Pergamon

0277-5387(95)00105-0

Polyhedron Vol. 14, No. 20-21, pp. 3051-3060, 1995

0277-5387/95 $9.50+0.00

DINUCLEAR NICKEL(II) COMPLEXES OF 2-HYDROXYACETOPHENONE ^{4}N-SUBSTITUTED THIOSEMICARBAZONES

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(*Received* 2 *December* 1994; *accepted* 24 *February* 1995)

Abstract—Dinuclear nickel(II) complexes with seven different 2-hydroxyacetophenone ^{4}N-substituted thiosemicarbazones have been prepared and characterized. IR, electronic, ^{1}H and ^{13}C NMR spectra of the thiosemicarbazones and their complexes have been obtained. Both the thiosemicarbazones and their nickel(II) complexes have considerable growth inhibitory activity against *Paecilomyces variotii*, but none against *Aspergillus niger*. Generally, the thiosemicarbazones are more active than their nickel complexes, but the 2-hydroxyacetophenone ^{4}N-dimethylthiosemicarbazone, H_2Ap4DM, is less active than [Ni(Ap4DM)]$_2$. The crystal structure of [Ni(Ap4DM)]$_2$ is included in this study.

Crystal structures for both salicylaldehyde thiosemicarbazone[1] and 2-hydroxyacetophenone thiosemicarbazone[2] have been reported, and both exist in the *E*-conformation with respect to the thiosemicarbazone's azomethine bond. There has been considerable interest shown in the metal complexes of both acetophenone and salicylaldehyde thiosemicarbazones; derivatives of the latter have received greater attention.[3]

Nickel(II) complexes of acetophenone, 4-aminoacetophenone and 4-acetylacetophenone thiosemicarbazones were prepared with both neutral and anionic thiosemicarbazone ligands and characterized by IR, magnetic and thermal data.[4] Also, solution thermodynamic parameters and stability constants have been determined for the nickel(II) complexes of 2-hydroxyacetophenone thiosemicarbazone.[5] Thus, there have been reports concerning aromatic thiosemicarbazones in which the aromatic ring is substituted,[6] but there have been few reports in which the thiosemicarbazone moiety is altered. One such study of complexes of a 2-hydroxyacetophenone thiosemicarbazone, where the ^{4}N-function of the thiosemicarbazone moiety is a part of a morpholine ring, has recently been reported.[7] Both the hydroxy and ^{2}N thiosemicarbazone protons are lost on complex formation for species having the general formula [Ni(ONS)X] ($X = NH_3$, H_2O), as well as [Ni(ONS)]$_2$, and the resulting complexes were characterized by spectral and magnetic measurements. More recently, a crystal structure of the dinuclear nickel(II) complex formed with 4-methyl-2-hydroxyacetophenone ^{4}N-dimethylthiosemicarbazone has been reported[8] with phenoxy bridging of the two four-coordinate nickel(II) centres. It is these dinuclear diamagnetic complexes that are of interest to us, and we report here the preparation, spectral characterization and antifungal activity of a

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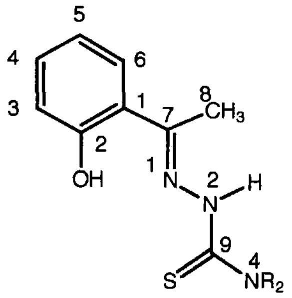
series of nickel(II) complexes of 2-hydroxyacetophenone ^{4}N-substituted thiosemicarbazones. We have recently communicated our studies[9] of the analogous dinuclear copper(II) complexes, and a comparison with those compounds is included in this report. Fig. 1 shows an *E* isomer and the symbols for the various thiosemicarbazones included in this study.

EXPERIMENTAL

The preparations and melting points of the 2-hydroxyacetophenone ^{4}N-substituted thiosemicarbazones are reported in our recent study of their copper(II) complexes.[9] The dinuclear nickel (II) complexes were prepared by dissolving the desired thiosemicarbazone (2 mmol) in ethanol (30 cm^3), followed by the dropwise addition of $Ni(OAc)_2$ (2 mmol) dissolved in ethanol (20 cm^3). The mixture was refluxed for *ca* 2 h and then slowly evaporated at 35°C until sufficient solid was formed; the mixture was filtered and the precipitate washed with cold isopropanol followed by anhydrous diethyl ether. Partial elemental analyses for each of the nickel(II) complexes were obtained from MicroAnalytics, Wilmington, Delaware, and are shown in Table 1. The physical and spectral methods of characterization, as well as the antifungal activity, of both the thiosemicarbazones and their nickel(II) complexes were carried out as described previously.[10]



^{4}N-substituent	symbol
NHMe	H_2Ap4M
NHEt	H_2Ap4E
NHPr	H_2Ap4P
$N(Me)_2$	H_2Ap4DM
$N(Et)_2$	H_2Ap4DE
$N(CH_2)_5$	H_2Appip
$N(CH_2)_6$	H_2Aphexim

Fig. 1. 2-Hydroxyacetophenone ^{4}N-substituted thiosemicarbazones

Crystals were grown by slow diffusion (−10°C) of diethyl ether into methylene chloride. The crystal, a blackish prism, of approximate dimensions 0.40 × 0.30 × 0.20 mm was measured on a Siemens P4 diffractometer using Mo-K_α. The unit-cell parameters were obtained from least-squares refinement of the setting angles of 34 reflections in the range $10.41 < 2\theta < 24.97$. Intensity data were collected at 293 K using a ω scan technique to a maximum of 2θ of 50°. Three reflections were chosen as intensity standards, being re-measured every 97 reflections. There was no significant variation in the intensity of these standards. A total of 2356 reflections were measured and processed in the usual way. Of 2109 independent reflections collected, 1378 were considered to be observed $[F > 4.0\sigma(F)]$ and were used in subsequent calculations. Reflections were corrected for absorption using Ψ-scan with a transmission factor min./max. of 0.4376/0.5129.

