Enantiomer Detection

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Enantioselective Precipitation and Solid-State Fluorescence Enhancement in the Recognition of α-Hydroxycarboxylic Acids**

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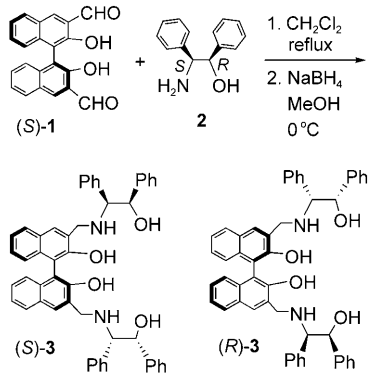
In classical chemical analysis, the two most convenient visual detection methods are color change and precipitate formation. Although significant progress has been made in the enantioselective recognition of chiral organic compounds over several decades,[1] very few examples of visual discrimination of enantiomers that rely only on color change have been reported.[2,3] Although the resolution of an organic racemate by treatment with an optically pure resolving agent often involves the enantioselective formation of an acid–base or a host–guest complex that may precipitate from solution,[4] enantioselective precipitation has not been utilized to date for the development of enantioselective sensors.

Chiral recognition is important in the study of drug molecules and other biologically relevant species because of the inherent chirality of biological systems.[1,5] In addition, fast and convenient analytical methods for chiral recognition are also useful for high-throughput chiral catalyst screening.[6] The enantioselective detection of α-hydroxycarboxylic acids has received attention because of the importance of this class of compounds in biological processes as well as in organic synthesis;[7] the various techniques that have been applied to the detection of these species include NMR, UV/Vis, and fluorescence spectroscopy.[8] Herein, we report a new acyclic chiral sensor that can be used to visually recognize the enantiomers of α-hydroxycarboxylic acids by enantioselective precipitation. In addition, the enantioselective precipitation generates strongly fluorescent particles and provides an additional quantitative method for enantioselective discrimination.

When (*S*)-3,3′-diformylbinol (binol = 1,1′-bi-2-naphthol),[9] (*S*)-**1**, is condensed with (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**2**) followed by reduction with $NaBH_4$, (*S*)-**3** is obtained as a white solid in 83% yield (Scheme 1). The specific optical rotation ($[\alpha]_D$) of (*S*)-**3** is $-24.5\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 1.15\times10^{-2}\ \mathrm{g\,cm^{-3}}$, CH_2Cl_2). The enantiomer (*R*)-**3** is also prepared by using the enantiomers of the starting materials.



Scheme 1. Preparation of the 1,1′-binaphthyl sensor (*S*)- and (*R*)-**3**.

We have studied the interaction of (*S*)-**3** with (*R*)- and (*S*)-mandelic acid (MA, $PhCH(OH)CO_2H$). When (*S*)-MA ($\geq 3.0\times10^{-3}$ M) is added to a solution of (*S*)-**3** (5.0×10^{-4} M) in benzene (containing 0.4 vol% dimethoxyethane, DME), the clear solution immediately becomes a white suspension (Figure 1a). Under the same conditions, when (*R*)-MA is added to a solution of (*S*)-**3** in the concentration range of 1.0×10^{-3}–8.0×10^{-3} M, the solution remains clear. When the enantiomer (*R*)-**3** is used, precipitation with (*R*)-MA is observed but not with (*S*)-MA (Figure 1b). This confirms the observed enantioselective precipitation.

The precipitate generated from the (*S*)-**3**/(*S*)-MA system can be isolated by filtration and is soluble in [D_6]acetone. The ^{1}H NMR spectrum of the precipitate shows that it contains (*S*)-**3** and (*S*)-MA in a 1:4 ratio. This ratio is independent of the initial ratio of the two components in solution. That is, four molecules of (*S*)-MA bind preferentially with one molecule of (*S*)-**3** to generate a stable precipitate from benzene.

Although the single-crystal X-ray structure of the precipitate could not be obtained, a powder X-ray diffraction study was conducted. It was found that (*S*)-**3** is amorphous and (*S*)-MA is crystalline, and that the precipitate of (*S*)-**3**/(*S*)-MA comprises a crystalline order with unit cells that are different from those of (*S*)-MA. This indicates that there is an organized self-assembly between (*S*)-**3** and (*S*)-MA during the precipitation.

