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STUDIES AND SYNTHESIS OF BIOLOGICAL ACTIVE MIXED LIGAND Zn (II) COMPLEXES

Chemistry

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ABSTRACT

Synthesis of mixed ligand Zn (II) complexes of the type [M (Q) (L)].2H2O have been carried out by using 8-hydroxyquinoline (HQ) as a primary ligand & N-and/or O-donar amino acids (HL) such as
L-valine, L-asparagine, L-glutamine, L-arginine and L-methionine as a secondary ligands. The characterization of metal complexes has been carried out on the basis of elemental analysis, electrical conductance, room temperature, magnetic susptebility measurements, spectral & thermal studies.
The electrical conductance studies of the complexes in DMSO (dimethyl sulphoxide) in 10-3 M concentration indicate their non-electrolytic nature. Room temperature magnetic susceptibility measurements specify that Zn (II) complexes are diamagnetic in nature . Electronic absorption spectra of the complexes show intra-ligand, charge transfer & d-d transition respectively. The thermal analysis data of the complexes indicate the presence of co-ordinated water molecules. FTIR spectra shows bonding of metal ions through N- and O- donar atoms of ligands molecules. Tube dilution and Agar cup methods were implemented for study the antibacterial activity of the complexes against the pathogenic bacteria Staphylococcus aureus, Corynebacterium diphtheriae, Salmonella typhi and Escherichia coli. The results have been compared with those of tetracycline, which was screened simultaneously & indicated mild antibacterial activity of the complexes.

KEYWORDS

Mixed ligand zinc complexes, synthesis, characterization and biological studies.

1. INTRODUCTION

Comprehensive research have studied for characterization, antimicrobial & toxicological activity of mixed ligand complexes of transition metal (1-6). Mixed ligand complexes plays a vital role in biological process (7,8). It has been found that a majority of the metal complexes with 8-hydroxyqunoline process biological activity (9-11). Amino acids are well known for their tendency to form complexes with metals having biological significance & metabolic enzymatic activities (12). Mixed ligand complexes has also been reported to show Anti-tumour activities (13, 14). The antibacterial & Anti-fungal properties of a range of Zinc (II) complexes have been evaluated against several pathogenic bacteria & fungi (15-16).

Therefore, it was considered to study the complexation & to determine the biological activity Zinc complexes. The present paper reports synthesis, characterization & antibacterial studies of the mixed ligand Zn (II) complexes prepared with 8-hydroxyqunoline (HQ) as a primary ligand & amino acids (HL) such as L-valine, L-asparagine, L-glutamine, L-arginine and L-methionine as a secondary ligands. The metal complexes have been characterized on the basis of elemental analysis & various physico-chemical techniques such as molar conductance, magnetic susceptibility, electronic spectra, IR spectra & thermal studies.

2. EXPERIMENTAL

2.1 Materials

Analytical grade Zinc (II) chloride dehydrate was used as such without further purification L-valine, L-asparagine, L-glutamine, L-arginine and L-methionine & 8-hydroxyqunoline were obtained from S.D. Fine chemicals, Mumbai, India. Solvents like ethanol, dimethyl sulphoxied & laboratory grade chemicals, whenever used were distilled & purified according to standard procedures (17,19).

2.2 Preparation of Mixed Ligand Complexes

Mixed ligand zinc (II) complexes were synthesized from zinc (II) chloride dihydrate, 8-hydroxy- quinoline (HQ) as a primary ligand and different amino acids (HL) such as L-valine, L-asparagine,L-glutamine, L-arginine and L-methionine as secondary ligand.

An aqueous solution (10 cm^3) of zinc (II) chloride dihydrate (136.29 mg, 1mmol) was mixed with ethanolic solution (10 cm^3) of 8-hydroxyquinoline (145 mg, 1mmol). The mixture was stirred and kept in a boiling water bath for 10 minutes. To this hot solution, an aqueous solution (10 cm^3) of amino acid (1 mmol) was added with constant stirring. The reaction mixture (1:1:1 molar proportion) was taken in water bath and heated for about 10 minutes till the temperature reached to 50^0C.