The structure was solved by the heavy atom method and refined by full-matrix least-squares with the Siemens SHELX-PLUS (PC version).[11,12] Complex atomic scattering factors were taken from the usual tabulations. Hydrogen atoms were included as fixed contributions and not refined. Their idealized positions were generated from the geometries about the attached carbon atoms, and they were assigned fixed thermal parameters of $U = 0.06$ Å^2 and a bond length of 0.96 Å (riding model). The final model converged as shown in Table 2. In the final difference Fourier map the highest peak was 0.46 e Å^{-3}.

RESULTS AND DISCUSSION

All complexes were prepared from boiling ethanolic solutions of nickel(II) acetates in order to promote formation of the dianion (*i.e.* loss of O$\underline{H}$ and ^{2}N$\underline{H}$ protons) on complexation and the resulting dinuclear complexes.[7] Table 1 shows that all of the complexes have been isolated free of acetato ligands. The water found in the analyses of two complexes is hydrate water since thermogravimetric analyses of dried samples show no mass loss until partial decomposition occurs well above 200°C, and bands attributable to the deformation modes of coordinated water are not observed in the complexes' IR spectra. The complexes are various shades of brown or olive green, diamagnetic, and non-electrolytes in DMF.

Table 1. Colours and partial elemental analyses of nickel(II) complexes of 2-hydroxyacetophenone ^{4}N-substituted thiosemicarbazones

Compound	Colour	%Found (%Calc.) C	H	N
Ni$_2$(Ap4M)$_2$	Dark brown	42.2(41.6)	4.0(4.2)	14.2(14.5)
Ni$_2$(Ap4DM)$_2$	Brown	46.0(45.0)	4.4(4.4)	15.5(14.3)
Ni$_2$(Ap4E)$_2$	Brown	44.6(44.9)	4.5(4.5)	13.6(14.3)
Ni$_2$(Ap4DE)$_2$·H$_2$O	Brown	47.8(47.2)	5.1(5.5)	12.5(12.7)
Ni$_2$(Ap4P)$_2$·H$_2$O	Dark brown	45.6(45.5)	4.6(5.1)	13.1(13.3)
Ni$_2$(Appip)$_2$	Brown	50.9(50.3)	5.3(5.1)	12.4(12.6)
Ni$_2$(Aphexim)$_2$	Olive green	51.9(51.8)	5.2(5.5)	12.0(12.1)

Table 2 shows a summary of crystal data and X-ray analysis information for [Ni(Ap4DM)]$_2$, and the interatomic distances and bond angles are listed in Table 3. A perspective view of [Ni(Ap4DM)]$_2$ is shown in Fig. 2 and the packing of the molecules in Fig. 3. In [Ni(Ap4DM)]$_2$ the anionic Ap4DM thiosemicarbazones act as tridentate ligands and coordinate to the nickel(II) atoms via the thiolato sulphur; the azomethine nitrogen, N(1), and the phenoxy oxygen atoms, which bridge to occupy the fourth coordination site, Fig. 2. There are no acetate counter ions indicating loss of both the OH and ^{2}NH hydrogens, and there are no relevant intermolecular interactions between dinuclear molecules. The crystallographic symmetry of the molecule is $0.5-x$, y and $-z$ and application of this operation to the x,y and z coordinates produces the other half of the dinuclear complex. The bridging oxygens are at different bond distances from the two nickel(II) centres [i.e. Ni—O = 1.853(5) and Ni(A)—O = 1.912(4) Å]. [Ni(Ap4DM)$_2$] is monoclinic and more symmetrical than the triclinic complex formed with 2-hydroxy-5-methylacetophenone ^{4}N-dimethylthiosemicarbazone, [Ni(5MAp4DM)]$_2$, but the two have very similar Ni—O bond distances {for [Ni(5MAp4DM)]$_2$: 1.851(3) and 1.912(4) Å}.[8] These bonds are considerably shorter than in a related copper(II) complex, [Cu(Aphexim)]$_2$, in which the bond lengths to the phenoxy oxygens are 1.923(4) and 1.967(4) Å.[9] These shorter bridging distances for [Ni(Ap4DM)]$_2$ compared with [Cu(Aphexim)]$_2$ causes a large tetrahedral distortion within the Ni—O—Ni(A)—O(A) function with a mean plane deviation of 0.2805 Å. This is considerably greater than 0.1223 Å which exists for the Cu—O—Cu(A)—O(A) core of [Cu(Aphexim)]$_2$,[9] and slightly greater than 0.2780 Å found for [Ni(5MAp4DM)]$_2$.[8] Also, mononuclear nickel(II) complexes (Table 4) with tridentate ONS[13] or NNS[14] ligands have longer Ni—S bonds, but shorter or comparable Ni—^{1}N bond distances to those of [Ni(Ap4DM)]$_2$ and [Ni(5MAp4DM)]$_2$.[8]

Table 2. Crystallographic data for [Ni(Ap4DM)]$_2$

Empirical formula	$C_{22}H_{26}N_6O_2S_2Ni_2$
Crystal colour, habit	Black, prismatic
Crystal size (mm)	0.40 × 0.30 × 0.20
Crystal system	Monoclinic
Space group	$I2/a$ (No. 15)
Unit-cell dimensions	a = 15.759(4) Å
	b = 8.233(2) Å
	c = 18.554(4) Å
	β = 95.46(2)°
Volume (Å^3)	2396.3(9)
Z	4
Formula weight	588
Density (calcd.) (g cm^{-3})	1.630
Absorption coefficient (cm^{-1})	17.79
F(000)	1216
Total no. of reflections measured	2356
No. of unique reflections (R_{int})	2109 (0.0274)
R	0.050
Rw	0.047

