

Self-assembly of dimeric tetraurea calix[4]pyrrole capsules

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Calix[4]pyrroles having extended aromatic cavities have been functionalized with 4 ureas in the *para* position of their *meso* phenyl substituents. This elaboration of the upper rim was completed in 2 synthetic steps starting from the $\alpha,\alpha,\alpha,\alpha$ -tetranitro isomer of the calix[4]pyrrole obtained in the acid catalyzed condensation of *p*-nitrophenyl methyl ketone and pyrrole. In dichloromethane solution and in the presence of 4,4'-bipyridine *N,N'*-dioxide the tetraurea calix[4]pyrrole dimerizes reversibly forming a cyclic array of 16 hydrogen bonds and encapsulating 1 molecule of bis-*N*-oxide. The encapsulated guest is bound in the cavity by hydrogen bonding to the 2 endohedral calix[4]pyrrole centers. Further evidence for dimerization of the tetraurea calix[4]pyrroles is provided by ¹H-NMR experiments and by the formation of mixed capsules.

calixpyrroles | hydrogen bonding | N-oxides

In the mid-1990s, Rebek and Böhmer independently reported the first examples of urea-containing noncovalent dimeric capsules **1**–**1** (Fig. 1) (1–3). These are based on the self-assembly of 2 calix[4]arene units **1** in which the so-called “cone-conformation” is fixed or favored (4, *) by the presence of ether functions in the lower rim (5, †). The 2 calixarene units dimerize through upper rim/upper rim interactions mediated by a self-complementary hydrogen bonding pattern based on 8 urea functionalities. Oriented in the same direction, all 8 ureas interact in a “head-to-tail” topology, which dictates the circular self-assembly. In such dimers, the 2 calixarene units are rotated relative to each other by 45° around their common axis and are held together by a seam of 16 hydrogen bonds that seal the resulting cavity. It is worth mentioning that other urea based dimeric systems that deviate from the rigid calixarenes have also been reported (6, 7).

Interest in the construction of molecular capsules by self-assembly and the study of their encapsulation properties has grown steadily since the first report appeared more than a decade ago (8, 9). Using hydrogen bonds, many different types of supramolecular capsules have been synthesized and studied, including examples of free-standing capsules composed of >2 molecular building blocks (10–14). In general, simple dimeric capsules, such as the ones derived from tetraurea calixarenes, are easier to characterize and manipulate in solution than multimolecular capsular aggregates. Nevertheless, even the design of self-assembled dimers becomes challenging if they are to have internal volumes capable of including >1 suitable sized guest and enclosing functionality to direct the organization of the housed guests. Although supramolecular capsules with internal volumes ranging from 200 to 1,500 Å³ have been prepared, there are very few examples in which the guest ordering within the molecular cavity has been controlled by factors other than simple steric constraints or weak nondirectional interactions with the molecular enclosure (15).

We report here the use of self-assembling tetraurea calix[4]pyrroles **2** (Fig. 1), which are easily synthesized and possess a sizable endohedral functionalized cavity, for the construction of dimeric capsules in which the included guest is bound through hydrogen bonding to donor sites located within the framework of the molecular enclosure.

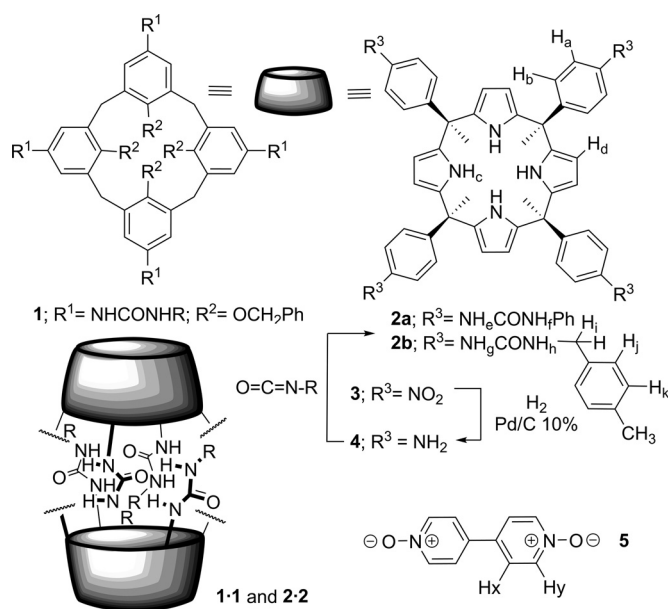


Fig. 1. Molecular structures of compounds **1**–**5**. The **1**–**1** and **2**–**2** dimers are shown schematically.

