PERKIN 2

Dimeric capsules of tetraurea calix[4]arenes. MD simulations and X-ray structure, a comparison

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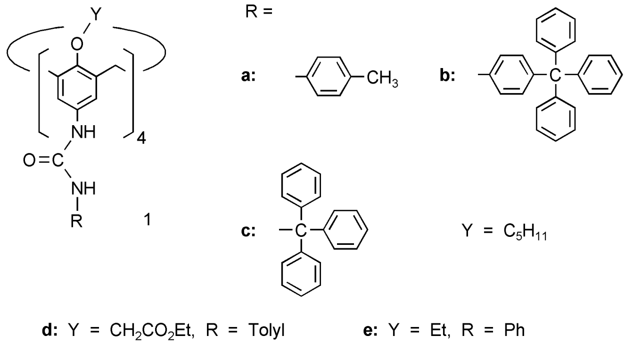
The single crystal X-ray structure of a homodimer of a tetra(tolylurea) calix[4]arene including a tetraethylammonium cation as guest shows an expansion of the capsule and a distortion of its shape, in comparison to the structure of a similar dimer with an encapsulated benzene molecule. Thus, only 8 of 16 possible hydrogen bonds are present in the hydrogen bonded belt holding together the two hemispheres. The encapsulated cation is disordered over two equivalent positions with two methyl groups pointing to the equator, while two methyl groups pointing to the poles form CH–π interactions with the inner surfaces of the calixarene cavities. MD simulations are in agreement with the distorted X-ray structure for a short simulation time of 1–2 ns with a given orientation of the included cation and approach for longer simulation times (9 ns) the fourfold symmetry found by ^{1}H NMR spectroscopy in solution.

Introduction

There is increasing interest in self-assembled structures[1] in which molecular building blocks are organized *via* reversible links. Especially capsules[2,3] formed by two or more building blocks with the inclusion of suitable guest molecules are highly attractive, since various applications may be envisaged, reaching from drug carrier systems to molecular reaction vessels,[4] to mention just two examples.

The dimerisation of calix[4]arenes substituted at their wide rim by four urea functions (**1**, Scheme 1) is now well established.[5] In such dimers two molecules are held together by a belt of hydrogen bonds between the interlocking urea functions, thus creating a closed cavity with an internal volume of about 200 Å^3. Although it has been stated that an "ideal guest" would occupy about 55% of the cavity,[6] neutral guests with volumes ranging from 73.5 Å^3 (benzene) up to 151 Å^3 (camphor) have been found in tetraurea dimers. If ammonium cations are used as guest, which enables easy detection of the capsules by ESI-MS,[7] the guest volume is usually at the upper limit (*e.g.*, 154 Å^3 for tetraethylammonium cations).



Scheme 1

In spite of the numerous examples realized synthetically, the structure of tetraurea dimers has so far been confirmed for only one example by a single crystal X-ray analysis.[8] The structure of these dimers has been initially deduced mainly from their ^{1}H NMR spectra and details of size and shape have been evaluated by MD simulations. Thus, a qualitatively satisfactory explanation was found for the experimentally established result, that homodimers of tritylphenylurea **1b** may contain toluene or benzene as guest, while the slightly smaller heterodimers of **1b** with tritylurea **1c** are formed only with benzene.[9] Homodimers of **1c** are predicted to be even smaller, in agreement with the fact that their formation can be induced only when tetramethylammonium cations (V = 89 Å^3) are offered as guest.[10] The strongly enhanced internal mobility of the hydrogen bonded belt observed for capsules with cationic guests, the directionality of which changes much faster than the dissociation/recombination, was also in satisfactory agreement with weaker hydrogen bonds predicted by MD simulations.[11] On the other hand, the formation of dimeric capsules of pentaurea calix[5]arenes has not (yet) been realized experimentally, although MD calculations lead to the same interaction energies per phenolic urea unit as calculated for tetraurea calix[4]arenes.[12] This example shows the limits which presently are encountered for predictions based on such computer simulations.

