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Synthesis of new chiral calix[4]arene diamide derivatives for liquid phase extraction of α-amino acid methylesters

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Abstract—The synthesis of chiral diamide derivatives of calix[4]arene from the reaction of *p-tert*-butylcalix[4]arene diester **1a** and calix[4]arene diester **1b** with various amino alcohols were reported. The ^{1}H and ^{13}C NMR, data showed that the compounds synthesized exist in the cone conformation. The extraction study properties of these new compounds **3a**,**b**–**4a**,**b** towards some selected α-amino acid methylesters are also reported.

1. Introduction

Calixarenes represent an important class of macrocyclic compounds due to their potential for forming host–guest complexes with numerous classes of compounds in supramolecular chemistry. To date, various calixarenes that possess ketone,[1] amine,[2] ester,[3] amide,[4] carboxylic acid[5] or other functional groups[6–11] have been synthesized for separation,[12] recognition,[13] discrimination[14] and catalysis.[15] Among them, chiral recognition, the process in which an enantiomerically pure host molecule, such as a chiral calixarene, selectively binds one of the enantiomers, is one of the more essential reaction processes occurring in living systems.[16] Therefore, chiral calixarenes have attracted increasing research interest in the fields of organic, biological and medicinal chemistry.

Chirality can be introduced into the calixarene platform either by attaching chiral units at one of the calix rims, or by synthesizing 'inherently' chiral derivatives, in which the nonplanarity of the molecule is exploited.[17a–c] Since the synthesis of calixarenes bearing chiral residues were first reported by Shinkai et al.,[17d] a large number of calix[4]arene derivatives have been prepared by introducing chiral substituents on the lower rim through the phenolic oxygens or at the *para* positions of the calix[4]arene skeleton.[17e,g] Among the most popular chiral building blocks used, amino acids,[18] peptides,[19] amino alcohols,[20] sugars,[21] tartaric acid esters,[22] binaphthyl,[23] glycidyl,[24] menthone[25] and guanidinium[26] groups offer a wide range of possibilities for providing calix[4]arenes with asymmetric features. Many of the chiral calix[4]arene derivatives have shown remarkable recognition properties toward achiral cations and anions,[27] however, more interestingly, some of them have exhibited significant chiral discrimination abilities for chiral guests such as organic ammonium salts, amino alcohols and amino acids.[28]

One of the most important features of amino acids is to assemble a large variety of proteins and enzymes. Therefore, they can be considered the fundamental constituents of a wide variety of biological macromolecules. In 1990, by employing a calix[6]arene derivative as a selective carrier, Chang et al. first reported the transport of *N*-benzoyl amino acids through a chloroform liquid membrane.[29a] Later, a series of carboxylic acid derivatives were used as host molecules for the quantitative extraction of amino acid methyl esters in a liquid–liquid extraction system.[29b] Furthermore, *p-tert*-butylcalix[*n*]arenes ($n = 6$ and 8) were investigated as carriers in a liquid membrane composed of a porous polymeric support.[29c] The chiral recognition of amino acids by calixarenes has also been reported.[29d,e] Recently, Yilmaz et al. developed chiral calix[4]arene derivatives as extractants for various amines and α-amino acid methylesters.[2a]

In a previous work, we reported the synthesis of calix[4]-arene derivatives bearing a chiral (azoxa)crown-7 moiety

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on the lower rim and chromogenic nitro groups at the upper rim.[17g,27a] Herein we report the synthesis of a novel chiral calix[4]arene platform with amide derivatives on their lower rim for quantitative extraction of α-amino acid methylesters in a liquid–liquid extraction system.

2. Results and discussion

2.1. Design and synthesis of the new chiral hosts

Herein, we have extended our previous studies[4,17g,27a] and report the synthesis of chiral amide derivatives using commercially available, inexpensive chiral amino alcohols. We have also explored the extraction properties of chiral calix[4]arene amide derivatives **3a**,**b** and **4a**,**b** towards some selected α-amino acid methylesters through the two-phase solvent extraction system. To achieve the desired goal, the diester derivatives of *p-tert*-butylcalix[4]arene **1a** and calix[4]arene **1b** were chosen as the precursors. The synthesis of compounds **1a** and **1b** was performed according to previously described methods;[4b] compounds **2a**–**4a** and **2b**–**4b** are reported for the first time. The synthetic route was conducted as shown in Scheme 1.

