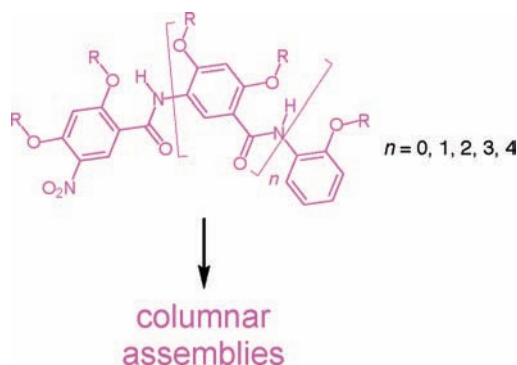# Aggregation and Columnar Assembly of Crescent Oligoamides

Yunfeng Zhang,[†] Kazuhiro Yamato,[‡] Kai Zhong,[†] Jin Zhu,[†] Jingen Deng,*,[†] and Bing Gong*,[‡]

Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041, China, and Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York 14260

bgong@chem.buffalo.edu

Received July 9, 2008

ABSTRACT

The aggregation and assembly of crescent oligoamides with two to six benzene residues are investigated. In chloroform, the pentamer and hexamer are found to associate into large aggregates. In the solid state, all oligomers examined associate into columnar assemblies via stacking interactions, as shown by X-ray diffraction data from single crystals and powder samples. The columnar assemblies of the pentamer and hexamer should contain hydrophilic channels defined by the constituent oligomers.

Unnatural oligomers that fold into well-defined conformations, i.e., foldamers, have attracted intense interest during the last ten years.[1] The majority of foldamers, such as the peptidomimetic α-aminoxy acid peptides,[2] β-,[3] γ-,[4] and δ-peptides,[5] peptoids,[6] and others with nonbiological backbones,[7] has focused on folding into secondary, mostly helical,[9a] structures. With many oligomers having well-defined conformations now being available, the assembly of foldamers into higher-order structures is attracting increasing attention.[8] We have developed a series of stably folded aromatic oligoamides based on backbone-rigidification enforced by intramolecular three-center hydrogen bonds.[9] Depending on its length, an oligoamide can adopt either a

[†] Chinese Academy of Sciences.
[‡] The State University of New York.
(1) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (c) Gong, B. *Chem.—Eur. J.* **2001**, *7*, 4336. (d) Huc, I. *Eur. J. Org. Chem.* **2004**, 17.
(2) Yang, D.; Ng, F. F.; Li, Z. J.; Wu, Y. D.; Chan, K. W. K.; Wang, D. P. *J. Am. Chem. Soc.* **1996**, *118*, 9794.
(3) (a) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071. (b) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913.
(4) (a) Hanessian, S.; Luo, X. H.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569–8570. (b) Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem.—Eur. J.* **2002**, *8*, 573.

(5) (a) Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parrill, A. L.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074. (b) Hungerford, N. L.; Claridge, T. D. W.; Watterson, M. P.; Aplin, R. T.; Moreno, A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3666.
(6) Kirshenbaum, K.; Barron, A. E.; Goldsmith, R. A.; Armand, P.; Bradley, E. K.; Truong, K. T.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4303.
(7) (a) Lokey, R. S.; Iverson, B. L. *Nature* **1995**, *375*, 303. (b) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793. (c) Cuccia, L. A.; Lehn, J. M.; Homo, J. C.; Schmutz, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 233.

crescent or a helical conformation. For example, short oligomers consisting of less than seven *meta*-linked benzene residues adopt a flat, crescent conformation.[10] The flat shape of the backbones is due to the planar arrangement enforced by highly favorable[11] intramolecular three-center H-bonds. Results from our own studies indicate that the three-center H-bonds we introduced are very robust and persist in both nonpolar and polar media.[12] Similar to the assembly of disclike aromatic molecules with large, flat surfaces,[13] these stably folded crescent oligoamides, with their flat surfaces of tunable areas, may also associate or aggregate based on surface–surface stacking interactions, leading to assemblies with anisotropic structures and properties. Herein, we describe results from our initial investigation on the association and assembly of a series of homologous crescent oligoamides both in solution and in the solid state.

