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Dynamic covalent assembly of tribenzotriquinacenes into molecular cubes†

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Molecular cubes constructed from catechol-functionalized tribenzotriquinacenes and 1,4-phenylene diboronic acids were synthesized in a one-pot procedure by crosslinking of 20 individual components through a dynamic covalent approach. Structural identity of the nanocubes was confirmed by mass spectrometry and 1H-NMR spectroscopy.

The formation of monodisperse molecular structures with ever increasing complexity is an ongoing desire in synthetic chemistry. Molecular cage compounds are intriguing examples for suchlike systems with dimensions in the nanometer regime. Over the last decades, hybrid systems assembled via metal coordination of appropriate organic linker molecules have been presented in large variety. However, reports on solely organic cages are far more limited in numbers since tedious multiple step synthesis hamper the efficient formation of highly complex systems. To circumvent these drawbacks, the concept of dynamic covalent chemistry offers the possibility of performing multiple reaction steps under reversible conditions giving easy access to complex structures under thermodynamic control. The most prominent reactions in this regard are the formation of imines and boronate esters from aldehydes and amines or boronic acids and 1,2-diols, respectively. Based on this approach, numerous examples of organic cage compounds have been presented in the literature in recent years. Potential applications can be found in the fields of host-guest chemistry or porous materials with reported BET surface areas of up to 3758 m²g⁻¹ for organic cages in the solid state. However, it is still challenging to obtain permanent porous materials and only a few examples of processing cage molecules into devices such as quartz microbalances or macroscopic inorganic porous beads have been reported. Since it was shown theoretically that any equilibrium states of dynamic molecular assemblies possess preferentially the highest possible symmetry, formation of Archimedean or Platonic solids should be preferred and as a matter of fact, solely organic representatives of tetrahedron, cube, octahedron or cuboctahedron were synthesized in the last decade. The factual shape of the cage is thereby encoded in the molecular symmetry of the implemented subunits. For instance, co-assembly of tritopic and ditopic building blocks in a 2:3 ratio is expected to yield either cuboctahedra (planar tritopic and ditopic molecules with tetrahedral angles) or cubes for trigonal corner units and linear ditopic struts. In contrast to the rich chemistry of octahedral metal complexes resulting in numerous examples for metal-organic systems, the chiral cubes synthesized by Xu and Warmuth from aldehyde-functionalized cyclotriveratrylenes and linear diamines are the only reported case for cubic organic cage compounds so far. The actual absence of further examples is most likely due to the lack of suitable organic building blocks featuring the required rectangular arrangement of three functional units. One rare example for such a molecular framework is the tribenzotriquinacene (TBTQ) scaffold possessing three condensed indane moieties. After being introduced by Kuck, functionalized TBTQ derivatives have been recently implemented into fullerene receptors, micro-porous polymers or mimics for odd-membered ring-defects in graphenes. However, despite the favourable rigid arrangement of up to three functional sites, there is only one reported example of a TBTQ-based cage compound and surprisingly, no attempts have yet been made to incorporate such derivatives as corner units into covalent organic cages with cubic symmetry.

Fig. 1 a) PM6-minimized model of 1 as a tritopic building block with an orthogonal arrangement of the peripheral catechol units; b) Formation of molecular cubes after reaction of eight tritopic corner units and twelve ditopic linear spacer units under dynamic covalent conditions; c) Synthesis of molecular cubes 4 from TBTQ derivative 2 and diboronic acids 3 in THF under water removing conditions.

Herein, we report on the synthesis of novel metal-free molecular cubes utilizing the formation of 24 boronate esters by crosslinking of catechol-functionalized tribenzotriquinacenes and 1,4-phenylene diboronic acids in a one-pot reaction.
Hexahydroxy TBTQ 1 has been recently used as a precursor for microporous polymers and based on the PM6-minimized model in Fig. 1, an angle of 89.3° could be calculated between two catechol units each indicating an almost rectangular orientation of the three indane moieties with respect to each other. As a matter of fact, this spatial arrangement of its functional groups identifies 1 as a well-suited precursor for the formation of molecular cubes via boronate ester formation with linear boronic acids. We therefore investigated the reaction of 1 with 1,4-phenylene diboronic acid 3a in a 2:3 molecular ratio in various solvents and under different reaction conditions. However, in all cases either no reaction occurred or rapid precipitation of presumably oligomeric side products was monitored by intermediates, we modified the apical position of the TBTQ moiety by introducing a butyl chain in 2 (see ESI† for synthetic procedures and characterization details) in order to enhance the solubility of both the starting material and oligomeric condensation products. Analogous to 1, reaction of 2 and 3a in a 2:3 molecular ratio in THF at room temperature resulted in an equilibrium of unreacted 1 and mono- to trisboronate esters as monitored by 1H-NMR spectroscopy for the TBTQ methine protons (see Fig. S11 ESI†).

