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Porphyrinoids

N-Confused and N-Fused *meso*-Aryl Sapphyrins**

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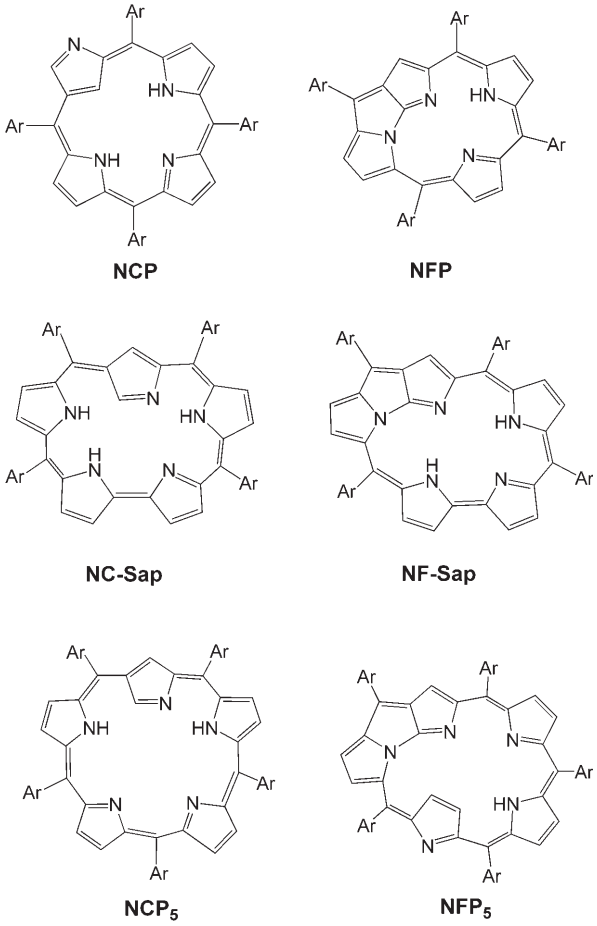
Mutation and selection are fundamental processes in the evolution of biosystems.[1] The generation of artificial mutants is a major strategy in biological science to enable properties of biomolecules to be exploited that have remained hidden under the natural conditions.[2] By using this as a guiding principle, we have been studying porphyrin analogues, especially the porphyrin mutants, namely N-confused porphyrin (**NCP**)[3] and other confused porphyrinoids,[4] including expanded porphyrins.[5] In particular, we have been trying to use a strategy to direct mutation (or evolution) to introduce one or more confused (that is, α,β′-linked) pyrrole ring(s) into the macrocycles. We have called this the confusion approach,[4a] and have aimed to create novel porphyrinoids that exhibit unique properties unseen in the standard porphyrins.

The mutant **NCP**, with a tetrapyrrolic framework, is less stable, both thermally and photochemically, than ordinary porphyrin. However, this instability turns to an advantage when **NCP** transforms into another species, such as N-fused porphyrin (**NFP**).[6] In the pentapyrrolic system, N-confused *meso*-aryl pentaphyrin (**NCP_5**) is unstable and exists as N-fused pentaphyrin (**NFP_5**) or doubly N-fused pentaphyrin.[7] In contrast, in the hexaphyrin system, the doubly N-confused dioxohexaphyrins are rather stable and can even be derived from standard hexaphyrins,[8] while the corresponding fused species have not yet been found. Here the question arises as to the relationship between the fate of the confused pyrrole ring and the size of the macrocycles, especially in the sapphyrin system, an intermediate compound between porphyrins and pentaphyrins, and perhaps the oldest member of the expanded porphyrin family.[9] Previously, we and the Chandrashekar research group reported diselena and dithia derivatives of N-confused *meso*-aryl sapphyrin;[10] however, the genuine *meso*-aryl N-confused sapphyrin remains an important synthetic target to clarify the intrinsic role of the confused pyrrole unit in the pentapyrrolic macrocycle. Herein



we report the first synthesis of N-confused all-aza-*meso*-aryl sapphyrin (**NC-Sap**) and N-fused sapphyrin (**NF-Sap**), and demonstrate the utility of the confusion approach in synthesizing porphyrin analogues.

