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Steric Decompression of Picket-Strapped Porphyrins for the Synthesis of Side-Differentiated Chelates

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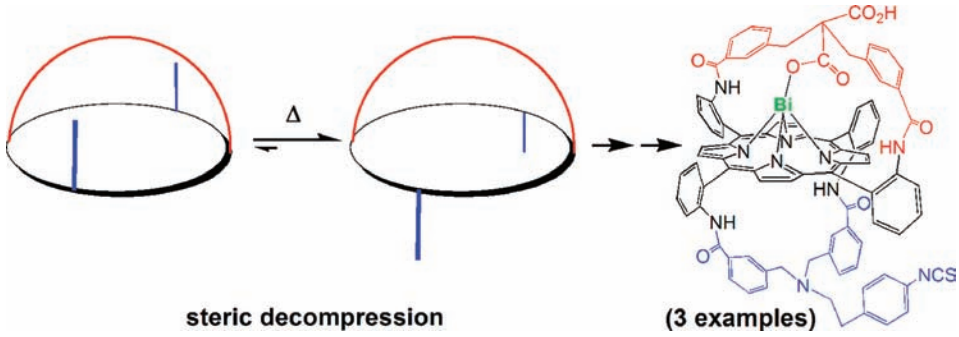
ABSTRACT



A general method to synthesize various αβαβ bis-strapped porphyrins, with a different functionalization on each side of the macrocycle, is described. The resulting new chelates may find applications as analogues of heme protein active sites, bifunctional chelates, or specific bis-chelating molecules with potential medical utility.

One of the main challenges facing organic chemists is the production of architecturally complex molecules in an easy, efficient, and economical way. This situation is particularly true in the domain of biomimetic heme analogues, with which chemists attempt to reproduce enzyme function with simple synthetic models.[1] Various structural features such as the presence and number of axial ligand(s), the selective functionalization of the proximal or distal side of the heme, and the nature of other functional groups at the periphery of the distal pocket are appropriate examples. However, in most cases, each side of the porphyrin has to be selectively derivatized to exhibit different functionalities. For instance, our research group has recently diverted the basic coordination properties of the porphyrinic core to complex metals such as bismuth(III) or lead(II) via the functionalization of tetra-aryl porphyrins.[2] To transform the initial ligand in a bifunctional chelate, a selective functionalization of the two sides is required. This possibility has been reported for the atropisomer αααβ of tetra-aminophenyl porphyrin[3] but not for the least abundant atropisomer αβαβ, which allows the tethering of two different functional groups, one on each side, with each group attached through two points.

Herein, we propose a general method to synthesize various αβαβ bis-strapped porphyrins (**1**, **2**, or **3**; Schemes 1 and 2) which can be used as analogues of heme protein active sites,[4] bifunctional chelates, or specific bis-chelating molecules with potential medical applications (Figure 1).[5]

