



# Pyridine-2,6-bisamide ligands and their copper(II) complexes

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## Abstract:

Pyridine-2,6-bisamide ligands can be readily prepared from either pyridine-2,6-dicarboxylic acid or the di(acid chloride) and a variety of amines. Early work in this lab has shown an interesting pH dependence of the copper(II) complexes of some of these ligands so a more detailed study has been undertaken to explore the acid-base properties of these precursor ligands (R = aryl or alkyl) as well as their copper(II) complexes. The redox activity of these complexes will also be considered.

## Introduction:

Copper complexes have been explored for a number of different applications. Although copper can participate in redox chemistry during various reactions, it is only generally stable in the +2 oxidation state and has a significant preference for square-planar and square-pyramidal geometries. This makes copper a convenient transition metal for ligand exploration.

When copper(II) is found in biological systems, it is often coordinated to the medium-to-hard nitrogen and oxygen donors of amino acid sidechains and the peptide backbone. In searching the literature, it was found that until recently ligands based upon a pyridine-2,6-bisamide backbone have received little attention despite their relative ease of synthesis and inexpensive starting materials.

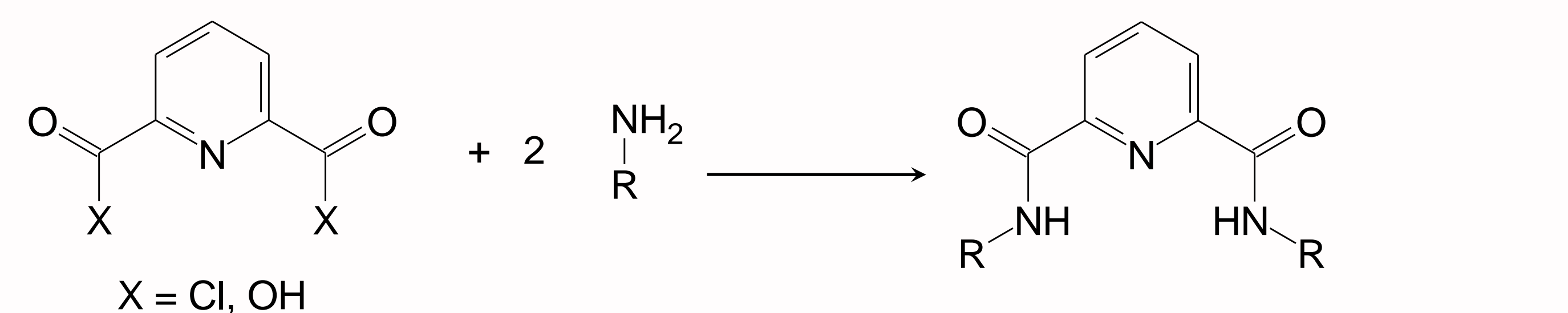
Early studies of aniline-derived ligands have shown a number of interesting properties, leading to continued research into this fruitful class of ligands.

## Ligand Families:

Initial efforts in this research are intended to screen a variety of ligand types in an effort find favorable candidates for further study. We have focused on a few classes of ligands.

### Pyridine bis-amide ligands:

This class of ligands offers a variety of readily available (and inexpensive) starting materials. This allows a large library of potential catalysts to be synthesized for screening. In reported studies, nitrogen-donor ligands have been shown to be excellent candidates for the oxidation of veratryl alcohol.



