New Form of Isomerism

Isomeric Constellations of Encapsulation Complexes Store Information on the Nanometer Scale**

*Alexander Shivanyuk and Julius Rebek, Jr.**

Isomers in chemistry are defined through constitution. Further stereochemical relationships between two molecules can be assigned through configuration and conformation, but collections of molecules can also show isomerism through their arrangements in space. We report here a new form of isomerism resulting from the encapsulation of three small-molecule guests in a cylindrical, reversibly assembled host. The mobility of the guests within the host is limited: the guest molecules are held in different constellations within the confined space. The various combinations and isomeric constellations of capsules are nanoscale data storage devices.

Encapsulation complexes are reversibly formed assemblies in which small-molecule guests are surrounded by a multimolecular host. The systems are held together by weak intermolecular forces comprising metal–ligand interactions and hydrogen bonding. The assemblies are dynamic; they form and dissipate on time scales ranging from milliseconds to hours. The mechanical barriers that constrain the molecules within molecules offer new possibilities for isomerism, first observed in covalently bound carcerands.[1] In reversibly bound encapsulation complexes,[2] the lifetime of the array is determined by the mobility of the guests, either within the capsule or through exchange with molecules outside, in solution. We report here isomeric constellations—arrangements of several molecules in space—that emerge when two different guests, are encapsulated within a cylindrical host.[3] Specifically, all combinations of chloroform and isopropyl chloride in the encapsulation complexes (Figure 1) can be identified by NMR methods. The isomerism is an emergent property of the assembly, rather than that of individual molecules. The phenomenon hints at applications in mechanistic organic chemistry through the selective solvation of reactants[4] and information storage at the molecular level.

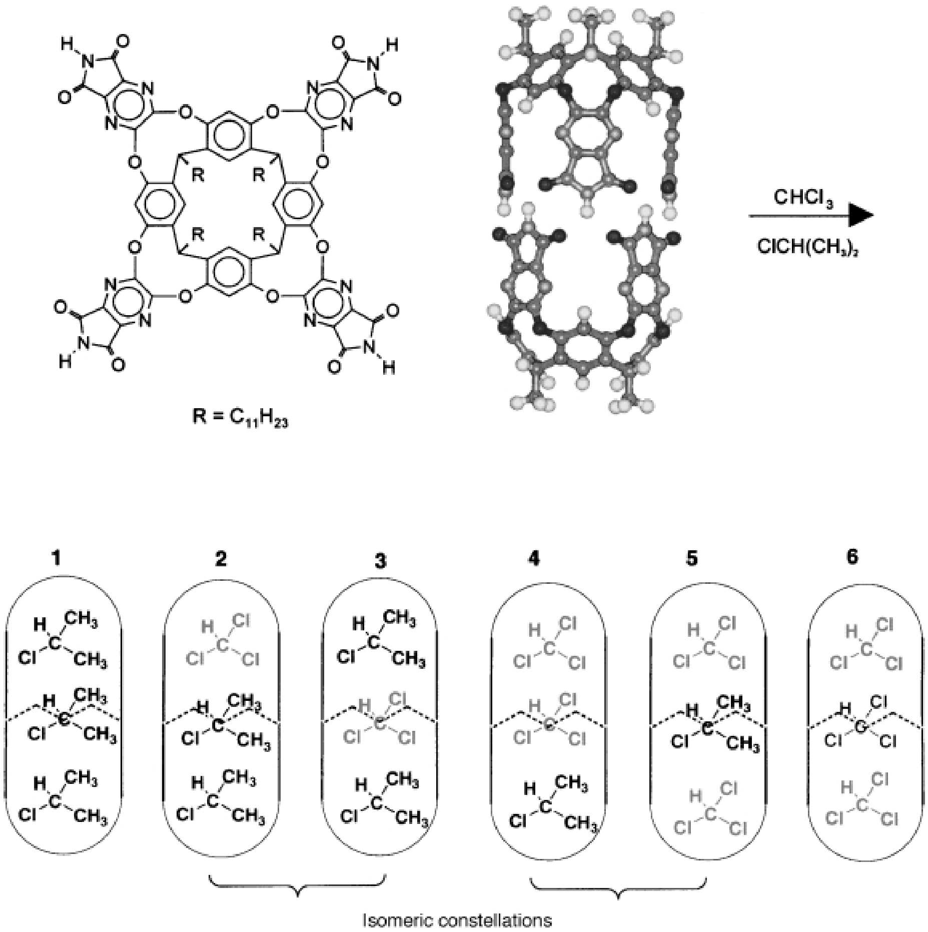

Figure 1. Top: Line drawing of the cavitand and a ball-and-stick representation of the self-assembled, cylindrical capsule. Bottom: the six different combinations of encapsulated $CHCl_3$ and $ClCH(CH_3)_2$.

