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Oligo-*m*-aniline Foldamers

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ABSTRACT

Nitrogen atoms showed intriguing properties such as, they can adopt sp^2 or sp^3 electronic configurations and form various degrees of conjugations with the adjacent aromatic rings depending on the electric nature of aromatic rings. Through deliberate combination of nitrogen atoms with aromatics of different electric nature, oligo-*m*-aniline foldamers were synthesized with a two-directional synthetic protocol. The synthesized hexamer and heptamer gave a snake-shape folding structure in the crystalline state. By means of 2D NOESY NMR experiments, both the hexamer and heptamer were found to adopt similar folding structures in solution as those in the solid state.

Folding is the central process of biological macromolecules such as proteins and DNA to carry out their biological functions. Inspired by the sophisticated structures and functions of the macromolecules, synthetic foldamers have attracted much attention since the end of last century.[1] In addition to the initial attempts to mimic the biological helical structure by designing unnatural peptide analogues, such as β, γ and δ-peptides,[1a,k,n,2] recent years have witnessed a growing interest in foldamers comprising aromatic building units.[1b–f,m,h] Among various artificial foldamers, oligoamides are the most extensively studied ones since moieties of amide units constitute effective hydrogen bond donors.[1b,d–f,h,3]

In the past decade, we have focused on the study of heteroatom-bridged calixaromatics, a new generation of macrocyclic host molecules in supramolecular chemistry.[4] It has been found that the bridging heteroatoms, such as nitrogen atoms, can adopt sp^2 or sp^3 electronic configurations and form various degrees of conjugations with the adjacent aromatic rings depending on the electronic nature of the aromatic rings, which results in the formation of different conformations and cavities.[3a,d,5]

Heteroatom-bridged calixaromatics are synthesized by the fragment coupling approach (FCA) and the one-pot reaction from readily available and simple aromatic dinucleophiles such as *m*-phenylenediamines and resorcinol derivatives, and aromatic dielectrophiles including 2,6-dibromopyridines, 4,6-dichloropyrimides and cyanuric chloride. Both methods are effective in the formation of macrocyclic compounds. This has led us to rationalize that the linear oligomeric precursors may adopt or fold to correct conformations prior to macrocyclization. To test our hypothesis, we synthesized several oligo-*m*-anilines and investigated their structures. Herein, we report an efficient two-directional synthetic method for the preparation of desired compounds. We also show that the resulting oligo-*m*-anilines adopt folding structure both in solid state and solution.

We initiated our synthesis by applying a two-directional fragment coupling approach. As illustrated in Scheme 1, nucleophilic aromatic substitution reaction of 2-*n*-butoxy-5-*tert*-butylbenzene-1,3-diamine **1** with 1,5-difluoro-2,4-dinitrobenzene **2** in the presence of DIPEA in THF at room temperature gave trimer **3** in a high yield of 83%. Further treatment of **3** with **2** under similar conditions afforded a pentamer **5** in a moderate yield. In addition to **5**, the reaction also gave a heptamer **7** in 8% yield. Similar reaction of **5** and **1** gave the desired hexamer **6** in 25% yield.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data and microanalysis (see Supplementary data, Figs. S9–S20). To put the structure beyond any doubt, and also to understand the structure at the molecular level, single crystals of compound **5–7** were cultivated. To our delight, single crystals of **6** and **7** were obtained and their structures were determined unambiguously. As illustrated in Figures 1 and 2, both compounds **6** and **7** formed a folding structure and some interesting structural features are worth addressing. First of all, in both cases the bridging nitrogen atoms adopted sp^2 electronic configuration and tended to conjugate with the electron deficient 2,4-dinitro-substituted benzene rings rather than electron rich 2-alkoxy-5-butyl-substituted benzene rings. In addition to conjugation effect, hydrogens attached on the bridging nitrogen atoms formed N–H. . .O hydrogen bondings with the neighbouring nitro groups, which enhanced the rigidity of dinitro-substituted *m*-phenylenediamine rings. Foldamers are therefore composed of larger and conjugated dinitro-substituted 1,3-phenylenediamine segments, and smaller *n*-butoxylated benzene units. It is noticeable

