Topochemistry

Borromean Rings: A One-Pot Synthesis

*Christoph A. Schalley**

Keywords:
self-assembly · structure elucidation · template synthesis · topochemistry

The aesthetics of beautiful molecules has been, and still is, a strong motivation for many chemists. Complex interwoven structures[1] such as catenanes, rotaxanes, and knots are even nowadays appealing because of their interesting topological properties, although their functions as molecular machines[2] have become more and more of the focus of interest.

The ability of chemistry to realize the mathematical zoo of knots (Figure 1),[3] at the molecular level still suffers from narrow limitations, and it is thus well-justified to consider the synthesis of trefoil knots as a major achievement.[4] Borromean rings possess an even more complex topology than the trefoil knot, thus making them a challenging target for chemical synthesis. This is reflected in the fact that they have only so far[5] been realized at the molecular level through the DNA nanoassembly methodology developed by Seeman and co-workers.[6] Consequently, the first chemical synthesis of Borromean rings by Stoddart, Atwood, and their co-workers[7] is certainly a highlight in supramolecular chemistry.

Borromean rings consist of three rings which are entangled in a way which prevents separation of the rings just by changing their shape (Figure 2). Opening one of the rings, however, makes the whole assembly fall apart. It is this property which has made the

Figure 1. A small selection from the mathematical zoo of knots.

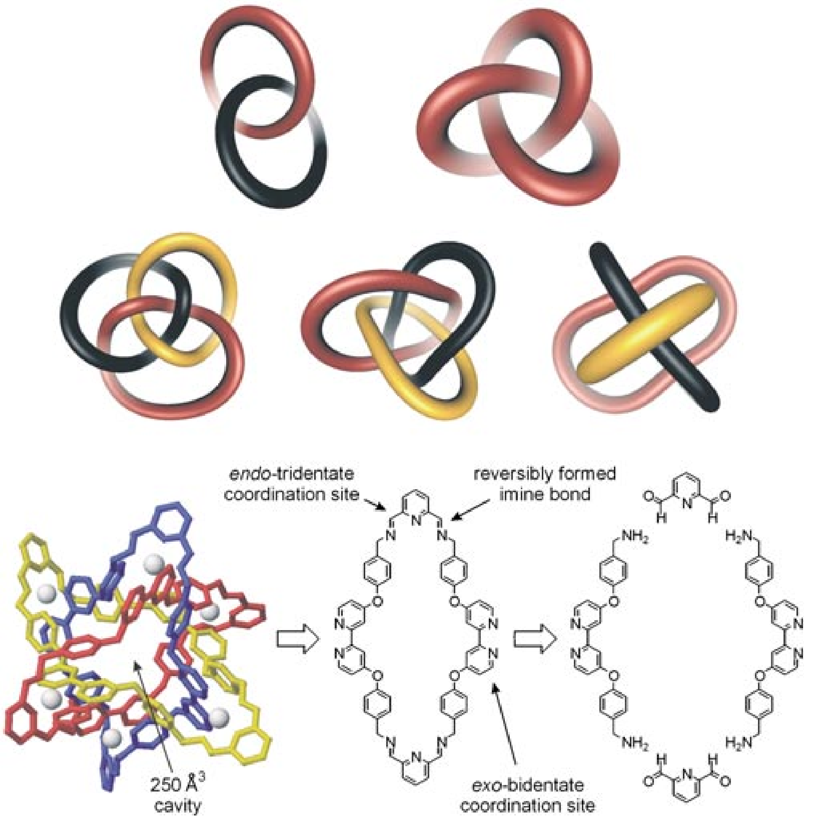

Figure 2. Top: Catenane (left) and trefoil knot (right). Center: Three views of Borromean rings. Bottom: Chemical realization of Borromean rings through self-organization.

---

[*] Priv.-Doz. Dr. C. A. Schalley
Kekulé-Institut für Organische Chemie
und Biochemie
Universität Bonn
Gerhard-Domagk-Strasse 1
53121 Bonn (Germany)
Fax: (+49) 228-735-662
E-mail: c.schalley@uni-bonn.de

DOI: 10.1002/anie.200460583

Borromean rings important in historical terms as a symbol for strength in unity.

