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Biased Helical Folding of Chiral Oligoindole Foldamers

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ABSTRACT

Oligoindole-based chiral foldamers have been synthesized by incorporating (*S*)- or (*R*)-1-phenylethylamine to both ends of the tetraindole scaffold. The oligoindoles fold into a helical conformation upon binding an anion by hydrogen bonds, which gives rise to an induced circular dichroism (CD) signal of large amplitude, implying the preferential formation of one helical isomer over another. Theoretical calculations suggest that the (*P*)-helix of the (*S,S*)-oligoindole 8a be more energetically stable than the corresponding (*M*)-helix.

Helical structures are commonly found in proteins and nucleic acids and are stabilized by the combination of various noncovalent forces such as hydrophobic interactions, van der Waals forces, hydrogen bonds, dipole−dipole forces, etc. Owing to the chiral nature of molecular blocks such as amino acids and nucleotides, one-handed helices of two possible helical isomers have been found in proteins and DNA. Much progress has been made over the past decade for the synthesis and characterization of foldamers mimicking secondary structures of biomacromolecules.[1,2] These efforts provided us with the opportunity to gain an insight into understanding the fundamental principles and factors that determine the structure and function of biomacromolecules. Moreover, if the conformation (folding vs unfolding, left- vs right-handed helix, etc.) can be reversibly controlled by external stimulation, the foldamer would be highly attractive for possible applications in molecular sensing, data storage, and optical devices.

A large number of synthetic oligomers capable of adopting a helical conformation have been reported,[1,2] and most of them fold into a racemic mixture of two helical isomers. For tuning the relative population of two different helices, many approaches have been reported, which can be classified broadly into two categories. One is to bind chiral guests to achiral foldamers, which results in the biased formation of two helical complexes.[3,4] Another is to introduce chiral segments to foldamers as a part of the backbones,[5] termini,[6,7]

(1) Hecht, S.; Huc, I. *Foldamers: Structure Properties and Applications*; Wiley-VCH: Weinheim, Germany, 2007.

(2) For reviews, see: (a) Li, Z.-T.; Hou, J.-L.; Li, C.; Yi, H.-P. *Chem. Asian J.* **2006**, *1*, 766–778. (b) Licini, G.; Prins, L. J.; Scrimin, P. *Eur. J. Org. Chem.* **2005**, *6*, 969–977. (c) Huc, I. *Eur. J. Org. Chem.* **2004**, *1*, 17–29. (d) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111–1239. (e) Schmuck, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2448–2452. (f) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232. (g) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4012. (h) Gong, B. *Chem. Eur. J.* **2001**, *7*, 4336–4342. (i) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287–296. (j) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180.

(3) (a) Goto, K.; Moore, J. S. *Org. Lett.* **2005**, *7*, 1683–1686. (b) Stone, M. T.; Moore, J. S. *Org. Lett.* **2004**, *6*, 469–472. (c) Heemstra, J. M.; Moore, J. S. *J. Org. Chem.* **2004**, *69*, 9234–9237. (d) Tanatani, A.; Hughes, T.; Moore, J. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 325–328. (e) Tanatani, A.; Mio, M. J.; Moore, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 1792–1793. (f) Prince, R. B.; Barnes, S. A.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 2758–2762.

