Selective Catalytic Oxidation of Substrates That Bind to Metalloporphyrin Enzyme Mimics Carrying Two or Four Cyclodextrin Groups and Related Metallosalens

Ronald Breslow,* Xiaojun Zhang, Ruo Xu, Milana Maletic, and Roland Merger

Department of Chemistry, Columbia University New York, New York 10027

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Although the speed of enzyme-catalyzed reactions is to be admired and imitated, the most useful enzyme catalytic property is its selectivity. Our invention of remote oxidation was inspired by the ability of enzymes to hold their substrates in such a geometry that reaction is directed to specific substrate atoms.[1] However, the use of a covalent link between substrate and catalyst prevented catalytic turnover. To avoid this problem, we created a metalloporphyrin catalyst carrying two additional metal ions as binding groups and indeed saw preferential oxidation of a substrate that could coordinate to the two metal ions and span the porphyrin unit.[2]

To broaden this work to encompass substrates lacking metal-coordinating binding groups, we have now synthesized porphyrins carrying four (**1**) and two (**2**) β-cyclodextrin rings that can bind substrates of appropriate length with two hydrophobic ends (Figure 1). We find that they indeed bind such substrates and their Mn(III) complexes achieve selective oxidation of the substrates with good catalytic turnover. However, the experimental details are critical for achieving high selectivity.

Compound **1** was synthesized (details of all syntheses are in Supporting Information) from *p*-(methylthio)benzaldehyde by oxidation to the sulfoxide and condensation with pyrrole to afford compound **3**. Pummerer rearrangement with trifluoroacetic anhydride and deacylation with triethylamine in methanol[3] afforded the tetrathiol, which was coupled with 6-iodo-6-deoxycycloheptamylose to afford **1**.[4] Compound **2** was prepared by condensing pyrrole with benzaldehyde to form a dipyrrylmethane and then linking this with *p*-(methylthio)benzaldehyde. This led to some shuffling of aryl groups, forming a precursor of the isomer (**2′**) of **2** in which the cyclodextrins are attached to neighboring phenyls.[5]

Stilbene substrates **4**−**11** were examined as ligands for **1**, **2**, and **2′** by titration calorimetry (details and results in Supporting Information). Ligand **9**, which can insert two *tert*-butylphenyl groups into two cyclodextrin rings of **1** and **2**, behaved as expected, affording a 2/1 complex with **1** and a 1/1 complex with **2**. Ligands **10** and **11** also gave 2/1 complexes with **1**, presumably with one complex across the top face of the porphyrin and the other across the bottom face. However, the longer stilbene derivatives **4**−**8** gave only 1/1 complexes with **1**, indicating that binding to one face of the porphyrin derivative causes some distortion that prevents binding of a second ligand.

The two *p*-nitrophenyl groups make **4** bind 18 times as strongly to **1** as does **7**, while the one *p*-nitrophenyl group in ligand **8** increases the binding over that of **7** by only 2.3-fold.

Table 1. Selectivity of Substrate Oxidations with Mn(III) Cyclodextrin Catalysts[a]

catalyst	substrate	additive (mM)	rel reactivity [b]
1-Mn	**5**		21
1-Mn	**4**		15
1-Mn	**4**	AdCOOH (1.9)[c]	45
1-Mn	**4**	AdCOOH (2.5)[c]	50
1-Mn	**4**	AdCOOH (5.3)[c]	25
1-Mn	**4**	*tert*-butylbenzoate (0.3)[d]	10
1-Mn	**4**	*tert*-butylbenzoate (5.0)[d]	5.5
2-Mn	**4**		16
2-Mn	**4**	AdCOOH (2.5)[c]	49
2-Mn	**4**	pyridine (9 and 18)	15
2-Mn	**4**	NaOAc (5.0)	9
2′-Mn	**4**		4
12	**5**		2
12	**4**		1

[a] With the two competing substrates at 0.5−1.0 mM and the catalyst at ca. 0.05 mM in pH 8.0 buffer at 25 °C, using iodosyl benzene as oxidant and carrying the conversion to less than 20%. [b] Relative to substrate **7**, by competition and analysis of the products using 500 MHz ^{1}H NMR, calibrated with authentic product samples. [c] Adamantane-1-carboxylic acid. The increase and then decrease of the ratio with increasing concentration of additive was confirmed independently. [d] *p-tert*-Butylbenzoic acid.

