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A New Class of Folding Oligomers: Crescent Oligoamides

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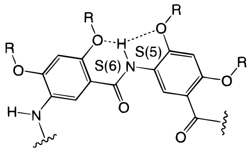
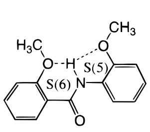
The assembly of well-defined protein secondary structures, leads to a bewildering array of tertiary structures.[1] As the first step toward developing artificial oligomers and polymers that fold like biomacromolecules, there is currently an intense interest in designing unnatural building blocks that adopt well-defined secondary structures.[2,3] Here we report a new class of oligoamides with backbones that adopt well-defined, crescent conformations.

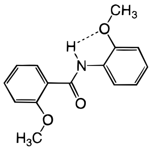


1

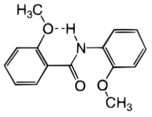
Our design is based on diaryl amide oligomers, shown as **1**. The presence of the three-center hydrogen bonding system consisting of the S(5) and S(6) type[4] intramolecularly hydrogen bonded rings should lead to rigidification of the amide linkage. Oligoamides containing such amide linkages should have a rigid backbone. With the two amide linkages on the same benzene ring being *meta* to each other, the resulting oligomer should have a crescent conformation.[5]



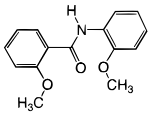
2 (0 kcal/mol)



2a (11.06 kcal/mol)

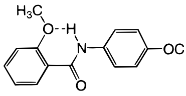


2b (14.51 kcal/mol)

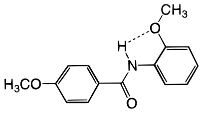


2c (27.37 kcal/mol)

Ab initio molecular orbital calculations (in vacuo) were performed on amide **2**.[6] Conformations **2a**−**b** are constrained to be planar. The relative energy of each conformation is shown in parentheses. The computational results indicated significant differences in the relative energies of the four conformations: **2** was overwhelmingly favored over the alternative conformations **2a**,**b**. The desired conformation, **2**, was planar and had two strong intramolecular hydrogen bonds with $O\cdots H = 1.87$ Å (S(6)) and 2.14 Å (S(5)), respectively.



2d



2e

^{1}H NMR studies in $CDCl_3$ indicated a significant downfield shift of the amide NH signal of **2** (10.60 ppm, independent of concentration) compared to those of the reference compounds **2d** (at 10 mM, 9.691 ppm) and **2e** (at 10 mM, 8.497 ppm), suggesting formation of the bifurcated hydrogen bonds. The conformation of **2** in solution was then examined by NOE difference spectroscopy (600 MHz, 300 K).[7] In $CDCl_3$, on saturating the amide-H signal, NOE enhancements were observed on both methoxy groups of the benzoate (δ 4.04; 1.14%) and the aniline (δ 3.92; 0.80%) residues. Interestingly, similar NOE enhancements were also detected in the polar solvent DMSO-d_6: on saturating the amide-H signal, enhancements on the benzoate and aniline methoxy signals were 1.05% and 0.64%, respectively. These results suggested the existence of the proposed S(5)- and S(6)-type hydrogen bonds and thus the proposed conformation of amide **2** in solution. More significantly, the fact that such a rigid conformation of **2** existed in the very polar solvent DMSO laid the foundation for the design of oligomers that adopt well-defined conformations in highly competitive solvents.

Crystals of amides **3** and **4** were grown from solutions in DMF by slow cooling. Figure 1 shows their X-ray structures.[7]

In the solid state, **3** showed the type of conformation as expected. Two intramolecular hydrogen-bonded rings, S(6) and S(5), were observed. The planes of the two aromatic rings in **3** were parallel to each other and to that of the amide group, resulting in a completely flat molecule with a rigid, curved conformation.

Four hydrogen bonded rings were observed in the structure of **4**. As a result, a crescent conformation with the two amide-O atoms turning inward was formed. These results indicated that (1) the S(5) and S(6) type intramolecular hydrogen bonds indeed prevailed in these structures and (2) the two amide O atoms, which pointed inward and might have repulsive interaction with each other, did not interrupt the overall curved conformation. This is significant since it is a critical structural requirement for longer analogues to adopt curved backbones. Amide **4** was overall flat.

