Shape-Selective Fluorescent Sensing Ensemble Using a Tweezer-Type Metalloreceptor

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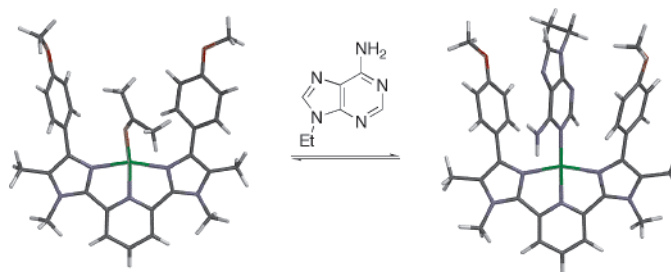# Shape-Selective Fluorescent Sensing Ensemble Using a Tweezer-Type Metalloreceptor

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ABSTRACT

A fluorescent sensing ensemble for pyridine-derived compounds is described. The receptor portion of the ensemble is prepared from a bisimidazole pyridine which coordinates copper to form a well-defined cavity. Small heteroaromatic guests such as adenine bind strongly in the cavity. The fluorescent response is provided by a dye which is coordinated to the receptor and quenched by the metal ion. The dye is released upon guest binding providing up to 25-fold fluorescence increases.

The molecular recognition of biologically important analytes continues to be a driving goal of supramolecular chemistry. Typically, artificial receptors are designed to recognize the intended guest using hydrogen bonding, ion−ion interactions, hydrophobic effects, metal−ligand interactions, covalent bonds, or some combination thereof. For molecular recognition under physiological conditions, hydrogen bonding is less important than other interactions, particularly the hydrophobic effect and metal−ligand interactions. We have been interested in the recognition of various classes of biological analytes including amines, carboxylates, and lipids.[1] As part of an effort to develop selective sensors for nucleotides, we report herein a metalloreceptor[2] for the recognition of heterocyclic aromatics, including adenine, which incorporates a shape-selective binding pocket with a molecular tweezer[3] design.

Metalloreceptors have become a valuable tool in supramolecular chemistry particularly with the advent of dye-displacement techniques which allow these receptors to be used as visible and fluorescent sensing ensembles.[4] Metal−ligand interactions offer strong association and defined geometries which are less solvent dependent than other noncovalent interactions. Our metallotweezer design is based on a pyridine bisimidazole[5] framework as shown in Scheme 1. The metal organizes a binding pocket between the appended aryl substituents with the metal ion at the base of this pocket allowing the guest to interact both with the ligand and the metal. This type of receptor is structurally related to

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(2) (a) Tobey, S. L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2003**, *125*, 14807−14815. (b) Haddou, H. A.; Sumaoka, J.; Wiskur, S. L.; Folmer-Andersen, J. F.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **2002**, *41*, 4014−4016. (c) Goodman, M. S.; Hamilton, A. D.; Weiss, J. *J. Am. Chem. Soc.* **1995**, *117*, 8447−8455. (d) Kim, K. H.; Song, R.; Kim, K. M. *J. Am. Chem. Soc.* **2003**, *125*, 7170−7171. (e) Kimura, E.; Ikeda, T.; Shionoya, M. *Pure Appl. Chem.* **1997**, *69*, 2187−2195. (f) Kickham, J. E.; Loeb, S. J.; Murphy, S. L. *Chem.−Eur. J.* **1997**, *3*, 1203−1213. (g) Nabeshima, T.; Nishida, D.; Akine, S.; Saiki, T. *Eur. J. Inorg. Chem.* **2004**, 3779−3782. (h) Cho, N. S.; Lee, C. H.; Kim, Y.-J.; Choi, J. S.; Kang, S. K. *Heterocycles* **2004**, *63*, 2827−2836.

(3) Zimmerman, S. C. *Top. Curr. Chem.* **1993**, *165*, 71−102.

(4) McCleskey, S. C.; Metzger, A.; Simmons, C. S.; Anslyn, E. V. *Tetrahedron* **2002**, *58*, 621−628.

