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SYNTHESIS OF L-CYSTEIC ACID BY INDIRECT ELECTROOXIDATION AND AN EXAMPLE OF PAIRED SYNTHESIS: L-CYSTEIC AND L-CYSTEINE FROM L-CYSTINE

G.Sanchez-Cano,V.Montiel and A.Aldaz

Departamento Química Física. Universidad de Alicante.
Apto. 99. 03080. Alicante. Spain

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SYNOPSIS: This paper studies the synthesis of l-cysteic acid from l-cystine by oxidation with electrochemically generated bromine in aqueous-HBr solution. High current efficiency and material yield were obtained. A very interesting process of paired synthesis has been proposed to obtain l-cysteic acid and l-cysteine from cystine that improves notably the economical parameters.

1-INTRODUCTION

The anodic cleavage of disulphides can be a very useful route for obtention of sulfonic derivates.

So, Bontempelli[1](1) and Fichter[2](2) obtained the following sulfonic acids :

$$(1)\qquad \mathrm{PhSSPh} \xrightarrow{\mathrm{Pt,anode}} \mathrm{PhSO_3H} \qquad 60\%$$

$$(2)\qquad \mathrm{HO_3SPhSSPhSO_3H} \xrightarrow{\mathrm{Pt,anode}} \mathrm{p\text{-}HO_3SPhSO_3H} \qquad 80\%$$

In analogous manner cysteic acid can be obtained by direct or indirect electrooxidation of l-cystine in aqueous solution. Because the reduction process occuring in the cathode can be used to obtain useful products a very interesting synthesis would be the paired synthesis of l-cysteine hydrochloride monohydrate and cysteic acid monohydrate obtained by cathodic reduction and anodic oxidation of l-cystine respectively.

Cysteic acid can be prepared by chemical oxidation of l-cystine in HCl solution using bromine as redox agent[3]. The procedure to carry out this reaction is summarized as follows: a solution with 50 ml. of concentrated HCl, 150 ml. of water, 24 grams of l-cystine(0.1 moles) and 80 grams of bromine(0.5 moles) is prepared. The solution is vigorously stirred during forty minutes. After concentration to dryness at reduced pressure and recrystallization,pure l-cysteic acid monohydrate is obtained. Material yield is between 80-90%:

$$(3)\qquad \underset{\text{l-cystine}}{\mathrm{RSSR}} + 5\mathrm{Br_2} + 6\mathrm{H_2O} \longrightarrow \underset{\text{l-cysteic}}{2\mathrm{RSO_3H}} + 10\mathrm{HBr}$$

$$\mathrm{R} = \mathrm{(CO_2H)CH(NH_2)CH_2}\text{-}$$

Recently the use of dimethylsulfoxide as oxidizing agent has been reported[4-5]. In order to liberate the l-cysteic acid the intermediated product ($\mathrm{RSO_3H\text{-}Me_2SO}$) is treated with methanol. Recrystallization from water gives l-cysteic acid monohydrate. Material yield 88%:

$$(4)\qquad \text{l-cystine} \xrightarrow[\text{cat.}]{\mathrm{Me_2SO}} \mathrm{RSO_3H\text{-}Me_2SO} \xrightarrow{\mathrm{MeOH}} \text{l-cysteic acid}$$

Different papers on the voltammetric behaviour of the anodic oxidation of l-cystine has been published [6] but no data are availables to be used in an electrochemical synthesis using a laboratory or a pilot cell.

Different experiments were carried out in order to obtain l-cysteic acid by direct electrochemical oxidation of l-cystine. The material yields found were low and mixtures of different products were obtained. For this reason a indirect synthesis of l-cysteic acid using electrogenerated bromine as oxidation agent was carried out.

This type of indirect or mediated electrosynthesis is very interesting not only from a basic point of view but because its industrial use avoids the inventory of redox agents that normally are expensives and dangerous for handling. Moreover this type of synthesis does not produce environmental problems due to the regeneration of the redox reagent or discharge either of oxidized or of reduced form in the effluents.

