Nanoscale Borromean Rings

STUART J. CANTRILL, KELLY S. CHICHAK,
ANDREA J. PETERS, AND J. FRASER STODDART*
*California NanoSystems Institute and Department of
Chemistry and Biochemistry, University of California,
Los Angeles, 405 Hilgard Avenue,
Los Angeles, California 90095-1569*

Received August 9, 2004

ABSTRACT
The molecular expression of topologically interesting structures represents a formidable challenge for synthetic chemists. The nontrivial link known as the Borromean rings has long been regarded as one of the most ambitious targets in this field. Of ancient provenance, this symbol comprises three interlocked rings in an inseparable union, but cut any one of the rings and the whole assembly unravels into three separate pieces. This Account delineates different strategies that can be applied to the formation of molecules possessing this distinctive topology, culminating with two successful syntheses of such compounds, thus cutting the Gordian knot of topological chemistry.

Introduction

The circle is one of the most ubiquitous and powerful symbols in human culture and has been so since time immemorial. With no beginning or end, this primeval metaphor for eternity is, in a conceptual or physical manifestation, relevant to many, the artist, the philosopher, the mathematician, the engineer, and the scientist to name but a few. Although perhaps apocryphal, the story of Kékulé's dream, in which the cyclic nature of benzene became apparent[1] to him, defines a point in history when chemistry, then still in its infancy, embraced rings. The synthesis and study of macrocycles evolved[2] thereafter, and the allure of tying together the ends of longer and longer molecular strands remains undiminished to this day.[3] Apart from the challenge posed by their synthesis, the properties of cyclic macromolecules[4] are just beginning to be explored. An obvious structural consequence of an appropriately sized cyclic architecture (molecular or otherwise) is the ability to link one or more additional rings to it to form a chain. Such a proposal, in a molecular context, was made[5] by Willstätter during a seminar in Zürich in the early part of the 20th century. Pioneering work by Lüttringhaus[6] in the field of macrocyclizations led to an attempt, reported in 1958, to synthesize a compound comprised of two linked rings, one of them being a cyclodextrin.[7] Although it was unsuccessful, the discussion of generic strategies targeting the synthesis of such compounds laid the foundations for those that followed. It was not until 1960, that the synthesis of the first [2]-catenane, a compound containing molecules comprised of two mutually interlocked rings, was reported by Wasserman.[8] This landmark in chemical synthesis spurred the pursuit of chemical topology[5,9] and topological stereochemistry[10] and resulted in the creation of many interwoven and interlocked molecular compounds.[11]

Whereas two rings can only be linked mechanically[12] in just one arrangement, i.e., a [2]catenane (**I**), much more complex topological constructs (e.g., **II**−**IV**) can be as-

* To whom correspondence should be addressed. Telephone: 310-206-7078. Fax: 310-206-1843. E-mail: stoddart@chem.ucla.edu.

Stuart J. Cantrill graduated with a B.Sc. in Chemistry and Bioorganic Chemistry from the University of Birmingham in the U.K. After receiving his M.Phil. from the same institution, he completed his Ph.D. studies with Fraser Stoddart at UCLA. After a 2-year sojourn at Caltech, as a postdoctoral scholar in the research group of Robert Grubbs, he returned to UCLA as a lecturer and research associate.

Kelly S. Chichak received his B.Sc. in Chemistry in 1994 and then obtained his Ph.D. in Organic Chemistry in 2001 from the University of Alberta under the supervision of Neil Branda. Currently, he is a postdoctoral scholar at UCLA in the Stoddart research group. His research interests include the design and synthesis of three-dimensional architectures and mechanically interlocked molecules by employing dynamic covalent chemistry and transition-metal templates.

Andrea J. Peters graduated from the University of Winnipeg with a B.Sc. in Chemistry in 1998. She received her Ph.D. Degree from Simon Fraser University in 2003 under the supervision of Neil Branda. She is currently at UCLA working as a postdoctoral scholar in the Stoddart research group. Her research interests include the design, synthesis, and study of dynamic supramolecular systems and novel photochromic systems.

J. Fraser Stoddart received all of his degrees (B.Sc., Ph.D., D.Sc.) from the University of Edinburgh. He presently holds the Fred Kavli Chair of Nanosciences at the University of California, Los Angeles, where he is also Director of the California NanoSystems Institute. His research interests relate broadly to the nature of the mechanical bond.
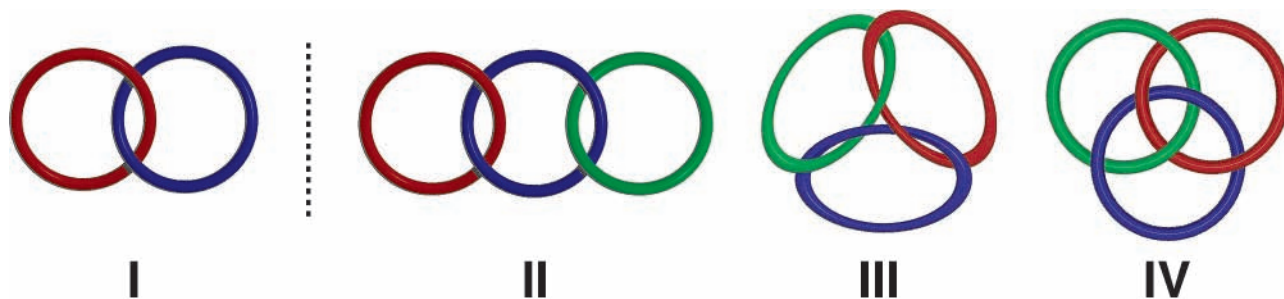
FIGURE 1. Some nontrivial two- and three-ring links, namely, (**I**) a [2]catenane, (**II**) a linear [3]catenane, (**III**) a cyclic [3]catenane,[14] and (**IV**) the Borromean rings.
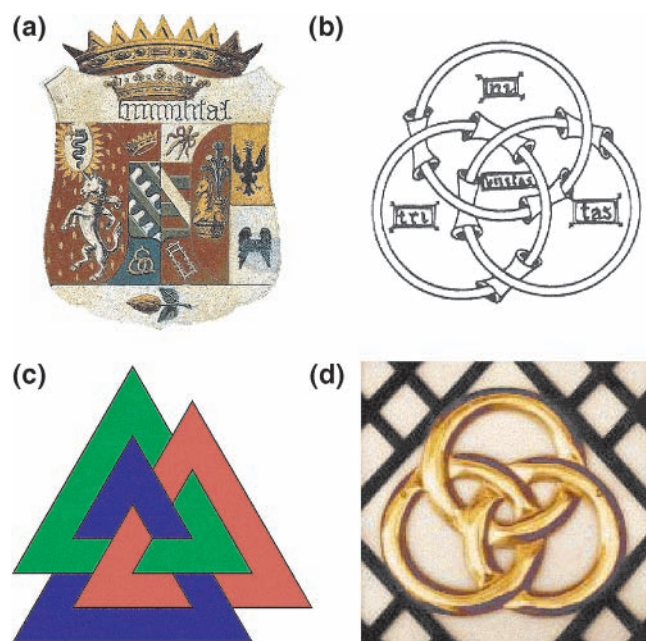

