Synthesis of Tripodal Phenol Porphyrins: A Modular Approach to Mimic Enzymes with a Cross-Linked Tyrosine

David Gueyrard, Amandine Didier, Christian Ruzié, Arnaud Bondon, Bernard Boitrel*

Université de Rennes1, UMR CNRS 6509, Institut de Chimie, 35042 Rennes Cedex, France
Fax +33(2)23235637; E-mail: Bernard.Boitrel@univ-rennes1.fr

Received 11 March 2004

Abstract: The synthesis of various tren [tris(2-aminoethyl)amine]-capped porphyrins incorporating a substituted phenol into different positions is reported. The conformations of the different ligands have been studied in solution by means of NMR spectroscopy.

Key words: porphyrins, spectroscopy, biomimetic synthesis, phenols, enzymes

The exergonic slow reductive cleavage of molecular oxygen through the four electron-four proton mechanism is essential for aerobic life on Earth.[1] This reduction results in the synthesis of ATP from ADP and inorganic phosphorus, the electrons flowing from NADH to O_2.[2,3] It is catalyzed by cytochrome *c* oxidase (CcO), a copper hemoprotein whose structure has been initially resolved by X-ray in 1995[4] and later refined.[5] The active site of the enzyme consists of two major components, a five-coordinated iron(II) porphyrin and a copper(I) complexed by three histidine residues, by which most of the synthetic models are inspired.[6] Accordingly, elucidating the fundamental aspects of dioxygen binding with heme and copper centers through the design and synthesis of functional analogs of CcO is crucial. In this respect, numbers of biomimetic models cleverly designed and skillfully made, have been reported, all of them having two proximal metal coordination sites favoring the binding of an O_2 molecule.[7] We have developed a series of ligands,[8] which resulted in the initiation and the verification of the idea that iron-only porphyrins can catalyze the clean reduction of dioxygen to water, when adsorbed at the surface of an electrode at physiological pH.[9] In fact, this crucial observation, initially controversial, but later confirmed and clearly explained,[10] demonstrates that the postulated μ-peroxo complex is not an essential intermediate for the four-electron reduction of oxygen, as long as electrons and protons can be rapidly delivered to the catalytic site of a synthetic model.[11]

Our conclusion, in agreement with recent spectroscopic results,[12] is also supported by Yoshikawa et al. who suggested that the peroxo-derivative could be protonated by the low pK_a Tyr_{244}, located in the closed environment of the coordination sphere of copper, forming a hydroperoxo adduct.[5] Besides, this Tyr_{244} represents an example of the

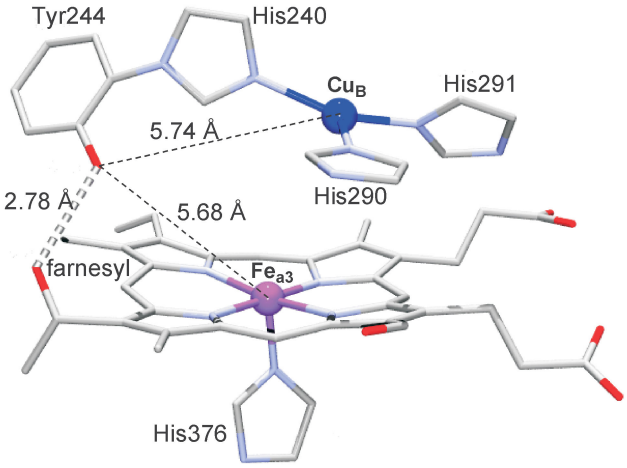
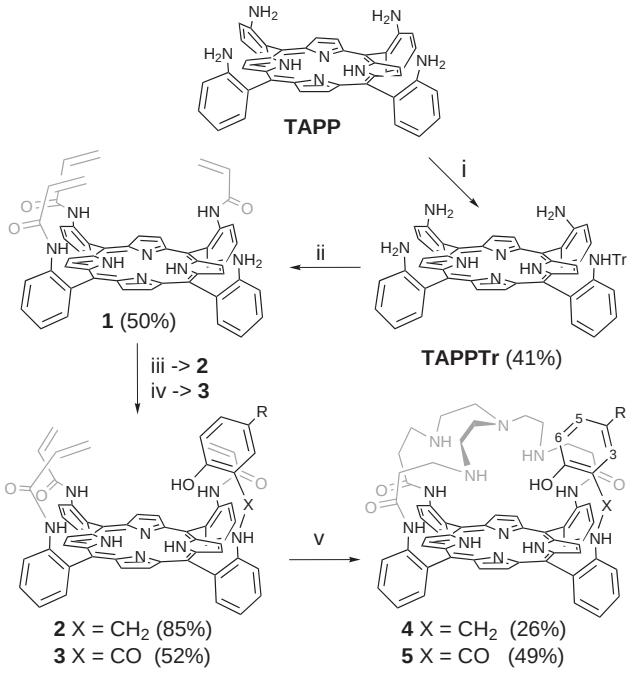


