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COPPER(II) COMPLEXES OF 2-BENZOYLPYRIDINE ^{4}N-SUBSTITUTED THIOSEMICARBAZONES

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Abstract—2-Benzoylpyridine ^{4}N-substituted thiosemicarbazones commonly coordinate as neutral tridentate ligands to give five coordinate $[Cu(HL)Cl_2]$ complexes when prepared in boiling isopropanol. However, when prepared in boiling ethanol, the anion (loss of the ^{3}N-hydrogen) coordinates as a tridentate ligand to give [CuLCl] complexes. Representative crystal structures of both stoichiometries have been determined. Spectral characterization of both the 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones and their copper(II) complexes includes IR, UV–vis, EPR and NMR studies. Growth inhibition studies of the thiosemicarbazones and their complexes were performed against two human pathogenic fungi.

Recently, there have been numerous studies of metal complexes of heterocyclic thiosemicarbazones.[1] Many of these have featured either 2-formylpyridine[2–5] or 2-acetylpyridine[6–9] thiosemicarbazones; there has been a single report concerned with the metal complexes of 2-benzoylpyridine thiosemicarbazone.[10] To our knowledge, no studies of the metal complexes of 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones have been completed. Here, we report a spectral study of a range of 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones (Fig. 1, which includes the symbols used throughout this work) and their copper(II) complexes. In addition, we include the molecular structure of $[Cu(HBz4P)Cl_2]$ and [Cu(Bzhexim)Cl], the growth inhibitory ability of these thiosemicarbazones as well as their copper(II) complexes against two fungi pathogenic to humans, and a comparison to the corresponding 2-formyl- and 2-acetylpyridine ^{4}N-substituted thiosemicarbazones and their complexes.

EXPERIMENTAL

The thiosemicarbazones were prepared by one of three methods: (1) refluxing (>20 h) of 2-benzoylpyridine (0.01 mol) with an equimolar amount of the available commercial (Aldrich) thiosemicarbazide (HBz4M and HBz4E) in 25 cm^3 of absolute ethanol; (2) mixing 2-benzoylpyridine (0.01 mol) with the desired amine (0.01 mol) in ethanol (40 cm^3), adding ^4N-methyl-^4N-phenyl-thiosemicarbazide (0.01 mol)[11] in small portions

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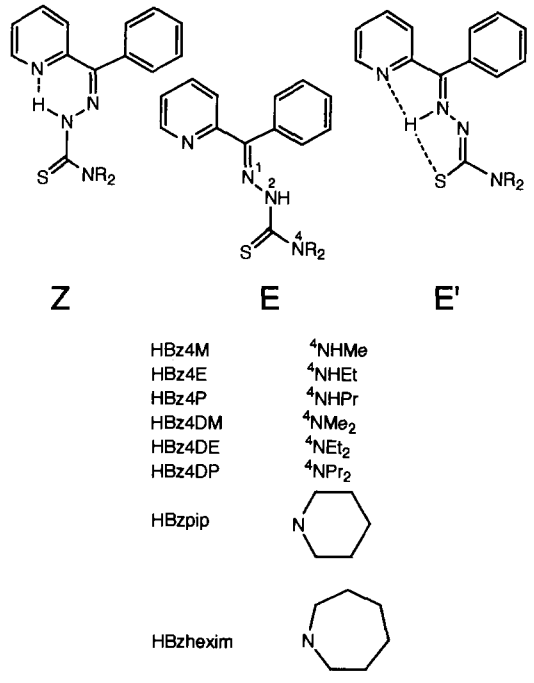

Fig. 1. 2-Benzoylpyridine ^{4}N-substituted thiosemicarbazones.

and refluxing with stirring continued for >20 h (HBz4DM, HBzDE, HBz4DP, HBzpip and HBzhexim); and (3) treating 2-benzoylpryridine hydrazone (0.01 mol; prepared by a 5 h ethanolic reflux of 2-benzoylpyridine and hydrazine monohydrate) with an isothiocyanate (0.01 mol) (HBz4P). On slow evaporation (35°C), and for some compounds, triturating with anhydrous diethylether, the resulting solids were filtered, washed with cold isopropanol and dried on a warm plate. The nature and purity of the thiosemicarbazones were confirmed by their ^{1}H and ^{13}C NMR spectra (Table 1) in DMSO-d_{16} and/or $CDCl_3$ using a Varian Gemini 300 MHz NMR Spectrometer. The complexes were prepared by mixing 1:1 stoichiometric ratios of the desired thiosemicarbazone (0.002 mol) and copper(II) chloride in boiling EtOH or Pr^{i}OH. The characterization of the complexes by spectral and physical properties, and the fungal growth inhibitory studies, were carried out as reported previously.[7–9, 12]

Crystals of $[Cu(HBz4P)Cl_2]$ were grown by slow evaporation of the EtOH filtrate from the preparation of [Cu(Bz4P)Cl], while those of [Cu(Bzhexim)Cl] were grown by diffusion of ether into a dimethyl sulphoxide solution. The selected crystals (dark green regular and dark brown needle for $[Cu(HBz4P)Cl_2]$ and [Cu(Bzhexim)Cl], respectively) were mounted in random orientation on a glass fibre and measured on a Seimens P4 Diffractometer. The structure of $[Cu(HBz4P)Cl_2]$ was solved by Siemens SHELXTL-PLUS (PC version) and [Cu(Bzhexim)Cl] by Direct Methods (SIR92),[13] and refined by the full-matrix least-squares technique. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in their calculated positions [d(C—H) = 0.96 Å]. Refinement of the parameters was accomplished by full-matrix least-squares using a riding model for hydrogen atoms with a fixed isotropic temperature factor ($U_{(iso)} = 0.06$ Å^2) and converged with $R = 0.047$ and $R_w = 0.043$ for the 2255 observed reflections for $[Cu(HBz4P)Cl_2]$ and $R = 0.058$ and $R_w = 0.062$ for the 2751 observed reflections for [Cu(Hzhexim)Cl]. The goodness-of-fits for $[Cu(HBz4P)Cl_2]$ and [Cu(Bzhexim)Cl] were 1.16 and 1.27, respectively. For a summary of crystal data, see Table 3.

