



Research Article

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Synthesis, Structural, Spectroscopic, Antimicrobial and Molecular modeling studies of a bis-chelating Sulphur containing Schiff base ligand

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ABSTRACT

Schiff bases have been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties. The biocidal effect of Schiff bases as well as its metal complexes is of interest due to their pharmacological activities. The azomethine linkage in Schiff bases is responsible for the biological activities. A class of ligands with more than one independent chelating sequence substituted on a single phenyl function exemplify bis – chelating ligands which can bind two metal ions simultaneously and form polynuclear complexes. The concept of bis- denticity becomes interesting to study if a variety of symmetric and unsymmetric bis-chelating systems are developed and employed in the formation of metal complexes. Biologically active Schiff base has been synthesized from 2,4-dihydroxy -5-acetylacetophenone and 2-aminothiophenol and characterized by IR, NMR and electronic spectral studies. The Schiff base geometry was evaluated using molecular calculation with argus lab software . The molecule is built and geometry optimization was done using molecular mechanics uniform force field (UFF) method. Molecular orbital calculations were performed with quantum mechanics based AM1 (Austin Model 1) approximation, for the synthesized ligand. The Schiff base functions as a binucleating, multidentate chelating agent and can coordinate via the deprotonated phenolic oxygen, azomethine nitrogen and sulphur atoms to the metal ion leading to two dimensional Schiff base polymers. The ligand has been evaluated for their antimicrobial potency, where the compound exhibited moderate to good potency.

Key words: bis-denticity, 2,4-dihydroxy -5-acetylacetophenone, 2-aminothiophenol, binucleating multidentate chelating agent, Schiff base polymers

INTRODUCTION

Schiff base compounds and their metal complexes have been extensively investigated due to their wide range of applications including catalysts [1], medicine [2,3] crystal engineering , anti-corrosion agents [4]. Schiff bases are studied widely due to their synthetic flexibility, selectivity and sensitivity towards the central metal atom; structural similarities with natural biological compounds and also due to presence of azomethine group(-N=CH-) which imports in elucidating the mechanism of transformation and racemization reaction biologically . Schiff bases have been reported to possess antimicrobial[5-9], antiviral[10], anticancer[11-14] and anti inflammatory activity [15]. Schiff bases having chelation with oxygen, nitrogen, sulphur etc. donors and their complexes have been used as drugs and reported to possess a wide variety of biological activities against bacteria, fungi, and certain type of tumors and also, they have many biochemical, clinical and pharmacological properties [16-18]. Imine or azomethine groups are present in various natural, naturally derived and non- natural compounds . The imine group present in such compounds has been shown to be critical to their biological activities [19].

A class of multidentate ligands developed from symmetric aromatic diketones have received investigation in our laboratory in view of their potentiality to simultaneously bind at least two metal ions with the help of two chelating sequences [20,21]. Such ligands have been designated as bis-chelating ligands. The metal complexes synthesized

from such ligands have been observed to possess interesting structural features like polymerism, antiferromagnetism and unusual geometries.

1,2,4,5 tetra substituted benzenes with all the four substitutions containing metal binding centres are of great synthetic interest as they can produce metal complex polymers.

Res-diacetophenone or 2,4-Dihydroxy-5-acetylacetophenone(DAAP) is a symmetric bisbidentate, 'O.O'-'O.O' donor and some bis bidentate / multidentate ligands can be synthesized by condensing $H_2 - DAAP$ with different amines. Infact some of such ligands can be tailor made or designed to drive metal ions into suitable / preferred coordination geometries.

As the proposed ligand possess hydroxy functions which can be deprotonated they constitute acidic metal binding centres which when associated with tri or other multidentate sequences are likely to form metal complexes of significant structural characteristics. Deprotonated phenolic groups can lead to bridging interactions with two or more metal ions and results in the formation of complexes which may exhibit exceptional magnetic properties .

EXPERIMENTAL SECTION

2.1. Chemicals and instrumentation

All the chemicals used for synthesis of the ligand precursors and the ligand were of Analar grade. The chemicals used in the synthesis were resorcinol,acetic anhydride, zinc chloride, charcoal, hydrochloric acid and o-amino thiophenol . Solvents used during the investigation include Methanol, Ethanol, Pet. ether Chloroform, Carbontetrachloride, Dimethyl Sulfoxide, Dimethyl formamide, 1,4 dioxane. These were purified by standard reported procedures.

