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Redox-Triggered Interconversion between Piperidine Chair Conformations in a Cu(I/II) Complex

Jing Zhang and James W. Canary*

Department of Chemistry, New York University, New York, New York 10003

canary@nyu.edu

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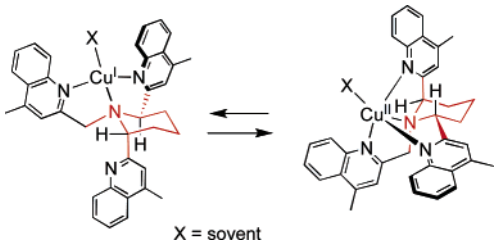
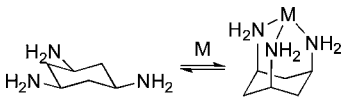
ABSTRACT



A redox-induced six-membered ring chair–chair conformational interconversion in a copper-coordinated *trans*-piperidine tripodal ligand is demonstrated. Each group of the 1,2,3-substituted ring can potentially ligate the metal; two equatorial groups ligate the metal in the Cu^{I} state leaving a disassociated, axial group. However, all three groups (two axial and one equatorial) ligate the metal in the Cu^{II} state. Exciton-coupled circular dichroism (ECCD) and 2D NMR were used to characterize the structures.

Interesting organic ligand conformational changes may occur upon complexation of metal ions. One classic example is the inversion of the chair conformation in *cis*,*cis*-1,3,5-triaminocyclohexane.[1] Upon chair inversion, three equatorial amine groups in the free ligand become axial to chelate a metal ion (eq 1). In this paper, we report a ligand containing



(1)

a six-membered piperidine ring triggered to interconvert between its two possible chair conformations by one-electron oxidation or reduction.

We previously described molecular redox switches[2,3] driven by the one-electron oxidation or reduction of a copper ion.[4] The two states of a copper ion display different coordination numbers in tripodal TQA (tris(2-quinolylmethyl)amine) complexes.[5] A dynamic NMR study of a methyl-substituted TQA Cu^{I} complex proved that one of the three arms is dissociated from metal coordination when the Cu^{II} ion is reduced to Cu^{I}. It also indicated that the steric effect of the methyl group provides control as to which arm of the ligand will be in motion.[6] Herein, we report a chiral TQA-based ligand **1** in which a piperidine ring links two of the quinoline arms. The different coordination number of

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Cu^{II} vs Cu^{I} provides the driving force for the ligand to adopt a higher energy chair conformation in the Cu^{II} complex.

Ligand **1** was constructed by a strategy involving the formation of a *trans*-piperidine moiety by tandem S_N2 substitution reactions from two components: the achiral primary amine **6** and the chiral dimesylate **10** (Figure 1). In

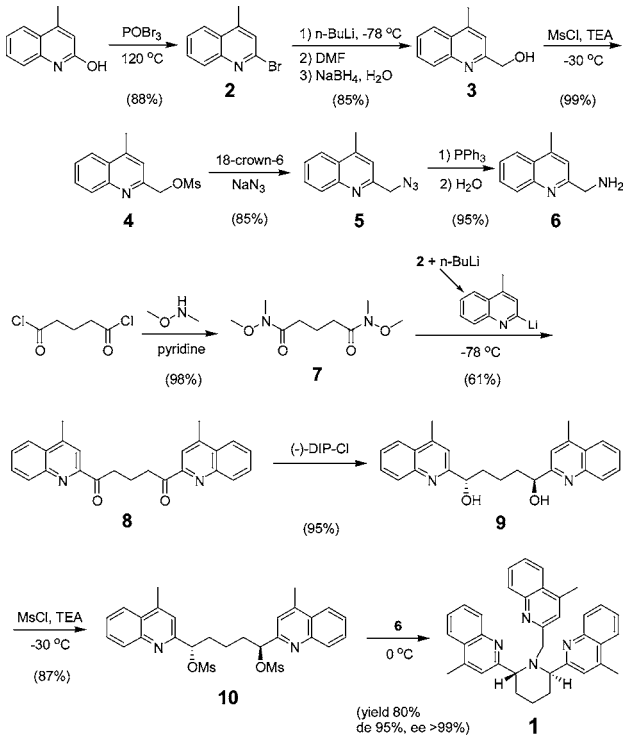

Figure 1. Synthetic route for ligand **1**.

