# Synthesis and Properties of *Upper Rim C*-Linked Peptidocalix[4]arenes

**Marcio Lazzarotto,[a][‡] Francesco Sansone,[a] Laura Baldini,[a] Alessandro Casnati,[a] Pietro Cozzini,[b] and Rocco Ungaro*[a]**

**Keywords:** Calixarenes / Chiral hosts / Amino acids / Supramolecular chemistry / Anion binding

*Cone* calix[4]arenes, functionalized with two or four L-alanine or L-phenylalanine units at the *upper rim*, have been synthesized. These compounds, in which the amino acids are attached to the calix[4]arene macrocycle through their carboxy groups, have been named *C*-linked peptidocalix[4]arenes. The solubility, conformational, and recognition properties of this novel class of chiral receptors are quite different from those previously reported for *N*-linked peptidocalix[4]arenes. The tetrafunctionalized phthaloyl derivatives **2** are soluble in low polarity media, whereas the corresponding acetyl and benzoyl derivatives **4** and **5** are completely insoluble in $CDCl_3$, suggesting a high degree of aggregation of the latter compounds. Protonation of the terminal amino groups of **3** results in positively charged water-soluble receptors, which represent the cationic counterparts of negatively charged, water-soluble, *N*-linked peptidocalix[4]arenes. The difunctionalized acetyl derivatives **9** are soluble in $CDCl_3$ and show a *pinched cone* conformation, which is mainly determined by intramolecular hydrogen bonding, as revealed by solvent-dependent $^1H$ NMR spectra and molecular modelling. In contrast to the *N*-linked analogues, which complex ammonium cations and carboxylic acids, the newly synthesized *C*-linked peptidocalix[4]arenes interact preferentially with anionic species.

## Introduction

The recognition of polar organic molecules of biological interest, such as carbohydrates[1] and amino acids,[2] is a topic of current interest in supramolecular chemistry. Particularly attractive in this field are the so called "hybrid" macrocyclic receptors,[3] which are characterized by the simultaneous presence of rather different binding groups, e.g. polar groups and hydrophobic cavities, which cooperate in the recognition process.

We have recently synthesized calix[4]arene derivatives functionalized at the *upper rim* (aromatic nuclei) with carbohydrate[4] (glycocalixarenes), amino acid[5] (*N*-linked peptidocalix[4]arenes), and (thio)urea[6] units, which represent examples of such *hybrid* receptors developed for the complexation of sugars, amino acids, and anions. We have also reported on the synthesis of calix[4]arenes bridged at the *upper rim* with small peptides, which show interesting *in vitro* antimicrobial activity[7] towards Gram-positive bacteria as a result of their ability to bind the D-alanyl-D-alanine residue.[8] Meanwhile, other groups have reported on the synthesis and properties of calixarenes and resorcinarenes functionalized with amino acids,[9] peptides,[10] and sugars.[11]

In this paper, we describe the synthesis and properties of *upper rim C*-linked peptidocalix[4]arenes **2**–**5** and **7**–**9**, which represent a novel class of chiral receptors in that the amino acid units are linked to the calix[4]arene platform through their carboxy groups rather than through nitrogen as in all previously described *N*-linked peptidocalix[4]arenes (Figure 1).[5,7–10] In designing these receptors, it was anticipated that they would show different conformational and binding properties as compared with their *N*-linked analogues.

## Results and Discussion

### Synthesis and Conformational Properties

#### Tetrafunctionalized Receptors

After several unsuccessful attempts to condense the tetraamino calix[4]arene[12] **1** with Cbz-L-alanine by applying various coupling protocols, we finally succeeded in obtaining compounds **2a**,**b** in good yields (60–65%) by reacting **1** with a slight excess of *N*-phthaloyl-L-alanine chloride or *N*-phthaloyl-L-phenylalanine chloride (Scheme 1).

The *N*-phthaloyl peptidocalixarenes **2a**,**b** were deprotected with hydrazine to furnish the tetraamino derivatives **3a**,**b**. Interestingly, the HCl salts of compounds **3a**,**b** are water-soluble at neutral pH and represent the cationic counterparts of water-soluble, anionic *N*-linked peptidocalix[4]arenes.[5] Subsequent reactions of **3a**,**b** with acetyl and benzoyl chlorides gave the tetraacetylated **4a**,**b** and tetrabenzoylated **5a**,**b** derivatives, respectively.

The phthaloyl-protected derivatives **2a**,**b** are soluble in $CDCl_3$ but give rise to rather broad signals in their $^1H$

[a] Dipartimento di Chimica Organica e Industriale dell'Università,
Parco Area delle Scienze 17/A, 43100 Parma, Italy
Fax: (internat.) + 39-0521/905472
E-mail: ungaro@ipruniv.cce.unipr.it
[b] Laboratorio di Modellistica Molecolare, Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica dell'Università,
Parco Area delle Scienze 17/A, 43100 Parma, Italy
Fax: (internat.) + 39-0521/905-557
E-mail: cozzi@unipr.it
[‡] Present address: Departamento de Quimica, Universidade Estadual de Ponta Grossa (UEPG),
Av. Dr. Carlos Cavalcanti,
4748, Ponta Grossa PR, 84030-000, Brazil

  1434–193X/01/0203–595 $ 17.50+.50/0 

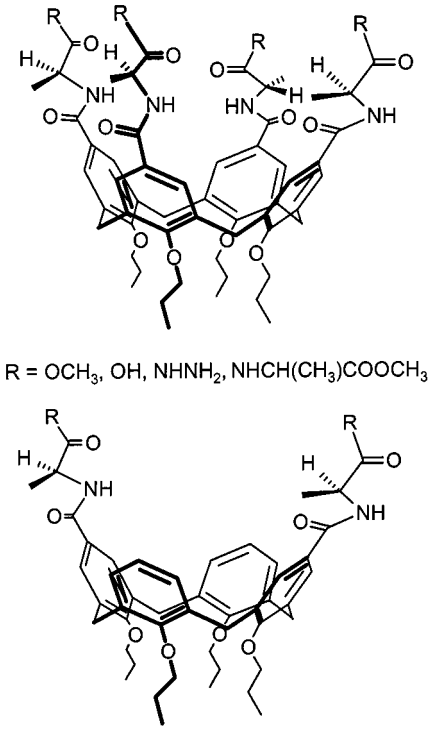



Figure 1. *N*-linked peptidocalix[4]arenes

NMR spectra that would seem to indicate aggregation, probably due to hydrogen bonding. In agreement with this hypothesis, the $^1$H NMR spectra of both compounds are sharp in [$D_6$]DMSO and clearly reveal the symmetrical $C_{4v}$ structure common to all tetrasubstituted *cone* calix[4]arenes.[13]

Both the acetylated **4a**,**b** and benzoylated **5a**,**b** derivatives were found to be completely insoluble in $CDCl_3$, slightly soluble in $CD_3CN$, and very soluble in DMSO, suggesting a more extensive aggregation of these compounds having two amide bonds in each chain as compared with **2a**,**b**. The broad $^1$H NMR signals observed in $CDCl_3$/$CD_3OD$ mixtures confirmed the tendency of these compounds to aggregate even in the presence of a small percentage of a polar solvent. This behaviour is in sharp contrast with that of *N*-linked peptidocalix[4]arenes, which were found to be freely soluble in low polarity media.[5a]

### Difunctionalized Receptors

By applying the same procedures as used to obtain **4a**,**b**, the difunctionalized analogues **9a**,**b** were synthesized in good overall yield starting from diamino-tetrapropyloxycalix[4]arene[14] **6** (Scheme 1).

Although both the phthaloyl and acetyl derivatives were found to have limited solubilities in $CDCl_3$, it was possible to study these compounds in this solvent. In contrast to the previously reported *N*-linked peptidocalix[4]arenes functionalized with alanine methyl ester units at the *upper rim*, the conformational behaviour of *C*-linked analogues **9a**,**b** shows significant changes on going from $CDCl_3$ to the more polar [$D_6$]acetone or [$D_6$]DMSO. In $CDCl_3$ (Figure 2 a), the relative positions of the signals due to the aromatic protons of the substituted (doublets at $\delta$ = 6.32 and 5.89) and unsubstituted (doublet and triplet at $\delta$ = 7.04 and 6.87, respectively) aromatic nuclei indicate that receptor **9a** adopts a *pinched cone* conformation with the two nuclei bearing the alanine units pointing inwards and the other two pointing outwards from the aromatic cavity. Moreover, the observed splitting into two doublets ($\delta$ = 3.13 and 3.10) of the signals due to the equatorial protons of the methylene bridge, attributed to the presence of the chiral substituents at the *upper rim*, indicates a significant degree of structural rigidity. In DMSO (Figure 2, b), a dramatic inversion is observed in the relative positions of the aromatic proton signals. Those attributable to the alanine substituted rings are shifted more than 1 ppm downfield (doublets at $\delta$ = 7.30 and 7.15), while those attributable to the unsubstituted aromatic nuclei are shifted ca. 0.5−0.8 ppm upfield (multiplet at $\delta$ = 6.40−6.28). Moreover, the equatorial protons give only a doublet ($\delta$ = 3.09), typical of achiral and symmetrically 1,3-disubstituted *cone* calix[4]arenes.[15]

Receptor **9b**, having two phenylalanine units, shows similarly solvent-dependent $^1$H NMR spectra.

