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Chiral single-stranded metallohelix: metal-mediated folding of linear oligooxime ligand

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Abstract—A linear tetraoxime ligand H_4L bearing chiral (*S*)-2-hydroxylpropyl groups at both ends was synthesized. Complexation between H_4L with Zn^{2+} and M^{n+} ($=Ca^{2+}$, Y^{3+}, La^{3+}) afforded helical trinuclear complex $[LZn_2M]^{n+}$. The helical sense was the most effectively induced when Ca^{2+} was used as the central metal M^{n+}.

In recent years, much interest has been focused on self-organized abiotic oligomers and polymers, which spontaneously form a helical structure with the aid of weak interactions.[1] Although labile metal–ligand bonds have been used to construct a number of self-organized double- and triple helicates,[2] there are few examples that have metal atoms in the helical main chain.[3] Such scaffold with a helical array of metal ions would be useful to make conducting nanocoils. We have been investigating single-helical oligometallic complexes that can be obtained from linear bis(salamo) **1a** and its longer analog.[4–6] Control of the helical sense of such metal-containing helices is important because sophisticated functions are expected from a combination of the intrinsic properties of metal complex moieties with the chiral helical structure. However, optical resolution of racemic helices is not suitable to obtain a one-handed form, when the helical complexes undergo reversible conformational interconversion between right- and left-handed (and non-helical) states. Instead, thermodynamic control can be used to obtain chiral helices. When the strand is placed in a chiral environment or is functionalized with an appropriate chiral auxiliary, one-handed helices can be preferentially formed.[7] In such cases, a rather small difference in thermodynamic stability between the two forms is sufficient for a predominant formation of one of the two forms. Thus, we designed a linear oligooxime ligand **1b** having (*S*)-2-hydroxypropyl groups as a chiral auxiliary (Chart 1). A one-handed helical structure is preferentially formed on complexation with zinc(II) and calcium ions.

The synthesis of ligand **1b** is shown in Scheme 1. The reaction of aldehyde **2**[8] with tosylate **3**[9] in the presence of cesium carbonate in DMF afforded **4** in 76% yield. The subsequent treatment of **4** with Pd–C/$HClO_4$ cleaved the protecting allyl and THP groups to give chiral salicylaldehyde **5** in 91% yield. The reaction of aldehyde **5** with excess 1,2-bis(aminooxy)ethane[10] in ethanol afforded monooxime **6**. The tetraoxime ligand **1b**[11] was obtained in 81% yield by the reaction of dialdehyde **7**[12] with 2 equiv of monooxime **6** in ethanol.

The complexation of **1b** ($=H_4L$) with zinc(II) acetate afforded trinuclear complex $[LZn_3]^{2+}$. The formation of 1:3 complex was clearly supported by spectroscopic titration and mass spectrometry (Fig. 1a). The homotrinuclear complex $[LZn_3]^{2+}$ was converted to a heterotrinuclear complex by the site-selective transmetalation strategy analogous to the methoxy derivative.[4] When

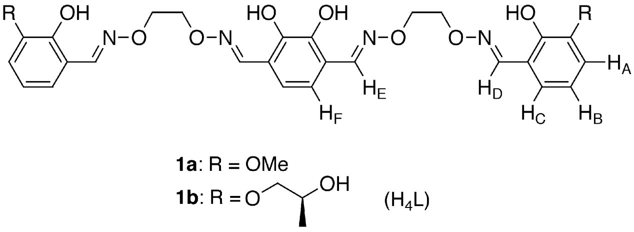

Chart 1.

Keywords: Oxime; Salamo ligand; Zinc complex; Helical structure; Chirality induction.