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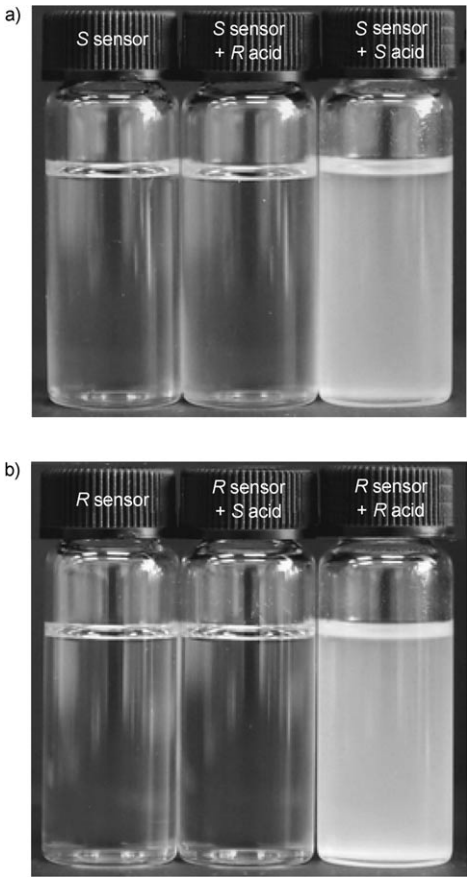

Figure 1. Photographs of (*S*)-**3** (a) and (*R*)-**3** (b) at 5.0×10^{-4} M with (*R*)- and (*S*)-MA (4.0×10^{-3} M) in benzene/0.4 vol% DME.

A scanning electron microscopy (SEM) image of the (*S*)-**3**/(*S*)-MA precipitate shows that the self-assembly of (*S*)-**3** and (*S*)-MA generates a porous structure (Figure 2). This is very different from the layered and closely packed crystalline structure of (*S*)-MA.

The fluorescence properties of (*S*)-**3** were studied. When a solution of (*S*)-**3** in benzene is excited at 341 nm, it shows a fluorescence signal at 439 nm with a shoulder at approximately 370 nm. Previously, we have shown that the 1,1′-binaphthyl-based compounds generally exhibit dual emission signals in the range of 350–450 nm with the short-wavelength peak attributed to the monomer emission and the long-wavelength peak to the excimer emission.[8g–j,10] When methanol is added to a solution of (*S*)-**3** in benzene, although almost no change in the UV/Vis spectrum of the solution is observed, its fluorescence spectrum shows that the ratio of the long-wavelength emission to the short-wavelength emission increases while the peak positions do not change. Thus, the increase in the polarity of the solvent might have increased the ease of excimer formation between the less polar aromatic rings of (*S*)-**3** upon excitation. When the concentration of (*S*)-**3** in benzene is decreased to 5.0×10^{-7} M, its excimer emission still dominates.

Comparison of the fluorescence spectra of the samples presented in Figure 1 a shows that the fluorescence signals of (*S*)-**3** and (*S*)-**3**/(*R*)-MA are very close to the baseline, but that of (*S*)-**3**/(*S*)-MA is enhanced over 950-fold at $\lambda_{em}=367$ nm (Figure 3). This dramatic fluorescence enhancement arises from the fluorescence of the precipitate of (*S*)-**3**/(*S*)-MA. Thus, the observed enantioselective precipitation is associated with a highly enantioselective fluorescence enhancement. The fluorescent responses of the enantiomeric sensor (*R*)-**3** to (*R*)- and (*S*)-MA confirm the high enantioselectivity.

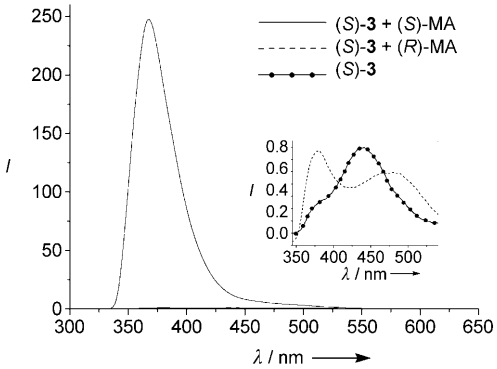

Figure 3. Fluorescence spectra of (*S*)-**3** (5.0×10^{-4} M) with (*R*)- and (*S*)-MA (4.0×10^{-3} M) in benzene/0.4 vol% DME ($\lambda_{exc}=341$ nm, slit width = 5.0/5.0 nm).

