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# Modular and Scalable Alluvial Cells for the Electroconversion of Poorly Soluble L-Cystine

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**ABSTRACT:** A new cell design for the electrochemical reductive cleavage of L-cystine to L-cysteine has been presented. The so-called alluvial cell exploits the low solubility of L-cystine as a substrate by reducing a cystine suspension at a porous cathode, dissolving only small quantities of the substrate and separating the fully dissolved product by filtration. This setup avoids corrosive, highly concentrated acidic electrolyte systems, which is beneficial for the lifetime of the plant and improves the energy efficiency of the process. Additionally, several alloys were established as novel electrode materials suitable for the electroconversion of cystine. The alluvial cell achieved an almost quantitative yield of L-cysteine upon optimization and was scaled up to a small pilot range, highlighting its technical relevance.

**KEYWORDS:** *electrosynthesis, disulfide reduction, alluvial cell, flow electrolyzer, L-cysteine, scale-up, pilot scale, green chemistry*

## INTRODUCTION

L-Cysteine is a proteinogenic amino acid with high technical significance because of its wide range of useful applications: It is employed in pharmaceuticals such as *N*-acetylcysteine or (*S*)-carboxymethyl-L-cysteine, in cosmetics, and in animal feed.[1−7] Moreover, it serves as a key precursor in the synthesis of peptides, lipoic acid, methionine, coenzyme A, and taurine.[8−13] Finally, L-cysteine is also crucial in the food industry, wherein it is applied as a dough softener for baking and as an ingredient in the Maillard reaction for creating meaty and savory flavors.[14−16]

Conventionally, L-cysteine is produced through acidic hydrolysis of animal material containing the protein keratin, like hair, feathers, or horn (Figure 1). However, this process results in complex reaction mixtures which are challenging to purify and leaves the thiol containing product highly susceptible to oxidation. Moreover, the waste disposal causes environmental and safety issues and the obtained L-cysteine is not vegan, which limits its use in food products.[17−19] Alternatively, different approaches for the biotechnological production of L-cysteine have been developed. In the late 1970s, the enzymatic bioconversion of DL-2-amino-$\Delta^2$-thiazoline-4-carboxylic acid by microorganisms of the *Pseudomonas* species was established, but industrial application of this method was limited due to the low enzymatic yield.[20−22] With the advancements in synthetic biology, direct bacterial-based fermentative processes for the synthesis of L-cystine and L-cysteine from glucose have been emerging since the late 1990s.[23−25] Especially Wacker Chemie AG has conducted research on the fermentative production of said amino acids and their derivatives using microorganisms and holds significant IP in this field.[26−28] The L-cystine obtained by a biotechnological fermentation process is natural and vegan (WACKER brand FERMOPURE), and therefore particularly suitable for applications in the pharmaceutical and food industry. Its monomer L-cysteine is then synthesized electrochemically by reductive cleavage of the disulfide bond (Figure 1).

Electrosynthesis has emerged as an attractive tool for sustainable organic synthesis and the generation of value-added products.[29−32] Since electrons serve as reagents, stoichiometric amounts of oxidizing or reducing agents can be avoided and reagent waste is minimized. Electrosynthesis can even be considered waste- and pollutant-free if electricity from sustainable sources is used.[33,34] Additionally, precise control of the electrolysis parameters results in an inherently safe process because simply turning off the electricity can prevent a thermal runaway of the reaction.[35,36] Moreover, electrosynthesis often enables reactions under mild reaction conditions and can achieve unique reactivity and selectivity, which is particularly valuable for the synthesis of value-added products.[37−42] The electrochemical reduction of L-cystine to L-cysteine is a well-known reaction that has been studied extensively and reviewed by Walsh et al. with a focus on cathode materials and current density.[43−49] More recent research by Waldvogel et al. covers systematic reaction optimization at metal cathodes using modern statistical methods.[50] Despite the large amount of research that has already been conducted on this reaction, there are still some drawbacks to the established reaction conditions. First, the reduction is usually carried out on toxic lead cathodes, which complicates downstream processing and approval for the use of the obtained cysteine in highly regulated areas. In addition,

