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# A Folded, Secondary Structure in Step-Growth Oligomers from Covalently Linked, Crowded Aromatics

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***Abstract:*** This study delineates general methods to create a new class of folded oligomers by covalently attaching overcrowded aromatics to each other. Crucial to observing the secondary structure in these oligomers was the employment of C-shaped linkers. These linkers preorganize the strands to form intramolecular hydrogen bonds. In solution, one- and two-dimensional $^1$H NMR data show well-defined columnar conformations. The side chains in these oligomers are critical for the secondary structure to emerge in solution. Using tris(dodecyloxy)phenethyl side chains in combination with *tert*-butyl side chains in the terminal subunit provides a soluble trimer and prevents intermolecular association above millimolar concentrations. This new folding motif, formed through a synergy between hydrogen bonds and $\pi$-stacking, is so robust that even dimers have secondary structure in solution.

## Introduction

In recent years, there has been intense interest in the design, synthesis, and study of abiotic oligomers of defined length that fold into well-defined secondary structures known as foldamers.[1] Crowded aromatics such as **1** (Figure 1a) were recently shown[2] to be a general method to create discotic-like liquid crystals[3] held together by hydrogen bonds.[4] Detailed below are the synthetic methods to covalently attach these mesogens to each other (Figure 1b) and data showing that *only* when certain linkers are employed do the oligomers fold into well-defined columnar conformations in solution. This new folded motif, formed through a synergy between hydrogen bonds[1] and $\pi$-stacking,[5] is so robust that even dimers have secondary structures in solution.

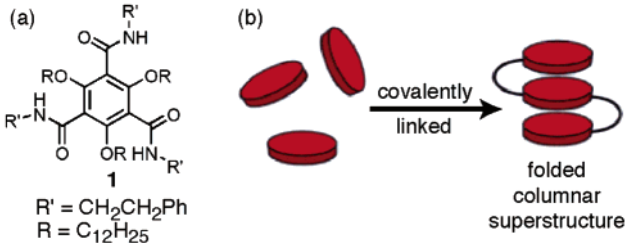



***Figure 1.*** (a) Previously reported mesogen.[2] (b) Schematic representing a covalently linked trimer of **1**.

## Results and Discussion

**Synthesis.** To screen for the efficacious linkers and side chains, a synthetic method is required that differentiates the amide side chains of **1**. The synthesis of the monoacid, diamides **6**−**8** is shown in Scheme 1.[6] The hexasubstituted aromatic core is prepared by a Lewis acid-induced double chloromethylation of methyl 2,4,6-tris(dodecyloxy)benzoate.[7] Conversion to diacetate **4**[8] followed by saponification and oxidation[9] produces the diacid, monoester **5**. The acid functions are coupled with

(1) For foldamers, see: (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4011. (c) Seebach, D.; Beck, A. K.; Rueping, M.; Schreiber, J. V.; Sellner, H. *Chimia* **2001**, *55*, 98−103.

(2) (a) Bushey, M. L.; Hwang, A.; Stephens, P. W.; Nuckolls, C. *J. Am. Chem. Soc.* **2001**, *123*, 8157−8158. (b) Bushey, M. L.; Hwang, A.; Stephens, P. W.; Nuckolls, C. *Angew.* Chem., Int. Ed. **2002**, *41*, 2828−2831. (c) Nguyen, T.-Q.; Bushey, M. L.; Brus, L. E.; Nuckolls, C. *J. Am. Chem. Soc.* **2002**, *124*, 15051−15054.

(3) For leading references on discotic liquid crystals, see: (a) Guillon, D. *Struct. Bonding* **1999**, *95*, 41−82. (b) Chandrasekhar, S.; Prasad, S.; Krishna, A. *Contemp. Phys.* **1999**, *40*, 237−245. (c) Chandrasekhar, Ranganath, G. S. *Rep. Prog. Phys.* **1990**, *53*, 57−84. (d) Boden, N.; Bushby, R. J.; Clements, J.; Movaghar, B. *J. Mater. Chem.* **1999**, *9*, 2081−2086.

