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Nonmonotonic Assembly of a Deep-Cavity Cavitand

Haiying Gan, Christopher J. Benjamin, and Bruce C. Gibb*

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148, United States

Supporting Information

ABSTRACT: The synthesis and assembly properties of a new water-soluble deep-cavity cavitand are discussed. For a homologous series of alkanes, the host can form a range of approximately isoenergetic 1:1, 2:1, and 2:2 complexes. As a result of this 'confluence' of binding and assembly the host displays an unusual, nonmonotonic, assembly profile. Thus, no or limited assembly is observed with methane through butane, pentane triggers assembly, and hexane through octane again does not promote assembly, whereas nonane and a larger guest again induce assembly. This unusual behavior is discussed in the context of the diversity of nodes of chemical systems (networks).

Complex systems possessing emergent phenomena are inherent to the world we live in.[1−3] Complexity in chemical systems arises from intricate networks of chemical entities[4−6] linked by both reversible and irreversible covalent bond formation and noncovalent interactions. Subsuming these networks, compartmentalization bestows a system with robustness; in other words it ensures that the system can lie far from equilibrium.[7] Chemistry is beginning to build an understanding of the different components of chemical systems. For example, it is adept at synthesizing molecules, the chemical entities that constitute the individual nodes of such networks and, more recently, have began to establish a variety of means by which external stimuli can switch nodes between one state and another (on and off).[8−14] Similarly, chemistry is also adept at controlling the kinetics and thermodynamics of molecular interactions, the individual links, or edges of networks.[15,16] Be that as it may, our appreciation of the different kinds of nodes that are components of complex chemical systems is limited; as is our appreciation of how different combinations of multiple nodes and edges engender network properties such as autoregulation or feed-forward loops.[4−6] Consequently, there is a need to both improve our understanding of biological systems[4] and devise wholly new *de novo* networks. Here we identify a water-soluble deep-cavity cavitand that functions as an unusual node. An examination of the binding of a homologous series of *n*-alkanes (C_1−C_{14})[17] reveals three possible supramolecular entities: 1:1, 2:1, and 2:2 host−guest complexes. The small energy differences between many of the different complexes leads to a 'confluence' at the node and an unexpected, nonmonotonic, assembly profile.

Deep-cavity cavitand **1a** (Scheme 1) was formed by an analogous procedure to that used in the synthesis of a cavitand **1b** (octa-acid) that has figured prominently in our research endeavors.[18,19] Briefly, known cavitand **2** was 'woven' with 3,5-dihydroxy-4-methylbenzyl alcohol (R = Me in structure) via an 8-fold Ullmann ether reaction to yield octol **3**. Oxidation then gave the crude product **1a**, which was purified by an esterification−hydrolysis procedure. Purification of octa-ester **4a** is the only step in the synthesis requiring chromatography and ensured the removal of impurities arising from both the weaving step and the oxidation of octol **3**. The cavitand **1a** differs from **1b**[20,21] by possessing four methyl groups that in part project into the hydrophobic cavity of the host but importantly also project into the hydrophobic rim of the host that is important in the predisposition[25] of these types of molecules to dimerize and form supramolecular capsules.[18,22−24] As a result of the latter, the predisposition of host **1a** for dimerization is reduced relative to the octa-acid **1b**. This was first apparent in the ^{1}H NMR spectrum of **1a** that showed sharp signals over the concentration range 1−3 mM (in D_2O buffered with 10−30 mM $Na_2B_4O_7$). In contrast, **1b** showed broad signals at concentrations above 2 mM (20 mM $Na_2B_4O_7$) indicative of partial assembly. That host **1a** is monomeric over the 1−3 mM concentration range was confirmed by pulse-gradient stimulated spin−echo (PGSE) NMR experiments[26] which reveal a diffusion rate of $D = (1.79−1.90) \times 10^{-6}$ cm^2 s^{-1}, corresponding to a hydrodynamic volume of between 6.3 and 7.6 nm^3.

