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Bernard Boitrel, Stéphane Le Gac. Match-mismatch effects in two-fold transfer of chirality within a Mobius metallo-receptor. *Chemical Communications*, 2020, 56 (64), pp.9166-9169. 10.1039/d0cc03877f. hal-02928633

HAL Id: hal-02928633

<https://hal.science/hal-02928633>

Submitted on 19 Nov 2020

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Match-Mismatch Effects in Twofold Transfer of Chirality within a Möbius Metallo-Receptor

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Twofold transfer of chirality has been investigated in a Möbius Zn(II) hexaphyrin metallo-receptor able to bind simultaneously two different chiral molecules. Match/mismatch effects influence the dynamic stereoselective twisting of the π -system, and allow tuning the induced chiroptical activity. Such an allosteric control is attractive to build up chirality sensing systems.

Chirality inherent to Möbius topology has recently regained interest, boosted by the booming of Möbius aromaticity.¹ As predicted by Heilbronner almost 60 years ago,² cyclic π -conjugated systems featuring half-a twist follow aromaticity rules opposite to planar systems, and therefore $4n$ Möbius (hetero)annulenes exhibit variable degrees of aromaticity.³ Major advances in the design of Möbius π -systems were accomplished over the last decade with the broad family of expanded porphyrins,^{4,5} that present several advantages: straightforward preparation, relatively good stability, wide range of metal coordination, strong light absorption (eventually in the NIR region), two-photon absorption, and last but not least, conformational flexibility that can be controlled via different stimuli. The latter property makes these macrocycles attractive to build up Möbius adaptative systems, such as molecular receptors that can feature induced-fit or allosteric processes.⁶ Indeed, the strong interplay between conformation, (anti)aromaticity, and chirality may afford large and tunable chiroptical activity variation, of particular interest for sensing systems. Mastering Möbius chirality is thus crucial to control and enrich the properties of ensuing molecular systems. To do so, transfer of chirality from a chiral source to a Möbius ring, aiming at asymmetric winding of the π -system, deserves intense investigations. To the best of our knowledge, only few systems have been reported to date, all involving a [28]hexaphyrin scaffold (Figure 1). Osuka et al. reported the very first asymmetric preparation of a Möbius hexaphyrin Pd(II) complex using a chiral palladium salt, with a moderate 23 % *e.e.* (Figure 1a).^{5c} In a different approach relying on *dynamic* transfer of

chirality,⁷ our group has shown more efficient stereoselective controls of the Möbius twist (up to 76 % *d.e.*), either from metal-bound molecules (Figure 1b)^{6a} or from covalently attached sources (Figure 1c).^{6c} Pursuing our efforts, we describe herein relatively simple Zn(II) hexaphyrin complexes undergoing twofold transfer of chirality upon simultaneous binding of two chiral molecules (Figure 1d), demonstrating an efficient allosteric tuning of the resulting chiroptical activity.

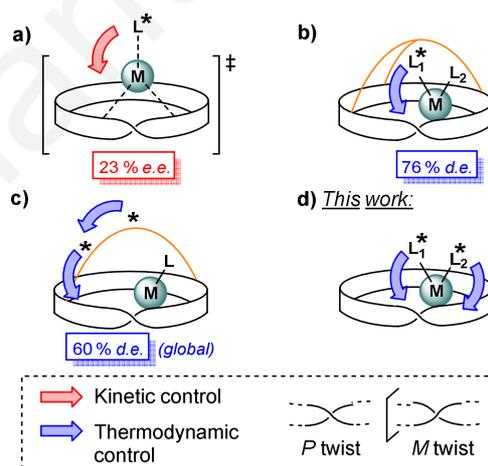
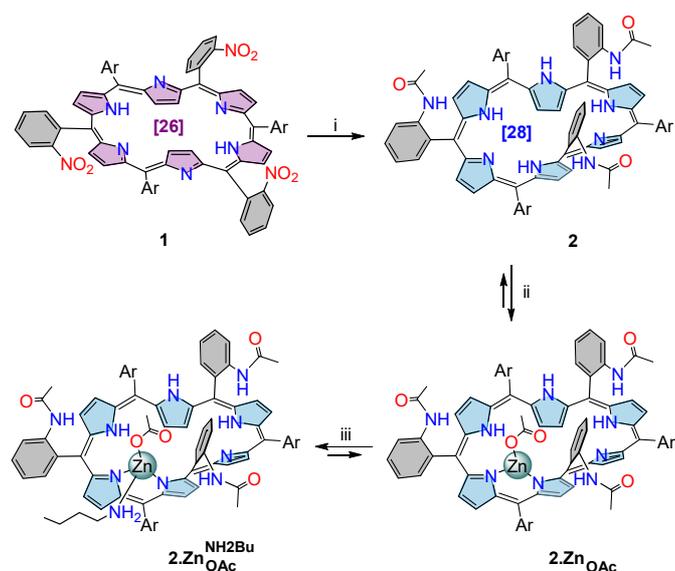


