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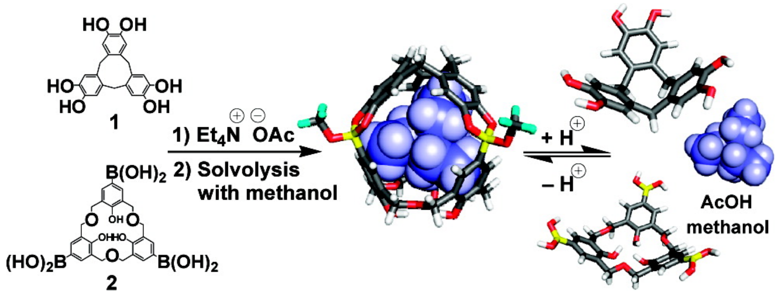

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# Ion Pair-Driven Heterodimeric Capsule Based on Boronate Esterification: Construction and the Dynamic Behavior

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Boronic acids[1] have attracted considerable interest in the field of molecular recognition in the development of boronic acid-based chemosensors for anions[2] and saccharides.[3] Boronic acids can rapidly and reversibly form cyclic boronate esters with diols[4] and also act as Lewis acid metal centers.[5] These properties led us to propose an anion sensor system based on anion-induced boronate esterification.[6] With this research we use anion-controllable reversible covalent bonding interactions in the construction of a chemically switchable molecular capsule.[7] Conventionally self-assembled molecular capsules have been developed using hydrogen bonding, ionic interactions, and metal ion coordination as well as combinations thereof.[8] Boron-containing compounds have previously been used as a structure-directing element (e.g., macrocycles,[9] helicates,[10] nanotubes,[11] porous covalent organic frameworks,[12] polymers[13]). However, to our knowledge, self-assembled molecular capsules via boronate esterfication have not been reported. Here, we describe an ion pair-driven heterodimeric capsule using cyclotricatechylene **1**[14] and boronic acid-appended hexahomotrioxacalix[3]arene **2**. Although **1** does not interact with **2** in a protic solution, the presence of $Et_4NAcO$ led to the quantitative production of a heterodimeric capsule as illustrated vide infra using NMR analysis, a direct result of the cooperative effect of acetate-induced boronate esterification and $Et_4N^+$ as a template. We also observed the reversible decomposition−reconstruction of the capsule using pH switching.

For our capsule we employed boronate ester bowl shaped **1** and **2** as modules. Compound **2** was prepared from tribromohexahomotrioxacalix[3]arene.[15] The capsule formation using **1** and **2** was investigated using $^1$H NMR in $CD_3OD-CD_3CN$ (4:1 v/v) (Figure 1); **1** has a rigid bowl-shaped structure, the methylene resonances producing an AB doublet of doublets at 4.602 ($J$ = 13.6 Hz) and 3.340 ppm ($J$ = 14.0 Hz), whereas the resonances ($H^2$, $H^3$) due to ethereal linkages of **2** displayed a singlet at 4.734 ppm (Figure 1b), clearly indicating that **2** exists in flexible conformation where the rate of the ring inversion is fast on the NMR time scale. Two singlets at 7.576 and 7.484 ppm can be assigned to the chemical shift of $H^1$; the spliting pattern may be due to solvent exchange on the boronic acid segments with methanol. No perturbation of the chemical shifts for **1** and **2** is caused by mixing them under these conditions (Figure 1c). However, when 3 equiv of $Et_4NAcO$ are added to the solution, the chemical shifts are changed (Figure 1d): (1) the resonances ($H^1$ and $H^a$) were shifted upfield to 7.226 and 6.446 ppm, respectively; (2) the protons ($H^2$, $H^3$) of **2** are a doublet at 4.701 ppm (d, $J$ = 9.2 Hz).[16] These results indicate that **2** interacts with **1** and that the conformation of **2** is frozen into a cone conformation. Furthermore, it is noteworthy that new signals appeared at 0.300 and −0.039 ppm, which can be assigned to the encapsulated $Et_4N^+$. These new peaks integrate in a 1:2 ratio with respect to the set of signals due to free $Et_4N^+$.

