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# Synthesis, characterization, structural analysis and DNA binding studies of nickel(II)–triphenylphosphine complex of ONS donor ligand – Multisubstituted thiosemicarbazone as highly selective sensor for fluoride ion

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ABSTRACT

A new kind of Ni(II) complex of the type, [Ni($PPh_3$)(**L**)](**1**), {where **L** = chemosensor thiosemicarbazone = 2-(3-bromo-5-chloro-2-hydroxybenzylidene)-*N*-phenyhydrazine-carbothioamide} have been synthesized and characterized by NMR, IR, UV–Vis spectroscopic methods and single crystal X-ray studies. Based on spectroscopic and X-ray crystallographic studies, a square planar structure has been proposed for the Ni(II) complex. The interaction between Ni(II) complex and CT-DNA has been investigated using UV–Vis, circular dichroism studies and gel electrophoresis. In UV studies, the observed strong hypochromism in absorption intensities and binding constant value ($K_b = 1.8 \times 10^5$) indicates significant interaction between the electronic states of the Ni(II) complex chromophore with that of DNA bases. With increasing concentration of Ni(II) complex, the peaks at 275 and 245 nm of CT-DNA are shifted to 1–2 nm without any change in the zero-cross over at 259 nm in circular dichroism studies. These observations suggest that the complex bind to DNA through a non-intercalative mode due to the waggling of three phenyl rings of triphenyl phosphine group. The Ni(II) complex display significant hydrolytic cleavage of circular plasmid pUC18 DNA. At high concentration, the Ni(II) complex almost promotes the maximum conversion of DNA from form I to form II along with the appearance of form III. The newly synthesized thiosemicarbazone compound is a promising system for the development of new colorimetric probes for the detection of anions. Anion sensing ability of the receptor (**L**) with halide ions ($F^-$, $Cl^-$, $Br^-$ and $I^-$) have been carried out in different solvents. The receptor shows a remarkable color change from colorless to dark orange in $CH_3CN$ solution on selective binding with fluoride ion. The anion recognition property of the receptor via hydrogen bonding interactions is monitored by UV–Vis titration and $^1H$ NMR spectroscopy.



## 1. Introduction

Thiosemicarbazones and their transition metal complexes have a wide range of biological activities, some of them are antiviral [1,2], antifungal [3], antibacterial [4,5], antitumor [6,7], anticancerogenic [8,9], antioxidant [10] and show insulin mimetic effects [11]. While *N*-heterocyclic thiosemicarbazones usually coordinate with a NNS donor set [12,13] and the ONS chelate structure is most common in metal–phosphine complexes of 2-hydroxyarylidene-thiosemicarbazones having sulfur as a terminal atom and one (or no) substituent on the $N^4$-nitrogen of the thioamide group [(CS)-$N^4$HR or (CS)-$N^4H_2$]. After the preparation of rhodium–triphenylphosphine catalytic system, [14], a large number of mixed-ligand complexes with various phosphines and classical ligands have been studied [15,16]. Metal–phosphine complexes of thiosemicarbazones have raised considerable interest because of their possible roles in stereoselective synthesis [17–20].

Numerous biological experiments have demonstrated that DNA is the primary intracellular target of many anticancer drugs, cancerogens and viruses [21,22]. Studies of small molecules, which react at specific sites along a DNA strand as reactive models for protein–nucleic acid interactions, provide routes towards rational drug design as well as means to develop sensitive chemical probes for DNA [23,24]. A number of metal complexes have been used as probes of DNA structure in solution, as agents for mediation of strand scission of duplex DNA and as chemotherapeutic agents [25–27]. Nickel element, an essential element involved in the life

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process can promote the absorption of iron element, the increase of red corpuscle and the synthesis of some amino-enzymes in body [28]. Nickel complexes have also drawn much attention due to their environmental toxicity, carcinogenic nature and chemotherapeutic property in the past years [29]. It has been found that these complexes can inhibit DNA repair by interfering with enzymes or proteins involved in DNA replication and/or DNA repair [30].

The synthesis of chemosensors for recognition and sensing of anions is of considerable significance [31]. In particular, the synthesis of colorimetric anion sensors is of great importance because 'visual detection' can offer qualitative and quantitative information [32]. Considerable efforts have been made to develop hydrogen-bonding donors/receptors containing imine [33–35], phenol [36–38], amide [39–41], urea [42–46], thiourea [47–52], imidazole ion [53], pyrrole [54] and 1,3,4-oxadiazole [55–57] subunits. Anions play an important role in a wide range of chemical and biological processes. Among the various anions, fluoride ion is one of the most significant because of its role in dental caries, clinical treatment for osteoporosis and toxicity resulting from its over accumulation in the bone [58,59] and association with hydrolysis of the nerve gas sarin [60,61]. Although compounds containing thiourea fragments have been widely used as anion receptor, this type simple and selective (for $F^-$) multi substituted thiosemicarbazone ligand system have not been explored much so far and herein we report the syntheses, spectral and X-ray structures of new thiosemicarbazone ligand and its triphenylphosphine nickel(II) complex with special reference to their biological and anion sensing ability.

## 2. Experimental

### 2.1. Materials and instrumentation

Bis(triphenylphosphine)-nickel(II)dichloride (Sigma–Aldrich), 3-bromo-5-chloro salicylaldehyde and N(4)-phenylthiosemicarbazide (Sigma–Aldrich), tetra butyl ammonium salts [$Cl^-$, $Br^-$, $I^-$, $F^-$] (Sigma–Aldrich), calf thymus DNA (Sigma), Tris–hydrochloride (SRL) and sodium chloride (SRL) were obtained commercially and used without further purification. Double distilled water was used for all the experiments. All reagents and solvents were analytical, spectroscopic grade and they were used without further purification. Thiosemicarbazone ligand (**L**) and its Ni(II) complex were prepared by reported literature methods.

