Metadynamics Simulations on the Key Factors of Handedness Induction for the N/C-Terminal Substituted Quinoline Oligoamide Foldamers

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Abstract

Metadynamics simulation has been used to describe the conformational energy landscapes of several helical quinoline oligoamides bearing β-pinene-derived pyridine at either the C or N terminus. Based on the experimental results, helix-sense preference for four types of foldamers with the chiral terminal group has been verified. To compare to the key factors of inducing handedness to helical-sense preference, a terminal group with three hydrogen bond sites is designed and corresponding foldamers are built. The calculated results show the delocalization effect and steric hindrance mainly responsible for a particular helix-sense preference for the investigated foldamers. The more hydrogen bonds between the terminal group and oligoamide units are formed, the more stable foldamers are.

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Keywords: Metadynamic, Helix, Chirality, Terminal group

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1. Introduction

Today, foldamers represent a rapidly growing ensemble of molecules in terms of diversity and chemical complexity. Foldamers can be as a bridge between the molecular chirality and recognize of biological molecules.

Many reports have shown that foldamers display biomimetic properties on reminiscent of allosteric proteins and receptor molecules[1-3]. Foldamers can translate chemical signals into conformation changes, and hence into chemical outputs such as control of reactivity and selectivity. Recent years, many potential bioactive foldamers have been discovered, quinoline oligoamides have been extensively demonstrated to adopt stable helical conformations in various solvents. Dr. Liu and her group members had reported some important foldamers with different terminal groups, and they found that the helix-sense bias of foldamers can really be predicted by analysing the interactions (hydrogen bond, steric and so on)[4-6], and the chirality of terminal group influences on the helix-sense of foldamers. A previous report found the steric and hydrogen bonds have important influences on the helical handedness of foldamer. So, it is benefit for the biological application of foldamers by synthesizing new foldamers with bioactive terminal group.

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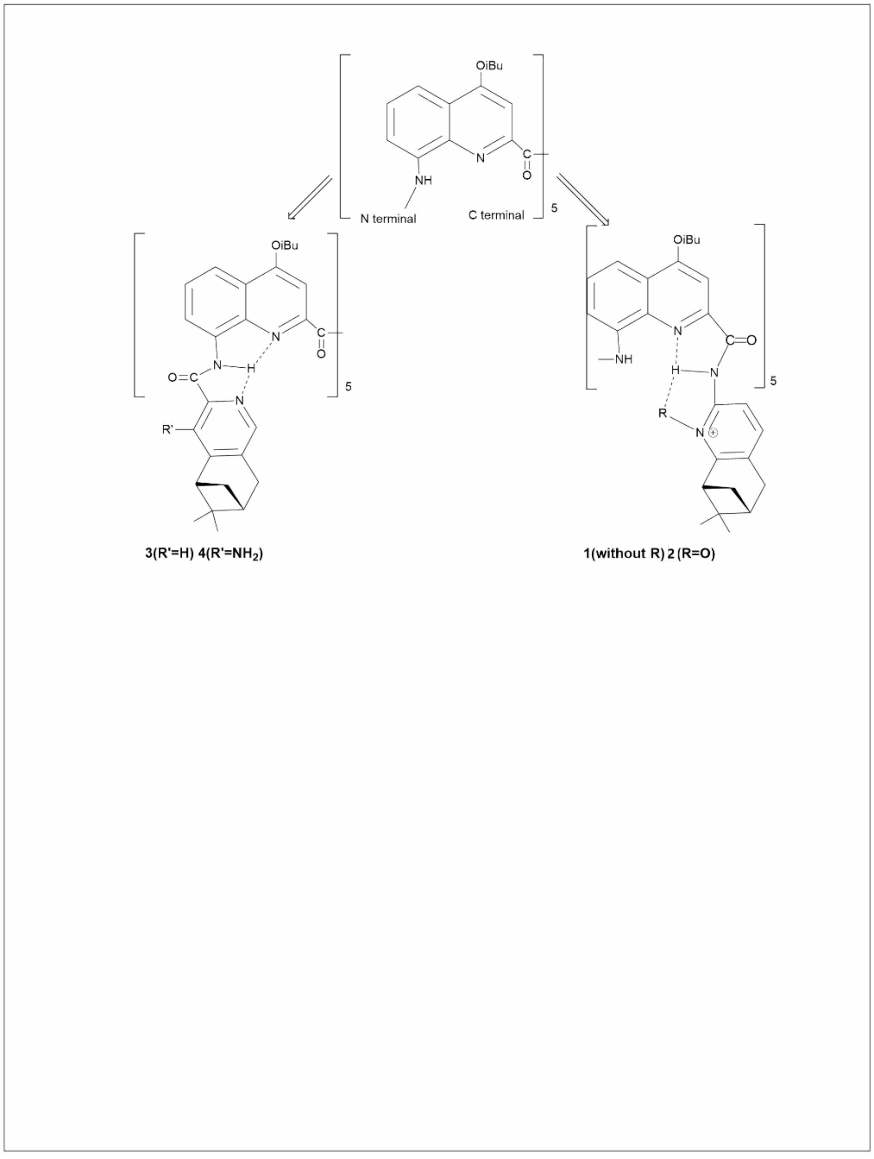