The distance between the Ni—Ni atoms in [Ni(Ap4DM)]$_2$ is 2.721(1) Å, slightly shorter than the 2.728(1) Å found for [Ni(5MAp4DM)]$_2$.[8] The non-bonding Cu—Cu distance in [Cu(Aphexim)]$_2$[9] is considerably longer [3.000(2) Å]. Each half of [Ni(Ap4DM)]$_2$ is more planar than found for [Ni(5MAp4DM)]$_2$,[8] but the mean plane deviation from the Ni—O(1)—N(1)—S—O(1A) plane is greater for the former, 0.0401 and 0.244 Å, respectively. Also, the five- [Ni—S—C(8)—N(2)—N(1)] and six-membered [Ni—N(1)—C(7)—C(1)—C(2)—O(1)] chelate rings deviate considerably from planarity; the mean deviation plane for the two rings is 0.0117 and 0.0362 Å, respectively. Further, the thiosemicarbazone moiety, in contrast to complexes of 2-acetylpyridine ^{4}N-substituted thiosemicarbazones,[13] shows a clear distortion from

Table 3. Bond lengths and bond angles for [Ni(Ap4DM)]$_2$

Ni(1)—S	2.134(2)	Ni(1)—O	1.853(5)
Ni(1)—N(1)	1.857(5)	Ni(1)—Ni(1A)[a]	2.721(2)
Ni(1)—O(A)	1.912(4)	S(1)—C(9)	1.749(7)
O—C(2)	1.367(7)	N(1)—N(2)	1.402(8)
N(1)—C(7)	1.327(7)	N(2)—C(9)	1.301(9)
N(3)—C(9)	1.342(9)	N(3)—C(10)	1.454(9)
N(3)—C(11)	1.441(9)	C(1)—C(2)	1.413(8)
C(1)—C(6)	1.421(9)	C(1)—C(7)	1.470(9)
C(2)—C(3)	1.391(10)	C(3)—C(4)	1.385(9)
C(4)—C(5)	1.373(10)	C(5)—C(6)	1.369(11)
C(7)—C(8)	1.499(9)		
S—Ni(1)—O	174.3(1)	S—Ni(1)—N(1)	88.5(2)
O—Ni(1)—N(1)	96.7(2)	S—Ni(1)—Ni(1A)	130.8(1)
O—Ni(1)—Ni(1A)	44.6(1)	N(1)—Ni(1)—Ni(1A)	129.3(2)
S—Ni(1)—OA	97.2(1)	O—Ni(1)—OA	77.2(2)
N(1)—Ni(1)—OA	172.1(2)	Ni(1A)—Ni(1)—OA	42.9(1)
Ni(1)—S—C(9)	94.9(2)	Ni(1)—O—C(2)	127.3(4)
Ni(1)—O—Ni(1A)	92.5(2)	C(2)—O—Ni(1A)	131.6(4)
Ni(1)—N(1)—N(2)	120.1(4)	Ni(1)—N(1)—C(7)	126.7(5)
N(2)—N(1)—C(7)	113.2(5)	N(1)—N(2)—C(9)	113.0(5)
C(9)—N(3)—C(10)	123.1(6)	C(9)—N(3)—C(11)	121.1(6)
C(10)—N(3)—C(11)	115.8(6)	C(2)—C(1)—C(6)	115.5(6)
C(2)—C(1)—C(7)	125.7(5)	C(6)—C(1)—C(7)	118.7(5)
O—C(2)—C(1)	120.7(6)	O—C(2)—C(3)	117.6(5)
C(1)—C(2)—C(3)	121.7(5)	C(2)—C(3)—C(4)	119.8(6)
C(3)—C(4)—C(5)	120.3(7)	C(4)—C(5)—C(6)	120.1(6)
C(1)—C(6)—C(5)	122.5(6)	N(1)—C(7)—C(1)	122.0(5)
N(1)—C(7)—C(8)	119.3(6)	C(1)—C(7)—C(8)	118.7(5)
S—C(9)—N(2)	122.9(5)	S—C(9)—N(3)	118.9(5)
N(2)—C(9)—N(3)	118.2(6)		

[a] Non-bonding distance.

planarity based on the angle between the two chelate rings [2.55(3)°]. There is also a distortion from planarity between the aromatic ring and the thiosemicarbazone moiety.

A comparison of the thiosemicarbazone moiety bond distances (Table 4) of [Ni(Ap4DM)]$_2$ to those of the uncoordinated 2-hydroxyacetophenone thiosemicarbazone, H_2Ap4DH,[2] shows that coordination lengthens the ^{7}C=^{1}N bond considerably [from 1.297(3) to 1.327(7) Å] and the ^{9}C=S bond substantially [from 1.692(2) to 1.739(7) Å], as would be expected on coordination of the azomethine nitrogen and thiol sulphur. The ^{2}N—^{9}C bond, which formally becomes a double bond in the complex, is shortened from 1.334(3) Å in H_2Ap4DH[2] to 1.301(8) Å in [Ni(Ap4DM)]$_2$. The remaining bonds of the thiosemicarbazone moiety listed in Table 4 are increased by 0.010 to 0.020 Å on coordination. The bond distances for the thiosemicarbazone moiety in [Ni(Ap4DM)]$_2$ are in excellent agreement with those reported for [Ni(DMAp4DM)]$_2$,[8] as are the metal–ligand bonds. However, the [Ni(Ap4DM)]$_2$ nickel–ligand bond distances are considerably shorter than the copper–ligand bonds of [Cu(Aphexim)]$_2$.[9] The bond distances for the thiosemicarbazone moiety in [Ni(Ap4DM)]$_2$ also reflect the stronger bonding to a nickel(II) centre, as was observed when comparing bond distances for [Cu(Lhexim)Br] and [Ni(Lhexim)Br].[13] Also, [Ni(Ap4DM)]$_2$ has larger bond angles (O—M—^{1}N and S—M—^{1}N) for its bichelate system than the dinuclear copper(II) complex.[9] Finally, [Ni(Ap4DM)]$_2$ and [Ni(DMAp4DM)]$_2$[8] have shorter metal–sulphur bond distances than a mononuclear nickel(II) complex with an ONS bichelate system, [Ni(Sa4Ph)(NH$_3$)].[14]

