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# Capsule-like Assemblies in Polar Solvents

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Calix[4]arene derivatives with four anionic groups at their upper rim form discrete 1:1 complexes with complementary calix[4]arene derivatives bearing four cationic groups at their upper rim. Each cation is bound by two anions, and vice versa, in a mutual chelate arrangement, reinforced by a network of ionic hydrogen bonds. These multiple electrostatic interactions lead to the formation of highly stable capsule-like assemblies even in polar protic solvents such as methanol and water. In the capsule interior a cavity is formed that is in principle large enough for the encapsulation of small aliphatic and aromatic guests (170−230 Å$^3$). Monte Carlo simulations in water reproducibly lead to the same regular opimized structures. These differ mainly by their inner volume and flexibility, as demonstrated by molecular dynamics calculations. Most half-spheres can be synthesized by way of the tetrakis(chloromethyl) or the tetrabromocalix[4]arene intermediate. Oppositely charged calix[6]arenes also form strong complexes, but no indication was found for a lock in the cone conformation. The formation of the ball-shaped complexes from calix[4]arene building blocks was studied with Job plots, NMR titrations, NOESY, and variable-temperature experiments, as well as ESI-MS measurements. Investigations aimed at the inclusion of various guest molecules were carried out with alcohols, sulfoxides, benzene derivatives, and ammonium, as well as pyrazinium guests. Although binding isotherms were generated with cationic guests, these must be considered to be loosely associated around the seam rather than included inside the capsule.

## Introduction

Functional self-organized structures are extensively used in Nature. Chemists have ever been attracted to this elegant concept but only in the past decade have they learned how to program well-designed building blocks which self-assemble into defined aggregates.[1] One of the major areas involves the preparation of spherical structures with an inner cavity: molecular capsules.[2] Is it feasible to imitate the viroid protein coat, which protects and transports the genetic material of the virus? A controlled release of drugs by artificial mimics might immediately be envisioned, along with numerous other fascinating applications. The field was opened with Rebek's seminal work on hydrogen-bonded capsules from self-complementary half-spheres,[3] followed by related developments in the groups of Reinhoudt, Shinkai, Böhmer, and others (Figure 1).[4] Recent advances include the use of transition metals and chelating ligands, which self-assemble into multinuclear complexes with an ever-increasing inner volume (Fujita, Stang).[5] These have been used as reaction chambers, examples for supramolecular isomerism, and much more.[6] However, especially those capsules relying on hydrogen bonds are limited to non-

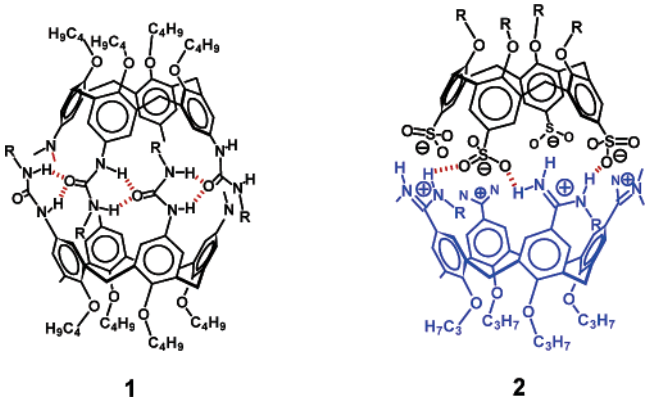

**FIGURE 1.** Self-assembled molecular capsules from self-complementary calix[4]arene tetraureas (**1**) and their ionic pendants (**2**) based on a combination of calix[4]arene tetrasulfonates with complementary calix[4]arene tetraamidinium counterions.

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polar solvents, usually chlorinated hydrocarbons, and even small amounts of DMSO or methanol completely disrupt the hydrogen bond pattern and lead to full dissociation of the container molecule into its components.[7] Very recently, the first capsules were reported which hold together by stronger ionic hydrogen bonds between resorcinarene units. These form 1:1 complexes even in polar protic solution.[8]

Nature often employs a cooperative combination of multiple electrostatic interactions between arginine or lysine residues and aspartates or glutamates on the neighboring subunits of virus particles (e.g., in the self-assembly of the tobacco mosaic virus); along similar lines we recently introduced a new concept for the construction of molecular capsule-like assemblies. The idea is a modular system of complementary half-spheres that relies on strong salt bridges in a self-reinforcing manner. Initially we focused on small, flexible, $C_{3v}$-symmetric building blocks for the generation of spherical 1:1 aggregates (Figure 2).[9] The next step included the construction of more rigid and highly preorganized half-spheres from calix[4]arenes.[10] The same idea was pursued by the group of Timmerman and Reinhoudt, who used amidinium-sulfonate calixarene ion pairs for the self-assembly of molecular capsule-like assemblies, which were highly stable in methanol/water mixtures (Figure 1).[11] They were also able to demonstrate the inclusion of tetraalkylammonium ions, such as acetylcholine, inside the cavity. We now present a complete account on the design, modeling, synthesis, binding properties, and characterization of our capsule-like assemblies based on calix[4]arene and calix[6]arene phosphonates, carboxylates, and ammonium and pyrazolium ions, as well as experiments aimed at the inclusion of various guests.

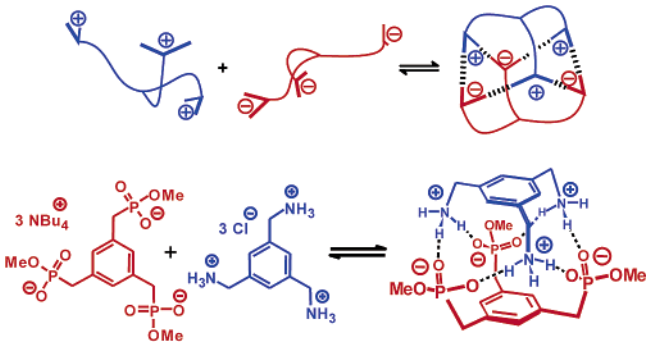


**FIGURE 2.** Top: Self-organization of flexible complementary tripods to $C_{3v}$ symmetrical spherical assemblies. Bottom: Realization of the concept with benzylic triammonium trisphosphonates.

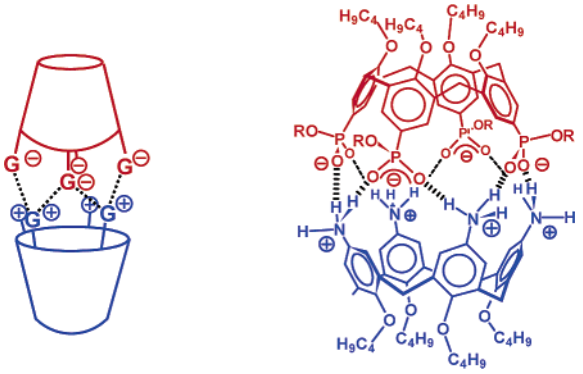


**FIGURE 3.** Left: Schematic representation of the concept of self-assembly between two rigid, complementary, oppositely charged half-spheres; each group $G^+$ or $G^-$ is engaged in a double chelate interaction. Right: Realization of the concept in tetraanionic and tetracationic calixarenes, here of the tetraphosphonate and tetraanilinium type.

## Results and Discussion

Calix[4]arenes with *O*-alkyl chains at their lower rims longer than *n*-propyl are preoriented in the *cone* or *partial cone* conformation, respectively. If the upper rim of one calixarene is adorned with four negatively charged groups, while the upper rim of a complementary half-sphere possesses four positively charged groups, both half-spheres should attract each other in polar solvents owing to multiple electrostatic interactions and finally interlock like two gear wheels. In the optimal conformation, each positive functionality is placed between two negatively charged groups and vice versa. The multiple chelate arrangement is furthermore reinforced by a network of ionic hydrogen bonds. In its interior, a relatively nonpolar cavity is formed, offering in principle space enough for small guests to be encapsulated (Figure 3).

