Shape Selective Alkane Hydroxylation by Metalloporphyrin Catalysts†

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Abstract: A series of manganese and iron porphyrins with sterically protected pockets are shown to be shape selective alkane hydroxylation catalysts. With iodosobenzene as oxidant, good regioselectivity is observed for hydroxylation of alkanes at the least hindered methyl group by using the very sterically hindered (5,10,15,20-tetrakis(2′,4′,6′-triphenylphenyl)-porphyrinato)manganese(III) acetate (MnTTPPP(OAc)) as catalyst; the moderately hindered (5,10,15,20-tetrakis(2′,4′,6′-trimethoxyphenyl)porphyrinato)manganese(III) acetate shows little selectivity toward terminal CH_3 hydroxylation but does show enhancement for the adjacent, $\omega - 1$, CH_2 site. Primary selectivity is dependent on the size and shape of the alkane substrate, with more bulky substituents giving greater primary selectivity. Substituting pentafluoroiodosobenzene or *m*-chloroperbenzoic acid as oxidants yields similar selectivity, thus conclusively demonstrating metal based oxidation via a common intermediate for these three systems. In contrast, *tert*-butyl hydroperoxide or 2,2,2-trifluoroethanol solubilized pentafluoroiodosobenzene show no primary carbon selectivity, and reaction product ratios are independent of the metalloporphyrin catalyst; this demonstrates that the site of oxidation with these oxidants is *not* metal based. The iron porphyrin derivatives also show good primary selectivity, although to a lesser degree than with the Mn derivatives, proving that these oxidations too are metal based. The regioselectivities for alkane hydroxylation shown by TTPPP derivatives are comparable to or better than those found for some isozymes of cytochrome P-450 which are responsible for primary alcohol biosynthesis from steroids, fatty acids, and alkanes.

The unequalled ability of enzymes to exhibit molecular recognition and to catalyze regioselective reactions has led to diverse efforts to design synthetic systems with similar capabilities. Such regioselectivity often originates from discrimination based on the size and shape of substrate molecules, i.e., shape selectivity. Two criteria apply: the first is the synthetic challenge in the design of a chemical species capable of molecular shape recognition; the second criterion requires that this synthetic host be capable of catalyzing a chemical transformation on the guest substrate while held in a specific orientation. Many guest–host systems, such as the cavitands,[1] calixarenes,[2] crown ethers,[3] lacunar macrocycles,[4] etc., have been synthesized, and some exhibit remarkable substrate recognition. None, however, are capable of catalyzing chemical reactions with the kind of regioselectivity typical of enzymatic reactions. In microporous extended solids, most notably zeolites, shape selective catalysis of hydrocarbon reforming has been successful and formed the basis for important industrial processes.[5] Nonetheless, the creation of homogeneous catalysts for shape selective transformations has remained unrealized.

Metalloporphyrins have been used as catalysts in a variety of oxidation reactions,[6] including olefin epoxidation and alkane hydroxylation, in attempts to mimic the enzymatic activity of cytochrome P-450. MnTPP(X) (where TPP is 5,10,15,20-tetraphenylporphyrinate(2−), and X can be Cl^-, Br^-, I^-, N_3^-, etc.) catalyzes the hydroxylation and halogenation of cyclohexane with iodosobenzene as oxidant.[7,8] A high spin d^2, Mn(V)–oxo complex has been suggested as one possible intermediate. Hill has isolated and characterized two other species formed during these reactions,[8] both of which are capable of oxidizing alkanes in solution: $(XMn^{IV}TPP(OIPh))_2O$ (X = Cl^-, Br^-) and $(N_3Mn^{IV}TPP)_2O$. The product distributions of *tert*-butylbenzene and norcarnane hydroxylations, as determined by Hill[7a] and Groves,[7b] respectively, are consistent with hydrogen atom abstraction and recombination, involving a radical, rather than a carbocation intermediate.

We[9] and others[10] have used metalloporphyrins with steric protection of the porphyrin faces as catalysts for the hydroxylation of cyclic and straight chain alkanes. In all cases involving modestly hindered porphyrins[9,10] (such as (5,10,15,20-tetrakis(2′,4′,6′-trimethoxyphenyl)porphyrinato)manganese(III) acetate, MnTTMPP(OAc), as shown in Figure 1), only very modest shape selectivity has proved possible: slight regioselectivity for secondary carbon vs. secondary carbon hydroxylation was observed, and no significant production of primary alcohols was seen. We report here that the *very* sterically crowded manganese(III) and iron(III) complexes of 5,10,15,20-tetrakis(2′,4′,6′-triphenylphenyl)-porphyrinate (the bis-pocket porphyrin, TTPPP, as in Figure 1) show good regioselectivity for primary hydroxylation of *n*-alkanes and remarkable shape selective hydroxylation of branched alkanes. This is reminiscent of some isozymes of cytochrome P-450 and of the nonheme-iron ω-hydroxylases, which are responsible for primary alcohol synthesis from the terminal hydroxylation of alkyl

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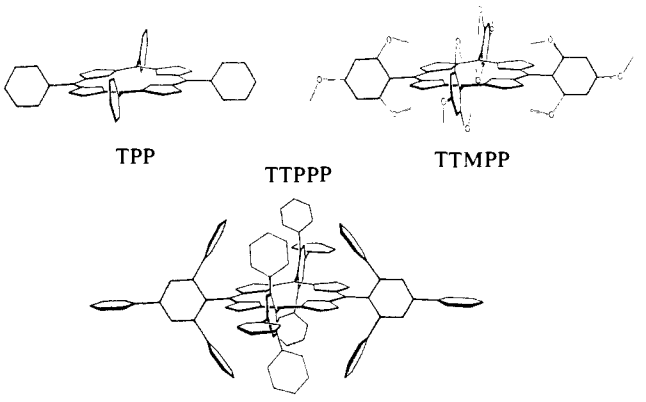

Figure 1. Diagrammatic representations of the porphyrins used in this study.

