Crystal-Driven Distortion of Ligands in Copper Coordination Complexes: Conformational Pseudo-Enantiomers

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Abstract: The ligand in [Cu(**6**)CH_3CN](ClO_4)$_2$ adopts two conformations that may be described as "pseudo-enantiomers" in that they possess approximately mirror-image molecular helicity, although they differ in the orientation of a single methyl substituent. The two conformations differ in energy as judged by analogy to other compounds studied previously, computation of the relative free energies of formation of the isomers, and measurement of solution circular dichroism spectra. The solid-state structures of both single enantiomer and racemic forms of the complex were determined by X-ray crystallography. In the chiral complex, a quasi-racemate was observed with both pseudo-enantiomeric conformers present in the asymmetric unit. Packing forces induce a higher energy conformation in order to achieve higher apparent symmetry in the solid state. In contrast, the racemic complex only displayed a single conformation corresponding to the lower energy one of the two observed in the single enantiomer structure.

Keywords: chirality · circular dichroism · conformation analysis · copper · solid-state structures

Introduction

Among the interesting issues currently being examined for crystal structures and morphology are the discernment of factors that influence solid-state structure[1] and the application of solid-state supramolecular chemistry to achieve asymmetric transformations and reactions.[2] Crystal structures of the enantiomers and of the racemic compound may exhibit similarities in the packing of the constituent molecules. Racemic crystals are generally more stable than crystals containing single enantiomers, with the difference in energy normally about -0.2 to -1 kcal mol^{-1}, but it can be as high as -2 kcal mol^{-1}.[2] The basis for this phenomenon has not been elucidated fully. One of the more widely accepted notions is that space groups containing inversion centers are favored.[1] In some cases this can lead to crystals with higher density[3–5] although not always.[2] In one interesting case, crystals of [(*R*)-1-cyanoethyl]bis(dimethylglyoximato)(4-methylpyridine)cobalt(III) crystallize with two crystallographically independent molecules in the asymmetric unit related by a pseudo inversion center. On irradiation with X-rays, the chiral center partially inverts, transforming one of the crystallographically independent molecules from configuration *R* to *S* and increasing the overall symmetry of the crystal structure.[6] A tendency to maximize symmetry in the crystal can result in interesting phenomena. For example, packing may give elements of pseudosymmetry, such as the formation of quasi-racemates, in which two different substances are structurally similar and quasi-enantiomeric.[2, 7]

In this paper, we report X-ray crystallographic data that provide an example in which the driving force for higher symmetry enforces a higher energy conformation of a molecule, which is difficult to characterize by other spectroscopic methods. There are well-documented cases in which the conformations of enantiomers are influenced by crystal packing forces. Structures of enantiopure and racemic amino acids have provided several interesting examples.[8] Structures of (+)- and (±)-ketopinic acids revealed a total of eight conformationally distinct contributors to the two structures, and these result from the low barriers to carboxyl rotation in this molecule.[9]

Chiral tripodal ligands related to tris[(2-pyridyl)methyl]amine (TPA, **1**) with an asymmetric center in one arm (e.g., **2**)[10] and their metal-ion complexes have been used as chiral solvating agents,[10] metal-ion sensors with multiple signals,[11] and redox chiroptical switches.[12–14] Related derivatives of α-amino acids and β-amino alcohols have been used in the assignment of absolute configurations.[15] The large ampli-

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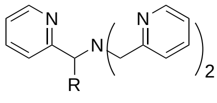
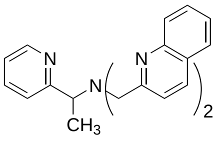


1 R = H
2 R = CH_3
3 R = Ph



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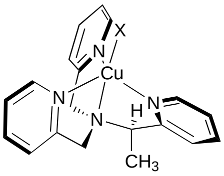

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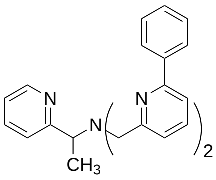

