Synthesis and characterization of durene-capped porphyrins and the crystal structure of a hemin derivative

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Received July 16, 1985


Sterically hindered porphyrins having a fully hydrophobic cavity have been prepared. The cavity is capped with a 2,3,5,6-tetramethylbenzene moiety containing at the 1,4-positions methylenes —(CH₂)₆— chains (n = 4, 5, 7) bonded at trans pyrrole rings of a porphyrin that is alkylated with methyl or ethyl groups at the other β-pyrorlic positions. The iron(III) chloride derivative of the 4,4-durene-capped base has been obtained as single crystals, and subjected to X-ray structural analysis. The typical high spin, square pyramidal geometry of five-coordinate hemin chlorides is maintained; the porphyrin core is strongly distorted and there is no interaction between the phenyl group of the strap and the iron.


On a préparé des porphyrines stériquement empêchées et possédant une cavité hydrophobe complète. La cavité est cappée par un tétraméthyl-2,3,5,6 benzène portant, dans les positions 1 et 4, des chaînes méthylenes —(CH₂)₆— où n = 4, 5, 7 lié aux cycles pyrroliques trans d’une porphyrine qui est alkylée par des groupements méthyle ou éthyle dans les autres positions β du pyrrole. On a obtenu un cristal unique du dérivé du chlorure de fer(III) de la base cappée par le durene-4,4 et on l’a soumis à une analyse par diffraction des rayons-X. La géométrie de pyramide carrée et à spin élevé qui est typique des chlorures d’hémines pentacoordonnées est maintenue; le noyau de la porphyrine est fortement déformé et il n’y a aucune interaction entre le groupement phénylé et le fer.

[Traduit par le journal]

There have been numerous attempts to prepare simple iron(II) porphyrin complexes which will reversibly bind oxygen in a manner analogous to hemoglobin and myoglobin (1–3). A major problem with the "readily available" protein-free model systems is that, in the presence of oxygen, an irreversible oxidation to μ-oxo-iron(III) dimers occurs; this autooxidation proceeds via the formation of a monomeric iron-dioxigen adduct, which subsequently reacts with a second iron(II) porphyrin unit (4). The synthesis of porphyrins with protective structures covering one face of the macrocycle has proved to be an effective way of inhibiting this "dimerization." Several such porphyrins have been synthesized, the best-known systems being the "picket-fence" (5) and "pocket" (6) porphyrins of Collman et al., the "capped" (7) porphyrins of Baldwin and co-workers, and the "cyclophane hemes" (8) of Traylor et al. In addition, model systems with steric hindrances on both faces of the porphyrin (the "basket-handle" porphyrins (9) of Momentenau et al.), as well as those with protective structures on one and appended imidazole ligand on the other side, have been prepared (10, 11).

Two fundamentally different approaches have been adopted for the synthesis of hindered porphyrins. The first is an extension of single-step coupling of benzaldehyde and pyrrole to produce meso-tetraphenylporphyrin (12). Aromatic aldehydes with potential amino groups as ortho-substituents are condensed with pyrrole and the protective structures are linked to the amino groups via amide linkages using appropriate acyl chlorides (5, 6). In a modification of this method, the protective structures are linked to the aromatic aldehydes at their ortho positions via ester or other functions, prior to the coupling with pyrrole (7, 9, 10). The most widely used approach to the synthesis of hindered porphyrins has been to condense, via ester or amide linkages, a diagonally β-substituted preformed porphyrin with a terminally bifunctional molecule carrying appropriate functional groups (8, 11, 13–15).

Porphyrins produced by such methods are limited, however, in the size of the cavity produced. In addition, truly hydrophobic cavities cannot be produced since the protective structures are linked to the porphyrin by polar amide, ester, or other linkages. An early attempt at the preparation of such a hydrophobic system using rigid dipyrromethene precursors resulted in very low yields during the cyclization step (16).

The synthetic route originally developed in this department to construct permanently deformed porphyrins (17, 18) appeared to be ideally suited for the synthesis of a sterically hindered porphyrin having a fully hydrophobic cavity.

