JOC Note

Chiral Mono Boronic Acid As Fluorescent Enantioselective Sensor for Mono α-Hydroxyl Carboxylic Acids

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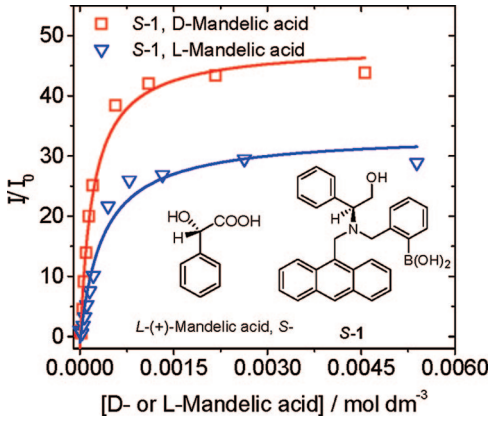
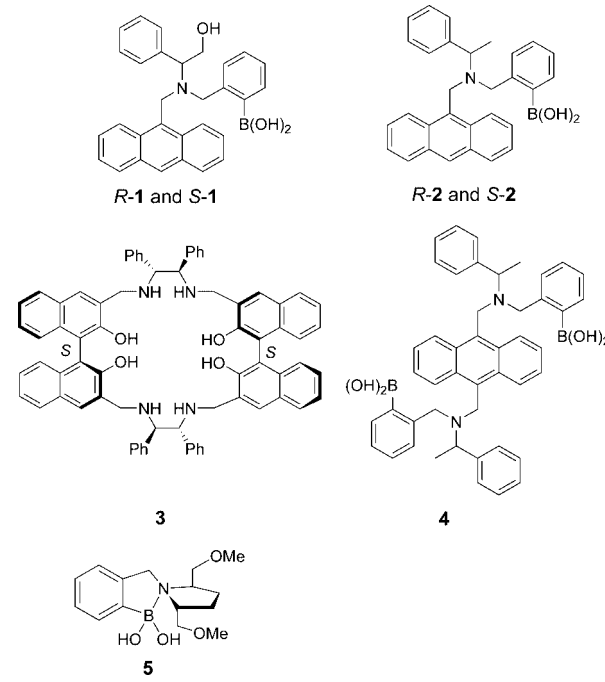


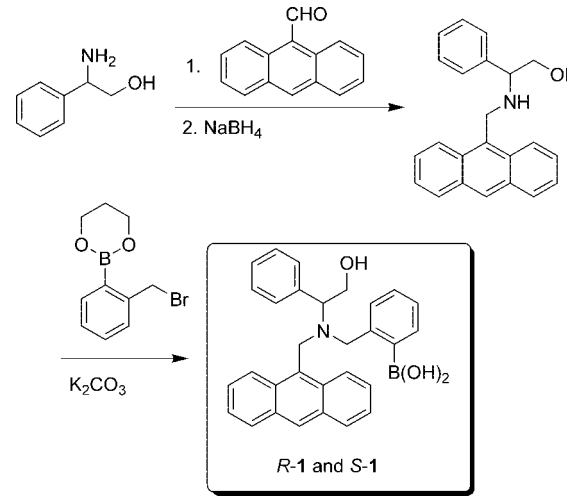
New mono boronic acid was found to be an enantioselective fluorescent chemosensor for mono α-hydroxyl carboxylic acids, such as mandelic acid and lactic acid. The chiral sensor shows lower background fluorescence, higher fluorescence enhancement, and enantioselective recognition kinetics toward mandelic acids and lactic acids.

