Available online at www.sciencedirect.com

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 12 (2004) 4673–4677

Bioorganic & Medicinal Chemistry

Cytochrome P-450 dependent monooxygenases model system: rapid and efficient oxidation of primary aromatic amines to azo derivatives with sodium periodate catalyzed by manganese(III) Schiff base complexes

Valiollah Mirkhani,[a,*] Shahram Tangestaninejad,[a] Majid Moghadam[b] and Maryam Moghbel[a]

[a] *Department of Chemistry, Isfahan University, Isfahan 81746-73441, Iran*
[b] *Department of Chemistry, Yasouj University, Yasouj 75914-353, Iran*

Received 20 April 2004; revised 15 June 2004; accepted 22 June 2004
Available online 24 July 2004

Abstract—Rapid and efficient oxidation of primary aromatic amines was investigated. Mn(III)-salophen catalyst can catalyze the oxidation of primary aromatic amines to azo derivatives with sodium periodate. The ability of various Schiff base complexes in this oxidation system was also investigated.

1. Introduction

Oxidation is one of the most important reactions for the metabolism of biotic substrates and many enzymes are known to catalyze various types of oxidation. Amongst such oxidizing enzymes, the heme-containing monooxygenase cytochrome P-450 has been most extensively studied.[1] Many metalloporphyrin complexes have been synthesized to reproduce the function of cytochrome P-450 and some well-designed iron(III) and manganese(III) porphyrins have been found to be efficient catalysts for *O*- and *N*-dealkylation,[2] olefine and arene epoxidation,[3,4] alkane hydroxylation,[5] and oxidation of nitroso[6] and primary aromatic amines to nitro derivatives.[7] Various single oxygen-atom donors such as iodosylbenzene, hypochlorites, potassium monopersulfate, and periodates have been used for this transformations.[8–13]

On the other hand, metal complexes of salen and salophen ligands also aroused the interest of synthetic chemists as model compounds for the active site of cytochrome P-450, since they have features in common with metalloporphyrins with respect to their electronic structure and catalytic activity. The electronic and steric nature of the metal complex can be tuned by introducing electron-withdrawing and electron-releasing substituents and bulky groups in the ligand. Manganese, chromium, nickel, and cobalt Schiff base complexes have been used as catalysts for oxidation reactions.[14–23]

Previously, we have reported the use of Mn(III)-salophen complexes in the alkene epoxidation and oxidative decarboxylation of carboxylic acids.[24,25] In continuation of our research in the oxidation of amines,[26,27] here we report the rapid and efficient oxidation of primary aromatic amines to azo derivatives with sodium periodate catalyzed by manganese(III) salophen complex.

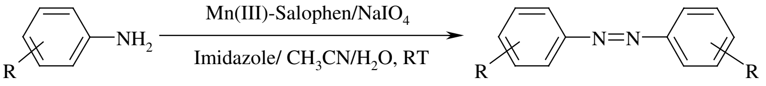
This catalytic system exhibits a high activity in the oxidation of primary aromatic amines with sodium periodate in 1:1 CH_3CN/H_2O mixture in the presence of imidazole as axial ligand (Scheme 1).

The type of metal ion and Schiff base and the nature of reactive intermediate were also investigated.

Keywords: Schiff base complexes; Primary aromatic amines; Periodate.

* Corresponding author. Tel.: +98-311-7932713; fax: +98-311-6689732; e-mail: mirkhani@sci.ui.ac.ir

doi:10.1016/j.bmc.2004.06.029



Scheme 1.

