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Bivalent transition metal complexes of cetirizine: Spectroscopic, equilibrium studies and biological activity

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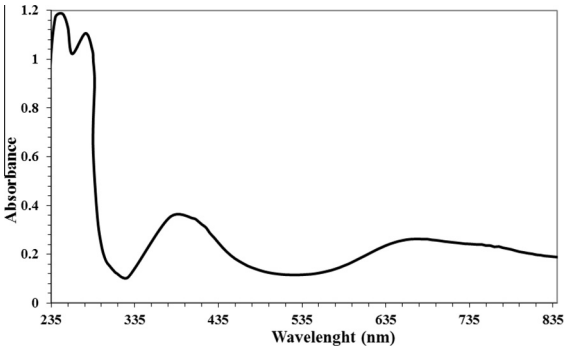
HIGHLIGHTS

- Transition metal complexes with cetirizine (CTZ) were synthesized and characterized.
- Protonation equilibria were calculated for (CTZ) and thermodynamics were discussed.
- Complex formation equilibria and speciation of binary M(II)–CTZ were investigated.
- The biological activity of the free CTZ and its metal-chelates were investigated.

GRAPHICAL ABSTRACT

Transition metal complexes of CTZ were synthesized and characterized by elemental analysis, magnetic susceptibility, molar conductance IR, EPR and UV–Vis studies. Metal complexes are formed in the 1:2 (M:L) ratio and have the general formula $[ML_2(H_2O)_2]\cdot nH_2O$, where M = Co (II), Ni (II) and Cu (II), L = CTZ. Both Ni(II) and Cu(II) complexes of CTZ are square planar while Co(II) – complex is tetrahedral.



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ABSTRACT

Metal complexes of cetirizine·2HCl (CTZ = 2-[2-[4-[(4-chlorophenyl)phenyl methyl]piperazine-1-yl]-ethoxy]acetic acid, dihydrochloride have been prepared and characterized by elemental analyses, IR, solid reflectance, magnetic moment, molar conductance, and UV–Vis spectra. The analytical data of the complexes show the formation of 1:2 [M:L] ratio, where M represents Ni(II), Co(II) and Cu(II) ions, while L represents the deprotonated CTZ ligand. IR spectra show that CTZ is coordinated to the metal ions in a monodentate manner through carboxylate-O atom. Protonation equilibria of CTZ and its metal complexation by some divalent metal ions were determined in aqueous solution at constant ionic strength (0.1 M NaCl) using an automatic potentiometric technique. Thermodynamic parameters for the protonation equilibria of CTZ were calculated and discussed. The stability order of M(II)–CTZ complexes were found to obey $Mn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+}$, in accordance with the Irving–Williams order. The concentration distribution of the complexes in solution is evaluated as a function of pH. The CTZ ligand and its metal complexes were screened for their biological activity against bacterial species (*Bacillus subtillis* RCMB 010067, *Staphylococcus aureus* RCMB 010028, *Pseudomonas aeuroginosa* RCMB 010043, and *Escherichia coli* RCMB 010052) and fungi *as* (*Aspergillus flavus* RCMB 02568, *Pencicillium italicum* RCMB 03924, *Candida albicans* RCMB 05031 and *Geotricum candidum* RCMB 05097). The activity data show that the metal complexes have antibacterial and antifungal activity more than the parent CTZ ligand against one or more bacterial or fungi species. MIC was evaluated for the isolated complexes.

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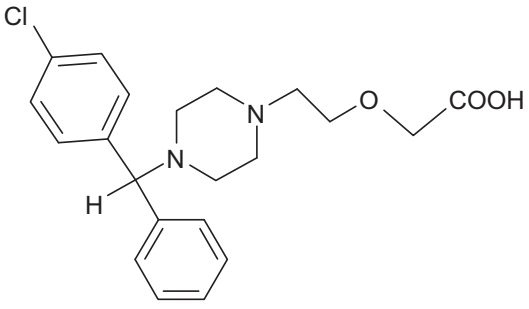
Introduction

Histamine was first identified as a major mediator in allergic reactions at the beginning of the last century [1]. H_1 antihistamines have been available for >50 years and are the drugs of initial choice for treatment of seasonal and perennial allergic rhinitis and urticaria. Newer drugs have been introduced during the past two decades with a lower spectrum of side effects. The most direct way to evaluate the potency of histamine blockade at the H_1 receptor is measurement of the ability of drugs to block the cutaneous response to histamine. The first large-scale comparison of first- and second-generation antihistamines was reported by Simons et al. [2], and they observed that the order of potency was cetirizine, terfenadine, loratadine, astemizole, chlorpheniramine, and placebo. Grant et al. [3] used a similar protocol and found a rank order of cetirizine, epinastine, terfenadine, ebastine, fexofenadine, loratadine, and placebo. Cetirizine (Zyrtec), the major metabolite of hydroxyzine, has become a popular therapeutic tool with high potency, minimal metabolism [4], and a low incidence of side effects [5]. The chemical name of cetirizine dihydrochloride (CTZ) is (RS)-2-[2-[4-[(4-chlorophenyl)phenyl methyl]piperazine-1-yl]-ethoxy]acetic acid, dihydrochloride (Scheme 1).

