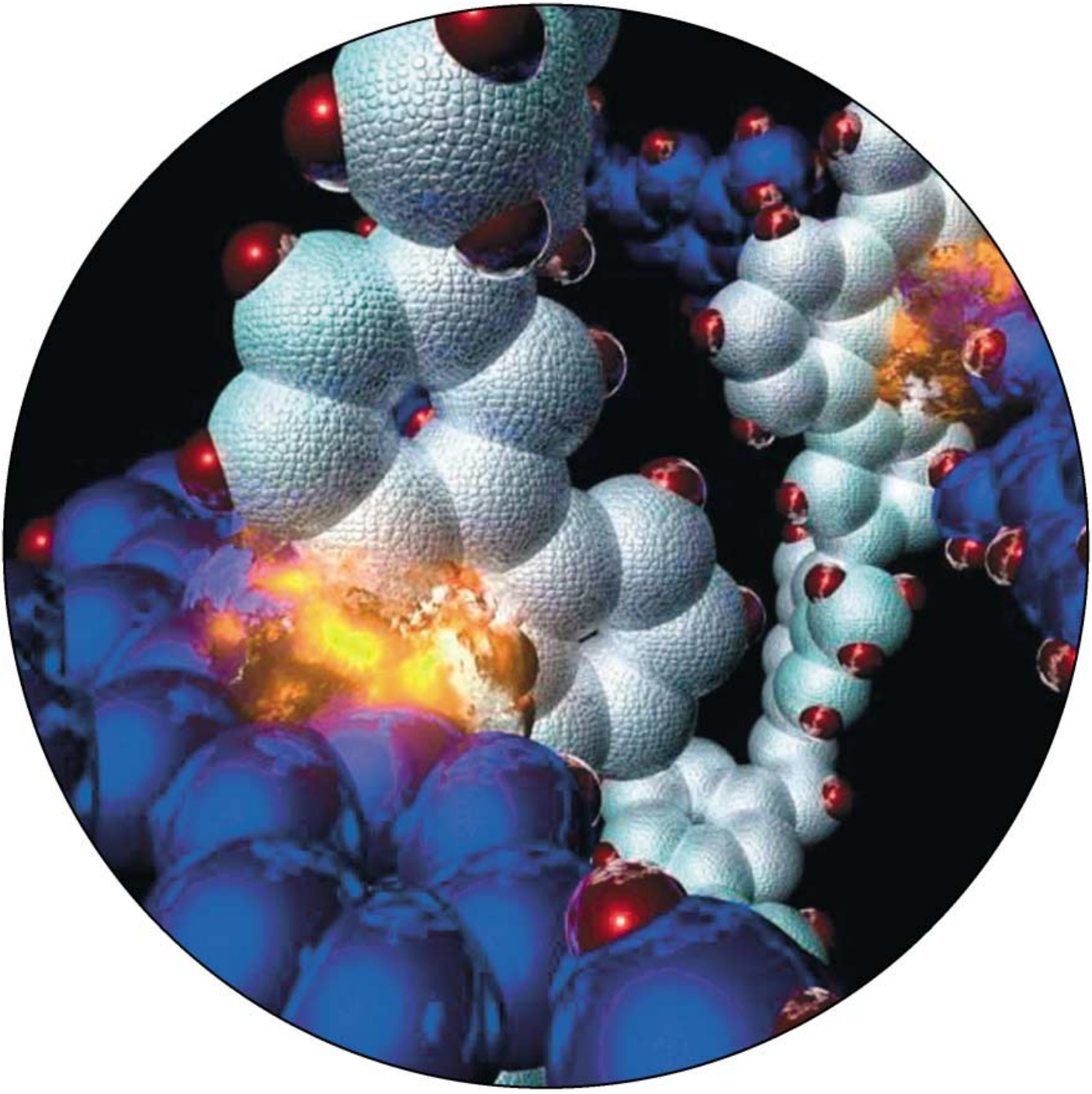
Communications



The Borromean link of three rings connected such that no two are concatenated is an exceptionally challenging target and any synthetic approach must address both representative and methodological aspects of the problem. Methodological advances toward an orthogonal two-ring target are detailed by J. S. Siegel et al. on the following pages.