Advantages of this ligand family:

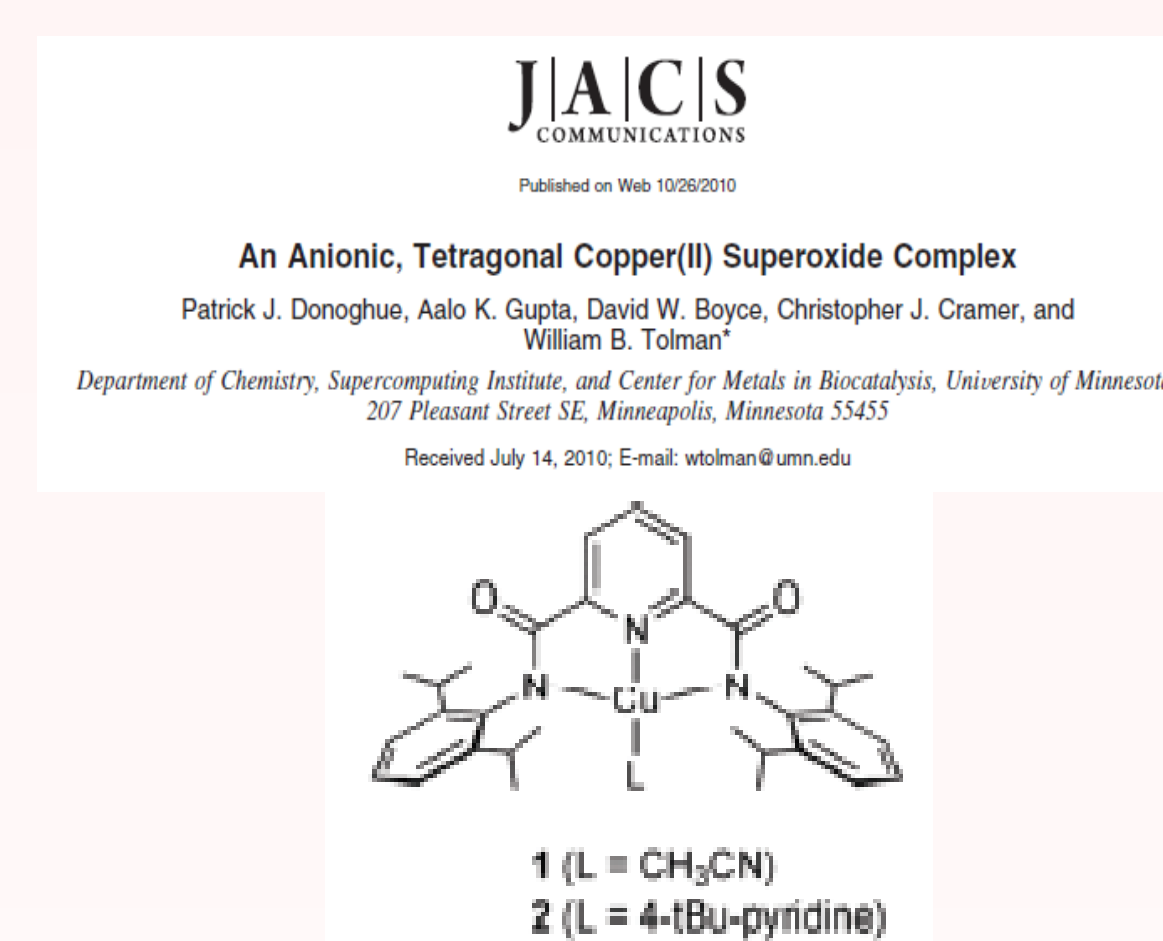
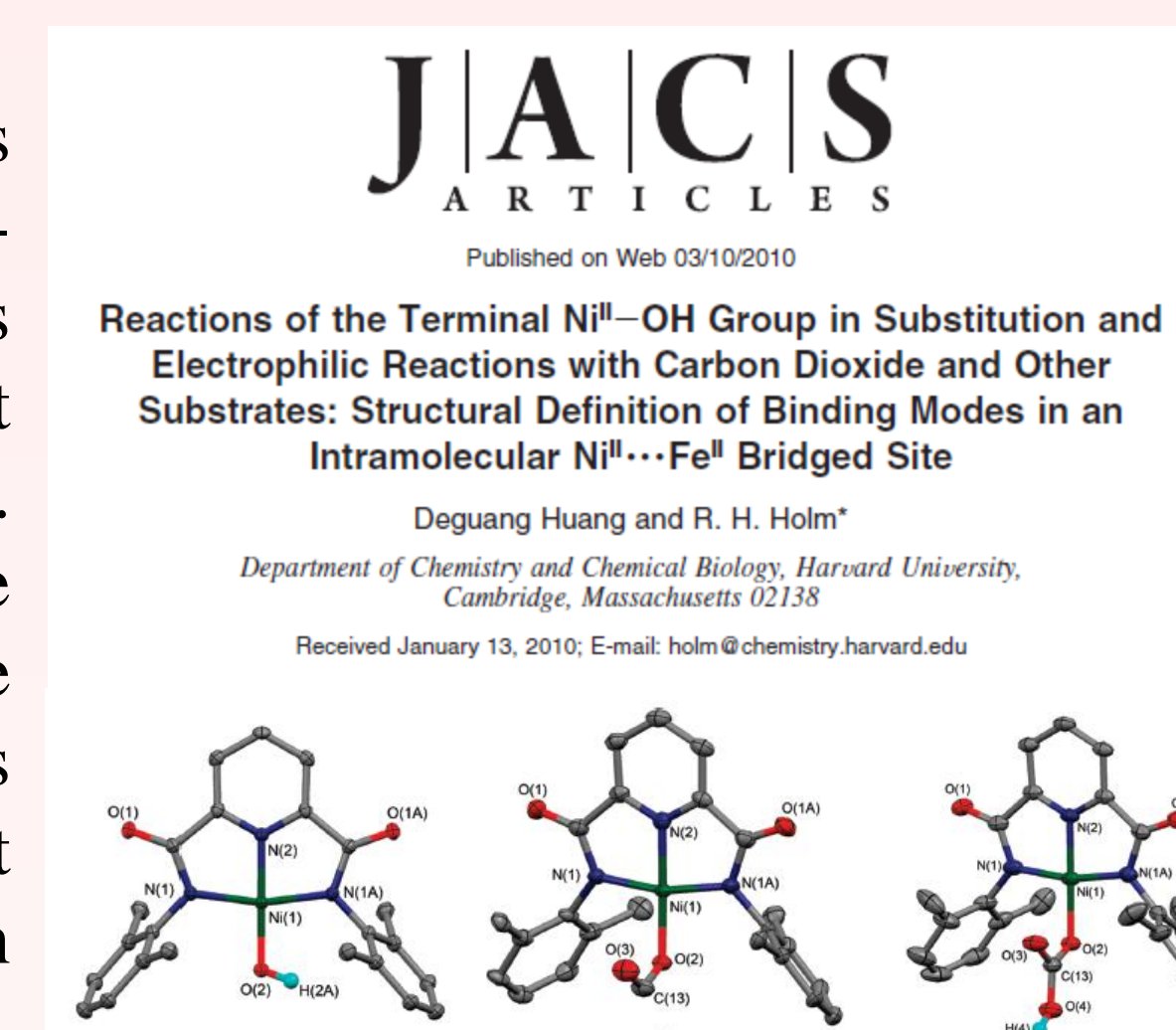
1. Wide variety of inexpensive primary amine starting materials
2. Relatively inexpensive acid chloride starting material
3. Relatively forgiving synthesis: air-stable, often crystallizable, chromatography-stable
4. Rigid *mer*/planar coordination environment
5. For 4-5 coordinate metal complexes, offers an open coordination site for exogenous ligand/substrate binding

