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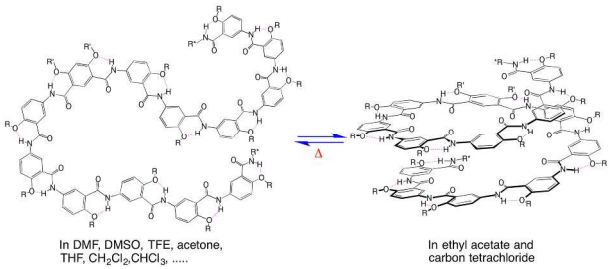

A 15-residue aromatic oligoamide with a backbone of increased flexibility exhibits solvent- and temperature-dependent folding and highly cooperative conformational transition.

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LETTER

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Aromatic Oligoamides with Increased Backbone Flexibility: Improved Synthetic Efficiencies, Solvent-Dependent Folding and Cooperative Conformational Transitions

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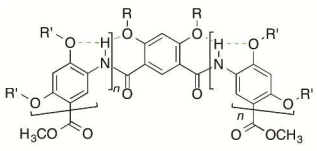
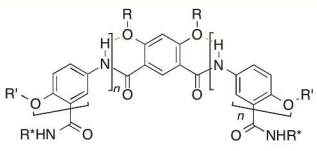
Aromatic oligoamides **2a**, **2b**, and **2c** of increasing chain lengths were prepared and further characterized for their folding behaviour. These oligomers were derived by relaxing the backbone-constraint of a series of oligoamides that fold into well-defined conformations. With their backbones of increased flexibility, the resultant **2a-c** were found to form in considerably improved efficiencies, and undergo highly cooperative folding that depends on chain length, solvents, and temperature.

Since the pioneering reports on unnatural folding oligomers, or foldamers, first appeared in 1996,[1] numerous systems of synthetic foldamers have been developed.[2] An especially attractive and powerful feature of synthetic foldamers is that a wide variety of building blocks can be incorporated. Indeed, the initially reported foldamers based on β-amino acids[1,3] soon inspired the development of various peptidomimetic foldamers consisting of monomeric residues such as those derived from γ-,[4] δ-[5] and other[6] unnatural amino acids. Another unique advantage of synthetic foldamers is that adjusting the combinations of various building blocks can greatly increase the diversity of backbones. As a result, the field quickly evolved from peptidomimetic foldamers having homogeneous backbones, i.e., those based on a single type of monomeric residues, to ones with heterogeneous backbones by incorporating different types of monomeric units.[7,8] Deviating even further away from peptidomimetic oligomers are abiotic foldamers consisting of aromatic basic units.[2c-2e] Examples of abiotic foldamers include, but not limited to, those consisting of pyridine-pyrimidine and aromatic heterocyclic,[9] arylene ethynylene,[10] aryl urea,[11] aryl amide[2d,2e,12] and hydrazide[13] residues.



1a: n = 2; **1b**: n = 4; **1c**: n = 6



2a: n = 2; **2b**: n = 4; **2c**: n = 6

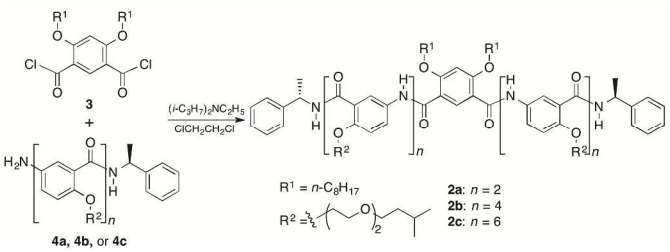
By constraining the backbones of aromatic oligoamides with a set of highly favourable three-center intramolecular hydrogen bonds, we developed foldamers containing non-collapsible cavities with precisely defined dimensions.[2d,12b-d,14] Oligoamides **1a-c** represent one class of such backbone-constrained foldamers we created. Studies by ourselves[14] and others[2e] revealed that intramolecular three-center H-bonds, especially the type shown by **1**,[15] along with those adopted in other systems, are very effective in restricting the conformational freedom of the corresponding oligoamide backbones, leading to folded structures that are persistent at elevated temperatures and in nonpolar and polar media.[12e] Based on this backbone-rigidifying strategy, aromatic oligoamides that fold into crescent or helical shapes having cavities of 8 to over 30 Å across were created.[12c] These highly stable foldamers, along with cavity-containing macrocycles having rigid backbones,[16] have well-defined cavities and large aromatic surfaces that result in interesting self-assembling,[17] molecular recognition,[18] and other[19] properties.