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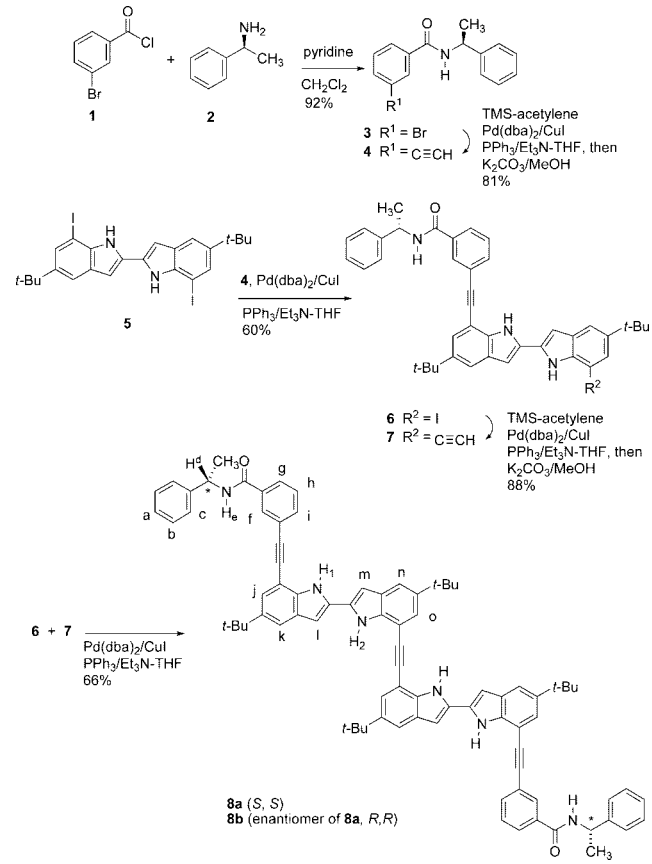
or side chains,[8,9] thus forming unequal ratio of two diastereomeric helices.

We have previously described oligoindoles capable of folding into a helical conformation upon binding a chloride ion via hydrogen bonding.[10] The oligoindoles fold to give a racemic mixture of two enatiomeric helices, the left- and right-handed. In order to induce the helical bias, we prepared chiral oligoindoles **8a** and its enantiomer **8b**, comprising a tetraindole backbone with (1*S*)- or (1*R*)-phenylethylamido units at both ends. ^{1}H NMR and circular dichroism (CD) spectroscopy clearly support the hypothesis that **8a** and **8b** adopt a helical structure upon binding an anion such as chloride by multiple hydrogen bonds. In particular, **8a** or **8b** alone exhibits almost no CD signal but the addition of an anion induces a strong Cotton effect, implying the preferential formation of one particular helix over another.

Scheme 1. Synthesis of Oligoindole **8a**



The synthesis of chiral oligoindole **8a** bearing the (*S*,*S*)-configuration at the benzylic positions of both ends is outlined in Scheme 1. Coupling of 3-bromobenzoyl chloride (**1**) with (1*S*)-phenylethylamine (**2**) gave **3** in 92% yield. Then, Pd(0)/CuI-catalyzed reaction[11] of **3** with trimethylsilyl(TMS)-ethyne, followed by removal of the TMS group under the basic conditions, gave **4** in 81% yield (two steps). Coupling of **4** with **5** (1.5 equiv) afforded **6** in 60% yield, part of which was in turn converted into **7**. Finally, **6** and **7** were combined to provide a chiral oligoindole **8a** in 66% yield.

The ^{1}H NMR spectrum of **8a** was unambiguously assigned by 2D ^{1}H−^{1}H COSY, TOCSY, and NOESY experiments (see Suppoting Information). The ^{1}H NMR spectrum of **8a** shows considerable changes in the chemical shift upon addition of tetrabutylammonium chloride (TBA^+Cl^-) (Figure 1).[12] First, the indole NH signals are largely downfield shifted from 10.83 and 10.89 ppm to 12.18 and 13.07 ppm as a result of hydrogen bonding. Second, signals for the amide NH and the benzoate CH^f are also downfield shifted by $\Delta\delta$

(4) (a) Abe, H.; Machiguchi, H.; Matsumoto, S.; Inouye, M. *J. Org. Chem.* **2008**, *73*, 4650–4661. (b) Waki, M.; Abe, H.; Inouye, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3059–3061. (c) Waki, M.; Abe, H.; Inouye, M. *Chem. Eur. J.* **2006**, *12*, 7839–7847. (d) Abe, H.; Masuda, N.; Waki, M.; Inouye, M. *J. Am. Chem. Soc.* **2005**, *127*, 16189–16196. (e) Inouye, M.; Waki, M.; Abe, H. *J. Am. Chem. Soc.* **2004**, *126*, 2022–2027. (f) Yi, H.-P.; Shao, X.-B.; Hou, J.-L.; Li, C.; Jiang, X.-K.; Li, Z.-T. *New J. Chem.* **2005**, *29*, 1213–1218. (g) Li, C.; Ren, S.-F.; Hou, J.-L.; Yi, H.-P.; Zhu, S.-Z.; Jiang, X.-K.; Li, Z.-T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5725–5729. (h) Hou, J.-L.; Shao, X.-B.; Chen, G.-J.; Zhou, Y.-X.; Jiang, X.-K.; Li, Z.-T. *J. Am. Chem. Soc.* **2004**, *126*, 12386–12394.

