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Original article

High antitumor activity of 5,7-dihalo-8-quinolinolato cerium complexes

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ABSTRACT

Three cerium complexes: $[Ce(ClQ)_4]$ (**1**) (H-ClQ = 5,7-dichloro-8-hydroxylquinoline), $[Ce(ClIQ)_4]\cdot CH_2Cl_2\cdot 0.5H_2O$ (**2**) (H-ClIQ = 5-chloro-7-iodo-8-hydroxylquinoline) and $[Ce_2(BrQ)_4(H\text{-}BrQ)(H_2O)_3Cl_2]\cdot 1.5H_2O$ (**3**) (H-BrQ = 5,7-dibromo-8-hydroxylquinoline) were synthesized. The structures of **1** and **2** are mononuclear whereas **3** has a binuclear structure. Compared with the H-ClQ, H-ClIQ and H-BrQ, complexes **1**–**3** exhibited significantly higher cytotoxicity (IC_{50} = 0.09–5.23 μM) to SK-OV-3 and BEL-7404, **1** and **2** exhibited higher cytotoxicity to NCI-H460. Most the complexes and ligands exhibited higher cytotoxicity than cisplatin. Complexes **1**–**3** are much more sensitive to SK-OV-3 than to human normal liver cell HL-7702. Their antitumor activities were achieved through cell apoptosis and arrest at G0/G1-phase. Studies on the binding properties of **1**–**3** to DNA indicate that intercalation is the most probable binding mode.

1. Introduction

Because of the success of cisplatin and related platinum complexes as anticancer agents, developing other active transition metal anticancer complexes with better efficiency has attracted the interests of many bioinorganic chemists [1–3]. Lanthanide complexes have caught the attention of medicinal chemists, because lanthanides manifest antitumor activity and could be developed into future anticancer drugs [4]. In the past two decades, a number of lanthanide complexes were synthesized and their cytotoxicities evaluated, such as La(III) complexes with 1,10-phenanthroline [5] and coumarine [6]; neodymium(III) complexes with 5-aminooritic acid [7]; cerium(III) complexes with coumarine [6] and Umbelliferone [8]. Among them, the cerium complexes have attracted special interests due to their great potential as anticancer agents [6,8].

On the other hand, heterocyclic compounds have been widely investigated for their anticancer activity. One such compound is clioquinol (5-chloro-7-iodo-quinolin-8-ol), a 8-hydroxyquinoline derivative, which displays anticancer activity *in vitro* and *in vivo* [9]. A series of anticancer studies of the combination of clioquinol or its derivatives with Cu(II) and Zn(II) ions as an ionophore have been conducted over the past decade by Dou, Shaw, Ding and Viale et al. [10–12]. In addition, insertion of halogen atoms to the ligands may increase membrane permeability and improve the affinity of the metal complex to molecular target [13]. Up to now, a series of researches on the cytotoxicity of 8-hydroxyquinoline and its derivatives' metal complexes against human cancer cell lines were reported [14–19]. In order to seek for cerium complexes with high antitumor activity, and to investigate the cytotoxic effect of the 8-hydroxylquinolines with different halogen atoms bound to cerium ion, herein we reported the synthesis and characterization of three new 5,7-dihalo-8-quinolinolato-cerium compounds (Scheme 1), their *in vitro* cytotoxicities against normal liver cells HL-7702 and tumor cells BEL-7404, SK-OV-3, NCI-H460, and the cell level assays for the interaction of the cerium complexes and DNA, as well as the binding properties of the cerium complexes to the potential target DNA.

