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# Hangman Salophens

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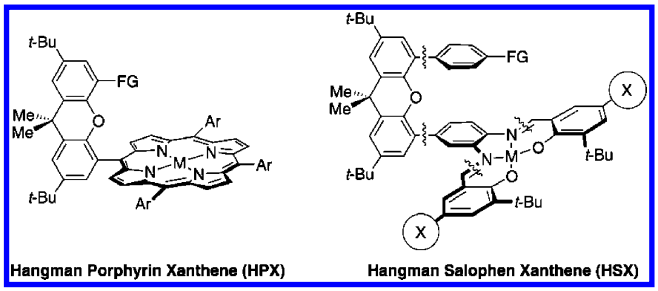
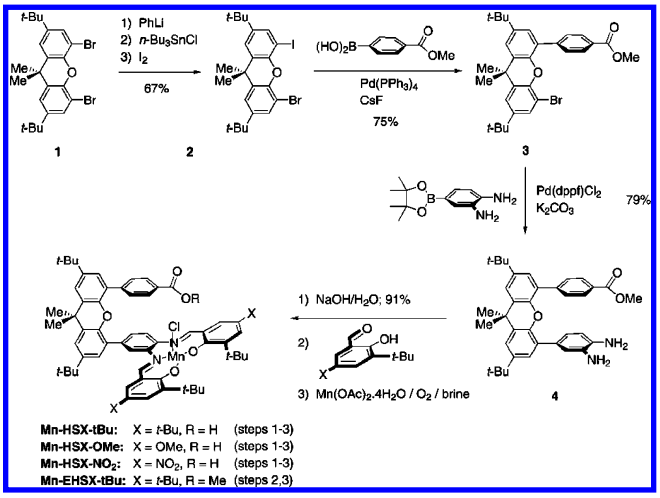
The bond-making and bond-breaking catalysis of small-molecule substrates in Nature are achieved by the coupled transport of both protons and electrons.[1−3] We have captured this proton-coupled electron transfer (PCET) catalysis by designing synthetic constructs that precisely position an acid−base functionality over the face of a redox cofactor (Chart 1). In the Hangman porphyrin xanthene (HPX),[4] the catalase and epoxidation activities of the protoporphyrin IX class of proteins and enzymes are emulated by using the acid functional group to unmask the reactive high-valent metal-oxo species by shuttling protons to a peroxide bound to the redox active metalloporphyrin.[5,6] Despite these advances, the elucidation of structure/reactivity relationships of PCET catalysis is difficult when porphyrins are used as the basal redox cofactor. Significant challenges are posed by the lengthy and tedious preparation of porphyrin platforms and their intractability to modular modifications. To develop a more versatile framework for studying PCET catalysis, we thought to replace the porphyrin with a salophen as the metal−supporting ligand.[7−9] We envisioned that the X groups of new Hangman salophen xanthene (HSX) ligands (Chart 1) could be utilized to easily tune the properties of the redox platform. In this communication, we show that HSX−metal complexes can be readily assembled in a modular fashion and that indeed HSX redox cofactors with properly tuned electronic properties can exhibit exceptional catalase-type reactivity.

***Chart 1***




***Scheme 1***




The synthesis of HSX−ligands, as outlined in Scheme 1 and described in Supporting Information, was designed about the strategic disconnects indicated in Chart 1. One of the challenges of the synthetic plan is the selective functionalization of the symmetric xanthene bridge starting from the commercially available xanthene dibromide **1**.[10−12] Using a two-step procedure, we could convert **1** to the asymmetric xanthene dihalide **2**.[13] Selective Suzuki cross-coupling of the more reactive aryl iodide bond with 4-methoxycarbonylphenylboronic acid incorporates the hanging carboxylic acid precursor to furnish **3**.[14] Subsequent cross-coupling of the remaining aryl bromide with *o*-phenylene diamine boronic acid ester affords **4**.[15] Hydrolysis of the methyl ester followed by condensation with the corresponding salicyl aldehyde and subsequent complexation with manganese diacetate provide the desired Hangman salophen manganese complexes in a modular fashion.

With a versatile synthetic route to the HSX framework in hand, we are ideally positioned to address whether PCET catalysis can be tuned by (i) the acid functional group and (ii) a redox-modulating X group. To probe these issues, we chose to investigate the PCET activation of O−O bonds by studying the disproportionation of $H_2O_2$, an important PCET process that is catalyzed by a variety of enzymes.[16] As Table 1 shows, very high turnover numbers (TON) for dioxygen production can be achieved at Mn−HSX platforms. The presence of a strong proton donor dramatically increases catalase-type reactivity. Whereas TON as high as 4372 can be achieved with Mn−HSX-*t*Bu, a relatively low TON is observed when the carboxylic acid functionality is replaced by an ester (Mn−EHSX-*t*Bu). Similarly, control experiments with the redox-only manganese salophen complex (Mn−Saloph-*t*Bu) as well as with a simple manganese salt ($Mn(OAc)_2{\cdot}2H_2O$) show low activity for disproportionation. The addition of an external $H^+$ source enhances TON of the parent salen complex as well as the Mn−EHSX-*t*Bu complex, but the activity remains far inferior to that of Mn−HSX-*t*Bu, which manages the proton by intramolecular transfer from the hanging functional group. An energy-minimized calculation of the hydroperoxide-bound Hangman salophen complex reveals that the hanging group is positioned over the face of the macrocycle and is

