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CYTOCHROME P-450 MODELLING OXYGENATION OF OLEFINS WITHIN THE SPACE-RESTRICTED CAVITY OF IRON "BINAP PORPHYRIN": RATE ENHANCEMENT IN THE PRESENCE OF IMIDAZOLE

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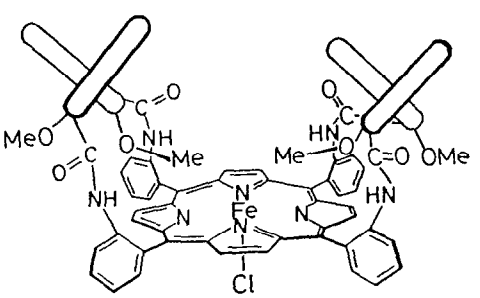
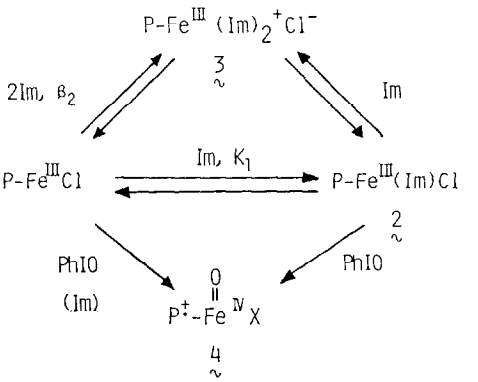
Abstract: In the presence of 1,5-diphenylimidazole, iron porphyrin modified by binaphthyl groups on one side exhibited increased rate in epoxidation of olefins and shape selective oxidation. Spectrophotometric study supports the inhibition of the formation of the six-coordinated bisimidazole complex. Oxidation within the modified cavity is proposed.

Modelling reaction of cytochrome P-450 monooxygenases is one of the recent topics in bioorganic chemistry and many reports relating mechanistic standpoint have been published so far in this field.[1] Very recently X-ray crystallographic analysis of cytochrome $P\text{-}450_{CAM}$ revealed the structural detail around the reaction center,[2] which possesses two different sites, i.e. a substrate/oxygen binding and a thiolate-ligand coordinating site. For construction of the modelling system which closely mimics the natural ones, the oxygenation reaction with iron porphyrin in the presence of a nitrogen (or more desirably a thiolate) base must be examined. As far as the use of iron porphyrins, the formation of the six-coordinated complexes is an unavoidable problem,[3,4] and the reports so far have been limited only to use symmetrical porphyrins excluding nitrogen bases.

We synthesized "BINAP porphyrin" (1) which possesses rigid backbones of binaphthyl groups as space-limiting walls and two alkoxy side arms closely locate to the central metal.[5] These auxiliary groups can cooperatively control substrate binding at the transition state of oxygenation and its catalytic reaction is expected to exhibit high shape selectivity. The added nitrogen base can coordinate only at the unhindered side not to lead an undesirable six-coordinate iron complex (3) and can block oxidation reaction at this side of the



1 $Fe[BINAP(OMe)_2]_2TPPCl$



Scheme 1.

porphyrin (Scheme 1). This will also be effective for the prevention of the formation of unreactive μ-oxo dimer. We report herein the successful oxygenation reaction of olefins with the iron "BINAP porphyrin" catalyst in the presence of the imidazoyl base. This is the first example of the rate enhancement in oxidation with the iron porphyrin-imidazole system.

