Molecular Motions within Self-Assembled Dimeric Capsules with Tetraethylammonium Cations as Guest

Myroslav O. Vysotsky,[a] Anca Pop,[a] Frank Broda,[b] Iris Thondorf,[b] and Volker Böhmer*[a]

Abstract: Hydrogen-bonded, dimeric capsules of calix[4]arenes substituted at the wide rim by four urea functions show unprecedented dynamic features when a tetraethylammonium cation is included as a guest. The seam of hydrogen bonds $C{=}O\cdots(HN)_2C{=}O$ in the equatorial region which holds the two calixarene counterparts together changes its directionality fast (at 25 °C), while the dimer itself is kinetically stable on the NMR time scale. An energy barrier of $\Delta G^{\neq} = 49.9\,kJ\,mol^{-1}$ (T_c 276 K) was estimated for this reorientation from variable-temperature (VT) NMR measurements. Lowering the temperature to about −50 °C restricts also the rotation of the encapsulated tetraethylammonium cation around a *pseudo* C_2-symmetry axis in the equatorial plane of the capsule, while its rotation around the C_4 axis is still fast. As a result of this restriction two ethyl groups of the tetraethylammonium cation point towards the "poles" of the capsule, while the other pair lies in the "equator" region. Variable-temperature ^1H NMR experiments led to a barrier of $\Delta G^{\neq} = 54.8\,kJ\,mol^{-1}$ (T_c 306 K) for the exchange of these different ethyl groups. Studies with the ternary complex formed by a C_{2v}-symmetrical tetraurea proved that both processes, reorientation of the hydrogen bonds and rotation of the guest, take place independently. Molecular dynamics simulations suggest that the capsule is strongly expanded by the larger tetraethylammonium cation in comparison with benzene as guest. Thus, on average only one $N{-}H\cdots O$ hydrogen bond is formed per urea function and the interaction energy between the two tetraurea calixarenes is less favorable by about $15\,kcal\,mol^{-1}$. This is overcompensated by an energy gain of about $36\,kcal\,mol^{-1}$ due to cation–π interactions. These results provide a rationale to understand the high stability of the complex inspite of the mobility of the hydrogen-bonded belt.

Keywords: calixarenes · conformation analysis · molecular dynamics · NMR spectroscopy · self-assembly

Introduction

Self-assembly can be used to construct molecular capsules[1, 2] which are able to include one or two[3] suitable organic molecules. It may be stated even, that well defined capsules are not formed without such a suitable guest.[4] Dimeric capsules based on tetraurea derivatives of calix[4]arene held together by a seam of 16 hydrogen bonds,[5] have been characterised mainly by NMR spectroscopy[6] and in one case also by X-ray analysis.[7] The use of tetraalkylammonium cations as guests opened the door for an analytical characterisation by ESI mass spectrometry,[8, 9] but surprisingly such dimeric capsules with cationic guests have not been studied thoroughly by NMR spectroscopy.[10]

While tetraureas such as **1** or **2** are C_{4v}-symmetric (as revealed by their NMR spectra monitored in hydrogen bond breaking solvents like DMSO), the symmetry of their capsules is reduced to S_8 (or C_4 in heterodimers) due to the directionality of the $C{=}O\cdots(HN)_2C{=}O$ hydrogen-bonded belt. The two *meta*-coupled doublets thus observed for the aromatic protons of the calix[4]arene part (separated by about 1.8 ppm) can be considered as the most typical NMR proof for the dimerisation. EXSY studies with the C_{2v}-symmetrical tetraurea **3** in benzene led to the conclusion that a reversal of the directionality does not occur within a dimer but only through its dissociation/recombination.[11]

It is well known that the encapsulated guest has a strong influence on the thermodynamic stability of the capsule.[6c, 12] Recently we could show, that also their kinetic stability is strongly dependent on the guest, changing for instance by nearly three orders of magnitude in going from encapsulated

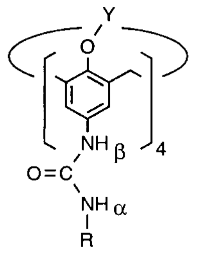
---

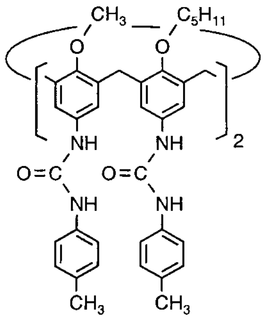
[a] Dr. V. Böhmer, Dr. M. O. Vysotsky, A. Pop
Fachbereich Chemie und Pharmazie, Abteilung Lehramt Chemie
Johannes-Gutenberg-Universität, Duisbergweg 10-14
55099 Mainz (Germany)
Fax: (+49) 6131 395419
E-mail: vboehmer@mail.uni-mainz.de

[b] F. Broda, Dr. I. Thondorf
Fachbereich Biochemie/Biotechnologie, Institut für Biochemie
Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Strasse 3
06099 Halle (Germany)

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author.

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001 0947-6539/01/0720-4403 $ 17.50+.50/0





3

1 Y = C_5H_{11}, R = Tolyl

2 Y = $C_{10}H_{21}$, R = n-C_6H_{13}

4 Y = CH_2CO_2Et, R = Tolyl

5 Y = Et, R = C_6H_5

chloroform to cyclohexane for complexes dissolved in cyclohexane.[13] We now found, that also the internal motions of the capsule are strongly influenced by the guest. In this article we describe the unexpected conformational behavior of the tetraethylammonium complexes of the self-assembled capsules formed by calixarenes **1**–**3**, studied by means of ^{1}H NMR spectroscopy and molecular dynamics (MD) simulations.

Results and Discussion

NMR studies

In $CDCl_3$ tetraurea **1** is present as a dimer with encapsulated $CDCl_3$ (Figure 1 a) indicated in the aromatic region by two strongly separated NH signals at $\delta = 9.3$ and 7.0 and two *meta*-coupled doublets for the aromatic protons of the calixarene skeleton at $\delta = 7.6$ and 5.9. Saturation of such a solution by tetraethylammonium tetrafluoroborate leads to a drastic change of the ^{1}H NMR spectrum of **1** (Figure 1 b). In the region of $\delta = 9-6$ only two sharp signals at $\delta = 9.0$ and 6.6 (ratio 1:3) are observed in addition to the two doublets of the tolyl groups. The down-field signal of one type of urea NH protons is in agreement with a hydrogen-bonded dimer, but could be explained also by strong hydrogen bonding to other acceptors (e.g. the anion). On the other hand, a single signal at $\delta = 6.6$ for the aromatic protons of the calixarene, accidentally superimposed with the second type of NH protons, is not in agreement with the typical picture found up to now for dimeric capsules. Up-field shifted signals for the tetraethylammonium cation (one broad signal at 0.9 (NCH_2) and one very broad signal at $\delta \approx -1.7$ (CH_3)) may be due to its encapsulation in a dimer, but could be also explained by its inclusion into the open cavity of a C_{4v}-symmetrical "monomeric" tetraurea,[14] eventually assisted by additional hydrogen bonding of NH groups to the anion (ion-pair complexation).

