Shape-selective Alkane Hydroxylation

Kenneth Suslick,* Bruce Cook, and Mary Fox

School of Chemical Sciences, University of Illinois at Urbana-Champaign, 505 S. Mathews Avenue, Urbana, Illinois 61801, U.S.A.

A series of sterically hindered manganese porphyrins have been used to catalyse shape-selective alkane hydroxylation, increasing the production of primary alcohols.

The ability of enzymes to exhibit unequalled substrate specificity has led to diverse efforts to design synthetic systems which will show substrate recognition, or shape- or regioselectivity.[1,2] Metalloporphyrins have been used as epoxidation and hydroxylation catalysts in an attempt to mimic the behaviour of cytochrome P450, with some degree of success.[3] We report here the remarkable enhancement of regioselectivity for catalytic alkane hydroxylation through the use of a series of sterically hindered manganese porphyrins. The preference observed for terminal, primary hydroxylation is reminiscent of the ω-hydroxylase enzymes.[4] As shown in Table 1, the selectivity observed for terminal hydroxylation of a number of alkanes (with iodosylbenzene as oxidant) increased dramatically as the steric bulk of the manganese porphyrin complex increased. Figure 1 shows schematically the increasing steric constraints of the unhindered 5,10,15,20-tetraphenylporphyrinate (TPP^{2-}),[5] moderately hindered 5,10,15,20-tetrakis-(2,4,6-trimethoxyphenyl)porphyrinate ($TTMPP^{2-}$),[6] and finally the extremely hindered 5,10,15,20-tetrakis(2,4,6-triphenylphenyl)porphyrinate ($TTPPP^{2-}$, the 'bis-pocket' porphyrin).[7] For the last, selectivity for terminal hydroxylation also increased significantly as the n-alkane chain length increased. The occurrence of such regioselectivity conclusively demonstrates the intimate involvement of the manganese porphyrin as the active site of hydroxylation of the alkanes when iodosylbenzene is the oxidant. In direct contrast, the use of alkyl hydroperoxides (*e.g.*, t-butyl hydroperoxide) does not produce any regioselectivity, and thus these oxidations must proceed through a radical chain mechanism in which the metalloporphyrin acts as an initiator.

Mn(TPP)(OAc) and Mn(TTMPP)(OAc) were synthesized by literature methods.[5,6] The 'bis-pocket' porphyrin H_2TTPPP was prepared by an improved synthesis using 2,4,6-collidine at 200 °C, as developed by Groves[3] for the tetramesitylporphyrin. The ^1H n.m.r. spectrum of H_2TTPPP at 360 MHz is first order, well resolved, and easily assignable to the expected structure shown in Figure 1: in CD_2Cl_2 *vs.* $SiMe_4$ δ −3.44 (s, 2H), 6.30 (t, 16H), 6.45 (t, 8H), 6.69 (d,

Table 1. Selectivity in the oxidation of alkanes with iodosylbenzene in the presence of manganese porphyrins.

Substrate	Catalyst	Products (% relative yield)				Rate[a]	Primary selectivity[b]
n-C_5H_{12}			3-ol	2-ol	1-ol		
	(A)		34	61	5	0.033	0.048
	(B)		28	68	4	0.51	0.039
	(C)		15	75	10	0.012	0.11
n-C_7H_{16}[c]		4-ol	3-ol	2-ol	1-ol		
	(A)	21(13)	40(37)	37(50)	2(<1)	0.44(2.7)	0.034(<0.01)
	(B)	15(14)	33(37)	49(49)	3(<1)	5.55(4.9)	0.052(<0.003)
	(C)	5(14)	17(42)	52(44)	26(<1)	0.19(1.4)	0.59(<0.042)
n-$C_{14}H_{30}$		4—7-ols	3-ol	2-ol	1-ol		
	(A)	64	17	17	1	0.71	0.040
	(B)	46	19	33	2	2.4	0.082
	(C)	31	15	37	17	0.46	0.82
(**1**)			(**3**)	(**4**)	(**5**)		
	(A)		91	9	<1	0.054	0.016
	(B)		85	11	3	1.3	0.027
	(C)		25	6	69	0.030	0.50
(**2**)				(**6**)	(**7**)		
	(A)			99	1	1.10	0.001
	(B)			98	2	1.46	0.003
	(C)			80	20	0.56	0.042

