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Synthesis of nano-scale shape-persistent macrocycles via hydrogen bonding-promoted formation of amide and hydrazone bonds

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ABSTRACT

This paper describes the synthesis of two series of rigid macrocycles from hydrogen bonding-induced folded aryl amide and hydrazone oligomers that bear two amines or one amine and one aldehyde. The diamines reacted with diacyl chloride to produce amide macrocycles, whereas the latter underwent self-coupling reactions to afford imine macrocycles. DFT calculations revealed that the new macrocycles possess rigid planar conformations and their cavity diameters were estimated to be 1.86 nm–2.75 nm.

1. Introduction

Pioneering works by Pedersen, Cram, and Lehn had triggered continued research on the synthesis of macrocyclic compounds and their discrete properties.[1,2] In particular rigid macrocycles have received considerable interest due to their predictable cavity and high co-planarity, which facilitate applications in molecular recognition and self-assembly.[3–16] In the past decade, the preorganization of precursors driven by continual intramolecular hydrogen bonds has been established as a useful strategy for the construction of aromatic amide, hydrazine, and urea macrocycles.[13–21] Many of the macrocycles have been revealed to complex molecular or ionic guests of matching size and binding sites or stack into well-defined supramolecular aggregates.[20,21] However, most of the reported macrocycles of this family have a small cavity. Examples of giant shape-persistent aromatic amide macrocycles with nano-scale cavity are relatively limited.[17d] Given the fact that shape-persistent giant aromatic macrocycles exhibit unique recognition, stacking, and photophysical properties,[22] it is still desirable for the development of new efficient approaches for obtaining giant aromatic macrocycles.

We previously reported the one-pot synthesis of 4-*mer* and 6-*mer* macrocycles from monomeric diamine and diacyl chloride precursors.[20c] The yields were generally good to high due to the existence of continuous intramolecular hydrogen bonds, which induced the last intermediate to fold for macrocyclization, as observed for other related amide macrocycles.[20] We also demonstrated that, via the formation of imine or hydrazone bonds under thermodynamic control,[23] many 6-*mer* macrocyclic and capsular architectures could be prepared in high to quantitative yields.[16,21] We herein describe that, by rational design of precursors, two new series of shape-persistent giant macrocycles, that is, 12-*mer* **1a**, 16-*mer* **1b**, 9-*mer* **2a**, and 12-*mer* **2b** (Fig. 1), can be prepared through the formation of amide or imine bonds from hydrogen bonded preorganized aromatic or hydrazide segments.

2. Results and discussion

2.1. Synthesis of macrocyles 1a and 1b

Diamines **3** and **4** (Fig. 2) were first prepared for the construction of new macrocycles by coupling with diacids. The two compounds were introduced with four and two sets of three-