Commercially available 1,4-bis(chloromethyl)-2,3,5,6-tetramethylbenzene (1) was converted into the diacid chlorides (2) using standard malonate chemistry. The incorporation of the durene strap into the porphyrin2 was initially carried out with the bis-pentanoic and heptanoic acid derivatives (2, n = 5 and 7), as outlined in the scheme. 2-Ethoxycarbonyl-3,5-dimethylpyrrole (3), prepared by the reductive condensation (19) of diethyl oximinomalonate with 2,4-pentanedione, was condensed with 2 to give the diketo bispyrrole (4), using a method previously employed for the preparation of covalently linked porphyrins (20). Diborane reduction, in THF, of 4 gave the bispyrrole ethyl ester (5, R = CO₂Et), which was transbenzylated (21) in refluxing benzyl alcohol and catalytic sodium benzyloxide. The benzyl ester (5, R = CO₂CH₂Ph) was converted to the dicyanovinyl protected derivative (6, R = CH₃) using standard

1All new compounds were characterized by satisfactory elemental analysis, and mass and nmr spectroscopy.
The solvent was removed and the residue washed with water and then chromatographed on alumina (activity V). Elution with CH₂Cl₂ gave the green μ-oxo dimer. Treatment of the eluate with 0.2 M HCl gave the hemin chloride, which was recrystallized from CH₂Cl₂/hexane (85% yield). Crystals of the hemin were prepared by the addition of methanol to a dichloromethane solution (0.1 M) to a ratio of 3:7 (v/v). Standing at room temperature for ~5 days yielded single crystals for X-ray structural analysis.

The molecular structure of the hemin shown in Fig. 1 indicates a very distorted porphyrin core, which results directly from the carbon "strap." Nevertheless, the square pyramidal coordination environment found about the Fe atom is typical of techniques (21–23). The intermediates in this sequence were unstable and neither isolated nor characterized. However, the dicyanovinyl group both protects the aldehyde function and provides a compound suitable for chromatographic purification.

The conversion of 6 (R = CH₃) to the chloromethyl derivative 6 (R = CH₂Cl) was carried out under conditions that allowed for an electrophilic, rather than a radical, reaction to favor competitive chlorination of the benzene substituents (24–28); chlorination in the dark using two equivalents of sulfuryl chloride in methylene dichloride at room temperature gave 6 (R = CH₂Cl), which was isolated and immediately condensed with the pyrrole 7 (17) to give 8 (R₁ = CH₂Cl). For 6 (R = CH₃), which was isolated and immediately decarboxylated and purified by chromatography. The overall yields of the porphyrin skeleton (210 CAN. 1. CHEM.

The reaction was followed by the appearance of a 280-nm band) gave 8 (R₁ = CH₂Cl/hexane). Crystals were prepared by the addition of methanol to a dichloromethane solution (0.1 M) to a ratio of 3:7 (v/v). Standing at room temperature for ~5 days yielded single crystals for X-ray structural analysis.

A crystal suitable for data collection was mounted in a thin-walled glass tube and centred on an Enraf–Nonius CAD4-F diffractometer. Accurate cell dimensions were determined by least-squares refinement of the setting angles of 25 accurately centred reflections (with 15° < 2θ < 20°) chosen from a variety of points in reciprocal space. The crystal system was found to be triclinic and consequently the space group was P1 or P1 (subsequent structure solution uniquely defined the space group as P1). A total of 5795 independent reflections were measured, of which 3271 were observed (Fo/σ(F) > 5σ(F)) and used in structure refinement. Lorentz and polarization corrections have been made. The Fe atom was located from the Patterson map, while all other non-hydrogen atoms were found from subsequent difference-Fourier maps. At this stage, the presence of a crystalization molecule of dichloromethane was detected in the unit cell, disordered in at least two different arrangements. The exact mode of this disorder is complicated and, although a number of chemically reasonable models were investigated, no satisfactory description of this volume could be made. We were able to minimize the electron density in this volume by fixing the "porphyrin" parameters and performing full-matrix least-squares refinement of the occupancies, coordinates, and temperature factors of two fractional dichloromethane molecules that overlapped at a common C site. Subsequent difference maps revealed clearly the positions of the hydrogen atoms of the porphyrin molecule (solvent hydrogens were not located). Refinement was continued by separation of the structure into three batches: batch 1 contained Fe(1), Cl(1), and the porphinato skeleton (248 variables); batch 2 consisted of the "strap" and peripheral methyl and ethyl groups (369 variables); and batch 3 was made up of the disordered solvent molecule (31 variables). A number of full-matrix least-squares cycles were performed on each batch alternately until the refinement had converged.