The electrochemical generation of bromine in acid medium or hypobromite in basic medium which reacts with a substrate to form the final product is a well-know method that has been succesfully used to produce a wide number of interesting reactions: aromatic and C=C bromination, methoxylation of THF and derivates, epoxydations and transformation of alcohols to aldehydes. Table I shows some specific examples of these reactions.

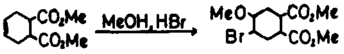
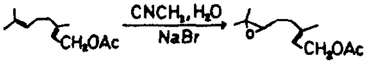
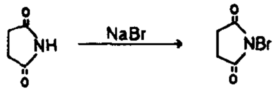
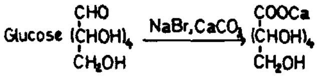
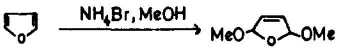
Indirect electrooxidation	Material %Yield	Ref.
P-xylene $\xrightarrow{AcOH,NaBr}$ Br-p-xylene	20	7
Naphtalene $\xrightarrow{AcOH,NaBr}$ Br-naphtalene	65	8
Phenol $\xrightarrow{HClO_4,NaBr}$ p-Br-phenol	52	9
	88	10
	82	11
trans-ØCH=CHØ $\xrightarrow[NH_4Br]{MeOH}$ ØCHBrCHBrØ ØCH(OMe)CHBrØ	30 17	12
		13
	66	14
 Glucose $\begin{matrix}CHO\\(CHOH)_4\\CH_2OH\end{matrix} \xrightarrow{NaBr,CaCO_3} \begin{matrix}COOCa\\(CHOH)_4\\CH_2OH\end{matrix}$	High	Sandoz-Chetano
	73	15

TABLE I

When mediated electrosynthesis is used to obtain a product, the choice of the redox agent plays a fundamental role. So, success in indirect electrooxidation or electroreduction requires a redox agent:

-which is soluble in the electrolysis media in both the high and low oxidation states.

-which is expected to undergo electrochemical regeneration with high current efficiency and chemical reaction with the substrate with high material yield.

-which can be easily separated from the products.

-which can be used without further purification when it has been regenerated.

-which can be used in the "in-cell method" although sometimes the "ex-cell method" in which the electrochemical and chemical steps are carried out in separate reactors, could be more interesting because it allows to optimize each step separately.

2-EXPERIMENTAL

The global process for the synthesis of l-cysteic acid involves two steps: formation of bromine (electrochemical step) and homogeneous reaction of this compound with l-cystine (chemical step).

Hydrogen bromide was employed as supporting electrolyte and to supply the bromine because it provides a good conductivity for the anolyte and because to carry out the chemical reaction in optima conditions a high concentration of protons is necessary. The partial and overall reactions are despicted in Figure 1.

FIGURE 1. Partial and overall reactions.

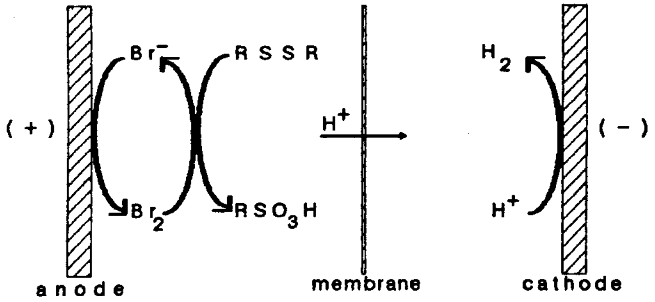
Anode: $10Br^- \longrightarrow 5Br_2 + 10e$

