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Anthracene Derivatives Bearing Thiourea and Glucopyranosyl Groups for the Highly Selective Chiral Recognition of Amino Acids: Opposite Chiral Selectivities from Similar Binding Units

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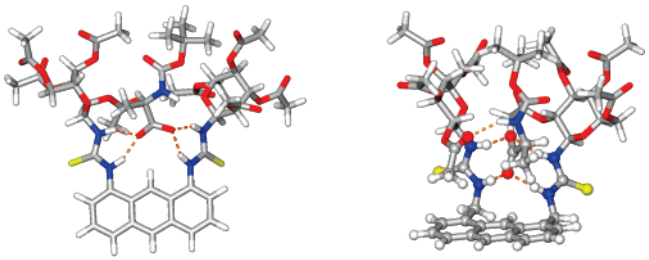

Two new anthracene thiourea derivatives, **1** and **2**, were investigated as fluorescent chemosensors for the chiral recognition of the two enantiomers of α-amino carboxylates. Especially, host **2** displayed K_L/K_D values as high as 10.4 with *t*-Boc alanine. Furthermore, the D/L selectivity of hosts **1** and **2** is opposite, even though both hosts bear the same glucopyranosyl units. These intriguing opposite D/L binding affinities by **1** and **2** were obtained without/with H-π interaction between anthrancene moiety and the methyl groups, which were explained by extensive high-level theoretical investigations taking into account the dispersion energy as well as the 2D-NMR chemical shifts.

The design and synthesis of chemosensors for the recognition or sensing of physiologically important anionic analytes has attracted considerable attention in recent years.[1] In particular, sensors based on anion-induced changes in fluorescence appear to be particularly attractive as a result of their simplicity and the high detection limit of the fluorescence.[2] Even though great effort has been devoted to chiral anion recognition,[3] fluorescent chemosensors for chiral anions with a sufficient selectivity are relatively rare.[4,5] Herein, we report new anthracene thiourea derivatives **1** and **2** (Figure 1) as fluorescent chemosensors for chiral recognition of the two enantiomers of α-amino carboxylates.

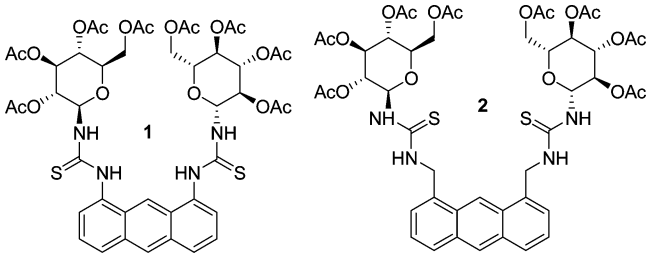

FIGURE 1. Structures of compounds **1** and **2**.

Previously, thiourea compounds derived from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate have been used for the recognition of simple anions[6] and dicarboxylates.[7] However, they have not been utilized for chiral recognition. 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate has also been utilized as a successful chiral derivatizing agent for the optical resolution of racemic amino compounds by forming two diastereomeric thiourea derivatives with racemic analytes.[8] In this instance, anthracene thiourea derivatives **1** and **2** containing a 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl group as a possible chiral barrier are expected to be useful for the chiral recognition of chiral anions.

Anthracene-based chiral chemosensors **1** and **2** were prepared simply by treating 1,8-diaminoanthracene[9] or 1,8-anthracenedimethanamine[10] with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

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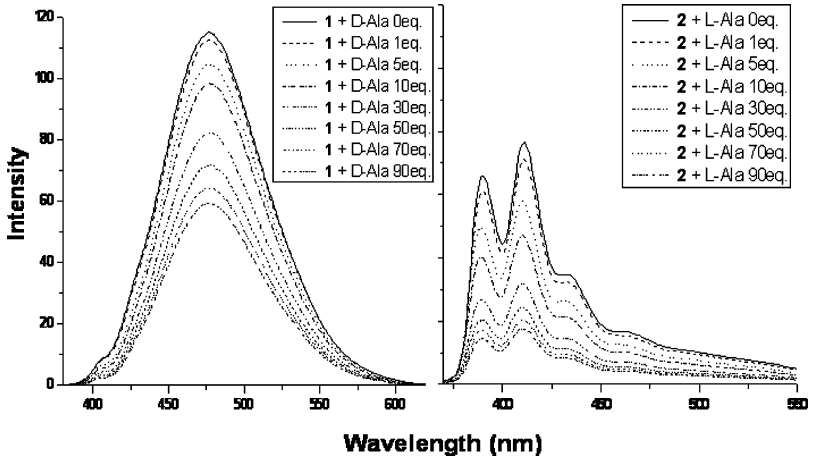

FIGURE 2. Fluorescent titrations of chemosensors **1** (10 μM) with D-DNB-alanine and **2** (10 μM) with L-DNB-alanine (tetrammonium salts) in acetonitrile.

isothiocyanate in 46% and 70% yield, respectively, after the column chromatography. The detailed synthesis and characterization of **1** and **2** are explained in Supporting Information.

