

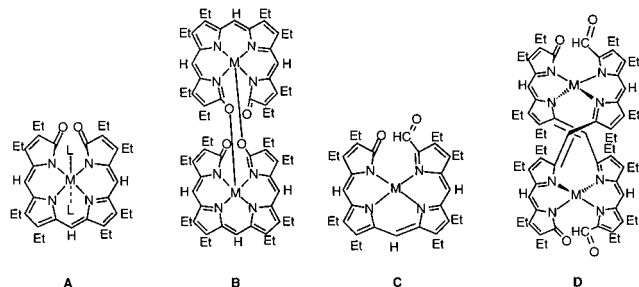
# A Linear Tetrapyrrole as a Binucleating Ligand with Copper(II). Coordination beyond the Usual M–N<sub>4</sub> Bonding

Richard Koerner, Marilyn M. Olmstead, Andrzej Ozarowski, and Alan L. Balch\*

Department of Chemistry, University of California, Davis, California 95616

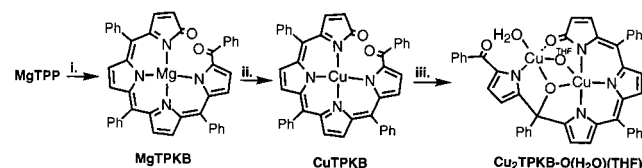
Received January 26, 1999

Heme degradation by heme oxygenase<sup>1</sup> and related processes produce a set of linear tetrapyrroles (biliverdin, formylbiliverdin, and bilirubin).<sup>2</sup> These linear tetrapyrroles cannot assume the MN<sub>4</sub> planar arrangement that is characteristic of metalloporphyrins. However, octaethylbiliverdin can form monomeric units (**A**) with helical M–N<sub>4</sub> coordination (with additional axial ligation possible),<sup>3</sup> or dimers (**B**)<sup>4</sup> which involve two tetrapyrroles that provide M–N<sub>4</sub>O coordination with the terminal oxygen atoms acting as bridges. Similarly, octaethylformylbiliverdin forms both helical monomers (**C**)<sup>5</sup> and dimers (**D**)<sup>6</sup> in which two tetrapyrroles provide M–N<sub>4</sub> coordination about two metal ions. Linear



tetrapyrroles (biliverdin, formylbiliverdin, and bilirubin) display biological activities, which frequently imply coordination to a metal center. Biliverdin, with antioxidant and antiviral activities,<sup>7</sup> is initially formed in heme oxygenase as an iron complex.<sup>1</sup> Formylbiliverdin may be a product from some heme oxygenases.<sup>8</sup> A related molecule has been found in senescent tree leaves.<sup>9</sup> Bilirubin is responsible for human jaundice<sup>1,2</sup> and is oxidized to a range of products by the multicopper enzyme bilirubin oxidase.<sup>10</sup> Degradation of metalloporphyrins by photo-oxidation produces tetrapyrrole metal complexes similar to natural heme degradation

## Scheme 1<sup>a</sup>



<sup>a</sup> (i) *hν*/air; (ii) Cu(OAc)<sub>2</sub>·4H<sub>2</sub>O; (iii) Cu(OAc)<sub>2</sub>·4H<sub>2</sub>O/Δ/acetone/18 h.

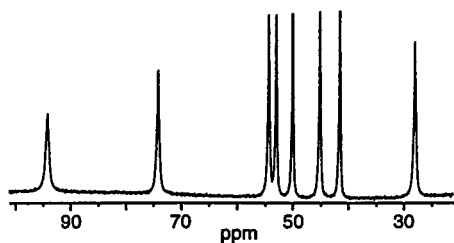
products.<sup>11</sup> Here we report the production of a complex in which a single linear tetrapyrrole unit is chemically modified and able to coordinate to two metal ions.

Magnesium tetraphenylketobiliverdin, Mg<sup>II</sup>(TPKB), from photo-oxidation of magnesium tetraphenylporphyrin<sup>12</sup> was transmetalated with Cu(OAc)<sub>2</sub>·H<sub>2</sub>O in methanol (Scheme 1). Chromatography on silica gel with 1% ethanol in dichloromethane produced brown-yellow Cu<sup>II</sup>(TPKB) {UV–vis in dichloromethane [ $\lambda_{\text{max}}$ , nm ( $\epsilon$ , L·cm<sup>−1</sup>·mol<sup>−1</sup>): 362 (3.2 × 10<sup>4</sup>), 478 (3.2 × 10<sup>4</sup>), 758 (7.3 × 10<sup>4</sup>)} and a small fraction of a blue compound. The yield of this blue compound, Cu<sub>2</sub>(TPKB-O)(H<sub>2</sub>O)(THF) [UV–vis in THF: 348 (5.0 × 10<sup>4</sup>), 558 (5.9 × 10<sup>3</sup>), 592 (1.8 × 10<sup>4</sup>), 642 (4.1 × 10<sup>4</sup>)], was greatly improved by treating Cu<sup>II</sup>(TPKB) with excess Cu(OAc)<sub>2</sub>·H<sub>2</sub>O in refluxing acetone for 18 h. This reaction occurs either under normal atmospheric conditions or under an atmosphere of purified dinitrogen. Thus dioxygen is not necessary for the formation of Cu<sub>2</sub>(TPKB-O)(H<sub>2</sub>O)(THF).

