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An Expeditious Synthesis of Tailed Tren-Capped Porphyrins

Pascale Even, Christian Ruzié, David Ricard, and Bernard Boitrel*

Université de Rennes1, Institut de Chimie, UMR CNRS 6509, Organométalliques et catalyse, 35042 Rennes Cedex, France

bernard.boitrel@univ-rennes1.fr

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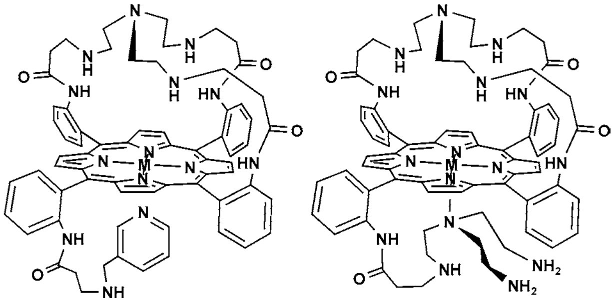
ABSTRACT



A one-pot two-step versatile synthesis of tailed tren-capped porphyrins has been achieved. The two resulting ligands demonstrate that this expeditious method can be applied to various axial bases to obtain highly functionalized macromolecules attractive for heme modeling purposes. Dioxygen binding of the pyridine-tailed iron complex is reported as a direct application.

The design and synthesis of close structural analogues is by essence a key step in biomimetic chemistry. Of particular interest, for dioxygen activation and/or transportation, the preparation of sophisticated porphyrins has become decisive for the investigation of functional models.[1] During the past 2 decades, various useful and powerful methods have been reported to achieve elaborated superstructures on the distal side of the porphyrin.[2] Among them, the congruent Michael addition of Collman was by far one of the most versatile methods,[3] followed some years later by the synthesis of chloroacetamido picket porphyrins.[4] Owing to these easy access methods, various ligands having a functionalized distal face could be prepared with good yields. On the other hand, the functionalization of the proximal face always required a sequence of protection/deprotection followed by an atropisomerization, which implied a much longer synthetic pathway with additionnal purification steps.[5]

We describe in this article a very direct method that makes it possible to introduce two different motifs on the two faces of a porphyrin: for instance, to functionalize the distal face and to bring a coordinating base that will be used later on as a fifth ligand for the iron atom of heme. Indeed, we have noticed that all syntheses ever reported and targeting tailed porphyrins started from the atropisomer αααα of tetra-

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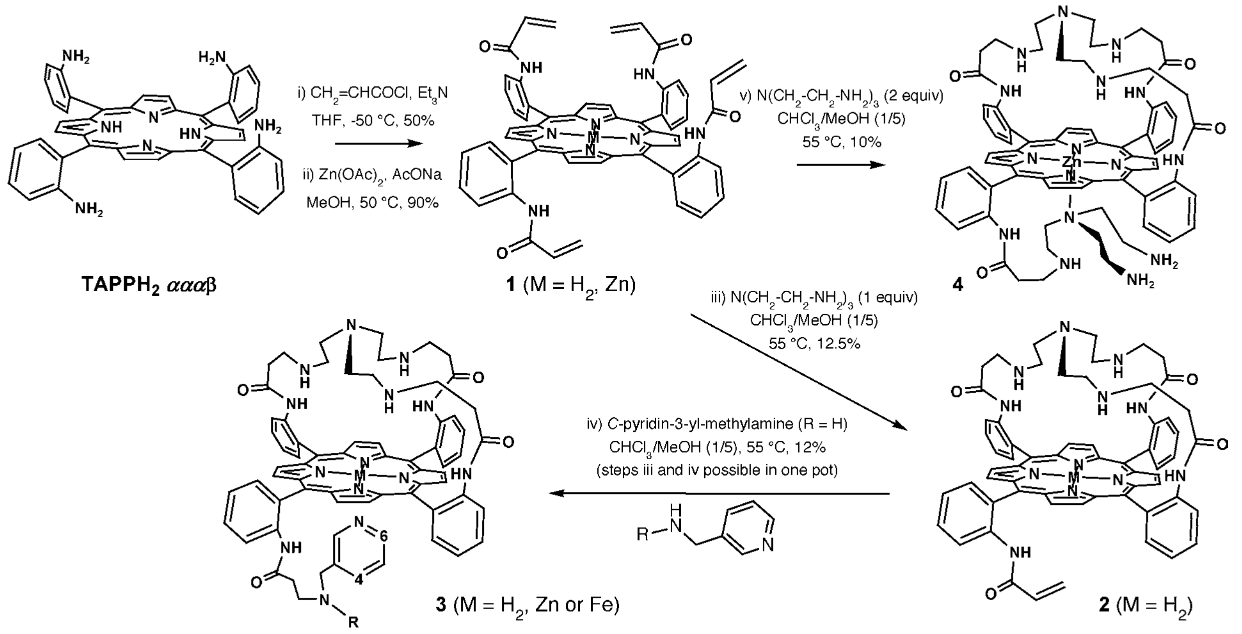
Scheme 1. Synthesis of Capped Porphyrins **3** and **4**