It is hoped that further studies on well defined model systems such as the tetraurea dimers **1·G·1** will improve these predictions. Especially a quantitative comparison of geometrical data obtained by modelling with those derived from the conformation found in the crystalline state seems necessary, to sharpen the computational tool, or to characterize its scope and limits.

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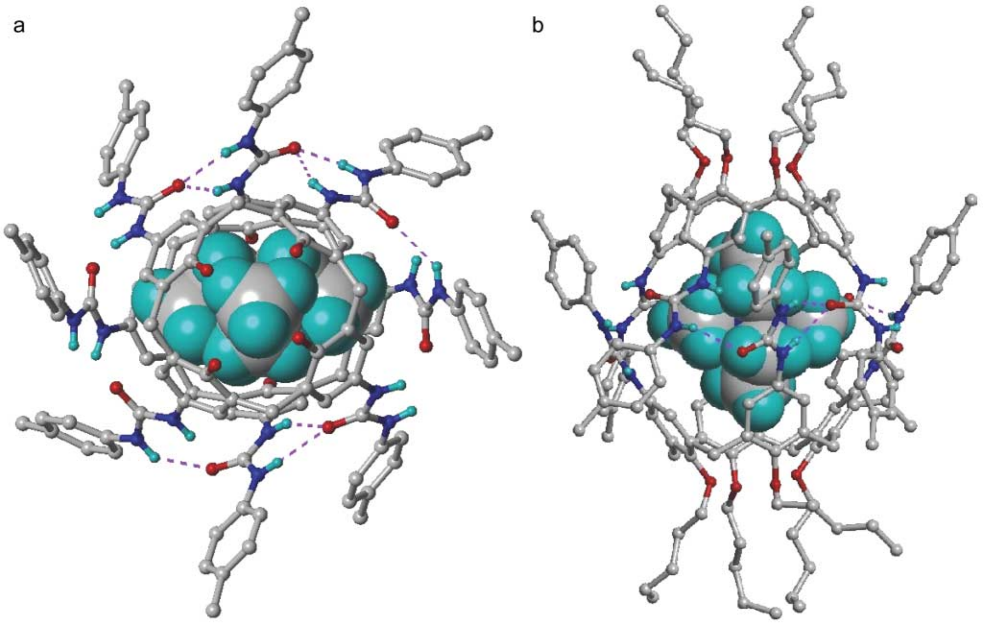

Fig. 1 Molecular conformation of **1a**·Et$_4$N$^+$·**1a** seen from a) the pole (the phenolic oxygens where the ether residues are omitted for clarity) and b) the equator (the hydrogen bonded urea belt). A space filling representation of the guest (the tetraethylammonium cation) is combined with a "ball and stick" representation of the dimeric capsule. Hydrogen bonds are indicated by dotted lines.

Reliable predictions by computer modelling clearly will be helpful for the (rational) design of further, more sophisticated self-assembled structures.

With this background, we discuss in this paper the single crystal X-ray structure of **1a**·Et$_4$N$^+$·**1a**·PF$_6^-$ and compare it with the predictions of MD simulations.

Crystal structure

Single crystals suitable for an X-ray structure determination were obtained by slow evaporation of a solution of **1a**·Et$_4$N$^+$·**1a**·PF$_6^-$ in dichloromethane/n-hexane.

A rough glance at the molecular conformation shown in Fig. 1 from two different perspectives reveals that the capsule formed by the two tetraurea molecules is completely filled by the tetraethylammonium guest. This is in contrast to the structure reported previously for a capsule with benzene as guest.[8] The higher mobility of the smaller benzene molecule within the capsule may be also the reason why it could not be located in the former case. In the present example a fixed position is found for the included tetraethylammonium cation, with two ethyl groups lying in the "equatorial plane" formed by the urea belt and two pointing into the calixarene cavities ("to the poles").