Anolyte: $5Br_2 + RSSR + 6H_2O \longrightarrow 2RSO_3H + 10H^+ + 10Br^-$

Membrane: $10H^+(\text{anolyte}) \longrightarrow 10H^+(\text{catholyte})$

Cathode: $10H^+ + 10e \longrightarrow 5H_2$

Overall: $RSSR + 6H_2O \longrightarrow 2RSO_3H + 5H_2$



Electrolysis was carried out at constant current in a divided filter-press cell with electrolyte flow perpendicular to the direction of the electric current. Three dimensional carbon electrodes of geometric area

4x5 cm^2 (the density current is referred to this area) were used. These electrodes are allocated inside the compartment between the current feeders and the membrane. The current feeders are graphite sheets of 7x9 cm^2 and 1 mm thick. The compartments have their own inlet and outlet tubes. The membrane used was a cationic ion-exchange membrane (Nafion 117). Both catholyte and anolyte were recirculated by means of pumps with a flow-rate of 1 liter/minute.

In all experiences the anolyte composition was an aqueous solution of HBr and l-cystine (volume 100 ml). In the experiment in which the synthesis of l-cysteic acid was optimized, the catholyte was always a solution of 4M sulphuric acid (volume 100 ml). For the paired synthesis the conditions will be described in section 3.2.

Cell voltage is a function of the specific electrolysis conditions, the values obtained were between 2 and 6 volts.

The end-point of the reaction was determined by the appearance of a slight brown coloration in the anolyte due to the presence of bromine(l-cystine conversion 100%). The residual bromine could be easily eliminated by purging with nitrogen.

No oxygen evolution from water oxidation ($H_2O = O_2 + 4H^+ + 4e$) appears and for this reason this reaction need not to considered in the reaction.

Figure 2 shows the elements of the cell without the three dimensional electrodes in order to simplify the figure. Figure 3 shows the complete electrolysis system employed and figure 4 presents the arrangement of the different measurement devices. (Figures 2-4 are shown in the next page).

Once electrolysis is finished, water and HBr were recovered by distillation at reduced pressure. After this, the residue was mixed with methanol at 5 °C and after 15 minutes, l-cysteic acid monohydrate was filtered off and rinsed with cold methanol. Finally, the product was recrystallizated from water. Identification was confirmed by comparing the IR, UV, H-RMN spectra with that of authentical material.

3-RESULTS

3.1 NON-PAIRED SYNTHESIS

By careful selection of the experimental conditions, it is possible to optimize the electrochemical parameters of the synthesis:

$$aA + \ldots + ne = bB + \ldots$$

CONVERSION : CV% = (moles A reacted / moles A initial)100
MATERIAL YIELD : MY% = ((a/b) moles B obtained/ moles A reacted)100
CURRENT EFFICIENCY: CE% = ((n/b) 96500 moles B obtained / Q)100
ENERGY COST: Kwh/Kg = V (n/b) (1/CE%) (1/MWB) 2680.5
PRODUCTION: Kg/m^2day = i CE% MWB (b/n) (1/11170)

Q: total charge circulated(C); V:cell voltage (V)
i: current density (mA/cm^2) ; MWB:molecular weight B

TABLE II

The initial experimental parameters selected were : HBr =2.6 M, RSSR = 0.42 M , T= 25 °C , i= 0.5 A/cm^2. In order to examine the influence of each variable on the synthesis one of them is changed and the influence of this change is studied.

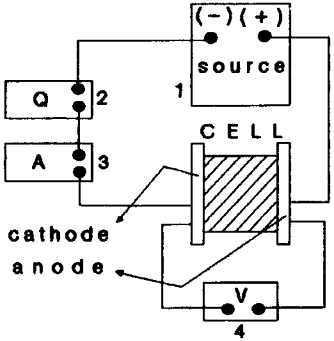


FIGURE 4. Schematic representation of the measurement systems. 1: power supply. 2: charge integrator. 3: ammeter. 4: voltmeter .

