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Molecular Borromean Rings

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The realization of the Borromean link in a wholly synthetic molecular form is reported. The self-assembly of this link, which is topologically achiral, from 18 components by the template-directed formation of 12 imine and 30 dative bonds, associated with the coordination of three interlocked macrocycles, each tetranucleating and decadentate overall, to a total of six zinc(II) ions, is near quantitative. Three macrocycles present diagonally in pairs, six *exo*-bidentate bipyridyl and six *endo*-diiminopyridyl ligands to the six zinc(II) ions. The use, in concert, of coordination, supramolecular, and dynamic covalent chemistry allowed the highly efficient construction, by multiple cooperative self-assembly processes, of a nanoscale dodecacation with an approximate diameter of 2.5 nanometers and an inner chamber of volume 250 Å³, lined with 12 oxygen atoms.

An object of particular interest in knot theory is known as the Borromean rings (BRs). It occurs in low-dimensional topology and is comprised (Fig. 1A) of three interlocked rings such that scission of any one ring leads to the other two falling apart. Although this symbol can be traced (1) back to early Christian iconography and Norse mythology, its proliferation on crests and statues commissioned by the Borromeo family in 15th-century Tuscany sealed its etymological fate. In addition to the symbol's having made cultural inroads into art and theology and heraldry, the last century witnessed its emergence on the scientific horizon in particle physics (2) and magnetism (3), as well as in the formidable challenge (4, 5) it presents to synthetic chemists in search of its molecular expression. In the wake of Wasserman's first synthesis (6) of

a compound—a [2]catenane—in which the molecules have two interlocked rings, the field of molecular topology has blossomed (7–9). Although more elaborate examples in chemical topology (10, 11) and topological stereochemistry (12, 13) have emerged (14, 15) in the shape of molecular knots, as well as catenanes, the BRs, with the exception of Seeman's seminal work (16) with single-stranded DNA, have proved to be elusive in a wholly synthetic molecular form (17–19).

Conceptually, there are two extreme synthetic strategies for the construction of molecular Borromean links: (i) a stepwise synthesis wherein the three rings are slotted into place by successive templation (20) one at a time and (ii) a strict self-assembly protocol (21, 22) that brings the components of the three rings together in one step under comprehensive template-directed control (20). A ring-by-ring (23–25) approach that is predominantly kinetically executed offers, in principle, access to a greater degree of structural diversity. Such an approach, however, courts the danger of being burdened by undesirable side reactions, particularly in the formation of the

third and final ring of the Borromean links where the geometrical demands associated with both noncovalent and covalent bond formation are likely to be high.

By contrast, an all-in-one strategy, which combines the virtues of reversibility, proofreading, and the error checking we associate with supramolecular (26) and dynamic covalent (27) chemistry with the geometrical precision afforded by coordination chemistry (28–30), allows the synthetic chemist to take up the gauntlet of assembling molecular BRs in the knowledge that thermodynamic control can be an efficient supplier of a complex product (27). Such a paradigm requires that each individual piece in the molecular self-assembly process is programmed so that the multiple molecular recognition between the pieces is optimized in a highly cooperative manner in the desired product. In our bid to facilitate the self-assembly of a BR compound, it was essential to ensure that cooperativity between π - π stacking interactions and coordination geometries was highly optimized. This crucial design element was satisfied computationally by molecular modeling. The manner in which the computer-aided design of the BR¹²⁺ dodecacation led directly to its synthesis in very high yields is rare in our own laboratories' experience.

The successful construction of a BR compound from individual pieces relies on the precise control of the six crossover points that can be identified in the Venn representation (Fig. 1A), where the like signs of the three outer nodes are opposite to those of the three inner nodes. Although these nodes define the topology of the final assembly, to conceive retrosynthetic disconnections it is advantageous to reorient the three interlocked rings so that they are mutually perpendicular in Cartesian space, as depicted in the orthogonal representation (Fig. 1B). With reference to any one of the three identical rings, the sequence of four alternating nodes (+/-/+/-) can man-

