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Selective Pairwise Encapsulation Using Directional Interactions

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The selectivity displayed by the majority of the self-assembled capsules capable of housing molecular species is usually restricted to the principle of size (packing) and shape exclusion.[1] On the one hand, this is a direct consequence of the almost exclusive use of aromatic panels to shape the capsule's interior.[2] On the other hand, the absence of internal polar groups can take part of the blame.[3] The lack of polar binding sites in the capsule's interior is also responsible for a certain degree of guest disorder and is reflected by the motions and even the exchange of position experienced by the encapsulated molecules.[4] In striking contrast to self-assembled capsules, enzyme active sites possess a remarkable degree of polar functionalization that controls both the binding selectivity and the ordering of included substrates. An approach to present polar functions to the encapsulated guest/s is based on the functionalization of the upper rim of resorcin[4]arenes, but examples of this methodology are still scarce in the literature.[5]

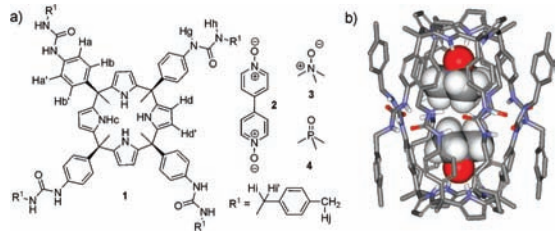

Figure 1. (a) Chemical structures of tetraurea **1** and guest molecules used in the study; (b) CAChe minimized structure of $\mathbf{3}_2\subset\mathbf{1}_2$.

Recently, we introduced an alternative strategy[6] by installing urea functions in the para positions of the α,α,α,α-stereoisomer of *meso*-tetraphenyl tetramethyl substituted calix[4]pyrrole **1** (Figure 1). Ureas have been widely used as agents for stabilizing calix[4]arene capsules,[7] and for governing the self-assembly of **1** into a dimeric molecular capsule with two endohedral hydrogen bond donor sites that converge on the interior. The dimerization of **1** was templated by the encapsulation of one molecule of 4,4′-pyridine bis-*N,N'*-oxide **2**. The application of $\mathbf{1}_2$ as a bimolecular reaction vessel requires coencapsulation of two guests. We describe here their use for the formation of ordered homo- and heteroencapsulation complexes that include two molecules within the capsule. Not unexpectedly, these assemblies turned out to be less stable thermodynamically than their three particle counterparts, but the endo-functionalized capsule $\mathbf{1}_2$ displays remarkably clear signs of selectivity during the encapsulation of the two isosteric guests **3** and **4**.

The synthesis of tetraurea calix[4]pyrrole **1** was previously described.[6] It exists as a single molecule in DMSO-d_6 but forms ill-defined aggregates in CD_2Cl_2 or $CDCl_3$ solution (Figure 2b). We used the crystal structure of $\mathbf{2}\subset\mathbf{1}_2$ to calculate a cavity volume of ~312 Å^3 for $\mathbf{1_2}$.[8] Molecular modeling studies indicated that the cavity is adequately filled if one molecule of trimethylamine *N*-oxide **3** is hydrogen-bonded to each of the two endohedral binding sites in the "poles" of $\mathbf{1_2}$. The packing coefficient for the quaternary complex $\mathbf{3}_2\subset\mathbf{1}_2$ is 0.5, very close to the ideal value of 0.55.[1c] The addition of 1 equiv of *N*-oxide **3** to a 1 mM suspension of **1** in CD_2Cl_2 resulted in the rapid dissolution of the mixture. The ^{1}H NMR spectrum of the solution showed sharp and well-resolved proton signals indicative of the formation of an ordered assembly and having the earmarks expected for a dimeric capsule with S_8 symmetry (Figure 2a). Four separate sets of doublets can be observed for the two ortho coupled protons of the *meso*-phenyl calixpyrrole substituent (a, a′, b and b′ in Figure 2a). The source of this asymmetry originates from the unidirectional sense of orientation of the urea groups and their slow interconversion on the ^{1}H NMR time scale. This urea belt directionality was already described by Rebek and Shimizu in related tetraurea calix[4]arene-based dimeric capsules.[9] However, the observation of this asymmetry in $\mathbf{1}_2$ also requires a slow rotation on the ^{1}H NMR time scale of the $C_{meso}-$phenyl bond. The head-to-tail directionality of the urea groups also mandates that each capsular assembly $\mathbf{1}_2$ incorporates two calixpyrrole monomers **1** which are chiral but cyclo-enantiomeric. By means of an EXSY experiment, we calculated an energy barrier of $\Delta G^{\ddagger} = 16.6$ kcal/mol for the change in direction of the urea belt. The chirality present in each monomer causes the two benzylic protons to become diastereotopic, and they are observed as two separated doublets exhibiting geminal coupling constant (proton i and i′ in Figure 2a). The phenyl urea proton (g) resonates at $\delta = 8.45$ ppm indicating a high degree of hydrogen bonding. The sharp singlet resonating at $\delta = 0.57$ ppm corresponds to the methyl protons of bound **3**. The methyl protons of free **3** appear at $\delta = 3.22$ ppm. The large complexation induced shift (CIS), $\Delta\delta = -2.65$ ppm, reveals that **3** is encapsulated and experiences the magnetic shielding provided by the four aromatic rings that shape the cavity. The integration ratio values for the proton signals of bound **3** and the capsule NHs provided clear evidence for the formation of a $\mathbf{3}_2\subset\mathbf{1}_2$ assembly. The pyrrole NHs of the capsular assembly resonate at $\delta = 10.06$ ppm, due to the formation of hydrogen bonds with the oxygen atom of encapsulated **3**. These interactions control the orientation of encapsulated **3** and reduce its motion to a rotation around its C_3 axis. In this way, the contacts between the two encapsulated **3** molecules are restricted to the methyl protons. Additional support for the formation of the $\mathbf{3}_2\subset\mathbf{1}_2$ assembly is derived from 2D NMR experiments (Supporting Information). The addition of 1 equiv of bis-*N,N'*-oxide **2** to a 1 mM CD_2Cl_2 solution containing the capsular assembly $\mathbf{3}_2\subset\mathbf{1}_2$ produces, within seconds, the complete exchange of the encapsulated guests and the appearance of a new set of proton signals corresponding to the $\mathbf{2}\subset\mathbf{1}_2$ assembly and free **3** (Supporting Information).

