Tripyrrin-armed isomaragdyrins: synthesis, heterodinuclear coordination, and protonation-triggered helical inversion†

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Oxidative ring closure of linear oligopyrroles is one of the synthetic approaches to novel porphyrinoids with dinuclear coordination sites and helical chirality. The spatial arrangement of the pyrrolic groups of octapyrro (P8) affected the position of the intramolecular oxidative coupling of the pyrrolic units; tripyrrin-armed isomaragdyrin analogue (1) containing a β,β-linked bipyrrole moiety was synthesized regioselectively in a high yield by using FeCl3. Ni2+-coordination at the armed tripyrrin site of 1 allowed the formation of diastereomeric helical twisted complexes (2A and 2B) and succeeding Cu2+-coordination at the macrocyclic core afforded heterodinuclear Ni2+/Cu2+-complexes (3A and 3B). Each of them comprised a pair of separable enantiomers, exhibiting P– and M–helices, respectively. Notably, diastereomeric interconversion from 2A to 2B was quantitatively achieved as a consequence of helical transformation under acidic conditions.

To build such large π-conjugated porphyrinoids, various approaches have been developed, mostly by acid-catalyzed condensation and organometallic cross-coupling reactions. Among them, oxidative ring closure of linear oligopyrroles could produce bipyrrole-containing porphyrinoids directly linked at the two terminal pyrroles in the ω–ω’ or ω–N modes (Fig. 1a). However, less investigation has been carried out on oxidative coupling between β,β’-pyrrolic C-Hs using a rational approach, which may be due to the intrinsic low reactivity of pyrrolic β-C-Hs compared to ω-C-Hs and the lower acidity of CHs than typical N-Hs. Moreover, the oligopyrranes commonly used in the oxidative ring closure reactions are usually too flexible to regulate the targeted reactive sites close to each other.

Inspired by the oxidative coupling reactions of tetraaza[8]circulenes (depicted in Fig. 1b) and tripyr fused porphyrin tapes where the reaction sites (i.e., β-pyrrolyl CHs) reside spatially in close proximity, we here report the synthesis of a novel β,β’-linked isomaragdyrin-based macrocycle (1) from a fully conjugated linear octapyrrole (P8) with terminal ω-acyl substituents by oxidative aromatic coupling using FeCl3. The octapyrrin P8 adopts a spiral conformation through its intrinsic hydrogen-bonding network, which resulted in positioning the specific CHs of pyrroles in close proximity. Indeed, two pyrrolic β-carbon atoms in P8 on rings A and E are close to each other with a short distance of 3.7 Å in the crystal (Fig. 1 and S24†), which enables a regioselective internal ring closure through the oxidative C–H coupling to afford a tripyrrin-armed pentapyrrolic macrocycle containing a β,β-linked bipyrrole moiety in high yield (Fig. 1c). Notably, the appended tripyrrin moiety and

Introduction

Recently, increasing attention has been focused on expanded porphyrin analogues bearing large π-conjugated oligo-pyrrolic scaffolds because of their diverse structural properties.† The expanded porphyrins can serve as unique ligands for multi-metal sensing components.

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Inspired by the oxidative coupling reactions of tetraaza[8]circulenes (depicted in Fig. 1b) and tripyr fused porphyrin tapes where the reaction sites (i.e., β-pyrrolyl CHs) reside spatially in close proximity, we here report the synthesis of a novel β,β’-linked isomaragdyrin-based macrocycle (1) from a fully conjugated linear octapyrrole (P8) with terminal ω-acyl substituents by oxidative aromatic coupling using FeCl3. The octapyrrin P8 adopts a spiral conformation through its intrinsic hydrogen-bonding network, which resulted in positioning the specific CHs of pyrroles in close proximity. Indeed, two pyrrolic β-carbon atoms in P8 on rings A and E are close to each other with a short distance of 3.7 Å in the crystal (Fig. 1 and S24†), which enables a regioselective internal ring closure through the oxidative C–H coupling to afford a tripyrrin-armed pentapyrrolic macrocycle containing a β,β-linked bipyrrole moiety in high yield (Fig. 1c). Notably, the appended tripyrrin moiety and
In the macrocycle 1, π-conjugation was disrupted, as evident from the blue-shifted absorption spectrum ($\lambda_{\text{max}} = 1073$ and 638 nm for P8 and 1, respectively) (Fig. S11†). The high resolution mass spectrum (HRMS) of 1 showed a molecular ion peak at $m/z = 2010.1192$ ($M^+$), consistent with a molecular formula of 1: $C_{69}H_{22}F_{40}N_{8}O_3$ (indicating the formal addition of a methoxy group to P8, i.e., loss of two hydrogens by oxidation with FeCl3), followed by the addition of MeOH). The $^1H$ NMR spectrum of 1 in CDCl3 indicates the unsymmetrical structure and shows two sets of signal patterns in the entire region, suggesting the presence of two conformational isomers in solution (Fig. S1 and S4†).14 For example, the signal of the OCH3 group appeared at $\delta = 3.19$ and 3.09 ppm with a ratio of 0.85 : 1 (calculated from the integral) for the two isomers. On the basis of the preliminary crystal structure of 1, a tripyrrin appended pentaphyrin structure consisting of a direct β,β-linkage between the terminal ring A and the middle ring E was verified (Fig. S25†). The unusual β,β-bonding mode tends to exhibit a significant distortion of the pentapyrrolic core similar to that observed in the tetrapyrryl corrinor.4d Notably, a methoxy group was found at the $\alpha$-position of one of the directly linked pyrroles (ring E), thus generating an sp$^3$ hybridized carbon linkage. The isosmaragdyrin macrocycle of 1 can thus be regarded as a nonaromatic derivative of modified isosmaragdyrin.