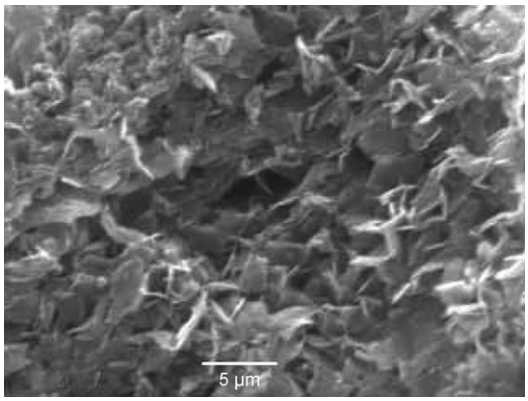

Figure 2. SEM image of the precipitate generated from (*S*)-**3** (5.0×10^{-4} M) and (*S*)-MA (4.0×10^{-3} M).

When the precipitate of (*S*)-**3**/(*S*)-MA is separated, the remaining solution exhibits very little fluorescence. The fluorescence microscopy images of the (*S*)-**3**/(*S*)-MA precipitate show that the solid particles of (*S*)-**3**/(*S*)-MA are strongly fluorescent upon UV irradiation (Figure 4). The solid particles of (*S*)-**3** have a much weaker fluorescence intensity and those of (*S*)-MA are nonfluorescent.

The greatly enhanced fluorescence of the (*S*)-**3**/(*S*)-MA precipitate compared with the solution is in sharp contradiction with the general observation that materials are normally less fluorescent in the solid state than in solution because close packing in the solid state often leads to self-quenching and excimer or exciplex formation.[12] Fluorescence enhancement in inclusion complexes and coordination polymer gels has been observed, but this has not been applied in enantioselective recognition.[13] The dramatically enhanced

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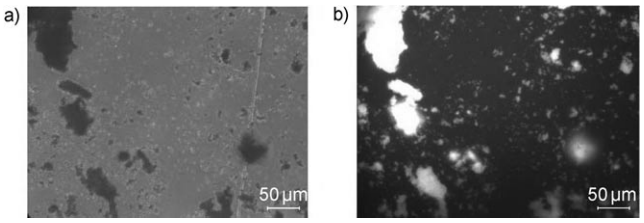


Figure 4. Topography image (a) and fluorescence image (b) of the precipitate formed from (*S*)-**3** (5.0×10^{-4} M) and (*S*)-MA (4.0×10^{-3} M).

fluorescence signal of the (*S*)-**3**/(*S*)-MA precipitate corresponds to the monomer emission of (*S*)-**3**, with almost no excimer emission (Figure 3). This observation, together with the NMR spectra, powder X-ray diffraction, and SEM studies of the precipitate indicate that the self-assembly of (*S*)-**3**/(*S*)-MA might have produced a highly organized material with each individual molecule of (*S*)-**3** separated by multiple (*S*)-MA molecules. There is no close-packing between the molecules of (*S*)-**3** in the precipitate, which should prevent the intermolecular interaction of (*S*)-**3** to generate the excimer and avoid self-quenching of the fluorophore. It is expected that there should be strong hydrogen bonding between the basic nitrogen atoms of (*S*)-**3** and the acidic proton of (*S*)-MA. This should suppress the photoinduced electron transfer fluorescence quenching caused by the lone pair of electrons on the nitrogen atom.[8g–j,10] In addition, in the solid particles of the (*S*)-**3**/(*S*)-MA complex, the structure of (*S*)-**3** should have much more restricted motion and thus act as a better fluorophore than in solution.

