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Solution and Solid-State Structural Study of the Copper(II) Complex of Diazepam

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The complex $Cu(L)_2Cl_2$ (L = 7-chloro-1,3-dihydro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-one, also known as diazepam) has been prepared and studied in solution and solid states. The complex crystallizes in the trigonal system (space group $R\bar{3}$) with a = 18.645 (2) Å and α = 117.52 (1)°. The structure was resolved by using 2594 reflections, by difference Fourier techniques, to a final R of 0.045, by least-squares refinement using anisotropic thermal parameters. The formula unit is $Cu(L)_2Cl_2(H_2O)_2 \cdot 0.33CHCl_3$. The metal atom is in a square-planar environment, coordinated to two nitrogens from the ligands (Cu–N = 1.990 (8) Å) and two chlorine atoms in a trans geometry (Cu–Cl = 2.27 (20) Å). The boat conformation of the seven-membered ring is maintained in the complex. The EPR and ^{13}C NMR results support a similar coordination of the Cu^{2+} ion in solution as that found in the solid state. The relation between the solid-state features and the solution properties is discussed.

Introduction

Among the 1,4-benzodiazepin-2-ones, one of them, commercially distributed as Valium, is widely prescribed for its high biological activity (see Figure 1). This class of psychotherapeutic drugs is extensively studied and used for its tranquillizing and sedative-hypnotic properties. Their muscle relaxant and anticonvulsant effects are also of current interest.

Research on the chemistry of this class of tranquillizers is active,[1,2] and recent work tries to relate molecular structures and biological activities.[2-4] It is widely accepted that geometrical factors can determine the chemical reactivity and resultant pharmalogical activity of compounds containing lactam rings.[5-10] In this respect, crystal and molecular structures of several 1,4-benzodiazepin-2-ones have been determined[4,10-14] and showed that the seven-membered rings retain similar boat conformations.

However, interactions between these drugs and metal ions have scarcely been investigated.[15] Nevertheless, it is well documented that metal complexes of ligands possessing biological activity are more active than the free ligands.[16,17] We now report on the coordinating behavior of diazepam in solution and solid state. In particular, the complexation effects of copper(II) on the conformation of the diazepin ring is discussed.

Experimental Section

Materials. The ligand diazepam (L), kindly supplied by Roche, was high purity grade and was used without further purification.

Preparation and Analysis. The X-ray sample has been obtained from a chloroform solution of stoichiometric amounts of the ligand (L) and hydrated copper chloride (2:1). Anal. Calcd for $CuC_{32}H_{26}O_2 \cdot 2(H_2O) \cdot 0.33(CHCl_3)$: Cu, 8.15; C, 50.25; H, 3.33; N, 7.28; Cl, 22.73. Found: Cu, 7.94; C, 51.28; H, 3.82; N, 7.59; Cl, 22.50.

NMR Study. The ^{13}C NMR study was carried out on 0.5 M $CDCl_3$ solutions of L with a variable metal ion concentration. The NMR spectra were recorded on a WH 90 Brucker spectrometer working at 22.62 MHz under standard conditions (^1H broad-band decoupling, spectrum width = 6000 Hz, number of scans varying between 5000 and 6000, 8K memory). The chemical shift values ($\delta C(i)$) are expressed in ppm relative to tetramethylsilane; a positive shift corresponds to an increase of the resonance frequency.

EPR Study. The EPR spectra were run on freshly prepared $CHCl_3$ solutions of $CuCl_2$ and L, using a flat quartz sample cell for liquid solutions. Low-temperature spectra were obtained as previously described.[18] All spectra were recorded on Varian E-9 or century series.

Crystallographic Study and Data Collection. The crystal of Cu(diazepam)$_2Cl_2(H_2O)_2 \cdot 0.33CHCl_3$ used for the X-ray study was mounted at the end of a glass fiber. Examination of this crystal by precesion methods using Kα radiation showed that it crystallizes in the trigonal system. Since no systematic absence was observed with rhombohedral axes, the possible space groups are R_3, $R\bar{3}$, $R32$, $R3m$, $R\bar{3}m$.

Cell constants and corresponding standard deviations at 24 °C were obtained from a least-squares refinement of the setting angles of 25 reflections automatically centered on an Enraf-Nonius CAD4 computer controlled diffractometer. Cell constants are a = 18.645 (2) Å and α = 117.52 (1)°.