Figure 1 Active site of CcO.

posttranslationally modified tyrosines in nature. Indeed, in CcO, Tyr_{244} is cross-linked to one of the copper-ligated histidines, His_{240}, indicative of radical chemistry at the active site.[13] This covalent linkage is expected to perturb both the redox potential of the tyrosyl radical (Y)[14] and pK_a of the phenol/phenolate as occurs for the redox-active, covalently cross-linked tyrosine in galactose oxidase (GO).[15] Nevertheless, in GO, the tyrosine is cross-linked with a cysteine residue and coordinates the copper, whereas it does not in CcO. The significant decrease of pK_a for ligands able to mimic the Cu_B coordination sphere has been reproduced[16] but so far, no synthetic model of CcO bearing a mimic of the triad heme a_3-Cu_B-Tyr_{244} has been designed and prepared. This observation could stem from both the synthetic difficulties and the complicated conformational control of the complete assembly, particularly for the orientation of the phenol group, as depicted in Figure 1 for the enzyme. Accordingly, the availability of copper-coordinating molecules bearing a mimic of cross-linked tyrosines, with a tunable pK_a and for which the coordination of the mimic to the copper cation could be allowed or not, becomes an exciting challenge.

In our ongoing projects devoted to the understanding of enzymatic catalytic cycles, we herein report the design and preparation of new ligands as potential models of enzymes that include a cross-linked tyrosine mimic such as CcO or GO, as well as the first insights of their conformational study.

SYNLETT 2004, No. 7, pp 1158–1162
Advanced online publication: 10.05.2004
DOI: 10.1055/s-2004-825589; Art ID: G07604ST



Scheme 1 Synthesis of tren-capped phenol porphyrins. R = NO_2; *Reagents*: i) trityl bromide, THF, Et_3N, 0 °C; ii) CH_2=CHCOCl, THF, Et_3N, –15 °C then TFA; iii) 2-hydroxy-5-nitrobenzaldehyde, $NaBH_3CN$, TFA, MeCN, r.t.; iv) 2-hydroxy-5-nitrobenzoic acid, DCC, DMAP, pyridine, r.t.; v) tren, MeOH/$CHCl_3$, reflux.

These new molecules have the obvious advantage of being closely related to our previously studied iron-copper analogs.[17] Recently, two pertinent examples of the His_3-Tyr-Cu motif have been published and their crystal structures reported.[18] Unfortunately, their assembly with a porphyrin remains a difficult task to be realized. Furthermore, on observing the active site of CcO in Figure 1, it appears that both metals (Cu_B and Fe_{a3}) are separated from the tyrosine hydroxyl by the same distance of 5.7 Å. On the other hand, Cu_B and the Tyr_{244} hydroxyl are diametrically opposed relative to the iron, and this spatial arrangement is quite difficult to reproduce.

