

Synthesis of Molecular Nanostructures by Multicomponent Condensation Reactions in a Ball Mill

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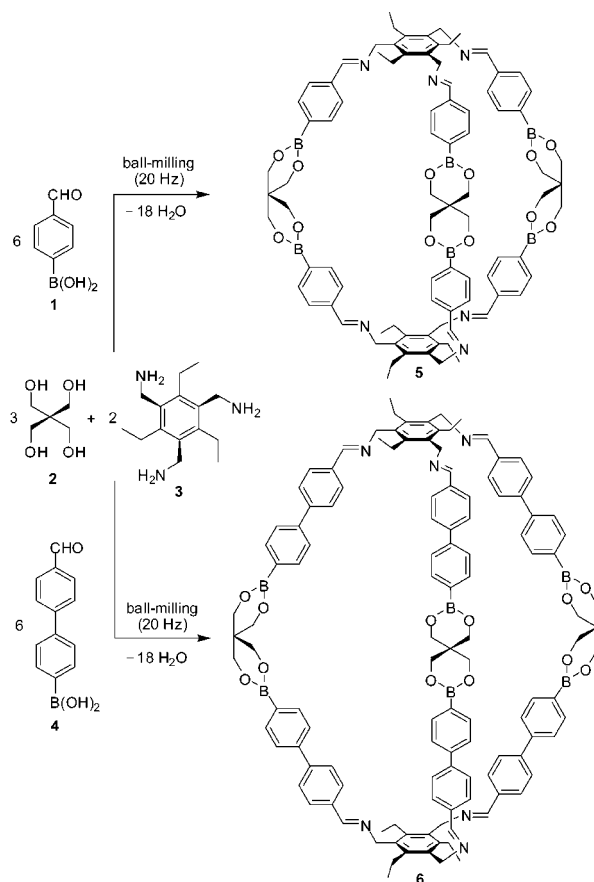
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Over the years, evidence has accumulated that a solvent-free synthesis promoted by grinding can be an interesting alternative to classical solution-based methods.¹ Obvious benefits are the reduced economic and ecological costs when working without a solvent. In addition, a solvent-free synthesis may display an increased rate and yield and a better selectivity.¹ From a practical point of view, it is advantageous to perform such syntheses in a ball mill, which allows efficient and fast grinding without physical efforts. Recent examples of reactions performed in a ball mill include asymmetric organocatalytic aldol reactions,² Knoevenagel condensations,³ oxidative aminations of aldehydes,⁴ Mn(OAc)₃-mediated cycloadditions,⁵ and the syntheses of protected nucleosides,⁶ glycosyl azides,⁷ and nitrones.⁸ Despite its success in organic synthesis, there are only a few reports about the utilization of grinding techniques for the construction of molecularly defined nanostructures.¹ Otera and co-workers, for example, have reported that the assembly of Pd(II)- and Pt(II)-based metallamacrocycles and cages can be accelerated by performing the reaction in the solid state using a mortar and pestle.⁹ More recently, the Chiu group has used ball-milling for the synthesis of a rotaxane.¹⁰ Below we describe the syntheses of two molecular cages. They were obtained by polycondensation of 11 building blocks in a ball mill. Evidence is presented that the ball mill syntheses are faster, cleaner, and more efficient than the corresponding solution-based reactions.