The purity of the ligand was tested by thin layer chromatography (TLC). Suitable solvent mixtures of ethyl acetate, benzene, carbontetrachloride etc, were used to develop chromatograms. The spots were identified by iodine vapour. Melting points of ligand was determined on Toshniwal hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Perkin Elmer Spectrum BX FT-IR spectrophotometer in the range $4000 - 400\text{ cm}^{-1}$ with samples prepared using KBr pellet.

$^1\text{H-NMR}$ data was obtained on Varian 1-200 MHz, using DMSO-d6 solutions.

The UV/Visible spectra were obtained from PerkinElmer Lambda 25 spectrophotometer.

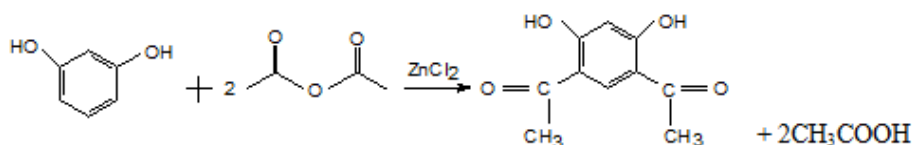
2.2. Synthesis of the Schiff base ligand

The ligand will be synthesized in the following steps.

1.Synthesis of 2, 4-Dihydroxy-5-acetylacetophenone (H_2 -DAAP) [23,24]

To a mixture of 10gms of freshly fused and powdered zinc chloride in 14ml of dry acetic anhydride, 10gms resorcinol was added while stirring. The resulting brown solution was heated gently on a flame to 140°C and maintained there for fifteen minutes. The resulting red viscous mass was cooled to room temperature and stirred with 80ml of dil. HCL (V/V 1:1 HCL).after a few minutes an orange red crystalline material which separated was filtered, washed thoroughly with water and dried. The dried product on repeated crystallization from methanol in presence of charcoal gave colorless long needles.

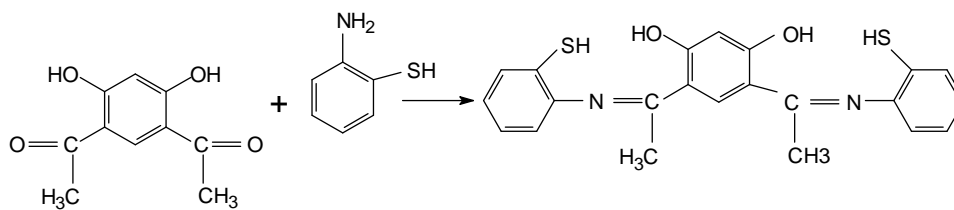
The over all reaction :



2. Synthesis of the ligand derived from 2, 4-Dihydroxy-5-acetylacetophenone and ortho- Amino thiophenol (H_2 -DAAAP)

To 0.05mol (9.7g) of $H_2 - DAAP$ dissolved in hot methanol, 0.1 mol (12.5ml) of ortho Amino thio phenol was added and refluxed for 3 hrs. After the completion of the reaction, water was added to produce the product. The compound was filtered washed with methanol and Petroleum ether and dried in vacuum.

Yield 80%



2.3. Molecular modeling studies

The Schiff base geometry was evaluated using molecular calculation with argus lab software . The molecule is built and geometry optimization was done using molecular mechanics uniform force field (UFF) method .

2.4. Biological Activity studies

The compound was tested for biological activity against different types of Gram-positive (Bacillus Subtilis ATTC 6051 and S. pyogones ATTC 12600) and Gram-negative bacteria (Escherichia Coli ATTC 11775 and Proteus Vulgaris ATTC 13315) and Fusarium Solani Martius and Aspergillus Niger Fungu. The sensitivity of a microorganism to antibiotics and other antimicrobial agents was determined by the assay plates which incubated at 28 °C for two days for yeasts and at 37 °C for one day for bacteria.

