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Ribose, galactose and glucose *bis*(thiosemicarbazone) complexes of copper(II) and nickel(II)

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Abstract—The *bis*(thiosemicarbazones) of glucose (GluTSCH$_2$), galactose (GalTSCH$_2$) and ribose (RibTSCH$_2$) were prepared and characterized by spectroscopic (^{1}H and ^{13}CNMR, UV, IR) methods. A complete assignment of the NMR signals was made using ^{1}H–^{1}H COSY; ^{13}C–^{1}H COSY; ^{13}C COLOC and NOEDIF techniques, complemented with theoretical calculations. Metal complexes with the general formula [M(*bis* TSC)], where M = Cu^{II}, Ni^{II} and *bis*TSC = anion of the monosaccharide *bis*(thiosemicarbazones), were prepared and characterized. The X-band ESR powder spectra of the copper(II) complexes show a rhombic distortion and the solution (DMF) ESR spectra indicate significant axial interaction with solvent molecules. The presence of the monosaccharide residue enhances the complexes' water solubility and increases their biological potential. © 1997 Elsevier Science Ltd

Keywords: bis(thiosemicarbazones); monosaccharide; copper; nickel.

Numerous biological activities have been reported for molecules with one or more thiosemicarbazone moieties [1], and these activities have often been related to their chelating properties [2]. *Bis*(thiosemicarbazones), having the two thiosemicarbazone moieties positioned so that the molecule is capable of acting as a tetradentate ligand, are excellent chelating agents and possess potentially important biological properties. H$_2$KTS, 3-ethoxy-2-oxobutyraldehyde *bis*(thiosemicarbazone), forms CuKTS *in vivo*, which is considered to be the intermediate in its antitumor activity [3]. Most thiosemicarbazones and their coordination compounds are highly hydrophobic and their low water solubility introduces experimental limitations in biological studies [4]. The introduction of a carbohydrate moiety to the thiosemicarbazone molecules should increase water solubility as well as cell membrane permeability. Horton [5] studied the *bis*(thiosemicarbazones) and their copper(II) complexes of D-arabinose, D-glucose and D-gulose. He observed *in vivo* antitumoral activity in murine L-1210 for the copper(II) complex of the glucose derivative, 3-deoxy-D-erythro-hexos-2-ulose *bis*(thiosemicarbazone). Additional studies of these *bis*(thiosemicarbazones) are merited, and here we report the synthesis and characterization of ribose (RibTSCH$_2$), galactose (GalTSCH$_2$) and glucose (GluTSCH$_2$) *bis*(thiosemicarbazones) (Fig. 1) and their nickel(II) and copper(II) complexes.

EXPERIMENTAL

All chemicals were of high purity and used as purchased from Fluka with the exception of *p*-toluidine

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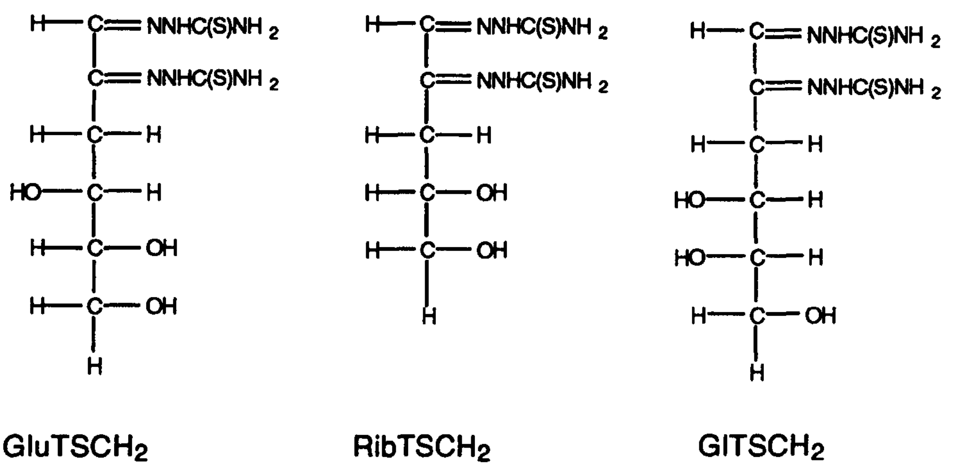