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Macrocycles

Synthetic Approaches to a Molecular Borromean Link: Two-Ring Threading with Polypyridine Templates**

*Jon C. Loren, Michito Yoshizawa, Richard F. Haldimann, Anthony Linden, and Jay S. Siegel**

The molecular Borromean link is one of the most challenging synthetic targets generated from molecular graphs[1] of complex topology.[2,3] Its structural complexity stems from the interweaving of three macrocycles such that no two of the macrocycles are concatenated nor covalently connected, yet collectively they form an integral molecular unit. The origins of this link in human culture go back to antiquity[4] and the novelty of its form has been richly discussed.[5] The design of molecular targets and retrosyntheses from topological graphs often correlate with a specific representation (often printed in two dimensions).[6,7] Three principal representations of the Borromean link that inspire targets for molecular design and synthesis are the Venn rings, chain rings, and orthogonal rings (Figure 1).[8] The Venn rings highlight threefold symmetry and embellish upon the triskelion[9] or related trefoil knot[10] precursor. The chain rings betray a rack[11] or grid[12] substructure from which functionalized end groups close the macrocycles. The orthogonal rings beseech a single-step template-driven synthesis[13] but readily succumb to a ring-by-ring retrosynthesis. From this humble strategy, we begin.

To illustrate a specific strategy, we look to an orthogonal-ring representation using metal coordination as the template method, built up by a kinetically selective reaction sequence (Figure 2). Two key structural intermediates along this synthetic route are the assembly of a principal base macrocycle with *endo*- or *exo*-oriented metal-binding sites and the completion of a threaded two-ring structure, in which the two rings are orthogonal and at least one of the two rings possesses a second set of metal-binding sites, compatible with the threading and knitting together of the third ring.

Macrocycles, abstracted as form **e** (cf. Figure 2), have substantial precedence in the literature;[14] however, the relatively simple conceptual extension to a bismacrocycle of form **c** (cf. Figure 2) represents a curious threaded-ring structure of which there are few examples.[15,16] Our

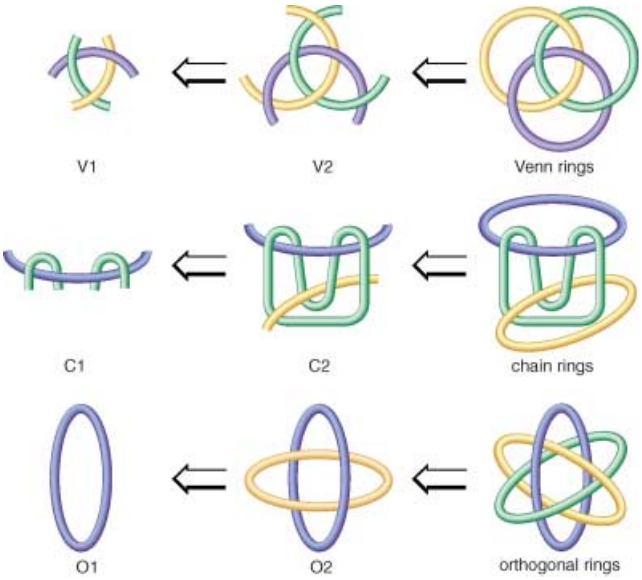

Figure 1. Three retrosynthetic representations of the Borromean link (Venn rings, chain rings, orthogonal rings).