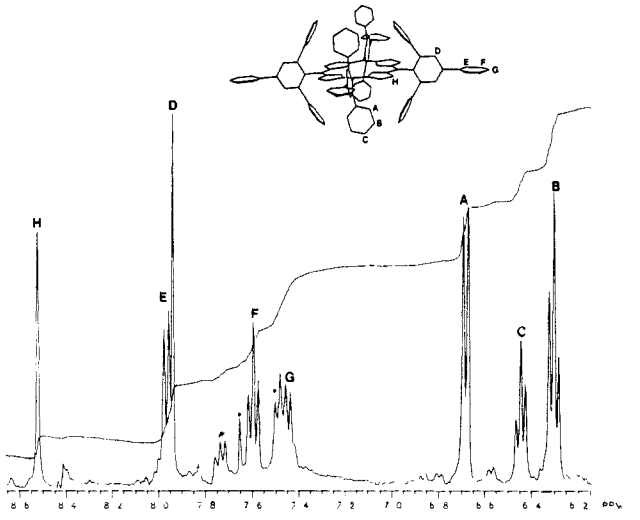

Figure 2. 360-MHz ^1H NMR of aromatic region of H_2TTPPP ($HDCCl_2$ reference). Marked impurity peaks are due to trace amounts of unreacted 2,4,6-triphenylbenzaldehyde.

chains (e.g., cholesterol, fatty acids, and *n*-alkanes). In fact, the regioselectivities of TTPPP derivatives are better than those of some isozymes of cytochrome P-450.

Experimental Section

Synthesis of Porphyrins and Metalloporphyrins. 5,10,15,20-Tetraphenylporphyrin (H_2TPP)[13] and 5,10,15,20-tetrakis(2′,4′,6′-trimethoxyphenyl)porphyrin (H_2TTMPP)[14] were synthesized as previously reported. 5,10,15,20-Tetrakis(2′,4′,6′-triphenylphenyl)porphyrin (H_2TTPPP) was prepared by condensing 2,4,6-triphenylbenzaldehyde and pyrrole (purified over CaH_2) with $Zn(OAc)_2$ as template in 2,4,6-trimethylpyridine[6k] or quinoline under nitrogen in a sealed stainless steel tube at 220 °C. The crude product was taken up into methylene chloride, extracted with 6 M HCl, and purified on silica gel with methylene chloride/hexanes as eluant. The purified chlorin was then oxidized with excess dichlorodicyanoquinone in benzene for 1 h. The benzene layer was extracted with a basic aqueous solution of $Na_2S_2O_4$. The previous characterization of the porphyrin's optical and fast atom bombardment mass spectra has been reported.[9,15] The ^1H NMR of H_2TTPPP is first order at 360 MHz[9] and is shown with assignments in Figure 2.

The manganese and iron acetates of TPP and TTMPP were made by their respective literature methods.[16,17] MnTTPPPBr and FeTTPPPI were synthesized as previously reported[9,15] and metathesized with aqueous NaOAc to yield the metalloporphyrin acetates. All metalloporphyrin derivatives were characterized by HPLC, ^1H NMR, fast atom bombardment mass spectrometry, and optical spectra.

Hydroxylations. Iodosobenzene and pentafluoroiodosobenzene were prepared by their literature methods.[18] All alkane substrates were purchased in their highest commercial purity and used without further purification. All reactions were run at 25 °C. In a typical reaction 45 μmol of oxidant was added to a solution of 0.5 mL of substrate, 0.5 mL of benzene, and 0.4 μmol of metalloporphyrin catalyst, and the reaction mixture was stirred under argon for 7 h. The mixture was then quenched with $NaHSO_3$, internal standard was added, and products were analyzed by capillary gas chromatography.

In order to make meaningful comparisons between various alkane substrates, we used several normalized selectivity indices. The primary selectivity index was defined as the ratio of the concentration of primary alcohol to secondary alcohols, normalized for the respective number of hydrogens. The following general formula was used: N[1° alcohol]/[2° alcohols], where N is equal to 1.00 for *n*-pentane, 1.33 for *n*-hexane, 1.67 for *n*-heptane, 2.00 for *n*-octane, 2.67 for *n*-decane, and 4.00 for *n*-tetradecane. Another useful parameter was the ω-1 selectivity index, which was defined as the ratio of the concentration of 2-alcohol (i.e., the ω − 1 position) to the other secondary alcohols, normalized for the relative number of hydrogens. The following formula applied: N[ω − 1 alcohol]/[other 2° alcohols], where N is equal to 0.50 for *n*-pentane, 1.00 for *n*-hexane, 1.50 for *n*-heptane, 2.00 for *n*-octane, 3.00 for *n*-decane, and 5.00 for *n*-tetradecane.

Kinetic Isotope Effect. $CH_3CD_2CH_2CD_2CH_3$ was synthesized by the literature method.[19] It was hydroxylated by using iodosobenzene and MnTTMPP(OAc) and the above conditions. The ratio of 2-pentanol to 3-pentanol observed in the hydroxylation of unlabeled pentane was divided by the ratio of 2-pentanol to 3-pentanol observed in the hydroxylation of pentane-d_4. This gave an observed kinetic isotope effect (k_H/k_D) of 3.5.

