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Synthesis, characterization, DFT calculations and molecular docking studies of metal (II) complexes

Anthony C. Ekennia [a, *], Aderoju A. Osowole [b], Lukman O. Olasunkanmi [c, d, e], Damian C. Onwudiwe [c, d], Olujide O. Olubiyi [f], Eno E. Ebenso [c, d]

[a] Department of Chemistry, Federal University Ndufu-Alike Ikwo (FUNAI), P.M.B 1010, Abakaliki, Ebonyi State, Nigeria
[b] Inorganic Unit, Department of Chemistry, University of Ibadan, Oyo State, Nigeria
[c] Material Science Innovation and Modelling (MaSIM) Research Focus Area, Faculty of Agriculture, Science and Technology, North-West University (Mafikeng Campus), Private Bag X2046, Mmabatho, South Africa
[d] Department of Chemistry, School of Mathematical and Physical Sciences, Faculty of Agriculture, Science and Technology, North-West University (Mafikeng Campus), Private Bag X2046, Mmabatho, 2735, South Africa
[e] Department of Chemistry, Faculty of Science, Obafemi Awolowo University, Ile-Ife, 220005, Nigeria
[f] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria

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ABSTRACT

Two novel ligands, 2-methyl-6-[(5-methyl benzothiazol-2-ylimino)-methyl]-2-methoxycyclohexa-1,5-dienol (HL_1) and 2-methyl-6-[(5-floro-benzothiazol-2-ylimino)-methyl]-2-methoxycyclohexa-1,5-dienol (HL_2) were synthesized from the condensation reaction of 2-hydroxy-3-methoxybenzaldehyde with 2-amino-6-methylbenzothiazole and 2-amino-6-florobenzothiazole respectively. Mononuclear Cu(II), Ni(II) and Co(II) complexes of the ligands were synthesized and characterized using elemental analysis, magnetic susceptibility, thermogravimetric, conductance, infrared and UV–visible spectroscopic measurements. The ^{1}H NMR, ^{13}C NMR, Dept-90 NMR spectroscopy of the ligands was also recorded to establish the formation of the Schiff bases. The analytical data of the complexes showed that the metal to ligand ratio was 1:1 for Cu(II), Ni(II) and Co(II) complexes of HL_1 and Cu(II) complexes of HL_2, while Ni(II) and Co(II) complexes of HL_2 was 1:2. The infrared spectral data showed that the chelation behaviour of the ligands towards transition metal ions was through phenolic oxygen and azomethine nitrogen atoms. Molar conductivity revealed the non-electrolytic nature of all chelates in DMSO solution. The geometry of the complexes was deduced from thermal, magnetic susceptibility and UV–visible spectroscopic results and was further confirmed with DFT calculations. The compounds were subjected to in-vitro antibacterial screening using agar well diffusion method on some clinically isolated Gram positive and Gram negative bacteria strains. The compounds showed varied antibacterial activities. Molecular docking studies were carried out to study the molecular interaction between the compounds and different enzymes of the bacterial strains. The antioxidant potentials of the compounds were studied using ferrous ion chelating assay and 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay. However, the complexes had better antioxidant potentials compared to the ligands.

1. Introduction

Schiff bases are a large group of chemical compounds with an azomethine group (C=N) in their composition, that have been reported to contain a catalog of biological potentials [1–8]. Precisely, O-vanillin (2-hydroxy-3-methoxy benzaldehyde) derived Schiff bases have been articulated as possessing antibacterial [9,10], antifungal [11], antimutagenic [12], comutagenic [13] and DNA interaction [14] properties. However, the chelation of Schiff bases with transition metal ions have been reported to improve the biological potentials of Schiff bases [15,16], hence, metal complexes of various Schiff bases are well renowned as antibacterial, antifungal, anticancer and antioxidant agents [17–19]. Remarkably, variation of substituents and spacer groups in the structure of Schiff bases confers different electronic (space configuration, electron density distribution and spectral), geometric and biological

* Corresponding author.
E-mail address: chemisttony@gmail.com (A.C. Ekennia).

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properties on their metal complexes [8], which could be well observed when subjected to computational studies. Consequently, structure related activity of a compound is an important aspect of drug design which involves the use of computational methods like DFT studies and molecular docking to give insight into a number of molecular properties such as electronic, geometric and as well as drug interactions with several biological proteins, nucleic acid and enzymes [20]. (see Schemes 1 and 2)

In our previous works we looked at synthesis and characterization of naphthaldehyde derived Schiff base metal complexes with floro and methyl substituent at the sixth position of 2-aminobenzothiazole moiety [21]. In our present work we want to explore both experimental and computational approaches to the study of O-vanillin derived Schiff base complexes with different substituents on the aromatic ring of the ligands.

2. Experimental

2.1. Materials

2-hydroxy-3-methoxybenzaldehyde (O-vanillin), copper(II) chloride dihydrate, nickel(II)chloride hexahydrate, cobalt(II)nitrate hexahydrate, 2-amino-6-methylbenzothiazole, 2-amino-6-florobenzothiazole, 2,2-Diphenyl-1-picrylhydrazyl, 1,10-phenantroline, iron(II) sulphate heptahydrate and triethylamine were purchased from BDH and Aldrich chemicals Germany and were used as received.