Fig. 1. Formulae of GalTSCH$_2$, RibTSCH$_2$ and GluTSCH$_2$.

and thiosemicarbazide which were recrystallized. The *bis*TSCH$_2$s were synthesized and purified by a procedure similar to that reported by Horton [5]. The 3-deoxyaldos-2-uloses were obtained by the reaction of the corresponding monosaccharide (0.011 mol) with *p*-toluidine (0.011 mol) in a slightly acid (1.2 mL of glacial acetic acid) hydroalcoholic solution (3 : 1) at 100°C for 30 min. A rearrangement of Amadori type takes place with the loss of a molecule of water. Then thiosemicarbazide (0.022 mole, 2 : 1 mole ratio) is added, the reaction maintained at 100°C for five hours and then refrigerated at 0°C overnight. Condensation with carbons 1 and 2 occurs to give the *bis*TSCH$_2$, as well as reduction of C$_3$ to a CH$_2$ group.

The nickel(II) and copper(II) complexes of the three *bis*TSCH$_2$s were prepared by dissolving the corresponding metal(II) acetate and a *bis*TSCH$_2$ in a 1 : 1 molar ratio in hot methanol. The mixture was stirred for three hours, left to cool, filtered and washed with ethanol. The complexes were recrystallized from hot methanol. The metal content was determined by atomic absorption spectrometry on a Pye Unicam SP-9 with hollow cathodic lamp and acetylene flame, and the analyses for the other elements was carried out on an Eager 200 analyzer.

The UV–vis absorption spectra were recorded with an Ultrospec III (Pharmacia-LKB) and Perkin–Elmer 330 spectrophotometer and the IR spectra with FT-IR PU-9800 (Phillips) and Perkin–Elmer 787 spectrometers as KBr tablets and nujol mulls, respectively. The ^{1}H and ^{13}C NMR spectra of the *bis*TSCH$_2$s and their nickel(II) complexes were obtained with a Bruker ACF 250 spectrometer in d^6-DMSO with TMS as reference. In addition, bidimensional spectra (^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY, ^{13}C COLOC) and NOEDIF were recorded for GluTSC. Theoretical calculations were carried out using the AM1 semi-empirical method, through the MOPAC program package. With the exception of the dihedral angle f involved in the Reaction Path Coordinate, all remaining geometric parameters were fully optimized. The ESR powder and solution spectra of the copper(II) complexes were recorded on a Varian E104 spectrometer at both room temperature and 77 K using a conventional insert Dewar with DPPH as reference.

RESULTS AND DISCUSSION

The colors and elemental analyses for the *bis*TSCH$_2$s and their complexes are shown in Table 1. The complexes are all 1 : 1 *bis*TSC : metal(II) center and have lost the N(2) hydrogens from each thiosemicarbazone moiety, which is consistent with tetradentate N$_2$S$_2$ coordination and the formation of three 5-membered chelate rings about the metal ions. Unfortunately, attempts to date to grow crystals for structural studies of these metal complexes have failed. However, the bonding to the metal ions is expected to be similar to that found for a nickel(II) complex of 2,3-butanedione *bis*(pyridylthiosemicarbazone) [6].

