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Influence of the size and geometry of the anion binding pocket of sugar–urea anion receptors on chiral recognition

Paulina Hamankiewicz [a], Jarosław M. Granda [b], Janusz Jurczak [a,b,*]

[a] Department of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland
[b] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

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ABSTRACT

Three new chiral urea-type anion receptors were synthesized from aromatic diamines and 1-amino-1-deoxyglucose. The anion binding properties of these receptors were studied using chiral carboxylates derived from mandelic acid and three α-amino acids. We found that the size of the anion binding pocket played an important role in chiral recognition processes. The best results were obtained for 1,8-diaminoanthracene and α-amino acid anions.

Since most compounds found in Nature are chiral (e.g., amino acids, peptides, terpenoids, sugars, etc.), it is essential to understand the interactions responsible for chiral differentiation in biological processes. In principle, chiral recognition is based on differences in the stability of diastereomeric host/guest complexes.[1] As many of these species exist at physiological pH as anions, we decided to investigate their chiral recognition using neutral synthetic receptors.

Among the common anion binding motifs typical for ligands often used in supramolecular chemistry (such as amide,[2] pyrrole,[3] indole,[4] and carbazole[5]), those with incorporated urea functionality[6] seemed to be the most promising building blocks for the synthesis of neutral receptors for anions. On the one hand, this is because a urea moiety can be readily incorporated into a wide range of anion binding receptors,[7] while on the other it is due to the specific geometry of hydrogen bond donors, which allows selective binding of carboxylates. For our chiral recognition studies we considered, as models, the three types of known receptors **1**–**3** shown in Figure 1.

In 2005, Gale and co-workers[8] reported the carboxylate binding properties of bis-urea anion receptor **1** (Fig. 1) with 1,2-diaminobenzene as an aromatic platform. This work showed that receptor **1** was selective for acetate and benzoate anions in DMSO + 0.5% H_2O. The Nam[9] and Tarr[10] groups, in turn, have studied a series of naphthalene urea anion receptors of type **2**. They examined the influence of the electronic effect of *para* substituents located on the phenyl ring of ligands **2** on the anion binding. Finally, Kim and Yoon[11] described fluorescent sensors for fluoride and pyrophosphate anions in which urea moieties were attached to anthracene at positions 1 and 8 (compounds of type **3**).

Based on these considerations, we resolved to design and synthesize three new chiral receptors **4**–**6**, using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isocyanate[12] and three different aromatic platforms: commercially available 1,2-diaminobenzene and 1,8-diaminonaphthalene, as well as 1,8-diaminoanthracene, which is known from the literature[13] (Scheme 1).[14] The receptors **4**,[15] **5**,[16] and **6**[17] (Fig. 2) were obtained in acceptable yields of 80%, 43%, and 55%, respectively.

The use of different aromatic platforms enabled us to construct receptors with binding pockets of varying size: the smallest for naphthalene, medium-size for benzene, and the largest for anthracene. We then investigated the influence of the size and shape of the anion binding site on the chiral recognition ability of the anion receptors **4**–**6** (Fig. 2).

In the first part of our investigation using chiral receptors, we examined achiral acetate and benzoate anions as guests. Anion binding studies were conducted applying ^{1}H NMR titration techniques in DMSO-d_6 + 0.5% H_2O at a constant concentration of receptor ($c = \sim 1 \times 10^{-2}$ M) and each titration was repeated twice. The results are collected in Table 1. Binding affinities were measured in terms of the anion complexation-induced resonance shift change of the urea NH protons. Binding constants were obtained using nonlinear regression of experimental data using the program HypNMR.[18] In line with previous findings for these anion binding

* Corresponding author. Tel.: +48 22 632 05 78; fax: +48 22 632 6681.
E-mail addresses: janusz.jurczak@icho.edu.pl, jjurczak@chem.uw.edu.pl (J. Jurczak).