Owing to the intrinsic pentaphyrin cavity and flexible oligopyrrin arm, isosmaragdyrin derivative 1 may bind two metal

Results and discussion

The oxidative cyclization of linear octapyrrin P8 was performed using 10 equivalents of anhydrous FeCl3 in CH₂Cl₂/MeOH for 24 h at room temperature. The β-positions of the spatially adjacent pyrrole units were regioselectively linked to afford 1 in a high yield of 88% (Scheme 1). The resulting macrocycle can be regarded as a novel isosmaragdyrin analogue (Fig. 1c).9

one of the outward-pointing pyrrolic nitrogen atoms of the macrocycle constitute a peripheral N4 coordination site and the isosmaragdyrin core serves as an internal N3 donor site, hence 1 provides hetero-bismetal chelation spheres. Taking advantage of this unique structure, metal-dependent complexation (with Ni$^{II}$ and Cu$^{II}$ ions) at both the peripheral and the iso-smaragdyrin cores successfully afforded helical diastereomeric mononuclear Ni$^{II}$ complexes (2A and 2B) and heterodinuclear Ni$^{II}$Cu$^{II}$ complexes (3A and 3B). Each of these complexes contains a pair of enantiomers exhibiting P- and M-helices, where all four optically pure isomers (i.e., M,R-x, P,R-x, P,S-x, and M,S-x; $x = 2$ or 3) have been successfully separated. Unprecedentedly, diastereomeric interconversion from 2A to 2B was quantitatively achieved by the addition of trifluoroacetic acid (TFA), thus enabling transformation between the P- and M-helices. These results provide a practical approach for developing novel porphyrinoids through oxidative ring closure at the spatially adjacent β-positions of elaborately designed conjugated oligopyrroles.
ions and exhibit unexpected properties, such as external-stimuli induced helical transfer.15 Actually, 1 allows the coordination of metal cations at the tripyrrin side chain (Scheme 1). When a methanol solution of 1 and 50 equiv. of Ni(OAc)₂·4H₂O was heated at reflux in the presence of NaOAc under anaerobic conditions, two greenish products, that is, isomeric mononuclear Ni²⁺ complexes 2A and 2B were obtained in 63% and 19% yields, respectively (Scheme 1). The HRMS of 2A and 2B showed essentially identical values of m/z = 2066.0459 and 2066.0432 (Fig. S18–S19†), respectively, indicating that the molecular formula is C₉₉H₂₀F₄₀N₈O₃Ni, which is consistent with the mononuclear Ni³⁺ chelate. Later the X-ray crystallographic analysis disclosed the structures of 2A and 2B with helical twists (Fig. 2a–d).16 The Ni³⁺ cation is wrapped with three N atoms from the tripyrrin unit (rings F–H) and the fourth N atom from the confused pyrrole (ring E), while the inner cavity of the macrocycle remains uncoordinated. The directly linked pyrrole rings A and E are located almost coplanar, and the rings C and H are at opposite sides of the mean plane defined by rings A and E in 2A. However, the rings C and H in 2B are arranged on the same side of the plane. Thus, 2A and 2B can be regarded as pseudo-trans and pseudo-cis conformations, respectively. The methoxy-attached pyrrolic α-carbon (i.e., C20) for 2A is sp² hybridized, which can be evidenced by the C20–C21, C20–C19, C20–O, and C20–N distances of 1.495(8), 1.536(7), 1.410(6), and 1.498(7) Å, respectively, typical values for C–C, C–O, and C–N single bonds.17 Similar bond lengths around C20 were also observed in 2B and the rough crystal structure of 1 (Fig. S25f). The pseudo-tetrahedral geometry of the sp³ carbon center can be further elucidated by the bond angles at C20 lying in the range from 103.7(4) to 111.6(4)°, which are close to 109.5°, a typical value for T₄ carbon atoms. Thus, C20 is a chiral center. Meanwhile, the helical structure of the tetrapyrrin (biliverdin-like) Ni³⁺ complex leads to another source of molecular chirality. As a result, there are four possible chiral isomers, namely, M,R-2, P,R-2, M,S-2, and P,S-2, where R and S represent the chirality of C20, and M (left-handed) and P (right-handed)18 denote the handedness of the biliverdin-like unit. Indeed, a pair of enantiomers, M,R-2 and P,S-2, was present in the crystals of the racemic compound 2A. Likewise, the racemic crystal 2B comprises enantiomers, P,R-2 and M,S-2. Hence, compounds 2A and 2B can be regarded as diastereomeric isomers.

