Reasons for the exclusive formation of heterodimeric capsules between tetra-tolyl and tetra-tosylurea calix[4]arenes†

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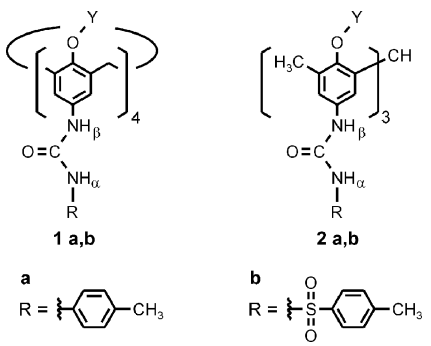
The selective heterodimerization of tetra-tolyl (**1a**) and tetra-tosylurea (**1b**) calixarenes, serendipitously found by Rebek *et al.* (R. K. Castellano, B. H. Kim and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1997, **119**, 12671–12672), has been used for the construction of highly sophisticated macrocycles and well-defined supramolecular assemblies. Regrettably, hitherto, neither the exact structure of these heterodimers nor the reason for their exclusive formation is known. We present molecular dynamics simulations using the AMBER force field in explicit chloroform solvent for the two homodimers, the heterodimer and the two uncomplexed tetra-urea calixarenes. The rigid rotation about the C–S–N–C bond of the tosylurea group has been calculated for a model compound (*N*-mesylformamide) at the RHF/6-31G* level of theory. The calculations suggest that the heterodimer **1a**·**1b** is energetically favored over the homodimers by a sterically relaxed conformation of the tosylurea hemisphere in **1a**·**1b**, by a moderate degree of reorganization of the hemispheres from the uncomplexed to the complexed state and by favorable interactions between the hemispheres. The tosylurea S=O groups are involved in the hydrogen bonding system which results in different sizes of the three capsules in increasing order **1a**·**1a** < **1a**·**1b** < **1b**·**1b**. To prove the computational predictions, ^{1}H NMR experiments have been carried out with solvents/guests differing in shape and size. The largest capsule **1b**·**1b** prefers the larger guests toluene and *p*-xylene while the latter is not encapsulated in the smallest capsule **1a**·**1a**.

Introduction

Interactions *via* hydrogen bonds are of fundamental importance for the structure and function of biological macromolecules or living systems as well as for the quality of technical products and in materials science. Often the understanding of more complex systems has been facilitated by studies with suitable models or model compounds. A very simple model for self-organization *via* hydrogen bonding is calix[4]arenes substituted at their wide rim by four urea groups.

Such tetra-urea calixarenes **1** form dimeric capsules **1**·**1** in apolar solvents, *e.g.* chloroform, benzene or cyclohexane. They are held together by a seam of eight pairs of intermolecular NH···O=C hydrogen bonds involving alternately urea functions of the two calixarenes.[1] The inclusion of a suitable guest, often a solvent molecule, is a necessary condition for the dimerization. The combination of two different tetra-ureas **1** in equimolar amounts usually results in the formation of homo- and heterodimers in a statistical ratio. Examples are known, however, where no heterodimers are formed, *e.g.* between a tetra-arylurea **1a** and a rigidified analogue derived from a bis-crown-3 calix[4]arene.[2] On the other hand it has been known for a long time that tetra-arylureas **1a** exclusively form heterodimers with tetra-tosylureas **1b** in a 1 : 1 mixture,[3] although both compounds **1a** and **1b** alone readily form homodimers. A tentative explanation for this behaviour was sought in the fact that the higher acidity of the tosylurea protons complements the basic oxygen of the tolylurea residue.[3]



This unexpected heterodimerization was used for the formation of regularly structured linear copolymers from bis-tetra-ureas *via* self-assembly.[4] More recently, well-defined dendritic assemblies were obtained in a similar manner using (*inter alia*) this selectivity.[5] Alkenyl residues attached to the urea functions can be intramolecularly connected *via* olefin metathesis, often followed by hydrogenation.[6] Again, heterodimers with **1b** could be used to control the regioselectivity, avoiding for instance connections across the calixarene cavity.[7] Bis-, tris- and tetraloop derivatives[8]

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† Electronic supplementary information (ESI) available: Geometric and energetic parameters of the monomers **1a** and **1b**, compounds used for the calculation of RESP charges and RESP derived charges for the constituting fragments of the tetra-tolyl and tetra-tosylurea calix[4]arenes **1a** and **1b**, histogram of the C–S–N–C dihedral angles of acyclic sulfonylureas in the Cambridge Structural Database and NOESY data for **1a**·**1b**. See http://dx.doi.org/10.1039/b708679b

of calix[4]arenes became available in this way, which were in turn converted to novel bis[2]-,[9] bis[3]- and cyclic [8]catenanes,[10] to fourfold rotaxanes[11] and (by hydrolysis of the urea functions) to huge macrocycles.[12] Therefore, the attempt to understand the reason for the exclusive formation of heterodimer **1a**·**1b** is not only an academic curiosity.

