# Velcrands with Snaps and Their Conformational Control

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**Abstract:** A novel class of self-folding velcrands was prepared that dimerize through intermolecular forces. Solvophobic interactions on extended π surfaces stabilize the dimer similar to *velcrands*, while eight hydrogen bonds act like *snaps* to hold the molecules together. The self-complementary array of hydrogen bonding sites were incorporated on the upper rim of a resorcinarene-based cavitand. A dramatic reorganization of shape and size of the internal cavity was manifested through changes in solvent polarity. Specifically, the equilibrium between the extended surface ($D_{2d}$ symmetry) and a deep cavity ($C_{4v}$ symmetry) could be manipulated in mixtures of aromatic solvents (or $CDCl_3$) and [$D_6$]DMSO. The switching of conformations and the dimerization motif are well-suited for the assembly of noncovalent polymeric materials.

**Keywords:** cavitands · dimerizations · hydrogen bonds · supramolecular chemistry · solvent effects

## Introduction

Self-complementary hydrogen bonding donor and acceptor sites, properly positioned on a curved molecular platform, play key roles in the self-assembly of dimeric capsules.[1] For example, calix[4]arenes functionalized with four urea groups at their upper rims dimerize in apolar solvents to form pseudo-spherical capsules,[2] and resorcinarene-based tetraimides form cylindrical capsules of nanometric dimensions.[3] Even in monomeric cavitands derived from **1** the cavity-forming process can be controlled by hydrogen bonding: octaamide **2** is held in the vaselike shape by a cooperative seam of *intramolecular* -C=O···H–N hydrogen bonds. This results in unusually high kinetic stabilities of their complexes (caviplexes). We call these molecules *self-folding cavitands.* [4] At first glance, the structures **3** and **4**, in which the amides at the rim of the vase are merely inverted, should also enjoy the benefits of intramolecular hydrogen bonding. Unexpectedly, this "isomerism" exposes a subtle self-complementarity: *intermolecular* hydrogen bonding between the secondary amide donors of one molecule and the diaryl ether acceptors of another occurs. Here, we describe in detail these systems and show how solvation causes a switch in conformations, between a cavity-forming vase and a flattened kitelike shape. These molecules represent self-folding cavitands of a new sort and a dimerization mode reminiscent of the velcrands is revealed for the first time: the dimer of $D_{2d}$ symmetry can reversibly dissociate into the $C_{2v}$ monomers and fold into the $C_{4v}$ symmetrical vase (Scheme 1). Factors controlling the switching—the folding and unfolding processes—will also be addressed.

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## Results and Discussion

Cavitands are synthetic structures with open-ended enforced cavities, based on Högberg's resorcinarenes (e.g, **1**).[5] In resorcinarene **1**, the eight hydroxy groups form a cyclic array of intramolecular hydrogen bonds that rigidify the structure and stabilize the "cone" conformation. When the resorcinol oxygen atoms in **1** are bridged with heteroarylene units (e.g. pyrazines or quinoxalines), deeper cavities result but the flexibility of the resorcinarene skeleton increases.[6–8] These cavitands fluctuate between $C_{4v}$ and $C_{2v}$ symmetries. Accordingly, their size and shape, and consequently their binding properties, were controlled by temperature. Cram et al. showed that for the unsubstituted resorcinarenes (**1**, R′ = H), the vase-shaped $C_{4v}$ conformer, with all of its four walls upwards, is preferred at $\geq$295 K.[6] The $C_{2v}$ conformer has the walls flipped outwards in a kitelike shape and is the dominant conformation at much lower temperatures. The interconversion barrier is typically 10–12 kcal mol$^{-1}$.[6] On the other hand, when 2′-substituted resorcinarenes (**1**, R′ = $CH_3$, $C_2H_5$) are condensed with heteroaryl dichlorides, only the $C_{2v}$ conformer is observed: the presence of the 2′-methyl or 2′-ethyl groups sterically destabilizes the vase.[6] Furthermore, the kite-shaped $C_{2v}$ conformer tends to dimerize in solution through solvophobic interactions; the $D_{2d}$ dimers are known as velcrands.[6]

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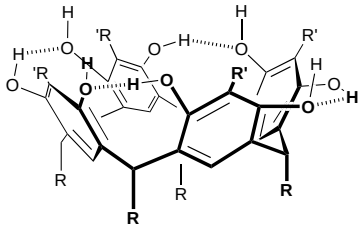
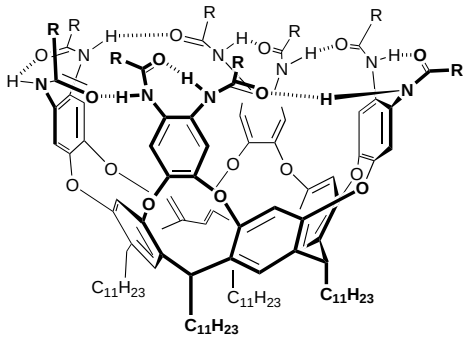
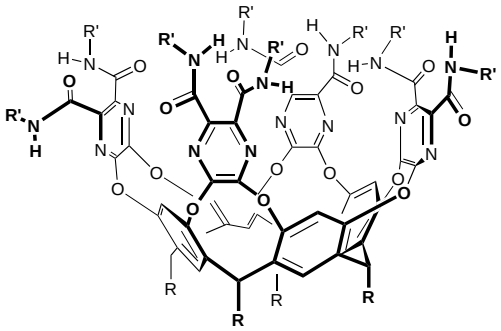


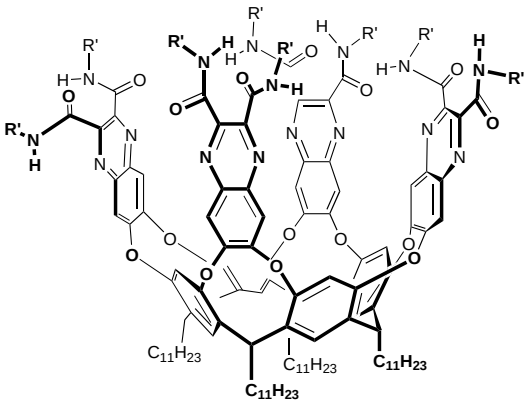
**1a** R = $CH_3$, R' = H
**1b** R = *n*-$C_{11}H_{23}$, R' = H
**1c** R = *n*-$C_9H_{19}$, R' = $CH_3$



**2** R = *n*-$C_7H_{15}$, $CH_2Cl$, *cyclo*-$C_6H_{11}$



**3a** R = $CH_3$, R' = *n*-$C_8H_{17}$
**3b** R = *n*-$C_{11}H_{23}$, R' = *n*-$C_8H_{17}$



**4a** R' = $CH_3$
**4b** R' = *n*-$C_4H_9$

**Abstract in Portuguese:** *Neste trabalho, uma nova classe de velcrantes flexíveis foi preparada. Esses velcrantes dimerizam de maneira não covalente, através de interações solvofóbicas e de oito ligações de hidrogênio cooperativas, que conectam a estrutura como botões de pressão. Para obter tal resultado, funções doadoras e aceptoras de ligações de hidrogênio, auto-complementares por natureza, foram posicionadas estrategicamente no aro superior de cavitantes, estruturas derivadas de resorcinarenos. A presença de ligações de hidrogênio intermoleculares, causa uma dramática reorganização no formato e nas dimensões da cavidade interna ao variar-se a polaridade do solvente. O equilíbrio entre estruturas de simetrias $D_{2d}-C_{4v}$ é controlado por adição de [$D_6$]DMSO a soluções dos velcrantes em solventes apolares ([$D_{10}$]p-xylene ou $CDCl_3$, por exemplo). Esse fenômeno representa um dispositivo conformacional, onde uma superfície estendida ($D_{2d}$) é transformada em uma cavidade de dimensões nanométricas ($C_{4v}$). O modelo estrutural e o modo de dimerização aqui apresentados, serão futuramente utilizados para a construção de polímeros auto-organizados, que podem ser despolimerizados simplesmente por aumento da constante dielétrica do meio.*

**Synthesis**: Shorter octaamide cavitands **3a, b** were prepared through the coupling of resorcinarene **1b** and 5,6-dichloropyrazine-2,3-dioctylcarboxamides **5**. Pyrazine **5** was prepared by reaction of 5,6-dichloropyrazine-2,3-dicarboxylic acid dichloride with two equivalents of *n*-octylamine (Scheme 2). Similarly, coupling of **1b** with four equivalents of methyl 5,6-dichloropirazine-2,3-dicarboxylate (**6**) afforded shallow octaester **7**. Deeper octaamide cavitands **4a, b** were synthesized according to a modular approach described by us recently:[8] bridging of the resorcinarene **1b** hydroxy groups was accomplished with 1,2-difluoro-4,5-dinitrobenzene, then, after reduction of the nitro functions, the octaamino cavitand module was immediately condensed with diethyl-2,3-dioxo-succinate. This produced deep octaester cavitand **8**. The compound was subsequently converted into amides **4a, b** simply by treatment with an excess of the appropriate amine in boiling EtOH. Compounds **9** and **10**, possessing 2′-$CH_3$ group in the resorcinol unit, were prepared along similar lines. Thus, reaction between **1c** and **5** gave **9**. Aminolysis of octaester **11** with *n*-butylamine afforded compound **10**. Model compound **12** (Scheme 2) was prepared for spectroscopic comparisons through the coupling of 4,5-dimethyl-1,2-phenylenediamine