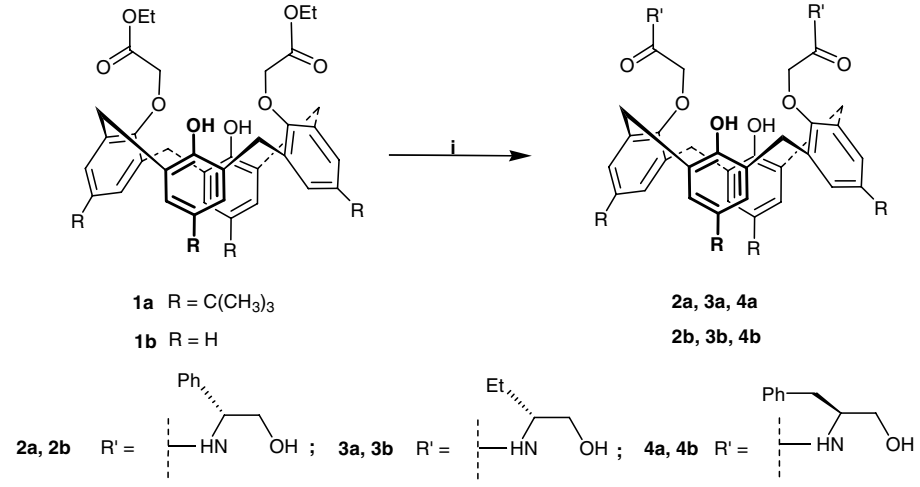
In the synthesis of *p-tert*-butylcalix[4]arene and calix[4]arene diamides, the aminolysis reaction of *p-tert*-butylcalix[4]arene and calix[4]arene diesters is a new method.[3b,c,4a] Thus, following the strategy outlined in Scheme 1, 5,11,17,23-tetra-*tert*-butyl-25,27-diethoxycarbonylmethoxy-26,28-dihydroxy calix[4]arene **1a** and 25,27-diethoxycarbonylmethoxy-26,28-dihydroxy calix[4]arene **1b** were refluxed with (*R*)-(−)-phenylglycinol, (*R*)-(−)-2-amino-1-butanol and (*S*)-(−)-2-amino-3-phenyl-propanol, respectively, in toluene/methanol (1:1) mixture to give the corresponding diamide derivatives of *p-tert*-butyl calix[4]arene and calix[4]arene **2a**–**4a** and **2b**–**4b** in 66–73% yields.

The new compounds **2a**–**4a** and **2b**–**4b** were characterized by a combination of ^{1}H NMR, ^{13}C NMR, IR, FAB MS and elemental analysis. The formation of the chiral diamide derivatives of *p-tert*-butyl calix[4]arene and calix[4]arene **2a**–**4a** and **2b**–**4b** were confirmed by the appearance of the characteristic amide bands at about 1660 cm^{-1}, and by the disappearance of the ester carbonyl band at about 1755 cm^{-1} in their IR spectra. The conformational characteristics of calix[4]arenes were conveniently estimated by the splitting pattern of the $ArCH_2Ar$ methylene protons in the ^{1}H and ^{13}C NMR spectroscopy.

