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METAL –CHELATOR THERAPY : STABILITY CONSTANTS OF TRANSITION METAL COMPLEXES OF PYRIMIDINE AND SULPHONAMIDE DRUGS

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ABSTRACT

Stability constant of metal complexes of pyrimidine and sulphonamides drugs were determined using spectrophotometric method. Stability constants of the complexes were determined at 25°C. Ionic strength was maintained constant using 0.1M KNO_3. Stoichometry of the complexes by Job's method showed that metal-drug ratio is 1 : 2. For the metal salts, the order of stability constant (β) was found to be Cu (II) > Fe (III) > Ni (II) > Co (II) > Zn (II) in accordance with lrving- Williams series. The overall stability constants (β) were found to be log 10.68, 5.5 and 4.8 for trimethoprim, sulphadiazine and sulphadimidine, respectively. The order of stability constant follows this trend: Trimethoprim > Sulphadiazine > Sulphadimidine. The stability constant data revealed that this ligand may be used as antidote or chelating agent for medical treatment of metals overload or poisoning.

Key words: Stability constant, Spectrophotometric, Pyrimidine, Sulphonamides, Job's method.

INTRODUCTION

Metal-drug complexes have been used as antidote since 1945, for chronic metal intoxication arising from therapy or household contamination or to hasten excretion of radioactive element.

These antidotes circulate in the blood stream without causing much depletion of the body's essential heavy metals[1]. Transition metals are non-essential heavy metals that are normally present in very low concentration in our environment. However, due to industrial uses of some of these metals, some people can be exposed to too much higher concentrations as a result of which they suffer many serious diseases[2,3]. Further more, diseases release

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metals into the blood stream. The concentration of these metals in blood and urine in human beings can be reduced by ligand therapy[4]. A lot of ligands have been used as antidote to combat metal poisoning. Dimercaptol is used to counter poisoning by compounds of gold and mercury[5]. The antidote is given intramuscularly every 4 hrs during the first day. Not only is the toxic nature of these elements masked by dimercaptol but they are excreted by the kidney. Bessman *et al.*[6] reported the use of calcium EDTA as an effective remedy for lead poisoining . The non-toxic penicillamine is effectively used to remove excess copper in patients suffering from Wilsons disease[7]. The use of ascorbic acid as a possible antidote for iron overload was demonstrated by Key Pour *et al.*[8] in reaction of ferric iron with ascorbic acid. Claim *et al.*[9] reported the use of desferrioxamine as potential iron chelators in condition related to iron overload. In order to investigate the metal- chelating ability of the ligands, stability constant of the compounds are determined. The stability constant depends on several parameters such as the electronegativity, hard or soft of the donor atoms in liquid structure, topology of ligand and the ionic radial, charge, hard or soft of the metal ion and its atomic number.[10]

This work is aimed at investigating the interaction of pyrimidine and sulphonamides drugs with some transition metals by determining their stability constants in order to assess their potentiality as antidotes for metal –overload or poisoining.

EXPERIMENTAL

All the chemicals were of analytical grade quality and their solutions were prepared in bidistilled water. Trimethoprim, sulphadiazine and sulphadimidine (Fluka, Sigma and Aldrich) were used without any additional purification. pH measurements of the analytes were made on an Elico pH meter (LI – 10) using glass and calomel electrodes. $CuCl_2.2H_2O$, $CoCl_2.6H_2O$, $FeCl_3.6H_2O$, $NiCl_2.6H_2O$ and $ZnCl_2$ were used as metal ion sources. UV-Vis spectra were obtained on Aquamate v4.60 Spectrophotometer.

Procedure

Determination of composition and stability constants of the complexes

Preparation of stock solution of ligand

Fresh stock solution of 5×10^{-2}M of sulphadiazine (SAZ), sulphadimidine (SAD) and trimethoprim (TMP) were prepared by dissolving the accurately weighed amount of SAZ (12.5 g/L in 0.1M NaOH), SAD (13.9 g/L in 0.1 MNaOH) and TMP (14.5 g/L in methanol).

Preparation of stock solution of metal salt

Fresh stock solution of 5 x 10^{-2}M of metal salt (Fe^{3+}, 13.5 g/L; Co^{2+}, 11.9 g/L; Ni^{2+}, 11.2 g/L; Cu^{2+}, 8.5 g/L; Zn^{2+}, 6.8 g/L) were prepared by dissolving accurate amount of metal salts in appropriate volume of water or methanol.