Our previous study aiming at the explanation of the observed selectivities by means of molecular dynamics (MD) simulations has proved unsuccessful.[13] Neither the interaction or complexation energies nor the geometries of the homodimers **1a**·**1a** and **1b**·**1b** differed significantly from those of the heterodimer **1a**·**1b**.

In contrast, by using RESP (restrained electrostatic potential fit)-derived partial charges,[14] instead of the Gasteiger–Hückel atomic point charges[15] utilized in the previous calculations, in combination with the AMBER 7 program suite[16] we were not only able to predict the selectivities observed for the dimerization of tritolyl (**2a**) and tritosyl (**2b**) derivatives of triphenylmethanes, but we could also verify the different hydrogen bonding patterns present in the respective dimers **2a**·**2a**, **2a**·**2b** and **2b**·**2b**.[17] Similarly, MD simulations of [2]rotaxanes derived from the heterodimer **1a**·**1b** proved to be in agreement with the experimental data.[11] Given the importance of the tolyl–tosylurea calixarene heterodimerization for the construction of larger supramolecular assemblies we decided to repeat the calculations for dimeric capsules from **1a** and **1b**.

In this paper we discuss the most probable reasons for the selective heterodimerization based on the results of the computer simulations and we present additional experimental evidence for the conclusions drawn from these calculations.

Results and discussion

The trajectories of the tolyl homodimer **1a**·**1a** reveal the usual bifurcated hydrogen bonding pattern between the NH and C=O groups of the urea residues (Fig. 1a). Statistical summarization of the hydrogen bonds present in the simulations shows that the two hemispheres are held together on average by 13.4 hydrogen bonds. The NH···O=C distances are somewhat shorter for the NH_α than for the NH_β protons, thus suggesting an unequal strength of the hydrogen bonds (Table 1). The inner volume of the capsule is on average 203 Å^3 with a pole–pole distance (defined by the centroids of the methylene carbon atoms) of 9.3 Å and an equatorial diameter (calculated from the radius of gyration of the urea carbonyl groups) of about 11.4 Å. This is in agreement with the crystal structures solved so far for such capsules[10,18] and, concerning the different strength of the hydrogen bonds, with the ^{1}H NMR data.[19]

The calculations of the tosyl homodimer **1b**·**1b** were started from the same bifurcated $(NH)_2\cdots O{=}C$ arrangement of the urea functions as in **1a**·**1a**. The inspection of the energy-minimized starting structure showed already the presence of four bifurcated hydrogen bonds between NH and O=S which were formed at the expense of four bifurcated NH···O=C hydrogen bonds. The NH···O=S and NH···O=C hydrogen bonds appear in an alternating order. This means that one hemisphere acts as a carbonyl acceptor while in the other the sulfonyl groups contribute to hydrogen bonding. This overall picture of hydrogen bonding was maintained during the MD simulation, but the NH protons switched several times between the O=C and O=S acceptor functions (Fig. 1c, see also Fig. 2). The direction of the hydrogen bonded belt remained constant. The fluctuation of the hydrogen bonding pattern, although slow on the MD timescale, may suggest that some steric strain present in one hemisphere is from time to time transferred the other hemisphere.

Since the overall shape of the capsule remains constant during the MD simulation irrespective of the toggling hydrogen bonding system, most energetical and geometrical parameters do not significantly change their values with time, such as the polar and equatorial extension of the capsule, the steric energy of the capsule, the interaction energies between the hemispheres and between host and guest (Tables 1 and 2). The alternating arrangement of hydrogen bonds is reflected in alternating values of the C–S–N–C dihedral angles as well as in alternating energies calculated for the two single hemispheres and for their interactions with the guest molecule (Fig. 2). The C–S–N–C dihedral angle of the sulfonamide group adopts an average value of about ±60° when the O=S function acts as the hydrogen bond acceptor and a value of around 180° when the adjacent urea carbonyl group accepts the hydrogen bond. Remarkably, the energy calculated for the former state is 20 kcal mol^{-1} higher for a single hemisphere than in the latter state (Table 2). This suggests that the C=O···HN hydrogen bonded hemisphere resides in a sterically and energetically unfavorable situation resulting from a strained arrangement of the tosylurea group.

Table 1 Average values for specific geometric parameters of the capsules, fluctuations in parentheses

	1a·**1a**	**1a**·**1b**	**1b**·**1b**
Cavity volume/Å^3	203	222	250
Number of hydrogen bonds[a]	13.4	14.8	15.4
Distance of the centroids of the methylene carbon atoms/Å	9.31 (0.21)	10.55 (0.16)	10.78 (0.24)
Equatorial diameter/Å[b]	11.45 (0.15)	9.37 (0.20)	10.85 (0.16)
$NH_\alpha\cdots O{=}C$ distance/Å	2.00 (0.19)	2.01 (0.16)	2.73 (0.47)/2.04 (0.22)[c]
$NH_\beta\cdots O{=}C$ distance/Å	2.08 (0.29)	1.97 (0.15)	3.63 (0.48)/2.36 (0.41)[c]
$NH_\alpha\cdots O{=}S$ distance/Å	—	2.39 (0.27)	2.29 (0.35)/3.15 (0.57)[c]
$NH_\beta\cdots O{=}S$ distance/Å	—	1.97 (0.16)	2.01 (0.28)/3.11 (0.78)[c]

[a] Obtained by statistical summarization over all snapshots with cut-off values of 2.75 Å for the NH···O distance and of 135° for the NH···O angle. [b] Calculated from the radius of gyration of the urea C=O groups. [c] Distances corresponding to the two different hydrogen bonding patterns (see text and Fig. 1c).

