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A thiolate ligand on a cytochrome P-450 mimic permits the use of simple environmentally benign oxidants for biomimetic steroid hydroxylation in water

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Abstract—Manganese porphyrin systems carrying cyclodextrin binding groups can regioselectively and stereoselectively hydroxylate bound steroid substrates, using iodosobenzene as oxidant, but hydrogen peroxide and other simple oxidants such as sodium hypochlorite are not effective in water. Thiol ligands were then added to the catalyst, both covalently attached and hydrophobically bound, and with these ligands hydrogen peroxide was now an effective oxidant.

We have described the hydroxylations of steroids directed by geometric control, in complexes of the substrates with cytochrome P-450 mimics that are based on manganese porphyrins carrying cyclodextrin binding groups.[1] In the earliest version, we saw that catalyst **1** could bind and hydroxylate substrate **2**—with two ester groups attached at C-3 and C-17 of the steroid—in water with iodosobenzene as the oxidant. The product was exclusively the diester of the 6α hydroxy steroid **3**, which was not further oxidized to a ketone because of the inaccessibility of the product 6β hydrogen in the complex. However, there were only eight turnovers before the catalyst was oxidatively destroyed. In a later version, catalyst **4**, the fluorines stabilized the catalyst against oxidative destruction and 187 catalytic turnovers were seen before the catalyst was destroyed (Fig. 1).[1c]

With the same catalyst **4**, we saw that oxidation of substrate with three binding ester groups attached to carbons 3, 6, and 17 led to hydroxylation at C-9 of the steroid.[1d] This selectivity reflected the new geometry in the complex of the substrate with three cyclodextrins of catalyst **4**. With a different catalyst we were also able to hydroxylate C-9 in a substrate carrying two binding ester groups at carbons 3 and 6, with only two binding interactions between substrate and catalyst.[1f] However, in all these cases we looked for the possible use of simpler oxidants, such as hydrogen peroxide, sodium hypochlorite, sodium chlorite, oxone (potassium persulfate), or peracetic acid, but they failed. These oxidants have been used previously in oxidations by metalloporphyrins,[2] but not in an aqueous system. Such oxidants are attractively convenient and cheap, and in many cases environmentally benign ('Green') but in our system only the stronger oxidant iodosobenzene was successful.

The mechanism of the catalyzed reactions ordinarily involves an oxygen atom transfer to the metal atom of the metalloporphyrins, followed by hydroxylation of the bound substrate by the metal oxo species, so the problem is apparently that the other oxidants tried were not strong enough to oxidize the metal to the oxo state in water. One solution is to find even stronger benign oxidants; the other is to make the metal oxidation easier. An electron donor ligand should accomplish this.

In the natural P-450 enzymes the iron porphyrin has a cysteine thiolate sulfur as the fifth ligand, while we had used imidazole as a fifth ligand (the oxygen is added to the sixth position), either simply in solution or covalently attached to the porphyrin system. We had used this imidazole as a way to block one face of the porphyrin, so that both the substrate and the added oxygen atom would be on the same porphyrin face for reaction. However, Woggon,[3] Battersby et al.,[4] Collman and Groh,[5] and Traylor et al.[6] have prepared some porphyrins with thiolates as the fifth ligand, and it was clear that the oxidation of the metal