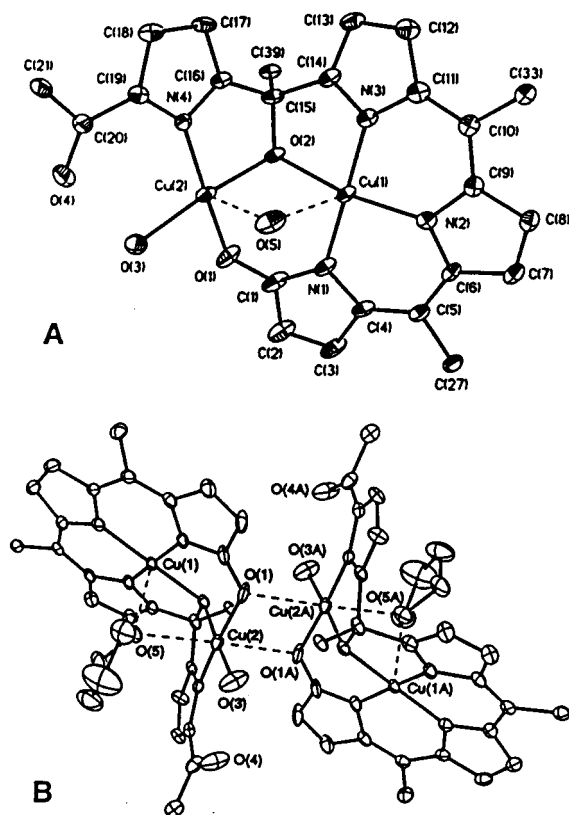
While the <sup>1</sup>H NMR spectra of most copper(II) complexes are broadened by the paramagnetic center to the extent that detection is impossible, Cu<sub>2</sub>(TPKB-O)(H<sub>2</sub>O)(THF) produces a well-resolved, paramagnetically shifted <sup>1</sup>H NMR spectrum. The downfield (100–25 ppm) portion of the <sup>1</sup>H NMR spectrum of Cu<sub>2</sub>(TPKB-O)(H<sub>2</sub>O)(THF) shows eight resonances with equal integrated areas (Figure 1). These are pyrrole resonances, since they are seen in the <sup>2</sup>H NMR spectrum of pyrrole-deuterated Cu<sub>2</sub>(TPKB-O-*d*<sub>8</sub>)(H<sub>2</sub>O)(THF) [from Mg<sup>II</sup>(TPP-pyrrole-*d*<sub>8</sub>)]. This spectrum provided the initial indication that Cu<sub>2</sub>(TPKB-O)(H<sub>2</sub>O)(THF) contained two copper(II) ions, since a number of other copper(II) complexes with both antiferromagnetically and ferromagnetically coupled metal ions display relatively easily observed <sup>1</sup>H NMR spectra.<sup>13</sup> Additionally, the variations in line width of these pyrrole resonances are indicative of the presence of two paramagnetic centers. The three broadest resonances probably belong to the pyrrole protons [on C(1), C(17), and C(13) (Figure 2)] that are situated between the two copper ions. The solution state magnetic susceptibility of Cu<sub>2</sub>(TPKB-O)(H<sub>2</sub>O)(THF) in CDCl<sub>3</sub> is 2.9  $\mu_B$  at 23 °C by the Evans technique.<sup>14</sup>

- (11) Furrhop, J.-H.; Mauzerall, D. *Photochem. Photobiol.* **1971**, *13*, 453.
- (12) Matsuura, T.; Inoue, K.; Ranade, A. C.; Saito, I. *Photochem. Photobiol.* **1980**, *31*, 23.
- (13) Satcher, J. H., Jr.; Balch, A. L. *Inorg. Chem.* **1995**, *34*, 3371. Holz, R. C.; Brink, J. M. *Inorg. Chem.* **1994**, *33*, 4609. Holz, R. C.; Brink, J. M.; Gobena, F. T.; O'Connor, C. J. *Inorg. Chem.* **1994**, *33*, 6086. Brink, J. M.; Rose, R. A.; Holz, R. C. *Inorg. Chem.* **1996**, *35*, 2878.

