

UV–Vis and EPR spectroscopic study of copper(II) complexes with bis(benzimidazol-2-yl) ligands

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Abstract

Copper(II) complexes with bis(benzimidazol-2-yl) ligands of the type $\text{Bz}(\text{CH}_2)_n\text{-X-(CH}_2)_n\text{Bz}$ (where Bz = benzimidazol-2-yl; X = O, S or CH_2 ; $n = 1, 2$) have been characterized in solution by UV–Vis and EPR spectroscopy. Mono complexes with O or S donor atom containing ligands have square-pyramidal stereochemistries, while bis complexes have pseudo-octahedral geometries with four nitrogen donors in the equatorial plane and the two heteroatoms occupying the apical positions. The mono and bis complexes with the ligand having X = CH_2 and $n = 2$ have distorted octahedral geometries with two molecules of solvents involved in the apical positions. The experimental results on the complexes with the ligand having X = CH_2 and $n = 1$ suggest that this ligand behaves as monodentate.

Introduction

The rationale for the 'copper approach' to the therapy of inflammatory disorder includes, among others, the administration of copper(II) complexes with 'copper-oriented' [1] ligands in order to overcome the problems concerned with the oral treatment of copper complexes and also to supplement the inflamed organism with a form of bioactive copper [2]. To this task, new anti-inflammatory complexes with polydentate ligands having donor groups less sensitive to the protonation have been analyzed. Among various tested copper derivatives significant anti-inflammatory activity has been found for a series of 1:1 adducts of CuX_2 (X = ClO_4 , Cl) with the tridentate mixed ligands NSNB C_2 (see formulae), which possess two benzimidazolyl and one thioetheral donor groups [3].

This work deals with a spectroscopic study of the coordination features of copper(II) ions with bis(benzimidazol-2-yl) ligands of the type $\text{Bz}(\text{CH}_2)_n\text{-X-(CH}_2)_n\text{Bz}$, where Bz = benzimidazol-2-yl; X = O, S or CH_2 ; $n = 1, 2$. All these ligands are potentially tridentate with the obvious exception of the ligands containing a central CH_2 group. This spectroscopic (UV–Vis and EPR) study in solution was carried out with the specific aim of gaining information about the geometry adopted by these

copper(II) complexes in view of the rationalization of the biological activity of these compounds as anti-inflammatory drugs. The different chain length (denoted C_1 or C_2) gives the ligand a different flexibility and probably a different way of approaching the copper(II) ion. Preparation, structural characterization by X-ray diffractometry and spectroscopic properties of copper(II) complexes with some of the ligands examined in this work have been previously reported [3a; 4].

Experimental

Preparation of the ligands

Ligands were prepared by condensation of the appropriate dicarboxylic acid with *ortho*-phenylenediamine, following various procedures. NSN– BC_2 and NSN– C_1 were prepared in boiling aqueous HCl [4], NCN– C_1 and NCN– C_2 in polyphosphoric acid at 200–240 °C [5], NON– C_1 in neat at 200 °C. The addition of dilute ammonia to the reaction mixture caused the separation of colored products, which were repeatedly purified by refluxing their methanolic solutions in the presence of decolorizing charcoal and finally recovered as colorless crystals upon addition of water. Yields ranged from 30–95%.

