Organic LETTERS

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pubs.acs.org/OrgLett

Controlling Helix Sense at N- and C-Termini in Quinoline Oligoamide Foldamers by β-Pinene-Derived Pyridyl Moieties

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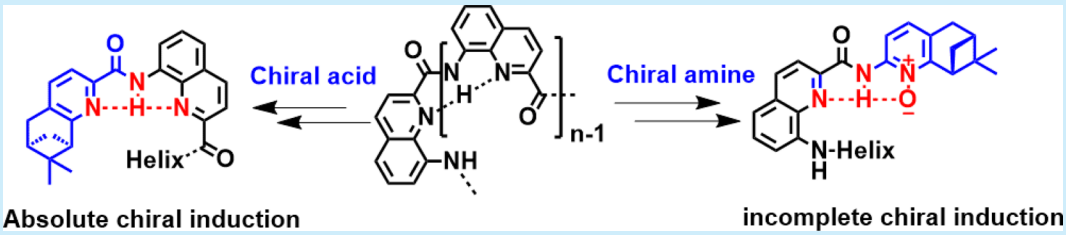
Supporting Information

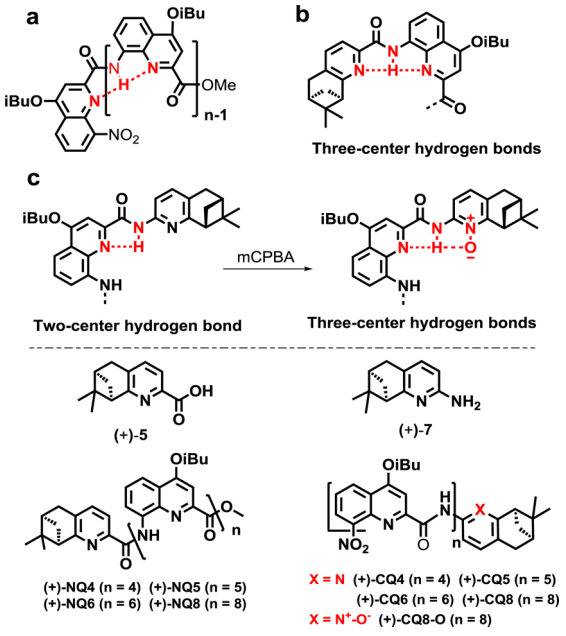


ABSTRACT: A series of quinoline oligoamide foldamers bearing a β-pinene-derived pyridyl group at the N-terminus or the C-terminus were synthesized, and the efficiencies of chiral inductions have been evaluated by ^{1}H NMR and CD spectra. The chiral inductions were quantitative when chiral pyridyl acid was appended at the N-terminus, but were inferior when chiral pyridyl amine was appended at the C-terminus. Unexpectedly, N-oxidation on the pyridine ring at the C-terminus does not notably enhance the chiral induction efficiency in spite of the presence of three-center hydrogen bonds.

The one-handed helicity of biomacromolecules, such as proteins and DNA, originating from their chiral monomers, plays a fundamental role in many biological processes such as DNA replication, asymmetric catalysis, and chiral transmissions of biological information. A variety of artificial oligomers termed as foldamers have been developed for understanding such chiral conformation in nature over the past two decades.[1] A foldamer consisting of achiral monomers, displaying an interconversion between the right- and left-handed helicity, is achiral. The strategies to bias one-handed preference including chiral inductions,[2−9] external stimuli,[3b,10−13] and cross-linking[14] have been receiving ever-increasing attention due to potentially practical uses in chiral sensing, chiral optical devices, and asymmetric catalysis.[15−17] Although a few examples have been reported on absolute control of one-handed helicity in aromatic foldamers, absolute control of helix sense at the N- and C-termini of aromatic peptides still presents a significant challenge.[9]

We envisioned that absolute control of helix sense could be achieved when chiral information was efficiently transferred with high-fidelity from chiral group to achiral foldamer backbone. Such chiral transfer can be realized by the combination of hydrogen bonds and steric interaction between chiral group and foldamer. For this end, oligoamides of 8-amino-2-quinolinecarboxylic acid, capable of folding into a helical conformation driven by a three-center hydrogen bond (Scheme 1), were chosen as model foldamers for investigating chiral induction because of its robust folded conformation and efficient synthetic procedures.[18] As for chiral induction moieties, we chose chiral β-pinene-derived pyridyl acid and amine because these chiral groups not only possess a large steric moiety inherited from the isoprenoid

Scheme 1. Structures of Quinoline Oligoamides with Chiral Inducing Groups at Termini



of β-pinene but also provide a pyridyl moiety able to form hydrogen bonds with the amide hydrogen (Scheme 1). These

