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Synthesis and Studies of a Super-Structured Porphyrin Derivative – A Potential Building Block for C*c*O Mimic Models

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A novel porphyrin complex that contains an Fe porphyrin linked to a tridentate ligand where a Cu ion could be coordinated was synthesized. The molecule also incorporated a tyrosine mimic attached to the porphyrin ring via a urea bond and was fully characterized. We studied the action of dioxygen on several porphyrin derivatives electrochemically with a rotating ring-disk electrode.

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Introduction

Cytochrome *c* oxidase (C*c*O), a membrane-bound metalloenzyme, is a member of the heme-Cu terminal oxidase superfamily. It is involved in the respiratory chains of mitochondria and aerobic bacteria and catalyzes the $4e^-/4H^+$ reduction of O_2 to H_2O.[1,2] The three-dimensional structures of C*c*Os from *Paracoccus denitricans*[3,4] and bovine heart[5–7] have recently been determined by X-ray diffraction. Their oxygen metabolic sites consist of three major components: heme, a Cu atom, and one tyrosine (Tyr) molecule. The three-dimensional structures of C*c*Os demonstrate that, as previously surmised from indirect evidence, the "distal" O_2-binding/activating site is composed of a myoglobin-type Fe center (heme a_3) and a Cu atom (Cu_B) with three histidine (His) ligands (Figure 1). Cu_B is located about 4.5 Å from heme a_3 and 1 Å away from the normal axis of the heme iron position. One of the three His residues coordinating to Cu_B is covalently cross-linked to a Tyr through the ε-nitrogen of His240 and C-6 of Tyr244 (the residue number is based on the bovine enzyme). The hydroxy group of the Tyr residue is within hydrogen–bonding distance of the dioxygen molecule bound to heme a_3. The arrangement of the active site residues has led to two different proposals for oxygen activation: (1) the oxy intermediate is protonated with the concomitant reduction of the complex by an electron from heme a_3 to give $Fe^{III}{}_{a3}$–O–O–H[2] or (2) without protonation and electron-transfer from heme a_3, the oxy form reacts with $Cu^I{}_B$ to give $Fe^{III}{}_{a3}$–O–O–Cu^{II}, where the bound oxygen is already in the peroxy state. The protonation of this bridging peroxy ligand is expected to induce heterolytic O–O cleavage. Several points have not yet been clarified including the participation of Cu_B in the oxygen activation reaction, the Tyr role and the characterization of transient species. Thus, the synthesis, characterization and studies of promising mimetic models and their evaluation toward molecular oxygen reduction are extremely challenging. Such studies have already been investigated by Karlin et al. with models bearing either a Tyr244 mimic or not. However, in such models, the triaza compound was attached only by one linker on the porphyrin.[8,9] In the present study, the Cu coordination sphere is attached to the heme via three urea bonds.

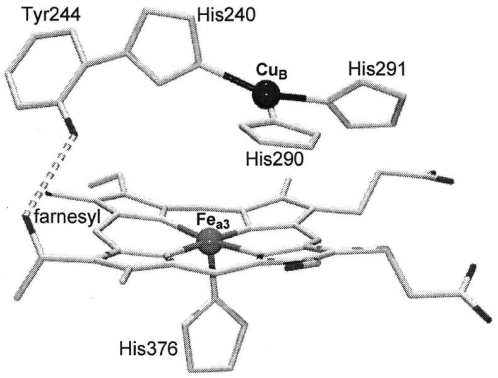

Figure 1. C*c*O-active center.

Results and Discussion

The porphyrin ring that constitutes the basic structural unit of the mimic derivative **1** is the 5,10,15,20-tetrakis(2-

