A Self-Assembled Cylindrical Capsule: New Supramolecular Phenomena through Encapsulation

Steffi K. Körner, Fabio C. Tucci, Dmitry M. Rudkevich, Thomas Heinz, and Julius Rebek, Jr.*[a]

Abstract: The synthesis and spectroscopic characterization of self-assembled cylindrical capsule **1a·1a** of nanometer dimensions is described. Encapsulation studies of large organic guest molecules were performed by using ^{1}H NMR sprectroscopy in [D_{12}]mesitylene solution. In addition to the computational (MacroModel 5.5, Amber* force field) analysis of the capsule's shape and geometry, an experimental approach towards estimation of the internal cavity dimensions is described. This involves using series of homologous molecular "rulers" (e.g. aromatic amides **5a–i**). The available space inside the capsule **1a·1a** can be estimated as 5.7 × 14.7 Å (error ±0.2 Å) with this technique. Dibenzoyl peroxide is readily encapsulated in [D_{12}]mesitylene and was shown to be stable to decomposition for at least three days at 70 °C inside the capsule. Moreover, **1a·1a** prevents the encapsulated peroxide from oxidizing Ph_3P or diphenyl carbazide present in solution. The normal chemical reactivity of the peroxide is restored by release from the capsule by DMF, a solvent that competes for the hydrogen bonds that hold the capsule together. The protection and release of encapsulated species augurs well for the application of capsules in catalysis and delivery.

Keywords: encapsulation · hydrogen bonding · molecular recognition · self-assembly · supramolecular chemistry

Introduction

The studies of molecular recognition in the last two decades has resulted in vast numbers of synthetic receptors for small molecule targets. The recognition complexes, held together by weak intermolecular forces, formed and dissipated rapidly and were characterized by a frequent change of partners.

As the field matured, the systems became increasingly sophisticated: receptors were tailored to contact larger fractions of the targets' surfaces, and completely surrounding the target became a realistic goal. Cryptands and spherands achieved this for ionic targets,[1] while cryptophanes and carcerands did the same for neutral molecules.[2] The latter, as carceplexes, allowed no change of partners since strong, covalent bonds held molecules within molecules.

Encapsulation complexes of self-assembled dimers are the most recent expressions of molecules-within-molecules.[3] They form reversibly on time scales of 10^{-3} to 10^3 s, somewhere near the middle of the spectrum defined by diffusion complexes at one end ($\approx 10^{-10}$ s) and carceplexes on the other ($\approx 10^{10}$ s). Recent developments have led to self-assembled capsules with cavities large enough to bind sizeable organic guests or even more than one guest molecule.[4, 5] These nanometric chambers are employed for bimolecular reactions and offer some promise in catalysis. Here we describe experimental details of the synthesis and characterization of an elongated capsule **1a·1a** (Figure 1) and introduce probes that reveal the behavior of larger guests *inside*—their dimensions and stability. Thereafter we describe pairwise interactions of smaller guests within the same capsule.

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Results and Discussion

Planning the synthesis of self-assembled capsule 1a·1a: Elsewhere we have dwelt on the need for molecular "curvature" for the synthesis of closed-shell assemblies and the structural modules that can provide it.[3] For the present case, we found ourselves in the unusual position of simplifying a known molecule rather than elaborating it. The perfect precedent was provided by the work of Cram on cavitands and velcrands,[6] derived from resorcinarenes (Scheme 1). The seemingly passive eight methyl groups in structure **1c** had been positioned with care and all are performing their functions: the *C*-methyl groups help stabilize the kitelike conformation **1c** and the *N*-methyl groups prevent aggrega-

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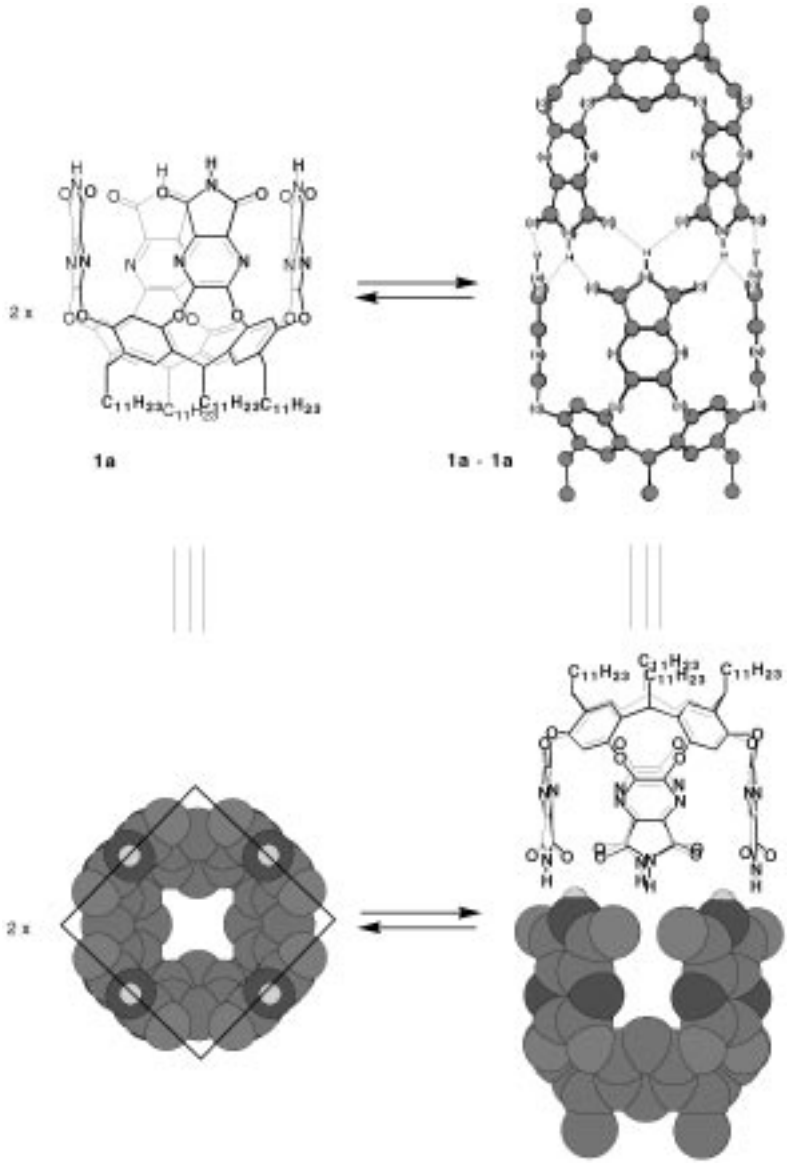

Figure 1. Self-assembly and structure of capsule **1** with two presentations of cavitand **1a** and the capsule. In the energy-minimized[12] (MacroModel 5.5, Amber* force field) structures, the long alkyl chains and CH hydrogens are omitted for viewing clarity. The cross-section of the molecule **1a** is a square at the pyrazine and the imide walls. The dimeric capsule is octagonal at the seam of the eight hydrogen atoms in the middle, and the capsule's shape involves two stacked square prisms rotated 45° from one another, each capped with another square pyramid also rotated at 45°.

tion through hydrogen bonding.[6b] The resulting molecule exposes large surface areas and dimerizes as a "velcrand" **1c**·**1c** through solvophobic forces.

Removal of the *C*-methyl groups was expected to permit the molecule to relax into a vaselike conformation (see, for example, **1b**, Scheme 1) and excision of the *N*-methyl groups would expose a series of hydrogen bond donors and acceptors (**1a**, Scheme 1). Because these sites are self-complementary, two such C_{4v} structures **1a** can be held together, rim-to-rim, by a seam of eight bifurcated hydrogen bonds. The result is a large "cylindrical" capsule **1a**·**1a** of nanometric dimensions (Figure 1 and Scheme 1).

Coupling of resorcinarene **2**[7] with four equivalents of 5,6-dichloropyrazine-2,3-dicarboxylic acid imide **3a** in DMF in the presence of Et_3N at 70–80 °C for 5–10 h afforded cavitand **1a** in 20–48% yield (Scheme 2). Analogously, N-methylated cavitand **1b** was prepared in 35% yield from resorcinarene **2** and 5,6-dichloropyrazine-2,3-dicarboxylic acid N-methylimide (**3b**). Imides **3a, b** were synthesized under acidic conditions by treatment of 5,6-dichloropyrazine-2,3-dicarboxylic acid anhydride with either ammonium chloride or *N*-methylammonium chloride in hot acetic anhydride. Model imide **4** was synthesized for spectroscopic comparisons from 3,5-di-*tert*-butylphenol and imide **3a**.