Thus it seemed clear that both ends of **4** bind into cyclodextrin rings of **1** and that **4** should be selectively oxidized by a catalyst based on **1** and probably by a catalyst based on **2**. This is what was observed.

Porphyrins **1**, **2**, and **2′** were converted to their Mn(III) complexes, which were used as catalysts[6] for the oxidations of substrates at ca. 1 mM with 0.5 equiv of iodosylbenzene. Authentic samples of the product epoxides were prepared, and competitive oxidations were performed with substrate mixtures. The conversion was carried to only 20%, and the product mixture was analyzed by ^{1}H NMR. All runs were performed two or more times; the reactivity ratios are listed in Table 1.

As the results in Table 1 show, there is an interesting effect of added adamantanecarboxylate, which up to a certain concentration raises the selectivity for the well-bound substrate (although at very high concentrations it decreases selectivity, since it can bind to the cyclodextrin rings and displace the bound substrate). It is known that hydrophobic carboxylate ions can bind to the Mn(III) in metalloporphyrins,[7] and we believe that this is happening here. When the substrate binds to catalyst **1-Mn** or **2-Mn** on one face of the porphyrin, there is a possibility that the oxo group goes to the other face and performs nonselective oxidation of substrates. The adamantanecarboxylate coordinates to that face and prevents such nonselective oxidation (Figure 2). It is large enough that it cannot be tolerated on the same face as the bound substrate, whereas acetate ion apparently has no such face selectivity, and we find that it actually decreases oxidation selectivity. As Table 1 shows, *p-tert*-butylbenzoate ion also decreases selectivity, presumably by competing for the cyclodextrin binding sites better than it performs the face shielding that we invoke for adamantanecarboxylate.

Our maximum oxidation selectivity, 50-fold or so, exceeds the binding selectivity of the desmetal porphyrin derivatives. This probably indicates that the weaker binding substrate **7** is

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(4) This catalyst was first revealed in the following: Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146−153.

(5) The sulfoxides were separated by preparative TLC and identified by the more symmetric ^{1}H NMR spectrum of the precursor of **2** compared with its isomer (see Supporting Information).

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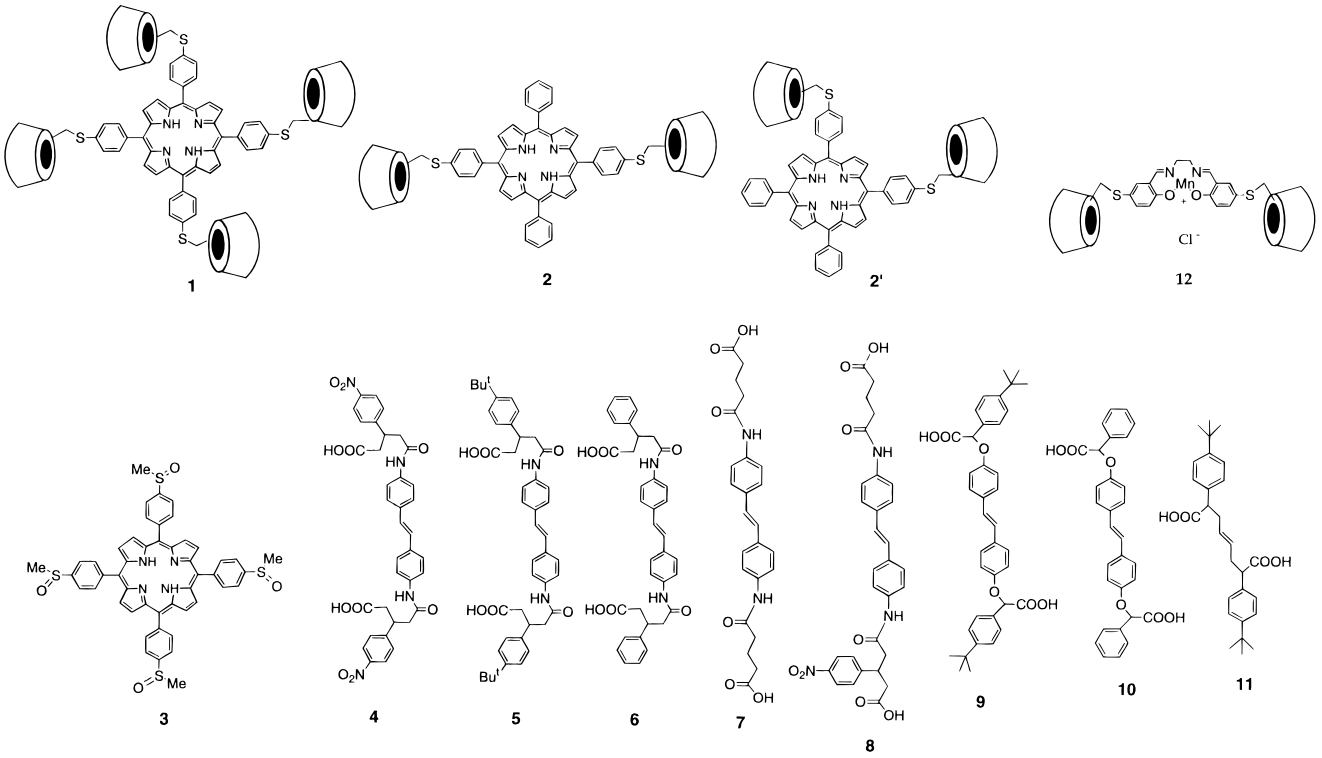

