

Synthesis and characterization of Cu(1,1,3,6,6,8-Hexamethyl-decahydro-3a,5a,8a,10a-tetra-azapyrene)Cl₂

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ABSTRACT

A novel Cu(II) complex, CuLCl₂ (L = 1,1,3,6,6,8-Hexamethyl-decahydro-3a,5a,8a,10a-tetra-azapyrene (tet-A tet)), has been formed by treatment of L with CuCl₂ dihydrate in methanol. Previously synthesized complexes of Cu(II) with tetracyclic tetraamines, which had been less sterically hindered, generally produced copper complexes with copper bound to only two non-adjacent nitrogens. The current complex has been formed in the presence of significant steric hindrance (six methyl groups) which necessitates major conformational changes to the ligand upon metal binding (two of the six-membered rings have the 'boat' conformation, rather than the free ligand all chair conformation). Additionally, the copper is bound to adjacent nitrogens – something never before encountered in a symmetric tetraamine of this kind, and probably induced by the steric hindrance of the methyl groups.

Keywords: *tetraaza-tetracycle, tetraamine, intermediate, enzyme active site, copper(II)*

INTRODUCTION

Copper(I) and copper(II) complexes of rigid bidentate amine ligands have recently gained attention in the modeling of multinuclear copper enzyme active sites (Cole 1996, DuBois 1997). This ligand type, along with the more prevalent tridentate ligands of Kitajima (Kitajima 1992, Kitajima 1994) and Tollman (Halfen 1996, Tollman 1997), have been used to study the oxidation of their Cu(I) complexes to produce Cu(II) or Cu(III) μ -hydroxo, μ -oxo, or μ -peroxo bridged dimers or even trimers that mimic active site geometries or reactivities.

This project was begun in order to increase the understanding of enzymatic active site geometries involving copper. New copper complexes of this type, might increase understanding of these active site structures and reactivities. The tetracyclic ligand used in this experiment is similar to several used in previous studies (Hubin 1999, Hubin 2001). The difference lies in the six methyl groups arranged about the periphery of the tetracycle.

Copper and palladium complexes with 1,4,8,11-tetra-azacyclotetradecane (Q14N4) have already been synthesized and characterized (Hubin 1998, Hubin 2001). The tet-A tetracycle (1,1,3,6,6,8-Hexamethyl-decahydro-3a,5a,8a,10a-tetra-azapyrene) differs from Q14N4 in the six methyl groups distributed around the macrocycle. It had been suggested that the additional steric hindrance, caused by the six methyl groups, would preclude complexation with either copper or palladium (Hubin 1999). As a result of this research, we hoped to complex the tet-A tetracycle with Cu²⁺.

MATERIALS AND METHODS

Materials:

Unless otherwise specified, all chemicals were purchased from national suppliers and were used without modification.

Physical Techniques:

Quantitative Technologies, Inc. performed elemental analyses. Mass spectra were measured by the Analytical Service of the University of Kansas on a VG ZAB HS spectrometer equipped with a xenon gun. The matrices used were NBA (nitrobenzyl alcohol) and TG/G (thioglycerol/glycerol). UV-VIS absorption was measured at McPherson College on a Varian Cary 50 Bio spectrometer. FT-IR spectra were collected at McPherson College on a Nicolet 320 Avatar on a KBr pellet sample. Magnetic measurements were taken on a Johnson-Matthey MSB I magnetic susceptibility balance. The crystal structure was obtained by Dr. Stephen Archibald at the University of Hull, in Hull, England. Data was collected on a Stöe IPDS-II imaging plate diffractometer.