Distilled water was used to dissolve all the metal salts for preparation involving sulphadiazine and sulphadimidine, while the methanol was used for trimethoprim.

Preparation of working solution

Dilute solution of the metal ions and drug solution under study were obtained by appropriate dilution of the stock solution. They were freshly prepared less than 5 hours before use.

Determination of the λ_{max} of the metal-ligand solution

The procedure described by Lee *et al.*[11] was modified and adopted.

A number of solutions were made by mixing different volumes of 8.00 x 10^{-3}M solution of each of the metal salts and 8.00 x 10^{-3}M of standard solution of each drug. The pH was adjusted to 7.4 and ionic strength was maintained constant using 0.1M KNO_3 at room temperature. The absorbance were scanned between 200-1100 nm to determine their λ_{max} using UV-Visible Spectrophotometer Aquamate V.60.

The absorption maximum, (λ_{max}) of the mixtures of metal ion and the drugs are shown in Table 1.

Determination of stoichiometry

Job's method of continuous variation was used[12,13]. Solutions of metal ions (M) and ligand, each 8.00 x 10^{-3}M were prepared and a series of mixtures containing X mL of the metal ion solution and (50 - X) mL of the ligand solution were made up to 50 mL volumetric flask. The absorbance of solution was taken at λ_{max} previously determined using UV-Visible Spectrophotometer Aquamate V4.60.

A plot of absorbance versus concentration of metal ion/metal ion plus ligand [(M)/(M)(L)] was drown.

Table 1: Stability contant data for various metal ligand systems in solutions

Ligands	Metal : Ligand	λ_{max} (nm)	M : L	Stability constant (log β)
Trimethoprim	Cu (II) TMP	650	1 : 2	11.27
	Fe (III) TMP	660	1 : 2	10.99
	Zn (II) TMP	255	1 : 2	10.00
	Ni (II) TMP	645	1 : 2	10.75
	Co (II) TMP	650	1 : 2	8.92
Sulphadiazine	Cu (II) SAZ	640	1 : 2	6.31
	Ni (II) SAZ	652	1 : 2	5.43
	Fe (III)SAZ	410	1 : 2	5.93
	Co (II) SAZ	540	1 : 2	5.29
	Zn (II) SAZ	274	1 : 2	3.92
Sulphadimidine	Cu (II) SAD	635	1 : 2	5.43
	Ni (II) SAD	675	1 : 2	5.03
	Fe (III) SAD	415	1 : 2	5.19
	Co (II) SAD	535	1 : 2	4.62
	Zn (II) SAD	282	1 : 2	4.20

Determination of stability constant

The stability constants of metal ions (Co^{2+}, Cu^{2+}, Zn^{2+}, Ni^{2+}, Fe^{3+}) with ligand (SAD, SAZ and TMP) were determined spectrophotometrically using the modified procedure of Hilderbrand and Benesi[13] as described by Lamsa *et al.*[14] & Rose and Drago[15]. A series of seven solutions were prepared with a constant concentration of metal ion [M_o] and variable ligand, [L_o] concentration at pH 7.4 with ionic strength (0.1M KNO_3). The reaction mixture was stirred continuously and allowed to stand for 15 minutes. The absorbance of each of the mixtures was taken at λ_{max} previously determined using UV-Visible Spectrophotometer

Aquamate V4.60. The stability constant, β was determined using Hilderbrand and Benesi equation[13].

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

Plot of M_o/A versus $1/L_o$ gives the $1/\varepsilon_c$ and slope $1/\beta\varepsilon_c$ from which β (stability constant) can be evaluated as shown in Figures 1-3.

RESULTS AND DISCUSSION

Stoichiometry of the complexes were determined from the plot of absorbance versus mole fraction. Job's method[12] was used to confirm the composition of the complexes. The results from Job's plot showed that Metal : TMP, Metal: SAZ and Metal: SAD metal to drug ratio is 1 : 2

Furthermore, the stability constants of the complexes of the drug were evaluated. The values of the stability constant (β) are calculated using Hilderbrand-Benesi equation[13] The Hilderbrand-Benesi plot (M/A vs. $1/L_o$) were linear. (Figures 1-3).

