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Catalytic O–O Activation Chemistry Mediated by Iron Hangman Porphyrins with a Wide Range of Proton-Donating Abilities

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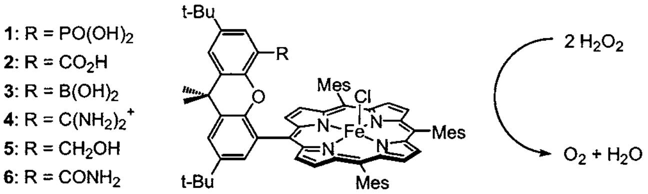
ABSTRACT



A library of hanging porphyrin xanthene (HPX) compounds containing pendant groups with various proton-donating abilities (pK_a ranging from ∼2 to 25) has been synthesized. Their corresponding chloroiron(III) complexes promote the catalase-like disproportionation of hydrogen peroxide. The overall activity and turnover numbers (TONs) are maximal for iron HPX complexes bearing acidic hydrogen-bond pendants. These results establish that careful control of intramolecular proton inventory can dramatically influence the catalytic activation of O–O bonds.

The coupled transport of both protons and electrons is needed by enzymes to achieve the bond-making and bond-breaking catalysis of small-molecule substrates.[1−8] Our interest in catalytic reactions mediated by proton-coupled electron transfer (PCET)[9−12] has led us to develop synthetic constructs where acid−base and redox functionalities are confined to a face-to-face arrangement on a single molecular scaffold.[13−15] For HPX (hanging porphyrin xanthene) and HPD (hanging porphyrin dibenzofuran) compounds, where a hydrogen-bond functionality may be precisely positioned, such platforms allow for detailed investigations of the PCET activation of O−O bonds in heme-based systems related to the protoporphyrin IX class of proteins and enzymes. We found recently that the catalase-like disproportionation of hydrogen peroxide is dramatically enhanced at a chloroiron(III) trimesitylporphyrin platform with the HPX scaffold containing a pendant carboxylic acid group (**2**); the HPX-CO$_2$H system has the proper span to bind peroxide oxidant, while the carboxylic

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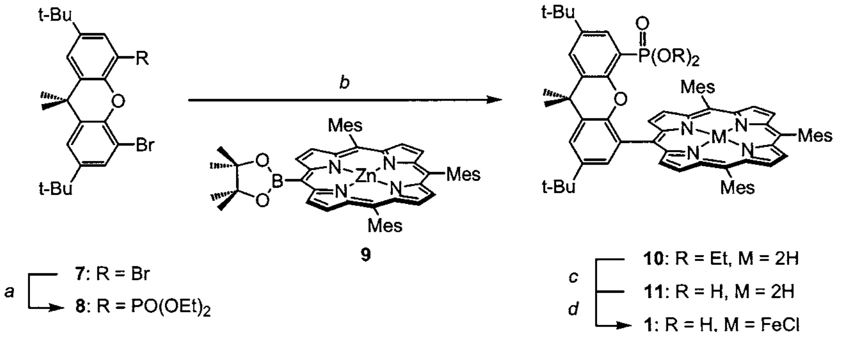
Scheme 1[a]



[a] Conditions: (a) (1) PhLi; (2) diethyl chlorophosphate. (b) (1) Na_2CO_3, $Pd(PPh_3)_4$; (2) 6 N HCl. (c) AcOH/H_2SO_4; (d) (1) $FeBr_2$, (2) aq NaCl/HCl.

acid group acts as an intramolecular shuttle to deliver proton equivalents for unmasking the reactive high-valent ferryl species.[13]

An intimate understanding of the contributions of PCET to O−O bond activation chemistry necessitates a systematic survey of catalyst systems that maintain a wide range of proton inventories. Toward this end, we now describe the synthesis, characterization, and H_2O_2 disproportionation chemistry of Hangman porphyrins bearing pendant groups with a wide range of different acid−base functionalities. These molecules afford precise control over the proton-donating ability of the pendant juxtaposed to the metalloporphyrin redox site, allowing us to determine the requirements for optimal catalase activity for the HPX system. Our findings reveal that the acidity of the hydrogen-bond pendant contributes greatly to the both the speed and stability of catalysts for proton-coupled O−O activation chemistry.

