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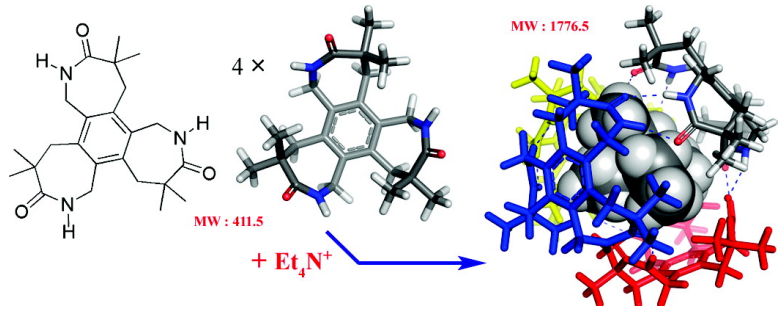

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Rational Design and Gas-Phase Characterization of Molecular Capsules by Self-Assembly of a Symmetric Hexasubstituted Benzene with Seven-Membered Lactams

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The hydrogen bond motif has been established as a powerful means for self-assembly of a wide variety of supramolecular aggregates.[1] This approach has been applied successfully in the construction of capsules[2] capable of engulfing suitable molecular guests. Once perfectly mastered, this method of crafting nanocontainers could ultimately lead to the appearance of "ideal" systems for (a) transporting drugs to specific cells or even cellular organelles or (b) catalyzing reactions by mimicking the active sites of enzymes.

One sophisticated tactic employed in this type of noncovalent synthesis utilizes subunits that have been encoded with the information necessary to predetermine the overall structure of the final supramolecule. Milestones in the still ongoing evolution of this methodology include the synthesis and characterization of various dimeric,[3] tetrameric,[4] hexameric,[5] and even larger cages.[6] Much of the work done in this area has relied upon various functional groups as "glue" to hold all the components together. Such components bearing the "sticky" groups belong to only a few well-defined structural families: (a) glycouryl derivatives,[3a–e,4a,6b] (b) cyclotriveratrylenes,[3j] and (c) calixarenes and related resorcinarenes and pyrogallolarenes.[3e–i,4b,5,6]

Here we introduce for the first time the use of *cis*-amides as gluing motifs for which the resulting weak interactions are sufficiently strong to impart supramolecular stability but nevertheless are sufficiently weak to allow reversibility as exists in biological systems. This has the potential to significantly augment the "tool-box" of the modern day supramolecular chemist. We employed an elegant small triamide **1** (Figure 1) that had been designed to self-assemble into simple dimers, or more interesting *T*, *O*, or *I* platonic solids.[7]

The core aryl cycle bears three lactams, whose ring size (7) had been chosen to force the *cis*-amides out of the plane defined by the central arene. This structural feature was confirmed by the crystal structure of the triallyl derivative **2** (Figure 1). DFT calculations showed that conformer **1a** having the same shape as **2** is more stable than C_3-symmetric **1b** (Figure 2) by a very slim preference of 0.43 kcal/mol. Not surprisingly, the dimeric capsule $\mathbf{1b}_2$ is more stable than its "pacman"-like conformer $\mathbf{1a}_2$. The huge difference of 6.15 kcal/mol between the two dimers is a direct consequence of the number of hydrogen bonds involved: six in $\mathbf{1b}_2$ and only four in its competitor.

We assessed the relative energies of the most evident capsules that can be built from **1a** and **1b** by AM1 calculations.[8] We found that each subunit **1a** would experience a gain in energy of 8.5, 10.5, and 9.1 kcal/mol by joining the $\mathbf{1b}_2$, $\mathbf{1b}_4$, and $\mathbf{1b}_8$ capsules. Since $\mathbf{1b}_4$ appears to be the most stable cage, we looked for a suitable guest that could fit inside.[9] Simple modeling suggested that Et_4N^+ fills the bill. The positively

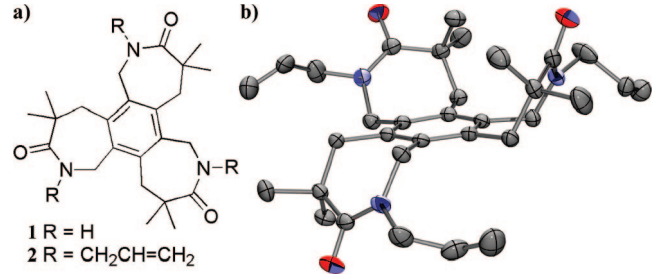

Figure 1. (a) Lactam **1** and its allyl derivative **2**. (b) Crystal structure of **2**.

