

Selective Oxidation of Thiols to Disulfides Catalyzed by Iron(III) – Tetra Phenyl Porphyrin Using Urea-Hydrogen Peroxide as Oxidizing Reagent

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Oxidation of thiols to disulfides catalyzed by iron(III) - tetra phenyl porphyrin Fe (TPP)Cl was investigated using urea-hydrogen peroxide adduct (UHP) as an oxidant in methanol as a solvent.

Key Words: Thiols, Fe (TPP) Cl, Urea hydrogen peroxide, disulfides.

Introduction

Conversion of thiols to disulfides is important from both biological and synthetic points of view¹⁻². In biological systems, thiols are oxidized by flavins, cytochromes and dehydroascorbic acid to control the cellular redox potential and prevent oxidative damage³⁻⁵. On the other hand, disulfides are important reagents in organic synthesis and can be used to prepare sulfinyl and sulfenyl compounds⁶⁻⁸. Several methods based on oxidative S-S coupling have already been reported⁹⁻³³. Some of these methods suffer from disadvantages such as long reaction times, limited availability of oxidant, toxicity of reagents and isolation of products. Therefore, the introduction of readily available, safe and stable reagents for oxidation of thiols to disulfides is still a necessity.

Today the development of an efficient model system resembling the activity of cytochrome P-450 has been one of the areas of most intense research activity³⁴⁻³⁵. Many metalloporphyrin complexes, mainly iron and manganese, proved to be able to catalyze oxidation reactions. Among the more biologically significant of these processes are *O*- and *N*-dealkylation³⁶, olefin and arene epoxidation³⁷⁻³⁸, alkane hydroxylation³⁹⁻⁴⁰, oxidation of nitroso⁴¹ and primary aromatic amines to nitro derivatives⁴². Various single oxygen-atom donors such as PhIO, ClO⁻, H₂O₂ or IO₄⁻ have been used for these transformations⁴³⁻⁵⁰. High yields and rates

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have been obtained with these biomimetic systems, making them useful for complete conversion of various substrates and potentially useful preparative oxidations in organic chemistry.

In the present paper we report iron(III) - tetra phenyl porphyrin **1** as a biomimetic catalyst for the oxidation of thiols to corresponding disulfides using urea hydrogen peroxide as a single oxygen donating compound. We have chosen urea hydrogen peroxide adduct **2** because it has been used as an odorless, safe, non-toxic and easy to use white crystalline powder that releases hydrogen peroxide locally on application in many reports. Over the past few years, several papers have been published on the use of urea hydrogen peroxide adduct **2** in oxidation reactions such as Baeyer-Villiger oxidation of ketones^{51–52}, oxidation of sulfides to sulfones⁵³, oxidation of aromatic aldehydes⁵⁴ and epoxidation of alkenes^{55–56}. Recently we reported the oxidation of imines to oxaziridines and nitrones using UHP **2** / maleic anhydride system⁵⁷. In these application, a urea-hydrogen peroxide **2** alone or in combination with carboxylic acid or anhydride as catalyst (rarely inorganic complex as co-catalyst) was produced as a mild and efficient oxidant^{58–59}.

Results and Discussion

Urea hydrogen peroxide (UHP) **2** as mentioned above has an active available oxygen content that can be used for different oxidation systems. Among the organic compounds, carboxylic acid or anhydrides have been used as a good mediator for the transfer of the active oxygen in these systems^{58–59}. Among the inorganic catalysts, metal Schiff-base complexes have been used widely as efficient catalysts for the oxidation of various substrates with hydrogen peroxide. For example, a Ti-(salen) catalyzed sulfoxidation reaction with UHP **2** in methanol at 0 °C⁶⁰ and cationic Co(III)-salen was used for Baeyer-Villiger oxidation in the presence of various hydrogen peroxide derivatives as oxidant in CH₂Cl₂ at room temperature⁶¹. An organic mediator such as maleic anhydride was required as co-catalyst for efficient epoxidation of alkenes in the presence of a Fe(TPP)Cl **1**/UHP system^{58–59}. During the search for a good mediator or catalyst that can transfer the active oxygen of UHP **2** to thiol oxidation systems, we found that Fe(TPP)Cl **1** suitably catalyzed oxidation of thiols to related disulfides in the presence of UHP **2** as oxidant (Figure 1).

