Alder trapping experiment[17] using ethyl vinyl ether to yield **5** (Scheme II).

The formation of the 1,4-dihydropyridine **2a** from the reaction of MDA with glycine methyl ester in the absence of added second aldehyde may be rationalized by the mechanism shown in Scheme III, where the very slow formation of acetaldehyde from the thermal cleavage of the amino alcohol (hydrated enaminal) **6** results in the eventual formation of an alkylidene MDA which can be trapped by a second molecule of enaminal. Malondialdehyde itself could behave as the "second aldehyde" in this reaction forming the alkylidene MDA **7** which would then result in the dihydropyridine **8**. However, **8** was not isolated in this reaction. In order to prove that dihydropyridine **2a** was not produced by the in situ decarbonylation of **8**, an authentic sample of **8** was prepared by an alternative route. It was found to be thermally stable under the conditions used to produce the 1,4-dihydropyridines.

We conclude from these initial studies that MDA is able to modify amino acid residues to fluorescent 1,4-dihydropyridines. These findings may be of significance in understanding the biological chemistry of MDA in vivo and may explain some of the spectral disparities reported earlier on the interaction of MDA with amino acids and proteins.[12,13] In addition, some of the dihydropyridines produced in this study may be of interest as fluorescent biological probes of the calcium channel in living systems.[18] Further studies on the dihydropyridines as well as the alkylidene malondialdehydes are in progress.

Acknowledgment. We thank the National Science Foundation for support of this research.

Supplementary Material Available: Tables of NMR (^1H and ^{13}C), UV, fluorescence, and mass spectral data for adducts (10 pages). Ordering information is given on any current masthead page.

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Drug-Metal Interactions: An Unusual Four-Membered Ring Copper Phenobarbital Complex

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Phenobarbital (**1**) is among the anticonvulsant drugs used in the treatment of most forms of epilepsy.[1,2] The drug may be administered orally, intramuscularly, or intravenously following which it is transported to the plasma. Since most of the labile copper in human plasma[3] is loosely bound to albumin, this metal can bind to amino acids and other chelating ligands. It is of interest, therefore, to determine the copper binding properties of phenobarbital and its sodium salt. Monodentate 2:1 copper complexes of barbiturates have been studied by various authors[4,5] using spectroscopic methods. During our studies of copper-phenobarbital interactions, a new type of a bidentate, 2:1 copper complex was obtained.

This report describes the synthesis, characterization, and the chemical structure of disodium bis(phenobarbiturato)copper(II), ($Cu^{II}(PB)_2$). The blue-green complex was prepared by combining methanolic solutions of $Cu^{II}Cl_2\cdot 2H_2O$ and sodium phenobarbital in a 1:2 molar ratio.[6,7] ESR and infrared data indicate that the copper atom is coordinated to two nitrogen atoms from each phenobarbital in a square-planar arrangement forming unusual four-membered rings. To our knowledge this is the first report on the synthesis and characterization of a copper complex containing this number of ring atoms.

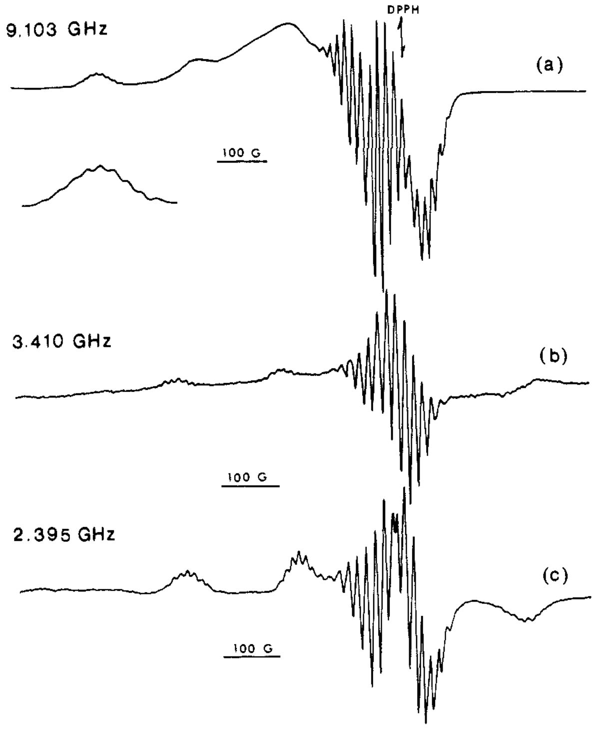
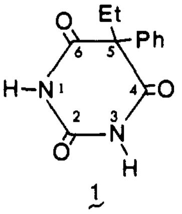


Figure 1. Multifrequency ESR spectra of $Cu^{II}(PB)_2$ complex in frozen MTHF glass at 77 K.

