Stereochemical Relationships between Encapsulated Molecules

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Molecule-within-molecule complexes provide physical organic chemistry with the means to study intermolecular forces,[1,2] to stabilize reactive intermediates,[3,4] and to probe the characteristics of the liquid state.[5] A new form of stereoisomerism, carceroisomerism, due to restricted tumbling of a guest bound within an asymmetric host[6] was also discovered. Larger container molecules are now available and feature cavities that can accommodate more than one guest.[7,8] These function as reaction chambers for some bimolecular processes[9] and can even form complexes-within-complexes.[10] One of these systems revealed an unusual form of isomerism due to spatial relationships between the encapsulated species, and we describe it here.

The system involves molecular capsule **1•1**[8] (Figure 1), which

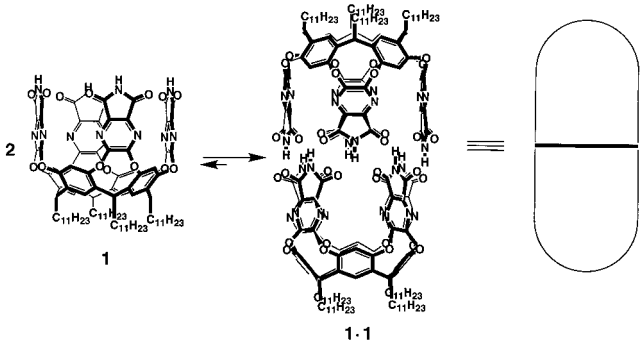

Figure 1. Two molecules of tetraimide (left) self-assemble through eight bifurcated hydrogen bonds into the cylindrical capsule **1•1** (center), which is represented by the cartoon (right).

is formed by the dimerization of tetraimide **1** in apolar organic solvents. The capsule is held together by hydrogen bonds and forms reversibly on time scales that range from hours to milliseconds. Because the capsule is cylindrical rather than spherical, guests experience and occupy various micro-environments along the cylinder's axis. The center, which is composed of eight imides, attracts—when possible—the more polar parts of

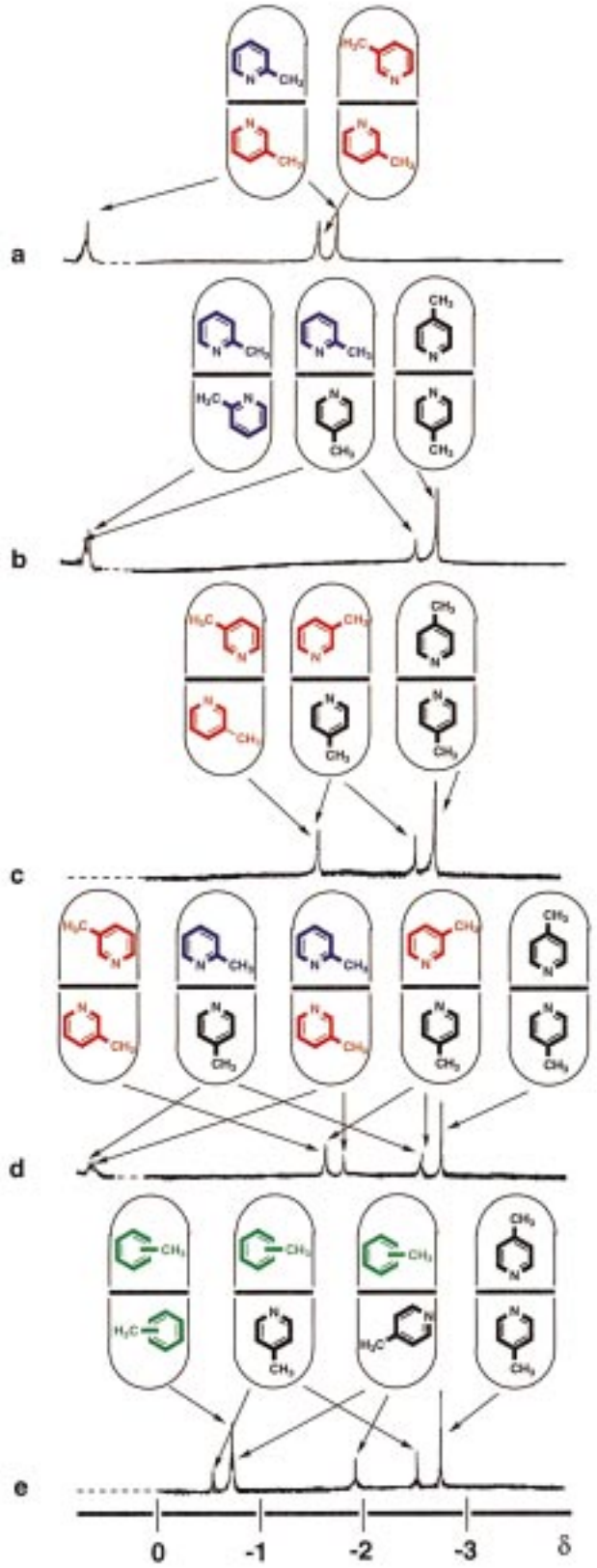

Figure 2. Upfield portion of the ^{1}H NMR spectrum (600 MHz) of homo- and heterocapsules, filled with picolines and toluene. In each experiment, equal amounts of the guests (ca. 30 equiv each) were added to a 0.5 mM solution of **1•1** in mesitylene-d_{12}, at 295 ± 1 K. (a) α- and β-picolines, (b) α- and γ-picolines, (c) β- and γ-picolines, (d) α-, β- and γ-picolines, (e) γ-picoline and toluene.

