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Sweet Anion Receptors: Recognition of Chiral Carboxylate Anions by D-Glucuronic-Acid-Decorated Diindolylmethane

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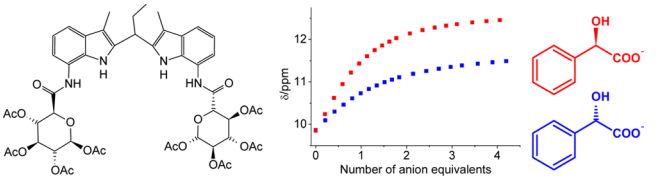
ABSTRACT



Anion receptors containing glucuronic acid were synthesized, and their anion binding ability studied. Chirality of anionic guests derived from mandelic acid and amino acids can be distinguished not only in terms of stability constants but also by significant differences in chemical shift changes for sugar moiety protons.

Molecular recognition, especially its chiral variants, plays an important role in many natural systems, for instance, the 2-deoxyribose-driven structure of the DNA double helix and the α-amino-acid-driven secondary structure of proteins.[1] Recently, much attention has been paid to chiral recognition and sensing by artificial systems containing stereogenic elements.[2] So far, two general approaches to these problems have been taken. The first one uses noncovalent host/guest interactions, which leads to chirality transfer to a host molecule having a signaling unit.[3] The other one applies to a covalent attachment of chiral moiety to a host backbone. The latter receptor type can recognize chiral guests by the difference in stability constants between the two diastereomeric complexes (*R*)-host/(*R*)-guest and (*R*)-host/(*S*)-guest.[4] In particular, hosts that can differentiate chiral anions have received increasing attention owing to the importance of anions in nature,[5] enantiomer separation processes,[6] applications in organocatalysis,[7] etc.

The field of anion recognition is relatively recent (when compared with early studied cations), having been explored seriously in the last 20 years, and has led to development of many neutral receptor motifs.[8] A common strategy involves the use of H-bond donors such as pyrroles,[9] indoles,[9] amides,[10] ureas,[11] etc., to coordinate a potential anionic

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guest. Among various anion binding pockets, derivatives of 2,2′-diindolylmethane of type **1** (Figure 1) draw a special attention for researchers seeking to construct an effective receptor for anions.[12] Such receptors have proven efficient even in very competitive solvents such as DMSO mixtures with water or methanol.[13] The diindolylmethane system has been also used as a selectivity controlling unit in transition-metal-catalyzed hydrogenation and hydroformylation reactions.[14]

Apart from amino acids, hydroxy acids, and terpenes, saccharides are an important part of the chiral pool.[15] They play a crucial role in many processes such as asymmetric synthesis and catalysis,[16] chiral recognition,[17] and chromatographic separation of enantiomers.[18] As such, simple monosacharides look to be the most potent source of chirality for planned receptors, useful in chiral recognition studies.

In this study we decided to pursue the idea of chiral recognition of anions by neutral receptors by synthesizing a hybrid, sugar-decorated receptor containing a diindolylmethane unit. As compound **1** can be easily functionalized by the formation of amide, readily available peracetylated D-glucuronic acid (**2**)[19] (Figure 1) was chosen to provide a source of chirality. Anion receptor **3** was prepared by treating 7,7′-diamino-2,2′-dindolylmethane (**1**) with acid chloride of **2** in 68% yield. The reference receptor **4** was synthesized in a similar manner from 7-aminoindole (Figure 1).

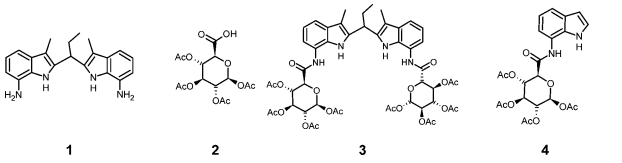

Figure 1. Structures of 7,7′-diamino-2,2′-dindolylmethane (**1**), peracetylated D-glucuronic acid **2**, and chiral anion receptors **3** and **4** investigated in this study.

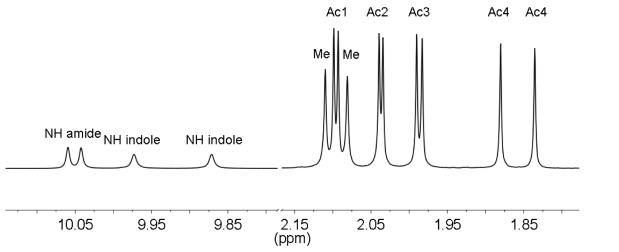

Figure 2. Fragment of 600 MHz ^{1}H NMR spectrum of receptor **3** in DMSO-d_6.

