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Self-assembly of a bis-urea macrocycle into a columnar nanotube

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A bis-urea macrocycle 1 was synthesized and shown to form extended nanotubular columns by X-ray crystallography.

There has been great interest in the development of new molecular building blocks that predictably self-assemble into three-dimensional nanoscale structures.[1] In particular, columnar or tube shaped structures have been sought for applications as sensors, templates for directed reactions, and in ion and small molecule transport systems.[2] A common design motif has been to identify macrocyclic building blocks that stack to form cylindrical assemblies (Fig. 1). The interior cavity size and integrity of the columns are ensured by the rigidity of the macrocyclic building blocks. Excellent examples in this regard are Ghadiri's cyclic peptides, Stang's molecular squares, and Moore's macrocyclic polyphenylenethynylenes.[3] We have designed a series of bis-urea macrocycles that are readily synthetically accessible and similarly self-assemble into columnar nanotubes. We report, herein, the synthesis and assembly of the first and smallest member of this family.

The guiding interaction in macrocycle **1** is the urea self-association. The topology of urea assembly is well understood. The ureas commonly form head-to-tail arrays based on 3-center hydrogen bonds from the NH's of the urea in one molecule to the carbonyl of the urea in the adjacent molecule which position the ureas 4.6 Å apart.[4] This strong hydrogen-bonding interaction has been used in self-assembled materials,[5] supramolecular assemblies,[6] and organic gelators.[7] Most of these have been acyclic systems and only a single demonstration of a macrocyclic assembly has been reported in which the ureas are part of the cyclic framework.[8]

In macrocycle **1**,† two *meta*-xylenes serve as rigid spacers. The macrocycle **1** was readily synthesized (Scheme 1). First the urea functionality was protected as a triazinanone **2**, inhibiting over-alkylation and premature self-assembly. Reaction of 5-*tert*-butyl-1,3,5-triazinan-2-one **2** with *meta*-dibromoxylene yielded the protected bis-urea **3**.[9] The enhanced solubility of the protected bis-urea **3** enabled facile isolation and purification. Deprotection with diethanolamine in methanol yielded bis-urea macrocycle **1**. Proton NMR analysis in DMSO of the deprotected **1** showed two broad peaks for the benzyl CH_2 groups centered at 4.6 and 3.8 ppm, consistent with slow flipping of the 16-membered ring. This dynamic conformational behavior is consistent with studies of the protected macrocyclic precursor **3** by Dave *et al.*[10]

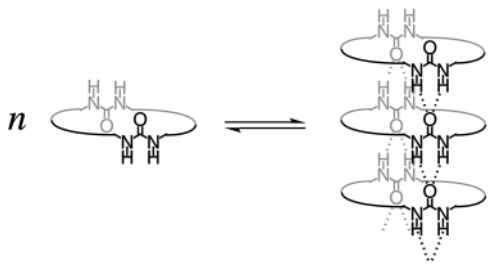
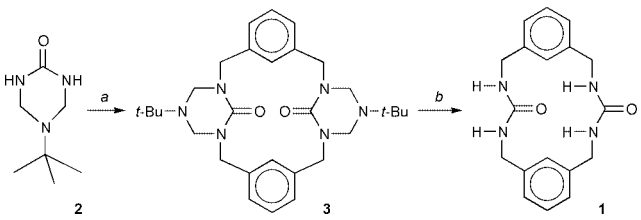


Fig. 1 Schematic representation of the self-assembly of rigid macrocyclic bis-ureas.



Scheme 1 Synthesis of bis-urea macrocycle **1**. *Reagents and conditions*: (a) *meta*-dibromoxylene, NaH, THF, 20%, (b) 20% diethanolamine, MeOH, reflux, 66%.

The solid-state molecular and assembled structures of bis-urea **1**‡ were examined by X-ray crystallographic analysis. The self-association of **1** was immediately apparent by its poor solubility characteristics. Single crystals suitable for X-ray diffraction were ultimately obtained upon slow cooling of **1** (135 °C to 25 °C) in a sealed tube of glacial acetic acid (100 mg/15 mL). The crystal structure of **1** reveals the expected bis-urea macrocycle (Fig. 2). The opposing urea functionalities are parallel but oriented oppositely, presumably to minimize the dipole moment. Most importantly, the ureas are not intramolecularly hydrogen-bonded and thus are free to form the designed macrocyclic stacks. The phenyl rings are tilted slightly out of the plane of the macrocycle, one pointing above and the other pointing below the plane of the macrocycle. The protons on C4 point inward, with an intramolecular H···H distance of 3.5 Å, filling most of the interior cavity.

The extended structure reveals that bis-urea units **1**§ stack on top of each other to form the desired supramolecular tubular structure. The bis-urea monomers are held together by the head-to-tail urea hydrogen-bonding motif extending along on both sides of the tube (Fig. 3). The three-centered hydrogen bonds have an N···O distance of between 2.82 and 3.01 Å and an H···O distance of 1.98 to 2.21 Å. This generates a spacing of 4.614 Å between the urea groups, consistent with other urea hydrogen-bonding systems. The urea monomers are aligned parallel but off-centered. The stacks are tilted 26° off of perpendicular as measured by the tilt in the ureas with respect to the macrocycle. This brings the aryl rings in adjacent macrocycles closer together within π-stacking distance (3.568 Å) while maintaining the longer urea–urea distance of 4.614 Å. The tilt also serves to orient the adjacent aryl rings in the more favorable offset aryl π-stacking geometry.[11]

In conclusion, the simple, symmetric bis-urea macrocycle **1**, assembles as designed into columnar structures. These extended

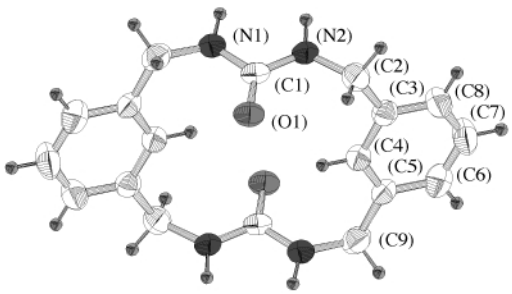


Fig. 2 ORTEP representation of bis-urea **1**.