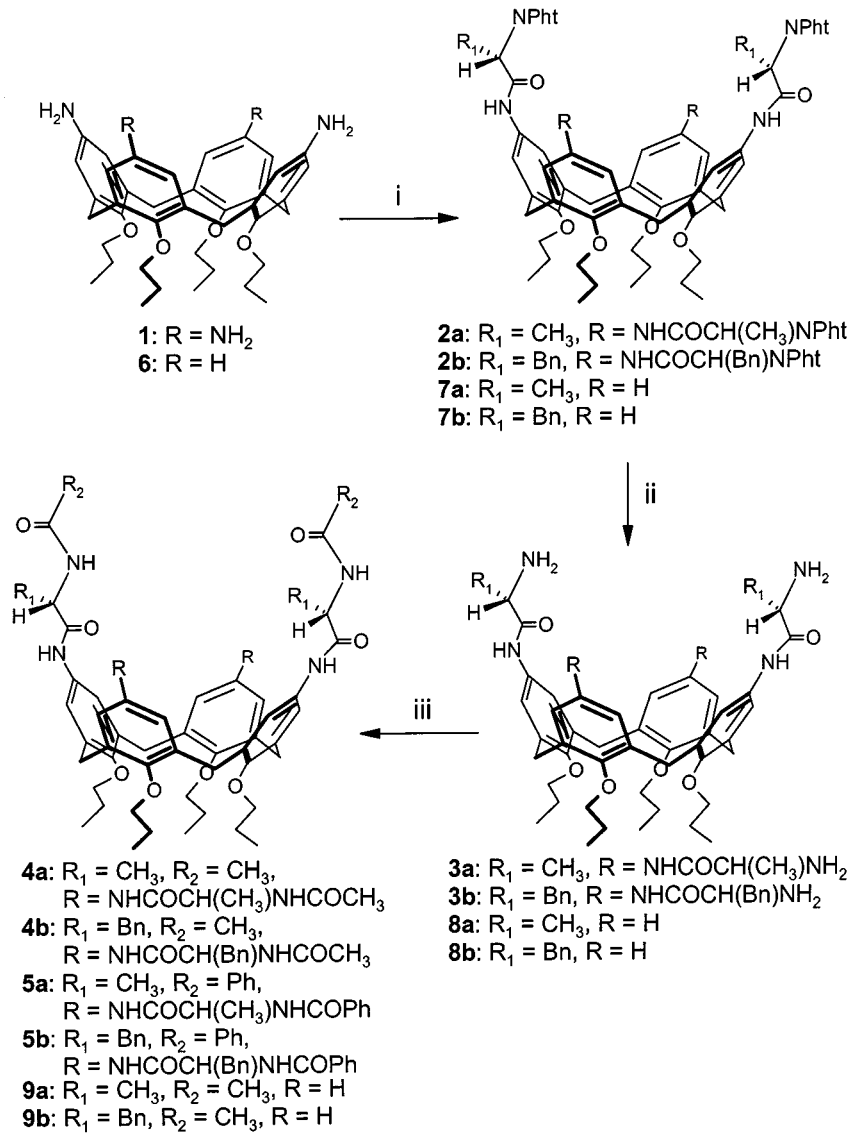
ESI and MALDI-TOF mass spectra of **9a** show the presence of peaks corresponding to a dimeric species. V.P.O. (vapour-pressure osmometry) molecular weight determination[16] in chloroform gave a mean molecular weight of 926, which is higher than that of the monomer (848.8) but significantly lower than that of the dimer (1697.6), thus indicating that the equilibrium between the two species is strongly shifted towards the monomer. At a concentration of $10^{-2}$ M, the upper solubility limit of receptor **9a** in chloroform, the dimeric species is present to an extent of 5−10%.

Taken together, these data suggest that the *pinched cone* conformation observed in $CDCl_3$ for compounds **9a**,**b** (Figure 3, A) arises as a result of intramolecular hydrogen bonding between the amino acid units.

In the absence of an X-ray crystal structure, a molecular modelling (MD) simulation was performed for peptidocalixarene **9a** in vacuo, using the simulated annealing conformational search method.[17] The calculations gave a series of type A (Figure 3) low-energy (from −8.1 to 20.5 kcal·mol$^{-1}$) conformations with one or two hydrogen bonds intramolecularly linking the amino acid units. The lowest-energy conformation (Figure 4) shows two interchain hydrogen bonds [$r(O_{100}\cdots H_{96}N_{87})$ = 1.730 Å, $\alpha(O_{100}\cdots H_{96}N_{87})$ = 156.5° and $r(O_{122}\cdots H_{103}N_{97})$ = 1.688 Å, $\alpha(O_{122}\cdots H_{103}N_{97})$ = 154.0°], in agreement with the hypothesis put forward on the basis of the $^1$H NMR spectroscopic data obtained in $CDCl_3$.

In [$D_6$]DMSO, the intramolecular hydrogen bonds are broken and the equilibrium between the two possible *pinched cone* conformations is shifted towards the *pinched cone* B (Figure 3).

The phthaloyl derivatives **7a**,**b** and their deprotected counterparts **8a**,**b** also show a preference for the *pinched cone* conformation B in $CDCl_3$, indicating that the peculiar conformational behaviour of the acetyl derivatives **9a**,**b** is due to intramolecular hydrogen bonding involving the ter-




Scheme 1. Reagents and conditions: (i) *N*-phthaloyl-amino acid chloride, $NEt_3$, dry $CH_2Cl_2$, room temp.; (ii) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; (iii) RCOCl, $NEt_3$, dry $CH_2Cl_2$, room temp.

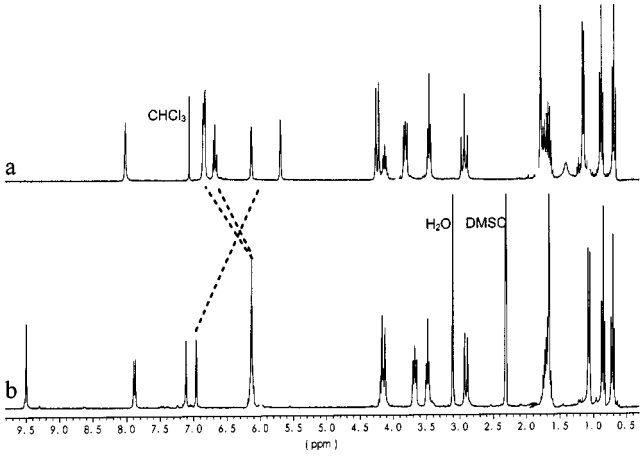



Figure 2. $^1H$ NMR spectra (300 MHz, 300 K) of compound **9a** in $CDCl_3$ (a) and $[D_6]$DMSO (b)

minal acetamide groups. This also explains the remarkable difference in behaviour compared with the *N*-linked peptidocalix[4]arenes, which show a preference for a type-B *pinched cone* conformation both in chloroform solution and in the solid state.[5a]

### Recognition Properties of *C*-Linked Peptidocalix[4]arenes

The recognition properties of the *C*-linked peptidocalix[4]arenes were investigated by $^1H$ NMR titration experiments.[18] The downfield shifts of the amide NH proton signals of the hosts at different host/guest ratios were analysed by nonlinear least-squares fitting procedures,[19] which led to the association constants presented in Table 1.

