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Efficient and Versatile Synthesis of New Porphyrins Bearing an N3O Moiety: Ligands for Mimicking Cytochrome *c* Oxidase

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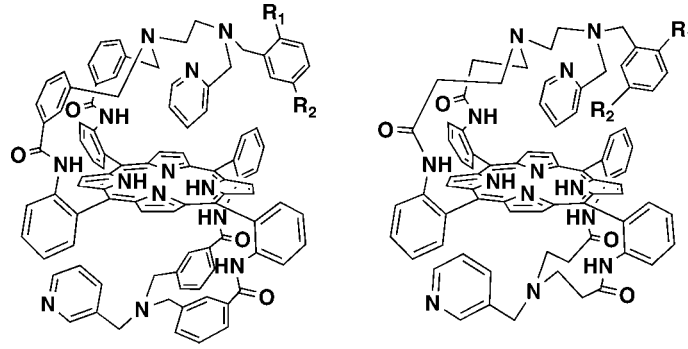
ABSTRACT



Two new generations of ligands for cytochrome *c* oxidase mimicking have been designed and synthesized via an efficient, convergent, and versatile synthesis. These porphyrins are functionalized with both an internal nitrogen base on one side and a triaza (N3) or a triaza-phenol (N3O) moiety on the other side, attached to the macrocycle by various spacers. Unlike tailed porphyrins, the triaza motif as well as the nitrogen base are linked by two points.

Dioxygen binding and activation are obviously two of the most important phenomena in aerobic biological systems.[1] Theses two reactions are illustrated in the activity of a paramount enzyme, cytochrome *c*-dioxygen oxido-reductase, commonly named cytochrome *c* oxidase (C*c*O).[2] The latter catalyzes the four-electron/four-proton reduction of dioxygen in water producing a proton gradient across the mitochondrial membrane.[3] The resulting electrochemical potential gradient provides the driving force needed by ATP synthase for the synthesis of ATP from ADP.

Indeed, dioxygen binding and reduction occur at a heterobinuclear site that is comprised of a heme a_3 and Cu_B in close proximity (Figure 1, left).[4] Additionally, one copper-ligated histidine ligand (His240) is covalently linked to a

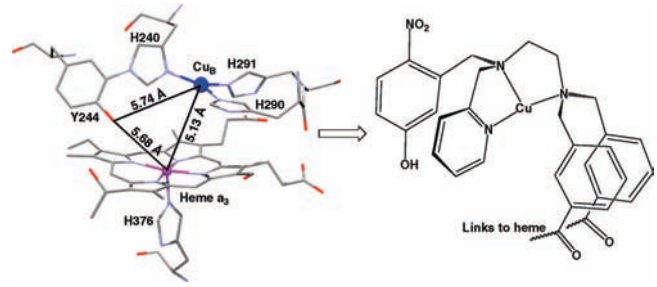


Figure 1. Cytochrome *c* oxidase active site (left) and subsequent design of a copper complex (right).

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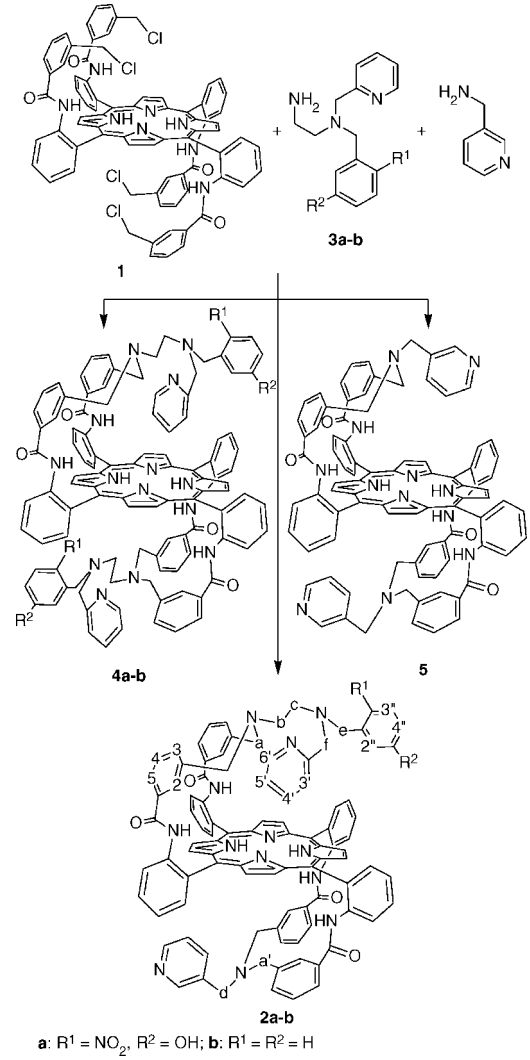
tyrosine side chain (Tyr244) according to a posttranslational modification.[5] This cross-linking is believed to decrease the pK_a value of the tyrosine residue around physiological pH, therefore allowing the transfer of a proton to the bound superoxo complex or the transfer of an electron via the formation of a tyrosyl radical or both. Since dioxygen reactivity of heme-copper complexes has attracted many synthetic modeling chemists, numbers of synthetic model compounds have been described to understand the key step of the reductive cleavage of the O−O bond.[6] For instance, Naruta et al. have described the first X-ray structure of an iron-η^2-copper-η^1-peroxo complex in which the copper ligand is based on a tetraza motif (TMPA).[7] However, Karlin et al. clearly demonstrated the influence of denticity (tetradentate versus tridentate) of the copper coordination sphere on the binding mode of dioxygen.[8] Nevertheless, few models incorporate all the structural features of the active site: (1) a heme possessing an intramolecular fifth ligand; (2) a flexible triaza ligand for copper I/II coordination, and finally (3) a mimic of Tyr244. On one hand, Collman et al. have reported the synthesis of such molecules,[9] one of them existing as a mixture of two isomers,[10] and on the other hand, Karlin et al. studied the reactivity of dioxygen on a model in which both entities, the heme and the phenol cross-linked tetraza complex, are not covalently linked.[11]