Spectroscopic characterization: The ^{1}H NMR spectra of **1a** in $CDCl_3$, [D_6]benzene, or [D_8]toluene show C_{4v} symmetry with one sharp set of signals for all groups of protons, and in particular a characteristic CH methine triplet at $\delta \approx 6$.[6a, 8] The spectra do not change within a 220–330 K temperature interval ([D_8]toluene, $CDCl_3$), indicating high conformational stability. The downfield N–H signals appear at $\delta > 9.5$ in noncompetitive solvents such as $CDCl_3$, [D_6]benzene, or [D_8]toluene (Table 1). In contrast, model imide **4** features its N–H resonance upfield at $\delta = 8$. The FT-IR spectrum of **1a** in $CHCl_3$ possesses exclusively a hydrogen-bonded, broad N–H stretching absorption at $\nu = 3332\ cm^{-1}$ at $\geq 3 \times 10^{-4}$ M concentrations.

According to molecular modeling (MacroModel 5.5, Amber* force field), the dimensions of capsule **1a**·**1a** are about 10 × 18 Å (from the centers of the most remote H atoms), one of the largest hydrogen-bonded capsules known.[9] The estimated volume[10] of the internal cavity is ≈460 Å^3 but its shape (see below) is unusual. Two benzene, two toluene or two $CDCl_3$ molecules fit nicely inside,[4] and we will address the occupancy of various solvents later. For the moment, the happily occupied capsule in these solvents was reluctant to take up other guests. We took advantage of the observations of Chapman and Still who first showed that a poorly accommodated solvent in a cavity could be easily replaced by a guest that fit well.[11] We have used this tactic in a number of studies where solvents too large or too small could promote encapsulation of an intended guest, even though the solvent's concentration was a hundred times greater than the guest's.

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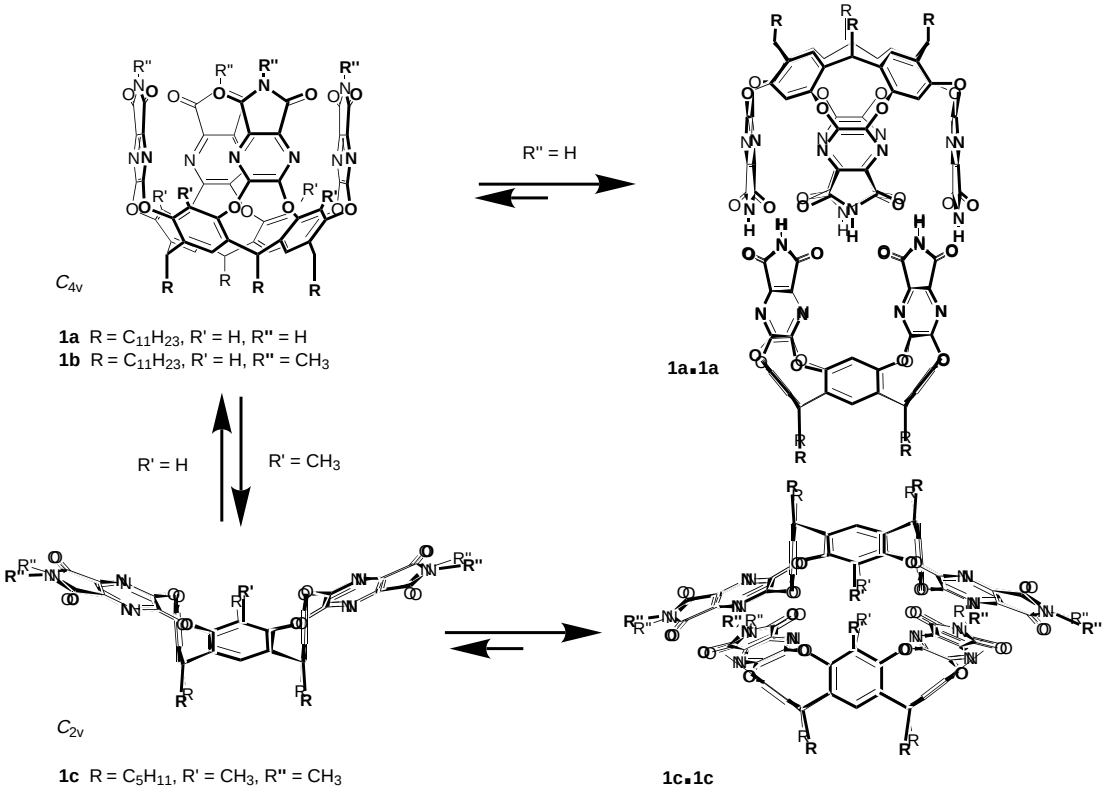
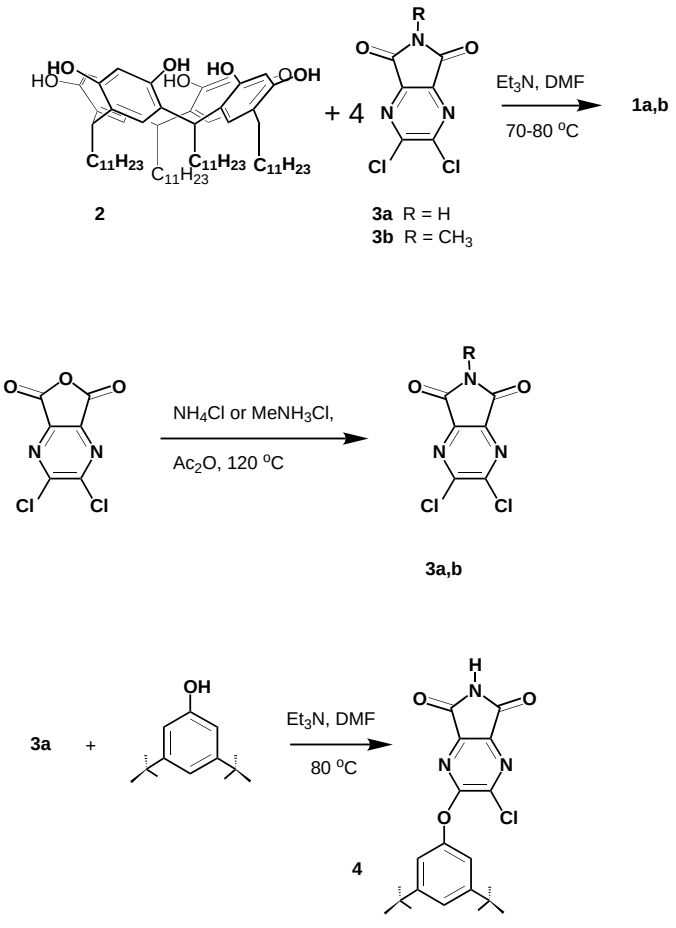


Scheme 1. Schematic representation of the $C_{4v} \rightleftharpoons C_{2v}$ conformational equilibria in cavitands **1a–c** and their dimerization.



Scheme 2. Synthesis of cavitands **1a, b** and imides **3a, b**, and **4**.

Table 1. Spectroscopic data for the imide N–H signal in **1a·1a** and **4.**[a]

Compound	Solvent	δ	$\tilde{\nu}$ [cm^{-1}][c]
1a[b]	$CDCl_3$	9.8	3332
	CD_2Cl_2	9.9	
	[D_6]benzene	10.5	
	[D_8]toluene	10.2	
	[D_{10}]-*p*-xylene	9.8	
	[D_6]DMSO	11.8[d]	
	[D_6]DMF/[D_{12}]mesitylene, 1:10	11.6[d]	
4	$CDCl_3$	7.7[e]	3416

[a] Measured at 295 K on 1×10^{-3} M solutions; estimated error $\delta = \pm 0.1$. [b] The spectra in apolar solvents are concentration independent within the range 1×10^{-4} to 2.2×10^{-2} M range. [c] In $CHCl_3$. [d] Monomeric species. [e] At 5×10^{-2} M, $\delta = 8.1$.

