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Synthesis of Crescent Aromatic Oligoamides

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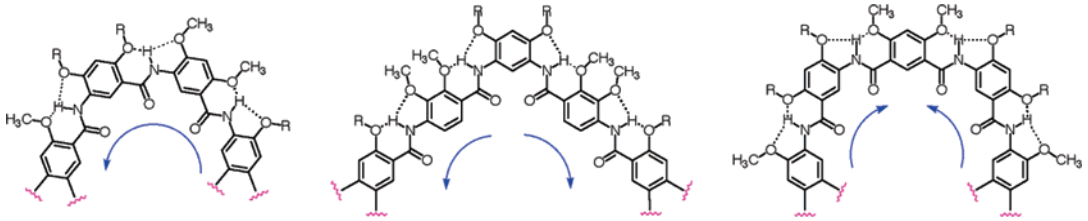

This article describes the synthetic procedures for the preparation of crescent (and helical) aromatic oligoamides developed in recent years in our laboratory. The large-scale preparation of a variety of monomers derived from various tetrasubstituted benzenes is presented. Three different strategies for constructing various oligomers consisting of meta- and meta/para-linked benzene residues are discussed. Factors affecting coupling efficiency and yields are analyzed. The developed synthetic methods have provided the basis for the preparation of longer oligomers and for the development of solid-phase synthesis.

Introduction

Intense interest in constructing foldamers, first coined by Gellman,[1] with well-defined secondary structures triggered the design and synthesis of a large number of artificial systems[1−4] such as aliphatic α-, *β*-, *γ*-, and *δ*-peptides,[4−13] and single-stranded and multistranded abiotic oligomers.[14−16] The challenges for folding synthetic oligomers include the ease of synthesis, folding stability, tunability, and the control of conformational changes under different environmental conditions that enable the

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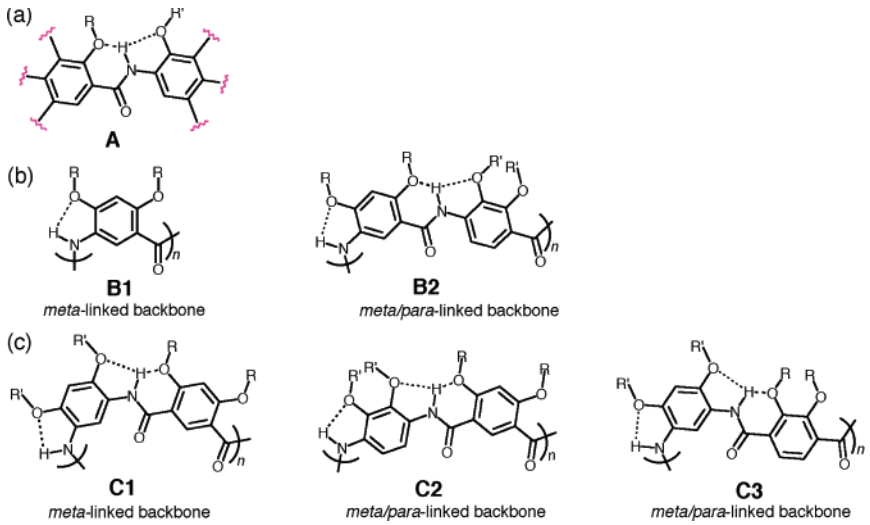

FIGURE 1. Design of backbone-rigidified aromatic oligoamides. (a) The three-center hydrogen bond that enforces the folding of the designed oligamides. (b) Oligoamides consisting of meta- (**B1**) or *meta*/*para*-linked (**B2**) aminobenzoic acid residues. (c) Oligoamides consisting of meta-linked diacid and diamine residues (**C1**), para-linked diamine and meta-linked diacid residues (**C2**), and meta-linked diamine and para-linked diacid residues (**C3**).

molecules to adopt various secondary structures or to undergo host−guest complexation.[17,18] Among the reported foldamer systems, aromatic oligoamides seem to be one class of promising candidates to satisfy many of these requirements,[19] some of which have already displayed interesting activities.[20,21]

Aromatic oligoamide foldamers were constructed based on anthranilic acids,[22,23] pyridines,[24,25] pyridine oxides,[22] pyrazines,[26] and so on. A few less studied aromatic oligomers were designed based on ureas[27] or hydrazides[28] without amide linkages. β-Sheetlike structures[29] and well-defined molecular duplexes[4,30−32] were established based on the combination of both α-peptide backbone and aromatic rings with alkoxy substituents to form adjacent hydrogen bonding.[29]

In recent years we reported a class of oligoamides with backbones that adopt well-defined, crescent conformations.[4,19,35−38] These oligomers are based on aromatic oligoamide backbones consisting of benzene rings that are meta- or meta/para-linked by secondary amide groups. The presence of a particularly robust three-center hydrogen bond[4a,36] involving each of the amide groups of these molecule leads to the rigidification of the amide linkages and thus the oligoamide backbone. As shown by general structure **A** (Figure 1a), the three-center H-bonds are introduced by placing ether oxygens in the vicinity of each amide hydrogen, leading to the formation of a three-center H-bond consisting of five- and a six-

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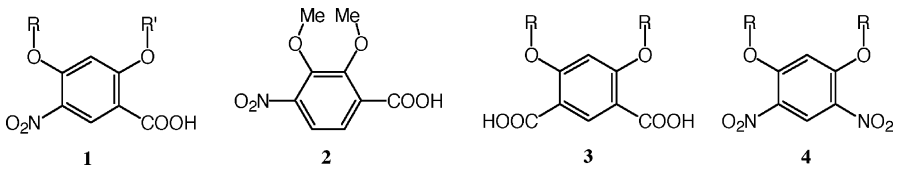

FIGURE 2. Building blocks prepared for constructing backbone-rigidified aromatic oligoamides.

membered H-bonded rings. Such backbone rigidification results in a crescent or helical conformation depending on the length of the oligomer. The aromatic oligoamides can be (1) oligomers consisting of building blocks derived from (*m*- or *p*-)aminobenzoic acids (Figure 1b), (2) co-oligomers of (*m*- or *p*-)benzenedicarboxylic acids and (*m*- or *p*-)phenylenediamines (Figure 1c), or (3) oligomers with backbones that mix the above two designs and the corresponding building blocks.

One unique feature of our oligoamide foldamers is the tuning of their interior and exterior diameters. This has been achieved by simply varying the ratio of meta- and para-linked benzene rings in an oligomer (e.g., **B2**, **C2**, and **C3** in Figure 1). The higher the ratio of the para-linked building blocks in an oligomer, the less curved the corresponding backbone and thus the larger the diameters. These backbone-rigidified foldamers are one of the few helical foldamer systems with large, well-defined, and systematically tunable interior cavity sizes (~10 and 30 Å).[35−38]

The successful synthesis of these foldamers relies on two factors: (1) efficient preparation of large quantities of building blocks (monomers) and (2) feasible strategies for coupling the building blocks and/or segments into oligomers of various length. In this paper we present a detailed account of the synthesis of these backbone-rigidified aromatic oligoamides.

