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Exclusive Self-Assembly of a Polar Dimeric Capsule between Tetraurea Calix[4]pyrrole and Tetraurea Calix[4]arene

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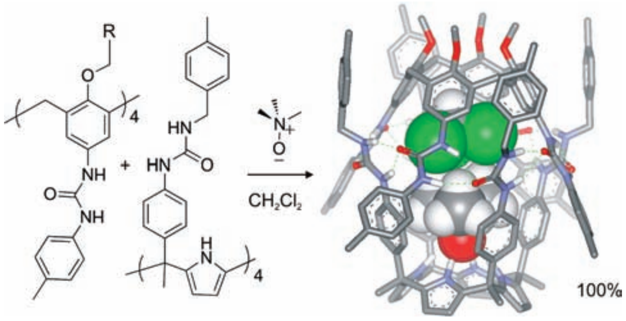
ABSTRACT



The exclusive self-sorting observed in the self-assembly process between tetraurea benzyl calix[4]pyrroles and tetraurea tolyl calix[4]arene to afford unprecedented hybrid dimeric capsules with polar interiors is described. The coencapsulation of a solvent molecule with an organic guest yields four particle aggregates in which the guests are confined and restricted into single hemispheres due to the polar requirements of the internal cavity.

By definition, a self-sorting chemical system must yield a product distribution that is different from the plausible composition of aggregates (complexes) estimated on the basis of statistical, chemical, and geometrical arguments.[1] The attractiveness of self-sorting to the synthetic chemist has to do with the possibility of self-assembling single species from a multicomponent library. The sorting process relies on the chemical information encoded in the structures of the molecules present in the mixture, which in turn is responsible for the type and number of intermolecular interactions established between them to produce the aggregates.[2,3] The discrimination process at work in molecular self-sorting is based on energetic differences between kinetically labile aggregates formed in solution (thermodynamic equilibration). Thus, chemical systems composed of dissimilar components establishing different types and/or numbers of interactions are "a priori" likely to produce a high degree of sorting.[1,4,5]

By the same token, systems containing structurally similar molecules represent a difficult challenge for the search of efficient self-sorting algorithms to be exploited even in the exclusive self-assembly of hybrid two component species.[6] Among others, this is the case encountered in the self-assembly process of heterodimeric supramolecular capsules derived from calix[4]arenes substituted by four

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(1) For the quantification of the degree of self-sorting in a chemical system, see: Mahata, K.; Schmittel, M. *J. Am. Chem. Soc.* **2009**, *131*, 16544.

(2) Ajami, D.; Schramm, M. P.; Volonterio, A.; Rebek, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 242.

(3) Ajami, D.; Hou, J. L.; Dale, T. J.; Barrett, E.; Rebek, J. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 10430.

(4) Schmittel, M.; Mahata, K. *Chem. Commun.* **2010**, *46*, 4163.

(5) Mahata, K.; Saha, M. L.; Schmittel, M. *J. Am. Chem. Soc.* **2010**, *132*, 15933.

(6) Alajarin, M.; Pastor, A.; Orenes, R. A.; Steed, J. W.; Arakawa, R. *Chem.—Eur. J.* **2004**, *10*, 1383.

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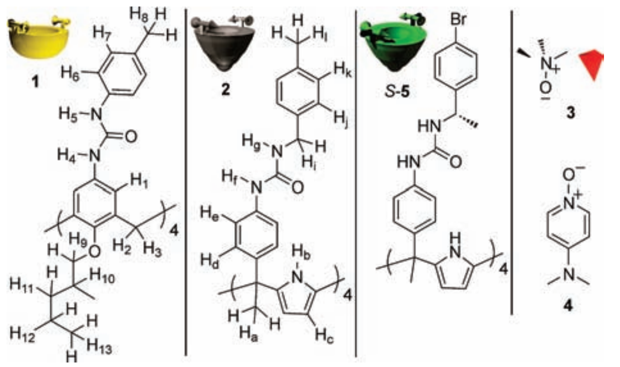