Our group is interested in the synthesis of complex molecular architectures based on boronic acids.^{11,12} In this context, we have recently reported a macrobicyclic structure that can be formed by a one-pot [6+3+2]-condensation reaction of 4-formylphenylboronic acid (**1**), Pentaerythritol (**2**), and tris(2-aminoethyl)amine (tren).^{11a} The solid state structure of the macrobicycle revealed a “collapsed” geometry with no accessible space inside the cage. To make larger and more expanded cage structures, we decided to exchange the flexible tren building block for the more rigid 1,3,5-trisaminomethyl-2,4,6-triethylbenzene (**3**).¹³ Furthermore, we wanted to test the incorporation of the extended biphenyl-based building block 4-(4-formylphenyl)phenylboronic acid (**4**).¹⁴ When 4-formylphenylboronic acid (**1**), Pentaerythritol (**2**), and the triamine **3** were heated for 2 h in ethanol using a Dean–Stark trap, we were able to isolate the desired cage **5** in 56% yield. Attempts to increase the yield by variation of the concentrations, the reaction time, or the workup procedure were not successful. Since alcohols are potentially problematic solvents for boronic acid–diol condensations,¹⁵ we investigated the same reaction in a mixture of THF and toluene (1:2). The heating of **1**, **2**, and **3** for 2 h under reflux using a Dean–Stark trap resulted in a significant amount of an insoluble product along with cage **5** (24% yield), which was contaminated with an incomplete condensation product. For reactions with the more elongated boronic acid **4**, we were also able to produce the desired cage **6** as evidenced by NMR spectroscopy and mass

spectrometry. But regardless of the solvent employed, the yield was low (<40%) and the product was always contaminated with a significant amount of an incomplete condensation product.

Scheme 1. Synthesis of the Cages **5** and **6** by Multicomponent Reactions in a Ball Mill



Boronate esters¹⁶ as well as imines¹⁷ can be prepared by solid-state reactions. This prompted us to investigate whether a ball mill could be used for the synthesis of cages **5** and **6**. And indeed, when the formylboronic acid **1** was ball-milled with the tetraol **2** and the triamine **3** for 1 h at 20 Hz, cage **5** was formed almost quantitatively (Scheme 1; for NMR and IR data, see the Supporting Information). The pure product was obtained in 94% yield after an additional heating step to remove the byproduct water (1 h at 80 °C in vacuum), followed by extraction with chloroform. Similarly, the larger cage **6** was formed in good yield by ball-milling for 1 h and subsequent heating. Small amounts of side products were easily separated by an extraction step with toluene to give **6** in an isolated

yield of 71%. The ball-milling procedures were thus by far superior to the solution-based methods that we have tested. The advantage is particularly important for the larger cage **6**, for which we were not able to obtain a pure product by reactions in solution.

The isolated cages **5** and **6** were characterized by multinuclear NMR spectroscopy and mass spectrometry. In addition, it was possible to obtain single crystals from 1,2-dichloroethane (**5**) or toluene solutions (**6**). Due to the size of the molecules, the lack of heavy atoms, and the presence of large amounts of disordered solvent molecules, the quality of the X-ray diffraction data was unfortunately low. But the overall geometry of the cages was clearly established (Figure 1). Both molecules have the shape of prolate spheroids with nearly coplanar triethylbenzene groups at the end of the molecules. The size of the small cage **5** is 1.7 nm × 2.3 nm (max. C-to-C distance) and that of the larger cage **6** is 1.9 nm × 3.1 nm. With its length of more than 3 nm, cage **6** is, to best of our knowledge, the largest macrocyclic structure based on boronic acids, which has been characterized by X-ray crystallography to date. Both compounds cocrystallize with significant amounts of solvent molecules. For compound **5**, it was possible to locate eight 1,2-dichloroethane molecules, six of which are found inside the cage. For cage **6**, the residual electron density points to the presence of at least eight cocrystallized toluene molecules. Due to severe disorder problems, the solvent-related electron density was treated with the SQUEEZE algorithm.¹⁸

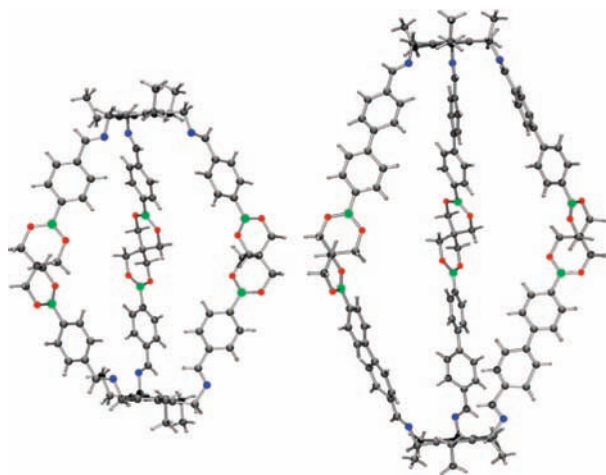


Figure 1. Molecular structures of the cages **5** (left) and **6** (right) in the solid state. Color coding: C, H: gray; O: red; N: blue; B: green. The cocrystallized solvent molecules are not shown for clarity.