We have established the efficient preparation of four different types of building blocks (Figure 2). These are synthesized based on our own methods, or by modifying precursors prepared based on previously reported procedures (**2**, **3**, **4**).[4,19,31,33,34,39−43] Compounds **1**−**3** have been prepared in 100-g quantities and **4** was obtained in multigram quantities. The nitro group of these monomers serves as the equivalent of a protected amino group and is converted into the latter by catalytic hydrogenation before oligomer synthesis.[41] These building blocks have been incorporated into the corresponding oligomers in a variety of different combinations, leading to crescent oligoamides with backbones of various curvatures and cavity sizes.[36−38]

Three strategies have been adopted for constructing oligomers.[13,14,19] One involves unidirectional chain growth by stepwise coupling of monomers derived from aminobenzoic acid (by reducing **1** and **2**), leading to "unsymmetrical" oligomers with two different (N and C) termini

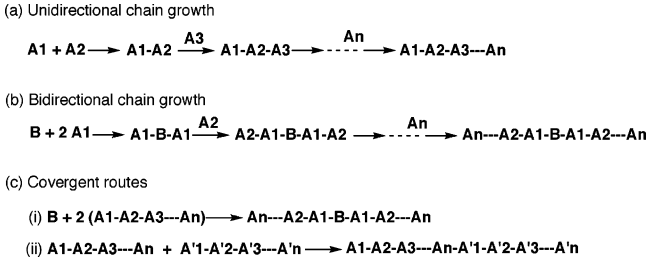

FIGURE 3. Coupling strategies for constructing folding aromatic oligoamides.

(Figure 3a). The second strategy starts chain growth by coupling monomers to a symmetrical central unit (Figure 3b). This bidirectional chain growth leads to symmetrical oligomers with two identical termini. The third strategy includes two possible convergent routes (Figure 3c): (1) two identical oligomer segments can be coupled with a symmetrical central residue, leading to symmetrical oligomers with two identical halves, and (2) two oligomer segments are coupled into a longer unsymmetrical oligomer.

Results and Discussion

A. Preparation of Building Blocks. Monomeric building blocks **1**−**4** (Figure 2) corresponding to meta- and para-linked residues have been prepared. These building blocks have been used extensively in constructing various oligomers that are described in this paper.

(1) Building Blocks 1. Two groups of building blocks **1** were prepared starting from the commercially available 2,4-dihydroxybenzoic acid. One group carries identical side chains (R = R′), and the other group bears two different side chains (R ≠ R′ = CH_3).

As shown in Scheme 1, nitration of 2,4-dihydroxybenzoic acid followed by esterification in methanol provided methyl ester **6** in a total yield of ~60%. Alkylation was carried out with the corresponding bromides or tosylate in DMF at 100 °C in the presence of K_2CO_3. Hydrolysis of the esters **7a**−**e** with aqueous NaOH or KOH followed by acidification led to acids **1a**−**e**.

Since ester **7f** contained two *tert*-butyl ester groups that are labile under strongly basic conditions, LiOH was employed for its hydrolysis. The hydrolysis in methanol was carried out for 15−18 h at room temperature, leading to the desired acid **1f** in a yield of 79%. It was noteworthy that longer reaction time may decrease the yield of **1f** with the removal of one or both *tert*-butyl groups. These side products were also observed when bases other than LiOH were used. For instance, with 4 equiv of NaOH, after the reaction mixture was stirred for 8 h at room temperature, the crude product was found to be a mixture containing two mono-*tert*-butyl esters, a triacid, and the desired product **1f** that was obtained in a yield of less than 20%. Among NaOH, LiOH, and $Ba(OH)_2$, only LiOH

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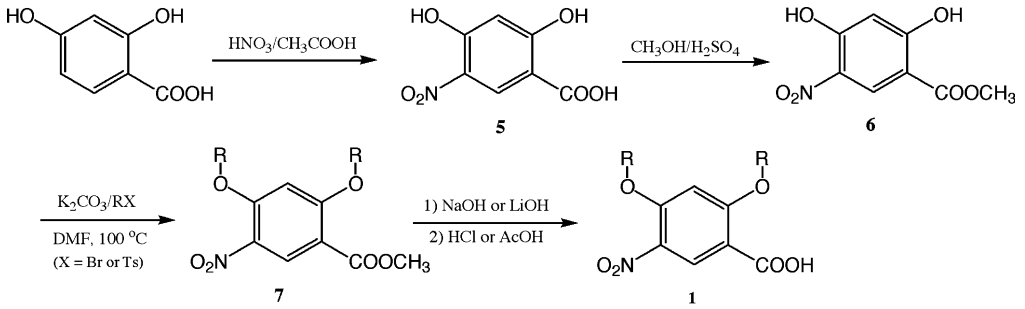
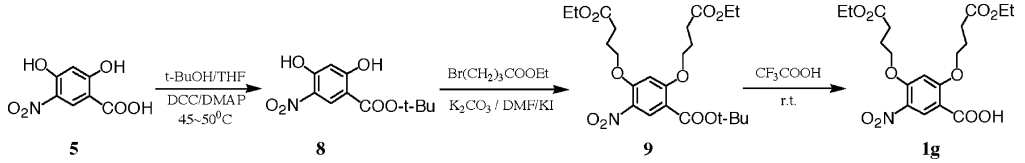
SCHEME 1. Synthesis of Building Blocks 1

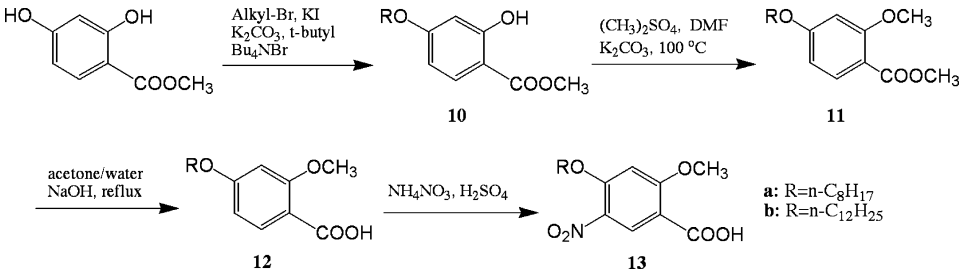


a: R = -CH_3; **b**: R = *n*-C_8H_{17}; **c**: R = *n*-$C_{12}H_{25}$; **d**: R = *i*-$CH_2CH(CH_3)_2$; **e**: R = -$(CH_2CH_2O)_3CH_3$; **f**: R = -$(CH_2)_3$COO-*t*-Bu

SCHEME 2. Synthesis of Building Block 1g



SCHEME 3. Synthesis of Building Blocks 13



gave a major spot on TLC (condition: 3.5−4 equiv of LiOH; 18 h at room temperature). In this case, controlling reaction time is crucial for the selective hydrolysis of the methyl ester while avoiding cleaving the *tert*-butyl ester groups. Due to the sensitivity of the *tert*-butyl ester groups to acid,[44] about 1 equiv of acetic acid (based on the amount of LiOH) was used to acidify the reaction mixture after the hydrolysis of **7f**.

