ORGANIC LETTERS

2006
Vol. 8, No. 22
5117−5120

Improving Foldamer Synthesis through Protecting Group Induced Unfolding of Aromatic Oligoamides

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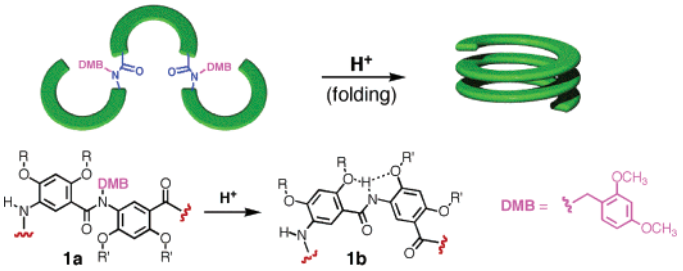
Received August 25, 2006

ABSTRACT



The hydrogen bond rigidified backbones of aromatic oligoamides are temporarily interrupted by replacing the amide hydrogens with the acid-labile 2,4-dimethoxybenzyl (DMB) group, which allows the efficient preparation of long folding oligomers that, upon removal of the DMB groups, fold into multiturn helices.

Unnatural folding oligomers, or foldamers, have attracted intense interest lately.[1−8] On the basis of backbone rigidification, we[9−11] and others[12−15] reported folding aromatic oligoamides in recent years. The folding oligomers we developed are forced into well-defined crescent or helical conformations by a three-center hydrogen bond.[16] The folded conformations of these molecules are particularly stable in various solvents and at elevated temperatures. Our oligoamide foldamers represent one of the few helical foldamer systems containing large, well-defined nanocavities with systematically tunable sizes.[17] Depending on its chain length,

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10.1021/ol062103d CCC: $33.50
Published on Web 10/05/2006

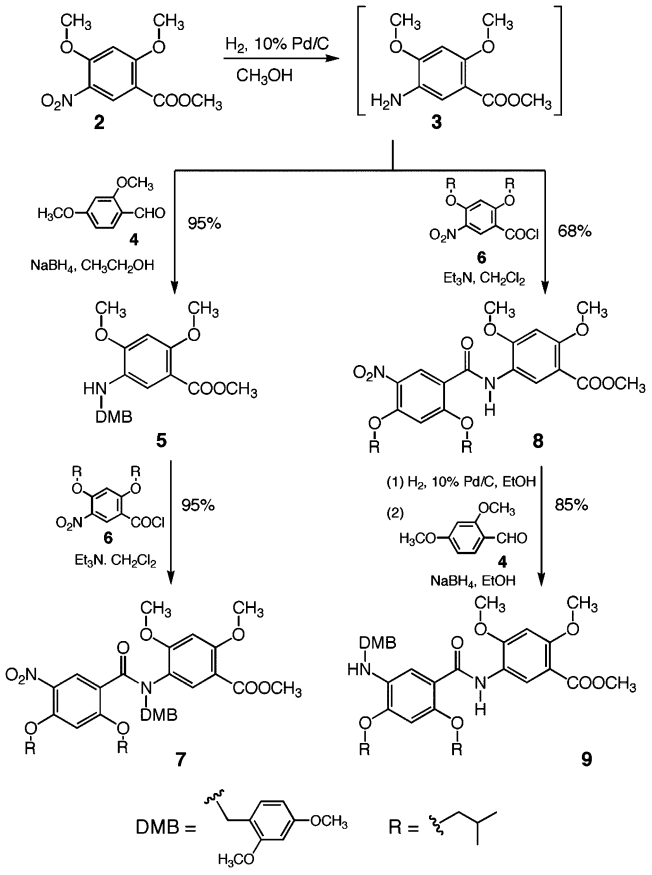
an oligomer can be regarded as either a broken "macrocycle" that can act as a receptor for cation and polar molecules or a folding helical nanotube that may find applications in designing pores and channels as well as receptors.

