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Synthesis of Macrocyclic Schiff Bases with Vanadium(V) Complexes and their Antibacterial and Antioxidant Properties

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ABSTRACT

Macrocyclic Schiff bases were synthesized and evaluated for their antibacterial activities against various bacteria and also for their antioxidant effects in vitro by nitric acid free radical scavanging assay. Ligands TSCB and HDCB were obtained by the condensation of the Benzil with Thiosemicarbazide and Hydrazine dihydrochloride respectively in ethanolic medium. Further their vanadium complexes were prepared by condensing synthesized ligands with vanadium salt. The synthesized compounds were characterized using IR, 1H- NMR, UV spectral datas together with elemental analysis, MP, TLC, MW, conductivities determinations.

Keywords: Macrocyclic ligands, Antioxidant Properties, Antibacterial Activities

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INTRODUCTION

The fast moving and expanding development in the chemistry of macrocyclic compounds as out lined by scientific backgrounds, interest and idiosyncrasies has been released due to their applicability in diverse areas of current interest mainly in coordination, bioinorganic and medicine chemistry.[1-3] Recently, it has been shown that the involvement of periodic elements particularly vanadium[4-5] with organic moieties having nitrogen and sulphur atoms plays a crucial role in designing a potential molecule of specific use. There has been a spectacular growth in the interest in vanadium complexes with macrocyclic Schiff bases as these represent one of the most biologically active classes of compounds, possessing a wide spectrum of pharmacological activities such as antibacterial, antifungal, antidiabetic, hypoglycemic, antihypertensive and analgesic properties.

Antioxidants are important in the prevention of human diseases. Antioxidant compounds may function as free radical scavengers, complexing agents for pro-oxidant metals, reducing agents and quenchers of singlet oxygen formation. Antioxidants are often used in oils and fatty foods to retard their autoxidation; therefore, the importance of search for natural antioxidants has greatly increased in the recent years.[6] These observations prompted us to synthesize some macrocyclic Schiff bases and their vanadium complexes and to investigate their structure, antibiological and antioxidant activities.

MATERIALS AND METHODS

AR grade chemicals, purified solvents and doubly distilled water were used throughout the experiments. The TLC was carried out on glass plates coated with silica gel activated at 50-60°C for 15-20 minutes. The plates were developed by exposure to iodine vapours. Melting points were determined on Sunsim electric melting point apparatus by open capillary method and are uncorrected. Molecular weights were determined by Rast Camphor method. Molar conductances of 10^{-3} M solution of the compounds were measured in DMF using EQ- 660A model.

The NMR spectral analysis was carried out at 27 °C on Bruker Advance 400 MHz FT NMR spectrometer. The chemical shifts (ppm) were referenced to TMS as internal standard. Electronic spectra of the compounds were recorded on a digital spectrophotometer. IR spectra of the samples were recorded on a Perkin–Elmer FTIR spectrophotometer as KBr discs. Elemental analysis was obtained on a Vario EL III Elementar Carlo Erba 1108.

Synthesis of Macrocyclic Schiff bases

An ethanolic solution of Benzil was mixed with the solution of Thiosemicarbazide and Hydrazine dihydrochloride in hot water (in equi molar ratio and in large amount of solvent) to give TSCB and HDCB ligands respectively. Both were constantly stirred for about 1 hour. The yellow solid precipitate was formed which was then filtered and recrystallised from ethanol and petroleum ether. (60-80°C)

Synthesis of Vanadium (V) complexes

Ethanolic solutions of prepared ligands were mixed with vanadium acetylacetone salt in ethanol in 1:1 molar ratio. The mixture was then refluxed for 6-7 hours on a water bath. The solid product obtained was filtered, washed and recrystallised with ethanol and dried *in vacuo*. As shown in fig1 & 2.

Fig 1: Expected Structure Oxovanadium complex of ligand HDCB

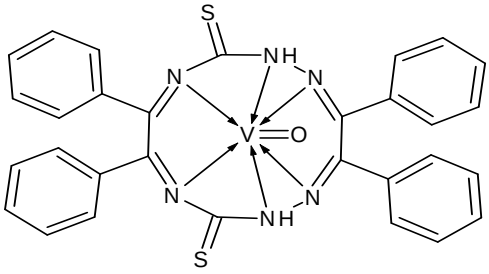
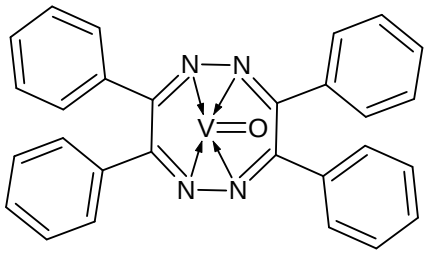