(5) (a) Hu, H.-Y.; Xiang, J.-F.; Yang, Y.; Chen, C.-F. *Org. Lett.* **2008**, *10*, 69–72. (b) Baruah, P. K.; Gonnade, R.; Rajamohanan, P. R.; Hofmann, H.-J.; Sanjayan, G. J. *J. Org. Chem.* **2007**, *72*, 5077–5084. (c) Zhong, Z.; Zhao, Y. *Org. Lett.* **2007**, *9*, 2891–2894. (d) Dong, Z.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 11850–11853. (e) Sugiura, H.; Nigorikawa, Y.; Saiki, Y.; Nakamura, K.; Yamaguchi, M. *J. Am. Chem. Soc.* **2004**, *126*, 14858–14864. (f) Zhao, X.; Jia, M.-X.; Jiang, X.-K.; Wu, L.-Z.; Li, Z.-T.; Chen, G.-J. *J. Org. Chem.* **2004**, *69*, 270–279. (g) Hill, D. J.; Moore, J. S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5053–5057. (h) Gin, M. S.; Moore, J. S. *Org. Lett.* **2000**, *2*, 135–138. (i) Gin, M. S.; Yokozawa, T.; Prince, R. B.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 2643–2644.

(6) (a) Hu, H.-Y.; Xiang, J.-F.; Yang, Y.; Chen, C.-F. *Org. Lett.* **2008**, *10*, 1275–1278. (b) Gillies, E. R.; Deiss, F.; Staedel, C.; Schmitter, J. M.; Huc, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 4081–4084. (c) Buffeteau, T.; Ducasse, L.; Poniman, L.; Delsuc, N.; Huc, I. *Chem. Commun.* **2006**, 2714–2716. (d) Dolain, C.; Jiang, H.; Leger, J.-M.; Guionneau, P.; Huc, I. *J. Am. Chem. Soc.* **2005**, *127*, 12943–12951. (e) Maurizot, V.; Dolain, C.; Huc, I. *Eur. J. Org. Chem.* **2005**, 1293–1301. (f) Jiang, H.; Dolain, C.; Leger, J.-M.; Gornitzka, H.; Huc, I. *J. Am. Chem. Soc.* **2004**, *126*, 1034–1035. (g) Dolain, C.; Maurizot, V.; Huc, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2738–2740.

(7) (a) King, E. D.; Tao, P.; Sanan, T. T.; Hadad, C. M.; Parquette, J. R. *Org. Lett.* **2008**, *10*, 1671–1674. (b) Li, C.; Wang, G.-T.; Yi, H.-P.; Jiang, X.-K.; Li, Z.-T.; Wang, R.-X. *Org. Lett.* **2007**, *9*, 1797–1800. (c) Dong, Z.; Karpowicz, R. J., Jr.; Bai, S.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 14242–14243. (d) Goto, H.; Heemstra, J. M.; Hill, D. J.; Moore, J. S. *Org. Lett.* **2004**, *6*, 889–892. (e) Cary, J. M.; Moore, J. S. *Org. Lett.* **2002**, *4*, 4663–4666. (f) Moriuchi, T.; Nishiyama, M.; Yoshida, K.; Ishikawa, T.; Hirao, T. *Org. Lett.* **2001**, *3*, 1459–1461.

(8) (a) Meudtner, R. M.; Hecht, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 4926–4930. (b) Khan, A.; Kaiser, C.; Hecht, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1878–1881. (c) Khan, A.; Hecht, S. *Chem. Eur. J.* **2006**, *12*, 4764–4774. (d) Sinkeldam, R. W.; Hoeben, F. J. M.; Pouderoijen, M. J.; Cat, I. D.; Zhang, J.; Furukawa, S.; Feyter, S. D.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 16113–16121. (e) Prince, R. B.; Moore, J. S.; Brunsveld, L.; Meijer, E. W. *Chem. Eur. J.* **2001**, *7*, 4150–4154. (f) Brunsveld, L.; Prince, R. B.; Meijer, E. W.; Moore, J. S. *Org. Lett.* **2000**, *2*, 1525–1528. (g) Prince, R. B.; Brunsveld, L.; Meijer, E. W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 228–230.