Much attention has been paid to the enantioselective molecular recognition of chiral analytes, especially α-hydroxyl acids.[1–6] To this end, hydrogen bonding based chiral fluorescent sensors for α-hydroxyl acids have been developed,[3,4,6] e.g., sensor **3** (Scheme 1).[3,7] In order to improve the chiral recognition,[8,9] *covalent* bonding based sensors are developed, such as sensor **4** and **5**.[10] The enantioselectivity of sensors **4** are good with bis or poly hydroxyl acids, such as tartaric acid and sugar acids but poor with mono α-hydroxyl acids, such as mandelic acids or lactic acids.[10] Recently, Anslyn et al. have shown that a mono boronic acid is effective for enantioselective recognition of mono α-hydroxyl acids, such as phenyl lactic acid (K_S/K_R = 2.8:1) (receptor **5**).[5] However, an alternative structural profile has to be found to develop an integrated chiral

SCHEME 1. Chiral Fluorescent Sensors for α-Hydroxyl Acids



SCHEME 2. Synthesis of Chiral Fluorescent Sensors 1



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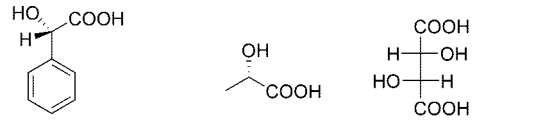
SCHEME 3. Analytes Used in the Study[a]



L-(+)-Mandelic acid, *S*- *L*-(+)-lactic acid, *S*- L-(+)-tartaric acid, (*R*,*R*)

[a] In each case only one enantiomer is shown.

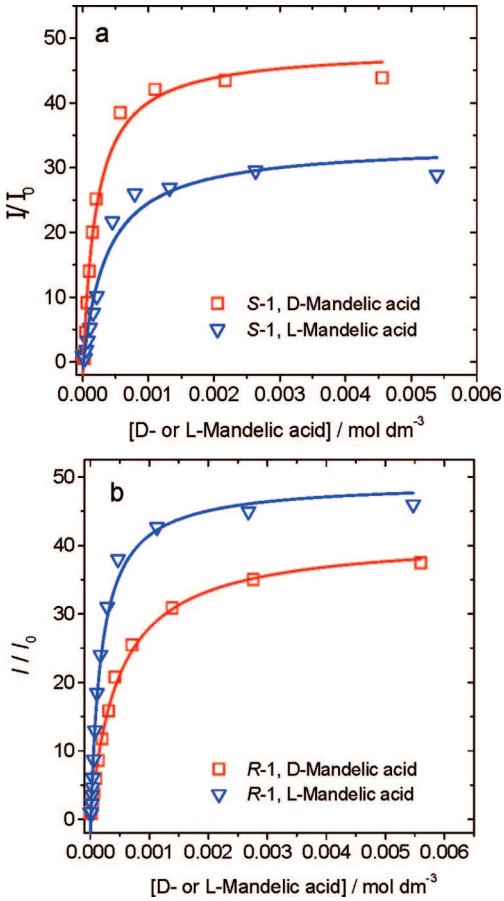


FIGURE 1. Relative fluorescence intensity of *S*-**1** (a) and *R*-**1** (b) versus concentration of with D- and L-mandelic acid; 3.99×10^{-6} mol dm^{-3} sensors in MeCN; $\lambda_{ex} = 351$ nm, $\lambda_{em} = 420$ nm; 20 °C.

fluorescent chemosensor (the binding of **5** was evaluated using a displacement assay).[2,5,11]

Chiral recognition requires multiple-point interaction.[12] We envision that by using an additional interaction, e.g., hydrogen binding, a mono boronic acid could be enantioselective toward mono α-hydroxyl acids. With this concept in mind we synthesized photoinduced electron transfer (PET) chiral sensor **1** (Schemes 1 and 2), and its chiral recogntion toward several representative α-hydroxyl acids (Scheme 3) was studied.

Sensor **1** was synthesized with 2-amino-2-phenyl-ethanol as chiral building blocks (Scheme 2).[10] *R*- and *S*-**1** were titrated with mandelic acid in MeCN (Figure 1). Enantioselective fluorescence enhancement was observed. With *S*-**1**, a binding constant (K) of $(5.04 \pm 0.77) \times 10^3$ M^{-1} was observed for D-mandelic acid, versus $K = (2.77 \pm 0.57) \times 10^3$ M^{-1} for