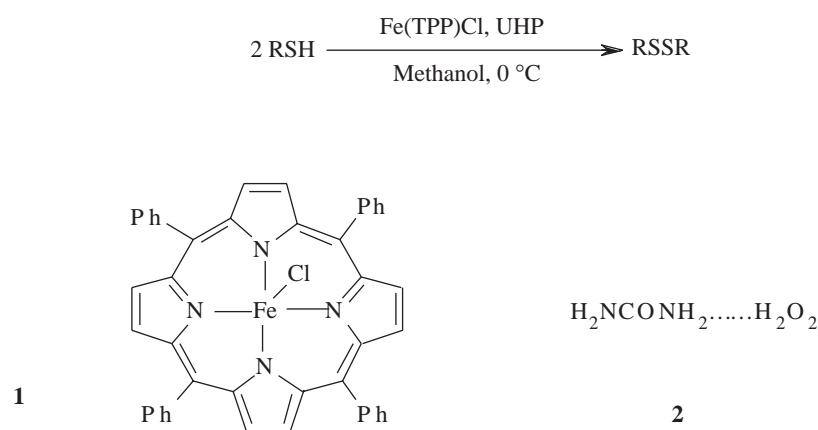


Figure 1

Initial studies were carried out on the exigency of a co-catalyst such as maleic anhydride on the conversion of 4-chlorothiophenol to bis (4-chlorobenzene) disulfide, but maleic anhydride did not have a considerable effect on the reaction's progress.

To study the effect of solvent, oxidation of 4-chlorothiophenol was performed in different solvents. As shown in Table 1, methanol is the best solvent due to the relatively good solubility of the catalyst and starting materials.

Table 1. Solvent effect on oxidative coupling of 4-chlorothiophenol with Fe (TPP) Cl/UHP at 0 °C.

Solvent	Completion time of reaction [min]	
	0 °C	RT
CH ₂ Cl ₂	100 ^a	140 ^a
CHCl ₃	100 ^a	140 ^a
CH ₃ OH	20 ^b	30 ^a
CH ₃ CN	60 ^b	60 ^a

^aThe reaction was not completed within time

^bThe reaction was completed within the time

Following the investigation of the axial ligand effect on catalyst activity, it was interesting that the absence or presence of the axial ligand on Fe (TPP) Cl **1** catalyst did not have a considerable effect on the conversion of thiols to disulfides. We suggest that the urea released during the progress of the reaction acts as an axial ligand.

The effect of catalyst amount was investigated using 1/100, 1/50, 1/25 and 1/15 molar ratios of Fe(TPP)Cl **1** in the conversion of 4-chlorothiophenol. The results revealed that a 1/50 molar ratio was optimum and a higher amount of catalyst did not have any effect on the completion of the reaction. The performance of our experiment showed relatively shorter reaction times at 0 °C. With above preliminary consideration of various effects, the results of oxidative coupling of some thiols are summarized in Table 2.

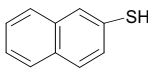
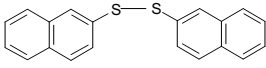
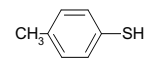
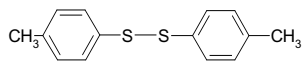
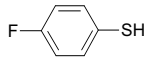
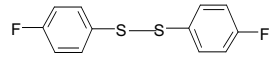
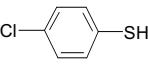
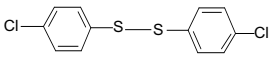
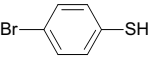
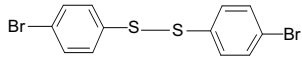
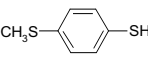
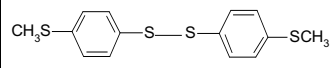
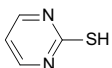
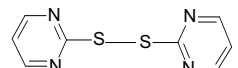
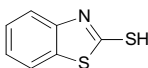
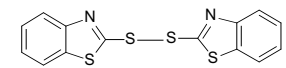
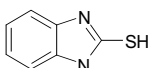
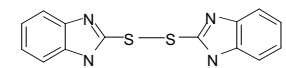
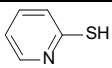
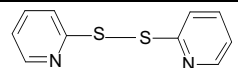
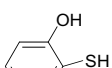
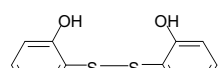
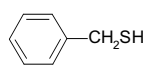
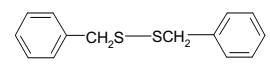
Entries 6-11 (Table 2) have 2 or more positions for the catalytic oxidation system. The thiols of entries 6 and 8 could undergo sulfoxidation or S-S oxidative coupling but the results showed that only S-S coupling occurred. Therefore the thiols of entries 7-10 could be subjected to the *N*-oxidation reaction but we obtained only corresponding disulfides. Therefore we think, in such cases this catalytic system in our conditions runs the selective oxidation of the SH-position of the thiols only to corresponding disulfides.

Generally in such systems the oxo-intermediate is considered a direct oxidant. Isolation and characterization of the oxo-intermediate is difficult but evidence, especially the severe color change of the catalyst during the reaction⁶²⁻⁶³, supports formation of [Fe^V(O)-TPP] **4** as oxo- intermediate in the presence of UHP **2**.

To pay attention to this evidence and other reported mechanisms⁵⁸⁻⁵⁹, the mechanism shown in Figure 2 is proposed for the oxidation of thiols.

