Published in final edited form as:

Chirality. 2011 January ; 23(1): 24–33. doi:10.1002/chir.20833.

A Stereodynamic Tripodal Ligand with Three Different Coordinating Arms: Synthesis and Zinc(II), Copper(I) Complexation Study

Jian Liang and James W. Canary*

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

Abstract

A tetradentate tripodal ligand containing a chiral center and three different coordinating arms was designed and synthesized. Its complexation properties with Zn^{II} and Cu^I were studied by NMR and optical spectroscopy. NMR experiments demonstrated the formation of two diastereomers, indicating the stabilization of the central tertiary amine configuration by metal coordination. The inversion of pyramidalization of the central tertiary amine of the ligand was found to be highly dependent upon metal ion, solvent, and temperature. Dynamic NMR measurements were used to estimate the energy of activation required for nitrogen atom inversion. Finally, absorption and circular dichroism measurements confirmed the expectation that metal complexes of the ligand gave rise to circular dichroism but that such spectra were not characterized by exciton-coupling, in contrast to previously described ligands containing two identical arms with strong chromophores.

Keywords

tripodal ligand; Variable temperature NMR; nitrogen inversion; dynamic exchange; coalescence

INTRODUCTION

Tetradentate tripodal ligands containing a central donor atom (N, P) attached to three arms capable of coordination to a metal¹ have been reported in which each of the arms also contains one or more donor atoms (N, O, S, P), linked to the central atom by an alkyl chain containing at least one carbon atom.² Such ligands have attracted considerable attention and have found applications in various research fields, including enzyme mimics,³ small molecule catalysis,⁴ catalytic polymerization,⁵ sensors,⁶ tools for absolute configurational assignment,⁷ and chiroptical molecular switches.⁸ So far, most reported nitrogen-centered tetradentate tripodal ligands had two or three identical coordinating arms and ligands with three different arms are rare.⁹ Reported tripodal ligands with three different arms did not contain additional chiral elements that would enable their isomerization to be studied easily.¹⁰

Among ongoing studies of stereodynamic coordination complexes from our laboratory,⁸ tripodal ligands with a tertiary amine central atom have played a central role. However, to date, we have not studied systems in which the central tertiary nitrogen atom was chiral. In the absence of special steric constraints, tertiary amines with three different substituents are

*Correspondence to: James W. Canary, Department of Chemistry, New York University, New York, NY 10003. james.canary@nyu.edu Phone: 212-998-8422 Fax: 212-995-4367.

Supplementary Material. Additional ¹H NMR spectra are included in supplementary material that can be accessed online at Wiley Interscience.

difficult to characterize as two enantiomers at ambient temperature due to the fast inversion rate of the central nitrogen atom.¹¹ In this study, a novel tripodal ligand with three different coordinating arms was designed and synthesized to explore the configurational control of the central tertiary amine (Scheme 1) with a view to explore this parameter as a potential design feature.

When heterocyclic chromophores, such as quinoline, were applied as coordinating arms, the tetradentate tripodal ligand formed propeller-shaped complexes with transition metal ions, such as Cu^{II} and Zn^{II} .¹² Coordinated heterocycles present an additional chiral element that must be taken into consideration: the orientation of coordinating arms. For example, in a tripodal ligand containing heterocyclic aromatic moieties such as shown in Figure 1, the planes of the heterocycles define a propeller with respect to the central axis (N-Zn-Cl) of the molecule. The propeller formed by the three arms can adopt left- and right-handed configurations.¹³ In the absence of any chiral center in the molecule, the propeller asymmetry yields a racemic mixture of enantiomers, and the propeller symmetry element cannot be observed. However, upon replacement of the methylene linker of one arm by a chiral methine linker, the tripodal ligand adopts a predominant propeller orientation upon complexation of metal ions and the handedness of the propeller is dictated by the absolute configuration of the carbon linker. The chiral carbon center biases the propeller-like conformation, fixing the orientation of the confined arms and resulting in the coupling of the chromophores and leading to strong exciton-coupled circular dichroism (ECCD) signals (Figure 1).¹⁴