[a] All reactions run at 25 °C. Rates are given as mol products (mol porphyrin)$^{-1}$ h^{-1}. In a typical experiment, 10 mg (45 μmol) of iodosylbenzene were added to 1 ml of a 1:1 v/v solution of substrate in C_6H_6 with 0.4 μmol of manganese porphyrin and the mixture was stirred under Ar for 7 h. The mixture was then quenched with $NaHSO_3$, internal standard added, and products analysed by capillary gas chromatography. Catalysts: (A), Mn(TPP)OAc; (B), Mn(TTMPP)(OAc); (C), Mn(TTPPP)(OAc). [b] The ratio of total primary alcohols to secondary (or tertiary) alcohols, normalized for the relative number of hydrogen atoms. [c] Data *in parentheses* refer to oxidations with *t-butyl hydroperoxide*. Bu^tOOH (0.25 mmol) was added to 1 ml of a 0.4 mM solution of manganese porphyrin, and the mixture stirred under Ar for 22 h. The mixture was then quenched with $Na_2S_2O_5$, internal standard added, and products analysed. Product yields are sums of the respective alcohols and ketones formed.

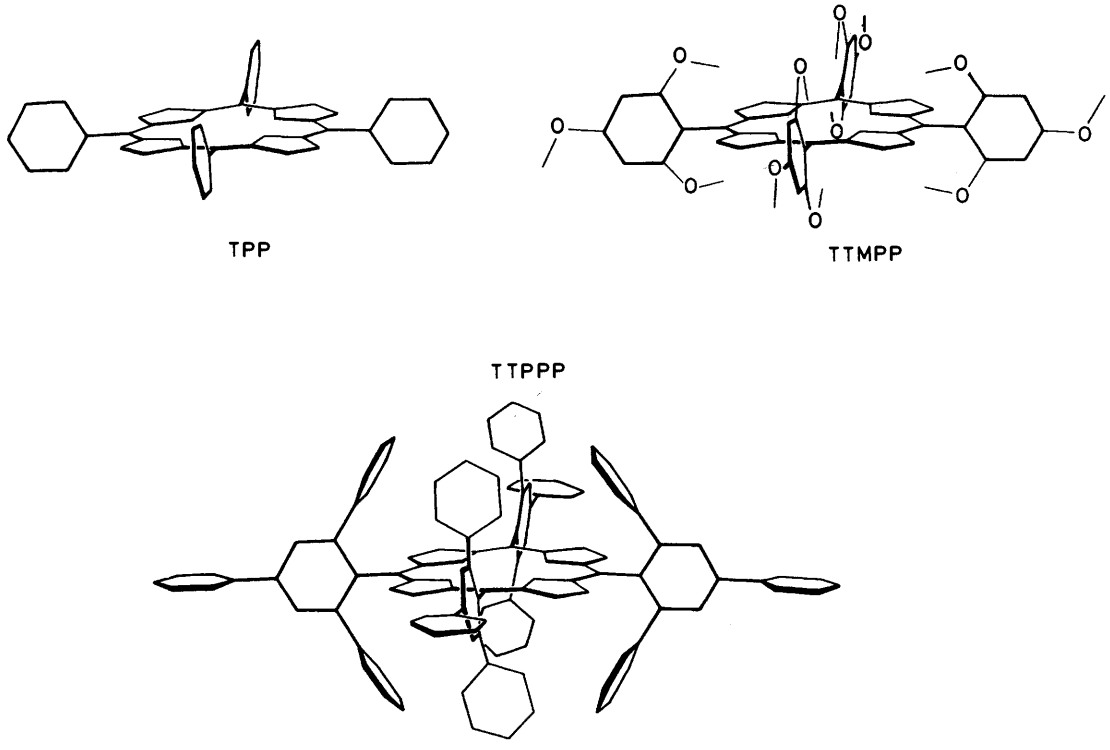
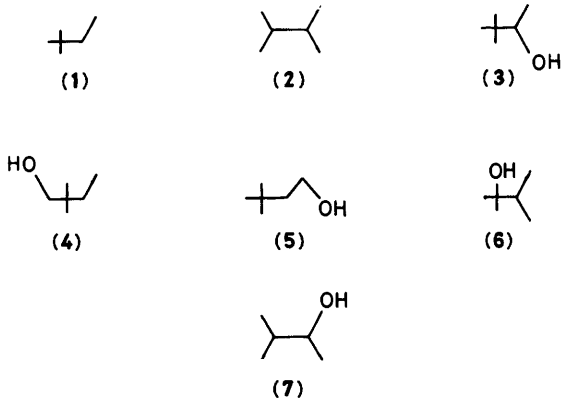