In Table 5 are listed the IR assignments of the bands that undergo significant change on coordination of the 2-hydroxyacetophenone thiosemicarbazone ligands. Coordination of the azomethine nitrogen causes $\nu(^7C{=}^1N)$ to shift by 20–40 cm^{-1} to lower frequencies,[10] but with the loss of the proton from ^{2}N, a new band due to $\nu(^2N{=}^9C)$

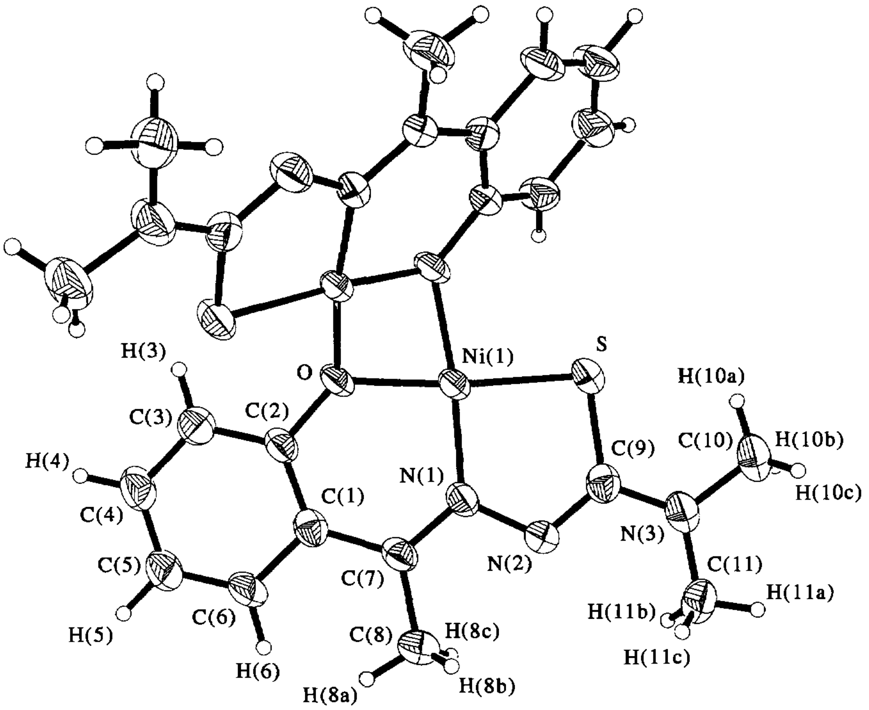


Fig. 2. ORTEP diagram for $[Ni(Ap4DM)]_2$.

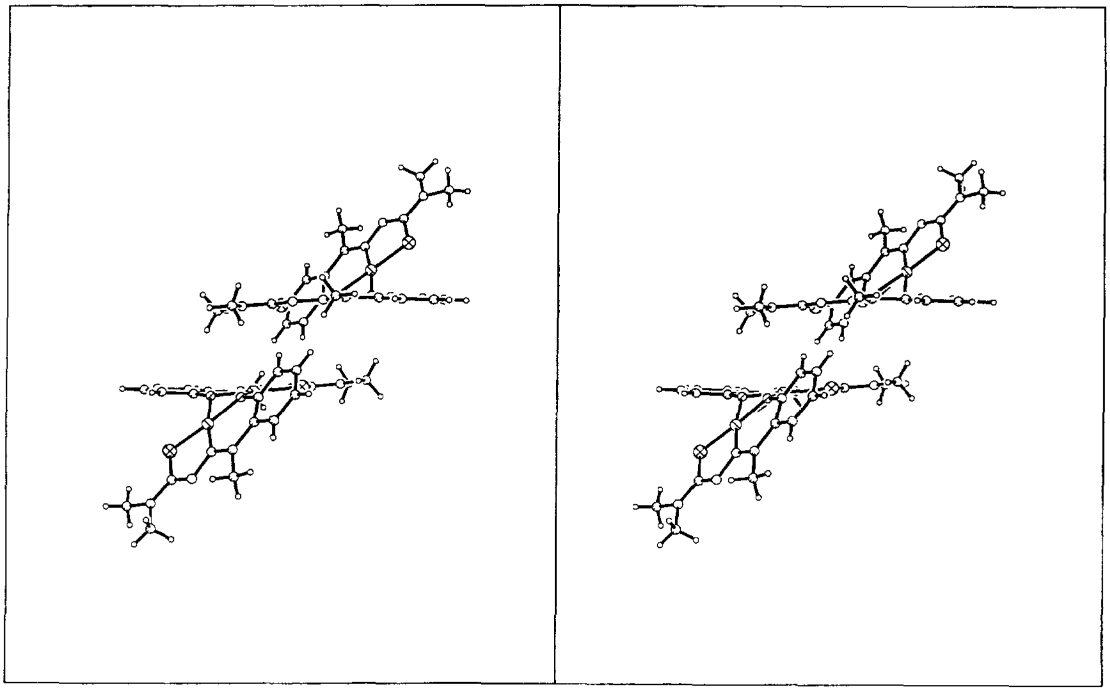


Fig. 3. Packing arrangement for $[Ni(Ap4DM)]_2$.