**Molecular Modeling.** In the gas phase, in chloroform, and even in water molecular modeling studies suggest a

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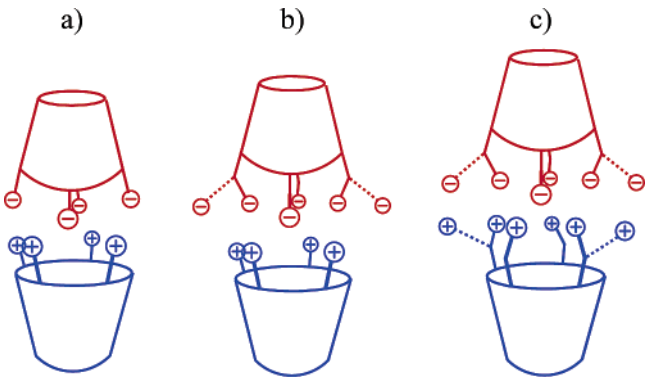


**FIGURE 4.** Schematic drawings of the three possible combinations of complementarily charged calixarene half-spheres: (a) two rigid half-spheres; (b) a rigid and a benzylic half-sphere; and (c) two benzylic half-spheres.

strong tendency for the formation of defined 1:1 aggregates, corresponding to a hollow ball with a seam of oppositely charged functional groups.[12] It has to be taken into consideration that in polar solution simple force-field calculations neglect strong solvent effects, in particular solvation entropy. In addition, the different flexibility of rigid and benzylic substituents on the upper rim (torsional entropy)[13] as well as dynamic effects are not taken into account by most calculations. Therefore, it is difficult to predict the relative stability of capsules even if they are self-assembled from quite similar components. This is, however, one of the advantages of non-self-complementary capsules over their (historical) predecessors: in a modular set of building blocks each half-sphere may be combined with almost any other, thus leading to a library of molecular capsule-like assemblies with different inner volumes and inclusion properties. After initial preoptimization of each half-sphere with molecular mechanics calculations, we performed Monte Carlo simulations of the ion pairs to find the preferred complex geometries. The best structures were always capsule-like assemblies; in selected examples they were finally subjected to a molecular dynamics calculation for 10 ps. Three obviously different classes of molecular capsule structures were produced: (a) two rigid half-spheres (their high degree of preorganization turns out to be favorable); (b) a rigid and a benzylic half-sphere (their high negative torsional entropies are unfavorable); and (c) two benzylic half-spheres (the high flexibility in the capsule seam makes these favorable for stability, but unfavorable for guest inclusion). Figure 4 shows a schematic representation of these classes, and Figure 5 contains the optimized structures derived from Monte Carlo simulations.[14]

These asthetically appealing and regular structures embrace a cavity with an inner volume between 170 and 230 Å$^3$.[15] For biologically relevant guest molecules, such as drugs and natural products, this space might be just a bit too confined. We therefore pursued an alternative idea parallel to the construction of preorganized capsules. It is well-known that even sterically demanding functionalities such as *tert*-butyl groups rotate freely through the inner part of the larger calixarenes. Thus, even with long-chain alkyl rests on the lower rim it is impossible to fix them in a *cone*-like conformation. However, if the mutual attraction of the oppositely charged, structurally disordered, larger calix[6+*n*]arenes would force them both into the *cone* conformation, a much larger cavity would develop offering space for guests, such as carbohydrates, cytostatic agents, etc.[16] Because they are more easily synthesized than their higher homologues, we focused on calix[6]arenes. The corresponding self-organized structures, which were calculated for the assemblies of two oppositely charged 1:1 calix[6]arenes by force-field calculations by using simple energy minimizations, looked at first glance very beautiful. Although their potential to form inclusion complexes with free glucose or tetrodotoxin and other alkaloids promised numerous potential applications (Figure 6), the subsequent Monte Carlo simulations distorted the energy-minimized structures and produced disordered assemblies. The regular *cone* conformation was never calculated to be at the thermodynamic minimum, as opposed to the calix[4]arenes. This is in accord with the findings of several other groups who reported a strong preference for 1,3,5-alternate structures for calix[6]arenes, which incidentally also gave capsules;[17] however, never was a capsule formed from calix[6]arene half-spheres with a regular *cone* conformation.[18] It seems that an inherent strain causes these molecules to avoid such a geometry.[19]

**Synthesis.** Chloromethylation[20] and subsequent $S_N2$ reaction led to a number of benzylic-substituted calixarenes. Depending on the choice of the nucleophile this route offers access to phosphonates, amines (via azides), and pyrazoles. Protonation with dilute HCl completes the synthesis of the cationic building blocks, whereas the phosphonates are selectively monodealkylated with LiBr in boiling acetonitrile (Figure 7).[21]

An alternative path starts with the 4-fold electrophilic bromination of the parent calixarene in its para posi-

(12) *MacroModel 7.0*; Schrödinger Inc., 2000; Force field: Amber*, water.

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(14) Rigid means direct connection of the respective ionic funtionality to the 4-position of each calixarene aromat; benzylic means connection via an additional methylene group.

(15) Height of the inner cavity (VDW surface), 8−10 Å; width, 7−8 Å. (a) Hamann, B. C.; Shimizu, K. D.; Rebek, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1329. (b) Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996**, 2533−2534. (c) Hayashida, O.; Sebo, L.; Rebek, J. *J. Org. Chem.* **2002**, *67*, 8291−8298. (d) Thondorf, I.; Broda, F.; Rissanen, K.; Vysotsky, M.; Böhmer, V. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1796−1800.

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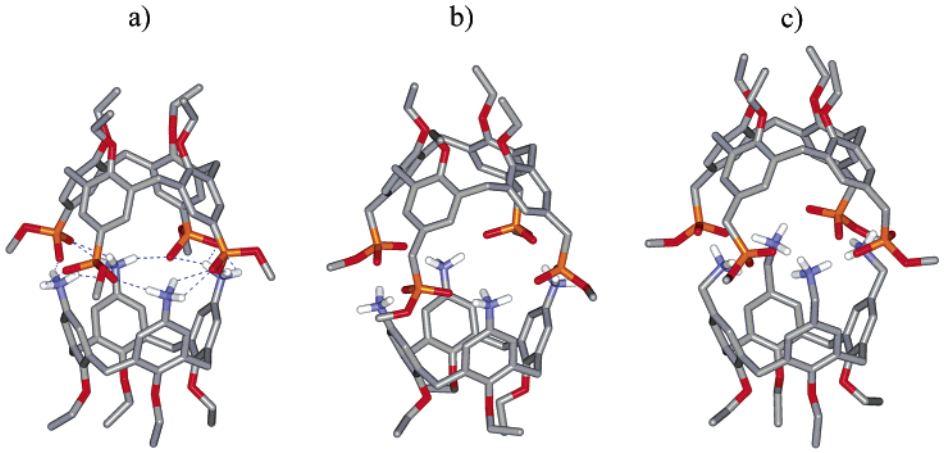


**FIGURE 5.** Three optimized structures corresponding to the above-mentioned cases of Figure 4: (a) tetraphosphonate-tetraanilinium assembly; (b) tetrabenzylphosphonate-tetraanilinium asssembly; and (c) tetrabenzylphosphonate-tetrabenzylammonium assembly. Monte Carlo simulations: MacroModel 7.0, Amber*, 3000 steps, water.

