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Chiral calix[4]azacrowns for enantiomeric recognition of amino acid derivatives

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ABSTRACT

In this study the synthesis of novel chiral calix[4]azacrown derivatives has been reported. The enantioselectivity of chiral receptors was investigated by using UV–vis spectroscopy. All the chiral calix[4]arene derivatives exhibited certain chiral recognition toward the enantiomers of phenylalanine (Phe-OMe·HCl) and alanine methyl ester hydrochlorides (Ala-OMe·HCl). As a chiral receptor, the furfuryl-armed calix[4]azacrown ether **7** has the best enantiomeric discriminating ability for α-amino acid ester hydrochlorides (up to K_L/K_D=2.08, $\Delta\Delta G_0$=−1.82 kJ mol^{-1}) in $CHCl_3$. The enantiomeric recognition abilities for guests are also discussed from a thermodynamic point of view.

1. Introduction

Molecular recognition is a fundamental property of various natural systems, based on the ability of a molecular receptor to form a complex preferentially with one of the enantiomers of a chiral molecule by noncovalent interaction such as hydrogen bonding, electrostatic interaction, and hydrophobic interaction.[1] Therefore, the chemical or biological activity of a compound often depends upon its stereochemistry in living organisms.

Amino acids and their derivatives are chiral organic molecules involved in a wide variety of biological processes, and also play an important role in the area of design and preparation of pharmaceuticals, as they are part of the synthesis process in the production of drug intermediates and protein-based drugs. Therefore the study of the enantiomeric recognition of these compounds is of particular significance for understanding the interactions between biological molecules and design of asymmetric catalysis systems, new pharmaceutical agents,[2] and separation materials.[3]

The rational design of receptors with chiral recognition ability for chiral amino acids is still receiving considerable attention, although numerous chiral macrocyclic receptors have been developed for amines, amino acids, and related compounds.[4]

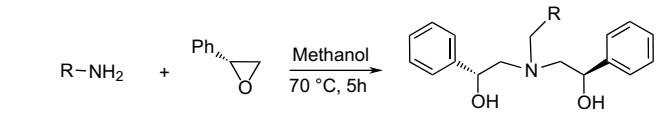
Among the several types of synthetic receptors for recognition, calixarenes offer a number of advantages in terms of their selectivity and efficiency of binding.[5,6] One of the most frequently used strategies for introducing chiral recognition ability into calixarenes is anchoring chiral subunits at either the lower or the upper rims of the calixarene macrocyclic ring. Chiral receptors that are based on the calixarene platform may have potential applications in the preparation, separation, and analysis of enantiomers. In this regard, investigations conducted on the synthesis and chiral recognition properties of chiral calix[4]arene derivatives have attracted considerable attention.[7]

In recent years, we have reported the synthesis of novel chiral calix[4]arenes containing various functionalities including crown[8] and azacrown ethers,[9] amides,[10] Schiff bases,[11] and quaternary ammonium salts[12] as well as their catalytic activities and enantiomeric recognition properties toward chiral amines, carboxylic acids, and amino acid derivatives. In the present study, we report the synthesis of novel calix[4]arene derivatives bearing a chiral azacrown-5 moiety at the lower rim and their recognition abilities for α-amino acid methyl esters by a UV–vis titration method in $CHCl_3$.

2. Results and discussion

2.1. Design and synthesis of calix[4]arene based receptors

Calix[4]azacrowns containing a calix[4]arene platform and an azacrown unit in their framework have received much attention because of their special structures and good complexing properties toward anions and cations.[13] In a recent study, we reported that the furfuryl-armed calix[4]azacrown ethers exhibited different chiral



R = Benzyl or furfuryl

1: **R** = Benzyl
2: **R** = Furfuryl

Scheme 1. Preparation of amino diols **1** (85%) and **2** (86%).

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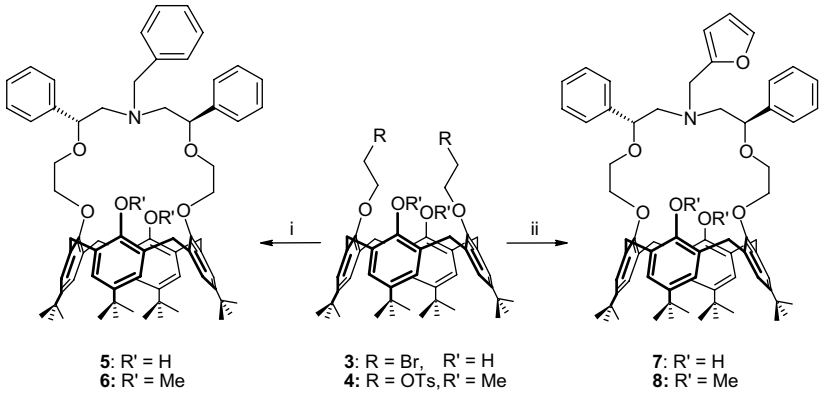