The NMR spectrum of isopropyl chloride $ClCH(CH_3)_2$ in the capsule using deuterated mesitylene as the solvent is shown in Figure 2a. Mesitylene is too large to be encapsulated and cannot compete with appropriately sized guests present at lower concentrations. Accordingly, the spectrum represents array **1**. The sharp, widely separated signals for guests in the two locations reflect the sizable energetic barrier that prevents the guest molecules from exchanging positions: they are too large to slip past each other while within the capsule. The rate of the exchange process is slow on the NMR time scale. The assignments were confirmed by NOE experiments. Irradiation of the upfield doublet gave NOEs with the

[*] Prof. Dr. J. Rebek, Jr., Dr. A. Shivanyuk
The Skaggs Institute for Chemical Biology and
Department of Chemistry
The Scripps Research Institute, MB-26
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2876
E-mail: jrebek@scripps.edu

[**] We are grateful to the Skaggs Institute of Research and the NIH (GM 50174) for support. A.S. is a Skaggs Postdoctoral Fellow. We are pleased to acknowledge illuminating discussions with Prof. A. Eschenmoser, Prof. P. Ballester, and Prof. J. Williamson. Technical help with NMR instrumentation was generously provided by Prof. M. Hennig.

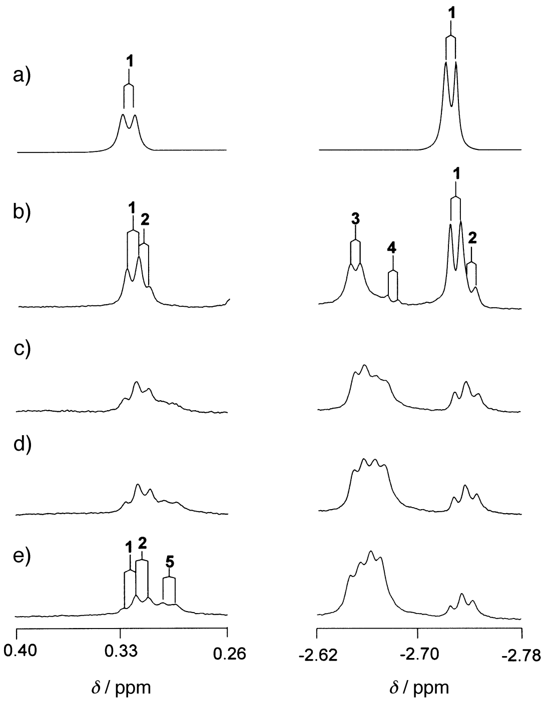

Figure 2. Upfield regions of the NMR spectra of the complexes (800 MHz; 298 K in [D_{12}]mesitylene (0.15 mL) and isopropyl chloride (0.3 mL)). The Initial concentration of the capsule is 2 mM. a) isopropyl chloride alone; array **1**. The furthest upfield doublet is assigned to the methyl groups of guests near the ends of the capsule, and the downfield doublet is assigned to methyl groups of the guest located near the middle. New arrays appear as the following volumes of $CDCl_3$ are added: b) addition of 0.05 mL $CDCl_3$. The isomeric constellations **2** and **3** arise as one guest is replaced and **4** appears as two guests are replaced from the $ClCH(CH_3)_2$-filled **1**; c) addition 0.15 mL $CDCl_3$. Array **4** increases at the expense of **1**, while the ratio **2**:**3** remains constant; d) addition of 0.3 mL $CDCl_3$; e) addition of 0.4 mL $CDCl_3$. Array **4** becomes the dominant $ClCH(CH_3)_2$-containing species, and its constellational isomer **5**, having a single $ClCH(CH_3)_2$ in the center of the capsule is identified.

resorcinarene hydrogen atoms, while irradiation of the downfield doublet showed NOEs only with the imide N–H signals. An energy-minimized structure for array **1** is shown in Figure 3a, where the van der Waals surfaces featured on the guests emphasize the constraints on their mobility within the capsule.