Results and Discussion

Calix[4]pyrroles, or *meso* octasubstituted porphyrinogens (16, 17), are macrocyclic species having an array of 4 NHs that act as a binding site for anionic and electron rich neutral guests in organic solvents (18). The formation of the complex, for example with a chloride anion, is usually accompanied by a change from the preferred alternate (1,2 or 1,3) conformation of the free calix[4]pyrrole core to the cone conformation (Fig. 2). Aryl extended calix[4]pyrroles are produced by substitution at each of the 4 *meso*-carbons with 1 aryl group (19). In the cone conformation, the $\alpha,\alpha,\alpha,\alpha$ isomers of aryl extended calix[4]pyrroles have a deep aromatic cavity suitable for including molecular

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*The monomeric form of the tetramethoxy urea derivative was only observed in the cone conformation.

†In reference 5, it has been shown that the existence of free hydroxyl groups in the lower rim enhances the 4-fold symmetry of the cone conformation through the formation of intermolecular hydrogen bonds assisting in the formation of dimeric tetraurea hydrogen bonding capsules even in polar solvents such as THF.

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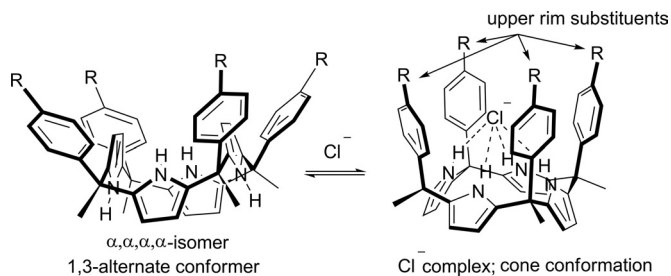


Fig. 2. Molecular structures of aryl extended calix[4]pyrroles. Conformational change of the $\alpha,\alpha,\alpha,\alpha$ -isomer from 1,3-alternate to cone promoted by chloride binding.

guests (Fig. 2). The aromatic cavity present in the cone conformation of aryl extended calix[4]pyrroles is deeper and more sizeable than that of a corresponding calixarene counterpart. Furthermore, and similarly to calixarenes, aryl extended calix[4]pyrroles possess an “upper rim,” surrounding the open end of their structure, which can be functionalized and further elaborated. However, in striking contrast with calixarenes, the deeper aromatic cavity of aryl extended calix[4]pyrroles is functionalized in its closed end with 4 converging NHs.

Simple molecular modeling studies suggested that tetraurea aryl extended calix[4]pyrroles constituted an ideal alternative to tetraurea calix[4]arenes for the construction of self-assembled dimeric capsules (Fig. 3). An aryl extended calix[4]pyrrole in the cone conformation positions the 4 urea substituents in the proper self-complementary orientation to induce self-assembly of hydrogen-bonded dimeric molecular capsule **2-2**. The structure of the dimer closely resembles the one derived from tetraurea calix[4]arenes, with all of the ureas oriented in the same direction and hydrogen-bonded to their neighbors, forming a total of 16 hydrogen bonds with reasonable geometric parameters. The size of the internal cavity in **2-2** is $\approx 321 \text{ \AA}^3$,[‡] representing approximately a 62% increase in internal volume with respect to the internal volume of **1-1** (198 \AA^3); this augurs well for the encapsulation of multiple guests. More importantly, the **2-2** dimer features 2 endohedral hydrogen-bonding donor sites that are located 12 \AA apart in a convergent orientation within the molecular enclosure and are not involved in the formation of the capsule framework. At first sight, these binding sites seem to be appropriate to order including guest(s) via hydrogen bonding.

Synthesis. The tetranitro aryl extended calix[4]pyrrole **3** was synthesized by acid condensation of pyrrole and 1-(4-nitrophenyl)ethanone in dichloromethane (20). Of the 4 possible configurational isomers, the $\alpha,\alpha,\alpha,\alpha$ -isomer was isolated after careful purification of the reaction mixture (column chromatography and crystallization) as a yellowish solid in 10% yield. Catalytic hydrogenation of tetranitro calix[4]pyrrole **3** using $\text{H}_2/10\% \text{ Pd-C}$ as catalyst in ethyl acetate afforded the corresponding tetraamine **4**. Thus, only 2 synthetic steps are required for the functionalization of the upper rim of the aryl extended calix[4]pyrrole with 4 *p*-amino groups. Subsequent reaction of tetraamine **4** with either phenyl isocyanate or *p*-methylbenzylisocyanate gave the corresponding tetraureas **2a** and **2b** (see Fig. 4 for the methanol solvate of **2b**) respectively in good yield.

