Practical synthesis and guest–guest communication in multi-hemicarceplexes†

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Single molecule hosts carrying three separately encapsulated guests are prepared in a seven step sequence in high overall yields.

Carceplexes and hemicarceplexes are special types of host–guest complexes in which guests are held very strongly within the confines of a fully encapsulating cage.[1–3] These closed-shell container molecules with their imprisoned guests are generally constructed through the covalent linking of two bowl shaped cavitand molecules in a rim-to-rim manner. Usually a single guest molecule is held within each host. "Cell-block" hosts comprising several incarcerated molecules, each confined within separate cages of a covalently-linked structure, should allow the investigation of some intriguing questions with potentially useful applications. For example, do guests incarcerated in different binding sites behave independently or can an induced change in the environment of one guest influence that of another? Bis-hemicarceplexes were first synthesised by Cram *et al.* through the covalent linking of two hemicarcerands.[4] More recently, Sherman *et al.* prepared bis- and tris-hemicarceplexes through the transannular shell closure of cavitand cyclic tetramers and hexamers, respectively.[5,6] Whilst both approaches are important advances, they are not without limitations. The former approach lacks generality since it requires a suitably functionalised hemicarcerand building block, whereas the latter approach is limited by prohibitively low yields of cyclic tetramer (15%) and hexamer (<1%) precursors. Furthermore, whilst the question of "communication" between guests has been raised,[4] to our knowledge no report of such a study has appeared. Herein we describe a new strategy for multi-hemicarceplex formation which employs selective lithium–halogen exchange technology in combination with Sherman's landmark templation method.[7] This robust approach leads to high overall yields for the

† Electronic supplementary information (ESI) available: experimental details and spectra. See http://www.rsc.org/suppdata/cc/b5/b504950d/

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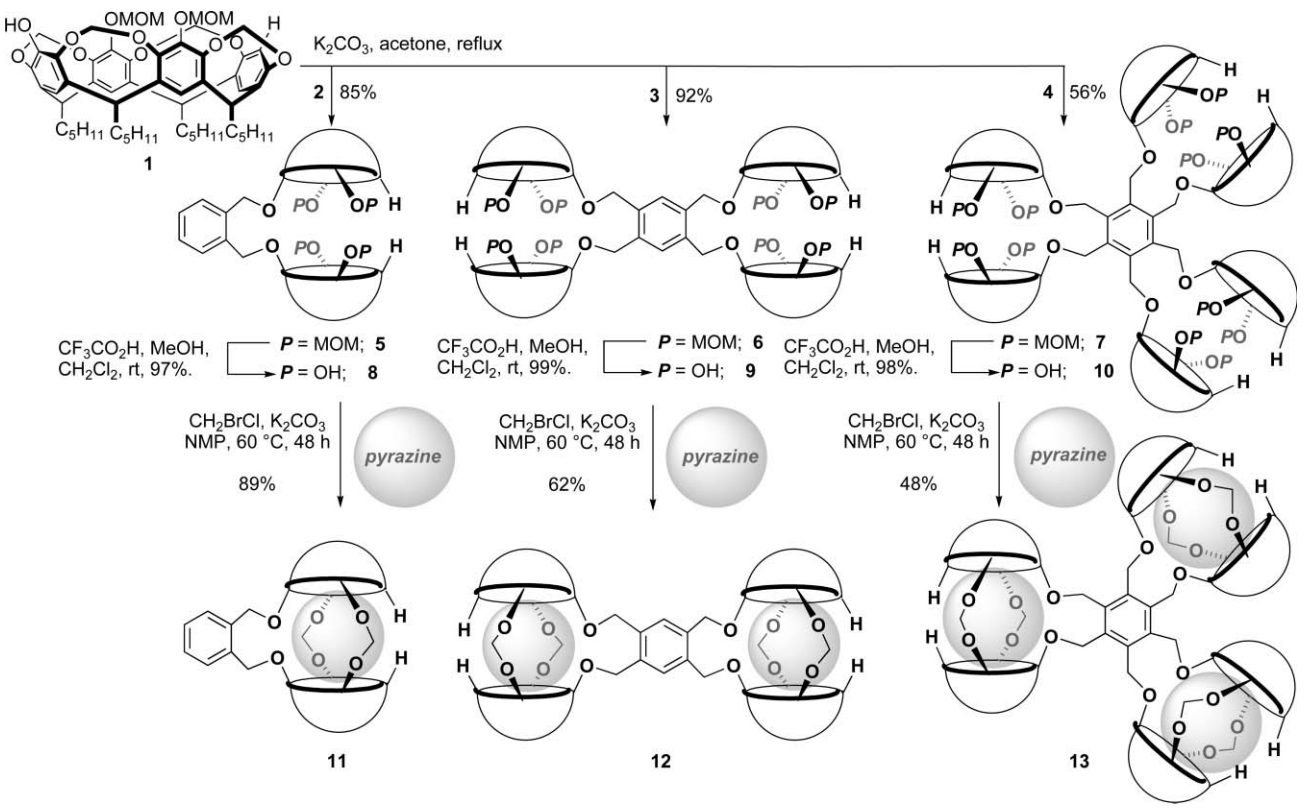


