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Barbiturate Copper Complexes: Preparation and Spectral Studies

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The preparation and spectral properties of copper(II) complexes of barbiturates are reported. Complexes of the general formula $Cu(II)B_2L_2$, *where* B = *phenobarbital or amobarbital; and* L = *pyridine, imidazole, or* H_2O *were synthesized. EPR and infrared data show that the copper atom is bound to the nitrogen atom of the barbiturate anion to form 2:1 barbiturate:copper complexes. The EPR spectra also indicate that all complexes have tetragonal symmetry* ($g_{\parallel} > g_{\perp} > g_e$) *with the unpaired electron in the* $d_{x^2-y^2}$ *orbital.*

Introduction

Barbiturates are among the most widely used drugs for the treatment of epilepsy [1, 2]. This class of antiepileptic drug is of special interest since many of them and their active metabolites form metal complexes.

Various metal complexes of barbiturates have been synthesized and studied in the past [3–8]. Levi and Hubley [9] prepared a series of twelve barbiturate copper complexes and on the basis of infrared spectral data suggested coordination of the barbiturate ligands to copper through an oxygen atom. Subsequent X-ray analyses of $Cu(barbital)_2L_2$ complexes, where L is pyridine or α-picoline, demonstrated that copper is bound to a deprotonated nitrogen atom of barbital and not to an oxygen atom [10–12]. Furthermore, it was shown that $Cu(barbital)_2L_2$ complexes have a square planar arrangement of coordinating atoms.

Recently, we communicated results consistent with the hypothesis that the active form of amobarbital is its copper complex, an effective anticonvulsant agent with potential advantages over the parent ligand [13]. Since changes in the electronic and/or steric environment around copper might be expected to alter anticonvulsant activity, other ligands such as water, pyridine, and imidazole were used to prepare ternary copper complexes of phenobarbital (5-ethyl-5-phenylbarbituric acid), and amobarbital (5-ethyl-5-isopentylbarbituric acid). Their synthesis and spectral characterizations are presented.

Experimental

Nujol mulls of complexes were used to obtain infrared spectra in the 4000 to 600 cm^{-1} region with a Beckman AccuLab 4 spectrophotometer. Potassium bromide discs were used to obtain spectra in the 600–250 cm^{-1} region with a Perkin-Elmer Model 457 spectrophotometer. Dimethylsulfoxide solutions were used to obtain ultraviolet-visible electronic spectra in the 200–800 nm region with a Shimadzu Model 200 spectrophotometer. EPR spectra were obtained on a Varian E-9 spectrometer operating at 9.1 GHz with 100 kHz modulation. The microwave frequency was measured using a Hewlett-Packard microwave frequency counter and the magnetic field was calibrated using a Magnion NMR-type gaussmeter. Elemental analyses were performed by M. H. W. Laboratories, Phoenix, Arizona.

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TABLE I. Assigned Infrared Absorption Bands (cm^{-1}) for the Copper(II) Complexes.

Compound	ν(C=O)			γ(N–H)	ν(Cu–N)
Phenobarbital	1772	1737	1710	850	
Cu(phen)$_2$(py)$_2$	1721	1660	1620	887	540, 585
Cu(phen)$_2$(imid)$_2$	1700	1600	1618	885	538, 580
Cu(phen)$_2$(H$_2$O)$_2$	1710	1660	1600		535, 555
Amobarbital	1754	1721	1695	855, 820	
Cu(amo)$_2$(py)$_2$	1710	1660	1600	848	510, 540
Cu(amo)$_2$(imid)$_2$	1710	1670	1590	848	510, 538
Cu(amo)$_2$(H$_2$O)$_2$	1710–1650 (broad)			850	520, 540

Bis(phenobarbiturato)diaquocopper(II) Trihydrate

A solution of $CuCl_2 \cdot 2H_2O$ (0.85 g, 5 mmol) in 30 ml H_2O was added dropwise to a solution of the sodium salt of phenobarbital (2.54 g, 10 mmol) in 150 ml H_2O, with constant stirring. The resulting sky-blue precipitate was filtered, washed with H_2O, and dried in air. *Anal.* Calcd for ($CuC_{24}H_{26}N_4O_8 \cdot 3H_2O$): C, 46.81; H, 5.20; N, 9.09. Found: C, 46.50; H, 5.13; N, 9.02.

