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Selective Anion Sensing by Chiral Macrocyclic Receptors with Multiple Hydrogen-Bonding Sites

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S Supporting Information

ABSTRACT: Chiral macrocycles featuring sulfonamide and/or amide groups as anion-binding sites were synthesized. X-ray crystal structures and DFT calculations have shown that they adopt different conformations that may lead to unique binding behavior. Indeed, various anions could be sensed by their colorimetric and/or fluorescence signal output. The chiral macrocycles showed chiral recognition for chiral anions. Furthermore, a multisensor array with two or four chiral receptors discriminated seven phosphate anions (AMP, ADP, ATP, CMP, GMP, Pi, and PPI) with 100% classification accuracy.

Chiral anions are species ubiquitous in nature where they play a number of key roles.¹ Therefore, highly selective and sensitive anion receptors and sensors are useful in a number of chemistry disciplines including biochemistry, physiology, and analytical chemistry.^{1,2} The importance of anion receptors as organocatalysts has been widely recognized.³ Consequently, new chiral anion receptors are highly desired. Anion–receptor recognition can be driven by hydrogen bonding, electrostatic interaction, and metal coordination.^{4–10} Hydrogen bonding, due to its relative strength (10–30 kJ/mol) and, most importantly, donor→acceptor directionality, occupies an important place in the receptor design. Various functional groups, such as amide,^{5a,d,e,6} sulfonamide,^{5c,7} pyrrole,⁸ urea,^{5c,9} and triazole,^{5b,d,10} have been used as hydrogen-bond donors. Wide implementation of chiral receptors for the detection and separation of anions is hindered by the lack of methods suitable for high-throughput screening. For example, ion chromatography is popular but has drawbacks, such as cost, and requires trained personnel. In contrast, optical methods such as UV–vis and fluorescence methods are generally sensitive and amenable to cost-effective high-throughput analysis. Toward this point, chiral anion receptors displaying analyte-induced change in color and/or fluorescence are required.

Chirabite-AR (**1**, Figure 1), a chiral macrocyclic host, has multiple H-bonding sites in the cavity as well as a fluorescent binaphthyl moiety enabling us to follow the recognition process using fluorescence. Recently, we have reported that **1** can bind various neutral guests.¹¹ In view of the importance of anion recognition we decided to explore the binding ability of **1** for chiral anions. Because the two amide NH groups of the lower segment of **1** are the principal H-bond donor sites,¹¹ we also

Figure 1. Chemical structures of Chirabite-AR (**1**) and sulfonamide congeners **2** and **3**. Only (*R*)-enantiomers are shown.

designed two sulfonamide congeners **2** and **3** (Figure 1) to strengthen the H-bond donor ability. The pyridine rings of **2** have been replaced by the benzene rings to yield receptor **3** because the Lewis basic pyridine rings of **2** might be unfavorable for the binding of anions (Lewis bases) and because fluorescence intensity might increase. The binaphthyl moiety is expected to impart chiral recognition in **1–3**.^{12,13} Here we report on the synthesis of **2** and **3**, X-ray crystal structures of **1** and **3**, and the anion recognition behavior of **1–3**. A multisensor array with (*R*)/(*S*)-**2** and (*R*)/(*S*)-**3** discriminated seven phosphate anions (AMP, ADP, ATP, CMP, GMP, Pi, and PPI) with 100% classification accuracy.

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Macrocycle **1** was prepared according to the literature,^{11a} while **2** and **3** were newly synthesized (Supporting Information (SI)). Single crystals of **1** and **3** were obtained by recrystallization from $\text{CHCl}_3/\text{EtOAc}$ and $\text{CHCl}_3/\text{hexane}$, respectively, and were subjected to X-ray crystallographic analysis (Figure 2). Figure 2 shows that **1** has a conjugated π -

Figure 2. X-ray crystal structures of (a) (R)-**1** and (b) (R)-**3**.

