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Studies on Mixed Ligand Complexes of Zinc (II) With Paracetamol and Amino Acids

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Abstract: *The Study was aimed at investigating the suitability of Paracetamol-amino acid novel metal (II) complexes. Synthesis of mixed ligand zinc (II) complexes of type [M(par)(L)].2H_2O have been carried out by using Analgesic drugs Paracetamol (par) as a primary ligand and Amino acid (HL) such as L-Valine, L-Threonine and L-Serine as a secondary ligand. Synthesized metal (II) complexes have been characterized on the basis of elemental analysis, electrical conductance, room temperature magnetic susceptibility measurement and spectral analysis which include UV, IR and XRD techniques. An electrical conductance studies indicates non-electrolyte nature and magnetic susceptibility measurement revealed paramagnetic nature of the complexes. UV spectra shows intra-ligand, charge transfer and d-d transition and IR spectra confirm bonding of metal ion through O or N donar ligands which further indicates complexation. The agar cup method and tube dilution method have been used to study antibacterial activity of the complexes against pathogenic bacteria such as Aureus, C. Diphtheriae, S.Typhi and E.coli.*

Keywords: Mixed Ligand Complexes, Paracetamol, Amino Acids, Metal ion

I. INTRODUCTION

The advancement of medicinal/bioinorganic chemistry has led to use of metal complexes and metal Nano-particles due to their imperative applications for the development of advance novel technologies which includes chemotherapeutics and diagnostics devices [1]. Amino Acids are well known for their tendency to form complexes with metals having biological significance and metabolic significance [2]. Mixed ligand complexes of copper and Zinc have also been reported to show Anti-tumor activities.[3-4].The antibacterial and anti- fungal property range of Zinc complexes have been evaluated against pathogenic bacteria and fungi [5] Paracetamol is found to be mild analgesic with weak anti-inflametoryactivity.it is commonly used for relief of ache and pain.[6].However overdose of paracetamol may causes liver damage [7], therefore it decided to synthesize mixed ligand analgesic drug-metal complexes with amino Acids which are characterized by their chemotherapeutic properties [8]. The present paper reports synthesis, characterization of mixed ligand Zn (II) complexes with paracetamol (Par) as primary ligand and Amino acids (HL) such as L-Valine, L-Threonine and L-Serine as secondary ligand and potential of such metal complexes as broad spectrum antibacterial agents in-vitro. This is continuation of the research activities of our group on search for biologically active metal (II) complexes that could serve as lead compounds in drugs research for pain management and analgesic and as flavoring agents in food and perfume antibacterial studies

II. EXPERIMENTAL

2.1 Materials

Analytical Grade (A.R) $ZnCl_2$. 2H_2O is used and amino acids such as L-valine , L-threonine ,L-serine are used from S.D.Fine Chemical Mumbai ,India .Solvents like ethanol, chloroform, DMSO (L.R grade) whenever used were distilled and purified according to standard procedure [9-11].All chemicals of high purity were used and purchased without any further purification

2.2 Preparation and Methods

Zn(II)Mixed ligand complexes ion is prepared by addingZn(II) ion solution over mixture ofParacetamol,primary ligand and Amino Acid, secondary ligand solutions at specific experimental conditions. For that, an aqueous solution (10cm^{-3}) of Zinc(II) chloride dehydrate (172.3mg, 1mmol), ethanolsolution(10cm^{-3}) of paracetamol (138mg, 1mmol) was added. The mixture was stirred and kept in boiling water bath for 10 min. To this hot solution, an aqueous solution (10cm^{-3}) amino

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acids solution (1mmol) was added with constant stirring. The mixture was again heated in a water bath. The complexes were obtained by raising pHof the reaction mixture by adding dilute ammonia solution. The mixture was cooled & solid complexes obtained were filtered, washed with water followed by ethanol. The complexes thus prepared were dried under vacuum.

2.3 Instrumentation

The Melting point of complexes was determined to ascertain their purity. The Melting point was measured using melting point electro thermal IAg100 apparatus. The complexes were analyzed for C, H,N& S contents on thermos Finnigan elemental Analyzer, Model No. FLASH EA 1112 Series at Department Of Chemistry, I.I.T. Mumbai. Metal content was estimated complex metrically by standard procedure [12-13].