Scheme 2. (i) and (ii) Chiral amino diol **1** or **2**, NaH, DMF, reflux (**5**, 42%; **6**, 54%).

recognition abilities toward the enantiomers of racemic mandelic acid and dibenzoyltartaric acid. These nitrogen binding sites, attached to the calix[4]arene platform could also serve as chiral receptors for the enantioselective recognition of amino acid methyl esters. For the desired goal, *p-tert*-butylcalix[4]arene derivatives **3** and **4** were chosen as the precursors, and the synthetic route is shown in Schemes 1 and 2 for the synthesis of furfuryl- and benzyl-armed chiral calix[4]azacrown ethers.

Thus, following the literature procedure,[14a,b] starting materials **1** and **2** were prepared by the ring opening of the (*R*)-styrene oxide with furfuryl- and benzylamine in high yields, respectively. The benzyl-armed calix[4]azacrowns obtained in 42 and 54% yields by the reaction of the *p-tert*-butylcalix[4]arene derivatives **3** or **4** with chiral amino diol **1** in DMF.

The products were characterized by a combination of ^{1}H NMR, ^{13}C NMR, FABMS, IR, and elemental analysis. The conformational characteristics of calix[4]arenes were conveniently estimated by way of the splitting pattern of the $ArCH_2Ar$ methylene protons in the ^{1}H and ^{13}C NMR spectroscopy.[15] ^{1}H and ^{13}C NMR data showed that newly synthesized chiral *p-tert*-butylcalix[4]arene derivatives **5** and **6** are in a cone conformation.

2.2. UV spectral titrations

It is well known that calix[*n*]arene derivatives act as receptors for ammonium cations through their aromatic cone cavity.[16] Calix[*n*]arenes exhibit a special ability for cation–π[17] interactions due to their preorganized aromatic rings. We have now extended these studies to the enantioselective recognition of α-amino acid methyl ester hydrochlorides by the chiral calix[4]azacrown derivatives **5**–**8**.

The binding constants (*K*) of inclusion complexes of above-mentioned chiral calix[4]arene receptors with amino acid methyl esters were determined on the basis of the differential UV spectrometry in chloroform.[18]

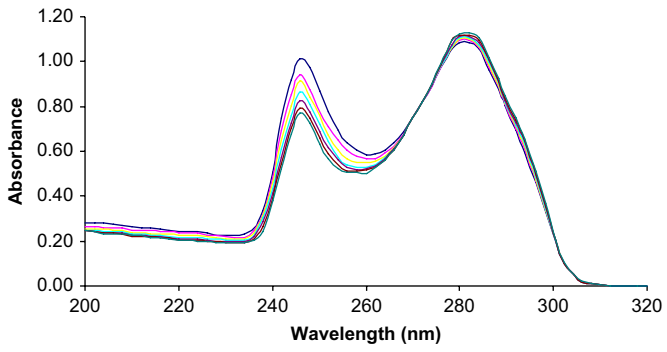

Figure 1. UV–vis spectra of **8** (2.0×10^{-4} mol dm^{-3}) in the presence of (D)-Ala-OMe·HCl (1.0–9.0×10^{-3} mol dm^{-3}) in chloroform solution at 25 °C.

Upon addition of (D)-Ala-OMe·HCl to the $CHCl_3$ solution containing chiral receptor **8** (2.0×10^{-4} mol dm^{-3}, 25 °C), the absorbance of **8** at 246 nm decreased and the one at 282 nm increased, with an isobestic point at 272 nm (Fig. 1). A similar spectral change was observed when other receptors were used as hosts and was believed to be due to hydrogen bonding and π–π stacking.

With the assumption of a 1:1 stoichiometry, the complexation of amino acid derivatives (G) with chiral calix[4]arene (H) is expressed by Eq. 1.

$$H + G \overset{K}{\rightleftarrows} H\cdot G \tag{1}$$

Under the conditions employed, the concentration of calix[4]-arene derivatives (2.0×10^{-4} mol dm^{-3}) is much smaller than that of amino acid derivatives, i.e., $[H]_0 \ll [G]_0$. Therefore, the stability constant of the supramolecular system formed can be calculated according to the modified Hildebrand–Benesi equation,[19] Eq. 2, where $[G]_0$ denotes the total concentration of amino acid, $[H]_0$ refers to the total concentration of calix[4]arene derivative, $\Delta\varepsilon$ is the difference between the molar extinction coefficient for the free and complexed calix[4]arene derivative, and ΔA denotes the changes in the absorption of the modified calix[4]arene on adding amino acid derivatives.

$$1/\Delta A = 1/K\Delta\varepsilon[H]_0[G]_0 + 1/\Delta\varepsilon[H]_0 \tag{2}$$

For all guest molecules examined, plots of calculated $1/\Delta A$ values as a function of $1/[G]_0$ values give good straight lines, supporting the 1:1 complex formation. Typical plots are shown for the complexation of compound **8** with (D)-alanine methyl ester in Figure 2.

