



PREPARATION AND CHARACTERIZATION OF SOME SCHIFF BASE MACROCYCLIC LIGANDS OF TRANSITION METAL COMPLEXES

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ABSTRACT

A novel macrocyclic multidentate Schiff base nitrogen donor ligand of transition metal complexes of the type $[M(C_{12}H_{20}O_8N_4)Cl_2]$ where $M = Cu(II), Ni(II)$ and $Co(II)$ was prepared via a templet approach and evaluated in vitro for their properties by performing minimum inhibitory concentration (MIC). The multinuclear macrocyclic-based complexes were prepared from the reaction of the corresponding metal chloride with the ligand. The mode of bonding and overall geometry of the compounds were determined through physicochemical and spectroscopic methods. Present study revealed tetrahedral geometry about Cu, Ni and Co atoms. However, square planar geometries have also been suggested for Cu(II) and Ni(II) complexes. Biological activity of the ligand and its metal complexes were studied. Results obtained indicate that growth and ergosterol content decreased significantly in the presence of the test compounds. The ligand offered remarkable viability in the range of 87–94% at a concentration of 25 IM. Ni(II) complex (KNi) was found to be the most active and least cytotoxic among all the compounds screened.

KEYWORDS : Metal complexes; Ergosterol, Cytotoxicity, Cytotoxic, Macrocyclic ligands.

Introduction

Macrocyclic species based on transition metal compounds and multidentate ligands has become an interesting field in chemistry. Now a days it has become the subject of extensive research due to their potential applications in building block macrocyclic-based chemistry,^{1,2} biomedical³ and environmental chemistry⁴. The chemistry of Schiff-base is an important field in coordination chemistry⁵. This is due to their ability to react with a range of metal ions forming stable complexes which have applications in different fields⁶. Schiff base complexes are considered to be among the most important stereo chemical models in main group and transition metal coordination chemistry due to their preparative accessibility and structural variety. Study of the interaction between drugs and transition metals is an important and active research area in bioinorganic chemistry. It is well known that the action of many drugs is dependent on the coordination with metal ions⁷.

A large number of Schiff bases and their complexes have been studied for their interesting and important properties, like the ability to reversibly bind oxygen, catalytic activity in the hydrogenation of olefins and transfer of an amino group, photochromic properties and complexing ability toward some toxic metals. The high affinity for the chelation of the Schiff bases toward the transition metal ions is utilized in preparing their solid complexes. Complexes based on Schiff-base ligands play important roles in biomedical^{8,9}, biomimetic, and catalytic systems and in supporting liquid crystalline phases.¹⁰

Schiff bases are potential anticancer drugs and, when administered as their metal complexes, the anticancer activity of these complexes is enhanced in comparison to the free ligand. Some biologically active Schiff base ligands like hydrazine-pyrrole-2-carboxaldehyde, hydrazine-furan-2-carboxaldehyde and hydrazine-thiophene-2-carboxaldehyde and their phenyl derivatives and their Co(II), Cu(II) and Ni(II) mixed complexes have been synthesized and characterized.

A number of Schiff-base complexes have been used as oxygen carriers to mimic complicated biological systems.^{7,11} Furthermore, metal complexes of chromium, manganese, nickel, copper, zinc, and ruthenium with a wide variety of Schiff-bases are active oxidants for stoichiometric conversion and have been used as catalysts for carbonylation, hydrogenation, hydroformylation, and epoxidation reactions. It is to explore the use of multidentate Schiff-base ligands for the building blocks of macrocyclic compounds. We describe here the formation of macrocyclic species of some phenoxo-bridged tetranuclear transition metal ions with the new macrocyclic Schiff-base. The ligand was derived via a template approach in which

ethylenediamine parts facilitated the linkage of the two units.

Candidiasis, a fungal disease caused by a diploid opportunistic fungal pathogen *Candida* proves to be life threatening mycoses fatal for immuno compromised patients, e.g. AIDS and transplantation surgery. A number of antifungal agents are available for the treatment of Candidal infections. Majority of them are polyenes such as Amphotericin B and Nystatin or the azoles, such as Itraconazoles and Fluconazole. Presently, use of standard antifungal therapies is scare due to the high toxicity, low efficacy rates, and drug resistance. Recent studies indicated C-albicans resistance to azoles or heptotoxicity and nephrotoxicity linked to polyene use, particularly amphotericin B. Therefore, present study was conducted to synthesize some macrocyclic tetradentate ligand based transition metal complexes and screen them for their properties.