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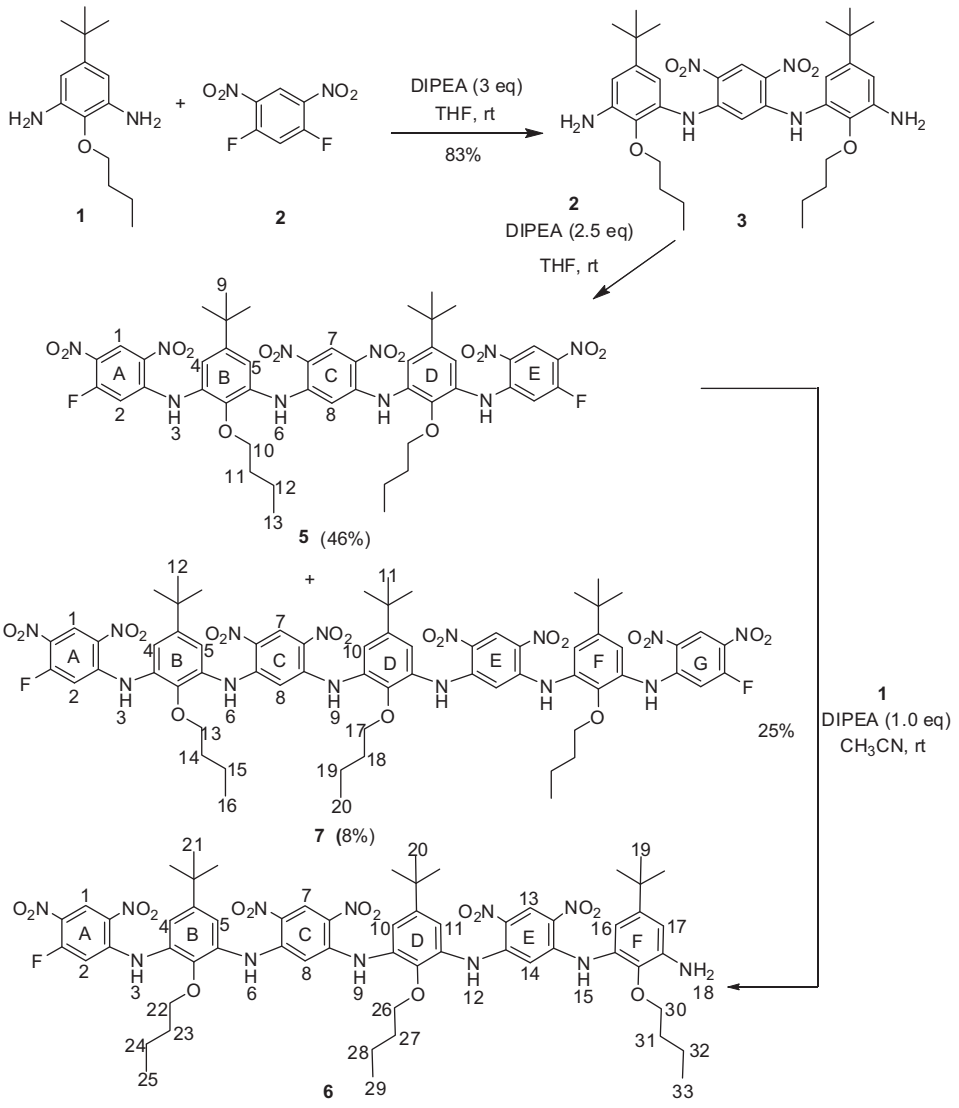

Scheme 1. Synthesis of oligomers **5**, **6** and **7**.

that the two fragments twist each other affording the dihedral angles in the range of 45–70°, which lead to the folding of the whole molecules (Figs. 1 and 2). It is also worth noting that the alkoxy and *t*-butyl substituents oriented to the same direction, acting as the side chains to further stabilize the folding structure. The *t*-butyl groups formed C–H...π interaction with the neighbouring benzene rings. The alkoxy substituents, on the other hand, tended to form Van der Waals interactions in the solid state (Fig. S1, A and Fig. S2, A). Moreover, the presence of bulky groups inhibited the mobility of the conformation because of the steric effect.