## Recent Reports:

Within the last year, two significant papers related to this work have been published in the Journal of the American Chemical Society. When we began working on this research, there were very few reported pyridine-2,6-bisamide ligands based upon simple amine precursors.

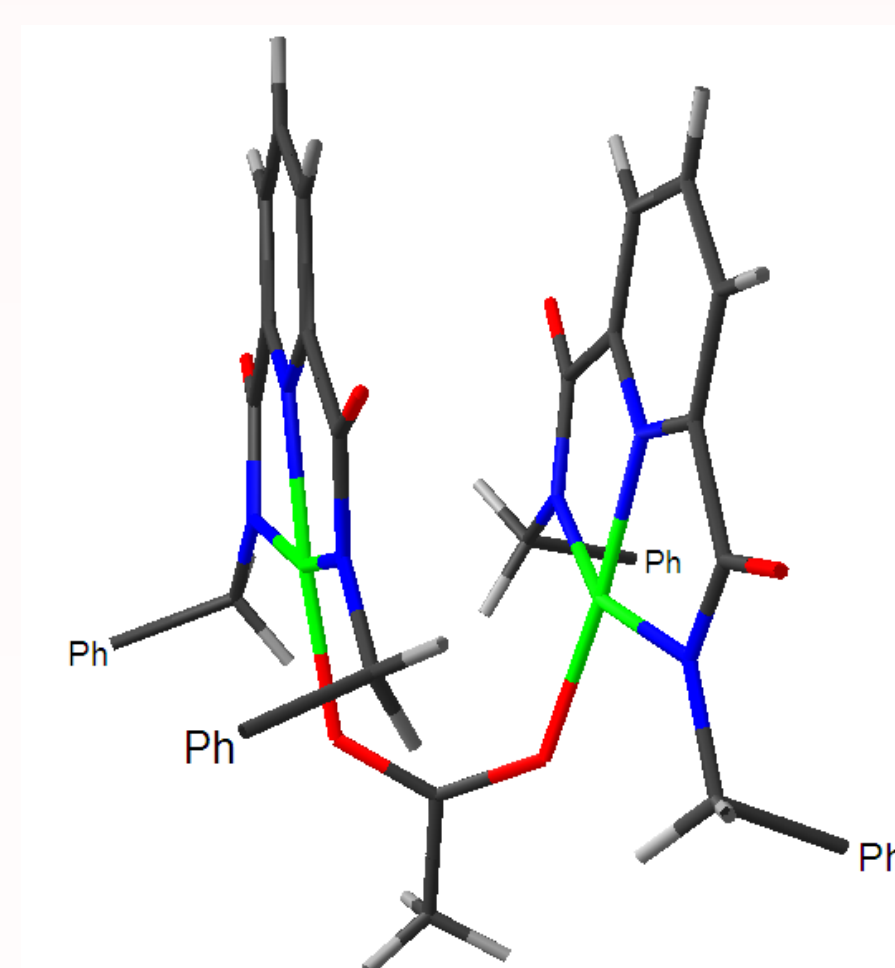
### The Ligand:

In March 2010, the Holm group from Harvard reported a series of nickel(II) complexes using the N,N'-Bis(2,6-dimethylphenyl)-2,6-pyridinedicarboxamide ligand. Although it was disappointing to see another group report this ligand, the report includes an alternate ligand cleanup that we hadn't tried. Washing the flash evaporated reaction mixture with hexane appears to effectively remove the triethylammonium chloride that is produced during reaction. Although the focus of this paper is on nickel(II) complexes, it provides valuable insight into ligand preparation as well as some of the coordination chemistry of the ligand.



### The Copper Complex:

In October 2010, the Tolman group from the University of Minnesota reported the copper complex of the closely related N,N'-bis(2,6-diisopropylphenyl)-2,6-pyridinedicarboxamide ligand. Once again, it was unfortunate to see this copper complex reported by another group, but this report provided some direction in the synthesis of these copper complexes from a group that has extensive experience with similar copper complexes.