plane in the lower segment, to which the binaphthyl moiety is orthogonal, and that the four amide NH groups are directed inside the macrocycle cavity. This structure is quite similar to that obtained by *ab initio* calculations.^{11b} Interestingly, a molecule of EtOAc used as solvent is included in the cavity of **1**, forming a rotaxane-like structure, where the O-atom of EtOAc is H-bonded with the amide NH groups of **1**. In contrast, **3** adopts a folded conformation with the binaphthyl moiety partially covering one side of the cavity; the four NH groups of **3** are not directed to the side of the cavity. This is due to the presence of the two sulfonamide groups intervening between the three π -systems in the lower segment. A CHCl_3 molecule is partially included in the calix-like cavity of **3** by CH/π and van der Waals interactions. DFT calculations indicated that **3** adopts the folded conformation even in the absence of the CHCl_3 molecule (SI). The solid state and DFT-optimized structures suggest that **1** and **3** would show quite different binding behavior. DFT calculations suggest that **2** adopts a similar but more folded conformation as compared with **3** (SI).

Initially, the binding of anions to the receptors was confirmed by electrospray ionization (ESI) mass spectrometry. The ESI-MS spectra showed the peaks of both the parent macrocycle and the anion–receptor complex (SI). Next, we attempted to determine the binding affinity of **1–3** for simple anions in $\text{DMSO}-d_6$ using NMR titrations. However, the nitrobenzamide and sulfonamide NH signals of **1–3**

disappeared upon addition of anions such as F^- , AcO^- , CN^- , and H_2PO_4^- , and in the case of F^- a new signal appeared at 16.1 ppm, which is assigned to HF_2^- . This suggests that the nitrobenzamide and sulfonamide NH groups in **1–3** may have been deprotonated. At the same time we noticed that solutions of receptor **1** were colored differently upon addition of anions, namely strong bases such as F^- , N_3^- , AcO^- , CN^- , and H_2PO_4^- . In particular, the addition of CN^- gave a deep reddish purple solution of **1**. Although CN^- -induced color changes have been reported for several receptors,¹⁴ the present color change is one of the most dramatic changes. On the other hand, **2** and **3** experienced little or no color change upon addition of anions. Instead, we found that **2** and **3** exhibited blue fluorescence upon UV irradiation (365 nm), although **1** did not. The absolute fluorescence quantum yields of **1**, **2**, and **3** in DMSO (excitation at 300 nm) were <1%, 6.9%, and 19.4%, respectively. It is likely that fluorescence from the binaphthyl group in **1** is quenched by the nitrophenyl group in **1**. Interestingly, the fluorescence of **2** and **3** was quenched by the addition of F^- , N_3^- , AcO^- , CN^- , or H_2PO_4^- (Figure 3).

Figure 3. (a) Color changes of **1** (15 mM) upon addition of anions (5.5 equiv) in DMSO. Fluorescence changes of (b) **2** (15 mM) and (c) **3** (15 mM) upon addition of anions (5.5 equiv) in DMSO. λ_{ex} = 365 nm. All anions were used as tetrabutylammonium salts.

Among them, N_3^- quenched the fluorescence of **2** but quenched that of **3** only slightly. Thus, N_3^- could be discriminated by using both **2** and **3**. Importantly, Figure 3 also indicates that **2** and **3** show slightly different responses even to AcO^- , CN^- , and H_2PO_4^- , which helps us to selectively detect these anions by using both **2** and **3**.

Because of the biological importance, we turned our attention to the anions of AMP, ADP, ATP, CMP, GMP, H_3PO_4 (Pi), and $\text{H}_4\text{P}_2\text{O}_7$ (PPI) (Figure 4). To evaluate the binding abilities of **1–3**, we determined the binding constants of **1–3** for the AMP and CMP anions by the NMR titration experiments (Table 1).^{11a,b} (R)-**1** showed no appreciable affinity for AMP and CMP anions, and the binding constants could not be determined. In contrast, (R)-**2** and (R)-**3** showed appreciable affinities for the AMP and CMP anions. Because the nucleotide anions used in this study are chiral, they are expected to show different affinities for (R)- and (S)-receptors. Indeed, AMP, bearing a purine base, exhibited a slightly higher affinity for (S)-**2**, while CMP, bearing a pyrimidine base,

Figure 4. Chemical structures of guests. The corresponding anions were used as tetrabutylammonium or sodium salts.