(4) Hydrogen bonds used to stabilize $\pi$-stacks: (a) Matsunaga, Y.; Miyajima, N.; Nakayasu, Y.; Sakai, S.; Yonenaga, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 207−210. (b) Brunsveld, L.; Zhang, H.; Glasbeek, M.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 6175−6182 and references therein. (c) Yasuda, Y.; Iishi, E.; Inada, H.; Shirota, Y. *Chem. Lett.* **1996**, *7*, 575−576. (d) Lightfoot, M. P.; Mair, F. S.; Pritchard, R. G.; Warren, J. E. *J. Chem. Soc., Chem. Commun.* **1999**, *19*, 1945−1946. (e) Ranganathan, D.; Kurur, S.; Gilardi, R.; Karle, I. L. *Biopolymers* **2000**, *54*, 289−295. (f) Paleos, C. M.; Tsiourvas, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1696−1711 and references therein. (g) Brienne, M. J.; Gabard, J.; Lehn, J. M.; Stibor, I. *J. Chem. Soc., Chem. Commun.* **1989**, *24*, 1868−70. (h) Goldmann, D.; Dietel, R.; Janietz, D.; Schmidt, C.; Wendorff, J. H. *Liq. Cryst.* **1998**, *24*, 407−411. (i) Ungar, G.; Abramic, D.; Percec, V.; Heck, J. A. *Liq. Cryst.* **1996**, *21*, 73−86. (j) Percec, V.; Ahn, C.-H.; Bera, T. K.; Ungar, G.; Yeardley, D. J. P. *Chem.- Eur. J.* **1999**, *5*, 1070−1083. (k) Malthete, J.; Levelut, A. M.; Liebert, L. *Adv. Mater.* **1992**, *4*, 37−41. (l) Pucci, D.; Veber, M.; Malthete, J. *Liq. Cryst.* **1996**, *21*, 153−155.

(5) Foldamers that utilize $\pi$-stacking: (a) see ref 1b. (b) Lokey, R. S.; Iverson, B. L. *Nature* **1995**, *375*, 303−305. (c) Tanatani, A.; Yamaguchi, K.; Azumaya, I.; Fukutomi, R.; Shudo, K.; Kagechika, H. *J. Am. Chem. Soc.* **1998**, *120*, 6433−6442.

(6) Spectra and experimental procedures are contained in the Supporting Information.

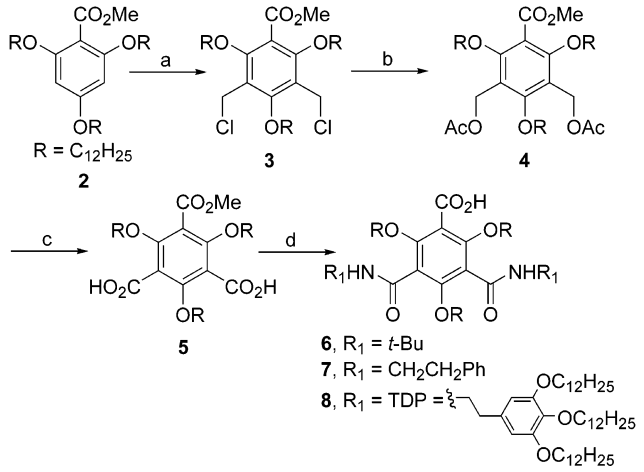
(7) By the method of: Schirch, P. F. T.; Boekelheide, V. *J. Am. Chem. Soc.* **1981**, *103*, 6873−6878.

(8) Similar to: (a) Wallenfels, K.; Witzler, F.; Friedrich, K. *Tetrahedron* **1967**, *23*, 1845−1855. (b) Anthony, J. E.; Khan, S. I.; Rubin, Y. *Tetrahedron Lett.* **1997**, *38*, 3499−3502.

