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Synthesis, crystal structure, DNA-binding properties and antioxidant activity of zinc(II) complexes based on the V-shaped bis(2-benzimidazol-2-ylmethyl)benzylamine ligand and its derivative

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ABSTRACT

Two V-shaped ligands, bis(2-benzimidazol-2-ylmethyl)benzylamine ($\mathbf{L^1}$) and its derivative bis(*N*-allylbenzimidazol-2-ylmethyl)benzylamine ($\mathbf{L^2}$) have been prepared. Reaction of two shaped-specific designed ligands with $Zn(pic)_2$ (pic = picrate) afforded two novel complexes, namely, $[Zn\mathbf{L^1}_2](pic)_2 \cdot 2MeCN \cdot Et_2O$ **1**, and $[Zn\mathbf{L^2}_2](pic)_2$ **2**. The ligands and Zn(II) complexes were characterized by elemental analysis, UV–Vis, IR spectroscopy. Single crystal X-ray diffraction revealed that two Zn(II) complexes have similar distorted octahedral coordination geometry, except that the degree of distortion is different. In order to explore the relationship between the structure and biological properties, the DNA-binding properties have been investigated by viscosity measurement, electronic absorption and fluorescence titration. The results suggested that the ligands and Zn(II) complexes bind to DNA *via* intercalative binding mode, and their binding affinity for DNA are also different. Moreover, two Zn(II) complexes also exhibited potential antioxidant properties *in vitro* studies, and the complex **1** reveal more effective than complex **2**.

1. Introduction

More and more attentions are being attracted by the research on transition metal complexes due to their extensive applications in wide ranging areas [1]. It is well known that metal ions present in complexes can accelerate the drug action and the efficacy of the organic therapeutic agents [2]. Over the past decades, the interaction between transition metal complexes and DNA has been extensively studied in this field. Transition metal complexes are currently being used to bind and react at specific sequences of DNA in a search for novel chemotherapeutics and probing DNA, and for the development of highly sensitive diagnostic agents [3,4]. Therefore, the research on the mechanism of the complexes interact with DNA are attracting more and more attention, which will potentially be useful in the design of such new compounds that can recognize specific site or conformation of DNA [4–6].

Nitrogen ligands have been extensively used in coordination chemistry [7,8], especially to obtain derivatives able to mimic structural, spectroscopic and catalytic features of active sites of metallo-enzymes [9–12]. As a class of typical heterocyclic ligand, benzimidazoles and their derivatives, including the designed ligands containing benzimidazole-based, due to the privileged structure and properties [13], exhibit wide-ranging antiviral activities [14], photochemical and photophysical properties [15,16], versatile coordination modes, and potential to form supramolecular aggregates through $\pi\cdots\pi$ stacking and hydrogen bonding [17–19]. Therefore, transition metal complexes containing benzimidazole-based ligands are a subject of intensive researches not only owing to their rich coordination chemistry but also due to a number of established and potential application areas [20,21], which gives the possibility for further research, such as design of structural probes and the development of novel therapeutics.

In the framework of our research project, mainly focus on dealing with the transition metal complexes containing benzimidazole-based ligands and exploring the reaction mechanism with DNA. In preceding paper [22–26], we have investigated the coordinating ability of various benzimidazole ligands and the corresponding transition metal complexes. In order to more clearly evaluate and understand the influencing factors on the DNA binding mechanism, the synthesis, characterization and DNA-binding activities of two zinc(II) complexes with different ligands are presented in this paper. Moreover, we therefore also conducted an investigation to verify whether two Zn(II) complexes have the antioxidant property.

2. Experimental

2.1. Materials and methods

All chemicals and solvents were reagent grade and were used without further purification. The C, H and N elemental analyses were determined by using a Carlo Erba 1106 elemental analyzer.

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Electrolytic conductance measurements were made with a DDS-307 type conductivity bridge using 3×10^{-3} mol L^{-1} solutions in DMF at room temperature. The IR spectra were recorded in the 4000–400 cm^{-1} region with a Nicolet FT-VERTEX 70 spectrometer using KBr pellets. Electronic spectra were taken on a Lab-Tech UV Bluestar spectrophotometer. The fluorescence spectra were performed on a LS-45 spectrofluorophotometer. The absorbance was measured with Spectrumlab 722sp spectrophotometer at room temperature. ^{1}H NMR spectra were recorded on a Varian VR300-MHz spectrometer with TMS as an internal standard.

