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A Practical Enantioselective Fluorescent Sensor for Mandelic Acid

Jing Lin, Qiao-Sheng Hu, Ming-Hua Xu, and Lin Pu*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319

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Application of luminescence to chiral recognition has been studied for over two decades.[1−4] Recently, the development of fluorescence-based enantioselective sensors for applications in chiral catalyst screening has also began to attract research attention.[4] Optically active compounds that can distinguish the enantiomers of chiral amines, amino alcohols, and carbohydrates by showing enantioselective fluorescence quenching or enhancement have been obtained.[2−4] The use of fluorescence in chiral recognition can potentially provide a real-time technique for the determination of the enantiomeric composition of chiral compounds.[5,6] In high through-put combinatorial screening experiments, this would be advantageous over current methods such as chromatography and NMR analyses.[7,8]

We have initiated a program to develop enantioselective fluorescent sensors for the recognition of chiral α-hydroxycarboxylic acids. α-Hydroxycarboxylic acids are found to be the structural units of many natural products and drug molecules. They can also serve as multifunctional precursors to a great variety of organic compounds.[9,10] Although significant progress has been made for the asymmetric synthesis of α-hydroxycarboxylic acids,[9,10] the search for highly enantioselective as well as practical catalysts in this area continues. This research endeavor should be greatly facilitated by employing the high through-put combinatorial technique.[10b] For this purpose, fluorescent sensors that can carry out an enantioselective recognition of α-hydroxycarboxylic acids and allow a rapid determination of their enantiomeric composition are highly desirable. Herein, we report our synthesis and study of a practically useful enantioselective fluorescent sensor for the recognition of an α-hydroxycarboxylic acid, mandelic acid.

We have designed the bisbinaphthyl molecule (*S*,*S*)-**1** for the fluorescent recognition of chiral α-hydroxycarboxylic acids (Scheme 1).[2,4a,b,11,12] Figure 1 shows a proposed structure of complex (*S*,*S*)-**1** + (*S*)-mandelic acid featured with three specific hydrogen bonds. The molecular modeling structure is energy-minimumized with the PCSpartan-Pro program using the semiemperical PM3 force field. The lone pair electron of the nitrogen atom in (*S*,*S*)-**1** is incorporated to quench the fluorescence of the molecule through an intramolecular photoinduced-electron-transfer (PIET) process.[13,14] After (*S*,*S*)-**1** complexes with the α-hydroxycarboxylic acid, the lone pair electrons of the nitrogen are no longer available for PIET, which should lead to fluorescence enhancement. Because the interaction of the sensor with the two enantiomers of the acid should generate two different diastereomeric complexes, different fluorescence enhancement is therefore expected.

Compound (*S*,*S*)-**1** was synthesized according to Scheme 1. Compound (*S*)-**2** (2.4 equiv), prepared from (*S*)-1,1′-bi-2-naphthol, was reacted with **3**[16] in the presence of K_2CO_3 in refluxing acetone to give the bisbinaphthyl compound (*S*,*S*)-**4** in 92% yield. After removal of the *p*-nitrophenylsulfonyl group of (*S*,*S*)-**4** with *p*-

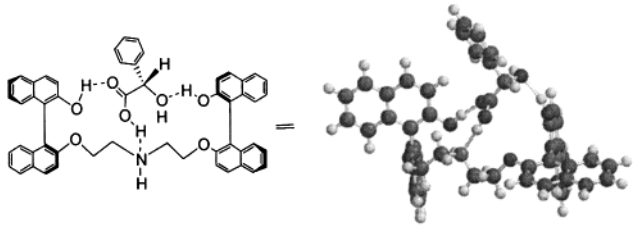
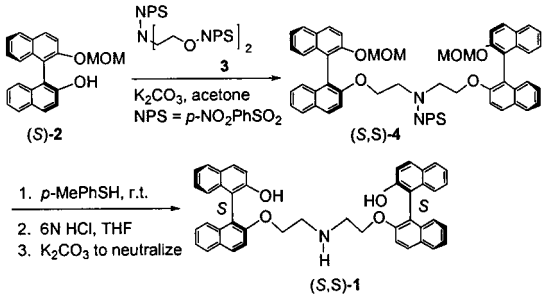


Figure 1. A proposed structure for complex (*S*,*S*)-**1** + (*S*)-mandelic acid.

Scheme 1. Synthesis of the Chiral Bisbinaphthyl Molecule (*S*,*S*)-**1**



MePhSH[17] and the MOM groups by acidic hydrolysis, the desired compound (*S*,*S*)-**1** was obtained in 73% yield over the two steps. The enantiomeric and diastereomeric purity of (*S*,*S*)-**1** were determined to be greater than 98%. The UV spectrum of (*S*,*S*)-**1** in methylene chloride solution displayed absorptions at λ_{max} 246, 280 and 334 nm. In the same solvent, this compound emitted at 367 nm when excited at 310 nm.