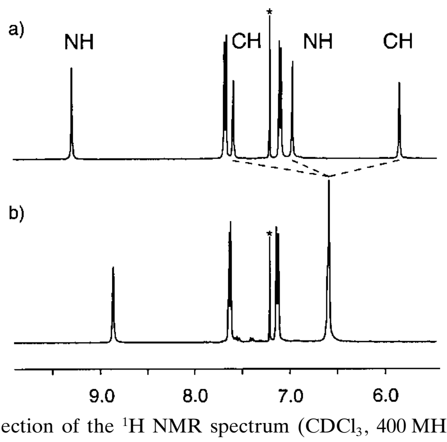


Figure 1. Section of the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, 25 °C) of a) [**1** · $CDCl_3$ · **1**], b) [**1** · Et_4N^+ · **1**]BF_4^-; (the solvent signal is indicated by an asterisk).

The integration of these guest signals, hampered by their broadness, indicated a ratio for **1**/Et_4N^+ of 2:1 rather than 1:1, and an additional proof for the dimeric structure of the complexes was found by the observation of heterodimers. The 1:1 mixture of ureas **1** and **2** extracted tetraethylammonium salts in a similar way and additional signals (e.g. two additional pairs of doublets for $ArCH_2Ar$, two additional broad triplets for OCH_2) are indeed observed in the ^{1}H NMR spectrum in complete agreement with the heterodimer [**1** · Et_4N^+ · **2**] (Figure 2). This unambiguously proves the existence of dimers which consequently must have apparent D_{4d} or C_{4v} symmetry (homo- and heterodimers, respectively) which means that the directionality of their hydrogen-bonded belt changes rapidly on the NMR time scale. From the existence of discrete homo- and heterodimers and from signals observed for uncomplexed Et_4N^+ ($\delta = 3.2$ (q, CH_2) and 1.2 (t, CH_3)), follows, that the capsules themselves are kinetically stable on the NMR time scale.[15] Therefore, the inversion of the directionality of the hydrogen bonds must occur in the present examples *within* the dimeric capsule and *not* through dissociation/recombination as observed before.

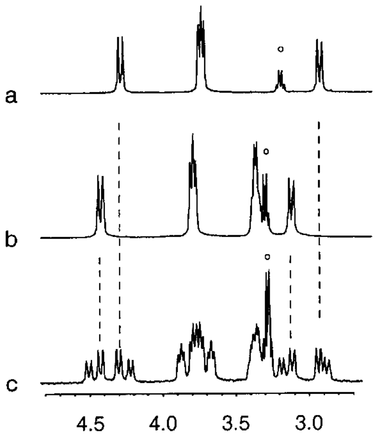


Figure 2. Section of the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, 25 °C) of a) [**1** · Et_4N^+ · **1**]BF_4^-; b) [**2** · Et_4N^+ · **2**]BF_4^-; c) mixture of [**1** · Et_4N^+ · **1**]BF_4^-, [**2** · Et_4N^+ · **2**]BF_4^- and [**1** · Et_4N^+ · **2**]BF_4^- (signals of free Et_4N^+ ions are marked by a circle).

Lowering the temperature leads to a splitting of the signals in the aromatic region, as shown in Figure 3 for the corresponding complex with Et_4N^+ PF_6^-. Most probably, this splitting is due to the directionality of the hydrogen-bonded system. The barrier for the exchange of the two directions (clockwise and counterclockwise when seen from one direction) was found to be 49.9 kJ mol^{-1} (at the coalescence

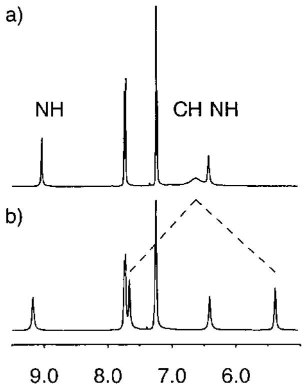


Figure 3. Section of the ^{1}H NMR spectrum (CDCl$_3$, 400 MHz) of a) [**1**$\cdot$Et$_4$N$^+\cdot$**1**]PF$_6^-$, 25 °C; b) [**1**$\cdot$Et$_4$N$^+\cdot$**1**]PF$_6^-$, -55 °C.

temperature $T_c = 276$ K) which is much lower than in case of the calixarene urea dimers with neutral organic molecules as guest, where two *meta*-coupled doublets were observed up to 100 °C.

As shown in Table 1 the chemical shifts (δ values) of the NH protons are smaller for the [**1**$\cdot$Et$_4$N$^+\cdot$**1**] complexes than for capsules with chloroform or benzene as guest. This upfield shift suggests weaker hydrogen bonding, which may be the reason for the observed rapid change of the directionality of the cyclic belt of hydrogen bonds (see below).

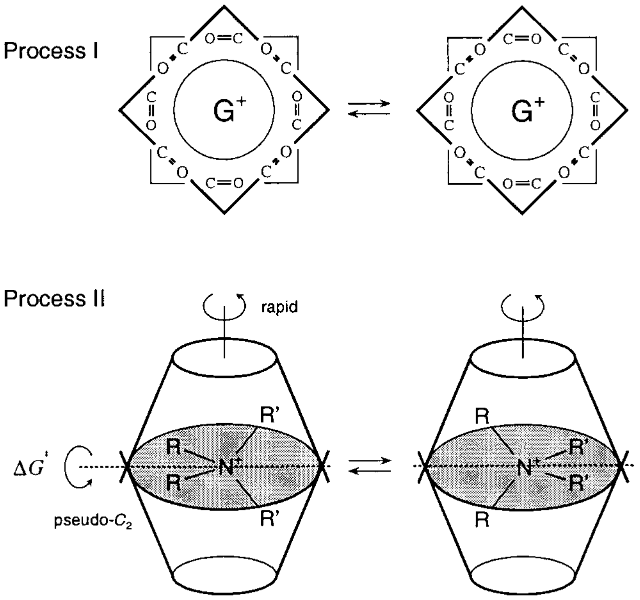
Table 1. Selected ^{1}H NMR data (in ppm) of hydrogen bonds in [**1**$\cdot$guest$\cdot$**1**] (CDCl$_3$, 400 MHz).

Complex	N-H$_\alpha$	N-H$_\beta$
[**1**$\cdot$Et$_4$N$^+\cdot$**1**]BF$_4^-$ (25 °C)	8.89	6.62
[**1**$\cdot$Et$_4$N$^+\cdot$**1**]PF$_6^-$ (25 °C)	9.04	6.42
[**1**$\cdot$Et$_4$N$^+\cdot$**1**]PF$_6^-$ (-55 °C)	9.16	6.42
[**1**$\cdot$CDCl$_3\cdot$**1**]	9.32	7.01
[**1**$\cdot$C$_6$D$_6\cdot$**1**] [a]	9.95	7.37
[**1**$\cdot$CHCl$_3\cdot$**1**][b]	9.49	7.05
[**1**$\cdot$C$_6$H$_6\cdot$**1**][b]	9.44	6.75

[a] In [D$_6$]benzene. [b] Values in [D$_{12}$]cyclohexane, taken from ref. [13].

