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Synthesis and chiral recognition properties of two novel chiral calix[4]arene tartaric ester derivatives

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Abstract—Two new chiral calix[4]arene derivatives containing tartaric acid ester moieties were synthesized. The chiral calix[4]arenes are in a '*cone*' conformation according to NMR spectroscopy. The chiral recognition capabilities of **1**–**4** toward the guests, 1,2-propanediol and serine methyl ester hydrochloride (SerOMe), were investigated (^{1}H NMR spectroscopy). The extraction properties of compounds **1** and **2** toward selected α-amino acid methyl esters were also studied.
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1. Introduction

Chirality is a property that often determines the actions and behavior of molecules. It is of a major concern in biological systems.[1] In nature, biomolecules exist in only one of the possible enantiomeric forms, for example, amino acids in the L-form and sugars in the D-form. Natural living systems are composed of chiral biological materials, and they interact with each stereoisomer of a racemic drug, respectively, as well as metabolize each enantiomer by way of a separate pathway to produce different pharmacological activities. Therefore, one stereoisomer may produce the desired therapeutic activities, while the other may be inactive or produce harmful effects. The study of enantiomeric recognition of chiral compounds such as amines, amino alcohols, and amino acids is of particular importance since these compounds are the basic building blocks of naturally occurring compounds.[2]

Among the several types of host molecules for recognition, calixarenes offer a number of advantages in terms of their selectivity and efficiency of binding. The introduction of chiral substituents on the lower rim through the phenolic oxygens or at the *para* positions of the calix[4]arene skeleton or by synthesizing 'inherently' chiral derivatives could, in turn, lead to the chirality of the artificial receptors. Chiral receptors that are based on the calixarene[3] 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[4] have attracted considerable attention.

Recognition of chirality can be evaluated and compared spectroscopically, chromatographically, and electrochemically. Among the available methods, NMR spectroscopy[5] has been shown to be a powerful tool for investigating the chiral recognition interaction between a chiral receptor and an analyte in the solution state.[6] Detailed information regarding the nature of these interactions and the structure of the complexes can be provided from the NMR experiments. NMR spectra of enantiomers in an achiral medium display the same chemical shifts. Enantiodifferentiation in the spectra requires the use of a chiral medium that converts the mixture of enantiomers into a mixture of diastereomeric complexes. These complexes are held together by weak intermolecular interactions such as van der Waals forces and/or hydrogen bonds.

In our previous work, we reported the synthesis of calix[4]arene derivatives bearing a chiral (azoxa)crown-7 moiety at the lower rim and chromogenic nitro groups at the upper rim.[7] Herein, we report the synthesis and recognition properties of the dinitro and dialdehyde derivatives of chiral

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calix[4]arenes bearing enantiomerically pure tartaric acid ester moieties.

2. Results and discussion

2.1. Design and synthesis of new chiral calix[4]arene derivatives

Starting reagents **1** and **2** were prepared from the reaction of (2*R*,3*R*)-2,3-di-(2-chloroacetoxy)-di-(1-methylethyl) succinate, and *p*-*tert*-butylcalix[4]arene/calix[4]arene according to the literature procedure[8] as shown in Scheme 1. Ungaro and Reinhoudt reported the selective[9] and ipso-nitration[10] of some calixarene derivatives, while Zheng et al.[11] reported the nitration of calixcrowns. Since the nitro group is a good functional group or auxochrome for the phenol ring, the nitration of **2** was studied. Calix[4]-arene tartaric ester was selectively nitrated with HNO_3 in glacial acetic acid at 0 °C to give **3** in a good yield (85%). The formyl group introduced selectively at the upper rim of the conformationally rigid calix[4]arenes is very versatile, since it can be easily transformed into other functional groups.[12,13] By way of a slight modification of the literature,[14] the dialdehyde derivative **4** was obtained in 62% yield.