[‡]The volume of the cavities were calculated using DeepView/Swiss-Pdb Viewer V 3.7 <http://www.expasy.org/spdbv/> and using the minimized structure of the **2-2** capsule obtained with *CAChe WorkSystem*, version 6.1.12.33; Fujitsu Limited. For the calculation of the volume in the **1-1**, the dimer the structure was obtained from the TIDWEI.cif file deposited in Cambridge Crystallographic Data Centre, www.ccdc.cam.ac.uk.

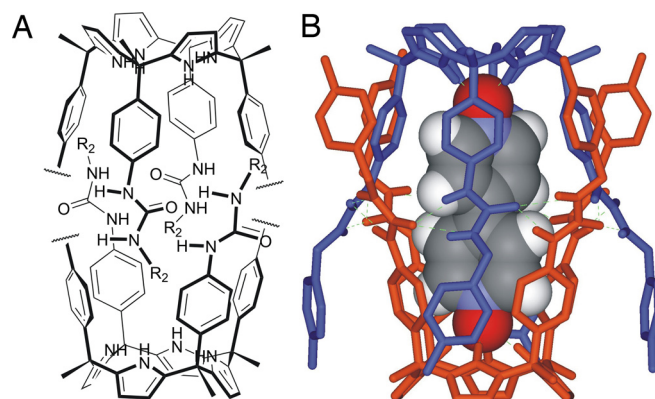


Fig. 3. Graphical representations of calix[4]pyrrole dimer assembly **2-2**. (A) Schematic view of the calix[4]pyrrole dimer assembly **2-2** and the head-to-tail urea belt. Some ureas are omitted for clarity. (B) Side view of the CAChe minimized structure of the **2b-2b** dimer (stick representation) containing an encapsulated bipyridine bis-*N*-oxide **5** (shown in CPK model). Nonpolar hydrogen atoms of **2b** are omitted for clarity.

Conformational Features of Calix[4]pyrroles. It is well known that calix[4]arenes have 4 conformations: cone, partial cone, 1,2-alternate, and 1,3-alternate (21). Due to the geometric resemblance between calix[4]arenes and calix[4]pyrroles it should be expected that calix[4]pyrroles could also adopt the same 4 major conformations. In fact, recent theoretical studies have shown that octaalkylcalix[4]pyrroles are extremely conformationally flexible molecules. “In silico,” these calix[4]pyrroles adopt mainly a 1,3-alternate conformation in all solvents, although the percentage of alternative conformations increases in polar solvents, especially in those with good hydrogen-bonding acceptor properties (22, 23). The results of molecular dynamics simulations indicate that calixpyrroles should not be viewed as rigid structures fixed in the 1,3-alternate conformation in the absence of coordination guest. Experimental and theoretical studies have also shown that, in nonpolar solvents, the binding of a chloride anion induces a conformational change in the calixpyrrole core

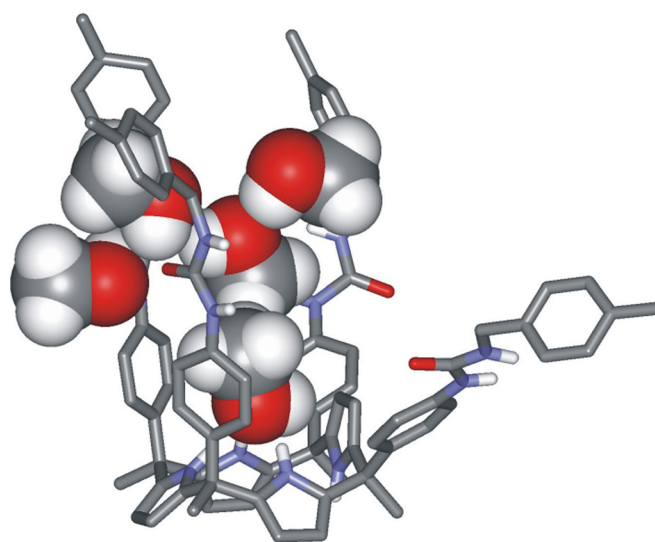


Fig. 4. X-ray structure of the methanol solvate of **2b**. The asymmetric unit contains 2 molecules of **2b**. In both of them the calix[4]pyrrole core adopts the partial cone conformation. Methanol molecules are shown in CPK representation, and **2b** is shown in stick view. Nonpolar hydrogen atoms of **2b** are omitted for clarity.