NMR spectra were recorded on a Perkin-Elmer 300 MHz spectrometer. Deuterated organic solvents along with tetramethylsilane (TMS) as the internal standard were used. FT-IR spectra (4000–400 $cm^{-1}$) of the Ni(II) complex and the thiosemicarbazone ligand (**L**) were recorded as KBr pellets with a Perkin-Elmer (Spectrum One) FT-IR spectrophotometer. UV–Vis spectra (600–250 nm) of the Ni(II) complex were obtained on a Shimadzu 2500 PC series UV–Vis spectrophotometer.

### 2.2. Crystallography

Suitable crystals for X-ray diffraction studies were grown from $CHCl_3$/ethanol mixture. The crystal data were collected at 287 K with Bruker Smart 1000 CCD Diffractometer using monochromated Mo Kα ($k$ = 0.7107300 Å) radiation. The data were collected and processed using SAINT and the structures were solved and refined by full matrix least square on $F^2$ using SHELXTL.

### 2.3. Spectroscopic studies on DNA interaction

#### 2.3.1. Electronic absorption spectra

All the experiments investigating the interaction of the Ni(II) complex with CT-DNA were carried out in Tris buffer (5 mM, pH 7.2). A solution of CT-DNA in the buffer gave a ratio of UV absorbance at 260 and 280 nm of about 1.8–1.9:1, indicating that the DNA was sufficiently free from protein [62]. The DNA concentration per nucleotide and polynucleotide concentration were determined by absorption spectroscopy using the molar extinction coefficient (6600 $M^{-1}$ $cm^{-1}$) at 260 nm [63]. The intrinsic binding constant $K_b$ for the interaction of Ni(II) complex with DNA has been calculated from the absorption spectral titration data. The intrinsic binding constant $K_b$ was determined from the Eq. (1) [64],

$$[DNA]/(\varepsilon_a - \varepsilon_f) = [DNA]/(\varepsilon_b - \varepsilon_f) + 1/K_b(\varepsilon_b - \varepsilon_f) \quad (1)$$

where [DNA] is the concentration of DNA in base pairs, the apparent absorption coefficient $\varepsilon_a$, $\varepsilon_f$ and $\varepsilon_b$ corresponds to $A_{obs}$/[M], the extinction coefficient of the free compound and the extinction coefficient of the compound when fully bound to DNA, respectively. Plot of [DNA]/($\varepsilon_a - \varepsilon_f$) versus [DNA] gave a straight line with a slope of 1/($\varepsilon_b - \varepsilon_f$) and an intercept of $1/K_b$ ($\varepsilon_b - \varepsilon_f$) and $K_b$ was determined from the ratio of the slope to intercept.

#### 2.3.2. CD spectra

Circular dichroic spectrum of DNA in the presence and absence of Ni(II) complex was recorded on a JASCO J-810 (163–900 nm) spectropolarimeter using a quartz cuvette of 1 mm optical path length at increasing complex/DNA ratio ($r$ = 0.1–0.3). Each sample solution was scanned in the range of 220–320 nm. Each CD spectrum was collected after averaging over at least four accumulations using a scan speed of 100 nm $min^{-1}$ and a 1 s response time from which the buffer background had been subtracted. [DNA] = 100 μM.

#### 2.3.3. DNA cleavage

The cleavage of DNA was monitored using agarose gel electrophoresis. In cleavage reactions supercoiled pUC19 DNA (500 ng) (form I) in 10% DMSO-5 mM Tris–HCl-50 mM NaCl buffer at pH 7.2 was treated with Ni(II) complex. The samples were incubated for 1 h duration at 37 °C. A loading buffer containing 25% bromophenol blue, 0.25% xylene cyanol and 30% glycerol (3 μL) was added and electrophoresis performed at 60 V for 5 h in Tris–acetate–EDTA (TAE) buffer (40 mM Tris-base–20 mM acetic acid–1 mM EDTA) using 1% agarose gel containing 1.01 g $mL^{-1}$ ethidium bromide. The cleavage products were irradiated at room temperature with a UV lamp (365 nm, 10 W) and analyzed with a BIORAD Model XI computer controlled electrophoresis power supply.

### 2.4. Preparation of the Schiff base ligand (**L**)(**1**)

The thiosemicarbazone ligand (**L**) was prepared by the following method: 3-bromo-5-chloro salicylaldehyde (3.0 mmol) in methanol (0.75 g) was stirred in a round bottom flask followed by drop wise addition of methanolic solution of 4-phenylthiosemicarbazide (3.0 mmol). The reaction mixture was stirred for 3 h. The resulting white solid was removed by filteration and washed with cold ethanol and dried *in vacuo* over anhydrous $CaCl_2$. M.p: 180 °C, yield: 80%.

### 2.5. Preparation of the Ni(II) complex (**2**)

A solution of [$NiCl_2(PPh_3)_2$], [0.131 g, 0.2 mmol] in methanol, was added to a solution of ligand (**L**) [0.105 g, 0.2 mmol] in dichloromethane. The mixture was refluxed in an inert (nitrogen) atmosphere for 4 h; the red color solution was allowed to stand for about 5 days at room temperature. After this period of time, the resulting dark-red solids were collected by filtration, washed with 10 ml on *n*-hexane and dried *in vacuo* over anhydrous $CaCl_2$. A sin-