Further metalation of 2A and 2B with Ni³⁺ ions did not proceed under the above conditions. Instead, the reaction of 2A and 2B with 10 equiv. of Cu(OAc)₂ in a mixture of CHCl₃/MeOH (1 : 1) at reflux for 2 h afforded hetero-dinuclear Ni³⁺/Cu²⁺ complexes, 3A and 3B, in the yields of 81% and 91%, respectively (Scheme 1). The molecular ion peaks at m/z = 2126.9590 and 2126.9608, respectively, agree with the dinuclear Ni³⁺Cu²⁺ coordination structures (Fig. S20 and S21f). The broad active EPR spectra of complexes, 3A and 3B, are consistent with the coordination of the paramagnetic Cu²⁺ ion (Fig. S22 and S23f).19 Incorporation of a Cu²⁺ ion into the inner N atoms of the macrocyclic core was also identified by X-ray crystallographic analysis (Fig. 2e–h).20 Notably, the Cu²⁺ cations in 3A and 3B coordinate to the nitrogen atoms of pyrrole rings B, C, and D in a T-shaped manner and the vacant site of the square-planar Cu²⁺ ion seems to be occupied by neighboring sp² carbons (Cu–C: 2.380–2.748 Å) presumably through Cu²⁺-arene interactions (Fig. S27 and S28f).20,21 From the viewpoint of molecular chirality, complex 3A has the same chirality as 2A, consisting of enantiomers M,R-3 and P,S-3 (Fig. 2e and f). Likewise, the crystals of 3B comprise enantiomers P,R-3 and M,S-3 (Fig. 2g and h).

The aforementioned addition of a methoxy group introduces a chiral center into the macrocycle of 1. To understand the chiroptical properties of the isosmaragdyrin derivatives, enantiomeric separation was conducted using a chiral HPLC column with a mixture of n-hexane/2-propanol as the eluent. A
pair of enantiomers of 1 (S-1 and R-1, respectively) was thus separated roughly in a 1 : 1 ratio (Fig. S2a†). The first fraction 1-I and the second 1-II displayed opposite Cotton effects in the circular dichroism (CD) spectra; they can be assigned as R-1 and S-1, respectively, judging from the data obtained experimentally and theoretically using time-dependent density functional theory (TD-DFT) calculations (Fig. S2b†). The absolute configuration of C20 remains intact during demetalation; that is, coordination of R-1 with NiII ions afforded a diastereomeric mixture of M,R-2 and P,R-2, while the corresponding reaction of S-1 likewise afforded P,S-2 and M,S-2. These diastereomers can be separated on conventional silica gel columns. Along this way, subsequent complexation of a CuII ion produced a pair of pure chiral isomers (M,R-3, P,R-3) and (P,S-3, M,S-3), respectively. According to the CD spectra of the resulting enantiomers 2 and 3 (Fig. S34–S37†), the intense Cotton effects were observed in the series of M,R-x and P,S-x (Δε = 400 M−1 cm−1) compared to those of M,S-x and P,R-x (Δε = 100 M−1 cm−1). These stereostructure-dependent spectral features could be rationalized by theoretical calculations (Fig. S39–S42†). The different strengths of Δε may reflect the extent of magnetic dipole transition moments for each electronic transition of the complexes.17

Unprecedentedly, it was found that the isomer 2A could be quantitatively converted to 2B upon treating with 1 equiv. of TFA in CH2Cl2 for 12 h (Scheme 1). TFA-induced stereo-transformation was further analyzed by CD, absorption and 1H NMR spectroscopy. Upon treatment with TFA, the CD spectrum of M,R-2 in CH2Cl2 was spontaneously changed to the same spectra obtained from the acidic solution of P,R-2 while retaining the stereochemistry (Fig. 3). Absorption spectroscopy also showed the clear conversion from 2A to 2B in the presence of TFA in CH2Cl2 or MeOH (Fig. S12, S13, and S15†). Whereas, the profile of 2B remained intact under the same conditions. The 1H NMR spectra also assisted in tracking the helix interconversion processes between 2A and 2B. When the solution of 2A in CD2Cl2 was treated with TFA, the signals of 2A gradually disappeared and subsequently, a new set of signals appeared identical to what is seen for 2B under acidic conditions (Fig. S8†). In CDCl3 or CD3CN, broadening of a specific NH peak for 2B was observed upon addition of TFA (Fig. S7 and S9†).

