Interaction of Co^{II}, Ni^{II} and Cu^{II} with Active Aldehyde Derivatives of Thiamine†

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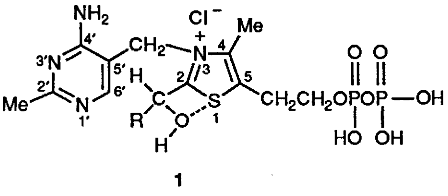
The reactions of the chloride salts of Co^{II}, Ni^{II} and Cu^{II} with the 'active aldehyde' derivatives of thiamine, 2-(α-hydroxybenzyl)- and 2-(α-hydroxycyclohexylmethyl-3-(4-amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium (hbt and hcmt), were studied in methanolic solutions. Compounds of formulae [Co(hbt)Cl$_3$], [Co(hcmt)Cl$_3$], [Ni(hbt)Cl$_3$]·2H$_2$O, [CuL′Cl$_2$]·H$_2$O and Cu$_2$(HL′)Cl$_4$·MeOH (L′ = thiochrome) were isolated as solid adducts and characterized by elemental analysis conductivity, magnetic susceptibility, IR, UV/VIS and ESR spectra. Pseudo-tetrahedral structures with the metal co-ordinated through the N(1′) site of the ligands are proposed for the first three complexes. Both copper complexes contain thiochrome produced by oxidation of thiamine by Cu^{II} and the first one is proposed to have a pseudo-tetrahedral structure with the metal again bonded through N(1′), while the second is proposed to be a mixed-valence compound, with possible formula [Cu^{I}(HL′)Cl]$^+$[Cu^{II}Cl$_3$(MeOH)]$^-$.

The active aldehyde derivatives of thiamine pyrophosphate, **1** are intermediates formed during its enzymatic action.[1–3]. It is known to catalyse either the decarboxylation of α-ketoacids or the formation of α-ketols.[4] For the enzymatic action of **1** *in vivo*, magnesium(II) ions are required.[4] Various other bivalent metal ions like Co^{II}, Zn^{II}, Cd^{II} and Ni^{II} are also known to be active *in vitro*.[4] In early solution studies [5–9] the bivalent metal ions were proposed to bind either through N(1′) of the pyrimidine moiety or the pyrophosphate group, linking the coenzyme with the substrate.

The first solid adducts prepared with thiamine and its phosphate esters involving a direct M–N(1′) bond were with Pt^{II} and Pd^{II} and their formation was explained as due to the high strength of these bonds.[10] Earlier attempts to prepare similar solid adducts [11–14] with various bivalent metal ions resulted in the formation of ionic salts of the type $[L]^{2+}[MX_4]^{2-}$, $[L]^{2+}[MX_3]^-{}_2$ or $[L]^+{}_2[MX_4]^{2-}$ (L = thiamine), due to the net positive charge on the ligand at N(3) and its easy protonation at N(1′) ($pK_a \approx 5$).[15]

Although there exist today eight crystal structure determinations of thiamine compounds involving direct metal–ligand bonds,[16–23] with the metal ions Pt^{II}, Rh^{II}, Zn^{II}, Cd^{II}, Cu^{II}, Co^{II} and Cu^{I}, the formation of such complexes is still not easy, thus not allowing the role played by the metal ions in the enzymatic reactions of thiamine to be known with certainty.

In the active aldehyde derivatives of thiamine on the other hand the positive charge on N(3) is partially delocalized on the sulphur atom of thiazole, which interacts with the oxygen atom of the substituent at C(2)[24,25] ($S^+ \cdots O^- < 3$ Å). In this way, the net positive charge of thiamine is partially neutralized. Working at a pH near the pK_a (≈ 5) of the N(1′) site, we should expect the easier formation of metal complexes with these ligands. This is in fact what was qualitatively found in the interaction of Zn^{II}, Cd^{II} and Hg^{II} with the active aldehyde derivatives 2-(α-hydroxybenzyl)- and 2(α-hydroxycyclohexylmethyl)-3-(4-amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium (hbt and hcmt), with the metals bound through the N(1′) site.[26]



