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A Helix–Turn–Helix Supersecondary Structure Based on Oligo(phenanthroline dicarboxamide)s

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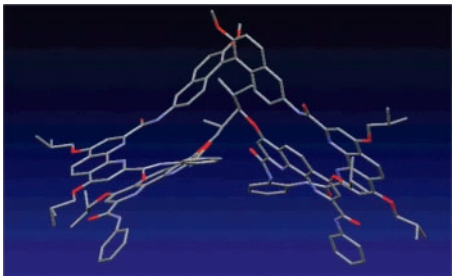
ABSTRACT



An artificial helix–turn–helix (HTH) supersecondary structure based on the oligo(phenanthroline dicarboxamide)s, in which the 2,2′-dimethoxy-1,1′-binaphthyl-6,6′-diamine subunit was utilized as the turn to impart a bias in the twist sense of the supersecondary structure, was reported. The HTH structure has been demonstrated by UV/vis, NMR, CD spectra, and X-ray crystal analysis.

Inspired by the fact that helices are not only key structural features of many biological macromolecules but are also important in material science,[1] much attention has been devoted during the past decade[2,3] to synthetic oligomers that could fold into stable, well-defined helical secondary structures. Recently, helical aromatic oligoamides[4] have attracted increasing interest for they feature a remarkable combination of structural predictability, stability, tunability, and ease of synthesis. Consequently, some helical foldamers based on oligoanthranilamides,[5] oligopyridine dicarboxamides,[6] quinoline-derived oligoamides,[7] and meta-connected diaryl amides[8] have been developed. However, the formation of distinct

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highly organized artificial structures from the assembly of several helical secondary elements is still a challenge.[9]

The helix−turn−helix (HTH) supersecondary structure composed of two helices connected by a turn is one of the simplest motifs with various important functions in DNA-binding protein.[10] However, few successful examples of artificial HTH systems have so far been reported.[11] Recently, we reported a new class of aromatic oligoamides based on phenanthroline dicarboxamides, which exhibited well-defined helical secondary structures in solution and in the solid state.[12] As part of continuing work, we herein report the first artificial aromatic oligoamide-based HTH supersecondary structure, in which a binaphthyldiamine moiety was inserted into the oligomer chains to impart a bias in the twist sense of the supersecondary structure. The design of the oligomers (±)-**1**−**3** and (*S*)-**1**−**3** was based on the oligo(phenanthroline dicarboxamide)s connected with (±)- or (*S*)-2,2′-dimethoxy-1,1′-binaphthyl-6,6′-diamine that could fold into a HTH motif (Figure 1).

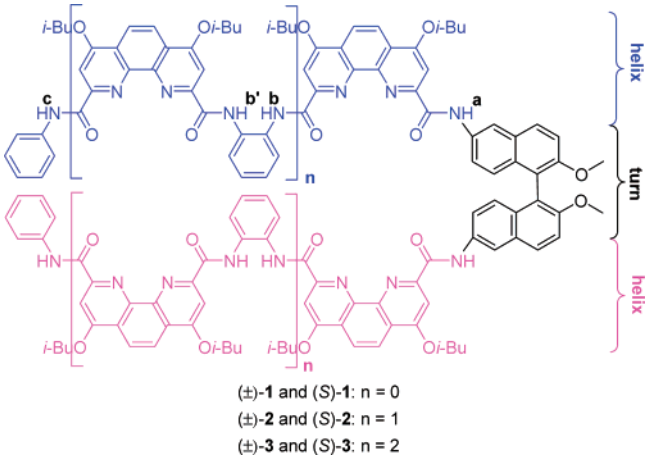
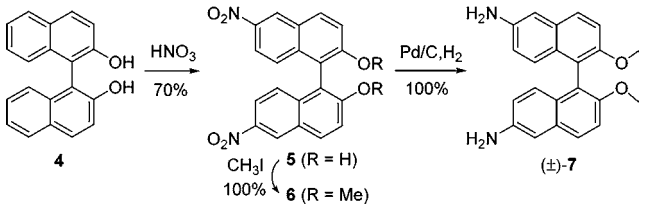


Figure 1. Chemical structures of oligomers **1**−**3**.

