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## Electrochimica Acta



# A homogeneous redox catalytic process for the paired synthesis of L-cysteine and L-cysteic acid from L-cystine

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#### ARTICLE INFO

Article history: Received 21 March 2011 Received in revised form 29 July 2011 Accepted 15 August 2011 Available online 9 September 2011

Keywords: L-Cystine L-Cysteine hydrochloride monohydrate L-Cysteic acid Cyclic voltammetry Paired electrolysis Redox catalyst

#### ABSTRACT

Redox catalytic process involved in the paired electrosynthesis of L-cysteine and L-cysteic acid from L-cystine is investigated by cyclic voltammetric technique and also confirmed by preparative electrolysis. The cyclic voltammetric behaviour shows that in the catholyte, in situ deposited tin (Sn) surface acts as a redox catalyst for the electro-reduction of L-cystine to L-cysteine whereas in the anolyte, the electro-generated bromine acts as a homogeneous redox mediator to enhance the electro-oxidation of L-cystine. L-Cysteine hydrochloride monohydrate (L-cysteine) and L-cysteic acid are prepared from L-cystine by preparative electrolysis with high purity and high yield using graphite cathode and DSA anode. At optimum concentration of L-cystine with 1:1 concentration ratio (catholyte:anolyte), the material yield obtained for L-cysteine is above 80% and that for L-cysteic acid is close to 60% in the paired electrosynthesis process in the batch operation. Scope for further experiments in conversion efficiency is also discussed. © 2011 Elsevier Ltd. All rights reserved.

#### 1. Introduction

Electrochemical synthesis of L-cytseine hydrochloride monohydrate (L-cysteine) by the electrochemical reduction of L-cystine is a well known commercial process [1]. However detailed investigations for understanding the reaction mechanism and improving process efficiency are still in progress. In 1994, Ralph et al. have reviewed the thermodynamic and kinetic aspects of L-cystine hydrochloride related redox processes [2]. The influence of electrodes and electrolytes on the electroreduction process efficiency was also evaluated [3]. Mercury plated copper and lead are some of the recommended cathode material for the commercial batch cell operation [4]. A flow cell process [5] and voltammetric reduction at mercury drop electrode [6] have also been reported by the same group. Hydrogen oxidation on a gas diffusion electrode has been proposed as the counter electrode reaction to achieve lower energy consumption [7].

Chemical oxidation of disulfides like L-cystine to L-cysteic acid by bromine and other oxidising agents is a well known commercial process [8,9]. In commercial electrosynthetic processes, pairing electrode processes has always been important. A range of paired electrode processes and their benefits and challenges in electrosynthesis were discussed [10,11]. In 1991, some preliminary experimental details of paired synthesis of the electrochemical oxidation of cystine in the anode compartment and electroreduction of the same compound in the cathode compartment were reported. 2M HCl and 3.9M HBr were used as the catholyte and anolyte respectively. 3D carbon material served as the anode as well as cathode. The overall efficiency claimed was around 70%. [12]. Though higher efficiency is claimed in a recent report of this paired synthesis [13], no further details on the process modification which led to such an improvement are available. Further basic studies as well as process optimization studies are required to develop this interesting process.

There is a considerable scope for improving the cathodic reduction as well as anodic processes individually. For example, though the cathodic process is efficient it employs Pd or mercury plated cathodes which require replacement. The anodic process efficiency itself needs to be established and improved further to achieve overall efficiency of the paired synthesis. The possibility of using simple commercially available electrodes like graphite cathode and DSA anode with additional redox mediators if necessary may also be looked into (Scheme 1).

The main objective of the present work is to study the voltammetric behaviour of L-cystine reduction as well as oxidation on glassy carbon electrode. The catalytic effect of  $SnCl_2$  salt on the cathodic reduction process is studied in detail. A few galvanostatic preparative experiments to establish the usability of graphite cathode with  $SnCl_2$  additive and DSA anode in the paired synthesis are also reported.





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<sup>0013-4686/\$ -</sup> see front matter © 2011 Elsevier Ltd. All rights reserved. doi:10.1016/j.electacta.2011.08.052



Scheme 1. Oxidation and reduction reaction of L-cystine.

