Effects of remote chiral centers on encapsulated molecules†

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Received (in Durham, UK) 3rd December 2007, Accepted 8th February 2008
First published as an Advance Article on the web 28th February 2008
DOI: 10.1039/b718595b

A guest encapsulated in a hybrid molecular assembly is affected by remote chirality attached to both capsular components; these effects span significant distances and become additive or subtractive, based on relative configurations.

The transfer of chiral information is typically achieved through two different means: through-bond, in which a chiral center transfers information to adjacent nuclei, or through-space, in which steric interactions influence recognition between two separate molecules. The dipole moment of a chiral molecule has been shown to be a function of both induced electric and magnetic fields.[1,2] This property manifests itself optically in a polarimeter and magnetically through the observation of non-equivalent chemical shifts by an NMR spectrometer. In the latter experiment, steric effects are almost exclusively invoked to explain spectra, as the magnetic component is easily overlooked, since intermolecular NOEs are rarely encountered.[3] Reversible encapsulation complexes can be employed to expose such effects, since their lifetimes permit the detection of phenomena that cannot be seen through diffusion encounters in solution. We have been concerned with the separation of the steric and magnetic aspects of chiral information transmitted from one molecule to another by placing physical barriers between them.[4] In related work, others have shown that chiral information can be transmitted from "donor" to "acceptor" over a distance corresponding to more than seven C–C sp^3 bonds.[5,6] We describe here the combined effects of two remote chiral donors on reversibly-encapsulated acceptors.

Recently, we demonstrated the self-assembly of a new hybrid capsule[7] from two different capsules,[8,9] in response to the presence of appropriate guests (Fig. 1). This was an exception to the rules of self-sorting;[10] thus the hybrid affords an opportunity to append different chiral elements to the top, bottom, or both parts of the capsule and to detect the effects on guests held inside.

We prepared resorcinarenes **1**, **3**, **5** and **7**, and cavitands **2**, **4** and **6** (Fig. 2) with remote chiral elements, as described earlier.[4] Guest **G** was selected to show a singlet for two acceptor nuclei (expected to be rendered diastereotopic) and to show a strong preference for the relative orientation as one of two carceroisomers.[11] On encapsulation in **1**·**2**, guest **G** preferred the orientation shown in Fig. 1 in excess of 8 : 1 (in the minor isomer, **G** is rotated 180°). The encapsulated *gem*-dimethyl protons appeared as a sharp singlet in the upfield region of the ^{1}H NMR spectrum.

First, we took chiral resorcinarene **3**, cavitand **4**, and the achiral components **1** and **2**, and examined the magnetic effects of all possible combinations on guest **G**. Hybrid assemblies **1**·**2**, **1**·**4**, **3**·**2** and **3**·**4** were studied, and compared using ^{1}H NMR spectroscopy (Fig. 3). The achiral capsule **1**·**2** is shown first (Fig. 3A), and illustrates that both hydroxyl groups of the resorcinarene **1** and the *gem*-dimethyl groups of **G** are chemical shift-equivalent (as expected in a non-chiral environment). Also, the guest is positioned as required: the toluic methyl of **G** is farther upfield in this major isomer (not shown) and thus resides in the cavitand half, as illustrated in Fig. 1. Next, in **3**·**2** (Fig. 3B), we modified the resorcinarene module to localize four chiral groups closest to our probe. The *gem*-dimethyl groups were rendered diastereotopic by the chiral centers of **3**, resulting in a $\Delta\delta = 0.022$. Also surprising was the differentiation that occurred in the resorcinarene's hydroxyl groups; its downfield signals separate with a $\Delta\delta = 0.192$. The small downfield signals are assigned to the minor carceroisomer. In **1**·**4** (Fig. 3C), we then placed the chiral elements at the "feet" of the hybrid capsule. As expected, the effects decreased because of the increased distance from donor to acceptor. A final comparison was provided by **3**·**4** (Fig. 3D), in which the observed $\Delta\delta$ values for the resorcinarene hydroxyl groups and the encapsulated guest was the mathematical sum of the two mixed capsules.

