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Communications

Molecular Engineering 3. Enhanced Molecular Recognition Properties of Lariat-Type Chiral Calix[4]crowns Having Binaphthyl Crown Unit on the Lower-Rim

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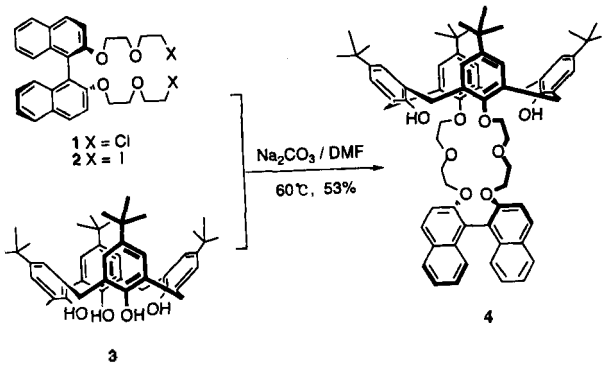
One of the main features of naturally occurring host molecules is their capacity for enantioselective recognition. Various attempts have been made to obtain synthetic chiral hosts capable of chiral recognition, but conclusive examples have not been reported yet.[1]

Calixarenes have been used as resources of attractive hosts whose efficiency and selectivity in metal ion, alkyl ammonium, and small molecule recognition have been controlled in terms of their ring size, conformation and the nature of the binding groups attached.[2] But even though chiral recognition and discrimination could be one of the main topics in calixarene chemistry, only a few examples of chiral recognition by calix[4]arene system have been reported.[3]

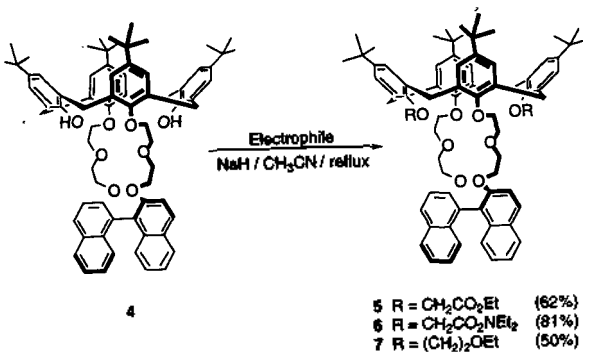
Chiral calix[4]arenes have been obtained by three different synthetic strategies; (1) calixarenes with chiral substituent, (2) asymmetric calixarenes, and (3) dissymmetric calixarenes. The first method is the most convenient route for chiral calixarenes, if the chiral pendant could be easily obtained in enantiomerically pure state and the derivatization reaction proceeds without racemization.[4] But usually simple attachment of a chiral unit cannot give a significant chiral barrier, because the chiral substituent used to direct divergently from the binding site. Asymmetric calix[4] arenes were also reported by Böhmer *et al.*,[5] Shinkai *et al.*,[6] and No *et al.*[7] Asymmetric calixarenes were obtained by incorporating different substituents on the lower- or the upper-rim or both, but the chiral resolution become difficult when the ring inversions, that is a racemization, occur during the reaction path way. Also the binding site used to be where no chiral barrier exists. Dissymmetric hosts are chiral but still have symmetry elements; a single n-fold axis (C_n symmetry) or a dihedral (D_n) symmetry. Dissymmetric hosts with a single n-fold axis are particularly attractive not only from the synthetic point of view[8] but also the high efficiency in enantioselection due to their multi recognition faces.[9] If a chiral substituent could be incorporated into a calix[4]arene by regiochemistry and conformation controlled reactions to give a dissymmetric host, it would be an efficient synthetic route of a chiral calix[4]arene with a good binding site and a significant chiral barrier.

The direct regioselective functionalization methods on the upper rim of calix[4]arene are quite rare.[10] But the lower rim of calix[4]arene provides excellent platform for the attachment of various functional groups.[2] The conformation of *O*-alkylated calix[4]arene can be controlled by the reaction conditions such as temperature, solvent, base, *p*-substituents of calix[4]arene, and the electrophile. Especially the templation effect of alkali metal cation of base is important for the distribution of product conformers. Also the regiochemistry of *O*-alkylation on the lower-rim can be controlled by the proper choice of base for the alkylation.[11] The regioselectivity arised from the different relative strength between the base and the subsequent residual intramolecular hydrogen bonds of calix[4]arene.

Chiral binaphthyl units have been used mostly frequently as chiral resources due to their chiral stability during the reactions as well as their versatility as skeletons of host.[12] CPK molecular model study shows that the distal incorporation of a chiral binaphthyl crown unit on the lower-rim of calix[4]arene would give a new chiral calix[4]crown



Scheme 1.