Table 1. Binding Constants of Hosts 1–3 for Anionic Nucleotides^a

receptor	K_a (M ⁻¹) ^b enantioselectivity ^c			
	AMP		CMP	
(R)-1	— ^d	—	— ^d	—
(R)-2	238	1.1 (S)	286	1.5 (R)
(S)-2	259		190	
(R)-3	258	1.1 (R)	270	1.2 (S)
(S)-3	228		326	

^aIn DMSO-*d*₆ at 22 °C. All anions were added as tetrabutylammonium salts. ^bThe K_a values were calculated by the nonlinear least-squares method. ^cRatio of the K_a values. ^dThe K_a value was too small to determine.

showed a 1.5-fold higher affinity for (R)-2. On the other hand, interestingly, AMP exhibited a higher affinity for (R)-3, while CMP showed a higher affinity for (S)-3. MM calculations suggest that the nucleotide anions take U-shaped conformations and that, in addition to double hydrogen bonds between the phosphate anion and the sulfonamide/amide groups, the nucleobase of AMP or CMP makes contact with the binaphthyl moiety of 2 or 3, which may lead to enantioselective binding (SI). Despite the small differences in affinity, we envisioned that 2 and 3 might sense and amplify the differences of various phosphate anions via fluorescence quenching as seen in Figure 3b and c. We performed fluorescence titrations. Figure 5 displays dramatic fluorescence spectral changes for (R)-2 upon addition of the AMP anion in an aqueous DMSO solution.¹⁵

Figure 5. Fluorescence titration of (R)-2 by AMP in an aqueous DMSO solution (water/DMSO = 3:97, v/v). λ_{ex} = 304 nm. $[AMP]$ = $(0-1.0) \times 10^{-4}$ M.

All of the above fundamental results encouraged us to investigate whether the multisensor array¹⁶ with (R)/(S)-2 and (R)/(S)-3 could discriminate the seven anions of AMP, ADP, ATP, CMP, GMP, Pi, and PPi (Figure 4). The assay was performed in the standard 1536-well microplate, the data were recorded with an automatic plate reader, and the output data were analyzed using linear discriminant analysis (LDA)¹⁷ with leave-one-out cross-validation. To our delight, LDA exhibited an excellent discrimination capability for these biologically important phosphates with 100% correct classification of all 160 data-points (20 data points for each of the seven analytes and control) (Figure 6). It should be noted that this four-sensor array could discriminate not only the number of phosphates but also types of base moieties.

Figure 6. LDA canonical score plots for the response of (R)-2, (S)-2, (R)-3, (S)-3 sensor array (the four-sensor array) to seven phosphates in an aqueous DMSO solution (water/DMSO = 1:9, v/v). The cross-validation routine shows 100% correct classification. $[guest]$ = 4.0×10^{-5} M.

Part of the motivation of this work was to establish the correlation between the structural feature of each sensor and the discriminatory power of the multisensor array, an effort that could provide important information for developing an effective analytical method for nucleotides. Toward that end, we analyzed the discriminatory power of the sensor arrays with various combinations of hosts. First, we attempted to discriminate the seven phosphates by using fluorescence responses arising from only one host. However, we could not achieve 100% correct classification. In contrast, the excellent resolution with 100% correct classification was achieved by the combination of two hosts ((R)-2 and (S)-2). Furthermore, the combination of (R)-2 and (R)-3 was also able to discriminate the seven phosphates with 100% classification. This implies that discrimination of the seven phosphates requires one enantiomeric host pair or a combination of two types of receptor (the two-sensor array), probably due to differential responses based on diastereomeric interactions as demonstrated in Table 1.

In summary, new macrocycles 2 and 3, with sulfonamide and amide groups in the cavity, were synthesized. The parent receptor 1 could detect anions by coloration, while 2 and 3 could detect anions by quenching of the fluorescence. As expected, the binding constants indicated that 2 and 3 showed higher affinities for anions than 1. Receptors 1–3 showed chiral recognition for chiral anions. Furthermore, we developed a sensor array using 2 and 3 capable of distinguishing seven phosphates in an aqueous DMSO solution with 100% classification accuracy. Further exploration of the microarray

using our macrocyclic hosts for chiral anion sensing is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The details of synthesis and characterization of new compounds, X-ray data, DFT and MM calculations, determination of binding constants, MS data, experimental details of microarray, canonical scores plots, and jackknifed classification matrices. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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