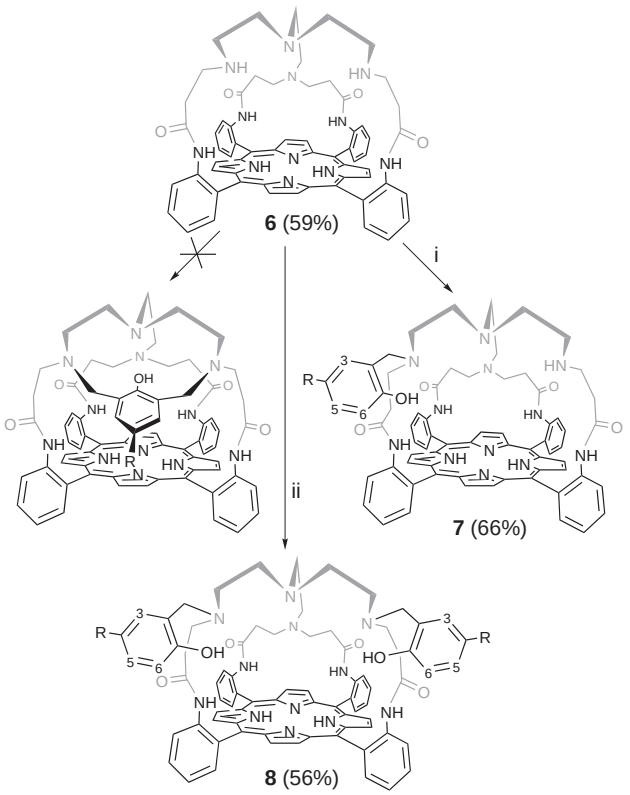
To do so, we chose the methodology that consists of tethering a phenol moiety bearing, for instance, an electron-withdrawing group in the *para*-position as described in Scheme 1. Indeed, if we were able to control the orientation of the hydroxyl group vs. the center of the cavity built by the tripodal architecture, this would provide a convenient way of organizing the surroundings of both metals. Moreover, two other structural features should be influenced by this stratagem. Firstly, owing to the substitution pattern of the porphyrin itself, the nitro phenol is attached to the macrocycle by *meso*-position 20 where the tripodal cap is off-center of diametrally opposed *meso*-position 5. Secondly, the further coordination of the copper cation by the phenol (or phenoxide) could be manipulated by the position of the hydroxy group on the aromatic picket. Our molecular mechanic modelling studies[19] indicate that this aromatic picket would have to come in close contact with the tren to allow the hydroxy group, in *ortho*-position to the amide linkage, to coordinate. On the other hand, when the hydroxy group is in *meta*-position to the amide linkage (position 6 in Scheme 1), this coordination should be possible.

Additionally, the two aromatic rings of the picket, conjugated through the amide bond on the porphyrin, are expected not to be coplanar as previously reported but to be twisted with a angle ranging from ca. 20 ° to 40 °.[20] Accordingly, the OH group should be slightly displaced on the side of the porphyrin as the Tyr_{244} OH is within the enzyme, maintained by a hydrogen bond with the farnesyl, instead of pointing straight to the center of the heme (Figure 1).

Thus, two new ligands have been prepared in which the phenol should not be able to coordinate the copper cation, once this one inserted in the tripodal cap, and so, these ligands appear to be potential synthetic models of CcO. They are closely related to one another as they only differ by the nature of their link to the *meso* aromatic ring of the porphyrin. As illustrated in Scheme 1, this link is benzylic for **4** and amidic in the case of **5**. We believe that this variation could have a significant influence on the spatial arrangment of the OH function. The synthesis of these two ligands begins with the preparation of porphyrin **1** bearing three acrylamide pickets[21] and one amino group, which is allowed to react either with 2-hydroxy-5-nitrobenzaldehyde in a reductive amination reaction or with 2-hydroxy-5-nitrobenzoic acid activated by DCC in pyridine.[22] The final capping reaction with tren reacting on the three acrylamide pickets is a common step for both porphyrins to afford compounds **4** and **5**.

On the other hand, when 2-hydroxy-5-nitrobenzyl bromide was grafted on porphyrin **6**, a second series of ligands was obtained. Depending on the ratio of benzyl bromide reagent vs. porphyrin, two porphyrins **7** and **8** were easily prepared with acceptable yields. However, in these two ligands, according to molecular mechanic modelling, the substituted phenol could coordinate the copper atom, once complexed in the tren because there is no means to control the spatial position of the phenol, that is presumably in free rotation around the tripodal cap. As already mentioned, such a coordination of a phenolate residue on copper exists in GO. In this topology, the porphyrin, with a redox and coordination inactive metal such as nickel(II), could be employed only as a structural framework, thereby providing a convenient opportunity of studing the reactivity of copper(I) –phenolate complexes, for which no intermolecular assembly will be possible. To obtain a ligand in which the conformation of the nitrophenol is dictated by the superstructure, we also tried to prepare a molecule that consists of the same type of substituted phenol (R = NO_2 in the present example) but attached on the tren motif by two points (Scheme 2).

Indeed, the nitrophenol would be strapped between the two secondary amines of porphyrin **6** with the OH group pointing directly toward the center of the cavity. Unfortunately, up to now, this synthesis failed even employing conditions as severe as heating porphyrin **6** with 2,6-di-



Scheme 2 Synthesis of substituted tren-capped porphyrins. R = NO_2; *Reagents*: 2-bromomethyl-4-nitrophenol (i: 1.1 equiv; ii: 2.2 equiv), Et_3N, THF, 60 °C.

bromomethyl-4-nitrophenol in DMF at 100 °C, but remains an interesting target.

