Peptide-Cavitands Based on Resorc[4]arenes − Synthesis and Structure

Carsten Berghaus[a] and Martin Feigel*[a]

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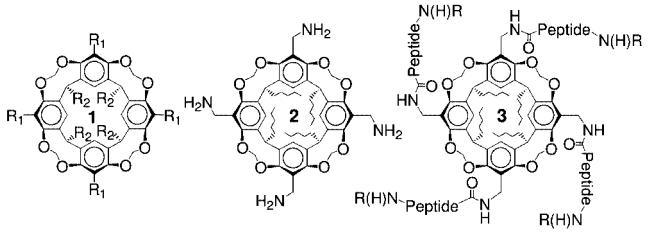
Amino acids and peptides were coupled to the four aminomethyl groups of the bridged resorc[4]arene **2**, resulting in peptide cavitands **3** of the general structure **2** [–Aa1-[Aa2-[Aa3]]–N(H)R]$_4$. These compounds contain either four amino acids (**3a**–**3d**: Aa1 = Gly, Val, Leu or Phe, R = H; **3e**, **3f**: Aa1 = Gly or Val, R = Z), four dipeptides (**3g**–**3l**: Aa1 = Gly, Aa2 = Gly, Val, Leu, Phe, Lys(Boc) or Pro, R = Z), four tripeptides (**3m**, **3n**: Aa1 = Gly, Aa2 = Val, Aa3 = Val or Met, R = Z) or four β-Ala dipeptides (**3o**, **3p**: Aa1 = β-Ala, Aa2 = Val or Leu, R = Z). The dipeptide and tripeptide cavitands **3g**–**3n**, which have a glycine bonded to the resorcarene core, form stable inclusion complexes with acetonitrile in chloroform solution. The free energy of complexation exceeds –5.9 kcal mol^{-1}. The exchange between complexed and free acetonitrile molecules is slow on the NMR spectroscopic time scale (298 K). NMR spectroscopic data suggest that the peptides in the acetonitrile complexes of **3g**–**3n** form a cyclic array of hydrogen bonds at the upper rim involving the glycine CO and NH groups.

Methylenedioxy-bridged resorc[4]arenes **1** are unique rigid bowl-shaped molecules designed to encapsulate small organic guests.[1−3] The backbone of these cavitands has been equipped with various substituents at the upper and the lower rim (R^1, R^2).[4−6] For example, aminomethyl-substituted derivatives **2** served as frames to construct anion and cation receptors.[7,8] While peptides have been attached to the upper rim of open, more-flexible calixarenes,[9−13] only a few reports exist where rigid cavitands have been modified with peptides. Sherman et al. connected peptides of helical conformation to the cavitand **1** using a thioether bridge at R^1.[14,15] Here, we report the synthesis and first structural characterization of peptide cavitands of the general structure **3** (Scheme 1) in which the *C*-termini of four short peptide chains are connected via amide bonds to the cavitand **2**.



Scheme 1

Our study was motivated by the unknown structure and functions of peptide cavitands. The four peptide chains fixed at the cavitand rim of **3** may adopt conformations and geometries not common in free peptides. The resulting structure may recognize protein surfaces, which is a feature that has been demonstrated for cyclopeptide-calixarenes.[9,10] Small peptides of complementary polarity and shape might be complexed by the peptide cavitands. Organic guests might be encapsulated in the chiral environment of the peptide cavitands and even artificial enzymes can be envisioned anchoring "catalytically active" peptide sequences at the rim of the cavitand. As a first object of such studies, the present work defines some conformational and structural rules for the peptide cavitands **3**.

Syntheses

The compounds **3a**−**3d** (Table 1) with one amino acid unit on each resorcinol ring were prepared by coupling the corresponding *N*-Boc-protected amino acids to the tetraamine **2**.[16] The activation by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) and *N*-hydroxybenzotriazole (HOBt) in dichloromethane gives reasonable yields (60−85%). The protecting Boc groups were removed using trifluoroacetic acid and the free amino derivatives **3a**−**3d** were precipitated from aqueous sodium hydroxide and recrystallized from acetonitrile. The Z-protected derivatives **3e** and **3f** were obtained by the same coupling procedure using Z-ValOH or Z-GlyOH as the peptidic component.

[a] Fakultät für Chemie, Ruhr-Universität Bochum, Universitätsstr. 150, 44780 Bochum, Germany
Fax: (internat.) + 49-(0)234/321-4497
E-mail: feigel@indi-f.nsc.ruhr-uni-bochum.de

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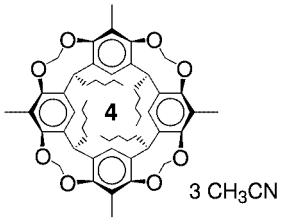
Table 1. Amino acid composition of the peptide cavitands **3a**−**3q**; the amino acids are noted in the sequence **2**[−Aa1−[Aa2−[Aa3]]−N(H)R]$_4$, where the *C*-terminus (Aa1) is connected to the aminomethyl groups of the cavitand **2**

	Aa1	Aa2	Aa3	R
3a	Gly	–	–	H
3b	Val	–	–	H
3c	Leu	–	–	H
3d	Phe	–	–	H
3e	Gly	–	–	Z
3f	Val	–	–	Z
3g	Gly	Gly	–	Z
3h	Gly	Val	–	Z
3i	Gly	Leu	–	Z
3j	Gly	Phe	–	Z
3k	Gly	Lys(Boc)	–	Z
3l	Gly	Pro	–	Z
3m	Gly	Val	Val	Z
3n	Gly	Val	Met	Z
3o	β-Ala	Val	–	Z
3p	β-Ala	Leu	–	Z

Di- and tripeptides were also be coupled to the tetraamine by using the EDC/HOBt protocol, but mixtures of diastereoisomers were obtained when the *C*-terminal amino acid (Aa1) is sensitive to base-catalysed epimerisation at the α-carbon atom. As expected, the compounds **3g**−**3p** (Table 1), derived from Z- (and Boc-)protected peptides with glycine or β-alanine at the C-terminus, were obtained as single isomers.

Crystal Structure of the Acetonitrile Complex 4

Compound **4** (Scheme 2) is an intermediate in the synthesis of the amino-substituted resorcarene **2**. Crystals of **4,** grown from acetonitrile, contain three acetonitrile molecules entrapped in the lattice, as shown by X-ray diffraction. Two of the acetonitrile molecules are located in close contact to the aliphatic pentyl chains and the third resides in the resorcarene bowl (Figure 1).



Scheme 2

It is interesting to note that the dipole moment of the acetonitrile molecule encapsulated in the resorcarene bowl points away from the center of the electron-rich aromatic units. The two other acetonitrile units compensate their dipole moments in an antiparallel arrangement to accommodate their lipophilic environment.