The pH of the mixture was raised by adding dilute ammonia solution in the reaction mixture and complex was obtained. Then the mixture was cooled and solid complex obtained was filtered, washed with water followed by ethanol. The complexes thus synthesized were dried under vacuum.

2.3 Instrumentation

The C, H, N & S elemental analysis of Zn (II) complexes were carried out on thermo Finnigan elemental Analyzer, Model No. FLASH EA 1112 Series at Department Of Chemistry, I.I.T., Mumbai. Metal content was estimated complexometrically by standard procedure (20,21).

The complexes were dissolve in DMSO (10^{-3}M) to measure Molar Conductance values on an Equiptronics Auto Ranging Conductivity Meter Model No. EQ -667 with a dip type conductivity cell fitted with platinum electrodes (cell constant= 1.0 cm^{-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^{-3}M) in the ultraviolet & visible region were recorded on Shimadzu UV/VIS-160 spectrometer using quartz cell of 1cm optical path at GNIRD, Mumbai.

Infrared spectra of all the ligands & there metal complexes were recorded in KBr discs on a Perkin-Elmer FTIR 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 the respected frequencies (22)

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 900^0C at heating rate of

10^{0}C per min.

2.4 Antibacterial screening

2.4.1 Agar Cup Method

Antibacterial screening of single compound against a number of organism or given organism against different concentrations of the same compound can be carried out by Agar Cup Method. Author studies reveals that this method is suitable for semisolid or liquid samples and was used in the present work.

In Agar Cup Method, a plate of sterile nutrient agar with the desired test strain was poured to a height of about 5 mm, allowed to solidify and a single cup of 8 mm diameter was cut from the center of the plate with a sterile cork borer. Thereafter the cup was filled with the sample solution of 1000 µg/cm3concentration. The test solution was allowed to diffuse in surrounding agar by keeping in refrigerator for 10 min and the plate was incubated at 370C for 24 hrs. 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 could be qualitatively studied.

2.4.2 Tube Dilution Method

The test compounds were subjected to in vitro screening against Staphylococcus aureus, Corynebacterium diphtheriae, Salmonella typhi and Escherichia coli using Muller Hinton broth as the culture medium.

The test compound (10 mg) was dissolved in DMSO (10 cm3) so as to prepare a stock solution of concentration 1000 µg/cm3. From this stock solution, aliquots of 50, 100, 150, 200 to ……, 1000 µg/cm3 was obtained in test broth.

Bacterial inoculums were prepared in sterilized Muller Hinton broth and incubated for 24 hrs. at 370C. The aliquots were dispensed (5 cm3) in each borosilicate test tube (150 x 20 mm). The bacterial inoculums 0.1 cm3 of the desired bacterial strain (Staphylococcus aureus, Corynebacterium diphtheriae, Salmonella typhi and Escherichia coli) containing 106 bacteria/cm3 was inoculated in the tube. The tubes were incubated at 370C for 24 hrs. and then examined for the presence or absence of the growth of the test organisms.

The lowest concentration which showed no visible growth was noted as minimum inhibitory concentration (MIC).Tetracycline was used as standard drug against Gram-positive and Gram-negative bacteria by similar screening procedure. The solvent DMSO was also tested as control to see that it did not affect the growth of the culture.