Results and Discussion

This study of shape selectivity uses three porphyrins with increasing steric protection of both faces of the macrocycle (Figure 1). We have succeeded in generating dramatic changes in regioselectivity for the formation of alcohols from alkanes as a function of steric constraint at the porphyrin periphery. These discussions will focus first on the regioselectivity for hydroxylation of alkanes shown by these three porphyrins, which span a very wide range of steric constraint. Then, we shall point out the use of shape selective catalysts as mechanistic probes to demonstrate the nature of the catalytic species and the site of the hydroxylation.

In order to use any catalyst for oxidation of hydrocarbons, it is important that the catalyst be oxidatively robust. This is generally *not* the case with simple metalloporphyrins. Although we have not yet done a full kinetic analysis of the rates of porphyrin degradation in these systems, we do have semiquantitative comparisons. In highly dilute manganese porphyrin solutions (10 μM), the half-lives of the metalloporphyrins upon addition of a large excess of oxidant are independent of oxidant concentration but strongly dependent on steric encumbrance at the meso position of the porphyrin. For iodosobenzene, pentafluoroiodosobenzene, or *m*-chloroperbenzoic acid, MnTPP(OAc) has a half-life of 5 min, MnTTMPP(OAc) of 10 min, and MnTTPPP(OAc) of 25 h. Thus, steric protection of the periphery of metalloporphyrins *dramatically enhances* the oxidative robustness of the catalyst. Electron-withdrawing substituents can have similar effects.[6k,l]

Shape Selectivity. The hydrogen atom abstraction–recombination mechanism has been demonstrated for at least some of the alkane hydroxylations catalyzed by metalloporphyrins. In the absence of steric considerations, then, regioselectivity will be determined by relative bond dissociation energies. Thus, with a

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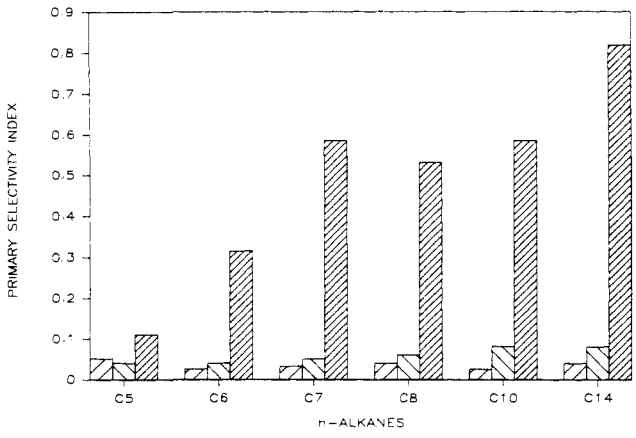

Figure 3. Primary selectivity index vs. *n*-alkane chain length; primary selectivity index is the ratio of primary to total secondary alcohols, normalized for the relative number of hydrogens. Reactions done in benzene under Ar with iodosobenzene as oxidant. (▨) MnTPP(OAc), (▧) MnTTPP(OAc), and (▩) MnTTPPP(OAc).

Table I. Yields of Hydroxylated Products from Heptane

catalyst	oxidant	yield[a] (%)
MnTPP(OAc)	C_6H_5IO	310
MnTTMPP(OAc)	C_6H_5IO	3900
MnTTPPP(OAc)	C_6H_5IO	130
MnTPP(OAc)	C_6F_5IO	530
MnTTMPP(OAc)	C_6F_5IO	1430
MnTTPPP(OAc)	C_6F_5IO	210
MnTPP(OAc)	*m*-$ClC_6H_4CO_3H$	280
MnTTMPP(OAc)	*m*-$ClC_6H_4CO_3H$	1000
MnTTPPP(OAc)	*m*-$ClC_6H_4CO_3H$	120
MnTPP(OAc)	C_6F_5IO/F_3CCH_2OH	200
MnTTMPP(OAc)	C_6F_5IO/F_3CCH_2OH	190
MnTTPPP(OAc)	C_6F_5IO/F_3CCH_2OH	210
MnTPP(OAc)	*t*-BuOOH	1900
MnTTMPP(OAc)	*t*-BuOOH	3400
MnTTPPP(OAc)	*t*-BuOOH	1000
FeTPP(OAc)	C_6H_5IO	220
FeTTMPP(OAc)	C_6H_5IO	1580
FeTTPPP(OAc)	C_6H_5IO	160

[a] Yields are based on metalloporphyrin, after 7 h. In the case of *t*-BuOOH, reported yields are the sums of the respective alcohols and ketones. Yields based on oxidant are not given, since excess oxidant was used.

sterically undemanding metalloporphyrin (such as MnTPP), one would expect (and observes) that the selectivity would be 3° ≫ 2° ≫ 1° and that there would be no statistically significant preference for one 2° site over another 2° site, etc. With sterically bulky catalysts, however, access of the alkane to the metal should be restricted to the more exposed C–H bonds, giving rise to shape selectivity.

The most difficult substrate for the demonstration of regioselectivity by any catalyst must be the *n*-alkanes, since they lack any functionality or polarity by which the catalyst may differentiate one site from another. Only relatively modest, anisotropic differences in the shape of the *n*-alkanes may allow for the distinction of one methylene from another or, even more challenging, for the selection of terminal methyl groups. As expected, MnTPP(OAc) catalysis of iodosobenzene hydroxylation of *n*-alkanes gives nearly exclusively 2° alcohols; the shallow pocketed metalloporphyrin, MnTTMPP(OAc), is only slightly better for the production of 1° alcohol (Figure 3 and Table II). With the deeply pocketed MnTTPPP(OAc), however, regioselectivity for the hydroxylation of the more sterically accessible methyl groups is observed.