Bis(phenobarbiturato)bispyridinecopper(II)

This complex was prepared according to a published method [9]. *Anal.* Calcd for ($CuC_{34}H_{32}N_6O_6$): C, 59.71; H, 4.68; N, 12.28. Found: C, 59.83; H, 4.83; N, 12.23.

Bis(phenobarbiturate)bisimidazolecopper(II) Dihydrate

Imidazole (0.34 g, 5 mmol) was added to a 70 ml aqueous solution of sodium phenobarbital (1.27 g, 5 mmol) with constant stirring. After several minutes a solution of $CuCl_2 \cdot 2H_2O$ (0.43 g, 2.5 mmol) in 50 ml H_2O, was added dropwise to the stirred solution. The purple precipitate was filtered, washed with H_2O, ethanol, and ether and air dried. *Anal.* Calcd for ($CuC_{30}H_{34}N_8O_8$): C, 51.61; H, 4.87; N, 16.04. Found: C, 51.16; H, 4.69; N, 16.27.

Bis(amobarbiturato)diaquocopper(II)

This complex was prepared as described for the synthesis of the phenobarbital analog, except that cupric acetate was used instead of cupric chloride. *Anal.* Calcd for ($CuC_{22}H_{38}N_4O_8$): C, 48.03; H, 6.91; N, 10.18. Found: C, 47.56; H, 6.23; N, 10.10. (See references [14–16] for discussions of difficulties in obtaining hydrogen analysis for hydrated copper complexes).

Bis(amobarbiturato)bispyridinecopper(II) Monohydrate

This complex was prepared as described for the synthesis of the phenobarbital analog. *Anal.* Calcd. for ($CuC_{32}H_{46}N_6O_7$): C, 55.68; H, 6.66; N, 12.17. Found: C, 55.44; H, 6.58; N, 12.02.

Bis(amobarbiturato)bisimidazolecopper(II)

This complex was prepared as described for the synthesis of the phenobarbital analog. *Anal.* Calcd for ($CuC_{28}H_{42}N_8O_6$): C, 51.72; H, 6.46; N, 17.23. Found: C, 51.40; H, 6.46; N, 17.27.

Results and Discussion

Infrared Spectra

Assigned C=O, N–H, and Cu–N absorption frequencies are tabulated in Table I. Three absorption bands in the regions of 1700 to 1721 cm^{-1}, 1660 to 1670 cm^{-1}, and 1590 to 1625 cm^{-1} are assigned as carbonyl stretching vibrations. All three bands are bathochromically shifted with respect to the positions observed for the free acid. Based upon reported values [17], the carbonyl stretching vibrations observed at 1772, 1737, and 1710 cm^{-1} for phenobarbital have been assigned to the 2-, 4-, and 6-carbonyl groups, respectively. Thus, we have assigned the high frequency carbonyl bands obtained for these copper complexes to the 2-position. The low frequency band is assigned to the 6-position and the middle band to the 4-carbonyl group. The fact that the carbonyl absorption frequencies in all of the barbiturate copper complexes are virtually the same suggests that the barbiturate anion is bound through nitrogen to copper. The structures of these complexes, based upon elemental analyses and infrared spectral data are shown in Fig. 1. A very strong absorption band at about 1710 cm^{-1} and a less intense broad band at 1600 cm^{-1} were observed for the Cu(phen)$_2$(H$_2$O)$_2$ complex. The dissimilarity in intensity of the carbonyl bands and the strong absorption band of one of the carbonyl groups in the Cu(phen)$_2$(H$_2$O)$_2$ complex, suggests that this carbonyl group is conjugated with the Cu–N bond resulting in enolization of the 4-carbonyl group.

TABLE II. Electronic Absorption Band Maxima (nm) for Copper(II) Complexes in DMSO Solution.

