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BIOMIMETIC OXIDATION OF ORGANIC SULFIDES WITH TPPFe(III)Cl/IMIDAZOLE/HYDROGEN PEROXIDE

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An enzyme model system, consisted with TPPFe(III)Cl/imidazole has been found to catalyze hydrogen peroxide dependent S-oxygenation and oxidative S-dealkylation of organic sulfides. This biomimetic reaction has been compared with the cytochrome P-450 catalyzed H_2O_2 dependent oxygenation.

While the mechanisms of various oxygenations of organic substrates involving cytochrome P-450 have been investigated extensively,[1] several model systems have been proposed for this enzyme.[2] Recently, we suggested that the oxyegnation of divalent sulfur compounds with cytochrome P-450 proceeds through one-electron transfer from the sulfenyl sulfur to the active centre (FeO^{3+}) of the enzyme to give the corresponding sulfenium radicals which eventually afford either sulfoxides, or mixture of sulfoxides and disulfides if the substituent X is electron-withdrawing.[3]

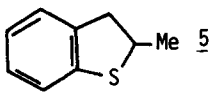
$$\mathrm{Ar\text{-}S\text{-}CH_2X} \xrightarrow{\text{cyt. P-450 } (FeO^{3+})} \mathrm{Ar\text{-}\overset{+\cdot}{S}\text{-}CH_2X} \begin{cases} \rightarrow \mathrm{Ar\text{-}\overset{O}{\overset{\uparrow}{S}}\text{-}CH_2X} + Fe^{3+} \\ \rightarrow 1/2\ \mathrm{ArSSAr} + \mathrm{XCHO} + Fe^{3+} \end{cases} \quad (1)$$

Cytochrome P-450 is also known to act as a peroxidase *in vitro* experiments; for example, some alkyl hydroperoxides and H_2O_2 can replace NADPH and molecular oxygen.[4] This paper deals with a model enzymatic reaction of peroxide dependent oxygenation of organic sulfides by a system consisted with TPPFe(III)Cl [chloro-*meso*-tetraphenylporphinatoiron(III)]/H_2O_2/imidazole.

To a solution of sulfide (1, 0.5 mmol) and TPPFe(III)Cl (0.025 mmol) in 15 ml of acetonitrile, hydrogen peroxide (30% aq. solution, 1 mmol) was added at room temperature. Monitoring of the reaction by both TLC and HPLC revealed that the oxidation took place smoothly, whereas in the absence of the catalyst only a trace amount of the sulfoxide was detected even after one day of incubation. The results are summarized in Table 1.

Table 1 Oxidation of Sulfides with H_2O_2 in The Presence of TPPFe(III)Cl at Room Temperature

substrate	system (eq.)[a]	solvent	time (h)	products (%)	
p-TolSCH$_3$ 1	TPPFe(III)Cl (0.05)	CH_3CN	<24	*p*-TolS(O)CH$_3$	(quant)
	TPPFe(III)Cl (0.25)	CH_3CN	1		(93)
	TPPFe(III)Cl (0.05)	CH_3CN-10% Im	0.5		(quant)
PhSCH$_2$Ph 2	TPPFe(III)Cl (0.05)	CH_3CN	<24	PhS(O)CH$_2$Ph	(quant)
PhSCH$_2$CN 3	TPPFe(III)Cl (0.10)	CH_3CN	2.5	PhS(O)CH$_2$CN (34)	PhSSPh (0.4)[b]
PhSCH$_2$COPh 4	TPPFe(III)Cl (0.10)	CH_3CN	2.5	PhS(O)CH$_2$COPh (35)	PhSSPh (5.8)[b]



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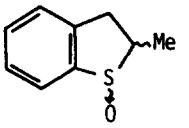