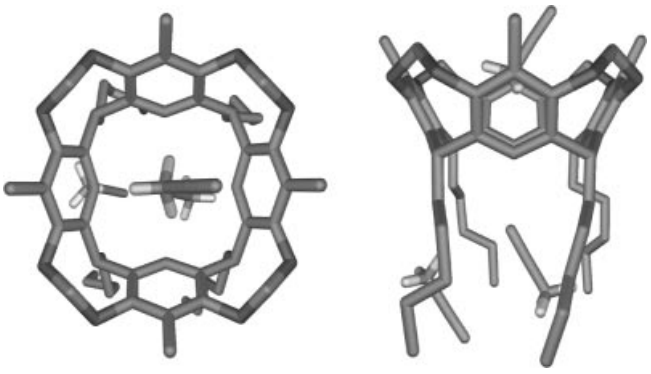


Figure 1. Top view and side view of the structure of **4**·3(CH_3CN) in the solid state; one acetonitrile molecule resides in the cavity of **4** and the other two are located at the pentyl chains

Several examples of solid-state structures of resorcarenes have been reported in which small organic guest molecules are included in the crystal.[2,17] The solvent molecules reside either in the bowl-shaped cavity formed by the four substituted benzene rings or are found in the lattice between the guest molecules. The solid-state structure of **4** exhibits both features in one structure.

Complexation of Acetonitrile by Peptide Cavitands 3 in Solution

The peptide cavitands listed in Table 1 were obtained as crystalline solids if the compounds were treated with acetonitrile during the synthetic workup. The ^{1}H NMR spectra of chloroform solutions of the compounds **3a**−**3f** and **3o**−**3p** display either no acetonitrile signal or a signal near δ = 2 ppm, the usual position of the methyl protons of acetonitrile. The spectra of the compounds **3g**−**3n**, however, having di- or tripeptides attached to the resorcarene bowl via glycine residues, each contains a sharp singlet for the methyl protons of acetonitrile at very high field (δ = −2.3 to −2.6 ppm, one equivalent). A typical spectrum is shown in Figure 2 (**3h**). Acetonitrile is added here in excess and an additional signal at 2 ppm is observed, which indicates that the exchange between free and bound acetonitrile is slow on the NMR spectroscopic time scale.

The location of the acetonitrile in the complex is reflected in the 2D-ROESY NMR spectra. As an example, an expanded region of the ROESY spectrum of **3i** is reproduced in Figure 3. Similar spectra were observed with the compounds **3h**−**3n**. The signal of the methyl protons of the complexed acetonitrile at δ = −2.4 ppm has cross-peaks with the four inner protons of the methylenedioxy bridges and the four para-protons of the resorcarene units. It is straightforward to conclude that the acetonitrile molecule resides within the resorcarene cavity in an orientation similar to that found in the solid-state structure of **4**. A schematic drawing of the complex is given in Figure 4 (left).

The rate of exchange of acetonitrile can be estimated roughly from the intensitiy of the exchange cross-peak in

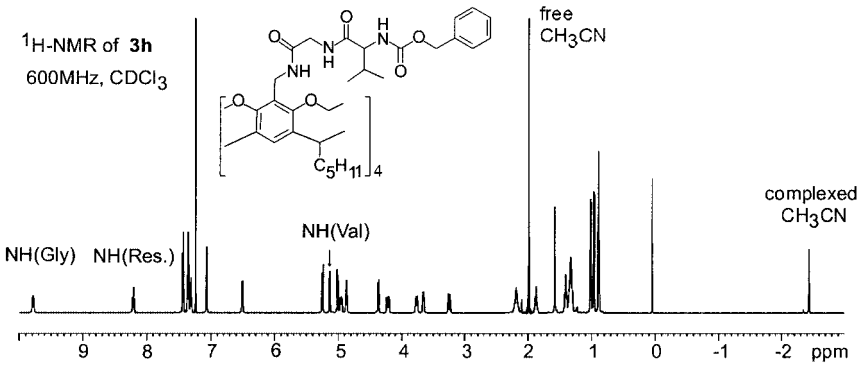


Figure 2. ^{1}H NMR spectrum of **3h** in $CDCl_3$ at 600 MHz with added acetonitrile

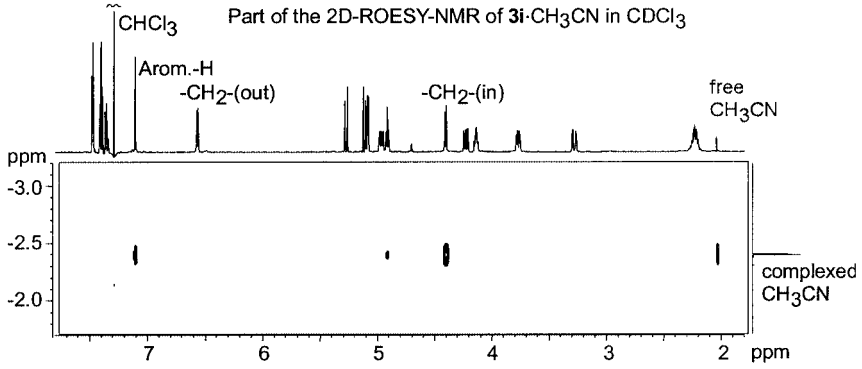


Figure 3. Part of the 2D-ROESY ^{1}H NMR spectrum of the **3i**·acetonitrile complex in $CDCl_3$; the cross-peak section of the methyl protons of complexed acetonitrile at $\delta = -2.4$ ppm is shown; the phase of the exchange cross-peak between the protons of free and complexed acetonitrile is opposite to the phase of the remaining signals

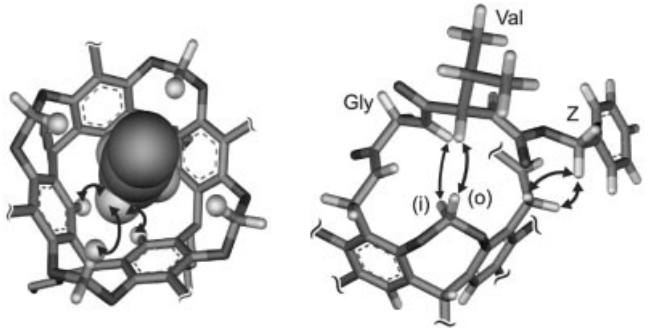


Figure 4. Significant NOE connectivities (black arrows) observed in the peptide-cavitand·acetonitrile complexes; the left drawing illustrates the position of the acetonitrile unit within the cavities of **3g**−**3n**; the right structural fragment is part of the NMR spectrum-derived conformation of the **3h**·acetonitrile complex (see Figure 5); long-range NOE contacts are indicated

2D-ROESY-spectra (Figure 3). The lower limit of the mean lifetime of acetonitrile within the complex is ca. 0.5 s, which gives a free energy of activation of $\Delta G^{\#}_{298} = 17$ kcal·mol^{-1}. Such high barriers of exchange of neutral guests have been observed in hydrogen-bonded dimeric resorcarene containers,[18] but they are rarely seen in open resorcarene monomers. An interesting example has been reported by Rebek et al. for a cavitand that is able to form a circular array of hydrogen bonds at the upper rim.[19]

