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Research Article

Molecular Docking, Fluorescence, Morphological, and Antimicrobial studies of Novel Schiff Base Ligand Derived from Glutaric Anhydride and its Nickel (II) Complex

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ABSTRACT

A new series of nickel (II) complex of the Schiff base derived from salicylaldehyde and 3,4-diaminobenzophenone with glutaric anhydride have been synthesized. These compounds have been characterized by molar conductivity measurements, infrared, and electronic spectra. The Schiff base ligand and its complex further identified by nuclear magnetic resonance (^{1}H NMR), ^{13}C NMR, scanning electron microscopy, energy-dispersive X-ray, fluorescence, and molecular docking study. Antimicrobial activity of the Schiff base ligand and their metal complex reveals that the Schiff base transition metal complex shows significant activity against some bacteria.

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INTRODUCTION

Schiff bases composed of N_2O_2 donor atoms are important chelating ligands for designing supramolecular synthons, medicinal, and catalytically useful metal complexes.[1-3] There has been enormous report directed toward the development of novel chemical compounds able to arrest or reverse the development of cancer.[4,5] Biological activities of transition metal complexes derived from Schiff base ligands are one of the most exhaustively studied topic in coordination chemistry. Furthermore, nickel is an important transition metal and its coordination compounds display interesting binding properties with proteins and nucleic acids.[6] The "N" and "O" containing Schiff base ligands and their nickel (II) complexes have become important due to their wide biological activity.[7-9]

The nickel (II) complex with N_2O_2 donor macrocyclic Schiff base ligand derived from 3,4-diaminobenzophenone with the glutaric anhydride and salicylaldehyde in same molar ratio has been developed using simple condensation process. This paper concentrates on the synthesis and biological activity of Schiff bases ligand and their nickel (II) complex.

EXPERIMENTAL SECTION

Reagents

The important chemicals used in the present study are given in Table 1. All chemicals employed in the present study were of analytical grade. Solvents employed were either of 99% purity or purified by standard laboratory procedures.[10]

Analytical methods

A variety of physicochemical methods have been employed to characterize the structure of organic Schiff base ligands and their metal complexes and in biological studies. A brief account of these methods is given below.

Physical methods

The infrared spectrum was recorded using KBr pellets in the range of 4400–400 cm^{-1}. UV-visible spectra of the ligand and the complexes were recorded on Perkin Elmer Lambda 3B UV-visible spectrophotometer in the range of 200–900 nm. The

Table 1: Important chemicals with specified make

Name of reagents	Manufacturer
Salicylaldehyde	LOBA Chemie Pvt., Ltd., Mumbai
3,4-Diaminobenzophenone, glutaric anhydride	Avra Synthesis Pvt., Ltd., Hyderabad
Nickel (II) nitrate hexahydrate	Merck, Germany

nuclear magnetic resonance (^{1}H NMR) spectra of the ligand and complex were recorded in Joel 500 MHz NMR spectrometer using $(CD_3)_2$ SO. The molar conductance of the ligands and the complexes was measured using 10^{-3} M solution of dimethyl sulfoxide (DMSO) at 25°C using an Elico CM-180 conductivity meter and Elico-type CC-03 conductivity cell of cell constant 1.05 cm^{-1}. Magnetic susceptibility of complex was measured at room temperature on a Gouy balance using $CuSO_4.5H_2O$ as a callibrant. SEM and energy-dispersive X-ray spectrometry (EDS) analyses were performed on Philips XL-30 scanning electron microscope (SEM) operating at 20 kV. Specimens for analysis were prepared by dusting the compounds on carbon tape.

The biological importance of the synthesized ligands is assessed by performing docking studies using AutoDock Vina PyRx software.[11] The docking calculations were performed using Run Vina and the binding affinity was used to determine the best-docked structure from the output. The predicted binding affinity is in kcal/mol. The fluorescence study of the nickel (II) complex was carried out using Perkin-Elmer LS 55 fluorescence spectrophotometer. The light source was xenon arc lamp and path length was 10 nm. The emission was carried out at 25°C using 10^{-4} M solutions in DMSO. Antimicrobial activity was investigated against four bacterial species: (i) Gram-positive bacteria: *Staphylococcus aureus* and *Enterococci* and (ii) Gram-negative bacteria: *Escherichia coli* and *Pseudomonas aeruginosa*.