Due to the solubility problems outlined in the previous section, the tetrafunctionalized receptors were studied in $[D_6]$DMSO solution (see Table 1). No complexation was observed for linear ammonium cations, *N*-protected amino acids, or carboxylic acids, whereas the corresponding an-

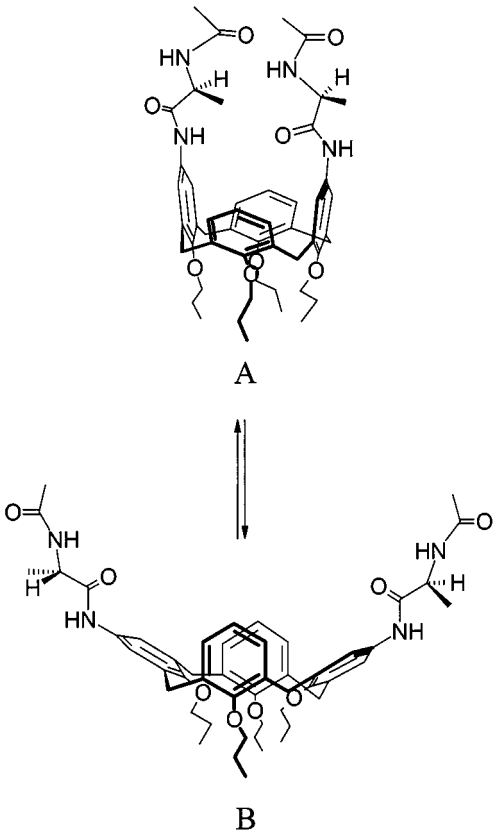



Figure 3. Interconversion between two *pinched cone* conformations in peptidocalix[4]arene **9a**

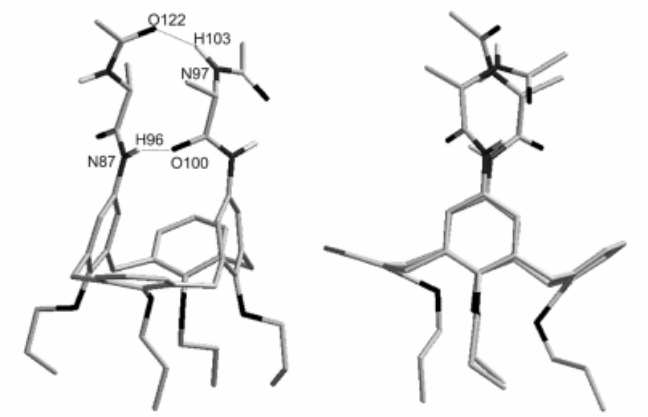



Figure 4. Two views of the energy-minimized structure of the *pinched cone* conformation A of peptidocalix[4]arene **9a**; hydrogen atoms are omitted with the exception of those of the amide NH groups

ionic forms were found to be complexed. The association constants are not very high because DMSO is a highly competitive solvent for hydrogen bonding. The data confirm that the *C*-linked peptidocalix[4]arenes do indeed show quite opposite recognition behaviour as compared to their *N*-linked counterparts, which complex carboxylic acids and ammonium cations but not anions in $CDCl_3$.[5a] We have thus reversed the recognition behaviour of peptidocalix[4]-arenes by changing the mode of attachment of the amino acid units to the calixarene platform.

Table 1. Association constants of selected peptidocalixarenes with various guests at 300 K

| Host | Solvent | Guest[a] | $K$ ($M^{-1}$)[b] |
|---|---|---|---|
| **4a** | [$D_6$]DMSO | acetate | 34 |
| | | benzoate | 12 |
| | | *N*-acetyl-L-alaninate | 14 |
| | | *N*-phthaloyl-L-alaninate | 17 |
| | | $Cl^-$ | 18 |
| | | $Br^-$ | no complexation |
| **2a** | [$D_6$]DMSO | acetate | 33 |
| **9a** | [$D_6$]DMSO | benzoate | 19 |
| | | benzoic acid | no complexation |
| **9a** | $CDCl_3$ | benzoate | 7 |
| | | benzoic acid | 49 |
| | | *N*-acetyl-L-alaninate | no complexation |
| **7a** | [$D_6$]DMSO | benzoate | 21 |
| | | acetate | 19 |
| | | $Cl^-$ | 4 |

[a] Anionic guests as tetra-*n*-butylammonium salts. – [b] The $K$ values are subject to errors of $\leq 10\%$.

In the *N*-linked peptidocalix[4]arenes, the greatest contribution to the binding is that of the carbonyl groups directly attached to the calixarene aromatic nuclei, whereas in the *C*-linked analogues the binding seems to involve only the NH groups in this position. This is indicated by the very similar association constants obtained for acetate in the case of receptor **4a** (34 $M^{-1}$) and the phthaloyl derivative **2a** (33 $M^{-1}$), even though the latter lacks the external amide NH groups. These groups are probably more exposed to solvation as compared with the "inner" NH groups in the vicinity of the apolar calixarene cavity.

The results obtained with the difunctionalized hosts also support this conclusion, the binding constant for benzoate, for example, being almost the same for the *N*-acetyl **9a** and the phthaloyl **7a** derivatives. The intramolecular hydrogen bonding present in the difunctionalized peptidocalixarenes **9a**,**b** results in peculiar behaviour for these hosts. In fact, the association constant between **9a** and benzoate in $CDCl_3$ (7 $M^{-1}$) is lower than that in [$D_6$]DMSO (19 $M^{-1}$), which is in contrast to the solvent effect often found with other host–guest systems interacting through hydrogen bonding.[2b–20] In the low donor solvent $CDCl_3$, the intramolecular hydrogen bonds have to be broken in order to allow anion binding to **9a**. A substantial rearrangement from the *pinched cone* conformation A to the other *pinched cone* B is indeed observed during titration experiments of **9a** with the benzoate anion. In fact, the signals due to the aromatic protons of the substituted rings of host **9a**, which are seen at $\delta = 6.32$ and 5.89 in the free ligand, are significantly downfield shifted to $\delta = 7.27$ and 7.19 when the host–guest ratio is 1:8.8. At the same time, the signals due to the protons of the unsubstituted aromatic nuclei are upfield shifted from $\delta = 7.04$ and 6.87 to $\delta = 6.37$ and 6.27, respectively.

## Conclusion

In this paper, we have shown for the first time that amino acids can be conveniently attached to the *upper rim* of *cone*

calix[4]arenes through their carboxy groups to give tetra- and difunctionalized *C*-linked peptidocalix[4]arenes.

Comparison of the chemical, conformational, and binding properties of this novel class of hybrid receptors with those of the previously reported *N*-linked peptidocalix[4]arenes reveals remarkable and interesting differences:

(i) The tetrafunctionalized *C*-linked peptidocalix[4]arenes show a much stronger tendency to aggregate and, as a consequence, their solubility in solvents of moderate polarity ($CDCl_3$, $CD_3CN$) is much lower as compared with that of their *N*-linked analogues.

(ii) The difunctionalized *C*-linked peptidocalix[4]arenes are subject to intramolecular hydrogen bonding, which stabilizes the *pinched cone* conformation A with a closed cavity, whereas the *N*-linked peptidocalix[4]arenes have a preference for the other *pinched cone* conformation B, characterized by an open, cleft-like cavity.

(iii) The *C*-linked peptidocalix[4]arenes seem to preferentially bind anions through hydrogen bonding, whereas the previously reported *N*-linked analogues mainly complex cationic acidic species.

(iv) The tetrafunctionalized *C*-linked peptidocalix[4]arenes **3a**,**b** have four terminal amino groups, protonation of which leads to positively-charged water-soluble receptors, whereas the *N*-linked water-soluble peptidocalix[4]arenes have negatively-charged carboxylate end groups. This fact could eventually lead to a completely different interaction mode of the two classes of receptors with biologically important hosts such as enzymes, DNA, etc.

The information collected with the present *C*-linked peptidocalix[4]arenes prototypes should prove useful for the design and synthesis of more complex hybrid receptors for the recognition of biologically relevant species.

## Experimental Section

**General:** Melting points were determined on an Electrothermal apparatus with samples in sealed tubes under nitrogen atmosphere. − $^1H$ and $^{13}C$ NMR spectra were recorded at 300 or 400 MHz and 25 or 75 MHz, respectively, on Bruker AC100, AC300, and AMX400 spectrometers (partially deuterated solvents were used as internal standards). − Mass spectra in CI mode ($CH_4$) were recorded on a Finnigan MAT SSQ710 spectrometer; MALDI-TOF MS experiments were carried out on a Perspective Biosystem Voyager DE-RP instrument. − Optical rotations were measured on a Perkin−Elmer 241 polarimeter using light of wavelength 589.3 nm. − TLC was performed on Merck silica gel 60 $F_{254}$, while for flash chromatography ICN 32−63 μm, 60-Å silica gel was used. − Amino acids were purchased from Sigma. − Molecular mass determinations were carried out using a vapour-pressure osmometer with samples in distilled HPLC-grade $CHCl_3$ at 36 °C in the concentration range 1.4−5.7 g·kg$^{-1}$; 25,26,27,28-tetrakis(*N,N*-diethylamino)carbonylmethoxycalix[4]arene[21] was used as a calibration standard. 5,11,17,23-Tetraamino-25,26,27,28-tetra-*n*-propyloxycalix[4]arene[12] **1** and 5,17-diamino-25,26,27,28-tetra-*n*-propyloxycalix[4]arene[14] **6** were synthesized from 5,11,17,23-tetranitro-25,26,27,28-tetra-*n*-propyloxycalix[4]arene[22] and 5,17-dinitro-25,26,27,28-tetra-*n*-propyloxycalix[4]arene,[23] respectively, according to literature procedures.