addition to the desired trans compound (80% yield), a cis compound was also collected as a byproduct (4% yield). The de for the products was 95% as determined by ^{1}H NMR, and the ee for the trans compound was >99% as determined by HPLC (chiral column, ChiralCel OJ-H). The stereochemistry of **1** was established by the stereoselective reduction of diketone **8** with (−)-DIP-Cl. The metal complexes were prepared in situ by mixing ligand **1** with corresponding perchlorate metal salts. Precipitation [Cu^{II}(**1**)$(ClO_4)_2$] or solvent evaporation [Cu^{I}(**1**)ClO_4 and Zn^{II}(**1**)$(ClO_4)_2$] offered solid samples.

Exciton-coupled circular dichroism (ECCD) has often been utilized to study conformational changes.[7a] As shown in Figure 2, the Cu^{II} complex, Cu^{II}(**1**)$(ClO_4)_2$, produced a very strong CD spectrum, with a positive first Cotton effect at 239 nm ($\Delta\epsilon = +687$ L cm^{-1} mol^{-1}) followed by a negative second Cotton effect at 227 nm ($\Delta\epsilon = -407$ L cm^{-1} mol^{-1}). The UV λ_{max} in this region is at 228 nm ($\epsilon = 12.3 \times 10^4$ L cm^{-1} mol^{-1}), with a shoulder at 238 nm ($\epsilon = 8.3 \times 10^4$ L cm^{-1} mol^{-1}). This spectrum can be assigned to ECCD, which originates from the spatial arrangement of the three chromophores defined by the chiral center.[7] The relevant quinoline transition is the ^1B_b band (225−227 nm, $\epsilon = 3.5 \times 10^4$

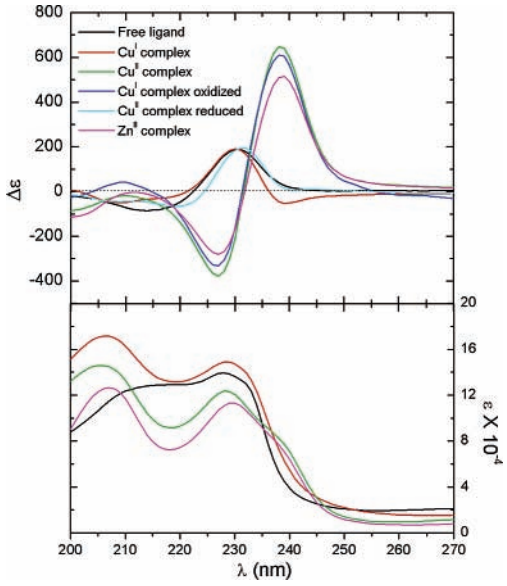

Figure 2. CD spectra of **1** (black), Cu^{I}(**1**)ClO_4 (red) and its oxidative product by air (blue), Cu^{II}(**1**)$(ClO_4)_2$ (green) and its reductive product by ascorbic acid (cyan), and Zn^{II}(**1**)$(ClO_4)_2$ (magenta) in acetonitrile.

to 4.0 × 10^4 L cm^{-1} mol^{-1}), which is polarized nearly parallel to the longitudinal axis.[8] The through-space exciton interaction of the quinolines held in proximity by the metal induces the splitting of the peaks in the CD and UV spectrum. A bisignated CD couplet and UV peak broadening for the Cu^{II} complex are clearly shown in Figure 2, and there are good correlations between the CD Cotton effects and UV absorbance maximum and shoulder (239 vs 238 nm, 227 vs 228 nm). The amplitude of this CD spectrum is very large ($A = 1094$ L cm^{-1} mol^{-1}).[5] The positive chirality indicated by ECCD is consistent with the *R,R* configuration of the ligand.

