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Experimental and Computational Probes of a Self-Assembled Capsule

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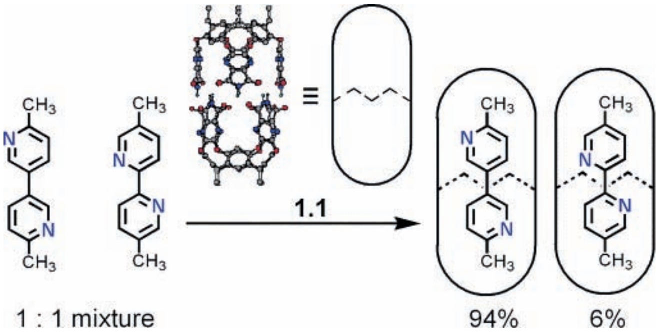
ABSTRACT



This research was undertaken to explore the interior surface of a synthetic receptor 1.1 with arylpyridines as guests. The interior surface differentiates the guests through the recognition of their nitrogen atoms. Experimental and computational analyses revealed that there is a delicate balance of attractions and repulsions between the host and the lone pairs of guests.

Self-assembled capsules provide spaces that are clearly defined with respect to size, shape, and chemical surface. As these are the principal considerations in molecular recognition, all which is required for encapsulation to occur is a good “fit” between the concave inner surface of the host capsule and the convex outer surface of the guest. The fit with respect to size usually involves filling a little more than half of the inner space of the host in the liquid phase.[1] The fit with respect to shape usually involves congruence but is not always predictable: several examples exist where guests contort themselves to higher energy conformations to better occupy the available space.[2] Because the fit with respect to chemical surface also provides surprises,[3] we have undertaken a mapping of the lining of a capsule **1.1** (Figure 1a) in some detail, and we report our findings here.

The cavity consists of an apolar resorcinarene at each tapered end and a polar seam of eight bifurcated hydrogen bonds that holds the two halves together in the middle.[4,5] Between these are four pyrazines provided by each half. The nonspherical shape of the capsule prevents tumbling of longer guest molecules such as biaryls and fixes their positions in

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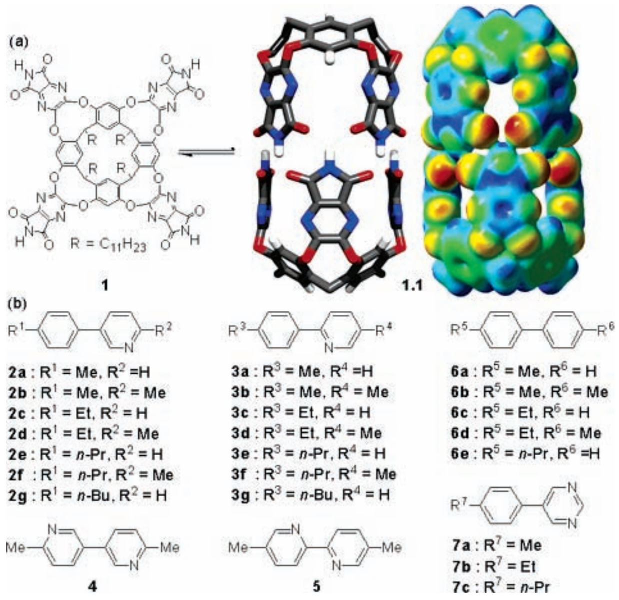

Figure 1. (a) Cavitand **1**, the dimeric cylindrical capsule **1.1** (some groups omitted for clarity), and a plot of total electron density (region of negative charge is red and region of positive charge is blue). (b) The probe guests for the exploration of the interior surface.

the space in a predictable way. We used a series of alkyl bipyridyls **2**−**5**, biphenyls **6**, and aryl pyrimidines **7** to probe the response of the capsule to lone pairs or C−H bonds directed to its various inner surfaces. The chemical shifts of the alkyl groups report on their contact with the resorcinarene ends.[6] They act as anchors for the rigid guests, and the positioning of the lone pairs is deduced by computations with the DFT method.[7] Where possible, the alkyl groups on the aryls *remote* from the heterocycle were used to minimize inductive effects of the nitrogen. Direct competition experiments with the various guests in Tables 1 and 2 gave the energetic consequences of the positioning, from which the following trends emerged.

The relative affinities **2a** > **6a** > **3a** and **2b** > **6b** > **3b** (which can be seen from entries 1−4 in Table 1) are interpreted as attractions of the lone pairs of **2a** and **2b** for some features of the capsule's interior. The encapsulation of the biphenyls **6a**,**b** relies on weak C−H/π interactions; the lone pairs of **2a** and **2b** must, accordingly, have stronger attractions, whereas the lone pairs of **3a**,**b** are positioned in a less-attractive environment. The affinities **4** ≫ **5** and **7a** > **2a** corroborate the attractions discussed above (Table 1, entries 5 and 6).