The structure of receptors **3** and **4** was confirmed by ^{1}H and ^{13}C NMR spectra. In the case of receptor **3**, two sets of signals were observed in the ^{1}H NMR spectrum for amide and indole NH's, δ = 9.87 and 9.97 ppm (for indole NH) and δ = 10.04 and 10.07 ppm (for amide NH), respectively (Figure 2). Protons H^1 and H^5 in the glucopyranose ring appeared as two well separated doublets, similarly as for acetyl and methyl groups of diindolylmethane. This has enabled complete assignment of ^{1}H and ^{13}C NMR spectra using COSY, HSQC, and HMBC experiments (for details see Supporting Information).

The binding properties of compounds **3** and **4** were studied under ^{1}H NMR controlled titrations at a constant concentration of receptor ($\sim 1 \times 10^{-2}$ M). In all cases, binding affinities were measured by anion complexation-induced resonance shift change upon addition of anionic guests in the form of tetrabutylammonium salts.[20] Substantial changes in the NMR spectra could be observed not only for indole and amide NH's, but also for protons belonging to the glucopyranose ring as well as to acetyl groups.

At the beginning of the binding investigations, receptor **3** was studied in order to compare the effect of chiral barrier on binding affinities. For this experiment, achiral anions of typical geometries, chloride, dihydrogenphosphate, acetate, and benzoate, were used, and the results are collected in Table 1.

Table 1. Association Constants and NH Shift Changes of Protons Involved in Hydrogen Bonding of Receptor **3** With Achiral Guests in DMSO-d_6 + 0.5% H_2O

anion[c]	K/M^{-1}[a]	$\Delta\delta_{max}$/ppm[d] NH indole	$\Delta\delta_{max}$/ppm[d] NH indole	$\Delta\delta_{max}$/ppm[d] NH amide	$\Delta\delta_{max}$/ppm[d] NH amide
Cl^-	95.1	1.55	1.39	0.33	−0.12
$H_2PO_4^-$	1500[b]	2.72	2.41	1.94	1.89
$PhCOO^-$	2421	2.75	2.38	0.71	0.55
AcO^-	>10^4	2.71	2.56	0.81	0.68

[a] Estimated error less than 10% [b] Slow binding equilibrium. [c] Used as tetrabutylammonium salts. [d] Asymptotic change in chemical shift obtained by nonlinear curve fitting.

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The addition of tetrabutylammonium chloride to receptor **3** causes a downfield shift for one of the amide NH protons and an upfield shift for the other (Table 1, entry 1). It appears that the receptor cavity is to small to accommodate the spherical chloride anion, which moreover suggests that receptor **3** lacks symmetry. Titration of receptor **3** with dihydrogenphosphate revealed slow complexation equilibrium on the NMR time scale (entry 2). In the case of two carboxylates, sterically demanding benzoate showed a binding constant of 2476 M^{-1} (entry 3), while acetate, the least spatially demanding, was found to bind anion receptor **3** more strongly with binding constant greater than 10 000 M^{-1} (entry 4).

The enantioselective recognition characteristics of hosts **3** and **4** were probed in the presence of model chiral anionic guests *S*(+)-mandelate ((*S*)-MA) or *R*(−)-mandelate ((*R*)-MA) in various solvents. In an effort to determine the binding constants for **3** with (*S*)-MA and (*R*)-MA, titrations were performed under standard conditions (DMSO-d_6 + 0.5% H_2O at 298 K), and the results are collected in Table 2.

Under the above conditions, receptor **3** showed a substantial decrease in binding affinity, roughly 10 times lower for enantiomeric mandelates, as compared with benzoate, and the binding constants were different for both enantiomers (cf. Table 1, entry 3 and Table 2, entries 1 and 2). (*R*)-MA was found to be bound with a larger binding constant, (*S*)-MA with smaller.

Table 2. Chiral Recognition of Mandelic Acid Anions

entry	anion[a]	ligand	K/M^{-1} [b]	solvent	K_R/K_S
1	(*S*)-MA	**3**	119	DMSO-d_6 + 0.5% H_2O	1.95
2	(*R*)-MA	**3**	233	DMSO-d_6 + 0.5% H_2O	
3	(*S*)-MA	**3**	58.6	DMSO-d_6 + 5% H_2O	2.01
4	(*R*)-MA	**3**	118	DMSO-d_6 + 5% H_2O	
5	(*S*)-MA	**3**	6147	MeCN-d_3	–[c]
6	(*R*)-MA	**3**	>10^4	MeCN-d_3	
7	(*S*)-MA	**4**	22.0	DMSO-d_6 + 0.5% H_2O	0.94
8	(*R*)-MA	**4**	20.7	DMSO-d_6 + 0.5% H_2O	
9	(*S*)-MA	**4**	693	MeCN-d_3	1.07
10	(*R*)-MA	**4**	740	MeCN-d_3	

[a] Anions used as tetrabutylammonium salts. [b] Estimated errors less than 10%. [c] Binding constants too large to be accurately compared.

