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ORIGINAL PAPER

Enhanced Enantioselective Recognition with Diastereoisomeric BINOL Based Chiral Fluorescent Boronic Acid Sensors

Qiuting Li · Huimin Guo · Yubo Wu · Xin Zhang · Yifan Liu · Jianzhang Zhao

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Abstract We prepared the diastereoisomers of BINOL based bisboronic acid chiral probes (the probes are with dual chirogenic centers) for enantioselective recognition of chiral analytes, such as tartaric acids, D-sorbitol, etc. We found the diastereoisomeric probes give different emission intensity-pH profiles, a phenomenon was reported, probably, for the first time. We found that with the second chirogenic center, the selectivity of the probes toward chiral analytes can be improved. For example, the diastereoisomeric probes give drastically different response to D-sorbitol, the same selectivity was not found for the BINOL bisboronic acid probes with single chirogenic center. Our result with the diastereoisomeric probes is helpful for design of new chiral molecular probes to enhance the selectivity of the boronic acid sensors toward chiral analytes.

Keywords Boronic acid · Chiral fluorescent chemosensors · BINOL

Introduction

Chirality is important for many aspects, such as pharmaceutical, synthesis of natural product and molecular recognition among the others [1]. Traditionally the chirality of organic compounds can be analyzed with NMR or gas/liquid chromatography, both methods are technically and instrumentally demanding. Recently fluorescent molecular probes are used for enantioselective detection of chiral compounds [2–7]. Normally the chiral molecular recognition is based on hydrogen bonding between the chiral molecular probe and the chiral analytes [8]. A few chiral probes based on covalent bonds emerged and will be promising for practical applications because these probes can be used in aqueous solutions, whereas the probes based on hydrogen bonding can not be used in aqueous solution [9–20]. However, the number of the probes based on covalent bond interaction for detection of organic molecules is limited [9]. Boronic acid probes are in particular interest due to its covalent bonding with sugars and α-hydroxyl carboxylic acids, thus the recognition of sugars or poly hydroxyl analytes with boronic acid probes can be performed in aqueous solution [12–14].

We have been interested in boronic acid probes for a while. Previously we used 1,1-bisnapthol (BINOL) based boronic acid sensors to enantioselectively recognize D- and L-tartaric acids [21]. Emission enhancement/diminishment was observed for the enantiomers of tartaric acids. We also prepared anthracene based bisboronic acids probes that show good enantioselectivity toward tartaric acids, sugar acids and sugar alcohols [22–24]. More recently, we found that carbazole based bisboronic acid probes show good enantioselectivity toward tartaric acids, as well as the novel

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d-PET effect (i.e. the fluorophore serves as the electron donor of the photo-induced electron transfer process) [16, 19, 20]. However, for all these chiral sensors, there is only a single chirogenic center. Inspired by the multi-hydrogen bonding motif of the natural glucose receptor, lactin [25]. we envision that by introducing an extra chirogenic center to the bisboronic acid probe molecules, the enantioselectivity of the boronic acid probes may probably be improved [26, 27]. To the best of our knowledge, however, no boronic acid sensors with dual chirogenic centers has been reported.

Herein we devised the BINOL based bisboronic acid probe **1**. Besides the BINOL's axial chirogenic center, we attached the second chirogenic center to the molecule by using the chiral methyl benzylamine (*R*- and *S*-) (Scheme 1). Thus four isomers were prepared, i.e. *R*,*R*-**1**, *R*,*S*-**1**, *S*,*R*-**1** and *S*,*S*-**1** (the first character denotes the chirogenic center of BINOL and the second character denotes the chirality of the methylbenzylamine). The synthesis of the chiral probes was outlined in Scheme 1. All the probes were obtained with satisfying yields. We found that the emission intensity-pH profile of the probes is different for the diastereoisomers. To the best of knowledge, this is the first time that such an emission intensity-pH profile was observed. Furthermore, the recognition of tartaric acids was performed and we found that the enantioselectivity of the BINOL bisboronic acid probes were altered with introduce of the second chirogenic center. For example, the diastereoisomeric probes show enantioselectivity on the recognition of the sorbitol.