MnTTPPP(OAc) also shows increasing primary selectivity for *n*-alkanes with increasing chain length (Figure 3 and Table II).

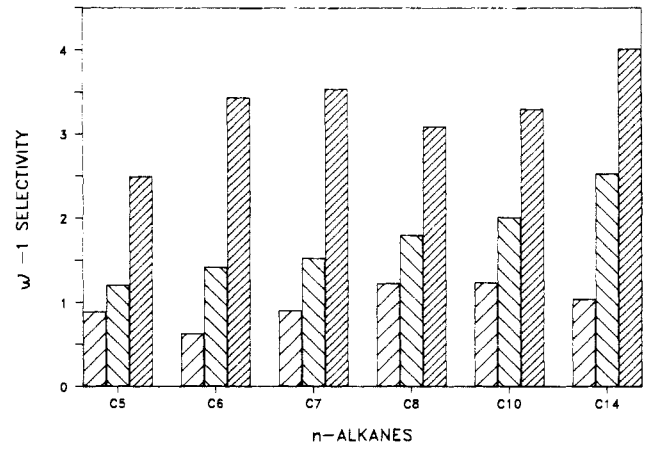

Figure 4. ω-1 Selectivity index vs. *n*-alkane chain length; ω-1 selectivity index is the ratio of ω-1 alcohol product to total other secondary alcohols normalized for the relative number of hydrogens. Reactions done in benzene under Ar with iodosobenzene as oxidant (▨) MnTPP(OAc), (▧) MnTTMPP(OAc), (▩) MnTTPPP(OAc).

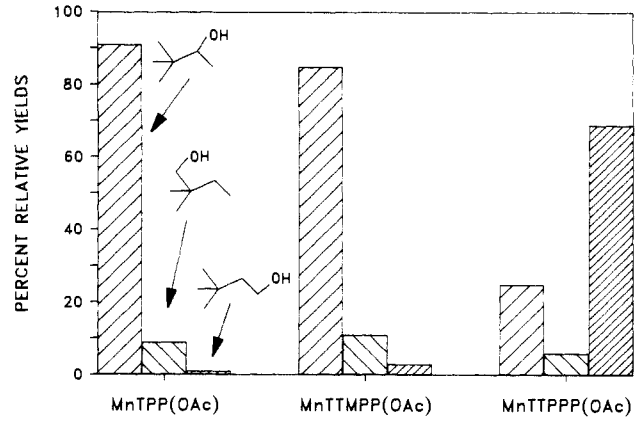

Figure 5. 2,2-Dimethylbutane hydroxylation using iodosobenzene as oxidant in benzene under Ar.

Relatively large increases in the primary selectivity index are observed as one goes from pentane to hexane to heptane, after which much smaller increases are observed with each added methylene unit. Thus, hexane marks the size limit for the "sideways" entry of *n*-alkanes into the pocket of this porphyrin; alkanes of larger size are restricted to an end-on approach. These experimental observations are consistent with both space-filling models and computer molecular modeling (ChemX Program Suite, Chemical Design, Ltd., Oxford, U.K.). The calculated pocket dimensions from such molecular modelling are 4.0 Å across by 5.0 Å deep, measured from the van der Waals surfaces, as shown in Figure 9.

More subtle differences in shape selectivity can be observed in the relative production of 2-ols from the *n*-alkanes. As shown in Figure 4, MnTPP(OAc) shows no preferene for this ω − 1 position, regardless of the chain length of the *n*-alkane. In contrast, MnTTMPP(OAc) (which exhibits only slight regioselectivity for primary hydroxylation) *does* show a significant selectivity for ω − 1 hydroxylation, which increases as the chain length increases. This selectivity is even greater for MnTTPPP(OAc) and is quite significant even for substrates as small as pentane. Therefore, the *observed* product distribution proves that even small alkanes enter in an oriented fashion.

Regioselectivity among primary sites of different steric environments is exhibited in the hydroxylation of branched alkanes. 2,2-Dimethylbutane is an especially interesting case,[20] since it has

(20) The hydroxylation of 2,2-dimethylbutane with iodosobenzene gave the following relative yields of 3,3-dimethylbutan-2-ol, 2,2-dimethylbutan-1-ol, and 3,3-dimethylbutan-1-ol, respectively: for MnTPP(OAc), 91%, 9%, <1%; for MnTTMPP(OAc), 85%, 11%, 3%; for MnTTPPP(OAc), 25%, 6%, 69%.

Table II. Selectivity in the Hydroxylation of *n*-Alkanes with C_6H_5IO

substrate	catalyst	products (% yield) 1-ol	2-ol	3-ol	4-ol[a]	primary selectivity[b]
n-C_5H_{12}	MnTPP(OAc)	5	61	34		0.048
	MnTTMPP(OAc)	4	68	28		0.039
	MnTTPPP(OAc)	10	75	15		0.11
n-C_6H_{14}	MnTPP(OAc)	2	38	60		0.027
	MnTTMPP(OAc)	3	57	40		0.041
	MnTTPPP(OAc)	19	62	18		0.31
n-C_7H_{16}	MnTPP(OAc)	2	37	40	21	0.034
	MnTTMPP(OAc)	3	49	33	15	0.052
	MnTTPPP(OAc)	26	52	17	5	0.59
n-C_8H_{18}	MnTPP(OAc)	2	37	32	28	0.041
	MnTTMPP(OAc)	3	46	29	22	0.064
	MnTTPPP(OAc)	21	48	16	15	0.53
n-$C_{10}H_{22}$	MnTPP(OAc)	1	29	21	49	0.027
	MnTTMPP(OAc)	3	39	25	33	0.066
	MnTTPPP(OAc)	18	43	13	26	0.58
n-$C_{14}H_{30}$	MnTPP(OAc)	1	17	17	64	0.040
	MnTTMPP(OAc)	2	33	19	46	0.082
	MnTTPPP(OAc)	17	37	15	31	0.82

[a] For *n*-decane, this also includes 5-decanol; for *n*-tetradecane, this also includes 5-tetradecanol, 6-tetradecanol, and 7-tetradecanol. [b] The ratio of total primary alcohol to total secondary alcohols normalized for the relative number of hydrogen atoms.