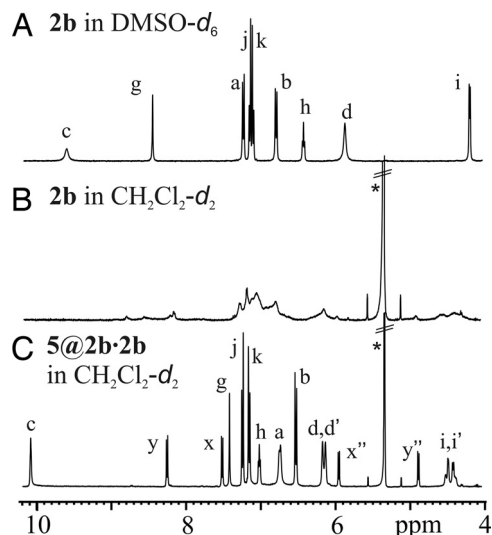


Fig. 5. Selected region of the $^1\text{H-NMR}$ spectra of a solution of **2b** in $\text{DMSO-}d_6$ (A), $\text{CH}_2\text{Cl}_2-d_2$ (B), and $\text{CH}_2\text{Cl}_2-d_2$ (C) containing excess bipyridine bis-*N*-oxide **5** (C). Primed numbers indicate diastereotopic protons, second primed numbers indicate protons corresponding to encapsulated **5**. See Fig. 1 for proton assignments. *, residual CH_2Cl_2 signal.

from the alternate conformation to the cone conformation (24). Although there are no detailed studies on the conformational features of aryl extended calixpyrroles, we (25, 26) and others (19) have observed that their chloride and fluoride complexes adopt the cone conformation in solution and in the solid state. This conformation has also been routinely observed in the crystal structure of aryl extended calixpyrroles grown from hydrogen bonding solvents (e.g., acetonitrile, acetone and *N,N*-dimethylformamide) (26, 27). In contrast, the few X-ray structures of aryl extended calixpyrroles from crystals grown in nonpolar solvents (e.g., dichloromethane) show that the calixpyrrole core is in the 1,3-alternate conformation (26). Taken together, these results suggest that the conformational features of aryl extended calixpyrroles could be considered analogous to those of the related octaalkyl calix[4]pyrroles. Thus, in nonpolar solutions aryl extended calixpyrroles mainly adopt a 1,3 alternate conformation that can undergo rapid interchange to the cone conformation when a suitable guest is placed close to the coordination site formed by the 4 convergent NHs (Fig. 2). The energetic cost associated with the conformational change is small, as has been observed in anion binding, and we anticipated that the preorganization to the cone conformation would not represent a major impediment to dimer self-assembly.

Dimer Assembly. Disappointingly, the $^1\text{H-NMR}$ spectra of 1 mM solutions of tetraureas **2a** and **2b** in $\text{CH}_2\text{Cl}_2-d_2$ show broad and unresolved signals that are spread all over the chemical shift proton scale (Fig. 5B). This observation is a clear indication that the formation of the expected **2:2** dimer did not take place and that ill defined aggregates are present in the dichloromethane solution (see GPC chromatogram of **2b** in the SI). In sharp contrast, the $^1\text{H-NMR}$ spectra of **2a** and **2b** in $\text{DMSO-}d_6$ reveal sharp and well resolved signals for all of the protons indicative of a time-averaged C_4 symmetry (Fig. 5A). Both $\alpha,\alpha,\alpha,\alpha$ -isomers display only one type of β -pyrrole resonance suggesting that the conformational exchange (cone to alternate), if operative, is fast on the $^1\text{H-NMR}$ timescale at room temperature or that the fluxional calixpyrrole is locked into a single conformation in this hydrogen bonding solvent. Characteristic of **2b** are the protons in the region of 6.0–10.0 ppm (Fig. 5A) where 1 singlet ($\delta = 8.45$ ppm, proton g) and 1 triplet ($\delta = 6.43$ ppm, proton h) for the urea