Synthesis of schiff base ligand (e)-6-((4-benzoyl-2-((e)(hydroxy-benzylidene)amino)phenyl)imino) tetrahydro-2h-pyran-2-one

The new Schiff base ligand was synthesized by following the literature procedure.[12-14] Glutaric anhydride, salicylaldehyde (1 mol), and 3, 4-diaminobenzophenone (1 mol) were added into 20 mL of absolute ethanol containing a few drops of concentrated hydrochloric acid in a 100 mL round-bottomed flask. The reaction mixture was refluxed for 2.30 h. It was then cooled and ice-cold water was added. The product so formed was filtered, washed, dried, and recrystallized from alcohol, yield 62%. Analysis: ($C_{25}H_{20}N_2O_4$). Calculated mass 412.44, observed mass 412.00. ^{1}H NMR: 10.25 ppm (1H, s, Ar-OH), 8.20 ppm (1H, s, CH=N), 7.04–7.80 ppm (m, Ar-H), 3.19 ppm (2H, t, CH_2), 2.50, ppm (2H, m, CH_2). ^{13}C NMR: 195.9 ppm (C=O), 158.4 ppm (CH=N), 113.0–132.9 ppm (Ar-C). Fourier transform infrared (FT-IR), KBr pellets (υ, cm^{-1}): 3290 υ(-OH str sharp band); 1730 υ(C=O for glutaric anhydride); 1547υ(C=N str); 3052 (CH-Ar str); electronic spectrum: Band absorbed around 267 and 350 nm.

Synthesis of schiff base Ni (II) complex

In Scheme 1, to a solution of Schiff base ligand (L_1) (0.1 g, 0.003 mol) in ethanol was added a solution of nickel nitrate hexahydrate (0.07 g, 0.003 mol), refluxed for 2.30 h. After refluxing, the mixture was filtered while hot. The filtrate was cooled for 1 day around 0°C. A brown-black product was obtained,[15] washed with ethanol, and then dried. The percentage of yield was 84. ^{1}H NMR: 8.16 ppm (1H, s, CH=N), 7.29–7.79 ppm (7H, m, Ar-H), 3.3–3.6 ppm (2H, s, H_2O) 2.50 ppm (2H, m, CH_2), and 2.92 ppm (2H, t, CH_2). ^{13}C NMR: 195.90 ppm (Ph-CO-Ph), 158.2 ppm (CH=N), and 115.0–135.5 ppm (C=C).

FT-IR, KBr pellets (υ, cm^{-1}): 3375 υ (broadband in H_2O), 1648 υ (C=O for benzophenone); 1537 υ (C=N str); 1384 (N-O str), 474υ (Ni-N), 545 υ (Ni-O); electronic spectrum: Band absorbed around 272, 395, 430 and 536 nm.

RESULTS AND DISCUSSION

In the present investigation, Schiff base macrocyclic ligands and their nickel (II) complex have been synthesized through condensation of aldehydes or ketones with primary amines (Schiff *et al*., 1864). The general mechanism has exhibited in Scheme 2.

The first step in this reaction is an attack of nucleophilic nitrogen atom of amine on the carbonyl carbon, resulting in a normally unstable carbinolamine intermediate. The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration. Typically, the dehydration of the carbinolamine is the rate-determining step of Schiff base formation and that is why the reaction is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and becomes non-nucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. Therefore, many Schiff base syntheses are best carried out at mildly acidic condition. The Schiff base ligand refluxed with various metal ions to form metal complexes.