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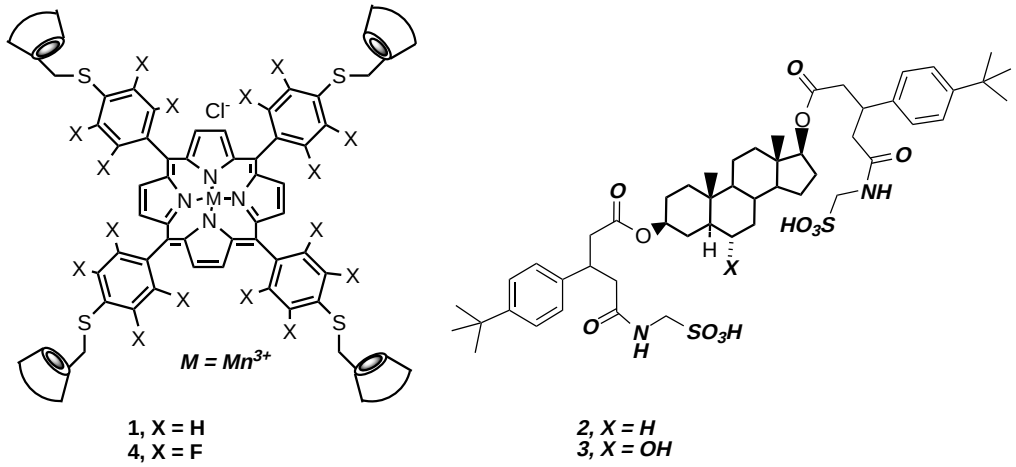
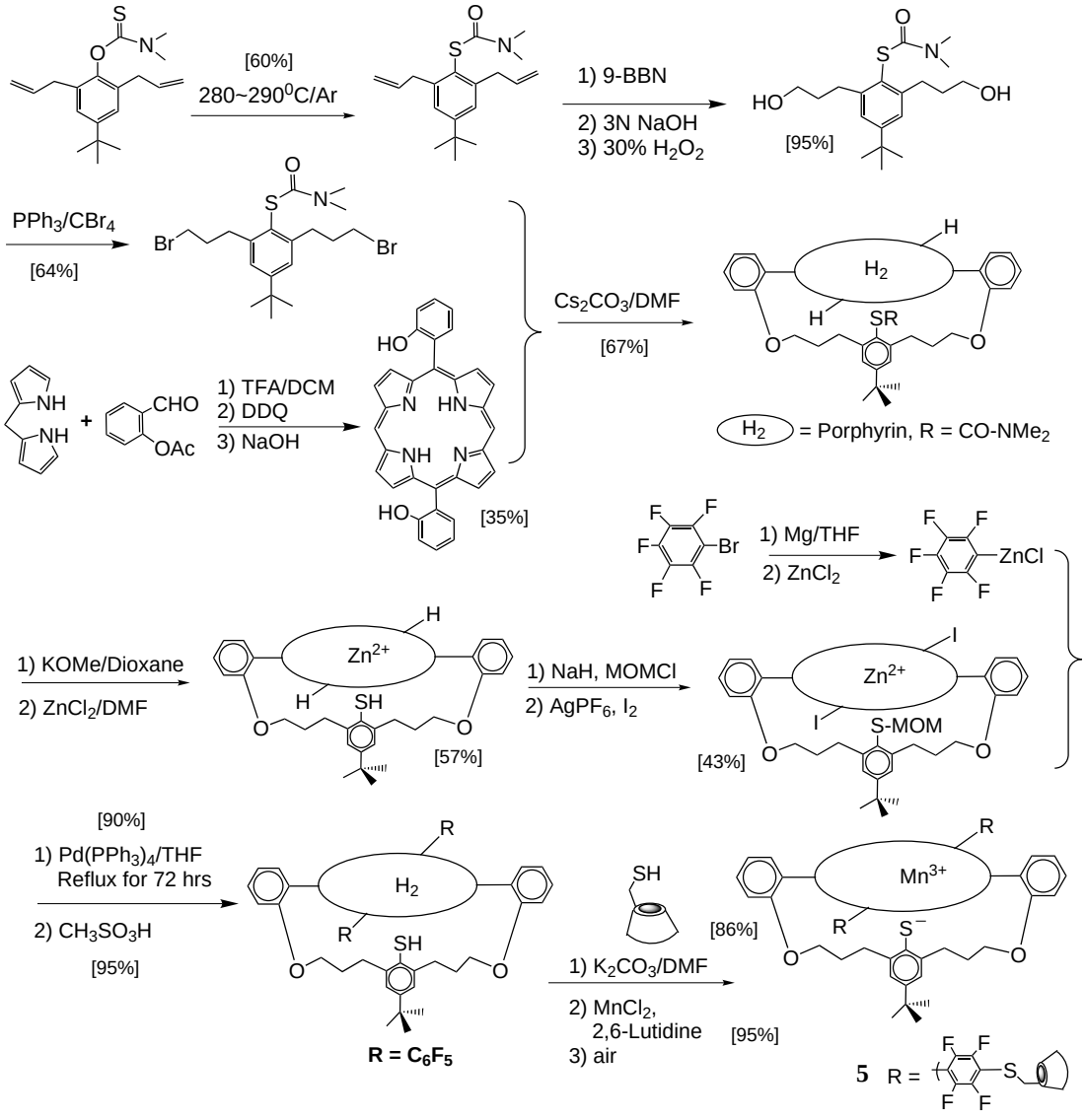


Figure 1.



Scheme 1.

to its oxo form would be assisted by the thiolate. The easily oxidized thiolate can be a much better electron donor to the oxo metal species than can imidazole or water ligands. Thus we set out to examine our catalysts with thiolates occupying the fifth coordination position of the metalloporphyrin.