Also shown in Figure 2 is that free ligand **1** gave a weaker, single-peak CD spectrum ($\Delta\epsilon = +199$ L cm^{-1} mol^{-1} at 231 nm), with UV λ_{max} at 228 nm ($\epsilon = 13.4 \times 10^4$ L cm^{-1} mol^{-1}). The Cu^{I} complex, Cu^{I}(**1**)(ClO_4), showed a CD spectrum ($\Delta\epsilon = +204$ L cm^{-1} mol^{-1} at 230 nm) very similar to that of the free ligand **1** but exhibited a slight negative Cotton effect at about 239 nm ($\Delta\epsilon = -63$ L cm^{-1} mol^{-1}). Changing the counterion from ClO_4^- to PF_6^- or SCN^- had little effect on the shape or intensity of the spectra. The dramatic changes in the CD spectra of the Cu^{II} and Cu^{I} complexes illustrate a remarkable redox-triggered chiroptical switch.[5]

The "on−off" modulation of the CD signal could be achieved using redox reagents. As shown in Figure 2, simply leaving the Cu^{I} complex in the air overnight oxidized it to a

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Cu^{II} complex, exhibiting a CD spectrum similar to that of the preformed Cu^{II} complex. After ascorbic acid was added to a solution of the Cu^{II} complex for 1 h, a spectrum similar to that of the authentic Cu^{I} complex was obtained.

The CD spectral differences must arise from different orientations of the chromophores that can be accounted for by analysis of the conformational behavior of the ligand. The strong amplitude of the Cu^{II} complex indicates that all three arms ligate the metal and offer three pairwise exciton interactions. To achieve this, the Cu^{II} complex must assume a C_3-like symmetry, and the quinoline chromophores must possess large projection angles with each other. The Cu^{I} complex, on the other hand, must adopt some other structure that is not apparent from analysis of the CD spectra. Models suggest a possible conformation for the Cu^{I} complex with one arm dissociated from the metal and the other two arms bound with a small projection angle.

The trans-substitution pattern on the piperidine allows either two equatorial and one axial substituents or one equatorial and two axial substituents, and the energy of the former is lower than that of the latter (Figure 3). However,

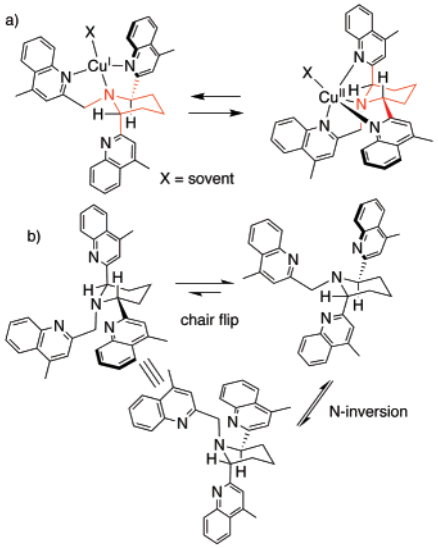

Figure 3. (a) Conversions between Cu^{I}(**1**) and Cu^{II}(**1**). (b) Free ligand conformational interconversions that result in exchange of two of the quinoline moieties.

coordination of all four nitrogen atoms of the ligand requires a conformation with two axial substituents. Presumably, Cu^{II} binds very strongly to the ligand and the favorable energy of tetradentate complex formation drives the ligand into a higher-energy conformation. The free ligand and the Cu^{I} complex, however, assume a lower-energy conformation that leaves one quinoline moiety remote from the metal ion.

Conformer searches using the Spartan program[9] were performed to give the lowest-energy conformers for the Cu^{II} complex (three arms coordinated) and the Cu^{I} complex (two arms coordinated). No low-energy conformation was found in which the quinoline attached to the CH_2 group was dissociated from the metal. The amplitude of ECCD is proportional to the angle between the chromophores. The projection angle between the quinolines for the Cu^{II} complex was $+58°$ and for the Cu^{I} complex was $-15°$. These data are consistent with the ECCD amplitude for the Cu^{II} and Cu^{I} complexes.

