

Tetramethoxy Calix[4]arenes Revisited: Conformational Control through Self-Assembly

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The concept of *preorganization* in molecular assembly has been well established, and its impact on synthetic supramolecular chemistry is profound.¹ Many natural systems thrive on the ability of inherently *flexible* molecules to self-organize. This process is promoted by a well-defined surrounding architecture and culminates in self-assembly.² The ability of a protein to find its thermodynamically most stable tertiary structure from a linear sequence of amino acids is an example. Also related is the ability of two flexible, complementary polynucleotide strands to form a double helix. In this paper we demonstrate how flexible molecules can reversibly self-assemble to give a *well-defined receptor cavity*.

The calix[4]arene skeleton³ was chosen as a vehicle for modeling such phenomena. The calixarene platform has recently been exploited for assembly by several laboratories.^{4,5} Research in our group has explored a unique dimeric binding mode for the calix[4]arene framework which provides for the encapsulation of small molecule guests.^{5,6} Specifically, urea functions placed on the upper rim of the calix[4]arene permit dimerization to occur through a head-to-tail hydrogen bonding pattern (Figure 1).

It is well-known that the calix[4]arenes interconvert between four discrete conformations in solution.^{3,7} This conformational flexibility can be controlled by alkylation of the phenolic oxygens with substituents larger than ethyl, i.e. reaction of the parent phenol with *n*-PrBr to give the tetrapropoxy derivative allows the isolation of three stable conformations: the cone (42%), partial cone (55%), and 1,3-alternate (3%).^{7b} We have recently explored derivative **1-1**, which uses benzyl ether substituents for such control.

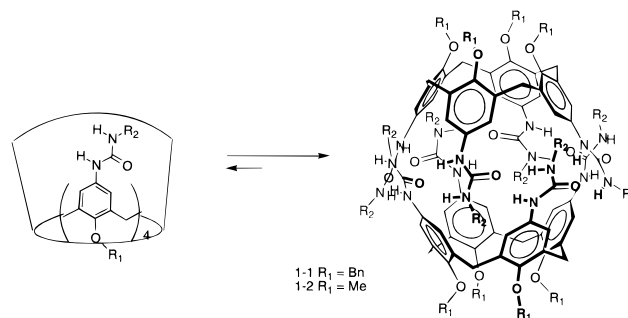


Figure 1. Dimerization of the tetraurea calix[4]arene.

In calixarene derivative **1-2** much smaller lower rim substituents are present. The tetramethoxy calix[4]arene has been well-studied and is defined as a “flexible” system.^{7,8} It freely interconverts between all four conformations, but the partial cone is the thermodynamically most favorable one.⁸ Specifically, in the parent *tert*-butyl system the difference in energy between the partial cone/cone isomers is ~ 1.5 kcal/mol, and the barrier to interconversion is on the order of 13 kcal.^{8c} We have found that *intermolecular hydrogen bonding through dimerization can be used to drive the conformational equilibrium exclusively to the cone conformer*. Since substitution on the upper rim of the calixarene is not known to substantially bias the conformational equilibria,³ the observed conformational selection (self-organization) can be attributed solely to hydrogen bonding effects.

Synthesis of the tetranitro derivative **1** of the tetramethyl ether followed well-established literature protocols.^{8a,9} Analysis of the ¹H NMR spectrum of **1** reveals a 96/4 mixture of the partial cone conformer to the cone. This is characteristically reflected by the two sets of AB doublets ($J = 14$ Hz) separated by 0.3 ppm arising from the cone and partial cone bridging methylene protons, respectively. These observations are in agreement with those obtained by Reinhoudt and co-workers.⁹ Reduction of **1** (Figure 2) with SnCl₂·2H₂O in EtOH gave **2** as the only product, which, nonetheless, featured broad ¹H NMR spectra in CDCl₃ and DMSO-*d*₆. This indicates that the tetraamine is conformationally flexible and possibly even aggregates in solution. Reaction of the tetraamine **2** with a variety of isocyanates at room temperature in CH₂Cl₂ was facile and occurred in most cases on the time scale of a few seconds. The analysis of the spectra of the resulting ureas (**3-5**, Figure 2) in a noncompetitive solvent such as C₆D₆ gave unequivocal results.¹⁰ In contrast to the broad, nondescriptive signals of the tetraamine, the spectra now offered sharp, characteristic splitting patterns. In the case of **3**, for example, only two doublets were visible at δ 3.07 and 4.30 ($J = 12$ Hz) for the *cone* bridging methylene protons and one sharp methoxy proton singlet appeared at δ 3.61. These