We have also prepared monomer **1g**, which carries two ethyl ester groups on its side chains (Scheme 2). Due to the similar reactivity of ethyl and methyl esters, methyl benzoate such as **6** cannot serve as a precursor for **1g**. The preparation of **1g** was realized via *tert*-butyl benzoates **8** and **9**.

The purity of acid **5** was found to be crucial for the successful preparation of *tert*-butyl ester **8**. The presence of even a trace amount of nitric acid (from the nitration step, see Scheme 1) in acid **5** led to a rather low yield (<15%) of **8**. Acid **5** of high purity can be obtained from its methyl ester **6** (Scheme 1), which was easily collected by filtration as a white solid. Hydrolysis of ester **6** provided the pure acid **5** as a white powder.

In addition to preparing building blocks of type **1** that carry two identical side chains, reaction conditions for preparing acids **13a** and **13b**, which carry two different side chains, have also been established. As shown in Scheme 3, instead of bearing two identical alkoxy groups on the same residue, **13a**,**b** bear a methoxy and another alkoxy group on the same benzene ring. The synthesis began with the alkylation of methyl 2,4-dihydroxybenzoate by adding 1.1 equiv of the alkyl bromide (or tosylate) in the presence of K_2CO_3, potassium iodide, and tetrabutylammonium bromide (or chloride). It was found that, under the above reaction conditions, the alkylation with alkyl bromide occurred preferentially at the hydroxyl group that is para to the methyl ester group, leading to **10a** and **10b**. Methylation of the remaining OH group was realized by using dimethyl sulfate in DMF, leading to esters **11a** and **11b**. Hydrolysis of esters **11a** and **11b** led to acids **12a** and **12b** by refluxing in acetone/NaOH (1 M) followed by acidification. The resulting acids were then nitrated by dissolving in concentrated H_2SO_4 and then adding 1.1 equiv of ammonium nitrate over 20 min at 0 °C. The precipitated pure products **13a**,**b** were collected by filtration in around 95% yield.

(2) Building Block 2. This compound was prepared by methylating the methyl esters of the known 2,3-dihydroxy-4-nitrobenzoic acid.[44,45] The resulting 2,3-dimethoxy-4-nitrobenzoate was hydrolyzed into the corresponding acid **2**.

(3) Building Blocks 3. These building blocks were synthesized starting from 4,6-dihydroxyisophthalic acid[31,33] **14** (Scheme 4a). Alkylation of diester **15** led to esters **16a**−**f**, which were converted into acids **3a**−**f** by hydrolysis.

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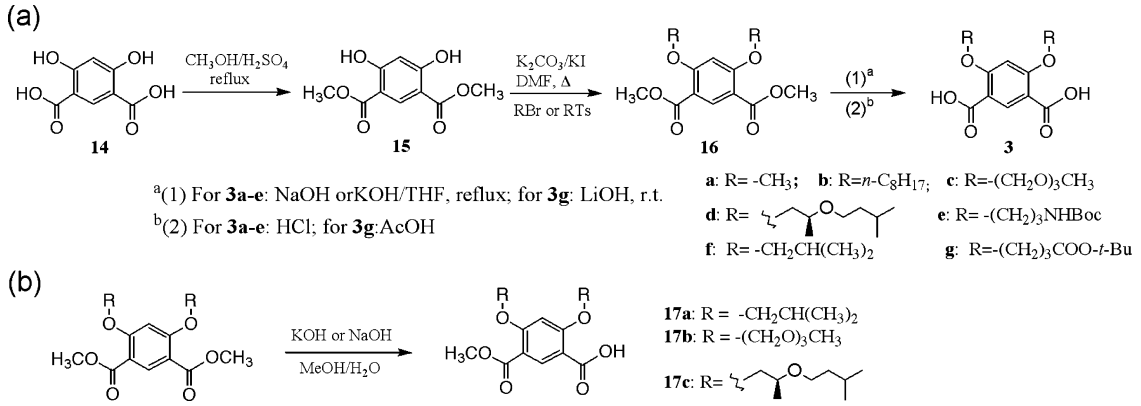
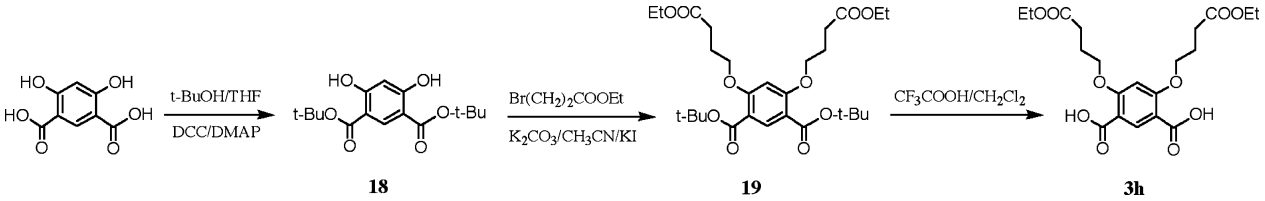
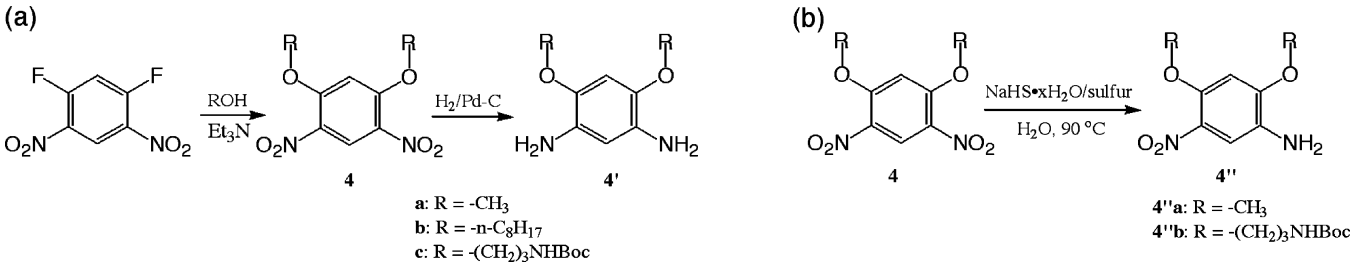
SCHEME 4. Synthesis of Building Blocks 3 and 17



SCHEME 5. Synthesis of Building Block 3h



SCHEME 6. Synthesis of Building Blocks 4, 4′, and 4″



The hydrolysis of ester **16g** with similar conditions for hydrolyzing **7g** (see Scheme 1) failed to give diacid **3g** as the major product. Among the separated products the one with only one methyl ester hydrolyzed was the major product (72%), together with a small amount of **3g** (5%) and the fully hydrolyzed tetraacid (10%). With shorter reaction time (15 h) the yield of **3g** was raised to about 15% but a significant amount of unreacted **16g** (26%) was recovered.

