Inorganic Chemistry
Communication

Control of Oxygen Atom Chirality and Chelate Ring Conformation by Protected/Free Sugar Hydroxyl Groups in Glucose-Pendant Dipicolylamine–Copper(II) Complexes

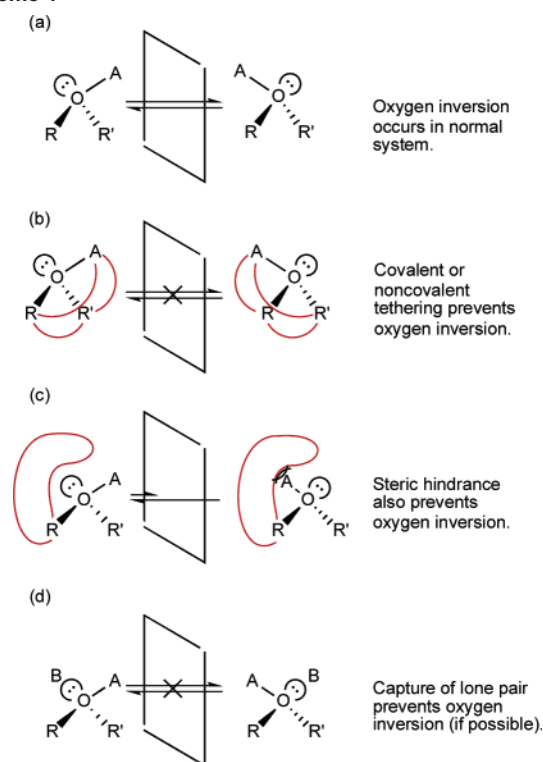**Yuji Mikata,* Yuko Sugai, and Shigenobu Yano***

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A pair of copper(II) complexes **1** and **2** exhibit an enantiomeric chiral center at the oxygen atom that coordinates to the metal center. The configurations of the oxygen atom chirality and the chelate ring conformation are simply controlled by protected/free hydroxyl groups of the sugar moiety, yielding mirror image CD spectra. In this system, repulsive and attractive forces are used to regulate chirality on the copper-coordinated oxygen atom both in the solid state and in solution.

When a unsymmetrical ether coordinates to a metal ion, chirality arises at the oxygen atom. This chirality would normally be unstable because the lone pair on the oxygen atom inverts via pyramidal inversion in a similar manner with the nitrogen atom of aliphatic amines[1] (Scheme 1a). In the case of nitrogen, however, this inversion can be substantially retarded on the metal ion coordination at the nitrogen atom, and the structure of asymmetric nitrogen and its inversion kinetics are extensively demonstrated in cobalt-(III)–,[2] nickel(II)–,[3] platinum(II)–,[4] and copper(II)[5]–amine complexes. Thus, to synthesize the complexes that exhibit a
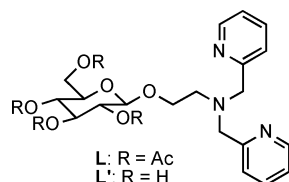
Scheme 1

(a) Oxygen inversion occurs in normal system.

(b) Covalent or noncovalent tethering prevents oxygen inversion.

(c) Steric hindrance also prevents oxygen inversion.

(d) Capture of lone pair prevents oxygen inversion (if possible).

chiral center at the oxygen atom, not only does strong coordination between ether oxygen atom and metal ion differentiate two lone pairs on the oxygen atom, but also adequate control of the configuration of the oxygen substituents is necessary. The strategy to fulfill these requirements includes the following: (1) tethering of substituents of the oxygen atom by a short linker to fix the oxygen configuration (Scheme 1b), (2) introduction of steric repulsion instead of attractive interaction by employing bulky substituents in proper orientation (Scheme 1c), and (3) capture of the oxygen

(1) (a) Wash, P. L.; Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2001**, *40*, 1221–1222. (b) Belostotskii, A. M.; Gottlieb, H. E.; Aped, P. *Chem. Eur. J.* **2002**, *8*, 3016–3026. (c) Belostotskii, A. M.; Gottlieb, H. E.; Shokhen, M. *J. Org. Chem.* **2002**, *67*, 9257–9266.