Borromean rings can be found throughout the history of mankind—from the vikings to christian iconography to far-East family emblems.[8] Their name originated from the inclusion of the rings in the fifteenth century crest of the Borromeo family from Milan. Figure 3 shows the rings on the entrance to the church San Sigismondo in Cremona in the dukedom of Milan.

Figure 3. The entrance door to San Sigismondo in Cremona, carved from walnut wood by Paolo and Giuseppe Sacca between 1536 and 1542. Reproduced with kind permission of Dr. Peter Cromwell.[8]

The fact that the Borromean rings fall apart if one of them is missing or cut was utilized as evidence for the topology of the DNA-based Borromean rings: enzymatic cleavage of one of the rings destroys the whole structure and results in the formation of three independent parts. What is an advantage for characterization is a problem for the synthesis of Borromean rings in the laboratory. Although precursors for catenanes and rotaxanes can be found relatively easily because they need to organize only two subunits into a suitable crossed arrangement, a total of six such crossing points need to be generated in the correct geometry for the synthesis of Borromean rings.

The latter can only be successful with a sophisticated template synthesis.[9] One possible synthetic strategy relies on the application of two different template effects and leads to a stepwise synthesis (Figure 4).[10] In the first step the second ring is moved into and bound by the first ring.[11] The second step involves the third ring being subsequently threaded into the complex by a second template effect in which all the geometric requirements necessary for the generation of Borromean rings are fulfilled. Such a strategy has the merit of structural variability: if two different templates are used successively, the three rings can be different from each other.

The other synthetic extreme, that is, an elegant one-pot synthesis utilizing self-assembly processes,[12] has now been used by Stoddart, Atwood, and coworkers.[7] Self-assembly requires reversible, multiple error-checking and error-correction steps that enable the system to reach its thermodynamic minimum. The retrosynthetic strategy and the building blocks used in this synthesis are shown in Figure 2. The condensation of the dialdehydes and diamines shown to form imines serves as the reversible bond-formation step in the macrocyclizations.[13] The resulting macrocycle bears two pairs of opposing *endo*-tridentate and *exo*-bidentate metal-coordination sites and has the overall oval shape required for the threading process.

Under template-free conditions, a complicated mixture of macrocyclic and linear oligomers would be expected to form from these building blocks. Therefore, the presence of transition-metal ions is required to form kinetically labile complexes with the coordination sites built into the macrocycles. Six zinc(II) ions are perfectly suited for this purpose; they template the formation of Borromean rings by binding to one of the exocyclic bipyridine units of one of the three macrocycles and to one of the tridentate endocyclic coordination sites of the next one, thus bridging one ring with the others and providing a way of threading the macrocycles into each other. After one macrocycle is encapsulated within another, nonsaturated coordination sites remain at the zinc ions, and these control the threading of the open-chain precursor of the third macrocycle. A final macrocyclization terminates the synthesis, with the product formed in a yield of about 90%.

The characterization was achieved by NMR spectroscopy, ESI mass spectrometry,[14] and crystal-structure analysis. In the solid state the Borromean rings have an S_6 symmetry. The Zn^{II} ions