Calf thymus DNA (CT-DNA) and ethidium bromide (EB) were purchased from Sigma–Aldrich. All the experiments involving interaction of ligands and Zn(II) complexes with CT-DNA were carried out in doubly distilled water buffer containing 5 mM Tris and 50 mM NaCl and adjusted to pH 7.2 with hydrochloric acid. A solution of CT-DNA gave a ratio of UV absorbance at 260 and 280 nm of about 1.8–1.9, indicating that the CT-DNA was sufficiently free of protein [27]. The CT-DNA concentration per nucleotide was determined spectrophotometrically by employing an extinction coefficient of 6600 M^{-1} cm^{-1} at 260 nm [28]. The stock solution of ligands and complexes were dissolved in DMF at the concentration 3×10^{-3} M.

Synthetic routine of ligands are showed in Scheme 1.

2.2. Synthesis

2.2.1. Synthesis of bis(2-benzimidazol-2-ylmethyl)benzylamine (**L^1**)

The **L^1** was synthesized following a slight modification of the procedure in Ref. [29]. (Yield: 74%); m.p.: 104–106 °C.*Anal.* Calc. for $C_{23}H_{21}N_5$: C, 75.18; H, 5.76; N, 19.06. Found: C, 75.31; H, 5.53; N, 19.15%. Λ_m(DMF, 297 K): 1.45 S cm^2 mol^{-1}. ^{1}H NMR (DMSO-d_6 400 MHz) δ/ppm: 3.47 (m, 2H, –CH_2–Ar), 3.85 (s, 4H, –CH_2-benzimidazol), 7.20 (m, 5H, H-benzene ring), 7.35–7.62 (m, 8H, H-benzimidazol ring). UV–Vis (λ, nm): 278, 284. FT-IR (KBr ν/cm^{-1}): 743, ν(*o*-Ar); 1271, ν(C–N); 1438, ν(C=N); 1622, ν(C=C).

2.2.2. Synthesis of bis(N-allylbenzimidazol-2-ylmethyl)benzylamine (**L^2**)

7.34 g (20 mmol) **L^1** with 1.56 g (40 mmol) potassium were put in tetrahydrofuran (150 mL), the solution was refluxed on a water bath for 4 h with stirring. Then, 4.84 g (40 mmol) allylbromide was added to this solution. With the dropping of allylbromide, the solution gradually became cream yellow. After that, the resulting solution was concentrated and cooled until pale yellow solid separating out, then the pale yellow precipitate was filtered, washed with massive water, and recrystallized from ethanol to give the ligand. Yield: 5.46 g (61%); m.p.:113–115 °C. *Anal.* Calc. for $C_{29}H_{29}N_5$: C, 77.82; H, 6.53; N, 15.65. Found: C, 78.02; H, 6.35; N, 15.71%. Λ_m(DMF, 297 K): 1.97 S cm^2 mol^{-1}. ^{1}H NMR (DMSO-d_6 400 MHz) δ/ppm: 3.45 (m, 2H, –CH_2–Ar), 3.85 (s, 4H, –CH_2-benzimidazol), 4.87–5.68 (m, 10H, –CH_2–CH=CH_2), 7.22 (m, 5H, H-benzene ring), 7.27–7.64 (m, 8H, H-benzimidazol ring). UV–Vis (λ, nm): 279, 286. FT-IR (KBr ν/cm^{-1}): 737, ν(*o*-Ar); 1265, ν(C–N); 1461, ν(C=N); 1643, ν(C=C).

