Polyhedron 30 (2011) 438–443

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Cu(II) and Zn(II) complexes with a fluoroquinolone antibiotic: Spectroscopic and X-ray absorption characterization

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ARTICLE INFO

Article history:
Received 6 September 2010
Accepted 4 November 2010
Available online 16 November 2010

Keywords:
Copper
Zinc
Antibiotic
Fluoroquinolone
Flumequine

ABSTRACT

The synthesis of two complexes with the antibiotic flumequine, $[Cu(Flumequine)_2(OH_2)_2]$ (**1**) and $[Zn(Flumequine)_2(OH_2)_2]\cdot H_2O$ (**2**) is reported. Their molecular structure was elucidated by combining various spectroscopic techniques. The EPR parameters combined with XAS data underline a tetragonal distorted octahedral geometry for the two complexes. The coordination occurs through the carbonyl and carboxylate oxygen atoms in the equatorial plane. The coordination sphere is completed by two water molecules in axial position.

1. Introduction

Flumequine (Fig. 1) is a drug used to treat bacterial infections. It kills bacteria by interfering with the enzymes involved in the DNA unwinding and duplication. It is an antibacterial first generation fluoroquinolone. Flumequine was used in veterinarian medicine to combat enteric infections (all infections of the intestinal tract), as well as to treat cattle, swine, chickens, and fish, but only in a limited number of countries. It was also used in France (and a few other European Countries) to treat urinary tract infections under the Apurone trade name. Due to the emergence of microbial resistance that results from the bacterial adaptations, the introduction of a new class of compounds named metallo-antibiotics seems to be a good alternative since they present comparable antimicrobial effects to that of free antibiotics, but with a lower microbial resistance.

Otherwise, it is known that many drugs possess modified pharmacological and toxicological properties when administrated in the form of metallic complexes. Recently, studies on the biological activity of quinolone metal complexes have appeared in the literature [1,2]. In a recent study, Soyogul et al. [3] underlined that a zinc supplementation increases the immunostimulatory effects of ciprofloxacine (fluoroquinolone) on polymorphonuclear functions of healthy young volunteers rather than elderly patients. In the last few years, the structure and physico-chemical properties of several compounds involving cinoxacine (quinolone) and ciprofloxacine with cobalt, copper, and zinc have also been reported [4–7]. All these compounds can be divided into complexes and ionic compounds. In the former, the most common bonding of ciprofloxacin to the metals is through the ring carbonyl group oxygen atom and one of the carboxylic oxygen atoms [8], whereas in the latter, only the ionic interaction between protonated quinolone and halometallato anions occurs [7–9].

In the present paper we report the synthesis of Cu(II) and Zn(II) flumequine complexes in a water–ethanol mixture. The green product and the uncolored one in the case of copper and zinc, respectively were analyzed using infrared, UV–Vis, NMR, and EPR spectroscopies, and X-ray absorption spectroscopy (XAS) including X-ray absorption near edge structure (XANES) and extended X-ray absorption fine structure (EXAFS). These techniques allowed to determine the coordination environment of the metallic cations, which is a key point in order to well understand their action mode. Moreover, although quinolones are highly toxic to mammalian cells in culture, its mechanism of cytotoxic action remains not known.

2. Results and discussion

2.1. Synthesis

The copper(II) and zinc(II) complexes were readily prepared using the same conditions by mixing a metallic salt ($Cu(NO_3)_2\cdot 3H_2O$ and $Zn(NO_3)_2\cdot 4H_2O$) aqueous solution with two equivalent of deprotonated flumequine in a basified ethanol–water mixture (%*v*/*v* = 40/60). KOH was used to deprotonate the ligand COOH group (Fig. 1). The copper complex was isolated as a green

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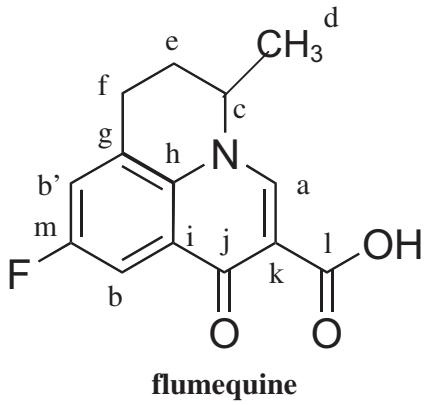
doi:10.1016/j.poly.2010.11.005



flumequine

Fig. 1. Schematic structure of the ligand (neutral form LH).

microcrystalline solid in relatively good yield (51%), whereas the zinc complex was uncolored (yield: 64%). In both cases, complexes were pure isolated and elementally analyzed. Each complex was characterized by IR, UV–Vis, NMR (for $Zn(NO_3)_2{\cdot}4H_2O$), and EPR (for $Cu(NO_3)_2{\cdot}3H_2O$) spectroscopies. Unfortunately, all attempts to obtain well-formed crystals suitable for X-ray determination have failed, thus copper and zinc complexes were structurally characterized by using X-ray absorption spectroscopy (XAS). TGA experiments were monitored under nitrogen atmosphere in the 20–300 °C temperature range. For the two complexes (**1**) and (**2**), the analytical data show a weight loss, which occurs in one step in the 50–100 °C temperature range corresponding to the loss of coordinated and uncoordinated water molecules. This weight loss corresponds to 5.7% in the case of complex (**1**), in agreement with the empirical formula $Cu(Flumequine)_2{\cdot}2H_2O$ (theoretical weight loss of 5.8%), and 8.7% for the complex $[Zn(Flumequine)_2{\cdot}2H_2O]{\cdot}H_2O$ (theoretical weight loss of 8.4%). A satisfactory elemental analysis was obtained for both complexes, which confirms the formation of 1:2 complexes (metal to ligand ratio) consistent with the neutral $Cu(Flumequine)_2(OH_2)_2$ and $[Zn(Flumequine)_2(OH_2)_2]{\cdot}H_2O$ species. These data allowed us to propose a six-coordinated copper(II) and zinc(II) ions with two water molecules in each case.