Based on a cell volume of 2611 Å^3 and six formula units per cell, the calculated density (1.49 g·cm^{-3}) is in good agreement with that of 1.50 (1) g·cm^{-3} obtained by flotation in bromoethane and 1-iodobutane medium.

Intensity data were collected, at 24 °C, with Mo Kα radiation, in a standard manner for this laboratory,[19] using a value of 0.02 for p, a parameter which prevents overweighing strong reflections.

The structure was solved in the centric $R\bar{3}$ space group by using the rhombohedral axis. The subsequent solution and refinement of the structure confirmed that the choice of the centric $R\bar{3}$ space group is correct. Positions for copper and chlorine atoms (but the ones of the solvent molecules) were deduced from the Patterson map, and these led to completion of the structure by standard difference Fourier and least-squares techniques.[20] Values of the atomic scattering factors and the anomalous terms for the copper and chlorine atoms were from the usual sources[21] and the effects of anomalous dispersion were included in the calculated structure factors.

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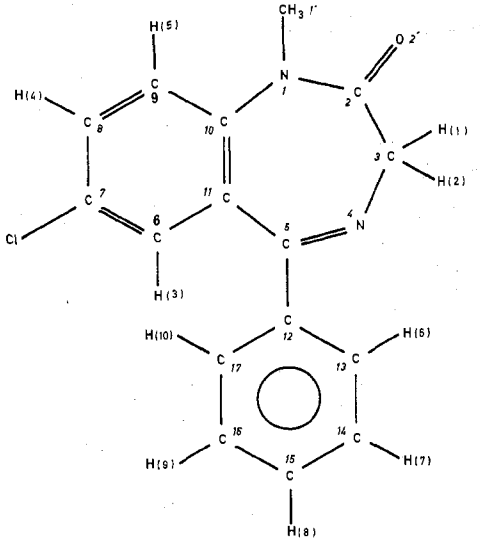

Figure 1. Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-one) = L.

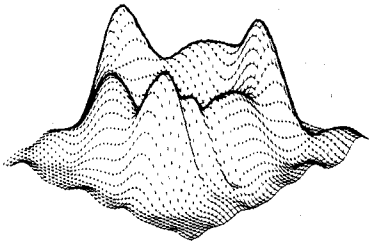

Figure 2. Fourier map showing the disorder of the solvent chlorine atom.

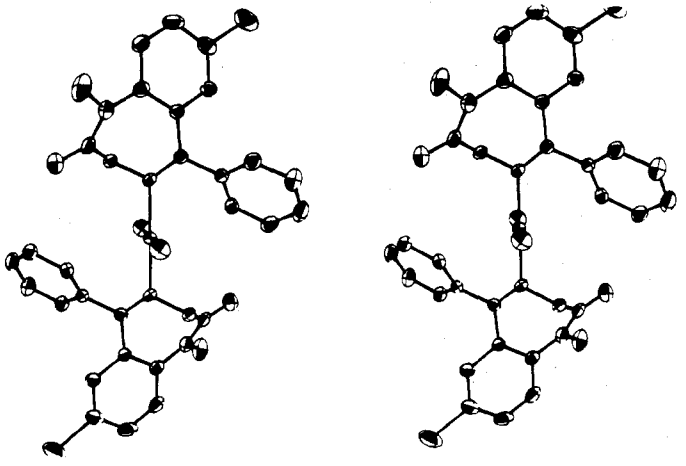

Figure 3. Stereoscopic view of the complex molecule.

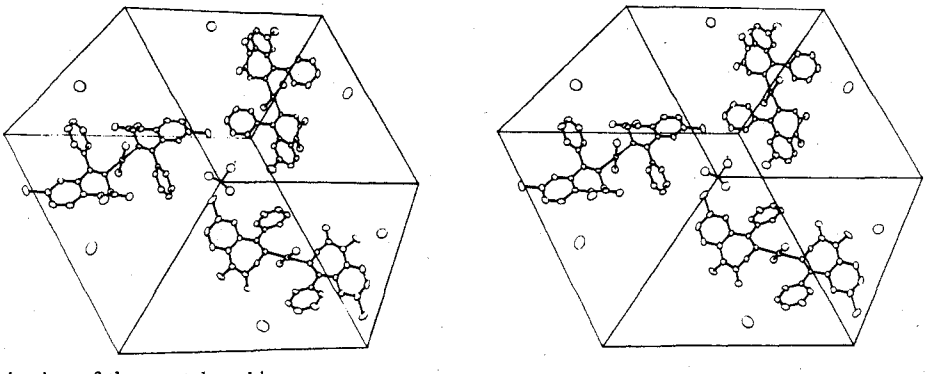

Figure 4. Stereoscopic view of the crystal packing.

