Supramolecular Isomerism in Caviplexes**

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Molecule-within-molecule complexes can exhibit subtle stereochemical relationships between host and guest. In complexes held together by covalent bonds such as carceplexes and cryptophanes,[1] a snug fit between host and guest can restrict molecular motions to an extent that different isomers, based on different orientations of the guest molecules inside the host, can be distinguished (Figure 1).[2] In complexes held together by hydrogen bonds such as self-assembling capsules,[3] related types of diastereomerism can also be observed.[4]

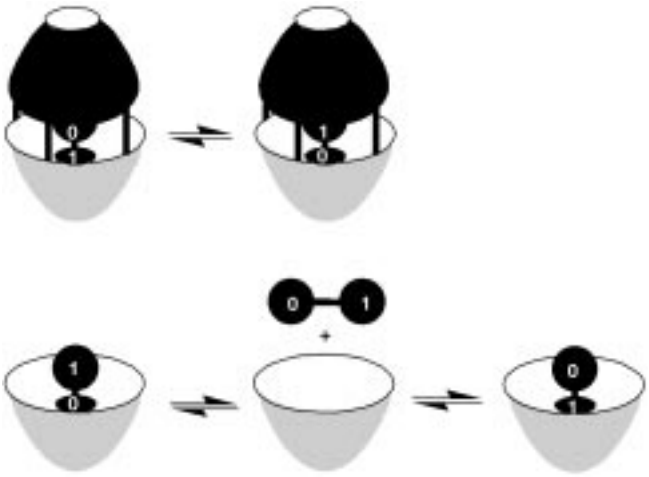

Figure 1. Top: stereoisomerism in carcerands (carceroisomerism). Bottom: stereoisomerism in cavitands. Symbols "0" and "1" represent different ends of the guest molecule.

In open-ended cavity-containing structures, such as cyclodextrins, cyclophanes, and cavitands, this kind of stereoisomerism is more difficult to detect.[5, 6] The kinetic stabilities of the complexes are low and guest exchange is generally rapid with respect to the timescale of the spectrometer. Recently, we described an exception: resorcinarene-based cavitands form complexes of high kinetic stabilities despite their open-ended structures and low binding affinities (Figure 2).[7] Here we report on their binding properties as they relate to stereoisomerism.

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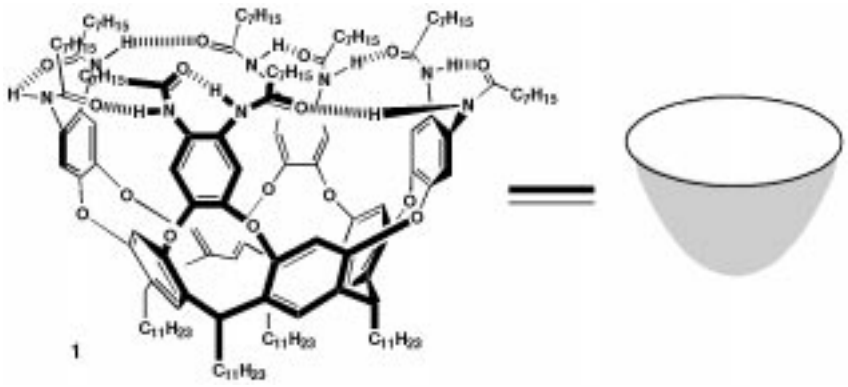

Figure 2. Cavitand **1** and its cartoon representation used elsewhere. Dashed lines indicate hydrogen bonds.

Cavitand **1** features a deep cavity that is maintained by intramolecular hydrogen bonding (Figure 2).[7] Guests of appropriate dimensions are bound within the cavity but their entrance and exit are accompanied by unfolding the vaselike conformation to the kitelike conformation. In the process, four interannular hydrogen bonds are broken and inversion of the seven-membered ring occurs. The resident guest is then exposed to molecules in the bulk solution for a supramolecular counterpart of a substitution reaction. The overall process proceeds with an activation energy of about 17 kcal mol^{-1} corresponding to a rate that is slow on the NMR timescale at room temperature. Accordingly, isomeric complexes can be directly observed in solution.

Alicyclic derivatives are particularly good complements for the cavity of **1**, and we screened a number of cyclohexyl and 1-adamantyl derivatives. The binding energies were generally not high ($-\Delta G \leq 3$ kcal mol^{-1} at 295 K in [D_{10}]-*p*-xylene), and excess guests were required to fully load the cavities at NMR concentrations. Molecules containing *both* 1-adamantyl and cyclohexyl fragments[8] were also evaluated by NMR spectroscopy and the results are summarized in Table 1.