This self-organized propeller property has been applied to the determination of absolute configurations of α -amino acids and β -amino alcohols.¹⁵ The derivation protocol afforded a consistent correlation between the absolute configuration of the chiral center and the sign of the ECCD spectra. According to our previous results, bis-quinoline derived tripodal ligands containing a single chiral center in one of the arms can give rise to ECCD signals upon complexation with Cu^{II} . However, similar Cu^{II} complexes of tris-pyridine derived tripodal ligands showed no indication of exciton coupling.¹⁴ In this study, a new tripodal ligand with two different chromophores (quinoline and pyridine) respectively installed onto two arms of the ligand was designed to test the extent of chromophore coupling with the expectation that no ECCD couplet should be observed since two suitable chromophores are required to observe the effect. L-methionine was chosen as the building block for the third arm containing a chiral center. In our previous study, methionine, methioninol and S-methyl cysteine showed inversion of helical propeller chirality when coordinating with transition metals in different oxidation states.¹⁶ This conformational differentiation results from the fact that borderline or predominantly hard metal ions (e.g., Cu^{II} , Zn^{II} , Co^{II}) favor coordination by oxygen, whereas soft metal ions (e.g., Cu^{I} , Ag^{I}) prefer softer sulfur atoms to be coordinated. The consequence of the propeller inversion is that opposite ECCD signals have been observed depending on the coordinated metal and its oxidation state, and conversion between mirror image ECCD couplets was accomplished by one-electron redox changes. It is intriguing to examine the possibility of conformational inversion of this tripodal ligand with three different arms coordinated by different types of metal ions. The introduction of a chiral carbon on the methionine arm also provides an NMR handle, which benefits the NMR investigation of configurations of central tertiary nitrogen by diastereomer formation.

Thus, when this new tripodal ligand coordinates a metal ion, at least three chiral elements appear in the complex: chiral carbon and nitrogen centers, and a propeller (orientation of arms). Technically, the metal ion also becomes chiral, but its configuration is inextricably associated with that of the nitrogen atom, so we will not consider it as a separate chiral center. Although this high density of stereochemistry may endow this complex with some

unusual properties, our primary goals in this study were to measure the equilibrium between different diastereomers associated with nitrogen atom inversion and the associated rates of conversion. These questions would be of critical importance, for example, in potential aggregated or oligomerized triggered complexes containing multiple stereodynamic centers.

RESULTS AND DISCUSSION

Synthesis

The synthetic route for tripodal ligand **1** is shown in Scheme 2 beginning with commercial N-Boc-L-methionine. An allyl ester was utilized offering mild and orthogonal deprotection conditions in contrast to methyl esters used previously.¹⁷ After removal of the Boc protecting group, L-methionine allyl ester **3** was alkylated with 1 equivalent of 2-(bromomethyl)quinoline **4**. The third arm was introduced by a further alkylation step with 2-picolyl iodide **6**. Finally, cleavage of the allyl ester protecting group was accomplished with Pd(PPh₃)₄ and morpholine (~80 % yield).

¹H NMR Studies of Zn^{II}-**1** complex

The paramagnetic Cu^{II} complex could not be examined by NMR. Since it was established previously by X-ray crystallographic analysis that the Cu^{II} and Zn^{II} complexes of very similar ligands are isomorphous,¹⁷ the Zn^{II} complex of the ligand was investigated which yielded excellent NMR data.¹⁸ In order to assign the NMR spectra of the free ligand and the complex, a series of two-dimensional NMR experiments were performed, such as COSY and HSQC (Figure S5, S6, S8, S9). In the ¹H-NMR spectra shown in Figure 2, there are remarkable differences between the free ligand and the Zn^{II} complex. In DMSO-d₆, the Zn^{II} complex shows two sets of peaks. Eight doublets in the 3.8-4.7 ppm region originate from eight diastereotopic methylene protons. This NMR pattern is in contrast to the NMR spectrum of the free ligand, which is consistent with rapid inversion of the tertiary amine nitrogen atom affording two sets of AB patterns for four methylene protons. In addition, for the free ligand, the proton attached to the chiral carbon atom has a chemical shift at 3.50 ppm; but for the Zn^{II} complex, two diastereotopic protons appear having shifts at 3.49 and 3.14 ppm respectively. The resonances in the proton NMR of the aromatic protons and the side chain in methionine are also split into two sets of peaks. These changes suggest that two diastereomers (Fig. 3) exist in solution with a ratio of 1 to 1 based on the integration. In principle, four isomers are possible (chiral N and propeller), but the presence of a chiral center on the methionine arm biases the helical propeller of the complexes. With “S”-configuration at the carbon center, a right-handed helix is favored in the Zn^{II} complex.¹² In other words, only one propeller arrangement exists, but two isomers with different N-configurations are formed in equal abundance. Hence the NMR results provide evidence of stabilized chiral configurations of central tertiary nitrogen once metal complexation occurs. Interestingly, when the NMR measurement is performed in DMF-d₇ at 25 °C, the Zn^{II}-**1** complex exhibited one set of peaks, though some peak broadening was detected (Figure S10). This different observation from the DMSO-d₆ experiment indicates that the isomer exchange rate is much faster in DMF-d₇ than in DMSO-d₆ at ambient temperature.