Efficient synthesis of relatively short oligomers that fold into crescents or helices of less than two turns has been developed by us.[18] However, the preparation of longer oligomers was met with increasing difficulty as the chain length extends. This is likely due to steric hindrance introduced by the folded (helical) conformation of the corresponding oligomers. One likely solution is to alter the folded conformation. This may be realized by replacing the amide hydrogen atoms with a protecting group that can be removed later, which interrupts the intramolecular H-bonding that rigidifies the backbone.

Thus, as shown by **1a**, when an amide hydrogen is replaced with the acid-labile 2,4-dimethoxybenzyl (DMB) group,[19] a modified amide group lacking the backbone-rigidifying intramolecular H-bond is obtained. Removing the DMB group with an acid such as trifluoroacetic acid (TFA) should restore the three-center H-bond, leading to **1b** that adopts the H-bond-enforced conformation.

Scheme 1 shows the synthesis of DMB-modified **7** and **9**. Hydrogenation of **2** led to amine **3**, which was treated with

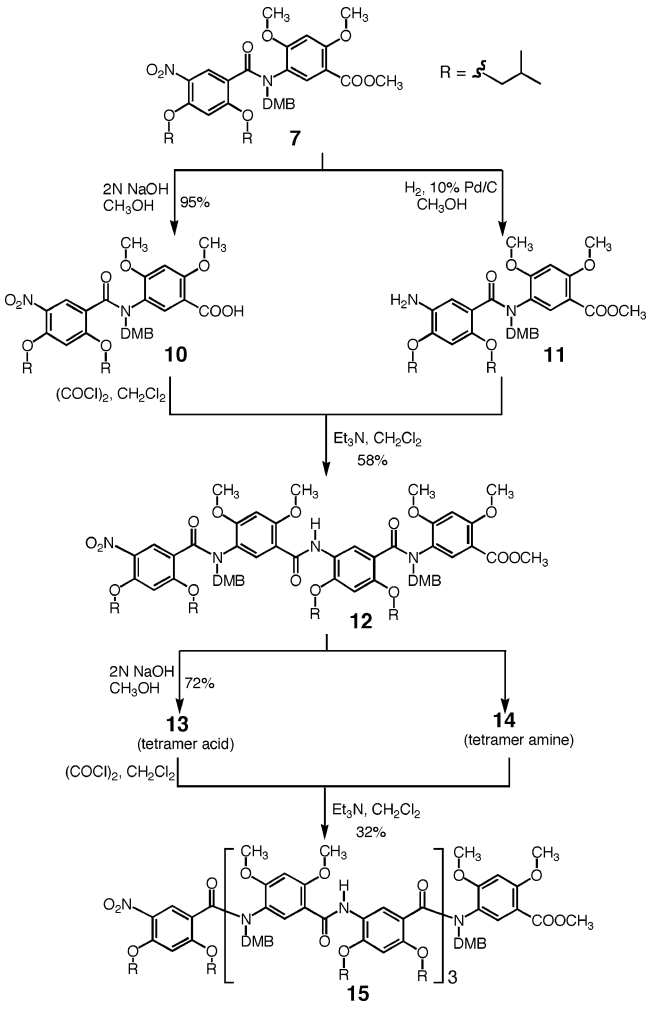
Scheme 1



the commercially available aldehyde **4**, leading to the intermediate Schiff base that was reduced with $NaBH_4$ into **5**. Acylating **5** with acid chloride **6** led to **7**, in which the DMB group is placed between two monomer units. Dimer **9**, with a DMB group at its N-terminus, was prepared by treating **3** with acid chloride **6**, leading to **8** that was converted into **9** by hydrogenation followed by reductive amination.

