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Helical Porphyrinoids

Enantioselective Induction of Helical Chirality in Cyclooctapyrroles by Metal-Complex Formation**

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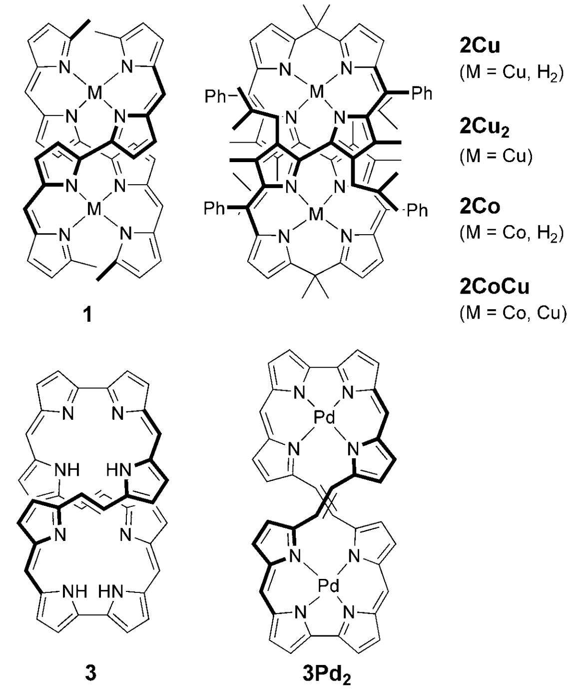
Linear oligopyrroles generate helical structural motifs that are of great interest in supramolecular chemistry.[1] Not only are helicates formed by the tetradentate coordination of bisdipyrrin ligands to a single metal, but two bisdipyrrin units assemble into dinuclear metal complexes of double helicates, such as **1** (Scheme 1).[2] Homohelicity induction in these helicates has been the focus of a number of studies in view of their application to chirality sensing and asymmetric catalysis. Helical chirality is usually controlled by introducing a chiral auxiliary to cause the generation of a particular helical form in diastereomeric excess. For example, the axial coordination of chiral amines to bilinone–zinc complexes and the addition of a homochiral binol linker or homochiral amide substituents to a bisdipyrrin skeleton led to the successful induction of homohelicity.[3,4] However, at present it is difficult to generate stereochemically stable double-helicate metal complexes. Furthermore, the enantioselective induction of helicate formation with a chiral promoter molecule in the absence of chiral auxiliaries has not been reported. This point is important, because the binding of a chiral guest to a host in a mixture of diastereomers would be too much complicated.

Stereochemically stable helicate metal complexes closely related to **1** can be prepared by using cyclooctapyrroles, such as **2**, in which π-conjugated bisdipyrrin units are linked by sp^3-hybridized carbon atoms (Scheme 1).[5] The figure-eight loop of cyclooctapyrroles is preorganized with metal-binding sites formed from four pyrrole nitrogen atoms. Mononuclear and dinuclear metal complexes of these macrocycles have been reported.[6] However, studies on the helical chirality of cyclooctapyrroles are limited.[7] Vogel et al. investigated the optical resolution of [36]octaphyrin(2.1.0.1.2.1.0.1) (**3**)[8] and its dinuclear palladium(II) complex **3Pd$_2$** by HPLC on a chiral phase, and the helicity of each enantiomer of **3Pd$_2$** was determined unambiguously by X-ray crystallography.[7a] However, the circular dichroism (CD) spectra of **3Pd$_2$** have not been reported, and there is some complexity derived from rotation about the bond between the pyrrole α carbon atom and the ethylene carbon atom in the ethylene-bridged bipyrrole moiety at the crossing point upon the conversion of **3** into **3Pd$_2$**. A conformational change due to rotation about this bond might be the reason why the order of HPLC elution of the two enantiomers was reversed after metal incorporation.



Scheme 1. Helical structures of bisdipyrrin dinuclear complexes.