Spectroscopic measurements

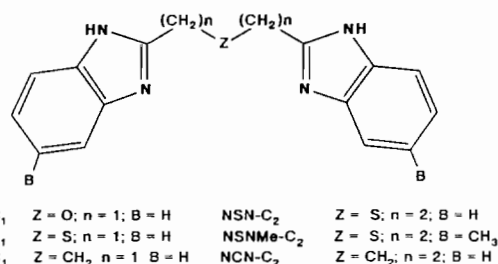
All EPR spectra were obtained with a Bruker ER 200 D X-band (c. 9.5 GHz) spectrometer. The magnetic field was carefully measured during any scan with the aid of the gauss meter ER 035 M which leaves markers at preselected values. DPPH free radical ($g = 2.0036$) was used to standardize the klystron frequency. All measurements were carried out at the temperature of 150 K by employing a standard low temperature apparatus. Aqueous methanolic solutions were 5 mM in $^{63}\text{Cu}(\text{NO}_3)_2$ and 5 mM in the ligand in the case of the mono complexes, or in excess of the ligand in the case of the bis complexes. In some cases DMSO was added to improve the solubility of the copper complexes. No dependence of the spin Hamiltonian parameters was observed on changing the composition of the solvent mixture; typical solvent mixtures were $\text{H}_2\text{O}-\text{CH}_3\text{OH}$ (30–70%) or $\text{H}_2\text{O}-\text{CH}_3\text{OH}-\text{DMSO}$ (20–50–30%).

Parameters for the EPR frozen solution spectra were obtained through computer simulation by using a modified program by Pilbrow [6] (MONOCLIN in its *trans* and *cis* version). Ultraviolet and visible optical spectra were recorded with a Perkin-Elmer 330 double-beam spectrophotometer at room temperature. Experiments were carried out on solutions having the same metal-to-ligand ratios of those employed in the EPR measurements by using natural copper(II) nitrate*.

Results

The general formulae of the ligands used in this work are summarized in Scheme 1. An EPR study was undertaken on the copper(II) complexes with these ligands. The spin Hamiltonian parameters associated with the EPR frozen solution spectra of the copper(II) mono and bis complexes are presented

*These complexes can be also prepared as solid compounds starting from methanolic solutions of the ligands, which copper(II) perchlorate ($[\text{Cu}^{2+}]:[\text{L}] = 2:1$ or $1:1$) was added to. The green solutions separated either yellow-green or blue-green copper(II) complexes of composition $[\text{Cu}(\text{L})_n](\text{ClO}_4)_2$ (with $n = 1, 2$) or colorless or pink-colored copper(I) derivatives of formula $[\text{Cu}(\text{L})(\text{ClO}_4)]$. Mono and bis complexes containing copper(II) can be easily isolated in the solid state with $\text{L} = \text{NSN}-\text{C}_1$, $\text{NSN}-\text{C}_2$ and $\text{NSNMe}-\text{C}_2$, whereas unexpectedly the formation of copper(I) derivatives was found with $\text{L} = \text{NON}-\text{C}_1$, $\text{NCN}-\text{C}_1$ and $\text{NCN}-\text{C}_2$. The copper(II) adducts with $\text{NSN}-\text{C}_1$ can be easily transformed into copper(I) derivatives by heating the green solution. On the contrary, the presence of excess ligands or the addition of significant amount of DMSO rapidly dissolved the copper(I) derivatives giving paramagnetic solution which contained the corresponding copper(II) adducts.



Scheme 1.

in Table 1. Shf structures due to two or four nitrogen atoms are often superimposed on the lowest field feature in the EPR spectra of both mono and bis complexes, respectively. Some typical EPR spectra run on frozen solution of these complexes are shown in Fig. 1(a) and (b). Optical studies in the UV-Vis region were undertaken, the results of which are reported in Table 2. Ligand field as well as ligand-to-metal charge transfer bands are shown by these complexes. One or two LF bands at different frequencies are clearly associated with the particular stereochemistries of these copper(II) complexes. LMCT bands below the intense internal ligand $\pi-\pi^*$ transition of the benzimidazolyl rings present maxima which are centered at average frequency values of 27600 ± 700 and $32600 \pm 700 \text{ cm}^{-1}$.