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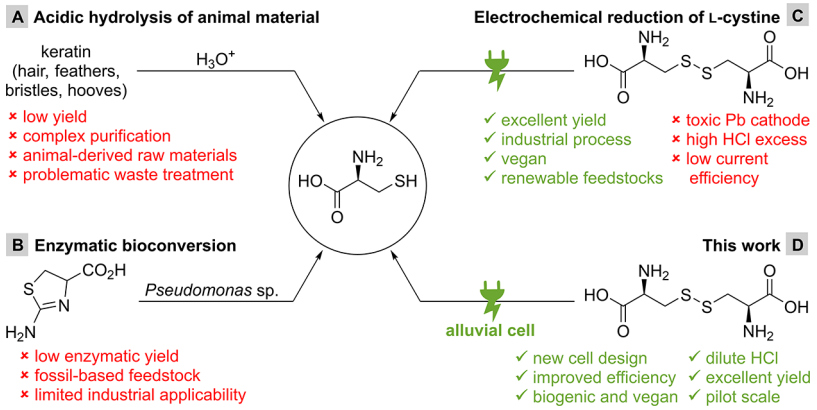


**Figure 1.** Comparison of different synthetic routes toward L-cysteine.

hydrochloric acid in very high concentrations is required as solvent due to the poor solubility of L-cystine, resulting in the need for HCl-resistant apparatuses and an elaborate workup procedure consisting of multiple evaporation and crystallization steps with all commonly employed electrolyzer architectures. Moreover, the efficiency of the reaction decreases significantly at high current densities due to the parasitic hydrogen evolution reaction, leading to a trade-off between the high space-time yield and high current efficiency.

To address these challenges, we envisioned a new cell design: the alluvial cell. Our design is based on the precoat layer cell (PLC) which was invented by BASF SE in the 1990s.[51−54] In the precoat layer cell, one electrode (e.g., the cathode) consists of an electrically conductive, porous support and a cathodically polarized layer formed thereon in situ by precoat filtration. Any electrically conductive material can serve as a cathodically polarized layer as long as it can be formed into a layer by alluviation against the support, which also allows for the use of finely dispersed catalysts without the need for complex processing to massive electrodes. The cathode can simply be exchanged by inversing the flow to resuspend and remove the old electrode material and using new electrode material in the filtration step before electrolysis. Originally, the precoat layer cell was employed for wastewater treatment, specifically for the recovery of metals and reductive decomposition of halogenated compounds. However, it also proved highly useful for both oxidation and reduction reactions in organic synthesis, e.g., indigo could be reduced starting from the substrate in its solid form in high yields up to 87%.[55−58] Therefore, we envisioned that a similar setup could also be used for the reduction of L-cystine in its solid form, which would allow for the use of dilute hydrochloric acid while also increasing the energy efficiency of the reaction. Herein, we developed the so-called alluvial cell for the electroreduction of L-cystine to L-cysteine (Figure 2). The reaction conditions were optimized using modern optimization tools based on regression methods, and the cell was scaled up from laboratory to small pilot scale.

## RESULTS AND DISCUSSION

The electroreduction of L-cystine was investigated in an alluvial cell as shown in Figure 3. The cathode material is alluviated at a glass frit as support and contacted with a lead-coated platinum wire to preserve the mechanical integrity of the reactor while also minimizing hydrogen evolution. A glass frit serves as a separator between the compartments, and a

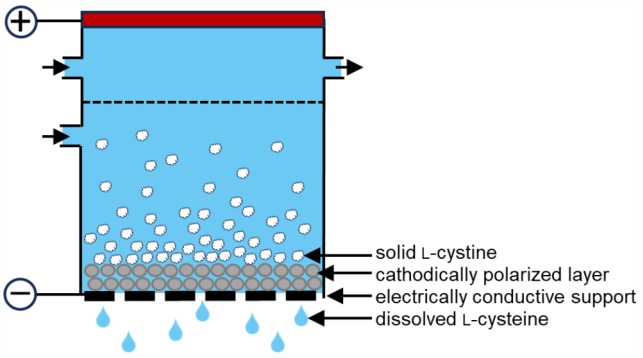


**Figure 2.** Schematic visualization of the operating principle of an alluvial cell for the electroreduction of L-cystine to L-cysteine.