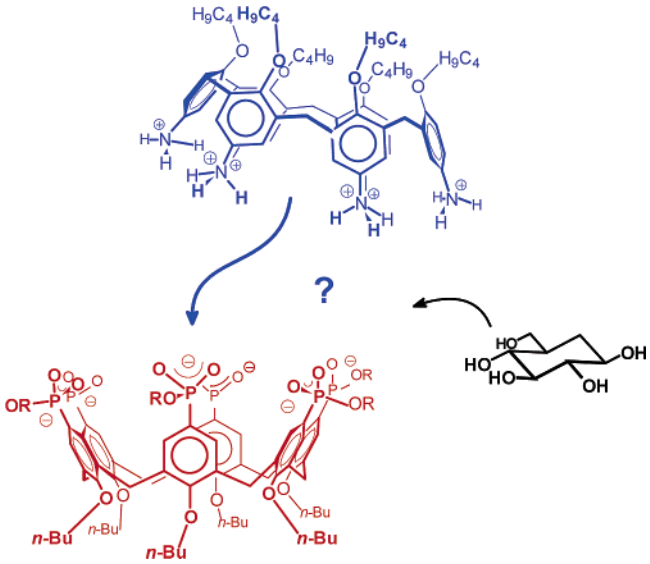


**FIGURE 6.** Putative 1:1 assembly between two calix[6]arene building blocks with oppositely charged functionalizations at the upper rims. According to molecular mechanics calculations, free glucose should be a potential guest for inclusion inside the large cavity.

tion,[22] followed by halogen−metal exchange and subsequent reaction with electrophiles. With a Ni(II) catalyst and triethyl phosphite the aromatic phosphonate was obtained,[23] while conversion to the organolithium compound and reaction with $CO_2$ furnished the tetracarboxylate.[24] Again, mild ester cleavage of the phosphonate ethyl ester was brought about by nucleophilic attack with LiBr in a dipolar aprotic solvent. The anilinium compound is accessible by nitration and subsequent catalytic hydrogenation.[25] Thus, a series of three cationic and three anionic building blocks was prepared (Figure 8).

The larger calix[6]arenes required much more drastic reaction conditions and markedly prolonged reaction times for complete (that is, 6-fold) conversion. Nevertheless, the above-outlined synthesis could be transferred to the benzylic dimethyl phosphonate[26] as well as the benzylic pyrazolium[27] derivatives in good yields. In this case, a 6-fold monodealkylation of the phosphonates with LiBr was no longer possible and led to considerable degradation of the calixarene backbone. Therefore, the hydrolysis was carried out with tetrabutylammonium hydroxide in water, giving the hexaanions in quantitative yield. The hexapyrazole could be protonated with stoichiometric amounts of 0.1 M HCl (Figure 9). All symmetrically functionalized calixarene derivatives displayed very simple and sharp NMR spectra with a single set of signals for identical aromatic units. All calix[4]arene derivatives have two well-separated doublets for the bridging methylene groups, and the diastereotopic splitting proves an overall calixarene cone conformation. By contrast, the $^1$H NMR spectrum of each calix[6]arene derivative only shows a broad averaged singlet for the six methylene groups. Here the conformational flexibility of the larger cyclophane is revealed, allowing even sterically demanding *O*-alkyl rests at the lower rim a free rotation through the macrocycle. In their ionic form all new compounds were highly soluble in water and methanol, but they did not dissolve at all in nonpolar organic solvents.

**Self-Assembly.** A first indication of strong interactions between oppositely charged calixarene half-spheres came from their 1:1 mixtures, which in most cases dissolved well in methanol, but precipitated from water. Interestingly enough, the supernatant solutions showed sharp NMR signals as well as negligible complexation-induced shifts in the aromatic region and for the aliphatic tail. From this, we concluded that calixarene tetracations and tetraanions do not aggregate by hydrophobic interactions between their electron-rich aromatic $\pi$-faces and/or their hydrophobic *O*-butyl groups. The drastic drop in solubility could then be explained by formation of a mutual chelate

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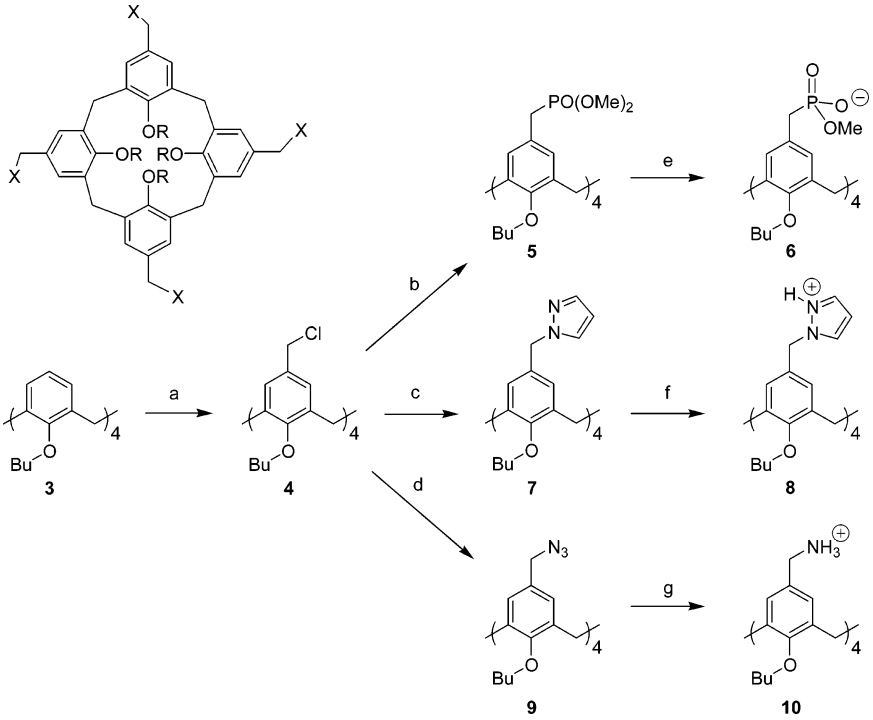


**FIGURE 7.** Synthetic route to the benzylic calix[4]arene half-spheres: (a) chloromethyloctyl ether, $SnCl_4$, 75%; (b) $P(OMe)_3$, 180 °C, 73%; (c) pyrazole, KOH, 91%; (d) $NaN_3$, 86%; (e) $[NBu_4]OH$, 93%; (f) HCl, 100%; and (g) $H_2$, Pd/C, HCl, 83%.

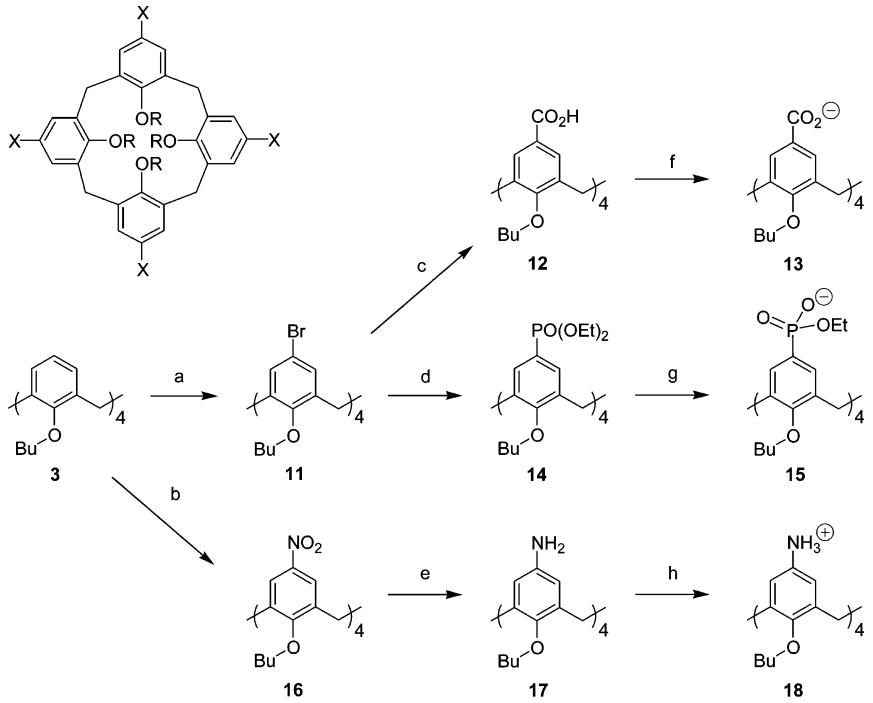


**FIGURE 8.** Synthetic route to the calix[4]arene half-spheres with functional groups directly attached to the 4-position: (a) NBS, 75%; (b) $HNO_3$, $H_2SO_4$, 65%; (c) *t*-BuLi, $CO_2$, 70%; (d) $NiCl_2$, $P(OEt)_3$, 62%; (e) $H_2$, Pd/C, 89%; (f) $[NBu_4]OH$, 90%; (g) LiBr, 90%; and (h) HCl, 100%.

