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Antioxidant, tautomerism and antibacterial studies of Fe(III)-1,2,4-triazole based complexes

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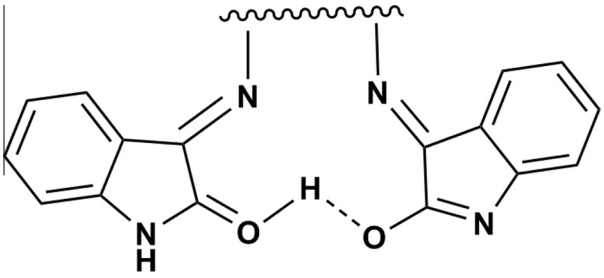
HIGHLIGHTS

- Structural characterization of Fe(III)-1,2,4-triazole based complexes.
- All the complexes were characterized by spectroscopy techniques.
- All the complexes were excellent interpretation and discussion.
- All the complexes show an effective antibacterial activity.

GRAPHICAL ABSTRACT

New Fe(III) complexes have been synthesized by 1,2,4-triazole based ligand complexes. FT-IR, ^{1}H and ^{13}H NMR studies reveal that the ligand (L_n) exists in the tautomeric enol form in both the states with intramolecular hydrogen bonding.



Keto-Enol Tautomerism

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ABSTRACT

New Fe(III) complexes have been synthesized by the reactions of ferric nitrate with Schiff base derived from 3-substituted phenyl-4-amino-5-hydrazino-1,2,4-triazole and indoline-2,3-dione. All these complexes are soluble in DMF and DMSO; low molar conductance values indicate that they are non-electrolytes. Elemental analyses suggest that the complexes have 1:1 stoichiometry of the type $[FeL_n(H_2O)(OH)]\cdot xH_2O$. Structural and spectroscopic properties have been studied on the basis of elemental analyses, infrared spectra, ^{1}H and ^{13}H NMR spectra, electronic spectra, magnetic measurements and FAB mass spectra. FT-IR, ^{1}H and ^{13}H NMR studies reveal that the ligand (L_n) exists in the tautomeric enol form in both the states with intramolecular hydrogen bonding. Magnetic moment and reflectance spectral studies reveal that an octahedral geometry has been assigned to all the prepared complexes. FRAP values indicate that all the compounds have a ferric reducing antioxidant power. The compounds 2 and 3 showed relatively high antioxidant activity while compound 1 and 4 shows poor antioxidant power. Also good antimicrobial activities of the complexes against *Staphylococcus aureus*, *Bacillus subtilis*, *Serratia marcescens*, *Pseudomonas aeruginosa* and *Escherichia coli* have been found compared to its free ligands.

Introduction

Triazoles and their derivatives are found to be associated with various biological activities, such as anticonvulsant, antifungal, anticancer, anti-inflammatory and antibacterial properties [1–9]. Several compounds containing 1,2,4-triazole ring are well known for drug synthesis [1]. 1,2,4-triazole containing amino group is also important for obtaining various Schiff base with well known

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antimicrobial properties [10–17]. Although many studies have investigated the antioxidant properties of resveratrol [18], there have been only a few reports of antioxidant and antiproliferative effects of hydroxyl-substituted Schiff bases.

Fe(III) complexes of Schiff bases are playing an important role in the development of coordination chemistry, which is evident in number of publications, including physicochemistry studies [19] and biological aspects [20–24]. Iron is one of the most important trace elements in the human body [25]. Increased iron availability in serum or tissues is associated with an increased risk of several tumors and may promote carcinogenesis [26]. Moreover, hereditary hemochromatosis is characterized by excess iron that causes tissue damage and fibrosis with irreversible damage to various organs [27]. Iron homeostasis is an important factor involved in neuroinflammation and progression of Alzheimer's disease [28].

In this study, Schiff base ligands and their Fe(III) complexes were synthesized and characterized by the analytical and spectroscopic methods. Antioxidant properties of the hydroxyl substituted Schiff base ligands were investigated. The antimicrobial activities of the ligands and their metal complexes were studied using the bacteria and yeast. The redox properties of the compounds were investigated by cyclic voltammetry. Thermal properties of the metal complexes were investigated in the 20–800 °C temperature range.

Materials and methods

Materials

The solvents were purchased from Merck and used without further purification. Ferric nitrate was purchased from Aldrich. The ligands were prepared as reported in literature [29]. Luria broth was purchased from Hi-media Laboratories Pvt. Ltd., India.