At the point where the positions of all atoms, but H, of the Cu(diazepam)$_2$Cl$_2$(H$_2$O)$_2$ moiety were known and refined with isotropic thermal parameters, a least-squares refinement using anisotropic thermal parameters was performed; the values of R and R_w were 0.055 and 0.104.

On the following difference Fourier map, ten of the eighteen hydrogen atoms and the solvent molecule were unambiguously located. The H atoms not found are the water molecules, solvent molecule, and methyl groups. In the next refinement cycle, the hydrogen atoms were introduced with a fixed contribution. The final values of R and R_w are 0.045 and 0.052.

The dimensions of the crystal were 0.6 × 0.4 × 0.4 mm, leading to a μR value of 0.57. So no absorption corrections were made.

The final atomic parameters, together with their standard deviations, are collected in Table I.

The very high value (24 Å^2) of the isotropic thermal parameter obtained for the chlorine atom of the solvent molecule indicates some kind of disorder for this molecule around the ternary axis. A difference Fourier map, performed when we omit the contribution of this molecule, shows an almost continuous electronic distribution around the ternary axis (see Figure 2) with three maxima corresponding to the position used in the final least-squares cycle.

Results and Discussion

Description and Discussion of the Structure. Figure 3 shows a stereoscopic perspective view of the molecule. The ligand is coordinated to the copper atom via its nitrogen atom N(4). The metal atom, which is a center of inversion for the whole molecule, has a square-planar environment being bonded to two nitrogen atoms of the diazepam ligands and two chlorine atoms. Values of bond distances and angles are given in Table II. They are in good agreement with those found for the free diazepam ligand[11] and do not lead to special comments.

It appears that the complexation of the diazepam molecule to the copper atom does not affect markedly its geometry. The most important variation is about the dihedral angle between the phenyl ring which is of 115° instead of 123.3° in the free ligand. The seven-membered ring conformation remains boat type. However, the comparison of torsion angles found for the free ligand and this complex (Table III) shows some interesting facts. The main effect of the complexation of the diazepam molecule is the symmetrization of the ring. Indeed, the boat conformation here is almost perfect as shown from the values of θ_{2-4}, θ_{4-5}, θ_{11-10}, and θ_{1-2} (−0.2°, −1.1°, −4.1°, and −4.7°, respectively).

The structure of the present compound consists of the packing of three molecules of CuL_2Cl_2, six molecules of water, and one solvent molecule (see Figure 4). The crystal cohesion seems to be mainly due to van der Waals interactions. Two hydrogen bonds, between the chlorine atom Cl(1) and the water molecule W(1), could be taken in account (Cl(1)^{i}–W(1)^{ii} = 3.17 Å; Cl(1)^{i}–W(1)^{iii} = 3.21 Å; W(1)^{ii}–Cl(1)^{i}–W(1)^{iii} = 93°). These equivalent positions are as follows: i = x, y, z; ii = $\bar{x}$, $\bar{y}$, $\bar{z}$; iii = $x - 1$, y, z. The shortest distance between diazepam molecules is C(3)^{i}–O(2′)^{iv} = 3.17 Å (iv = $1 + z$, x, y).