NHs and 4 doublets with *ortho* coupling for the tolyl residues ($\delta = 7.10$ and 7.15 ppm, protons k and j) and the aromatic protons ($\delta = 6.80$ and 7.23 ppm, protons b and a) of the calixpyrrole are observed. The 4 pyrrole NHs emerge as a singlet at $\delta = 9.60$ ppm (proton c) due to hydrogen bonding with the solvent. Not unexpectedly, the tetraureas **2a** and **2b** exist as single molecules in DMSO solution. Usually, only conformationally biased tetraurea calixarene subunits give rise to well-defined and thermodynamically stable dimeric capsules (28). A likely explanation for the lack of **2:2** capsule formation in dichloromethane may have to do with the fact that, although the structural information for assembly is present in the calixpyrrole tetraureas, the entropic and enthalpic price for the requisite conformational change and ensuing dimerization is not compensated by the formation of 16 hydrogen bonds in the assembled system. We already mentioned that the binding of anions and electron rich neutral guests produces a conformational change in the calixpyrrole core favoring the cone conformation. After screening a series of electron rich neutral compounds we came across pyridine *N*-oxides as effective guests capable of producing the desired conformational switch. Molecular modeling studies indicated that 4,4'-bipyridine bis-*N,N'*-oxide **5** was a perfect fit to fill the interior of the **2:2** capsule while being simultaneously bound through ditopic interactions with the 2 endohedral hydrogen-bonding donor sites (Fig. 3B). Accordingly, the addition of bipyridine bis-*N*-oxide **5** to a $\text{CH}_2\text{Cl}_2-d_2$ solution of calixpyrrole tetraurea **2b** produced a dramatic change in the $^1\text{H-NMR}$ spectra (Fig. 5C). After the addition of **5**, all proton signals corresponding to the calixpyrrole tetraurea **2b** became sharp and well resolved and were easily assigned. This observation constitutes the first indication that a discrete and well defined species had been formed in solution. Because the most typical proof for the dimerization of the calixarene tetraureas in solution was the observation of 2 separated *meta* coupled doublets for the calixarene aryl group, we looked for this asymmetry in the $^1\text{H-NMR}$ spectra of a $\text{CH}_2\text{Cl}_2-d_2$ solution of **2b** with **5**. Unfortunately, at room temperature, we did not observe this typical behavior assigned to capsule formation. We did, however, observe that the doublet of the calixpyrrole aryl proton *ortho* to the urea group (proton a in Fig. 5C) showed a significant broadening compared with the doublet of the *meta* proton (proton b in Fig. 5C) to which it is coupled. We were aware of the example described by Böhmer in which the splitting of the 2 signals for the proton *ortho* to the urea groups of the calixarene required lowering the temperature (29). Cooling our sample to 200 K lead to the expected splitting of the aromatic signal (see SI). Rebek pointed out (1) that the observation of such asymmetry in the tetraurea calixarene dimers is due to slow rotation around the arylcalixarene-urea bond, which in turn changes the directionality of the hydrogen-bonded belt of ureas. From the coalescence temperature, we calculated the barrier for the change of the direction of the urea belt in calixpyrrole dimer **2b·2b** to be 11.8 kcal·mol $^{-1}$. The desymmetrization of the benzyl protons of **2b** (proton i and i' in Fig. 5c), which exhibit a large geminal coupling constant, was already evident at room temperature and hinted to capsule formation. The room temperature $^1\text{H-NMR}$ spectrum of **5@2b·2b** also indicated a high degree of hydrogen bonding in the complex. The triplet of the benzyl urea proton was significantly shifted to $\delta = 7.03$ (proton h in Fig. 5C) compared with the chemical shift for the same signal observed in a strong hydrogen bonding solvent like $\text{DMSO-}d_6$ ($\delta = 6.43$ ppm, proton h in Fig. 5A). The phenyl urea proton resonates at $\delta = 7.43$ ppm (proton g in Fig. 5C), which also represents a significant downfield shift compared with the $\delta \approx 6.2$ ppm observed for diphenyl urea in diluted CDCl_3 solutions (30). Finally, the pyrrole NHs appeared at $\delta = 10.1$ ppm (proton c in Fig. 5C), that is, 0.5 ppm downfield shifted compared with its chemical shift in $\text{DMSO-}d_6$, a solvent known to hydrogen bond strongly with the NHs. Further support for the formation of the dimeric capsule arises from the observation of 2 doublets with *ortho* coupling at $\delta = 4.90$ and 5.97 ppm (protons y' and x'' in Fig. 5C) that were assigned to the protons

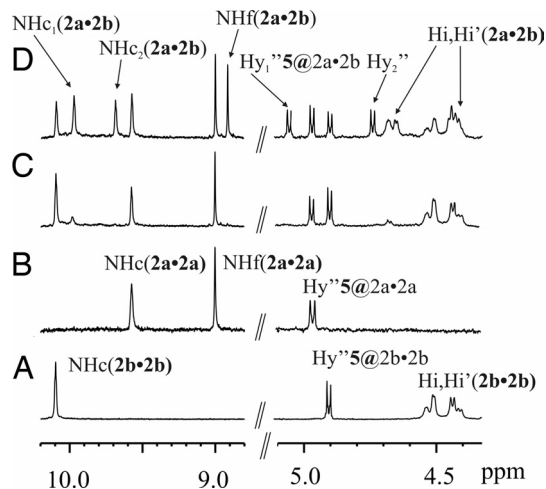


Fig. 6. Two selected regions of the ^1H -NMR spectra of the ternary complexes in $\text{CH}_2\text{Cl}_2-d_2$ solutions of homocapsule complex $5@2b\cdot 2b$ (A), homocapsule $5@2a\cdot 2a$ (B), and mixture of the 2 homocapsule complexes (C and D) at $t = 0$ h (C) and after 100 h have elapsed (D). Primed numbers indicate diastereotopic protons, second primed numbers indicate protons corresponding to encapsulated 5. In the heterocapsule $2a\cdot 2b$, the different type of protons are indicated by numbers. See text for details and Fig. 1 for assignment.

