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CHIRAL COMPLEXATION OF MULTIDENTATE *N*-HETEROCYCLIC PODAND LIGANDS BEARING HISTIDYL MOIETIES

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Abstract – Preorganized left- and right-handed helical conformations of the chiral pentadentate *N*-heterocyclic ligands bearing the podand histidyl moieties, *N*,*N*'-bis{(*S*)-(+)-1-methoxycarbonyl-2-(4-imidazoyl)ethyl}-2,6-pyridinedicarboxamide (L-BHisPA) and the D-isomer (D-BHisPA), induce the chiral complexation through spiral coordination of the pentadentate BHisPA to Cu(II) center to give L- and D-BHisPA-Cu(II) as a Λ and Δ enantiomorph, respectively. Each complex is connected by continuous intermolecular hydrogen bonds in a solid state to form a hydrogen-bonded macrocycle with left- or right-handed windmill-like arrangement, respectively. In the case of the Cu(II) complex (L-HisPA-Cu(II)) with the ligand bearing one histidyl pendant group, {(*S*)-(+)-1-methoxycarbonyl-2-(4-imidazoyl)ethyl}-2-pyridinecarboxamide (L-HisPA), each molecule is assembled in a solid state by continuous intermolecular hydrogen bonds and π-π interaction.

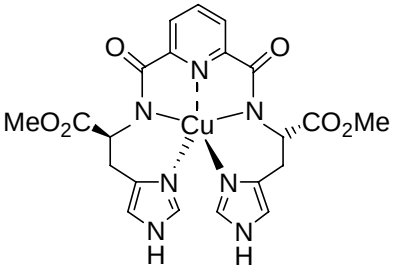
INTRODUCTION

Flexible podand ligands composed of a 2,6-pyridinedicarboxamide unit, which have σ-donor properties of the deprotonated nitrogens to stabilize a high oxidation state of a metal center, have been utilized to afford complexes possessing various metal geometries under different modes of coordination.[1] We have demonstrated that versatile catalytic systems for oxygenation reaction with molecular oxygen are achieved by utilization of transition metal complexes with the pentadentate *N*-heterocyclic podand ligands composed of a 2,6-pyridinedicarboxamide unit.[2] Multidentate coordination interaction of

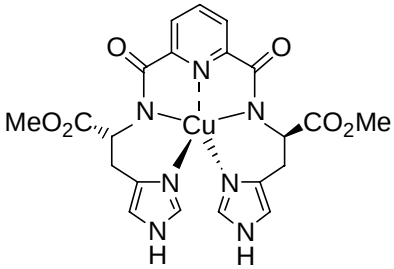
N-heterocyclic podand ligands has been revealed to be a critical factor for efficient oxygenation. Generally, complexation of a pentadentate podand ligand with a penta-coordinated transition metal gives rise to a pair of enantiomers (Λ and Δ enantiomorphs).[3] Introduction of chiral centers into the podand moieties is expected to induce chiral complexation with predetermined absolute configuration. However, such chiral complexation of pentadentate *N*-heterocyclic podand ligands composed of a 2,6-pyridinedicarboxamide unit has hitherto remained unclarified.[4, 5] On the other hand, the utilization of self-assembling properties of amino acid moieties, which possess chiral centers and hydrogen bonding sites, is considered to be a convenient approach to a highly ordered system. In a previous paper, *N*,*N'*-bis{(*S*)-(+)-1-methoxycarbonyl-2-(4-imidazoyl)ethyl}-2,6-pyridinedicarboxamide (L-BHisPA) and the D-isomer (D-BHisPA) have been demonstrated to form left- and right-handed helical conformations, respectively, through intramolecular hydrogen bonding and chirality of the podand histidyl moieties.[6] A preorganized left- or right-handed helical conformation of L- or D-BHisPA, respectively, is expected to induce chiral complexation together with self-organization. From these points of view, we focus on chiral complexation with L- and D-BHisPA possessing predetermined absolute configurations, and formation of a highly ordered self-assembly.

