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Enantioselective Recognition of Mandelic Acid with (*R*)-1,1-Bi-2-naphthol-Linked Calix[4]arene via Fluorescence and Dynamic Light Scattering

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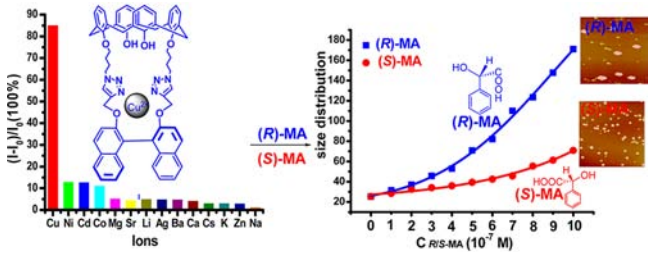
ABSTRACT



A chiral 1,1-bi-2-naphthol-derived calix[4]arene (1) was synthesized via a click reaction. Fluorescence spectra and dynamic light-scattering revealed that Cu(II)−1 complexes were generated in situ and exhibited remarkable enantioselectivity toward mandelic acid. Using this dynamic light-scattering technique, the detection sensitivity was improved almost 100-fold, with a detection limit of 2.0 × 10^{-7} M, compared with fluorescent methods.

Chiral recognition plays an important role in many fields of science and technology.[1] Because studies on chiral recognition contribute to an understanding of interactions among biological molecules, enabling the development of useful separation processes, catalysis, and sensing techniques, much consideration has been devoted to the design and synthesis of artificially enantioselective receptors and investigation of their applications.[2] Chiral discrimination has been achieved using various methods such as chiral HPLC,[3] capillary electrophoresis,[4] fluorescence,[5] colorimetric analysis,[6] and electrochemistry.[7] Although reasonable chiral discrimination has been achieved using these techniques, improving the sensitivity of chiral recognition

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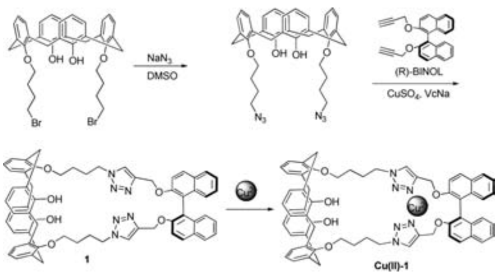
is essential and remains a challenging task. Dynamic light-scattering (DLS), because of its sensitive analysis of the size distribution of aggregates ranging from 0.5 nm to 10 μm,[8] is expected to be a feasible method for improving the sensitivity of analyte discrimination. To date, increased sensitivity of recognition via DLS characterization has been successfully accomplished in a few studies.[9]

Calixarenes, which are well-known representative host molecules, and also promising in molecular recognition, have attracted significant attention in supramolecular chemistry.[10] Calixarenes are amphiphilic molecules which can spontaneously assemble to form nanocapsules and nanoparticles.[11] For example, Lee et al. have reported supramolecular nanocapsules from amphiphilic calixarene assembly, and the aggregation behavior of calixarenes in solution has been investigated using DLS.[12] However, highly sensitive chiral recognition of calixarenes via DLS has not been achieved.

In this study, we synthesized a novel fluorescent calix[4]arene bearing a chiral 1,1′-bi-2-naphthol (BINOL) group and investigated its ion-binding properties and chiral recognition abilities with respect to mandelic acid (MA). MA is a structural unit of many natural products and drug molecules and is the multifunctional precursor of a variety of organic compounds.[13]

As shown in Scheme 1, (*R*)-BINOL-derived calix[4]arene **1** was synthesized in two steps.[14] All of the compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy, HDMS, and elemental analysis. The recognition ability of as-prepared **1** was investigated in detail, and **1** demonstrated highly selective binding toward Cu(II) to form a Cu(II)−**1** complex, resulting in prominent fluorescence quenching. Significantly, the as-obtained Cu(II)−**1** complex could be used as a fluorescent sensor for enantioselective recognition of MA with a fluorescence "turn on" mode. A specific DLS technique was employed, and the sensitivity of the chiral discrimination was improved 100-fold.

