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Mixed-ligand nickel(II) thiosemicarbazone complexes: Synthesis, characterization and biological evaluation

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ABSTRACT

The syntheses and characterization of some new mixed-ligand nickel(II) complexes {[Ni(L^1)(PPh_3)] (**1**), [Ni(L^1)(Py)] (**2**), [Ni(L^2)(PPh_3)]·DMSO (**3**), [Ni(L^2)(Imz)] (**4**), [Ni(L^3)(4-pic)] (**5**) and [{Ni(L^3)}$_2$(μ-4,4′-byp)]·2DMSO (**6**)} of three selected thiosemicarbazones {the 4-(p-X-phenyl)thiosemicarbazones of salicylaldehyde} (H_2L^{1-3}) (A, Scheme 1) are described in the present study, differing in the inductive effect of the substituent X (X = F, Br and OCH_3), in order to observe its influence, if any, on the redox potentials and biological activity of the complexes. All the synthesized ligands and the metal complexes were successfully characterized by elemental analysis, IR, UV–Vis, NMR spectroscopy and cyclic voltammetry. The molecular structures of four mononuclear (**1**–**3** and **5**) and one dinuclear (**6**) Ni(II) complex have been determined by X-ray crystallography. The complexes have been screened for their antibacterial activity against *Escherichia coli* and *Bacillus*. The minimum inhibitory concentrations of these complexes and their antibacterial activities indicate that compound **4** is the potential lead molecule for drug designing.

1. Introduction

Nickel(II) complexes with nitrogen and sulfur donor ligands are highly interesting [1–5] because several hydrogenases and carbon monoxide dehydrogenases [6] contain such nickel complexes as their active site. Thiosemicarbazones are an important class of N,S donor ligand which have considerable pharmacological interest due to their significant antibacterial, antiviral, antimalarial, antileprotic and anticancer activities [7–10]. Metal complexes of thiosemicarbazone ligands have shown variable bonding properties and structural diversity, along with promising biological implications and ion sensing abilities [9,11–17]. Among the transition metals, thiosemicarbazone complexes of nickel(II) also show marked and diverse biological [18–21] as well as catalytic activity [22,23], but there are a limited number of Ni(II) complexes reported with N1-substituted thiosemicarbazones [24–29].

Thiosemicarbazones obtained by condensation of ring-substituted 4-phenyl thiosemicarbazides with salicylaldehyde and substituted salicylaldehydes [30–33] form a class of versatile NS/NSO chelating ligands and are known to exhibit diverse biological activities [32]. However, not only the bioinorganic relevance of the complexes but also the chemistry of transition metal complexes of the thiosemicarbazones is receiving significant current attention because of the variable binding modes displayed by these ligands in their complexes [34–43]. The variable modes of binding of thiosemicarbazone ligands and the ability of nickel to take up different coordination environments (such as octahedral, square-planar and tetrahedral) has encouraged us to explore the coordination chemistry further, and herein we report the syntheses, X-ray structures and physical properties of some new mixed-ligand nickel(II) complexes of thiosemicarbazone ligands, with special reference to their antibacterial activity. Three thiosemicarbazones {the 4-(p-X-phenyl)thiosemicarbazones of salicylaldehyde} (H_2L^{1-3}) have been used, differing in the inductive effect of the substituent X (X = F, Br and OCH_3) in order to observe its influence, if any, on the redox potentials and biological activities of the complexes.

2. Experimental

2.1. Materials

Reagent grade solvents were dried and distilled prior to use. All other chemicals were reagent grade, available commercially and

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used as received. HPLC grade DMSO and CH_3CN were used for spectroscopic and electrochemical studies, and ethanol and methanol were used for the synthesis of the ligands and the metal complexes. Commercially available TEAP (tetra ethyl ammonium perchlorate) was properly dried and used as a supporting electrolyte for recording the cyclic voltammograms of the complexes.

2.2. Physical measurements

Elemental analyses were performed on a Vario ELcube CHNS Elemental analyzer. IR spectra were recorded on a Perkin-Elmer Spectrum RXI spectrometer. ^{1}H NMR spectra were recorded with a Bruker Ultrashield 400 MHz spectrometer using $SiMe_4$ as an internal standard. Electronic spectra were recorded on a Lamda25, Perkin-Elmer spectrophotometer. Electrochemical data were collected using a PAR Versastat-II instrument driven by E-CHEM software (PAR) at 298 K in a dry nitrogen atmosphere. Cyclic voltammetry experiments were carried out with Pt working and auxiliary electrodes, Ag/AgCl as the reference electrode and TEAP as the supporting electrolyte.

