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Constellational diastereomers in encapsulation complexes

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Three chiral guests in a cylindrical capsule led to six diastereomeric complexes.

Encapsulation complexes involve guests surrounded by self-assembled hosts. The translational motion of the guest is obviously limited by the mechanical boundaries of the host, but rotation of the guest is harder to restrict.[1] In self-assembled hosts large enough to surround two or more guests,[2–4] the shape of the hosts can determine the translational and rotational limitations of the guests. For example, in the hexameric resorcinarene capsule[5,6] the 8 benzene guests tumble and spin about all three axes and exchange positions freely.[7,8] Within the cylindrically shaped host, most guests are too large to squeeze past each other and the alternate arrangements in space of two different guests can create social isomers (Fig. 1).[9,10]

Since tumbling of the longer guest in the capsule is slow on the NMR timescale, the two isomers show different spectra. We introduce here a form of isomerism arising from the limited motion of enantiomeric guests within this host and use NMR methods to identify the resulting diastereomeric constellations.

The cylindrical capsule self-assembles in the presence of suitable solvents and encapsulates three molecules each of $CHCl_3$, dichloroethane or isopropyl chloride.[11] These guests are unable to exchange positions while inside the capsule and separate NMR signals are seen for the isomers.[12,13] Propylene sulfide also forms encapsulation complexes involving three guests in the capsule. Because of the asymmetric centers and the odd number of guests, each individual capsule is chiral.

The propylene sulfides (63 Å^3 each) fill some 45% of the space in the capsule, a low packing coefficient for liquids, but a high figure for gases. We prepared (*R*)-propylene sulfide from optically active (*S*)-propylene oxide and determined it to show 88% ee by the specific rotation {$[\alpha]_D^{20}$ +45.1° (neat)}.[14,15] Encapsulation of this (*R*)-propylene sulfide gave assignable signals in the upfield region of the ^{1}H NMR spectrum at 300 K (Fig. 3a). Two sets of methyl groups of the encapsulated guests were observed −2.59 ppm and 0.23 ppm, in a 2 : 1 ratio, respectively. The signals of the guests at the ends of the capsule are shifted much further upfield than the one in the center. The other protons of encapsulated propylene sulfides also had two sets of signals {CH_2 (−2.44, −1.74 and 0.64, 1.08 ppm) and CH (−1.67 and 1.49 ppm)} as identified by 1D GOESY experiments. A 2D NOESY spectrum showed cross peaks based on chemical exchange between encapsulated propylene sulfides and propylene sulfide in bulk solution; however, no cross peaks between upfield and downfield signals of the encapsulated guests were observed. These results indicated that the three guests in the capsule did not exchange their positions on the NMR time scale.

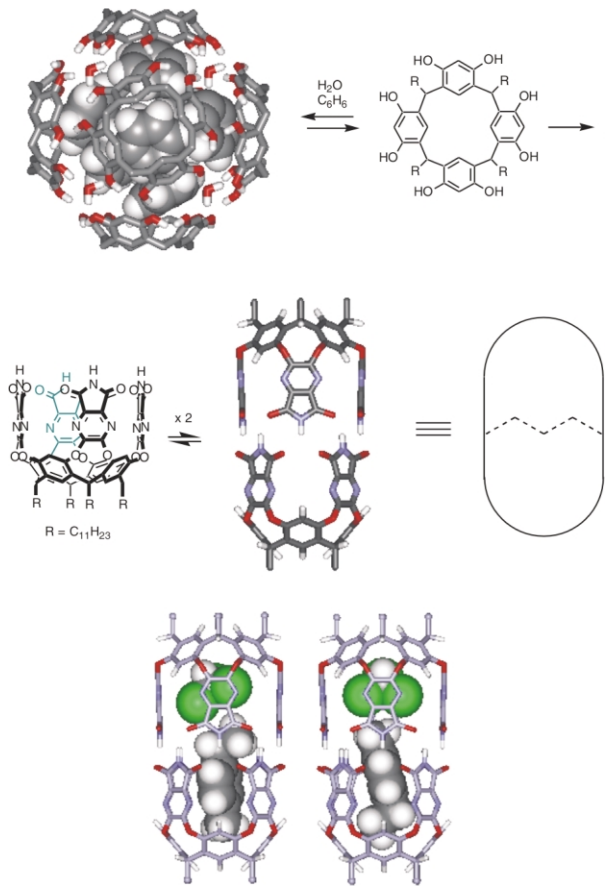

Fig. 1 Top: Line drawing of resorcin[4]arene monomer and space-filling model of eight benzenes in a hexameric capsule. Middle: Line drawing of subunit and ball-and-stick representation of the cylindrical capsule; cartoon representation used elsewhere is on the right. Bottom: Energy optimized structures (MM$^+$ force field) of isomeric encapsulation complexes of 4-ethyl toluene and chloroform.

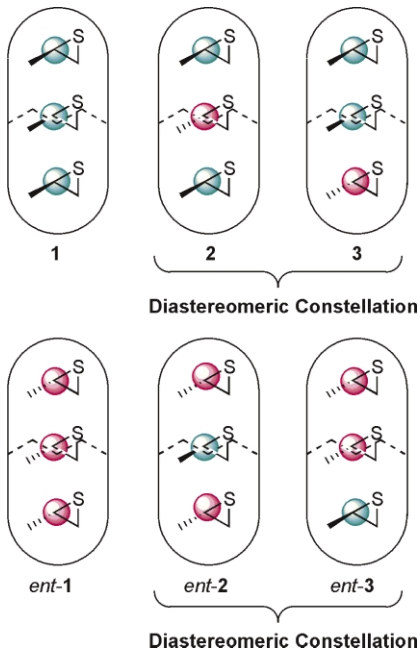

Fig. 2 The six different constellations of encapsulated (*R*) and (*S*)-proplylene sulfide.

