Synthesis, Characterization and Antibacterial Activity of Binuclear Complexes of Chiral Schiff Base 2,6-Bis (1S, 2R-2-Hydroxy-1-Methyl 2-Phenylethylimino)-4-Heptanone

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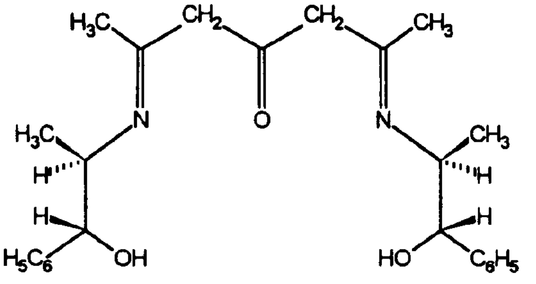
Summary: Binuclear complexes of VO(IV), Cr(II), Co(II), and Cu(II) with the title ligand were synthesized and characterized by elemental analysis and infrared spectra. The metal ions occupy the ONONO coordination sites of the ligand while acetates and two H_2O molecules are associated with each complex to satisfy the coordination requirements of the metal ions. The binuclear complexes have comparatively higher antibacterial activity as compared to their mononuclear analogs.

Introduction

Mono and polynuclear complexes of Schiff bases derived from condensation of diamines with triketones have been under investigation for some time [1,2]. These Schiff bases have two dissimilar N_2-O_2 and O_2-O_2 bonding compartments. These complexes have been described as models of polynuclear metalloenzymes which are active in biological systems. The bimetallic complexes of Schiff bases have been investigated for their magnetic exchange, structural phenomenon and reactivity studies [3]. Although chirality plays an important role in plants and biological systems, studies on complexes of chiral Schiff bases are scarce. Recently antibacterial studies on mononuclear complexes of a Schiff base *R*-pn$(BAA)_2$ have been reported from our laboratory [4]. Further, we have also reported the antibacterial effects of mononuclear VO(IV), Co(II), Ni(II) and UO_2(VI) with a new chiral Schiff base (*1S, 2R*-Nore)$_2$ DAA derived from condensation of norephedrine with diacetylacetone [5]. This ligand has two similar ONONO coordinating sites and can form binuclear complexes. It was observed that mononuclear complexes of this ligand have relatively stronger antibacterial activity as compared to free ligand. In continuation of our research pursuit, we report the synthesis and antibacterial effects of binuclear complexes of (*1S, 2R*-Nore)$_2$ DAA (I).



I (*1S,2R*-Nore)$_2$DAA

Results and Discussion

The chiral Schiff base (*1S, 2R*-Nore)$_2$DAA was prepared by condensing (+)-norephedrine with diacetylacetone in 2:1 mole ratio. The ligand (*1S, 2R* Nore)$_2$ DAA 1.5 H_2O has ONONO, two similar coordinating sites and binuclear complexes are formed filling both compartments. The VO(IV) complex is dirty green, Cr(II) complex is orange red while Co(II) and Cu(II) complexes are brown in colour.These complexes decompose between 110-202°C. (Table 1). The elemental analysis of these complexes fit the formulae $[V_2O_2LSO_4(H_2O)_2]$.4.5H_2O, $[Cr_2L(OAc)_2(H_2O)_2]$.H_2O, $[Co_2L(OAc)_2(H_2O)_4]$.3H_2O and $[Cu_2L(OAc)_2(H_2O)_4]$.3H_2O.

