J Incl Phenom Macrocycl Chem (2012) 74:361–368
DOI 10.1007/s10847-012-0123-y

ORIGINAL ARTICLE

Chiral calix[4]arenes bearing α-hydroxy amide units as membrane carriers for amino acid methyl esters

Mustafa Durmaz

Received: 2 January 2012 / Accepted: 2 February 2012 / Published online: 4 March 2012

Abstract Novel chiral calix[4]arene derivatives functionalized at the lower rim have been prepared from the reaction of *p-tert*-butylcalix[4]arene diamine or acylhydrazine derivative with mandelic acid or hydroxyisovaleric acid. The structures of these receptors were characterized by FTIR, ^{1}H, ^{13}C and 2D COSY NMR spectroscopy and elemental analysis. The transport of amino acid derivatives (phenylalanine, phenylglycine and tryptophan methyl ester hydrochlorides) was studied through bulk liquid membrane in the presence of chiral calix[4]arene derivatives. The receptors have been found to act as carriers for transport of aromatic amino acid methylesters from the aqueous source phase to the aqueous receiving phase. The transport rate and L/D selectivity of amino acid esters studied depend strongly upon the structure of the chiral receptors and guests. The best enantioselectivity was obtained in the case of phenylglycine methyl ester for all chiral carriers.

Keywords Chiral calix[4]arene · α-Hydroxy amide · Bulk liquid membrane · Amino acid methyl esters · Transport rate

Introduction

Chirality is a major concern in the design, discovery, development and marketing of new drugs [1–4]. This interest can be attributed largely to a heightened awareness that enantiomers of a racemic drug may have different pharmacological properties in terms of activity, potency, toxicity, transport mechanism and metabolic route. Thus, one stereoisomer may produce the desired therapeutic activities while the other may be inactive or, in worst cases, produce harmful effects [5]. Therefore, there is a great interest in obtaining those compounds with the required enantiopurity. Although a variety of methods are available to obtain enantiopure compounds, e.g., from natural sources, fermentation, or asymmetric synthesis, or by resolution of racemates, [6, 7] the separation of racemates is still the most important industrial approach for the preparation of enantiomerically pure compounds. Compared to other methods including crystallization, chromatography, and so forth extractive separation of liquid membrane is widely used in chiral separation process [8–10] due to its cost effectiveness, low energy demand, set-up simplicity and the possibility to be used in continuous mode.

Amino acids represent an important naturally occurring class of compounds and also known to be very useful building blocks in the production of drug intermediates and employed as reagents or catalytic agents in asymmetric synthesis [11]. Therefore the study of the enantiomeric recognition and separation of amino acids is of particular significance for understanding the transport process of these compounds through the cell membrane, design of asymmetric catalysis systems, new pharmaceutical agents [12], and separation materials [13].

In the literature, various types of receptors including cyclodextrins [14], cucurbit[n]urils [15], resorcin[4]arene [16], crown ethers [17], cryptands [18], macrocyclic pseudopeptides [19] or guanidine derivatives of sterols [20] reported on the chiral separation of biologically important molecules. Calixarenes as an important molecular scaffold

Electronic supplementary material The online version of this article (doi:10.1007/s10847-012-0123-y) contains supplementary material, which is available to authorized users.

M. Durmaz (✉)
Department of Chemistry, Ahmet Kelesoglu Faculty of Education, Konya University, Meram, Konya, Turkey
e-mail: mdurmaz42@yahoo.com

have been widely used for the construction of artificial host molecules, which have found applications in various fields [21–25]. Since they are emerging as a new class of synthetic macrocycles possessing extensive host–guest chemistry, chiral calixarenes are of particular importance for the enantioselective recognition and/or discrimination of chiral compounds. Although, many chiral calixarenes containing chiral residues at either the wide or the narrow rim have been prepared as chiral receptors and catalysts [26, 27], only a few calix[4]arene derivatives have been reported for the enantioselective transport of chiral compounds [28–30].

In a continuation of our recent studies in this field, we herein report the synthesis of novel calix[4]arene derivatives functionalized with chiral substituents at the lower rim and their potential applications as carriers in transport of amino acid methyl esters through bulk liquid membrane.

Experimental

General

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary. ^{1}H, ^{13}C and 2D COSY NMR spectra were recorded at room temperature on a Varian 400 MHz spectrometer in $CDCl_3$. IR spectra were obtained on a Perkin Elmer spectrum-100 FTIR spectrometer with the attenuated total reflection (ATR) technique and the absorption values are given as wavenumbers (cm^{-1}). UV/Vis spectra were measured with a Perkin Elmer Lambda 25 spectrometer. Optical rotations were measured on an Atago AP-100 digital polarimeter using a 1 dm cell. Elemental analyses were performed using a Leco CHNS-932 analyzer. An Orion 2 Star pH Benchtop pH meter was used for the pH measurements. 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.

Materials

All starting materials and analytical grade amino acid methyl esters: phenylalanine methyl ester hydrochloride (PhAlaOMe), phenylglycine methyl ester (PhGlyOMe) and tryptophan methyl ester hydrochloride (TrpOMe) were purchased from Fluka, Merck and Sigma-Aldrich and were employed without further purification. Chloroform (dielectric constant $\varepsilon_r = 4.81$) was distilled before use. 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 $MgSO_4$. All aqueous solutions were prepared with deionized water that had been passed through a Millipore milli-Q Plus water purification system.

Synthesis

Compounds **1** and **2** were synthesized according to the literature procedures [31, 32].