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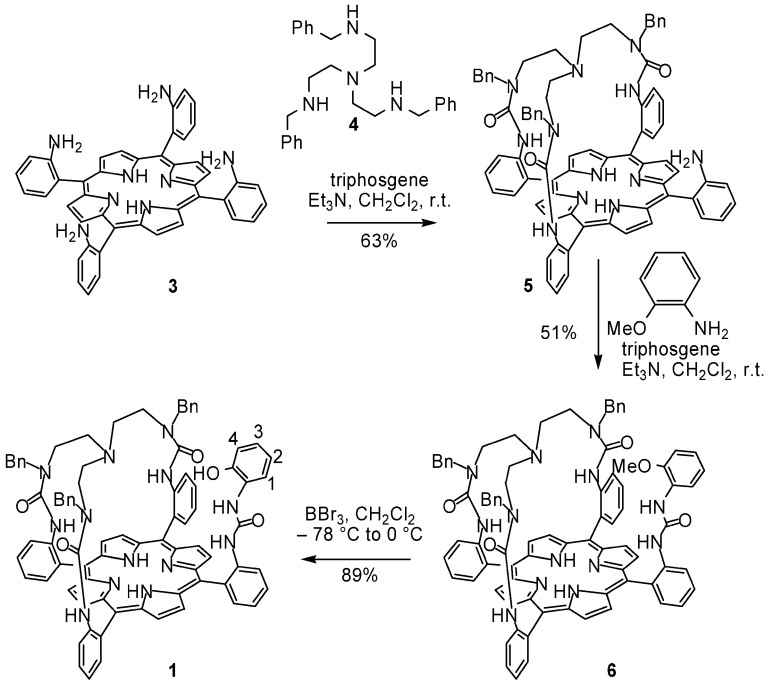
aminophenyl)porphyrin **3** (TAPP, Scheme 1). This particular porphyrin ring has been used for the synthesis of many biomimetic models owing to its easy preparation protocol as well as the possibility of anchoring various substitutes to the four amino groups. Extensive studies with regard to the separation, the interconversion and characterization of the four atropisomers of TAPP have been realized. For the synthesis of model **1**, we used the *α*,*α*,*α*,*α* atropisomer of **3**. In order to increase the proportion of the latter in the mixture, was used the method that consisted of refluxing the mixture of TAPP atropisomers with silica gel (SiO_2) in toluene.[10] With this procedure, 68% of the porphyrin was converted into the *α*,*α*,*α*,*α* isomer, and this yield can be improved by reprocessing the remaining mixture of atropisomers.

The host location (or substrate), in which the Cu will be coordinated, was N^1-benzyl-N^2,N^2-bis[2-(benzylamino)-ethyl]ethane-1,2-diamine (**4**). This substrate was prepared by a reaction between N^1,N^1-bis(2-aminoethyl)ethane-1,2-diamine (tren) and benzaldehyde in the presence of sodium borohydrate ($NaBH_4$).[11] Tren could also be used for the direct coordination of Cu. However, in our efforts to couple tren with porphyrin **3**, we observed the formation of many by-products. The formation of by-products was presumably due to the increased reactivity of the primary aliphatic amines of tren. Unlike in tren, the three secondary amines in **4** react slowly. By this procedure, the reaction between **4** and porphyrin **3** affords mainly the desired product **5**.

The following reactions for the synthesis of **1** are presented in Scheme 1. Initially, we performed the connection of **4** with porphyrin **3** via three urea bonds using the method of Collman et al.[12] For this purpose, we added to porphyrin **3** a suitable quantity of triphosgene in the presence of triethylamine. In this procedure, three of the four amino groups of porphyrin **3** were transformed to isocyano groups. We did not isolate the isocyano intermediate but reacted immediately with the three amino groups of **4** leading to the formation of porphyrin **5**. The presence of triethylamine was essential for the neutralization of the HCl produced during the reaction. In order to avoid the connection of one molecule of **4** with two different molecules of porphyrin, we added reagents simultaneously and slowly. The next step consisted in the attachment of the Tyr mimic moiety. We used 2-methoxyphenylamine to mimic the phenol of the Tyr. To porphyrin **5** we added triphosgene in the presence of triethylamine, and the isocyano intermediate that was formed reacted with 2-methoxybenzylamine, giving porphyrin **6** in a satisfactory yield (51%). We completed the synthesis of model **1** with the deprotection of the hydroxy group. We added an excess of boron tribromide (BBr_3) to a solution of porphyrin **6**, leading to the formation of model **1**. We characterized all the aforementioned derivatives (before the addition of any metal ion) by means of ^1H and ^{13}C NMR spectroscopy.