EPR Spectra were taken on a Bruker ESP300E spectrometer operating in the X-band by Dr. Andrew Borovik at the University of Kansas. Parameters are as follows: Conc.: 9.1 mM Temp: 77K Microwave Frequency: 9.319 Ghz Microwave Power: 0.619 mW Receiver Gain: 8.93 e+3 Mod. Frequency: 100 kHz Mod. Amplitude: 10.02 G

Synthesis of Diaminoethane Dihydrobromide [NH₂CH₂CH₂NH₂ • 2HBr]: To 100 mL of MeOH in an erlenmeyer flask, kept cool in an icebath, 20mL (0.15 mol) of Diaminoethane (DAE) was added. To this solution 70mL of concentrated HBr (0.32 mol) was added dropwise. The white precipitate that formed was filtered on a medium glass frit and was washed thrice with 10mL portions of n-butanol, then with copious amounts of ether. To the filtrate was added ether to precipitate a second crop of brominated salt that was filtered and washed with copious amounts of ether. Both crops were covered to prevent contamination and left in a fumehood to dry. Yield: 60.3g or 90.6% calculated by to DAE.

Synthesis of 5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetra-azacyclotetradeca-4,11-diene

Dihydrobromide Dihydrate (Curtis Macrocycle): To 280mL of acetone in a 500mL erlenmeyer flask were added 31.0g (0.14 mol) of the Brominated DAE salt and 9.3mL (0.14 mol) of DAE. This solution was stirred and heated to 45°C for ~45 minutes to facilitate the endothermic reaction. The solution was cooled, and the precipitate was filtered. It was washed first with cold acetone then with room temperature ether, and dried in vacuo. Yield: 52.5g (84.8%) of a slightly reddish powder.

Synthesis of *cis*- and *trans*- 5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetra-azacyclotetradecane

(tet-A and tet-B): To 100mL of MeOH in a 500mL erlenmeyer flask at 0°C was added 20.0g (0.05 mol) of the 5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetra-azacyclotetradeca-4,11-diene dihydrobromide dihydrate. To this solution were added 6g (0.15 mol) of NaOH and 7.1g (0.19 mol) of NaBH₄ alternately in small amounts. The solution was then stirred until all of the NaOH pellets had dissolved. The solution was heated to reflux for fifteen minutes then cooled to room temperature. To 200mL of water was added 10g (0.25 mol) of NaOH. The NaOH solution was then added to the first solution. This solution was stirred for one hour as a white precipitate formed. This was then filtered and washed with cold water and yielded 14.2g (92.2%) of an off-white, curdy precipitate (a racemic mixture of tet-A and tet-B). The precipitate was left in a fumehood to dry.

Separation of Diastereomers: To 150mL of MeOH in a 250 erlenmeyer flask was added the racemic mixture of tet-A and tet-B. The mixture was heated to reflux, filtered through celite, diluted again to 150mL, and heated to reflux again. The solution was removed from heat, and 108 mL of water was added. The solution was stirred and filtered through a fine frit, yielding 2.8g (54.9%) tet-A. Another 60mL of water were added to the solution, and the resulting precipitate (a mixture of tet-A and tet-B) was filtered. The filtrate was then evaporated to yield tet-B.

Synthesis of 1,1,3,6,6,8-Hexamethyl-decahydro-3a,5a,8a,10a-tetra-azapyrene (tet-A tet = L):

Into a round bottomed flask were added 2.7g (8.5×10⁻³ mol) of tet-A and 13mL of acetonitrile. The contents of the flask were stirred and flushed with N₂ for fifteen minutes. Next, 1.5 mL of glyoxal (40% by weight in water) was added to the flask. The contents of the flask were stirred and a temperature of 50-65°C was maintained for a period of three hours. During this time, the mixture became a transparent brown. The contents of the flask were evaporated, washed with chloroform, and filtered. The filtrate was then refrigerated to condense any remaining water. Finally, the solution was filtered and evaporated to remove the chloroform. The remaining compound (tet-A Tetracycle) had the characteristics of an oil or a wax depending upon its temperature.

