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Formation of a tris-capsule and a tris-carceplex from a cyclic six-bowl assembly†

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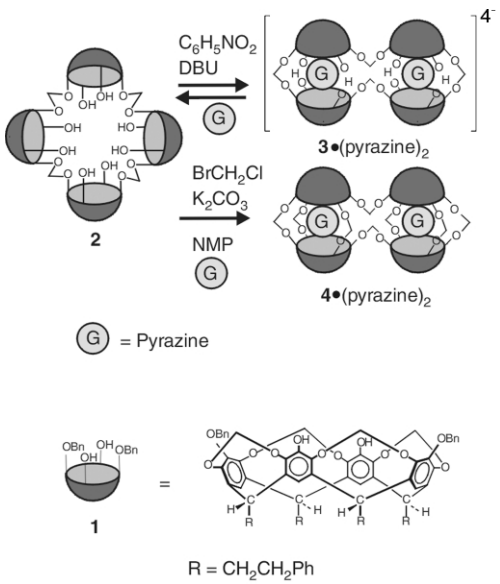
Received (in Columbia, MO, USA) 30th April 2002, Accepted 18th June 2002
First published as an Advance Article on the web 3rd July 2002

A macrocycle composed of six cavitands was assembled into a tris-capsule and a tris-carceplex, each of which encapsulates three guest molecules.

One of the current challenges in supramolecular chemistry is the use of non-covalent assembly processes to create complex structures.[1] Such structures may be reversible assemblies that have reasonable thermodynamic stability,[2–8] or they may be entirely covalent structures.[9–12] We have done extensive work studying the template effect in forming a carceplex[10] and have studied the corresponding reversible capsule.[5] Whereas the carceplex permanently entraps its template, the capsule binds the template reversibly, and is a good transition state model for formation of the carceplex. In these systems, two cavitands (akin to **1**) are brought together *via* charged hydrogen bonds and by the host–guest interactions, where the template is the guest. We found that we could apply this assembly process to cyclic tetramers of cavitands, **2**, to form both a bis-capsule (**3**)[6] and a bis-carceplex (**4**) (Scheme 1).[12] Bis-capsules **3**·(guest)$_2$, where guest is pyrazine or methyl acetate, form efficiently, according to the equilibria we observed by ^{1}H NMR spectroscopy.[6] Bis-carceplex **4**·(pyrazine)$_2$ formed efficiently as reflected by a 74% yield.[12] Here, we extend this work using hexamer **6** to see how this assembly process fares in bringing together six bridging molecules, three guest molecules, and a conformationally mobile host, while forming 12 new covalent bonds.

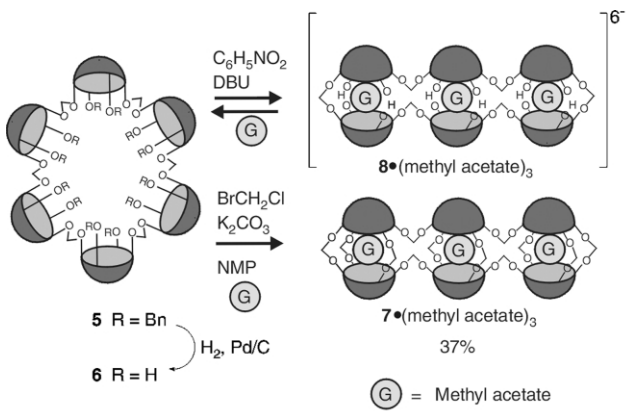
Hexamer **6** was obtained by hydrogenolysis (90% yield) of the corresponding hexabenzylated hexamer (**5**), which itself was obtained from cyclization of A,B-bis-benzyloxy diol **1** as a side-product (< 1% yield) in the formation of tetramer **2**.[12] Although the yield of **5** is low, it was readily available from reaction mixtures already in hand.



Scheme 1 Formation of bis-capsule **3**·(pyrazine)$_2$ and bis-carceplex **4**·(pyrazine)$_2$ from tetramer **2**.

We performed the same carceplex forming reaction on hexamer **6** as was done on tetramer **2**, with one small modification: we used methyl acetate as the template instead of pyrazine: ^{1}H NMR spectra with bound methyl acetate yield signals in an open window (< 0 ppm), whereas signals from the pyrazine are in the crowded 4.3 ppm region. Thus, reaction of hexamer **6** with CH_2BrCl in NMP in the presence of K_2CO_3 and 5 mol% methyl acetate gave tris-carceplex **7**·(methyl acetate)$_3$ in 37% yield (Scheme 2). How efficient is this assembly process? The 74% yield for bis-carceplex **4**·(pyrazine)$_2$[12] gives an average yield per new bond formed (eight) of 96%. The corresponding mono-carceplex yield of 87%[10] gives a yield per bond (four) of 97%. Here, the yield per bond (12) for tris-carceplex **7**·(methyl acetate)$_3$ is 92%. This is a good yield considering the complexity of the reaction. The somewhat lower than expected yield may be a result of the conformationally more flexible hexamer compared to the tetramer and/or the use of a slightly less effective template (pyrazine is 2.1 times better than methyl acetate).[10] However, caution must be taken at such an interpretation, as there are far more non-productive pathways from **6** to **7** than there are from **2** to **4**, or from the single cavitand to the mono-carceplex.[13] Thus, the assembly process to form **7**·(methyl acetate)$_3$ appears to be quite efficient.[13,14]