The nitrated and formylated products were characterized by a combination of ^{1}H NMR, ^{13}C NMR, FAB MS, 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]

Compounds **3** and **4** are chiral due to the formation of the chiral sub-ring on the lower rim of calix[4]arenes. ^{1}H and ^{13}C NMR data showed that new compounds are in the cone conformation. A typical AX pattern and two overlapped doublets were observed for the methylene bridge $ArCH_2Ar$ protons at 3.52 ($J = 12.9$ Hz, 2H), 3.65 ($J = 13.5$ Hz, 2H), and 4.20 ppm ($J = 12.7$ Hz, 4H) for **3** and 3.41 ($J = 12.8$ Hz, 2H), 3.52 ($J = 13.4$ Hz, 2H), and 4.13 ppm ($J = 13.8$ Hz, 4H) for **4** in ^{1}H NMR. The protons of the methylenes which are attached to the phenol oxygen, show an AB system coupling between 4.71 and 4.81 ppm for **3** and 4.60 and 4.73 ppm for **4**. This splitting pattern may relate to the presence of the chiral moieties in the molecules, as seen in other chiral calix[4]arenes.[4a,16]

Figures 1 and 2 show the UV–vis spectra of **3** and **4** in chloroform. Examination of the spectra showed broad absorption bands at 244, 330, and 242, 294 nm, respectively, suggesting in turn that compounds **3** and **4** could be used in recognition studies of cations, as sensors for anions and chiral molecules.

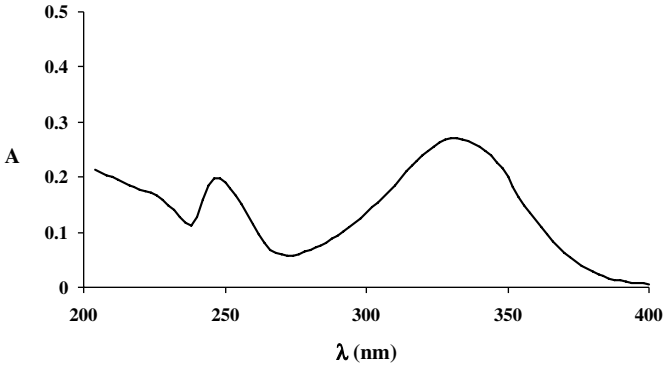


Figure 1. The UV–vis spectrum of compound **3**.

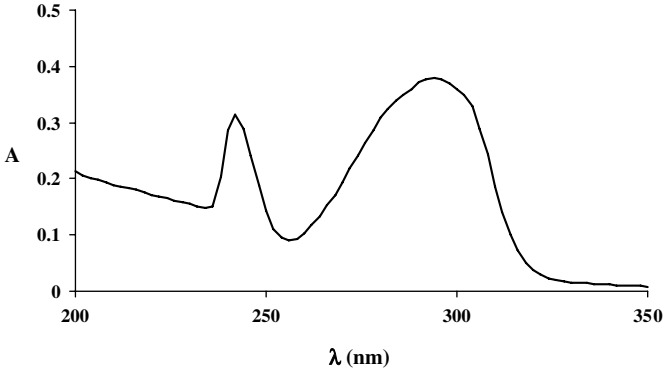
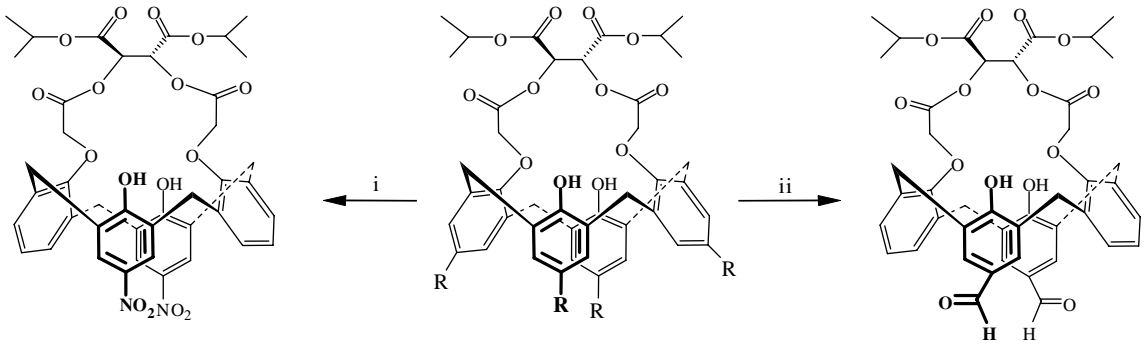


Figure 2. The UV–vis spectrum of compound **4**.

