Bipyridine Receptors as Metal Ligands

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Archeological evidence shows our industrial dependence on copper may date as far back as 8700 BCE when the metal began to be used for jewelry and, in combination with tin, early tools. In our homes, copper is integral to wiring, plumbing, heating, cooling, appliances, and telecommunications because of its high thermal and electrical conductivity and corrosion resistive properties. Our dependence on copper, however, does not always have benign consequences. The widespread use of cupric sulfate in pesticides[1] and waste from the electronics industry[2] are shifting natural copper levels. This imbalance is causing massive damage to ecosystems and generating growing environmental concern.[3] Humans need synthetic receptors designed to remove copper contamination safely and efficiently from our soil and water systems.

In addition to its uses in tools, copper is an essential bio-element,[4] vital to processes in all systems of the body. Health is dependent on delicate balances of ionic concentrations of copper, making the ability to test for molarity physiologically relevant. Recently, for example, medical researchers have been studying links between copper deficiencies and Alzheimer's disease.[5] Testing for the raised copper levels associated with Wilson's disease[6] may replace the current need to rely on a biopsy of the

liver for an accurate diagnosis. It may be possible to design the same chemosensors used for waste remediation to be adaptable as biomedical probes, capable of noninvasively determining copper molarity in organs and systems.

A supramolecular approach inspired by naturally occurring enzymes that selectively bind substrates[7] may provide a solution to the problems imposed by copper. It is possible to synthesize host molecules that utilize non-covalent interactions to aid in the complexation of specific guests. Just as a lock requires a distinctly shaped key, these systems target a precisely shaped ion. Recently, supramolecular receptors[8] have gained much attention because of their broad-range of usefulness in biomedical, chemical, environmental, and industrial fields.

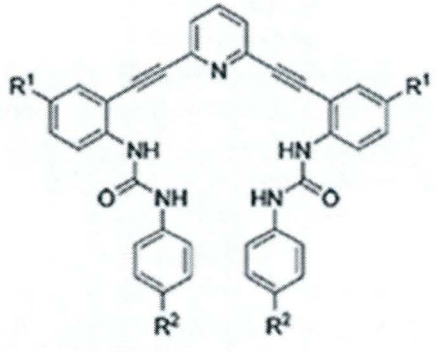

Figure 1: Model of 2,6-bis(2-anilinoethynyl)pyridine

Previous studies have demonstrated the biologically relevant aptitude of chemosensors built on a 2,6-bis(2-anilinoethynyl)pyridine core (Fig. 1) to sense anions such as chloride.[9] Although this class of anion sensors makes use of known metal coordinating moieties in their design, little

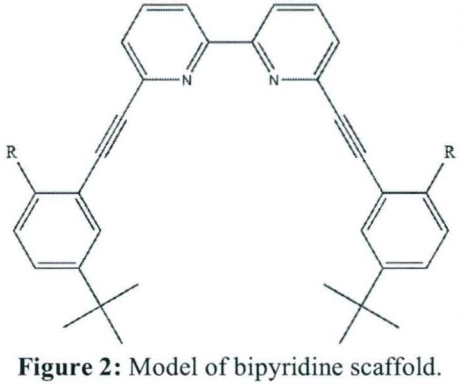

Figure 2: Model of bipyridine scaffold.

research has explored their ability to function as cation sensors.

This research explores a new receptor class built on a bipyridyl adaptation of 2,6-bis(2-anilinoethynyl)pyridine. This scaffold (Fig. 2) contains two articulate urea arms amenable to the addition of tailored functional groups for preferential binding based on the size and polarity of the targeted guests. Targeting ion-partners capable of cooperation, instead of cations or anions alone, increases selectivity and binding strength.[10] Receptors built on this bipyridyl core are ditopic with two lone pairs of electrons on the bipyridine nitrogen atoms capable of coordinating Lewis acidic guests and two urea groups able to form up four hydrogen bonds with anionic guests. For this study, our research focuses on bis(methoxy urea), which is a member of this bipyridine-based receptor class bearing 4-methoxyphenyl ureas, and its ability to function as a ligand for relevant metal salts (Fig. 3).