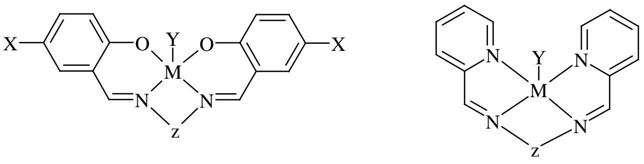
2. Results and discussion

2.1. Oxidation of primary aromatic amines with different metal Schiff base complexes

In a preliminary approach to the periodate anion activation by metal Schiff base complexes, we investigated the activity of various Schiff base complexes of Fe, Mn, Co, and Ni as metal ions. The obtained results on catalytic oxidation of *p*-toluidine with sodium periodate in the presence of different Schiff base complexes (Fig. 1) summarized in Table 1. The results indicated that the nature of the metal ion has an important role on the catalytic activity of Schiff base complexes. The iron, cobalt, and nickel complexes give small amount of the corresponding azo compound in the oxidation of *p*-toluidine. However, the use of manganese(III) complexes give higher oxidation product in the oxidation of *p*-toluidine.

In comparing the influence of Schiff base ligands on calatytic activity, the hindered Schiff base ligand, salophen, exhibits a significant greater catalytic power than the unhindered Schiff base ligand, salen. The similar situation have been observed with metalloporphyrin complexes and NaOCl as oxygen donors.[28]

Other oxygen-donors such as $KHSO_5$, NaOCl, and H_2O_2 were examined for oxidation of primary aromatic amines under various reaction conditions, but higher activity was observed with sodium periodate than with the other oxygen donors.



	M	z	X	Y
1	Mn	C_6H_4	H	Cl
2	Mn	C_6H_4	NO_2	Cl
3	Fe	C_6H_4	H	Cl
4	Co	C_6H_4	H	-
5	Ni	C_6H_4	H	-
6	Mn	$(CH_2)_2$	H	Cl
7	Fe	$(CH_2)_2$	H	Cl
8	Mn	C_6H_4	H	Cl
9	Fe	C_6H_4	H	Cl
10	Mn	$(CH_2)_2$	H	Cl
11	Fe	$(CH_2)_2$	H	Cl

Figure 1. Transition metal Schiff base complexes used in this study.

Table 1. Oxidation *p*-toluidine by various metal Schiff base complexes with sodium periodate

Schiff base	Yield (%)[a] after 10 min	Yield (%)[a] after 20 min	Yield (%)[a] after 30 min
1	95	96	98
2	33	35	38
3	8	8	8
4	8	9	9
5	7	8	8
6	14	16	17
7	8	10	13
8	29	31	34
9	8	8	9
10	16	19	23
11	9	9	11

[a] GC yields.

Table 2. Effect of solvent on oxidation of *p*-toluidine with Mn(salophen)/$NaIO_4$ system

Solvent	Yield (%)[a] after 5 min	Yield (%)[a] after 10 min
CH_3CN/H_2O	85	95
CH_3COCH_3/H_2O	42	57
CH_3OH/H_2O	17	27
CH_3CH_2OH/H_2O	25	32
$CHCl_3/H_2O$	3	3
CCl_4/H_2O	3	3

[a] GC yields.

2.2. Effect of solvent on the oxidation of *p*-toluidine

Among the 1:1 mixture of methanol, ethanol, acetone, acetonitrile (single phase systems), chloroform, and carbontetrachloride (two phase systems with Bu_4NBr as phase transfer catalyst) with water, the 1:1 acetonitrile/water mixture was chosen as the reaction medium, because metal Schiff base complexes are highly soluble in this solvent and higher azo yields were observed. The results were shown in Table 2.

2.3. Effect of axial ligand on the oxidation of *p*-toluidine

One important aspect of this catalytic system is the modification of the oxidation rate by addition of small amount of imidazole to the reaction mixture. The formation of azobenzene in the absence of axial ligand is very slow and the yields are always below 10%, whereas the amount of azobenzene reaches to 98% in the catalyzed reaction with the imidazole as the axial base.

The effect of different axial ligands upon the oxidation rate decreased in the order: imidazole = 1-methylimidazole > 4-*t*-buthylpyridine > 4-methylpyridine > 2-methylpyridine > pyridine.

2.4. Oxidation of primary aromatic amines with sodium periodate catalyzed by Mn(III)-salophen

The imidazole-modified Mn-salophen/$NaIO_4$ oxidizing system can be applied to oxidize a large number of primary aromatic amines in high to good yields at short times and room temperature. All experiments were carried out with 2 equiv of sodium periodate per 1 equiv of amine. As shown in Table 3, the yields are between 57% and 88% (isolated yields) and the product was azo derivative.