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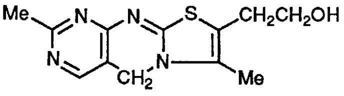
R = Ph or C$_6$H$_{11}$



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Continuing our studies on interactions of bivalent metal ions with the same derivatives of thiamine, hbt and hcmt, we report here their interactions with Ni^{II}, Co^{II} and Cu^{II}. Contrary to Co^{II} and Ni^{II} which form the usual MLCl$_3$ zwitterionic type complexes,[10,17,18,20,25,26] Cu^{II} oxidizes both ligands to thiochrome {2-(2,7-dimethyl-5*H*-pyrimido[4,5-*d*]thiazolo[3,2-*a*]pyridin-8-yl)ethanol} **2**, being reduced to Cu^{I}.[18,22]

Experimental

Methods.—The elemental analysis of the metals and chlorine were performed in our laboratory by complexometric and potentiometric titrations; analyses of C, N and H were carried out in the Analytical Laboratory of the University of Dortmund. Conductivity measurements were performed in a Metrohm E365 B Conductoscope. The magnetic susceptibility measurements were made by the Faraday method using

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† *Non-SI unit employed:* G = 10^{-4} T.

Table 1 Elemental analysis, molar conductance and magnetic susceptiblity data for the complexes

		Analysis (%)[a]						
Compound	Colour	M	Cl	C	N	H	Λ_M[b]/ S cm^2 mol^{-1}	μ_{eff}
$[Ni(hbt)Cl_3]\cdot 2H_2O$	Blue	10.5	18.1	40.1	9.5	4.5	17.2 (dmf)	3.96
		(10.3)	(18.6)	(39.9)	(9.8)	(4.7)	330.4 (water)	
$[Co(hbt)Cl_3]$	Blue	11.5	20.6	42.3	10.6	4.4	44.1 (dmf)	4.70
		(11.0)	(19.8)	(42.5)	(10.4)	(4.3)	335.2 (water)	
$[Co(hcmt)Cl_3]$	Blue	10.9	19.1	43.5	10.5	5.4	38.4 (dmf)	4.32
		(10.9)	(19.6)	(43.3)	(10.6)	(5.5)	292.8 (water)	
$[CuL'Cl_2]\cdot H_2O$	Dark green	14.6	17.5	34.5	13.0	3.5	17.8 (dmf)	2.21
		(15.3)	(17.1)	(34.7)	(13.5)	(3.9)	227.5 (water)	
$Cu_2(HL')Cl_4\cdot MeOH$	Yellow	22.1	25.8	27.7	9.8	3.1	71.1 (dmf)	0.65
		(22.5)	(25.2)	(27.7)	(9.9)	(3.4)	—	

[a] Calculated values are given in parentheses. [b] 10^{-3} mol dm^{-3} concentrations of the compounds were used; solvent in parentheses.

Table 2 Crystal-field parameters *Dr* for the Co^{II} complexes

	Energy (10^3 cm^{-1})			
Complex	A_2	E	Δ*	*Dr*
$[Co(hbt)Cl_3]$	5.21	7.06	1.85	0.185
$[Co(hcmt)Cl_3]$	5.14	6.97	1.83	0.183

* Energy difference for $^4E(T_2, P) \longleftarrow {}^4A_2(T_1,F)$, with the E bands the average of the two maxima.

$Hg[Co(NCS)_4]_2$ as reference. The IR spectra were recorded on a Perkin-Elmer model 580 spectrophotometer. The diffuse reflectance spectra were recorded on a Bausch Lomb Shimadzu spectronic 210 UV spectrophotometer, fitted with a standard reflectance attachment and spectroscopic grade MgO in the reference beam, at room temperature; also in a Cary 14 spectrophotometer as KBr pellets. Solution ultraviolet-visible spectra were recorded on a Hitachi 100-70 and on a Cary 14 spectrophotometer, using 1 cm rectangular quartz cells. The ESR spectra were obtained on a Varian Y-4502 spectrometer.

