Making Molecular Borromean Rings

A Gram-Scale Synthetic Procedure for the Undergraduate Organic Lab

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In 1892, Hermann Brunn spent hours drawing pictures of links *(1)* with one unique feature about them; namely, the breaking and removal of any one component of the links led to their complete disentanglement. Of all the possible "Brunnian links", a three-component version is, by far, the most famous. It even has its own namesake—the "Borromean rings" (BRs) in deference to the ennobled family of the Borromeos in Renaissance Italy in the 15th century who used the interlocked rings on their family crest (Figure 1A). Often employed as a symbol representing the unification of three different ideals, the aesthetic appeal of the BRs has transcended both cultural (Figure 1B) and disciplinary divides. It is to be found in Christian iconography (Figure 1C), as well as in famous works of art (Figure 1D). Calling on the Google search engine exposes over 25,000 hits for the "Borromean rings".

The key topological feature (Figure 2) of the BRs—the locking of the three rings together that relies on the presence of all three components—makes them not only a fitting family emblem, but also a challenging puzzle to scientists of all persuasions. The BRs' topology and, for some, the difficulties in constructing it, have captivated the minds of mathematicians *(2)* and physicists *(3)*, as well as chemists *(4, 5)*. In chemistry, the synthesis of the molecular BRs has just been accomplished in recent times *(6)*.

We have modified our reported experimental procedure *(7)* for the synthesis of molecular BRs to turn it into an experiment suitable for undergraduate students to pursue in an organic chemistry laboratory course. Herein, we describe a procedure that requires seven 4-hour blocks of time to allow undergraduate students to prepare the molecular BRs on a gram-scale in 90% yield.

Undergraduate students will be attracted to this training experience for all the same reasons that other researchers in different disciplines have been brought under the spell of the BRs—their unique topology and wide cultural appeal. Just as important as engaging students in the BRs is the fact that the making of the molecular BRs incorporates several important, yet nonetheless overlooked, areas of chemistry. They include, in addition to synthetic organic, physical organic, inorganic and metallo-organic chemistry, supramolecular, and dynamic covalent chemistry, all packaged up under the same umbrella in one project.

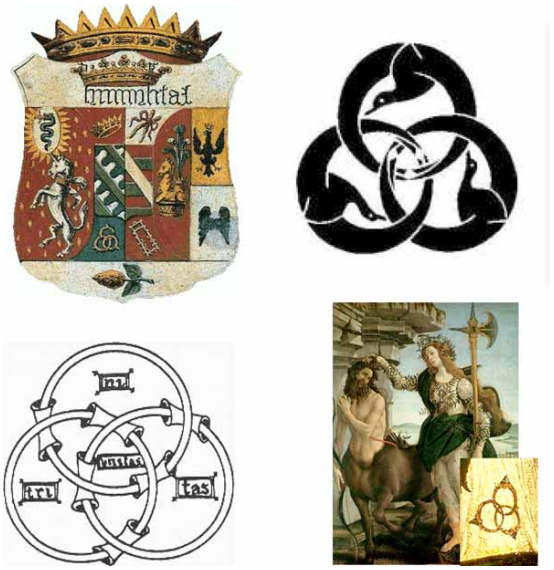


Figure 1. Examples of Borromean ring symbols are found everywhere—some of the most notable include their use in (A) the Borromeo family crest, (B) in Japanese family emblems, (C) in Christian iconography as a representation of the Holy Trinity, and (D) in Sandro Botticelli's *Pallas and the Centaur,* where the symbol adorns the gown of Pallas (detail shown in insert).

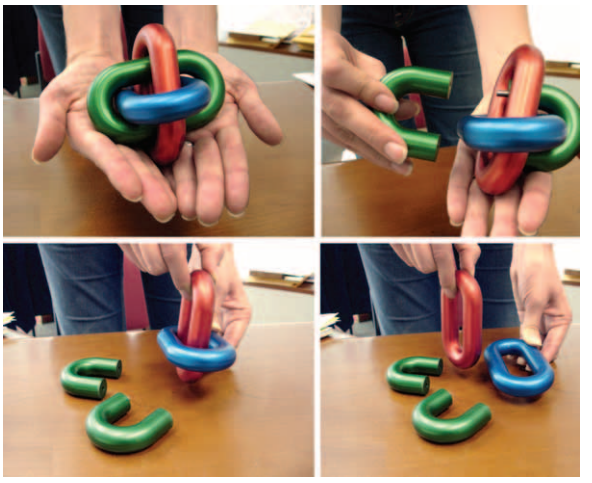


Figure 2. A demonstration of the BR topology. Although the intact Borromean rings are individually inseparable (top left), the cleavage of just one of the component rings results in the unlinking of the other two.