The syntheses of hanging porphyrin xanthene (HPX) compounds with tunable hydrogen-bond pendants are outlined in Schemes 1 (**1**) and 2 (**3**−**6**); compound **2** was available from previous studies.[13] Selective monolithiation of dibromide **7** with phenyllithium followed by quenching with diethyl chlorophosphate and aqueous workup provides diethylphosphonate **8** in 33% yield. Metal-catalyzed ($Pd(PPh_3)_4/Na_2CO_3$) cross coupling of **8** with boronate porphyrin **9**[16] using standard Suzuki conditions[17,18] furnishes diethylphosphono Hangman porphyrin **10** in moderate yield (46%). Deprotection of the ethyl groups of **10** under harsh acidic conditions affords **11** in 80% yield. Iron insertion into **11** with $FeBr_2$ followed by treatment with HCl affords the corresponding chloroiron(III) complex **1** in good yield (76%). The remaining porphyrins used in this study relied on **12** for the xanthene starting point. Bromoporphyrin **13** is synthesized from pyrrole, mesitaldehyde, and **12** in 25% yield using standard acid-catalyzed Lindsey conditions.[19] Zinc insertion into **13** followed by reaction with bis(neopentylglycolato) diboron[20] and acidic workup delivers boronic acid **14** in low yield (23%). Iron insertion into **14** with $FeBr_2$ followed by treatment with HCl affords the corresponding chloroiron(III) complex **3** in good yield (70%). Reaction of aldehyde **12** with hydroxylamine hydrochloride followed by treatment with selenium dioxide generates cyanide **15** in 70% yield.[21] Suzuki cross coupling of **15** and **9** delivers cyanoporphyrin **16** in good yield (74%). Iron insertion into **16** followed by reaction with Weinreb's amide reagent[22] furnishes amidinium porphyrin **4** in moderate yield (49%).[23] Reduction of ester porphyrin **18**[14] with $LiAlH_4$ produces alcohol porphyrin **19** in excellent yield (93%). Iron insertion into **18** and previously reported amide porphyrin **20** affords chloroiron(III) complexes **5** and **6** in high yields (>90%). Taken together, iron derivatives **1**−**6** afford a systematic set of Hangman catalysts with hydrogen-bond pendants displaying a wide range of acidities (pK_a from ∼2 to 25).[24,25]

Iron complexes **1**−**6** were evaluated for their catalase-like H_2O_2 disproportionation reactivity under biphasic, buffered conditions (pH 7) in the presence of 1,5-dicyclohexylimidazole at 25 °C. Oxygen evolution was monitored volumetrically and detected using a standard alkaline pyrogallol assay.[26] Two different organic solvent systems were employed: pure dichloromethane and a 3:1 methanol/dichloromethane mixture. With the exception of boronic acid **3**, which reacts with methanol to form the aprotic boronic methyl ester, the relative catalase reactivities of the iron Hangman systems are higher in the mixed methanol/dichloromethane solvent system than in pure dichloromethane. The results suggest that methanol, a protic solvent with a high dielectric