A few other interesting features of the intermolecular interactions of the folding oligomers are worth addressing. In the case of **6**, for example, the folding oligomers were linked with a dichloromethane molecule through C–H...π interaction between dichloromethane and 2-butoxy-5-*tert*-butylaniline moiety (Fig. S1, B), giving one dimensional infinite chain structure. In the two dimensional direction, two folding oligomers aligned head to tail, forming multiple π–π stackings between 2,4-dinitro-substituted benzene rings (Fig. S1, C). In the case of **7**, chloroform acted as the linker between the folding oligomers, forming Cl...O interaction with one molecule and C–H...O hydrogen bonding with another molecule. Similar to compound **6**, intermolecular multiple π–π stackings between 2,4-dinitro-substituted benzene rings are also observed in oligomer **7** (Fig. S2, B and C).

To study the structures of oligo-*m*-aniline compounds **5**, **6** and **7** in solution, we carried out two-dimensional (2D) NOESY NMR experiments. Compounds **5**–**7** gave well-resolved proton signals in their ^{1}H NMR spectra, and all signals were assigned based on peak intensity (integration) coupling patterns, deuteration experiments and NOE (see Supplementary data). We first examined the structure of **6** in solution, which was illustrated in Figure S3. Five N–^{1}H signals of **6** showed very different chemical shift values. Whereas protons H^6, H^9 and H^{15} gave similar chemical shifts at 9.94, 9.87 and 9.90, respectively, H^3 and H^{12} moved to downfield and upfield, respectively, giving the chemical shift value of 10.23 and 9.61. The changes of chemical shift of H^3 and H^{12} suggested that they are located in a local environment different from H^6, H^9 and H^{15}. Moreover, cross-peaks between protons of H^2 and H^4, H^3 and H^{12}, H^5 and H^8, H^8 and H^{10}, H^{11} and H^{14}, H^{14} and H^{16} were observed, which were in good agreement with the environment of protons in solid state, indicating the folding structure of **6** in solution (Fig. S3). In the case of **7**, cross-peaks between ^{1}H signals H^2