Since the CD Cotton effect is very important in a discussion on chirality, it seemed necessary to confirm the relationship between the helical handedness of cyclooctapyrroles and their CD Cotton effect. The macrocycle **3** contains a helicene-like bisdipyrrin π system surrounding each metal site and an ethylene-bridged bisdipyrrin π system connecting the two metal sites. Thus, the application of the exciton chirality method to predict the helical handedness of **3** on the basis of the CD Cotton effect is not straightforward.[9] The framework of **2**, in which a pair of electronically isolated bisdipyrrin chromophores cross over, may be better suited for the exciton

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chirality method. We describe herein the synthesis, optical resolution, and chiroptical properties of the stereochemically stable cyclooctapyrrole metal complexes **2M$_2$**. The helical chirality of **2M$_2$** was determined unambiguously on the basis of the theoretical simulation of the CD spectra by using the X-ray crystallographic data. Furthermore, we have found that metal sources with optically active carboxylate and amine ligands cause the enantioselective metalation of **2** to give helically asymmetric metal complexes with no chiral auxiliary.

Inversion of the figure-eight loop of the cyclooctapyrrole-free base **2** occurs through unwinding of the molecular twist and then rewinding in the opposite direction. This molecular motion was detected in variable-temperature ^{1}H NMR spectroscopic experiments in [D$_{10}$]*o*-xylene (see the Supporting Information). Two signals due to the diastereotopic methylene hydrogen atoms of the isobutyl groups, at $\delta = 3.0$ and 1.9 ppm at 60 °C, coalesced at temperatures over 120 °C. The inversion barrier was estimated to be at least 77 kJ mol^{-1} on the basis of the frequency difference ($\Delta\nu = 435$ Hz) and the coalescence temperature ($T_c > 393$ K). As interconversion between the enantiomeric forms is prohibited in their metal complexes, optical resolution of the complexes is possible. The treatment of the free base **2** with one molar equivalent of $Cu(OAc)_2{\cdot}H_2O$ in CH_2Cl_2–MeOH at room temperature for 1 h afforded a mononuclear copper(II) complex, **2Cu**, in 43 % yield, whereas the treatment of **2** with 10 molar equivalents of $Cu(OAc)_2{\cdot}H_2O$ in the presence of triethylamine at room temperature for 5 h gave a dinuclear copper(II) complex, **2Cu$_2$**, in 50 % yield. The absorption band in the visible region of the UV/Vis spectrum shifted from 541 to 570 and then 584 nm upon consecutive metalation of **2** with Cu (Figure 1 a). The mononuclear cobalt(II) complex **2Co** was also obtained in 85 % yield by the treatment of **2** with excess $Co(OAc)_2{\cdot}4H_2O$ at room temperature for 2 h. The treatment of **2Co** with excess $Cu(OAc)_2{\cdot}H_2O$ at room temperature afforded a heterodinuclear complex, **2CoCu**, in 78 % yield. The absorption band in the visible region of the UV/Vis spectrum shifted from 541 to 569 and then 591 nm upon consecutive metalation of **2** with Co and Cu (Figure 1 b).

X-ray crystallographic analysis of **2Cu**, **2Cu$_2$**, **2Co**, and **2CoCu** indicated that 2,2′-bipyrrole units in the *s-trans* conformation are located at the crossing point of the figure-eight loop, and that the metal atom is disordered between two sites in the complexes **2Cu**, **2Co**, and **2CoCu** (Figure 2). The side view of these complexes shows the rhombic cavity enclosed by four panels of the planar dipyrrin unit connected with two hinges in the form of bipyrrole C2–C2′ bonds and two *gem*-dimethyl-substituted bridging carbon atoms.

The dinuclear complexes **2Cu$_2$** and **2CoCu** were resolved by HPLC with a chiral column (Daicel chiralpak IB) by eluting with *n*-hexane/CH_2Cl_2 (40:1). The first fraction of **2Cu$_2$** showed positive CD signals at 697 and 496 nm and a negative CD signal at 583 nm (Figure 1 c). Similarly, the first fraction of **2CoCu** showed positive CD signals at 711 and 492 nm and a negative CD signal at 590 nm (Figure 1 d). Theoretical UV/Vis and CD spectra (Figure 3 a,b) were calculated on the basis of the atom coordinates obtained from the X-ray crystallographic structure of **2Cu$_2$** in the *M*,*M* helical form; all peripheral substituents were omitted (see the Supporting Information). The calculated spectra are in good agreement with the observed spectra for the enantiomer of **2Cu$_2$** eluted second in terms of band position and intensity. Furthermore, calculations based on time-dependent density