The additive effect of chiral groups of the same handedness—even at great distances from probe nuclei—led us to examine capsules of mixed handedness. A reasonable route to the enantiomers of **3** and **4** was not apparent, but

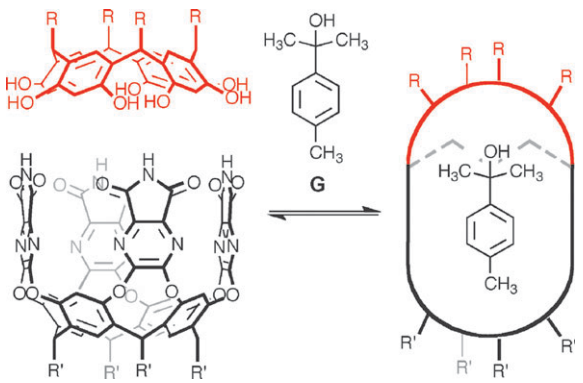

Fig. 1 Hybrid capsule assembly of resorcinarene (red) and cavitand (black) modules around template guest **G**.

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† Dedicated to Professor Jerry Atwood on the occasion of his 65th birthday.

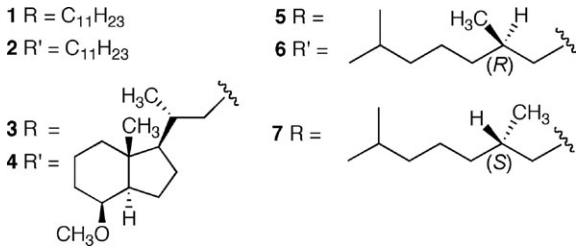

Fig. 2 Hybrid capsule building blocks. Odd numbers refer to resorcinarene functionalization (R), even numbers refer to cavitand functionalization (R′), as illustrated in Fig. 1.

resorcinarene **7** and the cavitand built upon it have been previously reported.[4] We prepared **7**'s antipode **5** uneventfully starting from commercial (*R*)-(+)-citronellol. The encapsulation of **G** in hybrid **5·2** showed only a modest differentiation (Fig. 4A), and was considerably attenuated compared to that of **3·2**. This is likely to be due to the differing number of stereogenic centers of the respective feet of **3** *vs.* **5**. In both cases, the distance between the closest chiral center and the guest should be the same, since a methylene spacer and an aromatic wall are common to both hybrids. An increased distance between donor and acceptor decreased the $\Delta\delta$ in **1·6** (Fig. 4B). When both halves of the capsule were chiral, we again saw a mathematical sum of the individual effects in **5·6** (Fig. 4C). The mixed-handed capsule **7·6** gave an effect somewhere in between that of the chiral resorcinarene module *vs.* the chiral cavitand module (Fig. 4A *vs.* Fig. 4B). The inherent

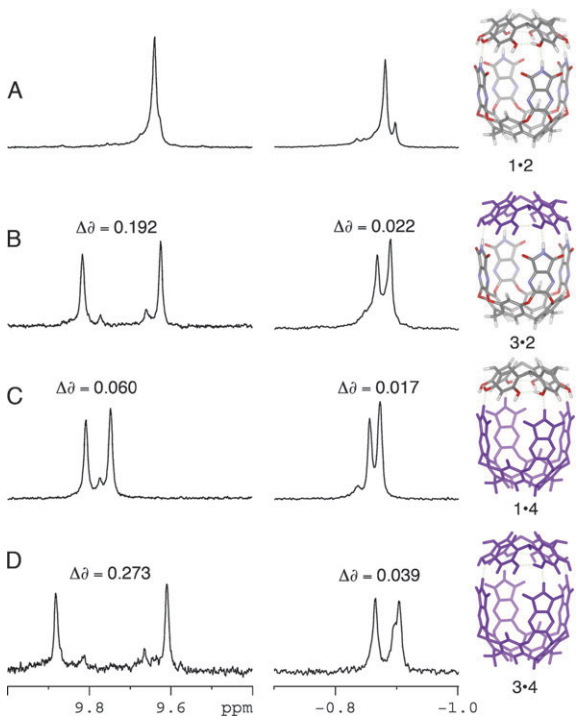

Fig. 3 Downfield (showing resorcinarene hydroxyl groups) and upfield (showing isopropyl group of guest **G**) regions of the ^{1}H NMR spectra of **1·2** (A), **3·2** (B), **1·4** (C) and **3·4** (D). Chiral non-racemic modules illustrated in purple. 0.5 mM of **1** or **3**, 3 mM of **2** or **4**, 40 mM of **G**, 600 MHz, 300 K, mesitylene-d_{12}.