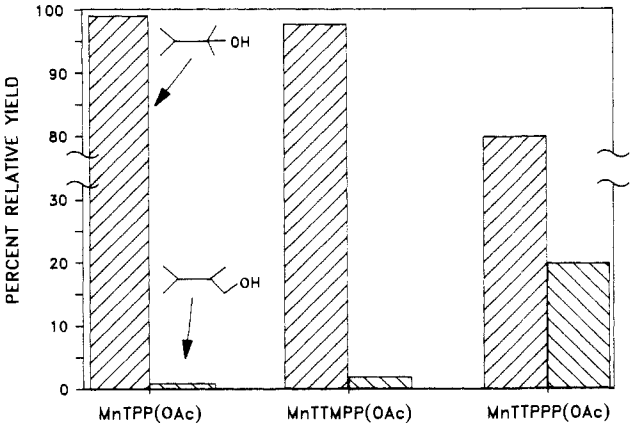

Figure 6. 2,3-Dimethylbutane hydroxylation using iodosobenzene as oxidant in benzene under Ar.

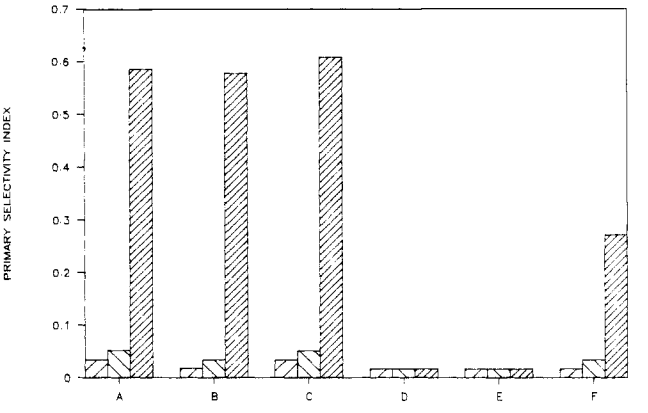

Figure 7. Primary selectivity index for various hydroxylating systems. A. Mn porphyrin catalyst + iodosobenzene as oxidant. B. Mn porphyrin catalyst + pentafluoroiodosobenzene as oxidant. C. Mn porphyrin catalyst + *m*-chloroperoxybenzoic acid as oxidant. D. Mn porphyrin as catalyst + trifluoroethanol solubilized pentafluoroiodosobenzene as oxidant (reactions done in 1 mL of benzene/heptane with 100 μL of trifluoroethanol; also done with CH_2Cl_2/F_3-EtOH/H_2O (80:18:2 v/v) as cosolvent). E. Mn porphyrin catalyst + *tert*-butylhydroperoxide as oxidant. F. Fe porphyrin catalyst + iodosobenzene as oxidant: (▽) M(TPP)(OAc), (◺) M(TTMPP)(OAc), (▨) M(TTPPP)(OAc),

both a 2° site and two quite distinctive 1° sites. As shown in Figure 5, the secondary alcohol is the predominant product (≈ 90%) from catalytic oxidation by either MnTPP(OAc) or MnTTMPP(OAc). With the deeply pocketed MnTTPPP(OAc), however, the steric inaccessibility of the 2° site is quite pronounced and 3,3-dimethylbutan-2-ol becomes only a minor product (<25%). Even more striking is the selectivity shown in favor of the most exposed methyl group (which gives 3,3-dimethylbutan-1-ol) and against the hindered *tert*-butyl group methyls (which give 2,2-dimethylbutan-1-ol). The ratio of the primary alcohols, weighted for their total number of hydrogens, increases from 0.3 to 0.89 to 34 to MnTPP(OAc), MnTTMPP(OAc), and MnTTPPP(OAc), respectively.[21] This very specific, enzyme-like, shape selection of the substrate by the catalyst gives rise to the impressive preferential hydroxylation of the sterically most accessible methyl group.

Selection for primary over tertiary hydroxylation is extremely difficult due to the large difference in bond dissociation energies. It is not surprising, then, that even with MnTTPPP(OAc), the principal product from hydroxylation of 2,3-dimethylbutane remains 2,3-dimethylbutan-2-ol, as seen in Figure 6. Nonetheless, there is a 40-fold increase in primary selectivity for MnTTPPP(OAc) compared to the less hindered porphyrin complexes, and the primary alcohol (2,3-dimethylbutan-1-ol) becomes a substantial, rather than trace, product.[22]

In these systems, one expects that terminal hydroxylation is induced by selectively slowing the rate of hydroxylation at the favored secondary and tertiary sites relative to hydroxylation at the more exposed primary site. Consistent with this, MnTTPPP(OAc) catalyzes hydroxylations at approximately half the rate of MnTPP(OAc) (Table I). The MnTTMPP(OAc) system however is unexpectedly 10-fold faster than MnTPP(OAc). This may be due either to high local polarity in the pocket or to electronic effects generated by the methoxy substituents.