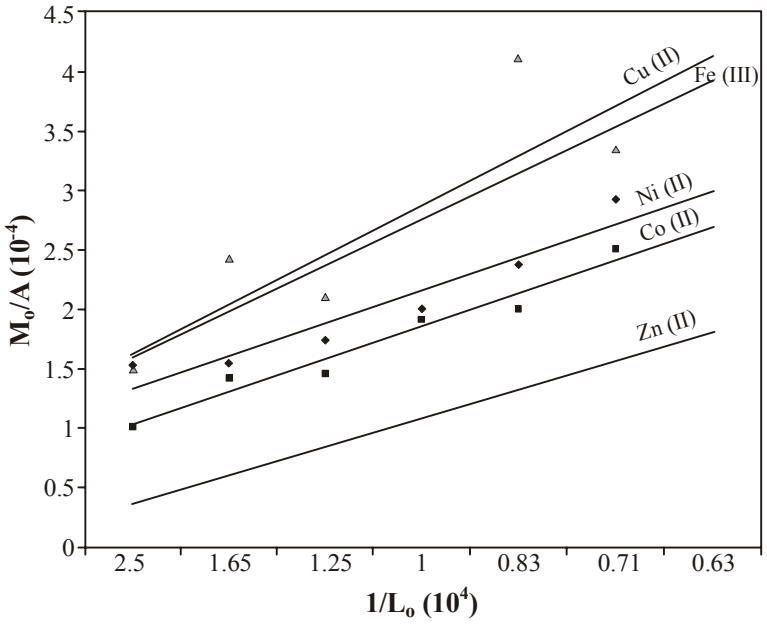

Fig. 1: Plot of stability constant data of interaction of metal ions with sulphadimidine

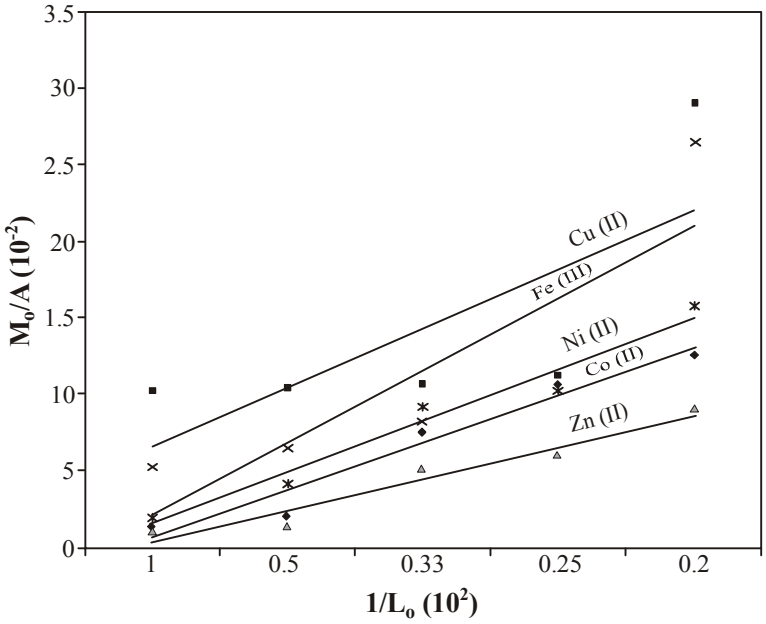

Fig. 2: Plot of stability constant data of interaction of metal ions with trimethoprim

