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Polypyridyl Ni(II) complex, $[Ni(tppz)_2]^{2+}$: Structure, DNA- and BSA binding and molecular modeling

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ABSTRACT

The mononuclear Ni(II) complex, $[Ni(tppz)_2]^{2+}$, where tppz is 2,3,5,6-tetra(2-pyridyl)pyrazine, has been prepared and characterized by elemental analysis, spectroscopic methods and single crystal X-ray structure analysis. The interaction of the complex with calf-thymus DNA (CT-DNA) has been monitored by UV–Vis, competitive fluorescence titration, circular dichroism (CD), voltammetric techniques and gel electrophoresis. The results have indicated that the complex binds to CT-DNA by three biding modes, *viz.*, electrostatic, groove and partial insertion of a pyridyl ring of the tppz ligand between the base stacks of double-stranded DNA. The molecular docking of the complex with DNA sequence $d(ACCGACGTCGGT)_2$ suggests two binding modes, *viz.*, groove and partial intercalative binding. The results have also shown good binding propensity of the complex to BSA. The molecular modeling has indicated that the binding mode of the complex to BSA is of hydrophobic forces and hydrogen bond interaction.

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1. Introduction

Polypyridyl transition metal complexes are attracting considerable interest due to peculiar electrochemical, spectroelectrochemical, magnetic, optical, and medicinal properties [1–3]. Some studies have recently found the efficiency of polypyridyl complexes as an electrochemical probe for nucleic acid sensing, particularly for CT-DNA [4], fluorescent probes for nuclear and protein components [5], DNA photocleavage agents [6,7], catalytic inhibitors (or poisons) of human topoisomerase IIα [6]. These complexes also exhibit good binding propensity to transporting proteins such as bovine serum albumin (BSA) [8] and transferrin (the key protein for the transport of Fe^{3+} in blood plasma) [9]. They also show cytotoxicity against cancer cell lines such as non-small lung carcinoma cell line (NCI-H460) [5], BEL-7402, hepG-2, MCF-7 [10] and cisplatin-resistant human ovarian and cervical cancer cell lines [11,12]. The polypyridyl ligand, 2,3,5,6-tetra(2-pyridyl)-pyrazine (tppz), and its complexes have received much attention because of their applications: in the construction of methanol fuel cells [13], in coordination polymers [14], in molecular sensors [15], for sequestering iron for disease prevention [16], and in photodynamic therapy [17].

Nickel is an essential trace metal involved in many biological process [18]. Nickel complexes have been receiving much attention due to biological applicability, such as antiepileptic [19], anticonvulsant [20], antibacterial [21], antifungal [21], antimicrobial [22] and anticancer/antiproliferative [23,24] activities. Nickel complexes can inhibit DNA repair mechanism due to interfering with enzymes or proteins synthesis involved in DNA replication or DNA repair [25]. Some polypyridyl Ni(II) complexes such as $[Ni(phen)_2(qdppz)]^{2+}$, $[Ni(phen)_2(dicnq)]^{2+}$ [26], $[Ni(phen)_2(PHPIP)](ClO_4)_2$ [4] and $[Ni(bipy)_2(phen\text{-}dion)](OAc)_2{\cdot}2H_2O$ [27] show good affinity in DNA binding to exert biological effects. DNA is a target molecule for cancer therapy, therefore, the experimental and theoretical investigations of interaction of DNA with suitable molecules is very important to the design of pharmaceutical molecules [28,29]. Many drugs are transported in the blood while bound to albumin. Therefore, investigation on the formation of complexes between protein and drugs is important to know the transport and mechanism of a drug in the body. Recently, it has been demonstrated that some metal complexes have high affinity for human serum albumin binding under physiological conditions to exhibit a variety of pharmacological properties [30]. In this study, we have used bovine serum albumin (BSA) as the protein model due to its medical importance, low cast, easy availability, intrinsic fluorescence emission, and structural homology with human serum albumin (HSA) [31].