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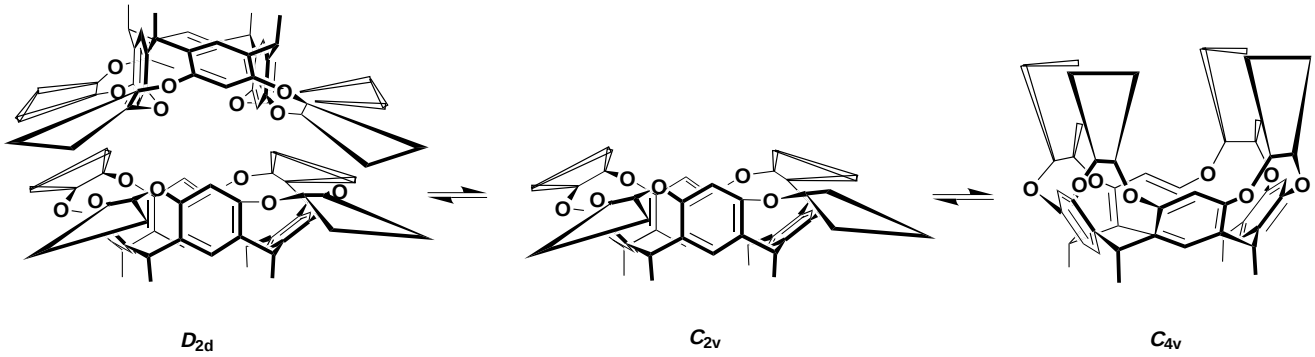
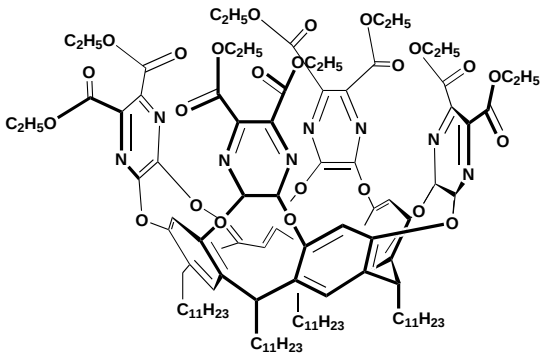
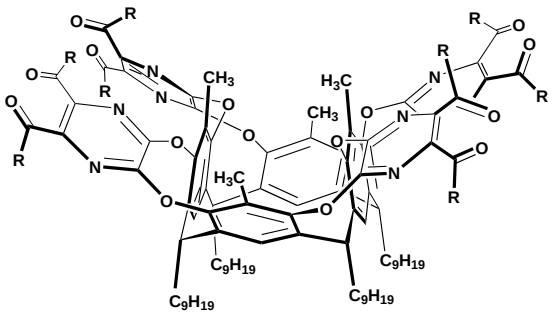


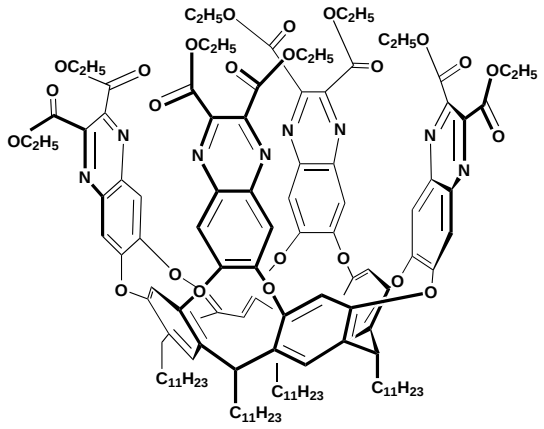

Scheme 1. Cartoon representation of the conformational switch in self-folding cavitands.



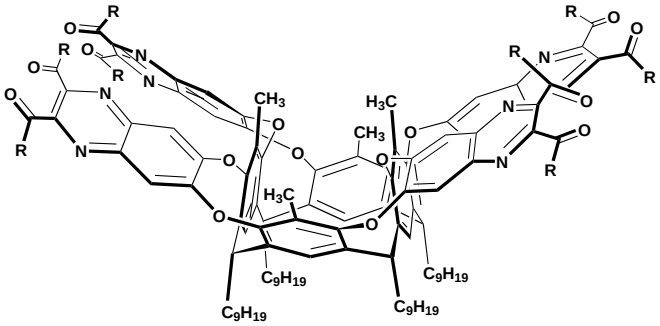
**7**



**9** R = NH-*n*-$C_8H_{17}$



**8**

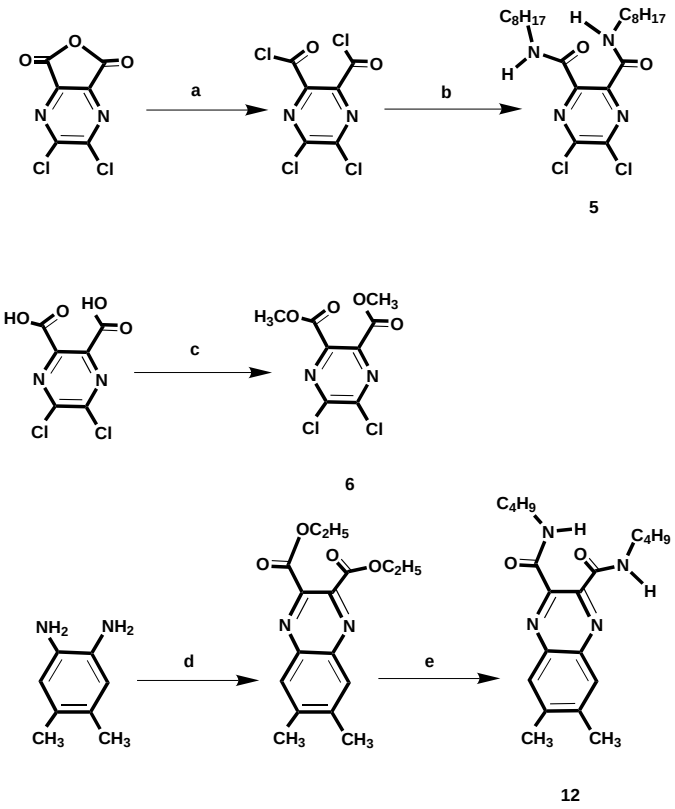


**10** R = NH-*n*-$C_4H_9$
**11** R = $OC_2H_5$

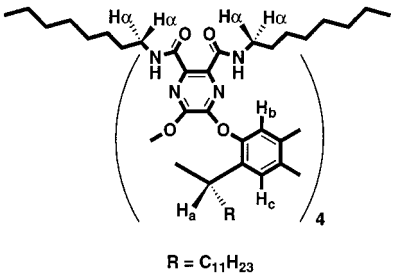
with diethyl-2,3-dioxo-succinate, followed by aminolysis with *n*-butylamine.

**Spectroscopic properties:** Since octacarboxamides **3a, b** and **4a, b** do not bear $CH_3$ substituents in the resorcinol 2′-position, they were expected to be in a vase $C_{4v}$ conformation at room temperature and above. Surprisingly, this was not the case and $C_{2v}$ symmetries were seen *exclusively* in their $^1$H NMR spectra in noncompetitive solvents ($CDCl_3$, [$D_6$]benzene, [$D_8$]toluene, [$D_{10}$]*p*-xylene). The characteristic doubled set of signals for all groups of protons (Figures 1 and 2) make these assignments unambiguous. In compounds **3a, b** one of the N-H signals was shifted far downfield, indicating strong hydrogen bonding in these solvents (Table 1). The $^1$H NMR spectra of extended octaamides **4a, b** in $CDCl_3$, [$D_6$]benzene, [$D_8$]toluene, and [$D_{10}$]*p*-xylene were broader (Figure 2), but also possessed downfield shifted N-H signals. The spectra sharpen upon addition of as little as 0.5% v/v of [$D_6$]DMSO.

The FTIR spectrum of **3b** (toluene, 295 K) showed a strong hydrogen-bonding absorption at 3300 $cm^{-1}$ and a less intense, nonaggregated one at 3405 $cm^{-1}$; this picture was concentra-



Scheme 2. Synthetic routes for the preparation of compounds **5**, **6**, and **12**. a) $PCl_5$, 170 °C, 1 h (82 %); b) $n$-$C_8H_{17}NH_2$, EtOAc/$H_2O$, $K_2CO_3$, room temperature, 1 h (89 %); c) MeOH, $H_2SO_4$, reflux, 17 h (82 %); d) diethyl-2,3-dioxosuccinate, EtOH, room temperature, 2 h (65 %); e) $n$-$C_4H_9NH_2$, EtOH, reflux, 41 h (67 %).



R = $C_{11}H_{23}$

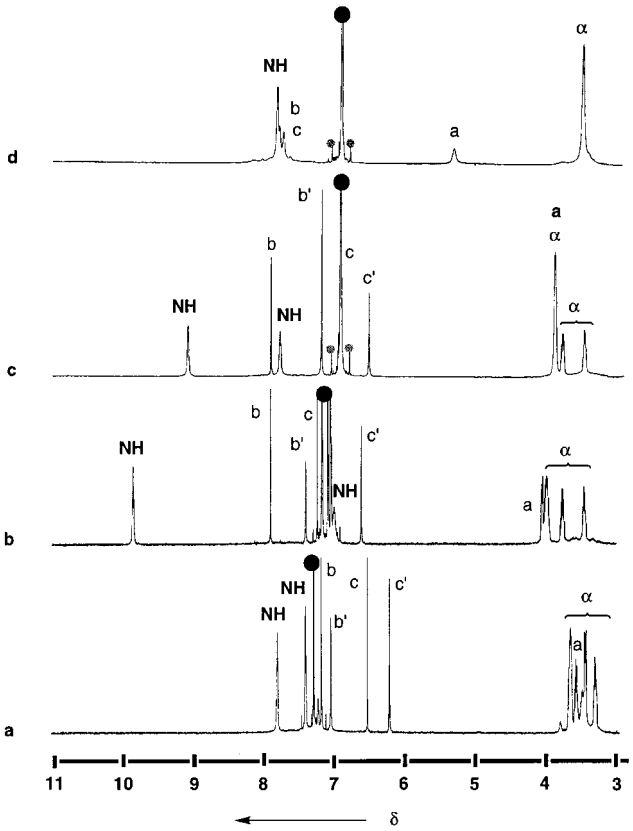


Figure 1. Downfield portion of the $^1$H NMR (600 MHz) of **3b** ($1 \times 10^{-3}$ M solution) in: a) $CDCl_3$, $295 \pm 1$ K; b) [$D_8$]toluene, $295 \pm 1$ K; c) [$D_{10}$]p-xylene, $295 \pm 1$ K, the compound symmetry did not change upon heating up to 380 K; d) [$D_{10}$]*p*-xylene + 12 % v/v [$D_6$]DMSO, $330 \pm 1$ K. Assignments were made based on COSY and ROESY experiments of derivatives. The solvent signals with corresponding satellites are marked "●".

