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Co(III) and Ni(II) complexes of an anthracene appended aroyl hydrazone: Synthesis, crystal structures, DNA binding and catecholase activity

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ABSTRACT

The Co(III) and Ni(II) complexes $[Co(L_2)_2(bpy)]Cl$ (**1**) and $[Ni(L_2)_2(phen)]$ (**2**) (where L_2 is a monoanionic bidentate hydrazone ligand and bpy = 2,2′-bipyridine, phen = 1,10-phenanthroline) have been synthesized and characterized by infra-red, UV–Vis, ESI-MS spectroscopies and elemental analyses. Complexes **1** and **2** were structurally characterized by single crystal X-ray diffraction. Structural analysis reveals a distorted octahedral coordination environment around the metal center with an MN_4O_2 chromophore [M = Co(III) and Ni(II)], with the hydrazone ligand acting as a monoanionic bidentate N, O-donor. Binding of complexes **1** and **2** with calf thymus DNA (CT-DNA) was investigated by UV–Vis absorption, fluorescence spectroscopy and viscosity measurements. Complex **1** shows excellent catecholase mimicking activity with 3,5-di-tert-butylcatechol (3,5-$DTBCH_2$) as the substrate. Kinetic measurements suggest the rate of catechol oxidation follows saturation kinetics with respect to the substrate and the k_{cat} value was found to be quite high, with a value of $1.00 \times 10^5\ h^{-1}$.

1. Introduction

The coordination chemistry of nitrogen–oxygen donor Schiff base ligands is a fertile area of inorganic research [1]. Aroyl hydrazones are quite interesting as they present a combination of donor sites, such as a protonated/deprotonated amide oxygen atom, imine nitrogen atom of the hydrazone moiety and an additional donor site (usually N or O) provided from the aldehyde or ketone forming the Schiff base [2–4]. Hydrazones form wide variety of complexes with chemical, structural, biological and industrial importance [2–10]. They have a variety of applications in biological and clinical fields, such as anti-bacterial, anti-fungal, anti-convulsing, anti-inflammatory, anti-malarial, analgesic, anti-platelets, anti-tuberculosis, anti-cancer and insecticidal activities [11–17]. These activities are attributed to the formation of stable chelate complexes with transition metals which catalyze physiological processes [18,19]. Recent studies have shown that a variety of transition metal complexes have significant potential as probes for sequence- and structure-specific DNA binding. Significant attention has centered upon metal complexes capable of binding DNA by intercalation, due to their strong DNA binding affinity and ease of detection of such binding using the change in luminescence properties. Metal complexes that exhibit interactions with DNA have been studied with the goal of developing probes for nucleic acid structures as well as chemotherapeutic agents [20].

Again, catechol oxidase is a copper containing enzyme whose activity is similar to that of tyrosinase, a related class of copper oxidase. Catechol oxidase carries out the oxidation of 1,2-diphenols, such as catechol, to *o*-quinones, using dioxygen (O_2). Hydrogen atoms removed from catechol combine with the oxygen to form water. The crystal structures of *met*- and *deoxy*- forms of catechol oxidase have enhanced the understanding of the mechanism of catecholase activity of tyrosinase and catechol oxidase. The mechanism of catechol oxidation by the natural enzyme was proposed by several workers, including prominent proposals by Solomon and Kerbs [21–24]. Apart from the large number of Cu(II) model complexes mimicking catecholase activity that have been reported in the literature, quite a number of Co(III/II) and Ni(II) complexes have also been reported to show catecholase-like activity, though their mechanistic aspects are not as clearly understood as that of the Cu(II)-model complexes [25].

In this paper we describe two mononuclear Co(III) and Ni(II) complexes of a hydrazone ligand, containing 2,2′-bipyridine (bpy)

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or 1,10-phenanthroline (phen) as a co-ligand. The ability of the complexes to bind calf-thymus DNA (CT-DNA) was studied by absorption spectroscopy and fluorescence quenching experiments. We also report the excellent catecholase-like activity of the Co(III) complex.

