b) A. Aggeli, M. Bell, N. Boden, J. N. Keen, T. C. B. McLeish, I. Nyrkova, S. E. Radford, A. Semenov, *J. Mater. Chem.* **1997**, *7*, 1135–1145; b) K. Janek, J. Behlke, J. Zipper, H. Fabian, Y. Georgalis, M. Beyermann, M. Bienert, E. Krause, *Biochemistry* **1999**, *38*, 8246–8252.

[17] T. C. Holmes, S. de Lacalle, X. Su, G. Liu, A. Rich, S. Zhang, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 6728–6733.

[18] J. H. Collier, B.-H. Hu, J. W. Ruberti, J. Zhang, P. Shum, D. H. Thompson, P. B. Messersmith, *J. Am. Chem. Soc.* **2001**, *123*, 9463–9464.

[19] J. D. Hartgerink, E. Beniash, S. I. Stupp, *Science* **2001**, *294*, 1684–1688.

[20] See, for example, a) D. A. Tirrell, M. J. Fournier, T. L. Mason, *MRS Bull.* **1991**, *16*, 23–28; b) J. C. M. van Hest, D. A. Tirrell, *Chem. Commun.* **2001**, 1897–1904, and references therein.

[21] Approaches for the incorporation of unnatural $\alpha$-amino acids include a) nonsense (stop codon) suppression,[22] b) the use of quadruplet (four-base) codons,[23] and c) the use of bacterial auxotrophs.[20]

[22] See, for example, a) V. W. Cornish, D. Mendel, P. G. Schultz, *Angew. Chem.* **1995**, *107*, 677–690; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 621–633; b) L. Wang, A. Brock, B. Herberich, P. G. Schultz, *Science* **2001**, *292*, 498–500.

[23] See, for example, a) T. Hohsaka, D. Kajihara, Y. Ashizuka, H. Murakami, M. Sisido, *J. Am. Chem. Soc.* **1999**, *121*, 34–40; b) B. Moore, B. C. Persson, C. C. Nelson, R. F. Gesteland, J. F. Atkins, *J. Mol. Biol.* **2000**, *298*, 195–209.

[24] Y. Tang, G. Ghirlanda, W. A. Petka, T. Nakajima, W. F. DeGrado, D. A. Tirrell, *Angew. Chem.* **2001**, *113*, 1542–1544; *Angew. Chem. Int. Ed.* **2001**, *40*, 1494–1496.

[25] W. A. Petka, J. L. Harden, K. P. McGrath, D. Wirtz, D. A. Tirrell, *Science* **1998**, *281*, 389–392.

---

# Of Molecular Gyroscopes, Matroshka Dolls, and Other “Nano”-Toys

## Christoph A. Schalley*

At the outset, let us stand up for playing. Often mistaken for a kid’s domain, playing opens up new fields of experience even for the “grown-ups”. Possibly, it is one of the prerequisites of the creative process, in the sense that dealing playfully with known ideas provides new ways of thinking. Scientists are no exception. On the contrary, in the area of supramolecular chemistry, with all the model-like realizations of macroscopic objects at a molecular level, the drive to play seems to be followed strongly.

That said, it is no suprise that second-sphere supramolecular complexes, that is, the inclusion of a guest in a host which is already encapsulated in an even larger host, have been compared to russian Matroshka dolls. However, such architectures have been realized only rarely so far, probably because of the difficulties inherent in the synthesis of appropriately sized host molecules which can incorporate an entire host–guest system. Several early examples have been observed by Vögtle and Müller, who described the co-crystallization of $\gamma$-cyclodextrin with coronates and cryptates in 1:1 und 2:1 ratios.[1] These so-called “cascade complexes” contain an alkali metal ion bound inside a crown ether or a cryptand, which—as later shown by X-ray crystal structure analyses[2]—are surrounded by one or two cyclodextrin molecules. Recently, a few other examples have been added, for example, hydrogen-bonded capsules which self-assemble reversibly in solution around an encapsulated cryptate (Figure 1)[3] as well as onionlike arrangements of fullerenes and carbon nanotubes.[4]