We examined the binding of the homologous series of the *n*-alkanes methane through *n*-tetradecane to cavitand **1a** using a combination of ^{1}H and PGSE NMR experiments. ^{1}H NMR confirmed guest binding or encapsulation as evidenced by high-field signals for the bound guest between 0 and −3.5 ppm. These experiments also confirmed the number and ratio of species formed by each guest and the ratio of the host and guest in the different complexes. The PGSE NMR experiments were used to determine both the extent of assembly and the stoichiometry of the complexes formed.

The smallest guest examined, methane, was observed to weakly bind to host **1a**. This was apparent from the appearance of a signal for the bound but fast exchanging guest at −0.02 ppm (Figure 1, cf. 0.2 ppm for free methane). This is in contrast to the corresponding host **1b** which showed no evidence of methane binding in a study of hydrocarbon gas separation.[17b] The binding of methane to host **1a** is stronger because the four methyl groups at the rim reduce the size of the binding pocket somewhat. In addition, the methyl groups narrow the portal to the pocket and undoubtedly increase the kinetic stability of the 1:1 complex. In the case of **1a**, diffusion NMR experiments confirmed that the complex possesses the same hydrodynamic volume (HV) as the free host (6.3 nm^3, Figure 2). The signals of the bound methyl groups of the guests ethane, propane, and

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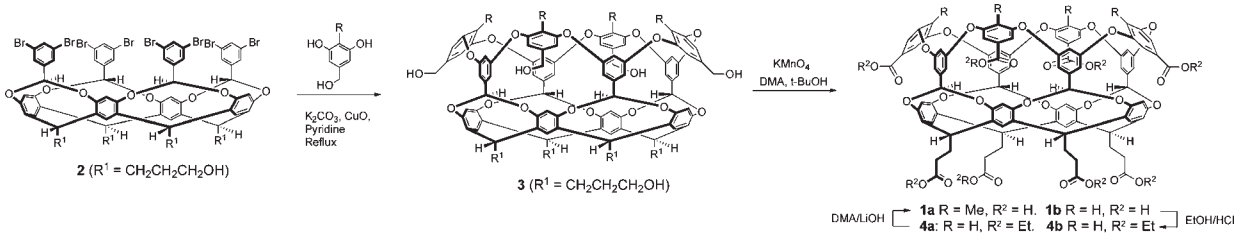
Scheme 1. Synthesis of Deep-Cavity Cavitand Host 1a



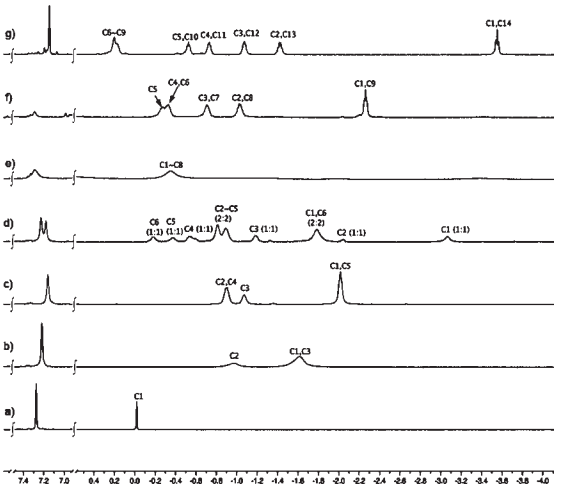


Figure 1. ^{1}H NMR spectra of the complexes formed between host **1a** and (a) methane; (b) propane; (c) *n*-pentane; (d) *n*-hexane; (e) *n*-octane; (f) *n*-nonane; and (g) *n*-tetradecane. Shown is the guest binding region (0.50 to −4.00 ppm) and the signal from the H atoms para to the acetal group in the host (ca. 7.20 ppm). All solutions were 1 mM complex in D_2O, 10 mM $Na_2B_4O_7$ buffer.