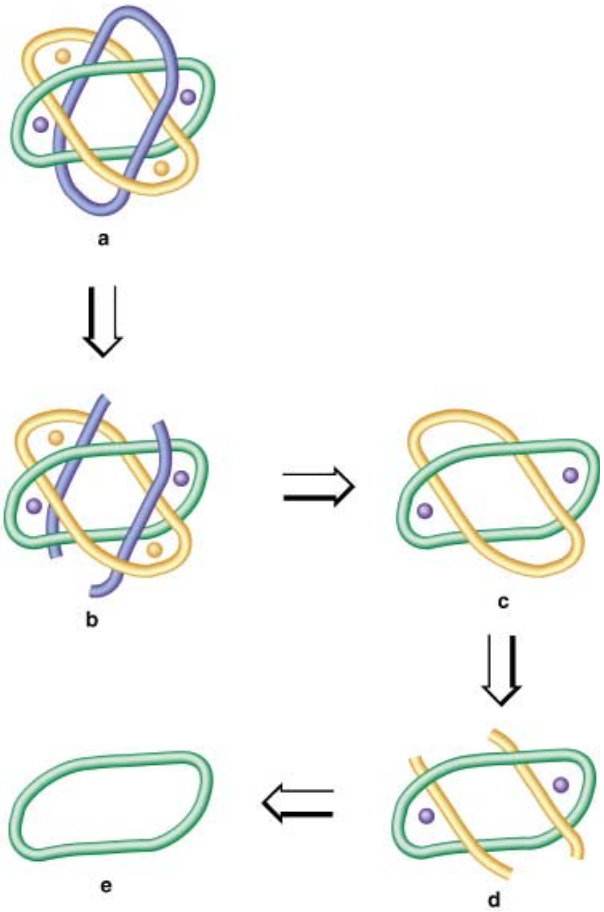

Figure 2. Retrosynthesis of a Borromean link from the orthogonal-ring representation.

[*] Prof. J. S. Siegel, Dr. A. Linden
Organic Chemistry Institute, University of Zürich
Winterthurerstrasse 190, 8057 Zürich (Switzerland)
Fax (+41) 1-635-6888
E-mail: jss@oci.unizh.ch

J. C. Loren, M. Yoshizawa, Dr. R. F. Haldimann
Department of Chemistry, University of California-San Diego
La Jolla, California 92093-0358 (USA)
Fax: (+1) 858-822-0386

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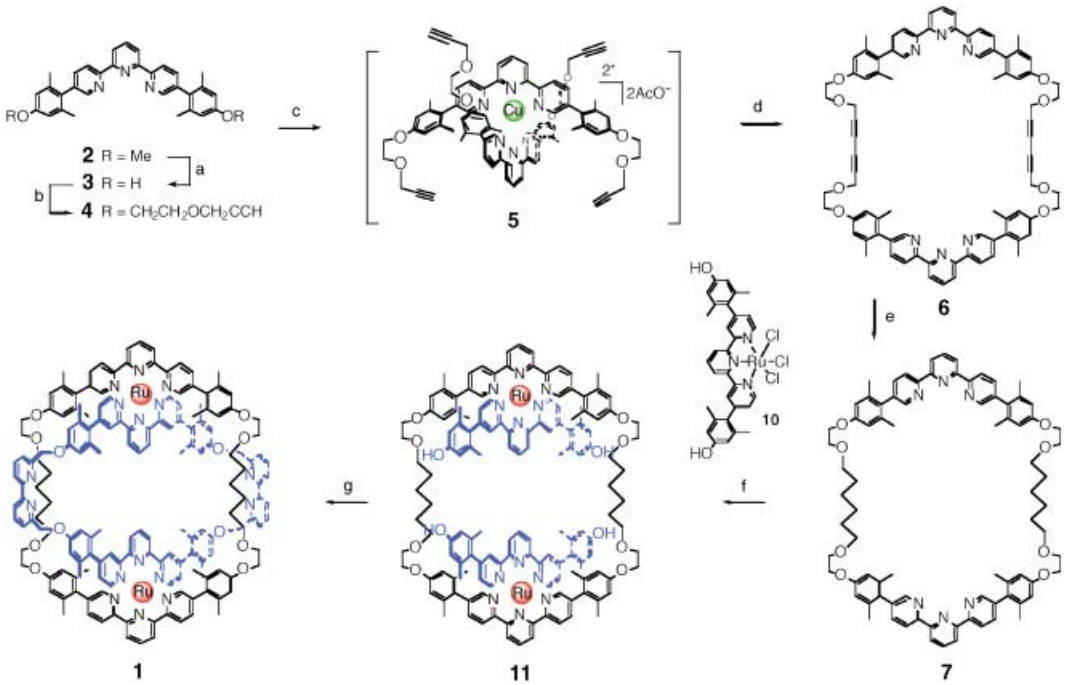
strategy focuses on those macrocycles with polypyridine units,[15,17] which would suit a metal-template-based retrosynthesis.

