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COMMUNICATION

Highly sensitive determination of enantiomeric composition of chiral acids based on aggregation-induced emission†

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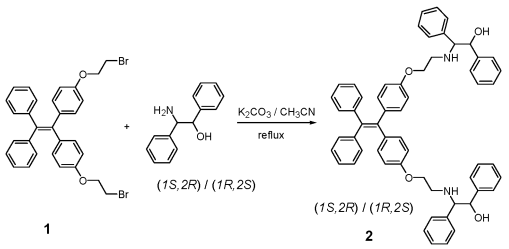
A new chiral tetraphenylethylene derivative with the AIE effect was synthesized and showed not only high enantioselectivity for a wide range of chiral acids but also a high sensitivity of 3.0×10^{-6} M scale. The enantiomeric purity of chiral acids could be quantitatively determined by this chiral sensor.

Chiral recognition through fluorescence change attracts keen interest because it can provide time-efficient, accurate, and sensitive enantiomeric determination of chiral reagents, catalysts, natural products and drugs.[1–3] However, to design and synthesize excellent fluorescent chiral receptors is still a challenge.[1–3] Recently, a new class of organic compounds with an aggregation-induced emission (AIE) or aggregation-induced emission enhancement (AIEE) have been developed[4] and shown to be highly selective and stable fluorescence sensors for biological and chemical analytes, such as for specific detection and quantitative analysis of carbon dioxide[4b] and D-glucose.[4c] Previously, we have demonstrated that chiral AIE carboxylic acids or amines can show exceptionally high enantioselectivity for chiral analytes, but the sensitivity was not high.[5] Pu and Hou[2a,b] also found enantioselective precipitation and solid-state fluorescence enhancement in the recognition of α-hydroxycarboxylic acids by 1,1′-bi-2-naphthol-amine receptors, but this chiral recognition was only obtained at a large concentration of 4.0×10^{-3} M. Recently, Zhu and Cheng *et al.*[2c] studied the effect of solvent polarity on the sensitivity of chiral recognition of α-hydroxy-carboxylic acids by salan sensors, and found that a considerable enantioselectivity could only be realized at a concentration of more than 1.0×10^{-4} M for the chiral acids in optimized solvents. Here we report that chiral tetraphenylethylene derivative **2** with the AIE effect displays not only high enantioselectivity for a wide range of chiral acids but also very high sensitivity. Even at a low concentration of 3.0×10^{-6} M scale, two enantiomers of a chiral acid can be efficiently discriminated.

Tetraphenylethylene (TPE) and its derivatives are well known for their excellent AIE effect.[4] Therefore, the known dibromoethoxy TPE **1**[6] was chosen to react with chiral auxiliary



Scheme 1 Synthesis of chiral AIE compounds (1*S*,2*R*)-**2** and (1*R*,2*S*)-**2**.

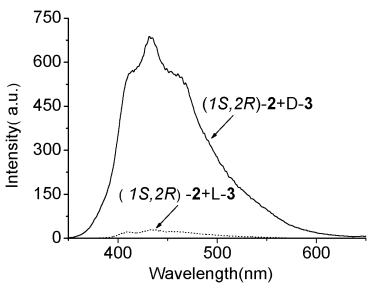


Fig. 1 Fluorescence spectra of a mixture of (1*S*,2*R*)-**2** and enantiomers of 2,3-di(*p*-toluoyl)tartaric acid **3** in chloroform. [(1*S*,2*R*)-**2**] = [**3**] = 5.0×10^{-4} M, λ_{ex} = 323 nm, ex/em slits = 10/10 nm.

(1*S*,2*R*)- or (1*R*,2*S*)-1,2-diphenyl-2-aminoethanol to give chiral AIE compounds (1*S*,2*R*)-**2** and (1*R*,2*S*)-**2** (Scheme 1). The test of mixed solvent confirmed that (1*S*,2*R*)-**2** and (1*R*,2*S*)-**2** were AIE compounds (Fig. S9, ESI†).