In the next stage, we performed the metalation reactions of both final derivatives **1** and **6**. For the metalation reactions of the porphyrin core, we used Fe bromide under anaerobic conditions in a glove box.[13] We observed a significant change in the color of the solution from purple to orange during the reaction, which is characteristic of the ferrous porphyrins. After completion of the reaction, and because column chromatography under anaerobic conditions is laborious, we exposed the solution to the atmosphere, and the Fe was immediately oxidized from the +2 to the more stable +3 oxidation state. During the oxidation of the Fe porphyrins by oxygen from the atmosphere, the formation of various oxygenated derivatives was possible



Scheme 1. Synthesis of ligand **1** bearing a phenyl group.

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including oxo (Fe–OH) and peroxo (Fe–O–O) moieties. The μ-oxo dimer (Fe–O–Fe) and the μ-peroxo dimer (Fe–O–O–Fe) also occurred. When the above-mentioned species were present together, they were difficult to separate. For this reason, we performed extractions with dilute HCl.[14] Under these conditions, we observed the exchange of the axial ligand of Fe as well as the splitting of the dimer units. Thus, we obtained exclusively monomeric species in which the Fe was pentacoordinate and had an axial Cl ligand. The structures of the synthesized Fe-only and Fe-Cu complexes as well as their phenol-protected analogues are presented in Figure 2. For the metalation reaction, we used a 10-fold excess of Fe dibromide. Under these conditions, the Fe could also coordinate to the location intended to host Cu. However, since we performed the extractions with dilute aqueous HCl, the nitrogen atoms of the Cu coordination site were protonated, leading to Fe liberation from that site.[15]

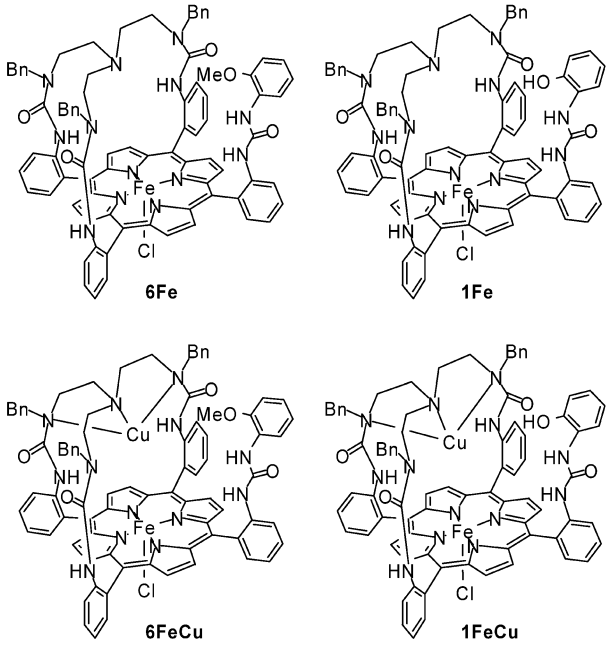


Figure 2. The metalated complexes with or without the protected phenol group. (The Cu counter anions are not represented).

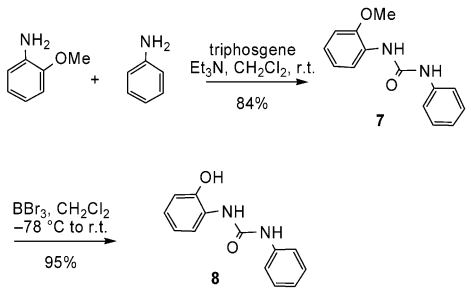
We confirmed the incorporation of Fe into the porphyrin ring by UV/Vis spectroscopy.[16] The Soret band of the porphyrin ring shifted to shorter wavelengths, which is characteristic of the binding of Fe with the four pyrrolic nitrogens. Moreover, we observed fewer Q bands as well as a decrease of the absorption coefficient (ε).

Due to the electronic configuration ([Ar] $3d^5$) of the Fe, it possesses unpaired electrons in both high-spin and low-spin complexes. Consequently, the proton signals in the ^{1}H NMR spectrum were spread from 80 ppm down to –10 ppm, giving broad peaks that were difficult to assign.[17] High-resolution mass spectrometry (HRMS) aided in the identification of the derivatives.