RESULTS AND DISCUSSION

To evaluate chiral complexation of the preorganized left- or right-handed helical conformation of L- on D-BhisPA, respectively, through spiral coordination with a penta-coordinated transition metal, complexation with $Cu(OAc)_2$ was examined. Treatment of L- and D-BHisPA with an equimolar amount of $Cu(OAc)_2$ in methanol led to the formation of L- and D-BHisPA-Cu(II), respectively. Otsuka, Sugiura, and Goto have already reported the crystal structure and spectroscopic properties of L-BHisPA-Cu(II).[5] The crystal structure of L-BHisPA-Cu(II) is almost the same as reported.[5] The observed crystal structure of D-BHisPA-Cu(II) revealed that the Cu(II) is coordinated by five nitrogens of the two deprotonated amide moieties, pyridyl group, and two imidazolyl rings (Figure 1). The two deprotonated amide moieties and pyridine ring are coplanar to form two five-membered chelate rings with



L-BHisPA-Cu(II)



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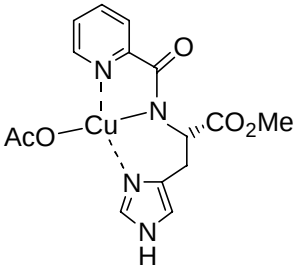

L-HisPA-Cu(II)