arrangement that shields the ionic groups from the solvent. A comparable behavior is well-known from zwitterionic amino acids at their isoelectric point. A second hint was provided by Job plots which consistently proved a clean 1:1 stoichiometry for all examined assemblies (Figure 10).[28] In principle, this result does not exclude the possibility of higher aggregates, although such highly ordered structures would be entropically unfavorable. ESI mass spectrometry turned out to be a valuable tool for the examination of these complexes. Not only could all single half-spheres be detected with high

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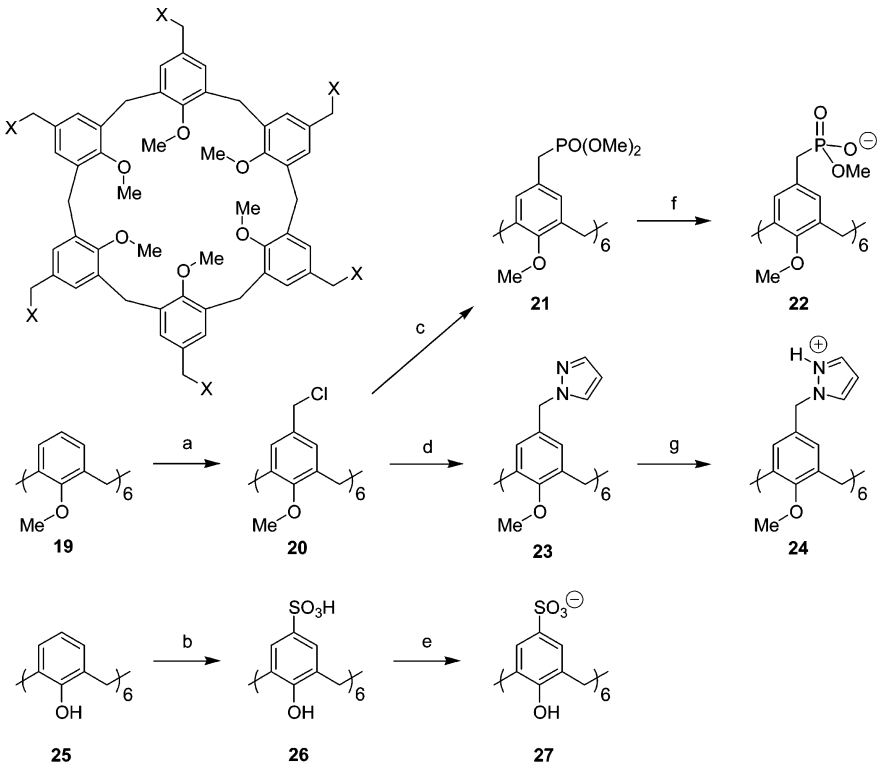


**FIGURE 9.** Synthesis of substituted calix[6]arene half-spheres: (a) chloromethyloctyl ether, $SnCl_4$, 90%; (b) $H_2SO_4$, 75%; (c) $P(OMe)_3$, reflux, 7 d, 53%; (d) pyrazole, 7 d, 72%; (e) $BaCO_3$, 100%; (f) $[NBu_4]OH$, 20 d, 100%; and (g) HCl, 100%.

intensities, but also every 1:1 aggregate furnished a prominent molecular ion peak. Usually, the assemblies produced the strongest peaks in the positive mass range, by picking up one alkali counterion from the solution. No molecular ion peaks for higher clusters were visible in the ESI spectra, whatever their charge state might be (Figure 10a). The only changes in the NMR spectra on complex formation were found in the neighborhood of the ionic groups; thus, signals of the aromatic meta protons, as well as the phosphonate ester groups, showed appreciable complexation-induced shifts. From these, binding curves were obtained by conventional NMR titrations and could be evaluated with nonlinear regression methods (Figure 10b).[29] In methanol, the aggregates hold together very strongly, with binding constants of $10^3$ to $10^5$ $M^{-1}$ (Table 1). The relatively broad range of binding constants for assemblies between various cationic species and the same anion suggests that affinities are influenced mainly by the choice of cationic and anionic headgroups on the upper rim. This, in turn, is a good indication for a specific ionic interaction that depends on acid strength, cation/anion distances, solvation entropies, and enthalpies. The best binders are doubly benzylic phosphonate and ammonium half-spheres, followed by the rigid aromatic phosphonates and anilinium calixarenes. Interestingly enough, this reflects the above-discussed groups for capsule-like assemblies shown in Figures 4 and 5. The p$K_a$ differences between the headgroups are equally important. It seems that the larger the p$K_a$ difference, the more stable the capsule-like assemblies. We determined the p$K_a$ values for two cationic building blocks by potentiometric titration and an analysis based on difference plots. Whereas the benzylammonium calixarene **10** shows a pronounced decrease in acidity from the first to the second protonation stage (p$K_a$ = 10.1, 9.4, 7.9, and 3.7, ±0.1), the p$K_a$ values for the more acidic anilinium calixarene **18** show a relatively narrow distribution.[30] In both cases, the cationic species are not fully protonated at neutral pH; however, the p$K_a$ differences toward the tetraphosphonate counterpart (p$K_a$ values around 2) are still large enough to ensure full formation of the ion pairs. Another factor adding to the thermodynamic stability of a capsule may be its rotational degrees of freedom; thus, the doubly benzylic functionalities create an entropically more favorable situation in capsules, where rotations around 8 benzylic bonds are possible without breaking the salt bridges. The molecular dynamics calculation shown in Figure 11 illustrates this drastically different mobility of the functional groups at the upper rim.

In a few cases, however, an unfavorable p$K_a$ difference resulted in mere proton transfer (**8** + **6**; **8** + **15**; **18** + **13**). Usually, this could be seen from very sharp "binding curves" pretending infinitely strong binding and large complexation-induced shifts that converged exactly at those saturation values known for the free bases. In these cases, dilution titrations were subsequently carried out in methanol, which produced smaller, but distinct, shifts that pointed to weaker interactions based on hydrogen

(29) (a) Schneider, H. J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442−6448. (b) Wilcox, C. S. In *Frontiers in Supramolecular Chemistry*; Schneider, H. J., Dürr, H., Eds.; VCH: Weinheim, Germany, 1991; pp 123−143.

(30) The first two protonation steps could be determined at p$K_a$ = 4.0 and 3.5 (±0.1), the last two had to be estimated between 4 and 5.5 due to increased precepitation. Potentiometric titrations were carried out in water/DMSO (benzylammonium) or water/methanol 2:1 (anilinium) solvent mixtures at 25 °C and an ionic strength of 0.1 M (KCl). For details of the analytical procedure, see: Kraft, A. *J. Chem. Educ.* **2003**, *80*, 554−559 and references cited therein.