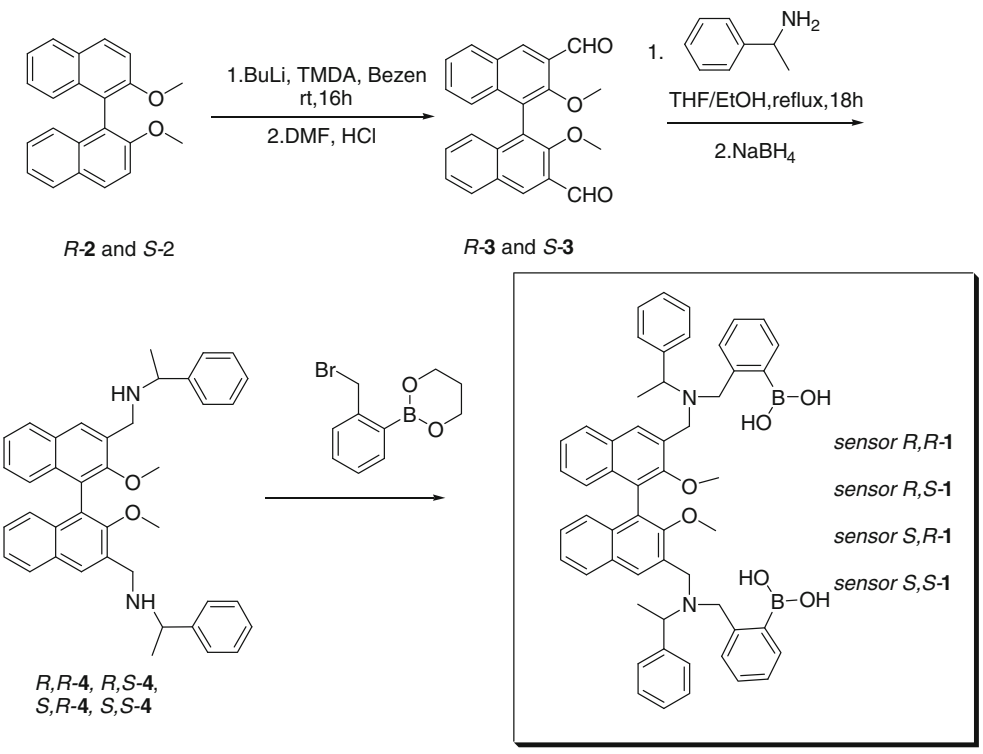
Experimental

Materials and General Methods

All the chemicals are analytical pure and were used as received. NMR spectra were taken on a 400 MHz Varian Unity Inova spectrophotometer. Mass spectra were recorded with Q-TOF Micro MS spectrometer. Fluorescence spectra were recorded on a JASCO FP-6500 or a Sanco 970 CRT spectrofluorometer.

(R)-and(S)2,2'-Dimethoxy-1,1'-dinaphthalene-3-carboxaldehyde (compound R-3 and S-3)

Under N_2 atmosphere, (*R*)-2, 2′-dimethoxy-1, 1′-binaphthalenean (2.4 g, 7.5 mmol) was suspended in dry benzene (60 mL). *N*,*N*,*N*′,*N*′-tetramethylethylenediamine(TMEDA) (1.08 g, 9.3 mmol) was added into the above solution. Then 4.5 mL (2.5 M, 11.3 mmol) n-BuLi/Hexane solution was added dropwise. The mixture was stirred at r.t. for 16 h. Then dry DMF (0.92 g, 0.75 mL, 9.6 mmol) was added in via syringe with ice bath cooling. After 30 min, the reaction was quenched with half-concentrated HCl (9 mL). The organic phase was washed with brine (2×30 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×30 mL). The organic phase was combined together and dried over Na_2SO_4. The solvent was removed in vacuum and the residual was purified with column chromatography



Scheme 1 Synthesis of the bisboronic acid probes with dual-chirogenic centers

(silica gel, CH_2Cl_2:CH_3OH=100:1, v/v). Yield: 920.0 mg, 32.9%. ^{1}H NMR (400 MHz, $CDC1_3$), δ 10.57(s, 2 H), δ 8.64(s, 2 H), δ 8.10-8.08(d, 2 H, *J*=8.0), δ 7.51–7.18(m, 6 H), δ 3.51(s, 6 H).

(R,R)-,(R,S)-,(S,R)-and (R,R)- N,N'-(2,2'-dimethoxy-1, 1'-binaphthalene-3,3'-diyl) bis(methylene) bis(1-phenylethanamine) (compound R,R-4, R,S-4, S,R-4 and S,S-4)

(*R*)-1-Phenylthanamine (0.52 g, 4.26 mmol) was added to (*R*)-2, 2′dimethoxy-1, 1′-binaphthalene-3- carboxyaldehyde (400 mg, 1.16 mmol) solution in absolute ethanol under nitrogen atmosphere, the reaction mixture was refluxed with stirring for 18 h. The solution was concentrated under reduced pressure and the residue was washed with 20 mL water. The aqueous solution was extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residual was purified with column chromatography (silica gel, CH_2Cl_2:CH_3OH= 20:1, v/v) and the solvent was removed under reduced pressure to give the amine as a yellow solid (*R*,*R*-4).Yield: 345.0 mg, 55.0%. ^{1}H NMR (400 MHz, $CDC1_3$),δ 7.86-7.83(t, 4 H), δ 7.40-7.11(m, 16 H), δ 4.00-3.97 (d, 2 H), δ 3.88-3.81(m,4 H), δ 3.24 (s, 6 H), δ 1.43 (d, 2 H, *J*=8 Hz). ESI-HRMS: m/z ($C_{40}H_{40}N_2O_2$ + H^+) calcd 581.3168, found 581.3182.