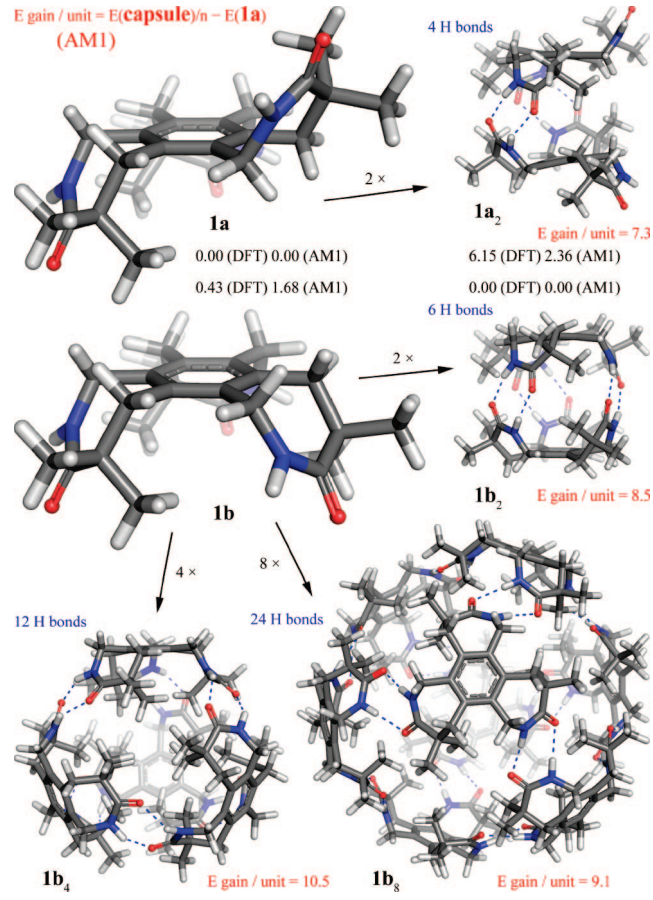

Figure 2. Calculated (AM1 and B3LYP/6-31G*) structures and relative energies (kcal/mol) of various monomers and their self-assembled objects.

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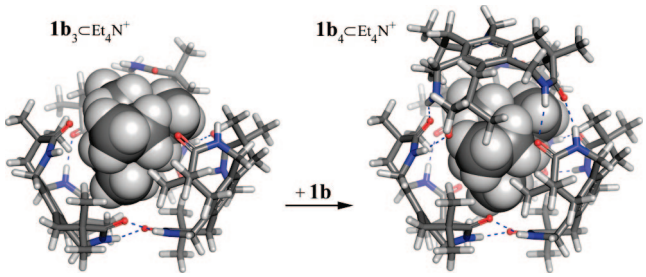

Figure 3. AM1 structures of $\mathbf{1b}_3{\subset}Et_4N^+$ and $\mathbf{1b}_4{\subset}Et_4N^+$.

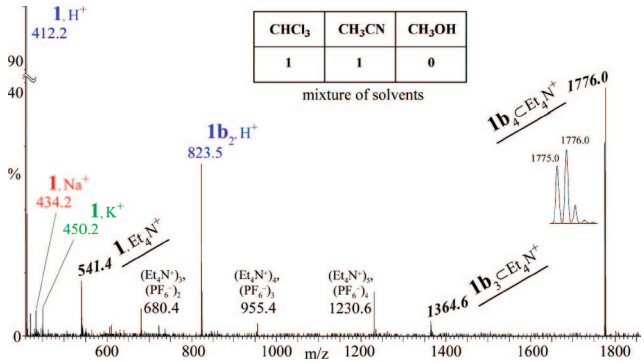

Figure 4. ESI spectrum of **1** and Et_4N^+,PF_6^- ($CHCl_3$ and CH_3CN). Satellite peaks around 1776.0 demonstrate the monocharged nature of $\mathbf{1b}_4{\subset}Et_4N^+$.