occurs in this same spectral region of the complexes. We have assigned the band at *ca* 1590 cm^{-1} to $\nu(^2N{=}^9C)$ and the band shifting from *ca* 1600 cm^{-1} in the thiosemicarbazones' spectra to *ca* 1570 cm^{-1} in the complexes' spectra to $\nu(^7C{=}^1N)$. Coordination of the azomethine nitrogen is also consistent with the presence of a band at 450–480 cm^{-1}, assignable to $\nu(NiN)$ for these complexes.[15] On loss of the ^2NH proton, coordination via the thiolato sulphur is indicated by a decrease in the frequency

Table 4. Comparison of bond distances (Å) and bond angles for thiosemicarbazones and representative metal complexes and complexes containing phenoxy bridging groups

Compound	^{7}C=^{1}N	^{1}N—^{2}N	^{2}N—^{9}C	^{9}C—S	^{3}N—^{9}C	Ref.
H$_2$Sa4DH	1.276(3)	1.380(4)	1.346(4)	1.689(4)	1.317(4)	1
H$_2$Ap4DH	1.297(3)	1.392(3)	1.334(3)	1.692(2)	1.322(3)	2
[Cu(Aphexim)]$_2$	1.306(8)	1.374(7)	1.313(8)	1.750(7)	1.313(9)	9
[Ni(Ap4DM)]$_2$	1.327(7)	1.402(8)	1.301(9)	1.749(7)	1.342(9)	This work
[Ni(DMAp4DM)]$_2$	1.325(5)	1.397(5)	1.298(5)	1.744(6)	not	8
	1.317(5)	1.394(5)	1.317(5)	1.736(5)	reported	
[Ni(Sa4Ph)(NH$_3$)]	1.316(10)	1.393(7)	1.333(10)	1.717(9)	1.357(10)	14
[Ni(Lhexim)Br]	1.33(1)	1.37(1)	1.31(1)	1.76(1)	1.33(1)	13

Compound	M—S	M—^{1}N	M—O	Ref.
[Cu(Aphexim)]$_2$	2.200(2)	1.938(5)	1.923(4)	9
			1.967(4)	
[Ni(Ap4DM)]$_2$	2.134(2)	1.857(5)	1.853(5)	This work
			1.912(4)	
[Ni(DMAp4DM)]$_2$	2.129(1)	1.855(5)	1.898(4)	8
	2.123(1)	1.860(4)	1.912(4)	
[Ni(Sa4Ph)(NH$_3$)]	2.166(2)	1.844(7)	1.858(6)	14
[Ni(Lhexim)Br]	2.155(4)	1.857(8)		13

Compound	S—M—O	S—M—^{1}N	O—M—^{1}N	M—S—^{9}C	M—^{1}N—^{2}N	Ref.
[Cu(Aphexim)]$_2$	166.1(1)	88.5(2)	93.0(2)	93.3(2)	118.5(4)	9
[Ni(Ap4DM)]$_2$	174.3(1)	89.0(2)	96.7(2)	94.9(2)	120.1(4)	This work
[Ni(DMAp4DM)]$_2$	173.5(1)	89.2(1)	96.6(2)	94.8(1)	119.7(3)	8
	173.1(1)		96.4(1)	95.1(1)	120.0(3)	
[Ni(Sa4Ph)(NH$_3$)]	176.0(2)	87.7(2)	96.2(3)	95.9(3)	121.5(5)	14
[Ni(Lhexim)Br]		87.9(3)		94.8(4)	122.2(7)	13

Table 5. IR assignments (cm^{-1}) for the 2-hydroxyacetophenone ^{4}N-substituted thiosemicarbazones and their nickel(II) complexes

Compound	ν(CN)	ν(CO)	ν(CS)	ν(MN)	ν(MO)	ν(MS)
H$_2$Ap4M	1600m	1220s	821sh			
Ni$_2$(Ap4M)$_2$	1588s	1155sh	740s	450m	410s	344w
H$_2$Ap4DM	1605sh	1218sh	813m			
Ni$_2$(Ap4DM)$_2$	1609sh, 1586s	1139m	736sh	465s	414m	355m
H$_2$Ap4E	1598sh	1230sh	808sh			
Ni$_2$(Ap4E)$_2$	1590sh, 1562sh	1142sh	740sh	480sh	450sh	315w
H$_2$Ap4DE	1604sh	1220m	818sh			
Ni$_2$(Ap4DE)$_2$	1587s, 1559s	1139sh	740s	478w	450sh	348w
H$_2$Ap4P	1615s, 1595sh	1218sh	817s			
Ni$_2$(Ap4P)$_2$	1600sh	1140sh	744sh	481w	454sh	346w
H$_2$Appip	1595sh	1236s	837sh			
Ni$_2$(Appip)$_2$	1588s, 1558s	1130sh	735s	475sh	462m	340w
H$_2$Aphexim	1598sh	1220s	835sh			
Ni$_2$(Aphexim)$_2$	1596s, 1567s	1132s	740s	481w	465m	328w

