Macrocycles

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Controlled Core-Modification of a Porphyrin into an Antiaromatic Isophlorin

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Abstract: *Partial core-modification of a porphyrin can be employed to synthesize the 20π antiaromatic isophlorin. Unlike the tetra-, tri-, and dipyrrole derivatives of a porphyrin, a monopyrrole porphyrin exhibits antiaromatic characteristics. It undergoes a two-electron reversible ring oxidation to yield the 18π aromatic dication. ^{1}H NMR analysis provides distinct evidence of the altered electronic characteristics through typical paratropic and diatropic ring current effects for the 4n and the (4n + 2) π-electron systems, respectively.*

Replacing one or two pyrrole units of a porphyrin (**1;** Figure 1) with other heterocycles such as furan or thiophene or selenophene is a well-established strategy to realize core-modified porphyrins (**2** and **3**).[1] Donor atoms such as O or S or Se in core-modified porphyrins alter the ligating properties while sustaining the structural features and electronic properties of the parent macrocycle. However, replacement of all four pyrroles by other heterocyclic units in a porphyrin yields antiaromatic 20π isophlorins (**4** and **5**) with similar structural characteristics but altered electronic properties.[2,3] A significant difference between porphyrin and isophlorin is observed in their reactivity towards protic acids. 20π isophlorins are characteristic organic molecules with pseudometal properties.[4] The compounds **4** and **5** undergo two-electron ring oxidation to yield the 18π aromatic dication. In contrast, 18π core-modified porphyrins exhibit nonredox protonation under similar reaction conditions. Since pyrrolic isophlorins are perceived to be unstable and nonplanar in nature,[5] the furan- and thiophene-derived macrocycles (**4** and **5**) represent the only stable and planar derivatives of the hypothetical 20π isophlorin **6**. In this regard, Woodward's hypothesis[6] of the unstable nature for the tetrapyrrolic system **6** stems from the pyrrole's ability to delocalize the π electrons through the nitrogen atoms. Hence a pyrrole-based 20π isophlorin remains a synthetic challenge to date.

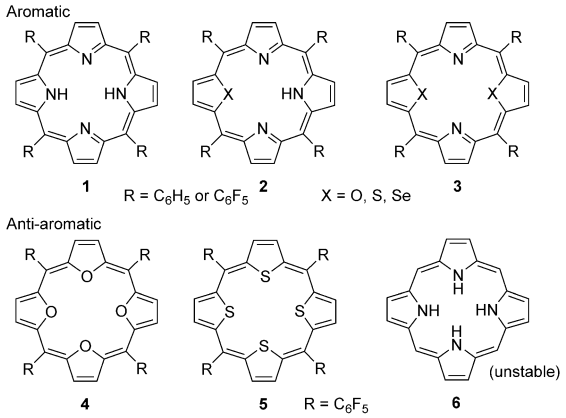
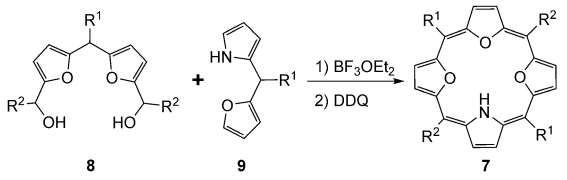


Figure 1. Chemical structures of the 18π porphyrin **1**, 18π core-modified porphyrins **2** and **3**, stable 20π tetraoxa- and tetrathiaisophlorins **4** and **5**, respectively, and the tetrapyrrolic 20π isophlorin **6**.

There have been sustained efforts towards the synthesis of core-modified porphyrins,[1,7] except for the synthesis of a monopyrrole derivative. The first inspection of the monopyrrole macrocycle 5,15-bis(phenyl)-10,20-bis(pentafluorophenyl)-21-aza-22,23,24-trioxa isophlorin (**7**) clearly indicates conjugation only across the carbon atoms, and is thus in stark contrast to the typical core-modified porphyrins. We perceived it as a case for an interesting investigation in the pursuit of a stable pyrrole derivative of the antiaromatic 20π isophlorin. Porphyrins with either one or two nonpyrrolic units can accommodate conjugation across the nitrogen atoms of the pyrrole. However, oxidizing the lone pyrrole nitrogen atom of **7** into an imine can only disrupt the conjugated pathway for a neutral macrocycle. Herein, we report the subtle control over core modification of a porphyrin to synthesize the first stable pyrrole-based antiaromatic 20π isophlorin along with the elucidation of its structural, electronic, and redox properties.