R,S-**4** was prepared with the similar method. Yield: 390.0 mg, 62.2%. ^{1}H NMR (400 MHz, $CDC1_3$), δ 7.93-7.83 (t, 4 H) δ 7.41-7.12 (m, 16 H), δ 3.93 -3.88 (t, 6 H), δ 3.22 (s, 6 H), δ 1.44 (d, 2 H, *J*=8.0 Hz). ESI-HRMS: m/z ($C_{40}H_{40}N_2O_2$ + H^+) calcd 581.3168, found 581.3181.

S,R-**4** was prepared with the similar method. Yield: 385.0 mg, 61.4%. ^{1}H NMR (400 MHz, $CDC1_3$), δ 7.92-7.84 (t, 4 H) δ 7.42-7.11 (m, 16 H), δ 3.92(s,4 H), δ 3.90-3.88 (t, 2 H), δ 3.22 (s, 6 H), δ 1.44 (d, 6 H, *J*=8 Hz). ESI-HRMS: m/z ($C_{40}H_{40}N_2O_2$ + H^+) calcd 581.3168, found 581.3167. *S,S*-**4** was prepared with the similar method. Yield: 393 mg, 62.67%.^{1}H NMR (400 MHz, $CDC1_3$), δ 7.86-7.84(m, 4 H), δ 7.41-7.11(m, 16 H), δ 3.97(d, 2 H, *J*=12), δ 3.89-3.81(m, 4 H), δ 3.24(s, 6 H), δ 1.43(d, 6 H, *J*=8.0 Hz), ESI-HRMS: m/z ($C_{40}H_{40}N_2O_2$ + H^+) calcd 581.3268, found 581.3267.