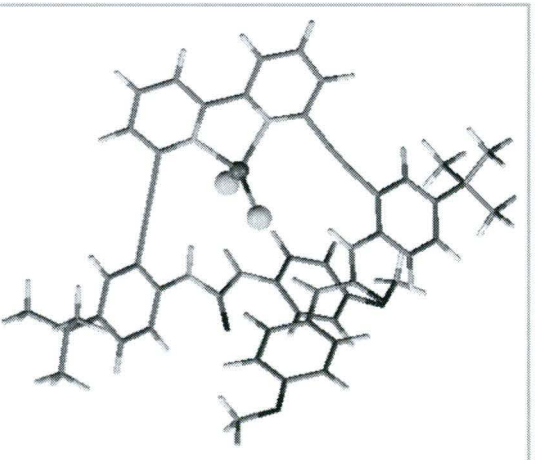

Figure 3: Model of bis(methoxy urea) coordinating with a water molecule.

One method to create molecular models is x-ray diffraction crystallography. By firing x-rays at organized crystals and studying the resulting diffraction pattern, we are able to generate a computational representation of the crystal's molecular structure. After slowly evaporating the chloroform-based solution, we obtained crystals suitable for analysis. Figure 4 shows that, in its solid state, the receptor forms an S-shaped conformation with two water mol-

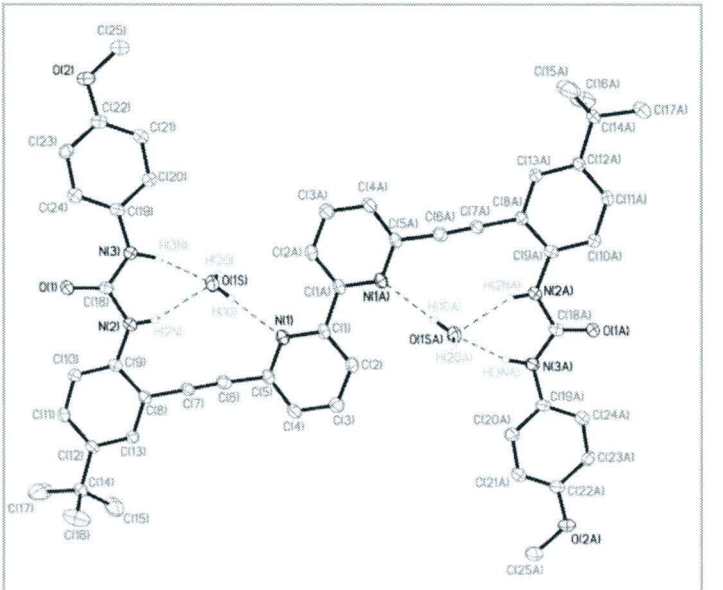

Figure 4: X-Ray crystal structure of bis(methoxy urea) with hydrogen-bonds to two water molecules.

ecules coordinated. This structure provided further confirmation that we successfully synthesized our desired molecule. The coordination of polar water molecules demonstrates the ability of this receptor to bind guests simultaneously via the bipyridyl and urea moieties.

We were interested in determining the ability of this receptor to function as a fluorescent sensor for metal salts. Initially, we screened a number of metal salts—copper chloride, $CuCl_2$; copper tetrafluoroborate, $Cu(BF_4)_2$; zinc bromide, $ZnBr_2$; zinc perchlorate, $Zn(ClO_4)_2$; and iron perchlorate, $Fe(ClO_4)_2$—in acetonitrile (MeCN) and measured the fluorescence of the free receptor and the receptor in the presence of metal salt. Unfortunately, we observed no visible fluorescence. Modifying the solvent system resulted in similar outcomes. These results indicate that this receptor is not well suited as a fluorescent sensor for the salts under study.