a: $R^1 = -CH_2CH_2OC(CH_3)_3$; $R^2 = -CH_3$
b: $R^1 = -CH_3$; $R^2 = -(CH_2CH_2O)_3CH_3$
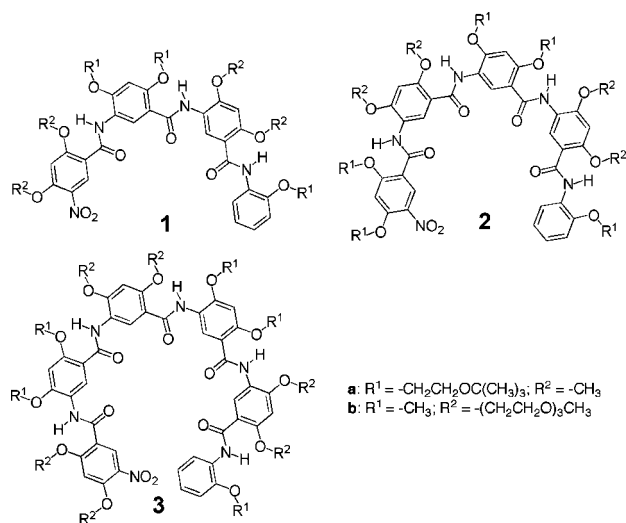
It was observed that oligoamides **1a**−**3a** showed a marked solubility difference in chloroform. Tetramer **1a** was readily soluble, and **2a** was soluble at up to 5 mM. In contrast, hexamer **3a** had a solubility of less than 2 mM. In addition, the line width of the ¹H NMR signals of these three oligomers increased from tetramer **1a** to pentamer **2a** and to hexamer **3a**.[14] These results indicate that aggregation of the oligomers is facilitated by stacking interaction that is proportional to the surface area of the molecules.

The aggregation of oligomers **1a**−**3a** in solution was then examined by using dynamic light scattering (DLS). All three oligomers appeared fully soluble when initially dissolved in chloroform (1 mM) at room temperature. DLS could not detect any aggregate in the solution of tetramer **1a**. In contrast, both pentamer **2a** and hexamer **3a** formed large

(8) (a) Mio, M. J.; Prince, R. B.; Moore, J. S.; Kuebel, C.; Martin, D. C. *J. Am. Chem. Soc.* **2000**, *122*, 6134. (b) Raguse, T. L.; Lai, J. R.; LePlae, P. R.; Gellman, S. H. *Org. Lett.* **2001**, *3*, 3963. (c) Lee, B. C.; Zuckermann, R. N.; Dill, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10999. (d) Qiu, J. X; Petersson, E. J.; Matthews, E. E.; Schepartz, A. *J. Am. Chem. Soc.* **2006**, *128*, 11338. (e) Bradford, V. J.; Iverson, B. L. *J. Am. Chem. Soc.* **2008**, *130*, 1517. (f) Petitjean, A.; Cuccia, L. A.; Schmutz, M.; Lehn, J. M. *J. Org. Chem.* **2008**, *73*, 2481.
(9) (a) Sanford, A. R.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649. (b) Gong, B. *Acc. Chem. Res.* **2008**, ASAP article. Web Release Date: 07-May-2008.

