20π antiaromatic isophlorins without mettallation or core modification


Abstract: Isophlorins (two-electron-reduced porphyrins) with 20π antiaromaticity have been synthesized by metallation or core modification (replacing the inner NHs with less bulky atoms) thus far. The core-modification number (CMN) is an important factor for the stability of isophlorins against their oxidation to porphyrins. However, isophlorins with small CMN (≤ 2), i.e., without significant core modification, are difficult to synthesize and important for understanding their structure–antiaromaticity relationships. Herein, we report the synthesis of free-base (metal-free) antiaromatic isophlorins with no core modification (CMN=0) for the first time in the literature. β-Tetracyanoporphyrins were successfully reduced by hydrazine to their corresponding isophlorins under aerobic conditions. These porphyrin/isophlorin transformations are reversible. Their structure and antiaromaticity were studied via 1H NMR and UV-vis/near-infrared absorption spectroscopy, X-ray diffraction and theoretical calculations.

Introduction

Isophlorins are two-electron-reduced species of porphyrins and were first proposed by Woodward in 1960 as intermediates in the synthesis of porphyrins (Figure 1a).[1,2] Isophlorins have 20π cyclic-conjugated electrons and, therefore, have an antiaromatic character. They are generally unstable and difficult to isolate because of their antiaromaticity and high sensitivity to oxidation. Isophlorin has four hydrogen atoms on each inner nitrogen atom of the macrocycle. Because of the steric hindrance of the hydrogen atoms, isophlorin exhibits the derivative from their planar antiaromaticity. Their further deformation by the N-alkylation affords stable isophlorin without antiaromatic character (Figure 1b).[3-6]

Planar and hence antiaromatic isophlorins have been synthesized by two approaches (Figure 1b). One approach is metallation. The two-electron reduction of Zn-tetraarylporphyrin produced an isophlorin with antiaromatic character, as revealed by 1H NMR studies.[7] In addition, tetravalent elements such as S[8] or Ge[8] or their analogs such as C=O[9] or B–B[10] have been used to obtain antiaromatic isophlorins. These isophlorins were highly air-sensitive and should be handled under an inert atmosphere. Another approach is core modification, which involves replacing the inner NHs with less bulky O or S atoms.[12–14] In particular, isophlorin derivatives with electron-withdrawing substituents, such as -CF3, were stable even under atmospheric conditions and exhibited strong antiaromaticity.[13,14] The core-modification approach inhibits π-conjugation of the heteroatoms and destabilizes the oxidized 18π aromatic system, thereby stabilizing the isophlorin. Therefore, the core-modification number (CMN) is an important factor for the stability of isophlorins. Synthesizing an isophlorin with a CMN of two or less is difficult; however, it is important for understanding the structure–antiaromaticity relationships of isophlorins.

![Diagram of Porphyrin and Isophlorin Formation](image-url)

Figure 1. (a) Proposed scheme for porphyrin formation by oxidation of porphyrinogen via the hypothetical intermediate isophlorin.[10] (b) Characterized and/or isolated isophlorins in the literature.[2–7,14]
Previously, we have reported the synthesis and antiaromaticity of β-tetracyano-21,23-dithiaisophlorin 1 (CMN=2) (Scheme 1).\[15] Weak reducing agents such as hydrazine were used to reduce the corresponding dithiaporphyrin 2 to its isophlorin 1, which was stable in the presence of the reducing agent even under atmospheric conditions. Moreover, the reduction of 2 to 1 was reversible. Using cyano groups as peripheral substituents increased the reduction potential of the porphyrin core and stabilized the antiaromatic isophlorin by π-conjugation. Based on this concept, in this study, we synthesized β-tetracyanoisoporphyrins 3a and 3b (CMN=0) via the reduction of β-tetracyanoporphyrins 4a and 4b, respectively, and studied their antiaromatic character. Although the synthesis, structure, and strong electron-accepting nature of β-tetracyanoporphyrins have been widely explored\[16-27] since the first report in 1973,\[28] their two-electron-reduced products, i.e., isophlorins, have not been isolated and explored, except for their UV-vis absorption studies during in situ electrolysis.\[18] In this study, isophlorins have been isolated by chemical reduction under ambient conditions. To the best of our knowledge, 3a and 3b are the first free-base isophlorins with a 20π antiaromatic character reported in the literature.