(9) A two-step oxidation sequence was used first to yield the bis(aldehyde) ((a) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *7*, 639−666) and then the bis(carboxylic acid) ((b) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888).


**10.1021/ja034001d CCC: $25.00** 

***Scheme 1*** [a]




[a] Reagents and conditions: (a) $ClCH_2OMe$, $ZnCl_2$; (b) AcONa, AcOH, Δ; (c) (i) KOH, rt; (ii) TPAP, NMO, 4-Å molecular sieves; (iii) $NaClO_2$, $NaH_2PO_4$, *t*-BuOH/2-methyl-2-butene; (d) (i) $SOCl_2$; (ii) $R_1NH_2$, $Et_3N$; (iii) KOH, Δ.

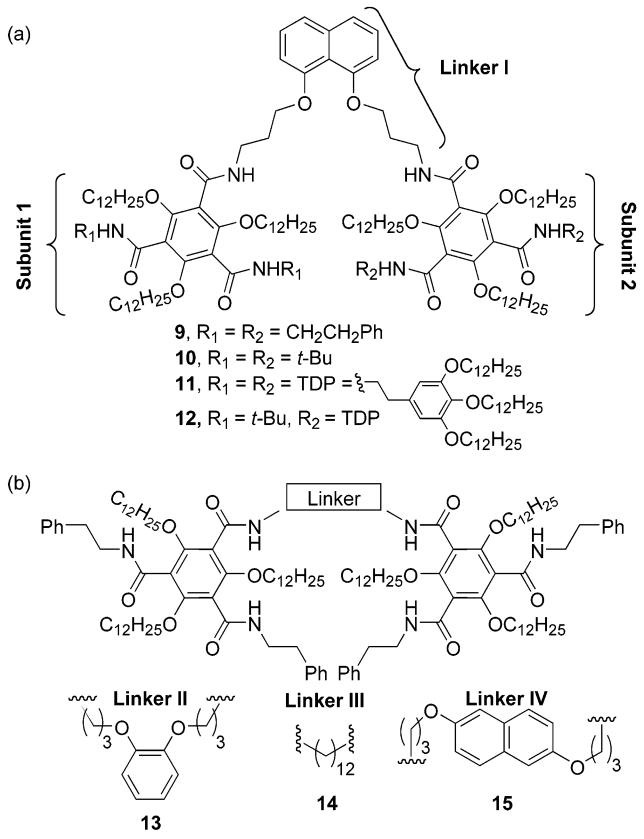


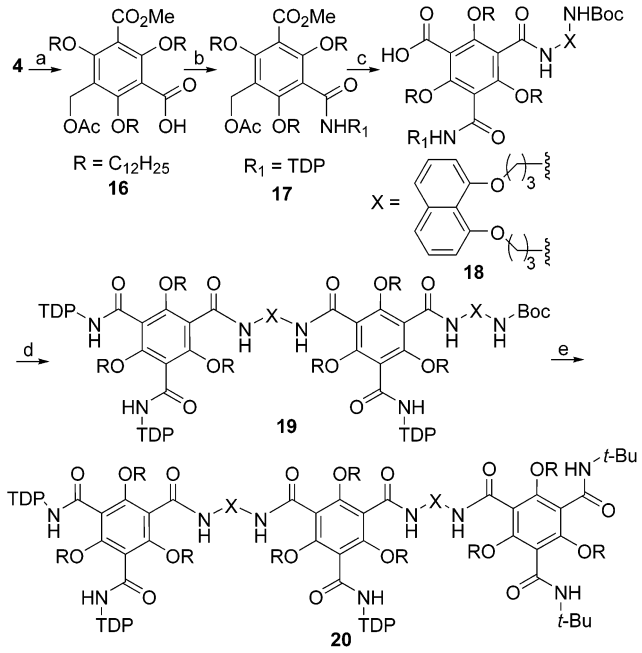

***Figure 2.*** (a) Homo- and heterodimers synthesized with linker **I**. (b) Homodimers with linkers **II**−**IV**.

amines, and the ester is saponified to yield the monoacids **6**−**8** in 31−36% yield from **2**.

