

Crystallographic Evidence of an Unusual, Pentagon-Shaped Folding Pattern in a Circular Aromatic Pentamer

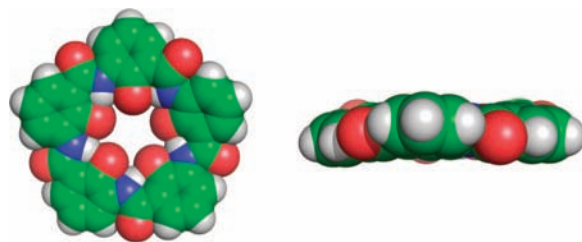
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ABSTRACT



Introduction of a continuous hydrogen-bonding network suppressed the conformational flexibility of an oligomeric backbone. Cyclization of a rigidified, suitably sized oligomer led to a circular aromatic pentamer. Its crystal structure determined by X-ray crystallography reveals a pseudo five-fold symmetric planarity in the solid state, which is quite unusual among all the previously described shape-persistent macrocycles and synthetic foldamers with biased conformations enforced by noncovalent forces.

In the unnatural world, structurally diverse molecular architectures with aesthetically pleasing five-fold (C_5) symmetry are mostly inorganic materials where the C_5 symmetry is available in pentagonal,^{1a,b} pentagonal bipyramidal,^{1c} pentagonal pyramidal,^{1d} pentagonal antiprismatic,^{1e} icosahedral,^{1e–g} and isopolyhedra^{1h} molecules as well as DNA nanostructures.¹ⁱ The C_5 symmetry is also readily

identifiable in all-carbon frameworks such as fullerenes,^{2a,b} carbon nanotubes,^{2c} and dodecahedrane,^{1g,2d} in metallic liquid^{2e} and quasicrystals^{2f,g} and in other nanoscale structures.^{2h–m} Examples of discrete C_5 -symmetric organic

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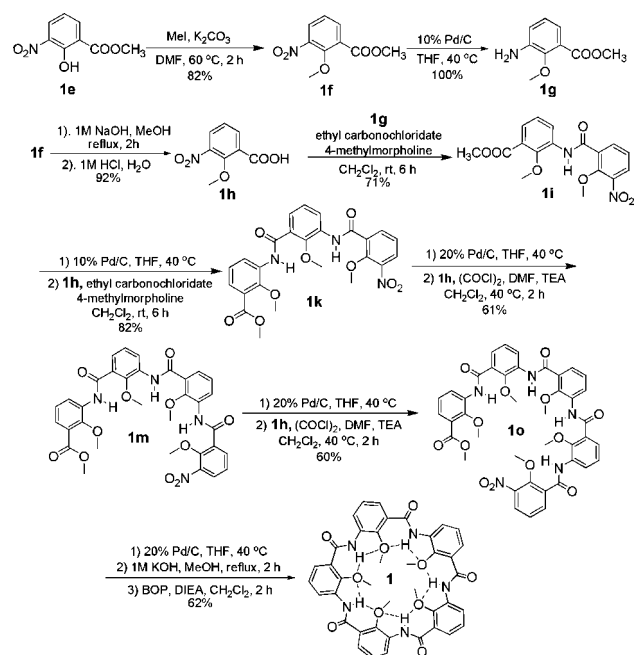
(1) For some selected examples, see: (a) Hasenkopf, B.; Lehn, J.-M.; Kneisel, B. O.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed.* **1996**, *35*, 1838. (b) Cai, M.; Marlow, A. L.; Fettingner, J. C.; Fabris, D.; Haverlock, T. J.; Moyer, B. A.; Davis, J. T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1283. (c) Rivard, E.; Steiner, J.; Fettingner, J. C.; Giuliani, J. R.; Augustine, M. P.; Power, P. P. *Chem. Commun.* **2007**, *46*, 4919. (d) Ellern, A.; Seppelt, K. *Angew. Chem., Int. Ed.* **1995**, *34*, 1586. (e) King, R. B. *J. Chem. Soc., Dalton Trans.* **2004**, 3420. (f) Muller, A. *Science* **2003**, *300*, 749. (g) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018. (h) Forbes, T. Z.; McAlpin, J. G.; Murphy, R.; Burns, P. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2824. (i) Chaput, J. C.; Switzer, C. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 10614.

