# A Waste-Free and Highly Effective Catalytic System for the Oxidation of Cysteine to Cystine

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Abstract A new three-component catalytic system, water/ionic liquid/metal phthalocyanine complex, was studied for the oxidition of cysteine to prepare cystine. It was found that the water/ 1-n-hexyl-3-methylimidazolium tetrafluoroborate ([hmim][BF<sub>4</sub>])/iron (II) phthalocyanine (Fe<sup>II</sup>Pc) system exhibited an excellent catalytic activity in the oxidition of cysteine. Cystine was obtained with 98% isolated yield in 12 h at the temperature of 80 °C. Further more, the catalytic system can be easily recovered and recycled in the following run without apparent reduction in catalytic activity.

Keywords Cysteine · Cystine · Ionic liquid · Metal phthalocyanine · Oxidation

## 1 Introduction

The highly selective oxidation is one of the major challenges in the synthesis of fine chemicals and intermediates [1]. The oxidation of cysteine to cystine is a fundamentally important laboratory and commercial procedure. Cystine, an important disulfide in biological chemistry, plays multiple roles in biochemical processes, including protecting cells against oxidative stress, maintaining cellular redox potentials and regulating metabolism and gene expression [2, 3]. Cysteine, one of the essential (R)-amino acids and one of the simplest biological thiols, can undergo oxidation

Cysteine, cystine, iron (II) phthalocyanine (Fe<sup>II</sup>Pc), iron (III) phthalocyanine (Fe<sup>III</sup>Pc), copper (II) phthalocyanine (Cu<sup>II</sup>Pc) and other reagents were of analytical reagent grade, purchased from Shanghai Chemical Reagent Co,.

either by metal ions or by nonmetallic oxidants to form the corresponding sulfinic acid or disulfide, depending on the oxidative capabilities of the oxidants. The selective oxidation of cysteine to cystine is conventionally carried out with stoichiometric amounts of metal ions such as  $[Fe^{III}(bpy)_2(CN)_2]^+[4], [Ir^{IV}Cl_6]^{2-}[5], [Co^{III}W_{12}O_{40}]^{5-}[6],$  $[Fe^{III}(CN)_6]^{3-}[7], [Co_2(CN)_{10}(O)_2]^{5-}[8], etc.$  From both economical and environmental points of view, the highly selective catalytic oxidation process that uses clean, inexpensive oxidants, e.g. molecular oxygen, for converting cysteine to cystine on an industrial scale has become an important objective for chemists. We herein report a novel homogeneous-heterogeneous catalysis process controlled by temperature for the oxidation of systeine to cystine with the high selectivity (Scheme 1). In the process, a catalytic system comprising Fe<sup>II</sup>Pc (Fig. 1a), water and the ionic liquid [hmim][BF<sub>4</sub>] (Fig. 1b) is employed, which is a homogeneous phase above 80 °C and turns into a heterogeneous phase at room temperature. Therefore, this catalytic system possesses the advantages of both homogeneous and heterogeneous catalytic reaction. The cystine can be isolated in a yield of 98% under moderate reaction conditions. Moreover, the catalytic system can be easily recovered and reused without apparent reduction in catalytic

activity. 2 Experimental

<sup>2.1</sup> Materials

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Fig. 1 The structure of FePc (a) and [hmim][BF<sub>4</sub>] (b)

Ltd and were used without further purification. 1-n-hexyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl) imide ([hmim][Tf<sub>2</sub>N]), 1-n-hexyl-3-methylimidazolium tetrafluoroborate ([hmim][BF<sub>4</sub>]), 1-n-decyl-3-methylimidazolium tetrafluoroborate ([dmim][BF<sub>4</sub>]), were synthesized according to the procedures reported in previous literatures [9, 10].

### 2.2 General Procedure

The oxidation of cysteine was carried out in an airproof stainless steel reactor (200 mL in volume) with a magnetic stirrer. In a representative reaction procedure, 0.242 g cysteine (2.0 mmol dissolved in 4 mL water) and 0.01 g FePc (dissolved in 1.0 g [hmim][ $BF_4$ ]) were charged into the autoclave respectively. Then the reactor was pressurized with oxygen (2.0 MPa) and the reaction system was stirred vigorously at 80 °C for 12 h. At the end of the reaction, the reactor was cooled to the ambient temperature and depressurized. A white solid was obtained by filtering, washing with distilled water and absolute ethanol, and drying overnight in vacuum at 40 °C. The product was identified by infrared spectroscopy, mass spectrometry and melting point measurement compared with authentic commercial samples. The catalytic system is easily separated by filtration and reused in the following run. Such procedure for the oxidation of cysteine can be described in Fig. 2.