This observation prompted us to synthesize a new triaza ligand bearing a Tyr244 mimic which could be attached by two linkers on a tetraaryl-porphyrin. Observing the active site of C*c*O, we have designed the molecule depicted in Figure 1 (right) in which a nitro-phenol is attached to a triaza ligand. Indeed, this nitro-phenol, with a pK_a of 7.5, represents a simple way to probe if the transfer of a proton to the superoxo complex is an important process for the catalytic activity. Moreover, this N3O ligand can be easily linked on a porphyrin. The properties of the phenol can also be modulated by varying the nature of the substituent in para position as well as the position itself of the OH group on the aromatic ring. Accordingly, we chose to functionalize tetrakis-*o*-aminophenyl porphyrin[12] (TAPP) $\alpha\alpha\beta\beta$ as this atropisomer allows the attachment of two different residues on the opposite sides of the porphyrin. For instance, we have already shown with an X-ray structure that a diethyl malonate group attached on each side of porphyrin **1** was oriented toward the center of the porphyrin.[13]

Furthermore, a commercially available compound such as *C*-pyridin-3-yl-methylamine can be bis-linked on the second face of the porphyrin, delivering a fifth ligand to the iron in future steps.[14] The syntheses of the desired compounds were achieved by using one-pot procedures in which two different nucleophiles were mixed with porphyrin **1**[15] in THF at 70 °C overnight (Scheme 1).

Scheme 1. Synthetic Route to Porphyrins **2a**,**b**



For instance, to obtain **2a** (11%), *C*-pyridin-3-yl-methylamine and compound **3a** were used to obtain both a nitrogen base and an N3O coordination sphere for copper, respec-

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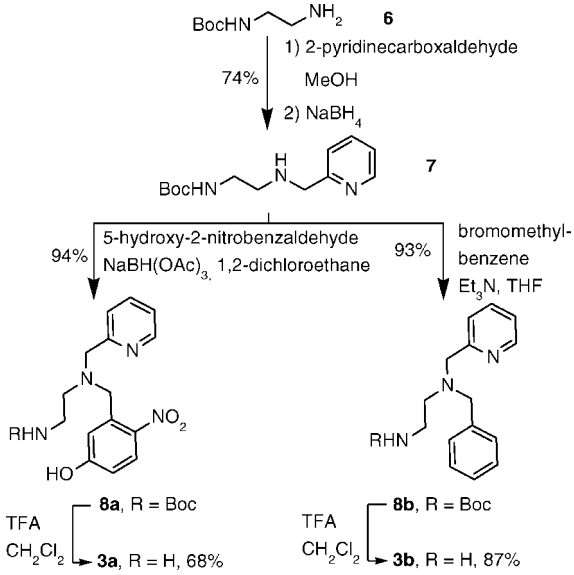
tively. But, obviously, two minor compounds were also formed as porphyrins **4a** (7%) and **5** (4%), leading to a global yield of 22%. For comparison purposes, the analogous compound of **2a** bearing a benzyl group instead of the benzyl nitro phenol residue, namely, **2b** (11%), has also been synthesized. Actually, as the synthesis of the tripods is convergent, it implies only one new step (Scheme 2). Briefly,