^{1}H NMR spectroscopy was used to test these structural hypotheses. Unable to observe spectra of the Cu^{II} complex due to its paramagnetism, the $Zn^{II}(ClO_4)_2$ complex of **1** was used instead of the $Cu^{II}(ClO_4)_2$ complex in the NMR studies. The Zn^{II} complex of **1** showed an ECCD spectrum similar to that for the Cu^{II} complex, suggesting a similar conformation.

There are remarkable differences among the free ligand, the Cu^{I} complex, and the Zn^{II} complex in the ^{1}H NMR spectra, suggesting different conformations in solution. The most obvious changes come from the two CH protons next to the quinolines on the chiral arms and the two CH_2 protons next to the quinoline on the achiral arm. The free ligand has one multiplet at 4.85 ppm for the two CH protons and AB pattern doublet peaks for the two CH_2 protons at very similar chemical shifts (3.89 and 3.85 ppm). The Cu^{I} complex gives widely separated CH proton peaks (6.03 vs 4.58 ppm) and relatively less-separated CH_2 doublet peaks (4.13 vs 3.77 ppm). The Zn^{II} complex also has four distinguishable peaks, but the separation of these two kinds of protons is reversed. The two CH protons are closer (4.71 vs 4.54 ppm), and the two CH_2 protons are more widely separated (4.64 vs 4.07 ppm). In the Zn^{II} complex, the two CH protons and one of the CH_2 protons are in almost the same chemical shift region (around 4.6 ppm), whereas in the Cu^{I} complex, all four protons are widely separated.

Comparison of the ^{1}H NMR spectra of the free ligand, the Cu^{I} complex, and the Zn^{II} complex supports the conformational model. In the free ligand, the two CH protons adjacent to the quinolines on the chiral arms are equivalent as a result of the interconversion of the two chair conformations, inversion of the nitrogen atom, and bond rotations. The two CH_2 protons next to the quinoline of the achiral arms are different due to the chiral environment but still close in chemical shift. Complexation with metals blocks the inversion of the tertiary nitrogen and differentiates all four protons. In the Cu^{I} complex, the achiral arm and one of the chiral arms ligate the metal, and the other chiral arm dissociates and points away from the metal, leaving the two CH protons in very different chemical environments. The CH proton of the unbound chiral arm lies in the shielding region of the quinoline group of the bound achiral arm, whereas the CH proton of the bound chiral arm is close to the quinoline on the unbound chiral arm and in its deshielding region. The two CH_2 protons are also more differentiated. The fixed conformation of the Cu^{I} complex leaves one proton in the more deshielding region than the other. For the Zn^{II} complex, all three arms are coordinated to the metal, and the molecule adopts a C_3-like symmetry. The two CH protons and one of the CH_2 protons are in a very similar chemical

(9) *Spartan 5.0*; Wavefunction, Inc.: Irvine, CA, 1997.

environment and, therefore, locate at the same chemical shift region in the ^{1}H NMR spectrum. The other CH_2 proton points toward the alkane part of the piperidine ring rather than toward the aromatic quinoline rings and has a chemical shift that is more downfield. Compared to the two bound quinolines of the Cu^I complex, the three quinolines of the Zn^{II} complex are further apart and have less effect on each other.

NOESY NMR spectra were also supportive of the conformational model. The NOESY spectrum of the Cu^I complex is shown in Figure 4, along with a structural model.