Titration of $CDCl_3$ into the capsule filled with isopropyl chloride generated the 800 MHz spectra shown in Figure 2b–e. The identification of constellational isomers **2** and **3** was possible in the upfield regions of the spectra (the regions representing $ClCH(CH_3)_2$ guests at the ends and the middle of the capsule). The first to appear are those in which one $ClCH(CH_3)_2$ is replaced by $CDCl_3$ (arrays **2** and **3**). A key to the assignment of the signals lies in the identical stoichiometries of these constellational isomers: the relative amounts of **2** and **3** need not be equal, but their ratio remains constant throughout the titration. Integration of the signals shows this requirement is met by the assignments indicated, with **3**:**2** = 2.5:1. The next arrays that emerge during the titration are the isomers with one $ClCH(CH_3)_2$ and two $CDCl_3$ guests, (**4** and

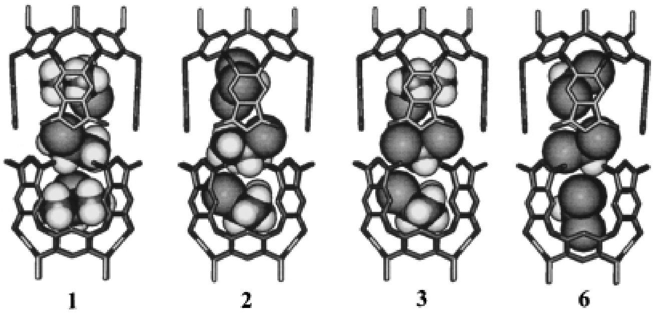

Figure 3. Energy-minimized structures of encapsulation complexes: **1**: $HCCl(CH_3)_2$ alone; **2** and **3**: constellational isomers of $CHCl_3{\cdot}2\,HCCl(CH_3)_2$; **6**: $CHCl_3$ alone. The van der Waals surfaces of the guests emphasize their inability to exchange places while within the capsule.

5) but only **4** appears in the furthest upfield region of the spectrum. Its constellational isomer **5** confines a single $ClCH(CH_3)_2$ guest to the middle of the capsule, and the appropriate region of the NMR spectrum is downfield (Figure 2c–e). Three arrays feature centrally located $ClCH(CH_3)_2$ guests: **1**, **2**, and **5**. Identification of **5** follows from the known resonance signal for **1** and that deduced for **2**.

With $CHCl_3$ as the only guest (array **6**) under these conditions, the same exchange characteristics hold; a signal occurs at $\delta = 3.52$ ppm for $CHCl_3$ molecules at the ends of the capsule, and a signal occurs at $\delta = 6.46$ ppm for the $CHCl_3$ in the center. A reverse titration in which $ClCH(CH_3)_2$ was added to the $CHCl_3$-filled capsule showed the initial appearance of signals for **4** and **5** followed by those for **2** and **3** in the NMR spectra (data not shown).

In addition to all the upfield signals for capsules containing isopropyl groups (**1**–**5**) described above, an equimolar mixture of $CHCl_3$ and $ClCH(CH_3)_2$ showed the appropriate downfield signals for encapsulated $CHCl_3$. Even the $CHCl_3$-filled capsule **6** can be identified, that is, all six combinations coexist at comparable concentrations for this pair of guests. This may appear as an unlikely result because the six combinations are not expected to have equal free energies and appear at different concentrations. The attractive forces—van der Waals and dipole–dipole interactions—between the guests and the host, and between the guests themselves are different for each arrangement. If the energetic difference between the most favored and least favored combinations exceeds 3 kcal mol^{-1}, less than 1% of the least favored isomer will be present at equilibrium at ambient temperature; NMR methods would be hard-pressed to detect both combinations. Specifically, only five of the six combinations of $CHCl_3$ with $ClCH_2CH_2Cl$ in the capsule could be observed, and generally, other solvent pairs tested showed even fewer isomeric constellations coexist. Yet the energies for the $CHCl_3$/$ClCH(CH_3)_2$ combinations are, evidently, well within 1 kcal mol^{-1} and all appear simultaneously.

The explanation lies in the nearly identical properties of these two guests. Their shapes, dimensions, and volumes are practically superimposable. For example, the volume of $CHCl_3$ is 73 Å^3 and that of $ClCH(CH_3)_2$ is 74 Å^3; any combination of three guests occupies about 53% of the capsule's internal space of 420 Å^3. The proper filling of space is an essential determinant of reversible encapsulation: guests that fill slightly more than half of the available space lead to the most stable complexes.[5] Either guest can interact favorably with the polar seam of hydrogen bonds that hold the capsule together through their modest dipole moments (1.15 **D** for $CHCl_3$ and 2.1 **D** for $ClCH(CH_3)_2$).

The different combinations and isomeric constellations introduced here represent information, temporarily stored in the form of a binary code. The symmetry of the capsule reduces the capacity to six bits from the eight expected. Long-term storage of data on the nanometric scale may follow when their arrangements can be precisely controlled, maintained, and retrieved. In the meantime, reversible assembly provides access to capsules with volumes capable of surrounding numerous guests.[6,7] The well-defined sizes and shapes of the cavities impose limitations on the motions of the guests, both internal, such as ring inversion[8,9] or external, such as molecular translation and tumbling.[10–12] Guest–guest interactions[13] offer even more possibilities for information storage and we explore them in the sequel.