(21) (a) The product distributions observed for the hydroxylation of 2,2-dimethylbutane by using MnTTPPP(OAc) are very similar to those reported for chlorination by using the very hindered *N*-chloro-2,2,6,6-tetramethylpiperidine as a chlorination agent. (b) Deno, N. C.; Pohl, D. G.; Spinelli, H. J. *Bioorg. Chem.* **1974**, *3*, 66.

(22) The hydroxylation of 2,3-dimethylbutane with iodosobenzene gave the following relative yields of 2,3-dimethylbutan-2-ol and 2,3-dimethylbutan-1-ol, respectively: for MnTPP(OAc), 99% and 1%; for MnTTMPP(OAc), 98% and 2%; for MnTTPPP(OAc), 80% and 20%.

(23) Bernardi, R.; Galli, R.; Minischi, F. *J. Chem. Soc. B* **1968**, 324.
(24) Groves, J. T.; McClusky, G. A.; White, R. E.; Coon, M. J. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 154.

Table III. Selectivity in Heptane Hydroxylation with Varoius Oxidants

oxidant	catalyst	products (% yield) 1-ol	2-ol	3-ol	4-ol	primary selectivity[a]
C_6H_5IO	MnTPP(OAc)	2	37	40	21	0.034
C_6H_5IO	MnTTMPP(OAc)	3	49	33	15	0.052
C_6H_5IO	MnTTPPP(OAc)	26	52	17	4	0.59
nC_6F_5IO	MnTPP(OAc)	1	36	45	18	0.017
C_6F_5IO	MnTTMPP(OAc)	2	51	36	11	0.034
C_6F_5IO	MnTTPPP(OAc)	26	50	17	8	0.58
m-$C_6H_4ClCO_3H$	MnTPP(OAc)	2	47	35	16	0.034
m-$C_6H_4ClCO_3H$	MnTTMPP(OAc)	3	51	33	14	0.051
m-$C_6H_4ClCO_3H$	MnTTPPP(OAc)	27	32	31	11	0.61
C_6F_5IO/F_3CCH_2OH	MnTPP(OAc)	1	44	38	17	0.017
C_6FIO/F_3CCH_2OH	MnTTMPP(OAc)	1	51	34	15	0.017
C_6F_5IO/F_3CCH_2OH	MnTTPPP(OAc)	1	48	36	15	0.017
t-BuOOH	MnTPP(OAc)	1	50	37	13	0.017
t-BuOOH	MnTTMPP(OAc)	1	49	37	14	0.017
t-BuOOH	MnTTPPP(OAc)	1	44	42	14	0.017
C_6H_5IO	FeTPP(OAc)	1	38	42	19	0.017
C_6H_5IO	FeTTMPP(OAc)	2	47	36	15	0.034
FeTTPPP(OAc)	FeTTPPP(OAc)	14	55	21	10	0.24

[a] The ratio of the total primary alcohol to total secondary alcohols normalized for the relative number of hydrogen atoms. In the case of t-BuOOH, the yields of corresponding ketones were added to those of the secondary alcohols.

Mechanistic Implications. The presence and degree of shape selectivity can be used as a mechanistic probe of the various porphyrin oxidation systems[6-8] (Figure 7 and Table III). The primary selectivity index for the hydroxylation of n-heptane with various oxidants in the presence of MnTTPPP(OAc) indicates whether the hydroxylation reaction occurs at the metal center or in the bulk solution. When pentafluoroiodosobenzene or m-chloroperbenzoic acid are used, the primary alcohol selectivities are very similar to those of iodosobenzene, which suggests that these three oxidants generate the same catalytically active species. It has been proposed that the active hydroxylating agent might be a metalloporphyrin–iodosobenzene complex.[8] This hypothesis is inconsistent with the *invariance* of the primary selectivity index observed with iodosobenzene, pentafluoroiodosobenzene, *and* m-chloroperoxybenzoic acid. Dimerization to form species similar to Hill's μ-oxo complexes[8] can also be ruled out as the catalytic species, since neither MnTTMPP nor especially MnTTPPP can form dimers. The kinetic isotope effect observed (3.5, as discussed earlier) shows that significant C–H bond breaking is taking place in the activated complex for manganese-catalyzed hydroxylation. This is consistent with the radical-like pathway proposed by Hill[7a] and Groves.[7b] Thus, the mechanism of hydroxylation in these systems is well-established: complete oxygen atom transfer from the iodosobenzene takes place to form a monomeric catalytic species which is capable of H-atom abstraction. These results are represented in the reaction scheme below, where XO is C_6H_5IO, C_6F_5IO, or m-$ClC_6H_4CO_3H$.

$$\text{Mn(Porph)(OAc)} + \text{XO} \rightarrow \text{OMn(Porph)(OAc)} + \text{X}$$

$$\text{RH} + \text{OMn(Porph)(OAc)} \rightarrow \text{R}\bullet + \text{HO–Mn(Porph)(OAc)}$$

$$\text{R}\bullet + \text{HO–Mn(Porph)(OAc)} \rightarrow \text{ROH} + \text{Mn(Porph)(OAc)}$$

No direct evidence for the coordination of the acetate is available; however, its dissociation is unlikely in nonpolar solvents. This scheme is not comprehensive; some involvement of carbenium ions, as an alternate path to radical abstraction, has also been suggested.[8b,10b]

Addition of 2,2,2-trifluoroethanol or other alcohols solubilizes iodosobenzene or pentafluoroiodosobenzene, by alcoholysis, and enhances the rate of olefin epoxidation by using iron porphyrins.[6j] When F_3CCH_2OH is added to the manganese porphyrin–pentafluoroiodosobenzene system, however, hydroxylation rates are diminished, and shape selectivity is no longer observed. Thus, the species responsible for hydroxylation in this system is not the same as in the unsolubilized iodosobenzene and is *not* localized at the metal center.