^{1}H and ^{13}C NMR data showed that compounds **2a**–**4a** and **2b**–**4b** have a cone conformation. A typical AX pattern was observed for the methylene bridge $ArCH_2Ar$ protons at 3.23 ($J = 13.0$ Hz), 3.42 ($J = 13.7$ Hz), 4.09 ($J = 13.7$ Hz), 4.26 ($J = 13.0$ Hz) for **2a**, 3.36 ($J = 13.2$ Hz), 3.54 ($J = 13.8$ Hz), 4.04 ($J = 13.8$ Hz) and 4.25 ($J = 13.2$ Hz) for **2b**, 3.21 ($J = 13.8$ Hz), 3.32 ($J = 13.0$ Hz), 4.01 ($J = 13.8$ Hz) and 4.28 ($J = 13.0$ Hz) for **3a**, 3.39 ($J = 12.0$ Hz), 3.58 ($J = 13.8$ Hz), 4.11 ($J = 13.8$ Hz) and 4.40 ($J = 12.0$ Hz) for **3b**, 2.90 ($J = 13.0$ Hz), 3.46 ($J = 13.5$ Hz), 3.91 ($J = 13.0$ Hz), 4.10 ($J = 13.5$ Hz) for **4a**, 2.97 ($J = 13.1$ Hz), 3.55 ($J = 13.8$ Hz), 3.84 ($J = 13.1$ Hz), 4.12 ($J = 13.7$ Hz) for **4b** in ^{1}H NMR. The high field doublets at 3.23, 3.42 for **2a**, 3.36, 3.54 for **2b**, 3.21, 3.32 for **3a**, 3.39, 3.58 for **3b**, 2.90, 3.46 for **4a**, 2.97, 3.55 for **4b** were assigned to the equatorial protons of the methylene groups, whereas the low field signals at 4.09, 4.26 for **2a**, 4.04, 4.25 for **2b**, 4.01, 4.28 for **3a**, 4.11, 4.40 for **3b**, 3.91, 4.10 for **4a**, 3.84, 4.12 for **4b** were assigned to the axial protons in ^{1}H NMR and two signals covering a range of 32.46 and 30.93 ppm in ^{13}C NMR.

2.2. Two-phase solvent extraction experiments

Two-phase solvent extraction studies were performed in order to examine the extraction behaviour of α-amino acid methylesters from the aqueous phase into the organic phase (CH_2Cl_2) by using novel chiral *p-tert*-butylcalix[4]arene and calix[4]arene diamide derivatives **3a**,**b**–**4a**,**b**. The results of the picrate extraction studies are summarized in Table 1. This data was obtained by using a dichloromethane solution of the ligands to extract ammonium picrates from the aqueous solution. The equilibrium



Scheme 1. Reagents and conditions: (i) the appropriate amino alcohol, toluene/MeOH (1:1), reflux, 72 h.

Table 1. Extraction percentage of selected α-amino acid methylesters with **3a**,**b**–**4a**,**b**[a]

Ligand	L-SerOMe	D-SerOMe	L-AlaOMe	D-AlaOMe	L-PheOMe	D-PheOMe
3a	53.4	54.5	52.2	53.1	48.3	49.6
3b	44.1	44.9	45.1	47.7	47.3	48.2
4a	59.4	66.8	54.0	62.4	54.9	56.7
4b	42.0	48.4	45.1	41.4	40.4	45.0

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

concentration of picrate in the aqueous phase was determined spectrophotometrically.

In this study, D- and L-α-amino acid methylesters were used in order to examine the effect of the size on their extraction efficiency. From the data given in Table 1, it was observed that all α-amino acid methylesters were highly extracted by **3a** and **4a** whereas **3b** and **4b** showed relatively lower extraction abilities. This implies the better preorganization of fixed **3a** and **4a** in the cone conformation in solution. Conversely **3b** and **4b** are significantly more flexible than **3a** and **4a**. The conformation of **3a** and **4a** have less flexibility because the *tert*-butyl groups lock them in the cone conformation in the liquid phase.