General procedure for the synthesis of chiral calix[4]arene derivatives **3–6**

N,N′-Dicyclohexylcarbodiimide (0.186 g, 0.9 mmol) was added slowly to a stirred solution of (L)-(+)-mandelic acid or (*S*)-hydroxyisovaleric acid (0.8 mmol), **1** or **2** (0.4 mmol) and *N*-hydroxysuccinimide (0.104 g, 0.9 mmol) in anhydrous THF (10 mL) at 0 °C under a nitrogen atmosphere. The cooling bath was removed and reaction mixture was stirred overnight, filtered and the cake of dicyclohexylurea washed with THF (2 × 5 mL). The solvent was removed under reduced pressure, and the residue dissolved with 10 mL ethyl acetate. The solution was extracted successively with saturated sodium carbonate, water, 2 M HCl, water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica gel eluting with hexane–ethyl acetate mixtures.

Chiral *p-tert*-butylcalix[4]arene α-hydroxy amide (**3**)

Yield 81%; white crystal; mp 97–99 °C; $\alpha_D^{25} = +83.0$ (*c* 4.64, $CHCl_3$). IR (cm^{-1}): 3344, 2954, 1655, 1530, 1485; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.89 (t, 2H, $J =$ 5.6 Hz PhCHCONH), 7.47–7.45 (m, 4H, ArH), 7.32–7.28 (m, 6H, ArH), 7.11–7.07 (m, 6H, ArH + ArOH), 6.78–6.75 (m, 4H, ArH), 5.14 (s, 2H, CHOH), 4.22 (d, 2H, $J = 13.1$ Hz, $ArCH_2Ar$), 4.09 (d, 2H, $J = 13.4$ Hz, $ArCH_2Ar$), 4.02–3.97 (m, 2H, OCH_2), 3.94–3.88 (m, 2H, OCH_2), 3.77–3.68 (m, 2H, $NHCH_2$), 3.50–3.42 (m, 2H, $NHCH_2$), 3.34 (d, 4H, $J = 13.3$ Hz, $ArCH_2Ar$), 2.31–2.24 (m, 2H, CH_2), 2.02–1.94 (m, 2H, CH_2), 1.33 (s, 18H, $C(CH_3)_3$), 0.95 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 173.8, 150.0, 149.8, 147.6, 143.0, 139.7, 132.6, 131.9, 128.7, 128.3, 128.1, 126.7, 126.2, 125.7, 125.6, 75.9, 74.7, 74.6, 38.1, 34.2, 31.9, 31.7, 31.2, 29.9, 29.0. Anal. Calcd for $C_{66}H_{82}N_2O_8$ (1031.39): C, 76.86, H, 8.01, N, 2.72%. Found: C, 76.93, H, 7.91, N, 2.64%.

Chiral *p-tert*-butylcalix[4]arene α-hydroxy amide (**4**)

Yield 74%; white crystal; mp 94–96 °C; $\alpha_D^{25} = -79.5$ (*c* 4, $CHCl_3$). IR (cm^{-1}): 3362, 2957, 1781, 1708, 1654, 1536,

1484; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.20–8.17 (m, 2H, CHCONH), 7.09 (d, 2H, J_{AB} = 2.4 Hz, ArH), 7.04 (d, 2H, J_{AB} = 2.4 Hz, ArH), 6.68 (d, 2H, J_{AB} = 2.4 Hz, ArH), 6.64 (d, 2H, J_{AB} = 2.4 Hz, ArH), 6.63 (s, 2H, ArOH), 4.20 (d, 2H, J = 13.1 Hz, ArCH_2Ar), 4.12–4.05 (m, 4H, OCH_2), 4.02–3.92 (m, 6H, NHCH_2 + ArCH_2Ar + CHOH), 3.50–3.45 (m, 2H, NHCH_2), 3.33 (dd, 4H J = 13.8, 13.2 Hz, ArCH_2Ar), 2.60 (bs, 4H, CHOH + CH$(CH_3)_2$), 2.25–2.17 (m, 2H, CH_2), 2.13–2.05 (m, 2H, CH_2), 1.30 (s, 18H, C(CH_3)$_3$), 1.07 (d, 6H, J = 6.9 Hz, CH_3), 0.87–0.86 (m, 24H, C(CH_3)$_3$ + CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.6, 172.5, 171.5, 150.5, 149.4, 147.5, 143.2, 132.4, 131.3, 128.5, 128.0, 126.3, 125.8, 125.5, 60.7, 38.9, 34.2, 34.1, 34.0, 31.9, 31.8, 31.6, 31.3, 31.1, 29.0, 25.6, 21.3, 20.0, 15.9, 14.4. Anal. Calcd for $C_{60}H_{86}N_2O_8$ (963.35): C, 74.81, H, 9.00, N, 2.91%. Found: C, 74.85, H, 9.07, N, 2.84%.

Chiral *p-tert*-butylcalix[4]arene α-hydroxy amide (**5**)

Yield 76%; white crystal; mp 114–116 °C; α_D^{25} = +31.4 (c 1, $CHCl_3$). IR (cm^{-1}): 3279, 2955, 1715, 1649, 1482; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.18 (s, 2H, PhCH-CONH), 9.76 (s, 2H, OCH$_2$CONH), 7.94 (s, 2H, ArOH), 7.56–7.33 (m, 10H, ArH), 7.09–6.94 (m, 8H, ArCH$_2$ArH), 5.25 (s, 2H, CHOH), 4.70, 4.45 (2xd, 4H, J = 15.1 Hz, ArOCH_2CONH), 4.23–4.12 (m, 4H, ArCH_2Ar), 3.38 (dd, 4H J = 13.2, 9.8 Hz, ArCH_2Ar), 1.26 (s, 18H, C(CH_3)$_3$), 1.09 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 170.7, 167.3, 149.5, 149.2, 148.7, 143.2, 139.0, 132.8, 132.7, 128.8, 128.5, 127.3, 127.2, 127.1, 126.6, 126.4, 125.9, 125.8, 74.3, 74.1, 34.4, 34.1, 31.8, 31.3. Anal. Calcd for $C_{64}H_{76}N_4O_{10}$ (1061.33): C, 72.43, H, 7.22, N, 5.28%. Found: C, 72.67, H, 7.14, N, 5.17%.