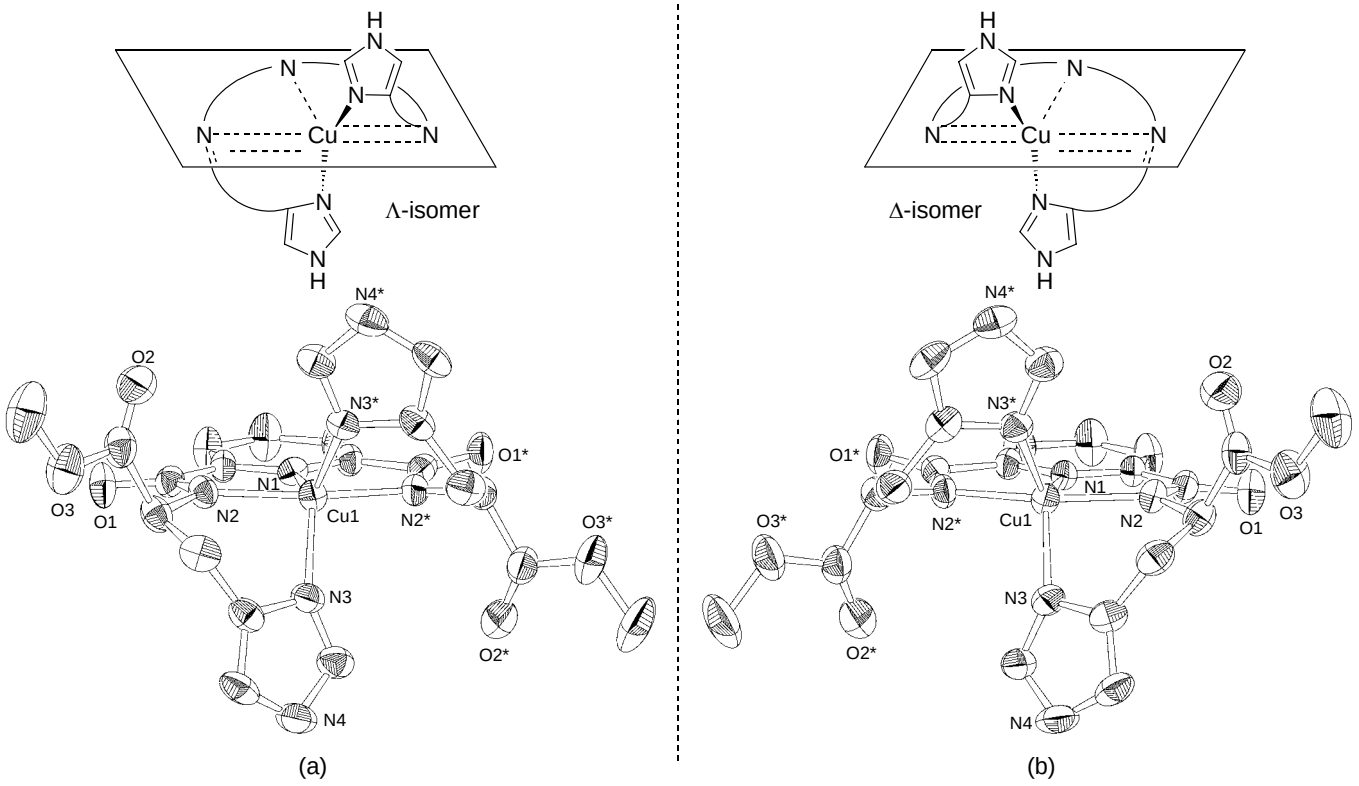

Figure 1. Molecular structures of (a) L-BHisPA-Cu(II) and (b) D-BHisPA-Cu(II) (Hydrogen atoms are omitted for clarity).

Table 1. Crystallographic Data for L-BHisPA-Cu(II), D-BHisPA-Cu(II), and L-HisPA-Cu(II)

	L-BHisPA-Cu(II)	D-BHisPA-Cu(II)	L-HisPA-Cu(II)
formula	$C_{21}H_{21}N_7O_6Cu$ $\cdot((CH_3CH_2)_2O$	$C_{21}H_{21}N_7O_6Cu$ $\cdot((CH_3CH_2)_2O$	$C_{15}H_{16}N_4O_5Cu$ $\cdot CCH_3OH$
fw	605.11	605.11	427.90
cryst syst	orthorhombic	monoclinic	orthorhombic
space group	$C222_1$ (No. 20)	$P2_1$ (No. 4)	$P2_12_12_1$ (No. 19)
a, Å	13.8216(6)	10.4739(2)	16.6576(9)
b, Å	15.4032(9)	13.8801(3)	16.923(1)
c, Å	13.7238(8)	10.5646(7)	13.9907(7)
β, deg		96.259(2)	
V, Å^3	2921.8(3)	1526.7(1)	3944.0(4)
Z	4	2	8
D_{calcd}, g cm^{-3}	1.376	1.316	1.441
μ(Mo Kα), cm^{-1}	8.01	7.67	11.46
T, °C	23	23	23
λ(Mo Kα), Å	0.71069	0.71069	0.71069
R^a	0.052	0.054	0.065
$R_w{}^b$	0.129	0.146	0.180

^{a} $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. ^{b} $R_w = [\Sigma w(F_o{}^2 - F_c{}^2)^2/\Sigma w(F_o{}^2)^2]^{1/2}$.

extended conjugation. Crystallographic data are shown in Table 1, with selected bond distances and bond angles listed in Table 2. It should be noted that the molecular structures of L-BHisPA-Cu(II) and D-BHisPA-Cu(II) are in good mirror image relationship and these are a Λ and Δ enantiomorph, respectively, due to the spiral coordination of the pentadentate BHisPA to Cu(II) center. The chiral complexation is found to be controlled by the configuration of the histidyl α-carbon atoms. A preorganized left- or right-handed helical conformation of L- or D-BHisPA, respectively, is considered to reflect on the chiral complexation.

Table 2. Selected Bond Distances (Å) and Angles (deg) for L-BHisPA-Cu(II), D-BHisPA-Cu(II), and L-HisPA-Cu(II)