The extraction data for **3a** were analyzed by a classical slope analysis method. Assuming the extraction of an ammonium cation ($R–NH_3^+$) by the receptor **3a** according to the following equilibrium:

$$[R–NH_3^+]_{aq} + [Pic^-]_{aq} + x[L]_{org} \rightleftharpoons [R–NH_3Pic(L)_x]_{org} \quad (1)$$

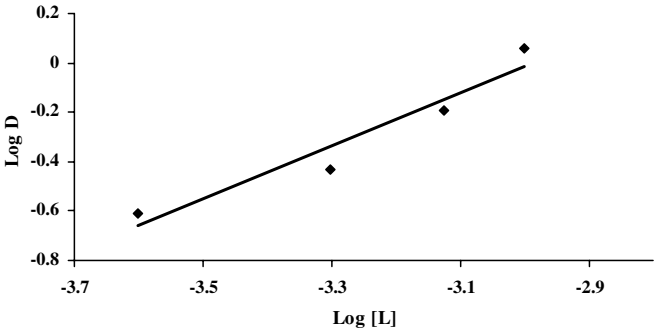


Figure 1. Log D versus log[L] for the extraction of D-SerOMe by **3a** from an aqueous phase into a dichloromethane phase at 25 °C.

The extraction constant K_{ex} is then defined by

$$K_{ex} = \frac{[R–NH_3Pic(L)_x]}{[R–NH_3^+][Pic^-][L]^x} \quad (2)$$

Eq. 2 can be rewritten as

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

where the distribution ratio D_A is defined as the ratio of concentrations of ammonium cation ($R–NH_3^+$) in two phases:

$$D_A = [R–NH_3Pic(L)_x]_{org}/[R–NH_3^+]_{aq} \quad (4)$$

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.

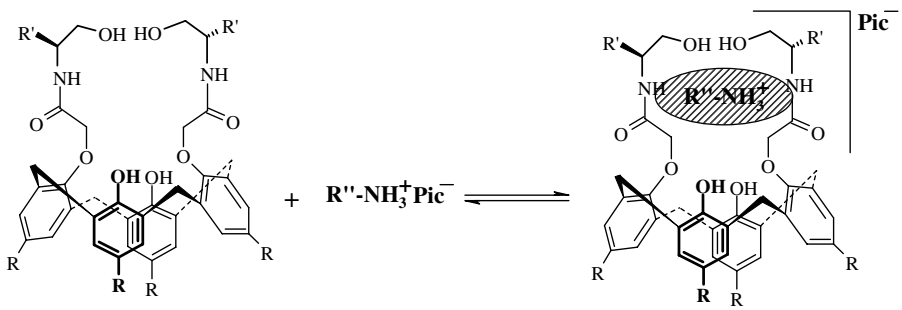
Figure 1 represents the extraction of **3a** into the dichloromethane phase at different concentrations for D-SerOMe. A linear relationship between $\log D_A$ versus log[L] was observed with a slope for ammonium ion by **3a**, which equals 1.07 suggesting that **3a** forms a 1:1 complex with an ammonium cation (Scheme 2). The analytical data of **3a** show that the complexation reaction takes place according to the following equilibrium:

$$(L)_{org} + (R–NH_3^+Pic^-)_{aq} \overset{K_{ex}}{\rightleftharpoons} (L, R–NH_3^+Pic^-)_{org} \quad (5)$$

According to the experimental data, if Eq. 3 is rearranged for **3a**, $\log K_{ex}$ can be calculated as the value 3.19 ± 0.2.

3. Conclusions

In this study, six chiral calix[4]arene amide derivatives **2a**,**b**, **3a**,**b** and **4a**,**b** have been synthesized by the aminolysis reaction of calix[4]arene esters. The enantioselective recogni-



Scheme 2. The proposed interactions of the diamide derivatives of calixarene with an ammonium cation belonging to an amino acid.

tion ability of the receptors was studied by UV/vis absorbtion spectroscopy. All receptors efficiently extracted α-amino acid methylesters, however they did not show any enantioselectivity towards selected α-amino acid methylesters.

4. Experimental

4.1. Reagents and general methods

Melting points were determined on a 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 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 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 starting materials and reagents 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 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 aqueous solutions were prepared with deionized water, which had been passed through a Millipore Milli-Q Plus water purification system.

