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Doubly *N*-Methylated Porphyrinoids

Wakana Naito,[†] Nobuhiro Yasuda,[‡] Tatsuki Morimoto,[§] Yasuteru Shigeta,[∥] Hikaru Takaya,[⊥] Ichiro Hisaki,[#] and Hiromitsu Maeda*[,†]

[†]Department of Applied Chemistry, College of Life Sciences, Ritsumeikan University, Kusatsu 525-8577, Japan

[‡]Research and Utilization Division, Japan Synchrotron Radiation Research Institute, Sayo 679-5198, Japan

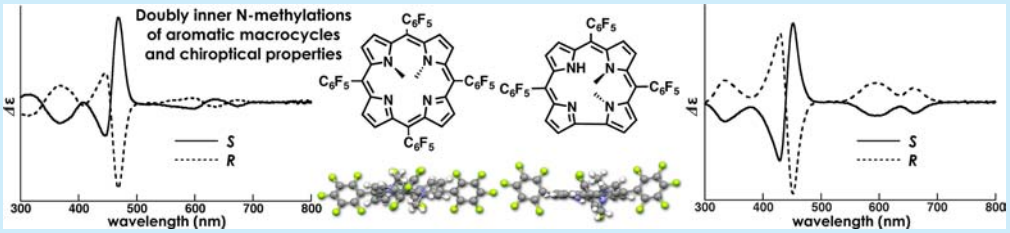
[§]Department of Applied Chemistry, School of Engineering, Tokyo University of Technology, Hachioji 192-0982, Japan

[∥]Department of Physics, Graduate School of Pure and Applied Sciences, University of Tsukuba, Tsukuba 305-8577, Japan

[⊥]International Research Center for Elements Science, Institute for Chemical Research, Kyoto University, Uji 611-0011, Japan

[#]Department of Material and Life Science, Graduate School of Engineering, Osaka University, Suita 565-0871, Japan

Supporting Information



ABSTRACT: Chirality-induced aromatic π-electronic macrocycles, porphyrin and corroles, were synthesized through doubly inner *N*-methylation through multistep and one-pot reactions, respectively. The exact structures of doubly *N*-methylated porphyrin and corroles were revealed by single-crystal synchrotron X-ray analysis, exhibiting two *N*-methyl groups located on neighboring pyrrole rings in up/down conformations. These doubly inner N-substitutions of the π-electronic macrocycles induced distorted geometries, resulting in chiroptical properties after optical resolutions.

The distortion of planar π-electronic molecules can induce chirality, resulting in interesting electronic and electro-optical properties. The symmetry of achiral π-electronic systems can be disrupted by the introduction of chiral substituents or by the interaction with chiral species.[1] Porphyrins, widely investigated 18π-electronic aromatic compounds,[2] are promising candidates for chirality induction by planarity distortion. As a fascinating example, inner-N-protonated forms of saddle-shaped porphyrins showed induced chirality by ion pairing with chiral carboxylates, resulting in chiral memory phenomena.[3] In contrast to peripheral β and *meso* substitutions, only a few examples of inner-N modifications have been reported.[4,5] Some doubly *N*-alkylated derivatives, i.e. β-alkylporphyrins[5b−d] and *meso*-tetraphenylporphyrin (TPP),[5e] were found to have two alkyl moieties on neighboring pyrrole rings in up/down conformations, as elucidated by ^{1}H NMR. Such inner N-substitutions, in opposite orientation to the porphyrin plane, induce chirality in the molecules by distortion of the π-conjugated macrocycles (Figure 1). However, the chiroptical properties such as circular dichroism (CD) of previously reported systems have not been explored.[6] The reported one-pot inner-N alkylation provides mixtures of various alkylated derivatives. In addition, the basicity of the inner-N sites was enhanced by inner-N alkylation; thus, a detailed investigation of the chiroptical properties of free-base states proved to be challenging. Moreover, the reported systems showed decreased stability due to the distortion from the planar

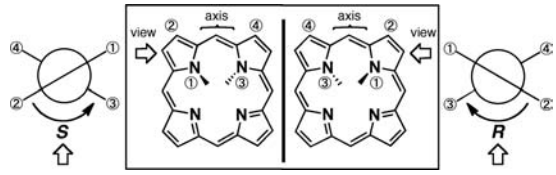


Figure 1. Conceptual diagram of chiral inner modified porphyrins showing enantiomers (center) and the definition of the *R*/*S* configurations, based on the axial chirality (left and right) as numbered according to the priorities, including a *meso* carbon in the "axis".

geometries. It is also noteworthy that the exact molecular structures of doubly *N*-alkylated porphyrins and related aromatic macrocycles have not been elucidated by, for example, single-crystal X-ray analysis. Thorough theoretical studies, which have not been previously conducted, would be helpful for understanding the electronic states of distorted π-electronic systems.