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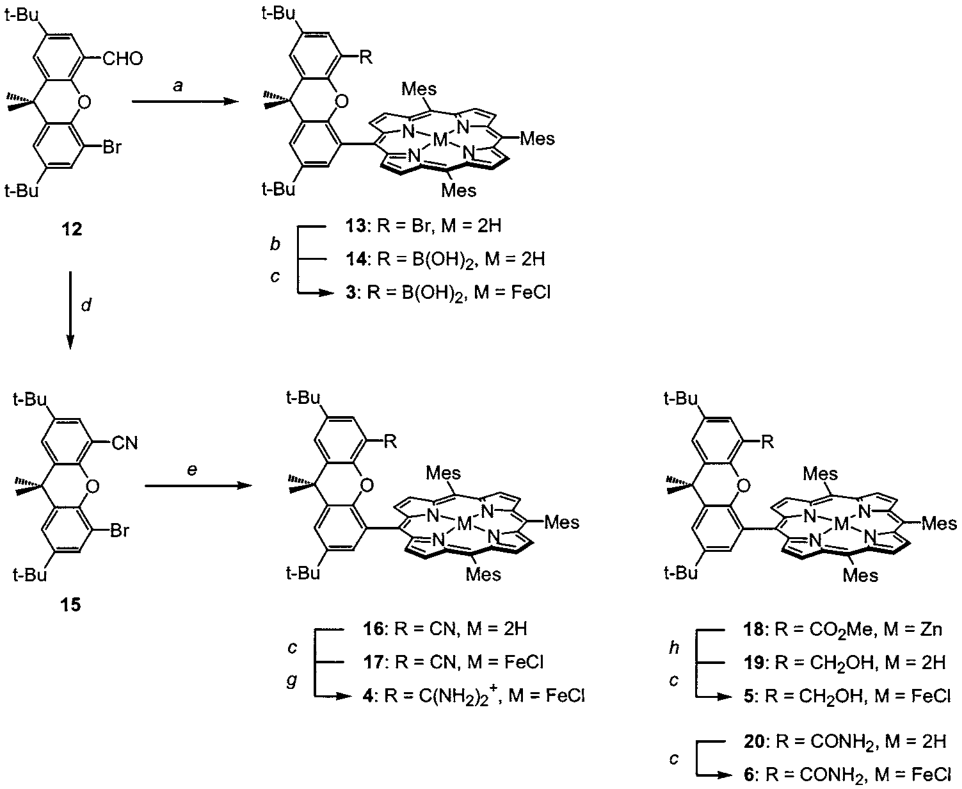
Scheme 2[a]



[a] Conditions: (a) (1) mesitaldehyde, pyrrole, $BF_3{\cdot}OEt_2$; (2) DDQ. (b) (1) $Zn(OAc)_2{\cdot}2H_2O$; (2) bis(neopentylglycolato) diboron, $Pd_2(dba)_3$, KOAc; (3) HCl. (c) (1) $FeBr_2$; (2) aq NaCl/HCl. (d) (1) $NH_2OH{\cdot}HCl$; (2) SeO_2. (e) (1) **9**, Na_2CO_3, $Pd(PPh_3)_4$; (2) 6 N HCl. (g) chloromethylaluminium amide. (h) $LiAlH_4$.

constant, assists in stabilizing a polar transition state to promote heterolytic over homolytic O−O cleavage of the ferric-hydroperoxide intermediate to generate the high-valent ferryl oxidant. Accordingly, subsequent kinetics and activity studies were performed in the 3:1 methanol/dichloromethane mixture.

The kinetics for H_2O_2 disproportionation catalyzed by **1**, **2**, **4**−**6**, and FeCl(TMP) in the latter solvent system were examined via video recording the collection of oxygen in a buret. The initial rates of H_2O_2 disappearance appear to follow first-order kinetics, and the apparent rate constant, k_i, is given in eq 1:

$$k_i = \frac{2.3}{ct}\log\frac{x_o}{x}\ \mathrm{M^{-1}\ s^{-1}} \qquad (1)$$

where x_o and x are the concentrations of H_2O_2 at time 0 and time t, respectively, and c is the concentration of the iron Hangman catalyst. The results collected in Table 1 show that the initial rates track the acidity of the pendant group, where a lower pK_a results in a higher initial rate constant. Strikingly, Hangman complexes bearing the most acidic pendants (phosphonic acid **1** and carboxylic acid **2**) exhibit initial rate constants that are 3 orders of magnitude greater than that of the baseline compound FeCl(TMP).