Partially hydrolyzing dimethyl esters **16** led to monomethyl ester acids **17a**−**c** (Scheme 4b). These are very useful intermediates for coupling steps that need to distinguish the two carboxyl groups of diacids **3**.

As shown in Scheme 5, monomer **3h**, with two base-labile ethyl ester groups on its side chains, was prepared by first treating the diacid with *tert*-butyl alcohol, which led to the di-*tert*-butyl ester **18** in a moderate yield (55%). Alkylating **18** with ethyl 3-bromopropionate in acetonitrile in the presence of K_2CO_3 and KI results in **19** (84%). Removing the *tert*-butyl groups of **19** with trifluroacetic acid provided the desired diacid **3h** in a total yield of 43.6%. The product was purified by simple recrystallization from EtAc/*n*-hexane (1:6).

(4) Building Blocks Based on 4. The ethers (**4a**−**c**) of dinitroresorcinols were prepared by treating the corresponding hydroxy compounds and the commercially available 1,3-difluoro-4,6-dinitrobenzene based on published procedures (Scheme 6).[46]

Dinitro compounds **4a**−**c** were converted into diamines **4′a**−**c** by catalytic hydrogenation. After removing solvent (methanol or DMF), the air-sensitive **4′a**−**c** were handled under an inert atmosphere (N_2 or Ar) and were usually used immediately in the subsequent coupling steps.

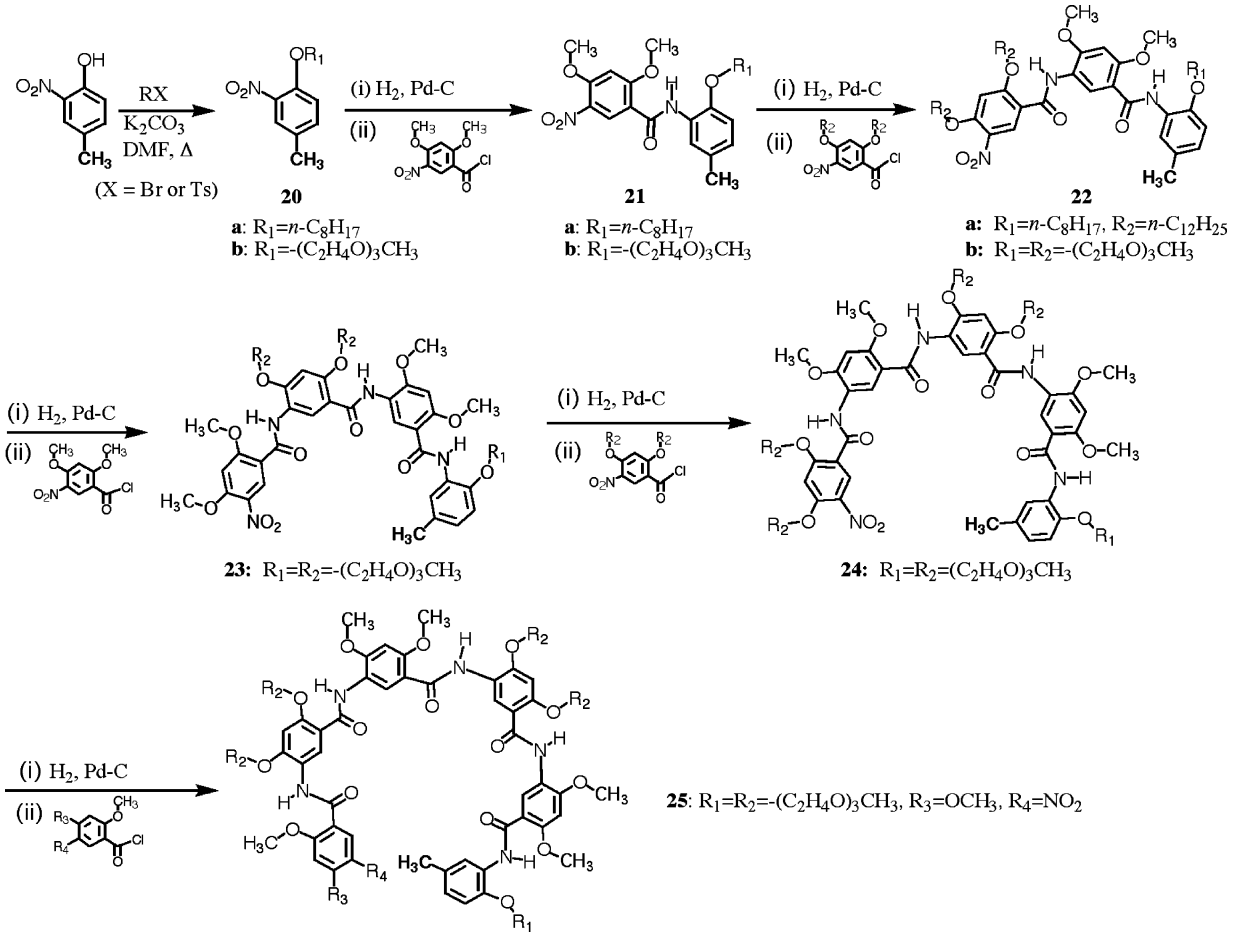
Selectively reducing one of the two nitro groups of **4a** with use of polysulfide ($NaSH{\cdot}xH_2O$ + sulfur) led to 2,4-dimethoxy-5-nitroaniline **4″a** in high (83%) yield.[15] The same procedure was used for the selective reduction of **4c**, leading to **4″b** (78%), which is indispensable for the stepwise construction of oligomers involving diacid and diamine building blocks.

B. Synethesis of Oligomers. The combination of meta- and para-disubstituted building blocks leads to oligomers with different curvatures that are determined by the ratio of meta- and para-linked residues. Depending on the orientations of the amide linkages, oligomers with either unsymmetrical or symmetrical backbones are obtained.

