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Stereochemical control of Zn(II)/Cu(II) selectivity in piperidine tripod ligands

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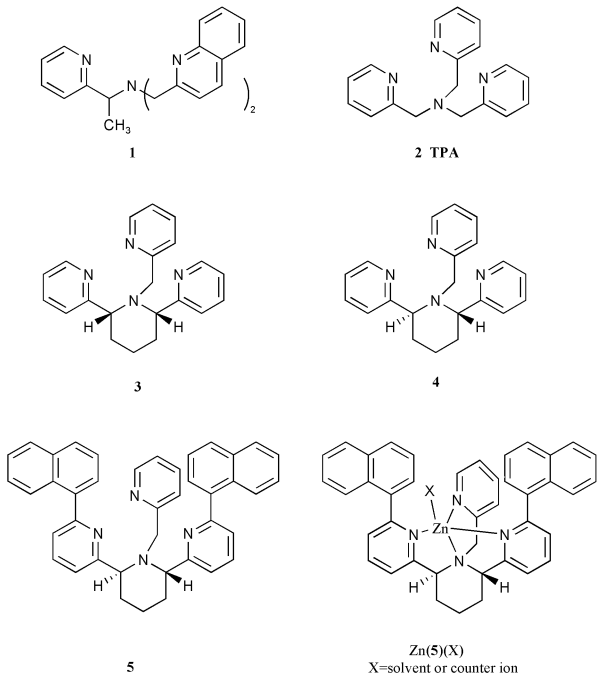
Received (in Colombia, MO, USA) 11th December 2001, Accepted 8th May 2002
First published as an Advance Article on the web 5th June 2002

Stereochemistry plays a major role in the selectivity toward zinc ion over copper(II) of some tripodal ligands with a central piperidine scaffold, one of which acts as a fluorescent zinc sensor with nanomolar sensitivity.

Zinc is an important element in most cells, and variation from normal concentration is associated with many diseases such as Alzheimer's syndrome.[1–4] Rapid analysis of trace metal cations requires both high sensitivity and selectivity. Fluorescent chemosensors, consisting of a recognition moiety and a signaling moiety, are particularly attractive for their inherently high sensitivity. One issue related to the recognition is that of interference by other metal ions. Many reported fluorescent chemosensors for Zn(II) suffer from interference by the binding of Cu(II), which commonly forms more stable complexes than Zn(II) with many ligands.[5–7] In a previous study,[8] recognition of Zn(II) by compound **1** benefited from both fluorescence



enhancement as well as chiroptical signal increase. However, Cu(II) was a significant competitor for Zn(II) in that system (as it is in many published systems). This paper presents an approach to engineering improved Zn(II)/Cu(II) selectivity controlling ligand stereochemistry.

Our idea was to increase the rigidity of the ligand scaffold by synthesizing piperidine analogues of **2**, which might be expected to destabilize Cu(II) binding compared to Zn(II). As a d^9 metal, the bonding in Cu(II) complexes is more covalent thus affording greater potential for differentiation due to ligand stereochemistry, while d^{10} Zn(II) is less demanding. A similar rationale was used to design ligands that stabilize Cu(I) over Cu(II).[9]

Compounds **3** and **4** were prepared[10] and the binding constants were determined by potentiometric titration.[11] For the *cis*-piperidine derivative **3**, Cu(II) and Zn(II) gave log β = 14.8 and 10.1, respectively, and for *trans*-ligand **4** the numbers were found to be 12.0 and 11.2. The parent compound TPA, **2**, shows log β = 16.15, compared to 11.00 for Zn(II).[12] Thus, the ratio of the association constants for the binding of Cu(II) over Zn(II) for **2**, **3** and **4** is 1.4×10^5, 5×10^4, and 6, respectively. While the *cis*-ligand **3** showed diminished binding for both Cu(II) and Zn(II), the *trans*-ligand **4** showed even worse binding of Cu(II) but slightly stronger binding of Zn(II) over TPA.

The differences in stability were estimated using PM3/tm calculations of the heat of formation of the $[M(L)Cl]^+$ (M = Cu(II), Zn(II)) complexes. A small difference was obtained for the Zn(II) complexes, 181.8 and 183.6 kcal mol^{-1} for **3** and **4**, respectively. A larger difference was observed for the Cu(II) complexes (106.8 and 112.6 kcal mol^{-1}). These calculations agree with the observation that the binding of Zn(II) is not much dependent on ligand stereochemistry, while for Cu(II), ligand **3** is preferred significantly. The computed structures show greater similarity of the $[Cu(TPA)Cl]^+$ Cu–N bond lengths in the complex with **3** than in **4**. Thus, *trans*-ligand **4** appears to distort the coordination sphere of the Cu ion, resulting in a less stable complex.