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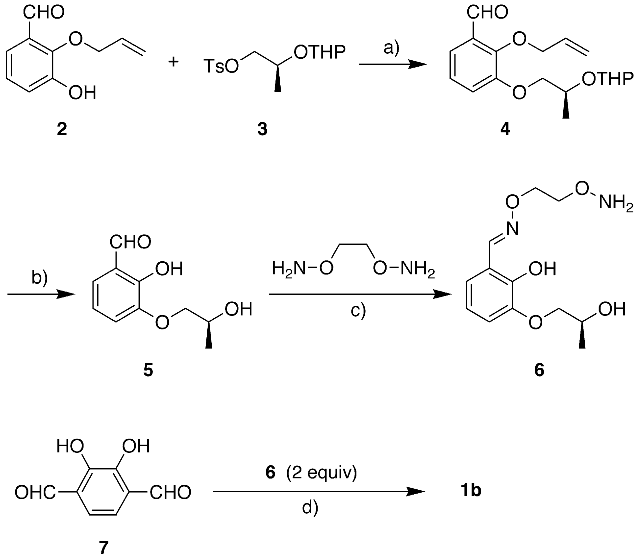
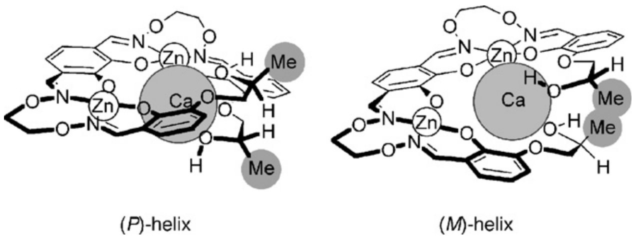


Scheme 1. Synthesis of chiral ligand **1b**. Reagents and conditions: (a) Cs_2CO_3, DMF, 60–65 °C, 76%; (b) 10% Pd/C, cat. $HClO_4$, MeOH, reflux, 91%; (c) EtOH, 55–60 °C, 43% and (d) EtOH, 50–55 °C, 81%.

1 equiv of calcium perchlorate was added to a solution of $[LZn_3]^{2+}$, about 81% of the zinc complex was converted to the heterotrinuclear complex. The addition of 2 equiv of calcium perchlorate was required for the complete (>97%) conversion. The formation of the heterotrinuclear complex was confirmed by the peaks at $m/z = 417.0$ for $[LZn_2Ca]^{2+}$ and 893.0 for $[LZn_2Ca(OAc)]^{+}$ in the ESI mass spectrum (Fig. 1b).

If the calcium complex $[LZn_2Ca]^{2+}$ has a helical structure similar to that of the methoxy analog,[4b] the complex is expected to exist as a mixture of two possible diastereomers, right- and left-handed forms (Scheme 2). However, the ^1H NMR spectrum in $CDCl_3/CD_3OD$ (1:1) at 293 K (Fig. 2) showed two singlets for the oxime protons (H_D, H_E), four signals for the aromatic protons (H_A, H_B, H_C, H_F), and one singlet for the methoxy proton (not shown in Fig. 2). This result can be attributed to the exclusive formation of one diastereomer, or the fast interconversion between the two diastereomers. The ^1H NMR spectra at lower temperatures clearly indicate the existence of two diastereomers, right- and left-handed helices. At 223 K, two sets of signals for all the protons were observed. At this temperature, one of the two diastereomers is preferentially formed (80:20). These two signals coalesce at higher temperatures due to a fast interconversion between the two species. The coalescence temperature was about 253 K, which corresponds to the helix inversion barrier $\Delta G^{\neq}$ of 52 kJ/mol.



Scheme 2. Two possible diastereomers of metallohelix $[LZn_2Ca]^{2+}$.