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ifest itself in the form of *exo/endo/* *exo/endo* binding sites in a wholly cross-complementary fashion. In a chemical context (Fig. 1C), transition metals can be embedded into these binding sites, thus ensuring complete three-dimensional control at all six such sites through a judicious choice of coordination geometry. Specifically, differentiation of the *exo* and *endo* binding sites at each of the six ring crossings can be established through the union (Fig. 1D) of bidentate and tridentate ligands around a five-coordinate metal ion. The requirements for flexibility and reversibility in the coordination spheres were met by using kinetically labile zinc(II) ions, each bound preferentially to one *exo*-bipyridyl and one *endo*-diiminopyridyl ligand. Ligands of this latter class have been used (28) to form macrocycles in the presence of metal-ion templates. It seemed propitious, therefore, to incorporate two of these *endo*-tridentate ligands, as a result of dynamic imine bond formation (27) between 2,6-diformylpyridine (DFP) and a diamine (DAB) harboring the incipient *exo*-bidentate ligands following a [2+2] macrocyclization (Fig. 1E).

Whereas in the absence of a metal-ion template, a complex mixture of polymeric and macrocyclic products is the likely outcome, introduction of zinc(II) ions is expected to template the formation of molecular BRs with maximal site occupancy (31) being honored. Molecular modeling (32) of the Borromean links, constructed from the appropriately interlocked arrangement of three of the [2+2] macrocycles, revealed only two molecular trinities stabilized by combinations of 12 π - π stacking interactions and 30 dative bonds, one with C_i ($= S_2$) symmetry and the other, shown in Fig. 1E, with S_6 symmetry.

Initial ^1H nuclear magnetic resonance (NMR) spectroscopic investigations, conducted in a CD_3OD solution containing equimolar amounts of DFP and DAB- $\text{H}_4\cdot 4\text{TFA}$ (TFA-trifluoroacetate), revealed that little or no reaction occurred at room temperature during several hours. Upon the addition of an equivalent of $\text{Zn}(\text{OAc})_2$ to the NMR tube, the spectrum changed dramatically, indicating that a reaction was occurring. To expedite the self-assembly process, the reaction mixture was heated under reflux for 3 days. Periodic monitoring of the ^1H NMR spectrum revealed that equilibrium was reached after 2 days, affording predominantly (90%) one highly symmetrical entity. To isolate sufficient quantities of the major product for characterization, the reaction was repeated on a preparative scale, resulting in a pale yellow powder that was crystallized from $\text{MeOH}/\text{Et}_2\text{O}$ to yield a pure crystalline sample. Electrospray ion-

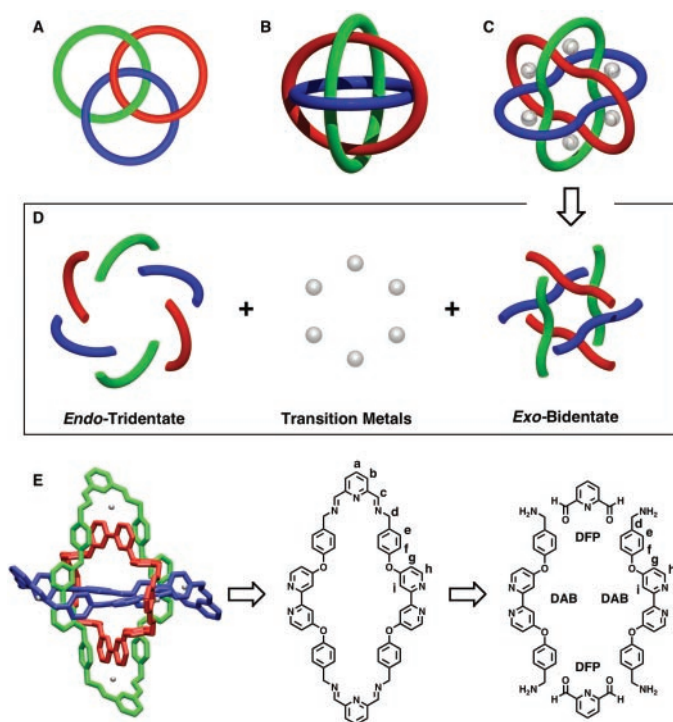
ization mass spectrometric (ESI-MS) analysis of this sample revealed three major peaks at mass-to-charge (m/z) ratios of 1465, 1070, and 834, corresponding to $[\text{M}-3\text{TFA}]^{3+}$, $[\text{M}-4\text{TFA}]^{4+}$, and $[\text{M}-5\text{TFA}]^{5+}$, respectively, a situation that is consistent with the proposed Borromean ring compound **BR** $\cdot 12\text{TFA}$.