aggregates as shown by DLS measurements (Figure 1). Consistent with the trend revealed by solubility difference
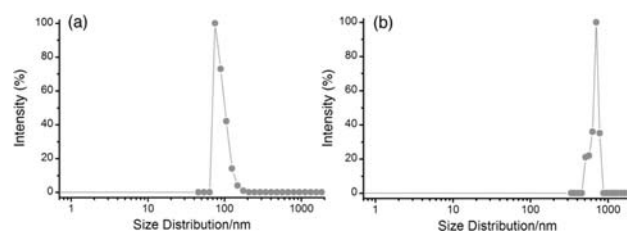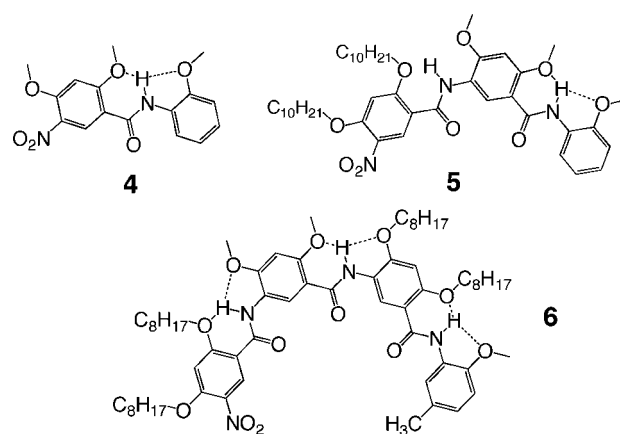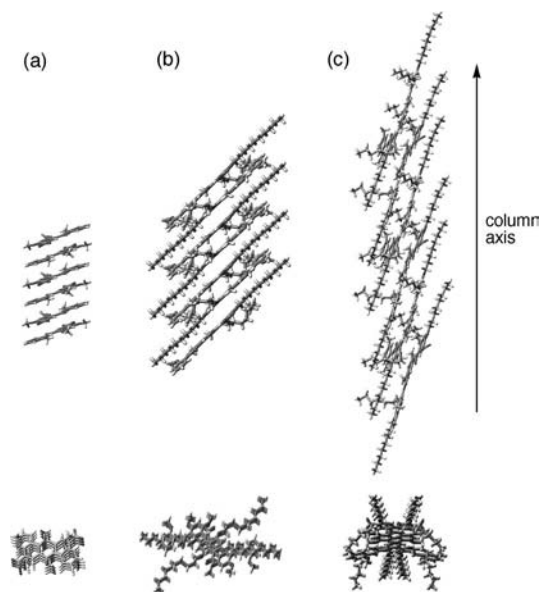

Figure 1. Results of dynamic light scattering measurements of (a) **2a** (1 mM) and (b) **3a** (1 mM), in chloroform at room temperature.

and changes of NMR line width, the aggregate formed by hexamer **3a** (around 700 nm, Figure 1b) is much larger than that formed by pentamer **2a** (around 90 nm, Figure 1a). Interestingly, DLS studies also revealed a time dependence for the aggregation of both **2a** and **3a**. Freshly prepared solution of **2a** or **3a** in chloroform did not show any detectable aggregation. In contrast, the size of the aggregate formed by **2a** or **3a** kept increasing until about 1 h after the solution was prepared. DLS measurements on the more soluble **2b** and **3a** also revealed large aggregates.[14] One explanation of the observed time dependence in the aggregation of these oligomers may be the anisotropic interaction of the molecules, which requires a proper orientation for effective intermolecular association to take place. The observed aggregation of oligoamides **2** and **3** is quite unusual and contrasts the behavior of oligomers having aromatic hydrocarbon backbones to which chloroform is a good solvent that discourages stacking interactions.[7b]

The above results clearly demonstrated the association of oligomers **2a** and **3a** in solution. To provide more insight into the assembly of crescent oligoamides, we decided to probe the assembly of these shape-persistent molecules in the solid state. The crystal structures of short oligoamides **4**−**6** were previously determined by us.[10] On the basis of the X-ray data, examining the packing of **4**−**6** revealed columnar assemblies formed by all three oligomers (Figure 2).

The column formed by dimer **4** consists of molecules that are stacked in a parallel, nearly eclipsed fashion, with the

Figure 2. Side and top views of columnar assemblies observed in the solid state structures of (a) dimer **4**, (b) trimer **5**, and (c) tetramer **6**.

plane of each molecule and that of the column being nearly perpendicular. In the columns formed by trimer **5** and tetramer **6**, the molecules are also parallelly stacked, with angles of ~45° and ~30°, respectively, between the long axes of the molecules and those of the corresponding columns. The distances between the planes of adjacent molecules in all columns are between 3.5 and 3.6 Å, indicating that aromatic stacking interactions are responsible for associating the molecules into the columns. The columns further assemble via van der Waals interaction between the numerous C−H bonds from aromatic rings and the alkyl side chains.