Discussion

A comparison between the magnetic parameters pertinent to the copper(II) complexes with the ligands of the C₂ series gives evidence for the differences in the method of coordination by NCN and NSN ligands (see Table 1). In particular, with the bidentate NCN ligand, the magnetic parameters are typical of axial copper(II) complexes in pseudo-octahedral stereochemistries. The shifts of g_{\parallel} and A_{\parallel} values going from the mono to the bis complex are not so marked as expected for the substitution of two solvent molecules from the equatorial plane with two nitrogen atoms of a bidentate ligand. There is no doubt that all nitrogen atoms are coordinated to copper(II) ion because of the shf structures present in the EPR spectra; there is probably a lack of stabilization owing to a poor chelate effect caused by the length of the chain connecting the two benzimidazolyl moieties. It is surprising that this ligand behaves as bidentate instead of giving rise to polymer species. This fact implies that the NCN-C₂ ligand is present in solution in some pre-organized form which makes it ready to chelate. A stacking interaction between the two benzimidazolyl groups could be responsible for this behaviour, as already found for other similar systems [7–9].

TABLE 1. Spin Hamiltonian parameters for $^{63}\text{Cu}(\text{II})$ complexes with bis(benzimidazol-2-yl) ether or thioether ligands

Complex	g_{\parallel} ± 0.002	A_{\parallel}^a ± 2	g_{\perp} ± 0.003	A_{\perp}^a ± 3	A_{\perp}^N ± 2	A_{\parallel}^N ± 2	shf ^b
C₂ series							
$[\text{Cu}(\text{NCN})]^{2+c}$	2.323	161	2.074	12		13	5
$[\text{Cu}(\text{NSN})]^{2+d}$	2.333	132	2.078	15		15	
$[\text{Cu}(\text{NSN-Me})]^{2+d}$	2.335	136	2.075	17		15	
$[\text{Cu}(\text{NCN})_2]^{2+c}$	2.306	165	2.063	18	10	14	9
$[\text{Cu}(\text{NSN})_2]^{2+d}$	2.264	183	2.053	22	13	16	9
$[\text{Cu}(\text{NSN-Me})_2]^{2+d}$	2.262	183	2.052	22	13	16	9
C₁ series							
$[\text{Cu}(\text{NCN})]^{2+d}$	2.350	130					
$[\text{Cu}(\text{NON})]^{2+c}$	2.337	157	2.064	10	11	14	5
$[\text{Cu}(\text{NSN})]^{2+d}$	2.331	158	2.060	10	11	14	5
$[\text{Cu}(\text{NON})_2]^{2+c}$	2.253	185	2.041	24	13	16	9
$[\text{Cu}(\text{NSN})_2]^{2+d}$	2.260	182	2.045	20	13	16	9

^aAll hyperfine coupling constants are in units 10^4 cm^{-1} . ^bNumber of lines due to nitrogen superhyperfine structure. ^c $\text{H}_2\text{O}-\text{CH}_3\text{OH}-\text{DMSO}$: 20–50–30%. ^d $\text{H}_2\text{O}-\text{CH}_3\text{OH}$: 30–70%.

When the central atom is a sulfur atom, the pattern is completely different. In fact, the mono complexes show spin Hamiltonian parameters which are typical of five coordinated copper(II) complexes in square-pyramidal geometries. The high g_{\parallel} values and low A_{\parallel} hyperfine coupling constant in the presence of two benzimidazolyl nitrogen donor atoms are direct evidence of the sulfur involvement in the coordination to the copper(II) ion, confirming that, with a central potentially coordinating heteroatom, these ligands behave as tridentate. Differences are also observed in the bis complexes among the NCN and NSNB series, the EPR spectra of the latter showing well-resolved shf structure on the lowest field peak (see Fig. 1) due to the interaction of the odd electron with four equivalent nitrogen nuclei. These differences in the magnetic parameters are to be ascribed to the coordination of the sulfur atoms in the two apical positions, this fact giving a greater stability to the copper(II) complexes (six-membered chelate rings, instead of ten). In particular, the lower g_{\parallel} and higher A_{\parallel} values are due to two different chromophores in pseudo-octahedral stereochemistries: CuN_4O_2 (oxygen atoms coming from solvent molecules in apical sites) with NCN ligand and CuN_4S_2 (sulfur atoms belonging to the ligand molecule in apical sites) with NSN or NSN-Me. Very little differences are present in the magnetic parameters as a consequence of methyl insertion in the benzimidazolyl group.