Comparison of the ^1H NMR spectrum of this crystalline material (Fig. 2B) with that of **DAB** $\cdot \text{H}_4\cdot 4\text{TFA}$ (Fig. 2A) (both spectra recorded in CD_3OD) reveals appreciable changes in the chemical shifts for the aromatic protons of the **DAB** fragment. Specifically, the resonances for H-e, H-f, H-g, and H-i are all moved upfield by as much as from 0.1 to 0.9 parts per million (ppm), indicating the occurrence of π - π stacking interactions, as predicted by the computational investigations carried out on the molecular Borromean ring (**BR**) surrogate. The averaged molecular symmetry (T_h) of this compound, which is fluxional on the ^1H NMR time scale at 50°C , is such that we would expect to see ^1H NMR signals for only one quadrant of one of the [2+2] macrocycles, because all three rings are equivalent. Inspection of the ^1H NMR spectrum shown in Fig. 2B reveals eight of the anticipated nine signals centered on δ 8.89 (H-c), 8.62 (H-a), 8.31 (H-b), 7.97 (H-i), 6.74/6.68 (H-e/f), 6.50 (H-g), and 4.84 (H-d). It is notable that the signal for H-g on

the bipyridyl ligand is broad but that the signal for the vicinal H-h proton has merged into the baseline between δ 7 and 8 ppm. A spectrum recorded at 50°C indicates that the signal for H-g becomes much sharper, whereas that for H-h emerges out of the baseline and resonates as a broad singlet, centered on δ 7.90 ppm. This temperature-dependent behavior suggests that a (co)-conformational change might be occurring within the **BR** $^{12+}$ dodecacation that is on the order of the ^1H NMR time scale at room temperature.

The x-ray crystallographic analysis (33) of **BR** $\cdot 12\text{TFA}$ reveals a molecular structure (Fig. 3, A to E) with S_6 symmetry wherein the three rings have the topology of a Borromean link. Each of the three equivalent rings adopts a chairlike conformation and, consequently, the **BR** $^{12+}$ dodecacation can be symmetry-related from half of one of the rings, which is 24.5 Å long from the tip of one pyridyl unit to the tip of the other. Molecular recognition is manifest in a mutually compatible manner. The three equivalent rings are held together by six Zn(II) ions, positioned 12.7 Å apart. They are each coordinated in a slightly distorted octahedral geometry to five N atoms (Zn-N bond lengths ranging from 2.10 to 2.24 Å with the *cis* N-Zn-N bond angles, ranging from 72.4° to 109.6°), with the sixth coordination site occupied by an O atom (Zn-O

Fig. 1. The Borromean rings (BRs) can be depicted in many ways, including a planar Venn representation (A) and a more informative orthogonal arrangement (B). At each of the six crossing points on this graph, it is possible to embed a templating feature [the silver spheres shown in (C)] to control the overall three-dimensional architecture in a molecular context. By employing transition metal ions to gather around themselves appropriate ligands in a prescribed fashion, one can envisage a relatively straightforward retrosynthetic disconnection of the BRs (D). The retrosynthesis in chemical terms (E) anticipates the use of an *exo*-bidentate bipyridyl ligand and an *endo*-tridentate diiminopyridyl ligand that is formed reversibly upon the reaction of DFP with DAB in a [2+2] macrocyclization. Molecular modeling (E, left) confirms that three such [2+2] macrocycles can be slotted together to form a highly stabilized assembly with a BR topology.



