J|A|C|S COMMUNICATIONS

Published on Web 01/29/2009

Pseudo-Capsule Assemblies Characterized by ^{19}F NMR Techniques

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Molecular recognition events in nature rely on combinations of weak intermolecular interactions comprising hydrogen bonds,[1] ionic,[2] and hydrophobic effects.[3] These forces and other polar attractions appear in synthetic receptors as well, but the weakest interactions—dispersion forces—seldom appear alone. We have now used them along with CH−π interactions to stabilize a new multicomponent assembly between cavitand host **1** (Figure 1) and ditopic guests **2** and **3a**−**c**. The clustered spectroscopic signals arising from these weak attractions required the use of ^{19}F NMR techniques to differentiate the species present in solution, and we describe these applications here.

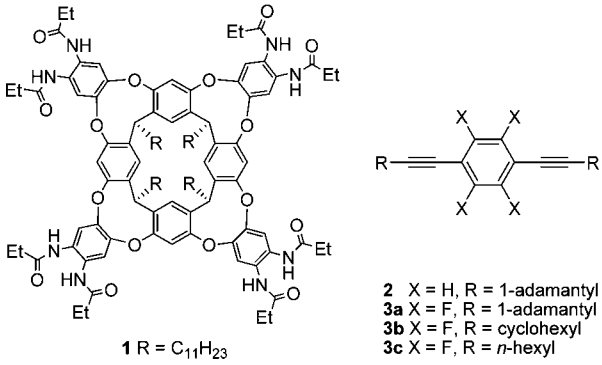


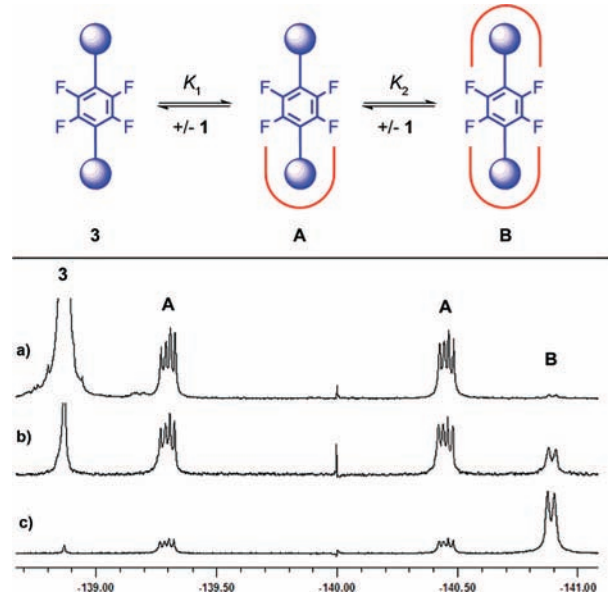
Figure 1. Host and guest structures.

Host **1** is a resorcinarene derived structure, stabilized in a vase conformation by a seam of intramolecular hydrogen bonds provided by the amide groups on the rim.[4] Adamantane derivatives are among the best guests for its hydrophobic cavity due to favorable CH−π interactions and the appropriate filling of the space inside **1**.[5] Accordingly, we expected that a guest containing two adamantyl groups connected by a suitably rigid linear linker would be an ideal ditopic ligand to bring two host molecules together. This could give rise to a new capsule-like assembly without any stabilizing contacts between the two cavitands.

Guests **2**[6] and **3a**−**c** were prepared by Sonogashira coupling reactions between the corresponding alkynes and 1,4-diiodobenzene derivatives. Although the binding of **2** within **1** could be observed readily by ^{1}H NMR in mesitylene-d_{12} (a noncompeting solvent), an accurate characterization of the system's stoichiometries was not possible: the two hydrophobic anchors experience almost identical upfield shifts[7] in either a 1:1 or a 2:1 complex, and the noncovalent interactions with the guest lacked diagnostic NH or CH NMR signals. The aromatic protons on the guest linker do experience upfield shifts on complexation, but they overlap with other aromatic signals from the host.

In contrast, fluorinated guest **3a** allowed resolution of the multiple species that appear in solution as the ^{19}F NMR spectrum is devoid of any interference by the cavitands' signals. The free guest appears as a singlet at δ −138.87 ppm in mesitylene-d_{12}, and upon mixing with **1**, three additional sets of resonances appear; they are shifted upfield by the shielded environment provided by the π systems of **1** (Scheme 1). The two doublets of doublets (J = 22.0, 11.5 Hz) at −139.30 ppm and −140.45 ppm result from desymmetrization of the A_4 spin system in **3a** into an AA′XX′ system and were assigned to a 1:1 complex **A** (Scheme 1). These resonances collapse again into a X_4 spin system (signals at −140.88 and −140.91 ppm) when the incorporation of a second host molecule renders the assembly symmetric and both sides of the aromatic linker experience the same shielding effect from the neighboring amide groups. The 2:1 complex (**B**) actually exists as an equal mixture of two cyclodiastereomers arising from a clockwise/clockwise or a clockwise/anticlockwise arrangement of the secondary amide groups at the rim of **1**[8] which interconvert slowly on the NMR time scale.[9] As expected, when the **1** to **3a** ratio in the mixture is gradually increased the formation of **B** is favored.

Scheme 1. Formation of Assemblies **A** and **B** and Evolution of the ^{19}F NMR Spectrum (300 K)[a]



[a] **1** to **3a** ratios are 0.16:1 (a), 1:1 (b), and 3:1 (c), respectively ([**3a**] = 5−6 mM).