The carbonyl region of the infrared spectrum of $Cu^{II}(PB)_2$ shows two bands of approximately equal intensity at 1625 and 1672 cm^{-1} and a weak band at 1710 cm^{-1}. All three bands are bathochromically shifted with respect to positions observed for the free acid.[8] In addition, a strong peak near 1620 cm^{-1} was observed which is not present in the free ligand. The infrared spectrum of the carbonyl region resembles in form and intensity patterns that reported for sodium phenobarbital.[8] For reference, the latter compound is based on an enolized C═O group in the 2-position[8] with a deprotonated nitrogen atom. In the copper complex under study, both nitrogen atoms are deprotonated resulting in resonance structure **2**. Thus, the three carbonyls would no longer be expected to have the same intensity and, based upon previous work,[8] the high-frequency weak C═O band is assigned to the 2-position. The two remaining carbonyls in the 4- and 6-positions, however, are in the same environment and are coupled



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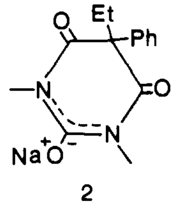

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[7] Anal. Calcd for $Na_2(CuC_{24}H_{22}N_4O_6\cdot 4H_2O)$: C, 44.77; H, 4.66; N, 8.70. Found: C, 44.52; H, 4.62; N, 8.74.

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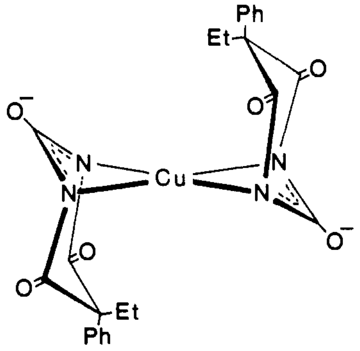

Figure 2. Proposed structure of Cu$^{\mathrm{II}}$(PB)$_2$ complex.

giving rise to symmetric and asymmetric carbonyl vibrations. The band at 1620 cm^{-1} is presumably due to a C=N bond conjugated to one of the carbonyl groups.

The ESR spectra of the complex recorded at liquid nitrogen temperature in methyltetrahydrofuran (MTHF) at three different microwave frequencies are shown in Figure 1. These spectra exhibit a typical copper hyperfine pattern with approximately axial symmetry ($g_{xx} = g_{yy}$). Splittings due to ^{63}Cu and ^{65}Cu were not resolved because of line broadening. In addition, no ESR signals were detected at half-field, $g = 4$, as would be expected from spin–spin interactions between two copper atoms. The X-band spectrum (Figure 1a) resembles that reported for Cu$^{\mathrm{II}}$TPP[9,10] and shows the splitting of the $M_I = -{}^3/_2$ of the parallel region into nine lines due to spin interactions with four neighboring nuclei, namely, nitrogen (^{14}N, $I = 1$) atoms. Low microwave frequency spectra, where strain broadening is reduced,[11-14] show well-resolved nitrogen hyperfine structures in both the $g_\parallel$ and $g_\perp$ regions. The nine-line pattern of the $M_I = -{}^3/_2$ and $M_I = -{}^1/_2$ of the parallel components supports strongly the coordination of four nitrogen atoms with a copper ion as shown in Figure 1b,c. Furthermore, the relative intensities are very close to those predicted for four nitrogens, which suggests that the four nitrogens are equivalent. The room temperature ESR spectrum also shows coupling to four nitrogens. The ESR parameters $g_\parallel$ and $A_\parallel$ were easily obtained from low-temperature spectra. The $g_\perp$ and $A_\perp$ values, on the other hand, were calculated from $g_\parallel$ and $A_\parallel$ and the isotropic values in solution ($g_{\mathrm{iso}} = (g_\parallel + 2g_\perp)/3$ and $a_{\mathrm{iso}} = (A_\parallel + 2A_\perp)/3$). The nitrogen hyperfine coupling constant in the $g_\perp$ region was approximated by $1/2^{1/2}[A_\parallel{}^{\mathrm{N}})^2 + (A_\perp{}^{\mathrm{N}})^2]^{1/2}$, the average in-plane value derived from the perpendicular lines. The ESR spin Hamiltonian parameters are $g_\parallel = 2.209$, $g_\perp = 2.04$, $A_\parallel{}^{\mathrm{Cu}} = 0.0192$ cm^{-1}, $A_\perp{}^{\mathrm{Cu}} = 0.0029$ cm^{-1}, $A_\parallel{}^{\mathrm{N}} = 0.0016$ cm^{-1}, and $A_\perp{}^{\mathrm{N}} = 0.0012$ cm^{-1}. These ESR parameters are similar to those obtained for Cu$^{\mathrm{II}}$TPP,[9,10] which indicates that, in general, the interactions are comparable. Furthermore, the ESR parameters obtained are characteristic of d^9 ions with an unpaired electron in the d$_{x^2-y^2}$ orbital ($g_\parallel > g_\perp > g_e$).