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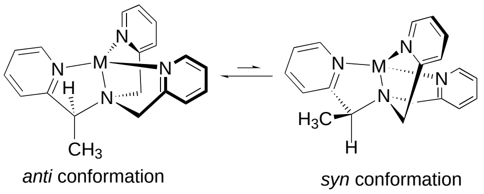
tudes of the observed chiroptical spectra upon which these applications are based derive from a conformational bias that fixes the geometry of the heterocyclic chromophores, resulting in strong circular dichroism spectra that yield useful stereochemical information.[16, 17] The complexation of a five-coordinate metal ion in a trigonal bipyramidal coordination geometry (e.g., $[M(L)X]^{n+}$, M = zinc(II) or copper(II), L = **2**, **3**, or **4**, X = counterion or solvent) results in the formation of a propeller-like orientation of the heterocyclic rings, and the orientation approximates an additional axial symmetry element (e.g., **5**). Complexation of metals with other coordination geometries does not generate the propeller structure and consequently does not result in strong CD spectra.[10]

Our previous studies examined complexes of **2**–**4**, with either a methyl or phenyl substituent on the asymmetric arm. We have suggested that two conformations are available to the substituted derivatives complexed with zinc(II) and copper(II) metal ions.[18] The two binding conformations available (Scheme 1) include the "*anti*" conformation, in which the α substituent points away from the pyridyl groups, and the "*syn*" conformation, in which the α substituent points towards one pyridyl group. The *syn* conformation should be less stable as a result of the presence of severe steric interactions between the α substituent and one of the pyridyl groups. Models suggest that the complex with a carbon-center configuration of "*R*" should display a left-handed propeller-like twist. For the complex $[Zn(\mathbf{2})Cl]^+$, there is a calculated preference for the *anti* conformation by 1–2 kcal mol^{-1} (Scheme 1).[19, 22] The existence of the *anti* conformer has been well established by the solid-state structures of enantiomerically pure[16] and racemic[19] chiral ligand–metal complexes and also by correlation between the chiroptical properties of the solutions with the estimated preferred conformations.[16] The unfavored *syn* conformation has been predicted by several calculations,[19, 22] but no experimental evidence for its existence has been available. Here we report the first direct experimental evidence for the *syn* conformation, observed in the solid-state structure of a copper(II) complex of ligand **6**. Comparison of the optically pure and racemic complexes suggests that the presence of the *syn* conformation may result from solid-state packing forces that seek to increase the symmetry of the crystal.



Scheme 1. Stereochemical depictions of chiral TPA binding conformations.

Results and Discussion

The ligands (*R*)-**6** and (*S*)-**6** and their complexes with $ZnCl(ClO_4)$ and CdI_2 were previously reported.[19] Crystals of $[Cu\{(R)\text{-}\mathbf{6}\}CH_3CN](ClO_4)_2$ suitable for X-ray crystallographic study were available previously, but the crystallographic analysis had been given low priority because novel structural features were not anticipated. Several other structures had been done in this series of compounds (although not with this particular ligand), and for all of the complexes previously studied, including both racemic and optically pure complexes, very similar structures were obtained with the ligands displaying only the *anti* conformation. However, we now report that the structure of $[Cu(\mathbf{6})CH_3CN](ClO_4)_2$ revealed unique and important features (see Table 1).

Table 1. Summary of crystal and refinement data.

	$[Cu\{(R)\text{-}\mathbf{6}\}CH_3CN](ClO_4)_2$	$[Cu(rac\text{-}\mathbf{6})CH_3CN](ClO_4)_2$
formula	$C_{33}H_{31}N_5Cl_2Cu$	$C_{33}H_{31}N_5Cl_2Cu$
M_w	760.09	760.09
crystal system	monoclinic	monoclinic
space group	$P2_1$	$P2_1/c$
a [Å]	11.692(4)	11.739(2)
b [Å]	19.852(1)	19.701(3)
c [Å]	14.501(8)	14.531(1)
α [°]	90.0	90.0
β [°]	96.09(4)	96.54(1)
γ [°]	90.0	90.0
V [Å^3]	3346.7(3)	3338.76(8)
Z	4	4
T [K]	298	298
no. of reflections collected	5343	20460
no. of unique reflections	5064	7585
R	0.070	0.069
R_w	0.1102	0.1026
GOF	2.51	1.07

