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Synthesis, spectral, computational and thermal analysis studies of metalloceftriaxone antibiotic

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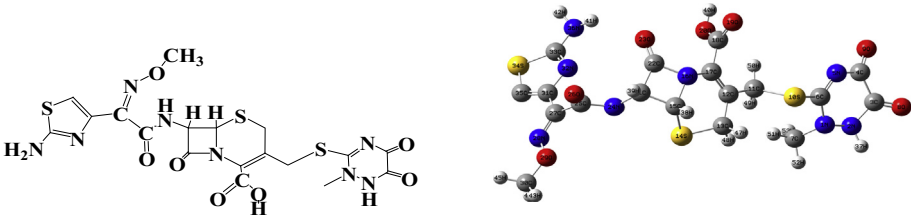
HIGHLIGHTS

- Binary and mixed metal complexes of ceftriaxone were synthesized and characterized.
- The ligand has different combination modes.
- Molecular modeling techniques and quantum chemical methods have been performed for ceftriaxone.
- The thermal behavior of the complexes was studied by TGA, DTA and DSC techniques.

GRAPHICAL ABSTRACT



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ABSTRACT

Binary ceftriaxone metal complexes of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II) and six mixed metals complexes of (Fe, Cu), (Fe, Co), (Co, Ni), (Co, Cu), (Ni, Cu) and (Fe, Ni) were synthesized and characterized by elemental analysis, IR, electronic spectra, magnetic susceptibility and ESR spectra. The studies proved that the ligand has different combination modes and all complexes were of octahedral geometry. Molecular modeling techniques and quantum chemical methods have been performed for ceftriaxone to calculate charges, bond lengths, bond angles, dihedral angles, electronegativity (χ), chemical potential (μ), global hardness (η), softness (σ) and the electrophilicity index (ω). The thermal decomposition of the prepared metals complexes was studied by TGA, DTA and DSC techniques. The kinetic parameters and the reaction orders were estimated. The thermal decomposition of all the complexes ended with the formation of metal oxides and carbon residue as a final product except in case of Hg complex, sublimation occurs at the temperature range 297.7–413.7 °C so, only carbon residue was produced during thermal decomposition. The geometries of complexes may be altered from O_h to T_d during the thermal decomposition steps. Decomposition mechanisms were suggested.

Introduction

Ceftriaxone has obtained high status among the cephalosporin drugs. Like other third generation cephalosporins, it is considerably less active than first generation drugs against gram-positive bacteria, but has a much broader spectrum of activity against gram-negative organisms. It is also effective against gram-negative anaerobes and Enterobacteriaceae (*E. coli, Enterobacter, Klebsiella pneumoniae*) Ceftriaxone exhibits high stability to beta-lactamases excluding those produced by *B. fragilis* and various strains of *Klebsiella*, *Proteus vulgaris*, and *Pseudomonas cepacia*. Ceftriaxone is effective in the treatment of various infections caused by susceptible organisms including [1].

Ceftriaxone (H_2ceftria) interacts with transition metal (II) ions to give [M(ceftria)] complexes (M = Mn, Co, Cu and Cd) and [Fe(ceftria)Cl] which were characterized by physicochemical and spectroscopic methods. The ligand acts as a dianionic pentadentate N_2O_3 chelating agent [2]. Iron, cobalt, nickel and copper complexes of

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ceftriaxone were prepared in 1:3 ligand: metal ratio to examine the ligating properties of the different moieties of the drug. The complexes were found to have high coordinated water molecules. The nujol mull electronic absorption spectra and the magnetic moment values indicated the O_h geometry of the metal ions in the complexes [3].

Masoud et al. reported the complexing properties and thermal behavior of some biologically active compounds [4–12]. In a sequel of continuation, the main interest of this article is studying the thermal behavior of ceftriaxone antibiotic and their metal complexes. The mechanism of decomposition is explained and the thermodynamic parameters are evaluated and discussed.

Iron ceftriaxone complex may be used for preventing or treating low levels of iron in the blood. Iron complex is a vitamin. It works by providing vitamins and iron to the body. Only small quantities of iron are absorbed in the small intestine at a time, and non-heme iron needs to be transformed into its ferrous form and bound to a transporter to pass from the gut into the bloodstream. Once in the bloodstream, iron is used in the bone marrow to make hemoglobin and the excess iron is stored as ferritin primarily in the liver and some in the spleen, Fig. 1.

