

Biomimetic models of nitric oxide synthase for the oxidation of oximes to carbonyl compounds catalyzed by water-soluble manganese porphyrins in aqueous solution

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ABSTRACT: A mild green and efficient approach for hydrogen peroxide oxidative converting oximes to the corresponding carbonyl compounds with a water-soluble manganese porphyrin as catalyst in water/acetone mixture has been developed. The water-soluble manganese porphyrin showed an excellent activity for the oxidative deoximation reactions of various oximes under ambient conditions in the absence of any additive. The oxidative deoximation was through the formation of high valent oxo-manganese species, which was confirmed by *in situ* UV-vis spectroscopy.

KEYWORDS: oxime; oxidation; water-soluble porphyrin; hydrogen peroxide.

INTRODUCTION

In the chemical industry, organic solvents should be avoided wherever possible [1]. Compared with organic solvents, water is a readily available, economic, safe, and environmentally-benign solvent [2]. Although the most complex form of organic compounds requires the construction of chemical bonds in an aqueous environment, water as a solvent was ruled out from organic reactions during the preceding decades [3].

Oximes are useful protecting groups and are widely used for the purification and characterization of carbonyl compounds [4]. Since oximes can also be prepared from non-carbonyl compounds, the generation of carbonyl compounds from them provides an alternative method for the preparation of aldehydes and ketones [5]. The reactions require organic solvent, drastic conditions and tedious procedures [6].

Metalloporphyrins as chemical models of cytochrome P450 and related monooxygenases have been used to carry out oxygenation and oxidation reactions of various organic compounds. However, most of the metalloporphyrins-mediated oxidations are conducted in organic solvents [7]. Therefore, the oxidations catalyzed by metalloporphyrins in water will be of great significance, which is closer to simulate the environments of the enzyme-mediated process [8]. A successful example of efficient controllable oxidation of alcohols to aldehydes or acids catalyzed by metalloporphyrins in water has been developed in our previous works [9].

We have reported the aerobic deoximation to the corresponding carbonyl compounds with manganese porphyrin in organic solvent with benzaldehyde as sacrificial reductant [10]. In order to avoid using organic solvent and sacrificial reductant for the deoximation, herein we report the aqueous oxidation of oximes catalyzed by *meso*-tetrakis(*N*-ethyl-4-pyridyl)manganese porphyrin (MnTEPyP) with hydrogen peroxide as oxidant (Scheme 1). The catalytic system has proved to be effective for the oxidation of oximes, which are commonly used as chemical models of nitric oxide synthase (NOS). Meanwhile, the process also provides a possible way for mimicking the aqueous oxidations of the numerous nitrogenous organic compounds in living organisms.

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Scheme 1. The oxidation of oximes to carbonyl compounds catalyzed by MnTEPyP

RESULTS AND DISCUSSION

Effect of MnTEPyP amount on the oxidation of cyclohexanone oxime

The catalytic activity of MnTEPyP with different amounts for oxime oxidation was investigated by using cyclohexanone oxime as the model substrate. The results are summarized in Table 1.

As shown in Table 1, only 12% of cyclohexanone oxime was converted in the absence of catalyst (entry 1). It was also observed that the conversion of cyclohexanone oxime was considerably enhanced when MnTEPyP was used. The conversion could reach up to 81% even if the amount of catalyst was only 0.5×10^{-3} mmol (entry 2), which indicated manganese porphyrin is crucial in oxidation reaction. With the increasing amount of catalyst from 1×10^{-3} to 5×10^{-3} mmol, no

Table 1. Effect of the amount of catalyst on the oxidation of oximes to carbonyl compounds^a

Entry	Amount of catalyst (× 10 ⁻³ mmol)	Conv., %	Yield, %	Selectivity, % ^b
1	0	12	10	83
2	0.5	81	72	89
3	1.0	90	83	92
4	2.0	92	84	91
5	3.0	92	85	92
6	5.0	93	84	90
7°	1.0	91	82	90
8 ^d	1.0	1	1	>99

^a Oxime (1 mmol), acetone/water (1 mL/5 mL), H₂O₂ (3 mmol), 60 °C, 30 min. ^b The by-product was benzonitrile. ^c Reaction time was 45 min. ^d Manganese acetate was used as catalyst.

significant difference was observed both for the conversion of cyclohexanone oxime and selectivity of cyclohexanone (entries 3–6). Also, no increased yield of cyclohexanone was obtained by prolonging reaction time to 45 min (entry 7). Therefore, the optimal amount of catalyst for the deoximation reaction was 1.0×10^{-3} mmol and the appropriate reaction time was 30 min. In addition, almost no reaction took place when the catalyst was replaced by manganese acetate with the same catalytic amount as metalloporphyrins (entry 8).