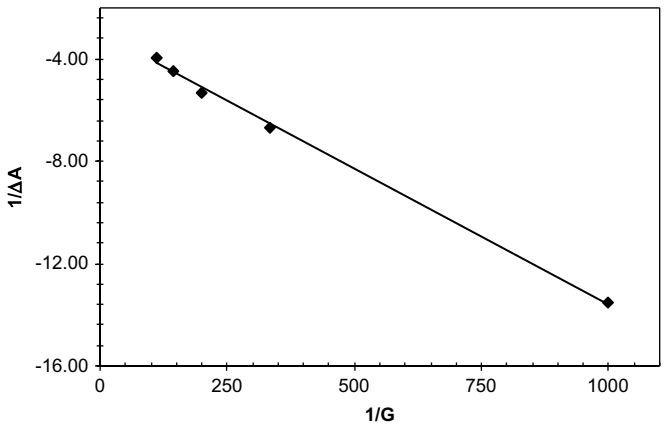

Figure 2. Typical Benesi–Hildebrand plot of $1/\Delta A$ versus $1/[G]_0$.

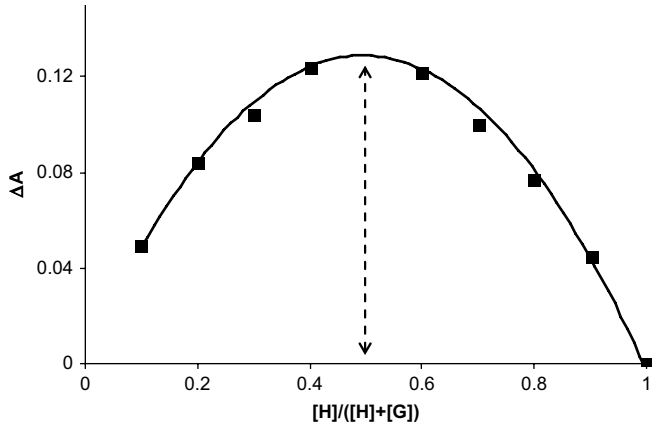

Figure 3. Job plot of **8** with D-Ala-OMe·HCl. The total concentration of the host and guest is 3.0×10^{-4} mol dm^{-3}.

In order to verify the 1:1 complexation, we used a Job plot experiment. Figure 3 illustrates that the **8**-D-Ala-OMe·HCl complex concentration approaches maximum when the molar fraction of [H]/([H]+[G]) is 0.5, suggesting that host **8** forms a 1:1 complex with D-Ala-OMe·HCl.

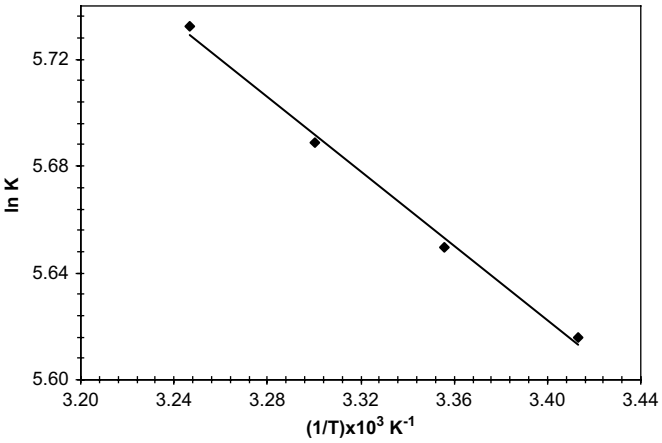

Figure 4. The plot of ln K versus $1/T$ for the host–guest complexation of **8** and D-Ala-OMe·HCl in $CHCl_3$.