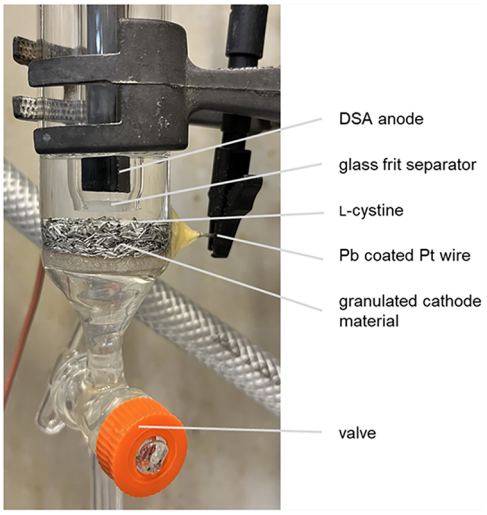


**Figure 3.** Initial alluvial cell design used for the screening of cathode materials.

dimensionally stable anode (DSA) is employed. To prevent cross-contamination of the electrolyte by ion diffusion through the frit, hydrochloric acid was used as both anolyte and catholyte. The gravity-induced flow is adjusted to roughly the same flow rate for all experiments with a valve below the support.

Electrolyses were conducted in 0.1 M hydrochloric acid, resulting in the bulk of the cystine remaining undissolved due to its low solubility of 0.017 mol $L^{-1}$ at pH 1.[59] As significant hydrogen evolution was observed in initial experiments, a low


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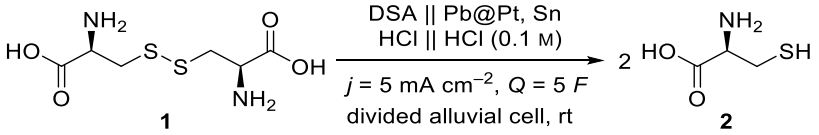
**Table 1. Screening of Cathode Materials and Further Optimization of the Electroreduction of L-Cystine to L-Cysteine in an Alluvial Cell**




| # | deviation from standard conditions | yield[a] |
|---|---|---|
| 1 | none | 40% |
| 2 | Pb powder | 21% |
| 3 | GC splinters | 25% |
| 4 | graphite beads | 17% |
| 5 | graphite felt | 18% |
| 6 | RVC | 25% |
| 7 | CuSn7Pb15 | 10% |
| 8 | Sn96Ag4 | 43% |
| 9 | Bi58Sn42 | 57% |
| 10 | Sn97Cu3 | 70% |
| 11 | Sn97Cu3, 0.3 M HCl | 90% |
| 12 | Sn97Cu3, 0.3 M HCl, 10 mA $cm^{-2}$, 4.0 *F* | 94% |
| 13 | Sn97Au3, 0.3 M HCl, 10 mA $cm^{-2}$, 4.0 *F* | 97% |
| 14 | Sn (0.1−0.8 mm), 0.3 M HCl, 10 mA $cm^{-2}$, 4.0 *F* | 94% |
| 15 | Sn (1−4 mm), 0.3 M HCl, 10 mA $cm^{-2}$, 4.0 *F* | 85% |

[a]Yield determined by $^1$H NMR spectroscopy using 1,4-dioxane as an internal standard.

