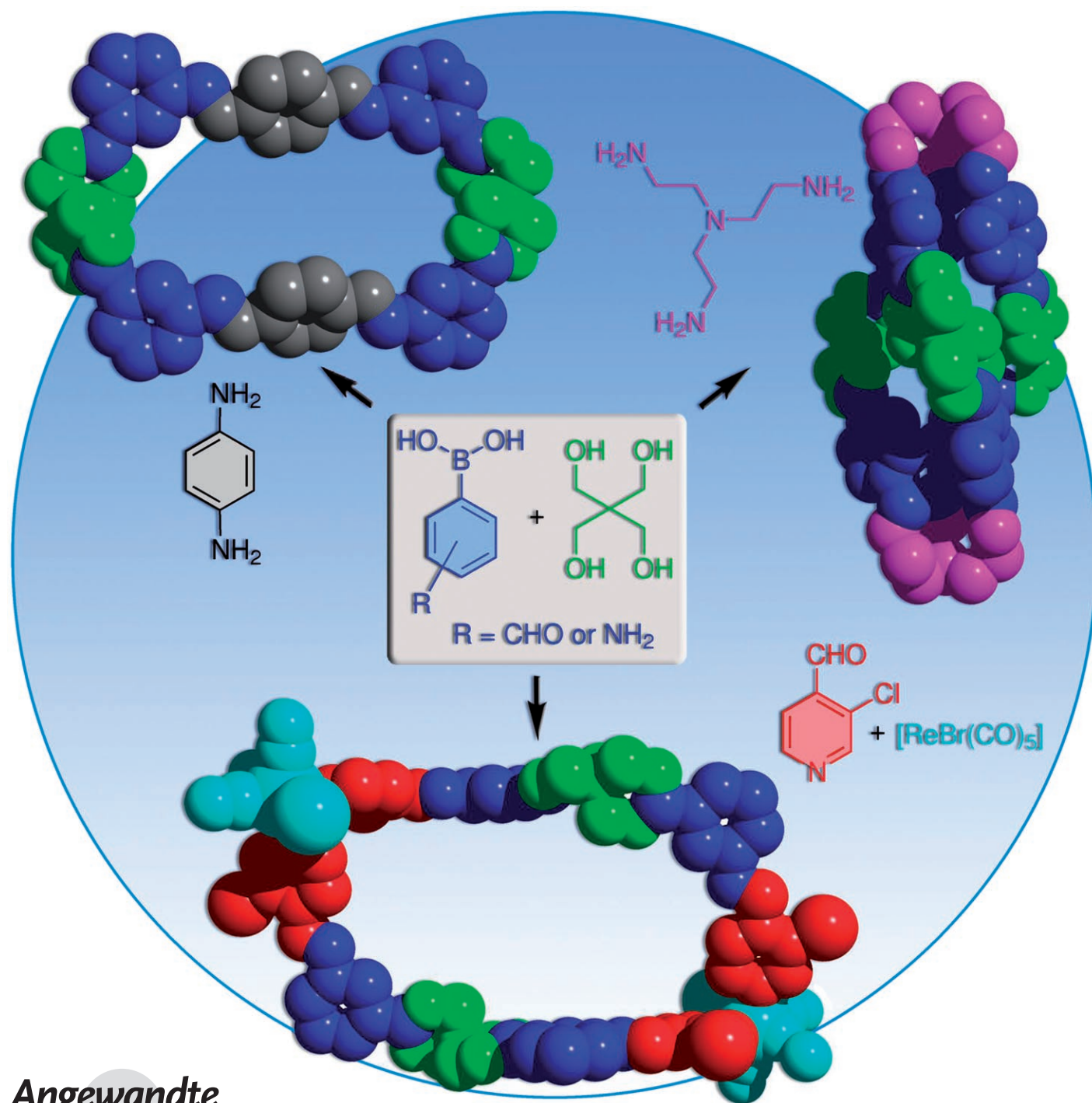


Multicomponent Assembly of Boronic Acid Based Macrocycles and Cages**

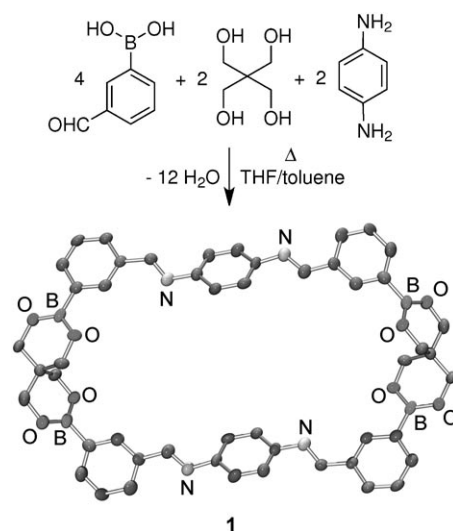
Nicolas Christinat, Rosario Scopelliti, and Kay Severin*



In nature, functional nanostructures are often formed by assembly of multiple, chemically distinct building blocks. The 30S subunit of bacterial ribosome, for example, is obtained by assembly of ribosomal RNA with 21 unique proteins.^[1] Synthetic supramolecular chemistry aims to use the principles of biomolecular self-assembly to construct artificial structures with interesting functions and properties. Although research in this area has been remarkably successful, the ability to assemble molecularly defined structures with three or more types of building blocks is still not very well developed. One strategy that has emerged is to control the assembly process with steric constraints. In supramolecular coordination chemistry, for example, sterically demanding ligands have been used to favor the formation of mixed-ligand aggregates over homoaggregates.^[2] Another option is the simultaneous utilization of different types of interactions. Reversible imine bond formation, for example, has been employed in parallel to metal–ligand interactions to form complex structures such as helicates, catenanes, and Borromean rings.^[3] Herein, we describe an extension of this approach. We show that aldehyde–amine condensation reactions and metal–ligand interactions can be combined with a third type of reversible interaction: the formation of boronic esters. This approach allows the assembly of boron-based macrocycles and cages of unprecedented size in one-pot reactions of simple building blocks.