The synthesis of N-confused 5,10,15,20-tetrakis(pentafluorophenyl)sapphyrin (**1**) was successfully achieved by both [5+0] and [3+2] routes from appropriate precursors (Scheme 1).[11] Briefly, N-confused pentapyrromethane **3** bearing four pentafluorophenyl groups was treated with NH_4Cl in acetonitrile at room temperature for 3 h, followed by oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), which resulted in the formation of **1** and N-fused 5,10,15,20-tetrakis(pentafluorophenyl)sapphyrin (**2**) as a side product. Purification of the crude reaction mixture by column chromatography on silica gel afforded **1** as a green solid in 6% yield and **2** as a red solid in less than 2% yield. Alternatively, **1** could also be prepared in 6% yield by the condensation between the biscarbinol derivative of N-confused tripyrromethane[12] **4** and 2,2-bipyrrole (**5**) in dichloromethane using trifluoroacetic acid (TFA) as a catalyst, followed by oxidation

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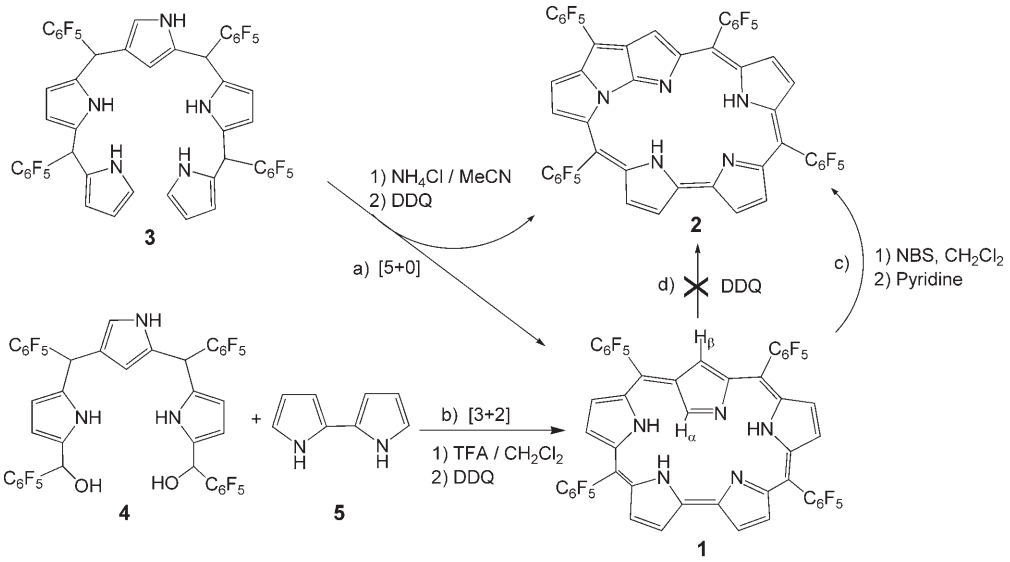


Scheme 1. The [5+0] and [3+2] routes for the synthesis of N-confused *meso*-aryl and N-fused sapphyrins (**1**, **2**, respectively).

with DDQ. The standard type of sapphyrin with four pentafluorophenyl groups was also prepared by the [3+2] route for comparison.[11] The MALDI-TOF mass spectrum of **1** shows the signal for the M^+ ion at m/z 1039, thus indicating the presence of a pentapyrrolic macrocycle. The signal for the M^+ ion for **2** appears at m/z 1037, which is two mass units less, thus reflecting the ring fusion. The structures of **1** and **2** were fully characterized by ^{1}H NMR spectroscopy (see below).