Chiral *p-tert*-butylcalix[4]arene α-hydroxy amide (**6**)

Yield 72%; white crystal; Mp 179–182 °C; α_D^{25} = –46.0 (c 2, $CHCl_3$). IR (cm^{-1}): 3286, 2957, 1712, 1671, 1479; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.12 (s, 2H, CHCONH), 9.63 (s, 2H, OCH$_2$CONH), 8.00 (s, 2H, ArOH), 7.09–7.07 (m, 4H, ArH), 7.01–6.98 (m, 4H, ArH), 4.87, 4.61 (2xd, 4H, J = 15.1 Hz, ArOCH_2CONH), 4.26 (dd, 4H J = 13.6, 13.0 Hz, ArCH_2Ar), 4.17–4.15 (m, 2H, CHOH), 3.47 (dd, 4H J = 13.7, 13.3 Hz, ArCH_2Ar), 2.67 (s, 2H, CHOH), 2.20–2.12 (m, 2H, CH$(CH_3)_2$), 1.27 (s, 18H, C(CH_3)$_3$), 1.10 (s, 18H, C(CH_3)$_3$), 1.03 (d, 6H, J = 6.9 Hz, CH_3), 0.93 (d, 6H, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 171.7, 166.8, 149.4, 148.9, 148.5, 143.0, 132.6, 132.5, 127.1, 126.8, 126.6, 126.1, 125.8, 125.6, 76.2, 74.1, 34.2, 33.9, 32.3, 31.9, 31.6, 31.0, 19.1, 16.0.Anal. Calcd for $C_{58}H_{80}N_4O_{10}$ (993.29): C, 70.13, H, 8.12, N, 5.64%. Found: C, 70.22, H, 8.01, N, 5.56%.

Transport experiments

Transport experiments were run at 25 °C in the custom-made, U-type glass tube for 24 h (Fig. 1). The bulk liquid membrane consisted of 10 mL of chloroform containing the chiral calixarene derivatives **3**–**6** at a concentration of 2×10^{-4} M. The membrane phase was stirred magnetically at 300 rpm. The source phase contains 5 mL of aqueous solution of amino acid methyl ester (Fig. 2) (the concentrations ranged between 2.0×10^{-4} and 7.0×10^{-3} M, depending of the amino acid methyl ester) at pH = 5.5 present in one arm (left in Fig. 1) whereas the aqueous receiving phase, 5 mL (pH = 1.5) is present in the other arm (right in Fig. 1). Blank tests indicated that the transport of guests was negligible. In order to determine the concentration of transported guests, corresponding samples were periodically withdrawn from the aqueous receiving phases in each experiment and the changes in concentrations of analytes were measured spectrophotometrically. All measurements were performed in triplicate under strict similar conditions to check reproducibility.

The flux (J) of each enantiomer was calculated according to the Eq. 1 [33, 34]:

$$J = \frac{V_r \Delta C_r}{At} \quad (1)$$

where t is the time in s, ΔC_r is the concentration difference of receiving phase, V_r the receiving volume of receiving phase and A is the effective membrane area. This is the flux from the start of the experiment till time t.

The enantioselectivity was calculated in terms of the flux ratio (α), corresponds to the flux of the one enantiomer with respect to the other enantiomer

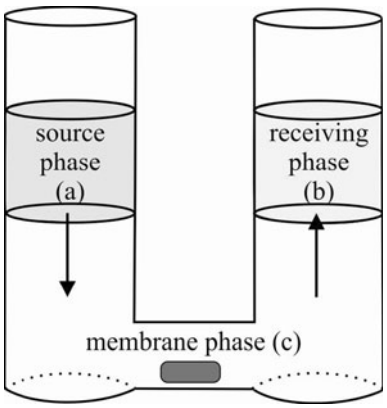


Fig. 1 Schematic device of the transport experiments. (*a*) Source phase (5 mL): amino acid methyl ester hydrochloride (pH = 5.5) (2×10^{-4} or 7×10^{-3} M); (*b*) Receiving phase (5 mL): pure water (pH = 1.5); (*c*) Organic membrane phase (10 mL): $CHCl_3$; carrier: chiral calix[4]arene derivatives (**3**–**6**) (2×10^{-4} M)

