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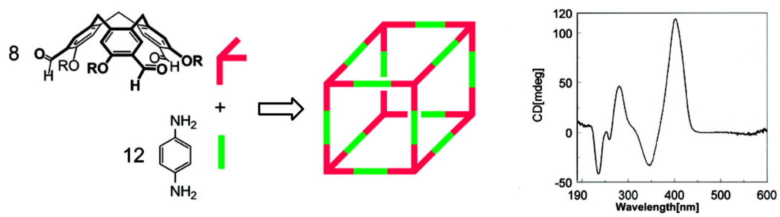

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Edge-Directed Dynamic Covalent Synthesis of a Chiral Nanocube

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Spherical molecules, whose shapes and symmetries parallel those of the regular or semiregular, convex polyhedra, also known as Platonic and Archimedian solids, are attractive synthetic targets and have the potential to encapsulate one or more guest molecules.[1] This creates opportunities for applications in delivery, separation, and as nanoreactors.[1b,c,2,3] Very recently, one-pot, multicomponent self-assembly approaches using hydrogen bonding or metal coordination chemistry have been developed that yield nanometer-sized capsules, of which many structurally represent Platonic or Archimedian polyhedra.[1b,4,5] Compared to more traditional covalent syntheses, these self-assembly approaches benefit from the reversibility of the hydrogen bond or metal−ligand interaction, which provides an error correction and proof-reading mechanism during the synthesis and ultimately yield the thermodynamic product.[1b,6]

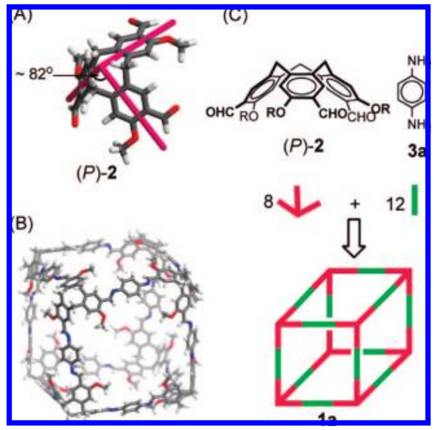
A coordination polyhedron can be assembled using different design strategies.[1b,4a–c] In an edge-directed synthesis, a polytopic building block forms the vertices of the polyhedron which are linked with linear spacers along the edges, leaving the faces open.[4b] Alternatively, in a face-directed assembly, the polyhedron is constructed from 2D panels, that occupy all or several of the faces, and these are linked together through metal coordination bonds.[4a,c] Conceptually, both strategies should also be applicable for multicomponent syntheses of covalent polyhedra, if suitable building blocks are connected via reversible, dynamic bonds, such as imines.[7,8] Here, we demonstrate the dynamic covalent synthesis of a polyimine nanocube using an edge-directed approach.[9]

A major challenge for the dynamic covalent synthesis of a cube is the identification of a suitable tritopic 90° corner unit that would yield a strain-free cube, but not the smaller tetrahedron or the larger dodecahedron. The latter are alternative 4 + 6 and 20 + 30 assemblies accessible from tritopic and linear building blocks.[4e,f]

Examination of X-ray structures of Collet's cyclotriveratrylenes (CTV)[10] suggested that C_3-trialkoxy-triformylcyclobenzylene **2** might be a suitable corner piece and may yield nanocube **1**, if 8 equiv of **2** are reacted with 12 equiv of a linear diamine, such as 1,4-phenylenediamine **3a** (Scheme 1C). In **2**, angles between the three lines that bisect each aryl unit and that cross at the C_3 axis are close to 90° (Scheme 1A). The chirality of **2** is an additional interesting feature and a unique homochiral product is only expected if **2** is enantiomerically pure or if the reaction proceeds with complete self-sorting such that only (*P*)-**2**s or (*M*)-**2**s are incorporated into the same cube.[11]

