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Self-Assembly of a Cavitand-Based Capsule by Dynamic Boronic Ester Formation**

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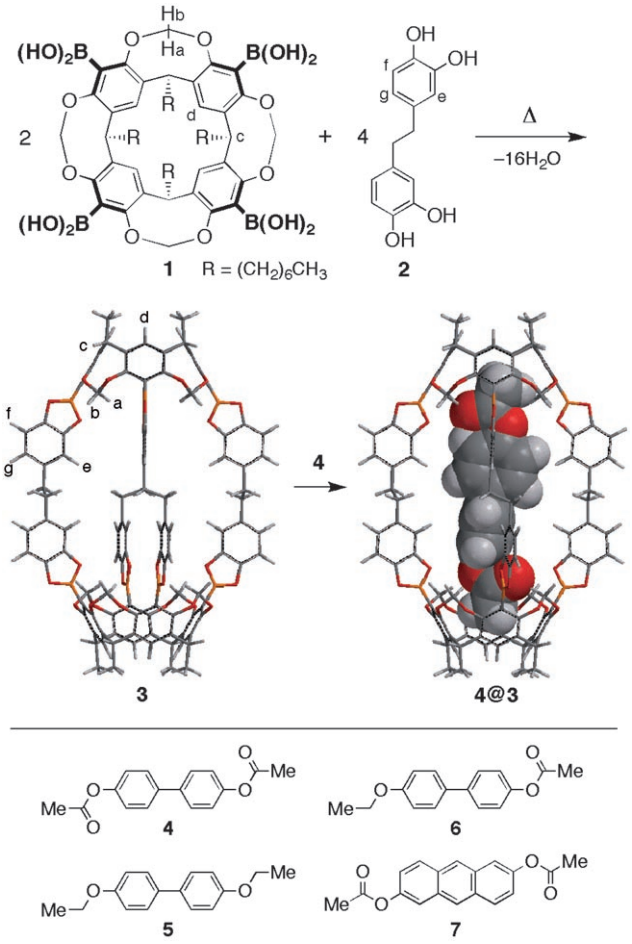
Carcerands and hemicarcerands, in which two calix[4]resorcinarene cavitands are held together by four covalent linkages, have been developed by Cram and others. They have attracted considerable attention from the viewpoint of stabilization of reactive intermediates and as microvesicles for drug delivery by the confinement of guest molecules inside the capsules away from bulk phases.[1] Error correction through thermodynamic equilibration, minimization of synthetic effort by use of modular subunits, and control of assembly processes through subunit design are characteristics of supramolecular approaches to self-assembly. On the basis of this concept, cavitand-based capsules have been constructed under thermodynamic control using noncovalent interactions such as hydrogen bonds,[2] metal coordination,[3] ionic interactions,[4] and solvophobic interactions.[5] As an alternative strategy, dynamic covalent chemistry offers great advantages in supramolecular syntheses because dynamic covalent bonds contain reversible covalent bond-forming and -breaking processes under thermodynamic control.[6] The reversibility of the imine bond-forming reaction has been applied to cavitand-based capsule synthesis.[7] Boronic ester formation is another reliable synthon for dynamic covalent chemistry.[8] Herein, we report the self-assembly of tetrakis(dihydroxyboryl) cavitand **1** (as a bowl-shaped aromatic cavity) and 1,2-bis(3,4-dihydroxyphenyl)ethane **2** into capsule **3** by dynamic boronic ester formation (Scheme 1).[9] Capsule **3** encapsulates one molecule of guest such as 4,4′-disubstituted-biphenyl or 2,6-disubstituted-anthracene derivatives in a highly selective recognition event. We also present the on/off control of capsule formation with guest encapsulation by removal/addition of methanol.

Taken in isolation, the cavitand tetraboronic acid **1**[2d,10] and the bis(catechol)-linker **2**[11] both have low solubilities in $CDCl_3$. However, a 2:4 heterogeneous mixture of **1** and **2** in $CDCl_3$ gave a homogeneous solution upon heating at 50 °C for 3 h and quantitatively produced capsule **3**, wherein two molecules of **1** at the polar positions are indirectly held together by eight boronic ester bridges involving four molecules of **2** at the equatorial positions (Scheme 1). A molecular model of **3**, calculated with Spartan '06[12] at the PM3 level, shows that **3** possesses an inner cavity of the approximate dimensions 8.4 Å × 19.4 Å (interatomic distance) and four equatorial portals of approximately 6.8 Å × 11.5 Å. Calculations suggest the linker unit adopts an approximate *anti*-conformation and the northern polar cavitand unit is twisted by ca. 12.4° with respect to the southern polar cavitand unit about a C_4 polar axis. The ^{1}H NMR spectrum of the reaction mixture showed a highly sym-



Scheme 1. Formation of capsule **3** from **1** and **2**. Molecular models of **3** and guest encapsulating capsule **4@3** are calculated at the PM3 level of Spartan '06.[12] The heptyl side chains of **1** are replaced by methyl groups. Guests **4**–**7** (bottom) have been encapsulated in **3**.