	L-BHisPA-Cu(II)	D-BHisPA-Cu(II)	L-HisPA-Cu(II) [a]	
Bond Distances				
Cu–N(1)	1.934(5)	1.981(4)	2.018(6)	2.001(6)
Cu–N(2)	2.000(4)	2.017(5)	1.970(6)	1.956(5)
Cu–N(3)	2.057(5)	2.077(6)	1.947(7)	1.961(6)
Cu–N(2*)	2.000(4)	2.049(6)		
Cu–N(3*)	2.057(5)	2.116(6)		
Cu–O(4)			1.958(5)	1.940(6)
Bond Angles				
N(1)–Cu–N(2)	79.5(1)	80.0(2)	81.7(2)	81.8(2)
N(1)–Cu–N(3)	127.1(1)	127.1(2)	174.6(2)	174.2(2)
N(1)–Cu–N(2*)	79.5(1)	78.6(2)		
N(1)–Cu–N(3*)	127.1(1)	126.9(2)		
N(2)–Cu–N(3)	88.9(2)	89.7(2)	93.3(2)	92.8(2)
N(2)–Cu–N(2*)	159.1(3)	158.6(2)		
N(2)–Cu–N(3*)	103.9(2)	103.5(2)		
N(3)–Cu–N(2*)	103.9(2)	103.8(2)		
N(3)–Cu–N(3*)	105.8(3)	105.9(2)		
N(2*)–Cu–N(3*)	88.9(2)	88.9(2)		
N(1)–Cu–O(4)			91.4(2)	92.1(2)
N(2)–Cu–O(4)			171.9(2)	171.5(2)
N(3)–Cu–O(4)			93.7(2)	93.5(2)

[a] Two independent molecules exist in an asymmetric unit.

Circular dichroism (CD) spectrometry is a useful tool to determine an ordered structure. The mirror image relationship of the CD signals around the d-d transition band of the Cu(II) center was observed between L- and D-BHisPA-Cu(II) in a solid state as shown in Figure 2a. The Cotton effects appear to be related to the chirality of the complexes. The similar CD spectra for L- and D-BHisPA-Cu(II) were

obtained in methanol solution as observed in solid states (Figure 2b), suggesting that L- and D-BHisPA-Cu(II) form a Λ and Δ enantiomorph, respectively, even in solution. The spiral coordination of the chiral pentadentate podand ligand, BHisPA, to the Cu(II) center is likely to induce the enantioselective complexation.

