ORGANIC LETTERS

2002
Vol. 4, No. 10
1687−1690

Self-Assembly of Molecular Capsules in Polar Solvents

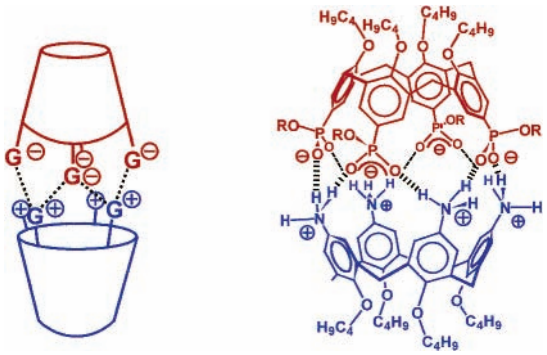
Reza Zadmard,[†] Thomas Schrader,*[,†] Thomas Grawe,[‡] and Arno Kraft*[,§]

Fachbereich Chemie, Universität Marburg, Hans-Meerwein-Strasse, 35032 Marburg, Germany, Institut für Organische Chemie und Makromolekulare Chemie, Universität Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany, and Department of Chemistry, Heriot-Watt University, Edinburgh EH14 4AS, United Kingdom

schradet@mailer.uni-marburg.de

Received February 22, 2002

ABSTRACT



We present a novel type of molecular capsule formed by self-organization of calix[4]arenes with several oppositely charged functional groups located at their upper rims. In highly polar solvents, the complementary half-spheres form stable 1:1 complexes with association constants of up to 7×10^5 M^{-1} in methanol. The cavity inside the capsules is large enough for the inclusion of small aliphatic or (hetero)aromatic guest molecules.

Self-organization of complementary moieties into new functional structures represents a fundamental process that is used extensively in Nature. Among others, the DNA double helix is formed spontaneously by the template-directed dimerization of complementary nucleic acid strands.[1] Chemists have recently designed various types of molecular capsules which self-assemble from smaller components by virtue of multiple noncovalent interactions.[2] However, most of these model systems rely on weak directed hydrogen bonds and are hence restricted to nonpolar solvents (for the few exceptions, see ref 3). We recently reported on a simple and versatile access to capsule-like complexes, which display a pronounced complex stability even in water.[4]

These noncovalent 1:1 complexes are composed of highly charged complementary building blocks based on ammonium (or amidinium) and phosphonate ions. The spheroidal complexes show high thermodynamic stability, with association constants K_a reaching 10^6 M^{-1} in methanol and in some

[†] Universität Marburg.
[‡] Universität Düsseldorf.
[§] Heriot-Watt University.

(1) (a) Pörschke, D.; Eigen, M. *J. Mol. Biol.* **1971**, *62*, 361−381. (b) Craig, M. E.; Crothers, D. M.; Doty, P. *J. Mol. Biol.* **1971**, *62*, 383−401.

(2) For an excellent review, see: (a) Conn, M. M.; Rebek, J. *Chem. Rev.* **1997**, *97*, 1647−1668. Some recent work on self-organized molecular capsules based on hydrogen bonds: (b) Heinz, T.; Rebek, J. *Nature* **1998**, *394*, 764−767. (c) Martin, T.; Obst, U.; Rebek, J. *Science* **1998**, *281*, 1842−1845. (d) Prins, L. J.; Huskens, J.; de Jong, F.; Timmermann, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498−502. (e) Hof, F.; Nuckolls, C.; Craig, S. L.; Martín, T.; Rebek, J. *J. Am. Chem. Soc.* **2000**, *122*, 10991−10996. (f) Rivera, J. M.; Craig, S. L.; Martín, T.; Rebek, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2130−2132.

10.1021/ol0257631 CCC: $22.00
Published on Web 04/20/2002

cases even exceeding 10^3 M^{-1} in water. The observed K_a values correlate well with the different degree of preorganization of the complexation partners. However, due to the relatively small size of the C_{3v}-symmetrical core unit, the cavity formed inside of these assemblies was too small for the inclusion of potential guest molecules. We have therefore transferred our concept to larger complementary structures with enough inner space for the accommodation of small aliphatic and aromatic guests.