Synthesis of Cu(1,1,3,6,6,8-Hexamethyl-decahydro-3a,5a,8a,10a-tetra-azapyrene)Cl₂:

To a round bottom flask were added 0.31g (0.001 mol) of the Tet A Tetracycle and 20mL of MeOH. To 10mL of MeOH was added 0.21g (0.002 mol) CuCl₂ • H₂O. The copper solution was added to the round bottom flask. The solution was then heated at reflux for sixteen hours. During the reaction, the solution's color changed from an initial dark green to a light red to a blue green upon cooling. This reaction yielded light green, needle-like crystals upon cooling. Mass Spec data: A FAB+ mass spectrum in NBA matrix exhibited a peak at m/z = 442 matching the mass of CuLCl₂. Elemental Analysis: Analytical Calculated: %C: 48.05 %H: 7.84 %N: 12.45. Found: %C: 48.04 %H: 7.64 %N: 12.33.

RESULTS AND DISCUSSION

Synthesis

The tet-A macrocycle was synthesized according to known methods (Hay 1975, Figure 1).

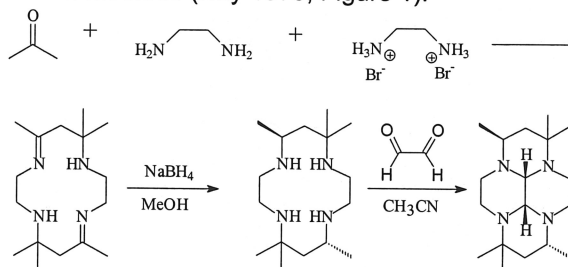


Figure 1

Condensation with glyoxal yielded the tet-A tetracycle ligand (L) (Hubin 1998, Figure 1). The tetracyclic nature of this tetraamine ligand makes it highly rigid. Its typical folded structure orients two nonadjacent nitrogens into the concave cleft while the other nonadjacent pair directs their lone pairs from the convex face. (Figure 2, methyl groups

omitted for clarity)

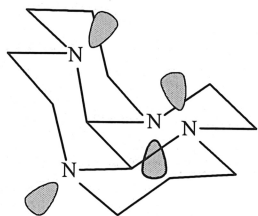


Figure 2

This ligand clearly could only coordinate a metal ion with the converging pair of nitrogens without major conformational adjustments. The result is a rigid bidentate ligand targeted for study of enzyme active sites. Previously, there have been no known metal complexes of this ligand. Despite the presence of six methyl groups around this ligand, which presents a steric challenge, the complexation with copper was rather simply done (figure 3). During the complexation reaction, the solution changed color from an initial dark blue, to a light red while heated and reacting, to a dark green upon cooling.

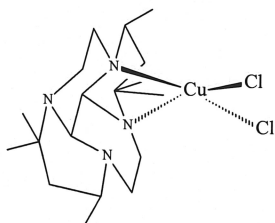
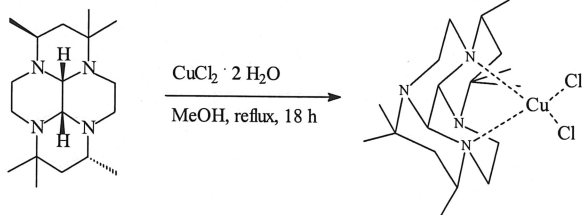


Figure 3

This reaction yielded an emerald green, needle-like crystalline solid. A powdered precipitate was obtained by adding excess ether to a saturated solution of the complex in dichloromethane.

Crystal Structure:

Determination of the crystal structure of the crystalline solid revealed that the copper had bonded to adjacent nitrogens (figure 4). This feature had been noted in only one other complex of ligands of this kind, a previously characterized asymmetric ligand (Hubin 2001, Figure 5).

Furthermore, of the four cyclohexanes within this novel complex, two exhibit the higher-energy, twist-boat conformation. This conformation is proposed to occur in an intermediate structure during inversion of the ligand from one diastereomer to another, but the

rings always revert to a 'chair' conformation according to any known crystal structures. (Riddell 1982) It should be noted that this same conformation was forced upon a similar ligand (Q14N4) by stepwise methylation of said ligand. (Hubin 1999) This leads to the hypothesis that the crystalline solid is a precipitated intermediate.