The free-energy change (ΔG) for inclusion complexes formed by chiral calix[4]azacrown derivatives and guest amino acid derivatives is calculated from the equilibrium constant K by Eq. 3 and is related to

$$\Delta G = -RT\ln K \quad (3)$$

and to the enthalpic and entropic changes (ΔH and ΔS) through the Gibbs–Helmholtz equation, Eq. 4. Combining Eqs. 3 and 4, we obtain Eq. 5, which describes the temperature dependence of K. Thus, plots of the ln K values as a function of the inverse of temperature gave good linear relationships for working temperature range (Fig. 4).

$$\Delta G = \Delta H - T\Delta S \quad (4)$$

$$\ln K = -\Delta H/RT + \Delta S/R \quad (5)$$

The association constants (K), the free-energy change ($\Delta\Delta G_0$) calculated from the slope and the intercept, and the thermodynamic parameters are summarized in Table 1, along with the enantioselectivity K_L/K_D for the complexation of D/L-amino acid esters by these hosts.

As can be recognized readily from Table 1, all the values of the enthalpy changes (ΔH°) and the entropy changes (ΔS°) of the resulting complexes are positive. These results indicate that the complexation of calix[4]arenes (**6**–**8**) with α-amino acid methyl esters examined is driven predominantly by the favorable entropic change, typically showing large positive entropy changes (ΔS°=54.66–103.27 J mol^{-1}) and somewhat smaller positive enthalpy changes (ΔH°=1.44–19.06 kJ mol^{-1}). One possible explanation for the complexation of the large entropy-driven is that both dissociated α-amino acid methyl esters and free calix[4]arene derivatives are heavily solvated by hydrogen-bonding interactions.

From the data shown in Table 1, all hosts have greater K values toward the enantiomers of Phe-OMe than Ala-OMe, a non-aromatic analog of Phe-OMe. This may be due to the fact that the chiral calix[4]azacrowns with an aromatic group attached to the nitrogen of the macrocyclic ring could have π–π interactions with that of Phe-OMe as an additional binding force. As a result, stronger binding was realized in all cases.

UV–vis spectroscopic studies indicate that chiral selectors **5** and **7** show strong binding and good recognition ability for the enantiomers of phenylalanine (Phe-OMe·HCl) and alanine methyl ester hydrochlorides (Ala-OMe·HCl).

Table 1
Binding constants (K), enantioselectivities (K_L/K_D), and thermodynamic parameters for the complexation of L/D-amino acid esters with the chiral receptors **5**–**8** in $CHCl_3$ at 25 °C

Entry	Host	Guest[a]	$K\times10^3$ (M^{-1})	K_L/K_D	$-\Delta G$ (kJ mol^{-1})	$-\Delta\Delta G$[b]	ΔH (kJ mol^{-1})	$\Delta\Delta H$[c]	ΔS (J mol^{-1})	$\Delta\Delta S$[d]
1	**5**	D-Phe-OMe·HCl	0.583±0.026	1.80	15.78±0.16	1.45	6.25±0.16	1.70	73.92±0.55	10.55
2	**5**	L-Phe-OMe·HCl	1.049±0.090		17.23±0.21		7.95±0.21		84.47±0.71	
3	**5**	D-Ala-OMe·HCl	0.315±0.024	1.13	14.25±0.26	0.30	7.23±0.26	3.50	72.08±0.85	12.72
4	**5**	L-Ala-OMe·HCl	0.356±0.027		14.55±0.36		10.72±0.36		84.80±1.21	
5	**6**	D-Phe-OMe·HCl	0.310±0.012	1.28	14.21±0.14	0.60	4.96±0.14	3.65	64.32±0.47	14.25
6	**6**	L-Phe-OMe·HCl	0.395±0.028		14.81±0.12		8.60±0.12		78.57±0.39	
7	**6**	D-Ala-OMe·HCl	0.109±0.008	1.02	11.62±0.20	0.09	16.08±0.20	2.98	92.96±0.67	10.31
8	**6**	L-Ala-OMe·HCl	0.111 ±0.021		11.71±1.20		19.06±1.20		103.27±3.99	
9	**7**	D-Phe-OMe·HCl	0.809±0.044	2.08	16.59±0.14	1.82	4.21±0.14	0.26	69.81±0.45	6.98
10	**7**	L-Phe-OMe·HCl	1.684±0.130		18.41±0.06		4.47±0.06		76.79±0.20	
11	**7**	D-Ala-OMe·HCl	0.419±0.017	1.27	14.96±0.03	0.59	1.44±0.03	0.89	55.04±0.09	4.97
12	**7**	L-Ala-OMe·HCl	0.532±0.014		15.55±0.04		2.33±0.04		60.01±0.15	
13	**8**	D-Phe-OMe·HCl	0.342±0.007	1.40	14.46±0.07	0.84	1.83±0.07	1.39	54.66±0.22	7.49
14	**8**	L-Phe-OMe·HCl	0.480±0.020		15.30±0.10		3.22±0.10		62.16±0.32	
15	**8**	D-Ala-OMe·HCl	0.284±0.014	1.09	14.01±0.29	0.22	5.82±0.29	2.43	66.52±0.96	8.89
16	**8**	L-Ala-OMe·HCl	0.311±0.009		14.22±0.21		8.25±0.21		75.42±0.69	

[a] Phe-OMe·HCl: phenylalanine methyl ester hydrochloride; Ala-OMe·HCl: alanine methyl ester hydrochloride.
[b] $\Delta\Delta G=\Delta G_L-\Delta G_D$.
[c] $\Delta\Delta H=\Delta H_L-\Delta H_D$.
[d] $\Delta\Delta S=\Delta S_L-\Delta S_D$.