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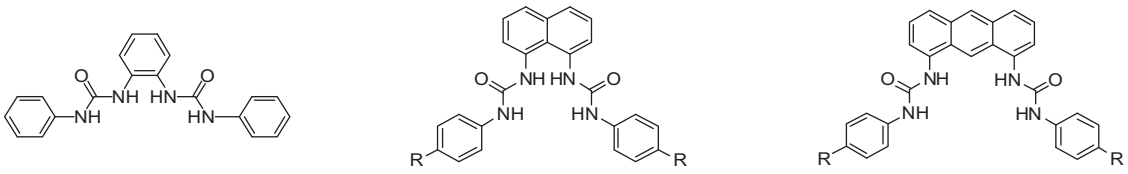
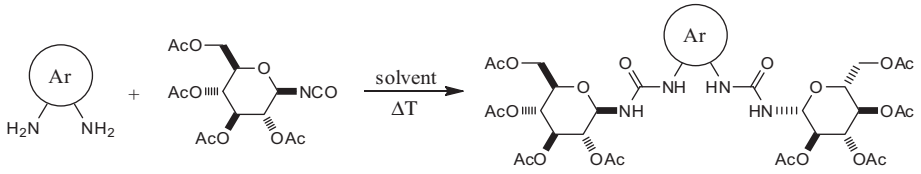


1 **2:** R = H, F, NO_2, OMe, CH_3 **3:** R = H, NO_2

Figure 1. Structures of anion urea-based receptors **1**–**3**.



Scheme 1. The general route to the chiral receptors.

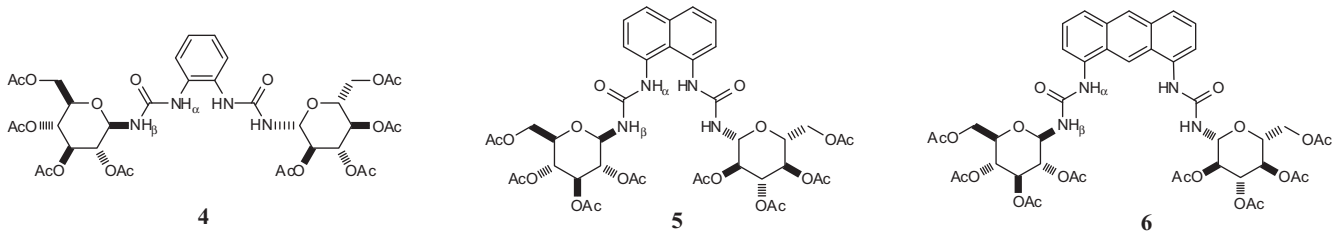


Figure 2. Structures of urea anion receptors **4**–**6**.

platforms, our experimental data fitted well into a 1:1 host/guest stoichiometry.

For each receptor we noted higher association constants (K_a) for the smaller acetate anion (Table 1, entries 1, 3, and 5). The best results were obtained with compound **6**, which had the most spacious anion binding site (entries 5 and 6), while receptor **5**, with the smallest anion binding pocket, was characterized by the lowest association constants K_a (entries 3 and 4).

We next used receptors **4**–**6** to explore chiral carboxylic anions. We selected tetrabutylammonium salts[19] of mandelic acid and Boc-*N*-amino acids, such as tryptophan (Trp), phenylalanine (Phe), and valine (Val). The results obtained for both enantiomers of each chiral guest are presented in Table 2.

The association constants obtained in all complexations of chiral guests by chiral receptors were lower than for pairs of chiral receptors and achiral guests (cf. Table 1). However, the values obtained for chiral partners were high enough to be applied for our studies. Both receptors **4** and **5**, possessing smaller binding pockets, were not satisfactory for chiral recognition of two of our model chiral guests (mandelic acid and tryptophan), affording low K_D/K_L values (entries 1–4 and 5–8, respectively). The relatively

Table 1
Association constants (K_a) of hosts **4**–**6** with achiral guests in DMSO-d_6 + 0.5% H_2O

Entry	Host	Guest[a]	K_a[b] (M^{-1})	$\delta_{max\ NH\alpha}$[c]	$\delta_{max\ NH\beta}$[c]
1	**4**	AcO^-	1283	9.62	8.48
2	**4**	$PhCOO^-$	444	9.73	8.53
3	**5**	AcO^-	954	10.75	8.50
4	**5**	$PhCOO^-$	212	10.95	8.81
5	**6**	AcO^-	7907	10.36	8.69
6	**6**	$PhCOO^-$	780	10.64	8.45

[a] Added as the tetrabutylammonium salt.
[b] Estimated error less than 10%.
[c] Asymptotic change in the chemical shift obtained by nonlinear curve fitting.