Comparison of this homogeneous oxidizing system with previously reported homogeneous metalloporphyrin systems[26] showed that in the Mn-salophen/$NaIO_4$ system the yields are higher than that metalloporphyrin/$NaIO_4$ systems and the reaction times are shorter, and in the case of heterogeneous metalloporphyrin system[27] the yields are similar whereas the reaction times are shorter.

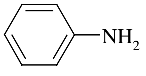
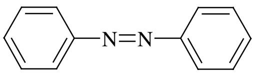
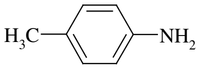
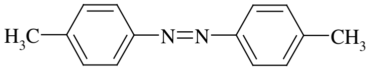
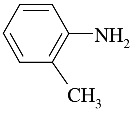
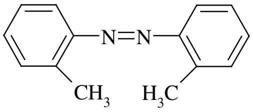
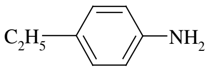
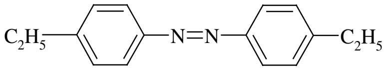
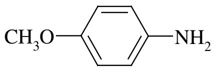
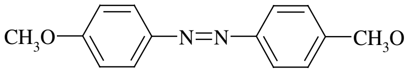
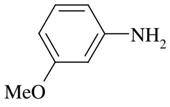
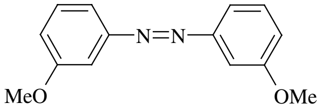
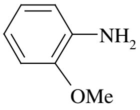
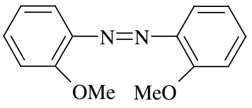
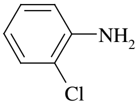
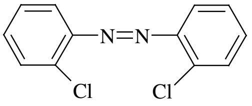
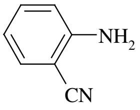
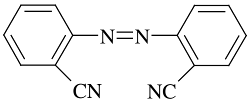
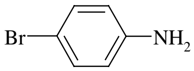
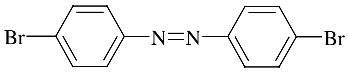
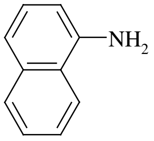
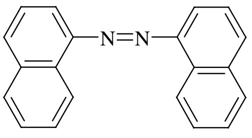
In the absence of manganese(III)-salophen catalyst, $NaIO_4$ has poor ability to oxidize primary aromatic amines at room temperature (4–10% yields).

At present, it is obscure to us to indicate the mechanism, but ^1H NMR, IR, and mass spectrometry confirmed the product.

2.5. Oxo manganese(V) species as the reactive intermediate

Although we have assumed the active manganese species to be reactive (salophen)Mn(V) oxo intermediate,

Table 3. Oxidation of primary aromatic amines to azo derivatives with $NaIO_4$ catalyzed by Mn(III)-salophen in the presence of imidazole

Row	Substrate	Products	Time (min)	Yield[a] (%)
1			10	82
2			10	88
3			10	83
4			10	88
5			10	85
6			10	83
7			10	82
8			30	65
9			30	69
10			30	61
11			30	57

[a] Isolated yields based on starting aromatic amine.

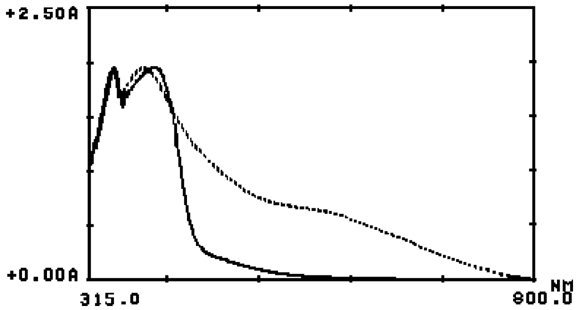


Figure 2. Absorption spectra of [Mn(III)-salophen]Cl in CH_3CN/H_2O. The dashed curve is the same solution immediately after reaction with excess $NaIO_4$.