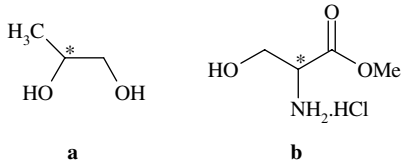


3 **1** R = $C(CH_3)_3$ **2** R = H **4**

Scheme 1. Reagents and conditions: (i) 70% HNO_3, glacial AcOH; (ii) $TiCl_4$, dichloromethyl methyl ether, $CHCl_3$.

2.2. Chiral recognition by ^{1}H NMR of host–guest complexes

NMR experiments were undertaken to assess the chiral recognition properties of ligands **1**–**4** by ^{1}H NMR. The racemic guests, 1,2-propanediol **a** and serine methyl ester hydrochloride (SerOMe) **b**, were chosen as probes (Fig. 3).



a **b**

Figure 3. Chemical structures of guests used in the experiments.

Figure 4 shows the ^{1}H NMR spectra for 1,2-propanediol **a** (10 mM) as a racemic mixture in the absence and presence of the chiral receptors **1**, **3**, and **4** (10 mM). When a solution of **a** (10 mM in $CDCl_3$) was gradually added to the 10 mM solution of **1** and **4** in $CDCl_3$, the OH proton signals of **a** moved upfield without displaying any resolution (Fig. 4C and D). ^{1}H NMR titration experiments with host **3** showed that the singlet at δ 4.39 ppm for the OH protons of the (*R*)- or (*S*)-forms of 1,2-propanediol **a** exhibited a gradual downfield shift with an increasing concentration of the guest, until the guest/host mole ratio reached 1:1; $\Delta\delta$ is 0.18 and 0.23 ppm toward the (*R*)- and (*S*)-forms of guest, respectively. This indicates that the interactions of host **3** with the (*R*)- and (*S*)-forms of *rac*-1,2-propanediol are different, resulting in two singlet resonances for the OH protons (Fig. 4B). It could be suggested that nitrated calix[4]arene bearing two phenolic moieties are strongly acidic and the interaction with guest **a** could be through intermolecular hydrogen bonding.

When a solution of receptor **2** (10 mM in $CDCl_3$) was treated with an equimolar amount of guest **b**, the CH proton of *rac*-SerOMe cleaved into two doublets of doublets with a downfield shift (from δ 3.84 to 4.03). This confirmed further that the enantioselective recognition had occurred between receptor **2** and the *rac*-SerOMe. Since the methine protons are adjacent to the ammonium cation, these protons must be significantly influenced by the oxygen of the chiral calix[4]arene platform. Moreover, the signals of the $-CH_2$ protons of guest **b** were shifted upfield, while –OMe proton signals moved downfield. This indicated that the interaction between the host and guest happened by way of multiple hydrogen bonds (Fig. 5).

Table 1 summarizes the chemical shift assignments of ^{1}H resonances for racemic guests **a**, **b**.

2.3. Extraction studies

In the present study, we used α-amino acid methyl esters, which had different molecular sizes in order to investigate the effect of size on their extraction efficiency, and supposed that both **1** and **2** could selectively extract α-amino acid methyl esters. Thus, two-phase solvent extraction studies were performed in order to examine the extraction behavior of α-amino acid methyl esters from the aqueous

