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Manganese Catalysts with Molecular Recognition Functionality for Selective Alkene Epoxidation

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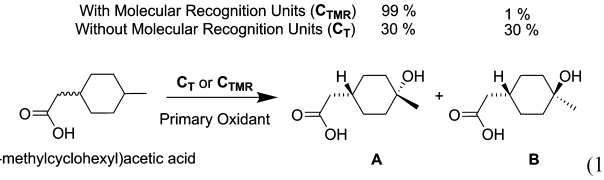
Selective epoxidation of alkenes is possible with a new manganese porphyrin catalyst, $\mathbf{C_{PMR}}$, that uses hydrogen bonding between the carboxylic acid on the substrate molecule and a Kemp's triacid unit. For two out of three olefin substrates employed, molecular recognition prevents the unselective oxidation of C−H bonds, and directs oxidation to the olefin moiety, giving only epoxide products. Weak diastereoselectivity is observed in the epoxide products, suggesting that molecular recognition affects the orientation of the catalyst-bound substrate. The previously reported manganese terpyridine complex $\mathbf{C_{TMR}}$ is shown to be a superior epoxidation catalyst to the porphyrin catalyst $\mathbf{C_{PMR}}$. Good conversion of 2-cyclopentene acetic acid (substrate **S2**) with $\mathbf{C_{PMR}}$ is consistent with molecular modeling, which indicates a particularly good substrate/catalyst match. Evidence suggests that hydrogen bonding between the substrate and the catalyst is critical in this system.

Introduction

Relatively few synthetic chemical systems combine molecular recognition and catalysis to achieve selective molecular activation.[1] Successful systems in this category have used a range of noncovalent interactions for substrate positioning including steric forces ("shape selectivity"),[2] molecular imprinting,[3] pi-stacking paired with solvophobic interactions,[4] and hydrogen bonding.[5] We recently reported[5,6] the regioselective and stereoselective oxidation of tertiary or benzylic C−H bonds using a molecular recognition catalyst $\mathbf{C_{TMR}}$, as shown in eq 1 and Figure 1. Hydrogen-bonding interactions between the substrate (2-(4-methylcyclohexyl) acetic acid) and the catalyst, both having -COOH molecular recognition units, position the substrate to allow the oxidation only at the Me−C-H position on the cyclohexane ring. As a result of molecular recognition, selectivity for hydroxylated product **A** increases and product **B** decreases with the molecular recognition catalyst, $\mathbf{C_{TMR}}$.



(1)

To test the generality of this type of molecular recognition catalysis, a new porphyrin catalyst $\mathbf{C_{PMR}}$ (Figures 1 and 2) was synthesized, along with new substrates for epoxidation. In contrast to our previous catalyst $\mathbf{C_{TMR}}$ (Figure 1), which contains two molecular recognition units per catalyst dimer,

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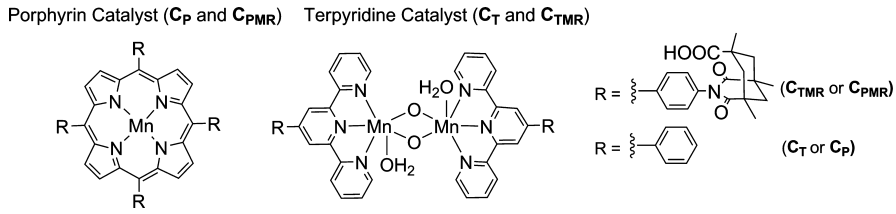


Figure 1. Porphyrin and terpyridine catalysts. Catalyst C_{PMR} and its activity are reported for the first time.

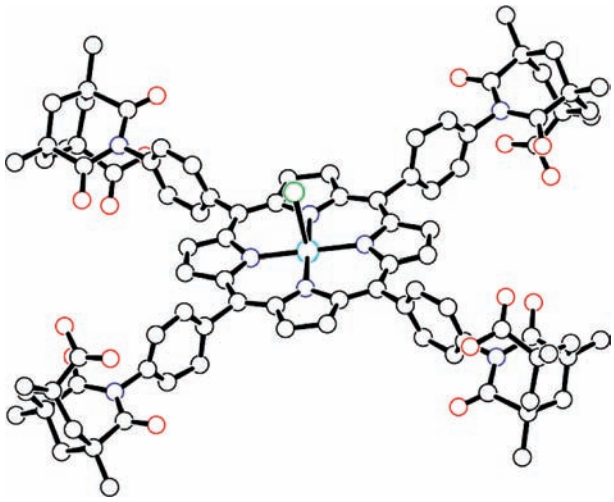
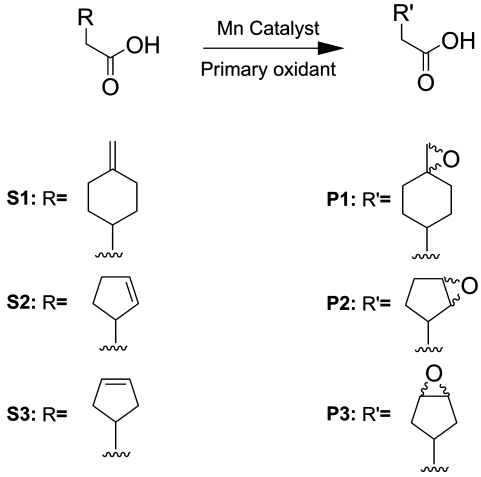


Figure 2. Conformation of the manganese(III) porphyrin C_{PMR} observed in the crystal structure. Four Kemp's triacid units form U-bends for hydrogen bonding to substrate molecules. (grey = C, dark blue = N, red = O, light blue = Mn, green = Cl).