The syntheses of cages **5** and **6** require the formation of 18 covalent bonds between 11 building blocks. The fact that such complicated multicomponent reactions based on dynamic covalent chemistry¹⁹ can be performed in a ball mill shows the potential of this technique for the construction of large nanostructures. It should be pointed out that the assembly of organic nanostructures via formation of imine^{20,21} or boronic ester bonds^{12,22} has received considerable interest in recent years. So far, these structures were generated almost exclusively by classical solution-based reactions. The results described above suggest that ball milling should be considered as a potentially very attractive alternative.

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Supporting Information Available: Experimental procedures and crystallographic data for **5** and **6** in cif format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For reviews see: (a) Rodri'guez, B.; Bruckmann, A.; Rantanen, T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2213–2233. (b) Garay, A. L.; Pichon, A.; James, S. L. *Chem. Soc. Rev.* **2007**, *36*, 846–855. (c) Braga, D.; Giuffreda, S. L.; Grepioni, F.; Pettersen, A.; Maini, L.; Curzi, M.; Polito, M. *Dalton Trans.* **2006**, 1249–1263. (d) Trask, A. V.; Jones, W. *Top. Curr. Chem.* **2005**, *254*, 41–70. (e) Braga, D.; Grepioni, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4002–4011. (f) Kaupp, G. *Top. Curr. Chem.* **2005**, *254*, 95–183. (g) Tanaka, K. *Solvent-free Organic Synthesis*; Wiley-VCH, Weinheim, 2003. (h) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159–2169. (i) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074.
- (2) (a) Rodri'guez, B.; Bruckmann, A.; Bolm, C. *Chem.—Eur. J.* **2007**, *13*, 4710–4722. (b) Rodri'guez, B.; Rantanen, T.; Bolm, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 6924–6926.
- (3) Trotzki, R.; Hoffmann, M. M.; Ondruschka, B. *Green Chem.* **2008**, *10*, 767–772.
- (4) Gao, J.; Wang, G.-W. *J. Org. Chem.* **2008**, *73*, 2955–2958.
- (5) Wang, G.-W.; Dong, Y.-W.; Wu, P.; Yuan, T.-T.; Shen, Y.-B. *J. Org. Chem.* **2008**, *73*, 7088–7095.
- (6) (a) Giri, N.; Bowen, C.; Vyle, J. S.; James, S. L. *Green Chem.* **2008**, *10*, 627–628. (b) Sikchi, S. A.; Hultin, P. G. *J. Org. Chem.* **2006**, *71*, 5888–5891.
- (7) Mugunthan, G.; Kartha, K. P. R. *J. Carbohydr. Chem.* **2008**, *27*, 294–299.
- (8) Colacino, E.; Nun, P.; Colacino, F. M.; Martinez, J.; Lamaty, F. *Tetrahedron* **2008**, *64*, 5569–5576.
- (9) Orita, A.; Jiang, L.; Nakano, T.; Ma, N.; Otera, J. *Chem. Commun.* **2002**, 1362–1363.
- (10) Hsu, C.-C.; Chen, N.-C.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7475–7478.
- (11) (a) Christinat, N.; Scopelliti, R.; Severin, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1848–1852. (b) Christinat, N.; Scopelliti, R.; Severin, K. *Chem. Commun.* **2008**, 3660–3662. (c) Christinat, N.; Croisier, E.; Scopelliti, R.; Cascella, M.; Röthlisberger, U.; Severin, K. *Eur. J. Inorg. Chem.* **2007**, 5177–5181. (d) Christinat, N.; Scopelliti, R.; Severin, K. *J. Org. Chem.* **2007**, *72*, 2192–2200. (e) Christinat, N.; Scopelliti, R.; Severin, K. *Chem. Commun.* **2004**, 1158–1159.