Scheme 1 Synthesis of mono-, bis- and tris-hemicarceplexes **11**, **12** and **13**. Cavitands (*cf.* **1**) are represented as cartoon bowls for clarity.

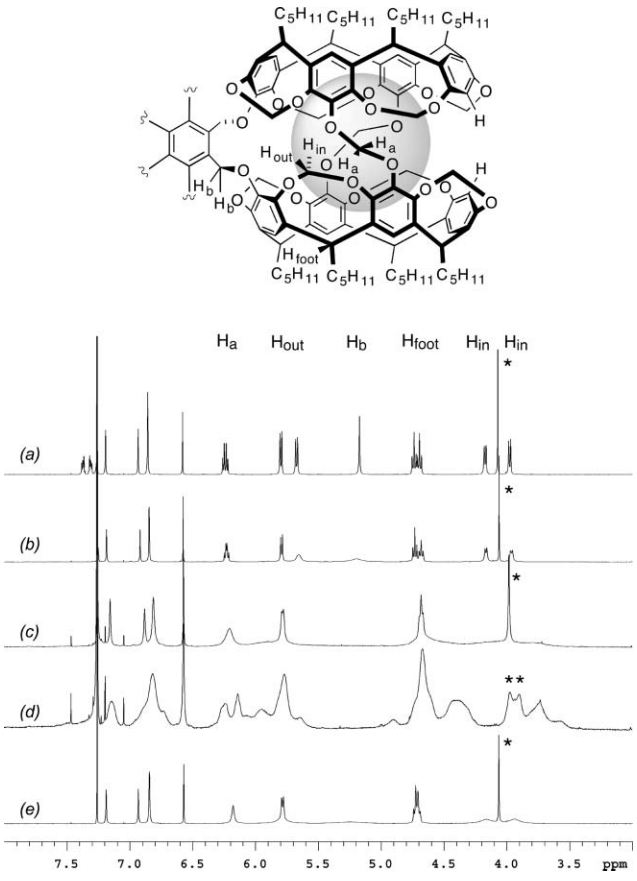
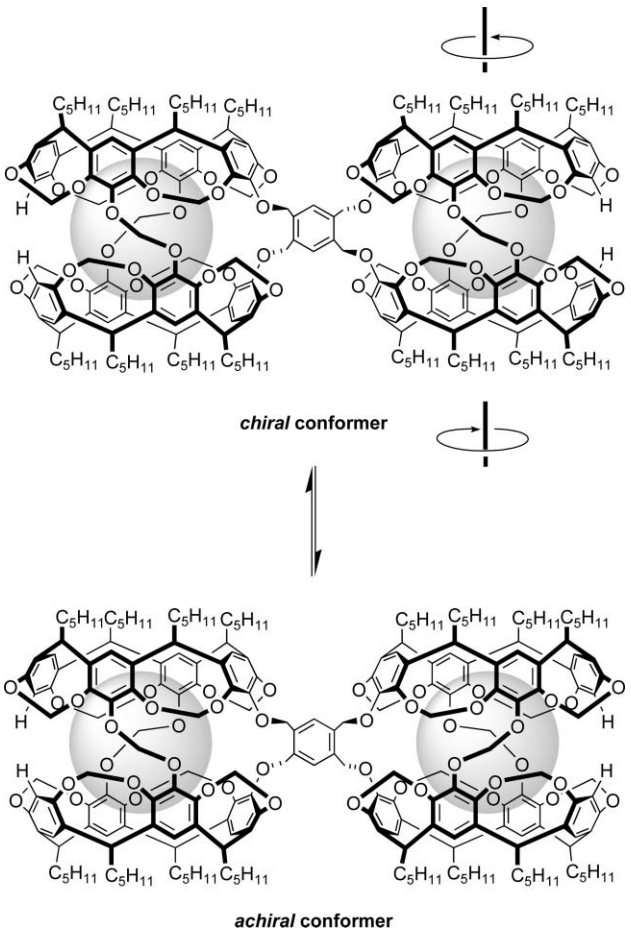


Fig. 1 500 MHz ^{1}H NMR spectra of the pyrazine hemicarceplexes in $CDCl_3$; *(a)* mono-hemicarceplex **11** at 25 °C; *(b)* bis-hemicarceplex **12** at 25 °C, *(c)* bis-hemicarceplex **12** at −25 °C; *(d)* bis-hemicarceplex **12** at −55 °C; *(e)* tris-hemicarceplex **13** at 25 °C. (Peaks marked * are encapsulated pyrazine.)