The free energy of complexation of acetonitrile by **3h** or **3i** in chloroform could not be determined precisely by integrations of NMR spectra. Dilute chloroform solutions of the peptide cavitands (10^{-2} to 10^{-3} M) containing one equivalent of acetonitrile each gave only a very tiny signal of free acetonitrile at the detection limits of integration of the NMR spectra. The association constant of the **3h**/acetonitrile complex was estimated from such a integration to be larger than 2×10^4 L·mol^{-1} at 298 K, which corresponds to a free energy of complexation of at least −5.9 kcal·mol^{-1}. This value is remarkably high for the complexation of acetonitrile in an organic solvent by an open cavitand.[20] A more-detailed kinetic and thermodynamic study is in progress, including the competing complexation of other small guests (e.g., dichloromethane) and the temperature-dependent NMR spectra of achiral dipeptide derivatives having sufficient solubility.[21]

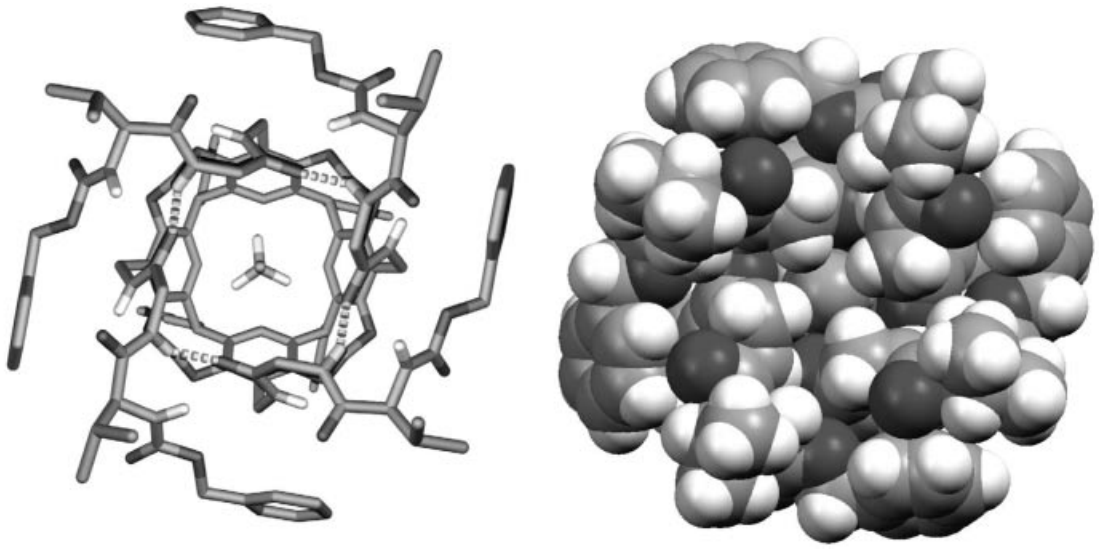


Figure 5. NMR spectrum-derived conformation of the **3h**·acetonitrile complex; the stick representation without CH hydrogen atoms (left) illustrates the circular array of hydrogen bonding; the CPK model (right) shows that the acetonitrile guest is deeply buried in the cavity; the CH_2 groups of four glycine units hinder the release of the guest

NMR Spectroscopy-Derived Conformations of the Peptide Chains in the Acetonitrile Complexes of 3h−3n

Short linear peptides usually exist in many low-energy conformations, so how does the fixing at the upper rim of the cavitand restrict their conformational space? The ^{1}H NMR spectra of the free peptide cavitands **3h**−**3n** obtained in the synthetic workup without the acetonitrile treatment (see above) exhibit broad lines and are not suitable for a conformational analysis. The NMR spectra of the acetonitrile complexes of **3h**−**3n**, however, consist of sharp lines and show substantial chemical shift dispersion so we expect relatively uniform conformations (see Figure 2). The chemical shifts of the glycine NH units of **3h**−**3n** are found between δ = 9.5 and 10 ppm in these cases. Obviously, those particular protons are involved in hydrogen bonding. Attempts to model a structure in which all glycine NH protons are hydrogen bonded result in a conformation of near-C_4 symmetry. The structure is given in Figure 5, using **3h** as an example. A circular array of hydrogen bonds is formed involving glycine amide protons and the glycine carbonyl oxygen atoms in neighboring peptide chains. Subsequently, the peptides fold into a wheel-like arrangement. Additionally, the structure shown in Figure 5 explains the several long-range NOE contacts found in the spectra of the acetonitrile complexes of **3h**−**3n**; e.g., the contacts between Val-αCH (Aa2) and the outer proton of the OCH_2O bridge, between Gly−NH (Aa1) and the inner proton of the OCH_2O bridge, and between the CH_2 protons of the Z group and the amidomethyl group of the resorcarene unit. Black arrows in Figure 4 (right drawing) illustrate these NOE contacts.

Extensive Monte Carlo calculations searching for low-energy conformations of the **3h**·acetonitrile complex using the MM3 or Amber force field within Macromodel[22] reproduce the hydrogen bonding of the Gly−NH unit, but not all the calculated structures of low energy maintain the C_4 symmetry. The NMR spectroscopy-derived structure in Figure 5 probably reflects an averaging over several less-symmetrical conformations of low energy.

NMR Spectroscopic Data of 3a−3g, 3o and 3p

The ^{1}H NMR spectra of the achiral glycine peptides **3a**, **3e** and **3g** contain very broad NMR spectroscopic signals of the enantiotopic methylene protons (298 K). The short structures **3a** and **3e** do not bind acetonitrile, but **3g**, substituted with Z-protected diglycines, forms a stable complex with acetonitrile in chloroform ($\delta_{MeCN} = -2.4$ ppm). The NMR spectroscopic signals of **3g** broaden further on cooling, but precipitation prevents further conformational analysis.

The compounds **3b**, **3c** and **3d** (which contain one chiral amino acid with a free N-terminus) do not complex with acetonitrile in chloroform solution. Their NMR spectra are not broadened by exchange (except for the amine moiety). NOE data and modeling studies suggest that these compounds also presumably form circular arrays of hydrogen bonds (using the free NH_2 and carbonyl groups of the chiral amino acid). Such an arrangement of free NH_2 groups, however, is obviously not sufficient to form stable acetonitrile complexes in chloroform.

The Z-protected valine derivative **3f** and the β-Ala-containing dipeptides **3o** and **3p** do not complex acetonitrile and exist probably as a mixture of different conformations, which is indicated by the broad signals in the NMR spectra.

CD Measurements

Figure 6 displays near-UV CD spectra of **3c**, **3f**, **3i** and **3n** measured in dilute acetonitrile solutions (0.5×10^{-4} M).

The orientation of the aromatic chromophores (the resorcarene core and the Z groups) should determine the shape of the CD curves in this region.