Boronic acids condense easily and reversibly with diols to form boronate esters. This reaction has been exploited widely in carbohydrate chemistry, where boronic acids are used to synthesize receptors and sensors or as protecting groups.^[4] The reversible formation of boronic esters has also been employed to build complex structures such as macrocycles,^[5] helicates,^[6] nanotubes,^[7] dynamic polymers,^[8] or porous covalent organic frameworks.^[9] We have recently shown that boronate ester based macrocycles with pendent aldehyde groups can be functionalized by reaction with amines to give dendritic nanostructures.^[10,11] This finding prompted us to investigate whether boronic ester and imine condensation reactions can be used simultaneously to construct large macrocyclic structures.

In a first set of experiments, we studied the reaction of formylphenylboronic acids with pentaerythritol and di- and triamines. When a THF/toluene solution of 3-formylphenylboronic acid, pentaerythritol, and 1,4-diaminobenzene was heated in a flask equipped with a Dean–Stark trap, we were able to isolate the macrocycle **1** in 44% yield (Scheme 1). As a side product, we obtained an insoluble material, which likely consists of polymeric condensation products.^[8]



Scheme 1. Formation of macrocycle **1** in a [4+2+2] condensation reaction. The graphic representation of the product is based on a crystallographic analysis. The hydrogen atoms and the solvent molecules (2CHCl_3) have been omitted for clarity. Thermal ellipsoids are shown at 50% probability.

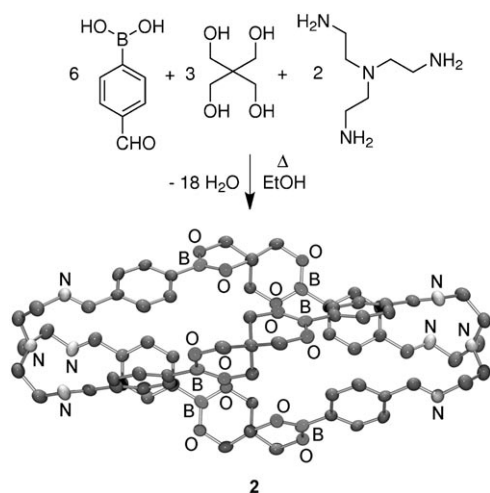
Macrocycle **1** was comprehensively characterized by NMR spectroscopy, elemental analysis, and single crystal X-ray crystallography.^[12] The high symmetry of **1** was reflected by the fact that only one set of signals in the NMR spectrum was observed for each of the different building blocks. The methylene protons of the boronate ester gave rise to a simple singlet in the ^1H NMR spectrum, thus indicating that the macrocycle possesses sufficient conformational flexibility to render them equivalent. The solid-state structure of **1** showed that the four imine bonds have the preferred *trans* geometry (Scheme 1). The diameter of the 42-membered macrocycle (maximum B...B distance) is 17.2 Å.