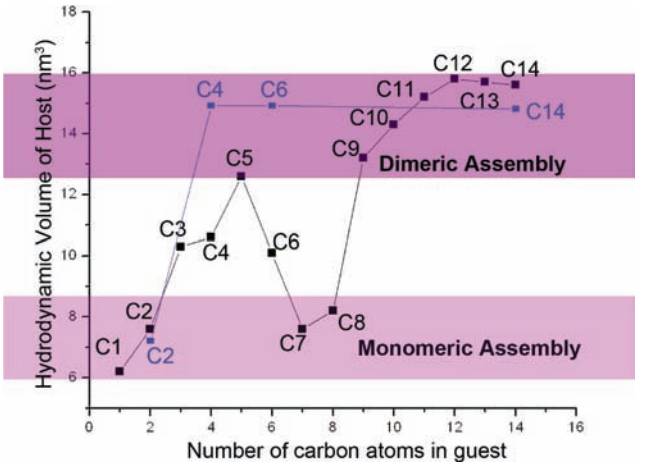


Figure 2. Graph of the hydrodynamic volume (HV) of the complexes formed between host **1a**/**b** and alkanes guests, against the number of carbon atoms in each guest. Data shown in black correspond to host **1a**. Data shown in blue correspond to the previously reported parent cavitand.[17a,b]

n-butane followed the expected monotonic trend appearing at −0.95, −1.62, and −1.95 ppm respectively (propane shown in Figure 1). These signals were broader than that of fast binding methane, an indication that exchange was slower and close to the (500 MHz) NMR time scale. In line with this notion, a competition experiment between methane and ethane revealed a K_{rel} for the latter of 3. Pertinent host signals also showed evidence of broadening (Supporting Information (SI)). The guest pentane continued this monotonic trend with a methyl signal at −2.02 ppm but showed sharper guest signals suggesting a kinetically more stable complex (Figure 1). Diffusion NMR studies focusing on both host and guest signals showed (Figure 2) that while the ethane complex was essentially monomeric (HV = 7.6 nm^3), propane and *n*-butane led to a mixture of 1:1 and 2:2 complexes (HV = 10.3 and 10.6 nm^3 respectively), while *n*-pentane led to mostly a 2:2 complex (HV = 12.6 nm^3). Returning to the ^{1}H NMR data (Figure 1), we attribute the broadening of bound guest signals in the case of propane to a combination of intermediate exchange rates between the free and the bound state in the 1:1 complex and intermediate exchange rates between the 1:1 and 2:2 complexes. The sharper signals for the pentane complex arise because there are only small amounts of the 1:1 complex, and exchange is slow on the NMR time scale in the case of the 2:2 complex. Unexpectedly, the ^{1}H NMR spectrum of the *n*-hexane indicates two, slow-exchanging complexes (Figure 1). A lack of baseline resolution in the host signals and broad signals from the bound guest precluded measuring the HV values of each species. However, an average HV value for the two species of 10.1 nm^3 (Figure 2) confirmed that these were the 1:1 and 2:2 host guest complexes. Integration of the bound host signals confirmed that these two entities exist in an approximate ratio of 1.8:1.[27] This break in the monotonicity of the extent of assembly continued with guests *n*-heptane and *n*-octane. Both guest signals and many of the host signals were again broad indicating intermediate exchange rates. Furthermore, the measured HV values for these complexes were essentially the same as that obtained for ethane (Figure 2). In other words, *n*-heptane and *n*-octane form 1:1 complexes with host **1a**. *n*-Nonane behaved very differently than *n*-octane, with the NMR experiments demonstrating that this guest is an efficient template for the formation of the corresponding 2:1 host−guest complex. More specifically, this second switch in the behavior of the host was evident from the ^{1}H NMR data (Figure 1), which showed a kinetically stable 2:1 complex, and the diffusion experiment that confirmed a capsule approximately the same size as that produced by pentane (HV = 13.2 nm^3, Figure 2). Finally, for *n*-decane through *n*-tetradecane there were monotonic shifts in both the bound guest methyl signals and the HV values reflecting the induced-fit 'swelling' of the host and concomitant increase in the packing coefficient (Figures 1, 2 and SI).