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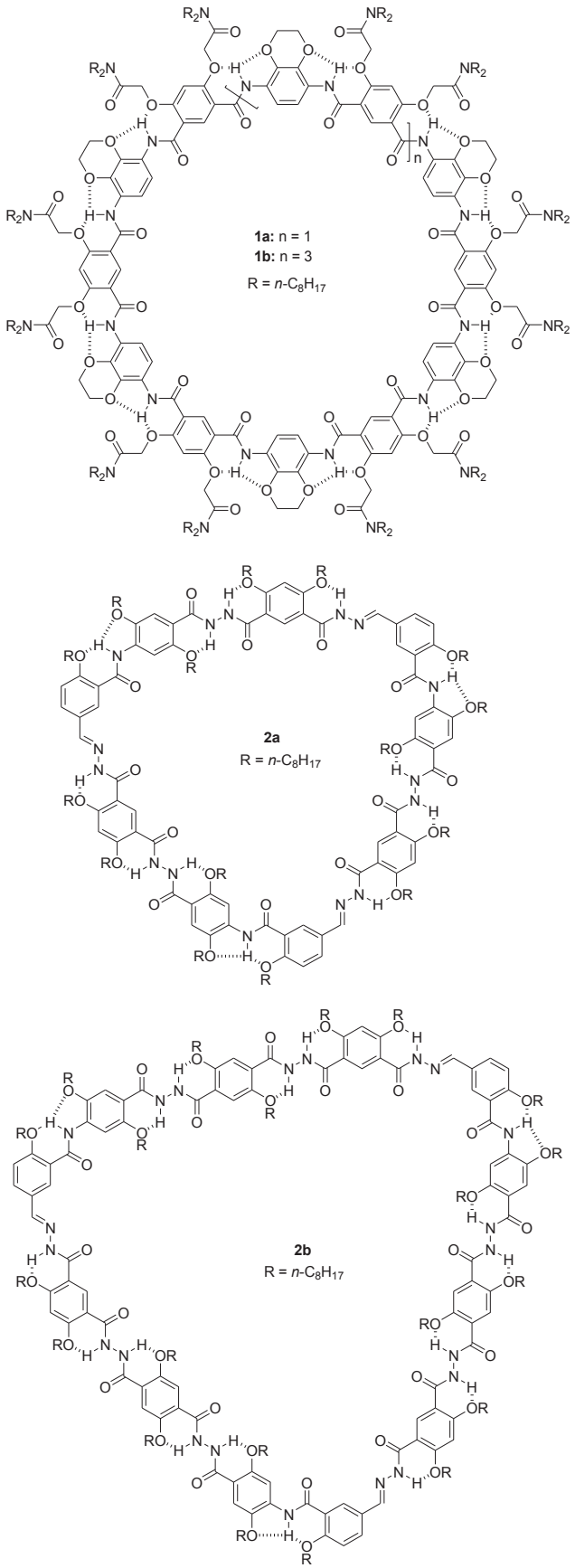


Fig. 1. The structures of giant macrocycles **1a**, **1b**, **2a**, and **2b**.

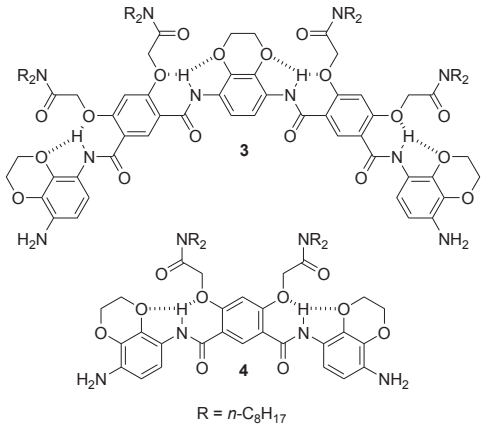


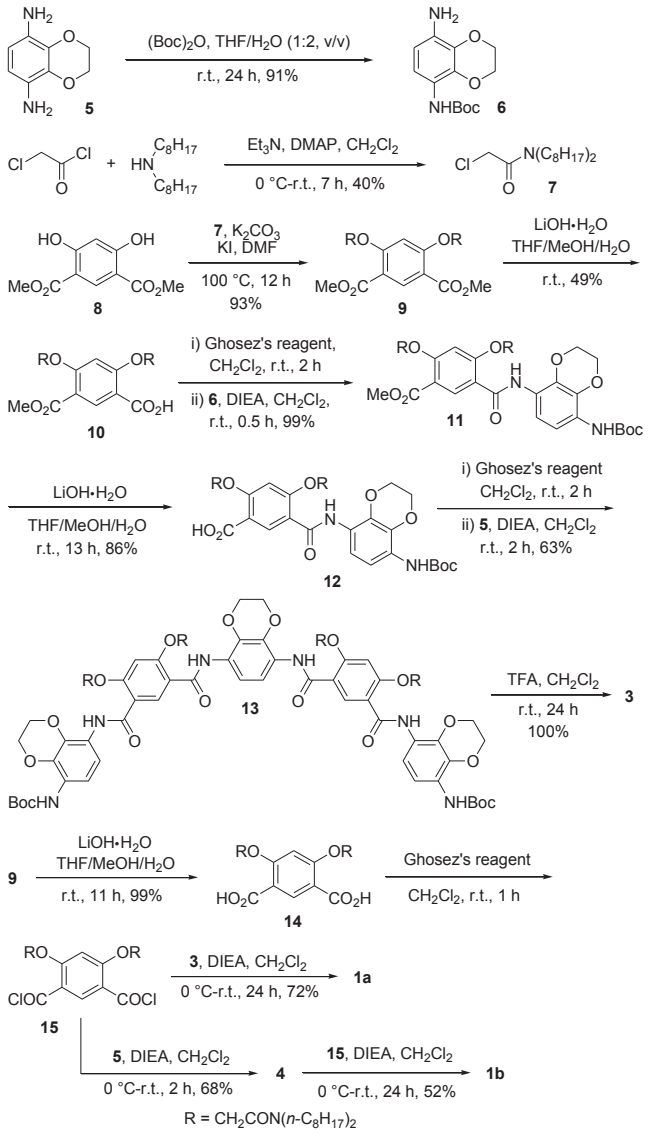
Fig. 2. Aromatic amide macrocycle precursors **3** and **4**.

