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Highly Efficient, One-Step Macrocyclizations Assisted by the Folding and Preorganization of Precursor Oligomers

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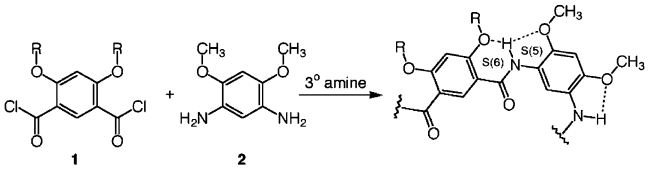
Macrocycles have attracted intense attention because of their widespread occurrence in nature, their unique properties, and applications.[1] Among the various methods developed for preparing macrocycles,[2,3] one-step, multicomponent cyclizations are particularly attractive because of the simplicity of the method and the easy availability of simple starting materials.[4] Except for systems that involve reversible covalent bond formation,[5] most one-step cyclizations described thus far are complicated by the entropically disfavored nature of the process, which usually leads to numerous side products and low yields of the targeted macrocycles. Consequently, tedious separation and purification steps usually accompany the isolation of the desired products. Shape-persistent macrocycles are structures with rigid, noncollapsible backbones and lumens of various sizes.[6] These structures are very interesting because of their unique properties that differ from their linear analogues. However, examples of these molecules are rare, mainly due to the difficulty in their preparation. Most of the shape-persistent macrocycles reported thus far have been based on the oligo(*meta*-phenylene ethynylene) backbone or its analogues. Similar to other one-step cyclizations, one-step syntheses led to very low yields of the *m*-PE cyclic hexamer.[7] Herein we report the highly efficient formation of a new class of shape-persistent, cyclic hexa(aramides) from the one-step macrocyclization of monomeric building blocks.

We previously developed backbone-rigidified folding oligomers,[8,9] including oligo(aramides). Lying at the center of our design of oligo(aramides) is a localized, three-center intramolecular hydrogen bond consisting of the S(5)- and S(6)-type rings that involves each of the backbone amide hydrogens. This three-center H-bond is highly stable, the presence of which limits the rotational freedom of the oligo(aramide) backbones. Depending on its chain length, a backbone-rigidified oligoamide adopts either a crescent or helical conformation. We decided to extend this strategy of enforcing globally folded conformations via localized H-bonding interactions into the design of folding polymers.



1 **2**

1a: R = -n-C_8H_{17}; **1b**: R = -$(CH_2)_3CO_2CH_2CH_3$; **1c**: R = -$(CH_2CH_2O)_3CH_3$

Thus, treating diacid chloride **1** with 4,6-dimethoxy-1,3-phenylenediamine **2** was expected to lead to AB-type poly(aramides) whose backbones should be rigidified by the three-center H-bonds that "lock" all of the amide groups. These poly(aramides), with their meta-linked benzene rings and the three-center H-bonds, should fold into curved, rigidified backbones adopting a hollow, helical conformation.

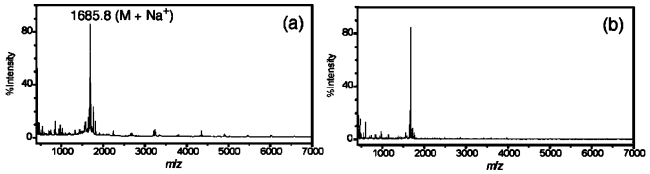


Figure 1. MALDI-TOF MS spectra of (a) the untreated mixture from the reaction between **1a** and **2** and (b) purified **3a**.

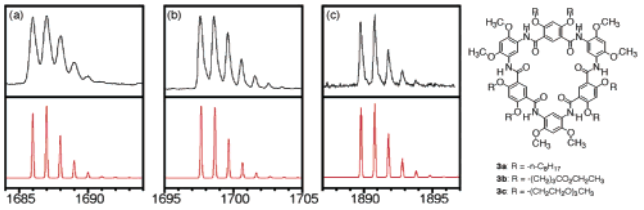


Figure 2. Isotope distribution of the $(M + Na)^+$ ions from MALDI-TOF (black) and computer simulation (red) of cyclic hexamers (a) **3a**, (b) **3b**, and (c) **3c**.