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Table 1. CH_3 Chemical Shifts (δ, ppm) for Encapsulated Guest−Molecules[a,b]

guest(s)	encapsulated species
α-picoline	0.58
β-picoline	−1.65
γ-picoline	−2.79
toluene	−0.78
α- + *β*-picolines	0.58, −1.88
α- + *γ*-picolines	0.60, −2.58
β- + *γ*-picolines	−1.65, −2.60
α-picoline + toluene	0.65, −0.84
β-picoline + toluene	−1.82, −0.49
γ-picoline + toluene	−1.95, −0.79 and −2.56, −0.56

[a] All encapsulation experiments were monitored by ^{1}H NMR spectroscopy (600 MHz, mesitylene-d_{12}, 295 ± 1 K). The spectra were taken at ca. 0.5 mM of **1•1** followed by addition of ca. 30 equiv of each guest. [b] The chemical shifts for the methyl groups in the bulk solution for toluene, α-, *β*-, and *γ*-picolines are, respectively: 2.11, 2.41, 1.78, and 1.76 ppm.

a guest, while the more hydrophobic parts of a guest molecule find themselves—perhaps by default—near the capsule ends. The chemical shift differences between guests in the bulk solution and those in the capsule are related to their positions in the cylinder. In the ^{1}H NMR experiment, α-, *β*- and *γ*-picolines gave complexes with two identical guests per capsule, homocapsules. When *γ*-picoline is encapsulated, the chemical shift of the methyl groups in the NMR spectrum places them near the ends of the cavity at −2.79 ppm (Table 1). The dipole involving the nitrogen, therefore, prefers the middle of the cavity, and at the methyl ends the change in shift ($\Delta\delta$) is maximal, 4.55 ppm! For the encapsulated *β*-picoline, the methyl chemical shift is −1.65 ppm ($\Delta\delta$ = 3.43 ppm), whereas with α-picoline, the methyl group is seen at 0.58 ppm ($\Delta\delta$ = 1.33 ppm) (Table 1). No evidence of line broadening was observed for any of the encapsulated heterocycles' signals on cooling; apparently, these guests spin along the long axis of the capsule but do not tumble about other axes.

When equal amounts of two different picolines were added to a mesitylene-d_{12} solution of **1•1**, in addition to the corresponding homocapsules, nonsymmetric heterocapsules were also formed, which are filled with two different guests. These guests are too large to move past each other within the capsule, and they can exchange their positions only by exiting the capsule and reentering it, a process that is slow on the NMR time scale. Accordingly, the capsule shows two sets of signals (two different ends) when two different guests are inside. The NMR assignment is shown in Figure 2 and is based on the data from Table 1. Moreover, when all three picolines were added to **1•1**, two homocapsules (*γ*-picoline and *β*-picoline filled) and three heterocapsules were clearly detected (Figure 2). Again, no dynamic processes were apparent in any of the spectra.

The situation is different for toluene. Encapsulated toluene shows one signal for the methyl group at −0.78 ppm. This must represent the weighted average chemical shift of all possible orientations for the two encapsulated guests.[8] When the sample is cooled, this signal disappears into the baseline (below 273 K) as may be expected for the dynamic process of tumbling, but no new upfield signals appear at temperatures down to the freezing point of the mesitylene-d_{12} solvent (233 K). Apparently, the favored species at low temperatures place the methyl groups nearer the center of the capsule. Even at 190 K (in toluene-d_8) the spectra indicated a symmetrically occupied capsule.

The peculiarity arises with the combination of toluene and *γ*-picoline: two (!) heterodimeric species were present at ambient temperature (Figure 2). Upon cooling of the sample to 0 °C, the peaks corresponding to toluene (−0.56 and −0.79 ppm) broadened and disappeared into the baseline, whereas the ones relative to the *γ*-picoline remained unchanged. The signals belonging to the host also remained unchanged. On heating, one of the signals for the encapsulated *γ*-picoline (−1.95 ppm) broadened and disappeared, whereas the other encapsulated *γ*-picoline signal (−2.56 ppm) remained. Accordingly, the same trend was observed for the signals of encapsulated toluene. Therefore, one of the isomers equilibrates to the other at higher temperatures. Neither of the other picolines showed dynamic behavior: a single heterodimeric species was observed for capsules containing toluene with α-picoline and toluene with *β*-picoline. In all cases the identities of the methyl signals for hetero-dimeric species were confirmed by experiments using toluene-d_8 and *γ*-picoline-*methyl*-d_3 as guests.

For the toluene/*γ*-picoline case, the chemical shifts for the *γ* methyls require their presence at the two positions shown in Figure 2e. In one isomer, the methyl group is deep in the hydrophobic end as shown by its ^{1}H NMR chemical shift (−2.56 ppm). The corresponding signal for the (tumbling) toluene is at −0.56 ppm. In the other isomer, the chemical shift of −1.95 ppm places the methyl group rather at the "meta" position (similar to the place it appears in *β*-picoline). The corresponding signal for the tumbling toluene in this case is at −0.79 ppm.

Why are there two isomers in this case? A tumbling molecule is likely to take up more of the capsule than a stationary one, and the co-guest picolines respond by getting out of the way. The new orientation of *γ*-picoline may reduce the space it takes up along the axis of the capsule. The cramped quarters allotted to *γ*-picoline result in an observable energetic barrier between its two conformations.

What is the relationship between the two isomers of the *γ*-picoline? They are diastereomers of a supramolecular sort reminiscent of carceroisomers, but they appear only in the presence of a second guest. More of these peculiar relationships are likely to emerge as the capsules become larger and able to accommodate more guest molecules, at which time some new nomenclature will be required to specify them. In the meantime, the control of guest orientations should lead to enhanced interactions or even reactions inside these cylindrical capsules. We are working toward these goals.

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