centered hydrogen bonding, respectively, which should induce the two appended amino units to point to one side of the backbones. The two compounds bear four and two *N*,*N*-di(*n*-octyl) acetamide side chains, respectively, which were expected to provide solubility for the resulting rigid macrocycles. 2,3-Dihydro benzo[*b*][1,4]dioxine-5,8-diamine was chosen as the diamine segment not only to expand the cavity of the resulting macrocycles, but also to maximize the strength of the hydrogen bonds it formed by minimize the possible steric hindrance produced by the ether chains.

For the synthesis of **3** (Scheme 1), diamine **5**[24] was first reacted with $(Boc)_2O$ in aqueous THF to afford **6** in 91% yield. Then, amide **7** was prepared from chloroacetyl chloride and di(*n*-octyl)amine in 40% yield. Treatment of diester **8**[25] with **7** in hot DMF in the presence of potassium carbonate produced **9** in 93% yield. This diester was then selectively hydrolyzed into **10** in 49% yield with lithium hydroxide in aqueous methanol and THF. The acid was then treated with Ghosez's reagent (1-chloro-*N*,*N*,2-trimethyl-1-propenyl amine) in dichloromethane to give rise to the corresponding acyl chloride. Without purification, this intermediate was reacted with **6** in dichloromethane to produce **11** in 99% yield. The ester was further hydrolyzed to **12** and the acid was converted into the corresponding acyl chloride under the similar reaction conditions. Treatment of the acyl chloride with excess of diamine **5** in dichloromethane afforded **13** in 63% yield.

This intermediate was then treated with trifluoroacetic acid in dichloromethane to yield **3** quantitatively. With this precursor in hand, compound **9** was further treated with excess of lithium hydroxide to produce **14** quantitatively. This diacid was then reacted with Ghosez's reagent to give the corresponding diacyl chloride **15**. Treatment of **15** with diamine **3** of the same molar equivalent in dichloromethane produced the 2+2 macrocycle **1a** in 72% yield. The mass spectrum of the crude product after workup did not exhibit the peak of 1+1, 3+3 or larger macrocycles, suggesting that the folded conformation of the intermediates formed from **3** and **15** substantially favored the formation of **1a** over other possible macrocycles. This result also confirms the stability of the intramolecular hydrogen bonds and thus the folded conformation of the intermediate for the last cyclization step.

For the synthesis of macrocycle **1b** (Scheme 1), diacyl chloride **15** was first reacted with diamine **5** to produce **4** in 68% yield. Further treatment of this diamine with **15** in dichloromethane produced the 4+4 macrocycle **1b** in 52% yield. Again, the mass spectrum of the crude product after workup did not exhibit the peak of other smaller or larger macrocycles, which also illustrated high cyclization selectivity.



