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Hydrogen bonded calixarene capsules kinetically stable in DMSO

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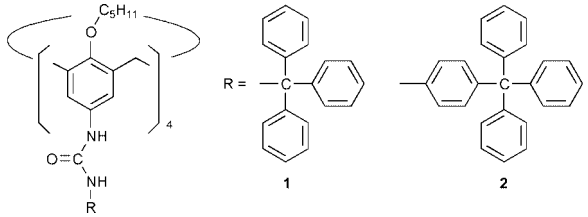
Half-life times up to 4 days in DMSO at room temperature are observed for the decomposition of dimeric capsules of urea substituted calix[4]arenes held together by a combination of hydrogen bonds, mechanical entanglement and cation–π interactions.

Natural macromolecules like proteins, DNA and RNA possess specific three-dimensional structures which determine their biological activity in complex sequences of intracellular transformations including recognition, catalysis and self-replication.[1] Their stability *in water* is achieved by a combination of numerous weak, noncovalent interactions such as hydrogen bonding, cation–π, π–π, and hydrophobic interactions.

Spatially well defined artificial hydrogen bonded assemblies which are thermodynamically or at least kinetically stable in highly competitive hydrogen bonding solvents such as water, DMF or DMSO are rare.[2,3] Recent examples are polymers formed by cooperative stacking of hydrogen-bonded pairs in water[4] and dimeric glycoluril capsules formed by self-assembly *via* hydrogen bonds in the presence of a hydrophobic guest in DMF.[5] In the latter case, the observation of signals of both the dimer and the monomer in the ^{1}H NMR spectra, indicated that the dimers are stable on the NMR time-scale. To our knowledge, this example is unique, although simpler systems like hydrogen bonded complexes of anions in d_6-DMSO which are stable on the NMR time-scale have been described.[6] In the following we disclose our first results on self-assembled dimers which possess high kinetic stability on a 'human time-scale' in a hydrogen bond breaking solvent like d_6-DMSO.

Calix[4]arenes bearing four urea functions at the wide rim, form dimeric capsules in appropriate nonpolar solvents.[7] These capsules are held together by a hydrogen bonded belt formed between the self-complementary urea units. A suitable guest, often a solvent molecule, must be included inside. The dimers are usually rapidly destroyed by small amounts (only up to 2%) of DMSO added to the apolar solvent, while kinetically very stable assemblies are available in the absence of competitive hydrogen bonding solvents.[8] We have demonstrated, for instance, that the mechanical entanglement of bulky residues like trityl (**1**) and *p*-tritylphenyl (**2**) attached to the urea



functions leads to dimers with kinetic stability on the 'human time-scale' ($\tau_{\frac{1}{2}}$ = 60 h for the heterodimer **1**·**2** in d_6-benzene).

MD simulations performed for **2**·**2**, **1**·**2** and **1**·**1** have shown[8a] that the inner volume of the capsule decreases in this row, and that the cavity size of the trityl urea dimer **1**·**1** would be too small for the inclusion of benzene. As predicted **1** does not form dimers in this solvent. However, we assumed that a small cation like tetramethylammonium could be a good template for the dimerisation of **1** (Fig. 1),[9] since favourable interactions

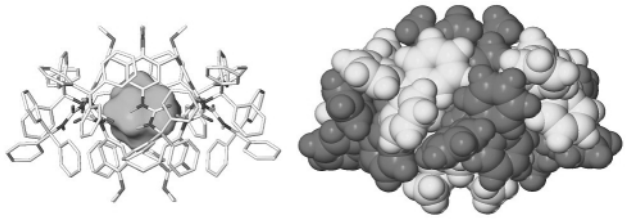


Fig. 1 Simulated structure of a dimer of **1** with Me_4N^+ as a guest.

between the cation and the extended π-basic cavity should additionally stabilise the ternary complex.

