Int J Pharm Bio Sci 2014 April ; 5 (2) : (P) 383 - 389

Research Article **Analytical Chemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

SYNTHESIS, SPECTRAL, THERMAL, ANTI MICROBIAL AND CATALYTIC ACTIVITY OF Zn^{2+} AND Cd^{2+} CHELATES WITH VALSARTAN.

PARASHAR H.MODH[1] AND JABALI J. VORA*[2]

[1.] Department of Chemistry, D.N.Science College,Dabhoi -391110 Gujarat India
[2.] Department of Chemistry, Hem. North Gujarat University,Patan-384265 Gujarat India

ABSTRACT

The metal chelates of Zn^{2+} and Cd^{2+}were prepared and characterized by physico-chemical analyses, Elemental analysis, UV - visible, IR, NMR and Thermal analyses. The probable structure has been assigned based on the above analysis. These complexes were used as catalyst for some selected redox and organic reactions. The antimicrobial activity of the ligand and their metal chelates were screened against various bacteria and fungi.

KEYWORDS: **Valsartan, Chelates of Zn^{2+} and Cd^{2+}, catalytic activity, antimicrobial activity**

JABALI J. VORA
Department of Chemistry, Hem. North Gujarat University,Patan-384265 Gujarat India

INTRODUCTION

The transition metal atoms of various soft and hard lewis acidity usually need to be satisfied in the most suitable fashion. Therefore hetero dentate ligands have great possibility to form polynuclear complexes.[1,2] Valsartan is a potent and specific competitive angiotensin II receptor antagonist (more commonly called an "ARB", which stands for Angiotensin Receptor Blocker) acting on AT1 subtype.[3] The study of different oxidation states in cobalt and their mono, di-and polynuclear chelates have been the centre of research because of their interesting synthetic, structural, spectroscopic, magnetic and opto electronic features.[4,5] The catalytic role of Zn constitutes Lewis acid activation of substrate stabilization of the leaving group and generation of a reactive nucleophile(Zn-OH).[6] There is a significant interest in the coordination chemistry of cadmium chelates because of the toxic environmental impact of cadmium. The militarization and immobilization of the cadmium in the environments and in some technical processes have been shown to depend significantly on the chelateation of the metal centre by chelating nitrogen donor ligands.[7] Dilipkumar et. all synthesized and characterized copper(II) ,cobalt(II) and chromium(III) complexes with 2,4,diamino-5-(3,4,5 trimethl-benzyl) pyrimidine and then characteterized by physicochemical and instrumental method.[8]

MATERIALS AND METHODS

Preparation of chelate

Analytical grade chemicals were used throughout the course of experimental work. Spectroscopic grade solvents were employed for recording the spectra. Zn(II) perchlorate and Cd(II) perchlorate were prepared in the laboratory of chemistry department, D.N. Science .college, Dabhoi. In the preparation of the metal chelates, the metal ion and the ligand were mixed in 1:1 molar ratio. Metal carbonate was added in a 0.02M perchloric acid until the effervescence stopped to prepare metal perchlorate solution. The synthesis of chelate was carried out by mixing a 0.01M M $(ClO_4)_2$ and 0.01M alcoholic solution of the ligand. (M=Zn^{II} Cd^{II}) The reaction mixture was refluxed for 3 hours at 90^0C temperature. After 3.0 hours, the reaction mixture was cooled. There was no immediate precipitation. pH of this solution was raised up to 6 using alkali solution which resulted in precipitation. The chelate was washed with a mixture of alcohol and water and then dried in oven at 50^0C to 60^0C temperature.