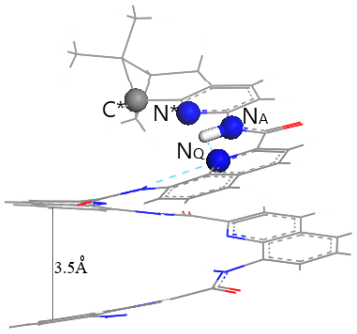
β -pinene is an optically active and racemic molecule, which presents in turpentine oils. It was demonstrated that when β-pinene synergizes with paclitaxel, they can suppress lung carcinoma cells. The geometrical structure of β -pinene with chiral atom has big space steric hindrance, which is benefit for the synthesis of chiral foldamers. Therefore, a lot of study has been reported on enantio-selective ofβ -pinene derived molecular [7,8]. In 2017, the study that β -pinene-derived pyridyl group can induce the handedness of oligoamide foldamers has been reported[9]. Experimental data has shown thatβ -pinene-derived pyridyl connecting with quinoline oligoamide behave better selection of handedness at N-terminal than at C-terminals. They had investigated three types of foldamers, and thought that hydrogen bond should be an obvious factors of helical handedness. However, it is reported that hydrogen bonds, steric hindrance and electrostatics are responsible for the helical handedness either in the C-terminal or N-terminal in some works [10,11]. In order to reveal the intrinsic reason for better selection of helix-sense at N-terminal than at C-terminal, six experimental synthesized and two designed oligoamide foldamers substituted by β -pinene have been investigated in this paper. Six synthesized oligoamides include four foldamers containing β -pinene-derived pyridyl amine at the C-terminal (**1a, 1b, 2a,** and **2b)** , two foldamers containing β - pinene-derived pyridyl carboxylic acid at the N-terminal (3a and **3b**). Two designed oligoamides include two foldamers containing three-center hydrogen bonds at N-terminal (**4a** and **4b**). Four types of foldamers (**1-4**) have been designed and they have been shown in **Scheme 1.** In foldamer **1**–**4** , **na** represents R chirality ofβ -pinene, **nb** represents S chirality of β -pinene. Because Zheng et al. have found that these foldamers are stable in chloroform ($CDCl_3$), $CDCl_3$ was selected as the solvent environment here. Based on the metadynamics simulations, the helical handedness of four types of foldamers withβ -pinene-derived pyridine has been calculated. From the data of the dihedral angle, rotation angle, and electronic orbitals constitutions of foldamers, the key factors of chiral induction toβ -pinene substituted foldamers have been analyzed and discussed.