of encapsulated 5. The corresponding protons for free 5 can be observed at $\delta = 7.53$ and 8.26 ppm (protons x and y in Fig. 5C). The observation of only 2 signals in the bound guest and their intense upfield complexation-induced shift is strong evidence for guest encapsulation in the symmetric cavity of the $2b\cdot 2b$ dimer. Furthermore, the largest anisotropy experienced by the pyridyl protons of bound 5 alpha to the *N*-oxide (proton y' in Fig. 5C, $\Delta\delta \approx 3.4$ ppm) indicates that they are deeply included inside the cavity while surrounded by the aromatic walls.

For the moment we cannot provide an accurate value for the association constant of the ternary complexes $5@2b\cdot 2b$. However, the fact that it is the exclusive species formed in a 1 mM solution even in the presence of excess 5 sets the lower limit of an estimated value for the complex stability in 10^7 M^{-2} . (The addition of $40 \mu\text{L}$ of $\text{DMSO}-d_6$ to $500 \mu\text{L}$ of a 1 mM solution of $5@2b\cdot 2b$ in $\text{CH}_2\text{Cl}_2-d_2$ is enough to break apart the capsular assembly and produce simple complexes of $5@2b$ with 1:1 stoichiometry.) The integration of the proton signals gave a 1:2 ratio of compounds bound 5 and 2, respectively, offering independent support for the dimeric structure of the termolecular complex. The observation of separated proton signals for free and bound 5 points out that, apart from its estimated thermodynamic stability, the ternary complex also exhibits high kinetic stability. The 2D NOESY experiments were performed to further characterize the kinetic stability of the system and to map out in more detail the complex geometry. Accordingly, no cross peaks were observed between the signals corresponding to free and encapsulated 5 at room temperature, indicating a high energy barrier for guest exchange. In the same experiment, several cross peaks corresponding to intermolecular NOE contacts were observed, which is in complete agreement with the proposed dimeric structure [e.g., strong cross peaks are observed between the methyl group of the tolyl substituent and the methyl groups and β -pyrrole protons of the calix (see SI)]. When a 1:1 mixture of tetraureas $2a$ and $2b$ in $\text{CH}_2\text{Cl}_2-d_2$ was treated with excess 5, in addition to the anticipated signals for the $5@2a\cdot 2a$ and $5@2b\cdot 2b$ ternary complexes, a new set of proton signals assigned to the formation of the heterodimer $5@2a\cdot 2b$ was immediately observed (Fig. 6D). This observation proves unambiguously the existence of dimers in solution. Furthermore, under these experimental conditions, the ratio of the proton

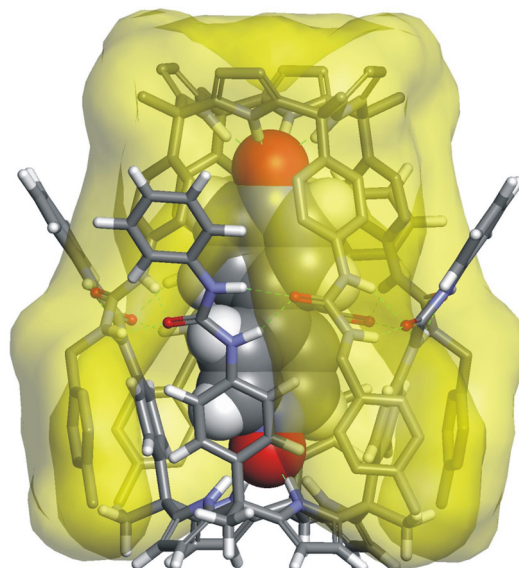


Fig. 7. Energy minimized structure of the heterodimeric capsule $2a\cdot 2b$ encapsulating 1 bipyrindine bis-*N*-oxide 5. Compound 5 is shown as CPK, the molecular component $2b$ is displayed as a VDW surface, and $2a$ is shown in stick representation. Some hydrogen atoms are omitted for clarity.

