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Interconversion between Möbius Chiroptical States Sustained by Hexaphyrin Dynamic Coordination

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Harnessing the chiroptical properties of molecular Möbius rings is motivated by fundamental aspects while challenged by synthetic difficulties. Focusing on Möbius aromatic Zn(II) hexaphyrin complexes, interconversion between two chiral states was achieved through binding and release of an amino ligand (forward/backward stimuli), leading to different chiroptical switching phenomena (amplification, on-off, inversion). The amine either supplies the chirality or behaves as an achiral effector regulating the Zn(II)-binding of a second (chiral) carboxylato ligand. These results highlight the Möbius [28]hexaphyrin scaffold as an attractive chiral switchable unit.

Chiroptical switches exhibit chiral states interconvertible by a stimulus input (chemical, redox, light...), each state having specific interactions with polarized light leading to changes in the chiroptical spectroscopic response.¹ Chiroptical switches have spread in many research fields, empowering significant implication in molecular recognition (sensing), information storage, optoelectronic materials, asymmetric catalysis.² In this context, whereas a wide range of (supra)molecular scaffolds supplying various types of stereogenic sources has been developed, it is worth to note that the chirality inherent to the Möbius topology³ (Figure 1a) has been scarcely investigated. Harnessing the chiroptical properties of molecular Möbius rings, and more particularly those featuring a 4n π -conjugated system giving rise to an aromatic character,^{4,5} remains of high fundamental interest but is challenged by synthetic difficulties. Whereas some scaffolds afford shape-persistent Möbius stereoisomers and thus a fix chirality,⁶ others allow conformational equilibrium between Möbius stereoisomers leading to a dynamic chirality. Some expanded porphyrins belong to both categories, as their native dynamic scaffold can be frozen by coordination chemistry.^{7,8} Focusing on

the regular [28]hexaphyrin which is intrinsically dynamic (Figure 1b),^{9,10} our group has developed Möbius Zn(II) metallo-receptors exhibiting strong interplay between aromaticity, guest recognition, and chirality transfer (Figure 1c).¹¹ These metal complexes are labile with the main advantage that both exogenous ligand binding and conformational isomerism are dynamic processes in solution at room temperature. *P/M* twist stereoselectivity can thus be readily addressed *in situ* in mild conditions upon addition of an adequate chiral source, eventually combined to the cooperative action of an achiral effector.^{11c,f,g} When two chiral sources are simultaneously bound to the metal center, two-fold transfer of chirality of increasing complexity (match-mismatch effects) allow to tune the chiroptical activity of the Möbius π -system (Figure 1c).^{11g,12} Pursuing our investigations, herein, we present our results towards chemically controlled, coordination driven, chiroptical switches from Möbius aromatic [28]hexaphyrin **1** (Scheme 1). This compound is functionalized by pentafluorophenyl and 2-acetamidophenyl substituents in alternate *meso* positions, a pattern suitable for both stability purposes and to establish a second sphere of coordination.^{11c,g}

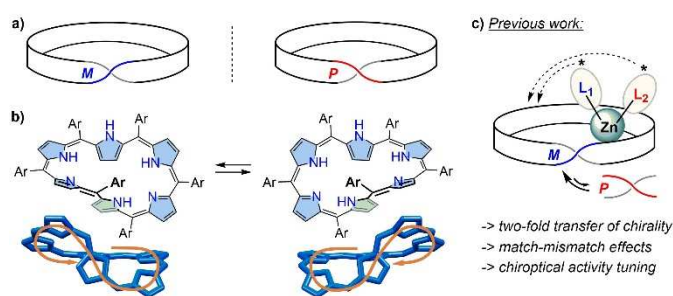
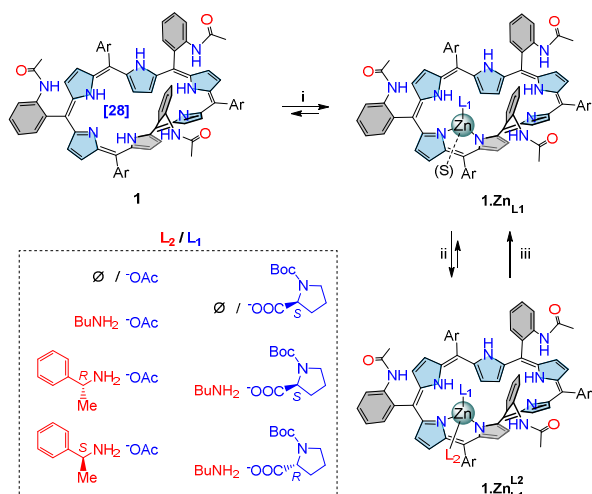