Scheme 1. The structures of the foldamer **1**–**4**

2. Results and Discussion

To obtain P or M helical bias of foldamers in the solvent, all investigated foldamers were put into a chloroform box. The metadynamics method was applied to investigate helical inversion of pentameric**1**–**4** in chloroform, and force field parameters specifically were optimized for the arylamides containing quinoline-based. Computations were systematically performed on each enantiomer to assess their reproducibility.

2.1. Helix handedness of oligomers (1a/1b) substituted byβ -pinene-derived pyridyl amine at C-terminal



Metadynamics studies of **1a/1b** (quinoline oligoamide pentamers substituted by β-pinene-

Figure 1. The free-energy profile of **1a Figure 2.** The structure of **1a**

derived pyridyl amine at C-terminal) indicated the same helical bias as the experimental results. **1a** possesses a (R) –β -pinene-derived pyridyl amine (Figure 1 right), yields a P helix as the global minimum. From the free-energy profile (FEP) of**1a** , it can see that P helix has about 2.3 $kcalmol^{-1}$ minima free energy. The

free-energy of M helix is 3.7 kcalmol^{-1} in **1a** , the energy gap is 1.4 kcalmol^{-1}, so the helical selectivity of 1**a** is not obvious. And **1b** has the same case**,**for **1b** (enantiomer of **1a**)**,** the M helix are more stable than P helix. **1b** possesses a (S) –β -pinene-derived pyridyl amine ⁽Supporting Information S1), yields an M helix as the global minimum, and minimum energy is about 2.08 kcalmol^{-1}. The free-energy of P helix is 3.5 in **1b.** Therefore, the helix handedness of**1a/1b** is mainly induced by the carbon atomic chirality ofβ -pinene-derived pyridyl amine. The structural features of the (P)-**1a** /(M)-**1b** were conducted by extracting conformations from the M-and P-helix using the 400 ns metadynamics trajectories. From the most stable structure of **1a** and**1b** (Supporting Information S2), it can get following structural parameters. The helical pitch of **1a** and **1b** is 3.5 Å and 3.6 Å. The terminal group (β -pinene-derived pyridyl amine) did not form any hydrogen bonds with quinoline oligoamide. That is, the hydrogen bond can not affect the helical handedness in**1a/1b** . Based on the analysis of the stable conformations of**1a/1b** , the two methyl groups of β -pinene both rotate to the out of helix, which can decrease the steric hindrance. Thus, the different between P and M is only from the angle degree of [?]N_Q-C_Q-C-N_A (figure 1 right) and [?]C_Q-C_Q-N_A-C. The figure 3 shows the structural analysis of **1a** . From Figure 3, it can see that the angle peaks of [?]N_Q-C_Q-C-N_A lie at $\pm$17° and [?]C_Q-C_Q-N_A-C lies at +-180deg for **1a** . The frequency of occurrence of [?]N_Q-C_Q-C-N_A is bigger than that of [?]C_Q-C_Q-N_A-C, it is revealed that the [?]N_Q-C_Q-C-N_A obviously determined the helix bias sense of foldamer. From Figure **4** , it can see that the angle

Figure 3. Dihedral angle distributions of **1a Figure 4.**The frequency of occurrence for

[?]N_Q-C_Q-C-N_A in**1a and 1b**

peaks of [?]N_Q-C_Q-C-N_A are 17deg in P-**1a** and P-**1b** , and it is -17deg in **M-1a**and **M-1b.** It means[?]N_Q-C_Q-C-N_A do significantly influence the helix handedness of foldamer. Because there is not formation of hydrogen bond between the terminal group and quinoline oligoamide, the steric hindrance effect and chiral atom should be the important factors on the helix handedness of **1a/1b** .