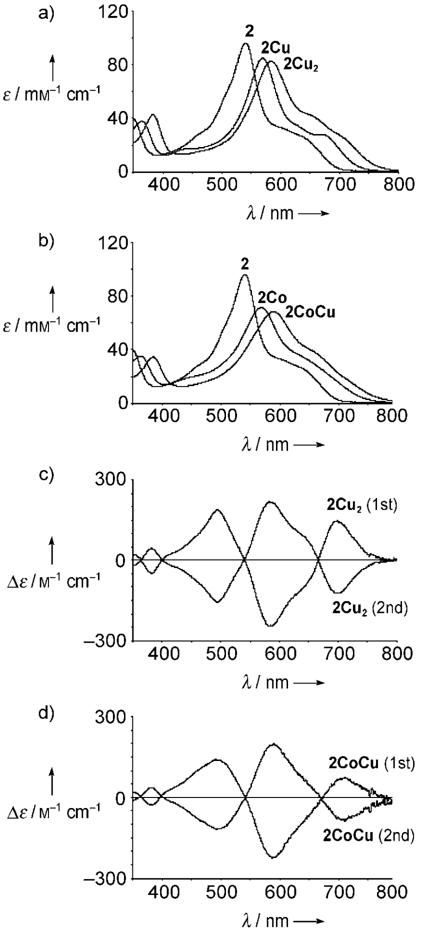


Figure 1. a) UV/Vis spectra of **2**, **2Cu**, and **2Cu$_2$** in CH_2Cl_2; b) UV/Vis spectra of **2**, **2Co**, and **2CoCu** in CH_2Cl_2; c) CD spectra of optically resolved **2Cu$_2$** (first (1st) and second (2nd) HPLC eluate) in CH_2Cl_2; d) CD spectra of optically resolved **2CoCu** (first and second HPLC eluate) in CH_2Cl_2.

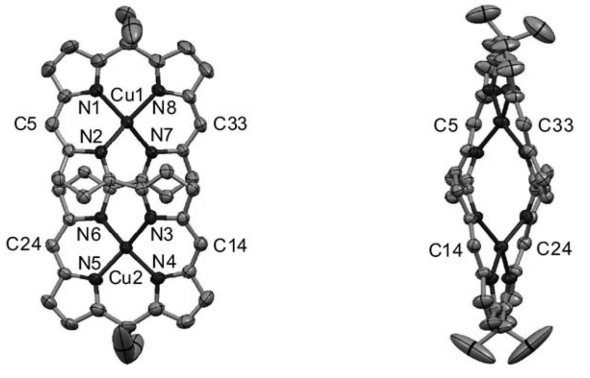


Figure 2. ORTEP drawings of **2Cu$_2$** at the 50 % level with atom numbering; left: top view, right: side view. Four phenyl substituents are omitted at C5, C14, C24, and C33, and eight alkyl substituents are omitted at the bipyrrole β positions.