Results and Discussion

β-Tetracyanotetraarylporphyrins 4a and 4b were synthesized using a modified synthesis of the dithia analog 2 from the literature.\[15] Similar to those of 2, the properties of 4 exhibited strong solvent dependence. The NMR and UV-vis absorption spectra of 4 in nonpolar solvents confirmed its 18π aromatic nature. In contrast, the NMR and UV-vis spectra recorded in dimethyl sulfoxide (DMSO) strongly suggested that 4 was spontaneously reduced by one electron to generate its anion radical. The 1H NMR spectrum of the reduced product of 4a in DMSO exhibited broader peaks than those in nonpolar solvents.

The redox potentials of 4a and 4b determined by cyclic and differential pulse voltammetry (Figure S6) are shown in Table 1. Both 4a and 4b exhibit two reversible reduction waves. In the nonpolar solvent CH3Cl2, the reduction potentials of 4a (−0.75 and −1.05 V) were −0.2 V more negative than those of 2 (−0.54 and −0.81 V). Those of 4b (−0.60 and −0.94 V) were more positive than those of 4a because of the effect of the electron-withdrawing trifluoromethyl substituents on 4b. In DMSO, the redox potentials of 4b were positively shifted (−0.47 and −0.74 V), indicating that the reduced states were more stable in DMSO. Similar solvent dependence was also reported by us for the dithia analog 2.\[15]

Table 1. Half-wave potentials (V vs Fe/Fc+) of 4a, 4b and 2. Potential values were obtained from differential pulse voltammetry (DPV).

<table>
<thead>
<tr>
<th>solvent</th>
<th>E_{ox1}</th>
<th>E_{red1}</th>
<th>E_{red2}</th>
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<tbody>
<tr>
<td>4a</td>
<td>CH3Cl2</td>
<td>0.92</td>
<td>−0.75</td>
</tr>
<tr>
<td>4b</td>
<td>CH3Cl2</td>
<td>1.0</td>
<td>−0.60</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>−0.81</td>
<td>−0.47</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>1.08</td>
<td>−0.54</td>
</tr>
</tbody>
</table>

[a] Data from ref 15. [b] Out of the potential window.

Similar to the reduction of 2, the reduction of 4a and 4b was performed to obtain the isophlorins [3a]2− and [3b]2−. The treatment of 4a and 4b with hydrazine monohydrate in DMSO resulted in a rapid color change from brown to reddish-purple, suggesting the formation of the corresponding isophlorin (Figure S5). However, the 1H NMR spectrum of the reduced product of 4a and NH4N2H2·H2O in [D2]DMSO was unclear (Figure S2b). In contrast, the 1H NMR spectrum of the reduced product of 4b (Figure 2) indicated that the antiaromatic isophlorin dianion [3b]2− was the sole product. A sharp signal for β protons was observed at 4.99 ppm, which was considerably upfield compared to that of 4b and comparable to that of [1]2−. Moreover, this signal was observed as a doublet with a small J value (1.7 Hz) owing to long-range coupling with the NH protons (Figure S3). A broad NH signal was observed at 16 ppm, and the integral ratio between the NH and β proton signals was 1:2. These results indicate that two NH protons were present in the product and were located on the nitrogen atoms of the unsubstituted pyrrole rings.

![Scheme 1. Redox transformations between 18π aromatic β-tetracyanoporphyrins and the corresponding 20π antiaromatic isophlorins.](image)

![Figure 2. 1H NMR (500 MHz) spectra of (a) 4b in CDCl3 and (b) [3b]2− generated by in situ reduction using NH4N2H2·H2O in [D2]DMSO.](image)

The unclear 1H NMR spectrum of the reduced product of 4a may be owing to the incomplete formation of [3a]2−, and the 19 π radical may exist in the solution as an equilibrium mixture.
Nonetheless, the formation of [3a]$^{2-}$ was accomplished using neat NH$_4$H$_2$O or ND$_3$:D$_2$O as solvents, as confirmed by $^1$H NMR analysis (Figure S2c).

The UV-vis/near-infrared (NIR) spectra of [3b]$^{2-}$ in DMSO/NH$_3$NH$_2$·H$_2$O (Figure 3) were similar to those of the previously reported dithia analog [1]$^{2-}$, with two absorption bands around 420 and 580 nm and a weak and broad absorption band in the 700–1100 nm region. Time-dependent density functional theory (TDDFT) calculations suggested that these absorption bands could be assigned to S$_2$$\rightarrow$S$_1$ (HOMO$\rightarrow$LUMO), S$_3$$\rightarrow$S$_4$ (HOMO$\rightarrow$LUMO+1), and S$_2$$\rightarrow$S$_2$ (HOMO–1$\rightarrow$LUMO) (Tables S2 and S3). Notably, the reduced product of 4a also afforded a similar spectrum to that of [3b]$^{2-}$ under the same conditions (Figure S5a) despite the incomplete formation of [3a]$^{2-}$ as suggested by $^1$H NMR analysis (Figure S2b). These results indicate that the redox interconversion is preferential towards the formation of the target product [3a]$^{2-}$; however, the equilibrium of [3a]$^{2-}$ with a small amount of incompletely reduced radical species causes significant broadening of signals in the $^1$H NMR spectrum.