(2) For some selected examples, see: (a) Kroto, H. W.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E. *Nature* **1985**, *318*, 162. (b) Fowler, P.; Manolopoulos, D. *An Atlas of Fullerenes*, 2nd ed.; Dover Publications: Mineola, NY, 2006. (c) Iijima, S. *Nature* **1991**, *354*, 56. (d) Paquette, L. A. *Chem. Rev.* **1989**, *89*, 1051. (e) Reichert, H.; Klein, O.; Dosch, H.; Denk, M.; Honkimäki, V.; Lippmann, T.; Reiter, G. *Nature* **2000**, *408*, 839. (f) Caspar, D. L. D.; Fontano, E. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14271. (g) Man, W. N.; Megens, M.; Steinhardt, P. J.; Chaikin, P. M. *Nature* **2005**, *436*, 993. (h) Okua, T.; Hiraga, K. *Diamond Relat. Mater.* **2000**, *10*, 1398. (i) Gunawidjaja, R.; Ko, H.; Jiang, C. Y.; Tsukruk, V. V. *Chem. Mater.* **2007**, *19*, 2007. (j) Johnson, C. L.; Snoeck, E.; Ezcurdia, M.; Rodríguez-González, B.; Pastoriza-Santos, I.; Liz-Marzán, L. M.; Hÿtch, M. J. *Nat. Mat.* **2007**, *7*, 120. (k) Sessler, J. L.; Seidel, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5134. (l) Li, Z. T.; Hou, J. L.; Li, C.; Yi, H. P. *Chem. Asian J.* **2006**, *1*, 766. (m) Zhang, W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4416.

molecules are more rare,³ particularly in the realm of conformationally defined (e.g., shape-persistent) macrocycles that have been designed to contain from two- to six- but not five-fold symmetries.⁴ The peripheral functionalization of these distinct easily modifiable organic templates that possess unusual pentagon-shaped topologies may lead to a good expectation in generating some useful functional materials such as quasicrystals,^{2g} DNA nanostructures,^{5a} virus capsid-like nanocontainers,^{5b} dendritic molecules,^{5c} discotic liquid crystals,^{5c,d} and hosts for organic/inorganic species. Furthermore, these rigid pentagon-shaped organic entities may be utilized to augment our ability in protein engineering and drug discovery that target biological pentamers found abundantly in Nature.⁶ For example, up to a ten million-fold gain in inhibitory activity against Shiga-like toxin, when compared to its univalent counterpart, has been achieved by a bifurcated pentavalent inhibitor that cross-links two identical toxin pentamers to form an inhibitor-sandwiched decameric ensemble.^{6h}

We describe here the synthesis and detailed characterization of a highly rigid and structurally well-defined circular aromatic pentamer **1** (Scheme 1). Excluding the five interior methoxy groups, the five identical aromatic building blocks meta-linked by secondary amide groups are nearly ideally disposed around a rotational axis of C_5 symmetry with internal angles of close to 108° and a geometric shape of a nearly planar pentagon. This five-fold folding pattern,