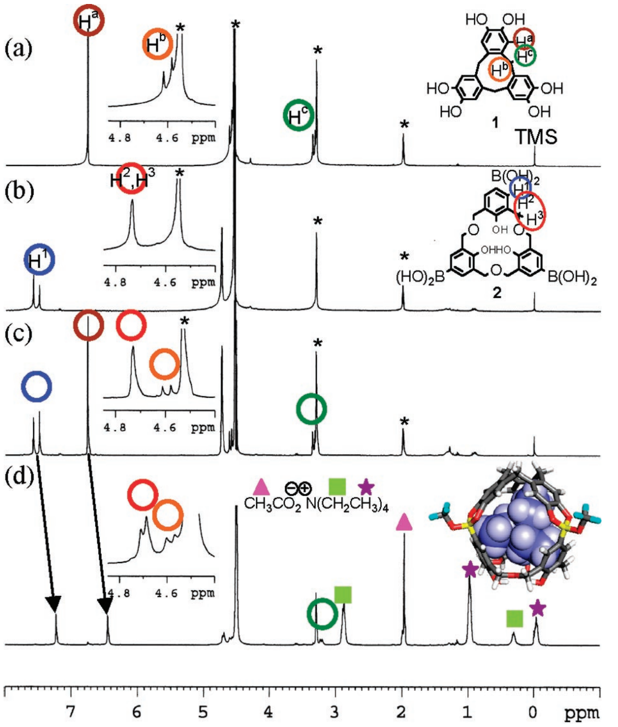

**Figure 1.** $^1$H NMR spectra (400 MHz, $CD_3OD-CD_3CN$ (4:1 v/v), 23 °C): (a) **1** (10 mM), (b) **2** (10 mM), (c) **1** (10 mM) and **2** (10 mM), (d) **1** (10 mM) and **2** (10 mM) with $Et_4NAcO$ (30 mM); signals with an asterisk (∗) represent residual peaks of solvents.

Assessment of the $Et_4NAcO$-triggered self-organization came from $^1$H, $^1$H ROESY spectroscopy. As expected, ROE cross-peaks were found between $H^a$ and $H^1$, indicating the production of capsular structure **1·2**. New peaks at approximately 0 ppm show exchange peaks with free $(CH_2CH_3)_4N^+$ protons. Further structural confirmation of the capsule was achieved through diffusion-ordered spectroscopy (DOSY).[17] The diffusion coefficients ($D$ values) of **1** and **2** in $[D]_6$-DMSO−$CD_3OD$ (4:1 v/v) involving $Et_4NAcO$ are identical within experimental errors ($8.9 \times 10^{-11}$ m$^2$ s$^{-1}$).[18] The resonances assigned to the encapsulated $Et_4N^+$ had nearly the same $D$ value as the capsule, being $8.5 \times 10^{-11}$ m$^2$ s$^{-1}$. These results clearly indicate that **1**, **2**, and $Et_4N^+$ exist as a single unit in solution, the average value being $8.8 \times 10^{-11}$ m$^2$ s$^{-1}$. The $Et_4N^+$ inside the cavity may be held by multiple C−H $\pi$ interactions with the proximal aromatic rings.[19] Although the role of $AcO^-$ is significant for the capsulation as inferred by Figure 1,[20] the $D$ value is much larger ($60 \times 10^{-11}$ m$^2$ s$^{-1}$), being consistent with that of free $Et_4NAcO$. We postulated that the $AcO-B^-(sp^3)$ dative bond is immediately subject to solvolysis in the protic media (methoxy insertion). Such a solvent insertion is known to be promoted owing to the increased electrophilicity of the boronate.[21] Indeed, ESI-MS

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***Table 1.*** The Capsule Stability Constants *K* in the Presence of Various Salts in MeOH−MeCN (4:1 v/v) at 25 °C[a]

| cation | anion | *K* ($M^{-1}$) |
|---|---|---|
| $Et_4N^+$ | $AcO^-$ | 11,000 ± 450[a] |
| $Me_4N^+$ | $AcO^-$ | 5,900 ± 600[a] |
| $K^+$ | $AcO^-$ | 1,100 ± 85[a] |
| $Et_4N^+$ | $F^-$ | 1,100 ± 130[a] |
| $Et_4N^+$ | $I^-$ | nd[b] |
| $K^+$ | $I^-$ | nd[b] |

[a] Three individual measurements were carried out. [b] The spectral change is too small to determine the *K* value; nd = not determined.

