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N-Naphthyl Peptoid Foldamers Exhibiting Atropisomerism

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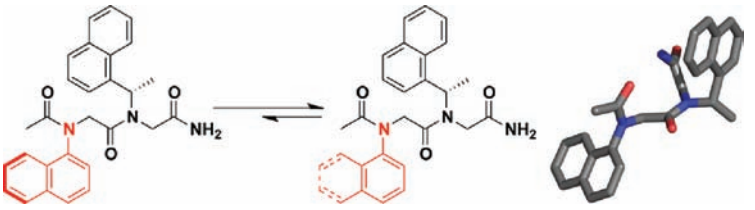
ABSTRACT



We introduce peptoid oligomers incorporating *N*-(1)-naphthyl glycine monomers. Axial chirality was established due to restricted rotation about the C–N(aryl) bond. Atropisomerism of both linear and cyclic peptoids was investigated by computational analysis, dynamic HPLC, and X-ray crystallographic studies.

Peptoids are a family of sequence-specific oligomers composed of diverse *N*-substituted glycine units.[1] Peptoids are an example of biomimetic foldamer compounds and can recapitulate many of the structural and functional attributes of polypeptides.[2] Peptoids are actively studied in the pursuit of folded oligomers that can display desirable biomedical, materials, or catalytic properties.[3] The peptoid backbone is typically achiral and lacks the ability to form hydrogen bond networks. The development of functional peptoids will necessitate an improved capability to design structural attributes, including chirality.

A variety of strategies have been employed to direct ordered peptoid conformations, including the incorporation of structure-inducing side chains[4,5] and oligomer macrocyclization.[6] The selection of different side chains can guide peptoid secondary structure features in a predictable manner.[5] Noncovalent interactions play a critical role in peptoid folding by dictating the energetically accessible dihedral angles for peptoid oligomers (Scheme 1A).[7] Peptoids incorporating bulky branched *N*-alkyl side chains, for example, adopt conformations featuring *cis*-amide bonds that resemble polyproline I helices.[8,9] Similarly, peptoids including *N*-aryl side chains establish *trans*-amide bonds resembling the polyproline II conformation (Scheme 1B).[10,11]

The lack of intrinsic backbone chirality confounds the formation of preferred handedness in peptoid secondary

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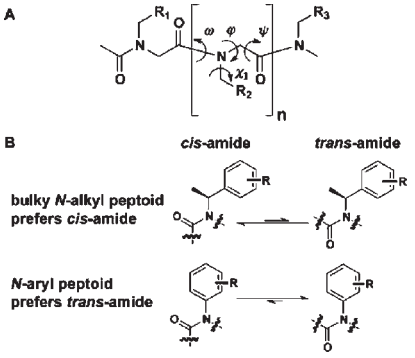
structures. Nevertheless, a suitable choice of side chain features can surmount this limitation. Bulky chiral *N*-alkyl side chains promote conformational ordering and can induce chirality in the peptoid backbone.[12] Handedness of the secondary structure may thus be dictated by the choice of side chain stereochemistry.[13]

Control of chirality has been demonstrated in a variety of folded oligomeric systems and does not necessarily require stereocenters in each of the monomer units.[14] One approach is to incorporate a chiral "sergeant", a specific chiral center capable of directing chirality throughout the oligomeric molecule.[15] Alternatively, handedness in folded oligomers can arise from the presence of other chiral elements, such as a chiral axis.[16]

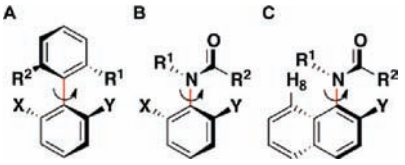
Atropisomerism is a stereochemical phenomenon in which the molecular chirality is established by virtue of restricted rotation around one or more bonds (Scheme 2A).[17] For congested tertiary anilides, electronic factors and steric hindrance can give rise to restricted rotation around the C−N(aryl) bond, promoting atropisomerism (Scheme 2B).[16,18] We have previously demonstrated that certain *N*-aryl peptoid oligomers incorporating bulky *ortho*-substituted anilide groups display chiral attributes due to atropisomerism.[16] *N*-aryl peptoids including *ortho*-iodo or *ortho*-*tert*-butyl anilide groups exhibit significant energy barriers to rotation about the stereogenic C−N(aryl) bond, allowing isolation of stable atropisomeric forms. Unfortunately, the synthesis of *ortho*-substituted *N*-aryl peptoids necessitates laborious solution phase chemistry and purification of intermediates.