Figure 1. (a) *M* and *P* enantiomers of a Möbius ring (singly twisted). (b) Equilibrium between the two enantiomers of a Möbius aromatic [28]hexaphyrin: energy barrier, ca. 8 kcal.mol⁻¹ (Ar = C₆F₅).^{9b,10} (c) Cartoon of a two-fold transfer of chirality in Möbius [28]hexaphyrin metallo-receptors.^{11g}

As summarized in Scheme 1, compound **1** forms mononuclear Zn(II) complexes in which the tetrahedral metal ion is bound to



Scheme 1. Zn(II) metallation of [28]hexaphyrin **1** (Ar = C₆F₅) in the presence of two different ligands (for the sake of clarity, only one possible isomer [Möbius conformation and 2-acetamidophenyl orientation] is displayed; for **1.ZnL₁**, '(S)' indicates the likely coordination of methanol; in the name **1.ZnL₁L₂**, L1 (L2) subscripted (/superscripted) correspond to inward (/outward) coordinations): i) Zn(OAc)₂ or Zn(OTf)₂/BocProOH, DIPEA, CDCl₃/CD₃OD 9:1; ii) BuNH₂ or MBA; iii) Boc₂O. Inset: different combinations of L₁/L₂ used in this study.

a dipyrin site, with two free coordination sites for the binding of two exogenous ligands: a carboxylato (L₁) oriented *inward*, and an amino (L₂) oriented *outward*.^{11g} For this study, we envisioned to control the chirality transfers from L₁ or L₂ by simple addition and protection of the amino ligand L₂, triggering interconversion between **1.ZnL₁** and **1.ZnL₁L₂** (Scheme 1). It is worth to note that these metal complexes exhibit hindered rotation of the 2-acetamidophenyl *meso* substituents, and thus correspond to dynamic mixtures of atropisomers (ESI).^{11g}

We chose to investigate two opposite situations depending on the external source of chirality, either the carboxylato (L₁^{*}) or the amino (L₂^{*}) ligand. Based on previous results, Boc-protected proline (BocProOH, Boc = *ter*-butyloxycarbonyl) and

methylbenzylamine (MBA) were selected, with different L₁/L₂ combinations as detailed in Scheme 1 (inset and ESI). In order to make the amino function of L₂ no longer available, we decided to test a classical Boc protection reaction since it generally occurs in mild conditions and tolerates well other functionalities.¹³ Prior to chiral ligands, the reaction conditions were optimized with the simple case of L₁/L₂ corresponding to AcO⁻/BuNH₂. All experiments were conducted in NMR tubes, in 9:1 CDCl₃/CD₃OD solutions at *ca.* 4 mM concentration.

Thus, **1.ZnOAc^{NH2Bu}** (Scheme 1) was formed upon mixing **1**, Zn(OAc)₂ (1.5 eq.), BuNH₂ (5 eq.) in the presence of DIPEA (5 eq., DIPEA = diisopropylamine), and subjected to reaction with different amounts of Boc₂O (1, 1.5 and 4 eq. relative to BuNH₂), leading to the following observations (ESI):

(i) The Boc protection is selective of the amino function of BuNH₂, proceeds cleanly, and gives back effectively **1.ZnOAc** along with the formation of BuNH₂Boc and *t*BuOH;¹⁴

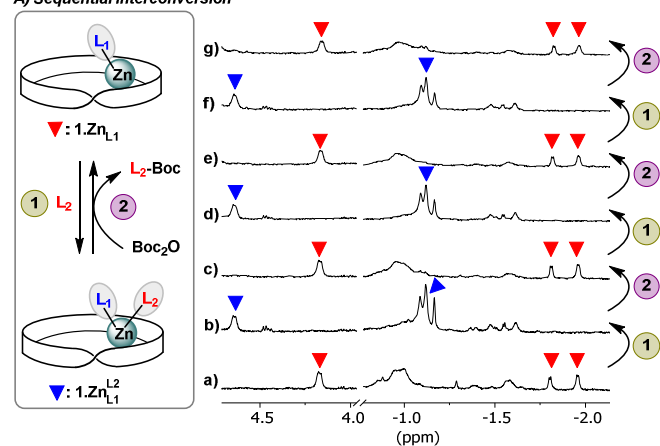
(ii) With 1 eq. of Boc₂O relative to BuNH₂, the Boc protection processes slowly and is not completed after 5 hours at room temperature (RT). Heating at 50 °C fastens the reaction, but ¹H NMR shows a new complex set of signals in the “non-aromatic” region (6–6.5 ppm), likely corresponding to hexaphyrin degradation;