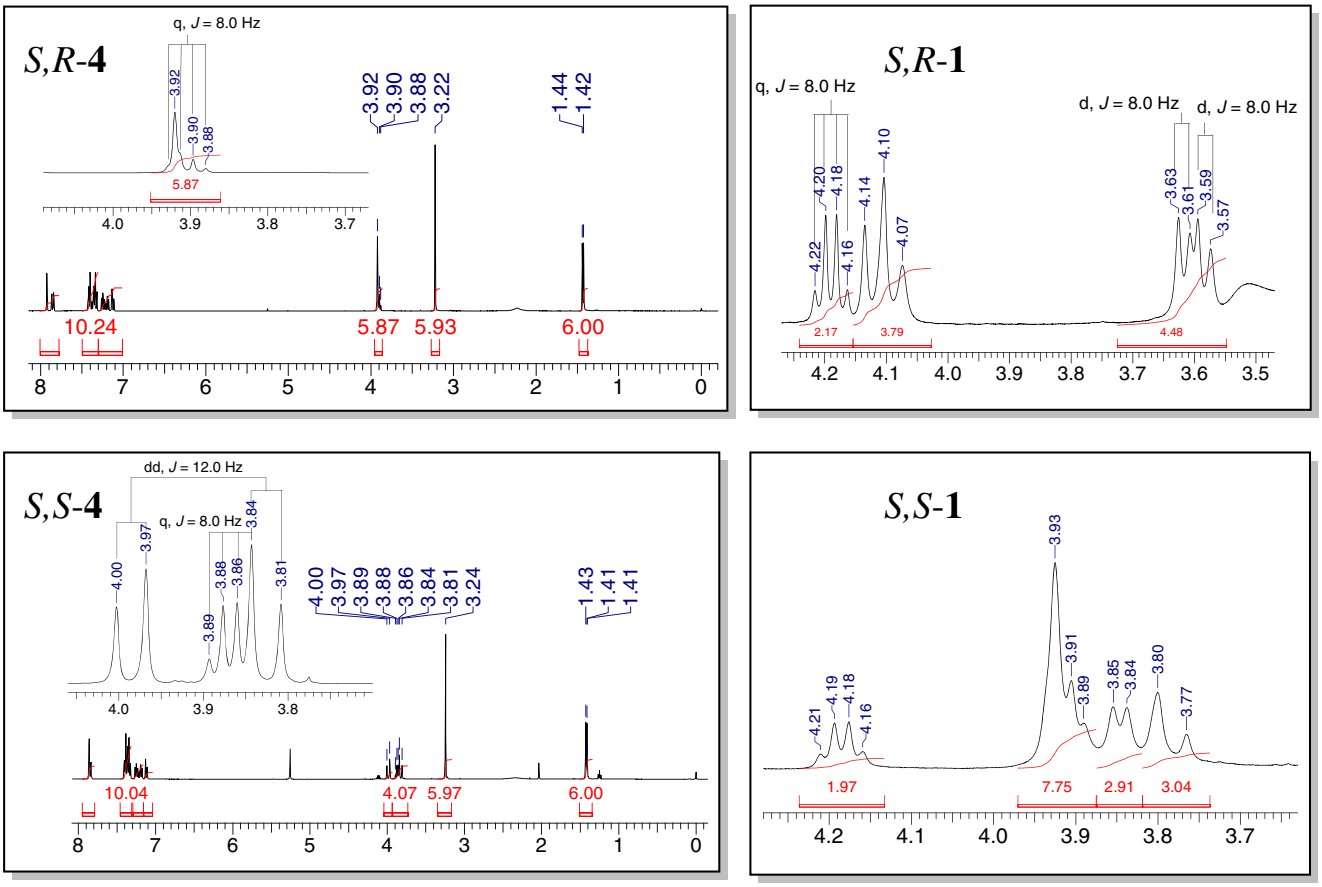


Fig. 1 ^{1}H NMR spectra of the *S,S*-**4** and *S,R*-**4** amine and partial ^{1}H NMR spectra of the sensors *S,S*-**1** and *S,R*-**1**: demonstration of the chiral steric environment of diastereoisomeric amines and the probes by the protons on methylene moiety

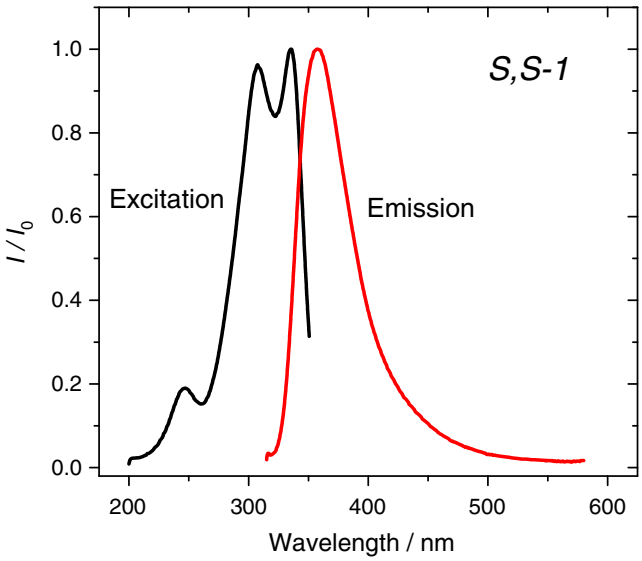


Fig. 2 Fluorescence excitation and emission spectra of *S,S*-**1**. λ_{ex}= 307 nm. λ_{em}=360 nm. $c=1.0\times10^{-5}$ mol dm^{-3} in 0.05 mol dm^{-3} NaCl (52.1% methanol in water)

(R,R)-,(R,S)-,(S,R)-and (R,R)-2,2'-(2,2'-dimethox)-1, 1'-binaphthyl-3,3'diyl,bis(methylene)bis (1-Phenylethyl), azanediyl, bis (methylene) bis(2,1-phenylene) bisboronic acid sensor (sensor R,R-1, R,S-1, S,R-1 and S,S-1)

At room temperature 4.4 equiv of 2-formylphenylboronic acid (214.0 mg, 1.42 mmol) was added to a solution of *R,R*-**4** (185.0 mg, 0.35 mmol) in 15 mL methanol. The system was stirred for 2 h and 10 equiv of $NaBH_4$ (0.65 g, 17.6 mmol) was added in several portions. The mixture was stirred for another 1 h. The solvent was removed under reduced pressure, and the resulting solid was dissolved in 20 mL of water and the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The organic phase was dried over sodium sulfate. The solvent was removed under vacuum and the crude product was purified with column chromatography (Al_2O_3, dichloromethane: methanol = 100: 1, v/v). The solvent was removed under reduced pressure and a white solid (*R,R*-**1**) was obtained. Yield: 130.0 mg, 48.2%. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD), δ 7.86-7.82 (m, 6 H), δ 7.36-7.09 (m, 22 H), δ 4.18 -4.17 (m, 2 H), δ 3.94-3.81 (m, 8 H), δ 3.00 (s, 6 H), δ 1.59 (d, 6 H, *J*=6.8 Hz). ^{13}C NMR(100 MHz, $CDCl_3$ + CD_3OD), δ 155.60,141.99,139.56, 136.25, 134.25,132.29, 131.44, 130.19, 130.12, 129.36, 128.25, 128.04, 127.67, 127.33, 126.38, 125.80, 124.74, 60.47, 57.96, 57.64, 47.94, 14.26. $[\alpha]_D^{25}$=+27.6 ° (*c*=0.25 in CH_2Cl_2). ESI-HRMS: m/z ($C_{54}H_{54}B_2N_2O_6$+ $2CH_3OH$ - $2H_2O$ + H^+) calcd 845.4297, found 845.4316.

