ORGANIC LETTERS

2001
Vol. 3, No. 10
1459−1461

Chiral Helicity Induced by Hydrogen Bonding and Chirality of Podand Histidyl Moieties

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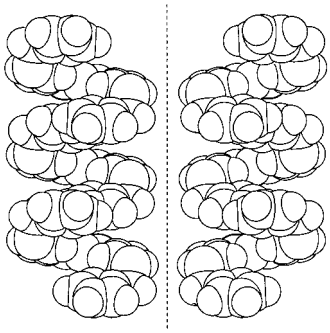
Received February 22, 2001

ABSTRACT



The single-crystal X-ray structure determination of *N*,*N*′-bis{(*S*)-(+)-1-methoxycarbonyl-2-(4-imidazolyl)ethyl}-2,6-pyridinedicarboxamide (L-BHisPA) and the D-isomer (D-BHisPA) derived from the corresponding chiral histidine revealed a left- and right-handed helical conformation, respectively, through intramolecular hydrogen bonding and chirality of the podand histidyl moieties. Furthermore, each helical molecule is connected by continuous intermolecular hydrogen bonds to afford a left- or right-handed helical assembly, respectively, in the crystal packing.

The utilization of self-assembling properties of amino acids is considered to be a convenient approach to a highly ordered system. The secondary structures such as α-helices, *β*-sheets, and *β*-turns, which play an important role in protein folding, are driven by hydrophobic interaction and hydrogen bonding of amino acids.[1] The highly ordered structures of these secondary structures are created in protein to fulfill the unique functions as observed in enzymes, receptors, etc.[1] We have already demonstrated that the introduction of dipeptide chains into the ferrocene scaffold permits chirality organization through the intramolecular interchain hydrogen bonding, in which a helical molecular arrangement is achieved in the crystal packing.[2] On the other hand, the 2,6-pyridinedicarboxamide scaffold has also been exploited for a building block to create helices.[3] Introduction of chiral amino acids

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10.1021/ol0100327 CCC: $20.00
Published on Web 04/19/2001

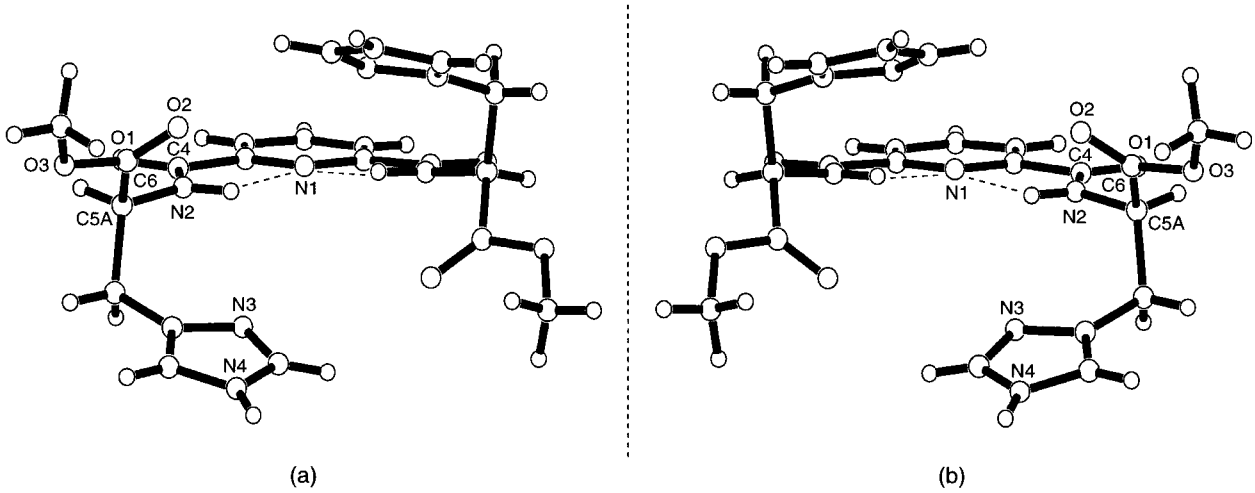
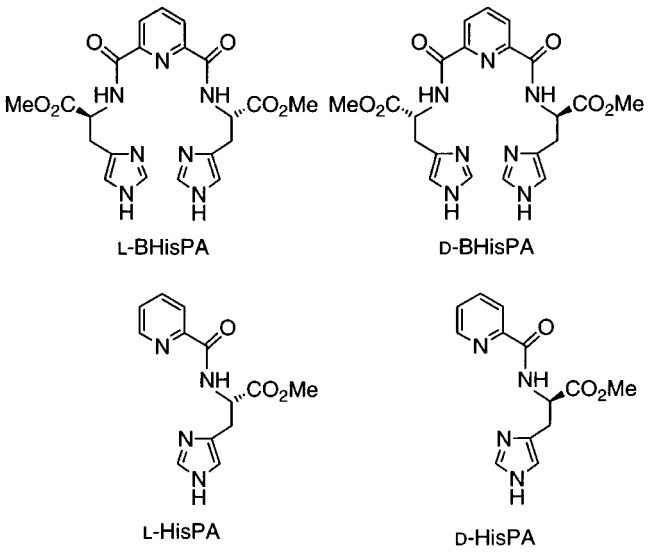


