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Original article

Synthesis, characterization, DNA binding properties and antioxidant activity of Ln(III) complexes with hesperetin-4-one-(benzoyl) hydrazone

Yong Li, Zheng-Yin Yang*, Ming-Fang Wang

College of Chemistry and Chemical Engineering and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

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ABSTRACT

Novel Ln(III) complexes with hesperetin-4-one-(benzoyl) hydrazone (H_4L) have been synthesized and characterized. Electronic absorption spectroscopy, fluorescence spectra, ethidium bromide displacement experiments, iodide quenching experiments, salt effect and viscosity measurements indicate that the ligand and Ln(III) complexes, especially the Nd(III) complex, strongly bind to calf thymus DNA, presumably via an intercalation mechanism. The intrinsic binding constants of the Nd(III) complex and ligand with DNA were 2.39×10^6 and 2.70×10^5 M^{-1}, respectively. Furthermore, the antioxidant activity of the ligand and Ln(III) complexes was determined by superoxide and hydroxyl radical scavenging method in vitro, which indicate that the ligand and Ln(III) complexes have the activity to suppress $O_2^{-\bullet}$ and $HO^{\bullet}$ and the Ln(III) complexes exhibit more effective antioxidant activity than the ligand alone.

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1. Introduction

It is well known that deoxyribonucleic acid (DNA) is an important genetic substance in organism. The regions of DNA involved vital processes, such as gene expression, gene transcription, mutagenesis and carcinogenesis [1]. Since DNA is an important cellular receptor, many chemicals exert their antitumor effects through binding to DNA thereby changing the republication of DNA and inhibiting the growth of the tumor cells, which is the basis of designing new and more efficient antitumor drugs and their effectiveness depends on the mode and affinity of the binding [2–5]. Therefore, the qualitative and quantitative analyses of the nucleic acids as the material base of genetic inheritance are becoming more and more important. Binding studies of small molecules to DNA are very important in the development of DNA molecular probes and new therapeutic reagents [6–8]. During the past decades, identifying small molecules that are capable of binding to DNA through an intercalation mode has attracted considerable interests [9]. Small molecule compounds would potentially be valuable tools in biotechnology, nanotechnology, therapeutic approaches and the study of nucleic acid conformations and then a large number of metal complexes with small molecule compounds as ligands are being used at the forefront of many of these efforts [10,11].

Some hydrazones and their metal complexes have diverse biological and pharmaceutical activities, such as antimicrobial, antituberculostatic, anticancer, antioxidant properties and so on [12–15]. Our previous studies indicate that naringenin hydrazones and their metal complexes possess better antitumor, antioxidant and cytotoxicity activities [16–18]. Furthermore, Schiff bases are an important class of ligands in coordination chemistry and are found to possess extensive applications in different fields, such as pharmacological field [19], which are able to inhibit the growth of several animal tumors [20]. Hesperetin (5,7,3′-trihydroxyl-4′-methoxyl-flavanone) is a kind of flavonoid which occurs ubiquitously in plants, fruits, flowers and foods of plant origin [21]. As an important bioactive Chinese traditional medicine, hesperetin has multiple biological and pharmacological activities, including antioxidant properties [22,23], inhibition of cancer development [24,25], effects on the blood-brain barrier [26,27], signal transduction pathways [28], etc. However, hesperetin hydrazones and their complexes have not been extensively investigated. Moreover, Our previous work clearly indicates that the lanthanide complexes possess better bioactivities, such as antioxidant activity, cytotoxic activity, DNA binding affinity and so on [16–18]. In addition, lanthanide ions are subjects of increasing interest in bioinorganic and coordination chemistry [29]. Lanthanide complexes with tetracycline, phenanthroline [30], adriamycin and pyridine [31,32] have been already synthesized as a probe to study nucleic acids.

In order to give a deep research to hesperetin ramifications and their lanthanide complexes, in this paper, we synthesized and characterized a novel ligand, hesperetin-4-one-(benzoyl) hydrazone

* Corresponding author. Tel.: +86 931 8913515; fax: +86 931 8912582.
E-mail address: yangzy@lzu.edu.cn (Z.-Y. Yang).