2.2. Ηελιξ ηανδεδνεσς οφ β-πινενε-δεριεδ πψριδψλ αμινε συβστιτυτεδ ολιγομερς 2α/2β ατ ˜-τερμιναλ

To find the proof of hydrogen bonds on the helix-sense bias of foldamer, Zheng [9] et al had synthesized the other foldamer **2** , in foldamer **2** , hydrogen bond O–H-N_A is formed between terminal group and quinoline-based amine (Figure 5). However, they found that the hydrogen bond O–H-N_A cannot enhance the helix-sense bias of foldamer. So we built foldamer**2** according to the experimental data and performed the dynamic calculation. From the results of metadynamics calculations, it can see that free-energy of **2a** (Supporting information S3) and**2b** only has little change compared to **1a** and**1b** , **2b** shows M helix with the global minimum, the minimum free-energy is about 2.47 kcalmol^{-1} (Figure 6). And the free-energy gap of **M** and **P** is 2.1 kcalmol^{-1}in **2b** . The structural parameters of**2a/2b** are similar to those of **1a/1b** . The helical pitch of **2a** and **2b** is 3.62 and 3.56Å, and the R chirality ofβ -pinene still induces a P helix, and S chirality induces the M helix in **2b** (Supporting information S4). Due to the similar structural parameters and free-energy gap between **1a/1b and 2a/2b** , it means that the hydrogen bond O–H-N_A does not obviously improve the selection of foldamer **2a/2b** .

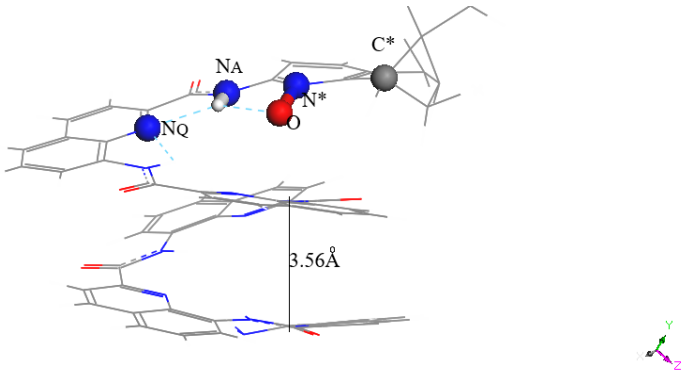
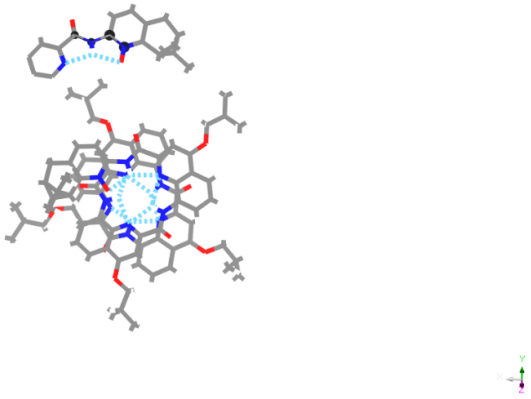


Figure 5. The structure of foldamer **2b Figure 6** . Free-energy profile of **2b**

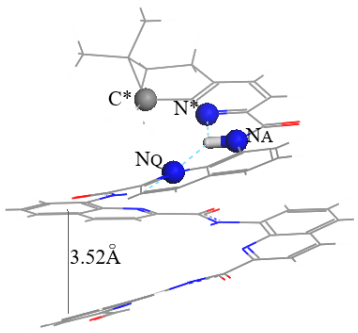


Of course, the distribution of dihedral angle [?]N_Q- C_Q- C-$N_A$and [?]C_Q-C_Q-N_A-C can make a distinction between the chirality of **2a** and **2b** . From Figure 7, it can be seen that the angle peaks of [?]N_Q-C_Q-C-N_A at $\pm 10^{\circ}$ for (P)-**2a** /(M)-**2b** . The angle peaks of [?]N_Q-C_Q-C-N_A for**2a/2b** are less than that in **1a/1b** , it due to two three-center hydrogen bonds O–H-N_A and N_Q–H-N_A improve the coplanar of [?]N_Q-C_Q-C-N_A(Figure 8). Based on above analysis, it shows that atomic chirality is the main factor on the helical selection of β -pinene-derived pyridyine

Figure 7. The three-center hydrogen bond in **2b. Figure 8.** The frequency of occurrence for N_Q-C_Q-C-N_A in**2a** and **2b**

substituted foldamer at C-terminal, and hydrogen bond just enhance the stable of foldamers **2a/2b** . However, the experimental found that the N-terminal substituted foldamers have better helical selection than C-terminal substituted foldamers. What is the intrinsic reason?