For the complexed adamantane derivatives, four sharp sets of signals are characteristically present at $\delta = 0.5$ to $\delta = -3$; for the complexed cyclohexanes, at least five broad signals are detected upfield of $\delta = 0$. Similar broadening was previously observed for encapsulated lactams,[7] and may be due to the chiral environment experienced by the complexed guest and its reduced tumbling. The case of **1**·*cyclo*-$C_6H_{11}NH_2\cdots HOC_6F_5$ represents an unprecedented "complex-within-a-caviplex".[9, 10] It is readily formed upon addition of pentafluorophenol to the [D_{10}]-*p*-xylene solution of cavitand **1** and cyclohexylamine, and is more stable than the corresponding **1**·*cyclo*-C_6H_{11}-NH_2 complex. Most likely the higher affinity is due to the increased acidity of the guest N–H protons; these are involved in hydrogen bonding to the circle of amides of the host. Inclusion of linear aliphatic chains and aromatic rings by **1** was not detected (Table 1, runs 1, 6).

The bis-adamantyl derivatives, showed two *diastereomeric* complexes (Figure 3, see also Table 1, runs 17, 18). As is the case with carceplexes,[2] these complexes differ by orientation of the guest molecule inside the cavity. They are too large to tumble freely within the cavity, but the symmetry of the vase is maintained and indicates that these guests are spinning

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Table 1. Encapsulation of guests by cavitand **1**.[a, b]

Run	Compound	Encapsulated site
1	$CH_3(CH_2)_5$-NH-C(O)-$(CH_2)_6CH_3$	[c]
2	Ad-NH_2	Ad
3	Ad-C(O)-Cl	Ad
4	Ad-CH_2C(O)-OC_6F_5	Ad
5	Ad-NH-C(O)-$(CH_2)_6CH_3$	Ad
6	Ad-NH-C(O)-C_6H_4-CH_3-*p*	Ad
7	Ad-CH_2C(O)-NH-$CH(CH_3)_2$	Ad
8	Ad-CH_2C(O)-NH-$CH(CH_3)CH_2CH_3$	Ad
9	Ad-CH_2C(O)-NH-$(CH_2)_5CH_3$	Ad
10	Ad-CH_2C(O)-NH-$CH(CH_3)CH_2OCH_3$	Ad
11	Ad-C(O)-NH-$CH(CH_3)CH_2CH_3$	Ad
12	Ad-C(O)-NH-$CH(CH_3)_2$	Ad
13	*cyclo*-C_6H_{11}-NH_2	Cycl
14	*cyclo*-C_6H_{11}-$NH_2\cdots HOC_6F_5$	Cycl
15	*cyclo*-C_6H_{11}-NH-C(O)-$(CH_2)_6CH_3$	Cycl
16	*cyclo*-C_6H_{11}-C(O)-NH-$(CH_2)_5CH_3$	Cycl
17	Ad-C(O)-NH-Ad	Ad + Ad′ (1:1)[d]
18	Ad-CH_2C(O)-NH-Ad	Ad + Ad′ (1:6)[d]
19	*cyclo*-C_6H_{11}-C(O)-NH-*cyclo*-C_6H_{11}	Cycl + Cycl′ (0:1)[d,e]
20	Ad-C(O)-NH-*cyclo*-C_6H_{11}	Ad + Cycl (2:3)[d]
21	Ad-NH-C(O)-*cyclo*-C_6H_{11}	Ad
22	Ad-CH_2C(O)-NH-*cyclo*-C_6H_{11}	Cycl
23	Ad-C(O)-NCH_3-*cyclo*-C_6H_{11}	Ad
24	Ad-CH_2C(O)-NH-$CH(CH_3)$*cyclo*-C_6H_{11}	Ad

[a] Determined by ^{1}H NMR spectroscopy (600 MHz, 295 K) in [D_{10}]-*p*-xylene. [**1**] $= 5 \times 10^{-4}$ M, guest concentration $\geq 5 \times 10^{-3}$ M. [b] Data collected from two or more independent experiments. [c] No kinetically stable complex was detected. [d] Determined by integration (error $\pm 10\%$); assignments followed from comparison with structurally related model compounds. [e] Line broadening renders this assignment ambiguous.