Preparation of the Ligands.—These were prepared according to the literature.[27]

Preparation of the Complexes $MLCl_3$ (M = Ni^{II} *or* Co^{II}, L = hbt *or* hcmt).—These blue complexes were prepared in a similar manner to that used for the analogous complexes of Zn^{II}, Cd^{II} and Hg^{II} already described, in alcoholic solutions.[26] Yields were 40–50%. The complex $[Ni(hcmt)Cl_3]$ could not be obtained free of KCl, NaCl or $[NMe_3H]Cl$.

Reactions of Cu^{II} *with* hbt *and* hcmt.—The reactions of $CuCl_2$ with equimolar amounts of both ligands (1 mmol), following the same neutralization procedure as described,[26] resulted in the formation of yellow compounds of stoichiometry $Cu_2(HL')Cl_4\cdot MeOH$ (L′ = thiochrome) in 20% yield. Under an ordinary atmosphere a green compound of formula $[CuL'Cl_2]\cdot H_2O$ was isolated in 40% yield.

Results and Discussion

The elemental analysis of the compounds (Table 1) isolated agree with the assigned formulae. Molar conductance values in dimethylformamide (dmf) solutions of the compounds $[Co(hbt)Cl_3]$, $[Co(hcmt)Cl_3]$, $[Ni(hbt)Cl_3]\cdot 2H_2O$ and $[CuL'Cl_2]\cdot H_2O$ are less than those corresponding to 1:1 electrolytes.[28] However, they increase with time indicating the replacement of more chlorides by dmf molecules. The compound $Cu_2(HL')Cl_4\cdot MeOH$ is a 1:1 electrolyte in dmf solutions. On the other hand, in aqueous solutions the replacement of the chloride takes place much faster by water molecules and the measured Λ_M values correspond to 1:3 electrolytes for the first three compounds and 1:2 for $[CuL'Cl_2]\cdot H_2O$.

The room-temperature magnetic susceptibilities of all the compounds except $Cu_2(HL')Cl_4\cdot MeOH$ are as expected for pseudo-tetrahedral structures. The value of $\mu = 0.65$ per Cu atom for the last complex, however, suggests either that one of the copper atoms is diamagnetic or that a metal–metal interaction may be present.[29]

The IR spectra of the two complexes of Ni^{II} and Co^{II} with hbt and that of Co^{II} with hcmt are completely identical (band by band) with those of the corresponding complexes of Zn^{II}, Cd^{II} and Hg^{II}, except for the metal–ligand bands.[26,30] They are therefore expected to be isostructural, corresponding to an *S* configuration of the ligands and direct M–N(1′) bonding, as in the case of the complex $[Hg(hbt)Cl_3]$.[26,30]

Both complexes $Cu_2(HL')Cl_4\cdot MeOH$ and $[CuL'Cl_2]\cdot H_2O$, on the other hand, show only one band at 1610 cm^{-1}, not removed upon deuteriation, which is therefore due to a ring stretching ν(C=N) of the pyrimidine ring. This implies the absence of an NH_2 group in these complexes. The bands at 3370 and 3400 cm^{-1} for these two complexes can be assigned to a co-ordinated water and to an NH imino group respectively. The compound $Cu_2(HL')Cl_4\cdot MeOH$ presents one additional band at 750 cm^{-1}, removed upon deuteriation, and assigned to an out-of-plane NH deformation.[31]

The bands at 260 and 295 cm^{-1} of the complex $Cu_2(HL')Cl_4\cdot MeOH$ may be assigned to ν(Cu–Cl) of an anionic $CuCl_3$ species.[11,32] The complexes $[HL]^+[CuCl_3(H_2O)]^-$, (L = *N,N′*-bimethylpiperazine or 2-aminopyridine) with a square-planar structure around Cu^{II} show bands near 310–320 and 265–275 cm^{-1}, tentatively assigned to the *trans* equatorial ν(Cu–Cl) vibrations, and to the ν(Cu–Cl) *trans* to the co-ordinated water molecule.[26] The present bands are analogously assigned. That at 320 cm^{-1}, of $Cu_2(HL')Cl_4\cdot MeOH$ could also be assigned to ν(Cu–Cl) of a CuL_2Cl_2 species[11] [L = 5-(2-hydroxyethyl)-4-methylthiazole] or to ν(Cu^I–Cl). The bands at 424 cm^{-1} of the remaining complexes suggests a pseudo-tetrahedral environment around the metals.