tion independent ($2 \times 10^{-2} - 1 \times 10^{-5}$ M). For **4b** the corresponding absorptions were at 3306 $cm^{-1}$ and 3411 $cm^{-1}$, also concentration independent ($2 \times 10^{-2} - 1 \times 10^{-5}$ M). Model bis-carboxamide-containing pyrazine **5** and quinoxaline **12** do not exhibit substantial hydrogen bonding in apolar solution, either between the adjacent amide fragments, or between the heterocyclic nitrogens and the amide N–H donors. The N–H chemical shift is upfield $\delta = 7$ (Table 1). In their FTIR spectra, only the nonaggregated N–H stretching absorptions were observed at 3430 $cm^{-1}$ in $CDCl_3$ and at 3410 $cm^{-1}$ in [$D_8$]toluene ($\leq 1 \times 10^{-2}$ M) for **5**, and at 3434 $cm^{-1}$ in $CDCl_3$ and at 3417 $cm^{-1}$ in [$D_8$]toluene ($\leq 1 \times 10^{-2}$ M) for **12** (Table 1).

Cavitands **7** and **8** showed the anticipated spectroscopic features of the vaselike $C_{4v}$ conformation,[6] and in their $^1$H NMR spectra only one set of signals for all groups of protons appears. The spectra of 2′-*methylated* cavitands **9, 10**, and **11** in various solvents showed the spectroscopic earmarks of the $C_{2v}$ kitelike conformation,[6] and two sets of signals were found for all groups of protons.

The unusual kite conformation in cavitands **3a, b** and **4a, b** is, most probably, due to the presence of eight secondary amides on their upper rims, but molecular modeling[9, 10] of only the monomeric forms does not offer a reasonable explanation of the observed $^1$H NMR and FTIR spectroscopic pictures. In the monomeric form of $C_{2v}$ symmetry, the hydrogen bonding sites are some distance from each other, and are unlikely to confer much stability to this conformation.

**Dimerization in solution:** The stable $C_{2v}$ structures of **3a, b** and **4a, b** exist, most probably, in equilibrium with their $D_{2d}$ dimers.[6] For the 2′-substituted $C_{2v}$ molecules these phenomena were well-studied by Cram et al.; solvophobic and entropic driving forces were found to be responsible for dimerization to velcraplexes in organic media.[6] For the cases at hand, MALDI mass spectrometry provided preliminary evidence that the dimerization was taking place (Table 2). For compound **3b**, the peak for the protonated monomer at *m/z* 2653, is accompanied with a peak for the dimeric structure at *m/z* 5307. The $CH_3$′-substituted octaamide **9** displayed a strong peak for the dimer at *m/z* 5187, along with the protonated monomer at *m/z* 2593. The MALDI mass spectrum of the extended octaamide **4b** also showed the dimerization in



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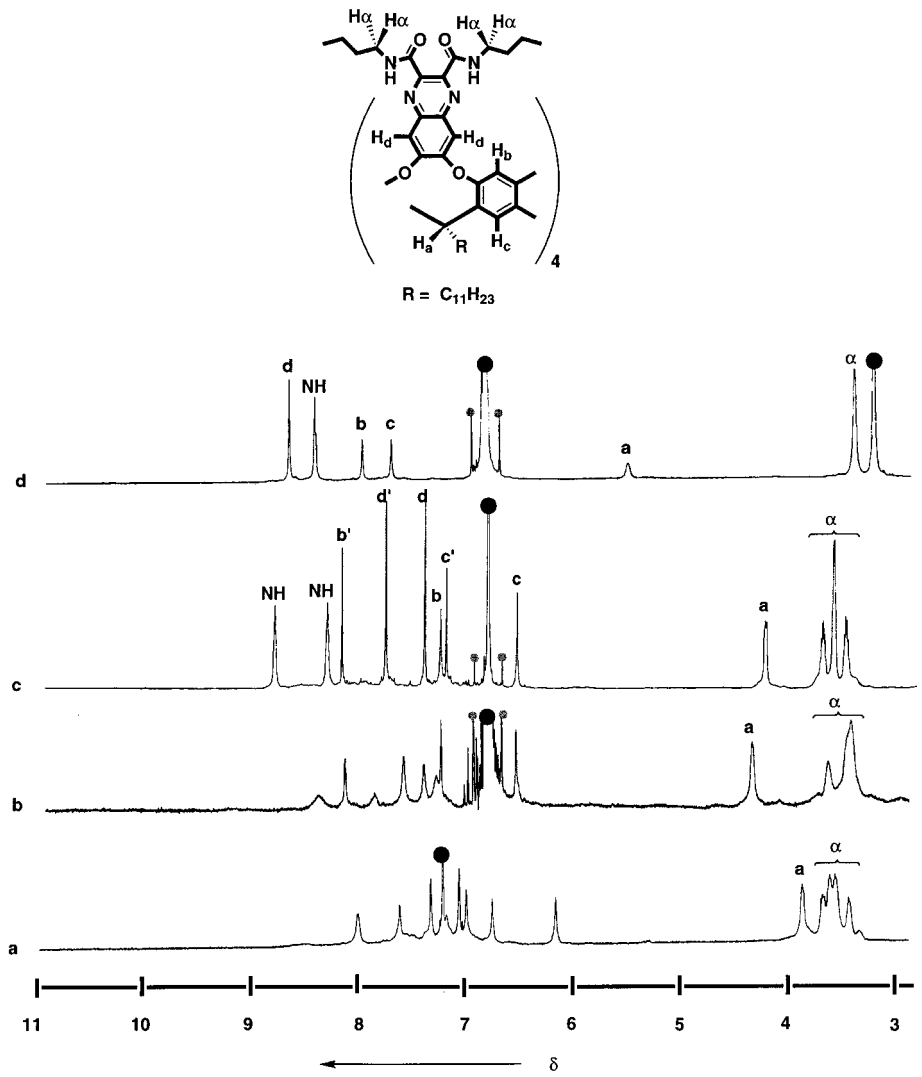


Figure 2. Downfield portion of the $^1$H NMR (600 MHz) of **4b** ($1\times10^{-3}$ M solution, $295\pm1$ K) in: a) $CDCl_3$; b) [$D_{10}$]*p*-xylene; c) [$D_{10}$]*p*-xylene + 3% v/v [$D_6$]DMSO; d) [$D_{10}$]*p*-xylene + 20% v/v [$D_6$]DMSO. Assignments were made based on COSY and ROESY experiments of derivatives. The solvent signals with corresponding satellites are marked as in Figure 1.

solution; beside the peak for the protonated monomer at *m/z* 2405, an intense (ca 50% of the base peak at *m/z* 2405) peak for the dimer at *m/z* 4811 was also observed. An analogous result was also obtained for the $CH_3$′-substituted extended octaamide **10**; peak at *m/z* 2347 and *m/z* 4694 were observed.

Further evidence for dimerization in solution came from $^1$H NMR studies. Mixing solutions of **3a** and **3b** in [$D_{10}$]*p*-xylene, containing 2% v/v of [$D_6$]DMSO, showed the corresponding homodimers **3a·3a** and **3b·3b**, along with heterodimer **3a·3b** (Figure 3). In particular, four different aromatic peaks—one for each homodimer and two for the heterodimer—were clearly seen. Most interestingly, the presence of the highly competitive [$D_6$]DMSO does not dissociate the dimers! In fact, in the absence of [$D_6$]DMSO the picture is broader, making it difficult to identify the peaks for each species in the spectrum. In short, in apolar solutions, dimers **3·3** and **4·4** are formed exclusively.

**Structural studies:** The important structural feature of the molecules **3** and **4** is a 2,3-dicarboxamido pyrazine (quinoxaline) fragment. Although modeling suggests that intramolecular hydrogen bonding between the -C(O)-NH and the pyrazine (quinoxaline) nitrogen atom is possible, the FTIR control experiments (vide supra) with models **5** and **12** ruled this out. On the other hand, there is an obvious electrostatic repulsion between the carboxamide oxygen and the pyrazine (quinoxaline) nitrogen, which forces both the -C(O)-NH out of the heterocyclic plane. Moreover, due to the repulsion between the two carbonyl oxygens, the -C(O)-NH groups are likely to be in a *trans* configuration with respect to the aromatic plane (Figure 4, left). The energy-minimized dimeric structures are presented in Figure 4. The two molecules are rotated 90° with respect to each other and extensive surface contacts are made. As a result, the four NH donors of one molecule appear in close proximity to the diaryl ether oxygen acceptors of the other. The N–H···O angle of about 170° is nearly ideal for the formation of eight intermolecular hydrogen bonds, which are like snaps that further hold the molecules in a dimer.