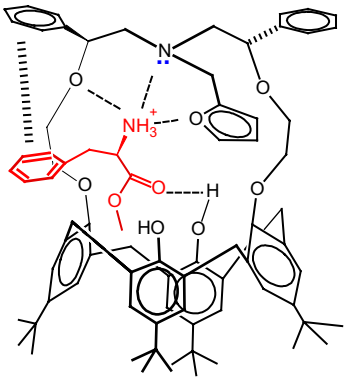

Figure 5. Proposed recognition mode of chiral calix[4]arene **5** toward a chiral amino acid methyl ester.

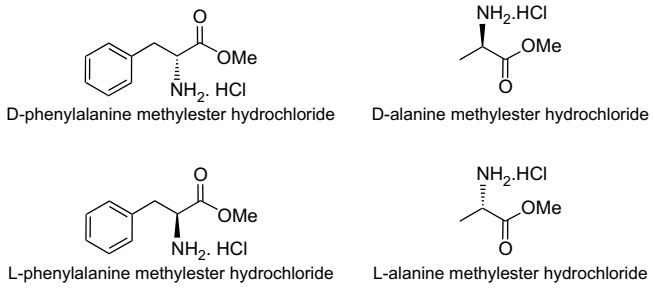

Figure 6. Chemical structures of guests employed.

Table 1 also shows the enantiomeric discrimination of a pair of α-amino acid ester hydrochlorides, characterized by the value of K_D/K_L, which are 1.13–2.08 or $\Delta\Delta G_0$ of −0.30 to −1.82 kJ mol^{-1} for chiral calix[4]arene receptors **5** and **7**. It was found that chiral host **5** gave stronger binding and better recognition ability for amino acid esters containing an aromatic group than for those possessing an aliphatic group, whereas receptor **7** exhibits the strongest binding and the best enantioselectivity for Phe-OMe·HCl, affording K_L/K_D of 1.27–2.08 or the $\Delta\Delta G_0$ of −0.59 to −1.82 kJ mol^{-1}. This is presumably due to multiple hydrogen bonding and π–π stacking interactions between the receptor and the aromatic side chain of amino acid.

The results revealed that the D/L-enantioselectivities are highly sensitive to the furan ring and phenolic-OH of the chiral receptors and shape of the substituted group in amino acid esters. The steric hindrance between the ammonium cation and aromatic moieties around the stereogenic centers of the host may also play an important role in chiral recognition and is expected to be minimized for the L-isomer in all cases. Therefore, the L-isomers of amino acid ester hydrochlorides form more favorable complexes with the chiral selectors than the D-isomers (Fig. 5).

The complexation of chiral calix[4]azacrowns with α-amino acid esters possibly occurs through interaction of the nitrogen atom in the azacrown loop and the quaternary ammonium cation in the α-amino acid esters. Noncovalent interactions between the guests and hydrogen bonding sites defined by ethylene oxygens, furan oxygen, and phenolic oxygen contribute to the stabilization of these complexes as well as π–π interactions.

3. Conclusion

In conclusion, novel calix[4]azacrown ethers were synthesized by the reaction of dibromo or ditosyl derivatives of *p-tert*-butylcalix[4]arene with a chiral diol. The enantioselective recognition of these receptors has been studied by UV–vis spectroscopy. Chiral selectors **5** and **7** show strong binding and some chiral recognition ability for the enantiomers of phenylalanine and alanine methyl ester hydrochlorides. The results indicate that the multiple hydrogen bonding, steric hindrance, structural rigidity or flexibility, and π–π stacking between the aromatic groups may be responsible for the enantiomeric recognition.

4. Experimental section

4.1. General

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Varian 400 MHz spectrometer in $CDCl_3$. IR spectra were obtained on a Perkin–Elmer 1605 FTIR spectrometer using KBr pellets. Optical rotations were measured on an Atago AP-100 digital polarimeter. The HPLC measurements were carried out on Agilent 1100 equipment connected with a Zorbax RX-C18 column. Elemental analyses were performed using a Leco CHNS-932 analyzer. FABMS spectra were taken on a Varian MAT 312 spectrometer.

