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Synthesis of an amide cyclophane building block of shape-persistent triangular molecular wedges

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Abstract—The synthesis of an amide cyclophane, which can be considered as the first generation of a family of triangular shape-persistent molecular wedges is described.

Macromolecular, nanoscale building blocks suitable for assembly to true hierarchical structures can be designed using three characteristic features that are found in proteins and are believed to enable their ability to work as molecular machines.[1] First, the building blocks should be chemically precise in composition. Second, they should posses a well defined, shape-persistent structure. And third, they should be chemically asymmetric. This asymmetry is the main difference between biological macromolecules and many synthetic macromolecular assemblies obtained through molding and replication techniques. As a consequence, assemblies made from synthetic macromolecules tend to be highly symmetric. We believe that in order to achieve a broader class of functional hierarchical assemblies, it will be necessary to have asymmetry introduced into the building blocks, in addition to having control over their size and shape.

An example of hierarchical assembly using these principles was demonstrated by Whitesides and co-workers with millimeter sized objects.[2–7] Asymmetry was introduced into polygons and polyhedra by chemically modifying top, bottom, and selected edges of the objects. The objects could be assembled at liquid–liquid interfaces and numerous assembly patterns could be achieved.

Here, we present the synthesis of a planar, shape-persistent macromolecular building block with built in asymmetry suitable for surface self-assembly. To minimize conformational flexibility, a ring structure with many sp^2 centers was synthesized. The ring structure consists of the symmetric units A_3 (benzene-1,3,5-tricarboxylic acid) and B_3 (1,3,5-triamino-benzene). With the help of orthogonal protecting group chemistry, selected functional groups on the A_3 and B_3 units can be substituted with groups that could direct the surface-assembly of the building blocks via weak noncovalent interactions between molecules. For synthetic simplicity, long alkyl chains have been used throughout the synthetic protocol as shown in Figure 1. Other substituents could be introduced in the same manner as the long alkyl chains leading to a building block with more asymmetry.

Earlier work on cyclic and planar building blocks has reported predominantly symmetric structures.[8–11] Equilateral triangular,[8] rectangular,[9,10] and square shaped[11] molecules have been studied and some have been used for surface assembly. Still and co-workers have reported low symmetry amide cyclophane structures, but the goal of those studies was to design hosts for molecular recognition rather than building blocks for macromolecular assembly.[8b,10b] We describe here a building block for isosceles triangular wedges. The synthesis of this first-generation (G1) triangular wedge is outlined in Figure 1. The synthesis was conducted in solution phase using orthogonal protecting group chemistry. First, one methyl ester of 1,3,5-benzene-tricarboxylic acid trimethyl ester **1** was selectively hydrolyzed as described elsewhere.[12] The free carboxylic acid of compound **2** was then reacted with di-*tert*-butyl-dicarbonate to yield the *tert*-buytl ester **3**. Selective hydrolysis of one methyl ester of compound **3** yields compound **4**.[13] Best yields