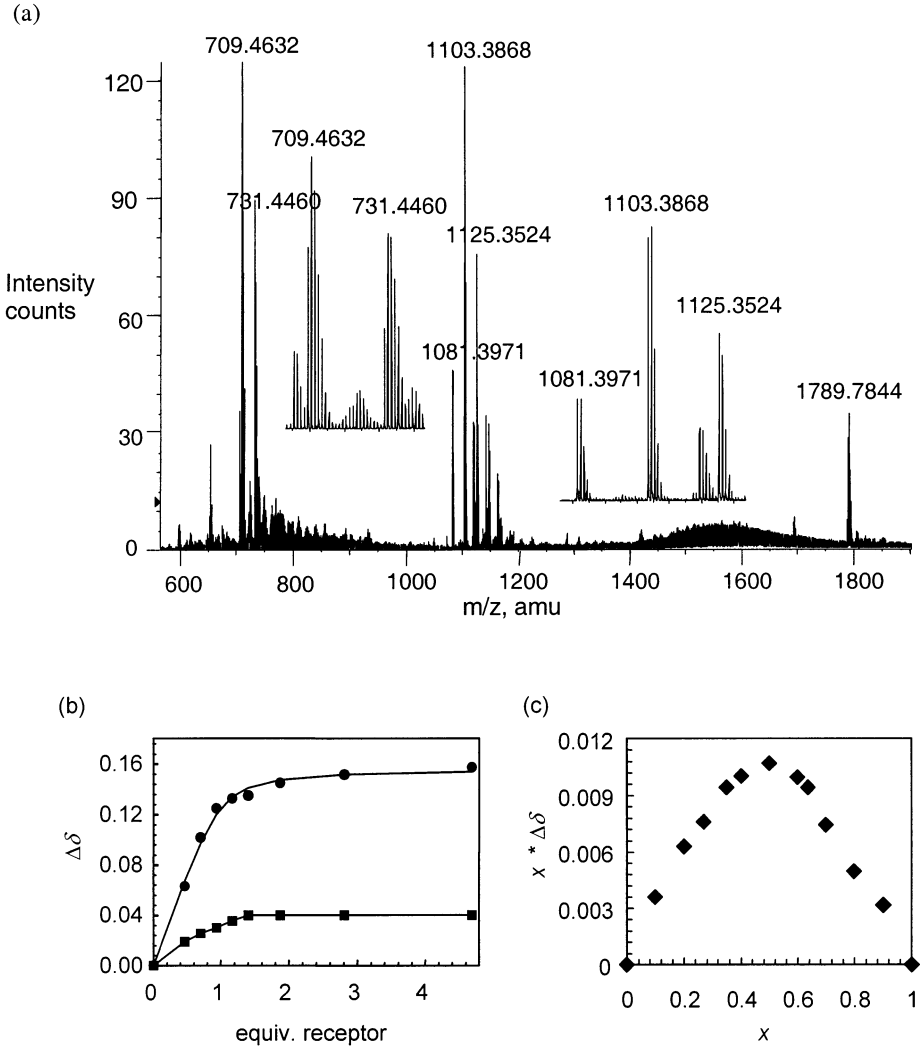


**FIGURE 10.** Evidence of capsule formation between tetracarboxylate **13**, tetraphosphonate **6** or **15**, and tetraammonium calix[4]arene half-spheres **10** or **18**: (a) ESI-MS spectrum (**15** + **18**), (b) NMR titration curves (**6** + **13**), and (c) Job plot (**6** + **10**). Positive ion ESI-MS: calcd for [**18** − 3H$^+$]$^+$, 710; calcd for [**15** + 5H$^+$]$^+$, 1081; calcd for [**15** + **18** + H$^+$]$^+$, 1792; all other peaks result from H$^+$/Na$^+$ exchange. No ion peaks were found beyond *m*/*z* 1800.

**TABLE 1. Binding Constants, $K_a$ [M$^{-1}$], and Gibbs Free Energies of Association [kcal mol$^{-1}$] in Methanol at 25 °C from NMR Titrations between All Possible Combinations of Calix[4]arene Half-Spheres**[a]

| 1:1 complex[b] | benzylphosphonate **6** | Δ*G*[c] | carboxylate **13** | Δ*G*[c] | phosphonate **15** | Δ*G*[c] |
|---|---|---|---|---|---|---|
| pyrazolium **8**[d] | (4 ± 0.1) × 10$^3$ | −4.8 | no shifts | − | (2 ± 0.6) × 10$^3$ | −4.4 |
| ammonium **10** | (4 ± 0.4) × 10$^5$ | −7.5 | (3 ± 1.1) × 10$^4$ | −6.0 | (7 ± 2.5) × 10$^5$ | −7.8 |
| anilinium **18** | (7 ± 1.0) × 10$^3$ | −5.2 | (7 ± 1.3) × 10$^3$ [d,e] | −5.2 | (1 ± 0.5) × 10$^4$ [f] | −5.4 |

[a] Unless stated otherwise. [b] Errors are standard deviations from the nonlinear regressions. [c] In kcal mol$^{-1}$. [d] Determined by dilution titration. [e] In DMSO-$d_6$. [f] In $D_2O/CD_3OD$ (1:4).

bonds. The resulting $K_a$ values were in the order of $10^2$ and $10^3$ M$^{-1}$. It is remarkable that these capsule-like assemblies hold together only by virtue of 8 hydrogen bonds without any ion pairs. Similar effects have been observed with pyridine-containing calixarenes in DMSO,[31] as well as with resorcinarenes in protic solvents (vide supra).[8]

When 1:1:2 mixtures of two different cationic half-spheres and a tetraphosphonate with comparable binding constants were cooled to −30 °C, no second set of NMR signals appeared for the anionic half-sphere at any temperature, indicating rapid exchange even at such a low temperature. Here, the ionic capsule-like assemblies are fundamentally different from the hydrogen-bonded assemblies examined in nonpolar solvents.[32] No intermolecular NOESY cross-peaks could be found between the complementary, oppositely charged half-spheres. Taken in conjunction with the observed sharp calixarene signals at all half-sphere ratios, this is a good indication

(31) (a) Vreekamp, R. H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 4282−4288. (b) Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 8255−8258.

(32) Two sets of signals appear in mixtures of related calixarene tetraureas: ref 4c.

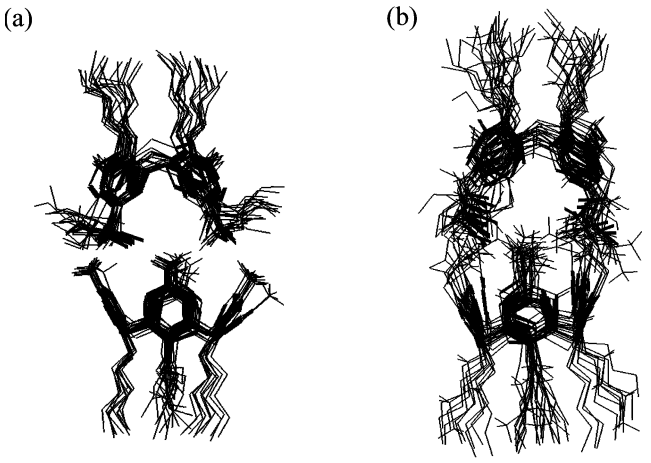


**FIGURE 11.** Molecular dynamics calculations for (a) rigid (**15** + **18**) and (b) doubly benzylic (**6** + **10**) capsule-like assemblies (MacroModel 7.0, water, 10 ps). Superimposition of 10 snapshots, successively taken every picosecond.

for the absence of any close contact between benzene walls or tails in aggregating half-spheres. On the other hand, the proposed binding pattern of alternating phosphonates and ammonium ions leads to minimum *CH*−*CH* distances of >4 Å that are hard to detect by NOESY. Timmerman et al. recently examined similar capsules with sulfonates and amidinium headgroups; they carried out extensive microcalorimetric measurements and found that capsule formation is mainly driven by entropy.[11] A comparable behavior has been found by us for the $C_{3v}$-symmetric spherical assemblies, and it can also be assumed to be the case for our phosphonate-ammonium based capsules; obviously, the release of solvent molecules from the polar functionalities at the upper rims is responsible for a marked increase in solvation entropy.