In order to complete the formation of a synthetic analogue of C*c*O, we performed the metalation reaction with Cu both on the final model and its analogue with a protected hydroxy group. We performed the metalation reactions using a Cu^{II} salt.[14] To a solution of the porphyrin derivatives in MeCN/ethanol, we added an eqimolar quantity of $[Cu(CO_2CH_3)_2]$ in MeCN. We heated the mixture at 55 °C for 5 min and isolated the desired derivative by precipitation with pentane. The final derivatives are depicted in Figure 2. The metalated Cu-Fe porphyrin derivatives obtained by the above-described procedure could not be submitted to further purification because the weak coordination of the Cu ion did not survive column chromatography. In this case also, we could not fully characterize the product by NMR spectroscopy due to the presence of Fe, which was still paramagnetic. Again, HRMS contributed to the identification of the formed complexes, and the results were in full agreement with the target structures.

In model **1**, the host molecule for Cu binding (**4**) was coupled with the porphyrin ring via three urea bonds. This type of link is expected to form a rigid ligand, as the tren residue is firmly held above the porphyrin. This conformation was supported by ^{1}H NMR spectroscopy, as several protons from **4** exhibited negative chemical shifts, indicating that they were shielded by the macrocycle. However, the phenyl ring that mimics the Tyr part of the enzyme is linked to the porphyrin entity by only one urea bond and is still somewhat mobile.

Many recrystallization efforts for derivatives **1**, **5**, and **6** have not provided the expected single crystals. The lack of any crystal data set as well the poorly resolved ^{1}H NMR spectra of **1Fe** and **1FeCu** due to the presence of the paramagnetic metal ion(s) drove us to a detailed study of derivatives **1** and **6**, as well as the synthesis of **8** (Scheme 2). A comparison of the ^{1}H and ^{13}C NMR spectroscopic data for derivatives **1** and **6** helped us to assign each peak to a corresponding proton. For **6**, we found the methoxy group at δ = 3.70 ppm, but the OH group of **1** was difficult to identify. In contrast, all the other signals of the OCH_3/OH-containing phenyl ring were clearly assigned. This is why we used **8** as a probe to investigate the conformation of the aromatic picket of **1**.



Scheme 2. Synthesis of **8** for the NMR comparison study.

Thus, we synthesized derivative **8** as a reference compound for the picket of porphyrin **1**. The synthetic pathway is described in Scheme 2. Aniline reacted first with triphosgene in the presence of triethylamine to give rise to the isocyano intermediate. The addition of 2-methoxyphenylamine

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followed. We stirred the mixture for 1 h, at which time derivative **7** formed. The next step involved the deprotection of the hydroxy group, which we achieved by the addition of boron tribromide to obtain derivative **8**.

Obviously, the phenolic proton would be a good probe candidate but is not reliable as it is mobile, exchangeable and its resonance frequency is temperature-dependent. On the other hand, the chemical shifts of the other phenyl ring protons such are indicative of their location in the shielding ring current of the macrocycle. From the values presented on Table 1 we observe that chemical shifts of these protons in **1** were smaller than those of the reference **8**, indicating that those protons were located above the porphyrin ring current. In addition, the most heavily shifted proton is H-4 (see Scheme 1 for the location), which is *ortho* to the hydroxy group. This observation favors an orientation of the phenyl ring with the hydroxy group pointed oriented toward the center of the molecule. Thus, in model **1**, the host ligand for the Cu ion as well the phenyl ring most likely adopts a favorable conformation for the catalyzed reduction of dioxygen.

Table 1. Comparative chemical shifts of the phenol protons for **1** and **8**.[a]

Entry		H-1	H-2	H-3	H-4
1	**1**	6.98	6.71	6.79	6.41
2	**8**	7.19	6.97	7.09	6.92
3	Δppm	–0.21	–0.26	–0.30	–0.51

[a] In $CDCl_3$.

We could not fully characterize the metalated compounds by NMR spectroscopy due to the presence of the Fe, which is paramagnetic. However, from the chemical shift of the pyrrole protons we determined the spin and the oxidation state of the Fe ion. In the ^1H NMR spectra of the metalated compounds **6Fe**, **6FeCu**, **1Fe**, and **1FeCu**, the chemical shift of the pyrrole protons was about 80 ppm. This value is characteristic of oxidized high-spin Fe-porphyrins. Therefore, we concluded that in all the synthesized models, the Fe was at the +3 oxidation state having an overall spin $S = 5/2$.