MIC of tetracycline was found to be 1.5 µg/cm3 against Staphylococcus aureus, 2.0 µg/cm3 against Corynebacterium diphtheriae, 1.5 µg/cm3 against Salmonella typhi and 2.5 µg/cm3 against Escherichia coli

3. RESULT & DISCUSSION

3.1 Characterization of Metal Complexes

The synthesis of mixed ligand Zn (II) complexes may be represented as follows:

$$ZnCl_2.2H_2O + HQ + HL \longrightarrow [Zn(Q)(L)].2H_2O + 2HCl$$

(Where, Q is deprotonated N and O donor primary ligand, 8-hydroxyquinoline and L is deprotonated

N and / or O donor secondary ligands, different amino acids)

All the complexes in general are colored, non-hygroscopic, thermally stable solids (Table 1 and 2). The complexes are insoluble in water and in common organic solvents such as ethyl alcohol, acetone, chloroform, etc., but partially soluble in DMF and DMSO. This insolubility of complexes hampered the molecular weight determination. Therefore molecular weights were computed using analytical data. All mixed ligand zinc (II) complexes are yellow in colour.

The elemental analysis data (Table 3) of metal complexes are consistent with their general formulation as 1:1:1 mixed ligand complexes of the type [Zn (Q)(L)].2H2O. The molar conductance values of the complexes in DMSO at 10-3 M concentration are low (< 1) indicating their non-electrolytic nature (23).

3.2 Magnetic studies

The magnetic moment of the mixed ligand zinc (II) complexes were calculated from the measured magnetic susceptibilities after employing diamagnetic corrections and revealed their diamagnetic nature (Table 4).

3.3 Electronic absorption spectra

The electronic spectra of metal complexes in DMSO were recorded in the UV-visible region

(Table 5). The spectra show three transitions in the range 273-280 nm (36630- 35714cm^{-1}), 335-339 nm (29801-29499 cm^{-1}) and 390-398 nm (25641-25126 cm^{-1}) ascribed $\pi \rightarrow \pi^{*}$ n $\rightarrow \pi^{*}$ and the charge transfer transitions (LMCT) from the ligands to the metal, respectively (24) As the term implies, these transitions involve electron transfer from one part of the complex to another which are fully allowed and hence give rise to much more intense absorption.

3.4 Infra –red spectra

The FTIR spectra of the metal complexes were recorded in KBr discs over the range 4000-400

cm^{-1}. These spectras of metal complexes were complicated due to the presence of numerous bands with varying intensities making, interpretation task quite difficult. However an attempt has been made to assign some of the important bands on the basis of reported infrared spectra of several N-and/or O-donar ligands, 8-hydroxyquinoline and their metal complexes (25-28).An important features of infrared spectra of the metal complexes is the absence of band ~ 3440 cm^{-1} due the O-H stretching vibration of the free O-H group of HQ. This observation leads to the conclusion that complex formation takes place by deprotonation of the hydroxyl group of HQ moiety takes place to form M-O bond.

A strong ν (CO) band observed in the range 1111-1105 cm^{-1} indicates the presence of oxine moiety in the complexes coordinated through its nitrogen and oxygen atoms as uninegative bidentate ligand.

The ν (C=N) mode observed at 1580 cm^{-1} in the spectra of free HQ ligand is found to be shifted to lower wave number in the range of 1500-1460 cm^{-1} in the spectra of complexes, which indicates the co-ordination through tertiary nitrogen donor of HQ.

The co-ordination through ring nitrogen atom of HQ with the metal has been confirmed on the basis of bands observed at the range of 508-504 cm^{-1} and 791-780 cm^{-1} that corresponds to in plane and out of plane ring deformation modes respectively. (9,10,25).

A (29-31) broad band observed in the region between 3300-3194 cm^{-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.

Broad bands observed at range 3193-3086 cm^{-1} and 3060-3052 cm^{-1} are assigned to N-H (asymmetric) and N-H (symmetric) vibrations respectively. In case of IR spectra of free amino acid these bands appear at the range of 3040 and 2960 cm^{-1}. This shift of N-H vibrations to higher wave numbers, suggest that in the formation of metal complexes, nitrogen atom of amino group co-ordinate to metal ion.

Co-ordination through the amino group of the amino acids has been further confirmed by the C-N symmetrical stretching frequency. It is observed at 950 cm^{-1} in the spectra of free amino acids and found to be shifted to lower wave numbers in the range of 914-910 cm^{-1} in the spectra of the complexes.