The $^1$H NMR spectra showed no diastereotopic splitting in the methylene region of calix[6]arene half-spheres upon complexation with 1 equiv of the oppositely charged building block from which we inferred that the complex structure must be disordered. Complexation-induced shifts were again found mainly in the neighborhood of the ionic groups, indicating electrostatic attraction as the main noncovalent attractive force. An NMR titration of the calix[6]arene hexaphosphonate **22** with the corresponding hexapyrazolium pendant **24** revealed complete proton transfer in methanol, as already observed before in the calix[4]arene series. However, in $D_2O$ the conformationally constrained hexammonium macrocycle **28** gave a well-defined 1:1 complex with a $K_a$ value of $5 \times 10^3$ $M^{-1}$, again without any conformational lock for the calix[6]arene. Binding experiments were also carried out between the calix[6]arene hexasulfonate **27** and the hexaaza analogue of 18-crown-6 **29** (Figure 12). At an exact 2:1 ratio between cyclophane and calixarene, a new set of sharp NMR signals occurred for the methylene groups. This pattern has been reported before for the hexasulfonate in a 2:1 complex with cobaltocenium guests.[33] Figure 13 shows the calculated structure of our proposed assembly, which is in good agreement with the structure postulated above. Although the 1,2,3-alternate cone forms a well-ordered complex with two azacrown units resembling a distorted sandwich, we found no evidence of a cavity for the inclusion of guests.

**Inclusion.** To investigate the ability of the calix[4]arene capsules to include guest molecules, we carried out numerous preliminary experiments. Usually the anionic half-sphere was first equilibrated with a potential guest molecule at ambient temperature for 2 h, followed by addition of the cationic half-sphere. $^1$H and $^{31}$P NMR spectra, as well as electrospray mass spectra, were measured after another 24 h to ensure complete equilibration in case of slow inclusion kinetics.[34] The guests were chosen from molecular modeling studies; only those guest molecules were used which did not lead to any distortion of the capsule structure during minimization. The structures of the guests varied from small, neutral, $C_2$-symmetric fragments over benzene derivatives and tetraalkylammonium ions to free zwitterionic amino acids (Figure 14).

Since small inclusion constants were expected, the guest-to-capsule ratio was varied systematically from 0.25 to 50 equiv. In all experiments, the capsule components were kept at an equimolar ratio and constant concentration so that only the cationic guest molecules displayed small complexation-induced shifts in the capsule components. The corresponding isotherms could be fitted according to a 1:1 model and produced binding constants of 300−500 $M^{-1}$ for $NMe_4^+$ (guest signals) and $10^3$ $M^{-1}$ for phenylalanine (capsule signals, Table 2). In principle, the positively charged guests could bind to the capsule-like assemblies in three possible ways: by inclusion inside the capsule; by loose association at the capsule's seam; and by opening of the capsule with subsequent inclusion into the anionic half-sphere (Figure 15). Since the capsules are far more stable ($\sim 10^5$ $M^{-1}$ in methanol) than the complexes of the respective cationic guests with the free anionic half-spheres ($\leq 10^3$ $M^{-1}$ in methanol), the last alternative can be ruled out. Inclusion of a guest inside the capsule should lead to distinct thermodynamically and mechanically stable ternary complexes, whereas a loose association of one or more guests around the seam should dissociate much more easily.[35] Apart from very small complexation-induced upfield shifts (below −0.1 ppm) in the guest molecules, we collected an increasing number of indications for the loose association mode. Contrary to the strong molecular ion peaks for each capsule combination, no peak could be detected for any ternary complex (10 ESI-MS experiments). In addition, no NOESY cross-peak could be identified between a guest and a capsule signal. An intriguing experiment was finally carried out, which settled the case (Figure 16). Inclusion of *N*-methylpyrazinium iodide and the *N*-methylated nicotinamide in the rigid tetraphosphonate anionic half-sphere **15** is accompanied by large upfield shifts of both the aromatic and the *N*-methyl protons of the pyrazine and nicotinamide derivative, because these guests are inserted into the cavity ($\Delta\delta_{sat}$ up to −3.2 ppm in methanol). A preformed 1:1 complex between *N*-methylpyrazinium

(33) Alvarez, J.; Wang, Y.; Gómez-Kaifer, M.; Kaifer, A. E. *Chem. Commun.* **1998**, 1455−1456 and 1457−1458.

(34) Hamann, B. C.; Shimizu, K. D.; Rebek, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1329.

(35) (a) Schalley, C. A.; Martín, T.; Obst, U.; Rebek, J. *J. Am. Chem. Soc.* **1999**, *121*, 2133-2138. (b) Schalley, C. A. *Mass Spectrom. Rev.* **2001**, *20*, 253−309.

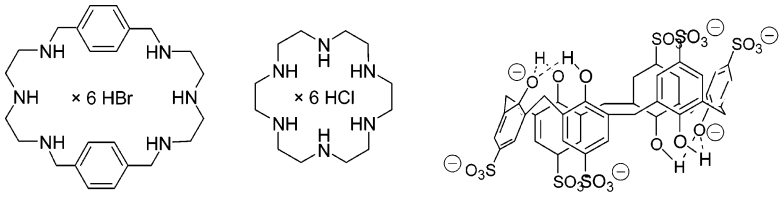


**FIGURE 12.** Left: Two noncalixarenic cationic complexation partners for calix[6]arene hexaanions. Right: 1,2,3-Alternate conformation of the calix[6]arene hexasulfonate as the octaanion.

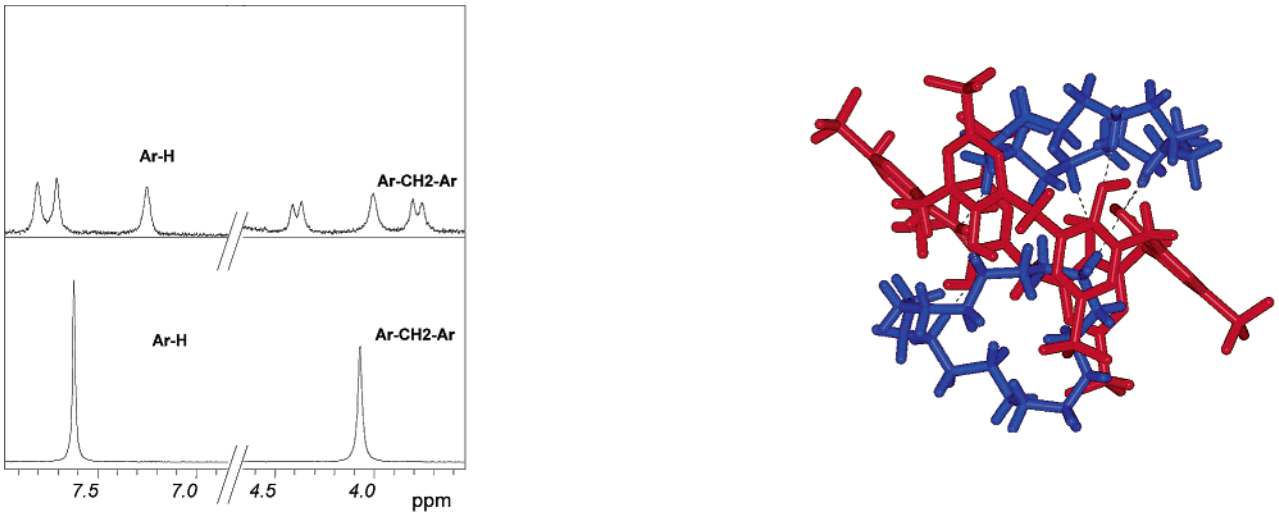


**FIGURE 13.** $^1$H NMR spectra of the aromatic and methylene region in $D_2O$ of the 2:1 complex **27** + **29** (with a pattern typical for a 1,2,3-alternate conformation, top) and, for comparison, of the free calix[6]arene hexasulfonate **27** (bottom). Right: Optimized structure of the proposed 2:1 complex.

