Journal of Photochemistry and Photobiology A: Chemistry 201 (2009) 183–190

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

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

DNA-binding properties studies and spectra of a novel fluorescent Zn(II) complex with a new chromone derivative

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ARTICLE INFO

Article history:
Received 12 June 2008
Received in revised form 23 October 2008
Accepted 24 October 2008
Available online 14 November 2008

Keywords:
Zn(II) complex
Chromone
Fluorescent properties
Calf thymus DNA
Intercalation mechanism

ABSTRACT

A new chromone derivative (6-ethoxy chromone-3-carbaldehyde benzoyl hydrazone) ligand (L) and its two transition metal complexes [Zn(II) complex and Ni(II) complex] have been prepared and characterized on the basis of elemental analysis, molar conductivity, mass spectra, UV–vis spectra and IR spectra. The Zn(II) complex exhibits light blue fluorescence under UV light, and the fluorescent properties of Zn(II) complex and the ligand in solid state and in different solutions (MeOH, DMF, THF and H_2O) were investigated. In addition, the interactions of the Zn(II) complex and the ligand with calf thymus DNA were investigated using UV–vis absorption, fluorescence, circular dichroic spectral methods and viscosity measurement. It was founded that both two compounds, especially the Zn(II) complex, strongly bind with calf thymus DNA, presumably via an intercalation mechanism.

1. Introduction

There has been considerable interest in the binding studies of small molecules to DNA. A more complete understanding of how to target DNA site would be valuable in the rational design of sequence-specific DNA-binding molecules of application in chemotherapy and highly sensitive DNA probe [1–3]. Given the structural flexibility and variable dimensionality, transition metal complexes play a key role in the development of new bound complex at a DNA site in recent years [4–10]. Basically, metal complexes interact with the double helix DNA in either a non-covalent or a covalent way. The former way includes three binding modes: intercalation, groove binding and external static electronic effects. Among these interactions, intercalation is one of the most important DNA-binding modes as it invariably leads to cellular degradation. Intercalative mode usually presents in compound of planar aromatic ring systems that occupy the space between two adjacent DNA base pairs. As both spectroscopic tags and functional models for the active centers, these complexes have been broadly used as foot-printing agents of both proteins and DNA.

Currently, due to their high antitumor activity and low toxicity, some natural products are being paid attention. Chromones are ubiquitous in nature especially in plants. These natural products are potentially antibacterial, anticancer, antioxidant, anti-inflammatory, and antiallergenic agents since they stimulate or inhibit a wide variety of enzyme systems as pharmacological agents [11,12]. Our previous work showed that 6-hydroxy chromone-3-carbaldehyde hydrazones and their Ln(III) complexes can bind to CT-DNA via intercalative mode, and their complexes have diverse spectral properties, certain antitumor and antioxidative activities [13–17]. It is well known that the different substituting group and conformation can affect the binding mode of compound with DNA.

Based on these evidences, in this study, we synthesized a novel chromone hydrazone ligand (6-ethoxy chromone-3-carbaldehyde benzoyl hydrazone) and its two transition metal complexes. We explored the binding mode of the ligand and Zn(II) complex with CT-DNA using spectroscopic and hydrodynamic methods. The fluorescent properties of Zn(II) complex in solid state and different solvents were also studied. The results should be extremely useful for understanding the mode of the complex with DNA as well as laying a foundation for the rational design of novel, powerful agents for probing and targeting nucleic acids. This study will be very helpful to examine the DNA conformation and structure.

2. Experimental

2.1. Materials

All chemicals used were of analytical grade and purchased from commercial vendors.

Calf thymus DNA (CT-DNA) was obtained from Sigma. UV–vis spectrometer was employed to check DNA purity 1.8–1.9:1 and

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doi:10.1016/j.jphotochem.2008.10.022

