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Two novel 2D waves copper(II) coordination polymer with the quinolone antimicrobial drugs ciprofloxacin: Synthesis, structure and biological evaluation

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ABSTRACT

Two novel coordination polymer $\{[Cu(Cip)]\cdot 2H_2O\}_n$ (**1**) and $\{[Cu_2(Cip)_2ClO_4(CH_3OH)]\cdot 0.5H_2O\}_n$ (**2**) (HCip = ciprofloxacin, Cip = deprotonated ciprofloxacin) have been synthesized and characterized by elemental analysis, infrared spectra and single-crystal X-ray diffraction. Both complexes **1** and **2** exhibit good binding propensity to human or bovine serum albumin protein (HSA or BSA) with relatively high binding constant values. UV and circular dichroism (CD) spectroscopies studies of the interaction of ciprofloxacin and its complexes with calf-thymus DNA (CT DNA) show that complex **2** exhibits higher binding constant to CT DNA ($K_b = 3.32 \times 10^6$) and the results indicate they interact with DNA mainly via intercalation. Fluorescence competitive studies with ethidium bromide (EB) reveal that the complexes could compete with EB and displace it to bind to DNA using the intercalative binding site.

1. Introduction

Quinolones are an important group of synthetic antibacterial agents structurally related to nalidixic acid, which are widely used in the treatment of different types of serious infections by targeting the bacterial type II DNA topoisomerases [1]. They also display chemopreventive and chemosuppressive effects in different cancers such as human breast, bladder, and prostate cancer cell lines [2]. Ciprofloxacin (HCip) (Scheme 1) is a potent and widely used antibiotic of the fluoroquinolone family. It demonstrates a broad spectrum of activity covering wild-type Gram-positive and Gram-negative bacteria. However, new molecules display higher intrinsic activity on Gram-positive bacteria, which becomes the main reasons for ciprofloxacin being restricted to infections in clinical indications [3]. In literature, metal-ciprofloxacin complexes have been reported, and the results suggested that metal ion coordination might be involved in the antibacterial activity of drug molecules and improve the drugs activity [4].

The importance of copper as a bio-metal is mainly focused on its biological role in proteins and its potential synergetic activity with drugs, besides it has a key role in the endogenous oxidative DNA damage associated with aging and cancer [5]. Some copper–quinolone complexes display potential antibacterial activity, good binding propensity to bovine or human serum albumin proteins [6], DNA gyrase inhibition and DNA cleavage activity [7], antiproliferative and anticancer properties [8]. Therefore, we present in this paper antibacterial activity and DNA- and Serum albumin binding properties of two copper(II) coordination polymer with ciprofloxacin.

Serum albumin is the most abundant protein in plasma and transports metal ions and metal complexes. Binding to proteins may lead to loss or enhancement of the biological properties of the original drug or provide paths for drug transportation. Therefore it is important to study the interaction of ciprofloxacin and its complexes with the serum albumin [9]. In this study, we investigated the affinity for bovine and human serum albumin proteins with ciprofloxacin and its complexes.

The study of the interaction of quinolones and their complexes with DNA is of great importance since their activity as antibacterial drugs is mainly focused on the inhibition of DNA replication by targeting essential type II bacterial topoisomerases such as DNA gyrase and topoisomerase IV [10]. As reported, DNA can provide three distinctive binding sites for quinolones and their metal complexes, namely, groove binding, electrostatic binding to phosphate group and intercalation [11–14]. In this paper we studied the interaction of the complexes with calf-thymus DNA (CT DNA) and the ability to

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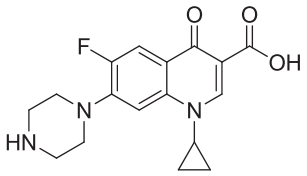

Scheme 1. Ciprofloxacin (HCip).

displace ethidium bromide (EB) from the classical DNA-intercalator EB performed.

