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Multicomponent Assembly of Cavitand-Based Polyacylhydrazone Nanocapsules

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Abstract: The thermodynamically controlled syntheses of different di-, tetra-, and hexacavitand polyacylhydrazone nanocapsules are reported. [2+4]-, [4+8]-, and [6+12]-nanocapsules assemble upon reacting a tetraformyl cavitand with two equivalents of isophthalic dihydrazide, or terephthalic dihydrazide in the presence of trifluoroacetic acid, whereby the building blocks are linked together through 8, 16, or 24 newly formed acylhydrazone bonds. Futhermore, the reaction of the tetraformylcavitands with different trigonal planar trihydrazides, simultaneously leads to the formation of [2+4]- and [6+8]-nanocapsules in varying ratios that depend on the cavitand to trihydrazide ratio and the nature of the cavitand and trihydrazide building blocks. The product ratios are rationalized with the different conformational strain of the acylhydrazone linkages in these nanocapsules. Diffusion NMR experiments with the hexacavitand polyacylhydrazone nanocapsules yield solvodynamic radii that range from 1.6 to 2.5 nm, consistent with estimates from force field calculations, and support, that these capsules have solvent filled, spherical interiors, the sizes of which approaches those of smaller proteins.

Keywords: cavitands · host–guest systems · hydrazones · molecular containers · nanocapsules

Introduction

Molecular container compounds are hollow nanospheres that allow encapsulation of one or more guest molecules and insulate the guest(s) from the bulk phase.[1] They have received much attention by the chemical community in part owing to their potential as nanoreactors,[2] in which otherwise fleeting reactive intermediates become persistent,[3] reactions are accelerated,[4] and regiochemistry,[4c,f,5] and selectivity are altered.[6] Furthermore, the investigation of energy and electron transfer through the shell of container molecules has increased understanding of these fundamental processes and may lead to novel applications in solar-energy conversion.[7] The development of self-assembly processes for the synthesis of nanocapsules using hydrogen bonding,[1d,f,8,9] metal-coordination,[1e,10,11] or other weak interactions[12] has given the field of molecular encapsulation a strong impetus. Self-assembly processes are under thermodynamic control, thus providing opportunities for capsule formation from multiple components in high yield.[13] Spontaneous assembly of nanoscopic covalent molecules from multiple reactants is possible with functional groups that react to form reversible covalent connections.[14] Such dynamic covalent syntheses benefit from proof reading and error correction mechanisms, which are the hall marks of self-assembly processes. Among different reversible bonds that have been utilized for dynamic covalent chemistry, imine and acylhydrazone bonds are particularly interesting and offer various possibilities for controlling kinetics of assembly and disassembly, stability and configuration. In addition, reduction permanently turns off the dynamic features and creates a new functionality (a secondary amine or hydrazide) for further chemical modification.[14a,b,15] For these reasons, dynamic covalent chemistry has received tremendous attention in the development of novel responsive materials,[14d,16] delivery devices,[17] and molecular libraries for drug discovery,[18] as well as in the target-oriented synthesis of topologically complex molecules,[15,19] such as knots,[20] catenanes,[19b,21] rotaxanes,[22] or polycyclic receptors.[16i,23]

Recently, we developed a rational design concept for the assembly of polycavitand nanocapsules using imine chemistry (Scheme 1).[24–26] For example, condensation of tetraformyl cavitand **1** with two equivalents of a kinked, 120° diamine unit (**5a**, **b**) or a rigid, linear, 180° diamine unit (**6a**) yields octaimine hemicarcerands (**2a**, **b**) or a hexadecaimine tetrahedral nanocapsule (**3a**) in close to quantitative yield.[24b,d,e,27] On the other hand, a cavitand-hexamer (**4a**) forms upon reaction of six cavitands **1** with eight planar, trigonal triamines (**7a**).[24a] The outcome of these assembly processes relies on the rigidity of the building blocks, their geometric features, and the imine bonds as linear connectors, whereby the preferred condensation products become strongly favored over other possible polycyclic or acyclic oligomers. In other words, each nanocapsule is preprogrammed into the specific combination of reactants. A disadvantage of imine bonds is their relatively small stability

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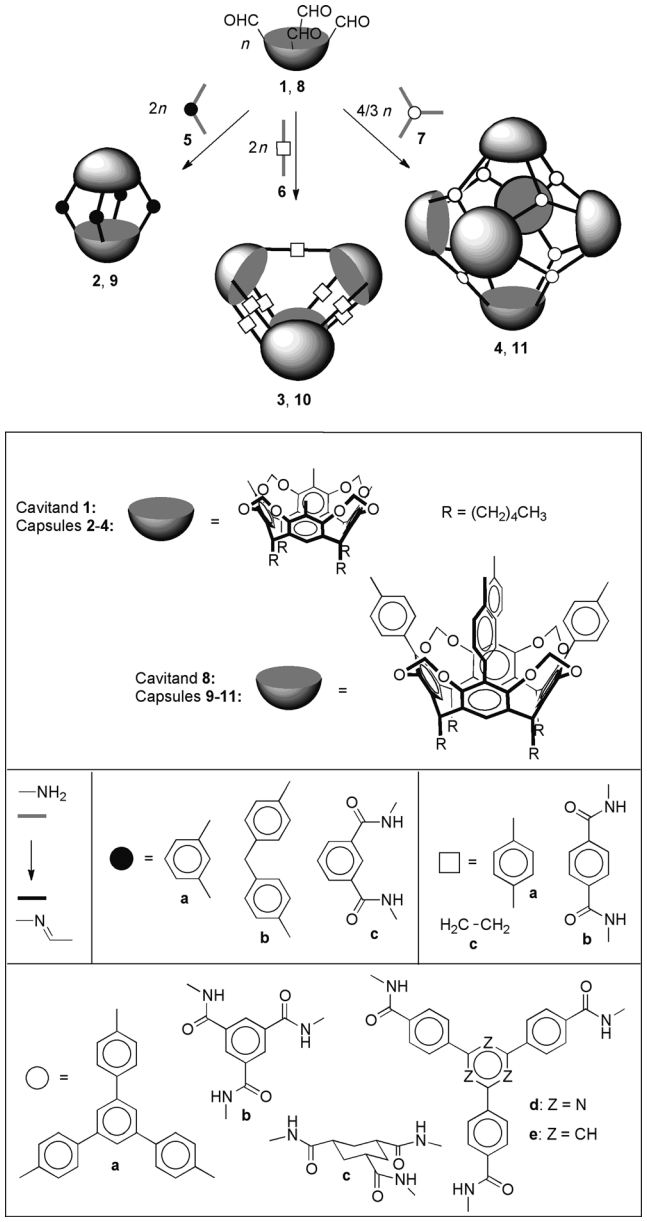


Scheme 1. Rational design of cavitand-based nanocapsules.

constants,[28] which limits their use in multicomponent assembly processes to organic media. On the other hand, related hydrazones, semicarbazones, and acylhydrazones, which form upon reactions of formyl groups with hydrazines [Eq. (1)], semicarbazide, or hydrazides, respectively, are thermodynamically more stable.[29] Aiming at future covalent assembly of nanocapsules in water, we have investigated the usefulness of acylhydrazone chemistry for the synthesis of cavitand-based hemicarcerands and larger nanocapsules.