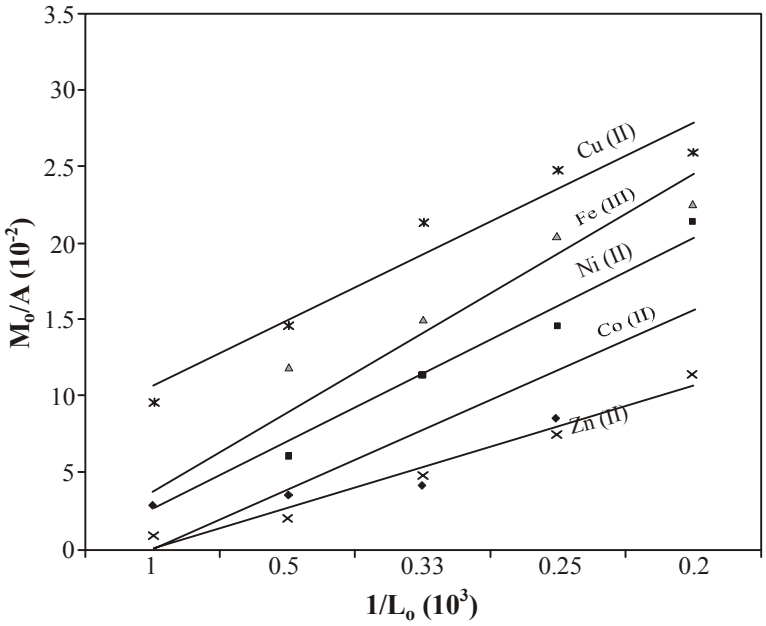

Fig. 3: Plot of stability constant data of interaction of metal ions with sulphadiazine

From the results of stability constants (Table 1) the order of stability constant and hence, reactivity of the ligands toward metal follows the trend Cu (II) > Fe (III) > Ni (II) > Co (II) > Zn (II). The stability constants are inversely proportional to the ionic radii of metals.

The order indicates that β values increases with decreasing ionic radius of the metals. The gradual decrease clearly showed that Irving-William rule[16] is strictly obeyed for all the complexes in solution. The most stable are the Cu (II) complexes and this is due to Jahn-Teller distortion. The Zn (II) complexes are the least stable and the reason for this is consistent with the fact that their CFSE = 0, Zn is d^{10} system. This finding is in agreement with the literature[17].

For example; the stability constant $\log^{\beta}$ of Cu (II)–SAZ, Fe (III)–SAZ, Ni (II)–SAZ, Co (II)–SAZ and Zn (II)–SAZ are 5.43, 5.19, 5.03, 4.62 and 4.20, respectively. The data also reveals that Fe^{3+} formed more stable complex with all the ligands compared to other metal ions except for Cu (II).The higher stability of Fe^{3+} complex of the drugs may be explained on the basis of differences in the charge of the metal ions. The high positive charge on the iron permits a closer approach of the ligand and better electrostatic attraction. This resulted in the formation of more stable complex with the ligands. However, a general rule is that trivalent metals form stronger bonds than divalent and monovalent ions[18]. This result further validate Irving and Rossotti[19] findings and confirmed that the basicity of the ligands is one of the factors governing the stability of chelates for a series of closely related ligands. The roles of basicity of the ligand and charge on metals as they affect stability constant are emphasized.

The stability constants of Cu (II), Fe (III), Ni (II), Co (II) and Zn (II) complexes of trimethoprim are compared with that of sulphadimidine and sulfadiazine complexes. It can be seen in Table 1 that the average stability constant (β) for the ligands were found to be log β 10.68, 5.5 and 4.8 for trimethoprim, sulphadiazine and sulphadimidine, respectively. The values of β show the order of stability and hence, reaction of the drug metals used to be Trimethoprim > Sulphadiazine > Sulphadimidine. The extra stability of trimethoprim with metals ion compared to other sulpha ligands is mainly due to high basicity of pyrimidine nitrogen and the presence of electron donating group (CH_3O) in trimethoprim molecule. The lower stability constant observed for the two sulfa drugs as compared to trimethoprim may be due to the effect of electron withdrawing group SO_2NH in the formers, which increases the acidity of NH amide.

Comparison of stability constant of sulphadiazine complexes with sulphadimidine indicates that the former is more stable than the latter probably due to the presence of electron withdrawing groups (CH_3) in the molecule of sulphadimidine, which reduces the stability[20].

CONCLUSION

The stability constant of the complexes were evaluated by method of Benesi-Hilderbrand. The highest stability constant was obtained for copper (II). This study established the affinity of these drugs toward copper (II) in contrast to other metal ions.The stability constants were found to be decreasing in the following order : $Cu^{2+} > Fe^{3+} > Ni^{2+} > Co^{2+} > Zn^{2+}$. The stability constants are inversely proportional to the ionic radii of metal ions. This finding is in agreement with lrving-Williams order. Inspection of data revealed that the order of stability constant and hence, reactivity towards metal ions is as follows. Trimethoprim > Sulphadiazine > Sulphadimidine, The trend is consistent with electron releasing, withdrawing effect and basicity of the ligand in the heterocyclic ring. This suggests that the ligands used in this study are good chelator agents and these drugs complexes can perhaps, be possible agents for the prevention of heavy metal poisoning in biological system.

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