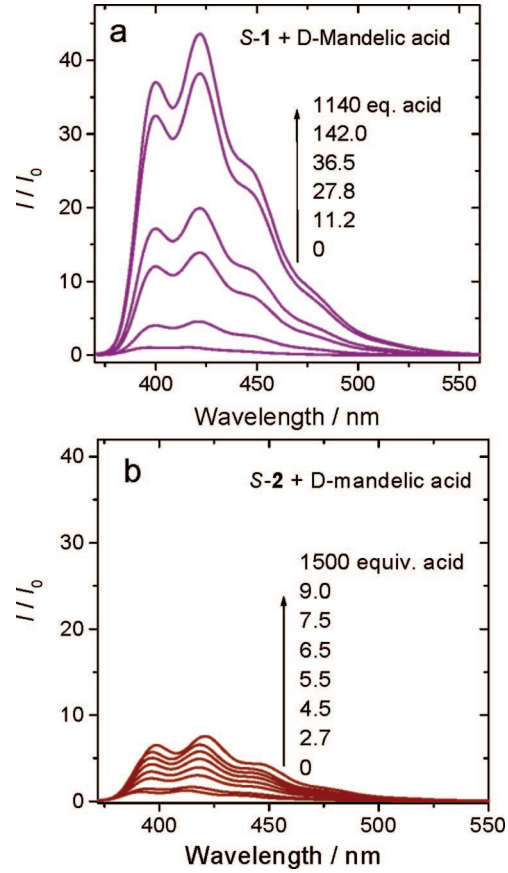


FIGURE 2. Normalized emission spectra of sensors *S*-**1** (a) and *S*-**2** (b) in the presence of D-mandelic acid; 3.99×10^{-6} mol dm^{-3} sensor in MeCN; $\lambda_{ex} = 351$ nm, 20 °C. To compare the fluorescence enhancement, the *y*-scales were set the same for a and b.

L-mandelic acid ($K_D/K_L = 1.8{:}1.0$). Thus the free energy difference of the diastereomeric complexes is $\Delta\Delta G° = 1.4 \pm 0.3$ kJ mol^{-1}.

To prove the enantioselectivity, *R*-**1** was also titrated with mandelic acid. A mirror effect was observed ($K_D/K_R = 1.0{:}2.7$, $\Delta\Delta G° = 2.4 \pm 0.3$ kJ mol^{-1}). These $\Delta\Delta G°$ values are comparable to those of macrocyclic ligands.[13]

Compound **2** is not enantioselective for mandelic acid (Figure S1). With *S*-**2**, K values of $(4.29 \pm 0.03) \times 10^4$ and $(4.49 \pm 0.03) \times 10^4$ M^{-1} were found for D- and L-mandelic acid, respectively, inferring that the extra hydroxyl group in **1** is essential for the enantioselectivity. We propose that an intramolecular hydrogen binding induced the enantioselectivity (see Supporting Information).

Lower background and higher enhancement of fluorescence were recorded for **1** compared with that of **2** (Figure 2). Compound **1** shows 30- to 40-fold fluorescence enhancement, versus only 6- to 7-fold observed for **2**.[19] Enhanced signal transduction may induce better detection limits.[14]

Enantioselective recognition of lactic acid is more challenging because the methyl group in it is less bulky than the phenyl group in mandelic acid, and the minor steric hindrance may attenuate the enantioselectivity.[5] However, titration shows that **1** is enantioselective toward lactic acid. With D-lactic acid, $K = (1.26 \pm 0.21) \times 10^3$ M^{-1} was observed for *S*-**1**, whereas for

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TABLE 1. Stability Constants, Fluorescence Enhancement (F) on Binding and Enantioselectivity (K_R:K_S) of Sensors *R*-1, *S*-1, *R*-2, and *S*-2[a]