![Figure 3](image-url) UV-vis/NIR absorption spectra of 4b in CHCl$_3$ (black) and [3b]$^{2-}$ in DMSO in the presence of NH$_3$NH$_2$·H$_2$O (1%) (red). The dashed line was magnified 10 times.

Similar to the oxidation of [1]$^{2-}$ to 2, [3a]$^{2-}$ and [3b]$^{2-}$ can undergo oxidation and transform into porphyrins 4a and 4b, respectively. During the attempted extraction of [3]$^{2-}$ in a DMSO/water solution by CHCl$_3$, [3]$^{2-}$ underwent oxidation by air to afford 4. This was evidenced by $^1$H NMR (Figures S2 and S4) and UV-vis/NIR (Figure S5) analyses.

Single crystals of the tetraphenylphosphonium (PPh$_4^+$) salts of isophlorins [3a]$^{2-}$ and [3b]$^{2-}$ were obtained by crystallization in a methanol solution of PPh$_4$Br. X-ray diffraction measurements revealed the molecular structures of [3a](PPh$_4$)$_2$ and [3b](PPh$_4$)$_2$ (Figure 4). The differential Fourier ([Fo$|$Fc]) map indicated that the two NH protons were located on the nitrogen atoms of the unsubstituted pyrrole rings. This result was consistent with $^1$H NMR analyses. Both [3a]$^{2-}$ and [3b]$^{2-}$ crystals exhibited small mean plane deviation values (0.13 and 0.02, respectively) (Table 2 and Figure S1), which were smaller than those for [1]$^{2-}$ (0.17), indicating that [3a]$^{2-}$ and [3b]$^{2-}$ have nearly planar conformations. Selected bond lengths are shown in Figure 5. The harmonic oscillator model of aromaticity (HOMA)$^{29,33}$ values of the crystal structures of [3a]$^{2-}$ and [3b]$^{2-}$ (Table 2) were within the range of typical antiaromatic porphyrinoids. The HOMA values of [3a]$^{2-}$ and [3b]$^{2-}$ for pathway A were smaller than those for pathway B, whereas the HOMA values of [1]$^{2-}$ for pathways A and B were comparable.

![Figure 4](image-url) Thermal ellipsoid representations (50% probability level) of the crystal structure of (a) [3a](PPh$_4$)$_2$ and (b) [3b](PPh$_4$)$_2$. PPh$_4$ cation and solvated molecules were omitted for clarity. C = gray, H = white, N = blue, and F = yellow.

![Figure 5](image-url) Selected bond lengths (Å) from the crystal structures of (a) [3a](PPh$_4$)$_2$ and (b) [3b](PPh$_4$)$_2$. 

![Figure 6](image-url)
Table 2. Mean plane deviation (mpd)[34] and harmonic oscillator model of aromaticity (HOMA) values for the crystal structures of [3a][PPh₄]₂, [3b][PPh₄]₂, and [1][PPh₄]²[35].

<table>
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<tr>
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<th>[3a][PPh₄]₂</th>
<th>[3b][PPh₄]₂</th>
<th>[1][PPh₄]₂</th>
</tr>
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<tr>
<td>mpd (Å)</td>
<td>0.13</td>
<td>0.02</td>
<td>0.17</td>
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<tr>
<td>HOMA(A)[36]</td>
<td>0.325</td>
<td>0.535</td>
<td>0.501</td>
</tr>
<tr>
<td>HOMA(B)[36]</td>
<td>0.545</td>
<td>0.652</td>
<td>0.525</td>
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The bond order of the cyanogroups upon reduction of 4 to [3]²⁻, evidenced by the crystal structure and IR spectra, was in agreement with that of a previously reported reduction of 2 to [1]²⁻.[15] The CN bond lengths of the cyanogroups in [3]²⁻ were longer than those in 4a[36] (Figure 5). The CN stretching peaks in the IR spectra of 4b and [3b]²⁻ were at 2222 and 2173 cm⁻¹, respectively, indicating a 49 cm⁻¹ shift in the peak (Figure S7). This result is attributed to the considerable contribution of the nonaromatic quinoidal resonance structures for [3]²⁻.[15]