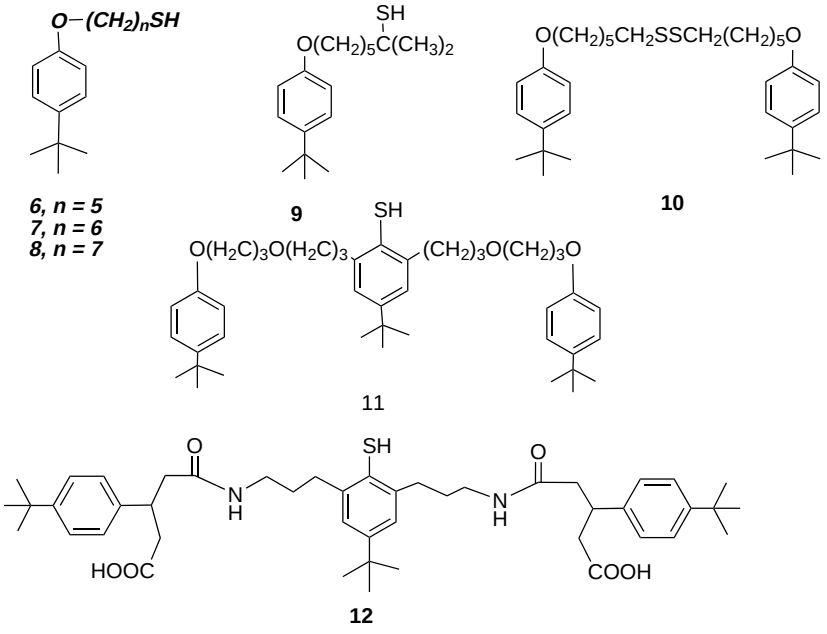
In our first new catalyst, we synthesized a manganese porphyrin **5** carrying a thiophenyl group covalently linked and bridged across the porphyrin system.[7] Our synthesis (Scheme 1) was based on that described by Wagenknecht and Woggon[3b] for a somewhat different porphyrin nucleus. With substrate **2** porphyrin **5** again afforded 6α hydoxylation, but now both sodium hypochlorite and hydrogen peroxide were successful as oxidants. The turnovers were modest—15 ± 1 with NaOCl and 10 ± 1 with hydrogen peroxide—perhaps reflecting in part that only two of the phenyl rings in the catalyst are perfluorinated (recall that catalyst **1** gave us only eight turnovers with iodosobenzene, raised to 187 with the perfluorinated catalyst **4**). The thiolate group is also of course a new oxidizable point in the catalyst. However, indeed the thiolate group made it possible to use more attractive oxidants.

We decided to use our perfluorinated catalyst **4**, with added thiol reagents. Simple thiols cysteine, thiolacetic acid, and *n*-hexylthiol added 1:1 with the catalyst led to no substrate oxidation with hydrogen peroxide. Then we took advantage of the fact that substrate **2** uses only two of the four cyclodextrins in **4** for binding. Computer models and some experimental evidence indicate that the bulky cyclodextrins alternate up and down relative to the porphyrin plane, so when the substrate is bound to two cyclodextrins on the top there are still two cyclodextrins on the bottom face available for ligand binding to a thiol.

In our first example we made three thiols **6**–**8** with the *tert*-butylphenyl group that binds strongly into β-cyclodextrin in water.[8] With 1 equiv of the thiols relative to catalyst **4** we saw no hydroxylation by hydrogen peroxide of substrate **2** with ligands **6** and **8**, but saw hydroxylation to form the 6α hydroxylated substrate with ligand **7**. This preference reflects an interesting geometric effect. The length of **7** is of course midway between that of **6** and **8**, but in addition the alkane chains in their fully extended conformations show alternating effects in the position of the thiol groups. There were 15 ± 1 turnovers, not changed if 2 equiv of **7** were used instead. By contrast, the more hindered ligand **9**[8] also potentiated hydrogen peroxide oxidation of the **4**/**2** complex at C-6α of the substrate, but with only two turnovers. The hindrance, designed to inhibit thiol oxidation, apparently also interferes with its metal coordination. The thiol oxidation product of **7**, disulfide **10**,[8] did not enable the hydrogen peroxide oxidation.

To use both of the cyclodextrins unoccupied by substrate **2** we synthesized two new ligands **11** and **12**. Ligand **11**[9] did not potentiate hydrogen peroxide oxidation with catalyst **4** and substrate **2**. Ligand **12**[9] did potentiate hydroxylation by hydrogen peroxide at C-6α of the substrate **2**, but with only 5 ± 1 turnovers. It is a little surprising that the triply bound thiols are not more effective than the doubly bound ones.

Thus, the thiolate ligands have indeed made it possible to use hydrogen peroxide as the oxidant for steroid hydroxylation, but the turnovers are not as large as one might hope. With further development, these systems could perhaps be attractive ways to carry out biomimetic hydroxylations of unactivated carbons, directed by the geometries of the catalyst/substrate complexes, and using inexpensive and environmentally benign oxidants.



Acknowledgments

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References and notes

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7. The immediate precursor, without the added manganese, had MS (MALDI) 3336 $[M+Na]^+$, the expected ^1H NMR spectrum, and UV–vis (nm, H_2O) 421 (Soret), 517, 555, 593, 650. Compound **5**, with the added manganese, had UV–vis (nm, H_2O) 468 (Soret), 560.
8. Compounds **6**–**8** had MS-CI $(M+H)^+$ of 253.2, 267.3, and 281.8, respectively. Compound **9** had MS-FAB of 294.2 $(M)^+$, compound **10** had MS-CI of 531.8 $(M+H)^+$.
9. Compound **11**, synthesized in a straightforward fashion, had MS-CI of 663.7 $(M+H)^+$. Compound **12** had MS (FAB) of 772.3 $(M)^+$. As with all such amides from the opening of the corresponding glutaric anhydride derivative, including the substrate **2** and the product **3**, this compound is a mixture of diastereomers with respect to the solubilizing chain.