2.3Ηελιξ-ηανδεδνεσς βιας οφβ-πινενε-δεριεδ πψριδψλ ςαρβοξψλις αςιδ-συβστιτυτεδ ο-λιγομερς 3α/3β ατ Ν-τερμιναλ



3is the β -pinene-derived pyridyl carboxylic acid substituted quinoline oligoamide foldamer at N-terminal. The computational results show that the free-energy difference is 4.77 kcalmol^{-1} between P-**3a** and M-**3a** . The R chirality of terminal atom still induces the P helix and S chirality of terminal atom still induces the M helix(Supporting information S6).

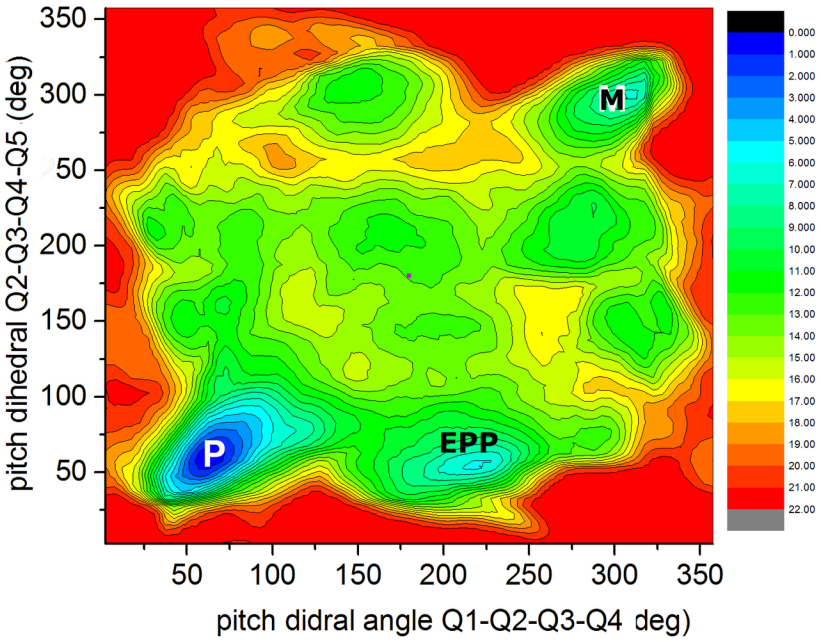
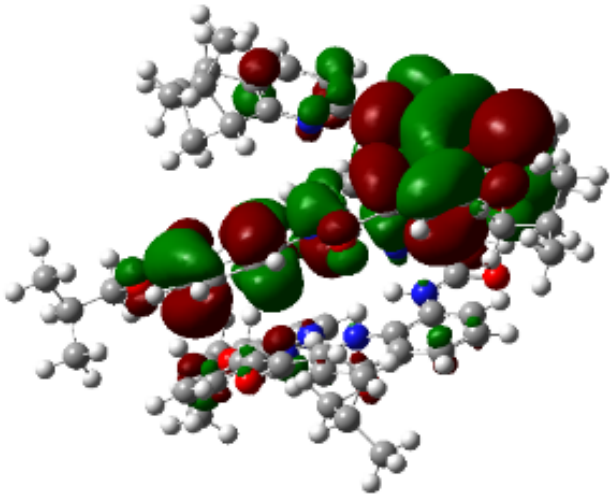
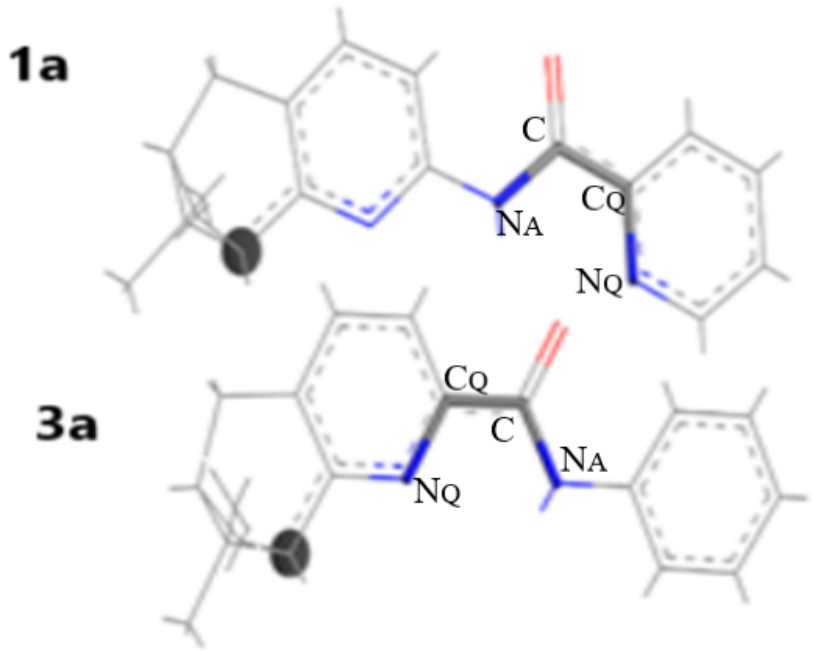