The anisotropy of the induced current density (AICD)[31] and the nucleus-independent chemical shift (NICS)[32,33] of [3a]²⁻ also confirm its antiaromatic character. The AICD plot for [3a]²⁻ revealed a counterclockwise ring current, as expected for antiaromatic π-systems (Figure 6). The contribution of the Cα,Cγ,Cγ atoms to the ring current was evidently small and that of nitrogen atoms was dominant. These results, along with the obtained HOMA values, suggest that conjugation pathway B (shown in Table 2) was more dominant than pathway A for both [3a]²⁻ and [3b]²⁻, whereas the contributions of pathways A and B were comparable for [1]²⁻. The NICS(0) values of [3a]²⁻ are listed in Table 3, which were comparable to those of [1]²⁻. These results suggest a similar antiaromatic character for [3a]²⁻ and [1]²⁻.

![Figure 6. Anisotropy of the induced current density (AICD) plot for [3a]²⁻ (isosurface value: 0.03).](image)

Table 3. Nucleus-independent chemical shift (NICS(0)) HF/6-311+G**//B3LYP/6-31+G** values for [3a][X = NH] and [1][X = S][36]

<table>
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<th>a</th>
<th>b</th>
<th>c</th>
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<tbody>
<tr>
<td>[3a]²⁻</td>
<td>4</td>
<td>2</td>
<td>-1</td>
<td>-2</td>
</tr>
<tr>
<td>[1]²⁻</td>
<td>6</td>
<td>5</td>
<td>-1</td>
<td>-1</td>
</tr>
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</table>

[a] All are NICSzz values. The values in parentheses are NICSxx values.

Conclusions

Free-base β-tetracyanoporphyrins are readily reduced by hydrazine under atmospheric conditions to afford β-tetracyanoisophlorin dianions with 20π antiaromatic character. Their structures were unambiguously confirmed by X-ray diffraction. The cyanogroups as the peripheral substituents on the isophlorin macrocycle and the electron-withdrawing substituents on the phenyl rings stabilized the reduced isophlorin. These porphyrin/isophlorin transformations are reversible. To the best of our knowledge, these isophlorins are the first antiaromatic isophlorins prepared without metallation or core modifications. We are currently synthesizing the metal complexes of these isophlorins to gain further insight into their structure–property relationships and to elucidate the properties of the obtained isophlorins.

Experimental Section

Instrumentation and Materials

1,3-Dimethyl-2-imidazolidinone (DMI) was distilled using CaH₂. All other chemicals were of reagent grade and were used without any further purification unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F₂54 plates. Column chromatography was performed using silica gel 60N (Kanto Chemical, spherical, neutral, 63–210 μm). All NMR spectral data were recorded on a JEOL ECA-500 (500 MHz) spectrometer at an ambient temperature (25 °C). Tetramethylsilane was used as the internal standard for ¹H NMR spectra, whereas CDCl₃ and [D₆]DMSO (δ = 77.0 and 39.5 ppm) were used as internal standards for ¹³C NMR spectra. High resolution electrospray ionization mass spectrometry (ESI HRMS) data were obtained using a Thermo Fisher Scientific Q-Exactive mass spectrometer. UV-vis/NIR spectral data were recorded on a Shimadzu UV-3150 spectrometer or HITACHI U-4100 spectrometer. IR spectral data were recorded on a JASCO FTIR 6100 spectrometer equipped with an attenuated total reflection
(ATR) unit. The melting points were determined using a Yanaco MP-S3 melting point apparatus. Cyclic and differential pulse voltammetry measurements were performed using an ALS 630E electrochemical analyzer in N2-saturated dry CH2Cl2 or DMSO solutions containing 0.1 M tetrabutylammonium hexafluorophosphate as a supporting electrolyte at ambient temperature (298 K). A conventional three-electrode cell was used with a glassy carbon working electrode, a platinum wire counter electrode, and a silver wire pseudo-reference electrode. Ferrocene was used as the internal standard in all the electrochemical experiments, and the reported potentials were corrected for the Fe/Fc+ couple.

Reduction of 4b and isolation of [3b][PPh4]2
To a solution of 4b in DMSO (or [D6]DMSO), a few drops of NH4H2N2H2·H2O were added until the color of the solution changed rapidly to reddish-purple. 1H NMR and UV-vis/NIR analyses revealed quantitative formation of [3a][PF6]−, potentially as a hydrazinium salt.