FIGURE 2. Symbols with the topology of the Borromean-link cross-cultural divides throughout history as can be visualized[15] by their use in (a) the crest of the Borromeo family of Renaissance Italy, (b) Christian iconography to represent the Holy Trinity, (c) Norse mythology as the Walknot (knot of the slain), and (d) Shinto symbolism, signifying the three realms of heaven, earth, and the underworld.

sembled with three (or more) rings, as exemplified (Figure 1) by van Gulick.[13] One of the most intriguing of the three-ring links is **IV**; no two rings are linked (i.e., catenated), yet all three remain, as a whole, inseparable. A significant corollary, therefore, is that, upon scission of any one ring, the entire assembly falls apart to give three separate components, namely, two free rings and a linear remnant of the cleaved ring. The use of motifs such as **IV** in their heraldic designs (Figure 2a) forever connected[15] the Borromeo family of Renaissance Italy[16] with this interweaving of three rings. To this day, links exhibiting this topology are commonly referred to as Borromean rings. Such symbols, however, significantly predate this period of history. Earlier examples (parts b–d of Figure 2) can be found[15,17] in Christian iconography and Norse mythology, as well as in ancient Asian engravings. In the general sense, this link is often emblematic of an entity which, as a whole, consists of three vital synergistic parts that, following removal of any one of the integral components,

cannot persist. Parallels with accepted dogma, either cultural, familial, or spiritual, are apparent, with the common tenet being that of "strength in unity". This fundamental message perhaps rationalizes the widespread yet independent adoption[18] of this imagery across both geographical and historical divides. Such allegory is also pertinent in a less abstract context and has been admitted into the scientific lexicon to describe more eloquently the properties of halo nuclei.[19]

In chemistry, the topology of the molecular Borromean rings poses a significant synthetic challenge. The rise of supramolecular chemistry[20] and the concomitant study of noncovalent bonding interactions has facilitated our ability to manipulate the geometry of multiple interacting and/or reacting components, so much so, that supramolecular assistance to covalent synthesis has become an invaluable paradigm[21] for the creation of interlocked molecules. Nevertheless, although the template-directed[22] synthesis of catenanes,[11] rotaxanes,[11,23] and knots,[11,24] is now routine, the unique disposition of the three noncatenated yet mutually interlocked rings of the Borromean-link topology introduces an even higher level of complexity. Here, we present a survey of possible retrosynthetic disconnections and review the state of the art in terms of the application of these pathways toward the ultimate goal, the synthesis of molecular Borromean rings.

Generic Strategies

A retrosynthetic analysis of the Borromean link (**IV**) reveals (Figure 3) four reasonable starting points (a–d) from which to mount a challenge on the synthesis of a compound with this exceptional topology. Although each pathway is not unique,[25] the initial supermolecules, a ring-in-ring complex (a), an interwoven braid (b), a tennis-ball seam complex (c), and double-threaded [3]pseudorotaxanes (d), define four distinct strategies for the construction of molecular Borromean rings. The ring-in-ring approach (a) relies initially upon the ability to thread perpendicularly one macrocycle through another. Once this threading is orchestrated, linear precursors of the final ring must be woven throughout the ring-in-ring supermolecule, ensuring the formation of a Borromean link upon macrocyclization. By contrast, a method (b) based on the multiple cyclization of acyclic fragments is also feasible. The braiding together of three molecular strands, in a highly specific fashion, affords an intertwined supermol-
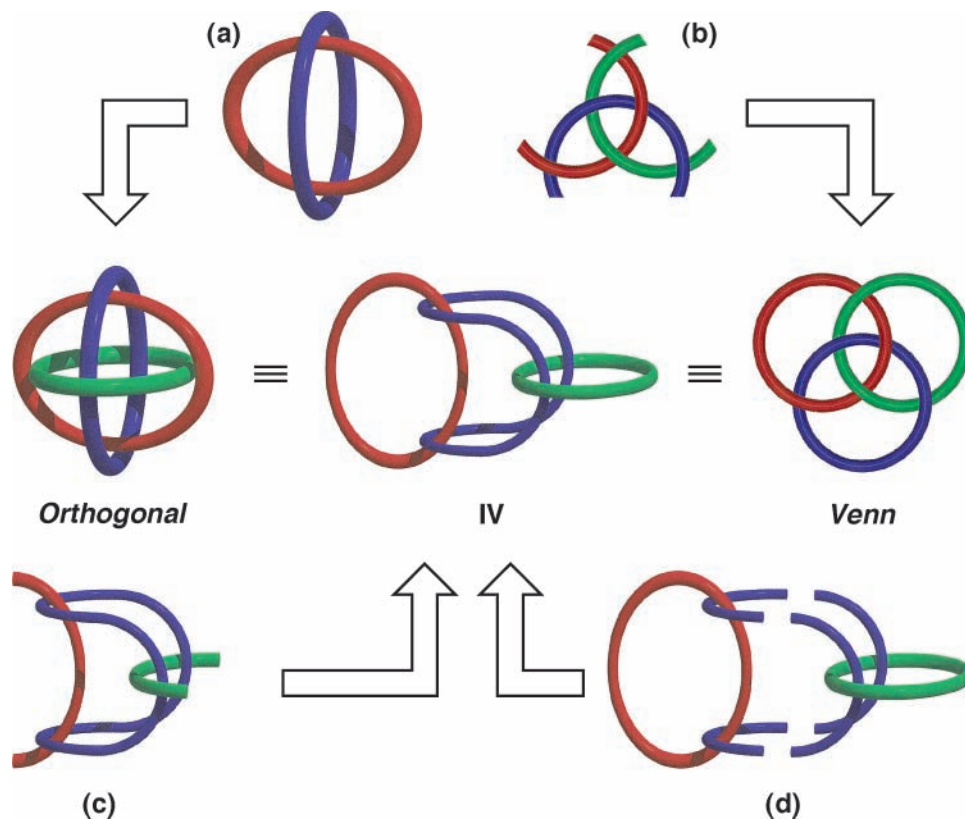
FIGURE 3. Generic strategies for the synthesis of Borromean-ring compounds (**IV**), which may also be depicted in *orthogonal* and *Venn* arrangements.

ecule harboring the crossing points that, following the appropriate triple macrocyclization, ultimately define the Borromean topology. The two other retrosynthetic disconnections are founded upon the ability to complex, in very different ways, a macrocyclic component with two linear ones. Assembly of a macrocycle and two linear guest molecules into a complex reminiscent, in part, of a tennis-ball seam (c) would, if followed by the appropriate double macrocyclization, afford a Borromean-ring compound. Alternatively, a double-threaded [3]pseudorotaxane is formed (d) when the two linear components both pierce the cavity of the macrocycle. Two of these supermolecules can be joined together, through the appropriate coupling of the acyclic guests, to form the desired Borromean architecture. The demands, common to each of these strategies, are not inconsiderable and dictate that a mastery of making both covalent and noncovalent bonds is paramount. Indeed, not only must the macrocyclizations proceed with high chemo- and/or regioselectivity, but also the relative spatial dispositions of the reacting fragments must be precisely controlled, i.e., high stereoselectivities must be attained to enforce the required toposelectivity.