Variable temperature NMR (VT-NMR, Figure 4) spectra of Zn^{II} complex were obtained in DMSO-d₆ over the temperature range from 25 °C to 155 °C and are shown in Figure 4 in which the coalescence of two sets of isomer peaks is clearly observed. First, from 65 °C to 125 °C, broadening and coalescence of NMR peaks were detected, as the rate of isomer exchange fell into the scale of NMR acquisition frequency. At 105 °C the two peaks from the proton of the chiral carbon center at 3.49 and 3.14 ppm merge into a broad peak at 3.3 ppm. With continued increase of the temperature from 125 °C to 155 °C the signals became sharp again with only the coalesced peak apparent. Similar transitions were observed for

aromatic protons and methylene protons. The VT-NMR experiment gives further proof that two diastereomeric Zn^{II} complexes are formed at ambient temperature. The transition energy was calculated to be 18.0 kcal/mol using the following equation:¹⁹

$$\Delta G_c^\ddagger = 2.3RT_c [10.32 + \log(T_c/K_c)] = 2.3RT_c [10.32 + \log(\sqrt{2}T_c/\pi\Delta\nu)]$$

in which, $T_c = 378\text{K}$ and $\Delta\nu = 0.35\text{ ppm} = 140\text{ Hz}$. The conversion rate therefore is 281 s^{-1} at 105°C .

To further demonstrate that the two diastereomers are in dynamic exchange, a 2D ROESY experiment with a mixing time of 200 ms was performed at 25°C . The expanded contour plot is shown in Figure S11. ROESY is the rotating frame NOESY and commonly used for monitoring exchange processes. Under these conditions, protons exchanging on the NMR time scale can be observed as off-diagonal signals. These exchange cross peaks can be easily identified because they have different phases compared to the regular cross peaks that arise from NOE. The cross peak appearing at 3.49 to 3.14 ppm corresponds to the interconversion of protons on the chiral carbons. The same peaks exhibited coalescence in the VT-NMR spectra, the same as cross peaks in the aromatic region. The ROESY spectra, therefore, further confirm that these protons are in dynamic exchange.

¹H NMR Studies of Cu^I-1 complex

To examine the complexation properties of ligand **1** to a soft metal ion, ¹H NMR studies of Cu^I-**1** complex were also performed (Fig. 5). The NMR signal assignment was accomplished with the aid of two-dimensional NMR (COSY) (Fig. S12). The free ligand showed similar chemical shifts in CD₃CN as in DMSO-d₆. However, there are significant differences between the NMR patterns of Cu^I-**1** and those of Zn^{II}-**1**. After coordination with Cu^I, the NMR signals still display as one set of peaks despite slightly downfield shifts of peaks from aromatic protons and methylene protons. This observation may suggest that in CD₃CN the two isomers of Cu^I-**1** complex have such a rapid exchange rate at ambient temperature that NMR measurement cannot distinguish them. To verify this hypothesis, a VT-NMR experiment was also conducted with the Cu^I-**1** complex (Fig. 6). Over the temperature range from 25°C to -45°C , broadening of aromatic peaks (7.31 - 8.25 ppm), methylene peaks (3.61 - 4.75 ppm) and chiral carbon peak (3.61 ppm) was observed. Splitting of the methylene peaks and some aromatic peaks also appeared at -45°C . Unfortunately, complete resolution of the decoalescing NMR signals was not reached within the temperature range of our measurement. Some peaks appear to coalesce around -10°C , but poorly resolved low temperature spectra prevent analysis of the energetics of interconversion. However, this VT-NMR measurement indicated the formation of two diastereomers of ligand **1** when coordinated with Cu^I ion (Fig. 7). Noteworthy is that the sulfide methyl peak at 2.05 ppm split into two peaks (1.95 and 2.12 ppm, the 2.12 ppm peak overlapped peaks from the methylene next to sulfur, but careful integration confirmed the assignment). This finding suggested, in contrast to the Zn^{II}-**1** complex, that the sulfide branch of methionine arm was involved in the complexation of **1** to Cu^I ion. When sulfur coordinated to the Cu^I ion, the different stereo-environments generated from the two diastereomers of Cu^I-**1** complex have a strong influence on the resonance of sulfide methyl protons.

UV/Vis Absorption and Circular Dichroism Spectra

The UV/Vis absorption spectra of ligand **1** and its copper complexes (Fig. 8A) in methanol display bands characteristic of quinoline and pyridine chromophores. All spectra show similar patterns with two major transitions (207 and 232 nm) and a set of poorly resolved

peaks at 250-330 nm. The absorption maxima for the copper complex shift to longer wavelengths around 234 nm compared with 228 nm for the free ligand. The CD spectra of the ligand and its complexes are shown in Figure 8B. While the free ligand has a UV spectrum similar to the complexes, its CD spectrum is of reduced intensity on the scale observed for the metal complexes. While the CD spectra of both the Cu^I and Cu^{II} complexes resemble a bisignate shape, the null does not correspond to the λ_{max} in the UV spectra. Furthermore, the CD amplitudes are much smaller than those of metal complexes of previously reported N,N-bisquinaldyl ligands. This indicates that, similar to N,N-bispicolyl derived tripodal ligands, ligand **1** did not give rise to ECCD upon complexation with the metal ions. Without an ECCD mechanism, no structural information about the complexes may be inferred from the sign or shape of the CD spectra.

