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First Synthesis of Single-"Strapped Cyclam-Porphyrins"

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***Abstract :** The first synthesis of strapped cyclam porphyrins is described ; these will be studied as dioxygen carriers as well as cytochrome C oxidase models. The original derivatives are characterized by mass spectrometry and ^{1}H NMR spectroscopy. The cofacial conformation of the two different macrocycles is confirmed by ^{1}H NMR data.*

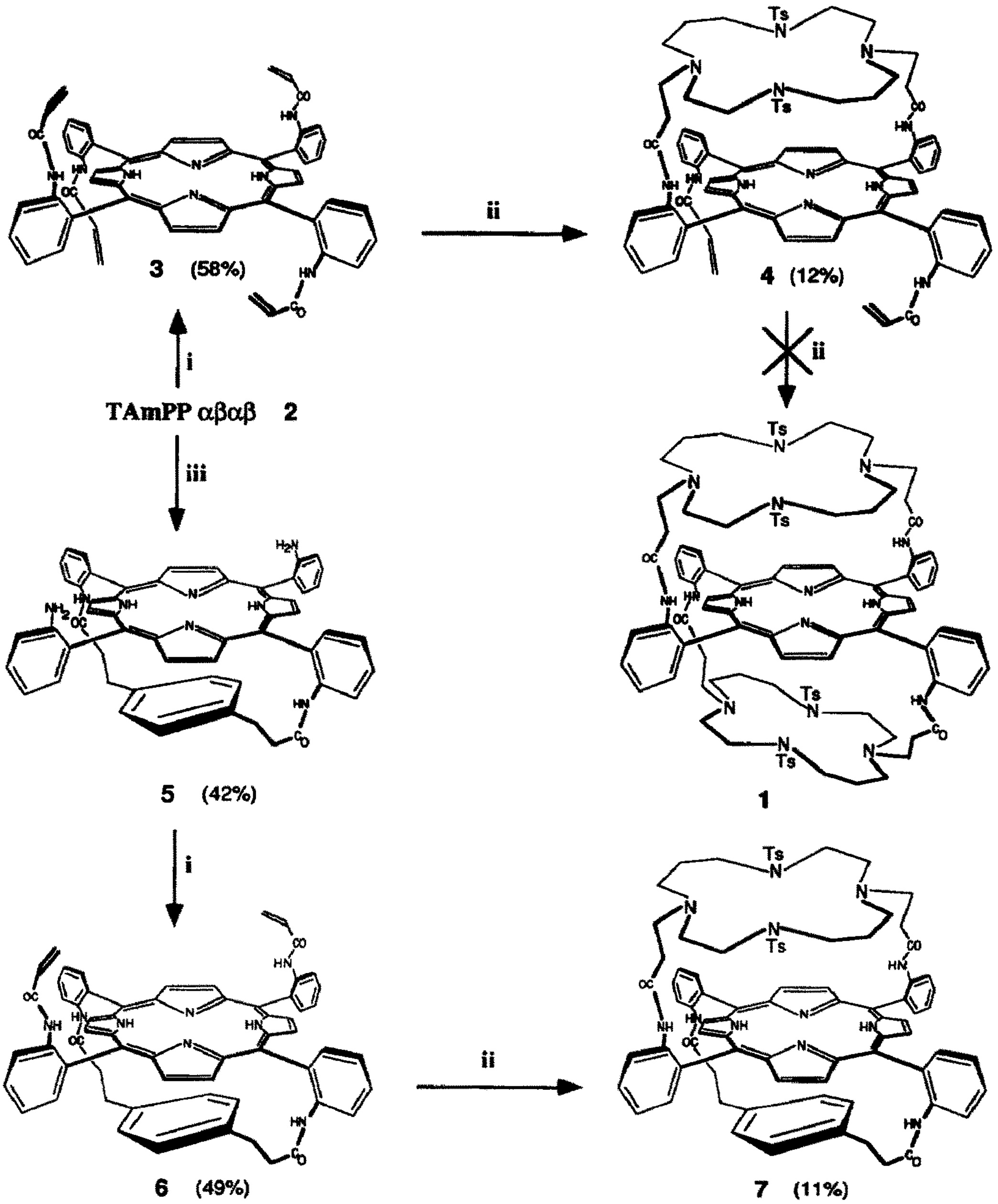
Cytochrome *C* oxidase is the respiratory enzyme that catalytically reduces O_2 to H_2O in mitochondria. Antiferromagnetic coupling between Fe(III) and Cu(II) in the oxygen-binding site is generally proposed[1] in order to explain the anomalous magnetic and spectroscopic properties of this enzyme. In spite of extensive studies, the active site structure of cytochrome *C* oxidase remains a controversial problem in chemistry. In most of the known models, either a ligand[2] bridges the two metal centers[3] or a molecular superstructure maintains the two metallic centers in close proximity.[4-7] Some of these models exhibit a weakly magnetically coupled heme-copper complex. We wish to report the synthesis of a new type of structure which unambiguously induces a cofacial geometry of two different macrocycles, *e.g.* a porphyrin and a cyclam. The only other instance of a molecule composed of these two macrocycles is ligated in a "tailed" structure, in which no magnetic interaction occurs.[7]