2.3. Synthesis of the ligands (H_2L^{1-3}) {H_2L^1 (4-(p-fluorophenyl) thiosemicarbazone); H_2L^2 (4-(p-bromophenyl) thiosemicarbazone) and H_2L^3 (4-(p-methoxyphenyl)thiosemicarbazone) of salicylaldehyde}

The thiosemicarbazides were prepared from distilled substituted aniline by a known method, reported ear1ier [44]. The Schiff base ligands, 4-(p-fluorophenyl)thiosemicarbazone (H_2L^1), 4-(p-bromophenyl) thiosemicarbazone (H_2L^2) and 4-(p-methoxyphenyl)thiosemicarbazone (H_2L^3) of salicylaldehyde were prepared in 80–90% yield by stirring an equimolar ratio of the substituted thiosemicarbazide with salicylaldehyde in methanol medium, using standard procedures [31]. The resulting compound was filtered, washed thoroughly with methanol and dried over fused $CaCl_2$. H_2L^1: Yield: 85%. *Anal.* calc. for $C_{14}H_{12}N_3SOF$: C, 58.13; H, 4.18; N, 14.52. Found: C, 58.15; H, 4.20; N, 14.51%. Main IR peaks (KBr, cm^{-1}): ν(O(1)–H) 3357 s, ν(N(1)–H) 3247 s, ν(N(2)–H) 3028 s, ν(C=C) 1605 s, ν(C(8)=N(3)) 1543 s, 1438 m, ν(C(7)=S(1)) 750 s. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.81 (s, 1H, –C(14)–O(1)H), 10.06 (s, 1H, –C(7)–N(1)H), 9.99 (s, 1H, –C(7)–N(2)H), 8.48 (s, 1H, –N(3)=C(8)–H), 8.11–6.81 (m, 8H, C_6H_4). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 176.52, 161.25, 158.54, 157.05, 140.52, 135.97, 135.95, 131.81, 128.54, 128.46, 127.48, 120.70, 119.66, 116.48. H_2L^2: Yield: 88%. *Anal.* calc. for $C_{14}H_{12}N_3SOBr$: C, 48.01; H, 3.45; N, 12.00. Found: C, 48.04; H, 3.40; N, 12.03%. Main IR peaks (KBr, cm^{-1}): ν(O(1)–H) 3307 s, ν(N(1)–H) 3297 s, ν(N(2)–H) 3098 s, ν(C=C) 1621 s, ν(C(8)=N(3)) 1522 s, 1412 m, ν(C(7)=S(1)) 752 s. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.88 (s, 1H, –C(14)–O(1)H), 10.09 (s, 1H, –C(7)–N(1)H), 9.96 (s, 1H, –C(7)–N(2)H), 8.49 (s, 1H, –N(3)=C(8)–H), 8.09–6.82 (m, 8H, C_6H_4). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 176.07, 157.17, 140.79, 139.09, 132.04, 131.85, 131.28, 129.12, 128.09, 127.53, 120.62, 119.63, 117.82, 116.51. H_2L^3: Yield: 87%. *Anal.* calc. for $C_{15}H_{15}N_3SO_2$: C, 59.78; H, 5.02; N, 13.94. Found: C, 59.75; H, 5.04; N, 13.91%. Main IR peaks (KBr, cm^{-1}): ν(O(1)–H) 3325 s, ν(N(1)–H) 3278 s, ν(N(2)–H) 3019 s, ν(C=C) 1623 s, ν(–C(8)=N(3)) 1563 s, 1457 m, ν(C(7)=S(1)) 749 s. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.70 (s, 1H, –C(14)–O(1)H), 10.07 (s, 1H, –C(7)–N(1)H), 9.95 (s, 1H, –C(7)–N(2)H), 8.47 (s, 1H, –N(3)=C(8)–H), 8.10–6.81 (m, 8H, C_6H_4), 3.76 (s, 3H, –C(4)–OCH_3). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 176.58, 157.32, 156.99, 140.29, 139.13, 132.51, 131.69, 131.06, 127.91, 127.53, 120.78, 119.67, 116.48, 113.69, 55.6.

2.4. Synthesis of the complexes {[Ni(L^1)(PPh_3)] (**1**); [Ni(L^1)(Py)] (**2**); [Ni(L^2)(PPh_3)]·DMSO (**3**); [Ni(L^2)(Imz)] (**4**), [Ni(L^3)(4-pic)](**5**) and [{Ni(L^3)}$_2$(μ-4,4′-byp)]·2DMSO (**6**)}

2.4.1. [Ni(L^1)(PPh_3)] (**1**)

To a solution of H_2L^1 (0.289 g, 0.100 mmol) in hot methanol, triethylamine (0.202 g, 0.2 mmol) was added, followed by solid $Ni(OAc)_2$ salt (0.248 g, 0.100 mmol) and triphenylphosphine (0.262 g, 0.100 mmol). The mixture was refluxed for 3 h and a clear reddish brown solution was obtained, which was filtered and allowed to evaporate at room temperature. Reddish brown colored crystals were obtained from the filtrate after 3–4 days. *[Ni(L^1)(PPh_3)]* (**1**): Yield: 67%. *Anal.* calc. for $C_{32}H_{25}FN_3NiOPS$: C, 63.18; H, 4.14; N, 6.91. Found: C, 63.13; H, 4.17; N, 6.87%. Main IR peaks (KBr, cm^{-1}): ν(N(1)–H) 3215 s, ν(C=C) 1627 s, ν(–C(8)=N(3)) 1542 s, 1408 m, ν(P–C) 1094 s, ν(C(7)–S(1)) 739 s. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.45 (s, 1H, –C(7)–N(1)H), 8.66 (s,1H, –N(3)=C(8)–H), 7.78–6.34 (m, 23H, C_6H_4).