Compound	λmax (ϵ_M)
Phenobarbital	251 (800), 258 (577), 263sh (490), 268sh[a] (360)
$Cu(phen)_2(py)_2$	252 (9700), 257sh (8670), 263sh (6950), 287sh (2200), 709 (70)
$Cu(phen)_2(imid)_2$	251 (7900), 287sh (2280), 638 (122)
$Cu(phen)_2(H_2O)_2$	251 (6900), 287sh (2200), 689 (60)
Amobarbital	249 (97), 265sh (50)
$Cu(amo)_2(py)_2$	253 (8430), 257sh (8100), 263sh (6600), 287sh (2350), 705 (80)
$Cu(amo)_2(imid)_2$	251 (3000), 287sh (1650), 620 (182)
$Cu(amo)_2(H_2O)_2$	252 (6700), 283sh (1450), 685 (70)

[a] Shoulder.

Furthermore, the disappearance of the N–H absorption band in the infrared spectrum of $Cu(phen)_2(H_2O)_2$ and the presence of: a) split OH stretching absorption bands near 3500 cm^{-1} and 3440 cm^{-1} [18], and b) a strong absorption band at 1210 cm^{-1} due to the C–O chromophore support the suggested enolization of the 4-carbonyl group. The other complex which contains an OH group, *i.e.* $Cu(amo)_2(H_2O)_2$, also shows a medium absorption band at 3440 cm^{-1} which is due to O–H stretching in water molecules.

All complexes and parent acids show a series of bands between 1600 and 600 cm^{-1}. The medium to strong absorption bands present in the range of 1295 to 1335 cm^{-1} have been assigned to C–N stretching vibrations. All compounds except $Cu(phen)_2(H_2O)_2$ showed absorption bands between 1408 and 1428 cm^{-1} and 848 to 887 cm^{-1} which were assigned to δ(N–H) and γ(N–H), respectively. In addition, the infrared spectra of complexes containing pyridine or imidazole ligands had absorptions characteristic of these ligands. Table I also lists the symmetric and asymmetric Cu–N stretching frequencies obtained for all of the barbiturate complexes. These bands appear in the 510 and 585 cm^{-1} region [4] and are at higher frequencies than amine and imine Cu–N absorption values [19]. This suggests that the Cu–barbiturate bond is stronger than the Cu–amine or Cu–imine bonds.

Electronic Spectra

The electronic spectra of copper(II) complexes in DMSO solution are summarized in Table II. At higher energies new absorption bands appeared between 283 and 287 nm in the spectra of these complexes. These bands were absent in the spectra of the barbiturates. In addition, these complexes show four bands at about 251, 258, 263, and 268 nm that are attributed to n → π or π → π* transitions originating within the barbiturate chromophore. The intensities of these absorptions increase upon complexation. The band between 283 and 287 nm was assigned to a charge transfer transition, since this band is absent from spectra of zinc barbiturates as well as the parent barbiturate ligands.

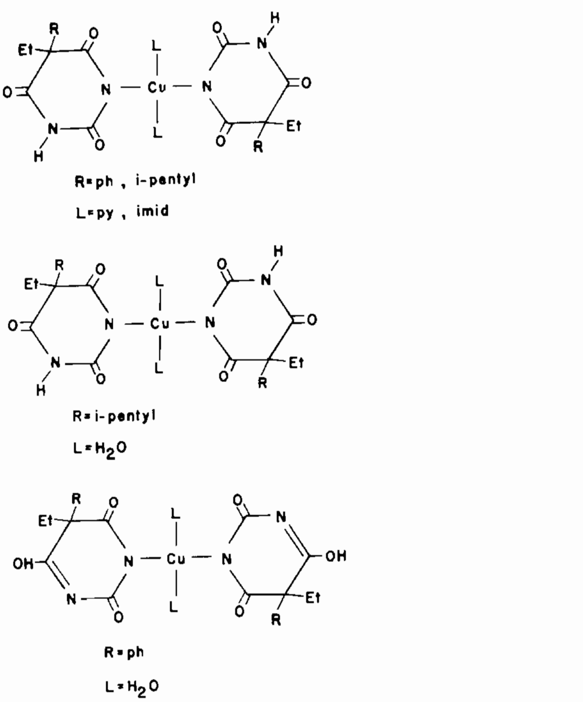

Fig. 1. The structures of copper(II) complexes of phenobarbital and amobarbital.