No changes are observed in the NMR spectrum, if a solution of **1** in CDCl$_3$ is saturated with a tetrapropyl- or tetrabutylammonium salt (Pr$_4$N$^+$BF$_4^-$ or Bu$_4$N$^+$PF$_6^-$) since these larger cations evidently cannot be included in a dimeric capsule. Additional signals appear with Me$_4$N$^+$PF$_6^-$. The complex spectrum indicates an inclusion of the smaller tetramethylammonium cation, but the capsules with CDCl$_3$ as guest are not completely replaced.[16, 17]

Temperature dependence was also found for the signals assigned to the guest.[18] With increasing temperature the two very broad signals at about $\delta = -0.4$ and -3.2 (found for [**1**$\cdot$Et$_4$N$^+\cdot$**1**]PF$_6^-$ at 25 °C) coalesce at 33 °C into one signal at about $\delta = -1.7$, while a temperature decrease leads to a slight down-field shift of the signal at $\delta = -0.40$ followed by an additional splitting into a pair of signals at about $\delta = -0.25$ and -0.30 below $T_c = 231$ K.[19] At low temperature these three signals in the high-field region are broad triplets and the gradient selected COSY spectrum recorded at -55 °C proves that the signal at $\delta = -3.45$ is coupled with two broad signals at $\delta = 0.34$ and 0.42, while the signals at $\delta = -0.25$ and -0.30 are coupled with two other signals at $\delta = 1.10$ and 0.90. This coupling pattern as well as the integral intensities at this temperature leave no doubts that the upfield signals in the region $\delta = 0$ to -3.50 really belong to the methyl groups of the encapsulated Et$_4$N$^+$ ion. The big difference in chemical shifts ($\delta = -0.25/-0.30$ vs. $\delta = -3.5$) indicates two very different environments for the methyl groups of the guest. It can be understood if one assumes an orientation where two residues R = Et of the Et$_4$N$^+$ ion are within the "*equatorial plane*" (the hydrogen-bonded belt), while the other two point towards the "*poles*" of the capsule (the π-basic cavity) and hence are much more shielded by the aromatic rings (see Scheme 1). An energy barrier of 54.8 kJ mol^{-1} ($T_c = 306$ K) is derived for the exchange R/R′ which most probably occurs by rotation around the pseudo-C_2 axis (Scheme 1), while the fourfold symmetry apparent from the host signals requires a fast rotation of the guest around the C_4 axis connecting the *poles.* The two signals observed at very low temperature in the region of $\delta = -0.3$ are explained by the absence of any symmetry plane through the nitrogen of the Et$_4$N$^+$ ion, when there is a directionality of the hydrogen-bonded system. This makes the two *equatorial* ethyl groups different from each other.



Scheme 1.

Still more detailed information was obtained from the C_{2v}-symmetrical calix[4]arene urea **3** which forms chiral dimers, present in solution, as a mixture of two enantiomers. The chirality in this case is caused only by the combination of the two monomers into a dimer while the directionality of the hydrogen bonds *does not* lead to additional isomeric structures, but only to a reduction of the symmetry from D_2 to C_2.[20] Thus, in principle the dimeric structure of the complex should follow directly from the NMR spectrum .

At 25 °C the NMR spectrum of [**3**$\cdot$Et$_4$N$^+\cdot$**3**]PF$_6^-$ (Figure 4a) shows four singlets for NH, four doublets for the aromatic protons of the tolyl residues, one singlet for methoxy and two singlets for tolyl methyl, and, in agreement with D_2

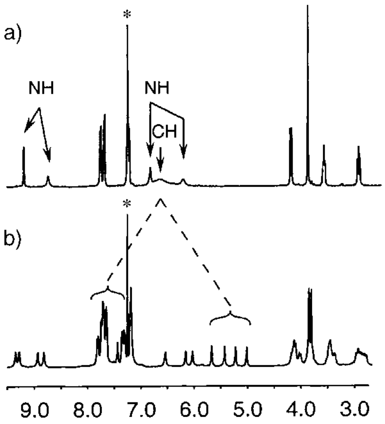


Figure 4. Section of the ^1H NMR spectrum ($CDCl_3$, 400 MHz) of a) [**3**·Et_4N^+·**3**]PF_6^-, 25 °C; b) [**3**·Et_4N^+·**3**]PF_6^-, –55 °C (the solvent signal is indicated by an asterisk).

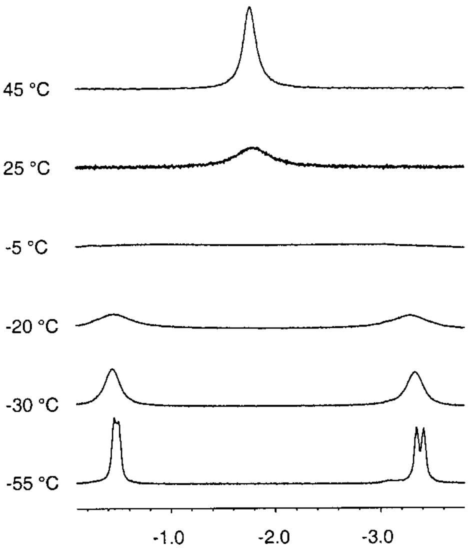


Figure 5. Section of the guest signals in the ^1H NMR spectrum ($CDCl_3$, 400 MHz) of [**3**·Et_4N^+·**3**]PF_6^- at different temperatures.

symmetry,[21] two pairs of doublets for the protons of the methylene bridges ($ArCH_2Ar$). The aromatic protons of the calixarene skeleton appear as one broad signal, indicating again a change in the directionality of the H-bonding system. The methyl groups of the included Et_4N^+ ion give one up-field signal at $\delta = -1.8$. With decreasing temperature this signal first ($T_c = -2\,°C$) splits into two broad signals at $\delta = -0.5$ and -3.4 (Figure 5). At lower temperature ($T_c = -25\,°C$) each of these signals splits again into a pair of broad multiplets (Figure 5) in agreement with the symmetry of a tetraethylammonium cation included in a *chiral* C_2-symmetrical dimer. The multiplicity of these signals is not expressed, but a COSY spectrum recorded at –55 °C proves that the signal at $\delta = -3.41$, attributed to one of the "*polar*" methyl groups, is coupled with one broad signal at $\delta = 0.24$, while the signal at $\delta = -3.34$, attributed to the other "*polar*" methyl group is coupled with two signals at $\delta = 0.14$ and 0.37, which correspond to two diastereotopic CH_2 protons within one "*polar*" ethyl group. The relative integral intensities of the three signals at $\delta = 0.37$, 0.24, and 0.14 are 1:2:1 (four protons). In a similar way, the CH_3 signal of one "*equatorial*" ethyl group at $\delta = -0.46$ is coupled with signals at $\delta = 0.82$ and 0.99, while the one at $\delta = -0.50$ is coupled with a signal at $\delta = 0.89$.

In the aromatic region (Figure 4b) four pairs of *meta*-coupled doublets can be assigned analogously in the COSY spectrum, superimposed in the low-field part by the tolyl signals. There are also eight signals for NH protons present in the ^1H NMR spectrum at –55 °C (Figure 4b), as well as two singlets for methoxy groups. All this is entirely in agreement with the C_2 symmetry of the [**3**·Et_4N^+·**3**]PF_6^- complex at this temperature, reflecting a directionality of the hydrogen bonding system which is frozen on the NMR time scale.

