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Nickel(II) complexes with 2-(pyridin-3-ylmethylsulfanyl)phenylamine and halide/pseudohalides: Synthesis, structural characterisation, interaction with CT-DNA and bovine serum albumin, and antibacterial activity

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ABSTRACT

A new series of hexacoordinated octahedral nickel(II) complexes of *2-(pyridin-3-ylmethylsulfanyl)phenylamine* (**L**) formulated as $[Ni(\mathbf{L})_4(X)_2]$ (**1**–**4**) [where X = Cl^- (**1**); NCO^- (**2**); N_3^- (**3**) and NCS^- (**4**)] has been synthesised and characterised by physicochemical, spectroscopic tools. Details of structural study of complex **1** using single crystal X-ray crystallography showed that distorted tetragonal environment around nickel(II) ion has been satisfied by four pyridinic-N donors of four organic moieties (**L**) and two chloride ions. All the complexes are redox active and the electrochemical study of the complexes showed only cathodic Ni^{II}/Ni^{I} redox couples in the range of −0.61 to −695 V *versus* Ag/AgCl. Interactions of **1** towards calf thymus-DNA by spectroscopic, viscosity-measurement and electrochemical study and towards bovine serum albumin (BSA) with the help of absorption and fluorescence spectroscopy were examined. Antibacterial activity of the complexes (**1**–**4**) studied by agar disc diffusion method showed the comparable inhibition activity of the nickel(II) complexes against some pathogenic bacteria namely *Escherichia coli*, *Vibrio cholerae*, *Streptococcus pneumonia*, *Shigella* sp. and *Bacillus cereus*.

1. Introduction

A considerable amount of attention is currently being shown in the synthesis of geometrically distorted nickel(II) complexes with mixed nitrogen and sulfur donor sets [1–4]. Nickel is present in the active sites of several important classes of metalloproteins, as either a homodinuclear or a heterodinuclear species. The active site of 2-mercaptoethanol-inhibited urease [5] contains two Ni centres bridged by thiolate donors, while thiolate bridging between Ni and Fe centres is present in the Ni/Fe hydrogenases [6–9]. The nickel coordination sphere in both of these metalloenzyme systems contains N and S donor atoms in unusual 5- or 6-coordinate arrangements with significant distortions from regular geometry. These distorted configurations often give rise to Ni centres with reversible Ni(II)/Ni(I) and Ni(III)/Ni(II) couples and low Ni(III)/Ni(II) redox potentials, characteristics which are crucial to the activity of the enzymes. These unusual structural and electronic features have led to increased interest in the synthesis of Ni (II) complexes with mixed N,S donating chelates as structural and spectroscopic models of the active sites.

As part of our continuous interest on nitrogen–sulfur polydentate chelators [10,11], here we report an account of nickel(II) complexes of *2-(pyridin-3-ylmethylsulfanyl)-phenylamine* (**L**) (*vide* Scheme 1). Four hexacoordinated octahedral nickel(II) complexes of *2-(pyridin-3-ylmethylsulfanyl)-phenylamine* (**L**) formulated as $[Ni(\mathbf{L})_4(X)_2]$ (**1**–**4**) [where X = Cl^- (**1**); NCO^- (**2**); N_3^- (**3**) and NCS^- (**4**)] were isolated using different the nickel(II) salts used as reactant, and characterised by physicochemical and spectroscopic tools along with the detailed structural characterisations of **1** by X-ray crystallography. The DNA and protein binding study of the nickel(II) complex (**1**) has been performed spectroscopically. Antibacterial activity of complexes (**1**–**4**) studied by agar disc diffusion method showed the comparable inhibition activity of the nickel(II) complexes against some pathogenic bacteria namely *Escherichia coli*, *Vibrio cholerae*, *Streptococcus pneumonia*, *Shigella* sp. and *Bacillus cereus*.

2. Experimental

2.1. Materials and physical measurements

All chemicals and reagents were obtained from commercial sources and used as received, unless otherwise stated. Solvents were distilled from an appropriate drying agent. The elemental

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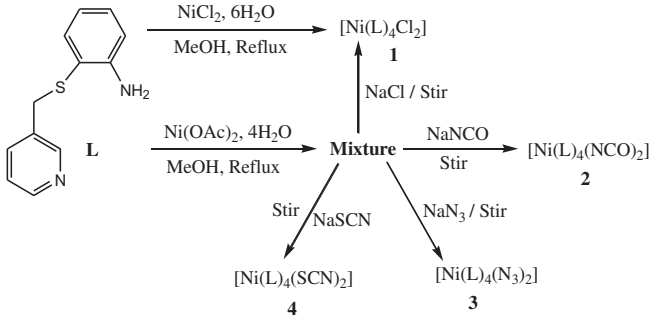

Scheme 1. Synthetic strategy of the complexes.

