

Synthesis, structure and DNA interaction of cobalt(III) bis-complexes of 1,3-bis(2-pyridylimino)isoindoline and 1,4,7-triazacyclononane

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Abstract

The complex $[\text{CoL}_2](\text{ClO}_4) \cdot \text{MeOH}$ (**1**), where HL is the tridentate 3N ligand 1,3-bis(2-pyridylimino)isoindoline, has been isolated and its X-ray crystal structure successfully determined. It possesses a distorted octahedral structure in which both the ligands are coordinated meridionally to cobalt(III) via one deprotonated isoindoline (L^-) and two pyridine nitrogen atoms. Interestingly, the average dihedral angle between pyridine and isoindoline rings is 25.9° , indicating that the ligand is twisted upon coordination to cobalt(III). The interaction of the complex with calf-thymus DNA has been studied using various spectral methods and viscosity and electrochemical measurements. For comparison, the DNA interaction of $[\text{Co}(\text{tacn})_2]\text{Cl}_3$ (**2**), where tacn is facially coordinating 1,4,7-triazacyclononane, has been also studied. The ligand-based electronic spectral band of **1** and the $\text{N}(\sigma) \rightarrow \text{Co}(\text{III})$ charge transfer band of **2** exhibit moderate hypochromism with small or no blue shift on interaction with DNA. The intrinsic binding constants calculated reveal that the monocationic complex ion $[\text{CoL}_2]^+$ exhibits a DNA-binding affinity lower than the tricationic complex ion $[\text{Co}(\text{tacn})_2]^{3+}$. The steric clashes with DNA exterior caused by the second L^- ligand bound to cobalt(III), apart from the lower overall positive charge on the $[\text{CoL}_2]^+$ complex, dictates its DNA-binding mode to be surface binding rather than partial intercalative interaction expected of the extended aromatic chromophore of deprotonated isoindoline anion. An enhancement in relative viscosity of CT DNA on binding to **1** is consistent with its DNA surface binding. On the other hand, a slight decrease in viscosity of CT DNA was observed on binding to **2** revealing that the smaller cation leads to bending (kinking) and hence shortening of DNA chain length. The electrochemical studies indicate that the DNA-bound complexes are stabilised in the higher Co(III) rather than the lower Co(II) oxidation state, suggesting the importance of electrostatic forces of DNA interaction.

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1. Introduction

The interaction of transition metal complexes with DNA has been extensively studied in the past few years in order to develop novel non-radioactive probes of DNA structure [1,2], new therapeutic agents that cleave

DNA [3–5] and DNA-mediated electron transfer reactions [6]. These complexes offer an opportunity to explore the effects of the central metal atom, the ligands and the coordination geometries on the binding event. By varying the ligands, it is possible to modify the mode of interaction of the complex with nucleic acids and facilitate individual applications [7–9]. The application of octahedral complexes has permitted the targeting of specific DNA sites by matching the shape, symmetry and functionality of the metal complex to that of the

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DNA target. There has also been increased interest in the study of metallointercalators, which play an important role in nucleic acids chemistry for their diverse applications such as foot-printing, sequence-specific binding and reactions, new structural probes, and therapeutic agents [2,6,10–18]. Further, the application of these molecules necessitates isolation of structurally analogous complexes with different shapes and electronic properties, investigation of their DNA-binding properties and then the precise understanding of the structural details of their mode of interaction with the target molecule, namely, double helical DNA.