Fig 2: Expected Structure Oxovanadium complex of ligand HDCB



Antibacterial activities

The *in vitro* biological screening effects of the investigated compounds were tested against the bacteria gram (+) viz *Staphylococus aureus*, *Bacillus licheniformis*, *Micrococcus luteus* and gram(-) *Escherichia coli*, (ATCC) by disc diffusion method using Muller Hinton agar nutrient as the medium. Stock solutions (100, 500 and 1000 ppm) were prepared by dissolving the compounds in DMF solution. The suspension of the microorganisms were spreaded on the solid medium using sterile swabs and then incubated at 37°C for 24 h. After incubation, zone of growth inhibition was measured and results were evaluated as mean ±SEM in table 2, also the IC_{50} values are shown in table 3. Ofloxacin was adopted as positive control.

Nitric oxide scavenging method

Nitric oxide (NO) was generated from sodium nitroprusside (SNP) and was measured by the Griess reagent. SNP in aqueous solution at physiological pH spontaneously generates NO, which interacts with oxygen to produce nitrite ions that can be estimated by the use of Griess Reagent. Scavengers of NO compete with oxygen leading to reduced production of NO. SNP (5mM) in phosphate buffer solution (PBS) was mixed with different concentration (50, 75, 100, 125µg/ml) of the compounds and incubated at 25 °C for 180 minutes. The samples from the above were reacted with Griess reagent (1% sulphanilamide, 0.1% naphthylethylenediamine dichloride and 3% phosphoric acid) in 1:1 ratio. The absorbance of the solution formed during the diazotization of nitrite with sulphanilamide and subsequent coupling with naphthylethylenediamine dichloride was read at 546 nm and referred to the absorbance of ascorbic Acid, used as a positive control treated in the same way with Griess reagent. The experiment was performed in triplicate (shown in table 4) and % scavenging activity was calculated using the formula (%) = Ao – A_1 / Ao x100 where Ao is control absorbance and A_1 is the absorbance of the sample. IC50 values were also calculated.

RESULTS AND DISCUSSION

The compounds were obtained as intensely colored, which exhibit their solubility in ethanol, DMF and DMSO. The yields of compounds were found in the range 60-75%. The MP of ligands were near 80°C while that of complexes was above 200°C thus confirming the coordination. Purity of compounds was confirmed as both ligands and complexes moves as a single spot indicating the presence of only one component. The compounds show no appreciable conductance which ranged from 4.0-10ohm^{-1} cm^{2} mol^{-1}, and this supports the hypothesis of their non-eletrolyte nature. The results of Rast Camphor method were found in accordance with

calculated value, establishing the monomeric nature of the compounds. Physical charactristics, microanalytical data of the compounds are given in table 1.

Table 1: Microanalytical datas of all compounds

COMPOUND	YIELD IN %	COLOR	MP IN °C	MW FOUND (CALC)	ELEMENT ANALYSIS FOUND (CALC) IN %					
					C	H	N	O	V	S
(TSCB) $C_{30}H_{22}N_6S_2$	65-70	Yellow	80	529 (530)	68.4 (67.9)	5.2 (4.1)	14.9 (15.8)	-	-	11.3 (12.0)
VANADIUM COMPLEX OF (TSCB) $C_{30}H_{22}N_6S_2OV$	70-75	Reddish black	Above 200	597 (598)	61.3 (60.2)	3.4 (3.6)	13.8 (14.0)	3.2 (2.6)	8.1 (8.6)	10.1 (10.7)
(HDCB) $C_{28}H_{20}N_4$	65-68	Yellow	80	410 (412)	80.1 (81.5)	5.7 (4.8)	14.1 (13.5)	-	-	-
VANADIUM COMPLEX OF (HDCB) $C_{28}H_{20}N_4OV$	70-72	Dark Green	Above 200	478 (480)	69.7 (70.0)	5.2 (4.1)	10.9 (11.6)	4.0 (3.3)	10.1 (10.8)	-

The UV spectra of ligand TSCB shows absorption maxima at 300nm and 360nm attributable to π- π* and n-π* transition respectively, in its complex first remains unchanged while second shows blue shift and a band appear at 310nm due to donation of lone pair of C=N group to vanadium atom. Ligand HDCB shows the same band at 310nm and 365nm while second appears at 320nm.

The IR absorption band of ligands in the region1590-1640cm-1 due to C=N indicates the compounds to be macrocyclic Schiff bases. In spectra of vanadium complexes, very sharp peak in region 970-990cm^{-1} suggests the presence of V=O bond. The band due to C=N has shifted to lower frequency in the complexes indicating the coordination through azomethine nitrogen. The absorption bands associated with other functional groups present all appeared in the expected regions. The 1H-NMR spectra of compounds exhibited a multiplet in the aromatic region at δ6.83-7.91 ppm corresponding to the Harom protons, which gets shifted downfield in their vanadium complexes.