Equilibrium state is reached after several minutes and no further changes were observed even over the course of several days. However, addition of 4Å molecular sieve led to quantitative conversion to a highly symmetrical product after five days as indicated by NMR analysis (see Fig. 2 and Fig. S18 ESI†). The reaction product could be precipitated with hexane and redissolved in CHCl₃ in which both precursors are completely insoluble. Subsequent filtration, removal of the solvent and drying in high vacuum gave cube 4b in 94% yield. Fig. 3d shows the MALDI TOF mass spectrum of a CHCl₃ solution revealing the formation of cube 4b as the only detectable species. As depicted in Fig. 4, 1H NMR spectroscopy shows only one set of signals for the individual protons indicating the high symmetry of the structure. Therefore, the successful formation of O₈ symmetrical molecular cubes 4b is the only plausible conclusion in accordance with both MS and 1H-NMR results. DOSY NMR spectroscopy of 4b showed all relevant signals with the same diffusion coefficient (see Fig. S20 ESI†) and from that we could calculate a diameter for the cage of 3.3 nm via the Stokes-Einstein equation. This finding is in good agreement with an PM6-optimized model of 4b exhibiting a diagonal corner-to-corner distance of 3.2 nm (see Fig. 3c). Altogether, these analytical findings are proofing the efficient formation of molecular cubes 4b.

In order to enhance the solubility of the molecular cages and to definitely prove the structural assignment as cubes with O₈ symmetry, we synthesized phenylene diboronic acid 3b with two butyl chains as additional solubilizing groups (see ESI† for synthetic procedures and characterization details). Again, mixing of 2 and 3b in a 2:3 ratio in THF-d₈ resulted in an equilibrium of several reaction intermediates, whereas subsequent addition of 4Å molecular sieve led to quantitative conversion to a highly symmetrical product after five days as indicated by NMR analysis (see Fig. 2 and Fig. S18 ESI†). The reaction product could be precipitated with hexane and redissolved in CHCl₃, a solvent in which both precursors are completely insoluble. Subsequent filtration, removal of the solvent and drying in high vacuum gave cube 4b in 94% yield. Fig. 3d shows the MALDI TOF mass spectrum of a CHCl₃ solution revealing the formation of cube 4b as the only detectable species. As depicted in Fig. 4, 1H NMR spectroscopy shows only one set of signals for the individual protons indicating the high symmetry of the structure. Therefore, the successful formation of O₈ symmetrical molecular cubes 4b is the only plausible conclusion in accordance with both MS and 1H-NMR results. DOSY NMR spectroscopy of 4b showed all relevant signals with the same diffusion coefficient (see Fig. S20 ESI†) and from that we could calculate a diameter for the cage of 3.3 nm via the Stokes-Einstein equation. This finding is in good agreement with an PM6-optimized model of 4b exhibiting a diagonal corner-to-corner distance of 3.2 nm (see Fig. 3c). Altogether, these analytical findings are proofing the efficient formation of molecular cubes 4b.

**Fig. 2** 1H-NMR monitoring (THF-d₈, 400 MHz, rt) of methine protons for reaction of 2 and 3b in a 2:3 molecular ratio (top: start of reaction, middle: after one day, bottom: after five days).

**Fig. 3** a) PM6-minimized model of molecular cube 4a with non-functionalized spacer units 3a; MALDI-TOF MS (TCNQ, solvent free, molecular ratio 4a:matrix 1:500) of 4a in the solid state; c) PM6-minimized model of molecular cube 4b with spacer units 3b containing butyl chains as solubilizing groups; d) MALDI-TOF MS (DCTB, CHCl₃) of 4b.
Due to the microcrystallinity of 4a, we investigated the potential porosity of the solid material. After redissolving the precipitate in MeOH, 0.9 equivalents of THF remained in the product (see Fig. S22 ESI†) even after drying for 24 hours at 50 °C in high vacuum. Thermogravimetric analysis of the dried solid revealed a weight loss of 11.5% between 100–200 °C (see Fig. S21 ESI†). This result was attributed to the removal of eight THF molecules per molecular cube 4a being in very good agreement with the amount of encapsulated THF determined by 1H-NMR. However, gas sorption measurements after washing the precipitate with dry THF and drying under high vacuum at 100 °C for 20 hours showed no significant porosity of the material. This findings indicate either kinetic hindrance of gas absorption or a structural collapse of the cubes after desolvation, a fact which is often observed for organic cage molecules.76 In ongoing work, we will address these issues and look for alternative activation protocols in order to preserve porosity of suchlike materials and gain more insight into the inner surfaces of the cubes.

In conclusion, we were able to synthesize molecular cubes 4a and 4b through the concerted formation of 24 boronate esters in a [8+12] cocondensation of twenty small molecule precursors in a dynamic covalent approach. These cage compounds are the first examples for purely organic cubes with the highest possible cubic symmetry Oh. Due to the easy and modifiable synthesis of TBTQ precursors 2 and linear diboric acids 3, this strategy will give access to a whole new family of structurally related cubic organic cage molecules and starting from lower symmetry analogues of the corner units also cuboid cages can be envisaged. Currently, we are working on the synthesis and characterization of modified cubes and cuboids in order to test the scope and potential of this Synthetic approach for dynamic covalent cube formation.

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**Notes and references**

22. *Spartan'14*, Wavefunction, Inc., Irvine, CA, USA.