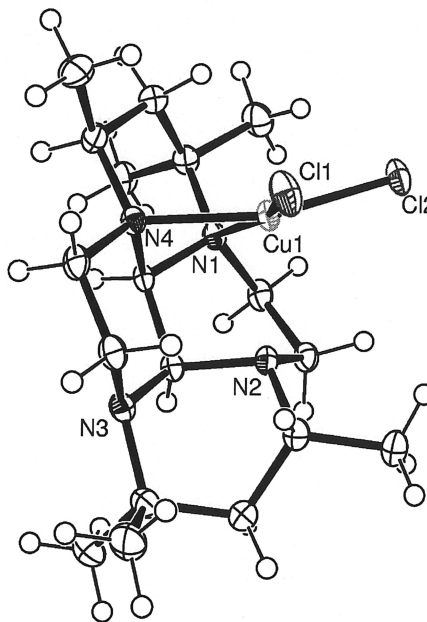
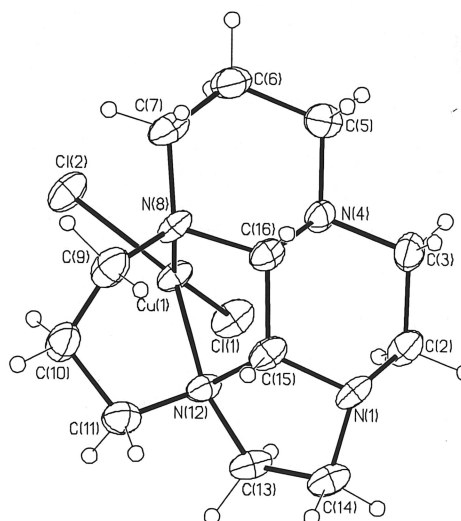


Figure 4
Figure 5



Electronic Structure:

Magnetic Moment. It was discovered that this ligand has a magnetic moment of 0.97, or roughly half the value it should have for a typical Cu(II) complex, which should have one unpaired electron. The cause for this result is still under investigation. One possible explanation is the hygroscopic nature of the complex. Additional water in the sample not accounted for would have the effect of lowering the observed magnetic moment. Because magnetic susceptibility was measured using the precipitated powder, a sample of the powder was sent for elemental analysis. Elemental analysis confirmed the results obtained from the analysis of the crystalline product.

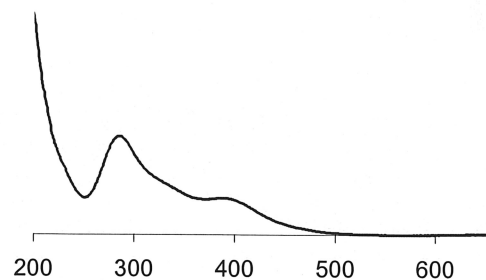
Electronic Structure. The electronic spectrum of CuLCl₂ was taken at 1.0 mM in acetonitrile. A spectrum typical of related complexes was obtained. Notable features include absorption bands at $\lambda_{\max} = 285$ nm ($\epsilon = 2,400$ M⁻¹ cm⁻¹) and $\lambda_{\max} = 389$ nm ($\epsilon = 900$ M⁻¹ cm⁻¹) which result from LMCT (ligand to metal charge transfer) between the chloride ligands and Cu. A third band was observed at $\lambda_{\max} = 748$ nm ($\epsilon = 52$ M⁻¹ cm⁻¹) resulting from a forbidden d-d transition of Cu²⁺. In UV-Vis scans of similar molecules, the band between 600-900 nm gives information about the bond angles of the copper atom. Shorter wavelengths tend to indicate a square planar conformation, whereas longer wavelengths indicate tetrahedral conformations (Hubin 2001). For this ligand, both the information obtained from the crystal structure and the electronic spectrum indicate a more square planar geometry. (Tables 1 and 2, Figure 6)

TABLE 1. Selected Bond Lengths (Angstroms)