Here, we address specifically, if substitution of the amino function in one of the building blocks against a hydrazide group ($C(O)NHNH_2$) is compatible with our nanocapsule design concept. We also explore the effect of inserting additional phenyl spacers into the cavitand's C_{aryl}–$C_{carbonyl}$ bond on the outcome of nanocapsule syntheses. Insertion of a phenyl unit will change the dihedral angle between the cavitand's aryl plane and the imine bond in **9**–**11**, which will change their conformational energy relative to that of other possible assemblies. Our results clearly show, that the acylhydrazone bond is a very promising dynamic covalent bond for the assembly of nanocapsules.

Results and Discussion

For our planned multicomponent syntheses of cavitand-based nanocapsules, the following considerations led to the choice of acylhydrazones as connectors for cavitand and linker building blocks. 1) Hydrazides can easily be prepared via reaction of esters with excess hydrazine hydrate and are very stable and storable in the solid state.

(1)

2) Most hydrazides with smaller R′ groups are water-soluble. 3) Typically, hydrazides have low pK_b values and are unprotonated at neutral pH.[29b] 4) Imine and hydrazone exchange can be accelerated via Brønsted acid, lantanide ion,[30] or covalent catalysis.[31] 5) Perhaps most importantly, acylhydrazones with R = aryl (Figure 1A) adapt predominately the *E*-s-*trans*-*anti* conformation in solution,[17] which results in a similar spatial arrangement of substituents R and R′ as in imines, and suggests that the above design concept should be applicable. Gas-phase computations of *N*-

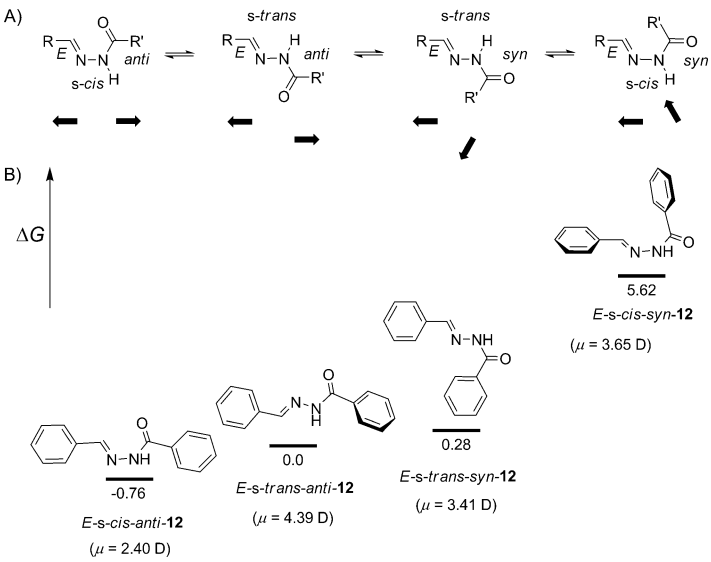
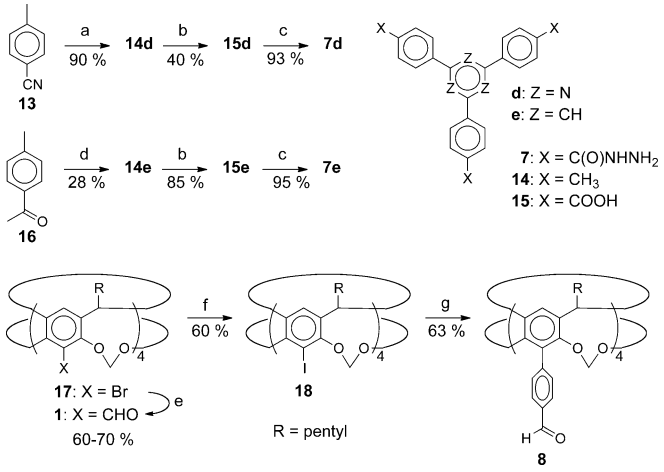


Figure 1. A) Main conformations of acylhydrazones. Only the *E*-s-*cis*-*anti* and *E*-s-*trans*-*anti* conformations are suitable "linear" connectors, as indicated by the arrows. B) Computed relative gas-phase free energies (B3LYP/6-31G(d) in kcal mol^{-1}) and dipole moments μ of *N*-benzoylphenylhydrazone **12** conformers.

benzoylphenylhydrazone **12** using density functional theory (B3LYP/6-31G(d)) support this conclusion.[32] Even though, the free energy of the *E*-s-*trans-anti*, *E*-s-*cis-anti*, and *E*-s-*trans-syn* conformers are within 1 kcal mol^{-1}, the *E*-s-*trans-anti* conformation should dominate in polar solvents. However, for some capsules, a strong conformational heterogeneity may result.

Synthesis of cavitands and linkers: Di- (**5c**, **6b**) and trihydrazides (**7b**, **c**) were prepared by heating the corresponding ethyl or methyl esters in hydrazine hydrate.[33] Trihydrazides **7d** and **7e** were prepared from *p*-toluonitrile and *p*-methylacetophenone, respectively, by means of acid-catalyzed cyclotrimerization, oxidation of the methyl groups to carboxylic acids, conversion of the carboxylic acid groups to acyl chlorides, and heating with hydrazine hydrate (Scheme 2).[34] Cavitand **1** was prepared according to published procedures.[27] For the synthesis of the extended cavitand **8**, we applied a Suzuki–Miyaura coupling. Palladium-catalyzed cavitand–aryl couplings had earlier been achieved using tetraiodocavitand **18** and arylboronic acids,[9l,p,11n,35] but required large excess of the boronic acids and almost stoichiometric amounts of palladium. In recent years, potassium aryltrifluoroborates have been shown to be superior alternatives to boronic acids, as they are more stable, and more reactive.[36] Thus, coupling of **18**[37] with stoichiometric amounts of potassium *p*-formylphenyltrifluoroborate in the presence of 5 mol% $Pd(OAc)_2/PPh_3$ (1:2) gave **8** in 63% yield after purification (Scheme 2). Under otherwise identical conditions, tetrabromocavitand **17** gave only small amounts of coupling products.