Scheme 1. Synthetic Route That Affords Pentamer **1**



(3) For a recent review on a C_5 -symmetric, bowl-shaped corannulene consisting of five benzene rings built around a five-membered ring, see: (a) Wu, Y.-T.; Siegel, J. S. *Chem. Rev.* **2006**, *106*, 4843; the regioselective substitution at its periphery is synthetically very challenging. For a phenyleneethynylene-based covalent pentacycle obtained as a side product with its point symmetry remaining unknown, see: (b) Zhang, W.; Moore, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 12796. For the metal-assisted templation of a roughly C_5 -symmetric, expanded porphyrin pentacycle (in this case, the metal-free organic pentacycle cannot be formed and isolated), see: (c) Day, V. W.; Marks, T. J.; Wachter, W. A. *J. Am. Chem. Soc.* **1975**, *97*, 4519. For a pyrrole-based macrocyclic pentaphyrin with its point symmetry remaining unknown, see: (d) Rexhausen, H.; Gossauer, A. *J. Chem. Soc., Chem. Commun.* **1983**, 275. For other organic molecules a local C_5 -symmetry, see: (e) Marks, T. J.; Stojakovic, D. R. *J. Chem. Soc., Chem. Commun.* **1975**, n/a, 28. (f) Cafeo, G.; Kohnke, F. H.; Parisi, M. F.; Nascone, R. P.; Torre, G. L.; Williams, D. J. *Org. Lett.* **2002**, *4*, 2695. (g) Sessler, J. L.; Anzenbacher, P., Jr.; Shriver, J. A.; Jursikova, K.; Lynch, V.; Marquez, M. *J. Am. Chem. Soc.* **2000**, *122*, 12061. (h) Dedek, P.; Janout, V.; Regen, S. L. *J. Org. Chem.* **1993**, *58*, 6553.

(4) For some recent reviews, see: (a) Li, Z. T.; Hou, J. L.; Li, C.; Yi, H. P. *Chem. Asian J.* **2006**, *1*, 766. (b) Zhang, W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4416. (c) Sessler, J. L.; Seidel, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5134.

(5) (a) Zimmermann, J.; Cebulla, M. P. J.; Monninghoff, S.; Kiedrowski, G. v. *Angew. Chem., Int. Ed.* **2008**, *47*, 3626. (b) Olson, A. J.; Hu, Y. H. E.; Keinan, E. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 20731. (c) Block, M. A. B.; Kaiser, C.; Khan, A.; Hecht, S. *Top. Curr. Chem.* **2005**, *245*, 89. (d) Sergeev, S.; Pisula, W.; Geerts, Y. H. *Chem. Soc. Rev.* **2007**, *36*, 1902.

(6) For some selected examples, see: (a) Emsley, J.; White, H. E.; O'Hara, B. P.; Oliva, G.; Srinivasan, N.; Tickle, I. J.; Blundell, T. L.; Pepys, M. B.; Wood, S. P. *Nature* **1994**, *367*, 338. (b) Brejc, K.; Dijk, W. J. v.; Klaassen, R. V.; Schuurmans, M.; Oost, J. v. d.; Smit, A. B.; Sixma, T. K. *Nature* **2001**, *411*, 269. (c) Bass, R. B.; Strop, P.; Barclay, M.; Rees, D. C. *Science* **2002**, *298*, 1582. (d) Merritt, E. A.; Zhang, Z.; Pickens, J. C.; Ahn, M.; Fan, E.; Hol, W. G. J. *J. Am. Chem. Soc.* **2002**, *124*, 8818. (e) Yao, N.; Coryell, L.; Zhang, D.; Georgescu, R. E.; Finkelstein, J.; Coman, M. M.; Hingorani, M. M.; O'Donnell, M. *J. Biol. Chem.* **2003**, *278*, 50744. (f) Becker, C. F. W.; Oblatt-Montal, M.; Kochendoerfer, G. G.; Montal, M. *J. Biol. Chem.* **2004**, *279*, 17483. (g) Traaseth, N. J.; Verardi, R.; Torgersen, K. D.; Karim, C. B.; Thomas, D. D.; Veglia, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 14676. (h) Kitov, P. I.; Sadowska, J. M.; Mulvey, G.; Armstrong, G. D.; Ling, H.; Pannu, N. S.; Read, R. J.; Bundle, D. R. *Nature* **2000**, *403*, 669.

possessing a good planarity, on the repeating structural motifs is quite unusual among all the hitherto reported conformationally defined macrocycles⁴ or synthetic foldamers⁷ with biased conformations enforced by noncovalent forces.