The ORTEP drawing of the enantiomerically pure complex is shown in Figure 1. Two asymmetric units were observed in the same unit cell. One displays a left-handed propeller twist with the methyl group pointing away from the pyridyl ring (i.e., **7**, *anti* conformation). The other one is right-handed with the methyl group pointing towards the pyridyl group (i.e., **8**, *syn* conformation). The copper ion displays distorted trigonal

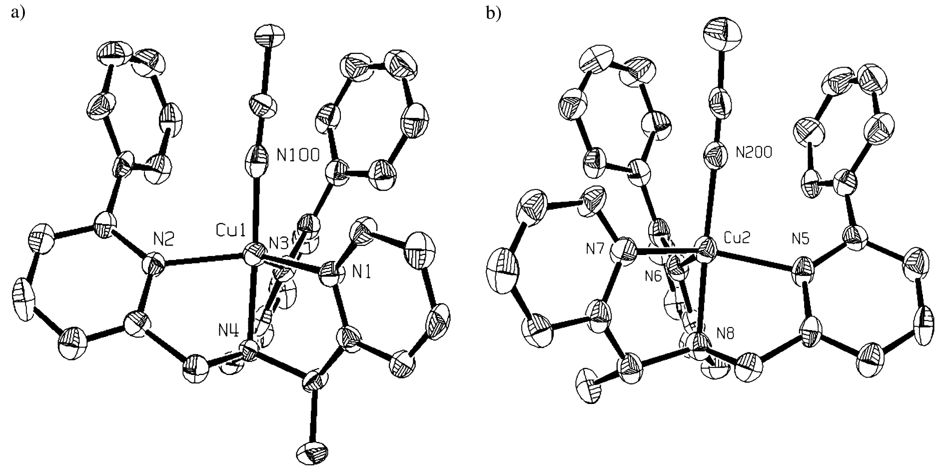
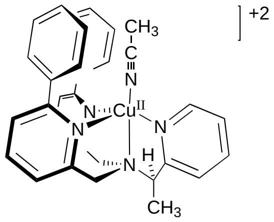


Figure 1. ORTEP diagram (30 % probability ellipsoids) of the complex [Cu{(*R*)-**6**}$CH_3CN](ClO_4)_2$. a) asymmetric unit with ligand in the *anti* conformation; b) ligand in the *syn* conformation.



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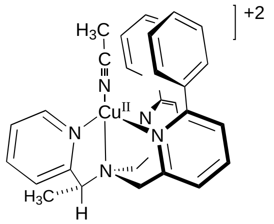

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bipyramidal geometry, in which the metal is 0.385 Å above the plane of the heterocyclic nitrogens (see Table 2).

The observation of both *anti* and *syn* conformations was surprising and at odds with our previous observations, so a calculation was done to estimate the relative energies. The structures of the complexes were calculated using semi-empirical calculations on the commercially available SPARTAN package of software. The initial geometries were generated from the crystallographic coordinates and minimized with geometry optimization by the PM3/tm semi-empirical method.[21] The structure with the ligand in the *anti*-conformation was found to be lower in energy than that with the *syn* conformation by 1.0 kcal mol^{-1}. These results are consistent with work on related Cu^{II} and Zn^{II} complexes, in which the substituent on the chiral arm of the ligand is methyl.[19]

Table 2. Selected bond lengths [Å] and angles [°] for the complex [Cu{(*R*)-**6**}$CH_3CN](ClO_4)_2$.

