CHEMISTRY LETTERS, pp. 1307-1310, 1994.

Ring Hydroxylations of Aromatic Amino Acid Derivatives and Toluene by Hydrogen Peroxide Catalyzed by Manganese Halogenated Porphyrins in CH_2Cl_2/H_2O and Lipid Bilayers

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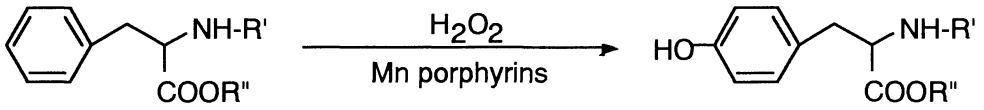
Manganese fluorinated porphyrins catalyzed the ring hydroxylation of phenylalanine derivatives and toluene with H_2O_2 and an enhanced hydroxylation was observed especially in phospholipid bilayers when imidazole was present. The hydroxylation depended upon the structures of porphyrins and substrates.

Synthetic porphyrin model studies are useful to provide an insight into possible reactions of porphyrin complexes such as occurs in mitochondoria membrane.[1] Porphyrin pigments play a key role in the oxidative electron transfer of membrane-bound enzymes such as cytochromes. Many oxidation systems have been reported to mimic cytochrome P-450-dependent monooxygenases with metalloporphyrins, in which alkene and alkane hydroxylations catalyzed by porphyrin complexes have been developed.[2-14] However, there has been little study of the ring hydroxylation of aromatic hydrocarbons catalyzed by porphyrin complexes to provide an insight into the structural effect of porphyrins in the reaction.[3,7,9] We now report the ring hydroxylations of phenylalanine derivatives **1** (Scheme 1) and toluene by H_2O_2 catalyzed by manganese halogenated porphyrins (Scheme 2) in CH_2Cl_2/H_2O and dipalmitoylphosphatidylcholine (DPPC) vesicle. The halogenated porphyrins

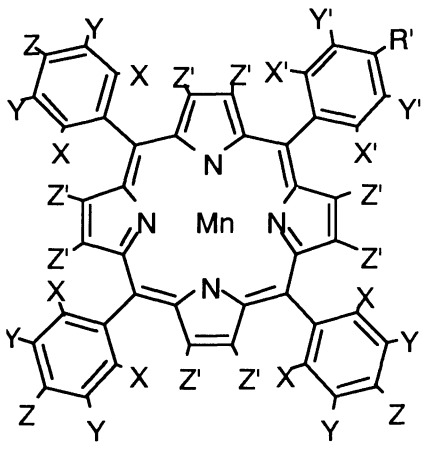


1 : L-N-Dc-PheOEt
R' = $-(CH_2)_9CH_3$, R" = $-CH_2CH_3$
L-N-Ac-PheOEt
R' = $-COCH_3$, R" = $-CH_2CH_3$
L-Phe
R' = -H , R" = -H

L-N-Dc-TyrOEt
R' = $-(CH_2)_9CH_3$, R" = $-CH_2CH_3$
L-N-Ac-TyrOEt
R' = $-COCH_3$, R" = $-CH_2CH_3$
L-Tyr
R' = -H , R" = -H

Scheme 1.

are stable against oxidant because of the steric effect of halogen portions on the porphyrin ring.[6,7,10,11] Manganese halogenated porphyrins were prepared as described in the previous papers.[1,3-7,10,11,16] The redox potential on glassy carbon electrode vs. SCE in DMSO containing 0.1 mol dm^{-3} TBAP for the manganese porphyrins follows in the order, $MnPFPPBr_8$ (+0.345 V) > $MnDCPPBr_8COOMe$ (+0.147 V) > MnPFPP



Scheme 2.

PE- :—C(=O)-N(H)-CH_2CH_2O-P(=O)(-O$^-$)-O-CH_2-CH(-OCOR)-CH_2OCOR

R = -$(CH_2)_{14}CH_3$

	X	Y	Z	Z'	X'	Y'	R'
$MnPFPPBr_8$	F	F	F	Br	F	F	F
MnPFPP	F	F	F	H	F	F	F
MnDFPP	F	H	H	H	F	H	H
MnDCPP	Cl	H	H	H	Cl	H	H
$MnDCPPBr_8COOMe$	Cl	H	H	Br	Cl	H	COOMe
MnFPP	H	H	F	H	H	H	F
PE-MnPFPP	F	F	F	H	H	H	PE

Table 1. Hydroxylation of Toluene by H_2O_2 Catalyzed by Manganese Halogenized Porphyrins in CH_2Cl_2/H_2O[a)]