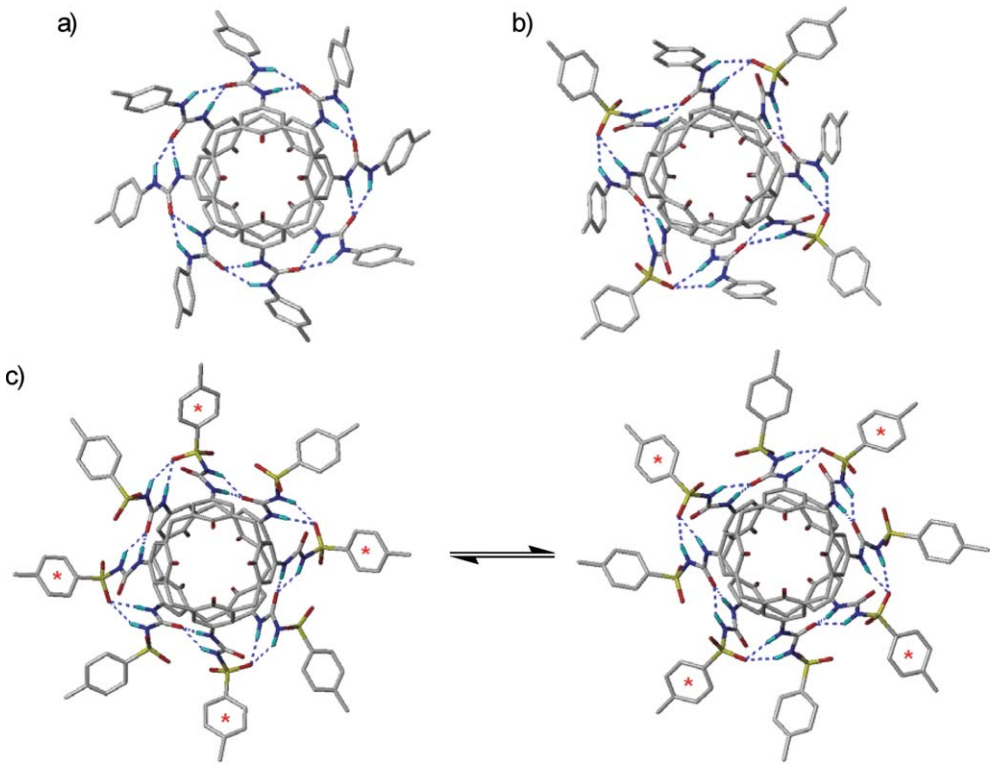


Fig. 1 Energy-minimized time-averaged structures of (a) **1a**·**1a**, (b) **1a**·**1b** and (c) **1b**·**1b** with the two different orientations of hydrogen bonds. Blue dashed lines denote hydrogen bonds. Hydrogen atoms bonded to carbon atoms and the pentyl groups at the narrow rim have been omitted for clarity. In (c) tosyl groups which accept hydrogen bonds via their S=O groups are marked with an asterisk.

Table 2 Average energy components[a] (kcal mol^{-1}) for the dimeric capsules

	E_{h1}	$\Delta E_{r,h1}$	E_{h2}	$\Delta E_{r,h2}$	ΔE_{h1_h2}	ΣE_{h_g}	$\Sigma E_{interact}$	$\Delta E_{complex}$
1a·**1a**	−380.0	24.4	−379.8	24.6	−121.4	−22.0	−143.4	−94.4
1a·**1b**	−381.3	23.1	−491.2	40.5	−158.9	−21.7	−180.7	−117.1
1b·**1b**	−465.6	66.1	−487.0	44.5	−169.2	−21.3	−190.5	−79.9

[a] E_{h1}, E_{h2}: energies of the two calixarenes within the assembly; $\Delta E_{r,h1}$, $\Delta E_{r,h2}$: reorganization energy of the calixarenes = $E_{h1,2}$ − $E_{h1,2}$(uncomplexed) ($E_{\mathbf{1a},uncomplexed}$ = −404.4 kcal mol^{-1}, $E_{\mathbf{1b},uncomplexed}$ = −531.7 kcal mol^{-1}); ΔE_{h1_h2}: interaction energy between the two tetra-urea subunits in the capsule; ΣE_{h_g}: sum of the interaction energies between the chloroform guest and the two tetra-urea calixarene units; $\Sigma E_{interact}$: sum of interaction energies; $\Delta E_{complex}$: complexation energy = $\Delta E_{r,h1}$ + $\Delta E_{r,h2}$ + $\Sigma E_{interact}$.

