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Social Isomers in Encapsulation Complexes

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Stereoisomerism in supramolecular chemistry assumes many forms. When a single guest is entirely surrounded by a host,[1] the cramped quarters impose both subtle and obvious limitations on mobility. The internal dynamics of the guest—rotation around amide bonds[2] or ring inversions[3,4]—may be slowed, and rotational freedom such as tumbling is curtailed.[5] We introduce here a new form of isomerism that arises when two different guests are confined to a cylindrical, self-assembled host capsule. The shape and dimensions of the capsule prevent the guests from exchanging positions or tumbling on the NMR time scale. The phenomenon depends on matching guest size and shape with that of the host and on the interaction of the two guest molecules. Accordingly, we term it social isomerism: the orientation of one guest depends on the presence and nature of the other.

The isomerism is related to one discovered by Reinhoudt in covalently bound carcerand hosts.[6] There, the hindered rotation of a tightly bound guest revealed carceroisomerism: dimethylacetamide or 1-methyl-2-pyrrolidinone adopt two distinct orientations in a small cavity lacking a center of symmetry. Here, a self-assembled capsule, a host capable of reversibly surrounding two molecules, leads to diastereomeric arrangements. Access to assemblies with more than two encapsulated guests will, inevitably, present even more complex isomeric possibilities.

The new form of isomerism appears in complexes of $\mathbf{1}_2$[7] during its coencapsulation of typical solvent guests with para-substituted toluene derivatives, for example, $CHCl_3$ with *p*-ethyl- toluene (Figure 1). Two isomeric complexes are observed. The chemical shifts in the NMR spectrum are those expected for a major diastereomer with the ethyl group near the middle of the capsule and a minor one with the ethyl function near the end. The resonances in the NMR spectrum are sharp and well separated (Figure 2a). The exchange rate between isomers is slow on the NMR time scale at 600 MHz at room temperature; a sizable energetic barrier exists between the social isomers. In principle, the isomers could interconvert if the two guests exchanged places while inside the capsule or if the *p*-ethyl-toluene tumbled within the capsule. In practice, these two guests cannot squeeze past each other. Elsewhere we have shown that the two halves of the capsule maintain their identities during exchange of guests this size,[8] but as related below, some tumbling can be induced at higher temperatures.

The direct observation of two different encapsulated guests is hardly commonplace.[9,10] The two different guests must represent a lower-energy combination than other available arrangements, and this requirement is not easily met in capsules with centrosymmetry. Several neutral molecules are co-encapsulated with *p*-ethyl-toluene as the primary guest, and the relative amounts of the two social isomers states is altered. (Table 1). Two complexes were also

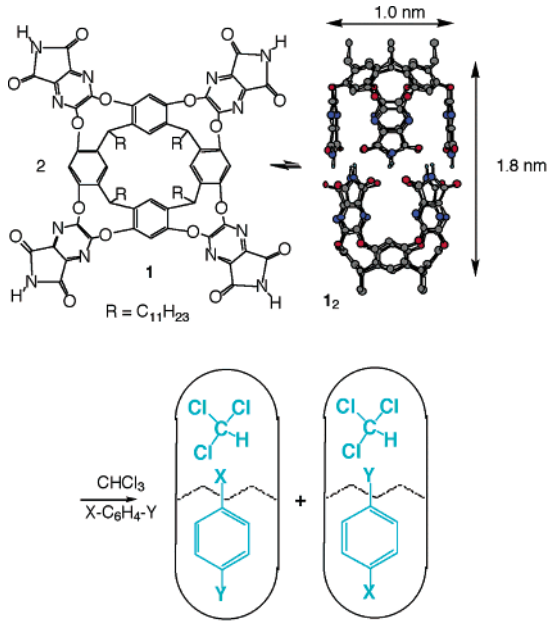

Figure 1. Line formula of subunit **1**; ball-and-stick and cartoon representations of capsule $\mathbf{1}_2$.

observed with 4-methylanisole as primary guests (Figure 2b). In all cases, the tolyl methyl group prefers the location shown in Figure 1, at the end of the capsule (in the cavity of **1**). The difference in energy between two diastereomeric capsules is modest and rarely exceeds 1 kcal/mol, a fortunate result since larger values would make the simultaneous observation of both isomers difficult. For the case at hand, the capsule's length encourages the pairing of a long guest with a short one, and the subtle energetic differences permit both social isomers to be present.