Diacid chloride **1a** (0.98 mmol) and diamine **2** (0.98 mmol) were dissolved in CH_2Cl_2 (7.5 mL each) and mixed in the presence of triethylamine (2.2 equiv) at −20 °C.[10] The reaction mixture was stirred and warmed to room temperature over a period of 4−6 h and was then heated under reflux for 24 h. After removing solvent, the remaining residue was examined by MALDI-TOF, which revealed a peak corresponding to a major product with a mass/charge ratio at 1686 (Figure 1a). Simple calculation showed that the mass of this major product was consistent with that of the cyclic hexamer **3a** ($C_{96}H_{138}N_6O_{18}$, 1663.0) plus a sodium ion. Pure cyclic hexamer **3a** was obtained in 69% as a white solid by washing the residue with methanol, water, acetone, and THF (Figure 1b). The identity of **3a** was confirmed by matching the isotope distribution of its $(M + Na^+)$ peak with the computer simulated one (Figure 2a). ^{1}H NMR spectrum of **3a** revealed signals corresponding to the aromatic and amide protons that were fully consistent with the symmetrical structure of **3a**.[10] Macrocycle **3a** was consistently obtained as the major product whether a solution of **1a** in CH_2Cl_2 was slowly added to that of **2** or whether the solutions of **1a** and **2** were mixed concurrently and quickly together. Similarly, cyclic hexamer **3b** ($C_{84}H_{102}N_6O_{30}$, 1674.7) was also obtained as the major product from the reaction of diacid chloride **1b** (2 mmol) in CH_2Cl_2 (10 mL) and diamine **2** (1.95 mmol) in the mixed solvent of CH_2Cl_2 and *N*,*N*-dimethylacetamide (2:1, 15 mL). Pure **3b** was isolated as a white solid in 82% yield after triturating with $CHCl_3$, followed by recrystallization from a mixed solvent containing DMF and THF.

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The structure of **3b** is confirmed by its ($M + Na^+$) peak (Figure 2b) and by its ^1H NMR spectrum.[10]

Although the original experimental conditions were adopted for preparing polymers and involved no high dilution conditions, macrocycles **3a** and **3b** were invariably obtained as the overwhelmingly major products. The observed yields compare favorably to most previously reported, templated, or untemplated one-step macrocyclizations. The reason for the highly efficient formation of **3a** and **3b** is obviously the preorganization of the backbones of the uncyclized precursors. Oligomers shorter than the hexamer could not cyclize easily because of the rigidity of their backbones. For the hexamer precursor, the folded backbone brought the amino and the acid chloride groups into close proximity, resulting in a rapid intramolecular cyclization. Given the irreversible nature of amide bond formation, the predominance of the cyclic hexamers and the scarcity of higher oligomers suggest that the uncyclized hexamers formed more rapidly than other higher oligomers. This contradicts conclusion from our kinetic analysis,[10] but could be rationalized by the H-bond-rigidified backbones of the intermediates. The rate of the bimolecular reactions between acid chlorides and amines leading to short oligomers (up to the hexamer) can be regarded as similar because of the lack of any strain in the transition states. In contrast, the bimolecular reactions leading to longer oligomers would involve the interaction of the reactive ends and the approach and overlap of the other two termini, of the curved oligomer precursors, which results in helical conformations of the transition states. Such helical conformations would be energetically more demanding than the completely "relaxed" transition states for forming the short oligomers.

The generality of the macrocyclization reactions was further examined by preparing the readily soluble **3c** ($C_{90}H_{126}N_6O_{36}$, 1866.8). Diacid chloride **1c** was treated with **2** under two conditions. (1) Solutions of **1c** (2.04 mmol) and **2** (2.04 mmol), in CH_2Cl_2 (17 mL each), were mixed together in the presence of triethylamine (2.2 equiv) at −20 °C. The reaction mixture was warmed to room temperature and heated under reflux. (2) To probe whether **3c** would still be the major product at a higher concentration that would favor the formation of higher oligomers, **1c** (1.95 mmol) and **2** (1.95 mmol), each dissolved in DMA (5 mL), were rapidly mixed in the presence of triethylamine (2.2 equiv) at −20 °C. The reaction mixture was warmed to room temperature, stirred overnight, refluxed for 24 h, and quenched by adding acetyl chloride and methanol. In both cases, the MALDI-TOF spectra[10] of the reaction mixtures indicated **3c** as the major product. These results demonstrated that the formation of the cyclic hexamers was indeed an inherently favorable process.

In the absence of the three-center intramolecular H-bonds, the corresponding oligoamide precursors are expected to adopt more flexible conformations, which should lead to a wider distribution of condensation products than reported here. Indeed, it was reported that, even under high-dilution conditions and in the presence of a template, the reaction of isophthaloyl chloride and *m*-phenylenediamine led to the isolation of an extremely insoluble cyclic hexamer in low (4 to 11%) yields along with numerous longer oligomers.[11]

The one-pot macrocyclization described here has provided a highly efficient method for preparing multigram quantities of a new class of shape-persistent macrocycles. We believe that the folding and preorganization of the uncyclized precursors are responsible for the abundance of the macrocycles. With their rigid backbones and large size, these new shape-persistent macrocycles could serve as building blocks for constructing a variety of covalent and noncovalent nanostructures. For example, with their flat aromatic surface and large interior cavity (~8 Å), the above cyclic hexamers could assemble into novel nanotubes. With their numerous side chains as synthetic handles, the macrocyles could serve as scaffolds for designing multivalent binders. The macrocycles, with their interior cavities decorated by amide O atoms, should serve as hosts for binding large cations and polar molecules.