(9) (a) Masu, H.; Sakai, M.; Kishikawa, K.; Yamamoto, M.; Yamaguchi, K.; Kohmoto, S. *J. Org. Chem.* **2005**, *70*, 1423–1431. (b) Zhao, X.; Schanze, K. S. *Langmuir* **2006**, *22*, 4856–4862.

(10) (a) Chang, K.-J.; Kang, B.-N.; Lee, M.-H.; Jeong, K.-S. *J. Am. Chem. Soc.* **2005**, *127*, 12214–12215. (b) Suk, J.-m.; Jeong, K.-S. *J. Am. Chem. Soc.* **2008**, *130*, 11868–11869.

(11) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.

(12) As a result of fast exchange on the ^{1}H NMR (400 MHz) time scale, time-averaged signals were observed at room temperature between all the possible conformational isomers of **8a** and complex **8a**·Cl^-. When the temperature was gradually lowered to −40 °C, the ^{1}H NMR signals were significantly broadened and not assignable.

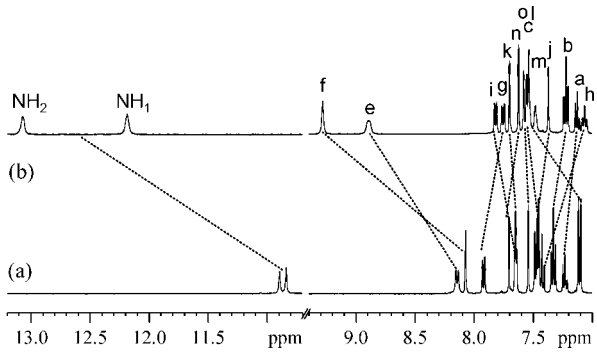


Figure 1. Partial ^{1}H NMR spectra (400 MHz, 10 mM acetone-d_6, 25 °C) of (a) **8a** and (b) **8a** + TBACl (3 equiv).

= 0.75 and 1.21 ppm, suggesting that these hydrogens also participate in hydrogen bonding with the chlordie ion. Third, the aromatic CH signals exhibit noticeable changes in the chemical shift ($\Delta\delta$ = ±0.1− 0.5 ppm), indicative of conformational reorganization. The 2D ^{1}H−^{1}H NOESY experiment with a mixture of **8a** and TBA$^+$Cl$^-$ (3 equiv) in acetone-d_6 gave clear evidence for the helical folding, showing characteristic NOE cross peaks between NH_1 and H^f, H^i and H^j, and H^b and H^n, which could not be observed in the absence of TBA$^+$Cl$^-$ (see Supporting Information).

CD spectroscopy has been widely used to reveal the helical chirality. In the absence of an anion, **8a** shows almost no CD signal in CH_2Cl_2 (5×10^{-5} M) at room temperature. Addition of TBA$^+$Cl$^-$ gives rise to strong positive CD signals centered at 296 nm (θ = 54 mdeg) and 395 nm (θ = 120 mdeg), corresponding to the absorption wavelengths of the benzoate and biindole segments, respectively. The intensity of the signal gradually increases and becomes saturated upon addition of approximately 1 equiv of the anion (Figure 3, top). The enantiomer **8b** display identical behaviors of the CD spectrum but the opposite Cotton effect (Figure 3, bottom). In addition, other anions such as bromide, iodide, azide, and nitrate also impart the induced CD signals with different ellipticities (see Supporting Information). These CD results suggest that chiral oligoindoles **8a** and **8b** form one of two possible helices, at least preferentially.