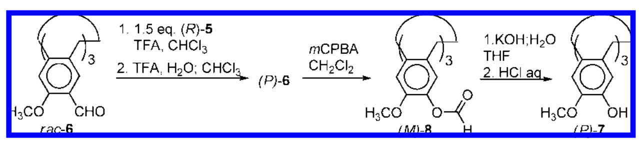
The asymmetric synthesis of (*P*)-**2** was achieved through a dynamic thermodynamic resolution, in which (*M*)-**2** is completely inverted.[10a] Heating racemic *rac*-**2** and two equiv of (*R*,*R*)-diaminocyclohexane (*R*)-**5** (99% ee) in $CHCl_3$ containing a catalytic amount of TFA (12 h; 80 °C) gave enantiomerically pure (*P*,*P*,*R*,*R*,*R*)-**4** (92% yield) together with small amounts of decomposition products (see also Figure S40, Supporting Information).[12] Precipitation of (*P*,*P*,*R*,*R*,*R*)-**4** and hydrolysis with TFA/water gave (*P*)-**2** (92% yield, >99% ee) and allowed recovery of (*R*)-**5**. We

Scheme 1 [a]



[a] Amber*-energy minimized structures of (*P*)-**2** (A) and (*all-P*)-**1a** (B) (hexadecyl groups are replaced with CH_3). (C) Design of nanocube **1a** from 8 tritopic 90° corners **2** (R = hexadecyl) and 12 ditopic 180° spacers **3a**.

Scheme 2. Resolution of **6** and Conversion of (*P*)-**6** into (*P*)-**7**



tentatively assign *P*-chirality to the resolved **2**, based on force field calculations (Amber*), which predict that (*P*,*P*,*R*,*R*,*R*)-**4** is the thermodynamic sink and 16.3 and 26.1 kcal mol^{-1} less strained than the other two isomeric (*P*,*M*,*R*,*R*,*R*)- and (*M*,*M*,*R*,*R*,*R*)-cryptophanes, respectively. We also resolved **6** using the same method and converted (*P*)-**6** into (*P*)-C_3-cyclotriguaiacylene (*P*)-**7** by Baeyer-Villager oxidation and subsequent basic hydrolysis (Scheme 2).[13] The CD spectrum of the reaction product was identical to that reported by Collet et al. for (*P*)(−)-**7**.[14] This experiment and the almost identical chiroptical properties of (*P*)-**6** and (*P*)-**2** support our configuration assignment of the latter.

When (*P*)-**2** (>99% ee) and **3a** were mixed in a 8:12 ratio in $CHCl_3$ containing 1 mol% TFA, homochiral nanocube (*all-P*)-**1a** formed in ∼90% yield together with ∼10% of diastereomeric heterochiral cubes containing (*M*)-**2** (Figure S41). The latter cubes result from partial inversion of (*P*)-**2** during the reaction.

The assignment of the major product to (*all-P*)-**1a** is based on its ^1H NMR spectrum, MALDI-TOF MS, gel permeation chromatogram, and diffusion properties: (1) The major ion in the MALDI-TOF MS has the correct mass-to-charge ratio for [(*all-P*)-**1a**+H]$^+$ at m/z = 9470.9 (calcd, 9471.7) (Figure 1A). (2) The ^1H NMR spectrum shows sharp singlets at δ 8.82, 7.15, 7.05, and 7.18 in a 24:24:24:48 ratio for the imine protons H1, the two cup aryl protons H2 and H4, and the linker aryl protons H3 (Figure 1B). This requires that all cups are identical and retain their C_3