Scheme 2. Synthesis of cavitands and hydrazides. Conditions: a) CF_3SO_3H, RT; b) HNO_3/H_2O, 220°C; c) 1. $SOCl_2$, reflux; 2. $NH_2NH_2{\cdot}H_2O$, reflux; d) $K_2S_2O_7$, H_2SO_4, 95°C; e) 1. *n*BuLi, −78°C, 2. DMF, 3. aq. NH_4Cl; f) 1. *n*BuLi, −78°C, 2. I_2; g) 4.1 equiv *p*-$KF_3BC_6H_4CHO$, 0.2 equiv $Pd(OAc)_2$, 0.4 equiv PPh_3; K_2CO_3, THF/H_2O, 110°C, sealed tube.

Reaction of cavitands 1 and 8 with isophthalic dihydrazide 5c: The reaction of **1** with slightly more than stoichiometric amounts of isophthalic dihydrazide **5c** (2.7 equiv)[38] in DMSO/chloroform containing two equivalents of trifluoracetic acid (TFA) reached equilibrium after about two days. This mixture contained approximately 30% hemicarcerand **2c** together with excess **5c** as judged from the ^{1}H NMR spectrum of the mixture (Figure 2A) and at least two other condensation products that have equal or lower molecular weight according to gel permeation chromatography (GPC). Upon further standing at room temperature, **2c** crystallized and could be isolated by filtration in 88% yield. The formation of hemicarcerand **2c** is support by its ^{1}H NMR (Figure 2B) and ^{13}C NMR spectra (Supporting Information), a strong signal for the $[M+Na]^+$ ion at $m/z = 2513.13$ with correct isotopic distribution in the MALDI-TOF mass spectrum, and X-ray diffraction studies. Substantially higher hemicarcerand yields were obtained in the condensation between extended cavitand **8** and **5c** under identical conditions as described for **2c**. Again, equilibrium was reached after two days leading to a mixture composed of only hemicarcerand **9c** and excess **5c** (Figure 2C). From this solution, **9c** crystallized in 85% yield (Figure 2D). NMR spectra and MALDI-TOF MS of **9c** are fully consistent with its structure and support a [2+4]-condensation product with eight newly formed acylhydrazone bonds.

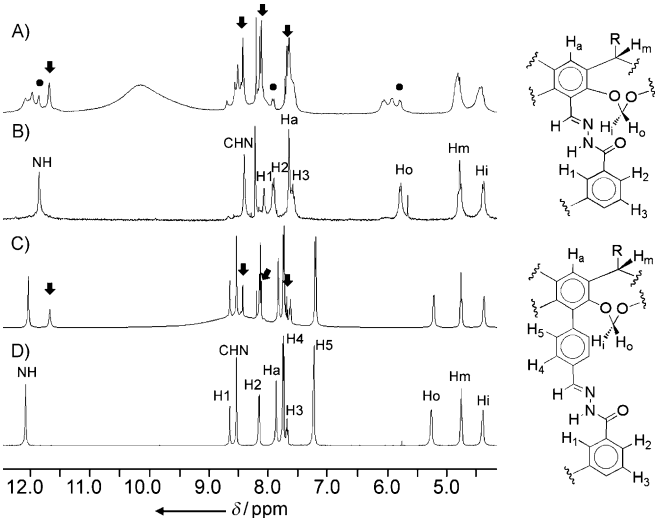


Figure 2. ^{1}H NMR spectra ($(CD_3)_2SO/CDCl_3$; 500 MHz; 25°C) of A) products formed in the reaction between **1** and **5c** (2.7 equiv) in the presence of TFA; B) **2c**; C) products formed in the reaction between **8** and 3 equivalents **5c** in the presence of TFA; and D) **9c**. Multiplets assigned to **2c** and **5c** in A) and C) are labeled with closed circles and arrows, respectively.

The outcome of both condensation reactions are rationalized with the design concept outlined in Scheme 1, according to which diamines or dihydrazides with an exact or close to 120° angle between the two C-NH_2 or N-NH_2 bonds have a high propensity to form [2+4]-hemicarcerand condensa-

tion products. A marked difference, however, exists between cavitand **1** and **8** in that the latter yields **9c** quantitatively in contrast to **2c**, which makes up only 30% of the condensation products observed in the reaction mixture; the 88% isolated yield is a consequence of its low solubility in the reaction mixture, which slowly shifts the equilibrium towards hemicarcerand formation. The different propensity to form hemicarcerands must be due to conformational strain in the linker groups of **2c** that is not presence in **9c**. This hypothesis is supported by X-ray crystallography and force field calculations.

X-ray quality crystals of **2c** were grown from a solution of **2c** in DMF/chloroform in the presence of trifluoro acetic acid (TFA) (Figure 3A,B). Hemicarcerand **2c** crystallizes in the space group *C*2/*c*. Four symmetry related copies of **2a** occupy the unit cell in addition to 64 DMF, 20 chloroform, and four water molecules. Each hemicarcerand cavity is filled with two chloroform, two DMF, and one water guest molecules (Figure 3A). Both chloroform guests occupy the upper and lower cavitand of **2c**. The two DMF molecules are located in the central part of the cavity and are stacked next to each other in an antiparallel fashion leading to favorable dipole–dipole interactions. The water sits close to an equatorial opening in the host shell, where it fills a small void at the interface between the DMF and one of the $CHCl_3$ guests and forms a hydrogen bond to a carbonyl group of a linker. If viewed along the pseudo-C_4 axis, **2c** has a paddle wheel structure (Figure 3B). All linker acylhydrazones and aryls are twisted in the same direction away from the planes that bisect each cavitand along the centers of opposite aryl units. Furthermore, the crystal structure shows that the eight acylhydrazones adapt a planar *E*-s-*trans-anti* conformation. To achieve this, a substantial increase of the aryl–imine torsional angles is required relative to that in *E*-s-*trans-anti*-**12**, whereby conjugation is reduced and conformational strain in **2c** increased (Figure 4). NMR data support that **2c** adapts a similar structure in solution. In the ^{13}C NMR spectrum of **2c**, the twist of the linkers leads to a

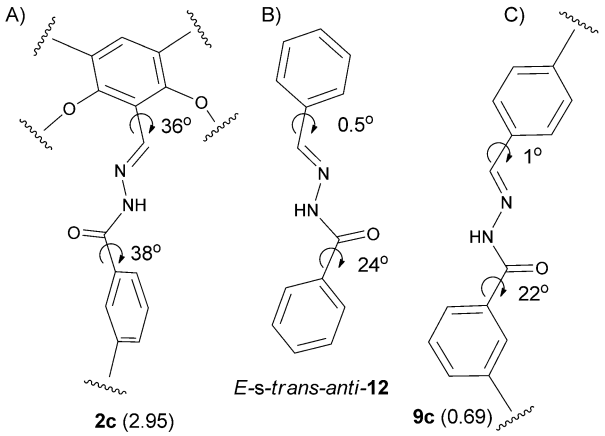


Figure 4. Comparison of *N*-aroylphenylhydrazone conformations in the crystal structures of **2c** (A) and the computed structure of **9c** (AMBER*, $CHCl_3$)[39] (C) and *E*-s-*trans-anti*-**12** (B3LYP/6-31G(d)) (B). Linker strain energy (kcal mol^{-1}) associated with the *N*-aroylphenylhydrazone units in **2c** and **9c** were computed (AMBER*, $CHCl_3$)[39] and are given in parenthesis.

