Communication

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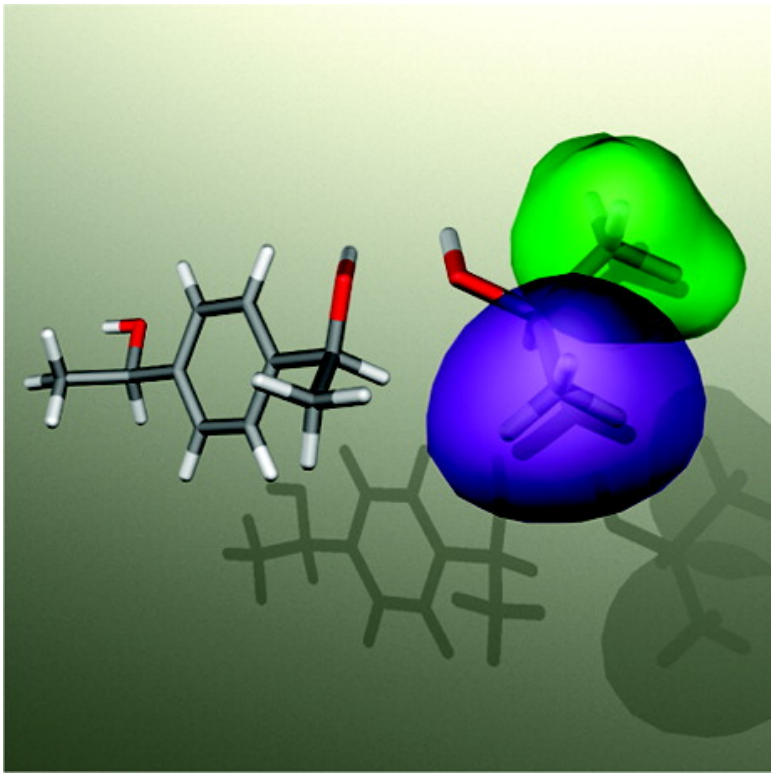

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Influence of Remote Asymmetric Centers in Reversible Encapsulation Complexes

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Molecular encounters in solution are short-lived and chaotic: two molecules collide more or less at random then diffuse apart to find new partners within nanoseconds. In contrast, for reversible encapsulation complexes such as **1·1** (Figure 1) the length of the encounter is nearly 1 second and the limited volume results in high concentrations (~4 M).[1,2] Moreover, the restricted sliding and tumbling of coencapsulated molecules make for arrangements that feature specific intermolecular contacts, stabilize reactive intermediates,[3] and lead to regioselective reactions.[4] Here we report the effects of remote asymmetric centers on two molecules held at such close range. We use NMR spectroscopy to reveal intermolecular phenomena that cannot be observed in bulk solution. Elsewhere, we have described the appropriate filling of space in **1·1**[5] and how guests can create chiral spaces in this achiral capsule.[6] These features are relevant to the question at hand: Can a guest **G** sense whether the remote site of the coencapsulated diol-**2** is *R* or *S*, that is, can **G** see "through" the nearby asymmetric environment and beyond the aromatic spacer to the other end of the capsule more than 10 Å away?

Diols[7] *meso*-**2**, (*S*,*S*)-**2**, and (*R*,*R*)-**2** were chosen to explore the effects of remote chirality using the identical constitution at each asymmetric center to make the comparisons more interpretable. A single molecule of **2** does not fill enough space in the capsule, but two such molecules cannot be accommodated. Accordingly, capsule formation can occur only when a complementary co-guest **G** is present with **2**. Diols **2** are too long to tumble within the capsule, so only one end of the diol is presented to the co-encapsulated **G** in each capsule. For example, isopropanol was coencapsulated with both *meso*-**2** and (*S*,S)-**2** (Figure 2). In both complexes the isopropyl methyl groups were rendered diastereotopic owing to the nearby chiral environment. With *meso*-**2** the $\Delta\delta$ for isopropanol's methyl groups is 0.21 ppm; with (*S*,*S*)-**2** the $\Delta\delta$ increased to 0.27 ppm. These results indicate that isopropanol's NMR signals are affected by the remote center. The encapsulation event brings the two guests together for a significant amount of time such that both the local and remote stereocenters are recorded by an achiral co-guest.[8] The imide N−H resonances of the capsule were also affected, but the effects were much smaller. The restricted confines of **1·1** afford an environment where an achiral molecule (*meso*-**2**) can desymmetrize another achiral molecule (isopropanol). These effects were not observed in the absence of **1·1**.[9]

