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SHORT COMMUNICATION

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Advances towards Aromatic Oligoamide Foldamers: Synthesis and X-ray Structures of Dimeric Arylopeptoids with Conformation-Directing Side Chains

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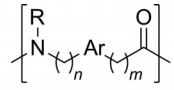
We have efficiently synthesized 36 arylopeptoid dimers with *ortho*-, *meta*-, and *para*-substituted aromatic backbones and *tert*-butyl or phenyl side chains. The dimers were synthesized by using a "submonomer method" on solid phase, by applying a simplified common set of reaction conditions. X-ray crystallographic analysis of two of these dimers disclosed that the *tert*-butyl side chain invokes a *cis* amide conformation with a comparatively more closely packed structure of the surrounding aromatic backbone while the phenyl side chain results in a *trans* amide conformation with a more open, extended structure of the surrounding aromatic backbone.

Introduction

Aromatic oligoamides assembled from aromatic amino acid building blocks in a "one-way sequence" fashion represent an intriguing subgroup of aryl-based foldamers.[1] Secondary structures have been reported for *N*-alkylated benzanilides,[2] benzanilides,[3] pyridylamides,[3f,3k,4] and oligoamides of quinolines,[5] naphthyridines,[6] aminophenoxy acetic acid,[7] and aminomethylphenyl acetic acid (Figure 1).[8] Depending on their nature, these aromatic oligoamides fold into spherand or crown ether-like structures,[3m,3o] crescent or helical structures,[2c,3j,3p–3r,4a–4e,5–8] or rod-like structures,[3h,3n] and they have furthermore been used as α-helix mimetics.[2a,2b,3a–3g,3i,3k,3l,4f,4g]

Amongst these foldamers, only the *N*-alkylated benzanilides carry side chains at the backbone amide nitrogen atoms. This may be a result of the often less straightforward synthetic pathways to *N*-alkylated aromatic oligoamides and because folding promoted by intramolecular hydrogen bonding involving backbone amide protons is not possible. Nevertheless, *N*-alkylation represents a conceptually simple strategy for greatly increasing the structural diversity of aromatic oligoamides as exemplified by *N*-alkylated aminomethylbenzamides[9] termed arylopeptoids (Figure 2).[10]



N-Alkylated benzanilide	(*n* = 0, *m* = 0, R = alkyl, Ar = Ph)
Benzanilide	(*n* = 0, *m* = 0, R = H, Ar = Ph)
Pyridylamide	(*n* = 0, *m* = 0, R = H, Ar = pyridine)
Quinoline	(*n* = 0, *m* = 0, R = H, Ar = quinoline)
Naphthyridine	(*n* = 0, *m* = 0, R = H, Ar = naphthyridine)
Aminophenoxy acetic acid	(*n* = 0, *m* = 1, R = H, Ar = phenol)
Aminomethylphenyl acetic acid	(*n* = 1, *m* = 1, R = H, Ar = Ph)

Figure 1. "One-way sequence" aromatic oligoamide foldamers.

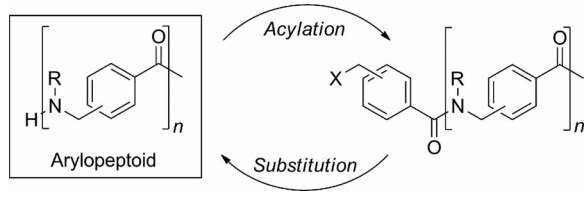


Figure 2. Arylopeptoids: *N*-alkylated aminomethylbenzamides.

The backbone structure of arylopeptoids allow for synthesis by using highly convenient "submonomer" approaches wherein the arylopeptoid residues are created in an iterative manner directly on the growing oligoamide chains with a unique acylation–substitution cycle (Figure 2). As a result of our recent efforts, arylopeptoids with *ortho*-,[10a] *meta*-,[10b–10d] or *para*-substitution pattern[10b–10d] in the backbone may now be synthesized efficiently both on solid phase, by use of either COMU-activated chloromethylbenzoic acids[10c] or chloromethylbenzoyl chlorides[10a,10b] in the coupling steps, as well as in solution.[10a,10d] These

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methods have enabled our recent discovery of the first biologically active arylopeptoids.[11]

NMR spectroscopic studies have furthermore enabled us to establish that most side chains give rise to the presence of *cis*/*trans* amide mixtures resulting in flexible structures and complex spectra.[10a,10b,10d] However, homooligomers carrying *tert*-butyl or phenyl side chains represent intriguing exceptions, because they produce simple NMR spectra. Extensive overlap in the aromatic region of the NMR spectra unfortunately hinders the extraction of conformational data, and we have hitherto not been successful in obtaining single crystals of any of these homooligomers. However, some limited conformational data can be obtained by performing NOESY studies on model arylopeptoid monomers,[10a,10b,10d] for which we have established that the *tert*-butyl side chain invokes a 100% *cis* conformation about the amide bond (Figure 3, left), while the phenyl side chain results in a 100% *trans* amide conformation (Figure 3, right).