While the backbone-constraining strategy has turned out to be very reliable in creating stably folded aromatic oligoamides, the high conformational stability of such foldamers imposes severe steric hindrance that hampers the preparation of longer oligoamides. For example, two symmetrical 9-residue oligomamides sharing the general structure of **1b** were obtained in yield of 37% and 38%, respectively by coupling the corresponding monomeric diacid chloride with the amino tetramers.[12c] In contrast, a symmetrical 13-residue oligomer having the same backbone of **1c** could only be obtained in a yield of 3.7% based on the same coupling strategy.[20] Although temporarily blocking the intramolecular three-center H-bonds led to longer oligomers with considerably improved yields,[20] this synthetic strategy is frustrated by the need of introducing blocking groups, which involves multiple synthetic steps even for the preparation of monomeric building blocks.

Herein we report the design, synthesis and initial examination of the folding of aromatic oligoamides **2a-c**, which can be regarded as being derived from **1** by removing the five-membered intramolecular H-bonds of the latter and thus have backbones that are only partially constrained by H-bonds. It was reasoned that, on one hand, with their rigid benzene residues that are *meta*-connected via rigid amide linkages,

oligoamides **2a-c** should still adopt folded, i.e., helical, conformations under proper conditions. On the other hand, with backbones that are less constrained than those of **1**, the folding of oligoamides **2** should be more dynamic (reversible), which alleviates steric hindrance caused by stably folded conformations and thus allows longer oligomers to form in improved efficiencies. It was found that, in comparison to aromatic oligoamides such as **1** that have fully constrained backbones, oligomers **2a-c** were obtained in considerably improved yields. The improvement in synthetic efficiency is most pronounced for the longest **2c**, which was obtained in a significantly improved yield as compared to fully constrained oligomers of a similar length. The folding of **2** was found to depend on chain length, the nature of solvents, and temperature.

Scheme 1. Synthesis of oligoamides **2a-c**.



The structures of **2a-c** are shown in Scheme 1. Oligoether side chains (R^2 groups) are introduced into **2** to render these oligoamides good solubility in multiple solvents. To facilitate the detection and characterization of folded conformations with circular dichroism (CD) spectroscopy, two chiral residues derived from (*S*)-(-)-1-phenylethylamine are introduced into **2a-c**. To be comparable with the synthesis of **1**, oligoamides **2a-c** were prepared by coupling diacid chloride **3** with the corresponding amino oligoamide precursors **4a**, **4b**, and **4c** which were prepared based on similar procedures we reported.[21]

Briefly, a solution of diacid chloride **3** (1 equiv.) dissolved in 1,2-dichloroethane was slowly added to a solution of amino oligomers **4a-c** (2 equiv.) and diisopropylethylamine (2.1 equiv.) in dichloroethane. After stirring at room temperature for one hour and then heated under reflux for 24 hrs, removing solvent and other volatile components left a residue that was purified with silica gel column chromatography to give **2a-c**.

Table 1. Reaction of amines **4a-c** with diacid chloride **3**.[a]

Entry	Amine 4	Solvent	Temp.	Yield of 2
1	**4a** (16 mM)	$ClCH_2CH_2Cl$	RT to 84 °C	53% (**2a**)
2	**4b** (16 mM)	$ClCH_2CH_2Cl$	RT to 84 °C	47% (**2b**)
3	**4c** (16 mM)	$ClCH_2CH_2Cl$	RT to 84 °C	27% (**2c**)

[a]The concentration of **3** is 8 mM in each of the reactions.