The synthesis of core-modified isophlorin **7** was achieved by a MacDonald-type condensation of the *meso*-phenyldifuran carbinol **8** with the modified dipyrromethane **9** (Scheme 1). An equimolar ratio of the reactants was stirred in dichloromethane under dark and inert conditions. The reaction was catalyzed by the addition of boron trifluoride ethereate and stirred for an hour. DDQ was added to the reaction mixture with continued stirring for two hours in a flask open to the atmosphere. The reaction mixture was



Scheme 1. Synthesis of the monopyrrole isophlorin **7**. $R^1 = C_6H_5$, $R^2 = C_6F_5$. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

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passed through a basic alumina column using dichloromethane/*n*-hexane as the eluent to isolate **7** as a yellowish-green solid in 10% yields.

This macrocycle was found to be stable under ambient conditions. It displayed an *m*/*z* value of 799.1194 (Cald. for $C_{44}H_{19}F_{10}NO_3$; 799.1205) in its ESI-TOF high-resolution mass spectrum (see the Supporting Information). The ^{1}H NMR analysis of **7** did not result in a well-resolved spectrum at room temperature. Interestingly, this macrocycle exhibited weak paramagnetic behavior in the solution state (see the Supporting Information) as confirmed from ESR spectroscopy. This behavior could be attributed to a possible spin contamination in the solution state leading to a biradical[8] system at room temperature. However, a typical paratropic ring current effect was observed in its ^{1}H NMR spectrum at 213 K (Figure 2). Overall, eight doublets, corresponding to the β-protons of the furan and pyrrole, were observed in the region between $\delta = 3$–1.8 ppm.

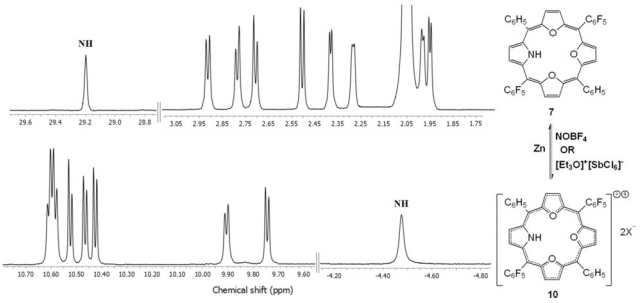


Figure 2. Partial ^{1}H NMR spectrum of **7** [recorded in $(CD_3)_2CO$ at 213 K] and **10** (recorded in CD_3CN at 298 K). In this spectrum X^- corresponds to the counteranion $[BF_4]^-$.

The ^{1}H-^{1}H COSY spectrum confirmed four sets of correlations amongst these eight doublets (see the Supporting Information). In addition to these signals a broad singlet was observed at $\delta = 29.2$ ppm corresponding to the pyrrole NH in the core of the 20π macrocycle. This assignment was further established by deuterium exchange upon the addition of D_2O (see the Supporting Information). These chemical-shift values signified strong paratropic ring current effects attributed to antiaromatic character marked by typical upfield shifts for the protons on the periphery of the macrocycle, and unusually large downfield signals for the protons at the center of the macrocycle. The structure of this macrocycle was unambiguously determined by single-crystal X-ray diffraction studies. It displayed a planar conformation for the antiaromatic 20π isophlorin (Figure 3). All the heteroatoms are pointed towards the center of the macrocycle, while the *meso*-phenyl rings are at a near-orthogonal orientation with respect to the mean macrocyclic plane. The unusual low-field resonance for the pyrrole NH at the center of the macrocycle further supported the strong paratropic ring current effect because of the delocalization of 20π electrons throughout the macrocycle. In addition to the two different *meso* substituents, the lone pyrrole reduces the symmetry of the macrocycle, which was supported by the eight distinct doublets for the protons on the four heterocyclic rings.