NMR spectra

The presence of a CH$_2$ (at C$_3$) group, formed on condensation of the thiosemicarbazide, is confirmed in the ^{1}H NMR spectra (and ^{13}C spectra, *vide infra*) by the appearance of two doublets at ~2.8 ppm (Table 2). The signals corresponding to the N*H* groups appear at approximately 10 and 12 ppm and the N*H*$_2$ groups at 7–8.5 ppm (Table 2). The assignment of N*H* and N*H*$_2$ is consistent with results found for 2,3-butanedione and pyruvaldehyde N(4)-substituted *bis*TSCs [6,7], and the assignments for the carbohydrate moieties are very similar to those reported by Horton [5]. The downfield chemical shifts of N*H* (10–12 ppm) indicate hydrogen bonding with d^6-DMSO.

NMR bidimensional analyses (^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY, ^{13}C COLOC) and NOE-DIFF were carried out for GluTSC in order to define its conformation

Table 1. Colors and elemental analyses (found/calcd) of the *bis*$TSCH_2$s and their nickel(II) and copper(II) complexes

Compound	Color	%C	%N	%H	%S	%M
$GalTSCH_2$	yellow	31.1	27.1	5.3	20.5	—
		31.2	27.2	5.0	20.7	
[Ni(GalTSC)]	dark green	26.5	23.2	3.5	17.9	16.5
		26.3	23.0	3.8	17.6	16.1
$[Cu(GalTSC]\cdot H_2O$	red brown	25.0	21.3	3.8	16.7	16.2
		24.8	21.7	3.6	16.5	16.4
$RibTSCH_2$	yellow	29.7	30.0	4.9	23.3	—
		30.2	30.2	5.0	23.0	
$[Ni(RibTSC)]\cdot H_2O$	dark green	24.2	23.9	3.2	18.4	16.4
		23.8	23.8	3.4	18.1	16.6
$[Cu(RibTSC)]\cdot H_2O$	red brown	19.4	19.8	2.4	14.2	14.6
		19.4	19.4	2.7	14.8	14.8
$GluTSCH_2$	yellow	31.2	27.2	5.2	20.8	—
		31.2	27.2	5.0	20.7	
[Ni(GluTSC)]	dark green	26.2	22.7	3.7	17.7	16.4
		26.3	23.0	3.8	17.6	16.1
$[Cu(GluTSC)]\cdot 2H_2O$	red brown	24.3	20.3	3.1	15.9	15.9
		23.7	20.7	3.4	15.7	15.7

Table 2. ^1H NMR assignments (ppm) of the *bis*$TSCH_2$s[a]

BisTSC	NH	NH_2	H-1	OH	H-(3,3′)
$GalTSCH_2$	10.70(s) 11.67(s)	7.78 7.93 8.38 8.33	7.65(s)	5.43(d) 4.82(d) 4.67(t) $^3J_{OH,H\text{-}4} = 5.1$ Hz $^3J_{OH,H\text{-}5} = 5.7$ Hz $^3J_{OH,H\text{-}6} = 5.7$ Hz	2.96(d.d) 2.68(d.d) $^2J_{3,3'} = 13.3$ Hz $^3J_{3,4} = 3.4$ Hz $^2J_{3',4} = 8.6$ Hz
$RibTSCH_2$	10.83(s) 11.68(s)	7.83 7.93 8.38 8.42	7.66(s)	5.74(d) 4.91(t) $^3J_{OH,H\text{-}4} = 3.9$ Hz $^3J_{OH,H\text{-}5} = 5.6$ Hz	2.95(d.d) 2.68(d.d) $^2J_{3,3'} = 13.7$ Hz $J_{3,4} = 2.9$ Hz $^2J_{3',4} = 7.5$ Hz
$GluTSCH_2$	10.70(s) 11.70(s)	7.71 7.92 8.33 8.37	7.70(s)	5.56(d) 4.92(d) 4.58(t) $^3J_{OH,H\text{-}4} = 5.5$ Hz $^3J_{OH,H\text{-}5} = 4.5$ Hz	3.02(d.d) 2.58(d.d) $^2J_{3,3'} = 13.7$ Hz $^3J_{3,4} = 2.3$ Hz $^2J_{3',4} = 8.6$ Hz