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Additional small signals observed in the vicinity of each signal could result from isomer **2** and **3**, but were too broad to assign at room temperature. At lower temperature, the methyl groups of encapsulated propylene sulfides at the ends of the capsule were particularly well resolved. When all isomers are present, four sets of methyl protons can be observed around −2.7 ppm: one set from isomer **1**, one set from isomer **2** and two sets from isomer **3**. Indeed, the ^{1}H NMR spectrum of encapsulated racemic guest at 243 K showed four well resolved doublets around −2.7 ppm (Fig. 3e). Isomer **3** seemed more stable than isomer **2** because intensities of those signals were similar. Assignment of those signals was completed by experiments using guests with varying enantiomeric excesses. Intensities of signals were sufficiently resolved to assign each isomer in case of 60% ee (Fig. 3c). The most intense signal resulted from isomer **1** which encapsulated three of the same enantiomers. The most upfield doublet and the most downfield doublet in this cluster of signals can be assigned as isomer **3**, with two different enantiomers of propylene sulfides at the ends of the capsule. The other, more intense signal must represent isomer **2**, with the same enantiomer at each end of the capsule. Further reducing the optical purity of guest caused an increase in the relative intensities of isomers **2** and **3** (Fig. 3d). The encapsulation complexes presented characteristic spectra that are dictated by the enantiomeric excess of the guests, and made it possible to estimate their optical purity without other information. This process could be applied to other small chiral molecules. For example, propylene oxide gave different spectra corresponding to its optical purity even though the resolution was insufficient for assignment of each isomer (spectra not shown).

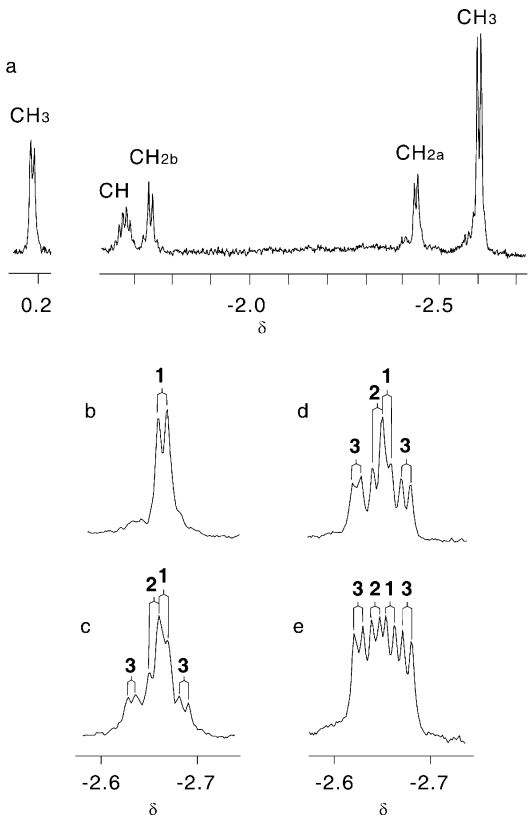

Fig. 3 Upfield region of the 1H NMR spectra (600 MHz) of encapsulation complexes of capsule (3 mM) in mesitylene-d_{12} (0.4 mL) and propylene sulfide (0.15 mL). a) (*R*)-Propylene sulfide (88% ee) at 300 K; encapsulated guests at the end of the capsule show CH_3 signals at −2.6 to −2.7 ppm, while the guest in the middle of the capsule shows the corresponding signal at ~0.23 ppm. b) (*R*)-Propylene sulfide (88% ee) at 243 K. c) (*R*)-Propylene sulfide (60% ee) at 243K. d) (*R*)-Propylene sulfide (30% ee) at 243 K. e) (±)-Propylene sulfide at 243 K.

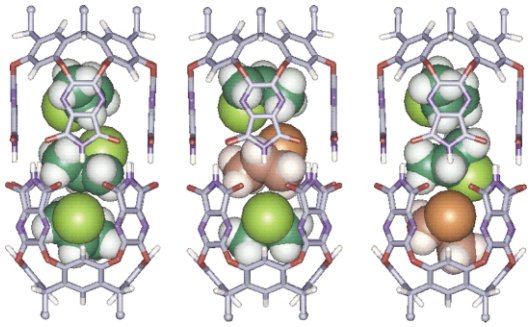

Fig. 4 Energy optimized structures (MM^+ force field) of encapsulation complexes: (*R*) isomer alone (left), (*R*)-(*S*)-(*R*) orientation (middle), (*R*)-(*R*)-(*S*) orientation (right).

In particular, the method could be useful for those small, chiral molecules that are difficult to resolve by HPLC or GC techniques.[16] In the future, a chiral host may allow determination of absolute configuration as well as optical purity. For now, the availability of the optically pure form allowed the identification of the diastereomeric constellations. Some energy minimized structures are shown in Fig. 4.

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