Indeed, when the urea **1** is refluxed for 2–4 weeks in dichloromethane in the presence of tetramethylammonium iodide or chloride an additional spot appears in the TLC (R_f = 0, instead of R_f = 1 for **1** with ethyl acetate as eluant) indicating the formation of charged species. A simple column separation allowed isolation of the compounds **1**·Me_4N^+·**1** I^- and **1**·Me_4N^+·**1** Cl^-— in 33 and 13% yield, respectively. The ^{1}H NMR spectrum in $CDCl_3$ shown in Fig. 2a clearly supports their structures by the sharp, low field shifted NH signals and one of two *meta*-coupled doublets characteristic for the aromatic protons of the calixarene in dimeric urea complexes.† The signal of the included tetramethylammonium cation is upfield shifted to δ −1.1 ppm due to shielding by the aromatic residues of the calixarene. The MALDI-TOF spectrum shows a peak at *m*/*z* 3886.8 (calc. for **1**·Me_4N^+·**1** 3886.7).

Surprisingly, the spectrum of the **1**·Me_4N^+·**1** I^- recorded in d_6-DMSO shows the same set of signals, typical for a dimeric structure, which slowly disappear while signals for the monomeric **1** and for the uncomplexed tetramethylammonium

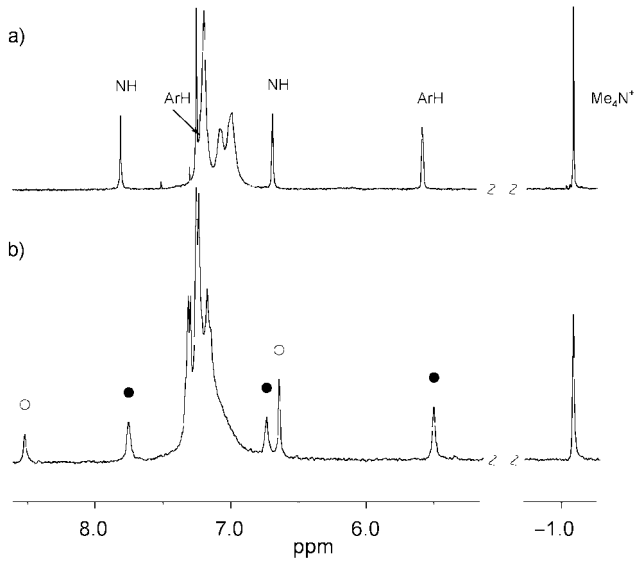


Fig. 2 Section of the ^{1}H NMR spectra (400 MHz) of **1**·Me_4N^+·**1** I^- recorded in $CDCl_3$ (a) and in d_6-DMSO after 1 day (b). Calixarene, amide and guest protons are indicated in (a), the disappearing signals of the dimer (●) and the growing signals of the monomer **1** (○) are marked in (b).

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cation appear (Fig. 2b). These spectral changes obey first-order kinetics. Activation parameters (Table 1) for the reaction: **1**·Me_4N^+·**1** $X^- \rightarrow$ 2 **1** + Me_4N^+ X^- were derived from Eyring plots (Fig. 3) in the 25–55 °C temperature range.

Table 1 Activation parameters for the decomposition of the capsules in d_6-DMSO

	1·Me_4N^+·**1** Cl^-	**1**·Me_4N^+·**1** I^-
$\Delta H^{\neq}$/kJ mol^{-1}	118.0 (± 6.5)	99.9 (± 2.6)
$\Delta S^{\neq}$/J K^{-1} mol^{-1}	49.0 (± 21)	−18.4 (± 8.2)
$\Delta G^{\neq}$/kJ mol^{-1} at 25 °C	103.4	105.6
$\tau_{\frac{1}{2}}$/hours at 25 °C	40	93

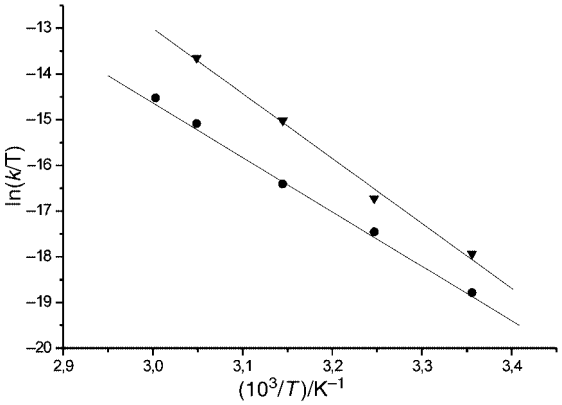

Fig. 3 Eyring plot for the decomposition of **1**·Me_4N^+·**1** I^- (●) and **1**·Me_4N^+·**1** Cl^- (▼) in d_6-DMSO.