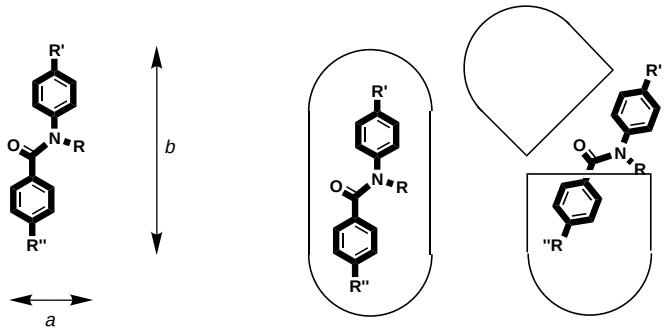
The largest deuterated solvent commercially available is [D_{12}]mesitylene (unfortunately, it is neither particularly well-deuterated nor free of other aromatic compounds), and modeling[12] suggested a tight fit in the capsule; the width of the solvent forces ruptures in the seam of the hydrogen bonds that gird the capsule. The NMR spectrum in this solvent shows assembly but a mixture of capsules, the major constituent of which is a capsule with two different halves is apparent. On more than one occasion we have been amazed at the capsule's ability to remove trace amounts of a well-fitting impurity and the occupancy of the capsule in [D_{12}]mesitylene is such an occasion. Happily, addition of guests to this solution gave clean spectra of the respective encapsulation complexes for which integration provided the stoichiometry. Accordingly, [D_{12}]mesitylene was used as a ^{1}H NMR solvent for subsequent studies.

As reported earlier,[4, 13] symmetrical guests such as bibenzyl (C_6H_5-CH_2-CH_2-C_6H_5), *p*-terphenyl (C_6H_5-C_6H_4-C_6H_5), dicyclohhexylcarbodimide, and *(E)*-4,4′-dimethylstilbene quickly (within seconds) replace the solvent(s) in the [D_{12}]mesitylene solution of **1a·1a**. The high symmetry of the capsule is restored as reflected by the ^{1}H NMR spectra. A new set of signals—shifted far upfield—emerges for the encapsulated species and integration gives a 1:1 stochiometry of the complexes. When larger guests were employed (see examples below), the capsule did not form: only [D_{12}]mesitylene aggregates were detected by ^{1}H NMR spectroscopy, and it is worthwhile to explore the questions regarding guest "size".

Space and molecular rulers: In molecular recognition the dimensions and shape of an internal cavity of synthetic receptors, cavitands, and carcerands can usually be estimated by molecular modeling or, more accurately, by X-ray crystallography. Lower technologies have also seen success as related by Cram with plaster of Paris and CPK models.[14] Depending on the program and parameters used, computer modeling can give varied results and always begs the question of where a molecule ends and space begins. Crystallographic data are not always available for the structure of interest, especially for the molecules that we have worked so hard to keep in solution. While we are delighted with Still's superbly accessible MacroModel,[12] an experimental approach was also desirable to probe how much of the space inside was available to guests. Accordingly, we used a homologous series of guests as *molecular rulers*: molecules with known and easily measurable size and shape, both of which can be progressively varied. Beginning with benzanilide, the amide nitrogen and *para* positions of the molecule were substituted with an increasing number of methylenes; that is the limit of resolution of the ruler is a CH_2 group.

The reasonably rigid *p*-[*N*-(*p*-Tolyl)]toluamide **5b** was shown to be an excellent guest for capsule **1a·1a**.[13] It is also complementary in shape and functionality and long enough to occupy a sizable fraction of the internal cavity. Intense intermolecular NOE contacts were observed between the resorcinol aromatic protons of **1a·1a** and both CH_3 groups of the encapsulated **5b**, indicating their positioning deep inside the capsule's resorcinarene terminii. Moreover, hydrogen bonding between the C(O)−NH fragment of **5b** and the seam of the capsule's imides is also likely. The width and length (e.g. *a* and *b*, Scheme 3) of amide **5b** can be estimated from molecular modeling and they are about 4.3 × 13.2 Å. Amide rulers **5a–i** were synthesized and used for the encapsulation studies (Table 2, Scheme 3, Figures 2 and 3).

The ^{1}H NMR spectra of the encapsulated guests **5b, c** and **5f** are presented in Figure 2. The large upfield shifts of the guest R′ and R″ alkyl groups ($\Delta\delta = -2$ to -4, $\Delta\delta \approx 4$) places them near the ends of capsule **1a·1a**. The aromatic signals of the encapsulated species are also seen. Interestingly, upon encapsulation of *N*-ethylated ruler **5f**, prepared from **5b** and ethyl iodide, the starting material (e.g. **5b**) was also detected inside the capsule (Figure 2). From the spectra, the ratio between **1a·5f·1a** and **1a·5b·1a** of about 1:2 was calculated. In the same sample, the concentration of **5b** in the bulk solution of **5f** was below the 600 MHz ^{1}H NMR detection limits! Again, **5b** is a much better guest than its bulkier derivative **5f**, and is removed from the solution as the complex (Figure 3).



5a R = H, R′ = CH_3, R″ = H
5b R = H, R′ = CH_3, R″ = CH_3
5c R = H, R′ = C_2H_5, R″ = CH_3
5d R = H, R′ = C_2H_5, R″ = C_2H_5
5e R = CH_3, R′ = CH_3, R″ = CH_3
5f R = C_2H_5, R′ = CH_3, R″ = CH_3
5g R = *n*-C_3H_7, R′ = CH_3, R″ = CH_3
5i R = *n*-C_4H_9, R′ = CH_3, R″ = CH_3

1a-5a-1a
1a-5b-1a
1a-5c-1a
1a-5e-1a
1a-5f-1a

1a + 5d
1a + 5g
1a + 5i

Scheme 3. Molecular rulers **5a–i** and the cartoon representation[4] of the capsule and its complexes used elsewhere in this paper.

Table 2. Calculated dimensions (*a*, *b*) of amides **5a–i**.[a]

Compound	*a* [Å]	*b* [Å]	Encapsulation
5a	4.3	12.3	+
5b	4.3	13.2	+
5c	4.3	14.7[b]	+
5d	4.3	15.7[b]	–
5e	4.5[b]	13.2	+
5f	5.7[b]	13.2	+
5g	6.8[b]	13.2	–
5i	8.0[b]	13.2	–

[a] The structures were energy-minimized by using MacroModel 5.5 with Amber* force field. MM2 and OPLS force field produced similar results within the error limits. The *a* distance for **5a–d** is the width of the aromatic ring, measured between the *ortho* protons with respect to the amide group; the C=O−H−N distance is 3.2 Å. For **5e–i**, the *a* distance was measured between the C=O oxygen atom and the most remote hydrogen atom in the N−H or N−Alk chain. The *b* distance was measured between the two most remote hydrogen atoms of the Ar−H or Ar−Alk chains. Centers of the atoms were used for the measurements. Estimated error ±0.2 Å due to the possible free rotation around C−C bonds and possible distortion inside the capsule. Only *Z* configurations of the C(O)−N bond were considered; the corresponding *E* conformers do not fit inside the capsule.[13] [b] Upper limit is given due to the possible free rotation around C−C bond and possible distortion inside the capsule.