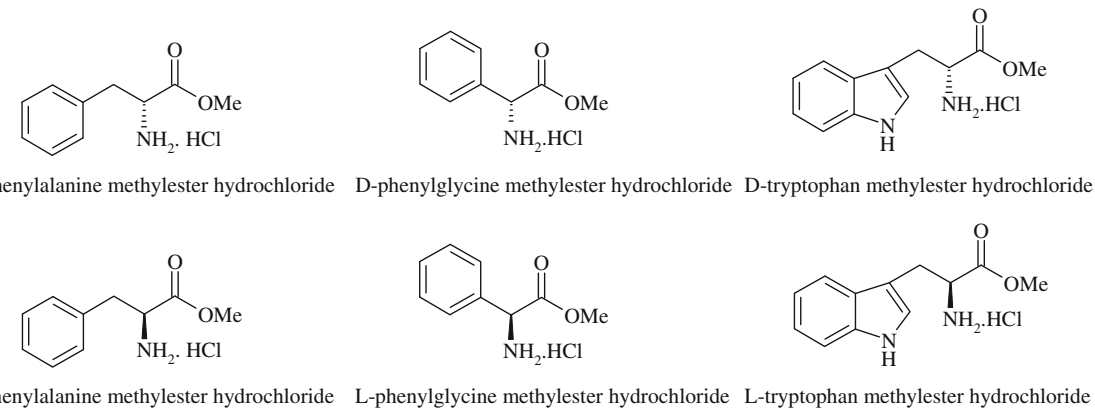


Fig. 2 Chemical structures of the amino acid methyl esters used throughout the experiments

$$\alpha = \frac{J_D}{J_L} \tag{2}$$

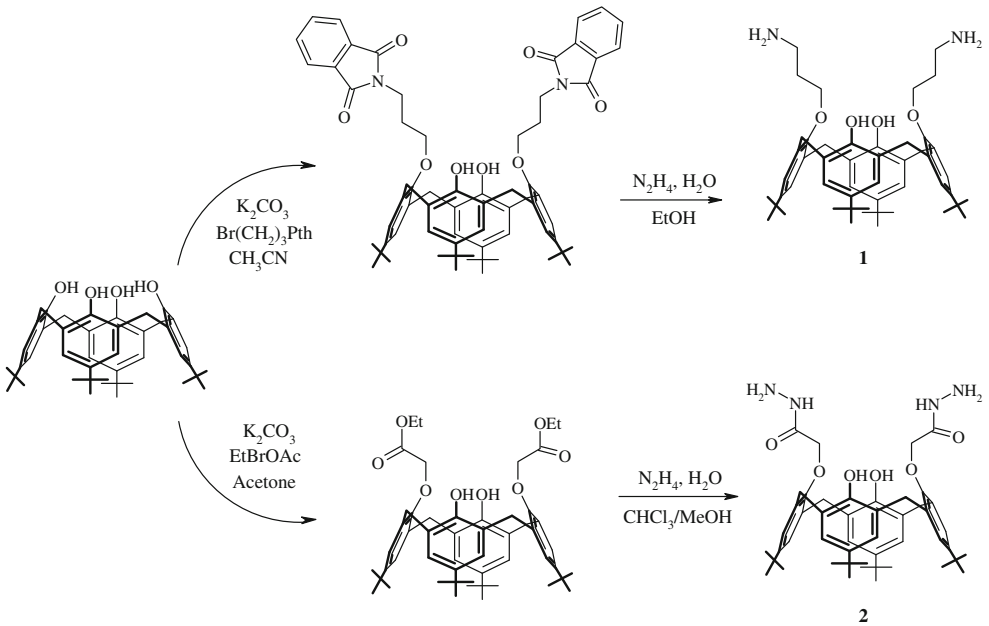
Results and discussion

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

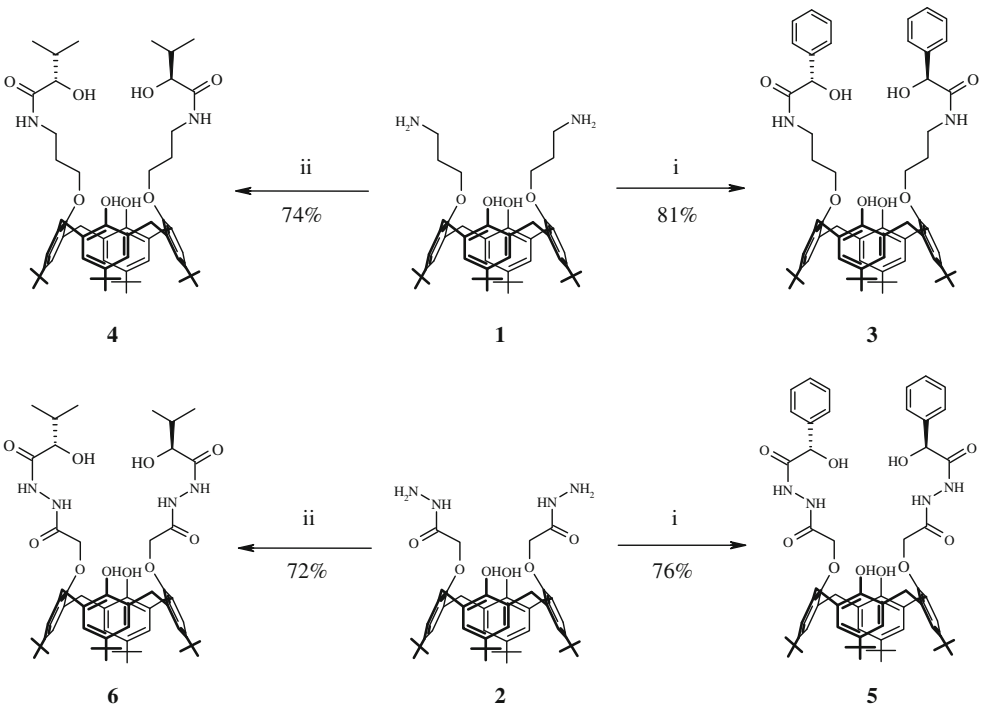
Chiral α- and β-hydroxy amides are useful building blocks for the synthesis of biologically active compounds and also used as chiral ligands in enantioselective reactions in the presence of Lewis acids [35, 36]. Calixarenes bearing α-hydroxy amide unit have received much attention because of their special structures and good complexing properties toward anions and cations [37]. In order to synthesize calix[4]arene α-hydroxy amides, first we have obtained diamino (1) and acylhydrazine (2) derivatives of calix[4]arene using known procedures in two steps starting from *p-tert*-butylcalix[4]arene (Scheme 1).