Received: February 20, 2017

DOI: 10.1021/acs.orglett.7b00510
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features will be in favor of chirality transfer from chiral group to foldamer. We expected that when chiral acid was attached at the N-termini of quinoline oligoamide foldamers, the amide hydrogen forms stable three-center hydrogen bonds between the adjacent quinoline and the chiral moiety (Scheme 1b), which restrict the rotation of the chiral pyridyl group, leading to a strong chiral induction. While chiral amine was attached at the C-terminus of quinoline oligoamide foldamers, there is a two-center hydrogen bond between the chiral group and the adjacent quinoline so that a weak chiral induction is anticipated. Importantly, pyridine N-oxidation[19] will provide an extra hydrogen bond acceptor so as to generate three-center hydrogen bonds (Scheme 1c), which should also produce a strong chiral induction.

Here we demonstrate our proof-of-concept design. Our ^{1}H NMR and circular dichroism (CD) investigations showed that β-pinene-derived pyridyl carboxylic acid is able to completely bias the helical sense of quinoline oligoamide foldamers at the N-terminus, but β-pinene-derived pyridyl amine is a much inferior chiral induction group at the C-terminus. Surprisedly, N-oxidation on the pyridine ring at the C-terminus did not significantly enhance the chiral induction efficiency.

Chiral β-pinene-derived pyridyl carboxylic acid (+)-**5** and amine (+)-**7** have been easily synthesized from its precursor β-pinene-derived pyridone.[20,21] The coupling reaction of (+)-**5** and amino-quinoline dimer via acid chlorides gave dimer (+)-**NQ2**, which was saponified and further coupled with the appropriate quinoline oligomeric amines to generate (+)-**NQ4**, (+)-**NQ5**, (+)-**NQ6**, and (+)-**NQ8** (named for the N-terminus) (Scheme 1). (+)-**CQ4**, (+)-**CQ5**, (+)-**CQ6**, and (+)-**CQ8** (named for the C-terminus) have been synthesized by the coupling of chiral amine (+)-**7** with amino-quinoline oligomers. The structures of these new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and MS spectra (Supporting Information).

The populations of two diastereomeric M and P helices can be assessed by a ^{1}H NMR spectrum if a foldamer is long enough to undergo slow interconversion on the NMR time scale. As shown in Figure 1, ^{1}H NMR spectra display only one set of signals for

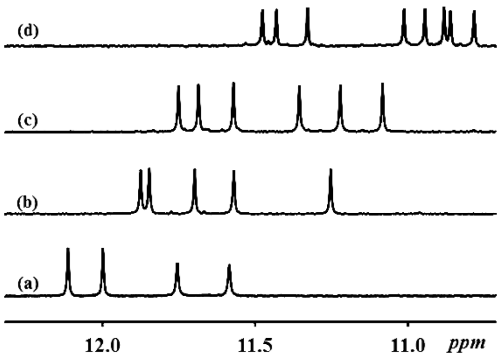

Figure 1. Parts of the 400 MHz ^{1}H NMR spectra of compounds: (a) (+)-**NQ4**; (b) (+)-**NQ5**; (c) (+)-**NQ6**; (d) (+)-**NQ8** in $CDCl_3$ at 25 °C.

(+)-**NQ5**, (+)-**NQ6**, and (+)-**NQ8**, assignable to either P or M diastereomers for (+)-**NQ5**, (+)-**NQ6**, and (+)-**NQ8** because previous studies showed that pentamer of quinoline oligoamide foldamer is long enough to undergo slow helix handedness inversion on the NMR time scale in $CDCl_3$ at 25 °C.[9a] Therefore, it is clear that the inductions of the helical sense are absolute in this solution for these long oligoamides. Additionally, the ^{1}HNMR spectra of (+)-**NQ8** showed only a single set of signals in polar solvents (Figure S1), such as DMSO-d_6 and pyridine-d_5, indicating that neither chiral induction nor helical stability is affected by the polarity of solvents.

In the case of (+)-**NQ4**, although ^{1}H NMR spectrum also displays only one set of signals (Figure 1a), a complete helical sense bias is unable to be claimed at this moment because tetramer shows fast helix handedness inversion on the NMR time scale in $CDCl_3$ at 25 °C.[18a,22] To further clarify the chiral induction efficiency of chiral pyridyl group in (+)-**NQ4**, variable-temperature (VT) NMR experiments were carried out from −80 to 100 °C and revealed only one set of signals detectable in the whole range of temperatures (Figures S2 and S3), hinting at an absolute helical sense bias for (+)-**NQ4**. The VT NMR experiments further strengthen the argument for diastereomeric purity of (+)-**NQ4** and also imply that the single set of NMR originates from either M or P diastereomeric (+)-**NQ4**.