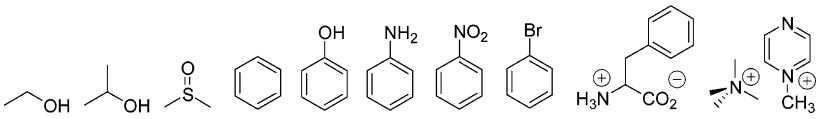


**FIGURE 14.** Examined potential guest molecules for the inclusion experiments.

**TABLE 2. Binding Constants between Preformed Molecular Capsule-like Assemblies and Cationic Guests as Determined by NMR Titrations in Methanol-$d_4$ at 20 °C**

| capsule | guest: TMA[a] | guest: phenylalanine[a] |
|---|---|---|
| anilinium **18** + phosphonate **15** | $(5 \pm 2) \times 10^{2}$ [b] | $(1 \pm 0.6) \times 10^{3}$ [b] |
| anilinium **18** + benzylphosphonate **6** | $(2 \pm 1) \times 10^{2}$ | no shifts |
| benzylammonium **10** + phosphonate **15** | $(4 \pm 2) \times 10^{2}$ | no shifts |

[a] $K_a$ [$M^{-1}$]. [b] Errors are standard deviations from the nonlinear regressions.

iodide and the tetraphosphonate was then treated with 1 equiv of the positively charged tetraanilinium half-sphere **18**. Immediately after the addition, the strong upfield shifts of all guest protons were reverted back to the chemical shifts of the free guests. Obviously, the highly stable capsule ($K_a \sim 10^5$ $M^{-1}$) was formed at the expense of the 1:1 assembly ($K_a \sim 10^3$ $M^{-1}$), and no guest was held within. If the guest had not been expelled, its upfield shifts would have been retained at least in part; on the contrary, the closing in of the lid would have caused even larger upfield shifts on the opposite side of the pyrazinium ring. Thus, we have to conclude that

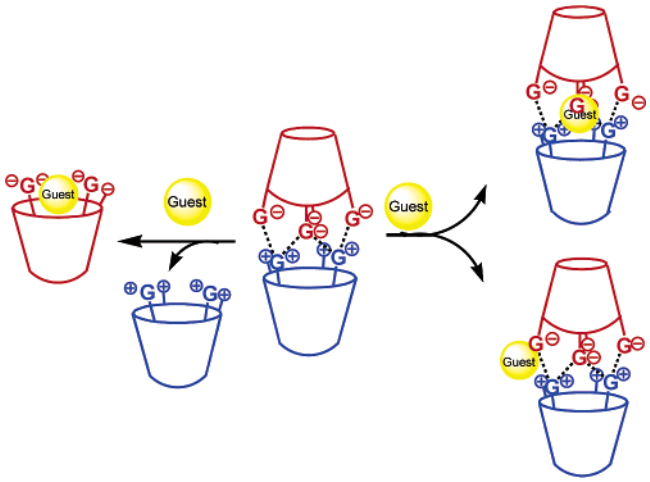


**FIGURE 15.** Three possible ways for cationic guest molecules to bind to the molecular capsule-like assemblies: inclusion in the isolated anionic half-sphere, inclusion in the capsule, and loose association around the seam.

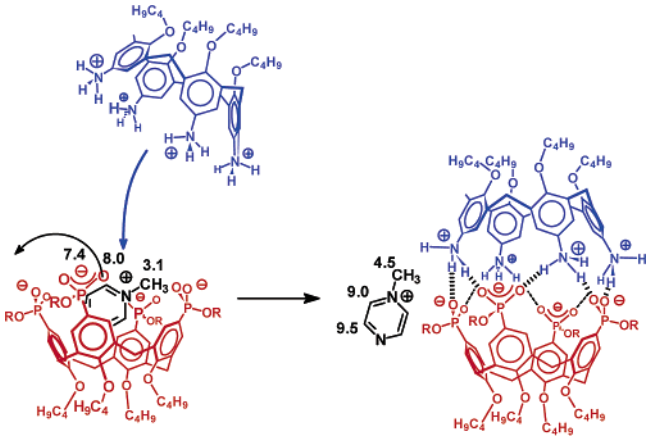


**FIGURE 16.** Inclusion of *N*-methylpyrazinium iodide inside the tetraphosphonate half-sphere **15** and its subsequent replacement by the tetraanilinium "lid". Note the drastic chemical shift changes in the guest molecule.

unfortunately no guest inclusion could be proven for the phosphonate-ammonium based molecular capsule-like assemblies. On the other hand, the clean substitution of *N*-methylpyrazinium cation by the tetracationic lid provides compelling evidence for the existence of a real capsule: the second half-sphere occupies the same space as the included monocationic guest, but it also forms a much more stable assembly. This competition experiment could be developed further into a quantitative method for the determination of binding constants. Even if a guest induces only small changes in chemical shift on complex formation with the tetraphosphonate calixarene host, large effects will be observed with the tetraphosphonate-pyrazinium complex. A similar method that relies on changes in the UV spectra has been reported recently by Anslyn et al. for the determination of citrate or tartrate anions in beverages.[36]

At this moment, we cannot offer a good explanation why our ionic capsule-like assemblies do not include any of the investigated guest molecules. Especially with tetramethylammonium ions, this behavior is clearly divergent from the sulfonate-amidinium capsules **(2)** previously presented by Timmerman and co-workers. Unlike in the case of Rebek's hydrogen-bonded capsules **(1)**, solvation effects will play a dominating role in polar solvents such as methanol and water. The highly charged capsule seam is definitely surrounded by a tightly packed solvation shell, which has to be stripped off if guests are to enter the cavity. According to molecular modeling studies, not even one water molecule will be tolerated in the chamber together with aromatic guests. Desolvation of hard ammonium and phosphonate functionalities might be more difficult than that of the softer sulfonates and alkylamidinium ions. We are currently synthesizing the corresponding ion pairs from calix[5]arenes, which also adopt a cone conformation. Their larger inner volume might be more suitable for the inclusion of guest molecules without the necessity of complete desolvation and also without severely restraining their degrees of translational freedom.

(36) (a) Metzger, A.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 649−652. (b) Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1999**, *38*, 3666−3669.

## Experimental Section

**General Information.** DMSO-$d_6$, deuterium oxide, and methanol-$d_4$ were purchased each in ≥99.8% purity. Thin-layer chromatography (TLC) analyses were performed on silica gel 60 $F_{254}$ with a 0.2 mm layer thickness. Preparative chromatography columns were packed with silica gel 60. All solvents were dried and freshly distilled before use.