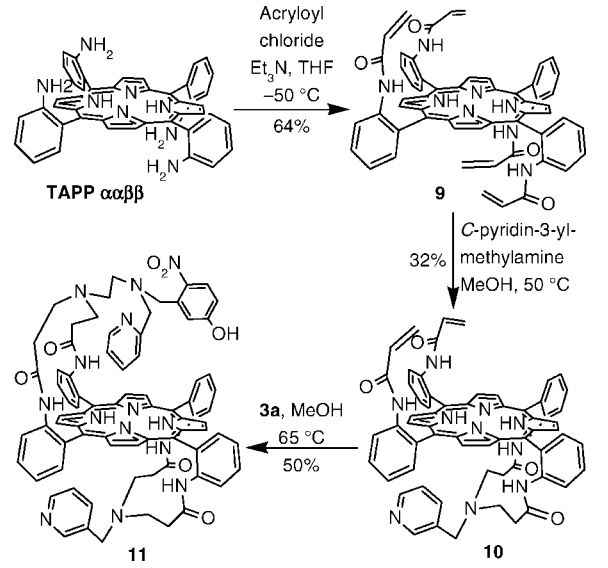
Scheme 2. Synthesis of New N3O and N3 Moieties



3a or **3b** was prepared starting from (2-amino-ethyl)-carbamic acid *tert*-butyl ester **6**.[16] In a first step, the third nitrogen atom of the future triaza compound is introduced by reductive amination of the primary amine of **6** to afford **7** (74%). A second alkylation of the same nitrogen atom leads to either **8a** (94%) or **8b** (93%) using either 5-hydroxy-2-nitro-benzaldehyde or bromomethyl-benzene. Exposure of the latters to TFA resulted in **3a** (68%) or **3b** (87%).

It should be mentioned that this convergent synthesis is efficient using various electrophilic picket porphyrins. We have tuned it for porphyrin **1** in which the pickets are quite rigid and preorganized (U-shaped pickets) as we wanted the resulting models to exhibit some preorganization both for the iron and the copper. For instance, Chang et al. were the first to demonstrate that such a 1,3-chloromethyl benzoyl link was properly preorganized to deliver an imidazole residue close to the iron of a porphyrin.[17] We reasoned that any structure delivered by two such linkers would be firmly maintained over the porphyrin. However, to dispose of analogous compounds exhibiting less preorganization, we applied the same synthesis to **9** (Scheme 3) that possesses

Scheme 3. Sequential Synthesis of Model Compound **8**



two acrylamide pickets per side and that should react according to a Michael addition.[18]

However, porphyrin **9** reacts differently from porphyrin **1**. For the former, we were able to isolate porphyrin **10** in which only one side of the porphyrin was functionalized by *C*-pyridin-3-yl-methylamine with a decent yield of 32%. This peculiar reactivity allowed us to graft the N3O synthon onto **10** in a final step to isolate with 50% yield the expected compound **11**.

As both series of porphyrins feature an internal nitrogen base as the fifth ligand of the metal in the porphyrin, it was crucial to verify that these new structures allow the coordination of their intramolecular fifth ligand. In the case of the series built-up with the acrylamide pickets, this coordination was verified on porphyrins **10Zn** and **11Zn** by the actual coordination of the pyridine derivative monitored by ^{1}H NMR spectroscopy (see Supporting Information for further details, S4−S5, S18). In the series prepared from porphyrin **1** bearing "U-shaped" pickets, the coordination of the internal nitrogen base was evidenced for both zinc complexes of porphyrin **5** in which the two sides of the macrocycle are equivalent and porphyrin **2b** bearing a pyridinyl base and a benzyl N3 ligand (Figure 2). With the proton NMR data of **2b** and **2bZn**, the coordination of the axial ligand on zinc is characterized by the upfield shift of the protons from the pyridinyl cycle but also by the deshielding of proton H_2' located in the position 2 of the "U-shaped" picket. In comparison, on the NMR spectra of porphyrins **5** and **5Zn** (Supporting Information, S3), proton H_2' is shifted from 3.81