Cu1–N100	1.96(2)	N100–Cu1–N4	173.2(5)
Cu1–N4	2.003(12)	N100–Cu1–N1	94.5(5)
Cu1–N1	2.016(12)	N4–Cu1–N1	83.5(5)
Cu1–N2	2.084(10)	N100–Cu1–N2	96.4(5)
Cu1–N3	2.162(13)	N4–Cu1–N2	80.9(5)
Cu1–N200	1.99(2)	N1–Cu1–N2	135.4(5)
Cu2–N8	2.005(14)	N100–Cu1–N3	107.3(6)
Cu2–N7	2.042(13)	N4–Cu1–N3	79.5(5)
Cu2–N5	2.102(11)	N1–Cu1–N3	109.8(5)
Cu2–N6	2.19(2)	N2–Cu1–N3	107.9(5)
		N200–Cu2–N8	171.0(6)
		N200–Cu2–N7	92.9(6)
		N8–Cu2–N7	83.6(5)
		N200–Cu2–N5	95.7(6)
		N8–Cu2–N5	81.2(5)
		N200–Cu2–N5	95.7(6)
		N7–Cu2–N5	136.0(5)
		N200–Cu2–N6	106.7(6)
		N8–Cu2–N6	109.7(5)
		N5–Cu2–N6	108.8(5)

The complex [Cu(*rac*-**6**)-$CH_3CN](ClO_4)_2$ shows lower energy peaks characteristic of trigonal bipyramidal copper(II) coordination[20] ($\varepsilon_{812} = 259$ and $\varepsilon_{635} = 85$; 0.82×10^{-3} M solution in acetonitrile), indicating retention of solid-state structure in solution. The molar conductance of [Cu(*rac*-**6**)$CH_3CN](ClO_4)_2$ in 0.82×10^{-3} M solution in acetonitrile indicates 1:2 electrolytic nature in solution. The complex [Cu(*rac*-**6**)$CH_3CN](ClO_4)_2$ shows a magnetic moment of 1.71 BM. The half wave potential for the complex [Cu(*rac*-**6**)$CH_3CN](ClO_4)_2$ measured by cyclic voltammetry (CV) in solution in acetonitrile (1 mM) gives a value of -0.093 V with a peak-to-peak separation 120 mV. The complex undergoes a quasireversible one-electron redox process with i_{pa}/i_{pc} approaching unity. The ferrocene/ferrocenium couple under the same conditions exhibited $E_{1/2} = 0.358$ V. These data are consistent with the molecular structure and coordination geometry of the metals that were observed in the X-ray structures.

Acquired UV/Vis (bottom) and CD (top) spectra of complex [Cu{(*R*)-**6**}]$(ClO_4)_2$ in acetonitrile are shown in Figure 2; they bear strong resemblance to analogous zinc(II) complexes of the same ligand.[14] While the UV/Vis spectra of the ligand and copper(II) complex are very similar with strong absorbances near 245 and 284 nm, the CD spectra are quite different, exhibiting a strong peak near 291 nm and a trough near 260 nm for the copper(II) complex, whereas the free ligand gives rise to a relatively weak Cotton effect. The free ligand has many conformations available, resulting in an ill-defined geometry. Complexation of a copper(II) ion induces a propeller-like shape, affording a much greater anisotropic environment, which leads to a larger CD amplitude. Spectra obtained from related complexes have been assigned to a coupled oscillator model,[17] but the present spectra do not satisfy the requirements for such an assignment.

At this point the computations and solution spectra appeared to be at odds with the X-ray data. At face value, one might infer from the X-ray data that the two conformations are of the same energy. The computations indicated a difference in conformational energy that would suggest a predominant population of the *anti* conformation. The solution circular dichroism spectra suggested that one conformational state was more significantly populated. Thus, all of the data pointed to the adoption of a predominant *anti* conformation except for the crystallographic structure. Indeed, the X-ray structure constituted the first evidence for the existence of the *syn* ligand conformation in α-substituted TPA deriva-

