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Study of the chemical chelates and anti-microbial effect of some metal ions in nanostructural form on the efficiency of antibiotic therapy "norfloxacin drug"

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ABSTRACT

This paper has reviewed the chemical and biological impact resulting from the interaction between norfloxacin (norH) antibiotic drug and two lanthanide (lanthanum(III) and cerium(III)) metal ions, which prepared in normal and nano-features. La(III) and Ce(III) complexes were synthesized with chemical formulas $[La(nor)_3]\cdot 3H_2O$ and $[Ce(nor)_3]\cdot 2H_2O$. Lanthanum and cerium(III) ions coordinated toward norH with a hexadentate geometry. The norH acts as deprotonated bidentate ligand through the oxygen atom of carbonyl group and the oxygen atom of carboxylic group. Elemental analysis, FT-IR spectral, electrical conductivity, thermal analysis (TG/DTA), X-ray powder diffraction (XRD) and scanning electron microscopy (SEM) measurements have been used to characterize the mentioned isolated complexes. The Coats–Redfern and Horowitz–Metzger integral methods are used to estimate the kinetic parameters for the major successive steps detectable in the TG curve. The brightness side in this study is to take advantage for the preparation and characterization of single phases of La_2O_3 and CeO_2 nanoparticles using urea as precursors via a solid-state decomposition procedure. The norH ligand in comparison with both cases (normal and nano-particles) of lanthanide complexes were screened against for antibacterial (*Escherichia Coli*, *Staphylococcus Aureus*, *Bacillus subtilis* and *Pseudomonas aeruginosa*) and antifungal (*Aspergillus Flavus* and *Candida Albicans*) activities. The highest antibacterial and antifungal activities data of the nano-particles complexes were observed with more potent than the free norH and normal lanthanide complexes.

1. Introduction

Antibiotics can interact with a variety of biomolecules, which may result in inhibition of the biochemical or biophysical processes associated with the biomolecules. This can be illustrated in the interaction of the peptide antibiotic polymyxin with glycolipids which affects membrane function [1].

The intercalation of the anthracyclines (ACs) into DNA base pairs which stops gene replication [2] in the imbedding of the lipophilic antibiotic gramicidin [3] and the insertion of the amphiphilic antibiotic protein into cell membrane [4] which disturb normal ion transport and trans-membrane potential of cells, in the inhibition of transpeptidase by penicillin which affects cell wall synthesis [5] and the inhibition of aminopeptidase by bestatin, amastatin, and puromycin which impairs many significant biochemical processes [6,7].

There are several families of antibiotics that require metal ions to function properly [2–7]. In some cases, metal ions are bound tightly and are integral parts of the structure and function of the antibiotics. Removal of the metal ions thus results in deactivation and/or change in structure of these antibiotics, such as bacitracin, bleomycin (BLM), streptonigrin (SN), and albomycin. In other cases, the binding of metal ions to the antibiotic molecules may engender profound chemical and biochemical consequence, which may not significantly affect the structure of the drugs, such as tetracyclines (TCs), ACs, aureolic acids, and quinolones.

When dealing with the interaction between drugs and metal ions in living systems, a particular attention has been paid to the interaction of metal ions with antibiotics. Antibiotics that interact with metal ions constituted a class of drugs which has been widely used in medicine both for human beings and animals [8,9]. In particular, the interaction between transition metals and β-lactamic antibiotics such as cephalexin had been recently investigated by several physicochemical and spectroscopic methods, and with detailed biological data [10–13]. Many drugs possess modified pharmacological and toxicological properties when

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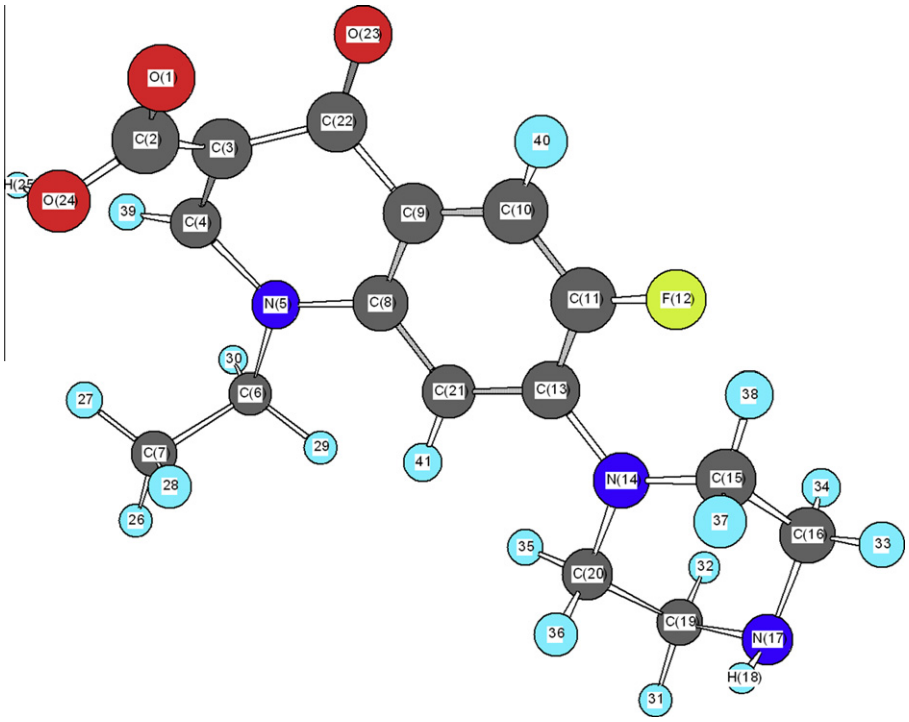