***R,S*-1** was prepared with the similar method. Yield: 135.0 mg, 50.0%. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ 7.92-7.83(m, 6 H), δ 7.38-7.08 (m, 22 H), δ 4.19-4.11 m, 6 H), δ 3.61-3.50 (m, 8 H), δ 3.13 (s, 6 H), δ 1.63 (d, 6 H, *J*=6.8). ^{13}C NMR(100 MHz, $CDCl_3$ + CD_3OD), δ 155.48, 141.84, 139.39, 136.17, 135.09, 134.12, 132.18, 131.55, 130.35, 130.05, 129.24, 128.13, 127.93, 127.55, 127.22, 126.27, 125.67. $[\alpha]_D^{25}$=50.5 ° (*c*=0.25 in CH_2Cl_2). ESI-HRMS: m/z ($C_{54}H_{54}B_2N_2O_6$ + CH_3OH - $2H_2O$ + H^+) calcd 845.4297, found 845.4310.

***S,R*-1** was prepared with the similar method. Yield: 106.0 mg, 39.2%. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD), δ 7.91-7.83(m, 6 H), δ 7.80-7.10 (m, 22 H), δ 4.21-4.10 (m, 6 H), δ 3.63-3.42 (m, 8 H), δ 3.13(s, 6 H), δ 1.63(d, 6 H, *J*=6.8 Hz). ^{13}C NMR (100 MHz,$CDCl_3$), δ 155.63,142.02,138.92, 136.33,134.31,131.60,130.47, 130.24,130.09, 129.49, 128.26, 128.01, 127.72, 127.31, 126.41, 125.86, 124.78, 60.52, 58.08, 58.57, 48.48, 16.04. $[\alpha]_D^{25}$ = − 49.6 ° (*c*=0.25 in CH_2Cl_2). ESI-HRMS: m/z ($C_{54}H_{54}B_2N_2O_6$ + CH_3OH-$2H_2O$ + H^+) calcd 845.4297, found 845.4280.

***S,S*-1** was prepared with the similar method. Yield: 120.0 mg, 44.4%. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD), δ 7.89-7.82(m, 6 H), δ 7.38-7.10(m, 22 H), δ 4.21-4.18(m, 2 H), δ 3.93-3.37(m, 12 H), δ 2.99(s, 6 H), δ 1.59(d, 6 H,

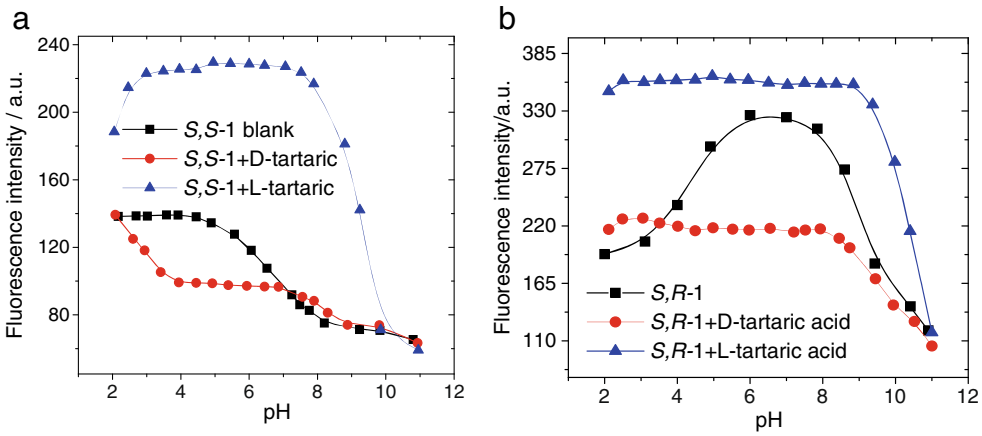


Fig. 3 Fluorescence intensity–pH profiles for the probes alone and in the presence of D- and L-tartaric acid. **a** *S,S*-**1**, $c=1.0\times10^{-6}$ mol dm^{-3} and (**b**) *S,R*-**1**. 2.3×10^{-7} mol dm^{-3} in 0.05 mol dm^{-3} NaCl solution (52.1% methanol in water), *c*(D-tartaric acid)=*c*(L-tartaric acid)=0.02 mol dm^{-3}, λ_{ex}=307 nm, λ_{em}=360 nm. 20 °C

