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A Chiral Perazamacrocyclic Fluorescent Sensor for Cascade Recognition of Cu(II) and the Unmodified α-Amino Acids in Protic Solutions

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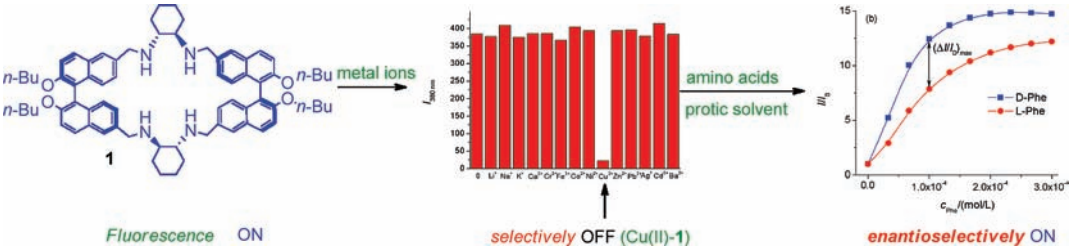
ABSTRACT



A novel chiral Perazamacrocyclic fluorescent sensor (1) was designed and synthesized. It can serve as a fluorescent turn-off sensor with high selectivity toward Cu(II) among 14 metal ions. Furthermore, though 1 exhibits no enantioselectivity, after adding Cu(II), the *in situ* generated Cu(II)-containing complex of 1 (Cu(II)-1) can exhibit remarkable fluorescent enhancement responses and considerable enantioselectivities toward unmodified α-amino acids in protic solutions *via* a ligand displacement mechanism; i.e. a cascade recognition of Cu(II) and unmodified α-amino acids has been achieved.

Chiral recognition plays an important role in many fields of science and technology.[1] Because studies on chiral recognition might contribute to the understanding of living systems, much effort has been devoted to the design and synthesis of artificial enantioselective receptors and their applications.[2] Among these studies, those on enantioselective recognition of amino acids and their derivatives are especially attractive, since they are fundamental molecules of life and are implicated in different biomolecular processes.[3] Though much research on the

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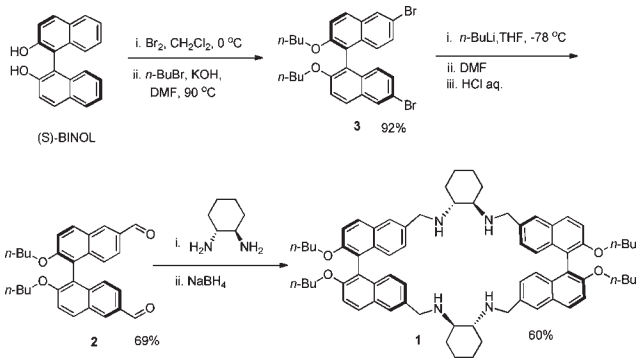
recognition of modified amino acids has been reported in recent years,[4] recognizing unprotected amino acids in protic solvent is still a challenge and only a few works have been reported to date.[5] Unlike other organic guest molecules, most amino acids exist as zwitterions and have poor solubility in aprotic organic solvent,[6] whereas in protic solvent the competition between solvent molecules and binding sites exists, not only preventing the formation of H-bonds between receptors and guest molecules but also resulting in low enantioselectivity.[1a,7]

Perazamacrocycles have been successfully applied in coordination chemistry, metal catalysis, ion recognition, supramolecular structures, material chemistry, and catalysis.[8] Recently, the research on the fluorescent and colorimetric molecular probes or chemosensors based on polyamines has prospered.[9] On the other hand, optically active 1,1′-Bi-2-naphthol (BINOL) and *trans*-cyclohexane-1, 2-diamine (*trans*-DACH) and their derivatives have been widely used in molecular recognition and asymmetric catalysis.[10] And some excellent enantioselective fluorescence sensors based on the building blocks of BINOL derivatives have been reported since chiral BINOL can effectively integrate chirality and the fluorescence property.[4b,11]

Scheme 1. Synthesis Route of **1**



In this paper, we synthesized a novel chiral perazamacrocycle **1** featuring BINOL and *trans*-DACH units which could serve as a fluorescent sensor for Cu(II). And the chiral recognition of the Cu(II)-containing complex of **1** toward unmodified α-amino acids in protic solutions was studied.