Considering these issues and unexplored aspects, the investigation of chiroptical properties requires carefully designed molecular structures, sophisticated synthetic strategies, and detailed chemical identifications, along with theoretical studies. Here, we report the syntheses, characterization, and properties of

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porphyrin and corroles with two methyl groups at the proximal inner-N sites (21- and 22-N) with up/down conformations.

One-step inner-N alkylation was previously reported for TPP by treatment with excess CH_3I at 100 °C in an autoclave.[5e] In this study, the porphyrin (F_5PP) possessing pentafluorophenyl (C_6F_5) groups at the *meso* positions was the framework of choice for decreasing the polarity of the corresponding *N*-alkyl derivatives such as **1** (Figure 2a) and also for augmentation of the

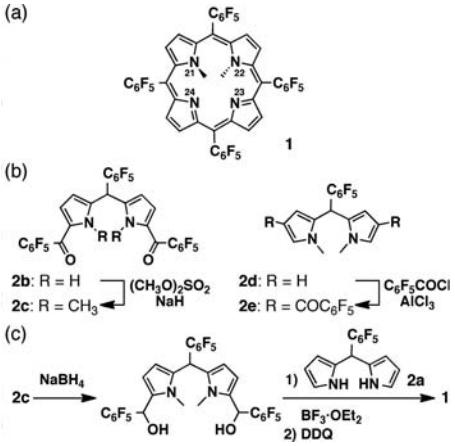

Figure 2. (a) Structure of *N*,*N*′-dimethyl-substituted porphyrin **1**, labeled with the N positions, represented as an *S*-form; (b) synthesis of *α*- and *β*-bis(pentafluorobenzoyl) **2c**,**e**; (c) synthesis of **1** from **2c**.

stabilities of the products along with reaction intermediates. First, inner-N methylation of F_5PP had been examined using an autoclave containing F_5PP, excess CH_3I, and K_2CO_3 at 100 °C in the absence of solvent, yielding a variety of *N*-alkylated derivatives. This observation led us to examine multistep reactions for the desired doubly *N*,*N*′-dimethyl macrocycle **1**.

An efficient synthetic route for **1** uses the [2 + 2]-type condensation of dipyrromethane **2a** and the hydroxymethyl form of *N*,*N*′-dimethyl *α*-bis(pentafluorobenzoyl) **2c**, both having a C_6F_5 unit at the *meso* position. It is important to introduce *meso* carbons as hydroxymethyl and precursory carbonyl units to the *N*,*N*′-dimethyl-substituted dipyrromethane in advance because the *α*-positions of *N*-methylpyrrole units are less reactive due to steric hindrance. The route starting from *α*-bis(pentafluorobenzoyl) **2b**[7] on treatment with dimethyl sulfate (2.2 equiv) in the presence of NaH afforded the desired compound **2c** in 47% yield (Figure 2b, left). On the other hand, another route through Friedel−Crafts reaction of pentafluorobenzoyl chloride with *N*,*N*′-dimethyldipyrromethane **2d**, which was prepared by the acid-catalyzed condensation of pentafluorobenzaldehyde and *N*-methylpyrrole, in the presence of $AlCl_3$ in refluxing 1,2-dichloroethane provided *β*-bis(pentafluorobenzoyl) **2e** in 17% yield instead of **2c** (Figure 2b, right).[8] The exact structures of **2c**−**e** were revealed by single-crystal X-ray analysis, showing, in particular, the exact locations of the pentafluorobenzoyl substituents in **2c** and **2e**.[9]

The acid-catalyzed [2 + 2]-type condensation of the hydroxymethyl (diol) form of **2c**, prepared by reducing **2c** using $NaBH_4$, and a counter dipyrromethane **2a** using $BF_3{\cdot}OEt_2$ and subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided **1** in 15% yield (from **2c**, two steps) (Figure 2c). The distortion of planarity in the up/down conformation of **1** can be initially discussed in terms of the dihedral angle of 30.3° for the *N*-methylated pyrrole ring to the macrocycle mean plane, defined by the 24 core atoms in the model optimized at B3LYP/6-31G(d,p).[10] Two basic inner-N sites are introduced in **1**, resulting in high polarity due to the location of the imine-type N sites located slightly out of the macrocycle plane, as seen in the dihedral angle of 14.7° for the unsubstituted pyrrole ring to the core plane. An aromatic moiety in **1** was suggested by the ^1H NMR spectrum in $CDCl_3$, wherein the singlet signal of *N*-methyl groups was observed at −4.87 ppm along with four sets of doublet signals ascribable to the peripheral *β*-CH appearing at 8.31, 8.30, 7.84, and 7.83 ppm at 25 °C, which were more clearly separated at −50 °C (Figure 3a). This