Nevertheless, these properties need to be confirmed through studies of the coordination chemistry of these new molecules. In a first approach, their conformations in solution have been scrutinized by proton NMR spectroscopy. A simple investigation consists of comparing the chemical shift of representative protons for both the raw nitrophenol derivative and the porphyrin (Table 1).

Table 1 Chemical Shifts of the Phenol Picket Protons

	H_3 (ppm)	H_5 (ppm)	H_6 (ppm)
2-Hydroxy-5-nitrobenzoic acid	8.55	8.33	7.15
5	8.56	7.39	5.38
2-Hydroxy-5-nitrobenzyl bromide	8.34	8.10	7.02
4	8.02	7.74	6.33
7	7.84	7.90	6.77
8	7.59	7.77	6.37

Obviously, the phenolic proton would be a good candidate but is not a reliable probe as it is mobile, exchangeable and temperature dependent. On the other hand, the chemical shift of a proton such as H_6 in the *ortho*-position of the hydroxy function, is indicative of its location in the shielding ring current of the macrocycle. This information is particularly important for porphyrins **4** and **5**, for which the steric hindrance of the tripodal cap could eject the OH to the outside of the cavity. To perform a comparison between the different superstructures, including compounds **7** and **8**, all the spectra were recorded in DMSO-d_6 at a temperature between 333 K and 363 K, depending on the best resolution obtained on a 500 MHz spectrometer. For instance, in the porphyrins **7** and **8**, the proton H_6 is found to be shifted upfield by an average value of δ = 0.4 ppm in comparison with 2-hydroxy-5-nitrobenzyl bromide. This slight shift is due to the lateral position of the aromatic ring attached to the tren motif. Moreover, H_3 experiences the same upfield shift, indicating that in fact, the benzyl residue is in free rotation with no privileged conformation. The same comparison is more instructive in the case of porphyrins **4** and **5**. Indeed, in comparison with the raw nitrophenol compound, H_6 is shifted upfield by δ = 0.7 ppm and 1.8 ppm in **4** and **5**, respectively. This observation is consistent with the fact that H_6 is oriented closer to the center of the cavity in **5** than in **4**. Additionally, the chemical shift of H_3 corroborates this observation as this proton, maintained in the periphery of the porphyrin, is not – or almost not – shifted upfield in porphyrins **5** and **4**. This first approach has been confirmed by the analysis of 2D ROESY spectra, from which more accurate information can be obtained.

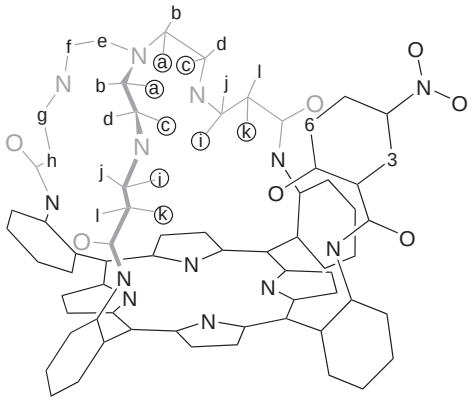


Figure 2 Detailed labeling of the aliphatic protons of **5** (for clarity, multiple bonds are omitted and protons exhibiting a ROE with H_6 are circled).

Indeed, for porphyrins **4** and **5**, if Figure 2 is representative of the actual conformation in solution, H_6 should induce strong ROE on the protons of the cap. As a matter of fact, for porphyrins **4** and **8**, there are only a few cross peaks in the spectra (data not shown) without any correlation between the protons of the phenyl ring bearing the hydroxy- and the nitro groups and the cap protons. Such an absence is in good agreement with a free rotation of this moiety. In contrast, with the more constrained porphyrin **5** a ROESY spectrum is obtained displaying several cross peaks (Figure 3). A more complete description of the molecular structure requires the full assignment of the protons, which has been performed using the combination of standard 2D experiments such as COSY, TOCSY,

heteronuclear H-C HSQC. The first comment concerns the high symmetry of the molecule as shown by the equivalence of the two branches of the tren surrounding the substituted phenol. Also remarkable is the strong high field shift of all the resonances of the methylene protons of the tren. This shielding must be related to a large movement of the tren toward the porphyrin plane. Finally, evidence for a major conformation with the hydroxy pointing toward the center of the macrocycle is given by the labelled strong ROE cross-peaks between the H_6 and four methylene groups of the tren (see Figure 2 for labelling of the molecule).