The diffuse reflectance and dmf solution spectra of the cobalt(II) complexes are in accord with pseudo-tetrahedral structures, as the splitting of the bands near 16 000 cm^{-1}, assigned to $^4A_2(T_1,P) \longleftarrow {}^4A_2(F)$, show (reduction of T_d to C_{3v} symmetry).[31,32] The same is true for the $[Ni(hbt)Cl_3]$ complex.

The crystal-field parameter *Dr* for the cobalt(II) complexes is a measure of the trigonal distortion from tetrahedral geometry and is obtained from the energy difference between the $^4E(T_1,F)$ and $^4A_2(T_1,F)$ states.[33,34] The present results are given in Table 2. They suggest that both complexes of Co^{II} show only a small trigonal distortion, compared to those with other similar ligands.[33,34]

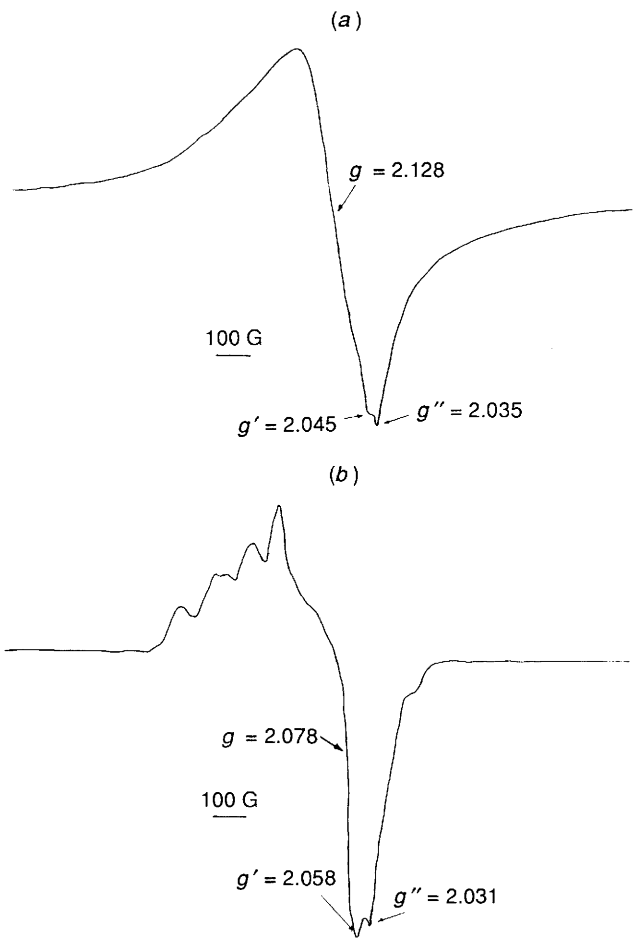

Fig. 1 (a) Powder ESR spectrum of the compound $Cu_2(HL')Cl_4 \cdot MeOH$ at 295 K and (b) ESR spectrum of the same compound in frozen dmf–toluene solution at 90 K

The complex $[CuL'Cl_2] \cdot H_2O$ shows a band at 13 680 cm^{-1} in the diffuse reflectance spectrum, assigned to the $^2T_2 \longleftarrow {}^2E$ transition of a distorted-tetrahedral environment.[11,32] Additional very weak bands observed in the near-IR region support this interpretation.[32,35] The band of this complex at *ca.* 20 500 cm^{-1} is assigned to a charge-transfer ($Cu^{II} \leftarrow Cl^-$) transition, at lower frequencies than that of $CuCl_4^{2-}$.[36]