Analytical TLC was performed using Merck prepared plates (silica gel 60 F_{254} on aluminum). Flash chromatography separations were performed on a Merck silica gel 60 (230–400 mesh). All reactions, unless otherwise noted, were conducted under a nitrogen atmosphere. All starting materials and reagents used were of standard analytical grade from Fluka, Merck, and Aldrich and used without further purification. Toluene was distilled from CaH_2 and stored over sodium wire. Other commercial grade solvents were distilled and then stored over molecular sieves. The drying agent employed was anhydrous $MgSO_4$.

Analytical grade α-amino acid methyl ester hydrochlorides were purchased from Aldrich and employed without further purification as guest molecules for the experiments, i.e., L-alanine methyl ester hydrochloride (L-Ala-OMe), D-alanine methyl ester hydrochloride (D-Ala-OMe), L-phenylalanine methyl ester hydrochloride (L-PheO-Me), and D-phenylalanine methyl ester hydrochloride (D-Phe-OMe) (Fig. 6).

4.2. Syntheses

Compounds **1**, **3**, and **4** were prepared according to previously described methods.[14a,20] The synthesis of **2**, **7**, and **8** has been already described by us.[14b]

*4.2.1. General procedure for the synthesis of compounds **5** and **6***

To a suspension of NaH (60% in mineral oil) (0.14 g, 3.56 mmol) in DMF (3 mL) was added a solution of **1** (0.31 g, 0.89 mmol) in DMF (5 mL) dropwise at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 2 h. Then **3** or **4** (0.89 mmol) in DMF (20 mL) was added slowly to the mixture. The mixture was stirred at room temperature for 2 days. DMF extract was evaporated and water (10 mL) added to the remaining residue. The mixture was extracted with CH_2Cl_2 (3×10 mL) and combined organic phase dried over $MgSO_4$. The solvent was evaporated and the crude product was obtained.

*4.2.1.1. N-Benzyl-5,11,17,23-tetra-tert-butyl-25,27-dihydroxy-26,28-(4′R,8′R-diphenyl-6′-aza-3′,9′,-dioxaundecane)-dioxycalix[4]arene (**5**).* The crude product was purified by flash chromatography on silica gel (EtOAc/hexane 1:15) to afford **5** as a white solid. Yield 42%; white crystal; mp 124–127 °C; $[\alpha]_D^{25}$ +24 (*c* 1, $CHCl_3$). IR (KBr): 3364, 3022, 2960, 2865, 1478, 1460, 1360, 1204, 1023, 871, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32–6.96 (m, 21H,

ArH and ArOH), 6.70–6.66 (m, 4H, ArH), 4.45 (d, 2H, J=12.9 Hz, ArCH_2Ar), 4.36 (d, 2H, J=13.1 Hz, ArCH_2Ar), 4.21 (t, 2H, J=5.7 Hz, –OCHPh), 3.98–3.88 (m, 4H, –OCH_2CH_2), 3.66–3.58 (m, 2H, PhCH_2N), 3.54–3.43 (m, 4H, –OCH$_2$CH_2), 3.26 (d, 4H, J=13.1 Hz, ArCH_2Ar), 3.10 (dd, 2H, J_1=5.9 Hz, J_2=5.7 Hz, –CHCH_2N), 2.98 (dd, 2H, J_1=5.6 Hz, J_2=5.6 Hz, –CHCH_2N), 1.27 (s, 18H, C(CH_3)$_3$), 0.83 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 150.1, 149.1, 145.5, 140.8, 139.9, 131.5, 131.4, 127.4, 127.2, 127.0, 126.9, 126.8, 126.7, 124.4, 124.3, 124.0, 75.7, 74.2, 65.9, 60.5, 32.8, 30.8, 30.4, 30.0, 28.7; FABMS m/z: (1071.29) $[M+Na]^+$. Anal. Calcd for $C_{71}H_{85}NO_6$ (1048.44): C, 81.34%; H, 8.17%; N, 1.34%. Found: C, 81.94%; H, 8.29%; N, 1.28%.