The monoacid, diamides **6**−**8** are coupled[10] with the primary diamines of linkers **I**−**IV** (shown in Figure 2) to yield homodimers **9**−**11** and **13**−**15**. A monoprotected version of linker **I** allowed the heterodimer **12** to be synthesized from coupling two different subunits, **8** and **6**.[6]

(10) By the method of: Xu, Y.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 4314−4322.

***Scheme 2*** [a]




[a] Reagents and conditions: (a) (i) KOH (1 equiv), rt; (ii) TPAP, NMO, 4-Å molecular sieves; (iii) $NaClO_2$, $NaH_2PO_4$, *t*-BuOH/2-methyl-2-butene; (b) $R_1NH_2$, EDC, HOAt, DMAP; (c) (i) KOH, Δ; (ii) BocNH-X-$NH_2$, EDC, HOAt, DMAP; (iii) TPAP, NMO, 4-Å molecular sieves; (iv) $NaClO_2$, $NaH_2PO_4$, *t*-BuOH/2-methyl-2-butene; (d) **8**-NH-X-$NH_2$, EDC, HOAt, DMAP; (e) (i) HCl in $Et_2O$; (ii) **6**, EDC, HOAt, DMAP.

The synthesis shown in Scheme 2 allows each of the amide side chains to be individually addressed so that higher oligomers can be constructed.[6] The monoalcohol results from hydrolysis of one of the acetate functions of **4**. This compound is then elaborated through a sequence similar to that used in Scheme 1 to produce the key bifunctional intermediate **18**. Through a coupling/deprotection strategy similar to what was used for heterodimer **12**, the trimer **20** can be synthesized. This route is universal and should allow for the synthesis of higher step-growth oligomers.

**Determination of Secondary Structure.** An energy-minimized molecular model[11] of a trimer that adopts a columnar motif due to the three hydrogen bonds between each subunit is shown in Figure 3. The linker used in this model is the 1,8-naphthalenediol-derived linker **I**. Models using linker **II** show a similar structure. Linker **IV**, derived from 2,6-naphthalenediol, serves as a control experiment, being too rigid and linear to allow intramolecular hydrogen bonds to form. An important feature of the models is that they display a folded motif if the linkers are linear alkyl (longer than 10 carbons) like **III** or curved and more rigid like **I** and **II**. The studies below test the importance of a C-shaped, preorganized linker.

Shown in Table 1 is a comparison of the amide $^1H$ resonances for the homodimers **9**−**11** and **13**−**15** and monomer **1**. Of the solvents tested (including acetone, benzene, chloroform, dichloromethane, DMF, and dimethyl sulfoxide), only THF-$d_8$ was able to dissolve each of the compounds listed in Table 1. For linker **I** or **II** with phenethyl side chains, the amide resonances occur around 8 ppm. However, the resonances for dimers with

(11) Molecular modeling was performed using MacroModel v.7.0 and the Amber* forcefield: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

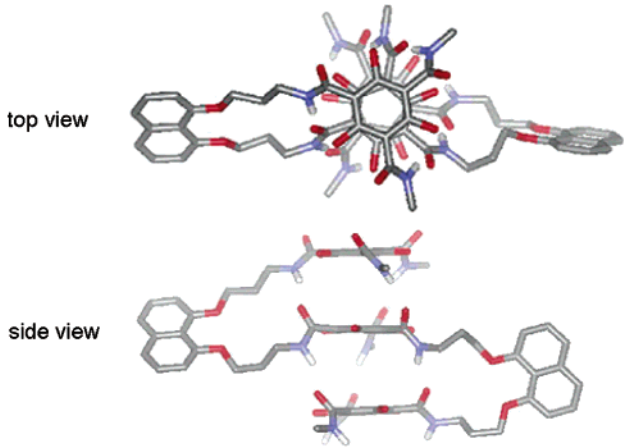



***Figure 3.*** Top and side views of an energy-minimized[11] computer model for a trimer that is tethered with a substituted naphthalene linker. The oligomer folds itself into a columnar conformation in solution (side chains omitted to clarify the view).

