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Efficient Synthesis of Hangman Porphyrins

Dilek K. Dogutan, D. Kwabena Bediako, Thomas S. Teets, Matthias Schwalbe, and Daniel G. Nocera*

Department of Chemistry, 6-335, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139-4307

nocera@mit.edu

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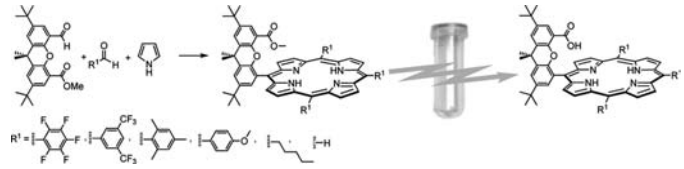
ABSTRACT



A two-step synthetic method has been designed to furnish hangman porphyrins in good yields from easily available starting materials. The use of the microwave irradiation technique has been found to be valuable for delivering the carboxylic acid hanging group in a much simplified and less time-consuming basic ester hydrolysis (4 h vs 7 days under harsh acidic conditions). The new route facilitates the synthesis of various hangman porphyrins that previously had limited or no access.

The activation of many small molecules requires the coupling of electrons to protons. In the absence of such coupling, large reaction barriers confront the conversion of the small molecule.[1−3] The challenge to effecting proton-coupled electron transfer (PCET) is in the management of the disparate tunneling length scales of the electron and proton.[4,5] Proton transfer is fundamentally limited to short distances, whereas the lighter electron may transfer over much longer distances. Hangman porphyrins manage the proton and electron extremely well by establishing the proton transfer distance with an acid−base group poised above the electron transfer conduit of the porphyrin macrocycle.[6,7] Electron[8] or energy[9] transfer to the macrocycle can be coupled to a short proton transfer to or from substrates bound within the hangman cleft. In this way, the hangman architecture captures the structural and functional relationships engendered by the amino acid residues in the distal cavities of heme hydroperoxidase enzymes. For example, a threonine residue on the distal side of cytochrome P450 (BM-3 structure) establishes a water channel by positioning a water molecule above the heme.[10] In hangman porphyrins, the hanging group assumes the structural role of threonine by preorganizing a water molecule above the hangman cleft.[11] Moreover, the diversity of biological redox processes performed by the heme enzymes is captured by hangman porphyrins. The active site in the enzyme, Compound I (Cpd I), which is two redox levels above Fe^{III} with a ferryl Fe^{IV}═O and associated radical,[12−14] is furnished by the heterolytic cleavage of the O−O bond of H_2O_2 or O_2.[12,15−18] A parallel oxygen activity

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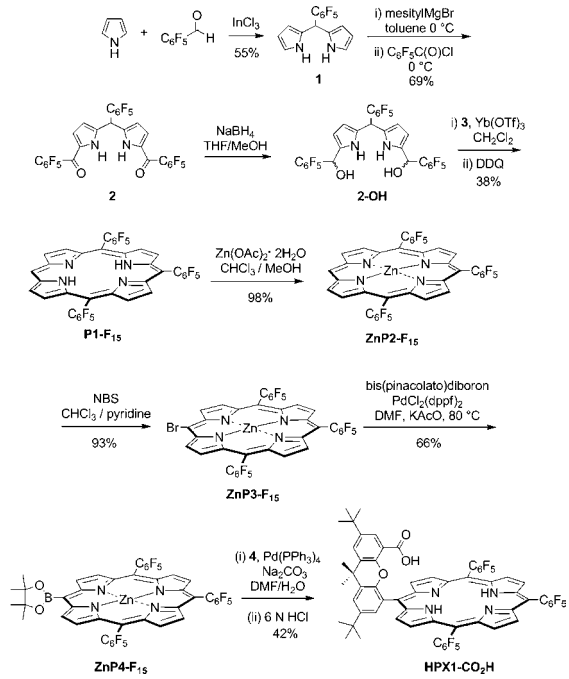
is observed within the cleft of hangman porphyrins.[19,20] Formation of Cpd I intermediate is accomplished by coupling proton transfer to a $2e^-$ heterolysis of an O−O bond. The incorporation of the hanging group enables multifunctional O−O activity at a single redox scaffold as is evocative of natural heme-dependent proteins, which employ a conserved protoporphyrin IX cofactor to affect a myriad of chemical reactivities.