(2) (a) Buckingham, D. A.; Marzilli, L. G.; Sargeson, A. M. *J. Am. Chem. Soc.* **1967**, *89*, 825–830. (b) Yano, S.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3486. (c) Yamaguchi, M.; Yano, S.; Saburi, M.; Yoshikawa, S. *Inorg. Chem.* **1980**, *19*, 2016–2021. (d) Ajioka, M.; Yano, S.; Matsuda, K.; Yoshikawa, S. *J. Am. Chem. Soc.* **1981**, *103*, 2459–2460. (e) Okamoto, K.; Okabayashi, M.; Ohmasa, M.; Einaga, H.; Hidaka, J. *Chem. Lett.* **1981**, 725–728. (f) Ishii, M.; Sato, S.; Saito, Y.; Nakahara, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3094–3098. (g) Kawaguchi, H.; Matsuki, M.; Ama, T.; Yasui, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 31–38. (h) Tsuboyama, S.; Shiga, Y.; Takasyo, Y.; Chijimatsu, T.; Kobayashi, K.; Tsuboyama, K.; Sakurai, T. *J. Chem. Soc., Dalton Trans.* **1992**, 1783–1789. (i) Sakagami, N.; Yasui, T.; Kawaguchi, H.; Ama, T.; Kaizaki, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 680–686.

(3) Murmann, R. K.; Barnes, C. L.; Barakat, S. *Polyhedron* **2001**, *20*, 431–440.

(4) Erickson, L. E.; Fritz, H. L.; May, R. J.; Wright, D. A. *J. Am. Chem. Soc.* **1969**, *91*, 2513–2518.

(5) (a) Liang, B.-F.; Margerum, D. W.; Chung, C.-S. *Inorg. Chem.* **1979**, *18*, 2001–2007. (b) Liang, B.-F.; Chung, C.-S. *Inorg. Chem.* **1980**, *19*, 1867–1871. (c) Lee, C.-S.; Wang, G.-T.; Chung, C.-S. *J. Chem. Soc., Dalton Trans.* **1984**, 109–114.

Chart 1

L: R = Ac
L′: R = H

lone pair by a Lewis acid (Scheme 1d). These strategies acting alone or in combination should result in a suitable system in which oxygen chirality can be stabilized in the molecule.

Here we report the isolation and characterization of a pair of copper(II) complexes **1** and **2**, which exhibit an enantiomeric chiral center at the oxygen atom that coordinates to the metal center. Novel sugar-pendant ligands **L** and **L′** (Chart 1) were developed for this objective. These ligands have a 2,2′-dipicolylamine (DPA)[6] unit that provides a suitable environment for coordination of the ether oxygen atom at the anomeric position to the metal center. As the basis for ligand design, repulsive and attractive forces are used to generate chirality on the copper-coordinated oxygen atom, simply controlled by protected/free hydroxyl groups of the sugar moiety. To the best of our knowledge, this is the first example of a pair of compounds that have a structurally characterized asymmetric oxygen with an enantiomeric configuration.

The newly developed ligand, 2-(*N,N*-bis(2-pyridylmethyl)-amino)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**L**), was prepared by the reaction of 2-bromoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[7] with dipicolylamine in dimethylformamide in the presence of potassium carbonate. Deprotection of the acetyl groups of **L** with sodium methoxide in methanol afforded 2-(*N,N*-bis(2-pyridylmethyl)-amino)ethyl β-D-glucopyranoside (**L′**) quantitatively. Characterization data for **L** and **L′** support the proposed structure of these compounds.[8]

The Cu[II] complexes, [Cu**L**(NO₃)]NO₃ (**1**) and [Cu**L′**(OAc)]-NO₃ (**2**), were obtained by mixing of ligands **L** and **L′** with copper nitrate trihydrate in methanol. Prismatic crystals of complex **1** were obtained directly from the reaction solution in 53% yield, whereas no precipitate appeared from the reaction mixture of **L′** with Cu(NO₃)₂·3H₂O. Evaporation of the solvent of the latter reaction mixture afforded a blue oily material. However, addition of acetic acid to either a methanol solution of this oily material or the reaction mixture of **L′** with Cu(NO₃)₂·3H₂O afforded blue crystals of complex **2** in ~15% yield. These complexes are soluble in water, methanol, and other polar organic solvents.