First, for evaluation of the coordinating ability of imidazoles to iron porphyrins, we examined spectroscopic studies on two imidazole derivatives, N-MeIm[6] and 1,5-Ph_2Im[6] as a less hindered and a bulky base, respectively. The addition of N-MeIm to FeTMPCl[6] in CH_2Cl_2 showed typical absorption of FeTMP(N-MeIm)$_2$Cl, of which equilibrium constant β_2 was estimated to be $\sim 8.0\times10^5$ M^{-2}.[7] Similarly, even the bulky imidazole ,1,5-Ph_2Im, showed preferential formation of the corresponding bisimidazole complex; K_1=180 M^{-1}, β_2=1.1×10^5 M^{-2} (Fig. 1). On the other hand, Fe[BINAP(OMe)$_2$]$_2$TPPCl **1** exhibited the marked contrast to FeTMPCl. Within the range up to 1,5-Ph_2Im =1.00×10^{-2} M, visible spectrum of **1** was completely the same as that of the imidazole-free solution.[8] To the solution containing 5.36×10^{-3} M 1,5-Ph_2Im, addition of N-MeIm showed the appearance of the six-coordinated complex (Fig. 2). As expected from CPK model study, the undesirable bisimidazole complex was concluded not to form and only the less bulky site would be blocked by this base, but the sterically unhindered imidazole can occupy the both axial positions. The following examination supports the importance of the auxiliary groups locating at the close position to the central metal for the avoidance of the preferential formation of the bisimidazole iron complex. As a typical hindered porphyrin, FeTpivPPCl[6,4a] showed easy formation of the corresponding bisimidazole complex with 1,5-Ph_2Im (β_2=8.5×10^4 M^{-2}), and the bulky groups which locate at the rather remote position from the

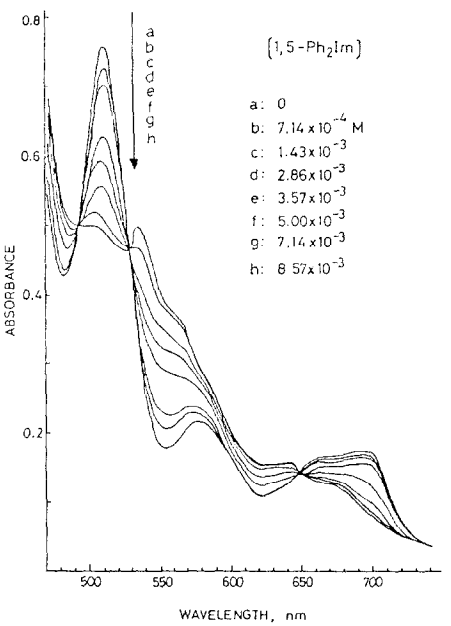


Fig. 1. Visible spectra change of 8.18×10^{-5} M FeTMPCl in the presence of varying amounts of 1,5-Ph_2Im in CH_2Cl_2 at 20 °C.

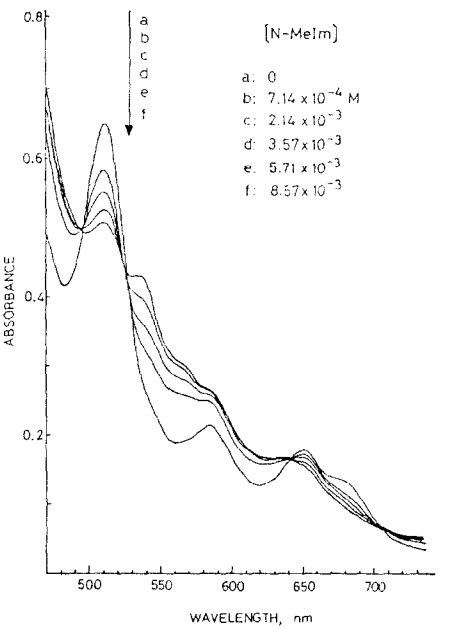


Fig. 2. ^{5}Visible spectra change of 8.18×10^{-5} M **1** in the presence of varying amounts of N-MeIm and 5.36×10^{-3} M 1,5-Ph_2Im in CH_2Cl_2 at 20 °C.

central metal are not effective for the inhibition of the second coordination of the imidazole.