The blue shift of the d-d band going from the mono to the bis NCN complexes is a clear indication of the coordination of a second NCN molecule to the copper(II) ion. The electronic absorption spec-

trum of $[\text{Cu}(\text{NSN})]^{2+}$ and $[\text{Cu}(\text{NSN-Me})]^{2+}$ consists of two well separated d-d bands clearly associated with the square-pyramidal geometry. In the case of the corresponding bis complexes one major band accompanied by a pronounced shoulder is present in the visible region. Ligand field spectra of this type have been assigned to copper(II) complexes in octahedral stereochemistry with a strong elongation of the bond distance along the z axis [10]. Diffractometric studies on complexes containing thioether sulfur apically bound to metal revealed that Cu-S bond distances range from 2.31 to 2.85 Å [11]. With regard to LMCT bands, since sulfur atoms are involved in the long axial Cu-L bonds, $\sigma(\text{S})$, $\pi(\text{S}) \rightarrow d_{\sigma}$ charge transfer absorptions are not expected; in general one would not see charge transfer absorptions from axially ligated ligands [12]. Thus, both LMCT bands, not always well-resolved in all complexes, are assigned due to $\pi_1(\text{N}) \rightarrow \sigma^*$ and $\pi_2(\text{N}) \rightarrow \sigma^*$, namely transitions from the benzimidazolyl nitrogen filled π molecular orbitals to the half-filled $d_{x^2-y^2}$. In some of these copper(II) complexes with sulfur containing ligands, Dagdigian *et al.* [4] have tentatively assigned these UV transitions to $\sigma(\text{S}) \rightarrow d_{\sigma}$ charge transfer. The synthesis of NCN and NON ligands in which the sulfur atom has been replaced by oxygen or carbon atoms allowed this point to be clarified: all the copper(II) complexes practically showed the same LMCT bands, which are only ascribable to $\pi(\text{N}) \rightarrow d_{\sigma}$ transitions.

The bis complexes with the ligands of the C₁ series with a central heteroatom are not very different from those with C₂ ligands. Slight differences are due to the different central heteroatoms, oxygen in the NON

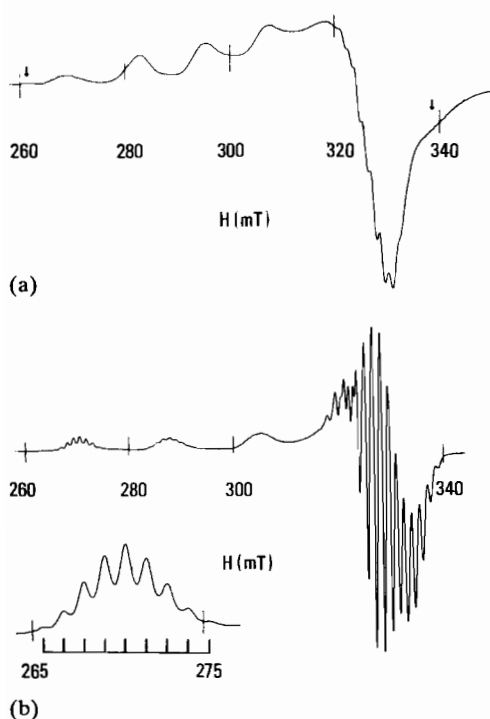
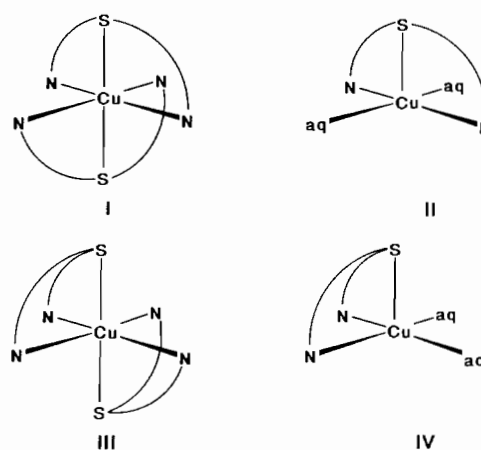