Compounds **1** and **2** were evaluated as chemosensors for various anionic species. Among anions such as $CH_3CO_2^-$, $H_2PO_4^-$, F^-, Cl^-, Br^-, and I^-, host **1** displayed a moderate selectivity for F^- in acetonitrile (Supporting Information). On the other hand, host **2** showed large chelation enhanced quenching (CHEQ) effects for $CH_3CO_2^-$, $H_2PO_4^-$, and F^- (Supporting Information).

Compounds **1** and **2** were then examined for chiral recognition with various amino acid derivatives. Tetrabutyl ammonium salts of *t*-Boc-amino acids and 3,5-dinitrobenzoyl (DNB)-amino acids, such as alanine (Ala), valine (Val), threonine (Thr), leucine (Leu), phenylglycine (Phg), and phenylalanine (Phe), were used for the binding study. Figure 2 explains the fluorescent titrations of chemosensors **1** (10 μM) with D-DNB-alanine and **2** (10 μM) with L-DNB-alanine in acetonitrile. Hosts **1** and **2** showed CHEQ effects with amino acids derivatives. These CHEQ effects for host **1** can be attributed to photoinduced charge transfer (PTC). A similar fluorescent quenching process due to the PTC has been previously reported.[11] On the other hand, fluorescent quenching effects of host **2** can be attributed to the PET process.[2c] The PET-induced quenching effects of thiourea or urea anthracene derivatives with anions have been also reported.[10,12]

Compared to the *t*-Boc series, DNB derivatives displayed larger fluorescent quenching effects, which are attributed to the quenching effect due to nitro groups in addition to the usual PET/PTC quenching effects. Fluorescent titration spectra of other amino acid derivatives are illustrated in Supporting Information. The quantum yield of host **1** was calculated as 0.095 in acetonitrile, and those with D-*t*-Boc-alanine and L-*t*-Boc-alanine were 0.039 and 0.044, respectively.[13] The quantum yields of **2**, **2** with D-*t*-Boc-alanine, and **2** with L-*t*-Boc-alanine were calculated as 0.057, 0.042, and 0.039, respectively.[13]

TABLE 1. Association Constants (M^{-1}) of Hosts 1 and 2 with *t*-Boc-Amino Acid Derivatives in Acetonitrile

	host **1**			host **2**		
guest	K_D (M^{-1})	K_D/K_L	K_L (M^{-1})	K_D (M^{-1})	K_L/K_D	K_L (M^{-1})
Ala	1.18×10^4	5.5	2.16×10^3	2.30×10^3	10.4	2.39×10^4
Val	8.02×10^3	4.3	1.85×10^3	1.67×10^3	7.0	1.17×10^4
Thr	1.85×10^4	4.1	4.54×10^3	7.57×10^3	7.8	5.90×10^3
Leu	1.26×10^4	2.0	6.27×10^3	9.93×10^3	3.1	3.09×10^4
Phg	1.11×10^4	1.1	1.00×10^4	2.13×10^3	1.5	3.12×10^3
Phe	1.00×10^4	1.2	8.41×10^3	3.20×10^3	2.6	8.42×10^3

TABLE 2. Association Constants (M^{-1}) of Hosts 1 and 2 with DNB-Amino Acid Derivatives in Acetonitrile

	host **1**			host **2**		
guest	K_D (M^{-1})	K_D/K_L	K_L (M^{-1})	K_D (M^{-1})	K_L/K_D	K_L (M^{-1})
Ala	4.73×10^3	5.9	8.06×10^2	1.39×10^3	6.6	9.20×10^3
Val	8.02×10^3	4.5	1.80×10^3	2.48×10^3	3.9	9.76×10^3
Thr	8.32×10^3	4.8	1.75×10^3	3.68×10^3	3.1	1.13×10^4
Leu	4.01×10^3	2.4	1.65×10^3	3.55×10^3	3.2	1.13×10^4
Phg	2.76×10^3	2.2	1.25×10^3	2.35×10^3	1.4	3.25×10^3
Phe	1.18×10^4	1.6	7.26×10^3	3.77×10^3	1.9	6.98×10^3

Fluorescent quenching effects (%) of host **1** with D- and L-*t*-Boc-phenylglycine were 12.2 and 12.3, respectively, and those of **2** with D- and L-*t*-Boc-phenylglycine were 22.5 and 26.1, respectively. On the other hand, fluorescent quenching effects (%) of host **1** with D- and L-DNB-phenylglycine were 43.1 and 37.0, respectively, and those of **2** with D- and L-DNB-phenylglycine were 66.6 and 63.9, respectively.