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metrical single species and disappearance of the OH groups from units **1** and **2** (Figure 1c vs. 1a, 1b), indicating the quantitative formation of **3**. The chemical shift changes of **3** relative to **1** and **2**, $\Delta\delta$ ($\delta_{complex}-\delta_{free}$), are 0.14, −0.20, 0.10, and 0.12 ppm for H_a-H_d of unit **1**, respectively, and 0.42, 0.49, and 0.45 ppm for H_e-H_g of unit **2**, respectively.

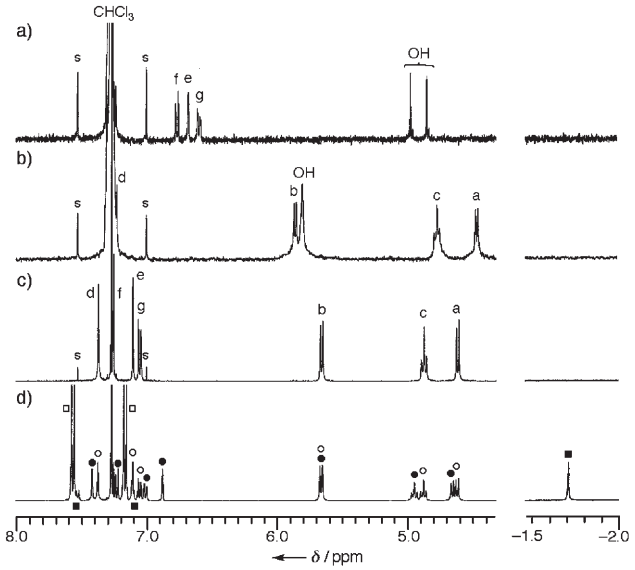

Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 23 °C): a) [**2**] = 10 mM if soluble (heterogeneous), b) [**1**] = 5 mM if soluble, c) capsule **3** (homogeneous after heating at 50 °C for 3 h, [**1**] = 5 mM and [**2**] = 10 mM), and d) **4@3**:free-**3** = 48:52 after heating [**3**] = 2.5 mM and [**4**] = 12.5 mM at 50 °C for 3 h, depicting peaks representing **3** from **4@3** (●), free **3** (○), **4** from **4@3** (■), and free **4** (□). The signals marked a–g are assigned in Scheme 1. The signals marked s are spinning sidebands of the residual solvent.

When 5 equiv of 4,4′-diacetoxybiphenyl **4** was added to a solution of **3** (2.5 mM) in $CDCl_3$, three species were independently observed after heating (Figure 1d); that is, 52% guest-free **3**, excess **4**, and 48% guest encapsulating capsule **4@3**. This result indicates that the exchange of **4** in and out of **3** is slow on the NMR time scale. The ^{1}H NMR signals of **4** encapsulated in **3** were shifted upfield by 4.04 ppm for the acetoxy protons and 0.04 and 0.06 ppm for the aromatic protons relative to those of free **4**. This result shows that the acetoxy groups are oriented to both aromatic cavity ends of **3** (Scheme 1). Based on the integration ratio, capsule **3** encapsulates one molecule of **4**. The association constant was estimated to be $K_a = 82\,M^{-1}$ in $CDCl_3$ at 23 °C. The van't Hoff plots gave thermodynamic parameters of $\Delta H° = -1.9$ kcal mol^{-1} and $\Delta S° = 2.3$ cal mol^{-1} K^{-1} (see Supporting Information, Figure S1).[13] Thus, the encapsulation of **4** in **3** in $CDCl_3$ is both enthalpically and entropically driven. By comparison, K_a for **3** with 4,4′-diethoxybiphenyl **5** was $8.1\,M^{-1}$.