Finally, we evaluated these derivatives as promising enzyme mimics electrochemically with a rotating ring disk electrode (RRDE) in the presence of molecular oxygen. Our purpose was to compare the catalytic activity of the newly synthesized compounds. The primary goal of this investigation was to shed light on the role of the hydroxy group delivered by one picket in the meso position of the porphyrin. More precisely, we wanted to know if its presence was essential for the $4e^-$ reduction of dioxygen to water. On the one hand, the main advantage of this technique is its ability to detect H_2O_2 by a ring current at the anode (made of a platinum ring). It is important to note that the H_2O_2 detected at the anode was produced by the reduction of dioxygen at the cathode (composed of a graphite disk) and had migrated dramatically. On the other hand, a disadvantage of this technique consists in the irreversible adsorption of the catalyst (the synthetic model) on the surface of the electrode. Indeed, there is no direct way to observe how the catalyst evolves during the catalytic process.

In order to carry out the electrochemical experiments, we adsorbed the molecules on the disk electrode, which was a section of a highly ordered graphite rod, with the planes of graphite being perpendicular to the surface of the electrode (edge-plane graphite electrode, EPGE). We scanned the potential of this modified graphite electrode from high to lower values so as to record the voltammogram for the reduction of O_2. The graphite electrode was surrounded by a platinum ring electrode, the potential of which we set at a fixed value (1.0 V) such that the H_2O_2 eventually produced at the disk was oxidized to O_2.

Figure 3 depicts the catalytic studies for the various complexes elaborated from ligand **1**. First, we studied complex **1Fe** without Cu. In this case (Figure 3, curve a), the reduction of dioxygen started at 0.05 V versus SCE. From the comparison with the $2e^-$ reduction wave on a bare EPGE, the number of electrons exchanged per O_2 molecule was 3.2. H_2O_2 is detected through its oxidation, as soon as O_2 is reduced, from the current increase at the platinum electrode encompassing the graphite disk. This means that the $2e^-$ and $4e^-$ reduction mechanisms occur simultaneously. From the study of model **1FeCu** (Figure 3, curve b), we observed that the presence of Cu ion did not seem to affect the catalytic ability of the complex. The number of the necessary electrons for the reduction process as well the potential did not significantly differ. We observed the most important change in the current on the platinum electrode (ring). However, this was attributed to the poisoning of the electrode from the catalyst molecules. The presence of catalyst molecules on the surface of the electrode led to measurement errors, as the observed current resulted not only from the reduction of H_2O_2 produced at the disk but also from the reduction of catalyst molecules. Models **1FeCu** and **1Fe**

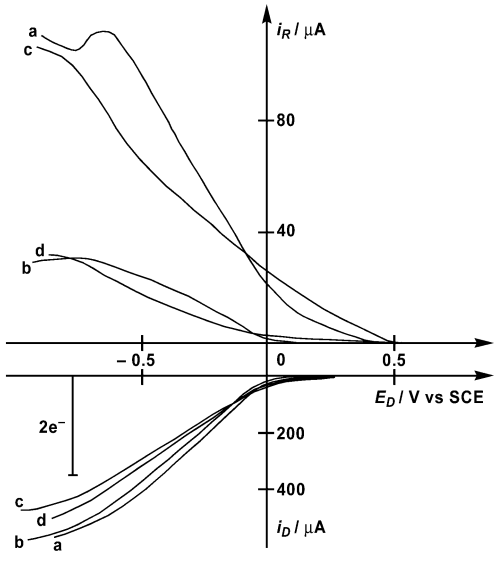

Figure 3. RRDE voltammograms (a: **1Fe**, b: **1FeCu**, c and d: 2nd scan for **1Fe** and **1FeCu**, respectively; bottom: disk current, top: ring current).

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were unstable and decomposed quickly after two successive scans. We also noticed a significant decrease in the current for the graphite electrode (disk, Figure 3, curves c and d) after the second scan, which we attributed to the decrease of the catalyst concentration on the surface of the electrode. This obstacle prevented us from further processing our analysis.