signal corresponding to the 3 dimers did not change with time. When the directionality of the hydrogen-bonded belt of ureas is in fast chemical exchange on the NMR timescale, as is the case at hand here, the homodimers have an apparent D_{4d} symmetry while the heterodimers are apparently C_{4v} symmetric. The $5@2a\cdot 2b$ dimer contains 2 different calixpyrrole units (Fig. 7). This change in symmetry was entirely reflected by the ^1H -NMR spectra and led to the observation of 2 different proton signals for the pyrrolic NHs and 4 different doublets for the protons of encapsulated 5 (Fig. 6D). The 2 doublets corresponding to the 2 different pyridyl protons alpha to the *N*-oxide function of 5, which are included in the 2 distinct calixpyrrole units of the $2a\cdot 2b$ dimer, can be readily observed in the upfield region of Fig. 6D. Two proton signals corresponding to diastereotopic benzylic protons of the $2b$ calixpyrrole unit in the heterodimer $2a\cdot 2b$ can also be observed in the equilibrated mixture. In striking contrast with the results presented above, when 2 $\text{CH}_2\text{Cl}_2-d_2$ solutions containing preformed homodimeric capsular complexes ($5@2a\cdot 2a$ and $5@2b\cdot 2b$) were mixed, the ^1H -NMR spectrum acquired immediately after mixing revealed the predominant existence of only homodimeric capsular complexes. Under these conditions, several hours elapsed until the formation of the heterodimer complex $5@2a\cdot 2b$ reached equilibrium. This observation suggests that the exchange of the calixpyrrole components of the $5@2\cdot 2$ complexes is slower than previously observed in calixarene analogs. Most likely, the hydrogen bonded guest 5, which is required to template the formation of the capsule, adds additional kinetic stabilization to the termolecular system. The high kinetic stability of the termolecular complex is also responsible for not having detected the presence of cross peaks due to guest exchange in the NOESY experiment. The final distribution of the 3 capsular dimers upon equilibration of the mixture was in complete agreement with the equilibrium constant value estimated statistically ($K = [5@2a\cdot 2b]/[5@2a\cdot 2a][5@2b\cdot 2b] = 4$). This result indicates that the 3 ternary complexes are isoenergetic.

Conclusion

We have prepared 2 self-complementary calix[4]pyrroles $2a\cdot b$ that, in nonpolar solvents and in the presence of an adequate template (i.e., 4,4'-bipyridine bis-*N,N'*-oxide 5), dimerize

through the formation of a circular belt of 8 hydrogen bonded ureas and additional hydrogen bonding interactions between the polar ends of **5** and the 2 binding sites of the calixpyrrole components. The overall result is the formation of a ternary inclusion complex showing very high thermodynamic and kinetic stability. Furthermore, the system presented here constitutes one of the few examples of supramolecular cages containing endohedral hydrogen bonding functionality for potential ordering included guests. Future achievements for capsules of this sort will include their templated formation in the presence of guests capable of producing tetramolecular complexes, and the formation of mixed calixarene-calixpyrrole tetraurea hybrid capsules.

Materials and Methods

General. All chemicals were purchased from commercial sources and used without further purification. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were taken on Bruker Avance 400 and 500 Ultrashield spectrometers. Mass analyses were performed on a Waters LCT Premier spectrometer (ESI mode).

The tetranitro $\alpha,\alpha,\alpha,\alpha$ isomer **3** was isolated in 10% yield as a pale yellow solid by slight modification of the experimental procedure described in ref. 20.

$^1\text{H-NMR}$ (500.1 MHz; CD_3CN ; 25 °C): δ 2.01 (s, 12H), 5.97 (d, 8H, $^4J_{\text{H-H}} = 2.7$ Hz), 7.23 (d, 8H, $^3J_{\text{H-H}} = 8.8$ Hz), 8.15 (d, 8H, $^3J_{\text{H-H}} = 8.8$ Hz), 8.12 (br s, 4H); HR-MS (ESI+ve) m/z calculated for $\text{C}_{48}\text{H}_{40}\text{N}_8\text{O}_8$ ($[\text{M} + \text{Na}]^+$) 879.2867, found 879.2856.

Preparation of Calix[4]Pyrrole Tetraamine (4). Crystallized tetranitro calix[4]pyrrole **3** (50 mg) was dissolved in 25 mL of ethyl acetate. The solution was filtered to remove any precipitate. The resulting solution was poured on a suspension of Pd/C (30 mg) in 3 mL of ethyl acetate. The reaction mixture was connected to a hydrogenation apparatus, purged twice with hydrogen, charged with a hydrogen pressure of 4 bars, and shaken during 3 h. The Pd/C suspension was filtered over celite and the resulting solution was evaporated to dryness under vacuum. The tetraamine calixpyrrole **4** was obtained as a white solid (40 mg, 92% yield).