2.2. Physical measurements

Electronic and IR (KBr disc) spectra were recorded on a Perkin-Elmer λ20 UV–vis and Perkin-Elmer FT-IR Spectrum BX spectrophotometers respectively. The elemental analysis was performed on an Elementar vario EL Cube set up for carbon, hydrogen, nitrogen and sulfur (CHNS) analysis. The percentage metal analyses were carried out using complexometric titration of the respective metal solutions against EDTA with murexide as an indicator. The thermal analysis was done using SDTQ 600 thermal instrument with alumina crucibles and heated at a rate of 10 °C min^{-1} under nitrogen atmosphere. Melting points (uncorrected) were determined using the Stuart scientific melting point SMP1 machine. NMR measurements were done with 300 MHz Bruker Advance III NMR spectrometer, room temperature magnetic moments and molar conductance measurements were recorded on Sherwood Susceptibility balance MSB Mark 1 and Hanna conductivity model H19991300 m respectively.

2.3. Syntheses

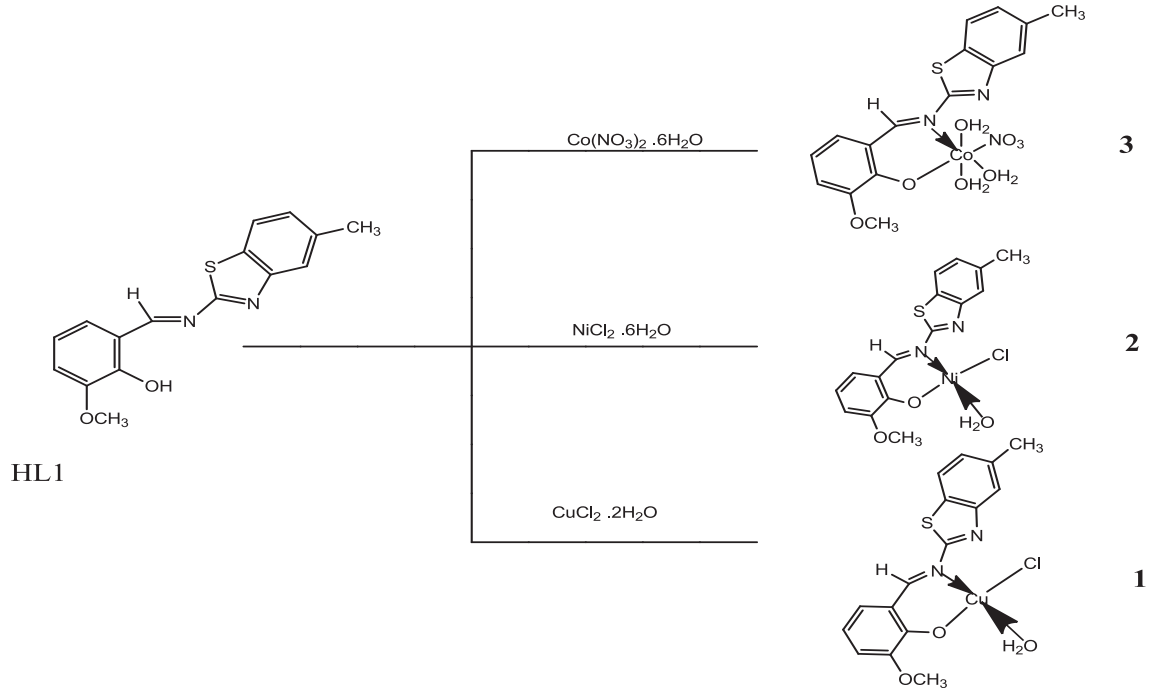
2.3.1. Synthesis of Schiff bases of 2-methyl-6-[(5-methyl-benzothiazol-2-ylimino)-methyl]-2-methoxycyclohexa-1,5-dienol (HL_1)

The ligand, HL_1 was synthesized by the addition of 2-amino-6-methylbenzothiazole (1.74 g, 8.90 mmol) to a stirring solution of 2-hydroxy-3-methoxybenzaldehyde (1.36 g, 8.90 mmol). Few drops of acetic acid were then added and the solution was refluxed for 3 h. The solution was allowed to cool to room temperature and the yellow precipitate formed was filtered, rinsed with methanol and recrystallized.

Yield 66%; m.p. > 166–168 °C; Yellow solid. Anal.Calcd for $C_{16}H_{14}N_2SO_2$ (%): C, 64.40; H, 4.74; N, 9.39; S, 10.75. Found (%): C, 64.69; H, 4.79; N, 9.69; S, 10.97. IR (ν, cm^{-1}): 3445br (OH), 3013, 3053 (Ar–CH), 1595sh (C=N), 1572sh(C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm):12.45(s, OH), 9.21(s, C=N), 6.89–7.90 (Ar–CH). ^{13}C NMR (300 MHz, DMSO-d_6, δ, ppm): 166.98 (s, H–C=N), 128.25–104.28 (Ar–CH). UV–visible (λ_{max}, nm): 276 (π–π^*), 395 (n–π^*).

2.3.2. Synthesis of Schiff bases of 2-methyl-6-[(5-floro-benzothiazol-2-ylimino)-methyl]-2-methoxycyclohexa-1,5-dienol (HL_2)

The ligand, HL_1 was synthesized by the addition of 2-amino-6-florobenzothiazole (1.50 g, 8.90 mmol) to a stirring solution of 2-



Scheme 1. Synthetic route for the synthesis of metal complexes of HL_1.