[a] H(4,5,6) are in the range $d = 3.2$–3.8 for the three *bis*TSCs.

and make a complete assignment of the signals of these *bis*$TSCH_2$s. The ^1H–^1H COSY spectrum of GluTSC confirms that the signals corresponding to NH_2 appear at 8.33 and 8.37 ppm, and couple with the NH protons at 11.68 and 10.68 ppm, respectively. The partial double bond character between the 8–9–10 and 8′–9′–10′ atoms (Fig. 1) is not the cause of such interaction, since it was not observed between the NH protons and the NH_2 protons at 7.71 and 7.92 ppm. A $^{13}C_{9(9')}$–$^1H_{8(8')}$ correlation in the ^{13}C–^1H COLOC spectrum, was observed between the 178.7–10.68 and 178.3–11.68 signals, assuming $^2J_s = C—N—H = 6$ Hz. NOE between $^1H_8$ and $^1H_3$ (at 2.58 ppm) and $^1H_{8'}$ and $^1H_1$ protons was observed. These results suggest that both thiosemicarbazone moieties are arranged in an E conformation, as shown in Fig. 2.

In order to confirm the conformational characteristics of this compound, semi-empirical AM1 calculations were performed. The AM1 optimized geometry shows that the interatomic distances between the protons H_1–$H_{8'}$, H_3–H_8 and H_1–H_3 are less than 3 Å. Therefore, these results are in complete agreement with the NMR results, except in the case of the last pair of protons. The fact that the H_1–H_3 protons do not present NOE suggests a free rotation through the C_1–C_2 bond. This was confirmed using a

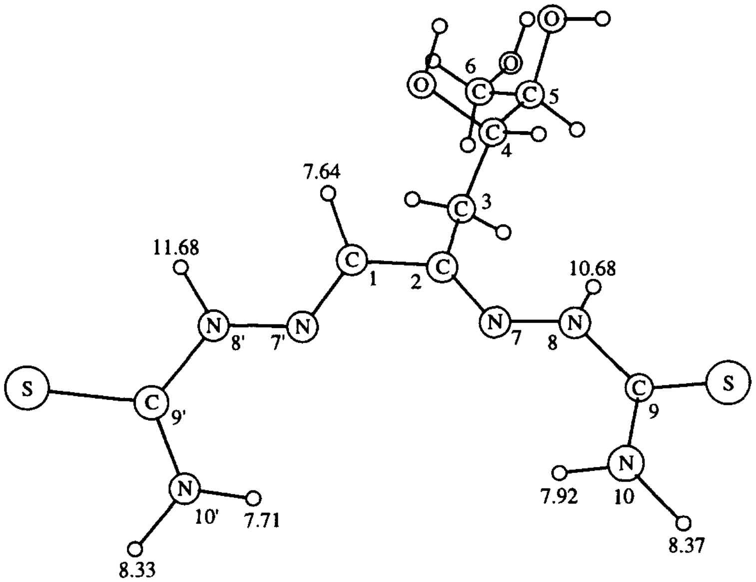

Fig. 2. 3-deoxy-D-erythro-hexos-2-ulosebis(thiosemicarbazone) (GluTSCH$_2$).

Reaction Path Coordinate calculation by which an energy difference of 1.2 Kcal/mol between the cis and trans conformers was obtained, with a rotational barrier of 3.3 Kcal/mol. Nevertheless, no free rotation is possible through the $C_{9(9')}$—$N_{8(8')}$ bond since a rotational barrier of 11.2(3) Kcal/mol was obtained for both thiosemicarbazone moieties. Therefore, the most stable isomer corresponds to that represented in Fig. 2, with both sulfur atoms oriented outward. This result agrees with the structure determined by single crystal X-ray diffraction for 2,3-butane *bis*(piperidinylthiosemicarbazone) [6].