#### 2. Experimental

#### 2.1. Cyclic voltammetric experiments

Cyclic voltammetric measurements were done using BAS IM6 Electrochemical Analyser (USA). In a three electrode undivided glass cell, glassy carbon (3 mm diameter), platinum foil and an aqueous saturated calomel electrode (SCE) served as working, counter and reference electrodes respectively. The cyclic voltammograms were recorded on Thales 3.18-USB software. Prior to the experiments, glassy carbon was polished with 4/0 emery sheets using alumina gel (0.05  $\mu$ m) and washed with distilled water. Further the electrode was sonicated for 5 min to remove adsorbed alumina. The test solutions were deaerated at least 30 min with N<sub>2</sub> before the start of the experiment to eliminate interfering oxygen. Reduction of L-cystine was carried out in HCl solution by adding a catalytic amount of stannous chloride. L-cystine oxidation was investigated in sulphuric acid medium with 10 mM HBr as catalytic additive. All experiments were performed at room temperature.

#### 2.2. Electrolysis of L-cystine

Galvanostatic electrolysis was conducted in a divided cell made up of PVC with 150ml capacity of catholyte and anolyte reservoirs separated by a proton permeable Nafion 324 membrane. A DC power supply was used for this constant current electrolysis. Graphite (surface area 18.6 cm<sup>2</sup>) and dimensionally stable anode (DSA) (surface area 11 cm<sup>2</sup>) were used as the cathode and anode respectively. DSA is a titanium substrate coated with titanium oxide and ruthenium oxide [14]. Potential was measured with SCE using externally connected multimeter. All the experiments were performed at room temperature. Both electrolyte solutions were kept at constant stirring (600 rpm) under a mechanical stirrer.

Electrochemical reduction was performed with L-cystine in 2 M HCl catholyte and 2 M HCl anolyte. Reduction was carried out without or by adding a small amount of  $SnCl_2$  (5 g/L) in to the catholyte solution. The reduction of L-cystine was monitored using UV-vis Spectrophotometer. Decreasing absorbance of L-cystine at 320 nm was the indication of the progress of the reaction, as shown in Fig. 1. After completion of electrolysis the catholyte solution was distilled under reduced pressure up to half of its initial volume and white crystalline product was obtained by cooling at 0–5 °C.

In the electrochemical oxidation, the anolyte composition was an aqueous solution of 3.9 M HBr and L-cystine. The end point of oxidation reaction was determined by the appearance of slight brown colour due to bromine evolution. UV–vis Spectrophotometer also shows a broad absorbance of the anolyte with a sharp peak at 420 nm (Fig. 2) due to excess generation of bromine. Anolyte solution was distilled to dryness and the residue cooled at 0–5 °C after adding chilled methanol to obtain white crystals of the oxidised product.

In paired electrolysis, reduction and oxidation was carried out in 2 M HCl and 3.9 M HBr as catholyte and anolyte respectively. A catalytic amount stannous chloride was added to the



**Fig. 1.** UV spectral monitoring of catholyte solution during the electroreduction of L-cystine at different intervals of time (a) 0, (b) 30, (c) 60, (d) 90 and (e) 120 min.

catholyte solution. Concentration ratio of L-cystine in the anolyte and catholyte compartment was varied. The end point was the excess generation bromine in the anolyte, which is monitored by UV-vis Spectrophotometer. Products from the catholyte and anolyte were separated using the above mentioned procedure. Purity of the compound was obtained from HPLC using a Shimpack ODS-18 column (125 mm  $\times$  4.5 mm) as stationary phase and the mobile phase consisted of 1% phosphoric acid buffer with 3% acetonitrile in water at a flow rate of 1 ml/min. Samples were analysed at a wavelength of 220 nm with a UV detector. Authentic samples were used to calculate the peak areas of corresponding



**Fig. 2.** UV spectral monitoring of anolyte solution during the electrooxidation of L-cystine at different intervals of time (a) 0, (b) 60, (c) 90 and (d) 120 min.