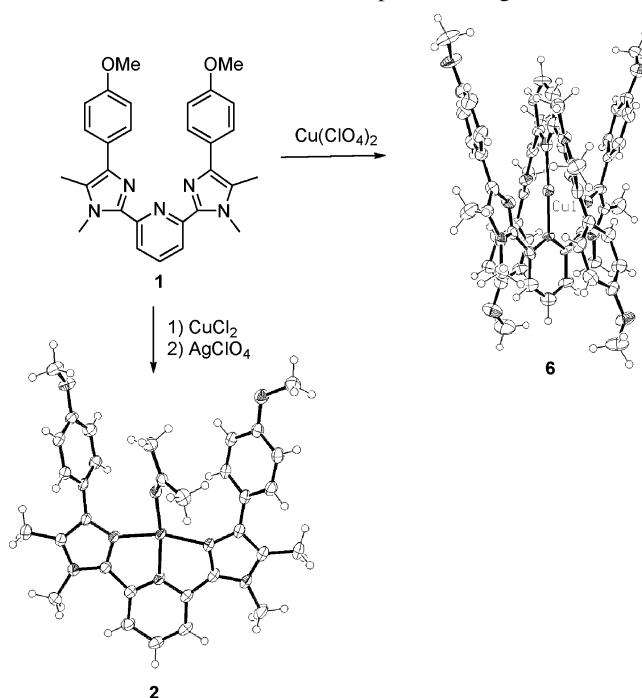**Scheme 1.** Recognition of Adenine by a Designed Metalloreceptor
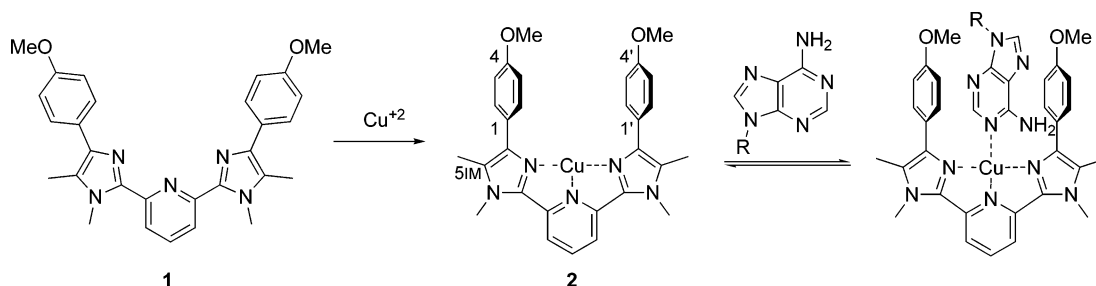
Lehn's aryl-substituted terpyridines.[6] The terpyridines themselves are competent receptors for aromatic guests; however, metal coordination distorts the alignment of the aryl groups producing a "pinch angle" which can inhibit guest binding.[7] In compound **2**, imidazole ligands were incorporated as they have good metal binding properties and the five-membered rings produce a coordination site in which the aryl substituents are arranged in a nearly parallel disposition (the vectors C1−C4 and C1′−C4′ are nearly parallel). Furthermore, the methyl substituent of the imidazole (5IM) provides steric buttressing of the anisole substituent, enforcing a near perpendicular anisole−imidazole arrangement, ideal for guest recognition. The receptor was designed with the expectation that, using a metal ion such as copper, the guest would fill the fourth coordination site of a square planar complex[8] and would have appropriate interactions with both the metal and the aromatic binding pocket. The remaining coordination sites on the metal could ultimately be useful for further host−guest interactions.

