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Metal Chelates of Ambidentate Ligand Cysteine and Antiulcer Drug Ranitidine

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The role of metal complexes in biological systems is of paramount importance. Mixed ligand complexes, wherein one ligand is a drug and another such an amino acid which makes part of the living system, can affect the activity of drug to a remarkable degree. Antiulcer drug is selected for the present study as it has potent donor atoms/groups in its structure while amino acids act as ambidentate ligand useful in formation of chelate rings involving various coordination sites. Mixed ligand complexes of ranitidine, an antiulcer drug and cysteine, an amino acid, with Mn(II), Co(II), Cu(II) and Zn(II) have been synthesised and characterised.

INTRODUCTION

Cysteine is one of the important, naturally occurring, biologically important ambidentate ligand manifested in the formation of chelate rings involving various coordination (N, S; O, S or N, O) sites[1]. Its importance is attached to study of the metal-sulfur bonds formed in processes like nonheme proteins[2] and blue copper proteins[3]. Cysteine has been used as a coligand to form mixed ligand complexes of ranitidine which is the most useful drug in the management of peptic and duodenal ulcer[4], having a substituted aromatic group and a polar "urea equivalent" group connected by a flexible chain[5]. It accelerates the healing of benign gastric ulcer.

Cysteine and ranitidine present a good set of coordinating sites in their structure and their coordination with various metal ions may affect their biological activity. The present paper describes the synthesis and characterisation of mixed ligand complexes of ranitidine and cysteine with metal ions Mn(II), Co(II), Cu(II) and Zn(II).

EXPERIMENTAL

The drug was obtained from Nicholas Peramal Limited and Glaxo Labs; other reagents used were of AnalaR grade.

The drug (1 mole) was dissolved in minimum quantity of ethanol, cysteine (1 mole) was dissolved in minimum quantity of liquor ammonia; metal salts were dissolved in distilled water. To the solution of cysteine, drug and metal salt solution were added gradually with continuous stirring and maintaining the pH

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at 9. The entire matrix was refluxed for 4 h over a water bath using air condenser. On cooling the complex sepaerated out which was filtered off and washed well with distilled water and dried in vacuum over fused calcium chloride.

IR spectra was recorded on Perkin-Elmer spectrophotometer model No. 14300. Thermal analysis was carried on thermal analyser Dupont 2100.

Elemental analysis was carried out at C.D.R.I. Lucknow. Metal was estimated gravimetrically. Particle sizes of various complexes and ligand were determined by the microscope ERNST Leitz Wetzlar Germany No. 538703, having eye-piece 10 x.x, objective 10/0.25 and fitted with ocular micrometer (Erma, Japan) and stage micrometer 0.01 mm (Erma, Japan).

RESULTS AND DISCUSSION

The compositions of the complexes are given in Table-1 indicating non-ionic nature.

IR Spectra: Bands near 3300–2500 cm^{-1} are due to (O—H) stretching of acid group which is in chelated state; this is confirmed by bands near 1728–1700 cm^{-1} due to (C=O) stretching vibrations[6]. These bands indicate that possibly cysteine has coordinated through N and S atoms. Bands near 650–460 cm^{-1} indicate metal-nitrogen linkages[7] which may be due to cysteine nitrogen-metal linkages, while bands near 630 cm^{-1} are due to metal-sulfur linkages suggesting that cysteine has coordinated through sulfur atom also. In case of complex of Co(II) additional bands were found near 3350–3320 cm^{-1} which may be due to coordinated water molecule supplemented by medium broad bands at 940 and 805 cm^{-1} due to rocking and wagging vibrations of water molecules[8].

Thermal Studies: The TGA studies indicate that complexes of ranitidine with various metal ions and cysteine decompose in two steps; the first decomposition starts from 175° to 200°C without any break-up to 275°C. The observed weight loss corresponds to loss of cysteine molecule and water molecule. The second step decomposition corresponds to loss of ranitidine molecule leading to the formation of metal oxide at 400°C. In case of Cu(II), Mn(II), Zn(II) and Co(II) complexes the weight of residue corresponds to the formation of Cu_2O, Mn_2O_3, ZnO and Co_2O_3 respectively. The Broido method was applied to TG data to determine the energy of activation and order of reactions[9].

DTG curves of the complex are of similar nature; in each case two peaks were obtained; as DTG curves presents the rate of weight change as a function of temperature, two peaks endothermic and exothermic are obtained (Table-2). The first peak corresponds to the weight loss of amino acid and moisture present in complex; while the second peak corresponds to the decomposition of complex, liberation of drug molecule and formation of metal oxide.