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With the aid of CPK models we interpret these results as follows. Guests methane through butane bind to the host but are small enough such that there is too much void space in the 2:2 complex and the 1:1 complexes are energetically preferred. These results are in contrast to the cavitand devoid of methyl groups at its rim (**1b**), which readily forms thermodynamically and kinetically stable 2:2 complexes with propane and butane (butane data shown in Figure 2). Hence, the methyl groups at the rim of **1a** reduce the relative stability of the capsular complex. On the other hand, the size of *n*-pentane is such that it leads to little void space in the 1:1 complex and dimerization to form a 2:2 complex is energetically preferred because this allows complete dehydration of the hydrophobic surfaces that form the dimerization interface. The guests *n*-hexane through *n*-octane are however too large to form stable 2:2 complexes and too small to form stable 2:1 complexes. As a result it is the 1:1 complex that is energetically preferred, especially in the case of *n*-heptane and *n*-octane. In contrast however, the still larger guests are of sufficient size to form a stable 2:1 host−guest complex; they do not form 1:1 complexes because a significant portion of the guest would remain hydrated in free solution.

Although guests of nine carbons or more are good templates for the formation of 2:1 host−guest capsular complexes, the limited predisposition of host **1a** to form a dimeric capsule means that many of the different supramolecular species that can form for the guests ethane through *n*-octane are approximately isoenergetic. This 'confluence' of supramolecular species is evident at both a 'local level', where more than one species is observed to exist in solution, and 'globally' in the nonmonotonicity of the diffusion data/assembly state. The confluence is all the more intriguing when it is recalled that a small energy difference of 0.5 kcal mol^{-1} establishes a 70:30 ratio of two equilibrated species, and that competition experiments involving guest binding in simple 1:1 host−guest systems frequently reveal $\Delta\Delta G^{\circ}$ values of 2−3 kcal mol^{-1} for guests differing only in a methylene group.[28,29] Hence for the guests ethane through *n*-octane, many of the 1:1, 2:1, and 2:2 complexes and assemblies observed here likely lie within 0−1.0 kcal mol^{-1} of each other, a range that is hard to engineer in a simple host−guests system.

The self-assembly of cavitands such as **1a** and **1b** can be envisioned in terms of Boolean logic. For example, a pair of selected guests (A and B) can be considered as inputs, while the output of the logic gate is either 0 (no assembly) or 1 (assembly into a 2:1 or 2:2 complex).[30] Hence, both **1a** and **1b** function as B gates (true whenever B is true) when guests inducing assembly are defined as B inputs. If an arbitrary threshold of 12 nm^3 (Figure 2) is chosen to define responses of 0 and 1, then for host **1a** the A inputs are methane to *n*-butane and *n*-hexane to *n*-octane, whereas the B inputs correspond to *n*-pentane and *n*-nonane through *n*-tetradecane. For host **1b**, an input of A corresponds to methane and ethane, and an input of B to guests propane and larger. Defining these systems as two-input, one-output gates does however fail to illustrate an important difference between hosts **1a** and **1b**; that is that when considering adjacent pairs in the homologous series, **1b** is only capable of differentiating between ethane and propane, whereas **1a** can differentiate between *n*-butane and *n*-pentane, *n*-pentane and *n*-hexane, and *n*-octane and *n*-nonane. Hence, it is perhaps more appropriate to consider the nine guests methane through *n*-nonane as unique inputs and treat the system as a nine-input, one-output gate (SI).

In conclusion, we have identified a host−guest system with an unusual nonmonotonic assembly profile. The system functions as an unusual switch because three different types of supramolecular species can be formed, and because many of these species are approximately isoenergetic. Considering the elaborate switching properties of many proteins it is likely that nodes displaying unusual properties are common, and even essential, to biological networks. With this notion in mind we are continuing our investigations of **1a** to determine the degree of control that is possible within such switching. We will report on these findings at a future date.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, ^{1}H NMR and PGSE experiments, and truth table. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
bgibb@uno.edu

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