Materials and Methods:

Organic reagents and solvents purchased from Sigma Aldrich, Merck and Loba Chemie were used without further purification. Melting point determination was performed by using a Mel-temp. instrument. Elemental analyses were performed on HeraeusVario EL (III) analyzer at the C.D.R.I., Lucknow. The results were within $\pm 0.3\%$ of the theoretical values. Electronic spectra were recorded on a Shimadzu UV 1601 PC UV-Visible spectrophotometer. IR spectra were recorded on Perkin-Elmer model 1600 FT-IR RX1 spectrophotometer as KBr discs. Far IR spectra were recorded as CsI pellets in the region $650-100\text{ cm}^{-1}$ using a JASCO FT-IR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on Bruker AVANCE 400 spectrometer using DMSO-d₆ as solvent with TMS as the internal standard. Positive and negative Thermal analysis (TG/DTA) data were studied under nitrogen atmosphere using a SII Ex Star 6000 TG/DTA 6300 instrument. Magnetic susceptibility measurements were carried out from a microanalysis laboratory by Gouy method at room temperature. Splitting patterns were designated as: s = singlet; d = doublet; dd = double doublet; t = triplet; m = multiplet. Chemical shift values are given in ppm.

Synthesis of Ligand:

25ml of ethanolic solution with tartaric acid and 25 ml of hot ethanolic solution of ethylene diamine (0.05 mol) were mixed slowly with constant stirring. This mixture was refluxed at 60–70°C for 6-7 hrs with few drops of concentrated hydrochloric acid. On keeping it overnight at 0°C a creamy white precipitate was formed, which was filtered, washed with ethanol and dried in vacuum over P₂O₅ and recrystallized from methanol. Yield: 76%; mp > 300°C; IR (KBr) cm^{-1} : 3444 (O-H), 3195(N-H), 3012 (C-H), 1618 (C=O), 1412 (C-N), 1064, 884, 773; ¹H NMR (300 MHz, d ppm from TMS in DMSO-d₆, 300 K): δ

11.68–12.57 (4H, Br N–H), δ 4.21–4.36 (s, 4H, C–H), δ 2.92–3.00 (s, 8H, C–H); ^{13}C NMR (CDCl₃) (δ , ppm): 172.5 (C=O), 38.06 (4CH₂); ESI MS (m/z) 346 [M]⁺, 349 [M⁺]⁺; Elem. Anal. Calcd. C = 41.37%, H = 5.72%, O = 36.74%, N = 16.07%; found C = 41.42%, H = 5.75%, O = 36.77%, N = 16.12%.

Synthesis of Cobalt(II) Complex:

A solution of CoCl₂·6H₂O (3m mol) dissolved in 20ml methanol was added drop wise to a methanolic solution (20ml) of the ligand (3m mol) with continuous stirring. The resulting solution was stirred for 6-7 hrs at 30^oC and the solution was reduced to half of its volume. It was then allowed to stand overnight in a refrigerator. A light pink product separated out, which was isolated by filtration under vacuum. It was washed thoroughly with hexane and dried in vacuum over fused CaCl₂. The compound was recovered in solid state. It was recrystallized from methanol. Yield: 66%; mp > 300^oC; UV-Vis (DMSO) cm⁻¹: 12,744–13,322, 16,886–17,486, 24,725–25,355; IR (KBr) cm⁻¹: 3444 (O–H), 3196 (N–H), 2975 (C–H), 1604 (C=O), 1367 (C–N), 1087, 883, 633, Far IR (Csl, cm⁻¹) 455 (Co–N), 344 (Co–S747 R). ¹H NMR (300 MHz, d ppm from TMS in DMSO-d₆, 300k): δ 11.71–12.61 (4H, Br, N–H), δ 4.22–4.40 (4H, C–H), δ 2.95–3.05 (8H, C–H), ^{13}C NMR (CDCl₃) (δ , ppm) 171.0 (C=O), 46.03 (4CH₂). ESI MS (m/z) 476 [M]⁺, 480[M²⁺]⁺.