Scheme 1. Substrates Used for Selective Epoxidation Reactions Catalyzed by Molecular Recognition Catalysts



C_{PMR} contains four U-turn motifs derived from Kemp's triacid to maximize the likelihood that at least one unit will always occupy each face of the porphyrin. As shown in previous work,[6] this design principle prevents reaction of unbound substrate because bound substrate molecules block the approach of unbound molecules. The substrates shown in Scheme 1 were designed to bind the molecular recognition units on catalysts C_{PMR} and C_{TMR}. Figure 3 shows how we expected selective epoxidation to be achieved for those substrates that are well-matched to the catalyst. Selective catalytic conversion is anticipated only if the olefin moiety of a bound substrate is correctly positioned relative to the catalyst active site. Depending on the orientation of the bound

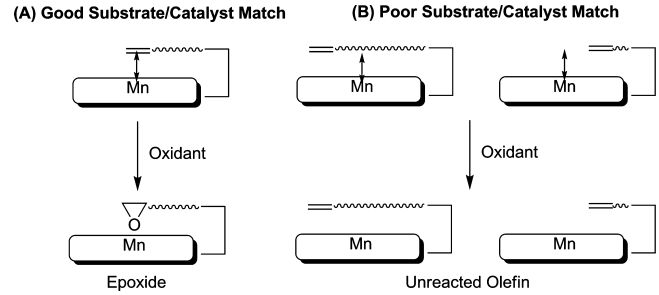


Figure 3. Epoxide is expected only in cases with a good substrate−catalyst match.

olefin with respect to the catalyst, diastereomeric selectivity could in principle also be observed. Substrates **S1**−**S3** were studied in this connection.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Spectrometers operating at 400 and 500 MHz, respectively. Chemical shifts are reported in parts per million (ppm) measured using the residual solvent peak as an internal standard. UV−visible spectra were recorded on a Cary 50 Bio Spectrophotometer. Solvents were degassed by standard Schlenk freeze-pump techniques, or by sparging with N_2.

Materials and Methods. All reagents were purchased from Sigma-Aldrich, except 2-cyclopentene acetic acid (**S2**), which was obtained from Acros. Epoxide standards for all products (**P1**−**P4**) were prepared by stirring 1 equivalent of the substrate (**S1**−**S4**) with 1.5 equiv. of 4-chloroperoxybenzoic acid (mCPBA) for 3−20 h, and purified using column chromatography (230−400 mesh silica gel, gradient of 30/70 − 60/40 EtOAc/Hexanes). **S4** was prepared by esterifying **S2** using TMS-diazomethane.[7] See the Supporting Information for procedure details and product characterization. All yields for manganese-catalyzed reactions were measured by NMR using 1,3,5-trimethoxybenzene as an internal standard.

Synthesis of Catalyst C_{PMR}. This porphyrin catalyst was synthesized according to Scheme 2. 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine (TPP, **1**) was converted to 5,10,15,20-(4-nitro)tetraphenyl-21*H*,23*H*-porphine (**2**) by direct nitration with sodium nitrite in strong acid via a modification of a known procedure.[8] Four equivalents of $NaNO_2$ (225 mg, 3 mmol) were

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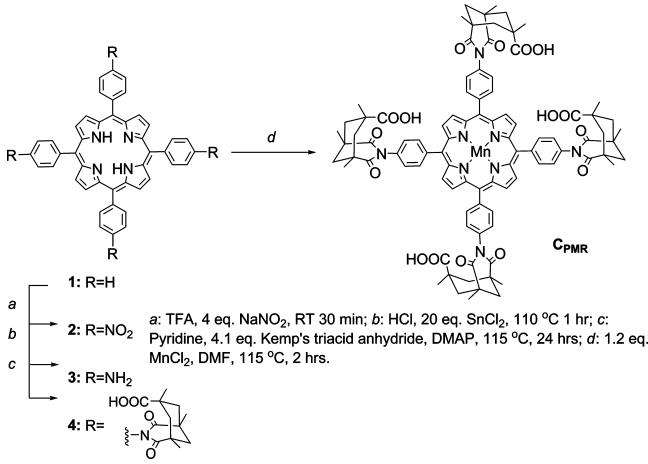
Scheme 2. Synthesis of Molecular Recognition Catalyst $\mathbf{C_{PMR}}$



added to a solution of TPP (500 mg, 0.814 mmol) in trifluoroacetic acid (ca. 300 mL). The mixture was stirred for 30 min and then extracted into dichloromethane. This method avoids the statistical mixtures found in the published procedure.[8] The organic phase was neutralized with a saturated solution of $NaHCO_3$, washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure (490 mg, 76% yield). All of this product **2** was then reduced to 5,10,15,20-(4-amino)tetraphenyl-21*H*,23*H*-porphine (**3**) by refluxing 5 equivalents of tin(II) chloride in HCl under nitrogen for 1 h to give the tetraamine **3** (224 mg, 54% yield), and extracted with dichloromethane after adjusting the pH to 8 using ammonium hydroxide. Compound **3** was further converted to **4** by refluxing in pyridine under nitrogen with 4.1 equiv. of Kemp's triacid anhydride chloride and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP, ca. 1 mg) for 24 h. The progress of the reaction was followed using ESI-MS and TLC (5% methanol in dichloromethane). Porphyrin **4** could be isolated by removing the pyridine under reduced pressure, and purified by flash chromatography using 5% MeOH in dichloromethane (446 mg, 86% yield). ^{1}H NMR (400 MHz, DMSO) δ 12.78 (br s, 4H), 8.90 (s, 8H), 8.27 (d, J = 8.1 Hz, 8H), 7.62 (d, J = 6.5 Hz, 8H), 2.66 (d, 8H), 2.39 (d, J = 13.3 Hz, 4H), 1.66 (d, J = 13.1 Hz, 4H), 1.47 (d, J = 13.4 Hz, 8H), 1.34 (s, 24H), 1.28 (s, 12H), −2.86 (br s, 2H). HRMS (ESI+) *m*/*z* predicted for m^{2+}, 782.8332; found, 782.8313.