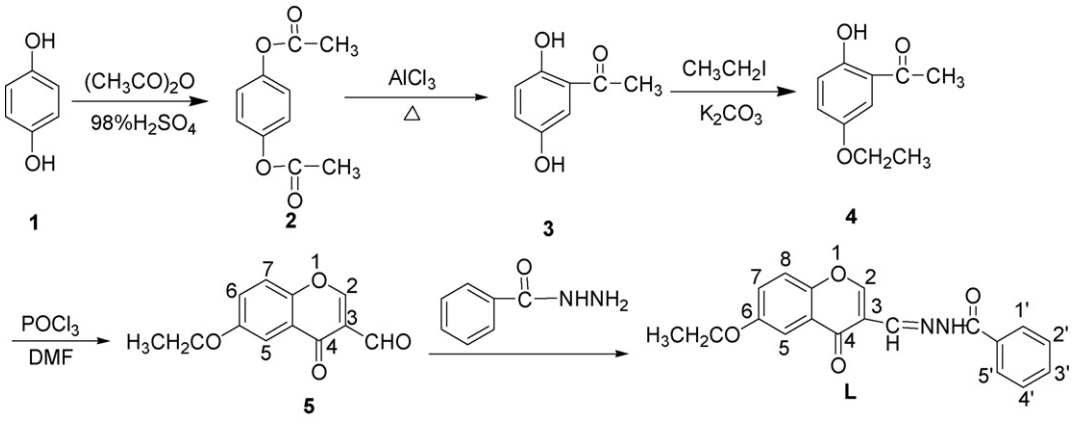

Fig. 1. Scheme of the synthesis of the ligand (L).

concentration ($\varepsilon = 6600\,M^{-1}\,cm^{-1}$ at 260 nm) [18–19]. All the experiments involving interaction of the compounds with DNA were carried out in doubly distilled water buffer containing 5 mM Tris [Tris (hydroxymethyl)-aminomethane] and 50 mM NaCl, and adjusted to pH 7.2 with hydrochloric acid.

2.2. Physical measurements

The metal ions were determined by EDTA (ethylene diamine tetraacetic acid) titration using xylenol orange as an indicator. Carbon, nitrogen and hydrogen analyses were determined using a Vario EL analyzer. Molar conductivity measurements were carried out with a DDS-11C type conductivity bridge using 1.0×10^{-3} mol/l solutions in methanol at 25 °C. IR spectra were recorded on a Thermo Mattson FT-IR instrument using KBr discs in the 4000–400 cm^{-1} region. The UV–vis spectra were recorded on a PerkinElmer Lambda-35 UV–vis (Ultraviolet and Visible) spectrophotometer. ^1H NMR spectrum was measured on a Bruker DRX-200 200-MHz spectrometer in solution with TMS as internal standard. Electrospray ionization (ESI) mass spectrometry was recorded on APEX II FT-ICR MS using methanol as mobile phase. Circular dichroism spectra of DNA were obtained by using JASCO J-810 spectropolarimeter operated at room temperature. Melting points were determined on a Beijing XT4-100X microscopic melting point apparatus. Fluorescence spectra and fluorescence quantum yields were obtained on a Shimadzu RF-5301 spectrophotometer at room temperature, and the latter used a quinine sulfate in 1 mol/l H_2SO_4 ($\Phi_f = 0.546$) [20] as a standard.

2.3. Preparation of ligand and complexes

2.3.1. Synthesis of the ligand (L)

The organic compounds **1**–**3** (Fig. 1) were prepared according to literature [21].

The organic compound **4** (Fig. 1): A mixture of **3** (7.60 g, 50 mmol), 60 mmol of the proper alkyl halide (10.46 g, 75.8 mmol), of anhyd. K_2CO_3 and acetone (220 ml) was heated at reflux for 2–3 d, with stirring. The mixture was filtered off, washed with acetone and the brown filtrate was concentrated to a solid. The solid was chromatographed on a silica gel column, eluting with acetate-petroleum ether (1:20) to give, after removal of solvents from the eluate collected, the nearly pure yellow crystals of compound **4**.

Yield: 70%. m.p.: 50 °C ([22] m.p.: 52 °C). Anal. Calcd for $C_{10}H_{12}O_{43}$: C, 66.65; H, 6.71. Found: C, 66.60; H, 6.80. ^1H NMR ($CDCl_3$): δ 11.84 (1H, s, OH), 7.64–7.33 (3H, m, PhH), 4.01 (2H, q, CH_2), 2.62 (3H, s, $COCH_3$), 1.42 (3H, t, CH_3). IR (KBr) cm^{-1}: ν (C=O) 1643, 1620, 1587, 1484.