A comparison of IR spectra of these bimetallic complexes with that of the ligand and monometallic complexes reveals that bands due to alcoholic (-OH) bending at 1048 cm^{-1}, carbonyl stretching at 1708 cm^{-1}, C=N at 1492 cm^{-1} and C-N-C at 1132 cm^{-1} have either been shifted or completely disappeared upon coordination with metal ions. The carbonyl stretching at 1708 cm^{-1} in the ligand is shifted to 1616 cm^{-1} in VO(IV) and Cu(II) while at 1654 and 1716 cm^{-1} in Cr(II) and Co(II) complexes, respectively. The alcoholic group (OH) vibration at 1048 cm^{-1} has been shifted to lower frequency between 1024-1046 cm^{-1} in these complexes. The C=N stretching band at 1492 cm^{-1} in the ligand is observed at 1448-1464 cm^{-1} in VO(IV) and Cr(II) complexes respectively whereas it is observed at 1560 cm^{-1} in the Cu(II) complex. Similarly C-N-C vibration at 1132 cm^{-1} in the ligand has been shifted to 1128 cm^{-1} in the VO(IV), Cr(II) and Cu(II) and at 1168 cm^{-1} in the Co(II) complexes. A strong band due to carboxylate ($C_2H_3O_2$) is also observed between 1340-1416 cm^{-1} in these complexes indicating the presence of coordinated acetate. A second band due to acetate stretching is identified between 652-668 cm^{-1} in two of these complexes. Further, vibrations due to phenyl ring bending at 753 cm^{-1} and bands due to Ar-H and C-H have not been shifted to any appreciable extent in most of these complexes. The characteristic stretching due to V=O is observed at 976 cm^{-1}. In the far IR, M-O stretching is observed between 536-624 cm^{-1} while bands due to M-N stretching are identified at 460 cm^{-1} and 418 cm^{-1} in VO(IV) complex. These observations indicate that both compartments are occupied by the metal ions.

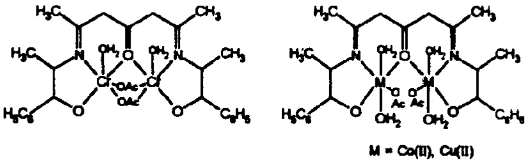
The elemental analyses show that 3-7 water molecules and two acetates are associated with these complexes. The VO(IV) complex is associated with a sulphate ion. It may be assumed that $[V_2O_2LSO_4(H_2O)_2]$4.5 H_2O, $[Cr_2L(OAc)_2(H_2O)_2]$.

Table - 1 Physical Constants and Prominent Infrared bands of the Bimetallic Complexes.

Complex	Physical State	Decom Pt. °C	Prominent Infrared bands (All bands reported as cm^{-1})											
			ν_{H_2O}	ν_{N-H}	ν_{C-H}	$\nu_{C=O}$	$\nu_{C=O}$ $+\nu_{C=C}$	$\nu_{C=N}$	Acetate Vib.	ν_{C-N-C}	OH bending	ν_{M-O}	ν_{M-N}	Others
$[V_2O_2L\ SO_4(H_2O)_2]$. 4.5H_2O	Green/ Amorphous	202	3420	3060	3032	1616	1544	1492 1448	-	1128	1036	536	460 428	$\nu_{V=O}$ 976
$[Cr_2L\ (OAc)_2\ (H_2O)_2]$. H_2O	Orange red/ Crystalline	152	3424	3148	3022	1659	1541	1464	1380	1128	1024	608	-	-
$[Co_2L\ (OAc)_2\ (H_2O)_4]$. 3$H_2O$	Brown/ Amorphous	110	3416	3088	3064	1716(w)	1576	-	1416 1340 668	1168	1024	616	-	-
$[Cu_2L\ (OAc)\ (H_2O)_4]$. 3H_2O	Brown/ Amorphous	130	3440	3084	3060 3028	1616	1584	1560	1408 1340 652	1180 1128	1048 1024	624	-	-

L - (*1S 2R* - Nore)$_2$ DAA

H_2O, $[Co_2L(OAc)_2(H_2O)_4]$. $3H_2O$ and $[Cu_2L(OAc)_2(H_2O)_4]$. $3H_2O$ all have octahedral geometry with H_2O occupying trans position in Co(II), Cr(II) Cu(II) complexes. In the VO(IV) complex the oxo group occupies a trans position to water. The $[CrL_2(OAc)_2(H_2O)_4]$. H_2O may have retained bridged acetates as shown (II) since the precursor $Cr_2(OAc)_4$. $2H_2O$ had bridging acetates.