Thus, we observed a higher selectivity for model **1** than for the other models in the $4e^-$ reduction of molecular oxygen to H_2O. For this reason, we performed further studies on the derivative in which a methyl group protects the hydroxy function. The difference between the results with **1** and **6** should provide evidence for the role of the proximal Tyr mimic in our derivatives. Actually, with **6** absorbed on the surface of the electrode, the results were consistent with those from model **1**, and we observed no difference. Consequently, the hydroxy group of these derivatives did not seem to participate in the reduction of dioxygen, as their catalytic activity and their stability remained unchanged when the hydroxy group was protected.

Conclusions

In conclusion, we tested the investigated molecules for their ability to reduce dioxygen in water on graphite electrodes in contact with an aqueous medium. Under these very specific conditions, although we observed a significant proportion of the $4e^-$ process, we found no clear influence of the hydroxy group of our model molecules on the proportion of the $4e^-$ versus $2e^-$ reduction of dioxygen. This lack of difference could come from the models themselves, in which the orientation of the hydroxy group might not be properly controlled. Further investigations of new derivatives as building blocks for efficient molecular models for C*c*O are needed. The complexity of the system requires very flexible and well-designed molecules in order to take into account all the involved parameters that could play a role in the catalytic activity.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded, unless otherwise specified, as deuterochloroform solutions using the solvent peak as an internal standard with a Bruker AMX-500 MHz spectrometer. UV/Vis spectra were recorded with a Shimadzu Multispec-1501 instrument. All electrospray mass spectrometric experiments were performed with an LCQ Advantage (ThermoElectron, San Jose, CA) mass spectrometer. HRMS was performed with a MS/MS ZABSpec TOF spectrometer at the University of Rennes I (C.R.M.P.O.). Thin-layer chromatography was preformed on silica gel 60 F_{254} plates. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 70–230 mesh ASTM). All dry solvents were dried by the appropriate technique. Organic extracts were dried with magnesium sulfate unless indicated otherwise. The evaporation of the solvents was accomplished with a rotary evaporator.

Porphyrin 1: To a solution of porphyrin **6** (25 mg, 0.02 mmol) in dry CH_2Cl_2 (20 mL), cooled to –78 °C, was introduced BBr_3 (1.0 M solution in CH_2Cl_2, 0.25 mL, 0.25 mmol). The mixture was stirred at –78 °C for 30 min and at 0 °C for 1 h. The reaction was quenched with MeOH (5 mL) and stirred for 10 min at 0 °C. The mixture was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), water (2 × 20 mL), and dried, and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography (10% MeOH in CH_2Cl_2) to give **1** as a purple solid (22 mg, 89%). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.97 (m, 2 H), 8.89 (d, J = 4.5 Hz, 2 H), 8.82 (s, 4 H), 8.54 (m, 2 H), 8.33 (d, J = 8.5 Hz, 1 H), 8.06 (m, 1 H), 7.83 (m, 7 H), 7.76 (m, 2 H), 7.69 (m, 1 H), 7.56 (t, J = 7.5 Hz, 1 H), 7.44 (t, J = 7.5 Hz, 1 H), 7.06 (m, 4 H), 6.98 (m, 7 H), 6.86 (m, 6 H), 6.79 (t, J = 7.5 Hz, 1 H), 6.71 (d, J = 7.5 Hz, 1 H), 6.41 (br. s, 4 H), 6.18 (br. s, 1 H), 4.67 (br. s, 2 H), 3.82 (s, 4 H), 2.99 (br. s, 2 H), 1.67 (m, 2 H), 0.99 (m, 2 H), 0.58 (br. s, 2 H), –1.42 (br. s, 2 H), –2.41 (s, 2 H), –2.57 (m, 2 H) ppm. R_f (CH_2Cl_2/MeOH, 9:1) = 0.41. HRMS (ES^+): calcd. for $C_{81}H_{70}N_{13}O_5$ $[M + H]^+$ 1304.5623; found 1304.5631. UV/Vis (CH_2Cl_2): λ (ε) = 422 (260.2), 516 (13.8), 549 (3.2), 588 (4.0), 646 (1.3) nm.