Next, we decided to destroy the three-center hydrogen bond network by protonation of the pyridine in the chiral group to see whether the chiral induction could be weakened. The protonation indeed led to the observation of two sets of new signals assignable to two diastereomers, as demonstrated by NMR for (+)-**NQ4** and (+)-**NQ6** (Figures S4 and S5), implying an incomplete chiral induction. The two sets of new signals could be reversely converted to the single set of signals by the sequential neutralization. Given that the parent foldamer could not be protonated as shown in the control experiments (Figure S6), we therefore believe that the protonation takes place in the chiral group and simultaneously breaks down the hydrogen bond network, which consequently causes the loss of chiral induction of helix sense.

The CD spectra of foldamers (+)-**NQ4**−(+)-**NQ8** in DCM (Figure 2) show strong positive Cotton effects in the absorption

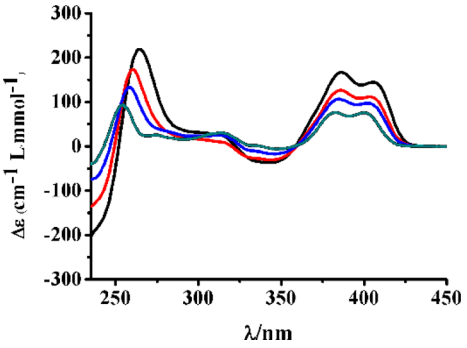

Figure 2. CD spectra of compounds (+)-**NQ4** (dark cyan), (+)-**NQ5** (blue), (+)-**NQ6** (red), and (+)-**NQ8** (black) in DCM.

region of the quinoline chromophores (350−420 nm), indicating a P handedness[2] induced by (+)-pinene-derived pyridyl group at N-terminus. The linear fitting of the $\Delta\varepsilon$ of (+)-**NQ4**−(+)-**NQ8** at 383 nm (Figure S12) illustrated that the intensity of the Cotton effect increased linearly with the growth of the chain length and that each compound had the same intensity ($\Delta\varepsilon$) per monomer, strongly suggesting that there is no loss of chiral induction of helix sense by (+)-pinene-derived pyridyl group at the N-terminus as the chain of foldamer is lengthened. This finding is consistent with the case in which the quantitative helical sense biases were induced by chiral camphanyl group.[9a] Finally, the CD signals of (+)-**NQ4** and (+)-**NQ6** disappeared upon the protonation and almost recovered to the original state upon the sequential neutralization (Figure S13). Again, these CD

DOI: 10.1021/acs.orglett.7b00510
Org. Lett. XXXX, XXX, XXX−XXX

results further support that the protonation damages the fidelity of the chirality transfer from the chiral group to the achiral foldamer, and the single set of NMR signals originates from either diastereomeric pure P or M helix rather than a mixture of M and P diastereomers with a fortuitous coincidence of all resonances.

We next examined the chiral induction efficiency of pinene-derived pyridyl amine at the C-terminus of aromatic peptides. The ^{1}H NMR spectra of (+)-**CQ5**, (+)-**CQ6**, and (+)-**CQ8** showed two sets of signals on the NMR time scale in $CDCl_3$ at 25 °C (Figure S7), revealing the existence of two diastereomers in $CDCl_3$. The *de* values of (+)-**CQ5**−(+)-**CQ8** were ca. 73% on the basis of NMR measurements. However, the ^{1}H NMR spectra showed only single set of signals for (+)-**CQ4** at 25 °C in $CDCl_3$. Given the incomplete chiral inductions in the cases of (+)-**CQ5**−(+)-**CQ8**, this phenomenon is attributed to the fast inversion of two diastereomers in the solution rather than the existence of single diastereomer, which was further confirmed by VT NMR experiments in which the single set of signals of (+)-**CQ4** decoalesced into two slowly exchanging constituent peaks when the temperature was cooled to 0 °C (Figure S8). The *de* value was calculated to be about 70%, which remained constant even the temperature decreased further.