As verified by other authors,[24] elemental analyses of calixarenes are very often incorrect because of the inclusion of solvent molecules and thus cannot be considered as an appropriate criterion of purity. Nevertheless, the identities of the reported compounds have been confirmed by their spectral data.

Molecular modelling was performed with SPARTAN and SYBYL software on a Silicon Graphics SI workstation. The TRIPOS force field[25] was used in conjunction with the standard parameters of the package. Simulated annealing[17] experiments were carried out using SYBYL version 6.5. Energy minimizations were carried out (Powell method[26]) until the root mean square of the gradient reached a value of 0.001 kcal·mol$^{-1}$·Å$^{-1}$. A distance-dependent dielectric constant was applied. Atomic charges were calculated by the Gasteiger−Hückel method.

**General Procedure for the Coupling of Aminocalix[4]arenes (1 and 6) with *N*-Phthaloyl Amino Acid Chlorides:** To a solution of the calixarene derivative (2.0 mmol) and $NEt_3$ (2.5 mmol for each $NH_2$ group) in dry $CH_2Cl_2$ (20 mL), a solution of the *N*-phthaloyl-amino acid chloride (1.25 mmol for each $NH_2$ group) in dry $CH_2Cl_2$ (0.5 mL for each mmol of amino acid) was added dropwise at 0 °C. The reaction was allowed to proceed for 1 h at room temp. It was then quenched by the addition of 0.1 N NaOH (15 mL) and the organic layer was separated. The aqueous layer was extracted twice more with $CH_2Cl_2$ (2 × 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated to dryness in vacuo.

**5,11,17,23-Tetrakis(phthaloyl-L-alanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (2a):** The pure compound was obtained by flash chromatography (hexane/AcOEt, 1:1, *v*/*v*). Yield: 1.89 g, 65%. White solid; m.p. 314−316 °C. − $[\alpha]_D^{25} = -19.0$ ($c$ = 0.5, $CHCl_3$). − $^1H$ NMR (300 MHz, [D$_6$]DMSO): δ = 9.61 (s, 4 H, NH), 7.95−7.85 (m, 16 H, phthaloyl), 6.98 and 6.92 (d, $J$ = 2.0 Hz, 4 H each, aromatic), 4.78 (q, $J$ = 7.2 Hz, 4 H, C*H*CH$_3$), 4.32 (d, $J$ = 12.6 Hz, 4 H, H$_{ax}$ of ArC*H*$_2$Ar), 3.78 (t, $J$ = 7.5 Hz, 8 H, OC*H*$_2$CH$_2$CH$_3$), 3.05 (d, $J$ = 12.6 Hz, 4 H, H$_{eq.}$ of ArC*H*$_2$Ar), 1.95−1.80 (m, 8 H, OCH$_2$C*H*$_2$CH$_3$), 1.58 (d, $J$ = 7.2 Hz, 12 H, CHC*H*$_3$), 0.93 (t, $J$ = 7.5 Hz, 12 H, OCH$_2$CH$_2$C*H*$_3$). − $^{13}C$ NMR (75 Hz, DMSO): δ = 167.4 and 166.9 (s, CO), 152.1 and 134.5 (s, aromatic), 133.9 (d, aromatic), 132.7, 131.8, and 123.0 (s, aromatic), 120.2 and 120.0 (d, aromatic), 76.5 (t, O*C*H$_2$CH$_2$CH$_3$), 48.9 (d, *C*HCH$_3$), 30.9 (t, Ar*C*H$_2$Ar), 22.5 (t, OCH$_2$*C*H$_2$CH$_3$), 15.2 (q, CH*C*H$_3$), 10.1 (q, OCH$_2$CH$_2$*C*H$_3$). − MS, CI(+): *m*/*z* = 1459.1 (100) [M$^+$ + H].

**5,11,17,23-Tetrakis(phthaloyl-L-phenylalanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (2b):** The pure compound was obtained by crystallization from $CH_2Cl_2$/hexane. Yield: 2.29 g, 65%. White solid; m.p. 175−177 °C. − $[\alpha]_D^{25} = -102.4$ ($c$ = 0.5, $CHCl_3$). − $^1H$ NMR (300 MHz, [D$_6$]DMSO): δ = 9.79 (s, 4 H, NH), 7.87−7.79 and 7.80−7.74 (m, 4 H each, phthaloyl), 7.20−7.05 (m, 20 H, aromatic H of phenylalanine), 7.02 and 6.99 (d, $J$ = 2 Hz, 4 H each, aromatic), 5.04 (dd, $J$ = 11.4, 4.8 Hz, 4 H, C*H*CH$_2$), 4.36 (d, $J$ = 12.6 Hz, 4 H, H$_{ax}$ of ArC*H*$_2$Ar), 3.81 (t, $J$ = 7.5 Hz, 8 H, OC*H*$_2$CH$_2$CH$_3$), 3.51 (dd, $J$ = 13.8, 4.8 Hz, 4 H, CHC*H*H), 3.43 (dd, $J$ = 13.8, 11.4 Hz, 4 H, CHCH*H*), 3.10 (d, $J$ = 12.6 Hz, 4 H, H$_{eq.}$ of ArC*H*$_2$Ar), 1.95−1.82 (m, 8 H, OCH$_2$C*H*$_2$CH$_3$), 0.95 (t, $J$ = 7.5 Hz, 12 H, OCH$_2$CH$_2$CH$_3$). − $^{13}C$ NMR (75 MHz, [D$_6$]DMSO): δ = 167.4 and 165.8 (s, CO), 152.2, 137.4, and 134.5 (s, aromatic), 134.0 (d, aromatic), 132.5 and 131.1 (s, aromatic), 128.6, 128.2, 126.4, 123.0, and 120.2 (d, aromatic), 76.5 (t, O*C*H$_2$CH$_2$CH$_3$), 55.0 (d, *C*HCH$_2$), 33.9 (t, CH*C*H$_2$), 30.9 (t, Ar*C*H$_2$Ar), 22.5 (t, OCH$_2$*C*H$_2$CH$_3$), 10.1 (q, OCH$_2$CH$_2$*C*H$_3$). − MS, CI(+): *m*/*z* = 1761.8 (100) [M$^+$].

**5,17-Bis(phthaloyl-L-alanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (7a):** The pure compound was obtained by crystallization from chloroform at 4 °C. Yield: 1.23 g, 60%. White solid; m.p. 245−247 °C. − $[\alpha]_D^{25} = -28.0$ ($c$ = 0.5, acetone). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.95−7.85 and 7.80−7.70 (2 m, 4 H each, phthaloyl), 7.83 (br. s, 2 H, NH), 7.07 (br. s, 4 H, aromatic), 6.34 (br. s, 6 H, aromatic), 5.06 (q, $J$ = 7.3 Hz, 2 H, C*H*$CH_3$), 4.38 (d, $J$ = 13.2 Hz, 4 H, $H_{ax}$ of ArC*H*$_2$Ar), 3.88 (br. t, 4 H, OC*H*$_2$$CH_2CH_3$), 3.71 (t, $J$ = 7 Hz, 4 H, OC*H*$_2$$CH_2CH_3$), 3.09 (d, $J$ = 13.2 Hz, 4 H, $H_{eq.}$ of ArC*H*$_2$Ar), 1.98−1.75 (m, 14 H, $OCH_2CH_2CH_3$ and $CHCH_3$), 1.02 (t, $J$ = 7.3 Hz, 6 H, $OCH_2CH_2CH_3$), 0.90 (t, $J$ = 7.5 Hz, 6 H, $OCH_2CH_2CH_3$). − $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 167.4 and 167.0 (s, CO), 158.7, 153.0, and 135.5 (s, aromatic), 134.3 (d, aromatic), 132.9, 132.4, and 131.8 (s, aromatic) 127.2 (d, aromatic), 123.0, 121.7, and 120.7 (d, aromatic), 76.5 and 76.1 (t, O*C*$H_2CH_2CH_3$), 48.8 (d, *C*H$CH_3$), 30.2 (t, Ar*C*$H_2$Ar), 22.9 and 22.4 (t, $OCH_2CH_2CH_3$), 15.1 (q, $CHCH_3$), 10.4 and 9.8 (q, $OCH_2CH_2CH_3$). − MS, CI(+): $m/z$ = 1025.6 (100) [M$^+$ + H].