To examine whether these stereochemical observations could be put to use in a fluorescent chemosensor, ligand **5** was prepared.[10] This compound contains the metal binding domain of *trans*-ligand **4** with a signaling domain consisting of two naphthalene moieties. This system works similarly to other photoinduced electron transfer (PET) chemosensors in that the

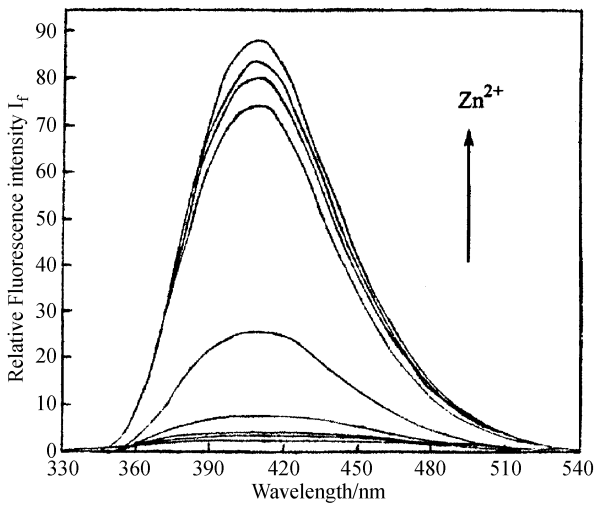


Fig. 1 Fluorescence response of compound **5** (1 μM) to buffered Zn^{2+}solutions. Spectra were acquired in 1% methanol aqueous solution (0.1 M KNO_3, 50 mM HEPES, pH 7.16, 25 °C) with excitation at 300 nm. The zinc ion concentration was buffered by 10 mM EGTA with total zinc concentration ranging from 0 to 9 mM. The spectra shown are for total Zn^{2+} at 0, 0.2, 0.4, 3, 4, 5, 6, 7 and 9 mM with corresponding free Zn^{2+} at 0, $10^{-10.29}$, $10^{-9.98}$, $10^{-8.97}$, $10^{-8.78}$, $10^{-8.60}$, $10^{-8.42}$, $10^{-8.23}$, $10^{-7.65}$ M, respectively.

DOI: 10.1039/b111259g

fluorescence of the naphthalene moieties is diminished in the absence of metal ion, but increases nearly 20-fold upon binding Zn(II), as shown in Fig. 1. In the free ligand, when the fluorophore is excited, a PET process can take place. The electron can transfer from the piperidine-N atom to the fluorophore, thereby quenching the fluorescence. Upon binding Zn(II), the oxidation potential of the amino-N atom increases significantly so that PET is checked and the fluorophore gives strong fluorescence. A Job plot of the fluorescence indicated stoichiometric binding, which was expected due to the similarity to other Zn(II) complexes.[13,14] The 1:1 log β of **5** for Zn(II) was found to be 9.3.

The sensitivity for Zn(II) was found to be nanomolar. A plot of the measured fluorescence intensity at 405 nm (near λ_{max}) against free Zn(II) resulted in a sigmoidal curve as shown in Fig. 2. This experiment utilized EGTA to control the free Zn(II) concentration. From this data, the lower detection limit of **5** toward Zn(II) is 1 nM and saturation is reached above 100 nM, suggesting that **5** is optimal for detecting Zn(II) concentration in the nanomolar range in water.

Finally, the issue of selectivity was assessed. We found that the biologically relevant metal ions have little or no influence on the sensing properties of compound **5**. The ions sodium (0.1 M), potassium (0.1 M), magnesium (1 mM), or calcium (1 mM) do not significantly change the fluorescence of **5** or Zn(**5**)$^{2+}$ at micromolar concentrations. As expected based on the studies of **3** and **4**, Cu(II) did compete with Zn(II) for **5**, resulting in the quenching of fluorescence by energy transfer between the paramagnetic metal ion and the fluorophore. A competition experiment with titration of Zn(**5**)$^{2+}$ with Cu(II) gave log β for Cu(II) = 10.6. Thus, the improved selectivity that had been found for ligand **4** was also observed with compound **5**.

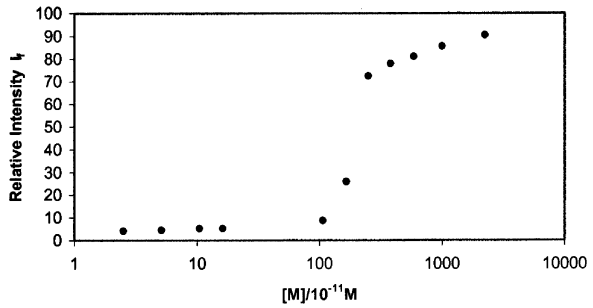


Fig. 2 Relative fluorescence intensity of compound **5** with different amount of Zn^{2+} at 405 nm. The conditions are the same as those of Fig. 1. The points shown are for total Zn^{2+} at 0, 0.2, 0.4, 0.6, 3, 4, 5, 6, 7, 8 and 9 mM, respectively.

In summary, we have shown that increasing ligand rigidity was able to improve the selectivity of Zn(II)/Cu(II) for **4**/**5** *vs.* **2** by a factor of 10^4. It seems likely that further rigidification of the receptor may yield even better selectivity.

We thank the National Science Foundation (CHE-0079072) for support of this work.

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