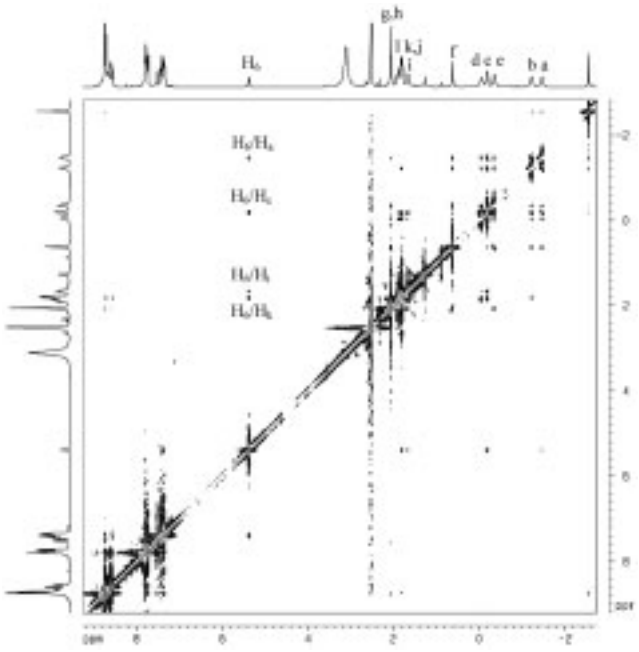


Figure 3 500 MHz ROESY spectrum of porphyrin **5**.

To conclude, four new tripodal phenol porphyrins bearing a cross-linked tyrosine mimic at different positions of the ligand, and with several orientations have been synthesized and studied by NMR spectroscopy. Owing to the simple design of these compounds, we should be able to modulate the position and the conformation of the substituted phenol moiety. Furthermore, the electron-withdrawing NO_2 group was employed, but we are currently preparing the analogs with an electron-donating OMe group, as the latter is expected to stabilize a radical in the *para*-position without conformational change in the superstructure.

Typical Experiments

Synthesis of 5: In a 500 mL round bottom flask under argon, 650 mg (0.708 mmol) of **TAPPTr**[23] and 1 mL of Et_3N were dissolved in 250 mL of freshly distilled THF, then acryloyl chloride (208 μL, 2.55 mmol) dissolved in 20 mL of THF was added dropwise at –15 °C over 10 min. Stirring was maintained during 10 min and then, the mixture was dried under vacuum. The residue was dissolved in 30 mL of CH_2Cl_2, and 3 mL of trifluoroacetic acid was added. After 2 h, the mixture was washed twice with 10 mL of aq NaOH (5%). The organic phase was concentrated by rotary evaporation and poured onto a 15 μm silica gel column (3 × 10 cm). The desired product was eluted with 0.6% MeOH/CH_2Cl_2. After evaporation to dryness, 330 mg of **1** were collected (yield = 50%).

In a 100 mL round bottom flask under argon, 80 mg (0.096 mmol) of **1**, DCC (39 mg, 0.191 mmol), DMAP (1 mg, 0.01 mmol) and 2-hydroxy-5-nitrobenzoic acid (35 mg, 0.191 mmol) were dissolved in 10 mL of freshly distilled pyridine. Stirring was maintained overnight and then, the mixture was dried under vacuum. The product was dissolved in $CHCl_3$ and poured onto a 15 μm silica gel column. The desired product was eluted with 0.7% MeOH/$CHCl_3$. After evaporation to dryness, 50 mg of **3** were collected (yield = 52%).