Metalloporphyrin $\mathbf{C_{PMR}}$ can be obtained by directly adding 1.2 equiv. of $MnCl_2$ dissolved in *N*,*N*-dimethylformamide (DMF) to the refluxing solution in the previous step. The mixture was refluxed until the reaction was complete according to UV−visible spectroscopy (ca. 2 h). Metalloporphyrin $\mathbf{C_{PMR}}$ was precipitated by pouring the reaction mixture into a 10-fold excess of cold water and filtered to give a dark green solid. The solid was then repeatedly dissolved in acetone, filtered, reprecipitated by adding hexane, and collected by filtration to remove impurities (338 mg, 80% yield going from **4** to $\mathbf{C_{PMR}}$; 28% net yield from **1**). Diffraction-quality crystals were obtained by cooling a concentrated (>4.5 mM) solution in acetonitrile, but these rapidly desolvated upon removal from the vessel. Figure 1 shows the connectivity of atoms in the porphyrin which was established from the low resolution X-ray determination of the structure from poorly diffracting crystals (see the Supporting Information for crystal data parameters). Paramagnetism in the Mn(III) complex prevented its characterization by NMR. HRMS (ESI+) *m*/*z* predicted (m^+ + H): 1616.5698, found 1616.5681. Elemental Anal. Predicted ($\mathbf{C_{PMR}}\cdot 4H_2O$): C, 64.34; H, 5.20; N, 6.76. Found: C, 64.09; H, 5.61; N, 6.50.

Terpyridine catalyst $\mathbf{C_T}$ was synthesized according to a previously published procedure,[16] and $\mathbf{C_{TMR}}$[5]was made using a procedure modified from that previously reported. The modifications were as follows. (1) Ligand synthesis: The ligand for catalyst $\mathbf{C_{TMR}}$ (**2** in the prior manuscript[5]) was synthesized from aminophenyl terpyridine (200 mg, 0.62 mmol) and Kemp's triacid anhydride chloride (200 mg, 1.25 equiv., 0.77 mmol) in freshly distilled pyridine (15 mL). After refluxing for 48 h under nitrogen, the mixture was poured into 150 mL of 0.05 N HCl and the product extracted with dichloromethane (3 × 10 mL). The organic layer was washed with brine, dried with $MgSO_4$ and the solvent removed (**Caution!** *Pyridine is toxic*.) under reduced pressure. The product was purified by dissolving the remaining residue in a minimal amount (ca. 5 mL) of dichloromethane, layering with an equivalent volume of pentane, and cooling to −10 °C. A brown solid was collected by filtration (194 mg, 63% yield). (2) Complex synthesis: Catalyst $\mathbf{C_{TMR}}$ (**1b** in the previous manuscript[5]) was synthesized as described previously,[5] but was recovered by removing the solvent under reduced pressure immediately after a dark solid was precipitated with excess solid KNO_3. Diethyl ether was added to the resulting solid to form a slurry, which was transferred to a frit and washed with excess cold water to remove the colorless inorganic salts. The remaining brown precipitate was collected and dried overnight under a vacuum and proved to be identical to the previously[5] fully characterized material.

Representative Epoxidation Procedures Using $\mathbf{C_T}$ and $\mathbf{C_{TMR}}$. To dissolve the catalyst, water (70 μL) was first added to the catalyst (0.6 μmol), followed by acetonitrile (0.1 mL). Over ca. 10 min, the catalyst dissolved on stirring and the remaining solvent MeCN (2.5 mL) was added. A solution of olefin (0.125 mmol) in 2.5 mL of acetonitrile was cooled to 0 °C. The catalyst solution was added followed by the dropwise addition of a solution of tetrabutylammonium oxone (1.6% active oxygen, 0.50 mmol) in 5.0 mL of acetonitrile. Once the addition was complete, the reaction mixture was warmed to ambient temperature and stirred for 4 h. The excess oxidant was removed by passing the reaction mixture through a 10 cm plug of silica gel, and eluting with 200 mL of a 5% acetic acid solution in ethyl acetate. The eluate was concentrated and the acetic acid was removed azeotropically with toluene under reduced pressure. The products were analyzed by NMR spectroscopy and the spectra compared with those of the independently prepared epoxide products.

Representative Epoxidation Procedures Using $\mathbf{C_P}$ and $\mathbf{C_{PMR}}$. An aliquot (200 μL) of a stock solution (5 mM) of porphyrin catalyst was injected into a degassed solution of CH_2Cl_2 containing 100 equivalents of substrate (0.1 mmol) and 500 equiv. (110 mg) of iodosylbenzene (PhIO). A rapid color change from green to orange was observed. The flask was covered with aluminum foil,

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and the solution stirred under nitrogen for 20 h. All product mixtures were analyzed by NMR spectroscopy.