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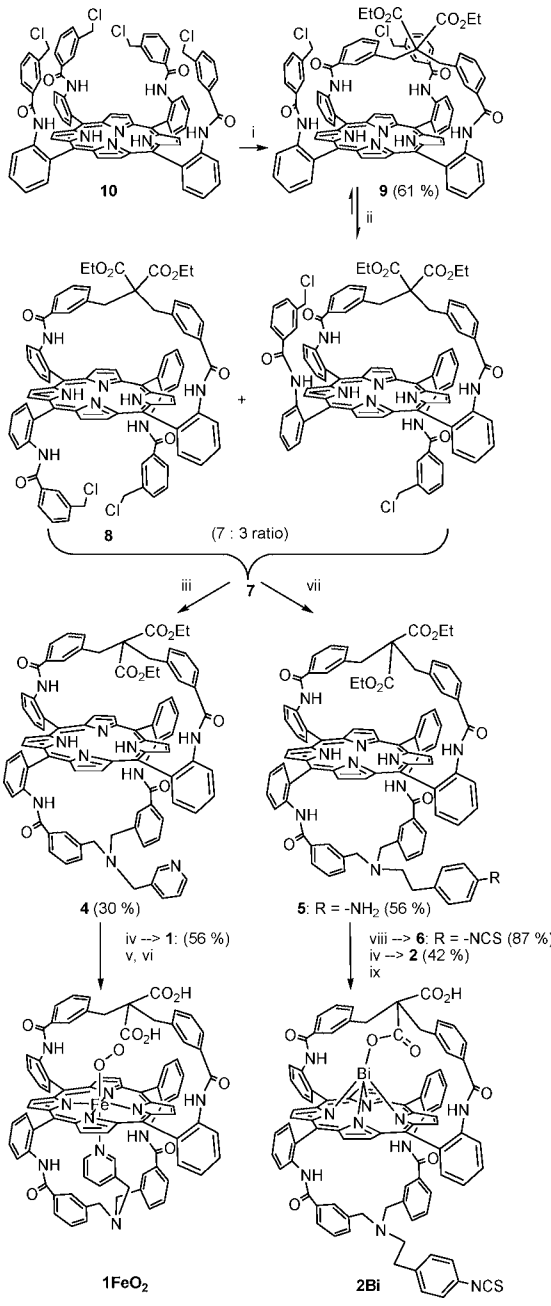
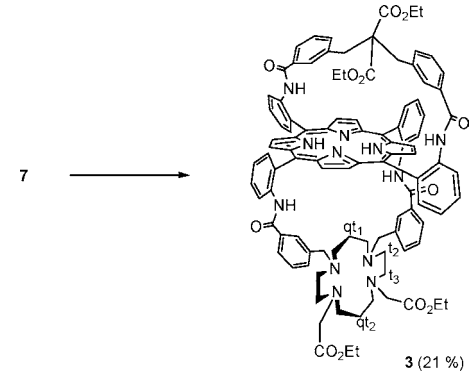
Scheme 1. Synthesis of Chelates **1** and **2** and Their Metallic Complexes[a]



[a] *Reagents and conditions.* i: diethyl malonate (10 equiv), EtONa, CH_2Cl_2, 2 h. ii: heating in toluene, 80 °C, 48 h. iii: *C*-Pyridin-3-yl-methylamine, NaI, K_2CO_3, THF, reflux overnight. iv: BBr_3, CH_2Cl_2, rt, overnight. v: Drybox,<2 ppm O_2, $FeBr_2$, reflux THF, 2 h. vi: Dioxygen. vii: 4-(2-Aminoethyl) benzenamine, NaI, K_2CO_3, THF, reflux 48 h. viii: Thiophosgen, $NaHCO_3$, $CHCl_3$, H_2O, 3 h, rt. ix: $Bi(NO_3)_3$, pyridine, rt.

Unlike the single-face hindered porphyrins of Momenteau[6] or the "jellyfish" porphyrins of Kyuno,[7] both synthesized from the atropisomer $\alpha\beta\alpha\beta$ of tetrakis-*o*-aminophenylporphyrin (TAPP), this method starts from the atropisomer $\alpha\alpha\alpha\alpha$, the abundance of which can be increased to 70%.[8] This method takes advantage of the 5,15-single-strapped structure of porphyrin **9**, obtained by reaction of 3-chloromethyl-benzoyl chloride with the $\alpha\alpha\alpha\alpha$ TAPP atropisomer

Scheme 2. Synthesis of Chelate **3**[a]



[a] *Reagents and conditions.* (11-Ethoxycarbonylmethyl-1,4,8,11-tetraaza-cyclotetradec-1-yl)-acetic acid ethyl ester, NaI, CH_3CN, K_2CO_3, 80 °C, 48 h.

