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# Synthesis, Characterization, and Antibacterial Activity of Complexes of (1*S*,2*S*)-N,N-1,2-Diphenylethylene-*bis*-(5-imino-1-phenyl-1,3-hexanedione)

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**Summary.** The synthesis and characterization of homobimetallic complexes of VO(IV), Cr(II), Co(II), Ni(II), and Cu(II) with the chiral *Schiff* base (1*S*,2*S*)-N,N-1,2-Diphenylethylene-*bis*-(5-imino-1-phenyl-1,3-hexa-nedione) is reported. The metal ions occupy both compartments of the ligand; water molecules fill the coordination spheres to provide an octahedral environment around the central atoms. The antibacterial activity of both mono- and bimetallic complexes against a number of *Gram*-positive as well as *Gram*-negative bacteria has been tested and is discussed.

**Keywords.** Transition metal complexes; Antibacterial activity; Chiral *Schiff* base.

## Introduction

Multinuclear complexes of ligands with the ability to bring two or more metal atoms into close proximity have been the subject of several investigations [1, 2]. Compounds of this kind obtained from metal ions and *Schiff* bases synthesized by condensation of diamines with triketones have turned out most suitable for the study of magnetic exchange as well as of spectroscopic and electrochemical properties [3, 4].

Complexes as mentioned above may be considered as model compounds for metalloenzymes in biological systems; therefore, stereochemistry is expected to play a vital role with respect to their mode of operation. Recently, mono- and bimetallic complexes of the chiral *Schiff* base 2,6-*bis*-(1*S*,2*R*)-(2-hydroxy-1-methyl-2-phenylethylimino)-1-heptanone have been shown to exhibit weak inhibitory effects [5]. In this contribution, the synthesis and antibacterial activity of binuclear complexes (**2**) of VO(IV), Cr(II), Co(II), Ni(II), and Cu(II) with (1*S*,2*S*)-N,N-1,2-diphenylethylene-*bis*-(5-imino-1-phenyl-1,3-hexanedione) (*S*,*S*-N,N-*stien*$(BAA)_2$, **1** [6]) and its mononuclear complexes is reported. The obtained compounds have been tested against a series of bacterial strains. The inhibitory effects of the complexes were found to be superior to those of the ligands for most of the bacteria studied.

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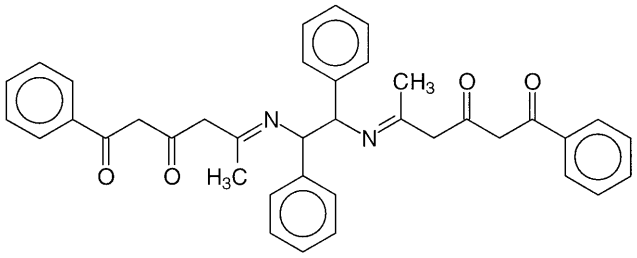
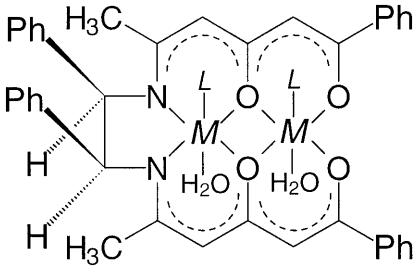


**1**



*M* = VO(IV), Cr(II), Co(II), Cu(II); *L* = $H_2O$, O (in case of the VO(IV) complex)

**2**

## Results and Discussion

Binuclear complexes of VO(IV), Cr(II), Co(II), Ni(II), and Cu(II) with the chiral *Schiff* base *S*,*S*-*stien*$(BAA)_2$ were synthesized by reacting the corresponding hydrated metal acetates with the ligand in a 2:1 ratio in aqueous acetone. The complexes widely differ in their colour and decompose between 150 and 230°C, $Cr_2L \cdot 8H_2O$ being the least stable one. They are fairly soluble in polar solvents like $CH_3OH$, $CH_3CN$, $(CH_3)_2SO$, *DMF*, and pyridine except for $(VO)_2L \cdot 3H_2O$ which is insoluble in methanol. Elemental analysis shows that two metal ions are coordinated with the ligand and anions are absent. These complexes are associated with different numbers of water molecules which was confirmed by thermal analysis in some cases.