Table 2
Association constants (K_a) of hosts **4**–**6** with chiral guests in DMSO-d_6 + 0.5% H_2O

Entry	Host	Guest[a]	K_a[b] (M^{-1})	K_D/K_L[c]	$\delta_{max\ NH\alpha}$[d]	$\delta_{max\ NH\beta}$[d]
1	**4**	*R*-PhCH(OH)COO^-	40	1.05	9.36	8.29
2	**4**	*S*-PhCH(OH)COO^-	38		9.43	8.24
3	**4**	D-TrpCOO^-	125	0.88	9.65	8.32
4	**4**	L-TrpCOO^-	141		9.67	8.28
5	**5**	*R*-PhCH(OH)COO^-	16	1.07	10.25	8.24
6	**5**	*S*-PhCH(OH)COO^-	15		10.21	8.17
7	**5**	D-TrpCOO^-	60	1.12	10.31	8.46
8	**5**	L-TrpCOO^-	51		10.49	8.36
9	**6**	*R*-PhCH(OH)COO^-	70	1.25	10.10	8.38
10	**6**	*S*-PhCH(OH)COO^-	56		10.15	8.47
11	**6**	D-TrpCOO^-	343	1.81	10.62	8.30
12	**6**	L-TrpCOO^-	190		10.41	8.45
13	**6**	D-PheCOO^-	483	2.07	10.47	8.28
14	**6**	L-PheCOO^-	233		10.33	8.37
15	**6**	D-ValCOO^-	644	2.42	10.51	8.29
16	**6**	L-ValCOO^-	266		10.35	8.44

[a] Added as the tetrabutylammonium salt.
[b] Estimated error less than 10%.
[c] For mandelate anions K_R/K_S was calculated instead of K_D/K_L.
[d] Asymptotic change in the chemical shift obtained by nonlinear curve fitting.

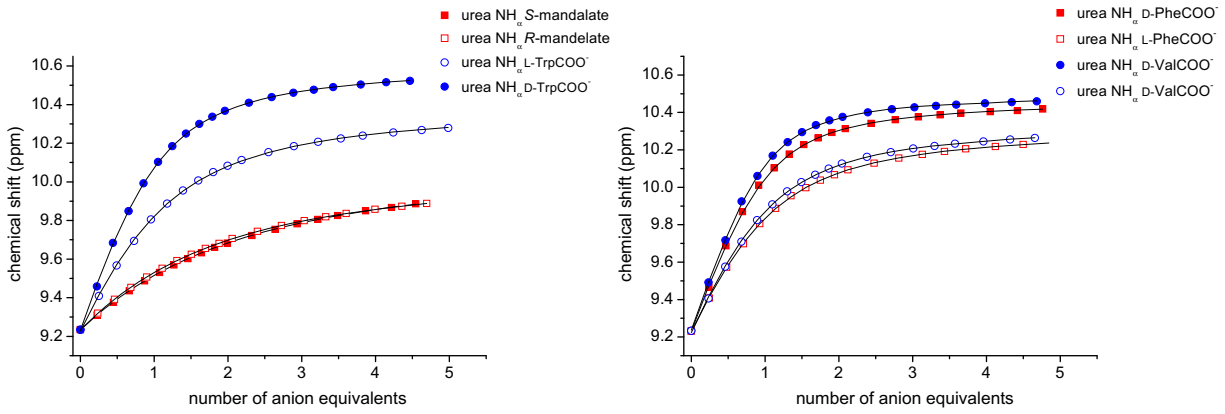


Figure 3. Comparison of the chemical shift changes for the urea NH_α proton of the ligand **6** upon addition of anions, *R*/*S* mandelates and L/D-tryptophan (left) and L/D-phenylalanine and L/D-valine (right). Points show experimental data; the black line is the fitted chemical shift data.