#### **3** Results and Discussion

It is well-known that molecular oxygen can be catalytically activated by transition metal phthalocyanine complexes



Fig. 2 The schematic representation of the catalytic system for aerobic oxidation of cysteine. Obviously, this process can facilitate the separation and purification of the product, the recovering and recycling of the catalyst and heightening the catalytic performance of the catalysts

[11–17]. However, the parent metal phthalocyanine complexes are less soluble in water and common organic solvents, which limit their application in catalysis [18]. To overcome this problem, the introduction of substituents at the periphery of the molecule has to be employed to make the phthalocyanine complexes soluble and suitable for homogeneous catalysis. And heterogeneous catalysts may be obtained by dispersion and fixation of phthalocyanine complexes onto different supports. However, these supported catalysts often suffer from drawbacks such as easily oxidative degradation under oxidation conditions and lower stability under higher temperatures [19, 20]. Thus there has been a growing demand for the development of fundamentally new and environmentally benign catalysis systems using metal phthalocyanine complexes as catalysts suitable for the industrial scale under moderate conditions with higher selectivity. Herein, the ionic liquid-water liquid-liquid system exhibits the fascinating characters. The controllable transformation between homogeneous and heterogeneous phase can be realized by changing temperature of the system. The metal phthalocyanine complex is dissolved in the homogeneous phase of ionic liquid-water mixture at high reaction temperature (80 °C), and in the ionic liquid phase of the ionic liquid-water heterogeneous phase system at low temperature (room temperature). The cysteine is soluble in water and homogeneous phase of ionic liquid-water and insoluble in ionic liquid phase. The product of reaction, cystine, is an undissolvable solid in these liquids (Fig. 2). So the reaction system comprises two phases, i.e., the aqueous solution of cysteine and the ionic liquid solution of the metal phthalocyanine complex before which is heated (Fig. 2a). Under heating and vigorous stirring, two parts are gradually blended into a homogeneous phase as described in Fig. 2b. The cysteine molecules fully contact the catalyst and oxygen in the homogeneous phase solution, which leads to effective oxidation of cysteine to cystine. In the course of the reaction, the cystine sinks to the bottom of the reactor as soon as it is produced. Thus, not only is the product easily separated but also the over-oxidation of the cystine is limited, and the higher selectivity for cystine can be obtained. At the end of reaction, the homogeneous system turns into three-layer heterogeneous system at ambient temperature. The top layer is the aqueous solution containing residue cysteine, the bottom layer is the product cystine, and the middle layer is the ionic liquid solution of the metal phthalocyanine complex (Fig. 2c).

To characterize behaviors of the catalytic system, the catalytic activities of the phthalocyanine complexes with central Fe<sup>3+</sup>, Fe<sup>2+</sup> and Cu<sup>2+</sup> cations were investigated in a water-ionic liquid [hmim][BF<sub>4</sub>] system, and the results were summarized in Table 1. The high yields of cystine were gotten in all the cases. However, the catalytic system containing Fe<sup>II</sup>Pc possessed the highest activity among them (entries 1–3 in Table 1). The previous investigations indicate that the active oxo-bridged intermediate of  $\mu$ -oxo Fe<sup>III</sup>Pc was produced in the oxidation system containing the Fe<sup>II</sup>Pc as catalyst and molecular oxygen as oxidant. However, in the same system, the active intermediate of  $O = Fe^{IV}Pc$  was produced when the  $Fe^{III}Pc$  was used as catalyst [21, 22]. The different catalytic efficiency among the phthalocyanine complexes in the reaction system reported herein may be ascribed to the different intermediates. This result indicated that the oxidation states and kinds of the central metal ions in the phthalocyanine complexes had some impact on the catalytic performance. The experimental results for influence of the amounts of catalyst on the reaction testified that the reaction yield increased as increasing the amount of catalyst and finally

Table 1 The oxidation of cysteine to cystine

Entry	Ionic liquid (g)	Catalyst (mg)	P(O <sub>2</sub> )(MPa)	Isolated yield (%)
1	[hmim][BF <sub>4</sub> ](1.0)	Fe <sup>II</sup> Pc(10.0)	2.0	98.0
2	[hmim][BF <sub>4</sub> ] (1.0)	Fe <sup>III</sup> Pc(10.0)	2.0	88.7
3	[hmim][BF <sub>4</sub> ] (1.0)	Cu <sup>II</sup> Pc(10.0)	2.0	82.3
4	[hmim][BF <sub>4</sub> ] (1.0)	Fe <sup>II</sup> Pc(15.0)	2.0	98.1
5	[hmim][BF <sub>4</sub> ] (1.0)	Fe <sup>II</sup> Pc (5.0)	2.0	70.1
6	[hmim][BF <sub>4</sub> ] (1.0)	Fe <sup>II</sup> Pc(10.0)	2.5	98.2
7	[hmim][BF <sub>4</sub> ] (1.0)	Fe <sup>II</sup> Pc(10.0)	1.5	83.5
8	[hmim][Tf <sub>2</sub> N] (1.0)	Fe <sup>II</sup> Pc(10.0)	2.0	22.7
9	[dmim][BF <sub>4</sub> ] (1.0)	Fe <sup>II</sup> Pc(10.0)	2.0	32.4
10	No ionic liquid	Fe <sup>II</sup> Pc(10.0)	2.0	13.5
11 <sup>a</sup>	[hmim][BF <sub>4</sub> ] (1.0)	Fe <sup>II</sup> Pc(10.0)	2.0	96.4