RESULTS AND DISCUSSION

The ^{1}H NMR spectral assignments for the pyridyl ring proton, ^{6}CH, as well as ^{3}NH and ^{4}NH, are listed for the eight 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones along with 2-benzoylpyridine in Table 1. Of the ring protons, ^{6}CH (followed by ^{4}CH) is the most sensitive to replacement of the carbonyl oxygen of 2-benzoylpyridine by the azomethine nitrogen and to hydrogen bonding by ^{3}NH of the thiosemicarbazone moiety. The magnitude of the downfield shift of ^{6}CH when converting 2-benzoylpyridine to a thiosemicarbazone is essentially the same for the various thiosemicarbazones. The thiosemicarbazones all show hydrogen bonding by ^{3}NH based on the presence of a peak at δ 13.62–14.54 in their spectra. The ^{4}N-dialkyl-thiosemicarbazones have this peak at lower field and this, along with their yellow colour, suggests the bifurcated E' isomer (Fig. 1). For the ^{4}N-alkyl-thiosemicarbazones the hydrogen bonding proton has $\delta < 14.00$, and their beige colour is consistent with the Z-isomer conformation shown in Fig. 1.[9,14–16] HBzpip is probably a mixture of the two isomers, 19.1% Z and 80.9% E' in $CDCl_3$ solution. Its yellow colour is consistent with this assignment. ^{4}NH is found in the δ 7.4–7.8 range for HBz4M, HBz4E and HBz4P, indicating this proton's non-involvement in hydrogen bonding.

Also included in Table 1 are the more important ^{13}C assignments [i.e. ^{6}C(ring), ^{2}C(ring), ^{7}C(azomethine) and ^{8}C(thioamide)]. In contrast to ^{6}CH, which is shifted considerably on conversion of the ketone to a thiosemicarbazone, ^{6}C is essentially unshifted for the thiosemicarbazones from its position in the spectrum of 2-benzoylpyridine. As would be expected, ^{2}C(ring) and ^{7}C(azomethine)

Table 1. ^{1}H and ^{13}C NMR spectral assignments (δ) and melting points of 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones

Compound	^{6}CH(d)	^{2}NH	^{4}NH	^{6}C	^{2}C	^{7}C	^{8}C	M.p. (°C)
2-Benzoylpyridine	8.149			147.1	153.6	191.9		42–44
HBz4M	8.773	13.709	7.412	148.4	142.3	152.1	178.9	181–182
HBz4E	8.833	13.640	7.764	148.6	142.3	152.4	178.1	146–148
HBz4P	8.742	13.622	7.731	148.3	142.1	152.0	177.9	82–84
HBx4DM	8.708	14.434		147.6	144.6	152.5	181.3	124–125
HBz4DE	8.697	14.579		147.4	144.7	152.8	179.6	102–105
HBz4DP	8.656	14.541		147.2	144.8	152.5	179.6	110–112
HBzpip[a]	8.772	14.231 13.719		147.9	143.8	152.2	180.6	114–117
HBzhexim	8.641	14.668		147.2	144.7	152.4	180.0	95–96

[a] 14.231 (19%), 13.179 (81%).

are shifted upfield by *ca* 10 and 40 ppm, respectively, on conversion from the ketone to the thiosemicarbazone. The chemical shift of ^{8}C at δ 177–180 is consistent with reports of the 2-formylpyridine[5,14] and 2-acetylpyridine[9,16] ^{4}N-substituted thiosemicarbazones. The melting points of these newly prepared thiosemicarbazones are included in Table 1 and, like the other heterocyclic thiosemicarbazones studied,[5–9,16] the bulkier ^{4}N-substituted thiosemicarbazones have the lowest melting points.

The information in Table 2 shows that both four- and five-coordinate complexes with an anionic (loss of the ^{3}NH) or neutral thiosemicarbazone ligand, respectively, can be isolated.[1,8,9,17] The isolation of the five-coordinate complexes can be enhanced by using isopropanol and less heating. Although isolation with anionic ligands is common for complexes of 2-acetylpyridine ^{4}N-dialkyl- and 3-azacyclothiosemicarbazones, it is considerably less common for the analogous thiosemicarbazones derived from 2-formylpyridine, unless base is added. Therefore, the mode of coordination of the 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones is more similar to the 2-acetylpyridine thiosemicarbazones than the 2-formylpyridine thiosemicarbazones.

The complexes are various shades of greens and brown, and those with the thiosemicarbazone coordinated as an anion {i.e. [Cu(NNS)Cl]} are non-electrolytes. The five-coordinate [Cu(HBz4E)Cl$_2$] has a molar conductivity approaching 1:1 electrolytic behaviour in DMF due to the partial substitution of one of the chloro ligands by solvent molecules. This observation for five-coordinate complexes involving neutral tridentate thiosemicarbazone ligands was reported previously based on the similarity of EPR and visible spectra of solu-

Table 2. Colours, partial elemental analyses, molar conductivities and magnetic susceptibilities of the copper(II) complexes of 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones

Compound	Colour	Found (calc.), %			Λ (ohm^{-1} cm^2 mol^{-1})	μ (B.M.)
		C	H	N		
[Cu(Bz4M)Cl]·H$_2$O	Bright green	45.5(45.5)	3.4(3.9)	14.6(14.5)	41	1.6
[Cu(HBz4E)Cl$_2$]·H$_2$O	Dark brown	41.2(41.2)	3.2(4.2)		70	1.7
[Cu(Bz4P)Cl]	Olive green	47.7(48.5)	3.9(4.3)	14.4(14.1)	<10	1.7
[Cu(Bz4DM)Cl]·1/2H$_2$O	Olive green	46.2(46.0)	3.8(4.1)	13.8(14.3)	<10	1.7
[Cu(Bz4DE)Cl]	Dark olive green	49.6(49.8)	4.6(4.6)	13.1(13.7)	<10	1.7
[Cu(Bz4DP)Cl]	Dark olive green	53.4(52.1)	5.2(5.3)	12.6(12.8)	50	1.5
[Cu(Bzpip)Cl]	Olive brown	51.0(51.2)	4.5(4.5)	12.6(13.3)	<10	1.7
[Cu(Bzhexim)Cl]	Olive brown	51.7(52.2)	4.9(5.1)		<10	1.7

tions of the four- and five-coordinate complexes of 2-formylpyridine thiosemicarbazones.[6] The four-coordinate complexes have normal magnetic moments, but the five-coordinate complexes have values lower than 1.7 B.M., indicating significant interaction between copper(II) centres. This interaction is via the basal chloro ligands to form dimers, which are further connected into chains by hydrogen bonds to the axial chloro ligands for [Cu(HBz4P)Cl_2] (see below).