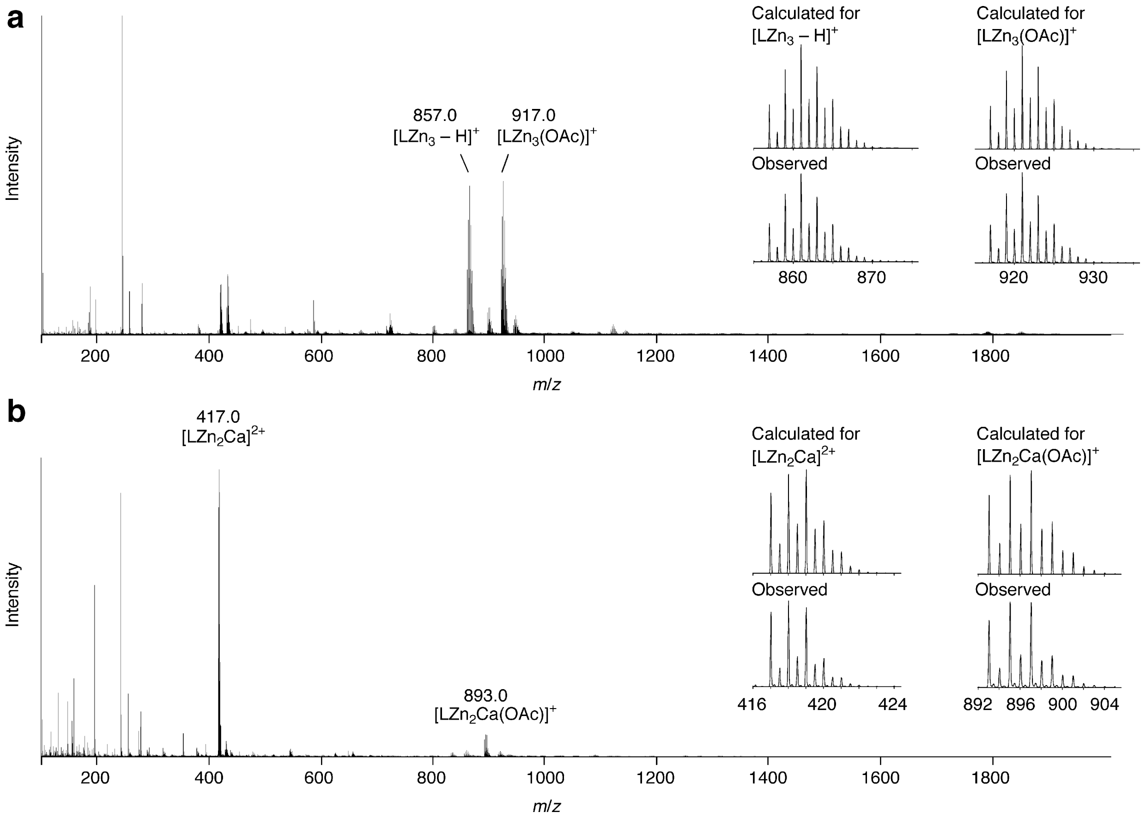


Figure 1. ESI-mass spectra of (a) $[LZn_3]^{2+}$ and (b) $[LZn_2Ca]^{2+}$.

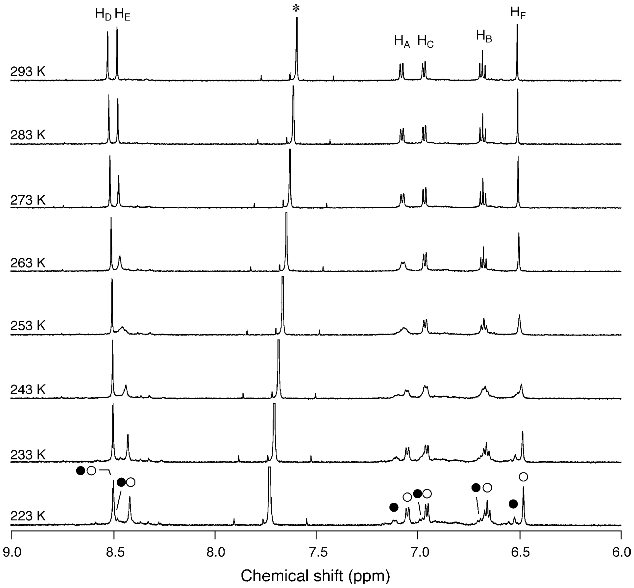


Figure 2. ^1H NMR spectra (600 MHz) of $[LZn_2Ca]^{2+}$ (1.0 mM) at varying temperatures (223–293 K) in $CDCl_3/CD_3OD$ (1:1). Signals of the two diastereomers are indicated with open and filled circles. Asterisk denotes the signal of chloroform. For assignment of signals, see Chart 1.