***Table 1.*** Amide $^1$H NMR Resonances for **1** and Homodimers **9**−**11** and **13**−**15**[a]

| | | linker | side chain | linker N–H/ppm | nonlinker N–H/ppm |
|---|---|---|---|---|---|
| monomer | **1** | | phenethyl | | 7.18 |
| dimer | **9** | **I** | phenethyl | 8.21 | 8.03 |
| | **10** | **I** | *t*-Bu | 7.63 | 6.67 |
| | **11** | **I** | TDP | 8.07 | 7.81 |
| | **13** | **II** | phenethyl | 8.08 | 7.97 |
| | **14** | **III** | phenethyl | 7.19 | 7.30 |
| | **15** | **IV** | phenethyl | 7.32 | 7.20 |

[a] For **9**−**11** and **13**−**15**, 1 mM, THF-$d_8$, 333 K. For **1**, 2 mM, THF-$d_8$, 333 K.

linkers **III** and **IV** and for the monomer **1** occur ∼1 ppm upfield. The large downfield shifts of amide resonances are diagnostic of hydrogen bond formation. Therefore, the C-shaped linkers with subunits derived from **7** are able to form intramolecular hydrogen bonds while the energetic cost is too great to reorganize the linear alkyl linker **III**.

Also demonstrated by the data in Table 1, the choice of side chain is critical for a folded conformation to be observed in solution. Oligomers initially synthesized employed the phenethyl side chains because they had proven effective in yielding regular columnar assemblies from **1**.[2] The bulkiness of the side chains for dimer **10** is too great, and its amide resonances are shifted upfield relative to **9** and **12** (shown for **12** in Figure 4a).

The tris(dodecyloxy)phenethyl (TDP) side chain was used to impart greater solubility to the oligomers,[12] and its amide resonances are downfield shifted similar to those from the subunit with phenethyl side chains. As an example of the solubilizing power of the TDP side chain, a trimer was initially synthesized with phenethyl side chains and proved to be soluble only below millimolar quantities in dichloromethane. In contrast, trimer **20** with the TDP side chains is soluble beyond 20 mM in dichloromethane.

Another strong indication that there are intramolecular hydrogen bonds in dimers with C-shaped linkers is their solubility profile. **9** and **11**−**13** are freely soluble in chloroform and dichloromethane while dimers with linear linkers (**14**, **15**) are almost insoluble in these solvents due to an extended intermolecular hydrogen bond network being formed.