Fig. 1. Frozen solution EPR spectra of $[\text{Cu}(\text{NSN-Me})]^{2+}$ (a) and $\text{Cu}(\text{NSN-Me})_2]^{2+}$ (b) both 5 mM in water-methanol mixture (30–70%) at 150 K. The two arrows in spectrum (a) indicate features due to slight amounts of free copper(II) and copper(II) bis complex ions. Spectrum (b) was obtained by using a ligand to metal ratio 4:1. Instrumental setting: (a) microwave frequency = 9.439 GHz, microwave power = 20 mW, modulation frequency = 100 KHz, field modulation amplitude = 5 mT, time constant = 0.5 s, scan time = 500 s; (b) microwave frequency = 9.387 GHz, microwave power = 20 mW, modulation frequency = 100 kHz, field modulation amplitude = 2.5 mT, time constant = 0.5 s, scan time = 500 s.

and sulfur in the NSN ligands. The chromophores are CuN_4S_2 and CuN_4O_2 in the pseudo-octahedral geometries typical of distorted tetragonal copper(II) complexes. Interestingly the mono complexes of the C_1 series show higher copper hyperfine coupling constants than those obtained in the case of the mono complexes with C_2 ligands, as if their central heteroatoms were not involved in the coordination to copper. On the contrary the similarities among the bis complexes of the C_1 and C_2 series of ligands and the g_{\parallel} almost equal to those of the mono complexes with C_2 ligands, in which the heteroatom is surely coordinated to copper, strongly suggest, also in this case, a square-pyramidal geometry. These differences can probably arise from two different ways of approaching the copper ion by the ligands. Actually, NSN- C_2 , which is a T-shaped ligand [4], coordinates copper with the two nitrogen atoms in *trans* positions of the equatorial plane, the sulfur

atom being linked apically (structure **II**). It is probable that in the C_1 series the shorter chain connecting the heteroatom to the benzimidazolyl moieties does not allow the same possibility and the two nitrogen atoms are forced to coordinate in *cis* positions of the equatorial plane (the best simulations have been obtained imposing a superhyperfine pattern due to two *cis* nitrogen nuclei), the Cu-S bond distance becoming longer (structure **IV**). This fact, which makes no or very little difference in the bis complexes in which all the coordination sites of the copper(II) tetragonal distorted octahedron are occupied (structures **I** or **III**), can be important in the mono complexes in order to achieve their peculiar stereochemistry.



A multispecies spectrum is obtained with NCN- C_1 on varying the amount of ligand dissolved in solution. However, in the presence of a slight excess of copper, a single species EPR spectrum can be obtained, whose parameters suggest that probably the two nitrogen atoms do not contemporarily coordinate. It is extremely important to point out the difference between NCN- C_2 and NCN- C_1 . The length of the chain interconnecting the two benzimidazolyl groups could become the critical factor which gives rise to these different behaviours. In other words the shorter chain in the NCN- C_1 ligand could probably prevent any possibility of pre-organized forms.