A comparison of the IR spectra of the complexes with those of the ligand reveals that bands due to C=O, C=N, and C–N–C stretching vibrations in the ligand are either shifted to lower frequency or disappear completely upon complexation (Table 1). A strong multiplet band at 1732 $cm^{-1}$ due to carbonyl stretching in the ligand appears as a weak band in the region of 1665–1724 $cm^{-1}$ in the VO(IV), Ni(II), and Cr(II) complexes, whereas it is not observed in the Co(II) and Cu(II) compounds. The C=N stretching band at 1522 $cm^{-1}$ in the ligand is shifted to 1446–1482 $cm^{-1}$ in the complexes; another characteristic band at 1158 $cm^{-1}$ due to C–N–C vibration in the ligand is shifted to 1173–1188 $cm^{-1}$. However, this band is

**Table 1.** Characterization of bimetallic complexes of *S*,*S*-*stien*$(BAA)_2$

| | Colour State | $T_{decomp}$/°C | Important IR bands/cm$^{-1}$ | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $\nu_{H_2O}$ | $\nu_{N-H}$ | $\nu_{C-H}$ | $\nu_{C=O}$ | $\nu_{C=O}+\nu_{C=C}$ | $\nu_{C=N}$ | $\nu_{C-N-C}$ | $\delta_{O-H}$ | $\nu_{M-O}$ | $\nu_{M-N}$ | $\nu_{V=O}$ |
| $[V_2O_2L(H_2O)_2]\cdot H_2O$ | pea-green crystalline | 230 | 3412 | 3246 | – | 1724 | 1521 | 1456 | 1188 | 1029 | 561 | – | 986 |
| $[Cr_2L(H_2O)_4]\cdot 4H_2O$ | orange-red amorphous | 150 | 3420 | 3238, 3060 | – | 1674 | 1536 | 1482 | 1182 | 1029 | 560 | – | – |
| $[Co_2L(H_2O)_4]$ | brown powder | 190 | 3412 | 3238 | 3004 | – | 1536 | 1452 | – | 1029 | 558 | – | – |
| $[Ni_2L(H_2O)_4]$ | brown micro-crystalline | 190 | 3432 | 3250 | 3010 | 1665 | 1554 | 1446 | 1182 | 1023 | 576 | – | – |
| $[Cu_2L(H_2O)_4]\cdot H_2O$ | greenish-brown powder | 172 | 3302 | 3248 | 3012 | – | 1518 | 1452 | 1173 | 1023 | 576 | 510 | – |

not observed in $Co_2L\cdot 4H_2O$. The presence of water in the complexes is indicated by the appearance of a broad band between 3302 and 3412 cm$^{-1}$ (OH stretching) and 1023 and 1092 cm$^{-1}$ (OH bending). A sharp strong band at 986 cm$^{-1}$ is assigned to V=O stretching in the divanadyl complex. In most of the complexes, *M*–O stretching vibrations are observed between 558 and 576 cm$^{-1}$; a band at 510 cm$^{-1}$ due to *M*–N stretching could be identified in the Cu(II) complex. As two metal ions are bound by the ligand and a number of water molecules are present, it is proposed that both compartments of the ligand are occupied by metal atoms with an octahedral environment (cf. **2**).

The antibacterial activity of the ligand and its mono- and binuclear complexes in *DMSO* was tested against a number of *Gram*-positive and *Gram*-negative bacteria. The ligand is a very weak inhibitor ($MIC = 640$–$1280$ μg/cm$^3$) against most of the bacteria studied. The mononuclear VO(IV) and $UO_2$(VI) complexes as well as the binuclear VO(IV) compound have no inhibitory effect against any of the investigated microorganisms. The other complexes exhibit inhibitory effects superior to that of the ligand against most of the strains. Generally, the activity of the ligand and its complexes is very weak (about 10%) as compared to that of a standard antibiotic like tetracycline ($MIC = 32$–$64$ μg/ml). For details, see Tables 2 and 3.

## Experimental

### *Materials and methods*

All metal salts, solvents, and reagents used were of analytical grade and used as obtained from commercial sources. 1-Phenyl-1,3,5-hexatrione ($H_2BAA$) and *S*,*S*-1,2-diaminodiphenylethane (*S*,*S*-*stien*) were prepared by literature methods [7]. The synthesis of *S*,*S*-*stien*$(BAA)_2$ and its mononuclear complexes $VOL\cdot(H_2O)$, $NiL\cdot H_2O$, $CuL\cdot 2H_2O$, and $UO_2L\cdot 2H_2O$ has already been reported [6]; $Cr_2(OAc)_4\cdot 2H_2O$ was synthesized according to Ref. [8]. The results of elemental analyses (Midwest Micro Labs, Indianapolis, IN, USA; metal [9], C, H, N) agreed with the calculated values within