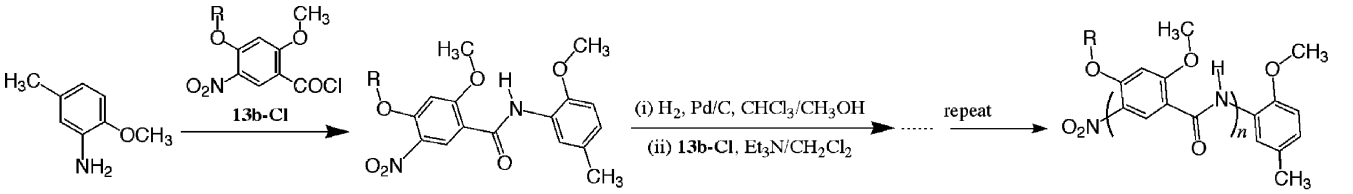
(1) Unidirectional, Stepwise Coupling. Coupling of substituted aminobenzoic acids (masked as nitrobenzoic acids) or their corresponding acid chlorides in a stepwise fashion leads to oligomers with amide linkages that orient in the same direction, resulting in oligomers with unsymmetrical (from the C to the N termini) backbones.

(46) Lehmann, F. P. A. *Tetrahedron* **1974**, *30*, 727.

SCHEME 7. Unidirectional Chain Extension Based on the Coupling of Acid Chlorides and Amines



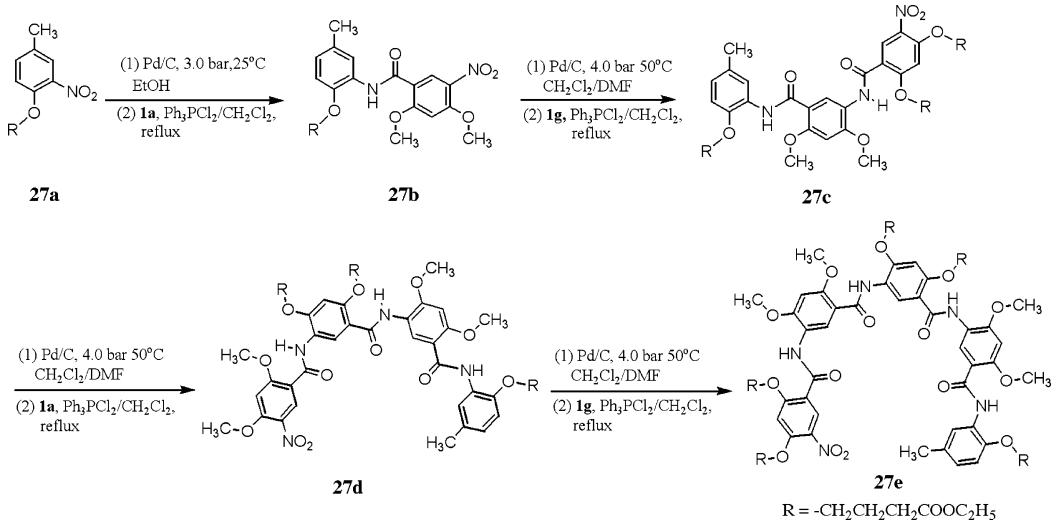
SCHEME 8. Unidirectional Chain Extension of Oligomers Consisting of the Same Residue 13b



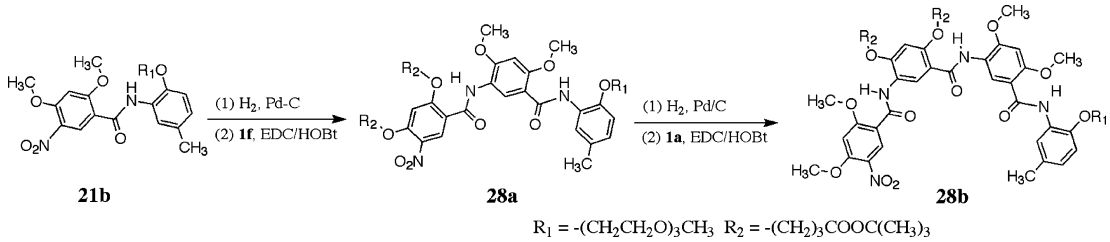
(i) Coupling of Acid Chlorides and Amines. This coupling strategy involves the incorporation of monomers **1** via their acid chloride[35] form (Scheme 7). The monomer acid chlorides were generated by treating the corresponding acids with thionyl chloride or oxalyl chloride. The preparation of a number of unsymmetrical oligomers from dimers **21** to hexamers **25** is shown in Scheme 7 to illustrate the stepwise coupling reactions. Yields of each coupling step ranged from 50% to 90%.

Due to the concern of undesirable steric interactions between bulky side chains flanking an amide group, residues carrying methyl with other bulkier side chains were placed on alternating residues along the backbones of the corresponding oligomers. This requires at least two different monomer acids or acid chlorides. With monomers such as **13a** or **13b** that carry a methyl and another bulkier side chain, homooligomers can be easily constructed by the repetitive coupling of the same building block. For example, starting from the commercially available 2-methoxy-5-methylaniline, homooligomers **26a**−**g** were constructed by the stepwise coupling of **13b** (via the corresponding acid chloride **13b-Cl**) to the amino-terminated oligomer intermediates (Scheme 8), which were generated by the hydrogenation of the nitro-terminated oligomers. Yields for each coupling step ranged from 60% to 80%. Generally, for each unit added to the oligomer chain, an additional 5 °C, as well as an additional 30 min of reaction time, was required for the completion of the reduction of the terminal nitro group. This trend plateaued at a reaction time of 4 h and a reaction temperature of 57 °C for oligomers beyond the hexamer. The reason behind this could be the increased bulkiness of the oligomers and thus the inaccessibility of the nitro groups upon the extension of the oligoarylamide chain. Solubility for all species of this series was good in chloroform. Of note, however, is octamer **26g**, which exhibited an NMR spectrum of very broad signals. This was probably due largely in part to the strong

SCHEME 9. Unidirectional Chain Extension with Ph_3PCl_2 as the Coupling Agent



SCHEME 10. Synthesis of Oligomers Containing Acid-Sensitive Side Chains



intermolecular aggregation of **26g** due to the large, well-defined aromatic surface formed by the helical conformation of this oligomer.

The purification of **26a**−**g** typically involved precipitating the oligomer products from chloroform by adding methanol, resulting in a >95% pure solid. Purity of the reacting reagents and intermediates was found critical, however, for preparing oligomers beyond the tetramer. Even trace impurities become serious contaminants beyond the hexamer (**26e**) stage, which often decreased the coupling yields from the ideal 70−90% range to 50% or below.