The synthesized complexes are soluble in DMF and DMSO. The molar conductance values for the macrocyclic Ni (II) complex (10^{-3}M) are determined in dimethyl sulphoxide at room temperature and the molar conductivity value of nickel (II) complex is 10.20 $\Omega^{-1}cm^2$ mol^{-1}.[16] The molar conductance of the complexes was found to be ranging from 14 ohm^{-1} cm^2 mol^{-1} to 22 ohm^{-1} cm^2 mol^{-1}.[17] On the basis of molar conductance measurements of the nickel (II) complex in DMSO corresponds to be non-electrolytic in nature of the complex. The magnetic moment of the nickel (II) complex at room temperature lies in the range of 2.94–2.96 B.M. The observed magnetic moment corresponding to two unpaired electrons which is in the range (2.94– 2.96 B.M) in tune with a high spin configuration and show the presence of an octahedral environment around the Ni (II) ion in the complexes.[18] Infrared spectra of ligand and metal complex are almost same with slight shift in peak position and varied intensity confirming the coordination of ligand to metal ions.

The band for C=N stretching of ligand was observed at lower frequency by 20–40 cm^{-1} in the metal complex, indicating

involvement of the azomethine nitrogen in the complex formation. The shift of the –OH band has appeared at 3291 cm^{-1} in the ligand, on complexation this band is disappeared, indicating deprotonation of the phenolic –OH by the complex. Weak bands at 500–550 cm^{-1} indicate Ni-O bond and a band in the region 430–490 cm^{-1} is due to Ni-N bond.[19] The electronic spectrum of ligand showed two bands, one in 267 nm and the other in 350 nm due to $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$.[20] On the other hand, the band corresponding to azomethine showed a slight shift to longer wavelength ongoing from ligand to complex, indicating coordination of ligand to metals through the azomethine moiety. The electronic spectrum of nickel (II) complex exhibits four absorption peaks. The first one is 272 nm might be due to $\pi \rightarrow \pi^*$; similarly, $n \rightarrow \pi^*$ and charge transfer spectra have been reported at 395 nm and 430 nm, respectively. The fourth band found at 536 nm can be focused to d-d transition.[21] The result of the finding exhibited octahedral geometry was found to nickel (II) complex.

Molecular docking studies

The PDB structure 4s1y[22] of human serum albumin is used for docking studies which play a key role in increasing the growth and productivity of cells and increases overall cell health. The best-docked complex selected has a binding score of −10.7 for nickel (II) complex of ligand which predicts a good inhibition. Figure 1 showed human serum albumin docked with ligand. The docked ligand interacts with the protein by forming four hydrogen bonds with the residues Lys195 *Å*, Asp451 *Å*, Arg222 *Å*, and Lys 92 *Å* with bond distances 3.12 *Å*, 3.49 *Å*, 3.21 *Å*, and 3.36 *Å*, respectively. The hydrogen bond showed in yellow line. Nickel (II) complex of ligand forms three hydrogen bonds with the protein in residues Glu292 *Å*, Lys 199 *Å*, and Gln196 *Å* with bond distances 3.20 *Å*, 3.17 *Å*, and 3.14 Å, respectively. The figure confirmed the nickel (II) ion coordinate with ligand. The nickel (II) complex of ligand is shown in Figure 2.

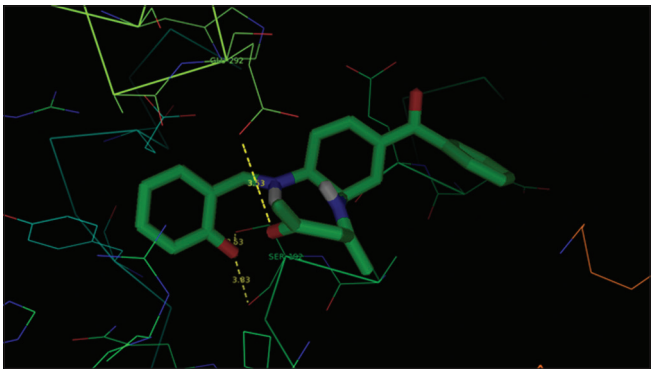


Figure 1: Ligand docked with 4s1y showing formation of hydrogen bond and distances