Since there are neither experimental nor theoretical studies of the geometry and energy of sulfonylureas published in the literature,[20] we checked the structures of sulfonylureas in the Cambridge Crystallographic Database,[21]‡ and we calculated the rotational barrier around the S–N bond at the RHF/6-31G* level of theory for the model compound *N*-mesylformamide. In the crystal structures, the C–S–N–C dihedral angles adopt only discrete values of ±60° (±20°) (see ESI†). The *ab initio* calculations show that only these two minima exist for the rotation around the S–N bond which correspond to the two possible synperiplanar arrangements of the N–H and S=O bonds (Fig. 3). The two minima are separated by two maxima at 0° and 180°, the energy difference between the maximum at 180° and the minima being about 9 kcal mol^{-1} for the model compound. Although we did not calculate the corresponding energy difference for the capsule **1b**·**1b** (due to the inherent molecule size limitations of the method used) it is reasonable to assume that the position of the maxima and minima is similar to the model system. Hence, the question arises why one hemisphere of the capsule always has to adopt such an energetically uncomfortable arrangement.

In contrast to the straight conformation of the tolylurea residues in **1a**·**1a** the presence of the sulfonyl group in **1b**·**1b** introduces a kink at the periphery of the capsule. A C–S–N–C dihedral angle of about ±60° implies that the tolyl ring is either backfolded in the direction of the capsule, leading to steric clashes with the calixarene skeleton of the second hemisphere, or it favorably extends into the equatorial plane of the capsule as shown in Fig. 1c. Since the two hemispheres of a tetra-urea capsule usually behave as mirror images the putative preferred arrangement would involve one hemisphere with C–S–N–C angles near +60° and the other with the corresponding angles near −60°. However, in this arrangement very close repulsive contacts occur between adjoining tolyl rings (Fig. 4). Therefore, in order to maintain the circular hydrogen

‡ Only acyclic sulfonylureas with a *trans*-configured S–N–C(=O)–N bond were considered in this analysis.

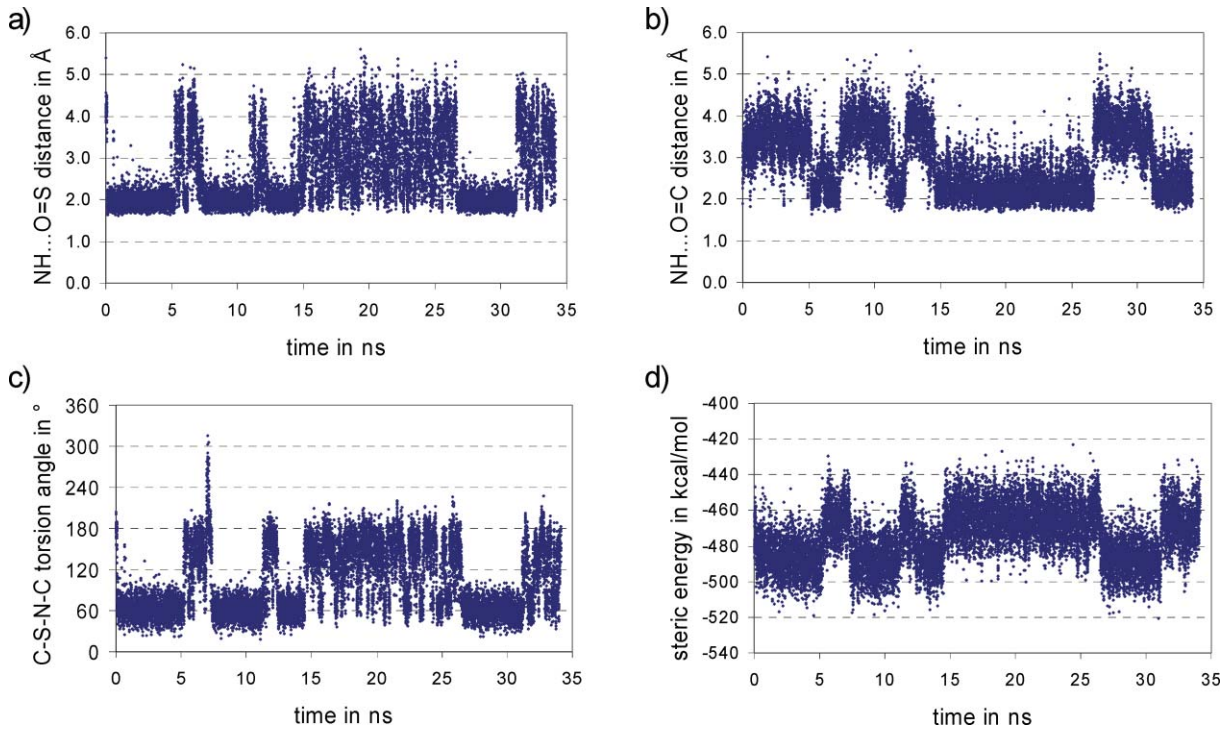
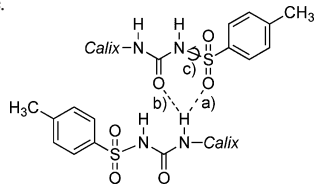


Fig. 2 (a) NH · · · O=S distance and (b) NH · · · O=C distance of the same NH proton in the time course of the MD simulation of **1b**·**1b** as an example of the alternating hydrogen bonding geometry, (c) C–S–N–C torsion angle of the tosylurea unit incorporating O=S and O=C of (a) and (b), respectively, as a function of time, (d) steric energy of the corresponding capsule hemisphere.