Figure 1. Transfer of chirality (red/blue arrows) in Möbius aromatic [28]hexaphyrin metal complexes: a) at the transition state of a metal insertion process [$M = \text{Pd(II)}$];^{5c} b) from a metal-bound molecule in a capped-hexaphyrin metallo-receptor [$M = \text{Zn(II)}$];^{6a} c) from two sources in covalently bridged hexaphyrin-cyclodextrin hybrids [$M = \text{Zn(II)}$];^{6c} d) from two metal-bound molecules in a hexaphyrin metallo-receptor [$M = \text{Zn(II)}$].

[28]Hexaphyrin **2** (Scheme 1), functionalized with 2-acetamidophenyl and pentafluorophenyl groups in alternate *meso* positions, was designed aiming at simpler receptors than those bearing a tripodal cap (Figure 1b).^{6a} This particular *meso*-substitution pattern affords electron withdrawing groups enhancing the hexaphyrin scaffold stability, and H bond donor moieties promoting Zn(II) complexation through a second sphere of coordination with amino/carboxylato ligands.^{6a} Compound **2** was prepared in one step from the known [26]hexaphyrin **1** (Scheme 1). Reduction of both the nitro groups by Pd(0)/C catalyzed hydrogenation, and the hexaphyrin

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Scheme 1. Synthesis of [28]hexaphyrin **2** (Ar = C₆F₅) and subsequent Zn(II) insertion in the presence of two different guest molecules (for the sake of clarity, only one possible isomer [Möbius conformation and 2-acetamidophenyl orientation] is displayed; for consistency with related previous work,^{6a} a monodentate coordination of OAc is arbitrarily depicted): i) H₂ (80 bars), Pd(0)/C, AcOEt, RT, 15 h; then AcCl, TEA, THF, 0 °C, 30 min; ii) Zn(OTf)₂, DIPEA, TBAOAc, CDCl₃/CD₃OD 9:1 (298 K); iii) BuNH₂ (298 K).

core ([26] → [28] π-system),^{6a} followed by an acylation reaction of the amino moieties with acetyl chloride, led to the desired [28]hexaphyrin **2** in moderate yield upon silica gel chromatography purification (23 %). HRMS analysis indeed confirmed the reduced state of the hexaphyrin scaffold featuring a [28] π-system. **2** exhibits an intense blue colour in solution, and its UV-vis absorption spectrum is characteristic of an aromatic species, with a sharp intense Soret-like band at 606 nm and four Q-like bands spanning from 730 to 1060 nm (SI).⁸ Its ¹H NMR spectrum in CDCl₃ exhibits marked broadening at 298 K, indicating a conformationally flexible compound (SI).⁹