Results

The new porphyrin catalyst $\mathbf{C_{PMR}}$ was successfully synthesized by directly nitrating tetraphenyl porphyrin (TPP) with sodium nitrite in strong acid,[9] followed by reduction to the amine with $SnCl_2$ and subsequent reaction with Kemp's triacid anhydride chloride. Managanese was incorporated into the porphyrin by refluxing $MnCl_2$ and the apoporphyrin in DMF and air oxidation converts Mn(II) to Mn(III). Crystallographic data (see Figure 2) shows that the desired complex was indeed obtained. Diffraction-quality crystals were obtained by cooling a concentrated solution (ca. 4.5 mM) in CH_3CN to −10 °C. However, rapid desolvation of the crystals prevented data collection sufficient for complete refinement. The connectivity of the metalloporphyrin and the chloride anion are shown in Figure 2, but the coordinates of the ca. 9 solvent molecules per porphyrin were undetermined. The terpyridine catalyst was synthesized using a modification to the previously reported method.[5]

Manganese porphyrins are well-known catalysts for both olefin epoxidation and C−H hydroxylation.[9] The commercially available olefin **S2,** and the synthetically available olefins **S1**, **S3**, and **S4** (see the Supporting Information) were substrates for the reactions shown in Scheme 1. Iodosobenzene (PhIO) and tetrabutylammonium oxone (TBAO) were the primary oxidants in the porphyrin and terpyridine systems respectively, while reaction with 4-chlorobenzoperoxoic acid (mCPBA) in the absence of metal was used to prepare the products **P1**−**P4**. Porphyrins are known to show higher activity in the presence of additives such as imidazole or pyridine bases that bind axially to the metal.[10] To avoid interference in the hydrogen-bonding, bases were avoided but 5 equiv. of pyridine *N*-oxide (PNO) enhanced the activity, presumably by acting as an axial ligand. Yields were also found to increase when reactions were run in the dark under a nitrogen atmosphere. Another variable affecting yield was the combination of the terminal oxidant and the catalyst. TBAO was the best oxidant for reactions using the terpyridine catalysts, but gave virtually no conversion with the manganese porphyrin catalysts. In contrast, the decarboxylation of ibuprofen was observed when tetrabutylammonium periodate was used with the porphyrin catalysts,[11] but was ineffective for oxidation with the terpyridine catalysts. In general, the Mn-terpyridine catalysts showed high conversion for all substrates (entries 3 and 4 in Tables 1−3), including >99% conversion for two of the three. In the absence of a manganese catalyst, no reaction between the olefins and PhIO or TBAO was found. Percent yield and the diastereomeric ratios (D.R.) of the products were compared for each of the substrates with the two control catalysts, $\mathbf{C_T}$ and $\mathbf{C_P}$, having no molecular recognition units, and $\mathbf{C_{TMR}}$ and $\mathbf{C_{PMR}}$. The relative configurations of the **P2** epoxide products were assigned by comparison to the products formed from the epoxidation of **S2** with mCPBA (see the Supporting Information). Because the presence of hydroxyl groups[12] and other hydrogen-bonding substituents[13] are known to direct the attack of mCPBA, the major isomer formed from the reaction of mCPBA with **S2** can be assigned as the syn isomer. Similarly, we tentatively assigned the major isomer formed from the reaction of **S3** and mCPBA as the syn isomer. Because of the remote location of the double bond in **S1**, however, we were unable to assume that such a directing effect would operate during the formation of **P1** and could not assign the relative stereochemistry for these products using this method. The matter was further complicated by the fact that the two isomers proved to be inseparable by both flash chromatography and by HPLC. Consequently, the relative stereochemistry of epoxides **P1** remains unassigned. Tables 1–3 list the diastereomeric ratios determined from the C−H shifts of the epoxide peaks in the NMR spectra.

Simple molecular models and MM2 calculations (Chem 3D) were used to predict the appropriate carboxylic acid-to-olefin distances for each substrate. These models suggest that substrates **S2** and **S3**, if aligned correctly, are both appropriate for catalyst $\mathbf{C_{PMR}}$, whereas **S1** is the best length match for $\mathbf{C_{TMR}}$. However, the orientation of the olefin with respect to the plane of the catalyst, which must be crucial for the diastereoselectivity, could not be accurately predicted. The catalytic data are shown in Tables 1−3.

Products from both control catalysts $\mathbf{C_P}$ and $\mathbf{C_T}$ gave NMR data of an unidentifiable mixture of oxidation

Table 1. Epoxidation of 2-(4-Methylenecyclohexyl) Acetic Acid (**S1**)

entry	catalyst	oxidant	additive	solvent	conv. (%)	yield (%)[c]	D.R.
1[a]	$\mathbf{C_P}$	Ph-I═O	PNO	CH_2Cl_2	40	n/d	n/d
2[a]	$\mathbf{C_{PMR}}$	Ph-I═O	PNO	CH_2Cl_2	<1	<1	4:1[d]
3[b]	$\mathbf{C_T}$	TBAO	none	$MeCN/H_2O$	>99	n/d	n/d
4[b]	$\mathbf{C_{TMR}}$	TBAO	none	$MeCN/H_2O$	>99	quant.	5:4

[a] Conditions: CH_2Cl_2 (20 mL), 1:5:100:500 catalyst:PNO:substrate:PhIO, N_2, dark, 25 °C. [b] Conditions: 0.3:1 H_2O:CH_3CN (9 mL), 0.5:100:400 catalyst:substrate:TBAO, 0 °C→25 °C. [c] Epoxide yields for control reactions could not be accurately determined due to overlapping peaks in the NMR spectrum of complex mixture of products. [d] Approximate value, due to low yield. D.R. = diastereomeric ratio, PNO = pyridine *N*-oxide, MeCN = acetonitrile. Conv. (%) = Percent conversion measured by internal standard in the NMR spectrum, n/d = not determined because of overlapping peaks or low yield. See eq 2.