In general, copper(II) complexes possess a low energy absorption band between 620 and 710 (ϵ_M = 60 to 182) which encompasses the range for copper d–d transitions. The spectral results indicate that the d–d is quite sensitive to the nature of the solvating ligand and suggest the following order in 10Dq: pyridine < H_2O < imidazole. Generally, on the basis of base strength, the following order is expected: DMSO < H_2O < pyridine < imidazole. On this basis the position of the diaquo complexes is anomalous. Differences in π-bonding can change this order, causing an increase in 10Dq. The EPR results indicate more extensive π-bonding in the pyridine complexes than in the imidazole complexes but this does not cause a change in the spectrochemical series as has been observed for some other complexes [21]. Since M → L π-bonding does not occur with H_2O, we suggest that the unexpected increase in 10Dq for the diaquo complexes is steric in origin. The EPR results for the diaquo complexes indicate a different geometry from the diamine complexes, probably

TABLE III. EPR Parameters for the Cu(II) Complexes at 120 K.

Compound	Solid			Frozen DMSO Solution			
	$g_\parallel$	$g_\perp$	$A_\parallel$(Cu) cm^{-1}	$g_\parallel$	$A_\parallel$(Cu) cm^{-1}	α^2	β_1^2
$Cu(phen)_2(py)_2$	2.20	2.045	n.r.	2.213	0.0201^a	0.83	0.54
$Cu(phen)_2(imid)_2$	2.21	2.048	n.r.	2.262	0.0183^a	0.83	0.75
$Cu(phen)_2(H_2O)_2$	2.215		$0.0212^{a,b}$	2.287	0.0164^a	0.80	0.78
$Cu(amo)_2(py)_2$	2.20	2.046	n.r.	2.220	0.0201^a	0.84	0.56
$Cu(amo)_2(imid)_2$	2.22	2.046	n.r.	2.258	0.0194^a	0.86	0.73
$Cu(amo)_2(H_2O)_2$	2.256		0.0181^a	2.218	0.0217^a	0.88	0.55

$^a A_\perp(N) = 0.0015\ cm^{-1}$. $^b A_\parallel(Cu) = 0.0198\ cm^{-1}$, $g_\parallel = 2.231$ at 300 K.

due to axial solvation. The smaller size of the H_2O ligand may also allow the diaquo complexes to be more planar than the diamine complexes which will lead to a higher d–d band energy [22].

Epr Spectra

X-band EPR spectra were obtained with solids and DMSO solutions at both room temperature and at 120 K. DMSO solutions of all samples gave poorly resolved spectra and were not helpful in elucidating structures at room temperature.

CuB_2L_2 Complexes

Solid state spectra of CuB_2L_2 (B = phenobarbital, amobarbital; L = pyridine, imidazole) were broad, unresolved, and axially symmetric with $g_\parallel > g_\perp > g_e$ consistent with a $d_{x^2-y^2}$ ground state and appreciable copper–copper dipole interaction causing line broadening. No signals were observed near g = 4 and $G = (g_\parallel - 2)/(g_\perp - 2)$ was greater than 4, indicating negligible exchange interaction [23, 24].

In frozen DMSO solution these four complexes gave well resolved spectra showing substantial superhyperfine structure in the $g_\perp$ region of the spectrum. Spectral parameters were rather similar, as shown in Table III. The EPR spectrum of $Cu(amo)_2(py)_2$ is shown in Fig. 2. The spectra indicate a tetragonal CuN_4 site with the unpaired electron in the $d_{x^2-y^2}$ orbital. The $g_\parallel$ ad $A_\parallel$ (Cu) values can be used to analyze the nature of the metal–ligand bonds. Using the method of Kivelson and Neiman [25] the parameter α^2, which is a term related to the covalent nature of the in-plane σ bonds, was found to be almost constant at about 0.84. If the experimental λ_{max} values for the d–d transitions are used to estimate E_{xz}, the parameter β_1^2, which can be related to the out-of-plane π bonding was found to be about 0.54 for the pyridine containing compounds and about 0.74 for the imidazole containing compounds. Thus π bonding is more extensive in the pyridine adducts.