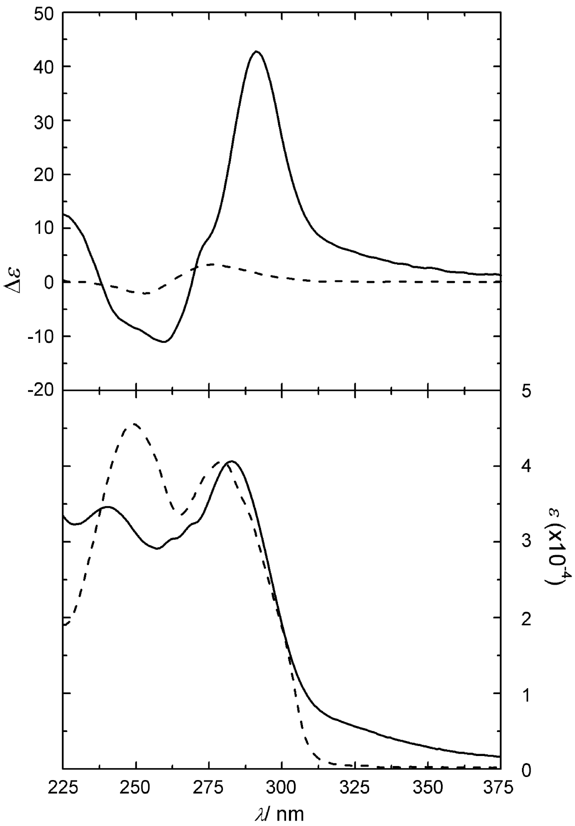

Figure 2. Circular dichroism (top) and UV (bottom) spectra of (*R*)-**6** (dashed) and [Cu{(*R*)-**6**}]$(ClO_4)_2$ (solid) in acetonitrile.

Table 3. Selected bond lengths [Å] and angles [°] for the complex [Cu(*rac*-**6**)CH_3CN]$(ClO_4)_2$.

Cu1–N5	1.982(5)	N5–Cu1–N1	173.4(2)
Cu1–N4	2.028(4)	N5–Cu1–N4	94.1(2)
Cu1–N1	2.011(4)	N1–Cu1–N4	83.0(2)
Cu1–N2	2.185(4)	N5–Cu1–N3	96.9(2)
Cu1–N3	2.092(4)	N1–Cu1–N3	81.0(2)
		N4–Cu1–N3	134.0(2)
		N5–Cu1–N2	106.4(2)
		N1–Cu1–N2	80.2(2)
		N4–Cu1–N2	110.5(2)
		N3–Cu1–N2	108.7(2)

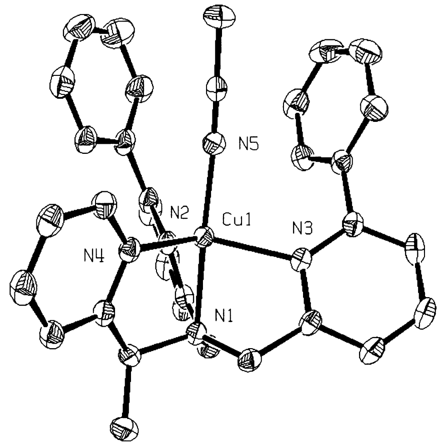

Figure 3. ORTEP diagram (30% probability ellipsoids) of the complex [Cu(*rac*-**6**)CH_3CN]$(ClO_4)_2$.

tives; previously the *syn* conformation was only predicted from several computational models and anticipated from analogy to TPA complexes.[19, 22] Under these circumstances, we considered whether some crystal-packing issue would lead to an anomalous observation in the X-ray structure.

Further examination of the two molecules in the asymmetric unit led to the observation that these molecules may be described as "pseudo-enantiomers".[23] Except for the configuration of the chiral carbon of the molecules of the asymmetric unit, the two structures are nearly mirror images. The twists of the two molecules are enantiomorphic, and this twist constitutes a large fraction of the overall shape of the molecule compared with the chiral carbon center. Deletion of the methyl groups, inversion of one molecule, and rigid superimposition of the complexes gave RMS (root mean square) = 0.037 Å for the Cu and N atoms and 0.141 Å for all heavy atoms. An interesting precedent for this type of behavior was reported recently for a series of organic salts.[24] In our case, it seems plausible that the crystal tries to achieve a higher symmetry by forcing one molecule into a higher conformation, achieving a higher pseudosymmetry (see footnote #57 in Brock and Dunitz).[1] To test our hypothesis, we prepared the racemic complex and determined the crystallographic structure. If the hypothesis were correct, then a higher symmetry space group should be observed with only one conformer.