Discussion

The data indicate the formation of complexes with several asymmetric features. Besides the chiral carbon center and the propeller twist, chelation of Zn^{II} greatly reduces the rate of nitrogen atom inversion. This results in the generation of two diastereomeric complexes that are formed in equal quantities. Although Cu^{II} complexes could not be studied by ¹H NMR, isomorphous Zn^{II} complexes produce data that indicate more facile nitrogen inversion in DMF than in DMSO. As the mechanism of the nitrogen atom inversion remains a matter of speculation, it is difficult to analyze solvent effects on its rate. Clearly, dissociation of the nitrogen atom from the tertiary nitrogen atom would facilitate its inversion. Molecular models suggest that such dissociation would also require dissociation of one or two of the chelating arms of the ligand. Multiple dissociations would almost certainly require intermediate associations of solvent molecules, and DMF would be expected to offer a steric advantage in the crowded ligand environment required for a multistep exchange process.²⁰ The Cu^I complex shows a much lower energy required for nitrogen atom inversion

It is not surprising that no diastereoselectivity is shown in complex formation. Even though the chiral carbon center is next to the nitrogen center, the pyridylmethyl vs. quinolylmethyl groups would be expected to be poorly differentiated in these complexes. As a result of the propeller twist of the complexes, one might imagine potential points of differentiation if the quinoline tilted towards the pyridine or the carboxylate in the complex, yet molecular models indicate that the distances are too large for such interactions to be observed.

MATERIALS AND METHODS

All solvents and reagents were purchased from commercial sources and used as received, unless noted otherwise. Solvents used in UV and CD studies were of spectrophotometric grade. UV-vis spectra were acquired on a Perkin-Elmer Lambda 40 spectrometer. Circular dichroism spectra were recorded on an AVIV model 202SF spectropolarimeter. NMR spectra were obtained on a Bruker 400 MHz FT-NMR spectrometer. ESI-MS spectra were acquired on an Agilent LC/MSD Trap XCT system. Elemental analysis was performed by Quantitative Technologies, Inc. 2-(Bromomethyl)quinoline (**4**) was prepared according to literature procedures.²¹ The coordination complexes were generally prepared by carefully mixing homogenous solutions of the ligand and the appropriate metal salt.

N-Boc-L-methionine allyl ester (**2**)

To a stirred solution of N-Boc-L-methionine (0.5 g, 2 mmol) in 12 ml of DMF was added 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (0.36 ml, 2.4 mmol) and allyl bromide (0.34 ml, 4.0 mmol) under Ar at 0 °C. The solution was stirred for 17 h at room temperature and then the solvent was removed under vacuum. The residue was dissolved in ethyl acetate and extracted with H₂O. The organic phase was washed with sat. brine and dried over anhydrous

Na₂SO₄. After removal of the solvent, the residue was subjected to column chromatography (silica gel, hexane/ethyl acetate 15:1) to yield 0.54 g (93%) of the compound as a colorless oil. ¹H-NMR (CDCl₃, 400 MHz): δ 5.89 (m, 1H), 5.32 (d, J = 17.4 Hz, 1H), 5.24 (d, J = 10.6 Hz, 1H), 5.17 (b, 1H), 4.61 (m, 2H), 4.41 (m, 1H), 2.52 (t, J = 7.6 Hz, 2H), 2.05-2.18 (m, 4H), 1.92 (m, 1H), 1.42 (s, 9H); ¹³C-NMR (CDCl₃, 100 MHz): δ 172.01, 155.34, 131.57, 118.92, 79.97, 66.00, 52.85, 32.18, 29.98, 28.31, 15.47; MS (ESI-MS) calcd. for C₁₃H₂₃NO₄S (m/z), 289.1; found, 312.1 (M + Na⁺).

N-quinaldyl-L-methionine allyl ester (5)

A solution of N-Boc-L-methionine allyl ester **2** (0.54 g, 1.87 mmol) in 12 ml TFA/DCM (1:3) was stirred for 2 h at room temperature and then the solvent was removed under vacuum. The residue (**3**) was used for the next step without further purification. ¹H-NMR (CDCl₃, 400 MHz): δ 8.45 (b, 2H), 5.90 (m, 1H), 5.35 (m, 2H), 4.69 (m, 2H), 4.27 (t, J = 5.9 Hz, 1H), 2.67 (t, J = 7.0 Hz, 2H), 2.27 (m, 2H), 2.09 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz): δ 169.20, 130.47, 120.21, 67.50, 52.34, 29.31, 29.01, 14.78; MS (ESI-MS) calcd. for C₈H₁₅NO₂S (m/z), 189.1; found, 190.0 (M + H⁺).