**Fig. 3.** Cyclic voltammograms of L-cystine reduction at glassy carbon electrode surface (a) 0.5 M HCl, (b) 10 mM L-cystine in 0.5 M HCl, (c) 4 mM SnCl<sub>2</sub> 0.5 M HCl and (d) 4 mM SnCl<sub>2</sub> 0.5 M HCl with different concentrations of L-cystine (i) 10 mM, (ii) 20 mM, (iii) 30 mM.

experimental products for yield calculations. Product was confirmed by NMR and FT-IR.

Data for L-cysteine HCl·H<sub>2</sub>O: <sup>1</sup>H NMR (CDCl<sub>3</sub>, Bruker-Biospin 400 MHz, (H) 4.221 (*t*,1H), 3.02,2.995 (CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, Bruker-Biospin 400 MHz, (C) 170.4 (C), 54.37 (CH), 23.88 (CH<sub>2</sub>). FT-IR (KBr):  $\upsilon$ =2551.3 cm<sup>-1</sup>(S-H bond), 1742.3 cm<sup>-1</sup>( $\alpha$ -amino acid hydrochloride).

Data for L-Cysteic acid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, Bruker-Biospin 400 MHz, (H) 4.356 (*t*,1H), 3.02,2.995 (CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, Bruker-Biospin 400 MHz, (C) 169.64 (C), 49.67 (CH), 49.09 (CH<sub>2</sub>). FT-IR (KBr):  $\upsilon$ =1126.7 cm<sup>-1</sup> (hydrated sulphonium salt), 870–840 cm<sup>-1</sup> (CH<sub>2</sub> rocking).

#### 3. Results and discussion

#### 3.1. Voltammetric studies

For electrochemical synthesis, it was proposed to employ graphite as cathode and DSA as anode. To understand the electrochemical process and role of catalyst employed, some basic voltammetric investigations were carried out on glassy carbon electrode.

Typical background current obtained in the cathodic direction on glassy carbon electrode in 0.5 M HCl is presented in Fig. 3a. It is noted that significant increase in background current due to the hydrogen evolution is observed only beyond -0.9 V vs SCE (Fig. 3b). In presence of 10 mM L-cystine gives a distinct reduction peak around -0.7 V vs SCE. Addition of 4 mM stannous chloride alone in 0.5 M HCl gives a reduction peaks around -0.6 V vs SCE (Fig. 3c) due to the electrodeposition of tin on to glassy carbon electrode as shown in Eq. (1).

$$\mathrm{Sn}^{2+} + 2e^{-} \to \mathrm{Sn} \tag{1}$$

On the reverse sweep a sharp anodic peak due to the dissolution of electrodeposited tin is also observed (Fig. 3c). In presence of 4 mM stannous chloride, L-cystine gives a distinct reduction peak around -0.6 V vs SCE which indeed is the reduction region of Sn<sup>2+</sup>



**Fig. 4.** Cyclic voltammetric response of glassy carbon electrode surface in 0.5 M HCl, (A) concentration effect of SnCl<sub>2</sub> absence of L-cystine (i) 2 mM, (ii) 4 mM, (iii) 6 mM, (iv) 8 mM and (v) 10 mM of SnCl<sub>2</sub> (B) concentration effect of SnCl<sub>2</sub> in presence 10 mM L-cystine (i) 2 mM, (ii) 4 mM, (iii) 6 mM, and (iv) 8 mM of SnCl<sub>2</sub>.

(Fig. 3d). The cathode peak current also increases linearly with increasing concentration of L-cystine (inset of Fig. 3) indicating that L-cystine is cathodically reduced on electrodeposited tin surface in the potential region corresponding to the deposition potential of Sn under the same experimental condition.