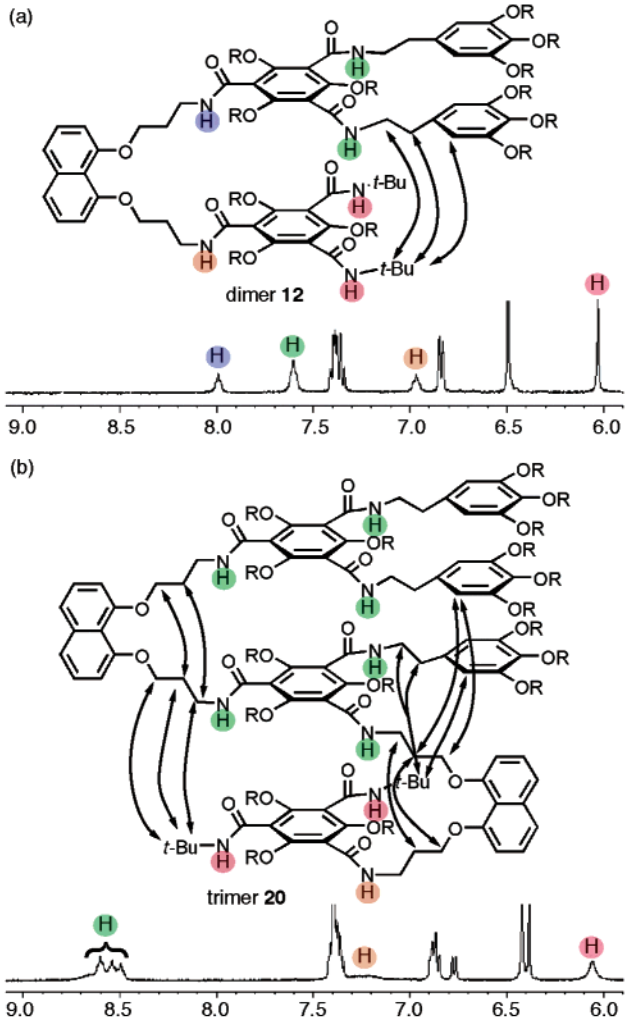



***Figure 4.*** NOE couplings and $^1$H NMR spectra (1 mM in $CD_2Cl_2$, 303 K) for (a) **12** and (b) **20**.

For the heterodimer **12** derived from two different subunits one with TDP and one with *tert*-butyl amide subunits, there are distinct sets of amide resonances, two upfield (∼6−7 ppm) and two downfield (∼7.6−8 ppm) shown in Figure 4a. The downfield amide resonances are derived from the TDP side-chain amides and *one* of the linker amides, and the far upfield-shifted resonances are from the *tert*-butyl amides and the remaining proton on the linker amide. This implies that the *tert*-butyl amides are able to act as the hydrogen bond acceptor through their carbonyls and the TDP amides act as the hydrogen bond donor and that each of the linker amides acts independently as a donor and as an acceptor. Dilution experiments on **12** reveal that its amide resonances are constant (within 0.015 ppm) between 3 and 0.2 mM.

Shown in Figure 4a is the result of a two-dimensional ROESY-NMR experiment for heterodimer **12** in $CD_2Cl_2$.[13] There are three NOE couplings between the TDP side chains (both the aromatic singlet and the two methylenes) and the *tert*-butyl side chains. In molecular models of an extended conformation, these protons are >10 Å from each other, much too far

(12) These side chains have proven useful in solubilizing other discotics; see refs 4i,j.

(13) By the procedure of: Bothner-By, A. A.; Stephens, R. L.; Lee, J.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811−813.

to display through space couplings, but are held ~2.3−2.7 Å apart by the intramolecular hydrogen bonds in the folded conformation.

In the $^1$H NMR spectrum (Figure 4b) for trimer **20**, nine amide protons reside in three sets of peaks. The set of overlapped resonances at 8.5−8.7 ppm is assigned to the six hydrogen-bonded amide protons in the top and middle subunits (the green circles in Figure 4b). Similar to dimer **12**, the resonances for the *tert*-butyl amides are far upfield-shifted, indicating that they are exposed to solvent. The $^1$H NMR spectrum is simple, implying that one conformation dominates the signal. The position of the amide resonances, ~0.6 ppm further downfield compared to similar protons in heterodimer **12**, indicates that the intramolecular amide hydrogen bonds are stronger in the heterotrimer than in the heterodimer. The origin of the strengthened hydrogen bonds is likely due to a cooperative mechanism where two of the subunits coming together preorganizes the system for hydrogen bonding to the third subunit.

Over a dozen unambiguous through-space NOE couplings, indicated in Figure 4b, were obtained for trimer **20** that confirm a folded columnar structure.[6] Dilution experiments for **20** show that its $^1$H NMR resonances are constant (within 0.015 ppm) from 0.2 mM to higher than 8 mM, meaning the trimer is less apt to form intermolecular aggregates than the dimer.

## Conclusion

This study delineates a general method to synthesize a new class of folded oligomers from crowded aromatics. Although, meta-disposed aromatic amides have been shown previously by Hunter to form intermolecular "zipperlike" complexes,[14] it appears unprecedented for them to fold in solution into columnar structures such as those from **12** and **20**. There are two critical ingredients to produce a stable columnar secondary structure from these oligomers: one, the linkers need to hold the subunits in proximity with each other, and two, the side chains need to be relatively unhindered.