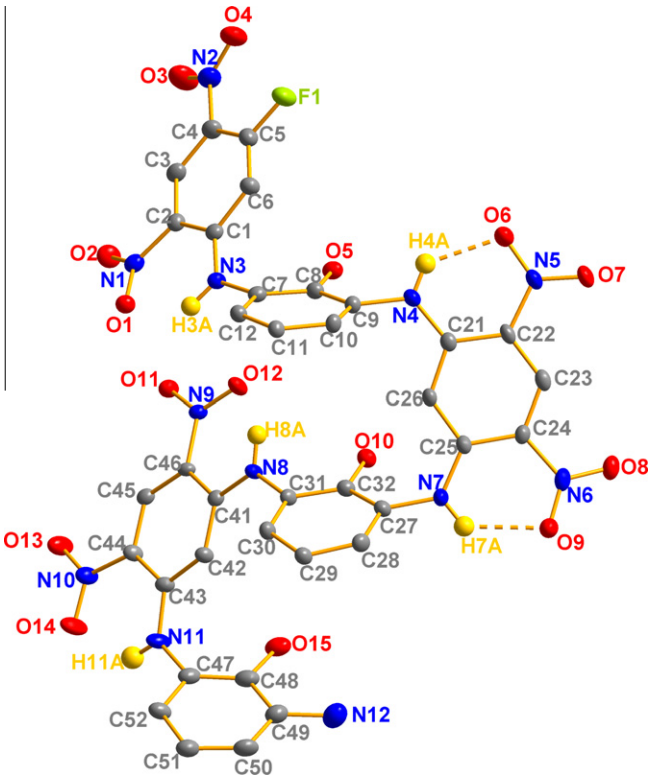

Figure 1. Crystal structure of **6**. Selected bond length [Å]: C1-N3 1.354, N3-C7 1.424, C9-N4 1.432, N4-C21 1.356, C25-N7 1.365, N7-C27 1.408, C31-N8 1.417, N8-C41 1.362, C43-N11 1.361, N11-C47 1.420; selected angle: <C1-N3-C7 125.46°, <C9-N4-C21 123.09°, <C25-N7-C27 124.42°, <C31-N8-C41 126.25°, C43-N11-C47 126.67°; hydrogen bond distances [Å]: O1…H3A 2.004, O6…H4A 1.979, O9…H7A 2.013, O12…H8A 2.001, O14…H11A 1.979; hydrogen bond angles: N3-H3A…O1 130.57°, N4-H4A…O6 130.59°, N7-H7A…O9 129.89°, N8-H8A…O12 129.32°, N11-H11A…O14 131.18°. The probability is 25%. *t*-Butyl, alkoxy substitutents, a aryl and alkyl hydrogens are omitted for clarity.

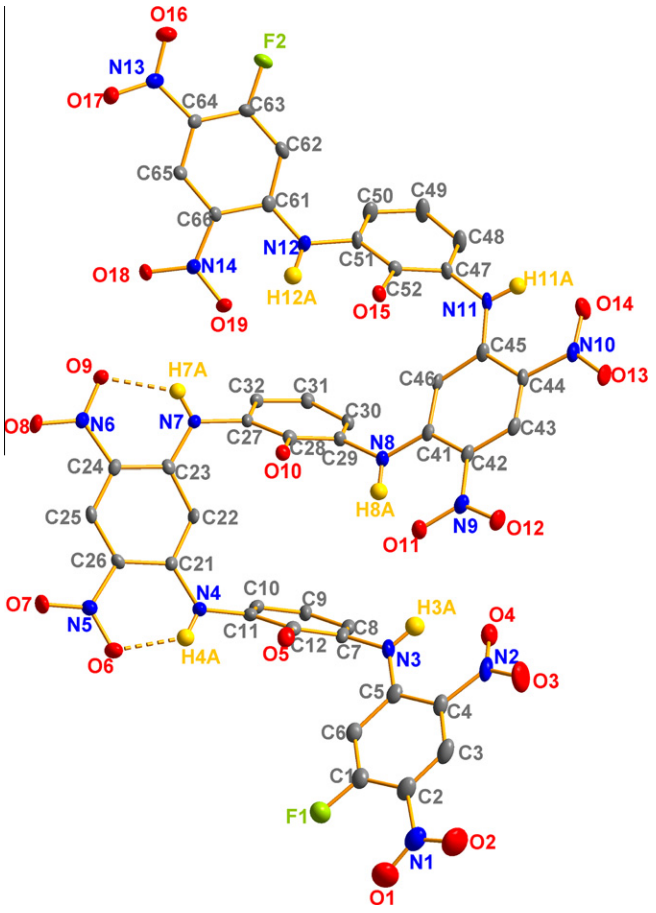

Figure 2. Crystal structure of **7**. Selected bond length [Å]: C61-N12 1.355, N12-C51 1.423, C47-N11 1.426, N11-C45 1.356, C41-N8 1.362, N8-C29 1.427, C27-N7 1.431, N7-C23 1.358, C21-N4 1.355, N4-C11 1.427, C7-N3 1.432, N3-C5 1.355; selected angle: <C61-N12-C51 127.96°, <C47-N11-C45 126.95°, <C41-N8-C29 125.43°, <C27-N7-C23 123.69°, C21-N4-C11 124.60°, C7-N3-C5 125.75°; hydrogen bond distances [Å]: O19…H12A 1.941, O14…H11A 1.965, O11…H8A 1.969, O9…H7A 2.011, O6…H4A 1.982, O4…H3A 1.993; hydrogen bond angles: N12-H12A…O19 133.83°, N11-H11A…O14 132.60°, N8-H8A…O11 131.53°, N7-H7A…O9 129.49°, N4-H4A…O6 131.04°, N3-H3A…O4 130.08°. The probability is 25%. *t*-Butyl, alkoxy substitutents, aryl and alkyl hydrogens are omitted for clarity.

