

Full Research Paper

## The Interaction of Sheep Genomic DNA with a Cobalt(II) Complex Containing *p*-Nitrobenzoate and *N,N'*-Diethylnicotinamide Ligands

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**Abstract:** The synthesized cobalt(II) complex, CoPNBDENA and the binding of this complex with sheep genomic DNA were investigated by UV–Visible absorption and viscosity techniques. Also the interaction of sheep genomic DNA with the complex was studied using the agarose gel electrophoresis method. The results indicated that the complex interacted with DNA. The nature of the binding seemed to be mainly an electrostatic interaction between DNA and the cobalt(II) complex. Other binding modes such as hydrogen bonds may also exist in this system. In this study, after the interaction of DNA– CoPNBDENA, it was observed that the migration of the DNA band became slow as the amount of cobalt(II) complex was increased. This clearly demonstrates that the CoPNBDENA complex neutralizes the negative charges of DNA.

**Keywords:** DNA-metal interaction, Cobalt(II) complex, Sheep genomic DNA, *p*-nitrobenzoate, *N,N'*-Diethylnicotinamid.

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## 1. Introduction

Deoxyribonucleic acid (DNA) plays a significant role in the life process, because it carries the inheritance information and leads the biological synthesis of proteins and enzymes through the replication and transcription of genetic information in living cells. DNA is especially a good target for metal complexes as it gives a wide variety of potential metal binding sites [1–4]. For example, the rich DNA electron bases and phosphate groups are suitable for direct covalent coordination at the metal centre. There are non-covalent binding behaviours such as hydrogen bonding and electrostatic binding in the grooved regions of the DNA, along with the intercalation of planar aromatic ligands in the stacked base pairs [5–11].

The factors that lead the binding modes show that the most important factor is the molecular shape [12]. Those complexes that best match with each other against the DNA helical structure indicate the highest binding affinity. Many useful applications of these complexes require that the complex bind to DNA through an intercalative mode with the ligand intercalating into the adjacent base pairs of DNA. However, the majority of such researches have concentrated on the complexes of Ru(II), yet lesser attention has been given to other metal complexes [12]. The interaction of DNA with transition metal complexes has got intensive attention in the last few years in order to develop new novel non-radioactive probes of DNA structure [12, 13], new therapeutic agents that cleave DNA [14–16] and DNA-mediated electron transfer reactions [17]. These complexes give an opportunity to discover the effects of the central metal atom, the ligands and the coordination geometries on the binding event. As to the different ligands, it is possible to change the mode of interaction of the complex with nucleic acids that makes easy individual applications [18–20]. The application of octahedral complexes has allowed the targeting of specific DNA sites by matching the shape, symmetry and functionality of the metal complex to that of the DNA target [21]. Because of the unusual binding properties and general photo-activity, these coordination compounds were available candidates as DNA secondary structure probe, photocleavers and antitumor drugs [22–25].

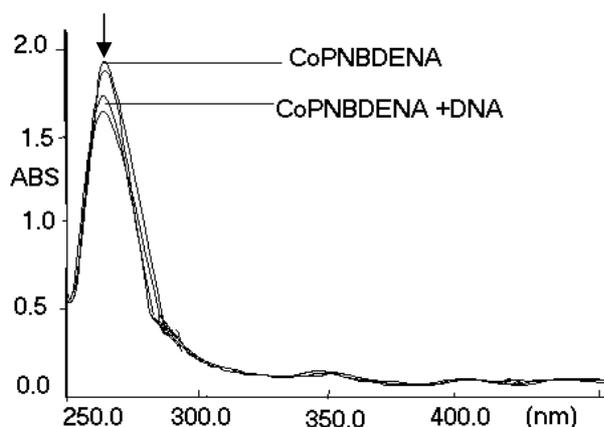
Cobalt was accepted as an essential metal element widely distributed in the biological systems such as cells and body, and thus the interaction of DNA with cobalt complex has attracted much attention [26]. Their binding properties of cobalt with calf thymus DNA were studied by several methods, and the experimental results showed that the size and shape of the intercalated ligand had an important effect on the binding affinity of the complexes with DNA [27]. Hisaeda and co-workers [28] discovered a new water-soluble dicobalt complex having two cobalt–carbon bonds and reported that this dicobalt complex showed higher ability for DNA cleavage in comparison with the corresponding monocobalt complex. Nair and co-worker [29] worked on the interaction of DNA with cobalt(II) tridentate complex, and the photocleavage studies showed that the cobalt(II) complex increased to nicking of DNA in the presence of plasmid DNA [29].