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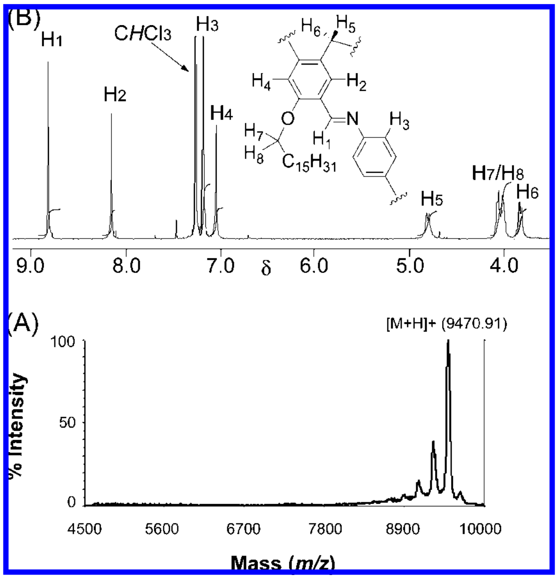
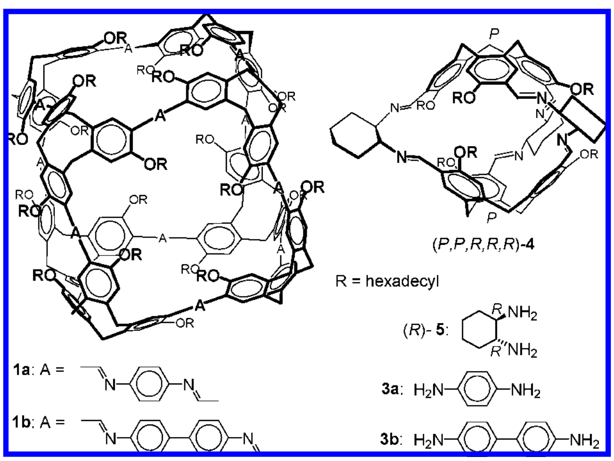


Figure 1. MALDI-TOF MS (A) and partial ^{1}H NMR spectrum (500 MHz; $CDCl_3$; 25 °C) (B) of (*all-P*)-**1a**.

Chart 1. Nanocubes **1a**,**b** and Chiral Cryptophane **4**



symmetry in **1a**, which is only possible for a cubic structure.[15] (3) Using DOSY experiments, we determined a diffusion constant of $D = 2.2 \pm 0.05 \times 10^{-10}$ m^{-2} s^{-1} for (*all-P*)-**1a** in $CDCl_3$ at 25 °C,[16] which suggests a molecular diameter of approximately 3.7 nm consistent with molecular dynamics (Figure S39). On the basis of force field calculations (Amber*), the edges and the C_3 axes of (*all-P*)-**1a** are, respectively, 1.7 and 2.9 nm long.

Our cube design principle should be general and should allow the preparation of other cubes from (*P*)-**2** and different linear diamines. Indeed, (*all-P*)-**1b** forms in similar yields as (*all-P*)-**1a** in the TFA-catalyzed reaction of (*P*)-**2** with benzidine **3b**. The same reactions as described above, however, carried with *rac*-**2** instead of (*P*)-**2**, gave complex mixtures of racemic diastereomeric nanocubes **1a** and **1b**, respectively. Because of the complexity of these mixtures, evidence for self-sorting could not be obtained.

In summary, we have demonstrated the dynamic covalent synthesis of chiral nanocubes using an edge-directed approach, in which eight tritopic C_3-triformylcyclobenzylene units occupy the cube vertices and are linked together along the edges with 12 linear diamines through 24 newly formed imine bonds. Our design differs from an earlier edge-directed coordination cube assembly, in which metal ions occupy the vertices[9a] and is closer related to Stang's assembly of a dodecahedron.[4f] We believe that our synthesis will inspire the self-assembly of CTV-based molecular cubes using hydrogen bonding and metal-coordination.[4g,17] The chirality of **1** suggests interesting recognition properties and possible applications in chiral separations, which have not been explored, yet. Furthermore, our cubes have dimensions that approach those of small globular proteins and may in fact be able to serve as alternative vessels for biomacromolecules.[18]