Another method to determine the ability of molecules to sense guests involved ultraviolet-visible (UV-Vis) spectrophotometry titrations.[11] Many molecules absorb ultraviolet or visible-spectrum light of various wavelengths. Generally, the host will absorb an amount of characteristic wavelengths that differs from the amount absorbed by the host-guest complex. Knowing the absorbance allows the use of Beer's Law to monitor the concentration of host present as we introduce a guest into solution. We obtained spectra by plotting absorbance measured in absorbance units (AU) against wavelength in nanometers (nm). By obtaining UV-Vis spectra after the repeated addition of small amounts of the guest molecule, we are able to follow the transition of free host to bound host in solution with increasing amounts of the guest. Aided by computer software we are

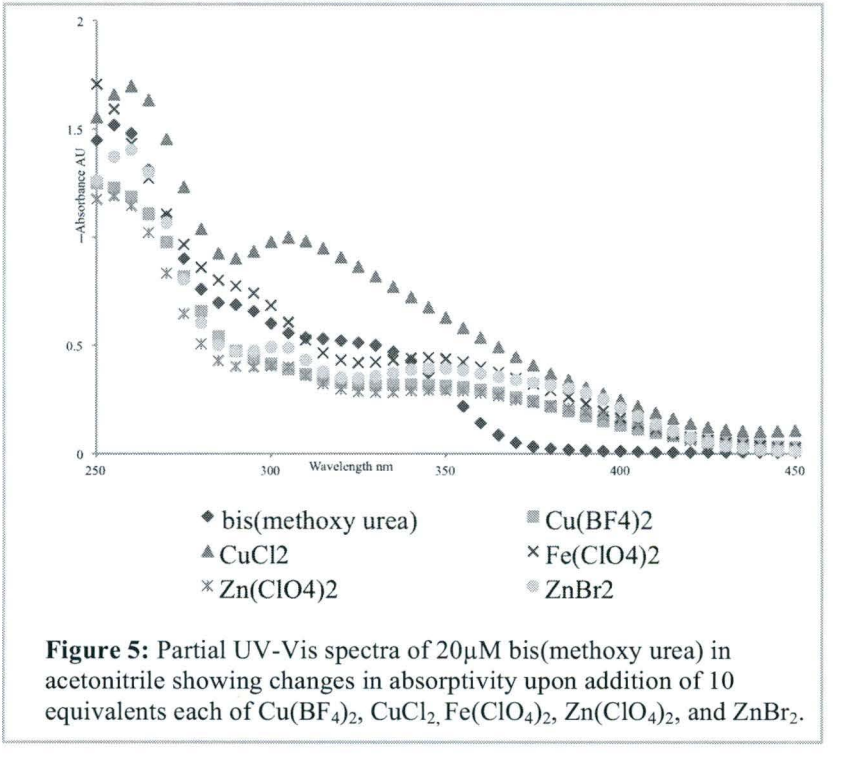

Figure 5: Partial UV-Vis spectra of 20μM bis(methoxy urea) in acetonitrile showing changes in absorptivity upon addition of 10 equivalents each of $Cu(BF_4)_2$, $CuCl_2$, $Fe(ClO_4)_2$, $Zn(ClO_4)_2$, and $ZnBr_2$.

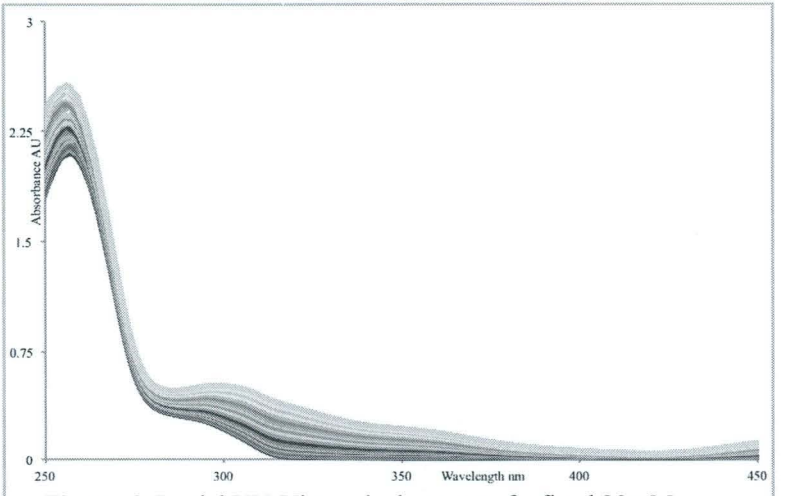

Figure 6: Partial UV-Vis stacked spectra of a fixed 20 μM concentration of bis(methoxy urea) in acetonitrile and increasing concentration of $CuCl_2$ from 0 to 200 μM (bottom to top)

able to extract from the data an association constant for the guest.