Table 2. Epoxidation of 2-Cyclopentene Acetic Acid (**S2**)

entry	catalyst	oxidant	additive	solvent	conv. (%)	yield (%)[c]	D.R.
1[a]	$\mathbf{C_P}$	Ph-I═O	PNO	CH_2Cl_2	20	9	1:0
2[a]	$\mathbf{C_{PMR}}$	Ph-I═O	PNO	CH_2Cl_2	15	14[d]	3:1[d]
3[b]	$\mathbf{C_T}$	TBAO	none	$MeCN/H_2O$	>99	6	>10:1[e]
4[b]	$\mathbf{C_{TMR}}$	TBAO	none	$MeCN/H_2O$	>99	63	>10:1[e]

[a] Conditions: CH_2Cl_2 (20 mL), 1:5:100:500 catalyst:PNO:substrate:PhIO, N_2, dark, 25 °C. [b] Conditions: 0.3:1 H_2O:CH_3CN (9 mL), 0.5:100:400 catalyst:substrate:TBAO, 0 °C→25 °C. [c] Epoxide yields for control reactions could not be accurately determined due to overlapping peaks in the NMR spectrum of complex mixture of products. [d] Values were measured at 3 h and found to have a 4% yield and a D.R of 3:1. [e] The minor isomer could not accurately be integrated because of poor signal:noise in the NMR spectrum; qualitatively, the epoxide ratios look the same. See eq 3.

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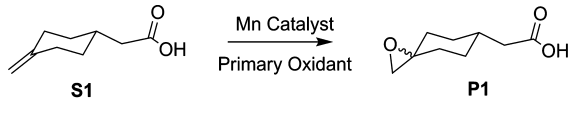
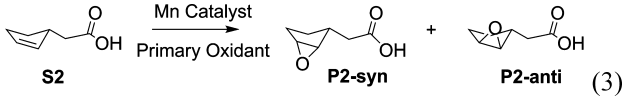


(2)

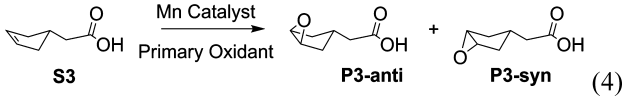
products for substrates. The product mixtures for both catalysts showed peaks shifted slightly downfield from the expected olefin positions, indicating that substrate oxidation, such as C−H hydroxylation, occurs at other sites on the molecule. However, when the molecular recognition catalysts $\mathbf{C_{PMR}}$ and $\mathbf{C_{TMR}}$ are used, only the epoxides are observed. This suggests that hydrogen-bonding between the catalyst and the substrate positions the olefin so that only the desired epoxidation reaction can occur. Molecular models show that substrate **S1** is the best match for catalyst $\mathbf{C_{TMR}}$, consistent with the excellent conversion observed. The low conversion with catalyst $\mathbf{C_{PMR}}$ is attributed to a length mismatch (Figure 3). Despite the low epoxide yield of **P1** from the porphyrin catalysts, it is clear from the NMR spectrum that both catalysts $\mathbf{C_{PMR}}$ and $\mathbf{C_{TMR}}$ favor the same diastereomer.



(3)

Substrate **S2** was predicted by our models to be a good match for catalyst $\mathbf{C_{PMR}}$, and indeed this olefin gave the highest conversion of all three substrates for this catalyst. Unlike the other substrates, the diastereomeric ratios for **P2** were determined for the control reactions (Table 2, entries 1 and 3), giving additional insight into the effects of molecular recognition. The major epoxide isomer is assigned as the syn isomer.[12,13] In the case of $\mathbf{C_{PMR}}$ versus $\mathbf{C_P}$, the D.R. is strongly affected, and the anti isomer is now observed. The D.R. does not change significantly with time; the diastereomers were in the same 3:1 ratio at 3 h and at 20 h. $\mathbf{C_T}$ and $\mathbf{C_{TMR}}$ show increased activity compared to the porphyrins: complete conversion and good epoxide yields are observed. However, in contrast to the change in diastereoselectivity observed for $\mathbf{C_{PMR}}$ versus $\mathbf{C_P}$, $\mathbf{C_{TMR}}$ shows a similar D.R. to $\mathbf{C_T}$.

Finally **S3**, like **S1**, gave an unidentifiable mixture of products with catalyst $\mathbf{C_P}$, but only epoxide products **P3** with molecular recognition catalyst $\mathbf{C_{PMR}}$ (see the Supporting Information for spectra). This is consistent with our previous report that bound substrate blocks the site and prevents unselective oxidation.[6] $\mathbf{C_T}$ and $\mathbf{C_{TMR}}$ were systematically more active than $\mathbf{C_P}$ and $\mathbf{C_{PMR}}$ for all the substrates, including **S3**, which gave complete conversion to olefin products. We tentatively assign the major product isomer from **S3** as syn. The D.R increases from 3:1 for $\mathbf{C_T}$ to 4:1 for $\mathbf{C_{TMR}}$, indicating that the preference for syn epoxidation is enhanced by molecular recognition.