As indicated in Fig. 2, the methylene groups of the ethyl residues are disordered over two positions with occupancies of 0.75 and 0.25, which obviously has no influence on the overall shape of the capsule. The shortest distances between equatorial methyl groups and two closest carbonyl groups (C197/C19D–C137 and C199/C19F–C159) are both 3.36 Å, while the distances between the polar methyl groups and the centroids of aromatic rings of the calixarenes vary between 3.45 Å and 3.88 Å (see Table 1), distances which are in agreement with CH–π interactions. The capsule possesses no symmetry element, and the inclination of the aromatic units with respect to the calixarene mean planes (defined by the carbons of the methylene bridges) varies irregularly between 109° and 130° (for calixarene I) and 114° and 125° (for calixarene II).

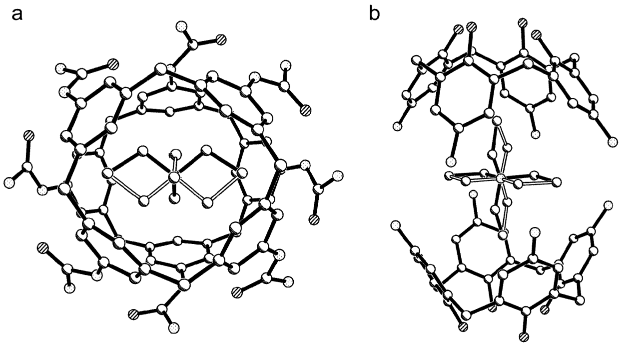

Fig. 2 Situation of the included cation, seen from the pole (a) and from the equator (b). While the N-atom and the methyl C-atoms are found at fixed places, the methylene C-atoms are disordered over two positions, indicated by thin lines for the lower populated position.

The larger guest (in comparison to benzene) strongly expands the capsule's dimensions. For instance, the "pole to pole" distance defined by the centroids of the methylene carbons is 10.5 Å as compared to 9.7 Å for **1d**·C$_6$H$_6$·**1d**. The inner diameter of the cavity (measured between the van der Waals surfaces) increases from 8 to 9 Å in the part of the equatorial region occupied by the two ethyl groups.

Hydrogen bonds between the urea functions are the main force holding together the two calixarenes of a capsule. In Table 2 the respective parameters are summarized. Due to the absence of any symmetry element, all hydrogen bonds are different. As usual, the N$_\alpha$–H groups attached to the tolyl residues form stronger hydrogen bonds (average distance N$_\alpha$ ··· O = 2.89 Å) than the N$_\beta$–H groups attached to the wide rim of the calixarene (average distance N$_\beta$ ··· O = 3.44 Å). Using arbitrary limits of N–H ··· O < 2.7 Å and N–H ··· O > 135° only 8 (of 16 possible) hydrogen bonds are formed, while by the same criterion all 16 hydrogen bonds were formed with benzene as guest.[10] This smaller number of hydrogen bonds must be the reason (or at least one of the reasons) for the rapid reorientation of the hydrogen bonded urea belt.[11] This should lead also to weaker attractive forces between the two calixarenes which seem to be compensated by cation-π interactions between the calixarenes and the included guest cation.

The crystal lattice may be considered of being composed of large monovalent cations and small spherical anions, a size relation which is just inverse to common inorganic salts or compounds where usually the anionic part is larger. The cations are arranged in a way which may be described as a closest hexagonal packing, which is distorted, however, due to the

Table 1 a) Shape of the two calixarenes, expressed by the inclination of the aromatic rings with respect to the calixarene mean plane. b) Distance of the two polar methyl groups of the included cation from the centroids of the aromatic rings

	Calixarene I X-ray	Calixarene II	Calixarene I Calcd.[a]	Calixarene II
a)				
Inclination/°	109	114	112	114
	130	125	126	124
	109	114	114	118
	125	118	127	111
b)				
Me–Ar distance/Å	3.45	3.59	3.57	3.51
	3.51	3.60	3.60	3.65
	3.84	3.64	3.60	3.72
	3.88	3.71	4.01	3.67

[a] Averaged over 726 snapshots, see computational methods.