Physical measurements

M.P. and TLC (solvent alcohol, tolene:methanol (7:3)) of all chelates were taken. TLC indicated single and separate spot confirming chelate formation. Molar conductance (equiptronic,EQ-667) indicated the nonionic character of chelates. Both the chelates were found to be diamagnetic.(by Goy's method).UV Visible spectra were measured on shimabzu spectrophotometer (UV 1800) Metal percentage of zinc chelate and cadmium chelate were determined by EDTA titration.[9]

RESULTS AND DISCUSSION

Table –1
Analyses and physical measurements

Compound (Color)	Formula Weight(gm) (M.P.)	Rf value (λ max)	Molar Conductance in methanol (μ mho.cm^{-1}) (Magnetic Susceptibility	Elemental Analysis %C Found (Calculated)	%H Found (Calculated)	%N Found (Calculated)	Metal Percentage %M Found (Calculated)
Ligand $[C_{24}H_{29}N_5O_3]$ (Colorless)	435.519 (115°C)	0.3690 (270nm)	0.00636 ---	66.81% (66.13%)	6.45% (6.66%)	15.93% (16.07)	----- ----
$[ZnC_{24}H_{31}N_5O_5]$ (Colorless)	534.939 (155°C)	0.4762 (284nm)	0.00864 Diamagnetic	52.82% (53.84%)	5.43% (5.84%)	12.23% (13.09%)	13.07% (12.22%)
$[CdC_{24}H_{29}N_5O_4]$ (Colorless)	563.938 (144°C)	0.4048 (265nm)	0.00824 Diamagnetic	50.15% (51.12%)	4.30% (5.18%)	11.33% (12.41%)	18.26% (19.93%)

Note;- All the compounds are soluble in alcohol

Infrared Spectra study

The IR spectra of the metal chelates and ligand were recorded in KBr pellets (Bruker, alpha). From this study, the band observed at 3425cm^{-1} and 3270cm^{-1} in the ligand due to N-H starching and –OH stretching. In both the chelates, the -OH and -NH stretching bands disappear showing co-ordination between metal and O,N atoms. The frequencies 2990cm^{-1}, 2961cm^{-1} and 2962cm^{-1} in the ligand, Zn chelate and Cd chelate respectively, indicate –CH stretching. The band at 1750cm^{-1} of the ligand is due to the C=O stretching. In the Zn and Cd chelates, it is shifted to 20-25cm^{-1} lower energy indicating coordination by the oxygen. At 1595cm^{-1} medium peak appeared in ligand and chelate due to the N=N which indicates the presence of azo group. The frequency of 830cm^{-1} and 761cm^{-1} observed in ligand and chelate due to the p-substituted benzene ring. The bands observed at ~1391cm^{-1} and ~1350cm^{-1} indicate the isopropyl group present in ligand and chelate. The bands at 3593cm^{-1}, 3585cm^{-1}, 3565cm^{-1} present in Zn chelate indicated the water of coordination.

NMR Study

The ^{1}H NMR spectra of ligand and chelate was recorded in $CDCl_3$ (Bruker, Avance II 400 NMR Spectrometer). ^{1}H NMR spectrum exhibited multiplet signals at δ 6.95-7.63 ppm which indicated the aromatic protons. The methyl proton of the $–CH_2$-CH_3 were observed at δ 1.4 ppm and its $–CH_2$ proton appeared at δ 4.02 ppm. A singlet is observed at δ 15.94 ppm due to the N-H proton but in the chelate -NH proton signal at δ 15.94 ppm disappeared. A broad signal at δ 12.50 ppm was observed due to –COOH proton while in the chelate this proton disappeared which showed that the –COOH and –NH group of the ligand participated in the coordination.