In this study, we concentrated on studies, concerning the interaction of DNA with a new  $[\text{Co}(p\text{-O}_2\text{NC}_6\text{H}_4\text{COO})_2(\text{C}_{10}\text{H}_{14}\text{N}_2\text{O})_2(\text{H}_2\text{O})_2]$ , trans-diaquabis(N,N'-diethylnicotinamide)bis(p-nitrobenzoato) cobalt(II), which has both para-nitrobenzoate and N,N'-diethylnicotinamide ligands in the coordination sphere. The binding properties of this CoPNBDENA with genomic DNA were studied using absorption, electrophoresis and viscosity experiments [30].

## 2. Results and Discussion

In the UV–Visible region, intense absorption bands, which appeared from 260 to 300 nm, are believed to charge transfer transitions. Electronic absorption spectra are initially used to study the binding of CoPNBDENA complex with genomic DNA. Moreover, increasing concentrations of the complex result in the obvious tendency of hyperchromism and shift of the absorption bands[31]. The absorption spectra of the complex CoPNBDENA in the absence and presence of genomic DNA, is shown in Figure 1. An electrostatic interaction between CoPNBDENA complex and the DNA can be predicted when it is based on the hyperchromism exhibited and shifted in absorbance of the cobalt complex. Because our complex contains the para-nitrobenzoate and N,N'-diethylnicotinamide ligands. However, the high hyperchromism effects observed suggest van der Waals contacts between the groups of PNBDENA of the complex [31]. The coordination bond of DNA base with cobalt can take place through replacement of ligands in the complex [32]. It should be reported that a favourable hydrogen bond may be formed between NH<sub>2</sub> in the complex and N of adenine or O of thymine in the DNA [31,32,33]

**Figure 1.** Absorption spectra of [Co(*p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>COO)<sub>2</sub>(C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] complex (15.4mM) in the absence and in the presence of DNA and increasing amounts of [DNA] = 0-10mM. Arrow shows that the absorbance changes upon increasing the DNA concentrations.



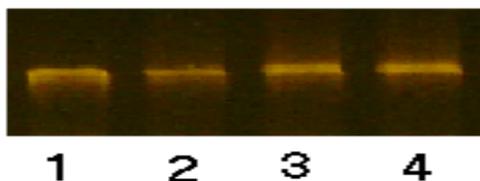
This shows that our cobalt(II) complex binds strongly with DNA compared with other ordinary cobalt(II) complexes known in the literature [31].

Gel electrophoresis study of [Co(*p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>COO)<sub>2</sub>(C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] complex provides visualization of the interaction of DNA and CoPNBDENA complex. Complex of a linearized genomic DNA with CoPNBDENA complex was formed at different concentrations, and agarose gel electrophoresis was subsequently carried out. Representative gel images are shown in Figure 2. While free DNA moves in the electric field toward the anode, the movement of DNA has been made slow due to the complex above. This study explains that the cationic unit of the complex is neutralizing the negative charges of DNA, thereby resulting in the formation of stable complex[35, 36]. It is reported that electroneutral complex with DNA is irrespective of the inherent amount of quarternization. This

may be because of the fact that all the nitro groups are charged by abstracting protons from the buffer[35, 36].

Tang and Szoka [34] and Bronich et al. [35] have reported that DNA-polycation complexes are formed as a result of ionic interactions between negatively charged phosphate groups of DNA and cationic groups of the polycation. Vinogradov et al. [36,37] have noticed that the binding between DNA and complex is considered to occur mainly through electrostatic interactions among the participating species. CoPNBDENA-DNA complex which is produced spontaneously resulting from the interaction of nitro groups of para-nitrobenzoate, amino groups of diethylnicotiamide with the phosphate groups of DNA. In order to substantiate the binding of the cobalt (II) complex to DNA, a gel retardation assay was conducted on DNA (Figure 2). Lane 1 is pure DNA not treated with any complex. Lanes 2–4 represent the DNA reacted with the cobalt(II) complex. In this study, due to the interaction of DNA–CoPNBDENA, the migration of the DNA band is made slow as the amount of cobalt(II) complex is increased. This clearly demonstrates that the CoPNBDENA complex is neutralizing the negative charges of DNA which could be made further easy because of the increase of p-nitrobenzoate groups and N,N'-diethylnicotineamide groups of CoPNBDENA complex.