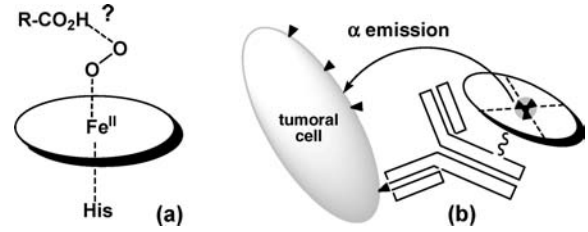


Figure 1. Useful porphyrinic chelates to (a) probe a hydrogen bond and (b) synthesize a bifunctional chelate.

(affording **10**) and subsequent reaction with the anion of diethyl malonate as previously reported (Scheme 1).[9] Indeed, when only 10 equiv of diethyl malonate is added, no porphyrin with straps attached on adjacent positions (5,10) is isolated. The key step in our method is a steric decompression of the strap of **9** by atropisomerization of the two remaining pickets. This decompression was easily achieved by heating the porphyrin in toluene at 80 °C for 48 h and resulted in **7**, a mixture of two atropisomers in a 7:3 ratio, based on proton NMR integration. The isomers could not be separated by the usual method of column chromatography on silica gel. However, we attributed the most abundant compound to the $\alpha\beta\alpha\beta$ atropisomer **8** and the least abundant to the $\alpha\alpha\alpha\beta$ atropisomer. This attribution was unambiguously confirmed by the synthesis of **8** starting from $\alpha\beta\alpha\beta$ TAPP (with a low overall yield of 1.4%, compared to 27% via the new method described above).

Without further purification, the atropisomeric mixture **7** was reacted in good yields with various nucleophilic reagents to functionalize the second face of porphyrin **8**, as shown in Scheme 1.

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For instance, the reaction with *C*-pyridin-3-yl-methylamine led to heme biomimetic model **4**, purified by silica gel chromatography from side products resulting from the addition of the nucleophilic reagent on each of the two remaining pickets of the monostrapped atropisomer $\alpha\alpha\alpha\beta$. Treatment of **4** with BBr_3 afforded porphyrin **1** while avoiding any decarboxylation reaction. As previously reported,[10] in the distal strap of **1**, the carboxylic groups may be directed either toward or pointing away from the porphyrin plane. Therefore, heme model **1** has been designed to probe the influence of an apical carboxylic group on dioxygen affinity. According to the Pauling hypothesis,[11] a hydrogen bond or even a dipole−dipole interaction with the superoxo complex is expected to increase the dioxygen affinity of the heme.[12] Such a hydrogen bond has also been evidenced in heme oxygenase proteins.[13] The only previous study with a carboxylic group close to the distal pocket of a model is a cobalt C-clamp porphyrin lacking a nitrogen base.[14] Conversely, both porphyrin models **4** and **1** exhibit a built-in fifth ligand. Thus, the influence of a hanging carboxylic group on the stability of the dioxygen adduct will be directly and easily studied providing the fact that iron(II) complexes **4** and **1** are five coordinate. This control of the coordination sphere was verified by characteristic UV−vis absorption bands (**4Fe**: 439, 564 nm; **1Fe**: 438, 545 nm) as well as proton NMR spectroscopy (see S30 and S38, Supporting Information). Indeed, both complexes **4Fe** and **1Fe** exhibit downfield-shifted signals around 50−60 ppm typical of paramagnetic S = 2 complexes, clearly verifying a five-coordination sphere. These complexes bind reversibly dioxygen without oxidation over several weeks as shown by CO trapping experiments (see S31 and S39, Supporting Information) and will be further investigated toward their dioxygen affinity.