2. Experimental

2.1. Materials and methods

The hydrazone ligand (E)-N-(anthracene-9-yl-methylene) benzohydrazide (L_2H) was prepared following a procedure described earlier [10]. Anthracene 9-aldehyde was purchased from Aldrich. All other chemicals and solvents were of reagent grade and used as such. Solvents for spectroscopic and cyclic voltammetry experiments were of HPLC grade obtained from Merck or Aldrich. Elemental analyses were performed on a Perkin-Elmer 2400 C, H, N analyser. Infrared spectra were recorded as KBr pellets on a JASCO FT-IR-460 spectrophotometer. UV–Vis spectra were recorded using a JASCO V-530 UV–Vis spectrophotometer. Electrochemical data were collected using a CH–instruments 1106A potentiostat. A three-electrode configuration, with Pt-working and auxiliary electrodes, and Ag/AgCl as reference electrode, was used. The potentials were calibrated against the ferrocene/ferrocenium couple (0.44 V versus the Ag/AgCl reference). All the electrochemical experiments were performed under a dry nitrogen atmosphere with millimolar concentrations of the samples dissolved in DMF containing 0.1 M TEAP as the supporting electrolyte. ^1H NMR spectra were recorded on a Bruker AVANCE DPX 300 MHz spectrometer using, $Si(CH_3)_4$ as an internal standard. ESI-MS spectra of the samples were recorded on a JEOL JMS 600 instrument. Viscosity measurements were performed at 25 °C using an Ubbelohde type viscometer.

2.2. Synthesis of the compounds

*2.2.1. $[Co^{III}(L_2)_2(bpy)]Cl$, (**1**)*

L_2H (0.325 g, 1 mmol) was dissolved in 35 ml MeOH, to which 1 mmol of triethylamine (0.101 g) was added. A solution of $CoCl_2{\cdot}6H_2O$ (0.118 g, 0.5 mmol) in MeOH (10.0 mL) was added dropwise to the ligand solution, which was stirred at room temperature. After one hour a methanolic solution of bpy (0.078 g 0.5 mmol) was slowly added to the reaction mixture, resulting in a deep brown colored solution. The reaction mixture was allowed to stir for another 2 h, after which the precipitate that formed was filtered, washed successively with 2 ml of MeOH and 10 ml diethyl ether, and then dried at room temperature. X-ray quality single crystals, having a deep brown color and square shape, of $[Co^{III}(L_2)_2(bpy)]Cl$ (**1**) appeared on slow evaporation of the filtrate at room temperature.

$[Co^{III}(L_2)_2(bpy)]Cl$ (**1**): *Anal.* Calc. for $C_{54}H_{38}N_6O_2ClCo$ (M.W. 897.28): C, 72.22; H, 4.24; N, 9.36. Found: C, 72.12; H, 4.34; N, 9.33%. MS: m/z: 861.2 $[(Co(L_2)_2(bpy)]^+$ (100%) (Fig. S1). Selected IR bands (cm^{-1}): 1601($\nu_{C{=}N{-}N{=}C\text{-}O-}$), 1166($\nu_{bpy(-C-H)}$), 733($\nu_{bpy(-C{=}N-)}$) (Fig. S2). Electronic spectrum in DMF solution λ_{max}/nm ($\varepsilon_{max}/M^{-1}\,cm^{-1}$): 938(22.5), 671(32.4), 401(21787), 371 (15974); Diffuse reflectance spectrum (Fig. S4) λ_{max}/nm: 944, 394, 362. ^1H NMR (DMSO-d_6 solution) δ/ppm (Fig. S3): 8.37 ($2H^{6a}$, d), 8.27–8.21 ($2H^{5a}$, m), 7.96 ($1H^4$, d), 7.84–7.82 ($2H^{5b}$, m), 7.68–7.67 ($5H^{8a,9a,10a,6b}$, m), 7.32 ($2H^{7,3}$), 6.90 ($1H^{11a}$, d), 6.68 ($1H^{2a}$,t), 6.60–6.58 ($2H^{1a,2b}$,m), 6.05 ($1H^{1b}$, d).

