A Molecular Leverage for Helicity Control and Helix Inversion

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S *Supporting Information*

ABSTRACT: The helical tetranuclear complex $[LZn_3La-(OAc)_3]$ having two benzocrown moieties was designed and synthesized as a novel molecular leverage for helicity control and helix inversion. Short alkanediammonium guests $H_3N^+-(CH_2)_nNH_3^+$ (n = 4, 6, 8) preferentially stabilized the P-helical isomer of $[LZn_3La(OAc)_3]$, while the longer guest $H_3N^+(CH_2)_{12}NH_3^+$ caused a helix inversion to give the M-helical isomer as the major isomer. The differences in the molecular lengths were efficiently translated into helical handedness via the novel *molecular leverage* mechanism using the gauche/anti conversion of the *trans*-1,2-disubstituted ethylenediamine unit.

Helical structures are frequently seen in functional biomolecules such as DNA and proteins. Their helical handedness principally depends on the chiral structures of their constituents, such as deoxyribose and amino acids. However, inversion of their helical handedness sometimes takes place.[1,2] Developing such a helix inversion system based on artificial molecular frameworks has been a fascinating research objective that has attracted many chemists. For example, there have been reports of artificial molecules or polymers whose handedness can be changed by external stimulation such as a change in temperature[3] or solvent,[4] redox reaction,[5] light irradiation,[6] addition of chemical species,[7] dissolution of crystals,[8] or various combinations of these stimulating events.[9]

In this study, we aimed to create a novel helix inversion system that is remotely driven using a *molecular leverage mechanism* (Figure 1). To date, various kinds of molecular machines[10] such as molecular shuttles and motors have been developed, and
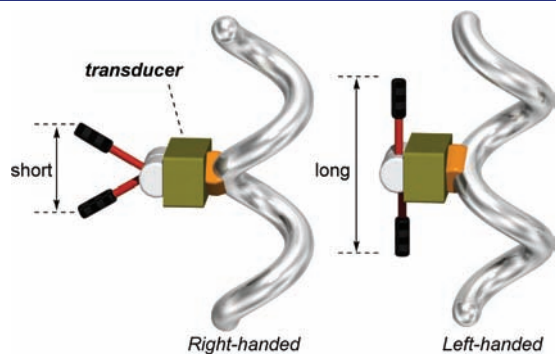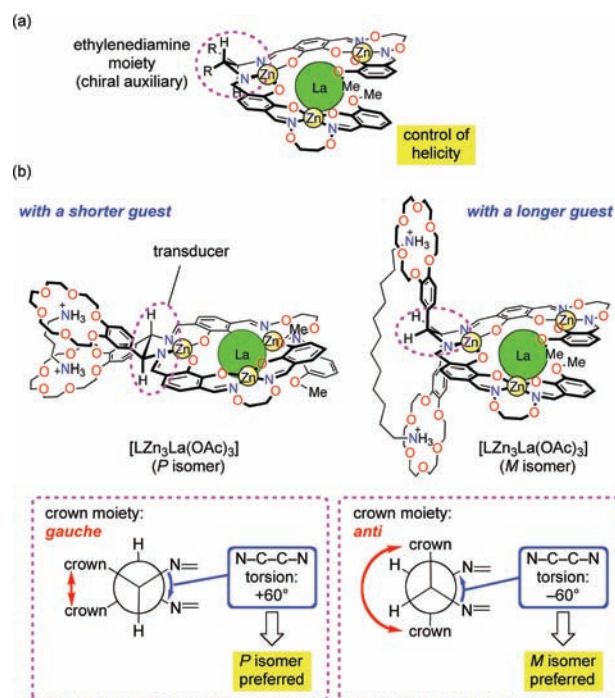

Figure 1. Concept of a molecular leverage mechanism for helix inversion.

Scheme 1. (a) Helicity Control of a Tetranuclear Complex by a Chiral Auxiliary; (b) Design of a Helical Metal Complex for Strategic Helix Inversion by a Molecular Leverage Mechanism
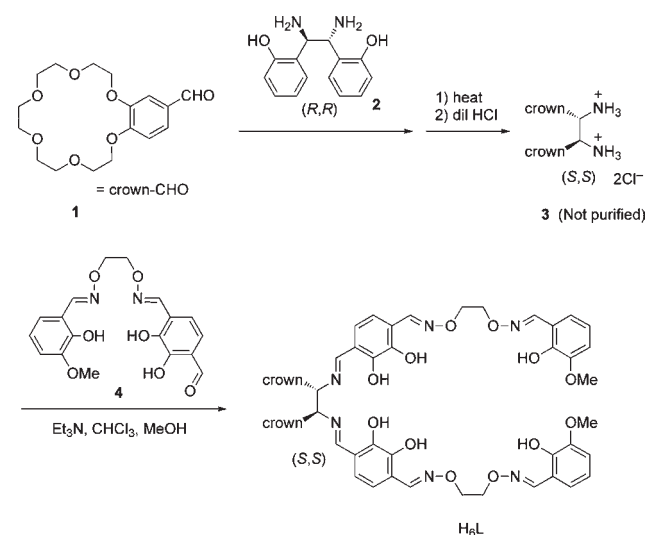

