Spectroscopic Study of Cu-Cimetidine Complex

R. A. JAMAL*, U. ASHIQ, AND Z.T.MAQSOOD
Department of Chemistry, University of Karachi, Karachi.

(Received 20th August, 2002, revised 15th March, 2003)

Summary: The interaction of Cimetidine with Copper was studied. An effective interaction with Copper was found during study. The formation constants and mole ratio of the resultant complex between Cimetidine and Copper was determined. Mole ratio was found to be ML_2 and M_2L in different conditions. Log βvalues of these complexes were 6.43 and 7.21 respectively.

Introduction

Cimetidine is used for the treatment of endoscopically or radiologically confirmed duodenal ulcers. It is also used in the treatment of pathological hypersecretory conditions. Preliminary studies also suggest that this agent may be effective in stress ulcers, peptic esophagitis and upper gastrointestinal bleeding. Cimetidine has a pka of 6.96. It competitively inhibits the action of histamine on the H_2 receptors of parietal cells, reducing gastric acid out put and concentration [1]. The most common side effects of Cimetidine are headache, dizziness, diarrhea and muscular pain. Cimetidine inhibits cytochrome P-450 and can slow metabolism of several drugs for example warfarine, quinidine and imipramine [2].

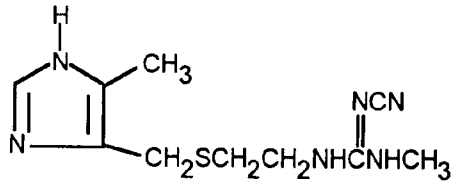
Metals play a vital role in a living system. It has been found that the activity of the biometals is very often attained through formation of complexes with different bioligands where the thermodynamic and kinetic properties of the complexes govern the mode of biological action. The catalytic roles, selectivity and specificity depend significantly on the properties of co-ordination compounds [3].

Copper is one of the trace element essential to the healthy life of many plants and animals [4-8]. Human diet usually includes between 2 to 5 mg of Copper per day [9].The adult body contain between 100 and 150 mg of Copper, the muscle mass having 64 mg, bones 23 mg and the liver 18 mg [10].

Copper (II) usually forms stable complex with N, O and S donor ligands for example Cu (II) makes square planar complex with ethylenediamine and bipyridine. In addition to the hexa aquo ion, the square planar such as [Cu $(acet)_2$] also forms. The biologically important imidazole system apparently behaves as a typical monodentate amine and in complex of the type Cu $(L)_4 X_2$ (X= I, Cl, NO_3) the ligand occupies four coplanar bonds around Copper, the anion making up the usual distorted octahedral arrangement [11-12].

Cimetidine have an imidizole ring with replaceable hydrogen. The log k value of this hydrogen is 6.96. Cimetidine have two parts, one is pentagon with two nitrogen at alternate corners and second is branched. Cyclic part has two nitrogen in which one nitrogen have a hydrogen. Long chain attached with the ring have four nitrogen and one sulphur group (Fig a).

So Cimetidine may behave as a poly dentate ligand and it can accommodate more than one metal.



2-Cyano-1-methyl-3-[2-[[(5-methyimidazol-4-yl)methyl]-thio]-ethyl]guanidine (Fig a)

$C_{10}H_{16}N_6S$

Metals play a vital role in a living system. Any misfunctioning of these metals can initiate a number of physiological abnormalities and symptoms of clinical disorders. These transition metal ions are also responsible for the proper functioning of different enzymes. It has been found that the activty of the biometals is very often attained through

*To whom all correspondence should be addressed.

formation of complexes with different bioligands. Cimetidine is a bio ligand which may chelate with metals and can create any abnormality in the body.

Results and Discussion

In solution Cu^{2+} was present as copper aquo complex (λmax=800nm) (Fig 1). H_2O behave as weak field ligand so Copper aquo complex act as labile complex, which can be easily replaced by Cimetidine. The complex of Cu^{2+} with Cimetidine (when ligand in excess) showed two absorption bands i.e. at 370 nm and 333 nm (Fig 2). With the increase in metal concentration absorption at 370nm gradually decreased (Fig 3) which confirm the different type of complex.

Two sets of solutions were studied. The first set involves Increasing ratio of ligand to metal, while the second set involves increasing ratio of metal to ligand. These ratios plotted against absorbance (Fig 4, 5) and the mole ratio were found to be ML_2 and M_2L, respectively.