(C, H, N) analyses were performed on a Perkin Elmer model 2400 elemental analyzer. Nickel analysis was carried out by Varian atomic absorption spectrophotometer (AAS) model-AA55B, GTA using graphite furnace. Electronic absorption spectra were recorded on a JASCO UV–Vis/NIR spectrophotometer model V-570. IR spectra (KBr discs, 4000 to 300 cm^{-1}) were recorded using a Perkin-Elmer FTIR model RX1 spectrometer. The room temperature magnetic susceptibility measurements were performed by using a vibrating sample magnetometer PAR 155 model. Molar conductances (Λ_M) were measured in a systronics conductivity meter 304 model using $\sim 10^{-3}$ mol L^{-1} solutions in appropriate organic solvents. Electrochemical measurements were performed using computer-controlled CH-Instruments (Model No. – CHI620D). All measurements were carried out under nitrogen environment at 298 K with reference to SCE electrode in dimethyl sulfoxide using [*n*-Bu_4N]ClO_4 as supporting electrolyte. The fluorescence spectra of EB bound to DNA were recorded in the Fluorimeter (Hitachi-4500).

2.2. Preparation of 2-(pyridin-3-ylmethylsulfanyl)phenylamine (*L*)

An ethanolic solution of 3-chloromethylpyridine, hydrochloride (3.28 g, 20 mmol) was added to 2-aminobenzenethiol (2.5 g, 20 mmol) in dry ethanol containing sodium ethoxide which is prepared by dissolving sodium (1.0 g, 43.4 mmol) in dry ethanol (25 mL) under cold conditions (0–5 °C). Then this mixture was allowed to stir at room temperature for 0.5 h and then it was refluxed for 3 h. The mixture was cooled to room temperature and then it was concentrated by rotary evaporation and extracted into dichloromethane (2 × 50 mL). The combined organic phases were washed with H_2O and then dried by anhydrous $MgSO_4$, and the solvent CH_2Cl_2 was removed by rotary evaporation. The product, *2-(pyridin-3-ylmethylsulfanyl)phenylamine* was obtained as a brownish yellow oil (3.1 g, 72%), which was subsequently purified by vacuum distillation for spectroscopic characterisation.

^{1}H NMR (δ, in $CDCl_3$): 8.52 (s, 1H on py), 8.48 (d, 1H on py), 7.58 (d, 1H on py), 7.19 (t, 1H on py), 6.95 (m, 2H), 6.55 (m, 2H), 4.31 (broad, NH2) and 3.99 (s, 2H). MS-EI$^+$: m/e, 216 (corresponds to M^+).

2.3. Preparation of [Ni(*L*)$_4$(X)$_2$] complexes (*1*–*4*)

The complexes were synthesised following a common procedure as described below. To a methanolic solution of nickel(II) acetate, tetrahydrate (249.0 mg, 1.0 mmol) was added to the solution of the organic compound (**L**) (864.0 mg, 4.0 mmol) in methanol (10 mL) in stirring condition at room temperature. The resulting mixture was refluxed for 3 h. To this solution aqueous solution of sodium chloride (117.0 mg, 2.0 mmol) (for **1**), sodium cyanate (130.0 mg, 2.0 mmol) (for **2**), sodium azide (130.0 mg, 2.0 mmol) (for **3**) and sodium thiocyanate (162.0 mg, 2.0 mmol) (for **4**) was added and stirring was continued for another 1 h. The volume of the solution was reduced at room temperature by slow evaporation. The product was collected by washing with cold methanol and water; and dried. The pure crystallised product was obtained from methanol.

Complex **1** was also prepared by refluxing the mixture of *2-(pyridin-3-ylmethylsulfanyl)-phenylamine* (**L**) (864.0 mg, 4.0 mmol) and nickel(II) chloride, hexahydrate (238.0 mg, 1.0 mmol) in methanol for 4 h. The product was collected by filtration and washing with cold methanol and water, and dried.