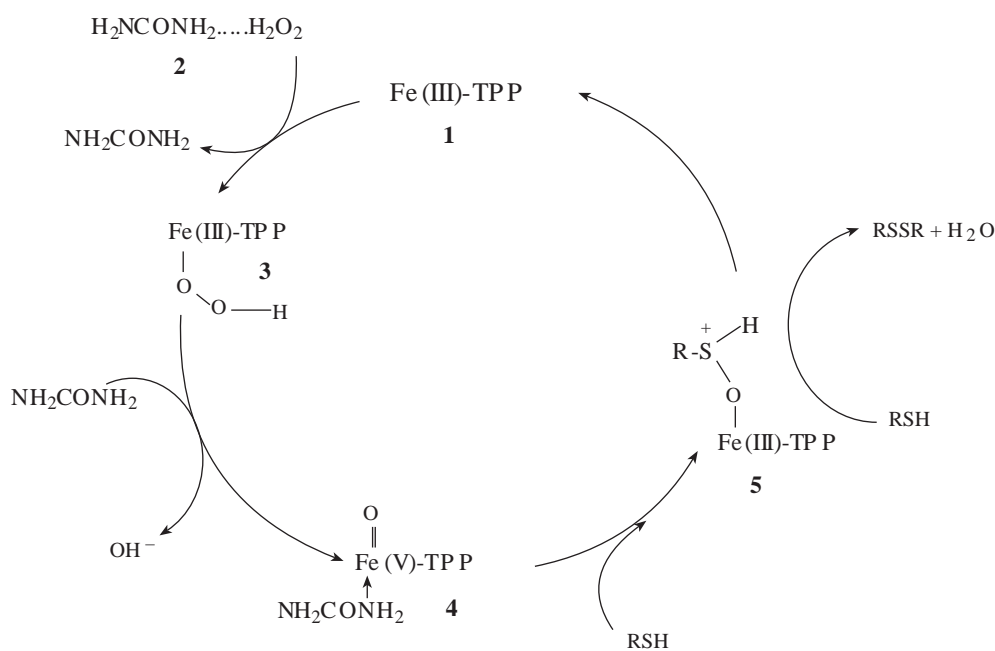
In Figure 2, Fe(TPP)Cl **1** is converted to hydroperoxy iron(III) porphyrin species **3** by H₂O₂ released from urea hydrogen peroxide adduct **2**; then with the entrance of urea as axial ligand, [Fe^V(O)-TPP] **4** is formed as a direct oxidant. However, hydroperoxy iron(III) porphyrin **3** can be assumed as the active species without the presence of oxo-compound **4**. In the next stage, RSH approaches oxidant species **4** and R-SHO-Fe (TPP) Cl is formed, which can release sulfenic acid RSOH as transient intermediate and regenerated Fe (TPP) Cl **1**. The reaction of RSOH with another RSH leads to RSSR. In another suggestion, it can be assumed that RSH is substituted at sulfur in the R SO⁺ HFe (TPP) Cl **5** to form RSSR, H₂O and **3**.

Table 2. Oxidative coupling of thiols using Fe (TPP) Cl/ 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 ⁹
2			10	91	43-44	44-45 ⁹
3			60	75	49-51	- ¹⁰
4			20	90	72-73	70-71 ⁹
5			10	95	90-92	91-93 ⁹
6			20	80	40-43	-**
7			30	82	133-135	134-136 ¹¹
8			90	65	177-179	177-180*
9			90	60	202-204	202-204 ¹²
10			40	80	55-56	55-57 ⁹
11			40	80	99-102	-**
12			20	90	69-71	69-70 ⁹

^a Refer to isolated yields. * Chemical and Reagents 2005-2007 Merck.

^{**} Identified with Mass and ¹H-NMR.


Figure 2

Conclusions

In this paper, we have described a facile, mild and biomimetic synthesis of symmetric disulfides using catalytic amounts of Fe (TPP) Cl **1** as a biotic model catalyst in the presence of UHP **2** as a stable, safe and non-toxic oxidant. The several advantages of this method, including high yields of products, short reaction times, inexpensive [catalytic amount of Fe(TPP)Cl **1** and non-necessity of axial ligand] and ease of isolation of products, make this reaction convenient and efficient.

Experimental Section General. Thiols and other chemicals were purchased from Aldrich, Fluka and Merck. UHP **2** was synthesized according to a previous report⁶¹. Fe (TPP) Cl **1** was prepared as previously described^{62–65}.

The reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with authentic samples prepared according to a previous method.^{9–12,14,66–67} IR spectra were recorded on FT-IR Jasco-680 and the ¹H-NMR spectra were obtained on a Bruker instrument 300 MHz model.

Typical experimental procedure. To a solution of 1 mmol (0.1445 g) of 4-chlorothiophenol in 10 mL of methanol were added 1 mmol (0.0941 g) of UHP **2** and 0.02 mmol (0.0141 g) of Fe (TPP) Cl **1** at 0 °C. Completion of 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 of n-hexane/chloroform (9:1) was added and filtered on silica gel. The solvent was removed under vacuum and 0.128 g of bis (4-dichlorobenzene) disulfide was obtained (90%), mp 72-73 °C {Lit.^{11d} mp 71-72 °C}.

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