The co-ordination of carboxylic acid group via oxygen with the metal ion may be indicated by the interpretation of the asymmetric and the symmetric mode of vibration of (COO-) band. The asymmetric (COO-) band of free amino acids i.e. 1610-1590 cm^{-1} is shifted to higher wave number, in the range 1643-1602 cm^{-1} and the symmetric (COO-) mode observed at 1400 cm^{-1} in the spectra of free amino acids is found to be shifted to lower wave number in the range of 1373-1370 cm^{-1}, in the spectra of complexes. In spectra of complexes indicating the co-ordination of the carboxylic acid group via oxygen with the metal ion.

The difference ($\nu_{asymmetric} - \nu_{symmetric}$) is in the range 270-232 cm^{-1} indicating that the M-O bond is purely covalent (32,33).

Some new bands of weak intensity observed in the regions of 615-600 cm^{-1} and at 410 cm^{-1} may be ascribed to the M-O and M-N vibrations respectively (29-33). It may be noted that these vibrational bands are absent in the infra-red spectra of HQ as well as amino acids. The M-O bond has much less covalent character than the M-N bond so the stretching bands of the former appear in low frequency region (34).

3.5 Thermal studies

The TG and DTA studies of the complexes have been recorded in the nitrogen atmosphere at the constant heating rate of 10^0C/ min. Thermal study on the mixed ligand Zinc complexes in controlled nitrogen atmosphere was carried out to understand stages and temperature range of decomposition. The most probable decomposition pattern of the complexes is proposed on the basis of the careful examination of TG and DTA curve. The thermo analytical data in Table 6.

The TG of the complexes shows that they are thermally quite stable to varying degree. The complexes shows gradual loss in weight due to decomposition by fragmentation with increasing temperature. The complexes with as L-valine, L-asparagine, L-glutamine, L-arginine and L-methionine as a secondary ligands show similar behavior in TG and DTA studies.

The thermograms of these complexes show the loss in weight corresponding to two water molecules in the temperature range 131-171^{0}C, followed by simultaneous weight loss in the range of 245-560^{0}C which is algebraic sum of weight loss due to both amino acid and 8-hydroxyquinoline moieties.

The DTA of the complexes display an endothermic peak in the range 131-171^{0}C which indicate the presence of two co-ordinated water molecules. As the temperature is raised, the DTA curve shows a broad exotherm in the range 245-560^{0}C attributed to simultaneous decomposition of amino acid and 8-hydroxyquinoline moieties present in the complexes. The formation of a broad exotherm is possibly due to simultaneous decomposition of ligand moieties and their subsequent oxidation to gaseous products like CO_2, H_2O, etc. (35-39).

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 610^{0}C indicates completion of the reaction. The ZnO formed was confirmed by X-ray diffraction pattern of the decomposed product (40).

3.6 Biological studies

All the metal complexes were screened against Staphylococcus aureus, Corynebacterium diphtheria, Salmonella typhi and Escherium coli.

The studies based on agar cup method revealed that the complexes are most sensitive against Staphylococcus aureus and Salmonella typhi and less sensitive against Corynebacterium diphtheria and Escherium coli (Table 7).

The minimum inhibitory concentration (MIC) of complexes (Table 8) ranges between 50-200 µg/mL. The complexes are found to be more active against, Corynebacterium diphtheria, Salmonella typhi and Escherium coli and less sensitive against Staphylococcus aureus. As compared to standard antibacterial compound, tetracycline, the complexes show moderate activity against selected strains of microorganisms (41). The biological activity of this complexes is due to bulky structure of the complexes.