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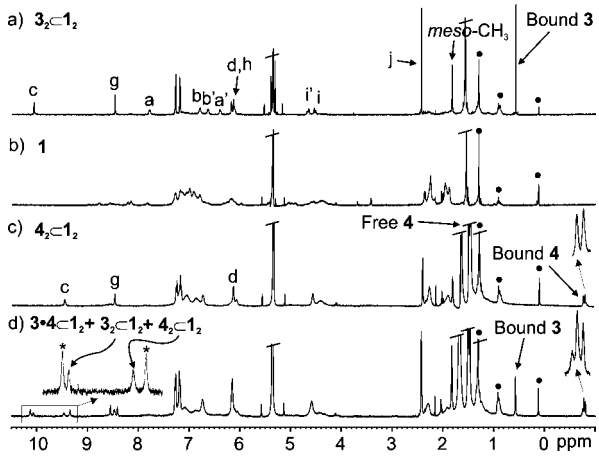

Figure 2. ^{1}H NMR spectra in CD_2Cl_2 at 298K of (a) capsule $\mathbf{3}_2\subset\mathbf{1}_2$, [**1**] = 1 mM, [**3**] = 1 mM; (b) **1**; (c) capsule $\mathbf{4}_2\subset\mathbf{1}_2$, [**1**] = 1 mM, [**4**] = 6 mM; (d) mixture of capsules, [**1**] = 1 mM, [**4**] = 6 mM, [**3**] = 0.5 mM. For proton assignments see Figure 1. Primed letters indicate diasterotopic protons; bullets (•) = impurity.

The relative thermodynamic stability of both assemblies was further investigated by competitive ITC experiments affording a stability constants ratio $K(\mathbf{2}\subset\mathbf{1}_2)/K(\mathbf{3}_2\subset\mathbf{1}_2)$ of 0.6 M. At first, it might be wrongly concluded that the four particle assembly is more "stable" since it has a greater *K*. Indeed, it is known that the relative stabilities of multiparticle hydrogen-bonded assemblies having a different numbers of components cannot be evaluated by direct comparison of *K* or $\Delta G°$ values, since these magnitudes do not include the effect of the concentration (and therefore of entropy).[10] The entropic advantage of $\mathbf{2}\subset\mathbf{1}_2$ with respect to $\mathbf{3}_2\subset\mathbf{1}_2$ dictates that an equimolar mixture of components will be largely in the form of the three particle assembly at concentrations lower than 0.6 M, as observed in the competitive ^{1}H NMR experiments described above (Supporting Information).