The molecular formulae of compounds were deduced from above discussions and these were found to be $C_{30}H_{22}N_6S_2$ for TSCB, $C_{28}H_{20}N_4$ for HDCB and $C_{30}H_{22}N_6S_2OV$ & $C_{28}H_{20}N_4OV$ for their respective vanadium complexes. Also, we proposed octahedral geometry for vanadium complexe of ligand TSCB and square planar geometry for vanadium complexe of ligand HDCB (as shown in fig 1&2). [8-9]

In the present study, we investigated the antibacterial properties of the compounds by the disk diffusion method at different concentration of 100, 500 &1000ppm against various bacteria. The screening results corroborated that all compounds exhibited antibacterial activities as shown in table 2. The results were further evaluated to determine the IC50 values by plotting the graph between % inhibitions with their respective concentrations. The results of this assay are outlined in Table 3. Results revealed that ligand TSCB was found to be more active than HDCB and was more potent against *Staphylococus aureus* with 0.50mg/ml IC50 value. On the other hand ligand HDCB was found to be most active against *Bacillus licheniformis* with having 0.52mg/ml IC50 value. From the results, we can also see that the complexes showed enhanced bactericidal effects compared with their respective ligands.

Table 2: Antibacterial Activities of all compounds
[Significance level P< 0.001, *P< 0.01. (n=3)]

Microorganism	Conc In ppm	Ligand (TSCB) (Mean±SEM)	Complex of (TSCB) (Mean±SEM)	Ligand (HDCB) (Mean±SEM)	Complex of (HDCB) (Mean±SEM)
E. coli(-)	100	15±0.289	16±0.551*	14±0.404	16±0.436
	500	22±0.115	24±0.603	22±0.578	24±0.493
	1000	29±0.173	31±0.440	27±0.200	32±0.152
S.aureus(+)	100	16±0.058	18±0.332	15±0.360	17±0.305
	500	23±0. 418	25±0.651	22±0.251	25±0.683
	1000	28±0.608	32±0.683	29±0.360	32±0.251
M.luteus(+)	100	14± 0.473*	16±0.404	15±0.569*	17±0.578*
	500	22± 0.416	27±0.305	22±0.513	25±0.173
	1000	29±0.529	31±0.416	28±0.625	31±0.289
B.licheniformis (+)	100	15±0.264	17±0.305	16±0.603*	18±0.473
	500	22±0.305	25±0.200	23±0.551	26±0.529
	1000	29±0.451	30±0.608	29±0.436	31±0.440

Table 3: IC_{50} values for antibacterial activities.

Compound	IC_{50}values (in mg/ml) against			
	E. coli(-)	S.aureus(+)	*M.luteus*(+)	*B.licheniforms* (+)
Ligand (TSCB)	0.55	0.50	0.56	0.58
Complex of (TSCB)	0.43	0.30	0.44	0.35
Ligand (HDCB)	0.58	0.58	0.58	0.52
Complex of (HDCB)	0.44	0.35	0.35	0.36

The compounds showed significant free radical scavenging action against nitric oxide (NO) induced release of free radicals at different concentration of (50,75, 100,125 µg/ml) Ascorbic acid was used as reference standard. The % inhibitions of compounds are shown in Table 4 as mean ±SEM of triplicates. The scavenging of NO by the compounds was increased in dose dependent manner i.e. it increases with the concentration. The results of IC50 values revealed that the metal complexes showed enhanced antioxidant activities. Ligands TSCB & HDCB and their complexes showed 110µg/ml, 154 µg/ml, 86 µg/ml and 94 µg/ml IC50 values respectively. These results denote the presence of antioxidant principles in the compounds.

CONCLUSION

The analytical data of all the complexes correspond to the general formula (ML)of the complexes. The spectral data are in good agreement with the proposed structures and are consistent with six-coordinated octahedral geometry for vanadium complex of ligand TSCB and four-coordinated square-planar geometry for vanadium complex of ligand HDCB.

From the results, we can also see that the complexes showed enhanced bactericidal effects compared with their respective ligands. The higher activity of the metal complexes may be owing to the effect of metal ions on the normal cell membrane. Metal chelates bear polar and nonpolar properties together; this makes them suitable for permeation to the cells and tissues. Changing hydrophilicity and lipophilicity probably leads to bring down the solubility and permeability barriers of cell, which in turn enhances the bioavailability of chemotherapeutics on one hand and potentiality at another.

Further investigation on the antioxidant and antibacterial effects clearly showed that the compounds had the potential to produce the desired antioxidants and antibacterials.

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