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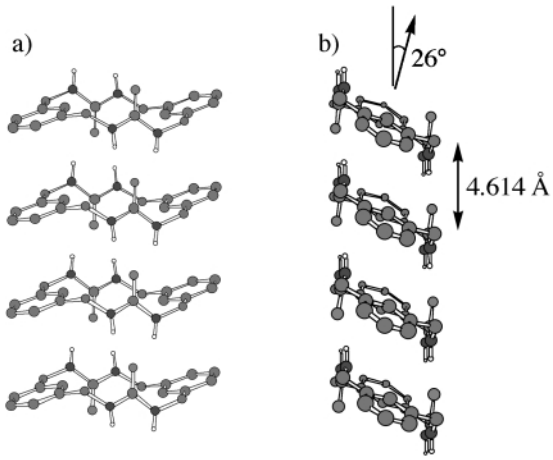

Fig. 3 X-Ray structures of bis-urea macrocycle **1**. The hydrogens have been omitted for clarity. Views alongside the tube showing (a) the 3-centered hydrogen bonding patterns and (b) the skewed orientation of monomers.

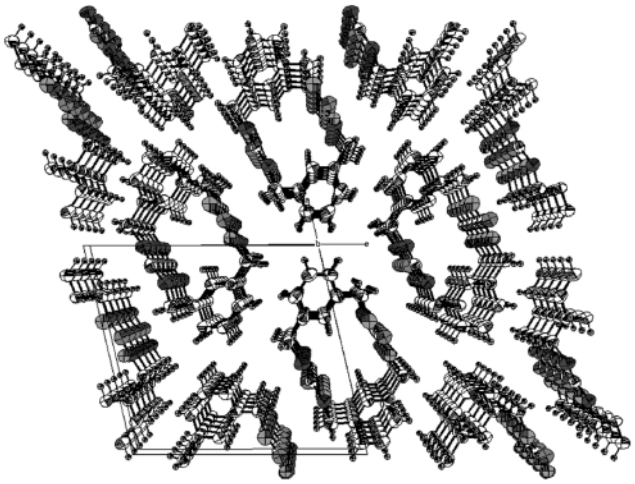

Fig. 4 Packing of the individual tubes highlights the potential channels that could be formed with macrocycles that have significant cavities.

tubes are held together by the urea–urea 3-centered hydrogen bonds and by aryl stacking interactions. Fig. 4 highlights the potential channels that may form with larger bis-urea macrocycles. We are currently focused on the synthesis and crystallization studies of larger analogues that would contain channels upon nanotubular assembly.

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Notes and references

† Synthesis of the protected bis-urea macrocycle: the triazone protected macrocycle was prepared from the *tert*-butyl triazone and *meta*-α,α′-dibromoxylylene according to the method described by Dave *et al.*[10]

‡ Synthesis of the bis-urea macrocycle **1**: the triazone protected macrocycle (0.26 g, 0.55 mmol) was stirred in MeOH (10 mL) and 20% diethanolamine (10 mL aqueous, pH 3) was added. The solution was heated at reflux overnight. A white precipitate formed. The reaction mixture was cooled and the crystals were collected by filtration and washed with water to yield 0.12 g (66%) of the urea cleft (**1**). The material was purified by crystallization from glacial acetic acid. ^{1}H NMR (300 MHz, DMSO) δ 7.30 (s, 2H), 7.16 (t, 2H, J = 7.4 Hz), 7.0 (d, 4H, J = 6.9 Hz), 6.46 (br s, 4H), 4.6 (v br m, 4H), 3.8 (v br m, 4H). ^{13}C NMR (75 MHz, DMSO) δ 158.0, 141.8, 127.5, 124.9, 123.3, 42.4. CHN analysis: C (calc.) 66.65 (found) 66.54, H (calc.) 6.21 (found) 6.25, N (calc.) 17.27 (found) 16.94%.

§ *Crystallographic data*: for **1**, 293 K $C_{18}H_{20}N_4O_2$, M = 324.38, monoclinic, space group $P2_1/n$, a = 12.808, b = 4.6145, c = 13.950 Å, β = 103.193°, U = 802.7 Å^3, Z = 2, D_c = 1.342 Mg m^{-3}, λ = 0.71073 Å (Mo-Kα), F(000) = 344. Bruker SMART APEX CCD-based diffractometer system, crystal size 0.22 × 0.03 × 0.02 mm^3, Θ_{max} = 23.29°, 4211 reflections measured, 1155 unique (completeness = 100%, R_{int} = 0.0686) and 618 were greater than 2σ(I). Corrections for Lorentz and polarization effects were also applied by SAINT. Final R_w = 0.0695 (all atoms). Conventional R = 0.0386.

CCDC reference number 166911. See http://www.rsc.org/suppdata/cc/b1/b102159c/ for crystallographic data in CIF or other electronic format.

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