Instruments

Elemental analysis (C, H, N) was performed using a 2400-II CHN analyzer (PerkinElmer, USA). Analyses of metal ions was carried out by dissolution of the solid complexes in hot concentrated nitric acid, further diluting with distilled water and filtered to remove the precipitated organic ligands. The remaining solution was neutralized with ammonia solution and the metal ions were titrated against EDTA. The melting point of all compounds was measured using the open capillary tube method. FT-IR spectra (400–4000 cm^{-1}) were recorded with a Spectrum GX-PerkinElmer spectrophotometer using KBr pellets. ^1H NMR and ^{13}C-NMR spectra of ligands were recorded on a model Advance 400 Bruker FT-NMR instrument using tetramethylsilane as internal standard and DMSO-d_6 as solvent. The fast atom bombardment (FAB) mass spectrum of the complexes was recorded at SAIF, CDRI, Lucknow with a JEOL SX-102/DA-6000 mass spectrometer at room temperature using argon/xenon as the FAB gas. Electronic spectra (200–1200 nm) were collected using a LAMBDA 19 UV–visible/near-infrared spectrophotometer.

Thermal stability and decomposition of the complexes were determined by TG and DTG using a model 5000/2960 SDT (TA Instruments, USA). The experiments were performed in N_2 atmosphere at a heating rate of 20 °C min^{-1} in the temperature range 20–800 °C. Sample sizes ranging in mass from 3 to 8 mg were heated in an Al_2O_3 crucible. Magnetic susceptibility measurements were obtained by Gouy's method using mercury tetrathiocyanato cobaltate(II) as a calibrant ($w = 16.44 \times 10^{-6}$ c.g.s. units at 20 °C). Diamagnetic corrections were made using Pascal's constant [30].

Synthesis of ligands [31]

Synthesis of 3-(substituted phenyl)-4-amino-5-hydrazino-1,2,4-triazole

A mixture of 3-(substituted phenyl)-4-amino-5-mercapto-1,2,4-triazole and $N_2H_4{\cdot}H_2O$ in ethanol was boiled under reflux for 4–5 h on a water bath. The reaction mixture was cooled at room temperature, within an hour the compound separated from the clear solution. It was filtered, washed and recrystallized in ethanol.

Synthesis of Schiff bases

A mixture of 3-(substituted phenyl)-4-amino-5-hydrazino-1,2,4-triazole and indoline-2,3-dione in 1:2 M ratio in an alcoholic medium containing a few drops of conc. HCl was refluxed for 5–6 h. The product separated on evaporation of the alcohol was recystallized in ethanol.

General procedure for the synthesis of complexes

A general procedure was followed to synthesize these complexes. The procedure involves the addition of the appropriate ligand (0.04 mol) to an aqueous ethanolic solution of $Fe(NO_3)_3{\cdot}9H_2O$ (0.04 mol) and sodium acetate (0.08 mol). The mixture was refluxed for 10–11 h on a water bath. Reddish brown or orange precipitate obtained was filtered, washed with ethanol and hot water and dried *in vacuo* at room temperature. The complexes were obtained as powdered material.

The details of the reactions along with the analytical data of the product are given in Table 1. The general reaction scheme is given in Fig. 1.

Minimum inhibitory concentration value

An antibacterial activity assay was performed on *Staphylococcus aureus*, *Bacillus subtilis*, *Serratia marcescens*, *Pseudomonas aeruginosa* and *Escherichia coli*. The antibacterial activity for the test compounds was tested to determine the bacteriostatic concentration, i.e. minimum inhibitory concentration (MIC) in terms micromoles. The MIC value was determined by broth dilution technique [32]. A preculture of bacteria was grown in LB (Luria broth) overnight at the most favorable temperature of each species. This culture was used as a control to examine if the growth of bacteria tested was normal. In a similar second culture, 20 µl of the bacteria as well as the tested compound at the desired concentration were added and monitored for bacterial growth by measuring turbidity of the culture after 18 h. If a certain concentration of a compound inhibited bacterial growth, half of the concentration of the compound was tested. This procedure was carried out up to the concentration which inhibited the growth of bacteria. The lowest concentration that inhibited bacterial growth was considered the MIC value. All equipments and culture media were sterilized [33].

Antioxidant studies

Ferric reducing antioxidant power (FRAP) was measured by a modified method of Benzie and Strain [34]. The antioxidant potentials of the compounds were estimated as their power to reduce the TPTZ-Fe(III) complex to TPTZ-Fe(II) complex (FRAP assay), which is simple, fast, and reproducible. FRAP working solution was prepared by mixing a 25.0 mL, 10 mM TPTZ solution in 40 mM HCl, 20 mM $FeCl_3.6H_2O$ and 25 mL, 0.3 M acetate buffer at pH 3.6. A mixture of 40.0 mL, 0.5 mM sample solution and 1.2 mL FRAP reagent was incubated at 37 °C for 15 min. Absorbance of intensive blue color [Fe(II)-TPTZ] complex was measured at 593 nm. The ascorbic acid was used as a standard antioxidant compound. The results are expressed as ascorbic equivalent