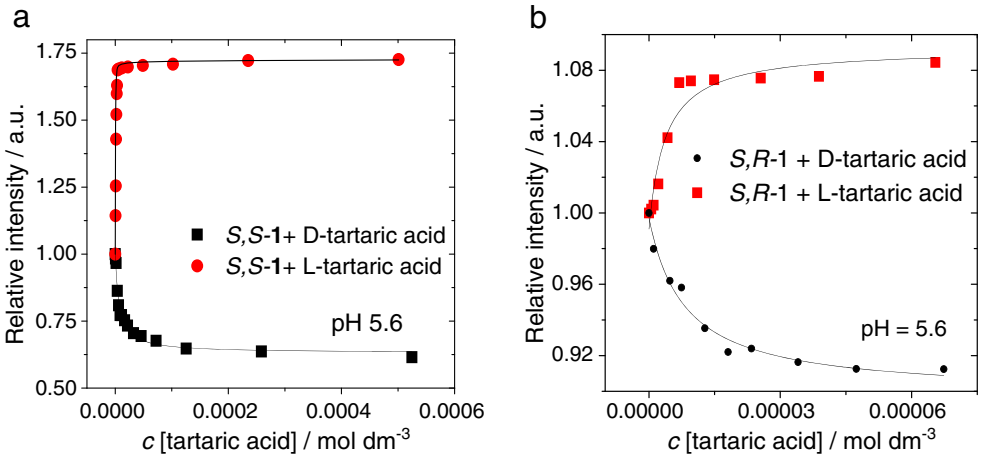


Fig. 4 Chiral discrimination of D- and L-tartaric acid by (**a**) *S,S*-**1** and (**b**) *S,R*-**1** (right) at pH=5.6. $c_{probes}=2.3\times10^{-7}$ mol dm^{-3}, in 0.05 mol dm^{-3} NaCl (52.1% methanol in water), $\lambda_{ex}=307$ nm. $\lambda_{em}=360$ nm. 20 °C

J=6.8 Hz). ^{13}C NMR(100 MHz, $CDC1_3$ + CD_3OD), δ 155.48, 141.84, 138.63, 136.20, 134.16, 131.48, 130.26, 130.06, 129.98, 129.35, 128.12, 127.87, 127.60, 127.18, 126.29, 125.71, 124.66, 123.60, 60.40, 57.82, 57.35, 48.29, 15.95. $[\alpha]_D^{25} = -23.7$ °(*c*=0.25 in CH_2Cl_2). ESI-HRMS: m/z ($C_{54}H_{54}B_2N_2O_6$ + CH_3OH-$2H_2O$ + H^+) calcd 845.4297, found 845.4328.

Results and Discussions

Synthesis BINOL was used as the starting material for the synthesis of the chiral probes (Scheme 1). First BINOL was methylated with methyl iodide. Then the methyl ether was formylated in the presence of BuLi and DMF. The chiral methylbenzylamine was used to prepare the chiral amine. Finally the boronic acid binding sites were introduced. Totally four probes were prepared, i.e. *R,R*-**1**, *R,S*-**1**, *S,S*-**1** and *S,R*-**1**. The chiral bisboronic acid molecular probes were obtained with satisfying yields.

We found that the chirogenic centers of the diastereoisomeric amines and the sensors can be indicated by the ^{1}H NMR spectra (Fig. 1). For example, the methylene protons of *S,R*-**4** gives peaks at about 3.9 ppm, infers that the chirogenic environment around the methylene protons are not strong. For the *S,S*-**4**, however, the methylene protons' signal is more resolved, thus propose that the chirogenic environment around the methylene protons are stronger than that in *S,S*-**4**. Difficult methylene proton signal profiles were observed for *S,R*-**1** and *S,S*-**1** (Fig. 1b). Thus we propose that it is possible to use the diastereoisomeric sensors to enantioselectively recognize the chiral analytes.

The emission and the excitation of the probe were studied (Fig. 2). The excitation is centered at 300 nm and 325 nm. A single emission band at 360 nm was observed. The Stokes shift is 53 nm. The small Stokes shift may be responsible for the asymmetric band shape of the emission (due to the inner-filter effect, i.e. the emission at the short wavelength side is re-absorbed by the probe molecules). The spectra are similar to the BINOL based molecular probes [21, 27].

