Sugar Thioureas as Anion Receptors. Effect of Intramolecular Hydrogen Bonding in the Carboxylate Binding Properties of Symmetric Sugar Thioureas

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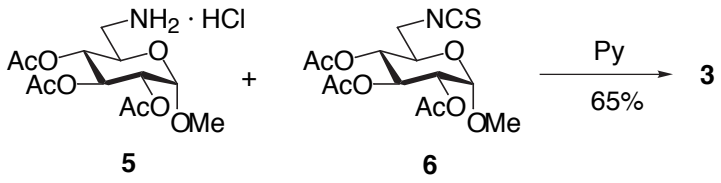
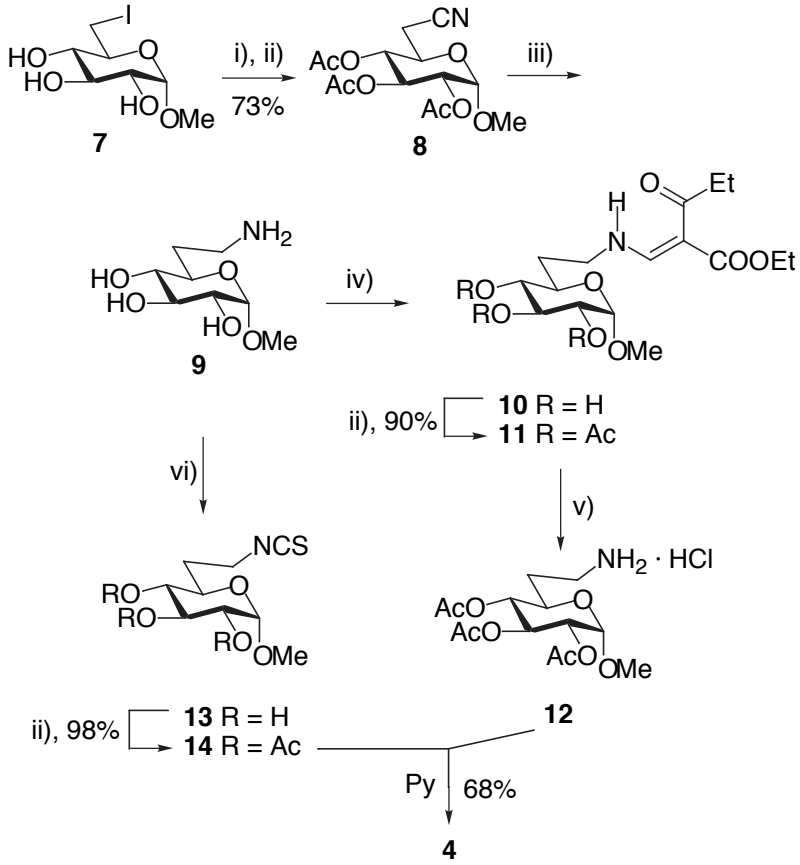
Supporting Information

Synthesis of Thioureido Sugar Receptors 1-4. Macrocycle **1** was prepared by coupling of 2,3,4,2',3',4'-hexa-*O*-acetyl-6,6'-dideoxy-6,6'-diisothiocyanato-α,α'-trehalose[1] and the corresponding hexa-*O*-acetylated 6,6'-diamino-6,6'-dideoxy-α,α'-trehalose dihydrochloride as previously reported.[2] Compound **2** was similarly obtained from the reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine hydrochloride.[3] The (6→6) and (7→7) thiourea tethered pseudodisaccharides **3** and **4** were obtained by nucleophilic addition of the selectively *O*-acetylated amino sugars **5**[4] and **12** with the corresponding isothiocyanates **6**[5] and **14**, respectively, according to Schemes 1 and 2.

Scheme 1



Scheme 2[a]



[a] Reagents: (i) 1. NaCN, DFM, 70 °C; (ii) Ac_2O-Py; (iii) borane-Me_2S complex; (iv) diethyl ethoxymethylenemalonate, MeOH, 40°C (74% from **8**); (v)Cl_2, CH_2Cl_2, 95%; (vi) $CSCl_2$, 80%.

