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Steric and Magnetic Asymmetry Distinguished by Encapsulation

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Chiral objects in achiral containers create chiral *spaces*. For meaningful (or measurable) consequences there is a requirement of scale: A single glove in a room or a single molecule in a flask is less likely to affect the behavior of the remaining space than a glove in a small box or a molecule in a nanoscale chamber. We recently provided an example of the latter by coencapsulation of styrene oxide with isopropyl chloride[1] (Figure 1). The guests are held in the host capsule for ca. 0.5 s, and a chiral guest has ample opportunity to provide an effective asymmetric environment for its coencapsulated partner. Accordingly, the encapsulated halide shows diastereotopic methyl groups in its NMR spectrum. The present research was undertaken to determine if a chiral element outside the capsule could influence the environment of the space inside. That is, can the methyl groups of a guest be observed diastereotopically only because of chirality outside of the capsule? We are aware of the desymmetrization of a space using chiral molecular capsules made of covalent bonds,[2] hydrogen bonds,[3] or metal/ligand interactions.[4] However, we are unaware of cases where an achiral space is affected by remote chiral elements. Here we show this effect.

The cylindrical capsule **1a**[5] (Figure 2) was chosen to explore the effect. This capsule **1a** forms reversibly in organic media when suitable guests are present. The lifetime of the host capsule is ~0.5 s, long enough to observe guests inside by conventional NMR techniques under ambient conditions. We synthesized a series of capsules **1b**−**f** from the respective octols **2b**−**f**, in which the number of asymmetric centers and their distance from the capsule varies. The shorter **1b** has the array of asymmetric centers one CH_2 group closer to the ends of the capsule than **1c**, while the longer **1d** has the array one CH_2 group further away. These were prepared from permethylated cholic acid following the procedure Kobuke[6] described for **2c**. In addition, the asymmetric environment provided by **1e** resembles that of **1b** but with fewer asymmetric centers. Finally, in **1f** only one asymmetric carbon is on each of the eight pendant chains with a single CH_2 spacer between capsule and the chiral center.

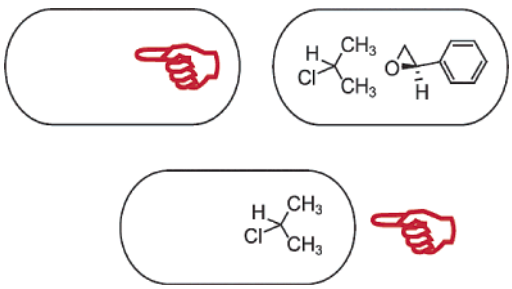

Figure 1. Top: (left) a chiral object (hand) in an achiral container leaves a chiral space; (right) the methyl groups of isopropyl chloride are diastereotopic in the coencapsulation complex with styrene oxide. Bottom: can a chiral center outside the capsule affect the behavior of the methyl groups of isopropyl chloride?

The number of guests and their general positions in the capsule were also varied: three isopropyl chlorides **4** are taken up by each capsule; a single isopropyl chloride **4** is coencapsulated with naphthalene **6** when both are present, and a single molecule each of the longer biphenyl derivatives **5**, **7**, and **8** are encapsulated (Figure 3). The capsules with three molecules of **4** show NMR signals for the guests at the ends of the capsule and a separate signal for the guest in the middle. The guests tumble freely but cannot exchange their positions while within the capsule.[7] The coencapsulation of **4** and **6** also features an isopropyl chloride at one end of the capsule, but the large size of the naphthalene limits the mobility of the smaller guest.[8] The length of **5** allows some sliding within the capsule, while this motion for the longer **7** and **8** is limited. The methyl groups of the isopropyl esters are forced deep into the ends of the capsule and are positioned close to whatever

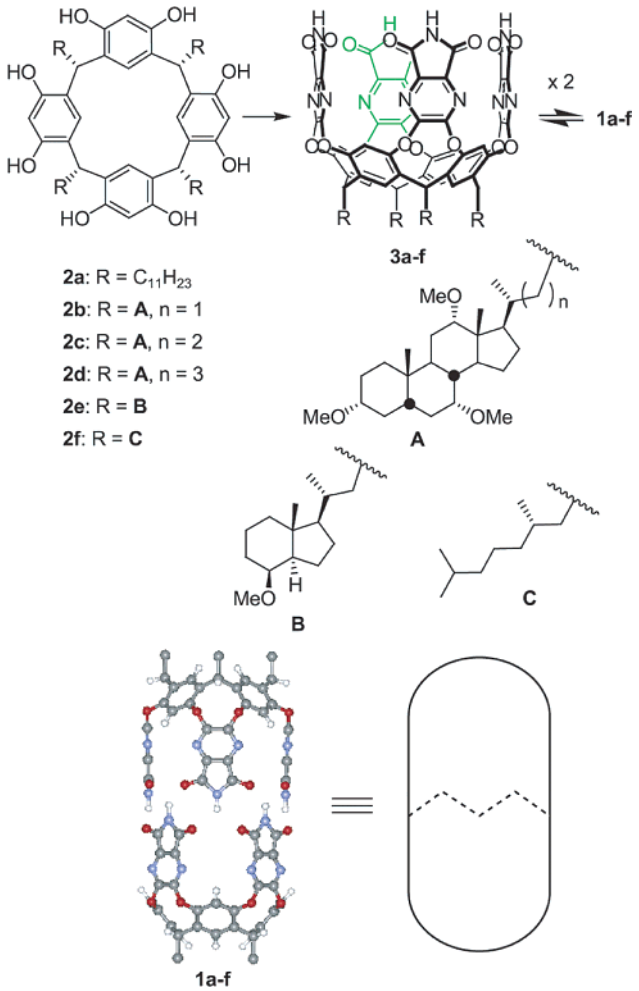

Figure 2. Synthesis of the capsule **1a**−**f**. A ball-and-stick representation of the dimeric capsule and its cartoon representation are also shown.