Ciprofloxacin usually coordinates to metal ion as a bidentate chelating ligand through two oxygen atoms [15]. In this study, we have synthesized two novel biological 2D waves-like copper(II) coordination polymer with the quinolone antimicrobial drugs ciprofloxacin, $\{[Cu(Cip)]\cdot 2H_2O\}_n$ (**1**) and $\{[Cu_2(Cip)_2ClO_4(CH_3OH)]\cdot 0.5H_2O\}_n$ (**2**), and characterized by elemental analysis, infrared spectra and single-crystal X-ray diffraction. Besides, we study the interaction of the complexes with calf-thymus DNA (CT DNA) by UV spectroscopy and circular dichroic (CD) spectra; the ability to displace ethidium bromide (EB) from the classical DNA-intercalator EB performed by fluorescence spectroscopy.

2. Results and discussion

2.1. Synthesis and spectroscopic study

The synthesis of the complexes were achieved via the reaction of ciprofloxacin, deprotonated with $NH_3\cdot H_2O$, with $Cu(NO_3)_2\cdot 3H_2O$ for **1**, or $Cu(ClO_4)_2\cdot 6H_2O$ for **2**.

In order to confirm the structure and deprotonation of the complexes, IR spectroscopy has been taken. A comparison of the IR spectra of the complexes with that of the free ligand revealed important features relating to the metal–ligand interactions. In the IR spectra of complexes **1** and **2**, the observed absorption band at 3530 (br, m) cm^{-1} attributed to the n(O–H) stretching vibration of HCip molecule has disappeared upon binding to the metal ion which is indicative of deprotonation of the carboxylate group. The bands at 1708(s) cm^{-1} and 1272(s) cm^{-1} attributed to the stretching vibrations $\nu(C{=}O)_{carboxylic}$ and $\nu(C{-}O)_{carboxylic}$, respectively, of the carboxylic moiety (–COOH) of ciprofloxacin. In complex **1**, shifted to 1570 and 1384, 1484 cm^{-1} assigned as antisymmetric, $\nu_{asym}(C{=}O)$, and symmetric, $\nu_{sym}(C{=}O)$, stretching vibrations of the carboxylato group, respectively. The difference $\Delta\nu = [\nu_{asym}(C{=}O) - \nu_{sym}(C{=}O)]$, a useful characteristic tool for determining the coordination mode of the carboxylate ligands, reaches a value of 186 and 86 cm^{-1}, which exhibits chelate and bridging coordination mode [16,17]. Complex **2** was similar characteristic absorptions of the carboxylate group. The vibration $\nu(C{=}O)_{ketone}$ is slightly shifted from 1624 cm^{-1} to 1628, 1629 cm^{-1} upon bonding. In the OH stretching region, both complexes exhibit a broad band at around 3445–3420 cm^{-1} indicative of the presence of lattice water molecules [18]. The strong band at 1085 cm^{-1} in **2** corresponds to a $\nu(ClO_4)^-$ vibration confirming the presence of a free ClO_4^- group.

The stability of complexes **1** and **2** in solution is important for biological studies. Complexes **1** and **2** are soluble at 1×10^{-5} M concentration level in the TBS at 25 °C contains 1% DMSO. The kinetic stability of both complexes was evaluated by UV–Vis absorption under this condition. The kinetic UV–Vis spectra of complexes **1** and **2** are showed in Fig. S1. Over the time course, the characteristic absorption of each complex showed hypochromicity but no bathochromic shift. The hypochromicity can be attributed to the gradual formation of aggregates of the complexes in solution, which will decrease their effective concentration for UV–Vis absorption [19].