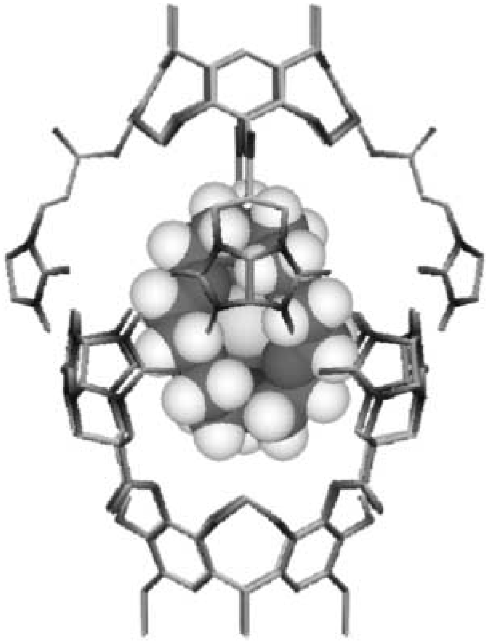


Figure 1. A dimeric, hydrogen-bonded capsule with an interior volume of almost 1000 Å$^2$ which reversibly encapsulates different cryptates in solution. The guest is depicted as a space-filling model (central sphere = K$^+$ ion inside the [2.2.2]cryptand), while the capsule is shown as tubes (for clarity, the solubilizing side chains have been omitted).

A particularly beautiful example has just been published by Day, Blanch, and co-workers.[5] This “gyroscane” (Figure 2) consists of a cucurbit[5]uril that is surrounded by a larger analogue, cucurbit[10]uril.[6] The particular aesthetics of this complex arise from the fact that both shells belong to the same class of compounds and thus provide a highly symmetrical compound. Upon crystallization from concentrated hydro-

---

[*] Dr. C. A. Schalley
Kekulé-Institut für Organische Chemie und Biochemie
Universität Bonn
Gerhard-Domagk-Strasse 1, 53121 Bonn (Germany)
Fax: (+49) 228-735662
E-mail: c.schalley@uni-bonn.de

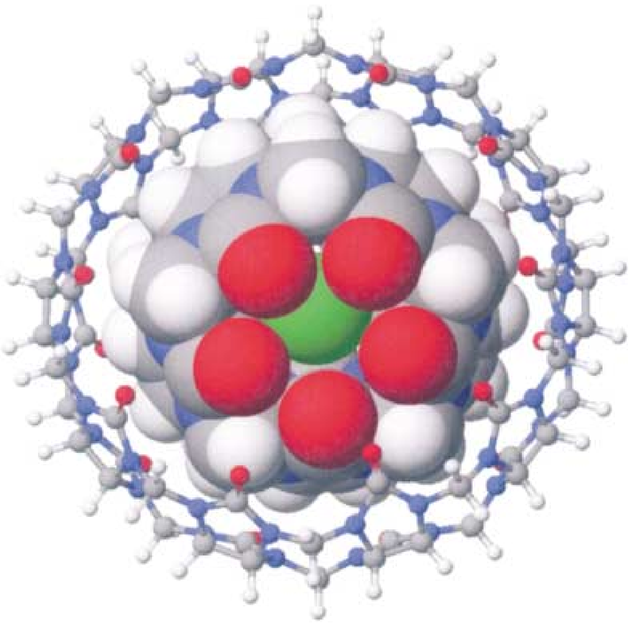


Figure 2. The cucurbit[5]uril inside the cucurbit[10]uril gyroscane encapsulates a chloride ion upon crystallization from concentrated HCl.