Effect of organic solvent on the oxidation of cyclohexanone oxime

As shown in Table 2, the conversion of cyclohexanone oxime was only 33% when the reac-

tion was conducted in aqueous medium, which could be attributed to the poor solubility of oxime in water (entry 1). Oxime might be dispersed well in the reaction media by adding one kind of organic solvent. Therefore, different organic solvents were checked for choosing the optimal reaction media. From Table 2, acetone was more favorable for the reaction compared with dimethylformamide, acetonitrile, methanol and ethanol (entries 2-5). It seems that the deoximation is related with the dielectric constant of solvent, in which solvent with large dielectric constant is not suitable for the oxidation in the presence of water-soluble manganese porphyrin. In addition, the mixture between water and organic solvent, that is homogeneously mixed or not, is important for the reaction. Although the dielectric constant of toluene is very low, the yield of cyclohexanone was only

 Table 2. Effect of organic solvent on the oxidation of oximes to carbonyl compounds^a

Entry	Solvent	Dielectric constant	Conv., %	Yield, % ^b
1	_		33	19
2	acetonitrile	37.5	24	19
3	dimethylformamide	36.7	32	19
4	methanol	32.6	35	25
5	ethanol	24.3	34	25
6	acetone	20.5	90	83
7	toluene	2.4	27	24
8°	acetone	20.5	78	63
9 ^d	acetone	20.5	82	76
10 ^e	acetone	20.5	75	73
11^{f}	acetone	20.5	57	53

^a Oxime (1 mmol), MnTEPyP (1×10^{-3} mmol), H₂O (5 mL), organic solvent (1 mL), H₂O₂ (3 mmol), 60 °C, 30 min. ^b The by-product was benzonitrile. ^{c-f} The volume of acetone is 0.5, 2, 3 and 5 mL, respectively.

27% when the reaction was carried out in water/toluene mixture medium (entry 7). It could be attributed to the formation of two phase system by adding toluene into the mixture, which is unfavorable to contact between catalyst and substrate.

The conversion of cyclohexanone oxime decreased with the increasing volume of acetone from 2 to 5 mL in the reaction system, coupled with the enhanced selectivity of cyclohexanone (entries 9–11). When 5 mL acetone was added to the mixture, only 57% of the substrate was converted. It could be understood that oxime might be enriched in acetone with the increasing amount, which retarded the interaction between catalyst and oxime.

Effect of temperature on the oxidation of cyclohexanone oxime

Effect of reaction temperature on the oxidation of cyclohexanone oxime to cyclohexanone catalyzed by MnTEPyP was also investigated. Results are summarized in Table 3.

As shown in Table 3, the conversion of cyclohexanone oxime is closely related with the reaction temperature. Almost no cyclohexanone oxime was converted to its corresponding product in the experiment that was carried out at 20 °C (entry 1). It was also observed that the conversion of cyclohexanone oxime was considerably enhanced with the increasing reaction temperature from 30 °C to 60 °C. However, the selectivity of cyclohexanone is minimally influenced by reaction temperature. With the elevated temperature from 60 °C to 70 °C, no obvious increase was observed for the conversion of cyclohexanone oxime, but it exhibited a slight decrease of cyclohexanone selectivity. Such results indicated that 60 °C was the optimal reaction temperature for the deoximation reaction catalyzed by MnTEPyP in the presence of hydrogen peroxide.

Oxidation of various oximes catalyzed by MnTEPyP in the presence of H_2O_2

Different substrates were examined for the oxidation catalyzed by the MnTEPyP in the presence of hydrogen

Table 3. Effect of temperature on the oxidation of oximes to carbonyl compounds^a

Entry	T, °C	Conv., %	Yield, %	Selectivity, % ^b
1	20	5	5	100
2	30	37	30	81
3	40	49	43	88
4	50	73	68	93
5	60	90	83	92
6	70	91	81	89

 $^{\rm a}$ Oxime (1 mmol), MnTEPyP (1 \times 10⁻³ mmol), acetone/water (1 mL/5 mL), H₂O₂ (3 mmol), 30 min. $^{\rm b}$ The by-product was benzonitrile.

peroxide, and the typical results are summarized in Table 4.