The macrocycle **6** can be synthesized in a multistep procedure from the previously reported terpyridine **2**[18] (Scheme 1). Elaboration of **2** into a related terpyridine **4** with alkyne-terminated side chains, proceeds by standard demethylation and realkylation methods. Terpyridine **4** forms an intermediate homoleptic copper(II) complex[19] with four dangling arms, terminating in alkynes. These arms are too short for the ends to form a [2]catanane, as seen in related work,[20] but are optimal to form the so-called "figure-eight" complex.[21] The combined one-pot operation of forming **5** from **4** and copper ions followed by addition of excess copper ion, under modified Eglinton conditions in ethanol without pyridine, leads directly to the 66-membered macrocycle **6** in over 90% yield. Hydrogenation of the diynes in **6** affords macrocycle **7**, which bears two *endo*-oriented terpyridines and saturated bridging arms. Preformation of the ruthenium complex **10** by standard methods[22] provides the reagent necessary to complex two 4,4″-diarylterpyridyl–Ru units (LRu) to macrocycle **7**, thus forming **11**. These LRu units serve as *exo*-oriented precursors of ring 2 threaded within ring 1. The ends of the 4,4″-aryl units are juxtaposed with each other and macrocyclization to form the threaded two-ring architecture **1** is effected by Williamson ether synthesis with the known biselectrophile 6,6′-bisbromomethyl-2,2′-bipyridine.[23] The bridging bipyridine units represent the *endo*-oriented portions of a tetrahedral or trigonal bipyramidal metal-binding site through which the third ring would ultimately be threaded, oriented, and cyclized.

Crystals of **1** were grown from acetone/diethyl ether as the PF_6 salt, and the crystal structure was elucidated in space group $P\bar{1}$ with molecules residing on C_i special positions (Figure 3).[24] The two rings are clearly threaded within one another in an orthogonal orientation. The largest dimension of the complex is roughly 29 Å from the hydrogen atoms in the saturated arm of ring 1 to their symmetry-related partners. The Ru–Ru span is 16.4 Å; on the outer ring (ring 1) the span from the *para*-hydrogen atom of the central ring of the terpyridine to its symmetry partner is approximately 27 Å. The dimensions of ring 2 are slightly smaller, with a long diagonal of 26.1 Å measured between manisyl aryl hydrogen atoms. The conformation of ring 1 is not planar and bows into a chair form. The two *endo*-oriented terpyridines of ring 1 sit in parallel planes, offset by about 5 Å. One might anticipate considerable uncertainty about the exact conformation of the saturated arms and this is supported by residual disorder, which required a two-conformation model for these arms in the crystal structure analysis. The conformation of ring 2 is also readily likened to a macrocyclic chair. The *exo*-oriented terpyridines sit in planes parallel to one another but shifted by roughly 6.5 Å. The bridging bipyridines, adopt the expected *anti* conformation in the absence of a metal. The idealized symmetry of ring 2 would be C_{2h}, with the twofold axis bisecting each of the 2,2′ bonds of each bipyridine, and the horizontal mirror plane bisecting the *exo*-oriented terpyridines. The structure shows that there is ample space for the arms of the third ring to be threaded inside of ring 2 and outside of ring 1. The dimensions of this third ring will again need to be over 20 Å to span even the smallest region of ring 1.



Scheme 1. Reaction conditions: a) molten py·HCl, 185 °C, 4 h, 97%; b) Cs_2CO_3, $TsOCH_2CH_2OCH_2CCH$ (2.2 equiv), DMF, 80 °C, 10 h, 69%; c) $Cu(OAc)_2{\cdot}H_2O$ (0.5 equiv), ethanol, room temperature, 1 h; d) 1) $Cu(OAc)_2{\cdot}H_2O$ (10.0 equiv), ethanol, high dilution, reflux, 72 h; 2) KCN (aq), CH_2Cl_2, 91%; e) H_2 80 psi, Pd/C (10%), ethanol/CH_2Cl_2 (1:1), 6 h, 91%; f) **10** (2.0 equiv), CH_2Cl_2/EtOH/ethylene glycol (2:2:1), reflux, 12 h, 65%; g) 6,6′-bisbromomethyl-2,2′-bipyridine (2.0 equiv), Cs_2CO_3, acetonitrile, reflux, 72 h, 49%.