***N,N'*-Bis(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosyd-6-yl)thiourea (3):** R_f 0.22 (1:1 EtOAc-hexanes); $[\alpha]_D$ +136.0 (*c* 0.9, CH_2Cl_2); FABMS: *m/z* 703 ([M+Na]+), 681 ([M+H]+); ^{1}H NMR (300 MHz, $CDCl_3$, 323 K) δ 6.67 (t, 2 H, $J_{NH,6a} = J_{NH,6b}$ 5.8 Hz, 2 NH), 5.47 (t, 2 H, $J_{2,3} = J_{3,4}$ 9.7 Hz, H-3), 4.94 (d, 2 H, $J_{1,2}$ 3.2 Hz, H-1), 4.89 (t, 2 H, $J_{4,5}$ 9.7 Hz, H-4), 4.79 (dd, 2 H, H-2), 4.00 (ddd, 2 H, $J_{5,6b}$ 5.8, $J_{5,6a}$ 2.7 Hz, H-5), 3.78 (ddd, 2 H, $J_{6a,6b}$ 14.8 Hz, H-6a), 3.50 (dt, 2 H, H-6b), 3.43 (s, 6 H, 2 OCH_3), 2.04, 1.97 (2 s, 18 H, 6 OAc); ^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K) δ 184.5 (CS), 170.0, 169.7, 169.6 (CO), 96.6 (C-1), 70.8 (C-2), 69.7 (C-4), 69.4 (C-3), 68.0 (C-5), 55.4 (OMe), 44.7 (C-6), 20.4, 20.3, 20.2 (Ac). Anal. Calcd for $C_{27}H_{40}N_2O_{16}S$: C, 47.64; H, 5.92; N, 4.11; S, 4.71. Found: C, 47.58; H, 6.00; N, 4.30; S, 4.78.

***N,N'*-Bis(methyl 2,3,4-tri-*O*-acetyl-6,7-dideoxy-α-D-*gluco*-heptopyranosyd-7-yl)thiourea (4):** R_f 0.42 (1:1 EtOAc-hexanes); $[\alpha]_D$ +121.9 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 323 K) δ 6.02 (t, 2 H, $J_{NH,7a} = J_{NH,7b}$ 4.9 Hz, 2 NH), 5.43 (t, 2 H, $J_{2,3} = J_{3,4}$ 10.2 Hz, H-3), 4.91 (d, 2 H, $J_{1,2}$ 3.6 Hz, H-1), 4.84 (t, 2 H, $J_{4,5}$ 10.2 Hz, H-4), 4.81 (dd, 2 H, H-2), 3.54 (ddd, 2 H, $J_{5,6b}$ 10.2, $J_{5,6a}$ 2.7 Hz, H-5), 3.66 (m, 2 H, H-7a), 3.46 (m, 2 H, H-7b), 3.39 (s, 6 H, 2 OMe), 1.89 (m, 2 H, H-6a), 1.72 (dq, 2 H, $J_{6b,7a} = J_{6b,7b}$ 10.2, $J_{6a,6b}$ 14.7 Hz, H-5), 2.04, 2.02, 1.97 (3 s, 18 H, 6 OAc); ^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K) δ 181.7 (CS), 170.0, 169.9, 169.8 (CO), 96.7 (C-1), 71.5 (C-4), 70.9 (C-2), 69.9 (C-3), 67.6 (C-5), 55.5 (OMe), 41.1 (C-7), 29.8 (C-6), 20.6, 20.5, 20.4 (Ac). Anal. Calcd for $C_{29}H_{44}N_2O_{16}S$: C, 49.14; H, 6.26; N, 3.95; S, 4.52. Found: C, 48.98; H, 6.10; N, 3.79; S, 4.33.