Scheme 1. (A) Dihedral Angles (ω, φ, ψ, and χ_1) for Peptoids and (B) Amide Bond Isomerization in *N*-Alkyl and *N*-Aryl Peptoids



We now evaluate whether the inclusion of *N*-(1)-naphthyl glycine monomers in peptoids may similarly provide restricted rotation due to *peri* interactions. The *peri* hydrogen atom (H_8) in the naphthyl ring could engender a C−N(aryl) rotational barrier of sufficient magnitude to generate atropisomerism (Scheme 2C). Additionally, the use of naphthyl amines to generate *N*-(1)-naphthyl peptoids may enable convenient solid phase synthesis using an established "submonomer" method.[19]

Scheme 2. Biaryl and Nonbiaryl Atropisomers: (A) Biphenyl, (B) Tertiary Anilide, and (C) *N*,*N*-Disubstituted *N*-Naphthylamide



Quantum mechanical modeling of the *N*-(1)-naphthyl peptoid minimal unit (**Mono-1**) indicates that conformational preferences are similar to those previously seen in *ortho*-substituted anilides.[16,20] In the low energy conformations, the naphthyl plane is oriented perpendicular to the plane of the backbone amide ($\chi_1 \approx \pm 100°$; Scheme 1A). The naphthyl group projects away from the following backbone carbonyl oxygen. This side chain rotamer is preferred by ~1.6 kcal/mol at the B3LYP/6-311+G** level of theory. Transition state energy calculations for rotation around the χ_1 dihedral angle of **Mono-1** yielded barriers of ~24−26 kcal/mol (see Supporting Information, SI). The calculated rotational barrier height is comparable to that previously observed in *ortho*-substituted *N*-aryl peptoid atropisomers[16] and indicates the potential for axial chirality in *N*-(1)-naphthyl peptoids.

We synthesized an *N*-aryl peptoid monomer (**Mono-2**) using 1-naphthyl amine as a synthon (Scheme 3A). Additionally, an *N*-aryl peptoid monomer incorporating the 2-naphthyl group was synthesized as a control (**Mono-3**). For the synthesis of the peptoid monomers, we used a solution phase synthesis protocol as previously described.[5,16]

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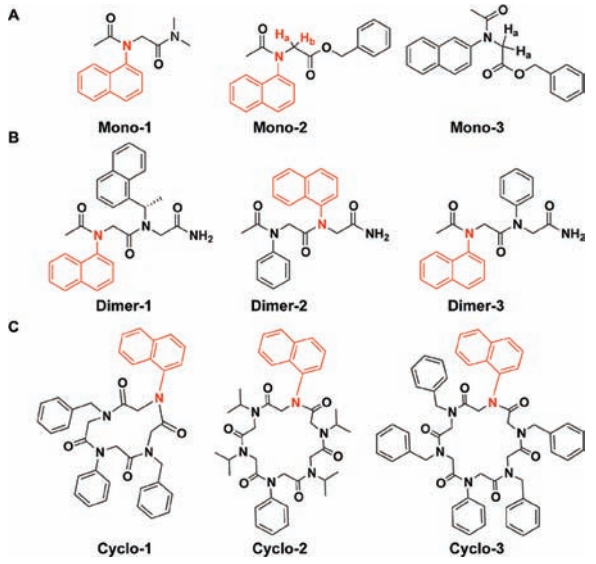
Scheme 3. Chemical Structures of Peptoid (A) Monomers, (B) Dimers, and (C) Macrocycles[a]



[a] *N*-1-Naphthyl groups are in red.

The presence of restricted rotation around the χ_1 dihedral angle was evaluated by NMR. For **Mono-2,** we observed that the backbone geminal methylene protons (Scheme 3A) were magnetically nonequivalent at 25 °C and appeared as doublet of a doublets (SI).[21] For **Mono-3** including the 2-naphthyl side chain, the geminal methylene protons were observed as a singlet.[22] This result indicates the importance of *peri* interactions in the *N*-(1)-naphthyl system to establish atropisomerism.