When chemical shift changes were tracked for indole protons, after the addition of mandelates, the titration curves showed a very interesting pattern: for the weaker bounded (*S*)-MA both indole protons behaved in the same way and exhibited similar shift changes (δ_{max}) of 11.81 and 12.15 ppm, respectively, after anion addition. On the other hand, for (*R*)-MA, the indole protons swapped places: the one proton that was the most upfielded in the free ligand (δ = 9.87 ppm) had the largest chemical shift after addition of (*R*)-MA (12.76 ppm), 0.8 ppm more than the second indole proton (11.94 ppm) (Figure 3).

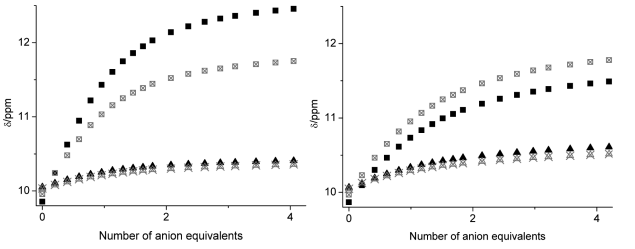

Figure 3. Comparison of binding isotherms of receptor **3** and *R*(−)-mandelate (left) and *S*(+)-mandelate (right) tetrabutylammonium salts in DMSO-d_6 + 0.5% H_2O. Chemical shift changes for indole (rectangle) and amide (triangle).

In addition, smaller but fairly observable chemical shift changes of protons in the glucopyranose ring, after anion addition, suggest different conformational changes of the receptor for each complex. For example, protons H^5 (neighboring to the carbonyl group of glucuronic acid), after addition of (*S*)-MA, were both down shielded by about 0.1 ppm. After addition of (*R*)-MA only one proton was down shielded. The protons H^5 were not differentiated by association of host **3** with achiral acetate anion (Figure 4).

Further, the structure of receptor **3** complexes with mandelates was investigated by 2D ROESY technique. ROESY spectrum of the receptor **3** and (*R*)-MA system shows correlations between aromatic protons of guest and sugar protons (H^3 and H^5). For weaker bounded (*S*)-MA additional cross peaks can be also found indicating deeper penetration of an anion into receptor **3** cavity. This is also reflected by different cross peak signals arising from mandelates α-proton and sugar moiety protons. The main correlation for (*R*)-MA was from proton H^5 located in a proximity to anion binding pocket. On the other hand, the main cross peak for (*S*)-MA α-proton was from hydrogen H^1 in anomeric position (for details see Supporting Information). Such results clearly suggest two distinct modes of anion binding. It may be concluded that receptor **3** geometry forces (*S*)-MA to interact with both sugar moieties while (*R*)-MA interacts only with one pyranose ring. This may also explain chemical shift changes of protons H^5 during titrations with mandelates shown in Figure 4.

To investigate the influence of the solvent, titrations of **3**, carried out in DMSO-d_6 + 5% H_2O and in MeCN-d_3, were compared. Increasing water content to 5% caused an expected decrease in binding constant for (*S*)-MA and (*R*)-MA (Table 2, entries 3 and 4), but it did not diminish the chiral recognition ability of receptor **3**. On the other hand, the use of a less polar solvent such as acetonitrile resulted in binding constants too large to be quantified

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(20) Binding constants were obtained using nonlinear regression of experimental data using the program HypNMR. All data fit well into a 1:1 binding model, and binding stoichiometry has additionally been confirmed by Job plots (for details see Supporting Information).

($K > 10\,000\ M^{-1}$, entries 5 and 6). The reference compound **4** was not able to differentiate between enatiomeric mandelates, with binding constants identical within the experimental error (entries 7−10).