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-α-D-*gluco*-heptopyranosiduronononitrile (8). To a solution of methyl 6-deoxy-6-iodo-α-D-glucopyranoside **7**[5] (1.8 g, 4.18 mmol) in dry DMF (30 mL) was added NaCN (0.41 g, 8.36 mmol). The solution was stirred overnigth at 70 °C, then concentrated and the residue acetylated with Ac_2O-pyridine (1:1, 30 mL) for 5 h. Conventional work-up and purification by column chromatography (1:1 EtOAc-toluene) gave **8** (1.0 g, 73%); $[\alpha]_D$ +42.6 (*c* = 1.8, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.45 (t, 1 H, *J* = 9.6 Hz), 4.95 (2, 1 H, *J* = 3.6 Hz), 4.88 (t, 1 H, *J* = 9.6 Hz), 4.86 (dd, 1 H, *J* = 3.6, 9.6 Hz), 4.04 (ddd, 1 H, *J* = 2.0, 4.0, 9.6 Hz), 3.43 (s, 3 H), 2.59 (dd, 1 H, *J* = 2.0, 10.0 Hz), 2.57 (dd, 1 H, *J* = 2.0, 10.0 Hz), 2.05, 2.05, 2.00 (3 s, each 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.9, 169.7, 169.6, 115.9, 96.6, 71.6, 70.4, 69.3, 65.0, 55.6, 20.5. Anal. Calcd. for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25. Found: C, 51.00; H, 5.72; N, 4.20.

Methyl 7-Amino-6,7-dideoxy-α-D-*gluco*-heptopyranoside (9). To a solution of **8** (1.88 g, 5.7 mmol) in dry 1,2-dimethoxyethane (60 mL), commercial borane-dimethyl sulfide complex (9.4 mL, 94 mmol) was added and the mixture was stirred under Ar at room temperature for 1 day. After cooling at 0 °C, MeOH (30 mL) was added dropwise and the mixture was stirred for 1 day before addition of water (20 mL). Evaporation of the solvents under reduced pressure and repeated coevaporation with MeOH afforded **9** as a hygroscopic white solid which was used in the next step

without further purification. ^{13}C NMR (75.5 MHz, D_2O): δ 99.3, 73.0, 72.9, 71.3, 69.8, 55.2, 36.9 and 28.4; FABMS *m/z* 230 (10 %, $[M+Na]^+$).

Methyl 6,7-Dideoxy-7-(2',2'-diethoxycarbonylvinyl)amino-α-D-*gluco*-heptopyranoside (10). To a solution of crude **9** (0.31 g, 1.50 mmol) in dry methanol (10 mL), diethyl ethoxymethylenemalonate (0.46 mL, 2.3 mmol) was added. The mixture was stirred at 40°C for 12 h and then concentrated. Column chromatography (20:1 CH_2Cl_2-MeOH) of the resulting syrup yielded **10** as a white solid (0.42 g, 1.11 mmol, 74%); $[\alpha]_D$ +45.7°(*c* = 2.4, MeOH); ^1H NMR (500 MHz, CD_3OD): δ 8.05 (s, 1H, =*CH*), 4.66 (d, 1 H, *J* = 3.8 Hz), 4.17, 4.11 (2q, 4 H, *J* = 7.1 Hz, O*CH*$_2$CH$_3$), 3.55 (dd, 1 H, *J* = 8.5, 9.4 Hz), 3.54 (m, 1 H), 3.54 (m, 2 H), 3.38 (dd, 1 H), 3.38 (s, 3 H, O*Me*), 3.07 (t, 1 H, *J* = 9.4 Hz), 2.15 (dtd, 1 H, *J* = 2.7, 14.4, 6.9 Hz), 1.69 (ddt, 1 H, *J* = 9.4, 6.9 Hz), 1.26, 1.25 (2t, 6 H, OCH$_2$*CH*$_3$); ^{13}C NMR (125.5 MHz, CD_3OD): δ 168.6 (*CO* chelated), 166.9 (*CO* free), 159.7 (=*CH*), 100.0, 88.2 (=*C*), 74.1, 73.5, 72.2 , 69.5, 59.3, 59.2 (2 C, O*CH*$_2$CH$_3$), 54.7 (O*Me*), 46.8, 32.0, 13.4 and 13.2 (2 C, OCH$_2$*CH*$_3$). Anal. Calcd. for $C_{16}H_{27}NO_9$: C, 50.92; H, 7.21; N, 3.71. Found: C, 50.80; H, 7.08; N, 3.60.