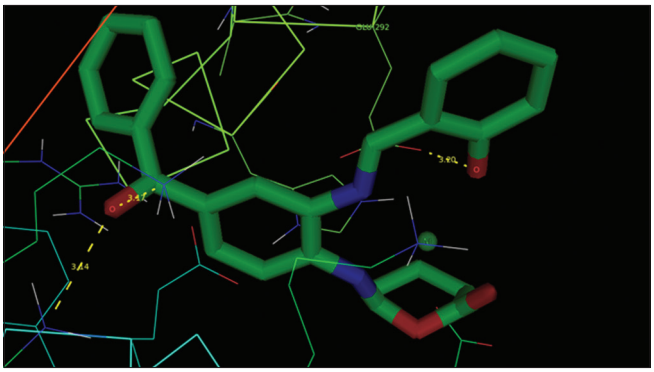
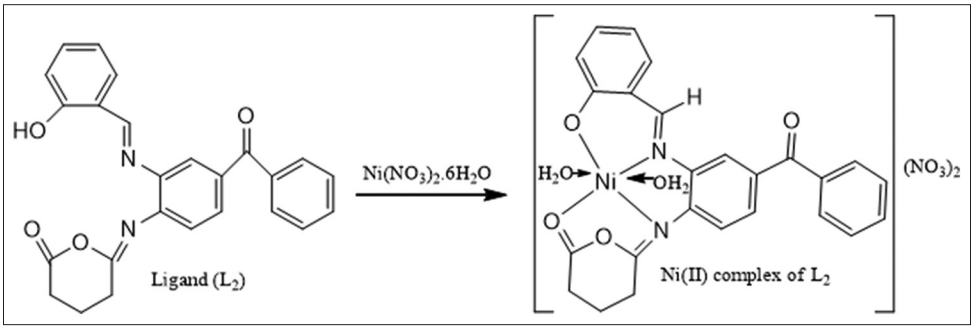
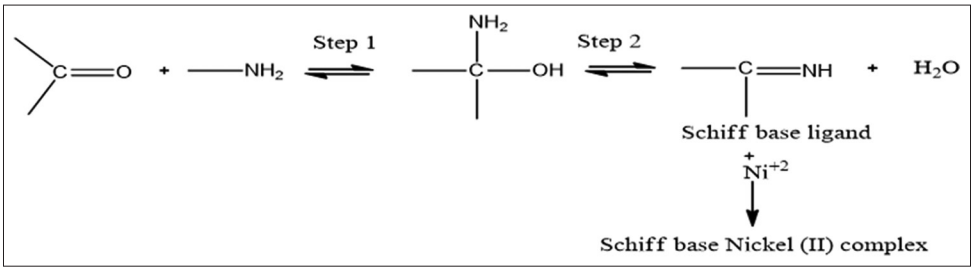


Figure 2: Nickel (II) complex of Schiff base ligand docked with 4s1y showing formation of hydrogen bond and distances



Scheme 1: Synthesis of nickel (II) complex of (E)-6-((4-benzoyl-2-((E)(hydroxy-benzylidene)amino)phenyl)imino) tetrahydro-2H-pyran-2-one



Scheme 2: Mechanism of Schiff base ligand and their nickel (II) complex formation

Morphology study

The surface morphology of nickel (II) complex has been examined using SEM analysis, which is observed that the nickel (II) complex is non-spherical shaped. SEM image of nickel (II) complex is shown in Figure 3.

Figure 4 showed the energy-dispersive X-ray spectrum of nickel (II) complex, which related to the perfect combination of the elements such as Ni, C, N, O, and H which constitute the complex can be evidence with this composition.

Fluorescence study

The emission wavelength of Nickel (II) complex appeared at 425 and 552 nm. The emission spectrum shows very strong emission at 552 nm and week emission at 425 nm.[23] The emission spectrum of nickel (II) complex is shown in Figure 5.

Antibacterial activity

The antimicrobial activity of ligands and their metal complexes was tested against a representative number of pathogenic organism, namely *S. aureus, Enterococci, P. aeruginosa,* and *E. coli,* using minimum inhibitory concentration method and the values are shown in Table 2.

The coordination of metal ion to the Schiff base influences the magnetic property and conductance which may also be a cause for the extensive biological characteristics of the complex. The azomethine bond also extends contribution for activity of the complexes.[24] As per the study on ZOI for ligand and their Nickel (II) complex found to have certain activity against the gram-positive and gram-negative bacteria.. Table 3 summarized the ZOI values of various Schiff base ligands and their nickel (II) complex. From these values indicate the complex more active than the ligand.