Ring-in-Ring Strategies

A ring-in-ring[26] strategy for the assembly of molecular Borromean rings was, to the best of our knowledge, first outlined in print by Busch[27] in a 1999 review on templated synthesis. This proposal (Figure 4) entails a ring-in-ring assembly in which the two aromatic rings of a bis-*para*-

phenylene crown ether are encircled by a bisbipyridinium cyclophane, a variation upon a well-established[28] π-donor/ π-acceptor recognition motif. As a consequence of this mode of complexation, in which the inner macrocycle is pinched together in its middle, the two oligoether portions of the crown ether are expected to form loops on opposite sides of the tetracationic cyclophane. Thereafter, each of these loops, themselves reminiscent of smaller crown ethers when constrained in this manner, should be able to accommodate secondary dialkylammonium ($R_2NH_2^+$) ions in a fashion analogous to another well-known[29] supramolecular threading motif. Subsequent [1+1] ring closure of the end-functionalized $R_2NH_2^+$ ion-containing components would afford a molecule with the Borromean-link topology. Although this specific scheme, as far as we know, remains a paper one, the delineation of the strategy undoubtedly represents a significant milestone in the development of the field. Indeed, Busch proceeds to speculate that metal–ligand interactions, with their inherently precise coordination numbers and geometries could facilitate the assembly of Borromean rings in molecular forms.

The ability of macrocyclic polyethers to bind $R_2NH_2^+$ ions has been investigated extensively by us[29b,30] and others[29a,31] during the past decade. The systematic variation in (i) the size of the cavity of the host and (ii) the geometry and number of $CH_2NH_2^+CH_2$ centers that define the guest has uncovered a reliable self-assembly algorithm[30] for the construction of interwoven supermolecules. Specifically, the propensity for bis-*para*-phenylene[34]-
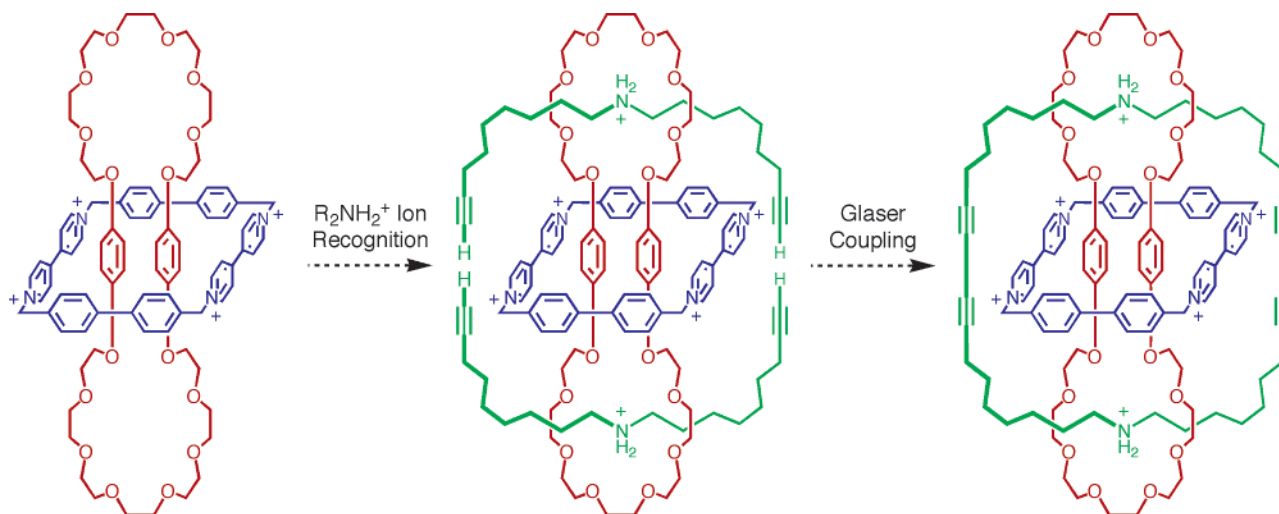
FIGURE 4. Busch's proposed[27] ring-in-ring synthesis of a Borromean-ring compound.

FIGURE 5. Conceptual advance[32] from a double-threaded [3]pseudorotaxane to a ring-in-ring complex based upon the interaction between crown ethers and secondary dialkylammonium ions.

crown-10 (BPP34C10) to host, within its cavity, two dibenzylammonium (DBA$^+$) cations foreshadows (Figure 5) the possibility of a ring-in-ring counterpart. Simply put, the notional linking of the ends of the DBA$^+$ ions in this double-threaded [3]pseudorotaxane ([BPP34C10·2DBA]$^{2+}$) begets a ring-in-ring complex. Consequently, a suitably proportioned dicationic macrocycle possessing two ammonium sites should also nestle quite comfortably inside the cavity of BPP34C10. This hypothesis was indeed vindicated when it was found[32] that the bismethylene-bridged bis-DBA$^+$ macrocycle **1**−H$_2$·2PF$_6$ forms a 1:1 complex with BPP34C10 in both the solution and solid states. Moreover, X-ray crystallography reveals that stabilization of this superstructure is achieved through the anticipated intercomponent N$^+$−H···O hydrogen-bonding interactions. In this case, the peripheral "loops" of the inner dicationic macrocycle do not protrude significantly beyond the mean plane of the crown ether belt, thereby precluding the penetration of the fragments necessary to construct the third and final ring of a Borromean ensemble. Nevertheless, this prototypical ring-in-ring species assuredly heralds the creation of similar 1:1 complexes in which BPP34C10 can be impaled reliably upon a range of dicationic macrocycles. By extension, the inclusion of expanded loop regions within these ammonium-ion-containing macrocycles would permit the threading of precursors of the third ring. Obviously, size is not the only

consideration; a template is required to direct the final macrocyclization and ensure that the connections are made with the appropriate selectivity. This requirement can be satisfied by locating complementary recognition sites, orthogonal to those that mediate the assembly of the initial ring-in-ring complex so as to avoid scrambling, in both the linear threading pieces and the expanded loop regions.