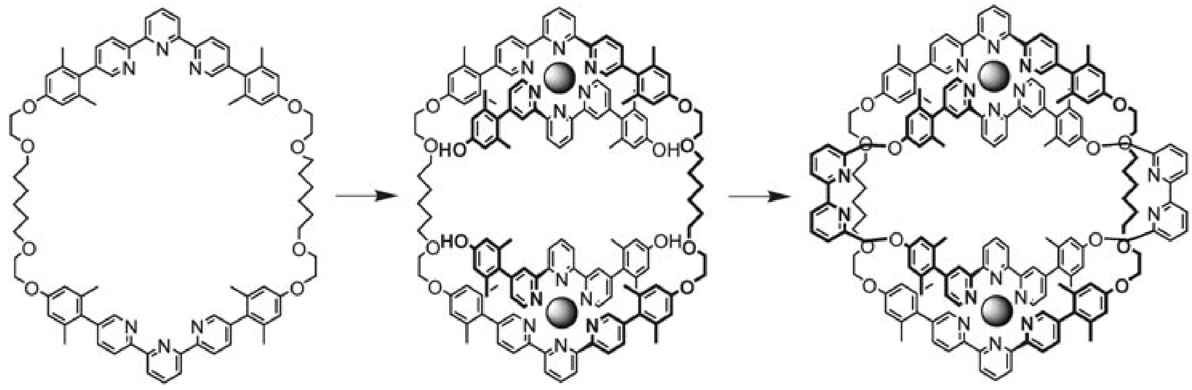

Figure 4. Stepwise synthesis of Borromean rings: Precursors and intermediates.

are 12.7 Å apart and have an almost octahedral coordination environment consisting of five nitrogen atoms and one oxygen atom from one of the triflate counterions. In addition to all their special topological features, the Borromean rings have a particular property that is highly interesting for supramolecular chemistry: They possess a cavity in their center with a volume of about 250 Å^3 which is defined by twelve oxygen atoms. ESI mass spectrometry as well as ^{1}H NMR experiments indicate the presence of an additional $\mathrm{Zn(CF_3SO_3)_2}$ ion triple as a guest inside the cavity.

In view of the cavity and the defined arrangement of six transition-metal ions, it will be interesting to follow the further development of the Borromean rings, which will likely take them far beyond their aesthetic structure into the world of functional materials.

---

[1] a) G. Schill, *Catenanes, Rotaxanes and Knots*, Academic Press, New York, **1971**; b) *Molecular Catenanes, Rotaxanes, and Knots* (Eds.: J.-P. Sauvage, C. Dietrich-Buchecker), Wiley-VCH, Weinheim, **1999**.

[2] a) V. Balzani, A. Credi, F. M. Raymo, J. F. Stoddart, *Angew. Chem.* **2000**, *112*, 3484; *Angew. Chem. Int. Ed.* **2000**, *39*, 3348; b) C. A. Schalley, A. Lützen, M. Albrecht, *Chem. Eur. J.* **2004**, *10*, 1072.

[3] Pictures of the knots were generated with the shareware program Knotplot by Rob Scharein: http://www.cs.ubc.ca/nest/imager/contributions/scharein/KnotPlot.html.

[4] a) C. O. Dietrich-Buchecker, J.-P. Sauvage, *Angew. Chem.* **1989**, *101*, 192; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 189; b) R. F. Carlina, C. Dietrich-Buchecker, J.-P. Sauvage, *J. Am. Chem. Soc.* **1996**, *118*, 9110; c) P. R. Ashton, O. A. Matthews, S. Menzer, F. M. Raymo, N. Spenzer, J. F. Stoddart, D. J. Williams, *Liebigs Ann.* **1997**, 2485; d) G. Rapenne, C. Dietrich-Buchecker, J.-P. Sauvage, *J. Am. Chem. Soc.* **1999**, *121*, 994; e) S. C. J. Meskers, H. P. J. M. Dekkers, G. Rapenne, J.-P. Sauvage, *Chem. Eur. J.* **2000**, *6*, 2129; f) O. Safarowsky, M. Nieger, R. Fröhlich, F. Vögtle, *Angew. Chem.* **2000**, *112*, 1699; *Angew. Chem. Int. Ed.* **2000**, *39*, 1616; g) H. Adams, E. Ashworth, G. A. Breault, J. Guo, C. A. Hunter, P. C. Mayers, *Nature* **2001**, *411*, 763; h) C. R. Woods, M. Benaglia, S. Toyota, K. Hardcastle, J. S. Siegel, *Angew. Chem.* **2001**, *113*, 771; *Angew. Chem. Int. Ed.* **2001**, *40*, 749; i) F. Vögtle, A. Hünten, E. Vogel, S. Buschbeck, O. Safarowsky, J. Recker, A. H. Parham, M. Knott, W. M. Müller, U. Müller, Y. Okamoto, T. Kubota, W. Lindner, E. Francotte, S. Grimme, *Angew. Chem.* **2001**, *113*, 2534; *Angew. Chem. Int. Ed.* **2001**, *40*, 2468; j) O. Lukin, W. M. Müller, U. Müller, A. Kaufmann, C. Schmidt, J. Leszczynski, F. Vögtle, *Chem. Eur. J.* **2003**, *9*, 3507.

