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Bis-Pocket Porphyrins without *meso*-Substituents: Tetramethyltetra(2,4,6-triisopropylphenyl)porphyrin I and Tetramethyltetraterphenylporphyrin I

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Abstract: A facile synthesis of meso-unsubstituted but doubly fenced porphyrins is described. The required pyrroles are made by the Barton-Zard method from 2,4,6-triisopropylbenzaldehyde and 2,6-diphenylbenzaldehyde. An X-ray structure confirms the type I pattern.

Synthetic porphyrin model compounds equipped with sterically shielding superstructures are the cornerstone of many important advances that successfully elucidated the hemoprotein chemistry in the last quarter of century.[1,2] Metalloporphyrins derived from such protected structures could escape from falling into the thermodynamically sink – μ-peroxo or μ-oxo bridging complex – when exposed to O_2 or "oxene" species and thus may behave more like the biological heme moiety encumbered in the protein pocket. Despite the impressive number (and fascinating names) of the protected porphyrins that are known today,[3] most are variations of a common molecular theme based on *meso*-tetraarylporphyrin owing to the synthetic accessibility. A very limited number of "cyclophane" porphyrins have been made in which the protective shielding is strapped across the face of porphyrin ring using side chains originating from β-pyrrole positions.[4] Even though such *meso*-unsubstituted porphyrins may be more desirable as spectroscopic models for biological hemes, the synthetic challenge involved in making these compounds has severely limited their utility. Recently, Barton and Zard have developed a convenient synthesis of a family of α-free pyrroles by the reaction of nitroalkenes and isocyanoacetates,[5] from which interesting β-alkyl- and arylporphyrins can be constructed.[6] We have adopted this approach and modified the procedure to achieve sterically hindered porphyrins with no *meso*-substituents. We report herein the synthesis of 1,3,5,7-tetramethyl-2,4,6,8-tetra(2,4,6-triisopropylphenyl)porphyrin (TMTIP) and 1,3,5,7-tetramethyl-2,4,6,8-tetraterphenylporphyrin (TMTTP).

The general synthetic strategy, incorporating the methods of Barton-Zard[5] and of Ono-Maruyama,[6] is illustrated in Scheme 1. 2,4,6-Triisopropylbenzene was formylated[7] by reaction with Cl_2CHOCH_3–$TiCl_4$ followed by hydrolysis to give **1a** which was then condensed with nitroethane in the presences of NH_4OAc to afford **2a** in 90% yield.[8] ^{1}H NMR of the singlet vinylogous proton at δ 8.08 ppm suggests that the nitro group *trans* to the aryl group was the only product obtained. The reaction of nitroalkene **2a** and ethyl isocyanoacetate was carried out in THF with an excess amount of DBU at room temperature for a minimum of 15 h in order to achieve a reasonable yield (60%) of the pyrrole **3a**. The m-terphenyl-2'-carboxaldehyde **1b**

Scheme 1
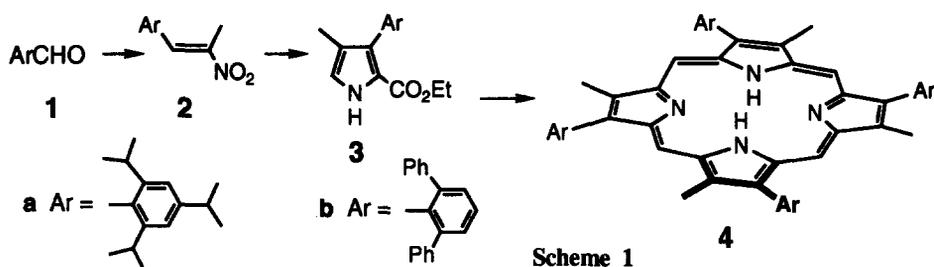
was obtained by phenyllithium addition to 2-fluorobiphenyl,[9] followed by quenching with DMF and hydrolysis. The conversion of **1b** to **2b** was similarly effected in neat nitroethane with an excellent yield. The pyrrole **3b**, however, could not be obtained by the same procedure using DBU as base; we found no evidence of pyrrole formation even after 2 days of reaction at elevated temperatures only to recover most of the unreacted **2b**. This problem was partially solved by employing a much stronger non-nucleophilic base than DBU to promoted the condensation. Thus, in the presence of stoichiometric amount of phosphazene base P_4-t-Bu (supplied by Fluka), **3b** was obtained in about 35% yield. Other bases such as sodium bis(trimethylsilyl)amide have been tested but the yields were even poorer.