Scheme 1. Synthesis of macrocycles **1a** and **1b**.

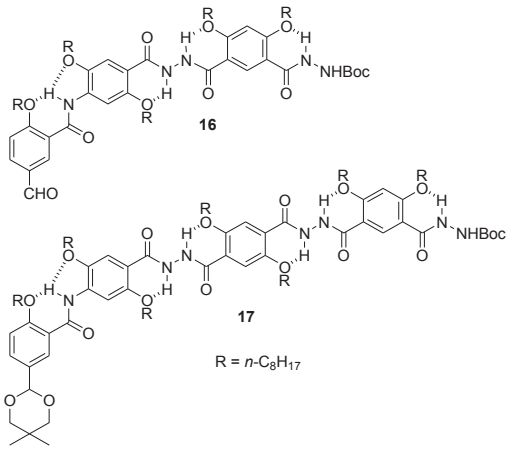
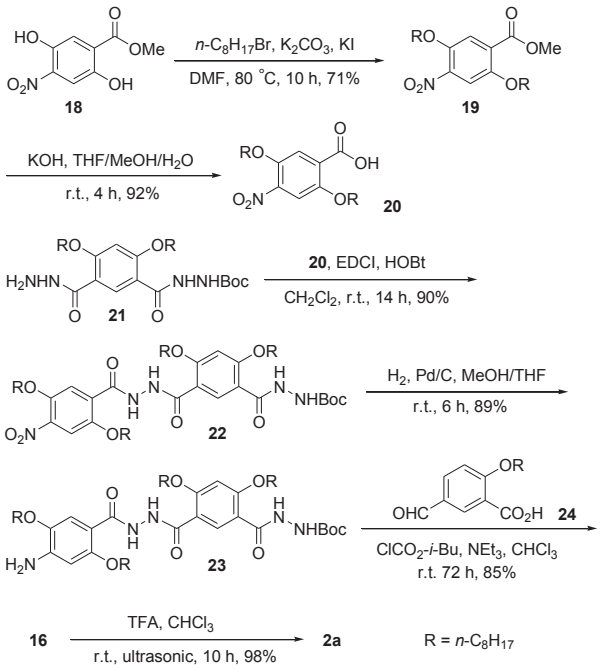


Fig. 3. Aromatic hydrazide macrocycle precursors **16** and **17**.



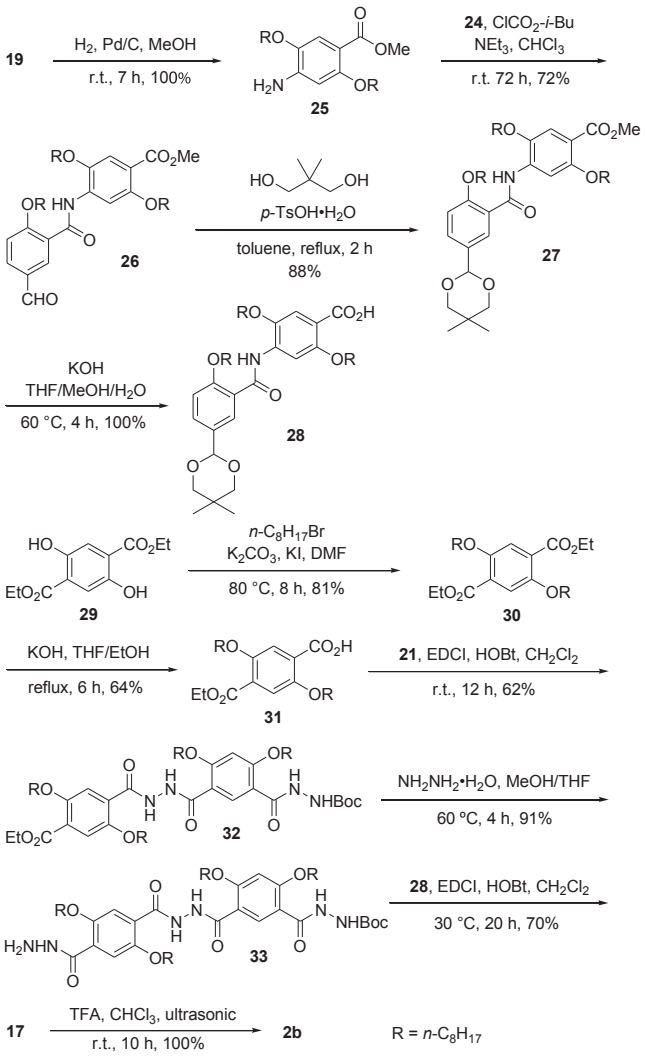
Scheme 2. Synthesis of macrocycle **2a**.