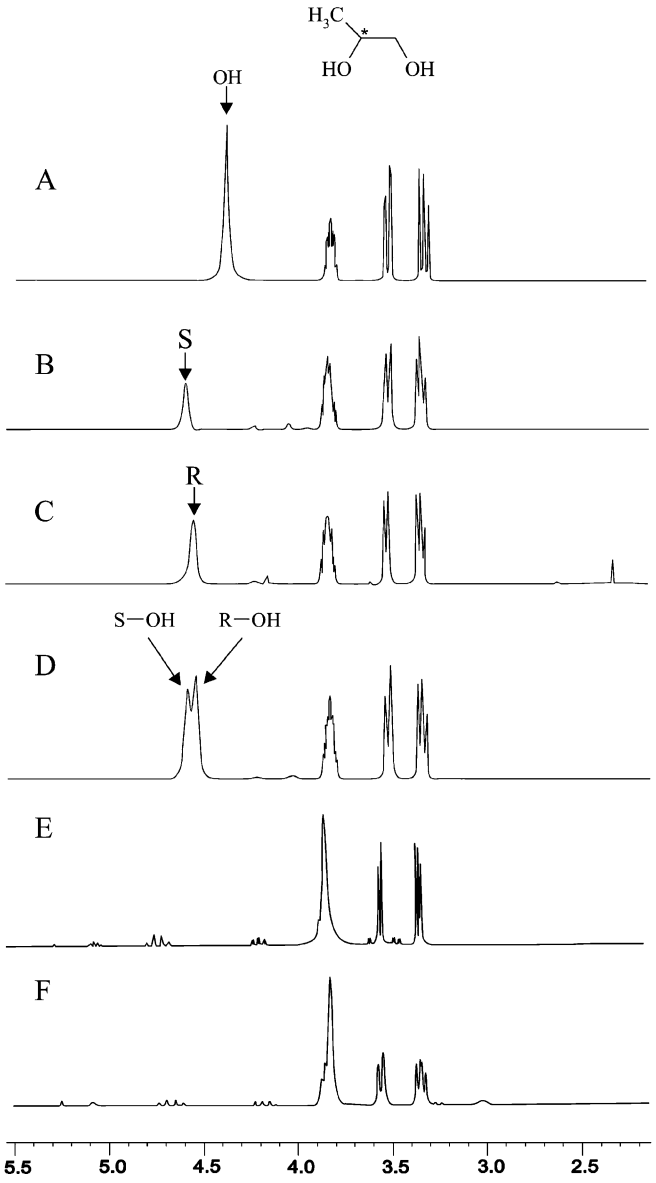


Figure 4. The 400 MHz ^{1}H NMR spectra (guest region) of 1,2-propanediol (**a**)/**1**, **2** and **4** complex with equimolar mixtures (10 mM each): (A) *rac*-**a**; (B) (*S*)-**a** with **3**; (C) (*R*)-**a** with **3**; (D) *rac*-**a** with **3**; (E) *rac*-**a** with **1**; (F) *rac*-**a** with **4** in $CDCl_3$ at 25 °C.

phase into the organic phase (CH_2Cl_2) by using chiral calix[4]arene derivatives **1** and **2**. The results of the picrate extraction studies are summarized in Table 2. These data were obtained by using a dichloromethane solution of the ligands to extract ammonium picrates from the aqueous solution. The equilibrium concentration of picrate in the aqueous phase was determined spectrophotometrically.[17]

It was observed that ammonium picrate extraction ratios did not change, in which compounds **1** and **2** did not display any selectivity toward α-amino acid methyl esters. The stoichiometry of the interaction between receptor **2** and D-AlaOMe was determined by a classical slope analysis method. Assuming the extraction of an ammonium cation ($R-NH_3^+$) by receptor **2** according to the following equilibrium:

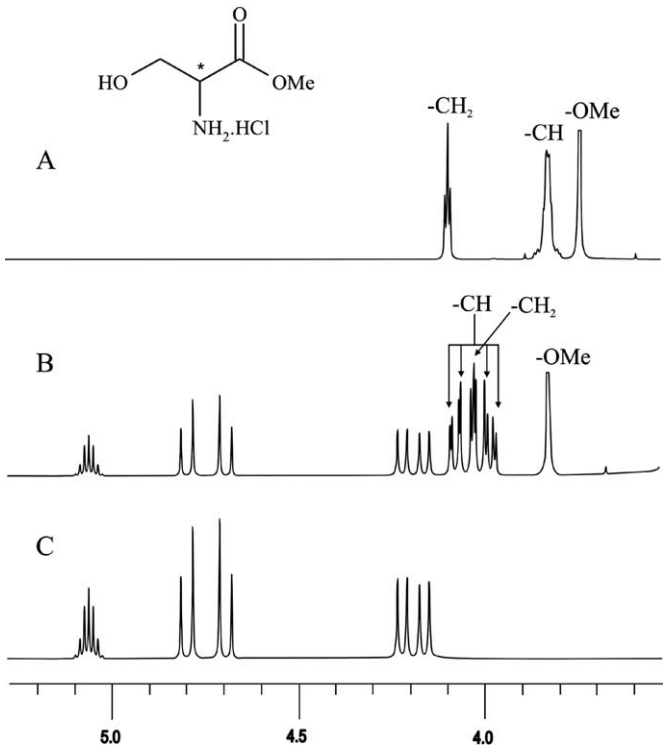


Figure 5. The 400 MHz ^{1}H NMR spectra (guest region) of *rac*-SerOMe—host **2** complex with equimolar mixtures (10 mM each). (A) *rac*-SerOMe; (B) *rac*- SerOMe with host **2**; (C) host **2**.

$$[\text{R–NH}_3{}^+]_{\text{aq}} + [\text{Pic}^-]_{\text{aq}} + x[\text{L}]_{\text{org}} \rightleftharpoons [\text{R–NH}_3\text{Pic(L)}_x]_{\text{org}}, \quad (1)$$

the extraction constant K_{ex} can then be defined as

$$K_{\text{ex}} = \frac{[\text{R–NH}_3\text{Pic(L)}_x]}{[\text{R–NH}_3{}^+][\text{Pic}^-][\text{L}]^x} \quad (2)$$

Eq. 2 can be rewritten as

$$\log D_{\text{A}} = \log K_{\text{ex}}\text{Pic} + x\log[\text{L}] \quad (3)$$

where the distribution ratio D_{A} is defined as ratio of concentrations of ammonium cation ($\text{R–NH}_3{}^+$) in two phases:

$$D_{\text{A}} = [\text{R–NH}_3\text{Pic(L)}_x]_{\text{org}}/[\text{R–NH}_3{}^+]_{\text{aq}} \quad (4)$$

Consequently, a plot of log D_{A} versus log[L] leads to a straight line whose slope allows the stoichiometry of the extracted species to be determined.

Figure 6 represents the extraction into dichloromethane at different concentrations of **2** for the ammonium ion. A linear relationship between log D_{A} versus log[L] was observed with a slope for ammonium ion by **2**, which equals 0.94, suggesting that **2** forms a 1:1 complex with an ammonium cation. The analytical data of **2** show that the complexation reaction takes place according to the following equilibrium:

$$(\text{L})_{\text{org}} + (\text{R–NH}_3{}^+\text{Pic}^-)_{\text{aq}} \overset{K_{\text{ex}}}{\rightleftharpoons} (\text{L, R–NH}_3{}^+\text{Pic}^-)_{\text{org}} \quad (5)$$

By using Eq. 5 for **2**, log K_{ex} a value of 3.01 ± 0.2 was obtained.

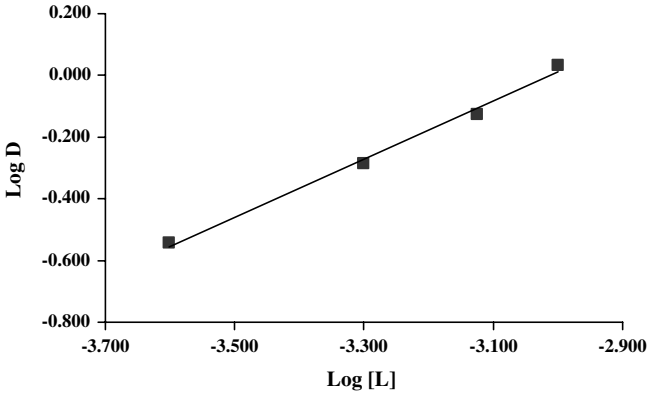


Figure 6. Log D versus log[L] for the extraction of D-AlaOMe by **2** from an aqueous phase into a dichloromethane phase at 25 °C.