Wider or longer amides **5d, g** and **i** were not encapsulated, only solvent-filled capsules were detected by ^{1}H NMR spectroscopy. From these experiments with amides **5a–i** (Table 2), the available space inside capsule **1a·1a** can reasonably be estimated as 5.7 × 14.7 Å (error ± 0.2 Å). This value is consistent with the poor fit of mesitylene (5.8 Å wide). Fullerenes (C_{60} and C_{70}; > 7 Å diameter) are also not complexed. When a longer guest was employed, such as *p*-quaterphenyl (C_6H_5-C_6H_4-C_6H_4-C_6H_5, 18.1 Å) only the solvent-filled capsules persisted. On the other hand, the capsule dimensions easily permit two benzene (ca. 5.0 Å length)

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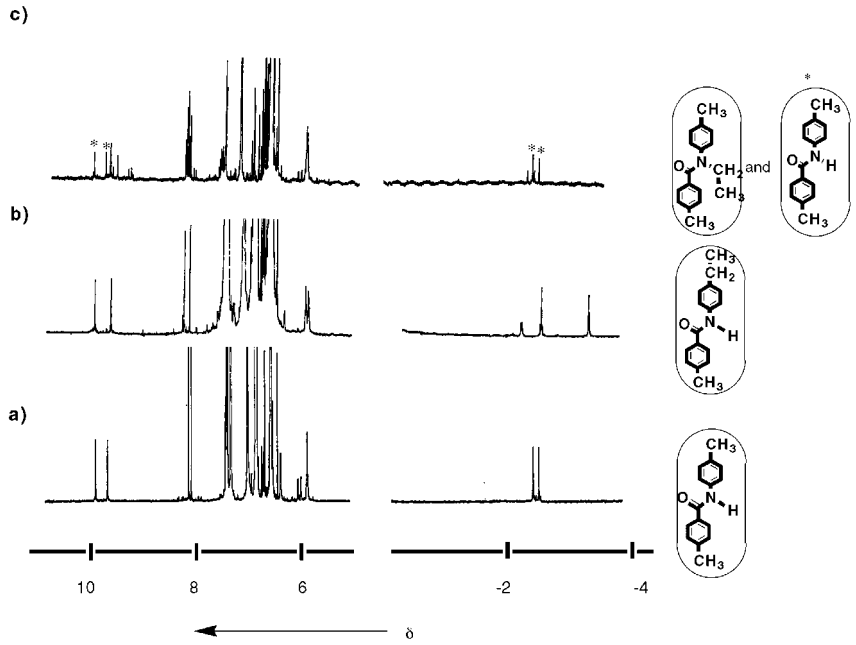

Figure 2. Portions of the ^{1}H NMR spectra in [D_{12}]mesitylene (600 MHz, 295 K): a) encapsulated anilide **5b**; b) encapsulated amide **5c**; c) encapsulated amide **5f;** the capsule containing **5b** is also present in this case and marked with "*". Downfield region ($\delta = 10$ to 8): the capsule imide N-H and aromatics are shown. Upfield region ($\delta = -2$ to -4): the guest CH_3 (s) signals and the C_2H_5 (q and t, $^3J(H,H) = 7.7$ Hz) group are shown. Alkyl peripheral groups and the partially deuterated solvent obscure the other regions of the spectra.

coverage at corners (Figure 1). The cross-section of the capsule varies along its length: octagonal at the seam of the eight hydrogens in the middle, square at the pyrazine and the imide walls, then shrinking squares at the tapered ends. Geometrically, the capsule's shape involves two stacked square prisms rotated 45° from one another, each capped with another square pyramid also rotated at 45°. Although the experimental data set is limited, flat and rigid molecules are not well suited to the interior. Neither anthracene nor 9,10-dihydroanthracene were encapsulated. Tetracene however was, so more stringent probes of the shape will be required.

Beside the variability in geometries, the capsule's features a range of microenvironments in chemical surfaces and magnetic properties. Almost all of the atoms that line the cavity are sp^2 hybridized with the p orbitals directed inward. Accordingly, the inner surface is a sheath of electrons that surround potential guests with a soft negative charge.

molecules to tumble freely inside. Toluene (ca. 5.5 Å maximal length) is close to the limit for tumbling (and there is spectroscopic evidence[5, 13] that this motion is slowed) but *p*-xylene (ca. 6.8 Å maximal length) exceeds the limit and must be oriented inside the capsule. It is also predictable that two aromatic molecules, each ≈3.5 Å thick, cannot squeeze past one another inside the capsule.

Shape: The dimeric capsule is not smoothly rounded as the cartoons suggest; rather, the flat aromatic walls of **1a**

There is a crude correlation between the ^{1}H NMR upfield shift for the *meta*-aromatic protons of the encapsulated guest and the guest's length (Figure 4, Table 3). For example, sizeable terphenyl (13.7 Å long) showed $\Delta\delta = 4.3$ for these protons upon encapsulation in [D_{12}]mesitylene, while for shorter bibenzyl (11.5 Å long) $\Delta\delta = 3.7$.

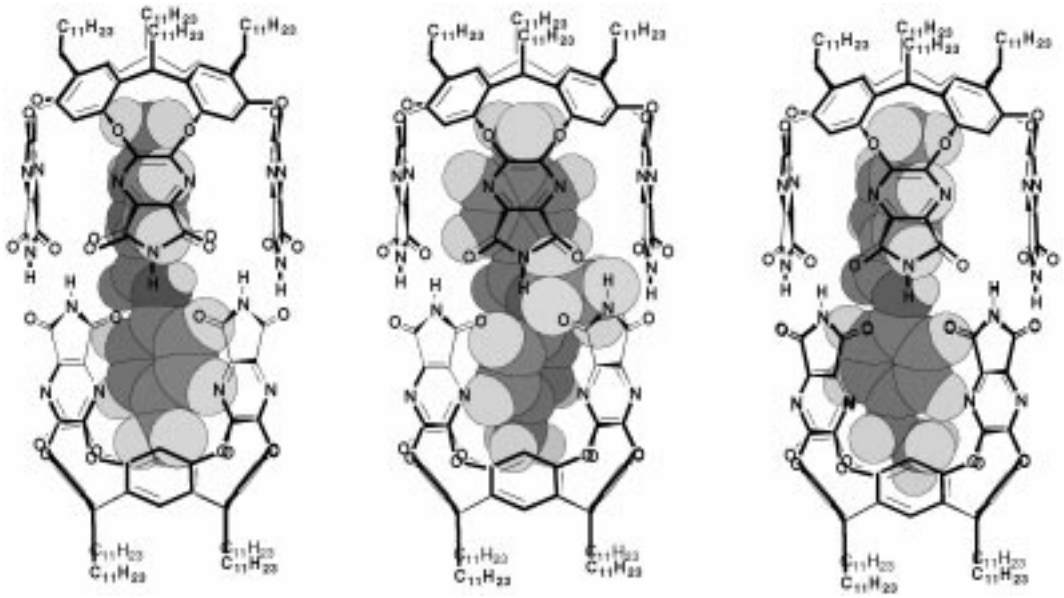

Figure 3. Artistic representations (CPK) of the molecular rulers **5b, 5f**, and **5c** inside the capsule. The energy-minimized[12] (MacroModel 5.5, Amber* force field) structures were used.

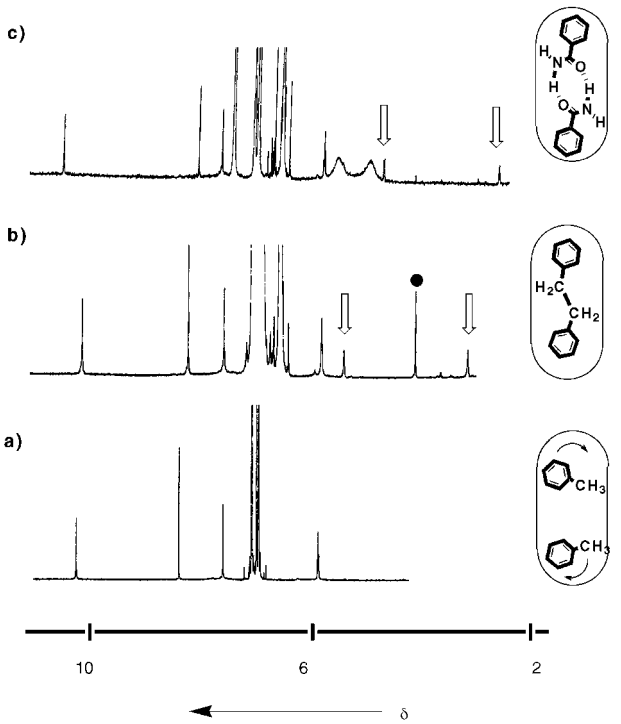

Figure 4. Portions of the ^{1}H NMR spectra (600 MHz, 295 K) of capsule **1a·1a**: a) in [D_8]toluene; b) in [D_{12}]mesitylene, encapsulated bibenzyl; c) in [D_{12}]mesitylene, encapsulated hydrogen-bonded dimer of benzamide. Downfield region ($\delta = 12$ to 8): the **1a** imide N–H and aromatics are shown. The guest *ortho*- (doublets) and *meta*- (triplets) aromatic signals are marked by arrows. The two "outside" benzamide N–H singlets are at $\delta = 5.8$. The residual CH_2Cl_2 is marked with "●".