In the $^1$H NMR spectra of compounds **3** and **4**, the two $CH_aH_{a'}NH$–C(O) groups on the pyrazine and quinoxaline rings are seen as magnetically nonequivalent, and their relationship is diastereotopic. This indicates hindered rotation caused by hydrogen bonds (Figures 1 and 2). The presence of dimers in solution was further supported by 2D ROESY experiments. Thus, for compound **3b** in [$D_{10}$]*p*-xylene, a through-space contact between the hydrogen bonding N–H ($\delta=9.0$) and the top aromatic CH of the resorcinarene skeleton was observed, which can only be intermolecular (ca. 2.5 Å). For the extended compound **4b**, the ROESY spectrum ([$D_{10}$]*p*-xylene/[$D_6$]DMSO, 97:3 v/v) showed the through-space contacts between one of the quinoxaline aromatic protons and both upwardly directed CH resorcinarene protons. This is also possible only in the dimer. The kitelike octaamides **9** and **10**, which feature a 2′-$CH_3$ substituent in the resorcinol rings (and are therefore fully expected to dimerize) showed $^1$H NMR spectroscopic behavior similar to octaamides **3a, b** and **4a, b** in noncompetitive solvents.

Accordingly, compounds **3**, **4**, **9** and **10** exist as $D_{2d}$ dimers in apolar solutions. To our knowledge, this type of velcraplex—

Table 1. Spectroscopic data (NMR and FTIR) for the amide NH signals in cavitands **3a, b**, **4a, b**, **9** and **10**, and model compounds **5** and **12** in various solvents.[a]

| Compound | Solvent | $\delta$ | $\nu$ |
|---|---|---|---|
| **3a**[b] | $CDCl_3$ | 7.9, 7.8 | |
| | [$D_{10}$]*p*-xylene | 9.1 br., 7.8 br. | |
| | benzene | – | 3400, 3286 |
| **3b**[b] | $CDCl_3$ | 7.8, 7.4 | |
| | [$D_{10}$]*p*-xylene | 9.1, 7.7 | |
| | [$D_8$]toluene | 9.8, 7.0 | 3405, 3300 |
| | [$D_6$]benzene | 10.0, 6.8 | |
| | [$D_{10}$]*p*-xylene + [$D_6$]DMSO, 9:1 | 8.1 | |
| **4a**[b] | $CDCl_3$ | 8.00 br., 7.2 br. | |
| | $CDCl_3$ + [$D_6$]DMSO, 19:1 | 8.1 br., 7.6 br. | |
| | benzene | – | 3409, 3303 |
| **4b**[b] | $CDCl_3$ | 8.1 br., 7.2 br. | 3429, 3304 |
| | $CDCl_3$ + [$D_6$]DMSO, 9:1 | 8.1, 7.6 | |
| | [$D_8$]toluene | – | 3411, 3306 |
| | [$D_{10}$]*p*-xylene + [$D_6$]DMSO, 199:1 | 8.7, 7.7 | |
| | [$D_{10}$]*p*-xylene + [$D_6$]DMSO, 97:3 | 8.9, 8.4 | |
| | [$D_{10}$]*p*-xylene + [$D_6$]DMSO, 4:1 | 8.5 | |
| **5** | $CDCl_3$ | 6.9 | 3430 |
| | [$D_8$]toluene | 6.2 | 3410 |
| **9**[b] | $CDCl_3$ | 8.2, 7.6 | |
| | [$D_6$]benzene | 9.5, 6.8 | |
| | [$D_{10}$]*p*-xylene | 9.8 br., 6.9 br. | |
| | [$D_{10}$]*p*-xylene + [$D_6$]DMSO, 9:1 | 9.5, 8.8 | |
| | [$D_8$]toluene | - | 3402, 3276 |
| | $CH_2Cl_2$ | - | 3418, 3259 |
| **10**[b] | [$D_6$]benzene | 8.6, 6.4 | |
| | $CH_2Cl_2$ | – | 3418, 3295 |
| **12** | $CDCl_3$ | 7.0 | 3434 |
| | [$D_8$]toluene | 6.7 | 3417 |
| | [$D_6$]benzene | 7.0 | |

[a] At $0.5 \times 10^{-3}$ M, $295 \pm 1$ K. [b] The spectra in apolar solvents are concentration independent within the $1 \times 10^{-4}$ to $1 \times 10^{-2}$ M range.

Table 2. Selected MALDI-MS Spectroscopic data for cavitands **3a, b**, **4a, b**, **9**, and **10**.

| Compound | Formula | Weight | Observed | |
|---|---|---|---|---|
| | | | monomer | dimer |
| **3a** | $C_{120}H_{168}N_{16}O_{16}$ | 2090 | 2092 | [a] |
| **3b** | $C_{160}H_{248}N_{16}O_{16}$ | 2651 | 2653 | 5307 |
| **4a** | $C_{120}H_{144}N_{16}O_{16}$ | 2066 | 2090 | [a] |
| **4b** | $C_{144}H_{192}N_{16}O_{16}$ | 2403 | 2405 | 4811 |
| **9** | $C_{156}H_{240}N_{16}O_{16}$ | 2593 | 2593 | 5187 |
| **10** | $C_{140}H_{184}N_{16}O_{16}$ | 2347 | 2347 | 4694 |

[a] Not detected.

stabilized by *both* solvophobic and hydrogen-bonding interactions—is without literature precedent, and we call these molecules "velcrands with snaps".

**Conformational switch:** The dimers of **3a, b** and **4a, b** displayed remarkable solution stability. That no monomeric species could be detected by $^1$H NMR spectroscopy within a wide temperature range in different solvents (including more competitive media, such as [$D_{10}$]*p*-xylene/[$D_6$]DMSO mixtures), indicates very high values of the dimerization constants ($K_D \geqslant 10^5\,M^{-1}$, $-\Delta G^{295} \geqslant 6.7$ kcal mol$^{-1}$). Although 2′-unsubstituted cavitands have *never before been found to form $C_{2v}$ dimers*,[6] the combination of dipole–dipole, van der Waals, and solvophobic attractions might still be responsible for the behavior of **3** and **4**. However, the structurally similar octaester cavitands **7** and **8**, lacking hydrogen donor sites, exist exclusively in the $C_{4v}$ conformation. Accordingly, intermolecular hydrogen bonding must be the main driving force for dimerization of **3a, b** and **4a, b** in noncompetitive solvents.

We found that **3a, b** and **4a, b** can eventually be converted to the vase $C_{4v}$ structures upon progressive addition of [$D_6$]DMSO to the corresponding nonpolar solution (Figures 1, 2, and 5). Titration of a solution of **3b** with [$D_6$]DMSO resulted in the disappearance of the $D_{2d}$ species with concomitant appearance of the $C_{4v}$ structure. One set of NMR signals for all groups of protons were observed. No other species were detected. Eventually, in $\geq 10$ % v/v of [$D_6$]DMSO in [$D_{10}$]*p*-xylene and $\geq 40$ % v/v of [$D_6$]DMSO in $CDCl_3$, the vase-shaped $C_{4v}$ conformer **3b** was observed exclusively, even though its $^1$H NMR spectrum was broad at room temperature. Similarly, when extended cavitand **4b** in [$D_{10}$]*p*-xylene was titrated with $\geq 16$ % v/v of [$D_6$]DMSO, a smooth conversion to the $C_{4v}$ vase resulted. In both cases, the two $CH_2NH$–C(O) groups of the pyrazine (quinoxaline) rings became magnetically equivalent (Figure 1d and 2d).

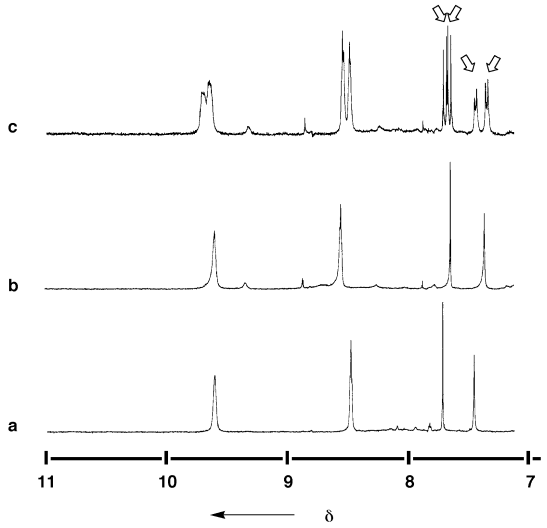


Figure 3. The heterodimerization experiment. Downfield region of the $^1$H NMR spectra ([$D_{10}$]*p*-xylene + 2 % v/v [$D_6$]DMSO, 600 MHz, $295 \pm 1$ K) of: a) cavitand **3b**; b) cavitand **3a**; c) 1:1 mixture of cavitands **3a** and **3b**. Concentrations were $1 \times 10^{-3}$ M for each compound. Some of the heterodimer aromatic signals are indicated by the arrows. Peak assignments were performed by varying the ratio [**3a**]:[**3b**].



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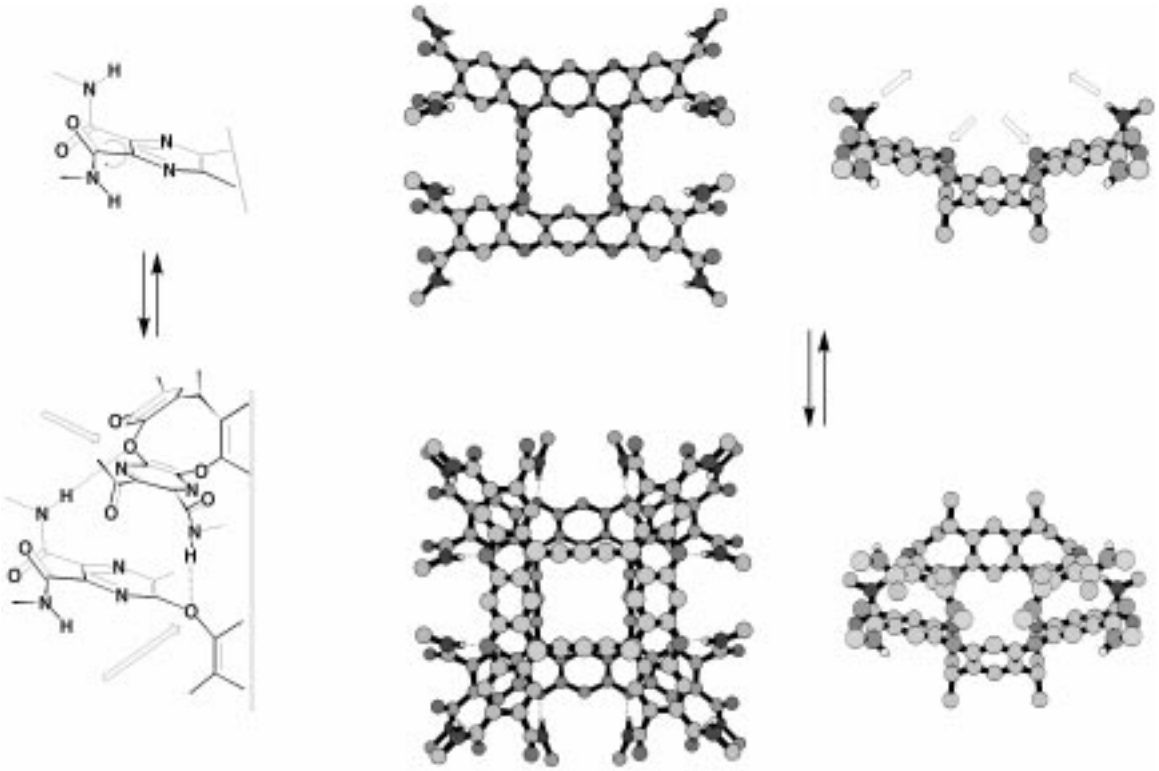