Then, treatment of **1** and **2** with enantiopure (L)-(+)-mandelic acid or (*S*)-hydroxyisovaleric acid in the presence of dicyclohexylcarbodiimide (DCC) and *N*-hydroxy-succinimide in dry THF led to the formation of the chiral calix[4]arene derivatives in good yields as shown in Scheme 2. Previously, Felix et al. reported a three step way for obtaining α-hydroxyamide derivative of calix[4]arene involving condensation of α-ketoacid chlorides with the diamino calix[4]arene, followed by a reduction process [38].

The products were fully characterized by a combination of ^{1}H, ^{13}C and 2D COSY NMR, FT-IR and elemental



Scheme 1 Synthesis of *p-tert*-butyl-calix[4]arene diamine (**1**) and acylhydrazine (**2**) derivatives



Scheme 2 Synthesis of chiral α-hydroxyamide derivatives of calix[4]arene **3–6**. Reaction conditions: (*i*) mandelic acid, DCC, *N*-hydroxysuccinimide, dry THF, 0 °C → rt.; (*ii*) hydroxyisovaleric acid, DCC, *N*-hydroxysuccinimide, dry THF, 0 °C → rt

analysis (see supplementary material). The cone conformation of all compounds were reflected in the characteristic AB system for the methylene groups bridging the aromatic rings in the ^{1}H and ^{13}C NMR spectra as expected in the light of the de Mendoza and Prados rule [39]. But surprisingly, there were two pairs of doublets at 7.09 and 7.04 as well as 6.68 and 6.64 ppm with coupling constants of 2.4 Hz, respectively for protons on phenol rings of the calixarene scaffold in the ^{1}H NMR spectrum of **4**. This result simply indicates that each phenol ring of **4** is not symmetrical. In addition, $ArCH_2Ar$ methylene groups showed three or four doublets instead of two doublets, which indicates that there are two different kinds of $ArCH_2Ar$ methylene groups. As previously reported in the literature [40, 41], this can be explained by the presence of chiral substituents and indicates a significant degree of structural rigidity.

Liquid membrane transport of amino acid methyl esters

In previous studies, some analytical applications of functionalized calix[4]arenes varyingly substituted by acid, azacrown or amido functions, glycolic chains and hydroxyl groups towards biological compounds have been reported [42–44]. Mainly the OH groups and amido functions known for their ability to form hydrogen bonds, oxygen-cation interactions and electrostatic interactions may play a role in binding of the amino acid esters. With the optical pure calix[4]arene derivatives bearing both hydroxyl groups and amido functions in hand, we then studied the transport ability of these receptors as enantioselective carries for aromatic amino acid methyl esters across liquid membranes.

For the initial studies, phenylalanine methyl ester hydrochloride (PhAlaOMe.HCl) was assayed for its enantiomeric transport with chiral receptors **3–6**. Chiral calix[4]arene derivatives showed the highest transport efficiency towards phenylalanine among all the amino acid esters studied (Fig. 3). This can attributed to the favorable π–π interaction between the phenyl group in PhAlaOMe.HCl and the aromatic moieties in carriers as well as hydrophobicity.

As shown in Fig. 4 as a representative sample, chiral receptor **3** shows not only good transport abilities for the enantiomers of PhAlaOMe.HCl but also recognize the chirality of the L- or D-isomer. Chiral macrocyclic carriers **3** and **6** showed relatively higher transport rate for the enantiomers of PhAlaOMe.HCl when compared with other receptors **4** and **5** where chiral calix[4]arene derivative **3**

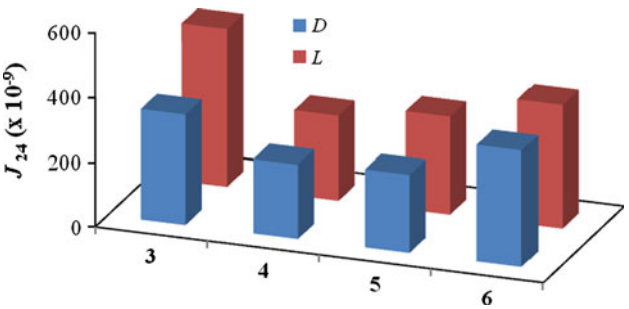


Fig. 3 Bar plots of fluxes of PhAlaOMe.HCl for hosts **3–6**

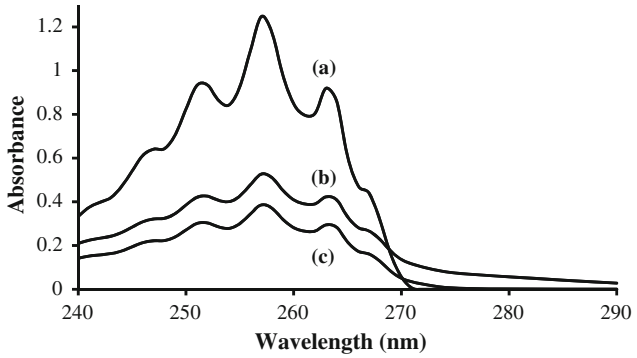


Fig. 4 UV-Vis spectrum of (*a*) 2.0×10^{-4} M PhAlaOMe.HCl; (*b*) Receiving phase of (L) PhAlaOMe.HCl after transport experiment with **3**; (*c*) Receiving phase of (D) PhAlaOMe.HCl after transport experiment with **3**