L-methionine allyl ester **3** (1.44 g, 7.62 mmol) and K₂CO₃ (3.15 g, 22.83 mmol) was stirred in 3 ml of dry DMF. After 20 min, 2-(bromomethyl)quinoline **4** (1.69 g, 7.61 mmol) in 3 ml of dry DMF was added to the reaction mixture. The solution was stirred for 6 h at 80 °C, when DMF was removed under vacuum. The residue was dissolved in methylene chloride and extracted with water. The collected organic layer was dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was subjected to column chromatography (silica gel, hexane/ethyl acetate 10:1) to yield 1.2 g (two step total yield 48%) of the compound as an oil. ¹H-NMR (CDCl₃, 400 MHz): δ 7.98 (m, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 6.9 Hz, 1H), 7.39 (m, 2H), 5.81 (m, 1H), 5.23 (d, J = 17.2 Hz, 1H), 5.13 (d, J = 10.6 Hz, 1H), 4.52 (m, 2H), 4.09 (d, J = 14.5 Hz, 1H), 3.94 (d, J = 14.5 Hz, 1H), 3.48 (m, 1H), 2.58 (m, 3H), 1.80-2.02 (m, 5H); ¹³C-NMR (CDCl₃, 100 MHz): δ 174.42, 159.76, 147.65, 136.38, 131.91, 129.40, 129.07, 127.53, 127.31, 126.08, 120.35, 118.66, 65.47, 60.03, 54.04, 32.84, 30.57, 15.37; MS (ESI-MS) calcd. for C₁₈H₂₂N₂O₂S (m/z), 330.1; found, 331.2 (M + H⁺).

N-quinaldyl-N-picolyl-L-methionine allyl ester (7)

To a solution 2-picolylchloride (1.16 g, 9.1 mmol) in 45 ml of acetone was added anhydrous NaI (2.22 g, 14.8 mmol). The mixture was heated to reflux under nitrogen for 2 h. The solvent was removed followed by addition of 200 ml of water and 200 ml of methylene chloride. The organic layer was separated and washed with 200 ml of sodium thiosulfate solution (5%). The collected organic phase was dried over anhydrous Na₂SO₄ and filtered. The solvent was removed and the residue was used for the next step without further purification. N-quinaldyl-L-methionine allyl ester **5** (1.2 g, 3.6 mmol) and K₂CO₃ (1.5 g, 10.9 mmol) in 2 ml of dry DMF was stirred at room temp for 30 min. The above 2-picolyl iodide **5** residue in 3 ml of dry DMF was added to the reaction mixture. The solution was stirred for 17 h at 50 °C before DMF was removed via vacuum. The residue was extracted with CH₂Cl₂ and H₂O, the organic phase was further washed with H₂O and sat. brine, and then dried over anhydrous Na₂SO₄. After removal of most of the solvent, the residue was subjected to column chromatography (alumina, hexane/ethyl acetate 8:1) to yield 0.54 g (35%) of the compound as an oil. ¹H-NMR (CDCl₃, 400 MHz): δ 8.52 (d, J = 4.8 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 6.9 Hz, 1H), 7.60 (m, 2H), 7.51 (t, J = 6.9 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.11 (t, J = 6.3 Hz, 1H), 5.98 (m, 1H), 5.39 (d, J = 17.2 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 4.68 (d, J = 5.8 Hz, 2H), 4.21 (m, 2H), 4.07 (s, 2H), 3.70 (m, 1H), 2.66 (m, 1H), 2.56 (m, 1H), 2.12 (m, 2H), 2.01 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz): δ 172.39, 160.28, 159.55, 149.16, 147.62, 136.36, 136.32, 132.10, 129.38, 129.07, 127.50, 127.32, 126.16, 123.07, 122.01,

120.90, 118.73, 65.34, 62.09, 58.10, 57.59, 30.97, 29.24, 15.22; MS (ESI-MS) calcd. for $C_{24}H_{27}N_3O_2S$ (m/z), 421.2; found, 422.1 ($M + H^+$).

N-quinaldyl-N-picolyl-L-methionine (1)