Even though oligomers[15] and polymers[16] of discotics have been previously synthesized, the affinity between the subunits is low, and folding does not occur in short polymer strands from substituted triphenylenes.[15] The affinity between the subunits in the oligomers created for this study is high, and even when they are only two subunits long, a well-defined solution conformation results. Unlike most foldamers,[1,5] each subunit of these oligomers is highly substituted and functional. Ongoing studies are derivatizing each subunit differently to see whether columns with programmed functionality can yield tertiary and quaternary structure in solution.

## Experimental Section

**Synthesis.** Synthetic details and characterization for **2**−**20**, diamine linkers **I**−**IV**, and the monoprotected linker from **I** are contained in the Supporting Information.

**$^1$H NMR Experiments from Table 1.** Solutions of homodimer studies were 1 mM in THF-$d_8$ for desired solubility. All spectra taken at 333 K were referenced relative to the isotopic impurity peak in THF-$d_8$ at 3.62 ppm. A small peak present in those spectra around 10.6 ppm originated from the solvent as evidenced by a control $^1$H NMR spectrum of blank THF-$d_8$. One-dimensional $^1$H NMR spectra of heterodimer **12** and trimer **20** were taken in $CD_2Cl_2$ at 1 mM and 303 K and were referenced relative to the isotopic impurity peak in $CD_2Cl_2$ at 5.36 ppm.

**COSY and ROESY Experiments.** Two-dimensional $^1$H NMR spectra were obtained on a Bruker DRX-500 spectrometer using standard Bruker pulse sequences, and the data were processed with Bruker XWin-NMR version 3.1 software. One-millimolar samples of dimer **12** and trimer **20** in $CD_2Cl_2$ were degassed by freeze−pump−thaw cycles[17] and placed in sealed NMR tubes. Proton signals were assigned from COSY[18] and ROESY[13] spectra. ROESY spectra were recorded with a mixing time of 250 ms and 54−62 scans. The COSY and ROESY spectra are given in the Supporting Information for **12** and **20**.

**Acknowledgment.** We acknowledge financial support from the Chemical Sciences, Geosciences and Biosciences Division, Office of Basic Energy Sciences, U.S. D.O.E. (DE-FG02-01ER15264) and U.S. National Science Foundation, Nanoscale Exploratory Research Grant (DMR-01-02467). This work is supported in part by the Nanoscale Science and Engineering Initiative of the National Science Foundation under NSF Award Number CHE-0117752. C.N. thanks the Beckman Young Investigator Program (2002) and the Dupont Young Investigator Program (2002). We thank Dr. Y. Itagaki (Columbia University) for assistance with the mass spectrometry.

**Supporting Information Available:** Preparation of **2**−**20**; COSY and ROESY NMR spectra for **12** and **20** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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(14) Bisson, A. P.; Carver, F. J.; Eggleston, D. S.; Haltiwanger, R. C.; Hunter, C. A.; Livingstone, D. L.; McCabe, J. F.; Rotger, C.; Rowan, A. E. *J. Am. Chem. Soc.* **2000**, *122*, 8856−8868.

(15) For a dimer from a traditional discotic, see: Tsukruk, V. V.; Bengs, H.; Ringsdorf, H. *Langmuir* **1996**, *12*, 754−757.

(16) For examples of discotic polymers, polymerized through their side chains, see: (a) Wang, T.; Yan, D.; Zhou, E.; Karthaus, O.; Ringsdorf, H. *Polymer* **1998**, *39*, 4509−4513. (b) Weck, M.; Dunn, A. R.; Matsumoto, K.; Coates, G. W.; Lobkovsky, E. B.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2741−2745.

(17) By the method of: Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*; Pergamon: Amsterdam, 1999.

(18) By the procedure of: Rance, M.; Sorenson, O. W.; Bodenhausen, G.; Wagner, G.; Ernst, R. R.; Wüthrich, K. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 479−485.