(iii) Using 1.5 eq. of Boc₂O relative to BuNH₂, a more convenient reaction time of *ca.* 2 hours at RT is needed to achieve a complete backward process. Note that without neither hexaphyrin nor Zn(II), these conditions lead to a much faster formation of BuNH₂Boc (< 15 min), indicating a decreased reactivity of the coordinated BuNH₂ in **1.ZnOAc^{NH2Bu}**;

(iv) Complex **1.ZnOAc** tolerates well a large excess of Boc₂O (20 eq., *i.e.* 4 eq. relative to BuNH₂), the reaction being complete after *ca.* 15 min at RT.

These observations allowed us to define two strategies for multiple *in situ* interconversions between **1.ZnOAc** and **1.ZnOAc^{NH2Bu}**, proceeding either sequentially or in “one-step” (Figure 2 A and B). For the first approach, **1.ZnOAc^{NH2Bu}** was

A) Sequential interconversion



B) “one-step” interconversion

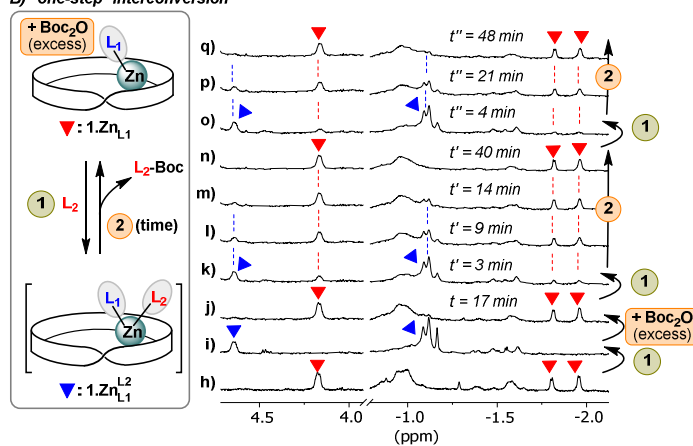


Figure 2. Partial ¹H NMR spectra (CDCl₃/CD₃OD 9:1, 298 K) related to the *in situ* interconversions between **1.ZnL₁** and **1.ZnL₁L₂** (L₁ = AcO⁻; L₂ = BuNH₂). A): two-step process with sequential addition of forward and backward agents; B): “one-step” process using a large excess of backward agent. Steps labelled “1” and “2” correspond to the addition of BuNH₂ and the addition and/or reaction with Boc₂O, respectively (ESI). Highlighted signals at 4.64 and 4.16 ppm (broad doublets) correspond to an ortho aromatic proton of a *meso* 2-acetamidophenyl group oriented *inward*, those at *ca.* -1.12 ppm (three singlets) to bound AcO⁻ ligands (L₁) oriented *inward*, and those at -1.80 and -1.96 ppm (broad doublets) to *inner* β-pyrrolic protons (ESI).^{11g}

generated from **1.Zn_{0Ac}** (Figure 2b, blue triangles) then allowed to react for *ca.* 2 h at RT with 7 eq. of Boc₂O, giving back **1.Zn_{0Ac}** (Figure 2c, red triangles). Second and third interconversions were achieved upon two successive additions of 7 eq. of BuNH₂ and 7 eq. of Boc₂O, with moderate fatigability (Figure 2d-g).¹⁴ In the second approach, **1.Zn_{0Ac}^{NH₂Bu}** (Figure 2i, blue triangles) reacted with 20 eq. of Boc₂O, rapidly giving back **1.Zn_{0Ac}** (Figure 2j, red triangles). Once done, 15 eq. of Boc₂O remain in solution. Then 5 eq. of BuNH₂ were added, and a ¹H NMR spectrum was immediately recorded (Figure 2k, 3 min after addition). It showed **1.Zn_{0Ac}^{NH₂Bu}** as major species together with traces of **1.Zn_{0Ac}**, and conversion of the former complex to the latter one rapidly took place (Figure 2l-n, 9 to 40 min after addition of BuNH₂). At this point, 10 eq. of Boc₂O remain in solution. Then, 5 other equivalents of BuNH₂ were added, leading again to the rapid formation and subsequent consumption of **1.Zn_{0Ac}^{NH₂Bu}** (Figure 2o-q). Thus, according to these two approaches, **1.Zn_{0Ac}^{NH₂Bu}** was generated either as a stable or transient species.¹⁵ Remarkably, in approach B, a second set of three additional interconversions was achieved *in situ* upon “refilling the tank” with 15 eq. of Boc₂O followed by three successive additions of 5 eq. of BuNH₂, leading in total to six interconversions (ESI).¹⁴