current density of 5 mA $cm^{-2}$ and an excess amount of applied charge of 5 *F* were chosen as standard conditions. Using these parameters, a screening of different porous cathode materials was performed, employing for example powders, granules or foams (Table 1). Out of the tested metal cathodes, tin granules achieved the highest yield with 40% (entry 1), surpassing lead powder which only resulted in 21% yield (entry 2). For applications in pharmaceuticals and food products, however, carbon-based cathodes would be preferred over metal cathodes.[60] Sadly, glassy carbon, graphite, graphite felt and RVC all performed significantly worse than tin with yields between 17% and 25% (entry 3−6). Since alloys such as leaded bronze have different properties than their metals in pure form, they were considered promising new cathode materials.[61] However, using leaded bronze as the cathode in our reaction resulted only in a yield of 10%. (entry 7). Binary tin silver and tin bismuth alloys showed more promising results with 43% and 57% yield, respectively (entry 8−9). To our delight, a significantly increased yield of 70% could be achieved with a binary tin copper alloy (entry 10). Using Sn97Cu3 as cathode material, the yield could even be increased to 90% by increasing the concentration of hydrochloric acid to 0.3 M (entry 11). This is probably due to the sharp increase of cystine solubility at pH < 1,[62] suggesting that the cystine needs to be dissolved in small quantities before it can be reduced. A further improvement to 94% yield could be achieved by increasing the current density to 10 mA $cm^{-2}$ and decreasing the amount of applied charge to 4 *F* (entry 12). When these optimized conditions were applied to Sn97Au3 and tin powder, comparable yields of 97% and 94% were achieved, respectively (entry 13−14). Tin granules with a larger particle size, however, led to a slightly lower yield of 85% (entry 15), suggesting that the size and possibly also the shape of the cathode material play an important role. This can be attributed to the active cathodic surface area which is dependent on the granule size. A larger surface area leads to a larger contact area with the undissolved cystine and a lower effective current density, reducing hydrogen evolution as side reaction, which results in a higher yield.

Notably, the aforementioned binary tin alloys, to the best of our knowledge, have not been used as cathode materials before. Therefore, they are promising new cathode materials also for the application as planar electrodes in regular flow cells using conventional conditions for cystine reduction. When a solution of cystine in 3 M HCl was employed in a standard flow cell, yields of up to 97% could be achieved (see the SI for detailed information). Under these conditions, however, corrosion of the plant because of the highly acidic electrolyte still remains a problem. The alluvial cell mitigates this problem by allowing the use of a substrate suspension in a dilute hydrochloric acid.

## Modular Setup

Despite these promising results, there were still drawbacks to the alluvial cell setup, such as the lead-coated Pt contact and the lack of measurable and reproducible flow rates. Therefore, a new setup was introduced to address these issues. The new alluvial cell, as shown in Figure 4, is modular, commercially available and includes several improvements to the previous cell: First, a stainless-steel frit serves as both porous support and electrical contact, substituting the lead-coated platinum wire. As separator, a Nafion N424 membrane is pressed between both compartments and inexpensive sulfuric acid is used as anolyte, resulting in oxygen evolution from the DSA anode which is a safer counter reaction than chlorine evolution.[63] Furthermore, the inlet of the new cell is connected to a membrane pump, enabling reproducible flow rates.

Transferring the same procedure and the previously optimized conditions from the initial cell to the new cell resulted in a yield of 81% when the electrolysis was conducted in a single-pass mode. Recycling the electrolyte once improved the yield to 86% and increased the conversion from 85% to 99%, indicating that batch recycling is necessary to achieve higher conversions. However, for the economically viable production of L-cysteine on an industrial scale, a current

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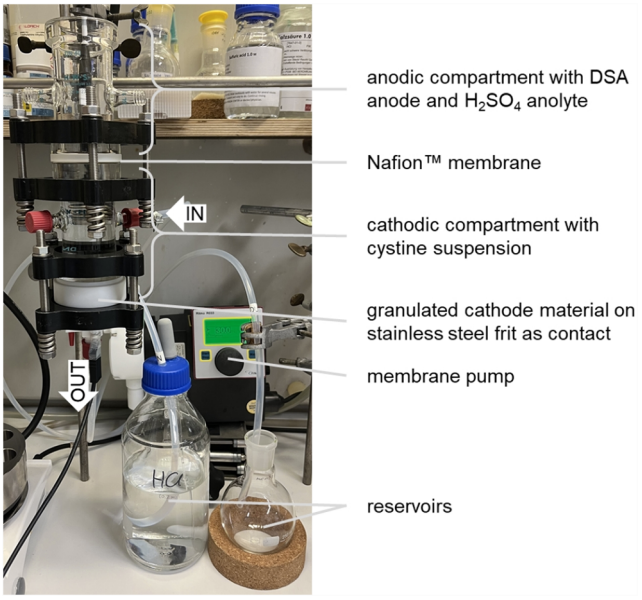