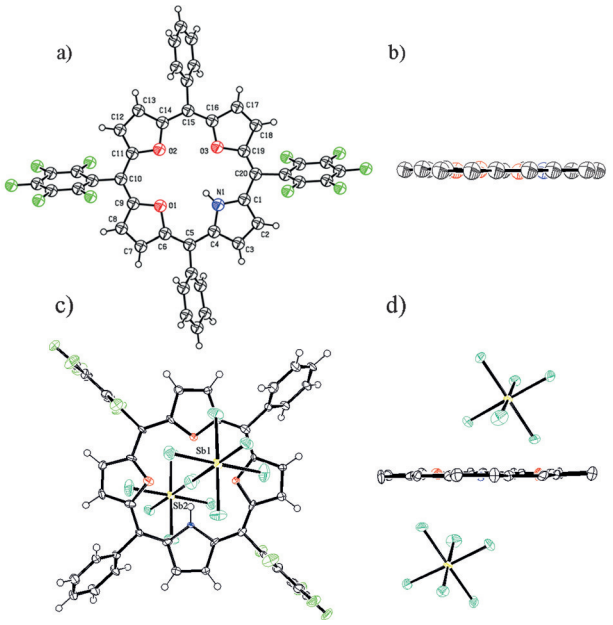
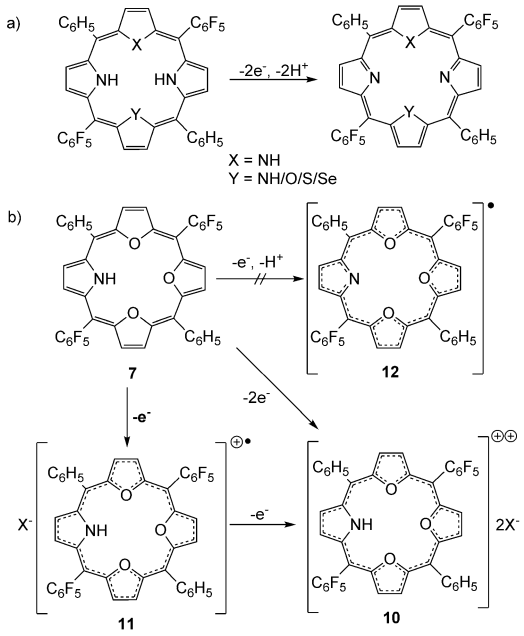


Figure 3. ORTEP plot of **7** and **10** (with two $[SbCl_6]^-$ counteranions).[12] a,c) top view and b,d) side view. Solvent molecules, *meso* substituents and hydrogen atoms (in side view) are omitted for clarity. Thermal ellipsoids shown at 50% probability.

We were more curious to explore the redox properties of this stable pyrrole-based antiaromatic isophlorin. While the oxidation of aromatic systems is known to yield a radical cation, antiaromatic macrocycles tend to undergo two-electron oxidation to the corresponding dication species.[9] As observed earlier,[1] the pyrrole NH is prone to oxidation so as to accommodate the nitrogen atom of the pyrrole in the conjugation (Scheme 2). It can be envisaged that the oxidation of **7** can yield either the 18π radical dication **12** or the 19π radical cation **11**. From our earlier reports, we have observed that salts such as $[Et_3O]^+[SbCl_6]^-$[10] and $[NO]^+[BF_4]^-$ are excellent oxidizing agents for antiaromatic systems.[9a] $[NO]^+[BF_4]^-$ was added to a solution of **7** in dichloromethane and stirred for ten minutes under nitrogen atmosphere. The solution displayed a subtle change from a yellowish-green to pink color upon oxidation. Pink-colored crystals were obtained in quantitative yield upon the evaporation of the solvent. The ESI-TOF high-resolution mass spectrum of these crystals displayed an *m*/*z* value of 399.5598 (Cald. for $[C_{44}H_{19}F_{10}NO_3]^{2+}$: 399.5602) corresponding to the dication of the macrocycle. Interestingly, this value suggested an oxidative process without altering the chemical composition of the macrocycle. The oxidation of the macrocycle by two electrons suggested the formation of an 18π aromatic dication. The dication **10** displayed a well-resolved ^{1}H NMR spectrum in deuterated acetonitrile at room temperature. Even though it displayed the same number of signals, the chemical-shift values for the protons of the heterocyclic rings varied significantly with respect to the neutral molecule **7**. In stark contrast to the upfield signals for **7**, the dication **10** displayed eight signals for the heterocyclic rings in the low-



Scheme 2. a) Oxidation of pyrroles if one or two heterocyclic rings are incorporated in the porphyrin framework. b) Stepwise one-electron oxidation of **7** to **10** when three pyrroles are replaced by furan. X^- corresponds to the counteranion ($[SbCl_6]^-$ or $[BF_4]^-$).

field region between $\delta = 10.6$ and 9.6 ppm (Figure 2). All the signals resonated as doublets and their multiplicity was confirmed from the ^1H–^1H COSY spectrum (see the Supporting Information). The appearance of the NH at a high field substantiated the aromatic character of the macrocycle as observed in mono-oxa/thia porphyrins. More importantly, the inner NH signal for the pyrrole ring displayed an incredible shift by nearly $\Delta\delta = 34$ ppm from $\delta = +29.2$ ppm in **7** to $\delta = -4.6$ ppm in **10**. This value is perhaps the largest difference for the NH signal amongst all the known core-modified porphyrins. The formation of this dication can be envisaged through two one-electron oxidations, with the intermediate **11** (Scheme 2), rather than the 19π radical **12**.