A second application of this synthetic strategy is represented by the facile synthesis of bifunctional chelates for the vectorization of α-emitter radionuclides. Indeed, it has been shown that a symmetrical bis-strapped porphyrin with the same type of malonate strap as **1** is able to coordinate a large cation such as bismuth(III), leading to a neutral complex.[10] In such a complex, the carboxylate group of one strap coordinates to porphyrin-bound bismuth. Therefore, this type of strap is adequate for a bismuth(III) chelation. On the other hand, a symmetrical chelate lacks the linkage function to attach to a targeting molecule such as a monoclonal antibody (Figure 1(b)). This goal provided the rationale for our synthesis of porphyrin **5**, by reaction of 4-(2-aminoethyl)benzenamine with a porphyrin mixture **7** in 56% yield. Subsequent steps consisted of activation of the aniline function with thiophosgene to obtain isothiocyanate **6** (87%), followed by ester hydrolysis with BBr_3 (56%) leading to bifunctional chelate **2**. The latter was metalated with bismuth nitrate to obtain **2Bi**, which exhibited the expected p-hyper-type UV−vis spectrum with the Soret band at 475 nm and a characteristic extra absorption at 358 nm.[15]

Finally, as our method turned out to be efficient for the nucleophilic reaction of a primary amino group with a bis-electrophilic picket porphyrin as described in Scheme 1, a bis-secondary amino function could also be added. Such a reagent is of interest in the case of a 1,11-dialkylated cyclam (Scheme 2). Indeed, this type of macrocycle selectively coordinates metals such as technetium (^{99m}Tc isotope), a γ-imaging radionuclide largely used in nuclear medical diagnostics.[16]