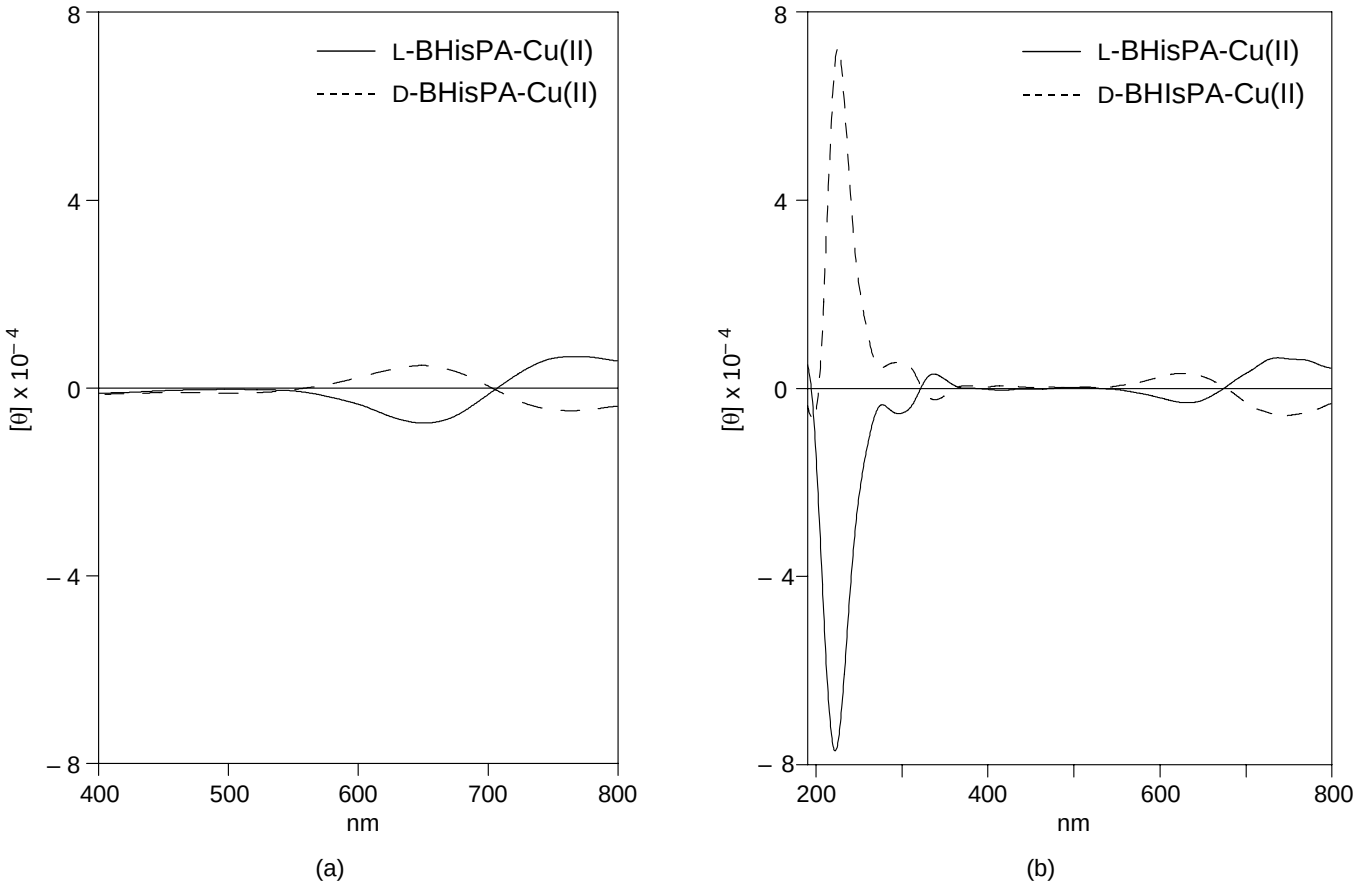

Figure 2. (a) CD spectra of L-BHisPA-Cu(II) and D-BHisPA-Cu(II) in a solid state as nujol mulls and (b) in methanol solution (1.0×10^{-4} M).

Another interesting feature is that each molecule of L-BHisPA-Cu(II) is connected by continuous intermolecular hydrogen bonds to form a hydrogen-bonded macrocycle with left-handed windmill-like arrangement as depicted in Figure 3a. It is in sharp contrast to the finding that D-BHisPA-Cu(II) exhibits right-handed windmill-like arrangement (Figure 3b). These molecular arrangements show a good mirror image relationship. The podand histidyl moieties are considered to induce the molecular aggregation. The utilization of self-assembling properties of the amino acid moieties is likely to be a convenient approach to such a highly ordered system.

On the contrary, the single-crystal X-Ray structure determination of the Cu(II) complex (L-HisPA-Cu(II)) with the ligand bearing one histidyl pendant group, {(*S*)-(+)-1-methoxycarbonyl-2-(4-imidazoyl)ethyl}-