The ORTEP drawing of [Cu(*rac*-**6**)CH_3CN]$(ClO_4)_2$ (see Table 3) is shown in Figure 3. Indeed only one molecule was observed in the asymmetric unit. The racemic complex crystallized in the $P2_1/c$ space group, while the chiral complex gave the $P2_1$ space group. The cell dimensions of the racemic complex are almost the same as those for the chiral complex. The bond lengths and bond angles are similar. The average distance between the copper(II) and the N atoms is 2.060 Å compared with that of 2.045 Å in the chiral complex. The complex gives a right-handed twist with the "*S*" chiral methyl group, which is in the *anti* conformation. No *syn* conformation is observed.

In conclusion, this study provides the first crystallographic evidence for the formation of the higher energy *syn* conformer of methylene-substituted TPA derivatives, a conformation previously only predicted from models. The presence of this conformer in the enantiomerically homogenous solid is at odds with the predicted relative energies and with solution chiroptical spectral data. Crystal packing forces appear to coerce adoption of the higher energy conformer. Similar packing phenomena have been reported in a variety of systems,[7, 24, 25] but we are not aware of an example showing conformational distortion as reported here. Indeed, crystallization of both racemic and enantiopure samples of compounds may be generally useful in cases in which conformational isomers are of interest.

Experimental Section

General methods: The room-temperature electron absorption spectra were recorded on a Perkin Elmer Lambda 40 UV/VIS spectrometer using quartz cuvettes (1 cm). Electrical conductivity measurements were carried out with a YSI Model 3200 conductivity instrument having a YSI model 3256 conductivity dip cell. The cell constant was 0.1 cm^{-1}. Room-temperature magnetic moments were determined by using a Johnson Matthey magnetic susceptibility balance (MSB-auto), which was calibrated with Hg[Co(SCN)$_4$]. Electrochemical experiments were carried out in a standard three-electrode apparatus with a glassy carbon working electrode, platinum foil auxiliary electrode, and Ag wire reference electrode. The measurements were performed at room temperature in solution in acetonitrile containing tetrabutylammonium hexafluorophosphate (TBAHP, 0.1M) as supporting electrolyte.

Synthesis: Synthesis of compound **6** was described previously.[19]

[Cu{(*R*)-6}CH$_3$CN](ClO$_4$)$_2$: Compound **6** (91.2 mg, 0.2 mmol) and Cu(ClO$_4$)$_2$·6H$_2$O (74.2 mg, 0.2 mmol) were dissolved in CH$_3$CN (3 mL). Diethyl ether was added to induce precipitation. The green precipitate was collected to give the complex (120 mg, 79%). X-ray quality crystals were obtained by recrystallizing the precipitate from solution in CH$_3$CN/diethyl ether. Elemental analysis calcd (%) for C$_{33}$H$_{31}$Cl$_2$CuN$_5$O$_8$: C 52.15, H 4.11, N 9.21; found: C 51.94, H 4.03, N 9.18.

[Cu(*rac*-6)CH$_3$CN](ClO$_4$)$_2$: The racemic complex was prepared by the same method. Elemental analysis: found: C 52.33, H 4.08, N 9.43.

X-ray data collection and structure refinement details: Crystals were mounted on glass fibers. The data for [Cu{(*R*)-**6**}CH$_3$CN](ClO$_4$)$_2$ were collected on a Rigaku AFC5R diffractometer and those for [Cu(*rac*-**6**)-CH$_3$CN](ClO$_4$)$_2$ on a CAD-4 Area Detector. Cell constants and other data collection parameters are given in Table 1. Further details including the complete listing of the fractional atomic coordinates, thermal factors, and bond lengths and angles are provided in the CCDC data. The structures were solved using SHELX-86 and refined with SHELX-93. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined.

CCDC-168268 and -168269 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

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