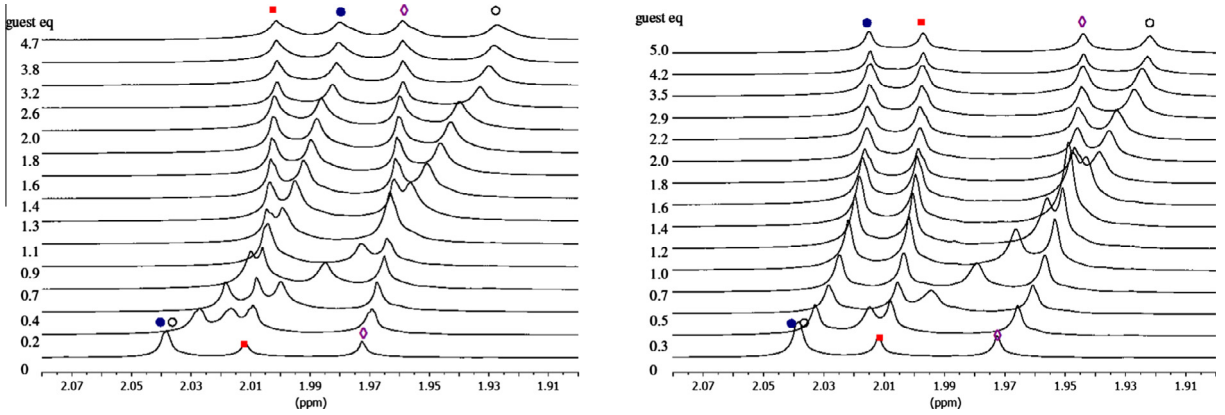


Figure 4. Excerpts of the stacked spectra from the ^{1}H NMR titrations of receptor **6** with tetrabutylammonium salts of Boc-L-tryptophan (left) and Boc-D-tryptophan (right) showing chemical shift changes of the acetyl groups.

good results for anthracene receptor **6** with mandelic acid (entries 9 and 10), encouraged us to investigate three representative amino acids as guests (entries 11–16), for which we obtained satisfactory results, with the best being for valine ($K_D/K_L = 2.42$). Figure 3 illustrates the relationship between the chemical shift changes for receptor **6** during titration with pairs of anions whose chirality was recognized and without chiral recognition (left), and between different pairs of anions with good chiral recognition (right).

Moreover, in the case of anions with chirality recognized by receptor **6**, noticeable chemical shift changes of the acetyl groups were observed. This behavior of the acetyl groups provided evidence that the sugar moieties in receptor **6** interact effectively with guest molecules. The chemical shift changes of the anion receptor **6** acetyl groups during titration with enantiomeric tryptophan anions are depicted in Figure 4. In each diastereomeric complex, the acetyl groups behaved differently. Such behavior was not seen for receptors **4** and **5**, which do not possess noticeable chiral recognition ability.

In conclusion, we have shown that the correct geometry of the anion binding pocket is required to make sugar-urea receptors effective in chiral recognition. Among three similar anion receptors **4**–**6**, only **6** showed noticeable chiral recognition for mandelic acid and amino acid anions. It appears that the optimum-sized anion binding pocket can pre-organize sugar moieties to interact effectively with guest molecules. This modulation of steric hindrance demonstrates itself in terms of the relative ratio of binding constants for small acetate and more sterically demanding benzoate (Table 1). This ratio was highest for receptor **6**, which possesses the most pronounced chiral recognition ability.