In the next step, we focused on the two complexes **1.Zn₁L₂** with L₁/L₂ = BocProO⁻/BuNH₂ and AcO⁻/MBA. The first situation, with the chiral source supplied by the carboxylato ligand, exhibits a positive cooperativity between the two ligands L₁* and L₂: without BuNH₂ (L₂), what is named **1.Zn₁** for simplicity reasons, corresponds to an ill-defined mixture of complexes, with only partial binding of BocProO⁻ (L₁*) in line with a higher steric hindrance than AcO⁻ (see ref 11g). However, upon addition of amino ligand L₂, a well-defined mixture is produced (two major species readily identified by ¹H NMR analysis, see ref 11g), with Zn(II)-bound L₂ and L₁* oriented outward and towards the Möbius ring (Scheme 1), respectively. Therefore, the transfer of chirality is more effective in the presence of L₂, resulting in almost a three fold enhancement of the electronic circular dichroism (ECD) intensity (Figure 3a, blue vs red plain line, L₁* = (S)BocProO⁻).¹⁶ In this case, the negative bisignate Cotton effects ($\lambda_{\text{max}} = 632/624 \text{ nm}$) indicate that both **1.Zn₁** and **1.Zn₁L₂** adopt a preferential *M* twist (left-handed helicity),^{11f} but with different magnitude.

Upon Boc protection of L₂ according to the above-described strategy “A” (Figure 3 inset, see the ESI for ¹H NMR studies), the system goes back to the ill-defined mixture named **1.Zn₁**, and the initial ECD signal is restored (Figure 3a, red dashed line). This interconversion corresponds to a reversible amplification phenomenon, the two chiral states having, at a given wavelength, ECD values of same signs but of different intensities. Although the system shows an obvious fatigability, *in situ* interconversion between those two states was realized three times, with either (S) or (R)BocProO⁻ (Figure 3b and ESI).¹⁴ It is worth to note that herein, the amino ligand acts as an achiral effector^{11c,f,g} that regulates the transfer of chirality to the twisted π -system by enhancing Zn(II)-binding of the external source of chirality, which is somehow reminiscent of allosteric modes of regulation in enzymes.¹⁷