recently, much attention has focused on molecular systems that can convert linear motion into rotary motion.[11] However, there have been no reports of a mechanism that can convert linear motion into helix inversion. To realize such a conversion, a rational and well-programmed mechanism should be incorporated into an invertible helix such as a labile helical metal complex,[12] which is flexible enough to undergo helix inversion upon capture of the external stimulus. We now report the first molecular machinery mechanism in which *molecular length* as an input is translated into *helical handedness* as an output by means of a novel leverage mechanism (Figure 1) based on the gauche/anti conversion of the *trans*-1,2-disubstituted ethylenediamine unit (Scheme 1).

The helix inversion strategy in this study was inspired by our previous study[13,14] of helicity control of single-helical tetranuclear complexes bearing a chiral auxiliary. In these complexes, the helicity of the preferred isomer depends on the relatively small chiral auxiliary, an ethylenediamine moiety, located at the

Scheme 2. Synthesis of H$_6$L

Figure 2. CD spectral changes of $[LZn_3La(OAc)_3]$ upon the addition of **G$_4$** in 1:1 chloroform/methanol at 0.02 mM concentration.

periphery of the molecule (Scheme 1a). Therefore, if we change the N−C−C−N torsion angle of the ethylenediamine moiety from +60° to −60° (or vice versa), we can invert the handedness of the helical scaffold of the tetranuclear complex moiety.

To realize this idea, we designed a helical metal complex equipped with a new *transducer mechanism* based on the (*S,S*)-*trans*-1,2-disubstituted ethylenediamine unit, whose helical handedness can be inverted by taking advantage of the host−guest interaction between the diammonium guests and 18-crown-6 substituents (Scheme 1b). When the complex recognizes a long (or short) diammonium guest, the two crown ether substituents are in the anti (or gauche) position relative to each other. This geometry corresponds to an N−C−C−N torsion angle of −60° (or +60°) in the ethylenediamine moiety, which defines the preferred handedness of the helical scaffold as *M* (or *P*). Using this *molecular leverage* mechanism, we can efficiently control the helical handedness by changing the molecular length of the diammonium guests.

The synthesis of the new tris(chelate) ligand H$_6$L bearing two 18-crown-6 moieties is shown in Scheme 2. Chiral diamine **3** bearing two 18-crown-6 moieties was synthesized by enantioselective [3,3]sigmatropy[15] using 4-formylbenzo-18-crown-6 (**1**)[16] and chiral diamine **2**. The reaction of diamine **3** with aldehyde **4**[17] afforded the H$_6$L ligand. Complexation of the H$_6$L ligand with zinc(II) acetate (3 equiv) and lanthanum(III) acetate (1 equiv) afforded the tetranuclear complex $[LZn_3La(OAc)_3]$ (Figures S1 and S2 in the Supporting Information). The formation of the tetranuclear species was confirmed by the electrospray ionization (ESI) mass spectrometry (m/z 1839.7 for $[LZn_3La(OAc)_2]^+$ and 890.3 for $[LZn_3La(OAc)]^{2+}$). The $[LZn_3La(OAc)_3]$ complex showed a UV−vis spectrum similar to that of the complex without crown moieties, indicating that the zinc(II) and lanthanum(III) ions are in the peripheral N_2O_2 and the central O_8 binding sites, respectively. The tetranuclear complex $[LZn_3La(OAc)_3]$ existed as a mixture of two diastereomers; the diastereomeric ratio was determined to be 75:25 in 1:1 $CDCl_3/CD_3OD$ using ^1H NMR spectroscopy. The helical handedness of the major isomer was determined to be *P* on the basis of the CD spectrum in 1:1 chloroform/methanol, which showed a positive Cotton effect at 352 nm (Figure S3).[13b] The relatively weak effect
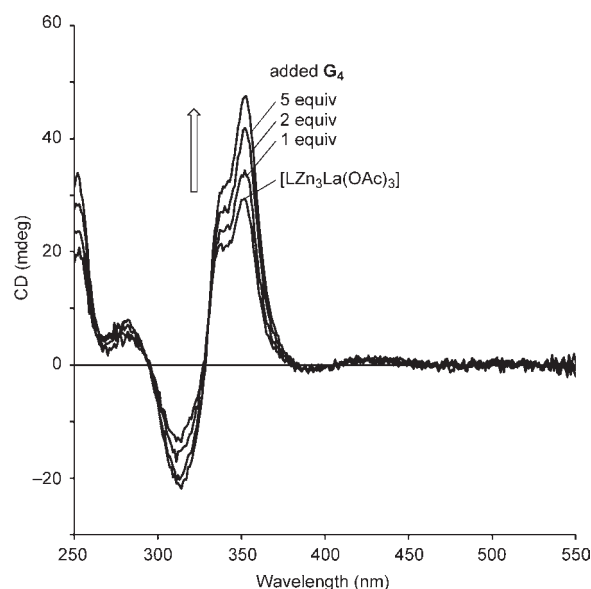
of the diamine unit as a chiral auxiliary (50% diastereomeric excess) presumably results from the fact that there is only a small difference in the two conformations (18-crown-6 moieties in the anti and gauche positions), which means that the arrangement of the crown moieties does not perfectly control the helicity.