Figure 6 shows a plot of $\Delta G^{\neq}$ versus the coalescence temperature T_c for different signals. It strongly suggests that in fact two different and independent dynamic processes are observed, namely the inversion of the directionality of the hydrogen bonded belt (process I) and the rotation of the tetraethylammonium cation around the pseudo-C_2 axis (process II). Process II is reported by the "large splitting" of the guest's methyl groups, while their "fine splitting" and the splitting of the host signals is caused by process I. Of course, the temperature range for $\Delta G^{\neq}$ is not large enough to determine accurately $\Delta H^{\neq}$ and $\Delta S^{\neq}$ from this plot. It clearly reveals, however, that one of the values does not belong to the remaining series.

It is worth to note that the barrier for the reorientation of the belt of hydrogen bonds is roughly the same for ureas **1** and **3**, while the barrier for the rotation of the tetraethylammonium cation decreases from 54.8 kJ mol^{-1} (T_c 306 K) (**1**) to 48.4 kJ mol^{-1} (T_c 271 K) (**3**). This might reflect a higher inner volume in the case of urea **3** where two pentyl residues of **1** have been replaced by the smaller methyl groups.

There remains the question, why in capsules with ammonium cations (e.g. Et_4N^+) as guest a rapid change of the direction of the hydrogen bonds occurs, in contrast to capsules with neutral guests. Such a process requires rotation around

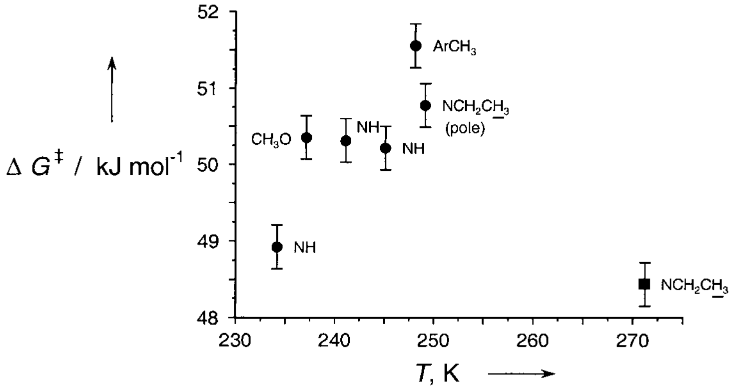


Figure 6. Energy barriers $\Delta G^{\neq}$ for the two rearrangement processes I (●) and II (■) versus the coalescence temperatures T_c of different signals in [**3**·Et_4N^+·**3**]PF_6^-.

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001

the Ar-NH-CO-NH- σ bonds and a passage of the negatively charged carbonyl oxygen through the interior of the capsule.[22] It can be easily understood, that a positively charged guest can lower the activation barrier for this rotation.

Molecular dynamics

To obtain more detailed information about the structure of the complexes and to gain a better understanding of their internal mobility we have performed molecular dynamics (MD) simulations of the model complex of [**5**$\cdot$Et$_4$N$^+$$\cdot$**5**] in a box of chloroform molecules and compared the results with the respective MD simulations of [**5**$\cdot$C$_6$H$_6$$\cdot$**5**].

The volume of the dimeric capsule accessible for a guest molecule is about 190–200 Å^3 as estimated from the only X-ray structure (**4**$\cdot$**4**) known so far and from molecular mechanics calculations.[7] While typical solvent guests such as chloroform ($V_{vdW} = 74.5$ Å^3) and benzene ($V_{vdW} = 73.5$ Å^3) occupy about 40% of the cavity, also the encapsulation of much larger guests such as camphor ($V_{vdW} = 151$ Å^3), myrtenol ($V_{vdw} = 144.4$ Å^3) or charged ammonium ions such as *N*-methylquinuclidinium ($V_{vdw} = 136.2$ Å^3) and tetraethylammonium ($V_{vdw} = 154$ Å^3) is evidently possible.[8, 23]

When the Et$_4$N$^+$ ion was docked into the interior of **4**$\cdot$**4** (coordinates taken from the X-ray structure) in the position anticipated from the experiment (see above) overlapping areas of the guest's and host's van der Waals surfaces in the equatorial region of the molecular capsule indicated that the cavity is much too narrow to properly accommodate the guest molecule. This necessarily means that the structure of the calixarene capsule containing the Et$_4$N$^+$ ion must differ from those formed with a benzene guest. The extent of this difference can be deduced from the comparison of several geometrical characteristics of the two ternary complexes [**5**$\cdot$Et$_4$N$^+$$\cdot$**5**] and [**5**$\cdot$C$_6H_6$$\cdot$**5**] calculated from the MD trajectories (Table 2).

Table 2. Average values for specific geometric parameters of the ternary complexes; fluctuations in parentheses.

	[**5**$\cdot$C$_6$H$_6$$\cdot$**5**]	[**5**$\cdot$Et$_4$N$^+$$\cdot$**5**]
cavity volume [Å^3][a]	ca. 190	ca. 224
number of hydrogen bonds[b]	14.0 (1.4)	7.6 (1.9)
extension pole to pole [Å][c]	9.6 (0.2)	10.5 (0.2)
extension at the equator [Å][d]	11.2 (0.7)	12.2 (0.3)
N–H$_\alpha$$\cdots$O distance [Å]	2.01 (0.2)	2.31 (0.4)
N–H$_\beta$$\cdots$O distance [Å]	2.45 (0.3)	2.86 (0.5)
inclination of calixarenes [°][e]	4.2 (2.1)	6.3 (6.3)
torsion angle C$_{Ar}$–NH$_\beta$ [°]	13.4 (10.6)	2.1 (12.7)

[a] Estimated from the average structure of the MD run. [b] Calculated using a cut-off value of 2.7 Å for the NH$\cdots$O=C distance and of 135° for the N–H$\cdots$O angle. [c] Distance of the two centroids of the bridging methylene carbon atoms. [d] Largest distance between opposite groups defining the equator of the capsule: the urea carbonyl carbon atoms in the case of [**5**$\cdot$C$_6$H$_6$$\cdot$**5**] and the peripheral nitrogen atoms for [**5**$\cdot$Et$_4$N$^+$$\cdot$**5**]. [e] Angle between the two mean planes defined by the bridging methylene carbon atoms.

Not unexpectedly, a substantial increase in the size of the molecular capsule occurs when Et$_4$N$^+$ is encapsulated instead of benzene (Figure 7). The inner volume, calculated from the average structures of the molecular dynamics runs,[24] increases by almost 20%. This expansion of the molecular capsule concerns both, stretching of the "*pole–pole*" distance ($\Delta d \approx 0.9$ Å) and the widening of the *equator* ($\Delta d \approx 1$ Å). Compared to [**5**$\cdot$C$_6$H$_6$$\cdot$**5**] the urea residues in [**5**$\cdot$Et$_4$N$^+$$\cdot$**5**] are drifted apart from each other which results in an elongation of the N–H$_\alpha$$\cdots$O=C distances and even in the disruption of the weaker[7] N–H$_\beta$$\cdots$O=C hydrogen bonds (Scheme 2). The two calixarene hemispheres of the molecular capsule in [**5**$\cdot$Et$_4$N$^+$$\cdot$**5**] are therefore linked together only by a seam of (on average) 7.6 hydrogen bonds between the peripheral N–H and C=O groups.