*4.2.1.2. N-Benzyl-5,11,17,23-tetra-tert-butyl-25,27-dimethoxy-26,28-(4′R,8′R-diphenyl-6′-aza-3′,9′,-dioxaundecane)-dioxycalix[4]arene (**6**).* The crude product was purified by flash chromatography on silica gel (EtOAc/hexane 1:20) to afford **6** as a white solid. Yield 54%; white crystal; mp 115–120 °C; $[\alpha]_D^{25}$ −2.5 (c 0.8, $CHCl_3$). IR (KBr): 3024, 2957, 2868, 1482, 1456, 1362, 1202, 1025, 870, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34–7.28 (m, 19H, ArH), 6.90–6.75 (m, 4H, ArH), 4.43 (d, 2H, J=13.1 Hz, ArCH_2Ar), 4.25 (d, 2H, J=13.0 Hz, ArCH_2Ar), 4.22 (t, 2H, J=5.7 Hz, –OCHPh), 3.99 (br, 6H, –OCH_3), 3.78 (br, 4H, –OCH_2CH_2), 3.68–3.62 (m, 2H, PhCH_2N), 3.54–3.47 (m, 4H, –OCH$_2$CH_2), 3.22 (d, 4H, J=12.9 Hz, ArCH_2Ar), 3.07 (dd, 2H, J_1=5.8 Hz, J_2=5.9 Hz, –CHCH_2N), 2.85 (dd, 2H, J_1=5.5 Hz, J_2=5.6 Hz, –CHCH_2N), 1.23 (s, 18H, C(CH_3)$_3$), 0.85 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.4, 150.9, 147.6, 142.4, 138.7, 132.5, 132.1, 128.6, 128.1, 127.9, 127.6, 127.1, 126.9, 125.3, 124.9, 124.3, 76.2, 75.4, 66.5, 61.2, 33.2, 31.2, 30.7, 30.4, 29.2, 22.9; FABMS m/z: (1099.37) $[M+Na]^+$. Anal. Calcd for $C_{73}H_{89}NO_6$ (1076.49): C, 81.45%; H, 8.33%; N, 1.30%. Found: C, 81.89%; H, 8.54%; N, 1.24%.

4.3. UV–vis spectral measurement

The recognition abilities of chiral calix[4]arenes with amino acid derivatives were determined on the basis of the differential UV spectrometry in chloroform. The UV–vis spectra were measured at 20, 25, and 30 °C with a thermostated cell compartment by Shimadzu 160 UV spectrometer. The same concentrations of guest solution were added to the sample cell and reference cell (light path=1 cm). The association constants were determined at 246 nm. The concentration of the hosts is 2.0×10^{-4} mol dm^{-3} with the concentration of added guest increasing between 1.0 and 9.0×10^{-3} mol dm^{-3}.

4.4. Evaluation of the stoichiometric ratio of the host–guest complex (Job plots)

The stoichiometry of the complex between chiral hosts **5**–**8** and enantiomers of amino acid methyl esters was determined by a continuous-variation plot (Job plot).[21] Stock solutions of hosts (7.5 mM) and guests (3 mM) in $CHCl_3$ were prepared. In ten 2.5-mL flasks, a portion of the host and guest solutions was added in such a way that their ratio changed from 0 to 1, keeping the total volume to 2.5 mL and the total concentration to 0.3 mM. The UV–vis spectra for each sample were measured by spectrometer.