According to the linear Benesi−Hilderand expression, the measured emission $[1/(F - F_0)]$ at 476 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 (Supporting Information). The 1:1 stoichiometry was further confirmed by Job plot (Supporting Information). The association constants of **1** and **2** with *t*-Boc-amino acids and DNB-amino acids are shown in Tables 1 and 2. For example, the association constants of **1** with D- and L-*t*-Boc alanine were calculated as 11800 and 2160 M^{-1}, respectively, and K_D/K_L was found to be 5.5. On the other hand, the association constants of **2** with D- and L-*t*-Boc alanine were calculated as 2300 and 23900 M^{-1}, respectively, and K_L/K_D was found to be 10.4. Even though there has been a report utilizing chiral boronic acid receptor for

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(13) The relative quantum yields were determined using 9,10-diphenylanthracene in degassed hexane ($\Phi = 0.96$).

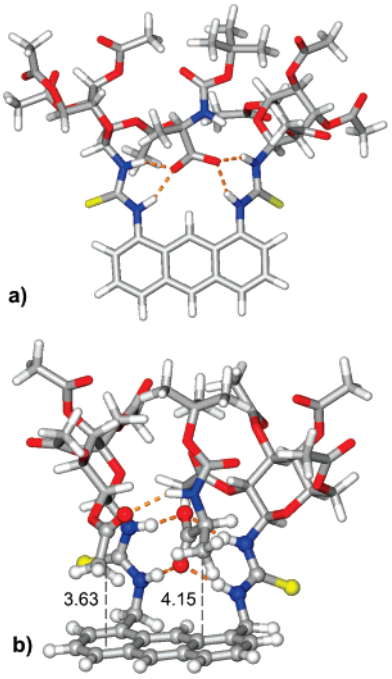

FIGURE 3. Optimized geometries of (a) **1**−D-t-Boc-alanine complex [at the B3LYP/6-31G* level] and (b) **2**−L-t-Boc-alanine complex [at the MP2/6-31G*//ONIOM(MP2/6-31G*+B3LYP/6-31G*) level, where the atoms at the MP2 level are shown in ball and stick model]. The H-π interactions are shown as grey dotted lines represented by distance (in Å) from the methyl carbon atom to the anthracene plane.

excellent chiral recognition of α-hydroxy acids,[14] the chiral selectivity of 10.4 is the highest value reported so far, which was obtained using an anion-selective receptor based on the hydrogen bonding interaction.

From the ^{1}H NMR experiments of host **2** (5 mM) with L/D-*t*-Boc-alanine (2 equiv) in CD_3CN, the two thiourea N−H peaks displayed a large downfield shifts ($\Delta\delta$ = 2.71 and 2.59 for L-alanine, $\Delta\delta$ = 2.67 and 2.48 for D-alanine), which supports the fluorescent data. More importantly, the peak for the methyl group of free alanine that appears at δ 1.22 ppm as a doublet moves to δ 0.97 ppm when 1 equiv of L-alanine was added to host **2**. On the other hand, in the case of D-alanine, the same peak moved to δ 1.10 ppm, which was also confirmed by ^{1}H−^{1}H COSY spectrum (Supporting Information). This suggests that there might be the H-π interaction[15] between the methyl group of alanine and the anthracene moiety, which can be a clue for the selectivity of **2** with L-alanine over D-alanine.

The opposite selectivity of hosts **1** and **2** with D/L-*t*-Boc-alanine was further demonstrated with theoretical calculations. **1**−D-*t*-Boc-alanine complex (Figure 3a) was found to be ∼0.5 kcal/mol more stable than that of **1**−L-*t*-Boc-alanine, which is slightly underestimated but comparable to the experimental selectivity (1.0 kcal/mol). **2**−L-*t*-Boc-alanine complex is 3.6 kcal/mol more stable than that of **2**−D-*t*-Boc-alanine complex. The H-π interaction alone contributes 2.7 kcal/mol in the gas phase (2.2 kcal/mol with counterpoise correction) and 2.3 (1.8) kcal/mol in acetonitrile toward the total energy differences, while the energy difference of ∼1 kcal/mol due to the H-bonding would nearly be nullified in polar solvents.[16] Even though the predicted total energy difference is ∼2 kcal/mol larger than the experimental free energy difference (1.4 kcal/mol), the calculations agree with the experiment, because the free energy difference is in general smaller than the total energy difference.[15]

In conclusion, we report highly selective fluorescent chemosensors for the chiral recognition of amino acids. Especially, host **2** displayed K_L/K_D values as high as 10.4 with *t*-Boc alanine. As far as we are aware of, this is the highest chiral selectivity obtained from anion-induced binding based on the hydrogen bonding interaction. Furthermore, the D/L selectivity of hosts **1** and **2** is opposite, even though both hosts bear the same glucopyranosyl units. These intriguing opposite D/L binding affinities by **1** and **2** were obtained without/with H-π interaction between anthrancene moiety and the methyl groups, which was explained by extensive high-level theoretical investigations taking into account the dispersion energy as well as the 2D-NMR chemical shifts.