	K		F[b]			
analytes	*R*-**1**	*S*-**1**	*R*-**1**	*S*-**1**	K_R:K_S	response selectivity[c]
D-mandelic acid	(2.11 ± 0.15) × 10^3	(5.04 ± 0.77) × 10^3	41.9 ± 1.1	49.1 ± 2.1	1.0:2.4	1.0:2.8
L- mandelic acid	(5.62 ± 0.64) × 10^3	(2.77 ± 0.57) × 10^3	50.4 ± 2.0	34.4 ± 2.2	2.0:1.0	3.0:1.0
D-lactic acid	(4.46 ± 0.57) × 10^2	(1.26 ± 0.21) × 10^3	42.5 ± 2.3	36.2 ± 2.0	1.0:2.8	1.0:2.4
L-lactic acid	(1.05 ± 0.14) × 10^3	(4.72 ± 0.82) × 10^2	44.3 ± 2.0	34.4 ± 2.4	2.2:1.0	2.9:1.0
D-tartaric acid	(8.51 ± 0.13) × 10^3	(8.88 ± 0.40) × 10^3	36.3 ± 0.4	27.8 ± 0.6	1.0:1.1	1.3:1.0
L-tartaric acid	(7.90 ± 0.37) × 10^3	(8.42 ± 0.31) × 10^3	31.5 ± 0.6	36.6 ± 0.4	1.0:1.1	1.0:1.2
	K		F[b]			
analytes	*R*-**2**	*S*-**2**	*R*-**2**	*S*-**2**	K_R:K_S	response selectivity[c]
D-mandelic acid	(4.20 ± 0.02) × 10^4	(4.29 ± 0.03) × 10^4	6.6 ± 0.1	7.7 ± 0.1	1.0:1.0	1.0:1.2
L-mandelic acid	(4.34 ± 0.02) × 10^4	(4.49 ± 0.03) × 10^4	7.0 ± 0.1	7.2 ± 0.2	1.0:1.0	1.0:1.0
D-lactic acid	(1.63 ± 0.07) × 10^4	(1.74 ± 0.08) × 10^4	7.0 ± 0.2	7.1 ± 0.2	1.0:1.0	1.0:1.0
L-lactic acid	(1.36 ± 0.07) × 10^4	(1.40 ± 0.07) × 10^4	6.7 ± 0.1	6.8 ± 0.2	1.0:1.0	1.0:1.1
D-tartaric acid	(3.25 ± 0.14) × 10^4	(3.35 ± 0.12) × 10^4	11.9 ± 0.6	11.2 ± 0.6	1.0:1.0	1.0:1.0
L-tartaric acid	(3.24 ± 0.12) × 10^4	(3.22 ± 0.14) × 10^4	10.5 ± 0.5	11.4 ± 0.6	1.0:1.0	1.0:1.1

[a] Constants determined by fitting a 1:1 binding model to I/I_0; determination coefficients $r^2 > 0.98$ in most cases. [b] Maximum fluorescence enhancement. [c] Response selectivity = (K(R)F(R))/(K(S)F(S)).

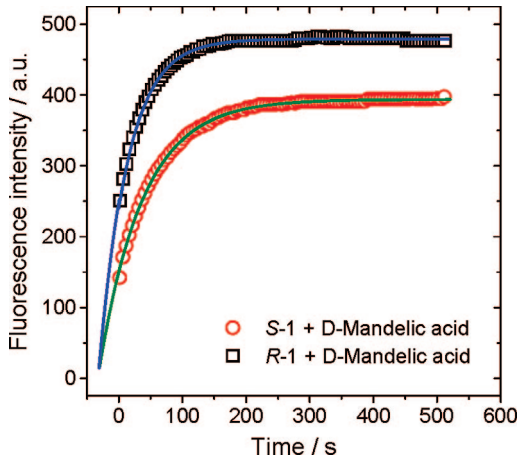

FIGURE 3. Enantioselective recognition kinetics of sensor-**1** on D-mandelic acid. c(*R*- and *S*-**1**) = 3.99 × 10^{-6} mol dm^{-3} in MeCN, c(D-mandelic acid) = 2.5 × 10^{-3} mol dm^{-3}. λ_{ex} = 351 nm, λ_{em} = 420 nm; 20 °C. For clarity, only 2% of the total recorded data points are shown. The squares and circles are experimental data, and the solid lines are exponential fitting (extrapolated to the intensity of the blank sensors).