- (1) Maines, M. D. *Heme Oxygenase: Clinical Applications and Functions*; CRC Press: Boca Raton, FL, 1992.
- (2) Falk, H. *The Chemistry of Linear Oligoporphyrins and Bile Pigments*; Springer-Verlag: Vienna, 1989.
- (3) (a) Balch, A. L.; Mazzanti, M.; Noll, B. C.; Olmstead, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 9114. (b) Balch, A. L.; Mazzanti, M.; Noll, B. C.; Olmstead, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 12206. (c) Attar, S.; Balch, A. L.; Van Calcar, P. M.; Winkler, K. J. *J. Am. Chem. Soc.* **1997**, *119*, 3317–3323. (d) Attar, S.; Ozarowski, A.; Van Calcar, P. M.; Winkler, K.; Balch, A. L. *Chem. Commun.* **1997**, 1115–1116.
- (4) Balch, A. L.; Latos-Grazynski, L.; Noll, B. C.; Olmstead, M. M.; Safari, N. *J. Am. Chem. Soc.* **1993**, *115*, 9056.
- (5) Koerner, R.; Olmstead, M. M.; Ozarowski, A.; Phillips, S. L.; Van Calcar, P. M.; Winkler, K.; Balch, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 1274–1284.
- (6) Struckmeier, G.; Thewalt, U.; Fuhrhop, J.-H. *J. Am. Chem. Soc.* **1976**, *98*, 278.
- (7) Stocker, R.; Yamamoto, Y.; McDonagh, A. F.; Glazer, A. N.; Ames, B. N. *Science* **1987**, *235*, 1043. Nakagami, T.; Tajiri, S.; Takahashi, M.; Yamanishi, K. *Microbiol. Immunol.* **1992**, *36*, 381. Mori, H.; Otake, T.; Morimoto, M.; Ueba, N.; Kunita, N.; Nakagami, T.; Yamasaki, N.; Tajiri, S. *Jpn. J. Cancer Res.* **1991**, *51*, 755.
- (8) Nakajima, H. *J. Biol. Chem.* **1963**, *238*, 3797. Nakajima, O.; Gray, C. H. *Biochem. J.* **1967**, *104*, 20.
- (9) Iturraspe, J.; Moyano, N.; Frydman, B. *J. Org. Chem.* **1995**, *60*, 6664.
- (10) Yokosuka, O.; Billing, B. *Biochim. Biophys. Acta* **1987**, *923*, 268.



**Figure 1.** Downfield region of the  $^1\text{H}$  NMR spectrum of  $\text{Cu}^{\text{II}}_2(\text{TPKB-O})(\text{H}_2\text{O})(\text{THF})$  at  $25.0\text{ }^\circ\text{C}$  in  $\text{CDCl}_3$  solution.



**Figure 2.** (A) Perspective view of  $\text{Cu}^{\text{II}}_2(\text{TPKB-O})(\text{H}_2\text{O})(\text{THF})$  with 50% thermal contours. O(5) is part of a bridging THF molecule, and O(3) is from a water molecule. Atoms C(21), C(27), C(33), and C(39) are the ipso carbon atoms of the phenyl groups which have been omitted for clarity. (B) Dimer produced by crystallization about a center of symmetry. Bond distances ( $\text{\AA}$ ): Cu(1)–N(1) 1.933(3), Cu(1)–N(2) 1.973(3), Cu(1)–N(3) 1.902(3), Cu(1)–O(2) 2.044(3), Cu(1)–O(5) 2.572(3), Cu(2)–N(4) 1.952(3), Cu(2)–O(1) 1.953(3), Cu(2)–O(1A) 2.514(3), Cu(2)–O(2) 1.938(3), Cu(2)–O(3) 1.969(4), Cu(2)–O(5) 2.503(3), Cu(1)–Cu(2) 3.173(1), Cu(2)–Cu(2A) 3.346(1), C(1)–O(1) 1.271(5), O(3)–O(4) 2.576(5), H(3A)–O(4) 1.725(6). Bond angles (deg): Cu(1)–O(2)–Cu(2) 105.61(12), Cu(1)–O(5)–Cu(2) 77.38(8), Cu(2)–O(1A)–Cu(2A) 96.21(11).