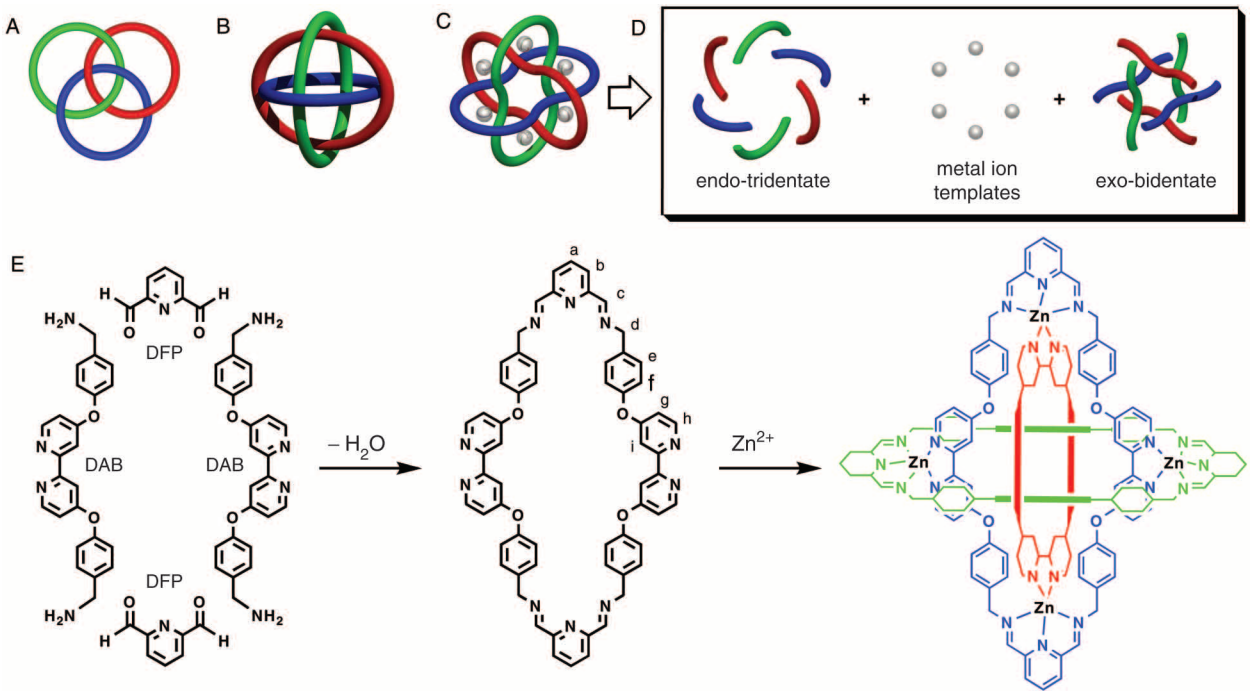


Figure 3. The BRs can be represented in a planar Venn diagram (A), where the alternating nodes relating to each of the rings to over/under/over/under are most apparent. The orthogonal (B) perspective reveals the three-dimensional relationship of each of the mutually perpendicular rings. In a chemical context (C) the transition metals are imbedded in the nodes, or binding sites. (D) Six endo-tridentate ligands, six transition metals, and six exo-bidentate ligands undergo an 18-component self-assembly process in one step to obtain the BRs. (E) The reversible reaction of diformylpyridine (DFP) with the diaminobipyridine (DAB) ligand in the presence of zinc acetate affords the molecular Borromean rings. The small letters on the macrocycle refer to the hydrogens seen in the ^{1}H NMR (Figure 5).

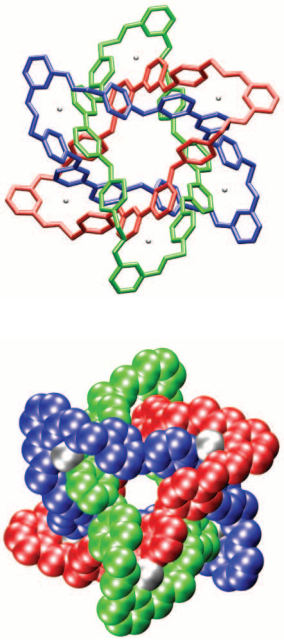


Figure 4. X-ray crystal structure of BR^{12+} viewed down the S_6 axis depicted in the (top) tubular and (bottom) space-filling representations. The TFA^- counterions and hydrogen atoms have been omitted for clarity. The solid-state structure was solved by Jerry L. Atwood and Gareth W. V. Cave at the University of Missouri-Columbia.