The Molar Conductance values were measured in DMSO (10^{-3}M) on an Equip-tronics auto ranging Conductivity Meter Model No.EQ -667 with a dip type conductivity cell fitted with platinum electrodes (cell constant= 1.0cm^{-1}). The room temperature magnetic susceptibility measurements of the complexes reported in the present study were made by the Guoy's method using Hg [Co (SCN)$_4$] as calibrant at Department of Chemistry, I.I.T., Mumbai. The electronic absorption spectra of all the complexes in DMSO solution (10-3M) in the ultraviolet & visible region were recorded on Shimadzu UV/VIS-160 spectrometer at GNIRD, Mumbai. Infrared spectra of all the ligands& their metal complexes were recorded in KBr discs on a PerkinElmer FT-IR spectrophotometer model 1600 in the region 4000-400 cm-1 at Department of Chemistry, I.I.T. Mumbai. The pellets were prepared taking necessary precautions to avoid moisture. The instrument calibration with respect to wave number and percent transmission was confirmed by recording the spectrum of standard polystyrene film. From the spectra,the characteristic groups were assigned by using respective IR frequencies[14].

The Thermogravimetric (TG) & Differential Thermal Analysis (DTA) measurements were carried out in controlled nitrogen atmosphere on a Perkin-Elmer Diamond TG-DTA instrument at the Department of Chemistry, I. I.T. Mumbai by recording the change in weight of the complexes on increasing temperature up to 900□ at heating rate of 10□ per min.

2.4 Antibacterial Screening

A. Agar Cup Method

In the Agar cup method, a single compound can be tested against number of organisms or a given organism against different concentrations of the same compound. The method was found suitable for semisolid or liquid samples & was used in the present work. In the Agar cup method, a plate of sterile nutrient Agar with the desired test strain was poured to a height of about 8mm diameter was cut from the center of the plate with a sterile core borer. Thereafter, the cup was filled with the sample solution of known concentration & the plate was incubated at 37□ for 24hrs. The extent of inhibition of growth from the edge of the cup was considered as a measure of the activity of the given compound. By using several plates simultaneously, the activities of several samples were quantitatively studied.

B. Tube Dilution Method

The test compound (10mg) was dissolved in DMSO (10cm^3) so as to prepare a stock solution of concentration 1000μg/mL. From this stock solution, aliquots of 50 to 1000μg/mL were obtained in testbroth. The test compounds were subjected to in- vitro screening against Staphylococcus Aureus, Corynebacterium Diphtheriae,PsedomonasAeruginosa & Escherichia coli using Muller Hinton broth as the culture medium. Bacterial inoculums were prepared in sterilized Muller Hinton broth incubated for 24hrs at 37□. They was dispersed (5cm^3) in each borosilicate test tube (150×20mm). The test sample solution was added in order to attain final concentration at 50 to 1000 μg/mL The bacteria inoculums 0.1cm^3 of the desired bacterial strain (S.aureus,C.diphtheriae, P.aeruginosa& E.coli) containing 106 bacteria/cm3were inoculated in the tubes. The tubes were incubated at 37□ for 24hr& then examine for the presence or absence of growth of the test organism. The lowest concentration which showed no visible growth was noted as minimum inhibitory concentration (MIC).

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III. Results and Discussion

3.1 Elemental Analysis and Conductivity Measurement

The physical properties and analytical data of the Zn (II) complexes are presented in table 1.Elementalanalysis data of the prepared complexes were represented in table 2. It is concluded that complexes were formed in 1:1:1 proportion of M,L_1& L_2. Their structures have been proposed on the basis of conductivity and magnetic moment measurements. The molar conductance of $1x10^{-3}$M solution of the complexes in DMSO were measured at 30^0C. The molar conductance values which found less than one indicate that the complexes are non-electrolytic in nature[15-16].

3.2 Magnetic Studies

The observed value of effective magnetic moment (μ_{eff}) of Zn (II) complexes at room temperature are given in Table 2. Magnetic moment values in BM ranging between (1.73-1.97) which explains the extreme environment and paramagnetic behaviour of Zn (II) complexes. The square planar geometry has been proposed for zinc complexes on the basis of conductivity and magnetic moment behaviour.