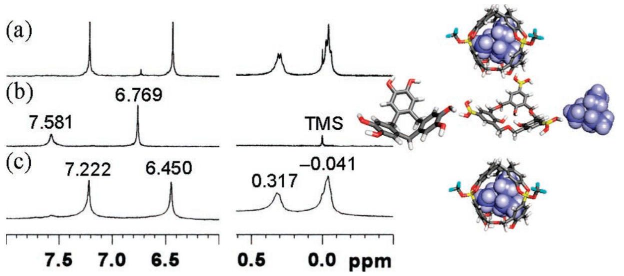

***Figure 2.*** Sections of the $^1H$ NMR spectra (400 MHz, 23 °C) of **1** (10 mM) and **2** (10 mM) in $CD_3OD-CD_3CN$ (4:1 v/v): (a) in the presence of 3 equiv of $Et_4NAcO$, (b) addition of 0.85 $\mu$L of 12 N HCl, and (c) subsequent $NaHCO_3$ addition.

measurements in negative mode displayed a significant molecular peak due to $[\mathbf{1}\cdot\mathbf{2}\cdot 2(Et_4N)\cdot 3(OMe)]_4^{4-}$ at 1151.63 (calcd, 1151.60) in MeOH at 100 °C (spray temperature). Taken together, this data confirms the formation of a heterodimeric capsule of **1** and **2**; it should be emphasized that the capsule formation via boronate esterification is driven by adding $Et_4N^+$ and $AcO^-$. Therefore we investigated capsule formation using different salts. When $Et_4NAcO$ is replaced with $Et_4NF$, $(n\text{-}Bu)_4NAcO$, or KI, the $^1H$ NMR spectra show ill-defined or no aggregates under similar conditions. Extensive investigations using UV−vis techniques furnished evidence for the selective ion-pair triggered capsule formation. The electric perturbation of **1** and **2** upon adding salts can be observed in the UV region wherein the isosbestic point at 250 nm could allow us to assume simple equilibration for the estimation of the capsule stability constant *K*; $\mathbf{H} + \mathbf{G} \rightleftarrows \mathbf{HG}$ where **H** is regarded as pre-capsule with three equivalent boronate-forming sites, **G** is the salt, and **HG** is desired capsule. Table 1 summarized the *K* values obtained by the titration upon adding several salts, which values increased with the following order: $Et_4N^+ > Me_4N^+ > K^+$ with $AcO^-$ salts and $AcO^- > F^- > I^-$ with $Et_4N^+$ salts, respectively. From these results, the capsulation is dictated mainly by size of the cation and basicity of the anion. In the former case, C−H $\pi$ interactions seem to play a significant role for the event.

Our next goal was to investigate whether the capsule formation could be dynamically controlled using a pH switch. When HCl was added to the solution of the $Et_4NAcO$-driven capsule, the resonances due to interior $Et_4N^+$ at ca. 0 ppm disappeared completely (Figure 2b), and each singlet at 7.581 and 6.769 ppm can be assigned to ArH of free **1** and **2**, respectively. The treatment with HCl resulted in the ejection of the guest upon collapse of the capsule. More interestingly, subsequent addition of $NaHCO_3$ allowed us to detect signals arising from the encapsulated $Et_4N^+$ (0.317 and −0.041 ppm; Figure 2c), thus restoring the capsule. The reversible boronate esterification allows us to control capsule assembly using pH switching.

In conclusion, we present for the first time selective ion pair-driven heterodimeric capsule formation using boronic acids.[22] The dynamic behavior is also controllable by changing the pH of the solution. These findings provide a potent way to develop materials which reversibly trap, store, and then deliver chemicals in a solution. On another front, this study has been driven by the conceptual novelty of the capsule formation. Thus, not only the related capsule with a larger cavity capable of accommodating chemically important guests[23] but also chromophore-appended capsule systems for the detection of dynamic behavior is currently a major target in the study.

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**Note Added After ASAP Publication.** Because of a production error, the formula $CD_3OD-CD_3CN$ in the caption of Figure 2 was incorrect in the version of the paper published November 16, 2007; the corrected version was published November 19, 2007.

**Supporting Information Available:** Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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