

# Summer Scholar Report

## *Stabilizing transition-metal-alkylthiolate bonds via secondary sphere hydrogen bonding*

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### Introduction

Sulfur is known to play a critical role in the function of metalloenzymes. Metal-sulfur bonds are ubiquitous in metalloenzymes both at active sites and secondary sites, and this project aims to quantify the underlying factors that stabilize these bonds so as to compare them to their biological counterparts<sup>1</sup>. For example the amino acid cysteine, which contains a thiol functional group, is often bound to metal ions through its sulfur atom<sup>1</sup>. Researchers at the University of Michigan have created the ligand of interest, H<sub>3</sub>thpa, and have bound copper and both chloride and fluoride to it.<sup>2,3</sup> The results show that the bond of copper to another ligand, e.g. anionic chloride, is stabilized by the H<sub>3</sub>thpa ligand. H<sub>3</sub>thpa complexes have also been used for studying the reduction of nitrite, a function performed in organisms by a class of enzymes known as nitrite reductases<sup>4</sup>. Investigation of different metals and the anionic alkylthiolate, a counterpart of cysteine, is of interest. Studying the ligand's secondary sphere effects on stability and reactivity provide insight into nature's tuning of biological metal-sulfur bonds, especially those with enzymatic function.

### Methods/Results

The synthesis of H<sub>3</sub>thpa involves three steps, all shown in Figure 1. The total yield for all three steps is ca. 18%. Due to this low overall yield, much time was spent preparing adequate quantities of H<sub>3</sub>thpa by running the three reactions shown in Figure 1 multiple times over.

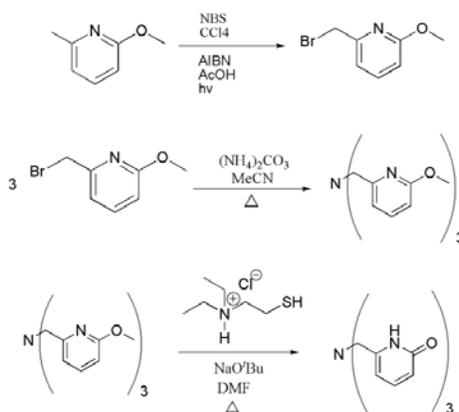
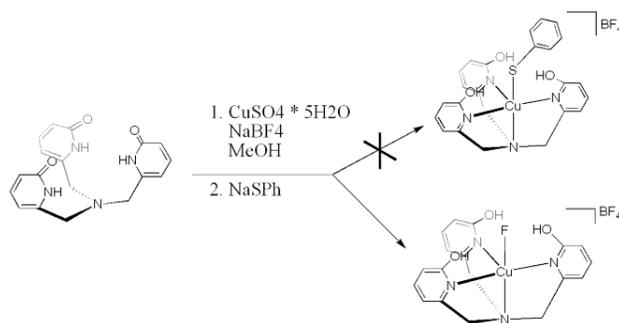
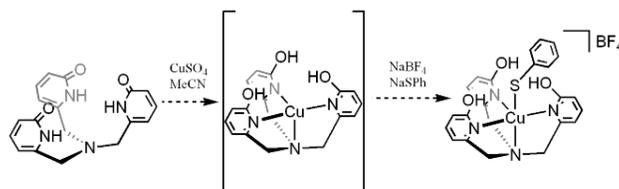


Figure 1: Synthetic Scheme to H<sub>3</sub>thpa

Once a suitable quantity of H<sub>3</sub>thpa was synthesized, a route towards [CuSPh(H<sub>3</sub>thpa)]BF<sub>4</sub> was investigated as shown in Figure 2. Rather than forming the desired product, the previously reported [CuF(H<sub>3</sub>thpa)]BF<sub>4</sub> was synthesized as determined by a single crystal X-ray diffraction experiment. This was unexpected, since the only possible fluoride source is from the counter ion BF<sub>4</sub><sup>-</sup>. Fluoride was indeed abstracted from the counter-ion BF<sub>4</sub><sup>-</sup> to create [CuF(H<sub>3</sub>thpa)]BF<sub>4</sub>; it was soon learned that fluoride can be abstracted from BF<sub>4</sub><sup>-</sup> in the presence of protic solvents<sup>5</sup>.