CONCLUSIONS

The formation of mononuclear nickel (II) complex is thermally stable. The complex was characterized by spectral

Table 2: Physicochemical and analytical data of the synthesized compounds

Compound	Mol. Wt.	M. P. (in °C)	Yield (%)	Color
Ligand	412	222–223	65	White solid
Nickel (II) complex	629	>300	84	Brownish-black solid

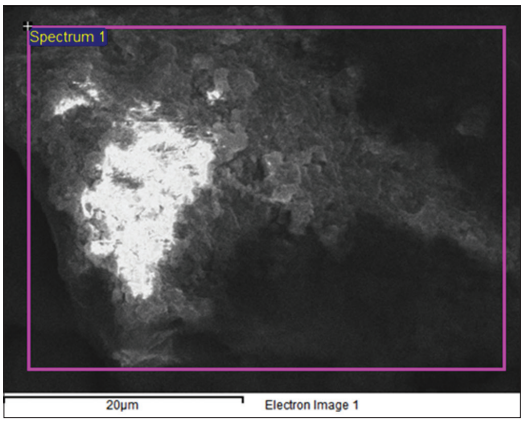


Figure 3: Scanning electron microscopy image of nickel (II) complex of (E)-6-((4-benzoyl-2-((E) (hydroxy-benzylidene) amino)phenyl) imino)tetrahydro-2H-pyran-2-one

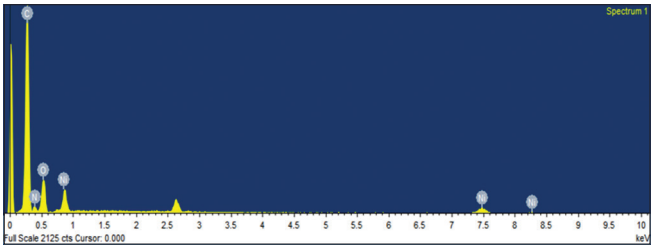


Figure 4: Energy-dispersive X-ray spectrum of nickel (II) complex of (E)-6-((4-benzoyl-2-((E)(hydroxy-benzylidene) amino)phenyl)imino) tetrahydro-2H-pyran-2-one

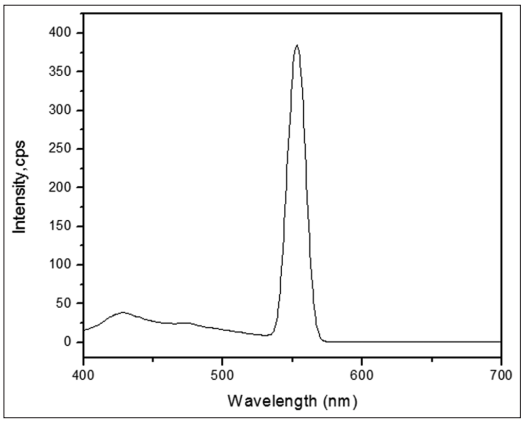


Figure 5: Emission spectrum of nickel (II) complex of (E)-6-((4-benzoyl-2-((E)(hydroxy-benzylidene)amino)phenyl)imino) tetrahydro-2H-pyran-2-one

Table 3: Antibacterial activity values of ciprofloxacin with Schiff base ligand and their nickel (II) complex

Compound	Gram-positive		Gram-negative	
	Staphylococcus aureus	*Enterococci*	*Pseudomonas aeruginosa*	*Escherichia coli*
	ZOI mm (%)			
Ligand	0.0	0.0	6 (24.0)	7 (25.9)
Nickel (II) complex	12 (46.1)	12 (50.0)	10 (40.0)	11 (40.7)
Control	-	-	-	-
Ciprofloxacin	26 (100)	24 (100)	25 (100)	27 (100)

*Activity of ciprofloxacin considered as 100% inhibition against selected pathogens, ZOI: Zone of inhibition

and analytical data. Based on the data, the complex has non-spherical octahedral geometry and at 525 nm arise the more emission. The antimicrobial studies carried out with the complex and ligand. These confirm that they are good antimicrobial agent, inhibition levels were determined.

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