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Chiral anion recognition by color change utilizing thiourea, azophenol, and glucopyranosyl groups

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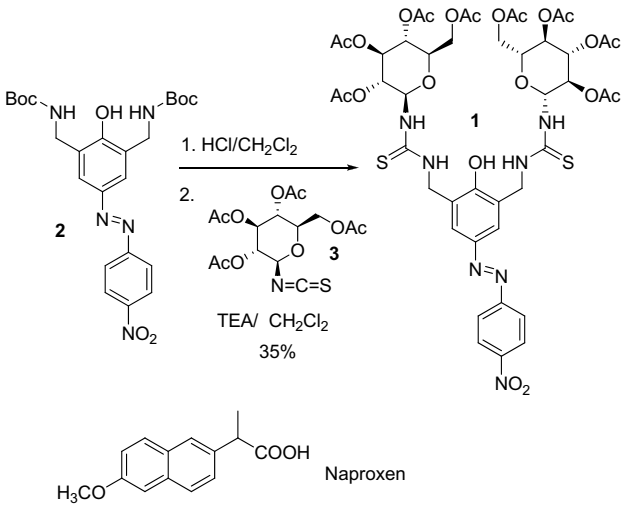
ABSTRACT

A new colorimetric anion sensor **1** was synthesized for the chiral recognition, which accommodates a combination of three different functional groups such as chromophore (azophenol dye), binding site (thiourea group), and chiral barrier (glucopyranosyl group). The colorimetric changes of host **1** with various α-amino carboxylates as well as chiral carboxylates such as naproxen were examined.

The anion-sensing based on molecular recognition has attracted considerable attention in recent years.[1] Even though great effort has been devoted to chiral anion recognition,[2] colorimetric chemosensors for chiral anions are relatively rare.[3] Herein, we report a new colorimetric sensor for chiral anion recognition, which accommodates a combination of three different functional groups, such as chromophore (azophenol dye), binding site (thiourea group), and chiral barrier (glucopyranosyl group). While 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate has been utilized as a successful chiral derivatizing agent for the optical resolution of racemic amino compounds[4] or for the recognition of simple anions[5] and dicarboxylates,[6] there has been only one example of sensor bearing this chiral barrier for the chiral recognition of amino acid derivatives.[7]

In the present study, the colorimetric changes of host **1** with various α-amino carboxylates as well as chiral carboxylates were examined. As high as 3.60 was observed for L/D selectivity of amino acid derivatives. Host **1** also displayed a moderate selectivity for the (*S*)-enantiomer of naproxen ([2-(6-methoxynaphth-2-yl)propionic acid]), a nonsteriodal anti-inflammatory drug (NSAID) over (*R*)-isomer. It is known that the pharmacological activity of (*S*)-isomer is greater compared to that of (*R*)-isomer. Even though several chiral synthetic receptors or chiral stationary phase have been reported so far,[9,10] the recognition of enantiomers of naproxen still remains a challenging task. Indeed, there has been only couple of examples so far, which were utilized as colorimetric or fluorescent receptors for the chiral recognition of naproxen.[9]

The synthetic scheme for host **1** was explained in Scheme 1. The intermediate **2** was synthesized using a reported procedure.[11] Removal of the Boc protecting group followed by the treatment of the resulting ammonium salt with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate **3** and triethylamine yielded host **1**[8] in 35% yield. The ^{1}H and ^{13}C NMR spectra of **1** are explained in the Supplementary data.



Scheme 1. Synthesis of host **1** and structure of naproxen.

The UV absorption changes of host **1** were examined for simple anionic species such as $CH_3CO_2^-$, $H_2PO_4^-$, F^-, Cl^-, Br^-, and I^-. Host **1** (40 μM) displayed a large bathochromic shift (~145 nm) with $CH_3CO_2^-$, F^-, and $H_2PO_4^-$ (40 μM) in acetonitrile (Fig. 1). This bathochromic shift can be attributed to the deprotonation of the azophenol, which can induce a photoinduced charge transfer (PTC).[11] Similar bathochromic shifts with anions are also reported for azophenol based receptors[12] and other chromophores.[13] Figure 2 explains the colorimetric changes of host **1** with these anions.