Heating a 2:4 mixture of **1** and **2** in C_6D_6 at 50 °C for 3 h did not give a homogeneous system, although **3** was quantitatively formed (Figure 2a and Figure S2). [13,14] In contrast, heating this mixture in the presence of 1 equiv of **4** relative to **1** gave a homogeneous solution and quantitatively produced **4@3**, as shown in Figure 2b. The IR spectrum of this reaction

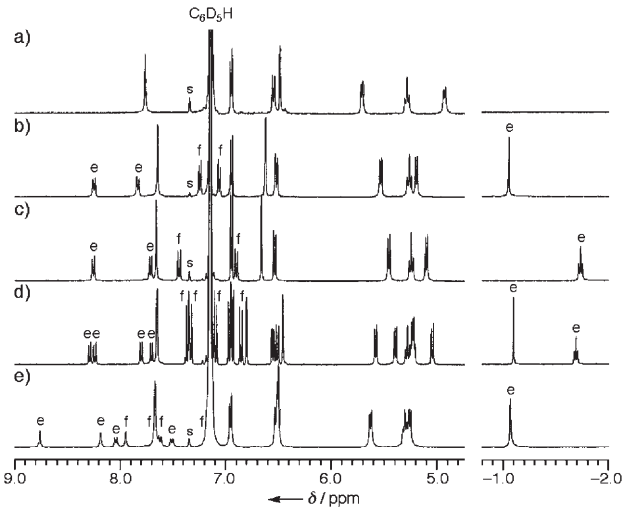

Figure 2. ^{1}H NMR spectra (400 MHz, C_6D_6, 23 °C): a) capsule **3** (heterogeneous after heating at 50 °C for 3 h, [**1**] = 5 mM and [**2**] = 10 mM), b) **4@3** + **4** (homogeneous after heating at 50 °C for 3 h, [**1**] = 5 mM, [**2**] = 10 mM, and [**4**] = 5 mM), c) **5@3** + **5**, d) **6@3** + **6**, and e) **7@3** + **7**. The signals marked "e and f" indicate peaks representing encapsulated and free guests, respectively. The signals marked "s" are spinning sidebands of the residual solvent.

mixture (after evaporation of solvents) showed the disappearance of the OH groups from **1** and **2**, indicating formation of the boronic ester, but not hydrogen bonds (Figure S3).[13] The ^{1}H NMR signals of **4@3** in C_6D_6 were shifted upfield by 2.85 ppm for the acetoxy protons and downfield by 1.01 and 0.78 ppm for the aromatic protons relative to those of free **4**. The association constant of **3** with **4** was estimated to be $K_a = 4.9\times10^5\,M^{-1}$ in C_6D_6 at 40 °C by a competitive encapsulation experiment with **5**. The ^{1}H NMR spectrum of **5@3** in C_6D_6 gave $\Delta\delta = -2.87$ (CH_3) and 0.18 ppm (CH_2) for the ethoxy groups and $\Delta\delta = 0.83$ and 0.82 ppm for the aromatic protons of **5** (Figure 2c), and $K_a = 1.30\times10^4\,M^{-1}$ at 40 °C. The thermodynamic parameters of **5@3** in C_6D_6 were $\Delta H° = -26.3$ kcal mol^{-1} and $\Delta S° = -65.2$ cal mol^{-1} K^{-1} (Figure S4),[13] indicating a major enthalpic contribution.

Thus, the association behavior of capsule **3** with a guest in C_6D_6 differs significantly from that in $CDCl_3$. The value of K_a(in C_6D_6)/K_a(in $CDCl_3$) for a guest encapsulated within **3** (guest@**3**) is approximately 1600–6000. The small K_a and considerable entropic contribution for guest@**3** in $CDCl_3$ (see above) strongly suggest that $CDCl_3$ acts as a guest competitor for **3**.[15] In fact, when pure **4@3**, which was prepared in benzene and dried in vacuo, was dissolved in $CDCl_3$, the release of **4** encapsulated in **3** into the bulk phase of $CDCl_3$ immediately occurred at 23 °C. The ratio of **4@3**:free-**3** was 60:40 after 3 min and 48:52 after 24 h, reaching an equilibrium (Figure S5).[13] This result agrees completely with that shown in Figure 1d.