The formation of **2** during the synthesis of **1** clearly shows that the ring fusion is a usual phenomenon among N-confused pentapyrrolic macrocycles.[7,8] Our synthetic studies show that **2** can be formed only as a side product when **1** is synthesized by a [5+0] route (path a). We found that **2** can also be made directly from **1** by following a similar strategy as used for the synthesis of **NFP**[6] (path c). Although the exact mechanism of ring fusion is still not known, a plausible explanation could be that the ring-fusion step occurs during the oxidation process of a sapphyrinogen intermediate through the nucleophilic attack of the adjacent pyrrolic N atom on the α-position of the inverted N-confused pyrrole unit. The occurrence of the ring-fusion step after oxidation of a confused sapphyrinogen is ruled out, since our efforts to make **2** by direct oxidation of **1** with DDQ were not successful (path d). Furthermore, the reaction conditions may not be favorable for ring fusion, since **2** was not obtained from a [3+2] route (path b).

The inverted structure of **1** in solution was inferred by the ^{1}H NMR chemical shifts of the signal for the inner CH (H_α) proton of the confused pyrrole ring at $\delta = 1.64$ ppm, signals for the three NH protons at $\delta = 0.78$, -0.92, and -2.48 ppm, and a signal for the outer CH (H_β) proton at $\delta = 10.24$ ppm (CD_2Cl_2, 183 K). The location of the three NH protons is not straightforward, but they are on the ordinary pyrrole moieties and not on the confused pyrrole ring. This is evident because the signal corresponding to the H_α proton was not affected by the addition of D_2O, a process that usually results in a smaller scalar coupling with the neighboring NH proton. The most probable tautomeric form derived from DFT calculations is shown in Scheme 1.[11] This tautomeric form is different from that of the previously reported dithiasapphyrin, which takes a less aromatic form.[5,10] For **1**, in accordance with the tautomeric structure above, a 22π aromatic system is indicated by the difference in the chemical shifts between the outer and inner protons ($\Delta\delta = 12.6$ ppm) in **1**, which is slightly less than that of the all-aza-*meso*-tetrakis(pentafluorophenyl)sapphyrin ($\Delta\delta = 14.8$ ppm),[11] but much higher than that of N-confused dithiasapphyrin ($\Delta\delta = 7.06$ ppm)[10] and the recently reported inverted β-alkylated sapphyrin ($\Delta\delta = 4.79$ ppm).[13] Reflecting the aromatic nature of **1**, two intense bands are observed in the Soret region at 395 and 497 nm in the absorption spectrum, and four small Q-type bands are observed at 625, 679, 750, and 871 nm (Figure 1).

On the other hand, **NF-Sap** (**2**), which is a higher homologue of **NFP**, lacks the ^{1}H NMR signal for the H_α proton of the confused pyrrole ring because of the ring fusion. The chemical shifts of the peripheral protons of the

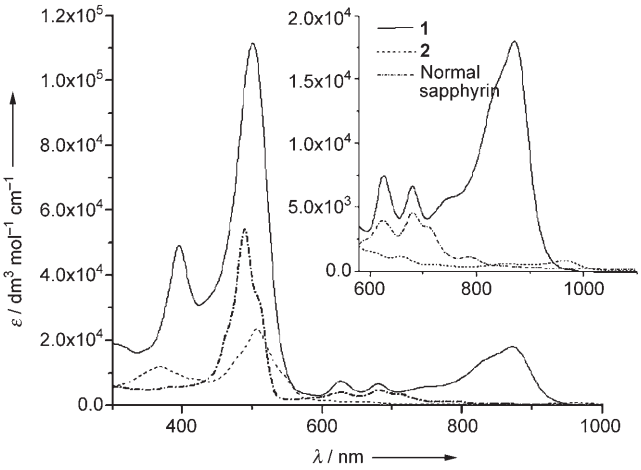


Figure 1. Absorption spectra of **1**, **2**, and *meso*-tetrakis-(pentafluorophenyl)sapphyrin in toluene.