2.2.3. Synthesis of [Zn**L^1**$_2$](pic)$_2$·2MeCN·Et_2O (**1**)

To a stirred solution of **L^1** (183.5 mg, 0.50 mmol) in hot EtOH (10 mL) was added Zn(pic)$_2$ (130.40 mg, 0.25 mmol) in EtOH (2 mL). A yellow crystalline product formed rapidly. The precipitate was filtered off, washed with EtOH and absolute Et_2O, and dried under vacuum. The crude product was dissolved in MeCN to form a yellow solution into which Et_2O was allowed to diffuse at room temperature. Yellow crystals of complex **1** suitable for X-ray measurement were obtained after several weeks. Yield: 176.5 mg (69%). *Anal.* Calc. for $C_{66}H_{58}N_{18}O_{15}Zn$: C, 56.27; H, 4.15; N, 17.90. Found: C, 56.43; H, 4.03; N, 17.76%. Λ_m(DMF, 297 K): 91 S cm^2 - mol^{-1}. UV–Vis (λ, nm): 279, 381. FT-IR (KBr ν/cm^{-1}): 744, ν(*o*-Ar); 1272, ν(C–N); 1364, ν(O–N–O); 1454, ν(C=N); 1612, ν(C=C).

2.2.4. Synthesis of [Zn**L^2**$_2$](pic)$_2$ (**2**)

Complex **2** was prepared in a similar way as described for complex **1**, but using **L^2** (223.5 mg, 0.50 mmol) in place of **L^1**. Yield: 207.5 mg (67%). *Anal.* Calc. for $C_{70}H_{62}N_{16}O_{14}Zn$: C, 59.35; H, 4.41; N, 15.82. Found: C, 59.16; H, 4.59; N, 15.74%. Λ_m(DMF, 297 K): 86 S cm^2 mol^{-1}. UV–Vis (λ, nm): 274, 281, 381. FT-IR (KBr ν/cm^{-1}): 746, ν(*o*-Ar); 1261, ν(C–N); 1365, ν(O–N–O); 1485, ν(C=N); 1631, ν(C=C).

Caution: Picrate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of the material should be prepared and handled with great care.

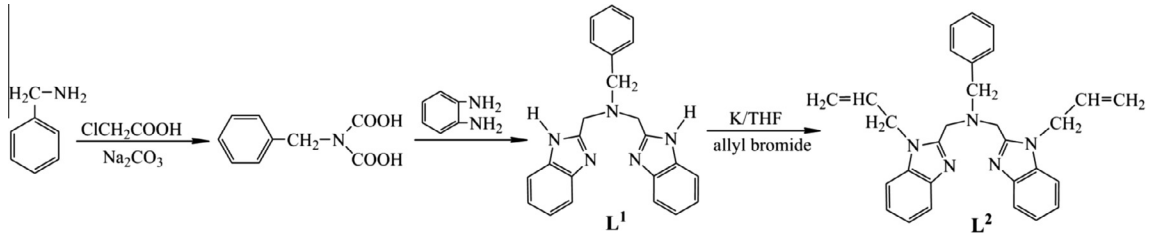
2.3. X-ray crystallography

A suitable single crystal was mounted on a glass fiber, and the intensity data were collected on a Bruker Smart CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 296 K. Data reduction and cell refinement were performed using the SMART and SAINT programs [30]. The structure was solved by Direct Methods and refined by full-matrix least-squares against F^2 of data using SHELXTL software [31]. All H atoms were found in difference electron maps and subsequently refined in a riding-model approximation with C–H distances ranging from 0.93 to 0.97 Å and U_{iso}(H) = 1.2 U_{eq}(C).

2.4. DNA-binding experiments

2.4.1. Viscosity titration measurements

Viscosity experiments were conducted on an Ubbelodhe viscometer, immersed in a water bath maintained at 25.0 ± 0.1 °C. The flow time was measured with a digital stopwatch and each sample was tested, three times to get an average calculated time. Titrations were performed for the compounds (3–30 μM), and each compound was introduced into CT-DNA solution (42.5 μM) present in the viscometer. Data were analyzed as $(\eta/\eta_0)^{1/3}$ versus the ratio of the concentration of the compound to CT-DNA, where η is the viscosity of CT-DNA in the presence of the compound and η_0 is the viscosity of CT-DNA alone. Viscosity values were calculated from the observed flow time of CT-DNA-containing solutions corrected from the flow time of buffer alone (t_0), $\eta = (t - t_0)$ [32].



Scheme 1. Synthetic routines of ligands.