As shown in Scheme 1, perazamacrocycle **1** was easily synthesized in 3 steps from (*S*)-BIONL.

The UV−vis and fluorescence spectra of perazamacrocycle **1** at various concentrations were studied (Figures S3−S4). The UV−vis spectra of **1** have no change in either the wavelengths or the shapes of the absorption signals and obey the Lambert−Beer Law well as the concentration increases from 0 to 2.5×10^{-5} mol/L, indicating that **1** does not form ground state intermolecular aggregates.[12] However, plots of fluorescent intensity vs concentration of **1** suggest that the suitable concentration of **1** for the fluorescent studies on recognition preferably should not be greater than 1×10^{-5} mol/L to avoid the violation of the Lambert−Beer Law.

We investigated the selective fluorionophoric properties of **1** toward Li^+, Na^+, K^+, Ca^{2+}, Cr^{3+}, Fe^{3+}, Co^{2+}, Ni^{2+} Cu^{2+}, Zn^{2+}, Pb^{2+}, Ag^+, Cd^{2+}, and Ba^{2+}. The fluorescence of **1** could be almost completely quenched only by $Cu(NO_3)_2$ (Figures 1 and 2). Job plots[13] analysis and the mass spectra of ESI and

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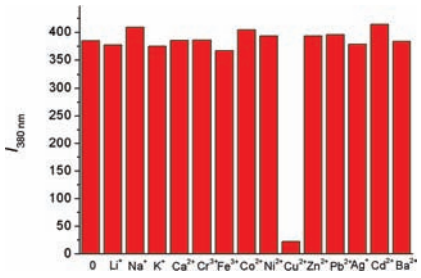


Figure 1. Fluorescence responses of **1** (1.0×10^{-5} mol/L, λ_{ex} = 331 nm) to various metal ions (2.0×10^{-5} mol/L) in methanol–water solutions (v/v = 1:1, 25 mM HEPES buffer, pH 7.3).

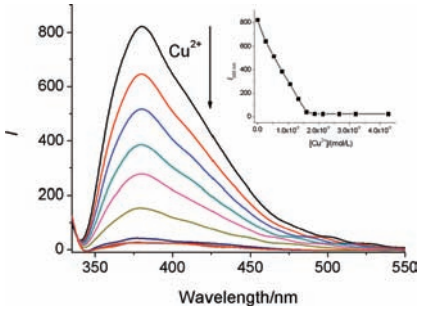
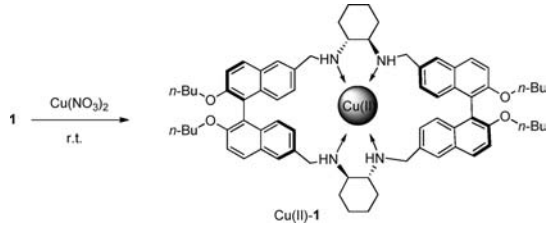


Figure 2. Fluorescence spectra of **1** (1.0×10^{-5} mol/L, λ_{ex} = 331 nm) in the presence of increasing amount of $Cu(NO_3)_2$ in a solution of MeOH/H_2O (v/v = 1:1), 25 mM HEPES buffered to pH 7.3. The inset features the dependence of the intensity emission at 380 nm on the concentration of Cu^{2+}.

Scheme 2. *In Situ* Formation of Cu(II)-Containing Complex of **1**



MALDI-TOF reveal that **1** and Cu(II) form a 1:1 complex Cu(II)-**1** (Figures S6–S7, Scheme 2). Moreover, the association constant (K) determined from the Job plot is up to 1.25×10^6 L/mol. With such a high selectivity and sensitivity, perazamacrocycle **1** could serve as a fluorescent ON-OFF sensor for Cu(II).