Knowledge of the physicochemical properties of a drug compound, e.g. its acid–base properties is important in the optimization stage of a drug development project. Commonly dissociation constants of drug compounds are determined by techniques such as titration by potentiometric in aqueous solution. Potentiometric titrimetry in aqueous solution is the most precise method for the determination of equilibrium constants. Stability constant values can also be predicted by computational methods. These techniques have certain advantages, for example calculations can be performed on large virtual compound libraries. Still, erroneous data are often predicted for complex and flexible drug compounds containing several functional groups. Furthermore, these calculations are based on parameters in data bases containing experimental data from the literature. Hence, sufficient data for new types of compounds, to give accurate predictions [6] may be missing [7]. Recently, complexation has often been used to influence biological processes that are metal dependent, at the same time; many drugs behave as ligands, coordinating biometals such as Co(II), Ni(II), Cu(II) and Mn(II) which affects their homeostasis. It can be assumed, therefore, that the action of at least some of the drugs used in the treatment of metal-dependent diseases can be explained on these grounds [8]. Additionally, binary and ternary complexes of transition metals are commonly found in biological media and may play important roles in processes as diverse as catalytic interaction of drugs with biomolecules, the uptake of iron by living organisms, the interaction of viruses with bacterial cell walls, etc. [9]. These create specific structures [10] and have been implicated in the storage and transport of active substances through membranes. The study of ternary complexes of transition metal ions with amino acids or peptides has been the focus of increasing research effort [11–13], which has revealed the role of metal ions at the molecular level. These types of complexes are implicated in the storage and transport of metal ions and of active substances through membranes. So, it is worthwhile to assemble information on their formation, stability, structure and on the mutual influence of two ligands bound to the same metal ion. In view of the above facts and in continuation of our published work on the coordination chemistry of bioactive ligands [14–23], this paper deals with the protonation equilibria of CTZ and its complexes with a number of 3d divalent metal ions (Mn(II), Co(II), Ni(II)and Cu(II)) and the thermodynamics of these systems. This was done through calculation of stability constants for their complexes at different temperatures. Additionally, ternary complexes involving Cu(II), cetirizine and some bio-relevant ligands have been investigated. This work is also extended to present some correlations between the thermodynamic functions and some of well-known properties of the metal ions. The study also includes a quantitative study of the formation equilibria of binary and ternary complexes of Cu(II) with CTZ and some bio-relevant ligands.



Scheme 1. Structural formula of cetirizine drug.

Experimental

Materials and reagents

Cetirizine was supplied by Merck Chem. Co. All metal salts used in this investigation $CuCl_2{\cdot}2H_2O$, $NiCl_2{\cdot}6H_2O$, $CoCl_2{\cdot}6H_2O$, $MnCl_2{\cdot}4H_2O$ were provided by Aldrich Chemicals Co. Metal salt solutions were prepared and standardized as described previously [24]. Carbonate-free NaOH solutions (titrant) was prepared by diluting the content of BDH concentrated volumetric solution vials. These solutions were systematically checked by titration against potassium hydrogen phthalate solution. All solutions were prepared in deionized H_2O.

Preparation of the solid complexes

Copper(II), Nickel(II) and Cobalt(II) complexes of the CTZ were prepared by direct mixing of 1 mmol of metal salt and the corresponding amount of 2 mmol of CTZ ligand and the equivalent amount of sodium bicarbonate required to neutralize the released protons. The metal chloride was dissolved in water and ligand was dissolved in ethanol and sodium bicarbonate in the smallest possible volume of water. The mixture was refluxed for 1–3 h. The formed solid complexes were separated by filtration and then washed several times with acetone and then diethyl ether. The solid complexes were dried in vacuum desiccator. The yield ranged from 71% to 74%. The complexes are soluble in ethanol, methanol, DMF and DMSO. The dried complexes were subjected to elemental and spectroscopic analysis.

Biological activity

Antimicrobial activity of the tested samples was determined using a modified Kirby–Bauer disc diffusion method [25]. Briefly, 100 μl of the test bacteria/fungi were grown in 10 ml of fresh media until they reached a count of approximately 108 cells/ml or 105 cells/ml for fungi [26]. 100 μl of microbial suspension was spread onto agar plates corresponding to the broth in which they were maintained. Isolated colonies of each organism that might be playing a pathogenic role should be selected from primary agar plates and tested for susceptibility by disc diffusion method of the National Committee for Clinical Laboratory Standards (NCCLS) [27]. Among the available media available, NCCLS recommends Mueller–Hinton agar due to: it results in good