Tris(2-benzylaminoethyl)amine (4): Benzaldehyde (1.7 mL, 16.5 mmol) was added dropwise to a solution of tris(2-aminoethyl)-amine (0.75 mL, 5 mmol) in dry MeOH (5 mL) at room temp. The resulting yellow solution was stirred for 1 h and then cooled in an ice bath. $NaBH_4$ (0.7 g, 19 mmol) was added portionwise, and the mixture was stirred for an additional 2 h at room temp. The reaction mixture was then diluted with water (10 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with aqueous HCl (1 N, 2 × 20 mL). The combined aqueous layers were extracted with diethyl ether (2 × 5 mL), and then made basic with solid K_2CO_3 to a pH > 10. The basic aqueous layer was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were dried and concentrated to give a pale yellow oil (1.67 g, 80%). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.25 (m, 15 H), 3.73 (s, 6 H), 2.66 (t, J = 6 Hz, 6 H), 2.57 (t, J = 6 Hz, 6 H), 1.84 (br. s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.5 (C), 128.4 (CH), 128.1 (CH), 126.8 (CH), 54.5 (CH_2), 54.0 (CH_2), 47.2 (CH_2) ppm. R_f (CH_2Cl_2/MeOH, 9:1) = 0.31.

Porphyrin 5: A mixture of tetraminoporphyrin **3** (67 mg, 0.10 mmol) and triethylamine (0.22 mL, 1.6 mmol) in dry CH_2Cl_2 (20 mL) was stirred for 1 h under argon at room temp. In another flask, tris(2-benzylamino ethyl)amine (**4**, 42 mg, 0.10 mmol) was dissolved in dry CH_2Cl_2 (20 mL) under argon. The two solutions were added simultaneous and slowly to a third flask, which contained dry CH_2Cl_2 (20 mL). The addition was competed in 1 h, and the resulting solution was stirred at room temp. for an additional 16 h. The reaction was monitored by thin-layer chromatography (4% MeOH in CH_2Cl_2). The residue was purified by column chromatography, and the desired porphyrin **5** was eluted with 6% ethyl acetate in CH_2Cl_2 to give a purple solid (73 mg, 63%). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.90 (d, J = 4.5 Hz, 4 H), 8.84 (d, J = 4.5 Hz, 2 H), 8.78 (m, 2 H), 8.54 (d, J = 7 Hz, 2 H), 8.40 (d, J = 8 Hz, 1 H), 7.81 (m, 6 H), 7.68 (t, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.55 (d, J = 7 Hz, 1 H), 7.41 (t, J = 7.5 Hz, 1 H), 7.17 (d, J = 7.5 Hz, 1 H), 7.12 (t, J = 7.5 Hz, 1 H), 7.00 (m, 5 H), 6.88 (m, 10 H), 6.42 (s, 2 H), 6.20 (s, 1 H), 4.90 (br. s, 2 H), 3.96 (s, 4 H), 3.57 (s, 2 H), 1.68 (m, 2 H), 1.21 (m, 4 H), 0.56 (m, 2 H), –1.12 (m, 2 H), –2.33 (m, 2 H), –2.50 (s, 2 H) ppm. R_f (CH_2Cl_2/EtOAc, 95:5) = 0.39. MS (EI): m/z = 1169.3 $[M + H]^+$, (100%) for $C_{74}H_{65}N_{12}O_3$. $C_{74}H_{64}N_{12}O_3$ (1169.38): calcd. C 76.01, H 5.52, N 14.37; found C 76.17, H 5.35, N 14.28. UV/Vis (CH_2Cl_2): λ (ε) = 422 (264.6), 516 (14.7), 549 (3.2), 588 (4.3), 646 (1.4) nm.

Porphyrin 6: A mixture of porphyrin **5** (25 mg, 0.02 mmol), triethylamine (6 μL, 0.04 mmol), and triphosgene (6 mg, 0.02 mmol) in dry

