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Synthesis, structure elucidation, biological screening, molecular modeling and DNA binding of some Cu(II) chelates incorporating imines derived from amino acids

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ABSTRACT

Three tridentate Schiff bases amino acids were prepared by direct condensation of 3-methoxysalicylaldehyde (MS) or 4-diethylaminosalicylaldehyde (DS) with α-amino acid ligands [L-phenylalanine (P), L-histidine (H) and DL-tryptophan (T)]. The prepared Schiff bases amino acids were investigated by melting points, elemental analysis, ^{1}HNMR and ^{13}CNMR, IR, UV–Vis spectra, conductivity and magnetic measurements analyses. Subsequently, copper was introduced and Cu(II) complexes formed. These complexes were analyzed by thermal and elemental analyses and further investigated by FT-IR and UV/Vis spectroscopies. The experimental results indicating that all Cu(II) complexes contain hydrated water molecules (except DSPCu complex) and don't contain coordinated water molecules. The kinetic and thermal parameters were extracted from the thermal data using Coast and Redfern method. The molar conductance values of the Schiff base amino acid ligands and their Cu(II) complexes were relatively low, showing that these compounds have non-electrolytic nature. Magnetic susceptibility measurements showed the diamagnetic nature of the Schiff base amino acid ligands and paramagnetic nature of their complexes. Additionally, a spectrophotometric method was determined to extract their stability constants. It was found that the complexes possess 1:2 (M:L) stoichiometry. The results suggested that 3-methoxysalicylaldehyde and 4-diethylaminosalicylaldehyde amino acid Schiff bases behave as monobasic tridentate ONO ligands and coordinate Cu(II) ions in octahedral geometry according to the general formula $[Cu(HL)_2]\cdot nH_2O$. To further understanding the structural and electronic properties of these complexes, Density Functional Theory (DFT) calculations were employed and provided a satisfactory description. The optimized structures of MST Schiff base ligand and its complex were calculated using DFT. The antimicrobial activity of the Schiff base ligands and their complexes were screened against some types of bacteria such as *Bacillus subtilis (+ve)*, *Escherichia coli (−ve)* and *Micrococcus luteus (+ve)* and some types of fungi such as *Asperagillus niger, Candida glabrata* and *Saccharomyces cerevisiae*. The results of these studies indicated that the metal complexes exhibit a stronger antibacterial and antifungal efficiency compared to their corresponding ligands. The complexes were screened for antiviral activity against a panel of DNA and RNA viruses. Minimum cytotoxic and minimum virus inhibitory concentrations of these complexes were determined. The mode of interaction between complexes and CT-DNA was monitored using absorption spectra, viscosity measurements and gel electrophoreses.

1. Introduction

The chemistry of metal-drug coordination compounds nowadays has a greater attention than before due to the importance needs particularly in designing more biologically active drugs [1]. Metal ions are known to affect the action of many drugs [2]. Several metal chelates are known to possess antimicrobial, antiviral and anticancer activity. In many cases, metal chelates have been found to be more antimicrobial than the chelating agents themselves [2–4]. Schiff bases ligands and their complexes have a variety of

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applications in clinical, analytical and industrial field [5,6].

Among these, heterocyclic Schiff base ligands and their complexes do have significant interest because of pharmacological properties [7]. Furthermore, the interaction of these complexes with DNA has gained much attention due to their possible applications as new therapeutic agents [8]. Some drugs show increased activity when administered as metal chalets and inhibit the growth of tumors [9]. The transition metal ions are responsible for the proper functioning of different enzymes. Certain drugs play a vital role as bio-ligands in the biological systems. Also, nitrogen bases such as (pyridine, pyrimidine and pyrazine) and amines such as (histamine, carbohydrates and different vitamins) have a vital role as bio-ligands. Metal complexes of Schiff base phenolates with favorable cell membrane permeability have been exploited in cancer multidrug resistance and used as antimalarial agents [10].

A number of diseases and their remedies are dependent on metabolism of inorganic constituents. The complexes of copper with Schiff bases have wide applications in food and dye industries, catalysis, fungicidal, agrochemical, antiradical activities and biological activities [11,12].

Cu(II) complexes are also attractive since Cu(II) is known to play a significant role in naturally occurring biological systems as well as a pharmacological agent. Copper is a biologically relevant element and many enzymes that depend on copper for their activity have been identified. The metabolic conversions catalyzed by most of these enzymes are oxidative.

This paper describes the synthesis of binary Cu(II) Schiff base amino acid complexes and characterization by various physical methods. Moreover, antimicrobial studies of the investigated Cu(II) complexes were performed against many types of bacteria, fungi and viruses. Moreover, the interaction between DNA and the synthesized Cu(II) complexes was performed by using absorption spectra, viscosity measurements and gel electrophoresis. 3-methoxysalicylaldehyde (MS) or 4-diethylaminosalicylaldehyde (DS) is the aldehyde that used in this investigation, the amino acids are L-phenylalanine (P), L-histidine (H) and DL-tryptophan (T).