Table 1. ^{1}H chemical shifts (ppm) of racemic guests in the absence and presence of hosts **1**–**4** at 25 °C in $CDCl_3$ or $CDCl_3$ + DMSO-d_6, respectively

Host	Guest	Free[a]	(*S*)-G[b]	$\Delta\delta$ (*S*)	(*R*)-G[b]	$\Delta\delta$ (*R*)	$\Delta\Delta\ \delta$[c]
3	**a**	4.39	4.62	−0.23	4.57	−0.18	0.05
1	**a**	4.39	3.82	0.57	3.82	0.57	0.00
2	**a**	4.39	4.35	0.04	4.35	0.04	0.00
2	**b** (–CH_2)	4.10	4.03	0.07	4.03	0.07	0.00
2	**b** (–OCH_3)	3.75	3.83	−0.08	3.83	−0.08	0.00
4	**a**	4.39	3.86	0.53	3.86	0.53	0.00

[a] [*rac*-**a**, **b**] = 10 mM.
[b] The chemical shifts were based on the spectra of *rac*-**a**, **b** (10 mM) in the presence of **1**–**4** (10 mM).
[c] Obtained by subtracting the Host–(*R*)-Guest value from the Host–(*S*)-Guest value.

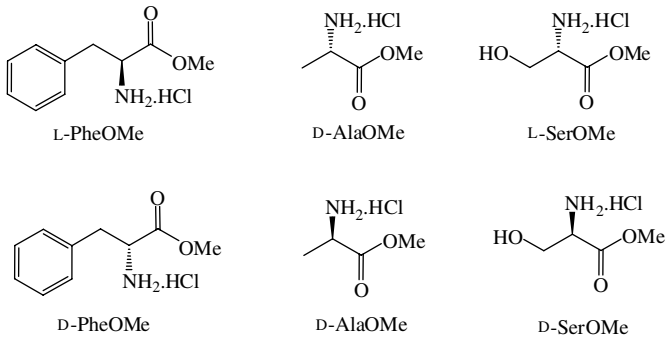
Table 2. Extraction percentage of selected α-amino acid methyl esters with[a] **1**–**2**

Ligand	L-SerOMe	D-SerOMe	L-AlaOMe	D-AlaOMe	L-PheOMe	D-PheOMe
1	39.8	40.9	35.9	42.6	40.1	39.5
2	42.9	44.4	47.4	64.7	45.4	44.5

Organic phase, dichloromethane, [ligand] = 1.0×10^{-3}; at 25 °C, for 1 h.
[a] Aqueous phase, [ammonium picrate] = 2.0×10^{-5}.

3. Conclusions

Herein, two new chiral calix[4]arene derivatives containing tartaric acid ester moieties were synthesized in excellent yields. The chiral recognition capabilities of **1**–**4** toward various racemic guests by ^{1}H NMR spectroscopy were investigated. Chiral host compounds **2**, **3**, and **4** showed enantiomeric recognition toward guest *rac*-SerOMe and 1,2-propanediol, respectively. Host **3** has a potential application for the assay and enantiomeric recognition of the above-mentioned α-amino acid methyl esters. The extraction properties of compounds **1** and **2** toward some selected α-amino acid methyl esters were also studied. The results showed that these compounds did not display any selectivity toward α-amino acid methyl esters.



Scheme 2. The chemical structure of α-amino acid derivatives used in the experiments.

4. Experimental

4.1. Reagents and general methods

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 using a Bruker 400 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. IR spectra were obtained on a Perkin–Elmer 1605 FTIR spectrometer as KBr pellets. Optical rotations were measured on A-Krüss Optronic polarimeter. FAB-MS spectra were taken on a Varian MAT 312 spectrometer. Elemental analysis data were performed on a Leco CHNS-932 analyzer.