core rings are in the range of $\delta = 7.5$ to 8.7 ppm, and the signals for the two inner NH protons appear as broad singlets at $\delta = 5.56$ and 8.30 ppm, which suggests a 22π aromaticity within the macrocycle. The large downfield shifts of the NH signals can be attributed to the presence of strong intramolecular hydrogen-bonding interactions in the cavity, where the distances between the neighboring nitrogen atoms are estimated from DFT calculations to be 2.62 and 2.92 Å (see Figure S17 in the Supporting Information). The absorption spectrum of **2** shows split Soret bands at 366 and 500 nm, and four small Q-type bands between 655 and 963 nm (Figure 1). Such long-wavelength absorption in the near-infrared region is a typical feature of N-fused porphyrinoids.[6,7]

Direct proof for the structure of **1** came from X-ray crystallographc analysis (Figure 2). Attempts to crystallize **1**

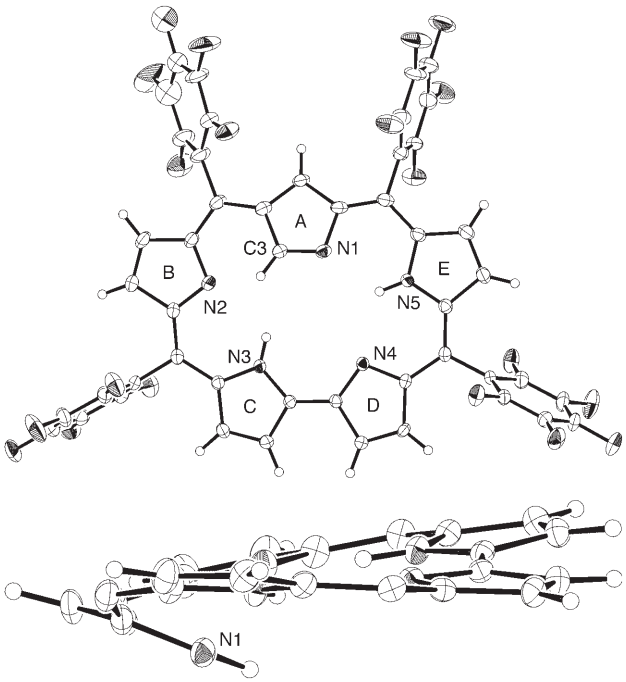


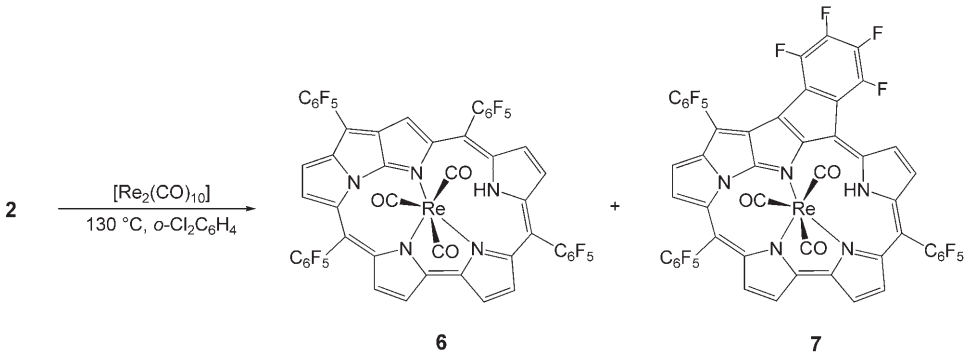
Figure 2. X-ray structures of $\mathbf{1}^-$: top: top view (the Bu_4N^+ ion and solvent molecules are not shown); bottom: side view showing the deviations of the N-confused pyrrole ring A from the plane of the macrocycle. The pentafluorophenyl groups are omitted for clarity. Thermal ellipsoids are shown at the 30% probability level.