Although the mechanism for the helical inversion is yet unknown, TFA-assisted protonation at the most probable imino nitrogen site of the isosmaragdyrin core of 2A and 2B could occur, which affected the hydrogen bonding network in the core and caused a conformational change, as inferred from the broadening of the NH signals of the resulting species in the 1H NMR spectrum (Scheme S1†). Intervening of the associated counter anion in this helical inversion sterically or through metal coordination could not be excluded.18 The solution of 2A or 2B in CD3CN reached an equilibrium state (the molar ratio 2A : 2B ≈ 3 : 2 from the integrals of the signals) by treatment with TFA (Fig. S10†). The solvent basicity may affect the protonation/deprotonation dynamics of the above system. In the case of CuII/NiII complexes, 3A and 3B reached equilibria in various media in the presence of acid. Demetallation of CuII ions of 3A and 3B seems to have occurred, judging from the resulting absorption spectra, especially in CH2Cl2 (Fig. S14–S16†).

The calculated energies of all conformers enabled the interpretation of the relative stability of the isomers.19 In particular, the pseudo-trans conformation of 2A has a favorable van der Waals interaction, whereas the pseudo-cis conformation of 2B has better coplanarity between the coordinating and non-coordinating moieties. As a result, the pseudo-cis conformation for 2B is more stable than the pseudo-trans one for 2A (Fig. 4), which is in contrast to the observation that the yield of 2A is much higher than that of 2B during the nickel complexation of 1. The nickel complex 2A could thus be a kinetically favorable product, while 2B is a thermodynamically favorable one. The conformation of the helical structure of 2 is unaffected by further metal coordination. For complexes 3, 3B is also more

Fig. 3 CD spectra of the complexes in CH2Cl2 in the absence (black line) and presence (red line) of TFA, (a) M,R-2, (b) P,R-2, (c) P,S-2, and (d) M,S-2.

Fig. 4 Relative energies between two conformers of (a) 2A and 2B, (b) 3A and 3B, (c) 2AH and 2BH, and (d) 3AH and 3BH. The energies of P,S-2, P,S-2H, P,S-3, and P,S-3H (corresponding to 2A, 2AH, 3A, and 3AH) were calculated relative to those of M,S-2, M,S-2H, M,S-3, and M,S-3H (corresponding to 2B, 2BH, 3B, and 3BH), respectively.
stable than 3A, but the net stabilization effect for 2 is more remarkable than that for 3 (ΔE = 13 kJ mol⁻¹ vs. 4.2 kJ mol⁻¹), which agrees with the ease of transformation for 2. The activation energy for this helical inversion process should be rather high, judging from the unidirectional helical changes, which might be relevant to the unusually high rotation barriers of the 3,3ᵗ⁻bipyrrole system.⁹⁸ Consistently, 2A/2B and 3A/3B were not observed to interconvert while using temperature-dependent CD measurements. On the other hand, we can see from Fig. 4c and d that the protonation of the free-base compound 2 and corresponding Cu complex 3 does not cause visible changes in the conformational structures of the initial non-protonated species, but the energy differences between P,S-2/3H and M,S-2/3H become smaller relative to the non-protonated cases (Fig. 1a and b). Hence, we can assume that protonation might also decrease the activation barrier for the helical inversion processes leading to easier equilibria between the protonated 2A/2B and 3A/3B species.

Conclusions

In summary, the β-positions of two pyrrole rings close to each other in the pre-organized framework of conjugated octapyrrin P8 were linked selectively and efficiently by the FeCl₃-promoted oxidative cyclization reaction. As a result, a tripyrrin appended to the synthesis of a diversity of porphyrinoids, particularly 3,3ᵗ⁻bipyrrole system. As a result, a tripyrrin appended to the synthesis of a diversity of porphyrinoids, particularly

Notes and references


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HPLC chart of 1 suggests the presence of two independent isomers in the solution state at room temperature (Fig. S1†), which is consistent with the observed two sets of NMR signals. These two isomers tend to interconvert quickly within the laboratory timescale.

11 CCDC 1509772 (1), 1430596 (2A), 1430597 (2B), 1430598 (3A), and 1430599 (3B) contain the supplementary crystallographic data for this paper.


17 The HOMO–LUMO energy gaps were obtained from DFT calculations and were in general agreement with the electrochemical data. See Fig. S29–S33, S43 and Table S1†.


19 All the calculations were achieved with Gaussian09 program package at the B3LYP/6-31G* level. See Supporting Information for calculation details.†