II

Antibacterial Study

The ligand (*1S, 2R* (Nore)$_2$ DAA) has very weak inhibitory effects against most of the bacteria studied. The bimetallic Cu(II) and Co(II) complexes of this ligand are found more active against a variety of bacteria in much lower concentration i.e. MIC 160 µg/ml against *P.Catgaris,Pseudomonas, K. Pneumoniae, Staphcoagulase, S. Paratyphium, Salmonella (sensitive), Pseudomonas and Enterobacter* [Table 2-3]. The VO(IV) complex is found active against *Solmonella (resistant) and Staphcoagulase* in the concentration range 320 µg/ml. A comparison of the activity of monometallic Cu(II) complex with that of the bimetallic analog shows that the bimetallic complex is active in lower concentration than its monometallic analog against most of the tested strains. The Cr(II) complex is not found active against any bacteria upto the concentration range of 1280 µg/ml.

It may be concluded from these studies that binuclear complexes of (*1S,2R*-Nore)$_2$ DAA are more active against a number of gram positive and gram negative bacteria as compared to mononuclear complexes or the ligand itself.

Experimental

a) Materials

All metal salts, solvents and other reagents used were of highest purity analytical reagent grade and obtained from commercial sources. These were used without further purification.

The synthesis of triketone 2,4,6-heptanetrione (H_2DAA) was carried out by a literature method [6]. The synthesis and characterization of 2,6-bis(*1S,2R*, 2-hydroxy-1-methyl-2-phenyl-ethylimino) 4-heptanone has already been reported [5]. The precursor $Cr_2(OAc)_4$. $2H_2O$ was prepared as reported [7].

b)Synthesis of Binuclear Complexes

(i) Diaquo sulphato 2,6-bis (*1S,2R*-2-hydroxy-1-methyl-2-phenylethylimino)4-heptana-todioxodi-

Table-2: Determination of minimum inhibitory concentration of (1*S*,2*R*-Nore)$_2$DAA and its complexes against gram positive bacteria (MIC µg/ml)

ORGANISM NO.	1	2	3	4	5	6	7
(1S,2R-Nore)$_2$DAA (L)	>	>	>	>	>	>	>
$[V_2O_2L_2(SO_4)(H_2O)_2]$	1280	640	1280	1280	1280	1280	1280
$[C_2L_2(OAc)_2(H_2O)_2]$ H_2O	>	>	>	>	>	>	>
$[Co_2L_2(OAc)_2(H_2O)_4]$ $3H_2O$	160	160	160	160	80	160	160
$[Cu_2L_2(OAc)_2(H_2O)_4]$. $3H_2O$	160	160	160	160	160	160	640

1. *Staphylococcus* AFIP-P-5283 2. *Staphcogulase* (-ive) 3. *Staphylococcus* AFIP-P-5381
4. *Streptococcus* Group-D 5. *Staphaureus* AFIP-P-5369 6. *Staphylococcus* (control)
7. *Escheridia coli*

Table-3: Determination of minimum inhibitory concentration of (1*S*,2*R*-Nore)$_2$DAA complexes against gram negative bacteria (MIC µg/ml

ORGANISM NO	1	2	3	4	5	6	7	8	9	10
(1S,2R-Nore)$_2$DAA (L)	>	1280	>	>	1280	>	>	>	>	>
$[V_2O_2L_2(SO_4)(H_2O)_2]$ $4.5H_2O$	1280	640	1280	320	640	320	320	1280	1280	1280
$[Cr_2L_2(OAc)_2(H_2O)_2]$. H_2O	>	>	>	>	>	>	>	>	>	>
$[Co_2L_2(OAc)_2(H_2O)_4]$. $3H_2O$	80	160	160	160	160	80	160	160	160	160
$[Cu_2L_2(OAc)_2(H_2O)_4]$. $3H_2O$	160	160	160	160	160	160	320	160	160	160

1. *Enterobacter* 2. *Salmonella*(resistant) 3. *Escheridia coli* 4. *Skalmonella thphimurium* 5. *Pseudomonas*
6. *Salmonella*(sensitive) 7. *Salmonella paratyphium* 8. *Proteus vulgaris* 9. *Pseudomonas*(control)
10. *Klepsiella pneumoniae*

vanadium (IV) 4.5 hydrate,
$[V_2O_2\ (1S,2R\text{-Nore})_2\ DAA)\ SO_4\,(H_2O)_2]$. 4.5 H_2O.