All of the reactions, unless otherwise noted, were conducted under a nitrogen atmosphere. Analytical TLC was performed using aluminum sheet Merck 60 F254 silica gel plates. Column chromatography separations were performed on Merck Silica Gel 60 (230–400 mesh). All of the starting materials and reagents which were used were of standard analytical grade from Fluka, Merck, and Aldrich, and used without further purification. Toluene was dried with calcium hydride and stored over a sodium wire. Other commercial grade solvents were distilled and then stored over 4 Å molecular sieves. The drying agent employed was anhydrous $MgSO_4$. All of the aqueous solutions were prepared with deionized water, which had been passed through a Millipore Milli-Q Plus water purification system.

Analytical grade α-amino acid methyl ester hydrochlorides were purchased from Aldrich and employed without further purification as guest molecules for the solvent extraction experiments, that is, L-alanine methyl ester hydrochloride (L-AlaOMe), D-alanine methyl ester hydrochloride (D-AlaOMe), L-phenylalanine methyl ester hydrochloride (L-PheOMe), D-phenylalanine methyl ester hydrochloride (D-PheOMe), L-serine methyl ester hydrochloride (L-SerOMe), and D-serine methyl ester hydrochloride (D-SerOMe) (Scheme 2).

4.1.1. (40*R*,50*R*)-5,17-Dinitro-25,27-dihydroxy-26,28-(40,50-di-1-methylethoxycarbonyl-30,60-dioxa-20,70-dioxooctylene)-dioxycalix[4]arene 3. To a slurry of 2.0 g (2.71 mmol) of **2** in 20 mL of glacial AcOH was added 5 mL of 70% HNO_3 in portions at 0 °C. The reaction mixture was stirred for 2 h and poured into ice-cold water, and the light yellow precipitate separated by filtration. This material was washed with cold water and triturated with MeOH to afford a single compound pure enough for subsequent reactions. An analytical sample was obtained by passing the product through a silica gel column ($CHCl_3$–*n*-hexane eluent), recrystallizing from $CHCl_3$–*n*-hexane (1:3), and stirring with MeOH to yield 1.91 g (85%) of a colorless solid. Mp 268–269 °C; $[\alpha]_D^{20} = +50.2$ (*c* 0.5, $CHCl_3$). IR (KBr): 3331 (OH), 1766 (OCO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm): 1.18 (d, 6H, $J = 6.2$ Hz, $CH(CH_3)_2$), 1.22 (d, 6H, $J = 6.2$ Hz, $CH(CH_3)_2$), 3.52 (d, $J = 12.9$ Hz, 2H, $ArCH_2Ar$), 3.65 (d, $J = 13.5$ Hz, 2H, $ArCH_2Ar$), 4.20 (t, 4H, $J = 12.7$ Hz, $ArCH_2Ar$), 4.71–4.81 (AB, d, 4H, $J = 16.1$ Hz, OCH_2CO), 5.09 (hep, 2H, $J = 6.3$ Hz, $OCH(CH_3)_2$), 6.25 (s, 2H, OC*H*), 6.96 (t, 2H, $J = 7.5$ Hz, Ar*H*), 7.09 (t, 4H, $J = 7.5$ Hz, Ar*H*), 8.05 (t, 4H, $J = 6.2$ Hz, Ar*H*), 9.07 (s, 2H, O*H*); ^{13}C NMR ($CDCl_3$): δ (ppm): 21.4, 21.5, 30.9, 31.4, 71.1, 71.6, 71.8, 124.7, 124.8, 126.9, 127.0, 128.1, 129.9, 130.2, 131.3, 132.0, 139.7, 149.7, 159.6, 164.8, 166.0. FAB-MS *m*/*z*: 852.3 $[M+Na]^+$. Anal. Calcd for $C_{42}H_{40}O_{16}N_2$ (829.4): C, 60.87, H, 4.86, N, 3.38. Found: C, 60.72, H, 4.68, N, 3.45.