The application of metallosupramolecular chemistry[33] to the challenge of generating ring-in-ring architectures soon followed, when Schmittel[34] reported the formation (Figure 6) of such mono- and dinuclear superstructures. Building upon his prior investigations[35] into the controlled self-assembly of heteroleptic bisphenanthroline metal complexes, he synthesized phenanthroline-containing macrocycles harboring either exo- or endotopic binding sites, representing molecular turns[27] that are divergent or convergent, respectively. Subsequent Cu^I-mediated association of two monophenanthroline macrocycles, one with an endotopic chelation site and the other with an exotopic one, afforded two examples of relatively compact yet also somewhat strained ring-in-ring complexes. The combination, however, of two significantly larger bis-phenanthroline macrocycles, one bearing two endocyclic binding sites and the other presenting two exocyclic ones, gave a more stable dicopper ring-in-ring superstructure, as evidenced by mass spectrometric and nuclear magnetic
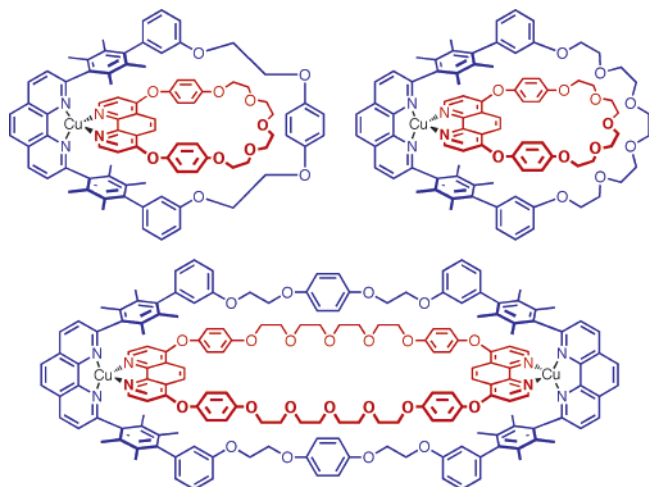
FIGURE 6. Schmittel's mono- and dinuclear ring-in-ring complexes[34] based upon macrocycles with exo (red) and endo (blue) phenanthroline recognition sites.

resonance (NMR) spectroscopic studies. Although Schmittel does not speculate as to the utility of these complexes, it is apparent that the principles that underpin this research could be exploited for the ring-in-ring syntheses of Borromean-ring compounds. The dinuclear complex could be adapted for this purpose. Incorporation of additional recognition elements, orthogonal to the phen−Cu^I−phen interaction, in the loops of each macrocycle, could facilitate threading of the components necessary for the construction of a third ring defining a Borromean topology for such a three-ring edifice.

These ring-in-ring strategies incorporate only recognition sites necessary for the mutual recognition of two macrocyclic components, no more and no less. The successful macrocyclization of the third ring of the Borromean link is necessarily dependent upon the precise orchestration of its precursors immediately prior to any ring-closing reaction. Satisfaction of this requirement can be achieved by installing additional recognition units in one−or ideally both for total control−of the constituent macrocycles of the ring-in-ring complex, to serve as templates for the formation of the third ring. This strategy is being pursued by Siegel,[36] who recently published his

road map (Figure 7) for a ring-in-ring synthesis. The first ring in this pathway is a 66-membered one, containing two endo-oriented terpyridine moieties, that is obtained in very high yield via an elegant "figure-eight" synthesis guided by the complexation of a Cu^{II} ion. Unlike the ring-in-ring approaches discussed previously, the second ring is constructed in situ; i.e., the first ring is used to template the formation of the second to afford, directly, a ring-in-ring complex. Two linear Ru^{II}-terpyridine complexes, bearing labile chloride ligands, skewer the cavity of the first ring. Displacement of the halides and association with the two endocyclic terpyridine moieties of the ring gives rise to two independent heteroleptic octahedral complexes. The subsequent capping of this double-threaded [3]pseudorotaxane intermediate with bipyridine-containing bridges not only creates the second ring of the assembly but also installs the extra recognition loops crucial for the successful knitting together of the third and final ring. Furthermore, the X-ray crystal structure of this intermediate reveals that the dimensions are such that there is ample space for the threading of linear components through the recognition loops that extend from either side of the ring-in-ring superstructure. It is only a matter of time before the successful implementation of this approach for the synthesis of a compound with the Borromean-link topology is reported.

All-in-One Strategies

By contrast with the stepwise macrocyclizations characteristic of the ring-in-ring approaches, all-in-one strategies achieve the knitting together of all three rings of the Borromean link in one fell swoop. The successful implementation of this comprehensive protocol, however, necessitates the careful selection and design of the acyclic precursors. These building blocks must be programmed to recognize one another in a selective fashion, ensuring their unambiguous union to form molecular Borromean rings. This methodology is arguably best-suited for the construction of homomacrocyclic Borromean-ring compounds, i.e., ones in which all three rings are identical, because selectivity issues are minimized in this case. On
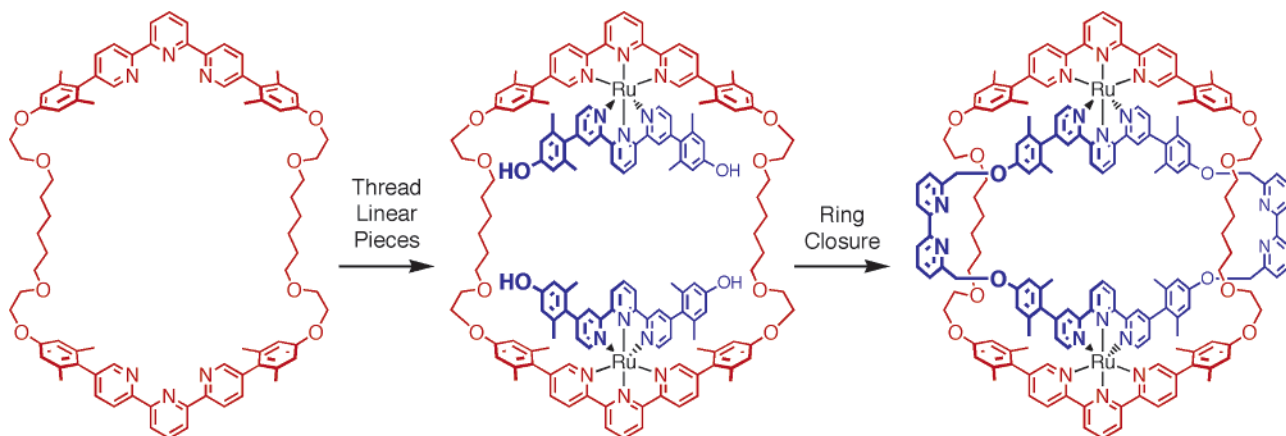

FIGURE 7. Synthesis[36] of Siegel's ring-in-ring complex, in which two endo bipyridyl ligands await the threading of the components necessary for construction of the final ring of a molecular Borromean link.

the other hand, heteromacrocyclic Borromean links, i.e., those comprised of at least two different rings, can conceivably[36] be accessed by the stepwise ring-in-ring approach. Nonetheless, as the following example demonstrates, the all-in-one approach can, given exquisite control, produce a heteromacrocyclic Borromean link.