In a 250 mL two-neck round bottom flask under argon, 250 mg (0.090 mmol) of **3** were dissolved in 90 mL of a mixture $CHCl_3$–MeOH (1:5) degazed during 2 h. The solution was heated at 55 °C. With a syringe, 16 μL (0.096 mmol) of tris-2-aminoethylamine were slowly added. Stirring was maintained during 5 h and then, the mixture was dried under vacuum. The product was dissolved in CH_2Cl_2 and poured onto a 15 μm silica gel column. The desired product was eluted with 5–10% MeOH/CH_2Cl_2/$NH_{3\,(g)}$. After evaporation to dryness, 50 mg of **5** were collected (yield = 49%). ^{1}H NMR (500 MHz, DMSO-d_6, 363 K): δ = 11.03 (broad s, 3 H, NH), 8.75 (d, 4 H, *J* = 4.5 Hz, $H_{\beta pyr}$), 8.73 (d, 2 H, *J* = 4.8 Hz, $H_{\beta pyr}$), 8.71 (d, 2 H, *J* = 4.8 Hz, $H_{\beta pyr}$), 8.67 (broad d, 2 H, H_{aro}), 8.60 (d, 2 H, *J* = 8.0 Hz, H_{aro}), 8.56 (d, 1 H, *J* = 3.2 Hz, H_3), 7.83–7.45 (m, 4 H, H_{aro}), 7.73 (dd, 1 H, *Jo* = 7.0 Hz, *Jm* = 1.5 Hz, H_{aro}), 7.52 (dd, 2 H, *Jo* = 7.5 Hz, *Jm* = 1.8 Hz, H_{aro}), 7.43 (td, 2 H, *Jo* = 7.5 Hz, *Jm* = 1.8 Hz, H_{aro}), 7.37 (td, 2 H, *Jo* = 7.5 Hz, *Jm* = 1.8 Hz, H_{aro}), 7.35 (dd, 1 H, *Jo* = 9.0 Hz, *Jm* = 3.2 Hz, H_5), 5.38 (d, 2 H, *J* = 9.0 Hz, H_6), 2.06 (m, 4 H, H_g/H_h), 1.88 (m, 2 H, H_l), 1.80 (m, 4 H, H_j/H_k), 1.66 (m, 2 H, H_i), 0.62 (t, 2 H, *J* = 9.0 Hz, H_f), –0.06 (t, 2 H, *J* = 9.0 Hz, H_d), –0.20 (m, 2 H, H_c), –0.36 (t, 2 H, *J* = 9.0 Hz, H_e), –1.23 (m, 2 H, H_b), –1.46 (m, 2 H, H_a), –2.52 (s, 2 H, –NH_{pyr}). HRMS (ESI-MS): calcd *m/z* = 1148.4895 for $C_{66}H_{62}N_{13}O_7$ $[M + H]^+$; found: 1148.4877. UV/Vis ($CHCl_3$/MeOH 10%): λ_{max} = 423 (ε/dm^3 mol^{-1} cm^{-1} 323400), 519 (16800), 550 (3900), 590 (4700) and 646 (1900) nm.

