Bis (salicylaldehyde-1, 2-phenylene diimine)Mn(III) chloride (Mn(III)-salophen) catalysed oxidation of thiols to symmetrical disulfides using urea hydrogen peroxide (UHP) as mild and efficient oxidant

Bahador Karami[a]*, Morteza Montazerozohori[a] and Mohammad Hossein Habibi[b]

[a]*Department of Chemistry, Yasouj University, Yasouj 75914-353, Iran*

[b]*Department of Chemistry, Isfahan University, Isfahan 81745-117, Iran*

A variety of thiols were oxidised efficiently by a catalytic amount of Mn(III)-salophen **1** in the presence of urea hydrogen peroxide adduct **2** as a convenient and mild oxidant to afford the corresponding disulfides in high yields in quite short reaction times.

Keywords: Mn(III)-salophen, oxidation, UHP, thiols, disulfides

Disulfides play a crucial role from the synthetic chemical point of view and in biological systems they control the cellular redox potential and prevent oxidative damage.[1,2] In biological systems flavins, cytochromes and dehydroascorbic acid are used as the oxidant for thiol to disulfide conversion. From the view of experimental chemistry, several oxidative methods have been used for the synthesis of disulfides from thiols and protected thiols and these include the use of redox dyes, diazocompounds, sulfoxides, halogens, H_2O_2, $KMnO_4$/$CuSO_4$, DMSO/I_2, sodium perborate, $[Fe_4S_4(SR)_4]^{2-}$ and electrochemical methods.[3] Today chemists are interested in mimicing biological systems because of their high efficiency and mild conditions. In this direction, many efficient enzymatic model systems such as metal porphyrins and metal-tetradentate Schiff base complexes have been used for the oxidation of organic compounds in the presence of various oxidants.[4-10] Metal complexes of salen and salophen ligands 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 mimicing P-450 in various reactions, in their electronic structure and catalytic activity.

Over the past few years, several papers have been published on the use of urea hydrogen peroxide adduct **2** in oxidation reactions because it is an odourless, safe, non-toxic and easy to use white crystalline powder which releases hydrogen peroxide locally on application in many reports. For instance rhenium complex[11] and Ti-(salen) and Co-(salen)[12a] have been used, respectively, for catalytic sulfoxidation and Baeyer-Villiger oxidation of organic compounds using UHP **2** and other hydrogen peroxide adducts as oxidants at 0°C or room temperature. Although manganese Schiff base complexes have been used as biomimetic catalysts in several oxidation methods, further developments of their application in this category of reaction continues to be of importance. Recently we reported oxidation of imines to oxaziridines and nitrones using a UHP **2**/maleic anhydride system.[13] In all of these applications, urea–hydrogen peroxide **2** alone or in combination with a catalyst or organic mediator has been shown to be a mild and efficient oxidant.[14]

In the present paper we report that Mn(III)-salophen **1** is a biomimetic catalyst for the oxidation of thiols to the corresponding disulfides using urea hydrogen peroxide **2** as the single oxygen-donating compound in methanol at 0°C in the presence of imidazole as axial ligand.

Result and discussion

During the search for a good mediator or catalyst that can transfer the active oxygen of UHP **2** to the thiol oxidation systems, we found that Mn(III)-salophen **1** suitably catalyses oxidative coupling of thiols to related disulfides in the presence of UHP **2** as oxidant (Scheme 1). Important factors that were investigated are as follows.

Initial studies were carried out using a co-catalyst such as maleic anhydride for conversion of 4-chlorothiophenol into bis(4-chlorobenzene)disulfide, but maleic anhydride did not have considerable effect on the reaction progress. Also other co-catalysts such as acetic anhydride and trifluoroacetic anhydride showed the same results.

For inspection of the solvent effect, oxidation of 4-chlorothiophenol was performed in different solvents. As shown in Table 1 we found that methanol was the best solvent for our conditions, due to the relatively good solubility of catalyst and starting materials.

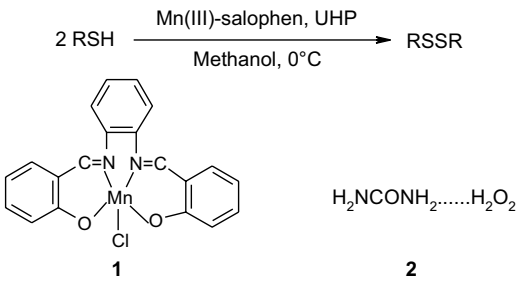
Conversion of thiols into disulfides in the absence of an axial ligand led to very poor yields (below 10%), whereas transformation was almost complete with imidazole as axial ligand. The imidazole was chosen based on the previously studies on the various donor compounds considered as axial ligands.[4-10]