Vapor diffusion of *n*-pentane into a tetrahydrofuran (THF) solution of the complex yielded crystals suitable for X-ray

diffraction.<sup>15</sup> The structure of  $\text{Cu}^{\text{II}}_2(\text{TPKB-O})(\text{H}_2\text{O})(\text{THF})$  is shown in the upper part of Figure 2. The two copper sites, Cu(1) and Cu(2), are bridged by the modified tetrapyrrole ligand and a weakly coordinated THF, O(5). Cu(2) is also ligated by a terminal water molecule, O(3). The hydrogen atoms on the terminal water ligand were found on a difference map, and one, H(3A), is hydrogen-bond intramolecularly to the keto oxygen, O(4). The conversion of  $\text{Cu}^{\text{II}}(\text{TPKB})$  to  $\text{Cu}^{\text{II}}_2(\text{TPKB-O})(\text{H}_2\text{O})(\text{THF})$  involves the introduction of a bridging oxy group, O(2), at C(15), which presumably comes from water in the solvent and in the copper salt. Individual  $\text{Cu}^{\text{II}}_2(\text{TPKB-O})(\text{H}_2\text{O})(\text{THF})$  molecules crystallize about a center of symmetry. This weak dimerization produces the tetracopper center shown in the lower part of Figure 2 and results in the formation of two rather long [2.514(3)  $\text{\AA}$ ] bonds between Cu(2) and O(1A) and Cu(2A) and O(1).

Magnetic data collected over the temperature range 1.8–50 K revealed that the ground state of the tetranuclear unit in the solid must be a singlet as judged by the decrease of  $\chi T$  with decreasing temperature. The magnetic data were fit using the Heisenberg–Dirac–Van Vleck Hamiltonian:  $H = J_a(S_{\text{Cu}(1)}S_{\text{Cu}(2)} + S_{\text{Cu}(1A)}S_{\text{Cu}(2A)}) + J_bS_{\text{Cu}(2)}S_{\text{Cu}(2A)}$ .

The best fit was achieved with  $J_a = 8.4\text{ cm}^{-1}$ ,  $J_b = 15.7\text{ cm}^{-1}$ , temperature independent paramagnetism =  $126 \times 10^{-6}\text{ emu}$ , and 30% of monomeric impurities. The high content of monomeric impurities is attributed to the ready loss of tetrahydrofuran from the solid and disruption of the tetranuclear structure.

Evidence for the addition of water to tetraphenylketobiliverdin was deduced earlier on the basis of spectroscopic data. Only a mononuclear zinc complex of this modified tetrapyrrole was reported which was presumed to have simple  $\text{ZnN}_4$  coordination.<sup>16</sup> The propensity for nucleophilic attack on this tetrapyrrole leads to the suggestion that, as enzyme substrates (e.g., in the copper enzyme bilirubin oxidase),<sup>17</sup> linear tetrapyrroles may undergo attack by an enzyme-based nucleophile, for example, a metal-bound hydroxyl group.

**Acknowledgment.** This work was supported by the U.S. National Institutes of Health (Grant GM 26226). The authors thank Dr. Peter Kalvins for assistance with the magnetic data.

**Supporting Information Available:** X-ray crystallographic files in CIF format for  $\text{Cu}^{\text{II}}_2(\text{TPKB-O})(\text{H}_2\text{O})(\text{THF}) \cdot 0.75\text{THF} \cdot 0.25\text{H}_2\text{O}$ . This material is available free of charge via the Internet at <http://pubs.acs.org>.

IC9901113

- (14) Evans, D. F.; James, T. A. *J. Chem. Soc., Dalton Trans.* **1979**, 723.
- (15) Blue parallelepipeds of  $\text{Cu}_2\text{C}_{44}\text{H}_{30}\text{N}_4\text{O}_3 \cdot 1.75\text{C}_4\text{H}_8\text{O} \cdot 0.25\text{H}_2\text{O}$  crystallize in the triclinic space group  $P\bar{1}$  with  $a = 11.314(2)\text{ \AA}$ ,  $b = 14.073(3)\text{ \AA}$ ,  $c = 15.165(3)\text{ \AA}$ ,  $\alpha = 108.04(3)^\circ$ ,  $\beta = 105.95(3)^\circ$ ,  $\gamma = 92.54(3)^\circ$ ,  $V = 2185.2(8)\text{ \AA}^3$ ,  $Z = 2$ . Refinement of 5897 reflections (based on  $F^2$ ) with 572 parameters converged to  $wR2 = 0.1551$  [conventional  $R1$  [5291 reflections with  $I > 2\sigma(I)$ ] is 0.0551].
- (16) Cavaleiro, J. A. S.; Hewlins, M. J. E.; Jackson, A. H.; Neves, M. G. P. M. S. *Tetrahedron Lett.* **1992**, 33, 6871. Cavaleiro, J. A. S.; Neves, M. G. P. M. S.; Hewlins, M. J. E.; Jackson, A. H. *J. Chem. Soc., Perkin Trans.* **1990**, 1937.
- (17) Solomon, E. I.; Sundaraman, U. M.; Machonkin, T. E. *Chem. Rev.* **1996**, 96, 2563.