Synthesis of 7: In a 100 mL round bottom flask under argon, 200 mg (0.193 mmol) of **6**,[11] 2-bromomethyl-4-nitrophenol (53.6 mg, 0.231 mmol) and 0.2 mL of Et_3N were dissolved in 50 mL of freshly distilled THF. The solution was heated at 65 °C overnight and then dried under vacuum. The product was dissolved in $CHCl_3$ and poured onto a 15 μm silica gel column. Compound **8** was eluted first with 5.6% MeOH/$CHCl_3$ then the desired product **7** was eluted with 6.4% MeOH/$CHCl_3$. After evaporation to dryness, 168 mg of **7** were collected (yield = 66%). ^{1}H NMR (500 MHz, DMSO-d_6, 363 K): δ = 10.93 (broad s, 1 H, NH), 9.42 (broad s, 1 H), 9.24 (broad s, 1 H), 8.90 (d, 1 H, *J* = 5.0 Hz, $H_{\beta pyr}$), 8.89 (d, 1 H, *J* = 4.5 Hz, $H_{\beta pyr}$), 8.79 (d, 1 H, *J* = 5.0 Hz, $H_{\beta pyr}$), 8.76 (d, 1 H, *J* = 5.0 Hz, $H_{\beta pyr}$), 8.69 (broad s, 1 H), 8.67 (d, 1 H, *J* = 4.5 Hz, $H_{\beta pyr}$), 8.63 (d, 1 H, *J* = 4.5 Hz, $H_{\beta pyr}$), 8.55 (d, 1 H, *J* = 4.5 Hz, $H_{\beta pyr}$), 8.51 (d, 1 H, *J* = 4.5 Hz, $H_{\beta pyr}$), 8.24 (dd, 1 H, *Jo* = 7.5 Hz, *Jm* = 1.5 Hz, H_{aro}), 8.01 (d, 1 H, *J* = 8.0 Hz, H_{aro}), 7.97 (d, 1 H, *J* = 8.0 Hz, H_{aro}), 7.90 (dd, 1 H, *Jo* = 9.0 Hz, *Jm* = 3.0 Hz, H_5), 7.87 (td, 1 H, *Jo* = 7.5 Hz, *Jm* = 1.5 Hz, H_{aro}), 7.84 (d, 1 H, *J* = 3.0 Hz, H_3), 7.83–7.75 (overlapping m, 6 H, H_{aro}), 7.70 (td, 1 H, *Jo* = 7.5 Hz, *Jm* = 1.5 Hz, H_{aro}), 7.64 (td, 1 H, *Jo* = 7.5 Hz, *Jm* = 1.5 Hz, H_{aro}), 7.71 (d, 1 H, *J* = 6.5 Hz, H_{aro}), 7.48 (td, 1 H, *Jo* = 7.5 Hz, *Jm* = 1.5 Hz, H_{aro}), 7.45 (td, 1 H, *Jo* = 7.5 Hz, *Jm* = 1.5 Hz, H_{aro}), 7.41 (td, 1 H, *Jo* = 7.5 Hz, *Jm* = 1.5 Hz, H_{aro}), 7.64 (td, 1 H, *Jo* = 7.5 Hz, *Jm* = 1.5 Hz, H_{aro}), 6.77 (d, 2 H, *J* = 9.0 Hz, H_6), 3.18 (s, 2 H, CH_{2benz}), 2.43 (m, 1 H, -CH_2-), 2.24 (m, 1 H, -CH_2-), 2.10–1.75 (overlapping m, 7 H, -CH_2-), 1.62 (m, 4 H, -CH_2-), 1.18 (m, 2 H, -CH_2-), 0.87 (m, 2 H, -CH_2-), 0.72 (m, 1 H, -CH_2-), 0.50 (m, 1 H, -CH_2-), –0.08 (m, 1 H, -CH_2-), –0.22 (m, 1 H, -CH_2-), –0.48 (m, 2 H, -CH_2-), –0.58 (m, 1 H, -CH_2-), –1.14 (m, 1 H, -CH_2-), –1.20 (m, 1 H, -CH_2-), –1.63 (m, 1 H, -CH_2-), –2.45 (m, 1 H, -CH_2-), –2.57 (s, 2 H, -NH_{pyr}). HRMS (ESI-MS): calcd *m/z* = 1188.5208 for $C_{69}H_{66}N_{13}O_7$ $[M + H]^+$; found: 1188.5195 (1 ppm). UV/Vis ($CHCl_3$/MeOH 10%): λ_{max} = 423 (ε/dm^3 mol^{-1} cm^{-1} 301200), 517 (15400), 550 (4200), 589 (4900) and 645 (2000) nm.

Acknowledgment

The authors thank MENRT (A.D.) and Région Bretagne (C.R.) for financial support.