In addition to 4,4′-diacetoxybiphenyl **4** and 4,4′-diethoxybiphenyl **5**, capsule **3** also encapsulates 4-acetoxy-4′-ethoxybiphenyl **6** and 2,6-diacetoxyanthracene **7** (Figure 2d and e). In contrast, encapsulations of 4-ethoxy-4′-methoxybiphenyl, 4-ethoxy-4′-*n*-propoxybiphenyl, 4-acetoxy-4′-methoxybi-

phenyl, and 4,4′-bis(methoxycarbonyl)biphenyl were not detected in C_6D_6. Thus, **3** strictly discriminates a one-carbon atom difference in guests, as well as functional groups. The encapsulation ability of guests in **3** increased in the order **5** (relative binding ability = 1) < **6** (5.9) < **7** (8.8) < **4** (38.2), as evaluated by competitive encapsulation experiments (Figure S6). [13]

The on/off control of capsule formation with guest encapsulation was achieved by chemical stimulus; namely, the removal and addition of methanol (Figure 3).[16] Addition of 5% CD_3OD (1000 equiv) to a solution of **4@3** in C_6D_6 caused immediate dissociation of the boronic ester bonds of **3** to release **4** and to produce **1**-(methanol)$_n$ adducts and **2** (Figure 3a vs. 3b, 3c). This mixture was restored to the original **4@3** by vacuum drying at room temperature and then heating in C_6D_6 at 50 °C for 3 h (Figure 3d and e).

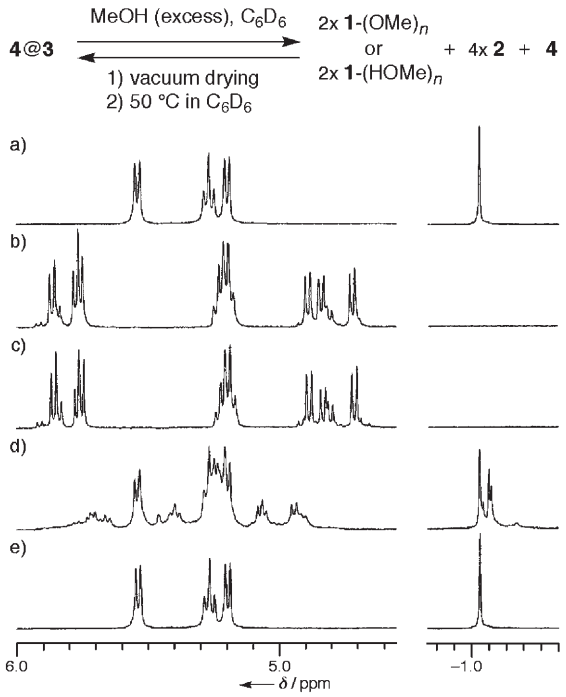

Figure 3. On/off control of capsule formation with guest encapsulation by removal/addition of methanol. ^{1}H NMR spectra (400 MHz, 23 °C): a) **4@3** (2.5 mM) in C_6D_6, b) after 3 min of **4@3** in 5% (v/v) CD_3OD-C_6D_6 (1000 equiv of CD_3OD), c) **1** (5 mM) in 5% (v/v) CD_3OD-C_6D_6, d) vacuum-dried sample b in C_6D_6 (heterogeneous), and e) after heating sample d in C_6D_6 at 50 °C for 3 h.

In summary, we have demonstrated 1) the self-assembly of cavitand-based capsule **3** by dynamic boronic ester formation, 2) guest encapsulation by **3** with a highly selective recognition event, 3) a significant solvent effect for guest encapsulation, and 4) the on/off control of capsule formation with guest encapsulation by the removal and addition of methanol. Our next projects are the elucidation of the guest encapsulation process of **3** (constrictive vs. intrinsic binding),[17] and asymmetric guest recognition of a chiral capsule[18] to be derived from **1** and incorporating a C_2 symmetric chiral bis(catechol) linker in place of **2**.

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[12] Spartan '06, Wavefunction Inc., Irvine CA (USA), **2006**
[13] See the Supporting Information.
[14] The solubility of **3** in C_6D_6 at 23 °C was 1.3 mM based on the ^{1}H NMR integration ratio with *p*-dimethoxybenzene as an internal standard.

[15] In the ^{1}H NMR spectra of **3** in $CHCl_3$ even at −55 °C with $CDCl_3$ sealed in a capillary for NMR deuterium locking or a mixture of **3** and 100 equiv of $CHCl_3$ in C_6D_6, no signal of $CHCl_3$ encapsulated in **3** was observed. These results suggest small K_a and very fast exchange of $CHCl_3$ in and out of **3** on the NMR time scale.

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