The bisimidazole ligand **1** was synthesized as shown in Scheme 2. Anisaldehyde was condensed with formamide and

Scheme 2. Synthesis of Ligand **1**

toluene sulfinic acid to afford isocyanate **3** upon dehydration.[9] Cycloaddition of **3** with the methyl imine of acetaldehyde gave imidazole **4**.[10] The imidazole was brominated and stannylated followed by coupling with dibromopyridine to

generate the final ligand **1**. Reaction of ligand **1** with copper perchlorate produced the 2:1 complex **6** (Scheme 3). Forma-

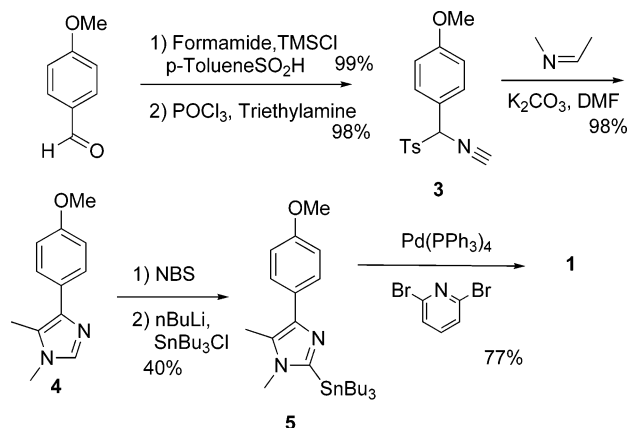**Scheme 3.** Coordination Properties of Ligand **1**[a]

[a] Perchlorate counterions are omitted from the ORTEP plots for clarity.

tion of the dimeric complex is not surprising given that the ligand is also a good guest for the first formed metallo-

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(9) Sisko, J.; Mellinger, M.; Sheldrake, P. W.; Baine, N. H. *Tetrahedron Lett.* **1996**, *37*, 8113−8116

(10) Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y. H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinski-Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem.* **2002**, *45*, 1697−1711.

receptor. To circumvent this coordination preference, **1** was treated with copper chloride to produce the 1:1 complex followed by anion exchange using silver perchlorate to generate the metalloreceptor **2**.

The geometry and stoichiometry of binding were determined by X-ray analysis. For example, crystallization of **2** with 1 equiv of pyridine gave complex **7** (Figure 1). As
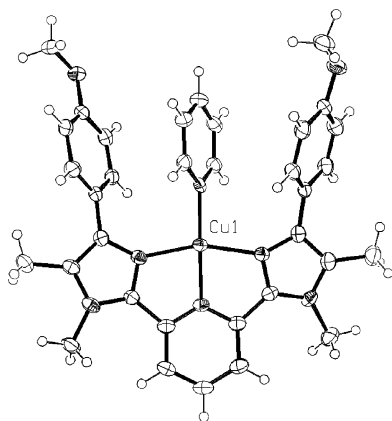

Figure 1. ORTEP plot of complex **7**. Perchlorate counterions are omitted for clarity.

anticipated, the metal adopts a square planar geometry in which the anisole rings are splayed at an angle of 24.2° (angle between the C1−C4 and C1′−C4′ vectors). The torsional angle between each anisole ring and its adjacent imidazole ring is 52.6°, in which the two anisole groups are nearly parallel aligned with each other and the guest. Thus, the metalloreceptor has a pocket which is ideally suited for recognition of heteroaromatic guests.

Guest recognition by complex **2** was then explored spectroscopically. The absorption spectrum of compound **2** has a $\lambda_{max} = 386$ nm in acetone solvent which increases slightly upon the addition of guests. To assess binding constants more easily, a fluorescence dye displacement assay was developed. Dimethylaminostyrylpyridine (DMASP) is a common fluorophore whose emission is largely quenched upon association with the receptor due to spin−orbit coupling with the copper ion.[11] The binding of DMASP by the receptor ($K_a = 1.1 \times 10^5$ M^{-1}) was determined by absorption and fluorescence titrations (Figure 2a). Addition of guests to a mixture of DMASP and complex **2** produces a 25-fold fluorescence increase as the DMASP is released from the metal (Figure 2b). Thus, the combination of **2** and DMASP makes an efficient sensing ensemble for aromatic ligands with an excellent fluorescent response.