Earlier we reported that coencapsulation of two chiral molecules in **1·1** showed diastereoselection.[5,10] The coencapsulation of chiral propylene oxide **3** with diols **2** has this potential as well. Encapsulation of (*R*)-**3** with (*S*,*S*)-**2** (Figure 3A) or (*S*)-**3** and (*S*,*S*)-**2** (Figure 3B) shows different upfield ^{1}H NMR spectra for the methyl group of **3**. These differences are due to the influence of both the local and remote asymmetric centers of **2**. To determine diastereoselectivity, *rac*-**3** was coencapsulated with (*S*,*S*)-**2** (**C**) demonstrating that (*S*)-**3** is preferentially encapsulated with (*S*,*S*)-**2** over (*R*)-**3** (dr, 1.3:1). Next, we coencapsulated *meso*-**2** with (*S*)-**3** (**D**). In this experiment (*R*,*S*)-**2** (*meso*-**2**) can adopt two different orientations inside the capsule, which gives rise to two different observed

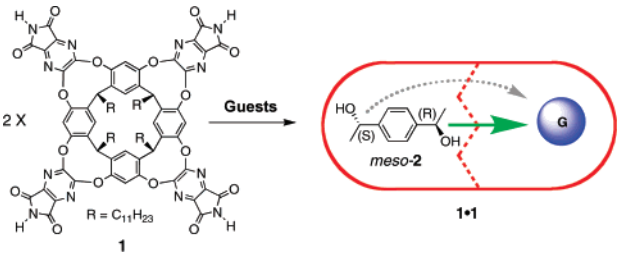

Figure 1. Chemical structure of cavitand **1** and schematic representation of the cylindrical capsule **1·1** with encapsulated guest *meso*-**2** and co-guest "**G**". The influence of chirality from steric effects and close contacts on guest **G** are represented with a green arrow; the gray dashed arrow is used to represent the magnetic effects of the remote center.

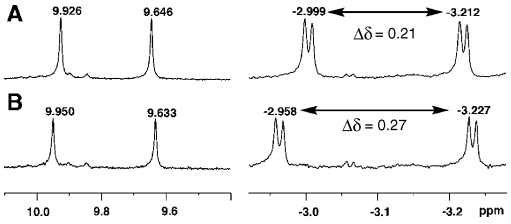

Figure 2. Downfield (showing capsule imide resonances) and upfield (showing encapsulated isopropanol) regions of the ^{1}H NMR spectra of isopropanol coencapsulated with *meso*-**2** (A), (*S*,*S*)-2 (B), (1.8 mM **1·1**, 36 mM isopropanol, 36 mM *meso*-**2**, or (*S*,*S*)-**2**, 300 K, mesitylene-d_{12}).

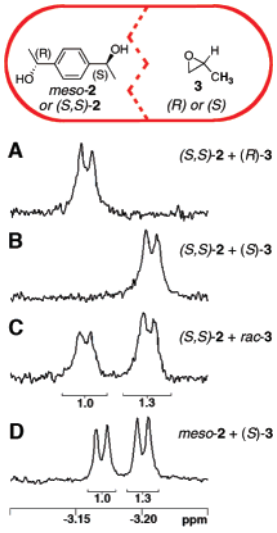

Figure 3. Upfield regions of the ^{1}H NMR spectra of (*R*)-propylene oxide **3** coencapsulated with (*S*,*S*)-**2** (A), (*S*)-**3** and (*S*,*S*)-**2** (B), *rac*-**3** and (*S*,*S*)-**2** (C), and (*S*)-**3** and *meso*-**2** (D).

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Table 1. Chemical Shift Data for the Upfield Region of the ^{1}H NMR Spectra of Propylene Oxide **3** Coencapsulated with **2**[a]

entry	guests	δ (ppm)
1	(*S*,*S*)-**2** + (*R*)-**3**	−3.158
2	(*R*,*S*)-**2** + (*R*)-**3**	−3.169
3	(*S*,*S*)-**2** + (*S*)-**3**	−3.207
4	(*R*,*S*)-**2** + (*S*)-**3**	−3.201

[a] The stereochemical designators under "guests" indicate relative orientation of asymmetric centers inside the capsule based on our assignments (300 K, 1.5 mM **1·1**, 36 mM **2,** 86 mM **3**, mesitylene-d_{12}).