To this end, we synthesized a modular set of tetracationic and tetraanionic building blocks based on calix[4]arenes, which had been fixed in their cone conformation by spacious protecting groups at their lower rim (Figure 1). These half-spheres are in most cases readily accessible from known precursors by standard procedures: The main synthetic route starts from *n*-butyl-protected free calix[4]arene **3**[5] which is chloromethylated in one pot to give **4**.[6] This key intermediate is treated with trialkyl phosphite and subsequently monodealkylated to furnish the first anionic building block **5** as a benzylic tetraphosphonate.[7] Reaction of **4** with sodium azide followed by reduction with hydrogen over Pd/C gives the benzylic tetramine **6**. If pyrazole is used instead, almost quantitative formation of the tetrapyrazolyl calixarene **7** is observed (Figure 2).

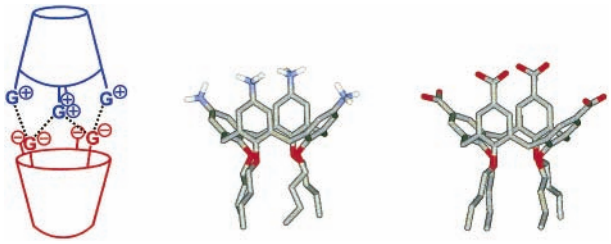


Figure 1. Extension of the above-discussed concept of self-organization of complementary half-spheres to calix[4]arenes: more charges, preorganization and inner space of the molecular capsules. Right: energy-minimized structure of a tetracarboxylate and a tetraammonium half-sphere. Note the symmetrical open cone conformation ideally preorganized for self-assembly to the capsule.

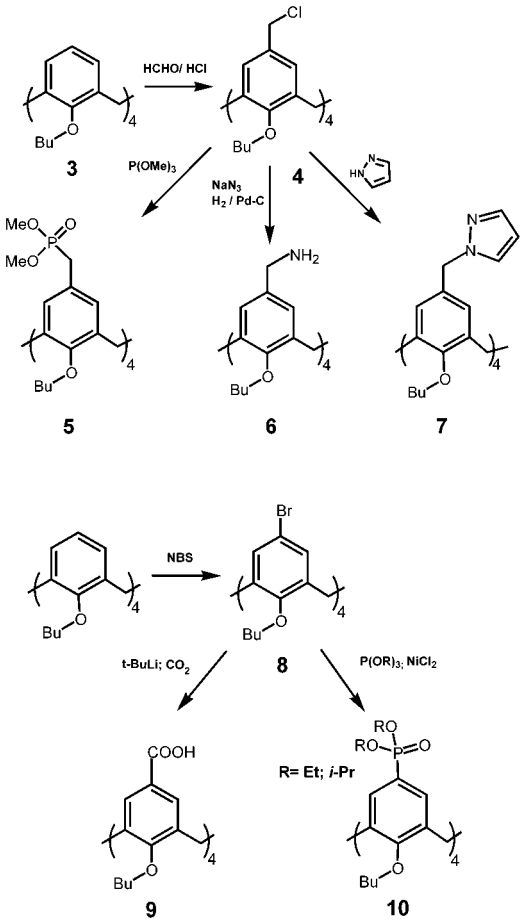


Figure 2. Synthesis of the anionic and cationic building blocks **5**−**10**.

A higher degree of preorganization is achieved if the ionic functionality is attached directly to the calixarene's benzene ring. Two anionic building blocks were prepared by way of the tetrabromo derivative **8**, which itself emerges from **3** after NBS bromination.[8] Bromine−lithium exchange on **8** with *t*-BuLi proceeds smoothly; the phenyllithium intermediate is then efficiently trapped by gaseous CO_2 to give the tetracarboxylate **9**.[9] In a nickel-II-catalyzed cross-coupling reaction at elevated temperatures, it was possible to attach also the phosphonate group directly to the upper rim of the calix[4]arene skeleton; treatment of bromide **8** with dialkyl phosphites followed by selective monodealkylation produced the third anionic half-sphere **10**.[10] Finally, the aniline equivalent of calix[4]arene **11** was synthesized by ipso-nitration of the *tert*-butyl precursor of **3**, followed by conversion of the nitro group into the aromatic amine by hydrogenation over Pd/C (Figure 3).[11] All these half-spheres

(3) Exceptions—molecular capsules in water based on metal chelates: (a) Takeda, N.; Umemoto, K.; Yamaguchi, K.; Fujita, M. *Nature* **1999**, *398*, 794−796. (b) Olenyuk, B.; Whiteford, J. A.; Fechtenkötter, A.; Stang, P. J. *Nature* **1999**, *398*, 796−798. Molecular capsules in polar solvents based on hydrogen bonds: (a) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Chem. Commun.* **2001**, 1890−1891. (b) Shivanyuk, A.; Rebek, J. *Chem. Commun.* **2001**, 2374−2375. (c) Atwood, J. L.; Barbour, L. J.; Jerga, A. *Chem. Commun.* **2001**, 2376−2377.