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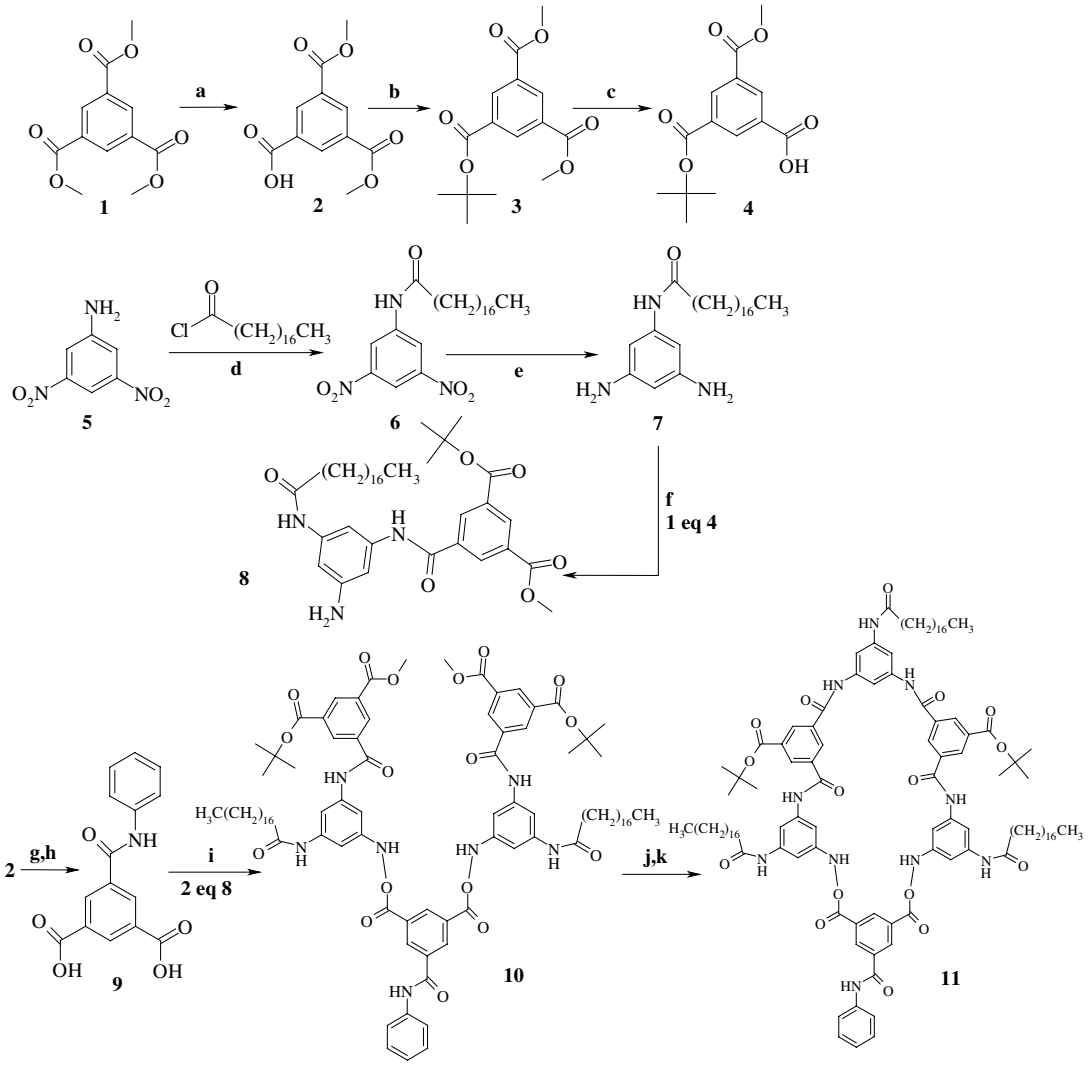

Figure 1. (a) NaOH (0.9 equiv), EtOH/H_2O, 60%; (b) di-*tert*-butyl-dicarbonate, DMAP, THF, 91%; (c) NaOH (0.9 equiv), DMF/H_2O; (d) THF, 2,6-lutidine, 97%; (e) Pd (5%) on act. C, H_2 (950 psi), quant.; (f) DCC, HOBT, DIEA, DMF, 50 °C, 34%; (g) 2,6-lutidine, DCC, HOBT, DMF, quant.; (h) NaOH, DMF/H_2O, 87%; (i) HOBT, DCC, DIEA, DMF, 50 °C 52%; (j) NaOH, DMF/H_2O, 93%; (k) **7**, HOBT, DCC, DIEA, DMF, 50 °C, 6%.

for this reaction were achieved by reacting a 23.9 mM solution of compound **3** in DMF/H_2O (70/1) with 0.9 equiv NaOH. Compound **4** has one free carboxylic acid that can be used for an amide coupling reaction in later synthetic steps. The other two carboxylic acids are protected with orthogonal protecting groups.

3,5-Dinitro-aniline **5** was reacted with stearoyl chloride to yield compound **6**. The two nitro groups were hydrogenated to afford di-amine **7**. Compound **7** was directly used in the next synthesis step due to its oxidation lability. By coupling (DCC/HOBT) compound **7** with 1 equiv of compound **4**, compound **8** (A_3B_3 unit) was obtained.[14] This reaction has low yield since compound **4** can react with both amines of compound **7** resulting in a mixture of products that was separated by column chromatography on silica. Alternatively, one amine group of **7** was protected with an alloc protecting group by reacting **7** with allyl chloroformate. This reaction has low yield for the exact same reasons as mentioned above. The alloc protecting group can be removed later with 1,3-dimethylbarbituric acid and $[(C_6H_5)_3P]_4Pd$ as a catalyst.

Compound **2** was coupled (DCC/HOBT) with aniline and the two methyl esters were hydrolyzed to yield **9**. Aniline was chosen to simulate the attachment of A_3 to the solid phase resin. The two unprotected carboxylic acids of **9** were coupled with 2 equiv of **8**. Excess of DCC (4.2 equiv) and HOBT (8.0 equiv) as well as moderate heating (50 °C) had to be employed in order to obtain **10**. After hydrolyzing the methyl esters of **10**, compound **7** could be used to close the ring under dilution principle conditions. As with **10**, long reaction times and excess of coupling reagents DCC (8 equiv) and HOBT (16 equiv) were employed. Compound **10** and **7** were added in millimolar concentrations to the coupling agents at 50 °C over the course of 20 h.[15] The reaction had 6% yield, which is not an untypical yield for ring closing reactions of high membered rings.