Table 3 is a summary of the crystallographic data for [Cu(HBz4P)Cl_2] and [Cu(Bzhexim)Cl], and their interatomic distances and bond angles are listed in Tables 4 and 5, respectively. Perspective views of [Cu(HBz4P)Cl_2] and [Cu(Bzhexim)Cl] are shown in Figs 2 and 3, and the packing of the molecules in Figs 4 and 5.

Both the neutral and anionic thiosemicarbazones bond as tridentate ligands and coordinate to the central metal atom via the pyridyl nitrogen N(1), the azomethine nitrogen N(2) and the thione/thiolato sulphur atoms with the fourth (and fifth) coordination site occupied by chlorine atom(s) (Figs 2 and 3). For [Cu(HBz4P)Cl_2] the thiosemicarbazone ligand occupies three basal positions and one of the chlorines the fourth basal position of the square pyramidal structure. The copper atom is positioned 0.253(1) Å above the plane of the four basal ligands towards the chlorine atom. The bond angles of the *trans* donor atoms [i.e. S,N(1) and Cl(1),N(2)] are both >160° and the thiosemicarbazone bite angles are less than 90°, i.e. N(1)—Cu—N(2) = 79.0° and S—Cu—N(2) = 84.5°. The second chlorine atom has bond angles with the basal plane between 90.7° [Cl(2)—Cu—N(1) = 90.7°] and 100.7° [Cl(1)—Cu—Cl(2) = 100.7°], forming the larger angles with the two bulkier basal atoms (i.e. sulphur and chlorine). Thus, the apical chlorine, Cl(2), is slightly bent off-axis from the axial position of a regular square pyramid. Cl(2) has a considerably longer bond, 2.660 Å, than the basal chlorine, Cl(1), which has a bond distance of 2.236 Å. Each molecule has

Table 4. Bond lengths (Å) for [Cu(HBz4P)Cl_2] and [Cu(Bzhexim)Cl]

[Cu(HBz4P)Cl_2]			
Cu—Cl(1)	2.236(2)	Cu—Cl(2)	2.660(1)
Cu—S	2.287(2)	Cu—N(1)	2.038(4)
Cu—N(2)	2.001(4)	S—C(8)	1.698(5)
N(1)—C(2)	1.342(6)	N(1)—C(6)	1.346(7)
N(2)—N(3)	1.356(5)	N(2)—C(7)	1.293(7)
N(3)—C(8)	1.366(7)	N(4)—C(8)	1.320(6)
N(4)—C(9)	1.456(8)	C(2)—C(3)	1.372(9)
C(3)—C(4)	1.370(9)	C(4)—C(5)	1.395(7)
C(5)—C(6)	1.386(8)	C(6)—C(7)	1.478(6)
C(7)—C(1′)	1.475(7)		
[Cu(Bzhexim)Cl]			
Cu—Cl	2.225(3)	Cu—S	2.235(3)
Cu—N(1)	2.015(7)	Cu—N(2)	1.968(7)
S—C(9)	1.750(9)	N(1)—C(2)	1.312(11)
N(1)—C(6)	1.370(11)	N(2)—N(3)	1.358(9)
N(2)—C(7)	1.295(10)	N(3)—C(8)	1.336(10)
N(4)—C(8)	1.342(10)	N(4)—C(10)	1.487(11)
N(4)—C(15)	1.452(11)	C(2)—C(3)	1.396(12)
C(3)—C(4)	1.378(15)	C(4)—C(5)	1.388(13)
C(5)—C(6)	1.384(12)	C(6)—C(7)	1.473(11)
C(7)—C(16)	1.519(12)		

Table 3. Crystallographic data for [Cu(HBz4P)Cl_2] and [Cu(Bzhexim)Cl]

	[Cu(HBz4P)Cl_2]	[Cu(Bzhexim)Cl]
Empirical formula	$C_{16}H_{18}Cl_2CuN_4S$	$C_{19}H_{21}ClCuN_4S$
Colour: habit	Dark green prism	Dark brown needle
Crystal size (mm)	0.32 × 0.24 × 0.20	0.20 × 0.27 × 0.72
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
Unit cell dimensions	a = 12.227(3) Å	a = 14.961(3) Å
	b = 12.175(2) Å	b = 12.885(2) Å
	c = 13.876(2) Å	c = 10.356(7) Å
	β = 111.91(1)°	β = 97.27(2)°
Volume	1916.3(7) Å^3	1980.3(14) Å^3
Z	4	4
Formula weight	432.8	436.4
Density (calc.)	1.500 g cm^{-3}	1.464 g cm^{-3}
Absorption coefficient	1.532 mm^{-1}	1.353 mm^{-1}
F(000)	884	900

Table 5. Bond angles (°) for [Cu(HBz4P)Cl_2] and [Cu(Bzhexim)Cl]