2.2. Spectroscopic characterization of complexes

The IR spectra of the complexes are consistent with the presence of coordinated carboxylic and carbonyl moieties. Indeed, there is a shift of these ν(C=O) vibrations from 1723 cm^{-1} (broad strong signal) in the free ligand to 1625 cm^{-1} and 1583 cm^{-1} for the copper complex and to 1624 cm^{-1} and 1579 cm^{-1} for the zinc complex. Both complexes exhibit a broad band around 3400 cm^{-1} and 3450 cm^{-1}, which is caused by the OH vibration of coordinated and uncoordinated water molecules. These trends are similar to those reported for complexes with other (fluoro)quinolones [10]. The electronic absorption spectrum of the copper(II) complex in solid state exhibits one asymmetric broad absorption band in the visible region with a maximum at 788 nm. This band due to a d–d transition, which is assigned to the $^2B_{1g} \rightarrow {}^2A_{2g}$ transition, is in accordance with a distorted octahedral geometry of the copper(II) metallic center with a CuO_6 chromophore [11].

The ^{1}H NMR spectrum of the zinc(II) complex (Fig. 2) recorded in DMSO-d_6 evidences the disappearance of the carboxylic proton signal of the ligand at 15.11 ppm, in accordance with a coordination through the carboxylic moiety. Thus, in order to pertinently compare the flumequine and zinc(II) complex NMR spectra, the flumequine spectrum was also recorded in NaOD medium (DMSO-d_6 with added NaOD). The complex formation provokes important downfield shifts of H_a and H_c protons (0.20 and 0.09 ppm, respectively) and to a less extent of H_b and $H_{b'}$ aromatic protons (0.03 ppm), which confirms the implication of the carboxylic moiety in the coordination to the metallic cation. The chemical shift of the other protons is not modified.

The paramagnetic copper(II) cation gave, as might be expected, nonrecordable ^{1}H NMR spectrum. Thus, an EPR spectrum was recorded in ethanolic solution at 100 K (Fig. 3). Due to line broadening caused by the anisotropy of the g factors and hyperfine interactions and by the interaction of the Cu(II) centers with

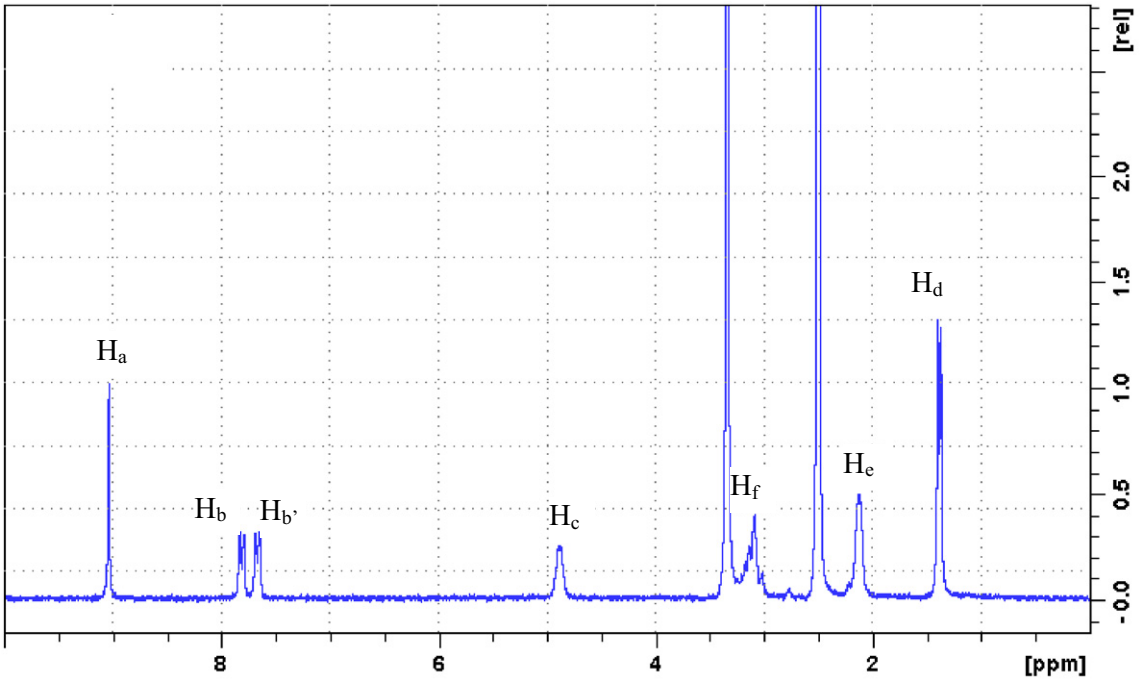


Fig. 2. ^{1}H NMR spectrum of $[Zn(Flumequine)_2(OH_2)_2]{\cdot}H_2O$ complex recorded in DMSO-d_6 at 298 K.