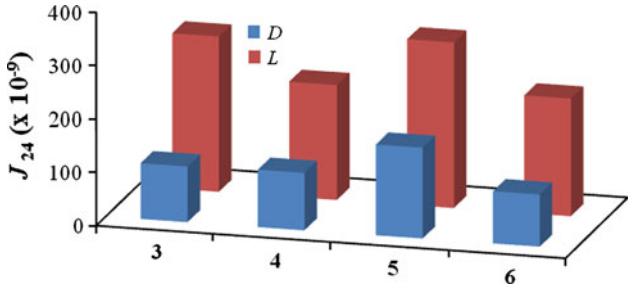


Fig. 5 Bar plots of fluxes of PhGlyOMe.HCl for hosts **3–6**

exhibited the best enantioselectivity affording a flux ratio of (L/D) 1.43.

In the case of phenylglycine methyl ester (PhGlyOMe.HCl), as compared with PhAlaOMe.HCl, it lacks a methylene spacer between the amine group and the aromatic ring, the transport sequence has been found that the order of carriers is **5** > **3** > **6** > **4**. The enantiomer designated L form had a relatively higher flux in all cases investigated, which is probably due to the more complementary structure of L-enantiomer with receptors. The highest L/D selectivity was observed with hosts **3** and **6**, affording flux ratios of 2.77 and 2.23 respectively. From the data displayed in Fig. 5 and Table 1, chiral receptors **3** and **5** which both have a phenyl group instead of the isopropyl group showed considerable higher transport rates.

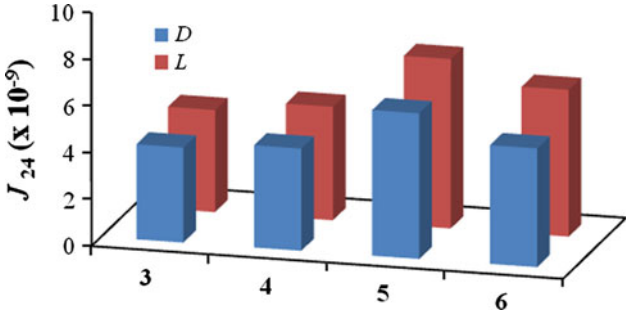


Fig. 6 Bar plots of fluxes of TrpOMe.HCl for hosts **3–6**

The facilitated transport of tryptophan methyl ester hydrochloride through a liquid membrane was also studied in the presence of chiral calix[4]arene derivatives. As can be seen from Table 1 and Fig. 6, all macrocyclic carriers showed significantly lower transport rates and selectivities for the enantiomers of TrpOMe.HCl than other amino acid esters. While the best transport rate was obtained when chiral calix[4]arene derivative **5** was employed as carrier, the best enantioselectivity was obtained with receptor **6** with a flux ratio value of 1.24.

All macrocyclic carriers showed much higher transport rate for the enantiomers of PhAlaOMe.HCl and PhGlyOMe.HCl than the enantiomers of TrpOMe.HCl, indicating that there may be stronger interaction between carrier and PhAlaOMe.HCl and PhGlyOMe.HCl induced by hydrogen bonds, charge transfer as well as π–π interaction. The enantiomer designated L form had higher flux values than that of the D form in all cases investigated. The chiral carriers **3–6** are generally similar in that all contain hydrogen bonding sites defined by carbonyl oxygen, amide nitrogen, and α-hydroxy groups at roughly similar positions with respect to the phenoxy oxygen. With chiral carrier **4**, relatively low transport rates and selectivities were observed for amino acid esters. This might be related to the lack of π–π stacking between aromatic moieties and results to the weak steric interactions of those substituents with the amino acid ester molecule. As in the case of receptors **3**

Table 1 Transport data through liquid membrane

	D-Trp-OMe.HCl	L-TrpOMe·HCl		D-PhAlaOMe.HCl	L-PhAlaOMe.HCl		D-PhGlyOMe.HCl	L-PhGlyOMe.HCl	
Host	$J_{24} \times 10^{-9}$ (mol × m^{-2} × s^{-1})		α_T	$J_{24} \times 10^{-9}$ (mol × m^{-2} × s^{-1})		α_T	$J_{24} \times 10^{-9}$ (mol × m^{-2} × s^{-1})		α_T
3	4.08 ± 0.16	4.38 ± 0.19	1.07 (L)	341.08 ± 1.76	488.00 ± 1.99	1.43 (L)	105.23 ± 0.74	291.07 ± 1.41	2.77 (L)
4	4.39 ± 0.18	4.87 ± 0.20	1.11 (L)	230.09 ± 1.35	261.86 ± 1.60	1.14 (L)	108.43 ± 0.83	214.95 ± 1.19	1.98 (L)
5	6.25 ± 0.25	7.28 ± 0.27	1.17 (L)	241.60 ± 1.55	302.16 ± 1.61	1.25 (L)	171.23 ± 1.10	310.58 ± 1.59	1.81 (L)
6	5.10 ± 0.18	6.30 ± 0.26	1.24 (L)	359.31 ± 1.87	381.70 ± 1.83	1.06 (L)	98.52 ± 0.74	220.06 ± 1.18	2.23 (L)

J_{24} = Flux of transported amino acid methyl esters after 24 h (mol m^{-2} s^{-1}); α_T = ratio of fluxes: higher/lower flux; TrpOMe.HCl = Tryptophan methyl ester hydrochloride; PhAlaOMe.HCl = Phenylalanine methyl ester hydrochloride; PhGlyOMe.HCl = Phenylglycine methyl ester hydrochloride

(D) or (L) indicates the preferential form of enantiomers

and **5**, the introduction of a phenyl group affects considerably the transport rate and enantioselectivity. This could be attributed to the favorable π–π interactions between the phenyl moiety of the carrier and the aromatic fragment of the guest.