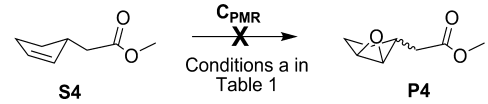
(4)

Table 3. Epoxidation of 3-Cyclopentene Acetic Acid (**S3**)

entry	catalyst	oxidant	additive	solvent	conv. (%)	yield[c] (%)	D.R.
1[a]	$\mathbf{C_P}$	Ph-I=O	PNO	CH_2Cl_2	55	n/d	n/d
2[a]	$\mathbf{C_{PMR}}$	Ph-I=O	PNO	CH_2Cl_2	1	<1	2:1[d]
3[b]	$\mathbf{C_T}$	TBAO	none	MeCN/H_2O	>99	quant.	3:1
4[b]	$\mathbf{C_{TMR}}$	TBAO	none	MeCN/H_2O	>99	quant.	4:1

[a] Conditions: CH_2Cl_2 (20 mL), 1:5:100:500 catalyst:PNO:substrate:PhIO, N_2, dark, 25 °C. [b] Conditions: 0.3:1 H_2O:CH_3CN (9 mL), 0.5:100:400 catalyst:substrate:TBAO, 0 °C→25 °C. [c] Epoxide yields for control reactions could not be accurately determined due to overlapping peaks in the NMR spectrum of complex mixture of products. [d] Approximate value, because of low yield. See eq 4.

Scheme 3. Reaction of Methyl 2-(cyclopent-2-enyl)acetate with $\mathbf{C_{PMR}}$ Yields No (<1%) Epoxide



To probe the importance of hydrogen bonding between $\mathbf{C_{PMR}}$ and the substrate, the substrate **S2** was esterified using diazomethane to yield substrate **S4**.[14] When the reaction in Scheme 3 was run, no epoxide (<1% yield) was observed in the NMR spectrum.

The lower conversion of <1% for ester **S4** compared with the 15% conversion for substrate **S2** (Table 2) indicates that molecular recognition forces enhance reactivity with the porphyrin. The importance of hydrogen bonding for selectivity with catalyst $\mathbf{C_{TMR}}$ has been fully explored in previous work.[6]

Carboxylic acids such as AcOH reduce molecular recognition selectivity for $\mathbf{C_{TMR}}$,[6] so we looked at their effect on $\mathbf{C_{PMR}}$. Unfortunately, at high concentrations (20 equiv. per substrate) the AcOH appears to inhibit the catalysis, perhaps by binding to the metal or blocking the site. With cyclooctene as substrate (Table 4), control experiments show that an excess of acetic acid (entry 3, 20 equiv. to substrate) decreased the reaction yield compared to one or no equivalents of acetic acid (entries 1 and 2). To determine whether this was caused by steric hindrance of acetic acid bound to the catalyst receptors, bulky *tert*-butyl benzoic acid was also used in excess (entry 4) and found to have a similar effect. The observation of some activity indicates that steric hindrance does not completely block access to the metal, but that it plays some role. This is different to the previously reported results for $\mathbf{C_{TMR}}$, where acetic acid was shown to disrupt hydrogen bonding between the substrate and the catalyst with a linear concentration dependence.[6] These results, together with the control experiment with ester **S4** and $\mathbf{C_{PMR}}$, suggest that the activity observed with substrate **S2** is due to molecular recognition, and not a favorable influence of the carboxylic acid on the reaction mechanism.

In addition to epoxidation, porphyrins are known to hydroxylate C−H bonds.[9] To compare the new porphyrin catalyst $\mathbf{C_{PMR}}$ to our previously published terpyridine catalyst,[5] ibuprofen was used as a substrate as shown in

(14) Furniss, B. R.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longman: London, 1996.
(15) Komuro, M.; Nagatsu, Y.; Higuchi, T.; Hirobe, M. *Tetrahedron Lett.* **1992**, *33*, 4949, and personal communication.

Table 4. Epoxidation of Cyclooctene in the Presence of Acetic Acid with $\mathbf{C_{PMR}}$[a]

entry	additive	equivalents	epoxide yield (%)
1	none	0	24
2	acetic acid	1	23
3	acetic acid	20	10
4	*t*-Bu benzoic acid	20	12

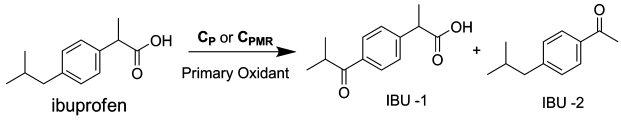
[a] Experimental conditions are as described in Table 1, but with added carboxylic acid. *t*-Bu = 4-*tert*-butyl.

Table 5. Oxidation of Ibuprofen Using $\mathbf{C_{PMR}}$[a]

oxidant	Mn(III) porph	% yield IBU-1	% yield IBU-2
periodate	$\mathbf{C_P}$	4	43
periodate	$\mathbf{C_{PMR}}$	16	55
iodosobenzene	$\mathbf{C_P}$	6	56
iodosobenzene	$\mathbf{C_{PMR}}$	7	18

[a] Reaction conditions: CH_2Cl_2 (5 mL) 1:5:100:500 catalyst:PNO:substrate:oxidant, N_2, dark, 25 °C, 12 h. See eq 5.

eq 5. Ibuprofen can undergo oxidation at either of its benzylic positions to give products **IBU-1** or **IBU-2**. We had expected that hydrogen-bonding interactions with $\mathbf{C_{PMR}}$ would favor product **IBU-1**. In contrast to our previous success with ibuprofen and $\mathbf{C_{TMR}}$, and despite model building and computational predictions suggesting a good match, only poor selectivity and conversion was observed for $\mathbf{C_{TMR}}$ (Table 5). With tetrabutylammonium periodate (Table 5, Entries 1 and 2), increased oxidation at the benzylic bond distal to the carboxylic acid could be achieved only but with an increase in oxidative decarboxylation. With iodosobenzene as primary oxidant, overoxidized products were observed with $\mathbf{C_{PMR}}$. These findings are consistent with the results of Hirobe et al.,[15] showing that oxidative decarboxylation of ibuprofen occurs preferentially to C−H bond oxidation when an iron porphyrin is used. With isobutylbenzene, very little oxidation (<10%) was observed under a variety of conditions. This suggests that the manganese terpyridine catalyst $\mathbf{C_T}$ is far superior to $\mathbf{C_P}$ for the hydroxylation of C−H bonds.