Our bottom-up pentameric molecular design lies in the preceding literature observations that suggest to us the likelihood for the amide linkages to display a breathing-type behavior in bond angles, resulting in the backbone being curved toward the hydrogen bonded (H-bonded) side.^{7f,8} We reasoned that an oligomeric backbone incorporating an inward-pointing, continuous H-bonding network might require less than six benzene units per turn. As such, the end-to-tail cyclization of a rigidified, crescent acyclic pentamer into a circular form as sketched in pentamer **1** might not impose too much angle strain on the molecular backbone and so a planar conformation with a smaller cavity may result. Following this speculation, a total of four conformations of circular pentamer **1**, depending on the orientation

(7) For some recent reviews, see: (a) Gellman, S. H. *Foldamers: A manifesto*. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Gong, B. *Chem. Eur. J.* **2001**, *7*, 4336. (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (d) Sanford, A. R.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649. (e) Cheng, R. P. *Curr. Opin. Struct. Biol.* **2004**, *14*, 512. (f) Huc, I. *Eur. J. Org. Chem.* **2004**, *17*. (g) Sanford, A. R.; Yamato, K.; Yang, X.; Yuan, L.; Han, Y.; Gong, B. *Eur. J. Biochem.* **2004**, *271*, 1416. (h) Licini, G.; Prins, L. J.; Scrimin, P. *Eur. J. Org. Chem.* **2005**, 969. (i) Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. *Nat. Chem. Biol.* **2007**, *3*, 252. (j) Hecht, S. M.; Huc, I. *Foldamers: Structure, Properties and Applications*; Wiley-VCH: Weinheim, Germany, 2007. For some recent examples of H-bond rigidified macrocycles, see: (k) Yuan, L.; Feng, W.; Yamato, K.; Sanford, A. R.; Xu, D.; Guo, H.; Gong, B. *J. Am. Chem. Soc.* **2004**, *126*, 11120. (l) Jiang, H.; LRger, J.-M.; Guionneau, P.; Huc, I. *Org. Lett.* **2004**, *6*, 2985. (m) Sanford, A. R.; Yuan, L.; Feng, W.; Flowersb, K. Y. R. A.; Gong, B. *Chem. Commun.* **2005**, n/a, 4720. (n) Zhang, A. M.; Han, Y. H.; Yamato, K.; Zeng, X. C.; Gong, B. *Org. Lett.* **2006**, *8*, 803-806.

(8) Gong, B.; Zeng, H.; Zhu, J.; Yuan, L.; Han, Y.; Cheng, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11583-11588.

of interior methoxy groups, were fully optimized using density functional theory at the B3LYP/6-31G* level.⁹ Energy minimum is found for circular conformer bearing five methoxy groups spatially arranged in an up–down–up–down–up fashion. All of the other three conformers with alternative side chain orientations are energetically less stable by 2.5–7.5 kcal/mol. The energy-minimized conformer adopts almost flat disk geometry with an appreciable cavity size. Prompted by this encouraging observation and using the well-established amide coupling methods, circular pentamer **1** was prepared from commercially available salicylic acid in 15 steps (Scheme 1).⁹

A first indication for achieving the synthesis of circular pentamer **1** came from the examination of ¹H NMR spectroscopy (Figure 1). At 1 mM, the ¹H NMR spectrum of **1** revealed five sets of proton signals corresponding to the methoxy groups (4.09 ppm) and aromatic (9.00, 8.02, and 7.45 ppm) and amide protons (10.89 ppm) that are in excellent agreement with the symmetrical structure of **1**. In particular, the amide protons of **1** resonating at the very low field⁹ (10.88–10.89 ppm over a concentration range of 0.1–10 mM) are a diagnostic indicator of the presence of strong H-bonding interactions,^{8,10} consisting of both S(5)- and S(6)-type intramolecular H-bonds that lead to the rigidification of the amide linkages and a crescent aromatic backbone. The apparent lack of aggregation in **1** as evidenced by concentration-independent ¹H NMR chemical shifts may be attributed to the sticking-out orientation of the five interior methoxy methyl groups (Figure 4) that prevent the possible intermolecular aggregation from happening.