Guest stability: In self-assembled capsules, the exchange between complexed and free guest species is usually fast on the human time scale, but slow on the NMR time scale (≈ 0.5 to $1\ s^{-1}$).[15] In contrast, covalently sealed carcerands show very high kinetic stability. Their complexes, the carceplexes, can stabilize highly reactive species (cyclobutadiene, benzyne, etc.) inside.[16] Once formed, the "hot" encarcerated species can even react with the walls of the carcerand. We report here a somewhat different situation: a supramolecular cage effect. Encapsulation not only protects the species, benzoyl peroxide, from external reagents but also from its thermal decomposition. It can be stored inside the capsule for a long time, then released—when needed—to the bulk solution (Figure 5).

The dimensions of benzoyl peroxide are $\approx 4.3 \times 13.2$ Å (Table 3) and it is readily encapsulated by **1a·1a** (Figure 6a) in [D_{12}]mesitylene. Once inside, it can be stored for weeks at room temperatures. We found that the encapsulated benzoyl peroxide possesses chemical properties *different* from those in a bulk solution:

1) Inside capsule **1a·1a** benzoyl peroxide is stable for at least three days at 70 °C in [D_{12}]mesitylene, while in the absence of **1a·1a** it decomposes within about 3 h under those conditions.[17]
2) Benzoyl peroxide readily oxidizes Ph_3P present in [D_{12}]mesitylene to $Ph_3P{=}O$ at room temperature at millimolar concentrations (50% within ca. 2 h, ^{1}H and ^{31}P NMR control, Figure 6d). In contrast, no reaction occurs when benzoyl peroxide is inside the capsule and Ph_3P is outside.
3) The encapsulated benzoyl peroxide can be slowly replaced by *p*-[*N*-(*p*-tolyl)]toluamide (**5b**) within 3–5 days (Figure 6b), by *p*-[*N*-methyl-*N*-(*p*-tolyl)]toluamide (**5e**) within weeks, or by the highly competitive hydrogen bond acceptor DMF within seconds (Figure 6c). The DMF competes for the inner hydrogen bond donors in the

Table 3. Calculated length *b* and chemical shifts of the aromatic protons of the encapsulated species.[a]

Compound	*b* [Å]	*ortho*-, δ ($\Delta\delta$)	*meta*-, δ ($\Delta\delta$)
C_6H_5-CH_2-CH_2-C_6H_5	11.5	5.5 (2.5)	3.4 (3.7)
(E)-stilbene[b]	11.7	5.7 (1.6)	3.3 (3.8)
benzoyl peroxide	13.2	5.4 (2.4)	3.0 (4.0)
C_6H_5-C_6H_4-C_6H_5	13.7	5.0 (2.4)	2.9 (4.3)
benzamide (dimer)	14.7	4.8 (2.7)	2.8 (4.2)
C_6H_5-C_6H_4-C_6H_4-C_6H_5	18.1	[c]	[c]

[a] The structures were energy-minimized using MacroModel 5.5 with Amber* force field. The *b* distance was measured between the two most remote hydrogens of the Ar–H fragments. Centers of the atoms were used for the measurements. Measured in [D_{12}]mesitylene at 1×10^{-3} M of **1a**. Estimated error $\delta = \pm 0.1$. [b] No *(Z)*-stilbene encapsulated. [c] No encapsulation.

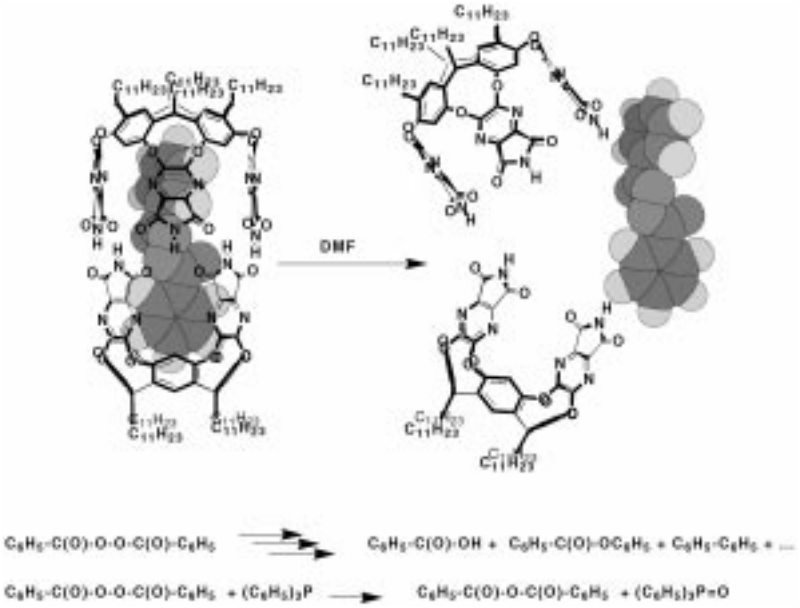

Figure 5. Schematic representation of the encapsulated benzoyl peroxide and its release by DMF. The energy-minimized[12] (MacroModel 5.5, Amber* force field) structures were used. Two chemical processes studied are shown: thermal decomposition and oxidation of Ph_3P.

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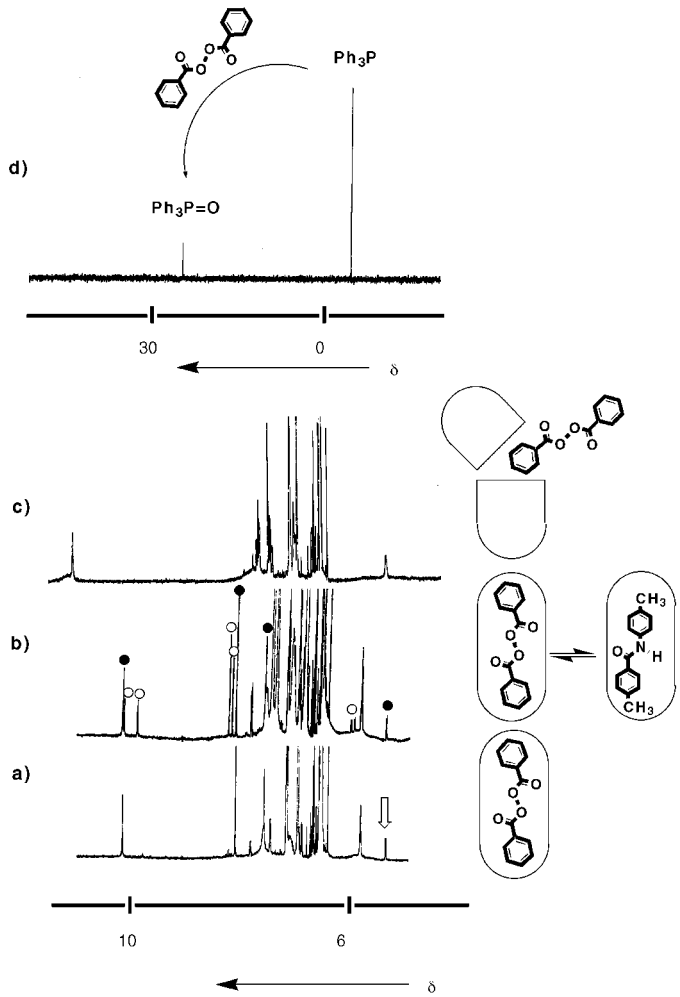

Figure 6. Stability of the encapsulated benzoyl peroxide. Portions of the NMR spectra in [D_{12}]mesitylene: a) ^{1}H NMR (600 MHz, 295 K) spectrum of the encapsulated benzoyl peroxide; the spectrum did not change upon heating the sample at 70 °C for three days; b) exchange between benzoyl peroxide and amide **5b**, after about 43 h (^{1}H NMR, 295 K). The capsule with benzoyl peroxide is marked with "●", and the capsule with **5b** is marked with "o"; c) solution as in Figure 6a after addition of 1–2% (vol) DMF; d) typical ^{31}P NMR (243 MHz, 295 K) spectrum of oxidation of Ph_3P to Ph_3P=O by benzoyl peroxide.

assembly and only monomeric cavitand **1a** can be detected; no encapsulated benzoyl peroxide remains.