(5)

Discussion

In the initial design phase, we used molecular models to determine which substrates should be well-matched to the catalyst structure. In the experimental work, we found that well-matched substrates for molecular recognition catalysts $\mathbf{C_{TMR}}$ and $\mathbf{C_{PMR}}$ do indeed show selective epoxidation. Unexpectedly, both porphyrin catalysts, $\mathbf{C_P}$ and $\mathbf{C_{PMR}}$, showed poor conversion. Detailed comparison showed that the terpyridine catalysts are systematically more active than the porphyrins. Unlike the situation for $\mathbf{C_{TMR}}$ in C−H hydroxylation, the diastereoselectivity was only modest, but both catalysts favored the same epoxide.

Olefin Conversion. Two factors seem to improve the yield of the epoxides **P1**−**P3**. First, minimal steric hindrance is required for good access to the metal in epoxidation. This is illustrated by the lower conversion of all substrates with the sterically more hindered molecular recognition catalyst $\mathbf{C_{PMR}}$versus the $\mathbf{C_P}$ control. The second factor, well-matched hydrogen bonding between the catalyst and the substrate, as shown in Figure 3, is necessary for a good yield. Both **S1** and **S3** show unselective oxidation when the catalyst molecular recognition units are absent, but highly specific epoxidation when the molecular recognition units are present. This is best explained by catalyst-substrate recognition. No conversion at all occurs when ester **S4** is exposed to the reaction conditions using $\mathbf{C_{PMR}}$, in contrast with the good conversion observed for the corresponding acid, **S2**. We ascribe this to the ester abolishing the hydrogen bonding only possible with the carboxylic acid form of the substrate. However, we cannot exclude the possibility that other unexpected factors, such as catalyst−catalyst interactions, affect the epoxide yield.

Diastereoselectivity and Olefin Orientation. The best evidence for molecular recognition affecting diastereoselectivity in these systems is shown by **P2**, where D.R.'s are shifted from 1:0 for the control catalyst $\mathbf{C_P}$ to 3:1 for $\mathbf{C_{PMR}}$ (Table 2, entries 1 and 2). These differences are much smaller than we previously found for C−H hydroxylation, and we offer the following tentative explanation to account for these results.

The orientation of the face of the olefin with respect to the plane of the catalyst is expected to be an important factor in achieving diastereoselectivity. When a substrate is positioned over the metal via hydrogen bonding with the catalyst, only one face of the olefin is exposed to the catalyst and therefore one product is expected. After oxidation of the olefin to the epoxide, the product must dissociate from the catalyst to allow another substrate to bind.

One explanation for the weak diasteroselectivity observed for both catalysts is that the olefin needs to be positioned roughly perpendicular to the plane of the catalyst in the oblique docking pattern shown in Figure 4. Both faces of the olefin are exposed and either can be attacked. Thus for **P2**, one diastereomer is only slightly favored by molecular recognition (Table 2, entries 2 and 4), when compared to the case where molecular recognition is absent (Table 2, entries 1 and 3). In principle, better selectivity could be achieved with better control over the substrate's orientation.

Orientational differences and steric effects may also explain the lack of conversion of **S3** with $\mathbf{C_{PMR}}$, despite our models indicating a good match. After binding the catalyst, the olefin in **S3** may not be parallel to the porphyrin plane in the reactive conformation as we had modeled, but somewhat rotated. In our model, rotating the cyclopentene ring causes a steric clash with the porphyrin. Indeed, the traces of **P3** isomers have a nearly equivalent ratio, as Figure 4 indicates.

(16) (a) Limburg, J.; Vrettos, J. S.; Liable-Sands, L. M.; Rheingold, A. L.; Crabtree, R. H.; Brudvig, G. W. *Science* **1999**, *283*, 1524. (b) Limburg, J.; Vrettos, J. S.; Chen, H.; de Paula, J. C.; Crabtree, R. H.; Brudvig, G. W. *J. Am. Chem. Soc.* **2001**, *123*, 423.

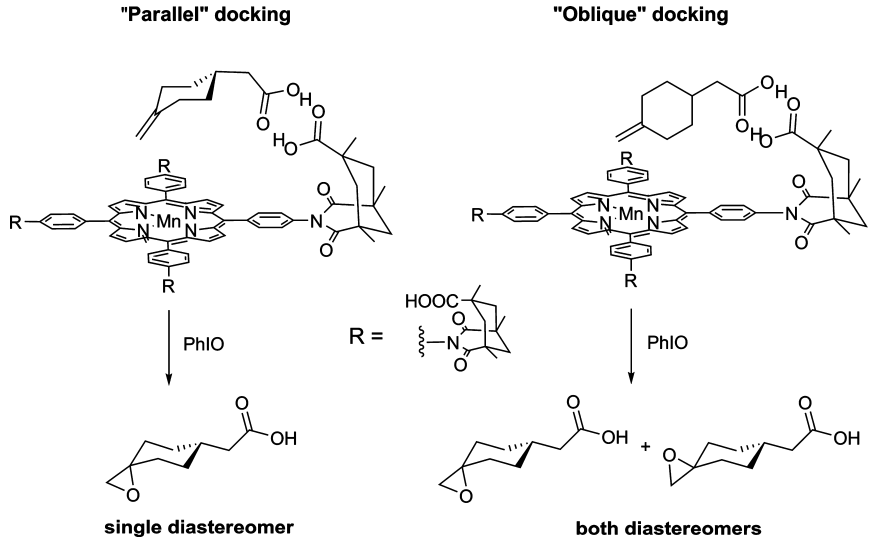


Figure 4. Orientation effects of the substrate. Different products may arise from different positioning.