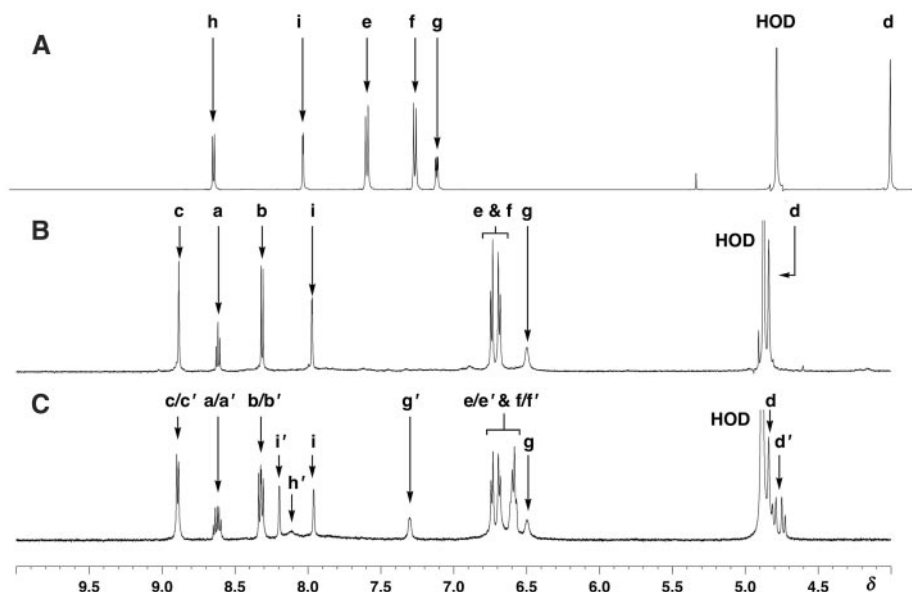
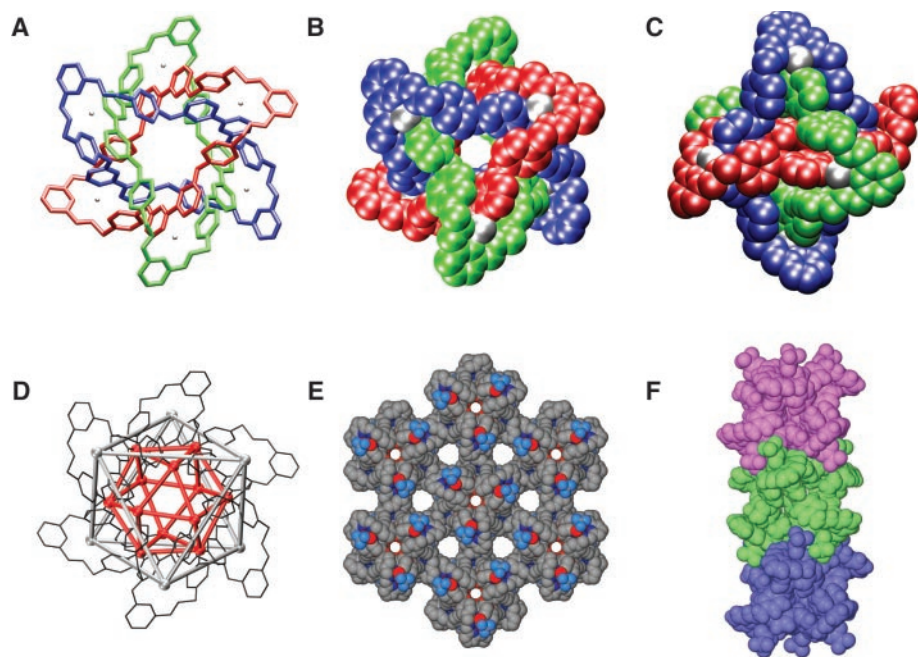


Fig. 2. The ¹H NMR spectra (CD₃OD, 298 K) of (A) the *exo*-bidentate ligand-containing starting material DAB-H₄·4TFA (500 MHz), (B) the molecular Borromean rings BR·12TFA (600 MHz), and (C) an inseparable mixture of “empty” and “filled” Borromean rings, namely BR·12TFA and Zn@BR·14TFA, respectively (600 MHz). The letters a to i are defined for BR¹²⁺ with respect to the appropriate protons on the structural formulas shown in Fig. 1E. Primed letters represent the corresponding protons in Zn@BR¹⁴⁺.