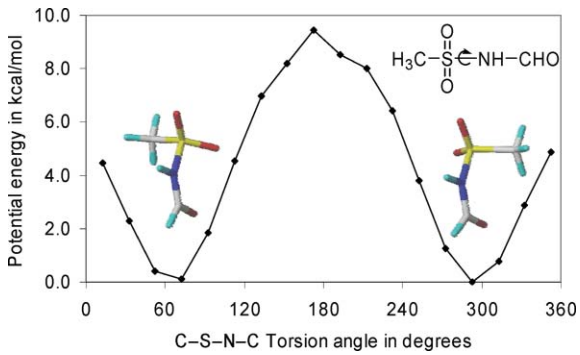


Fig. 3 Potential energy for rigid rotation about the S–N bond in *N*-mesylformamide at the RHF/6-31G* level of theory.

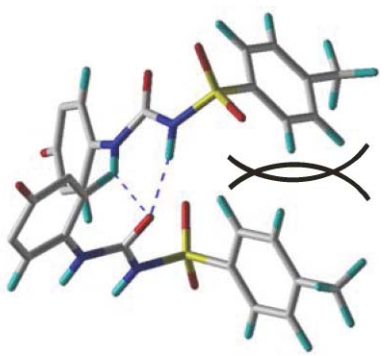


Fig. 4 Repulsion of the tolyl rings in a putative low-energy structure of **1b**·**1b** with C–S–N–C dihedral angles of +60° and −60°. The view is along the long axis of the capsule; only two building blocks belonging to different hemispheres are shown.

bonding system in **1b**·**1b**, the tosyl groups of one of the two hemispheres must necessarily adopt an energetically unfavorable arrangement characterized by C–S–N–C dihedral angles near 180°.§ The energy price paid for the higher conformational energy is compensated by the favorable interaction between the two capsule hemispheres (most probably due to favorable hydrogen bonding, see Table 2) which is commensurate with the fact that the tetra-tosylurea calixarene **1b** forms in solution a homodimer in the absence of the tolylurea calixarene **1a**.

The capsule **1b**·**1b** is held together on average by 15.4 hydrogen bonds, the strongest being formed between the NH_β proton and O=S as well as between the NH_α proton and O=C. This modified hydrogen bonding pattern results in an elongation of the capsule along the pole–pole axis by about 1.5 Å in comparison to **1a**·**1a**,

§ It should be noted that similar steric repulsions exist also for circular hydrogen bonding patterns involving either exclusively NH · · · O=C or NH · · · O=S contacts.

while the equatorial diameter is marginally smaller (Table 1). The space available for a guest molecule in the interior of the capsule is on average 250 Å^3, which is nearly 50 Å^3 more than in the case of **1a**·**1a**. Hence, a bigger guest molecule should be able to occupy the cavity of **1b**·**1b** (see below).

In the heterodimer **1a**·**1b** a stable hydrogen bonding pattern is formed consisting of four bifurcated hydrogen bonds between the tolyl NH protons and the O=S functions and four bifurcated hydrogen bonds between the tosyl NH protons and the carbonyl oxygens of the tolylurea groups (Fig. 1b). This hydrogen bonding motif emerges from the $(NH)_2 \cdots O{=}C$ pattern of the starting structure during the equilibration period of the simulation and it does not change during the production period. On average, 14.8 hydrogen bonds are formed between the two hemispheres. Three of the four hydrogen bonding contacts ($NH_\beta \cdots O{=}C/O{=}S$, $NH_\alpha \cdots O{=}C$) are of comparable strength while the fourth ($NH_\alpha \cdots O{=}S$) is somewhat weaker (Table 1). The tosylurea units adopt a low-energy state corresponding to a C–S–N–C dihedral angle of around ±60°.

The alternating arrangement of two different kinds of hydrogen bonds causes an asymmetric shape of the capsule. Thus, the two hemispheres are rotated by 40° (and by 50° in the other direction) against each other while the corresponding angles are near 45° in **1a**·**1a** and **1b**·**1b**. The participation of the S=O groups, which are further apart from the calixarene skeleton than the C=O groups, in the hydrogen bonding scheme causes an elongation of the capsule along its longitudinal axis by about 1 Å compared to **1a**·**1a** while it contracts the equatorial region by about 2 Å. The cavity of the capsule **1a**·**1b** is about 20 Å^3 larger than that of **1a**·**1a** which would approximately correspond to the volume of a methyl group. Bearing in mind that toluene preferentially orients its methyl group in the direction of the polar region[22] (the region of the calixarenes) it may be anticipated that *p*-xylene, which is considered to be a poor guest[1] of **1a**·**1a** (see also below), could be a suitable guest for **1a**·**1b**. Moreover, given the different size of the homo- and heterodimers from **1a** and **1b**, it might be possible to influence the formation of homo- *vs.* heterodimers by means of careful guest selection.