Table 1. Observed Initial Rate Constant (k_i) for Catalase-like H_2O_2 Disproportionation Catalyzed by Iron Hangman Complexes **1**, **2**, **4**−**6**, and FeCl(TMP) in 3:1 Methanol/Dichloromethane at 25 °C

catalyst	pK_a[a]	k_i ($M^{-1}\ s^{-1}$)
1	1.8	84 ± 17
2	4.2	83 ± 17
4	11.6	9 ± 2
5	15.4	1.4 ± 0.3
6	25.0	0.9 ± 0.2
FeCl(TMP)		0.03 ± 0.01

[a] Tabulated pK_a values are estimated from phenyl derivatives.[24,25]

The overall catalytic activities in turnover numbers (TONs) for Hangman porphyrins **1**−**6** and FeCl(TMP) are presented in Figure 1. The total TON depends on both the intrinsic reactivity and stability of the iron complex for H_2O_2 disproportionation. Carboxylic acid congener **2** exhibits the greatest overall reactivity of the Hangman catalysts surveyed due to its combination of high intrinsic reactivity and stability. For example, due to differences in their relative catalytic stabilities, **1** and **2** display disparate total TONs despite their similar intrinsic reactivities (initial rates); catalyst **1** is decomposed within 5 min with the addition of

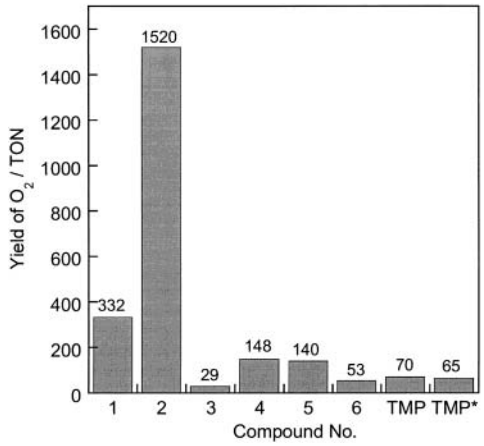


Figure 1. Turnover numbers (TONs) for oxygen release from H_2O_2 dismutation catalyzed by iron Hangman complexes **1**−**6** and FeCl(TMP) in 3:1 methanol/dichloromethane at 25 °C. TMP denotes FeCl(TMP) and TMP* denotes FeCl(TMP) and 1 equiv of benzoic acid. Error bars for TONs (not shown) are approximately ±10%.

0.11 mL of 30% H_2O_2, while **2** remains active after 15 min with over three times as much peroxide added.

Our results demonstrate that the proton-coupled activation of O−O bonds by Hangman porphyrins is markedly dependent on the acidity of the hydrogen-bond pendant. The overall observed activity for the catalase-like disproportionation of hydrogen peroxide has major contributions from both the intrinsic reactivity and stability of the catalyst system. The intrinsic reactivities of the Hangman systems directly track their acidity; pendants with lower pK_a values lead to higher initial rates for H_2O_2 dismutation. However, the overall catalase activity is maximal for the iron Hangman porphyrin bearing a carboxylic acid pendant ($pK_a \sim 4.2$), and the observed TON decreases when the pK_a of the pendant group is higher or lower than this optimum value. The stability of the catalyst is related to the heterolytic dispensation of the peroxo by proton transfer versus O−O bond homolysis, which generates reactive radical species that are debilitating to the catalyst lifetime and attendant TON. We reason that hydrogen-bond pendants with higher pK_a values are less competent to provide the required protons for heterolytic O−O bond activation, while the conjugate base of the more acidic phosphonic acid functionality ($pK_a < 2$) is less effective at accepting protons during the catalytic cycle. The successful synthesis and catalytic evaluation of a systematic set of Hangman porphyrins now sets the stage for more detailed mechanistic investigations of proton-coupled O−O activation chemistry, with particular interest toward spectroscopic identification of peroxo and oxo intermediates and their acid−base reactivity. Efforts along these lines are in progress.

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Supporting Information Available: Synthetic procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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