	Products / μmol							
	phenol products of toluene				side chain oxidation products of toluene			
Mn porphyrin	o-cresol	p-cresol	total[b)]	o/p ratio	$PhCH_2OH$	PhCHO	PhCOOH	total[c)]
$MnPFPPBr_8$	17.7	8.5	26.2 (13.1)	2.1	—[d)]	0.8	—[d)]	0.8 (0.4)
MnPFPP	6.7	4.9	11.6 (5.8)	1.4	6.2	6.0	1.0	13.2 (6.6)
MnDFPP	2.4	1.9	4.3 (2.2)	1.3	12.9	14.7	5.5	33.1 (16.6)
MnDCPP	0.3	0.5	0.8 (0.4)	0.6	102	51.0	110	263 (132)
$MnDCPPBr_8COOMe$	1.7	1.5	3.2 (1.6)	1.1	8.8	4.8	1.0	14.6 (7.3)

a) The hydroxylations were done by three times. Yield determination by HPLC was made by using calibration curves with acetophenone as an internal standard. b) Total products of aromatic ring hydroxylation. Parenthesis is turn over number. c) Total products of methyl group hydroxylation. Parenthesis is turn over number. d) not determined.

(-0.070 V) > PE-MnPFPP (-0.105 V) > MnDFPP (-0.127 V) > MnDCPP (-0.182 V) > MnFPP (-0.213 V). L-N-Dc-PheOEt, L-N-Ac-PheOEt, L-N-Dc-TyrOEt, L-N-Ac-TyrOEt and N-decanoyl-L-histidine methyl ester (Dec-L-HisOMe) were synthesized as described previously .[15] Hydroxylations of toluene catalyzed by manganese halogenated porphyrins with 31% H_2O_2 were carried out in CH_2Cl_2/H_2O (2.6 cm^3 : 0.8 cm^3) during 2 h at 40 °C under the following conditions; catalyst (2 μmol), oxidant (31% H_2O_2, 0.8 cm^3), substrate (6.0 mmol), and imidazole (140 μmol). In the reaction, imidazole was used as a cocatalyst as it has been shown to have a beneficial effect in oxidations by H_2O_2.[5] The reaction products were identified by the methods of GC-MS and HPLC. Hydroxylation of toluene gave cresol which comes from the direct hydroxylation of the aromatic ring and benzylalcohol, benzylaldehyde, and benzoic acid which come from the side chain oxidation. Table 1 sum-

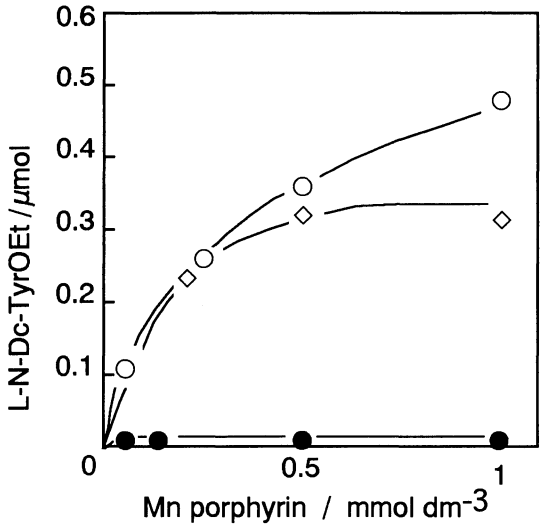


Fig. 1. Changes in conversion to tyrosine product, L-N-Dc-TyrOEt as a function of MnPFPP concentration in DPPC vesicle and CH_2Cl_2 / H_2O_2.
(O):MnPFPP in DPPC vesicle,
(◇): PE-MnPFPP in DPPC vesicle,
(●):MnPFPPin CH_2Cl_2 / H_2O.

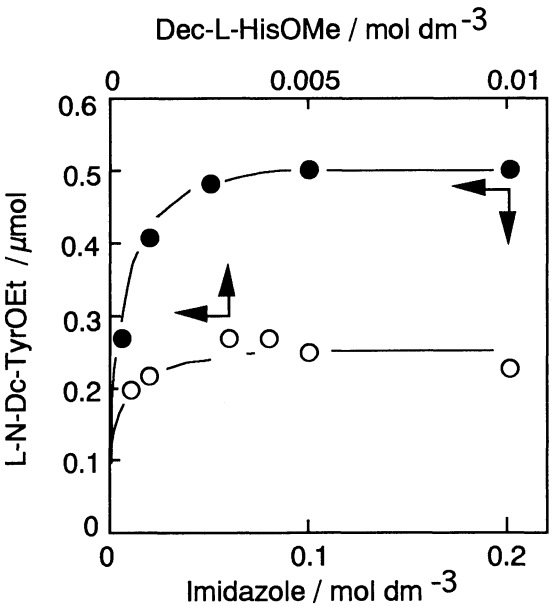


Fig. 2. Changes in conversion to tyrosine product, L-N-Dc-TyrOEt as a function of imidazole or Dec-L-His-OMe concentration in DPPC vesicle containing MnPFPP.
(O) : Dec-L-HisOMe, (●) : Imidazole.