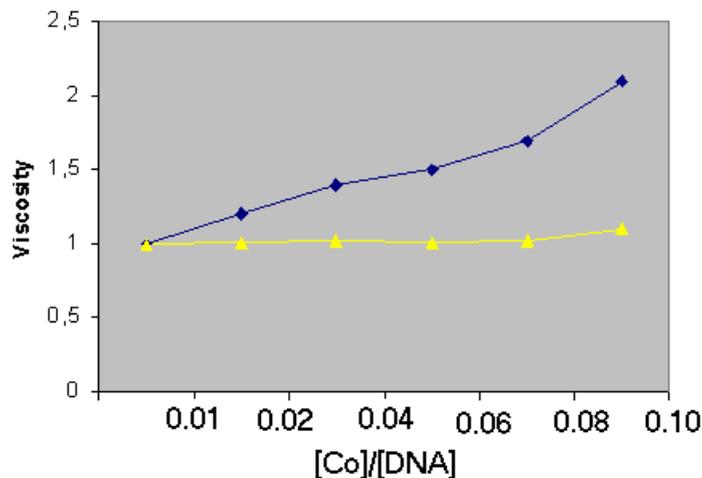
**Figure 2.** Analysis of complex formation between DNA and CoPNBDENA by agarose gel electrophoresis. Gel retardation assay of genomic DNA by CoPNBDENA. Lane 1: untreated genomic DNA alone, Lanes 2–4: DNA + CoPNBDENA complex in the concentration of 15.4, 0.154 and 0.0154mM. An increasing concentration of the complex was added to DNA in 45mM Tris-borate and 1mM EDTA at pH 8.0. The mixture was then analyzed on a 1% agarose gel in Tris-borate buffer (45mM, pH 8.0) containing 1mM EDTA.



The experiment gave signs that untreated DNA does not represent any cleavage in the dark (see lane 1). Similarly, DNA nicking was not observed for genomic DNA treated with CoPNBDENA in the dark experiments (see lanes 1, 2–4).

To further make clear the interaction between the complex and DNA, viscosity measurements were studied. Optical photophysical studies are not enough to explain a binding between DNA and the complex. A classical intercalation model results in lengthening the DNA helix, as base pairs are separated to accommodate the binding ligand, leading to the increase of DNA viscosity. The effect of  $[\text{Co}(p\text{-O}_2\text{NC}_6\text{H}_4\text{COO})_2(\text{C}_{10}\text{H}_{14}\text{N}_2\text{O})_2(\text{H}_2\text{O})_2]$  on the viscosity of DNA is shown in Figure 3. When the ratio of Co(II) complex to DNA increase,  $[\text{compound}]/[\text{DNA}]$ . CoPABDENA can increase the viscosity of DNA, which indicates that the compound binds to DNA by intercalation of the aromatic ring into the base pairs of DNA. Not only does this result give sign of an intercalative binding mode of the complex, but it is also in agreement with the pronounced hypochromism, bathochromism of the complex in the presence of DNA [25].

**Figure 3.** Effect of increasing amounts of  $[\text{Co}(p\text{-O}_2\text{NC}_6\text{H}_4\text{COO})_2(\text{C}_{10}\text{H}_{14}\text{N}_2\text{O})_2(\text{H}_2\text{O})_2]$  ( $\blacklozenge$ ), on the relative viscosities of goose genomic DNA ( $\nabla$ ),  $[\text{DNA}] = 0.5 \text{ mM}$ , at  $30.0 (\pm 0.1) \text{ }^\circ\text{C}$



### 3. Experimental

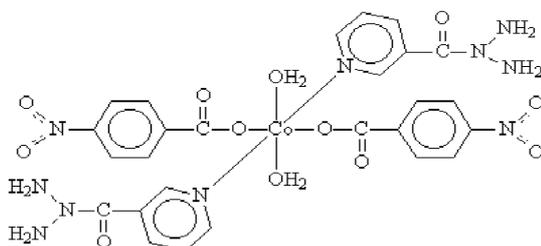
#### 3.1. Materials and methods

Cobalt sulphate ( $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ ) heptahydrate, sodium *p*-nitrobenzoate,  $N,N'$ -diethylnicotinamide, and all common solvents and reagents were purchased commercially from Aldrich and Sigma and used without further purification. Genomic DNA obtained from the blood sample was used as well. All experiments involving the interaction of the complex with DNA were conducted in Milli-Q water, and all solutions were prepared with Milli-Q water. The spectroscopic titration was performed in the buffer (10 mM NaCl 50mM Tris-HCl, pH 7.3) at room temperature. A solution of DNA in the buffer gave a ratio of UV absorbance at 265 and 285 nm showing that the DNA was almost free of protein [13].