Figure 1. Line drawing structures of the tetraurea calix[4]arene **1**, the tetraurea calix[4]pyrroles **2**, **5**, and guests **3**, **4** with their schematic representation.

urea groups on the upper rim and fixed in the cone conformation.[7] To the best of our knowledge, three different strategies have been reported for the efficient self-sorting assembly of heterodimeric capsules from equimolar binary mixtures of tetraurea calix[4]arenes involving the tetratolyl derivative **1** (Figure 1): (a) the mixture of tetratolyl urea with tetratosyl urea in $\mathrm{CDCl_3}$,[7-9] (b) the mixture of tetratolyl urea with a tetraurea derivative of valine or isoleucine in $\mathrm{C_6D_6}$,[10] and (c) the mixture of the tetratolyl urea with tetraureas that bear loops between adjacent urea groups in $\mathrm{CDCl_3}$.[11,12] While in the latter case the discrimination process is clearly based on structural and thermodynamic factors (maximum site coordination and largest number of species),[13] in the former two cases, thermodynamic contributions including those with the solvent are considered.

Herein, we describe an unprecedented *exclusive* self-sorting system that involves tetratolyl urea **1** and affords a molecular dimeric capsule with a polar interior. In striking contrast with the reports mentioned above for self-sorting of heterodimeric tetraurea calix[4]arene capsules which rely on differences in the functionalization of the urea groups of the two components, our approach is based on the use of different although related molecular scaffolds in the core of the two tetraurea components: tolyl calix[4]arene **1** and benzyl calix[4]pyrrole **2**. The cone conformation of **2** affords a much deeper and polar aromatic cavity with respect to **1** but displays a close similarity in the spatial disposition of the urea groups.

Molecular modeling studies indicate that the heterodimeric capsule **1•2** features good complementarity between the urea groups involved in the hydrogen bonding belt that stitches both components together in the hybrid capsule (Figure 2b).

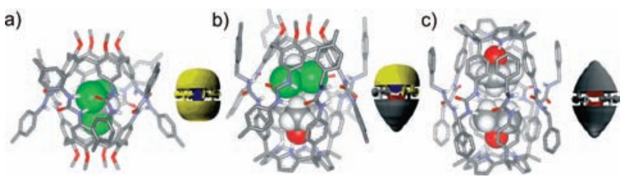

Figure 2. CAChe minimized structures for the capsular assemblies: (a) $\mathrm{CDCl_3}\subset\mathbf{1}\cdot\mathbf{1}$; (b) $\mathrm{CHCl_3}\bullet\mathbf{3}\subset\mathbf{1}\bullet\mathbf{2}$; (c) $\mathbf{3}\bullet\mathbf{3}\subset\mathbf{2}\bullet\mathbf{2}$ and their schematic representation.

Recently, we reported the dimerization of tetraurea calix[4]pyrrole **2** induced by the pairwise encapsulation of trimethylamine-*N*-oxide **3** to yield homocapsule **2•2** with a cavity volume of 340 Å^3 (Figure 2c).[14,15] The included *N*-oxides are selectively oriented within the internal cavity of **2•2** through hydrogen bonding with the four pyrrole NH's located at each of the two closed ends of the capsular assembly. On the other hand, chloroform is a typical guest of tetraurea calix[4]arene capsule **1•1** and complements nicely its cavity size and lipophilicity (Figure 2a).[16,17] The hybrid assembly **1•2** is expected to exhibit host properties that differ from the parent capsules, it has one polar hemisphere, and the internal volume is 280 Å^3. While chloroform has an approximate volume of 75 Å^3 and that of the *N*-oxide **3** is close to 80 Å^3, the coencapsulation of $\mathrm{CDCl_3}$ and **3** into the heterodimeric capsule **1•2** seems to be a perfect cocktail ($PC = 52\%$) to fulfill Rebek's 55% packing coefficient rule for the liquid state, as well as a perfect match to the polarity requirements of the interior.[18]