2. Materials and methods

All chemicals reported here, such as 3-methoxysalicylaldehyde ($C_8H_8O_3$) (MS), 4-diethylaminosalicylaldehyde ($C_{11}H_{15}O_2N$) (DS), amino acids[L-Phenylalanine (P), DL-Tryptophan (T), L-Histidine (H)], Calf thymus DNA (CT − DNA), and the metal salt [copper acetate ($Cu(CH_3COO)_2$. H_2O), were purchased from Sigma–Aldrich and used as received.

2.1. Characterization of the prepared Schiff base amino acid ligands and their complexes

Melting points for the isolated ligands and decomposition points for their complexes were monitored on a melting point apparatus, Cimarec 3 Thermolque. The carbon, hydrogen, and nitrogen contents were determined on a Perkin Elmer (2400) CHNS analyzer. IR spectra (4000–400 cm^{-1}) were recorded on Shimadzu FT-IR model 8101 spectrometer using KBr pellets. ^{1}HNMR and ^{13}CNMR spectral measurements were determined by using a BRUKER, using DMSO as an internal reference. The TG/DT analyses were recorded on Shimdzu corporations 60H at 10°min^{-1}. The UV–Vis spectra were recorded on a PG spectrophotometer model T + 80 at 298 K. Magnetic susceptibility measurements of the metal complexes were done on a Gouy balance at room temperature using $Hg[Co(SCN)_4]$ as a calibrant. Molar conductance was measured on an Elico CM-180 conductometer using 1 mmol l^{-1} solutions in DMF. A HANNA 211 pH meter at 298 K equipped with a CL-51B combined electrode was used for pH measurements, calibrated against standard buffers (pH 4.02 and 9.18) before measurements. Quantum chemical calculations for 3-methoxysalicyaldehyde and tryptophan (MST) ligand structure were performed using MOPAC2000 [13] with WinMOPAC 2.0 [14] as a graphic interface. At the beginning, structure the starting material was optimized with the eigenvector-following routine (EF) [15] using the semi-empirical PM3 method [16,17]. To investigate the 3D structure and molecular stability for the Cu-MST complex accurate density functional theory (DFT) calculations were done using Gaussian 03 software package [18]. Calculations were carried out at DFT level of theory with pseudo potential functions, 6-311G (p,d) [19] basis set for ligand atoms, and LANL2DZ [20] basis set with effective core potential (ECP) for Cu ion. Antimicrobial screening was carried by using agar well diffusion. Viscosity measurements were performed by using viscometer immersed in a thermo stated water bath maintained at 25 °C. Gel electrophoresis was visualized under UV a transilluminator and photographed with a Panasonic DMC-LZ5 Lumix Digital Camera.

2.2. Synthesis of Schiff base amino acids

To a stirred solution of 3-methoxysalicylaldehyde or 4-diethylaminosalicylaldehyde (5 mmol, 0.76 g, 0.995 g respectively) in ethanol, 40 ml of the appropriate (L-Phenylalanine (P), DL-Tryptophan (T), L-Histidine (H)) (5 mmol, 0.825 g, 1.045 g, 1.02 g respectively) was added. The resultant mixture in each case was heated under reflux for 2 h. The solid products were collected by filtration, washed with hot ethanol, dried at room temperature and finally stored in an air tight sample vial for further use [21].

2.3. Complexes preparation

Aqueous solutions of the amino acids were prepared by dissolving (5 mmol, 0.825 g, 1.045 g, 1.02 g respectively in 40 ml of aqueous-ethanol mixture) of each (P, T, H). Each of the solutions was mixed with 3-methoxysalicylaldehyde (5 mmol, 0.76 g, 50 ml hot ethanol) or 4-diethylaminosalicylaldehyde (5 mmol, 0.995 g, 50 ml hot ethanol). Then the mixture was stirred at 70 °C for 1 h. Cu(II) acetate mono hydrate solution of (2.5 mmol, 0.5 g in 40 ml aqueous-ethanol mixture) was added to the previous mixtures. The color changed from yellow to (green for MSTCu, dark green for DSPCu and bright brown for DSHCu) after stirring at room temperature for 3 h. The obtained products were evaporated over night. The obtained solid products were filtered, washed with water, and dried in vacuum over anhydrous $CaCl_2$ [2,3,22]. The structures of the investigated Schiff base amino acid ligands and their complexes are shown in Table 1.

2.4. Magnetic susceptibility measurements

The magnetic susceptibility measurement is one of the most useful methods available to the coordination chemists for studying the electronic structure of a transition metal complex. It provides fundamental information about the bonding and stereochemistry of the metal complexes [23]. The magnetic properties of the coordination compounds are based on the effect of the ligands on the spectroscopic terms of the metal ions. The susceptibility per gram atom of a paramagnetic metal ion in a particular compound is determined by measuring the molar susceptibility of the compounds and applying diamagnetic corrections for the other ions or molecules in the compounds. The diamagnetic corrections can be determined by various methods [24], however Pascal's constants are more often used to calculate the corrections. The magnetic susceptibility and moments can generally be calculated by using the following relationships [25].