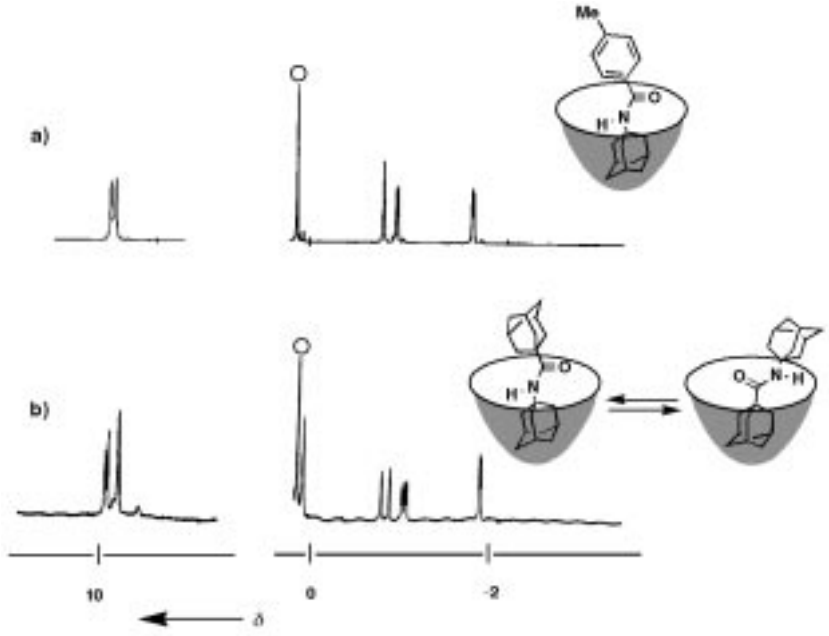

Figure 3. Portions of the ^{1}H NMR spectra in [D_{12}]mesitylene (600 MHz, 295 K). The caviplex **1** amide N–H signals are shown in the downfield region and the guest signals are shown in the upfield region. The internal standard singlet is marked "o". a) bound Ad-NH-C(O)-C_6H_4-CH_3-*p*; b) bound Ad-C(O)-NH-Ad; two diastereomeric complexes are seen in a ratio of about 1:1.

rapidly about the long axis of the assemblies. Mixed adamantyl–cyclohexyl amides (Table 1, runs 20–24), however, gave caviplexes, where, in general, either adamantyl or cyclohexyl fragments appeared in the ^{1}H NMR upfield region (see for example, Figure 4b,c). As an exception, Ad-C(O)-NH-*cyclo*-C_6H_{11} (Table 1, run 20) gave a mixture of two caviplexes (Figure 4d). The corresponding NMR data (Table 1, runs 20–22) showed the selectivity of the cavity to be: {Ad-NH-C(O)-; *cyclo*-C_6H_{11}-NH-C(O)-} $\gg$ {Ad-C(O)-NH-; Ad-CH_2C(O)-NH-; *cyclo*-C_6H_{11}-C(O)-NH-}. This grouping suggested that the origin of the selectivity was in the amide linker of the guest, and molecular modeling[11] supported the notion that the guest NH proton and/or the carbonyl group is involved in hydrogen bonding to the circle of amides in the host (Figure 5). The two sharp C(O)-NH singlets of the cavitand **1** undergo significant changes and broadening upon complexation (Figure 4). In the experiment, substitution of the NH proton by CH_3 (as in Ad-C(O)-NCH_3-*cyclo*-C_6H_{11}, Figure 4d,e; Table 1, runs 20 and 23) led the encapsulation of the adamantyl end, exclusively. In short, chemical methylation switches one orientation to another.

A number of forces can be used to control a guest's positioning within its host: proton transfer, electron transfer, light, and solvent polarity have proved useful in this context.[12] These systems process information through molecular recognition. Our current efforts are directed toward increasing informational content in caviplex formation for applications in catalysis and separations.