R-**1**, K = (4.46 ± 0.57) × 10^2 M^{-1} (K_R/K_S = 1:2.8). L-Lactic acid was also tested, and a mirror effect was observed (Figure S3, Supporting Information). With **2**, no enantioselectivity was found (Figure S4). To the best of our knowledge, **1** is the first fluorescent enantioselective mono boronic acid sensor for mono α-hydroxyl acids, such as mandelic acid. The ee values of mandelic acids was determined with **1** (Figure S5).[10]

The recognition of **1** and **2** toward chiral acids is summarized (Table 1). Compared with **2**, lower binding constants were observed for **1**. The enantioselectivity of **1** toward chiral mono α-hydroxyl acids may be due to the additional hydrogen binding of the hydroxyl group with the boron center. Recognition of **1** in aqueous solution was carried out, but no enantioselectivity was found.

The binding of **1** on chiral acids was found to be slow at room temperature, as time-dependent fluorescence enhancements were observed with addition of analytes.

Interestingly, the recognition is kinetically enantioselective (Figure 3). Exponential regression of the time course curves gives the apparent formation (binding) rate constants (K_{app}). For *R*-**1**-D-mandelic acid complex, K_{app} = (2.24 ± 0.00) × 10^{-2} s^{-1}, while for *S*-**1**-D-acid complex, K_{app} = (1.45 ± 0.00) × 10^{-2} s^{-1}. Thus the enantioselectivity on the formation rate constants of diastereomeric complexes is 1.5:1.0. With L-mandelic acid, enantioselectivity of 1.0:1.4 was observed (Figure S6).

With lactic acid, simillar enantioselectivity was found (Figure S7), e.g., K_{app} = (1.24 ± 0.00) × 10^{-2} s^{-1} for *S*-**1**-D-lactic acid versus K_{app} = (1.50 ± 0.00) × 10^{-2} s^{-1} for *R*-**1**-D-acid was observed (enantioselectivity = 1:1.2). With tartaric acid, no enantioselectivity was found (Figure S8). For **2**, the fluorescence enhancements reach the maximum instantlaneously on addition of acids (Figure S9).

We propose that the slow kinetics of the recogntion is due to the break of the intramolecular boronic acid ester structure. Without this extra process, the recognition will be fast, which is proved with sensor **2** (Figure S9).

Usually molecular recognition is thermodynamically controlled, but in some cases kinetic recognition can be decisive, such as recognition events involving DNA.[15,16] Such kinetically controlled recognition is widely used in chiral kinetic resolutions[17,18] but has rarely been employed in the development of chemosensors.[19–21] We propose that the enantioselective binding kinetics is due to the difference of the activitation energy to form the two diastereoisomers. Further investigation of such an enantioselective kinetics is underway in our laboratories.

The single crystal X-ray structure of **1** illustrates an intramolecular boronate ester structure (Figure 4, mono ester of methanol; effort to obtain a single crystal of sensor−analyte complex failed), with a B−N distant of 2.819 Å. Such long distance rules out a direct B−N interaction,[22] as the typical B−N

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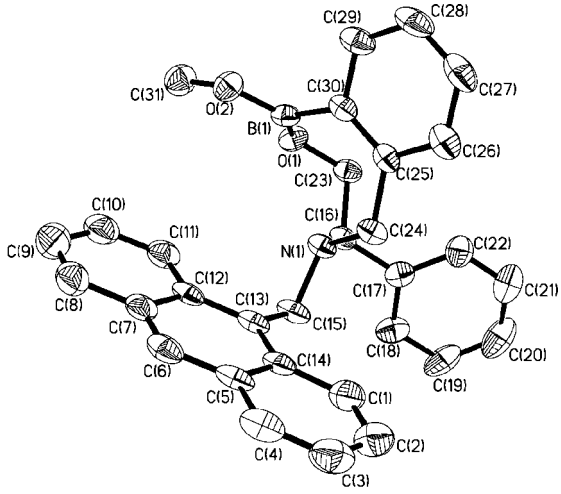

FIGURE 4. ORTEP view of the single crystal structure of *R*-**1**. Thermal ellipsoids are drawn at the 30% probability level, and the hydrogen atoms are omitted for clarity.

distance is much shorter, e.g., 1.747 Å.[23] The lack of B−N interaction (due to the formation of intramolecular boronate esters) may be responsible for the lower background fluorescence.[2] Binding with analytes induces a bridged B−N interaction and leads to enhanced fluorescence.[10b] This structure can be used to design new boronic acid fluorescent chemosensors with lower background fluorescence and higher fluorescence enhancement in the presence of analytes.