2.8 ppm chemical shift difference between diastereotopic arylcarbons C3 and C3′, most likely due to a field effect induced by the imine electron lone pairs. This effect is still felt at C2 and C2′. From the chemical shift difference $\Delta\delta = \delta_{C2} - \delta_{C2'} = 0.28$ ppm at 50 °C, we estimated $\Delta G^{\ddagger}_{323K} \geq 16.2$ kcal mol^{-1} as the lower limit of the free energy of activation for the switching motion that leads to a change in twisting sense of the linkers (Figure 5).

X-ray quality crystals of **9c** were grown from solutions of the complex in DMSO/chloroform, also containing TFA, by slow evaporation of the solvent. Unfortunately, due to the small crystal size and the large cavity of **9c**, which is filled with mostly disordered solvent molecules, the quality of the structure was too low for publication. Therefore, the energy-minimized structure of **9c** (Amber*; $CHCl_3$,[39] Figure 3C,D) will be used in the further discussion. Like **2c**, **9c** shows a

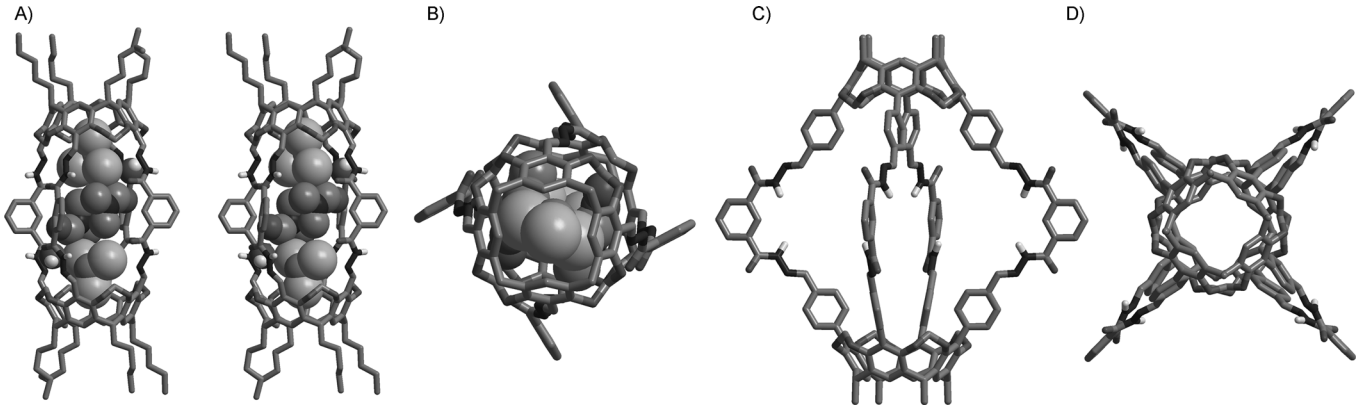


Figure 3. A) Stereoview of a stick model of the crystal structure of **2c**⊂$[CHCl_3]_2[(CH_3)_2NCHO]_2[H_2O]$ viewed perpendicular to the pseudo-C_4 axis. B) Stick models of the crystal structure of **2c**⊂$[CHCl_3]_2[(CH_3)_2NCHO]_2[H_2O]$ viewed along the pseudo-C_4 axis. C) and D) Stick models of energy-minimized structures of **9c** (C, D; Amber*, $CHCl_3$) viewed perpendicular to and along its polar C_4 axis, respectively. Encapsulated guests are shown as space filling representation. Non-polar hydrogens are omitted for clarity. Appending pentyl groups are omitted in B) for clarity or are replaced with methyl groups in C) and D).

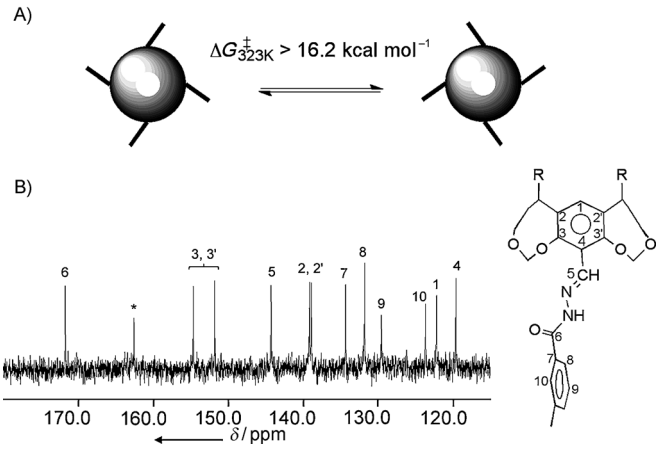


Figure 5. A) Cartoon drawing of the top view of **2c** showing the dynamics of linker flips. B) Partial ^{13}C NMR spectrum of **2c** (125 MHz, $CDCl_3$, 25 °C). Signal marked with an asterisk is assigned to $HC(O)N(CH_3)_2$ impurity.