Initially, we screened several biologically relevant metal salts to determine which guests produced a meaningful response using UV-Vis. A 5 mM stock-solution of bis(methoxy urea) was prepared using MeCN in a volumetric flask. Aliquots of stock solutions of bis(methoxy urea) were diluted with the same solvent in a separate volumetric flask to yield a solution of approximately 500 μM concentration. In each case, we transferred 2 ml of this solution to a cuvette and used the remainder to generate the guest stock solution to maintain a constant host concentration throughout the titration. We used Hamilton gas tight syringes to add aliquots of the guest solution to the host solution in the cuvette and obtained spectra using UV-Vis. We acquired and removed a baseline sample of MeCN from each spectrum. In Figure 5, the diamonds represent the signal from bis(methoxy urea). Overlaid with the plot of bis(methoxy urea) are signals from five solutions containing 20 μM receptor-MeCN solution and 200 μM of either

$CuCl_2$, $Zn(ClO_4)_2$, $Cu(BF_4)_2$, $Fe(ClO_4)_2$, or $ZnBr_2$. All of the plots from the metal salts are relatively close together with similar slopes except for $CuCl_2$, represented with triangles, that shows a substantially higher absorption. Changes in the levels of absorbance can indicate shifts from host to host-guest complexes, although inconclusive, merit further research.

We conducted several titration experiments at various concentrations by incrementally adding $CuCl_2$ into solutions of the bipyridyl receptor in MeCN. Each time there was a substantial linear increase in absorbance (Fig. 6) but no isosbestic point indicating a clean transition from the host to host-guest complex.

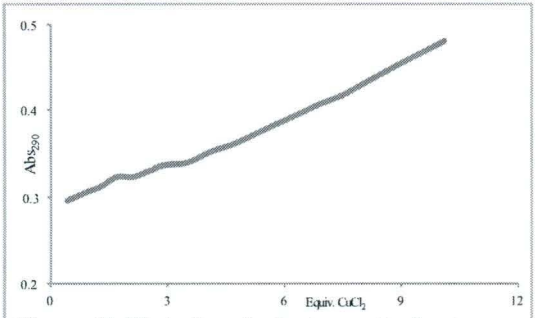

Figure 7: Plot of equivalent guest to host concentration versus absorbance in AU of 290 nm light

In order to monitor titrations we plotted equivalence of guest to host versus absorption of a single wavelength. To confirm coordination, the graph should increase as guest is introduced into solution and then level off as the host becomes saturated, creating a curved line. Figure 7 is a plot of 290 nm measured in the titration from Figure 6. Although the shifts in data were interesting, there was no saturation point indicating an alternative host-guest interaction.

We repeated the previous studies, replacing $CuCl_2$ with $Cu(BF_4)_2$. As tetrafluoroborate is a non-coordinating counter anion, we were able to study the effect of copper cation alone. The results were markedly different for this system (Fig. 8), in that there was a red-shift upon the addition of a minimal amount of salt, but no substantial additional shift with increasing concentrations of the cation.

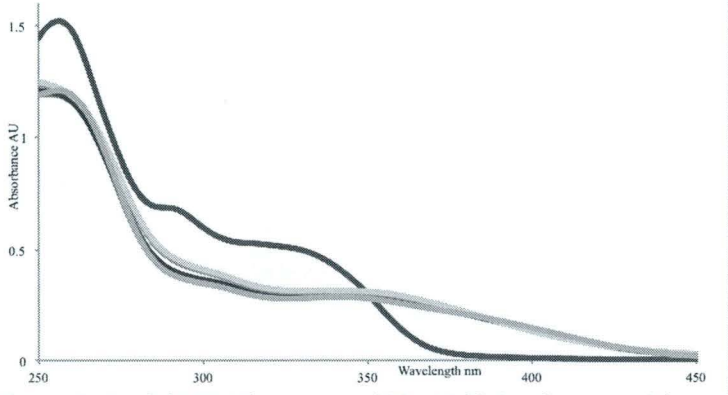

Figure 8: Partial UV-Vis spectra of 20 μM bis(methoxy urea) in acetonitrile showing shifting absorbance in response to increasing guest concentration during titrations from 0 (top dark grey line) to 200 μM $Cu(BF_4)_2$.