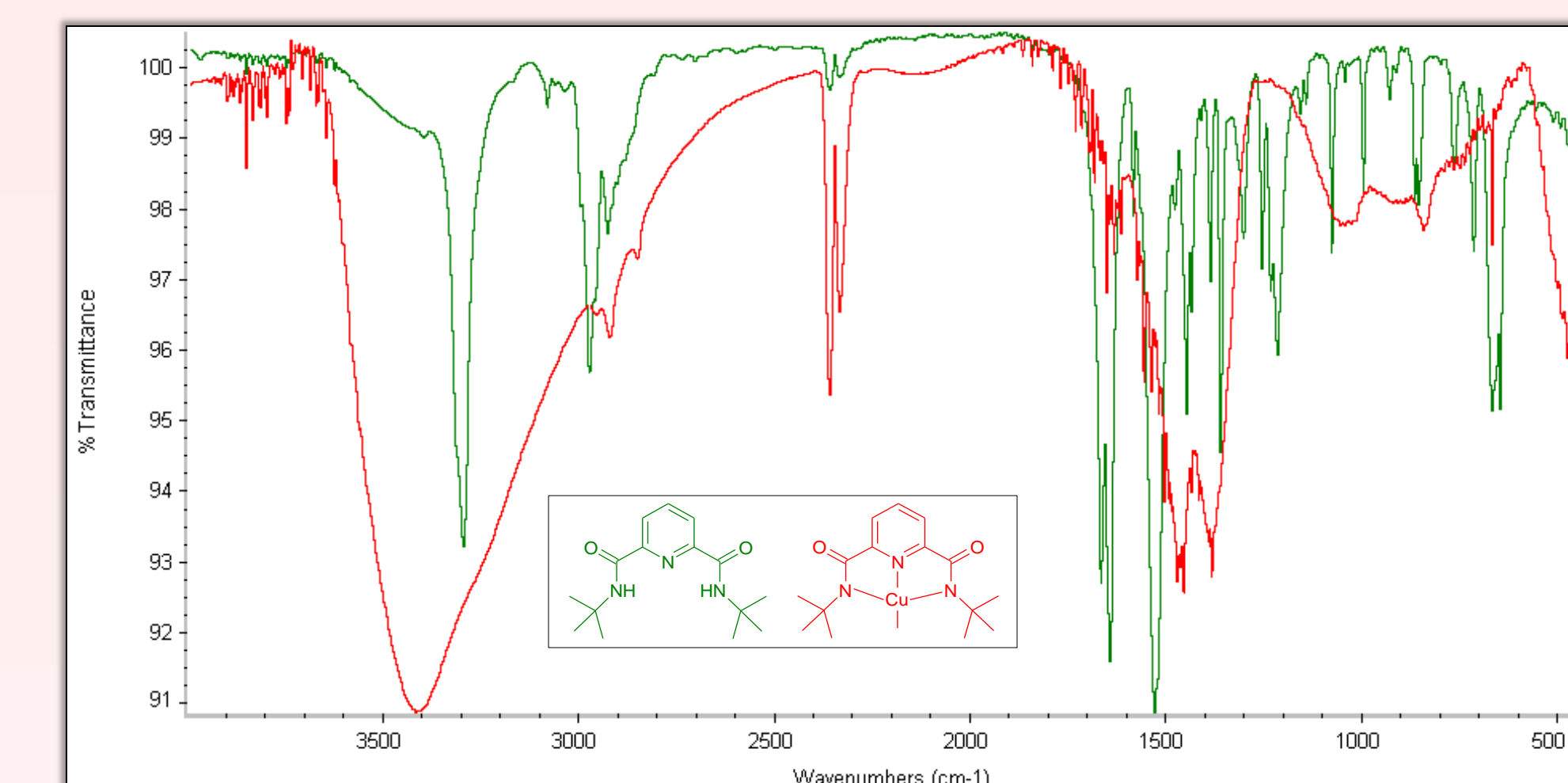
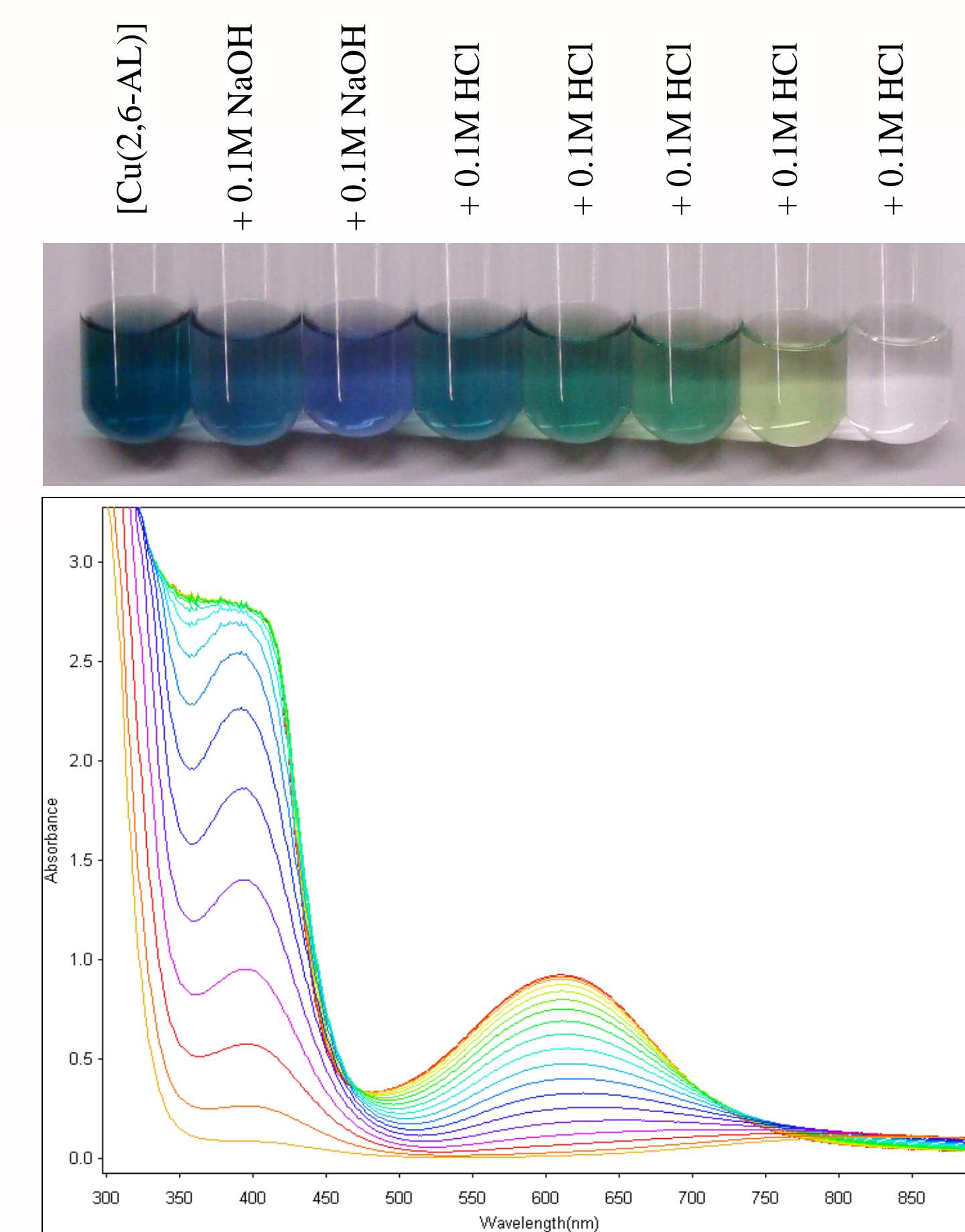