During these cycles, hydrogen atoms were constrained with respect to their parent carbon atoms (C—H = 0.95(2) Å; H—C—H = 110(2)°; C—C—H = 110(2)°) and an overall isotropic temperature factor was refined for (i) methyl hydrogens, (ii) methylene hydrogens, and (iii) "Co" hydrogens. The final cycle of refinement, with all hydrogen and solvent parameters fixed and the coordinates and anisotropic thermal parameters of the non-hydrogen atoms allowed to vary, produced essentially no shifts (Δ(shift/e.s.d.) = 2.52) and gave final agreement factors of R = 0.038 and R₁ = 0.048 for 470 variables. The final difference map contained a number of residual peaks (0.18–0.40 e Å⁻³) in the solvent region and two peaks (0.28 and 0.31 e Å⁻³) close to Fe(1). Weights were derived on the basis of trends in w² as a function of sin θ/λ and F₀ (Table 1). Atomic scattering factors including anomalous dispersion were taken from Tables for X-ray Crystallography (29). Final positional and Uiso temperature factors are given in Table 2. Anisotropic, thermal parameters, hydrogen parameters, bond parameters, mean-planes data, and structure factor listings have also been deposited (Tables 3–7).

Data reduction and initial structure solution were performed using "The NRC VAX crystal structure system" (30), whereas the latter stages of structure solution and refinement were carried out using "CRYSTALS, Oxford University" (31). All calculations were performed using an "in-house" VAX750 computer.

![Diagram of the hemin](https://example.com/hemin_diagram.png)
other high spin Fe(III) porphyrins that do not contain a "strap" (33) (Table 8). The Fe(I)—Cl(I) distance of 2.232(1) Å is close to the value of 2.218(6) Å found for [Fe(proto)Cl] (34) and the distance from Fe(I) to the centre of the phenyl ring of 5.615 Å indicates no interaction between the phenyl group of the "strap" and Fe(I).

The distortion of the porphinato skeleton found here is not as marked as found in the related deformed free-base porphyrin with short-strap bridging reported earlier (18, 35). The angle between rings 2 and 4 is 68.5° compared with 73.1° found in the related deformed free-base porphyrin. Mean-plane calculations for 10 (Table 10) (36) and bond twist (t\textsubscript{twist}) parameters (36) for the porphinato skeleton (Table 9) suggest that strain induced by the strap is distributed throughout the entire molecule rather than being localized within the two "strapped" pyrrole rings. Mean-plane data determined for each pyrrole ring further support distribution of strain throughout the molecule, viz. the "strapped" C atoms C(2) and C(12) within rings 1 and 3, respectively, lie well out (0.06–0.10 Å) of the plane defined by the other atoms in their rings. Also, C\textsubscript{8} atoms in pyrrole rings 2 and 4 lie out of plane with respect to the other ring members, in a direction towards the "strap."

Bond distances and angles around the porphinato skeleton are remarkably similar to those found in other "undistorted" nonstrapped XFe(III) porphyrins (Table 10) (37, 38). The bond parameters for the "strap" and alkyl substituents do not appear unusual. Transannular parameters indicate that the central porphinato cavity has contracted as a result of binding to Fe(I), e.g. N(1)—N(3) and N(2)—N(4) are 3.965(5) and 4.016(5) Å, respectively, cf. 4.003(4) and 4.241(4) Å in a severely distorted porphyrin (35).

Acknowledgements

This work was supported by the U.S. National Institutes of Health (AM 17989) and the Natural Sciences and Engineering Research Council of Canada.


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