These experimental observations are consistent with a predominant aromatic Möbius conformation undergoing fluxional equilibrium (fast exchange process on the NMR time scale), as previously observed with related compounds.^{5b,6a,10} Atropisomerism involving the *meso* 2-acetamidophenyl groups likely contributes as well to this ill-resolved ¹H NMR spectrum. Zn(II) insertion in **2** was investigated by ¹H NMR experiments in 9:1 CDCl₃/CD₃OD. In the presence of DIPEA, addition of Zn(OTf)₂ led only to partial consumption of **2** affording minor unidentified species with non-trivial resonances in the highfield region (Figure 2b). In contrast, subsequent addition of TBAOAc led instantaneously to complete disappearance of **2** and to the formation of several species featuring dissymmetric patterns (Figure 2c), the two major ones (*ca.* 1:1 ratio) being partially characterized by 2D NMR spectra. They display three sets of β-pyrrolic protons, around -2 ppm (blue triangles, *inner* β-pyr), 4.5 ppm (green triangles, *twisted* β-pyr) and 7-8 ppm (red triangles, *outer* β-pyr). These patterns correspond to aromatic Möbius conformations, rigidified on the NMR time scale by Zn(II) complexation, with a typical diatropic ring current shielding the inside and deshielding the outside of the hexaphyrin core.^{5b,6a} 2D ROESY NMR experiment indicates that shielded signals at -1 ppm correspond to acetate molecules oriented inward (Figure 2c, blue dot, Δδ = -2.9 ppm), in agreement with the binding of a 'ZnOAc' moiety at a dipyrin site (Scheme 1, **2.ZnOAc**), as in related tren-capped hexaphyrin complexes.^{6a,11} The 2-acetamidophenyl group adjacent to the *twisted* pyrrole (bound to zinc) is projected towards the hexaphyrin core and thus experiences partial shielding (Figure 2c, orange dots). This feature likely reinforces the dissymmetry at the level of the metal centre. More detailed NMR characterization is hampered by the complexity of the spectrum.¹²

Subsequent addition of BuNH₂ led to a new set of NMR patterns with at least the three major species retaining the characteristic resonances of Zn(II) Möbius complexes with a 2-acetamidophenyl group projected towards the hexaphyrin