RESULTS AND DISCUSSION

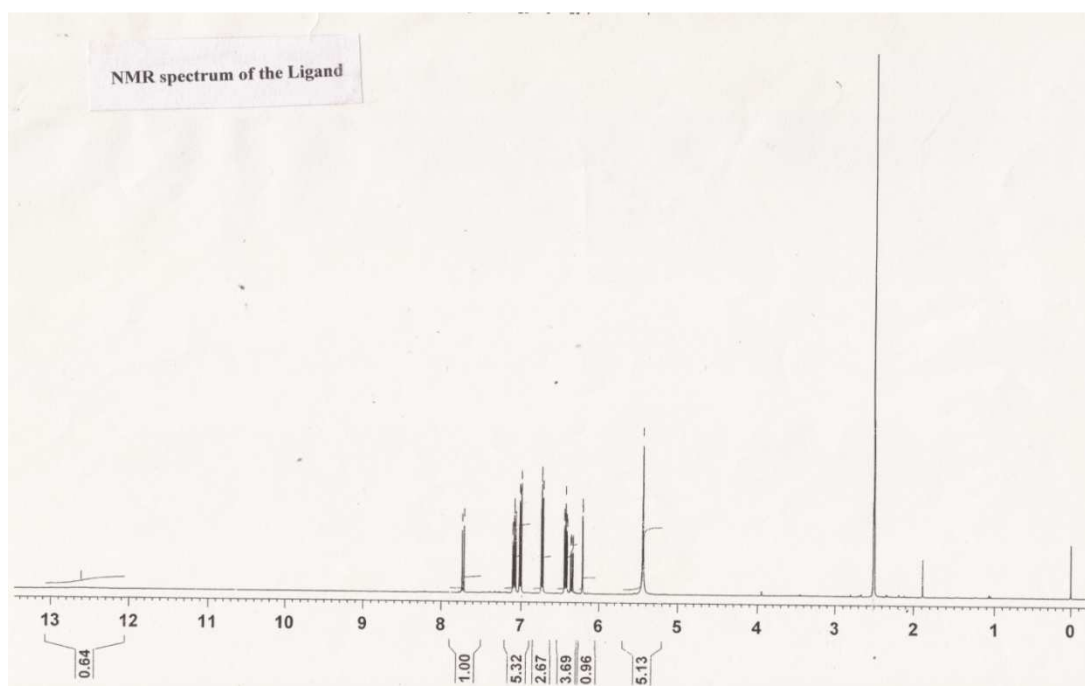
The prepared ligand is soluble in hot methanol, DMF and DMSO. The melting point of the ligand was found to be 175°C.

The analytical data obtained for H₂-DAAAP suggests its molecular formula to be C₂₂H₂₀N₂S₂Which is in close match with the expected structure. The data also suggests 1:2 condensation of 2, 4-Dihydroxy-5-acetylacetophenone with ortho-Aminothiophenol. Fig (1)

The LC mass spectrum of the ligand shows a peak at m/z 377 which is attributed to M+1 peak which corresponds to the molecular weight of the ligand 376.

3.1. NMR studies

The ¹NMR spectrum of the Ligand shows a signal at δ2.5 which corresponds to six protons of H₃C-C=N group. Complex multiplet in the region δ7.2 – 6.4 correspond to benzene protons. The signal at δ5.4 correspond to SH protons. The signal corresponding to the phenolic OH adjacent to azomethine moiety is indicated at δ12.6. The D₂O exchange studies also further confirm the structure.



3.2. IR Studies

The IR spectrum of H₂-DAAP shows characteristic bands assignable to O-H, C=O, C-O and C=C which are indications of the functional group of the target molecule. The broad band from 3500 to 2700 cm⁻¹ is due to the strong intra and intermolecular hydrogen bonded O-H stretching frequency of the phenolic group, which is also supported by the medium band at 1243 cm⁻¹ of its bending mode frequency. The band at 3074 cm⁻¹ is assigned to C-H stretching frequency of the aromatic group, besides its bending mode is observed at 839 cm⁻¹, which is a relatively sharp band. However, the band at 2929 cm⁻¹ can be assigned to CH stretching of the methyl group and its bending mode is observed at 1370 cm⁻¹. The band at 1646 cm⁻¹ corresponds to C=O stretching frequency of the carbonyl group. The bands that appeared at 1588 and 1490 cm⁻¹ can be assigned to C=C of the benzene aromatic ring.

The strong band that is located at 1258 cm⁻¹ can be assigned to C-O stretching of the phenolic group.

The IR spectrum of the ligand H₂-DAAAP shows the characteristic bands of the vibration frequencies of the functional groups such as O-H, C=N, C-O, S-H, C=C.