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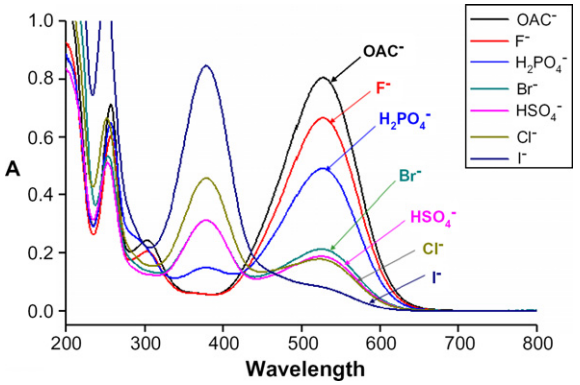

Figure 1. The UV absorption changes of compound **1** (40 μM) with various anions (1 equiv) in acetonitrile.

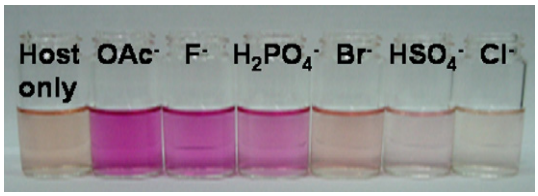

Figure 2. The color changes of compound **1** (40 μM) with various anions (1 equiv) in acetonitrile.

Compounds **1** were then examined for chiral recognitions with various amino acid derivatives. Tetrabutyl ammonium salts of

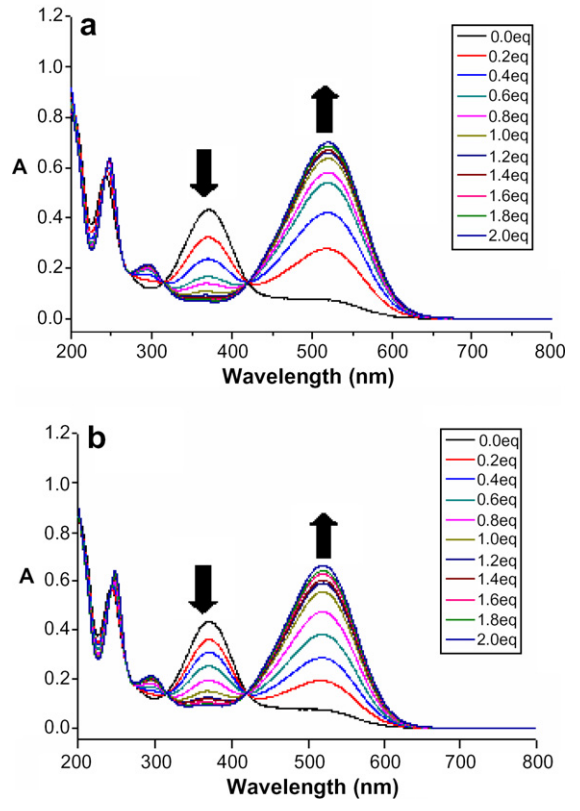

Figure 3. UV titrations of compound **1** (20 μM) with L-*t*-Boc-threonine (a) and D-*t*-Boc-threonine in acetonitrile.

Table 1
The association constants (M^{-1}) of hosts **1** with *t*-Boc-amino acid derivatives in acetonitrile

Guest	K_D (M^{-1})	K_D/K_L	K_L (M^{-1})
Phenylglycine	3.80×10^4	1.16	3.27×10^4
Leucine	2.98×10^4	2.22	1.34×10^4
Valine	1.64×10^4	1.43	1.15×10^4
Threonine	6.89×10^4	3.13	2.20×10^4
Alanine	2.28×10^3	3.60	6.33×10^2

Table 2
The association constants (M^{-1}) of hosts **1** with DNB-amino acid derivatives in acetonitrile