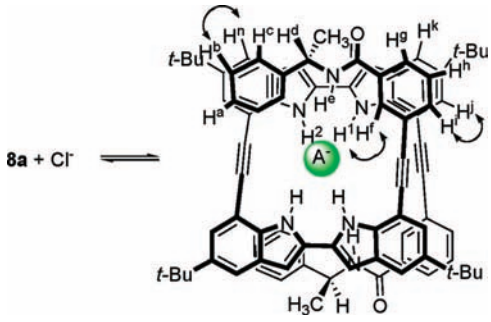


Figure 2. Proposed structure of complex **8a**·Cl$^-$ with the NOE correlation shown in the 2D ^{1}H−^{1}H NOESY spectrum.

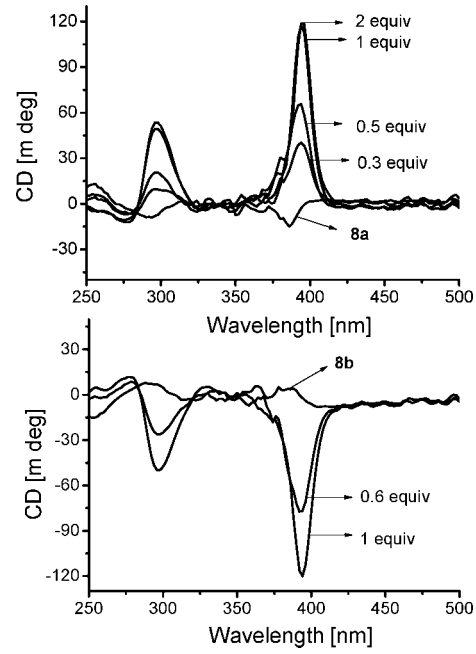


Figure 3. Changes in CD spectra of **8a** (top) and **8b** (bottom) (0.05 mM) upon addition of TBACl in CH_2Cl_2 at 24 ± 1 °C.

The association constants between **8a** and anions were quantitatively measured by UV−vis titration experiments. Each titration was carried out by increasing the amount of tetrabutylammonium anion to constant concentration (1.0×10^{-5} M) of **8a** in 99:1 (v/v) CH_2Cl_2/MeOH at 21 ± 1 °C. Nonlinear least-squares fitting[13] of the titration curve gave the association constants (K_a ± 15%); 2.9×10^5 M^{-1} for Cl$^-$, 6.2×10^4 M^{-1} for Br$^-$, 2.6×10^2 M^{-1} for I$^-$, 4.4×10^4 M^{-1} for NO_3^-, and 8.5×10^5 M^{-1} for N_3^-. Job plots suggest that **8a** forms 1:1 complexes with all the anions (see Supporting Information).

To find out which of the two possible helices of complex **8a**·Cl$^-$ was more energetically stable, we conducted theoretical calculations in the gas phase using hybrid ab initio methods with the Gaussian 03 package.[14] First, structure optimization was performed with the HF/3-21G method for both cases. Using the optimized structures, we performed

(13) (a) Long, J. R.; Drago, R. S. *J. Chem. Educ.* **1982**, *59*, 1037–1039. (b) Connors, K. A. *Binding Constants*; John Wiley & Sons: New York, 1987.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford CT, 2004.

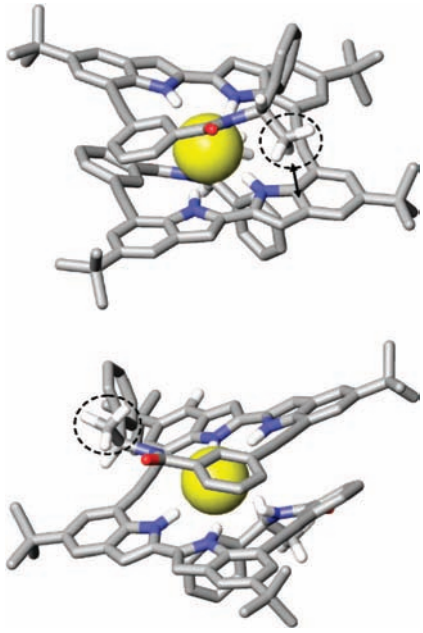


Figure 4. Energy-minimized structures of the (*P*)-helix (top) and the (*M*)-helix (bottom) of **8a**·Cl^- (Gaussian 03 package). For clarity, all the hydrogens are omitted except the indole NHs, bezylic hydrogen, and methyl group in the dotted circle.