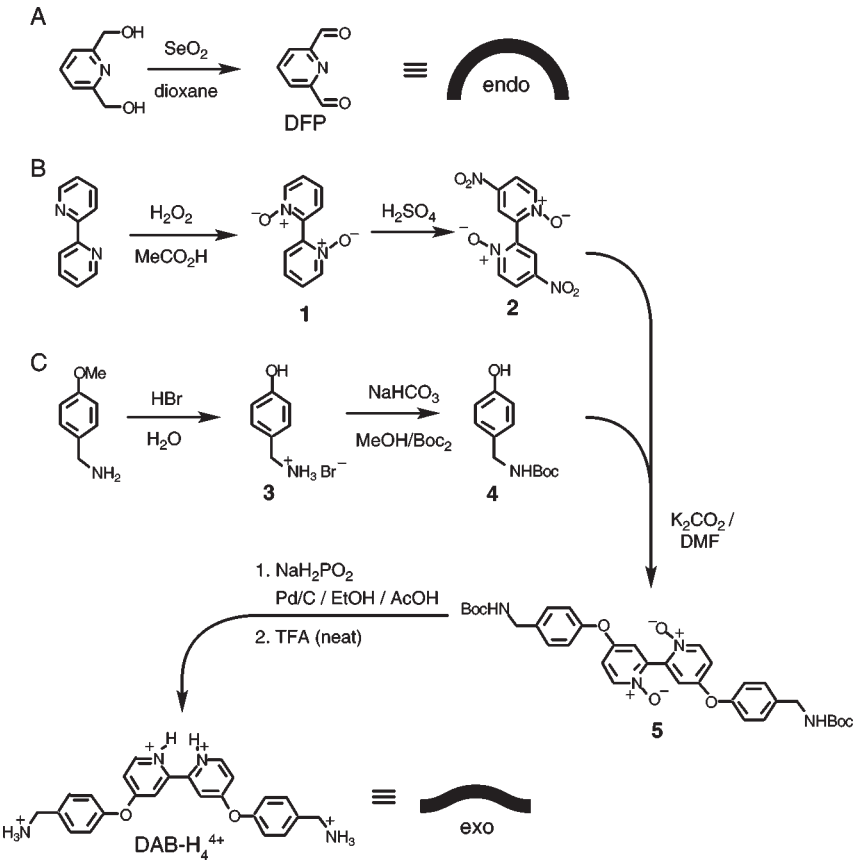
From the vantage point of a chemist, the alternating nodes evident (Figure 3A) in the Venn diagram of the BRs can be appreciated by examining the orthogonal representation (Figure 3B) and analyzing the relative relationships ("inside" and "outside") of the rings with respect to each other. Our recent successes *(6)* in forming the molecular BRs relies upon using transition-metal ions as templates (Figures 3C and D) to preorganize endo (inside) and exo (outside) ligands around the ions. In the event, the reaction can be made to go in 95% yield on a gram scale. Single crystals can be obtained from the crude powder by vapor diffusion of diethyl ether into a methanolic solution of the BRs. The X-ray crystal structure is shown in Figure 4 with the BRs oriented so that the S_6 axis of symmetry is apparent.

For a seemingly complex structure, the molecular BRs are made from very simple starting materials and reagents. The overall efficiency of the reaction makes the experimental procedure attractive to instructors operating on a tight budget. It costs[1] just under $14 for one student to produce 120 mg of the molecular BRs. This quantity[2] is more than adequate for characterization purposes.

Experimental Procedure

Hazards

This synthesis requires the use of chemicals that are toxic (selenium dioxide, methanol, methanol-d_4, ethanol, dichloromethane, *N,N′*-dimethylformamide, di-*tert*-butyldicarbonate



Scheme I. Synthesis of the diformylpyridine endo ligand (DFP) and the exo diaminobipyridine (DAB) ligand.

and zinc acetate), corrosive (hydrogen bromide and hydrogen peroxide, and acetic, nitric, sulfuric and trifluoroacetic acids), and flammable (ethyl acetate, hexane, Pd/C, and dioxane). Students should be encouraged to look up the MSDS data for all the solvents and reagents as part of their prelab training.

Equipment

The following items of equipment are required: Pasteur pipets, spatulas, round-bottom flasks (50, 25, and 10 mL), a three-necked round-bottom flask (25 mL), beakers (25 and 50 mL), graduated cylinders (10 and 100 mL), magnetic stirrer–hot plate, sonicator, heating mantle, stir bars, condensers, drying tube, Büchner funnel, Hirsch funnel, filter flask, filter paper, chromatography column, rotary evaporator, and NMR tubes.