Figure 4. Energy-minimized[9] structures of both monomeric and dimeric **3**. The long alkyl chains and some CH bonds have been omitted for viewing clarity. The *trans* orientation adopted by the vicinal carboxamide groups upon dimerization is depicted on the left side of the figure. The self-complementary sites are indicated by the arrows.

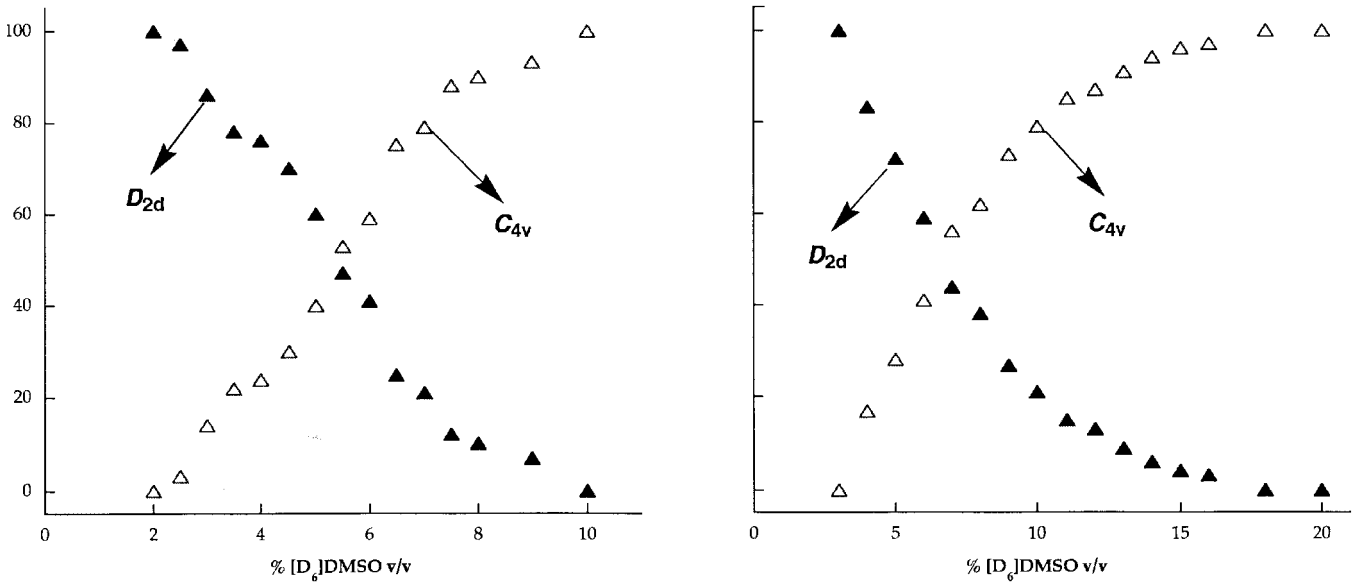


Figure 5. The NMR titration curves for compounds **3b** (left) and **4b** (right) in [$D_{10}$]*p*-xylene with [$D_6$]DMSO added in increments at $295 \pm 1$ K. The ratios $D_{2d}/C_{4v}$ were obtained by integration of the methine ($CH_a$) triplets.

Accordingly, a dynamic conformational equilibrium—*folding* and *unfolding*—takes place. At least two processes are involved. First, dissociation of the dimer to a monomeric kitelike structure occurs. Then, a subsequent $C_{2v}-C_{4v}$ equilibrium takes place.

In the absence of hydrogen bonding, the $C_{2v}-C_{4v}$ interconversion for the structures related to **3** and **4** requires an activation energy of $\approx 10-12$ kcal mol$^{-1}$.[6] With eight cooperative hydrogen bonds, this process must require significantly more energy. In the case of the 2′-methylated molecules, even at 70% v/v of [$D_6$]DMSO in $CDCl_3$ the dimeric velcraplex **9·9** is not completely dissociated into its monomer! The monomeric **9** however does not interconvert to the $C_{4v}$ conformer.

The vase $C_{4v}$ conformers **3a, b** and **4a, b** doubtlessly accommodate solvent/guest molecules in their internal cavity, whereas their kite $C_{2v}$ conformers and the dimeric velcra-

plexes do not posses a cavity of any size. The conformational switch results in significant reorganization of the solution: the large $C_{2v}$ surface orients many solvent molecules, whereas the $C_{4v}$ cavity is, in principle, able to trap a few of the solvent molecules in its interior (Figure 6). The dimensions of vase-like cavitands **3a, b** and **4a, b** are 8 Å × 11 Å and 8 Å × 14 Å, respectively; the latter one is among the largest known for a monomeric, open-ended molecule.[11] Molecular modeling[9] accommodates four molecules of $CHCl_3$, or three molecules of benzene or toluene in their interior. To date, no strong complexation with simple aromatic and aliphatic compounds has been detected in [$D_6$]DMSO/[$D_{10}$]*p*-xylene mixtures. Even so, the effect of solvation on the cavities was readily detected: solvent(guest)-induced $^1$H NMR shifts of up to 0.2 ppm were observed for the protons on the resorcinarene skeleton and the walls. Apparently, rapid solvent–guest exchange takes place in the open-ended cavitands **3a, b** and **4a, b**, when no seam of hydrogen bonds is available to stabilize the vase form. This behavior is similar to that observed by Dalcanale et al. for quinoxaline-based cavitands also lacking hydrogen bonds.[7, 8]

## Conclusion

A new generation of self-folding cavitands has been prepared. These can switch conformations and their behavior is due to intermolecular hydrogen bonding. A highly extended surface can now be reorganized into a deep cavity in a controlled way—by changing the solvent polarity (Scheme 1 and Figure 6 ).

The high kinetic and thermodynamic stability of the $D_{2d}$ dimers—velcrands with snaps—stabilized by hydrogen bonding, van der Waals interactions, and solvophobic forces directly points at their applications for the formation of noncovalent polymers.[12] We are currently exploring these possibilities.

## Experimental Section

**General:** Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. $^1$H NMR (600 MHz) and $^{13}$C NMR (151 MHz) spectra were recorded on a Bruker DRX-600 spectrometers. The chemical shifts were measured relative to residual non-deuterated solvent resonances. Fast atom bombardment (FAB) mass spectra were obtained with a VG ZAB-VSE double focusing high-resolution mass spectrometer equipped with a cesium ion gun; *m*-nitrobenzyl alcohol (NBA) was used as a matrix. For high-resolution mass spectral data (HRMS-FAB), for compounds with molecular weight $\leq$500, the measured masses always agreed to $\leq$5 ppm with the calculated values. For compounds with significantly higher molecular weight ($\geq$2000), slightly lower resolution ($\leq$10 ppm) was achieved.[13] Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry experiments were performed on a PerSeptive Biosystems Voyager-Elite mass spectrometer with delayed extraction, using 2,5-dihydroxybenzoic acid (DHB) as a matrix. FTIR spectra were recorded on a Perkin Elmer Paragon 1000 PC FT-IR spectrometer. Silica gel chromatography was performed with Silica Gel 60 (EM Science or Bodman, 230–400 mesh). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under a dry nitrogen atmosphere. Compounds **1a–c**[5] and **8**[8] were synthesized in accord with the literature protocols. Molecular modeling was performed using the Amber* force field in the MacroModel 5.5 program.[9]

**5,6-Dichloropyrazine-2,3-dicarboxylic acid dichloride**: 5,6-Dichloropyrazine-2,3-dicarboxylic acid anhydride[6c] (876 mg, 4.0 mmol) and $PCl_5$