marized the results of the hydroxylations catalyzed by manganese halogenated porphyrins, where MnFPP showed no catalytic activity because the porphyrin easily decomposed itself during the reaction. The total side chain oxidation products on toluene increase in the order, MnDCPP >> MnDFPP > $MnDCPPBr_8$ > MnPFPP > $MnPFPPBr_8$, while the total phenol products increase in the order, $MnPFPPBr_8$ >> MnPFPP > MnDFPP > $MnDCPPBr_8$ > MnDCPP. The chemoselectivity of the hydroxylation depends on the porphyrin structure, implying that electron-deficient and fluorinated porphyrin such as $MnPFPPBr_8$ and MnPFPP catalyzes selectively the aromatic ring hydroxylation, while MnDCPP catalyzes selectively the side chain oxidation.

Furthermore, we used these fluorinated porphyrins to provide an insight into the ring hydroxylation of toluene and aromatic amino acid derivatives in lipid bilayers. The hydroxylation was carried out for 2 h at 40 °C under the following conditions; catalyst (0-2.5 μmol), oxidant (16% H_2O_2,1 cm^3), substrate (50 μmol), and imidazole (0-0.4 mmol) or Dec-L-HisOMe (0-0.02 mmol) in DPPC vesicle [DPPC (55 μmol), pH 7.0, 0.1 mol dm^{-3} phosphate buffer (1.0 cm^3)], where the concentration of the substrates in DPPC vesicle is lower by a part of 10^2 in comparison to that in CH_2Cl_2/H_2O as described above. $MnPFPPBr_8$ and $MnDCPPBr_8COOMe$ could not be immersed into the lipid bilayer because of steric effect of the bromo portions on the porphyrin ring. The reaction products, tyrosine derivatives, were identified by the methods of LC-MS or HPLC. Other by-products were observed but not identified. For an example, Fig. 1 illustrates changes in conversion to L-N-Dc-TyrOEt as a function of the concentration of manganese fluorinated porphyrins in DPPC vesicle and CH_2Cl_2/H_2O when [imidazole] / [MnPFPP] = 50. MnPFPP and PE-MnPFPP catalyzed the ring hydroxylation of L-N-Dc-PheOEt with increasing the concentration of porphyrin complexes in DPPC vesicle, but MnPFPP showed no or little catalytic activity on the hydroxylation in CH_2Cl_2/H_2O, where PE-MnPFPP can be more embedded into

the lipid bilayer by 10 times in comparison to MnPFPP. This acceleration on the hydroxylation catalyzed by PE-MnPFPP in the lipid bilayer is of interest to provide a model for the oxidative electron transfer of membrane-bound enzymes. Similar hydroxylations were observed in the ring hydroxylation of L-N-Ac-PheOEt catalyzed by MnPFPP and PE-MnPFPP in DPPC vesicle, in which the yield of the ring hydroxylation was a part of tenth in comparison to that of L-N-Dc-PheOEt (data not shown). No or less ring hydroxylation was observed in the hydroxylations of toluene and L-Phe catalyzed by MnPFPP and PE-MnPFPP in DPPC vesicle. These results suggest that the hydrophobic moiety of the substrate plays an important role on the ring hydroxylation in DPPC vesicle. Figure 2 illustrates changes in conversion to the tyrosine product, L-N-Dc-TyrOEt as a function of the concentration of imidazole or Dec-L-HisOMe in DPPC vesicle. The tyrosine derivative increased with increasing the concentration of imidazole or Dec-L-HisOMe and then showed a maximum value when [imidazole] / [MnPFPP] = 50 or [Dec-L-HisOMe] / [MnPFPP] = 5. This result indicates that the concentration of imidazoles plays a crucial role in the hydroxylation in which imidazole is more efficient than Dec-L-HisOMe at the high concentration as shown in Fig. 2. The role of imidazole is likely to be as in Mansuy's paper,[5] in which manganese porphyrins decompose H_2O_2 and transfer one oxygen atom to alkanes presumably via high valent Mn(IV)=O or Mn(V)=O intermediate only when imidazole is present.

In conclusion, manganese fluorinated porphyrins catalyzed the ring hydroxylation of toluene and aromatic amino acid derivatives, **1** with H_2O_2 and the hydroxylation of **1** was enhanced in phospholipid bilayers when imidazole was present. The hydroxylation depended upon the structures of the porphyrins and substrates.

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16) Mass spectra indicated MnPFPPBr$_8$ (M=1658), MnPFPP (M=1027), MnDFPP (M=811), MnDCPP (M=943), MnDCPPBr$_8$COOMe (M=1564), and PE-MnPFPP (M=1622).

(Received March 28, 1994)