Firstly the pH titration of the *S,S*-**1** and *S,R*-**1** was studied (Fig. 3). For *S,S*-**1**, normal pH titration curve of the Wolff type of boronic acid sensors was observed [12]. The emission at acidic pH is stronger than that of neutral and basic pH. The apparent pK_a value is 6.65. Novel chiral recognition fluorescence transduction was observed, e.g. in acidic pH region, the emission intensity was decreased in the presence of D-tartaric acid, but the emission was intensified in the presence of L-tartaric acid. Such an emission enhancement/diminishment against the enantiomers of the chiral analytes was rarely reported. Previously we reported the first example of such as enantioselective molecular recognition transduction with BINOL boronic acid

Table 1 Binding constants (M^{-1}) of the diastereoisomeric bisboronic acid probes with the analytes

sensor	pH=5.6		pH=7.0	
	L-tartaric acid	D-tartaric acid	L-tartaric acid	D-tartaric acid
S,S-1	$(9.88\pm2.20)\times10^5$	$(1.54\pm0.21)\times10^5$	$(1.14\pm0.10)\times10^5$	$(1.45\pm0.13)\times10^4$
S,R-1	$(2.67\pm1.00)\times10^5$	$(1.22\pm0.28)\times10^5$	$(5.26\pm1.65)\times10^4$	$(6.45\pm0.82)\times10^4$
R,R-1	$(1.27\pm0.70)\times10^5$	$(4.18\pm1.86)\times10^5$	$(2.58\pm0.75)\times10^3$	$(6.43\pm1.11)\times10^4$
R,S-1	$(2.95\pm0.56)\times10^2$	$(2.50\pm0.50)\times10^4$	$(1.33\pm0.49)\times10^5$	$(3.41\pm1.06)\times10^4$

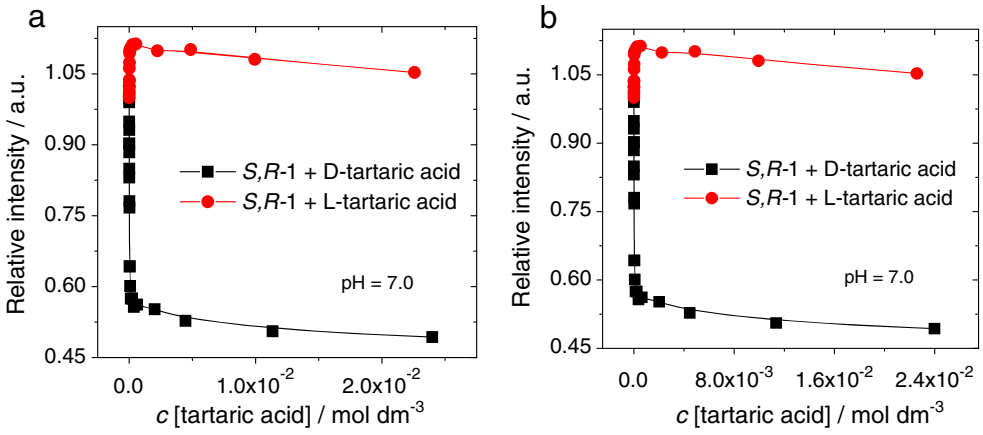


Fig. 5 Chiral discrimination of D- and L-tartaric acid by (**a**) *S*,*S*-**1** and (**b**) *S*,*R*-**1** at pH=7.0. c=2.3×10^{-7} mol dm^{-3}, in 0.05 mol dm^{-3} NaCl (52.1% methanol in water), λ_{ex}= 307 nm. λ_{em}=360 nm. 20 °C

probes and tartaric acid [21]. Recently we also observed this phenomena for a carbazole based chiral bisboronic acid probe [16].

Interestingly, different pH titration profile was observed for the diastereoisomer, *S*,*R*-**1** (Fig. 3b). The pH titration curve gives a maximum in the neutral pH region, but gives weak emission in both the acidic and the basic region. The two apparent pK_a values of *S*,*R-1* were determined as ca. 9.0 and 5.0. For enantiomeric probes, strictly the same pH titration profiles were observed [16, 22]. The different pH titration profile of *S*,*S*-**1** and *S*,*R*-**1** can be rationalized by the fact that they are diastereoisomers, not enantiomers. Diastereoisomers can give different properties, such as solubility. We propose that the different pH titration profile of *S*,*S*-**1** and *S*,*R*-**1** is due to the diastereoisomerity of the two probes. To the best of knowledge, this is probably the first time that such a phenomenon was reported. This novel response can be used to develop new sensing motifs for chiral probes.

The enantioselective covalent bond interaction between the probes and tartaric acid was proved by the concentration titration (Fig. 4). For example, the emission intensity was increased with increasing the concentration of L-tartaric acid, but decreased with increasing the concentration of D-tartaric acid (Fig. 4a). The binding constants of *S*,*S*-**1** with *D*- and *L*-tartaric acid are (1.54±0.21)×10^5 M^{-1} and (9.88±2.20)×10^5 M^{-1}, respectively (Table 1). Thus the enantioselectivity is 1:6.4.

With the diastereoisomer, i.e. *S*,*R*-**1**, the fluorescence transduction profile is reversed. However, the binding constants of the *S*,*R*-**1** with D- and L-tartaric acids are different from that of *S*,*S*-**1**. This difference is attributed to the presence of the second chirogenic center in the probes, i.e. the enantioselectivity can be affected by the second chirogenic center in the probe molecule.