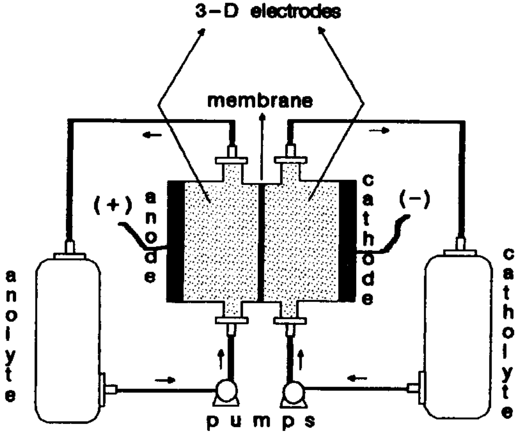
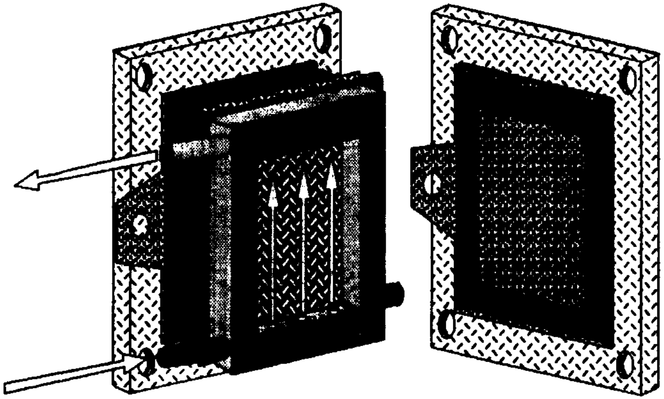


FIGURE 3. Experimental set-up.



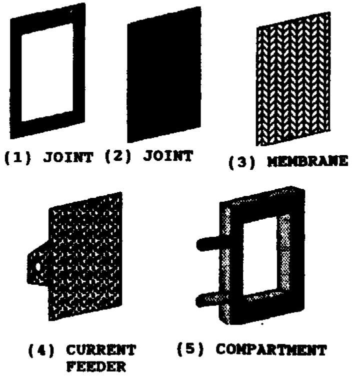


FIGURE 2. Schematic representation of the laboratory cell.

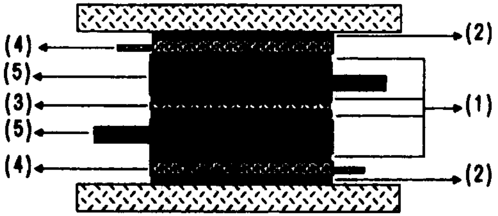


Table III (next page) summarizes the reactions that were carried out in order to optimize the synthesis. A decrease in l-cystine concentration increases l-cysteic acid yield. This yield also increases with increasing temperature and HBr concentration. When density current both higher or lower that 0.5 A/cm^2 is used, the material yield diminished.

Based on these results, the following conditions were selected:

HBr = 3.9M, T=45 °C, i=0.5 A/cm^2, RSSR= 0.42M

It should be mentioned that the total quantity of l-cystine added into the anolyte was equivalent to 0.42 M but in order to maintain a low l-cystine concentration, this quantity was added throughout the experience.

The optimized economical parameters were :

CV%	MY%	CE%	Kg/m^{2}day	Kwh/Kg
100	81	84	140	2.79

3.2 PAIRED SYNTHESIS

The hydrogen evolution as cathodic reaction is a not desirable reaction because its lack of economical interest for small productions. It should be more interesting to use both electrodic reactions simultaneously. In this manner two products could be obtained. However, sometimes is difficult to carry out the two reactions under compatible experimental conditions.