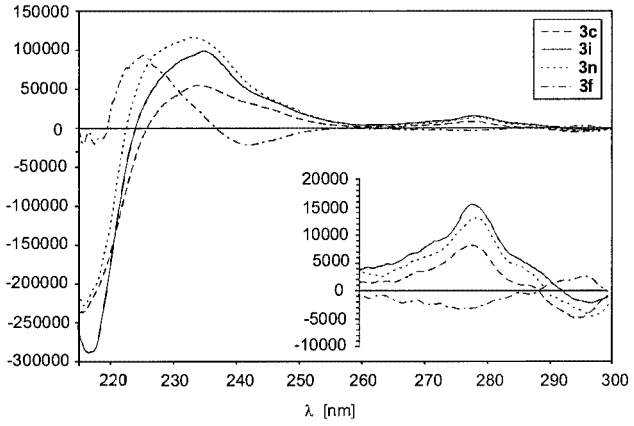


Figure 6. Near-UV CD spectra of **3c**, **3i**, **3n** and **3f** measured in acetonitrile (0.5×10^{-4} M); the inset is a vertical expansion of the region 260−300 nm

Compounds **3c** [**2**(−Leu)$_4$], **3i** [**2**(−Gly−Leu-Z)$_4$] and **3n** [**2**(−Gly−Val−Met-Z)$_4$] display positive bands at 235 and 275 nm. Of these compounds, **3i** and **3n** belong to the group of structures that contain a C-terminal glycine unit and form stable acetonitrile complexes associated with a circular array of hydrogen bonds (see above). Compound **3c** (without a Z group) is probably also in a conformation that allows circular hydrogen bonds (see the NMR spectroscopy discussion above). It is straightforward to conclude that the near-UV CD pattern observed for **3c**, **3i** and **3n** results from a similar chiral environment of the resorcarene unit. The compound **3f** [**2**(−Val-Z)$_4$] gives a different CD pattern of reduced intensity in agreement with the observation that the NMR spectroscopic data do not indicate any preferred conformation (see above). In summary, the CD spectra reflect the conformations derived from the NMR spectroscopic data.

Conclusion

The dipeptide- and tripeptide-modified cavitands **3g**−**3n** form remarkably stable inclusion complexes with acetonitrile in chloroform solution. The dynamics of the exchange between the complexed and free acetonitrile is slow on the NMR spectroscopy timescale, which is a feature that is very unusual for open cavitands (not carcerands). The NMR spectroscopic data (supported by CD measurements) suggest that the acetonitrile complexes of the compounds contain a circular array of hydrogen bonds involving the CO and NH groups of the glycine units connected to the upper rim of the cavitand. We assume that the rigid hydrogen-bonded structure must open partially to release the encapsulated acetonitrile molecule. The complex is formed if a C-terminal glycine unit (Aa1) is connected via an amide bond to the second amino acid unit (Aa2). Obviously, the chirality (L) of Aa2 determines the orientation of the circle of hydrogen bonds.[23] Additionally, the structure in Figure 5 suggests that side chains of the L-amino acids at the Aa1 position (other than glycine) will prevent the indicated hydrogen bonding.

The enclosed small guest (acetonitrile) occupies the cavitand cavity, stabilizes the hydrogen-bonded peptide arrangement, and induces — together with the geometric requirements of the cavitand rim — the defined conformation of the four attached peptides. It is this orientation that makes the system interesting for recognition studies.

Molecular guests substantially larger than acetonitrile will not fit in the cavity. A systematic study of the complexation properties of **3** is not the purpose of this paper, but preliminary studies show that a dichloromethane molecule is encapsulated and a larger chloroform molecule is not.[21]

Several differences are noted when we compare the systems **3g**−**3n** with published peptide calixarenes.[11,13,24] The association constant for the complexation of acetonitrile found in our study is at least one order of magnitude higher than the association constants reported for various guests of peptide calixarenes. Even peptide calixarenes having charges opposite to the charge of their guests are complexed more weakly. The exchange between the free and complexed guests is fast on the NMR spectroscopic time scale in the complexes of peptide calixarenes; the exchange is slow in the system reported here. A circular arrangement of hydrogen bonds has not been reported for peptide calixarenes up to now − more differences between peptide calixarenes and peptide resorcarenes might be listed. The peptides in the published calixarene systems, however, are bonded to amino or carboxyl substituents directly attached at the aromatic rings of the calixarenes; our system uses aminomethyl substituents at this position. The differences in conformation and complexation described above may well be based on this differing local geometry and not on the difference in structure between the calixarene and the cavitand core.

Further work is in progress to synthesize derivatives of **3** with extended peptides containing additional binding sites to modulate the binding of larger guests. The combinatorial approach to such binders will also include non-natural amino acids and combinations of D- and L-amino acids.

Experimental Section

General Remarks: The following spectrometer were used: ^{1}H NMR spectra — Bruker DRX 400 and 600 MHz; FAB mass spectra — VG AutoSpec; ESI-mass spectra — Bruker Esquire 3000plus; CD spectra — Jasco 700. Commercially available protected amino acids were obtained from Nova Biochem and Fluka. Boc- or Z-protected di- and tripeptides were prepared as methyl esters by using standard peptide coupling procedures and then were converted into their corresponding carboxylic acids by basic hydrolysis with lithium hydroxide.

General Procedure A. Coupling of Boc- or Z-Protected Amino Acids and Peptides to 2: The corresponding Boc- or Z-protected amino

acid or peptide (2.5 mmol), EDC·HCl (0.497 g, 2.5 mmol) and HOBt (0.338 g, 2.5 mmol) were stirred in a solution of dichloromethane (50 mL) at 0 °C for 1 h. A suspension of **2** (0.466 g, 0.5 mmol) and triethylamine (0.28 mL, 2 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 0 °C for a further 24 h (the solutions were kept at 25 °C in case of Z-protected peptides with glycine at the terminus). The solvent was evaporated in vacuo and the residue taken up in ethyl acetate (75 mL). The ethyl acetate solution was washed with 10% $NaHSO_4$ (25 mL), 5% $NaHSO_4$ (2 × 25 mL), saturated sodium bicarbonate (3 × 25 mL) and brine (25 mL), and then dried with anhydrous Na_2SO_4. The filtered organic phase was used in the following workup procedures [B or C].

General Procedure B. Preparation of 3a−3d: The solvent of the solution prepared in procedure A was evaporated in vacuo and then the residue was taken up in dichloromethane (40 mL) and treated with trifluoroacetic acid (20 mL). The solvent was evaporated in vacuo. The addition and removal of dichloromethane was repeated several times. The remaining yellow solid was transferred to the top of a short column of silica gel (Si60, 1.5 × 10 cm), which was washed with dichloromethane and ethyl acetate. The product was than eluted with methanol. The methanolic solution was slowly added to 1 N NaOH and then the precipitate that formed was filtered off and recrystallized from acetonitrile.

General Procedure C. Preparation of 3e−3n and 3o−3p: The solvent of the solution prepared in procedure A was evaporated in vacuo, the residue suspended in *n*-hexane, and the mixture heated under reflux for 1 h. The suspension was filtered and the precipitate dried in vacuo. The material was either recrystallized from acetonitrile or washed further with acetonitrile or *n*-hexane (see below).