For the isolation of [3b][PF6]−, 4b (20.8 mg, 21.1 μmol) was dissolved in 1.25 mL of NH4H2N2H2·H2O/DMSO (1:4 v/v). A saturated solution of tetraphenylphosphonium bromide in methanol was gently poured into the resulting solution and left to stand for 1 day. Then, the precipitated microcrystals of [3b][PPh4]2 were collected by filtration and dried under vacuum to afford [3b][PPh4]2 as brown microcrystals (20.4 mg, 12.2 μmol, 58%). M.p. (PPh4 salt): >300 °C; 1H NMR (hydrazinium salt, 500 MHz, [D6]DMSO + 1% NH4H2N2H2·H2O): δ = 16.49 (s, 2H), 7.50 (d, J = 8.1 Hz, 8H), 7.09 (d, J = 7.9 Hz, 8H), 4.99 ppm (d, J = 1.7 Hz, 4H); 13C NMR (hydrazinium salt, 125 MHz, [D6]DMSO + 1% NH4H2N2H2·H2O): δ = 154.1 (Cq), 144.9 (Cq), 144.4 (Cq), 131.8 (CH), 133.5 (CH), 127.1 (q), 127.9 (CH), 126.6 (CH), 125.5 (q, 125.1 (CH), 124.5 (q), 123.8 (CH), 115.9 (Cq), 109.4 (Cq), 97.1 ppm (Cq); IR (PPh4 salt, ATR): ν̃ = 3401, 1367, 1313, 1300, 1298, 1161, 1088, 1066, 958, 950, 857, 835, 807, 779, 753, 720, 689, 669 cm−1; UV-Vis/NIR (hydrazinium salt, DMSO + 1% NH4H2N2H2·H2O): δmax (Log ε) = 353 (shoulder, 4.36), 376 (4.47), 405 (4.66), 428 (4.84), 499 (shoulder, 4.27), 537 (4.64), 581 (4.84), 728 (shoulder, 3.13), 824 nm (shoulder, 2.94); Elemental analysis (PPh4 salt) calc (%) for C60H56N2P2F2I2O: C 71.34; H 3.83; N 6.66; found: C 71.50; H 3.87; N 6.78.

X-ray crystal structure determinations
Single crystals of [3a][PPh4]2 and [3b][PPh4]2 suitable for X-ray diffraction study were obtained by slow diffusion of tetraphenylphosphonium bromide in methanol to a solution of [3a][PF6]− and [3b][PF6]− (just reduced by NH4H2N2H2·H2O) in methanol. Single-crystal X-ray diffraction data were collected on a Rigaku XtaLAB Synergy Custom Diffractometer using multilayer mirror monochromated Mo-Kα radiation (λ = 0.71073 Å) by the ω scan mode. The crystal was cooled by a stream of cold N2 gas. Collection, indexing, peak integration, cell refinement, and scaling of the diffraction data were performed using CrysalisPro 1.171.40.75a software (Rigaku OD, 2020). The data were corrected for Lorentz and polarization effects, and empirical absorption correction was applied. The structures were solved using SHELXTL[34] programs and refined by full-matrix least-squares calculations on F2 (SHELXL).[35] All non-hydrogen atoms were modeled anisotropically. All hydrogen atoms were placed in idealized positions and refined using a riding model [Uiso(H) = 1.2Uiso(C)].

The crystallographic data are summarized in Table S1. CCDC 2163554 ([3a][PPh4]2), and 2163553 ([3b][PPh4]2) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

DFT calculations
All calculations except for AICD were carried out using the Gaussian 16 program package (Revision C.01).[36] Geometries of all models were optimized by the DFT method at the B3LYP/6-31+G(d,p) level. Frequency calculations were performed to confirm that the optimized geometries were not in the saddle points but stable points. Charge distribution was calculated by NBO6.

Nucleus-independent chemical shifts (NICS) values were calculated at the GIAO-HF/6-311+G(d,p) level. The anisotropy of the current-induced density (ACID) calculations were performed using the Gaussian 09 program package (Revision E.01)[37] at the B3LYP/6-31+G(d,p) level using the CSGT method and analyzed using the AICD 2.0.0 program.

Acknowledgments
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Keywords: antiaromaticity • redox chemistry • isophorons • structure elucidation • porphyrinoids

Conflict of Interest: The authors have no conflicts of interest to declare.

References


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