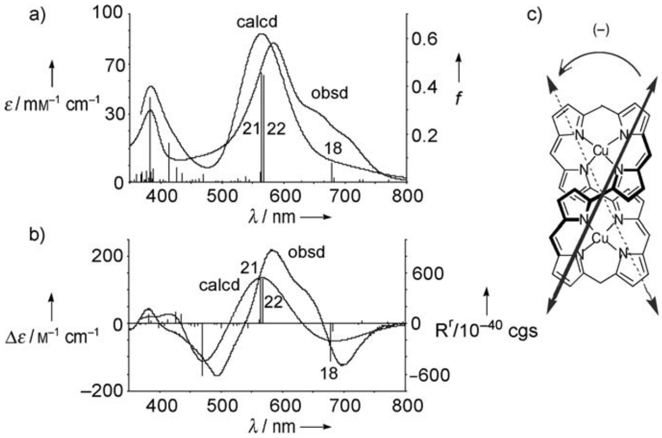


Figure 3. a) Theoretical and experimental UV/Vis spectra; b) theoretical and experimental CD spectra; c) coupling electronic transitions that give rise to the absorption band 18 and the sign of the corresponding Cotton effect in the left-handed cyclooctapyrrole *M*,*M* enantiomer. The theoretical spectra were calculated for the macrocyclic core of (*M*,*M*)-**2 Cu$_2$**, and the experimental spectra were recorded for the enantiomer of **2 Cu$_2$** that was eluted second by HPLC. The bars indicate the positions and oscillator strength (*f*) or rotary strength (R^r) of the transitions (18, 21, 22) calculated by TDDFT.

functional theory (TDDFT) revealed that the electronic transitions along the long axes of the π-conjugated bisdipyrrin chromophores connecting the two copper sites are responsible for the absorption band 18 in the theoretical UV/Vis spectra. Since this absorption band correlates with a negative sign in the theoretical CD spectrum, the absolute configuration of **2 Cu$_2$** determined by calculation is in agreement with that determined on the basis of the CD exciton chirality method. In the figure-eight screw shown in Figure 3 c, the transition in the front bisdipyrrin chromophore couples with the transition in the back bisdipyrrin chromophore. When the coupling dipole direction is counterclockwise, as for the *M*,*M* enantiomer, a negative Cotton effect can be predicted according to the CD exciton chirality method.[9] Thus, *M*,*M* helicity was assigned to the enantiomer of **2 Cu$_2$** eluted second from the HPLC column.

We reported previously that porphyrinoids can be induced to adopt a particular unidirectional helical conformation preferentially by protonation with optically active carboxylic acids.[7b,10] In fact, the addition of 200 equivalents of (*S*)-(+)-mandelic acid to a solution of **2** in CH_2Cl_2 caused the appearance of a CD spectrum that is quite similar to that of (*M*,*M*)-**2 Cu$_2$** (see the Supporting Information). This result led us to investigate the enantioselective formation of stable cyclooctapyrrole metal complexes. The copper(II) salt prepared by the addition of (*S*)-(+)-mandelic acid sodium salt (4 equiv) in MeOH to $CuCl_2{\cdot}2\,H_2O$ in water was used as the metal source. The treatment of copper(II) (*S*)-(+)-mandelate (30–40 equiv) with **2** in CH_2Cl_2 for 24 h resulted in the formation of a mixture of **2 Cu** and **2 Cu$_2$**. The CD spectrum of the product **2 Cu$_2$** showed a negative first Cotton effect at 697 nm. The *ee* value of **2 Cu$_2$** based on the CD intensity (12 % *ee*) was in good agreement with that determined by HPLC analysis (14 % *ee*). Complex **2 Cu** formed in this experiment showed negative CD signals at 669 and 484 nm and a positive CD signal at 564 nm. These wavelengths are only slightly blue-shifted (12–28 nm) relative to those of **2 Cu$_2$**, which suggests that the monocopper complex also has *M*,*M* helicity. This monocopper complex was converted into the dicopper complex by using excess $Cu(OAc)_2{\cdot}H_2O$ in the presence of triethylamine at room temperature. CD analysis of the product verified the *ee* value of 12 %. Thus, the *ee* value was not affected by the second metalation process to give **2 Cu$_2$**. The reaction of **2** with the copper(II) carboxylate derived from (*R*)-(−)-mandelic acid led to **2 Cu$_2$** with 13 % *ee* and with a positive first Cotton effect at 697 nm.