Table I. Positional and Anisotropic Thermal Parameters ($\times 10^3$) and Their Estimated Standard Deviations for $Cu(L_2)Cl_2(H_2O)_2 \cdot 0.33CHCl_3$[a,b]

atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cu	0	1/2	1/2	11.3 (2)	11.5 (2)	11.6 (2)	10.1 (1)	10.3 (1)	10.4 (1)
Cl(1)	−0.2525 (1)	0.2389 (1)	0.2510 (1)	11.0 (2)	11.9 (2)	12.3 (2)	9.0 (2)	9.3 (2)	9.4 (2)
Cl(2)	0.4918 (2)	0.6904 (2)	0.6939 (2)	29.5 (4)	33.5 (4)	26.8 (4)	27.0 (4)	24.9 (4)	28.5 (4)
Cl(3)	0.116 (1)	0.049 (1)	0.124 (1)	24.9 (4)[c]					
N(1)	0.4146 (5)	0.1634 (5)	−0.1141 (5)	14.4 (9)	15.6 (9)	16.1 (9)	13.5 (8)	13.8 (8)	13.9 (9)
C(1)′	0.3056 (7)	0.0010 (6)	−0.2575 (6)	16 (1)	9.0 (10)	14 (1)	10.3 (10)	13 (1)	7.5 (10)
C(2)	0.4928 (6)	0.2668 (7)	−0.0859 (7)	15 (1)	18 (1)	15 (1)	16 (1)	14 (1)	15.1 (1)
O(2)′	0.4718 (5)	0.2284 (5)	−0.1752 (5)	26.4 (10)	25.4 (10)	23.2 (9)	23.7 (9)	23.2 (9)	21.8 (9)
C(3)	0.6064 (6)	0.4311 (6)	0.0633 (6)	14.1 (10)	16 (1)	17 (1)	13.8 (10)	14.1 (10)	15 (1)
N(4)	0.5144 (4)	0.4225 (4)	0.0415 (4)	11.2 (7)	12.9 (8)	11.8 (8)	11.1 (7)	10.1 (7)	11.0 (7)
C(5)	0.4471 (6)	0.3620 (6)	0.0445 (6)	10.6 (9)	10.1 (9)	9.0 (8)	9.1 (8)	8.5 (8)	8.4 (8)
C(6)	0.4757 (6)	0.3282 (6)	0.1620 (6)	12.0 (9)	12.0 (9)	13.0 (10)	11.9 (9)	10.2 (9)	11.1 (9)
C(7)	0.4858 (6)	0.2719 (7)	0.1868 (6)	13 (1)	16 (1)	14 (1)	12 (1)	11.0 (10)	13 (1)
C(8)	0.4767 (7)	0.1856 (7)	0.1180 (7)	17 (1)	20 (1)	22 (1)	16 (1)	16 (1)	20 (1)
C(9)	0.4576 (6)	0.1555 (6)	0.0238 (7)	16 (1)	16 (1)	20 (1)	15 (1)	16 (1)	16 (1)
C(10)	0.4461 (6)	0.2095 (6)	−0.0061 (6)	9.6 (9)	10.5 (9)	12.3 (9)	8.8 (8)	9.1 (8)	9.8 (9)
C(11)	0.4571 (5)	0.2989 (6)	0.0662 (6)	9.6 (9)	10.6 (9)	10.9 (9)	8.9 (8)	8.8 (8)	9.5 (8)
C(12)	0.3637 (6)	0.3625 (6)	0.0327 (5)	11.1 (9)	10.8 (9)	10.1 (8)	9.7 (8)	9.4 (8)	9.3 (8)
C(13)	0.4233 (6)	0.4909 (6)	0.1068 (6)	14.7 (10)	15 (1)	12.9 (10)	13.3 (10)	12.6 (9)	12.3 (9)
C(14)	0.3408 (8)	0.4878 (7)	0.0910 (7)	21 (1)	19 (1)	16 (1)	19 (1)	17 (1)	16 (1)
C(15)	0.1992 (8)	0.3561 (9)	0.0023 (7)	18 (1)	23 (1)	17 (1)	19 (1)	16 (1)	17 (1)
C(16)	0.1427 (7)	0.2319 (7)	−0.0677 (7)	15 (1)	16 (1)	16 (1)	13 (1)	13 (1)	13 (1)
C(17)	0.2244 (6)	0.2352 (6)	−0.0521 (6)	14 (1)	14 (1)	13.1 (10)	12.5 (10)	12.1 (9)	11.5 (9)
C(18)	0	0	0	4.1 (6)[c]					
W(1)	0.5632 (7)	0.0431 (7)	−0.0712 (7)	59 (2)	51 (2)	59 (2)	49 (2)	55 (2)	50 (2)

atom	x	y	z	B, Å²	atom	x	y	z	B, Å²
H(1)	0.671	0.502	0.085	3.5	H(6)	0.525	0.585	0.171	4.2
H(2)	0.672	0.467	0.148	3.5	H(7)	0.383	0.581	0.143	5.2
H(3)	0.481	0.386	0.211	3.7	H(8)	0.137	0.351	−0.011	5.0
H(4)	0.482	0.145	0.136	4.9	H(9)	0.044	0.140	−0.127	6.3
H(5)	0.456	0.099	−0.019	5.1	H(10)	0.182	0.144	−0.103	4.4