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(H_4L, Fig. 1) and its Ln(III) complexes. We described a comparative study of the interaction of novel Ln(III) complexes and the ligand with calf thymus DNA (CT DNA) using electronic absorption spectroscopy, fluorescence spectra, ethidium bromide experiments, iodide quenching experiments, salt effect and viscosity measurements for the first time. The antioxidant activity of the ligand and its Ln(III) complexes was also investigated. Information obtained from our study would be helpful to understand the mechanism of interactions of hesperetin hydrazones and their complexes with nucleic acid and should be useful in the development of potential probes of DNA structure and conformation, and new therapeutic reagents for some certain diseases.

2. Results and discussion

2.1. Structure of the Ln(III) complexes

The complexes were prepared by direct reaction of ligand with the appropriate mole ratios of Ln(III) nitrate in acetone. The yields were good to moderate. The desired Ln(III) complexes were separated from the solution by suction filtration, purified by washing several times with ethanol. The complexes are air-stable for extended periods and soluble in DMSO and DMF; slightly soluble in ethanol and methanol; insoluble in benzene, water and diethyl ether. The molar conductivities of the complexes are around 73.9–88.1 S cm^2 mol^{-1} in DMF solution, showing that all complexes are 1:1 electrolytes [33]. The elemental analyses and molar conductivities show that formulas of the Ln(III) complexes conform to $[Ln(H_4L)_2(NO_3)_2]NO_3$ [Ln(III) = La, Sm, Dy, Yb and Nd].

The IR spectra of the complexes are similar. IR spectra usually provide a lot of valuable information on coordination reactions. All the spectra are characterized by vibrational bands mainly due to the NH, C═O, C═N and NO_3 groups. The ν (N–H) appears at 3362 cm^{-1} for the ligand, and this peak shifts at 3386 cm^{-1} or so for the complexes. The ν (C═O) vibration of the free ligand is at 1642 cm^{-1}; for the complexes, the peak shifts to 1610 cm^{-1}, $\Delta\nu_{(ligand-complexes)}$ is equal to 32 cm^{-1}. In the complexes, the band at 555 cm^{-1} or so is assigned to ν (M–O). It demonstrates that the oxygen of carbonyl has formed a coordinative bond with the lanthanide ions [34]. The band at 1604 cm^{-1} for the free ligand is assigned to the ν (C═N) stretch, which shifts to 1570 cm^{-1} for its complexes, $\Delta\nu_{(ligand-complexes)}$ is equal to 34 cm^{-1}. Weak bands at 410 cm^{-1} or so are assigned to ν (M–N) in the complexes. These shifts and new bands further confirm that the nitrogen of the imino-group bonds to the lanthanide ions [35]. The absorption bands of the coordinated nitrates were observed at about 1479 (ν_{as}) and 870 (ν_s) cm^{-1}. The ν_3 free nitrates appear at 1384 cm^{-1} or so in the spectra of the Ln(III) complexes. In addition, the separation of the two highest frequency bands $|\nu_4 - \nu_1|$ is approximately 160 cm^{-1}, and accordingly the coordinated NO_3^- ion in the complexes is a bidentate ligand [36].

The ^{1}H NMR spectra of the ligand and its La(III) complex are assigned as follows: H_4L (DMSO-d^6, 200 MHz), δ (ppm) 2.51 (1H, dd, J = 12.3, 17.0 Hz, 3(a)-H), 2.88 (1H, dd, J = 3.0, 17.0 Hz, 3(e)-H), 3.77 (3H, s, –OCH_3), 5.06 (1H, dd, J = 3.0, 12.3 Hz, 2-H), 5.87 (1H, d, J = 2.2 Hz, 6-H), 5.93 (1H, d, J = 2.2 Hz, 8-H), 6.93 (3H, br, 2′, 5′, 6′-H), 7.52 (2H, dd, J = 1.8, 7.4 Hz, 3″, 5″-H), 7.54 (1H, dd, J = 7.4, 11.6 Hz, 4″-H), 7.88 (2H, dd, J = 1.8, 11.6 Hz, 2″, 6″-H), 9.09 (1H, s, 3′-OH), 9.99 (1H, s, 7-OH), 11.12 (1H, s, –NH–C═O), 13.06 (1H, s, 5-OH). $[Ln(H_4L)_2(NO_3)_2]NO_3$: (DMSO-d^6, 200 MHz), δ (ppm) 2.74 (2H, dd, J = 8.0, 16.2 Hz, 3(a)-H), 2.90 (2H, dd, J = 2.2, 16.2 Hz, 3(e)-H), 3.85 (6H, s, –OCH_3), 5.50 (2H, dd, J = 2.2, 8.0 Hz, 2-H), 5.58 (2H, d, J = 2.2 Hz, 6-H), 5.87 (2H, d, J = 2.2 Hz, 8-H), 6.92 (6H, br, 2′, 5′, 6′-H), 7.45 (4H, dd, J = 2.0, 7.6 Hz, 3″, 5″-H), 7.85 (2H, dd, J = 7.6, 13.4 Hz, 4″-H), 7.96 (4H, dd, J = 2.0, 13.4 Hz, 2″, 6″-H), 9.06 (2H, s, 3′-OH), 10.00 (2H, s, 7-OH), 11.12 (2H, s, –NH–C═O), 13.07 (2H, s, 5-OH). In the complex, the –OH-5 hydrogen still exists. The hydrogen of the ═NNH– group is also detected and there are no hydrogens replaced by the metal ion, which is also supported by the IR spectra.