The half-life slightly depends on the counter anion and reaches 93 hours at 25 °C in the case of iodide, which is unprecedented for such a hydrogen bonded assembly to our knowledge. This high kinetic stability of the capsules in d_6-DMSO suggests that the mechanical entanglement of the bulky trityl residues protects the belt of 16 hydrogen bonds from access by DMSO (*cf.*, Fig. 1).[10]

The signals of the trityl groups in the ^{1}H NMR spectrum are broad at 25 °C and split into several broad signals in the case of **1**·Me_4N^+·**1** Cl^- in CD_2Cl_2 at −50 °C (Fig. 4), in contrast to the monomeric **1**. The overall symmetry of the capsule remains S_8 as deduced from the presence of only two NH and two ArH signals for the calixarene skeleton. Six signals of the trityl groups are sufficiently resolved to distinguish clearly cross-peaks corresponding to two different phenyl groups in the gradient selected COSY spectrum. The pattern of the spectrum proves the fast rotation of the phenyl groups.‡ Thus, the splitting of the signals must be due to the slow rotation of the entire trityl groups around the C–N bonds. Models suggest that this rotation must occur in a concerted way for all of the eight trityl groups.

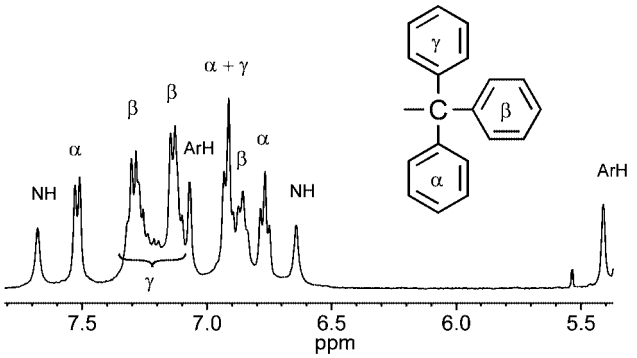

Fig. 4 Section of the ^{1}H NMR (−50 °C, CD_2Cl_2, 400 MHz) of **1**·Me_4N^+·**1** Cl^-. Calixarene and amide protons are marked with NH and ArH respectively. Two low-field shifted signals of the phenyl group (assigned 'β') overlap with signals of the third phenyl ring ('γ').

In conclusion, we have described an unprecedented example of a molecular capsule self-assembled *via* a belt of hydrogen bonds, showing kinetic stability on 'the human time-scale' in the hydrogen bond breaking solvent d_6-DMSO. This kinetic stability is caused, to a large extent, by the mechanical entanglement of bulky, *noncyclic* residues (trityl groups) attached to the urea functions which hinder the access of solvent to the hydrogen bonded belt. We propose to call this type of molecule 'anchoranes' since — in contrast to 'rotaxanes'§ — noncyclic structural elements or residues are mechanically entangled similar to an anchor holding a ship due to its interlocking with noncyclic structures on the bottom of the sea.

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Notes and references

† In gradient selected-COSY spectra there are cross-peaks from this signal to another *meta*-coupled doublet overlapped with signals of trityl groups.
‡ Only *two* cross-peaks between three signals of the rings α or β are observed. If rotation about the C–C bond were slow on the NMR time-scale, five signals would be expected for each phenyl group.
§ Although 'rotaxanes' are topologically not exactly defined like catenanes, the concept of (pseudo)rotaxanes has proved to be very fruitful.

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