For porphyrin synthesis from pyrroles such as **3**, Ono et al.[6] recommended the reduction of the 2-carboxylic ester group by $LiAlH_4$ to a pyrrylmethanol which is isolated first and then cyclized with methylal in the presence of an acid catalyst (e.g. p-TsOH). We found that this procedure is unreliable and often gives poor results with our sterically hindered pyrroles. Since pyrrole-2-methanol already contains all the carbon elements for building up a porphyrin ring, it is not necessary to utilize additional aldehyde group if the reaction is carried out in a mild manner to curtail the elimination of the hydroxymethyl group as formaldehyde. Thus, the pyrrole ester (0.5 g) was reduced by $LiAlH_4$ in THF; after quenching with ethyl acetate and small amount of water, the reaction mixture was evaporated to near dryness. To this residue, without further work-up, acetic acid (100 mL) was added, and the mixture was heated to reflux without protection of air for 3 h. Good yields of porphyrin **4a** (55%) and **4b** (48%) were obtained by this method. ^{1}H NMR of both porphyrin products revealed a sharp singlet for their *meso*-protons, attesting to the fact that only the type-I isomer was produced.[10] Undoubtedly the steric bulk of the aryl group has a major influence in directing the pyrrole cyclization as less hindered phenyl substituents invariably result in a mixture of scrambled patterns (type I, II, III, and IV).[6]

Metal insertions to porphyrin **4a** and **4b** can be accomplished by standard methods (e.g. MCl_2 in hot DMF). A crystalline Zn(II) complex of **4a** was obtained from $CHCl_3$/MeOH, and the X-ray structural study of this methanol chelated complex $C_{84}H_{100}N_4Zn(CH_3OH) \cdot CHCl_3$ has allowed a thorough characterization of this bis-pocket shaped porphyrin.[11] As shown in Fig. 1, the phenyl rings are nearly perpendicular to the porphyrin plane with the 2,6-isopropyl groups oriented in an expected conformation of having the two methyl groups pointing away from the pyrrole. The cavity created by the surrounding "fence" seems to be spacious enough to allow unhinderd access to the metal center. The fence itself is about 2.5 Å tall (from the porphyrin plane), which is sufficient to prevent μ-oxo Fe(III) dimer formation. The inability for **4a** to form Fe(III)-O-Fe(III) is evidenced by the fact that when paramagnetic high-spin Fe(III)-Cl (^{1}H NMR of the ring Me at 48

ppm at 23 °C) is treated with aqueous NaOH, or basic alumina, instead of the typical antiferromagetically coupled, essentially diamagnetic μ-oxo dimer, a new paramagnetic species (Me, δ at 37 ppm) is obtained, which is identified to be Fe(III)-OH. The Fe(II) complex of **4a**, when exposed to O_2 at room temperature, rapidly oxidizes (to yield Fe(III)-OH), suggesting that the isopropyl fence is not bulky enough to prevent autoxidation. On the other hand, the Fe(II) complex of **4b** binds O_2 at 20 °C and is stable in py/toluene solution, indicating that the metal center in this system, similar to that in Suslick's "bis-pocket" heme,[12] is amply shielded to protect the coordinated O_2; further detail will be reported in due course.
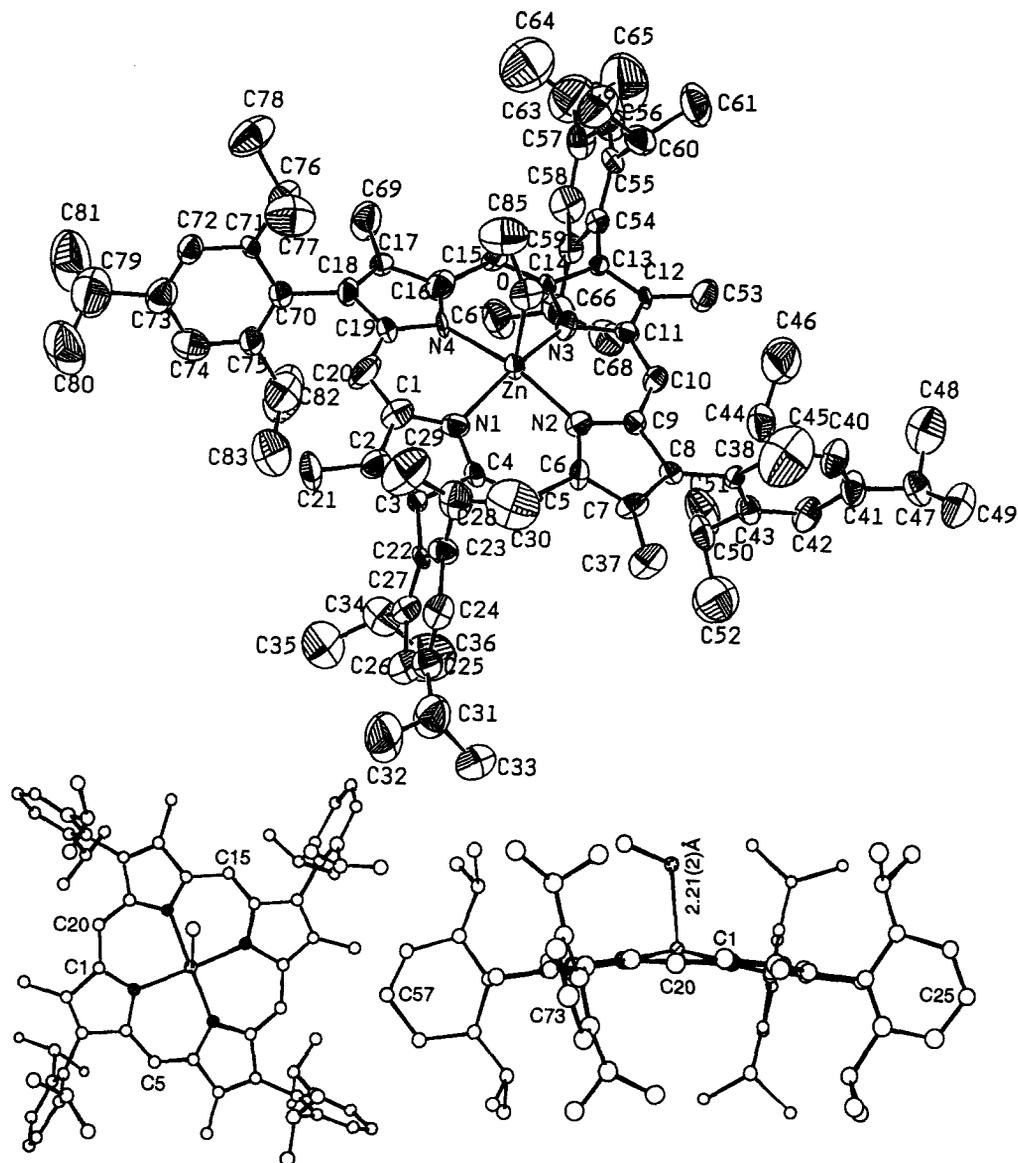