Reagents

All solvents and reagents can be used as received from Aldrich (Milwaukee, WI) and VWR (San Dimas, CA). Per student, this laboratory requires 2,2′-bipyridine (0.25 g); 30% H_2O_2 (0.5 mL); AcOH (2.75 mL); fuming H_2SO_4 (0.7 mL); 4-methoxybenzylamine (1.00 g); 48% HBr (2.6 mL); $NaHCO_3$ (0.60 g); di-*tert*-butyldicarbonate (0.41 g); K_2CO_3 (0.23 g); NaH_2PO_2 (0.30 g); Pd/C (60 mg); 2,6-pyridinedimethanol (60 mg); SeO_2 (50 mg); TFA (5 mL); $Zn(OAc)_2$ (50 mg).

Synthesis

The synthesis (Scheme I) of the BR ligand precursors, the diformylpyridine (DFP) and diaminobipyridine (DAB) ligands, constitute three independent sets of reactions that can be easily carried out in parallel if it helps the student meet an otherwise tight schedule. The three sets of reactions are the synthesis of DFP (A in Scheme I), which ultimately becomes the endo ligand; the synthesis of the middle portion of the exo DAB ligand (B in Scheme I), that is, the dinitrobis-*N*-oxide, **2**; and the synthesis of the benzylamine derivative, **4** (C in Scheme I), that will subsequently be coupled to compound **2**.

To contain the time-demanding synthetic effort, DFP can be purchased[3] and a group effort can be employed to synthesize the DAB ligand where one half of the class assume responsibility for the synthesis of the dintrobis-*N*-oxide, **2**, while the other half of the class makes the benzylamine derivative, **4**. By sharing compounds **2** and **4**, everyone in the class would complete the nucleophilic aromatic substitution of the two nitro groups in **2** to produce quantities of the bis-*N*-oxide of the protected DAB ligand for the assembly of the BRs.

Procedure

The procedure described below, and in the Supplemental Material,[W] reveals that the yields (shown in parentheses) obtained by the undergraduate students are significantly lower

than those reported in the literature *(6)*. These yields are a result of modifications made to the procedures that make it possible for undergraduate students to work under typical classroom time constraints (e.g., a 4-h lab period).

The synthesis (Scheme I) of the bipy component begins with the oxidation of 2,2′-bipyridine (97%), followed by nitration of the product **1** (58%) to produce 4,4′-dinitro-2,2′-bipyridyl-*N,N′*-dioxide, **2**. The synthesis of the other half of the ligand begins with the demethylation of the methyl ether function in 4-methoxybenzylamine, (32%), followed by boc-protection (88%) of the amino function.

4,4′-(*tert*-Butyl(4-hydroxybenzyloxy)carbamate)-2,2′-bipyridyl-*N,N′*-dioxide (5)

Add solid K_2CO_3 (0.23 g, 1.7 mmol) to a stirred solution of **4** (0.26 g, 1.2 mmol) and **2** (0.13 g, 0.5 mmol) in anhydrous DMF (1 mL) under an argon atmosphere in a 10-mL round-bottom flask. Heat the reaction mixture at 80 °C for 20 h. Stop the heating and transfer the solution to a 50-mL round-bottom flask and allow it to cool to room temperature. Remove the solvents under reduced pressure to obtain a yellowish-brown residue. Add H_2O (30 mL) to the residue and sonicate until a suspended solid is produced. Filter the solid, wash with H_2O (3 × 5 mL), and dry to afford a yellowish-brown solid. Dissolve the solid in CH_2Cl_2 (20 mL) and dilute with EtOAc (30 mL). Bring this solution to a boil and concentrate to 30 mL. After compound **5** precipitates from the mixture upon cooling, collect it by filtration. Dry the light yellow powder under vacuum. Yield: 53%.

4,4′-Bis-(4-*tert*-butyl-*N*-phenoxycarbamate)-2,2′-bipyridine (boc-DAB)

In one portion, add an excess of NaH_2PO_2 (0.30 g, 3.3 mmol) to a three-neck 25-mL round-bottom flask equipped with a condenser containing a stirred suspension of **5** (0.29 g, 0.5 mmol) and 10% Pd/C (0.06 g) in 75/15 EtOH/AcOH (6 mL). Seal the reaction flask with a balloon to prevent the loss of the H_2 gas that evolves from the decomposition of NaH_2PO_2. Heat this mixture at 70 °C for 20 h. Upon cooling to room temperature, filter the reaction mixture through celite. Wash the filter cake with CH_2Cl_2 (3 × 10 mL). Combine the filtrates and reduce the volume to 5 mL under reduced pressure, giving a dark yellow-brown solution. Neutralize the AcOH by adding solid $NaHCO_3$ (0.6 g) in H_2O. After concentrating the solution to dryness, suspend the resulting beige product in H_2O. Collect the product by filtration, wash with H_2O (3 × 10 mL), and dry. Recrystallize the crude product from EtOAc/hexanes (15 mL/15 mL) to afford the boc-DAB ligand as a yellowish-brown solid. Yield: 68%.