5,11,17,23-Tetrakis[glycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3a): Boc−Gly−OH (0.438 g, 2.5 mmol) was used in procedure A followed by B (recrystallization from acetonitrile). Yield: 0.539 g (83%). White solid; m.p. > 250 °C (dec.). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.91 (br. s, 4 H, Ar−CH_2N*H*), 7.55 (s, 4 H, Ar−H), 5.89 (br. d, 4 H, O−CH_2−O), 4.61 (t, 4 H, Ar_2CH−pentyl), 4.35 (br. d, 4 H, O−CH_2−O), 4.14 (s, 8 H, Ar−C*H*$_2$NH), 3.02 (br. s, 8 H, Gly−CH_2), ca. 3.0 (very br. s, Gly−NH_2 and H_2O), 2.33, 1.38, 1.29, 0.87 (4m, 44 H, C_5H_{11}) ppm. MS (FAB): *m*/*z* (%) = 1183.6 (46) [**3a** + Na]$^+$, 1160.6 (27) [**3a**]$^+$. $C_{64}H_{88}N_8O_{12}$·2H_2O (1197.5): calcd. C 64.19, H 7.74, N 9.36; found C 63.86, H 7.73, N 8.91.

4(24),6(10),12(16),18(22)-Tetramethylenedioxy-2,8,14,20-tetrapentyl-5,11,17,23−tetrakis[L-valinylamidomethyl]resorc[4]arene (3b): Boc-L-Val−OH (0.543 g, 2.5 mmol) was used in procedure A followed by B (recrystallization from acetonitrile). Yield: 0.544 g (75%). White solid; m.p. 205−208 °C (dec.). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.85 (t, 4 H, Ar−CH_2N*H*), 7.04 (s, 4 H, Ar−H), 6.04 (d, 4 H, O−CH_2−O), 4.74 (t, 4 H, Ar_2CH−pentyl), 4.67 (dd, 4 H, Ar−C*H*$_2$NH), 4.43 (d, 4 H, O−CH_2−O), 3.94 (dd, 4 H, Ar−C*H*$_2$NH), 3.05 (br. m, 4 H, Val-αH), 2.21 (m, 4 H, Val-βH), 2.17, 1.38, 1.32, 0.90 (4m, 44 H, C_5H_{11}), 1.47 (br. s, 8 H, Val−NH_2), 0.93, 0.78 (2d, 24 H, Val−CH_3) ppm. MS (FAB): *m*/*z* (%) = 1351.7 (8) [M + Na]$^+$, 1329.7 (11) [M + H]$^+$. $C_{76}H_{112}N_8O_{12}$·H_2O (1347.7): calcd. C 67.73, H 8.53, N 8.31; found C 67.06, H 8.61, N 8.31.

5,11,17,23−Tetra[L-leucinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylene-2,8,14,20-tetrapentyldioxyresorc[4]arene (3c): Boc-L-Leu−OH (0.578 g, 2.5 mmol) was used in procedure A followed by B (recrystallization from acetonitrile). Yield: 0.573 g (75%). White solid; m.p. 222−225 °C (dec.). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.17 (dd, 4 H, Ar−CH_2N*H*), 7.02 (s, 4 H, Ar−H), 6.10 (d, 4 H, O−CH_2−O), 4.85 (dd, 4 H, Ar−C*H*$_2$NH), 4.75 (t, 4 H, Ar_2CH−pentyl), 4.49 (d, 4 H, O−CH_2−O), 3.82 (dd, 4 H, Ar−C*H*$_2$NH), 3.12 (br. m, 4 H, Leu-αH), 1.67 (m, 4 H, Leu-βH), 1.57, 1.26 (2m, 2 × 4 H, Leu−CH_2), 2.16, 1.39, 1.32, 0.89 (4m, 44 H, C_5H_{11}), 1.75 (br. s, 8 H Leu−NH_2), 0.91 (d, 12 H, Leu−CH_3), 0.84 (t, 12 H, Leu−CH_3) ppm. MS (FAB): *m*/*z* (%) = 1407.5 (13) [M + Na]$^+$, 1386.5 (25) [M + H]$^+$. $C_{80}H_{120}N_8O_{12}$·2H_2O (1421.9): calcd. C 67.58, H 8.79, N 7.88; found C 67.83, H 9.13, N 8.26.

4(24),6(10),12(16),18(22)-Tetramethylenedioxy-2,8,14,20-tetrapentyl-5,11,17,23-tetra[L-phenylalanylamidomethyl]resorc[4]arene (3d): Boc-L-Phe−OH (0.578 g, 2.5 mmol) was used in procedure A followed by B (recrystallization from acetonitrile). Yield: 0.549 g (60%). White solid; m.p. 185−188 °C (dec.). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.78 (t, 4 H, Ar−CH_2N*H*), 7.22−7.09 (m, 20 H, Phe−Ar−H), 7.04 (s, 4 H, Ar−H), 6.01 (d, 4 H, OCH_2O), 4.74 (t, 4 H, Ar_2CH−pentyl), 4.62 (dd, 4 H, Ar−C*H*$_2$NH), 4.42 (d, 4 H, OCH_2O), 3.97 (dd, 4 H, Ar−C*H*$_2$NH), 2.55 (m, 4 H, Phe-αH), 3.42, 3.12 (2dd, 2 × 4 H, Phe−CH_2), 2.17, 1.39, 1.33, 0.90 (4m, 44 H, C_5H_{11}), 1.24 (br. s, 8 H Phe−NH_2) ppm. MS (FAB): *m*/*z* (%) = 1544.4 (3) [M + Na]$^+$, 1522.0 (2) [M + H]$^+$. $C_{92}H_{112}N_8O_{12}$·3H_2O (1576.9): calcd. C 70.1, H 7.60, N 7.11; found C 69.68, H 7.11, N 7.05.

5,11,17,23-Tetrakis[benzyloxycarbonylglycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3e): Z-Gly−OH (0.523 g, 2.5 mmol) was used in procedure A followed by C (recrystallization from dichloromethane/acetonitrile). Yield: 0.789 g (93%). White solid; m.p. 212−216 °C. ^{1}H NMR (600 MHz, $CDCl_3$, approx. 10 equiv. CH_3CN added): δ = 7.63 (br. s, 4 H, Ar−CH_2N*H*), 7.34−7.21 (m, 20 H, Z-Ar−H), 6.95 (s, 4 H, Ar−H), 6.60 (t, 4 H, Gly−NH), 5.98 (d, 4 H, OCH_2O), 5.07 (s, 8 H, Z-CH_2−O), 4.68 (t, 4 H, Ar_2CH−pentyl), 4.29 (d, 4 H, OCH_2O), 4.23 (br. s, 8 H, Ar−C*H*$_2$NH), 3.48 (br. d, 8 H, Gly−C*H*$_2$), 2.10, 1.32, 1.21, 0.83 (3m, 44 H, −C_5H_{11}), 1.94 (s, CH_3CN), 1.46 (s, H_2O) ppm. MS (FAB): *m*/*z* (%) = 1719.2 (8) [M + Na]$^+$. $C_{96}H_{112}N_8O_{20}$·2H_2O (1734.0): calcd. C 66.5, H 6.74, N 6.46; found C 66.13, H 6.69, N 6.91.