Figure 1. (a) Molecular structures of L-BHisPA and (b) D-BHisPA.

into this scaffold can be designed to afford a chiral molecular arrangement.[4] Histidine has the advantage of forming an ordered structure on the basis of the chiral center and an additional hydrogen bonding site of the imidazolyl group. From these points of view, we herein report that the chiral helicity of *N*,*N*′-bis{1-methoxycarbonyl-2-(4-imidazolyl)-ethyl}-2,6-pyridinedicarboxamide induces a self-assembled helix in the crystal packing, which provides a key procedure to construct highly ordered structures by using amino acids.

N,*N*′-Bis{(*S*)-(+)-1-methoxycarbonyl-2-(4-imidazolyl)-ethyl}-2,6-pyridinedicarboxamide (L-BHisPA) was synthesized from 2,6-pyridinedicarboxylic acid dichloride and L-histidine methyl ester.[5] The single-crystal X-ray structure determination of L-BHisPA confirmed a left-handed helical conformation through chirality of the histidyl moieties and intramolecular hydrogen bonding between NH (amide) and N (pyridine) (NH···N, 2.230 Å) to give five-membered hydrogen-bonded rings as depicted in Figure 1a.[6] To elucidate the capability of the 2,6-pyridinedicarboxamide bearing podand histidyl moieties to induce the chiral molecular conformation, the crystal structure of D-BHisPA derived from D-histidine methyl ester was investigated. It should be noted that a right-handed helical conformation was formed in the crystal structure of D-BHisPA.[7] Similar intramolecular hydrogen bondings between NH (amide) and N (pyridine) (NH···N, 2.291 Å) were observed in this helical structure (Figure 1b). The molecular structures of L-BHisPA and D-BHisPA are in a good mirror-image relationship, indicating conformational enantiomers.[8] The propensity to form the chiral helicity appears to be controlled by the configuration of the histidyl α-carbon atoms.



Another interesting feature is that each molecule of L-BHisPA is connected by continuous intermolecular hydrogen bonds to give a left-handed helix (*M*-form) as shown

(4) (a) Yu, Q.; Baroni, T. E.; Liable-Sands, L.; Yap, G. P. A.; Rheingold, A. L.; Borovik, A. S. *Chem. Commun.* **1999**, 1467. (b) Karle, I. L.; Ranganathan, D.; Kurur, S. *J. Am. Chem. Soc.* **1999**, *121*, 7156.