**5,17-Bis(phthaloyl-L-phenylalanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (7b):** The pure compound was obtained by flash chromatography ($CH_2Cl_2$/MeOH, 70:1, *v*/*v*). Yield: 1.41 g, 60%. White solid; m.p. 196−198 °C. − $[\alpha]_D^{25} = -32.7$ ($c$ = 0.5, acetone). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.01 (br. s, 2 H, NH), 7.85−7.78 and 7.78−7.68 (m, 8 H, phthaloyl), 7.40−7.07 (m, 14 H, aromatic H of calixarene and phenylalanine), 6.24 (br. s, 4 H, aromatic), 5.25 (t, 2 H, $J$ = 8.4 Hz, C*H*$CH_2$), 4.39 (d, 4 H, $J$ = 13.2 Hz, $H_{ax}$ of ArC*H*$_2$Ar), 3.92 (br. t, 4 H, OC*H*$_2$$CH_2CH_3$), 3.75−3.60 (m, 8 H, $CHCH_2$ and OC*H*$_2$$CH_2CH_3$), 3.09 (d, 4 H, $J$ = 13.2 Hz, $H_{eq.}$ of ArC*H*$_2$Ar), 1.99−1.78 (m, 8 H, $OCH_2CH_2CH_3$), 1.04 (t, 6 H, $J$ = 7.4 Hz, $OCH_2CH_2CH_3$), 0.88 (t, 6 H, $J$ = 7.1 Hz, $OCH_2CH_2CH_3$). − $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 167.5 and 162.5 (s, CO), 157.5, 155.5, and 137.0 (s, aromatic), 136.6, 134.3, 133.1, 131.4, 131.0, 129.0, 128.8, 127.6, 127.1, 123.6, 122.2, and 120.7 (d, aromatic), 77.2 and 76.8 (t, O*C*$H_2CH_2CH_3$), 57.3 (s, *C*H$CH_2$), 35.1 (t, CH*C*$H_2$), 31.0 (t, Ar*C*$H_2$Ar), 23.4 and 23.0 (t, $OCH_2CH_2CH_3$),10.7 and 10.0 (q, $OCH_2CH_2CH_3$). − MS, CI(+): $m/z$ = 1178.8 (100) [M$^+$ + H].

**General Procedure for Removal of the Phthaloyl Group:** A mixture of the phthaloyl-protected peptidocalixarene (1.0 mmol) and hydrazine monohydrate (2.5 mmol for each phthaloyl group) in absolute ethanol (40 mL) was refluxed for 2 h. It was then cooled to room temp., the solvent was evaporated, the residue was treated with 0.1 N NaOH (20 mL), and then extracted with $CH_2Cl_2$ (2 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness in vacuo.

**5,11,17,23-Tetrakis(L-alanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (3a):** The pure compound was obtained by trituration with $Et_2O$. Yield: 0.80 g, 85%. White solid; m.p. 256−259 °C. − $[\alpha]_D^{25}$ = 15.0 ($c$ = 0.5, ethanol). − $^1$H NMR (300 MHz, $CD_3OD$): δ = 6.97 and 6.73 (2 d, $J$ = 2.2 Hz, 4 H each, aromatic), 4.46 (d, $J$ = 12.6 Hz, 4 H, $H_{ax}$ of ArC*H*$_2$Ar), 4.35 (q, $J$ = 6.9 Hz, 4 H, C*H*$CH_3$), 3.85 (t, $J$ = 7.5 Hz, 8 H, OC*H*$_2$$CH_2CH_3$), 3.07 (d, $J$ = 12.6 Hz, $H_{eq.}$ of ArC*H*$_2$Ar), 2.00−1.85 (m, 8 H, $OCH_2CH_2CH_3$), 1.29 (d, $J$ = 6.9 Hz, 12 H, $CHCH_3$), 1.01 (t, $J$ = 4.7 Hz, 12 H, $OCH_2CH_2CH_3$). − $^{13}$C NMR (75 MHz, $CD_3OD$): δ = 175.8 (s, CO), 154.5, 136.3, 136.2, and 133.4 (s, aromatic), 122.1 and 121.8 (d, aromatic), 78.2 (t, O*C*$H_2CH_2CH_3$), 51.9 (d, *C*H$CH_3$), 32.2 (t, Ar*C*$H_2$Ar), 24.4 (t, $OCH_2CH_2CH_3$), 21.6 (q, CH*C*$H_3$), 10.8 (q, $OCH_2CH_2CH_3$). − MS, CI(+): $m/z$ = 937.8 (70) [M + H$^+$], 892.8 (100) [M$^+$ − $NH_2CHCH_3$].

**5,11,17,23-Tetrakis(L-phenylalanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (3b):** The pure compound was obtained by trituration with $Et_2O$. Yield: 1.05 g, 85%. White solid; m.p. 134−136 °C. − $[\alpha]_D^{25}$ = 12.6 ($c$ = 0.5, ethanol). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.90 (s, 4 H, NHCO), 7.35−7.20 (m, 12 H, aromatic H of phenylalanine), 7.17 (d, $J$ = 7.3 Hz, 8 H, aromatic H of phenylalanine), 7.06 and 6.75 (2 d, $J$ = 2.1 Hz, 4 H each, aromatic), 4.45 (d, $J$ = 13.1 Hz, 4 H, $H_{ax}$ of ArC*H*$_2$Ar), 3.84 (t, $J$ = 7.5 Hz, 8 H, OC*H*$_2$$CH_2CH_3$), 3.57 (dd, $J$ = 9.4, 3.6 Hz, 4 H, $CHCH_2$), 3.31 (dd, $J$ = 13.6, 3.6 Hz, 4 H, CHC*H*), 3.17 (d, $J$ = 13.1 Hz, 4 H, $H_{eq.}$ of ArC*H*$_2$Ar), 2.66 (dd, $J$ = 13.6, 9.4 Hz, 4 H, CHC*H*), 2.01−1.90 (m, 8 H, $OCH_2CH_2CH_3$), 0.99 (t, $J$ = 7.4 Hz, 12 H, $OCH_2CH_2CH_3$). − $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 172.1 (s, CO), 153.4, 137.9, 135.0, and 131.5 (s, aromatic), 129.2, 128.7, 126.8, and 120.7 (d, aromatic), 76.9 (t, O*C*$H_2CH_2CH_3$), 56.8 (d, *C*H$CH_2$), 41.0 (t, CH*C*$H_2$), 31.2 (t, Ar*C*$H_2$Ar), 23.1 (t, $OCH_2CH_2CH_3$), 10.2 (q, $OCH_2CH_2CH_3$). − MS, CI(+): $m/z$ = 1241.5 (90) [M$^+$ + H], 1120.5 (100) [M$^+$ − $H_2NCHCH_2Ph$].

**5,17-Bis(L-alanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (8a):** The pure compound was obtained by flash chromatography ($CH_2Cl_2$/$CH_3OH$, 100:1, *v*/*v*). Yield: 0.57 g, 74%. White solid; m.p. 226−228 °C. − $[\alpha]_D^{25}$ = 3.7 ($c$ = 0.5, acetone). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 9.21 (s, 2 H, NH), 7.28 and 7.20 (2 d, $J$ = 2.5 Hz, 2 H each, aromatic), 6.31 (br. s, 6 H, aromatic), 4.42 (d, $J$ = 13.2 Hz, 4 H, $H_{ax}$ of ArC*H*$_2$Ar), 3.94 (br. t, 4 H, OC*H*$_2$$CH_2CH_3$), 3.70 (t, $J$ = 4.9 Hz, 4 H, OC*H*$_2$$CH_2CH_3$), 3.60 (q, $J$ = 6.9 Hz, 2 H, C*H*$CH_3$), 3.13 (d, $J$ = 13.2 Hz, 4 H, $H_{eq.}$ of ArC*H*$_2$Ar), 1.97−1.84 (m, 8 H, $OCH_2CH_2CH_3$), 1.44 (d, $J$ = 6.9 Hz, 6 H, $CHCH_3$), 1.06 (t, $J$ = 7.3 Hz, 6 H, $OCH_2CH_2CH_3$), 0.87 (t, 6 H, $J$ = 7.5 Hz, $OCH_2CH_2CH_3$). − $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 173.2 (s, CO), 155.5, 154.2, and 136.9 (s, aromatic), 133.4, 131.6, 127.6, 122.1, and 120.1 (d, aromatic), 77.2 and 76.9 (t, O*C*$H_2CH_2CH_3$), 51.2 (d, *C*H$CH_3$), 31.0 (t, Ar*C*$H_2$Ar), 23.4 and 22.9 (t, $OCH_2CH_2CH_3$), 21.8 (q, CH*C*$H_3$), 10.7 and 10.0 (q, $OCH_2CH_2CH_3$). − MS, CI(+): $m/z$ = 765.6 (85) [M$^+$ + H], 721.5 (35) [M$^+$ − $NH_2CHCH_3$], 694.1 (100) [M$^+$ − $NH_2CH(CH_3)CO$].