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Supporting Information Available: Experimental procedures and compound characterization. Chiral HPLC chromatograms and CD spectra of (*P*)-**2**, (*P*)-**6** and (*all-P*)-**1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018. (b) Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev.* **2000**, *100*, 853. (c) Cram, D. J.; Cram, J. M.; *Container Molecules and their Guests*; Royal Society of Chemistry: Cambridge, U.K., 1994.
(2) (a) Warmuth, R. *J. Incl. Phenom.* **2000**, *37*, 1. (b) Lützen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1000. (c) Warmuth, R.; Makowiec, S. *J. Am. Chem. Soc.* **2007**, *129*, 1233. (d) Natarajan, A.; Kaanumalle, L. S.; Jockusch, S.; Gibb, C. L. D.; Gibb, B. C.; Turro, N. J.; Ramamurthy, V. *J. Am. Chem. Soc.* **2007**, *129*, 4132. (e) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Science* **2007**, *316*, 85. (f) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251.
(3) Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2006**, *128*, 16498.
(4) (a) Fujita, M.; Tominaga, M.; Hori, A.; Therrien, B. *Acc. Chem. Res.* **2005**, *38*, 371. (b) Caulder, D. L.; Raymond, K. N. *Acc. Chem. Res.* **1999**, *32*, 975. (c) Seidel, S. R.; Stang, P. J. *Acc. Chem. Res.* **2002**, *35*, 972. (d) Fujita, M.; Oguro, D.; Miyazawa, M.; Oka, H.; Yamaguchi, K.; Ogura, K. *Nature* **1995**, *378*, 469. (e) Beissel, T.; Power, R. E.; Raymond, K. N. *Angew. Chem., Int. Ed.* **1996**, *35*, 1084. (f) Olenyuk, B.; Levin, M. D.; Whiteford, J. A.; Shield, J. E.; Stang, P. J. *J. Am. Chem. Soc.* **1999**, *121*, 10434. (g) Ronson, T. K.; Fisher, J.; Harding, L. P.; Hardie, M. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9086.
(5) (a) Rebek, J., Jr *Angew. Chem., Int. Ed.* **2005**, *44*, 2068. (b) Wyler, R.; de Mendoza, J.; Rebek, J., Jr *Angew. Chem., Int. Ed.* **1993**, *32*, 1699. (c) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469.
(6) (a) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, Germany, 1995. (b) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **1996**, *35*, 1154.
(7) Liu, Y.; Liu, X.; Warmuth, R. *Chem.—Eur. J.* **2007**, *13*, 8953.
(8) (a) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898. (b) Lehn, J.-M. *Chem.—Eur. J.* **1999**, *5*, 2455.
(9) (a) For coordination cubes: Roche, S.; Haslam, C.; Adams, H.; Heath, S. L.; Thomas, J. A, *Chem. Commun.* **1998**, 1681. (b) Johannessen, S. C.; Brisbois, R. G.; Fischer, J. P.; Grieco, P. A.; Counterman, A. E.; Clemmer, D. E. A. *J. Am. Chem. Soc.* **2001**, *123*, 3818.
(10) (a) Collet, A. *Tetrahedron* **1987**, *43*, 5725. (b) Collet, A.; Gabard, J.; Jacques, J.; Cesario, M.; Guilhem, J.; Pascard, C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1630.
(11) For leading references related to self-sorting see: (a) Wu, A.; Isaacs, L. *J. Am. Chem. Soc.* **2003**, *125*, 4831. (b) Mukhopadhyay, P.; Wu, A.; Isaacs, L. *J. Org. Chem.* **2004**, *69*, 6157. (c) Rowan, S. J.; Reynolds, D. J.; Sanders, J. K. M. *J. Org. Chem.* **1999**, *64*, 5804.
(12) At room temperature, no decomposition products are observed, but the reaction required 3 weeks to reach completion.
(13) Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153.
(14) Canceill, J.; Collet, A.; Gabard, J.; Gottarelli, G.; Spadat, G. P. *J. Am. Chem. Soc.* **1985**, *107*, 1299.
(15) A cube with inverted CTVs, whose concave surface would be at the outer surface, can be ruled out since it would require *cis*-imine bonds that would raise the conformational energy far beyond that of (*all-P*)-**1a**.
(16) Wu, D.; Chen, A.; Johnson, C. S., Jr *J. Magn. Reson. A* **1995**, *115*, 260.
(17) Sumby, C. J.; Hardie, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6395.
(18) (a) Erben, C. M.; Goodman, R. P.; Turberfield, A. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7414. (b) Seebeck, F. P.; Woycechowsky, K. J.; Zhuang, W.; Rabe, J. P.; Hilvert, D. *J. Am. Chem. Soc.* **2006**, *128*, 4516.

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