The reactions were carried out with 0.242 g cysteine (2.0 mmol) (dissolved in 4 mL water) at 80  $^\circ C$  for 12 h

<sup>a</sup> Reused at the 6th time

approached to the invariant (entries 1, 4-5). The results in entries 1, 6–7 in Table 1 illustrated that the yield of cystine evidently increased with the increase of oxygen pressure below 2.0 MPa and its change was unobvious when oxygen pressure was further increased above 2.0 MPa. The yield of cystine increased by only 0.2% when the oxygen pressure increased from 2.0 to 2.5 MPa. This may be because the dissolved amount of the oxygen in the reaction medium almost reached the maximum under 2.0 MPa and the extra increase in the pressure of oxygen had less effect on the concentration of oxygen. As shown in entries 1, 8-10, the ionic liquid played an important role in the highly effective oxidation reaction of cysteine and the best result was obtained by using [hmim][BF<sub>4</sub>] as an ionic liquid phase. It may be ascribed to that [hmim][Tf<sub>2</sub>N] and [dmim][BF<sub>4</sub>] were water-immiscible and [hmim][BF4] was water-miscible at/above 80 °C. The possibility of recycling of the aqueous-ionic liquid catalyst system was also examined. After the product was separated from the reaction system at the end of each reaction, the used catalytic system was recharged with cysteine into the reactor and the reaction was conducted once again. The isolated yield of 96.4% was maintained after the aqueous-ionic liquid catalyst system was repeatedly used for 6 times (entry 11).

#### 4 Conclusion

A novel method was established in this work to obtain cystine by the oxidation of cysteine in the water-ionic liquid catalytic system containing the metal phthalocyanine complexes. The method possesses several advantages as follows: (1) It is a very clean process without production of the wastes; (2) The procedure is simple and easy for the separation of the catalytic system and the product by simple filtration; (3) The catalytic system is highly effective and to be easily recycled. So this is an organic synthesis process conforming to the fundamental principles of green chemistry and can provide a novel way to prepare cystine in chemical industry.

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#### References

- Sheldon RA, Kochi JK (1981) Metal-catalyzed oxidations of organic compounds. Academic Press, New York
- Jacob C, Giles GI, Giles NM, Sies H (2003) Angew Chem Int Ed 42:4742–4758
- 3. Hand CE, Honek JF (2005) J Nat Prod 68:293–308
- 4. Wang X, Stanbury DM (2008) Inorg Chem 47:1224-1236

- 6. Ayoko GA, Olatunji MA (1983) Polyhedron 2:577-582
- Bridgart GJ, Fuller MW, Wilson IR (1973) Dalton Trans 1274– 1280
- Ghosh SK, Saha SK, Ghosh MC, Bose RN, Reed JW, Gould ES (1992) Inorg Chem 31:3358–3362
- 9. Huddleston JG, Visser AE, Reichert WM, Willauer HD, Broker GA, Rogers RD (2001) Green Chem 3:156–164
- 10. Fadeev AG, Meagher MM (2001) Chem Commun 295
- 11. Hassanein M, Abdo M, Gerges S (2008) J Mol Catal A Chem 287:53–56
- Shaabani A, Farhangi E, Rahmati A (2008) Appl Catal A Gen 338:14–19
- 13. Murahashi S, Zhou XG, Komiya N (2003) Synlett 3:321-324

- 14. Sharma VB, Jain SL, Sain B (2003) Tetrahedron Lett 44:383-386
- 15. Villemin D, Hammadi M, Hachemi M (2002) Synth Commun 32:1501–1515
- Sorokin AB, Mangematin S, Pergrale C (2002) J Mol Catal A Chem 182:267–281
- Woltinger J, Backvall JE, Zsigmond A (1999) Chem Eur J 5:1460–1467
- 18. Alexande B, Sorokin AT (2000) Catal Today 57:45-59
- Chauhan SMS, Kumar A, Srinivas KA (2003) Chem Commun 2348–2349
- 20. Ebadi A, Safari N, Peyrovi MH (2007) Appl Catal A Gen 321:135-139
- 21. Monacelli F, Viola E (2006) J Porph Phtha 10:13-21
- 22. Chen MJ, Fremgen DE, Rathke JW (1998) J Porph Phtha 2: 473–482