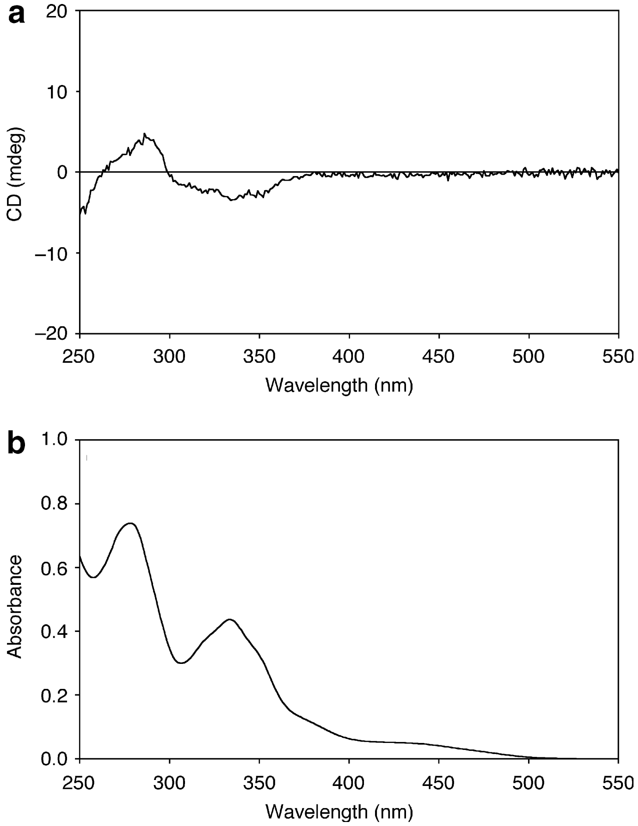


Figure 3. CD and UV–vis absorption spectra of $[LZn_2Ca]^{2+}$ (0.02 mM) at 293 K in chloroform/methanol (1:1).

Analogously, complexes $[LZn_2M]^{n+}$ ($M = Y^{3+}$, La^{3+}) were formed by the transmetalation method. ^1H NMR titration and ESI-mass spectra clearly indicated the complete conversion to the heterotrinuclear complexes. The ^1H NMR spectra of $[LZn_2Y]^{3+}$ and $[LZn_2La]^{3+}$ showed sharp signals at room temperature. The fact indicates that the interconversion of the helical complexes takes place in a similar fashion. At 223 K, two sets of signals corresponding to the right- and left-handed helices were observable. The ratio of the two species was 56:44 for $[LZn_2Y]^{3+}$ and 53:47 for $[LZn_2La]^{3+}$. The result indicates that there is only a slight difference in thermodynamic stability between the right- and left-handed forms of $[LZn_2M]^{n+}$ ($M = Y^{3+}$, La^{3+}). Thus, the chirality induction was the most effective when Ca^{2+} was used as the central metal M^{n+}. The conformation of $[LZn_2M]^{n+}$ is possibly affected by the pendant (*S*)-2-hydroxypropyl group, which may form direct coordination bonds with the metal centers or make hydrogen bonds with counter anions on the metal centers. The M^{n+} dependency of the diastereomeric ratio may be reflected by the non-covalent interactions involving the pendant (*S*)-2-hydroxypropyl group.

In general, chiral helicenes show the Cotton effect around the wavelength of π–π transition bands, because they have a helically arranged conjugated system.[13] The CD spectrum of the metallohelicene $[LZn_2Ca]^{2+}$ recorded in a chloroform/methanol solution showed a bisignate Cotton effect, negative at 334 nm and positive at 286 nm (Fig. 3). The observed CD signals can be assigned to the helically arranged π-system of the ligand chromophore, because the (*S*)-2-hydroxypropyl group has no absorption around these wavelengths. Observation of the CD signal is consistent with the preferential formation of one of the two diastereomers of the helical heterotrinuclear complex $[LZn_2Ca]^{2+}$. Consequently, the terminal (*S*)-2-hydroxypropyl groups of the ligand effectively affect the sense of the single-stranded helix.

In conclusion, a linear tetraoxime ligand bearing chiral (*S*)-2-hydroxylpropyl groups at both ends formed helical trinuclear complexes with Zn^{2+} and the central metal M (=Ca^{2+}, Y^{3+}, La^{3+}). The ratio of the right- and left-handed forms of $[LZn_2M]^{n+}$ depends on the central metal M^{n+}; the helical sense was the most effectively induced when Ca^{2+} was used as the central metal M^{n+}. The trinuclear complex with a helical π-system would be a useful building block for molecular nanocoil that has a helical array of metal ions. Further investigation on the regulation of helicity of a longer-chain strand is now in progress.

Acknowledgment

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References and notes

1. (a) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011; (b) Huc, I. *Eur. J. Org. Chem.* **2004**, 17–29.