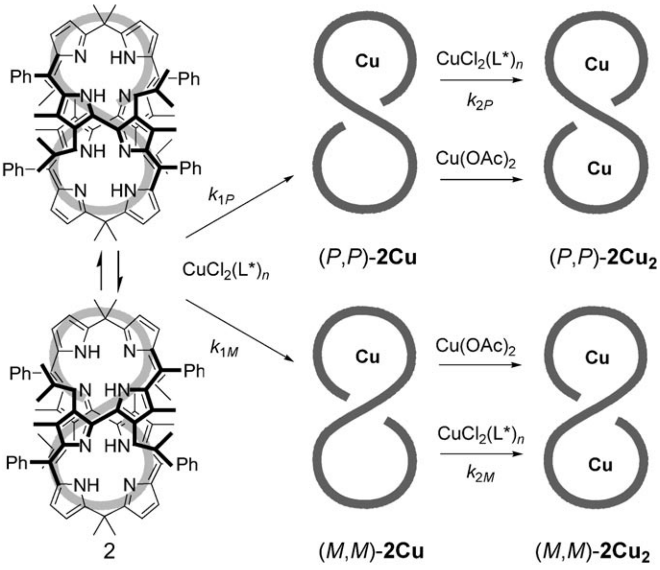
Optically active amines were used under homogeneous reaction conditions for the asymmetric synthesis of **2 Cu** and **2 Cu$_2$** in a much shorter reaction time than the 24 h required for the complete conversion of **2** under the heterogeneous reaction conditions with mandelic acid. When **2** was added to a solution of (*R*)-(+)-1-(1-phenyl)ethylamine (10 equiv) and $CuCl_2{\cdot}2\,H_2O$ (5 equiv) in CH_2Cl_2, **2** reacted completely to give **2 Cu** in 2 h. However, the *ee* value for helical chirality was very small (Table 1, entry 1). An increase in the concentration of (*R*)-(+)-1-(1-phenyl)ethylamine (80 equiv) retarded the metalation reaction, but the *ee* value of **2 Cu** was improved to 13 % (Table 1, entry 2). The use of a large excess of a mixture of (*R*)-(+)-1-(1-phenyl)ethylamine and $CuCl_2{\cdot}2\,H_2O$ in a 2:1 ratio at low temperature further improved the *ee* value of **2 Cu** (Table 1, entry 4).

Table 1: Asymmetric synthesis of **2 Cu** in the presence of (*R*)-(+)-1-(1-phenyl)ethylamine.[a]

Entry	Molar ratio (amine/Cu/**2**)	*t* [h]	*T* [°C]	CD sign (669 nm)	*ee* [%][b] (**2 Cu**)
1	10:5:1	2	RT	+	2
2	80:5:1	5	RT	+	13
3	800:400:1	0.25	RT	+	11
4	800:400:1	1.5	0	+	19

[a] A solution of **2** (0.07–0.28 μM) in CH_2Cl_2 was treated with $CuCl_2{\cdot}2\,H_2O$ and the amine. [b] The *ee* value was determined by using $|\Delta\varepsilon_{583}-\Delta\varepsilon_{496}|$ as an index after conversion into **2 Cu$_2$** with $Cu(OAc)_2{\cdot}H_2O$.

As noted above, the rates for the first metal-insertion process to give (*M*,*M*)-**2 Cu** and (*P*,*P*)-**2 Cu** (k_{1M} and k_{1P}, respectively) are dependent on the temperature and the amount of the optically active amine used (Table 1 and Scheme 2). To gain insight into the effect of the optically active amine on the second metalation step, a racemic mixture of **2 Cu** was treated with (*R*)-(+)-1-(1-phenyl)ethylamine (10 equiv) and $CuCl_2{\cdot}2\,H_2O$ (5 equiv) in CH_2Cl_2. Although these reaction conditions do not lead to a remarkable difference between k_{1M} and k_{1P} (Table 1, entry 1), an *ee* value of 33 % was observed for the *P*,*P* helical form of **2 Cu$_2$** in the initial stages of the second metalation step (Table 2, entry 1). Thus, the rate (k_{2P}) for the metal insertion into (*P*,*P*)-**2 Cu** is twice as high as the rate (k_{2M}) for the metal insertion into (*M*,*M*)-**2 Cu**. As the metalation proceeds, (*P*,*P*)-**2 Cu** is consumed faster, which is consistent with the development of an excess of the *M*,*M* helical form of **2 Cu**. Thus, 72 % *ee* was observed for the *M*,*M* helical form of **2 Cu** in the final stage of the metalation (Table 2, entry 5). These results show that



Scheme 2. Metalation of **2** and **2 Cu** with an optically active metal source. L* = (*R*)-(+)-1-(1-phenyl)ethylamine.