[a] In our labeling scheme, Cl(3) and C(18) belong to the chloroform molecule. [b] The form of the anisotropic thermal parameters is $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}kl + \beta_{23}kl)]$. [c] B, Å².

Table II. Bond Distances (Å) and Angles (Deg) for the Heavy Atoms[a]

Cu-N(4)	1.990 (8)	C(11)-C(10)	1.41 (2)
Cu-Cl(1)	2.27 (20)	C(1)-N(1)	1.41 (2)
N(1)-C(1′)	1.50 (9)	C(11)-C(6)	1.40 (1)
N(1)-C(2)	1.37 (3)	C(6)-C(7)	1.380 (9)
C(2)-O(2′)	1.21 (1)	C(7)-Cl$_2$	1.74 (1)
C(2)-C(3)	1.51 (9)	C(7)-C(8)	1.38 (2)
C(3)-N(4)	1.475 (8)	C(8)-C(9)	1.36 (1)
N(4)-C(5)	1.29 (1)	C(9)-C(10)	1.405 (9)
C(5)-C(11)	1.468 (8)	C(5)-C(12)	1.473 (7)
N(4)-Cu-Cl	90.9 (1.3)	C(5)-C(11)-C(6)	117.1 (9)
N(1)-C(2)-C(3)	115 (2)	C(11)-C(6)-C(7)	119.8 (9)
C(1′)-N(1)-C(2)	117 (2)	C(6)-C(7)-Cl(2)	118.8 (9)
N(1)-C(2)-O(2′)i	122 (3)	C(6)-C(7)-C(8)	121.3 (6)
O(2′)-C(2)-C(3)	122 (1.5)	Cl(2)-C(7)-C(8)	120 (1)
C(2)-C(3)-N(4)	108 (4)	C(7)-C(8)-C(9)	119 (1)
C(3)-N(4)-C(5)	119.1 (7)	C(8)-C(9)-C(10)	121.7 (9)
N(4)-C(5)-C(11)	121.9 (5)	C(9)-C(10)-C(11)	118.3 (6)
C(5)-C(11)-C(10)	123.4 (5)	C(10)-C(11)-C(6)	119 (1)
C(11)-C(10)-N(1)	123 (1)		

[a] Figures in parentheses are estimated standard deviations.

Table III. Torsion Angles (Deg) for the Free and Complexed Ligand[a]

definition	symbol	for free ligand	for complexed ligand	|Δ|
N(1)-C(2)-C(3)-N(4)	θ_{2-3}	−65.0	−70.5	5.5
C(2)-C(3)-N(4)-C(5)	θ_{3-4}	74.7	73.7	1
C(3)-N(4)-C(5)-C(11)	θ_{4-5}	−2.9	−1.1	1.8
N(4)-C(5)-C(11)-C(10)	θ_{5-11}	−40.3	−40.6	0.3
C(5)-C(11)-C(10)-N(1)	θ_{11-10}	−3.2	−4.1	0.9
C(11)-C(10)-N(1)-C(2)	θ_{10-1}	51.8	47.6	4.2
C(10)-N(1)-C(2)-C(3)	θ_{1-2}	−13.5	−4.7	8.8
N(1)-C(2)-N(4)-C(5)	θ_{2-4}	5.6	−0.2	5.8
N(4)-C(5)-C(12)-C(13)	τ_{5-12}	−23.2	−37.9	14.7
C(11)-C(5)-C(12)-C(13)	τ'_{5-12}	154.0	139.4	14.6
C(1′)-N(1)-C(10)-C(11)	τ_{1-10}	−141.6	−139.7	1.9
C(1′)-N(1)-C(10)-C(9)	τ'_{1-10}	36.5	36.2	0.3
C(1′)-N(1)-C(2)-C(3)	τ_{1-2}	179.6	−177.5	2.9
O(2′)-C(2)-N(1)-C(10)	τ_{2-1}	174.6	175.3	0.7
O(2′)-C(2)-C(3)-N(4)	τ_{2-3}	113.3	109.4	3.9
O(2′)-C(2)-N(1)-C(1′)	τ_{2-1}	1.3	2.5	1.2