As shown in Table 4, the oxidations of most oximes occurred smoothly to afford the corresponding carbonyl compounds by MnTEPyP in the presence of hydrogen peroxide selectively. Among the cyclic oximes, cyclohexanone oxime was more efficiently oxidized than other cyclic oximes such as cyclooctanone and cyclopentanone oximes, which required longer reaction time or higher reaction temperature (entries 1–3).

The catalytic system also presented high activity for the conversion of aromatic oximes to carbonyl compounds. For example, 82% of benzaldoxime could be converted to the corresponding benzaldehyde (76%) in 5 h at 90 °C (entry 4). It seems that the oxidation efficiency for this catalytic system was dependent on the electronic property of substrates. The main product obtained was nitrile for the substrates with electron-withdrawing groups at *ortho*-position (entries 6,7). However, the oxidation efficiency was not affected by electron-denoting group of substrate (entry 5). Such extremely different results should be attributed to different electronic atmosphere of C=N bond [10]. Steric structure almost has no effect on the conversion of oximes, while it is favorable for the selectivity of carbonyl compound (entries 8,9).

Plausible mechanism for the oxidation of oxime catalyzed by MnTEPyP

For the selective oxidation of hydrocarbons or other organic compounds, the application of iron porphyrins in combination of hydrogen peroxide is particularly extensive [11]. It is suggested that reaction of hydrogen peroxide with iron(III) porphyrins results in the formation of an iron(IV) oxo species or iron(IV) π -radical cations, which are the active species for the oxidation [12]. In the present deoximation catalyzed by manganese porphyrins, as mentioned above, water-soluble manganese porphyrin (MnTEPyP) is essential for the reaction in the presence of hydrogen peroxide. The presence of manganese-oxo porphyrin was confirmed by *in situ* UV-vis spectra for the oxidation of cyclohexanone oxime. The spectrophotometer was programmed to acquire UV-vis spectrum every 5 min.

As shown in Fig. 1, the initial characteristic absorption peaks of MnTEPyP were at 464 and 562 nm. After adding H_2O_2 and cyclohexanone oxime into the reaction system, *in situ* determination revealed that the characteristic absorption peak of MnTEPyP weakened gradually, suggesting the consumption of oxidant active species (Mn^{IV}=O) by substrate [13]. In addition, color changes of the reaction mixture from dark green to tinge also indicate valence change of manganese. GC analysis of these reactive products revealed the formation of cyclohexanone, indicative of the presence of active oxidation species.

In the metalloporphyrins-catalyzed oxidation of oximes with various oxidants, the formation mechanism of Mn-oxo active species is quite different. For the aerobic

Entry	Oxime	Product	T, °C	Time, h	Conv., %	Yield, %
1	N ^{OH}	O	60	0.5	90	83
2	N ^{_OH}		60	2.5	96	87
3	N-OH		90	5	96	82
4	N ^{OH} H	O H	90	5	82	76
5	OH N OH	ОН	90	5	91	87
6	OH N NO ₂		90	5	52	22 30
7	OH N		90	5	47	19 26
8	N_OH	O C	90	5	98	98
9b	HON	° C	90	5	95	95

Table 4. Oxidation of various oximes catalyzed by MnTEPyP in the presence of $\mathrm{H_2O_2^{\,a}}$

^a Oxime (1 mmol), MnTEPyP (1 × 10^{-3} mmol), acetone/water (1 mL/5 mL), H₂O₂ (3 mmol). ^b Acetone (2 mL).



Fig. 1. *In situ* UV-vis spectra of MnTEPyP in the solution of cyclohexanone oxime oxidation in the presence of hydrogen peroxide (time scan: 5 min). Cyclohexanone oxime (1 mmol), H_2O_2 (3 mmol), MnTEPyP (1 × 10⁻³ mmol), acetone/water (1 mL/5 mL), 60 °C

deoximation catalyzed by MnTPPCl as reported previously [10], the active species (Mn^{IV}=O) was generated *via* a radical process coupled with the sacrifice of benzaldehyde as a reductant. While, for the deoximation reaction of hydrogen peroxide with MnTEPyP, Mn(IV) oxo species was generated by the homolytic cleavage of Mn(III) hydroperoxide species, which was formed by the reaction of hydrogen peroxide with manganese porphyrins [14].