isomers. By comparing the diastereoselectivity via the isomeric ratios observed in Figure 3C and D, we were able to assign all the peaks (see Supporting Information (SI)). The magnitude of diastereoselection using *meso*-**2** and (*S*)-**3** is identical to that observed for the combination of (*S*,*S*)-**2** and *rac*-**3** thus we infer that the major social isomer[11] in Figure 3D is the one in which the (*S*)-center of *meso*-**2** is situated in the center of the capsule near (*S*)-**3**. This result is expected if direct steric contacts between propylene oxide and the local stereocenter of **2** cause the selection. We used our assignment to calculate the remote effects of chirality on **3** (Table 1). Entries 1 and 3 correspond to Figure 3A and 3B, respectively. Entry 4 was assigned based on the arguments just listed such that the major diastereomer in Figure 3D is the (*R*,*S*)-**2** + (*S*)-**3**. The minor diastereomer is then (*S*,*R*)-**2** + (*S*)-**3** which would give the same chemical shift as its enantiomeric complex (*R*,*S*)-**2** + (*R*)-**3**, hence our assignment in entry 2. As a result, the effect of the remote stereocenter can be quantified by comparing entries 1 and 2 ($\Delta\delta$ 0.11 ppm) and entries 3 and 4 ($\Delta\delta$ 0.06 ppm).

When all three stereocenters have the same absolute configuration, **3** experienced the greatest shielding and is found farthest upfield (Figure 3B, Table 1 entry 3).

The arrangements are supramolecular diastereomers that, as a matter of course, have different properties, but the long distances between the relevant nuclei make the NMR results striking. Distortions of the capsule by guests might give such long-range effects through an induced chiral host conformation, but no such distortion was detectable in CD spectra (see SI). To remove the effect of the local asymmetric center we prepared (*S*)-1-(4′-hydroxyphenyl)ethanol, **4** (see SI).[12] Coencapsulation of **4** with **3** resulted in the major social isomer that positioned the phenolic hydroxyl near the center of capsule **1·1** and isolating the remote asymmetric center. The NMR spectrum of the assembly of (*S*)-**3** and (*S*)-**4** showed an upfield signal at −3.07 ppm for **3**, whereas encapsulation of (*R*)-**3** and (*S*)-**4**, showed the signal at −3.03 ppm (see SI). Again, the remote stereocenter exerts differentiation of the chemical shifts of these diastereomers. The sensing of remote chirality in *covalently* linked molecules is common: for example, an asymmetric center seven C−C sp^3 bond lengths away in a helical structure could be detected.[13] Additionally, a supramolecular assembly using Xe in a cryptophane revealed that an asymmetric center seven covalent bonds away could be differentiated.[14] Finally, observations with a self-assembled cylindrical capsule **1·1** with chiral "feet" also yielded success in separating the magnetic from the steric effects of chirality.[15] The walls of the capsule align the diols and fix their asymmetric centers in space such that **G** is presented with their steric and magnetic effects for a prolonged time—some 10^9 times longer than they would as diffusion complexes in solution. These effects are based on the handed matching ((*S*,*S*)-**2**) or mismatching (*meso*-**2**) of the asymmetric diol centers and that gives rise to different magnetic asymmetric environments felt by the encapsulation partners. To the best of our knowledge, this remote intermolecular interaction has not been otherwise observed. The differentiation we observe due to the remote asymmetric functions of **2** on its encapsulation partner **G** cannot be explained by steric arguments: the relevant centers are separated by a benzene ring and the proximal asymmetric function. So what gives rise to this phenomenon? We propose that these remote effects are strictly magnetic. The induced dipole moment responsible for chiral electro-optical effects has an often overlooked magnetic component,[16] but recent experiments have also demonstrated that a chiral molecule can induce a chiral solvent structure.[17]

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Supporting Information Available: Experimental data for experiments discussed but not illustrated in the text are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For experiments using acetone or CH_2Cl_2 as coguests, see the SI.
(9) *Meso*-**2** and (*S*,*S*)-**2** or (*R*,*R*)-**2** had almost superimposable ^{1}H NMR spectra (CDCl3, 600 MHz). When we titrated isopropanol with (*R*,*R*)-**2** in the absence of **1·1**, a slight upfield shift of isopropanol's methyl groups occurred. Diastereotopic splitting was not observed.
(10) For instance, (*S*)-mandelic acid was shown to prefer (*R*)-2-butanol over the (*S*)-isomer by 1.3:1.
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