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Enantioselective Recognition of α-Hydroxycarboxylic Acids and *N*-Boc-Amino Acids by Counterion-Displacement Assays with a Chiral Nickel(II) Complex

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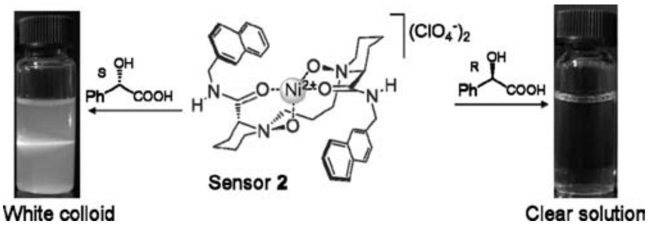
ABSTRACT



A new chiral sensor based on an *N*,*N*′-dioxide nickel(II) complex was prepared, which could visually recognize a series of chiral α-hydroxycarboxylic acid enantiomers by coordination and self-assembly forming into nanospheres or nanofibers. With the help of various techniques, the morphology structures of the colloid or suspension were obtained and the counterion-displacement assays were also confirmed. In addition, this metal complex could act as a highly enantioselective fluorescence sensor to recognize *N*-Boc-amino acids and chiral α-hydroxycarboxylic acids.

The study of chiral recognition provides a compelling rationale for understanding the interactions of biological molecules,[1] developing a useful separation process,[2] catalysis,[3] and sensing.[4] During the past decades, considerable efforts have been devoted to design of time-efficient chiral sensors through electrochemical and optical detection.[5] Apparently, visual detection methods such as color change and precipitate formation, which are more convenient and direct, have been scarcely reported.[6] Significant attention has been focused on chiral recognition of α-hydroxycarboxylic acids for their bioactivity.[4,7b] Generally, intermolecular noncovalent bonds such as hydrogen bonding are crucial in chiral recognition of those compounds

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(6) For examples of enantioselective color changing, see: (a) Folmer-Andersen, J. F.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **2005**, *127*, 7986–7987. (b) Tsubaki, K.; Tanima, D.; Nuruzzaman, M.; Kusumoto, T.; Fuji, K.; Kawabata, T. *J. Org. Chem.* **2005**, *70*, 4609–4616. (c) Kaneda, T.; Hirose, K.; Misumi, S. *J. Am. Chem. Soc.* **1989**, *111*, 742–743. For examples of enantioselective precipitation or gel, see: (d) Liu, H. L.; Hou, X. L.; Pu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 382–385. (e) Zheng, Y. S.; Ran, S. Y.; Hu, Y. J.; Liu, X. X. *Chem. Commun.* **2009**, 1121–1123. (f) Chen, X.; Huang, Z.; Chen, S. Y.; Li, K.; Yu, X. Q.; Pu, L. *J. Am. Chem. Soc.* **2010**, *132*, 7297–7299.

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between the host and the guest.[5] Encouraged by great success of Anslyn's indicator-displacement assays[7] and Wolf's competitive binding assays,[8] we envision that the chiral metal complex catalysts could also supply efficient enantioselective recognition opportunity in counterion-displacement assays. Herein, we wish to describe the first example of a chiral *N*,*N*′-dioxide-nickel(II) complex, which has been well developed by our group in asymmetric catalysis, as chemosensor to visually recognize a series of chiral α-hydroxycarboxylic acid enantiomers by coordination and self-assembly forming into nanospheres or nanofibers. Fluorescence recognition of α-hydroxycarboxylic acids and *N*-Boc-amino acids has also been realized by the chiral complex sensor.

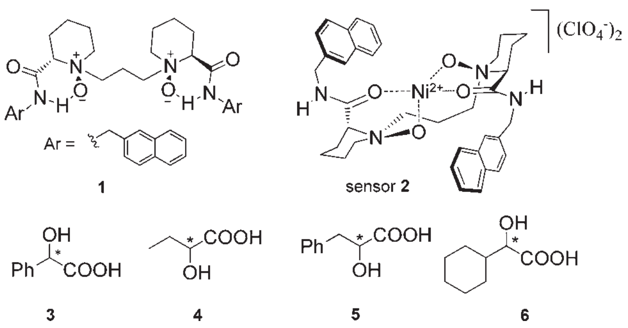

Figure 1. Structures of chiral sensor and chiral acids screened.