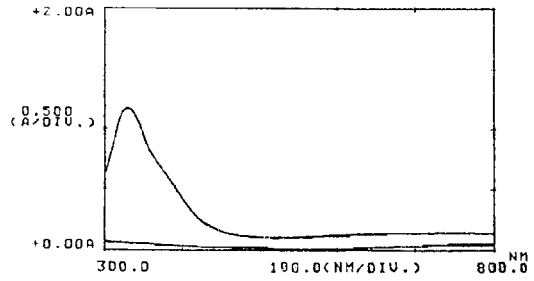


Fig 1: Spectrum of Copper (II) solution, in the presence and absence of drugs

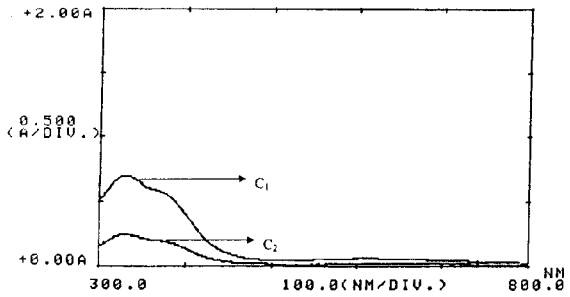


Fig.2. Spectrum of Copper Cimetidine complex(when ligand in excess)

Cimetidine have an imidizole ring with replaceable hydrogen. The log k value of this hydrogen is 6.96

In complex molecule, over all ratio of ligand to metal is 1: 2, as confirmed earlier, so the over all reaction is.

$$M + L \longrightarrow ML \quad (1)$$

$$M + 2L \longrightarrow ML_2 \quad (2)$$

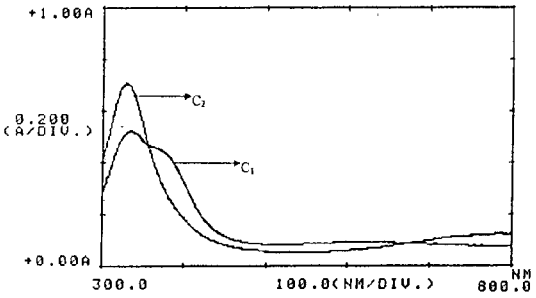


Fig.3. Spectrum of Copper Cimetidine complex (when metal in excess)

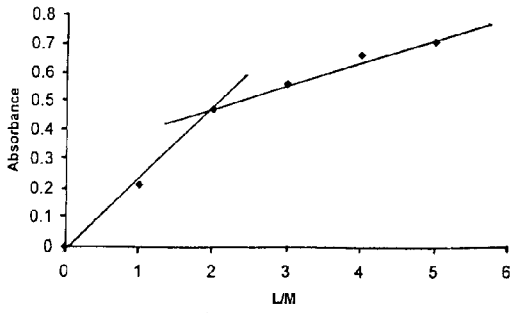


Fig.4. Plot of the mole ratio of Cu- Cimetidine complex (when ligand in excess)

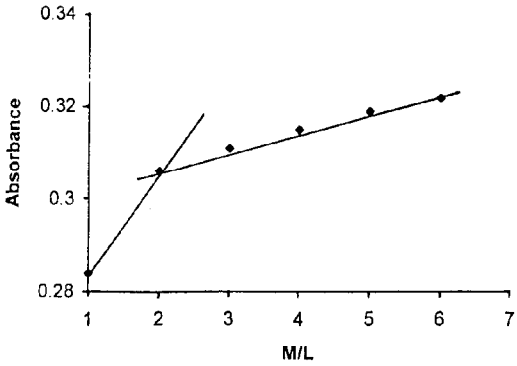


Fig.5. Plot of the mole ratio of Cu- Cimetidine complex (when metal in excess)

These expression can be expressed in another way also

$$\beta_1 = \frac{[ML]}{[M][L]} \quad (3)$$

$$\beta_2 = \frac{[ML_2]}{[M][L]^2} \quad (4)$$

With the help of absorbance and molar extinction coefficient values, concentrations of complexes were calculated. By subtracting this concentration from added metal concentration one can get remaining metal concentration $[M_R]$ and then remaining ligand concentration $[L_R]$. Stability constant were calculated (Table 1) by using this formula

$$\beta ML_2 = \frac{[ML_2]}{[M_R][L_R]^2}$$

The log β of ML_2 complex is found to be 6.43.