Table 1. Competitive Encapsulations between Methylated Biaryls of Guest A and B[a]

entry	guest A	guest B	ratio[b]
1	**2a**	**3a**	91:9
2	**2a**	**6a**	73:27
3	**2b**	**3b**	90:10
4	**2b**	**6b**	62:38
5	**4**	**5**	94:6
6	**2a**	**7a**	25:75

[a] [1] = 4 mM, [guest A] = [guest B] = 50 mM, 0.6 mL of mesitylene-d_{12}, at 300 K. [b] The ratio of host−guest A complex to host−guest B complex. Determined by ^{1}H NMR (600 MHz).

Table 2. Various Pairwise Competitions of Two Guests C and D[a]

entry	guest C	guest D	ratio[b]
1	**2c**	**3c**	25:75
2	**2c**	**6c**	23:77
3	**2d**	**3d**	30:70
4	**2d**	**6d**	25:75
5	**2e**	**3e**	13:87
6	**2e**	**6e**	26:74
7	**2f**	**3f**	18:82
8	**2g**	**3g**	38:62
9	**2c**	**7b**	85:15
10	**2e**	**7c**	91:9

[a] [1] = 4 mM, [guest C] = [guest D] = 50 mM, 0.6 mL of mesitylene-d_{12}, at 300 K. [b] The ratio of host−guest A complex to host−guest B complex. Determined by ^{1}H NMR (600 MHz).

The methyls of **2a** and **2b** are slightly deeper ($\Delta\delta = -4.8$ ppm) in the cavitand ends than those of **6a** and **6b** ($\Delta\delta = -4.6$ ppm, on average) and much deeper than those of **3a** and **3b** ($\Delta\delta = -4.2$ ppm). As shown in Figure 2, the $\Delta\delta$ for methyl protons of encapsulated R$_1$ and R$_2$ for **2a**,**b** and **3a**,**b** is large when compared to those for **2c**−**g** and **3c**−**g**. Again, the lone pairs of **2a** and **2b** find an electronic fit that matches the remote methyl's position in the cavitand end, and **3a** and **3b** drift away from the end because their lone pairs are poorly accommodated. The DFT calculations were performed for encapsulated **2a**, **2b**, **3a**, **3b**, and **6b** to

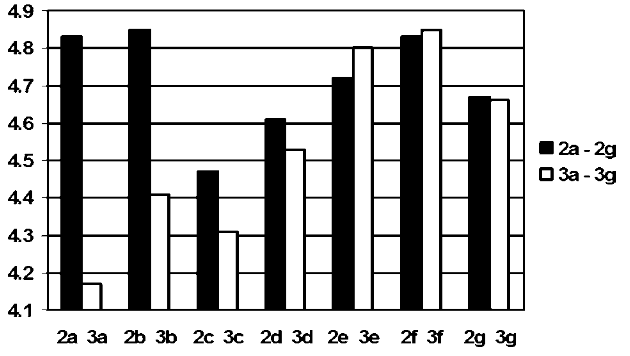

Figure 2. $\Delta\delta$ (vertical line) for methyl protons of encapsulated R^1 and R^3 in mesitylene-d_{12}.

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compute the position of these guests inside the capsule (Figure 3). Comparison of the nitrogen positions between **2a** and **3a** showed that the lone pair of **2a** is directed at the gap between the lone pairs on the pyrazine nitrogens and the imide oxygens, but that of **3a** is directed at the imide oxygen lone pairs. Semiempirical calculated (AM1) positions of guests **4**, **5**, and **7a** also showed similar positions of the nitrogen atoms (Figure 4).

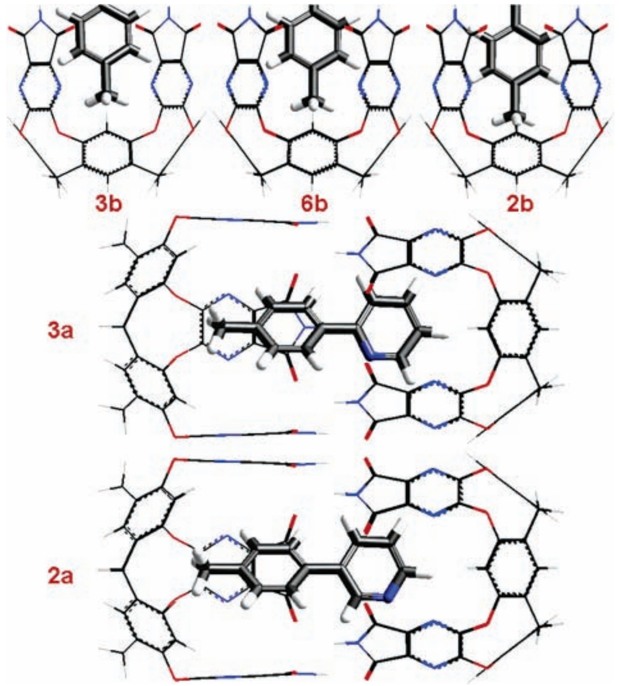

Figure 3. DFT (B3LYP/6-31G*) calculated[8] positions of guests inside cylindrical capsule **1.1** (some groups omitted for clarity).