In the present study, we have synthesized a mononuclear nickel(II) complex, $[Ni(tppz)_2]^{2+}$, where tppz is 2,3,5,6-tetra(2-pyridyl)pyrazine. The complex was characterized by elemental analysis, spectroscopic methods (UV–Vis and IR) and single crystal

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X-ray structure analysis. The binding property of the complex with calf-thymus DNA (CT-DNA) under physiological conditions has been studied using different analytical methods such as UV–Vis spectrophotometry, ethidium bromide displacement assay (measured by emission quenching), circular dichroism (CD), cyclic voltammetry (CV), differential pulse voltammetry (DPV) and gel electrophoresis assay. Furthermore, UV–Vis, fluorescence and CD have been used to evaluate the binding behavior of the complex with BSA. In addition, the interaction of the uncoordinated tppz ligand with DNA and BSA has been studied by UV–Vis titration and the results were used to indicate the role of metal ion in the biological activity of the Ni(II) complex. Finally, the molecular docking studies were performed to obtain detailed binding information of the Ni(II) complex with DNA and BSA.

2. Experimental

2.1. Materials and methods

All chemicals and solvents were of high purity and used without any further purification. Highly polymerized calf-thymus DNA (CT-DNA) and bovine serum albumin (BSA) (Sigma) were utilized as received. The solutions of CT-DNA gave a UV absorbance ratio (260 over 280 nm) of more than 1.8, indicating the purity of DNA [32]. Tris(hydroxymethyl)-aminomethane (Tris) buffer and ethidium bromide (3,8-diamino-5-ethyl-6-phenylphenanthridinium bromide, EthBr) were of analytical reagent grade and obtained from Merck. Double-distilled deionized water was used for preparation of all solutions. The stock solution of CT-DNA was prepared by dissolving DNA in 10 mM Tris buffer and 10 mM NaCl at pH 7.2. The DNA concentration per nucleotide was determined by absorption spectroscopy using the molar absorption coefficient ($\varepsilon = 6600\ M^{-1}\ cm^{-1}$) at 260 nm [33]. The stock solutions were stored at 4 °C and used within 4 days.

Elemental analysis (C, H and N) were performed by using a Leco, CHNS-932 elemental analyzer. Fourier transform infrared spectra were recorded on a FT-IR JASCO 680-PLUS spectrometer in the region of 4000–400 cm^{-1} using KBr pellets. Electronic absorption spectra were recorded on a JASCO 7580 UV–Vis–NIR spectrophotometer. Steady state luminescence measurements were performed on a SHIMADZU RF-5000 spectrofluorimeter for DNA interaction studies and a JASCO spectrofluorimeter (FP 6200) for BSA interaction studies. Voltammetric experiments were performed on a SAMA Research Analyzer M-500. All measurements were carried out in a 15 mL cell which was fitted with a Teflon lid incorporating a three-electrode system comprising of a platinum electrode (Φ = 2 mm) as the working electrode, a platinum wire as the auxiliary electrode and a silver wire as the pseudo-reference electrode. The platinum working electrode surface was freshly cleaned with alumina polish on a micro cloth before each scan and was rinsed with double-distilled water between each polishing step. The solutions were deoxygenated by purging with dry N_2 prior to measurements for 10 min and kept under a nitrogen atmosphere throughout all the procedures. Circular dichroism (CD) spectra were measured on a JASCO J-810 spectropolarimeter in a 1 mm path length cylindrical quartz cell. Each sample was scanned from 350 to 190 nm at a speed of 200 nm min^{-1}. The spectral and electrochemical data were collected at the ambient temperature.

