



Synthesis and spectral characterization of 2-((2-hydroxybenzylidene)amino)-2-methylpropane-1,3-diol derived complexes: Molecular docking and antimicrobial studies



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ABSTRACT

A series of four homo-dinuclear transition metal complexes with stoichiometry $[M_2(HL)_2(H_2O)_2]$ [$M = Fe$ (1), Co (2), Ni (3) and Cu (4)]; $H_3L = 2-((2-hydroxybenzylidene)amino)-2-methylpropane-1,3-diol$ has been prepared. Ligand (H_3L) was obtained by the condensation of 2-amino-2-methyl-1,3-propanediol (H_2ampd) with salicylaldehyde. The complexes (1–4) are characterized employing elemental analysis, FTIR, ESI mass, 1H & ^{13}C NMR, EPR, UV Visible, TGA, cyclic voltammetry, and magnetic studies. Spectral data ascertained the bonding features and the geometry of the complexes and revealed that all the complexes adopt distorted octahedral geometry with high spin state of metal ions. Thermal and ESI mass data confirmed the proposed stoichiometry of the complexes. Cyclic voltammetric (CV) studies ascertain the formation of M^{II}/M^{III} quasi-reversible redox couples in solution. The antimicrobial activities of the present complexes have been examined against few bacteria (*E. coli*, *B. subtilis*, *S. aureus* and *S. typhimurium*) and fungi (*C. albicans*, *A. fumigatus* and *P. marneffeii*) suggesting that the present compounds show moderate to high antimicrobial properties. Among all the compounds tested, complex (4) exhibited highest antibacterial as well as antifungal activity. Molecular docking studies of the free ligand and the complexes are performed with BDNA (PDB ID: 1BNA) and the results of docked models indicate that ligand as well as the complexes (1–4) can efficiently bind with DNA receptor with free energy of binding (FEB) values of -206.0 (H_3L), -234.0 (1), -238.4 (2), -241.0 (3) and -236.5 (4) $kJ\ mol^{-1}$. Complex (3) shows the highest binding ability (with binding energy of $-241.0\ kJ\ mol^{-1}$) while the ligand (H_3L) binds with DNA with least extent. The order of binding efficiency is $3 > 2 > 4 > 1 > H_3L$.

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1. Introduction

The coordination chemistry of the complexes involving Schiff base ligands having O,N,O donor groups and a number of metal ions has become area of much focus due to the versatility of Schiff base ligands [1,2]. Schiff base on treating with transition metal ions produces mono as well as polynuclear complexes, which have been widely employed in material science and medicine. The Schiff base complexes may incorporate planar aromatic or flexible polydentate ligands. The chemistry of bimetallic complexes with the Schiff base ligands are most convincing way to illustrate the possibility to

control the number and the nature of the metal ions within the same molecular unit [3]. The interest was mainly motivated by the extremely interesting synthetic procedure “combination of multi-dentate ligands with transition metals has resulted in the preparation of a diverse range of complicated architectures”, leads to numerous binuclear complexes with wide applications in many significant areas such as magneto-chemistry, binuclear reactivity, catalysis, optical properties, and bioinorganic chemistry [3–5]. The Schiff bases are often used to stabilize unusual oxidation states and provide good solubility in polar solvents [6]. Intermolecular interactions between the same molecules result in the generation of di and oligomers as well as extended networks [7].

A number of mono and dinuclear complexes have been derived previously from the Schiff base ligands obtained on condensation of salicylaldehyde or derivative of salicylaldehyde with different

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amines [8]. In the mononuclear complexes, transition metal ion occupies the different donor groups with [N,O] type cavity. In some of the binuclear complexes of transition metal ions, one water molecule is coordinated to occupy the remaining site of the octahedron, resulting in the formation of the product [9]. Again, there are also a few non-hydrated compounds of the same metal ions derived from the similar ligands [10]. The homo-binuclear systems having oxygen bridging obtained with tri-asymmetric ligands derived from the amino polyalcohol as a ligand backbone are important because its Schiff base derivatives are versatile ligands in terms of donor properties and so are able to form higher nuclearity compounds. The condensation reaction of salicylaldehyde with 2-amino-2-methylpropane-1,3-diol [H₂ampd, with N,O,O set of donor atoms], proved as good scaffold due to its potential binding modes to metal centre as well as participation in hydrogen bonding interactions, affords Schiff bases that can act as multi-dentate ligand, forming metal complexes via oxygen bridging. The metal ions are hosted into the O,N,O [11] set of donor atoms. Hydroxyl-rich Schiff base ligand have synthetic flexibilities, structural varieties, and potential applications and, therefore, such tri- and tetradentate Schiff base ligands are often used for the synthesis of such homo, bi and multinuclear metal ion complexes [12]. Furthermore, great deals of interest for binuclear metal complexes have been demonstrated to display effective antioxidant, and the antimicrobial activities. We have therefore synthesized and characterized homodinuclear Schiff base complexes which have been screened for antimicrobial properties. Moreover molecular docking studies are performed to investigate the effect of the complexes on DNA receptor [13].