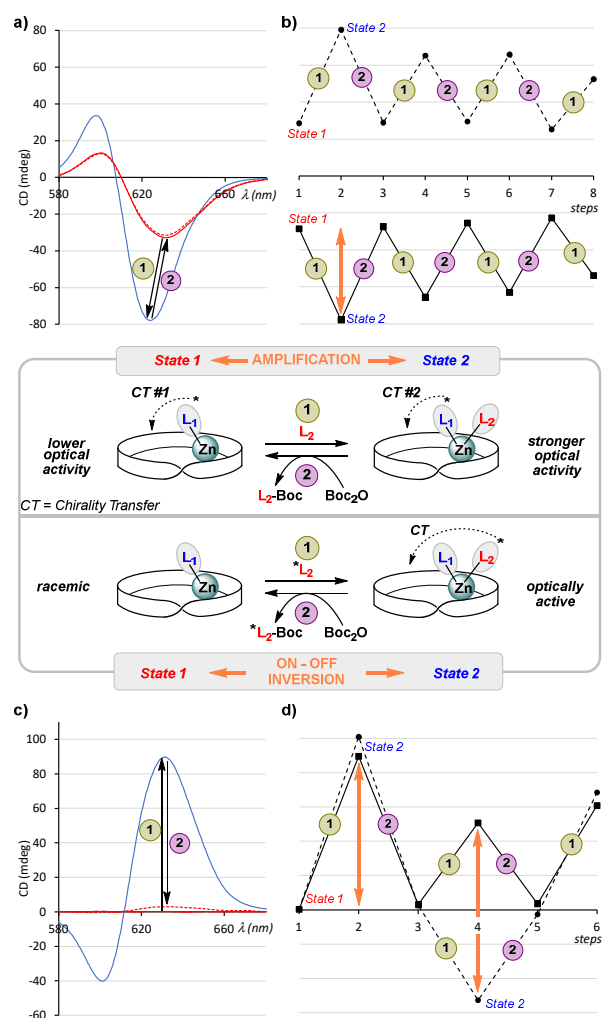


Figure 3. Changes in ECD spectra (CHCl₃/CH₃OH 9:1) related to **1.Zn₁/1.Zn₁L₂** interconversions, with the source of chirality supplied either by L₁ [upper part, L₁* = (S) or (R)BocProO⁻ and L₂ = BuNH₂] or L₂ [lower part, L₁ = AcO⁻ and L₂* = (S) or (R)MBA]: a) amplification phenomenon owing to the cooperative Zn(II)-binding of L₁* and L₂, that drives the efficiency of the transfer of chirality to the Möbius ring; b) changes in ECD values at 624 nm when three transformation cycles were run, with L₁* of opposite configuration [dashed/plain lines: L₁* = (R)/(S)BocProO⁻]; c) on-off phenomenon lying on the addition and protection of the chiral source L₂* [L₂* = (S)MBA]; d) changes in ECD values at 632 nm illustrating an inversion phenomenon upon addition of L₂* of opposite configuration [L₂* = (S)MBA except in step 3 → 4, dashed line, L₂* = (R)MBA].

The second situation, with the chiral source supplied by the amino ligand, behaves differently although it also shows positive cooperativity. Indeed, whereas small size ligand AcO⁻ (L₁) binds to Zn(II) without L₂*, the presence of L₁ is mandatory for the binding of L₂* (MBA) to Zn(II) (a putative complex “**1.Zn₁L₂**” has never been observed).^[11g] In ECD spectroscopy, **1.Zn_{0Ac}** is silent (racemic) but shows an intense signal upon addition of (S)MBA, the positive bisignate Cotton effect ($\lambda_{\text{max}} = 632 \text{ nm}$) indicating that **1.Zn_{0Ac}(S)MBA** preferentially adopts a *P* twist (Figure 3c, blue line vs red plain line).^{11f} The *in situ* Boc protection of the bulky (S)MBA (Figure 3 inset) revealed more difficult than for BuNH₂ and, in order to maintain reasonable reaction times, the above-described approach B was applied. However, in that case, a large excess of Boc₂O (~20 eq.) had to be kept constant to complete the backward process, the

transient complex **1**.Zn_{OAc}^{(S)MBA} exhibiting a longer life-time. In optimized conditions, this interconversion between **1**.Zn_{OAc} and **1**.Zn_{OAc}^{(S)MBA} was realized four times (¹H NMR experiments, ESI).¹⁴ As a result of the Boc protection of (S)MBA, an almost complete disappearance of the ECD signal was observed (Figure 3c, red dashed line), the forth and back process corresponding to an on-off chiroptical phenomenon different from the amplification one of Figure 3a. Note that a lower ECD intensity is reached for “state 2” of the second interconversion process (Figure 3d, plain line, step 4), due to the transient nature of **1**.Zn_{OAc}^{(S)MBA}. Remarkably, the second interconversion can be realized with L₂* of opposite configuration, *i.e.* with (R)MBA, leading to a reverse preferential twisting of the π-system (**1**.Zn_{OAc}^{(R)MBA}: *M* twist favored), as inferred from the ECD values of opposite signs (Figure 3d, dashed vs plain lines, step 4). This particular situation thus generates a chiroptical inversion phenomenon, and several ECD sign inversions were realized *in situ* upon sequential additions/removals of stereogenic sources of opposite configuration (Figure 3d, dashed line, steps 2, 4, 6: *M* twist favored → *P* twist favored → *M* twist favored). To the best of our knowledge, interconverting at will the *P/M* twist of a Möbius π-conjugated system is unprecedented.

In conclusion, the dynamic nature of the Möbius aromatic π-system of **1** was successfully harnessed evidencing different chiroptical regulation phenomena: amplification, on-off, inversion. The unique Zn(II) coordination behavior of **1** featuring selective and cooperative ligand-metal binding processes under thermodynamic control, associated to an *in situ* protection sequence, allows to choose and tune the role of the ligands (chirality supplier or achiral effector), and thus to play with chirality transfers at work. The particular Möbius [28]hexaphyrin scaffold therefore provides an interesting chiral switchable unit, which strongly deserves to be further investigated in sensing systems and catalysis. More robust Möbius [28]hexaphyrin switches with various modes of control (light, redox), exhibiting a single species for a given ECD state, are currently being studied in our laboratory.

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