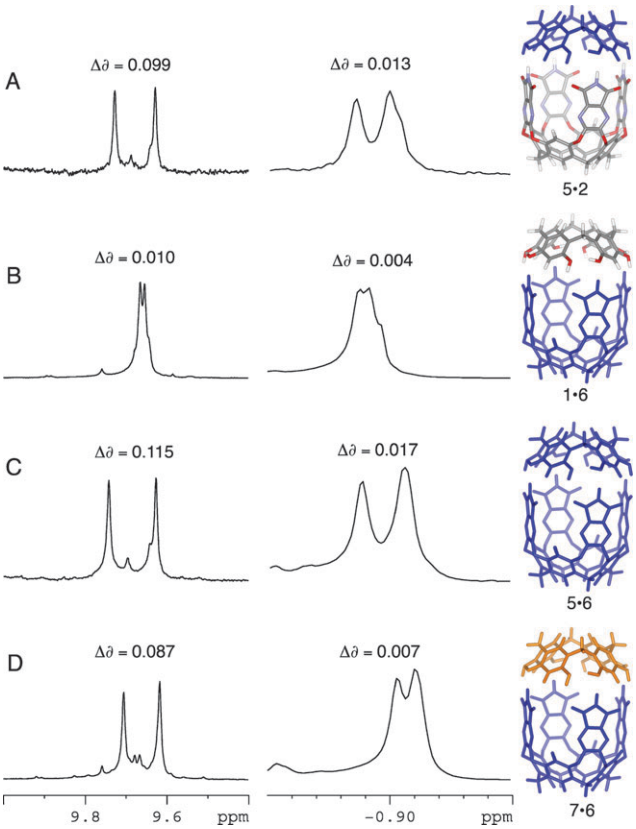

Fig. 4 Downfield (showing resorcinarene hydroxyl groups) and upfield (showing isopropyl group of guest **G**) regions of the ^{1}H NMR spectra of **5·2** (A), **1·6** (B), **5·6** (C), and **7·6** (D). Chiral non-racemic (*R*) modules illustrated in blue, (*S*) in orange, achiral in grey. 0.5 mM of **1**, **5** or **7**, 3 mM of **2** or **6**, 40 mM of **G**, 600 MHz, 300 K, mesitylene-d_{12}.

inaccuracy of $\Delta\delta$ at this resolution leads us to the tentative conclusion that the effects of mixed handedness are *subtractive*. The downfield hydroxyl groups 0.099 (Fig. 4A) − 0.010 (Fig. 4B) = 0.089 can be compared to the measured 0.087 (Fig. 4D), and the results are in good agreement. From the perspective of the guest, the calculated difference of 0.013 − 0.004 = 0.009 is also reasonable when compared to the measured value: 0.007 (Fig. 4D).

These results are consistent with additive or subtractive effects based on handedness and distance. It remains to be determined precisely which of the two diastereotopic nuclei is which. This may be of significance in terms of the sign of $\Delta\delta$ for a given assembly. One could imagine that the 'pro-*R*' and 'pro-*S*' methyl groups invert their relative locations as a function of the handedness or location of external chiral elements. We currently have no evidence to suggest that this is the case, but future syntheses should resolve this proposal. More challenging will be the providing of a theoretical account that can be used to explain these results. The four chiral centers found in **5** and **6** relay their information to an encapsulated guest, despite having a small chiral dipole moment. The addition of more chiral centers, as found in **3** and **4**, makes this point clear. In both cases, however, significant distances exist between these chiral elements and the acceptor. Perhaps even more interesting is how these effects work in tandem.

This hybrid assembly represents an advance in encapsulation methodology. Appropriate guests can serve as templates, resulting in exclusive hybrid formation, in preference to dimeric cavitand and hexameric resorcinarene capsules. This hybrid system also provides predictable orientation of the guest in the host and affords the opportunity to place specific functional groups in close proximity to encapsulated guests, if not directly in contact with them.[12] Applications of hybrid assemblies and a more detailed account of the theoretical aspects encountered herein[13] will be reported in a sequel to this article.

We are grateful for financial support from the Skaggs Institute and the NIH (GM50174). M. P. S. is a Skaggs Postdoctoral Fellow. We thank Dr Dariush Ajami for helpful discussions and Dr Siddhartha Shenoy for compound **7**.

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