**5,17-Bis(L-phenylalanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (8b):** The pure compound was obtained by flash chromatography ($CH_2Cl_2$/$CH_3OH$, 70:1, *v*/*v*). Yield: 0.64 g, 70%. White solid; m.p. 183−185 °C. − $[\alpha]_D^{25}$ = −5.5 ($c$ = 0.5, acetone). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 9.17 (s, 2 H, NH), 7.40−7.16 (m, 16 H, aromatic H of phenylalanine), 7.22 and 7.14 (2 d, $J$ = 2.2 Hz, 2 H each, aromatic), 6.36 (br. s, 6 H, aromatic), 4.44 (d, $J$ = 13.2 Hz, 4 H, $H_{ax}$ of ArC*H*$_2$Ar), 3.93 (br. t, 4 H, OC*H*$_2$$CH_2CH_3$), 3.73 (m, 6 H, OC*H*$_2$$CH_2CH_3$ and C*H*$CH_2$), 3.39 (dd, $J$ = 13.5, 3.5 Hz, 2 H, CHC*H*H), 3.13 (d, $J$ = 13.2 Hz, 4 H, $H_{eq.}$ of ArC*H*$_2$Ar), 2.78 (dd, $J$ = 13.5, 9.6 Hz, CHCH*H*), 2.01−1.84 (m, 8 H, $OCH_2CH_2CH_3$), 1.09 (t, $J$ = 7.2 Hz, 6 H, $OCH_2CH_2CH_3$), 0.92 (t, $J$ = 7.5 Hz, 6 H, $OCH_2CH_2CH_3$). − $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 171.5 (s, CO), 155.5, 154.2, 136.6, 133.5, and 131.4 (s, aromatic), 129.3, 128.8, 127.6, 126.9, 122.1, and 120.2 (d, aromatic), 76.8 and 76.5 (t, O*C*$H_2CH_2CH_3$) 56.8 (d, *C*H$CH_2$), 40.7 (t, CH*C*$H_2$), 31.0 (d, Ar*C*$H_2$Ar), 29.6, 23.3, and 22.9 (t, $OCH_2CH_2CH_3$), 10.6 and 10.0 (q, $OCH_2CH_2CH_3$). − MS, CI(+): $m/z$ = 916.6 (45) [M$^+$], 796.5 (90) [M$^+$ − $NH_2CHCH_2Ph$], 769.5 (100) [M$^+$ − $NH_2CH(CH_2Ph)CO$].

**General Procedure for the *N*-Acylation of Peptidocalixarenes 3a,b and 8a,b:** To a solution of the calixarene derivative (0.5 mmol) and $NEt_3$ (2.0 mmol for each amino acid unit) in dry $CH_2Cl_2$ (20 mL), a solution of the acyl chloride derivative (2.5 mmol for each amino acid unit) in dry $CH_2Cl_2$ (2 mL) was added at 0 °C. The reaction mixture was stirred for 2 h at room temp., and then quenched by

the addition of 0.1 N NaOH (10 mL). The organic layer was separated, washed with water (2 × 10 mL) and 1 N HCl, dried over $MgSO_4$, and concentrated to dryness.

**5,11,17,23-Tetrakis(acetyl-L-alanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (4a):** The pure compound was obtained by trituration with $CH_2Cl_2$. Yield: 0.50 g, 90%. White solid; m.p. 241−243 °C. − $[\alpha]_D^{25} = -12.0$ ($c$ = 0.5, ethanol/DMSO, 1:3). − $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.66 (s, 4 H, NHPh), 8.00 (d, $J$ = 7.2 Hz, 4 H, N*H*CH), 7.14 and 6.84 (d, $J$ = 2.1 Hz, 4 H each, aromatic), 4.36 (d, $J$ = 12.6 Hz, 4 H, $H_{ax}$ of ArC$H_2$Ar), 4.30 (q, $J$ = 6.9 Hz, C*H*CH$_3$), 3.80 (t, $J$ = 7.2 Hz, 8 H, OC$H_2$CH$_2$CH$_3$), 3.09 (d, $J$ = 12.6 Hz, 4 H, $H_{eq.}$ of ArC$H_2$Ar), 2.00−1.85 (m, 8 H, OCH$_2$C$H_2$CH$_3$), 1.83 (s, 12 H, CH$_3$CO), 1.19 (d, $J$ = 6.9 Hz, 12 H, CHC$H_3$), 0.96 (t, $J$ = 7.8 Hz, 12 H, OCH$_2$CH$_2$C$H_3$). − $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 170.6 and 168.8 (s, CO), 151.9, 134.0, 133.9, and 132.8 (s, aromatic), 119.9, 119.5 (d, aromatic), 76.4 (t, O*C*H$_2$CH$_2$CH$_3$), 48.7 (d, *C*HCH$_3$), 30.8 (t, Ar*C*H$_2$Ar), 22.5 (t, OCH$_2$*C*H$_2$CH$_3$), 22.4 (q, *C*H$_3$CO), 18.2 (q, CH*C*H$_3$), 10.1 (q, OCH$_2$CH$_2$*C*H$_3$). − MS, CI(+): $m/z$ = 1106.5 (80) [M$^+$ + H], 993.4 (100) [M$^+$ − CH$_3$CONHCH(CH$_3$)CO].

**5,11,17,23-Tetrakis(acetyl-L-phenylalanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (4b):** The pure compound was obtained by trituration with $CH_2Cl_2$. Yield: 0.60 g, 85%. White solid; m.p. 238−240 °C. − $[\alpha]_D^{25}$ = 48.6 ($c$ = 0.5, ethanol). − $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.89 (s, 4 H, NHPh), 8.10 (d, $J$ = 8.2 Hz, 4 H, N*H*CH), 7.35−7.10 (m, 24 H, aromatic), 6.81 (d, $J$ = 2.1 Hz, 4 H, aromatic), 4.60−4.50 (m, 4 H, C*H*CH$_2$), 4.38 (d, $J$ = 12.6 Hz, 4 H, $H_{ax}$ of ArC$H_2$Ar), 3.82 (t, $J$ = 7.3 Hz, 8 H, OC$H_2$CH$_2$CH$_3$), 3.12 (d, $J$ = 12.6 Hz, 4 H, $H_{eq.}$ of ArC$H_2$Ar), 2.97 (dd, $J$ = 13.7, 3.9 Hz, 4 H, CHC*H*H), 2.73 (dd, $J$ = 13.7, 10.4 Hz, CHCH*H*), 2.00−1.85 (m, 8 H, OCH$_2$C$H_2$CH$_3$), 1.74 (s, 12 H, CH$_3$CO), 0.98 (t, $J$ = 7.2 Hz, 12 H, OCH$_2$CH$_2$C$H_3$). − $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 169.6 and 169.0 (s, CO), 152.0, 137.9, 134.1, 133.9, and 132.8 (s, aromatic), 129.0, 127.9, 126.2, 120.2, and 119.7 (d, aromatic), 76.5 (t, O*C*H$_2$CH$_2$CH$_3$), 54.6 (d, *C*HCH$_2$), 37.7 (t, CH*C*H$_2$), 30.9 (t, Ar*C*H$_2$Ar), 22.6 (t, OCH$_2$*C*H$_2$CH$_3$), 22.3 (q, *C*H$_3$CO), 10.1 (q, OCH$_2$CH$_2$*C*H$_3$). − MS, CI(+): $m/z$ = 1408.7 (80) [M$^+$], 1219.8 (100) [M$^+$ − CH$_3$CONHCH(CH$_2$Ph)CO].