The above results indicate that analogues of amides **2**−**4** with longer backbones should adopt a well-defined, curved conformation. Tetramer **5** in solution was thus investigated by 2D (NOESY) ^{1}H NMR ($CDCl_3$, 800 MHz, 300 K) spectroscopy. At 50 mM, the amide NH signals of **5** appeared at δ 9.58, 9.90, and 10.13 as three well-separated peaks. As shown in Figure 2, two cross-peaks corresponding to each of the three amide protons were observed: one with a methoxy group and the other with its neighboring octyloxy α-methylene group. Such contacts suggested the formation of bifurcated hydrogen bonds between an amide proton and its neighboring alkoxy-O atoms, which provided the

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(1) Branden, C.; Tooze, J. *Introduction to Protein Structure*, 2nd ed.; Garland Publishing: New York, 1998.

(2) For a recent review, see: Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.

(3) For recent examples, see: (a) Appella, D. H.; Christianson, L. A.; Karle. I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 6206. (b) Gong, B.; Yan, Y.; Zeng, H.; Skrzypcak-Jankun, E.; Kim, Y. W.; Zhu, J.; Ickes, H. *J. Am. Chem. Soc.* **1999**, *121*, 5607. (c) Gin, M. S.; Yokozawa, T.; Prince, R. B.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 2643. (d) Yang, D.; Qu, J.; Li, B.; Ng, F.-F.; Wang, X.-C.; Cheung, K.-K.; Wang, D.-P.; Wu, Y.-D. *J. Am. Chem. Soc.* **1999**, *121*, 589. (e) Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569. (f) Seebach, D.; Abele, S.; Stifferlen, T.; Hänggi, M.; Gruner, S.; Seiler, P. *Helv. Chim. Acta* **1998**, *81*, 2218. (g) Armand, P.; Kirshenbaum, K.; Goldsmith, R. A.; Farr-Jones, S.; Barron, A. E.; Truong, K. T.; Dill, K. A.; Mierke, D. F.; Cohen, F. E.; Zuckermann, R. N.; Bradley, E. K. *Proc. Natl. Acad. Sci. U.S.A* **1998,** *95*, 4309.

(4) Berstein, J.; Davis, R. E.; Shimoni, L.; Chang, N.-L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1555.

(5) Hamilton et al. reported oligomers generated from anthranilic acid, pyridine-2,6-dicarboxylic acid, and 4,6-dimethoxy-1,3-phenylenediamine units, in which intramolecular H-bonds enforce a helical (or curved) conformation: Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587.

(6) (a) The Jaguar program[6b] was used to obtain relative energies of the optimized structures. Geometry optimizations were carried out at the B3LYP/6-31G(d) level, whereas the LMP2/6-311G(d) method was used for single point energy calculations. See Supporting Information for computational details. (b) Jaguar v3.0, Schordinger, Inc.: Portland, OR, 1997.

(7) The X-ray data of **3** and **4** are given in the Supporting Information. Additional NMR spectra are also included in the Supporting Information.

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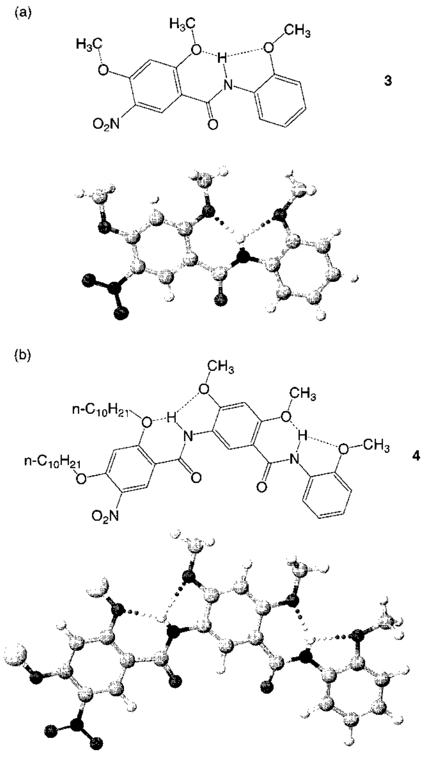


Figure 1. (a) X-ray structure of **3**. (b) X-ray structure of **4**. The decyl groups in **4** are replaced with dummy atoms for clarity of view.