2.4.2. [Ni(L^1)(Py)] (**2**), [Ni(L^2)(PPh_3)]·DMSO (**3**), [Ni(L^2)(Imz)] (**4**) and [Ni(L^3)(4-pic)] (**5**)

Complexes **2**–**5** were prepared following the same procedure as complex **1**. Reddish brown crystals of Complex **3**, suitable for X-ray crystallography were obtained by slow evaporation from DMSO.

[Ni(L^1)(Py)]: (**2**):Yield: 70%. *Anal.* calc. for $C_{19}H_{15}FN_4NiOS$: C, 53.68; H, 3.56; N, 13.18. Found: C, 53.65; H, 3.59; N, 13.16%. Main IR peaks (KBr, cm^{-1}): ν(N(1)–H) 3229 s, ν(C=C) 1613 s, ν(–C(8)=N(3)) 1521 s, 1417 m, ν(C(7)–S(1)) 736 s. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.47 (s, 1H, –C(7)–N(1)H), 8.35 (s, 1H, –N(3)=C(8)–H), 8.84–6.59 (m, 13H, C_6H_4). *[Ni(L^2)(PPh_3)]·DMSO* (**3**): Yield: 65%. *Anal.* calc. for $C_{34}H_{31}BrN_3NiO_2PS_2$: C, 54.64; H, 4.18; N, 5.62. Found: C, 54.69; H, 4.19; N, 5.78%. Main IR peaks (KBr, cm^{-1}): ν(N(1)–H) 3257 s, ν(C=C) 1624 s, ν(–C(8)=N(3)) 1545 s, 1425 m, ν(P–C) 1098 s, ν(C(7)–S(1)) 747 s. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.58 (s, 1H, –C(7)–N(1)H), 8.69 (s, 1H, –N(3)=C(8)–H), 7.77–6.35 (m, 23H, C_6H_4), 2.54 (s, 6H, DMSO). *[Ni(L^2)(Imz)]* (**4**): Yield: 68%. *Anal.* calc. for $C_{17}H_{14}BrN_5NiOS$: C, 42.99; H, 2.97; N, 14.74. Found: C, 42.95; H, 2.99; N, 14.72%. Main IR peaks (KBr, cm^{-1}): ν(N(1)–H) 3251 s, ν(C=C) 1619 s, ν(–C(8)=N(3)) 1556 s, 1428 m, ν(C(7)–S(1)) 741 s. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.60 (s, 1H, –C(7)–N(1)H), 8.71 (s,1H, –N(3)=C(8)–H), 7.03–6.79 (m, 12H, C_6H_4). *[Ni(L^3)(4-pic)]* (**5**) : Yield: 67%. *Anal.* calc. for $C_{21}H_{20}N_4NiO_2S$: C, 55.90; H, 4.47; N, 12.42. Found: C, 55.87; H, 4.43; N, 12.46%. Main IR peaks (KBr, cm^{-1}): ν(N(1)–H) 3263 s, ν(C=C) 1622 s, ν(–C(8)=N(3)) 1542 s, 1430 m, ν(C(7)–S(1)) 739 s. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.23 (s, 1H, –C(7)–N(1)H), 8.19 (s, 1H, –N(3)=C(8)–H), 8.68–6.57 (m, 12H, C_6H_4), 3.69 (s, 3H, –C(4)–OCH_3), 2.37 (s, 3H, 4-pic-CH_3).

2.4.3. [{Ni(L^3)}$_2$(μ-4,4′-byp)]·2DMSO (**6**)

To a solution of H_2L^3 (0.301 g, 0.100 mmol) in hot methanol, triethylamine (0.202 g, 0.2 mmol) was added, followed by solid $Ni(OAc)_2$ salt (0.248 g, 0.100 mmol) and 4,4′-bipyridine (0.078 g, 0.050 mmol). The mixture was refluxed for 3 h and a clear reddish brown solution was obtained, which was filtered and allowed to evaporate at room temperature. Reddish brown crystals suitable for X-ray crystallography were obtained from DMSO by slow evaporation. Yield: 65%. *Anal.* calc. for $C_{44}H_{46}N_8Ni_2O_6S_4$: C, 51.38; H, 4.51; N, 10.89. Found: C, 51.43; H, 4.50; N, 10.84%. Main IR peaks (KBr, cm^{-1}): ν(N(1)–H) 3268 s, ν(C=C) 1624 s, ν(–C(8)=N(3)) 1524 s, 1416 m, ν(C(7)–S(1)) 741 s. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.25 (s, 1H, –C(7)–N(1)H), 8.27 (s, 1H, –N(3)=C(8)–H), 9.00–6.59 (m, 12H, C_6H_4), 3.70 (s, 3H, –C(4)–OCH_3).