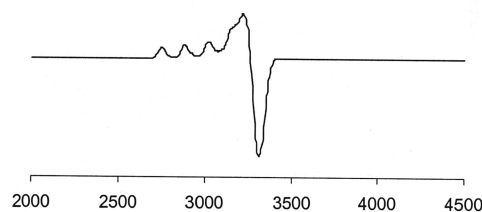
Cl(1)-Cu(1)	2.2505(4)
Cl(2)-Cu(1)	2.2374(5)
N(1)-Cu(1)	2.1835(12)
N(4)-Cu(1)	2.0828(13)

TABLE 2. Selected Bond Angles (degrees)

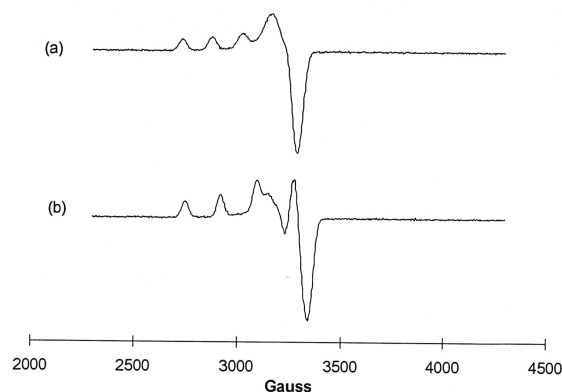
N(4)-Cu(1)-N(1)	65.13(4)
N(4)-Cu(1)-Cl(2)	156.68(4)
N(1)-Cu(1)-Cl(2)	97.40(3)
N(4)-Cu(1)-Cl(1)	97.90(3)
N(1)-Cu(1)-Cl(1)	163.02(3)
Cl(2)-Cu(1)-Cl(1)	99.072(17)

**Figure 6**

EPR. The electron paramagnetic resonance spectrum of CuLCl₂ was obtained in a frozen 1:1 MeCN/toluene solution at 77K (Figure 7). No simulation studies were carried out, but the general appearance of the spectrum indicated some rhombic character. EPR studies of related complexes have been carried out (Hubin 2001). Those ligands binding through non-adjacent nitrogens typically have a characteristic appearance, while the one other example of ligand binding through adjacent nitrogens is quite different (Figure 8b). The present complex,



having its ligand bound through adjacent nitrogens, resembles the most structurally similar example. (Figure 8a)

Figure 7**Figure 8**

As a result of this study, the first metal complex of

this ligand and a complex of the copper binding with adjacent nitrogens was produced. In previous experiments, the boat conformation was produced in one six-membered ring of a similar ligand by successive methylation of the nitrogens. In this experiment, the boat conformation was a result of the metal binding to the ligand. This would tend to indicate that the copper-nitrogen bonds are relatively strong, since a clearly unfavorable ligand conformation is stabilized by complexation.

It is notable that the spectroscopic and structural parameters of this complex are rather commonplace for copper complexes. However, the ligand conformation and binding are strikingly different from copper complexes of related ligands. Clearly the ligand has adapted its structure in order to bind copper instead of forcing changes on the copper in order for it to bind the ligand.

CONCLUSIONS

A novel Cu(II) complex with a rigid bidentate ligand has been synthesized. Copper is bound to adjacent Nitrogens in this particular molecule. This binding mode has only been seen in one asymmetric molecule of this type before; while, binding of the 'parent' of this tetracycle was seen to occur with opposite nitrogens. A similarly interesting and unusual aspect of this complex is that while two of the rings are in the stable boat conformation, the other two rings have adopted a twist-boat conformation. An explanation for these two phenomena could be that the initial binding of the copper to the complex requires that the tetracycle be in the process of inverting (due to the kinetic energy absorbed during the heating). The copper latches onto the first Nitrogen atom to be exposed, and subsequently binds to the only other Nitrogen atom available to it. Additional studies will build on the complex described above in order to produce dimers that more closely resemble enzymatic active sites in structure and reactivity.

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