A significant energy barrier about a stereogenic C–N-(aryl) bond can permit the separation of atropisomeric conformers.[16,23] We observed that **Mono-2** can be resolved by chiral HPLC allowing enantioseparation into (*M*)-**Mono-2** and (*P*)-**Mono-2**, on Chiralpak AD stationary phase (Figure 1). Dynamic HPLC (DHPLC) can be performed at variable temperatures, providing a means to determine enantioconversion barriers. At 20.0 °C, baseline separation of (*M*)-**Mono-2** and (*P*)-**Mono-2** was observed. Upon increase of the temperature, characteristic changes in the HPLC elution profiles were observed due to on-column racemization (Figure 1). Computational fitting of the experimentally obtained DHPLC elution profiles[23] gave an activation energy for the atropisomerization ($\Delta G^{\ddagger}$) of 23.0 kcal/mol at 25.0 °C, consistent with the computational evaluation of **Mono-1** (*vide supra*). This activation energy is comparable to the energy barriers determined previously for *ortho*-substituted *N*-aryl peptoid atropisomers.[16] A van't Hoff plot of the DHPLC data obtained for **Mono-2** gave $\Delta H^{\ddagger} = 18.7$ kcal/mol and $\Delta S^{\ddagger} = -14.5$ cal/K mol, indicating a highly organized transition state.

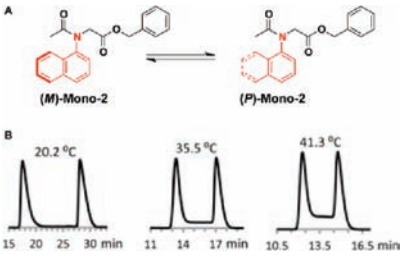


Figure 1. Dynamic HPLC studies of peptoid **Mono-2**. (A) Enantiomerization of **Mono-2** atropisomeric forms. (B) Variable temperature HPLC profiles of **Mono-2**.

The results from the study of the peptoid monomers allowed us to pursue atropisomeric features in peptoid dimers incorporating the *N*-(1)-naphthyl side chain. We synthesized a hybrid *N*-alkyl/*N*-aryl peptoid (**Dimer-1**, Scheme 3B) and two *N*-aryl peptoids (**Dimer-2** and **Dimer-3**). The linear peptoids were synthesized on solid phase using "submonomer" methods, as described previously, and then purified by HPLC (SI).[10,19]

In the absence of a chiral controlling influence, the ratio of *P* and *M* conformers of peptoid **Mono-2** are equally populated at room temperature (Figure 1A). However, it is possible to alter the relative population of interconverting atropisomers.[24] To this end, we obtained **Dimer-1** featuring the chiral (*S*)-*N*-(1-naphthylethyl) side chain at the *C*-terminus and the axially chiral *N*-(1)-naphthyl side chain at the *N*-terminus. This would presumably bias the *N*-aryl atropisomers of **Dimer-1** such that one conformer might predominate (Figure 2A). Below 15 °C, baseline separation of **Dimer-1** was observed. Upon further increase of temperature, on-column diastereomerization was observed. At 31.3 °C, the ratio of the diastereomers was estimated as 1.4:1 (Figure 2B). Based on DHPLC analysis of the elution profile obtained at this temperature, the activation energy and the rate for the diastereomerization of the major to the minor atropisomer were calculated as 23.0 kcal/mol and 0.0104 min^{-1}, respectively (SI). Thus, the relative energies of the axially chiral anilide rotamers can be influenced by an adjacent stable stereogenic center.[25]

Two *N*-aryl dimers (**Dimer-2** and **Dimer-3**, Scheme 3B) were prepared to further explore axial chirality in peptoid oligomers. **Dimer-2** and **Dimer-3** were synthesized incorporating the *N*-(1)-naphthyl side chain at the C-terminus or N-terminus, respectively. **Dimer-2** atropisomers could be resolved by chiral HPLC. The activation energy for isomerization of the atropisomers was comparable to the energy barrier for **Dimer-1** ($\Delta G^{\ddagger} = 21.9$ kcal/mol at 25 °C, SI). In contrast to **Dimer-1**, the ratio of enantiomers (*P* and *M* forms) of **Dimer-2** was 1:1 at ambient temperature, indicative of an equal population of interconverting atropisomers. **Dimer-3** atropisomers could similarly be separated by chiral HPLC. These results establish that peptoid

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dimers incorporating the *N*-(1)-naphthyl side chain at either the *N*-terminus or *C*-terminus can form stable atropisomers.