[a] For a torsion angle of the chain ABCD, the sign is positive if, when looking from B to C, a clockwise motion of atom A would superimpose it on atom D. For the free ligand, the x coordinate for the C(10) atom (in our labeling scheme) is false. We have assumed a coordinate giving a correct geometry for the chlorophenyl ring.

The fact that the chloroform molecule is isolated in the cell, leading to no hydrogen bond, could explain satisfactorily that it exhibits an almost free rotation around the ternary axis.

Magnetic Resonance Studies. The ^{13}C NMR spectrum obtained from a freshly prepared 0.5 M $CDCl_3$ solution of L is shown in Figure 5a. It shows 14 peaks. The peaks corresponding to C(7) and C(12) are not visible on Figure 5a because they are marked by the peaks corresponding respectively to C(6) and C(13,17). The assignments have been deduced from several observations[22] dealing with the $^nJ_{C-H}$ coupling constants and the chemical shifts themselves. They are listed in Table IV. The introduction of increasing quantities of Cu^{2+} ions in the previous solution induces a systematic perturbation of the resonance conditions of the ligand (L) C(*i*) nuclei (see Figure 5b,c,d). In Figure 5b, the peaks corresponding to C(3) and (C(12), C(13,17)) show an important decrease in intensity and attendant broadening. The same effect is still visible for the C(11) peak. It is weak for the C(2) and C(5) peaks. In Figure 5b,c spectra, we can see an important increase of the previously observed effects;

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Table IV. Chemical Shifts (ppm/Me_4Si) of L

chemical shifts	+169.8	+168.9	+142.6	+138.2	+131.5	+130.6	+130.0
assignments	C(2)	C(5)	C(10)	C(11)	C(8)	C(15)	C(7)
chemical shifts	+129.8	+129.4	+129.2	+128.4	+122.6	+56.9	+34.8
assignments	C(6)	C(13,17)	C(12)	C(14,16)	C(9)	C(3)	C(1′)

Table V. EPR Parameters for CuL_2Cl_2

conditions	$g_{\parallel}$	$g_{\perp 1}$	$g_{\perp 2}$	$\bar{g}$
solid state, 295 K	2.205	2.058	2.027	2.097
$CHCl_3$ solution, 295 K				2.110
$CHCl_3$ solution, 77 K, X-band	2.20	2.06	2.035	2.113
$CHCl_3$ solution, 110 K, Q-band	2.225	2.072	2.041	2.113

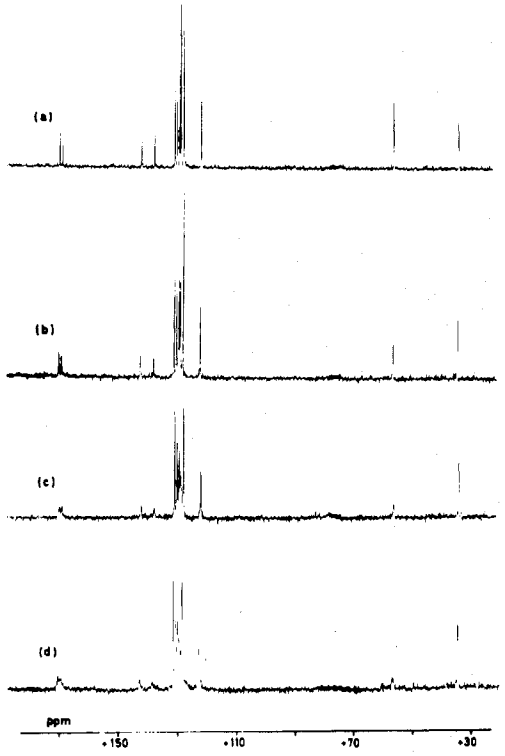

Figure 5. (a) ^{13}C NMR spectrum of the free ligand L. (b)–(d) ^{13}C NMR spectra of L with increasing quantities of $CuCl_2$.

furthermore, C(10), C(6), C(9) and C(14,16) are also affected. Finally, only (C(1′) and C(8) remain practically unchanged after Cu^{2+} addition (see Figure 5d). These observations are, as a whole, quite consistent with coordination of the metal ion by the N(4) nitrogen of the ligand and exclude other coordination possibilities.