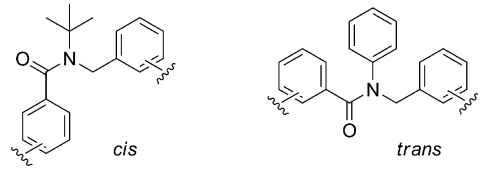
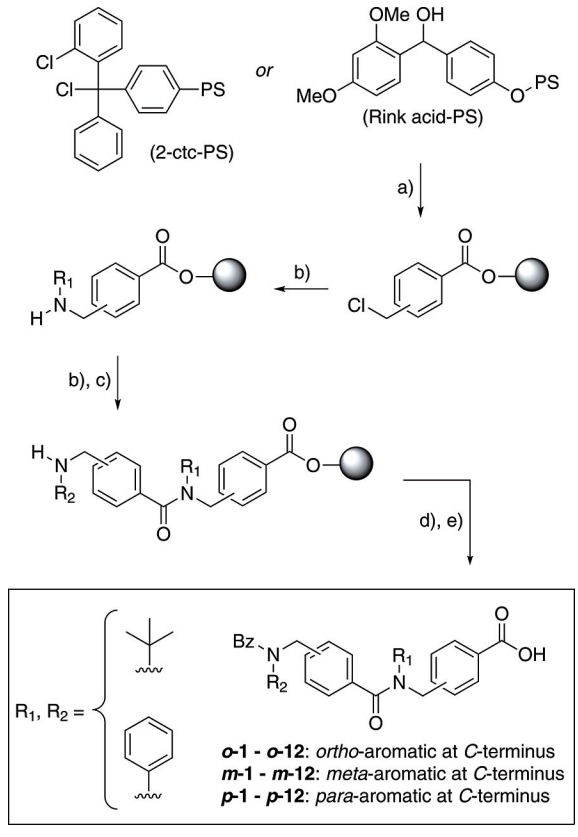


Figure 3. *cis* and *trans* amide conformations found in model arylopeptoid monomers.

Obtaining single crystals for X-ray analysis of arylopeptoid fragments with *tert*-butyl or phenyl side chains would represent a substantial advance towards the possible future design of foldamers based on arylopeptoids. During our previous work we have observed that monomers with free acids at the *C*-terminus often display a high level of crystallinity, which therefore prompted us to investigate the possibility for crystallizing the corresponding dimeric arylopeptoids.

Results and Discussion

We synthesized a library comprising all 36 possible combinations of dimers with an *ortho*-aromatic (***o***-series), *meta*-aromatic (***m***-series), or *para*-aromatic (***p***-series) substitution at the *C*-terminus, *ortho*-, *meta*-, or *para*-aromatic substitution at the *N*-terminus, and *tert*-butyl or phenyl side chains (Scheme 1, see Supporting Information for details). This is the first time arylopeptoids with mixed *ortho*-, *meta*-, and *para*-substituted backbones have been synthesized and studied. The ***o***-series was synthesized by using a Rink acid polystyrene resin,[10a] while the ***m***- and ***p***-series were synthesized by using a 2-chlorotrityl chloride (2-ctc) polystyrene resin.[10b] Loading onto these resins was performed as we have previously described.[10a,10b] In order to facilitate the library synthesis, we applied a set of simplified chain elongation conditions (Scheme 1). Thus, the substitution reactions were all performed by using either aniline (20 equiv., 4 M in DMSO) at 50 °C for 3 h or *tert*-butylamine (20 equiv., 2 M in DMSO) at 50 °C for 1 h. Acylation or capping after substitution with aniline was carried out by using 2-, 3-, or 4-(chloromethyl)benzoyl chloride or benzoyl chloride (3 equiv., 0.5 M in CH_2Cl_2) in the presence of DIPEA (6 equiv.) at room temp. for 1 h. Acylation or capping after substitution with *tert*-butylamine was carried out by using 2-, 3-, or 4-(chloromethyl)benzoyl chloride or benzoyl chloride (6 equiv., 1.0 M in CH_2Cl_2) in the presence of DIPEA (12 equiv.) at room temp. for 1 h, except when the acylating reagent or the residue to be acylated was an *ortho*-substituted aromatic group, in which case the reaction time was extended to 3 h. The dimers were cleaved from the resins by using CH_2Cl_2/HFIP (4:1) for 1 h and purified by preparative HPLC as described previously.[10a,10b] With these methods, the 12 dimers of the ***p***-series were obtained in 34–58% purified yield (≥ 94% purity) and the 12 dimers of the ***m***-series were obtained in 51–69% purified yield (≥ 95% purity). The 12 dimers of the ***o***-series were obtained in a more varied 15–48% purified yield (≥ 83% purity; 11 of