The effect of catalyst amount was investigated using 1/100, 1/50, 1/25 and 1/15 molar ratios of Mn(III)-salophen **1** to substrate on the conversion of 4-chlorothiophenol. The results revealed that a 1/15 molar ratio was optimum and that higher amounts of catalyst had no improved effect on the reaction time. Therefore this molar ratio was applied in all experiments. Also, 1/30 molar ratio of imidazole to substrate (or 1/2 molar

Table 1 Solvent effect on oxidative coupling of 4-chlorothiophenol with Mn(III)-salophen/UHP at 0°C

Solvent	Completion time of reaction/min	
	0°C	RT
CH_2Cl_2	140[a]	140[a]
$CHCl_3$	140[a]	140[a]
CH_3OH	30[b]	30[a]
CH_3CN	60[b]	60[a]

[a]The reaction was not completed within time given.
[b]The reaction was completed within time given.



1 **2**

Scheme 1

* Correspondent. E-mail: karami@mail.yu.ac.ir; karamivk@yahoo.com

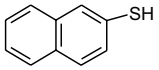
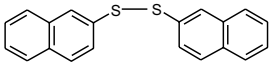
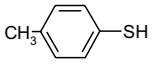
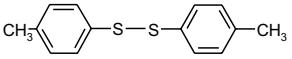
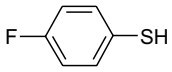
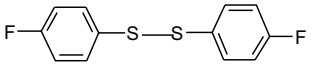
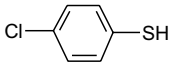
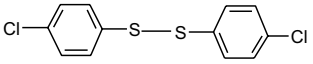
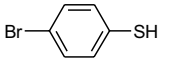
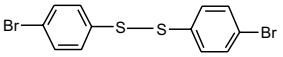
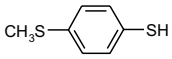
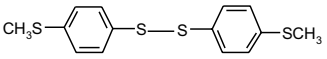
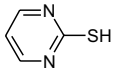
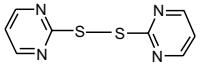
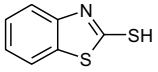
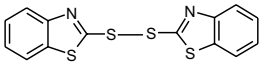
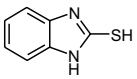
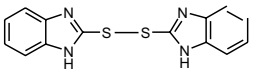
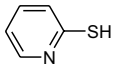
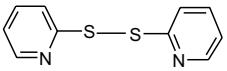
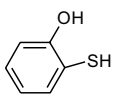
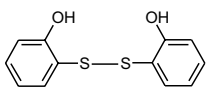
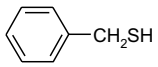
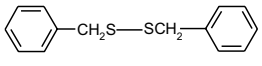
ratio of imidazole to **1**) was obtained as optimum, among the 1/15, 1/30 and 1/45 molar ratios. Based on the literature, oxidation reactions containing UHP **2** as oxidant were done at 0°C, room temperature and, rarely, at reflux. Performance of our experiment in these conditions, showed relatively shorter reaction times at 0°C than at the other temperatures because of the higher efficiency of UHP **2** at 0°C. After the above preliminary consideration of various effects, the results of oxidative coupling of some thiols are summarised in Table 2.

Generally in such systems an oxo-intermediate is considered to be the direct oxidant. Isolation and characterisation of such an oxo-intermediate is difficult but evidence, especially severe colour change of catalyst (light brown to deep brown) during the reaction[10,15] supports the formation of [Mn^{V}(O)-salophen] **4** as the oxo-intermediate in the presence of UHP **2**.

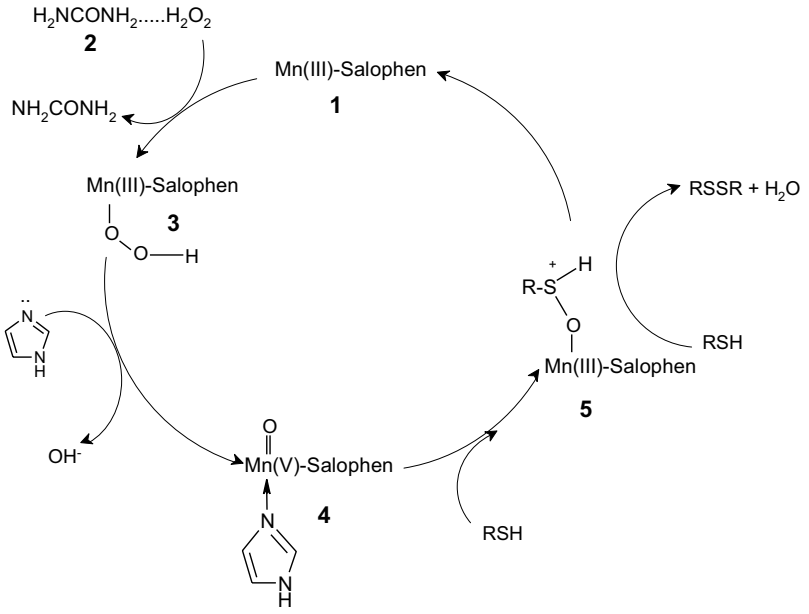
Based on our observations and another reported mechanism,[14] the mechanism shown in Scheme 2 is proposed for the oxidation of thiols under our reaction conditions.