Scheme 1. Synthetic Route to **1**



The fluorescence spectrum of **1** (λ_{ex} = 300 nm) in CH$_3$CN exhibited a characteristic emission band at 361 nm. As Figure S4 (Supporting Information) shows, the fluorescence of **1** was almost completely quenched by Cu(ClO$_4$)$_2$. The binding constant of **1** with Cu^{2+} was calculated using the Benesi−Hildebrand equation, and the corresponding association constant K_a was found to be 7.38×10^5 M^{-1}.[15] Job plots analysis and MALDI-TOF MS spectra show that **1** and Cu(II) form a 1:1 complex Cu(II)−**1**, and the ^{1}H NMR spectrum of Cu(II)−**1** shows that the Cu^{2+} ion of the Cu(II)−**1** complex is located in the cavity formed by the nitrogen-rich triazole (Figures S5−S9, Supporting Information).

To further investigate the chiral recognition performance of the Cu(II)−**1** complex, (*R*)- and (*S*)-MA were tested using the complex, which was first prepared in situ by mixing **1** and Cu^{2+} in a 1:1 ratio.[16] When the Cu(II)−**1** complex was treated with (*R*)- or (*S*)-MA, significant fluorescence enhancement was observed in both cases. Evident enantioselectivity can be observed from the degree of fluorescence increase. As shown in Figure 1, in CH$_3$CN, the fluorescence intensity of the Cu(II)−**1** complex (1×10^{-5} M) increased 6.35-fold on addition of (*R*)-MA (1×10^{-4} M). However, (*S*)-MA (1×10^{-4} M) only increased the fluorescence intensity of the Cu(II)−**1** complex 4.87-fold; that is, the enantiomeric fluorescence difference ratio, ef [ef = $(I_R - I_0)/(I_S - I_0)$], is 1.69. This large difference in enantiomeric fluorescence enhancement makes Cu(II)−**1** a useful sensor for the enantioselective recognition of chiral (*R*)-MA. The analogs tartaric acid and malic acid were also investigated. All of the *R* analogues increased the fluorescence recovery (Figures S10 and S11, Supporting Information); that is, results on fluorescence responses similar to those of MA were displayed. However, in contrast, MA gives much better

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enantioselectivity, and extensive investigations of the chiral discrimination of MA have been carried out.

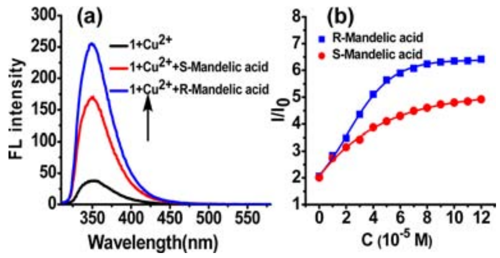

Figure 1. (a) Fluorescence variation (λ_{ex} = 300 nm) of **1** (1×10^{-5} M) added to Cu(II) (2×10^{-5} M) (black line) and the as-formed Cu(II)−**1** complex added to (*R*)-MA (1×10^{-4} M) (blue line) and (*S*)-MA (1×10^{-4} M) (red line), respectively. (b) Titration curves of the rate of fluorescence change (I/I_0) in different concentrations of (*R*)-MA (blue line) and (*S*)-MA (red line) in CH_3CN. That is, the enantioselective recognition of MA has been achieved.

To determine whether the enantioselectivity of MA is reflected in the nanostructural features, AFM studies were performed on Cu(II)−**1**, {[Cu(II)−**1**] + (*R*)-MA}, and {[Cu(II)−**1**] + (*S*)-MA}. The corresponding micrographs and particle size distributions are shown in Figure 2. Cu(II)−**1** is composed of spherical particles in the size range 25−35 nm (Figure 3a). When (*R*)-MA is added to Cu(II)−**1**, the size of the particles increases significantly to 447−572 nm, and the particles become nonspherical (Figure 3b). For {[Cu(II)−**1**] + (*S*)-MA}, the particle size increases to 149−233 nm, and the shape remains spherical (Figure 3c). This large difference in nanostructural features also confirms that Cu(II)−**1** is a useful sensor for enantioselective recognition of chiral (*R*)-MA.

