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A Reversible Reaction Inside a Self-Assembled Capsule

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Substrates at enzyme active sites are temporarily isolated from others in the bulk water solvent. The structured environments at these sites are complementary to reactive intermediates and the high-energy transition states that lead to them, and they have maximum binding to the transition state. This is regarded as the quintessential feature of enzyme catalysis. Synthetic structures can also stabilize reactive species by isolating them. The unstable species may be short-lived intermediates in chemical reactions or high-energy conformations of otherwise stable molecules. The earliest example was the stabilization of cyclobutadiene[1] in a cage molecule permanently held together through covalent bonds. Reversibly formed capsules, self-assembled through metal/ligand interactions, can also isolate and temporarily stabilize reactive species; they allow the direct observation of the stabilized molecules under ambient conditions, at equilibrium and in the liquid phase. Species, such as siloxanes,[2] phosphine carbonyl adducts,[3] and organometallics have been stabilized.[4] Hydrogen bonded capsules, such as **1** (Figure 1), stabilize peroxides[5] and high-energy helical conformations of normal alkanes.[6] We have now observed amplification and stabilization of otherwise unfavored forms in ring/chain isomerization reactions. These indicate that reversible reactions can take place within encapsulation complexes.

The amplification within **1·1** can be directly observed by NMR spectroscopy through its effect on the ring/chain isomerizations shown in Figures 2 and 3. The Schiff's base **2** is the major form in mesitylene-d_{12} solution, but the oxazine **3** is by far the dominant form within the capsule. Likewise, the dimethylamino variant **5**, the major isomer in equilibrium with **4** in solution, becomes the exclusive guest of the capsule.

The in−out *exchange* of encapsulated and free molecules of this size takes hours at these conditions.[7] A number of *p*-substituted aldehydes were converted to their tautomeric Schiff's bases according to literature procedures. They all showed nearly exclusive encapsulation of their corresponding ring forms.

Does the isomerization reaction take place within the capsule, outside in solution, or both? The interconversion of **2** and **3** takes place relatively slowly under these conditions. For example, **2** can be prepared in crystalline form,[8] and a freshly prepared solution in mesitylene-d_{12} shows less than 10% **3** present within 5 min. Equilibrium is reached after 2 h. Yet, the encapsulation of **2** and **3** takes place rapidly under these conditions. Both freshly prepared and equilibrated solutions of **2** gave the same results on addition of the capsule: in the few minutes needed to acquire an NMR spectrum, the capsule was more than 90% occupied by the heterocycle **3**. It is likely that **2** and **3** interconvert within the capsule, but EXSY experiments with mixing times from 0.1 to 1 s did not show cross-peaks for encapsulated **2** and **3**. Accordingly, the time scale for interconversion is >1 s. To check on the possibility of acid catalysis of the interconversion by the imide

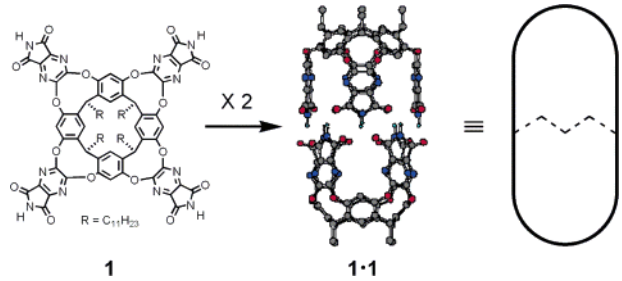

Figure 1. Two cavitands self-assemble through hydrogen bonding into a cylindrical capsule **1·1**. Two representations of the capsule are shown. In the center is the energy-minimized (MacroModel 5.5, Amber* force field) structure **1·1**; the long alkyl chains and CH hydrogen atoms are omitted for viewing clarity. Right: the cartoon representation.

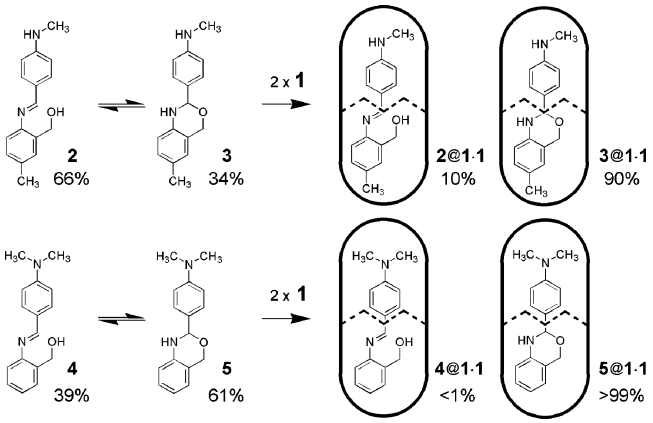

Figure 2. Encapsulation experiments of **2**/**3** and **4**/**5** isomerization. The encapsulations were carried out with the guest (2.70×10^{-3} mmol) and **1** (10 mg, 5.94×10^{-3} mmol) in mesitylene-d_{12} (1.5 mL). The ratios were determined by ^{1}H NMR (600 MHz, 300 K).

protons of the capsule, we examined the rate of the ring/chain tautomerism with a commercially available imide,[9] but no catalysis was seen.