**Figure 2:** Formation of [CuF(H<sub>3</sub>thpa)]BF<sub>4</sub>



**Figure 3:** Proposed synthetic route to formation of [CuSPh(H<sub>3</sub>thpa)]BF<sub>4</sub> employing aprotic conditions

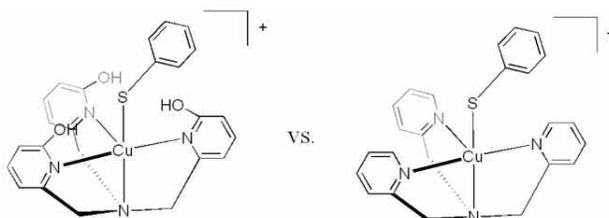
Armed with this information, a second reaction was attempted using similar reaction conditions to Figure 2, but toluene was used instead of methanol. To also reduce the risk of fluoride abstraction, CuSO<sub>4</sub>·5H<sub>2</sub>O was flame-dried to give anhydrous CuSO<sub>4</sub> as the copper source for this and future reactions. The reaction was run at elevated temperature to aid in the dissolution of the ionic substances present. Yield was poor for this reaction and the product was a black solid- this is not typical of the copper complexes previously reported<sup>2</sup>. Seeking a more reliable method, acetonitrile solvent was used due to its higher polarity vs. toluene. The ionic compounds dissolved much more readily in acetonitrile and the reaction did not require heating; the reaction scheme can be seen in Figure 4. One major concern is the risk of deprotonation of H<sub>3</sub>thpa to give a dimer. It has been shown

that a weak base, such as acetate, is able to deprotonate H<sub>3</sub>thpa to give a metal-H<sub>3</sub>thpa dimer.<sup>4</sup> Thiophenolate is a stronger base than acetate, so this is a possibility that needs to be considered when characterizing the product.

### Future Work

Once [CuSPh(H<sub>3</sub>thpa)]BF<sub>4</sub> has been synthesized and characterized, an alkylthiolate will be bound in place of the thiophenolate. Thiophenolate is first being tested since we theorize that the delocalization of sulfur electron density to its phenyl ring will provide a more favorable chance at binding to the copper metal center. The surrounding three hydrogen bond donors pull additional electron density from the sulfur. Alkylthiolates are of interest due to similarity to the cysteine residue found near the active site at metalloenzymes.

The synthesis of complexes containing tris(2-pyridylmethyl)amine (tpa) instead of H<sub>3</sub>thpa will also be investigated as shown in Figure 4. The direct impact of hydrogen bonding can be evaluated by comparing the bond lengths/bond angles from crystal structure data, by evaluating the redox potentials of the metal centers as determined by cyclic voltammetry, and by changes of the electronics of the metal center as determined by UV-Vis spectroscopy.



**Figure 4:** *CuSPh(H<sub>3</sub>thpa)<sup>+</sup> left and CuSPh(tpa)<sup>+</sup> right. Structure differences provide useful comparison for the effect of hydrogen bonding on the sulfur-copper bond.*

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### References

- (1) Solomon, E. I.; Gorelsky, S. I.; and Dey, A. Metal–thiolate bonds in bioinorganic chemistry. *J. Comput. Chem.* 2006, 27 (12), 1415–1428.

- (2) Moore, C.; Quist, D.; Kampf, J.; Szymczak, N. A 3-Fold-Symmetric Ligand Based on 2-Hydroxypyridine: Regulation of Ligand Binding by Hydrogen Bonding. *Inorg. Chem.* **2014**, 53 (7), 3278-3280.
- (3) Moore, C.; Szymczak, N. Redox-induced fluoride ligand dissociation stabilized by intramolecular hydrogen bonding. *Chem. Commun.*, **2015**, 51, 5490-5492
- (4) Moore, C.; Szymczak, N. Nitrite reduction by copper through ligand-mediated proton and electron transfer. *Chem. Sci.*, **2015**, 6, 3373-3377.
- (5) Kannan, S.; Moody, M.; Barnes, C.; Duval, P. Fluoride abstraction and reversible photochemical reduction of cationic uranyl(VI) phosphine oxide complexes. *Inorg. Chem.*, **2006**, 45 (23), 9206-9212.