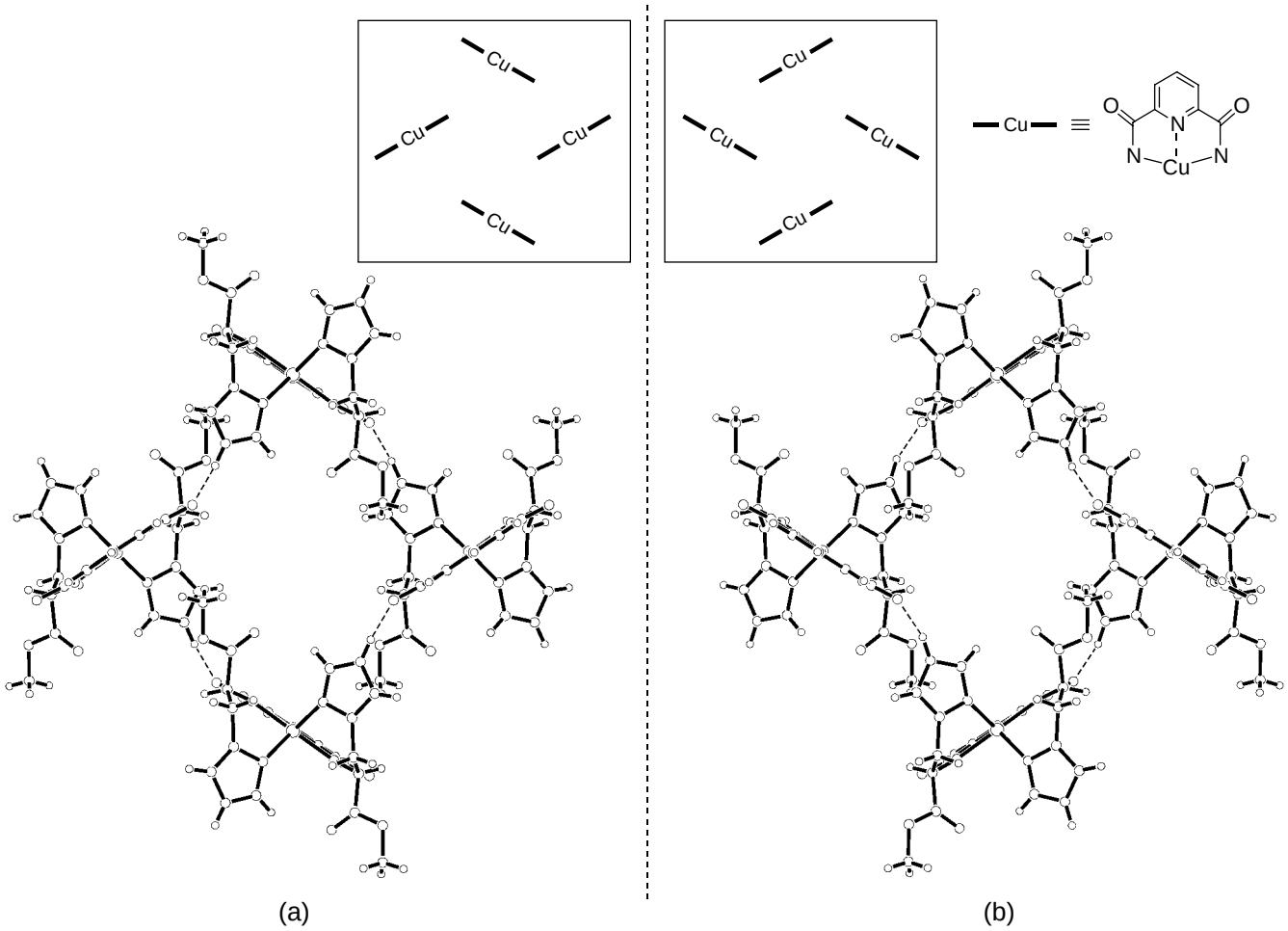

Figure 3. A portion of a layer containing the macrocyclic assembly of crystal packing of (a) L-BHisPA-Cu(II) and (b) D-BHisPA-Cu(II).

2-pyridinecarboxamide (L-HisPA), indicates a little distorted square planar geometry at Cu(II) substituted with the amide nitrogen of L-HisPA (N(2)-Cu-O(4), 171.9°) as shown in Figure 4. Two independent molecules exist in an asymmetric unit to form the π-stack dimer by face-to-face overlap between the pyridyl moieties. In the crystal packing of L-HisPA-Cu(II), each molecule is connected to two neighboring molecules by intermolecular hydrogen bonds, forming a hydrogen-bonded network (Figure 5a). Furthermore, a hydrogen-bonded network was assembled by π-π interaction between the pyridyl moieties (Figure 5b). The Cotton effects around the d-d transition band of Cu(II) center as observed in L- and D-BHisPA-Cu(II) were not detected in the case of L-HisPA-Cu(II).