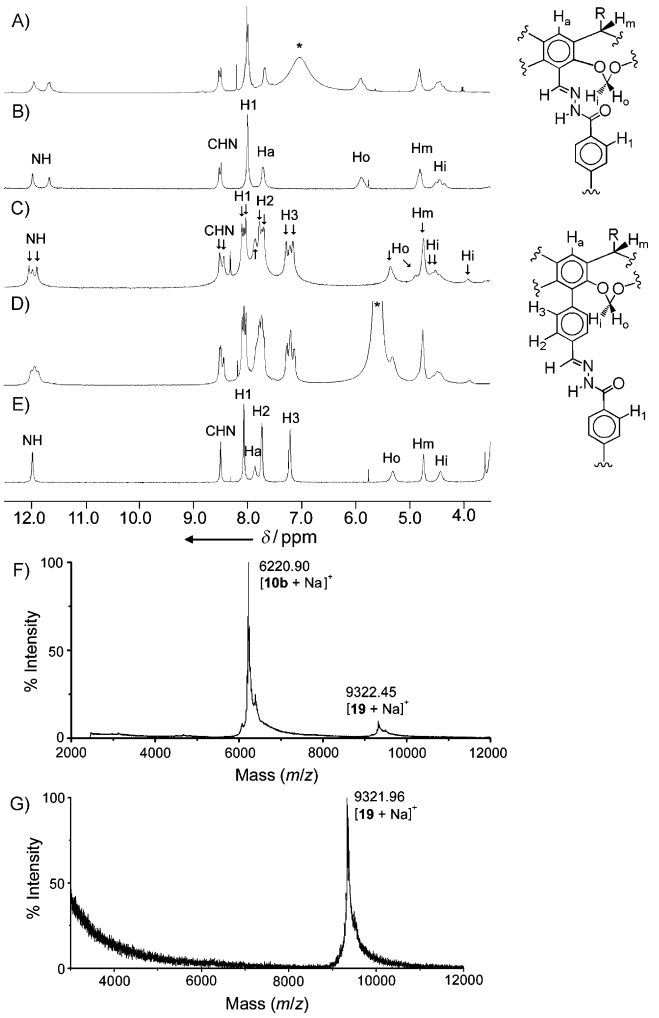
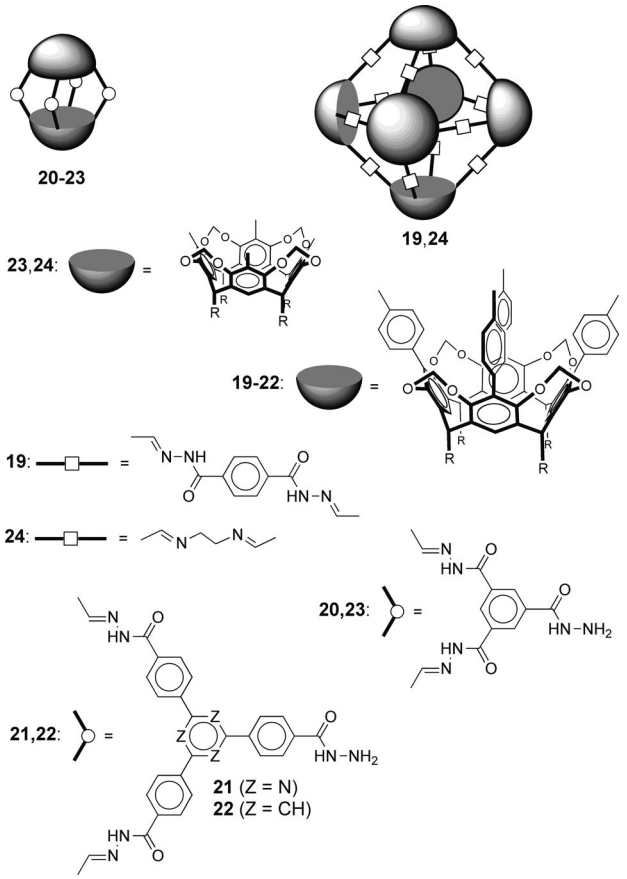


Figure 6. A)–D): ^{1}H NMR spectra ($(CD_3)_2SO/CDCl_3$ (2:1) 500 MHz; 25 °C) of products formed in the reaction between **1** and two equiv **6b** in the presence of TFA (A; * marks $CF_3CO_2^-H_3O^+ + H_2O$ signal), of **3b** (B) and of products formed in the reaction between **8** and two equiv **6b** in the presence of TFA after two days (C; ↓ are signals assigned to **10b**) and 60 days (D). E) ^{1}H NMR spectrum ($(CD_3)_2SO$; 500 MHz; 25 °C) of pure **19**. F) MALDI-TOF MS (THAP matrix) of mixture C, showing signals for $[\mathbf{10b}+Na]^+$ and $[\mathbf{19}+Na]^+$. G) MALDI-TOF MS (THAP matrix) of crystallized **19**.

paddle wheel structure, if viewed along the polar C_4 axis, but has pseudo-D_{4d} symmetry and a nearly spherical cavity. The structure is consistent with the NMR data of **9c** as well as its diffusivity $D = (1.05 \pm 0.01) \times 10^{-6}$ cm^{2}s^{-1} in $CDCl_3/(CD_3)_2SO$ (1:2) at 25 °C. Using the Stoke–Einstein equation, we estimate a solvodynamic diameter of 2.4 nm, which is close to the cavitand-center to cavitand-center distance $d = 1.9$ nm in the X-ray structure of **9c**. The acylhydrazones adapt a planar *E*-s-*trans-anti* conformation with the carbonyl groups pointing away from the cavity. Based on force-field calculations (Amber*, $CHCl_3$),[39] we estimate a 2.26 kcal mol^{-1} higher strain energy per linker group in **2c** as compared to **9c**, which is primarily a result of different torsions in both linkers (Figure 4). As a consequence, linker cleavage by means of intermolecular transimination with excess free **5c** will be less favorable for **9c** than for **2c**. We believe that partially opened structures constituted part of the product mixture observed in the condensation of **1** and **5c** and are absent in the same reaction of **8** (Figure 2A, C).[40] These conclusion are consistent with the outcome of reactions between cavitands **1** and **8** with aryltrihydrazides **7b–e**, in which variations in the linker conformational energies explain the propensity of a particular cavitand–aryltrihydrazide combination to assemble into hexacavitand nanocapsules (see below).

Reaction of cavitands 1 and 8 with terephthalic dihydrazide 6b: Based on the outcome of reactions between **1** with rigid, linear diamines such as **6a** or benzidine, which gave quantitatively tetrahedral [4+8]-condensation products (**3**),[24b] a similar nanocapsule is expected for the condensation of **1** with two equivalents of the linear dihydrazide building block **6b**. Indeed, the ^{1}H NMR spectrum of this reaction mixture showed that tetrahedral **3b** is the main condensation product (>95%) and partially crystallized from the reaction mixture in 36% yield (Figure 6A,B). The formation of **3b** is supported by a strong $[M+Na]^+$ signal in MALDI-TOF MS at $m/z = 5004.26$, and the observation of two NH signals at $\delta = 11.97$ and 11.65 ppm (ratio 8:8), two imine protons at $\delta = 8.52$ and 8.49 ppm (ratio 8:8) and three H_i, ratio 4:8:4, at $\delta = 4.51$, 4.44 and 4.35 ppm consistent with the structure and C_{2d} symmetry of **3b**.