4) When about 1–2% (v/v) of DMF was added to the [D_{12}]mesitylene solution of [**1a**·benzoyl peroxide·**1a**], containing 10 equivalents of Ph_3P, a redox reaction occurred within minutes and the formation of Ph_3P=O was readily detected by ^{31}P NMR spectroscopy.
5) The [D_{12}]mesitylene solution of [**1a**·benzoyl peroxide·**1a**], containing 8–10 equivalents of Ph_3P, was stored at 70 °C for 10 h. According to ^{31}P NMR spectroscopy, no Ph_3P=O was formed. However, when about 1–2% (v/v) of DMF was then added to the cooled solution, the reaction occurred.
6) Capsule **1a**·**1a**, charged with benzoyl peroxide, is stable in [D_{12}]mesitylene containing 1–2% (vol) of acetic acid for about 10 h. Even when an excess 1,5-diphenylcarbazide is present (a widely used colorimetric reagent for peroxide determination[17]), no color changes occur within hours (Figure 7). Larger quantities of acetic acid (= 5% (vol)) open the capsule within seconds, and the released benzoyl peroxide oxidizes 1,5-diphenylcarbazide, producing intense bright-pink color ($\lambda = 555$ nm).

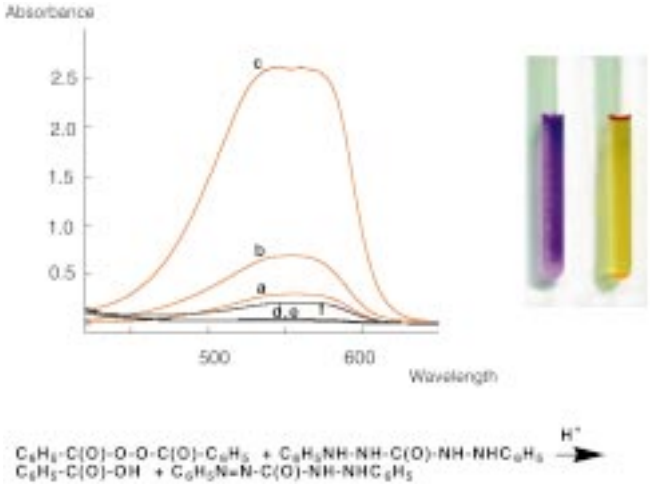

Figure 7. Colorimetric detection of diphenylcarbazone ($\lambda_{max} = 555$ nm) by oxidation of diphenylcarbazide with benzoyl peroxide in mesitylene in the presence of CH_3COOH (1–2% vol). Portion of the UV/Vis spectra (2.7×10^{-5} M benzoyl peroxide, 295 K). No capsule added: a) after 2 h; b) after 8 h; c) after 17 h. Cavitand **1a** (2.5×10^{-4} M) added: d) after 2 h; e) after 8 h; f) after 17 h. Diphenylcarbazide was used in a large excess ($\approx 1 \times 10^{-3}$ M). Photograph of the mesitylene solutions, used in the UV/Vis experiments (1 h after mixing). Left: no capsule added. Right: with the capsule.

How is benzoyl peroxide protected from thermal decomposition? One possibility is that dissociation to two benzoyloxy radicals is prevented inside the capsule. The alternative is that dissociation takes place, but recombination is much faster than decarboxylation and hydrogen abstraction processes. Labeling studies with ^{18}O isotope could distinguish between these possibilities, but that isotope's commercial availability is unpredictable—the experiment must wait.

Conclusion

The encapsulation complexes allow the isolation of single molecules from the bulk solution for spectroscopic characterization. Their isolation is temporary and reversible but their behavior inside the capsule can be profoundly different from their solvated states. The cavity's dimensions can be probed by a number of techniques, and experimental rulers are complementary to computational ones. The nonspherical capsules limit the rotational freedom of guests and suggest that two encapsulated species will enjoy special stereochemical relationships with one another. We will report on these developments in due course.

Experimental Section

General: Melting points (m.p.) were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker DRX-600 (600 MHz) and AM-300 (300 MHz)

spectrometers at 295 K. The ^{13}C and ^{31}P NMR spectra were measured on a Bruker DRX-600 (151 and 243 MHz, respectively) spectrometer at 295 K. The fast atom bombardment (FAB) positive-ion mass spectra were obtained with a VG ZAB-VSE or a PerSeptive Biosystems Voyager-Elite mass spectrometer equipped with a cesium-ion gun. FT-IR spectra were recorded on a Perkin-Elmer Paragon 1000PC FT-IR spectrometer. UV/vis spectra were recorded on a Perkin-Elmer UV/VIS Lambda 12 spectrometer. All commercially available chemicals were used without further purification unless otherwise specified. Resorcinarene **2**, 5,6-dichloropyrazine-2,3-dicarboxylic acid anhydride, and 5,6-dichloro-pyrazine-2,3-dicarboxylic acid methylimide were prepared following literature procedures.[6b, 7]

Molecular mechanics (MM2*, Amber* force-field) calculations were performed with MacroModel 5.5.[12]

5,6-Dicarboxylic acid imide 3a: A mixture of 5,6-dichloropyrazine-2,3-dicarboxylic acid anhydride (1.00 g, 4.57 mmol) and ammonium chloride (435 mg, 8.13 mmol) in acetic anhydride (1.15 mL) was heated in a closed flask at 120 °C for 20 min. The cooled crystalline mixture was washed with water and dried in vacuo. Flash chromatography (SiO_2, EtOAc, $R_f = 0.83$) afforded the product **3a** (466 mg, 47%) as a white solid. M.p. >300 °C; ^1H NMR ([D$_6$]DMSO): $\delta = 12.31$ (s, 1H, NH); ^{13}C NMR ([D$_6$]DMSO): $\delta = 164.1$ (C=O), 151.0 (arom), 145.4 (arom); FT-IR (KBr): $\tilde{\nu} = 3515, 3278, 2352, 1876, 1806, 1762, 1740, 1714, 1542, 1388, 1366\ cm^{-1}$; ESI-MS: *m/z*: 218 [$M^+ - H$] (calcd for $C_6HCl_2N_3O_2$ 218).

Cavitand 1a: Triethylamine (146 μL) was added to a solution of resorcinarene **2** (132.6 mg, 0.12 mmol) and 5,6-dichloropyrazine-2,3-dicarboxylic acid imide (**3a**) (122.9 mg, 0.56 mmol) in DMF (4.7 mL). The reaction mixture was heated at 80 °C for 5 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 (25 mL) and water (25 mL). The organic layer was separated and dried over $MgSO_4$. The product **1a** (98 mg, 48%) was isolated after flash chromatography (SiO_2, EtOAc/hexane, 4:1) as a pale-yellow solid. M.p. >270 °C; ^1H NMR ($CDCl_3$): $\delta =$ 9.79 (s, 4H, NH), 8.09 (s, 4H, arom), 7.37 (s, 4H, arom), 5.64 (t, $^3J(H,H) =$ 7.9 Hz, 4H, CH-methine), 2.25 (m, 8H, alkyl), 1.20 (m, 72H, alkyl), 0.83 (t, $^3J(H,H) = 7.5$ Hz, 12H, CH_3); ^1H NMR (CD_2Cl_2): $\delta = 9.89$ (s, 4H, NH), 8.21 (s, 4H, arom), 7.41 (s, 4H, arom), 5.68 (t, $^3J(H,H) = 7.9$ Hz, 4H, CH-methine), 2.34 (m, 8H, alkyl), 1.29 (m, 72H, alkyl), 0.89 (t, $^3J(H,H) =$ 6.8 Hz, 12H, CH3); ^1H NMR ([D$_6$]benzene): $\delta = 10.50$ (s, 4H, NH), 8.37 (s, 4H, arom), 7.60 (s, 4H, arom), 5.92 (t, $^3J(H,H) = 8.0$ Hz, 4H, CH-methine), 2.30 (m, 8H, alkyl), 1.34 (m, 72H, alkyl), 0.93 (t, $^3J(H,H) = 7.1$ Hz, 12H, CH_3); ^1H NMR ([D$_8$]toluene): $\delta = 10.20$ (s, 4H, NH), 8.38 (s, 4H, arom), 7.61 (s, 4H, arom), 5.93 (t, $^3J(H,H) = 8.0$ Hz, 4H, CH-methine), 2.35 (m, 8H, alkyl), 1.36 (m, 72H, alkyl), 0.99 (t, $^3J(H,H) = 7.0$ Hz, 12H, CH_3); ^1H NMR ([D$_6$]DMSO, 295 K): $\delta = 11.83$ (s, 4H, NH), 7.20 (s, 4H, arom), 3.74 (t, $^3J(H,H) = 7.4$ Hz, 4H, CH-methine), 2.10 (br m, 8H, alkyl), 1.15 (m, 72H, alkyl), 0.83 (t, $^3J(H,H) = 7.0$ Hz, 12H, CH_3); ^1H NMR ([D$_6$]DMSO, 350 K): $\delta = 11.55$ (s, 4H, NH), 7.31 (s, 4H, arom), 7.13 (s, 4H, arom), 3.84 (t, $^3J(H,H) = 7.3$ Hz, 4H, CH-methine), 2.19 (m, 8H, alkyl), 1.22 (m, 72H, alkyl), 0.86 (t, $^3J(H,H) = 6.9$ Hz, 12H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 163.2$ (C=O), 158.6, 152.8, 142.9, 137.2, 124.6, 119.1, 34,4, 32.5, 32.2, 30.0, 29.9, 29.7, 28.2, 23.0, 14.4; FT-IR ($CHCl_3$, 1.5×10^{-3} M): $\tilde{\nu} = 3333$ (NH), 2921, 2861, 1797, 1733, 1600, 1480, 1445, 1385, 1351 cm^{-1}; FT-IR ($CHCl_3$, 3×10^{-4} M): $\tilde{\nu} = 3334$ (NH) cm^{-1}; MALDI-MS: *m/z*: 1686 [M^+] (calcd for $C_{96}H_{108}N_{12}O_{16}$ 1686); HRMS-FAB: *m/z*: 1949.6290 ([$M - H$]$^-$+2Cs$^+$) (calcd for $C_{96}H_{108}N_{12}O_{16}$ 1949.6037).