An additional series of Schiff's bases **6a**−**e** (Figure 4) were prepared from the corresponding salicyl aldehydes and anilines. None of these showed the presence of their heterocyclic tautomers **7a**−**e** in mesitylene-d_{12} solution within the limits of NMR detection, in accord with literature precedent for the unsubstituted case, **6a**.[10]

Addition of the capsule showed only the encapsulated Schiff's bases for **6b** and **6c**. However, **6d** showed a minor encapsulated species, identified as the corresponding heterocycle **7d** (Figure 5), as it showed the characteristic NMR signatures of the cyclized product. Specifically, geminal couplings of the hydrogens indicated were 14.4 Hz as is known for other molecules of this sort. A similar result occurred with the methoxy-substituted derivative **6e**, the cyclized molecule was present *inside* the capsule but not *outside* in bulk solution. This suggests that the open chain molecule is encapsulated, and it cyclizes inside the capsule; that is, the reversible

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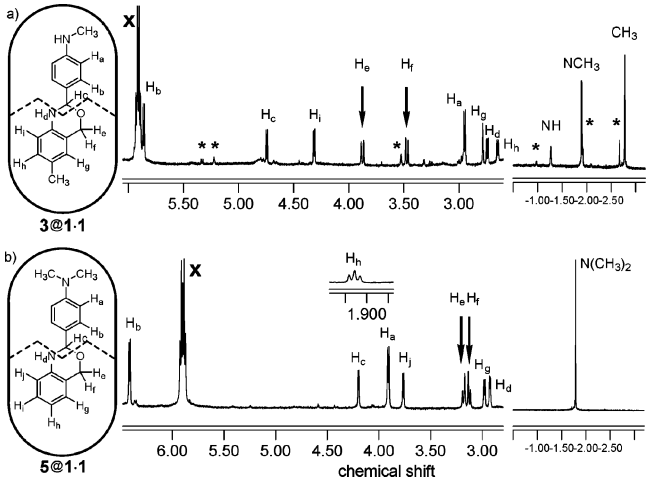

Figure 3. Portions of ^{1}H NMR spectra of encapsulated **2**/**3** and **4**/**5** isomerization (600 MHz, 300 K, mesitylene-d_{12}): (a) the peaks of **3@1·1** and **2@1·1** are labeled with letters and asterisks, respectively; (b) a detectable amount of **4@1·1** was not formed, and all protons of **5@1·1** (except H_i which overlapped with peaks of solvent or **1·1**) are assigned. The peaks labeled x are CH methines in **1·1**. (The AB-shaped peaks H_e and H_f identify the heterocyclic guests, pointed with arrows; the complete assignments of NMR spectra and $\Delta\delta$ between free and encapsulated species are available in the Supporting Information.)

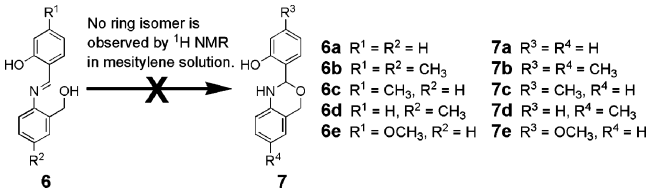

Figure 4. Schiff's bases **6a**−**e**. In mesitylene-d_{12} at 300 K, **6a**−**e** show no sign of cyclization to corresponding isomers **7a**−**e**.

chemical reaction takes place within the capsule. Perhaps the conformational restrictions within the capsule drive this equilibrium to detectable amounts of cyclized form. The *ortho* hydroxyl function may also facilitate the interconversion through intramolecular acid/base catalysis. In any case, the heterocycle form is amplified and stabilized within the structured solvent sphere that is the wall of the capsule.

The temperature dependence of the encapsulated equilibrium of Figure 5 showed that the equilibrium constant remained unchanged over nearly 100 K (spectra in Supporting Information). It indicates a process for which $\Delta H \sim 0$ and ΔG is determined by the entropy term ΔS. Defining K = **6d/7d** = 6.7, the ΔS is 3.76 eu. This is of the correct sign as cyclization reactions are generally known to reduce entropies.

It should be possible to amplify intermediates in bimolecular actions, such as hemiacetal formation. Typically, the hemiacetal cannot be observed in bulk solution, but the amplified concentrations within the capsule—where each component enjoys a 4 M concentration—could stabilize and constrain the tetrahedral form to the degree that it could be observed. The limited space in a capsule and an enzyme's cavity represent similar structured

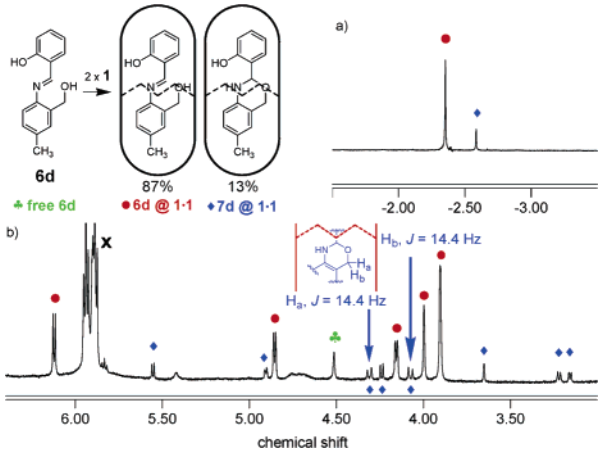

Figure 5. Portions of ^{1}H NMR spectrum of encapsulated **6d** (600 MHz, 300 K, mesitylene-d_{12}): (a) in upfield portion, two encapsulated CH_3 groups are situated at δ −2.35 and −2.59; (b) in mid-field portion, the AB-shaped peaks of **7d@1·1**, H_a and H_b, are situated at δ 4.31 and 4.07, pointed with arrows. The peaks labeled x are CH methines in **1·1**.

environments, from which bulk solvents are largely excluded. The similarities to enzyme active sites may be stronger than first believed.

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Supporting Information Available: Temperature dependence of the encapsulated equilibrium, chemical shifts and $\Delta\delta$ of **3@1·1** and **5@1·1**, and corroborative data of encapsulation experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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