Next, we investigated whether this approach can be used to build cage-like structures. Towards this goal, we replaced 1,4-diaminobenzene with tris(2-aminoethyl)amine (tren). Unfortunately, the polycondensation reaction with 3-formylphenylboronic acid and pentaerythritol resulted in a product of very low solubility, which prevented further characterization. When 4-formylphenylboronic acid was used, however, we were able to obtain a product (**2**) that displayed good solubility in chloroform (Scheme 2). The ^1H NMR spectrum of **2** was again indicative of a highly symmetrical structure, with one set of signals for each of the three types of building blocks. Confirmation that we had obtained the desired cage structure came from ESI mass spectrometry and single crystal X-ray crystallography. The quality of the results of the latter was very low, but the connectivity and the overall geometry were clearly established (Scheme 2).^[13] The macrobicyclic **2** was formed by condensation of six boronic acid molecules, three pentaerythritol molecules, and two triamine molecules ([6+3+2] condensation). It should be pointed out that the obtained yield of 82% is quite remarkable, given that the one-pot synthesis of **2** requires the formation of 18 covalent bonds. The cage has the form of an ellipsoid with a length of 20.5 Å (maximum N...N distance). The three boronate ester chains

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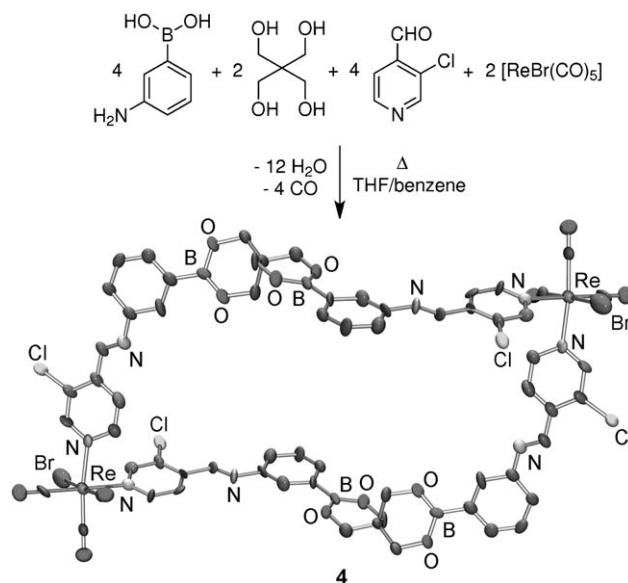
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 2. Formation of cage **2** in a [6+3+2] condensation reaction. The graphic representation of the product is based on a crystallographic analysis. The hydrogen atoms and the solvent molecules (4 CHCl₃) have been omitted for clarity. Thermal ellipsoids are shown at 35% probability.

wrap around each other in a slightly helical fashion. The macrobicycle **2** can be classified as a cryptand.^[14] Related tren-based cryptands have been prepared by [3+2] condensation reactions with simple dialdehydes,^[15] but the reported structures are significantly smaller than that of **2** ($d(\text{N}\cdots\text{N}) \approx 10 \text{ \AA}$).^[15c] Preliminary experiments indicate that cage **2** can act as a dinucleating ligand for copper(I). When two equivalents of [Cu(CH₃CN)₄(PF₆)] in acetonitrile were added to a chloroform solution of **2**, the quantitative formation of the cryptate [Cu₂(**2**)(PF₆)₂] was observed, as evidenced by ¹H NMR spectroscopy and ESI mass spectrometry. Most likely, the Cu⁺ ions are bound to the N atoms of the cage, as was observed for smaller tren-based cryptands.^[15d,16]