[Cu(HBz4P)Cl_2]			
Cl(1)—Cu—Cl(2)	100.7(1)	Cl(1)—Cu—S	94.3(1)
Cl(2)—Cu—S	100.5(1)	Cl(1)—Cu—N(1)	99.0(1)
Cl(2)—Cu—N(1)	90.7(1)	S—Cu—N(1)	160.7(1)
Cl(1)—Cu—N(2)	165.0(1)	Cl(2)—Cu—N(2)	94.2(1)
S—Cu—N(2)	84.5(1)	N(1)—Cu—N(2)	79.0(2)
Cu—S—C(8)	97.2(2)	Cu—N(1)—C(2)	127.5(4)
Cu—N(1)—C(6)	113.6(3)	C(2)—N(1)—C(6)	118.8(5)
Cu—N(2)—N(3)	119.0(3)	Cu—N(2)—C(7)	118.4(3)
N(3)—N(2)—C(7)	122.0(4)	N(2)—N(3)—C(8)	117.8(4)
C(8)—N(4)—C(9)	125.0(5)	N(1)—C(2)—C(3)	122.1(5)
C(2)—C(3)—C(4)	119.6(5)	C(3)—C(4)—C(5)	119.2(6)
C(4)—C(5)—C(6)	118.3(5)	N(1)—C(6)—C(5)	122.0(4)
N(1)—C(6)—C(7)	115.7(5)	C(5)—C(6)—C(7)	122.3(5)
N(2)—C(7)—C(6)	113.0(4)	N(2)—C(7)—C(1′)	124.9(4)
C(6)—C(7)—C(1′)	122.0(5)	S—C(8)—N(3)	121.3(3)
S—C(8)—N(4)	123.0(4)	N(3)—C(8)—N(4)	115.8(4)
N(4)—C(9)—C(10)	110.0(5)	C(9)—C(10)—C(11)	112.2(5)
C(7)—C(1′)—C(2′)	119.1(4)		
[Cu(Bzhexim)Cl]			
Cl—Cu—S	96.9(1)	Cl—Cu—N(1)	97.7(1)
S—Cu—N(1)	165.2(2)	Cl—Cu—N(2)	176.3(2)
S—Cu—N(2)	84.7(2)	N(1)—Cu—N(2)	80.8(3)
Cu—S—C(8)	95.5(2)	Cu—N(1)—C(2)	128.0(6)
Cu—N(1)—C(6)	112.9(5)	C(2)—N(1)—C(6)	119.1(7)
Cu—N(2)—N(3)	123.4(5)	Cu—N(2)—C(7)	117.1(5)
N(3)—N(2)—C(7)	119.5(6)	N(2)—N(3)—C(8)	111.8(6)
C(8)—N(4)—C(10)	120.0(7)	C(8)—N(5)—C(15)	123.1(7)
C(10)—N(4)—C(15)	116.1(7)	N(1)—C(2)—C(3)	123.1(9)
C(2)—C(3)—C(4)	118.5(8)	C(3)—C(4)—C(5)	118.9(8)
C(4)—C(5)—C(6)	119.8(8)	N(1)—C(6)—C(5)	120.6(7)
N(1)—C(6)—C(7)	114.2(7)	C(5)—C(6)—C(7)	125.1(8)
N(2)—C(7)—C(6)	114.9(7)	N(2)—C(7)—C(16)	123.6(7)
C(6)—C(7)—C(8)	121.5(7)	S—C(8)—N(3)	124.4(6)
S—C(8)—N(4)	119.5(6)	N(3)—C(8)—N(4)	116.0(7)
N(4)—C(10)—C(11)	112.4(8)	C(10)—C(11)—C(12)	116.3(11)
C(11)—C(12)—C(13)	125.6(17)	C(12)—C(13)—C(14)	133.6(15)
C(13)—C(14)—C(15)	123.4(11)	N(4)—C(15)—C(14)	112.8(9)

a sixth donor, a Cl(I) from an adjacent molecule, which has a Cu—Cl bond distance of 2.72(1) Å; thus, the molecule is a dimer and each Cl(2) is positioned so that it interacts weakly with N(3)H and N(4)H of the closest of the copper(II) centres of an adjacent dimer, resulting in a weakly held lattice of dimeric copper(II) complexes. The phenyl ring is turned out of the plane to reduce steric interaction with the pyridyl ring, as well as for packing reasons, and the N(4)-propyl group is out of the plane of the thiosemicarbazone moiety.

For [Cu(Bzhexim)Cl] the thiosemicarbazone ligand occupies three positions and the chlorine the fourth position of an approximate square plane. The bond angles of the trans donor atoms [i.e. S,N(1) and Cl(1), N(2)] are both $>160°$ and the thiosemicarbazone bite angles are less than 90°, i.e. N(1)—Cu—N(2) = 80.8° and S—Cu—N(2) = 84.7°, which are marginally greater than for [Cu(HBz4P)Cl_2]. This distortion is due to the restricted bite angles of the thiosemicarbazone ligand rather than the bulkiness of the chlorine atom because the analogous angles are essentially the same for [Cu(Lhexim)Br], where Lhexim is the anion of 2-acetylpyridine 3-hexamethyleneiminylthiosemicarbazone.[17] The bite angles for [Cu(Lpip)Br] (Lpip = anion of 2-acetylpyridine 3-piperidylthiosemicarbazone)[17] are also similar to the above two complexes. The phenyl ring in [Cu(Bzhexim)Cl] is again turned out of the coordination

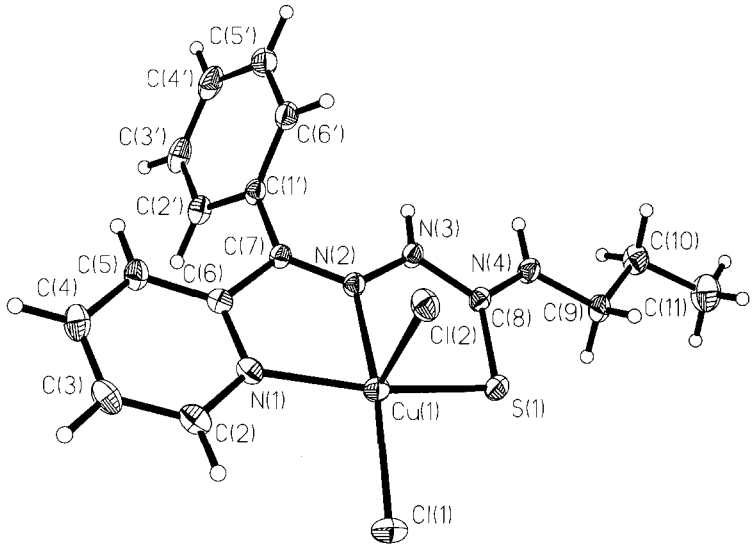

Fig. 2. Perspective view of [Cu(HBz4P(Cl$_2$].

plane with weak interactions between its C(19) hydrogen, as well as the C(4) hydrogen of the pyridyl ring and a chlorine on an adjacent molecule; the hexamethyleneiminyl ring is also bent away from the coordination plane.