Weaker N–H$_\alpha$$\cdots$O=C hydrogen bonds in the Et$_4$N$^+$ complex are also reflected by the chemical shifts for NH protons

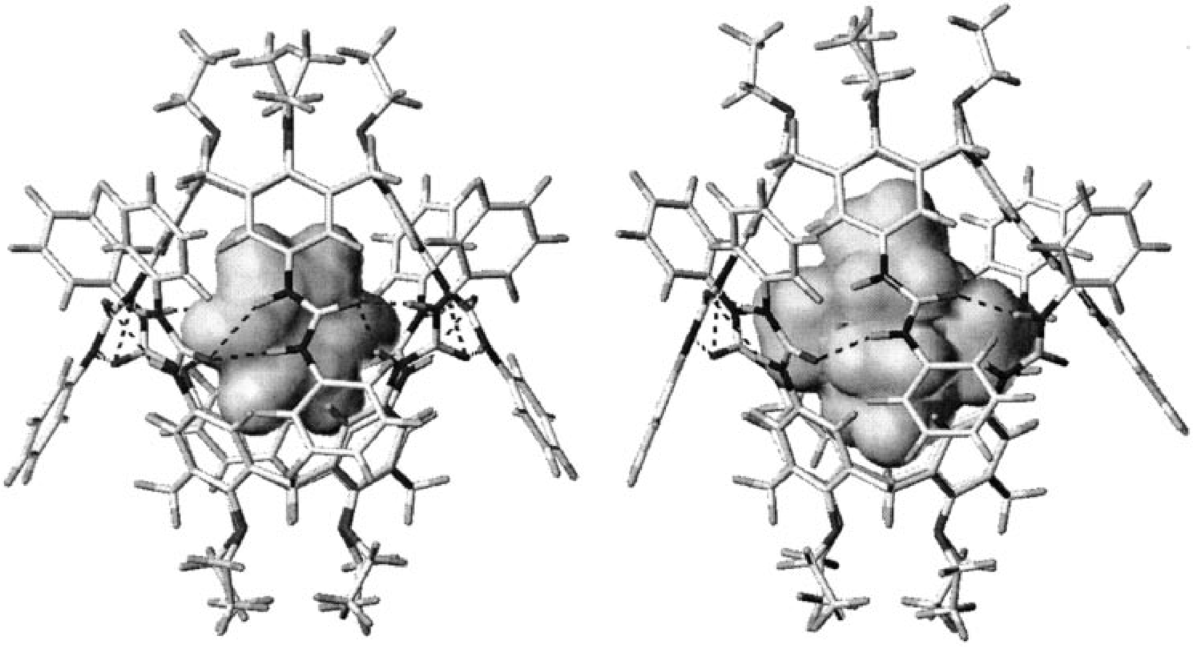
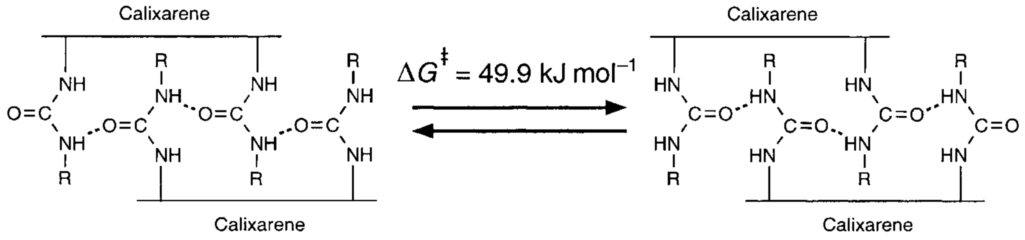


Figure 7. AMBER-minimized average structures of the MD runs of [**5**$\cdot$C$_6$H$_6$$\cdot$**5**] (left) and [**5**$\cdot$Et$_4N^+$$\cdot$**5**] (right). The van der Waals volume is indicated for the guest, while only the skeleton is shown for the dimeric host. Hydrogen bonds are represented by dashed lines.



Scheme 2.

reported in Table 1. No direct values are available for the benzene complex in $CDCl_3$ (the conditions taken for the simulation), due to its low kinetic stability, while the values obtained in C_6D_6 are generally down-field shifted. However, the complex with chloroform may be taken for comparison instead, since in [D_{12}]cyclohexane (the same is true for $CDCl_3$ containing 5% C_6D_6) both complexes show nearly the same value for N–H$_\alpha$. In principle the same trends are observed for the chemical shifts of protons N–H$_\beta$.

The results of the energy component analyses (Table 3) are in line with these observations. When Et_4N^+ is accommodated instead of benzene the interaction energy between the two calixarene monomers of the capsule is less favourable by about 13 kcal mol^{-1} corresponding to somewhat more than 2 kcal mol^{-1} per lacking hydrogen bond. The average energy of the dimer simultaneously increases by about 20 kcal mol^{-1}, thus indicating that in addition to the weakening of the hydrogen-bonding system also a steric strain of approximately 7 kcal mol^{-1} is excerted on the molecular capsule by the bulky tetraethylammonium cation. The host–guest interaction is, however, more favourable by 36 kcal mol^{-1} in [**5** · NEt_4^+ · **5**] than in [**5** · C_6H_6 · **5**] which is sufficient to compensate for the energy loss resulting from the reorganisation of the capsule. This large energy gain by encapsulation of the Et_4N^+ guest can be rationalised by attractive non-covalent forces between the cation and the extended π-basic cavity of the calixarenes as well as the negatively charged carbonyl oxygen atoms which turn toward the cavity (cf., Table 1).[25]

Table 3. Average energy components of the ternary complexes (in kcal mol^{-1}); fluctuations in parentheses.

[**5** · C_6H_6 · **5**]	[**5** · Et_4N^+ · **5**]	
steric energy of the dimer	142.9 (9.6)	162.3 (10.2)
interaction energy [**5**–**5**][a]	– 78.2 (2.3)	– 65.2 (3.8)
interaction energy [**5** · guest · **5**][b]	– 20.3 (1.3)	– 56.6 (2.8)
interaction energy complex – solvent	– 190.7 (7.3)	– 194.5 (7.0)

[a] Interaction energy between the two monomers in the dimeric capsule. [b] Interaction energy between the guest and the dimeric capsule.

Conclusion

The results of the MD simulations indicate significant differences in the properties of calixarene capsules accommodating either a benzene or a tetraethylammonium guest. While the former is held together by a seam of (ideally) 16 hydrogen bonds between the self-complementary urea units around the equator, in the latter this hydrogen bonding system is dramatically weakened due to the expansion of the capsule by encapsulation of the bulky guest but additional "cation ⋯ π" interactions provide enough energy to keep the two hemispheres together.[26] It seems therefore that a change in the directionality of the hydrogen bonding system follows different mechanisms in the two ternary complexes: a dissociation/recombination mechanism[11] when hydrogen bonding is the main factor for the stability of the capsule, and rotation of the urea residues within the dimeric structure when nondirectional attractive forces between the calixarene hemispheres and the guest contribute significantly to the stability of the assembly.