However, this diastereomeric ratio of the right- and left-handed isomers was changed by molecular recognition of the alkanediammonium guests $H_3N^+(CH_2)_nNH_3^+(TsO^-)_2$ (**G$_n$**; $n = 4, 6, 8, 10, 12$) at the 18-crown-6 sites. It is well-known that 18-crown-6 derivatives can strongly interact with a primary alkylammonium cation in the cavity. We expected that a shorter alkanediammonium guest **G$_n$** would shorten the distance between the two 18-crown-6 moieties while a longer one would extend it.

When the short guest **G$_4$** was added to a solution of $[LZn_3La(OAc)_3]$ in 1:1 chloroform/methanol, the Cotton effect of the $[LZn_3La(OAc)_3]$ at 352 nm increased (Figure 2). The intensity increased by up to 61% relative to that of $[LZn_3La(OAc)_3]$ itself when 5 equiv of **G$_4$** was present. The binding constant for the 1:1 host−guest complexation was calculated to be log K_a = 4.36 (K_a in M^{-1}). Since the absorption spectra did not significantly change upon host−guest complexation, this increase can be ascribed to the change in the *P/M* diastereomeric ratio. The major isomer (the *P* isomer) was preferentially stabilized by the recognition of the diammonium guest **G$_4$**. In contrast, the addition of a monoammonium cation, $C_{12}H_{25}NH_3^+Cl^-$, did not change the CD spectrum at all. Therefore, the change in the CD spectrum upon the addition of **G$_4$** can be attributed to binding of the guest in a bridging fashion. The change in the diastereomeric ratio was confirmed by NMR spectroscopy. When 2 equiv of **G$_4$** was added, the 75:25 ratio changed to 85:15. The increase in the diastereomeric excess from 50% to 70% is responsible for the increase in the CD intensity.

Similar changes were observed in the case of the longer guests **G$_6$** and **G$_8$**. The CD intensities increased by 50% and 35% when 5 equiv of **G$_6$** and **G$_8$**, respectively, were added (Figure S4). In contrast, no change was observed upon the addition of **G$_{10}$**. It

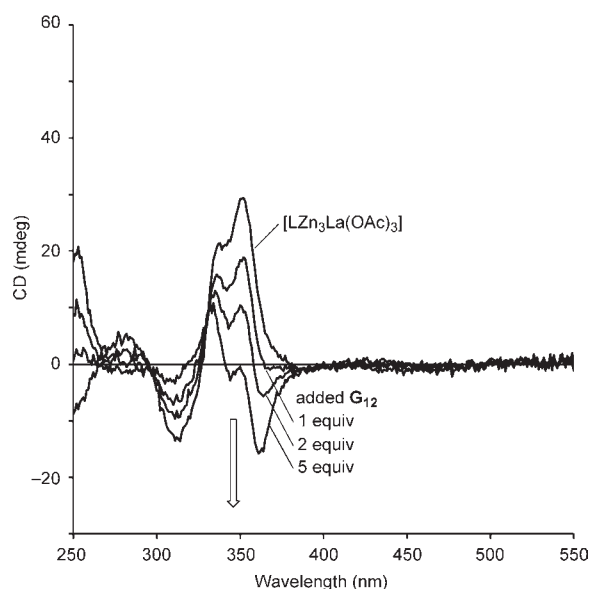**Figure 3.** CD spectral changes of $[LZn_3La(OAc)_3]$ upon the addition of G_{12} in 1:1 chloroform/methanol at 0.02 mM concentration.
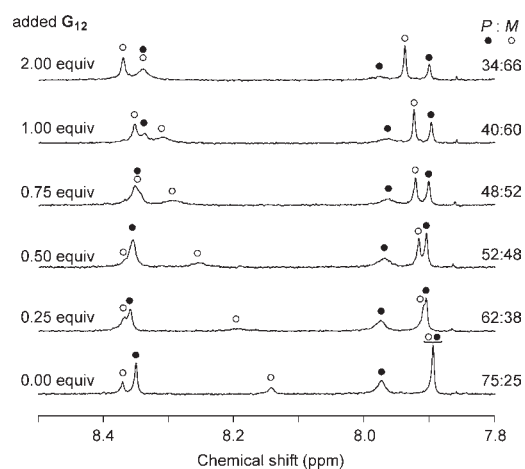