Hendrickson *et al.*[18] reported chromium(III) and iron(III) complexes with both thione and thiolato thiosemicarbazones of pyruvic acid bonded to the same metal centre. The bichelate bond angles for the two forms of the thiosemicarbazone are very similar [i.e. thione, O—Cr—N = 79.5°, N—Cr—S = 81.9°; thiolato, O—Cr—N = 81.1°, N—Cr—S = 81.7°]. The two forms have the greatest differences in bond distances for bonds attached to C(9) [thione, N(3)—C(9) = 1.359 Å, C(9)—N(4) = 1.307 Å and C(9)—S = 1.717 Å; thiolato, N(3)—C(9) = 1.335 Å, C(9)—N(4) = 1.337 Å and C(9)—S = 1.741 Å]. Recently, Padhye and co-workers[19] also found that small, but consistent, differences occur in the bond angles and distances for the thione and thiolato forms of 2-ketobutyric acid thiosemicarbazone in its chromium(III) and cobalt(III) complexes. A comparison of [Cu(HBz4P)Cl$_2$] to [Cu(Bzhexim)Cl] shows that the Cu—N(1), Cu—N(2) and Cu—Cl(1) bond distances are longer for the former, as expected for a five- compared to a four-coordinate copper(II) complex. The Cu—Cl bond distances {basal Cu—Cl for [Cu(HBz4P)Cl$_2$]} are in closest agreement and differ by only *ca* 0.01 Å. As would be expected, the largest difference in the copper–donor atom bond distance for these two

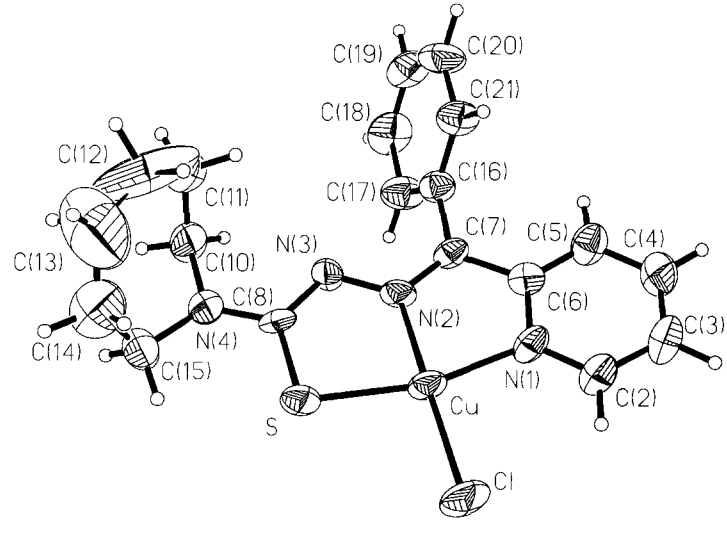

Fig. 3. Perspective view of [Cu(Bzhexim)Cl].

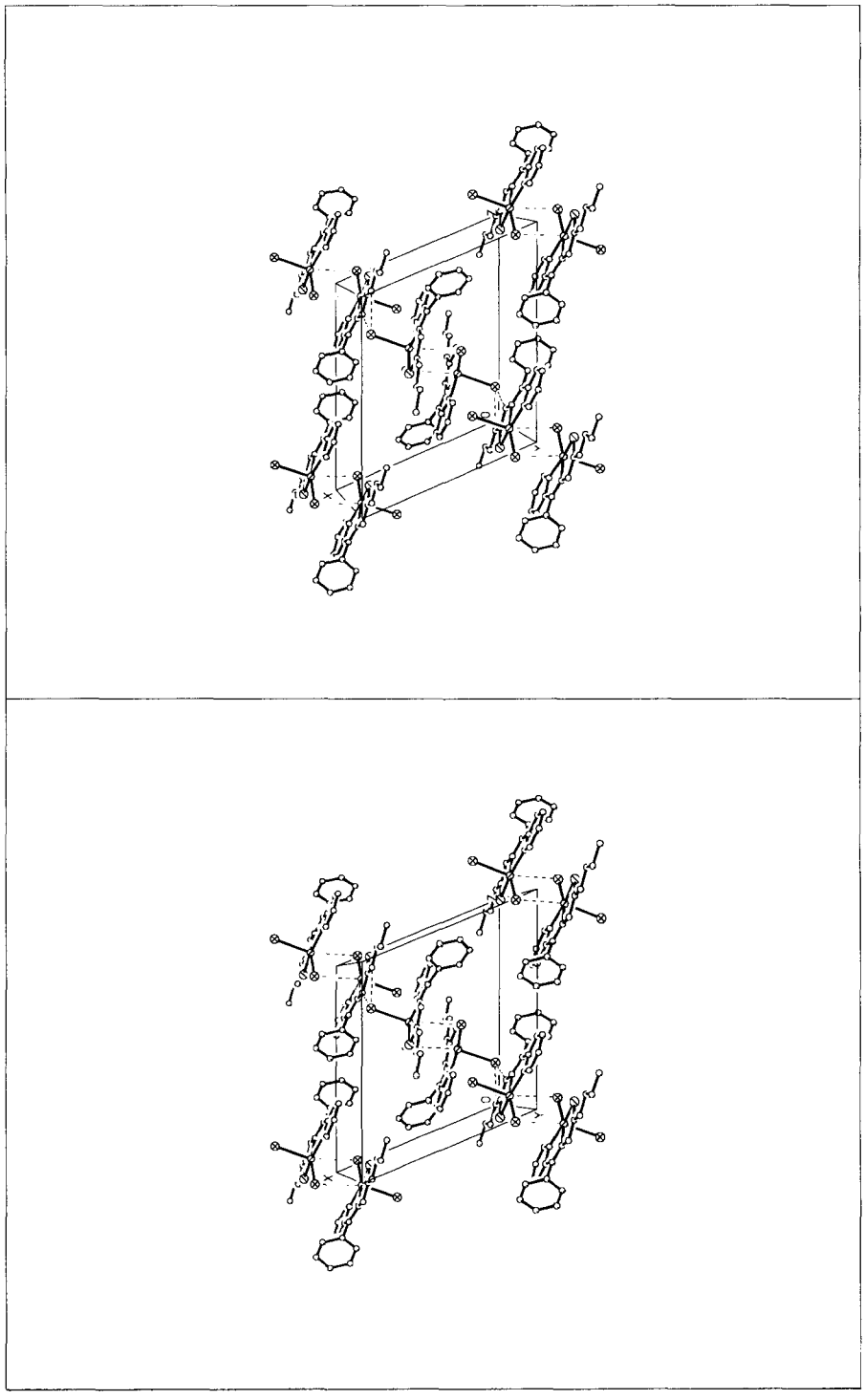

Fig. 4. Packing arrangement for [Cu(HBz4P)Cl_2].

