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Nickel complexes of some thiosemicarbazones: Synthesis, structure, catalytic properties and cytotoxicity studies

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ABSTRACT

Reaction of salicylaldehyde thiosemicarbazone (H_2L^1), 2-hydroxyacetophenone thiosemicarbazone (H_2L^2) and 2-hydroxynaphthaldehyde thiosemicarbazone (H_2L^3) with $Ni(ClO_4)_2{\cdot}6H_2O$ afforded dimeric complexes of type $[\{Ni(L)\}_2]$. Reaction of these complexes with triphenylphosphine (PPh_3), pyridine (py) and 4,4′-bipyridine (bpy) has yielded complexes of type $[Ni(L)(PPh_3)]$, $[Ni(L)(py)]$ and $[\{Ni(L)\}_2(bpy)]$, respectively, which have also been obtained from reaction of the thiosemicarbazones with $Ni(ClO_4)_2{\cdot}6H_2O$ and PPh_3 or pyridine or 4,4′-bipyridine. Structures of the $[\{Ni(L)\}_2]$ complexes have been optimized by DFT calculations. Crystal structures of $[Ni(L^2)(PPh_3)]$, $[Ni(L^2)(py)]$ and $[\{Ni(L^1)\}_2(bpy)]$ have been determined. In all these complexes thiosemicarbazone is coordinated to nickel as ONS-donor. All these complexes show characteristic ^1H NMR spectra and intense absorptions in the visible and ultraviolet region. Cyclic voltammetry on the complexes shows one irreversible oxidation on the positive side of SCE, and one irreversible reduction on the negative side. The mixed-ligand nickel complexes are found to be efficient catalysts for Heck type C–C coupling reactions. *In vitro* cytotoxicity screenings of the six mononuclear nickel complexes have been also carried out in a human tumor cell lines, viz. breast carcinoma cell line (MCF-7). $[Ni(L^3)(py)]$ shows the lowest LD_{50} value. An apoptosis study in MCF-7 with all the complexes confirms that at concentrations near LD_{50} they induce apoptosis.

1. Introduction

The chemistry of thiosemicarbazone complexes of the transition metal ions has been receiving significant current attention, primarily because of the bioinorganic relevance of the complexes [1–9]. A large majority of the thiosemicarbazone complexes have found wide medicinal applications owing to their potentially beneficial biological (viz. antibacterial, antimalarial, antiviral and antitumor) activities [10–18]. Systematic studies on the binding of thiosemicarbazones of selected types to different transition metal ions are of considerable importance in this respect. However, we have been exploring the chemistry of transition metal complexes of the thiosemicarbazones [19–31], mainly because of the variable binding mode displayed by these ligands in their complexes, and the present work has emerged out of this exploration. Herein we have chosen three potentially tridentate thiosemicarbazones, viz. thiosemicarbazones of salicylaldehyde, 2-hydroxyacetophenone and 2-hydroxynaphthaldehyde (Chart 1). These ligands are abbreviated in general as H_2L, where H_2 stands for the two dissociable protons, the phenolic proton and the hydrazinic proton. Individual ligand abbreviations are shown in Chart 1. Salicylaldehyde thiosemicarbazone (as well as the two other ligands) is usually expected to bind to a metal center, via dissociation of two acidic protons, as a dianionic tridentate ONS-donor forming stable chelate **I**, and this mode of binding has been truly observed by us in its complexes of rhodium [27], iridium [25], palladium [23] and platinum [24]. However, upon reaction with $[Ru(PPh_3)_3Cl_2]$ salicylaldehyde thiosemicarbazone has displayed a rather unusual coordination mode (**II**), where, in spite of having the phenolic oxygen as a potential donor site, it binds to ruthenium as a bidentate NS-donor forming a four-membered chelate ring [30]. The ruthenium-bound thiosemicarbazone in **II** has been utilized further for the construction of an interesting ruthenium–nickel heterometallic assembly (**III**), where all the five available donor atoms in the thiosemicarbazone ligand are engaged in coordination along with bridging mode of binding from the sulfur to nickel [28]. This variable mode of binding of salicylaldehyde thiosemicarbazone (and related ligands) has encouraged us to explore its coordination chemistry further, and herein we have chosen nickel as the metal center to interact with the selected thiosemicarbazones. One reason behind the choice of this particular metal center is its ability

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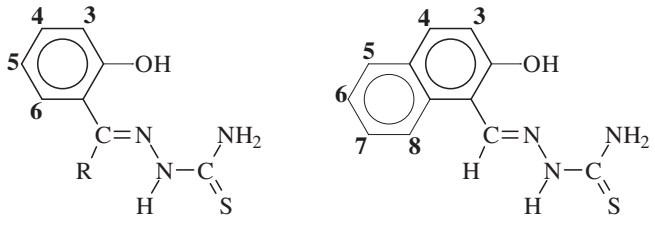
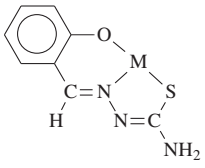


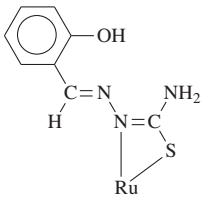
H_2L^1 (R = H)
H_2L^2 (R = CH_3)
H_2L^3

Chart 1.