aminophenyl porphyrin (TAPP).[6] Thus, at some point, either an atropisomerization or a selective protection of the amino function being unique on one side of the porphyrin had to be performed.[7] A second posssibility consists of reducing[8] only one nitro group of a 2,6-dinitro-mesophenyl group or acylating only one amino function after reduction of the two nitro functions.[9] On the other hand, very little is known about the few tris(2-aminoethyl)amine (tren)-capped tailed porphyrins described in the literature.[10] As we wanted to investigate various properties as the dioxygen binding for the analogous compounds of "arbor" porphyrins,[11] with a built-in proximal ligand, we synthesized such porphyrins according to the synthetic pathway described in Scheme 1. After purification on silica gel of the atropisomer $\alpha\alpha\alpha\beta$ of TAPPH$_2$ which exists at 50% in the mixture, the reaction of acryloyl chloride led to the $\alpha\alpha\alpha\beta$ Michael acceptor with a yield of 60%. As this porphyrin exhibits a face with only one picket, the latter is much more reactive than in the case of the $\alpha\alpha\alpha\alpha$ atropisomer. To avoid any possible polymerization, we have found that the addition of acryloyl chloride on the porphyrin mixture cooled to −50 °C was optimal. In a second step, 1.1 equiv of tren was heated at 55 °C in a CHCl$_3$/MeOH mixture. At this step, the yield was not very high (12.5%) as probably the single Michael acceptor has a tendency to react with the nucleophilic reagents in the mixture and particularly the resulting secondary amino functions of the cap. However, this low yield was counterbalanced by the third step that could also be achieved in a "one-pot" fashion. Indeed, at this stage, free-base porphyrin **2** can either be isolated or allowed to further react with 5 equiv of *C*-pyridin-3-yl-methylamine, leading to tailed porphyrin **3**.

When steps iii and iv were performed in one pot, the overall yield was 12%, whereas when the third step was realized separately, after a column chromatography to isolate **2**, the same yield decreased down to 1.5%!

To improve the latter reaction, the same synthesis was investigated with both porphyrin **1Zn** and benzyl-pyridin-3-ylmethyl-amine (R = benzyl, Scheme 1). Indeed, with zinc inside the porphyrin core, a template effect with the nitrogen base to be tethered could be expected. Furthermore, benzyl-pyridin-3-ylmethyl-amine should be more reactive toward the 1,4 addition than its primary amine counterpart, namely *C*-pyridin-3-yl-methylamine. Unexpectedly, this reaction did not afford **3Zn** with R = benzyl. This observation is consistent with the fact that this particular secondary amine is too much hindered to be attached on the porphyrin.