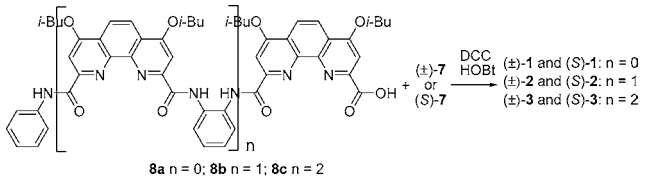
Compound 2,2′-dimethoxy-1,1′-binaphthyl-6,6′-diamine (±)-**7** could be conveniently synthesized by the nitration of the racemic binaphthol **4**, then alkylation with methyl iodide and catalytic hydrogenation in the presence of Pd/C (Scheme 1). With dicyclohexylcarbodiimide (DDC) and 1-hydroxy-

Scheme 1. Synthesis of Compound (±)-**7**



benzotriazole (HOBt) as coupling reagent, the oligomers (±)-**1**−**3** were synthesized in excellent yields by the condensation reactions of the appropriate monoacid **8** with the diamine (±)-**7** (Scheme 2). Following a method similar to the

Scheme 2. Synthesis of Oligomers (±)-**1**−**3** and (*S*)-**1**−**3**



above, the oligomers (*S*)-**1**−**3** could also be obtained by the reaction of the monoacid **8** and the optically pure (*S*)-2,2′-dimethoxy-1,1′-binaphthyl-6,6′-diamine[13] in the presence of DCC and HOBt. The structures of new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, MS spectra, and elemental analysis.[14]

We first examined the intramolecular interactions of the oligomers through the absorption spectra for the formation of helical structures that will lead to stacking of phenanthroline units. Consequently, the UV/vis spectra of the oligomers (±)-**1**−**3** were recorded in CH_3CN and shown in Figure 2. The UV/vis spectra of (±)-**1**−**3** display the absorption maxima at 348, 329, and 325 nm, respectively. With the increased number of phenanthroline rings from (±)-**1**−**3**, a slight blue-shift was observed, which might be attributed to the torsional distortions in phenanthroline rings. Moreover, the values of the molar absorptivity for (±)-**1**−**3** were found to be 4.8×10^4, 6.9×10^4, and 8.2×10^4 M^{-1} cm^{-1}, respectively. As expected, a hypochromic effect with an increased number of phenanthroline rings was shown, which implied that the helical ordering and $\pi-\pi^*$ stacking of the phenanthroline units in (±)-**2** and (±)-**3** might exist. To rule out intermolecular association, the ϵ for each oligomer was determined by using a range of concentrations.[14] For each compound, Beer's law behavior was observed, which indicated that the oligomers were in an ordered conformation consistent with the helix formation.[15]

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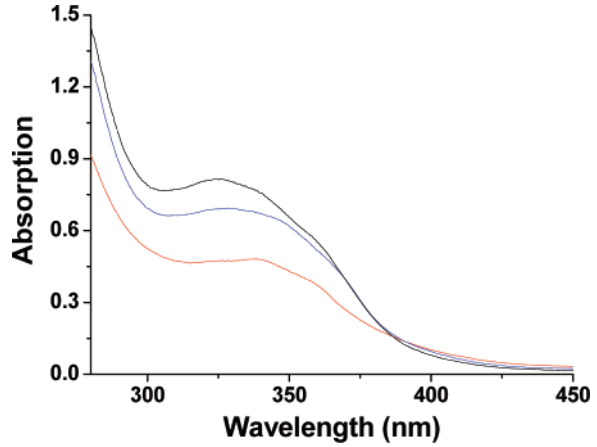

Figure 2. UV−vis spectra of the molecular strands (±)-**1** (red), (±)-**2** (blue), and (±)-**3** (black) in CH_3CN ($c = 10^{-5}$ M).