References

(1) Ferguson-Miller, S.; Babcock, G. T. *Chem. Rev.* **1996**, *96*, 2889.
(2) Lehninger, A. L. In *Biochemistry, the Molecular Basis of Cell Structure and Function*, 2nd ed.; Worth Publishers, Inc.: New York, **1975**.
(3) Zubay, G. L. In *Biochemistry*; Addison-Wesley Publishing Company, Inc.: Reading, USA, **1983**.
(4) Tsukihara, T.; Aoyama, H.; Yamashita, E.; Tomizaki, T.; Yamaguchi, H.; Shinzawa-Itoh, K.; Nakashima, R.; Yaono, R.; Yoshikawa, S. *Science* **1995**, *269*, 1069.
(5) (a) Yoshikawa, S.; Shinzawa-Itoh, K.; Nakashima, R.; Yaono, R.; Yamashita, E.; Inoue, N.; Yao, M.; Fei, M. J.; Libeu, C. P.; Mizushima, T.; Yamaguchi, H.; Tomizaki, T.; Tsukihara, T. *Science* **1998**, *280*, 1723. (b) Iwata, S.; Ostermeier, C.; Ludwig, B.; Michel, H. *Nature* **1995**, 660.
(6) Collman, J. P.; Boulatov, R.; Sunderland, C. J. In *The Porphyrin Handbook*, Vol. 11; Kadish, K. M.; Smith, K. M.; Guilard, R., Eds.; Academic Press: Boston, **2003**.
(7) (a) Collman, J. P.; Herrmann, P. C.; Boitrel, B.; Zhang, X. M.; Eberspacher, T. A.; Fu, L.; Wang, J. L.; Rousseau, D. L.; Williams, E. R. *J. Am. Chem. Soc.* **1994**, *116*, 9783. (b) Sasaki, T.; Naruta, Y. *Chem. Lett.* **1995**, 663. (c) Collman, J. P. *Inorg. Chem.* **1997**, *36*, 5145. (d) Baeg, J. O.; Holm, R. H. *Chem. Commun.* **1998**, 571. (e) Tani, F.; Matsumoto, Y.; Tachi, Y.; Sasaki, T.; Naruta, Y. *Chem. Commun.* **1998**, 1731. (f) Collman, J. P.; Fu, L.; Herrmann, P. C.; Wang, Z.; Rapta, M.; Broring, M.; Schwenninger, R.; Boitrel, B. *Angew. Chem. Int. Ed.* **1998**, *37*, 3397. (g) Kopf, M.-A.; Karlin, K. D. *Inorg. Chem.* **1999**, *38*, 4922. (h) Collman, J. P.; Rapta, M.; Broring, M.; Raptova, L.; Schwenninger, R.; Boitrel, B.; Fu, L.; L'Her, M. *J. Am. Chem. Soc.* **1999**, *121*, 1387.
(8) Andrioletti, B.; Boitrel, B.; Guilard, R. *J. Org. Chem.* **1998**, *63*, 1312.
(9) Ricard, D.; Andrioletti, B.; L'Her, M.; Boitrel, B. *Chem. Commun.* **1999**, 1523.
(10) Collman, J. P.; Shiryaeva, I. M.; Boulatov, R. *Inorg. Chem.* **2003**, *42*, 4807.
(11) Ricard, D.; L'Her, M.; Richard, P.; Boitrel, B. *Chem.–Eur. J.* **2001**, *7*, 3291.
(12) Fabian, M.; Wong, W. W.; Gennis, R. B.; Palmer, G. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 13114.
(13) Blomberg, M. R. A.; Siegbahn, P. E. M.; Wikstrom, M. *Inorg. Chem.* **2003**, *42*, 5231.
(14) (a) Proshlyakov, D. A.; Pressler, M. A.; Babcock, G. T. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8020. (b) Proshlyakov, D. A.; Pressler, M. A.; DeMaso, C.; Leykam, J. F.; DeWitt, D. L.; Babcock, G. T. *Science* **2000**, *290*, 1588. (c) MacMillan, F.; Kannt, A.; Behr, J.; Prisner, T.; Michel, H. *Biochemistry* **1999**, *38*, 9179.
(15) (a) Stubbe, J.; van der Donk, W. A. *Chem. Rev.* **1998**, *98*, 705. (b) Klinman, J. P. *Chem. Rev.* **1996**, *96*, 2541.
(16) (a) McCauley, K. M.; Vrtis, J. M.; Dupont, J.; van der Donk, W. A. *J. Am. Chem. Soc.* **2000**, *122*, 2403. (b) Collman, J. P.; Wang, Z.; Zhong, M.; Zeng, L. *J. Chem. Soc., Perkin Trans. 1* **2000**, *8*, 1217. (c) Cappuccio, J. A.; Ayala, I.; Elliott, G. I.; Szundi, I.; Lewis, J.; Konopelski, J. P.; Barry, B. A.; Einarsdottir, O. *J. Am. Chem. Soc.* **2002**, *124*, 1750.
(17) (a) Didier, A.; L'Her, M.; Boitrel, B. *Org. Biomol. Chem.* **2003**, *1*, 1274. (b) Didier, A.; Ricard, D.; L'Her, M.; Boitrel, B. *J. Porphyrins Phthalocyanines* **2003**, *7*, 281.
(18) Kamaraj, K.; Kim, E.; Galliker, B.; Zakharov, L. N.; Rheingold, A. L.; Zuberbuhler, A. D.; Karlin, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 6028.
(19) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) All the geometry optimizations were performed by using the MM+ force field. This force field is an extension of MM2 developed by Allinger.
(20) Zimmer, B.; Bulach, V.; Drexler, C.; Erhardt, S.; Hosseini, M. W.; De Cian, A. *New J. Chem.* **2002**, *26*, 43.
(21) Collman, J. P.; Zhang, X.; Herrmann, P. C.; Uffelman, E. S.; Boitrel, B.; Straumanis, A.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 2681.
(22) Selwood, D. L.; Livingstone, D. J.; Comley, J. C. W.; O'Dowd, A. B.; Hudson, A. T.; Jackson, P.; Jandu, K. S.; Rose, V. S.; Stables, J. N. *J. Med. Chem.* **1990**, *33*, 136.
(23) Collman, J. P.; Brauman, J. I.; Collins, T. J.; Iverson, B. L.; Lang, G.; Pettman, R. B.; Sessler, J. L.; Walter, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 3038.