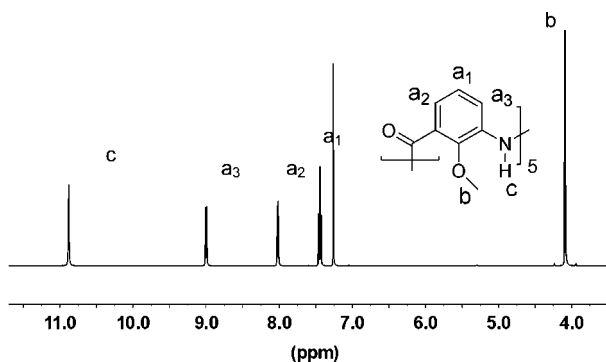


Figure 1. ¹H NMR spectrum (500 MHz, 298 K, CDCl₃) of pentamer **1** at 5 mM.

The electron ionization mass spectrum of pentamer **1** showed the molecular ion peak as a major peak (745.5) that matches its predicted mass losing one electron (C₄₀H₃₅N₅O₁₀, 745.7). Its identity was unambiguously confirmed by an excellent matching between the experimentally obtained high resolution mass of **1** (745.2387) and the calculated one

(745.2384), and between the isotope distribution pattern of the obtained high resolution mass with the computer-simulated one (Figure 2).

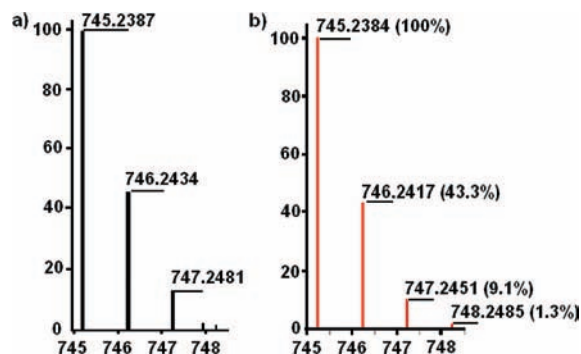
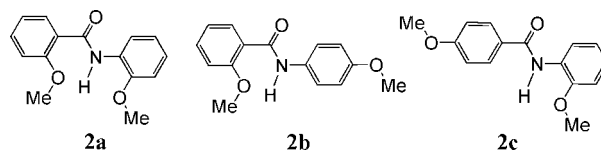


Figure 2. (a) Experimental (HRMS-EI) and (b) computer-simulated isotope distribution patterns of the M⁺ radical cations of circular aromatic pentamer **1**.

The elucidation of the folded conformation of **1** in solution was aided by carrying out the two-dimensional (2D) NOESY (Figure 3a, CDCl₃, 500 MHz, 500 ms, 298 K) experiment. At 5 mM, a very strong NOE cross-peak between interior methoxy protons *b* and amide protons *c* was observed with intensity comparable to the diagonal autocorrelation peak intensity. This contrasts sharply with the observation of a very weak NOE intensity between aromatic protons *a*₂ or *a*₃ and amide protons *c*, clearly supporting the curved, circular conformation for **1** where the methoxy protons stay much closer to the amide protons than to the aromatic protons. The 2D NOESY spectrum of **1** recorded in CDCl₃/DMSO-*d*₆ (Figure 3b, 2:8 v/v, 500 MHz, 298 K, 5 mM) displayed the same NOE intensity pattern as that observed in CDCl₃, suggesting the preservation of folded circular conformation in **1** in a polar environment that is highly competitive in disrupting the typical H-bonding interactions.

To quantitatively measure the stability of these intramolecular three-center H-bonds, amide proton-deuterium (H-D) exchange experiment was performed on **1** at 2 mM (Figure 3).⁹ The half-life of H-D exchange for the amide protons in **1** that contains a continuous H-bonding network was determined to be 25 h. This value agrees well with those (>7 h) of H-bond enforced amide protons previously determined on **2a** (12.7 h), fragment of **1**, and on an aromatic nonamer under identical conditions. For comparison, the corresponding dimers **2b** and **2c** that contain only one two-center H-bond have half-lives of 17 and 9 min, respectively.¹⁰ Such comparison points to a much higher stability of amide protons in pentamer **1** compared with those in **2b** and **2c**.



(9) See Supporting Information.

(10) Yuan, L.; Zeng, H.; Yamato, K.; Sanford, A. R.; Feng, W.; Atreya, H. S.; Sukumaran, D. K.; Szyperski, T.; Gong, B. *J. Am. Chem. Soc.* **2004**, *126*, 16528.