5,11,17,23-Tetrakis[benzyloxycarbonyl-L-valinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]xarene (3f): Z-L-Val−OH (0.628 g, 2.5 mmol) was used in procedure A followed by C (recrystallization from dichloromethane/acetonitrile). Yield: 0.866 g (90%). White solid; m.p. 118 −121 °C. ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 7.40−7.31 (m, 20 H, Z-Ar−H), 7.17 (s, 4 H, Ar−H), 6.48 (br. s, 4 H, Ar−CH_2N*H*), 5.88 (br. d, 4 H, OCH_2O), 5.75 (br. m, 4 H, Val−NH), 5.14 (d, 4 H, Z-CH_2O), 4.96 (d, 4 H, Z-CH_2O), 4.78 (t, 4 H, Ar_2CH−pentyl), 4.61 (br. m, 4 H, Ar−C*H*$_2$NH), 4.42 (br. d, 4 H, OCH_2O), 4.12 (br. m, 4 H, Ar−C*H*$_2$NH), 4.06 (br. m, 4 H, Val-αH), 2.26 (m, 8 H, Ar_2CH−C*H*$_2$−butyl), 2.05 (br. m, 4 H, Val-βH), 2.00 (s, 3 H, CH_3CN), 1.61 (very br. s, ca. 8 H, H_2O), 1.46, 1.39 [m, 24 H, Ar_2C−CH_2−(C*H*$_2$)$_3$−CH_3], 0.96 [t, 12 H, Ar_2CH−$(CH_2)_4$−C*H*$_3$], 0.91 (d, 24 H, Val-CH_3) ppm. MS (FAB): *m*/*z* (%) = 1884.6 (2) [M + Na]$^+$. $C_{108}H_{136}N_8O_{20}$·CH_3CN·5H_2O (1997.4): calcd. C 66.15, H 7.52, N 6.31; found C 65.80, H 7.39, N 6.53.

5,11,17,23-Tetrakis[benzyloxycarbonylglycinylglycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3g): Z-GlyGly−OH (0.669 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 0.67 g (68%). White solid; m.p. 135−137 °C. ^{1}H NMR [600 MHz, $CDCl_3$, the data listed below describe the set of

signals (ca. 70% intensity) that belongs to the **3g**/CH_3CN complex; the spectrum contains also broad and partially hidden signals of a minor component in chemical exchange with the acetonitrile complex (probably free **3g**, 30% intensity, data not listed) and an intense H_2O signal at δ = 1.52 ppm]: δ = 9.50 [br. s, 4 H, Gly(Aa1)−NH], 7.60 (br. s, 4 H, Ar−CH_2N*H*), 7.44, 7.39, 7.29 (3m, 20 H, Z-Ar−H), 7.09 (s, 4 H, Ar−H), 6.39 (d, 4 H, OCH_2O), 5.69 [br. s, 4 H, Gyl(Aa2)−NH], 5.23 (s, 8 H, Z-CH_2O), 4.83 (t, 4 H, Ar_2CH−pentyl), 4.37 (d, 4 H, OCH_2O), 4.30 (very br. s, 8 H, Ar−CH_2NH), 3.87 [br. s, 8 H, Gly(Aa2)−CH_2], 3.60 [very br. s, 8 H, Gly(Aa1)−CH_2], 2.24, 1.39, 1.32, 0.89 (4m, 44 H, C_5H_{11}), −2.42 (s, 3 H, CH_3CN) ppm. MS (FAB, scan 400−2100): *m*/*z* (%) = 1947.6 (100) $[M + Na]^+$. $C_{104}H_{124}N_{12}O_{24}$·$CH_3CN$·$4H_2O$ (2039.3): calcd. C 62.43, H 6.67, N 8.93; found C 62.76, H 6.79, N 8.45.

5,11,17,23-Tetrakis[benzyloxycarbonyl-L-valinylglycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3h): Z-L-ValGly−OH (0.553 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 0.71 g (68%). White solid; m.p. 143−145 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.79 (dd, 4 H, Gly−NH), 8.22 (d, 4 H, Ar−CH_2N*H*), 7.45, 7.36, 7.31 (3m, 20 H, Z-Ar−H), 7.06 (s, 4 H, Ar−H), 6.51 (d, 4 H, OCH_2O), 5.25 (d, 4 H, Z-CH_2O), 5.14 (d, 4 H, Val−NH), 5.01 (d, 4 H, Z-CH_2O), 4.96 (dd, 4 H, Ar−CH_2NH), 4.87 (t, 4 H, Ar_2CH−pentyl), 4.37 (d, 4 H, OCH_2O), 4.22 (dd, 4 H, Gly−CH_2), 3.76 (dd, 4 H, Ar−CH_2NH), 3.66 (dd, 4 H, Val-αH), 3.24 (dd, 4 H, Gly−CH_2), 1.88 (m, 4 H, Val-βH), 2.18 1.41, 1.33, 0.89 (4m, 44 H, C_5H_{11}), 1.02, 0.97 (2d, 24 H, Val−CH_3), −2.43 (s, 3 H, CH_3CN) ppm. MS [ESI (pos.), scan 400−3000]: *m*/*z* (%) = 2093.5 (50) $[M]^+$, 1047.7 (55) $[M + H]^{2+}$. $C_{116}H_{148}N_{12}O_{24}$·$CH_3CN$·$3H_2O$ (2189.6): calcd. C 64.73, H 7.23, N 8.32; found C 64.77, H 7.58, N 8.27.

5,11,17,23-Tetrakis[benzyloxycarbonyl-L-leucinylglycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20−tetrapentylresorc[4]arene (3i): Z-L-LeuGly−OH (0.553 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 0.956 g (89%). White solid; m.p. 186−188 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.65 (dd, 4 H, Gly−NH), 8.11 (dd, 4 H, Ar−CH_2N*H*), 7.43−7.29 (m, 20 H, Z-Ar−H), 7.06 (s, 4 H, Ar−H), 6.52 (d, 4 H, OCH_2O), 5.22 (d, 4 H, Z-CH_2O), 5.08 (d, 4 H, Z-CH_2O), 5.03 (d, 4 H, Leu−NH), 4.93 (dd, 4 H, Ar−CH_2NH), 4.87 (t, 4 H, Ar_2CH−pentyl), 4.37 (d, 4 H, OCH_2O), 4.18 (dd, 4 H, Gly−CH_2), 4.10 (m, 4 H, Leu-αH), 3.72 (dd, 4 H, Ar−CH_2NH), 3.23 (dd, 4 H, Gly−CH_2), 2.19, 1.40, 1.32, 0.89 (4m, 44 H, C_5H_{11}), 1.56−1.59 (m, 12 H, Leu-βH, Leu-γH), 1.00, 0.93 (2d, 24 H, Leu−CH_3), −2.40 (s, 3 H, CH_3CN) ppm. MS [ESI (pos.), scan 400−3000]: *m*/*z* (%) = 1074.5 (93) $[M]^{2+}$. $C_{120}H_{156}N_{12}O_{24}$·$CH_3CN$·$H_2O$ (2189.6): calcd. C 64.73, H 7.23, N 8.32; found C 64.77, H 7.58, N 8.27.