Received: August 5, 2002
Revised: October 29, 2002 [Z19884]

[1] P. Timmerman, W. Verboom, F. C. J. M. van Veggel, J. P. M. van Duynhoven, D. N. Reinhoudt, *Angew. Chem.* **1994**, *106,* 2437 – 2440; *Angew. Chem. Int. Ed. Engl.* **1994**, *33,* 2345 – 2347.
[2] F. C. Tucci, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 4928 – 4929.
[3] T. Heinz, D. M. Rudkevich, J. Rebek, Jr., *Nature* **1998**, *394*, 764 – 766.
[4] C. K. Regan, S. L. Craig, J. I. Brauman, *Science* **2002**, *295*, 2245 – 2247.
[5] A. S. Mecozzi, J. Rebek, Jr., *Chem. Eur. J.* **1998**, *4*, 1016 – 1022.
[6] J. Chen, J. Rebek, Jr., *Org. Lett.* **2002**, *4*, 327 – 329.
[7] M. K. Ebbing, M.-J. Villa, J.-M. Malpuesta, P. Prados, J. de Mendoza, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4962 – 4966.
[8] B. M. O'Leary, R. M. Grotzfeld, J. Rebek, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 11 701 – 11 702.
[9] R. G. Chapman, J. C. Sherman, *J. Org. Chem.* **2000**, *65*, 513 – 516.
[10] D. J. Cram, J. M. Cram, J. M. *Container Molecules and Their Guests* (Ed.: F. Stoddart), The Royal Society of Chemistry, London, **1994**.
[11] A. Jasat, J. C. Sherman, *Chem. Rev.* **1999**, *99*, 931 – 968.
[12] M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647 – 1668.
[13] A. Shivanyuk, J. Rebek, Jr., *J. Am. Chem. Soc.* **2002**, *124*, 12 074– 12 075.

Modular-Assembled Bowls and Crowns

Modular Cavity-Tunable Self-Assembly of Molecular Bowls and Crowns as Structural Analogues of Calix[3]arenes**

Shu-Yan Yu, Hui Huang, Hong-Bo Liu, Zhong-Ning Chen, Rongben Zhang, and Makoto Fujita*

The construction of container molecules is still an interesting topic in organic synthesis, particularly bowl-shaped molecules, such as calixarenes, because of their potential applications in a variety of areas of supramolecular chemistry.[1] In contrast to the inorganic approach, metal-directed self-assembly has been widely employed to construct well-defined metal–organic container molecules.[2] Metal-assembled bowl-shaped molecules that are structural analogues of calixarenes, such as metallacalix[3]arenes,[3] metallacalix[4]arenes,[4] and others[5,6] have attracted considerable attention. We obtained a metal–organic nanobowl by self-assembly,[7] which was found to assemble in aqueous media to form a dimeric capsule that contains a large hydrophobic pocket inside the framework.[8] This pocket served as a reaction container for a highly stereoselective [2+2] photodimerization of olefins.[9] These findings inspired us to develop structurally and functionally new container molecules with calixarene features to conform with certain molecular architectures, and various reactions. In addition, we noted that among the few inorganic analogues of calixarenes, conformational conversion usually occurred because of the flexibility of the ligand, and because of distortion of the coordination geometry, as found in some metallacalix[3]arenes (with partial cone conformer),[6] and metallacalix[4]arenes (with isomers).[4] Therefore, self-assembled metallacalixarenes with single rigid conformations (i.e., cone conformer, bowl form, and *all-syn* conformation) are

[*] Prof. Dr. S.-Y. Yu, H. Huang, Dr. H.-B. Liu, Prof. Dr. R. Zhang
State Key Laboratory of Polymer Physics and Chemistry
Center for Molecular Science
Institute of Chemistry
Chinese Academy of Sciences
Beijing 100080 (P.R. China)
Fax: (+86) 10-6255-9373
E-mail: syu@infoc3.icas.ac.cn

Prof. Dr. Z.-N. Chen[+]
State Key Laboratory of Structural Chemistry
Fujian Institute of Research on the Structure of Matter
Chinese Academy of Sciences
Fuzhou 350002 (P.R. China)

Prof. Dr. M. Fujita
Department of Applied Chemistry
Graduate School of Engineering
The University of Tokyo
bunkyo-ku, Tokyo 113-8656 (Japan)

[+] Crystal structure analysis.

[**] The project supported by National Natural Science Foundation of China No. 90206013.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  0044-8249/03/11506-0710 $ 20.00+.50/0