#### 3.2. Synthesis of *Diaquabis(N,N'-diethylnicotinamide)bis(p-nitrobenzoato)cobalt(II) complex*

$[\text{Co}(p\text{-O}_2\text{NC}_6\text{H}_4\text{COO})_2(\text{C}_{10}\text{H}_{14}\text{N}_2\text{O})_2(\text{H}_2\text{O})_2]$ , *trans*-diaquabis( $N,N'$ -diethylnicotinamide)bis(*p*-nitrobenzoato)cobalt(II) complex was synthesized (Fig. 4) [30]. The complex was prepared by 0.01 mol  $[\text{Co}(p\text{-O}_2\text{NC}_6\text{H}_4\text{COO})_2(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$  and 0.02 mol of diethylnicotinamide in 100 mL water. The solution was filtered and set aside for crystallization at ambient temperature for a few days. Pink crystals were obtained [30]. Elemental analysis were carried out on a LECO CHNS 932 analyzer. The theoretical contents of C, H and N were calculated for  $[\text{Co}(p\text{-O}_2\text{NC}_6\text{H}_4\text{COO})_2(\text{C}_{10}\text{H}_{14}\text{N}_2\text{O})_2(\text{H}_2\text{O})_2]$  (%): C, 53.14; H, 5.70; N, 10.33, analytical results were found (%): C, 49.76; H, 5.78; N, 10.34.

**Figure 4.** Chemical structure of  $[\text{Co}(p\text{-O}_2\text{NC}_6\text{H}_4\text{COO})_2(\text{C}_{10}\text{H}_{14}\text{N}_2\text{O})_2(\text{H}_2\text{O})_2]$ .



### 3.4. Physical measurements

Absorption spectra were recorded on a UV–Vis Heyλios Range of UV-Visible spectrophotometer spectrophotometer using cuvettes of 1 cm path length. For the absorption spectra, an equal solution of DNA was added to both complex solution and reference solution to eliminate the absorbance of DNA itself. The DNA concentration per nucleotide was determined by absorption spectroscopy using the known molar extinction coefficient value of 6600 M<sup>-1</sup> cm<sup>-1</sup> at 260 nm [27,28,29,31]. Absorption titrations were carried out by using [Co(*p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>COO)<sub>2</sub>(C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>], (CoPNBDENA), complex concentration to which increments of the DNA stock solution were added. CoPNBDENA complex and DNA solutions were allowed to incubate for 1 h before the absorption spectra were recorded. The electrophoretic mobilities of the complex/DNA at different complex concentrations were determined by gel electrophoresis using 1.0% agarose gel in a buffer consisting of 45mM Tris-borate and 1mM EDTA at pH 8.0. Experiments were run at 50 V for 2 h. DNA was visualized under UV illumination by staining the gels with ethidium bromide overnight at room temperature.

Viscosity experiments were carried out using an Ubbelodhe viscometer maintained at a constant temperature of 30 °C in a thermostatic bath [23]. A digital stopwatch was used to measure six times the flow time, and each sample was measured six times, and an average flow time was calculated. Data were illustrated as  $(\eta/\eta_0)^{1/3}$  versus binding ratio [24], where  $\eta$  is the viscosity of DNA in the presence of complex, and  $\eta_0$  is the viscosity of DNA alone [25].

### 3.5. DNA-binding experiments

The DNA-binding experiments were carried out at room temperature. CoPNBDENA, [Co(*p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>COO)<sub>2</sub>(C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>], complex were used as the source of reactive. MilliQ water was used to prepare the solutions of complex. The pH of the solutions was fixed to 7.3 by adding slowly NaOH solution. The solution of genomic DNA in the buffer consisting of 1mM Tris-HCl at pH 7.3, 1mM NaCl and 1mM EDTA was used [29]. DNA was allowed to interact with the metal complex. In order to compare the effect of interaction of the metal complex between DNA and CoPNBDENA complex–DNA, solutions were allowed to incubate for 24 h before the absorption spectra were recorded. For the gel electrophoresis experiments, genomic DNA was treated with CoPNBDENA in 50 mM Tris–HCl, 20 mM NaCl buffer, pH 7.3. The samples were electrophoresed for 3 h at 50 V on a 0.8% agarose gel in tris–acetic acid–EDTA buffer. The gel was stained with 0.5 μg/mL ethidium bromide and then photographed under UV light [38].

## Conclusion

The DNA binding of cobalt complex containing the *p*-nitrobenzoate and *N,N'*-diethylnicotinateamide ligands has been studied by absorption spectroscopy, gel electrophoresis and viscosity methods. The binding of cobalt(II) complex to DNA seems stronger than ordinary cobalt(II) complex. This may be due to the presence of cobalt(II) complex molecular units and free amino groups in a single molecule which cooperatively help the binding to DNA between each other.

## Abbreviations

[Co(p-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> COO) <sub>2</sub> (C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	CoPNBDENA
Tris	tris-(hydroxymethyl) aminomethane
CoPNBDENA	diaquabis(N,N'-diethylnicotinamide)bis(p-Nitrobenzoato) cobalt(II)

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