Fig. 1. The structural formula of norH antibiotic drug.

administered in the form of metallic complexes. Probably the most widely studied cation in this respect is Cu(II), for which a host of low-molecular-weight Cu(II) complexes have been proved beneficial against several diseases such as tuberculosis, rheumatoid arthritis, gastric ulcers, and cancers [14–17]. There has been a tremendous growth in the study of drugs from quinolone family, which began with the discovery of nalidixic acid some over 40 years ago. Since then, the exponential growth of this family had produced more than ten thousand analogues [18]. Norfloxacin is considered the best of the third generation quinolone family. There are several reports regarding the synthesis and crystal structure of metal complexes with quinolone derivatives [19–22]. Quinolone antibiotics could participate in the formation of complexes in a number of ways [23–27]. When in acidic media, quinolones are usually singly and/or doubly protonated making them unable to coordinate to the metal cations and, in such cases, only electrostatic interaction are observed between the drug and the metal ions [27,28].

Similar to the case of "metalloproteins," these antibiotics are dubbed "metalloantibiotics" which are the title subjects of this study. Metalloantibiotics can interact with several different kinds of biomolecules, including DNA, RNA, proteins, receptors, and lipids, rendering their unique and specific bioactivities. In addition to the microbial-originated metalloantibiotics, many metalloantibiotic derivatives and metal complexes of synthetic ligands also show antibacterial, antiviral, and anti-neoplastic activities which are also briefly discussed to provide a broad sense of the term "metalloantibiotics". There are several metal–norH complexes and their biological activities studies have been reported [23–28], although, the literature survey failed to have any information about the comparison between biological activities of metal ions in nanoparticles coordinated with norH ligand and the normal norH complexes towards metal salts. So interested in this paper is developing a modular form of the effectiveness of antibiotics on the biological effects resulting from the interaction between the lanthanum and cerium ions in nano-structural fashion and norH antibiotic ligand.

2. Experimental

2.1. Reagents

Urea, $CeCl_3{\cdot}7H_2O$, $LaCl_3{\cdot}6H_2O$ and methanol solvent were obtained from Aldrich Company. Norfloxacin drug (Fig. 1) was received from Fluka chemical company. All chemicals used in this study were of analytically reagent grade and used without further purification.

2.2. Synthesis of Ce(III) and La(III)–nor complexes

2.2.1. A normal preparation method

In usual experiment 3 mmol of norH suspended in 30 mL of methanol was mixed with another solution containing 1 mmol of the $CeCl_3{\cdot}7H_2O$ or $LaCl_3{\cdot}6H_2O$ in 10 mL distilled water. The reaction mixture was then basified by adding ammonia solution (5%, V/V) and was kept at 80–90 °C for about 4–5 h. The reaction mixture was maintained basic by adding ammonia solution from time to time. The product obtained as a precipitate was collected by filtration and washed with a mixture of methanol/water (50:50). The product thus obtained was dried (90 °C) under vacuum over anhydrous calcium chloride.

2.2.2. Method of nano-particles preparation

Preparation is in four steps they can be summarized as follows with sequence equations:

i. $MCl_3 \cdot xH_2O + \text{Urea} \xrightarrow{\text{ca. } 80\ ^\circ C} Ln_2(CO_3)_3 \cdot xH_2O$ (first step) [29,30] (where M = Ce(III) or La(III)).
ii. $M_2(CO_3)_3 \cdot xH_2O \xrightarrow{\text{ca. } 800\ ^\circ C} CeO_2/La_2O_3$ (second step).
iii. $CeO_2/La_2O_3 + HCl\ (\text{conc.}) \xrightarrow{\text{ca. } 80\ ^\circ C} CeCl_3/LaCl_3$ (third step).
iv. $LnCl_3 + \text{norH} \rightarrow [Ln(\text{nor})_3] \cdot xH_2O$.

The first step of preparation was discussed previously [29,30] as follows: $Ln_2(CO_3)_3{\cdot}6H_2O$ (Ln=La and Ce) were prepared by mixing aqueous solutions (100 mL) of 0.01 M of the respectively