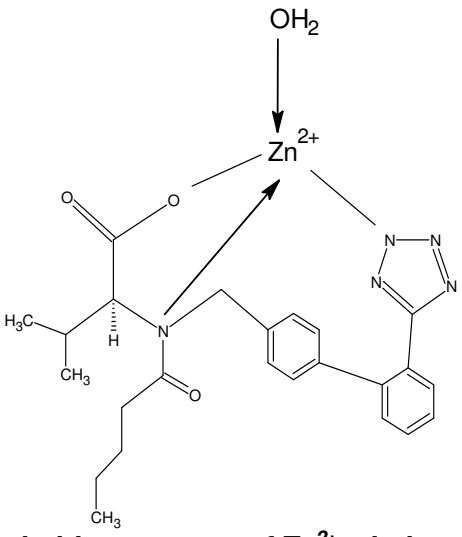
Thermal study

TGA analysis was carried out using Perkin Elmer, Pyris 1 TGA. In the chelate, there are two types of water molecules associated, one of them lattice water and second coordinated water. At the low temperature (60-120^{0}C), the lattice water will be lost and coordinated water molecule will be lost at high temperature (150-200^{0}C).[10] The thermo gravimetric analysis indicates the removal of water of coordination and crystallization for the chelate. In the Zn chelate at 100^0 C temperature 16.69 gm weight loss occurred which indicated that one H_2O molecule of crystallization with Zn chelate. And at the 150^{0}C temperature 11.05 gm weight loss occurred which indicates that one H_2O molecule coordinated with Zn chelate. In the Cd chelate at 100^0 C temperature 23.21 gm weight loss occurred which indicates that one H_2O molecule of

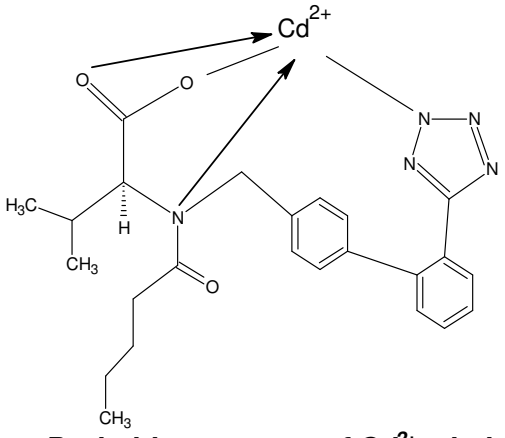
crystallization is present with Cd chelate, and at 150^0C temperature 1.08 gm weight loss occurred which indicated that there is no any water molecule coordinated with Cd chelate.

Table –2
TGA Analysis of chelates

Compound	Found			
	100ºC		150ºC	
	gm	%	Gm	%
Zn	16.69	3.33	11.05	2.21
Cd	23.21	4.24	5.93	1.08



Probable structure of Zn^{2+} chelate



Probable structure of Cd^{2+} chelate

From the spectral data, it can be seen that the zinc ion is probably coordinated by two oxygens and one nitrogen atom of the ligand valsartan and one water molecule coordinate to form a four coordinate chelate. Cadmium ion is coordinated by two nitrogens and two oxygens of the ligand to form a four coordinate chelate.

Antibacterial study

In antibacterial study, the inhibitory effects of the synthesized chelates on the growth of various microorganisms are listed in Table 3, 4, 5 and 6. Minimum inhibitory concentrations of these compounds were determined by literature method.[11] In the present study the antibacterial activity of the ligand as well as chelates have been studied against *E.Coli., S.Aureus,S .Pyogenus, P.Aeruginosa* by agar cup method and the anti fungal activity against *C.Albicans,A.Niger and A.Clavatus* also have been studied. It was observed that the antibacterial activity of the ligand either increased or remained same when it was chelated with Zn^{2+} and Cd^{2+} metal ions. The anti bacterial activity of Zn chelate was found to be equal to that of ampicilin against *S.Aureus* and *P.Aeruginosa*. Zinc chelate showed less activity against *S.Pyogenus* and *E.Coli.* compared with the standard antibiotics. The anti bacterial activity of Cd chelate was found higher to that of Ampicilin against *S.Aureus*. Cd chelate showed less activity against *S.Aureus, S.Pyogenus, P.Aeruginosa, E.Coli* compared to the standard antibiotics.

Table –3
Antibacterial Activity of ligand and chelates

Name of the compound		Minimal Inhibition Concentration (µg/ml)			
SR. No.	Code No.	*E.Coli* MTCC 443	*P.Aeruginosa* MTCC 441	*S. Aureus* MTCC 96	*S.Pyogenus* MTCC 442
1	Ligand	250	500	500	500
2	Zn chelate	500	100	250	>1000
3	Cd chelate	125	250	50	>1000

Table – 4
Antibacterial activity of standard antibiotics

Standard drug	Minimal Inhibition Concentration (µg/ml)			
	E. Coli	*P.Aeruginosa*	*S.Aureus*	*S.Pyogenus*
--	MTTC 443	MTCC 441	MTCC 96	MTCC 442
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