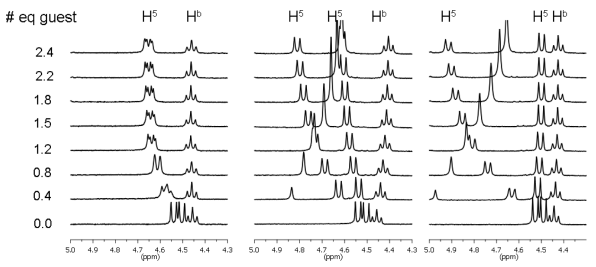

Figure 4. Stacked plots from ^{1}H NMR titrations of host **3** with acetate (left) *S*-mandelate (middle) and *R*-mandelate (right). H^5 protons in glucopyranuronic ring, H^b bridging proton in diindolylmethane in DMSO-d_6 + 0.5% H_2O.

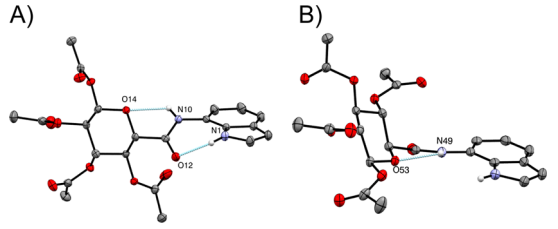

Figure 5. Fragments A and B in crystal structure of receptor **4** in *anti* and *syn* conformation. The atomic displacement parameters are at 50% probability level. Hydrogen atoms have been omitted for clarity.

In order to gain insight into the structural factors responsible for chiral recognition, we tried to grow crystals of **3** suitable for X-ray analysis, yet despite many attempts we were unable to obtain a single crystal. We therefore turned our attention to compound **4**, which gave a single crystal appropriate for X-ray analysis. There are two distinct motifs, shown in Figure 5A and B, present in the same crystal structure and differing in conformation of the pyranose ring with respect to an indole fragment (*syn* vs *anti*).

Consideration of the *anti* conformation of the compound **4** (Figure 5A) revealed that amide NH as well as indole NH were involved in intramolecular hydrogen bonding interactions. The indole NH participates in a hydrogen bond with the carbonyl group of glucuronic acid (d_{N1-O12} = 2.743 Å), while amide NH is involved in a hydrogen bond with the anomeric oxygen atom ($d_{N10-O14}$ = 2.706 Å). A similar observation was reported earlier for secondary anilides of glucuronic acid.[21] In the *syn* conformation (Figure 5B) amide NH, as in former case, is involved in intramolecular hydrogen bonding ($d_{N49-O53}$ = 2.612 Å) with the anomeric oxygen atom. The glucopyranose ring is almost perpendicular to the indole moiety and thus shields one face of compound **4**. These two motifs are connected by a hydrogen bond of indole NH fragment A and the acetyl group of fragment B, forming 1-D hydrogen bond network. These intramolecular hydrogen bonds look to play a crucial role in preorganizing the host molecule.

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Table 3. Chiral Recognition of Amino Acids by Receptor **3**

entry	anion[a]	K/M^{-1} [b]	K_R/K_S
1	Boc-*N*-D-Trp-COO^-	227	2.57
2	Boc-*N*-L-Trp-COO^-	88.0	
3	Boc-*N*-D-Val-COO^-	305	2.42
4	Boc-*N*-L-Val-COO^-	126	
5	Boc-*N*-D-Phe-COO^-	224	2.40
6	Boc-*N*-L-Phe-COO^-	93.3	

[a] Anions used as tetrabutylammonium salts. [b] Stability constants in DMSO-d_6 + 0.5% H_2O obtained from ^{1}H NMR titrations. Estimated errors less than 10%.

To broaden the field of our investigation, we decided to use several *N*-protected amino acid anions as guests. Three *N*-Boc-protected amino acids were used, tryptophane, valine, and phenylalanine, and the results are shown in Table 3.

The anion receptor **3** prefers D-enantiomers in all cases studied. Stability constants for these enantiomers were in every case (Table 3, entries 1−6) at least twice as big as for L-amino acids. For titrations of receptor **3** with amino acids, similar characteristics were observed to those obtained for the recognition of enantiomeric mandelates.

To summarize, receptor **3**, being a sugar derivative of diindolylmethane was synthesized and characterized for the first time. We demonstrated the chiral recognition ability of receptor **3** and its preference for carboxylates having *R* configuration on the α carbon atom. Additionally, we found that enantiomeric anions can be differentiated not only by the difference in stability constants but also by chemical shift changes after the addition of enantiomeric guests to receptor **3**.

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Supporting Information Available. Complete experimental procedures, Job plots, description of ^{1}H NMR titrations, crystallographic data for **4** (CCDC 943660). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.