Synthesis of Nickel(II) Complex:

This compound was also synthesized by the above same procedure except that NiCl₂·6H₂O was used instead of CoCl₂·6H₂O. A light green product was obtained which was recrystallized from methanol. Yield 62%; mp > 300^oC; UV-Vis (DMSO) cm⁻¹: 11,666; 13,355; 14,664; 19,123; 24,394; IR (KBr) cm⁻¹: 3418(O–H), 3192 (N–H), 2977 (C–H), 1604 (C=O), 1386 (C–N), 1063, 811, 614, Far IR (Csl, cm⁻¹) 466 (Ni–N), 344 (Ni–Cl). ¹H NMR (300 MHz, d ppm from TMS in DMSO-d₆, 300 k): δ 11.71–12.60 (4H, Br, N–H), δ 4.23–4.35 (4H, C–H), δ 2.96–3.10 (8H, CH₂). ^{13}C NMR (CDCl₃) (d, ppm) 176.5 (C=O), 49.50 (4CH₂).

Synthesis of Copper(II) Complex:

This compound was also synthesized by the above same procedure except that CuCl₂·2H₂O was used instead of CoCl₂·6H₂O. A sky blue product was obtained, which was recrystallized from methanol. Yield: 67%; mp > 300^oC; UV-Vis (DMSO) cm⁻¹: 13,826–14,394; 18,894–19,367; 24,872–25,437; IR (KBr) cm⁻¹: 3420 (O–H), 3190 (N–H), 2977 (C–H), 1600 (C=O), 1390 (C–N), 1077, 886, 646, Far IR (Csl) cm⁻¹: 433 (Cu–N), 337 (Cu–Cl). ¹H NMR (300 MHz, δ ppm from TMS in DMSO-d₆, 300 k): δ 11.75–12.64 (4H, N–H), δ 4.22–4.38 (4H, C–H), δ 2.98–3.12 (8H, C–H); ^{13}C NMR (CDCl₃) (δ , ppm): 174.9(C=O), 44.82 (4CH₂).

Results and discussion:

Some macrocyclic tetradentate nitrogen donor (N₄) ligand 6,7,14,15-tetrahydroxy-1,4,9,12-tetraazacyclohexadecane-5,8,13,16-tetrone based transition metal complexes of the type [M(C₁₂H₂₀O₈N₄)Cl₂] where M = Cu(II), Ni(II) and Co(II) were isolated with considerable yields. The structure of the ligand and its metal complexes were established using various spectroscopic studies. The analytical data of these compounds are in good agreement with their composition. The compounds do not undergo any weight loss up to 255^oC, 245^oC, 250^oC respectively, which suggest their fair thermal stability. The structure of all complexes was established by comparing spectral data (IR, UV-Vis and ¹H NMR) with their respective ligands and was further supported by their ESI MS and thermo gravimetric analysis.

Electronic spectra:

Cobalt(II) Complex:

The electronic spectrum of the mononuclear cobalt(II) complex exhibits absorption bands in the range 12,744–13,316; 16,886–17,488 and 24,724–25,352 cm⁻¹, which may be assigned to ⁴T_{1g}(F) → ⁴T_{2g}(F), ⁴T_{1g} → ⁴A_{2g} and ⁴T_{1g}(F) → ⁴T_{1g}(P) transitions, respectively, suggesting an octahedral geometry around a Cobalt(II) ion, in the complexes under study. Furthermore, the magnetic moment measurements recorded at room temperature

lie at 4.98 BM. This value is indicative of an octahedral geometry of these complexes.

Copper(II) Complex:

The electronic spectrum of the mononuclear copper(II) complex recorded at room temperature, in DMF solution, shows broad band absorption in the range 13,822–14,390; 18,890–19,364 and 24,892–25,43 cm⁻¹, which may be assigned to ²B_{1g} → ²A_{1g} and ²B_{1g} → ²E_g transition and it is in conformity with octahedral geometry, an indication of the most probable geometric configuration of the synthesized metal complexes is their magnetic moment values. So, it has been further confirmed by the magnetic moment measurements, room temperature values lying at 1.98 BM corresponding to the presence of one unpaired electron and it supports an octahedral geometry.

Nickel(II) Complex:

The magnetic moment of the Ni(II) complex at room temperature lies at 2.98 BM. These values are in tune with high spin configuration and show the presence of an octahedral environment around the Ni(II) ion. The electronic spectra of the nickel(II) complex showed transition bands at 11,666; 13,352 and 14,664 cm⁻¹ which are assigned to the transition ³A_{2g} → ³T_{2g}, 19,122; 24,392 cm⁻¹ which are assigned to the transition ³A_{2g} → ³T_{1g}(F). These bands indicate an octahedral geometry around the nickel(II) ion in its complex.