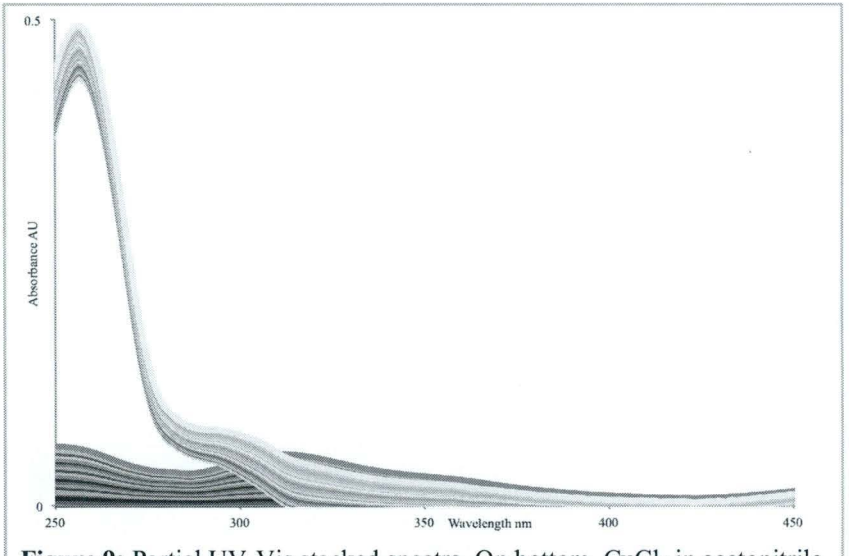

Figure 9: Partial UV-Vis stacked spectra. On bottom, $CuCl_2$ in acetonitrile, without a host, increasing concentration from 0 to 12.5 μM. On top, a fixed 5 μM concentration of bis(methoxy urea) in acetonitrile and increasing concentration of $CuCl_2$ from 0 to 12.5 μM (bottom to top).

We studied $CuCl_2$ by slowly increasing the ratio of guest to host and then repeated the trial with the same increments of guest but no host present (Fig. 9). This showed that $CuCl_2$ guest was absorbing in the range of the host molecule and interfering with the titration experiments. We remedied this problem by calculating what the absorbance of copper chloride should be at each titration point based on the molar absorptivity at a single wavelength (290 nm) and subtracting that value from the observed absorbance at the specified wavelength. The resulting graph revealed a decreasing curved line indicating coordination (Fig. 10). Future work will involve further calculations to account for how metal salt absorption may affect quantitative results.

This study has provided direction for future experimentation with this receptor class. Future studies will include bis(nitro urea) bearing 4-nitrophenyl urea groups and other adaptations to target other metal salts with this bipyridine core. These preliminary qualitative results have suggested bis(methoxy urea) may have copper specificity, but it is necessary to further explore these interactions.

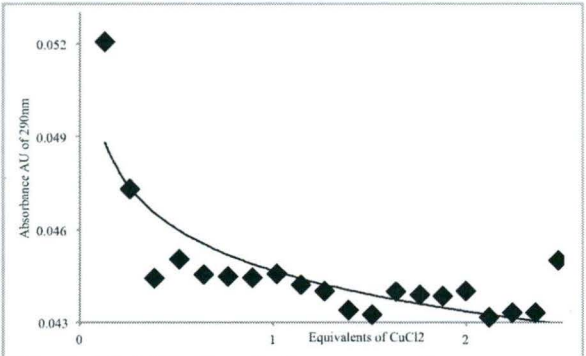

Figure 10: Plot of equivalent guest to host concentration versus adjusted absorbance values in AU of 290 nm light.

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