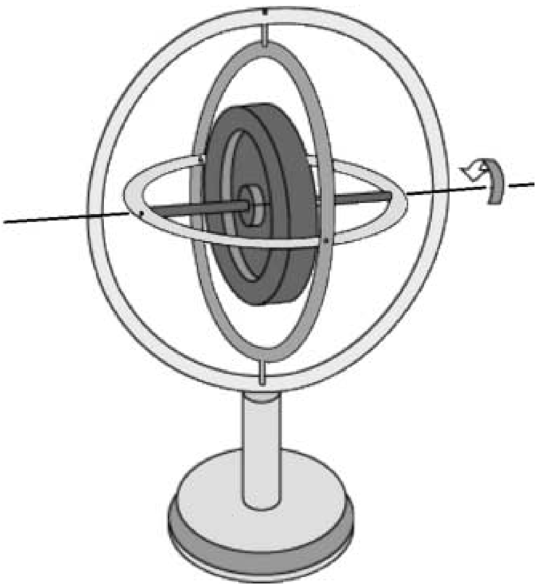
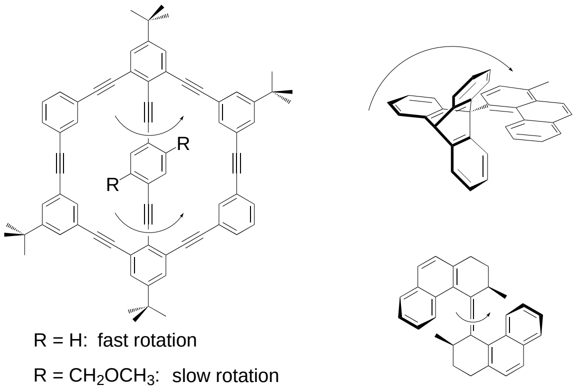


Figure 3. In a gyroscope, the macrocyclic precursor of the gyroscane, the central wheel can rotate freely. When the wheel spins, the conservation of angular momentum prevents the axis from changing its direction even if the framework is moved.

chloric acid, the inner cavities of these complexes are filled with a chloride ion, while water molecules or $H_3O^+$ ions cover the two portals of the inner cucurbituril and bridge the rims of the two macrocycles by hydrogen bonding. The plane of the inner ring is tilted significantly (64°) against that of the outer macrocycle.

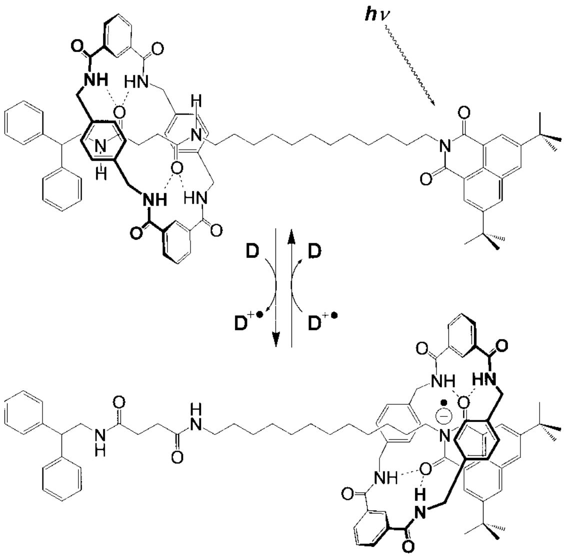
The molecule-in-molecule-in-molecule motif is not the only characteristic feature of this arrangement of the two rings. An almost completely free motion of the smaller cycle within the larger one can be demonstrated by $^1H$ and $^{13}C$ NMR spectroscopy and computer modeling studies. Both rings can rotate relative to each other in the same plane, but the rotational axis of the inner cucurbituril can also be tilted against that of the outer cucurbit[10]uril macrocycle. This special kind of unprecedented mobility probably emerges from a combination of the rigidity of the glycoluril subunits and their concave curvature perpendicular to the planes of the macrocycles. It is analogous to that of a gyroscope (Figure 3) and consequently led to the authors' suggestion to coin this type of complex "gyroscane". Gyroscopes are not only known as toys. They are also used for precise measurements of rotational movements and serve as means of stabilization in space stations such as the legendary MIR. At the same time, the inner macrocycle is mechanically trapped inside the outer ring: While the rotations inside the cavity are fast on the NMR time scale and provide averaged signals, the exchange of cucurbit[5]uril against a $^{13}C$-labeled analogue added to the sample solution proceeds relatively slowly and requires about one hour. These properties place the gyroscane in a series with other "molecular machines",[7] for example, the "turnstile" described by Bedard and Moore,[8] the Kelly "ratchet",[9] or Feringa's overcrowded, light-switchable (*cis*/*trans*) double bonds that are appropriately equipped with chirality elements to provide unidirectionality (Scheme 1).[10] Other molecular machines utilize rotaxanes for rotational and shuttling motion; a recent example is shown in Scheme 2.[11]