The social isomerism observed above allowed additional NMR experiments to address the guest exchange rate with bulk solvent and the tumbling rate within the cavity. Irradiation of the methyl signals of bulk 4-ethyltoluene at 295 K with a mixing time of 0.4 s resulted in no NOE's with the corresponding signals inside the capsule. When the temperature was increased to 323 K and the mixing time increased to 2 s, the expected exchange NOE's were observed. The saturation of signals of the more upfield shifted methyl groups (295 K, 0.4 s) resulted in the exchange NOE with their less shielded counterparts, while no effect was detected on the signals of corresponding methyl groups of bulk 4-ethyltoluene. Accordingly, in−out exchange is considerably slower than guest tumbling. Unexpectedly, the saturation of the methyl signal of the less shielded ethyl group with a mixing time of 2 s resulted in NOE with the singlet at 2.94 ppm corresponding to the co-encapsulated $CHCl_3$ molecule. In the optimized structures of this complex (Figure

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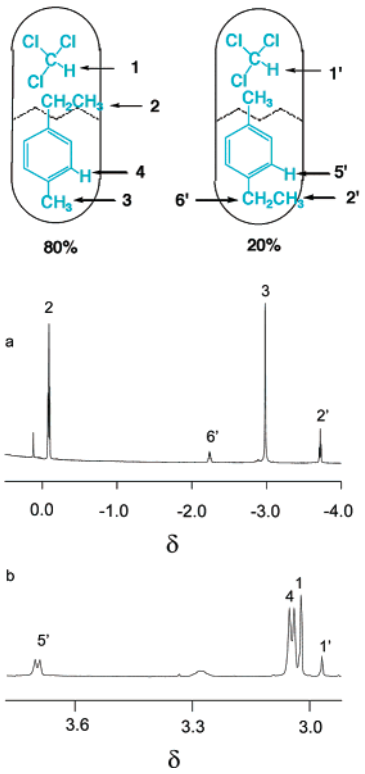

Figure 2. (a) The upfield window of the ^{1}H NMR spectrum of 4-ethyltoluene and $CHCl_3$ in $\mathbf{1}_2$ at 295 K (600 MHz, mesitylene-d_{12}, [$\mathbf{1}_2$] = 4 mM). (b) The midfield region of the same spectrum at higher amplitude. The assignments for the signals are shown in the cartoons.

Table 1. Coencapsulated Guests of $\mathbf{1}_2$, the Ratio of Social Isomers, Corresponding $\Delta\Delta G$ Values, and Packing Coefficients (PC)

guest 1	guest 2	Me-in[a]/ Me-Out	ΔΔG (kcal/mol)	PC
4-ethyltoluene	CH_2Cl_2	3:1	0.6	44
"	$CHCl_3$	4:1	0.8	49
"	CH_2ClCH_2Cl	4:1	0.8	49
"	Benzene	6:1	1.0	49
"	Cyclohexane	13:1	1.4	54
4-methylanisole	$CHCl_3$	4:1	0.8	46
"	CH_2Cl_2	5:1	0.9	42

[a] Refers to the position of the methyl in the cavitand of the resorcinarene substructure of the capsule as shown in Figure 3 (top, right).

3, top right) the distance between the methyl protons of the ethyl group and the chloroform molecule is 3.6 Å which can allow the intermolecular NOE. To the best of our knowledge this is the first observation of NOE between two different co-encapsulated guest molecules.

The motions of guests within encapsulation complexes are limited in a number of senses, and the social interactions of two guests result in the isomerism seen here: The orientational preference of one guest depends on the presence of the co-guest. As is apparent from the table, the presence of a large co-guest favors the isomer with the methyl near the ends of the cavity. This may reflect a better fit of the methyl group in that space or more attractive interactions of the ethyl group with the co-guest. The energetic differences are sufficiently small that their origins are clouded. Even so, there are sure to be parallels in enzymology, where both components of a bimolecular reaction must present their reactive groups face-to-face for catalysis to occur. The nonspherical shape of $\mathbf{1}_2$ and its capacity to encapsulate even more than two guests present other novelties of isomerism in chemistry, and these are explored in the sequel.

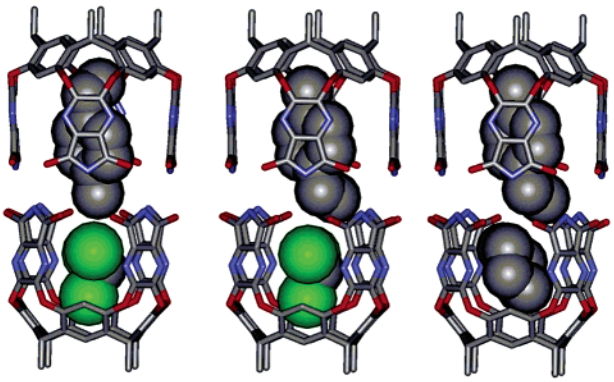

Figure 3. MM optimized (MM+ force field[11]) structures of encapsulation complexes of guests in $\mathbf{1}_2$: left, 4-ethyl toluene and $CHCl_3$ (ethyl in the cavity of **1**); center, 4-ethyl toluene and $CHCl_3$ (methyl in the cavity of **1**); right, 4-ethyl toluene and cyclohexane; All hydrogens and the peripheral alkyl groups of **1** have been removed for viewing clarity.

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