**Figure 4.** Modular and commercially available alluvial cell used for the optimization via Design of Experiments.

density of at least 100 mA $cm^{-2}$ is required. When we applied this current density to the alluvial cell, a significant drop in the yield to 57% was observed due to parasitic hydrogen evolution. Fortunately, increasing the number of cycles from 2 to 15 resulted again in a yield of 91%, indicating that the detrimental effect of higher current densities can be mitigated effectively with a larger number of cycles.

## Design of Experiments

In order to further improve the yield, we systematically screened the continuous reaction parameters using a Design of Experiments (DoE) approach, which is a powerful statistical tool providing deeper insights into the influence and interaction of various parameters with a minimum number of experiments.[64] Initially, a $2^{4-1}$ fractional factorial design was performed to investigate the concentration of hydrochloric acid ($c_{HCl}$), the number of cycles, the current density ($j$), and the amount of applied charge ($Q$). In the tested range, only the concentration of HCl and the number of cycles had a significant influence on the yield, whereas the amount of applied charge and the current density did not have a significant effect. Since the main effect plots suggested curvature, the design was extended to include star points, resulting in a face-centered central composite design. After response optimization, an optimized set of reaction conditions was obtained that yielded 98% of L-cysteine (Scheme 1). Remarkably, no more than the theoretically needed amount of applied charge was necessary for an almost quantitative yield.

## Scale-Up to Pilot Scale

The scale-up alluvial cell system shown in Figure 5 comprised a sulfuric-acid-driven anode loop and a cathode loop supplied

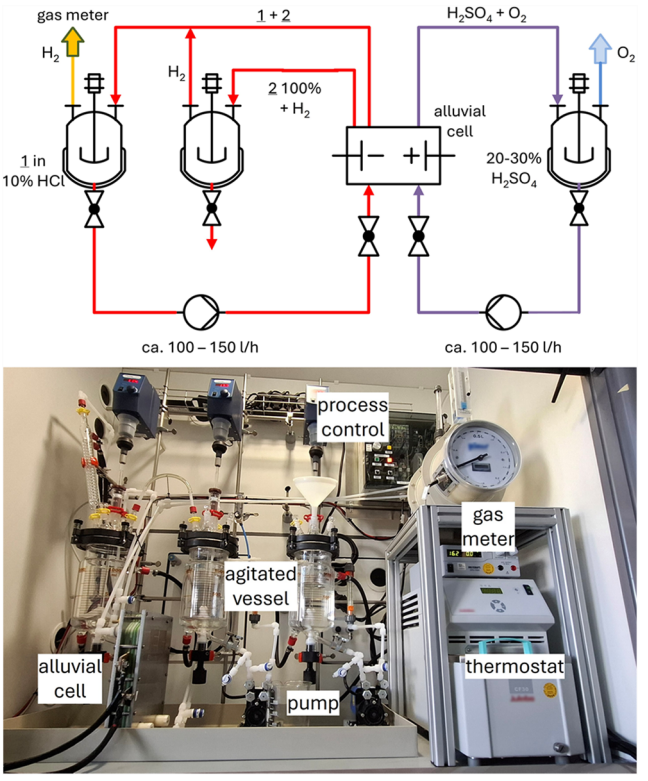
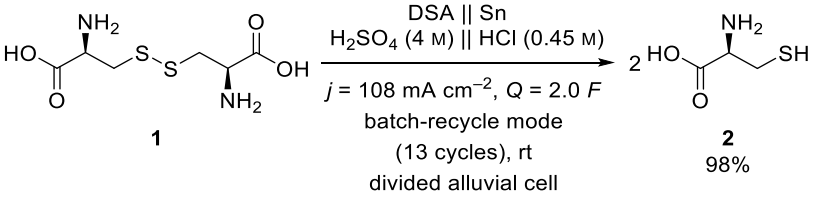