Table 2 Hydrogen bonding parameters for the X-ray structure, the total MD run (9 ns) and for a selected subset of the MD simulation (characterized by a uniform position of the Et_4N^+ guest, averaged over 726 snapshots = 1.452 ns)

	Distance/Å $N_\alpha H \cdots O$	Distance/Å $N_\alpha \cdots O$	Angle/° $N_\alpha H \cdots O$	Distance/Å $N_\beta H \cdots O$	Distance/Å $N_\beta \cdots O$	Angle/° $N_\beta H \cdots O$
X-ray	2.43	2.98	150	3.44	3.84	112
	2.18	2.88	139	2.83	3.52	138
	2.15	2.95	154	2.12	2.92	154
	2.42	2.97	122	3.13	3.58	115
	2.17	2.87	138	3.02	3.51	118
	1.98	2.82	165	2.78	3.49	141
	1.95	2.78	163	2.21	2.98	150
	2.26	2.84	125	3.17	3.70	122
mean	2.19	2.89	144	2.84	3.44	131
MD, 1.452 ns	2.47	3.18	132	3.00	3.67	126
	2.09	2.98	151	2.54	3.37	140
	2.07	2.98	153	2.46	3.32	144
	2.18	3.04	147	2.74	3.54	139
	2.58	3.20	125	3.23	3.86	124
	2.15	3.00	144	2.58	3.35	135
	2.12	2.98	145	2.58	3.37	137
	2.64	3.26	124	3.43	4.06	125
mean	2.29	3.08	140	2.82	3.57	134
MD, 9 ns	2.29	3.08	140	2.84	3.59	133
	2.28	3.07	140	2.80	3.55	133
	2.31	3.08	139	2.86	3.60	133
	2.28	3.07	140	2.80	3.54	134
	2.29	3.07	140	2.81	3.56	134
	2.30	3.08	139	2.86	3.60	133
	2.24	3.05	143	2.74	3.51	135
	2.28	3.07	140	2.79	3.54	134
mean	2.28	3.07	140	2.81	3.56	134

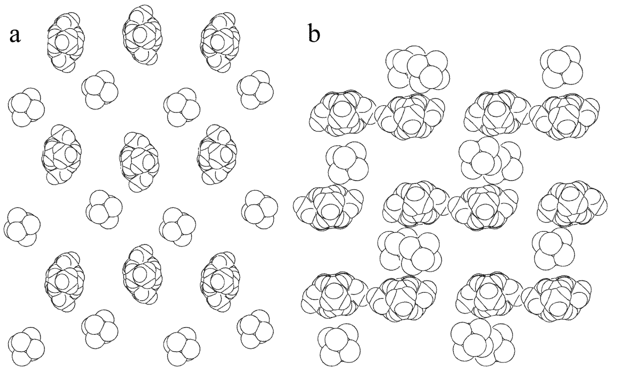

Fig. 3 Packing of Et_4N^+ and PF_6^- (the calixarenes are omitted for clarity) seen along the *x* axis (a) and the *y* axis (b).

"non-spherical" shape of the cationic capsule. Fig. 3 shows the packing of Et_4N^+ and PF_6^- (the calixarenes are omitted) from two directions. The PF_6^- anions reside in the octahedral holes, forming a kind of primitive hexagonal lattice. In other words, each anion is octahedrally surrounded by six capsules, while the anions around a capsule occupy the corners of a distorted trigonal prism (Fig. 4).

Molecular dynamics simulations

MD simulations of the model compound **1e**·Et_4N^+·**1e** have been carried out for 9 ns in a rectangular box of chloroform molecules. In the starting structure the guest molecule was oriented in such a manner that two ethyl groups were pointing to the poles while the other two were oriented towards the equatorial region.