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CH_2Cl_2 (30 mL) was stirred for 1 h under argon at room temp. 2-Methoxybenzylamine (5 mg, 0.04 mmol) was then added, and the stirring was continued overnight. The resulting mixture was purified by column chromatography (10% ethyl acetate in CH_2Cl_2) to give **6** as a purple solid (14 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.91 (m, 2 H), 8.86 (d, J = 4.5 Hz, 2 H), 8.79 (s, 4 H), 8.55 (d, J = 6.5 Hz, 2 H), 8.35 (d, J = 8.5 Hz, 1 H), 8.10 (br. s, 1 H), 8.00 (d, J = 7 Hz, 1 H), 7.90 (m, 3 H), 7.82 (m, 4 H), 7.67 (t, J = 7.5 Hz, 2 H), 7.60 (t, J = 7.5 Hz, 1 H), 7.45 (m, 2 H), 7.09 (br. s, 1 H), 6.93 (m, 9 H), 6.82 (m, 7 H), 6.64 (d, J = 7 Hz, 1 H), 6.57 (t, J = 7.5 Hz, 1 H), 6.46 (br. s, 3 H), 5.91 (br. s, 1 H), 4.77 (br. s, 2 H), 3.91 (s, 4 H), 3.61 (s, 3 H), 2.98 (br. s, 2 H), 1.52 (m, 2 H), 0.98 (m, 2 H), 0.67 (br. s, 2 H), –1.42 (m, 2 H), –2.50 (s, 2 H), –2.60 (br. s, 2 H, H-13) ppm. R_f (CH_2Cl_2/EtOAc, 9:1) = 0.38. MS (EI): m/z = 1318.7 $[M + H]^+$, (100%) for $C_{82}H_{72}N_{13}O_5$. $C_{82}H_{71}N_{13}O_5$ (1318.53): calcd. C 74.70, H 5.43, N 13.81; found C 74.80, H 5.35, N 13.68. UV/Vis (CH_2Cl_2): λ (ε) = 422 (262.2), 516 (14.1), 549 (3.2), 588 (4.2), 646 (1.4) nm.

Porphyrin 6Fe: Under an inert atmosphere, porphyrin **6** (30 mg, 0.025 mmol) and Fe(II) bromide (54 mg, 0.25 mmol) were added to a Schlenk flask. The addition of deoxygenated THF (6 mL) gave a red solution. The mixture was stirred overnight at 55 °C and then opened to the air and cooled to room temp. The solvent was then removed under vacuum, and the resulting powder was dissolved in $CHCl_3$ (20 mL) and washed with HCl (2 N, 1 × 25 mL) and saturated $NaHCO_3$, dried, filtered, and concentrated under vacuum. The resulting crude product was purified by chromatography (0–6% MeOH in chloroform). The product was eluted at 2% MeOH in chloroform to give **6Fe** as a brown-purple solid (29 mg, 84%). R_f (CH_2Cl_2/MeOH, 9:1) = 0.40. HRMS (ES^+): calcd. for $C_{82}H_{69}FeN_{13}O_5$ $[M - Cl]^+$ 1371.4894; found 1371.4899. UV/Vis (CH_2Cl_2): λ (ε) = 417 (74.0) nm.

Porphyrin 1Fe: The insertion of the iron was carried out according to the procedure described for **6Fe**. R_f (CH_2Cl_2/MeOH, 9:1) = 0.37. HRMS (ES^+): calcd. for $C_{81}H_{67}FeN_{13}O_5$ $[M - Cl]^+$ 1357.4738; found 1357.4743. UV/Vis (CH_2Cl_2): λ (ε) = 417 (75.3) nm.

Porphyrin 6FeCu: To a solution of porphyrin **6Fe** (7 mg, 5.5 μmol) in MeCN (4 mL) was added Cu acetate [6.0 μmol, from a standard solution of 50 mg of $Cu(CH_3COO)_2$ in 25 mL of MeCN], and the mixture was stirred at 60 °C for 10 min. The solvent was then removed under vacuum, and the resulting solid was dissolved in $CHCl_3$. Upon the addition of pentane, the complex precipitated. The solid was filtered and washed with pentane, giving **6FeCu** as a brown-purple solid (7.5 mg, 97%). R_f (CH_2Cl_2/MeOH, 9:1) = 0.40. HRMS (ES^+): calcd. for $C_{82}H_{69}CuFeN_{13}O_5$ $[M - Cl]^+$ 1434.4190; found 1434.4181. UV/Vis (CH_2Cl_2): λ (ε) = 417 (60.9) nm.

Porphyrin 1FeCu: The insertion of copper was performed according to the procedure described for **6FeCu**. R_f (CH_2Cl_2/MeOH, 9:1) = 0.37. HRMS (ES^+): calcd. for $C_{81}H_{67}CuFeN_{13}O_5$ $[M - Cl]^+$ 1420.4034; found 1420.4049. UV/Vis (CH_2Cl_2): λ (ε) = 417 (61.3) nm.

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR spectra for all new compounds.

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