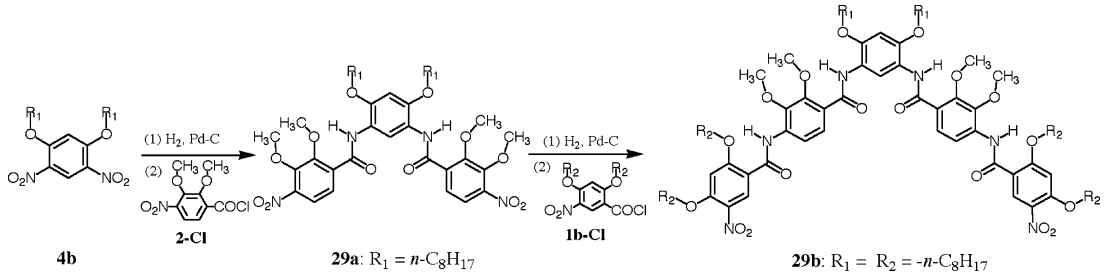
(ii) Coupling of Acids and Amines. Coupling reagents such as EDC, DCC, and HATU have also been successfully applied for the synthesis of short oligomers. As chain length increased, the coupling rate was found to decrease. One coupling reagent, dichlorotriphenylphosphorane (Ph_3PCl_2),[47] led to efficiency comparable to that demonstrated by acid chlorides. Thus, stepwise coupling of monomer acids with amino-terminated oligomers in the presence of Ph_3PCl_2 led to satisfactory yields for the preparation of homologues **27b**−**e**, which bear ethyl ester groups on their side chains (Scheme 9).

While the synthesis of oligomers **27b**−**e** could also employ the coupling of acid chlorides and amines, acid chlorides become incompatible with monomers and intermediates bearing acid-sensitive groups, such as ether, ester, or carbamate functionality containing the *tert*-butyl group. In such cases, acid chlorides usually led to unsatisfactory results. For example, the synthesis of trimer **28a** and tetramer **28b**, both of which contain two *tert*-butyl ester groups, was achieved by using the coupling reagent EDC in the presence of triethylamine (Scheme 10). Using the acid chloride of monomer **1d**, even in the presence of an excess amount of triethylamine, led to significantly reduced coupling yield. The reduction of **28a** in $CHCl_3$/ethanol (2:1, v/v) under normal conditions of hydrogenation (H_2, 4 Pa, Pd−C, 50 °C, 3 h) gave a complicated mixture with a small amount of the desired product. This was most likely due to the removal of the *tert*-butyl groups by the trace amount of acid (e.g., HCl) from the dehydrochlorination of chloroform or in Pd−C. Trimer **28a** was successfully reduced by hydrogenation in the same mixed solvent in the presence of 30 equiv of 4-aminopyridine. After hydrogenation, 4-aminopyridine was easily removed by filtering through a pad of silica gel. Coupling of the reduced trimer with monomer **1a** using EDC led to tetramer **28b** in satisfactory yield.

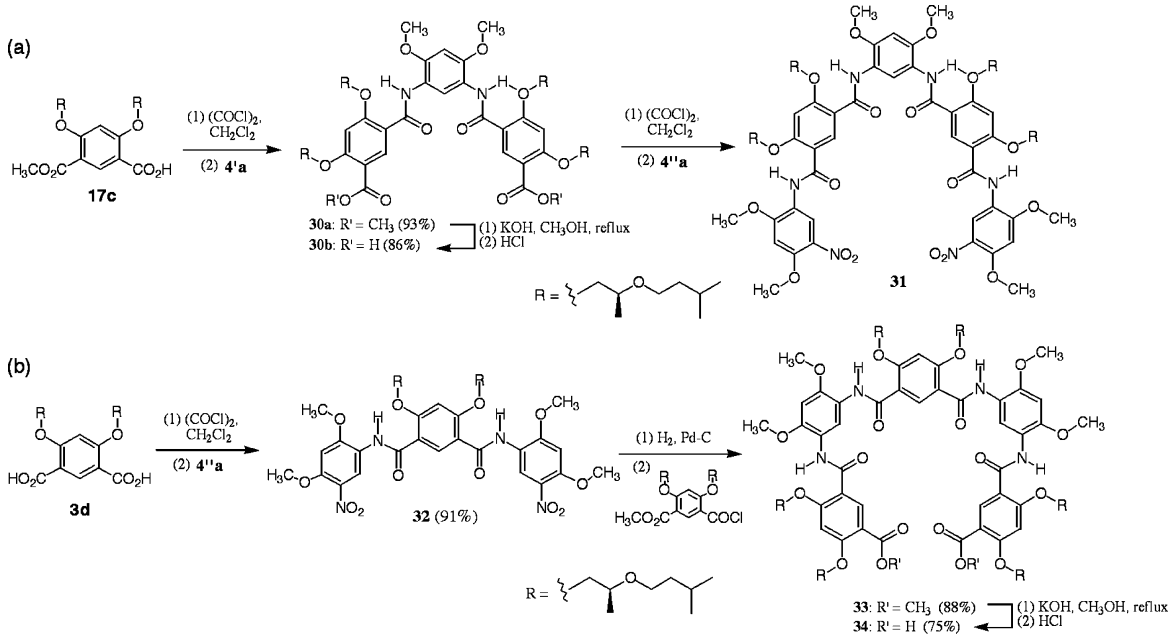
(2) Factors Affecting Coupling Efficiency. (i) Protonation of Amine Intermediates. Although the reduction of monomers with nitro groups such as **20a**,**b** can be performed easily by hydrogenation under mild conditions (room temperature, 1 atm), the hydrogenation of trimer and longer oligomers became increasingly sluggish, which usually required elevated temperature and pressure. Another observation was that during our early investigation of amide coupling reactions, the yield of each coupling step fluctuated significantly, ranging from ~80% to ~40%. The amine precursors obtained from hydrogenation, if washed with aqueous sodium bicarbonate before being coupled to acids or acid chlorides, usually led to better yields.

(47) Azumaya, I.; Okamoto, T.; Imabeppu, F.; Takayanagi, H. *Tetrahedron* **2003**, *59*, 2325.