$^1\text{H-NMR}$ (400 MHz; CD_3CN ; 25 °C). δ 1.82 (s, 12H), 5.96 (d, 8H, $^4J_{\text{H-H}} = 2.6$ Hz), 6.52 (d, 8H, $^3J_{\text{H-H}} = 8.2$ Hz), 6.65 (d, 8H, $^3J_{\text{H-H}} = 8.2$ Hz), 8.01 (s, broad 4H); HR-MS (ESI+ve) m/z calcd for $\text{C}_{48}\text{H}_{44}\text{N}_4$ ($[\text{M} + \text{Na}]^+$) 699.3464, found 699.3473.

General Procedure for the Synthesis of Calix[4]Pyrrole Tetraureas. The corresponding isocyanate (0.21 mmol) was added dropwise to a solution of the

tetraamine **4** (40 mg; 0.05 mmol) in CHCl_3 (8 mL). The reaction mixture was stirred at room temperature during 2 h. After that time, 40 mL of methanol were added to the mixture. The chloroform was removed under vacuum and the resulting methanol solution was slowly evaporated to induce the precipitation or crystallization of the tetraurea calixpyrrole. Yields ranged from 50 to 70%.

Compound 2a. $^1\text{H-NMR}$ (400 MHz; DMSO; 25 °C): δ 1.77 (s, 12H), 5.95 (bs, 8H), 6.84 (d, 8H, $^3J_{\text{H-H}} = 8.67$ Hz), 6.91 (t, 4H, $^3J_{\text{H-H}} = 7.48$ Hz), 7.19 (t, 8H, $^3J_{\text{H-H}} = 8.27$ Hz), 7.31 (d, 8H, $^3J_{\text{H-H}} = 8.67$ Hz), 7.37 (d, 8H, $^3J_{\text{H-H}} = 8.27$ Hz), 8.53 (br s, 4NH), 8.55 (br s, 4NH), 9.54 (br s, 4NH); HR-MS (ESI+ve) m/z calcd for $\text{C}_{76}\text{H}_{68}\text{N}_{12}\text{O}_4$ ($[\text{M} + \text{Na}]^+$) 1235.5384, found 1235.5371.

Compound 2b. $^1\text{H-NMR}$ (400 MHz; DMSO; 25 °C): δ 1.75 (s, 12H), 2.25 (s, 12H), 4.20 (d, 8H, $^3J_{\text{H-H}} = 5.84$ Hz), 5.87 (br s, 8H), 6.43 (t, 4NH, $^3J_{\text{H-H}} = 5.84$ Hz), 6.79 (d, 8H, $^3J_{\text{H-H}} = 8.4$ Hz), 7.10 (d, 8H, $^3J_{\text{H-H}} = 8.17$ Hz), 7.15 (d, 8H, $^3J_{\text{H-H}} = 8.17$ Hz), 7.23 (d, 8H, $^3J_{\text{H-H}} = 8.4$ Hz), 8.45 (s, 4NH), 9.60 (br s, 4NH); HR-MS (ESI+ve) m/z calcd for $\text{C}_{84}\text{H}_{84}\text{N}_{12}\text{O}_4$ ($[\text{M} + \text{Na}]^+$) 1347.6636, found 1347.6615.

Preparation of Capsule 5@2.2. In a typical capsule formation experiment, a small amount of solid bipyridine bis-*N*-oxide **5** was added to a 1 mM dichloromethane solution of **2**. The mixture was sonicated during 5 min to induce the solubilization of **5**. The final suspension was filtered to remove the non dissolved solid, and the $^1\text{H-NMR}$ spectrum of the solution was acquired.

Preparation of Heterocapsule 5@2a.2b. Two 1 mM solutions of **2a** and **2b** were prepared in dichloromethane. Two different procedures were used to obtain the heterocapsule. In the first procedure, an equimolar solution of **2a** and **2b** was prepared by mixing equal volumes of stock 1 mM solutions. To the equimolar mixture was added a small amount of solid **5** and, after sonication and filtration, the $^1\text{H-NMR}$ spectrum of the solution was acquired. In the second procedure, a small amount of solid **5** was added to each of the two 1 mM stock solutions. After sonicating the suspensions for 5 min, they were filtered to remove undissolved material. Next, a solution mixture was prepared by mixing equal volumes of the two 5@2.2 stock solutions. Several $^1\text{H-NMR}$ spectra of the solution mixture were acquired at different times.

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