Hydrogen-Bonding Interactions and Reactive Site Protection. The importance of hydrogen bonding is highlighted by comparing the data for **S2** and **S4** (Table 2 and Scheme 3). Substrate **S2** is the only one to give measurable amounts of epoxide for $\mathbf{C_{PMR}}$, which we ascribe to its good match with the catalyst. If hydrogen bonding were not important, the same trend should be observed with the methyl ester **S4**, with the olefin similarly located with respect to the carbonyl group. However, no conversion is observed for this substrate with $\mathbf{C_{PMR}}$, which we ascribe to the steric clash between the alkyl groups surrounding the porphyrin and the ester, together with the absence of hydrogen bonds. Again, steric effects also seem to play a role.

As in our previous work,[6] we attempted to disrupt the hydrogen bonding interactions between $\mathbf{C_{PMR}}$ and the substrate using excess acetic acid. However, the high concentrations of acid required for these experiments shut down activity in the porphyrin system, as shown by Table 4. With acetic acid in excess (20:1 olefin) in the epoxidation of cyclooctene, reactivity decreased. It therefore seems unlikely that the presence of the carboxylic acid moiety in substrates **S1**−**S3** alters reactivity independent of hydrogen bonding forces. The lack of complete inhibition of $\mathbf{C_{PMR}}$ by *tert*-butyl benzoic acid highlights an important difference from $\mathbf{C_{TMR}}$. This may be attributed to differences in the cavity size or flexibility of the two catalysts (this difference is discussed in the next section).

The likely cause of the decrease in yield is a steric interaction between the bound acetic acid, and the free olefin. We have previously reported a similar inhibition effect for $\mathbf{C_{TMR}}$,[6] but the effects are less drastic than in C−H hydroxylation. As previously reported, this same principle also plays a role in the selectivity by preventing unbound molecules from accessing the metal. Without molecular recognition, substrates can be oxidized unselectively. In contrast, when a substrate is bound to the catalyst by hydrogen bonds, it can protect the site and prevent unselective oxidation. Catalysts $\mathbf{C_{TMR}}$ and $\mathbf{C_{PMR}}$ give only epoxides when used with **S1**−**S3**, which can be explained by this principle.

Terpyridine vs Porphyrin Catalysts. There was a considerable difference between the terpyridine and the porphyrin catalysts. The terpyridine catalyst gave complete conversion for two of the three substrates, whereas the porphyrin catalysts consistently gave lower conversions. Appending the Kemp's triacid groups to the porphyin also consistently suppressed conversion, yet had no effect on conversion for the terpyridine catalysts. Furthermore, in our hands the porphyrin was unable to oxidize both benzylic C−H bonds in ibuprofen, whereas the terpyridine catalysts can do so in high yield. That the terpyridine catalyst is a superior oxidation catalyst is not surprising because it is also capable of oxidizing water to dioxygen.[16] Further mechanistic and computational work will be needed to address this point.

Recent computational and experimental results suggest that the rigidity and flexibility of the substrate and catalyst play important roles in deciding regio- and stereoselectivity.[17] Some of the observed differences between the two systems may, therefore, be due to the difference in rigidity of the porphyrin macrocycle and the terpyridine dimer. Finally, we found that the choice of primary oxidant had great impact on the different catalysts. For example, no oxidation was observed with TBAO in the porphyrin system, and PhIO showed no activity with $\mathbf{C_T}$ and $\mathbf{C_{TMR}}$. This is consistent with a previous report by Furia et al.[18]

Conclusion

A new porphyrin catalyst, $\mathbf{C_{PMR}}$, bearing four U-turn hydrogen-bonding molecular recognition motifs has been synthesized and used for the selective epoxidation of olefins. For two out of three substrates, molecular recognition prevents unselective oxidation of C−H bonds and directs oxidation to the olefin, giving only epoxide products.

(17) Manuscript in preparation.

(18) Campestrini, S.; Furia, F. D.; Labat, G.; Novello, F. *J. Chem. Soc., Perkins Trans. 2* **1994**, 2175.

Furthermore, unselective oxidation of unbound substrate was prevented. The Mn-Terpy catalyst $\mathbf{C_{TMR}}$ gave complete conversion of all substrates, showing it to be a superior oxidation catalyst to $\mathbf{C_{PMR}}$. Good conversion of substrate **S2** by $\mathbf{C_{PMR}}$ is indicative of a good substrate/catalyst match compared to other substrates, and is predicted by molecular models. Low diastereoselectivity is attributed to the orientation of the olefin as it is held in the porphyrin pocket.

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Supporting Information Available: Detailed procedures for the syntheses and characterization of substrates **S1** and **S3**−**S4** and the products **P1**−**P4**; partial crystallographic data; NMR spectra of product mixtures for **S2** using $\mathbf{C_P}$ and $\mathbf{C_{PMR}}$ (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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