Cavitand 1b: Obtained analogously to **1a** from resorcinarene **2** and 5,6-dichloropyrazine-2,3-dicarboxylic acid methylimide (**3b**) in DMF. The product (222.4 mg, 35%) was isolated after flash chromatography (SiO_2, first EtOAc/hexane, 1:1, then EtOAc) as a white glassy solid. ^1H NMR ($CDCl_3$, 330 K): $\delta = 7.59$ (s, 4H, arom), 7.03 (s, 4H, arom), 4.50 (t, $^3J(H,H) = 7.4$ Hz, 4H, CH-methine), 3.23 (s, 12H, *N*-CH_3), 2.15 (m, 8H, alkyl), 1.31 (m, 72H, alkyl), 0.90 (t, $^3J(H,H) = 7.2$ Hz, 12H, CH_3); ^1H NMR ($CDCl_3$, 295 K): $\delta = 7.58$ (s, 4H, arom), 7.00 (s, 4H, arom), 4.32 (br, 4H, CH-methine), 3.25 (s, 12H, *N*-CH_3), 2.12 (m, 8H, alkyl), 1.31 (m, 72H, alkyl), 0.89 (t, $^3J(H,H) = 7.2$ Hz, 12H, CH_3); HRMS-MALDI: *m/z*: 1741.8676 [M^++H] (calcd for $C_{100}H_{116}N_{12}O_{16}$ 1741.8711).

5-Chloro-6-(3′,5′di-*tert*-butylphenoxy)pyrazine-2,3-dicarboxylic acid imide (4): Triethylamine (60 μL) was added to a solution of 3,5-di-*tert*-butylphenol (94.6 mg, 0.46 mmol) and 5,6-dichloropyrazine-2,3-dicarboxylic acid imide (**3a**) (50.0 mg, 0.23 mmol) in DMF (2 mL). The reaction mixture was heated at 80 °C for 5 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 (25 mL) and water (20 mL). The organic layer was separated and dried over $MgSO_4$. The product **4** (28.7 mg, 32%) was isolated after flash chromatography (SiO_2, EtOAc/hexane, 1:1) as a white solid. ^1H NMR ($CDCl_3$, 5×10^{-2} M): $\delta = 8.08$ (s, 1H, NH), 7.36 (t, $^3J(H,H) = 1.5$ Hz, 1H, arom), 7.02 (d, $^3J(H,H) = 1.5$ Hz, 2H, arom), 1.33 (s, 18H, $C(CH_3)_3$); ^1H NMR ($CDCl_3$, 9×10^{-4} M): $\delta = 7.73$ (s, 1H, NH), 7.36 (t, $^3J(H,H) = 1.5$ Hz, 1H, arom), 7.02 (t, $^3J(H,H) = 1.5$ Hz, 2H, arom), 1.33 (s, 18H, $C(CH_3)_3$); FT-IR ($CHCl_3$, 3×10^{-3} M): $\tilde{\nu} = 3416$ (NH), 2961, 2907, 2866, 1791, 1757, 1612, 1525, 1478, 1451, 1420, 1363, 1349 cm^{-1}; FT-IR ($CHCl_3$, 3×10^{-4} M): $\tilde{\nu} = 3416$ (NH) cm^{-1}; HRMS-FAB: *m/z*: 140.1231 [M^++Na] (calcd for $C_{20}H_{22}ClN_3O_3$ 410.1247).

***p*-[*N*-(*p*-Ethylbenzene)]toluamide (5c):**[18] *p*-Toluoyl chloride (0.69 mL, 5.2 mmol) was added dropwise to a solution of *p*-ethylaniline (0.62 mL, 5 mmol) and K_2CO_3 (1.38 g, 10 mmol) in EtOAc/H_2O (30 mL, 1:1). The reaction mixture was stirred at room temperature for 3 h. After the addition of CH_2Cl_2 (300 mL), the organic layer was separated, dried over $MgSO_4$, and evaporated in vacuo. Recrystallization of the residue from *i*PrOH gave **5c** as white crystals (0.8 g, 67%). M.p. 139–140 °C (MeOH); ^1H NMR ($CDCl_3$): $\delta = 7.83$ (br, 1H, NH), 7.75 (d, $^3J(H,H) = 8.0$ Hz, 2H, arom), 7.53 (d, $^3J(H,H) =$ 8.4 Hz, 2H, arom), 7.26 (d, $^3J(H,H) = 8.0$ Hz, 2H, arom), 7.18 (d, $^3J(H,H) = 8.4$ Hz, 2H, arom), 2.63 (q, $^3J(H,H) = 7.5$ Hz, 2H, Ar-CH_2), 2.41 (s, 3H, CH_3), 1.23 (t, $^3J(H,H) = 7.5$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 165.6, 142.2, 140.5, 135.6, 132.2, 129.4, 128.3, 127.2, 120.3, 28.3, 21.5, 15.7$; FT-IR ($CHCl_3$, 2×10^{-3} M): $\tilde{\nu} = 3439, 3030, 2967, 1670, 1611, 1593, 1516, 1500, 1411, 1317, 834\ cm^{-1}$; HRMS-MALDI-FTMS: *m/z*: 240.1394 [M+H$^+$] (calcd for $C_{16}H_{17}NOH$ 240.1388).

***p*-[*N*-(*p*-Ethylbenzene)]ethylbenzamide (5d):** Obtained analogously to **5c** from *p*-ethylbenzoyl chloride (1.69 g, 10 mmol), *p*-ethylaniline (1.24 mL, 10 mmol), and K_2CO_3 (2.76 g, 20 mmol) in EtOAc/H_2O (50 mL, 1:1). Yield 2.0 g (79%). M.p. 129–130°C (cyclohexane); ^1H NMR ($CDCl_3$): $\delta = 7.78$ (d, $^3J(H,H) = 8.0$ Hz, 2H, arom), 7.77 (br, 1H, *N*-H), 7.54 (d, $^3J(H,H) =$ 8.2 Hz, 2H, arom), 7.30 (d, $^3J(H,H) = 8.0$ Hz, 2H, arom), 7.19 (d, $^3J(H,H) =$ 8.2 Hz, 2H, arom), 2.71 (q, $^3J(H,H) = 7.6$ Hz, 2H, Ar-CH_2), 2.63 (q, $^3J(H,H) = 7.6$ Hz, 2H, Ar-CH_2), 1.27 (t, $^3J(H,H) = 7.6$ Hz, 3H, CH_3), 1.23 (t, $^3J(H,H) = 7.6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) $\delta = 165.6, 148.4, 140.5, 135.6, 132.4, 128.3, 128.2, 127.1, 120.3, 28.8, 28.3, 15.7, 15.3$; FT-IR ($CDCl_3$, 2×10^{-3} M): $\tilde{\nu} = 3435, 3023, 2966, 2928, 2870, 1666, 1609, 1590, 1519, 1500, 1404, 1314, 1257, 852, 833\ cm^{-1}$; HRMS-MALDI-FTMS: *m/z*: 254.1553 [M+H$^+$] (calcd for $C_{17}H_{19}NOH$ 254.1545).