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(17) **Selected Data for 1, 2, and 3**. A typical reaction for the addition of nucleophilic reagents on **7** is described for the synthesis of **3**. In a 100 mL round-bottom flask equipped with a stir bar, (11-ethoxycarbonylmethyl-1,4,8,11-tetraaza-cyclotetradec-1-yl)-acetic acid ethyl ester (0.23 mmol, 85 mg) is dissolved in 50 mL of acetonitrile. Porphyrinic mixture **7** (0.15 mmol, 200 mg) is added together with NaI (0.61 mmol, 91 mg) and K_2CO_3 (0.92 mmol, 127 mg). During 48 h, the mixture is heated at 80 °C. The mixture is cooled and evaporated under reduced pressure, and the residue is purified by silica gel column chromatography. The desired compound is eluted with a mixture of 0.5% of MeOH in $CHCl_3$ and obtained in 21% yield (20 mg). Spectroscopic data for **1**: ^{1}H NMR (DMSO-d_6, 313 K, 500 MHz) δ 9.01 (2H, s, βpyr), 8.89 (2H, s, βpyr), 8.82 (8H, m, βpyr, aro, NHCO), 8.50 (2H, d, J = 8.50 Hz, aro), 8.39 (2H, d, J = 7.5 Hz, aro), 8.34 (2H, d, J = 7.5 Hz, aro), 8.32 (1H, d, J = 4.5 Hz, pyr_6), 8.20 (3H, m, NHCO, pyr_2), 7.93 (2H, t, J = 7 Hz, J = 9 Hz, aro), 7.88 (2H, t, J = 8.0 Hz, J = 9.5 Hz, aro), 7.74 (2H, t, J = 7.5 Hz, J = 7.5 Hz, aro), 7.69 (2H, t, J = 6.5 Hz, J = 8.5 Hz, aro), 7.4 (2H, d, J = 7.5 Hz, $aro_{6'}$), 7.1 (1H, d, J = 6.5 Hz, pyr_4), 7.1 (1H, dd, J = 4.5 Hz, J = 6.5 Hz, pyr_5), 7.03 (2H, t, J = 7.5 Hz, J = 8 Hz, $aro_{5'}$), 6.97 (4H, d, J = 8.0 Hz, $aro_{4'}$, $aro_{6'}$), 6.87 (4H, m, J = 7.5 Hz, J = 7.5 Hz, J = 8.0 Hz, $aro_{4'}$, $aro_{5'}$), 5.2 (2H, s, $aro_{2'}$), 5.02 (2H, s, $aro_{2'}$), 2.8 (2H, s, CH_{2pyr}), 2.03 (4H, bs, CH_{2bz}), 1.74 (4H, bs, CH_{2bz}), −2.52 (2H, s, NH_{int}). ESI-HRMS: calcd m/z = 1351.4830 $[M + H]^+$ for $C_{85}H_{63}N_{10}O_8$, found 1351.4855. UV−vis (CH_2Cl_2): λ/nm ($10^{-3}\varepsilon$, dm^3 mol^{-1} cm^{-1}) 425 (324.0), 517 (14.0), 552 (3.9), 590 (4.1), 647 (1.0). TLC silica gel: Rf = 0.4 (MeOH/CH_2Cl_2; 2/8). **1Fe**: ESI-HRMS calcd m/z = 1403.38667 $[M - H]^-$ for $C_{85}H_{59}N_{10}O_8{}^{56}Fe$, found 1403.3943. UV−vis (benzene): λ/nm (% of absorbance): 438 (100%), 545 (12%). **2**: ^{1}H NMR (DMSO-d_6, 323 K, 500 MHz) δ 8.82 (8H, s, βpyr), 8.78 (2H, s), 8.68 (1H, s), 8.63 (3H, m), 8.38 (4H, m), 8.16 (2H, m), 7.87 (4H, m), 7.68 (2H, t, J = 7.5 Hz), 7.62 (2H, t, J = 7.4 Hz), 7.45 (2H, d, J = 7.5 Hz), 7.19 (1H, d, J = 7.9 Hz), 7.11 (1H, d, J = 8.2 Hz), 6.96 (4H, m), 6.89 (2H, m), 6.76 (3H, m), 6.70 (2H, d, J = 7.4 Hz), 6.63 (1H, m), 5.16 (2H, s, $H_{2'a}$), 5.04 (2H, s, $H_{2'}$), 2.08 (6H, m, CH_{2a}, CH_{2abz}), 1.96 (2H, t, J = 6.6 Hz, CH_{2b}), 1.76 (4H, s, CH_{2bz}), −2.47 (2H, s, NH_{int}). ESI-HRMS: calcd m/z = 1421.4707 $[M + H]^+$ for $C_{88}H_{65}N_{10}O_8S$, found 1421.4706. UV−vis (CH_2Cl_2): λ/nm ($10^{-3}\varepsilon$, dm^3 mol^{-1} cm^{-1}) 427 (343.0), 518 (16.9), 553 (5.5), 590 (5.7), 647 (2.3). TLC silica gel: Rf = 0.4 (CH_3CO_2H/MeOH/CH_2Cl_2; 1/1/8). **2Bi**: ESI-HRMS: calcd m/z = 1627.4276 $[M + H]^+$ for $C_{88}H_{62}N_{10}O_8S$, found 1627.4280. UV−vis (CH_2Cl_2): λ/nm (% of absorbance): 358 (32.6%), 475 (100%), 604 (15.4%), 649 (16.1%). **3**: ^{1}H NMR ($CDCl_3$, 298 K, 500 MHz): δ 9.12 (2H, d, J = 8.03 Hz, H_3), 8.95 (4H, d, J = 4.87 Hz, βpyr), 8.93 (4H, d, J = 4.58 Hz, βpyr), 8.74 (2H, d, J = 8.3 Hz, H_{3a}), 8.04 (2H, d, J = 7.7 Hz, H_{aro}), 8.00 (2H, s, NHCO), 7.95 (4H, d, J = 7.7 Hz, H_{aro}), 7.91 (2H, t, J = 8.3 Hz, H_{aro}), 7.73 (2H, d, J = 7.7 Hz, H_{aro}), 7.59 (2H, d, J = 6.6 Hz, H_{aro}), 7.56 (2H, d, J = 7.2 Hz, H_{aro}), 7.51 (2H, s, NHCO), 7.02 (2H, t, J = 7.7 Hz, H_{aro}), 6.97 (2H, d, J = 7.7 Hz, H_{aro}), 6.78 (2H, d, J = 7.4 Hz, H_{aro}), 6.66 (2H, d, J = 8.3 Hz, H_{aro}), 6.62 (2H, s, $H_{2'a}$), 6.58 (2H, t, J = 7.7 Hz, H_{aro}), 5.02 (2H, s, $H_{2'}$), 4.05 (4H, qd, J = 7.0 Hz, CH_{2c}), 3.11 (4H, s), 2.79 (4H, s, CH_{2bz}), 2.51 (4H, t, J = 6.3 Hz, t_4), 2.41 (4H, t, J = 6.3 Hz, t_3), 2.10 (4H, t, t_2), 1.79 (4H, bs, CH_{2bz}), 1.43 (2H, m, qt_2), 1.34 (4H, bs), 1.18 (6H, t, J = 7.0 Hz, CH_{3cycl}), 1.03 (4H, t, t_1), 0.41 (2H, m, qt_1), −0.46 (6H, t, J = 7.0 Hz, CH_{3strap}), −2.42 (2H, s, NH_{int}). ESI-HRMS: calcd m/z = 1671.7505 $[M + H]^+$ for $C_{101}H_{99}N_{12}O_{12}$, found 1671.7511. UV−vis (CH_2Cl_2): λ/nm ($10^{-3}\varepsilon$, dm^3 mol^{-1} cm^{-1}) 647 (2.1), 590 (4.6), 551 (4.2), 517 (16.8), 424 (271.6). TLC silica gel: Rf = 0.25 (MeOH/CH_2Cl_2; 0.4/8).