Next, we examined iron porphyrin-catalyzed epoxidation of olefins with iodosobenzene.[9] In the presence of excess amounts both of the oxidant and of olefins, every run exhibited linear pseudo-first order behavior. Rate and turnovers for the epoxidation of simple olefins were shown in Table 1. As observed in the spectroscopic study the added imidazole exhibited the marked effect on the oxidation rate. The catalytic activity of FeTMPCl in the presence of 0.01 M 1,5-Ph_2Im extremely decreased in 0.15-0.018 amplitude (compare entries 1 and 2, 8 and 9, respectively), while the catalyst 1 showed increase in epoxidation rates. Turnover number and selectivity also incresed in accord with the concentration of the nitrogen ligand. However, N-methylimidazole, which favors the six-coordinated complex with 1, exhibited the inhibitory properties of the epoxidation (entry 5). FeTpivPPCl also exhibited marked decrease in the epoxidation rate by the addition of the diphenylimidazole (entries 6 and 7). These kinetic results completely coincided with those obtained by the above spectrophotometric study. Competitive epoxidation of olefins would sensitively reflect the steric environment around the central metal at the oxygen transfer stage. When FeTMPCl was used as a catalyst, an 1:1 mixture of 2,3-dimethyl-2-butene and styrene (overall 2.0 mmol olefins with 0.01 M 1,5-Ph_2Im, under the same conditions as shown in Table 1) preferentially gave

Table 1. Catalytic Epoxidation of Olefins with Iron Porphyrins.[a]

Run	Catalyst	Olefin	1,5-Ph_2Im / M	Epoxide rate turnovers·s^{-1}	Epoxide turnovers after 2 h	Epoxide selectivity/ %[b]
1	FeTMPCl	Cyclooctene	0	6.0	4.0×10^3	100
2			0.01	0.91	1.2×10^3	100
3	1		0	3.1	1.9×10^3	96
4			0.01	5.6	3.3×10^3	100
5			0.1[c]	1.0	5.1×10^2	64
6	$FeT_{piv}PPCl$		0	∿ 4	4.4×10^2	-
7			0.01	0.04	1.9×10^3	100
8	FeTMPCl	Styrene	0	8.6	2.9×10^3	93[d]
9			0.01	0.16	6.2×10^2	90[d]
10	1		0	3.7	1.9×10^3	77[d]
11			0.01	4.1	2.3×10^3	95[d]
12			0.1	4.5	2.0×10^3	94[d]
13	FeTMPCl	2,3-Dimethyl-2-butene	0	6.6	1.2×10^3	68
14	1		0.01	4.4	2.0×10^3	72

[a] Experimental conditions: in CH_2Cl_2 (1.0 ml) with the catalyst (1.0×10^{-4} mmol); olefin (2.0 mmol), iodosobenzene (0.5 mmol) and n-tridecane (GC standard) at 20 °C. [b] Selectivity is based on mmol of epoxide/ mmol of oxidant consumed. [c] N-Methylimidazole was used. [d] 5 - 6 % of phenylacetaldehyde was detected by ^{1}H-NMR.

2,3-dimethyl-2,3-epoxybutene (5) (>93% selectivity) over the formation of styrene oxide (6). The selectivity obtained in this reaction well accorded with the highly electrophilic nature of the intermediate iron oxo complex and the electron-rich olefin was preferentially oxidized regardless of its bulkiness. The steric hindrance caused by the mesityl groups is moderate for appearance of substrate shape selectivity.[10,11] The reversed selectivity (5:6 = 45:55), however, was observed in the catalytic reaction with 1. The bulky olefin is less favorable for oxygen transfer within the space-restricted cavity. Thus, the results obtained also support the oxidation reaction occurs at the modified site of 1 and the added imidazole blocks the oxidation at the unmodified one. We would like to propose the importance of the steric environment close to the central metal for controlling the shape selectivity.

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5. The synthetic detaile of "BINAP porphyrin" will be reported elsewhere.
6. Abbribation: TMP; meso-tetramesitylporphyrin dianion, TpivPP; meso-tetra(α,α,α,α-o-pivalamidophenyl)porphyrin dianion, N-MeIm; N-Methylimidazole, 1,5-Ph_2Im; 1,5-diphenylimidazole.
7. For the determination of the equiliblium constants, K_1 and β_2, see ref. 3c.
8. The similarity of the visible spectra of P-Fe^{III}Cl and the monoamine adduct 2 is known, see ref. 3c, p.5556.
9. Since iodosobenzene is an insoluble polymer, it is not possible to exclude the dependence of the rate on the concentration of the oxidant. However, since different olefins are epoxidized at different rates and the rates of epoxidation of all olefins examined were linear, it is concluded the rate observed are not regulated by the concentration of PhIO.
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