*2.2.2. $[Ni^{II}(L_2)_2(phen)]{\cdot}2CH_2Cl_2$ (**2**)*

L_2H (0.325 g, 1 mmol) was dissolved in 35 ml MeOH, to which 1 mmol of triethylamine (0.101 g) was added. To the above solution a solution of $NiCl_2{\cdot}6H_2O$ (0.117 g, 0.5 mmol) in MeOH (10.0 mL) was added dropwise with stirring at room temperature. After one hour a methanolic solution of 1,10-phenanthroline monohydrate (0.099 g 0.5 mmol) was added slowly to the reaction mixture, giving a shiny green colored solution. The reaction mixture was stirred for another two hours and the precipitate that formed was filtered under suction, washed successively with 2 ml of MeOH, and 10 ml diethyl ether. Green square shaped X-ray quality single crystals of $[Ni^{II}(L_2)_2(phen)]{\cdot}2CH_2Cl_2$ (**2**) were obtained by diffusion of diethyl ether into a CH_2Cl_2 solution of the complex.

$[Ni^{II}(L_2)_2(phen)]{\cdot}2CH_2Cl_2$ (**2**): *Anal.* Calc. for ($C_{58}H_{42}Cl_4N_6NiO_2$) (M.W. 1055.49): C, 65.94; H, 3.97; N, 7.95. Found: C, 65.85; H, 3.82; N, 7.91%. Selected IR bands (cm^{-1}): 1586($\nu_{C{=}N{-}N{=}C{-}O}-$), 1120($\nu_{phen(-C-H)}$), 726($\nu_{phen(-C{=}N)}$) (Fig. S2). Electronic spectrum in DMF solution λ_{max}/nm ($\varepsilon_{max}/M^{-1}\,cm^{-1}$): 915(70.2), 553(82.2), 392(17715), 372(16179), 353(13100); Diffuse reflectance spectrum (Fig. S5) λ_{max}/nm: 913, 563, 380.

2.3. X-ray structural determinations

Data for $[Co(L_2)_2(bpy)]Cl$ (**1**) were collected on an 'Oxford Supernova' diffractometer at 150 K. Data for $[Ni(L_2)_2(phen)]{\cdot}2CH_2Cl_2$ (**2**) were collected using a 'Bruker SMART' CCD area diffractometer at 100(2) K. Cu Kα (λ = 1.54184 Å) and Mo Kα (λ = 0.71073 Å) radiations were used for complexes **1** and **2**, respectively. The structures were solved by direct methods using SIR92 for **1** [26] and SHELEXS-97 [27] for **2**, and they were refined by full-matrix least-squares on F^2 using SHELX 97 [28]. The non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed at calculated positions and refined using isotropic displacement parameters. Empirical absorption corrections were applied. A summary of the crystallographic data and the refinement details are collected in Table 1.

2.4. DNA-binding experiments

2.4.1. Absorption spectroscopic studies

The DNA-binding experiments were performed at 25 ± 0.2 °C. The DNA concentration was determined by its UV absorbance at 260 nm after 1:1000 dilution using $\varepsilon = 6600\ M^{-1}\,cm^{-1}$ [29]. The UV absorbance ratio at 260 and 280 nm (A_{260}/A_{280}) of 1.85 indicated that the DNA was sufficiently free of protein contamination [30]. The DNA stock solution was stored at 4 °C in the dark and

Table 1
Crystal data and refinement details of **1** and **2**.

Compound	1	2
Formula	$C_{54}H_{38}ClCoN_6O_2$	$C_{58}H_{42}Cl_4N_6NiO_2$
Formula weight	897.28	1055.49
Crystal size (mm)	0.56 × 0.13 × 0.034	0.28 × 0.24 × 0.18
T (K)	150(2)	100(2)
Crystal system	monoclinic	hexagonal
Space group	*P*21/*n*	*P*6(5)
a (Å)	10.5475(17)	10.7701(3)
b (Å)	17.236(4)	10.7701(3)
c (Å)	24.856(4)	71.416(4)
α (°)	90.00	90.00
β (°)	92.659(14)	90.00
γ (°)	90.00	120.00
D_{calc} ($g\,cm^{-3}$)	1.320	1.466
μ (mm^{-1})	3.914	0.682
F(000)	1856	3264
Total reflections	16123	32691
Unique reflections	7862	7477
Observed data [$I > 2\sigma(I)$]	4055	6976
R_{int}	0.1196	0.0319
R_1, wR_2 [$I > 2\sigma(I)$]	0.1154, 0.2691	0.0328, 0.0635
R_1, wR_2 (all data)	0.1698, 0.3049	0.0379, 0.0650
Data/restraints/parameters	7862/0/577	7477/1/642
Goodness-of-fit (GOF) on F^2	1.04	1.019