Although commonly recognized as a repository for the genetic blueprint of living organisms, DNA also serves as an effective construction material. This medium, most notably exploited by Seeman[37] for the creation of numerous nonnatural DNA nanostructures, has many attractive features. In particular, the predictable hydrogen-bond-mediated Watson−Crick base pairing between DNA molecules harboring complementary base sequences represents a powerful self-assembly paradigm. Furthermore, biotechnology has given rise to a battery of techniques that allow us to create and subsequently manipulate DNA strands in a highly efficient and specific manner, whether linking them together, tearing them apart, or twisting them this way or that. Significantly, the fact that double-stranded DNA does not exist as a simple ladder structure, rather it winds itself into a helix, is fundamentally important in a topological context. Each double-helical turn represents a crossing point, characterized as either positive or negative, depending upon the handedness of the helix, that is equivalent to the "node" or "unit tangle" common to the field of topology. Using this relationship, the construction of different nucleic-acid-based topological species can be achieved by the judicious linking together of combinations of right- and/or left-handed double-helical DNA, denoted as B- and Z-DNA, respectively.

The traditional planar Venn representation of the Borromean rings can be redrawn (Figure 8) such that all of the nodes are replaced by one and a half turns of a double helix. The three inner helices are right-handed,

whereas the three outer ones are left-handed, reflecting the equal number of positive and negative crossings that define a Borromean link. This "polar projection" can be deformed continuously into a "three-dimensional" representation that reveals a more obvious retrosynthetic disconnection, involving the ligation of two stable three-arm junctions, one constructed from B-DNA and the other from Z-DNA. Using this strategy, Seeman[38] designed and synthesized six single DNA strands and assembled them separately into the two required junctions, before they were combined and annealed to form a DNA Borromean link.[39] This landmark in topological chemistry represents the first molecular expression of the Borromean rings and arises from a braiding approach, equivalent to that first suggested by van Gulick.[13] Each ring of this heteromacrocyclic DNA Borromean link contains a different hairpin motif, each harboring a site that is targeted by a specific restriction enzyme. This design feature allows for the conclusive characterization of the product and confirms the expected topology. When, in turn, each ring of the link is cleaved, only its own linear debris and the other two separate, i.e., noncatenated rings, remain, an innate and defining feature of such an assembly.

In addition to this hydrogen-bonding approach, the interweaving of acyclic molecular strands, resulting in the formation of complex architectures, can also be mediated[40] by metal−ligand interactions. In isolation, the six crossing points depicted (Figure 3) in the orthogonal representation of the Borromean rings can be equated with mononuclear metal−ligand complexes in which two rings of the Borromean link furnish the necessary ligands, one exocyclic and one endocyclic. Overall, this model (top of Figure 9) requires, therefore, that each component macrocycle of the Borromean link be comprised of a sequence of four alternating (exo/endo/exo/endo) che-
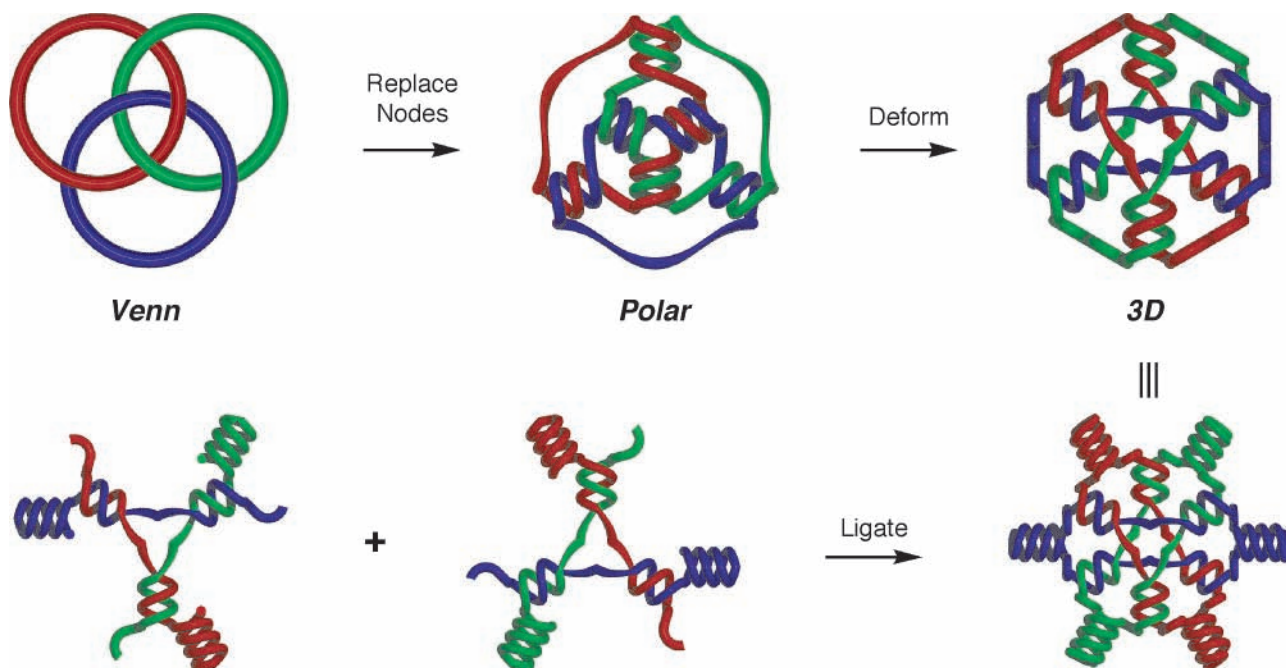

FIGURE 8. (Top) Translation and deformation of the *Venn* Borromean link into a *3D* structure with double-helical regions. (Bottom) Synthetic approach[38] for the formation of a DNA Borromean-ring compound from the ligation of two three-arm junctions.
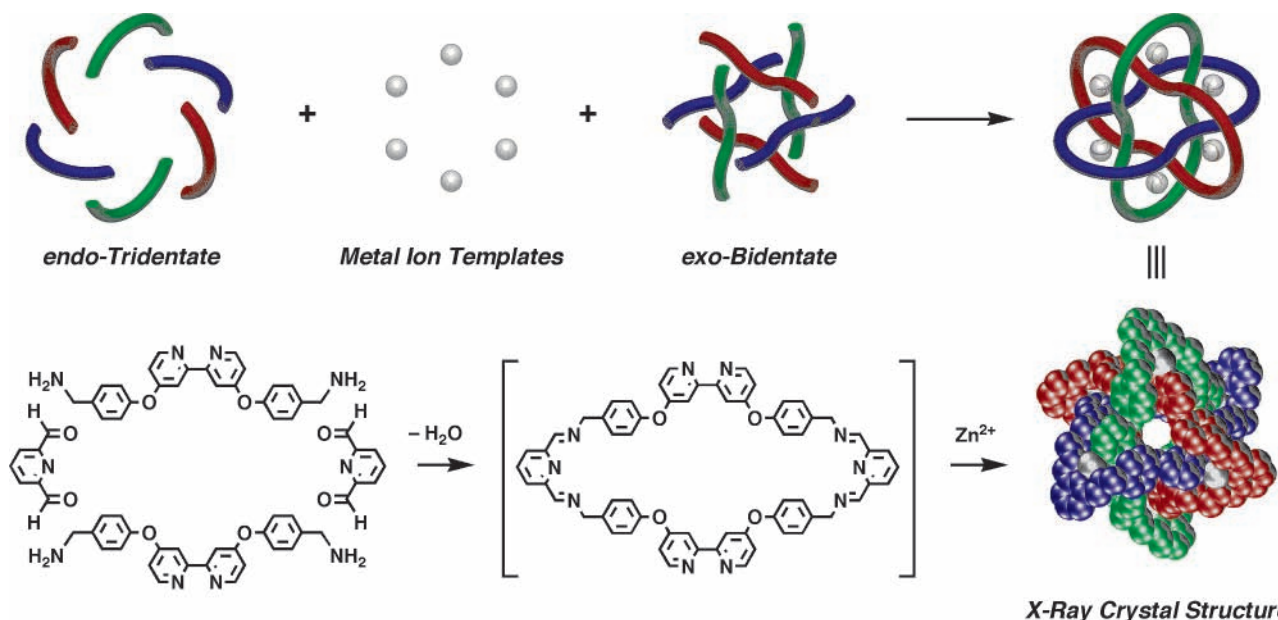
FIGURE 9. (Top) Schematic assembly of a Borromean link from a combination of *endo-tridentate* and *exo-bidentate* ligands around *metal ion templates*. (Bottom) Reversible reaction of 2,6-diformylpyridine with a diamine, containing a dipyridyl binding site, in the presence of zinc acetate affords[42] a molecular Borromean link.