The complex $Cu_2(HL')Cl_4 \cdot MeOH$, on the other hand, presents three distinct maxima in dmf solutions, at 6460, 7000 and 9800 cm^{-1}, assigned to the $^2E \longleftarrow {}^2B_2$, $^2B_1 \longleftarrow {}^2B_2$ and $^2A_1 \longleftarrow {}^2B_2$ transitions, in a D_{2d} 'flattened' tetrahedral geometry.[32,35] The charge-transfer band ($Cu^{II} \leftarrow Cl^-$) is observed near 22 000 cm^{-1}. This may indicate the presence of a $CuCl_3^-$ species in this complex, since this wave number is higher than for $[CuL'Cl_2] \cdot H_2O$, but lower than for $CuCl_4^{2-}$.[36]

Both complexes $[CuL'Cl_2] \cdot H_2O$ and $Cu_2(HL')Cl_4 \cdot MeOH$ show a band near 27 000 cm^{-1} due to the presence of thiochrome, which itself presents a band at 27 000 cm^{-1} (369 nm).[37] This band does not exist in the spectra of the other complexes.

The powder ESR spectrum of $[CuL'Cl_2] \cdot H_2O$ is almost isotropic. It shows almost no temperature dependence with $g = 2.160$ at 295 K and $g = 2.158$ at 100 K. Similar spectra were found in frozen dmf–toluene solutions. The absence of any band in the regions of 1600 and 4600 G suggests a monomeric nature for this compound.[38,39]

The powder ESR spectrum of $Cu_2(HL')Cl_4 \cdot MeOH$ is also nearly isotropic with a main g value of 2.128 at 295 K and 2.129 at 100 K. More peaks are observed near the main g value ($g' = 2.045$ and $g'' = 2.035$ in the 295 K spectrum). In frozen dmf–toluene solutions the main g value is found at 2.078 at 90 K with additional peaks, $g' = 2.058$ and $g'' = 2.031$ (see Fig. 1). The additional g values may indicate the presence of a second weak paramagnetic nucleus. Here again there were no bands near 1600 and 4600 G, characterizing dimers.[38,39]

Based on the above experimental data a pseudo-tetrahedral structure, with the three chloride ions and the ligand [bonded through N(1′)] around the metals, may be proposed for the complexes $[Co(hbt)Cl_3]$, $[Co(hcmt)Cl_3]$ and $[Ni(hbt)Cl_3]$ and *S* configurations for the ligands.[26,30] The structure of the two copper complexes, on the other hand, involves thiochrome, most probably co-ordinated to the metal again *via* the N(1′) site. Of these, $[CuL'Cl_2] \cdot H_2O$ most probably has a pseudo-tetrahedral structure, while $Cu_2(HL')Cl_4 \cdot MeOH$ is a mixed-valence compound, containing independent copper-(I) and -(II) species, and may best be formulated as $[Cu^I(HL')Cl]^+[Cu^{II}Cl_3(MeOH)]^-$ with the $[Cu^{II}Cl_3(MeOH)]^-$ moiety corresponding to a 'flattened' tetrahedral D_{2d} structure.

Furthermore, the present study confirms again the more facile formation of complexes of first-row transition metals active *in vitro*[4] with the active aldehyde derivatives of thiamine than with thiamine itself,[11–14,26,30] bonded through the N(1′) site. The easy loss of the substituent group at the C(2) position of thiazole in hbt and hcmt in their reactions with Cu^{II}, resulting in oxidation to thiochrome, also supports the hypothesis of the intervention of the bivalent metal ions in the enzymatic action of thiamine, after the formation of the 'active aldehyde' intermediates.[26]

Finally, the isostructural nature of the copper(II) and nickel(II) compounds, to those of the Group IIB metals, with the ligands in the *S* configuration once more points out the importance of this conformation in the liberation of the C(2) substituent to form the final product (aldehyde), following the formation of the M–N(1′) bonding.[26]

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