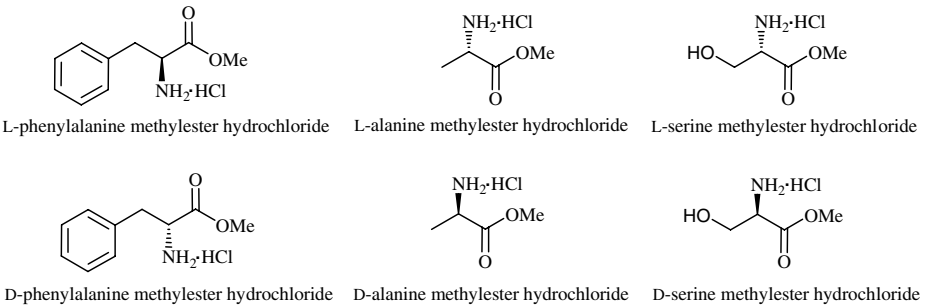
Analytical grade α-amino acid methylester hydrochlorides were purchased from Aldrich and employed without further purification as guest molecules for the solvent extraction experiments: L-alanine methylester hydrochloride (L-AlaOMe), D-alanine methylester hydrochloride (D-AlaOMe), L-phenylalanine methylester hydrochloride (L-PheOMe), D-phenylalanine methylester hydrochloride (D-PheOMe), L-serine methylester hydrochloride (L-SerOMe) and D-serine methylester hydrochloride (D-SerOMe) (Scheme 3).

4.2. General procedure for the synthesis of compounds 2a–4a and 2b–4b

An appropriate amino alcohol (20.0 mmol) was dissolved in 1:2 toluene/MeOH mixture (60 mL) and added dropwise to a solution of either 25,27-diethoxycarbonylmethoxy-26,28-dihydroxycalix[4]arene **1** or 5,11,17,23-tetra-*tert*-butyl-25,27-diethoxycarbonylmethoxy-26,28-dihydroxycalix-[4]arene **2** and (4.0 mmol) in 20 mL toluene with continuous stirring at room temperature for about 30 min. The reaction mixture was refluxed and the reaction was monitored by TLC. After the substrate had been consumed, the solvent was evaporated under reduced pressure and the residue triturated with MeOH to give a crude product. The crude products were purified by flash chromatography and recrystallized.

4.2.1. Compound 2a. The crude product was purified by flash chromatography (SiO_2, eluent EtOAc/hexane 1:1) and recrystallized from EtOAc/hexane, as white crystals; yield 73%; $[\alpha]_D^{20} = -8.7$ (c 0.3, $CHCl_3$). Mp: 130–133 °C. IR (KBr, cm^{-1}): 3340 (OH), 1664 (CO); ^{1}H NMR ($CDCl_3$): δ 9.40 (d, 2H, $J = 6.7$ Hz, N*H*), 7.32 (s, 2H, ArO*H*), 7.29–7.23 (m, 4H, Ar*H*), 7.15–7.00 (m, 10H, Ar*H*, ph), 6.78 (d, 4H, $J = 13.2$ Hz, ArH), 5.22 (t, 2H, O*H*), 4.90 (d, 2H, $J = 15.1$ Hz, CH_2OH), 4.26 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 4.16 (d, 2H, $J = 15.1$ Hz, CH_2OH), 4.09 (d, 2H, $J = 13.7$ Hz, ArCH_2Ar), 3.88 (s, 4H, OCH_2CO), 3.82 (t, 2H, –NHC*H*–ph), 3.42 (d, 2H, $J = 13.7$ Hz, ArCH_2Ar), 3.23 (d, 2H, $J = 13.0$ Hz, ArCH_2-Ar), 1.31 (s, 18H, C(CH_3)$_3$), 0.93 (s, 18H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 169.62 (*C*=O), 150.01, 149.61 (Ar*C*), 139.23, 132.43, 132.26, 129.06, 128.49, 128.25, 127.86, 127.50, 127.13, 126.96, 126.75, 125.97, 125.60, 125.18 (Ar*C*H), 75.00, 65.81 (O*C*H$_2$), 56.56 (*C*H), 32.46, 31.80 (Ar*C*H$_2$Ar), 10.65, 10.22 (*C*H$_3$); FAB-MS m/z: (1026.4) $[M+Na]^+$. Anal. Calcd for $C_{64}H_{78}N_2O_8$ (1003.34): C, 76.62; H, 7.84; N, 2.79. Found: C, 76.57; H, 7.69; N, 2.62.