Also in the case of the ligands belonging to the C_1 series the optical data for the copper(II) complexes are in agreement with the EPR results. The discussion of these data follows that outlined in the case of the copper(II) complexes with the C_2 ligands. In fact two LF transitions are present (except for the case of the NCN ligand) in the visible region as well-resolved bands or shoulders, whereas two LMCT ones are seen in the UV region. The LF transitions are shifted to higher frequencies with respect to those seen in the case of the copper(II) complexes

TABLE 2. Optical data for copper(II) complexes with bis(benzimidazol-2-yl) ether or thioether ligands

Complex	LF*	LMCT*
C₂ series		
[Cu(NCN)] ²⁺	14000(50)	26700(550), 32800(1500)
[Cu(NCN) ₂] ²⁺	16500(70)	29000(1200), 33300(1600)
[Cu(NSN)] ²⁺	11100(124), 15100(183)	27200(2900), 32800(3100)
[Cu(NSN) ₂] ²⁺	11500(72), 15700(150)	27400(3000)
[Cu(NSN-Me)] ²⁺	11100(131), 15000(181)	27600(2600)
[Cu(NSN-Me) ₂] ²⁺	11600(68), 15900(122)	27400(3100)
C₁ series		
[Cu(NCN)] ²⁺	12400(46)	27600(1200), 32800(1700)
[Cu(NSN)] ²⁺	14100(60), 15800(57)	27900(1700), 31600(1800)
[Cu(NSN) ₂] ²⁺	13900(41), 17300(72)	
[Cu(NON)] ²⁺	13300(63), 16400(37)	29000(1400), 32700(1750)
[Cu(NON) ₂] ²⁺	14800(100), 17400(129)	29400(1200)

*Units of ν_{\max} are in cm^{-1} ; the molar absorption coefficient ($\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$) is given in parentheses.

of the C₂ series and this fact could be probably ascribed to two factors: (i) five-membered chelate rings are obtained with the NSN-C₁ and NON-C₁ ligands both in the mono and in the bis complexes; (ii) the axial linkage of sulfur or oxygen donor atoms is probably weaker (compare the A_{\parallel} values extracted from the EPR spectra in the mono complexes among the two series of the ligands) than that experienced in the case of the C₂ ligands and, as a consequence, the equatorial field due to two or four nitrogen donors is much stronger. A separate case has to be considered for the complex [Cu(NCN-C₁)]²⁺, which exhibits a broad LF band centered at 12 400 cm^{-1} . This low frequency value, comparable with that of the free copper(II) ion is in agreement with the EPR results. An optical absorption spectrum run on the same solution, in the presence of an excess of NCN-C₁ ligand, showed no distinctive maximum, but a continuous absorption going from 11 000 to 16 000 cm^{-1} , thus meaning that many complex species with different coordination levels contemporarily contribute to the overall Vis spectrum. In the UV region, two high frequency bands centered at exactly the same frequency as those observed for [Cu(NCN-C₁)]²⁺ give evidence that at least one of the benzimidazolyl nitrogen donors is always coordinated to the copper(II) ion. These data indirectly confirm the EPR results. In other words NCN-C₁ probably acts as a monodentate ligand.

Conclusions

This work reports another example of bidentate ligands which, despite the fact that they are expected to give thermodynamically unstable complexes, produce stable copper(II) macro-chelates, owing to some

pre-organization of the ligand in solution. As shown by the EPR spectra of the mono and bis copper(II) complexes with NCN-C₂, this ligand is coordinated to the metal through the two benzimidazolyl nitrogen donors, giving rise in both cases to ten-membered chelate rings. Closely related examples have already been reported in the literature [7–9], for mono and bis copper(II) complexes with cyclo-(L-histidyl-L-histidyl) [7, 8] or for the [CuLH₋₁] species of some tetrapeptides having prolyl residues [9] (L = Phe-Gly-Pro-Tyr, Tyr-Gly-Pro-Phe).

The results of this study point that the peculiar stereochemistry found for the solid [Cu(NSN-C₂)]²⁺ species [4] is also achieved in solution (structure II) and that a similar stereochemistry is common to the [Cu(NSN-C₁)]²⁺ and [Cu(NON-C₁)]²⁺, but with the two nitrogen donor atoms in *cis* position (structure IV). These square-pyramidal five-coordinated species with two replaceable solvent molecules in the equatorial plane and a sixth apical free position, could account for the particular pharmacological properties of this class of compounds [3].

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