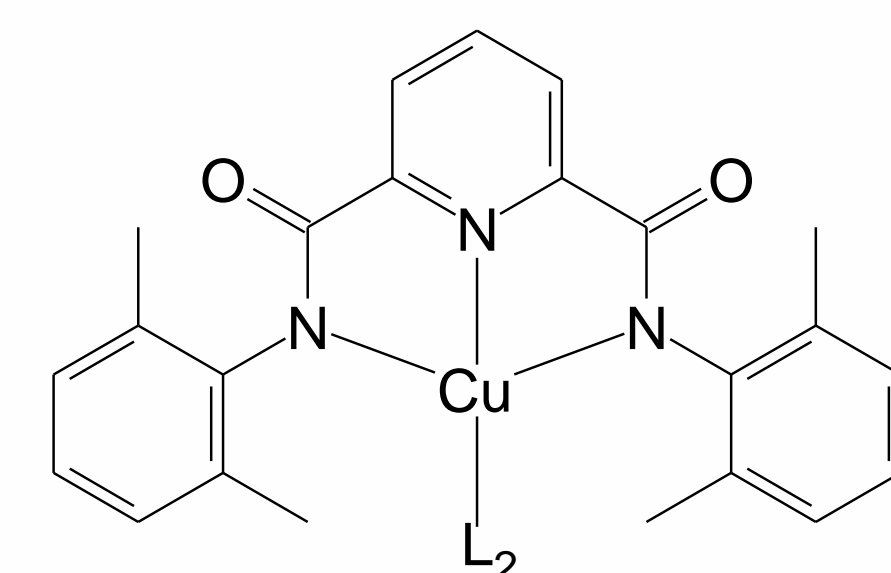