2.2. Synthesis of macrocycles 2a and 2b

We previously reported that hydrogen bonding-induced pre-organization of aromatic amide or hydrazide precursors that bear aldehyde and/or amine or monoacylhydrazine units could drive them to condense into 6-*mer* macrocycles through the formation of imine or hydrazone bonds at room temperature in high or nearly quantitative yield after the reactions reached thermodynamic equilibrium.[16,21] To further expand the scope of this approach, we also prepared compounds **16** and **17** (Fig. 3) to investigate their self-condensation to produce shape-persistent macrocycles after the *tert*-butoxycarbonyl (Boc) and 2,2-dimethylpropane-1,3-diol protecting groups were removed with acid. For both compounds, *n*-octyl groups were introduced to provide solubility in organic solvents.

For the synthesis of **16** (Scheme 2), **18**[26] was first alkylated in DMF to afford **19** in 71% yield. The ester was then hydrolyzed with potassium hydroxide in aqueous methanol and THF in 92% yield. The resulting acid **20** was then coupled with **21**[27] in dichloromethane in the presence of EDCI and HOBt to produce **22** in 90% yield. Palladium-catalyzed hydrogenation of **22** in methanol and THF afford **23** in 89% yield. The amine was then coupled with **24**,[21b] which was activated with *iso*-butyl chloroformate in chloroform to generate **16** in 85% yield. Finally, **16** underwent self-coupling in chloroform under ultrasonic in the presence of TFA to give **2a** in 98% yield. The crude product obtained from the last reaction after workup did not exhibit the peak of other macrocycles, showing that, similar to the shorter analogues, the extended conformation of **16** remarkably favored the formation of the 9-*mer* macrocyclic structure.

Encouraged by the high yield of **2a** formed from **16**, we further prepared the longer precursor **17** that also possesses an extended conformation (Scheme 3). Thus, compound **19** was first hydrogenated to afford **25** quantitatively in methanol, which was catalyzed by Pd/C. The amine was then coupled with **24**, also activated with *iso*-butyl chloroformate, to produce **26** in 72% yield. The aldehyde was then protected by 2,2-dimethyl-1,3-dipropanol in refluxed toluene in the presence of *p*-toluenesulfonic acid. The resulting intermediate **27** was quantitatively hydrolyzed to afford **28** in aqueous methanol and THF with potassium hydroxide as the base. With **28** being in hand, compound **30** was prepared in 81% yield



Scheme 3. Synthesis of macrocycle **2b**.

from the reaction of **29**[28] with *n*-octyl bromide in hot DMF in the presence of potassium carbonate and potassium iodide. Treatment of **30** with potassium in THF and ethanol under reflux afforded **31** in 64% yield. The acid was then coupled with **21** in dichloromethane in the presence of EDCI and HOBt to give **32** in 62% yield. The ester was further reacted with hydrazine in methanol and THF under reflux to produce **33** in 91% yield. This hydrazine derivative was then coupled with **28** in dichloromethane in the presence of EDCI and HOBt to afford **17** in 70% yield. In the presence of TFA, the solution of **17** stirred in chloroform under ultrasonic yielded macrocycle **2b** in quantitative yield. The fact that both **2a** and **2b** were generated exclusively shows that the dynamic imine chemistry based macrocyclization could occur more selectively because of the feature that the reactions were of thermodynamic control.