Scheme 1. Molecular turnstile (left), ratchet (top right), and overcrowded double bond (bottom right) as miniature machines. The arrows indicate the rotation of the respective molecule parts. In the example shown at the right side, unidirectionality can be induced by the implementation of suitable chirality elements.

As a third topic, the synthesis is briefly discussed. At first sight this appears to be rather unspectacular, since formation of gyroscane proceeds with low selectivity and a lot of side products. Also, the acid-catalyzed condensation of formaldehyde and glycoluril is easily explained with respect to its mechanism. However, this seemingly boring facade hides at least one intriguing aspect: A mere statistical inclusion of the smaller ring would be so unlikely that there must be a better explanation for the formation of gyroscane. On one hand, the reversible exchange of the cucurbit[5]uril inside the cavity against a free, isotopically labeled analogue is feasible, even if it is only slow. Thus, the exchange barrier is low enough to make the gyroscane a kinetically labile species. On the other hand, NMR experiments, even after longer time intervals, show no sign of cucurbit[5]uril being liberated from the complex. Consequently, the formation of gyroscane is ther-

1433-7851/02/4109-1514 $ 20.00+.50/0



Scheme 2. A light-driven molecular shuttle. **D** corresponds to an electron donor present in solution.

modynamically favorable and the binding constant must be high; the authors report a value of $>10^6\,\mathrm{M}^{-1}$. Rather strong noncovalent binding interactions between the two macrocycles must exist; the encapsulation is thus not purely mechanical. One can easily speculate that the same intermolecular forces already play a pivotal role during the formation of gyroscane, which would then proceed through template control.[12] The generation of linear, not yet cyclized oligomers would then (among others) yield 10-mers, which could wrap around a cucurbit[5]uril macrocycle and place the ends to be connected in proximity. The ring closure of the large ring would then be favored. In this respect, highly interesting questions remain that invite a more detailed study of the gyroscane: What is the nature of the noncovalent forces between the two rings? What is the exact mechanism of the formation of gyroscane? Which template is involved? Are there other analogous compounds with different ring sizes or is the combination of cucurbit[5]uril and cucurbit[10]uril the only one with a suitable size complementarity?[5b]

The gyroscane example demonstrates how dealing playfully with chemistry and even the reconstruction of toys and macroscopic machines from everyday life at the molecular level leads to thrilling chemical problems. Finding solutions often leads to a significant increase in our chemical knowledge. Furthermore, the clear visible trend from structural chemistry to the implementation of function also becomes clear. Those who would like to interpret this statement in favor of fundamental science are invited to do so.

---

[1] F. Vögtle, W. M. Müller, *Angew. Chem.* **1979**, *91*, 676–677; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 623–624.

[2] a) S. Kamitori, K. Hirotsu, T. Higuchi, *J. Chem. Soc. Chem. Commun.* **1986**, 690–691; b) S. Kamitori, K. Hirotsu, T. Higuchi, *J. Am. Chem. Soc.* **1987**, *109*, 2409–2414; c) S. Kamitori, K. Hirotsu, T. Higuchi, *Bull. Chem. Soc. Jpn.* **1988**, 3825–3830.

[3] a) A. Lützen, A. R. Renslo, C. A. Schalley, B. M. O'Leary, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 7455–7456; b) B. M. O'Leary, T. Szabo, A. Lützen, N. Svenstrup, C. A. Schalley, M. Schäfer, J. Rebek, Jr., *J. Am. Chem. Soc.* **2001**, *123*, 11519–11533.