First, we investigated the self-sorting of the chemical system composed of the two tetraureas **1**, **2** and *N*-oxide **3** in $\mathrm{CDCl_3}$. As mentioned above, in $\mathrm{CDCl_3}$ solution, tetraurea calix[4]arene **1** readily assembles into a dimeric assembly that encapsulates one solvent molecule, $\mathrm{CDCl_3}\subset\mathbf{1}\bullet\mathbf{1}$.[16] The octaurea dimer **1•1** features S_8 symmetry, and this is reflected in the desymmetrization of the aryl (H_1 and H_1') protons (Figure 3c). The source of this asymmetry is the unidirectional sense of orientation adopted by all the urea groups in the **1•1** capsule and their slow rotation about the aryl-urea bond on the NMR time scale. The equimolar mixture of the required amounts to

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(7) Rudzevich, Y.; Vysotsky, M. O.; Bohmer, V.; Brody, M. S.; Rebek, J.; Broda, F.; Thondorf, I. *Org. Biomol. Chem.* **2004**, *2*, 3080.

(8) Castellano, R. K.; Kim, B. H.; Rebek, J. *J. Am. Chem. Soc.* **1997**, *119*, 12671.

(9) Thondorf, I.; Rudzevich, Y.; Rudzevich, V.; Bohmer, V. *Org. Biomol. Chem.* **2007**, *5*, 2775.

(10) Castellano, R. K.; Nuckolls, C.; Rebek, J. *J. Am. Chem. Soc.* **1999**, *121*, 11156.

(11) Rudzevich, Y.; Rudzevich, V.; Klautzsch, F.; Schalley, C. A.; Bohmer, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 3867.

(12) Rudzevich, Y.; Rudzevich, V.; Bohmer, V. *Chem.—Eur. J.* **2010**, *16*, 4541.

(13) Kramer, R.; Lehn, J. M.; Marquisrigault, A. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5394.

(14) Gil-Ramirez, G.; Chas, M.; Ballester, P. *J. Am. Chem. Soc.* **2010**, *132*, 2520.

(15) Ballester, P.; Gil-Ramirez, G. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 10455.

(16) Shimizu, K. D.; Rebek, J. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12403.

(17) Mogck, O.; Paulus, E. F.; Bohmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996**, 2533.

(18) Mecozzi, S.; Rebek, J. *Chem.—Eur. J.* **1998**, *4*, 1016.

produce a 1 mM solution of tetraurea calix[4]pyrrole **2** and *N*-oxide **3** in $CDCl_3$ shows proton signals (Figure 3a) in accordance with those assigned to the four particle homodimer capsule $\mathbf{3}_2\subset\mathbf{2}\bullet\mathbf{2}$ assembled in CD_2Cl_2.[14] When 2 equiv of tetraurea calix[4]arene **1** were added to the above solution, the ^{1}H NMR analysis of the mixture revealed the presence of three different sets of proton signals (Figure 3b).