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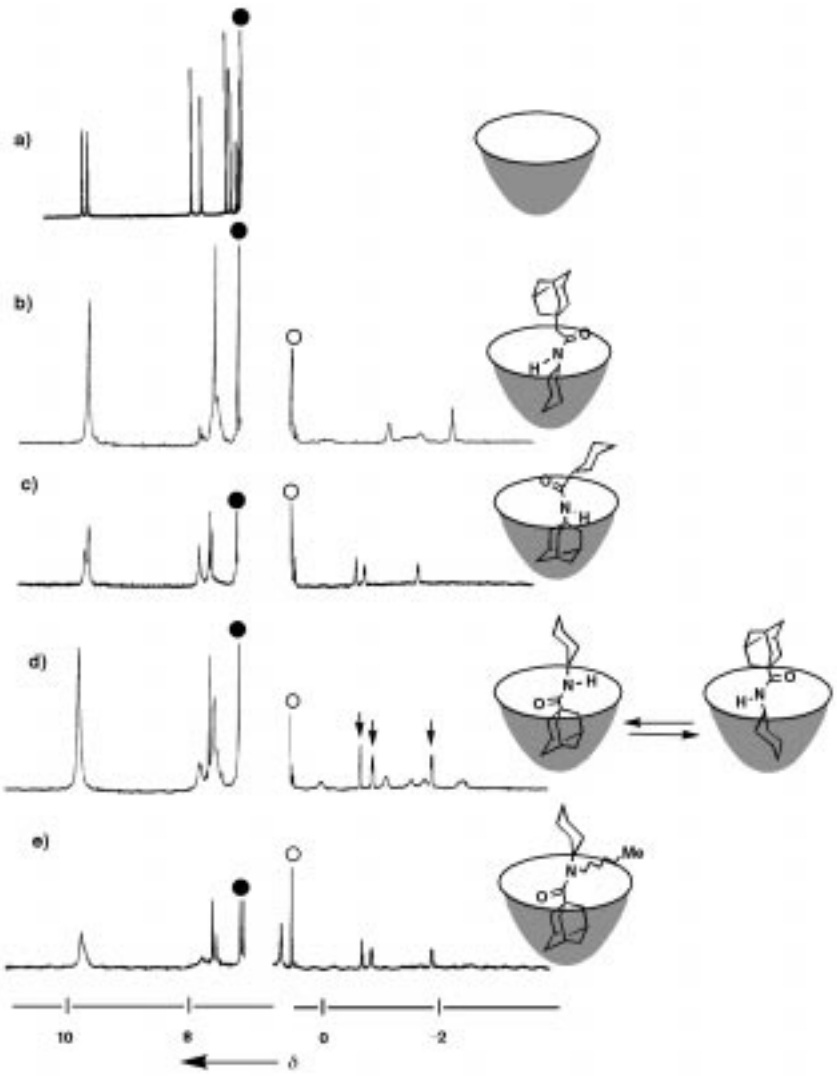

Figure 4. Downfield and upfield regions of the ^{1}H NMR spectra in [D_{10}]-*p*-xylene (600 MHz, 295 K): a) "empty" cavitand **1**; b) bound Ad-CH_2C(O)-NH-*cyclo*-C_6H_{11}; c) Ad-NH-C(O)-*cyclo*-C_6H_{11}; d) bound Ad-C(O)-NH-*cyclo*-C_6H_{11}. Two diastereomers are shown, and the Ad-end set is marked by arrows; e) bound Ad-C(O)-NCH_3-*cyclo*-C_6H_{11}. The solvent signal and the internal standard singlet are marked "●" and "o", respectively.

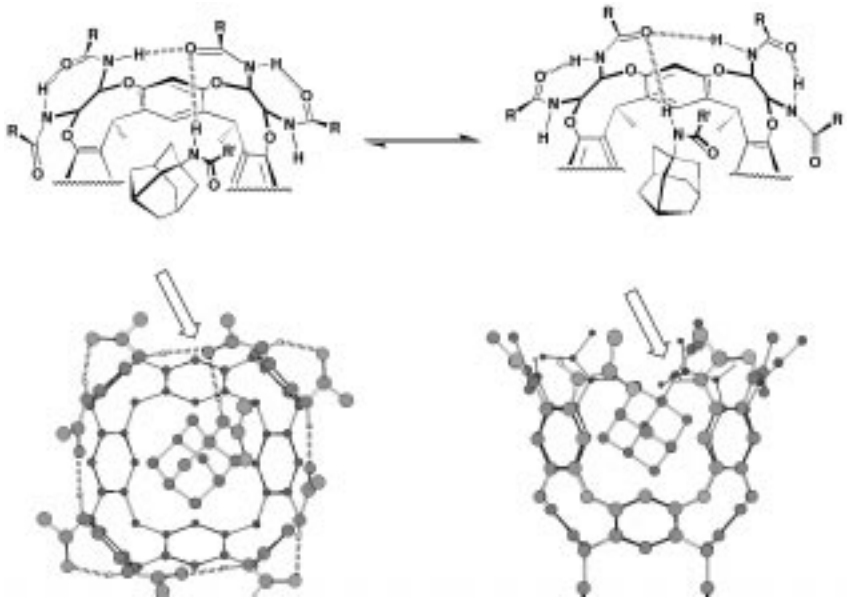

Figure 5. Schematic representation of hydrogen bonding in the caviplexes and two views of the energy-minimized[11] structure of caviplex **1** with Ad-NH-C(O)-CH_3. Long alkyl chains and CH hydrogens have been omitted for viewing clarity. A hydrogen bond between the guest and **1** is indicated by the arrow.

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[8] All compounds synthesized were fully characterized by FT-IR, high-resolution ^{1}H and ^{13}C NMR spectroscopy and high-resolution FAB mass spectrometry. Pure amides were obtained as colorless solids in 75 – 90% yields after crystallization, using textbook procedures of peptide chemistry. Complexation experiments were performed on a Bruker DRX-600 spectrometer (600 MHz) in [D_{10}]-*p*-xylene and [D_{12}]mesitylene at 295 K.

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