Inspection of the trajectories revealed that the tetraethylammonium guest slowly rotates (on the MD timescale) around the axis connecting the two poles of the capsule (Fig. 5a). Corresponding to the S_8-symmetrical structure of the capsule eight preferred, energetically equivalent orientations exist for the guest which differ by an angle of 45°. Not unexpectedly, an exchange between the polar and equatorial positions of the

Table 3 Summary of geometric parameters in X-ray and calculated structures

	1d·C_6H_6·**1d** X-ray	**1e**·C_6H_6·**1e** Calcd.	**1a**·Et_4N^+·**1a** X-ray	**1e**·Et_4N^+·**1e** Calcd.[a]
Cavity volume/Å^3 [b]	*ca.* 202	*ca.* 190	*ca.* 230	*ca.* 224
Number of H-bonds	16	14	8	8
Extension pole to pole/Å [c]	9.7	9.6	10.5	10.4
Inner diameter at the equator/Å [d]	8.0	8.0	9.0/10.0	9.0/10.5
N_α–H ··· O distance/Å	2.01	2.01	2.19	2.29
N_β–H ··· O distance/Å	2.34	2.45	2.84	2.82
Inclination of calixarenes/° [e]	0.0	4.2	4.4	6.0
Torsion angle C_{Ar}–N_βH/°	8.5	13.4	17.5	4.7

[a] Averaged over 726 snapshots, see computational methods. [b] Estimated as described in ref. 8. [c] Distance of the two centroids of the bridging methylene carbon atoms. [d] Measured between opposing van der Waals surfaces. In the case of Et_4N^+ due to the ellipsoidal shape two values for the minimum and maximum diameter are given. [e] Angle between the two mean planes defined by the bridging methylene carbon atoms.

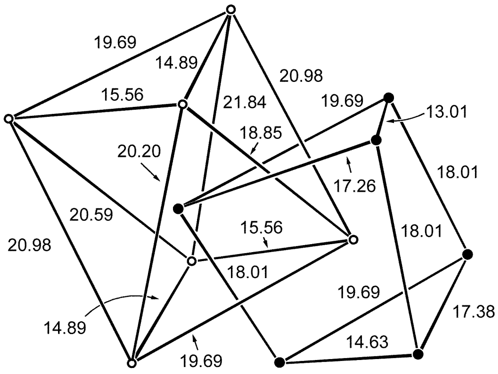

Fig. 4 The co-ordination sphere of cations and anions represented by N (open circles) and P atoms (filled circles) with the P–P and N–N distances in Å. P–N distances (in Å): 10.272, 11.491, 12.518, 13.944, 14.611, 16.849.

ethyl groups could not be detected.† The rotation of the guest inside the capsule leads to an averaging of the geometrical parameters dependent on the equatorial extension of the capsule. Ideally, if the MD simulation would be long enough, an equalization of the N_α–H ··· O and N_β–H ··· O distances and angles as well as of the inclination angles should be observed. During the time period used for the present MD simulation no complete equalization was obtained (Table 2). The structure of the capsule averaged over 9 ns corresponds, however, almost to S_8 symmetry. In contrast, the shape of the capsule is completely asymmetric for a particular time interval with a *uniform position* of the guest (Fig. 5b) which is in agreement with the present X-ray structure. This asymmetry concerns primarily the arrangement of the urea functions characterised by N–H ··· O distances and angles yet also the inclination of the calixarene aromatic rings to the mean macrocyclic plane (Tables 1 and 2).

The molecular dynamics simulations also reflect the extension of the capsule by the bulky guest. Table 3 gives a comparison between selected geometrical data of the X-ray structures of **1d**·C_6H_6·**1d** and **1a**·Et_4N^+·**1a**·PF_6^- and the analogous values for **1e**·G·**1e** from MD simulations. Like in the X-ray structure, the extension of the two ethyl "arms" of the guest towards the equatorial region results in the deformation of the capsule's equator from the circular shape found when benzene is included as guest to a more ellipsoidal contour. The urea groups flanking the two ethyl groups are bent outwards which leads to a complete or almost complete disruption of the associated hydrogen bonds while the remaining urea groups form the typical head-to-tail hydrogen bonds present in the X-ray structure[8] of **1d**·C_6H_6·**1d**. An average of eight hydrogen bonds (for the cut-off values *vide supra*) between the two hemispheres was calculated from the MD trajectories. In contrast to the hydrogen bonding situation described here averaging over the whole simulation time revealed eight N_α–H ··· O hydrogen bonds while there is no appreciable hydrogen bonding between the N_β protons and the carbonyl oxygens (Table 2). This observation is in agreement with the solution ^{1}H-NMR spectrum of **1a**·Et_4N^+·**1a** where the N_β protons display an upfield shift in comparison to **1a**·C_6H_6·**1a**[11] and it is also commensurate with the fact that the hydrogen bonded belt in **1a**·Et_4N^+·**1a** rapidly changes its directionality.