CONCLUSION

A preorganized left- or right-handed helical conformation of the chiral pentadentate *N*-heterocyclic

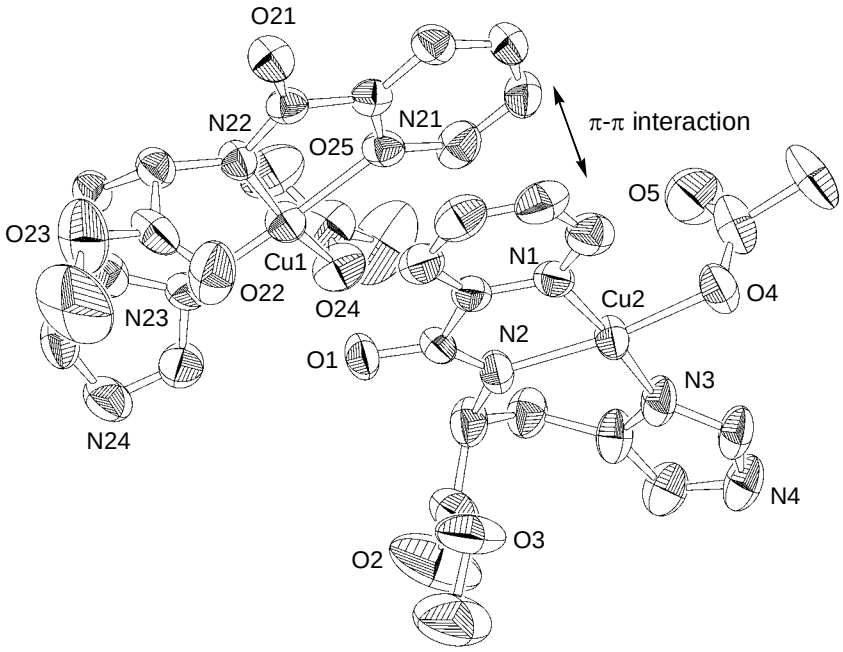

Figure 4. Molecular structure of L-HisPA-Cu(II) (Hydrogen atoms are omitted for clarity).

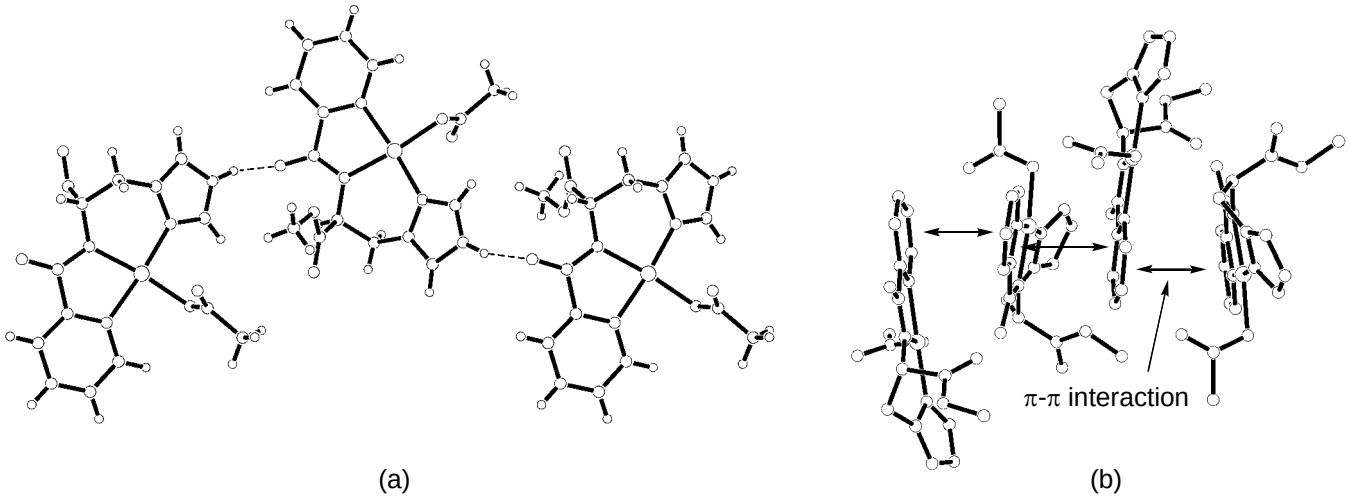

Figure 5. (a) A portion of a layer containing a hydrogen-bonded network and (b) the π-stack of L-HisPA-Cu(II) in the crystal packing.

ligands composed of the 2,6-pyridinedicarboxamide scaffold and the podand histidyl moieties was found to induce the chiral complexation. The propensity to form the chiral complexes is considered to be controlled by the configuration of the histidyl α-carbon atoms. Another noteworthy feature of the chiral ligands is their strong tendency to form the chiral self-assemblies through intermolecular hydrogen bondings in solid states. Architectural control of the molecular assemblies is achieved by the amino acid units possessing chiral centers and hydrogen bonding sites. Studies on the application of the chiral complexation to chiral recognition and asymmetric reaction are now in progress.