The system could be further characterized by implementing various NMR techniques in the ^{19}F dimension. The ^{19}F DOSY experiment[10] shows decreasing diffusion coefficients for the free guest (D = 859 μm^2 s^{-1}), complex **A** (D = 509 μm^2 s^{-1}), and complex **B** (D = 412 μm^2 s^{-1}) according to the increase in size of each molecular species in this series (Figure 2a). The ^{19}F ROESY[11] (318 K) spectrum clearly shows the stepwise formation of **A** and **B** from **1** and **3a** (Figure 2b). Off-diagonal peaks arising from

10.1021/ja809224p CCC: $40.75

chemical exchange can be observed between the free guest signal and the resonances assigned to **A** which in turn correlate to the far upfield signals assigned to **B**. The latter also have a correlation with the free guest peak which probably accounts for a dissociative process of **B** into **1** and **3a**. The slow interconversion between the three species on the NMR time scale allows the extraction of association constants from the spectra by simple integration. The intrinsic binding constant for the first equilibrium process (K_1^i)[12] was found to be larger than that for the second one (K_2^i) but the same order of magnitude. This suggests only modest steric clashes exist between the ethyl groups on the two cavitand rims. Kinetic data can also be extracted from ^{19}F EXSY[13] experiments, and the 18.1 kcal/mol barriers obtained this way for the dissociation of both **A** and **B** compare well to the values previously calculated by ^{1}H EXSY[5] and coalescence experiments.[4a]

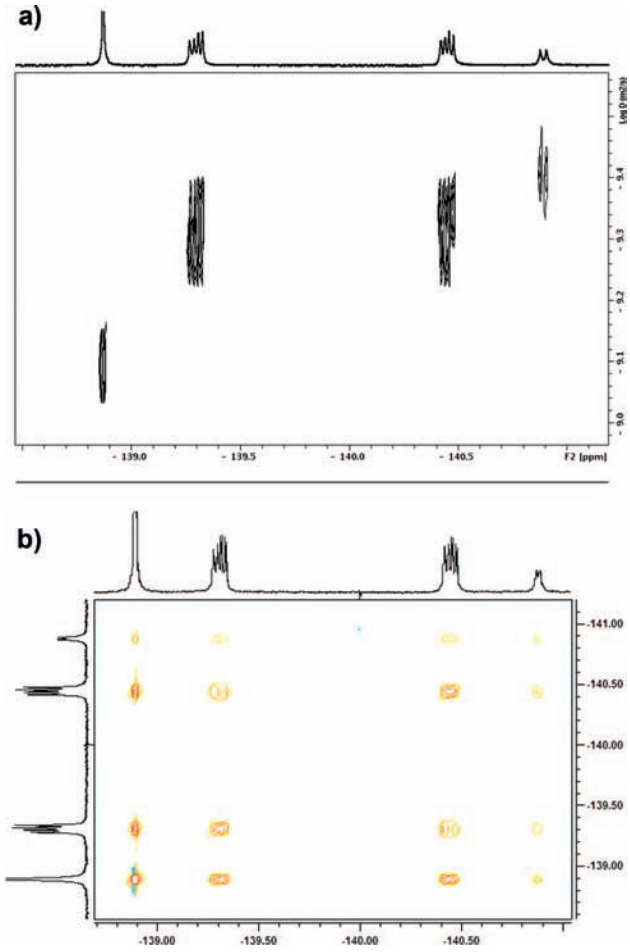


Figure 2. (a) ^{19}F DOSY spectrum displaying different diffusion coefficients (D) for **3a**, **A**, and **B**. (b) ^{19}F ROESY spectrum (318 K) showing chemical exchange between these species.

Binding experiments of related guests **3b** and **3c** lacking the adamantane anchor illustrate the importance of dispersion and CH/π attractions in the formation of **B**. The cyclohexyls of **3b** have the size and shape to fit deeply in the space but are not as attractive as the adamantyl groups for **1**.[14] As a result, the binding event is less effective in overcoming the entropic (and perhaps steric) penalties of bringing the three components together. Linear aliphatic residues such as the *n*-hexyl groups in **3c** can only properly fill the cavity if they coil into a higher energy conformation.[15] Consequently, no binding was observed with the *n*-alkanes.

Table 1. Intrinsic Binding Constants[a] with Host **1**

guest	K_1^i (M^{-1})[b]	K_2^i (M^{-1})[b]
3a	565 ±5	220 ±5
3b	120 ±2	24 ±2
3c	–[c]	–[c]

[a] $K_1 = 2K_1^i$, $K_2 = {}^1/_2K_2^i$, see ref 12. [b] In mesitylene-d_{12}, [**1**] = 5−6 mM. [c] Binding not observed.

The case of **3a** establishes that a guest can be more or less completely surrounded in an assembly lacking direct attractions between host subunits. This type of self-assembly would find applications in template synthesis when reaction conditions are incompatible with, for example, hydrogen bonds. In addition, the present study showcases the advantages of ^{19}F NMR spectroscopy in the characterization of complex supramolecular systems. The ^{19}F nucleus has a much broader range of chemical shift than the proton yet offers the same applications of NMR techniques in the ^{19}F dimension.

Acknowledgment. We are grateful to the Skaggs Institute and NIH (GM 27953) for support. We thank Dr. Laura Pasternack for NMR assistance and Dr. Richard J. Hooley for helpful discussions. A.L. thanks Fundación Ramón Areces (Spain) for a postdoctoral fellowship. P.R. is a Swedish Knut and Alice Wallenberg Postdoctoral Fellow.

Supporting Information Available: Synthesis and characterization data for guests **2** and **3a**−**c**, additional information for the ^{19}F NMR experiments including fitting curves for DOSY calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA809224P