Scheme 2 Twistomerisomerism in bis-hemicarceplex **12**. Twisting in the right hand chamber causes switch from one diastereomer to the other, invoking a change in environment of guest in left hand chamber.

synthesis of a new family of multi-hemicarceplexes and hydrogen-bonded capsules. We also demonstrate that within these complexes, a change in the environment of one captive guest is felt by the other prisoners.

The key building block for practical multi-hemicarceplex formation, unsymmetrically functionalised cavitand **1**, was prepared from the corresponding tetrabromocavitand through a four step synthetic route in 34% overall yield involving regioselective lithium–bromine exchange with *n*-BuLi.[8] Cavitand phenol **1** was united with 1,2-bis(bromomethyl)benzene **2**, 1,2,4,5-tetrakis(bromomethyl)benzene **3**, and hexakis(bromomethyl)benzene **4** to form xylylene-linked cavitand dimer **5**, tetramer **6** and hexamer **7**, respectively (Scheme 1). Hydrolysis of the MOM ethers gave the corresponding phenols **8**, **9** and **10**, the precursors for hemicarceplex shell closure. Pleasingly, upon reaction with bromochloromethane and potassium carbonate in the presence of pyrazine,[7] the desired mono-, bis- and tris-hemicarceplexes **11**, **12** and **13** were obtained in excellent yields after standard column chromatography on SiO_2. A yield of 48% for tris-hemicarceplex **13** from dodecaphenol **10** is remarkable since it involves the formation of twelve covalent bonds, in the process encapsulating three guest molecules. Comparable yields of mono- (83%) and tris-hemicarceplex (40%) were obtained with dioxane as template. ^{1}H NMR spectra of the family of hemicarceplexes at room temperature are strikingly similar [Fig. 1*(a)*, *(b)* and *(e)*].

In addition to host signals, they exhibit a resonance for encapsulated pyrazine at δ 4.05 ppm, characteristically shifted a considerable distance upfield from that of the free guest.[7] Interestingly, whereas mono-hemicarceplex **11** exhibits a sharp NMR spectrum at ambient temperature, those of the bis- and tris-complexes are increasingly broad. The signals most strongly affected are those of the benzylic protons (H_b), two of the four outer acetal protons (H_{out}) and the inner acetal protons (H_{in}). As the temperature is lowered, much more complex spectra are obtained for bis- and tris-hemicarceplexes **12** and **13**. [Spectra for **12** are depicted in Fig. 1*(b)*, *(c)* and *(d)*.] This behaviour results from a decrease in the rate of interconversion between two diastereomeric twistomers:[9] structures related through a twisting motion of one hemisphere of one hemicarceplex moiety with respect to the other hemisphere. In mono-hemicarceplex **11**, this conformational change interconverts two enantiomeric complexes. In the bis- and tris-hemicarceplexes **12** and **13**, two diastereomeric complexes result, since the sense of twisting for a pair of hemicarceplex groups within the same molecule can be in the same direction or opposed (Scheme 2). At low temperatures, two distinct signals are visible for encapsulated pyrazines at δ 3.9 and