Acknowledgment

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14. *General procedure for receptor preparation:* 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl isocyanate (2 mmol) was added in one portion to a solution of the diamino derivative (1 mmol) in dry toluene or CH_2Cl_2 (10 ml) under an argon atmosphere. The mixture was stirred for 1–2.5 h at RT or at reflux, and then the solvent was evaporated and the crude product dissolved in CH_2Cl_2 (10 ml). The organic layer was washed with 0.1 M HCl (5 ml), saturated $NaHCO_3$ solution (5 ml), and H_2O (5 ml). The organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue was purified by flash chromatography (EtOAc/hexane/MeOH, 100:100:1, v/v).
15. *Compound* **4**: The reaction mixture was stirred at RT for 2 h in toluene. White powder (683 mg, 80%). mp 82–85 °C. [α] = +18.1 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 2H, NH), 7.50 (dd, *J* = 6.0, 3.6 Hz, 2H, ArH), 7.30 (d, *J* = 9.8 Hz, 2H, NH), 7.02 (dd, *J* = 6.1, 3.6 Hz, 2H, ArH), 5.37 (t, *J* = 9.5 Hz, 2H), 5.31 (t, *J* = 9.5 Hz, 2H), 4.91 (t, *J* = 9.7 Hz, 2H), 4.84 (t, *J* = 9.5 Hz, 2H), 4.15 (dd, *J* = 12.3, 4.8 Hz, 2H), 4.10–4.02 (m, 2H), 3.97 (d, *J* = 10.3 Hz, 2H), [14H in the region 5.37–3.97 belong to the sugar moieties], 2.00 (d, *J* = 1.0 Hz, 12H, Ac), 1.99 (s, 6H, Ac), 1.94 (s, 6H, Ac); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.05, 169.49, 169.45, 169.34, 154.66, 130.65, 123.75, 123.45, 78.46, 72.81, 71.71, 70.39, 68.04, 61.85, 20.54, 20.46, 20.41, 20.32; HRMS (ES+) *m*/*z* = 877.2581 $(M+Na)^+$, calcd for $C_{36}H_{46}N_4O_{20}Na$ = 877.2603; elemental analysis, calcd for $C_{36}H_{46}N_4O_{20}$: C 50.6, H 5.4, N 6.5, found: C 50.2, H 5.5, N 6.4.
16. *Compound* **5**: The reaction mixture was refluxed for 1 h in CH_2Cl_2. White powder (389 mg, 43%) mp 186–188 °C. [α] = +48.2 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 2H, NH), 7.71 (d, *J* = 7.5 Hz, 2H, ArH), 7.47 (d, *J* = 6.8 Hz, 2H, NH), 7.42 (t, *J* = 7.7 Hz, 2H, ArH), 6.78 (d, *J* = 9.7 Hz, 2H, ArH), 5.43–5.28 (m, 4H, sugar H), 4.99 (t, *J* = 9.7 Hz, 2H), 4.91 (t, *J* = 9.5 Hz, 2H), 4.37 (dd, *J* = 12.2, 3.6 Hz, 2H), 4.12–4.00 (m, 4H), [14H in the region 5.43–4.00 belong to the sugar moieties], 2.05 (s, 6H, Ac) 1.99 (s, 6H, Ac), 1.98 (s, 6H, Ac), 1.93 (s, 6H, Ac); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.20, 169.54, 169.49, 169.30, 155.32, 135.68, 134.05, 125.67, 125.41, 123.52, 122.76, 79.01, 72.95, 72.22, 70.52, 67.73, 61.49, 20.58, 20.52, 20.43, 20.36; HRMS (ES+) *m*/*z* = 927.2759 $(M+Na)^+$, calcd for $C_{40}H_{48}N_4O_{20}Na$ = 927.2760; elemental analysis, calcd for $C_{40}H_{48}N_4O_{20}\cdot H_2O$: C 52.1, H 5.5, N 6.1, found: C 52.1, H 5.4, N 5.9.
17. *Compound* **6**: The reaction mixture was refluxed for 2.5 h in CH_2Cl_2. Brown solid (525 mg, 55%) mp 235–238 °C. [α] = −22.5 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 2H, NH), 8.77 (s, 1H, ArH), 8.57 (s, 1H, ArH), 7.90 (d, *J* = 7.4 Hz, 2H, ArH), 7.77 (d, *J* = 8.4 Hz, 2H, ArH), 7.54–7.42 (m, 2H, ArH), 7.37 (d, *J* = 9.9 Hz, 2H, NH), 5.47 (dt, *J* = 11.3, 9.5 Hz, 4H), 4.99 (dt, *J* = 15.5, 9.6 Hz, 4H), 4.22 (dd, *J* = 12.2, 4.8 Hz, 2H), 4.16 (d, *J* = 9.8 Hz, 2H), 4.01 (d, *J* = 12.2 Hz, 2H), [14H in the region 5.47–4.01 belong to the sugar moieties], 2.04 (s, 12H, Ac), 2.01 (s, 6H, Ac), 1.98 (s, 6H, Ac), ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.04, 169.67, 169.54, 169.38, 154.38, 134.28, 131.66, 127.27, 125.73, 124.54, 122.64, 115.83, 113.66, 78.36, 72.78, 71.83, 70.34, 68.13, 61.96, 20.57, 20.51, 20.46, 20.37; HRMS (ES+) *m*/*z* = 977.2944 $(M+Na)^+$, calcd for $C_{44}H_{50}N_4O_{20}Na$ = 977.2916; elemental analysis, calcd for $C_{44}H_{50}N_4O_{20}\cdot 0.5H_2O$: C 54.8, H 5.3, N 5.8, found: C 54.7, H 5.4, N 5.7.
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19. Tetrabutylammonium salts of anions were prepared by the addition of 1 equiv of Bu_4NOH to 1 equiv of a carboxylic acid or amino acid dissolved in the MeOH. After evaporating the MeOH in vacuo, the salts were dried under high vacuum over P_2O_5.