Table –5
Antifungal Activity of ligand and chelates

Name of the compound		Minimal fungicidal Concentration (µg/ml)		
SR. No.	Code No.	*C. Albicans* MTCC 227	*A. Niger* MTCC 282	*A. Clavatus* MTCC 1323
1	Ligand	500	>1000	>1000
2	Zn chelate	200	500	500
3	Cd chelate	500	>1000	>1000

Table –6
Antifungal Activity of standard antibiotics

Standard drug	Minimal Fungicidal Concentration (µg/ml)		
Drug	*C.Albicans*	*A. Niger*	*A. Clavatus*
--	MTCC 227	MTCC 282	MTCC 1323
	Microgram / ml		
Nystatin	100	100	100
Greseofulvin	500	100	100

Kinetic study

Three redox reactions were selected, potassium persulphate ($K_2S_2O_8$) with potassium iodide (KI), potassium bromate ($KBrO_3$) with potassium iodide (KI) and hydrogen peroxide (H_2O_2) with potassium iodide (KI).

$$K_2S_2O_8 + 2KI \longrightarrow 2K_2SO_4 + I_2$$
$$KBrO_3 + 6KI + 6HCl \longrightarrow KBr + 6KCl + 3H_2O + 3I_2$$
$$H_2O_2 + 2KI + H_2SO_4 \longrightarrow K_2SO_4 + I_2 + 2H_2O$$

These three reactions were carried with an addition of Zn and Cd chelates as a catalyst and without addition of chelate. Out of three reactions Zn and Cd chelates were able to increase the reaction rate to greater extent for the reaction of BrO_3^- + I^- in acidic medium. For the remaining two reactions, H_2O_2 with I^- and $S_2O_8^{2-}$ with I^- in acidic medium, addition of the 1% Zn and Cd chelate resulted in increase in the reaction rate. Data indicated that the enhancement of the reaction rate of $KBrO_3$ with I^- was highest compared to other two reactions.

Table –7
Reaction Rates with and without chelates

Reaction	k without chelate	k with Zn chelate	k with Cd chelate	% Increase in reaction rate at T = 305 K (Zn chelate)	% Increase in reaction rate at T = 305 K (Cd chelate)
$K_2S_2O_8$ + KI	$6.7928x10^{-5}$	$7.7048x10^{-5}$	$7.5806x10^{-5}$	13.43%	11.60%
$KBrO_3$ + KI	$1.5237x10^{-3}$	$1.8283x10^{-3}$	$1.7732x10^{-3}$	19.99%	16.37%
H_2O_2+ KI	$3.0696x10^{-4}$	$3.5084x10^{-4}$	$3.4918x10^{-4}$	14.30%	13.75%

Catalytic Study

4.6 gm of NaOH was mixed with 3.7ml of nitrobenzene and 24 ml methanol in 250ml round bottom flask. The mixture was refluxed for 3 hours in water bath with vigorous shaking. Then methanol is distilled off and the reaction mixture is dumped in cold water and the mixture is made acidic with HCl. The azoxybenzene separates as heavy oil and on stirring solidifies. The product is filtered and washed with water.

$$4C_6H_5NO_2 + 3CH_3OH + 3NaOH \longrightarrow 2C_6H_5NO{:}NC_6H_5 + 3HCOONa + 6H_2O$$

This is a standard organic preparative reaction[12] which should be carried out for 3 hours for getting 55.55% yield. When this reaction was carried out for 2 hours, 51.94% yield was obtained without any catalyst. The same reaction was carried out using 1% catalytic amount of the Zn and Cd catalyst, It gave 60.55% and 56.94% yield respectively. Thus, 16.57% increase in reaction yield was observed with catalytic amount of Zn chelate and 9.63 % increase in reaction yield was observed with a catalytic amount of Cd chelate.