A detailed assignment of the signals corresponding to the protons and carbon atoms in the carbohydrate moieties was also achieved, as shown in Tables 2 and 3. The fact that the sulfur atoms are directed outward explains why the free *bis*TSCH$_2$s are much less water soluble than their metal complexes, because the metal coordination fixes the position of the sulfur atoms inward. The greater water solubility of the complexes is suggested on the basis of calculation of the dipole moments for the two conformations of *bis*GluTSCH$_2$. For the conformation with the sulfur atoms inwards $m_D = 9.1$ D, while for the other conformer $m_D = 1.4$ D.

The N(2)*H* signals in the ^{1} NMR spectra of the nickel(II) complexes disappear, indicating the dissociation of these protons on coordination resulting in a $N_2S_2^{2-}$ ligand. The other main characteristic of the NMR spectra of the Ni^{II} complexes is in the NH_2 protons for which only two broad signals appear at slightly higher fields (i.e. 7.5 and 7.6 ppm) compared to the uncoordinated *bis*TSCH$_2$s. A significant shift to lower fields is observed for the C_1 and C_2 resonances in the ^{13}C spectra of the nickel(II) complexes compared to the *bis*TSCH$_2$s. This is due to the deshielding effect of coordination via the two azomethine nitrogen atoms of the two TSC moieties. The C_9 and $C_{9'}$s atoms are shifted only slightly, which is similar to the results for other *bis*TSCH$_2$s [6,7], and probably attributable to considerable back π-bonding by the nickel(II). Also, the resonances for C_3, which are positioned far upfield and consistent with loss of oxygen during the reduction, are shifted to lower field on complexation. Even though C_3 is β to noe of the coordinating nitrogens, its shift is larger compared to the $C_{9'}$ which are α to the coordinating sulfur atoms. Further, the effect of coordination is seen (Table 3) along the monosaccharide chain with alternating shifts to lower and higher field (i.e. C_4, C_5 and C_6) with the magnitude of the shifts diminishing with distance from C_2.

Table 3. ^{13}C NMR assignments (ppm) of the *bis*TSCH$_2$s and their nickel(II) complexes

Compound	C_9=S	$C_{9'}$=S	C_1=N	C_2=N	$C_4C_5C_6$	C_3
GalTSCH$_2$	178.8	178.4	142.3	149.3	70.0; 73.0; 62.0	29.3
[NiGalTSC]	180.4	178.5	146.1	156.6	68.9; 75.0; 63.0	31.9
RibTSCH$_2$	178.4	178.0	142.0	148.7	70.5; 64.9	29.1
[NiRibTSC]	180.4	178.5	146.0	155.9	68.7; 65.7	32.1
GluTSCH$_2$	178.7	178.3	142.1	149.6	70.8; 74.6; 62.9	28.7
[NiGluTSC]	180.4	178.5	145.6	156.3	67.8; 73.7; 62.4	31.9

Table 4. Electronic (H_2O, solid) and IR spectral assignments (cm^{-1}) of the *bis*TSCH_2s and their nickel(II) and copper(II) complexes

	UV–vis (log ε)		IR	
Compound	Intraligand and charge transfer	ν(d–d)	$\nu(CN)+\delta(NH_2)$	ν(CS)
GalTSCH_2	30000 (5.19)	—	1610	835
NiGalTSC	38500 (4.61) 25300 (4.28)	15270 (2.79)	1627, 1560	775
solid		17540 13530		
GuGalTSC	39800 (4.20) 32900 (4.38)	21460 (3.77)	1620, 1614, 1582	780
solid		20280 15800		
RibTSCH_2	30100 (5.01)	—	1610	830
NiRibTSC	38900 (4.45) 25400 (4.01)	15240 (2.99)	1622, 1603, 1565	780
solid		16950 13850		
CuRibTSC	39800 (4.06) 32800 (427)	21410 (3.71)	1640, 1600, 1565	785
solid		20280 18730 16080		
GluTSCH_2	30200 (4.91)	—	1640, 1600	830
NiGluTSC	38900 (4.27) 25400 (3.84)	15310 (2.55)	1640, 1560	775
solid		17240 13890		
CuGluTSC	39700 (4.26) 32900 (4.38)	21410 (3.77)	1620, 1582, 1570	780
solid		20830 16780		