We further obtained a crystal structure[16] of the oligomer (±)-**2** from a solution of CH_2Cl_2/*i*-PrOH through a slow evaporation at room temperature, which provided direct evidence for the formation of the HTH supersecondary structure. As shown in Figure 3a,b, the oligomer (±)-**2** consisted of two regular helices linked by a binaphthyldiamine moiety, which resulted in an angle of 72° between the two helix segments, and subsequently formed a HTH motif. The network of intramolecular hydrogen bonds sets the conformation of each rotatable bond over the entire strand, and the high curvature of the strands leads to a complete turn for each helix in (±)-**2**. Both helical pitches are about 3.4 Å, which are consistent with those of helical foldamers we reported before.[12] Moreover, a pair of right- and left-handed helical strands are presented in the unit cell (Figure 3c). Two left-handed helices are always associated with the (*S*)-binaphthyldiamine, while two right-handed helical secondary structures are connected by the *R*-binaphthyldiamine. Interestingly, we also found that each oligomer includes three *i*-PrOH molecules. Two of them are presented at the outside ends of the two helices, while it might be due to the spatial interaction that only one *i*-PrOH molecule at the inside end was observed (Figure 3c). The multiple intermolecular hydrogen bonds between the *i*-PrOH molecules and the helices may play an important role in the stability of the helical foldamer.[14]

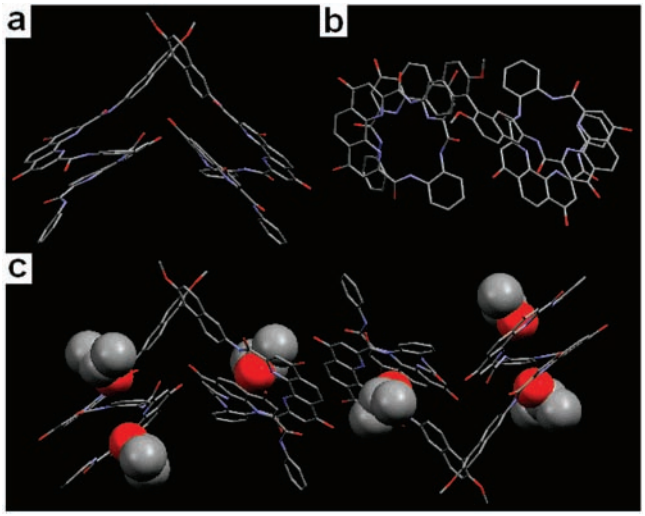

Figure 3. (a) Side view and (b) top view of crystal structure and (c) crystal packing of (±)-**2**. Solvent molecules not involved in the interactions with the helices, isobutyl chains, and hydrogen atoms were omitted for clarity.

To obtain more insights into the HTH structure, we further used the (*S*)-binaphthyldiamine as the turn to synthesize the oligomers (*S*)-**1**−**3**. Compared with racemic foldamers, the ^{1}H NMR spectra of (*S*)-**1**−**3** feature sharper peaks. With the help of the TOCSY spectrum, the peaks of NH protons in (*S*)-**2** could be assigned. A NOESY experiment of (*S*)-**2** in $CDCl_3$ was then carried out, which displayed the expected correlations for the formation of a helical structure in solution.[14] As shown in Figure 4, a cross-peak between two aryl NH protons was observed, which is consistent with the helical structure.

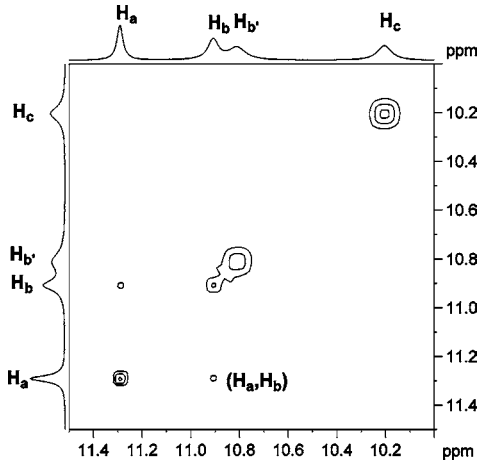

Figure 4. Partial NOESY spectrum of (*S*)-**2** in $CDCl_3$.