Our initial attempt to prepare a porphyrin such as the model **1** relied on reaction of the suitable diacyl chloride and the αβαβ atropisomer of the tetraamino-phenyl porphyrin **2**.[8a] To this end, the 1,4,8,11-tetra-azacyclotetradecane-4,11-ditosyl 1,8-dipropionic (or diacetic) acid[9] was synthesized but the activation of the dicarboxylic acids (*e.g.* into diacyl chloride, dianhydride, *etc.*) according to well established methods[10] failed. We then decided to apply the previously described synthesis of Weiss *et al.*[7] , which is based on a 1,4 addition reaction, with the 1,4,8,11-tetra-azacyclotetradecane-1,8-ditosyl[9] (named for clarity diTs cyclam) (Scheme 1) and the porphyrin **3** as the Michael acceptor. The starting materials were totally recovered even after long reaction times at room temperature!

Although such additions of secondary amines do not generally require any catalyst, some examples in the literature report successful methods of using a catalyst to induce a nucleophilic reaction in a Michael-type addition. In this particular series, we found that 1,8-bis-(dimethylamino)-naphthalene (DMAN) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzes the addition of the diTs cyclam on the porphyrin **3** to yield the single strapped cyclam-porphyrin **4** (Figure 1) (12% based on starting porphyrin **3** , 19% relative to transformed porphyrin **3**) whereas catalysts such as Triton-B or fluoride anions failed.[11a] Under the same

Scheme 1 : Synthetic strategy leading to "Strapped cyclam-porphyrins"

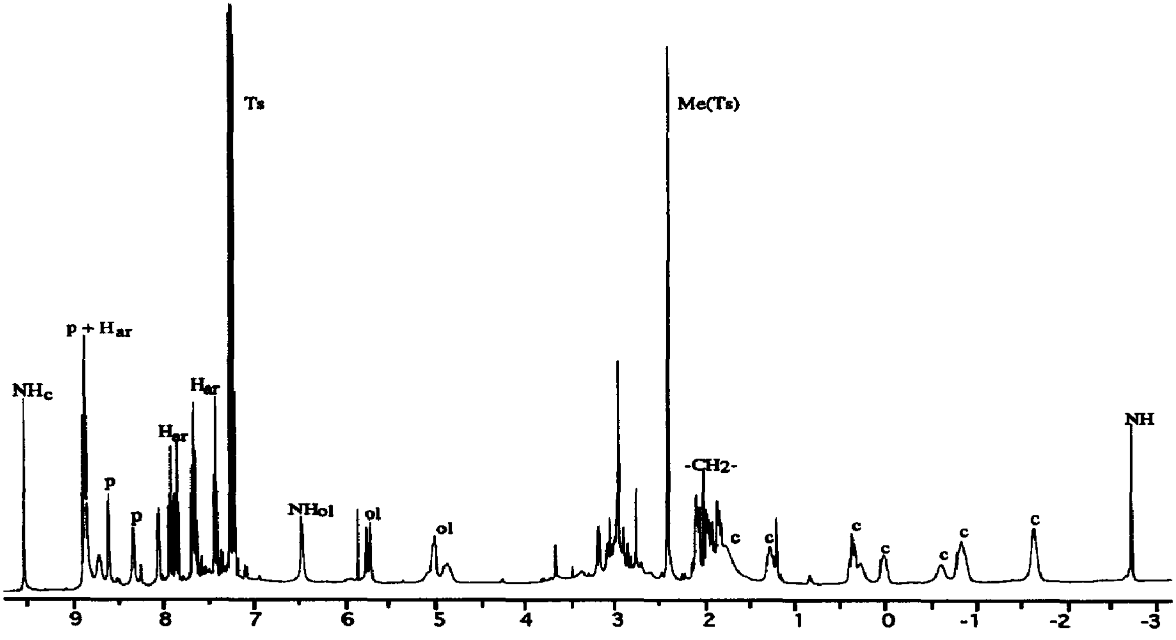
i : acryloyl chloride, N-methyl piperidine, anhydrous THF ; ii : diTs cyclam, DMAN, EtOH
iii : *p*-phenylene dipropionyl chloride, N-methyl piperidine, anhydrous THF, high dilution.