4.2.2. Compound 2b. The crude product was purified by flash chromatography (SiO_2, eluent CH_2Cl_2/acetone 10:1) and recrystallized from CH_2Cl_2/MeOH, as white crystals; yield 69%; $[\alpha]_D^{20} = -30$ (c 0.5, $CHCl_3$). Mp: 156–157 °C. IR (KBr, cm^{-1}): 3312 (OH), 1664 (CO). ^{1}H NMR ($CDCl_3$): δ 9.48 (d, 2H, $J = 6.4$ Hz, N*H*), 7.76 (s, 2H, ArO*H*), 7.30–7.24 (m, 4H, Ar*H*) 7.18–7.13 (m, 6H,



Scheme 3. The chemical structure of α-amino acid derivatives used in experiments.

Ar*H*, ph), 7.12–7.08 (m, 4H, Ar*H*, ph), 6.94–6.88 (m, 4H, Ar*H*), 6.82–6.72 (m, 4H, Ar*H*), 5.24 (t, 2H, O*H*), 4.92 (d, 2H, $J = 15.2$ Hz, CH_2OH), 4.25 (d, 2H, $J = 13.2$ Hz, ArCH_2Ar), 4.22 (s, 4H, OCH_2CO), 4.20 (d, 2H, $J = 15.2$ Hz, CH_2OH), 4.04 (d, 2H, $J = 13.8$ Hz, ArCH_2Ar), 3.89 (t, 2H, –NHC*H*–ph), 3.54 (d, 2H, $J = 13.8$ Hz, ArCH_2Ar), 3.36 (d, 2H, $J = 13.2$ Hz, ArCH_2Ar); ^{13}C NMR ($CDCl_3$): δ 169.39 (*C*=O), 151.88, 151.82 (Ar*C*), 138.58, 132.60, 132.55, 130.14, 129.26, 129.11, 128.68, 128.53, 127.70, 127.65, 126.97, 126.92, 126.40, 120.39 (Ar*C*H), 74.9, 66.1 (O*C*H$_2$), 56.6 (*C*H), 32.04, 31.62 (Ar*C*H$_2$Ar); FAB-MS *m/z*: (801.9) $[M+Na]^+$ (calcd 861.8). Anal. Calcd for $C_{48}H_{46}N_2O_8$ (778.89): C, 74.02; H, 5.95; N, 3.59. Found: C, 74.26 H, 5.87; N, 3.42.

4.2.3. Compound 3a. The crude product was purified by flash chromatography (SiO_2, eluent CH_2Cl_2/acetone 10:1) and recrystallized from CH_2Cl_2/MeOH, as white crystals; yield 71%; $[\alpha]_D^{20} = -9.3$ (*c* 0.4, $CHCl_3$). Mp 243–246 °C. IR (KBr, cm^{-1}): 3365 (OH), 1656 (CO). ^{1}H NMR ($CDCl_3$): δ 8.94 (d, 2H, $J = 7.3$ Hz, N*H*), 7.45 (s, 2H, ArO*H*), 7.18 (s, 4H, Ar*H*), 6.98 (s, 4H, Ar*H*), 4.85 (d, 2H, $J = 15.0$ Hz, CH_2OH), 4.59 (t, 2H, O*H*), 4.28 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 4.16 (d, 2H, $J = 15.0$ Hz, CH_2OH), 4.04 (s, 4H, OCH_2CO), 4.01 (d, 2H, $J = 13.8$ Hz, ArCH_2Ar), 3.80 (q, 4H, CH_2CH$_3$), 3.64 (p, 2H, –NHC*H*Et), 3.32 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 3.21 (d, 2H, $J = 13.8$ Hz, ArCH_2Ar), 1.22 (s, 18H, C(CH_3)$_3$), 0.93 (s, 18H, C(CH_3)$_3$), 0.88 (t, 6H, CH$_2$CH_3), 0.85 (t, 6H, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$): δ 169.42 (*C*=O), 151.95, 151.79 (Ar*C*), 132.51, 132.33, 132.22, 130.21, 129.34, 129.12, 128.53, 127.81, 127.58, 126.95, 126.71, 126.18, 125.92, 125.62 (Ar*C*H), 74.95, 64.51 (O*C*H$_2$), 53.49 (*C*H), 31.62, 30.95 (Ar*C*H$_2$Ar), 24.09 (*C*H$_2$), 10.73, 10.45 (*C*H$_3$); FAB-MS *m/z*: (930.4) $[M+Na]^+$. Anal. Calcd for $C_{56}H_{78}N_2O_8$ (907.25): C, 74.14; H, 8.67; N, 3.09. Found: C, 74.22; H, 8.71; N, 3.13.