As chelating ligands, amino acids are highly associable with many metal ions, especially with Cu(II).[14] Thus, they

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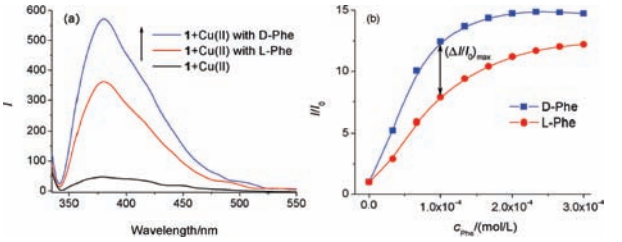

Figure 3. (a) Fluorescence spectra of **1**+Cu(II) ($(1 \times 10^{-5}) + (2 \times 10^{-5})$ mol/L, λ_{ex} = 331 nm) with D- or L-Phe (1×10^{-4} mol/L) and (b) plots of (I/I_0) vs Phe concentration during the titration of **1**+Cu(II) with D- or L-Phe (λ_{ex} = 331 nm, λ_{em} = 380 nm) in a solution of MeOH/H_2O (v/v = 1:1), 25 mM HEPES buffered to pH 7.3.

probably are able to associate with Cu(II) and displace the ligand **1** in Cu(II)-**1**, which may conduce to the recovery of the fluorescence quenched by Cu(II). On the other hand, since **1** is chiral, one enantiomer of an amino acid may have more efficiency in displacing **1** and result in more fluorescence enhancement than another. Keeping these in mind and encouraged by the recent brilliant achievements of Anslyn's indicator-displacement assays[15] and competitive binding assays such as Wolf's[16] and Feng's,[4a,17] we further studied the chiral recognition of the *in situ* generated Cu(II)-containing perazamacrocyclic complex of **1** (Cu(II)-**1**) toward unmodified amino acids.

Initially, 1 equiv of Cu(II) was added to **1** and the resulting mixture was engaged in the recognition of enantiomers of phenylalanine (Phe) (Figure S8). Both enantiomers of Phe could induce apparent fluorescence enhancement responses, whereas D-Phe is more effective than L-Phe. The maximal fluorescence enhancement ratio I_{Dmax}/I_0 reached 1.87, and $(\Delta I/I_0)_{max}$ = 0.27. That is to say the expected enantioselective fluorescent enhancement sensing has been achieved.

Noting that 1 equiv of Cu(II) could not quench the fluorescence of **1** to a minimum (Figure 2), we employed 2 equiv of Cu(II) to ensure thorough quenching and then performed enantioselective recognition studies. While the mixture of **1** and Cu(II) (1:2) was titrated with Phe (Figure 3), the flourescence enantioselectively increased as expected. To our surprise, I_{Dmax}/I_0 and $(\Delta I/I_0)_{max}$ amazingly increased to 14.9 and 4.9 respectively, which are much higher than 1.87 and 0.27 obtained previously. This suggests that **1**+Cu(II) (1:2) is superior to **1**+Cu(II) (1:1) and could result in great enhancement of both sensitivity and enantioselectivity. Whereafter, the enantiomers of other four amino acids alanine (Ala), valine (Val), proline (Pro), and (PG) were engaged in the titration experiments (Figures S9–S12, Table 1). The enantioselective fluorescence responses are similar to that of Phe, and in

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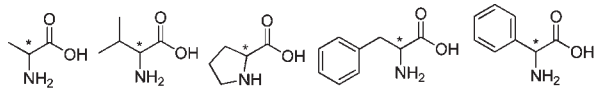
Table 1. Amino Acids Employed in Enantioselective Sensing Studies and the Sensitivities and Enantioselectivities of **1**+Cu(II) towards Them[a]



c_{Cu}/c_1	Amino acids	I_{Dmax}/I_0	$(\Delta I/I_0)_{max}$
1	Phe	1.87	0.27
2	Phe	14.9	4.6
	Ala	13.2	1.4
	Val	12.4	1.9
	Pro	14.1	3.2
	PG	9.7	1.6

[a] $c_1 = 1 \times 10^{-5}$ mol/L, in a solution of MeOH/H_2O (v/v = 1:1), 25 mM HEPES buffered to pH 7.3