4.35 gm (0.01 mole) of the ligand dissolved in 50 ml of acetone was brought to boiling. An aqueous solution containing 0.02 mole of vanadyl sulphate was added dropwise to the boiling ligand solution. The resulting green solution was refluxed for 15-20 minutes for completion of reaction. The solution was concentrated to a small volume (10 ml) upon which the complex precipitated. The product was separated, washed with acetone, ether and dried. Anal. Calcd. for $V_2O_2\ C_{25}H_{30}\ N_2O_3\ SO_4$. 6.5 H_2O. C 39.85, H 5.75, N 3.72, V 15.75% Found: C 39.55 H 4.86 N 3.86 V 16.77%.

(ii) Diaquo-diacetato 2,6-bis (*1S, 2R*-2-hydroxy-1-methyl-2-phenylethylimino) 4-hepta-natodi chromium (II) hydrate.
$[Cr_2(1S,\ 2R\text{-Nore})_2\ DAA)\ (OAc)_2(H_2O)_2]$. H_2O.

A methanol solution of 3.75 gm of $Cr_2(OAc)_4$. $2H_2O$ was slowly added to the ligand solution in acetone (4.35 gm, 0.01 mole) with stirring under nitrogen atmosphere. The colour of reaction solution was immediately changed to orange red which was stirred for 1 hour at room temperature. The reaction mixture was slowly concentrated at room temperature. The precipitated product was filtered, washed with acetone, ether and dried. Anal. Calcd. for $Cr_2C_{25}H_{30}N_2O_3\ (C_2H_3O_2)_2$. $3H_2O$ C 51.02 H 6.20 N 4.10 % Found: C 50.95 H 6.06 N 3.67 %.

(iii) Tetraaquo-diacetato 2,6-bis(*1S,2R*-2-hydroxy-1-methyl-2-phenylethylimino)4-hepta-natodi cobalt (II) trihydrate
$[Co_2(1S,\ 2R\text{-Nore})_2\ DAA)\ (OAc)_2\ (H_2O)_4]$.$3H_2O$.

To a boiling acetone solution of 4.35 gm (0.01 mole) of the ligand was added aqueous solution of 4.98 gms (0.02 mole) of hydrated cobalt(II) acetate in minimum solvent. The complex precipitated out upon refluxing the solution for one hour, which was filtered, washed with acetone, ether and dried. Anal. Calcd. For $Co_2C_{25}H_{30}N_2O_3\ (C_2H_3O_2)_2$. $7H_2O$ C 45.31 H 6.5 N 3.64 Co 15.33% Found: C 45.36, H 5.74 N 3.28 Co 15.6 %.

(iv) Tetraaquo diacetato-2,6-bis(*1S,2R*-2-hydroxy-1-methyl-2-phenylethylimino)4-hepta-natodicopper(II) trihydrate,
$[Cu_2(1S,\ 2R\ \text{Nore})_2\ DAA)\ (OAc)_2\ (H_2O)_4]$.$3H_2O$.

A 50 ml acetone solution of 4.35 g (0.01 mole) of the ligand was brought to boiling. An aqueous solution of 3.98 gm (0.02 mole) of copper (II) acetate was slowly added with constant stirring followed by 1.00 ml of triethylamine. The reaction mixture was refluxed for 15-20 minutes during which green bimetallic complex precipitated. The product was filtered, washed several times with acetone, ether and dried, Anal. Calcd. For $Cu_2C_{25}H_{30}N_2O_3\ (C_2H_3O_2)_2$. $7H_2O$ C 44.78 H 6.48 N 3.60 Cu 16.34% Found: C 44.70 H 5.63 N 3.15 Cu 16.81%.

Instrumentation

The elemental analysis were obtained from Midwest Microlab Indianapolis, Indiana, U.S.A. The metal contents were determined by literature methods on Shimdzu model 120-2 spectrophotometer using 10 mm quartz cells. The melting points were determined on MP-D melting point apparatus using sealed capillary tubes. Infra-red spectra of solid complexes in KBr disc were recorded on Perkin Elmer model 1710 FTIR Spectrophotometer.

Antibacterial Activity Studies

The complexes dissolved in DMSO were screened out for antibacterial effects. Minimum inhibitory concentration of the complex was determined using double dilution method. Daully's multipoint inoculator was used for the application of inoculum. The details of the procedure are reported earlier [5].

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