Oligoamides **2a-c** were obtained in satisfactory to acceptable yields (Table 1). In comparison to oligoamides represented by general structures **1**, oligoamides **2a-c**, with their partially constrained backbones, were all obtained in considerably improved yields. For example, with 15 benzene residues, oligoamide **2c**, which is in fact longer than an analogous 13-residue oligomaide that was formed in 3.7% yield,[20] was obtained in a much higher yield than the latter. The observed formation of **2**, especially **2c**, clearly demonstrates that increasing the flexibility of aromatic oligoamide backbones can indeed improve the synthetic efficiency of the corresponding oligomers. By optimizing the coupling efficiencies and/or by including methods such as solid-phase synthesis, homologues of **2** that are much longer than currently known aromatic oligoamides with fully constrained backbones should become available.

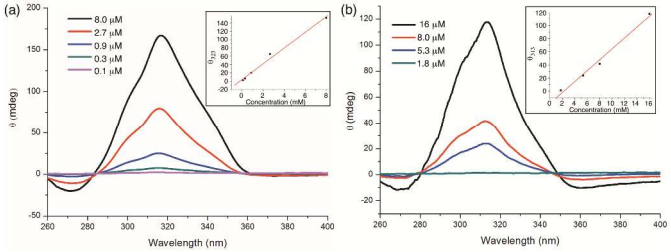


Figure 1. CD spectra of **2c** (a) in CCl_4 and (b) in ethyl acetate, measured at room temperature and at different concentrations. Inset in (a): Plots of the ellipticity of **2c** at 323 nm versus concentration in CCl_4; inset in (b): Plots of the ellipticity of **2c** at 313 nm versus concentration in ethyl acetate.

The folding of **2a–c** was investigated by recording their CD spectra in a number of different solvents, including DMF, DMSO, 2, 2, 2-trifluoroethanol, acetone, ethyl acetate, THF, 1, 2-dichloroethane, methylene chloride, chloroform, and CCl_4, in which these oligomers are readily soluble. The shortest **2a**, which can make about one turn if adopting a helical conformation, shows no CD signal in any of these solvents. Surprisingly, oligomer **2b**, which has 11 benzene residues and could fold into a helix with well over one turn, also failed to give any CD signal. In contrast, the longest **2c**, which gives a helix of over two turns if folds, does give CD spectra with a well-defined shape in CCl_4 (Figure 1a) in a wide concentration range. Interestingly, CD spectra with very similar shapes were also observed for **2c** in ethyl acetate (Figure 1b), a solvent that is much more polar than CCl_4 while having no similarity to the latter. In fact, the same positive Cotton effect is revealed by the CD spectra of **2c** recorded at different concentrations in both CCl_4 and ethyl acetate, with a minimum at 273 nm and a maximum at 323 nm in the former (Figure 1a), and a minimum at 274 nm and a maximum at 313 nm in the latter solvent (Figure 1b). In contrast, in 2, 2, 2-trifluoroethanol, a solvent that promotes secondary-structure formation in peptides,[22] oligomer **2c** also failed to give any observable CD signal, suggesting that the solvent-dependent folding of **2c** involves factors that are very different from those for the folding of peptides.

Plotting the ellipticity of the maxima at 323 nm (in CCl_4) or 313 nm (in ethyl acetate) against concentrations of **2c** reveal linear correlations (Figure 1, insets), confirming that the observed intensity change is because of variation of concentration, rather than a change of folded conformation or due to aggregation. The CD spectra of **2c**, which share the same shape in both CCl_4 and ethyl acetate at different concentrations, demonstrate that this oligoamide folds into a chiral conformation in which chirality is transferred from the UV-silent side chains to chirally positioned backbone chromophores. Given that its backbone consists of *meta*-linked monomeric residues,

oligoamide **2c** should fold into a conformation that is similar to those of fully constrained aromatic oligoamides such as **1**,[12e] i.e., a hollow helix of over two turns with a pitch of approximately 6.5 units.

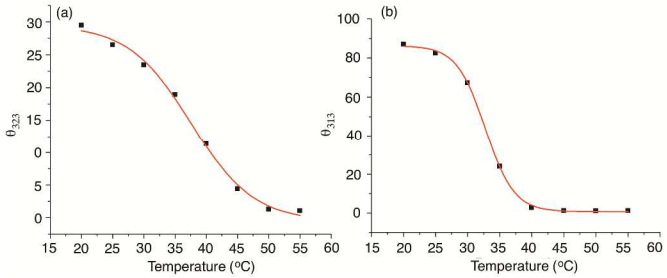


Figure 2. Plots of the ellipticity (mdeg) of **2c** (a) in CCl_4 (1.6 μM) at 323 nm and, (b) in ethyl acetate (3.2 μM) at 313 nm as a function of temperature.