**5,17-Bis(acetyl-L-alanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (9a):** The pure compound was obtained by trituration with hexane and subsequent crystallization from $CHCl_3$ at 4 °C. Yield: 0.25 g, 60%. White solid; m.p. 180−182 °C. − $[\alpha]_D^{25}$ = −17.3 ($c$ = 0.5, acetone). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.21 (s, 2 H, NHPh), 7.04 (d, 4 H, $J$ = 7.3 Hz, aromatic), 7.03 (d, 2 H, $J$ = 7.5 Hz, N*H*CH), 6.87 (t, $J$ = 7.3 Hz, 4 H, aromatic), 6.32 and 5.89 (2 d, $J$ = 2.1 Hz, 2 H each, aromatic), 4.43 (d, $J$ = 13.4 Hz, 4 H, $H_{ax}$ of ArC$H_2$Ar), 4.40−4.35 (m, 2 H, C*H*CH$_3$), 4.01 (br. t, 4 H, OC$H_2$CH$_2$CH$_3$), 3.65 (t, $J$ = 6.8 Hz, 4 H, OC$H_2$CH$_2$CH$_3$), 3.13 and 3.10 (2 d, $J$ = 13.4 Hz, 2 H each, $H_{eq.}$ of ArC$H_2$Ar), 1.98 (s, 6 H, CH$_3$CO), 1.98−1.82 (m, 8 H, OCH$_2$C$H_2$CH$_3$), 1.34 (d, $J$ = 6.9 Hz, 6 H, CHC$H_3$), 1.07 and 0.88 (2 t, $J$ = 7.4 Hz, 6 H each, OCH$_2$CH$_2$C$H_3$). − $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.69 (s, 2 H, NHPh), 8.07 (d, $J$ = 7.2 Hz, 2 H, N*H*CH), 7.30 and 7.15 (2 d, $J$ = 2.1 Hz, 2 H each, aromatic), 6.40−6.28 (m, 4 H, aromatic), 4.35−4.28 (m, 2 H, C*H*CH$_3$), 4.33 (d, $J$ = 13.5 Hz, 4 H, $H_{ax}$ of ArC$H_2$Ar), 3.87 (br. t, 4 H, OC$H_2$CH$_2$CH$_3$), 3.67 (t, $J$ = 6.9 Hz, 4 H, OC$H_2$CH$_2$CH$_3$), 3.09 (d, $J$ = 13.4 Hz, 4 H, $H_{eq.}$ of ArC$H_2$Ar), 1.95−1.80 (m, 8 H, OCH$_2$C$H_2$CH$_3$), 1.85 (s, 6 H, CH$_3$CO), 1.25 (d, $J$ = 7.2 Hz, 6 H, CHC$H_3$), 1.04 (t, $J$ = 7.2 Hz, 6 H, OCH$_2$CH$_2$C$H_3$), 0.92 and 0.90 (2 t, $J$ = 7.8 Hz, 3 H each, OCH$_2$CH$_2$C$H_3$). − $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 170.8 and 170.4 (s, CO), 157.6, 153.4, and 136.2 (s, aromatic), 134.0, 130.2, 128.9, 123.3, and 121.9 (d, aromatic), 77.1 and 76.7 (t, O*C*H$_2$CH$_2$CH$_3$), 48.9 (d, C*H*CH$_3$), 31.1 and 29.6 (t, Ar*C*H$_2$Ar), 23.3 and 22.8 (t, OCH$_2$*C*H$_2$CH$_3$), 23.0 (q, *C*H$_3$CO), 17.5 (q, CH*C*H$_3$), 10.6 and 9.7 (q, OCH$_2$CH$_2$*C*H$_3$). − MS, CI(+): $m/z$ = 848.6 (100) [M$^+$].

**5,17-Bis(acetyl-L-phenylalanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (9b):** The pure compound was obtained by crystallization from $CH_2Cl_2$ at 4 °C. Yield: 0.28 g, 55%. White solid; m.p. 195−197 °C. − $[\alpha]_D^{25}$ = −5.7 ($c$ = 0.5, acetone). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.98 (br. s, 2 H, NHPh), 7.32−7.20 (m, 6 H, aromatic H of phenylalanine), 7.20−7.12 (m, 4 H, aromatic H of phenylalanine), 6.96 (br. d, 4 H, aromatic), 6.85 (br. d, 2 H, N*H*CH), 6.83 (t, $J$ = 7.2 Hz, 2 H, aromatic), 6.30 and 5.82 (2 d, $J$ = 2.0 Hz, 2 H each, aromatic), 4.62−4.54 (m, 2 H, C*H*CH$_2$), 4.40 (d, $J$ = 13.2 Hz, 4 H, $H_{ax}$ of ArC$H_2$Ar), 3.98 (br. t, 4 H, OC$H_2$CH$_2$CH$_3$), 3.66 (t, $J$ = 6.9 Hz, 4 H, OC$H_2$ CH$_2$CH$_3$), 3.18−2.95 (m, 4 H, CHC$H_2$), 3.11 and 3.07 (2 d, $J$ = 13.2 Hz, 2 H each, $H_{eq.}$ of ArC$H_2$Ar), 2.00 (s, 6 H, CH$_3$CO), 2.00−1.78 (m, 8 H, OCH$_2$C$H_2$CH$_3$), 1.05 (t, $J$ = 7.4 Hz, 6 H, OCH$_2$CH$_2$C$H_3$), 0.88 (t, $J$ = 7.5 Hz, 6 H, OCH$_2$CH$_2$C$H_3$). − $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 171.9 and 170.6 (s, CO), 157.4, 153.3, and 136.0 (s, aromatic), 134.0, 129.3, 128.7, 128.4, 126.7, 123.6, 122.1, and 121.7 (d, aromatic), 77.1 and 76.7 (t, O*C*H$_2$CH$_2$CH$_3$), 54.7 (d, *C*HCH$_2$), 37.9 (t, CH*C*H$_2$), 30.9 (t, Ar*C*H$_2$Ar), 23.3 and 22.8 (t, OCH$_2$*C*H$_2$CH$_3$), 23.1 (q, *C*H$_3$CO), 10.6 and 9.8 (q, OCH$_2$CH$_2$*C*H$_3$). − MS, CI(+): $m/z$ = 1000.6 (100) [M$^+$].

**5,11,17,23-Tetrakis(benzoyl-L-alanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (5a):** The pure compound was obtained by trituration with hexane. Yield: 0.58 g, 85%. White solid; m.p. 310−311 °C. − $[\alpha]_D^{25}$ = 86.4 ($c$ = 0.5, ethanol/DMSO, 1:1). − $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.77 (s, 4 H, NHPh), 8.45 (d, $J$ = 7.2 Hz, 4 H, N*H*CH), 7.89 (d, $J$ = 8.4 Hz, 8 H, benzoyl), 7.52 (t, $J$ = 7.2 Hz, 4 H, benzoyl), 7.44 (t, $J$ = 7.6 Hz, 8 H, benzoyl), 7.20 and 6.85 (d, $J$ = 2.1 Hz, 4 H each, aromatic), 4.60−4.45 (m, 4 H, C*H*CH$_3$), 4.36 (d, $J$ = 12.6 Hz, 4 H, $H_{ax}$ of ArC$H_2$Ar), 3.80 (t, $J$ = 7.4 Hz, 8 H, OC$H_2$CH$_2$CH$_3$), 3.09 (d, $J$ = 12.6 Hz, 4 H, $H_{eq.}$ of ArC$H_2$Ar), 2.00−1.82 (m, 8 H, OCH$_2$C$H_2$CH$_3$), 1.33 (d, $J$ = 7.1 Hz, CHC$H_3$), 0.95 (t, $J$ = 7.3 Hz, 12 H, OCH$_2$CH$_2$C$H_3$). − $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 170.6 and 165.9 (s, C=O), 151.9, 134.1, 133.9, and 133.0 (s, aromatic), 131.2, 128.1, 127.4, 120.0, and 119.5 (d, aromatic), 76.5 (t, O*C*H$_2$CH$_2$CH$_3$), 49.5 (d, *C*HCH$_3$), 31.2 (t, Ar*C*H$_2$Ar), 22.6 (t, OCH$_2$*C*H$_2$CH$_3$), 18.0 (q, CH*C*H$_3$), 10.1 (q, OCH$_2$CH$_2$*C*H$_3$). − MS, CI(+): $m/z$ = 1353.7 (10) [M$^+$], 1178.9 (100) [{M − BzNHCH(CH$_3$)CO}$^+$].