Figure 1 shows the solid-phase structures of complexes **1** and **2**, which were elucidated by X-ray crystallography.[8,9] Ligands **L** and **L′** both act as a tetradentate *N,N,N,O* donor
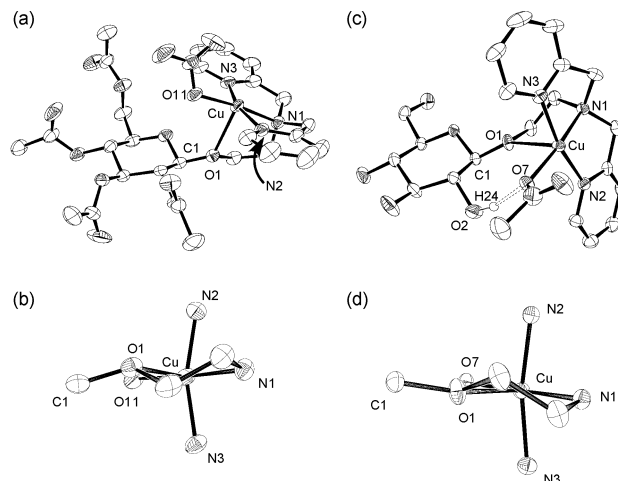

Figure 1. ORTEP drawings of complexes **1** ([Cu**L**(NO₃)]NO₃) and **2** ([Cu**L′**(OAc)]NO₃): (a) cationic portion of **1**, (b) coordination environment around copper center and configuration of anomeric oxygen atom of **1**, (c) cationic portion of **2** (dotted line indicates hydrogen bond), (d) coordination environment around copper center and configuration of anomeric oxygen atom of **2**. Selected bond lengths: (**1**) Cu1−N1 2.042(3) Å, Cu1−N2 1.970(2) Å, Cu1−N3 1.974(2) Å, Cu1−O1 2.413(2) Å, Cu1−O11 1.953(2) Å; (**2**) Cu1−N1 2.043(3) Å, Cu1−N2 1.995(3) Å, Cu1−N3 1.979(3) Å, Cu1−O1 2.546(2) Å, Cu1−O7 1.916(2) Å.

atom system by use of DPA nitrogen and anomeric oxygen atoms. Coordination of one counterion (nitrate for **1** or acetate for **2**) to copper is also evident in the monocationic five-coordinate Cu[II] complex. The three nitrogen atoms of the DPA unit are coordinated to the Cu[II] center in a meridional fashion leading to the coordination environment around the copper metal as distorted square-pyramidal, having an anomeric oxygen atom as the apical ligand. The bond distances are similar to those reported in the literature for Cu[II] complexes containing DPA.[10] The τ value proposed by Addison et al. on the basis of bond angles[11] is calculated to be 0.18 for **1** and 0.07 for **2**, demonstrating that the copper center in **1** is slightly shifted toward the apical ligand from the basal plane. Figure 1b,d demonstrates the inversion of absolute configuration of the anomeric oxygen atom coordinated to the copper center. Complex **1** has an *R*-configuration for the oxygen center and a λ-gauche conformation for the five-membered chelate ring in the linker ethylene chain, whereas complex **2** exhibits an *S*-configuration for

(6) (a) Glerup, J.; Goodson, P. A.; Hodgson, D. J.; Michelsen, K.; Nielsen, K. M.; Weihe, H. *Inorg. Chem.* **1992**, *31*, 4611−4616. (b) Palaniandavar, M.; Mahadevan, S.; Kökerling, M.; Henkel, G. *J. Chem. Soc., Dalton Trans.* **2000**, 1151−1154.

(7) Davis, B. G.; Maughan, M. A. T.; Green, M. P.; Ullman, A.; Jones, J. B. *Tetrahedron: Asymmetry* **2000**, *11*, 245−262.

(8) See Supporting Information.

(9) Crystal data for **1**: monoclinic, space group *P*2₁, *a* = 10.0348(7) Å, *b* = 13.5631(9) Å, *c* = 12.4213(10) Å, β = 95.336(4)°, *V* = 1683.2(2) Å³, *Z* = 2, *T* = −100 °C, 13153 data collected, 3968 data with *I* > 2σ(*I*). The structure was solved by direct methods (SIR-92) and refined by full-matrix least-squares methods on *F*². All hydrogen atoms except methyl group were found and treated as a riding model. *R* = 0.033, *wR*2 (all data) = 0.073, GOF = 0.951. Crystal data for **2**·CH₃OH: monoclinic, space group *P*2₁, *a* = 8.7208(7) Å, *b* = 16.3103(11) Å, *c* = 9.8981(8) Å, β = 104.383(4)°, *V* = 1363.8(2) Å³, *Z* = 2, *T* = −100 °C, 10571 data collected, 3188 data with *I* > 2σ(*I*). The structure was solved by direct methods (SIR-92) and refined by full-matrix least-squares methods on *F*². All hydrogen atoms except solvent methanol were found and treated as a riding model. *R* = 0.033, *wR*2 (all data) = 0.086, GOF = 0.947.