[(salophen)Mn^V=O], by comparing the present spectral observation with the previous reports,[28] we could not isolate this active species. It is pertinent to point out that to date no (salophen)Mn(V) oxo species have yielded to structural characterization, although Groves et al. and others have characterize oxo manganese(V) porphyrin complexes in recent years.[29]

When a clear brown solution of Mn(III)-salophen in acetonitrile is treated with sodium periodate, it immediately turns dark. The appearance of a new absorption band (with $\lambda_{max} = 520–530$ nm, Fig. 2) is strongly reminiscent of the spectral change obtained during the conversion of the Mn(III)-salophen cation to the corresponding oxo manganese(V) species. Upon standing, the dark brown solution fades to the original light brown within 10 min. When the same experiment is carried out in the presence of *p*-toluidine, the dark brown solution immediately changed to its original light brown color.

3. Experimental

Schiff base complexes 1–11 (Fig. 1), were prepared as described by Boucher[30] or by the more recently modified methods.[11,31,32] Amines were obtained from Merck or Fluka and were passed through a column containing active alumina to remove peroxidic impurities. The electronic absorption spectra were recorded with a Shimadzu UV-160 spectrophotometer. ^1H NMR spectra were obtained with a Brucker AW80 (80 MHz) spectrometer. GLC analyses were performed on a Shimadzu GC-16A instrument using a 2 m column packed with silicon DC-200 or Carbowax 20M. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer.

3.1. General procedure for oxidation of primary aromatic amines to azo derivatives

All of the reactions were carried out at room temperature in a 25 mL flask equipped with a magnetic stirring bar. A solution of sodium periodate (2 mmol in 5 mL H_2O) was added to a mixture of amine (1 mmol), Mn-salophen (0.067 mmol), and imidazole (0.067 mmol) in CH_3CN (5 mL). Progress of the reaction was monitored by TLC. After the reaction was completed, the reaction products were extracted with CH_2Cl_2 (20 mL) and were purified by silica gel plate or silica gel column (eluent: $CCl_4–Et_2O$). The identities of products were confirmed by IR and ^1H NMR spectral data.

4. Conclusions

Although many oxidation systems that mimic cytochrome P-450 dependent monooxygenase have been reported, Mn(III)-salophen/$NaIO_4$ catalytic system have the following advantages: (i) short reaction time; (ii) high efficiency for the oxidation of amines; (iii) ease of preparation of the catalyst.

In comparison with other reported Schiff-base oxidation systems, performance of the novel Mn(III)-salophen/$NaIO_4$ system can be described as outstanding. Therefore, in the list of suitable oxidants able to behave like single oxygen donor to Schiff base complex, sodium periodate is among the most efficient.

Acknowledgements

The partial support of this work by Isfahan University Council of Research is acknowledged.