**Figure 5.** Process scheme (top) and picture (bottom) of the scale-up alluvial cell system.

with an L-cystine (**1**) feed that was pumped into the cell. The setup enabled operation using either dissolved or suspended L-cystine. In the experiments reported herein, an L-cystine suspension was employed, prepared by partially dissolving 217 g of L-cystine in 600 g of 3.2 M HCl. The cell featured two cathode outlets: one delivering the cysteine product stream and a second recirculating loop for the combined L-cystine/L-cysteine stream (**1** + **2**). The cathode side of the electrolysis cell was divided into two chambers by a porous electrode. Catholyte was supplied through the inlet into one chamber and withdrawn via outlets from both chambers. As a result, the catholyte flow was split into a tangential part along the surface of the porous cathode and a transverse fraction passing through the porous electrode (Figure 6). The process was carried out in batch mode, with the volume flows from the catholyte outlets being combined and returned to the catholyte inlet via a buffer tank until a sufficiently high cysteine concentration was achieved.

**Scheme 1. Optimized Conditions for the Electroreduction of L-Cystine to L-Cysteine in an Alluvial Cell as Obtained after the Optimization Using Design of Experiments**



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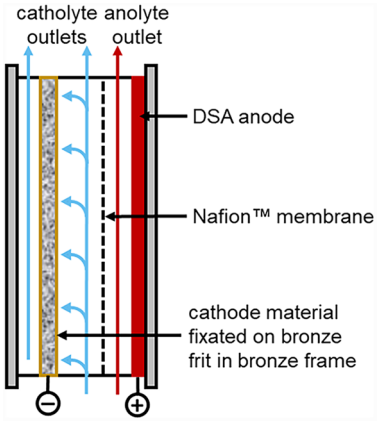


**Figure 6.** Schematic representation of the alluvial cell implemented in the pilot plant at Wacker Chemie AG.

Compared with the laboratory cell (Figure 4), several improvements were implemented. A dedicated outlet for hydrogen evolution was installed, enabling controlled gas venting and quantitative analysis using a gas meter. In addition, the electrolyte flow rate was precisely controlled both upstream and downstream of the cell.

The alluvial cell was based on a commercially available electrochemical flow cell (Electrical, type Electro MP Cell). The design featured an electrode area of 100 $cm^2$ and incorporated a Nafion N424 membrane, a reinforced cation exchange membrane with a thickness of approximately 0.38 mm. An iridium mixed metal oxide (Ir-MMO) coated titanium electrode was employed as anode, while the modular architecture of the cell enabled a highly flexible implementation of different cathode concepts, including beds of metal particles, metal frits or foams, as well as metallic or carbon-based structures. A key advantage over the laboratory cell was that the distance between the electrodes could be significantly reduced (adjustable between 2 mm and 16 mm, depending on the selected frames, spacers, and the overall configuration of the cell).

In an initial approach, a Sn granulate cathode (see Figure 7) was employed, resulting in only near-complete conversion of cystine to cysteine at an applied charge of 4 *F* when operating at a current density of 200 mA $cm^{-2}$. In addition to the incomplete conversion, this electrode configuration proved to be insufficiently stable, leading to significant tin dissolution and contamination of the product solution with approximately 1% Sn. As an alternative, a bronze frit cathode bearing an electrochemically deposited Sn sponge (prepared from $SnCl_2$ in HCl at 50 mA $cm^{-2}$ for 5 h) was evaluated. Under identical operating conditions, complete cystine conversion was achieved at an applied charge of 3 *F*, demonstrating improved electrochemical performance relative to the granulate-based cathode. Nevertheless, residual tin impurities were still detected in the product solution (~0.02% Sn), exceeding the specified limit for heavy metals (<10 ppm).