Table -8
%yield with and without catalyst

Temperature	% yield without catalyst	% yield with Zn catalyst	% yield with Cd catalyst	% increase in yield with Zn catalyst	% increase in yield with Cd catalyst
360 K	51.94%	60.55	56.94%	16.57%	9.63%

CONCLUSION

This ligand was chelated with perchlorates of Zn^{2+} and Cd^{2+} ions. This Zn and Cd chelates were characterized by elemental analyses IR., NMR, T.G.A., UV visible spectroscopy etc. Then after two different types of study were carried out for these chelates. It was found that the chelates successfully increased the rates of all the selected redox reactions and the % yield increased and also the time requirement decreased. Antibacterial as well as the anti fungal study of these chelates was carried out. Some chelates gave better and comparable anti microbial activities.

ACKNOWLEDGEMENT

The authors thank SAIF, Chandigarh, CIMF dept. of chemistry, Hemchandracharya North Gujarat University, Patan and SICART, Vallabh vidyanagar for instrumental analyses.

REFERENCES

1. Rhett Kempe, Henrik Noss,Torsten Irrgang; Towards f and d electron interactions in amido metal complexes,Journal of organometallic chemistry,647 (1,2):12-20,(2002).
2. Z.Pan; M.T.Gamer and P.W.Roesky ; Copper(I) and Gold(I) complexes with

N,N'-Bis(diphenylphosphino)-2,6 diamino pyridine as ligand synthesis and molecular structure,Z. anorg.Allg.Chem ,632**,**744-748 (2006)

3. Raja Rajeswari K, Abbulu K.Sudhakar M.;Development,characterization and stability study of solid dispersion of valsartan,journal of chemical and pharmaceutical research,3(1):180-187(2011)
4. A.A.Khandar,B.Shaabani,F.Belas and A.Bakhtari; Synthesis, characterization,electrochemical and spectroscopic investigation of cobalt(III) schiffbase complexes with axial amine ligands the layered crystal structure of $[Co^{III}$(salophen)(4-picoline)$_2]ClO_4.CH_2Cl_2$,Inorganica chimica acta, 360(10),3255-3264 (2007)
5. Santokh S. Tondon S.D. Bunge, R.rakosi, Z.Xu and L.K. Thomson; Self assembly of mixed-valence Co(II) and Ni(II) clusters: azide-bidged 10single chain coordination polymers comprised of tetra nuclear units,tetranuclear Co(II) complexes, ferromagnetically coupled azide bridged tetra nuclear and hexa nuclear Ni(II) complexes:synthesis structural and magnetic properties:the international journal for inorganic organometallic and bioinorganic chemistry, Dalton trans issue 33 6536-6551(2009).
6. Andrea Erxleben and jolente Herman ;lournal of the chemical society,Dalton transactions,4,569-575 (2000).
7. James N. ,Wolfgang Lindner,Geoffrey Davies,David E. Seitz, Barry L. Karge ;rsolution of the optical isomers of dansyl amino acids by reversed phase liquid chromatography with optically active metal chelate additives, Anal. Chem. 51,433-435 (1979)
8. Copper(II),Cobalt(II) and Chromium (III) complexes of 2,4 diamino-5-(3,4,5 trimethoxy-benzyl) pyrimidine : Synthesis characterization and influence of copper(II) complex on germination of legume seeds. Dilip R Kulkarni,Mukund R. Mulley, Jijabhau K. Roadge, Madhavrao N. Deshpande and Swati S. Ardhapurkar International journal of pharmaceutical and bio science, 1(2), 1-13, (2010)
9. "A Textbook of quantitative inorganic analysis" Elementary instrumental analysis Arthur I. Vogel Third edition, 961(1964) The English language book society and Longmans Green and co. ltd.(1964)
10. A.P.Mishra, M.Khare; Non-isothermal degradation and kinetic parameters of some Schiff base complexes,journal of Indian chemical society,77(8): 367-370 (2000).
11. J.M. Andrews; Determination of minimum inhibitory concentration ,journal of Antimicrob. Chemotherapy, Vol 48 suppl. 51,(2001).
12. F.G.Mann and B.C.Saunders, " Practical Organic Chemistry"4th edition Orient Longman , 212-213,Pearson Education Ltd,U.K.(2009).