Table 2: Conversion of racemic **2 Cu** into **2 Cu₂** with $CuCl_2 \cdot 2H_2O$ in the presence of (*R*)-(+)-1-(1-phenyl)ethylamine at room temperature.[a]

Entry	*t* [h]	**2 Cu**		**2 Cu₂**		Molar ratio
		CD sign (669 nm)	*ee* [%][b]	CD sign (697 nm)	*ee* [%][b]	**2 Cu/2 Cu₂**
1	3	−	3	+	33	9:1
2	9	−	15	+	29	6:4
3	12	−	25	+	25	5:5
4	16	−	36	+	19	3:7
5	24	−	72	+	6	1:9

[a] A solution of **2 Cu** (0.36 μM) in CH_2Cl_2 was treated with the amine and $CuCl_2 \cdot 2H_2O$ in an amine/$CuCl_2 \cdot 2H_2O$/**2** molar ratio of 10:5:1. [b] The *ee* value was determined by using $|\Delta\varepsilon_{583} - \Delta\varepsilon_{496}|$ as an index after conversion into **2 Cu₂** with $Cu(OAc)_2 \cdot H_2O$ if necessary.

kinetic resolution may be a potential approach to the preparation of metal porphyrinoids with high optical purity.

The unique figure-eight loop structure of cyclooctapyrroles has potential application to the synthesis of chiral functional materials. For this purpose, an understanding of the chiroptical properties of cyclooctapyrroles on the basis of their structure is of great importance. Mononuclear cobalt(II) and copper(II) complexes and homo and heterodinuclear complexes of a cyclooctapyrrole with two *gem*-dimethyl-substituted bridging carbon atoms were prepared in this study. The crossing of discrete bisdipyrrin chromophores in the figure-eight loop is an advantageous structural feature for the determination of the absolute configuration on the basis of the exciton chirality method. The absolute configuration was confirmed by the theoretical CD spectrum calculated for (*M*,*M*)-**2 Cu₂** on the basis of X-ray crystallographic data. The induction of excess unidirectional helicity in the metalation processes not only gives insight into the mechanism of chirality transfer but also provides a convenient method for the preparation of optically active metal cyclooctapyrroles for further applications.

Experimental Section

2 Cu₂ (50% yield): UV/Vis (λ_{max} (logε), CH_2Cl_2): 384 (4.63), 584 (4.92), 660 (shoulder, 4.61), 711 nm (shoulder, 4.38); ESIMS: *m*/*z* calcd for $C_{86}H_{88}N_8Cu_2$: 1360.58; found: 1360.30; magnetic moment (Evans method, $CDCl_3$): 3.14; elemental analysis: calcd (%) for $C_{86}H_{88}N_8Cu \cdot C_6H_{14} \cdot H_2O$: C 75.43, H 7.16, N 7.65; found: C 75.51, H 6.94, N 7.65. Recrystallization from CH_2Cl_2/hexane gave crystals for X-ray crystallographic analysis. Crystal data: $C_{92}H_{102}N_8Cu_2 \cdot 2C_6H_{14}$, $M_r = 1533.07$, triclinic, space group *Pca2₁*, $a = 22.2077(16)$, $b = 16.1092(12)$, $c = 22.2493(16)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 7959.7(10)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.279$ Mg m^{-3}, $\mu(Mo_{K\alpha}) = 0.589$ mm^{-1}, $T = 296(2)$ K, crystal size: $0.50 \times 0.40 \times 0.10$ mm. A total of 15899 unique reflections were collected ($3.62 < 2\theta < 54.72°$) by using graphite-monochromated $Mo_{K\alpha}$ radiation. The structure was solved by the direct method by using the SHELX97 package. The positions of all non-hydrogen atoms were refined anisotropically (930 parameters). All hydrogen atoms were placed at ideal positions and included in the refinement. $R_1 = 0.0427$, $wR_2 = 0.1051$ for 13648 reflections with $I > 2.00\sigma(I)$; $R_1 = 0.0546$, $wR_2 = 0.1156$ for all data; GOF (on F^2) = 1.041. CCDC 698457 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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