4.1.2. (40*R*,50*R*)-5,17-Diformyl-25,27-dihydroxy-26,28-(40,50-di-1-methylethoxycarbonyl-30,60-dioxa-20,70-dioxooctylene)-dioxycalix[4]arene 4. A solution of 1,1-dichloromethylmethylether (5.1 mmol) in chloroform (10 mL) was added to a solution of compound **2** (0.3 mmol) in chloroform (5 mL) with stirring at room temperature, followed by the addition of titanium tetrachloride (5.1 mmol). The reaction mixture was stirred for an additional 2 h and then treated with water (3 mL) and MeOH (1 mL). The organic layer was separated, washed twice with water (2 × 15 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was recrystallized from EtOAc/*n*-hexane. Yield 62% (1.48 g); mp: 203–206 °C; $[\alpha]_D^{20} = +28.2$ (*c* 0.3, $CHCl_3$). IR (KBr): 3354 (OH), 1762, 1683 (OCO), 1600 (CHO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) 0.97 (d, $J = 6.2$ Hz, 6H, $CH(CH_3)_2$), 1.04 (d, $J = 6.3$ Hz, 6H, $CH(CH_3)_2$), 3.41 (d, $J = 12.8$ Hz, 2H, $ArCH_2Ar$), 3.52 (d, $J = 13.4$ Hz, 2H, $ArCH_2Ar$), 4.13 (t, $J = 13.1$ Hz, 4H, $ArCH_2Ar$), 4.60–4.73 (AB, d, $J = 16.1$ Hz, 4H, OCH_2CO), 4.94 (hep, $J = 6.24$ Hz, 2H, $OCH(CH_3)_2$), 6.16 (s, 2H, OC*H*), 6.73 (t, 2H, $J = 7.6$ Hz,

ArH), 6.94 (d, 4H, $J = 7.4$ Hz, ArH), 7.55 (d, 4H, $J = 6.5$ Hz, ArH), 8.84 (s, 2H, OH), 9.67 (s, 2H, –CH); ^{13}C NMR ($CDCl_3$): δ (ppm): 20.9, 21.2, 21.5, 31.0, 31.4, 31.6, 71.0, 71.7, 71.8, 126.7, 127.5, 128.7, 129.7, 129.9, 130.9, 131.3, 132.6, 149.8, 159.6, 165.0, 166.4, 170.0, 171.0. FAB-MS m/z: 817.8 $[M+Na]^+$. Anal. Calcd for $C_{44}H_{42}O_{14}$ (794.8): C, 66.49, H, 5.33. Found: C, 66.63, H, 5.28.

4.2. Analytical procedure

In NMR titrations, host compounds **1**–**4** dissolved in dry $CDCl_3$ and the stock solutions of guests' **a**, **b** were prepared by dissolving in dry $CDCl_3$. However, owing to the partial solubility of the *rac*-SerOMe in $CDCl_3$, a few drops of dry DMSO-d_6 (2% in each case) were added to the stock solution to prepare a homogeneous solution of the guest. Upon addition of the guest solution to the 10 mM host solution, upfield or downfield chemical shifts and the resolutions of resonances for various protons of guest compounds were observed.

Picrate extraction experiments were performed following Pedersen's procedure. A 10 mL portion of a 2.0×10^{-5} M aqueous picrate and a 10 mL portion of 1.0×10^{-3} M solution of calixarene **1** or **2** in CH_2Cl_2 were vigorously agitated in a stoppered glass tube with a mechanical shaker for 2 min, then magnetically stirred in a thermostated water-bath at 25 °C for 1 h, and finally left to stand for an additional 30 min. The concentration of the picrate ion remaining in the aqueous phase was then determined spectrophotometrically at 357 nm. Blank experiments showed that no picrate extraction occurred in the absence of calixarene. The percentage extraction (E%) was calculated as

$$(E\%) = A_0 - A/A_0 \times 100$$

where A_0 and A are the initial and final concentrations of the amino acid methyl ester hydrochlorides picrate before and after the extraction, respectively.

To prepare the ammonium picrates, an aqueous solution of α-amino acid methyl ester hydrochloride salt was treated with a saturated Na_2CO_3 solution and extracted three times with CH_2Cl_2. The organic phase was dried over $MgSO_4$. The solvent was evaporated until dryness to give pure α-amino acid methyl ester. α-Amino acid methyl ester and picric acid in the molar ratios of 1:1 were then dissolved in deionized water. Thus, the stock solution was diluted to 2.0×10^{-5} M and was used in liquid–liquid extraction experiments.

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