lation sites. In essence, such requirements are just those of the metallosupramolecular ring-in-ring strategies discussed[34,35] earlier. In contrast, however, introducing the aspect of reversibility by performing the covalent as well as the noncovalent assembly under thermodynamic control allows for all three rings to be synthesized in one pot. If complete cross complementarity between the exo and endo sites (i.e., exo only matches with endo and vice versa) is achieved, successful ring closing of all three rings should result in the formation of molecular Borromean rings. Furthermore, the use of dynamic covalent chemistry[41] introduces the all-important element of error checking whereby "incorrect" products fall victim to a thermodynamic proof-reading step wherein their components are cycled back into an equilibrating mixture, which, if the system has been designed correctly, should ultimately afford the stable Borromean-ring structure. We have been pursuing such a strategy since 1999, by employing[42] tridentate 2,6-bisiminopyridyl and bidentate 2,2-bipyridyl moieties as the endo and exo ligands, respectively. This choice of ligands not only facilitates the selective formation of heteroleptic five-coordinate complexes, i.e., satisfying the necessary endo/exo complementarity, but also provides the required dynamic covalent bond, namely, the carbon–nitrogen double bonds, i.e., imines. Once the correct spacing between the recognition sites had been determined using computer-aided molecular modeling, the desired diamine ligand was synthesized in five steps in an overall yield of 42%. This ligand was subsequently reacted, in boiling methanolic solution, with 2,6-diformylpyridine in the presence of zinc acetate (bottom of Figure 9) affording, in ~80% yield without chromatography, the hexanuclear[43] Borromean-ring compound. The structure was characterized in solution (NMR spectroscopy) and in the gas phase (electrospray ionization mass spectrometry), and its interlocked nature was confirmed

unambiguously by X-ray crystallography, which reveals the formation of a nanoscale Borromean link measuring roughly 2.5 nm across. In addition, this structure possesses an inner chamber, with a volume of 250 Å^3, lined with 12 oxygen atoms and, as such, is reminiscent of Cram's spherands.[44] Indeed, when the assembly of these Borromean rings is performed in 95% ethanol, there is strong evidence suggesting that the cavity is occupied partially with a seventh Zn^{II} ion.

Conclusions

On account of the endless fascination the Borromean rings hold far beyond the realms of chemistry; they have long been considered a holy grail for synthetic chemists inspired by topology and committed to extending the influence of the mechanical bond beyond catenanes, rotaxanes, and knots. And indeed, as the saying goes, there is more than one way to skin a cat! Conceptually, the [3]-pseudorotaxane and tennis-ball seam complexes offer viable routes for the formation of Borromean-ring compounds, and the successful implementation of either of these methods simply awaits the creative exploitation of appropriate molecular recognition paradigms. The stepwise ring-in-ring strategies will undoubtedly result in the formation of Borromean-ring compounds, but with heavy investments in the more traditional aspects of synthesis, it is difficult to envision such approaches yielding large quantities of material. Nevertheless, such protocols perhaps offer a greater degree of structural control, thereby allowing easier access to systems comprised of at least two different rings. Comprehensive template-directed, all-in-one strategies represent the most efficient and indeed successful approaches to date. Seeman's clever manipulation of DNA sequences resulted in the first known example of molecular Borromean rings. The smallest known Bor-

romean link to date resulted from an all-in-one synthetic strategy that combines the virtues of reversibility, proof reading, and error checking that we associate with supramolecular and dynamic covalent chemistry, together with the geometrical guidance and precision that we entrust to coordination chemistry. We are confident that a new era in topological chemistry is dawning. More chemical examples of Borromean links await discovery[45] and creation.[46]