complexes is the Cu—S bond. For [Cu(HBz4P)Cl_2] this bond is 2.287(2) Å and for [Cu(Bzhexim)Cl] 2.235(3) Å. Similarly, the S—C(8) bond is shorter, 1.698(5) Å, in [Cu(HBz4P)Cl_2] than for [Cu(Bzhexim)Cl], 1.750(9) Å. For C(7)—N(2), the azomethine bond, the distances are 1.293 and 1.295 Å for [Cu(HBz4P)Cl_2] and [Cu(Bzhexim)Cl], respectively. This similarity indicates that the coordination number is the determining factor for differences for Cu—N(2) in the two complexes {2.001(4) and 1.968(7) Å for [Cu(HBz4P)Cl_2] and [Cu(Bzhexim)Cl], respectively} rather than a

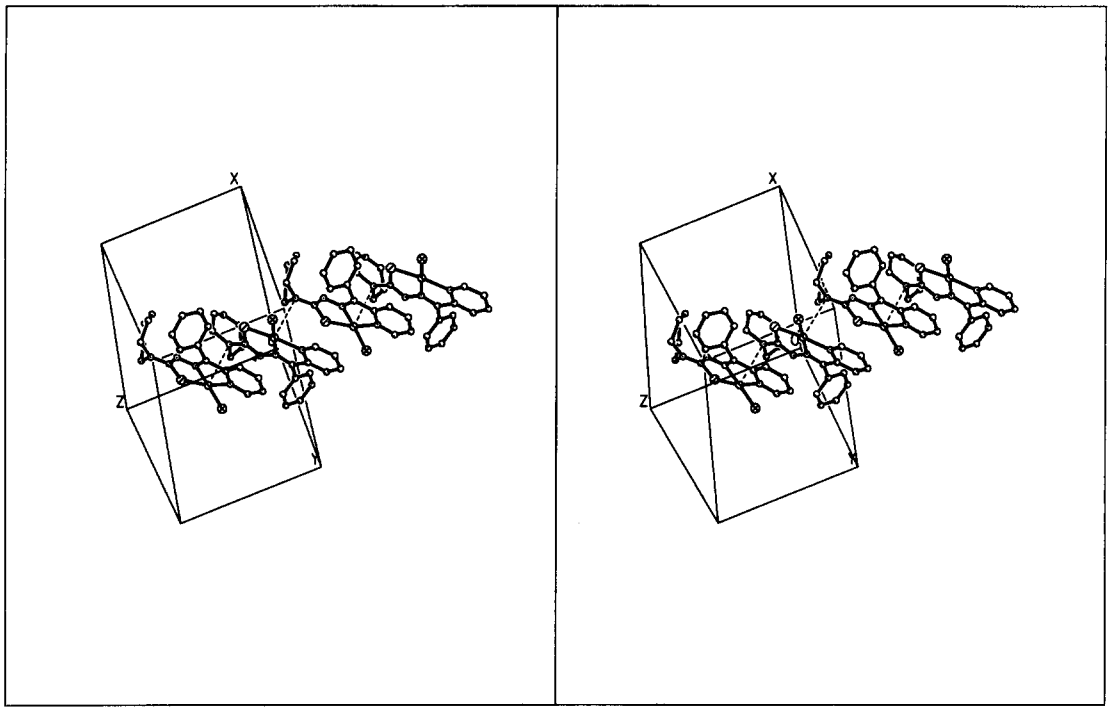

Fig. 5. Packing arrangement for [Cu(Bzhexim)Cl].

change in the electron density in the thiosemicarbazone moiety.

Table 6 includes selected bond distances and angles of other heterocyclic ^{4}N-substituted thiosemicarbazone complexes that have been reported recently. Although the differences are small, the complexes of the present study have longer C(7)=N(2) and shorter N(2)—N(3) bond distances than copper(II) complexes of 2-acetylpyridine thiosemicarbazones. This is likely due to the greater steric requirements of the phenyl ring compared to the methyl group. Like other copper(II) complexes of thiosemicarbazones with bulky azacyclo groups involving N(4), [Cu(Bzhexim)Cl] has a longer N(4)—C(9) bond than [Cu(L4M)Br],[20] but shorter than [Cu(Lhexim)Br].[17] The three metal–donor atom bond distances are essentially the same for [Cu(Bzhexim)Cl] and [Cu(Lhexim)Br] and both are considerably longer than the bond distances found for [Ni(Lhexim)Br].[17] The bichelate bond angles are largest for those complexes in which the thiosemicarbazone has the bulkier hexamethyleneiminyl substituent and are smallest for [Cu(Hbz4P)Cl_2].

The assignments for the IR spectral bands useful for determining the ligand's mode of coordination are listed in Table 7. ν(C=N) of the thiosemicarbazone moiety (1572–1591 cm^{-1}) generally

Table 6. Comparison of thiosemicarbazone moiety bond lengths (Å) and angles (°) for metal(II) heterocyclic ^{4}N-substituted thiosemicarbazone complexes

Compound	C(7)—N(2)	N(2)—N(3)	C(9)—N(4)	S—Cu—^{1}N	S—Cu—^{2}N	^{1}N—Cu—^{2}N	Ref.
[Cu(HBz4P)Cl_2]	1.293	1.356	1.320	160.7	84.5	79.0	This work
[Cu(Bzhexim)Cl]	1.295	1.358	1.342	165.2	84.7	80.8	This work
[Cu(L4M)Br][a]	1.288	1.363	1.315	164.8	84.7	80.5	20
[Cu(Lpip)Br][b]	1.28	1.39	1.37	162.5	84.3	80.6	17
[Cu(Lhexim)Br][c]	1.275	1.373	1.377	165.3	85.1	80.5	17
[Ni(Lhexim)Br][c]	1.33	1.37	1.33	170.4	87.8	82.7	17

[a] L4M = anion [loss of N(3) proton] of 2-acetylpyridine ^{4}*N*-methylthiosemicarbazone.
[b] Lpip = anion [loss of N(3) proton] of 2-acetylpyridine 3-piperidinylthiosemicarbazone.
[c] Lhexim = anion [loss of N(3) proton] of 2-acetylpyridine 3-hexamethyleneiminyl-thiosemicarbazone.