Figure 4. ^1H NMR spectral changes of $[LZn_3La(OAc)_3]$ upon the addition of the longer guest G_{12} (400 MHz, 1:1 CDCl$_3$/CD$_3$OD, 1 mM). The P/M ratios were determined by deconvolution of the peak profiles.

appeared that the intensity change was smaller as the chain length increased.

However, the longer guest G_{12} had a drastically different effect. The addition of G_{12} to the solution resulted in a decrease in the Cotton effect at 352 nm followed by inversion (Figure 3). When 5 equiv of the guest was present, the CD spectrum showed a significant negative Cotton effect at 362 nm. This strongly indicated that the binding to G_{12} caused inversion of the helical handedness, with the M isomer becoming preferred. The ESI mass spectrum of $[LZn_3La(OAc)_3]$ in the presence of G_{12} showed peaks at m/z 680.7, 718.0, and 755.4 for $[LZn_3LaX_2 \cdot H_3N\text{-}(CH_2)_{12}NH_3]^{3+}$ (X = OAc, OTs), indicating the formation of 1:1 host–guest complex.

To study the inversion in more detail, the complexation was investigated using ^1H NMR spectroscopy. The addition of guest G_{12} resulted in changes in the mole fractions of the P and M

Scheme 3. Equilibrium Constants for P/M Isomerization and Guest Binding of $[LZn_3La(OAc)_3]$
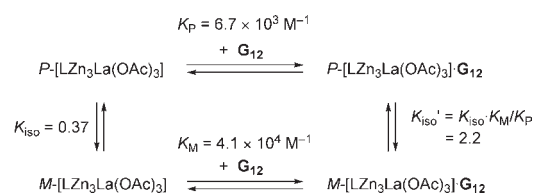
isomers as well as the chemical shifts (Figure 4). Upon the addition of G_{12}, the mole fraction of the P isomer decreased and that of the M isomer increased. The P/M ratio of 75:25 changed to 34:66 upon the addition of 2 equiv of G_{12}. This corresponds to a reversal of the diastereomeric excess from 50% to −32%. The equilibrium constants for P/M isomerization and guest binding (Scheme 3), which were determined by nonlinear least-squares regression of the NMR data, clearly showed the reversal of the P/M preference ($K_{iso} = 0.37$ to $K_{iso}' = 2.2$) upon guest binding and a 6-fold higher guest-binding affinity of the M isomer relative to the P isomer.

Consequently, binding of G_{12} to $[LZn_3La(OAc)_3]$ produces helical handedness opposite to that for G_4 binding. As we expected, the longer guest G_{12} extends the distance between the two 18-crown-6 moieties to make the N–C–C–N torsion angle negative, which stabilizes the M isomer of the helix. On the other hand, the shorter guest G_4 keeps the distance short, resulting in a positive N–C–C–N torsion angle and stabilization of the P isomer. The difference in the *molecular lengths* is efficiently transferred into a change in *helical handedness*.

This reported helix inversion system is of interest as the first molecular transducer that changes linear motion (extension and contraction) into helix inversion (right-handed and left-handed). The conversion between the anti and gauche forms of the *trans*-1,2-disubstituted ethylenediamine unit enables this strategic helix inversion. The basic concept of this mechanical helicity inversion could also be applied to the switching of a variety of chiral functions. The combination of this system with other mechanical motions such as molecular shuttles and cranks would lead to well-controlled molecular machinery on the nanometer scale.

■ ASSOCIATED CONTENT

ⓢ Supporting Information. Synthetic procedure for $[LZn_3La(OAc)_3]$, ^1H NMR spectra of H$_6$L and $[LZn_3La(OAc)_3]$, and CD spectra of $[LZn_3La(OAc)_3]$. This material is available free of charge via the Internet at http://pubs.acs.org.

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