Another set of solution, in which ligand concentrations were kept constant, was also examined spectrophotometrically. The remaining ligand and metal concentrations were calculated in the same way and the value of stability constant was calculated (Table 2) by using formula

$$\beta M_2L = \frac{[M_2L]}{[M_R]^2[L_R]}$$

The log β value of M_2L complex is found to be 7.21.

Table.1.Data for formation costant of Cu-Cimetidine complex (when ligand in excess) concentration of metal = 3×10^{-4}M

[L]x 10^3 M	Abs	Remaining metal x 10^5 M	Remaining ligandx 10^5 M	βML_2 x $10^{-6}M^{-2}$
0.3	0.221	22.60	0.15	-
0.6	0.439	15.40	0.30	9.82
0.9	0.605	9.84	0.49	8.31
1.2	0.661	7.90	0.76	4.76
1.5	0.704	6.65	1.03	3.34
1.8	0.706	6.48	1.32	2.04
2.1	0.707	6.44	1.62	1.37
2.4	0.708	6.40	1.92	1.00

Table.2. Data for formation constant of Cu-Cimetidine complex (when metal in excess) concentration of ligand = 3×10^{-4}M

[M]x 10^3 M	Abs	Remaining metal x 10^4 M	Remaining ligandx 10^5 M	βM_2L x 10^{-7} M^{-2}
0.3	0.285	-	-	-
0.6	0.306	0.44	2.2	0.06
0.9	0.311	3.3	1.73	0.15
1.2	0.315	6.2	1.37	5.3
1.5	0.319	9.2	1.00	3.4
1.8	0.322	12.1	0.73	2.7
2.1	0.324	15.1	0.55	2.3

Experimental

Stock solution of metal having 0.01M concentration was prepared in deionized distilled water by dissolving calculated amount of AR grade reagent. Different dilutions of the stock solutions were then made according to the requirements.

Stock solutions of ligands were prepared in deionized distilled water. Spectroscopic method was used for the characterization of complex.

For determination of λmax of complexes, two solutions were prepared. First one has 1 ml metal (0.01M) and 9 ml ligand solution (0.01M), while the other have 9 ml metal (0.01M) and 1 ml ligand solution (0.01M). These solutions were taken in glass cuvets and spectra were recorded in the range of 300-800nm on shimadzu UV160A using water as blank.

In the complexation study, experiment comprise two set of solutions, first in which the concentration of the metal kept constant and concentration of ligand changed by 1 ml difference through 1 - 9 ml while in the second set of solution ligand kept constant and concentration of metal changed by 1 ml difference through 1-9 ml. Spectra of these solutions were recorded in the wavelength range of 300 - 800 nm. It was assumed with the help of spectra that at high metal concentration ML_2, ML_3, ML_4 do not exist similarly at high ligand concentration M_2L is quiet rare.

References

1. T.G Keith, : *Gastrointestinal and liver drugs*, Chap 39 in Remington, 18th edition.pg 780.
2. Churchill Living Stone: *Therapeutic drugs*, vol 1 (A-H) C 215 (1999).
3. A K. Das : *Medical Aspects of Bio Inorganic Chemistry*, Regional Engineering College . Durgapur, CBS Publishers and Distributer, India, (1989).

4. W.Stiles : *Trace Elements in plants*, 3rd ed, Cambridge U.P (1961).
5. M. Borys, *Wiad. Bot*, **8**(1964)205; *Biol. Abstr* (1965)29208.
6. E . J. Hewitt : *Ann. Rev. plant physiology*. **2**, (1951)25.
7. F.C. Steward (ed.) : *plant physiology*, vol.(III). Academic press (1963).
8. H. M. Fox and G. Vevers : *The nature of Animal colours*, Sidgwick and Jackson, London (1960).
9. A.G. MASSEY : *Copper*, in *Comprehensive inorganic chemistry*, Volume **3**, Chapter 27, pg 3, Published by Pergamon Press, University of Technology, Laugh borough.
10. H.I.Scheinberg, *Federation Proceedings*, **20** 179 (1961).
11. H. Montgomery and E.C.Lingafelter: *J.Phys. Chem.* **64**, 831 (1960).
12. W.J.Eilbeck, F.Holmes and A.E.Under hill : *J.Chem. Soc.* (1967A).