"Hangman" Porphyrins for the Assembly of a Model Heme Water Channel

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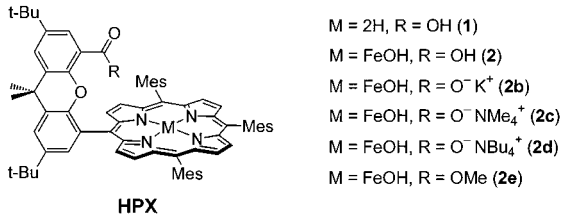
The heme unit is one of the most ubiquitous and versatile cofactors found in Nature.[1,2] The amazingly diverse reactivities displayed by heme-dependent enzymes (e.g., O_2 transport and storage,[3,4] single outer-sphere electron transfer,[5] metabolic oxidation reactions[6,7] and O_2 reduction[8,9]) are governed by subtle and precise changes in the microenvironments imposed by the tertiary structures of the folded proteins surrounding the active site porphyrinic cores. In many cases, this exquisite control is exerted by noncovalent interactions such as hydrogen bonding; an exemplary system is provided by the cytochrome P450 enzymes.[7] Crystallographic studies of this family of monooxygenases give evidence for the presence of internal solvent water channels that finely tune heme electronic structure and redox potential, as well as providing a possible proton-relay pathway during multielectron catalysis.[10−14] However, the challenge of constructing structural and functional models[15−23] for such complex, noncovalent aggregates outside the biological milieu poses a daunting task for the synthetic chemist. In this communication, we introduce novel, minimalist heme/water channel models composed of porphyrins and distal hydrogen-bonding groups anchored in a cofacial manner to a rigid spacer. These pillared "Hangman" porphyrins have the distinct ability to orient exogenous water in a controlled fashion via hydrogen bonding in the solid state and in solution, as well as affording a monomeric iron(III) hydroxide porphyrin to be characterized by single-crystal X-ray analysis.

Scheme 1



Our interest in the proton-coupled activation of small molecules[24,25] has led us to recently develop methods for the facile assembly of new symmetric cofacial bisporphyrins based on dibenzofuran (DPD)[26] and xanthene (DPX)[27] spacers that exhibit variable pocket sizes with minimal lateral displacements. A similar approach may be used to produce asymmetric cofacial architectures in which the rigid xanthene scaffold is used to "hang" a hydrogen-bonding functionality over the porphyrin macrocycle (HPX = hanging porphyrin xanthene, Scheme 1). Porphyrin H_2(HPX−CO_2H) (**1**) is synthesized via a mixed-aldehyde condensation under standard Lindsey conditions.[28,29] The carboxylic acid complex provides access to a wide variety of functional groups; for example, ester and amide derivatives are readily prepared from **1**. Metalation of **1** with $FeBr_2$ followed by alkaline workup affords the corresponding monomeric iron(III)−hydroxide complex FeOH(HPX−CO_2H) **2**. The steric buttressing provided by the flanking mesityl groups precludes the formation of bisiron(III) μ-oxo dimers.[18,30−32] The ^{1}H NMR of **2** is consistent with its formulation as a hydroxide species; the downfield chemical shifts of the β-pyrrole resonances (80.79, 82.40 ppm) are indicative[31] of a monomeric high-spin Fe(III) porphyrin.

The structure of **2** is confirmed by single-crystal X-ray analysis (Figure 1); a number of notable features merit discussion here. To the best of our knowledge, we are unaware of another reported crystal structure of a monomeric iron(III) hydroxide porphyrin.[33] Furthermore, it is interesting to note that the hydrogen-bonding network promotes selective binding of the axial hydroxide ligand to the distal side of the HPX platform. The complex adopts a distorted square pyramidal geometry with the pentacoordinate Fe elevated 0.4947 Å out of the N4 plane and an average $Fe-N_{pyrrole}$ bond length of 2.075 Å. The $Fe-O_{hydroxide}$ bond length of 1.868 Å is shorter than the Fe−O distances found for Fe(III)−aqua

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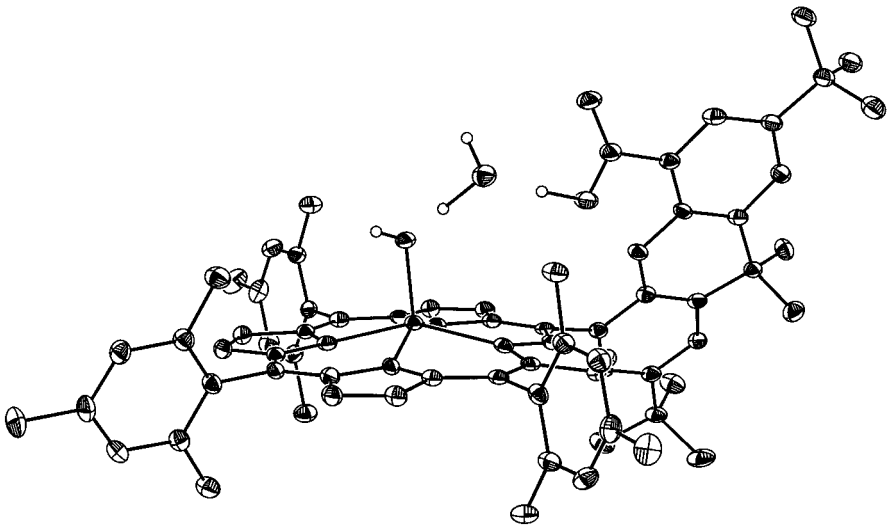