Preliminary results from potential of mean force (PMF) calculations[27] suggest that this rotation proceeds preferably by the passage of the C=O group through the interior of the capsule while the passage of the NH groups requires a higher energy. In keeping with these simulation results is the observation that the experimentally determined energy barrier for the inversion of the H-bond direction is also dependent of the anion present. A passage of the NH hydrogens through the outer sphere of the capsule could be easily influenced by interactions with the anion. We presently study this anion influence more in detail.

It may be generally stated that the hydrogen-bonding system of such tetraurea capsules represents a valuable model system to study the thermodynamic and kinetic properties of hydrogen bonds, by far the most frequently used "tool" for self-assembled supramolecular structures in nature.

Experimental Section

NMR studies

$CDCl_3$ (stabilized over silver wool, 99.8% of deuterium, Fa. Merck) was used for the spectroscopic studies. The ^1H NMR spectra were measured on a Bruker DRX400 Avance (400.13 MHz) spectrometer. The complexes used for the variable temperature ^1H NMR measurements were prepared by refluxing a 2:1 mixture of ureas **1** or **3** (50–70 mg) and tetraethyl ammonium hexafluorophosphate with 5 mL of chloroform (p.a. grade) for 2 h, followed by evaporation and drying in the vacuum of an oil pump. Variable temperature ^1H NMR measurements were conducted at a complex concentration of 5 mM. Experiments with a slight excess (10%) of one of the components, ammonium salt or urea, did not show differences in the coalescence temperatures, while a larger excess of the ammonium salt led to measurable deviations. The Gutowsky–Holm[28] and Arrhenius equations were used to calculate $\Delta G^{\ddagger}$ at coalescence temperatures.

5,11,17,23-Tetra-[*N'*-tolyl-*N*-ureido]-25,26,27,28-tetrapentyloxycalix[4]arene [1 · Et_4N^+ · 1]BF_4^-: ^1H NMR (25 °C): δ = 8.89 (s, 8H; NH), 7.66 and 7.16 (2 × d, ^3J = 8.2 Hz, 32H; ArH$_{tol}$), 6.62 (s, 24H; ArH$_{cal}$ + NH), 4.30 and 2.94 (2 × d, ^2J = 11.7 Hz, 16H; ArCH$_2$Ar), 3.76 (t, ^3J = 8.2 Hz, 16H; OCH$_2$), 2.26 (s, 24H; ArCH$_3$), 1.93–1.89 (m, 16H; CH$_2$), 1.4–1.36 (m, 16H; CH$_2$), 1.32 – 1.23 (m, 16H; CH_2), 0.96 (t, $^3J = 7.0$ Hz, 24H; CH_3), 0.92 (br m, 8H; NCH_2*), – 1.67 (br m, 12H; CH_3*). Signals of the included guest are marked by an asterisk.

5,11,17,23-Tetra-[*N*′-hexyl-*N*-ureido]-25,26,27,28-tetradecyloxycalix[4]arene [$\mathbf{2}\cdot\mathbf{Et_4N^+}\cdot\mathbf{2}$]$\mathbf{BF_4}^-$: ^{1}H NMR (25 °C): $\delta = 6.93$ (s, 16H; ArH_{cal}), 6.76 (s, 8H; NH), 6.51 (br s, 8H; NH), 4.44 and 3.13 ($2\times$d, $^2J = 12.4$ Hz, 16H; $ArCH_2Ar$), 3.79 (t, $^3J = 7.2$ Hz, 16H; OCH_2), 3.34 (q, $^3J = 5.6$ Hz, 16H; NCH_2), 1.96 (m, 16H; CH_2), 1.64 (m, 16H; CH_2), 1.50 – 1.00 (m, 176H; CH_2), 0.91 (br m, 8H; NCH_2*), 0.87 (br t, 48H; CH_3), – 1.70 (br m, 12H; CH_3*).

5,11,17,23-Tetra-[*N*′-tolyl-*N*-ureido]-25,26,27,28-tetrapentyloxycalix[4]arene [$\mathbf{1}\cdot\mathbf{Et_4N^+}\cdot\mathbf{1}$]$\mathbf{PF_6}^-$: ^{1}H NMR (25 °C): $\delta = 9.04$ (s, 8H; NH), 7.73 and 7.24 ($2\times$d, $^3J = 8.2$ Hz, 32H; ArH_{tol}), 6.62 (br s, 16H; ArH_{cal}), 6.42 (s, 8H; NH), 4.30 and 2.92 ($2\times$d, $^2J = 12.0$ Hz, 16H; $ArCH_2Ar$), 3.76 (t, $^3J = 8.0$ Hz, 16H; OCH_2), 2.27 (s, 24H; $ArCH_3$), 1.94 – 1.87 (m, 16H; CH_2), 1.44 – 1.35 (m, 16H; CH_2), 1.32 – 1.26 (m, 16H; CH_2), 1.11 (br m, 4H; NCH_2*), 0.96 (t, $^3J = 7.3$ Hz, 24H; CH_3), 0.8 (br m, 4H; NCH_2*), – 0.4 (br m, 6H; CH_3*), – 3.2 (br m, 6H; CH_3*); ^{1}H NMR (– 55 °C): $\delta = 9.16$ (s, 8H; NH), 7.73 and 7.24 ($2\times$d, $^3J = 7.2$ Hz, 32H; ArH_{tol}), 7.65 and 5.38 (br s, 16H; ArH_{cal}), 6.42 (s, 8H; NH), 4.21 and 2.89 ($2\times$d, $^2J = 10.5$ Hz, 16H; $ArCH_2Ar$), 3.76 (br m, 16H; OCH_2), 2.25 (s, 24H; $ArCH_3$), 1.87 (br m, 16H; CH_2), 1.33 (m, 16H; CH_2), 1.21 (m, 16H; CH_2), 1.10 (br m, 4H; NCH_2*), 0.91 (t, $^3J = 7.0$ Hz, 24H; CH_3), 0.42 and 0.34 ($2\times$ br m, 4H; NCH_2*), – 0.25 and – 0.30 ($2\times$ br t, 6H; CH_3*), – 3.45(br t, 6H; CH_3*).