Fig. 3. Different structural and superstructural representations of the BR¹²⁺ dodecacation(s) in the solid state as deduced from x-ray crystallography carried out on single crystals of BR·12TFA. In the case of the illustrations of the single BR¹²⁺ dodecacation, the three equivalent macrocycles are featured, as tubular and space-filling representations, in the three primary colors, green, red, and blue. The six Zn(II) ions are depicted in silver. (A) Tubular representation viewed down the S₆ (and collinear C₃) axis of BR¹²⁺. (B) Space-filling representation of A, showing the pore with a diameter of 2.08 Å in BR¹²⁺, which leads to an inner chamber. (C) Space-filling representation of BR¹²⁺, highlighting the mutually orthogonal arrangement of the three interlocked macrocycles adopting chairlike conformations wherein the distance from the tip of one pyridyl ring to the other, in any given macrocycle, is 24.5 Å. Multiple π–π stacking interactions are evident to the extent that all six equivalent bipyridyl ligands are sandwiched between six pairs of flanking phenolic rings, such that the plane-to-plane separations are 3.61 Å in one direction and 3.66 Å in the other. In addition, there are six [C–H⋯π] interactions (H⋯π distance 2.78 Å) between H-h on all of the bipyridyl ligands and the faces of the six pyridyl rings. The coordination sphere around each of the six equivalent Zn(II) ions exhibits distorted octahedral geometry, with a single TFA⁻ anion (not shown) occupying the sixth coordination site in all cases. (D) A stick representation of BR¹²⁺, upon which are superimposed a platonic solid (i.e., the silver octahedron with its vertices defined by the six Zn(II) ions and having edges that are all equal to 12.7 Å) and a slightly distorted Archimedean solid [i.e., the red cuboctahedron with its vertices defined by 12 O atoms (each 5.1 Å distant from the centroid of BR¹²⁺) that line the inner chamber of BR¹²⁺ and with a volume of ~250 Å³]. (E) Space-filling representation of the hexagonal array of six individual columnar stacks of three BR¹²⁺ dodecacations clustered around a central column viewed down the *c* direction of the crystal lattice, showing the TFA⁻ anions (red and blue) coordinated to the



Zn(II) ions. Neighboring BR¹²⁺ dodecacations are held together by intermolecular π–π stacking interactions (3.31 Å) between matching pairs of pyridyl rings. The small channels that run through the center of the superstructures are separated by 22.5 Å, and the large channels, which are 4.2 Å in diameter, are filled with Zn(II)-coordinated TFA⁻ anions (not shown) and separated from each other by 13.0 Å. (F) Space-filling representation of three interdigitated BR¹²⁺ dodecacations present in superstructural columns that run through the crystal in the *c* direction. Each BR¹²⁺ (green) in the columnar array is linked above (purple) and below (blue) itself by six [C–H⋯O=C] hydrogen bonds (with a [H⋯O] distance of 2.52 Å), which arise from an interaction between H-g in one BR¹²⁺ and the carbonyl oxygen atom of a Zn(II)-bound TFA⁻ anion in the neighboring BR¹²⁺. The distance within the columns between the centers of repeating BR¹²⁺ dodecacations is 16.3 Å.

bond length of 2.06 Å and *cis* O–Zn–N bond angles, ranging from 89.0° to 99.3°) belonging to aTFA⁻ anion with a disordered trifluoromethyl group. The six equivalent bipyridyl ligands are sandwiched unsymmetrically between six pairs of phenolic rings, such that the π–π stacking distance is 3.61 Å in one direction and 3.66 Å in the other. The BR¹²⁺ dodecacation contains an inner chamber (34) of volume 250 Å³ lined with the van der Waals surfaces of 12 O atoms that are oriented in the form of a cuboctahedral array toward the center of the chamber, which contains species that give rise to nonresolved and diffuse electron density.

At a supramolecular level, the BR¹²⁺ dodecacations are arranged (Fig. 3E) in hexagonal arrays with close (3.31 Å) intermolecular π–π stacking interactions between pairs of pyridyl rings in adjacent dodecacations, which form (Fig. 3F) columnar arrays in the orthogonal *c* direction that are stabilized by six [C–H⋯O=C] interactions between each BR¹²⁺ dodecacation, the centers of which are 16.3 Å apart. The six cylindrical channels that surround each col-

umn have a diameter of 4.2 Å and are filled with [ZnTFA₄]²⁻ counterions.