A solution of N-quinaldyl-N-picolyl-L-methionine allyl ester **7** (0.42 g, 1 mmol) in dry THF (11 ml) was treated with morpholine (1 ml, 10 mmol) and $Pd(PPh_3)_4$ (114 mg, 0.1 mmol), and stirred for 12 h at room temp before removal of the solvent under vacuum. The residue was dissolved in 200 ml of CH_2Cl_2 and washed with 0.1 M HCl. The aqueous layer was neutralized with sat. $NaHCO_3$ until pH = 6–7, and then extracted with CH_2Cl_2 . The organic phase was dried over Na_2SO_4 . After removal of most of the solvent, the residue was chromatographed (silica gel, DCM/MeOH 50:1) to yield 0.3 g (79%) of the product. 1H -NMR ($CDCl_3$, 400 MHz): δ 8.49 (d, J = 4.2 Hz, 1H), 8.13 (m, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.55 (m, 2H), 7.39 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.14 (t, J = 6.3 Hz, 1H), 4.36 (s, 2H), 4.16 (m, 2H), 3.85 (m, 1H), 2.70 (m, 2H), 2.36 (m, 1H), 2.10 (m, 1H), 2.06 (s, 3H); ^{13}C -NMR ($CDCl_3$, 100 MHz): δ 175.31, 159.92, 158.95, 148.18, 146.39, 137.64, 137.28, 130.18, 127.73, 127.62, 127.37, 126.72, 123.11, 122.45, 120.46, 63.97, 56.92, 56.05, 31.31, 28.38, 15.24; 1H -NMR (DMSO- d_6 , 400 MHz): δ 8.48 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 8.6 Hz, 1H), 7.95 (m, 2H), 7.73 (m, 2H), 7.58 (m, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.23 (t, J = 6.3 Hz, 1H), 4.13 (m, 2H), 3.98 (m, 2H), 3.50 (m, 1H), 2.45–2.64 (m, 2H), 1.98 (m, 2H), 1.92 (s, 3H); ^{13}C -NMR (DMSO- d_6 , 100 MHz): δ 173.90, 160.43, 159.45, 148.72, 146.82, 136.52, 136.34, 129.41, 128.39, 127.73, 126.92, 126.10, 122.65, 122.10, 120.81, 61.43, 57.30, 56.79, 30.26, 28.68, 14.31; MS (ESI-MS) calcd. for $C_{21}H_{23}N_3O_2S$ (m/z), 381.2; found, 382.2 ($M + H^+$).

$[Zn^{II-1}]ClO_4$

(CAUTION! Perchlorate salts of metal complexes with organic ligands are potentially explosive. They should be handled in small quantities and with caution.) To a methanolic solution of $Zn(ClO_4)_2 \cdot 6H_2O$ (48.8 mg, 0.131 mmol in 5 ml methanol) was added a solution of compound **7** (50 mg, 0.131 mmol in 5 ml methanol). The solution was stirred for 30 min. An off-white precipitate was filtered and dried under vacuum to yield 52.5 mg (74%) of the complex. 1H -NMR (DMSO- d_6 , 400 MHz): δ 8.88 (d, J = 5.2 Hz, 1H), 8.76 (m, 2H), 8.68 (d, J = 8.5 Hz, 1H), 8.58 (d, J = 4.6 Hz, 1H), 8.54 (d, J = 8.5 Hz, 1H), 8.16 (m, 2H), 8.04 (d, J = 7.7 Hz, 1H), 7.98 (m, 2H), 7.87 (t, J = 7.7 Hz, 1H), 7.68–7.79 (m, 4H), 7.62 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.34 (t, J = 6.4 Hz, 1H), 4.52–4.60 (m, 2H), 4.29–4.49 (m, 3H), 4.08–4.23 (m, 2H), 3.97 (d, J = 17.2 Hz, 1H), 3.49 (m, 1H), 3.14 (m, 1H), 2.90–3.01 (m, 2H), 2.59–2.78 (m, 2H), 2.26–2.39 (m, 2H), 2.15 (s, 3H), 2.13 (s, 3H), 1.98–2.10 (m, 2H); ^{13}C -NMR (DMSO- d_6 , 100 MHz): δ 173.43, 173.38, 159.58, 157.56, 155.68, 154.67, 148.06, 147.17, 144.61, 144.23, 141.62, 141.43, 140.34, 140.04, 131.97, 131.56, 128.77, 128.51, 128.39, 127.80, 127.50, 126.11, 125.73, 125.12, 124.87, 124.12, 123.83, 122.16, 121.50, 67.83, 64.13, 59.77, 55.30, 55.23, 54.66, 32.31, 26.21, 25.74, 14.56, 14.46; Elemental Anal. Calcd. for $C_{21}H_{22}ClN_3O_6SZn \cdot 0.5H_2O$: C, 45.50; H, 4.18; N, 7.58; Found: C, 45.80; H, 3.77; N, 7.47; MS (ESI-MS) calcd. for $C_{21}H_{22}N_3O_2SZn$ (m/z), 444.1; found, 444.1.

$[Cu^I-1]PF_6$

Compound **7** (10 mg, 0.026 mmol) and $Cu^I(CH_3CN)PF_6$ (20 mg, 0.053 mmol) were mixed in 2 ml of CD_3CN in a glove box and the solution was allowed to stand for 30 min. The filtrate was used for NMR measurements. 1H -NMR (CD_3CN , 400 MHz): δ 8.65 (b, 1H), 8.38 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.81 (m, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.38 (m, 2H), 4.48 (m, 2H), 4.26 (m, 2H), 3.61 (m, 1H), 2.80 (m, 1H), 2.54 (m, 1H), 2.15 (m, 2H), 2.05 (s, 3H); MS (ESI-MS) calcd. for $C_{21}H_{23}N_3O_2SCu$ (m/z), 444.1; found, 444.1.