Scheme 1. Solid-phase submonomer synthesis of arylopeptoid dimers. *Reagents and conditions*: (a) ***o***-series: Rink acid polystyrene resin, $ClCH_2ArCOCl$ (3.0 equiv., 0.5 M), DMAP (3.0 equiv.), DIPEA (3.0 equiv.), CH_2Cl_2, room temp., 20 min; ***m***-/***p***-series: 2-chlorotrityl chloride polystyrene resin, $ClCH_2ArCOOH$ (1.2 equiv., 0.14 M), DIPEA (6.0 equiv.), CH_2Cl_2, room temp., 1 h. (b) R = Ph: $PhNH_2$ (20 equiv., 4.0 M), DMSO, 50 °C, 3 h; R = *t*Bu: $tBuNH_2$ (20 equiv., 2.0 M), DMSO, 50 °C, 1 h. (c) $ClCH_2ArCOCl$ (3.0 equiv., 0.5 M or 6.0 equiv., 1.0 M), DIPEA (6.0 or 12.0 equiv.), CH_2Cl_2, room temp., 1 h or 3 h. (d) BzCl (3.0 equiv., 0.5 M or 6.0 equiv., 1.0 M), DIPEA (6.0 or 12.0 equiv.), CH_2Cl_2, room temp., 1 h or 3 h. (e) HFIP/CH_2Cl_2 (1:4), room temp., 1 h. See Supporting Information for yields and purities.

the 12 dimers were isolated in ≥ 96% purity), and although optimization might increase these yields and purities, we did not investigate these options, as we obtained sufficient material for full characterization and crystallization.

As expected, NMR spectra of all dimers showed the presence of a single conformer only (see Supporting Information). However, overlap of signals in the aromatic region unfortunately hinders conformational analysis. Crystallization of the 36 dimers was then investigated from a range of different solvents and solvent compositions. We succeeded in obtaining suitable crystals of two of the dimers: ***m*-2** of the *meta*-series (Figure 4, top left), which is constructed of two *meta*-residues both carrying *tert*-butyl side chains, and ***o*-4** of the *ortho*-series (Figure 4, top right), which is constructed of two *ortho*-residues carrying a *tert*-butyl side chain on the first residue and a phenyl side chain on the second. Crystals of dimer ***m*-2** were obtained by slow concentration from a solution of approximately 10 mg of the compound in 1 mL of $CDCl_3$ containing a few drops of MeOD, while crystals of ***o*-4** were isolated by slow concentration from a solution of approximately 10 mg of the compound in 1 mL of CH_2Cl_2/$CHCl_3$ (2:1) containing a few drops of MeOH.

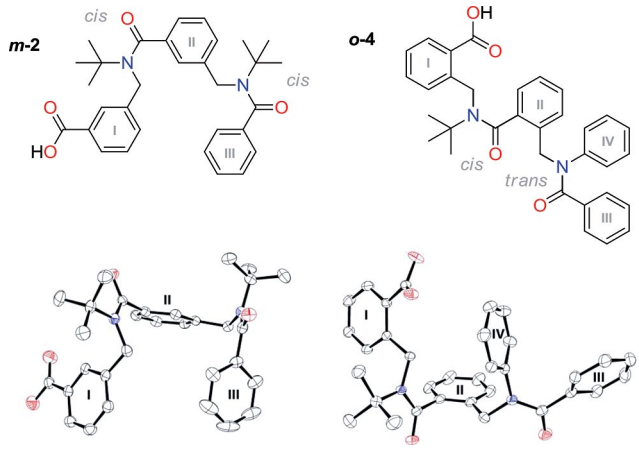


Figure 4. X-ray structures of dimers ***m*-2** and ***o*-4**.