When the self-assembly process was repeated in 95% ethanol, we noted (Fig. 4) the appearance of additional peaks in the ESI mass spectrum at *m/z* 1563 and 1143 corresponding to [M-3TFA]³⁺ and [M-4TFA]⁴⁺, respectively, a situation that can be explained if an additional Zn·2TFA is associated with BR·12TFA. We propose that the central electron-rich cavity, decorated with 12 donor O atoms, and so qualitatively reminiscent of Cram's spherands (35), hosts the seventh Zn(II) ion. This hypothesis is supported by an ¹H NMR spectrum (Fig. 2C) that shows an additional set of signals—some of which correspond to protons (H-c/c', H-b/b', and H-a/a') on the periphery of the molecule and overlap with those for BR·12TFA—attributable to another highly symmetrical species that we propose is Zn@BR·14TFA, i.e., a seventh Zn(II) ion occupies the central electron-rich cavity of BR¹²⁺. Of further importance is that resonances corresponding to the protons H-i' and H-g', located much closer to the core of the molecule, are influenced most in their chemical shifts by the incarcerated guest.

The ability to produce gram quantities of highly soluble hosts that can locate a range of different transition metals in an insulated octahedral array around an inner heteroatom-lined chamber, which can provide a welcoming home for many dif-

ferent guest species, suggests numerous ideas in which these BR compounds could be exploited as highly organized nanoclusters in a materials setting such as spintronics (36) or in a biological context such as medical imaging (37).

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- To our knowledge, the only known case of molecular BRs consists of single-stranded DNA derived by ligating a right-handed B-DNA three-arm junction and a left-handed Z-DNA three-arm junction. The molecule is comprised of three individual rings of 196, 206, and 216 nucleosides in which each arm of the junctions contains 1.5 turns of DNA, see (38).
- For a metallic microstructure possessing the BR topology, see (39).
- Examples of Borromean links within 2D and 3D arrays

have been identified retroactively in certain coordination polymers, see (40).