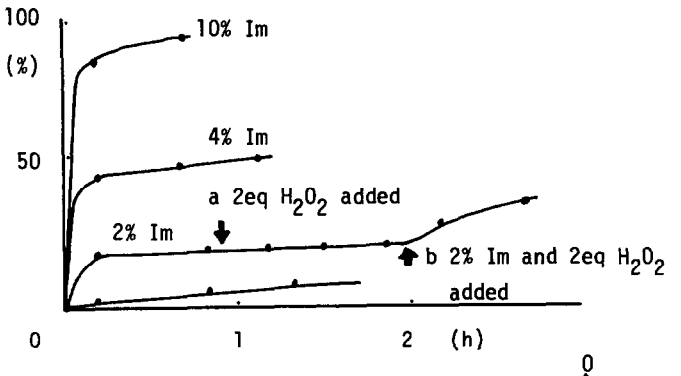
			Trans : *cis*	
TPPFe(III)Cl (0.05)	$CHCl_3$-10% Im	1	76 : 24	(93)
Purified cyt. P-450/NADPH/O_2	Buffer (pH 7.4)		81 : 19[9]	
Microsomes/H_2O_2	Buffer (pH 7.4)		78 : 22	
mCPBA	$CHCl_3$		53 : 47[9]	
$NaIO_4$	H_2O-CH_3COCH_3		52 : 48[9]	

In all cases, 2 eq. of hydrogen peroxide was used. a) Based on sulfide used. b) Starting materials were recovered in 60% for 3 and 55% for 4.

Imidazole was found to accelerate the oxidation extremely, but not found to be absolutely essential. However, imidazole was found to be an essential compound of our model system when the oxidation was carried out in chloroform instead of acetonitrile as illustrated in Fig 1. The rates of oxidation depended on the amount of imidazole added. The oxidation of thioanisole was almost completed within 10 min in the presence of 0.1 equimolar amount of imidazole (to sulfide), however, the reaction stopped at 20% completion when only 0.04 equimolar amount of imidazole was used. Additional imidazole-hydrogen peroxide (b in Fig 1) started the reaction again to completion, indicating that some of imidazole was consumed during the reaction.

In the oxygenation of *p*-tolyl methyl sulfide (1) and benzyl phenyl sulfide (2), the corresponding sulfoxides were found to be produced as the sole products, however, alkyl sulfides each having an acidic α-methylene group such as 3 and 4 gave not only the corresponding

Fig 1 Oxidation of Thioanisole with TPPFe(III)Cl/ Imidazole/H_2O_2 System in $CHCl_3$ at Room Temperature



$$PhSCH_3 + {}^{4.8\%}TPPFe(III)Cl + {}^{2eq}H_2O_2 + Im \longrightarrow PhS(O)CH_3$$

sulfoxides as the S-oxidation products but also diphenyl disulfide as the S-dealkylation product. Such a dual mode of the oxidation is well consistent with that of the oxygenation with cytochrome P-450 of alkyl sulfides each bearing an acidic α-methylene (eq. 2),[3] suggesting clearly the involvement of the sulfenium radicals in this enzyme model reaction as in the

$$Ar\text{-}S\text{-}CH_2X \xrightarrow{TPPFe(III)Cl\text{-}H_2O_2} \begin{cases} Ar\text{-}S(O)\text{-}CH_2X & \text{(S-oxidation)} \\ 1/2\ ArSSAr + XCHO & \text{(S-dealkylation)} \end{cases} \quad (2)$$

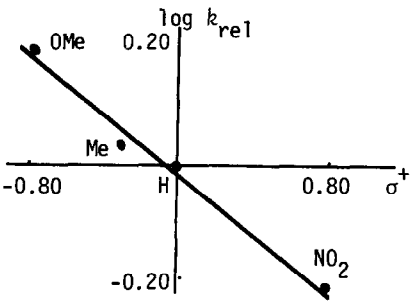
real enzymatic reaction (eq. 1).[5-7] In search for evidence to support further the involvement of the sulfenium radical, polar effect of *para*-substituent on the rate of sulfoxidation of thioanisole has been examined (Table 2 and Fig 2). As was expected, the electron-releasing substituent accelerated the S-oxidation and log k_{rel}'s can be correlated nicely with either the one-electron oxidation potentials of the corresponding sulfides or Brown-Okamoto's σ^+-constants ($\rho^+ = -0.26$) but not with the Hammett σ-constants, whereas the rates of the oxidations of the same compounds by simple electrophilic oxidation of sulfides by hydrogen peroxide have been known to be correlated with σ-values but not with σ^+-values.[8] This is in keeping with the polar substituent effect ($\rho^+ = -0.16$)[5,6] observed in the enzymatic S-oxygenation of the same compounds with purified cytochrome P-450, isolated from phenobarbital pretreated rabbit liver.