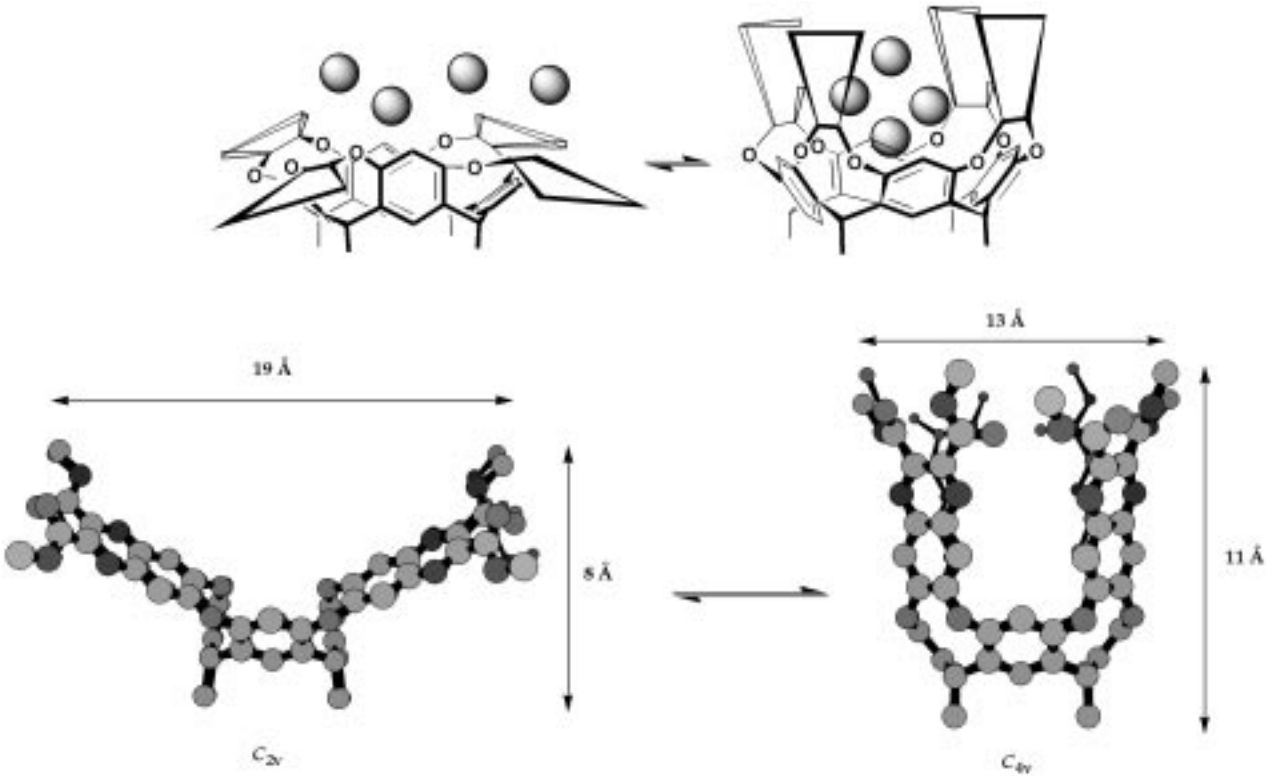


Figure 6. Top: solvent reorganization upon folding (cartoon representation). Bottom: energy-minimized structures[9] of **4** in the $C_{2v}$ and $C_{4v}$ conformations, with the approximate dimensions. The alkyl chains and the CH bonds have been omitted for clarity.



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(886 mg, 4.3 mmol) were heated at 170 °C for 1 h. The reaction mixture was cooled and the $POCl_3$ formed during the reaction was removed under vacuum. The dark residue was distilled under vacuum using a kugelrhor apparatus (≈1 mmHg/170–200 °C) to yield the title compound as a colorless oil (900 mg, 3.3 mmol; 82 %). The compound was used without further purification.

**5,6-Dichloropyrazine-2,3-dioctyl carboxamide (5)**: To a rapidly stirred mixture of $K_2CO_3$ (2.07 g, 15.0 mmol), water (15 mL), EtOAc (15 mL), and *n*-octylamine (1.07 mL, 6.5 mmol) at room temperature was added a solution of the diacid chloride above (900 mg, 3.3 mmol) in EtOAc (2 mL) over a period of 5 min. The resulting biphasic mixture was stirred for 40 min at room temperature. The organic layer was then separated, washed with brine (20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum to yield a yellow solid (1.36 g, 2.9 mmol; 89 %) that was pure enough to be carried on to the next step. M.p. 147–149 °C; $^1$H NMR ($CDCl_3$): $\delta = 7.12$ (t, $^3J$(H,H) = 5 Hz, 2H), 3.41 (q, $^3J$(H,H) = 7 Hz, 4H), 1.61 (m, 4H), 1.35–1.25 (m, 20H), 0.86 (t, $^3J$(H,H) = 7 Hz, 6H); $^{13}$C NMR ($CDCl_3$): $\delta = 162.77$, 147.09, 144.68, 40.43, 32.02, 29.44, 27.20, 22.95, 22.86, 14.38, 14.29; FTIR (film): $\tilde{\nu} = 3418$, 3277, 2928, 2854, 1677, 1530, 908, 733 cm$^{-1}$; HRMS-FAB: *m/z*: 459.2309 [*M*+H$^+$] (calcd for $C_{22}H_{36}Cl_2N_4O_2H$ 459.2294).

**Octaamide cavitand 3a**: To a solution of octol **1a** (55 mg, 0.10 mmol) and **5** (207 mg; 0.45 mmol) in anhydrous DMF (5 mL) was added anhydrous $K_2CO_3$ (138 mg, 1.00 mmol). The resulting solution was stirred for 72 h at room temperature, during which time a suspension was formed. The solids were filtered, washed thoroughly with water, and chromatographed on silica gel (3:2 v/v hexanes:EtOAc as eluent). The desired compound was isolated as a white solid (103 mg, 0.05 mmol; 50 %). M.p. > 270 °C; $^1$H NMR ($CDCl_3$): $\delta = 7.80$ (s, 4H), 7.55 (s, 4H), 7.18 (s, 2H), 7.13 (s, 2H), 6.56 (s, 2H), 6.30 (s, 2H), 3.68–3.62 (m, 8H), 3.53–3.52 (m, 4H), 3.51–3.49 (m, 4H), 3.29–3.27 (m, 4H), 1.73–1.29 (m, 108H), 0.92–0.87 (m, 24H); $^{13}$C NMR ($CDCl_3$): $\delta = 163.37$, 162.97, 152.45, 150.55, 149.63, 145.28, 142.17, 139.12, 134.23, 130.42, 127.75, 121.20, 116.79, 109.57, 40.47, 40.24, 31.94, 31.90, 31.70, 31.44, 29.67, 29.58, 29.51, 29.36, 29.29 (br), 28.71, 27.59, 27.34, 27.15, 22.68, 22.65, 22.58; FTIR (benzene): $\tilde{\nu} = 3400$, 3286, 2925, 2854, 1656, 1542, 1524, 1405, 1335, 890 cm$^{-1}$; MALDI-MS: *m/z*: 2092 [*M*+H]$^+$ (calcd for $C_{120}H_{168}N_{16}O_{16}H$ 2091.8); HRMS-FAB: *m/z*: 2222.1685 [*M*+Cs]$^+$ (calcd for $C_{120}H_{168}N_{16}O_{16}Cs$ 2222.1879).

**Octaamide cavitand 3b**: Prepared as described for **3a** using resorcinarene **1b** (110 mg, 0.10 mmol), **5** (207 mg, 0.45 mmol), anhydrous DMF (5 mL), and anhydrous $K_2CO_3$ (138 mg, 1.00 mmol). Compound **3b** was purified by chromatography (78:22 v/v hexanes:EtOAc as eluent). The product was obtained as a pale yellow solid (98 mg, 0.04 mmol; 40 %). M.p. 225–230 °C; $^1$H NMR ($CDCl_3$): $\delta = 7.79$ (t, $^3J$(H,H) = 5 Hz, 4H), 7.39 (t, $^3J$(H,H) = 5 Hz, 4H), 7.17 (s,2H), 7.03 (s,2H), 6.51 (s, 2H), 6.20 (s, 2H), 3.64–3.61 (m, 8H), 3.55–3.50 (m, 4H), 3.45–3.40 (m, 4H), 3.30–3.26 (m, 4H), 1.94–1.18 (m, 176H), 0.92–0.86 (m, 36H); $^1$H NMR ([D$_8$]toluene): $\delta = 9.76$ (s, 4H), 7.87 (s, 2H), 7.37 (s, 2H), 7.20 (s, 2H), 7.00 (s, 4H), 6.57 (s, 2H), 3.99–3.97 (m, 4H), 3.94–3.91 (m, 8H), 3.69–3.67 (m, 4H), 3.39–3.36 (m, 4H), 2.00–1.19 (m, 176H), 1.01–0.89 (m, 36H); $^1$H NMR ([D$_{10}$]*p*-xylene): $\delta = 9.35$ (t, $^3J$(H,H) = 5 Hz, 4H), 7.87 (s, 2H), 7.51 (s, 4H), 7.23 (s, 2H), 7.16 (s, 2H), 6.50 (s, 2H), 3.87–3.83 (m, 12H), 3.70–3.68 (m, 4H), 3.38–3.36 (m, 4H), 2.05–1.10 (m, 176H), 1.00–0.95 (m, 36H); $^1$H NMR ([D$_6$]benzene): $\delta =$ 9.98 (s, 4H), 7.85 (s, 2H), 7.36 (s, 2H), 7.20 (s, 2H), 6.84 (s, 4H), 6.55 (s, 2H); 3.97–3.94 (m, 8H), 3.89–3.87 (m, 4H), 3.65–3.63 (m, 4H), 3.37–3.35 (m, 4H), 2.15–2.09 (m, 8H), 1.96–1.89 (m, 4H), 1.78–1.70 (m, 4H), 1.67–1.64 (m, 8H), 1.45–1.05 (m, 152H), 0.95–0.90 (m, 36H); $^{13}$C NMR ([D$_{10}$]*p*-xylene + 12 % v/v [D$_6$]DMSO): $\delta = 164.03$, 153.51, 151.20, 144.08, 138.02, 126.66, 118,08, 33.02, 32.89, 30.82, 30.76, 30.71, 30.66, 30.47, 30.40, 30.36, 28.86, 28.29, 23.60, 23.57, 20.93, 14.77; FTIR (toluene): $\tilde{\nu} = 3407$, 3292, 1657, 1404, 905 cm$^{-1}$; MALDI-MS: *m/z*: 2653 [*M*+H$^+$] (calcd for $C_{160}H_{248}N_{16}O_{16}H$ 2652.9), 5307 [$M_2$+H$^+$] (calcd for $C_{320}H_{496}N_{32}O_{32}H$ 5304.7); HRMS-FAB: *m/z*: 2782.8399 [*M*+Cs$^+$] (calcd for $C_{160}H_{248}N_{16}O_{16}Cs$ 2782.8139).