4.2.4. Compound 3b. The crude product was purified by flash chromatography (SiO_2, eluent CH_2Cl_2/acetone 10:1) and recrystallized from CH_2Cl_2/MeOH, as white crystals; yield 72%; $[\alpha]_D^{20} = -24$ (*c* 0.5, $CHCl_3$). Mp 226–230 °C. IR (KBr, cm^{-1}): 3317 (OH), 1655 (CO). ^{1}H NMR ($CDCl_3$): δ 9.10 (d, 2H, $J = 7.3$ Hz, N*H*), 7.99 (s, 2H, ArO*H*), 7.13–7.07 (m, 6H, Ar*H*), 6.85–6.81 (m, 3H, Ar*H*), 6.77–6.72 (m, 3H, Ar*H*), 5.00 (d, 2H, $J = 15.0$ Hz, CH_2OH), 4.60 (t, 2H, O*H*), 4.40 (d, 2H, $J = 12.0$ Hz, ArCH_2Ar), 4.26 (d, 2H, $J = 15.1$ Hz, CH_2OH), 4.23 (s, 4H, OCH_2CO), 4.11 (d, 2H, $J = 13.8$ Hz, ArCH_2Ar), 3.79 (p, 2H, –NHC*H*Et), 3.72 (q, 4H, CH_2CH$_3$), 3.58 (d, 2H, $J = 13.8$ Hz, ArCH_2Ar), 3.39 (d, 2H, $J = 12.0$ Hz, ArCH_2-Ar), 0.88 (t, 6H, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$): δ 169.49 (*C*=O), 151.93, 151.81 (Ar*C*), 132.86, 132.78, 132.62, 130.25, 129.66, 129.32, 129.05, 128.99, 128.63, 127.89, 127.69, 127.51, 126.48, 120.64 (Ar*C*H), 75.03, 64.64, 64.40 (O*C*H$_2$), 53.84 (*C*H), 31.88, 31.70 (Ar*C*H$_2$Ar), 23.98, 23.81 (*C*H$_2$), 10.66, 10.28 (*C*H$_3$); FAB-MS *m/z*: (705.9) $[M+Na]^+$. Anal. Calcd for $C_{40}H_{46}N_2O_8$ (682.82): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.43; H, 6.85; N, 4.14.