The organic compound **5** (Fig. 1): compound **4** (3.60 g, 20 mmol) was dissolved in DMF (40 ml), then $POCl_3$ (20 ml) was added to the above solution at 0 °C. The mixture solution was stirred at room temperature overnight. The solution was allowed to stir at 100 °C for 1 h. The mixture was added to ice water yielding a precipitate, which was filtered off, washed with water and dried. Then the solid was chromatographed on a silica gel column, eluting with ethyl acetate-petroleum ether (1:30) to give, after removal of solvents from the eluate collected, the nearly pure yellow compound **5**.

Yield: 60%. m.p.: 134–135 °C. Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.60; H, 4.70. ^1H NMR ($CDCl_3$): δ 10.41 (1H, s, CHO), 8.53 (1H, s, 2-H), 7.64–7.33 (3H, m, 5, 7, 8-H), 4.16 (2H, q, CH_2), 1.47 (3H, t, CH_3). IR (KBr) cm^{-1}: ν (C=O) 1700, ν (CHO) 1640.

The ligand (L) (Fig. 1) was synthesized as follows. An ethanol solution containing benzoyl hydrazone (1.36 g, 10 mmol) was added dropwise to another ethanol solution containing **5** (2.31 g, 10 mmol). The mixture was stirred for 1 h at room temperature yielding a precipitate, which was filtered off, washed with ethanol and dried in a vacuum. The solid was recrystallized from ethanol to yield a yellow solid and then dried.

Yield: 80%. m.p.: 159 °C. Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79, N, 8.33. Found: C, 67.80; H, 4.85; N, 8.27. HRMS [CH_3OH, m/e]: 337.1194 (calcd for $C_{19}H_{17}N_2O_4$: 337.1188). ^1H NMR (DMSO): δ 11.93 (1H, s, NH), 8.63 (1H, s, 2-H), 8.81 (1H, s, CH=N), 7.94–7.41 (8H, m, 5, 7, 8-H, PhH (2′,3′,4′)), 4.16 (2H, q, CH_2), 1.37 (3H, t, CH_3). HRMS [CH_3OH, m/e]: 337.1194 (calcd for $C_{19}H_{17}N_2O_4$: 337.1188). IR (KBr) cm^{-1}: ν $(C{=}O)_{(hydrazonic)}$ 1650, ν $(C{=}O)_{(carbonyl)}$ 1626, ν (C=N) 1602. UV λ_{max} (MeOH) nm (ε): 213 (27,730), 291 (15,590), 321 (17,370), 410 (12,780).

2.3.2. Synthesis of the complexes

The ligand (L) (0.17 g, 0.5 mmol) was dissolved in acetone (10 ml) when refluxed on an oil-bath at 70 °C with stirring. To this solution was added dropwise a solution of $Zn(NO_3)_2{\cdot}6H_2O$ (0.15 g, 0.5 mmol) in acetone (5 ml). Immediately, a large amount of white precipitate appeared. The precipitate was separated from the solution by centrifuge, purified by washing several times with acetone and dried for 24 h in a vacuum. The Ni(II) complex was also synthesized as the above method.

Zn(II) complex $[ZnLNO_3]NO_3$: color: white, yield: 80%. Anal. Calcd for $C_{19}H_{16}N_4O_{10}Zn$: C, 43.41; H, 3.07; N, 10.66; Zn, 12.44. Found: C, 43.14; H, 2.91; N, 10.44; Zn, 12.70. HRMS [CH_3OH, m/e]: 462.0243 (calcd for $C_{19}H_{16}N_3O_7Zn$: 462.0280), 399.0276 (calcd for $C_{19}H_{15}N_2O_4Zn$ 399.0323). IR (KBr) cm^{-1}: ν $(C{=}O)_{(hydrazonic)}$ 1640, ν $(C{=}O)_{(carbonyl)}$ 1612, ν (C=N) 1579, ν_1 (NO_3) 1487, ν_0 (NO_3) 1384, ν_4 (NO_3) 1321, ν (M–O) 577, ν (M–N) 427. UV λ_{max} (MeOH) nm (ε): 202 (57,270), 329 (14,940), 410 (20,410). Λm ($S\,cm^2\,mol^{-1}$): 140.7.