The DMB-modified monomer **5**, together with **7** and **9**, allows the efficient preparation of oligomers with DMB groups placed on the oligoamide backbones. As shown by Scheme 2, the DMB-modified **7** was converted into acid **10**

Scheme 2



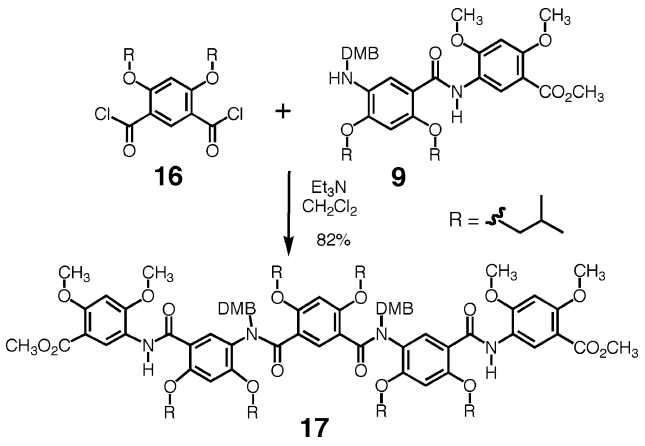
by hydrolysis and into amine **11** by hydrogenation. Acid **10** was converted into its acid chloride that was coupled to **11**, leading to tetramer **12**. Hydrolysis and hydrogenation of **12** led to the acid **13** and the amine **14**, respectively. Coupling **13** and the acid chloride of **14** led to octamer **15** in an isolated yield of 32%.

(18) Yuan, L. H.; Sanford, A. R.; Feng, W.; Zhang, A. M.; Zhu, J.; Zeng, H. Q.; Yamato, K.; Li, M. F.; Ferguson, J. S.; Gong, B. *J. Org. Chem.* **2005**, *70*, 10660.

(19) N-Substitution of a secondary amide by the 2,4-DMB group was reported to induce a conformational change that promoted ring-closing metathesis. See: Creighton, C. J.; Reitz, A. B. *Org. Lett.* **2001**, *3*, 893.

Surprisingly, hydrogenation of octamer **15** under various conditions, such as elevated temperatures and increased pressure, failed to reduce the nitro group into the desired amino group. Efforts to crystallize **15** have not succeeded. Instead, single crystals of **7**, and those of pentamer **17** (Scheme 3), were obtained. These crystal structures provide

Scheme 3



insight into the unexpected difficulty encountered in the seemingly straightforward reduction of **15**.

In the crystal structures of **7** and **17**, the presence of the DMB groups leads to crowded conformations. To avoid steric hindrance due to the presence of the DMB group, the two benzene rings attached to the amide carbonyl group and the N atom are almost perpendicular to the plane of the amide group. In the structure of **7**, the ester group sits in between the aromatic rings of the aniline and the benzyl moieties, whereas the nitro group is more exposed. For **17**, the two tertiary amide groups, with their DMB groups, lead to an overall zigzagged conformation. Instead of being in close proximity as would be expected from the corresponding folded pentamer with a H-bond-rigidified backbone, the two ester groups point away from each other. In the solid-state structures of both **7** and **17**, the DMB-modified tertiary amide groups adopt the cis conformation.

The structures of **7** and **17** (Figure 1) suggest that a proper combination of DMB-modified and H-bonded amide groups is necessary to expose the termini of an oligomer. Too many DMB groups may result in an overcrowded structure that prevents the reacting group from being shielded away from the catalyst and other reagents. It is reasoned that, to expose the end group(s), one DMB group should be incorporated for every three to five residues, which should lead to a modified oligomer with short H-bond-rigidified segments segregated by DMB-modified amide groups.

Several oligomers bearing one DMB group were prepared in good yields (Scheme 4). Tetramer **19** was prepared by coupling the acid chloride and the amine derived from **10** and **18**. Starting from **19**, acid chlorides **20** and **6** were sequentially coupled to the corresponding precursor oligomers, which afforded pentamer **21**, hexamer **22**, and hep-