***n*-Methyl octacarboxamide cavitand 4a**: To a flask containing octaester **8** (20 mg, 9.2 μmol) was added methylamine (4 mL of a 2.0 M solution in MeOH). The flask was sealed and the mixture was stirred at room temperature for 24 h. The system was then heated in an oil bath at 70 °C for 3 h. After cooling, the volatiles were removed under vacuum and the residue was purified by preparative thin-layer chromatography (PTLC, plate thickness 0.5 mm; 9:1 v/v EtOAc:MeOH as eluent). The title compound was obtained as a white solid (4 mg, 1.9 μmol; 21 %). M.p. > 250 °C; $^1$H NMR ($CDCl_3$): $\delta = 7.99$ (s, 4H), 7.51 (s, 4H), 7.40 (s, 4H), 7.17 (s, 4H), 7.10 (s, 2H), 7.05 (s, 2H), 6.81 (s, 2H), 6.24 (s, 2H), 3.92 (t, $^3J$(H,H) = 7 Hz, 4H), 3.27 (s, 12H), 3.17 (s, 12H), 1.88–1.79 (m, 8H), 1.26–1.05 (m, 72H), 0.83 (t, $^3J$(H,H) = 7 Hz, 12H); $^1$H NMR ($CDCl_3$ + 5 % v/v [D$_6$]DMSO): $\delta = 8.11$ (s, 4H), 7.61 (s, 4H), 7.40 (s, 2H), 7.31 (s, 4H), 6.98 (s, 4H), 6.95 (s, 2H), 6.70 (s, 2H), 6.14 (s, 2H), 3.81 (t, $^3J$(H,H) = 7 Hz, 4H), 3.13 (s, 12H), 3.04 (s, 12H), 1.90–1.75 (m, 8H), 1.17–0.96 (m, 72H), 0.72 (t, $^3J$(H,H) = 7 Hz, 12H); $^1$H NMR ([D$_6$]DMSO, 350 K): $\delta = 8.29$ (s, 8H), 8.23 (br., 8H), 7.58 (s, 4H), 7.36 (s, 4H), 4.79 (br., 4H), 2.85 (d, $^3J$(H,H) = 5 Hz, 24H), 2.31–2.27 (m, 8H), 1.29–1.17 (m, 72H), 0.86 (t, $^3J$(H,H) = 7 Hz, 12H); $^{13}$C NMR ([D$_6$]DMSO, 350 K): $\delta = 164.63$, 153.20, 152.35, 146.55, 139.55, 138.00, 132.60, 124.45, 119.76, 30.73, 30.10, 28.50, 28.39 (br), 28.10, 26.58, 25.33, 21.46, 13.20; FTIR (benzene): $\tilde{\nu} = 3409$, 3303, 2925, 2845, 1674, 1396, 1220, 850, 806 cm$^{-1}$; MALDI-MS: *m/z*: 2069 [*M*+H]$^+$ (calcd for $C_{120}H_{144}N_{16}O_{16}H$ 2068); HRMS-FAB: *m/z*: 2198.0121 [*M*+Cs]$^+$ (calcd for $C_{120}H_{144}N_{16}O_{16}Cs$ 2198.0001).

***n*-Butyl octacarboxamide cavitand 4b**: A 25 mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar was charged with octaester **8** (50 mg, 23.0 μmol), absolute EtOH (10 mL), and *n*-butylamine (1 mL, 10.0 mmol). The resulting mixture was heated under reflux while the consumption of the starting material was monitored by TLC (3:2 v/v hexanes:EtOAc). The reaction was deemed complete after 19 h. The volatiles were removed under vacuum and the residue was chromatographed (3:2 v/v hexanes/EtOAc as eluent). The product was obtained as a yellowish solid (27 mg, 11.3 μmol; 49 %). M.p. > 270 °C; $^1$H NMR ([D$_{10}$]*p*-xylene + 3 % v/v [D$_6$]DMSO, $C_{2v}$): $\delta = 8.88$ (s, 4H), 8.39 (s, 4H), 8.26 (s, 2H), 7.85 (s, 4H), 7.49 (s, 4H), 7.33 (s, 2H), 7.28 (s, 2H), 6.62 (s, 2H), 4.31–4.29 (m, 4H), 3.77–3.75 (m, 4H), 3.67–3.65 (m, 8H), 3.57–3.55 (m, 4H), 2.20–2.10 (m, 8H), 1.88–1.84 (m, 32H), 1.67–1.62 (m, 8H), 1.57–1.52 (m, 8H), 1.29–1.09 (m, 68H), 1.05 (t, $^3J$(H,H) = 7 Hz, 12H), 0.91 (t, $^3J$(H,H) = 7 Hz, 12H); $^1$H NMR ([D$_{10}$]*p*-xylene + 20 % v/v [D$_6$]DMSO, $C_{4v}$): $\delta = 8.74$ (s, 8H), 8.51 (t, $^3J$(H,H) = 5 Hz, 8H), 8.06 (s, 4H), 7.79 (s, 4H), 5.59 (m, 4H), 3.49–3.46 (m, 16H), 2.53–2.48 (m, 8H), 1.70–1.66 (m, 16H), 1.48–1.44 (m, 32H), 1.29–1.25 (m, 56H), 0.99 (t, $^3J$(H,H) = 7 Hz, 24H), 0.90 (t, $^3J$(H,H) = 7 Hz, 12H); $^{13}$C NMR ([D$_6$]DMSO + 30 % v/v $CDCl_3$): $\delta = 164.51$, 153.41, 152.58, 147.02, 138.30, 132.86, 125.00, 120.16, 113,10, 38.67, 34.42, 31.28, 31.00, 30.54, 29.13, 28.99, 28.73, 27.05, 22.06, 19.60, 13.81, 13.55; FTIR ($CDCl_3$): $\tilde{\nu} = 3429$, 3304, 2959, 2929, 2856, 1671 cm$^{-1}$; MALDI-MS: *m/z*: 2405 [*M*+H]$^+$ (calcd for $C_{144}H_{192}N_{16}O_{16}H$ 2404.2), 4811 [$M_2$+H]$^+$ (calcd for $C_{288}H_{384}N_{32}O_{32}H$ 4807.5); HRMS-FAB: *m/z*: 2534.3612 [*M*+Cs]$^+$ (calcd for $C_{144}H_{192}N_{16}O_{16}Cs$ 2534.3757).

**Dimethyl 6,7-dimethyl-2,3-quinoxalinedicarboxylate**: 4,5-Dimethyl-phenylenediamine (136 mg, 1.00 mmol) was dissolved in absolute EtOH (5 mL) and diethyl-2,3-dioxosuccinate (404 mg, 2.00 mmol) was added dropwise by syringe. The resulting mixture was stirred for 2 h at room temperature, then the solvent was evaporated under vacuum. The residue was chromatographed (4:1 v/v hexanes/EtOAc as eluent) to give the title compound as a white solid (196 mg, 0.65 mmol; 65 %). M.p. 119–121 °C; $^1$H NMR ($CDCl_3$): $\delta = 7.95$ (s, 2H), 4.51 (q, $^3J$(H,H) = 7 Hz, 4H), 2.50 (s, 6H), 1.44 (t, $^3J$(H,H) = 7 Hz, 6H); $^{13}$C NMR ($CDCl_3$): $\delta = 165.02$, 143.71, 143.22, 140.33, 128.61, 62.63, 20.55, 14.16; FTIR ($CH_2Cl_2$): $\tilde{\nu} = 2977$, 2933, 1735, 1550, 1480, 1286, 1198, 1137, 1071, 872 cm$^{-1}$; HRMS-FAB: *m/z*: 303.1347 [*M*+H]$^+$ (calcd for $C_{16}H_{18}N_2O_4H$ 303.1345).

***N2*,*N3*-Dibutyl-6,7-dimethyl-2,3-quinoxalinedicarboxamide 12**: Dimethyl 6,7-dimethyl-2,3-quinoxalinedicarboxylate (100 mg, 0.33 mmol) was suspended in absolute EtOH (4 mL) and then *n*-butylamine (200 μL, 2.00 mmol) was added. The mixture was heated under reflux for 41 h. The volatiles were removed under vacuum and the remaining solid triturated with EtOH to give the product as a beige solid (80 mg, 0.22 mmol; 67 %). M.p. 147–149 °C; $^1$H NMR ($CDCl_3$): $\delta = 7.70$ (s, 2H), 7.16 (t, $^3J$(H,H) = 5 Hz, 2H), 3.52 (q, $^3J$(H,H) = 7 Hz, 4H), 2.46 (s, 6H), 1.67 (quint, $^3J$(H,H) = 7 Hz, 4H), 1.45 (sext, $^3J$(H,H) = 7 Hz, 4H), 0.96 (t, $^3J$(H,H) = 7 Hz, 6H); $^1$H NMR ([D$_8$]toluene): $\delta = 7.62$ (s, 2H), 6.67 (s, 2H), 3.39 (q, $^3J$(H,H) = 7 Hz, 4H), 2.03 (s, 6H), 1.48–1.44 (m, 4H), 1.34–1.29 (m, 4H), 0.88 (t, $^3J$(H,H) = 7 Hz, 6H); $^{13}$C NMR ($CDCl_3$): $\delta = 165.18$, 158.40, 145.61, 142.50, 139.46, 128.00, 39.66, 31.42, 20.42, 20.16, 13.75; FTIR ($CDCl_3$): $\tilde{\nu} =$ 3434, 2961, 2934, 2875, 1672, 1527, 1483; HRMS-FAB: *m/z*: 357.2294 [*M*+H]$^+$ (calcd for $C_{20}H_{28}N_4O_2H$ 357.2291)

**Dimethyl 5,6-dichloropyrazine-2,3-dicarboxylate (6)**: To a solution of 5,6-dichloropyrazine-2,3-dicarboxylic acid (1.19 g, 5.00 mmol) in MeOH

(15 mL), concentrated $H_2SO_4$ (0.5 mL) was added dropwise. The resulting mixture was heated under reflux for 17 h. Upon cooling, the mixture was poured onto ice water and extracted with EtOAc. The organic layer was washed with diluted aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, and filtered. After evaporation, **6** was obtained as a thick colorless oil (1.09 g, 4.11 mmol; 82%). $^1$H NMR ($CDCl_3$): $\delta =$ 3.98 (s, 6H); $^{13}$C NMR ($CDCl_3$): $\delta =$ 162.86, 148.82, 141.80, 53.74; FTIR (film): $\tilde{\nu} =$ 3009, 2956, 2855, 1751, 1522, 1440, 1264, 1176, 1097, 961, 913, 837, 815, 785 cm$^{-1}$; HRMS-FAB: *m/z*: 264.9713 $[M+H]^+$ (calcd for $C_8H_6Cl_2N_2O_4H$ 264.9783).