Table1. Empirical formula, molecular weight, colour of the Zinc complexes studied

No.	Complex	Empirical Formula	Molecular Weight	Colour
1	[Zn(Q)(Val)].2H_2O	$ZnC_{14}H_{20}O_5N_2$	361.72	Yellow
2	[Zn (Q)(Asp].2H_2O	$ZnC_{13}H_{13}O_6N_3$	376.69	Yellow
3	[Zn (Q)(Glu].2H_2O	$ZnC_{14}H_{19}O_6N_3$	390.72	Yellow
4	[Zn (Q)(Arg)].2H_2O	$ZnC_{15}H_{23}O_5N_5$	418.78	Yellow
5	[Zn (Q)(Met)].2H_2O	$ZnC_{14}H_{20}O_5N_2S$	393.79	Yellow

Q represents the deprotonated primary ligand-8-hydroxyquinoline, where as Val,Asp,Glu,Arg. & Met. represent deprotonated secondary ligands: L-valine, L-asparagine, L-glutamine, L-arginine and L-methionine respectively.

Table 2.Decomposition Temperature & P^H of the Zinc complexes studied

No.	Complex	Decomposition Temperature (^{O}C)	pH
1	[Zn(Q)(Val)].2H_2O	249	6.89
2	[Zn (Q)(Asp].2H_2O	248	6.98
3	[Zn (Q)(Glu].2H_2O	266	7.04
4	[Zn (Q)(Arg)].2H_2O	260	6.97
5	[Zn (Q)(Met)].2H_2O	262	7.00

Abbrevations see Table 1.

Table 3. Elemental analysis data of Zinc complexes.

No.	Complex	Elemental Analysis Found (Calculated)				
		% M	% C	% H	% N	% S
1	[Zn(Q)(Val.)].2H_2O	18.07 (18.08)	46.47 (46.48)	05.56 (05.58)	07.74 (07.75)	---
2	[Zn(Q)(Asp.].2H_2O	17.35 (17.36)	41.44 (41.45)	04.56 (04.56)	11.15 (11.16)	---
3	[Zn (Q)(Glu.].2H_2O	16.74 (16.74)	43.02 (43.03)	04.89 (04.91)	10.75 (10.76)	---
4	[Zn(Q)(Arg)].2H_2O	15.60 (15.61)	43.01 (43.02)	05.53 (05.55)	16.73 (16.73)	---
5	[Zn(Q)(Met.)].2H_2O	16.59 (16.61)	42.68 (42.70)	05.12 (05.13)	07.11 (07.12)	08.12 (08.14)

Abbriviations see Table 1.

Table 4. Molar conductance, Magnetic moments of Zinc complexes.

No.	Complex	Xg	Xm	Molar conductance (Mhos cm^2 mol^{-1})	µeff. (B.M.)
1	[Zn(Q)(Val.)].2H_2O	-1.21 x 10^{-6}	-4.42 x 10^{-3}	0.028	Diamagnetic
2	[Zn (Q)(Asp.].2H_2O	-4.82 x 10^{-6}	-1.72 x 10^{-3}	0.026	Diamagnetic
3	[Zn(Q)(Glu.].2H_2O	-6.67 x 10^{-6}	-2.49 x 10^{-3}	0.019	Diamagnetic
4	[Zn(Q)(Arg)].2H_2O	-4.83 x 10^{-6}	-1.75 x 10^{-3}	0.025	Diamagnetic
5	[Zn(Q)(Met.)].2H_2O	-1.61 x 10^{-6}	-5.72 x 10^{-3}	0.014	Diamagnetic

Abbrevations see Table 1.

Table 5. Electronic Spectral Data of Zinc (II) Complexes

No.	Complex	λ (nm)	ν (cm^{-1})	Proposed Assignments
1	[Zn(Q)(Val.)].2H_2O	273	36630	π → π*
		335	28851	n → π*
		390	25641	Charge transfer
2	[Zn (Q) (Asp.].2H_2O	278	35971	π → π*
		339	29499	n → π*
		395	25316	Charge transfer
3	[Zn(Q)(Glu.].2H_2O	280	35714	π → π*
		338	29586	n → π*
		397	25189	Charge transfer
4	[Zn(Q)(Arg)].2H_2O	279	35842	π → π*
		338	29586	n → π*
		398	25126	Charge transfer
5	[Zn(Q)(Met.)].2H_2O	274	36496	π → π*
		338	29586	n → π*
		396	25253	Charge transfer

Abbrevations see Table 1.