2. (a) Lehn, J.-M. *Supramolecular Chemistry, Concepts and Perspectives*; VCH: Weinheim, 1995; (b) Piguet, C.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005–2062.
3. For examples, (a) Stone, M. T.; Moore, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5928–5935; (b) Ikeda, M.; Tanaka, Y.; Hasegawa, T.; Furusho, Y.; Yashima, E. *J. Am. Chem. Soc.* **2006**, *128*, 6806–6807.
4. (a) Akine, S.; Taniguchi, T.; Nabeshima, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4670–4673; (b) Akine, S.; Taniguchi, T.; Saiki, T.; Nabeshima, T. *J. Am. Chem. Soc.* **2005**, *127*, 540–541; (c) Akine, S.; Matsumoto, T.; Taniguchi, T.; Nabeshima, T. *Inorg. Chem.* **2005**, *44*, 3270–3274.
5. H_2salamo = 1,2-bis(salicylideneaminooxy)ethane, see: (a) Akine, S.; Taniguchi, T.; Nabeshima, T. *Chem. Lett.* **2001**, 682–683; (b) Akine, S.; Taniguchi, T.; Dong, W.; Masubuchi, S.; Nabeshima, T. *J. Org. Chem.* **2005**, *70*, 1704–1711.
6. For examples, of helical salen complexes, see: (a) Dai, Y.; Katz, T. J.; Nichols, D. A. *Angew. Chem., Int. Ed.* **1996**, *35*, 2109–2111; (b) Zhang, H.-C.; Huang, W.-S.; Pu, L. *J. Org. Chem.* **2001**, *66*, 481–487; (c) Furusho, Y.; Maeda, T.; Takeuchi, T.; Makino, N.; Takata, T. *Chem. Lett.* **2001**, 1020–1021; (d) Mizukami, S.; Houjou, H.; Nagawa, Y.; Kanesato, M. *Chem. Commun.* **2003**, 1148–1149; (e) Zhang, F.; Bai, S.; Yap, G. P. A.; Tarwade, V.; Fox, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 10590–10599.
7. Yagi, S.; Morinaga, T.; Nomura, T.; Takagishi, T.; Mizutani, T.; Kitagawa, S.; Ogoshi, H. *J. Org. Chem.* **2001**, *66*, 3848–3853.
8. van Staveren, C. J.; van Eerden, J.; van Veggel, F. C. J. M.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1988**, *110*, 4994–5008.
9. Cowie, J. M. G.; Hunter, H. W. *Makromol. Chem.* **1990**, *191*, 1393–1401.
10. Dixon, D. W.; Weiss, R. H. *J. Org. Chem.* **1984**, *49*, 4487–4494.
11. Synthesis of ligand **1b**. A solution of dialdehyde **7** (20.8 mg, 0.13 mmol) in ethanol (5 mL) was added to a solution of oxime **6** (67.5 mg, 0.25 mmol) in ethanol (5 mL). The mixture was heated at 50–55 °C for 1 h. After cooling, the solvent was removed under reduced pressure. The crude product was purified by recrystallization from chloroform/hexane to afford ligand **1b** (67.8 mg, 81%) as colorless crystals, mp 112–113 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 6H), 3.19 (br s, 2H), 3.83 (dd, $J = 9.7$, 8.4 Hz, 2H), 4.04 (dd, $J = 9.7$, 2.8 Hz, 2H), 4.16–4.24 (m, 2H), 4.47–4.52 (m, 8H), 6.80 (s, 2H), 6.84 (t, $J = 7.6$ Hz, 2H), 6.88 (dd, $J = 7.6$, 2.0 Hz, 2H), 6.97 (dd, $J = 7.6$, 2.0 Hz, 2H), 8.25 (s, 4H), 9.61 (s, 2H), 9.95 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.35 (CH_3), 66.05 (CH), 73.03 (CH_2), 73.28 (CH_2), 76.41 (CH_2), 117.03 (C), 117.73 (C), 117.89 (CH), 119.73 (CH), 120.72 (CH), 123.88 (CH), 145.73 (C), 147.20 (C), 148.07 (C), 151.21 (CH), 151.84 (CH). Anal. Calcd for $C_{32}H_{38}N_4O_{12}H_2O$: C, 55.8; H, 5.9, N, 8.1. Found: C, 55.8; H, 6.0; N, 7.6.
12. Akine, S.; Taniguchi, T.; Nabeshima, T. *Tetrahedron Lett.* **2001**, *42*, 8861–8864.
13. Martin, R. H.; Marchant, M. J. *Tetrahedron* **1974**, *30*, 343–345.