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(10) Selected –NH region ¹H NMR and MS data for compounds **3-6**: **3** (C₆D₆; 250 Hz) δ 7.36 (s, NH_a), 9.53 (s, NH_b); MS (FAB) calcd for C₆₀H₅₂F₄N₈O₈ 1088.3844, found 1088.3847. **4** (C₆D₆; 250 Hz) δ 7.07 (t, NH_a), 7.98 (s, NH_b); MS (FAB) calcd for C₆₈H₁₀₄N₈O₈ 1160.7977, found 1160.7978. **5** (C₆D₆; 250 Hz) δ 7.46 (s, NH_a), 9.74 (s, NH_b); MS (FAB) calcd for C₆₄H₆₄N₈O₈ 1072.4847, found 1072.4833. **6** MS (FAB) calcd for C₁₆H₂₆N₂O₂ 278.1994, found 278.1996.

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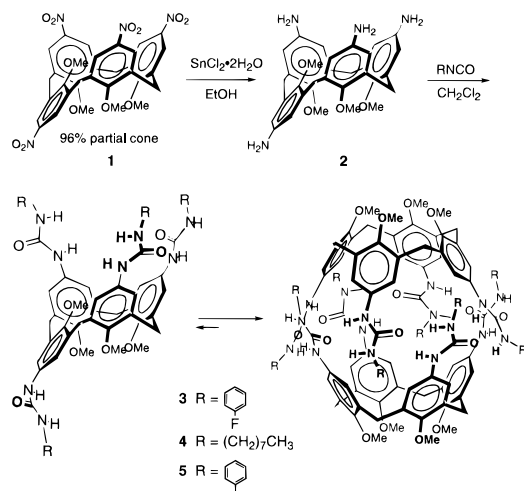


Figure 2. Observed shift in conformational equilibria due to intermolecular hydrogen bonding.

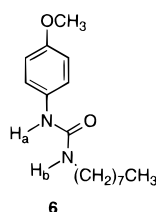


Figure 3.

results suggest complete selection of the cone conformer, presumably through self-assembly.

It is now established that dimerization of urea substituted calix[4]arenes results in downfield ^1H NMR shifts of the urea protons.^{4–6} Of particular interest is the shift of the NH_b proton (Figure 3) in the aryl derivatives to extremely low field, i.e. δ 9.53 for **3** and δ 9.74 for **5** in C_6D_6 . A model compound **6** was prepared for chemical shift comparison by reaction of *p*-anisidine with octyl isocyanate (Figure 3). This is the functional group equivalent of **4**. The two $-\text{NH}$ protons of this compound resonate at δ 4.34 and 6.28 in C_6D_6 (these shifts are concentration dependent and vary 0.5 ppm in a concentration range of 1–10 mM). As further evidence for dimerization, the corresponding calixarene **4** features the same protons at δ 7.07 and

7.98 (these shifts are essentially concentration independent). Although the spectral data obtained are very telling, the properties of the dimers formed could also be compared with that of known species. For example, a 50/50 mixture of **4** and **5** was made with the intention of synthesizing the corresponding heterodimer. The spectrum of **4** and **5** did in fact show three distinct species.^{5b} The representative peaks of the known dimers were easily identified and the ones that remained were reasonably assigned the heterodimer. There is also recent evidence of dimerization in the solid state.¹¹

Preliminary encapsulation studies were performed with **5**. After dissolving the sample in toluene- d_8 and adding benzene, a small peak was observed in the ^1H NMR spectrum representative of encapsulated benzene (δ 4.04). These findings are consistent with work previously published in the group.^{5,6} Finally, additional evidence for dimerization and encapsulation can be obtained from ESI-MS studies, which definitively show a host/guest (chloroform) complex of **5**.¹²

The unique behavior of these systems is not in their dimerization, but the means by which it occurs. Conversion of the 96% partial cone **1** to 100% cone **3–5** by intermolecular forces is not difficult to rationalize: The information for assembly is present in nascent form and the enthalpic and entropic prices of dimerization are well paid for by the formation of up to 16 hydrogen bonds in the self-assembled system. Previously, only conformationally biased subunits had given well-defined cavities through self-assembly,¹³ whereas flexible precursors had not.^{2b,14} The present results argue well for an increased range of subunit architectures and the design of potentially “functional” cavities.

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(11) V. Böhmer, unpublished.

(12) Compound **5** was dissolved in chloroform and showed an intense $[2\text{M} + \text{Na}^+]^+$ peak at m/z 2169.9 and a $[2\text{M} + \text{Na}^+ + \text{CHCl}_3]^+$ peak at m/z 2289.0, 119 mass units higher than the dimer alone. In methanol the dimer was not detected. We gratefully acknowledge this spectrometry performed by Lisa Marzilli and Prof. Paul Vouros at Northeastern University; details will be published elsewhere.

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