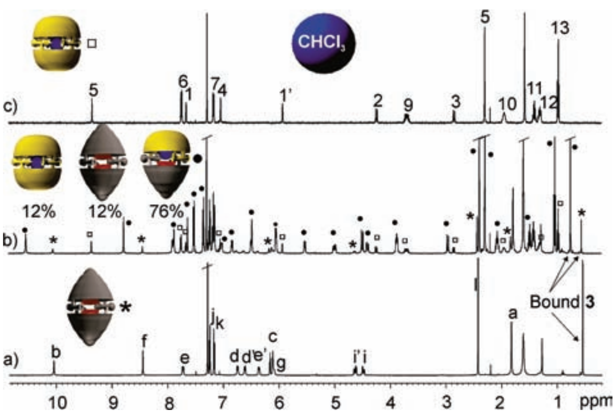

Figure 3. ^{1}H NMR spectra in $CDCl_3$ at 298 K of (a) $\mathbf{3}\bullet\mathbf{3}\subset\mathbf{2}\cdot\mathbf{2}$; (b) mixture of $\mathbf{3}\bullet\mathbf{3}\subset\mathbf{2}\bullet\mathbf{2}$ with 2 equiv of **1**; and (c) $CDCl_3\subset\mathbf{1}\bullet\mathbf{1}$. In Figure 3b the proton signals of $\mathbf{3}\bullet\mathbf{3}\subset\mathbf{2}\bullet\mathbf{2}$ are indicated with an asterisk, those of $CDCl_3\subset\mathbf{1}\bullet\mathbf{1}$ with a square, and the signals corresponding to $\mathbf{3}\subset\mathbf{1}\bullet\mathbf{2}$ with a black circle.

An in-depth study of the spectrum allows the assignment of two of the sets of protons to the known dimeric capsules $CDCl_3\subset\mathbf{1}\cdot\mathbf{1}$ and $\mathbf{3}\bullet\mathbf{3}\subset\mathbf{2}\bullet\mathbf{2}$. The remaining set contains the number of protons signals with chemical shift values and multiplicities expected for the heterodimeric capsule $\mathbf{3}\subset\mathbf{1}\bullet\mathbf{2}$ (*vide infra*). Based on integration of selected proton signals the percentage of assemblies $CDCl_3\subset\mathbf{1}\bullet\mathbf{1}/\mathbf{3}\subset\mathbf{1}\bullet\mathbf{2}/\mathbf{3}\bullet\mathbf{3}\subset\mathbf{2}\bullet\mathbf{2}$ can be roughly calculated as 12%, 76%, and 12% respectively. A plausible estimate of the expected statistical distribution of products is complicated: the three assemblies have different energies, and they involve different numbers of particles. In any case, the high percentage obtained for the heterodimeric assembly $\mathbf{3}\subset\mathbf{1}\bullet\mathbf{2}$ in conjunction with the possible coencapsulation of one solvent molecule in the aggregate's interior prompted us to evaluate the self-sorting of the system in CD_2Cl_2.

The ^{1}H NMR spectrum of the calix[4]arene **1** in CD_2Cl_2 shows broad and uninterpretable bands hinting to disruption of capsule formation in this solvent (Figure 4a).[19] However, the ^{1}H NMR spectrum in CD_2Cl_2 of a 1 mM solution containing equimolar amounts of **1**, **2** and **3** showed the existence of a single set of proton signals (Figure 4b) that do not correspond to $\mathbf{3}\bullet\mathbf{3}\subset\mathbf{2}\bullet\mathbf{2}$ (Figure 4c). The chemical shifts of the signals were almost coincident with those corresponding to the heterodimeric assembly $\mathbf{3}\subset\mathbf{1}\bullet\mathbf{2}$ in the $CDCl_3$ experiment. Diagnostic signals of the assembly assigned to the heterocapsule $\mathbf{3}\subset\mathbf{1}\bullet\mathbf{2}$ include, for the calix[4]arene component, the downfield shift experienced by the NH proton of the urea residue resonating at δ (H_5) = 8.7 ppm, due to strong hydrogen bonding, and the characteristic splitting of the aryl (H_1 and H_1') protons, analogous to the one observed for the $CDCl_3\subset\mathbf{1}\cdot\mathbf{1}$ assembly. This splitting is due to the asymmetry produced by the unidirectional orientation of the ureas in the heterodimer. For the calix[4]pyrrole moiety, the benzyl protons (H_i and H_i') become diastereotopic also due to this asymmetry.