In summary, a mono boronic acid as an intergrated fluorescent chemosensor for chiral recognition of mono α-hydroxyl acids is reported. The new sensor displays fluorescence OFF−ON character, and its recognition of hydroxyl acids is an enantioselective slow process. The structural profile of the sensor may be used for design of new enantioselective fluorescent boronic acid sensors for chiral mono α-hydroxyl acids.

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Experimental Section

***R*-1**: a mixture of 2-phenyl-2-(anthracen-9-ylmethylamino)-ethanol (0.3 g, 0.92 mmol), K_2CO_3 (0.51 g, 3.67mmol), and 2-(2-bromomethylphenyl)-1,3,2-dioxaborinane (0.374 g, 1.47 mmol) in dry MeCN was refluxed for 8 h. The reaction mixture was cooled to room temperature, diluted HCl was added, and the mixture was stirred for further 1 h (to ensure the deprotection of the boronic acid group). The solvent was removed under vacuum, the residue was taken up with 10 mL H_2O, the aqueous phase was extracted with DCM (3 × 30 mL), and the organic phase was washed with brine (2 × 20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was applied to column chromatography (silica gel, DCM/MeOH, 20/1, v/v). A light yellow powder was obtained, yield 38.0%. ^{1}H NMR ($CDCl_3/CD_3OD$, 400 MHz, TMS): δ 8.45 (s, 1 H), 8.27 (d, 2 H, J = 8.0 Hz), 7.98 (d, 2H, J = 8.0 Hz), 7.40−7.52 (m, 5 H), 7.23−7.27 (m, 1 H), 7.13−7.18 (m, 4H), 6.79 (d, 1H, J = 8.0 Hz), 6.64 (br, 2H), 5.17 (d, 1H, J = 12.0 Hz), 4.88 (d, 1H, J = 12.0 Hz), 4.50−4.54 (m, 1 H), 3.95−4.05 (m, 2 H), 3.76−3.88 (m, 2 H). ESI-MS: *m*/*z* (positive ion mode) calcd for $C_{30}H_{27}BNO_2$ ($[M - H_2O + H]^+$) 444.2135, found 444.0978; calcd for $C_{30}H_{29}BNO_3$ ($[M + H]^+$) 462.2240, found 462.1042.

***S*-1**: synthesized by the same methods. ^{1}H NMR ($CDCl_3/CD_3OD$, 400 MHz, TMS): δ 8.45(s, 1 H), 8.27 (d, 2 H, J = 8.0 Hz), 7.97 (d, 2H, J = 8.0 Hz), 7.40−7.52 (m, 5 H), 7.23−7.27 (m, 1 H), 7.14−7.18 (m, 4H), 6.79 (d, 1H, J = 8.0 Hz), 6.62 (d, 2H, J = 8.0 Hz), 5.17 (d, 1H, J = 12.0 Hz), 4.88 (d, 1H, J = 12.0 Hz), 4.50−4.55 (m, 1 H), 3.95−4.06 (m, 2 H), 3.82−3.87 (m, 2 H). TOF ESI-MS (positive ion mode): calcd for $C_{31}H_{29}BNO_2$ [M + CH_3OH − $2H_2O$ + H] 458.2291, found 457.9589; calcd for $C_{62}H_{56}B_2N_2NaO_4$ ($[2M + 2CH_3OH - 4H_2O + Na]^+$) 937.4324, found 936.8504.

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Supporting Information Available: Experimental details, spectra of the sensors, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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