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- A neutral BR surrogate was constructed within the input mode of MacroModel 4.0 by aligning orthogonally the three identical [2+2] macrocycles in initially planar conformations. Six generic atoms (Z type) were placed between each set of *exo*-bipyridyl and *endo*-diiminopyridyl coordination sites and then subjected to energy minimization in the absence of counterions by using the Polak-Ribière Conjugate Gradient (PRCG) method and the AMBER* forcefield.
- Single crystals suitable for x-ray crystallographic analysis were grown by vapor diffusion of *n*-Bu₂O into a CF₃CH₂OH solution of BR·12TFA. A colorless single crystal was attached with oil to a thin glass fiber. Crystal data for [(C₆₂H₄₆N₁₀O₄)₃(ZnCF₃CO₂)₆]·3[Zn(CF₃CO₂)₄], *M*_r = 5608.0, trigonal, *a* = *b* = 38.937(5) Å and *c* = 32.604(8) Å, *V* = 42,809(13) Å³, space group R $\bar{3}c$, *Z* = 6, ρ_{calc} = 1.305 g cm⁻³, $\lambda(\text{MoK}\alpha)$ = 0.70930 Å, *F*(000) = 16920, *T* = 173(1) K, 10,598 unique reflections ($2\theta \leq 56^\circ$), of which 2587 were observed [*I*_o > 2σ(*I*)]. Final *R* factors: *R*₁ = 0.1656, *wR*₂ = 0.5151 for 381 parameters. Data was collected on a Bruker SMART 1000 CCD diffractometer with MoK α radiation using the ω-scan mode. Data were corrected for absorption with the SADABS program, and structure solution and refinement were performed with the SHELX-97 software package. All nonhydrogen atoms and nonguest molecules were refined anisotropically, whereas the hydrogen atoms were included at geometrically calculated positions and allowed to ride on their parent atoms. Details of the x-ray structure determination are available from the Cambridge Crystallographic Data Centre (CCDC), deposition number CCDC 231701. This data can be obtained free of charge from www.ccdc.cam.ac.uk/contents/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax, (+44)1223-336-033, e-mail, deposit@ccdc.cam.ac.uk.
- The cuboctahedron's volume was calculated by mapping out the 3D space of the largest sphere that can be placed inside the cavity with its centroid and wall boundary defined by the Cartesian coordinates of 12 O atoms allowing for their van der Waals radii. The calculations were performed using MCAVITY, a program that is freely available at www.x-seed.net/cavity.html.
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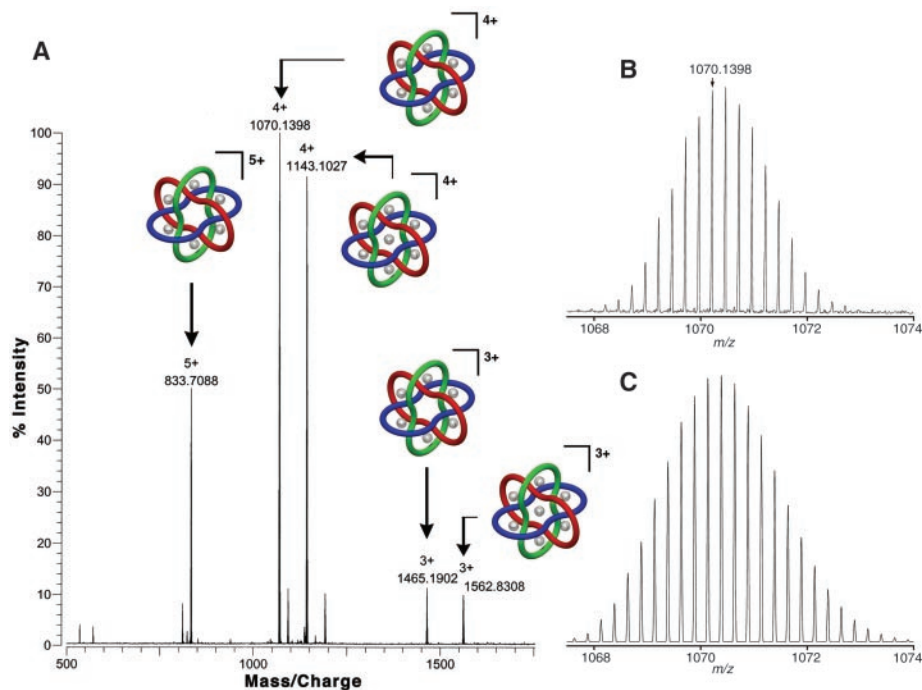


Fig. 4. (A) The ESI mass spectrum of a mixture of BR·12TFA and Zn@BR·14TFA. (B) The expanded isotopic distribution pattern for [M-4TFA]⁴⁺, which correlates well with the calculated distribution shown in (C).

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Supporting Online Material

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Materials and Methods

SOM Text

Scheme S1

References

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Multiple Catenanes Derived from Calix[4]arenes

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A multicatenane is described in which two belts consisting of four annelated rings attached to the wide rims of two calix[4]arenes are interwoven in such a way that each ring of one belt penetrates two adjacent rings of the other belt and vice versa. The key step of the synthesis of this [8]catenane is the exclusive formation of preorganized heterodimers between a multimacrocylic tetraurea calix[4]arene and an "open-chain" tetraurea calix[4]arene containing eight ω -alkenyl groups. When a tetraurea calix[4]arene containing four alkenyl groups is used, a bis-[3]catenane is formed analogously.

Topologically interesting molecules represent a permanent challenge for synthetic chemists (1). Möbius strips (2), various knots (3), K5 molecules (4), or first steps toward Borromean rings (5) may be cited as a somewhat arbitrary selection of examples. The interest is justified not only by the potential application of such systems, which has already been demonstrated for rotaxanes (6) and catenanes in the areas of molecular devices [for reviews, see (7–9)] and information storage (10, 11), but also because, in nature, topologically nontrivial forms of DNA play a crucial role in the correct replication and translation processes (12). An increasing understanding of the preorganization of suitable precursor molecules by reversible bonds ("self-assembly") is responsible for the rapid progress in this area.