In Scheme 2, Mn (III)-salophen **1** is converted into [Mn^{V}(O)-salophen**]** **4** by H_2O_2 released from urea hydrogen peroxide adduct **2**, and **4** is the direct oxidant that affords a hydroperoxy manganese species **3**. Also hydroperoxy manganese could be

Table 2 Oxidative coupling of thiols using Mn(III)-salophen/UHP at 0°C in methanol

Run	Thiol	Disulfide	Reaction Time/min.	Yield[a]/%	M.P./°C	
					Found	Literature
1			10	90	144–146	142–145 [3d]
2			10	91	43–44	44–45 [3d]
3			60	82	49–51	– [3b]
4			30	90	72–73	70–71 [3d]
5			10	95	90–92	91–93 [3d]
6			20	80	40–43	–[b]
7			60	76	133–135	134–136 [3e]
8			30	65	177–179	177–180*
9			60	63	202–204	202–204 [3f]
10			40	78	55–56	55–57 [3d]
11			40	80	Oil	– [b]
12			20	90	69–71	69–70 [3d]
13	*n*-BuSH	$(n\text{-BuS})_2$	30	85	Oil	Oil [3d]
14	Cyclo-$C_6H_{11}SH$	$(Cyclo\text{-}C_6H_{11}S)_2$	30	83	Oil	Oil [3d]

[a]Refers to isolated yields.
[b]Characterisation (formerly tentative) by mass spectrometry and ^1H NMR.



Scheme 2

considered as the active species without the presence of oxo-compound **4**,[16] but the necessity of an axial ligand for the convenient progress of the reaction (an axial ligand stabilises oxo-intermediate **4)** supports **4** as an important oxidant in our reactions. In the next stage, RSH approaches oxidant species **4** and R–SHO–Mn(III)-salophen **5** is formed that can release sulfenic acid RSOH as a transient intermediate and regenerate Mn(III)-salophen **1**. Reaction of RSOH with another RSH leads to RSSR as a major product with H_2O.

In summary in this paper, we have described a facile, mild and biomimetic synthesis of symmetrical disulfides using catalytic amounts of Mn(III)-salophen **1** in the presence of UHP **2**, a stable, safe and non-toxic oxidant. Several advantages of this method, including the high yields of products, short reaction times, low expense (catalytic amount of Mn(III)-salophen **1**) and ease of isolation of the products make this reaction convenient and efficient.

Experimental

Thiols and other chemicals were purchased from Aldrich, Fluka and Merck. UHP **2** was synthesised according to a previous report.[17] Mn(III)-salophen **1** was prepared by a previously described method.[18]

The reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with those in the literature.[3] IR spectra were recorded on an FT-IR JASCO-680 instrument and the ^{1}H NMR spectra were obtained on a 300 MH_Z Brucker instrument.

Typical experimental procedure: To a solution of 1 mmol (0.1445 g) of 4-chlorothiophenol in 10 ml methanol, 1 mmol (0.0941 g) UHP **2**, 0.067 mmol (0.0168 g) Mn(III)-salophen **1** and 0.033 mmol (0.0022 g) imidazole were added at 0°C. Completion of the oxidation reaction was followed by TLC (*n*-hexane: ethyl acetate, 7:3 and carbon tetrachloride: ethyl acetate, 8:2). After completion of the reaction, the solvent was evaporated under vacuum at room temperature and then 10 ml *n*-hexane/chloroform (9:1) was added and the whole filtered on silica gel. The solvent was removed under vacuum and 0.128 g bis(4-chlorobenzene) disulfide was obtained (90%), m.p. 72–73°C {Lit,[3d] m.p. 71–72°C}.

Spectrosopic identification of product, entry **6**: ^{1}H NMR(d_6-DMSO): 7.11(m, *J** = 8 Hz, 4H), 6.81 (m, *J** = 8 Hz, 4H), 2.91(s, 6H) ppm [for AA'XX' system $J^* = J_{23} + J_{25}$].

Mass (*m/z*): 155, 157, 310, 311, 312.

Spectroscopic identification of product, entry **11**: ^{1}H NMR ($CDCl_3$): 7.4(dd, 2H, *J* = 7.1, 3.5 Hz), 7.2(m, 2H), 6.9(m, 2H), 6.8(dd, 2H, *J* = 6.2, 3.1 Hz), 6.2(bs, 2H) ppm.

Mass (*m/z*): 125, 127, 250, 251, 252.

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