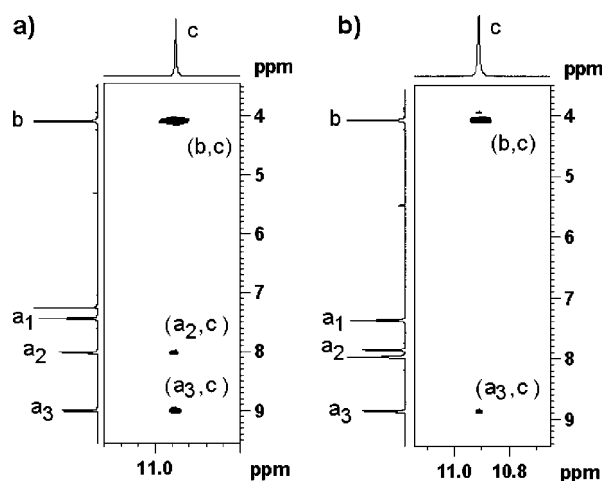


Figure 3. NOEs between the amide protons **c** and their adjacent interior methoxy protons **b** revealed by the NOESY (5 mM, 500 MHz, 298 K, mixing time 500 ms) spectra of pentamer **1** in (a) CDCl_3 and (b) $\text{CDCl}_3/\text{DMSO-}d_6$ (2:8 v/v).

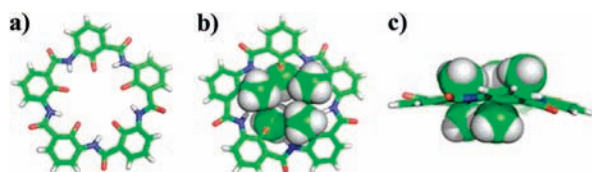


Figure 4. Crystal structure of pentamer **1**: (a) top view with interior methoxy methyl groups omitted for clarity of view, (b) top view, and (c) side view both with methoxy methyl groups in CPK representations.

The X-ray quality single crystals of **1** were grown by slow evaporation of **1** in mixed solvents containing methanol and dichloromethane (1:1 v/v). The molecule folds into an almost planar disk arrangement of nearly perfect C_5 symmetry in solid state (Figure 4), remarkably similar to the *ab initio* calculated structure at the level of B3LYP/6-31G*.⁹ All five

methoxy oxygen atoms and amide protons point inward and contribute to the formation of a continuous intramolecularly H-bonded network ($\text{NH}\cdots\text{OMe} = 2.2\text{--}2.4$ and $1.9\text{--}2.0$ Å for S(5) and S(6) intramolecular H-bonds, respectively) that encloses a cavity of 2.85 Å in radius (or 1.45 Å after deducting a covalent radius of 1.4 Å for oxygen atom) defined by five methoxy oxygen atoms. The methyl groups form two hydrophobic caps made up of three and two methyl groups, respectively, covering either side of the pentamer plane. Such hydrophobic caps apparently prevent **1** from binding to metal cations such as Na^+ (~ 1.0 Å), K^+ (~ 1.4 Å), etc. In view of the fact that the radius of the majority of cations stays below 1.4 Å, replacement of one or more methoxy groups with hydroxyl groups should open up the cavity for the selective, tight binding to cations of varying types. Further exquisite modifications at both the exterior and interior may lead to sizable complexation/inclusion capacities and opportunities.

In summary, the structural characterization by both a 2D NOESY study and an X-ray diffraction method has led to the observation of an unusual five-fold folding topology in an almost disk-like macrocyclic foldamer **1**. Its relative ease of synthesis and modular nature make other closely related structural variations highly sensible. These pentagon-shaped molecules may serve as good templates in the construction of either chemically or biologically relevant supramolecular nanoarchitectures with interesting material properties^{5b} or biological activities.^{6d,h}

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Supporting Information Available: Synthetic procedures for pentamer **1** and a full set of characterization data including crystallographic data (CIF), ^1H NMR, ^{13}C NMR, MS, UV-vis, IR, H-D exchange, and molecular modeling. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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