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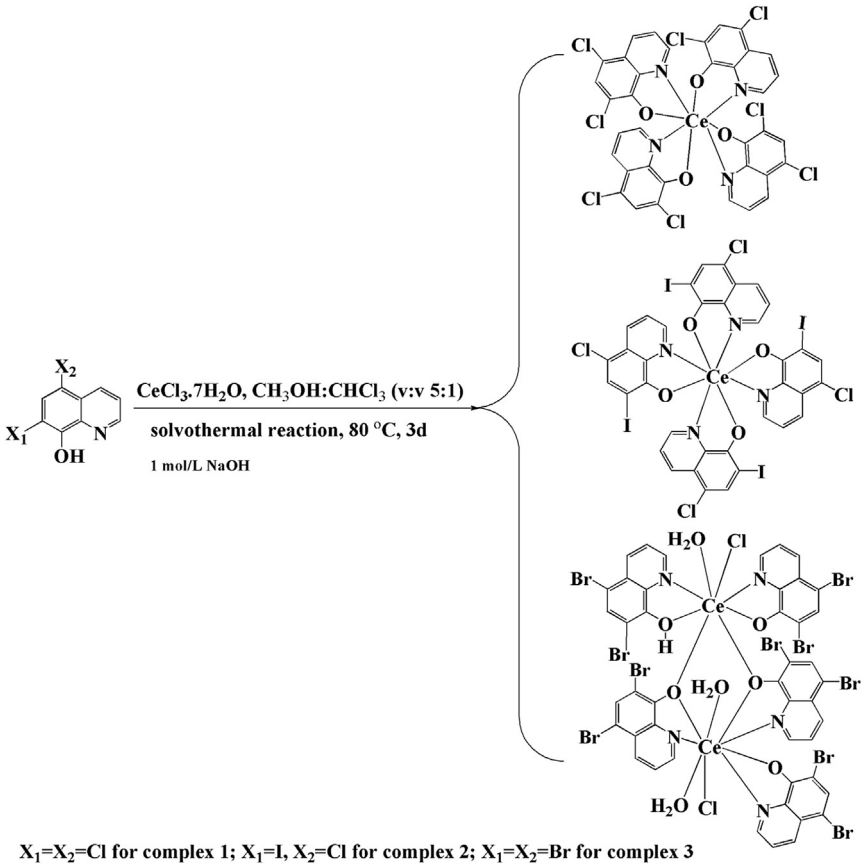

Scheme 1. Synthesis route of complexes **1**–**3**, the solvents are omitted for clarity.

2. Results and discussion

2.1. Chemistry

2.1.1. Synthesis

Under alkaline and solvothermal conditions, each of the three dihalo-substituted 8-hydroxylquinolines reacted with $CeCl_3 \cdot 7H_2O$ to give the three different cerium complexes. In complexes **1** and **2**, four dihalo-substituted 8-hydroxylquinoline molecules were deprotonated to form ClQ^- or $ClIQ^-$ anions to coordinate to Ce atom, and the Ce(III) was oxidized to Ce(IV). In complex **3**, four H-BrQ ligands deprotonated to form anions and one H-BrQ molecule remained coordinated to Ce(III) centers. The structures of the complexes were confirmed by X-ray diffraction analysis, IR, ^{1}H NMR and ^{13}C NMR.

2.1.2. Crystal structure

The single-crystal X-ray diffraction analyses for complexes **1**–**3** revealed that their structures are different. Complexes **1** and **2** have mononuclear structures whereas complex **3** has a binuclear structure. We here describe their structures in detail. Selected bond lengths are reported in Table S1.

Complexes **1** and **2** have mononuclear structures as shown in Figs. 1 and 2. The Ce(IV) atom is octa-coordinated by four N and four O atoms from ClQ^- or $ClIQ^-$ ligands, forming a distorted dodecahedral geometry. In addition, complex **2** contains $Ce(ClIQ)_4$, one CH_2Cl_2 and $0.5H_2O$ solvent molecules. Complex **3** consists of $Ce_2(BrQ)_4(H\text{-}BrQ)(H_2O)_3Cl_2$ and $1.5H_2O$ solvent molecules. **3** is a binuclear structure as shown in Fig. 3 and the Ce centers possess different coordination numbers. Ce(1) is nona-coordinated with the coordination sphere filled by three N and three O from three BrQ^-, two O from two aqua ligands and one Cl^-, in which two μ_2-O (O2, O3) from BrQ^- bridge the Ce(2). Ce(2) is octa-coordinated and surrounded by two N and two O from one BrQ^- and one H-BrQ, one O from one aqua, one Cl^-, as well as the two μ_2-O that bridge the Ce(1). The coordination geometry for Ce(1) and Ce(2) are tricapped distorted trigonal prism and distorted dodecahedron, respectively. The average Ce–O bond length for complexes **1**, **2**, **3** are 2.219, 2.238, 2.486 Å, while the average Ce–N bond length for complexes **1**, **2**, **3** are 2.649, 2.605, 2.745 Å, respectively, both of which showing

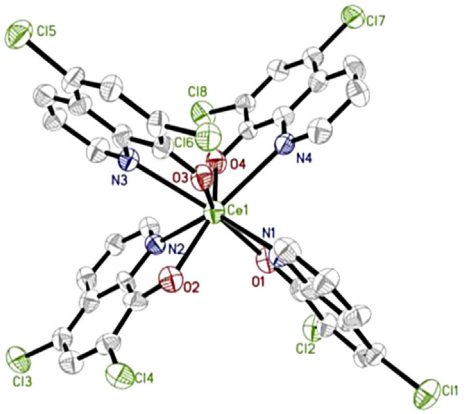

Fig. 1. An ORTEP drawing of complex **1** with atom numbering scheme. Thermal ellipsoids for non-hydrogen atoms are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.