Besides, when porphyrin **3** was prepared as the free base and zinc was inserted to obtain **3Zn**, proton NMR spectroscopy clearly demonstrated that the pyridine (R = H, Scheme 1) was able to coordinate the metal in the porphyrin. For instance, The two protons H$_4$ and H$_6$ that exhibit a signal at 7.67 and 4.52 ppm for the free-base porphyrin **3H$_2$** appear at 6.22 and 2.45 ppm, respectively (see Supporting Informa-

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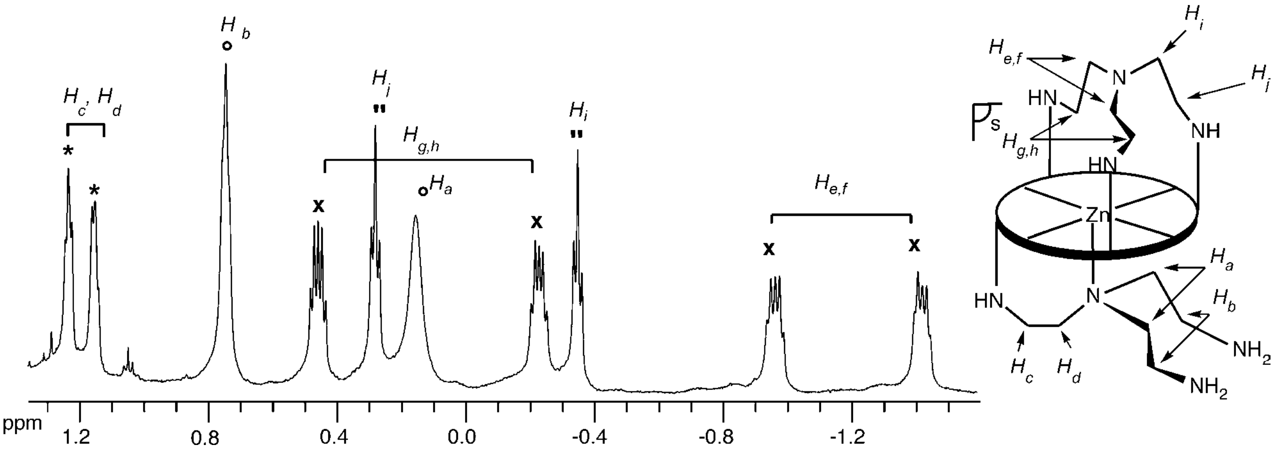

Figure 1. Chemicals shifts and assignments of the signals from the tailed tren unit in **4Zn**.

tion for more details). Actually, this observation is also true for the iron(II) porphyrin **3Fe** as, at first glance, iron insertion in **3H$_2$** led to a S = 2 five-coordinate spectrum typical of a complex in which the internal methyl-pyridine acted as the fifth ligand (Figure 2).[12]

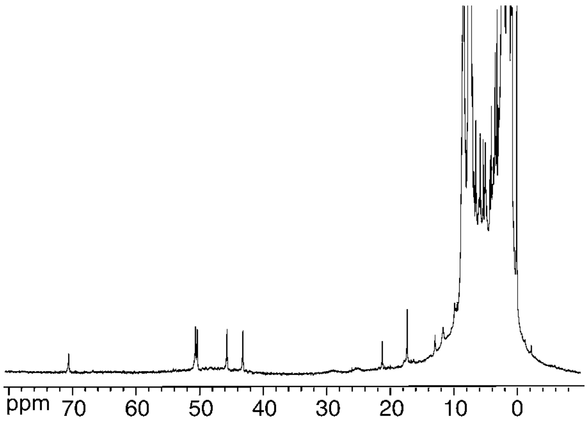

Figure 2. ^1H NMR spectrum of five-coordinate complex **3Fe** ($CDCl_3$, 298 K).

Furthermore, the nucleophilic reagent to be attached on the proximal side has not to be an aromatic amine as a pyridine or imidazole derivative. In fact, we were also able to attach a second tren molecule as the axial ligand for the zinc in the porphyrin. Indeed, if porphyrin **1Zn** was allowed to react with 2 equiv of tren, the tailed-tren porphyrin **4Zn** was purified (10%) and fully characterized in solution by ^1H NMR spectroscopy (Figure 1). As expected for such a compound, the coordinated tren motif exhibits a specific signature in the aliphatic domain. The two major differences with the distal tren are, first, the less negative chemical shifts of the various protons and, second, the multiplicity of these protons that appear not well resolved as the motion of the tren is less restricted when grafted by only one linker than by three linkers on the distal side.