and H^4, H^5 and H^6, H^3 and H^8, H^8 and H^{13}, H^2 and H^{13}, H^5 and H^{11}, H^3 and H^9, H^3 and H^{10}, H^4 and H^{14} were found in Figure 3 and Figure S4, also agreeing well with the folding structure in the solid state. Noticeably, the long distance NOE between H^5 and H^{11}, H^3

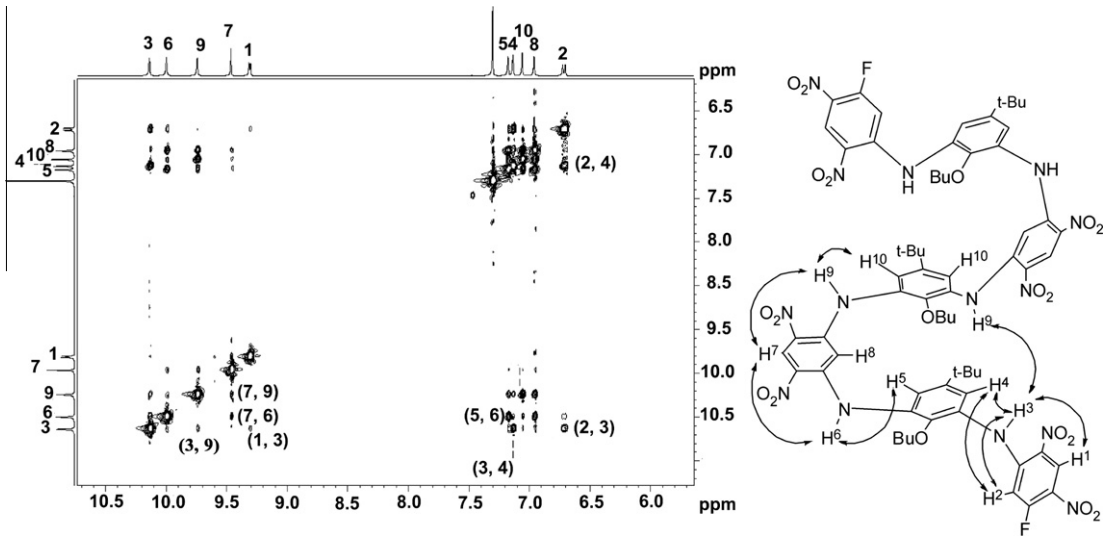

Figure 3. 2D NOESY NMR spectrum of **7**. The 2D NOESY NMR experiment was carried out at 223 K with the concentration of **7** being 0.025 M and mixing time 800 ms, respectively.

and H^9, H^3 and H^{10} further evinced the folding structure in solution (Fig. 3 and Fig. S4). It is worth addressing that the intensity of the cross-peak between N–^{1}H signals H^3 and H^9 in **7** is stronger than that of H^3 and H^{12} in **6**, indicating the result of two set of N–H contacts. The structure of **5** in solution was also examined by means of NOESY NMR spectrum. From Figure S5, several cross-peaks were observed, such as H^2 and H^4, H^3 and H^4, H^5 and H^6, H^3 and H^{10}, H^6 and H^{10}, H^2 and H^9, H^4 and H^9, H^5 and H^6. Though the NOE between H^2 and H^9, H^8 and H^9 indicated they are closely neighboured in the structure, it is hard to conclude that **5** existed in a folding form in solution.