The packing of **4**−**6** suggests that forming columnar assemblies may be a common feature for these crescent oligoamides in the solid state. Thus, higher homologues of **4**−**6**, such as oligomers **2** and **3**, with their larger surface areas, not only aggregate in solution as shown by **2a** and **3a** but also may associate into columnar assemblies in the solid state. Columnar assemblies of pentamer **2** and hexamer **3** are particularly interesting because with their increasingly enclosed cavities the assembled structures should have hydrophilic channels running down the columns. Since repeated efforts to grow single crystals of the analogues of

(10) (a) Zhu, J.; Parra, R. D.; Zeng, H.; Skrzypczak-Jankun, E.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 4219. (b) 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. (c) Yuan, L. H.; Zeng, H. Q.; Yamato, K.; Sanford, A. R.; Feng, W.; Atreya, H. S.; Sukumaran, D. K.; Szyperski, T.; Gong, B. *J. Am. Chem. Soc.* **2004**, *126*, 16528.

(11) Rozas, I.; Alkorta, I.; Elguero, J. *J. Phys. Chem. A* **1998**, *102*, 9925.

(12) Parra, R. D.; Zeng, H. Q.; Zhu, J.; Zheng, C.; Zeng, X. C.; Gong, B. *Chem.−Eur. J.* **2001**, *7*, 4352.

(13) Kumar, S. *Chem. Soc. Rev.* **2006**, *35*, 83.

(14) Please see Supporting Information for more details.

2 and **3** that bear short alkyl side chains have failed to yield single crystals amenable to X-ray analysis, the assembly and packing of **2b** and **3b** in the solid state were investigated using other techniques.

The X-ray powder diffraction patterns of the solid sample of **2b** directly prepared from solution by evaporation of solvent (CH_2Cl_2) failed to indicate large-scale organization.[14] Oligomer **2b** was then thermally treated under nitrogen by being placed between two glass plates and heated to become an isotropic liquid with an oil bath (150−200 °C). Stress was then applied to the molten sample by slightly pulling the upper glass plate along the plane of the glass plate unidirectionaly.[15] The treated sample was rapidly cooled in liquid nitrogen and was subsequently allowed to warm to room temperature. The XRD diffraction pattern indicates a highly ordered phase (Figure 3a). The presence of an
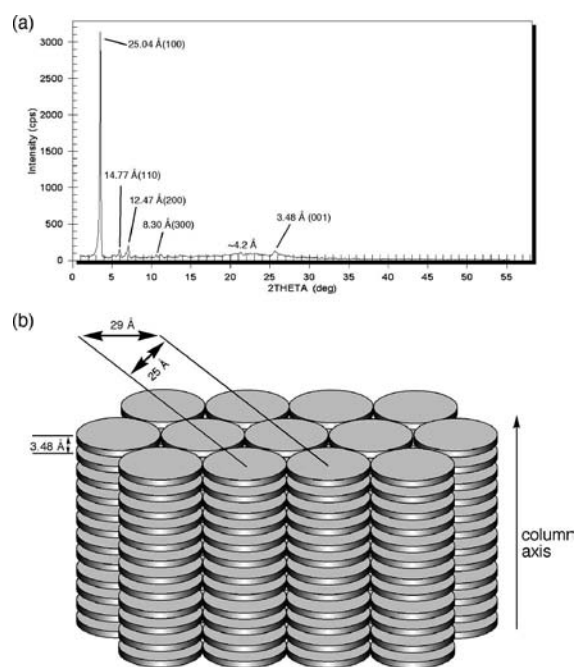

Figure 3. (a) Diffractogram of the thermally treated solid sample of pentamer **2b**. (b) Schematic drawing of the columnar packing of **2b** and the hexagonal lattice. The hexagonal lattice parameter *a* is 28.9 Å. This cartoon does not imply the actual stacking axis geometry which is currently unknown.

overwhelmingly dominant peak at 25 Å and the paucity of other peaks in the diffractogram of **2b** are characteristic of columnar assemblies formed by disclike molecules.[16] The ratios of the *d*-spacings of the dominant peak at 25 Å, along with the weaker peaks at 14.77 and 12.47 Å ($1:1/\sqrt{3}:0.5$), are consistent with those from a two-dimensional hexagonal lattice (Col_{hd}),[16] based on which a lattice parameter of *a* = 28.9 Å is obtained (Figure 3b). Parameter *a* is the diameter of the column which is consistent with the molecular dimension of **2b**. In addition, the broad maximum at ~4.2 Å is often observed with columnar discotic liquid crystals and can be assigned to the distance between the packed side chains of **2b**. The presence of a distinct peak at 3.48 Å can

be attributed to the interplanar reflections between the flat backbones of the molecules, which suggests relatively strong stacking interactions between the backbones of the molecules in the columns and indicates the existence of periodicity along the columns.