References and notes

1. (a) Coon, M. J.; White, R. E. In *Dioxygen Binding and Activation by Metal Centers*; Spiro, T. G., Ed.; Wiley: New York, 1980; p 73; (b) White, R. E.; Coon, M. J. *Annu. Rev. Biochem.* **1980**, *49*, 315.
2. Lindsay Smith, J. R.; Mortimer, D. N. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1743.
3. Appelton, A. J.; Evans, S.; Lindsay Smith, J. R. *J. Chem. Soc., Perkin Trans. 2*, **1996**, 281.
4. Hoffman, P.; Robert, A.; Meunier, B. *Bull. Soc. Chim. Fr.* **1992**, *129*, 85.
5. (a) Maldotti, A.; Bartocci, C.; Varani, G.; Molinari, A.; Battioni, P.; Mansuy, D. *Inorg. Chem.* **1996**, *35*, 1126; (b) Dolphin, D.; Traylor, T. G.; Xie, L. Y. *Acc. Chem. Res.* **1997**, *30*, 251.
6. Jorgenson, K. A. *J. Chem. Soc., Chem. Commun.* **1987**, 1405.
7. Tollari, S.; Vergani, D.; Banfi, S.; Porta, F. *J. Chem. Soc., Chem. Commun.* **1993**, 442.
8. Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786.
9. Bortolini, O.; Meunier, B. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1967.
10. Meunier, B.; Cuilmel, E.; De Carvallho, M. E.; Poiblane, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668.
11. (a) Mohajer, D.; Tangestaninejad, S. *J. Chem. Soc., Chem. Commun.* **1993**, 240; (b) Mohajer, D.; Tangestaninejad, S. *Tetrahedron Lett.* **1994**, *35*, 945.
12. Wohler, D.; Gitzel, J. *Makromol. Chem., Rapid Commun.* **1988**, *9*, 229.
13. (a) Leonard, D. R.; Lindsay Smith, J. R. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1917; (b) Leonard, D. R.; Lindsay Smith, J. R. *J. Chem. Soc., Perkin Trans. 2* **1991**, 25.
14. Srinivasa, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.
15. Siddall, T. L.; Miyaura, N.; Huffman, J. C.; Kochi, J. K. *J. Chem. Soc., Chem. Commun.* **1983**, 1185.

16. Ganeshpure, P. A.; Satish, S. *J. Chem. Soc., Chem. Commun.* **1988**, 981.
17. Rihter, B.; Masnovi, J. *J. Chem. Soc., Chem. Commun.* **1988**, 35.
18. Chellamani, A.; Alhaji, N. M. I.; Rajagopal, S.; Sevvel, R.; Srinivasan, C. *Tetrahedron* **1995**, *51*, 12677.
19. Chellamani, A.; Alhaji, N. M. I.; Rajagopal, S. *J. Chem. Soc., Perkin Trans. 2* **1997**, 299.
20. Koola, J.; Kochi, J. K. *J. Org. Chem.* **1987**, *52*, 4545.
21. Koola, J.; Kochi, J. K. *Inorg. Chem.* **1987**, *26*, 908.
22. Kinneary, J. F.; Wagler, T. R.; Burrows, C. J. *Tetrahedron Lett.* **1988**, *29*, 877.
23. Querci, C.; Strologo, S.; Ricci, M. *Tetrahedron Lett.* **1990**, *31*, 6577.
24. Tangestaninejad, S.; Mirkhani, V. *Asian Chem. Lett.* **1998**, *4*, 788.
25. Mirkhani, V.; Tangestaninejad, S.; Moghadam, M.; Moghbel, M. *Bioorg. Med. Chem.* **2004**, *12*, 903.
26. (a) Habibi, M. H.; Tangestaninejad, S.; Mirkhani, V. *J. Chem. Res. (S)* **1998**, 648; (b) Habibi, M. H.; Tangestaninejad, S.; Mirkhani, V. *Asian Chem. Lett.* **1998**, *2*, 107.
27. Mirkhani, V.; Tangestaninejad, S.; Moghadam, M.; Karimian, Z. *J. Chem. Res. (S)*, **2003**, 792.
28. (a) Chellamani, A.; Alhaji, N. M. I.; Rajagopal, S.; Sevvel, R.; Srinivasan, C. *Tetrahedron* **1995**, *51*, 12677; (b) Chellamani, A.; Alhaji, N. M. I.; Rajagopal, S. *J. Chem. Soc., Perkin Trans. 2* **1997**, 299.
29. (a) Groves, J. T.; Lee, J.; Marla, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 6269; (b) Collins, T. J.; Gordon-Wylies, W. *J. Am. Chem. Soc.* **1989**, *111*, 4511.
30. Boucher, L. J. *J. Inorg. Nucl. Chem.* **1974**, *36*, 531.
31. Chen, D.; Martell, A. E. *Inorg. Chem.* **1987**, *26*, 1026.
32. Trivedi, B. M.; Bhattacharya, P. K.; Ganeshpure, P. A.; Satish, S. *J. Mol. Catal.* **1992**, *75*, 109.