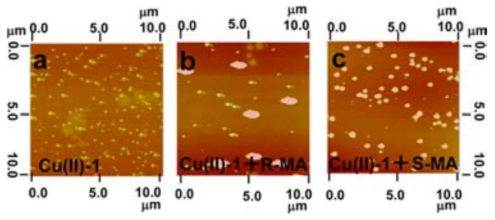

Figure 2. AFM images of Cu(II)−**1** added to (*R*)-MA and (*S*)-MA: (a) Cu(II)−**1** alone, (b) Cu(II)−**1** with (*R*)-MA, and (c) Cu(II)−**1** with (*S*)-MA.

Based on the above analysis, a possible mechanism of enantioselective recognition is proposed. The fluorescence recovered by adding MA was the result of suppression of PET quenching in the Cu(II)−**1** system. The observed enantioselective size in the AFM images was the result of preferential complexation between Cu(II)−**1** and (*R*)-MA, and in this case, larger aggregates were formed. The characteristic changes observed in the fluorescence spectra during the sensing of Cu^{2+} and followed by (*R*)/(S)-MA are represented schematically in Figure S13 (Supporting Information).

Although chiral recognition of MA is achieved through monitoring of fluorescence signatures, compared to other examples,[17] the sensitivity of the detection is not much improved (the detection limit is 2×10^{-5} M), which may limit its potential applications. To solve this problem, we used DLS to improve the sensitivity of the assay toward MA. It is known that DLS is a powerful method for determining small changes in particle sizes, and can be used to detect size changes in nanoparticles. As shown in Figure 3, the diameter of the Cu(II)−**1** complex particles (1×10^{-5} M) increased 6.74-fold on addition of (*R*)-MA (1×10^{-6} M). However, (*S*)-MA (1×10^{-6} M) only increased the diameter of the Cu(II)−**1** particles 2.79-fold, that is, the enantioselectivity could be detected by DLS. Quantitative analysis of MA was achieved using a plot of the size distribution versus the concentration of MA from 1.0×10^{-7} to 1×10^{-6} M, as shown in Figure 3. The titration curves show that the detection limit of the enantioselectivity measured using DLS is 2.0×10^{-7} M (Figure S14, Supporting Information). As a result, the detection sensitivity was improved almost 100-fold compared with that of the fluorescent method. The results described here demonstrate that the complex Cu(II)−**1**, with a chiral cavity, assembled into well-defined and tunable nanoparticles that increase significantly in diameter on addition of MA. In this chiral recognition system, calixarene plays a very important role. First, calixarene **1** is an amphiphilic molecule which can be expected to spontaneously assemble to form nanoparticles. Second, the calixarene framework was coordinated with chiral binaphthyl groups to construct a chiral cavity for the enantioselective recognition of MA.

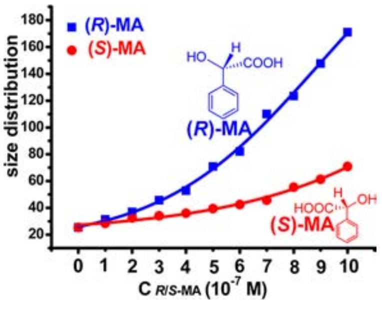

Figure 3. Size distribution curves of Cu(II)−**1** with changes in concentration of (*R*)-MA (blue line) and (*S*)-MA (red line).

In summary, we have designed and synthesized a versatile chiral calixarene derivative, **1**. Cu(II)−**1** was generated in situ and exhibited excellent enantioselective recognition

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of MA with a fluorescence "turn on" mode. Furthermore, significantly improved sensitivity of chiral discrimination of MA was achieved using a DLS technique, which may provide a novel and effective way of enhancing the sensitivity of enantioselective recognition for other analytes.

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Supporting Information Available. Experimental details, NMR spectra of all the components, fluorescence spectra, and other data mentioned in this paper.This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.