Table 7. IR spectral assignments (cm^{-1}) of 2-benzoyl ^{4}N-substituted thiosemicarbazones and their copper(II) complexes

Compound	ν(CN)	ν(CS)	ρ(py)	ν(CuN)	ν(CuS)	ν(CuCl)
HBz4M	1577m	811s	589m			
HBz4E	1575m	810s	588m			
HBz4P	1577m	819s	588s			
HBz4DM	1591m	810m	589s			
HBz4DE	1579s	792m	595s			
HBz4DP	1573s	795s	598sh			
HBzpip	1572s	792s	597s			
HBzhexim	1576sh	791s	596sh			
[Cu(Bz4M)Cl]	1555m	720s	632sh	460m	346m	305
[Cu(HBz4E)Cl_2]	1560m	739m	622vw	457m	346m	315sh
						308s
[Cu(HBz4P)Cl_2]	1585m	728m	632m	455w	344m	312m
						291w
[Cu(Bz4P)Cl]	1573m	719s	633m	460w	345m	315vs
[Cu(Bz4DM)Cl]	1582s	742m	618m	455m	340m	305s
[Cu(Bz4DE)Cl]	1582s	738m	619m	446m	338m	305s
[Cu(Bz4DP)Cl]	1586s	745m	610m	448m	342s	298s
[Cu(Bzpip)Cl]	1569s	741s	600m	462m	347s	290s
[Cu(Bzhexim)Cl]	1560m	738s	619m	450m	342m	312vs

shifts to lower energy in the spectra of the complexes (1555–1586 cm^{-1}), indicating coordination of the azomethine nitrogen (^{1}N). In complexes containing the anionic ligand, a band due to $\nu(^8C{=}{}^3N)$ is often resolved in the 1590–1600 cm^{-1} region. We have assigned a band in the range 446–462 cm^{-1} to ν(CuN) for the azomethine nitrogen in the spectra of the complexes. Recent studies[21] have assigned a number of bands as having contributions from ν(C=S) in a complex of methylpyruvate thiosemicarbazone, but the many ring vibrations contribute to the complexity of the spectra in the present thiosemicarbazones, which makes bands other than the thioamide IV band difficult to assign. This latter band appears in the range 791–811 cm^{-1} in the spectra of the thiosemicarbazones and shifts to 719–745 cm^{-1} in the complexes' spectra, indicating coordination of the thiolato/thione sulphur atom. Bands in the 338–347 cm^{-1} region have been assigned to ν(Cu—S).[22] Coordination of the pyridine nitrogen is indicated by a positive shift of the ring deformation band found below 600 cm^{-1} in the spectra of the thiosemicarbazones to above 600 cm^{-1} in the complexes' spectra. ν(CuCl) is assigned to a strong band or bands at *ca* 300 cm^{-1} at the lower end of the region associated with terminal chloro ligands.[23] Consistent with their five-coordinate nature, the neutral ligand complexes have two assignable ν(CuCl) bands. Complexes with neutral thiosemicarbazones are five-coordinate, and their bonding involves NNS tridentate ligands and both chlorines, in agreement with the crystal structure determined for [Cu(HBz4P)Cl_2].

Each thiosemicarbazone has a peak in the range 27,400–30,670 cm^{-1} in its solid state spectrum that is assignable to an $n \rightarrow \pi^*$ transition of the pyridine moiety (Table 8). Some of the thiosemicarbazones have a second band at somewhat lower energy due to an $n \rightarrow \pi^*$ transition associated with the thiosemicarbazone moiety.[24] The presence of the *E'* isomer (bifurcated hydrogen bond with conjugated thiosemicarbazone moiety) is primarily responsible for this band.[25] It is more easily assignable in DMF or DMSO solution and is stronger and more distinct in the spectra of the ^{4}N-dialkyl-thiosemicarbazones and 3-azacyclothiosemicarbazones than the ^{4}N-alkyl-thiosemicarbazones. For example, in DMF, HBz4DM shows a well defined peak at 25,700 cm^{-1} ($\log \varepsilon = 3.00$) and for HBzhexim this band is at 23,879 cm^{-1} with $\log \varepsilon = 3.31$.

The electronic spectra of the copper(II) complexes have the $n \rightarrow \pi^*$ band of the pyridyl ring at *ca* 31,000 cm^{-1}. Additional bands are present in the 20,000–27,000 cm^{-1} range that are assignable to $S \rightarrow Cu^{II}$ and $py \rightarrow Cu^{II}$ charge-transfer transitions.[24,26] Bands in the range 27,000–31,000 cm^{-1} may have contributions from $Cl \rightarrow Cu^{II}$ change-transfer transitions.[27] The broad solid state *d–d* band (14,680–17,540 cm^{-1}) does not have a resolved shoulder(s) in any of these complexes. The band maximum is comparable in energy to that found for the complexes of either 2-formylpyridine

Table 8. Electronic spectra (cm^{-1}) of 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones and their copper(II) complexes

Compound	Intraligand and charge transfer				$\nu(d\text{–}d)$
HBz4M	27,400				
HBz4E	28,410				
HBz4P	28,410	25,840			
HBz4DM	28,570	27,030			
HBz4DE	28,820	23,150			
HBz4DP	28,570	22,730			
HBpip	30,300	27,250	23,260		
HBzhexim	30,670	27,550			
[Cu(Bz4M)Cl]	32,050	27,780	22,730		14,680
[Cu(HBz4E)Cl_2]	31,060	27,170	22,870	21,370	15,130
[Cu(Bz4P)Cl]	31,450	27,770	24,270		17,180
[Cu(Bz4DM)Cl]	31,250	25,000	21,980		17,540
[Cu(Bz4DE)Cl]	30,860	28,090	22,370		17,390
[Cu(Bz4DP)Cl]	31,250	26,670	22,220		16,130
[Cu(Bzpip)Cl]	31,740	24,630	22,220		16,670
[Cu(Bzhexim)Cl]	31,450	26,740	21,830		16,840

Table 9. EPR spectral parameters of the copper(II) complexes of 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones

Compound	Temp.	g_1 or $g_\parallel$	g_2	g_3 or $g_\perp$	g_{av}
[Cu(Bz4M)Cl] solid	RT[a]	2.179		2.052	2.094
	77 K	2.176		2.050	2.092
[Cu(HBz4E)Cl_2] solid	RT	2.052		2.115	2.094
	77 K	2.052		2.115	2.094
[Cu(Bz4P)Cl] solid	RT	2.122	2.054	2.033	2.070
	77 K	2.118	2.052	2.031	2.067
[Cu(Bz4DM)Cl] solid	RT	2.129	2.065	2.034	2.076
	77 K	2.129	2.065	2.035	2.076
[Cu(Bz4DE)Cl] solid	RT	2.139	2.050	2.037	2.075
	77 K	2.147	2.046	2.033	2.075
[Cu(Bz4DP)Cl] solid	RT	2.150		2.041	2.070
	77 K	2.143	2.043	2.035	2.074
[Cu(Bzpip)Cl] solid	RT	2.151		2.036	2.074
	77 K	2.153		2.033	2.073
[Cu(Bzhexim)Cl] solid	RT	2.141		2.040	2.074
	77 K	2.138		2.041	2.073

[a] Room temperature.

or 2-acetylpyridine thiosemicarbazones. For example, [Cu(4DP)Cl][5] and [Cu(L4DP)Cl],[7] complexes of 2-formyl- and 2-acetylpyridine ^{4}*N*-dipropylthiosemicarbazone, respectively, have their solid state *d–d* band maxima at 16,530 and 17,770 cm^{-1} with a shoulder at 14,710 cm^{-1}, while [Cu(Bz4DP)Cl] shows this band at 16,130 cm^{-1}.