***p*-[*N*-Methyl(*p*-tolyl)]toluamide (5e)**:[19] Powdered KOH (2.24 g, 40 mmol) in DMSO (20 mL) was stirred for 5 min. Then amide **5b** (2.25 g, 10 mmol) and methyl iodide (1.85 mL, 30 mmol) were added. After stirring at room temperature for 20 min, the reaction mixture was poured into water (200 mL), and extracted with CH_2Cl_2 (3×200 mL). The combined organic phases were washed with water (5×100 mL), dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography (SiO_2, hexane/EtOAc, 4:1, $R_f = 0.16$) afforded the product **5e** (2.28 g, 95%) as a white solid. M.p. 92 °C; ^1H NMR ($CDCl_3$): $\delta = 7.70$ (d, $^3J(H,H) = 8.1$ Hz, 2H, arom), 7.02 (d, $^3J(H,H) = 8.1$ Hz, 2H, arom), 6.96 (d, $^3J(H,H) = 8.1$ Hz, 2H, arom), 6.92 (d, $^3J(H,H) = 8.1$ Hz, 2H, arom), 3.45 (s, 3H, *N*-CH_3), 2.28 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 171.2, 143.1, 140.1, 136.6, 130.2, 130.0, 129.3, 128.8, 127.1, 38.8, 21.6, 21.2$; FT-IR ($CHCl_3$, 2×10^{-3} M): $\tilde{\nu} = 1629$ (C=O), 1612, 1581, 1572, 1514, 1427, 1370, 1301 cm^{-1}; MS-FAB: *m/z*: 240 [M^++H] (calcd for $C_{16}H_{17}NO$ 240); HRMS-FAB: *m/z*: 240.1382 [M^++H] (calcd for $C_{16}H_{17}NO$ 240.1388).

***p*-[*N*-Ethyl(*p*-tolyl)]toluamide (5f)**: Prepared analogously to **5e** from powdered KOH (1.12 g, 20 mmol), toluamide **5b** (1.13 g, 5 mmol), and ethyl iodide (0.80 mL, 10 mmol) in DMSO (10 mL). Yield 1.11g (87%) of a colorless oil after flash chromatography (silica gel, hexane/EtOAc 85:15). ^1H NMR ($CDCl_3$): $\delta = 7.19$ (d, $^3J(H,H) = 8.0$ Hz, 2H, arom), 7.00 (d, $^3J(H,H) = 8.0$ Hz, 2H, arom), 6.93 (d, $^3J(H,H) = 8.0$ Hz, 2H, arom), 6.89 (d, $^3J(H,H) = 8.0$ Hz, 2H, arom), 3.93 (q, $^3J(H,H) = 7.0$ Hz, 2H, *N*-CH_2), 2.26 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.19 (t, $^3J(H,H) = 7.0$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) $\delta = 170.0, 140.7, 139.3, 136.2, 133.4, 129.6, 128.7, 128.2, 127.5, 45.4, 21.2, 20.9, 12.8$; FT-IR (film, NaCl): $\tilde{\nu} = 3029, 2974, 2931, 2871, 1643, 1610, 1571, 1511, 1442, 1414, 1117, 821, 750\ cm^{-1}$; HRMS-MALDI-FTMS: *m/z* 254.1542 [M+H$^+$] (calcd for $C_{17}H_{19}NOH$ 254.1545).

***p*-[*N*-Propyl(*p*-tolyl)]toluamide (5g)**: Prepared analogously to **5e** from powdered KOH (1.12 g, 20 mmol), toluamide **5b** (1.13 g, 5 mmol), and propyl bromide (0.91 mL, 10 mmol) in DMSO (10 mL). Yield 1.14g (85%)

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of a colorless oil after flash chromatography (silica gel, hexane/EtOAc 85:15). ^{1}H NMR ($CDCl_3$): $\delta = 7.18$ (d, ^3J(H,H) = 7.9 Hz, 2H, arom), 7.00 (d, ^3J(H,H) = 7.9 Hz, 2H, arom), 6.93 (d, ^3J(H,H) = 7.9 Hz, 2H, arom), 6.90 (d, ^3J(H,H) = 7.9 Hz, 2H, arom), 3.84 (t, ^3J(H,H) = 7.6 Hz, 2H, *N*-CH_2), 2.26 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.63 (m, ^3J(H,H) = 7.6 Hz, 2H, CH_2), 0.92 (t, ^3J(H,H) = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) $\delta = 170.3$, 141.0, 139.3, 136.1, 133.5, 129.6, 128.7, 128.2, 127.5, 52.0, 21.3, 20.9, 20.8, 11.3; FT-IR (film, NaCl): $\tilde{\nu} = 3029$, 2964, 2926, 2873, 1643, 1610, 1573, 1511, 1436, 1385, 1122, 827, 750 cm^{-1}; HRMS-MALDI-FTMS: *m/z*: 268.1697 [*M*+H$^+$] (calcd for $C_{18}H_{21}NOH$ 268.1701).

***p*-[*N*-Butyl(*p*-tolyl)]toluamide (5i)**: Prepared analogously to **5e** from powdered KOH (224 mg, 4 mmol), toluamide **5b** (225 mg, 1 mmol), and butyl iodide (0.23 mL, 2 mmol) in DMSO (2 mL). Yield 233 mg (83%) of a white solid after flash chromatography (silica gel, hexane/EtOAc 85:15). M.p. 61–63 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.17$ (d, ^3J(H,H) = 7.8 Hz, 2H, arom), 7.01 (d, ^3J(H,H) = 7.8 Hz, 2H, arom), 6.94 (d, ^3J(H,H) = 7.8 Hz, 2H, arom), 6.90 (d, ^3J(H,H) = 7.8 Hz, 2H, arom), 3.87 (t, ^3J(H,H) = 7.6 Hz, 2H, *N*-CH_2), 2.27 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 1.61-1.57 (m, 2H, CH_2), 1.37–1.33 (m, 2H, CH_2), 0.90 (t, ^3J(H,H) = 7.3 Hz); ^{13}C NMR ($CDCl_3$) $\delta = 170.3$, 141.1, 139.4, 136.1, 133.5, 129.6, 128.8, 128.3, 127.5, 50.3, 29.7, 21.3, 21.0, 20.2, 13.9; FT-IR (film $CHCl_3$, NaCl): $\tilde{\nu} = 3023$, 2956, 2928, 2861, 1641, 1610, 1511, 1385, 1124, 827, 750 cm^{-1}; HRMS-MALDI-FTMS: *m/z*: 282.1853 [*M*+H$^+$] (calcd for $C_{19}H_{23}NOH$ 282.1858).

Benzoyl peroxide stability measurements: In a typical NMR experiment, a solution of **1a** (2.6×10^{-3} M), benzoyl peroxide (2.9×10^{-4} M), and PPh_3 (2.9×10^{-3} M), when applicable, in [D_{12}]mesitylene was placed in a 5 mm NMR tube and analyzed by ^{1}H and/or ^{31}P NMR spectroscopy at 295 K in equal time intervals (0.5 to 1 h). All measurements were performed at least in triplicate, and good reproducibility was observed.

Decomposition of capsule **1a·1a**, charged with benzoyl peroxide, in the presence of 1,5-diphenylcarbazide diphenyl in mesitylene solution, containing 1–2% (vol) of acetic acid, was monitored by ^{1}H NMR and UV/Vis spectroscopy and visually (Figure 7) at 295 K. In the UV/Vis spectra (2.7×10^{-5} M benzoyl peroxide, 2.5×10^{-4} M **1a**), absorption intensity changes at $\lambda = 555$ nm were followed. All blank experiments were performed under the same conditions, but without cavitand **1a**.

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