The three-dimensional structures of the two dimers were then determined by X-ray crystallography (see Supporting Information for details).[12] Dimer ***m*-2** (Figure 4, bottom left), crystallizes in the triclinic space group $P\bar{1}$. The conformations of both amide moieties are *cis* [torsion angles: –3.6(4)°, 14.0(4)°], which confirms our previous findings from NMR spectroscopic studies on model monomers regarding the *tert*-butyl side chain.[10a,10b,10d] Importantly, these findings allow us for the first time to establish that the *cis*-amide-directing action of the *tert*-butyl side chain in model arylopeptoid monomers is likewise extended to an arylopeptoid dimer. The *tert*-butyl side chain leads to a relatively compact structure about the amide moiety where the two surrounding backbone aromatic rings are nearly perpendicular to one another [the dihedral angle between rings I and II is 89.86(9)° and that between rings II and III is 86.81(10)°], and the distances between the branching points of the aromatic rings are 3.666(4) Å (between ring I and II) and 3.644(4) Å (between ring II and III). We propose that steric effects of the bulky *tert*-butyl side chain cause the amide to adopt the observed *cis* conformation, which enables the *tert*-butyl side chains to point outwards from the twist created by the two surrounding backbone aromatic rings. The carboxylic acid moiety is slightly bent out of the plane of the aromatic ring [6.3(4)°]. Dimer ***o*-4** (Figure 4, bottom right) crystallizes in the monoclinic space group $P2_1/n$. The observed amide conformations likewise confirm and extend our previous findings from NMR spectroscopic studies on model arylopeptoid monomers:[10a,10b,10d] A *cis* conformation is observed at the first amide moiety that carries a *tert*-butyl side chain [torsion angle: –6.4(2)°], while the second amide moiety, which carries a phenyl side chain, adopts a *trans* conformation [torsion angle: –179.9(1)°]. Analogous to ***m*-2**, the *tert*-butyl side chain leads to a compact structure about the amide moiety where the two surrounding backbone aromatic rings are close to perpendicular [the dihedral angle between rings I and II is 76.75(4)°], and the distance between the branching points of the aromatic rings is 3.696(2) Å. The phenyl side chain, on the other hand, leads to a more open, extended conformation [the dihedral angle between rings II and III is 53.35(5)°, and the distance between the branching points of the aromatic rings is 4.671(2) Å (between ring II and III)]. The *trans* amide conformation causes the phenyl side chain to point inwards into the twist created by the two surrounding backbone aromatic rings. We speculate that the *trans* amide preference may be because the *N*-phenyl side chain is less bulky than the *N*-methylbenzyl group and because of the electronic repulsion between the carbonyl lone pair and the phenyl π-electrons.[13] The carboxylic acid moiety of ***o*-4** is bent out of the plane of the aromatic ring [–35.2(2)°], presumably because of the *ortho*-substitution. See Supporting Information for details regarding the crystal packing of the two dimers.

Conclusions

We have used a common set of simplified reaction conditions for efficient submonomer solid-phase synthesis of a library of 36 dimeric arylopeptoids with *ortho*-, *meta*-, and *para*-substituted aromatic backbones and *tert*-butyl and phenyl side chains. Arylopeptoids with mixed *ortho*-, *meta*-, and *para*-substituted backbones have been synthesized and studied for the first time. Also for the first time, we succeeded in obtaining single crystals suitable for X-ray crystallographic studies of two of the dimers: Amides with a *tert*-butyl side chain were found to adopt a *cis* amide conformation, while an amide with phenyl side chain was found to adopt a *trans* amide conformation. These results thus confirm and extend our previous findings from NMR spectroscopic studies on model arylopeptoid monomers. We furthermore found that the phenyl side chain in the crystallized dimers results in a comparatively more open, extended backbone structure where the phenyl side chain points inwards into the twist created by the surrounding

aromatic backbone, while the *tert*-butyl side chain results in a more closely packed structure that enables the *tert*-butyl side chains to point outwards from the twist created by the two surrounding backbone aromatic rings. We believe that these findings represent an important advance for future development and design of arylopeptoid-based foldamers, and we will report our progress in due time.

Supporting Information (see footnote on the first page of this article): General experimental methods, experimental procedures and characterization data, methods used for analytical and preparative HPLC, HPLC profiles and NMR spectra of synthesized arylopeptoid dimers, detailed X-ray crystallographic analysis of dimers ***m*-2** and ***o*-4**.

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