(80–100 cm^{-1}) of the thioamide IV band found at *ca* 840 cm^{-1} in the thiosemicarbazones' spectra and also by the presence of a band in the range 310–350 cm^{-1}, assignable to ν(NiS).[16] The phenolic oxygen, on loss of the OH proton, occupies the third and fourth (through bridging) coordination sites. This causes ν(CO) a 60–80 cm^{-1} shift to lower wave numbers from *ca* 1250 cm^{-1} in the thiosemicarbazones' spectra, which is consistent with a bridging phenolic oxygen.[17] A band in the 420–460 cm^{-1} range in the spectra of the complexes is assignable to ν(MO) for the bridging phenolato oxygen.[18]

The ^{1}H NMR spectral assignments for both the thiosemicarbazones and some of their nickel(II) complexes are included in Table 6. The potential for hydrogen bonding of the ring OH and/or the ^{2}NH protons allows for the possibility of different isomers[19] for the various thiosemicarbazones depending on electronic and steric effects. The spectrum of H_2Ap4M indicates an absence of hydrogen bonding with OH, ^{2}NH and ^{4}NH found at 10.78, 8.83 and 6.92 ppm, respectively. However, the NMR spectrum of H_2Ap4DM shows a strong signal at 12.54 ppm and a weaker signal at 12.22 ppm, which together integrate for one hydrogen atom and are assignable to hydrogen bonding OH. Further, ^{2}NH at 8.27 ppm is upfield in the spectrum of H_2Ap4DM from 8.83 ppm for H_2Ap4M. Similarly, H_2Ap4DE shows the OH peak at 12.53 ppm and the ^{2}NH peak at 8.35 ppm consistent with the presence of a single hydrogen-bonding (i.e. OH) isomer. The 3-azacyclothiosemicarbazones (i.e. H_2Appip and H_2Aphexim) have similar spectra to H_2Ap4DM and H_2Ap4DE. H_2Ap4P, like H_2Ap4M, has a single non-hydrogen bonding isomer, but H_2Ap4E shows peaks consistent with about 1/3 being a hydrogen bonding isomer (i.e. OH).

Consistent with their loss on complexation, the peaks due to OH and ^{2}NH are absent in the ^{1}H NMR spectra of the nickel(II) complexes. Coordination of the phenolic oxygen causes small shifts of the ring protons and the acetyl methyl, $^{8}CH_3$, and the ^{4}NH protons also shift on coordination of the azomethine nitrogen and thiolato sulphur. For example, a comparison of the ^{1}H NMR spectra of [Ni(Ap4P)]$_2$ and H_2Ap4P shows small upfield shifts for ^{3}CH, ^{4}CH, ^{5}CH and ^{4}NH, indicating increased electron density at these sites on complexation, but downfield shifts for ^{6}CH and ^{8}CH, indicating decreased electron density due to coordination via the phenoxy oxygen and azomethine nitrogen, respectively. All of these signals shifted to a much greater extent in the analogous copper(II) complexes.[9] There is a distinct difference in the positions of the NMR signals on complexation for ^{4}N-alkyl- compared with ^{4}N-dialkyl- and 3-azacyclothiosemicarbazones. For example, on complexation ^{3}CH shifts upfield for the ^{4}N-alkyls (Ap4M, Ap4E and Ap4P), but downfield for the others (Ap4DM, Ap4DE, Appip and Aphexim). The nature of the ^{4}N-substituent (i.e. alkyl or dialkyl/azacyclo) of the thiosemicarbazones affects the chemical shifts of the other ring hydrogens and

Table 6. ^{1}H NMR ($CDCl_3$) assignments of 2-hydroxyacetophenone ^{4}N-substituted thiosemicarbazones and their nickel(II) complexes

Compound	OH	^{3}CH	^{4}CH	^{5}CH	^{6}CH	^{8}CH	^{2}NH	^{4}NH
H_2Ap4M	10.78	6.98	7.32	6.93	7.47	2.39	8.83	6.85
H_2Ap4DM	12.54(94.3%)	7.00	7.27	6.85	7.37	2.28	8.27	
	12.22(5.7%)							
H_2Ap4E	10.77(62.2%)	6.99	7.32	6.82	7.58	2.38	8.63	6.82
	12.60(37.8%)	6.93	7.25	6.77	7.49		8.33	
H_2Ap4DE	12.53	7.03	7.28	6.86	7.40	2.17	8.35	
H_2Ap4P	10.83	6.97	7.30	6.84	7.46	2.39	8.79	6.84
H_2Appip	12.10	6.98	7.28	6.88	7.42	2.32	8.22	
H_2Aphexim	12.68(85.4%)	7.01	7.26	6.83	7.36	2.28	8.36	
	12.64(14.6%)					2.17	8.30	
$Ni_2(Ap4M)_2$		6.75	7.11	6.64	7.55	2.71		6.37
$Ni_2(Ap4DM)_2$		7.09	7.09	6.77	7.36	2.46		
$Ni_2(Ap4E)_2$		6.76	7.11	6.64	7.56	2.71		6.38
$Ni_2(Ap4DE)_2$		7.08	7.08	6.75	7.33	2.45		
$Ni_2(Ap4P)_2$		6.76	7.12	6.65	7.56	2.71		6.42
$Ni_2(Appip)_2$		7.08	7.10	6.77	7.35	2.46		
$Ni_2(Aphexim)_2$		7.09	7.09	6.76	7.35	2.45		

$^8C\underline{H}_3$ {e.g. for $[Ni(Ap4M)]_2$, $^8C\underline{H}_3 = 2.71$ ppm and for $[Ni(Ap4M)]_2$, $^8C\underline{H}_3 = 2.45$ ppm}.