The catalytic effect of SnCl<sub>2</sub> addition may be either due to the reduction of L-cystine on the electrodeposited Sn surface through adsorption mechanism or redox catalysis of Sn<sup>2+</sup>/Sn redox intermediates. The later mechanism appears to be operative for the following reasons. (i) The electroreduction of L-cystine occurs in the same potential where Sn<sup>2+</sup> reduction takes place. (ii) The cathodic peak found to shift cathodically with increasing concentration of L-cystine rather than anodically. This suggests that non-nernstien or blocking type of adsorption behaviour of L-cystine reduction on the Sn surface. (iii) In contrast Sn<sup>2+</sup> reduction peak is found to shift in anodic direction with increasing Sn<sup>2+</sup> concentration showing the nernstien behaviour as shown Fig. 4A. Quiet interestingly the anodic peak potential shift is more pronounced with increasing concentration of Sn<sup>2+</sup> in presence of 10 mM L-cystine (Fig. 4B). The increase in peak current values with Sn<sup>2+</sup> concentration is also higher in presence of L-cystine. The peak potential and peak current values in the absence and presence of L-cystine are also compared in Fig. 5A and B respectively. These observations suggest that in presence of 10 mM L-cystine, the effective concentration of Sn<sup>2+</sup> enhances significantly near the electrode surface through the following redox catalytic reaction sequence where RSSR refers to L-cystine.

$$Sn^{2^+} + 2e^ Sn$$
  
 $Sn + RSSR + 2H^+ \rightarrow 2RSH + Sn^{2^+}$  (2)

At sufficiently negative potential, the deposited Sn reaches the steady state value which is the proportional to initial  $\text{Sn}^{2+}$  concentration. Hence on the reverse sweep, the anodic dissolution peak observed depends only on the initial concentration on of  $\text{Sn}^{2+}$  taken (Fig. 4A and B) and does not depend on L-cystine concentration (Fig. 3d).

The electrochemical oxidation of L-cystine to L-cysteic acid was also evaluated using cyclic voltammetry on glassy carbon electrode in  $0.5 \text{ M H}_2\text{SO}_4$ . In this medium increase in anodic background due to oxygen evolution is noticed beyond 1.3 V vs SCE (Fig. 6a). In



Fig. 5. Plot of (A) potential vs concentration of Sn<sup>2+</sup> and (B) current vs concentration of Sn<sup>2+</sup> in presence and absence of 10 mM  $_L$ -cystine.



**Fig. 6.** Cyclic voltammograms of L-cystine oxidation at glassy carbon electrode surface (a)  $0.5 \text{ M} + 2SO_4$ , (b) 10 mM L-cystine in  $H_2SO_4$ , (c) 10 mM HBr in  $0.5 \text{ M} + 2SO_4$  and (d) 10 mM HBr in  $0.5 \text{ M} + 2SO_4$  with different concentrations of L-cystine (i) 10 mM, (ii) 20 mM, (iii) 40 mM, (iv) 60 mM.

presence of 10 mM L-cystine the anodic background limit itself is shifted to more positive potentials probably due to the blocking of oxygen evolution reaction by adsorbed L-cystine molecules. A distinct anodic oxidation peak due to the oxidation of L-cystine molecule is indeed observed around 1.6 V vs SCE (Fig. 6b). The cyclic voltammogram behaviour of 10 mM HBr in 0.5 M H<sub>2</sub>SO<sub>4</sub> is shown in Fig. 6c. The redox peak due to Br<sup>-</sup>/Br<sub>2</sub> redox couple are distinctly visible. The anodic peak due to the oxidation of Br<sup>-</sup> occur around 1.1 V vs SCE (Fig. 6c). In presence of Br<sup>-</sup> the anodic oxidation peak due to the L-cystine is shifted to 1.3 V vs SCE (Fig. 6d) from 1.6 V vs SCE in the absence of Br<sup>-</sup> (Fig. 6b). The anodic peak current around 1.3 V vs SCE also increases with increasing concentration of L-cystine (inset of Fig. 6). Electro-generated bromine acts as a homogeneous redox mediator in the overall oxidation of L-cystine to L-cysteic acid (Eqs. (3) and (4)).

$$10Br^- \rightarrow 5Br_2 + 10e^- \tag{3}$$

$$5Br_2 + RSSR + 6H_2O \rightarrow 2RSO_3H + 10H^+ + 10Br^-$$
 (4)