in the presence of tetrabutylammonium fluoride resulted in an ion pair [$\mathbf{1}^-\cdot Bu_4N^+$] in the crystal, with **1** present in a deprotonated anionic form and a tetrabutylammonium ion associated as a counter cation.[14,15] In the crystal, $\mathbf{1}^-$ and Bu_4N^+ stack in an alternate fashion to form a single strand. The sapphyrin core in $\mathbf{1}^-$ is slightly distorted from a least-squares plane consisting of 29 (N1–C24) atoms (plane **I**), with a mean deviation of 0.271 Å. The confused pyrrole ring (ring A) is inverted and significantly tilted with respect to the core plane. The tilting angles (°) of the pyrrole rings (A–E) to the plane **I** are: A, 27.5; B, 4.3; C, 5.9; D, 9.6; E, 13.3. The two pyrrole rings C and E possess protonated nitrogen atoms (NH) while the other three rings (A, B, and D) contain imino-type nitrogen atoms (N).[16] The distances N1···N5, N4···N5, and N2···N3 are 2.693, 2.683, and 2.856 Å, respectively, which are within hydrogen-bonding distances.

Previously, Latos-Grażyński and co-workers reported that *meso*-tetraphenylsapphyrin takes an inverted conformation in the neutral form, but changes to a planar form (that is, with all the N atoms pointing inward) upon protonation.[9c] To see whether the ring flipping is a general property in the *meso*-aryl sapphyrin system, the protonation behavior of **1** was examined. The ^{1}H NMR spectrum of monoprotonated **NC-Sap** ($\mathbf{1}^+$), which was obtained by the addition of one equivalent of TFA in CD_2Cl_2 at 183 K, shows signals for the four inner NH and inner α-CH (H_α) protons at $\delta = -1.05$, -1.61, -2.32, -3.03, and -0.75 ppm, respectively, and the signal for the outer β-CH (H_β) proton at $\delta = 11.01$ ppm. Further addition of acid (5 equiv) afforded the diprotonated form of **NC-sap** ($\mathbf{1}^{2+}$) which shows signals for five NH protons at $\delta = 5.30$ (overlapped with CH_2Cl_2; $\delta = 5.88$ ppm in $CDCl_3$ at 223 K), -2.13, -2.56 (2H), and -3.11 ppm, and the signals for the inner CH and outer CH protons at 2.14 and 11.05 ppm, respectively. The observed NH signal at $\delta = 5.30$ ppm is assigned to that of the inverted confused pyrrole ring on the basis of the difference in the chemical shift from that of the inner CH (H_α) proton ($\Delta\delta$ = ca. 3 ppm). These data indicate that, in contrast to the standard *meso*-aryl sapphyrin, ring flipping of the confused pyrrole of **1** does not take place in the protonated states.

To gain insight into the conformation and the location of the NH atoms in **1**, DFT calculations were performed on all the tautomers in various ionic states (monoanionic, neutral, monocationic, and dicationic), but with the pentafluorophenyl groups replaced by hydrogen atoms or phenyl groups for simplicity. The most stable inverted tautomers in each ionic state and their relative energies compared to those of standard sapphyrin are shown in Figure S18 in the Supporting Information. The calculations show that **1** prefers the inverted structures except in diprotonated $\mathbf{1}^{2+}$.[17] Since the planar conformation of the skeleton in all the ionic states was found by calculations to be more stable, it appears that steric hindrance from the *meso*-aryl groups is more significant in the planar conformation than in the inverted one.[11] Furthermore, it is noteworthy that the total energy of $\mathbf{1}^-$ is lower than that of the corresponding standard sapphyrin (ΔE in kcal mol^{-1}): -1.2 (anion), $+2.6$ (neutral), $+5.0$ (monocation), $+8.3$ (dication)), which suggests that **1** is more acidic than the standard sapphyrin. As illustrated in the X-ray structure, the intramolecular hydrogen bonds of the inverted confused pyrrole ring in the core may contribute significantly to the stabilization of $\mathbf{1}^-$.