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References and notes

1. (a) Marchi-Artzner, V.; Artzner, F.; Karthaus, O.; Shimomura, M.; Ariga, K.; Kunitake, T.; Lehn, J.-M. *Langmuir* **1998**, *14*, 5164–5171; (b) Bohanon, T. M.; Caruso, P.-L.; Denzinger, S.; Fink, R.; Mobius, D.; Paulus, W.; Preece, J. A.; Ringsdorf, H.; Schollmeyer, D. *Langmuir* **1999**, *15*, 174–184; (c) Hartley, J. H.; James, T. D.; Ward, C. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3155–3184; (d) Pu, L. *Chem. Rev.* **2004**, *104*, 1687–1716; (e) Ludwig, R. *Microchim. Acta* **2005**, *152*, 1–19; (f) Hembury, G. A.; Borovkov, V. V.; Inoue, Y. *Chem. Rev.* **2008**, *108*, 1–73; (g) Homden, D. M.; Redshaw, C. *Chem. Rev.* **2008**, *108*, 5086–5130.
2. *The Design of Drugs to Macromolecular Targets*; Beddell, C. R., Ed.; Wiley: Chichester, UK, 1992.
3. *Chromatographic Separations Based on Molecular Recognition*; Jinno, K., Ed.; VCH: Weinheim, 1996.
4. (a) Fitzmaurice, R. J.; Kyne, G. M.; Douheret, D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841–864; (b) You, J.-S.; Yu, X.-Q.; Zhang, G.-L.; Xiang, Q.-X.; Lan, J.-B.; Xie, R.-G. *Chem. Commun.* **2001**, 1816–1817; (c) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–386; (d) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250; (e) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488–1508; (f) Casnati, A.; Sansone, F.; Ungaro, R. *Acc. Chem. Res.* **2003**, *36*, 246–254; (g) de Namor, A. F. D.; Cleverley, R. M.; Zapata-Ormachea, M. L. *Chem. Rev.* **1998**, *98*, 2495–2525.
5. (a) Vicens, J.; Böhmer, V. *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Kluwer: Boston, MA, 1991; (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713–745.
6. Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713–1734.
7. (a) Tuntulani, T.; Thavornyutikarn, P.; Poompradub, S.; Jaiboon, N.; Ruangpornvisuti, V.; Chaichit, N.; Asfari, Z.; Vicens, J. *Tetrahedron* **2002**, *58*, 10277–10285; (b) Diamond, D.; McKervey, M. A. *Chem. Soc. Rev.* **1996**, *25*, 15–24; (c) Kim, S. K.; Lee, S. H.; Lee, J. Y.; Lee, J. Y.; Bartsch, R. A.; Kim, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 16499–16506.
8. Karakucuk, A.; Durmaz, M.; Sirit, A.; Yilmaz, M.; Demir, A. S. *Tetrahedron: Asymmetry* **2006**, *17*, 1963–1968.
9. (a) Sirit, A.; Karakucuk, A.; Memon, S.; Kocabas, E.; Yilmaz, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3595–3600; (b) Sirit, A.; Kocabas, E.; Memon, S.; Karakucuk, A.; Yilmaz, M. *Supramol. Chem.* **2005**, *17*, 251–256.
10. (a) Kocabas, E.; Karakucuk, A.; Sirit, A.; Yilmaz, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1514–1520; (b) Kocabas, E.; Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. *Chirality* **2008**, *20*, 26–34.
11. (a) Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2322–2327; (b) Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. *Tetrahedron: Asymmetry* **2007**, *18*, 900–905.
12. Bozkurt, S.; Durmaz, M.; Yilmaz, M.; Sirit, A. *Tetrahedron: Asymmetry* **2008**, *19*, 618–623.
13. (a) Oueslati, I.; Thuéry, P.; Shkurenko, O.; Suwinska, K.; Harrowfield, J. M.; Abidi, R.; Vicens, J. *Tetrahedron* **2007**, *63*, 62–70; (b) Queslati, I. *Tetrahedron* **2007**, *63*, 10840–10851; (c) Banthia, S.; Samanta, A. *Org. Biomol. Chem.* **2005**, *3*, 1428–1434; (d) Kim, J. S.; Shon, O. J.; Ko, J. W.; Cho, M. H.; Yu, I. Y., II; Vicens, J. *J. Org. Chem.* **2000**, *65*, 2386–2392.
14. (a) Prabagaran, N.; Abraham, S.; Sundararajan, G. *ARKIVOC* **2002**, *7*, 212–226; (b) Demirtas, H. N.; Bozkurt, S.; Durmaz, M.; Yilmaz, M.; Sirit, A. *Tetrahedron: Asymmetry* **2008**, *19*, 2020–2025.
15. (a) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161–170; (b) Gutsche, C. D. In *Calixarenes Revisited*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998.
16. (a) Mutihac, L.; Buschmann, H.-J.; Tudorescu, A.; Mutihac, R. *J. Inclusion Phenom. Macrocyclic Chem.* **2003**, *47*, 123–128; (b) Mutihac, L.; Buschmann, H.-J.; Mutihac, R.-C.; Schollmeyer, E. *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, *51*, 1–10.
17. (a) Arnecke, R.; Böhmer, V.; Cacciapaglia, R.; Cort, A. D.; Mandolini, L. *Tetrahedron* **1997**, *53*, 4901–4908; (b) Meadows, E. S.; De Wall, S. L.; Barbour, L. J.; Gokel, G. W. *J. Am. Chem. Soc.* **2001**, *123*, 3092–3107.
18. (a) Ogasahara, K.; Hirose, K.; Tobe, Y.; Naemura, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3227–3236; (b) Mohammed-Ziegler, I.; Poór, B.; Kubinyi, M.; Grofcsik, A.; Grün, A.; Bitter, I. *J. Mol. Struct.* **2003**, *650*, 39–44.
19. Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
20. (a) Li, Z.-T.; Ji, G.-Z.; Zhao, C.-X.; Yuan, S.-D.; Ding, H.; Huang, C.; Du, A.-L.; Wei, M. *J. Org. Chem.* **1999**, *64*, 3572–3584; (b) Kerdpaiboon, N.; Tomapatanaget, B.; Chailapakul, O.; Tuntulani, T. *J. Org. Chem.* **2005**, *70*, 4797–4804.
21. Job, P. *Ann. Chim. (Paris)* **1928**, *9*, 113–203.