(10) (a) Murakami, T.; Hatakeyama, S.; Igarashi, S.; Yukawa, Y. *Inorg. Chim. Acta* **2000**, *310*, 96−102. (b) Palaniandavar, M.; Butcher, R. J.; Addison, A. W. *Inorg. Chem.* **1996**, *35*, 467−471. (c) Ugozzoli, F.; Massera, C.; Lanfredi, A. M. M.; Marsich, N.; Camus, A. *Inorg. Chim. Acta* **2002**, *340*, 97−104.

(11) Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Verschoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, 1349−1356.
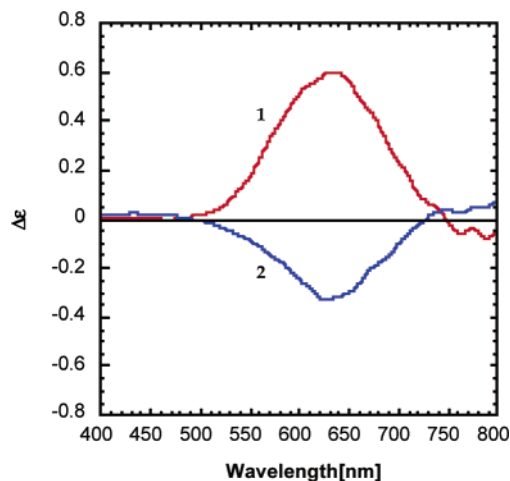
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Figure 2. CD spectra of complexes **1** and **2** in MeOH.

the oxygen center and a δ-gauche conformation for the five-membered chelate ring. Since the sum of the three bond angles around the anomeric oxygen atom is 342° for **1** and 355° for **2**, the chiral environment around oxygen atom is more apparent in complex **1**.

Complexes **1** and **2** also display characteristic CD spectra (Figure 2) in methanol solution. These complexes exhibit a nearly mirror image Cotton effect in the copper metal d−d transition region, indicating the observations that chelate ring conformation and/or absolute configuration at the ligated ether oxygen of these complexes is chiral and the metal coordination environments of the two complexes are nearly enantiomeric as evidenced by X-ray crystallography. This demonstrates that the anomeric oxygen-bound species found in the solid phase for **1** and **2** retain their asymmetric environment around the metal center in methanol solution to exhibit the Cotton effect observed in the CD spectrum. Recently, Sigel et al. reported that the intramolecular equilibrium forming a five-membered chelate by the ether oxygen is of great significance even in water for copper complexes of phosphate ligands with an ether moiety as a weakly coordinating second site.[12] Since the structure of our complexes has great relevance to Sigel's system, the Cotton

effect observed in the present study indicates the significant equilibrium to the asymmetric coordination of the ether oxygen to the metal center in methanol solution.

In the X-ray structure of complex **2**, a hydrogen bond is found between the hydroxyl group at the 2-position of sugar moiety and the acetate oxygen bound to the copper atom (Figure 1c). This effect freezes the configuration of the chiral oxygen atom and should be the driving force of generation of chirality around the copper center. On the other hand, the acetyl group in complex **1** at the same position avoids the close approach of the copper center toward the 2-positon of the sugar moiety, leading the oxygen chirality to the opposite configuration.

In conclusion, both the absolute configuration of the copper-bound oxygen atom and the configuration of the chelate ring around the metal center are remote-controlled by protected/free hydroxyl groups of the sugar-pendant DPA ligand. In this system, the hydroxyl group at the 2-position of the carbohydrate moiety plays a crucial role for regulation of the stereochemistry around the metal center, via the interplay of steric and hydrogen-bonding interactions. These results could serve as a general method for the introduction and stabilization of chirality at an oxygen atom, as well as aid in the molecular design and the control of the configuration of groups of interest by modification just at a remote site of a molecule. Further, the confirmation of the existence of the asymmetric oxygen upon coordination could promise great assistance in elucidating the reaction mechanism for metalloenzymes.

Supporting Information Available: Crystallographic data for **1** and **2**, and preparations and characterization data for **L**, **L′**, **1**, and **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For recent reviews: (a) Sigel, H. *Chem. Soc. Rev.* **2004**, *33*, 191−200. (b) Sigel, H.; Kapinos, L. E. *Coord. Chem. Rev.* **2000**, *200−202*, 563−594.