When (*S*,*S*)-**1** was treated with (*R*)- or (*S*)-mandelic acid, a large fluorescence enhancement was observed as expected due to the suppressed PIET fluorescence quenching when the amine nitrogen of (*S*,*S*)-**1** was protonated by the acid. We also observed that this fluorescence enhancement was highly enantioselective. In benzene solution [containing 2% dimethoxyethylene (DME)], the fluorescence intensity of (*S*,*S*)-**1** (9.5×10^{-5} M) was increased to 2.87 times that of the original value by (*S*)-mandelic acid (5.0×10^{-3} M), but only to 1.75 times by (*R*)-mandelic acid (5.0×10^{-3} M). The net fluorescence intensity increase of (*S*,*S*)-**1** by (*S*)-mandelic acid was 2.49 times that by (*R*)-mandelic acid, i.e., $(I_S - I_0)/(I_R - I_0) = 2.49$. Such a large difference in fluorescence enhancement makes this sensor practically useful for the enantioselective recognition of the chiral α-hydroxycarboxylic acid.

When (*S*,*S*)-**1** (9.5×10^{-5} M) was treated with mandelic acid in the concentration range of 5.0×10^{-3} to 2.0×10^{-2} M, the fluorescence enhancement of the sensor followed a Benesi−Hildebrand type equation.[18] Thus, the association constant of (*S*,*S*)-**1** + (*S*)-mandelic acid was found to be 348 M^{-1}, and that of (*S*,*S*)-**1** + (*R*)-mandelic acid 163 M^{-1}. This indicates that the complex (*S*,*S*)-**1** + (*S*)-mandelic acid is more stable than the complex (*S*,*S*)-**1** + (*R*)-mandelic acid by ca. 0.45 kcal/mol ($\Delta\Delta G$). The interaction of (*S*,*S*)-**1** with (*S*)-mandelic acid in C_6D_6 (containing 2% DME)

* Address correspondence to this author. E-mail: lp6n@virginia.edu.

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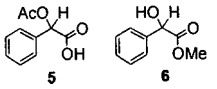
was also studied by using ^{1}H NMR spectroscopy. It was observed that the methine proton signal of (*S*)-mandelic acid at δ 5.16 was shifted downfield upon interaction with the sensor. In a 9:1 sensor/acid solution, the methane signal was observed at δ 5.28. A Job plot was obtained on the basis of the NMR study that indicates the formation of a 1:1 complex between the sensor and the acid.[19]

The fluorescence enhancement of (*R*,*R*)-**1**, the enantiomer of (*S*,*S*)-**1**, in the presence of (*R*)- and (*S*)-mandelic acid was studied under the same conditions as (*S*,*S*)-**1**. It showed that (*R*)-mandelic acid enhanced the fluorescence of (*R*,*R*)-**1** much greater than (*S*)-mandelic acid. That is, there is a mirror image relationship between the fluorescence enhancement of (*R*,*R*)-**1** and (*S*,*S*)-**1** in the presence of mandelic acid. This confirms that the observed different fluorescence enhancement between the two enantiomers of mandelic acid is indeed due to chiral recognition by the fluorescent sensor.

We also studied the interaction of (*S*,*S*)-**1** with compounds (*R*)- and (*S*)-**5**. Both (*R*)- and (*S*)-**5** were found to greatly enhance the fluorescence of (*S*,*S*)-**1** under conditions similar to the use of mandelic acid. However, essentially no enantioselectivity in the fluorescence enhancement was observed. Compound **6** was also used to interact with sensor (*S*,*S*)-**1**. In the presence of racemic **6** (5.0×10^{-3} M in benzene containing 2% DME), there was almost no fluorescence enhancement at all for (*S*,*S*)-**1** (9.5×10^{-5} M). The study of **5** and **6** demonstrates that both the hydroxyl group and the carboxylic acid group of mandelic acid are important for the enantioselective fluorescence enhancement of the sensor. This is consistent with the proposed multiple hydrogen bonding structure between the sensor and mandelic acid.



5 **6**

The fluorescence of (*S*,*S*)-**1** in the presence of mandelic acid with various enantiomeric composition was studied. A linear relationship between I/I_0 and the percent of the *S* component of mandelic acid was observed. Thus, the enantiomeric composition of the α-hydroxycarboxylic acid can be readily determined by measuring the fluorescence intensity of sensor (*S*,*S*)-**1** in the presence of the substrate. We are currently studying the use of this sensor in the combinatorial screening of chiral catalysts for the asymmetric synthesis of α-hydroxycarboxylic acids.

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Supporting Information Available: Synthesis and characterization of sensor (*S*,*S*)-**1**, sample preparation for fluorescence measurement, fluorescence spectra of (*S*,*S*)-**1** with/without mandelic acid, Benesi−Hildebrand plots, a Job plot, and a fluorescence intensity versus enantiomeric composition plot (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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