The interaction of transition metal complexes of polypyridyl ligands with DNA has been extensively studied due to their cationic character and stability in aqueous solution. Efforts have been directed towards design of complexes containing modified 2,2'-bipyridine (bipy) or 1,10-phenanthroline (phen) ligands that bind DNA primarily via base-pair intercalation [19–25]. Though Co(III) polypyridyl complexes [26–29] possess interesting metallointercalation and DNA cleavage properties in addition to binding selectivity, they have not attracted as much attention as Cu(II) [30–33] or Ru(II) complexes [34–38]. In our laboratory, we have already studied the DNA-binding properties of $[\text{Co}(5,6\text{-dmp})_3]^{3+}$ (5,6-dmp = 5,6-dimethyl-1,10-phenanthroline) and the mixed ligand cobalt(III) complexes containing bipy, phen, 5,6-dmp and imp (imidazo[4,5-f][1,10]-phenanthroline). We have shown that these complexes display interesting and varying DNA-binding properties and a few of them have the potential to change the conformation of CT DNA [27]. This prompted us to investigate the DNA-binding properties of the cobalt(III) bis-complex of 1,3-bis(2-pyridylimino)isoindoline (HL, Scheme 1) with extended π -aromatic ring system. This tridentate ligand is interesting since the isoindoline ring, which is almost coplanar with the two pyridine rings, is expected to insert itself partially into DNA base pairs leading to intercalative interaction. So we have isolated the complex $[\text{CoL}_2](\text{ClO}_4) \cdot \text{MeOH}$ (**1**), determined its X-ray crystal structure and investigated its mode and extent of DNA binding. We have also isolated

the cobalt(III) bis-complex $[\text{Co}(\text{tacn})_2]\text{Cl}_3$ (**2**), where tacn (1,4,7-triazacyclononane) is a facially coordinating ligand without a planar aromatic moiety unlike the above meridionally coordinating isoindoline. It would be interesting to look at the difference in DNA-binding behaviour of the complexes caused by the difference in ligand architecture of the complexes.

So we have investigated the interaction of the complexes **1** and **2** with calf-thymus DNA (CT DNA) using a variety of spectral methods and viscometric and cyclic voltammetric measurements.

2. Experimental

2.1. Materials

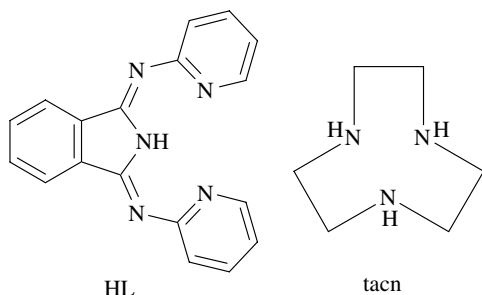
Disodium salt of calf-thymus DNA (Sigma), phthalonitrile, 2-aminopyridine, cobalt(II) perchlorate hexahydrate (Aldrich) and 1,4,7-triazacyclononane (Fluka) were used as received. The complex $[\text{Co}(\text{tacn})_2]\text{Cl}_3$ (**2**) was prepared according to the literature procedure [39]. Common solvents, such as ethanol, methanol and 1-butanol were used after distillation. Milli Q water was used for the preparation of the buffers. All the experiments involving CT DNA were carried out in aqueous 50 mM NaCl/5 mM Tris HCl [tris(hydroxymethyl)aminomethane hydrochloride] buffer at pH 7.1.

2.1.1. Synthesis of 1,3-bis(2-pyridylimino)isoindoline (HL)

The ligand was prepared according to the literature procedure [40]. In a round-bottom flask, phthalonitrile (1.28 g, 10 mmol), 2-aminopyridine (1.97 g, 21 mmol) and calcium chloride (0.1 g, 1 mmol) in 1-butanol (20 mL) were heated at reflux for 48 h. On cooling the solution, a crystalline solid (HL) was isolated. The crude ligand was then recrystallised from ethanol–water solution to obtain X-ray quality crystals. Yield, 0.93 g (31%). The identity of the compound was established by ^1H NMR spectrum and X-ray crystallography. The crystal structure is in good agreement with that reported recently [41].

2.1.2. Syntheses of complexes

2.1.2.1. Synthesis of $[\text{CoL}_2](\text{ClO}_4) \cdot \text{MeOH}$ (1**).** The complex was prepared according to the procedure reported in the literature with slight modifications [42]. To a solution of the ligand (0.29 g, 1 mmol) in methanol (15 mL) was added dropwise a solution of cobalt(II) perchlorate hexahydrate (0.18 g, 0.5 mmol) in methanol (2 mL) with constant stirring. The orange coloured precipitate was removed by filtration and the filtrate allowed to stand. The orange coloured solution turned



Scheme 1.

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