The ligand field transition energies which are characteristic of the d–d transitions were estimated from visible absorption spectra of Cu$^{\mathrm{II}}$(PB)$_2$. From the spectra obtained in Me$_2$SO, the following values were determined and subsequently used as ligand field transition energies: $\Delta E_{xz} = 23920$ and $\Delta E_{xy} = 15800$ cm^{-1}. These energies and the ESR parameters can be used to determine the nature of the metal–ligand bonds. From the approaches of Roberts and Koski[15] and Kivelson and Neiman,[16] the bonding coefficients α^2, $\beta_1{}^2$, and β^2 were calculated. On the basis of these bonding parameters, the following is proposed: (1) the in-plane σ bonding is moderately covalent with $\alpha^2 = 0.80$, (2) the in-plane π bonding is moderately covalent with $\beta_1{}^2 = 0.71$, and (3) the out-of-plane π bonding is moderately covalent with $\beta^2 = 0.77$.

The structure proposed for this complex based on the spectroscopic evidence presented above is shown in Figure 2. As indicated above, the fact that no ESR signals were detected at $g = 4$, expected for a copper–copper interactions, was used to rule out a dimer. In addition, the ESR data confirmed the fact that the copper atom is bound to four equivalent nitrogens in a square-planar arrangement. There are two reasonable configurations, chair or boat, for the barbiturate ligands in this complex. It is proposed that the barbiturates are in chair forms and the Cu—N bonds are diequatorial with regard to the chelate plane.

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Oxidation of Organocuprates with Nitroarenes: "Higher Order" Cyanocuprates Are Different[1]

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Organocuprates prepared from CuCN have been described as "higher order" *ate* complexes, R$_2$Cu(CN)Li$_2$,[2] thus implying that they are *qualitatively* different from previous organocuprates prepared from CuI or CuBr, traditionally represented[3] as R$_2$CuLi and now termed "lower order". While some of the yields obtained by using CuCN-derived cuprates are somewhat better *quantitatively* than those obtained with reagents made from CuI or CuBr,[4] such observations are not sufficient to establish that these reagents are fundamentally different. By studying their oxidation, a reaction heretofore not applied to the cyanocuprates, we have been able to obtain definitive evidence that they are, in fact, significantly different from the cuprates prepared from CuI.

Whitesides et al.[5] reported that organocuprates (prepared from CuI) are oxidized by dioxygen, CuCl$_2$·TMEDA, or nitrobenzene to yield the dimer (R–R) of the organic residue (R). We have studied the oxidation of mixed cuprates, RR′CuLi, where R = Bu (*n*-butyl) and R′ = Pe (*n*-pentyl), were chosen to minimize electronic and steric differences. Of the dozen oxidizing agents screened,[6] the dinitrobenzenes gave the best results in terms of the highest yields, and tetrahydrofuran (THF) proved to be the best solvent.[7] The results for the oxidation of cuprates derived

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