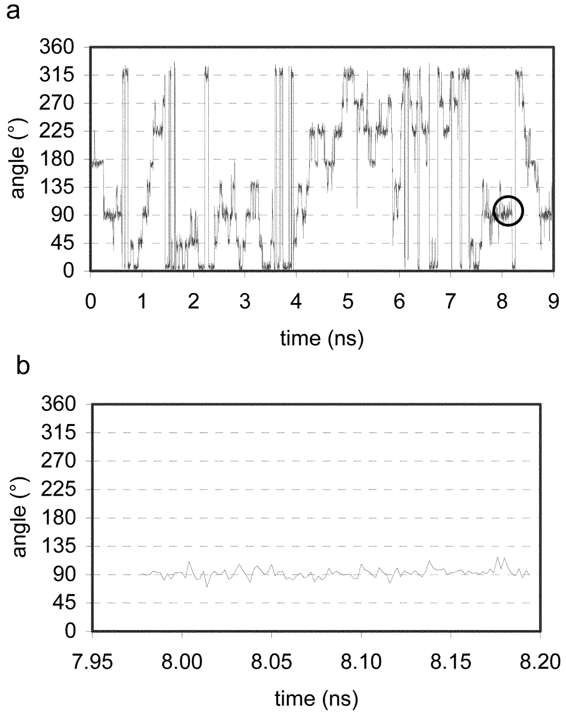

Fig. 5 Plots of the angle between the axes defined by the equatorial methyl carbon atoms of Et_4N^+ and by the centres of two opposing aromatic rings of the calixarene skeleton for (a) the whole simulation time and (b) a selected subset of the trajectories (marked by a circle in (a)) with uniform orientation of the guest which was used for the averaging of geometrical parameters in comparison to the X-ray structure.

Conclusions

The inclusion of the bulky tetraethylammonium cation in molecular capsules composed of tetraurea calix[4]arenes strongly expands the capsule's dimensions compared to the ternary complex with benzene as guest. The circular hydrogen bonded belt holding the two hemispheres together is sub-

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† NMR investigations[11] furnished a barrier of 54.8 kJ mol^{-1} for this process which corresponds to $k = 2821$ s^{-1} and $t_{1/2} = 2.46 \times 10^{-4}$ s. Under the conditions used for the MD simulations (see experimental part) and assuming that a simulation time of 30 ps requires roughly a CPU time (AMD Athlon MP 1600+, 1.4 GHz) of 1 h the first observation of the polar/equatorial exchange can be statistically expected after 935 years!

stantially weakened which may explain the fast change of its directionality observed in the ^{1}H-NMR spectrum. The results obtained by molecular dynamics simulations are in good agreement with the experimental data. Both the asymmetry of the capsule found in the crystal structure and the symmetry of the capsule observed on the NMR timescale are reflected by the calculations if different time periods are considered and the guest orientation is taken into account.‡ Important structural parameters such as the size of the capsule and the geometry of the hydrogen bonding scheme can be predicted by computational simulations which thus offer a valuable tool for the rational design of self-assembled systems.