**Cavitand 7**: Anhydrous $K_2CO_3$ (690 mg, 5.0 mmol) was added to a solution of resorcinarene **1b** (552 mg, 0.50 mmol) and diester **6** (600 mg, 2.25 mmol) in anhydrous DMF (25 mL). The mixture was stirred at room temperature for 46 h, then poured onto acidic water (pH $\approx$1). The solid was filtered, rinsed with water, and dried under vacuum. The residue was chromatographed (3:1 v/v hexanes:EtOAc as eluent) and the title compound was obtained as a white solid (185 mg, 0.10 mmol; 20%). M.p. 155–158 °C ; $^1$H NMR ($CDCl_3$, 330 K): $\delta =$ 7.20 (s, 4H), 6.83 (s, 4H), 3.98 (s, 24H), 3.88 (t, $^3J$(H,H) = 7 Hz, 4H), 2.10–2.05 (m, 8H), 1.32–1.27 (m, 72H), 0.92–0.90 (m, 12H); $^1$H NMR ([D$_6$]benzene): $\delta =$ 7.87 (s, 4H), 7.37 (s, 4H), 5.25 (br., 4H), 3.62 (s, 24H), 2.16–2.14 (m, 8H), 1.40–1.20 (m, 72H), 0.95 (t, $^3J$(H,H) = 7 Hz, 12H); $^{13}$C NMR ([D$_6$]benzene): $\delta =$ 164.00, 153.25, 152.55, 141.17, 135.97, 124.33, 118.57, 53.17, 35.80, 33.00, 32.75, 30.54, 30.52, 30.50, 30.39, 30.31, 30.25, 28.33, 23.51, 14.75; FTIR ($CDCl_3$): $\tilde{\nu} =$ 2955, 2928, 2855, 1742, 1601, 1548, 1482, 1446, 1418, 1342, 1277, 1215, 1193, 1145 cm$^{-1}$; HRMS-FAB: *m/z*: 2005.8279 $[M+Cs]^+$ (calcd for $C_{104}H_{128}N_8O_{24}Cs$ 2005.8096).

**Cavitand 9**: Anhydrous $K_2CO_3$ (138 mg, 1.00 mmol) was added to a solution of resorcinarene **1c** (105 mg, 0.10 mmol) and **5** (207 mg, 0.45 mmol) in anhydrous DMF (5 mL). The mixture was stirred at room temperature for 46 h, then poured onto acidic water (pH about 1). The solid was filtered, rinsed with water, and dried under vacuum. The residue was chromatographed (9:1 v/v hexanes:EtOAc as eluent) and the title compound was obtained as a white solid (53 mg, 0.02 mmol; 20%). M.p. >250 °C; $^1$H NMR ($CDCl_3$): $\delta =$ 8.67 (br., 4H), 7.40 (br., 4H), 6.91 (s, 2H), 5.99 (s, 2H), 3.66–3.62 (m, 4H), 3.54–3.51 (m, 4H), 3.50–3.46 (m, 4H), 3.38–3.30 (m, 8H), 2.46 (s, 6H), 2.17–2.05 (m, 8H), 1.87–1.70 (m, 16H), 1.69 (s, 6H), 1.43–1.14 (m, 136H), 0.89–0.74 (m, 36H); $^1$H NMR ([D$_6$]benzene, 330 K): $\delta =$ 9.52 (s, 4H), 7.22 (s, 2H), 6.80 (s, 4H), 6.36 (s, 2H), 3.99–3.94 (m, 8H), 3.73–3.70 (m, 8H), 3.35–3.40 (m, 4H), 2.99 (s, 6H), 2.40 (s, 6H), 2.10–1.90 (m, 12H), 1.85–1.80 (m, 4H), 1.70–1.55 (m, 16H), 1.45–1.10 (m, 136H), 0.96–0.90 (m, 36H); $^{13}$C NMR ($CDCl_3$): $\delta =$ 164.10, 163.03, 151.24, 150.02, 149.88, 144.75, 142.81, 139.38, 134.33, 129.64, 126.66, 122.35, 119.02, 118.51, 40.59, 40.53, 37.83, 32.33, 31.92, 31.90, 31.86, 29.92, 29.65, 29.58, 29.49, 29.43, 29.33, 29.24, 29.03, 27.41, 27.22, 27.14, 22.71, 22.68, 22.65, 14.09, 14.08, 11.31, 11.02; FTIR ($CH_2Cl_2$): $\tilde{\nu} =$ 3418, 3259, 2925, 2854, 1652, 1559, 1546, 1405, 1071 cm$^{-1}$; MALDI-MS: *m/z*: 2593 $[M+H]^+$ (calcd for $C_{156}H_{240}N_{16}O_{16}H$ 2594.9), 5187 $[M_2+H]^+$ (calcd for $C_{312}H_{480}N_{32}O_{32}H$ 5188.7); HRMS-FAB: *m/z*: 2726.7765 $[M+Cs]^+$ (calcd for $C_{156}H_{240}N_{16}O_{16}Cs$ 2726.7513).

**Cavitand 11**: The corresponding octaamino compound[4] (1.30 g, 0.89 mmol) was dissolved in EtOH (30 mL) and to the resulting solution, diethyl-2,3-dioxosuccinate (1.02 g, 5.05 mmol) was added dropwise. Within 5 min of the addition, a precipitate formed. The mixture was stirred for 12 h at room temperature. The yellow solid was filtered, washed with EtOH, and dried under vacuum. Yield = 1.48 g (0.69 mmol; 78%). M.p. >250 °C; $^1$H NMR ($CDCl_3$): $\delta =$ 8.04 (s, 4H), 7.73 (s, 4H), 7.00 (s, 2H), 6.06 (s, 2H), 4.54 (q, $^3J$(H,H) = 7 Hz, 8H), 4.50 (q, $^3J$(H,H) = 7 Hz, 8H), 3.99–3.96 (m, 4H), 2.52 (s, 6H), 2.39 (s, 6H), 1.99–1.90 (m, 8H), 1.48–1.42 (m, 24H), 1.25–1.10 (m, 56H), 0.85 (t, $^3J$(H,H) = 7 Hz, 12H); $^{13}$C NMR ($CDCl_3$): $\delta =$ 164.81, 164.54, 153.73, 153.56, 151.08, 150.95, 144.28, 142.18, 140.10, 137.82, 134.43, 130.02, 124.26, 122.48, 121.17, 118.85, 118.12, 115.33, 62.76, 62.59, 36.75, 31.79, 31.66, 29.43, 29.39, 29.19, 26.88, 22.61, 14.10, 14.05, 11.21, 10.93; FTIR ($CH_2Cl_2$): $\tilde{\nu} =$ 2925, 2854, 1740, 1603, 1480, 1203, 1018; HRMS-MALDI-FTMS: *m/z*: 2152.0012 $[M+Na]^+$ (calcd for $C_{124}H_{144}N_8O_{24}Na$ 2152.0190).

**Octacarboxamide cavitand 10**: Octaester **11** (50 mg, 23.4 μmol) was suspended in EtOH (10 mL) and *n*-butylamine (1 mL, 10 mmol) was added. The mixture was heated under reflux for 18 h after which time the volatiles were removed under vacuum. The residue was purified by PTLC (plate thickness 1 mm; 95:5 v/v $CH_2Cl_2$:MeOH as eluent). The title compound was obtained as a pale yellow solid (16 mg, 6.8 μmol; 29%). M.p. >250 °C; $^1$H NMR ([D$_6$]benzene): $\delta =$ 8.66 (t, $^3J$(H,H) = 5 Hz, 4H), 7.88 (s, 4H), 7.54 (s, 4H), 7.40 (s, 2H), 6.55 (s, 2H), 6.45 (t, $^3J$(H,H) = 6 Hz, 4H), 4.61–4.59 (m, 4H), 3.89–3.48 (m, 16H), 3.40 (s, 6H), 2.63 (s, 6H), 2.21–1.98 (m, 8H), 1.85–1.52 (m, 16H), 1.26–1.13 (m, 72H), 1.02–0.89 (m, 36H); FTIR ($CH_2Cl_2$): $\tilde{\nu} =$ 3418, 3295, 2960, 2925, 2854, 1665, 1528, 1480, 1374, 1216, 1057 cm$^{-1}$; MALDI-MS: *m/z*: 2347 $[M]^+$ (calcd for $C_{140}H_{184}N_{16}O_{16}$ 2347.1), 4694 $[M]_2^+$ (calcd for $C_{280}H_{368}N_{32}O_{32}$ 4694.2); HRMS-FAB: *m/z*: 2478.3285 $[M+Cs]^+$ (calcd for $C_{140}H_{184}N_{16}O_{16}Cs$ 2478.3131).

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