Figure 1. Diagrammatic representations of the series of sterically hindered porphyrins.



16H), 7.46 (t, 4H), 7.60 (t, 8H), 7.94 (s, 8H), 7.97 (d, 8H), and 8.52 (s, 8H). Metallation of H_2TTPPP required the refluxing of anhydrous $MnBr_2$ with H_2TTPPP in mesitylene under Ar for 48 h, followed by anion metathesis with aqueous NaOAc. The electronic spectrum showed bands at 391, 415, 496, 608, and 648 nm; the positive ion fast-atom-bombardment mass spectrum showed the expected $P + 1$ pseudo-parent ion.

Good regioselectivity for primary *vs.* secondary or tertiary hydroxylation is demonstrated by Mn(TTPPP)(OAc), whereas Mn(TTMPP)(OAc) shows only slight improvement over the unhindered Mn(TPP)(OAc). Mn(TTPPP)(OAc) also shows increasing primary selectivity for n-alkanes with increasing chain length: enhancements in the normalized selectivity [compared to Mn(TPP)(OAc)] are 2-, 17-, and 21-fold for n-pentane, n-heptane, and n-tetradecane, respectively. In the case of the sterically demanding 2,2-dimethylbutane (**1**), this increase in selectivity is > 30-fold, and primary alcohols account for 75% of the total products formed. With 2,3-dimethylbutane (**2**), a 40-fold increase in primary selectivity is observed when compared to the even more easily abstracted tertiary hydrogen atoms.

Regioselectivity among different possible primary (or secondary) sites on the substrate is also observed. For example, 2,2-dimethylbutane (**1**) presents two separate primary positions: the less hindered one leads to 3,3-dimethylbutan-1-ol (**5**), and the more hindered to 2,2-dimethylbutan-1-ol (**4**). The ratio of these two increases from 0.1 for Mn(TPP)(OAc), to 0.31 for Mn(TTMPP)(OAc), to 12 for Mn(TTPPP)(OAc). We can make similar comparisons for hydroxylation of the secondary positions of n-alkanes: for example, the ratio of pentan-2-ol to pentan-3-ol increases from 1.8, to 2.4, to 5.0 as the porphyrins become more hindered, consistent with the greater accessibility of the $\omega-1$ methylene group.

In these systems, one expects that terminal hydroxylation is induced by selectively slowing the rates of hydroxylation at the favoured secondary and tertiary sites relative to hydroxylation at the desired primary site. Consistent with this, Mn(TTPPP)(OAc), with its increased steric demands, catalyses hydroxylations at approximately half the rate of Mn(TPP)(OAc) (Table 1). The Mn(TTMPP)(OAc) system, however, is unexpectedly 10-fold faster than Mn(TPP)(OAc); this may be due either to high local polarity in the pocket or to electronic effects generated by the methoxy substituents.

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