pK^H)

The average number of proton associated with ligand (nA) was determined from free acid & ligand titration curve . These nA values were used to determine pK^H values by pointwise calculation method as well as half integral method(plot n A vs pH)[6]. pK^H values were also checked by linear plot method(lognA/1-nA) & was found in good agreement & given in table 1.

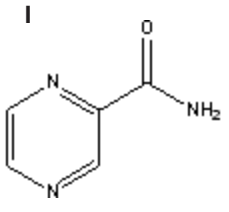
Table 1: Proton ligand (pK^H)and Metal ligand stability constants(LogK) of Mn(II) Co(II) Ni(II) Cu (II) and Zn(II) complexes with pyr, iso and etb drugs in aqueous solution at 30 ±1 ^{0}C, Ionic strength =0.1M ($NaClO_4$).

Drugs	pK_2^H	pK_1^H	LogK				
			Mn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)
Pyr	6.71	-	3.77	3.81	4.34	4.70	4.00
Iso	3.32	.80	4.63	4.66	5.11	6.52	5.71
Etb	6.48	-	4.44	4.62	4.68	6.14	4.47

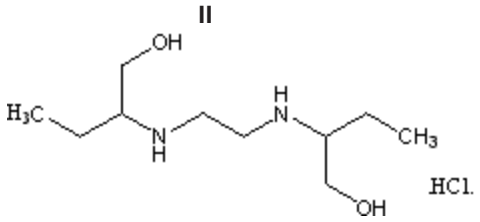
It is found that pyrazinamide & ethambutol-HCl gives only one pK^H due to deprotonation of only one proton during complexation . In general ligands can be represented as HL & dissociated as $HL \rightleftharpoons H^+ + L^-$. Unlike above , isoniazid ligand gives two pK^H values due to two dissociable protons. One may be from (- NH_2) & other be from (:Na") group.The pK^H values indicates that pyrazinamide has strong basic strength than etb. & iso. This might be due to inductive & mesomeric effect of carbonyl group and availability of lone pairs of electrons of pyrazine nitrogen atoms (pyr>Etb>Iso.). In ethambutol HCl it is decreased due to steric effect and in isoniazid found weak due to strong electron withdrawing (-CONH) group[7].

Metal Ligand Stability Constants(LogK)

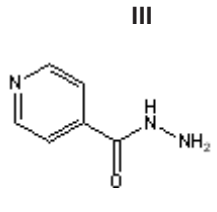
LogK were calculated for Mn(II), Co(II), Ni(II), Cu(II)and Zn(II) transition metal ions by pointwise calculation method as well as half integral



PYR



ETB



ISO

method (n- vs pl) . The values of n-(metal ligand formation number) & pl(free ligand concentration) were calculated by Irving Rossoti expression [8]. The logK values of transition metal ions with all ligands are given in table-1.

The low values of stability constants show that the interaction of drugs with metal ions is ionic[9]. The pH of hydrolysis was determined for each metal ion to know complex formation before hydrolysis of metal ions. Considerable displacement of metal complex curve from reagent curve along volume axis is an evidence for complex formation.

The highest value of n at the pH of precipitation was around one, indicating the formation of 1:1 complex for all metal ions. Further with the use of very dilute solution of metals, possibility of formation of polynuclear complexes may be ruled out.

Irving & Williams plotted logK vs atomic number of Mn(II)……Zn(II) & showed that stability increases with increasing atomic number up to the end of transition series and then falls at zinc. It was tested by plotting logK vs atomic number and found that order of stability constants are in accordance with the Irving & Williams series [Mn(II) ‹ Co(II) ‹ Ni(II) ‹ Cu (II) › Zn(II)].

This order is particularly valid for most oxygen & nitrogen donar ligands[10]. The order of stability constant for all the three ligands are as follows

PYR = Mn(II) < Co(II) ‹ Ni(II) ‹ Cu (II) › Zn(II)
ISO =Mn(II) < Co(II) ‹ Ni(II) ‹ Cu (II) › Zn(II)
ETB= Mn(II) < Co(II) <Ni(II) ‹ Cu (II) › Zn(II). The plot of logK vs Atomic No. is shown in fig-1.

Plot of logK of various metal ions with second ionization potential [11] , electro negativity, & reciprocal of ionic radii were drawn and results were found in quite good with that observed by earlier worker [12]. From table 1 it is clearly found that order of stability of metal complexes for all three drugs follows the order of basic strength of ligands i.e. logK=pyr>etb>iso.

Low values of pK^H indicate that these drugs are complexes forming species around 7.00 pH which would be optimum physiological conditions. This may favor binding of drugs with nucleic acid of cell via transition metal in the human body and this may affect the structure and function of nucleic acid which helps in the transportation of drugs to the site of its physiological action [13]

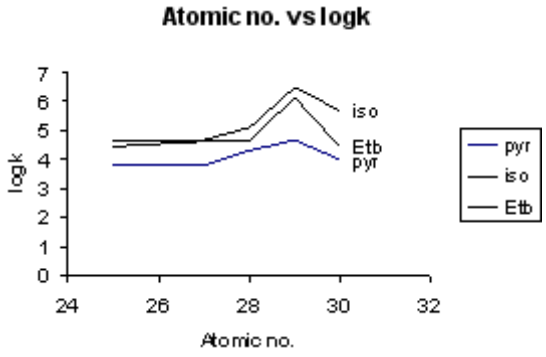


Fig. 1: curves showing atomic number vs logK of transition metals (Mn(II) Co(II) Ni(II) Cu (II) Zn(II)for various ligands

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REFERENCES

1. Thomas G, Medicinal Chemistry- John Wiley & Son Ltd. London 256 (2003).
2. (a). Mukherjee G.N & Ghosh T.K., *Indian J. of Chem.,* 30 A 1033-1037 (1991).
(b) Mukherjee G.N. & Ghosh T.K., *Jour. of Ind. Chem. Soc,* **68**: 194-196 (1991).

(c) Magare B.K.,Farooqui M.N. and Ubale M.B.,*Natl Acad Sci Lett* **31**(11& 12): 353 (2008).

3. Vogels I Text Book Of Quantitative Chem. Analysis, 6th Ed, Pearson Edu. Ltd. Singapore.
4. Irving H & Rossoti H.S., *J Chem. Soc,* 3397 (1953).
5. Peter Sykes "A Text Book Of Reaction Mechanism", Orient Longman, New Delhi, 65-76 (1982,)
6. Irving H. and Rossoti H.S. *J., Chem, Soc*., 2904 (1954)
7. Purushottam B. Chakrawarti, B. Srivastava,& B. L. Vijayvargia. *J. Ind. Chem., Soc*, **70**: 158 (1993).
8. Irving H. and Williams R.J.P., *J., Chem, Soc.,* 3192 (1953).
9. Irving H. and Williams R.J.P., *Nature*, 162 and 746 (1946).
10. Martell A.E. and Calvin, " Chemistry Of Metal Chelate Compounds", Prentice, Hall, New York. (1956) , Calvin M.and Melchoir N.C., *J. Amc. Chem. Soc*. **70**: 3270 (1948).
11. Chakrawarty P.B. *et. al, Ind J Chem.,* **19**A: 84 (1980).