CONCLUSION

A novel tetradentate tripodal ligand with three different coordinating arms was designed and synthesized. Its complexation with Zn^{II} and Cu^{I} ions was studied with the aid of NMR and optical spectroscopy. Variable temperature NMR studies of the free ligand, Zn^{II} and Cu^{I} complexes demonstrated the formation of two diastereomers of the complex, which experienced a temperature-dependent dynamic exchange. Absorption and CD spectra showed that the pyridine and quinoline chromophores did not give rise to ECCD upon the ligand complexation with the metal ions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Contract grant sponsor: National Science Foundation; Contract grant numbers: CHE-0848234, CHE-0234863, CHE-0116222, and DUE-0126958. Contract grant sponsor: National Institutes of Health; Contract grant numbers: GM076202 and C06 RR-16572-01.

LITERATURE CITED

1. Blackman AG. The coordination chemistry of tripodal tetraamine ligands. *Polyhedron*. 2005; 24:1–39.
2. Nagao H, Komeda N, Mukaida M, Suzuki M, Tanaka K. Structural and Electrochemical Comparison of Copper(II) Complexes with Tripodal Ligands. *Inorg Chem*. 1996; 35:6809–6815. [PubMed: 11666847]
3. Parkin G. The bioinorganic chemistry of zinc: synthetic analogues of zinc enzymes that feature tripodal ligands. *Chem Commun*. 2000; 1971–1985
4. a Chufán EE, Mondal B, Gandhi T, Kim E, Rubie ND, Moënne-Loccoz P, Karlin KD. Reactivity studies on $\text{Fe}^{\text{III}}\text{-(O}_2^{2-})\text{-Cu}^{\text{II}}$ compounds: Influence of the ligand architecture and copper ligand denticity. *Inorg Chem*. 2007; 46:6382–6394. [PubMed: 17616124] b Hitomi Y, Ando A, Matsui H, Ito T, Tanaka T, Ogo S, Funabiki T. Aerobic catechol oxidation catalyzed by a bis(μ -oxo)dimanganese(III,III) complex via a manganese(II)–semiquinone complex. *Inorg Chem*. 2005; 44:3473–3478. [PubMed: 15877428] c Yamaguchi M, Kousaka H, Izawa S, Ichii Y, Kumano T, Masui D, Yamagishi T. Syntheses, characterization, and catalytic ability in alkane oxygenation of chloro(dimethyl sulfoxide)ruthenium(II) complexes with tris(2-pyridylmethyl)amine and its derivatives. *Inorg Chem*. 2006; 45:8342–8354. [PubMed: 16999434] d Nagataki T, Ishii K, Tachi Y, Itoh S. Ligand effects on Ni^{II} -catalysed alkane-hydroxylation with *m*-CPBA. *Dalton Trans*. 2007; 1120–1128. [PubMed: 17339995] e Mas-Ballesté R, Que L Jr. Iron-catalyzed olefin epoxidation in the presence of acetic acid: Insights into the nature of the metal-based oxidant. *J Am Chem Soc*. 2007; 129:15964–15972. [PubMed: 18052063] f Klotz KL, Slominski LM, Hull AV, Gottsacker VM, Mas-Ballesté R, Que L Jr. Halfen JA. Non-heme iron(II) complexes are efficient olefin aziridination catalysts. *Chem Commun*. 2007; 2063–2065
5. Kawaguchi H, Matsuo T. Aryloxide-based multidentate ligands for early transition metals and f-element metals. *J Organomet Chem*. 2004; 689:4228–4243.
6. a Dai Z, Canary JW. Tailoring tripodal ligands for zinc sensing. *New J Chem*. 2007; 31:1708–1718. b Masaki ME, Paul D, Nakamura R, Kataoka Y, Shinoda S, Tsukube H. Chiral tripode approach toward multiple anion sensing with lanthanide complexes. *Tetrahedron*. 2009; 65:2525–2530.
7. Holmes AE, Simpson SA, Canary JW. Stereodynamic coordination complexes. Dependence of exciton coupled circular dichroism spectra on molecular conformation and shape. *Monatsh Chem*. 2005; 136:461–475.
8. Canary JW. Redox-Triggered chiroptical molecular switches. *Chem. Soc. Rev*. 2009; 38:747–756. [PubMed: 19322467]