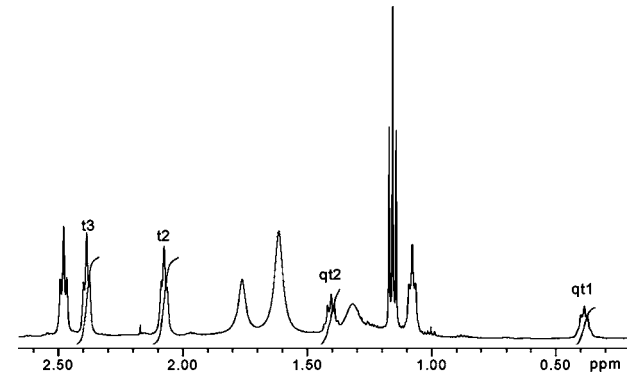

Figure 2. 500 MHz proton NMR spectrum ($CDCl_3$, 298 K, aliphatic domain) of chelate **3**.

Therefore, synthesis of macrotetracycle **3** (Scheme 2) via the reaction of (11-ethoxycarbonylmethyl-1,4,8,11-tetraaza-cyclotetradec-1-yl)-acetic acid ethyl ester (1,11-diester cyclam) with porphyrins **7** was performed, and **3** was isolated in 21% yield.

The proton NMR spectrum of **3** unambiguously indicates that the cyclam unit adopts on average a perpendicular orientation relative to the main porphyrinic plane, as evidenced by the high upfield shift of particular methylene signals, while the other signals appear at the expected chemical shifts. For example, the two triplets at 2.41 ppm (t_3) and 2.10 ppm (t_2) and, even more significantly, the two characteristic quintuplets at 1.43 ppm (qt_2) and 0.41 ppm (qt_1) demonstrate this effect (Figure 2). Thus, porphyrin **3** is a timely illustration of a molecule exhibiting two selective coordination sites, which could be of interest in medical applications for concomitant imaging and therapeutic purposes.

In summary, an efficient and versatile route to new highly functionalized porphyrinic chelates has been developed via the steric decompression of a single strapped bis-picket porphyrin. As this methodology relies on steric repulsion of a 5,15-strap pinched between two pickets, it could possibly be extended to the incorporation of groups that are more hindered than diethyl malonate. We are currently studying these possible extensions as well as the coordination properties of these various chelates.[17]

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

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