Similarly, XRD measurements of the powder sample of hexamer **3b** prepared by removing solvent from solution did not reveal any ordered phase. In contrast, XRD measurements of thermally treated solid sample of **3b** prepared in the same way as that used for **2b** revealed diffraction patterns that share the general features (see Supporting Information).[14] An overwhelmingly dominant peak at ~28 Å and the dearth of other prominent peaks are associated with the diffracto-grams of thermally treated **3b**,[14] suggesting that molecules of **3b** also stack into columnar structures. A peak at ~3.5 Å corresponding to interplanar reflections between the flat backbones of **3b** can be observed in each case. Thus, the diffractograms of **3b** strongly suggest that **3b** also forms columnar structures in the solid state. Unfortunately, the obtained diffractograms of **3b** do not allow the peaks to be properly indexed.

The XRD results suggest that, similar to the assembly of their shorter homologues **4−6** and that of discotic liquid crystals, the molecules in the thermally treated solids of **2b** and **3b** are ordered into columns that further pack on a hexagonal lattice.
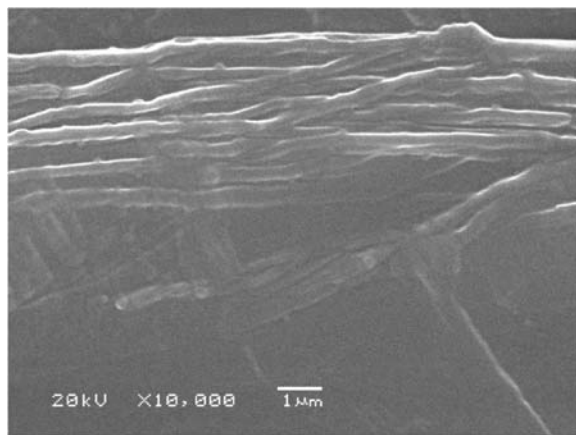

Figure 4. Scanning electron micrograph of the thermally treated sample of **2b**.

Figure 4 shows the SEM image of the thermally treated sample of **2b**. Fibers with lengths over several micrometers were observed.[14] In addition, these fibers seem to be rigid

and have a narrow distribution of diameters that are between 0.3 to 0.4 μm (average 0.35 μm). The SEM image provided additional evidence that is consistent with the highly aniso-tropic nature of the assembly formed by **2b**.

In summary, oligoamides **2a** and **3a** showed an obvious tendency to self-assemble in solution, as demonstrated by solubility difference, changes of NMR line width, and the formation of nanosized aggregates. The aggregation of these two oligomers in solution is presumably due to stacking interactions promoted by the flat, well-defined oligoamide backbones. However, the fact that aggregation was observed in chloroform which normally discourages aromatic stacking interactions suggests the possibility of a stacking mechanism unique to this and analogous systems. In the solid state, the columnar packing of short crescent oligoamides **4−6** is revealed by examining X-ray data obtained from the corre-sponding single crystals. The columnar and hexagonal packing of pentamer **2b** is clearly indicated by X-ray diffraction patterns and SEM image. The diffraction patterns of the solid sample of hexamer **3b** share the same general features shown by those of **2b**, suggesting that **3b** also packs into columns. These initial results have demonstrated the strong association and anisotropic, columnar packing of crescent oligoamides, which have provided the basis for the subsequent study and elucidation of the supramolecular assemblies of these molecules. With their persistent flat shape and easily modifiable side chains that allow the introduction of more directional intermolecular interactions such as H-bonding, crescent oligoamides offer a set of readily available and tunable nanosized building blocks that should lead to the creation of new nanoporous structures with uniform, hydrophilic channels. The corresponding objective is being pursued and will be reported in due course.

Supporting Information Available: ^{1}H NMR spectra, diffractograms, SEM images, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801410F

(15) The sample of **2b** was similarly treated but without being subjected to such stress gave very similar diffraction patterns that can be indexed to a hexagonal lattice (see Supporting Information).

(16) Prasad, S. K.; Rao, D. S. S.; Chandrasekhar, S.; Kumar, S. *Mol. Cryst. Liq. Cryst.* **2003**, *396*, 121.