Scheme 2.

with C_2 symmetry. Moreover its residual two distal hydroxyls could be converted to various additional side-arms to give lariat-type chiral calix[4]crowns. Their synthesis and preliminary molecular recognition properties were reported.

(R)-(+)-Binaphthol ($[\alpha]^{21}$ +34°, c=1, THF) was treated with 2-(2-chloroethoxy)ethane tosylate in K_2CO_3/DMSO mixture at 55-60 °C to give (R)-2,2'-bis-(2-(2-chloroethoxy) ethoxy)-1,1'-binaphthalene **1** (Scheme 1). Chiral Binaphthols are known optically stable at 100 °C for 24 h in dioxane-water.[12] Chloro-compound **1** was treated with NaI in MEK solution at 55-60 °C to give (R)-2,2'-bis-(2-(2-iodoethoxy) ethoxy)-1,1'-binaphthalene **2**. This chiral compound **2** was incorporated at the 1,3-position of the lower rim of *p-tert*-butylcalix[4]arene **3** to give a new chiral host **4**[13] (53%) in DMF/Na_2CO_3 mixture.

The ^{1}H NMR spectrum of host **4** shows that it is a cone-structured, 1,3-bridged and chiral calix[4]crown. *p-tert*-Butyl protons appeared as two singlets at 1.30 (18H) and 0.96 (18H). But methylene protons bridging aryls appeared as two doublets at δ 4.32 for H_{endo} (4H, J=13.2 Hz) and at δ 3.28 for H_{exo} (4H, J=13.2 Hz). Also ethyleneoxy protons appeared as more than 6 multiplets (δ 3.25(2H), 3.56(2H), 3.80(4H), 3.86(4H), 4.22(2H), 4.41(2H)). The chirality of **4** was also confirmed by its CD spectra shown in Figure 1. FAB$^+$ MS spectrum, FT-IR and elementary analyses as well as a sharp mp (132-133 °C) of host **4** also supported the proposed structure.

If host **4** were 1,2-bridged and then asymmetric, the proton peaks should be much more complex. For example, aryl-bridging methylene proton's peaks should be split into three kinds in 1:2:1 ratio. If host **4** were 1,3-bridged partial cone and also asymmetric, the *t*-butyl peaks should be split into three kinds in 1:2:1 ratio. But if host **4** were 1,3-bridged alternative conformer, methylene proton peaks might appear similarly, which case is not known to occur for *p-tert*-butylcalix[4]arene in the similar reaction conditions.[11] Also in this case there should be several significant chemical shift changes due to reorganized benzene units, which were not observed.

Host **4** has two residual hydroxy groups which can be functionalized to side-arms to increase binding efficiencies. Accordingly, lariat-type chiral hosts **5**,[14] **6**,[15] and **7**[16] in the cone conformation, which has ester, amide, or ether side-arms respectively, were synthesized (Scheme 2). Treatment of host **4** with ethyl bromoacetate in NaH/CH_3CN mixture at 65 °C afforded host **5** (62%). Also reaction of **4** with 2-chloro-N,N-diethyl acetamide, or 2-chloroethyl ethyl ether in NaH/NaI/CH_3CN mixture at 65 °C afforded **6** (81%), or **7** (50%) in good yields. Cone conformation of hosts **5**, **6** and **7** were confirmed by ^{1}H NMR spectra which showed similar patterns to those of host **4**. Also CD spectra of these host in Figure 1 gave the similar pattern of Cotton effect due to the same chirality of binaphtyl group. Other characteristic results from FAB-MS, FT-IR and elementary analyses corresponded to those anticipated.

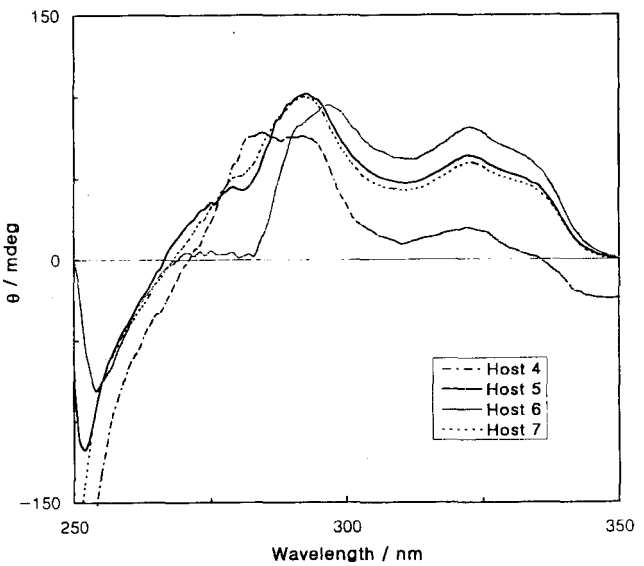


Figure 1. CD spectra of Host **4-7** at 25 °C ([**4**]=1×10^{-4} M in $CHCl_3$, [**5**]=[**6**]=[**7**]=1×10^{-4} M in CH_2Cl_2).

