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Biomimetic Oxidation of Diphenyl Sulfide with Metalloporphyrin–O_2–$NaBH_4$ System

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A P-450 model system consisting of metallo-*meso*-tetraphenylporphyrins, O_2 and $NaBH_4$ in basic solution is described. It has three remarkable features; 1) dioxygen is activated on a metalloporphyrin; 2) the reductant is used effectively, *i.e.*, the efficiency of the reductant, calculated on the assumption that two electrons are consumed to produce an active two-electron oxidant in the catalytic cycle, is 37%; 3) the life of the catalyst is extremely long for a P-450 model system. The maximum turnover is 336.

When *meso*-tetraphenylporphyrinatomanganese(III) chloride (1) was used as a catalyst in this system, diphenyl sulfide was oxidized stepwise to diphenyl sulfoxide and then to diphenylsulfone. When *meso*-tetraphenylporphyrinatoiron(III) chloride (2) was used as a catalyst, diphenyl sulfide was oxidized quantitatively to diphenyl sulfoxide.

Keywords P-450 model; oxidation; sulfide; *meso*-tetraphenylporphyrinatomanganese(III) chloride; *meso*-tetraphenylporphyrinatoiron(III) chloride; sulfoxide

In the generally accepted catalytic cycle for P-450, an oxo-iron(V) species or oxo-iron(IV) porphyrin π-cation radical is produced by transfer of two electrons and one dioxygen. Difficulties in binding and reduction of dioxygen can be bypassed by the addition of exogenous oxygen sources such as RCO_3H and PhIO.[1]

Studies on the oxidation of sulfides with metalloporphyrins have dealt with the shunt mechanism except for that of Santa *et al.*, because of the difficulty, that in this catalytic cycle, the oxo-metallo species must oxidize a substrate in the presence of a large excess of reductant.[2–7] In the oxidation of sulfides it is particularly important to choose the reductant carefully because the oxidation product of sulfides, sulfoxides, may be easily reduced to sulfides again. Sulfoxides are not reduced with $NaBH_4$, though $NaBH_4$ can reduce *meso*-tetraphenylporphyrinatomanganese(III) chloride (**1**) or *meso*-tetraphenylporphyrinatoiron(III) chloride (**2**).[8]

In this paper we wish to describe a biomimetic oxidation of a sulfide with **1** or **2** and $NaBH_4$ as a model compound of P-450 dnd reductant, respectively. Tabushi and Koga reported that exposure of cyclohexene to the **1**–O_2–$NaBH_4$ system in benzene–ethanol at room temperature and gave cyclohexanol and cyclo-hexenol.[9] This system was applied to biomimetic oxidation of diphenyl sulfide, but the reaction was very slow, contrary to our expectation. Then the solvent was switched to benzene–methanol–H_2O, and NaOH was added to accelerate the reaction.

Results

Oxidation of sulfides with the O_2–$NaBH_4$ System In a typical run, compound **1** (0.02 mmol), diphenyl sulfide (0.1 ml, 0.06 mmol) and diphenyl as an internal standard were dissolved in a solvent (10 ml, benzene, methanol, and 4% aqueous NaOH (3 : 7 : 1)) and $NaBH_4$ (3 mmol) was added to the solution. The reaction mixture was stirred at room temperature with bubbling O_2 gas. Twenty-five μl aliquots of the reaction mixture were taken at appropriate time-intervals, and diluted with benzene (0.5 ml). The products and the substrate were monitored by gas chromatography. Most of the diphenyl sulfide was oxidized to diphenyl sulfoxide in 7 h, and a part of which was also oxidized further to diphenylsulfone, as shown in Fig. 1.

No reaction occurred in the absence of $NaBH_4$ or **1**. A similar result was obtained when thioanisole was used as a substrate instead of diphenyl sulfide, but the total yields of products did not reach 100% (Fig. 2).

When **2** was used instead of **1**, only diphenyl sulfoxide was formed with only a trace of diphenylsulfone. The selectivity of **2** is superior to that of **1**. When *meso*-tetraphenylporphyrinatocobalt(II) was used instead of **1**, the reaction scarcely proceeded.

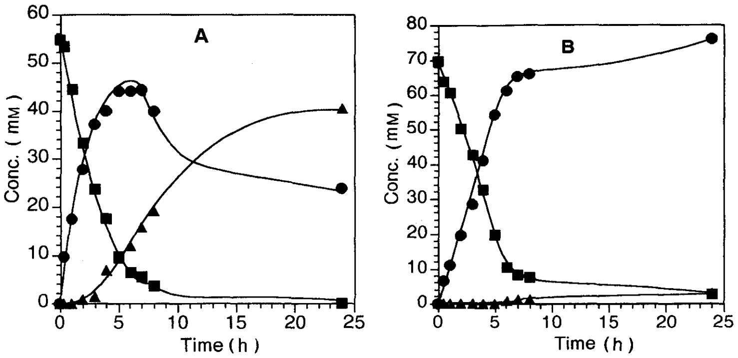

Fig. 1. Selective Oxidation of Diphenyl Sulfide with P-450 Model System (TPPMn(III)Cl (A)/TPPFe(III)Cl (B), $NaBH_4$, O_2, in C_6H_6–MeOH–NaOH); Ph_2S (■), $Ph_2S=O$ (●), Ph_2SO_2 (▲).