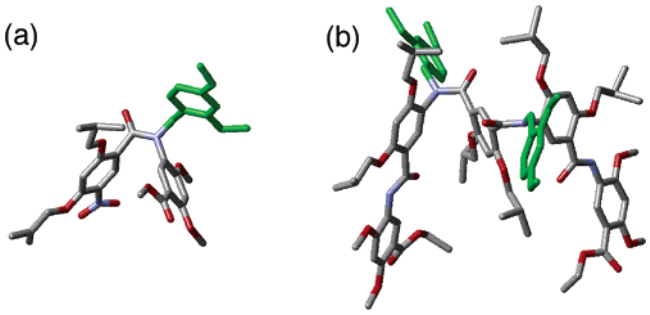
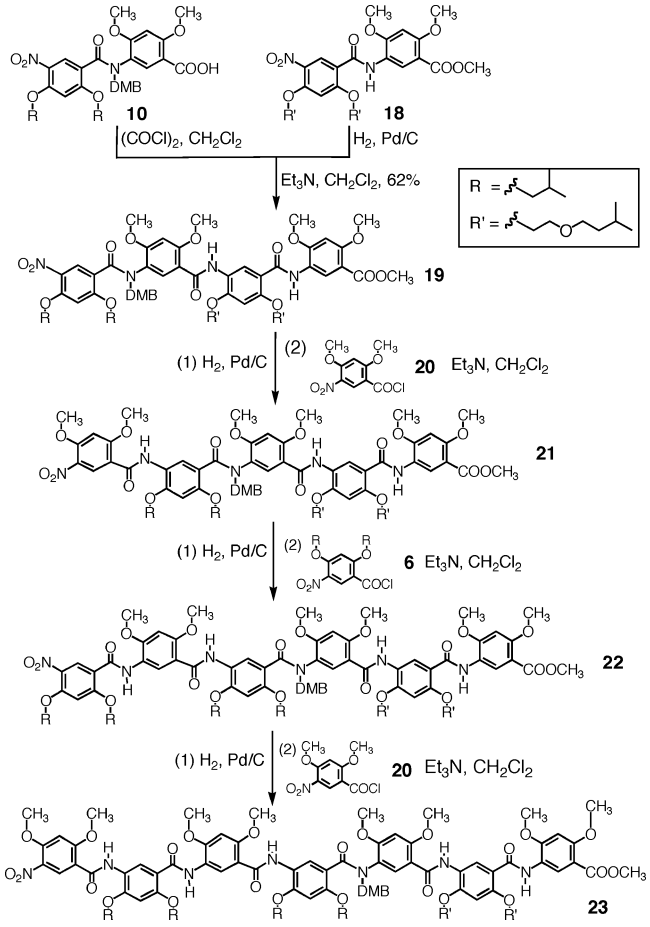


Figure 1. Crystal structures of DMB-modified (a) dimer **7** and (b) pentamer **17**. The DMB group is shown in green. The H atoms are removed for clarity.

tamer **23**. Compared to the aromatic oligoamides lacking the DMB group, which often show poor solubility when carrying short alkyl side chains, oligomers **19** and **21**−**23** all have excellent solubility in nonpolar and polar solvents such as CH_2Cl_2, $CHCl_3$, and DMSO. As the chain length extends, the coupling efficiencies showed only small changes. These results suggest that removing the three-center H-bond from just one of the amide groups of an otherwise backbone-

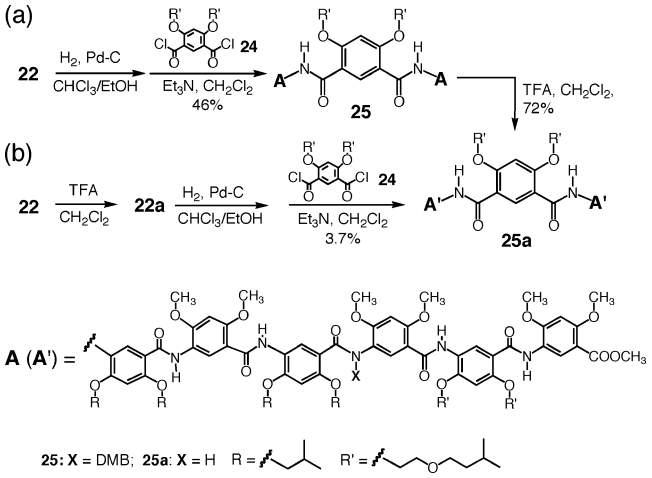
Scheme 4



rigidified oligomer can significantly alter its property by altering the flat oligoamide backbone.