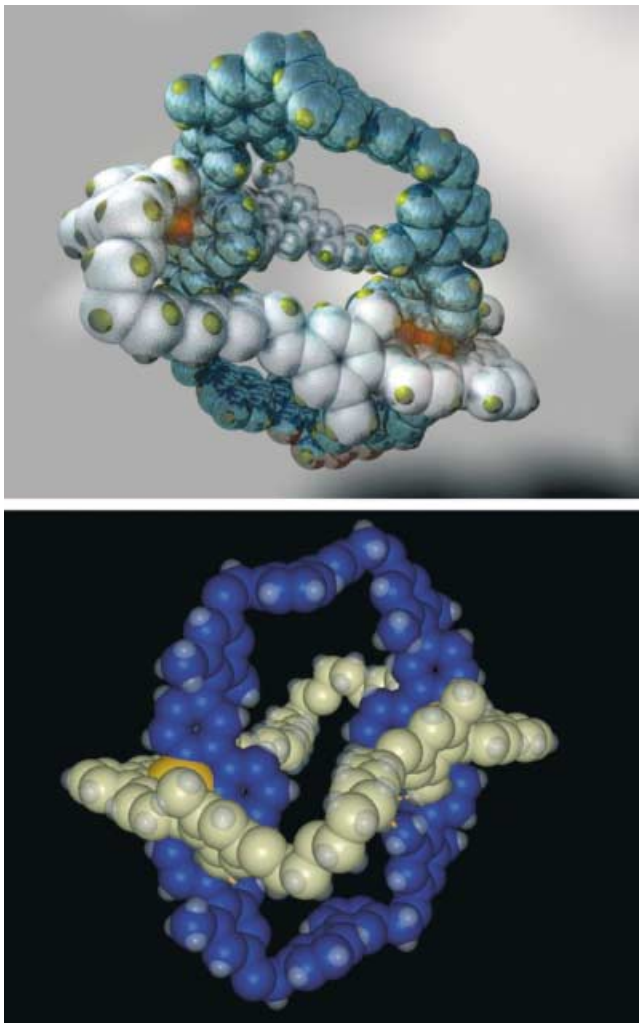
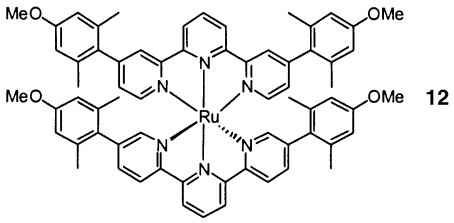


Figure 3. Space-filling model of the crystal structure of **1**: colored to emphasize connectivity; aspect to show chair form of ring 1 (bottom)

The photophysical and electrochemical properties of **1**, relative to its parent mono ruthenium heteroleptic complex **12**, indicate that the ruthenium centers behave independently of one another (Table 1). Excitation near 312 nm results in



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what appears to be a ligand-centered emission at 407 and 419 nm for **1** and **12**, respectively. These values coincide with the emission wavelength range of the free ligands.[18] Excitation at 480 nm results in no detectable emission for either. Cyclic voltametry (CV) shows only quasi-reversible behavior, and electrodeposition occurs on the electrodes after multiple scans for both **1** and **12**.

Table 1: UV/Vis, fluorescence, and electrochemical reduction potentials for **1** and **12**.

	UV/Vis[a]		Fluorescence (λ)[a]		
	λ_{abs}	$\log \varepsilon$	Excitation	Emission	$E_{1/2}$ [V][b]
1	201	5.6	312	407	0.99
	273	5.0			
	312	5.1			
	480	4.4			
12	202	5.0	313	419	0.95
	271	4.8			
	313	5.9			
	480	4.1			

[a] In acetonitrile. [b] 0.1 M tetrabutylammonium hexafluorophosphate in acetonitrile vs $Ag/AgNO_3$ in acetonitrile.

The synthesis of the two-ring intermediate en route to a Borromean link in the orthogonal-ring representation marks a milestone. The challenge of this target lead to a highly efficient strategy for the synthesis of macrocycle **7**, which in turn made 100 mg quantities of **1** readily accessible. The elucidation of the structure of **1** provides evidence that the molecule adopts a structure close to the idealized scheme and, more importantly, gives insight into the stereochemistry and structural dimensions necessary to assemble the last ring of the Borromean link. Beyond the mere technical details, these studies illustrate an important aspect of the pursuit of chemistry: the human conception of molecular structure.[31]

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