Figure 9 . The structure of **3a** **Figure 10.** The FEP graph of **3a**



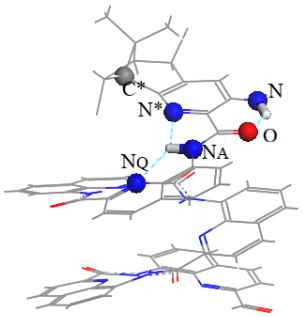


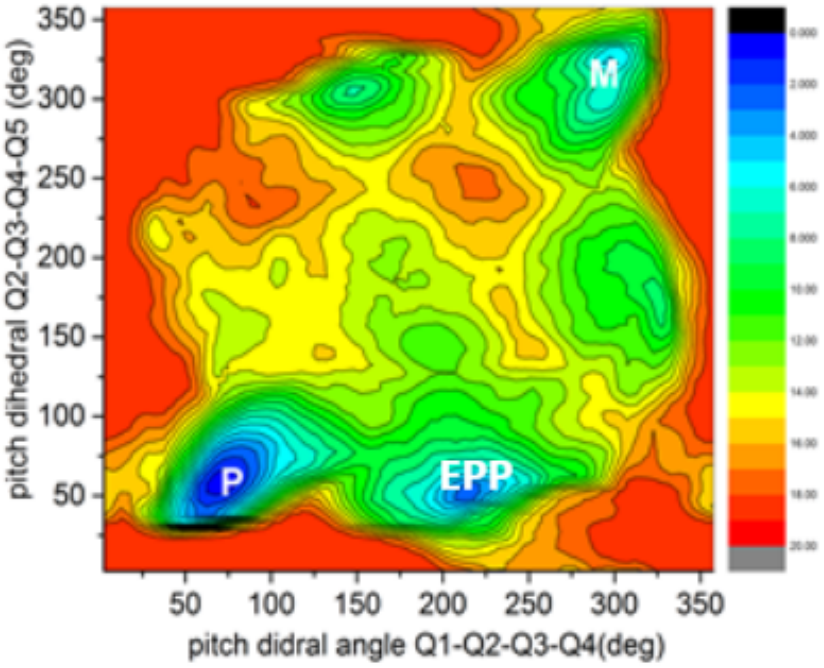
Foldamer **3a** (Figure 9) is consistent with **1a** and**2a** , and the helical pitch is 3.52Å and 3.74 Å.Two three-center hydrogen bonds(N^*–H-$N_A$and N_A-H–N_Q) were formed between the terminal β -pinene-derived pyridyl carboxylic with quinoline oligoamide, the hydrogen bonds length are 2.28 Å and 2.09 Å, the bond angles are 107.9° and 106.8°, respectively. Interestingly, the distribution of N_Q-C_Q-C-N_A shows that angle peaks at +-10deg, which is consistent with **2** . That is, three-center hydrogen bonds do improve coplanar of [?]N_Q-C_Q-C-N_A. Next, the investigation was locked at the character of dihedral angle [?]N*-C*-C=O in **3a.**