Experimental

Synthesis of mono metal complexes

Nine simple metal–ceftriaxone complexes were prepared in a similar manner. The inorganic salts [Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) as chlorides] were dissolved in 10 ml bidistilled water. Ligand was dissolved in bidistilled water. The molar amount of the metal chloride salt was mixed with the calculated amount of the ligand using different mole ratios (M:L) viz. 1:1 and 2:1. In each case, the reaction mixture reflux for about 5 min then left over-night, where the precipitated complexes were separated by filtration, then washed several times with a mixture of EtOH–H_2O and dried in a vacuum desiccator over anhydrous $CaCl_2$. The analytical results are given in Table 1.

Synthesis of mixed metals complexes

Six mixed metals complexes of ceftriaxone were prepared by dissolving 1 mmol of the first metal chloride and 1 mmol of the second metal chloride in 10 ml of bidistilled water. The resulting mixed solution added to the ligand (1 mmol in 10 ml bidistilled water). The reaction mixture reflux for about 10 min where colored complexes formed, filtered and washed several times with a mixture of EtOH–H_2O then dried in a vacuum desiccator over anhydrous $CaCl_2$. The analytical results of the isolated mixed metals complexes, Table 1, depicted the formation of complexes with different stochiometries 1:1:2, 2:1:4 and 2:1:2 (M_1, M_2, L respectively). All of these complexes have melting point >300 °C. Elemental analysis C, H, N and S contents of all the synthesized complexes were analyzed by the usual methods [13]. The metal contents were determined based on atomic absorption technique using model 6650 Shimadzu-atomic absorption spectrophotometer and complexometrically with standard EDTA solution using the appropriate indicator as reported [14]. The analysis of chloride contents of the complexes were determined by applying the familiar Volhard method [13].

Physical measurements

The KBr disc infrared spectra of the ligand and their complexes were measured over the frequency range 200–4000 cm^{-1} using Perkin-Elmer Spectrophotometer model. The UV–Vis spectra of the solid complexes were measured in Nujol mull spectra [15]. Molar magnetic susceptibilities, corrected for diamagnetism using Pascal's constants were determined at room temperature (298 K) using Faraday's method. The instrument was calibrated with $Hg[Co(SCN)_4]$. ESR spectra were recorded with a reflection spectrometer operating at (9.1–9.8) GHZ in a cylindrical resonance cavity with 100 KHZ modulation. The g values were determined by comparison with DPPH signal. Differential thermal analysis (DTA), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) were carried out using a Shimadzu DTA/TGA-50. The rate of heating was 10 °C/min and the atmospheric nitrogen rate flow was 20 ml min^{-1}.

Computer analysis programs

Applying Hyper chemistry computer program using PM3 semi-empirical and Molecular Mechanics Force Field (MM+) methods to calculate theoretically the Quantum Chemical Parameters [16].

Results and discussion

IR spectra of ceftriaxone (H_4L) and their simple metal complexes

From IR spectra of ceftriaxone simple complexes represented in Table 2, one could notice that:

1. Ceftriaxone complexes, Table 2 showed broad bands in the 3400.22–3580.99 cm^{-1} region in all prepared complexes suggesting coordination with water. It seemed from the elemental analysis of the complexes and thermal analysis that all complexes contain water molecules in their structures. This is evident by ν_{OH}, Table 2. However, coordinated water in these complexes is indicated by the appearance of metal-oxygen bands attributable to rocking modes at 464.22–495.61 cm^{-1} region [10].
2. The band of N—H stretching vibration of the hydrogen bonded NH_2 group appeared at 3428.00 cm^{-1} in spectra of ceftriaxone. This band appeared in all simple complexes but overlapped with ν_{O-H} of H_2O broad bands.
3. Generally the ring carbonyl absorption frequency shifted to higher wave numbers as the ring became more and more strained. The lactam (C=O) band appeared at 1742.64 cm^{-1} in the spectrum of ceftriaxone which is shifted in the simple

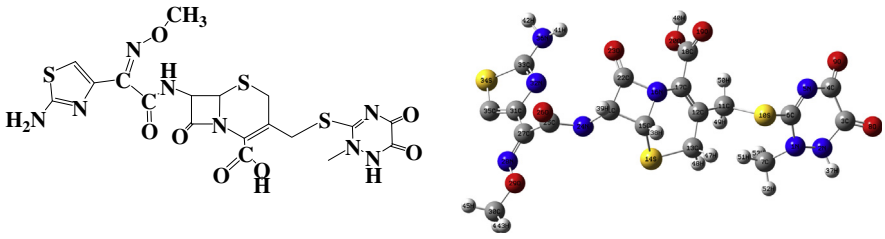

Fig. 1. Structure and molecular modeling of ceftriaxone (H_4L).