(4) Grawe, T.; Schrader, T.; Gurrath, M.; Kraft, A.; Osterod, F. *Org. Lett.* **2000**, *2*, 29−32. Grawe, T.; Schrader, T.; Gurrath, M.; Kraft, A.; Osterod, F. *J. Phys. Org. Chem.* **2000**, *13*, 670−673. Other ball-shaped assemblies stabilized by multiple electrostatic interactions: (a) Lee, S. B.; Hong, J.-I. *Tetrahedron Lett.* **1996**, *37*, 8501−8504. (b) Fiammengo, R.; Timmerman, P.; de Jong, F.; Reinhoudt, D. N. *Chem. Commun.* **2000**, 2313−2314. (c) Hamilin, B., Jullien, L., Derouet, C., Herve' du Penhoat, C., Berthault, P. *J. Am. Chem. Soc.* **1998**, *120*, 8438−8447.

(5) (a) Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1985**, *51*, 742−745. (b) Chawla, H. M.; Srinivas, K. *Indian J. Chem.* **1993**, *32B*, 1162−1164.

(6) Ikeda, A.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, *116*, 3102−3110.

(7) Schrader, T. *J. Org. Chem.* **1998**, *63*, 264−272.

(8) Nuckolls, C.; Hof, F.; Martin, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 10281.

(9) (a) Conner, M.; Janout, V.; Regen, S. L. *J. Org. Chem.* **1992**, *57*, 3744−3746. (b) Larsen, M.; Jorgensen, M. *J. Org. Chem.* **1996**, *61*, 6651−6655.

(10) Kal'chenko, V. I.; Atamas', L. I.; Pirozhenko, V. V.; Markovskii, *J. Gen. Chem. USSR (Engl. Transl.)* **1992**, *62*, 2161−2162.

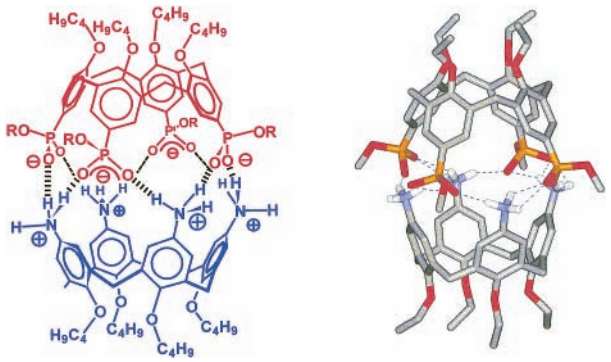


Figure 3. Proposed structure of the complex between tetraphosphonate **10** and tetraaniline **11** according to a Monte Carlo simulation in water (MacroModel 7.0, OPLS-AA, 1000 steps).

carried four positive or negative charges on their upper rim, but they differed in the number of rotatable bonds and, more importantly, the pK_a values of their functionalities. All of them were soluble in methanol and most of them in water. Force field calculations in water[12] were carried out for all possible nine combinations and invariably led to assemblies with the same binding pattern: A tetracationic building block attracted a tetraanionic counterpart and formed an alternating array of positive and negative charges, connected by a network of hydrogen bonds. This arrangement was always calculated to be much more stable than that of the simple ion pairs lacking the mutual chelate arrangement. It should be emphasized that all charged functional groups except the pyrazoles were chosen as sterically small ligands capable of forming hydrogen bonds in two directions.

A first hint for the formation of complexes with a defined composition came from Job plots between numerous combinations of half-spheres **5**−**11** in methanol: in all cases a perfect 1:1 stoichiometry was detected on the basis of NMR experiments.[13] The corresponding complexation-induced shifts of *CH*-protons were small but distinct and reproducible. Since capsule formation does not bring *CH*-protons of one calixarene in close proximity to those of the other, large changes in chemical shifts cannot be expected. No line-broadening was observed, so that clustering of the amphiphilic calixarene bowls to oligomeric or even polymeric aggregates seems unlikely. Unfortunately, the 1:1 complexes were often insoluble in water and in some cases precipitated even from methanol. However, by this procedure the aggregates could be obtained completely free of all counterions and in an analytically pure form. ESI-MS offered another indication for the formation of molecular capsules: in several cases, a molecular ion peak was found for the 1:1 complex, but no peaks could be detected for 2:2 or even higher aggregates. Molecular ion peaks were normally strong in the negative mass range but could also be found in the positive range, indicating that the complexes remained intact even with a net excess charge (Figure 4).