References

(1) Kékulé's dream reputedly involved visions of a serpent biting its own tail, the ancient Ouroboros, a symbol commonly associated with alchemy. For a glimpse of the debate on the origin of the benzene structure, see Rocke, A. J. Waking up to the Facts—The Cyclical Structure of Benzene is a Landmark Achievement in Chemistry—But Who Should Rightfully be Credited with its Discovery? *Chem. Brit.* **1993**, *29*, 401–402, and a reply: Noe, C. R.; Bader, A. *Chem. Brit.* **1993**, *29*, 402.
(2) Pedersen, C. J. The Discovery of Crown Ethers (Noble Lecture). *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021–1027. Although the title of this article is repeated faithfully from the source, it refers to his Nobel lecture!
(3) *Large Ring Molecules*; Semlyen, J. A., Ed.; John Wiley and Sons: Chichester, U.K., 1996.
(4) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. An "Endless" Route to Cyclic Polymers. *Science* **2002**, *297*, 2041–2044.
(5) Frisch, H. L.; Wasserman, E. Chemical Topology. *J. Am. Chem. Soc.* **1961**, *83*, 3789–3795.
(6) Lüttringhaus, A.; Cramer, F.; Prinzbach, H.; Henglein, F. M. Cyclisationen von Langkettigen Dithiolen. *Liebigs Ann. Chem.* **1958**, *613*, 185–198.
(7) For a successful catenation of a cyclodextrin, see Armspach, D.; Ashton, P. R.; Moore, C. P.; Spencer, N.; Stoddart, J. F.; Wear, T. J.; Williams, D. J. The Self-Assembly of Catenated Cyclodextrins. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 854–858.
(8) (a) Wasserman, E. The Preparation of Interlocking Rings: A Catenane. *J. Am. Chem. Soc.* **1960**, *82*, 4433–4434. (b) Schill pioneered the covalent-template-directed approach to catenane synthesis. See Schill, G. Umwandlung einer Triansa-Verbindung in eine Catena-Verbindung. *Chem. Ber.* **1967**, *100*, 2021–2037.
(9) Tauber, S. J. Absolute Configuration and Chemical Topology. *J. Res. Nat. Bur. Stand. A* **1963**, *67*, 591–599.
(10) (a) Sokolov, V. I. Topological Ideas in Stereochemistry. *Russ. Chem. Rev.* **1973**, *42*, 452–463. (b) Walba, D. M. Topological Stereochemistry. *Tetrahedron* **1985**, *41*, 3161–3212.
(11) (a) Schill, G. *Catenanes, Rotaxanes, and Knots*; Academic Press: New York, 1971. (b) Amabilino D. B.; Stoddart, J. F. Interlocked Molecules. *Chem. Rev.* **1995**, *95*, 2725–2828. (c) Sauvage, J.-P.; Dietrich-Buchecker, C. *Molecular Catenanes, Rotaxanes, and Knots: A Journey Through the World of Molecular Topology*; Wiley–VCH: Weinheim, Germany, 1999.
(12) There are, however, other considerations, such as the degree of twisting in either of the two rings, when contemplating two-ring links. In a simple two-crossing [2]catenane-link, both rings are flat. If, however, one of the rings contains a half-twist, then a doubly interlocked [2]catenane is obtained. See Nierengarten, J.-F.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. Synthesis of a Doubly Interlocked [2]Catenane. *J. Am. Chem. Soc.* **1994**, *116*, 375–376. This interlocked molecule is one of the many elegant examples that Sauvage has introduced since 1983 into the arena of topological chemistry using metal ion templation. See Dietrich-Buchecker, C. O.; Sauvage, J.-P.; Kintzinger, J.-P. Une Nouvelle Famille de Molecules: Les Metallo-Catenanes. *Tetrahedron Lett.* **1983**, *24*, 5095–5098.
(13) van Gulick, N. Theoretical Aspects of the Linked Ring Problem. *New J. Chem.* **1993**, *17*, 619–625. This manuscript was written in 1960 and circulated as a preprint after being rejected by *Tetrahedron* as "not being chemistry" before finally being published in 1993. For a commentary, see Walba, D. M. Preface to van Gulick Paper. *New J. Chem.* **1993**, *17*, 618.
(14) For a cyclic [3]catenane, such as that depicted by structure **III**, there are four possible topological stereoisomers. In this two-dimensional representation, the crossing of any two rings is equivalent to one-half-turn of a helix. In this case, the sense of all three helices is right-handed, i.e., *PPP*. The structure in which all three helices are left-handed (*MMM*) is a nonsuperimposable mirror image of **III**; i.e., it is a topological enantiomer. A topologi-

(15) Cromwell, P. R.; Beltrami E.; Rampichini, M. The Borromean Rings. *Math. Intelligencer* **1998**, *20*, no. 1, 53–62. This article has been expanded and adapted into a webpage, see http://www.liv.ac.uk/~spmr02/rings/index.html.
(16) Although named after the Borromeo family, this linked symbol is also associated with other prominent Italian families of the period (for details, see ref 15). Most notable amongst these is the Medici family of Florence, whose connection with this imagery is immortalized in Botticelli's painting, Pallas and the Centaur. Finished in 1482, this piece of art, commissioned by Lorenzo di Piero de'Medici, otherwise known as Lorenzo the Magnificent, depicts Pallas (Athena) taming a centaur, a motif that is thought to be allegorical of wisdom triumphing over instinct. Significantly, the gown worn by Pallas is decorated with three- and four-component links, with the former akin to the Borromean rings, which were symbols of the Medici family. This painting now hangs in the Uffizi Gallery in Florence. We thank Joanne Wright in the Department of Fine Arts at the University of Nottingham for bringing this association to our attention.
(17) Siegel, J. S. Chemical Topology and Interlocking Molecules. *Science* **2004**, *304*, 1256–1258.
(18) Rings with the Borromean-link topology have been fashioned into logos of numerous organizations, including (i) the Ricordi Music Company, (ii) the Pisa Research Corporation, in which a Mobiüs strip is intertwined with the three-ring link, and (iii) the Ballantine Brewery of Newark, NJ. For a more comprehensive list, consult ref 15. Interestingly, it has been observed (Nickon, A.; Silversmith, E. F. *Organic Chemistry—The Name Game*; Pergamon Press: New York, 1987; pp 156–157) that, in the 1950s, students in Harvard's research laboratories would refer to "ballantine compounds" when describing Borromean-ring structures.
(19) Austin, S. M.; Bertsch, G. F. Halo Nuclei. *Sci. Am.* **1995**, *272*, 90–95.
(20) Lehn, J.-M. *Supramolecular Chemistry—Concepts and Perspectives*; Wiley–VCH: Weinheim, Germany, 1995.
(21) Fyfe, M. C. T.; Stoddart, J. F. Synthetic Supramolecular Chemistry. *Acc. Chem. Res.* **1997**, *30*, 393–401.
(22) (a) *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley–VCH: Weinheim, Germany, 2000. (b) Breault, G. A.; Hunter, C. A.; Mayers, P. C. Supramolecular Topology. *Tetrahedron* **1999**, *55*, 5265–5293. (c) Hubin, T. J.; Busch, D. H. Template Routes to Interlocked Molecular Structures and Orderly Molecular Entanglements. *Coord. Chem. Rev.* **2000**, *200*, 5–52.
(23) A rotaxane is a molecule comprised of a linear dumbbell-shaped component—bearing bulky end groups—around which one or more macrocycles are trapped. Although remote from mathematical concepts such as topology—the molecular graph of a rotaxane is, without exception, planar (see ref 10b)—rotaxanes are usually associated with their interlocked brethren, i.e., catenanes, as a consequence of structural similarity exhibited by those two archetypal classes of mechanically-linked compounds. The first reported synthesis of a rotaxane appeared less than a decade after that announcing the first catenane, see Harrison, I. T.; Harrison, S. The Synthesis of a Stable Complex of a Macrocycle and a Threaded Chain. *J. Am. Chem. Soc.* **1967**, *89*, 5723–5724.
(24) (a) Dietrich-Buchecker, C.; Sauvage, J.-P. Synthetic Molecular Knots. *New J. Chem.* **1992**, *16*, 277–285. (b) Dietrich-Buchecker, C.; Sauvage, J.-P. A Synthetic Molecular Trefoil Knot. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 189–192. (c) Lukin, O.; Vögtle, F. Knotting and Threading of Molecules: Chemistry and Chirality of Molecular Knots and Their Assemblies. *Angew. Chem., Int. Ed.* In press.
(25) Regardless of which pathway is chosen, the final step in the synthesis of any molecular expression of the Borromean link is the ring closure of the third ring. The nature of the intermediate that exists immediately prior to this post-assembly covalent modification may differ in a geometric sense; i.e., it may or may not incorporate a ring-in-ring motif, but the topology is the same and necessarily remains independent of the pathway, otherwise the product would not be the Borromean rings!
(26) Herein, the term "ring-in-ring" describes a complex in which one macrocyclic component is threaded through another such that their mean planes are approximately perpendicular to each other. For examples of the more familiar "macrocycle-within-macrocycle" juxtaposition, in which the mean planes of the rings are roughly coincident, see (a) Kim, S.-Y.; Jung, I.-S.; Lee, E.; Kim, J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. Macrocycles Within Macrocycles: Cyclen, Cyclam, and their Transition Metal Complexes Encapsulated in Cucurbit[8]uril. *Angew. Chem., Int. Ed.*