Using *tert*-butylhydroperoxide as an oxidant, rapid alkane hydroxylation occurs, but no change in selectivity is observed as the manganese porphyrin catalyst is varied. Therefore, with this oxidant, hydroxylation is *not* taking place at the metal center; rather, it must be due to a free radical chain pathway, initiated by the metalloporphyrin. The regioselectivity observed by this radical chain shows little primary product, and the predominant secondary product is at the $\omega - 1$ methylene position similar to that reported for the radical chlorination of n-heptane.[23]

When *iron* porphyrin complexes are used as catalysts, with iodosobenzene as oxidant, shape selectivity is still observed, as shown in Figure 7. Thus, for both Mn and Fe porphyrins, substrate oxidation is taking place in close proximity to the metal center. Primary selectivity, however, is diminished in all three porphyrin systems for iron relative to manganese. The diminution in selectivity may be due either to electronic differences between the two different oxometalloporphyrin intermediates or to differences in the steric constraints present during the transition state of H-atom abstraction. The diminished selectivity does suggest that in the transition state more C–H bond breaking is occurring with the iron system than with the manganese. This conclusion is confirmed by the relative isotope effects observed for iron (11.5 for cytochrome P-450[24] and 12.9 for FeTPP(Cl) with iodosobenzene[10c]) as compared to manganese (3.5).

The amount of steric contact generated between substrate and metalloporphyrin during hydroxylation may be determined from the relative rates of 1° vs. 2° alcohol production for TTPPP relative to TPP with either Mn or Fe. This change is the energy associated with the greater steric contact of TTPPP over TPP with the substrate. For n-heptane hydroxylation, this calculated energy is 1.6–1.7 kcal/mol for *either* metal systems.

Comparisons to Enzymatic Hydroxylation. There are two classes of ω-hydroxylases (i.e., enzymes which hydroxylate terminal methyl groups of alkyl chains): a nonheme iron monooxygenase found in bacteria[12] and specific isozymes of cytochrome P-450 found, for example, in yeast and in mammalian liver and kidney mitochondria.[11] With in vivo substrates (e.g., fatty acids and cholesterol steroids), the regioselectivities can be quite striking: the ratio of $\omega/(\omega-1)$ hydroxylation of capric acid by kidney cytochrome P-450, for example,[11b] can be as high as 20.

Direct comparisons to enzyme regioselectivity in alkane hydroxylation are difficult, due to the paucity of published data, the variations of one isozyme to another, and the weakness of alkane binding in the enzyme active site. Nonetheless, data are available[11] for the hydroxylation of hexane and heptane by rat liver microsomal cytochrome P-450. The regioselectivities shown for these

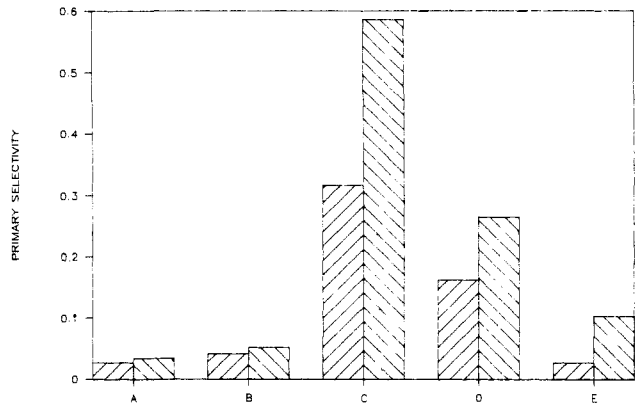

Figure 8. Primary selectivity index of synthetic porphyrins vs. cytochrome P-450 for *n*-hexane and *n*-heptane. A. MnTPP(OAc) with C_6H_5IO. B. MnTTMPP(OAc) with C_6H_5IO. C. MnTTPPP(OAc) with C_6H_5IO. D. Uninduced rat liver microsomal cytochrome P-450. E. Phenobarbital induced rat liver microsomal cytochrome P-450. (▨) *n*-hexane, (▧) *n*-heptane.

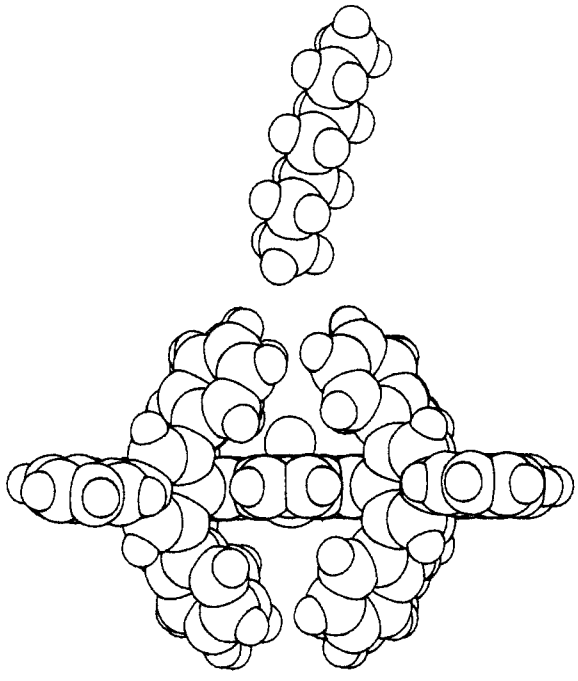

Figure 9. Computer generated molecular model of the approach of *n*-heptane to a putative $M(TTPPP)(O)^+$ intermediate. For the sake of clarity, the atomic radii shown are only 0.8 of the van der Waals radii.

n-alkanes, however, is not nearly as high as that shown for fatty acids. The primary selectivity, as defined earlier, of rat liver microsomal P-450 (uninduced) is 0.16 for hexane and 0.26 for heptane, as compared to 0.32 and 0.59, respectively, for MnTTPPP(OAc) with C_6H_5IO. Upon treatment with phenobarbital, different and less selective isozymes of cytochrome P-450 are induced, with primary selectivities of 0.03 for hexane and 0.10 for heptane.[11] These data, together with those of the synthetic porphyrins, are shown in Figure 8.