Experimental Section

Compound 1. 1,8-Diamino anthracene was synthesized from 1,8-donitroanthraquinone following a reported procedures.[9] To a stirred solution of 1,8-diaminoanthracene (0.1 g, 0.48 mmol) in 5 mL of methlyene chloride was added dropwise a solution of 2,3,4,6-tetra-*O*-acetyl-*β*-D-glycopyranosyl-isothiocynate (GITC) (0.37 g, 0.95 mmol). The mixture was refluxed for 2 h under nitrogen gas. The reaction mixture was filtered through a filter paper, and the resulting solution was dried with Na_2SO_4. After solvent was evaporated under vacuum, the crude product was purified by flash chromatography (ethyl acetate/hexane/methanol = 1:1:0.1) to afford the product **1** (0.22 g, 0.22 mmol, 46%) as a brown solid: mp 162−164 °C; $[\alpha]_D^{16}$ −29.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR (acetone-d_6, ppm) δ 1.94 (s, 12H), 1.96 (s, 6H), 1.99 (s, 6H), 4.00−4.12 (m, 4H), 4.35 (dd, J = 4.8 Hz, 2H), 4.95−5.05 (m, 4H), 5.41 (t, J = 9.3 Hz, 2H), 6.01 (t, J = 9.0 Hz, 2H), 7.53−7.61 (m, 7H), 8.09 (d, J = 8.1 Hz, 2H), 8.72 (d, J = 16.5 Hz, 2H), 9.73 (s, 1H); ^{13}C NMR (CD_3CN, ppm) δ 19.99, 20.07, 20.12, 29.75, 29.84, 62.10, 68.68, 71.13, 73.30, 73.53, 83.14, 115.36, 125.71, 127.95, 128.63, 132.93, 134.06, 169.48, 169.64, 170.41, 184.28, 206.15; IR (KBr) cm^{-1} 3356.50, 2929.34, 1752.98, 1536.99, 1370.18, 1230.36, 1038.48, 599.75; HR-ESI-MS m/z = 987.2653 $(M + H)^+$, calcd for $C_{44}H_{51}N_4O_{18}S_2$ = 987.2632.

Compound 2. 1,8-Bis(aminomethyl)anthracene was synthesized from 1,8-bis(hydroxymethyl) anthracene following a reported procedure.[10] To a stirred solution of 1,8-bis(aminomethyl)anthracene (0.1 g, 0.42 mmol) in 20 mL of methlyene chloride was added dropwise a solution of GITC (0.33 g, 0.85 mmol). The mixture was stirred for 1 h under nitrogen gas at room temperature. Solvent was evaporated under vacuum, and the crude product was purified by flash chromatography (ethyl acetate/hexane/methanol = 1:1:0.1) to afford the product **2** (0.30 g, 0.30 mmol, 70%) as a yellow solid: mp 160−162 °C; $[\alpha]_D^{16}$ −13.2 (*c* 0.1, $CHCl_3$); ^{1}H NMR (acetone-d_6, ppm) δ 1.84 (s, 6H), 1.94 (s, 6H), 1.96 (s, 6H), 1.99 (s, 6H), 3.99−4.07 (m, 4H), 4.26 (dd, J = 4.5 Hz, 2H), 4.93−5.04 (m, 4H), 5.39 (t, J = 9.6 Hz, 2H), 5.49 (d, 4H), 6.00 (t, J = 6.9 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 7.7 Hz, 2H), 7.57 (d, J = 6.9 Hz, 2H), 7.93 (t, 2H), 8.03 (d, J = 8.1 Hz, 2H), 8.61 (s, 1H), 8.92 (s, 1H); ^{13}C NMR (CD_3CN, ppm) δ 20.10, 20.17, 20.24, 46.63, 62.13, 68.57, 71.08, 73.47, 78.52, 82.34, 118.35, 125.44, 125.76, 128.20, 128.41, 129.82, 131.97, 134.40, 170.18, 170.38, 170.61, 171.00, 184.42; IR (KBr) cm^{-1} 3360.35,

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2925.34, 1547.59, 1377.89, 1234.22, 1037.52, 600.72; HR-ESI-MS m/z = 1015.2987 $(M + H)^+$, calcd for $C_{46}H_{55}N_4O_{18}S_2$ = 1015.2946.

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Supporting Information Available: Fluorescent and ^1H and ^{13}C NMR spectra of compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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