(5) The selected data are as follows. L-BHisPA: mp 198−199 °C (uncorrected); IR (KBr) 3394, 3126, 1743, 1666 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.23 (d, 2H, J = 7.5 Hz), 8.12 (t, 1H, J = 7.5 Hz), 7.57 (s, 2H), 6.93 (s, 2H), 4.93 (dd, 2H, J = 8.7, 5.1 Hz), 3.76 (s, 6H), 3.36−3.19 (m, 4H); EI-MS *m*/*z* 469 (M^+). Anal. Calcd for $C_{21}H_{23}N_7O_6 \cdot H_2O$: C, 51.74; H, 5.17; N, 20.11. Found: C, 51.57; H, 5.01; N, 20.16. D-BHisPA: mp 198−199 °C (uncorrected); IR (KBr) 3394, 3126, 1743, 1666 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.23 (d, 2H, J = 7.5 Hz), 8.12 (t, 1H, J = 7.5 Hz), 7.57 (s, 2H), 6.93 (s, 2H), 4.93 (dd, 2H, J = 8.7, 5.1 Hz), 3.76 (s, 6H), 3.36−3.19 (m, 4H); EI-MS *m*/*z* 469 (M^+). Anal. Calcd for $C_{21}H_{23}N_7O_6 \cdot H_2O$: C, 51.74; H, 5.17; N, 20.11. Found: C, 51.51; H, 4.78; N, 19.83. L-HisPA: mp 174−175 °C (uncorrected); IR (KBr) 3348, 3116, 1728, 1658 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.62 (ddd, 1H, J = 5.4, 1.8, 0.9 Hz), 8.05 (ddd, 1H, J = 7.5, 1.5, 0.9 Hz), 7.94 (td, 1H, J = 7.5, 1.8 Hz), 7.63 (s, 1H), 7.54 (ddd, 1H, J = 7.5, 5.4, 1.5 Hz), 6.89 (s, 1H), 4.91 (dd, 1H, J = 7.2, 5.4 Hz), 3.74 (s, 3H), 3.25−3.21 (m, 2H); EI-MS *m*/*z* 274 (M^+). Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.56; H, 5.21; N, 20.26. D-HisPA: mp 174−175 °C (uncorrected); IR (KBr) 3348, 3116, 1728, 1658 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.62 (ddd, 1H, J = 5.4, 1.8, 0.9 Hz), 8.05 (ddd, 1H, J = 7.5, 1.5, 0.9 Hz), 7.94 (td, 1H, J = 7.5, 1.8 Hz), 7.63 (s, 1H), 7.54 (ddd, 1H, J = 7.5, 5.4, 1.5 Hz), 6.89 (s, 1H), 4.91 (dd, 1H, J = 7.2, 5.4 Hz), 3.74 (s, 3H), 3.25−3.21 (m, 2H); EI-MS *m*/*z* 274 (M^+). Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.89; H, 5.06; N, 20.38.

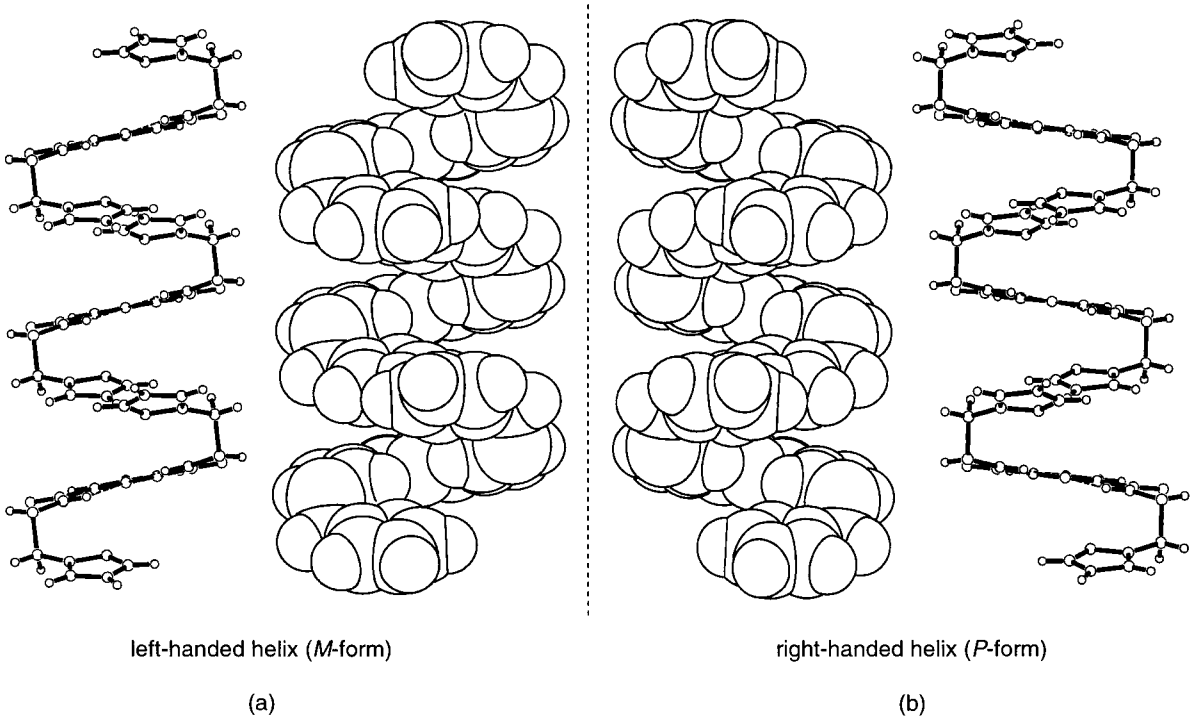


Figure 2. (a) A portion of a layer containing the helical assembly of crystal packing of L-BHisPA and (b) D-BHisPA (methyl ester moieties are omitted for clarity). Each helical molecule is connected by continuous intermolecular hydrogen bonds to induce chiral helicity.