Interestingly, **NF-Sap** (**2**) undergoes further fusion during metalation. When **2** was treated with [$Re_2(CO)_{10}$] in *o*-dichlorobenzene at reflux for 12 h, the Re^I complexes **6** and **7** were obtained in yields of 7 and 55%, respectively, after column chromatography (Scheme 2). The X-ray structure of the major product **7** shows a peculiar [5.5.5.5.6] domino-fused penta-ring system, which is formed by connection between the β-carbon atom of the tricyclic ring and the *ortho* position of the *meso*-pentafluorophenyl group of **6** (Figure 3).[14] The Re center is connected to the central nitrogen atom (N1) of the fused ring and two bipyrrole nitrogen atoms (N2, N3),



Scheme 2. Formation of Re complexes **6** and **7** of **NF-Sap** derivatives.

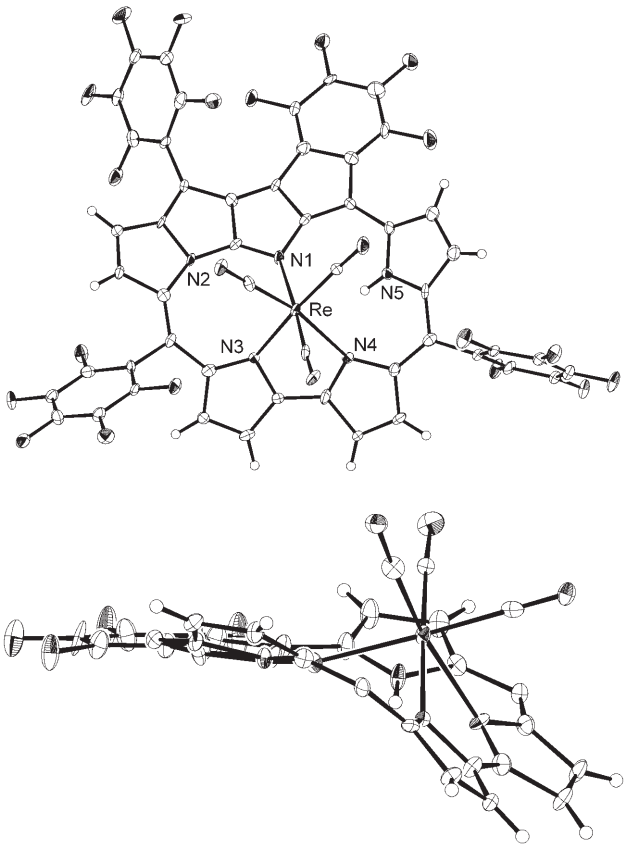


Figure 3. X-ray structure of **7**: top: top view; bottom: side view. Nonfused pentafluorophenyl groups are omitted for clarity. Thermal ellipsoids are shown at the 30% probability level.

with bond lengths of 2.285, 2.150, and 2.334 Å, respectively, which are slightly longer than those in the Re^{I} complex of **NFP** (avge: 2.13 Å).[6b,c] The effect of the extension of the π system in **7** is seen in the absorption spectrum, where broad bands appear in the Soret region at 403, 484, and 564 nm, while the edge of the Q-type bands exceeds 1300 nm in toluene.[11]

In general, when the system becomes destabilized, the perturbed system starts to gradually move to a stable state. The introduction of a confused pyrrole ring into the sapphyrin framework destabilizes the macrocycle and forces the molecule (**NC-Sap**) to undergo reaction (namely, fusion) to give **NF-Sap**. When an additional perturbation (that is, metalation) is supplied, the mutated **NF-Sap** can further transform into a domino-fused sapphyrin bearing a fused penta-ring that has novel absorption properties. In the case of N-confused porphyrinoids, the confused pyrrole ring is usually more reactive than other α,α′-linked pyrrole rings in the macrocycle because of the exposed electron-rich α (and β) positions, which are susceptible to ring fusion. On the other hand, in some cases the inverted confused pyrrole ring could stabilize the system by intramolecular hydrogen bonding, as seen in $\mathbf{1}^{-}$ and doubly N-confused dioxohexaphyrins.[8] Thus, the repeated introduction of confused rings in the macrocycles would eventually lead to the stable confused porphyrinoids, whose properties are useful. Thus, we believe our confusion approach method will become a powerful strategy to access these novel functional molecules in the near future.

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