Under similar conditions, the reaction of the extended cavitand **8** with two equivalents of **6b** gave a slightly different outcome. After two days, the ^{1}H NMR spectrum and the MALDI TOF of the reaction mixture showed formation of two capsules that make up >95% of all products. Both were isolated in a combined yield of 78% by precipitation with methanol. We assign the major product to tetrahedral **10b**, which formed in an approximate 6:1 ratio together with octahedral hexacavitand capsule **19** (Scheme 3). Consis-



Scheme 3. Octahedral nanocapsule **19** and **24** and hemicarcerands **20**–**23**.

tent with these assignments are the observation of [**10b**+Na]$^+$ and [**19**+Na]$^+$ ions at correct mass-to-charge ratio as major signals in the MALDI-TOF MS of the products (Figure 6F). However, when the reaction mixture was allowed to stand at room temperature for a longer time, the ratio [**10b**]/[**19**] slowly decreased from 6:1 to 6:5 after two months by means of a slow equilibration.[41] From this mixture, pure **19** crystallized and was isolated in 56% yield (Figure 6D, E, and G). The ^{1}H NMR spectrum of pure **19** is fully consistent with its octahedral symmetry and shows one signal each for NH, H_{imine}, H_1, H_a, H_2, H_3, H_o, H_m, and H_i of **19** at $\delta = 11.97$, 8.49, 8.06, 7.85, 7.73, 7.21, 5.31, 4.74, and 4.43 ppm, respectively in a ratio 1:1:2:2:2:1:1:1. Deconvolution of the ^{1}H NMR spectrum shown in Figure 6C, allowed assignment of all multiplets to protons of **10b** and **19**, which supports the structure of **10b**. For example, two signals for NH, H_{imine}, H_1, H_2, and H_3, each in a 1:1 ratio, are observed at $\delta = 12.05$, 11.89, 8.52, 8.44, 8.10, 8.03, 7.77, 7.70, 7.28, and 7.15 ppm, respectively and three signals for H_o and H_i, each in a 1:2:1 ratio, are observed at $\delta = 5.35$, 5.35 and 4.89 ppm and at $\delta = 4.58$, 4.52 and 3.92 ppm, respectively (Figure 6C).

In contrast to **3b**, for which evidence of formation of a related octahedral hexacavitand capsule could not be obtained in the ^{1}H NMR spectrum and MALDI TOF of the reaction mixture, **10b** and **19** must have comparable thermodynamic stabilities in solution. In earlier studies, we observed a similar octahedral [6+12]-capsule **24** in the condensation of **1** with two equivalents of ethylene-1,2-diamine in $CHCl_3$, which formed in 82% yield, together with small amounts ($\approx$5%) of the tetrahedral [4+8]-capsule **3c** (Schemes 1 and 3). In THF, only **3c** was observed (35% yield). Our rationale for the formation of these nanocapsules, rather than the corresponding hemicarcerand **2d** ([2+4]-condensation capsule), was: 1) the lower conformational energy of the 1,2-diazaethylene units in the larger capsules, in which they can adapt the anti conformation, as opposed to **2d**, which requires gauche conformations, and 2) the different ability of the solvent ($CHCl_3$ versus THF) to solvate the lowest energy linker conformations in **20** and **3c**. Increasing the preference for the *anti* conformation as in ethylene-1,2-bis(4′anilide) (H_2N-C_6H_4-$CH_2CH_2C_6H_4$-NH_2) or using a rigid, linear diamine, such as **6b** or benzidine, gave quantitatively a tetrahedral [4+8]-condensation capsule. Thus, cavitand **1** inherently prefers to form tetrahedral nanocapsules with linear diamine components. This preference is confirmed with the exclusive formation of **3b** and has also been observed in cavitand-based metal-coordination capsules.[11a] It can be rationalized with the geometry of the cavitand building block, in which adjacent and opposing aryl–carbonyl bonds form angles of 44 and 63.8°, which are too small for a strain-free octahedron (60 and 90°) with a rigid diamino linker and better suited for a smaller capsule.[42] However, the formation of **19** in the condensation of **8** with **6b**, suggests that with increasing flexibility the inherent preference for the [4+8]-capsule vanishes and that larger [6+12]-condensation capsules become accessible.

Reaction of cavitands 1 and 8 trihydrazides 7b–e: We also investigated the possibility to assemble hexacavitand nanocapsules **4** and **11** through the acid-catalyzed reaction of six equivalents of **1** or **8** with eight equivalents of C_3-symmetric trihydrazides (**7b–e**; Scheme 1). Reactions were carried out in DMSO/$CHCl_3$ solvent mixtures in the presence of excess TFA. Hexacavitand capsules **4b** and **11c** were the only observable condensation products in the reaction of **1** with **7b** and of **8** with **7c** based on ^{1}H NMR spectra and MALDI-TOF MS of the reaction mixtures (Figure 7). Both capsules **4b** and **11c** crystallized from the reaction mixture and could be isolated in 44 and 48% yield respectively. The ^{1}H NMR spectra of **4b** and **11c** are also consistent with their structure (Figure 7B and Supporting Information), but show strong signal broadening especially for **4b**, which we explain with a conformational heterogeneity resulting from different orientations of the 24 acylhydrazone fragments and with the formation of different diastereomeric hexacavitand products **11c**. Hexacavitand nanocapsule **11e** was again the major product in the reaction of six equivalents of **8** with slightly more than eight equivalents of **7e**, but formed together with small amounts of the [2+4]-condensation product **22** (Scheme 3). The latter could be removed by treating the reaction mixture with polymer-bound 3-benzyloxybenzaldehyde allowing isolation of pure **11e** in 80% yield. Again, **11e** gave a MALDI-TOF MS and ^{1}H NMR spectrum consis-

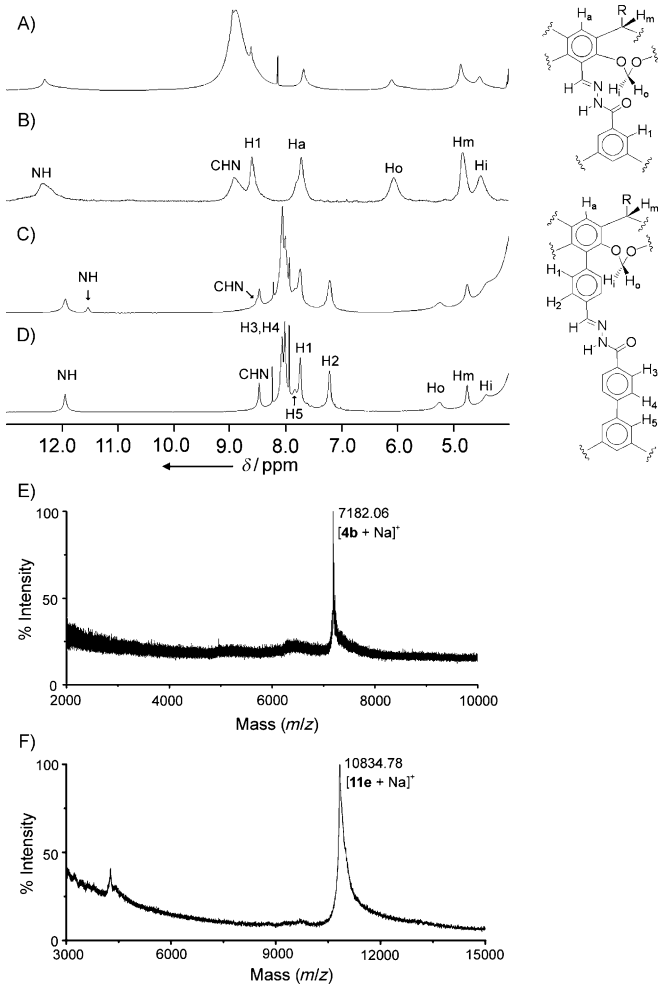


Figure 7. Partial ^{1}H NMR spectra of A) products formed in the TFA-catalyzed reaction of **1** (6 equiv) with **7b** (8 equiv), B) crystallized **4b**; C) **11e** and **22** (ratio 2:1) formed in the TFA-catalyzed reaction of **8** (6 equiv) with **7e** (ca. 9 equiv), and D) purified **11e**. MALDI-TOF MS (THAP) of E) **4b** and F) **11e**.