Methyl 2,3,4-Tri-*O*-acetyl-6,7-dideoxy-7-(2',2'-diethoxycarbonylvinyl)amino-α-D-*gluco*-heptopyranoside (11). Conventional acetylation of **10** (0.36 g, 0.96 mmol) with Ac_2O-pyridine (1:1, 6 mL) followed by purification by column chromatography (1:1 AcOEt-Hex) gave **11** (0.43 g, 0.86 mmol, 90%), $[\alpha]_D$ +66.8°(*c* = 2.8, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 9.25 (m, 1 H, *NH*), 7.92 (d, 1H, *J* = 14.1 Hz, =*CH*), 5.39 (t, 1 H, *J* = 9.5 Hz), 4.90 (d, 1 H, *J* = 3.6 Hz), 4.81 (dd, 1 H, *J* = 9.5 Hz), 4.81 (t, 1 H, *J* = 9.5 Hz), 4.18, 4.12 (2q, 4 H, *J* = 7.1 Hz, O*CH*$_2$CH$_3$), 3.81 (td, 1 H, *J* = 3.3, 9.5 Hz), 3.45 (m, 2 H), 3.35 (s, 3 H, O*Me*), 2.02, 1.99, 1.96 (3s, 9 H, CO*Me*), 1.78 (m, 2 H), 1.26, 1.25 (2t, 6 H, OCH$_2$*CH*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.4, 170.2, 170.1 (3 C, *CO*Me), 169.0 (*CO* chelated), 166.5 (*CO* free), 160.1(=*CH*), 97.0, 90.2 (=*C*), 72.2, 71.2, 70.1, 66.9, 60.1, 59.8 (2 C, O*CH*$_2$CH$_3$), 56.0 (O*Me*), 46.5, 32.1, 20.9, 20.8 (3 C, CO*Me*), 14.7 and 14.6 (2 C, OCH$_2$*CH*$_3$). Anal. Calcd. for $C_{22}H_{33}NO_{12}$: C, 52.48; H, 6.61; N, 2.78. Found: C, 52.30; H, 6.63; N, 2.69.

Methyl 2,3,4-Tri-*O*-acetyl-7-amino-6,7-dideoxy-α-D-*gluco*-heptopyranoside hydrochloride (12). Into a solution of **11** (0.32 g, 0.63 mmol) in CH_2Cl_2 (10 mL) dry Cl_2 was bubbled for 30 min. The solvent was removed under reduced pressure and the resulting syrup was washed with diethyl oxide (2 x 10 mL) to yield **12** (0.23 g, 0.60 mmol, 95%) as a white solid; $[\alpha]_D$ +105.7°(*c* = 0.8, CH_2Cl_2); ^1H NMR (500 MHz, 313 K, $CDCl_3$): δ 6.60 (bs, 3 H, *NH*$_3$Cl), 5.41 (t, 1 H, *J* = 9.7 Hz), 4.96 (d, 1 H, *J* = 3.5 Hz), 4.90 (t, 1 H, *J* = 9.7 Hz), 4.86 (dd, 1 H), 3.90 (td, 1 H, *J* = 9.7, 2.8 Hz), 3.40 (s, 3 H, O*Me*), 3.14 (t, 2 H, *J* = 6.6 Hz), 2.11 (m 1 H), 2.05, 2.02, 1.98 (3s, 9 H, CO*Me*) and 1.96 (m, 1 H); ^{13}C NMR (125.5 MHz, 313 K, $CDCl_3$): δ 170.0 (3C, *CO*Me), 96.7, 71.4, 70.8, 69.8, 67.6, 55.8 (O*Me*), 36.9, 28.4, 20.7, 20.6 and 20.5 (3 C, CO*Me*). Anal. Calcd. for $C_{14}H_{24}NO_{12}Cl$: C, 45.47; H, 6.54; N, 3.79. Found: C, 45.19; H, 6.23; N, 3.58.