4.2.5. Compound 4a. The crude product was purified by flash chromatography (SiO_2, eluent CH_2Cl_2/acetone 10:1) and recrystallized from CH_2Cl_2/MeOH, as white crystals; yield 66%; $[\alpha]_D^{20} = -14.3$ (*c* 0.4, $CHCl_3$). Mp 242–244 °C. IR (KBr, cm^{-1}): 3370 (OH), 1660 (CO). ^{1}H NMR ($CDCl_3$): δ 9.00 (d, 2H, $J = 7.3$ Hz, N*H*), 7.39 (s, 2H, ArO*H*), 7.09–6.99 (m, 10H, Ar*H*), 6.97 (s, 4H, Ar*H*), 6.75 (s, 4H, Ar*H*), 4.93 (d, 2H, $J = 15.0$ Hz, CH_2OH), 4.48 (t, 2H, O*H*), 4.31 (s, 4H, OCH_2CO), 4.10 (d, 2H, $J = 13.5$ Hz, ArCH_2Ar), 4.07 (d, 2H, $J = 14.9$ Hz, CH_2OH), 3.91 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 3.52 (t, 2H, –NHC*H*–ph), 3.46 (d, 2H, $J = 13.5$ Hz, ArCH_2Ar), 2.90 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 2.84 (s, 4H, CH_2–ph), 1.30 (s, 18H, C(CH_3)$_3$), 0.94 (s, 18H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 169.59 (*C*=O), 149.80, 148.06 (Ar*C*), 137.63, 132.52, 132.26, 129.12, 128.32, 128.18, 126.88, 126.74, 126.25, 126.12, 125.44, 124.90 (Ar*C*H), 74.90, 64.17 (O*C*H$_2$), 52.57 (*C*H), 31.65, 30.93 (Ar*C*H$_2$Ar), 10.43, 10.17 (*C*H$_3$); FAB-MS *m/z*: (1054.4) $[M+Na]^+$. Anal. Calcd for $C_{66}H_{82}N_2O_8$ (1031.40): C, 76.86; H, 8.01; N, 2.72. Found: C, 76.91; H, 8.12; N, 2.78.

4.2.6. Compound 4b. The crude product was purified by flash chromatography (SiO_2, eluent CH_2Cl_2/acetone 10:1) and recrystallized from CH_2Cl_2/MeOH, as pale yellow crystals; yield 70%; $[\alpha]_D^{20} = -26.9$ (*c* 0.2, $CHCl_3$). Mp 120–124 °C. IR (KBr, cm^{-1}): 3331 (OH), 1654 (CO). ^{1}H NMR ($CDCl_3$): δ 9.01 (d, 2H, N*H*), 7.24 (s, 2H, ArO*H*), 7.09 (d, 2H, Ar*H*, *meta*), 7.04–6.94 (m, 10H, Ar*H*), 6.84 (d, 2H, Ar*H*, *meta*), 6.75 (t, 2H, Ar*H*, *para*), 6.69 (t, 2H, Ar*H*, *para*), 4.96 (d, 2H, $J = 15.0$ Hz, CH_2OH), 4.50 (t, 2H, O*H*), 4.30 (s, 4H, OCH_2CO), 4.12 (d, 2H, $J = 13.7$ Hz, ArCH_2Ar), 4.05 (d, 2H, $J = 15.0$ Hz, CH_2OH), 3.84 (d, 2H, $J = 13.1$ Hz, ArCH_2Ar), 3.49 (t, 2H, –NHC*H*–ph), 3.55 (d, 2H, $J = 13.8$ Hz, ArCH_2Ar), 2.97 (d, 2H, $J = 13.1$ Hz, ArCH_2Ar), 2.88 (s, 4H, CH_2–ph); ^{13}C NMR ($CDCl_3$): δ 169.38 (*C*=O), 151.88, 151.78 (Ar*C*), 137.41, 132.94, 132.76, 130.26, 129.42, 129.19, 129.05, 128.92, 128.50, 128.38, 127.14, 126.37, 120.52 (Ar*C*H), 75.03, 64.39 (O*C*H$_2$), 52.56 (*C*H), 31.84, 31.68 (Ar*C*H$_2$Ar); FAB-MS *m/z*: (830.0) $[M+Na]^+$. Anal. Calcd for $C_{50}H_{50}N_2O_8$ (806.96): C, 74.42; H, 6.25; N, 3.47. Found: C, 74.49; H, 6.30; N, 3.48.

4.3. Analytical procedure

Picrate extraction experiments were performed following Pedersen's procedure: 10 mL of 2.0×10^{-5} M aqueous picrate and 10 mL of 1.0×10^{-3} M solution of calixarene (**3a**–**4a** and **3b**–**4b**) 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 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*%) has been calculated as

$$(E\%) = A_0 - A/A_0 \times 100 \quad (6)$$

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

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