As shown in Fig. 1, Fig. S10–S18 (ESI†) and Table 1, the chiral recognition ability of (1*S*,2*R*)-**2** was tested for a large number of chiral acids. It was noticed that (1*S*,2*R*)-**2** was especially suitable for chiral diacids probably due to two amine groups connected to it. For 2,3-di-*p*-toluoyltartaric acid **3**, the mixture of (1*S*,2*R*)-**2** and D-**3** produced precipitates but that of (1*S*,2*R*)-**2** and L-**3** gave a solution in chloroform. The suspended precipitates strongly fluoresced while the solution did not (Fig. 1). The fluorescence intensity ratio or enantioselectivity (I_1/I_2 in Table 1) resulted from two enantiomers of **3** was 25. For 2,3-dibenzoyltartaric acid **4**, malic acid **5**, *N*-Boc-glutamic acid **6** and *N*-Cbz-aspartic acid **7**, (1*S*,2*R*)-**2** also exhibited a high enantioselectivity from 20, 14, 20 to 12, respectively (Table 1).

The AIE compound (1*S*,2*R*)-**2** also exhibited excellent chiral recognition between two enantiomers of chiral monocarboxylic acids (Fig. S14–S17, ESI†). The enantioselectivity was 5.0, 13,

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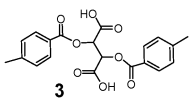
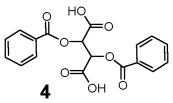
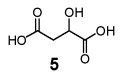
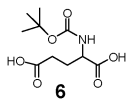
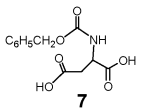
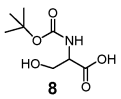
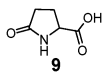
Table 1 The enantioselectivity (I_1/I_2) of (1*S*,2*R*)-**2** resulted from two enantiomers of chiral acids

No.	Acids	I_1/I_2	State[a]
1	 **3**	25 (D/L)	Pre/Sol[b]
2	 **4**	20 (D/L)	Pre/Sol[b]
3	 **5**	14 (D/L)	Sus/Sol[c]
4	 **6**	20 (D/L)	Sus/Sol[c]
5	 **7**	12 (D/L)	Sus/Sol[c]
6	 **8**	5.0 (D/L)	Sus/Sol[d]
7	 **9**	13 (D/L)	Sus/Sol[c]
8	 **10**	46 (*R*/*S*)	Sus/Sol[e]
9	 **11**	16 (*S*/*R*)	Sus/Sol[c]
10	 **12**	5.6 (D/L)	Sus/Sol[d]

[a] Enantiomer 1/enantiomer 2, Pre = precipitates; Sus = suspension; Sol = solution. Fluorescence intensity (*I*) was measured at λ_{max}. [b] In $CHCl_3$. [c] In H_2O/THF. [d] In CH_2Cl_2. [e] In CH_2Cl_2/hexane.

46, and 16 for *N*-Boc-serine **8** and pyroglutamic acid **9** as well as convenient α-hydroxycarboxylic acids, mandelic acid **10** and 2-chloromandelic acid **11**, respectively (Table 1). In addition, even for a strong acid, camphorsulfonic acid **12**, (1*S*,2*R*)-**2** could also discriminate its two enantiomers with a good enantioselectivity of 5.6 (Fig. S18 (ESI†) and No. 10 in Table 1).

The enantioselectivity between two enantiomers of chiral acids could change as concentration and solvent(s) were changed. In chloroform, all mixtures of (1*S*,2*R*)-**2** and L-**3** from 1.0×10^{-4} M to 1.0×10^{-3} M were a clear solution, but those of (1*S*,2*R*)-**2** and D-**3** appeared as a suspension when the concentration was more than 3.0×10^{-4} M. The enantioselectivity increased from 25, 95 to 160 when concentration increased from 5.0×10^{-4}, 8.0×10^{-4} to 1.0×10^{-3} M. In the range of concentration less than 3.0×10^{-4} M, almost no fluorescence intensity difference for two enantiomers was observed (Fig. 2A). If a mixed solvent of chloroform and hexane was used, high enantio selectivity could be obtained at lower concentration. In chloroform mixed with hexane (volume ratio 1 : 2), the enantioselectivity