To get more insight into the conformation of the new hydrogen bonded macrocycles and to estimate the size of their cavity, computer simulations with GAUSSIAN09 program for the model compounds with methoxyl groups were further carried out for all the four macrocycles. The lowest-energy conformations were optimized with the M062X/6-31G(d,p) calculation method,[29] using the GAUSSIAN09 program. As shown in Fig. 4, all the alkoxyl oxygen atoms were engaged in intramolecular hydrogen bonding, which forced the macrocyclic backbone to form a well-defined rigid conformation. The diameter of the four macrocycles was estimated to ca. 1.94, 2.75, 1.86, and 2.65 nm, respectively. Notably, the 12-

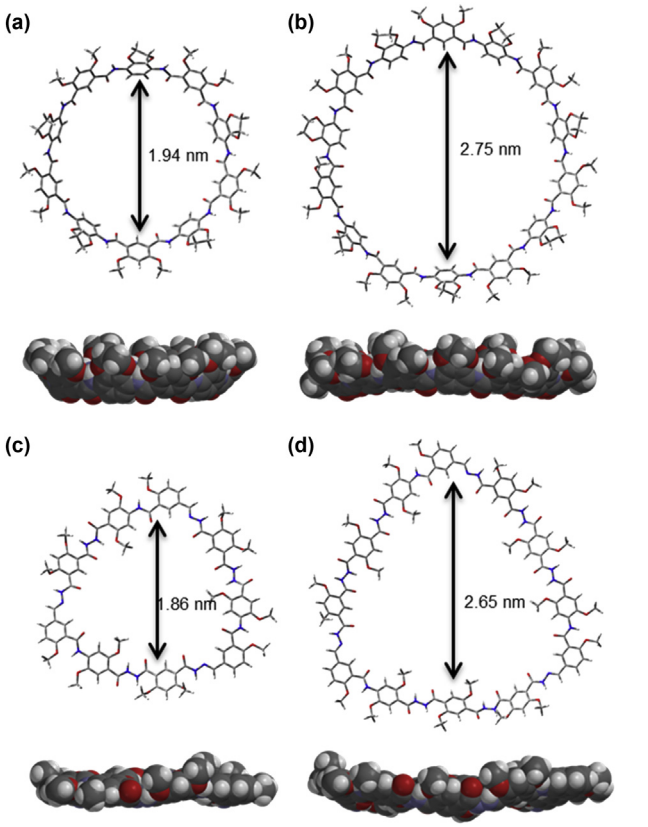


Fig. 4. Top and side views of the structures of macrocycles (a) **1a**, (b) **1b**, (c) **2a**, and (d) **2b** optimized at the M062X/6-31G(d,p) level. For simplicity, all the long side chains are replaced with methoxyl groups.

residue **1a** has a conformation resembling a shallow bowl, while the 16-residue **1b** gave rise to a flat backbone, which implies that the latter's aromatic backbone has a small ring tension. In contrast, both 9-residue **2a** and 12-residue **2b** have a slightly twisted triangular planer conformation, which may be attributed to the similarity of the extended aromatic backbone of the precursors.

3. Conclusions

We demonstrate that sizable macrocycles can be prepared from rationally designed aromatic amide or hydrazide precursors by making use of strong intramolecular hydrogen bonding to induce the precursors to adopt preorganized conformation for macrocyclization through the formation of 3–8 amide or hydrazone bonds. The selectivity of both approaches is high, but the yield of the second approach is much higher and the macrocycles can be formed quantitatively, which illustrates the robustness of this dynamic imine chemistry based macrocyclization strategy. The new rigid giant aromatic macrocycles have a cavity of nano-scale size. We are investigating the insertion of the new shape-persistent macrocycles into lipid membrane and the possibility of transporting large organic molecules.

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