UV spectra

In the UV spectra of the three *bis*TSCH_2s in DMSO (Table 4) only one band is observed at ~28,300 cm^{-1} (log ε ~ 5). This greatly resembles the UV band reported for H_2KTS at 27,800 cm^{-1} [2] and is a combination of the $n \rightarrow \pi^*$ transitions of the azomethine and thione portions of the two thiosemicarbazone moieties. On complexation a portion, based on the lower molar absorptivities in the complexes, of the $n \rightarrow \pi^*$ combination band of the uncomplexed *bis*(thiosemicarbazones) shifts to higher energy (i.e. *ca* 39,000 cm^{-1}). The higher energy band is likely due to the azomethine $n \rightarrow \pi^*$ transition and the thione $n \rightarrow \pi^*$ band evidently merges with a $S \rightarrow M^{II}$ charge transfer band for both the copper(II) and nickel(II) complexes at *ca* 32,000 cm^{-1} and 25,000 cm^{-1}, respectively. The energies and intensities of the $d \rightarrow d$ bands are typical for planar N_2S_2 for both the nickel(II) and copper(II) complexes (Table 4) [6,7]. For example, no $d \rightarrow d$ transitions were detected below 10,000 cm^{-1} for the nickel(II) complexes, which suggests planar stereochemistry. In solution we were able to identify only a single band for each complex, but solid state mulls allowed observation of more than one $d \rightarrow d$ band for the copper(II) complexes and showed two bands (i.e. *ca* 17,000 and 13,500 cm^{-1}) for the nickel(II) complexes. These solid state spectra are similar to the spectra found for the complexes of 2,3-butanedione and pyruvaldehyde N(4)-substituted thisemicarbazones [6,7].

IR spectra

The IR spectra of the *bis*TSCs show a band at ~830 cm^{-1} (Table 4), assignable to the thioamide IV band, which is the only band involving ν(C═S) that is easily assignable in these spectra. In the spectra of the metal complexes, the thioamide IV vibration shifts to lower frequencies indicating loss of double bond character and coordination via the thiolato sulfurs. The ν(C═N) vibration region is complicated by the appearance of a second band due to $\nu\{N{=}C(S)\}$.

Compared to ν(C═N) in the free ligand, the $\nu\{N{=}C(S)\}$ band is usually found at slightly higher energies (i.e. 1590–1605 cm^{-1}) [6] in the complexes. Thus, we assign the band due to ν(C═N) in the 1560–1582 cm^{-1} in the spectra of the complexes, consistent with previous studies [6,7]. The metal ligand bands, ν(MN) and ν(MS), are found in the 450 and 340 cm^{-1} regions, respectively, consistent with results of other *bis*TSC complexes [6,7].

Electron spin resonance spectra

The ESR parameters obtained for the polycrystalline samples at room temperature and 77 K are

Table 5. Powder ESR spectral parameters of the copper(II) complexes of the *bis*TSCH$_2$s