For all synthetic details about the syntheses of the calix[4]arene halfspheres, see Supporting Information of Zadmard et al.[10]

**5,11,17,23,29,35-Hexa(1-pyrazolylmethyl)-37,38,39,40,-41,42-hexamethoxycalix[6]arene (23).** Chloromethylmethoxycalix[6]arene **21** (200 mg, 198 μmol) was treated with pyrazole (360 mg, 5.28 mmol), 40% aqueous sodium hydroxide (3.5 mL), 1 M aqueous tetrabutylammonium hydroxide (4 drops), and benzene (20 mL). The resulting solution was refluxed for 7 days. The product was extracted with dichloromethane, and the combined organic layers were evaporated to dryness. The remaining solid was purified by column chromatography over silica gel ($CHCl_3$/acetone 1:1). Yield 170 mg (142 μmol, 72%); $R_f$ (ethyl acetate/EtOH 1:1) 0.56; mp 106 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 18H), 3.88 (s, 12H), 4.83 (s, 12H), 6.19 (t, $J$ = 2 Hz, 6H), 6.70 (s, 12H), 7.17 (d, $J$ = 2 Hz, 6H), 7.48 (d, $J$ = 2 Hz, 6H); $^1$H NMR (300 MHz, $CD_3$-OD) δ 3.34 (s, 18H), 3.91 (s, 12H), 4.93 (s, 12H), 6.24 (s, 6H), 6.76 (s, 12H), 7.39 (d, $J$ = 1.5 Hz, 6H), 7.45 (d, $J$ = 1.5 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 30.3, 55.2, 60.5, 105.6, 128.6, 129.0, 131.8, 134.4, 19.3, 156.0; MS (FD, $CH_2Cl_2$) $m/z$ 1200 ($M^+$), 1223 ($M + Na^+$). Anal. Calcd for $C_{72}H_{72}N_{12}O_6 \cdot H_2O$: C, 70.92; H, 6.12; N, 13.78. Found: C, 70.52; H, 5.95; N, 12.48.

**5,11,17,23,29,35-Hexa(1-pyrazolylmethyl)-37,38,39,40,-41,42-hexamethoxycalix[6]arene Hexahydrochloride Salt (24).** Pyrazolylcalixarene **23** (100 mg, 71.0 μmol) was stirred with an excess of 2 M hydrochloric acid for 1 h until the calixarene was completely dissolved. The solvent was evaporated, and the resulting solid was thoroughly dried in vacuo. Yield 100%; mp 124 °C; $^1$H NMR (300 MHz, $CD_3OD$) δ 3.34 (s, 18H), 3.94 (s, 12H), 5.21 (s, 12H), 6.53 (s, 6H), 6.90 (s, 12H), 7.88 (s, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 31.2, 55.8, 61.2, 108.4, 130.0, 130.2, 131.6, 136.2; MS (FD, MeOH) $m/z$ 1241 ($M - 5$ HCl)$^+$, 1202 ($M - 6$ $Cl^- - 5$ $H^+$).

**37,38,39,40,41,42-Hexamethoxy-5,11,17,23,29,35-hexa-(dimethoxyphosphorylmethyl)calix[6]arene (21).** Hexachloromethylmethoxycalix[6]arene **20** (300 mg, 297 μmol) was refluxed for 7 d with $P(OMe)_3$ (35 mL) at 140 °C. Excess $P(OMe)_3$ was removed in vacuo. The remaining solid was dissolved in hot methanol (3 mL), and water (50 mL) was added. The product precipitated as a white solid after 48 h at 4 °C. The crude product was purified further by column chromatography ($CH_2Cl_2$/MeOH 10:1), $R_f$ 0.13. Yield 210 mg (160 mmol, 53%); mp 104 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.84 (d, $J$ = 21.2 Hz, 12H), 3.36 (s, 18H), 3.58 (d, $J$ = 10.9 Hz, 36H), 3.89 (s, 12H), 6.82 (s, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 30.3, 31.8 (d, $J$ = 137.0 Hz), 52.7 (d, $J$ = 6.7 Hz), 60.3, 126.2 (d, $J$ = 9.5 Hz), 130.2 (d, $J$ = 6.2 Hz), 134.3 (d, $J$ = 3.4 Hz), 155.3; $^{31}$P NMR (81 MHz, $CDCl_3$) δ 29.73; MS (FD, MeOH) $m/z$ 1454 ($M + H^+$), 1476 ($M + Na^+$). Anal. Calcd for $C_{66}H_{90}O_{24}P_6 \cdot 2H_2O$: C, 53.23; H, 6.36. Found: C, 52.99; H, 6.11.

**37,38,39,40,41,42-Hexamethoxy-5,11,17,23,29,35-hexa-(hydroxymethoxyphosphoryl)methylcalix[6]arene, Tetrabutylammonium Salt (22).** A solution of the dimethoxyphosphorylmethylcalix[6]arene **21** (54 mg, 37 μmol) in water (75 mL) was treated with 1 M aqueous tetrabutylammonium hydroxide (225 μL, 225 μmol). The mixture was refluxed for 20 d. After evaporation of the solvent and drying in vacuo, the product was obtained as a colorless, hygroscopic solid in quantitative yield. Mp 210 °C; $^1$H NMR (300 MHz, $D_2O$) δ 0.91 (t, $J$ = 7.6 Hz, 72H), 1.26−1.39 (m, 48H), 1.56−1.66 (m, 48H), 2.82 (d, $J$ = 20.2 Hz, 12H), 3.09−3.18 (m, 48H), 3.13 (s, 18H), 3.40 (d, $J$ = 10.3 Hz, 18H), 3.90 (s, 12H), 6.93 (s, 12H); $^{13}$C NMR (75 MHz, $D_2O$) δ 13.3, 19.6, 23.6, 30.7, 33.4 (d, $J$ = 127.5

Hz), 52.2 (d, $J$ = 6.2 Hz), 58.5, 60.6, 130.8, 130.9, 134.5, 154.3; $^{31}$P NMR (81 MHz, $D_2O$) $\delta$ 26.71; HRMS (ESI negative, MeOH/$H_2O$) $m/z$ 683.1488 $(M + 4\ H^+)^{2-}$, 803.7913 $(M + 3\ H^+ + Bu_4N^+)^{2-}$, 924.9323 $(M + 2\ H^+ + 2\ Bu_4N^+)^{2-}$, calcd for $C_{60}H_{77}O_{24}P_6^-$ 1367.3231.

**Encapsulation of Guests.** Ten NMR tubes were each filled with 0.35 mL of a solution of the anionic half-sphere ($c = 10^{-3}$–$10^{-4}$ M) in $CD_3OD$. The guest compound was dissolved in the same solvent, and the resulting solution was added at ambient temperature in increasing amounts from 0.25 to 50 equiv to the anionic half-sphere solutions. After 2 h, the cationic half-sphere (0.35 mL; $c = 10^{-3}$–$10^{-4}$ M) was finally added. $^1$H NMR spectra spectra was measured after another 24 h to ensure complete equilibration in the case of slow inclusion. The association constants were calculated by nonlinear regression methods, assuming a 1:1 stoichiometry.

**Competition Experiment with *N*-Methylpyrazinium Iodide.** A $10^{-3}$ M equimolar solution of the rigid tetraphosphonate calix[4]arene half-sphere **15** and *N*-methylpyrazinium iodide in methanol-$d_4$ was characterized by its $^1$H NMR spectrum. Then 1 equiv of the rigid tetraanilinium calix[4]arene half-sphere **18** was added directly to the NMR tube. After 1 h of equilibration, another $^1$H NMR spectrum was recorded and compared with the first one. Large chemical downfield shift changes to the values of the free guest indicated its complete expulsion from the anionic half-sphere (*N*-methyl, 3.1 ppm → 4.5 ppm; H-2, 8.0 ppm → 9.0 ppm; H-3, 7.4 ppm → 9.5 ppm.)

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**Supporting Information Available:** NMR titrations and Job plots of all calix[6]arene complexes discussed in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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