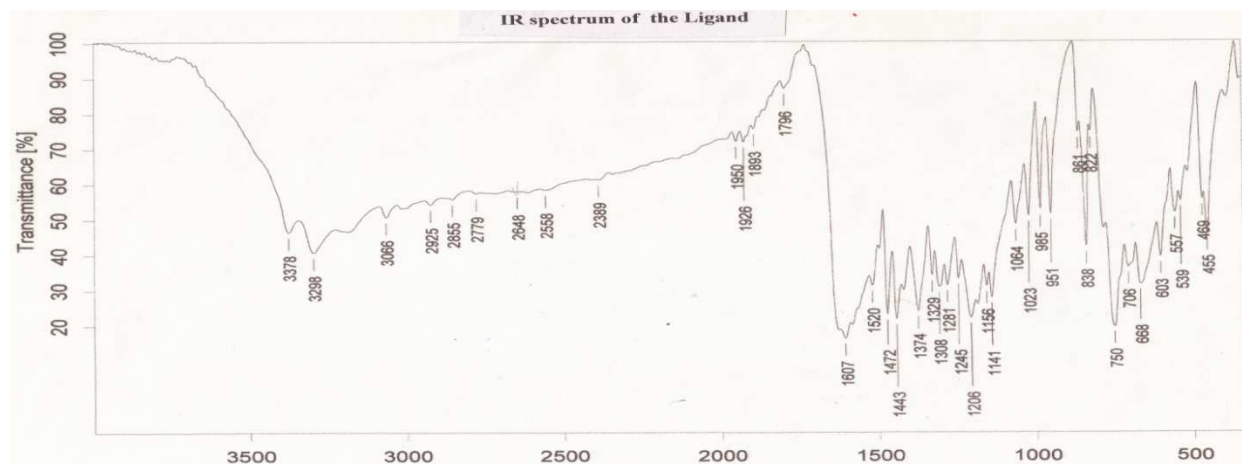
The band appearing at 3378 cm⁻¹ can be assigned to the phenolic O-H and band at 2648 cm⁻¹ can be assigned to ν S-H. The small bands at around 3066 and 2925 cm⁻¹ could be assigned to C-H stretching frequency of the benzene ring and the methyl group respectively. The sharp band located at 1607 cm⁻¹ is attributed to C=N stretching of the azomethine group. While the C=C stretching of the aromatic ring is observed at 1472 cm⁻¹.

The band at 1206 cm⁻¹ may be assigned to C-O stretching of the phenolic group. Bands at 1329 cm⁻¹ and 951 cm⁻¹ correspond to the bending frequencies of O-H phenolic group and S-H groups. The band at 838 cm⁻¹ may be due to ν C-S.

The infrared spectra of the ligand precursor and the ligand are summarized in table 1.

Table - 1 Characteristic Infrared frequencies of H₂-DAAP and H₂-DAAAP in Cm⁻¹

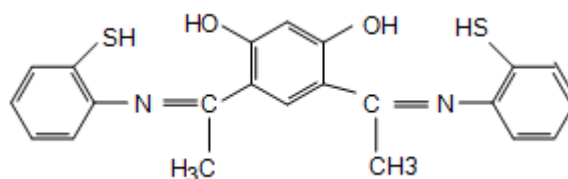
Compound	ν O-H	ν S-H	ν (C=N)	ν (C=O)	ν (C-O)
DAAP	3500-2700	-	-	1645	1258
Ligand	3378	2648	1607	-	1206



3.3. UV/Visible Studies

The electronic transition study of the free ligand was carried out in methanol. Three distinct bands were observed at 280 - 275 nm; 350 - 334 nm and 450 - 421 nm. The first two bands correspond to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of the azomethinechromophore [25,26] respectively.

Based on the above obtained spectral data the proposed structure of the Schiff base is

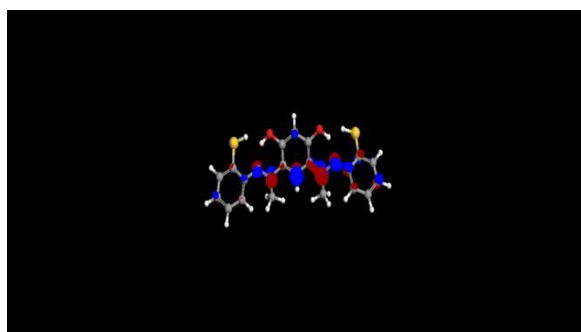
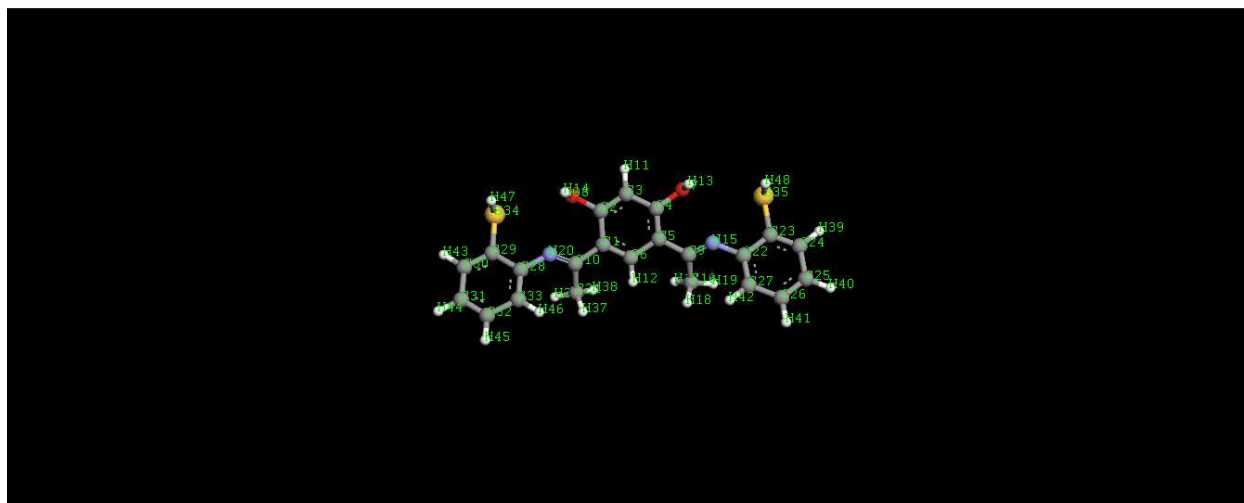