Compound	Temp	g_1	g_2	g_3	g_{iso} or g_{av}	G
[CuGalTSC]	R*T*	—	—	—	2.055	
	77K	—	—	—	2.052	
[CuRibTSC]	R*T*	2.109	2.047	2.032	2.063	2.8
	77K	2.102	2.047	2.026	2.058	2.8
[CuGluTSC]	R*T*	2.112	2.048	2.022	2.061	3.2
	77K	2.122	2.047	2.018	2.062	3.7

presented in Table 5. The spectra recorded at 77 K are very similar to the room temperature spectra indicating no significant change in stereochemistry. The broad isotropic feature found for solid CuGalTSC suggests a significant interaction between copper(II) centers. The powder ESR spectra of CuRibTSC and CuGluTSC have a rhombic distortion with $g_1 > g_2 > g_3 > 2$ indicative of complexes with a $d_{x^2-y^2}$ ground state. The rhombic signal is probably a consequence of the bulkiness of the carbohydrate moiety, as well as its tendency to form intermolecular hydrogen bonds. In such cases the g-values can be related by the expression $G = (g_{\parallel}-2)/(g_{\perp}-2)$ assuming $g_1 = g_{\parallel}$ and $(g_2+g_3)/2 = g_{\perp}$) [8]. As expected, G is less than four (Table 5) for the two complexes with resolved spectra indicating that exchange interaction between the copper centers is considerable in the polycrystalline solid. This is consistent with weak bridging by the coordinated sulfur atoms to neighboring copper(II) centers that is common to 4-coordinate copper(II) complexes containing sulfur [6,7]. The larger interaction is observed for CuRibTSC, which could be due to it having the smaller carbohydrate moiety.

The ESR parameters in DMF solution are very similar for the three compounds (*ca* $g_0 = 2.060$ at room temperature and $g_{\parallel} = 2.134$ and $g_{\perp} = 2.026$ at liquid nitrogen temperature). However, the frozen DMF g-values are different from those found for the powder compounds, suggesting significant axial interaction with the DMF molecules (i.e. the larger values for $g_{\parallel}$ compared to the powder g_1 values indicate even greater axial bonding in the frozen solution). All the copper(II) spectra have four well defined copper hyperfine lines (*ca* $A_0 = 89$ G at room temperature and $A_{\parallel} = 175$ G and $A_{\perp} = 35$ G, $A_{av} = 82$ G in frozen solution) and five superhyperfine lines (1 : 2 : 3 : 2 : 1) due to two nitrogen donor atoms $\{A_{iso}(\mathrm{N}) = 14.5$ G at room temperature, $A(\mathrm{N}) = 13$ G and $A(\mathrm{N}) = 16$ G in frozen solution$\}$. In methanol similar well resolved spectra were also recorded. A typical ESR spectrum at room temperature in DMF is shown in Fig. 3. The covalency parameter, $\alpha^2 \approx 0.6$, for these complexes suggests appreciable covalent character in the metal-ligand bonds. Also indicating extensive covalency are the Racah parameters of $k_{\parallel} = 0.55$ and $k_{\perp} = 0.62$ for [Cu(gluTSC)], which indicate that in-plane π-bonding is more important than out-of-plane π-bonding.

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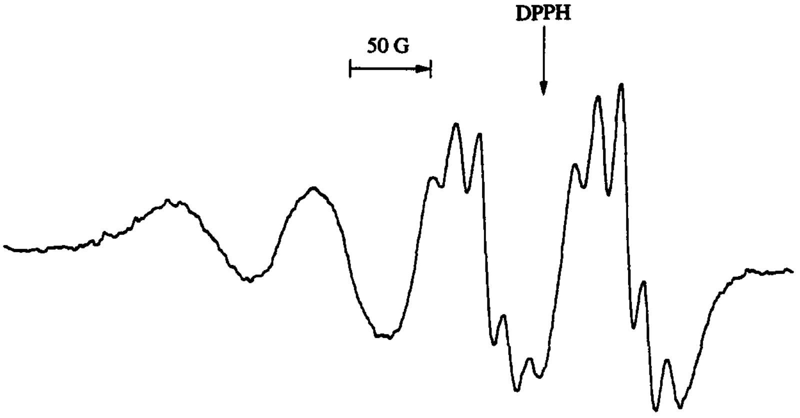

Fig. 3. Room-temperature X-band ESR spectrum of CuGalTSC in DMF.

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