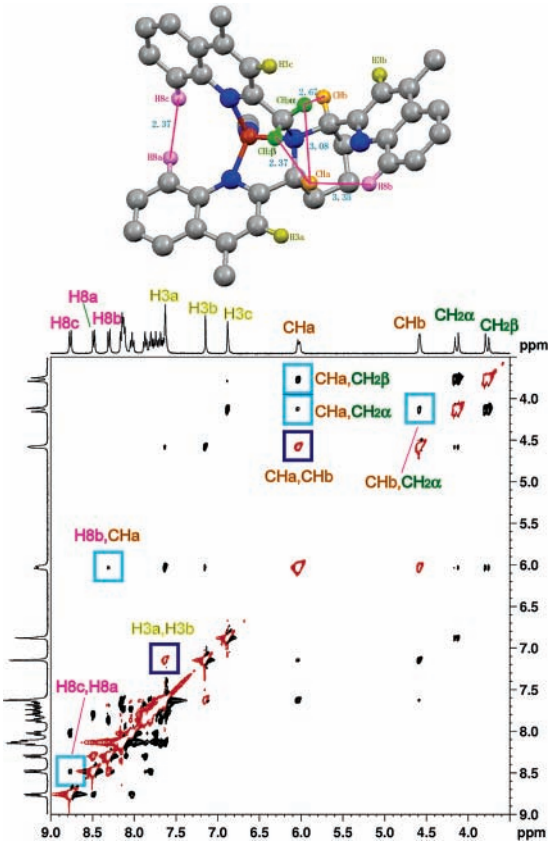

Figure 4. NOESY spectrum (in CD_3CN) and structural model of Cu^I(**1**)ClO_4. The cross-peaks shown in cyan frames indicate through-space interaction between arms, and the cross-peaks shown in blue frames indicate exchange between the arms. The structural model was calculated using the semiempirical method PM3(tm).

In this NOESY spectrum, the negative cross-peaks (shown in black) indicate the through-space NOE correlations, and the positive cross-peaks (shown in red) indicate exchange processes.[10] There are five cross-peaks that indicate unique through-space correlations between the arms for the Cu^I complex. Hydrogen 8a (the H8 proton of the quinoline on the bound chiral arm) is close to H8c (the H8 proton of the quinoline on the bound achiral arm), but neither of these two H8 protons is close to H8b (the H8 proton of the quinoline on the unbound chiral arm). However, this H8b is close to CHa (the CH proton of the quinoline on the bound chiral arm). The two CH_2 protons on the achiral arm also showed an interesting difference. $CH_2\alpha$ (one of these CH_2 protons) is close to both of the two CH protons (CHa and CHb), and $CH\beta$ (the other CH_2 proton) is only close to one of the CH protons (CHa). All of these NOESY through-space correlations can be found in the structural model for the Cu^I complex (Figure 4). In the NOESY spectrum of the Zn^{II} complex, the H8 proton of any quinoline is not close to any other H8 proton, and only one of the CH_2 protons of the achiral arm is close to one of the CH protons of the chiral arms. There is also no unique through-space interaction shown between the arms of the free ligand.

Besides the negative signals, useful positive cross-peaks were shown for the CH protons (CHa with CHb), H3 protons (H3a with H3b), and H8 protons (H8a with H8b) of the two chiral arms (Figure 4). This indicates that either of the two quinolines on the chiral arms can bind with the Cu^I while the other dissociates; therefore, there are two identical Cu^I complexes in solution. Each chiral arm may be dissociated or associated, resulting in an exchange cross-peak in the NOESY spectrum. This exchange process also explains why each CH proton (CHa and CHb) showed NOE to the H3 proton of both chiral arms (H3a and H3b). The ROESY spectrum of the Cu^I complex confirmed the exchange aspects of the NOESY spectrum.

In conclusion, a new redox-triggered chair conformational change based on a *trans*-piperidine rigidified tripodal ligand **1** was demonstrated. The Cu^I complex of ligand **1** showed an induced CD or weak ECCD spectrum, whereas the Cu^{II} complex showed a very strong ECCD spectrum. The switching of the circular dichroic signal was caused by the conformational change of the ligand. As indicated by ^{1}H NMR and NOESY spectra and computation, only one arm in the Cu^I complex occupies the axial position, along with the other achiral arm, to coordinate to the metal. In the Cu^{II} complex, two arms adopt the axial position and all three arms ligate the metal. Besides potential application as redox-triggered materials such as optical displays or molecular electronics, this well-defined Cu(I/II) redox couple may also be of interest with respect to redox active metalloenzymes and catalysts.[11]

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Supporting Information Available: Experimental details and spectroscopic data of **1** and various Cu^I(**1**) and Cu^{II}(**1**) complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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