Experimental

Crystallography

Fragile single crystals have been obtained by slow evaporation of the solution of a urea complex in a dichloromethane/hexane mixture. Crystallographic measurements were carried out at 173.0(1) K using an Enraf Nonius Kappa-CCD diffractometer, MoKα radiation. The structure was solved by direct methods, full matrix least-squares refinement on F^2, with no absorption correction. The disordered methylene carbons (C294, C296, C298 and C300) with occupancy of 0.25 have been refined isotropically. $C_{170}H_{216}Cl_4F_6N_{17}O_{16}P$, $M = 3044.13$, crystal size 0.30 × 0.30 × 0.40 mm, monoclinic, space group $P2_1/n$, $a = 19.685(5)$, $b = 35.565(5)$, $c = 23.159(5)$ Å, $\beta = 92.553(5)°$, $V = 16197(6)$ Å^3, $Z = 4$, $D_c = 1.247$ g cm^{-3}, $\mu = 0.157$ mm^{-1}, 27283 reflections, 18947 independent, $R_{int} = 0.0321$, $R1 = 0.0905$, $wR2 = 0.1870$ for $I > 2\sigma I$, 1963 parameters, largest diff. peak and hole: 0.688 and −0.635 e Å^{-3}.§

Computational methods

The initial geometry of our model was obtained from the crystal structure of **1d**·C_6H_6·**1d**[8] by replacing the benzene guest by the Et_4N^+ cation and by converting the tolylurea and methylethoxycarbonyl residues into phenylurea and ethyl residues, respectively. Atomic point charges were calculated using the Gasteiger–Marsili[13] method.¶ The structure was solvated with 822 chloroform molecules in a rectangular box using the LEaP program of AMBER 5[14,15] and subjected to 5000 steps of minimisation followed by a 30 ps belly dynamics (300 K, 1 bar) for solvent relaxation.

Subsequently, a 9 ns MD simulation at 300 K and 1 bar with 1 fs time step was performed. Snapshots were recorded every 2 ps. The initial temperature was set to 200 K. The Berendsen temperature coupling algorithm[16] was employed using separate couplings for the solvent and solute with a 0.5 ps coupling time in both cases. Pressure control was achieved by using the experimental value for the compressibility of chloroform (100 × 10^{-6} bar^{-1}) and by setting the pressure relaxation time to 1.0 ps. Bonds containing hydrogen were constrained to their equilibrium length using the SHAKE algorithm.

The minimisation, MD simulations and the analysis of the results were performed using AMBER 5. Parameters were taken from the parm96 parameter set complemented by the following additions: bond lengths and angles for the urea groups were derived from 6-31G**/MP2[17] calculations and a torsional barrier for C_{Ar}–N of 8.0 kcal mol^{-1} was used. Some missing parameters for the calixarene were taken from ref. 18. Chloroform parameters (four-site model) were adopted from the literature[19] 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}.

In order to obtain the geometrical parameters listed in Tables 2 and 3 the MD trajectories were clustered with respect to the angle between the axes defined by the methyl carbon atoms of Et_4N^+ and by the centres of two opposing rings of the calixarene skeleton. Subsequently, using the CARNAL module of AMBER 5 the corresponding values were calculated for the cluster containing most (726) snapshots with uniform orientation of the guest molecule.

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‡ It should be noted that the symmetry of **1a**·Et_4N^+·**1a** observed by NMR spectroscopy is D_{4d} due to the rapid change of the directionality of the hydrogen bonded system while the average symmetry obtained from the MD simulations is S_8 with a fixed directionality of hydrogen bonds.

§ CCDC reference number 190630. See http://www.rsc.org/suppdata/p2/b2/b207082k/ for crystallographic files in CIF or other electronic format.

¶ The assignment of RESP charges (C. I. Bayly, P. Cieplak, W. D. Cornell and P. A. Kollman, *J. Phys. Chem.*, 1993, **97**, 10269; W. D. Cornell, P. Cieplak, C. I. Bayly and P. A. Kollman, *J. Am. Chem. Soc.*, 1993, **115**, 9620.) to ternary complexes of tetraurea calix[4]arenes leads to an overestimation of electrostatic interactions which results in the shrinking of the capsules and the drastic shortening of hydrogen bonds which is in contradiction to the experimental data known so far.