The introduction of the acid−base hanging group into the hangman architecture is challenging. Over the years, we[21−23] and others[24,25] have developed methods for the facile assembly of porphyrins onto dibenzofuran (DPD) and xanthene (DPX) spacers. However, introduction of the hanging group is not facile and proceeds via hydrolysis of protected groups such as esters over long times and in low yields.[26] In this report, we describe stepwise and statistical synthetic methods for delivering new hangman porphyrin xanthenes (HPX). The use of microwave irradiation in the latter route is especially effective for deprotecting the nascent hanging group. The new methods should provide easy access to hangman porphyrins that have heretofore limited or no access.

1. Stepwise Synthesis of Hangman Porphyrins. Hangman porphyrins have the A_3B motif. Scheme 1 shows the synthesis of the **HPX1-CO$_2$H** exemplar.

Scheme 1. Stepwise Synthesis of **HPX1-CO$_2$H**

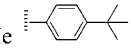
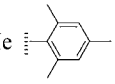
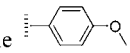
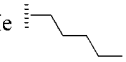


5-Pentafluorophenyl dipyrromethane **1**[27] and 1,9-diacyldipyrromethane **2**[28] were synthesized according to reported procedures with slight modifications. Reduction of **2** gave the corresponding dipyrromethane dicarbinol (**2-OH**), which upon condensation[29] with dipyrromethane **3**[27] gave the corresponding porphyrin **P1-F$_{15}$** in 38% yield. Subsequent metalation[30] and regioselective α-bromination[31] afforded porphyrin **ZnP2-F$_{15}$** in 98% yield. Bis(pinacolato)diboron was coupled with **ZnP2-F$_{15}$** by applying the Miyaura reaction[32] to afford porphyrin **ZnP3-F$_{15}$**. Cross-coupling of **ZnP3-F$_{15}$** with 4-hydroxycarbonyl-5-bromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene **4**,[33] under Suzuki reaction conditions, afforded the previously reported **HPX1-CO$_2$H** with a 3% overall yield. To synthesize porphyrins in larger quantities, shorter time periods, and fewer steps, statistical condensation procedures were explored.

2. Statistical Synthesis of Hangman Porphyrins. The HPX library shown in Table 1 was constructed using the statistical and more concise synthetic pathway depicted in Scheme 2. Compound **5**, which serves as a common synthon for the construction of a variety of hangman porphyrins, was synthesized by following reported procedures.[26] In all cases, the standard high-dilution Lindsey condition[34] is employed for the porphyrin synthesis. The acid-catalyzed condensation of **5** with pentafluorobenzaldehyde and pyrrole afforded the corresponding porphyrinogen. In situ $6e^-/6H^+$ oxidation of the latter with DDQ afforded the hangman porphyrin with a methyl ester hanging group (**HPX1-CO$_2$Me**) in 34% yield. *meso*-Tetrakis(pentafluorophenyl)porphyrin **F$_{20}$-TPP** was also isolated as a side product in 4% yield. Single crystals of **F$_{20}$-TPP** were obtained by slow evaporation of hexane and CH_2Cl_2. The structure (Figure S1) shows an almost planar macrocycle with the aryl groups twisted considerably out of plane (~83°) owing to steric clashing.

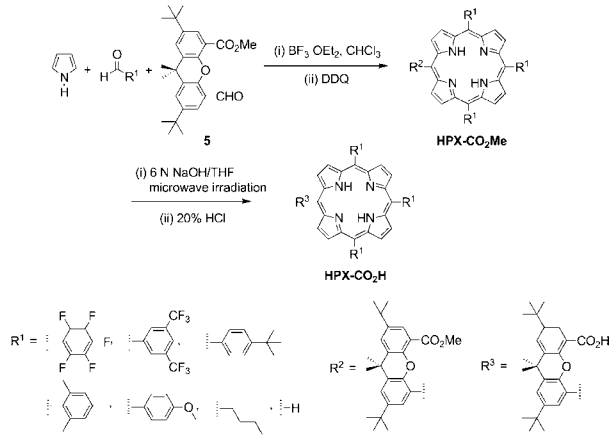
The hydrolysis of a methyl ester to the corresponding carboxylic acid has been performed under acidic conditions.[35]