***Table 1.*** Turnover Numbers for the Dismutation of $H_2O_2$ Catalyzed by Manganese Salophen Complexes

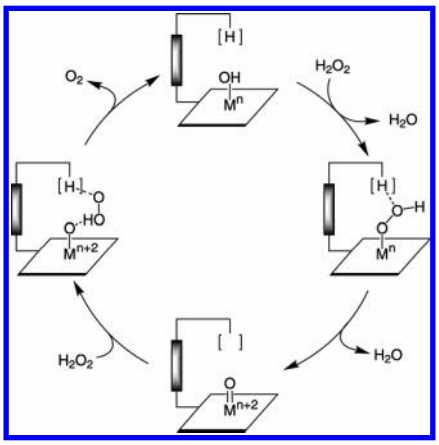
| catalyst | $O_2$ yield/TON[a] |
|---|---|
| Mn−HSX-*t*Bu | 4372 |
| Mn−EHSX-*t*Bu | 98 |
| Mn−EHSX-*t*Bu[b] | 373 |
| Mn−Saloph-*t*Bu | 86 |
| Mn−Saloph-*t*Bu[b] | 472 |
| $Mn(OAc)_2{\cdot}2H_2O$ | 62 |

[a] After 1 h. [b] In presence of 1 equiv of benzoic acid.



10.1021/ja042849b CCC: $30.25 

***Scheme 2***




able to hydrogen bond to substrate (Table S1 and Figure S1, Supporting Information).

The data listed in Table 1 are consistent with the proposed mechanism for the catalase activity of chloroperoxidases.[16] Scheme 2 adapts the mechanism for the Hangman architecture. Coordination of $H_2O_2$ to the metal results in a putative metal-bound hydroperoxide, which is converted into a Compound I intermediate by proton−assisted heterolytic O−O bond cleavage. Deprotonation of $H_2O_2$ followed by its oxidation by the high-valent metal-oxo furnishes $O_2$ and the reduced catalyst. The enhancement in TON for the Mn−HSX-*t*Bu catalyst is consistent with the proton-assisted heterolytic O−O bond cleavage and/or the base-assisted production of $O_2$, thus accounting for the proton dependence of the PCET catalysis.

We next explored whether the PCET catalysis of Scheme 2 is affected by the electronic perturbation of the redox site. This issue has not been probed for porphyrin-based Hangman platforms owing to the difficulty associated with modifying the macrocycle. Conversely, aromatic ring substituents on salen platforms are known to influence the electronic properties of the metal and in turn dictate the outcome of catalysis.[17] Indeed, the electronic spectra of a series of substituted HSX−manganese complexes reveal a strong substituent effect. The absorption spectra of the Mn−HSX complexes (Figure S2) are distinguished by a low energy band in the visible absorption spectrum similar to that observed for *N*,*N*′-di(3-*tert*-butyl-5-methylsalicylidene) cyclohexanediamine manganese(III) chloride in $CH_2Cl_2$.[18] The band exhibits a significant red-shift along the series X = $NO_2$ ($\lambda_{max}$= 460 nm) < *t*Bu ($\lambda_{max}$= 490 nm) < OMe ($\lambda_{max}$= 511 nm). This trend parallels the increasing electron donation of the X group and therefore is consistent with a salophen ligand-to-metal charge transfer parentage for the absorption band. Strikingly, these differently substituted HSX−manganese complexes display dramatic reactivity differences in $H_2O_2$ dismutation. As illustrated by the reaction profile of Figure 1, electron-donating substituents significantly enhance catalyst performance. Mn−HSX-OMe (TON = 4580) catalyzes the complete conversion of $H_2O_2$ in ∼20 min, whereas a catalyst bearing a less donating substituent (X = *t*Bu) converts 64% of substrate in the same time (TON = 3060). On the other hand, little to no reactivity is observed for Mn−HSX-$NO_2$ (TON = 81, 2% conversion). The presence of an electron-donating group on the salophen of HSX platform[19] appears to stabilize the high-valent manganese-oxo intermediate against decomposition and/or facilitates the heterolytic cleavage of the O−O bond.

In conclusion, we have synthesized Hangman salophens as a new ligand scaffold for PCET catalysis. The Hangman salophens are distinguished from typical salophen constructs by the presence of an intramolecular proton-transfer network, which is able to couple

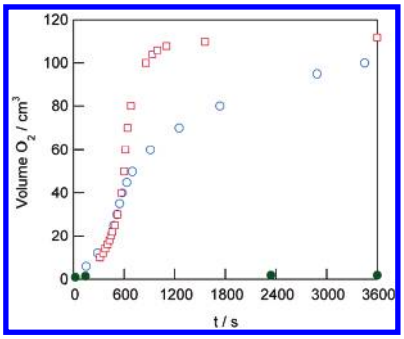



***Figure 1.*** Effect of electronic tuning on catalase-type reactivity in HSX−Mn complexes: Mn−HSX-OMe (red □), Mn−HSX-*t*Bu (blue ○), Mn−HSX-$NO_2$ (●).

to the redox processes occurring at the salophen platform. We show here for $H_2O_2$ dismutation that a strong proton-donating hanging group, working in concert with an electron-rich redox platform, is essential for the activation of the O−O bond by PCET. In this way, the Hangman salophens significantly contribute to investigations of PCET catalysis because their modular design allows for the two crucial components of a PCET reaction—acid−base and redox properties—to be tuned with facility. Accordingly, Hangman salophens uniquely enrich the scope of multielectron PCET reactions associated with catalytic bond-making and bond-breaking chemistry of small molecule substrates.

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**Supporting Information Available:** Synthesis, characterization, and DFT calculations of Hangman salophens. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Control experiments without a proton donor on a Hangman salophen possessing electron-donating groups (Mn-EHSX-OMe) also show little activity.

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