The solid, freshly ground polycrystalline powder of the complex yields a well-resolved EPR spectrum, even at room temperature. Three principal g values can be determined in a straightforward manner, and these combine to an average $\bar{g}$ value of 2.097 (Table V). Chloroform or dichloromethane solutions of the complex have similar features, with resolved copper nuclear hyperfine structure as well as ligand hyperfine splitting (see Figure 6). The average g value obtained in chloroform is 2.110, with a copper hyperfine splitting of 85 G. The smaller 13 G splitting observed on the high-field absorption cannot be assigned to a specific nucleus, as the number of lines does not coincide with that expected for two nitrogens or two chlorines alone. Frozen chloroform solutions also reveal ligand hyperfine splittings on the $g_{\perp}$ part of the spectrum. The fourth line of the $g_{\parallel}$ absorption is absent from the spectrum as is often the case with copper complexes, and the $g_{\perp}$ absorption is in fact the overshoot line. The g values were therefore obtained by a computer-simulation program (see Figure 7). The best fit parameters include a line width of 20 G, and an unobserved $A_{\perp}$ hyperfine near 45 G, to account for the width of the overshoot line.

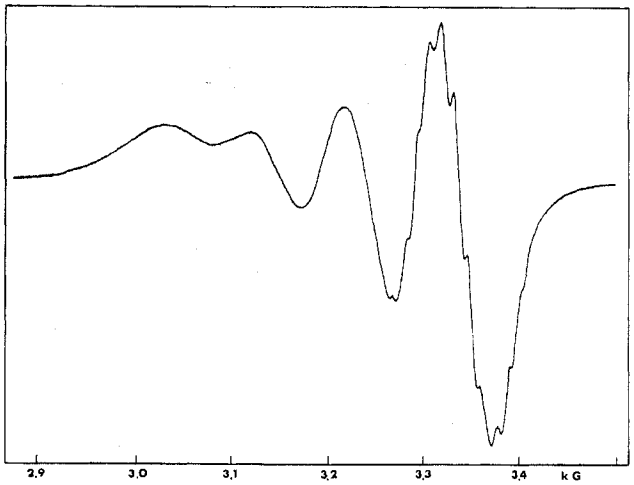

Figure 6. EPR spectrum of CuL_2Cl_2 in $CHCL_3$ solution. Microwave frequency = 9.476 GHz.

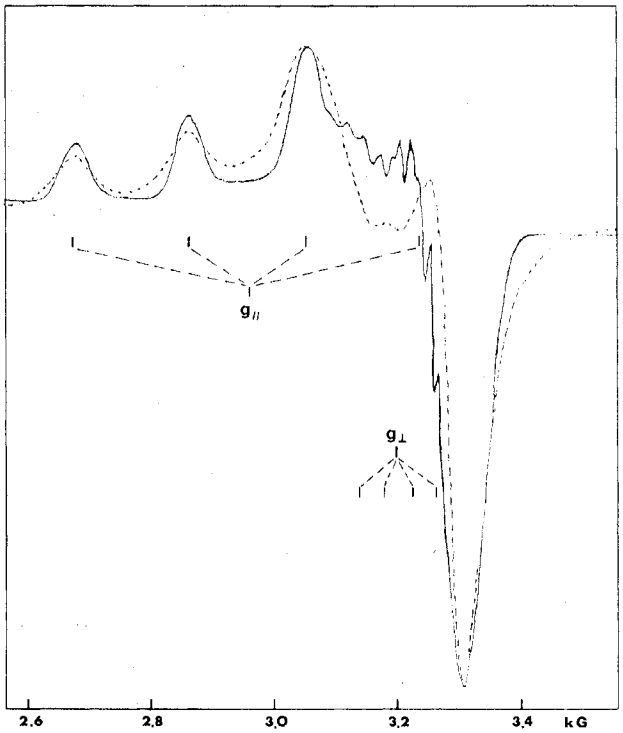

Figure 7. EPR spectrum of CuL_2Cl_2 in $CHCl_3$, 77K. Microwave frequency = 9.361 GHz. (···) Simulated spectrum with $g_{\parallel} = 2.20$, $g_{\perp 1} = 2.06$, $g_{\perp 2} = 2.035$, $A = 180$ G, and $B = C = 45$ G.