in Figure 2a. Noteworthy is that an opposite helically ordered molecular assembly, a right-handed helix (*P*-form), was formed in the crystal packing of D-BHisPA (Figure 2b). On the contrary, such chiral helicity was not observed in the pyridinecarboxamide derivatives bearing one histidyl pendant group, {(*S*)-(+)-1-methoxycarbonyl-2-(4-imidazolyl)ethyl}-2-pyridinecarboxamide (L-HisPA) and D-isomer (D-HisPA).[9] A hydrogen-bonded network was only formed in the crystal packing, wherein each molecule is connected to four neighboring molecules by intermolecular hydrogen bonds (Figures S2−S7, Supporting Information). The structural difference between BHisPA and HisPA existed in the torsion angle ϕ_1 defined as C(4)−N(2)−C(5A)−C(6) (L-BHisPA, −131.7°; D-BHisPA, 131.9°; L-HisPA, −102.7°; D-HisPA, 102.2°). The helical arrangement requires rotation of the pendant chains, resulting in the above-mentioned torsion angles. The podand histidyl moieties of the pyridinedicarboxamide scaffold are likely to play an important role in creating the helical arrangement.

In conclusion, the intramolecular hydrogen bondings and chirality of the podand histidyl pendant groups on the 2,6-pyridinedicarboxamide scaffold allow induction of the chiral helicity, creating the left- or right-handed helical assembly by the connection of each helical molecule through continuous intermolecular hydrogen bonds in the crystal packing. Studies on the application of chiral helicity to molecular recognition and asymmetric reaction are now in progress.

Acknowledgment. Thanks are due to the Analytical Center, Faculty of Engineering, Osaka University, for the use of the NMR and MS instruments.

Supporting Information Available: Tables of X-ray crystallographic data for L-BHisPA, D-BHisPA, L-HisPA, and D-HisPA. ORTEP figures and crystal packings for L-HisPA and D-HisPA. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Crystal data for L-BHisPA: $C_{21}H_{23}N_7O_6 \cdot H_2O$, fw = 487.47, orthorhombic, space group $C222_1$ (No. 20), a = 12.317(1) Å, b = 9.1373(9) Å, c = 22.507(2) Å, V = 2533.1(4) Å^3, Z = 4, D_{calcd} = 1.278 g cm^{-3}, R = 0.089, R_w = 0.211.

(7) Crystal data for D-BHisPA: $C_{21}H_{23}N_7O_6 \cdot H_2O$, fw = 487.47, orthorhombic, space group $C222_1$ (No. 20), a = 9.105(1) Å, b = 12.297(1) Å, c = 22.403(3) Å, V = 2508.4(5) Å^3, Z = 4, D_{calcd} = 1.291 g cm^{-3}, R = 0.074, R_w = 0.183.

(8) The mirror image of the CD signals between L-BHisPA and D-BHisPA was obtained (Figures S1, Supporting Information), suggesting that a chiral molecular conformation based on an ordered structure through intramolecular hydrogen bondings and chirality of the histidyl moieties is present even in solution.

(9) Crystal data for L-HisPA: $C_{13}H_{14}N_4O_3$, fw = 274.28, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.650(2) Å, b = 16.262(2) Å, c = 8.872(2) Å, V = 1392.2(3) Å^3, Z = 4, D_{calcd} = 1.308 g cm^{-3}, R = 0.091, R_w = 0.136. D-HisPA: $C_{13}H_{14}N_4O_3$, fw = 274.28, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.6490(6) Å, b = 16.3212(9) Å, c = 8.8998(6) Å, V = 1401.6(1) Å^3, Z = 4, D_{calcd} = 1.300 g cm^{-3}, R = 0.038, R_w = 0.128.