Compare with [?]N*-C*-N-H dihedral angle in **1** and**2** , rotation of [?]N*-C*-C=O is more difficult than that of [?]N*-C*-N-H. In addition, the electronic delocalization effect was found between bond C=O and pyridine ring of terminal group. The delocalization can be proved by three bonds length. As Figure 11 shows that **3a**and **1a** has the same bonds N_Q-C_Q, C_Q-C, and C-N_A, but the bonds length of N_Q-C_Q, C_Q-C, and C-N_A are 1.3521 A, 1.4972 A and 1.3720 A in **3a** , respectively, which are shorter than those in **1a** (1.3698, 1.5529, and 1.4330). Furthermore, the orbital properties of the terminal group also show the delocalization properties of terminal group in**3a** . The terminal group has contributions in the HOMO orbital of**3a** , but terminal group has no contribution in the HOMO orbital of **1a** (Figure 12). It is worthwhile noting that a metastable state **EPP** (Q1-Q2 is extended, Q2-Q3 and Q3-Q4 are P helix) has been found in the FEP of **3a** (Figure 10), the free-energy of**EPP** is about 2.7kcalmol^{-1}. That is, when the P helix of **3a** converts to M helix, it needs cross a metastable state EPP. And the metastable state also results in the big free-energy gap between P- **3a** and M-**3a** , it is the main reason that**3a** has better helical selection than **1a** . Based on the above discussion, we conclude that the electronic delocalization effect influences the selection of helical handedness, and the delivery of chirality in the conjugated chains is easier than in unconjugated system, which corresponds to some experimental results [12-15].

Figure 11 . The structure of N_Q-C_Q -C -N_A.**Figure 12** The HOMO orbital distribution.

2.4 Ηελιξ-ηανδεδνεσς βιας οφ β-πινενε-δεριεδ πψριδψλ ςαρβοξψλις αςιδ-συβστιτυτεδ ολιγομερς 4α/4β ατ Ν-τερμιναλ





From investigation of foldamer **1, 2** and **3,** it is found that the three-center hydrogen bonds between the terminal group and oligomers are found both in **2** and **3,** but the helical selection is Figure 13. The FEP of **4a** Figure 14. The structure of **4a**

better in **3** than in **2** . To further investigates the relation between hydrogen bonds and helical