Table 6. Thermal data of Zinc complexes

No.	Complex	Temperature range for loss of water molecules ©	Weight loss due to water		Temperature range for loss of 8HQ & amino acid (C)	Weight loss due to 8HQ & amino acid	
			Found	Calculated		Found	Calculated
1	[Zn(Q)(Val.)].2H_2O	135-171	10.02	09.96	248-552	72.00	71.96
2	[Zn(Q)(Asp.].2H_2O	139-169	09.87	09.56	252-557	73.10	73.07
3	[Zn(Q)(Glu.].2H_2O	140-165	09.35	09.22	246-560	74.20	74.04
4	[Zn(Q)(Arg.)].2H_2O	131-165	08.75	08.60	249-558	75.80	75.78
5	[Zn(Q)(Met.)].2H_2O	143-170	09.25	09.15	245-552	74.35	74.24

Abbrevations see Table 1.

Table 7. Antibacterial activity (mm) of Zinc complex by Agar Cup Method

No.	Complex	Test			
		S.aureus	C.diphtheriae	S. typhi	E.coli
1	[Zn(Q)(Val.)].2H_2O	25	14	20	13
2	[Zn(Q)(Asp.].2H_2O	23	15	24	14
3	[Zn(Q)(Glu.].2H_2O	26	18	24	12
4	[Zn(Q)(Arg.)].2H_2O	24	16	23	12
5	[Zn(Q)(Met.)].2H_2O	22	12	22	13
6	Tetracycline	30	25	26	26

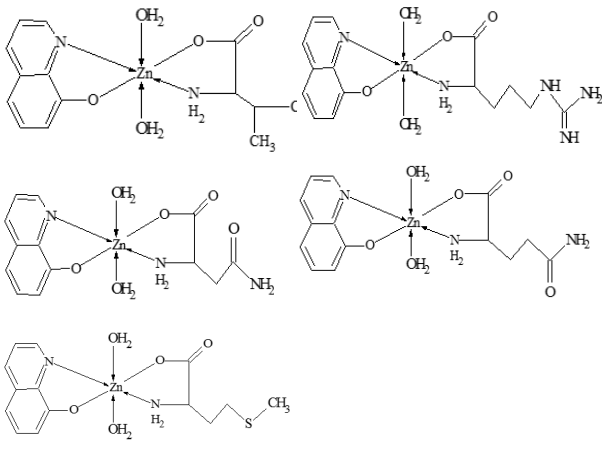
Abbreviations see Table 1.

Table 8. MIC(mg/ml)data of Zinc complexes.

No.	Complex	S.aureus	C.diphtheriae	S. typhi	E.coli
1	[Zn(Q)(Val.)].2H_2O	50	200	100	50
2	[Zn(Q)(Asp.].2H_2O	50	150	50	50
3	[Zn(Q)(Glu.].2H_2O	50	150	50	100
4	[Zn(Q)(Arg.)].2H_2O	50	150	100	150
5	[Zn(Q)(Met.)].2H_2O	50	200	100	50

Abbreviations see Table 1.

On the basis of the physico-chemical studies, the bonding and structure for the Zinc complexes may be represented as shown as below.



4. CONCLUSIONS

The higher decomposition temperature of the complexes indicate a strong metal-ligand and electrical conductance studies show non-electrolytic nature of the complexes. Magnetic studies indicate diamagnetic 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-donar atoms of the two ligands. Thermal analysis confirms the presence of co-ordinated water molecules.

The antibacterial study shows that complexes are found to be more active against Staphylococcus aureus and Salmonella typhi as compared to Corynebacterium diphtheria and Escherium coli. As compared to standard antibacterial compound, tetracycline, the complexes show moderate activity against selected strains of microorganisms . The biological activity of this complexes is due to bulky structure of the complexes.

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