charged host−guest complex $\mathbf{1b}_4{\subset}Et_4N^+$ (Figure 3) is a good candidate for detection by electron spray ionization (ESI) technique.[5b,10]

A diluted solution of **1** and Et_4N^+,PF_6^- in a hydrogen bond promoting solvent was first examined by ESI (Figure 4). A huge peak around 1776 in the spectrum was attributed to the desired complex $\mathbf{1b}_4{\subset}Et_4N^+$ (no ESI evidence was observed for host−guest complexes involving the larger cation n-Bu_4N^+). This signal does not correspond to a van der Waals driven aggregate because a similar experiment with **2** (deprived of hydrogen bond donors) yielded no equivalent species $\mathbf{2}_4{\subset}Et_4N^+$. Less intense signals were observed for $\mathbf{1},Et_4N^+$ and $\mathbf{1b}_3{\subset}Et_4N^+$. The latter appears to be a trimeric cavitand templated by Et_4N^+ (Figure 3). Since the dimeric capsule cannot accommodate any guest of significant size, the complex $\mathbf{1}_2,Et_4N^+$ is consequently nonexistent. Other observed species involving **1** can be summarized by the simple formula $\mathbf{1}_n,M^+$ (n = 1, 2 and M = H, Na, K).

In a second set of ESI experiments, we explored the stability of $\mathbf{1b}_4{\subset}Et_4N^+$ by adding CH_3OH, to disrupt hydrogen bonds (Figure 5). The peak at 1776 was still present, whereas all peaks corresponding to smaller $\mathbf{1}_n,Et_4N^+$ (n = 1, 3) combinations had totally disappeared. Even further addition of CH_3OH to reach a 1/1/1 ratio of $CHCl_3$, CH_3CN, and CH_3OH was unable to completely eradicate the presence of that signal. These first two measurements attest that $\mathbf{1b}_4{\subset}Et_4N^+$ is a stable supramolecule indeed. Finally, a large quantity of $CHCl_3$ was added to revert back to a hydrogen bond inducing solvent. We witnessed an increase in the intensity of the signal around 1776, suggesting that formation and dismantling of $\mathbf{1b}_4{\subset}Et_4N^+$ is a reversible process than can be modulated by the solvent medium.

In conclusion, we present here the first example of a very simple C_3-symmetric lactam self-assembling into a robust tetrameric capsule capable of inviting guests of reasonable size such as Et_4N^+. It provides a novel prototype that can be easily

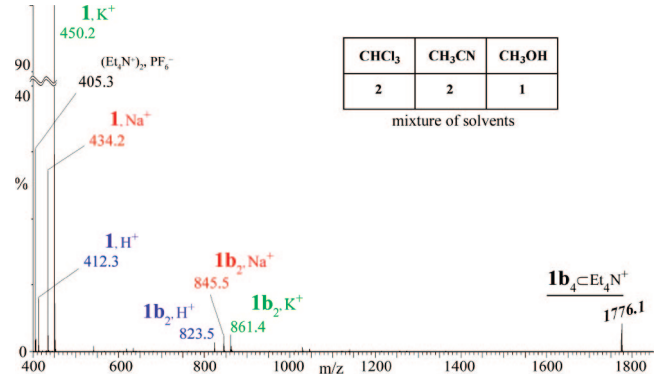

Figure 5. ESI spectrum of **1** and Et_4N^+,PF_6^- ($CHCl_3$, CH_3CN, and CH_3OH).

tuned-up by grafting side chains or groups to the three *gem*-dimethyl handles. More exploration is still underway to see if larger octameric capsules can be templated by well-chosen molecules.[9]

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Supporting Information Available: Crystal data of **2**, mdl mol files for **1** and related capsules, a mpg file for the *T* capsule $\mathbf{1b}_4$. This material is available free of charge via the Internet at http://pubs.acs.org.

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