It has been proven that there was strong intramolecular H-bonding within *N*,*N*′-dioxide in our previous studies.[9] However, when a metal ion was added, a new tetradentate *N*,*N*′-dioxide-metal complex was generated, in which, based on X-ray analyses, the conformation of the ligand changed to facilitate the four oxygen atoms bonding to the central metal.[10] Sensor **2** was prepared from ligand **1** containing hydrophobic units of naphthyl as a stable green powder (Figure 1 and Supporting Information). Excitingly, when mandelic acid (*S*)-**3** was added ($\geq 1 \times 10^{-3}$ M) to a solution of sensor **2** (2.5×10^{-3} M) in acetonitrile, a white suspension began to form. If the suspension was illuminated with a 650 nm laser, an obvious Tyndall effect appeared that indicated the suspension behaved as a colloid (Figure 2a), whereas the mixture of (*R*)-**3** ($\geq 1 \times 10^{-3}$ M) and sensor **2** (2.5×10^{-3} M) gave rise only to a clear solution that seemed to be unchanged with even a 100-times excess of (*R*)-**3** (0.1 M). Similarly, a mixture of the *S*-enantiomer of α-hydroxybutyric acid **4**, 3-phenyllactic acid **5**, or hexahydromandelic acid **6** with sensor **2** also produced suspensions when 2-propanol was used as cosolvent together with acetonitrile (Figure 2b–d). Afterward, the enantiomer of sensor **2** was prepared and interacted with acids **3**–**6** under the same condition. A colloid or suspension of (*R*)-acids was observed, and clear solution was related to the (*S*)-acids (see Supporting Information). Therefore, the enantioselective generation of a colloid or suspension and visual discrimination of the enantiomers of each acid could be established. It is noted to be the first example of the metal complex as visual chiral sensor to recognize a series of chiral α-hydroxycarboxylic acids.

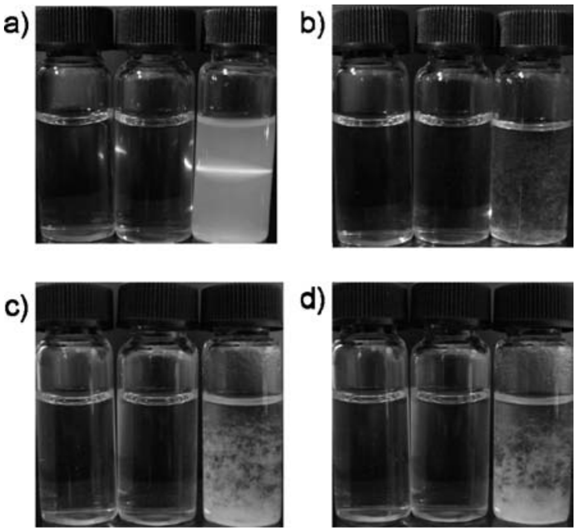

Figure 2. Photographs of sensor **2** at 2.5×10^{-3} M with chiral α-hydroxycarboxylic acids. (a) **3** in acetonitrile (5×10^{-3} M); (b) **4** in acetonitrile/5 vol % 2-propanol (5×10^{-3} M); (c) **5** in acetonitrile/10 vol % 2-propanol (1×10^{-2} M); (d) **6** in acetonitrile/10 vol % 2-propanol (5×10^{-3} M). From left to right in each picture are the solutions of **2**, **2**-(*R*)-acid, and **2**-(*S*)-acid.

The surface ultrastructure of these colloids or suspensions was confirmed by scanning electron microscopy (SEM). It revealed that the colloid from (*S*)-**3**/sensor **2** was 150 nm diameter nanospheres, which were very uniform and connected to each other to form a self-assembly web-like pattern (Figure 3a). Interestingly, the SEM images of suspensions of (*S*)-**4**/sensor-**2**, (*S*)-**5**/sensor-**2**, and (*S*)-**6**/sensor **2** were also different from the crystalline structure of sensor **2** (Supporting Information). Further studies of the spherical morphology for (*S*)-**3**/sensor-**2** were ensured by TEM images, which showed the nanospheres were solid instead of hollow and were compact in the center of the spheres but

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(10) In our previous studies, according to the ^{1}H NMR spectroscopy of **1**, the NH proton of *N*,*N*′-dioxide showed a strong deshielding effect at 10.886 ppm due to the strong hydrogen bond between *N*-oxide and the NH proton. Comparatively, after coordinating with metal, the X-ray crystal structure of *N*,*N*′-dioxide-Ni(II) and *N*,*N*′-dioxide-Sc(III) showed that the *N*,*N*′-dioxide behaves as a tetradentate ligand with both carbonyl oxygens and oxygens of *N*-oxide coordinating to metal center. The two amide groups stretched up and down on the opposite site, which acted as a good hydrogen bond acceptor. This indicated that the N-H from **1** and sensor **2** were complete difference. Thus **1** had no special phenomenon by adding chiral α-hydroxycarboxylic acids.