The ionophoric properties of hosts **5**, **6** and **7** were measured by the picrate extraction method.[17] Aqueous picrate solution (1.0×10^{-3} M) was extracted with organic host solution ($CHCl_3$, 1.0×10^{-3} M) at 25 °C. The extracted picrate concentration was calculated from the residual picrate concentration in aqueous solution, because the λ_{max} of picrate and binaphthyl unit of these hosts were overlapped.

Table 1 and 2 show the results of cation binding study. Table 1 shows the association constants ($\log K_a$) and Table 2 shows the binding free energies ($-\Delta G$/kJmol^{-1}). The values of analogues **8**, **9**, and **10** (Figure 2) obtained by the same method[17] were added for comparison.

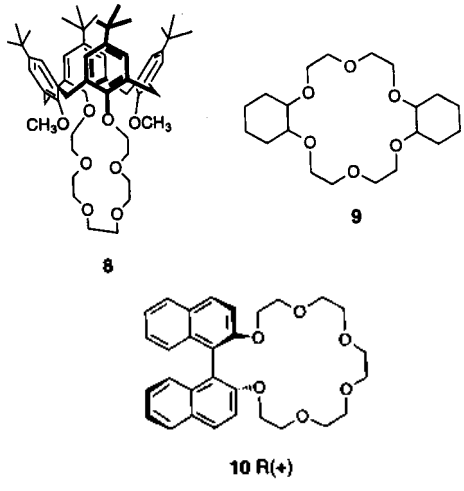
All the lariat calix[4]crowns showed enhanced binding abilities for alkali metal, primary and tert-butyl ammonium ions compared to analogues **8** and **10**. Analogue **9** is the

Table 1. Association Constants ($\log K_a$) for Complexes of Hosts with Alkali Metal, Ammonium and *t*-Butyl Ammonium Picrate in $CHCl_3$ Saturated with H_2O at 25 °C

Host	$\log K_a$ (M^{-1})						
	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	*t*-$BuNH_3^+$
5	6.8	6.2	6.2	6.5	6.7	6.5	5.1
6	7.3	7.2	6.9	6.8	6.8	6.5	5.2
7	6.7	6.1	6.0	6.5	6.6	6.5	5.1
8[18]	4.7	4.6	5.2	5.3	6.5	-	-
9[17b]	4.3	5.4	8.3	6.7	6.3	7.8	5.1
10[17c]	3.5	5.0	6.3	-	5.4	5.9	-

Table 2. Binding Free Energie ($-\Delta G$ $kJmol^{-1}$) for Complexes of Hosts with Alkali Metal, Ammonium and *t*-Butyl Ammonium Picrate in $CHCl_3$ Saturated with H_2O at 25 °C

Host	$-\Delta G$ ($kJmol^{-1}$)						
	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	*t*-$BuNH_3^+$
5	39.0	35.6	35.5	37.1	38.1	37.3	29.0
6	41.6	41.0	39.3	38.7	39.0	37.3	29.6
7	38.3	35.0	34.1	36.8	37.9	37.3	28.8
8[18]	26.8	26.4	29.7	30.6	37.2	-	-
9[17b]	30.2	36.5	47.5	38.4	35.8	44.8	39.6
10[17c]	20.1	28.6	37.2	-	31.0	33.6	-



8

9

10 R(+)

Figure 2. Structure of hosts **8**[18], **9**[17b], and **10**[17c].

most strong binder for K^+, NH_4^+, or *t*-$BuNH_3^+$. Among the lariat calix[4]crowns, host **6** was the strongest and host **7** was the weakest in general. The effect of side arms as additional ligands increased in order of amide > ester > ether. For the alkali metal cations, analogues **9** and **10** showed peak binding at K^+ and analogue **8** at Cs^+. But those new hosts gave two peak binding patterns, the highest for Li^+ and the second for Cs^+, which implies that the host's overall size-fit binding competes with the host's regional binding. When the size of guest becomes larger, it binds to host in overall size-fit binding mode. But when the size of guest becomes smaller, it binds to a regional part of host, which seems to occur easily due to the partially coiled chiral binaphtyl unit. Also those new hosts showed substantial affinity for ammonium ions, which suggests their potential