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources and were further purified by the standard methods, if necessary. Melting points were determined on a Yanagimoto Micromelting Point Apparatus and were uncorrected. Infrared spectra were obtained with a Perkin Elmer Model 1605 FT-IR. ^{1}H NMR spectra were recorded on a Varian MERCURY 300 (300 MHz) spectrometer and a Varian Unity Inova 600 (600 MHz) one with tetramethylsilane as an internal standard. Mass spectra were run on a JEOL JMS-DX303HF mass spectrometer. L-BHisPA, D-BHisPA, and L-HisPA were prepared according to the method reported in a previous paper.[5]

L-BHisPA-Cu(II) and D-BHisPA-Cu(II)

A mixture of L- or D-BHisPA (93.5 mg, 0.20 mmol) and $Cu(OAc)_2$ (36.3 mg, 0.20 mmol) in methanol (5.0 mL) was stirred under argon at rt for 8 h. A blue solid was obtained by evaporation of the methanol solution in vacuo. L-BHisPA-Cu(II) or D-BHisPA-Cu(II) was isolated quantitatively by recrystallization from methanol/ether. L-BHisPA-Cu(II): mp 253-254 °C (decomp); IR (KBr): 3094, 1745, 1573 cm^{-1}. MS (FAB): *m*/*z* = 532 (M^++1). Anal. Calcd for $C_{21}H_{21}N_7O_6Cu\cdot H_2O$: C, 45.94; H, 4.22; N, 17.86. Found: C, 45.80; H, 3.94; N, 17.53. D-BHisPA-Cu(II): mp 253-254 °C (decomp.); IR (KBr): 3094, 1745, 1573 cm^{-1}. MS (FAB): *m*/*z* = 532 (M^++1). Anal. Calcd for $C_{21}H_{21}N_7O_6Cu\cdot H_2O$: C, 45.94; H, 4.22; N, 17.86. Found: C, 46.27; H, 4.17; N, 17.55.

L-HisPA-Cu(II)

A mixture of L-HisPA (27.4 mg, 0.10 mmol) and $Cu(OAc)_2$ (18.2 mg, 0.10 mmol) in methanol (5.0 mL) was stirred under argon at rt for 8 h. A blue solid was obtained by evaporation of the methanol solution in vacuo. L-HisPA-Cu(II) was isolated in 78% yield by recrystallization from methanol/ether. Mp 178-179 °C (decomp); IR (KBr): 3077, 1742, 1579, 1562 cm^{-1}. MS (FAB): *m*/*z* = 338 $[M\text{-}OAc+1]^+$. Anal. Calcd for $C_{15}H_{16}N_4O_5Cu\cdot 0.5H_2O$: C, 44.50; H, 4.23; N, 13.84. Found: C, 44.20; H, 4.01; N, 13.77.

CD Measurements

CD spectra were recorded using a JASCO J-720 spectropolarimeter in the deaerated methanol solution with the concentration (1.0×10^{-4} M) under argon at 25 °C.

X-Ray Structure Analysis

All measurements for L-BHisPA-Cu(II), D-BHisPA-Cu(II), and L-HisPA-Cu(II) were made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo Kα radiation. The

structures of L-BHisPA-Cu(II), D-BHisPA-Cu(II), and L-HisPA-Cu(II) were solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The H atoms involved in hydrogen bonding were located in electron density maps. The remainder of the H atoms were placed in idealized positions and allowed to ride with the C atoms to which each was bonded. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-165930 for L-BHisPA-Cu(II), CCDC-165931 for D-BHisPA-Cu(II), and CCDC-165932 for L-HisPA-Cu(II). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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