2.2. Crystal structure description

2.2.1. Crystal structure of $\{[Cu(Cip)]\cdot 2H_2O\}_n$ (**1**)

The crystal structure of the compound is shown in Fig. 1. The crystallographic data for complex **1** are showed in Table 1, and selected bond distances and angles are listed in Table 2. Cu^{II} is in a distorted tetragonal pyramid geometry, with two oxygen atoms of a ciprofloxacin (Cu1–O1 = 1.940(7) and Cu1–O2 = 1.961(8) Å), an oxygen atoms of a water molecule (Cu1–O2W = 1.981(19) Å) and a nitrogen atom of the second ciprofloxacin (Cu1–N3C = 2.025(8) Å) occupying the equatorial plane. An oxygen atom of the third ciprofloxacin (Cu1–O3D = 2.203(8) Å) occupies the axial position.

The distances of Cu1–O3D is much longer than that of Cu1–O(1,2), It is obvious that the interaction between Cu1 and O3D is weaker than others. The long Cu1–O3D distance may be related to different C–O interaction, the distances of O3–C1 band (1.244(13) Å) is shorter than that of O1–C3 band (1.268(11) Å) and O2–C1 band (1.252(13) Å). The Cu1–N3C band distance (2.025(8) Å) is similar to that in other reported copper–quinolone complex [20].

The two-dimensional waves-like structure of complex **1** are shown in Figs. S2 and S3. There are two remarkable features: firstly, ciprofloxacin acts as uniqueness bridging polydentate ligand to copper atoms, secondly, ciprofloxacin behaves as quadridentate ligand coordinated to copper atom via a nitrogen atom of the piperazinyl ring, two oxygen atoms of carboxylate and an oxygen atom from quinolone ring.

2.2.2. Crystal structure of $\{[Cu_2(Cip)_2ClO_4(CH_3OH)]\cdot 0.5H_2O\}_n$ (**2**)

The crystal structure of the compound is shown in Fig. 2. The crystallographic data for complex **2** are showed in Table 1, and selected bond distances and angles are listed in Table 3. One of the Cu atoms, Cu1, in a distorted tetragonal pyramid geometry, with three oxygen atoms of two ciprofloxacin (Cu1–O1A = 1.914(8), Cu1–O3A = 1.967(8) and Cu1–O5 = 1.984(8) Å) and an oxygen atom of a water molecule (Cu1–O2W = 1.987(9) Å) occupying the equatorial plane. An oxygen atom of the second water molecule (Cu1–O1W = 2.335(12) Å) occupies the axial position. The geometry around the second Cu atom is octahedral, with two oxygen atoms of a ciprofloxacin (Cu2–O4 = 1.927(7) and Cu2–O19 = 1.937(8) Å), two nitrogen atoms of two different ciprofloxacin (Cu2–N2 = 2.021(8) and Cu2–N3 = 2.027(8) Å) occupying the equatorial plane. An oxygen atom of the second water molecule (Cu2–O3W = 2.025(8) Å) and an oxygen atom of perchlorate anion (Cu2–O16 = 2.781(11) Å and O3W–Cu2–O16 = 170.7(3)°) are on the axial positions. The distances between copper atoms and nitrogen atoms are similar to complex **1**. However, they are shorter than that in previously reported structures of mixed copper–ciprofloxacin ternary complexes [21]. Furthermore, it is different of the distances between copper atoms and oxygen atoms. Compared to complex **1**, the distances between copper and oxygen atoms of water molecules are longer than complex **1**. Therefore, the interaction between copper and water molecules is weaker in complex **2**. Besides, the distances between carboxylate oxygen atoms and copper atom are shorter in complex **2**. It may be related to the different two-dimensional structures of the complexes.

The two-dimensional waves-like structure of complex **2** are shown in Figs. S4 and S5. In complex **2**, ciprofloxacin behaves as quadridentate ligand coordinated to copper atom via a nitrogen atom of the piperazinyl ring and all oxygen atoms.

This bonding mode was novel, and to the best of our knowledge, in quinolone drug interactions toward metal ions. Therefore, the remarkable feature is that ciprofloxacin in **2** exhibits mixed-