Enantioselective Recognition of Calix[5]arene-based Artificial Receptor Bearing Chiral Macrocycle for Chiral Ethyltrimethylammonium Salts

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(Received June 14, 2007; CL-070647; E-mail: haino@sci.hiroshima-u.ac.jp)

Calix[5]arene-based artificial receptor **1** capped with chiral macrocycle **4** was synthesized and showed strong binding toward ethyltrimethylammonium salts via cation/π and hydrogen-bonding interactions. The calix[5]arene cavity provided the dissymmetric guest-binding environment in which chiral guests **6**–**14** were encapsulated in an enantioselective fashion.

Enantioselective recognition is a long-standing issue in the field of supramolecular chemistry.[1,2] It involves preferred recognition of an enantiomeric molecule out of its racemic mixtures. Discrimination of a chiral center of a molecule requires additional constraint, creating an effective chiral environment, compared to achiral molecular recognition. Much effort has been devoted to employing the steric and electronic interactions to create a chiral environment in which one of the racemic mixtures can be preferentially bound.

We have reported calix[5]arene-based artificial receptors,[3] capable of taking up a guest molecules into its cavity through noncovalent interactions: van der Waals, CH/π, etc. In this paper, we present chiral calix[5]arene-based receptor **1** equipped with chiral macrocycle **4**[4] of isophthalic acid and (1*S*,2*S*)-*trans*-1,2-diaminocyclohexane, providing additional constraint to produce the dissymmetric guest-binding space in the calix[5]arene cavity (Figure 1).

Synthesis of **1** started from known diaminocalix[5]arene **2**[5] (Figure 2). Coupling reaction of **2** and *N*-*t*-butyloxycarbonyl-L-leucine with 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide and 1-hydroxy-7-azabenzotriazole in dichloromethane proceeded at 40 °C to give **3** in 38% yield (Figure 2). Treatment of **3** with trifluoroacetic acid in dichloromethane afforded the ammonium salt, which was subjected to coupling reaction with **4** in the presence of diisopropylethylamine at 60 °C in dimethylformamide to furnish desired host **1** in 32% yield (Figure 2).

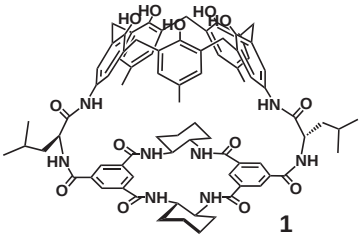


Figure 1. Chiral calix[5]arene-based receptor **1**.

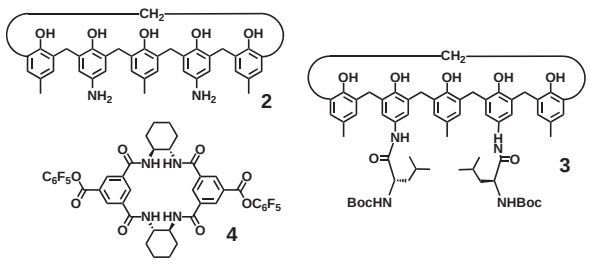
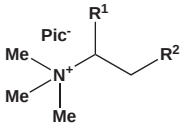


Figure 2. Synthetic intermediates.



5: R^1=H, R^2=OAc
6: R^1=Ph, R^2=H
7: R^1=Ph, R^2=OAc
8: R^1=Ph, R^2=OH
9: R^1=Me, R^2=OAc
10: R^1=Me, R^2=OH
11: R^1=*i*-Pr, R^2=OAc
12: R^1=*i*-Pr, R^2=OH
13: R^1=CH_2Ph, R^2=OAc
14: R^1=CH_2Ph, R^2=OH

Figure 3. Cationic guests.

Chemical structures of all guests used in the binding studies with **1** are shown in Figure 3. The complexation behavior of achiral guest **5** with **1** was studied in order to gain an insight into its binding manner. Titration experiment of **5** with **1** at 293 K in chloroform was carried out using absorption spectroscopy. Job's plots confirmed the 1:1 stoichiometry of the host–guest complex. The curve-fitting analysis gave an association constant (K_a: $13000 \pm 1000\,M^{-1}$) (Table 1). The structural information of the complex was given by ^1H NMR titration experiment in chloroform–d_1. Upon the addition of **1** to a solution of **5**, the guest protons showed the significant upfield shifts (Me–N: −2.13, N–CH_2: −2.16, OCH_2: −1.51, C(O)Me: −0.34 ppm). Characteristic upfield shifts of the methyl and methylene protons adjacent to the nitrogen atom, and the decreased values of the protons distant from the nitrogen atom, indicate that the trimethylammonium group stays deep inside the cavity of the calix[5]arene to create cation/π interaction.[6]

Enantioselective recognition of **1** for guests **6**–**14** was studied. The encapsulation of **6** was driven only by cation/π interaction to the π-basic cavity of **1** in an enantioselective fashion. It indicated that **6** recognized the dissymmetric binding environment of **1** only by noncovalent interactions. The preferential

Table 1. Association constants K_a ($dm^3 \cdot mol^{-1}$) of guests **5**–**14** at 298 K in chloroform