Magnetic Moment: The μ_{eff} values of Co(II) complexes indicate high spin octahedral stereochemistry with 4.72 B.M. magnetic moment[10]. μ_{eff} for Cu is 2.22 B.M. suggesting an octahedral arrangement. μ_{eff} for Mn(II) complex indicates high spin tetrahedral stereochemistry[11] with B.M. of 5.9 while complex of Zn(II) is diamagnetic in nature.

Particle size analysis: Particle size characteristics[12, 13], particularly in the case of sparingly soluble drugs, have a profound influence on their rate of absorption in the stomach or gastrointestinal tract, and hence on their efficacy when administered orally. The results of particle size analysis of ranitidine and its complexes are given in Table-1. The particle sizes of complexes are smaller than the parent drug. The smaller particle size of complexes may enhance the absorption of complexes in comparison to the parent drug, which may lead to increase in potency of the drug, if given in complex form.

TABLE-1

ANALYTICAL DATA AND PHYSICAL DATA OF COMPLEXES

S. No.	Compound (Colour)	Metal % found (calcd)	μ_{eff} (B.M.)	Particle size (in microns)	Yield (%)
1.	[Ran Cu(Cys)$_2$SO$_4$] (Black)	9.0 (9.1)	2.22	3–12	52.50
2.	[Ran Mn(Cys)]SO$_4$ (Brown)	9.3 (9.3)	5.9	3–7	59.63
3.	[Ran Zn(Cys)]SO$_4$ (Off white)	12.2 (10.9)	Dimagnetic	3–14	65.86
4.	[Ran Co(Cys)(H$_2$O)$_2$](NO$_3$)$_2$ (Pink)	8.79 (9.92)	4.72	3–9	54.39
5.	Ranitidine	—	—	3–14	–

All compounds gave satisfactory C, H and N analysis carried out at C.D.R.I. Lucknow.

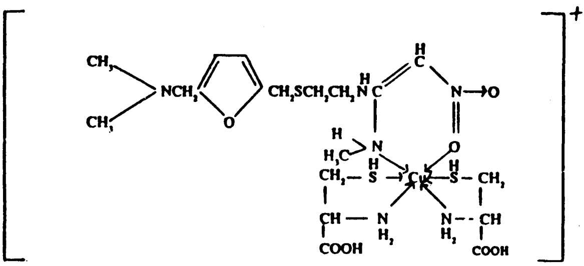
TABLE-2

THERMAL DATA OF MIXED LIGAND COMPLEXES OF RANITIDINE AND CYSTEINE WITH Cu(II), Mn(II), Zn(II), Co(II)

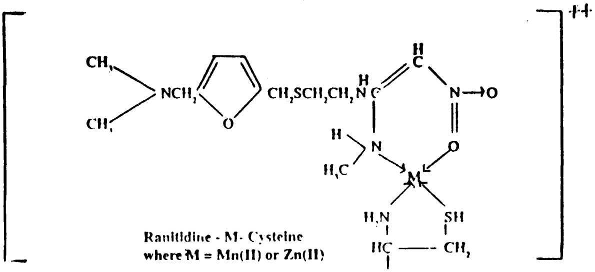
S. No.	Compound	Ist Step Decomposition obsd. (calcd.)	2nd Step Decomposition obsd. (calcd.)	Activation Energy	Order of Reaction	1st Decomposition Maxima of DTG (TM) (°C)	2nd Decomposition Maxima of DTG (TM) (°C)
1.	[Ran Cu(Cys)$_2$SO$_4$]	37.59 (33.60)	18.00 (20.00)	17.500	1	200	350
2.	[Ran Mn(Cys)]SO$_4$	19.50 (20.75)	22.40 (26.85)	3.185	1	300	400
3.	[Ran Zn(Cys)]SO$_4$	21.20 (20.30)	15.00 (13.60)	2.540	1	300	375
4.	[Ran Co(Cys)(H$_2$O)$_2$](NO$_3$)$_2$	23.00 (26.60)	21.90 (27.90)	5.120	1	325	375

Ran = Ranitidine

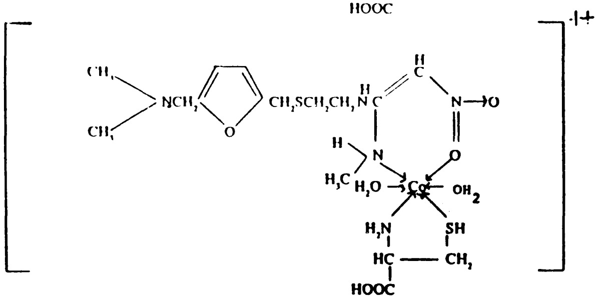
On the basis of above findings the following structures are proposed:



Ranitidine - Cu- Cysteine



Ranitidine - M- Cysteine
where M = Mn(II) or Zn(II)



Ranitidine - Co- Cysteine

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