9. Thomas F, Gellon G, Gautier-Luneau I, Saint-Aman E, Pierre JL. A structural and functional model of galactose oxidase: Control of the one-electron oxidized active form through two differentiated phenolic arms in a tripodal ligand. *Angew Chem Int Ed.* 2002; 41:3047–3050.
10. Abufarag A, Vahrenkamp H. A tripod ligand with 3 different legs and some chiral zinc-complexes thereof. *Inorg Chem.* 1995; 34:3279–3284.
11. Wolf, C. Dynamic stereochemistry of chiral compounds: principles and applications. Royal Society of Chemistry; 2008.
12. Castagnetto JM, Canary JW. A chiroptical enhanced fluorescent chemosensor. *Chem Commun.* 1998; 203-204
13. a Canary JW, Allen CS, Castagnetto JM, Chiu YH, Toscano PJ, Wang Y. Solid state and solution characterization of chiral, conformationally mobile tripodal ligands. *Inorg Chem.* 1998; 37:6255–6262. b Castagnetto JM, Xu X, Berova ND, Canary JW. Absolute configurational assignment of self-organizing asymmetric tripodal ligand-metal complexes. *Chirality.* 1997; 9:616–622. [PubMed: 9329182]
14. Zahn S, Canary JW. Cu(I/II) Redox control of molecular conformation and shape in chiral tripodal ligands: Binary exciton-coupled circular dichroic states. *J Am Chem Soc.* 2002; 124:9204–9211. [PubMed: 12149026]
15. Zahn S, Canary JW. Absolute configurations of *N,N*-dialkyl α -amino acids and β -amino alcohols from exciton-coupled circular dichroism spectra of Cu(II) complexes. *Org Lett.* 1999; 1:861–864. [PubMed: 10823214]
16. a Zahn S, Canary JW. Electron-induced inversion of helical chirality in copper complexes of *N,N*-dialkylmethionines. *Science.* 2000; 288:1404–1407. [PubMed: 10827947] b Barcena HS, Holmes AE, Zahn S, Canary JW. Redox inversion of helicity in propeller-shaped molecules derived from *S*-methyl cysteine and methioninol. *Org Lett.* 2003; 5:709–711. [PubMed: 12605496] c Das D, Dai Z, Holmes A, Canary JW. Exploring the scope of redox-triggered chiroptical switches: Syntheses, x-ray structures, and circular dichroism of cobalt and nickel complexes of *n,n*-bis(arylmethyl)methionine derivatives. *Chirality.* 2008; 20:585–591. [PubMed: 18196593]
17. Zahn S, Debasis D, Canary JW. Redox-induced ligand reorganization and helicity inversion in copper complexes of *N,N*-dialkylmethionine derivatives. *Inorg Chem.* 2006; 45:6056–6063. [PubMed: 16842014]
18. Zhang J, Canary JW. Redox-triggered interconversion between piperidine chair conformations in a Cu(I/II) complex. *Org Lett.* 2006; 8:3907–3910. [PubMed: 16928035]
19. Lambert, JB.; Shurvell, HF.; Lightner, DA.; Cooks, RG. Organic Structural Spectroscopy. Prentice-Hall, Upper Saddle River; New Jersey: 1998.
20. a Koide M, Suzuki H, Ishiguro S. Solution equilibria of zinc (II) and cadmium (II) complexes with 2, 2'-bipyridine in *N,N*-dimethylacetamide at 25°C. *Journal of Solution Chemistry.* 1996; 25:1261–1270. b Chung CL, Lim KT, Canary JW. The influence of phenyl substituents on the redox potentials of sterically hindered tripodal ligand/copper complexes. *Supramol Chem.* 1995; 5:39–43.
21. Wei N, Murthy NN, Chen Q, Zubieta J, Karlin KD. Copper(I)/dioxygen reactivity of mononuclear complexes with pyridyl and quinolyl tripodal tetradentate ligands: Reversible formation of Cu:O₂ = 1:1 and 2:1 adducts. *Inorg Chem.* 1994; 33:1953–1965.

Scheme 1.

Two stabilized stereoisomers formed after metal coordination of a nitrogen-centered tetradentate tripodal ligand with three different coordinating arms. (A) Racemic mixture of enantiomers; (B) One chiral arm offered two diastereomers.

Fig. 1.
(A) Left-handed propeller (clockwise orientation of quinoline transition dipoles) gives rise to a positive couplet in ECCD. (B) Inversion of helicity by one-electron oxidation/reduction.

Scheme 2.
Synthesis of the tripodal ligand **1**.

Fig. 2.
 ^1H -NMR spectra of ligand **1** (A) and its complex with Zn^{II} (B) in DMSO-d_6 .

Fig. 3.
Two diastereomers of Zn^{II} -**1** complex in dynamic exchange in DMSO-d_6

Fig. 4.
Selected VT-NMR spectra of the Zn^{II}-1 complex in DMSO-d₆

Fig. 5.
 ^1H -NMR spectra of **1** (A) and its Cu^{I} complex (B) in CD_3CN

Fig. 6.
VT-NMR spectra of Cu^I-**1** complex in CD₃CN

Fig. 7.

Two diastereomers of Cu^I-**1** complex in dynamic exchange in CD₃CN

Fig. 8. UV/Vis (A) and CD (B) spectra of the ligand and its copper complexes (0.5 mM) recorded in methanol at 25 °C.