To probe the efficiency of preparing longer oligomers from DMB-modified precursors, a convergent route[18] involving the coupling of an amino-terminated oligomer to a diacid was adopted. As shown in Scheme 5a, hexamer **22**, after

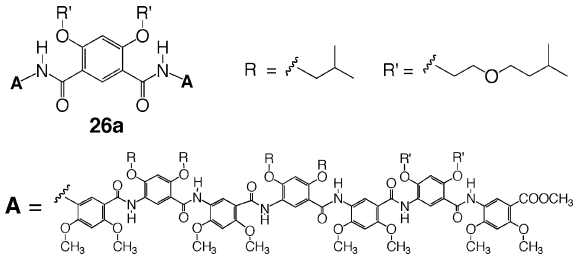
Scheme 5



being reduced into its amino analogue, was treated with 0.5 equiv of diacid chloride **24**. Symmetrical 13mer **25** was obtained in 46% yield. The two DMB groups of **25** were then removed in CH_2Cl_2 using trifluoroacetic acid (TFA), which led to backbone-rigidified 13mer **25a** that should fold into a helix with ~2 turns[11] in 72% yield.

The efficiency of the strategy involving DMB-modified oligomers was also demonstrated by preparing 13mer **25a** on the basis of an alternative route (Scheme 5b). In this case, the DMB group of **22** was removed first, leading to **22a** that should adopt a rigidified, nearly flat and crescent conformation in which the two termini lie in close proximity. Hexamer **22a** was then reduced, followed by coupling to **24**, which led to **23a** in a very poor (3.7%) yield. Repeating the same coupling led to similar low yields. This is in sharp contrast to the yield of 13mer **25** and the overall yield of **25a** shown in Scheme 5a, which suggest that for a folded oligomer precursor of a sufficient length (~1 turn) steric hindrance indeed played a major role in retarding its reactivity. Obviously, in this case (Scheme 5b), the H-bond-rigidified conformation of oligomer **22a** is not in rapid equilibrium with an unfolded state, such as the scenario described by the Curtin−Hammett principle that would lead to an efficient formation of **25a**. This conclusion is also consistent with our previous observation[11] that this class of backbone-rigidified foldamers adopts a very stable, folded conformation.

On the basis of the same procedures shown in Scheme 5a, coupling the amino-heptamer derived from **23** to diacid chloride **24** led to 15mer **26**. The DMB groups of **26** were then removed, giving backbone-rigidified 15mer **26a**, which should fold into a helix of ~2.5 turns, in a satisfactory overall yield.[20]



In the ^{1}H NMR spectrum of **22a**, the signals of the amide (9.5−10.5 ppm) and the aromatic (6.2−6.8 and 8.6−9.3 ppm) protons are well-resolved,[20] which are the same as those of the backbone-rigidified folding oligoamides we reported.[9−11] Comparing the aromatic and amide proton signals of **25a** and **26a** to those of **22a** shows that the signals of the longer oligomers are increasingly overlapped and broadened.[18,20] Nevertheless, the corresponding aromatic and amide protons of **25a** and **26a** still appear in the same regions as those of **22a**,[20] suggesting that **25a** and **26a** are also rigidified and therefore fold in the same way as shorter oligomers. A two-dimensional (NOESY) ^{1}H NMR spectrum of **26a** shows extensive NOEs between the amide and alkoxy protons,[20] which further support the presence of the three-center H-bonds and thus the folded conformation.

Oligomer **26a** represents the longest meta-linked oligoamide we have prepared. Before adopting the current strategy, the longest meta-linked aromatic oligomer of this series that we prepared was a symmetrical undecamer.[11] Given the efficiency demonstrated in the preparation of the oligomers and the good solubility and reactivity of the DMB-modified precursors and with further optimized reaction conditions, it is expected that much longer oligomers will be prepared. This strategy of conformation−alteration should also facilitate the preparation of folding aromatic polyamides, which has been hampered by the exclusive formation of macrocycles.[21]

Acknowledgment. Grateful acknowledgment is made to the NSF (CHE-0314577 to B.G.) and ONR (N000140210519 to B.G.) for support.

Supporting Information Available: Synthetic procedures and 1D and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062103D

(20) See Supporting Information for details.

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