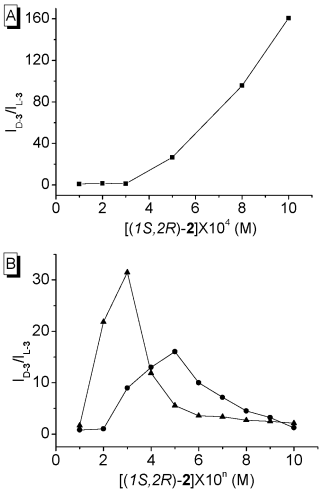


Fig. 2 Change of fluorescence intensity ratio for two enantiomers of **3** with concentration of (1*S*,2*R*)-**2** in different solvent(s): (A) $CHCl_3$; (B) ▲ concentration axis $n = 5$, $CHCl_3$/hexane 1 : 2; ● concentration axis $n = 6$, $CHCl_3$/hexane 1 : 4 (V/V). [D-**3**]/[(1*S*,2*R*)-**2**] = [L-**3**]/[(1*S*,2*R*)-**2**] = 1 : 1.

initially increased from 2.1 to 31 and then decreased from 31 to 1.7 when concentration decreased from 1.0×10^{-4} M to 1.0×10^{-5} M (Fig. 2B, ▲). At a concentration of 3.0×10^{-5} M, the mixture of (1*S*,2*R*)-**2** and L-**3** became a solution but that of (1*S*,2*R*)-**2** and D-**3** remained a suspension. Therefore, the highest enantioselectivity (31, D/L) was obtained at this concentration. Even at 2.0×10^{-5} M, (1*S*,2*R*)-**2** also led to a high enantioselectivity of up to 22. But at 1.0×10^{-5} M, it had only 1.7.

When the volume ratio of chloroform and hexane was decreased to 1 : 4, (1*S*,2*R*)-**2** could discriminate the two enantiomers even at a concentration of 10^{-6} M scale. As shown in Fig. 2B (●), the enantioselectivity initially increased from 1 to 16 and then decreased from 16 to 1.2 when concentration of the mixture of (1*S*,2*R*)-**2** and one enantiomer of **3** decreased from 1.0×10^{-5} M to 1.0×10^{-6} M. The maximum of enantioselectivity appeared at 5.0×10^{-6} M and it was still up to 9.0 even at 3.0×10^{-6} M. Unlike those at high concentration, all mixtures of (1*S*,2*R*)-**2** and enantiomers of **3** seemed to be almost a clear solution at a low concentration of 10^{-6} M scale. However, even under a portable 365 nm UV lamp, the mixture of (1*S*,2*R*)-**2** and D-**3** emitted strong blue light but that of (1*S*,2*R*)-**2** and L-**3** showed no fluorescence.

^{1}H NMR titration of (1*S*,2*R*)-**2** with D-**3** or L-**3** was carried in *d*-chloroform (Fig. S20–S23, ESI†). From the Job plots, it was found that both D-**3** and L-**3** formed a 1 : 1 complex with (1*S*,2*R*)-**2**. The association constants of (1*S*,2*R*)-**2**–D-**3** complexes and (1*S*,2*R*)-**2**–L-**3** complexes were 6.3×10^4 M^{-1} and 1.3×10^5 M^{-1}, respectively, demonstrating a different binding force when D-**3** and L-**3** interacted with (1*S*,2*R*)-**2** respectively. FE-SEM images disclosed that the suspension of (1*S*,2*R*)-**2**–D-**3** complexes was pod-like nano-rods with about 80 nm width and 350 nm length, while the solid resulted from dryness of the solution of (1*S*,2*R*)-**2**–L-**3** complexes was irregular lamella (Fig. S24 and S25, ESI†). Importantly, ESI^+ mass spectra of the mixture of **2** and **3** in chloroform not only showed a strong peak of **2**–**3** complexes (m/z 1229.5, M + 1) but also obvious one of $\mathbf{2}_2$–$\mathbf{3}_2$ tetramers (m/z 2459.1, M + 3) (Fig. S26–S29, ESI†), indicating oligomers composed of **2** and **3**