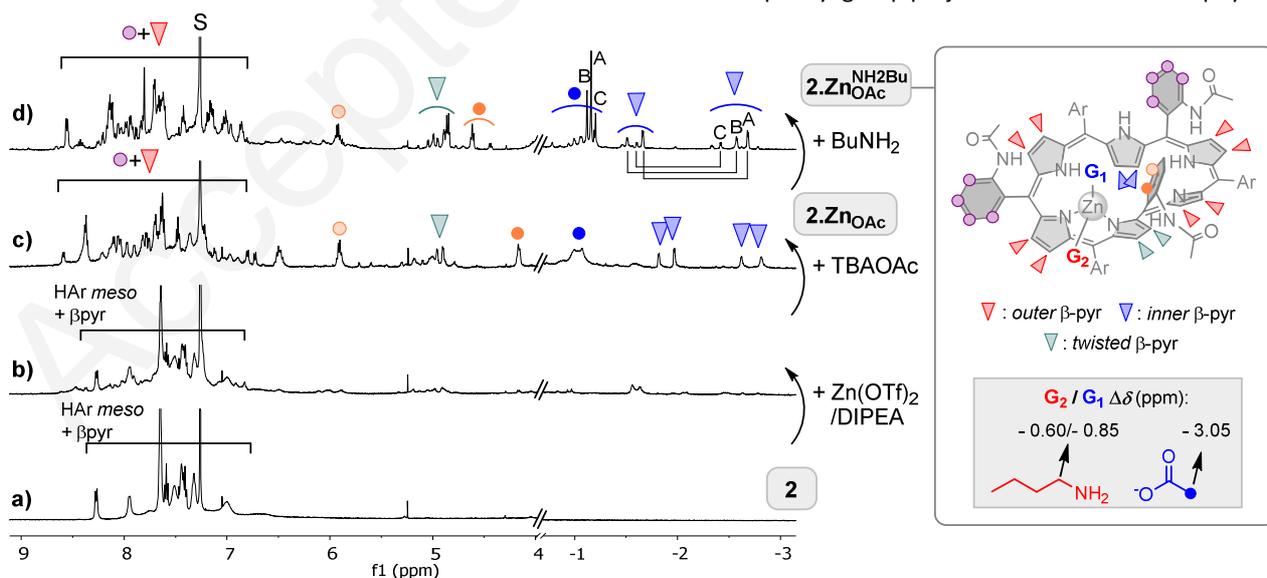


Figure 2. ^1H NMR study of the metallation of **2** with Zn(II) ($\text{CDCl}_3/\text{CD}_3\text{OD}$ 9:1, 298 K, 500 MHz): a) **2** at 4.4 mM; b) upon addition of 1.5 equiv. of $\text{Zn}(\text{OTf})_2$ and 5 equiv. of DIPEA; c) upon addition of 3 equiv. of TBAOAc; d) upon addition of 5 equiv. of BuNH_2 (at 278 K; signals labelled "A", "B" and "C" belong to the three major species). S = solvent. Inset: $\Delta\delta = \delta_{\text{bound}} - \delta_{\text{free}}$.

core (Figure 2d, labelled "A", "B" and "C").¹³ In addition to a Zn(II) acetato ligand oriented inward ($\Delta\delta \sim -3$ ppm, Figure 2 inset), 2D ROESY NMR experiment (SI) evidences concomitant binding of a butylamino ligand, oriented outward. Indeed, only the protons in α position of the coordinated nitrogen atom undergo slight shielding ($\Delta\delta \sim -0.7$ ppm, Figure 2 inset), consistently with an aliphatic chain pointing away from the inner core of the Möbius hexaphyrin (Scheme 1, **2**. $\text{ZnOAc}^{\text{NH}_2\text{Bu}}$). These observations are in agreement with related tren-capped hexaphyrin complexes, in which a 4-coordinate Zn(II) (tetrahedral geometry) orients carboxylato and amino ligands respectively inward and outward.^{6a} During the course of our investigations towards twofold transfer of chirality to the Möbius twisted π -system, we

collected interesting results with two other ligands, N-Boc protected (*S*)-Proline (BocProOH) as *inward* guest and (*R/S*)-methylbenzylamine (MBA) as *outward* guest. With their resulting complexes, ^1H NMR spectroscopy does not provide direct access to chirality induction (*d.e.* values) due to too complex sets of NMR patterns arising from atropisomerism. In contrast, electronic circular dichroism (ECD) spectroscopy is a straightforward and efficient method to evaluate and compare *P/M* twist stereoselectivity, since atropisomers of the same *P* (*/M*) configuration will simply sum up their CD spectra. To assess twofold transfer of chirality, five situations were thus compared by both ^1H NMR and ECD spectroscopies (Figure 3a-e), all generated from the same mixture of **2**, DIPEA and $\text{Zn}(\text{OTf})_2$ ($\text{CDCl}_3/\text{CD}_3\text{OD}$ 9:1, 298 K):