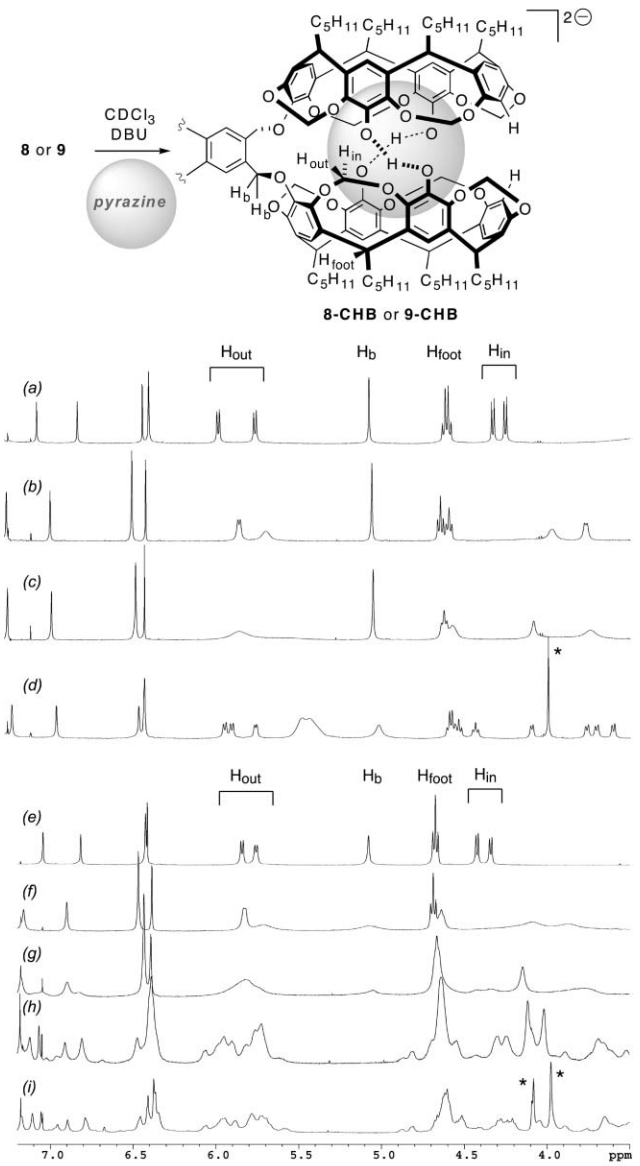


Fig. 2 500 MHz ^{1}H NMR spectra of the CHB complexes in $CDCl_3$ *(a)* bis-cavitand **8** and DBU at 25 °C; *(b)* bis-cavitand **8**, DBU and pyrazine at 50 °C; *(c)* bis-cavitand **8**, DBU and pyrazine at 25 °C *(d)* bis-cavitand **8**, DBU and pyrazine at −40 °C; *(e)* tetrameric-cavitand **9** and DBU at 25 °C; *(f)* tetrameric-cavitand **9**, DBU and pyrazine at 50 °C; *(g)* tetrameric-cavitand **9**, DBU and pyrazine at 25 °C; *(h)* tetrameric-cavitand **9**, DBU and pyrazine at −40 °C; *(i)* tetrameric-cavitand **9**, DBU and pyrazine at −55 °C. (Peaks marked * are encapsulated pyrazine.)

4.0 ppm, *i.e.* one signal for each diastereomeric complex [Fig. 1*(d)*].‡

Similar results are obtained with reversible charged hydrogen bonded (CHB) capsules[10] derived from tetraphenol **8** and octaphenol **9**, the relevant ^{1}H NMR spectra of which are reproduced in Fig. 2. Upon addition of pyrazine to a deuterated chloroform solution of host **8** and DBU, a new CHB complex is observed [*cf.* Fig. 2*(a)–(c)*]. Capsule **8-CHB** exists as a pair of enantiomeric twistomers. At 50 °C these twistomers are rapidly interconverting, thus a time-averaged spectrum is observed. At −40 °C, this interconversion is slow on the ^{1}H NMR timescale, hence the apparent plane of symmetry is broken and protons from each hemisphere of the host become non-equivalent [Fig. 2*(d)*]. Nevertheless, the protons from the pyrazine guest give rise to a sharp singlet at *ca.* 4.0 ppm.

Upon addition of pyrazine to a deuterated chloroform solution of tetrameric-cavitand **9** and DBU, the pyrazine CHB complex is the only species observed in solution [*cf.* Fig. 2*(e)*, *(f)* and *(g)*]. Given the complexity of the low temperature ^{1}H NMR spectrum of **8-CHB**, the convoluted nature of that of **9-CHB**, with its two diastereomeric bis-capsules, is not surprising. Even so, as witnessed with bis-hemicarceplex **12**, two relatively sharp singlets due to encapsulated pyrazine at *ca.* δ 3.9 and 4.1 ppm are visible in the spectrum of **9-CHB** at −55 °C [Fig. 2*(h)* and *(i)*].

It is hardly remarkable that encapsulated guests in diastereomeric complexes experience different environments. It is noteworthy, however, that a conformational change within *one* cage of **12** or **9-CHB** is causing a change in the environment of *the other* encapsulated guest. Such a property is worthy of further scrutiny.

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Notes and references

‡ In addition to the increased complexity observed upon cooling, certain host and guest signals of CHB complexes and hemicarceplexes shift upfield [see Fig. 1*(b)*, *(c)* and *(d)*]. This interesting phenomenon has been observed previously.[11]

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