Tris-carceplex **7**·(methyl acetate)$_3$ was characterized as follows: MALDI-MS gave a strong signal at 6494 *m/z* (**7**·(methyl acetate)$_3$·Na$^+$ = 6492). The ^{1}H NMR spectrum of **7**·(methyl acetate)$_3$ in C_6D_6 at 57 °C contains signals at −0.09, −0.33, −1.70 and −1.91 ppm (Fig. 1), which integrate in a 1:2:1:2 ratio, and account for 18 protons when integrated against the host signals.[15] Based on integration, we assign the signals at −0.09 and −1.70 ppm to methyl acetate trapped in the inner cavity, and those at −0.33 and −1.91 ppm to guests trapped in the two outer cavities. When a sample of **7**·(methyl



Scheme 2 Formation of tris-capsule **8**·(methyl acetate)$_3$ and tris-carceplex **7**·(methyl acetate)$_3$ from hexamer **6**.

† Electronic supplementary information (ESI) available: assembly number discussion, and experimental details for the preparations and characterizations of **5**–**8**. See http://www.rsc.org/suppdata/cc/b2/b204089a/

DOI: 10.1039/b204089a

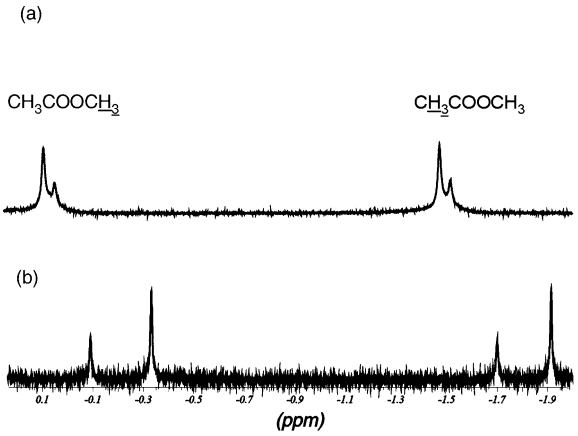


Fig. 1 Upfield region of the ^{1}H NMR spectra (400 MHz) of (a) tris-capsule **8**·(methyl acetate)$_3$ (2.52 mM hexamer **6**, 17.7 mM DBU and 27.9 mM methyl acetate) in nitrobenzene-d$_5$ at 127 °C, (b) tris-carceplex **7**·(methyl acetate)$_3$ in C_6D_6 at 57 °C.

acetate)$_3$ was heated in nitrobenzene-d$_5$ at 150 °C for five days, no loss of guest was observed, which justifies the term carceplex for **7**·(methyl acetate)$_3$.

When hexamer **6** was dissolved in nitrobenzene-d$_5$ in the presence of 7 mol equiv. of DBU, the ^{1}H NMR spectrum yields very broad signals. Upon addition of methyl acetate, the host signals remain broad, but two new signals of equal intensity appear at 0.0 and −1.5 ppm, which we assign to the bound guests. At 127 °C, these two signals each resolve into two signals that integrate in 2 : 1 ratios (Fig. 1(a)) and account for a total of 18 protons with respect to the host. Although the host signals remain somewhat broad, it is clear that tris-capsule **8**·(methyl acetate)$_3$ formed. The broad host signals are likely a result of the fluctional nature of the large host. Addition of less than a stoichiometric amount (< 3 mol equiv.) of methyl acetate gives the same number of signals and chemical shifts as when an excess amount of the guest is used. This observation indicates that guest binding in tris-capsule **8** is cooperative, that is, **8**·(methyl acetate)$_n$, where n = 1 or 2, are probably not generated in appreciable quantities. A similar cooperativity was observed with bis-capsule **3**·(guests)$_2$.[6]

We have demonstrated that hexamer **6** can be used to make a tris-capsule and a tris-carceplex. The tris-capsule is held together by charged hydrogen bonds, whereas the tris-carceplex contains its guests *via* covalent linkages. Although the yields are getting lower on going from synthesis of one to two to three carceplexes, the efficiency of the assembly process still appears to be high. Indeed, a more sophisticated method of evaluating their efficiency is surely needed.[13] We can differentiate the guests in the outer *vs*. the central chambers by their chemical shifts and by integration. Such handles may allow us to probe guest–guest communication as well as the dynamics within each chamber. It would also be interesting to probe the orientatation and mobility of the chambers with respect to each other.

We thank NIH (GM 56104) and NSERC (Canada) for support of this work. We thank Professor D. Dolphin for use of his chromatotron, and Y. Terazono for help with its operation.

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13 For analyses of yield/efficiency using assembly numbers, see ESI†and C. L. D. Gibb and B. C. Gibb, *J. Supramol. Chem.*, 2001, **1**, 39.
14 As guest selectivity has been studied in detail with the single carceplex/capsule system (refs. 5 and 10) we did not repeat such experiments on the present system. Undoubtedly, we would see similar selectivity; as the two carceplex/capsule system manifested similar selectivity to the single carceplex/capsule system (refs. 11 and 12).
15 The host signals of **7**·(methyl acetate)$_3$ are very broad at room temperature and moderately broad at 57 °C in benzene-d$_6$. The extent of intra- and inter-chamber conformational twisting is presently unknown, but it is likely responsible for the broad spectra. The bis-carceplex/capsule system manifests similar spectral properties to the present system (refs. 11 and 12). For studies on guest orientation and host and guest dynamics in the single chamber system, see: R. G. Chapman and J. C. Sherman, *J. Org. Chem.*, 2000, **65**, 513.