2001, *40*, 2119−2121. (b) Day, A. I.; Blanch, R. J.; Arnold, A. P.; Lorenzo, S.; Lewis, G. R.; Dance, I. A Cucurbituril-Based Gyroscane: A New Supramolecular Form. *Angew. Chem., Int. Ed.* **2002**, *41*, 275−277.

(27) Hubin, T. J.; Kolchinski, A. G.; Vance, A. L.; Busch, D. H. Template Control of Supramolecular Architecture. *Adv. Supramol. Chem.* **1999**, *5*, 237−357. Prior to this report, in partial satisfaction of UCLA doctoral degree requirements, one of us presented a not dissimilar ring-in-ring strategy. See Cantrill, S. J. The Synthesis of Borromean Rings. UCLA Original Research Proposal, December 15, 1998.

(28) Raymo, F. M.; Stoddart, J. F. Self-Assembling Cyclobis(paraquat-4,4′-biphenylene). *Pure Appl. Chem.* **1996**, *68*, 313−322.

(29) (a) Kolchinski, A. G.; Busch, D. H.; Alcock, N. W. Gaining Control Over Molecular Threading: Benefits of Second Coordination Sites and Aqueous−Organic Interfaces in Rotaxane Synthesis. *J. Chem. Soc., Chem. Commun.* **1995**, 1289−1291. (b) Ashton, P. R.; Campbell, P. J.; Chrystal, E. J. T.; Glink, P. T.; Menzer, S.; Philp, D.; Spencer, N.; Stoddart, J. F.; Tasker, P. A.; Williams, D. J. Dialkylammonium Ion/Crown Ether Complexes: The Forerunners of a New Family of Interlocked Molecules. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1865−1869.

(30) Cantrill, S. J.; Pease, A. R.; Stoddart, J. F. A Molecular Meccano Kit. *J. Chem. Soc., Dalton Trans.* **2000**, 3715−3734.

(31) (a) Takata, T.; Kihara, N. Rotaxanes Synthesized from Crown Ethers and Sec-Ammonium Salts. *Rev. Heteroat. Chem.* **2000**, *22*, 197−218. (b) Jones, J. W.; Gibson, H. W. Ion Pairing and Host−Guest Complexation in Low Dielectric Solvents. *J. Am. Chem. Soc.* **2003**, *125*, 7001−7004.

(32) Chiu, S.-H.; Pease, A. R.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. A Ring-in-Ring Complex. *Angew. Chem., Int. Ed.* **2002**, *41*, 270−274.

(33) (a) Fujita, M. Metal-Directed Self-Assembly of Two- and Three-Dimensional Synthetic Receptors. *Chem. Soc. Rev.* **1998**, *27*, 417−425. (b) Leininger, S.; Olenyuk, B.; Stang, P. J. Self-Assembly of Discrete Cyclic Nanostructures Mediated by Transition Metals. *Chem. Rev.* **2000**, *100*, 853−907.

(34) Schmittel, M.; Ganz, A.; Fenske, D. Ring-in-Ring Structures from Phenanthroline Macrocycles with Exo- and Endotopic Binding Sites. *Org. Lett.* **2002**, *4*, 2289−2292.

(35) Schmittel, M.; Ganz, A.; Fenske, D.; Herderich, M. Heteroleptic Silver(I) and Zinc(II) Bis(phenanthroline) Complexes. *J. Chem. Soc., Dalton Trans.* **2000**, 353−359.

(36) Loren, J. C.; Yoshizawa, M.; Haldimann, R. F.; Linden, A.; Siegel, J. S. Synthetic Approaches to a Molecular Borromean Link: Two-Ring Threading with Polypyridine Templates. *Angew. Chem., Int. Ed.* **2003**, *42*, 5702−5705.

(37) Seeman, N. C. Nucleic Acid Nanostructures and Topology. *Angew. Chem., Int. Ed.* **1998**, *37*, 3220−3238.

(38) Mao, C.; Sun, W.; Seeman, N. C. Assembly of Borromean Rings from DNA. *Nature* **1997**, *386*, 137−138.

(39) Whereas the simplest Borromean link possesses 6 crossing points, Seeman's DNA Borromean rings have 18 crossings. The specific emblem of the Borromeo family is the first in a series of such links in which the number of crossings is a multiple of 6. This DNA congener, therefore, is the third in the series. For a discussion on this family of links, see Liang, C.; Mislow, K. On Borromean Links. *J. Math. Chem.* **1994**, *16*, 27−35.

(40) Hasenknopf, B.; Lehn, J.-M.; Boumediene, N.; Leize, E.; van Dorsselaer, A. Kinetic and Thermodynamic Control in Self-Assembly: Sequential Formation of Linear and Circular Helicates. *Angew. Chem., Int. Ed.* **1998**, *37*, 3265−3268.

(41) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. Dynamic Covalent Chemistry. *Angew. Chem., Int. Ed.* **2002**, *41*, 898−952.

(42) (a) Chichak, K. S.; Cantrill, S. J.; Pease, A. R.; Chiu, S.-H.; Cave, G. W. V.; Atwood, J. L.; Stoddart, J. F. Molecular Borromean Rings. *Science* **2004**, *304*, 1308−1312. (b) Schalley, C. A. Borromean Rings: A One-Pot Synthesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 4399−4401.

(43) For a related structure, see Dolomanov, O. V.; Blake, A. J.; Champness, N. R.; Schröder, M.; Wilson, C. A Novel Synthetic Strategy for Hexanuclear Supramolecular Architectures. *Chem. Commun.* **2003**, 682−683.

(44) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, U.K., 1994.

(45) Examples of Borromean links have been identified retroactively in some coordination polymers. See Carlucci, L.; Ciani, G.; Proserpio, D. M. Borromean Links and Other Non-Conventional Links in "Polycatenated" Coordination Polymers: Re-examination of some Puzzling Networks. *CrystEngComm* **2003**, *5*, 269−279.

(46) For a metallic microstructure possessing the Borromean topology, see Wu, H.; Brittain, S.; Anderson, J.; Grzybowski, B.; Whitesides, S.; Whitesides, G. M. Fabrication of Topologically Complex Three-Dimensional Microstructures: Metallic Microknots. *J. Am. Chem. Soc.* **2000**, *122*, 12691−12699.