Spectra recorded at higher microwave frequency (see Figure 8) confirmed the calculated g value anisotropy. Indeed, three principal absorptions were observed, each with a different hyperfine splitting. $g_{\parallel}$ centered at $g = 2.225$, showed the four-line structure of square-planar copper complexes, with $A_{\parallel} = 178$ G, conforming to a ground-state configuration with the unpaired electron in the $d_{x^2-y^2}$ orbital. One $g_{\perp}$ absorption at $g = 2.041$ showed a well-defined five-line pattern expected for two equivalent nitrogen nuclei. The relatively large coupling constant of 16 G corresponds, according to one theory, to a very small deviation from axial symmetry. The other $g_{\perp}$

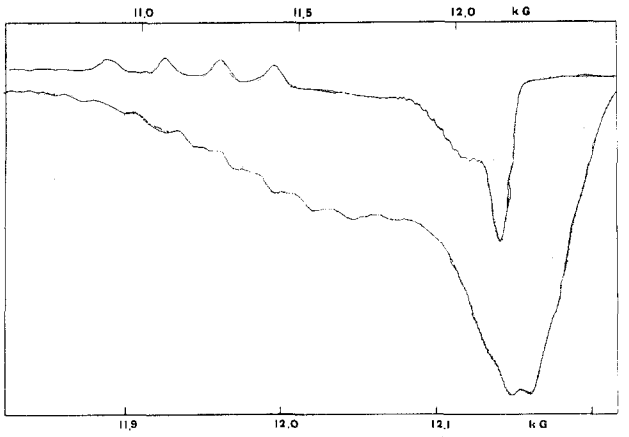

Figure 8. EPR spectrum of CuL_2Cl_2 in $CHCl_3$, 110 K. Microwave frequency = 34.622 GHz. Lower line: expanded spectrum showing the ill-resolved hyperfine structure.

absorption at $g = 2.072$ has ill-resolved hyperfine structure. Seven lines are expected for coupling with two equivalent chlorine nuclei of spin $^3/_2$, but as the two naturally occurring isotopes have different coupling constants, some interference is expected. Furthermore, one cannot rule out second-order effects or some resolution of copper $A_\perp$ hyperfine structure. In any case, chlorine and nitrogen couplings are observed and this explains the complicated pattern observed in the room-temperature liquid solution spectra. This was confirmed by the fact that $CuBr_2$ also reacted to yield a similar complex, but with a much larger hyperfine interaction, as expected.

The data provide evidence that the unpaired electron is delocalized on to the ligands. Well-resolved Cl and Br hyperfine structures have been resolved previously in mixed complexes with only one "covalently" bonded halogen.[23] Provided the hyperfine and **g** tensors are coaxial, the results support the conclusion that the ligands are strongly bonded to the copper and remain in a square-planar trans configuration, even in solution. This is interesting, as most authors agree that, due to the plasticity of the copper coordination sphere, spectra–structure relationships are usually unwarranted for solution studies[24] even though the correlations are generally accurate for the solid state.

Conclusion

In conclusion, the environment around the copper(II) ion is similar in solution and solid states and is quite typical for this metal ion. We believe the phenyl rings of the ligand effectively block the usual axial elongated octahedron type coordination site. This steric hindrance is responsible for the stoichiometry of the complex, no other copper/ligand ratio other than 2:1 being found, contrary to other copper amine systems.[25] This can also explain the square-planar solid-state structure and the resolution of the ligand hyperfine structure in the solution EPR spectra, due to slow exchange of the ligands. This encourages us to extend our work to other solution studies in order to more fully characterize the coordinating behavior of this type of ligand. We anticipate in vivo comparative biological tests for metal complexes of these drugs should lead to other interesting results.

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Registry No. $Cu(L)_2Cl_2 \cdot 2H_2O \cdot 0.33CHCl_3$, 72175-01-0.

Supplementary Material Available: A listing of structure factor amplitudes (8 pages). Ordering information is given on any current masthead page.

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