With increasing size of the remote alkyls (Table 2, entries 1−8), the lone pairs of **2c**−**2f** are forced into a destabilizing environment (**6c**, **6d** $>$ **2c**, **2d**) whereas those of **3c** and **3d** move to a neutral environment (**6c**, **6d** $\sim$ **3c**, **3d** $>$ **2c**, **2d**). The affinities **2c** $>$ **7b** and **2e** $\gg$ **7c** corroborate the repulsions discussed above (entries 9 and 10). The positions of **2c**, **2e**, **3c**, and **3e** inside the capsule are shown in Figure 4. The lone pairs of **2c** and **2e** are directed at pyrazine nitrogens or the resorcinarene, and that of **3e** was located in the gap between the lone pairs on the pyrazine nitrogens and the imide oxygens.

What other structural features of **1.1** are responsible for the repulsions and attractions? The cavity is lined with π bonds, and none of the heterocycles should be preferred to the carbocycles. Their repulsion is most apparent near the tapered ends where four aromatics of the resorcinarenes converge to give an electron-rich surface. Accordingly, the longer guests of the **2** series (**2c**−**2g**) and the **7** series (**7b** and **7c**) are unwelcome in this environment.

The attractions are less obvious. At first glance, the only obvious complements to the lone pairs of the guests are the hydrogens of the imides. Yet, the structures in Figures 3 and 4 show this cannnot be the case. The nearest lone pairs are those in **5** and in the **3** series, yet **3a** and **3b** experience a repulsion and, on moving away as in **3c** and **3d**, the interactions become neutral. Apparently, the carbon atoms between the carbonyls and the pyrazine nitrogens of the host are sufficiently electron poor to attract well-positioned guest lone pairs. This may be related to the attractions of dipoles and lone pairs to carbonyls recently exposed by Diederich.[9]

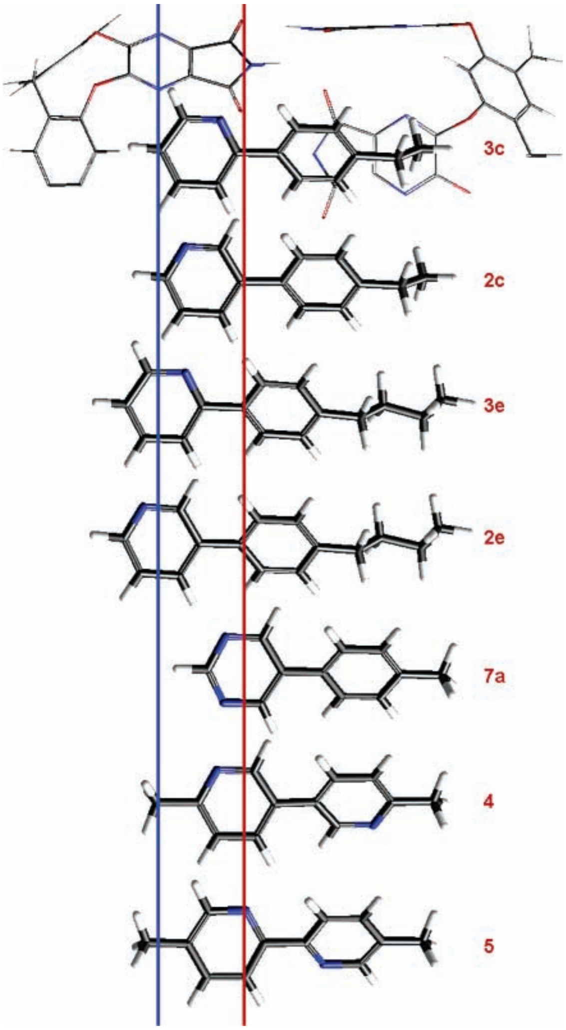

Figure 4. Semiempirical calculated (AM1) positions of guests (**2c**, **2e**, **3c**, **3e**, **4**, **5**, and **7a**). Note the alignments of the pyridyl nitrogens with imide oxygens (red line) and pyrazine nitrogens (blue line) of the capsule (some groups omitted for clarity).

Whatever the source, the relative affinities and the NMR chemical shifts of these guests provide the experimentally determined parameters for encapsulation. The calculations can then be used to position the guest with sub-Angstrom detail. This scale and the spaces of the capsule are not always

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experimentally accessible. Both experiment and calculation are required to give a consistent picture of these complexes.

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Supporting Information Available: Experimental details and ^{1}H NMR spectra of all guests in **1.1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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