Conclusion

In conclusion, novel chiral calix[4]arene α-hydroxy amides were synthesized by the reaction of *p-tert*-butylcalix[4]arene diamine or acylhydrazine derivative with enantiopure carboxylic acids. The transport abilities of these receptors towards amino acid esters have been studied by UV-Vis spectroscopy. The receptors exhibited different transport abilities and enantioselectivities towards the enantiomers of guests. Amongst the amino acid esters investigated, the highest enantioselectivities were observed for PhGlyOMe.HCl with chiral calix[4]arene derivatives. The results indicate that steric hindrance, structural rigidity or flexibility and π–π stacking between the aromatic groups may be responsible for the enantioselective transport.

Acknowledgement This work was supported by Konya University.

References

1. Beckett, A.H.: Chirality and its importance in drug development: what are the issues? Biochem. Soc. Trans. **19**, 443–446 (1991)
2. Caldwell, J.: Through the looking glass in chiral drug development. Modern Drug Discov. **2**, 51–60 (1999)
3. Agranat, I., Caner, H., Caldwell, J.: Putting chirality to work: the strategy of chiral switches. Nat. Rev. Drug Discov. **1**, 753–768 (2002)
4. Eichelbaum, M., Gross, A.S.: Stereochemical aspects of drug action and disposition. Adv. Drug Res. **28**, 1–64 (1996)
5. Scott, A.K.: Stereoisomers and drug toxicity: the value of single stereoisomer therapy. Drug Saf. **8**, 149–159 (1993)
6. Sheldrake, G.N., Crosbyb, J., Collins, A.N.: Chirality in industry II: developments in the manufacture and applications of optically active compounds. Wiley, New York (1997)
7. Steensma, M., Kuipers, N.J.M., Haan, A.B.D., Kwant, G.: Identification of enantioselective extractants for chiral separation of amines and aminoalcohols. Chirality **18**, 314–328 (2006)
8. Xie, R., Chu, L.Y., Deng, J.G.: Membranes and membrane processes for chiral resolution. Chem. Soc. Rev. **37**, 1243–1263 (2008)
9. Yang, L., Chen, X.Q., Jiao, F.P.: Extractive resolution of racemic mandelic acid through a bulk liquid membrane containing binary chiral carrier. J. Braz. Chem. Soc. **20**, 1493–1498 (2009)
10. Jirage, K.B., Martin, C.R.: New developments in membrane-based separations. Trends Biotechnol. **17**, 197–200 (1999)
11. Ibrahem, I., Sundén, H., Dziedzic, P., Rios, R., Córdova, A.: Asymmetric amplification in the amino acid-catalyzed amino acid derivative synthesis. Adv. Synth. Cat. **349**, 1868–1872 (2007)
12. Beddell, C.R.: The design of drugs to macromolecular targets. Wiley, Chichester (1992)
13. Jinno, K.: Chromatographic separations based on molecular recognition. VCH, Weinheim (1996)
14. Ferreira, Q., Coelhoso, I.M., Ramalhete, N., Marques, H.M.C.: Resolution of racemic propranolol in liquid membranes containing TA-β-cyclodextrin. Sep Sci Technol **41**, 3553–3568 (2006)
15. Jeon, Y.J., Kim, H., Jon, S., Selvapalam, N., Oh, D.Y., Seo, I., Park, C.-S., Jung, S.R., Koh, D.-S., Kim, K.: Artificial ion channel formed by cucurbit[n]uril derivatives with a carbonyl group fringed portal reminiscent of the selectivity filter of K^+ channels. J. Am. Chem. Soc. **126**, 15944–15945 (2004)
16. Yoshino, N., Satake, A., Kokuke, Y.: An artificial ion channel formed by a macrocyclic resorcin[4]arene with amphiphilic cholic acid ether groups. Angew. Chem. Int. Ed. **40**, 457–459 (2001)
17. Buschmann, H.-J., Mutihac, L.: Complexation, solvent extraction, an transport through liquid membrane of protonated peptides using crown ethers. Anal. Chim. Acta **466**, 101–108 (2002)
18. Buschmann, H.-J., Mutihac, R.-C., Schollmeyer, E.: Complex formation of crown ethers and cryptands with alkali metal and ammonium ions in chloroform. J. Solut. Chem. **38**, 209–217 (2009)
19. Miyake, H., Yamashita, T., Kojima, Y., Tsukube, H.: Enantioselective transport of amino acid ester salts by macrocyclic pseudopeptides containing *N,N′*-ethylene-bridged-dipeptide units. Tetrahedron Lett. **36**, 7669–7672 (1995)
20. Urban, C., Schmuck, C.: Active transport of amino acids by a guanidiniocarbonyl-pyrrole receptor. Chem. Eur. J. **16**, 9502–9510 (2010)
21. Alpaydin, S., Saf, A.O., Bozkurt, S., Sirit, A.: Kinetic study on removal of toxic metal Cr(VI) through a bulk liquid membrane containing *p-tert*-butylcalix[4]arene derivative. Desalination **275**, 166–171 (2011)
22. Mutihac, L., Lee, J.H., Kim, J.S., Vicens, J.: Recognition of amino acids by functionalized calixarenes. Chem. Soc. Rev. **40**, 2777–2796 (2011)
23. Kim, L., Hamdi, A., Stancu, A.D., Souane, R., Mutihac, L., Vicens, J.: Selective membrane transport of amino acids by functionalised calix[4]arenes. J. Incl. Phenom. Macrocycl. Chem. **66**, 55–59 (2010)
24. Mutihac, L., Mutihac, R.: Liquid–liquid extraction and transport through membrane of amino acid methylesters by calix[n]arene derivatives. J. Incl. Phenom. Macrocycl. Chem. **59**, 177–181 (2007)
25. Bayrakci, M., Ertul, S., Yilmaz, M.: Transportation of poorly soluble drug molecules from the organic phase to the aqueous phase by using phosphorylated calixarenes. J. Chem. Eng. Data **56**, 4473–4479 (2011)
26. Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J. (eds.): Calixarenes 2001. Kluwer, Dordrecht (2001)
27. Sirit, A., Yilmaz, M.: Chiral calixarenes. Turk. J. Chem. **33**, 159–200 (2009)
28. Okada, Y., Kasai, Y., Nishimura, J.: The selective extraction and transport of amino acids by calix[4]arene-derived esters. Tetrahedron Lett. **36**, 555–558 (1995)
29. Durmaz, M., Bozkurt, S., Naziroglu, H.N., Yilmaz, M., Sirit, A.: Chiral calix[4]arenes bearing aminonaphthol moieties as membrane carriers for chiral amino acid methyl esters and mandelic acid. Tetrahedron Asymmetr. **22**, 791–796 (2011)
30. Oshima, T., Inoue, K., Furusaki, S., Goto, M.: Liquid membrane transport of amino acids by a calix[6]arene carboxylic acid derivative. J. Membr. Sci. **217**, 87–97 (2003)
31. Lin, Y., Leydier, A., Metay, E., Favre-Reguillon, A., Bouchu, D., Pellet-Rostaing, S., Lemaire, M.: Synthesis of original capping