Table 3. Binding Constants (K_a) for the Complexes of Hosts **4**, **5**, **6**, and **7** with Hydrochloride Salts of α-Amino Acid Methyl Ester in $CHCl_3$ at 25 °C ([H]=1.0×10^{-6} M, λ_{ex}=332 nm, λ_{em}=380 nm)

Amino acid ester	K_a ($\times10^{-3}$ M^{-1})				K_D/K_L	
	4	**5**	**6**	**7**	**4**	**5**
L-Val-OMe	6.89	9.15	6.83	5.00		
L-Leu-OMe	12.1	10.4	8.35	9.07		
L-Ile-OMe	12.8	10.3	9.09	8.58		
D-Phe-OMe	8.99	9.24	-	-		
L-Phe-OMe	2.79	5.14	-	-	3.22	1.80
D-Trp-OMe	8.31	5.36	-	8.04		
L-Trp-OMe	3.94	-	-	6.70	2.11	-

binding ability for amino acid ester·HCl salts. But the selectivities in overall were relatively low due to the large binding site. The highest binding energy ($-\Delta G$) was observed as 41.6 $kJmol^{-1}$ of host **6** for Li^+, and the lowest was observed as 28.8 $kJmol^{-1}$ of host **7** for *t*-$BuNH_3^+$.

The preliminary chiral recognition properties were measured by spectrofluorometric titration method. The association constants (K_a) were calculated using Benesi-Hildebrand equation[19] and summarized in Table 3. Host **4** showed the larger affinities in general and the largest selectivity (3.22) for D/L Phe. Lariat host 5 showed better affinity for amino esters having relatively small 2-alkyl groups (L-Val *vs.* L-Leu, L-Ile or Phe *vs.* Trp), which implies that the bulky side arms would rather inhibit the approach of guest having large alkyl group.

In conclusion, distal hydroxyl groups of *t*-butylcalix[4]arene were efficiently connected with chiral binahpthyl unit to give new chiral calix[4]crowns **4**, **5**, **6**, and **7**. Significant binding abilities of these hosts were observed by picrate extraction experiment and spectrofluorophotometric titration method. All the new hosts showed high binding abilities for alkali metal, primary and tert-butyl ammonium ions. But the selectivity was relatively low due to the large binding site. These lariat-type calix[4]crowns show the significant chiral recognition abilities and the $K_{a,D\text{-}Phe}/K_{a,L\text{-}Phe}$ by host **4** was 3.22.

Currently the spectra of chiral recognition properties and the binding mode of these chiral hosts are being observed.

Acknowledgment. The financial support from Ministry of Education, Korea (BSRI-96-3437) is gratefully acknowledged.