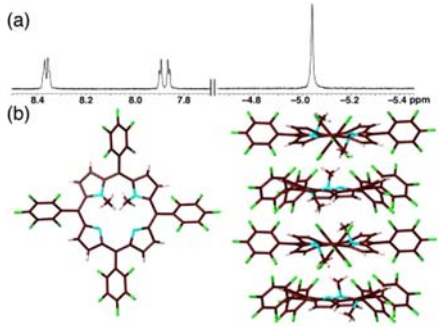

Figure 3. (a) ^1H NMR of **1** in $CDCl_3$ at −50 °C; (b) single-crystal X-ray analysis of **1** as top (left) and side stacking (right) views of the (*S*)-type isomer as a representative, wherein atom color codes of brown, pink, yellow green, and blue refer to carbon, hydrogen, fluorine, and nitrogen, respectively.

aromatic feature can be correlated with the nucleus-independent chemical shift (NICS)[11] of −13.08 ppm at the center of **1**, defined as the averaged position of the 24 core atoms, as estimated at B3LYP/6-31G(d,p).[10] The ^{13}C NMR of **1** showed a signal at 31.54 ppm ascribable to the inner N-Me. In addition, the UV/vis absorption spectrum of **1** in CH_2Cl_2 showed the Soret band at 454 nm and the Q bands at 562 and 627 nm as maxima, which were red-shifted compared with those of F_5PP (411 nm for the Soret band and 505 and 582 nm for the Q bands) because of the less symmetrical geometry in **1**. Furthermore, the fluorescence emission of **1** excited at 454 nm in CH_2Cl_2 showed a maximum at 720 nm at rt.

The exact molecular structure of **1**, which has the desired up/down conformation, was revealed by the synchrotron-radiation X-ray analysis at BL38B1 (SPring-8) for the needle-shaped single crystals prepared from a CH_2Cl_2/MeOH solution of the racemic state (Figure 3b).[10] Interestingly, a quarter of the macrocycle was observed due to the symmetrical geometry in the crystal with the disordered *N*-methyl groups, exhibiting the up/down orientation on the neighboring pyrroles. This results in the estimation of the dihedral angles of 31.3° and 12.6° for the *N*-methylpyrrole and unsubstituted pyrrole rings, respectively, to the macrocycle mean plane defined by the 24 core atoms. The N−C bond in the *N*-methylpyrrole part shows a dihedral angle of 16.9° to the pyrrole plane, suggesting the contribution of the sp^3 property at the pyrrole nitrogen. In the solid state, the disordered geometry of **1** cancels out the chirality of each molecule. Furthermore, **1** forms the stacking structure based on the segregation of core units and peripheral C_6F_5 moieties with the stacking distance and rotation angle of 4.75 Å and 29.4°, respectively, between the two neighboring planes. The obtained up/down conformation in **1** was consistent with the theoretical study at B3LYP/6-31G-(d,p),[10] exhibiting the more stable up/down conformation at

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21.68 kcal/mol rather than the achiral up/up conformation as their parent structures. Although the starting **2c** may provide both of the conformations, the up/up conformation cannot be synthesized, theorized to be a result of its lower stability.

Like porphyrin, corrole is a well-known functional π-electronic molecule with 18π aromaticity with a less symmetric structure,[13] resulting in chirality induction even by a single inner-N alkylation.[14] In addition, corrole can form four regioisomers and eight stereoisomers (counting a pair of enantiomers as a single stereoisomer) by dimethyl substitution at the inner-N sites. Before the trial, the smaller size of the inner core in corrole, as compared to porphyrin, had seemed less suitable for one-pot *N*-methylation. However, tris(pentafluorophenyl)corrole (F_5PC) was converted to a dimethyl derivative **3a** in 71% yield, without the formation of other regioisomers, by treatment with CH_3I (excess) in the presence of K_2CO_3 in refluxing acetone (Figure 4a). This result can be ascribable to the difficult first *N*-