- (12) For reviews about boronic acids in molecular self-assembly, see: (a) Fujita, N.; Shinkai, S.; James, T. D. *Chem. Asian J.* **2008**, *3*, 1076–1091. (b) Höpfl, H. *Struct. Bonding (Berlin)* **2002**, *103*, 1–56.
- (13) Wallace, K. J.; Hanes, R.; Anslyn, E.; Morey, J.; Kilway, K. V.; Siegel, J. *Synthesis* **2005**, 2080–2083.
- (14) Moorthy, J. N.; Natarajan, R.; Venugopalan, P. *J. Org. Chem.* **2005**, *70*, 8568–8571.
- (15) (a) Nishimura, N.; Kobayashi, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6255–6258. (b) Zhu, L.; Shabbir, S. H.; Gray, M.; Lynch, V. M.; Sorey, S.; Anslyn, E. V. *J. Am. Chem. Soc.* **2006**, *128*, 1222–1232.
- (16) (a) Schnürch, M.; Holzweber, M.; Mihovilovic, M. D.; Stanetty, P. *Green Chem.* **2007**, *9*, 139–145. (b) Kaupp, G.; Naimi-Jamal, M. R.; Stepanenko, V. *Chem.—Eur. J.* **2003**, *9*, 4156–4161.
- (17) (a) Kaupp, G.; Naimi-Jamal, M. R. *Eur. J. Org. Chem.* **2002**, 1368–1373. (b) Kaupp, G.; Schmeyers, J.; Boy, J. *Tetrahedron* **2000**, *56*, 6899–6911. (c) Schmeyers, J.; Toda, F.; Boy, J.; Kaupp, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 989–993.
- (18) Van der Sluis, P.; Spek, A. L. *Acta Crystallogr., Sect. A* **1990**, *46*, 194–201.
- (19) (a) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wieter, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711. (b) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952.
- (20) For reviews, see: (a) Borisova, N. E.; Reshetova, M. D.; Ustyniuk, Y. A. *Chem. Rev.* **2007**, *107*, 46–79. (b) Meyer, C. D.; Joiner, C. S.; Stoddart, J. F. *Chem. Soc. Rev.* **2007**, *36*, 1705–1723. (c) Vigato, P. A.; Tamburini, S.; Bertolo, L. *Coord. Chem. Rev.* **2007**, *251*, 1311–1492. (d) MacLachlan, M. J. *Pure Appl. Chem.* **2006**, *78*, 873–888.
- (21) For selected recent examples, see: (a) Xu, D.; Warmuth, R. *J. Am. Chem. Soc.* **2008**, *130*, 7520–7521. (b) Luo, J.; Lei, T.; Xu, X.; Li, F.-M.; Ma, Y.; Wu, K.; Pei, J. *Chem.—Eur. J.* **2008**, *14*, 3860–3865. (c) Boden, B. N.; Hui, J. K.-H.; MacLachlan, M. J. *J. Org. Chem.* **2008**, *73*, 8069–8972. (d) Mastalerz, M. *Chem. Commun.* **2008**, 4756–4758. (e) Skowronek, P.; Gawronski, J. *Org. Lett.* **2008**, *10*, 4755–4758.
- (22) For selected recent examples, see refs 11, 15a, and: (a) Hutin, M.; Bernardinelli, G.; Nitschke, J. R. *Chem.—Eur. J.* **2008**, *14*, 4585–4593. (b) Kataoka, K.; James, T. D.; Kubo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 15126–15127. (c) Iwasawa, N.; Takahagi, H. *J. Am. Chem. Soc.* **2007**, *129*, 7754–7755. (d) Barba, V.; Villamil, R.; Luna, R.; Godoy-Alcántar, C.; Höpfl, H.; Beltram, H. I.; Zamudio-Rivera, L. S.; Santillan, R.; Farfán, N. *Inorg. Chem.* **2006**, *45*, 2553–2561.

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