Enantioselective recognition of the tartaric acids was also observed at pH 7.0 (Fig. 5). For example, with *S*,*S*-**1**, fluorescence enhancement was observed with L-tartaric acid, but the fluorescence emission was quenched in the presence of D-tartaric acid (Fig. 5a). With the *S*,*R*-**1** (Fig. 5b), however, the recognition profile is reversed, that is, the quenching is more significant that that with *S*,*S*-**1**. The binding constants were collected in Table 1.

We also used the chiral probes with dual-chirogenic centers to recognize larger analytes, such as D-sorbitol. We

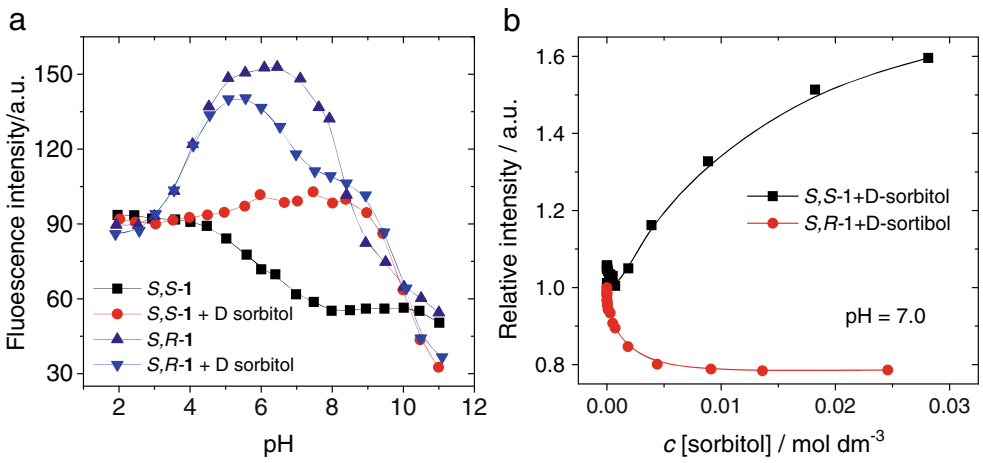


Fig. 6 Recognition of D-sorbitol with the sensors. **a** Fluorescence intensity–pH profiles for *S*,*S*-**1**, *S*,*R*-**1**. **b** Chiral discrimination of D- sorbitol by *S*,*S*-**1** and *S*,*R*-**1** at pH=7.0. c_{probes}=2.3× 10^{-7} mol dm^{-3}, in 0.05 mol dm^{-3} NaCl (52.1% methanol in water), λ_{ex}= 307 nm. λ_{em}=360 nm. 20 °C

expected that with the second chirogenic center and more stereo hindered binding pockets the enantioselective recognition of D-sorbitol may be achieved. The pH titration of the probes in the presence of D-sorbitol were studied (Fig. 6a). For the *S,S*-***1***, the emission in the neutral and basic pH region was intensified. For the *S*,*R*-**1**, however, the emission intensity is nearly un-changed. Thus the diastereoisomeric probes *S*,*S*-**1** and *S*,*R*-**1** give significant different binding with D-sorbitol. Thus the diastereoselectivity is good. This different response was proved by the concentration titration (Fig. 4b). With increasing the concentration of D-sorbitol, the emission of the *S*,*S*-**1** was enhanced but the emission of *S*,*R*-**1** was decreased. This sensing profile is in stark contrast to the previously reported BINOL chiral probes, which show no selectivity toward D-sorbitol. The enantiomers of the probes, i.e. *R,R*-**1** and *R,S*-**1** were also studied and similar results were observed (see Supporting Information).

To the best of our knowledge, this is the first time that diastereoisomeric boronic acid probes were reported. We noticed that BINOL based diastereoisomeric probes have been reported [26]. However, those reported probes are based on hydrogen bonding interaction, not covalent bonding. No pH titration of the diastereoisomeric probes was reported and our result is the first one that shows different pH-emission intensity profiles for the diastereoisomeric fluorescent molecular probes.

Conclusions

In summary, diastereoisomeric BINOL based fluorescent boronic acid probes (i.e. the probe molecules are with dual chirogenic centers) were prepared and the interaction between the probes and the sugar acids (such as tartaric acid and sorbitol) were studied. We found that the diastereoisomers of the chiral probes show different emission-pH profiles, which is in stark contrast from the enantiomeric probes. Furthermore, we found that the selectivity on tartaric acid was enhanced by the second chirogenic center. Our results are helpful for design of diastereoisomeric boronic acid sensors to enhance the selectivity of the enantioselective molecular recognition.

Supporting Information Available

General experimental methods, ^{1}H and ^{13}C NMR data of the compounds and photophysical data. This material is available free of charge via the Internet.

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