3.3 Electronic Spectra

The electronic spectra of the metal complexes were recorded in 10^{-3}DMSO at 30^0C.(Table 4) The spectra show three transitions in the range 272-280 nm(36765-35714cm^{-1}), and333-339 nm (30030-29762cm^{-1}) and 386-398nm (25907-25126cm^{-1})ascribed $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and the charge transfer transitions(LMCT) from the ligands to the metal, respectively[17-19]. All those band shows bathochromic shift in complexes in comparing to ligands indicating the coordination process.

3.4 FTIR Studies

The FTIR spectra of the metal complexes were recorded in KBrdiscs over the range 4000-400 cm^{-1}. Some important frequencies are shown in table 4. Various absorption band were seen in spectra of ligands and metal complexes. Some of this band in these ligand disappeared from complex while some of the bands were shifted. This phenomenon indicates coordination of metal to ligands leads to form metal complexes.

The strong and medium band at3467,3452$cm^{-1}$and 3412.08, 3527cm^{-1} in paracetamol and valine were due tov (OH). This band in paracetamol and valine found to be disappearing in metal complexes this clearly indicates complexations of metal ion through phenolic oxygen of paracetamol.

There is a sharp band in the range of 1622-1595cm^{-1} in paracetamol which assign due to ν(CO) stretching vibration. This bands was found to shiftto 1759-1553cm^{-1} in metal complexes conforming complexation of metal ion through carbonyl oxygen of paracetamol. Furthermore, there are new absorption bands in the range of 596-504cm-1 in metal complexes which were absent in ligand this band were assigned to ν(M-O) and not ν(M-N) as absorption band at 440-425cm^{-1} were absent. The broad band at 3500 cm^{-1} in the metal complexes were assign to ν(OH) of coordinated water

By comparing the spectra of free amino acids, it has been proved that there is decrease in the N-H stretching frequency on complex formation[20-21]. Character and strength of the M-N bond has been correlated to the shift of N-H stretching band. A[22-24] broad band observed in the region between 3300-3194cm^{-1} due to asymmetric and symmetric O–H stretching modes and a weak band in the range 1578-1570 cm^{-1} due to H–O–H bending vibrations indicating presence of water molecules further confirmed by thermal studies.

3.5 XRD

Like most of the metal organic complexes, these complexes also decompose to a fine powder of metal oxide i.e. ZnO. The constant weight plateau in TG after 610C indicates completion of the reaction. The ZnO formed was confirmed by X-ray diffraction pattern of the decomposed product [25].

Table 1: Empirical formula, molecular weight, colour of the Zinccomplexes studied

Sr. No	Complex	Empirical Formula	Molecular Weight	Colour	pH
1	[Zn(Par)(Val)].$2H_2O$	$ZnC_{13}H_{23}O_6N_2$	368.748	Yellow	6.89
2	[Zn(Par)(Thr)].$2H_2O$	$ZnC_{12}H_{21}O_7N_2$	370.721	Yellow	6.97
3	[Zn(Par)(Ser)].$2H_2O$	Zn $C_{11}H_{19}O_7N_2$	356.574	Yellow	7.00

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Par. represents the deprotonated primary ligand paracetamol, whereas Val, Thr& Ser. represent deprotonated secondary ligands: L-valine, L-threonine &L-Serine respectively.

Table 2: Elemental analysis data, molar conductance & magnetic moments of Zn(II) complexes

Sr. No.	Complex	Elemental Analysis Found(Calculated)					Molar conductance (Mhoscm2mol-1)	μeff. (B.M.)
		%M	%C	%H	%N	%S		
1	[Zn(Par)(Val)].2H_2O	17.73 (17.75)	42.34 (42.30)	06.28 (06.30)	07.59 (07.60)	---	0.021	1.94
2	[Zn (Par)(Thr)].2H_2O	17.64 (17.65)	38.87 (38.90)	05.70 (05.75)	07.59 (07.63)	---	0.019	1.97
3	[Zn (Par)(Ser)].2H_2O	18.34 (18.32)	37.23 (37.24)	05.36 (05.40)	07.85 (07.87)	---	0.020	1.90

Abbreviations see Table 1.