When the amount of $NaBH_4$ was reduced to 0.3 mmol (half the amount of diphenyl sulfide), the yields of diphenyl sulfoxide and diphenylsulfone were 72% and 0.9%, respectively. Sodium borohydride is an 8-electron reductant, and two electrons and 4 electrons are needed to produce diphenyl sulfoxide and diphenylsulfone from diphenyl sulfide, respectively. Since two electrons are consumed to produce a two-electron-oxidant, oxo-metallo(V) species, in the P-450 catalytic cycle, the efficiency of the reductant was 37%.

In order to clarify the catalytic cycle, we used Mn(III) DMB-PBP Cl, which is one of the "picnic-basket" porphyrinatomanganese(III) chlorides and whose bridging group was 2,6-dimethylbenzoate.[10] DMB-PBP has a pocket whose size is too small to allow diphenyl sulfide to enter. The fifth ligand of Mn(III) DMB-PBP Cl is outside the pocket.[11] When Mn(III) DMB-PBP Cl was used in place of **1**, the oxidation scarcely proceeded and only a little (5—7 mM) diphenyl sulfoxide was obtained in both the presence and absence of *N*-methylimidazole. These results show that the sulfides were oxidized on **1** and **2**, and are consistent with the speculation that the oxidant may be the oxo-metallo(V) species and not free activated oxygen.

A maximum turnover number of 336 was obtained when the amount of diphenyl sulfide was increased to 2.5 mmol and that of **1** was decreased to 0.001 mmol. In this case, only diphenyl sulfoxide was formed as a product. When **2** was used instead of **1**, a turnover number of 263 was obtained. The life of **1** was longer than that of **2**.

Mass Spectrometry A 4% aqueous NaOH solution was prepared with $H_2{}^{18}O$ whose isotopic enrichment was 99.8% and used as one of components of the reaction solvent. A 10 μl aliquot of the reaction solvent was subjected to TLC. The appropriate spot was scraped off and then extracted with acetone. After filtration of the organic solution, mass and high-resolution mass spectra were taken. The spectrum of the acetone solution was very similar to that of $(Ph)_2S^{16}O$ and the signal at 202.0466 ($C_{12}H_{10}OS$) was observed in the high-resolution mass spectra. The signal of $(Ph)_2S^{18}O$ was not detected. This supports the hypothesis that the origin of the oxygen atom in diphenyl sulfoxide is dioxygen.

Visible Spectrometry Visible spectra were obtain in a solvent (benzene–methanol (3 : 7)) containing **1** or **2** respectively. Addition of *N*-methylimidazole to the solution containing **1** changed the spectra slightly. Addition of NaOH caused a bigger change, especially in the ranges of 350—420 and 550—650 nm. Addition of *N*-methylimidazole to the solution of **1** and NaOH did not change the spectra. Addition of *N*-methylimidazole to the solution containing **2** increased the absorption at 415 nm and slightly decreased that at 337 nm, but no marked change of the spectrum of the solution containing **2** was seen upon addition of *N*-methylimidazole or NaOH.

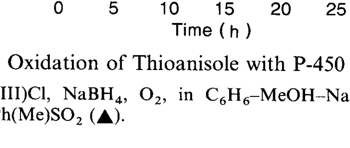

Fig. 2. Selective Oxidation of Thioanisole with P-450 Model

System (TPPMn(III)Cl, $NaBH_4$, O_2, in C_6H_6–MeOH–NaOH); PhSMe (■), Ph(Me)S=O (●), $Ph(Me)SO_2$ (▲).