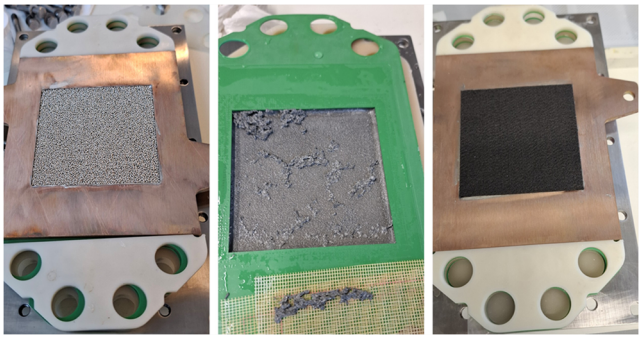

**Figure 7.** Pictures of the three porous cathode types evaluated in the scale-up system: Sn granulate (left), Sn sponge (center), and carbon felt (right).

To avoid tin contamination of the product solution altogether, we subsequently investigated a carbon felt cathode. This electrode type exhibited particularly high efficiency, enabling complete L-cystine conversion at an applied charge of only 2.4 *F* under the same operating conditions (Table 2).

**Table 2. Applied Charge until Full Conversion of 1 to 2 for Cathodes Evaluated in the Scale-Up Alluvial Cell System (100 $cm^2$ Electrode Area) at 200 mA $cm^{-2}$ Current Density**

| # | cathode evaluated | applied charge until full conversion of **1** to **2** |
|---|---|---|
| 1 | Sn granulate | 4.0 *F*[a] |
| 2 | Sn sponge | 3.0 *F* |
| 3 | carbon felt | 2.4 *F* |

[a]Near-complete conversion.

On top of that, optimization of the interelectrode distance to 8 mm led to a pronounced reduction in the specific energy consumption to approximately 1.0 Wh $g^{-1}$ cysteine, while enabling operation at current densities of up to 400 mA $cm^{-2}$ without exceeding a mean cell voltage of ~5 V. Under these optimized conditions, the process could be operated stably and reproducibly, achieving productivities of up to 200 g $h^{-1}$.

Investigations into the influence of L-cystine feed purity on the purity of electrolytically produced L-cysteine suggested that the presence of fermentation residues may lead to clogging of the porous electrodes, potentially resulting in system failure. In addition, electrolysis of crude L-cystine in the alluvial cell configuration is likely to induce foaming, giving rise to challenges similar to those encountered under conventional operating conditions (with excess hydrochloric acid). In any case, processing of crude L-cystine in the alluvial cell would necessitate downstream purification of the product solution to remove residual biomass and metal impurities originating from fermentation in order to meet product specification requirements.

## CONCLUSIONS

The alluvial cell was established as a new cell design for the electroreduction of L-cystine to L-cysteine. This setup exploits the low solubility of L-cystine in diluted hydrochloric acid by alluviating the undissolved substrate at a granulated or mesh cathode and filtering the product during the electrolysis. During the optimization, several binary tin alloys were discovered as novel electrode materials suitable for the electroreduction of L-cystine. Furthermore, the alluvial cell allows the use of dilute HCl, as opposed to the 6 M HCl employed in current industrial processes, which significantly increases the safety of the process and mitigates problems associated with acidic corrosion. Moreover, the cystine reduction in the alluvial cell shows a significantly improved Faradaic efficiency, rendering the process more economical. The technical relevance of the alluvial cell was demonstrated by a scale-up to a small pilot plant, achieving a productivity of




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up to 200 g $h^{-1}$. Finally, carbon felt can serve as an alternative cathode to tin, eliminating any trace metal impurities while maintaining excellent electrochemical efficiency. Overall, the alluvial cell has proved to be a highly useful setup for the electroreduction of L-cystine to L-cysteine even on a technical scale and has great potential for further applications in electroorganic syntheses with poorly soluble substrates.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.6c00197.

General information, electrochemical setups, optimization data, and experimental procedures. (PDF)

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### Author Contributions

S.R.W. and S.H. conceived the project. M.S.L., R.B., and R.K. conducted experiments and analyzed and interpreted the results. M.S.L., S.H., and S.R.W. wrote and reviewed the manuscript. S.R.W. and S.H. supervised the project. All authors have given approval to the final version of the manuscript.


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### Notes

The authors declare no competing financial interest.

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## ■ ABBREVIATIONS

DoE, Design of Experiment; DSA, dimensionally stable anode; GC, glassy carbon; MMO, mixed metal oxide; RVC, reticulated vitreous carbon

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