The effect of the enantiomeric composition of MA on the fluorescence enhancement of the sensor is studied. Figure 5, curve a shows the fluorescence enhancement of (*S*)-**3** (5.0×10^{-4} M, benzene/0.4 vol% DME) in the presence of (*S*)-MA in the concentration range of 0–4.0×10^{-3} M. It shows that the fluorescence enhancement starts when the concentration of (*S*)-MA is greater than 2.0×10^{-3} M. Figure 5, curve b shows the fluorescence enhancement of the same sensor solution in the presence of the substrate containing both (*S*)- and (*R*)-

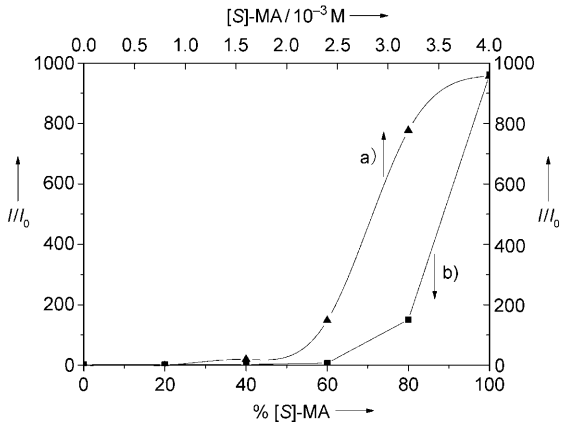
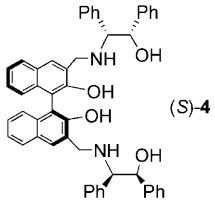


Figure 5. Fluorescence enhancement of (*S*)-**3** (5.0×10^{-4} M, benzene/0.4 vol% DME) in the presence of (*S*)-MA (curve a, top scale) and the enantiomeric mixture of MA at 4.0×10^{-3} M (curve b, bottom scale). $\lambda_{exc}=341$ nm.

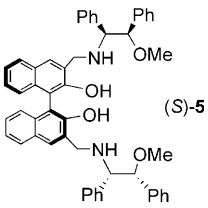
MA at a total acid concentration of 4.0×10^{-3} M. It shows that the fluorescence enhancement of (*S*)-**3** starts when the proportion of the *S*-enantiomer of MA is greater than 60%. Thus, the sensor will be useful to determine the enantiomeric composition of the samples that have greater than 60% enantiomeric purity, that is, greater than 20% *ee*. When (*S*)-MA is present in excess, (*S*)-**3** will be used and when (*R*)-MA is present in excess, (*R*)-**3** will be used. The samples that have an almost racemic composition ((50 ± 10)% *R* or *S*) will not show significant fluorescence enhancement. One explanation for this is that the binding between the two enantiomers in the racemic MA might be stronger than their interaction with the sensor. This should also contribute to the difference between curve a and curve b in Figure 5.

The interaction of compound (*S*)-**3** with (*R*)- and (*S*)-hexahydromandelic acid ($C_6H_{11}CH(OH)CO_2H$), an aliphatic α-hydroxycarboxylic acid, was also studied. A similar enantioselective precipitation and solid-state fluorescence enhancement to that of (*S*)-**3** with (*R*)- and (*S*)-MA occurred.

We have prepared compound (*S*)-**4**, a diastereomer of (*S*)-**3**, from the reaction of (*S*)-**1** with (1*S*,2*R*)-2-amino-1,2-diphenylethanol followed by reduction. When (*S*)-**4** is treated



(*S*)-**4**



(*S*)-**5**

with (*R*)- or (*S*)-MA in benzene (containing 0.4 vol% DME), no precipitate is observed. A similar result occurred when the methylated compound (*S*)-**5** was treated with (*R*)- or (*S*)-MA. These observations demonstrate that both the chiral configurations of the binol and amino alcohol units in (*S*)-**3** are important for the observed enantioselective precipitation and that the hydrogen bonding of the amino alcohol hydroxy protons should be involved.

In summary, a visual chiral recognition of the enantiomers of α-hydroxycarboxylic acids has been achieved by enantioselective precipitation. We have also found that the observed enantioselective precipitation is associated with a dramatic (over 950-fold) solid-state fluorescence enhancement. Through the use of various techniques including NMR, UV/Vis, and fluorescence spectroscopy, X-ray diffraction, SEM, and fluorescence microscopy, insights into the structure of the precipitate and its strong fluorescence have been acquired. The enantioselective fluorescence enhancement of the sensor makes its possible to determine the enantiomeric composition of the acid. Further study of this class of sensors for the recognition of other substrates is under way.

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