Figure 1. Molecular structure of **2** with thermal ellipsoids drawn at the 35% probability level. Crystals were obtained from slow evaporation of a saturated pentane solution.

porphyrins (~2.04 Å)[34,35] and Fe porphyrin dimers that contain bent, bridging hydroxo ligands (1.92−1.95 Å),[36] but significantly longer than those found in corresponding Fe(III) μ-oxo dimers (1.73−1.82 Å).[1,37] The values for all these parameters are consistent with data obtained for other five-coordinate high-spin Fe(III) porphyrin derivatives.[1,37]

Even more striking is the water molecule bound between the distal xanthene carboxylic acid and iron porphyrin hydroxide by two hydrogen bonds. The short O−O distances of 2.581 and 2.670 Å from the water to the carboxylic acid and the iron hydroxide, respectively, attest to the stability of this unique hydrogen-bonded scaffold. To accommodate the bridging water molecule, the xanthene pillar rotates along the porphyrin macrocycle, forming a dihedral angle of 59.8°.

Preliminary results suggest that the water remains bound in solution as well as in the solid state, and that this binding is chemically reversible. Titration of **2** with a slight excess of various bases results in facile replacement of the carboxylic acid proton with the corresponding cations (K^+ **2b**, NMe_4+ **2c**, NBu_4+ **2d**).[29] The solution spectra of carboxylates **2b** and **2c** are nearly identical to that of **2**, displaying Soret absorptions at 419 nm with tailing, low-intensity Q-band shoulders at 490, 550, and 655 nm. In contrast, the spectrum of carboxylate **2d**, containing the sterically bulky NBu_4^+ cation, is distinguished from the rest of the series by a broadened Soret band at 419 nm and a well-defined Q-band doublet at 576 and 622 nm (Supporting Information, Figure S1). This absorption profile is identical to Fe(TMP)OH[31] and to the methyl ester derivative of **2**, Fe(HPX−CO_2Me)OH (**2e**), which does not support a water bound within a hydrogen-bonding network. Compound **2** is recovered quantitatively upon addition of a slight excess of water to **2d**. These solution data are consistent with the reversible binding of a directed water as observed in the crystal structure of **2**.

High-valent ferryl−HPX complexes (analogous to Compounds I and II of heme oxygenases[6,7]) may be generated by low-temperature chemical oxidation depending on solvent and reaction temperature. Treatment of **2** (λ_{max} = 419 nm, ϵ = 142 000 M^{-1} cm^{-1}) with mCPBA in THF at −61 °C yields a deep red solution with an absorption spectrum consistent with the formation of an iron(IV)−oxo porphyrin (Supporting Information, Figure S2), displaying a Soret band of increased intensity (λ_{max} = 418 nm, ϵ = 170 000 M^{-1} cm^{-1}) and a distinctive Q-band centered at 555 nm.[38] Similarly, reaction of Fe(HPX−CO_2Me)OH (**2e**) or Fe(TMP)OH with mCBPA under these conditions give deep red products with nearly identical spectral profiles. Oxidation of Fe(HPX−COOH)Cl, Fe(HPX−CO_2Me)Cl, or Fe(TMP)Cl with mCPBA or PhIO in dichloromethane at −78 °C affords emerald green complexes that exhibit absorption spectra characteristic of iron(IV)−oxo porphyrin cation radical species (Supporting Information, Figure S2).[18] The spectra feature broad, blue-shifted Soret bands of decreased intensity ($\lambda_{max} \approx$ 406 nm, $\epsilon \approx$ 70 000 M^{-1} cm^{-1}), and weak, tailing absorptions at 600−700 nm indicative of porphyrin cation radicals.

The HPX system, with its ability to bind water in a controlled manner via noncovalent hydrogen bond interactions, provides a remarkably minimalist model platform for the heme water channel assembly found in the cytochrome P450 enzymes. The success of this architecture is highlighted by the structure of **2**, a crystallographically characterized monomeric iron(III) hydroxy porphyrin. With the synthetic versatility available to modify the porphyrin ring and its distal organic functionality, it should be possible to probe detailed structure/function relationships for these and related compounds. The generation of the ferryl forms of **2** demonstrates the suitability of the HPX platform for participation in redox reactions of small molecule substrates. In particular, the exceptional ability of these "Hangman" porphyrins to juxtapose water and hydroxy units offers a unique opportunity to explore proton-coupled O−O bond forming and cleavage chemistry using these molecular templates. Efforts along these lines are in progress.

Acknowledgment. This paper is dedicated to the memory of Professor Gerald T. Babcock, whose vision has and will continue to inspire biologists and chemists in their studies of O_2/H_2O activation. C.J.C. gratefully acknowledges the National Science Foundation for a predoctoral fellowship. We thank Drs. M. Pink and V. Young, Jr. at the University of Minnesota X-ray Crystallographic Laboratory for solving the structure of **2**, and Professor K. S. Suslick for enlightening discussions and sharing results prior to publication. The National Institutes of Health GM 47274 provided funding for this work.

Supporting Information Available: Absorption spectra for titration of **2** with NBu_4OH and for Compounds I and II analogues of **2**, thermal ellipsoid representations, tables of crystal data, atomic coordinates, bond lengths and angles, anisotropic thermal parameters and hydrogen coordinates for compound **2** (PDF). X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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