Methyl 6,7-Dideoxy-7-isothiocianato-α-D-*gluco*-heptopyranoside (13). To a heterogeneus mixture of amine **12** (1.19 g, 5.75 mmol) in 1:1 H_2O-acetone (30mL) and $CaCO_3$ (2.3 g, 23 mmol) was added Cl_2CS (1.32 g, 0.88 ml, 11.5 mmol). The mixture was vigorously stirred

for 2 h at room temperature and then concentrated. The residue was purified by column chromatography (CH_2Cl_2-MeOH 9:1→6:1) to afford **13** (1.14 g, 80%); $[\alpha]_D$ +2080 °(*c* = 0.7, CH_2Cl_2); IR (KBr) 3362, 3206, 2924, 2182, 2120, 1352, 1138, and 1045 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 4.65 (d, 1 H, *J* = 3.7 Hz), 3.76 (td, 1 H, *J* = 5.3, 9.2 Hz), 3.68 (td, 1 H, *J* = 6.6 Hz), 3.65 (td, 1 H, *J* = 9.5, 2.2 Hz), 3.59 (t, 1 H, *J* = 9.5 Hz), 3.42 (s, 3 H, O*Me*), 3.40 (dd, 1 H), 3.08 (t, 1 H, *J* = 9.5 Hz), 2.26 (dddd, 1 H, *J* = 14.6 Hz), 1.70 (dddd, 1 H); ^{13}C NMR (125.5 MHz, CD_3OD): δ 131.4 (*NCS*), 101.1, 75.4, 74.8, 73.5, 69.0, 55.8 (O*Me*), 42.5 and 33.1; FABMS *m/z* 272 (100 %, $[M+Na]^+$). Anal. Calcd. for $C_9H_{15}NO_5S$: C, 43.36; H, 6.07; N, 5.62; S, 12.86. Found: C, 43.45; H, 6.18; N, 5.50; S, 12.63.

Methyl 2,3,4-Tri-*O*-acetyl-6,7-dideoxy-7-isothiocianato-α-D-*gluco*-heptopyranoside (14). Conventional acetylation of **13** (0.5 g, 2.0 mmol) with Ac_2O-pyridine (1:1, 8 mL) gave **14** (0.735 g, 98%); $[\alpha]_D$ +13.7°(*c* = 1.0, CH_2Cl_2); IR (KBr) 2938, 2182, 2110, 1735, 1370, 1223, and 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.47 (t, 1 H, *J* = 9.5 Hz), 4.92 (d, 1 H, *J* = 3.6 Hz), 4.84 (dd, 1 H), 4.84 (dd, 1 H, *J* = 9.8 Hz), 3.93 (ddd, 1 H, *J* = 2.5, 10.5 Hz), 3.74 (ddd, 1 H, *J* = 9.2, 5.4, 14.3 Hz), 6.68 (ddd, 1 H, *J* = 6.5, 4.5 Hz), 3.43 (s, 3 H, O*Me*), 2.08, 2.07, 2.01 (3s, 9 H, CO*Me*), 1.94 (dddd, 1 H, *J* = 14.2 Hz) and 1.77 (dddd, 1 H); ^{13}C NMR (125.5 MHz, $CDCl_3$): δ 170.0, 169.8, 169.7 3 C, *CO*Me), 130.9 (*NCS*), 96.4, 71.8, 70.8, 69.7, 65.1, 55.4 (O*Me*), 40.9, 31.4 and 20.5 (3 C, CO*Me*). Anal. Calcd. for $C_{15}H_{21}NO_8S$: C, 47.99; H, 5.64; N, 3.73; S, 8.54. Found: C, 48.10; H, 5.72; N, 3.73; S, 8.29.

Binding Studies. $CDCl_3$ used for binding experiments was deacidified and partially dried by storage over basic alumina. Stock solutions of each host (1.4 or 0.5 mM) were prepared by dissolving the host in $CDCl_3$. Stock solutions of TBA benzoate and acetate (10-15 mM) were prepared from the stock solution of the host in order to have a constant concentration of the host during titration. Binding constants were determined by adding in portions via microsyringe a solution of guest to a solution of host. The ^1H NMR spectrum of each solution was recorded, and the chemical shift of the NH (**1**) or sugar protons (**2**-**4**) obtained at 12-15 different host-guest concentration ratios were used in an iterative least-squares fitting procedure.

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