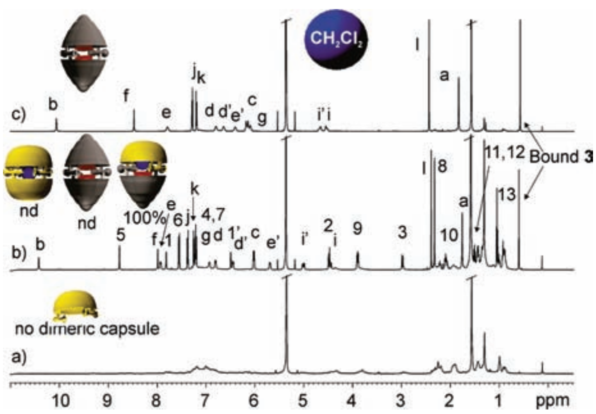

Figure 4. ^{1}H NMR spectra in CD_2Cl_2 at 298 K of (a) calix[4]arene **1**; (b) hybrid capsule $\mathbf{3}\subset\mathbf{1}\bullet\mathbf{2}$, and (c) homocapsule $\mathbf{3}_2\subset\mathbf{2}\bullet\mathbf{2}$. nd = not detected.

It is worth noting that the proton signals of the aromatic protons of the *meso* phenyl substituents of the calix[4]pyrrole component (H_e and H_e', H_d and H_d') are also desymmetrized. This is due not only to the unidirectional orientation of the ureas and its slow rotation but also to the slow rotation of the C_{meso}–phenyl bond, caused by steric congestion with the included *N*-oxide guest **3**. The pyrrole NH's appear at δ = 10.5 ppm due to strong hydrogen bonding with the oxygen atom of **3**. The protons of **3** resonate below 1 ppm testifying the deep inclusion of this guest within the aromatic cavity of the calix[4]pyrrole component. DOSY NMR experiments are indicative of the presence of a single species in solution (see Supporting Information (SI)). Identical diffusion coefficients are observed for both calix[4]arene and calix[4]pyrrole components (5.6×10^{-10} m^2 s^{-1}). More importantly, the observation of the same diffusion coefficient for bound **3** and the tetraureas points to the inclusion of the *N*-oxide inside the hybrid capsule. In addition, a 2D ROESY experiment reveals intermolecular contacts between the methyl protons of bound **3** and the aromatic and NH protons of **2**. Cross-peaks between key protons of **1** and **2** are also detected (SI). The space proximity between these proton adds additional support to the formation of hybrid assembly $\mathbf{3}\subset\mathbf{1}\bullet\mathbf{2}$ in solution.

The obtained results demonstrate that the solvent plays an important role in the self-sorting of the system.

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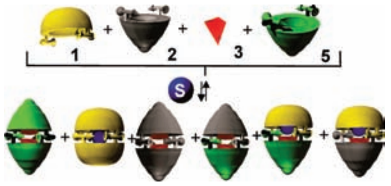
(19) Rudzevich, Y.; Vysotsky, M. O.; Bohmer, V.; Brody, M. S.; Rebek, J.; Broda, F.; Thondorf, I. *Org. Biomol. Chem.* **2004**, *2*, 3080.