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13. (4) mp 132-133 °C; FT-IR (KBr) 3414 cm^{-1} (ν_{OH}) ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J*=9.0 Hz, BiNAP-Ar*H*), 7.84 (2H, d, *J*=8.1 Hz, BiNAP-Ar*H*), 7.46 (2H, d, *J*=9.1 Hz, BiNAP-Ar*H*), 7.44 (2H, s, ArO*H*), 7.30 (2H, t, *J*=7.3 Hz, BiNAP-Ar*H*), 7.24-7.17 (4H, m, BiNAP-Ar*H*), 7.11, 7.01, 6.83, 6.75 (each d, *J*=2.2 Hz, each 2H, Ar*H*), 4.41, 4.22 (each m, each 2H, CH_2CH_2 OBiNAP), 4.32 (4H, d, *J*=13.2 Hz, *endo*-ArC*H*Ar), 3.86-3.76 (m, 8H, CH_2OCH_2), 3.56 (m, 2H, $ArOCH_2CH_2$), 3.28 (4H, d, *J*=13.2 Hz, *exo*-ArC*H*Ar), 3.25 (2H, t, $ArOCH_2CH_2$), 1.30 (18H, s, $(CH_3)_3C$), 0.955 (18H, s, $(CH_3)_3C$); FAB$^+$ MS (3-nitrobenzyl alcohol) m/z 1075 (M^+, 100%). Anal. Calcd for ($C_{77}H_{82}O_8$+CH_3OH): C, 79.17; H, 7.83. found: C, 79.38; H, 8.00.
14. (5) mp 139-140 °C; FT-IR (KBr) 1730 cm^{-1} ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J*=9.0 Hz, BiNAP-Ar*H*), 7.78 (2H, d, *J*=8.1 Hz, BiNAP-Ar*H*), 7.47 (2H, d, *J*=9.1 Hz, 2H, BiNAP-Ar*H*), 7.24 (2H, t, *J*=7.3 Hz, BiNAP-Ar*H*), 7.12 (2H, t, BiNAP-Ar*H*), 7.00 (2H, d, *J*=8.1 Hz, BiNAP-Ar*H*), 6.96 (4H, d, *J*=5.7 Hz, Ar*H*), 6.42 (4H, d, *J*=5.8 Hz, Ar*H*), 4.41-3.89 (24H, m, $ArOCH_2CH_2OCH_2CH_2$, *endo*-ArC*H*Ar, OCH_2CO, OCH_2CH_3), 3.67-3.56 (4H, m, $ArOCH_2CH_2$), 3.29-3.23 (4H, two d, *J*=13.2 Hz, *exo*-ArC*H*ArO), 1.21 (s, 18H, $(CH_3)_3C$), 1.07 (t, 6H OCH_2CH_3), 0.76 (s, 18H, $(CH_3)_3C$); FAB$^+$ MS (3-nitrobenzyl alcohol), m/z 1246 (M^+, 52%), 1269 (M+Na$^+$, 100%). Anal. Calcd for ($C_{80}H_{94}O_{12}$+CH_3OH+CH_3CN): C, 75.48; H, 7.71. found: C, 75.42; H, 8.01.
15. (6) mp 147-149 °C; FT-IR (KBr) 1652 cm^{-1} ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, *J*=9.0 Hz, BiNAP-Ar*H*), 7.83 (2H, d, *J*=8.1 Hz, BiNAP-Ar*H*), 7.56 (2H, d, *J*=9.1 Hz, BiNAP-Ar*H*), 7.28 (2H, t, *J*=7.3 Hz, BiNAP-Ar*H*), 7.17 (2H, t, *J*=7.6 Hz, BiNAP-Ar*H*), 7.10 (2H, d, *J*=2.2 Hz, BiNAP-Ar*H*), 7.07 (4H, s, Ar*H*), 6.41 (4H, s, Ar*H*), 4.46-4.04 (20H, m, $ArOCH_2CH_2OCH_2CH_2$, OCH_2CO and *endo*-ArC*H*Ar), 3.79-3.70 (m, 4H, ArO CH_2CH_2), 3.34-3.22 (m, 8H, NCH_2CH_3), 3.13 (t, 4H, *J*= 13.2 Hz, *exo*-ArC*H*ArO), 1.31 (s, 18H, $(CH_3)_3C$), 1.02 (m, 12H, NCH_2CH_3), 0.76 (s, 18H, $(CH_3)_3C$); FAB$^+$ MS (3-nitrobenzyl alcohol), m/z 1323 (M+Na$^+$, 100%). Anal. Calcd for ($C_{84}H_{104}N_2O_{10}$+CH_3OH): C, 76.54; H, 8.16; N, 2.10. found: C, 76.68; H, 8.21; N, 1.96.
16. (7) mp 139-140 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, *J*=9.0 Hz, BiNAP-Ar*H*), 7.90 (2H, d, *J*=8.1 Hz, BiNAP-Ar*H*), 7.58 (2H, d, *J*=9.1 Hz, BiNAP-Ar*H*), 7.65 (2H, t, *J*=7.3 Hz, BiNAP-Ar*H*), 7.22 (2H, t, *J*=7.6, Hz, BiNAP-Ar*H*), 7.15-7.12 (6H, m, 2H of BiNAP-Ar*H* and 4H of Ar*H*) 6.47 (4H, d, *J*=5.8 Hz, Ar*H*), 4.46 (4H, dd, *J*=13.2 Hz, *endo*-ArC*H*Ar) 4.30-3.69 (24H, m, $ArOCH_2CH_2OCH_2CH_2O$ and $ArOCH_2CH_2OCH_2CH_3$), 3. 46 (4H, q, *J*=8.1 Hz, OCH_2CH_3), 3.13 (4H, dd, *J*=13.2 Hz, *exo*-ArC*H*ArO), 1.33 (18H, s, $(CH_3)_3C$), 1.17 (6H, t, OCH_2CH_3), 0.86 (18H, s, $(CH_3)_3C$); FAB$^+$ MS (3-nitrobenzyl alcohol), m/z 1218 (M^+, 100%), 1241 (M+Na$^+$, 23%). Anal. Calcd for ($C_{80}H_{98}O_{10}$): C, 78.78; H, 8.1. found: C, 78.51; H, 8.26.
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