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Supporting Information Available: Experimental details and NMR and MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Meng, Q. C.; Hesse, M. *Top. Curr. Chem.* **1992**, *161*, 107. (b) Sessler, J. L.; Burrell, A. K. *Top. Curr. Chem.* **1992**, *161*, 177. (c) Bernhardt, P. V.; Moore, E. G. *Aust. J. Chem.* **2003**, *56*, 239.

(2) For reviews, see: (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Knops, P.; Sendhoff, N.; Mekelburger, H. B.; Vogtle, F. *Top. Curr. Chem.* **1992**, *161*, 3. (c) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469. (d) Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767. (e) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898. (f) Gibb, B. C. *Chem.−Eur. J.* **2003**, *9*, 5180.

(3) For recent examples, see: (a) Lee, C. W.; Choi, T. L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224. (b) Li, X. H.; Upton, T. G.; Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2003**, *125*, 650. (c) Meutermans, W. D. F.; Bourne, G. T.; Golding, S. W.; Horton, D. A.; Campitelli, M. R.; Craik, D.; Scanlon, M.; Smythe, M. L. *Org. Lett.* **2003**, *5*, 2711.

(4) (a) Krakowiak, K. E.; Izatt, R. M.; Bradshaw, J. S. *J. Heterocycl. Chem.* **2001**, *38*, 1239. (b) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Science* **2002**, 590. (c) Janvier, P.; Bois-Choussy, M.; Bienayme, H.; Zhu, J. P. *Angew. Chem, Int. Ed.* **2003**, *42*, 811.

(5) (a) Dhawan, B.; Chen, S.-I.; Gutsche, C. D. *Makromol. Chem.* **1987**, *188*, 951. (b) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827. (c) Rowan, S. J.; Brady, P. A.; Sanders, J. K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2143. (d) Gawronski, J.; Kolbon, H.; Kwit, M.; Katrusiak, A. *J. Org. Chem.* **2000**, *65*, 5768. (e) Smith, A. B., III; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990. (f) Zhao, D. H.; Moore, J. S. *J. Org. Chem.* **2002**, *67*, 3548.

(6) (a) Zhao, D. H.; Moore, J. S. *Chem. Commun.* **2003**, 807. (b) Hoger, S. *Chem.−Eur. J.* **2004**, *10*, 1320. (c) Moore, J. S.; Zhang, J. S. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 922. (d) Höger, S.; Meckenstock, A. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2713.

(7) (a) Staab, H. A.; Neunhoeffer, K. *Synthesis* **1974**, 424. (b) Ge, P. H.; Fu, W.; Herrmann, W. A.; Herdtweck, E.; Campana, C.; Adams, R. D.; Bunz, U. H. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3607.

(8) (a) Gong, B. *Chem.−Eur. J.* **2001**, *7*, 4336. (b) Sanford, A. R.; Gong B. *Curr. Org. Chem.* **2003**, *7*, 1649. (c) Sanford, A. R.; Yamato, K.; Yang, X. W.; Yuan, L. H.; Han, Y. H.; Gong, B. *Eur. J. Biochem.* **2004**, *271*, 1416.

(9) (a) Yang, X. W.; Yuan, L. H.; Yamato, K.; Brown, A. L.; Feng, W.; Furukawa, M.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2004**, *126*, 3148. (b) Yang, X. W.; Martinovic, S.; Smith, R. D.; Gong, B. *J. Am. Chem. Soc.* **2003**, *125*, 9932. (c) Yang, X. W.; Brown, A. L.; Furukawa, M.; Li, S.; Gardinier, W. E.; Bukowski, E. J.; Bright, F. V.; Zheng, C.; Zeng, X. C.; Gong. B. *Chem. Commun.* **2003**, 56. (d) Gong, B.; Zeng, H. Q.; Zhu, J.; Yuan, L. H.; Han, Y. H.; Cheng, S. Z.; Furukawa, M.; Parra, R. D.; Kovalevsky, A. Y.; Mills, J. L.; Skrzypczak-Jankun, E.; Martinovic, S.; Smith, R. D.; Zheng, C.; Szyperski, T.; Zeng, X. C. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11583. (e) Parra, R. D.; Zeng, H. Q.; Zhu, J.; Zheng, C.; Zeng, X. C.; Gong, B. *Chem.−Eur. J.* **2001**, *7*, 4352. (f) Zhu, J.; Parra, R. D.; Zeng, H.; Skrzypczak-Jankun, E.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 4219.

(10) See Supporting Information for experimental details and NMR and MS spectra.

(11) Kim, Y. H.; Calabrese, J.; McEwen, C. *J. Am. Chem. Soc.* **1996**, *118*, 1545.

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