handedness of foldamers. We designed a -NH_2 connected with pyridine ring of the terminal group (Scheme 1), and -NH_2 formed another hydrogen bond (N-H–O) with quinoline amide. When this modifiedβ -pinene-derived pyridine connects with N-terminal quinoline oligoamide, the foldamer **4**were designed, and **4a/4b** represents P-helix/M-helix. Based on the metadynamic calculation, the FEP of **4a** and **4b** were get. The results show that R chirality ofβ -pinene still induced the P helix, S chirality still induced M helix. FEP shows that the difference between the free-energy P-**4a** and M-**4a** is 6.7 kalmol^{-1}, there is the bigger free-energy gap for**4** than for **3** (Figure 13). When the R-chiral atom induces the P type structure, the new hydrogen bond N-H–O is formed. The bond length of N-H–O is 1.96 Å with bond angle of 150°. Thus, together with two inherent three-center hydrogen bonds (N_Q–H-N_A and N^*–H-N_A), there are three hydrogen bonds in **4a** (Figure 14). When the angle [?]N_Q-C_Q-C-N_A is rotated, which needs overcome a big free-energy barrier due to three hydrogen bonds are destroyed. It is proved the more hydrogen bonds of the terminal group, the more stability of foldamer **4** . In another hand, the rotation of [?]N_Q-C_Q-C-$N_A$can induce another hydrogen bond N–H-N_A, the hydrogen bond length is 1.789 A, the bond angle is 109deg. So there should have a stable conformer**4c** (Supporting information S7). The distributions of dihedral angle show the angle peaks of [?]N_Q-C_Q-C-N_A at +-10degfor (P)-4a/(M)-4b. And a metastable state **EPP** also is found in FEP of **4a** , the minimum free-energy of **EPP** is 4.3kcalmol^{-1}, and it is similar to foldamer **3** . From the calculated data, it can see that the chiralβ -pinene connect with oligomers at N-terminal has the better selection of helix than at the C-terminal. The reason mainly comes from two aspects, one reason is that delocalization effect is found betweenβ -pinene derivatives with quinoline oligomers at N-terminal (foldamer **3** and **4)** , and the delocalization effect improves the delivery of chirality, resulting in the better helical selection of **3** and **4** than **1** and**2** (β -pinene substituted at C-terminal). Another reason is that β -pinene has big steric hindrance, it is difficult to rotate between different helical handedness once there are more hydrogen bonds. For foldamer **3a** , the delocalized bond improved the selection of chirality, delocalization effect is the key

factors. The free-energy gap of **4a** became the bigger than that of **3a** , which is due to the more hydrogen bond to strengthen the helical stability of

4a.

3. Conclusion

In conclusion, using the metadynamic methods, we prove an experiment results that the β -pinene connects with quinoline oligomers at N-terminal has the better helical induction than at C-terminal. However, the intrinsic reason is rather electronic delocalization and steric effect than hydrogen-bond effect. Especially, β -pinene is chiral group of huge steric hindrance, which can induce the helix preference of foldamer, but the chiral delivery of chiral atom is affected by steric hindrance and delocalized effect. When the β -pinene connects with oligomer units at the C-terminal, the dihedral angle [?]N_Q-C_Q-C-N_A is far away from chiral carbon of pinene, which cannot effectively induce the helix bias of foldamer. Even an additional hydrogen bond is added at C-terminal, which still no obviously improve the helical selection. That is, for foldamer **1** and **2** with β -pinene derivative at C-terminal, the hydrogen bonds rarely affect the helical selection of foldamer. When the β -pinene connects with it at N-terminal, chiral carbon of β -pinene can form the conjugated bond with N_Q-C_Q-C-$N_A$bond, it is benefit for the delivery of chirality. The chiralβ -pinene forms the more hydrogen bonds with quinoline oligoamide, the foldamers are more stable. Therefore, the free-energy profiles (FEPs) of **1**–**4** show that there is a small free energy barrier between P and M for foldamers **1** and **2** , but in FEPs of**3** and **4,** free-energy has large difference between P and M, the foldamer **4a** with more hydrogen bond has the bigger free-energy gap between P helix and M than **3a** has.

4. Experimental Section

We carried out all-atom molecular dynamic simulations (300–500 ns) in chloroform. Combined with the metadynamics free-energy method, force field parameters specifically optimized for the quinoline-based arylamides was calculated by our method [16,17]. This method accelerates the simulation by adding small repulsive potentials ("hills") to the underlying free energy landscape, thus gradually biasing the system to escape energy minima and explore the wide conformational space. From metadynamics simulations, we determined the free energy of the oligomers with respect to two Control Variables (CVs) to generate two-dimensional free free-energy profiles (FEPs). At least one CV in each metadynamics simulation is chosen to be a pitch dihedral angle. This angle defined by the centers of masses of four consecutive quinoline rings ("Q") (Scheme 1). Identify the handedness of the helix: a positive dihedral angle for right-handed (P) and a negative angle for left-handed (M) helices. The metadynamics computational methods had been successfully used to predict and explain helix handedness bias in the context of helically folded aromatic oligoamides in previous reports. All simulations were carried out using the AMBER-18 package [18].

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