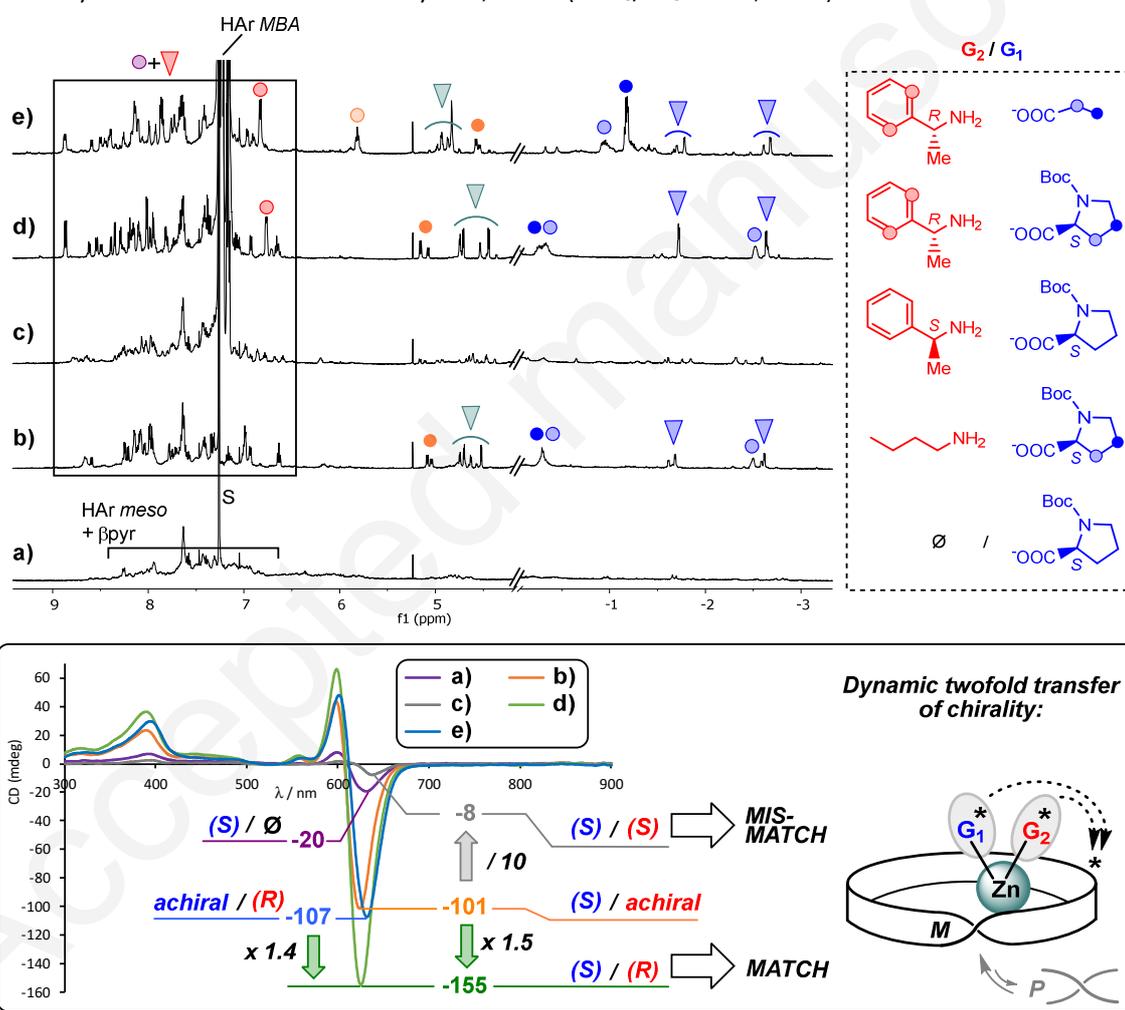


Figure 3. Assessment of the *P/M* stereoselective formation of Möbius isomers, from ^1H NMR (top) and ECD (down) studies. Metallation of **2** with $\text{Zn}(\text{OTf})_2/\text{DIPEA}$ ($\text{CDCl}_3/\text{CD}_3\text{OD}$ 9:1, 298 K, 500 MHz) performed in the presence of different guest molecules: a) (*S*)-BocProOH; b) BuNH_2 and (*S*)-BocProOH; c) (*S*)-MBA and (*S*)-BocProOH; d) (*R*)-MBA and (*S*)-BocProOH; e) (*R*)-MBA and EtCO_2 . S = solvent. Proton labelling: same as Figure 2. NMR initial concentration of **2**: 4.4 mM; ECD total concentration of **2**: 44 μM ($\Delta\epsilon$ values and proportions of each species are not accessible).

(i) Whereas addition of (*S*)-BocProOH led to an ill-defined NMR spectrum and an ECD one of weak intensity (Figure 3a), subsequent introduction of BuNH_2 led to the expected mixture

of Zn(II) Möbius complexes with (*S*)-BocProOH *inward* and BuNH_2 *outward* (Figure 3b; $\Delta\delta$ values in the SI).^{14,15} An important 5-fold increase of the ECD intensity ($\lambda = 624$ nm), displaying negative

cotton effect, indicates marked chirality transfer favouring a *M* twist.¹⁶ Such a behaviour corresponds to a cooperative process, requiring concomitant binding of the two guests;