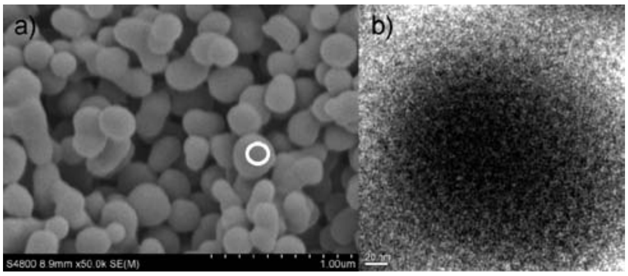

Figure 3. (a) SEM images of self-assembly objects from the interaction of sensor **2** (2.5×10^{-3} M) with (*S*)-**3** (5×10^{-3} M) in acetonitrile. (b) A magnified TEM image of the part circled by a white line in panel a.

gradually became less dense moving outward (Figure 3b). On the basis of the powder X-ray diffraction (XRD), it was found that sensor **2** was amorphous. The colloid of (*S*)-**3**/sensor **2** contained only two broad peaks at low scattering angles, and a sharp peak was not obtained (Supporting Information). This confirmed that the spherical aggregate was disordered on the short-range scale but was self-assembly ordered on the long-range.[11] Together with the TEM images, these experiments revealed that the sizes of the nanoparticles from the nanospheroid were irregular.

Although the NMR spectrum and crystal of the colloid could not be obtained, the solid state IR spectrum revealed the guest would coordinate with nickel(II) of sensor **2** to form a new complex (Supporting Information). Different from ligand or indicator displacement assays by Anslyn and Wolf,[7,8] we proposed that the guest tended to enantioselectively exchange the counterion of the host. The chiral acid **3** as mandelate anion might be able to coordinate to the central metal of the sensor **2** by displacing the orginal counterion ClO_4^- from the sensor **2**; EI-HRMS experiments supported this hypothesis (Supporting Information). The acquired critical ions $[[\mathbf{1} + Ni^{2+} + (S)\text{-}\mathbf{3}] - H]^+$ in the EI-HRMS spectrum of sensor **2**/(*S*)-**3** indicated that ClO_4^- was replaced by (*S*)-mandelate anion through the effective bonding of the two oxygens to nickel. The molecules of the new complex containing host−guest self-assembled into a colloid as a result of solvent effects. Comparative testing showed that no colloid was generated when sensor **2** was treated with methyl mandelate in acetonitrile.[12] However, when (*R*)-**3** was mixed with the sensor, no signals of new complexes were detected and ClO_4^- was still bonded to the metal, which was confirmed by critical ions $[\mathbf{1} + Ni^{2+} + ClO_4^-]^+$. Because of the mismatched chiral environment and steric factor, it was too difficult for (*R*)-**3** to approach the center of sensor **2** (see Supporting Information), so $[[\mathbf{1} + Ni^{2+} + (R)\text{-}\mathbf{3}]\text{-}H]^+$ was absent in the EI-HRMS spectrum of sensor **2**/(*R*)-**3**. Meanwhile, the $\pi-\pi$ interaction from the phenyl group of chiral acid **3** with the naphthyl moiety from the sensor and hydrophobic effect also might play an important role in forming colloid.

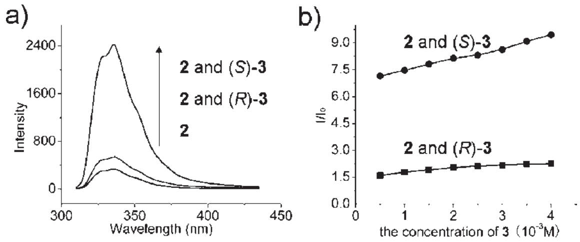

Figure 4. (a) Fluorescence spectra of sensor **2** at 1×10^{-3} M with/without (*S*)-**3** and (*R*)-**3** (5×10^{-4} M) in acetonitrile. (b) Fluorescence responses of sensor **2** at 1×10^{-3} M in acetonitrile toward (*S*)- and (*R*)-**3**.