Guest	K_a	*R*:*S*	Guest	K_a	*R*:*S*
5	13000 ± 1000		***R*-10**	4700 ± 200	2.2:1.0
***R*-6**	2400 ± 100	1.0:2.0	***S*-10**	2100 ± 200	
***S*-6**	4900 ± 200		***R*-11**	17000 ± 2000	1.9:1.0
***R*-7**	9800 ± 1000	1.0:1.5	***S*-11**	9000 ± 1000	
***S*-7**	15000 ± 2000		***R*-12**	21000 ± 1000	2.4:1.0
***R*-8**	12000 ± 1000	1.0:1.4	**S-12**	8600 ± 800	
***S*-8**	17000 ± 2000		***R*-13**	32000 ± 5000	1.6:1.0
***R*-9**	20000 ± 1000	2.0:1.0	***S*-13**	20000 ± 2000	
***S*-9**	10100 ± 800		***R*-14**	26000 ± 3000	3.7:1.0
			***S*-14**	7100 ± 900	

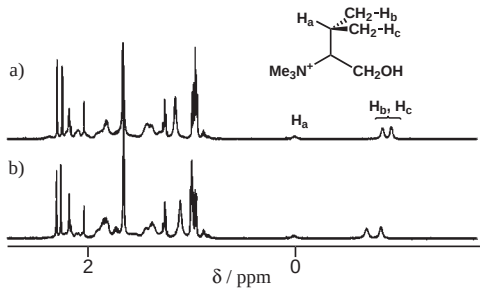


Figure 4. ^{1}H NMR spectra of a) *R*-**12** and b) *S*-**12** (2.0×10^{-3} mol/L) with 1.5 eq. of **1**.

binding of the R isomers to **1** was observed for **9**–**14**. 2-Hydroxyethyltrimethylammonium salts showed slightly higher selectivity than the corresponding 2-acetoxy salts, suggesting that the hydrogen-bonding interaction between the host and guest most likely play a key role in the chiral discrimination. The highest enantioselectivity was achieved in the complexation between **14** and **1**.

The complexation induced shift changes of the guest protons were measured when **12** was encapsulated within the cavity of **1** (Figure 4). In both isomers, the substituent protons H_a, H_b, and H_c appeared in the clear window higher than 0.5 ppm, and their complexation induced upfield shifts were more than -2 ppm, indicating that the protons stayed in the highly shielded region of the five phenolic rings of the calix[5]arene.

While the structures of the complexes remain to be determined, molecular modeling of the host–guest complex is informative. The molecular mechanics calculation of the complexes of **1** with *R*-**12** or *R*-**14** was carried out by MacroModel V.9.1 using OPLS2005 force field together with the GB/SA solvation for $CHCl_3$.[7] In the complex structure of **1** and *R*-**12**, the guest hydroxy group forms the hydrogen bond to one of the carbonyl groups of the macrocyclic amide (Figure 5a). The trimethylammonium and the isopropyl groups stay deep inside the calix[5]arene cavity, facing toward the phenolic rings. The calculated structure of the host–guest complex rationalized that the proton signals of the isopropyl group showed the large upfield shifts. Apparently, the steric interaction between the isopropyl group and the aromatic rings should drive the enantioselective binding of the guest within the dissymmetric cavity of the host. The calculated result of the complex with *R*-**14** suggests that the guest creates the hydrogen-bonding and cation/π interactions to **1** as seen in the complex with *R*-**12** (Figure 5b). In addition, the guest aromatic ring adopts the parallel arrangement to one of the phenolic rings to form π–π stacking interaction, which should play a key role in the enantioselective recognition within the dissymmetric cavity.

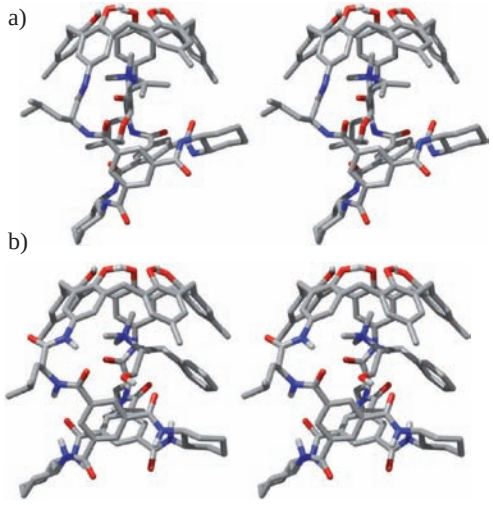


Figure 5. Stereoplots of the calculated complex structures of **1** with a) *R*-**12** or b) *R*-**14**.

In summary, we demonstrated the synthesis and enantioselective recognition of calix[5]arene-based chiral host **1**. The host took up the ethyltrimethylammonium salts into its π-basic cavity via cation/π, hydrogen-bonding, and van der Waals interactions. The chiral guests recognized the dissymmetric cavity of the host to provide the enantioselective binding.

This work was supported by a Grant-in-Aid for Scientific Researches (B) and in a Priority Area "Super-Hierarchical Structures" for the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are grateful to Inamori, Kurata, and Ogasawara Foundations for financial support.

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Published on the web (Advance View) July 14, 2007; doi:10.1246/cl.2007.1054