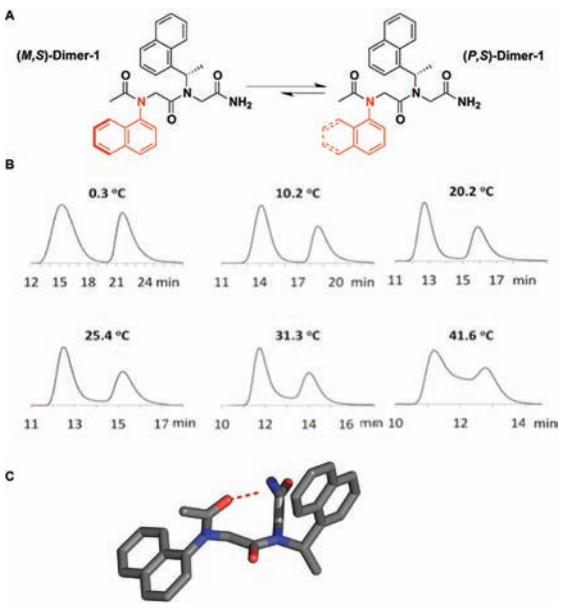

Figure 2. Dynamic HPLC and X-ray studies of peptoid **Dimer-1**. (A) Diastereomerization of **Dimer-1**. (B) Variable temperature HPLC profiles of **Dimer-1**. (C) X-ray structure of (*P*,*S*)-**Dimer-1** (red dashed line indicates hydrogen bond).

The peptoid **Dimer-1** was crystallized from ethanol by slow evaporation. The **Dimer-1** crystal was monoclinic and corresponded to the chiral space group $P2_1$. We observed one exclusive diastereomeric form (*P*,*S*) of **Dimer-1** in the solid state (Figure 2C, SI). To our knowledge, this is the first crystal structure for a linear *N*-aryl/*N*-alkyl hybrid peptoid. As observed for other *N*-aryl peptoid monomers,[10] the *N*-(1)-naphthyl monomer unit features a *trans*-amide bond with $\omega = 176.3°$. Correspondingly, the *N*-alkyl peptoid unit (S)-*N*-(1-naphthylethyl) monomer includes a *cis*-amide bond with $\omega = -1.9°$. **Dimer-1** features an intramolecular hydrogen bond between the carbonyl oxygen at the *N*-terminus and the NH_2 group of the amidated C-terminus, suggestive of a reverse turn motif (Figure 2C). Both the *N*-terminal (*N*)-1-naphthyl and C-terminal (*S*)-*N*-(1-naphthylethyl) monomer positions include predictable dihedral angles as evaluated previously by X-ray studies and molecular modeling (SI).[7,9−11] In addition, the overall conformation of **Dimer-1** corresponds to the low energy structure as modeled by calculation performed at the M052X/6-311+G** level of theory (SI).

We sought to establish atropisomerism in large peptoid macrocycles. We prepared three macrocycles from corresponding linear peptoids as previously described (Scheme 3C).[26] The tetramer sequence **Cyclo-1** and two hexamer sequences **Cyclo-2 and Cyclo-3** were synthesized incorporating a *N*-(1)-naphthyl side chain. For both **Cyclo-1** and **Cyclo-2,** chiral HPLC resolved the atropisomeric forms at room temperature (SI). Crystals were obtained for the cyclic hexamer **Cyclo-3** by slow evaporation in ethanol. **Cyclo-3** was monoclinic and crystallized in space group $P2_1/n$. The crystal structure of **Cyclo-3** displays two *trans*-amides at *N*-aryl positions 3 and 6, (Figure 3) and *cis*-amide bonds at the *N*-alkyl positions (1, 2, 4 and 5). The ω, φ, and ψ dihedral angles conform to the previously determined X-ray structure of a cyclic hexamer *N*-alkyl/*N*-aryl peptoid (SI).[10] Substantial disorder was observed in the side chains of **Cyclo-3**. The disorder prohibited a complete analysis of the (χ_1) side chain dihedral angles, which were investigated further by computational modeling (SI). The chiral features that may be established by atropisomeric peptoid macrocycles remain an intriguing topic for future studies.[27]

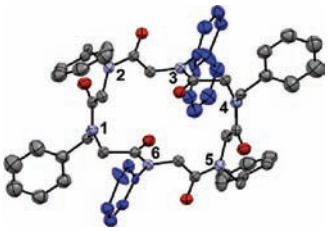

Figure 3. X-ray structure depicting a conformer of **Cyclo-3**.

Peptoids provide an attractive platform to evaluate the relationship between the sequence and structure of folded oligomeric molecules. We demonstrate that chirality can be established in peptoids in the absence of formal stereocenters. Peptoids incorporating the *N*-(1)-naphthyl side chain can exhibit axial chirality. We observed significant barriers to rotation around the C−N(aryl) bond. The slow isomerization rates allowed separation of linear and cyclic peptoid atropisomers by chiral HPLC. These advances will provide new strategies to define peptoid conformations and facilitate the development of more elaborate peptoid architectures.

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Supporting Information Available. Additional information regarding characterization of peptoids by HPLC, DHPLC, ESI−MS, NMR and computational studies. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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