Discussion

Santa *et al.* recommended the use of a protic solvent with iron porphyrin as a catalyst for the reductive activation of molecular oxygen because μ-oxo dimer formation was effectively suppressed and molecular oxygen was reductively activated.[2,12] They also reported that addition of a small amount of base increased the yield, but did not explain why. The results of visible spectrometry can be summarized as follows. Addition of *N*-methylimidazole changed the spectra of the solution containing **1** or **2** in the absence of NaOH, but not in the presence of NaOH. When NaOH is present in the reaction mixture, the 5th ligand should be replaced with a hydroxyl ion, which is more basic than *N*-methylimidazole or chloride ion. The following schemes are suggested for oxidation of sulfides with the **1**–O_2–$NaBH_4$ and **2**–O_2–$NaBH_4$ systems in basic solution. Compound **1** or **2** is converted to the hydroxy complex by replacement of the chloride ion with hydroxyl ion when the reaction mixture is prepared. One electron reduction of 5-coordinate hydroxy complexes with $NaBH_4$ is followed by binding of dioxygen to generate the superoxo form. A second one-electron reduction yields the metallo peroxo species. A proton catalyzes the heterolysis of the O–O bond with concomitant generation of the reactive oxidant and a molecule of H_2O. The S-oxygenation of sulfides consists of electron transfer and oxygen transfer as shown in the P-450 catalytic cycle.[4,13] One-electron transfer from sulfides to the oxidant (C) generates cation redicals. A cation radical generated from diphenyl sulfide goes quantitatively to the oxo-transfer stage. A part of the cation radical generated

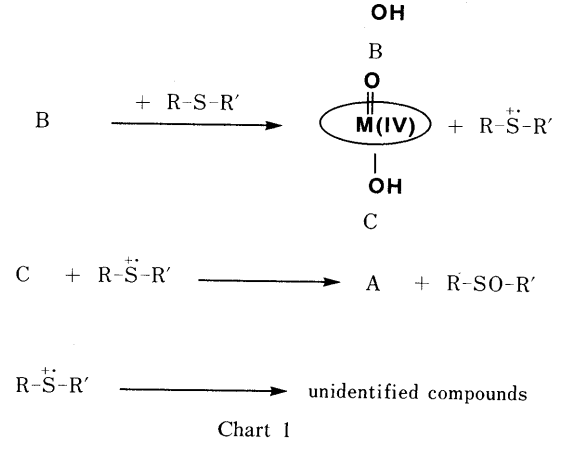

Chart 1

from thioanisole is decomposed to unidentified products by loss of a proton from the carbon atom attached to the sulfur atom.[14] This is the reason why the total of the yields of methyl phenyl sulfoxide and methylphenylsulfone does not reach 100%.

Oae pointed out that sulfides tended to be oxidized with electrophilic oxidants owing to the lone electron pair, while sulfoxides were not oxidized with electrophilic oxidants but were with nucleophilic ones owing the positive charge.[15] Fe has higher electronegativity than Mn, so the oxidant made from Fe has lower nucleophilicity. This is responsible for the sharp selectivity. Owing to the weaker reducing power of $NaBH_4$, the **1**–O_2–$NaBH_4$ and **2**–O_2–$NaBH_4$ systems both gave higher turnover and reductant efficiency as compared with than Fe(III)TPP–O_2–$Na_2S_2O_4$. Sodium dithionite is a strong reductant in a basic medium and reduces not only metalloporphyrins but also reactive oxidant generated in the catalytic cycle.

In conclusion, the **1**–O_2–$NaBH_4$ and **2**–O_2–$NaBH_4$ systems mimic the monooxygenation of sulfide best among the reactions so far known. The selectivity of **2** is superior to that of **1**, but the life of **1** is longer than that of **2**.

Experimental

Apparatus Mass spectra were obtained with a Hitachi M-2000. A Shimadzu GC-14A was used for gas chromatography.

Material Organic solvents were purified as described previously.[11] Mn(III) DMB-PBP Cl was prepared by the known method.[10] ^{18}O-Labeled diphenyl sulfoxide was prepared by the known method, but 99.8% enriched water was used instead of 1.5% enriched water.[16] The mass spectrometric signal ratio of ^{16}O-diphenyl sulfoxide *vs.* [^{18}O]-diphenyl sulfoxide was 1/0.6.

Oxidation of Diphenyl Sulfide Compound **1** (14 mg), diphenyl sulfide (0.1 ml) and diphenyl (92 mg) as an internal standard were dissolved in a solvent (10 ml, benzene, methanol, and 4% aqueous NaOH (3 : 7 : 1)) and $NaBH_4$ (0.1 g) was added to the solution. The reaction vessel was wrapped with black paper. The reaction mixture was stirred at room temperature with bubbling O_2 gas (5—7 ml/min). Twenty-five μl aliquots were taken at appropriate time-intervals, and diluted with benzene (0.5 ml). The products and the substrate were monitored by GC (column, Silicon OV-101, Uniport HP).

Mass Spectrometry A 4% aqueous NaOH solution was made of NaOH (0.4 g) and $H_2{}^{18}O$ whose isotopic enrichment was 99.8% and used as one of the components of the reaction solvent. The reaction mixture was prepared and allowed to react as mentioned above. Three hours later, the reaction mixture (10 μl) was spotted on a silica gel TLC plate and the plate was developed with benzene–methanol (9 : 1). The appropriate spot was scraped off and then extracted with acetone. After filtration, mass and high resolution mass spectra of the acetone solution were taken.

References and Notes

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