single point calculations with B3LYP/3-21G and MP2/3-21G methods to compare the energy of the helices. This kind of structure optimization-single point hybrid calculation is widely used due to its relatively accurate results yet inexpensive computation cost.[15] For all cases, the (*P*)-helix is more stable than the (*M*)-helix by 24 kJ/mol (HF/3-21G), 19 kJ/mol (HF/3-21G//B3LYP/3-21G), and 16 kJ/mol (HF/3-21G//MP2/3-21G). In the left-handed (*M*)-helix, the methyl substituent at the benzylic position is eclipsed to the adjacent carbonyl group, while the benzylic hydrogen is oriented toward the helical strand (Figure 4). On the other hand, the hydrogen atom and methyl group are oppositely placed in the right-handed (*P*)-helix. As a result, the methyl substituent is directed toward the aromatic strand to exert CH$\cdots\pi$ interactions with the indole surface, which appears to be primarily responsible for the stabilization of the (*P*)-helix over the (*M*)-helix.[16] This kind of interactions has been known to play an important role in the folding and binding processes of natural and artificial molecules.[17]

In conclusion, an oligoindole-based foldamer with chiral termini folds into a helical conformation upon binding an anion by hydrogen bonds. The chirality of the terminal group has been effectively transferred on the folding process, thus leading to the preferential formation of one helical isomer, as demonstrated by circular dichroism (CD) spectroscopy. According to the theoretical calculation, the (*P*)-helix of complex **8a**·Cl^- bearing (*S*,*S*)-configuration is more stable than the corresponding (*M*)-helix. We are currently attempting the synthesis of a chiral foldamer possessing a larger helical cavity able to accommodate chiral species such as carboxylates and phosphates. This may allow us to reveal foldamer-based chiral recognition as well as to develop a a helicity-switching molecular system responsive to a chiral substrate.

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Supporting Information Available: Synthesis and characterization of oligoindole **8a** and **8b**. 1D and 2D NMR spectra, UV−vis, CD spectra, and theoretical caculations. This material is available free of charge via the Internet at http//www.pubs.acs.org.

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(15) (a) Garau, C.; Frontera, A.; Quinonero, D.; Costa, A.; Ballester, P.; Deya, P. M. *Chem. Phys.* **2004**, *303*, 265–270. (b) Burda, J. V.; Leszczynski, J. *Inorg. Chem.* **2003**, *42*, 7162–7172. (c) French, A. D.; Johnson, J. P. *Can. J. Chem.* **2006**, *8*, 603–612. (d) Frison, G.; Ohanessian, G. *J. Comput. Chem.* **2008**, *29*, 416–433.

(16) To further examine the significance of the CH$\cdots\pi$ interaction, we carried out more simulations. The (*P*)-helix has been destabilized by $\Delta E =$ 102 kJ/mol upon replacing the benzylic methyl group with hydrogen, while the (*M*)-helix has been greatly stabilized when the benzylic hydrogen is changed into the methyl group. For details, see Supporting Information

(17) (a) Burley, S. K.; Petsko, G. A. *Trends Biotechnol.* **1989**, *7*, 354–359. (b) Kim, E.-I.; Paliwal, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 11192–11193. (c) Jennings, W. B.; Farrell, B. M.; Malone, J. F. *Acc. Chem. Res.* **2001**, *34*, 885–894. (d) Grossmann, G.; Potrzebowski, M. J.; Olejniczak, S.; Ziólkowska, N. E.; Bujacz, G. D.; Ciesielski, W.; Prezdo, W.; Nazarov, V.; Golovko, V. *New J. Chem.* **2003**, *27*, 1095–1101. (e) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250. (f) Bhayana, B.; Wilcox, C. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6833–6836. (g) Carroll, W. R.; Pellechia, P.; Shimizu, K. D. *Org. Lett.* **2008**, *10*, 3547–3550. (h) Fischer, F. R.; Schweizer, W. B.; Diederich, F. *Chem. Commun.* **2008**, 4031–4033.