SCHEME 11. Bidirectional Chain Extension from a Central Diamine Residue



SCHEME 12. Bidirectional Chain Extension Based on Diacid and Diamine Units

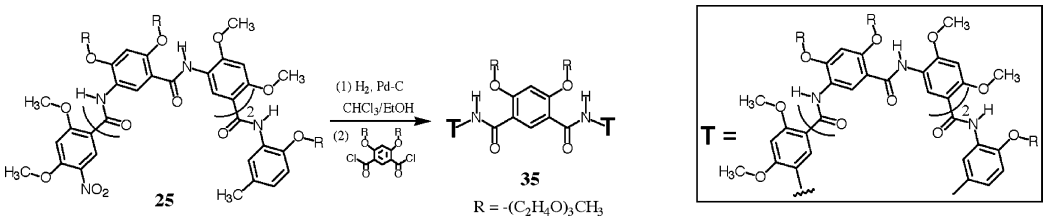


When dimer **21b** (Scheme 7) was reduced by hydrogenation, it was found that the residue (a white solid) obtained after removing the solvent was only sparsely soluble in CH_2Cl_2. This white solid, which was quite soluble in ethanol, turned out to be the protonated form of the reduced product (i.e., amino dimer). It gradually dissolved into CH_2Cl_2 upon addition of triethylamine. Obviously, acid (HCl) from the dehydrochlorination of which, or from the Pd−C catalyst was responsible for the protonation of the amine. In fact, it is a general phenomenon that both the free amine and the corresponding salt were obtained after the hydrogenation of a nitro compound, with the former accounting for a small fraction of the hydrogenated product. The free amine form, which is critical to achieving satisfactory coupling yields, can be generated by adding an excess of triethylamine or washing with aqueous $NaHCO_3$ right before the coupling steps. Another method that avoided the formation of protonated amines from hydrogenation involved using DMF as the solvent, in which case no amine salt was detected. However, using DMF as the solvent for hydrogenation is not practical since most of the oligomers with alkyl side chains have very limited solubilities in this solvent, and completely removing DMF is difficult due to its high boiling point.

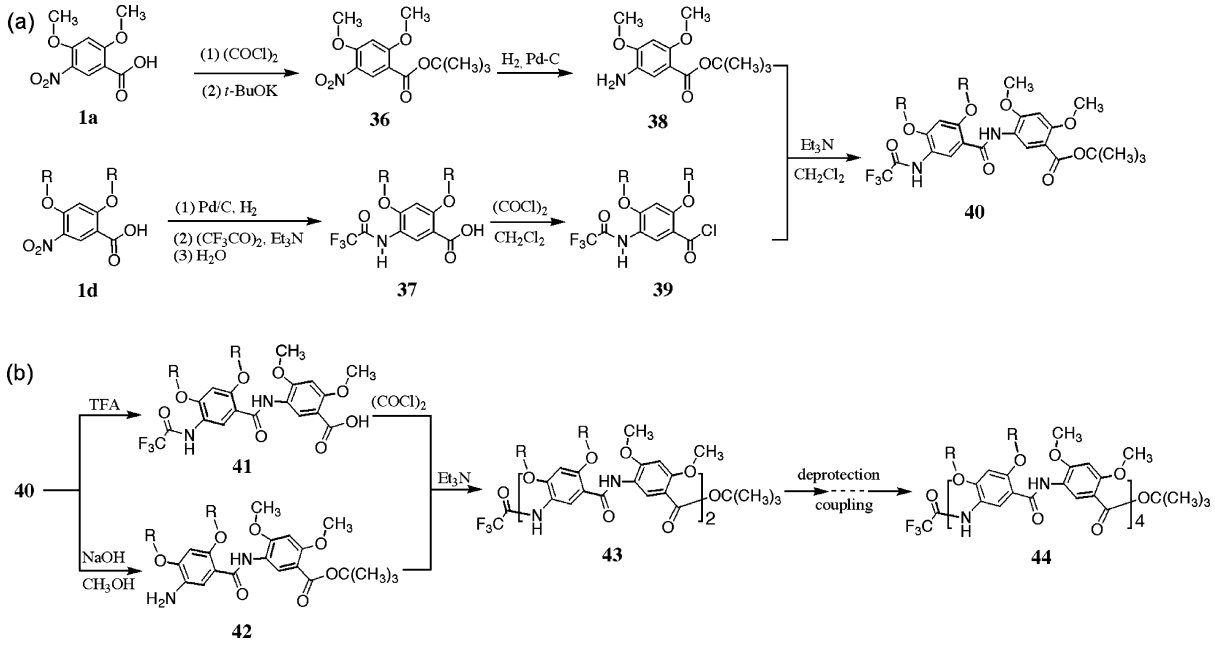
(ii) Coupling Methods. Coupling reactions involving monomer acid chlorides and oligomer amines generally led to better coupling yields than reactions using standard coupling reagents such as DCC and EDC. It was reported[47] that dichlorotriphenylphosphorane (Ph_3PCl_2) was an effective coupling reagent for forming hindered tertiary benzanilides from the corresponding substituted benzoic acids and *N*-monoalkylated anilines. An advantage of this reagent is that it requires no other additive for the coupling reaction.[47] As already shown in Scheme 9, oligomers **27b**−**e** were prepared in satisfactory yields with Ph_3PCl_2. Compared to generating monomer acids with oxalyl chloride, the coupling method involving Ph_3PCl_2 was straightforward and much more convenient. Oligomers **27b**−**e** were obtained by simply mixing three reagents (amine, acid, and Ph_3PCl_2) together and refluxing for 12 to 30 h in methylene chloride or chloroform. The yield based on free amine is comparable to that with acid chlorides. Therefore Ph_3PCl_2 could be a very promising, inexpensive reagent for constructing aromatic oligoamides of the type developed by us. The synthesis of longer oligomers based on this reagent is currently being explored.

(3) Bidirectional, Stepwise Coupling. Coupling acids to a substituted phenylenediamine will lead to chain growth in two opposite directions, leading to oligomers with two identical halves. Compared to the above-discussed unidirectional coupling, this strategy allows the synthesis of symmetrical oligomers of the same length with only half of the coupling steps. As shown in Scheme 11, pentamer **29b** was prepared in two coupling

SCHEME 13. Synthesis of the Symmetrical 35 by Coupling Two Identical Fragments to a Diacid Unit



SCHEME 14. Synthesis of Unsymmetrical Oligomers by Segment Condensation



steps starting from monomer **4b**. This strategy is particularly useful for preparing meta/para-linked oligomers that require more residues to complete a helical turn than the all-meta-linked oligomers.

On the basis of the same strategy, pentamers **31** (Scheme 12a) and **34** (Scheme 12b) were obtained by coupling the corresponding diacids and diamines. The adoption of monoacid **17c** and nitroaniline **4″a** was the key for the success of the stepwise coupling shown in Scheme 12. Continuing the coupling steps should lead to AB-type oliogmers longer than the pentamers. Pentamers **31** and **34**, with their preorganized backbones, should readily undergo ring-closing when treated with the corresponding diacid or diamine, leading to shape-persistent six-residue macrocycles[4,19,37] with specifically incorporated functional groups.