Table 1. Statistical Synthesis of Hangman Porphyrin Xanthene (HPX) under Microwave Irradiation

Porphyrin	R^1	% Yield[a]	Porphyrin	% Yield[b]
HPX1-CO$_2$Me		34	HPX1-CO$_2$H	32
HPX2-CO$_2$Me		23	HPX2-CO$_2$H	22
HPX3-CO$_2$Me		33	HPX3-CO$_2$H	25
HPX4-CO$_2$Me		39	HPX4-CO$_2$H	38
HPX5-CO$_2$Me		28	HPX5-CO$_2$H	27
HPX6-CO$_2$Me		24	HPX6-CO$_2$H	23
HPX7-CO$_2$Me		18	HPX7-CO$_2$H	17

[a] Porphyrin formation was performed under modified Lindsey conditions. The yield calculations were given based on aldehyde **5**. [b] Overall yield for steps a and b of Scheme 2.

Scheme 2. Statistical Synthesis of Hangman Porphyrin Xanthene (HPX-CO_2H)



The reaction required refluxing **HPX1-CO_2Me** in a mixture of acetic acid and sulfuric acid (4:1) under N_2 in the dark for 7 days. Basic hydrolysis of a methyl ester of **HPX5-CO_2Me** has also been shown to afford the hangman porphyrin with carboxylic acid hanging unit in 3 days under reflux with argon;[26] for the electron-withdrawing porphyrins described herein (e.g., **HPX1-CO_2Me** and **HPX2-CO_2Me**), no reaction was observed after 2 weeks. In an attempt to curtail reaction times, we turned our attention to microwave synthesis.[36−39] Efficient hydrolysis of the ester functionality of **HPX1-CO_2Me** using 6 N NaOH and microwave irradiation was achieved in 4 h with 98% yield. The statistical porphyrin synthesis afforded the target porphyrin **HPX1-CO_2H** in four steps with 29% isolated overall yield, which is 9× higher yield than that obtained from the stepwise route of Scheme 1. This promising result prompted us to investigate generality of Scheme 2 for the synthesis of hangman porphyrins with meso groups of varying electronic and steric properties.

The condensation reaction, step a in Scheme 2, proceeded smoothly for all listed R^1 substituents. The progress of the microwave-induced basic hydrolysis was monitored with thin-layer chromatography; optimized powers and irradiation times for each reaction are given in the Supporting Information. The reaction was allowed to proceed until all starting porphyrin was consumed and no decomposition products were observed. Reaction times were found to be highly dependent on the properties of the meso substituent. Whereas deprotection of the methyl ester was achieved in 4−6 h for hangman porphyrins bearing electron-withdrawing meso groups, porphyrins bearing electron-releasing meso substituents required ∼16 h of microwave irradiation for complete consumption of starting material. This slower reaction time is likely a result of retarded nucleophilic attack by hydroxide anion on the more electron-rich macrocycles. Zinc, manganese, and cobalt insertion was promoted by microwave irradiation;[40] the metalation of the porphyrin proceeds at >90% yield. The overall yields of hangman porphyrins delivered via this new strategy set out in Scheme 2 are satisfactory (see Table 1).

Crystals of **ZnHPX2-CO_2H** that were suitable for X-ray analysis were obtained from hexanes/CH_2Cl_2 mixtures. The structure of an isolated molecule of **ZnHPX2-CO_2H** is shown in Figure 1. The Zn(II) ion is elevated 0.239 Å out of the N4 plane, and an average $Zn-N_{pyrrole}$ bond length of 2.05 Å is observed. The meso substituents at the 5,15 positions are twisted between 58° and 65° out of the macrocyclic plane, whereas the aryl substituent opposite the xanthene backbone is twisted 87°. The elevation of the Zn(II) ion from the N4 plane and exaggerated twisting of the meso-15 substituent can be understood when the complete structure of **ZnHPX2-CO_2H** is considered. As shown in Figures S2 and S3, **ZnHPX2-CO_2H** assumes a dimeric arrangement that is supported by a hydrogen bonding network occurring between a trapped water molecule and the carboxylic hanging groups. The trapped water molecule is almost equidistant to both zinc atoms (2.39 and 2.43 Å) and is also hydrogen bonded to carboxylic oxygen atoms with $O_{H_2O}-O_{carbonyl}$ distances of 2.78 Å. The carboxylic acid groups of the xanthene backbones, which exhibit significant bending