Some interesting examples[16] of this type of synthesis have been reported (figure 5):

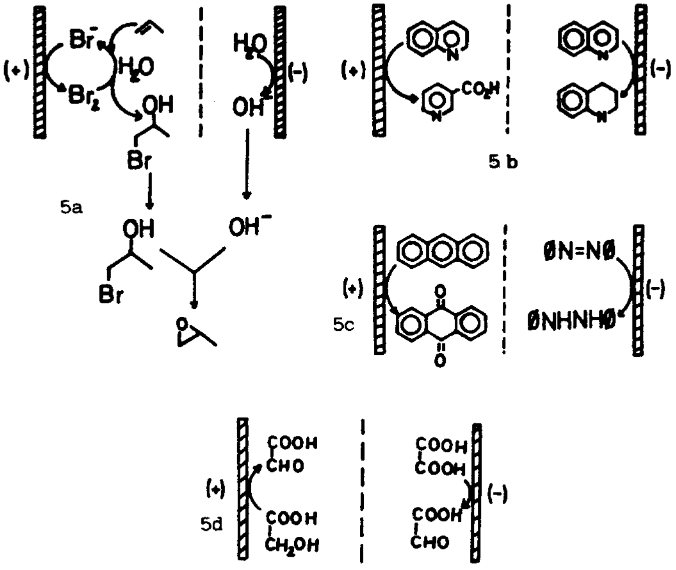


FIGURE 5

TABLE III

PARAMETERS FIXED	T(°C)	MY(%)	CE(%)	Kg/m^2day	Kwh/Kg
1-cystine 0.42 M HBr 2.6 M i 0.5 $A.cm^{-2}$	12	47	52	86	4.83
	25	57	62	103	3.93
	45	60	65	108	3.41

PARAMETERS FIXED	HBr	MY(%)	CE(%)	Kg/m^2day	Kwh/Kg
1-cystine 0.42 M Temperature 25 °C i 0.5 $A.cm^{-2}$	1.3 M	17	20	33	17.2
	2.6 M	57	62	103	3.93
	3.9 M	61	66	110	3.48

PARAMETERS FIXED	RSSR	MY(%)	CE(%)	Kg/m^2day	Kwh/Kg
Temperature 25 °C HBr 2.6 M i 0.5 $A.cm^{-2}$	0.21 M	70	74	123	3.00
	0.42 M	57	62	103	3.93
	0.84 M	30	35	58	4.45

PARAMETERS FIXED	$A\ cm^{-2}$	MY(%)	CE(%)	Kg/m^2day	Kwh/Kg
1-cystine 0.42 M HBr 2.6 M Temperature 25 °C	0.2	52	57	38	3.27
	0.5	57	62	103	3.93
	0.75	51	56	140	5.89

OPTIMUM CONDITIONS	MY(%)	CE(%)	Kg/m^2day	Kwh/Kg
1-cystine 0.42 M , HBr 3.9 M Temp. 45 °C, i=0.5 A/cm^2	81	84	140	2.79

MY=Material Yield CE=Current Efficiency

Kg expressed as cysteic acid monohydrate

In general, paired electrosyntheses are divided in three cases:

1.Both the anodic and cathodic reactions are employed to give the final product (figure 5a).

2.The anodic and cathodic reactions lead to two different organic products being the starting product the same for both electrode reactions (figure 5b) or different (figure 5c).

3.The anodic and cathodic reaction lead to the same product (figure 5d).

The paired syntheses can be academically very elegant and industrially are very interesting because the cost of the process is shared between two products and the production per cell is increased.

After some research, it was decided to try as the cathodic reaction the reduction of l-cystine. This electroreduction has been related in the bibliography and the process have reached the commercial scale[17-20] .