The complexes begin to decompose at 298 °C or so and there are three exothermic peaks appear around 298–646 °C. The corresponding TG curves show a series of weight loss. Under 200 °C, there are no endothermic peaks and no weight loss on the corresponding curves. It indicates that there are no crystal or coordinate solvent molecules. While being hated to 800 °C, the complexes become their corresponding oxides and the residues are in accordance with calculations.

The study of the electronic spectra in the ultraviolet and visible (UV–vis) ranges for the Ln(III) complexes and ligand was carried out in Tris–HCl buffer solution. The electronic spectra of the free ligand have a strong band at λ_{max} = 328 nm and a medium band at λ_{max} = 285 nm. The complexes also yield two bands, and the two bands are shifted to 343 and 291 nm or so. These indicate that the Ln(III) complexes are formed.

The electrospray ionization (ESI) mass spectra of Sm(III) and Dy(III) complexes were made. The mass spectra of Sm(III) and Dy(III) complexes show peaks at 991 and 1002 which can be assigned to the fragments [Sm(III) complex–$3NO_3$–H]$^{2+}$ and [Dy(III) complex–$3NO_3$–2H]$^+$, respectively.

Since the crystal structures of the Ln(III) complexes have not been obtained yet, we characterized the complexes and determined its possible structure by elemental analyses, molar conductivities, IR spectra, ^{1}H NMR, TG/DTA, mass spectra and UV–vis spectra. The ligand and lanthanide ions can form mononuclear ten-coordination $[Ln(H_4L)_2(NO_3)_2]NO_3$ [Ln(III) = La, Sm, Dy, Yb and Nd] complexes with 1:2 metal-to-ligand stoichiometry at the Ln(III) centers (Fig. 2).

2.2. Magnetic properties

Effective magnetic moments were calculated from the molar magnetic susceptibilities [49]. Dy(III) complex ($\Delta\nu$ = 42.0 Hz) has a magnetic moment of 12.60 B.M., as predicted for a high spin f^9 system with five unpaired electrons. However, La(III) complex ($\Delta\nu$ = 0) is diamagnetic as expected for a f^0 configuration. Magnetic moments for Nd(III) complex ($\Delta\nu$ = 4.5 Hz), Sm(III) complex ($\Delta\nu$ = 1.5 Hz) and Yb(III) complex ($\Delta\nu$ = 7.2 Hz) are 0, 3.84, 1.85 and 4.65 B.M., respectively. These results are consistent with the calculated values.

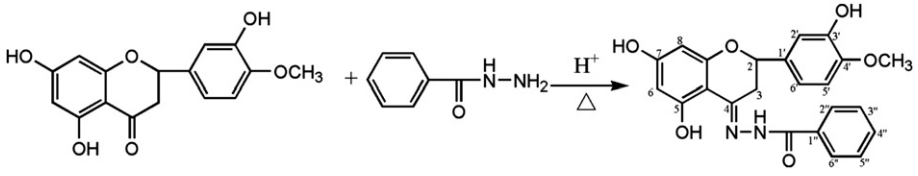

Fig. 1. Scheme of the synthesis of the ligand (H_4L).

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