The fluorescent property of *N*,*N'*-dioxide **1** and sensor **2** was studied. Fluorescence spectrum of *N*,*N'*-dioxide **1** in acetonitrile showed very strong emission intensity at 336 nm on excitation at 300 nm, in contrast to a low intensity of metal complex **2** exhibited at the same condition. The strong fluorescence quenching of sensor **2** might be due to metal-to-ligand charge transfer that was discovered by UV spectra experiments (see Supporting Information).[13] Subsequently, chiral recognition of several chiral α-hydroxycarboxylic acids and *N*-Boc-amino acids was investigated by sensor **2** at relative lower concentration in which no suspension was observed for all systems. Notably, highly enantioselective fluorescent response to acid **3** was found: the enantiomer (*S*)-**3** (5×10^{-4} M) greatly enhanced the fluorescence intensity of sensor **2**, but the (*R*)-**3** (5×10^{-4} M) did little. The enantiomeric fluorescence difference ratio, ef was 10.3 (Figure 4a).[14] This fluorescent enhancement might also be attributed to displace of the counterion of sensor **2** by chiral acid which was supported by UV expriments (Supporting Information). On the other hand, the interaction between acid **3** and sole *N*,*N'*-dioxide **1** was negligible, which corresponded to the nondiscrimination of the enantiomers and little response even in the presence of a large excess of ligand **1**.[6f,7,8] Then, the fluorescent interaction of acid **3** with the enantiomer of sensor **2** was also studied to support the enantioselective recognition. The "reverse image" relationship of the enantioselective fluorescence enhancement was obtained, and recognition curves over the concentration range 5×10^{-4} to 4×10^{-3} M of both enantiomer sensors were shown (Figure 4b and Supporting Information).[15]

Further investigation of chiral recognition by sensor **2** of other α-hydroxycarboxylic acids and *N*-Boc-amino acids was performed with the best ef summarized in Table 1.

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[11] Fireman-Shoresh, S.; Popov, I.; Avnir, D.; Marx, S. *J. Am. Chem. Soc.* **2005**, *127*, 2650–2655.

[12] Afterward, chiral recognition response of methyl mandelate and sensor **2** in acetonitrile was detected by fluorescence spectrum. As visual recognition, there was little discrimination between them.

[13] (a) Geoffroy, G. L.; Isci, H.; Litrenti, J.; Mason, W. R. *Inorg. Chem.* **1977**, *16*, 1950–1955. (b) Mason, W. R., III; Gray, H. B. *J. Am. Chem. Soc.* **1968**, *90*, 5721–5729. (c) Cowman, C. D.; Ballhausen, C. J.; Gray, H. B. *J. Am. Chem. Soc.* **1973**, *95*, 7873–7875.

[14] ef = $(I_L - I_0)/(I_D - I_0)$.

[15] The ee determination of the substrate **3** is shown in Supporting Information.

Table 1. Results for the Enantioselective Fluorescent Responses of Sensor **2** to the Chiral Acids

entry	acid	solvent	concn (M)	ef
1	**3**	acetonitrile	5.0×10^{-4}	10.3
2[a]	**4**	acetonitrile	4.0×10^{-3}	4.5
3[b]	**5**	acetonitrile	7.0×10^{-3}	2.6
4[c]	**6**	acetonitrile	4.0×10^{-3}	5.0
5	*N*-Boc-Glu	acetonitrile	2.5×10^{-4}	6.9[d]
6	*N*-Boc-Ser	acetonitrile	3.5×10^{-3}	3.5
7	*N*-Boc-Thr	acetonitrile	2.0×10^{-3}	2.4
8	*N*-Boc-Phe	acetonitrile	4.0×10^{-3}	2.0

[a] Solvent containing 5% 2-propanol. [b] Solvent containing 3% 2-propanol. [c] Solvent containing 10% 2-propanol. [d] ef = $(I_D - I_0)/(I_L - I_0)$

Both α-hydroxycarboxylic acids and *N*-Boc-amino acids could enhance the fluorescent intensity of sensor **2** to some extend. The results confirmed that sensor **2** demonstrated highly enantioselective fluorescent responses toward the *S*-enantiomer except for *N*-Boc-Glu (Supporting Information).

In summary, we have developed a chiral *N*,*N*′-dioxide nickel(II) complex sensor for colloid or suspension chiral recognition of a series of chiral α-hydroxycarboxylic acids by enantioselective self-assembly forming into nanofibers or nanospheres. With the help of various techniques, the morphology structure of the colloid or suspension has been obtained. This complex can also act as a highly enantioselective fluorescence sensor to recognize *N*-Boc-amino acids. As an excellent asymmetric catalyst extended to chiral sensors, it is a new way to enrich the new type of sensors and develop potential applications of those ligands. Further studies for recognizing other substrates are underway.

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Supporting Information Available. Experimental procedures, synthesis of compounds, EI-HRMS, IR, SEM, TEM, XRD, NMR and fluorescence spectra. This material is available free of charge via the Internet at http://pubs.acs.org.