#### 3.2. Preparative electrolysis

Some preparative scale experiments were carried out under the optimum condition reported in the literature to establish the usability of graphite cathode with SnCl<sub>2</sub> additive and DSA anode in the cathodic reduction, anodic oxidation and paired synthesis process. In the cathodic reduction process, initial L-cystine concentration could be as high as 0.5 M. The cathode current density in the range of 150–250 mA/cm<sup>2</sup> could be applied. The material yield up to 90% could be achieved in the batch operation at ambient temperature in presence of 5 g/L SnCl<sub>2</sub>. In the absence of SnCl<sub>2</sub> the material yield was found to be only 75%. The competitive hydrogen evolution however is quite significant especially towards the end of electrolysis as H<sub>2</sub> bubbles were noticed near the cathode surface. Hence the overall current efficiency was found to be around 60%. The current efficiency was also found to decrease with lower initial when the reactant concentration once again due to competitive hydrogen evolution. The progress of electrolysis however could be monitored by UV absorption at 320 nm until the reactant concentration reaches nearly zero (Fig. 1).

The anodic oxidation of L-cystine to L-cysteic acid is relatively more complex. The absorption in the UV region is due to bromine as well as L-cystine (Fig. 2). Moreover, the galvanostatic electrolysis could not be continued until 10 F/mole of electric charge is passed. Depending on the reaction conditions, significant bromine evolution is noticed much earlier. It appears that the oxidation of L-cystine to L-cysteic acid can proceed only in the presence of large excess of reactant. As the reactant concentration decreases, the electro-generated bromine evolves at the anode surface. Hence the overall conversion efficiency remains low.

In the paired electrolysis, the concentration ratio between catholyte and anolyte compartment is another important factor that can influence the overall efficiency. Theoretically electroreduction of L-cystine requires 2 F/mole while electro-oxidation requires 10F/mole. Hence the concentration ratio should be 5:1. In practice however, apart from solubility differences between HCl and HBr media, the conversion efficiencies also depend significantly on this ratio as shown in Table 1. At very high anolyte concentration (1:2) the anodic process efficiency drops substantially due to reactant concentration depletion in the catholyte. At very high concentration (5:1) the cathodic process efficiency found to be low. At optimum concentration (1:1) the material yield for L-cysteine is above 80% and that for L-cysteic acid is close to 60%. For a successful operation of paired synthesis, optimum reactant concentration should be maintained both in the anolyte and catholyte compartments. This is indeed possible in a flow reactor.

#### Table 1

Yield and current efficiency obtained in paired synthesis of L-cysteine and L-cysteic acid from L-cystine (anode: DSA, cathode: graphite, current density: 200 mA/cm<sup>2</sup>, duration of electrolysis-2 h). Temperature: 25 °C, stirring: 600 rpm.

S. No.	Ratio of L-cystine (catholyte: anolyte)	Material yield (%)		Current efficiency (%)	
		L-Cysteine	L-Cysteic acid	L-Cysteine	L-Cysteic acid
1	1:2	79	32	25.94	53.36
2	1:1	82.91	57.24	60.12	54.24
3	2:1	64.37	58.01	55.18	49.82
4	5:1	43.95	61.35	48.20	53.65

#### 4. Conclusion

The present investigation clearly indicates that a redox mediated paired synthesis of L-cysteine and L-cysteic acid from the same raw material L-cystine. Simple commercially available graphite cathode and DSA anode may be employed for the above system. In-situ electro-generated Sn can act as a mediator for cathodic process and HBr can act as a redox mediator for anodic process. Cyclic voltammetric measurements suggest such a redox catalytic mechanistic pathway. Further optimization studies are indeed necessary for achieving commercial viability. However the potential energy efficient (both anodic and cathodic reactions are useful) and environment friendly (avoiding the use of Br<sub>2</sub> liquid and discharge of bromide) nature of the process justifies further efforts in this area.

#### Acknowledgements

The authors thank the Director, Central Electrochemical Research Institute, Karaikudi for his support and encouragement. K. Firoz Babu thanks CSIR-New Delhi for the research fellowship.

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