The CD spectra demonstrated that (+)-**CQ4**−(+)-**CQ8** also prefer a P helical conformation (Figure S14), showing that pinene-derived pyridyl amine (+)-**7** attached at the C-terminus is also able to induce a P helix but with a smaller amplitude of $\Delta\varepsilon$ values in comparison with pinene-derived pyridyl acid (+)-**5** attached at the N-terminus under the same conditions. This can lead the conclusion that chiral induction at the N-terminus is more efficient than that at the C-terminus due to the more stable hydrogen bond network at the N-terminus. This observation is consistent with the previous study of oligomers of α-amino-isobutyric acid (Aib), which adopt 3^{10} helix.[4b]

The previous investigations show that the half-life of helix inversion of chiral octamer of quinoline oligoamide is long enough to allow separation of two diastereomers by chromatography.[2] As expected, the pair of diastereomers of (+)-**CQ8** appeared as two distinct spots on TLC at room temperature, allowing a successful separation of the two diastereomers by regular silica gel chromatography. ^{1}H NMR spectra of the diastereomers were recorded just after separation and revealed that the major diastereomer was pure, but the minor one was not (Figure S9). An attempt to further purify the minor diastereomer failed. The major diastereomers progressively convert to the minor ones, and equilibrium is reached after 1 day at room temperature (Figure S15). The handedness of the major diastereomer of (+)-**CQ8** is assigned as P helicity according to CD experiments.[2]

N-Oxidation was chosen to generate an extra hydrogen bond acceptor because it should not notably affect the helical structure of quinoline-derived oligoamides.[19] The oxidation of (+)-**CQ8** was tested first in the presence of 8 equiv of *m*-CPBA. NMR experiments revealed that the oxidation was over in less than 30 min by monitoring the peak of amide hydrogen at 9.17 ppm close to chiral group and that original two sets of signals disappeared gradually with simultaneous appearance of two sets of new signals in low field rather than one set of signals as expected (Figures 3 and S10), hinting that the chiral induction is not absolute either. Mass spectrometry show N-oxidation only occurred on the chiral pyridyl ring (Figure S20) because no oxidation on quinoline rings was detected in the control experiments (data not shown). However, we also tested the

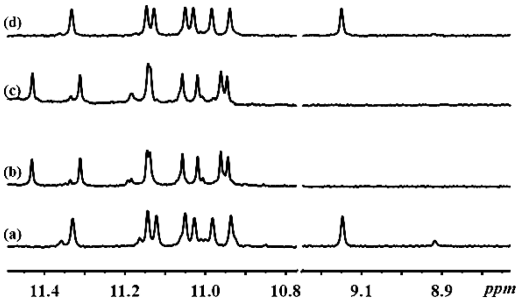

Figure 3. Parts of the 400 MHz ^{1}H NMR spectra of (a) (+)-**CQ8**; (b) (+)-**CQ8** in the presence of 8 equiv of *m*-CPBA in 12 h; (c) (+)-**CQ8-P** in the presence of 8 equiv of *m*-CPBA in 1 day; and (d) (+)-**CQ8-P** in $CDCl_3$ at 25 °C.

oxidation on diastereomeric pure (+)-**CQ8-P** (**P** helix) under the same condition. NMR monitoring display that the oxidation of (+)-**CQ8-P** was also completed in less than 30 min and the oxidized product (+)-**CQ8−P-O** appeared simultaneously. However, another set of minor signals set to appear over 25 min (Figures 3 and S11), implying that the major P helix of (+)-**CQ8-O** is able to partially convert into M helix of (+)-**CQ8-O**. Thus, it is not surprised that the final products are almost the same in the both cases due to interconversion as demonstrated by NMR and CD spectra (Figures 3 and S16). The *de* values of (+)-**CQ8** and (+)-**CQ8-O** were determined to 73% and 80% on the basis of CD measurements, respectively (Table S1), indicating that although the oxidation generates an extra hydrogen acceptor for forming three-center hydrogen bonds, it poses a slight effect on chiral induction. The chiral induction at the C-terminus is weaker than that at the N-terminus and may be attributed to the different stability of three-center hydrogen bonds at the both termini. Finally, the half-lives of helices for approach to equilibrium were found to be 223 and 172 min for (+)-**CQ8** and (+)-**CQ8-O**, respectively (Figures S18 and S19; Table S2 and S3).

In summary, we have demonstrated controlling helical sense of quinoline oligoamide foldamers at the N- and C-termini by β-pinene-derived pyridyl moieties. The present studies reveal that the chiral inductions were absolute at the N-terminus but incomplete at the C-terminus, which suggests that chiral induction is great if a chiral input is applied at the N-terminus rather than at the C-terminus. Our investigations highlight a great challenge to obtain absolute helical sense at the C-terminus, which is an ongoing project in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00510.

Experimental procedures, characterization of synthesized oligomers, and additional data (PDF)

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DOI: 10.1021/acs.orglett.7b00510
Org. Lett. XXXX, XXX, XXX−XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21472015, 21511130061, and 21332008).

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DOI: 10.1021/acs.orglett.7b00510
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