Such a mechanism provides evidence in favor of resonance stabilization for an antiaromatic isophlorin even in the presence of pyrrole rings. This structure represents the first example for oxidation of a stable pyrrole derivative of a 20π isophlorin to an 18π dication without deprotonating the pyrrole NH. Even though such a two-electron oxidation is known for other 20π isophlorins, both states for any given isophlorin could not be characterized comprehensively, as only one of them was found to be stable under ambient conditions. The β-substituted thia/oxa/selena isophlorins were found to be stable as porphyrin dications,[2] whereas the tetraphenyl tetraoxaisophlorin was found to resist oxidation to the corresponding 18π dication.[3a] The structure of **10** was unambiguously determined through single-crystal X-ray diffraction studies (Figure 3c,d). The macrocycle was found to sustain a planar conformation. Its dicationic behavior was confirmed by the presence of two $[SbCl_6]^-$ counter anions, one above and one below the plane of the macrocycle. More significant was the presence of NH to validate the two-electron oxidation through an intermediate 19π cation radical (Scheme 2). We also employed DFT calculations to estimate the nucleus independent chemical shift (NICS)[11] value for both **7** and **10**. The antiaromatic **7** was found to have a large positive NICS(0) value of $\delta = +27.6$ ppm, while **10** corresponded to a negative value of $\delta = -13.8$ ppm. These values are in complete agreement for the oxidation of **7** to its corresponding aromatic dication **10**.

Electronic absorption spectroscopy provided further insight into the optical properties for these systems (Figure 4). The neutral macrocycle **7** displayed a relatively

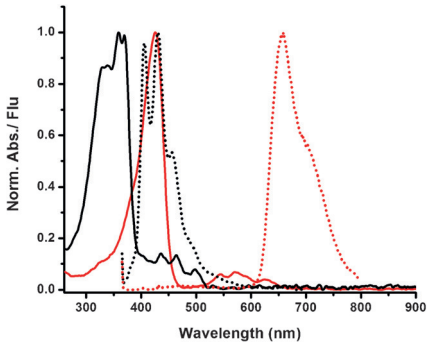


Figure 4. Normalized electronic absorption spectra (solid line) and emission spectra (dotted line) of **7** (black) and **10** (red) recorded in dichloromethane at room temperature.

intense and split absorption for the Soret-like band at $\lambda =$ 359 nm ($\varepsilon = 108\,700$) and 369 nm (10 700) with three weak absorptions in the region between $\lambda = 430$–500 nm. Upon oxidation, the Soret-like absorptions for **10** were found to be more intense and red-shifted as a split band at $\lambda = 426$ nm (223 550), with weak bands in the region between $\lambda = 540$ to 625 nm. The change in the absorption is found to be similar to that observed for the 20π tetraoxaisophlorins, thus supporting the two-electron oxidation to the aromatic 18π dication. It was also observed that **7** exhibited significant emission at $\lambda =$ 410 and 434 nm when excited either at $\lambda = 360$ or 370 nm, with a quantum yield (Φ) of 2.2% in dichloromethane, and **10** displayed a weak ($\Phi = 1.2$) but strong red-shifted emission at $\lambda = 650$ nm, which is very much similar to that observed for tetraphenyl porphyrins. Cyclic voltammetry studies revealed two reversible reductions and oxidations, with a Δ_{redox} of 1.18 V. More significantly, **7** displayed a relatively lower oxidation potential compared to that of the tetraphenyl porphyrin and *meso*-tetra(pentafluorophenyl)teraoxaisophlorin.[3] These lower oxidation values were found to be quasireversible in nature. In an attempt to reduce the dication to the 20π antiaromatic isophlorin, **10** was treated with reducing agents such as $FeCl_2$ and sodium. Neither of them yielded **7**. However, it could be reduced to **7** by the addition of zinc dust. This change was observed by electronic absorption spectroscopy. Based on our earlier reports,[9] we suspect that the fluorines of the pentafluorophenyl groups might interfere with sodium metal in the reduction mechanism. It was also observed that the dication of $[SbCl_6]^-$ undergoes a quick reduction in comparison to the $[BF_4]^-$ salt.

In summary, we have synthesized the first stable pyrrole derivative of the 20π antiaromatic isophlorin. Now, partial core modification of porphyrin can be employed as a convenient synthetic strategy to realize various other isomers of this isophlorin. The two-electron oxidation of the antiaromatic macrocycle to the aromatic dication has been unambiguously proven through experimental and computational studies. The compound **7** represents a macrocycle with a structural resemblance to the parent tetrapyrrole isophlorin, **6**, which undergoes a reversible two-electron oxidation. The chemical reversibility of the two-electron oxidation of an isophlorin to a porphyrin has been established for the first time. Further studies are in progress to assess the ability of **7** as an antiaromatic ligand to complex metal ions.

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[12] CCDC 1443655 (**7**) and 1445017 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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