Figure 1. Structures.

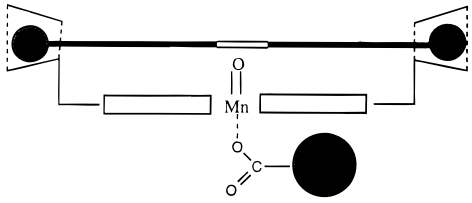

Figure 2. Schematic diagram of a substrate binding into two cyclodextrins of a Mn(III) porphyrin. The Mn carries an oxygen that will add to the substrate double bond, and the opposite face is shielded by adamantanecarboxylate.

not as reactive even within its complex as is substrate **4**, which binds to put the double bond atop the Mn oxo group. The isomer **2′-Mn** gave very poor selectivity, supporting our proposal that the effective binding geometry is that shown in Figure 2, with the substrate spanning the porphyrin ring.

Catalyst **1-Mn** shows good turnover as well as good selectivity. With an excess of substrate and oxidant we have run the epoxidation of **4** to 40 turnovers, and the catalyst was then recovered in good yield unchanged. Although the reaction slows somewhat because of product inhibition, since the product can also bind to **1-Mn**, this indicates that catalysts **1-Mn** and **2-Mn** have practical potential.

In our earlier work using metal coordination to bind substrates, we also examined metallosalen catalysts.[2] Metallosalens have been used for a number of interesting selective epoxidation reactions, along with mechanistic studies.[8−20] Thus, we examined the metallosalen bis-cyclodextrin catalyst **12**. It showed good binding selectivity but was not as good as an epoxidation catalyst and not as selective between substrates, including shorter substrates selected to fit the shorter catalyst **12** (Table 1). Thus the metalloporphyrins **1-Mn** and **2-Mn** are better catalysts for our purposes than was this metallosalen. This may reflect the formation of metallooxetane intermediates in salen catalysis[19,20] but not in porphyrin catalysis. The rigid binding of substrates into both cyclodextrin rings of **12** could block metallooxetane formation, judging from models.

The interest in catalysts **1-Mn** and **2-Mn** will be even greater if they can perform regioselective hydroxylations at saturated carbons, as covalently attached manganese porphyrins do.[21] However, even at this stage their ability to bind substrates selectively and then oxidize them with good turnover makes them interesting mimics of oxidative enzymes.[22]

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Supporting Information Available: Synthesis and characterization of new compounds, and binding and oxidation procedures and data (18 pages). See any current masthead page for ordering and Internet access instructions.

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