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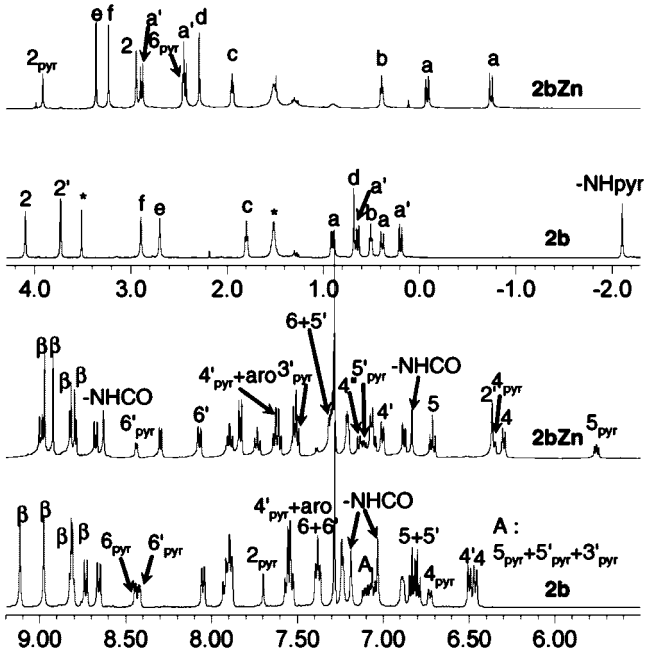

Figure 2. ^{1}H NMR of compounds **2b** and **2bZn** (500 MHz, $CDCl_3$, 323 K): pyr refers to the aminomethyl pyridyl residues.

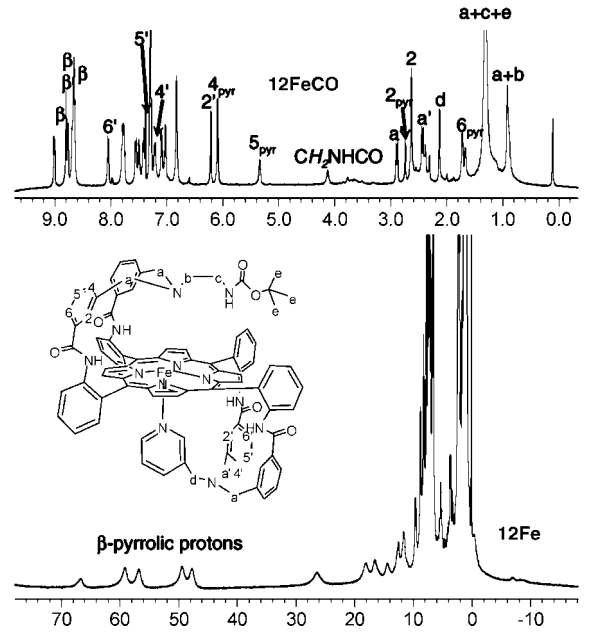

Figure 3. ^{1}H NMR of compounds (a) **12Fe** and (b) **12FeCO** (500 MHz, $CDCl_3$, 298 K).

ppm downfield to 4.78 ppm. Moreover, the signal due to H_2' and those from the pyridine cycle are sharp for the free-base porphyrin and become large and unresolved for the zinc porphyrin. These observations are consistent with the fact that the strap has to be moved away from the center of the porphyrin to allow the coordination of the axial base.

Additionally, the coordination of this internal nitrogen base was also observed in this series with iron inside the porphyrin. For this purpose, we have studied the behavior of the iron complex of porphyrin **12** (Figure 3), the analogue of porphyrins **2a** or **2b**, but resulting from the addition of *C*-pyridin-3-yl-methylamine on one side and (2-amino-ethyl)-carbamic acid *tert*-butyl ester **6** on the other one. As this type of porphyrin will be further studied as bimetallic iron−copper complexes, in a first step, it is crucial to verify first that the iron-only complex can form a five-coordinate complex with the built-in nitrogen base and second that the former can coordinate a small molecule as dioxygen or carbon monoxide in the sixth coordination site of iron(II). Again, these two phenomena can be easily probed by proton NMR spectroscopy. Indeed, it is well established that five-coordinate high-spin ($S = 2$) iron(II) complexes exhibit a typical proton pattern on NMR spectra with β-pyrrolic protons downfield-shifted at around 50−60 ppm[14,19] (Figure 3, bottom) and that coordination of carbon monoxide on such complexes leads to a six-coordinate diamagnetic complex for which a regular spectrum is observed (Figure 3, top).

In summary, owing to a versatile synthesis, we have prepared three porphyrins, **2a**, **2b**, and **11**, that exhibit important structural features for future C*c*O modeling, as a built-in nitrogen base and a flexible triaza-benzyl residue or a triaza-benzylphenol residue both suspended over the center of the porphyrin via a strap attached on adjacent meso positions. This particular geometry is expected to allow some flexibility to the linked structures. Porphyrin **11** possesses the same functions on both sides of porphyrin **2a** but without preorganization, due to aliphatic spacers instead of 1,3-aromatic linkers. The phenol residue of the distal structure can easily be substituted by different groups. The reactivity toward dioxygen as well as spectroscopic characterization of these models are currently under investigation.

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Supporting Information Available: Experimental section and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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