**Table 2.** *MIC* values of *S,S-stien*$(BAA)_2$ and its complexes against *Gram*-positive bacteria ($\mu g \cdot cm^{-3}$)

| | *Enterobacter* | *Salmonella* (resistant) | *Escherichia coli* | *Salmonella thphimurium* | *Pseudomonas* | *Salmonella* (sensitive) | *Salmonella paratyphium* | *Proteus vulgaris* | *Pseudomonas* (control) | *Klepsiella pneumoniae* |
|---|---|---|---|---|---|---|---|---|---|---|
| *S,S-stien*$(BAA)_2$ | 1280 | 1280 | 1280 | 1280 | 640 | 1280 | 1280 | 640 | 1280 | 1280 |
| [VO*L*$(H_2O)$] | – | – | – | – | – | – | – | – | – | – |
| [$V_2O_2$*L*$(H_2O)_2$] · $H_2O$ | – | – | – | – | – | – | – | – | – | – |
| [$Cr_2$*L*$(H_2O)_4$] · $H_2O$ | 320 | 640 | 640 | 640 | 640 | 320 | 320 | 320 | 320 | 640 |
| [$Co_2$*L*$(H_2O)_2$] · $H_2O$ | 1280 | 1280 | 1280 | – | – | 640 | – | – | 1280 | – |
| [Ni*L*] · $H_2O$ | 640 | 640 | 640 | 640 | 640 | 640 | 640 | 640 | 640 | 640 |
| [$Ni_2$L$(H_2O)_4$] | 640 | 640 | 640 | 640 | 640 | 640 | 320 | 640 | 640 | 640 |
| [Cu*L*$(H_2O)_2$] | 640 | 640 | 1280 | 1280 | – | 1280 | – | 1280 | – | 1280 |
| [$Cu_2$*L*$(H_2O)_4$] · $H_2O$ | 640 | 640 | 1280 | 1280 | 1280 | 1280 | 1280 | 1280 | 1280 | 1280 |
| [$UO_2$*L*$(H_2O)$] · $H_2O$ | – | – | – | – | – | – | – | – | – | – |

**Table 3.** *MIC* values of *S,S-stien*$(BAA)_2$ and its complexes against *Gram*-negative bacteria ($\mu g \cdot cm^{-3}$)

| | *Staphylococcus* AFIP-P-5283 | *Staphcogulase (-ve)* | *Staphylococcus* AFIP-P-5381 | *Streptococcus* group-D | *Staphaureus* AFIP-P-5369 | *Staphylococcus* (control) | *Escherichia coli* (control) |
|---|---|---|---|---|---|---|---|
| *S,S-stien*$(BAA)_2$ | 640 | 1280 | 640 | 1280 | 1280 | 640 | 1280 |
| [VO*L*$(H_2O)$] | – | – | – | – | – | – | – |
| [$V_2O_2$*L*$(H_2O)_2$] · $H_2O$ | – | – | – | – | – | – | – |
| [$Cr_2$*L*$(H_2O)_4$] · $H_2O$ | 320 | 640 | 640 | 640 | 640 | 640 | 640 |
| [$Co_2$*L*$(H_2O)_2$] · $H_2O$ | 1280 | 1280 | – | – | 1280 | – | 1280 |
| [Ni*L*] · $H_2O$ | 320 | 640 | 640 | 640 | 640 | 640 | 640 |
| [$Ni_2$*L*$(H_2O)_4$] | 320 | 320 | 640 | 640 | 640 | 640 | 640 |
| [Cu*L*$(H_2O)_2$] | 640 | 640 | – | – | 1280 | – | 1280 |
| [$Cu_2$*L*$(H_2O)_4$] · $H_2O$ | 640 | 640 | 1280 | 1280 | 1280 | 1280 | 1280 |
| [$UO_2$*L*$(H_2O)$] · $H_2O$ | – | – | – | – | – | – | – |

experimental error. Melting points: MT-MPD apparatus; IR spectra: KBr discs, Perkin-Elmer 1710 FT spectrometer.

*Syntheses*

*$[V_2O_2(S,S\text{-}stien(BAA)_2)(H_2O)_2] \cdot H_2O$ ($V_2O_2C_{38}H_{32}N_2O_4 \cdot 3H_2O$)*

The ligand (5.24 g, 0.01 mol) dissolved in 50 $cm^3$ acetone was heated to boiling, and an aqueous solution of $VO^{2+}$ (0.02 mol) was slowly added. Complexation was accompanied by the formation of a green precipitate. The mixture was refluxed for 20–25 min and then filtered, and the residue was washed with acetone and ether and dried. Yield: 72%.