conditions, transformation of 4 into the desired porphyrin 1 could not be achieved but led only to oligomers or polymers and the unreacted starting materials. In light of this, we decided to follow the same synthetic pathway starting from the singly-hindered porphyrin 5 already described by Momenteau *et al.*.[8b] Thus, the reaction of one equivalent of *p*-phenylene dipropionyl chloride and 2 leads to the single strapped porphyrin 5 in a 42% yield ; this reaction was followed by condensation of two equivalents of acryloyl chloride in anhydrous THF with N-methyl piperidine as a base to afford the macrocycle 6. Finally, treatment of a solution of 6, diTs cyclam and DMAN in ethylic alcohol gives the model 7 in a 11% yield.

Most surprising is the successful synthesis of the single-face protected porphyrin 4 (which can potentially be functionalized by another porphyrin like 5, leading to a tri-macrocyclic compound) without any trace of compound 1. Compounds 4 and 7 are able to coordinate two metallic centers ; thus, incorporation of iron and copper should lead to cytochrome *C* oxidase models or, in the case of the dicobalt complexes, to dioxygen carriers. Work is in progress to improve this type of synthesis and to study the characteristic properties of these new compounds.

Figure 1: 400 MHz ^{1}H NMR spectrum of porphyrin 4.($CDCl_3$ / 10^{-3}M , chemical shifts in ppm relative to $CDCl_3$ at 7.25ppm)



NH$_c$: amide protons on the cyclam side ; p: β pyrrolic protons ; H$_{ar}$: *meso*-aromatic protons as four triplets and four doublets ; Ts: aromatic protons of the tosyl group ; NH$_{ol}$: amide protons on the olefin side ; ol: olefinic protons ; Me(Ts): methyl of the tosyl group ; $-CH_2-$: aliphatic protons of the strap ; c: protons of the cyclam macrocycle.

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Notes

All new compounds gave satisfactory spectroscopic data (^1H NMR, MS) ; ^1H NMR spectra as shown in figure 1 were elucidated by two-dimensional COSY sequences.

UV Visible data : wavelengths given in nm with the molar extinction coefficient into brackets ($10^{-3}.\varepsilon, dm^3\ mol^{-1}\ cm^{-1}$) **3:** 419 (254.5), 513 (14.6), 545 (3.6), 586 (4.9), 643 (1.2) ; **4:** 422 (272.3), 514 (14.8), 549 .(5.0), 587 (4.7), 646 (1.6) ; **6:** 419 (215.7), 512 (24.6), 542 (5.7), 583 (7.6), 639 (2.8) ; **7:** 421 (229.6), 513 (23.1), 546 (13.6), 585 (13.5), 642 (10.2).

NMR data : chemical shifts given in ppm, coupling in Hertz.

7: **NHc**: 9.61, 2H, s ; **Har**: 8.90, 2H, d, J=8.4 ; **p**: 8.83, 4H, s broad ; **p**: 8.65, 2H, d, J=4.4 ; **p**: 8.46, 2H, broad ; **Har**: 8.18, 2H, d, J=7.3 ; **Har**: 8.09, 2H, d, J=8 ; **Har**: 7.88, 2H, t, J=7.6 ; **Har**: 7.79, 2H, t, J=7.3 ; **Har**: 7.67, 2H, t, J=7.4 ; **Har**: 7.48, 2H, d, J=7.2 ; **Har**: 7.30, 2H, t, J=7.8 ; **Har(Ts)**: 7.37, 4H, dd, J=8.4 ; **NHs**: 5.68, 2H, s ; **Har(s)**: 4.07, 4H, s ; **Me(Ts)**: 2.45, 6H,s ; **CH_2(c)**: from 2.16 to 2.00, m, 8H ; **c**: 1.48, 4H, broad ; **CH_2(s)**: 1.30, 4H, t, J=6.4 ; **CH_2(s)**: 0.87, 4H, t, J=6.8 ; **c**: 0.40, 4H ; 0.01, 2H ; -0.55, 2H ; -0.79, 4H ; -1.69, 4H, broad ; **NH**: -2.69, 2H, s.

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