## Copper complexes:

At this point, we have had the most success with the pyridine bis-amide ligand family. Early syntheses focused on the benzyl derivative which ultimately formed X-ray quality crystals. Determination of the structure showed that this complex exists as an acetate bridged dimer in the solid state. Although this complex was readily synthesized, solubility and stability issues precluded significant further study. In an effort to address these problems, various aniline derivatives were explored.

After some initial complications with ligand syntheses, these aniline-based ligands resulted in a number of complexes with similar properties, as expected.

The copper complex of the pyridine-bis-2,6-dimethylaniline derived ligand displays interesting behavior upon pH change. When the complex as synthesized is dissolved and acidified, the color progressively disappears. This color change is reversible upon addition of base. The nature of this color change is currently being investigated further.



Solid-state IR spectra comparison of the t-butylamine ligand (green) with the resulting copper complex (red). Attention should be paid to the appearance of a broad OH peak in the complex spectrum. Both samples consisted of well-dried solid samples in KBr pellets, so the presence of the significant OH stretch implies a coordinated water or hydroxide.

Qualitative testing of the t-butyl complex did not show the same pH-dependent color change as the 2,6-dimethylphenyl derivative. This implies that the color change is due in part to the rigid steric demands of the 2,6-dimethylphenyl compared to the t-butyl derivative. The differing solubilities of the two derivatives could also contribute.

## Challenges:

There are a number of challenges in this synthetic scheme. While these are not exceptionally surprising, they have slowed progress on a number of fronts.

### Ligand Synthesis Using Pyridine-2,6-bis(Acid Chloride):

The reaction generates HCl so an organic base is required. Triethylamine works well during the synthesis but has been difficult to separate from the intended product. Pyridine also works well in the synthesis, and can be easier to remove from some of the products, but any residual pyridine clutters the aromatic region of the NMR spectrum.

### Ligand Synthesis Using Pyridine-2,6-bis(Carboxylic Acid):

This synthesis can be catalyzed by triphenylphosphite, but yield and purity have not been optimized.

### Alkyl vs. Aromatic Derivatives:

All of the mono- and di-methyl derivatives based upon aniline have similar solubility and behavior; the alkyl series (ethyl, isopropyl, tertbutyl) have significantly different solubilities which require different purification procedures for each one.

### Copper(II) Complexes:

The open coordination site is necessary for potential applications of these complexes as catalysts, but it presents a challenge in synthesis of the copper(II) complexes. The choice of copper(II) salt has the potential of providing a coordinating ligand, as was seen in the crystal structure of the benzyl derivative shown at left.

The choice of base used in the synthesis is also critical. It must be a strong enough base to deprotonate the amide nitrogens, but many likely bases can coordinate to copper(II). In addition to the acetate bridged dimer shown at left, the presence of hydroxide can lead to either terminal or bridging hydroxo-complexes. This is likely the cause of the pH dependent color change, although this phenomenon has not been fully explored.

## References:

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