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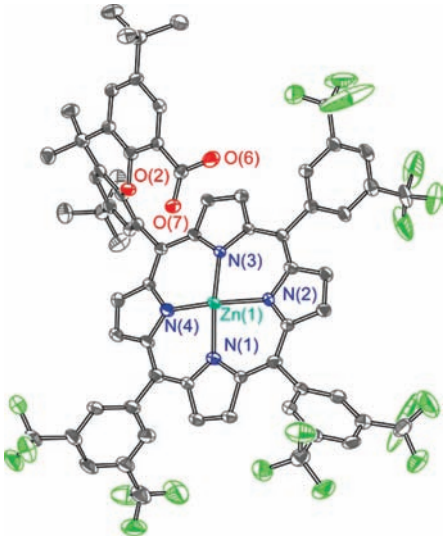

Figure 1. Crystal structure of **ZnHPX2-CO_2H** showing only half of the dimer. Thermal ellipsoids are drawn at the 50% probability level.

(148°), are aligned on the same side of the dimer and show a common hydrogen bonded dimeric motif with an O−O distance of 2.66 Å. The Zn−$N_{pyrrole}$ metrics are consistent with distorted square pyramidal geometry of pentacoordinate Zn(II) porphyrin derivatives.[41] The high degree of twisting of the aryl substituent opposite the xanthene backbone is a result of steric congestion in the dimer structure. This dimeric array is not prevalent in all hangman structures. For instance, as shown in Figure S4, **HPX5-CO_2H** crystallizes as a monomer. The proton of the carboxylic acid group forms a six-membered ring by hydrogen bonding (d($O_{xanthene}$···H) = 1.91 Å) to the oxygen of xanthene. This structural motif has been observed previously for hangman amide complexes.[42]

Cyclic voltammograms (CVs) of **F_{20}-TPP** and hangman porphyrins in CH_3CN generally show two reversible reduction waves at −1.19 to −1.37 V vs Fc^+/Fc for the first reduction and −1.65 to −1.83 V vs Fc^+/Fc for the second reduction (Figure S10f). The replacement of one pentafluorophenyl meso substituent of the TPP framework by the xanthene scaffold typically shifts the reduction potentials cathodically by ∼200 mV. **ZnHPX1-CO_2H** shows one reduction wave at −1.71 V that is accompanied by a prefeature in the initial scan at more positive potentials (Figure S11g); this behavior is consistent with adsorption of porphyrin on the electrode. Of greater interest are the CVs of the Co HPX1 series of compounds (Figure S13c). **CoHPX1-CO_2Me** exhibits two reversible waves at −1.15 and −2.19 V vs Fc^+/Fc, whereas **CoHPX1-CO_2H** shows a reversible initial reduction at −1.20 V. However, the second reduction at E_{peak} = −2.0 V is irreversible. The reduction of Co(II) macrocycles in the presence of a proton is often accompanied by Co(III) hydride formation.[43] The hangman scaffold provides a source for such a proton, and the results suggest that the **CoHPX-CO_2H** compounds may support hydrogen evolution chemistry. Studies to investigate this possibility are now underway.

The synthetic route described here is a general method for the practical synthesis of hangman porphyrins (1) from easily available starting materials, (2) in two steps, (3) in good yields, and (4) with abbreviated reaction times (4−16 h). Twelve new hangman porphyrins have been prepared with meso substituents that perturb the electronic properties of the macrocycle. The ability to tune the electronic properties of the hangman macrocycle by the synthetic method described here, and obtain them in good yields, will be useful for exploiting hangman active sites for small molecule activation.

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Supporting Information Available: Characterization data and detailed descriptions of the syntheses of all compounds. X-ray crystallographic files for porphyrins (CIF) are also provided as separate files. This material is available free of charge via the Internet at http://pubs.acs.org.

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