We recently have shown that the preorganization of tetraurea calix[4]arenes (Scheme 1, formula 1) in hydrogen-bonded dimers (13) (Fig. 1) can be used to synthesize novel bis-[2]catenanes by metathesis reaction between alkenyl groups attached to the urea residues R (14). A "statistical approach" with homodimers (1_2) led to three possible topological isomers: bis-[2]catenanes (5 to 12%), doubly bridged mono-[2]catenanes (26 to 32%), and tetrabridged capsules (10 to 15%). However, the bis-[2]catenane is the only identified reaction product when heterodimers of prefab-

ricated double-loop derivative 3 with a tetraurea of type 1 (bearing 5-hexenyloxy chains instead of 7-octenyloxy chains) are reacted (15). Here, we show how such double-loop derivatives 3 and analogous tetra-loop derivatives 4 (16) of calix[4]arenes can be used as building blocks for novel multicatenanes.

"Open-chain" tetraureas 1 and 2 exist as well-defined homodimers in aprotic solvents

(Fig. 2A). Tetraureas of type 3 and 4 do not homodimerize (Fig. 2B), because this would necessarily lead to a sterically unfavorable overlap of the loops. Thus, a solution of a 1:1 mixture of 4 and 1 or 2 in apolar solvents contains exclusively the heterodimers 1·4 or 2·4 as the only species that can be detected by proton nuclear magnetic resonance (¹H NMR) spectra (Fig. 2C), because this is the only way by which all urea functions can be involved in the usual belt of 16 NH···O=C hydrogen bonds (17).

Metathesis reaction of such pseudorotaxane-like heterodimers (18) under the conditions described before (15, 19) leads (after hydrogenation) to a single reaction product 5 or 6, as schematically represented in Fig. 1B (reactions a and b).

Both compounds were isolated in >50% yield after a simple purification by column chromatography and recrystallization. Their unprecedented multicatenane structure was unambiguously proved by electrospray ionization mass spectrometry (20) and ¹H and ¹³C NMR. Compound 6, especially, shows in apolar solvents the usual S₈ symmetry of a homodimer of type (1)₂ with two (and only two) singlets for NH protons and two

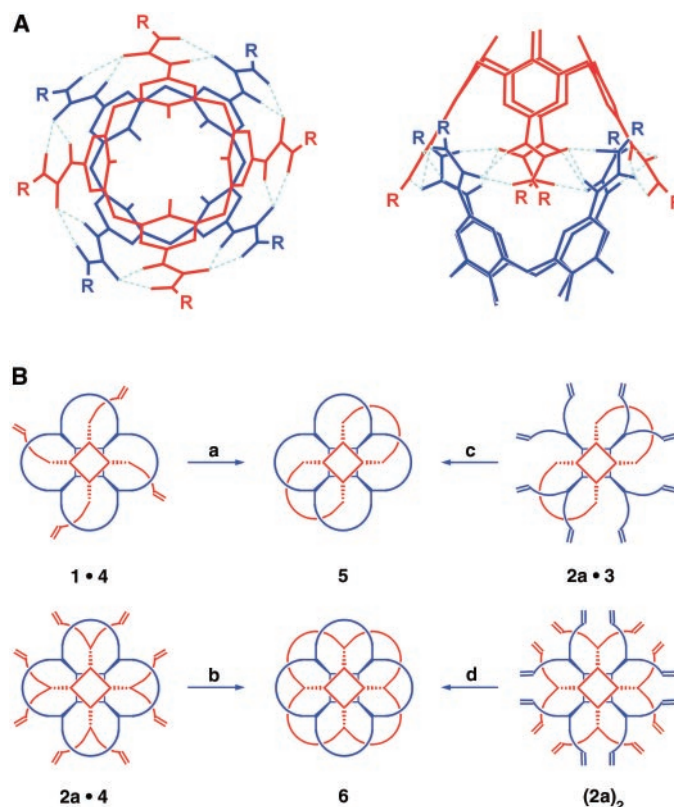


Fig. 1. (A) Hydrogen-bonded dimer of a tetraurea calix[4]arene 1 or 2, showing the mutual orientation of the urea residues R. Ether groups are omitted for clarity. (B) Schematic representation of the synthesis of multicatenanes 5 and 6 by metathesis reaction of selectively formed heterodimers 1·4 and 2a·4 followed by hydrogenation (reactions a and b). While reaction d led to a complicated mixture of products, reaction c (which has not yet been checked) seems at least an alternative to a, although wrong connections between double bonds are possible for c in contrast to a.

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