The energetical analysis of the trajectories recorded for the three capsules and the uncomplexed calixarenes (Table 2) indicates that the high-energy conformation of a single hemisphere in the homodimer **1b**·**1b** is not the sole reason for the exclusive formation of heterodimer **1a**·**1b**. The difference in the complexation energies $\Delta E_{complex}$ calculated for the equilibrium **1a**·**1a** + **1b**·**1b** ⇌ 2(**1a**·**1b**) favors the heterodimer **1a**·**1b** over the two homodimers by 59.9 kcal mol^{-1}, which is almost three times the energy difference between the two different conformations of **1b** in the complex **1b**·**1b**.

The complexation energies $\Delta E_{complex}$ can be directly related to the free enthalpies of complexation $\Delta G_{complex}$ provided that different entropic contributions to $\Delta G_{complex}$ can be neglected due to the similarity of the systems. Two major components contribute to the overall complexation energy: the reorganization energy which is necessary to convert the constituting individual molecules from the uncomplexed to the complexed state and the interaction energies between the capsule hemispheres and between host and guest. The reorganization energies ΔE_r (Table 2) are substantially higher for the tosylurea calixarenes **1b** than for the tolyl calixarenes **1a** indicating that different interactions must be present in the free calixarenes. Inspection of the trajectories stored for **1a** and **1b** showed that they adopt pinched cone conformations in their uncomplexed state, which are stabilized by hydrogen bonding between opposite urea functions.[23] While in **1a** a single bifurcated $NH \cdots O{=}C$ hydrogen bond is formed, two bifurcated $NH \cdots O{=}S$ hydrogen bonds in **1b** tightly connect opposite rings (Fig. 5). It is therefore obvious that the rearrangement from the pinched cone conformation to the C_4 symmetrical cone conformation present in the capsules requires a much higher energy for the tosylurea calixarene **1b** than for the tolylurea derivative **1a**.

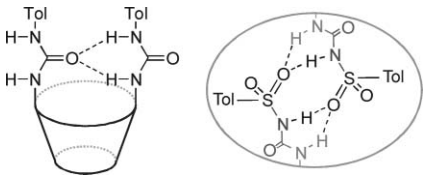


Fig. 5 Hydrogen bonding geometry of the monomers **1a** (left, sideview) and **1b** (right, view from the top).

The interaction energies (Table 2) favor the heterodimer over the two homodimers by about 25 kcal mol^{-1}. While the host–guest interaction energies are nearly identical, the energies for the interactions between the two hemispheres increase in the order **1b**·**1b** < **1a**·**1b** < **1a**·**1a**. This order parallels the average number of hydrogen bonds present in the capsules (Table 1). Additionally, attractive π–π interactions of the tilted-T type[24] (average ring-center–ring-center distances of 6.3 Å for **1a**·**1b** and 6.6 Å for **1b**·**1b**, respectively) are formed between adjacent aromatic rings attached to the urea functions. This type of interaction is only possible in **1a**·**1b** and **1b**·**1b** due to the kinked shape of the tosylurea group, whereas in **1a**·**1a** the straight form of the tolylurea group prevents such interactions.

NMR experiments

Taking into account the results obtained by the MD simulations, *p*-xylene was examined as a potential guest for the homodimers **1a**·**1a**, **1b**·**1b** and the heterodimer **1a**·**1b**. All attempts to dissolve **1a** or **1b** in pure *p*-xylene-d_{10} failed, whereas an addition of one drop of non-deuterated benzene led (after heating) to the clear solutions. As expected, the ^{1}H NMR spectrum of the tetra-tolylurea **1a** showed only the capsule with included benzene (Fig. 6a). A single dimer was also found in the case of tetra-tosylurea **1b**, however, no signal of encapsulated benzene was observed, suggesting that *p*-xylene is included as the guest (Fig. 6b).

For the preparation of the heterodimer **1a**·**1b** the solutions described above were mixed together. Immediately after mixing, the initial homodimers **1a**·C_6H_6·**1a**, **1b**·C_8D_{10}·**1b** and two heterodimers **1a**·C_6H_6·**1b**, **1a**·C_8D_{10}·**1b** were detected in the spectrum (Fig. 6c). After 1 h only the heterodimers remained in the mixture (Fig. 6d).

To prove the potential inclusion of *p*-xylene, **1a** and **1b** were dissolved in $CDCl_3$ and 15% of non-deuterated *p*-xylene was added to the each solution. The spectrum of the tetra-tolylurea **1a** did not change and no resonances corresponding to the encapsulated *p*-xylene were observed (Fig. 7a). In contrast, a second set of calixarene protons and two additional peaks at 5.36 and −2.22 ppm appeared for the tetra-tosylurea **1b**, clearly showing that *p*-xylene is included in the cavity (Fig. 7b). The same experiment in benzene also showed two different sets of signals