Following the methodology employed in section 3.1, new reactions have been carried out in order to optimize the electrochemical reduction of l-cystine. The following optima conditions were selected:

RSSR= 1.0 M, HCl = 2.3 M, i= 0.5 A/cm^2, T= 45 °C

The anolyte was a solution of 4M sulphuric acid and consequently the anode reaction was the oxygen evolution ($H_2O=O_2+4H^++4e$). The electrolysis was ended when the l-cystine was consumed (100% conversion). The economical parameters for the synthesis of l-cysteine were:

CV%	MY%	CE%	Kg/m^{2}day	Kwh/Kg
100	94	92	700	1.04

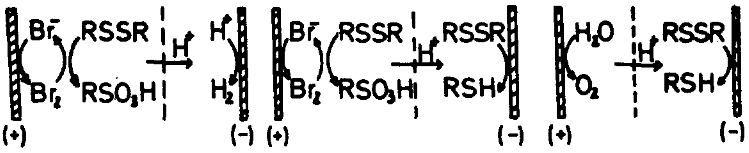
The choice of HCl as supporting electrolyte is due to that l-cysteine is normally sold as l-cysteine hydrochloride monohydrate.

The isolation of l-cysteine-HCl-H_2O is achieved when the solution is concentrated to dryness at reduced pressure, and the residual material is recrystallized from water.

Figure 6 (next page)shows the global process-flow for the paired synthesis. The starting materials are l-cystine and water and final products are l-cysteic acid and l-cysteine.

Table IV compares the results for the paired and the individuals syntheses.

TABLE IV



anolyte / catholyte	anolyte / catholyte	anolyte / catholy
HBr=3.9M / H_2SO_4=4M	HBr=3.9M / HCl=2.3M	H_2SO_4=4M / HCl=2.3
RSSR=0.42M / ---	RSSR=0.42M / RSSR=1.0M	--- / RSSR=1.
i=0.5 A/cm^2	i=0.5 A/cm^2	i=0.5 A/cm^2
T=45C	T=45C	T=45C
CV%=100	CV%=100	CV%=100
Voltage=3.41V	Voltage=2.68V	Voltage=6.12V
140Kg/m^{2}day	(140+700)Kg/m^{2}day	700Kg/m^{2}day
2.79Kwh/Kg	0.46Kwh/Kg	1.04Kwh/Kg

FIGURE 6. Process-flow for the paired synthesis. Partial and overall reactions.

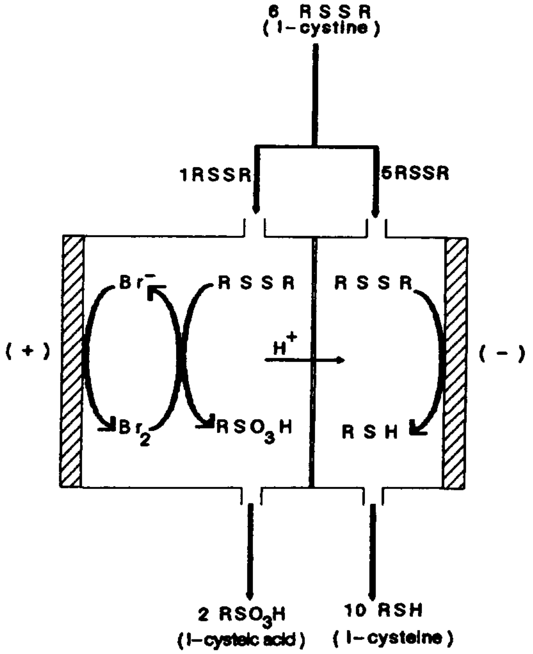
Anode: $10Br^- \longrightarrow 5Br_2 + 10e$

Anolyte: $5Br_2 + RSSR + 6H_2O \longrightarrow 2RSO_3H + 10H^+ + 10Br^-$

Membrane: $10H^+(\text{anolyte}) \longrightarrow 10H^+(\text{catholyte})$

Cathode: $5RSSR + 10H^+ + 10e \longrightarrow 10RSH$

Overall: $6RSSR + 6H_2O \longrightarrow 2RSO_3H + 10RSH$



Due to the different current efficiences in the cathodic (92%) and anodic processes (84%), in order to obtain a 100 % conversion of the l-cystine both in the catholyte and in the anolyte, the following volume ratio for the conditions given in table IV must be obeyed: catholyte / anolyte = 2.3 .

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