(4) Convergent Synthesis of Oligomers. (i) Coupling Two Identical Amino-Terminated Oligomers to a Diacid Chloride. Another strategy for constructing long oligomers with reduced coupling steps involves the coupling of oligomer fragments. We described previously the preparation of symmetrical nonamers and undecamers by coupling unsymmetrical oligomers,[19,37] which in turn were prepared by stepwise coupling to a central diacid (or the corresponding diacid chloride). Longer oligomers were also prepared based on this strategy in solution. For example (Scheme 13), 13mer **35** was obtained in reasonable yields by treating hexamer **25** with the corresponding diacid chloride. Similar to the bidirectional coupling strategy shown in Schemes 11 and 12, oligomer **35** obtained by this convergent route is symmetrical, consisting of two identical halves. In fact, a meta/para-linked 21mer represents the longest oligomer we have prepared so far.[37] Our previous 2D NMR studies showed that this 21mer folded into a helical conformation with a large (>30 Å) interior cavity.[37] These oligomers, with their tri(ethylene glycol) side chains, had good solubility in polar solvent such as DMSO, DMF, or mixed solvent of DMSO and methanol.

(ii) Segment Condensation of Short Oligomers. Another convergent approach involves the coupling of two oligomer precursors, one carrying a terminal carboxyl group and the other bearing a terminal amino group. Our earlier attempts to couple nitro-terminated oligomer acids to amino-terminated oligomers were met with limited success, which was most likely due to the stacking of the oligomer precursors. The above-discussed synthetic strategies use the nitro group as the equivalent of a protected amino group. The need to reduce the nitro group before each coupling step introduces an extra step that inevitably compromises the overall yield of a multistep oligomer synthesis. It was also discovered that the hydrogenation of nitro-terminated oligomers became increasingly sluggish as the backbone of the oligomers extended. In addition to that issue, the hydrogenation step is also incompatible with the solid-phase synthesis of oligoamides currently being developed. To develop efficient solution and solid phase synthetic strategies, the amino and carboxyl functionalities of the building blocks and intermediates need to be protected by using different

groups that can be easily removed under orthogonal conditions.

As shown in Scheme 14, acids **1a** and **1d** were converted into amino ester **38** and acid chloride **39**, respectively. Coupling of **38** and **39** in the presence of triethylamine led to dimer **40**. Deprotection of **40** with trifluoroacetic acid (TFA) and NaOH in methanol gave acid **41** and amino ester **42**, which were coupled via acid chloride into tetramer **43** in a yield of 76%. Repeating the deprotection and coupling procedures on tetramer **43** led to octamer **44** as indicated by MALDI-TOF. Conditions for preparing higher oligomers are being pursued. The coupling strategy as shown in Scheme 14 has provided a convergent method for the rapid preparation of long oligomers by doubling the chain length of the oligomers in each coupling cycle. The orthogonal reactivities of TFA-amido and *tert*-butyl groups are critical for the success of this approach. The high efficiency of the coupling reactions bodes well for applying these monomer and dimer building blocks to solid-phase synthesis that is being developed.

Conclusions

The methods developed by us for synthesizing folding aromatic oligoamides over the past several years are summarized in this article. The availability of a series of monomers in large quantities has provided the basis for the preparation of oligomers with curved backbones of different curvatures. These tetrasubstituted monomers, along with many of the intermediates developed during the synthesis, should also be useful for many other synthetic purposes. The three coupling strategies have led to the preparation of oligomers of various length. These oligomers fold into crescent and helical conformations containing internal hydrophilic cavities from 9 to 30 Å across. The efficient solution synthesis of these oligomers bodes well for the preparation of longer oligomers and for solid-phase synthesis that is being developed.

Experimental Section

General Procedures: (1) Preparation of Disubstituted Methyl Ester with Different Side Chains. A mixture of 2,4-dihydroxy-5-nitrobenzoic acid methyl ester **6** (1 equiv) or **15** (1 equiv) and potassium carbonate (2.5−3.0 equiv) in DMF was heated at 60 °C with stirring for 1−2 h. Then alkyl bromide (2.2 equiv) and potassium iodide (1% of alkyl bromide) were added followed by heating at 90−100 °C for about 2 days. In the case of **7a** CH_3I was used, no KI was added, and the temperature was kept around 38 °C throughout the reaction. The reaction mixture was filtered while hot and the solid left was extracted with ethyl acetate. The filtrate and the extract were combined. After removing the solvent under reduced pressure, the remaining residue was dissolved in methylene chloride, washed with brine and water, and dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 afforded the desired product.

(2) Preparation of Acid Chloride from the Corresponding Acids. To a solution of acid (1.0 equiv) and oxalyl chloride (1.2 to 1.5 equiv) in dry CH_2Cl_2 were added one or two drops of DMF. The mixture was stirred for 20 min at room temperature and then refluxed for an additional 30−50 min. The solvent was evaporated and the resulting acid chloride was dissolved in dry CH_2Cl_2, then the solvent was evaporated to remove any excess oxalic chloride. The residue was used for the next coupling step.

(3) Hydrolysis of Methyl Esters. A mixture of compounds **7a**−**f** or **16a**−**f** (1 equiv) in MeOH (or THF, water) and sodium hydroxide (or potassium hydroxide, lithium hydroxide) (2 to 2.5 equiv) dissolved in water was refluxed for 2−12 h. Workup followed either of the two methods: (A) Water (ca. twice of the solvent used) was added to cause precipitation while acidifying with HCl. After removing part of the solvent, the solid was collected, washed with water, and triturated with methanol to give the desired acid. (B) The mixture was acidified followed by removing most of the solvent, and the residue was extracted twice with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the desired product.

(4) Hydrogenation of Nitro Compounds. The general procedure for the preparation of the amines from the corresponding monomer and oligomers (dimers and beyond) bearing a nitro group by catalytic hydrogenation is as follows:

To a mixture of nitro compounds, 10% Pd/C (10−20 wt % of nitro compound) and chloroform, was added methanol. (**Caution**! Direct addition of methanol to the Pd/C without wetting the catalyst with solvent may cause fire!) The solution was purged with hydrogen, and shaken under an atmosphere of hydrogen gas at the appropriate temperature for a period of time from one to several hours until only amine appeared on TLC, which is signaled in most cases by the color change of spots caused by oxidation under UV lamp or in air. The mixture was then filtered and the solvent evaporated. The residue consisting usually of both free amine and amine salt was treated according to the following two procedures: (A) It was dissolved in CH_2Cl_2, and triethylamine was added to the solution with stirring to convert any amine salt to free amine, followed by immediate coupling with acid chloride. (B) The solution of the residue was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to dryness to afford the crude amine (>90%), which was used without further purification for the next step. For each subsequent higher nitro-oligomer an additional 5 °C increment of reaction temperature and an additional 20−30 min of reaction time were required.

Synthetic procedures for the preparation of various oligomers, along with analytical and characterization data, can be found in the Supporting Information.

Acknowledgment. We thank the National Institutes of Health for support (R01GM63223).

Supporting Information Available: Specific synthetic procedures for certain compounds; analytical and spectral characterization data of compounds discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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