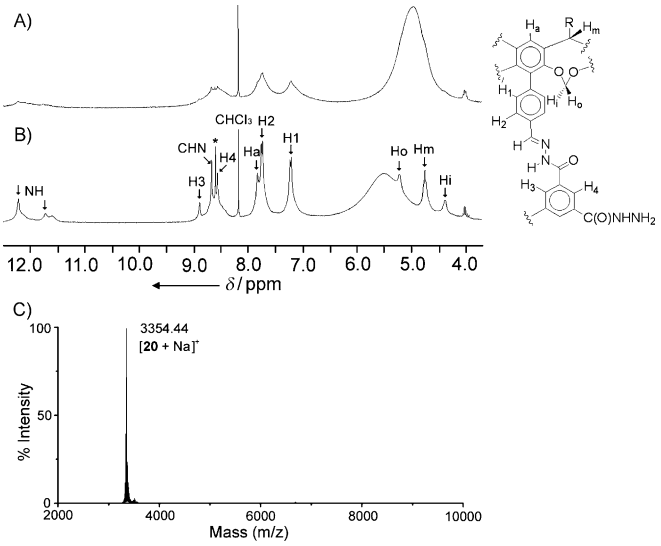


Figure 8. ^{1}H NMR spectra of products formed in the reaction of **8** (6 equiv) with A) 8.4 and B) 12.8 equiv of **7b**. Signals assigned to **20** are marked with arrows. C) MALDI-TOF MS (THAP) of reaction mixture showing only $[\mathbf{20}+\mathrm{Na}]^+$ ions.

tent with its structure. Contrary to these nanocapsule syntheses, the reaction of six equivalents of **8** with eight equivalents of trihydrazides **7b** or **7d** failed to produce the corresponding hexacavitand capsules **11b** and **11d**, respectively. Instead, GPC and MALDI-TOF MS of the reaction mixtures supported formation of larger oligomeric products (MW > 25 000) together with small amounts (< 10 %) of [2+4]-condensation products **23** and **21** (Scheme 3). The latter hemicarcerands became the major products when the cavitand to trihydrazide ratio was increased from 6:8 to 6:12 (Figure 8 and Supporting Information).

Hemicarcerand formation may compete with hexacavitand nanocapsule formation since the angle between two reacting hydrazide groups in **7a–e** is appropriate for a [2+4]-condensation. The propensity of the different trihydrazides to yield hexacavitand capsules and/or hemicarcerands can be rationalized with the linker strain in these capsules and with the tendency to maximize the number of intramolecular hydrazone linkages. We estimated the strain associated with improper acylhydrazone conformations in the hexacavitand nanocapsules and hemicarcerands from energy-minimized structures (AMBER*, $CHCl_3$) by comparing the conformational energy of each linker with that of its lowest energy conformation. Results are summarized in Table 1.

Table 1. Linker strain in energy minimized structures of hexacavitand nanocapsules **4b** and **11b**,**d**,**e** ([6+8]-capsules) and hemicarcerands **20**–**23** ([2+4]-capsules).[a]

Entry	[6+8]-Capsule	Strain [kcal mol^{-1}]	[2+4]-Capsule	Strain [kcal mol^{-1}]	Δ[b]
1	**4b**	2.51	**23**	2.95	−0.44
2	**11b**	2.95	**20**	0.69	2.26
3	**11d**	1.37	**21**	0.37	1.00
4	**11e**	1.06	**22**	0.91	0.15

[a] Amber*, $CHCl_3$.[39] [b] Δ = strain ([6+8]-capsule) − strain ([2+4]-capsule); in kcal mol^{-1}.

Based on these strain estimates, formation of a hexacavitand capsule is favored for the reaction of **1** with trihydrazide **7b**. Inserting a phenyl unit into the cavitand's aryl–CHO bond increases linker strain in the [6+8]-condensation capsule and reduces strain in the [2+4]-condensation capsule beyond that of the former capsule, such that **20** becomes the only identifiable product in the reaction of **8** with **7b**. For the same reason, reaction of **8** with **7d**, which is an extended version of **7b**, does not yield the [6+8]-condensation capsule **11d**. Our strain calculations predict similar linker strain in hexacavitand capsule **11e** and the corresponding hemicarcerand **22**. In this case, the observed product ratio is best rationalized with the tendency of this cavitand–trihydrazide system to maximize the amount of hexacavitand capsule **11e**, which has a higher ratio of intra-/intermolecular hydrazone bonds than **23**, and to minimize the amount

of free trihydrazide **7e**. For a reactant ratio [**8**]/[**7e**] of about 6:9, a capsule ratio [**11e**]/[**22**] approximately 3:1 is predicted, which is close to the observed 4:1 ratio.[43] Pure **22** is predicted for a ratio [**8**]/[**7e**] of about 6:12. Consistently, the amount of **22** increased relative to that of **11e**, if the amount of trihydrazide **7e** was increased. Likewise, pure **11e** should form for an exact reactant ratio [**8**]/[**7e**] of 6:8. Unfortunately, lowering the ratio from 6:9 towards 6:8 resulted in extensive gelation of the reaction mixture shortly after addition of TFA to the reactants, which prevented further equilibration. In this system, a small excess of **7e** is needed to break down larger reaction intermediates that would otherwise give rise to gel formation.[44]

Diffusivity and size of polyhydrazone nanocapsules: We measured the diffusivity D of nanocapsules **4b**, **9c** and **11c**, **e** by DOSY experiments. Results are listed in Table 2 together with D of **4a** and solvodynamic radii of model spheres that would have the same diffusion constants according to the Stokes–Einstein equation.

Table 2. Diffusion constant D, solvodynamic diameter $2r$ and computed longest cavitand-cavitand distance d of nanocapsules **4a**,**b**, **9c**, **11c**,**e** and **19** and viscosity η.