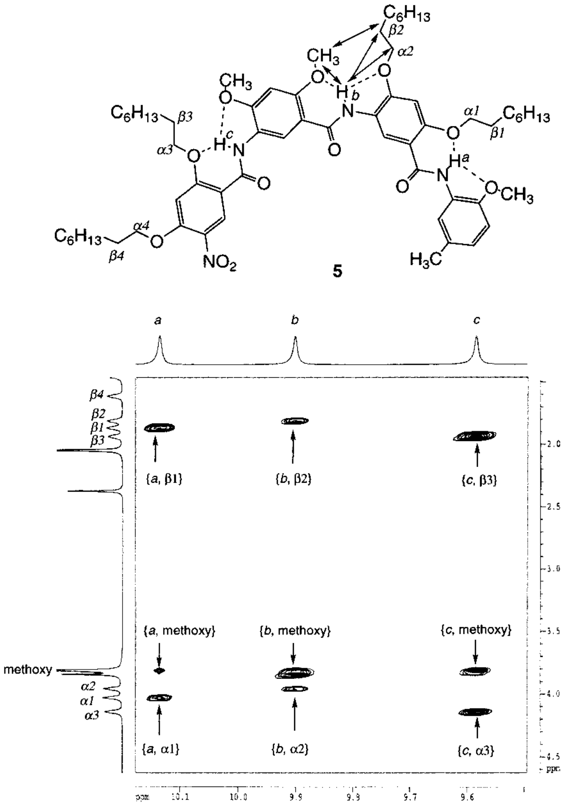
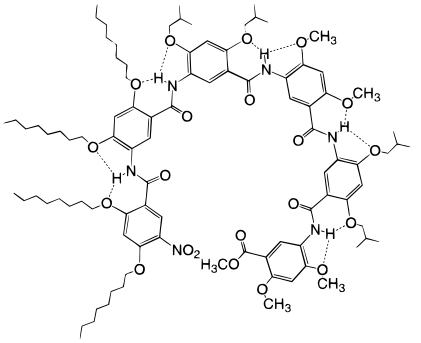


Figure 2. NOESY spectrum of **5** in $CDCl_3$ (800 MHz, mixing time: 0.3 s). The contacts between amide H*b* and the other protons as determined by NOESY spectroscopy are indicated in the structure. Amide H*a* and H*c* show the same set of contacts. Arrows in the spectrum show contacts depicted in the text.

most diagnostic evidence for the curved conformation of **5**. Besides, the NOESY spectrum of **5** also revealed contacts between the methoxy protons and the *β*-methylene protons of the octyloxy groups, providing additional, unequivocal evidence for the proposed curved conformation.[7]



6

The conformation of hexamer **6**, which should make almost a full circle and thus a nearly closed cavity, was probed by NOESY ($CDCl_3$, 800 MHz, 280 K) studies.[7] At 25 mM, the five amide NH signals of **6** appeared as three groups of peaks: *δ* 9.51 and 9.54 (two partially overlapped peaks, 2H), *δ* 9.69 (single peak, 1H), and *δ* 9.82 and 9.84 (two partially overlapped peaks, 2H). On the basis of results from **5**, each amide proton should have two cross-peaks corresponding to the three-center hydrogen bonds. The NOESY spectrum of **6** revealed exactly 10 cross-peaks between the amide protons and the protons of the alkoxy α-methylene and methoxy groups (3.6 to 4.4 ppm). Two of the four cross-peaks corresponding to the two NH signals at around *δ* 9.82 and 9.84 were not completely resolved, but can be clearly identified. These 10 cross-peaks, corresponding to two contacts for each amide proton, clearly support the curved conformation shown here for **6**.[8]

In summary, we have described a series of oligoamides with well-defined, curved backbones. The persistence of the three-center hydrogen bonds which lead to the rigidification of the backbones has been established. These compounds can be prepared from readily available starting materials based on well-established, highly efficient amide chemistry. These oligoamides have inherent folding propensities: the conformations of their backbones depend only on the presence of local intramolecular hydrogen bonds between amide linkages and their adjacent alkoxy groups. The curved backbone confirmation should thus be resilient toward structural variation on the −OR groups. More significantly, the curved backbone should lead to the formation of a large (~10 Å in **6** based on computer modeling[9]), hydrophilic cavity. On the basis of this new motif, a variety of folding structures with interior cavities can be envisioned. For example, oligomers such as **6** can be viewed as acyclic "macrocycles" that may selectively bind to metal ions and small molecules.[10] Oligomers with more than six rings (or residues) should fold into a new class of helices with large, interior cavities.

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Supporting Information Available: Synthetic procedures, NOE difference spectra of **2**, NOESY spectra of **5** and **6**, and tables of X-ray data for **3** and **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Compounds **2**, **3**, **4**, and **6** gave satisfactory results on spectral and elemental analysis. Data from the characterization of **2**−**6** are included in the Supporting Information.

(9) The energy minimization was performed on a Macintosh computer using the CaChe Program (Oxford Molecular, MM2 force field).

(10) Vögtle, F.; Weber, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 753.