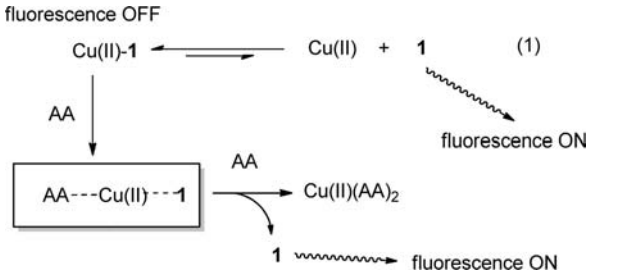
most cases, the resulting I_{Dmax}/I_0 is above 10. The results also suggest that the increase of bulk of the group in the α-position of amino acids might be beneficial to the enhancement of enantioselectivity. To the best of our knowledge, Cu(II)-**1** is the first reported metal-containing perazamacrocycle sensor which can exhibit remarkable fluorescent enhancement responses and considerable enantioselectivities toward unmodified α-amino acids in protic solutions.

It is interesting to find that the excess metal ions could lead to the enhancement of enantioselectivity. A possible explanation (Scheme 3) might be that the excess Cu(II) (2 equiv) could drive the balance of eq 1 to move to the left, which not only ensures the quenching of fluorescence to a minimum but also promotes the formation of chiral coordination complex Cu(II)-**1** and keeps the chiral ligand displacement proceeding according to the reported machanism.[15] Thus, enhanced sensitivity and enantioselectivity could be observed.

While **1** without Cu(II) was treated with the enantiomers of Phe (Figure S13), the fluorescence intensity decreased as the concentration of Phe increased. Even upon addition of 200 equiv of Phe, the difference between the fluorescence responses of two enantiomers remains very small, indicating the indispensability of Cu(II) for chiral recognition. Furthermore, the consistency of fluorescent responses of **1** toward two enantiomers also verifies that the distinctly different fluorescent responses measured from ligand displacement arises from enanioselective recognition and is not due to impurities.

The influence of the enantiomeric composition of Phe on the fluorescence intensity was investigated. As shown in Figure 4, the intensity of fluorescence enhanced while adding D-Phe or an enantiomeric mixture of D-Phe. With the same amount of D-Phe the enantiomeric mixture (curve a) causes greater fluorescence enhancement than an optically pure D-Phe (curve b) dose. There is a fairly linear relationship between I/I_0 and the percent of the D-Phe component ($R = 0.998$, Figure S14), which indicates that the enantioselective ligand displacement method can be effectively applied for the enantiomer composition determination of amino acids.

Scheme 3. Possible Mechanism of Ligand Displacement



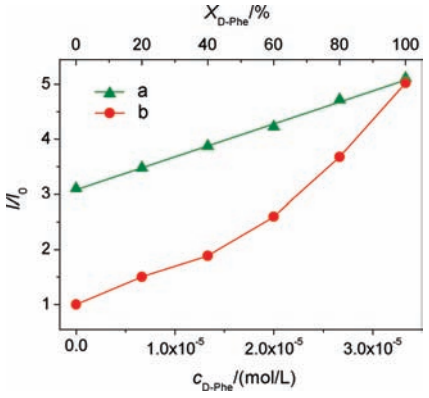


Figure 4. Fluorescence enhancement of **1**+Cu(II) ($(1 \times 10^{-5}) + (2 \times 10^{-5})$ mol/L) in the presence of the enantiomeric mixture of Phe at 3.3×10^{-5} mol/L (curve a, top scale) and pure D-Phe (curve b, bottom scale) ($\lambda_{ex} = 331$, $\lambda_{em} = 380$ nm) in a solution of MeOH/H_2O (v/v = 1:1), 25 mM HEPES buffered to pH 7.3.

In conclusion, we designed and synthesized a versatile chiral perazamacrocycle **1** which can serve as a fluorescent turn-off sensor for Cu(II) and exhibit good selectivity among 14 metal ions. Furthermore, though **1** exhibits no enantioselectivity, after addition of Cu(II), the *in situ* generated Cu(II)-**1** can exhibit remarkable fluorescent enhancement responses and considerable enantioselectivities toward unmodified α-amino acids in protic solutions *via* a ligand displacement mechanism; i.e. a cascade recognition of Cu(II) and unmodified α-amino acids has been achieved.

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Supporting Information Available. Fluorescence, UV–vis spectroscopic plots, and data mentioned in above paragraphs; ^1H and ^{13}C NMR spectra of all new compounds as well. This material is available free of charge via the Internet at http://pubs.acs.org.