to take up different coordination environments (such as octahedral, square-planar and tetrahedral), which makes its coordination chemistry very interesting. The other, and more attractive, reason is the demonstrated ability of its complexes to catalyze C–C cross-coupling reactions [32–34]. While various types of palladium complexes are being widely utilized as catalysts for such cross-coupling reactions [34–38], much less attention has been paid to the less expensive nickel complexes. Thus, while the primary objective of this present work has been to prepare nickel complexes of the chosen thiosemicarbazones (Chart 1) and find out binding mode of the thiosemicarbazones in the complexes, the other objective has been to explore catalytic properties of the complexes. Besides, by virtue of being complexes of thiosemicarbazone ligands, the targeted nickel complexes are expected to serve as cytotoxic agents, and hence exploration of their cytotoxicity has also been included as another objective of this study. Reactions of the selected thiosemicarbazones with $Ni(ClO_4)_2{\cdot}6H_2O$, taken as the source of nickel, under different experimental conditions have afforded a family of mononuclear and dinuclear complexes. The chemistry of these complexes is reported in this paper with special reference to their formation, structure and, catalytic and cytotoxic properties.



I



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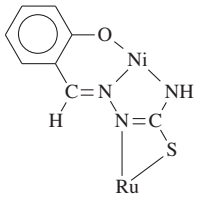

III

Table 1
Crystallographic data for [Ni(L^2)(py)].

Empirical formula	$C_{14}H_{14}N_4OSNi$
fw	345.05
Space group	Monoclinic, $P2_1/c$
a (Å)	8.0988(3)
b (Å)	7.1970(2)
c (Å)	25.3321(8)
α (°)	90
β (°)	93.636(2)
Y (°)	90
V (Å^3)	1473.56(8)
Z	4
λ (Å)	0.71073
Crystal size (mm^3)	0.19 × 0.20 × 0.22
T (K)	296
μ (mm^{-1})	1.461
R_1[a]	0.0476
wR_2[b]	0.1995
Goodness-of-fit (GOF)[c]	0.73

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.
[b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 \Sigma w(F_o^2)]^{1/2}$.
[c] GOF $= [\Sigma(w(F_o^2 - F_c^2)^2)/(M - N)]^{1/2}$, where M is the number of reflections and N is the number of parameters refined.

2. Experimental

2.1. Materials

Salicylaldehyde, 2-hydroxyacetophenone and 2-hydroxynaphthaldehyde were obtained from S.D. Fine-chem, Mumbai, India. Thiosemicarbazide was procured from Loba Chemie, Mumbai, India. The thiosemicarbazone ligands (H_2L^1, H_2L^2 and H_2L^3) were prepared by condensing equimolar amount of the respective aldehyde or ketone with thiosemicarbazide in hot ethanol. Tetrabutylammonium hexafluorophosphate (TBHP) purchased from Aldrich, and AR grade acetonitrile procured from Merck (India), were used in electrochemical work. All other chemicals and solvents were reagent grade commercial materials and were used as received.

2.2. Preparation of the complexes

The [{Ni(L)}$_2$] complexes (L = L^1, L^2 and L^3) were prepared by following a general procedure. Specific details are given below for a particular complex.

[{Ni(L^1)}$_2$]. To a solution of H_2L^1 (53 mg, 0.27 mmol) in hot ethanol (30 mL) was added triethylamine (55 mg, 0.54 mmol) followed by $Ni(ClO_4)_2{\cdot}6H_2O$ (100 mg, 0.27 mmol). The mixture was heated at reflux for 3 h. [{Ni(L^1)}$_2$] precipitated as a brown solid, which was collected by filtration, washed thoroughly with ethanol and then dried in air. Yield: 87%. *Anal.* Calc. for $C_{16}H_{14}O_2N_6S_2Ni_2$: C, 38.14; H, 2.78; N 16.69. Found C, 38.24; H, 2.89; N, 16.52%. Mass: 505, [M+H]$^+$. ^{1}H NMR (d^6-DMSO, 300 MHz)[1]: δ = 5.73 (2NH_2), 6.35 (2 C5–H), 7.07 (2 C6–H), 7.27 (2 C4–H), 7.52 (2 C3–H), 7.91 (2 azomethine-H).

[{Ni(L^2)}$_2$]. Yield: 91%. *Anal.* Calc. for $C_{18}H_{18}O_2N_6S_2Ni_2$: C, 41.11; H, 2.28; N, 15.99. Found C, 41.24; H, 2.16; N, 16.09%. Mass: 533, [M+H]$^+$. ^{1}H NMR (d^6-DMSO, 300 MHz) [1] δ = 2.28 (2CH_3), 5.66 (2NH_2), 6.18 (2 C5–H)}, 6.85 (2 C6–H)}, 7.15 (2 C4–H)}, 7.50 (2 C3–H)}.

[{Ni(L^3)}$_2$]. Yield: 83%. *Anal.* Calc. for $C_{24}H_{18}O_2N_6S_2Ni_2$: C, 47.73; H, 2.98; N, 13.92. Found C, 47.51; H, 3.15; N, 14.04%. Mass: 605, [M+H]$^+$. ^{1}H NMR (d^6-DMSO, 300 MHz)[1] δ = 5.79 (2NH_2), 6.23 (2 C5–H)}, 7.00 (2 C6–H)}, 7.19 (2 C7–H)}, 7.30 (2 C8–H)}, 7.71 (2 C4–H)}, 7.89 (2 C3–H)}, 8.09 (2 azomethine-H).

[1] Chemical shifts are given in ppm. Multiplicity of the signals did not resolve in all the spectra. Multiplicity of the signals (wherever resolved) along with the associated coupling constants (J) are given in parentheses. Overlapping signals are marked with an asterisk. The numbering in the coordinated thiosemicarbazone ligands is given according to, Chart 1.