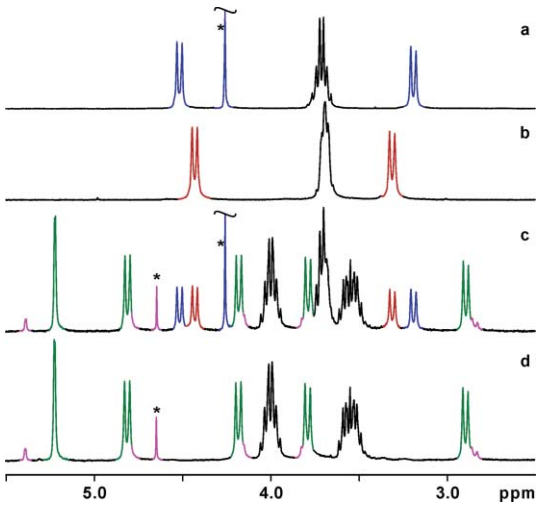


Fig. 6 Parts of the ^{1}H NMR spectra (*p*-xylene-d_{10}, 3% of C_6H_6) of (a) **1a**, (b) **1b**, (c) 1 : 1 mixture of **1a** and **1b** immediately after mixing, (d) 1 : 1 mixture of **1a** and **1b** 1 h after mixing. Colour code: **1a**·C_6H_6·**1a** blue, **1b**·C_8D_{10}·**1b** red, **1a**·C_6H_6·**1b** pink, **1a**·C_8D_{10}·**1b** green; the signals of the included benzene are marked with *.

belonging to the dimers **1b**·C_6D_6·**1b**, **1b**·C_8H_{10}·**1b** (Fig. 7c) and the included *p*-xylene.

To distinguish between the internal volumes of the capsules **1a**·**1a**, **1a**·**1b** and **1b**·**1b**, solvents that differ slightly in shape/size were offered as guests. All pairwise combinations (50 : 50 mol%) of benzene, toluene and *p*-xylene were checked, the results for *p*-xylene-d_{10}–C_6D_6 are shown in Fig. 8. The results, which demonstrate an obvious difference in the sizes of the three dimers, are summarized in Table 3.

The smallest dimer **1a**·**1a** is not able to accept *p*-xylene as a guest and forms only the homodimer **1a**·C_6H_6·**1a** even if only traces of

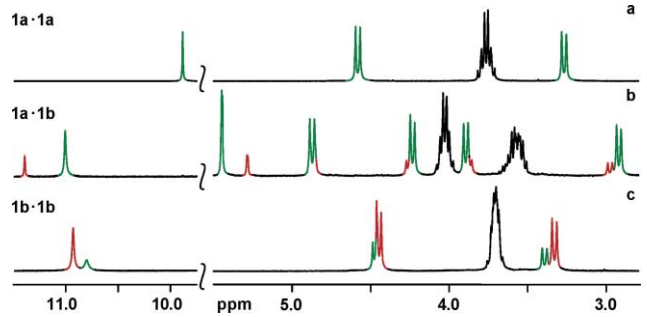


Fig. 8 Sections of the ^{1}H NMR spectra (*p*-xylene-d_{10}–C_6D_6, 50 : 50 mol%) of **1a**·**1a**, **1a**·**1b** and **1b**·**1b**. Dimers with included C_6D_6 are shown in green, dimers with included *p*-xylene in red.

benzene are present (Fig. 6a). Benzene is also a favorable guest *vs.* toluene, since 87% of the **1a**·**1a** homodimers formed in a 1 : 1 mixture of the respective solvents contained C_6H_6 as the guest.

The slightly larger heterodimer **1a**·**1b** can include each of the proposed solvent molecules. Although benzene or toluene seem to be the better guests in comparison to *p*-xylene, there is no clear difference between either of them.

The largest capsule **1b**·**1b** clearly prefers to include the larger guests toluene or *p*-xylene in comparison to benzene. In the case of the guest pair *p*-xylene–toluene the smaller toluene is still preferred. However, for all three guest pairs there is an increasing tendency to include the larger guest when going from the smallest capsule **1a**·**1a** *via* the heterodimer **1a**·**1b** to the largest capsule **1b**·**1b**.

Experimental

All molecular dynamics simulations were performed using the AMBER 7 software package and the *gaff* parameter set.[16] The initial geometry of the monomers and dimers was obtained

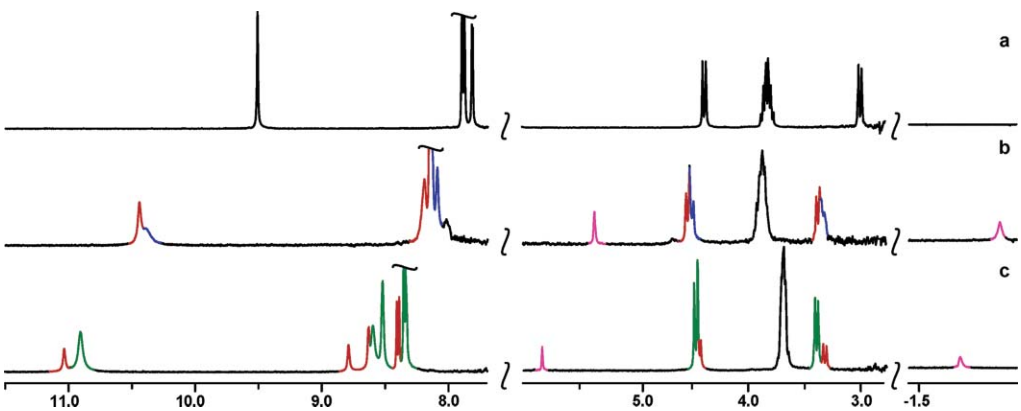


Fig. 7 Parts of the ^{1}H NMR spectra (with 15% of *p*-xylene) of (a) **1a** in $CDCl_3$, (b) **1b** in $CDCl_3$, (c) **1b** in C_6D_6. Colour code: **1b**·C_8H_{10}·**1b** red, **1b**·$CDCl_3$·**1b** blue, **1b**·C_6D_6·**1b** green, included *p*-xylene pink.