**5,11,17,23-Tetrakis(benzoyl-L-phenylalanylamino)-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (5b):** The pure compound was obtained by trituration with hexane. Yield: 0.66 g, 80%. White solid; m.p. 285−287 °C. − $[\alpha]_D^{25}$ = 116.4 ($c$ = 0.5, DMSO). − $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 10.09 (s, 4 H, NHPh), 8.60 (d, $J$ = 8.2 Hz, 4 H, NHC*H*), 7.84 (d, $J$ = 7.4 Hz, 8 H, aromatic H of phenylalanine), 7.53 (t, $J$ = 7.2 Hz, 4 H, aromatic H of phenylalanine), 7.50−7.31 (m, 20 H, aromatic), 7.31−7.12 (m, 12 H, aromatic), 6.83 (d, $J$ = 2.0 Hz, 4 H, aromatic), 4.87−4.73 (m, 4 H, C*H*CH$_2$), 4.43 (d, $J$ = 12.1 Hz, 4 H, $H_{ax}$ of ArC$H_2$Ar), 3.87 (t, $J$ = 7.3 Hz, 8 H, OC$H_2$CH$_2$CH$_3$), 3.18 (d, $J$ = 12.1 Hz, 4 H, $H_{eq.}$ of ArC$H_2$Ar), 3.18−2.94 (m, 8 H, CHC$H_2$), 2.08−1.90 (m, 8 H, OCH$_2$C$H_2$CH$_3$), 1.02 (t, $J$ = 7.3 Hz, 12 H, OCH$_2$CH$_2$C$H_3$). − $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 169.7 and 166.0 (s, CO), 151.9, 138.3, 134.2, 133.9, 132.9, and 131.2 (s, aromatic), 129.1, 128.1, 127.9, 126.2, 120.3, and 119.6 (d, aromatic), 76.6 (t, O*C*H$_2$CH$_2$CH$_3$), 55.5 (d, *C*HCH$_2$), 37.2 (t, CH*C*H$_2$), 30.9 (t, Ar*C*H$_2$Ar), 22.6 (OCH$_2$*C*H$_2$CH$_3$), 10.1 (OCH$_2$CH$_2$*C*H$_3$). − MS,

CI(+): *m/z* = 1656.9 (10) [$M^+$], 1405.5 (100) [$M^+$ – BzNHCH($CH_2$Ph)CO].

## Acknowledgments

We thank the M.U.R.S.T. ("Supramolecular Devices" Project) and the C.N.R. (M.U.R.S.T. Chimica Legge 95/95 "Agenti di contrasto, di shift e sonde luminescenti") for financial support. The *Centro Interdipartimentale di Misure dell'Università di Parma* is also gratefully acknowledged for the use of NMR and mass spectrometers. Marcio Lazzarotto wishes to acknowledge the CAPES, Brasilia (Brazil), for a fellowship.

[1] A. P. Davis, R. S. Wareham, *Angew. Chem. Int. Ed.* **1999**, *38*, 2978–2996.
[2] [2a] W. C. Still, *Acc. Chem. Res.* **1996**, *29*, 155–163. – [2b] H.-J. Schneider, F. Eblinger, M. Sirish, *Adv. Supramol. Chem.* **2000**, *6*, 185–216 and references therein.
[3] J. M. Coterón, C. Vicent, C. Bosso, S. Penadés, *J. Am. Chem. Soc.* **1993**, *115*, 10066–10076.
[4] [4a] A. Marra, M.-C. Scherrmann, A. Dondoni, A. Casnati, P. Minari, R. Ungaro, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2479–2481. – [4b] A. Dondoni, A. Marra., M.-C. Scherrmann, A. Casnati, F. Sansone, R. Ungaro, *Chem. Eur. J.* **1997**, *3*, 1774–1782.
[5] [5a] F. Sansone, S. Barboso, A. Casnati, M. Fabbi, A. Pochini, F. Ugozzoli, R. Ungaro, *Eur. J. Org. Chem.* **1998**, 897–905. – [5b] F. Sansone, S. Barboso, A. Casnati, D. Sciotto, R. Ungaro, *Tetrahedron Lett.* **1999**, *40*, 4741–4744.
[6] [6a] J. Scheerder, M. Fochi, J. F. J. Engbersen, D. N. Reinhoudt, *J. Org. Chem.* **1994**, *59*, 7815–7820. – [6b] J. Scheerder, J. F. J. Engbersen, A. Casnati, R. Ungaro, D. N. Reinhoudt, *J. Org. Chem.* **1995**, *60*, 6448–6450. – [6c] A. Casnati, M. Fochi, P. Minari, A. Pochini, M. Reggiani, R. Ungaro, *Gazz. Chim. Ital.* **1996**, *126*, 99–106. – [6d]A. Casnati, L. Pirondini, N. Pelizzi, R. Ungaro, *Supramol. Chem.*, in press.
[7] A. Casnati, M. Fabbi, N. Pelizzi, A. Pochini, F. Sansone, R. Ungaro, E. Di Modugno, G. Tarzia, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2699–2704.
[8] L. Frish, F. Sansone, A. Casnati, R. Ungaro, Y. Cohen, *J. Org. Chem.* **2000**, *65*, 5026–5030.
[9] T. Nagasaki, T. Tajiri, S. Shinkai, *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 407–411.
[10] [10a] B. C. Gibb, A. R. Mezo, A. S. Causton, J. R. Fraser, F. C. S. Tsai, J. C. Sherman, *Tetrahedron* **1995**, *51*, 8719–8732. – [10b] Y. Hamuro, M. C. Calama, H. S. Park, A. D. Hamilton, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2680–2683. – [10c] H. S. Park, Q. Lin, A. D. Hamilton, *J. Am. Chem. Soc.* **1999**, *121*, 8–13.
[11] [11a] S. J. Meunier, R. Roy, *Tetrahedron Lett.* **1996**, *37*, 5469–5472. – [11b] R. Roy, J. M. Kim, *Angew. Chem. Int. Ed.* **1999**, *38*, 369–372. – [11c] T. Fujimoto, C. Shimizu, O. Hayashida, Y. Aoyama, *J. Am. Chem. Soc.* **1997**, *119*, 6676–6677. – [11d] Y. Aoyama, Y. Matsuda, J. Chuleeraruk, K. Nishiyama, K. Fujimoto, T. Fujimoto, T. Shimizu, O. Hayashida, *Pure Appl. Chem.* **1998**, *70*, 2379–2384.
[12] A. M. A. van Wagenigen, E. Snip, W. Verboom, D. N. Reinhoudt, H. Boerrigter, *Liebigs Ann./Recueil* **1997**, 2235–2245.
[13] A. Arduini, M. Fabbi, M. Mantovani, L. Mirone, A. Pochini, A. Secchi, R. Ungaro, *J. Org. Chem.* **1995**, *60*, 1454–1457.
[14] P. Timmerman, H. Boerrigter, W. Verboom, D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 103–111.
[15] [15a] C. D. Gutsche, *Calixarenes Revisited*, in *Monographs in Supramolecular Chemistry* (Ed.: J. F. Stoddart), The Royal Society of Chemistry, Cambridge, U.K., **1998**. – [15b] J.-D. van Loon, A. Arduini, L. Coppi, W. Verboom, A. Pochini, R. Ungaro, S. Harkema, D. N. Reinhoudt, *J. Org. Chem.* **1990**, *55*, 5639–5646. – [15c] E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, A. Abu El-Fadl, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1990**, *112*, 6979–6985.
[16] E. E. Schrier, *J. Chem. Ed.* **1968**, *45*, 176–180.
[17] S. R. Wilson, W. Cui, J. W. Moskowitz, K. E. Schmidt, *J. Comp. Chem.* **1991**, *12*, 342–349.
[18] C. S. Wilcox, in *Frontiers in Supramolecular Chemistry and Photochemistry* (Eds.: H.-J. Schneider, H. Durr), VCH, Weinheim, **1991**, 123–145.
[19] D. J. Leggett, *J. Chem. Ed.* **1983**, *60*, 707–710.
[20] [20a] T. H. Webb, C. S. Wilcox, *Chem. Soc. Rev.* **1993**, 383–395. – [20b] E. Fan, A. van Arman, S. Kincaid, A. D. Hamilton, *J. Am. Chem. Soc.* **1993**, *115*, 369–370.
[21] A. Casnati, Y. Ting, D. Berti, M. Fabbi, A. Pochini, R. Ungaro, D. Sciotto, G. G. Lombardo, *Tetrahedron* **1993**, *49*, 9815–9822.
[22] W. Verboom, A. Durie, R. J. M. Egberink, Z. Asfari, D. N. Reinhoudt, *J. Org. Chem.* **1992**, *57*, 1313–1316.
[23] E. Kelderman, L. Dehaeg, G. J. T. Heesink, W. Verboom, J. F. J. Engbersen, N. F. van Hulst, A. Persoons, D. N. Reinhoudt, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1075–1077.
[24] V. Böhmer, K. Jung, M. Schön, A. Wolff, *J. Org. Chem.* **1992**, *57*, 790–792. – C. D. Gutsche, K. A. See, *J. Org. Chem.* **1992**, *57*, 4527–4539.
[25] M. Clark, R. D. Cramer III, N. Van Opdenbosch, *J. Comp. Chem.* **1989**, *10*, 982–1012.
[26] M. J. D. Powell, *Math. Programming* **1977**, *12*, 241–254.

Received July 24, 2000
[O00376]