5,11,17,23-Tetrakis[benzyloxycarbonyl-L-phenylalanylglycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3j): Z-L-PheGly−OH (0.931 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 0.891 g 78%. White solid; m.p. 148−150 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.27 (m, 4 H, Gly−NH), 8.02 (m, 4 H, Ar−CH_2N*H*), 7.46−7.20 (m, 40 H, Z-Ar−H, Phe−Ar−H), 7.01 (s, 4 H, Ar−H), 6.36 (d, 4 H, OCH_2O), 5.22 (d, 4 H, Z-CH_2O), 5.14 (d, 4 H, Phe−NH), 5.05 (d, 4 H, Z-CH_2O), 4.91 (dd, 4 H, Ar−CH_2NH), 4.82 (t, 4 H, Ar_2CH−pentyl), 4.23 (m, 4 H, Phe-αH), 4.20 (d, 4 H, OCH_2O), 3.70 (m, 8 H, Ar−CH_2NH, Gly−CH_2), 3.02−2.93 (2dd, 8 H, Phe−CH_2), 2.66 (dd, 4 H, Gly−CH_2), 2.15, 1.38, 1.30, 0.87 (4m, 44 H, C_5H_{11}), −2.58 (s, 3 H, CH_3CN) ppm. MS [ESI (pos.), scan 400−3000]: *m*/*z* (%) = 1142.8 (20) $[M]^{2+}$. $C_{132}H_{148}N_{12}O_{24}$·$CH_3CN$·$H_2O$ (2345.7): calcd. C 68.61, H 6.57, N 7.76; found C 68.21, H 6.64, N 7.64.

5,11,17,23-Tetrakis[benzyloxycarbonyl-ε-*tert*-butyloxycarbonyl-L-lysinylglycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3k): Z-L-Lys(Boc)-Gly−OH (1.068 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 0.978 g (75%). White solid; m.p. 125−127 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.73 (m, 4 H, Gly−NH), 8.15 (m, 4 H, Ar−CH_2N*H*), 7.43−7.29 (m, 20 H, Z−Ar−H), 7.06 (s, 4 H, Ar−H), 6.47 (d, 4 H, OCH_2O), 5.28 (br. m, 8 H, Lys-αNH, Lys-εNH), 5.22 (d, 4 H, Z-CH_2O), 5.02 (d, 4 H, Z-CH_2O), 4.93 (br. m, 4 H, Ar−CH_2NH), 4.86 (t, 4 H, Ar_2CH−pentyl), 4.37 (d, 4 H, OCH_2O), 4.15 (br. dd, 4 H, Gly−CH_2), 3.97 (m, 4 H, Lys-αH), 3.75 (br. m, 4 H, Ar−CH_2NH), 3.26 (br. d, 4 H, Gly−CH_2), 3.16, 2.93 (2m, 8 H, Lys-εCH_2), 2.19 (m, 8 H, Ar_2CH−CH_2−butyl), 1.67, 1.63 (2m, 8 H, Lys-βCH_2), 1.50−1.2 [m, 40 H, Lys-γCH_2 and Lys-δCH_2, Ar_2CH−CH_2−(CH_2)$_3$−CH_3], 1.36 (s, 36 H, Boc−CH_3) 0.89 [t, 12 H, Ar_2CH−$(CH_2)_4$−CH_3], −2.46 (s, 3 H, CH_3CN) ppm. MS [ESI (pos.), scan 400−3000]: *m*/*z* (%) = 1304.8 (44) $[M]^{2+}$. $C_{140}H_{192}N_{16}O_{32}$·$CH_3CN$·$2H_2O$ (2712.2): calcd. C 63.77, H 7.40, N 8.78; found C 63.28, H 7.38, N 8.81.

5,11,17,23-Tetrakis[benzyloxycarbonyl-L-prolinylglycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3l): Z-L-ProGly−OH (0.765 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 0.719 g (69%). White solid; m.p. 159−161 °C. ^{1}H NMR [600 MHz, $CDCl_3$; one dominant conformation (ca. 90%, C_4 symmetry) is observed and one or more minor conformations having broad NMR spectroscopic signals. NOe-signals between the Z-CH_2 protons and the Pro-δH indicate *trans*-proline peptide bonds in the dominant conformation. The following data describe the signals of this major form]: δ = 9.84 (dd, 4 H, Gly−NH), 8.47 (t, 4 H, Ar−CH_2N*H*), 7.43−7.29 (m, 20 H, Z-Ar−H), 7.11 (s, 4 H, Ar−H), 6.49 (d, 4 H, OCH_2O), 5.31 (d, 4 H, Z-CH_2O), 5.10 (d, 4 H, Z-CH_2O), 4.97 (dd, 4 H, Ar−CH_2NH), 4.92 (t, 4 H, Ar_2CH−pentyl), 4.44 (d, 4 H, OCH_2O), 4.25 (m, 8 H, Pro-αH and Gly−CH_2), 3.85 (dd, 4 H, Ar−CH_2NH), 3.59 (m, 8 H, Pro-δH), 3.28 (dd, 4 H, Gly−CH_2), 2.23 (m, 8 H, Ar_2CH−CH_2−butyl), 2.20−1.80 (m, 24 H, Pro-βH and Pro-γH), 1.45, 1.37, [2m, 24 H, Ar_2CH−CH_2−(CH_2)$_3$−CH_3], 0.94 [t, 12 H, Ar_2CH−$(CH_2)_4$−CH_3], −2.38 (s, 3 H, CH_3CN) ppm. MS [ESI (pos.), scan 400−3000]: *m*/*z* (%) = 2086.5 (100) $[M]^+$, 1043.6 (36) $[M]^{2+}$. $C_{120}H_{156}N_{12}O_{24}$·$CH_3CN$·$3H_2O$ (2181.5): calcd. C 64.97, H 6.88, N 8.34; found C 64.70, H 7.21, N 8.05.

5,11,17,23-Tetrakis[benzyloxycarbonyl-L-valinyl-L-valinylglycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3m): Z-L-Val- L-ValGly−OH (1.054 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 1.058 g (85%). White solid; m.p. 165−168 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.61 (dd, 4 H, Gly−NH), 8.00 (t, 4 H, Ar−CH_2N*H*), 7.38−7.26 (m, 20 H, Z-Ar−H), 7.02 (s, 4 H, Ar−H), 6.48 (d, 4 H, OCH_2O), 6.18 [br. d, 4 H, Val(2)−NH], 5.36 [br. d, 4 H, Val(3)−NH], 5.12 (br. s, 8 H, Z-CH_2O), 4.99 (dd, 4 H, Ar−CH_2NH), 4.81 (t, 4 H, Ar_2CH−pentyl), 4.34 (d, 4 H, OCH_2O), 4.11 (dd, 4 H, Gly−CH_2), 4.01 [m, 4 H, Val(1)-αH], 3.82 [dd, 4 H, Val(2)-αH], 3.73 (dd, 4 H, Ar−CH_2NH), 3.21 (dd, 4 H, Gly−CH_2), 2.14 [m, 12 H, Ar_2CH−CH_2−butyl, Val(1)-βH], 1.91 [m, 4 H, Val(2)-βH], 1.38, 1.30, [2m, 24 H, Ar_2CH−CH_2−(CH_2)$_3$−CH_3], 1.02−0.92 [m, 48 H, Val(1)−CH_3, Val(2)−CH_3], 0.88 [t, 12 H, $Ar_2CH(CH_2)_4$−CH_3], −2.47 (s, 3 H,

CH_3CN) ppm. MS [ESI (pos.), scan 400−3000]: *m/z* (%) = 1244.4 (47) $[M]^{2+}$. $C_{136}H_{184}N_{16}O_{28}\cdot CH_3CN\cdot 2H_2O$ (2568.1): calcd. C 64.54, H 7.50, N 9.27; found C 64.21, H 7.55, N 8.92.