[5] Metallic microknots and Borromean Rings have been generated on a micro- to millimeter scale by chemical means. Their fabrication relies on the electrodeposition of a metal on two suitably patterned cylinders, and finally producing a junction between the two cylinders at the right parts of their surfaces. Removing the cylinders finally yields the desired microknots: H. Wu, S. Brittain, J. Anderson, B. Grzybowski, S. Whitesides, G. M. Whitesides, *J. Am. Chem. Soc.* **2000**, *122*, 12691.

[6] a) C. Mao, W. Sun, N. C. Seeman, *Nature*, **1997**, *386*, 137; the synthesis of trefoil and figure-eight knots based on DNA and RNA have also been reported: b) S. M. Du, B. D. Stollar, N. C. Seeman, *J. Am. Chem. Soc.* **1995**, *117*, 1194; c) H. Wang, R. J. Di Gate, N. C. Seeman, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 9477.

[7] K. S. Chichak, S. J. Cantrill, A. R. Pease, S.-H. Chiu, G. W. V. Cave, J. L. Atwood, J. F. Stoddart, *Science* **2004**, *304*, 1308; for a report on this publication, see J. S. Siegel, *Science*, **2004**, *304*, 1256.

[8] P. R. Cromwell, E. Beltrami, M. Rampichini, *Mathematical Intelligencer* **1998**, *20*, 53.

[9] a) T. J. Hubin, A. G. Kolchinski, A. L. Vance, D. H. Busch, *Adv. Supramol. Chem.* **1999**, *5*, 237; 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; d) M. Kogej, P. Ghosh, C. A. Schalley, *How to thread a string into the eye of a molecular needle: Template-directed synthesis of mechanically interlocked molecules* in *Strategies and Tactics in Organic Synthesis*, *Vol. 4* (Ed.: M. Harmata), Elsevier, Amsterdam, **2004**, p. 171.

[10] Precursors for the synthesis of Borromean rings have been reported previously: J. C. Loren, M. Yoshizawa, R. F. Haldimann, A. Linden, J. S. Siegel, *Angew. Chem.* **2003**, *115*, 5880; *Angew. Chem. Int. Ed.* **2003**, *42*, 5702.

[11] a) M. Schmittel, A. Ganz, D. Fenske, *Org. Lett.* **2002**, *4*, 2289; b) S.-H. Chiu, A. R. Pease, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **2002**, *114*, 280; *Angew. Chem. Int. Ed.* **2002**, *41*, 270.

[12] a) G. M. Whitesides, J. P. Mathias, C. T. Seto, *Science* **1991**, *254*, 1312; b) D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154; c) J.-M. Lehn, *Chem. Eur. J.* **2000**, *6*, 2097; d) M. Albrecht, *Chem. Rev.* **2001**, *101*, 3457.

[13] a) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem.* **2002**, *114*, 938; *Angew. Chem. Int. Ed.* **2002**, *41*, 898; reviews: b) P. A. Brady, J. K. M. Sanders, *Chem. Soc. Rev.* **1997**, *26*, 327; c) J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455.

[14] For MS studies aimed at the structural characterization of topologically interesting molecules, see also a) C. A. Schalley, *Int. J. Mass Spectrom.*, **2000**, *194*, 11; b) C. A. Schalley, *Mass Spectrom. Rev.* **2001**, *20*, 253.