Meanwhile, we reported in the previous paper the stereochemistry of S-oxidation of unsymmetrical sulfides.[9] Thus, in order to compare the stereochemistry of S-oxidation of unsymmetrical sulfide by the enzyme model system with that by cytochrome P-450 enzyme system, we have carried out the oxidation of 2-methyl-2,3-dihydro-4,5-benzothiophene (5), which has

Table 2 Comparison of Kinetics with One Electron Oxidation Potential (Ep)

X-C$_6$H$_4$-S-CH$_3$	log k_{rel}	Ep[5] (volt *vs* SCE)
X = MeO	0.20	1.26
Me	0.03	1.41
H	0	1.53
NO_2	-0.21	1.85

Fig 2 Relationship between σ^+-Constants and log k_{rel} of *p*-Substituted Thioanisole Derivatives



The oxidation was carried out in $CHCl_3$ containing 0.1 equimolar amount of imidazole.

been shown to give the most distinct isomer ratio of the oxygenated products in the real enzymatic oxygenation of unsymmetrical sulfide.[9] The results are listed in Table 1 together those with the enzymatic system and also with nonenzymatic chemical oxidants, *i.e.*, *m*-chloroperbenzoic acid and sodium metaperiodate. The formation of the *trans*-5-sulfoxide was found to predominate over that of the *cis*-isomer in both the enzymatic and biomimetic oxidations to the same extent. The isomer ratio of the resultant sulfoxides is clearly different from those of oxidations of 5 by chemical oxidants such as *m*CPBA and $NaIO_4$. Thus, our biomimetic oxidation is quite similar to the enzymatic oxygenation in the three points, i) duality of the reaction path; ii) polar substituent effect on rate; iii) stereoselectivity, suggesting that the enzyme model reaction proceeds through the same mechanistic path as that of the enzymatic oxygenation, we postulated earlier.[3,5-7]

References

1) "Cytochrome P-450", R. Sato and T. Omura Eds., Kodansha Ltd., Tokyo (1978); R.E. White and M.J. Coon, Ann. Rev. Biochem., 49, 315 (1980). 2) T. Matsuura, Tetrahedron, 33, 286 (1977); C.K. Chang and D. Dolphin,"Bioorganic Chemistry", E.E. van Tamelen Ed., Vol 4, p. 37, Academic Press, New York (1978); J.T. Groves, T.E. Nemo, and R.S. Myers, J. Am. Chem. Soc., 101, 1032 (1979); J.T. Groves, M. Nakamura, T.E. Nemo, and B.J. Evans, *ibid.*, 103, 2884 (1981); C.K. Chang and M.-S. Kuo, *ibid.*, 101, 3413 (1979); I. Tabushi and N. Koga, *ibid.*, 101, 6456 (1979). 3) Y. Watanabe, T. Numata, T. Iyanagi, and S. Oae, Bull. Chem. Soc. Jpn., 54, 1163 (1981). 4) E.G. Hrycay and P.J. O'Brien, Arch. Biochem. Biophys., 153, 480 (1972); B.W. Griffin, C. Marth, Y. Yasukochi, and B.S. S. Masters, *ibid.*, 205, 543 (1980). 5) Y. Watanabe, T. Iyanagi, and S. Oae, Tetrahedron Lett., 21, 3685 (1980). 6) Y. Watanabe, T. Iyanagi, and S. Oae, Bull. Chem. Soc. Jpn., in press (1982). 7) Y. Watanabe, T. Iyanagi, and S. Oae, Tetrahedron Lett., in press (1982). 8) G. Modena and L. Mariola, Gazz. chim. ital., 87, 1306 (1957). 9) T. Takata, M. Yamazaki, K. Fujimori, Y.H. Kim, S. Oae, and T. Iyanagi, Chem. Lett., 1980, 1441.

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