(ii) Addition of EtCO₂H and (*R*)-MBA led to a similar result, *i.e.* Zn(II)-bound carboxylato and amino ligands are respectively oriented *inward* and *outward* and support transfer of chirality favouring a *M* twist (Figure 3e, same CD spectrum as Figure 3b). Thus, chirality transfer can proceed from *inward* [(*S*)-BocProO⁻] or *outward* [(*R*)-MBA] guests with comparable efficiency, provided that their complementary (achiral) guest is present (respectively BuNH₂ and EtCO₂);

(iii) Addition of (*S*)-BocProOH and (*S*)-MBA, that respectively favour *M* and *P* twists, led to an ill-defined ¹H NMR spectrum¹⁷ and to an ECD spectrum of weak intensity (Figure 3c; 10-fold decrease vs Figure 3b). In contrast, addition of (*S*)-BocProOH and (*R*)-MBA, that both favour a *M* twist, led to a very well defined ¹H NMR spectrum (two predominant Möbius Zn(II) complexes in *ca.* 2:1 ratio, Figure 3d), and to an ECD spectrum of higher intensity than those of the two separated chiral ligands (Figure 3d, 50 % increase vs Figure 3b and 3e). Hence, an *inward* guest favouring a *M* twist exhibits a mismatch effect with an *outward* guest favouring a *P* twist, leading to weak recognition and poor diastereoselectivity, but exhibits a match effect with an *outward* guest also favouring a *M* twist, leading to a remarkable increase of the diastereoselectivity. The same trend is observed when comparing (*R*)-MBA and (*S*)-BocProOH vs EtCO₂H (Figure 3d vs 3e, match effect).

These match-mismatch effects evidence an overall communication between the two sources of chirality, meaning that chirality transfers do not take precedence over one another. This feature nicely allows up or down regulation of the chiroptical activity of the Möbius π-system owing to allostereism, relying on the configuration of the two guests. This phenomenon, to date restricted to Möbius porphyrinoids, is possible because of the conformational equilibrium between the two Möbius enantiomers, allowing (twofold) transfer of chirality under thermodynamic control. Such dynamic metallo-receptors featuring highly responsive chiroptical activity are attractive to build up chirality sensing systems.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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- Low temperature ¹H and ¹⁹F NMR spectra (down to 190 K) did not afford a single sharp signature, but rather multiple patterns with shielded signals, consistently with a mixture of Möbius aromatic conformations frozen on the NMR time scale, see the SI.
- An energy barrier of *ca.* 9 kcal/mol was calculated for the benchmark *meso*-hexakis(pentafluorophenyl)[28]hexaphyrin, see: K. S. Kim, Z. S. Yoon, A. B. Ricks, J.-Y. Shin, S. Mori, J. Sankar, S. Saito, Y. M. Jung, M. R. Wasielewski, A. Osuka and D. Kim, *J. Phys. Chem. A*, 2009, **113**, 4498-4506.
- An alternative outward coordination of AcO⁻ was not detected by 2D ROESY NMR in the present conditions (see the SI), although it cannot be ruled out for minor species lacking 2D NMR correlations.
- The UV-vis-NIR absorption spectrum of **2.ZnOAc** is characteristic of a Möbius aromatic [28]hexaphyrin, the Soret-like band being red shifted compared to **2**, see the SI.
- Roughly, the same ratio of A, B and C (4:2.5:1) is measured from different signals (*inner* and *twisted* β-pyrrolic protons, CH₃ protons of the acetato ligands, aromatic protons of the *meso* 2-acetamidophenyl substituent oriented inward).
- Note that an incomplete metalation is observed in the present conditions, which is likely due the steric hindrance of BocProO⁻ larger than that of AcO⁻.
- The inward orientation of (*S*)-BocProO⁻ is deduced from (i) important Δδ values (up to -4.37 ppm) and (ii) NOE correlations with the inward oriented *meso* 2-acetamidophenyl group adjacent to the *twisted* pyrrole bound to zinc (see the SI). Two predominant Möbius complexes are present in *ca.* 1.5:1 ratio.
- For a definition of *M* and *P* stereodescriptor, see ref 6c.
- More investigations are needed to analyze this mixture.