3.4. Molecular Modeling Studies

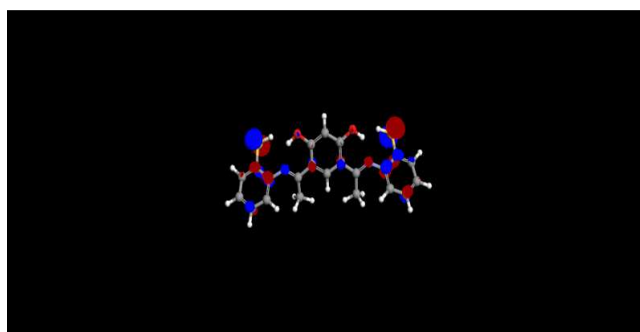
The Schiff base geometry was evaluated using molecular calculation with argus lab software . The molecule is built and geometry optimization was done using molecular mechanics uniform force field (UFF) method . Molecular orbital calculations were performed with quantum mechanics based AM1 (Austin Model 1) approximation, for the synthesized ligand. The Self consistent field (SCF) energy value and heat of formation ΔH_f for the optimized geometry are shown below.

Final SCF Energy = -96791.36 kcal/mol

Heat of Formation= -21.45 kcal/mol



LUMO



HOMO

3.5. Biological activity

In testing the antibacterial and antifungal activity of the compound we used more than one test organism to increase the chance of detecting antibiotic principles in tested materials. The sensitivity of a microorganism to antibiotics and other antimicrobial agents was determined by the assay plates which incubated at 28 °C for two days for yeasts and at 37 °C for one day for bacteria. The compound was tested for biological activity against different types of Gram-positive (Bacillus Subtilis ATTC 6051 and S. pyogones ATTC 12600) and Gram-negative bacteria (Escherichia Coli ATTC 11775 and Proteus Vulgaris ATTC 13315) and FusariumSolaniMartius and Aspergillus Niger Fungu.

The following results are obtained as listed in Table 2:

Table 2 Biological activity and MIC₅₀ of the ligand

Sample	Fungus		Bacteria			
			G. -ve		G. +ve	
	<i>F. solani</i>	<i>A.Niger</i>	<i>E.Coli</i>	<i>P.Vulgaris</i>	<i>B.Subtilis</i>	<i>S.Pyogones</i>
Ligand	1.1	0.9	-ve	-ve	-ve	-ve
MIC ₅₀	>100µg/mL	>100µg/mL	-ve	-ve	-ve	-ve

Bacteria: The Schiff base ligand is found to have no biological activity against all tested bacteria.

Fungus: Schiff base ligand shows antifungal activity against *F. solani* and *A. niger*. From the Table, ligand is found to have high sensitivity against *F. solani* than *A. niger*.

CONCLUSION

The ligand is of significant synthetic interest from chelation point of view. As the chelating functions are present on the opposite sides of the benzene ring, they are likely to produce polynuclear complexes. They are likely to provide a variety of donor systems for coordination like ON and S for efficient metal binding reactions. Further the ligand can behave as symmetric bis-bidentate and multidentate system. The Schiff base ligand is found to have no biological activity against all tested bacteria.

but shows antifungal activity against *F. solani* and *A. niger*. The ligand is found to have high sensitivity against *F. solani* than *A. niger*.

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