*$[Cr_2(S,S\text{-}stien(BAA)_2)(H_2O)_4] \cdot 4H_2O$ ($Cr_2C_{38}H_{32}N_2O_4 \cdot 8H_2O$)*

A methanolic solution of 1.87 g (0.005 mol) of $Cr_2(OAc)_4 \cdot 2H_2O$ was slowly added to the ligand solution (2.92 g, 0.005 mol) in acetone with gentle stirring under nitrogen. The reaction mixture instantly changed to orange red and was slowly heated to reflux. After 20–25 min the oily product was separated and redissolved in ethanol. An orange-red product was obtained upon slow evaporation of the solvent which was recrystallized from ethanol. Yield: 78%.

*$[Co_2(S,S\text{-}stien(BAA)_2)(H_2O)_4]$ ($Co_2C_{38}H_{32}N_2O_4 \cdot 4H_2O$)*

To 50 $cm^3$ of a boiling acetone solution of the ligand (5.84 g, 0.01 mol), an aqueous solution of 5.98 g (0.02 mol) of hydrated $Co(OAc)_2$ was added slowly. The reaction mixture was refluxed for 30 min during which time an oily product was formed. which was separated and dissolved in ethanol. Upon slow evaporation of the ethanol at room temperature, the brown complex precipitated; it was filtered, washed with ether, and dried. Yield: 80%.

*$[Ni_2(S,S\text{-}stien(BAA)_2)(H_2O)_4]$ ($Ni_2C_{38}H_{32}N_2O_4 \cdot 4H_2O$)*

The preparation of the Ni complex was carried out analogously to that of the Co compound by reacting 5.84 g (0.01 mol) of the ligand in acetone with an aqueous solution of 4.6 g (0.02 mol) of hydrated nickel(II) acetate. Yield: 68%.

*$[Cu_2(S,S\text{-}stien(BAA)_2)(H_2O)_4] \cdot H_2O$ ($Cu_2C_{38}H_{32}N_2O_4 \cdot 5H_2O$)*

50 $cm^3$ of a solution of 5.84 g (0.01 mol) of the ligand was refluxed for 5 min and an aqueous solution of 3.98 g (0.02 mol) of hydrated copper(II) acetate was added. The complex precipitated upon refluxing the mixture for 1 h and subsequent concentration to a small volume. The product was separated, washed with acetone and ether, and dried. Yield: 67%.

*Antibacterial screening*

These complexes are insoluble in water; however, they easily dissolve in *DMSO* which has no inhibitory effects upon bacteria. *Dowley*'s multipoint inoculator was used for application of bacteria on predried *Mueller-Hinton* plates containing the complexes.

1.280 g of the ligand and the metal complexes were dissolved in a minimum quantity of *DMSO* and diluted to 5 $cm^3$. A series of eight test tubes was prepared containing 1280, 640, 320, 160, 80, 40, 20, and 10 μg of ligand or complex per $cm^3$ of agar solution. Sterilized test tubes and pipettes were used throughout. Nutrient agar solution was prepared in distilled water and autoclaved. 1 $cm^3$ of

ligand or complex solution was transferred to a sterilized 20 $cm^3$ flask and diluted to 20 $cm^3$ with agar solution. This was then transferred to a labelled petri dish and covered. The plates thus prepared were refrigerated.

The test organisms were subcultured on blood agar, *MacConkey* agar, and nutrient agar plates and incubated at 37°C aerobically and anaerobically for 24 h. The bacteria were reidentified by screening methods before subjecting to *MIC* studies. From nutrient agar plates, samples were inoculated in 2 $cm^3$ of *Mueller-Hinton* broth in *Bijon* bottles and incubated at 30°C aerobically for 18–24 h. Just prior to the test, the turbidity was adjusted to $10^5$–$10^6$ CFU/$cm^3$ (*Kirby-Bauer* standard) by diluting the suspension with sterile *Mueller-Hinton* broth. 0.5 $cm^3$ of this broth culture of each test strain were transferred into each well of the multipoint inoculator.

*Dowley's* multipoint inoculator was used for application of the inoculi. The specimens were divided into batches. The bacteria were inoculated on prepared *Mueller-Hinton* agar plates containing predried test compounds. The plates were allowed to dry at room temperature for 10–15 min after inoculation and then incubated aerobically for 10–24 h at 37°C. The *MIC* cited is the lowest concentration of test compound at which no growth of organism was visible to the unarmed eye.

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