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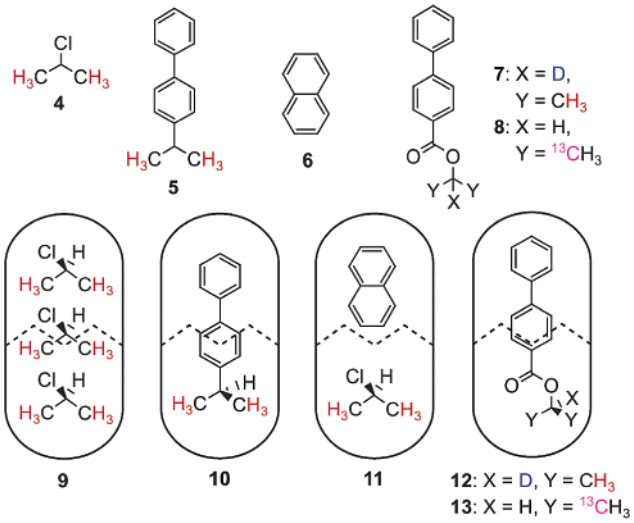

Figure 3. Guests and inclusion complexes.

Table 1. $\Delta\delta$ between Diastereotopic Methyl Groups of Encapsulated Species[a]

	complex	9	10	11	12	13
	PC[b]	53%	45%	47%	50%	50%
	$\Delta\delta$ between diastreotopic methyl groups [Hz]					
host	**1b**	0	5.9	16.1	13.2	13.8[c]
	1c	0	0	0	4.4	0[c]
	1d	0	0	0	0	
	1e	<2	7.3	19.1	14.7	16.1[c]
	1f	0	0	6.6	5.9	8.0[c]

[a] Capsule: 1 mM, guest: excess, mesitylene-d_{12}: 0.6 mL, 300 K, 600 MHz. [b] PC was calculated on the basis of the volumes which were minimized with the program Hyperchem 7.0, Hypercube Inc., 2002, at semiempirical PM3 level and calculated with WebLab Viewer Pro 4.0 by Molecular Simulation, Inc. [c] ^{13}C NMR (Apt) experiment (150 MHz).

anisotropy is on offer from the asymmetric centers just outside. The deuterated derivative **7** simplifies (and amplifies) the signals of the methyl groups in its ^{1}H NMR spectra, whereas the labeled **8** offered the advantages of ^{13}C NMR spectroscopy. The results of the spectroscopy are summarized in the Table 1.

None of the guests in capsule **1d** showed any evidence of the anisotropy of its exterior asymmetric centers. Nor did any capsules containing only **4**. Yet the influence of the chiral centers outside capsules **1b**, **c**, **e**, and **f** was clearly present inside and experienced by other guests. Specifically, Figure 4 shows the ^{1}H NMR signals for the methyl groups of **7** in all of the capsules. A singlet appears only in the achiral **1a** and the capsule with the most distance between asymmetric centers and the cavity **1d**. The other cases show diastereotopic methyl groups. The distance between external asymmetric centers and the cavity is a factor as is the mobility of the guests within since neither the longest spacer of capsule **1d** nor the freely tumbling guest **4** showed any evidence of desymmetrization. Unexpectedly, the sheer number of asymmetric centers is insufficient (there are 88 in **1b**−**d** but only 8 in **1f**).

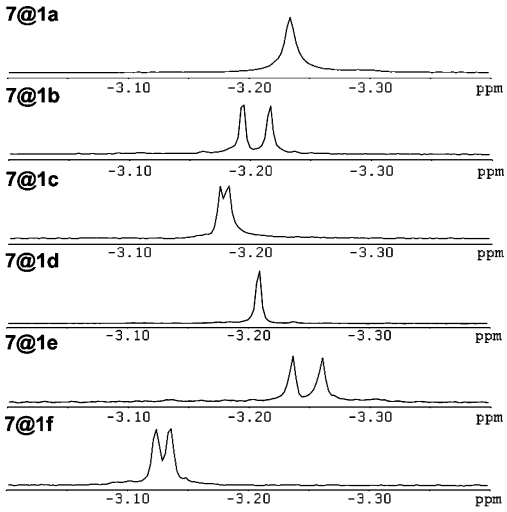

Figure 4. Upfield region of the ^{1}H NMR spectra (600 MHz, 300 K) of encapsulation complexes of **1a**−**f** (1 mM) in mesitylene-d_{12} (0.6 mL) and the guest **7** (1.5 μL).

In summary, we detected the effect of chiral elements outside the capsule through the desymmetrization study where there is no direct contact between the guest and asymmetric centers.[9] For the present, the search for the origins of biological homochirality could be expanded to include influences such as those shown here that are more remote than previously thought possible.

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Supporting Information Available: Synthetic details and spectroscopic data for all of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) It is conceivable that the asymmetric centers somehow affect the shape of the capsule. The many negative results (zeroes in the table) argue against this possibility.

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