[4] a) H. W. Kroto, *Nature* **1992**, *359*, 670–671. b) J. Cumings, A. Zettl, *Science* **2000**, *289*, 602–604.

[5] a) A. Day, R. J. Blanch, A. P. Arnold, S. Lorenzo, G. R. Lewis, I. Dance, *Angew. Chem.* **2002**, *114*, 285–287; *Angew. Chem. Int. Ed.* **2002**, *41*, 275–277; another example for a ring-in-ring arrangement appeared in the same issue: b) S.-H. Chiu, A. R. Pease, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **2002**, *114*, 280–284; *Angew. Chem. Int. Ed.* **2002**, *41*, 270–274. Very recently, a publication on molecular compasses and gyroscopes appeared: c) Z. Dominguez, H. Dang, M. J. Strouse, M. A. Garcia-Garibay, *J. Am. Chem. Soc.* **2002**, *124*, 2389–2399.

[6] Homologues of cucurbit[6]uril have recently been described for the first time: J. Kim, I.-S. Jung, S.-Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi, K. Kim, *J. Am. Chem. Soc.* **2000**, *122*, 540–541. The binding properties of cucurbit[6]uril have been reviewed previously: W. L. Mock in *Comprehensive Supramolecular Chemistry, Vol. 2* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, J.-M. Lehn), Pergamon, Oxford, **1996**, pp. 477–493.

[7] Review: V. Balzani, A. Credi, F. M. Raymo, F. J. Stoddart, *Angew. Chem.* **2000**, *112*, 3484–3530; *Angew. Chem. Int. Ed.* **2000**, *39*, 3348–3391.

[8] T. C. Bedard, J. S. Moore, *J. Am. Chem. Soc.* **1995**, *117*, 10662–10671.

[9] a) T. R. Kelly, I. Tellitu, J. P. Sestelo, *Angew. Chem.* **1997**, *109*, 1969–1971; *Angew. Chem. Int. Ed.* **1997**, *36*, 1866–1868; b) T. R. Kelly, H. De Silva, R. A. Silva, *Nature* **1999**, *401*, 150–152; c) review: T. R. Kelly, *Acc. Chem. Res.* **2001**, *34*, 514–522.

[10] a) N. Koumura, R. W. J. Zijlstra, R. A. van Delden, N. Harada, B. L. Feringa, *Nature* **1999**, *401*, 152–154; review: b) B. L. Feringa, *Acc. Chem. Res.* **2001**, *34*, 504–513; for the relation of chirality and unidirectional rotation in molecular motors, see also c) C. A. Schalley, K. Beizai, F. Vögtle, *Acc. Chem. Res.* **2001**, *34*, 465–476.

[11] A few recent examples may suffice: a) N. Armaroli, V. Balzani, J.-P. Collin, P. Gaviña, J.-P. Sauvage, B. Ventura, *J. Am. Chem. Soc.* **1999**, *121*, 4397–4408; b) P. R. Ashton, R. Ballardini, V. Balzani, A. Credi, K. R. Dress, E. Ishow, C. J. Kleverlaan, O. Kocian, J. A. Preece, N. Spencer, J. F. Stoddart, M. Venturi, S. Wenger, *Chem. Eur. J.* **2000**, *6*, 3558–3574; c) A. M. Brouwer, C. Frochot, F. G. Gatti, D. A. Leigh, L. Mottier, F. Paolucci, S. Roffia, G. W. H. Wurpel, *Science* **2001**, *291*, 2124–2127.

[12] Recent reviews dealing with template synthesis: a) N. V. Gerbeleu, V. B. Arion, J. Burgess, *Template Synthesis of Macrocyclic Compounds*, Wiley-VCH, Weinheim, **1999**; b) *Templated Organic Synthesis* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **2000**; c) T. J. Hubin, D. H. Busch, *Coord. Chem. Rev.* **2000**, *200–202*, 5.