Figure 1. X-ray crystal structure of Zn(II)TMTIP with MeOH as axial ligand; the bottom two views have the 4-isopropyl groups deleted for clarity. The out-of-N_4 plane displacement of Zn is 0.30(2) Å.

These two examples demonstrate a facile approach to hindered porphyrins bearing perhaps even more biological relevance than the traditional TPP-based model compounds. For example, this type of bis-pocket porphyrins is uniquely suitable as model for studying reactions occurring at the heme *meso*-position, e.g. heme oxygenase catalyzed heme degradation[13] and peroxidase reactions with certain drugs.[14]

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8.   Typical procedure: Equal amounts (0.01 mol) of aldehyde and NH_4OAc were heated to reflux in nitroethane (20 mL) overnight. The solvent was removed and the residue was washed with CH_2Cl_2 and water and crystallized from CH_2Cl_2/hexane.

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10. ^{1}H NMR δ ($CDCl_3$, 300 MHz)

      4a: 9.65 (s, 4 H), 7.38 (s, 8 H), 3.21 (s, 12 H), 3.19 (hep, 4 H, J=6.8 Hz), 2.79 (hep, 8 H, J=6.7 Hz), 1.51 (d, 24 H, J=6.9 Hz), 1.11 (d, 24 H, J=6.8 Hz), 0.96 (d, 24 H, J=6.8 Hz), -3.32 (s, 2 H).

      4b: 9.27 (s, 4 H), 7.75 (m, 12 H), 7.05 (m, 24 H), 6.6 (m, 16 H), 2.86 (s, 12 H), -4.2 (s, 2 H).

11.   X-ray diffraction data were collected on a Nonius diffractometer at 25 °C (λ = 0.7107 Å). $C_{84}H_{100}N_4Zn(CH_3OH) \cdot CHCl_3$ crystal dimensions: 0.05 x 0.25 x 0.50 mm; monoclinic, space group $P2_1/c$; a = 17.578(5) Å, b = 15.380(5) Å, c = 31.092(8) Å, β = 90.94(3)°; V = 8404(4) Å^3, Z= 4. The structure was solved by direct method using the NRC-VAX package. All non-hydrogen atoms were refined anisotropically; final R_f = 0.122. The thermal vibrations of the isopropyl groups no doubt contributed to the rather mediocre R-value.

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