In summary, we have synthesized the first examples of oligo-*m*-aniline foldamers through a fragment coupling protocol. As revealed by X-ray crystallography, the hexamer and heptamer give a snake-shape folding structure in the crystalline state. On the basis of 2D NOESY NMR experiments, both hexamer and heptamer adopt similar folding structures as those in the solid state.

Acknowledgments

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Supplementary data

Supplementary data (experimental details, full characterization of products, crystal structures, 2D ^{1}H NMR NOESY spectra, ^{1}H and ^{13}C NMR of the products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.050.

References and notes

1. (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173; (b) Huc, I. *Eur. J. Org. Chem.* **2004**, 17; (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893; (d) Gong, B. *Acc. Chem. Res.* **2008**, *41*, 1376; (e) Li, Z.-T.; Hou, J.-L.; Li, C. *Acc. Chem. Res.* **2008**, *41*, 1343; (f) Saraogi, I.; Hamilton, D. *Chem. Soc. Rev.* **2009**, *38*, 1726; (g) Nakano, T.; Okamoto, Y. *Chem. Rev.* **2001**, *101*, 4013; (h)*Foldamers: Structure, Properties and Applications*; Heeht, S., Huc, I., Eds.; Viley-VCH: Weinheim, 2007; (i) Bautista, A. D.; Craig, C. J.; Harker, E. A.; Schepartz, A. *Curr. Opin. Chem. Biol.* **2007**, *11*, 685; (j) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219; (k) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366; (l) Juwarker, H.; Jeong, K.-S. *Chem. Soc. Rev.* **2010**, *39*, 3664; (m) Ni, B.-B.; Yan, Q.; Ma, Y.; Zhao, D. *Coord. Chem. Rev.* **2010**, *254*, 954; (n) Martinek, T. A.; Fülöp, F. *Chem. Soc. Rev.* **2012**, *41*, 687; (o) Schafmeister, C. E.; Brown, Z. Z.; Gupta, S. *Acc. Chem. Res.* **2008**, *41*, 1387.
2. (a) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054; (b) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J., Jr; Gellman, S. H. *Nature* **1997**, *387*, 381; (c) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, *21*, 2015; (d) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1595; (e) Zhao, X.; Jia, M.-X.; Jiang, X.-K.; Wu, L.-Z.; Li, Z.-T.; Chen, G.-J. *J. Org. Chem.* **2004**, *69*, 270.
3. (a) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 446; (b) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529; (c) Berl, V.; Huc, I.; Khoury, R.; Krische, M.; Lehn, J.-M. *Nature* **2000**, *407*, 720; (d) Zhu, J.; Parra, R. D.; Zeng, H.; Skrzypczak-Jankun, E.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 4219; (e) Jiang, H.; Léger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448; (f) Gan, Q.; Bao, C.; Kauffmann, B.; Grélard, A.; Xiang, J.; Liu, S.; Huc, I.; Jiang, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1715; (g) Hu, H.-Y.; Xiang, J.-F.; Yang, Y.; Chen, C.-F. *Org. Lett.* **2008**, *10*, 69.
4. For reviews on heteracalixaromatics see: (a) Wang, M.-X. *Chem. Commun.* **2008**, 4541; (b) Maes, W.; Dehaen, W. *Chem. Soc. Rev.* **2008**, *37*, 2393; (c) Tsue, H.; Ishibashi, K.; Tamura, R. *Top. Heterocycl. Chem.* **2008**, *17*, 73; (d) Wang, M.-X. *Acc. Chem. Res.* **2012**, *45*, 182; (e) Thomas, J.; Rossom, W. V.; Hecke, K. V.; Meervelt, L. V.; Smet, M.; Maes, W.; Dehaen, W. *Chem. Commun.* **2012**, *48*, 43; (f) König, B.; Fonseca, M. H. *Eur. J. Inorg. Chem.* **2000**, 2303.
5. Wang, M.-X.; Zhang, X.-H.; Zheng, Q.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 838.