Nevertheless, assuming that the coencapsulation of one solvent molecule in the hybrid capsule **3**⊂**1•2** is reasonable (see Figure 2b), it remains unclear to what extent the observed level of self-sorting is mandated by the difference in the filling of the capsule's space with CD_2Cl_2 (*PC* = 48%) instead of $CDCl_3$ (*PC* = 54%) or by other factors also influenced by the solvent, i.e. destabilization of homocapsule **1•1** in CD_2Cl_2. In trying to answer this question, we selected 4-dimethylaminopyridine *N*-oxide **4** as potential substitute to induce the assembly of the hybrid capsule **1•2**. In terms of size, guest **4** is not suitable to template the formation of the calix[4]pyrrole homocapsule **2•2** in any of the two solvents, biasing the system to only two possible capsules, **1•1** and **1•2**. Importantly, molecular modeling shows both a perfect fit for **4** (see SI) within the cavity of the hybrid capsule **1•2** (*PC* = 43%) and that no additional space is conceivable for the coencapsulation of a solvent molecule (*PC* for **4•**CD_2Cl_2⊂**1•2** = 63%). The results of self-sorting obtained with the chemical system composed by **1**, **2**, and **4** are almost identical to the ones reported using **3**, that is, the exclusive formation of the **4**⊂**1•2** heterocapsule in CD_2Cl_2 and a high level of self-sorting toward the same aggregate in $CDCl_3$ (SI). These results suggest that the exclusive assembly of the hybrid capsule **1•2** in CD_2Cl_2, to a major extent, is driven not by the solvent assistance in adequately filling its cavity but by the maximization of the available intermolecular interactions as a result of the disruption of the **1•1** capsule in this solvent. Finally, we performed additional self-sorting experiments using a more elaborate chemical system containing in addition the chiral tetraurea calix[4]pyrrole *S*-**5**. We have shown previously that the self-sorting of *S*-**5** with achiral **2**, induced by encapsulation of two molecules of **3**, is both exclusive and diastereoselective yielding heterodimer **3•3**⊂(*M•S*,*P*)-**2•5**.[20] The outcomes of the self-sorting experiments for the elaborate system are summarized in Table 1. The hybrid capsule **3**⊂**1•5** is always obtained as a mixture of diastereoisomers **3**⊂(*M•S*,*P*)-**1•5** and **3**⊂(*P•S*,*M*)-**1•5**, and the diastereomeric ratio is solvent dependent. In CD_2Cl_2, when 2 equiv of **1** are used the self-sorting of the system is exclusive toward the two possible hybrid assemblies, **1•5** and **1•2**. When only 1 equiv of **1** is used the excess of tetraurea calix[4]pyrroles self-assembles into the heterodimeric capsule **2•5**. Most likely, in $CDCl_3$ the high stability of the homocapsule **1•1** prevents the complete disproportionation of the heterodimer **2•5** into hybrid capsules **1•5** and **1•2**.

Table 1. Results Obtained in the Self-Sorting Experiments with the Chemical System Containing Three Tetraureas



S	**5•5**	**2•2**	**1•1**	**1•5**	**2•5**	**1•2**	Equivalents **1, 2, 3, 5**
$CDCl_3$	nd[a]	14	<2	34	17[b]	34	1, 1, 2, 1[c]
CD_2Cl_2	nd	nd	nd	46	27	27	1, 1, 2, 1
	nd	nd	nd	nd	50[b]	50	2, 1, 2, 1
	nd	nd	–	–	**100**[b]	–	1, 0, 1, 1

[a] nd = not detected. Estimated errors are >10%. [b] Mixture of diastereoisomers. [c] A suspension is formed.

In conclusion, the discovery of exclusive self-sorting in the assembly of hybrid molecular capsule between tetraurea calix[4]arene **1** and tetraureas calix[4]pyrroles **2** or **5** represents another step toward the functionalization of the interior of molecular capsules. The level of self-sorting can be modulated from efficient to exclusive using a solvent (CD_2Cl_2) that disrupts the formation of one of the possible homocapsules. The capsules described here constitute rare examples of fully closed dimeric assemblies in which the two hemispheres are differently functionalized. The coencapsulation of a solvent molecule with guest **3** yields four particle aggregates in which the guests are confined and restricted into single hemispheres.[21] The molecular recognition and positioning of the guests within the two different capsules' hemisphere relies on polar interactions and not only on size or shape. We intend to explore the control of the size and function of the internal cavity of the hybrid capsules through the use of derivatives of **3** functioning as a *prosthetic group*.

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Supporting Information Available. CAChe minimized structures of **4**⊂**1•2**, **3**⊂(*M•S*,*P*)-**1•5**, and **3**⊂(*P•S*,*M*)-**1•5**; 2D ^{1}H NMR spectra in CD_2Cl_2 solution of heterocapsule **3**⊂**1•2**; 1D ^{1}H NMR spectra of the self-sorting experiments performed with **4** as guest and those reported in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Chas, M.; Gil-Ramirez, G.; Escudero-Adan, E. C.; Benet-Buchholz, J.; Ballester, P. *Org. Lett.* **2010**, *12*, 1740.

(21) Shivanyuk, A.; Rebek, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 684.