Assignments of the ^{13}C NMR signals (Table 7) for the thiosemicarbazone moiety are based on those of Koch,[20] as well as previous studies from our laboratory.[10] Two sets of peaks are present for a number of the carbons of H_2Ap4E, indicating the presence of two isomers for this thiosemicarbazone, signals consistent with its ^1H spectrum. The ^{13}C NMR spectra of these thiosemicarbazones are essentially unchanged with varying ^4N-substituents. One notable exception, however, is the upfield shift for ^8C (acetyl methyl group) with increasing bulkiness of the ^4N-substituent. This suggests that the conformation about the ^9C—^4N bond, which has a bond distance closer to that of a double bond than a single bond,[13] is such that these larger substituents attached at ^4N are in close proximity to the acetyl carbon, ^8C.

For the aromatic ring the largest shifts are for ^5C when comparing each of the uncomplexed thiosemicarbazones with their nickel(II) dinuclear complexes (e.g. 117.2 ppm to 114.9 ppm for H_2Ap4DM and $[Ni(Ap4DM)]_2$, respectively). ^7C (azomethine) and ^8C also shift downfield due to coordination of the azomethine nitrogen [e.g. 152.6 and 12.3 ppm for H_2Ap4DE and 155.8 and 17.1 ppm for $Ni_2(Ap4DE)_2$, respectively]. The downfield shift of azomethine carbon, ^7C, is consistent with results found for cobalt(III) complexes of 2-acetylpyridine ^4N-substituted thiosemicarbazones,[21] although the magnitude of the shift is considerably less for these nickel(II) complexes consistent with lower formal charge on the metal centre.

On coordination the ^2NH proton is lost resulting in the thione sulphur becoming a coordinated thiolato function and ^9C is shifted upfield considerably in the complexes. For example, this peak is found at 180.3 ppm and 171.8/169.8 for H_2Ap4DM and $[Ni(Ap4DM)]_2$, respectively. The presence of two peaks for ^9C for $[Ni(Ap4M)]_2$, $[Ni(Ap4DM)]_2$ and $[Ni(Ap4E)]_2$ is due to slight differences for the two thiosemicarbazone moieties in solution; possible explanations are unequal addition of solvent molecules to axial sites or partial decomposition in solution as we observed for $[Cu(Aphexim)]_2$.[9] Slight differences for two apparently identical coordinated thiosemicarbazones have been observed in crystal structure studies of bis(isoquinoline-1-carboxaldehyde thiosemicarbazonato)nickel(II) monohydrate[22] and bis(acetylpyrazine ^4N-dimethylthiosemicarbazone)nickel(II).[23] For the cobalt(III) complexes ^9C, the thiol carbon, is little shifted on complexation.[21] On coordination of the sulphur, the electron density would be expected to be lost from ^9C, similar to ^7C, but back π-bonding is greater for the thiolato function than the azomethine function. The back π-bonding causes the upfield shift and is more significant for a divalent nickel(II) than a trivalent cobalt(III).

Each thiosemicarbazone and nickel(II) complex shows a ring $\pi \rightarrow \pi^*$ band at *ca* 40 000 cm^{-1} (not

Table 7. ^{13}C NMR assignments of the 2-hydroxyacetophenone thiosemicarbazones in $CDCl_3$ and their nickel(II) complexes

Compound	^1C	^2C	^3C	^4C	^5C	^6C	$^7\underline{C}{=}N$	$^8\underline{C}H_3$	$^9\underline{C}{=}S$
H_2Ap4M	119.0	157.4	118.4	128.4	117.6	132.0	153.5	14.0	178.8
H_2Ap4DM	119.3	158.0	118.4	126.7	117.2	129.9	143.9	13.6	180.3
H_2Ap4E	119.4	158.7	118.4	127.1	117.5	131.0	142.2	13.9	179.0
	119.8	157.5		128.4		131.9	152.1	14.3	177.7
H_2Ap4DE	119.2	158.6	118.5	127.3	118.2	131.1	152.6	12.3	178.9
H_2Ap4P	119.3	157.5	119.7	128.4	117.5	131.9	153.6	14.1	177.7
H_2Appip	119.8	158.5	118.9	127.7	117.9	131.3	153.3	12.8	184.2
$H_2Aphexim$	119.2	158.5	118.5	127.4	118.0	131.0	153.4	12.5	179.1
$Ni_2(Ap4M)_2$[a]		158.7	120.6	128.8	114.9	130.0	157.4	17.9	171.9 168.2
$Ni_2(Ap4DM)_2$[a]	120.4	158.8	119.9	128.8	114.9	129.9	156.5	17.3	171.8 169.8
$Ni_2(Ap4E)_2$[a]	120.5	158.8	120.3	128.8	114.9	129.9	157.1	17.7	171.8 167.5
$Ni_2(Ap4DE)_2$[a]	120.5	158.9	119.7	128.8	114.8	129.8	155.8	17.1	167.9
$Ni_2(Appip)_2$[a]	120.4	159.1	119.8	128.9	114.9	130.0	156.7	17.3	169.4
$Ni_2(Aphexim)_2$[a]	120.5	158.9	119.6	128.8	114.8	129.8	155.7	17.1	168.4

[a] d^6-DMSO.

Note: $Ni_2(Ap4P)_2$ did not yield an acceptable spectrum.