The $\omega - 1$ selectivities are much more distinctive for both uninduced and phenobarbital-induced rat liver microsomal P-450: with hexane, 5.7 and 4.2; with heptane, 8.0 and 6.6. This compares to $\approx$3.5 for MnTTPPP(OAc) with C_6H_5IO. Much less selective isozymes of mammalian P-450 also exist; upon induction with benzpyrene or methylcholanthrene, the primary selectivity drops to nearly 0, and the $\omega - 1$ selectivity approaches 1.

One may see from these comparisons that our most hindered porphyrin, TTPPP, is as shape selective as the best isozymes of microsomal cytochrome P-450. These data do suggest that the active site is relatively open in phenobarbital-, benzpyrene-, and methylcholanthrene-induced P-450. It will prove interesting to compare the relative sizes of binding sites in various enzymes to the synthetic analogues, as structures become available.

Conclusions

Shape selectivity for the hydroxylation of alkanes has been demonstrated by using very sterically hindered metalloporphyrins as catalysts. FeTTPPP(OAc) and MnTTPPP(OAc) show remarkable enhancements for primary hydroxylation of branched and *n*-alkanes, unprecedented in nonbiological catalysis and comparable to ω-hydroxylase enzymes. The diminished primary selectivity shown by iron porphyrin complexes relative to manganese suggests that in the transition state more C–H bond breaking is occurring with iron than with manganese. With substrates having sterically different methyl groups (such as 2,2-dimethylbutane), these porphyrin catalysts are capable of distinguishing between those sites in a very specific fashion. In addition, the steric protection of the porphyrin periphery dramatically increases the catalyst's oxidative robustness.

The presence and degree of shape selectivity is offered as conclusive proof of direct metalloporphyrin involvement during the actual hydroxylation of substrates with the iodosobenzene, pentafluoroiodosobenzene, and *m*-chloroperoxybenzoic acid (but *not* with *tert*-butylhydroperoxide or alcohol-solubilized iodosobenzene) as oxidants. Such shape selectivity will be a useful tool for mechanistic studies of other metalloporphyrin catalyzed oxidations.[25]

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Registry No. *t*-BuOOH, 75-91-2; PhIO, 536-80-1; C_6F_5IO, 14353-90-3; *m*-$ClC_6H_4C(O)OOH$, 937-14-4; CF_3CH_2OH, 75-89-8; H_2TTPPP, 85390-97-2; MnTPP(OAc), 58356-65-3; MnTTMPP(OAc), 98827-71-5; MnTTPPP(OAc), 98827-70-4; FeTPP(OAc), 33393-26-9; FeTTMPP(OAc), 104350-59-6; FeTTPPP(OAc), 104350-60-9; $CH_3(CH_2)_4OH$, 71-41-0; $CH_3(CH_2)_2CH(OH)CH_3$, 6032-29-7; $CH_3CH_2CH(OH)CH_2CH_3$, 584-02-1; $CH_3(CH_2)_5OH$, 111-27-3; $CH_3(CH_2)_3CH(OH)CH_3$, 626-93-7; $CH_3(CH_2)_2CH(OH)CH_2CH_3$, 623-37-0; $CH_3(CH_2)_6OH$, 111-70-6; $CH_3(CH_2)_4CH(OH)CH_3$, 543-49-7; $CH_3(CH_2)_3CH(OH)CH_2CH_3$, 589-82-2; $CH_3(CH_2)_2CH(OH)(CH_2)_2CH_3$, 589-55-9; $CH_3(CH_2)_7OH$, 111-87-5; $CH_3(CH_2)_5CH(OH)CH_3$, 123-96-6; $CH_3(CH_2)_4CH(OH)CH_2CH_3$, 589-98-0; $CH_3(CH_2)_3CH(OH)(CH_2)_2CH_3$, 589-62-8; $CH_3(CH_2)_9OH$, 112-30-1; $CH_3(CH_2)_7CH(OH)CH_3$, 1120-06-5; $CH_3(CH_2)_6CH(OH)CH_2CH_3$, 1565-81-7; $CH_3(CH_2)_5CH(OH)(CH_2)_2CH_3$, 2051-31-2; $CH_3(CH_2)_{13}OH$, 112-72-1; $CH_3(CH_2)_{11}CH(OH)CH_3$, 4706-81-4; $CH_3(CH_2)_{10}CH(OH)CH_2CH_3$, 1653-32-3; $CH_3(CH_2)_9CH(OH)(CH_2)_2CH_3$, 1653-33-4; D_2, 7782-39-0; *n*-pentane, 109-66-0; *n*-hexane, 110-54-3; *n*-heptane, 142-82-5; *n*-octane, 111-65-9; *n*-decane, 124-18-5; *n*-tetradecane, 629-59-4; 5-decanol, 5205-34-5; 5-tetradecanol, 21078-83-1; 6-tetradecanol, 6836-39-1; 7-tetradecanol, 3981-79-1; 2,4,6-triphenylbenzaldehyde, 85390-98-3; pyrrole, 109-97-7.

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