Circular dichroism (CD) spectroscopy is a useful tool to investigate the secondary structure of peptides and synthetic oligomers.[17] So we also carried out the CD experiments of oligomers (*S*)-**1**−**3**. The results showed that the CD spectra

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(16) Crystal data for the foldamer (±)-**2**: $C_{144}H_{148}Cl_2N_{16}O_{21}$, M = 2509.68, triclinic, space group $P\bar{1}$, a = 18.171(3) Å, b = 18.429(3) Å, c = 22.747(5) Å, α = 85.308(10)°, β = 77.267(9)°, γ = 70.020(10)°, V = 6983(2) Å^3, Z = 2, T = 113(2) K, 24500 reflections measured, 17506 independent, giving R_1 = 0.1170, wR_2 = 0.3476 for observed unique reflection ($I > 2\sigma(I)$), and R_1 = 1393, wR_2 = 0.3774 for all data.

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of (*S*)-**1**−**3** in acetonitrile are dependent on chain length. As shown in Figure 5, the observed signal of (*S*)-**1** is mainly

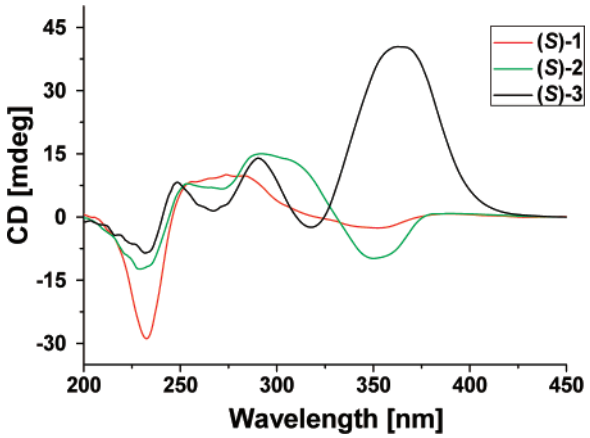

Figure 5. CD spectra of the molecular strands (*S*)-**1** (red), (*S*)-**2** (green), and (*S*)-**3** (black) in CH_3CN ($c = 10^{-5}$ M).

due to the chiral binaphthol unit in the chain.[18] The oligomer (*S*)-**2** gives a negative Cotton effect at 350 nm due to the $\pi-\pi^*$ electronic transition of the phenanthroline moiety, which demonstrated an ordered putative helical and the two helical segments with the same helicity (M-*S*-M). For the longer analogue (*S*)-**3**, it was interestingly found that a strong positive Cotton effect at 363 nm arising from the phenanthroline moiety was observed, which implied that the P-*S*-P should be the major isomer due to the possible spatial interaction between the two helices of the M-*S*-M isomer in (*S*)-**3**. Furthermore, the increase in the molar CD ($\Delta\epsilon$) from (*S*)-**2** to (*S*)-**3** (factor of 4.1) is much larger than the increase in UV/vis absorption coefficient ϵ (factor of 1.2), which indicated a marked amplification of the optical activity in (*S*)-**3**.[9c,17b]

In summary, we have presented the first artificial aromatic oligoamide based HTH supersecondary structure, which was composed of two helical secondary structures based on oligo(phenanthroline dicarboxamide) strands connected with a binaphthyldiamine as the turn. The HTH structures have been demonstrated by UV/vis, NMR, CD spectra, and X-ray crystal analysis. Our results showed that the stepwise synthetic strategy could be devised to access abiotic, conformationally defined architectures that to some extent mimic proteins. Future work will be focused on the new highly organized artificial structures based on the oligo(phenanthroline dicarboxamide) helical foldamers and their potential applications in molecular recognitions.

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Supporting Information Available: Synthesis and characterization data of the new compounds, copies of ^1H and ^{13}C NMR spectra for the new compounds, TOCSY and NOESY spectra of (*S*)-**2**, UV spectra of (±)-**1**−**3** and CD spectra of (*S*)-**1**−**3**, and an X-ray crystallographic file (CIF) for (±)-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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