*Complex **1**:* [Ni(**L**)$_4$(Cl)$_2$]: $C_{48}H_{48}N_8S_4Ni_1Cl_2$: *Anal.* Calc: C, 57.83; H, 4.74; N, 11.16; Ni, 5.82. Found: C, 57.94; H, 4.82; N, 11.26; Ni, 5.89%. IR (cm^{-1}): $\nu_{C=N}$, 1478; ν_{C-S}, 752. Magnetic moment (μ, B.M.): 3.10. Conductivity (Λ_o, ohm^{-1} cm^2 mol^{-1}) in DMF: 44. Yield 80–85%.

*Complex **2**:* [Ni(**L**)$_4$(NCO)$_2$]: $C_{50}H_{48}N_{10}Ni_1S_4O_2$: *Anal.* Calc: C, 59.54; H, 4.72; N, 13.82; Ni, 5.74. Found: C, 59.60; H,4.76; N, 13.90; Ni, 5.82%. IR (cm^{-1}): $\nu_{C=N}$, 1480; ν_{C-S}, 756, $\nu_{NCO,}$ 2184. Magnetic moment (μ, B.M.): 3.06. Conductivity (Λ_o, ohm^{-1} cm^2 mol^{-1}) in DMF: 42. Yield 75–80%.

*Complex **3**:* [Ni(**L**)$_4$(N$_3$)$_2$]: C_{48} H_{48} $N_{14}S_4Ni_1$: *Anal.* Calc.: C, 57.26; H, 4.70; N, 19.42; Ni, 5.78. Found: C, 57.22; H, 4.76; N, 19.47; Ni, 5.82. IR (cm^{-1}): $\nu_{C=N}$, 1479; ν_{C-S}, 750, ν_{N3}, 2049. Magnetic moment (μ, B.M.): 3.08. Conductivity (Λ_o, ohm^{-1} cm^2 mol^{-1}) in DMF: 48. Yield 80–85%.

*Complex **4**:* [Ni(**L**)$_4$(SCN)$_2$]: $C_{50}H_{48}N_{10}S_6Ni_1$: *Anal.* Calc: C, 57.72; H, 4.64; N, 13.41; Ni, 5.58. Found: C, 57.77; H, 4.62; N, 13.47; Ni, 5.64%. IR (cm^{-1}): $\nu_{C=N}$, 1478; ν_{C-S}, 754, $\nu_{NCS,}$ 2081. Magnetic moment (μ, B.M.): 3.09. Conductivity (Λ_o, ohm^{-1} cm^2 mol^{-1}) in DMF: 40. Yield 75–85%.

2.4. X-ray crystal structure analysis

Crystal data and details of data collection and refinement for complex **1** was summarised in Table 1. Suitable single crystals for X-ray diffraction analysis of **1** were grown at ambient temperature by slow evaporation of a methanolic solution. Diffraction data of **1** was collected at room temperature on a Nonius DIP-1030H system, by using Mo Kα radiation (λ = 0.71073 Å). Cell refinement, indexing and scaling of the data set were performed using programs DENZO and SCALEPACK [12]. The structure was solved by direct methods and subsequent Fourier analyses and refined by the full-matrix least-squares method based on F^2 with all observed reflections [13]. The contribution of hydrogen atoms at calculated positions were included in final cycles of refinement. All the calculations were performed using the WINGX System, Ver. 1.80.05 [14].

2.5. DNA binding experiments

Tris–HCl buffer (pH 7.0) solution prepared using deionised and sonicated HPLC grade water (Merck) was used in all the experiments involving CT-DNA. The CT-DNA used in the experiments was sufficiently free from protein as the ratio of UV absorbance of the solutions of DNA in tris–HCl at 260 and 280 nm (A_{260}/A_{280}) was almost ≈1.9 [15]. The concentration of DNA was determined with the help of the extinction coefficient of DNA solution [16]. Absorption spectral titration experiment was performed by keeping constant the concentration of the nickel(II) complex and varying the CT-DNA concentration.

In the ethidium bromide (EB) fluorescence displacement experiment, 5 μL of the EB tris–HCl solution (1.0 mmol L^{-1}) was added to 1.0 mL of DNA solution (at saturated binding levels) [17], stored in the dark for 2.0 h. Then the solution of the nickel(II) complex was titrated into the DNA/EB mixture and diluted in tris–HCl buffer to 5.0 mL to get the solution with the appropriate Ni(II) complex/CT-DNA mole ratio. Before measurements, the mixture was shaken up