The coordination of the tertiary amine of the proximal tren was definitely confirmed by the chemical shifts since if it was not effective, all of the methylene groups of the tren would appear at much lower fields.

The possibility of synthesizing a tren-capped tailed iron(II) porphyrin such as **3Fe**, in only three steps, allowed us to study straightaway the influence of the nitrogen base principally on the dioxygen affinity of this type of dioxygen carrier. Thus, the iron was inserted in the free-base **3H$_2$**. We employed the method that consists of heating the free-base porphyrin with iron bromide without any base to avoid the metalation of the tripod that could likely coordinate iron.

The dioxygen affinity was directly measured by UV−visible spectroscopy according to the method reported by Drago[13] and reinvestigated in the case of porphyrins by Collman.[14] Thus, using a tonometer, by adding increasing quantities of diluted dioxygen in nitrogen to a solution of **3Fe**, at 25 °C in toluene, $P_{1/2}(O_2) = 1/K_{O_2} = 1.6 \times 10^{-5}$ Torr was measured. The reversibilty of the gas binding was monitored after the measure by forming the carbon monoxide adduct (Figure 3). It was also probed by bubbling argon through the tonometer and by recording several UV−visible spectra. However, since the affinity of **3Fe** for dioxygen is very high, it was difficult to obtain the original absorption of the five-coordinate UV−vis spectrum because of solvent evaporation. As the reaction is very slow, the UV−vis spectrum of the dioxygen adduct was recorded after at least 1 week to verify that the absorption was not modified and

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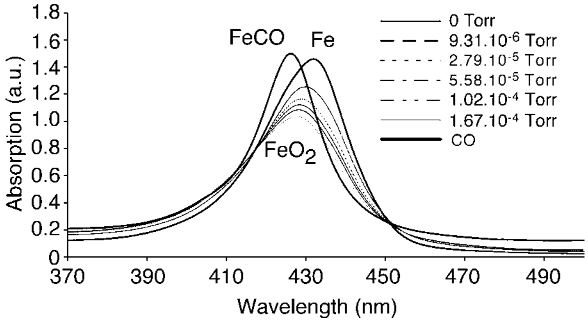

Figure 3. UV−vis monitoring upon coordination of O_2 and CO on **3Fe**. Intermediate O_2 partial pressures are tabulated.

hence that the equilibrium was actually reached. This $P_{1/2}(O_2)$ value compares with that reported for a related compound lacking the built-in nitrogen base, for which we measured a $P_{1/2}(O_2) = 9.8 \times 10^{-5}$ Torr.[11b] It is worth noting that although for the latter, 1000 equiv of 1,2-dimethylimidazole was used as the iron fifth ligand, the affinity for dioxygen was not very different than that measured with an intramolecular base. However, these dioxygen affinities are very high but the equilibrium is so slow to be reached (>12 h) that it prevents any possible application for these complexes. On the other hand, further functionalizations[15] of the secondary amines of the distal cap clearly show that a hydrogen bond cannot be the single decisive feature to explain these dioxygen affinities. It is plausible that the “cage” structure of the tripod could be itself responsible for these dioxygen affinities, but this hypothesis needs to be confirmed.

In summary, we have demonstrated in this work that a direct access to highly functionalized molecules was possible starting from the $\alpha\alpha\alpha\beta$ atropisomer of TAPP. Although the yields are not very high, as this methodology can be performed as a two-step one-pot synthesis and considering the complexity of the resulting structures, it deserves to be employed. Indeed, it allows a direct investigation of the gas binding properties of various types of synthetic dioxygen carriers. Additionally, the modular approach with only two steps will open up new possibilities for the proximal ligand of heme models. Incidentally, we have been able to synthesize an iron(II) porphyrin that exhibits the highest O_2 affinity reported to date.

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Supporting Information Available: Experimental procedures and full spectroscopic data, including 1D and 2D NMR spectra of the various new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) To be published elsewhere.