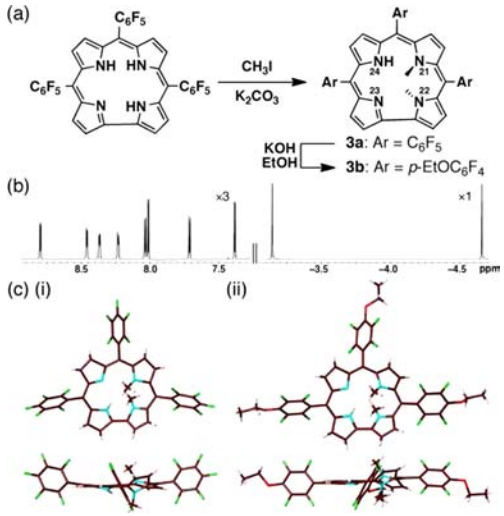

Figure 4. (a) Synthesis of **3a**,**b**, which are represented as *S*-forms and labeled with the N positions, from F_5PC; (b) ^{1}H NMR of **3a** in $CDCl_3$ at 20 °C; (c) single-crystal X-ray analysis (top and side views) of (i) **3a** (one of the disordered structures) and (ii) **3b** as *S*-forms as representatives, wherein an atom color code, which is same as that of Figure 3, of red refers to oxygen.

methylation, whose achievement enables the facile second *N*-methylation. It was difficult to convert **3a** to the trimethyl derivative even under more vigorous conditions.

Introduction of two nonequivalent methyl groups at the inner-N sites was suggested by two upfield ^{1}H NMR signals at −3.14 and −4.66 ppm in $CDCl_3$ (20 °C), whereas eight independent β-CH signals were observed at 8.80−7.38 ppm as doublets (Figure 4b). ^{13}C NMR of **3a** showed signals at 30.60 and 30.05 ppm ascribable to two methyl groups. The two different *N*-methyl chemical shifts excluded two regioisomers possessing the methyl units at the 21- and 24-N sites (on the bipyrrole unit) and the 22- and 23-N sites (on the dipyrrin unit). The aromatic character is correlated with the NICS value (−12.74 ppm at B3LYP/6-31G(d,p)) of **3a**.[10] The UV/vis absorption spectrum of **3a** in CH_2Cl_2 showed the Soret and Q bands at 432 and 594 nm, respectively, which were red-shifted in comparison to those of F_5PC with the Soret band at 407 nm and the Q bands at 561 and 604 nm. On the other hand, the fluorescence emission of **3a** excited at 432 nm in CH_2Cl_2 showed a maximum at 682 nm, whose intensity was significantly enhanced at lower temperatures. Furthermore, *p*-fluorine moieties in C_6F_5 units of **3a** can be readily converted to *p*-ethoxy-substituted **3b** by treatment with EtOH in the presence of KOH (Figure 4b).

The exact locations of the N-substituents, 21- and 22-N sites, and also the up/down conformation were revealed by single-crystal synchrotron X-ray analysis of **3a**,**b**, whose single crystals were obtained from CH_2Cl_2/MeOH for the racemic states, at BL40XU (SPring-8) (Figure 4c).[15] Although disorder of *N*-methyl moieties in **3a** resulted in the two possible candidates with those at the 21- and 22-N and the 21- and 23-N sites, the latter has been excluded by the analysis of **3b** that showed no disordered structures. The dihedral angles of *N*-methylpyrrole units with 21- and 22-N in **3a**, defined by the 23 core atoms, were 16.3° and 35.9° (22.8° and 39.1° in the other disordered structure), respectively, whereas those in **3b** were 28.7° and 31.7°, respectively. Similar to **1**, the N−C bonds in the *N*-methylpyrrole parts of **3a** show dihedral angles of 35.2°/18.9° and 29.1°/20.7° to the pyrrole planes. These conformations, exhibiting the larger distortion of the *N*-methylpyrrole ring at the bipyrrole unit, are also observed in the optimized structure of **3a** at B3LYP/6-31G(d,p) showing the dihedral angles of 26.0° and 36.4° for the pyrroles with 21- and 22-N units, respectively. The packing structures can be controlled by the substituents on the *meso*-aryl moieties; **3a** formed stacking columns in a parallel orientation, while **3b** provided zigzag stacking assemblies. Furthermore, in contrast to **1**, **3a**,**b** have a proton at an inner-N site, resulting in the more stable isomers with two methyl units at the neighboring pyrroles. Notably, **3a** was selectively obtained by a one-pot reaction from F_5PC under mild reaction conditions.[16]