Guest	K_D (M^{-1})	K_D/K_L	K_L (M^{-1})
Phenylglycine	6.48×10^4	1.10	5.90×10^4
Leucine	9.95×10^4	2.17	4.59×10^4
Valine	2.65×10^4	1.42	1.86×10^4
Threonine	5.15×10^4	1.17	4.39×10^4
Alanine	4.35×10^3	2.55	1.70×10^3

t-Boc-amino acids and DNB(dinitrobenzyl)-amino acids, such as alanine (Ala), valine (Val), threonine (Thr), leucine (Leu) and phenylglycine (Phg), were used for the binding study. Figure 3 explains the UV titrations of chemosensor **1** (20 μM) with L-*t*-Boc-threonine (Fig. 3a) and D-*t*-Boc-threonine (Fig. 3b) in acetonitrile. According to the linear Benesi–Hilderand expression, the measured absorption $[1/(A - A_0)]$ at 523 nm varied as a function of amino acids in linear relationship ($R \cong 0.9995$), indicating the ~1:1 stoichiometry between amino acids and hosts (Supplementary data). The 1:1 stoichiometry was further confirmed by Job plot (Supplementary data). The association constants of **1** with *t*-Boc amino acids and DNB-amino acids are explained in Tables 1 and 2. As shown in Tables 1 and 2, in general, host **1** displayed a larger K_a value with L-amino acid derivatives than that with D-isomers. For example, the association constants of **1** with L- and D-*t*-Boc threonine were calculated as 68,900 and 22,000 M^{-1}, respectively, and K_L/K_D was found to be 3.13 (Table 1). *t*-Boc or DNB group was introduced due to the solubility problem. However, these *t*-Boc or DNB derivatives displayed a higher L/D selectivity than deprotected amino acids, which means that large *t*-Boc or DNB group is needed to interact with chiral barrier (glucopyranosyl unit). ^{1}H NMR experiments of **1** (2 mM) with D-*t*-Boc valine (1 equiv) in DMSO-d_6 displayed a distinct downfield-shift of guest amide (NH) hydrogen from 5.73 to 6.81 ppm (Supplementary data), which can be attributed to that an amide hydrogen of guest can make a H-bonding with phenolic oxygen of host. In addition, a small upfield-shift (0.2 ppm) of isopropyl group of the guest was observed.

Host **1** was further examined with chiral carboxylates such as naproxen, 2-phenylpropionic acid, and 2-hydroxybutyric acid. The association constants were determined by UV–visible titration in acetonitrile and analyzed by the Benesi–Hilderand expression (Supplementary data). As shown in Table 3, the chiral carboxylate anions showed the larger association constants for (*S*)-enantiomers than those for (*R*)-enantiomers. 2-Phenylpropionic acid displayed the K_S/K_R as high as 2.95. Host **1** also displayed a moderate selectivity for the (*S*)-enantiomer of naproxen, a nonsteriodal anti-inflam-

Table 3
The association constants (M^{-1}) of host **1** with chiral carboxylates in acetonitrile

Chiral carboxylate	K_S (M^{-1})	K_S/K_R	K_R (M^{-1})
Naproxen	3.59×10^3	1.86	1.93×10^3
2-Phenylpropionic acid	8.25×10^3	2.95	2.79×10^3
2-Hydroxybutyric acid	2.21×10^4	1.32	1.67×10^4