Based on these observations, a plausible reaction mechanism for the deoximation with water-soluble manganese porphyrin (MnTEPyP) as catalyst was proposed (Fig. 2). The reaction mechanism could involve the use of oxo-manganese intermediate generated from the reaction between manganese porphyrin and hydrogen peroxide. An adduct (a) could be generated from the nucleophilic attack of the high-valent oxo species to C=N bond, which produces the corresponding carbonyl compounds by decomposition. For the oximes with electron-withdrawing groups at *ortho*-position (entries 6,7, Table 4), nitrile was obtained as another main product. Such oximes may



Fig. 2. Plausible reaction mechanism of the deoximation catalyzed by MnTEPyP in the presence of hydrogen peroxide

tend to be protonated firstly, followed to yield nitrile *via* dehydration step.

The metalloporphyrins-catalyzed aerobic oxidations are always carried out with sacrificial additives under atmospheric pressure. To avoid using additives, the oxidations should be conducted under high pressures [15]. The present deoximation was conducted not only under ambient conditions, but also conducted in the absence of any additives. The reaction could also provide some evidences to explore the metabolism of nitrogenous organic compounds in living organisms.

EXPERIMENTAL

Oximes with analytical grade were obtained from Aldrich or Fluka Chemical Company without further purification unless indicated. Pyrrole was purified before use. UV-vis spectrum was recorded on a Shimadzu UV-2450 spectrophotometer. Mass spectra were obtained on a Shimadzu LCMS-2010A. Elemental analysis data were obtained on Vario EL III. Other solvents were all of analytical grade.

MnTEPyP (*meso*-tetrakis(*N*-ethylpyridinium-4-yl)manganese porphyrin) catalysts were prepared according to previously reported procedures [9, 16]. The structure of MnTEPyP was confirmed by elementary analysis, mass spectra and UV-vis spectra, respectively.

$$\label{eq:mntepyp} \begin{split} & [\text{Mntepyp}]^{4+} \text{. EI-MS: } \textit{m/z} \ 787. \ UV-vis \ (H_2O): \ \lambda_{max}, \\ & \text{nm} \ (\log \epsilon) \ 464 \ (2.48), \ 559 \ (1.25), \ 675 \ (0.87), \ 769 \ (0.54). \\ & \text{Anal. calcd. for} \ [\text{Mntepyp}]^{4+} \ C, \ 44.50; \ H, \ 3.42; \ N, \ 8.65. \\ & \text{Found: } C, \ 44.67; \ H, \ 3.51; \ N, \ 8.49. \end{split}$$

General procedures for the catalytic oxidation of oximes to carbonyl compounds. All reactions were carried out in a 25 mL flask equipped with a magnetic stirrer bar under air. Water (5 mL), acetone (1 mL), oxime (1 mmol), MnTEPyP (1 × 10^{-3} mmol), and 30% H₂O₂ (3 mmol) were mixed at 60 °C while stirring for 30 min. The product for each reaction was analyzed with GC (Shimadzu GC-2010 plus) and GC-MS (Shimadzu GCMS-QP2010 plus) with naphthalene as an internal standard after the extraction with ethyl acetate at an interval of 5 min.

CONCLUSION

In summary, an environmentally friendly protocol has been developed for the catalytic oxidation of oximes to give carbonyl compounds. The MnTEPyP-based catalytic system has proven to be effective in the deoximation with hydrogen peroxide as a terminal oxidant. The oxidation of cyclohexanone oxime by MnTEPyP in water/ acetone mixture (5/1, v/v) gave oxidative product up to 83% yield. Various oximes could be successfully converted. The oxidative deoximation was through the formation of high valent oxo-manganese species, which was confirmed by *in situ* UV-vis spectroscopy. A plausible mechanism for the oxidative deoximation has been proposed. The reaction is conducted under atmospheric pressure in the absence of any additive, which has the application prospects and provides a possible way to explore the aqueous oxidations of the nitrogenous organic compounds in living organisms.

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