Electrochemical analyses revealed a profound influence of the introduction of two inner-N methyl groups on the electronic structure of the macrocycles. Cyclic voltammetry (CV) showed that **1** (+0.75 V vs Fc/Fc^+) was more easily oxidized than F_5PP (+1.06 V vs Fc/Fc^+) by ca. 0.31 V. In contrast, the first reduction wave of **1** was observed at −1.30 V, comparable to F_5PP (−1.31 V). These results indicate that the introduction of two methyl groups to the core destabilizes the HOMO level, and in turn, induces the red shifts of the Soret and Q bands as seen in UV/vis absorption spectra. The increasing HOMO level and almost constant LUMO level could be supported by the theoretical calculation,[10] where the HOMO level of **1** is higher than that of F_5PP by ca. 0.37 V and the LUMO levels are comparable to each other. In addition, another significant difference is the less reversibility of the reduction waves of **1** than F_5PP, owing to the more distorted less stable structure by the two inner methyl groups. On the other hand, it is not easy to compare electrochemical properties of **3a** and F_5PC, because F_5PC displayed quasi-reversible or irreversible waves, in sharp contrast to the reversible oxidation and reduction waves of **3a**. Thus, it is clear that the introduction of methyl groups into the corrole core suppressed the protonation and deprotonation processes at the core, which brings about complicated redox waves in the CVs.[17]

Optical resolutions of **1** and **3a** were achieved by chiral HPLC (Daicel CHIRALPAK IA) with *n*-hexane containing *i*PrOH and ethylenediamine (5% and 0.1%, respectively) for **1** and with *n*-hexane containing *i*PrOH and diethylamine (0.1% for each) for **3a** as eluents. Optically pure **1** and **3a**, which kept their chiral configurations after heating in refluxing toluene for 12 h, exhibited Cotton effects in CD (Figure 5). In **1**, the first fraction showed the negative and positive signs in the Soret band region with the maxima at 445 and 468 nm, respectively, along with the negative, positive, and negative signs at Q-bands (597, 632, and

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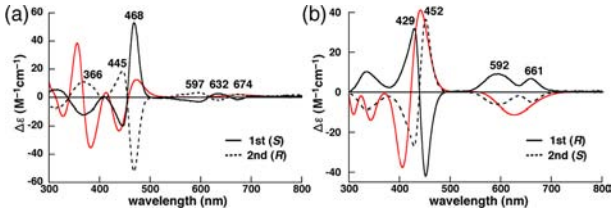

Figure 5. CD spectra of (a) **1** and (b) **3a** in CH_2Cl_2 at 20 °C as the first (solid lines) and second (broken lines) fractions on chiral HPLC and the corresponding theoretical spectra for each (*S*) isomer (red lines).

674 nm) in CH_2Cl_2. Whereas in **3a**, the first fraction showed the positive and negative signs in the Soret band region with maxima at 429 and 452 nm along with the positive signals at Q bands (592 and 662 nm) in CH_2Cl_2. The intensities of the CD signals of **1** and **3a** were enhanced at low temperatures due to the more rigid distorted geometry. The CD spectra for **1** and **3a** with *S*-configurations, predicted by TD-DFT calculations at LC-BLYP(μ = 0.20)/6-31++G(2d,2p)//B3LYP/6-31G(d,p) with C-PCM (CH_2Cl_2) for both ground and vertical excited state calculations,[10,18] were consistent with the observed CD spectra for the first and second fractions, respectively (Figure 5). Such chiroptical properties were ascribable to the distorted π-conjugated units rather than the directions of *N*-methyl moieties. Interestingly, the transitions at around 450 nm in **3a** can be theoretically assigned as the intramolecular charge-transfer (CT) excitations from HOMO−1 localized at the *meso*-aryl rings to LUMO and LUMO+1 localized at the core macrocycle, whereas those in **1** are ascribable to the excitations with the changes in the MO, such as HOMO−3 and HOMO−4, localized at the macrocycle.

In summary, this study showed the introduction of alkyl (methyl) substituents at the inner-N sites of the aromatic macrocycles such as porphyrin and corroles by multistep and one-pot reactions, respectively. The locations and orientations of the introduced two N-substituents were revealed by single-crystal synchrotron X-ray analysis. Optical resolutions of the doubly *N*-methylated macrocycles resulted in the observations of CD Cotton effects, whose differences according to macrocycle structures can be explained by theoretical studies. Introduction of other functionalities to the inner-N sites would provide fascinating chiral π-electronic systems exhibiting chiroptical properties, and their design and syntheses are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01377.

Synthetic procedures, spectroscopic data, and theoretical study (PDF)

Crystallographic data (CCDC 1420135−1420141) (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: maedahir@ph.ritsumei.ac.jp.

Notes

The authors declare no competing financial interest.

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