Table 3 The ratio between dimers formed in the two-component solution mixtures (50 : 50 mol%; $c = 8 \times 10^{-3}$ M, 25 °C)

Solvent		Homodimer **1a**·**1a**		Heterodimer **1a**·**1b**		Homodimer **1b**·**1b**	
A	B	**1a**·A·**1a**	**1a**·B·**1a**	**1a**·A·**1b**	**1a**·B·**1b**	**1b**·A·**1b**	**1b**·B·**1b**
p-Xylene-d_{10}	Toluene-d_8	—	100	15	85	28	72
p-Xylene-d_{10}	C_6D_6	—	100	19	81	78	22
Toluene-d_8	C_6D_6	13	87	54	46	84	16

from earlier MD simulations,[13] but the ethyl ether groups at the narrow rim used in these calculations were replaced by pentyl ether groups. A chloroform molecule was placed as a guest inside the capsule. Charges (see ESI†) were derived following the standard RESP procedure[14] from a 6-31G* electrostatic potential calculated with the Gaussian98 program[25] and the assemblies were transferred into the LEaP format. Subsequently, a rectangular box of chloroform molecules (approximately 14 Å solvent layer thickness on each side) was added. For the chloroform solvent model, the corresponding parameters of AMBER 7 were used.[26] Missing parameters for the ca–os–c3 and n–s6–ca bond angles were defined by analogy to the corresponding c–os–c3 and o–s6–ca parameters, respectively, included in the *gaff* parameter set of AMBER 7. The solvated structures were subjected to 5000 steps of minimization followed by a 30 ps belly dynamics (300 K, 1 bar, 1 fs timestep) for solvent relaxation and a 100 ps equilibration period. Subsequently, MD simulations were performed in an NTP (300 K, 1 bar) ensemble (constant number of particles, constant temperature and pressure) for 3 ns (**1a**), 9 ns (**1b**, **1a**·**1a** and **1a**·**1b**) and 34 ns (**1b**·**1b**) using a 1 fs time step. Constant temperature and pressure conditions were achieved by the weak coupling algorithm and isotropic position scaling. Temperature and pressure coupling times of 0.5 ps and 1.0 ps, respectively, and the experimental compressibility value of 100×10^{-6} bar^{-1} for chloroform were used. The particle mesh Ewald (PME) method[27] was applied to treat long-range electrostatic interactions, and the van der Waals interactions were truncated by using a cut-off value of 12 Å. Bonds containing hydrogen atoms were constrained to their equilibrium length using the SHAKE algorithm. Snapshots were recorded every 2 ps.

Geometrical and energetic analyses of the trajectories were carried out with the carnal and anal modules of AMBER 7. Analysis of hydrogen bonding was conducted by measurement of distances and angles between potential donor and acceptor sites for each snapshot of the trajectory followed by statistical summarization. Graphical analysis of the results was performed with the SYBYL program.[28] Internal volumes of the cavities were calculated with the MOLCAD module of SYBYL using the Fast Connolly Channel algorithm with a probe size of 1.4 Å.

The calculation of the rotational barrier around the S–N bond was carried out for *N*-mesylformamide at the 6-31G* level of theory with the Gaussian98 program. This basis set was considered adequate for sulfonamides.[29] The step size was 20° and the corresponding dihedral angle (C–S–N–C) was kept fixed while all other coordinates were optimized.

Conclusions

Although frequently used in self-assembly processes and in covalent syntheses based on this self-assembly the reason(s) for the exclusive formation of heterodimers between tetra-tosylurea calix[4]arenes **1b** and tetra-tolylurea calix[4]arenes **1a** remained obscure. Based on molecular dynamics simulations we could give for the first time a reasonable explanation for this heterodimerization which is consistent in itself. For electronic and mainly for steric reasons the homodimer **1b**·**1b** of a tetra-tosylurea consists of two molecules with different conformation and considerably different energy. The heterodimer **1a**·**1b**, which contains the tetra-tolylurea **1a** in the usual conformation, can be formed only with the energetically favored conformation of the tetra-tosylurea **1b**. Hence all tetra-tosylurea molecules can assume the favorable conformation if only heterodimers are present, while half of the tetra-tosylurea molecules are held in the unfavorable conformation in the homodimer. MD simulations alone are not a proof. However, from these simulations further conclusions followed for the size of the dimeric capsules, which in turn could be verified by the inclusion of differently sized solvent molecules as guests, which concludes a self-consistent explanation.

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