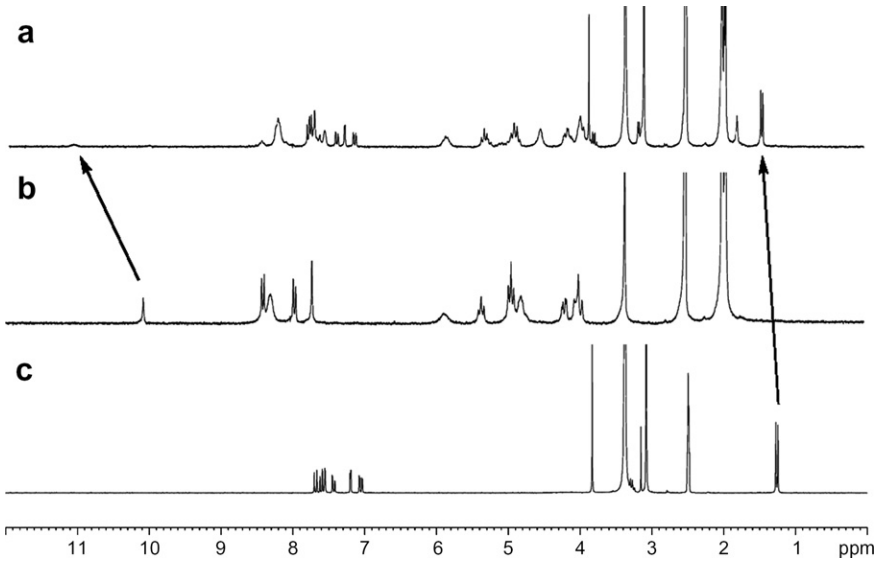

Figure 4. The partial ^{1}H NMR (250 MHz) spectra in DMSO-d_6; (a) **1** (2 mM) upon the addition of (*S*)-naproxen (0.6 equiv), (b) **1** only (2 mM), (c) (*S*)-naproxen only.

matory drug (NSAID) over (*R*)-isomer. It is known that the pharmacological activity of (*S*)-isomer is greater compared to that of (*R*)-isomer.

To examine the chemical shift changes of host **1** as well as naproxen, ^{1}H NMR experiments were performed in DMSO-d_6 (Fig. 4). As shown in Figure 4, OH peak in the host moved from 10.1 to 11.1 ppm and methyl group in the guest moved from 1.30 to 1.43 ppm upon the addition of (*S*)-naproxen (0.6 equiv).

In conclusion, we report a new colorimetric sensor for chiral anion recognition such as α-amino carboxylates as well as chiral carboxylates such as naproxen. Our host **1** accommodates a combination of three different functional groups, such as chromophore (azophenol dye), binding site (thiourea group), and chiral barrier (glucopyranosyl group). As high as 3.60 was observed for the D/L selectivity of host **1**, which can be attributed to the glucopyranosyl unit (chiral barrier) of the host.

Acknowledgments

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Supplementary data

Supplementary data (NMR and UV spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.055.

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8. *Compound* **1**. Compound **2** was dissolved in 15 mL of methylene chloride in 100 ml two-necked round flask. HCl gas was introduced to this solution to remove the Boc group. 0.29 g of ammonium intermediate was obtained after filteration of the resulting precipitate. The resulting ammonium intermediate (0.20 g, 0.99 mmol) was then dissolved in 20 ml of methylene chloride in 100 ml round-bottomed flask. To the solution were added triethylamine (0.4 ml, 2.37 mmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (0.46 g, 1.18 mmol). The whole solution was stirred for 10 h at room temperature under an argon atmosphere. The reaction mixture was washed with 1 N HCl solution, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane/methanol: 1/2/0.1) to afford compound **1** (0.26 g, 35%) as a yellowish solid: mp 152.8–154.2 °C; $[\alpha]_D^{16.4}$ 84.4 (*c* 0.5, $CHCl_3$); IR (KBr) cm^{-1} 3349, 1751, 1548, 1375, 1230, 1039; ^{1}H NMR (CD_3CN, ppm) δ 8.32 (d, 2H, J = 7.2 Hz), 7.92 (d, 2H, J = 8.9 Hz), 7.80 (s, 2H), 7.38 (m, 2H), 7.01 (d, 2H, J = 8.1 Hz), 5.33 (t, 2H, J = 9.5 Hz), 4.98 (td, 4H, J_1 = 9.9 Hz and J_2 = 2.6 Hz), 4.82 (br s, 4H), 4.18 (dd, 2H, J_1 = 12.4 Hz and J_2 = 5.2 Hz), 4.01 (dd, 2H, J_1 = 12.3 Hz and J_2 = 2.2 Hz), 3.9 (ddd, 2H, J_1 = 9.9 Hz, J_2 = 5.0 Hz and J_3 = 2.3 Hz), 1.93 (m, 24H); ^{13}C NMR (CD_3CN, ppm) δ 183.2, 170.0, 169.9, 169.5, 169.3, 157.2, 155.6, 148.1, 145.3, 125.6, 124.8, 124.5, 122.6, 81.6, 72.6, 72.2, 70.2, 67.9, 61.5, 43.8, 19.6, 19.6, 19.6; MALDI-TOF-MS 1102.3 ($M+Na^+$) calcd for $C_{44}H_{53}N_7O_{21}S_2$ 1102.3 ($M+Na^+$).
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