To further enlarge the scope of this synthetic approach, we investigated whether it is possible to simultaneously combine three types of reversible interactions, namely imine and boronic ester condensations as well as metal–ligand interactions. We thus treated 3-aminophenylboronic acid with pentaerythritol, 4-formylpyridine, and [ReBr(CO)₅]. The last building block was chosen because it is known to be a versatile starting material for the formation of [ReBr(CO)₅(N-donor ligand)₂] complexes.^[17] Heating a solution of this mixture in THF/benzene in a flask equipped with a Dean–Stark trap resulted in the formation of a yellow solid (**3**). The analytical data (IR, ¹H, ¹³C, and ¹¹B NMR spectroscopy) of this complex were in agreement with the desired macrocyclic structure. Attempts to obtain additional evidence by mass spectrometry or crystallography were not successful. We therefore repeated the reaction with 3-chloro-4-formylpyridine instead of 4-formylpyridine. Following a similar procedure, a yellow complex (**4**) was obtained in 58% yield (Scheme 3). Fortunately, the introduction of the chloro substituents allowed us to obtain single crystals of sufficient quality to perform a crystallographic analysis.^[18] The result confirmed that a metallamacrocyclic structure had formed. Two independent but structurally very similar complexes are



Scheme 3. Formation of macrocycle **4** in a [4+4+2+2] reaction. The graphic representation of the product is based on a crystallographic analysis. The hydrogen atoms and the solvent molecules (3 C₂H₄Cl₂) have been omitted for clarity. Thermal ellipsoids are shown at 50% probability.

present in the crystal (half of each complex in the asymmetric unit). Each macrocycle contains two {ReBr(CO)₃} fragments. The bromide and the carbonyl ligand *trans* to the bromide are statistically disordered in a ratio of 7:3.^[19] The two {ReBr(CO)₃} fragments are connected by two bridging ligands, each of which is the condensation product of two boronic acid molecules, two 3-chloro-4-formylpyridine molecules, and one pentaerythritol molecule. The one-pot synthesis of complex **4** thus requires the formation of 12 covalent and 4 metal–ligand bonds. With a ring size of 52 atoms and a diameter of approximately 24 Å (Re⋯Re distance),^[20] complex **4** is by far the largest boron-based macrocycle described to date.

The results described above are evidence that multi-component condensation reactions can be used to construct nanometer-sized macrocycles and cages in one-pot reactions from very simple starting materials. The key to success is the simultaneous utilization of different types of reversibly formed bonds that are largely independent of each other. Boronate esters and imines appear to be ideally suited in this regard. The four-component syntheses of **3** and **4** show that metal–ligand interactions can be used as a third type of bond to further increase complexity.

The structural diversity that is accessible with this approach seems to be very high. Instead of pentaerythritol, for example, other rigid tetraols such as bicyclo-[2.2.1]heptane-2,3,5,6-tetraol could be employed. The modular nature and the fact that the coupling reactions are reversible should also be of interest for studies in the context of dynamic combinatorial chemistry.^[21]

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$c = 20.60(2) \text{ \AA}$, $\alpha = 97.48(7)^\circ$, $\beta = 107.74(9)^\circ$, $\gamma = 101.23(8)^\circ$, $V = 4876(9) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.476 \text{ g cm}^{-3}$, $\mu = 3.628 \text{ mm}^{-1}$, $F(000) = 2116$, crystal dimensions $0.61 \times 0.33 \times 0.14 \text{ mm}^3$, $T = 100(2) \text{ K}$, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$, $\theta = 3.31\text{--}22.99^\circ$, $-16 \leq h \leq 16$, $-18 \leq k \leq 18$, $-22 \leq l \leq 22$, 55052 reflections collected, 13133 independent reflections, $R_{\text{int}} = 0.1471$, $R_1 = 0.1079$ [$I > 2\sigma(I)$], $wR_2 = 0.3088$ (all data), largest difference peak $3.842 \text{ e \AA}^{-3}$, largest difference minimum $-3.067 \text{ e \AA}^{-3}$. Structure solution and refinement by SHELX97 (G. M. Sheldrick, SHELX97, Programs for Crystal Structure Analysis, University of Göttingen, Göttingen (Germany), 1998). Hydrogen atoms were placed in calculated positions using the riding model. CCDC-667830 contains the supplementary crystallographic data

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