5,11,17,23-Tetra-[*N*′-tolyl-*N*-ureido]-25,27-dimethoxy-26,28-di-pentyloxy-calix[4]arene [$\mathbf{3}\cdot\mathbf{Et_4N^+}\cdot\mathbf{3}$]$\mathbf{PF_6}^-$: ^{1}H NMR (25 °C): $\delta = 9.18$ (s, 4H; NH), 8.72 (s, 4H; NH), 7.75 and 7.25 ($2\times$d, $^3J = 8.2$ Hz, 16H; ArH_{tol}), 7.68 and 7.18 ($2\times$d, $^3J = 8.2$ Hz, 16H; ArH_{tol}), 6.82 (br s, 4H; NH), 6.8 – 6.4 (br s, 16H; ArH_{cal}), 6.20 (s, 4H; NH), 4.19 and 2.94 ($2\times$d, $^2J = 10$ Hz, 8H; $ArCH_2Ar$), 4.19 and 2.91 ($2\times$d, $^2J = 11.7$ Hz, 8H; $ArCH_2Ar$), 3.87 (s, 12H; OCH_3), 3.60 – 3.56 (m, 8H; OCH_2), 2.28 (s, 12H; $ArCH_3$), 2.26 (s, 12H; $ArCH_3$), 1.89 (m, 8H; CH_2), 1.65 (m, 8H; CH_2), 1.40 (m, 8H; CH_2), 0.95 (t, $^3J = 7.3$ Hz, 12H; CH_3), 0.70 (br m, 8H; NCH_2*), – 1.80 (br m, 12H; CH_3*); ^{1}H NMR (– 55 °C): $\delta = 9.35$ (s, 2H; NH), 9.28 (s, 2H; NH), 8.93 (s, 2H; NH), 8.82 (s, 2H; NH), 7.8 – 7.6 (m, 16H; ArH_{tol}), 7.76 and 5.43 ($2\times$ br d, 4H; ArH_{cal}), 7.71 and 5.23 ($2\times$ br d, 4H; ArH_{cal}), 7.62 and 5.67 ($2\times$ br d, 4H; ArH_{cal}), 7.43 and 5.02 ($2\times$ br d, 4H; ArH_{cal}), 7.3 – 7.1 (m, 18H; ArH_{tol} + NH), 6.54 (s, 2H; NH), 6.16 (s, 2H; NH), 6.03 (s, 2H; NH), 4.2 – 4.00 (m, 8H; $ArCH_2Ar$), 3.86 (s, 6H; OCH_3), 3.81 (s, 6H; OCH_3), 3.5 – 3.3 (m, 8H; OCH_2), 2.9 – 2.7 (m, 8H; Ar-CH_2-Ar), 2.31 (s, 12H; $ArCH_3$), 2.27 (s, 6H; $ArCH_3$), 2.19 (s, 6H; $ArCH_3$), 1.89 (m, 8H; CH_2), 1.33 (m, 16H; CH_2), 0.89 (br t, 12H; CH_3), 1.03 – 0.74 (m, 4H; NCH_2*),0.35 (br m, 1H; NCH_2*), 0.24 (br m, 2H; NCH_2*), 0.05 (br m, 1H; NCH_2*), – 0.46 and – 0.50 ($2\times$ br m, 6H; CH_3*), – 3.34 and – 3.41 ($2\times$ br m, 6H; CH_3*).

Computational methods

Calixarene model complexes [$\mathbf{5}\cdot NEt_4^+\cdot\mathbf{5}$] and [$\mathbf{5}\cdot C_6H_6\cdot\mathbf{5}$] were created by modification of the crystal structure[7, 29] of $\mathbf{4}\cdot\mathbf{4}$ using the SYBYL[30] software suite. Point charges were assigned by the Gasteiger-Marsili algorithm.[31] The structures where then transferred to the LEaP format of AMBER 5[32, 33] and solvated in a cubic box of 822 ([$\mathbf{5}\cdot NEt_4^+\cdot\mathbf{5}$]) and 920 ([$\mathbf{5}\cdot C_6H_6\cdot\mathbf{5}$]) chloroform molecules, respectively. The resulting models were subjected to 5000 steps of minimisation and subsequently to a 30 ps belly MD simulation (300 K, 1 bar) to accomplish relaxation of the solvent.

All minimisations and MD simulations were carried out with AMBER 5. We employed the parm96 parameter set with the following additions. Chloroform parameters (four-site model) were adopted from the literature[34] with minor modifications: $r_{vdW(Cl)}$ and $r_{vdW(C)}$ were set to 1.925 and 2.109 Å, respectively, and the force constant for the Cl-C-Cl bending term was set to 70.0 kcal mol^{-1} rad^{-2}. Some missing parameters for the calixarene were taken from reference [35]. Geometrical parameters for the urea units (see Supporting Information) were derived from 6 – 31G**/MP2[36] calculations on *N*,*N*′-dimethylurea and the torsional parameters were estimated from the ab initio rotational barrier.

The MD simulations were performed at 300 K and 1 bar pressure for 500 ps with 200 K initial temperature and 1 fs time step. The nonbonding cutoff was set to 12 Å. Temperature coupling was achieved using the Berendsen algorithm[37] with different scaling for solute and solvent and by setting the coupling time to 0.5 ps in both cases. The pressure coupling time was set to 1.0 ps. Bonds containing hydrogen were constrained using SHAKE. Coordinates were recorded every 200 fs for later analysis.

Acknowledgement

We thank Prof. J. Okuda for generous access to the Bruker DRX 400 Avance instrument and Dr. B. Mathiasch for his technical assistance during the NMR experiments. The financial support from the Deutsche Forschungsgemeinschaft (Bo523/14 – 1, Th 520/5 – 1) is gratefully acknowledged.

---

[1] Self-assembled capsules via hydrogen bonding: a) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647 – 1668; b) R. G. Chapman, G. Olovsson, J. Trotter, J. C. Sherman, *J. Am. Chem. Soc.* **1998**, *120*, 6252 – 6260; c) L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469 – 472.

[2] Self-assembled capsules through metal – ligand interactions: a) O. D. Fox, N. K. Dalley, R. G. Harrison, *J. Am. Chem. Soc.* **1998**, *120*, 7111; b) B. Olenyuk, M. D. Levin, J. A. Whiteford, J. E. Shield, P. J. Stang, *J. Am. Chem. Soc.* **1999**, *121*, 10434; c) O. D. Fox, M. G. B. Drew, P. D. Beer, *Angew. Chem.* **2000**, *112*, 140 – 144; *Angew. Chem. Int. Ed.* **2000**, *39*, 136 – 140; d) A. J. Terpin, M. Ziegler, D. W. Johnson, K. N. Raymond, *Angew. Chem.* **2001**, *113*, 161 – 164; *Angew. Chem. Int. Ed.* **2001**, *40*, 157 – 160; e) M. Ziegler, J. L. Brumaghim, K. N. Raymond, *Angew. Chem.* **2000**, *112*, 4285 – 4287; *Angew. Chem. Int. Ed.* **2000**, *39*, 4119 – 4121; f) T. N. Parac, M. Scherer, K. N. Raymond, *Angew. Chem.* **2000**, *112*, 1288 – 1291; *Angew. Chem. Int. Ed.* **2000**, *39*, 1239 – 1242.

[3] a) T. Heinz, D. M. Rudkevich, J. Rebek, Jr., *Angew. Chem.* **1999**, *111*, 1206 – 1209; *Angew. Chem. Int. Ed.* **1999**, *38*, 1136 – 1139; b) F. C. Tucci, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 4928 – 4929; c) A. Shivanyuk, K. Rissanen, E. Kolehmainen, *Chem. Commun.* **2000**, 1107 – 1108.