BR·12TFA and Zn/BR·14TFA

Dissolve the compound boc-DAB (0.14 g, 0.24 mmol) in trifluoroacetic acid (TFA) (10 mL) in a 25-mL round-bottom flask and stir the solution at room temperature for 30 min. Remove the TFA by rotary evaporation under reduced pressure followed by subsequent additions and removals of MeOH (3 × 10 mL), leaving a pink tar. Add $Zn(OAc)_2$ (43.0 mg, 0.24 mmol) to stirred *i*-PrOH (10 mL) containing the freshly deprotected DAB ligand, followed by the addition of DFP (32.0 mg, 0.24 mmol). *Ensure that all components are completely dissolved before proceeding. Sonicate if necessary.* Fit the flask with a condenser and heat the reaction mixture at 60 °C for 20 h to produce an off-white precipitate. Remove the precipitate by filtration and wash with *i*-PrOH (3 × 5 mL), Et_2O (3 × 5 mL), and dry to afford the title compound as a mixture of BR·12TFA and Zn/BR·14TFA (80:20) as a pale gray powder. Yield: 86%.

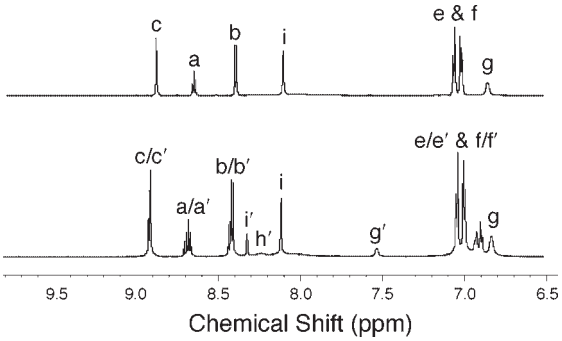


Figure 5. ^{1}H NMR Spectra (CD_3OD, 298 K, 600 MHz) of (top) BR·12TFA, where only six zinc ions are present and (bottom) BR·12TFA and Zn/BR·14TFA with an extra zinc ion occupying the cavity within the core. The hydrogen labels are identified in Figure 3.

Characterization

Belonging to the S_6 point group, the molecular BRs are highly symmetrical and have simple ^{1}H NMR spectra. The spectrum of BR·12TFA is shown in Figure 5. Occasionally two sets of peaks appear in the spectrum, indicating that a seventh zinc ion has found its way into the cavity of the BR, affording Zn/BR·14TFA.

Summary

The undergraduate curriculum inherently lags behind graduate-level research. Oftentimes, undergraduates are conducting experiments that were introduced 30 or more years ago. By way of contrast, the molecular BRs are still undergoing detailed investigations *(8)* in our group. In assembling and analyzing the BRs, students are exposed to fundamental concepts, symmetry point groups, metal–ligand dative bond formation, synthetic organic chemistry, and dynamic covalent chemistry. As the conceptual basis for BR formation stretches across so many subdisciplines of chemistry, we believe that this experiment would serve as a nice capstone project to culminate any comprehensive organic laboratory course.

[W]Supplemental Material

The following material for the instructors is available in this issue of *JCE Online:* (i) cost analysis tables providing a spreadsheet of the necessary materials and their current prices; (ii) a spreadsheet with all the ratios entered into one document so that a instructor can determine the quantities of chemicals needed for each class; (iii) a full experimental section containing further details of the synthetic procedures; (iv) suggested test or prelab questions about the BR self-assembly process; and (v) suggested demonstration activities to aid the instructor in describing the BR topology.

Notes

1. A table of the required chemicals and the corresponding prices is provided in the Supplemental Material.[W]

2. The undergraduates in our laboratory have completed the procedure on a gram-scale. Procedures for both the gram-scale and 120 mg-scale are provided in the Supplemental Material.[W]

3. The purchase of DFP ($292.00/g) is optional and may be helpful for those with limited time, but larger budgets. We have included the procedure to synthesize DFP in one step from 2,6-pyridinedimethanol as the more cost-effective route (see the Supplemental Material[W]).

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Borromean Rings are featured on the cover of this issue. See page 738 of the table of contents for a description of the cover.