Table 3: IR Spectral values of Zn (II) complexes

S. N.	Complex/Ligand	-C=C	-C-N	-O-H	-C=O	-N-H	C-O	M-N (AA)	-M-O (Par,AA)
1	Paracetamol	1444.68 -566.20	1107.14-1257.89	3467,3452	1622,1595	3382 str. 1566 b	1012.63	-	-
2	Amino acid	-	11909.07-1255.66	3412.08-3527.80 str.	1687 1755.2	-	1026.13-1141.86	-	-
3	[Zn(Par)(Val)].2H_2O	1442.83-1562.27	1107.14-236.37	1371.39 (Phb)	1658.85	3330.21	1014.56	410	596,504 600
4	[Zn(Par)(Thr)].2H_2O	1430.3-1550.77	1109.07-321.24	1325.10	1666.5	3332.7	1011.63	419	596,503 610
5	[Zn (Par)(Ser)].2H_2O	1440.83-566.06	-	1321.24 (Phb)	1656.9	3327.21	1016.49	420	596,417 605

Table 4: Electronic Spectral Data of Zn (II) Complexes

Sr. No.	Complex	λ (nm)	ν (cm- 1)	Proposed Assignments
1	[Zn(Par)(Val)].2H_2O	272	36765	$\pi \rightarrow \pi^*$
		336	29752	$n \rightarrow \pi^*$
		288	25773	Charge transfer
2	[Zn(Par)(Thr)].2H_2O	280	35714	$\pi \rightarrow \pi^*$
		333	30030	$n \rightarrow \pi^*$
		386	25907	Charge transfer
3	[Zn (Par)(Ser)].2H_2O	274	36496	$\pi \rightarrow \pi^*$
		334	29940	$n \rightarrow \pi^*$
		394	25381	Charge transfer

Table 5: Antibacterial activity (mm)of zinc complex by agar cup method

Sr. No.	Complex	Test			
		S.aureus	C.diphteriae	S.typhi	E.coli
1	[Zn(Par)(Val)].2H_2O	22	12	14	14
2	[Zn(Par)(Thr)].2H_2O	19	13	16	13
3	[Zn (Par)(Ser)].2H_2O	19	11	19	11

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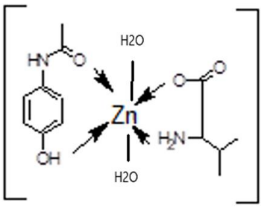
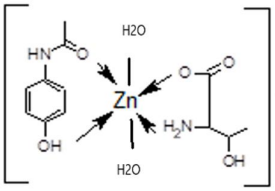
Table 6: MIC (mg/ml) data of zinc complexes

Sr. No.	Complex	S.aureus	C. diphtheriae	S. typhi	E.coli
1	[Zn(Par)(Val)].2H_2O	50	100	50	100
2	[Zn(Par)(Thr)].2H_2O	50	100	100	100
3	[Zn (Par)(Ser)].2H_2O	50	150	50	50

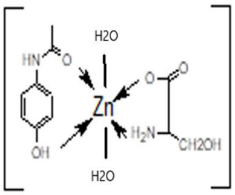
The proposed structures for the complexes are,



[Zn(par)(val)].2H_2O



[Zn(par)(Thr].2H_2O



[Zn(par)(ser].2H_2O

IV. Biological Studies

All the metal complexes were screened against Staphylococcus aureus, Corynebacterium diphtheriae, Salmonella typhi and Escherichia coli. The studies based on agar cup method revealed that the complexes are sensitive against S. aureus and S. typhi as compared to C. diphtheria and E.Coli. The minimum inhibitory concentration (MIC) of metal complexes ranges between 50-150 µg/cm^3. The results show that, as compared to the activity of metal salts and free ligands the metal complexes show higher activity (Table 5 and 6). On the basis of the physico-chemical studies. All the complexes observed good antimicrobial activities. The tested mixed ligand complexes showed higher activities against selected strain microorganism so they are potential antimicrobial agents.

V. Conclusion

The method has been used to synthesis a mixed paracetamol-amino acid drug metal complexes where both the paracetamol and the amino acid found to act as a bidentate ligand. An electrical conductance studies shows non-electrolyte nature and magnetic studies indicate paramagnetic nature of the complexes. Electronic absorption spectra of the complexes show intra-ligand and charge transfer transitions. IR spectra show bonding of the metal ion through N-and O-donor atoms of the two ligands. The antibacterial study shows that complexes are found to be more active against S.aureus and P.aeruginosa as compared to C.diphtheria and E.coli compared to standard antibacterial compound, tetracycline, and the complexes show satisfactory activity against selected strains of microorganisms, so they are poetical anti-microbial agents.

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