2.2. Synthesis of $[Ni(tppz)_2](PF_6)_2 \cdot CH_3CN$

A solution of $Ni(NO_3)_2 \cdot 6H_2O$ (58 mg, 0.2 mmol) in DMF (8 mL) was added dropwise to a solution of tppz (155 mg, 0.4 mmol) in DMF (10 mL) with vigorous stirring. The resulting mixture was stirred at room temperature for 24 h. The solvent was removed by a rotary evaporator and the remaining brown solid, $[Ni(tppz)_2](NO_3)_2$, was washed with cold ethanol several times and then air dried. The brown solid was dissolved in a minimum amount of water and precipitated from solution as the hexafluorophosphate salt by the addition of excess amount of NH_4PF_6. The brown precipitate, $[Ni(tppz)_2](PF_6)_2$, was collected by suction filtration, rinsed with cold water and diethyl ether, and then air dried. For further purification, the brown microcrystalline precipitate was recrystallized by slow evaporation of a 3:1 acetonitrile/toluene solution of the complex. After 1 week at room temperature, shiny red crystals of $[Ni(tppz)_2](PF_6)_2 \cdot CH_3CN$ suitable for X-ray crystallography were formed. The crystals were washed with cold toluene and air dried (yield 81%; 182 mg). *Anal.* Calc. for $C_{50}H_{35}F_{12}N_{13}NiP_2$ (MW = 1166 g/mol): C, 51.48; H, 3.02; N, 15.61. Found: C, 51.73; H, 3.06; N, 15.72%. UV–Vis (CH_3CN) λ_{max}/nm ($\varepsilon/M^{-1}\ cm^{-1}$): 795 (33); 427 (475); 355 (54362); 299 (54575); 197 (122137).

2.3. X-ray structure determination

The X-ray measurement of the complex was made on a Bruker–Nonius X8 ApexII diffractometer equipped with a CCD area detector by using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at 296(2) K. Unit cell parameters were determined by the least-squares calculations with θ angles ranging from 2.35° to 24.72° for $[Ni(tppz)_2](PF_6)_2 \cdot CH_3CN$. The structure was solved by direct method and refined by full-matrix least-squares against F^2 in anisotropic (for non-hydrogen atoms) approximation. Hydrogen atoms were located from the difference Fourier syntheses and placed in geometrically calculated positions (C–H = 0.93 or 0.96 Å). All hydrogen atom positions were refined in an isotropic approximation in the riding model with $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}$(methyl C). Structure solution and refinement were carried out using SHELXS*97* and SHELXL*97* program packages [34], respectively, giving a final R_1 = 0.0680, wR_2 = 0.1689 for $[Ni(tppz)_2](PF_6)_2 \cdot CH_3CN$. The complete conditions of the data collection and structure are given in Table 1.

2.4. DNA binding experiments

All DNA binding experiments, unless otherwise noted were carried out in 10 mM Tris buffer and 10 mM NaCl at pH 7.2. A stock solution of tppz was prepared by dissolving the ligand in an

Table 1
Crystal data and structure refinement for $[Ni(tppz)_2](PF_6)_2 \cdot CH_3CN$.

Chemical formula	$C_{50}H_{35}F_{12}N_{13}NiP_2$
Formula weight	1166.52
T (K)	296(2)
Crystal system	orthorhombic
Space group	*Pca*2(1)
a (Å)	27.5392(10)
b (Å)	11.0445(3)
c (Å)	33.3343(15)
V (Å^3)	10138.9(6)
Z	8
Absorption coefficient (mm^{-1})	0.541
D_x (Mg/m^3)	1.528
F (000)	4736
θ ranges (°)	2.35–24.072
Reflections collected	50101
Independent reflections (R_{int})	16949 (0.0539)
Data/restraints/parameters	16949/1/1407
Goodness-of-fit (GOF) on F^2	1.018
Final *R* indices	R_1 = 0.0680, wR_2 = 0.1689
R indices (all data)	R_1 = 0.0985, wR_2 = 0.1957
Range of *h*, *k*, *l*	−30/33, −13/9, −30/41

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