To self-assemble the capsular aggregate $\mathbf{4}_2\subset\mathbf{1}_2$ using the same procedure as for $\mathbf{3}_2\subset\mathbf{1}_2$ led to broad and poorly defined protons signals in the ^{1}H NMR spectrum. Surprisingly, we detected a well-resolved doublet resonating at $\delta = -0.8$ ppm that we assigned to encapsulated **4**. Further addition of **4** (6 equiv Figure 2c) resulted in the emergence of well-defined signals for some of the protons of **1**. Separate signals for the methyl protons of free and bound **4** also became evident. The protons of free **4** appear at $\delta = 1.49$ ppm. The intensity of the signal assigned to encapsulated **4**, $\delta = -0.8$ ppm, grew considerably after the addition. Both signals are doublets with $^3J_{H-P} = 12.60$ Hz confirming the assignment. The NH signals appear at $\delta = 9.5$ ppm, somewhat upfield shifted when compared with the NH signal in $\mathbf{3}_2\subset\mathbf{1}_2$, suggesting weaker hydrogen bonding interactions. On the other hand, one of the urea protons (g) appears at the exact chemical shift as seen in $\mathbf{3}_2\subset\mathbf{1}_2$. Likewise, the chemical shifts of the aromatic protons of the benzylic residues and the β-pyrrolic protons in the new assembly are almost coincident with $\mathbf{3}_2\subset\mathbf{1}_2$. The integration ratio for the proton NHs to bound **4** reveals a 1:1 stoichiometry. Altogether, these results suggest that the assembly of $\mathbf{4}_2\subset\mathbf{1}_2$ has taken place but with a somewhat weaker thermodynamic and kinetic stability compared to $\mathbf{3}_2\subset\mathbf{1}_2$. For example, we could not observe the characteristic desymmetrization of the benzyl protons of **1** (proton i) or the asymmetry in the *meso*-phenyl protons (a, b) both of which are earmarks of capsule formation. The signals of these protons are broad. Most likely, this is due to an intermediate exchange in the ^{1}H NMR scale of the directionality of the urea belt caused by the reduced kinetic stability of the $\mathbf{4}_2\subset\mathbf{1}_2$ assembly.

We also investigated capsule formation in the presence of both guests **3** and **4** in solution. Rebek has shown that the coencapsulation of two distinct molecules leads to different chemical shifts for the included guests when compared to the chemical shift values of encapsulated homopairs.[11] The addition of only 0.5 equiv of **3** to the CD_2Cl_2 solution containing **1** (1 mM) and 6 equiv of **4** was sufficient to produce three new proton signals in the NH region. One of the new signals was easily assigned to the NH protons of $\mathbf{1}_2$ in the $\mathbf{3}_2\subset\mathbf{1}_2$ assembly. The other two, marked with an asterisk in Figure 2d, correspond to the two different NH protons of the assembly encapsulating the heteropair $\mathbf{3}\cdot\mathbf{4}\subset\mathbf{1}_2$. The observed splitting of signals in the upfield region is also consistent with the interpretation of heteroencapsulated pairs: A new doublet emerges in the region of -0.8 ppm corresponding to encapsulated **4** in the heteropair. Additional experiments with 2.5 equiv of **4** and 0.5 equiv of **3** alter the distribution of species favoring the formation of $\mathbf{3}_2\subset\mathbf{1}_2$. Under these conditions, the singlet corresponding to encapsulated **3** in the hetero assembly $\mathbf{3}\cdot\mathbf{4}\subset\mathbf{1}_2$ is also resolved (Supporting Information).

In conclusion, we have shown that the self-assembly of tetraurea calixpyrrole **1** into dimeric capsules is induced by the complexation of trimethyl *N*-oxide **3** and trimethyl phosphine oxide **4** yielding four particle assemblies, $\mathbf{3}_2\subset\mathbf{1}_2$ and $\mathbf{4}_2\subset\mathbf{1}_2$, respectively. A heteromolecular assembly ($\mathbf{3}\cdot\mathbf{4}\subset\mathbf{1}_2$) is also generated when both guests are present in solution. All the multiparticle capsules are highly stable thermodynamically and kinetically. The coencapsulation of two molecules of *N*-oxide **3** produces the more stable aggregate. These results represent rare examples of dimeric capsules capable of orienting guests within the enclosure using weak hydrogen-bonding interactions. In addition, the functionalization of the capsule's interior features guest selectivity beyond the controls of size or shape exclusion. Our current efforts are directed toward the use of the capsule to induce a chemical reaction between two suitably functionalized *N*-oxides.

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Supporting Information Available: Additional NMR spectra, detailed experimental procedures, and data analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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