Nanocapsule	ϕ[a]	η [cP][b]	D [10^{-6} cm^{2}s^{-1}]	$2r$[c] [nm]	d[d] [nm]
4a[e]	0	0.539	2.08 ± 0.05	3.9	3.05
4b	0.781	1.75	0.72 ± 0.03	3.2	2.51
9c	0.673	1.88	1.05 ± 0.01	2.4	1.93
11c	0.73	1.82	0.56 ± 0.01	4.3	3.52
11e	1	2.18	0.40 ± 0.02	5.0	4.63
19	0.594	1.66	0.62 ± 0.01	4.2	4.27

[a] Ratio $(CD_3)_2SO/((CD_3)_2SO + CDCl_3)$. [b] From reference [45]. [c] Computed using the Stokes–Einstein equation. [d] Distance between the centers of cavitands on opposite sides of AMBER* energy-minimized structures. [e] From reference [46].

The newly synthesized nanocapsules show solvodynamic diameters that range from 2.5 to 5 nm and are consistent with estimates of the molecular sizes of **4a**,**b**, **9c** and **11c**,**e** based on AMBER*-minimized structures (Figure 9). The structures predict cavity diameters d that range from 2 to 4.6 nm and are of comparable size to the largest known coordination capsules.[10e,11d,r] Interestingly, the deviation between measured solvodynamic diameter $2r$ and computed capsule diameter, which is approximately the cavity diameter d plus 8–9 Å to account for the appending pentyl groups, is largest for **19** and decreases in the order **19** > **11e** > **11c** ≈ **4b**. This suggests, that the [6+8]-condensation capsules are less flexible as compared to the [6+12]-capsule, which, due to its mode of construction, should be easier deformed and compressed. Therefore, the former design should be superb for capsule assembly in aqueous solution and may provide large hydrophobic cavities in water.

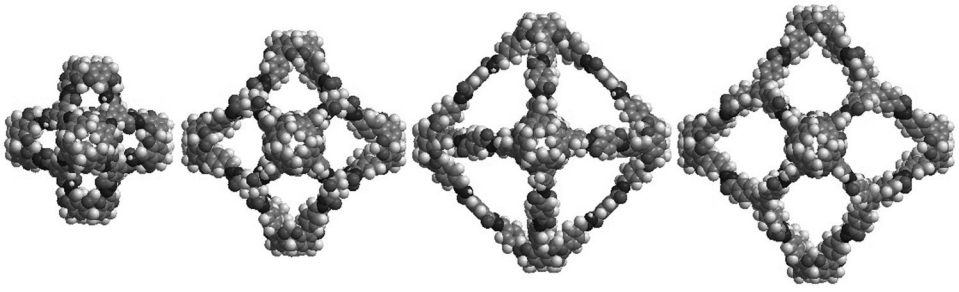


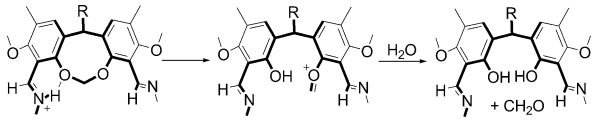
Figure 9. Space-filling models of energy-minimized structures (AMBER*, vacuum) of **4b**, **11c**, **19**, and **11d** (left to right) showing the relative size of these hexacavitand nanocapsules, whose cavity diameter ranges from 2.5 to 4.6 nm.

Conclusion

In summary, we have demonstrated that the nanocapsule design strategy outlined in Scheme 1 is applicable not only to polyimine nanocapsules, but also to polyacylhydrazone nanocapsules and allows the assembly of molecular spheres with cavity diameters that range from 2–4.5 nm. These capsules are of comparable sizes to those of the largest known coordination capsules. Furthermore, our studies highlight the interplay between linker strain and yield of hexacavitand nanocapsules and hemicarcerands and underline the importance of careful choice of building blocks in order to avoid/minimize formation of other capsules as side products. These considerations should also be applicable to the synthesis of other dynamic covalent nanocapsules involving for example imine or boronic ester chemistry.[24a,25a,d] The high sensitivity of capsule yields towards small variations in linker torsional strain is reminiscent to recent observations by Fujita and co-workers in the assembly of giant coordination nanocapsules, in which small geometrical changes in one of the building blocks led to substantial different assemblies with respect to size and number of components.[10e] This underlines the difficulty to predict the outcome of multicomponent assemblies, in which different assemblies are possible. On the other hand, it has been the basis for the discovery of new assemblies.

With respect to their properties, polyacylhydrazone nanocapsules have several advantages over related polyimine nanocapsules. 1) The higher thermodynamic stability constant of the acylhydrazone bond with respect to the imine bond suggests that these nanocapsule syntheses should be possible in water and that capsules will be more stable in water compared to their polyimine analogues. 2) A major advantage of cavitand-based polyacylhydrazone nanocapsules over most polyimine capsules that have been prepared in our group is their acid-stability. In earlier cavitand-based polyimine nanocapsule syntheses, acid-catalyzed cleavage of acetal groups of the cavitand building blocks during the

nanocapsule assembly has been a major problem and has led to substantial reduction in yield. The sensitivity of polyimine capsules towards acid cleavage depended on the aryl–C(H)=N torsional angle and was faster in larger tetra- and hexacavitand nanocapsules relative to octaimine hemicarcerands, which led us to propose intramolecular acid catalysis by the iminium ion [Eq. (2)].



(2)

Due to the substantial lower basicity of the acylhydrazones—the pK_a of an acylhydrazonium ion is estimated to be below zero—the acylhydrazones are essentially not protonated under our assembly conditions (0.1–0.2 M trifluoroacetic acid) and acetal cleavage was not detected even after several weeks. This allowed complete equilibration of the system and slow crystallization of product nanocapsules from the reaction mixture. Current efforts in our laboratory are directed towards the synthesis of water-soluble polyhydrazone nanocapsules and the exploration of their molecular recognition properties.

Experimental Section

For details of the synthesis and characterization of the compounds prepared herein, please see the in the Supporting Information

Acknowledgements

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[40] Based on the GPC of the reaction mixture leading to **2c**, byproducts have a similar molecular weight as **2c**. There are no products with more than two cavitands present in the mixture.

[41] If a 6:1 mixture of **10b** and **19** is heated to 80 °C for three weeks, an equilibrium is reached with showing a 1:1 ratio of both capsules.

[42] In the tetrahedral [4+8]-condensation capsules formed with **6a** and **6b**, the linkers have still some conformational strain.

[43] A ratio [**11e**]/[**22**] = 4:1 ratio is predicted for a ratio [**8**]/[**7e**] = 6:8.8.

[44] In preliminary experiments with a derivative of **8**, that lacks the tendency to form gels in its condensation reaction with **7e**, exclusive formation of the corresponding [6+8]-condensation capsule is observed for the ideal 6:8 reactant ratio. Junling Sun, Ralf Warmuth, unpublished results.

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