Using the standard methods for displacement assays,[12] the binding of adenine was found to be quite strong (Table 1).

(11) (a) Hortlatá, M. A.; Fabbrizzi, L.; Marcotte, N.; Storneo, F.; Taglietti, A. *J. Am. Chem. Soc.* **2003**, *125*, 20−21. (b) Bonizzoni, M.; Fabbrizzi, L.; Piovani, G.; Taglietti, A. *Tetrahedron* **2004**, *60*, 11159−11162.

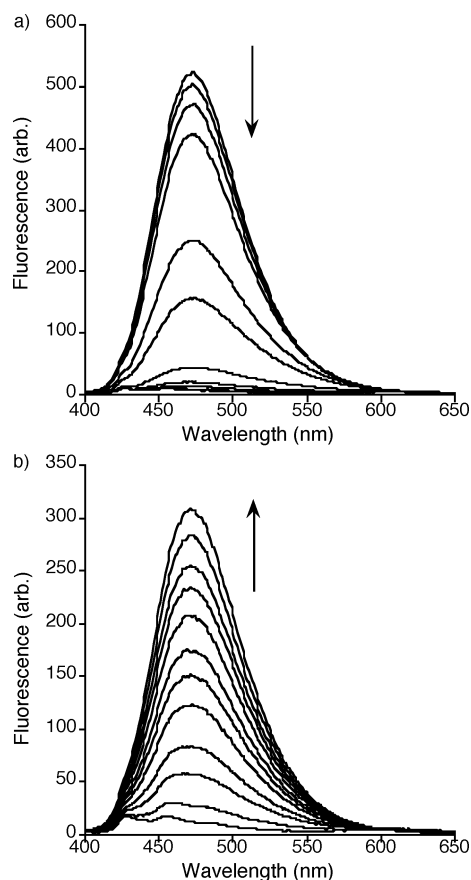(12) Connors, K. A. *Binding Constants*; John Wiley and Sons: New York, 1987; pp 175−177.

Figure 2. Fluorescent titration data ($\lambda_{ex} = 384$ nm) for (a) addition of complex **2** to DMASP (10 μM) in acetone and (b) addition of pyridine to a solution of complex **2** (40 μM) and DMASP (10 μM) in acetone.

Unfortunately, other alkyl nucleobases were not sufficiently soluble in acetone for binding constants to be determined. To probe the selectivity of the receptor, several other nonbiological guests were assayed. The data demonstrate that the receptor is very shape selective in that flat aromatic guests such as adenine bind well and larger guests (lutidine and piperidine) do not bind to any measurable extent. Among

Table 1. Binding Constants for Guests with Compound **2** in Acetone

guest	K_a (M^{-1})[a]
ethyl-adenine	8.8×10^4
4-(dimethylamino)pyridine	5.1×10^6
pyridine	2.6×10^4
pyridine-2-aldehyde	2.3×10^4 [b]
isonicatinamide	1.7×10^4
4-cyanopyridine	1.1×10^3
benzene	8.6×10^2
lutidine	—[b]
piperidine	—[b]

[a] Error in K_a is ±15% based on triplicate titration. [b] Determined by UV titration.

the guest with appropriate shape, the trends in binding affinity follow the electronics of the guest, with the more electron-rich guests binding tighter. Interestingly, the electron-poor pyridine-2-aldehyde binds nearly as well as pyridine itself due to coordination of the aldehyde oxygen with the metal.[13] Indeed, simple aromatics such as benzene bind without any metal coordination, though with much lower affinity. Thus, both the metal affinity and shape complimentarity are important for guest selection.

In summary, a novel molecular tweezer system has been developed which utilizes metal coordination at the bottom of a defined shape-selective cavity. This methodology is currently being extended to water-soluble systems with expanded binding pockets and carefully crafted metal coordination sites with a view toward the preparation of very selective sensors for biologically important analytes.

Supporting Information Available: Experimental procedures including characterization data and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) As observed in the solid-state structure; see Supporting Information.

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