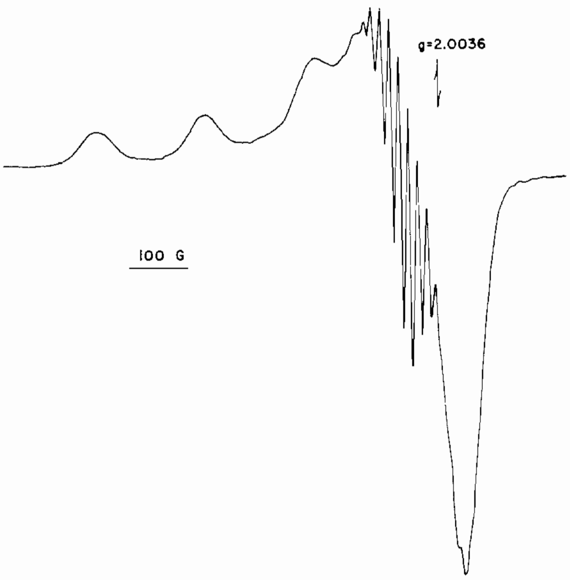

Fig. 2. EPR spectrum of $Cu(amo)_2(py)_2$ in frozen DMSO solution.

$CuB_2(H_2O)_2$ Complexes

In the solid state these complexes gave spectra with resolved copper hyperfine splitting, indicating that there is little interaction between adjacent copper ions. Representative EPR spectra of $Cu(phen)_2(H_2O)_2$ and $Cu(amo)_2(H_2O)_2$ are shown in Fig. 3. $Cu(phen)_2(H_2O)_2$ also showed resolved nitrogen hyperfine structure in the $g_\perp$ region of the spectrum. The EPR parameters of this complex were also slightly temperature dependent, $A_\parallel$(Cu) increasing by 0.0014 cm^{-1} as the temperature was decreased from 300 K to 120 K. The EPR parameters indicate a tetragonal copper site. The two complexes have significantly different EPR parameters. $Cu(amo)_2(H_2O)_2$ has parameters consistent with a CuN_2O_2 site [26] but $Cu(phen)_2(H_2O)_2$ has parameters that

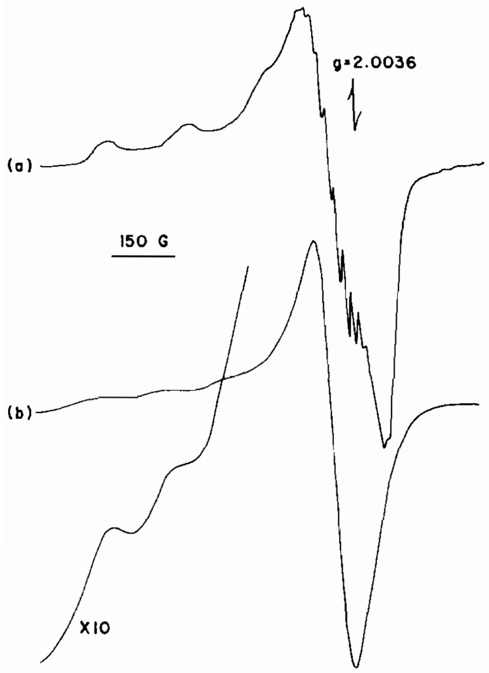

Fig. 3. EPR spectra in solid state at 120 K of (a) $Cu(phen)_2(H_2O)_2$ and (b) $Cu(amo)_2(H_2O)_2$.

are more like a CuN_4 site. This fact, plus the fact that the EPR parameters for this complex are temperature dependent, indicates that two additional water molecules may be coordinated in the axial positions, an observation consistent with the microanalytical data which indicate three water molecules of crystallization.

In frozen DMSO solution, spectra of $Cu(phen)_2(H_2O)_2$ showed that three species were present. These are attributed to $Cu(phen)_2(H_2O)_2$, $Cu(phen)_2(H_2O)(DMSO)$, and $Cu(phen)_2(DMSO)_2$. This was confirmed by adding increasing amounts of water which led to the expected changes in relative intensity of the three species. Even in DMSO solution, however, the major species is the diaquo complex. This species has the EPR parameters expected for a tetragonal CuN_2O_2 site and shows the nitrogen hyperfine pattern in the $g_\perp$ region that is expected for two nitrogen ligands with $A_\perp(N)$ approximately half $A_\perp(Cu)$ as is commonly found for such complexes. The $Cu(amo)_2(H_2O)_2$ complex showed no tendency to undergo solvolysis but the EPR parameters are similar to those of the phenobarbital complex in the solid state rather than the phenobarbital complex in frozen DMSO solution. We attribute this to a stronger interaction of the solvent along the axial positions.

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