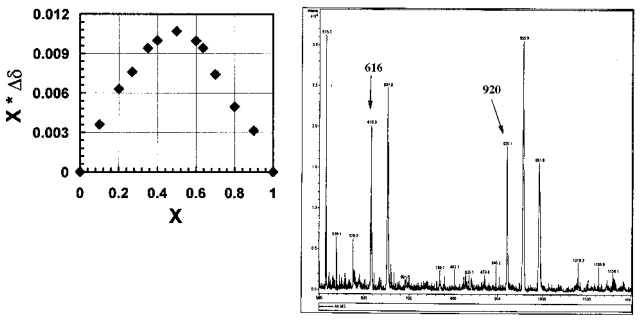


Figure 4. (a, left) Job plot for complex formation between tetraphosphonate **10** and tetraamine **6** in methanol. (b, right) ESI-MS for the same 1:1 complex from a 10^{-7} M solution in methanol (negative mass range (calcd for M^{2-} 920; calcd for M^{3-} 616; the other peaks represent chloride adducts); no peaks are found beyond $m/z = 1200$.

NMR titrations were then carried out for all nine possible combinations of cationic with anionic building blocks (Figure 5). Complexation-induced shifts of *CH*-protons of up to 0.25

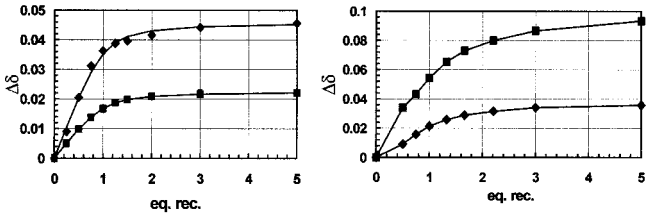


Figure 5. NMR titration curves for complex formation between tetraphosphonate **10** and tetraamine **6** (left) or tetraphosphonate **10** and tetraaniline **11** (right).

ppm were produced in methanol. The resulting binding curves gave a good fit with a 1:1 binding isotherm and were analyzed by standard nonlinear regression methods.[14] The resulting K_a values varied between 10^3 and 10^5 M^{-1} in methanol (Table 1). In four cases, the cationic part was so acidic that proton transfer to the anionic part occurred. This could be proven in two ways: first the final shifts for all *CH*-protons of the cationic building blocks were exactly identical with those of their free bases. Second, the binding curve showed a sharp kink at 1.0 equiv and the respective nonlinear regression calculated an almost infinite binding constant without reaching convergence during the fit pro-

(11) Jakobi, R. A.; Böhmer, V.; Grüttner, C.; Kraft, D.; Vogt, W. *New J. Chem.* **1996**, *20*, 493.
(12) MacroModel 7.0, Schrödinger Inc., 2000; force-field: OPLS-AA.
(13) (a) Job, P. *Compt. Rend.* **1925**, *180*, 928. (b) Blanda, M. T.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626.
(14) (a) Schneider, H. J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442. (b) Wilcox, C. S. In *Frontiers in Supramolecular Chemistry*; Schneider, H. J., Ed.; Verlag Chemie: Weinheim, 1991; p 123.

Table 1. Binding Constants K_a [M^{-1}] Resulting from NMR Titration Experiments between Anionic and Cationic Calix[4]arene Half-Spheres in Methanol at 25 °C[a]

1:1 complexes[b]	benzyl-phosphonate **5**	carboxylate **9**	phosphonate **10**
ammonium **6**	$(4 \pm 0.4) \times 10^5$	$(3 \pm 1.1) \times 10^4$	$(7 \pm 2.5) \times 10^5$
pyrazolium **7**[c]	$(1 \pm 0.1) \times 10^5$	no shifts	$(2 \pm 0.6) \times 10^3$
anilinium **11**	$(7 \pm 1.0) \times 10^3$	$(7 \pm 1.3) \times 10^3$ [c,d]	$(1 \pm 0.5) \times 10^4$ [e]

[a] Unless stated otherwise. [b] Errors are standard deviations from the nonlinear regressions. [c] Determined by dilution titration. [d] d_6–DMSO. [e] D_2O/MeOD = 1:4.