[4] For instance, the dimerisation of C_{2v}-symmetrical tetraesters derived from resorcarenes is induced by tropylium cations: A. Shivanyuk, E. F. Paulus, V. Böhmer, *Angew. Chem.* **1999**, *111*, 3091 – 3094; *Angew. Chem. Int. Ed.* **1999**, *38*, 2906 – 2909.

[5] J. Rebek, Jr., *Chem. Commun.* **2000**, 637 – 643.

[6] a) K. D. Shimizu, J. Rebek, Jr., *Proc. Nat. Acad. Sci. USA* **1995**, *92*, 12403 – 12407; b) O. Mogck, V. Böhmer, W. Vogt, *Tetrahedron* **1996**, *52*, 8489 – 8496; c) B. C. Hamman, K. D. Shimizu, J. Rebek, Jr., *Angew. Chem.* **1996**, *108*, 1425 – 1427; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1326 – 1329.

[7] O. Mogck, E. F. Paulus, V. Böhmer, I. Thondorf, W. Vogt, *Chem. Commun.* **1996**, 2533 – 2534.

[8] a) C. A. Schalley, R. K. Castellano, M. S. Brody, D. M. Rudkevich, G. Siuzdak, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 4568 – 4579; b) C. A. Schalley, *Int. J. Mass Spectr.* **2000**, *194*, 11 – 39.

[9] Other dimeric and tetrameric self-assembled capsules were characterised analogously a) C. A. Schalley, T. Martín, U. Obst, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 2133 – 2138; b) F. Hof, C. Nuckolls, J. Rebek, Jr., *J. Am. Chem. Soc.* **2000**, *122*, 4251 – 4252.

[10] Only one ^{1}H NMR spectrum was published in ref. [8a], from which the dimeric structure of the complex can be hardly deduced.

[11] O. Mogck, M. Pons, V. Böhmer, W. Vogt, *J. Am. Chem. Soc.* **1997**, *119*, 5706 – 5712.

[12] L. Frish, S. E. Matthews, V. Böhmer, Y. Cohen, *J. Chem. Soc. Perkin Trans. 2* **1999**, 669 – 671.

[13] M. O. Vysotsky, V. Böhmer, *Org. Lett.* **2000**, *2*, 3571 – 3574.

[14] Such an inclusion with kinetically stable (NMR time scale) complexes was observed for calix[5]arenes: F. Arnaud-Neu, S. Fuangswasdi, A. Notti, S. Pappalardo, M. F. Parisi, *Angew. Chem.* **1998**, *110*, 120 – 122; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 112 – 114.

[15] From the appearance of signals for the heterocomplex [$\mathbf{1}\cdot Et_4N^+\cdot\mathbf{2}$] in a freshly prepared mixture of [$\mathbf{1}\cdot Et_4N^+\cdot\mathbf{1}$]$PF_6^-$ and [$\mathbf{2}\cdot Et_4N^+\cdot\mathbf{2}$]$PF_6^-$ ($c = 2.10^{-3}$ M); a half-life time of about 15 min could be estimated at room temperature.

[16] This is in agreement with selectivities observed in ESI-MS studies, see ref. [8a].

[17] In CD_2Cl_2 predominantly capsules with included Me_4N^+ are observed, and a barrier of $\Delta G^{\neq} = 54.5 \pm 0.4$ kJ mol^{-1} ($T_c = 298$ K) can be estimated from preliminary measurements for the reorientation of the hydrogen bonded belt. This indicates, that obviously already the

positive charge of the guest lowers the energy barrier for the passage of the carbonyl group through the interior of the capsule. Studies for a series of cations with different size are in progress.

[18] For the dynamics of the encapsulated cyclohexane within self-assembled capsules see: B. M. O'Leary, R. M. Grotzfeld, J. Rebek, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 11701–11702.

[19] In the same temperature range the up-field signal at $\delta = -3.15$ shifts further to $\delta = -3.44$.

[20] For a general discussion of the symmetry properties see: M. Vysotsky, C. Schmidt, V. Böhmer, *Adv. Supramol. Chem.* **2000**, *7*, 139–233.

[21] This is in contrast to the capsule with $CDCl_3$ as guest, which shows C_2-symmetry similar to the spectrum reported in ref. [11].

[22] Alternatively the NH hydrogen atoms could pass the interior which intuitively is less likely with a cationic guest.

[23] R. K. Castellano, B. H. Kim, J. J. Rebek, *J. Am. Chem. Soc.* **1997**, *119*, 12671–12672.

[24] For the estimation of the cavity volume see ref. [7].

[25] For a review on cation$\cdots\pi$ interactions in calixarenes see: P. Lhotak, S. Shinkai, *J. Phys. Org. Chem.* **1997**, *10*, 273–285.

[26] Tetraethylsilane, as a non-charged model for the tetraalkylammonium cation is not included as guest.

[27] Results of the PMF calculations will be published in due course.

[28] H. S. Gutowsky, C. H. Holm, *J. Chem. Phys.* **1956**, *25*, 1228.

[29] Refcode TIDWEI in the Cambridge Structural Database (F. H. Allen, O. Kennard, *Chemical Design Automation News* **1993**, *8*, 31–37).

[30] SYBYL 6.6 Tripos Inc., 1699 South Hanley Rd., St. Louis, Missouri, 63144, USA.

[31] J. Gasteiger, M. Marsili, *Tetrahedron* **1980**, *36*, 3219–3288.

[32] a) S. J. Weiner, P. A. Kollman, D. A. Case, U. C. Singh, C. Ghio, G. Alagona, S. Profeta, P. Wiener, *J. Am. Chem. Soc.* **1984**, *106*, 765–784; b) S. J. Weiner, P. A. Kollman, D. T. Nguyen, D. A. Case, *J. Comput. Chem.* **1986**, *7*, 230–252.

[33] D. A. Case, D. A. Pearlman, J. W. Caldwell, T. E. Cheatham III, W. S. Ross, C. L. Simmerling, T. A. Darden, K. M. Merz, R. V. Stanton, A. L. Cheng, J. J. Vincent, M. Crowley, D. M. Ferguson, R. J. Radmer, G. L. Seibel, U. C. Singh, P. K. Weiner, P. A. Kollman, AMBER 5, **1997**, University of California, San Francisco.

[34] W. L. Jorgensen, J. M. Briggs, M. L. Contreras, *J. Phys. Chem.* **1990**, *94*, 1683–1686.

[35] a) P. A. Kollman, G. Wipff, U. C. Singh, *J. Am. Chem. Soc.* **1985**, *107*, 2212–2219; b) P. D. J. Grootenhuis, P. A. Kollman, *J. Am. Chem. Soc.* **1989**, *111*, 2152–2158; c) P. D. J. Grootenhuis, P. A. Kollman, L. C. Groenen, D. N. Reinhoudt, G. J. Van Hummel, F. Ugozzoli, G. D. Andreetti, *J. Am. Chem. Soc.* **1990**, *112*, 4165–4176.

[36] Jaguar 3.5, Schrödinger, Inc., Portland, OR, **1998**.

[37] H. J. C. Berendsen, J. P. M. Postma, W. F. Van Gunsteren, A. Di Nola, J. R. Haak, *J. Chem. Phys.* **1984**, *81*, 3684–3690.

Received: March 1, 2001 [F3100]

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001