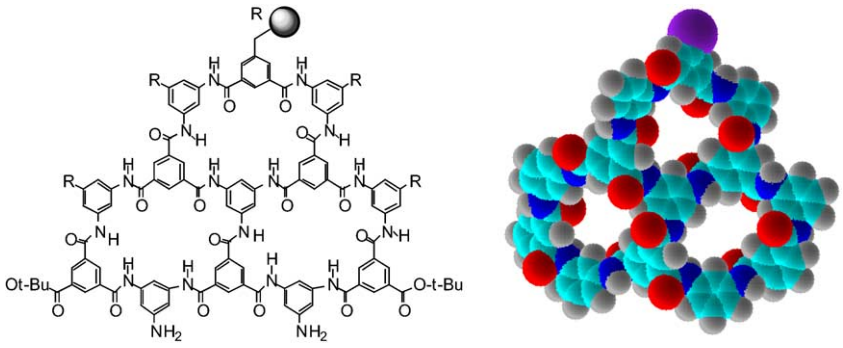

Figure 2. Left: Structure of a second generation (G2) molecular wedge. Right: Energy-minimized (PC Macromodel) space filling model of the building block.

The significance of synthesizing cyclophane **11** from **8** is that the synthesis may in principle be extended, by sequential coupling of suitably protected A_3B_3 units like **8**, to make higher generation number wedges. To do this, we are currently trying to improve the yield in the ring closing step by synthesizing the molecule on solid phase with stochiometric amounts of reactants at high dilution. Our future plans are to extend the synthesis to higher generation number isosceles triangular wedges as illustrated in Figure 2.

Acknowledgements

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13. ^{1}H NMR (acetone-d_6) δ 8.80 (m, 3H, aromatic), 3.98 (s, 3H, methoxy), 1.65 (s, 9H, *tert*-butyl); ^{13}C NMR (acetone-d_6) δ [166.17, 165.92, 164.52] (ester carbons), [134.92, 134.68, 134.57, 134.08, 132.60, 132.17] (benzene carbons), 82.84 (*tert*-butyl carbon), 53.03 (methoxy carbon), 28.30 (methyl carbons); (APCI)$^-$ MS ([M−H]$^-$ = 279.
14. ^{1}H NMR (THF-d_8) δ 9.56 (s, 1H, amide), 8.75 (s, 1H, amide), 8.66 (m, 3H, aromatic), 7.30 (m, 1H, aromatic), 6.86 (m, 2H, aromatic), 4.52 (s, 2H, amine), 3.92 (s, 3H, methoxy), 2.24 (t, J = 7.5 Hz, 2H, methylene), 1.62 (s + m overlaid, 9 + 2H, *tert*-butyl, methylene), 1.30 (s, 28H, methylene), 0.88 (t, J = 6.8 Hz, 3H, methyl); ^{13}C NMR (THF-d_8) δ [170.62, 165.48, 164.14, 163.90] (amide and ester carbons), [149.48, 140.94, 140.32] (phenyl carbons from 1,3,5-benzene-tricarboxylic acid), [137.62, 133.00, 132.77, 132.27, 131.07] (phenyl carbons from 1,3,5-triaminobenzene), [101.31, 100.02] (phenyl carbons from 1,3,5-triamino-benzene), 81.73 (*tert*-butyl carbon), 52.00 (methoxy carbon), [37.30, 32.30, 30.09, 30.03, 30.01, 29.78, 29.74, 27.69, 22.99] (methylene carbons), 13.87 (methyl carbon); 2D HMQC NMR verifies structure; (APCI)$^+$ MS [M+H]$^+$ = 652.
15. ^{1}H NMR (THF-d_8) δ 10.14 (m, 5H, amide), 9.81 (s, 1H, amide), 9.30 (s, 4H, amide), 8.80 (m, 9H, aromatic), 8.47 (s, 3H, aromatic), 8.18 (s, 6H, aromatic), 7.85 (m, 2H, aromatic), 7.34 (m, 2H, aromatic), 7.08 (m, 1H, aromatic), 2.35 (t, J = 7.3 Hz, 6H, methylene), 1.66 (s + m overlaid, 18 + 6H, *tert*-butyl, methylene), 1.29 (s, 84H, methylene), 0.88 (m, 6H, methyl); (MALDI) MS calcd for $C_{113}H_{156}N_{10}O_{14}$ [M+Na$^+$] 1901.51, found 1901.49.