2. Experimental

2.1. Materials

All the reactions were carried out under aerobic conditions. Analytical grade solvents and reagents were purchased from commercial sources and used without further purification.

2.2. Physico-chemical methods and instrumentation

Elemental analyses of the compounds were obtained from a Thermo quest CE instruments (CHN) EA/110 model. Melting points was determined by open capillary method and are uncorrected. The IR spectra (KBr pellets) were collected on a Perkin Elmer Model spectrum GX spectrophotometer operating at 400–4000 cm⁻¹. Absorption spectroscopic measurements were carried out at room temperature; using a Perkin-Elmer Lambda-25 UV–visible spectrophotometer in 10⁻³ M solution in CH₃OH, cu-vettes of 1 cm path length. Electrospray ionization mass spectrometry (ESI–MS) spectra were performed on a Q–TOF micromass spectrometer. ¹HNMR and ¹³CNMR spectra were recorded on a BrukerAvance II 400 NMR spectrometer from Punjab, university Chandigarh, India. Thermal gravimetric analysis (TGA) data were recorded from room temperature up to 600 °C at a heating rate of 20 °C/min. The data were obtained using a Shimadzu TGA-50H instrument. Magnetic susceptibility was measured by magnetic susceptibility balance, Sherwood scientific Cambridge U. K. at room temperature.

2.3. Cyclic voltammetry studies

Cyclic voltammetry (CV) was performed on EG&G PAR 273 Potentiostat/Galvanostat an IBM PS-2 computer with EG&G M270 software for data acquisition. The three-electrode cell configuration comprised of, a platinum sphere, a platinum plate and Ag(s)/AgNO₃ were used as working, auxiliary and reference electrodes,

respectively. The supporting electrolyte used was [nBu₄N]·ClO₄. Platinum sphere electrode was sonicated for 2 min in dilute nitric acid, dilute hydrazine hydrate and then in double distilled water to remove the impurities. The solutions were deoxygenated by bubbling research grade nitrogen gas and an atmosphere of nitrogen was maintained over the solution during measurements.

2.4. Molecular model computations

CSChem-3D-MM2 software has been used to get the minimum energy perspective plots for the geometry of the ligand and the complexes (1–4) [14]. This provided the most stable (ground state) arrangement of the ligand environment around the metal ions.

2.5. Antibacterial studies

Disc diffusion method [15] was employed to evaluate and compare the antibacterial activity of the four complexes against *E. coli*, *B. subtilis*, *S. aureus* and *S. typhymurium*. The 5 mm (diameter) discs of Whatman No. 1 filter paper were sterilized by heating at 140 °C for 1 h. The discs were placed in nutrient agar medium after being soaked separately in each of the four complexes (1–4) at two concentrations of 1 mg/mL and 100 mg/mL and ciprofloxacin (used as standard). Inverted plates were incubated at 30 ± 1 °C for 24 h and zones of inhibition zone were measured. To determine Minimum inhibitory concentrations (MICs), ~ 5 × 10⁵c.f.u of actively dividing bacteria cells were inoculated in nutrient broth containing two-fold serially diluted amount of complexes and controls and incubated for 24 h at 37 °C. The highest dilution or the lowest complex concentration at which growth (measured spectrophotometrically) gets arrested was recorded as MIC. To determine the minimum bacterial concentration (MBC) which corresponds to the lowest complex concentration required to kill 99.9% of the inoculums, 0.1 mL of each inoculum was spread on agar plates and c.f.u. were counted after incubation at 35 °C for 18–24 h.

2.6. Antifungal studies

Antifungal activities of the test complexes (1–4) were evaluated by agar diffusion method [16] against clinical isolates of *C. albicans*, *A. fumigatus* and *P. marneffeii* in DMSO. A suspension of fungal spores was prepared in normal saline and plated on agar media containing peptone (1%), D-glucose (4%) and agar (2%) in distilled water (pH ~5.7). Plates were incubated at 37 °C for 3–4 days. Greseofulvin was used as control in this assay to compare the inhibition zones formed. MIC and minimum fungicidal concentration (MFC) were similarly determined.

2.7. Molecular docking studies

Molecular docking was performed using Hex 8.0.0 program [17]. The PDB format of ligand and complexes was obtained from chemdraw (MM2) energy minimized file and by converting its file using Mercury software. The crystal data of the B-DNA dodecamer, d(CGCGAATTCGCG)₂ (PDB ID: 1BNA) were downloaded from the Protein Data Bank. The water molecules were removed from the 1BNA using chimera 1.10.2 before performing docking calculations.

3. Synthesis

3.1. Preparation of the Schiff base ligand (H₃L)

The preparation of Schiff base ligand (H₃L) used in this work is shown in Scheme 1. (H₃L) was obtained by the refluxing 2-amino-2-methyl-1,3-propanediol (H₂ampd) (5.0 mmol) with

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