cedure. However, in most of these cases dilution titrations still produced small chemical shifts resulting in a saturation curve with K_a values between 10^2 and 10^3 M^{-1} in methanol. We conclude that after proton transfer the arrangement of acidic and basic groups around the upper rim of the calixarenes is still favorable for simultaneous formation of relatively strong hydrogen bonds; similar effects have been observed with pyridine-containing calixarenes in DMSO.[15] Several factors seem to influence the overall free binding enthalpy between the oppositely charged half-spheres. Large pK_a differences between both half-spheres usually lead to the highest binding constants. Thus the tetrabenzylammonium cation **6** (pK_a in water around 9) and both tetraphosphonate anions **5** and **10** (pK_a in water around 2) form the most stable complexes with their respective counterparts. The less basic tetraaniline **11** (pK_a in water around 4) as well as the less acidic tetracarboxylic acid **9** (pK_a in water around 5) are not completely ionized in protic solvents and lead to weaker interactions (Figure 6). With the least basic tetrapyrazole (pK_a in water around 2.5) proton transfer occurs in every case, leading to purely hydrogen-bonded capsules.

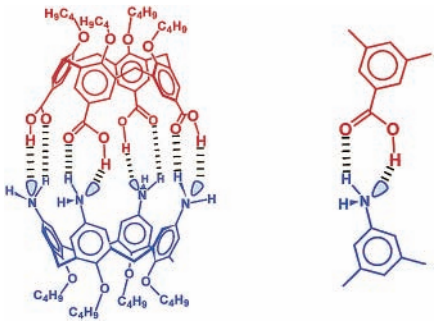


Figure 6. Left: proton transfer between tetracarboxylate **9** and tetraaniline **11** before dilution titration produces a weaker complex relying solely on hydrogen bonds. Right: six-membered hydrogen-bonded ring.

With our permutations between rigid and benzylic half-spheres, three different kinds of molecular capsules have been generated (Figure 7, a–c). They differ in their entropy balance:[16] while two flexible benzylic units allow simultaneous rotation of the anionic and the cationic group around the benzylic C–C bond even in the complex, the combination of a rigid with a flexible half-sphere severely restricts the torsional rotation of the benzylic part; otherwise the electrostatic attraction would be lost. By contrast, the combination of two rigid building blocks offers the highest degree of preorganization and should also lead to a favorable entropy balance. This may be the reason for a disappointingly low K_a for **11·5**, while the highly preorganized capsule **11·10** gives a high K_a even in aqueous methanol.

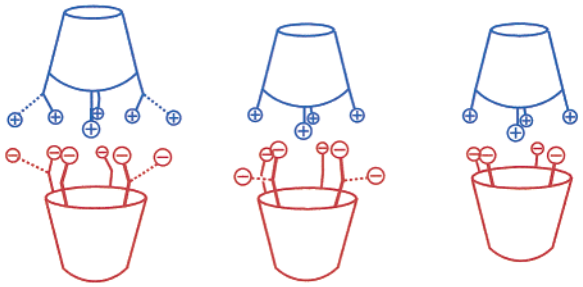


Figure 7. Schematic drawing of the three kinds of molecular capsules formed from flexible and rigid elements: (a) two flexible half-spheres, (b) a flexible and a rigid half-sphere, (c) two rigid half-spheres.

Finally, it became clear from microcalorimetric measurements of the tripodal 1:1 aggregates that the solvation enthalpy and entropy can override the complexation enthalpy and the torsional entropies.[17]

In the future, we will carry out extensive microcalorimetric investigations with the various kinds of molecular capsules; the most promising candidates will be equilibrated with a large variety of polar organic guest molecules. Their inclusion might be used for the protection of sensitive compounds, for the transport and possibly controlled release of drugs, for catalysis inside the capsule, and for many other purposes.

Acknowledgment. We thank Prof. Dr. G. Wulff (Universität Düsseldorf) for generous support during the past three years of T. Grawe's Ph.D. work. We thank the Deutsche Forschungsgemeinschaft for financial support.

Supporting Information Available: Experimental procedures, NMR titration tables and curves, Job plots. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0257631

(15) (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.

(16) For a discussion of entropy changes in multivalent complexations, see: (a) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754–2794. (b) Mammen, M.; Shakhnovich, E. I.; Deutch, J. M.; Whitesides, G. M. *J. Org. Chem.* **1998**, *63*, 3821–3830. (c) Jeyaraj, D. A.; Yadav, V. K.; Parvez, M.; Gauniyal, H. M. *J. Org. Chem.* **1998**, *63*, 3831–3837.

(17) Positive ΔH and ΔS values in tripodal aggregates: Grawe, T.; Schrader, T.; Kraft, A. Submitted. In general, positive entropies and enthalpies are often found in complexes relying on ion pairs.