5,11,17,23-Tetrakis[benzyloxycarbonyl-L-methionyl-L-valinyl-glycinylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy2,8,14,20-tetrapentylresorc[4]arene (3n): Z-L−Met-L-ValGly−OH (1.099 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 1.086 g (83%). White solid; m.p. 143−147 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.64 (br. d, 4 H, Gly−NH), 8.09 (t, 4 H, Ar−CH_2N*H*), 7.37−7.27 (m, 20 H, Z-Ar−H), 7.02 (s, 4 H, Ar−H), 6.74 (br. s, 4 H, Val−NH), 6.42 (d, 4 H, OCH_2O), 5.52 (br. d, 4 H, Met−NH), 5.13 (br. s, 8 H, Z-CH_2O), 4.97 (dd, 4 H, Ar−C*H*$_2$NH), 4.80 (t, 4 H, Ar_2CH−pentyl), 4.43 (br. m, 4 H, Met-αH), 4.32 (d, 4 H, OCH_2O), 4.11 (dd, 4 H, Gly−C*H*$_2$), 3.76 (m, 8 H, Val-αH, Ar−C*H*$_2$NH), 3.20 (dd, 4 H, Gly−C*H*$_2$), 2.66 (m, 8 H, Met-γH), 2.20−1.85 (m, 20 H, Ar_2CH-CH_2−butyl, Met-βH, Val-βH), 2.10 (s, 12 H, Met−CH_3), 1.42−1.25, [m, 24 H, $Ar_2CH-CH_2-(CH_2)_3-CH_3$], 1.00, 0.94 (2d, 24 H, Val−CH_3), 0.89 [t, 12 H, $Ar_2CH-(CH_2)_4-CH_3$], −2.46 (s, 3 H, CH_3CN) ppm. MS [ESI (pos.), scan 400−3000]: *m/z* (%) = 1308.8 (25) $[M]^{2+}$. $C_{136}H_{184}N_{16}O_{28}S_4\cdot CH_3CN\cdot 4H_2O$ (2731.4): calcd. C 60.68, H 7.16, N 8.72; S 4.70, found C 60.06, H 7.42, N 9.16, S 4.78.

5,11,17,23-Tetrakis[benzyloxycarbonyl-L-valinyl-β-alanylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3o): Z-L-Val-βAla−OH (0.806 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 0.946 g (88%). White solid; m.p. 211−213 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37−7.25 (m, 20 H, Z-Ar−H), 7.19 (br. s, 4 H, β-Ala−NH), 7.10 (s, 4 H, Ar−H), 6.35 (br. s, 4 H, Ar−CH_2N*H*), 5.95 (br. d, 4 H, OCH_2O), 5.74 (br. s, 4 H, Val−NH), 5.13 (d, 4 H, Z-CH_2O), 5.06 (d, 4 H, Z-CH_2O), 4.76 (t, 4 H, Ar_2CH−pentyl), 4.38 (br. d, 4 H, OCH_2O), 4.37−4.20 (br. m, 8 H, Ar−C*H*$_2$NH), 4.04 (br. m, 4 H, Val-αH), 3.49 [br. s, 8 H, β-Ala−CH_2(β)], 2.36 [br. s, 8 H, β-Ala−CH_2(α)], 2.20, 1.43, 1.36, 0.93 (4m, 44 H, C_5H_{11}), 2.11 (br. m, 4 H, Val-βH), 1.70 (br. s, 8 H, H_2O), 0.97, 0.92 (2d, 24 H, Val−CH_3) ppm. MS [ESI (pos.), scan 400−3000]: *m/z* (%) = 1074.4 (100) $[M]^{2+}$. $C_{120}H_{156}N_{12}O_{24}\cdot 4H_2O$ (2222.7): calcd. C 64.85, H 7.44, N 7.56, found C 63.67, H 7.31. 7.67.

5,11,17,23-Tetrakis[benzyloxycarbonyl-L-leucinyl-β-alanylamidomethyl]-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorc[4]arene (3p): Z-L-Leu-βAla−OH (0.838 g, 2.5 mmol) was used in procedure A followed by C (recrystallized from acetonitrile). Yield: 0.959 g (87%). White solid; m.p. 148−152 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38−7.25 (m, 20 H, Z-Ar−H), 7.19 (br. s, 4 H, β-Ala−NH), 7.09 (s, 4 H, Ar−H), 6.18 (br. s, 4 H, Ar−CH_2N*H*), 5.94 (br. d, 4 H, OCH_2O), 5.69 (br. s, 4 H, Leu−NH), 5.16 (d, 4 H, Z-CH_2O), 5.07 (d, 4 H, Z-CH_2O), 4.76 (t, 4 H, Ar_2CH−pentyl), 4.37 (br. s, 4 H, OCH_2O), 4.36 −4.25 (m, 8 H, Ar−C*H*$_2$NH), 4.21 (br. s, 4 H, Leu-αH), 3.46 [br. s, 8 H, β-Ala−CH_2(β)], 2.32 [br. s, 8 H, β-Ala−CH_2(α)], 2.20, 1.43, 1.36, 0.93 (4m, 44 H, C_5H_{11}), 1.90 (br. s, 3 H, CH_3CN), 1.65 (s, 2 H, H_2O), 1.71−1.55 (m, 12 H, Leu-βH, Leu-γH), 0.95 (br. m, 24 H, Leu−CH_3) ppm. MS [ESI (pos.), scan 400−3000]: *m/z* (%) = 2205.8 (6) $[M]^+$, 1102.5 (100) $[M]^{2+}$. $C_{124}H_{164}N_{12}O_{24}\cdot CH_3CN\cdot H_2O$ (2265.8): calcd. C 66.79, H 7.52, N 8.04; found C 66.94, H 7.74, N 8.12.

X-ray-Crystallographic Study of 4: Crystal data: Colorless prism, size 0.5 × 0.5 × 0.3 mm, empirical formula $C_{56}H_{72}O_8\cdot 3(C_2H_3N)$, mass 996.30. Cell dimensions: *a* = 12.022(8), *b* = 12.894(8), *c* = 19.765(13) Å, α = 79.649(12), β = 74.956(12), γ = 73.734(12) °, *V* = 2821(3) Å^3, triclinic, space group $P\bar{1}$, *Z* = 2, *d* = 1.173 Mg·m^{-3}. Data collection: Bruker axs CCD-1000 area detector, Mo-K_α radiation, graphite monochromator, ω scan, *T* = 203 K. Θ_{max} = 27.58, 17281 reflections measured, 12346 independent, 8080 observed [$I > 2\sigma(I)$], intensities [R_{merg} = 0.1086 (F^2)]. μ = 0.077 mm^{-1} no absorption correction. Structural analysis and refinement: Full matrix refinement with calculated hydrogen positions, 652 parameter, F_o= 1076, *R* = 0.1086, R_w = 0.3024, program SHELXLS 97.

CCDC-203527 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

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