Consistent with the relatively high energy *d–d* band maxima for the four-coordinate copper(II) complexes of 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones, their solid state EPR spectra generally have low values for $g_\parallel$ (and g_{av}). There is little difference between the room and liquid nitrogen temperature *g*-values, indicating no significant change in the stereochemistry of the coordination spheres on cooling. [Cu(Bz4M)Cl] has the highest value for $g_\parallel$ and [Cu(Bz4P)Cl] the lowest, but many of the complexes have rather low values for $g_\parallel$, indicating strong coordination as well as a significant degree of covalent bonding. Compared to

Table 10. Growth inhibitory activity of 2-benzoylpyridine ^{4}N-substituted thiosemicarbazones and their copper(II) complexes against *Aspergillus niger* and *Paecilomyces variotii*

Compound	200[a]	400	600	1000	1600
Aspergillus niger					
[Cu(Bz4P)Cl]	6.0[b]	6.0	6.0	6.0	6.2
HBz4DM	6.0	6.5	11.5	14.8	16.0
HBz4DE	6.0	6.0	8.3	8.8	10.7
HBz4DP	7.5	8.2	8.6	8.4	9.5
[Cu(Bz4DP)Cl]	6.0	6.5	7.0	7.0	8.0
HBzpip	7.0	8.0	9.0	10.7	13.0
[Cu(Bzpip)Cl]	8.0	8.7	9.5	10.0	8.7
HBzhexim	7.2	7.5	7.2	9.3	10.2
[Cu(Bzhexim)Cl]	7.8	8.7	9.2	9.3	9.5
Paecilomyces variotii					
[Cu(Bz4M)Cl]	7.0	10.5	11.0	16.3	17.3
[Cu(HBz4E)Cl_2]	14.0	15.2	17.6	20.5	21.7
HBz4P	6.7	8.2	9.0	10.2	12.7
[Cu(Bz4P)Cl]	8.2	10.0	11.7	13.5	14.3
HBz4DM	6.0	9.0	16.7	18.0	23.0
HBz4DE	6.0	8.8	11.7	12.0	17.3
HBz4DP	11.4	11.7	12.4	13.5	14.0
[Cu(Bz4DP)Cl]	7.8	9.3	9.5	10.8	11.5
[Cu(Bzpip)Cl]	14.0	14.7	14.5	16.3	16.0
HBzhexim	10.3	9.2	10.3	11.7	12.3
[Cu(Bzhexim)Cl]	12.2	12.0	13.0	12.7	13.0

[a] μg cm^{-3}

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

[Cu(4DP)Cl][5] and [Cu(L4DP)Cl],[7] complexes of 2-formyl- and 2-acetylpyridine ^{4}*N*-dipropylthiosemicarbazone, which have $g_\parallel = 2.169$ and 2.154 respectively, [Cu(Bz4DP)Cl] has $g_\parallel = 2.150$. Therefore, the phenyl group does affect the coordination sphere to a small extent by virtue of its greater bulkiness (compared to hydrogen and CH_3). The bulkier phenyl group likely blocks additional bonding by sulphur or chlorine atoms of adjacent copper(II) centres. The phenyl group's electron withdrawing ability seems to be unimportant to the strength of the coordinate bonds. A reversed spectrum ($g_\perp > g_\parallel$) for five-coordinate [Cu(HBz4E)Cl_2] suggests that the stereochemistry is closer to trigonal bipyramid than square pyramid.

[Cu(Bz4DM)Cl] and [Cu(Bzhexim)Cl] in chloroform yield diluted copper(II) spectra with $g_o = 2.080$ and 2.079, respectively. Both are somewhat greater than their powder g_{av} values, which may be due to the change of medium and not representative of any stereochemical change. The frozen $CHCl_3$ spectrum was not resolvable.

Many of these thiosemicarbazones and their copper(II) complexes are inactive or only slightly active at inhibiting the growth of *Aspergillus niger* (Table 10; those showing no activity are omitted); HBz4DM and HBzpip are the most active thiosemicarbazones and [Cu(Bzpip)Cl] and [Cu(Bzhexim)Cl] are the most active copper(II) complexes. There is more inhibitory activity against *Paecilomyces variotii*. In some instances the same copper(II) complexes are active, but the thiosemicarbazones inactive (e.g. HBz4M and HBz4E). In contrast, some thiosemicarbazones are active, but their copper(II) complexes are inactive e.g. [Cu(Bz4DM)Cl] and [Cu(Bz4DE)Cl]. The bulkier thiosemicarbazones, HBz4DP, HBzpip and HBzhexim, are active both as uncomplexed thiosemicarbazones and as copper(II) complexes. On dissolution in DMSO, the solvent for the antifungal testing, the five-coordinate complexes having bulkier ligands lose the more weakly held chloro ligand. Therefore, for these complexes the species being tested is a four-coordinate complex.

The 2-formyl- and 2-acetylpyridine ^{4}*N*-dipropylthiosemicarbazone complexes analogous to [Cu(Bz4DP)Cl] {i.e. [Cu(4DP)Cl] and [Cu(L4DP)Cl]} at a concentration of 200 μg cm^{-3} show the following growth inhibition zones: 32.5 and 21.0 cm, respectively, against *Paecilomyces variotii*. Therefore, the substituent attached to C(7) must play a significant role in these compounds' growth inhibitory activity, since [Cu(Bz4DP)Cl] has an inhibition zone of only 7.8 cm at a concentration of 200 μg cm^{-3}.

Supplementary material

Atomic coordinates have been deposited with the Director, Cambridge Crystallographic Data Centre.

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