IR Spectra:

Macrocyclic Ligand:

IR spectrum of the ligand does not exhibit any band corresponding to the free primary amine group. The absence of a broad absorption band in the region 3111–2511 cm⁻¹ a characteristic for (O–H) group of carboxylic acid and presence of an absorption band in the region 1677–1777 cm⁻¹ a characteristic for the carbonyl group (>C=O) in tartaric acid, indicates that the -OH group of tartaric acid was detached from the -COOH group to form a bond between carboxyl carbon atom and amino group nitrogen of ethylenediamine also suggests complete condensation of the reactants and the elimination of water molecule. This has been confirmed by the appearance of a strong signal at 1422 cm⁻¹ which may be attributed to the C–N bond.¹² A sharp medium intensity band observed at 3188 cm⁻¹ may be assigned to t(N–H) of the secondary amine group. The ligand also shows a signal for the >C=O at 1620 cm⁻¹ and C–H at 3012 cm⁻¹ vibrations. The low frequency of >C=O group as compared to acetone (1715 cm⁻¹) is attributed to resonance with lone pair of the nitrogen.

Complexes:

Molar conductance measurements of the complexes in DMF correspond to non-electrolytic nature. Thus, the complexes may be formulated as [M(K)Cl₂] where M = Ni(II), Co(II), and Cu(II) and K is [(C₁₂H₂₀O₈N₄)]. The shifting in the band of t(C–N) toward the lower wave number in the metal complexes indicates that coordination takes place through the nitrogen of the t(C–N) group, hence implying that the ligand (K) is tetradentate. This indicates the flow of electron density toward the metal atom through the C–N group. This has been finally established through far IR spectra by the appearance of new signals seen at 480, 472, 454 cm⁻¹ in the spectra of metal complexes which gives us clear proof for the presence of metal–nitrogen bond in Co(II), Ni(II), and Cu(II) complexes, respectively. Other vibrating signals seen at 344, 336 and 332 cm⁻¹ in the spectra of metal complexes give us proof of the presence of metal–chlorine bond in Co(II), Ni(II) and Cu(II) complex, respectively.

¹H NMR Spectra:

The ¹H NMR spectrum of the ligand shows a broad signal in the range 11.66–12.55 ppm which is attributed to amide >CO–N–H, (4H) and does not show any signal corresponding to the primary amine. A signal appearing in the range 4.22–4.37 ppm has been ascribed to methylene protons O=C–N–CH₂, (8H), whereas C–H (4H) protons appear in the range 2.96–3.12 ppm. The NMR spectrum of the ligand is consistent with the single species present in the solution, since

only one set of signals is observed in the ligand. These proton signals undergo down field shifting in all the metal complexes of the ligand, because of the paramagnetic effect of metal(II) ions and hence support the coordination of the ligand toward the metal ions and also the macrocyclic nature of the product¹³.

The thermal analysis (TG/DTA) of the ligand and its metal complexes was recorded under nitrogen atmosphere at the heating rate of 10^oC/min. The ligand is stable up to 215^oC. Synthesis, characterization and biological screening S747 and shows a continuous weight loss up to 380^oC. Therefore the whole ligand¹⁴⁻¹⁵ gets decomposed in a single step. The DTA of the ligand shows two endothermic peaks; one broad endothermic peak at 228^oC with a shoulder at 210^oC, which corresponds to the melting and the first inflexion point. The second inflexion on the DTA curve occurs at 352^oC which represents a small weight loss step from 362^oC to 380^oC.

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Conclusion:

Present work is able to synthesize a new series of macrocyclic tetradentate nitrogen donor (N₄) ligand 6,7,14,15-tetrahydroxy-1,4,9,12-tetraazacyclohexadecane-5,8,13,16-tetrone based transition metal complexes of the type [M(C₁₂H₂₀O₈N₄)Cl₂] where M = Cu(II), Co(II) and Ni(II) and screened them for their anticandidal property by performing minimum inhibitory concentration (MIC) along with ergosterol composition assay against the tested candida species. Antimicrobial results showed that metal complexes have high killing activity compared to the ligand. MIC values decreases almost stoichiometrically with multiplication of structure. A whole line of current antifungals target ergosterol biosynthesis pathway or its end product which is unique to fungi. At respective MIC values Ni(II) complex leads to enormous reduction in ergosterol content followed by Cu(II) complex, Co(II) complex and the ligand, respectively.

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