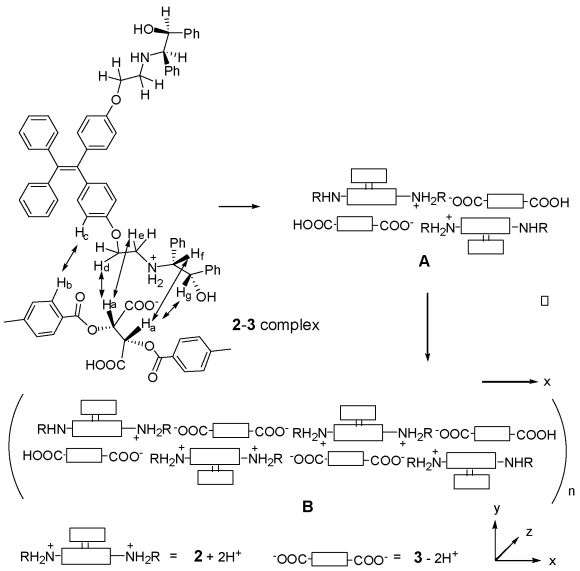


Fig. 3 The main intermolecular NOEs between **2** and **3** in **2–3** complexes and probable mechanism of aggregates formation.

in a 1 : 1 ratio could be easily produced. Due to acid–base interaction of carboxylic and amino groups, methine protons of the acid were close to protons of two alkanoic chains connected to amino groups and showed intermolecular NOEs between H_a–H_d, H_a–H_e, H_a–H_f, and H_a–H_g in 2D NOESY spectra of **2–3** complexes. Exceptionally, there were obvious intermolecular NOEs between the toluoyl protons of the acid and the protons of the substituted phenyl ring of the TPE part in **2** (between H_b–H_c) (Fig. 3 and Fig. S30–S33 (ESI†)), indicating that the toluoyl group of the acid was close to the TPE part of **2**. No intermolecular NOEs between methyl protons of the toluoyl group and phenyl protons of the TPE part were found. Therefore, the **2–3** complex formed by approach of the acid **3** to the amine **2** from exterior of two amino groups of **2**, rather than between two amino groups of **2** (Fig. 3). The intermolecular NOEs also excluded the diacid **3** from forming a bridge between two molecules of **2**. The **2–3** complex formed by acid–base interaction can be converted into a tetramer complex **A** by dipole–dipole attraction of two acid–base ion pairs and hydrogen bonds (Fig. 3). By further acid–base interaction at the *x* direction, tetramer complexes **A**s form a 1D network **B**, which can stack side by side at *y* and *z* directions to give a 3D nano-rod. If the acid is monoacid, the resultant tetramer complex could stack from the *z* direction by hydrogen bonds of acid–base ion pairs to give a 1D network, which could arrange side by side to give aggregates. This probable self-assembly of acid–base complexes can be found in recent literature[7] and in crystal structure of the complex of (1*S*,2*R*)-2-amino-1,2-diphenylethanol and (*1R*)-camphor-10-sulfonic acid we have obtained (unpublished). In case the interaction force between the tetramer complexes is not enough, or the tetramer is easily soluble in solvents, the 1D network cannot form, which will lead to no aggregates. Due to different binding force of two enantiomers to (1*S*,2*R*)-**2**, and different solubility of **2–3** complexes or tetramers from two enantiomers, one enantiomer results in aggregates, another leads to no or less aggregates. In aggregates, the intramolecular rotation of (1*S*,2*R*)-**2** leading to fluorescence quench is limited, therefore, it will emit strong fluorescence. The more it aggregates, the stronger it emits.

The chiral recognition by chiral AIE compound **2** at very low concentration could be used for quantitative determination of enantiomeric composition of chiral acids. Due to inherent chiral recognition, when (1*R*,2*S*)-**2** was used as chiral amine, the interaction of chiral acids with (1*R*,2*S*)-**2** resulted in a contrary enantioselective aggregation compared with (1*S*,2*R*)-**2**. When 3.3×10^{-5} M solutions of **3** with varying enantiomeric ratios were tested with (1*S*,2*R*)-**2** at the same concentration (Fig. S34, ESI†), the fluorescence intensity increased with increasing molar percentage of D-**3** in two enantiomers of **3**. The fluorescence intensity change was sensitive to the variation of enantiomeric composition, especially at low molar percentage less than 10% of D-**3**. Similarly, the fluorescence intensity of the same experiment with (1*R*,2*S*)-**2** increased with increasing molar percentage of L-**3**. It also had a sharp increase as long as a little amount of L-**3** was added into D-**3**, demonstrating the high sensitivity of the chiral sensor. As a result, the enantiomeric purity of chiral acid **3** could be obtained from any one of two standard curves drawn from the above two tests with (1*S*,2*R*)-**2** and (1*R*,2*S*)-**2**, respectively.

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