calixarenes with DTPA fragment. J. Incl. Phenom. Macrocycl. Chem. **61**, 187–193 (2008)
32. Maity, D., Chakraborty, A., Gunupuru, R., Paul, P.: Calix[4]arene based molecular sensors with pyrene as fluoregenic unit: effect of solvent in ion selectivity and colorimetric detection of fluoride. Inorg. Chim. Acta **372**, 126–135 (2011)
33. Jiao, F., Chen, X., Hu, W., Yang, L., Huang, K.: Enantioselective transport of R-clenbuterol through a bulk liquid membrane containing O,O′-dibenzoyl-(2S, 3S)-tartaric acid. J. Braz. Chem. Soc. **18**, 804–809 (2007)
34. Raizada, P., Vyas, V., Sharma, U.: Liquid membrane extraction and transport of amino acids using calix[6]arene. Indian J. Chem. Tech. **17**, 267–273 (2010)
35. Kakei, H., Nemoto, T., Ohshima, T., Shibasaki, M.: Efficient synthesis of chiral α- and β-hydroxy amides: application to the synthesis of (R)-fluoxetine. Angew. Chem. Int. Ed. **43**, 317–320 (2004)
36. Blay, G., Fernandez, I., Hernandez-Olmos, V., Marco-Aleixandre, A., Pedro, J.R.: Enantioselective addition of dimethylzinc to aldehydes catalyzed by *N*-substituted mandelamide-Ti(IV) complexes. Tetrahedron Asymmetr. **16**, 1953–1958 (2005)
37. Danil de Namor, A.F., Chaaban, J.K., Abbas, I.: Cation/anion recognition by a partially substituted lower rim calix[4]arene hydroxyamide, a ditopic receptor. J. Phys. Chem. A **110**, 9575–9584 (2006)
38. Sdira, S.B., Felix, C., Giudicelli, M.-B., Vocanson, F., Perrin, M., Lamartine, R.: Synthesis, structure and anion binding properties of lower rim α-hydroxyamide calix[4]arene derivatives. Tetrahedron Lett. **46**, 5659–5663 (2005)
39. Jaime, C., Mendoza, J.D., Prados, P., Nieto, P.M., Sanchez, C.: ^{13}C NMR chemical shifts. A single rule to determine the conformation of calix[4]arenes. J. Org. Chem. **56**, 3372–3376 (1991)
40. Ben Sdira, S., Felix, C.P., Giudicelli, M.-B.A., Seigle-Ferrand, P.F., Perrin, M., Lamartine, R.: Synthesis and structure of lower rim C-linked N-tosyl peptidocalix[4]arenes. J. Org. Chem. **68**, 6632–6638 (2003)
41. Zheng, Y.-S., Ran, S.-Y., Hu, Y.-J., Liu, X.-X.: Enantioselective self-assembly of chiral calix[4]arene acid with amines. Chem. Commun. **9**, 1121–1123 (2009)
42. Hamdi, A., Souane, R., Kim, L., Abidi, R., Mutihac, L., Vicens, J.: Extraction behaviour of amino acid esters by functionalized calix[4]arenes. J. Incl. Phenom. Macrocycl. Chem. **64**, 95–100 (2009)
43. Enache, I.V., Mutihac, L., Othman, A.B., Vicens, J.: Calix[4] azacrowns as ionophores for liquid–liquid extraction and facilitated transport of biological supramolecular complexes. J. Incl. Phenom. Macrocycl. Chem. **71**, 537–543 (2011)
44. Medvedovici, A., Albu, F., Hamdi, A., Souane, R., Kim, L., Mutihac, L., Vicens, J.: Mass spectrometric behavior of functionalized calix[4]arenes: the screening ability of host–guest complex formation with amino acid methyl esters. J. Incl. Phenom. Macrocycl. Chem. **71**, 545–555 (2011)