Table 8. Solid-state electronic spectra (cm^{-1}) of the 2-hydroxyacetophenone thiosemicarbazones and their nickel(II) complexes

Compound	$n \rightarrow \pi^*$	L → M	$d \rightarrow d$
H_2Ap4M	33 900, 29 500		
Ni_2(Ap4M)$_2$	33 560	26 320, 21 980	17 540sh
H_2Ap4DM	34 970, 29 850		
Ni_2(Ap4DM)$_2$	32 260	27 030, 21 740	16 950sh
H_2Ap4E	33 000, 29 500		
Ni_2(Ap4E)$_2$	32 260	26 180, 21 500	17 090sh
H_2Ap4DE	33 330, 29 070		
Ni_2(Ap4DE)$_2$	30 300	26 320, 19 610	16 390sh
H_2Ap4P	33 450, 29 590		
Ni_2(Ap4P)$_2$ · H_2O	34 250	27 030, 21 740	15 630sh
H_2Appip	34 130, 28 570		
Ni_2(Appip)$_2$	30 300	27 030, 23 810	16 530sh
H_2Aphexim	33 220, 29 500		
Ni_2(Aphexim)$_2$	32 250	28 250, 23 360	16 390sh

included in Table 8) and an $n \rightarrow \pi^*$ band at *ca* 33 000 cm^{-1}. A second $n \rightarrow \pi^*$ band, which is found between 29 000 and 30 000 cm^{-1} in the uncomplexed thiosemicarbazones' spectra, which involves transitions within the thiosemicarbazone moiety, merges with the first $n \rightarrow \pi^*$ band in the spectra of the nickel(II) complexes. Two ligand-to-metal charge-transfer bands are in the 26 000–28 000 and 19 000–23 000 cm^{-1} ranges. The former band is due to the S → Ni^{II} transitions based on studies of previous copper(II) thiosemicarbazone complexes,[9,24] and its energy is dependent on the steric requirements of the ^{4}N-substituents. That is, thiosemicarbazones with bulkier ^{4}N-substituents have this band at somewhat higher energies. The band in the 19 000–23 000 cm^{-1} range involves bridging phenoxy O → Ni^{II} transitions by analogy to the dinuclear copper(II) complexes.[9] Each complex has a broad *d–d* combination band that appears as a shoulder on the intraligand and charge-transfer bands. These nickel complexes show a trend of increasing size of the ^{4}N-substituent and lower energy of the *d–d* band maximum, presumably due to weakening of the coordinate bonding with increased bulkiness of the ligands. That is, [Ni(Ap4M)]$_2$ > [Ni(Ap4E)]$_2$ > [Ni(Ap4P)]$_2$; [Ni (Ap4DM)]$_2$ > [Ni(Ap4DE)]$_2$ and [Ni(Appip)]$_2$ > [Ni(Aphexim)]$_2$.

Table 9. Activity of the 2-hydroxyacetophenone thiosemicarbazones and their nickel(II) complexes against *Paecilomyces variotii*

Compound	200[a]	400	600	1000	1600
H_2Ap4M	10.00[b]	20.2	21.0	22.5	22.7
Ni_2(Ap4M)$_2$	6.0	6.0	6.0	6.0	6.0
H_2Ap4DM	11.3	17.7	20.2	20.5	21.8
Ni_2(Ap4DM)$_2$	24.5	28.3	28.5	28.7	28.2
H_2Ap4E	21.7	23.7	26.2	26.0	28.2
Ni_2(Ap4E)$_2$	6.0	6.0	6.0	6.0	
H_2Ap4DE	39.8	40.8	40.7	41.0	40.3
Ni_2(Ap4DE)$_2$	7.0	7.3	7.2	7.0	6.3
H_2Ap4P	23.5	26.0	28.0	27.3	28.7
Ni_2(Ap4P)$_2$ · H_2O	6.5	7.2	7.3	7.2	6.8
H_2Appip	30.5	29.5	29.7	28.5	29.3
Ni_2(Appip)$_2$	26.0	29.7	29.8	30.0	29.3
H_2Aphexim	23.5	26.5	27.8	27.3	26.6
Ni_2(Aphexim)$_2$	25.8	25.0	20.1	24.2	29.0

[a] ug cm^{-3}.

[b] mm diameter of growth inhibition zone (6.0 = no inhibition).

Table 9 shows the growth inhibitory activity of the uncomplexed thiosemicarbazones and their nickel(II) complexes against *Paecilomyces variotii*. The uncomplexed thiosemicarbazones are significantly more active than their nickel(II) complexes with the exception of H_2Ap4DM, H_2Appip and H_2Aphexim, and for most compounds there is little difference in the activity over the concentration range studied. The uncomplexed thiosemicarbazones retain their activity down to less than 20 μg cm^3 L against *Paecilomyces variotii*, but they and their nickel(II) and copper(II)[9] complexes show no activity against *Aspergillus niger*. H_2ApDE is the most active of the uncomplexed thiosemicarbazones and the trends in activity are as follows: H_2Ap4M < H_2Ap4E < H_2Ap4P; H_2Ap4DM < H_2Ap4DE; H_2Appip > H_2Aphexim. Although all of the copper(II) complexes of these ligands show significant activity against *Paecilomyces variotii*, the following nickel(II) complexes are more active than their copper(II) analogues: [Ni(Ap4DM)]$_2$, [Ni(Appip)]$_2$ and [Ni(Aphexim)]$_2$. H_2Ap4DM, H_2Appip and H_2Aphexim all have some activity against certain cell lines in the National Cancer Institute anti-tumour screening program, but on repeat testing none were shown to have sufficient activity to warrant further consideration. These three thiosemicarbazones along with [Ni(Ap4DE)]$_2$ and [Ni(Appip)]$_2$ were found to be inactive in the *in vitro* anti-HIV primary screen also carried out at the National Cancer Institute.

Supplementary material. Atomic coordinates have been deposited with the Director, Cambridge Crystallographic Data Center.

Acknowledgements—Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society for the partial support of this research. JV-M thanks Universidad Nacional Autonoma de Mexico PAPIIT Program (IN1038393) and Consejo Nacional de Ciencia y Tecnologia (3920-E).

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