The fact that only **2c** folds into a helical architecture suggests that, to adopt a stably folded conformation, the stacking of aromatic rings and amide linkages is the most likely driven force for the folding of this oligomer. The length of **2c** allows the formation of a helix with over two turns, in which all the aromatic residues and amide groups of **2c** engage in stacking interaction. Such an arrangement provides sufficient stabilization for **2c** to adopt a compact helical conformation. As a result, in spite of the distinctly different properties of CCl_4 and ethyl acetate, oligoamide **2c** still fold similarly.

To probe the denaturation of **2c**, CD spectra in CCl_4 and ethyl acetate were recorded as a function of temperature and were found to have the same shape as those shown in Figure 1.† The loss of folded structure is indicated by decreasing ellipticity at 323 nm (in CCl_4) and 313 nm (in ethyl acetate), respectively, with rising temperature. The change in ellipticity is then plotted as a function of temperature (Figure 2). Consistent with the unfolding of a well-defined conformation, the CD signals of **2c** in CCl_4 or ethyl acetate are very insensitive to change of temperature. In CCl_4, an obvious transition at above 30 ℃ is observed and a sharp transition occurs at above 15 ℃ in ethyl acetate. Based on these data, "melting temperatures" of 38 ℃ and 18 ℃ can be estimated for **2c** in CCl_4 and ethyl acetate, respectively.

Plotting the change in ellipticity as a function of temperature as shown in Figure 2 reveals reverse sigmoidal curves reminiscent of highly cooperative conformational transitions,[23] i.e., the folding of oligomer **2c** does not involve a gradual conformational change. Instead, the abrupt change shown by the reverse sigmoidal curves points to a completely unfolded or completely folded state for **2c**. Such cooperative transitions are usually associated with bio-foldamers, such as peptides and small, rapidly folding globular proteins.[24] Thus, the folding of **2c**, like that of bio-oligomers, involves weak but strongly coupled individual interactions that act cooperatively through the conformational and covalent geometry of the oligoamide chain.

In summary, modifying aromatic oligoamides **1** leads to **2** with backbones of increased flexibility. Compared to **1**, the reduced rigidity of the backbones of **2** alleviates steric hindrance that would be associated with stably folded conformations, leading to considerably improved yields for these oligomers. Due to the enhanced backbone flexibility of **2**, only the longest **2c** adopts folded conformations in CCl_4 and ethyl acetate. At this moment, it is not yet clear what factors are responsible for the observed solvent-dependent folding of **2c**. Nevertheless, the folding of **2c** raises interesting questions on the folding of this class of oligomers, which warrants additional, detailed study. The highly cooperative nature observed for the conformational transition between the folded and unfolded states of **2c** closely mimics bio-foldamers, which bodes well for developing more stable, longer homologs of this series. Besides, adjusting the overall flexibility of a backbone by tuning the ratio of fully and partially constrained amide linkages should lead to the contorl of folding propensity and stabilities for the corresponding oligoamides. Systematic synthetic and structural studies are being pursed on this new generation of foldamers. The corresponding results will be reported in due course.

Experimental

General procedure for synthesis of oligoamides 2a-c

Diacid chloride **3** (0.038 mmol) dissolved in dichloroethane (1.8 mL) was added dropwise into a solution of the corresponding amino oligomer precursor (0.076 mmol) and diisopropylethylamine (0.08 mmol) in dichloroethane (3 mL) at room temperature. The final concentrations of **3** and **4a**, **4b**, or **4c** were 8 mM and 16 mM, respectively. The reaction mixture was stirred at room temperature for one hr, and was then heated under reflux for 24 hrs. After removing solvent *in vacuo*, the remaining residue was purified with column chromatography (silica gel, $CHCl_3/CH_3OH$ (60/1, v/v)).

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Notes and references

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† Electronic Supplementary Information (ESI) available: NMR, UV and additional CD spectra. See DOI: 10.1039/b000000x/

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