

# A Microflow Electrolysis Cell for Laboratory Synthesis on the Multigram Scale

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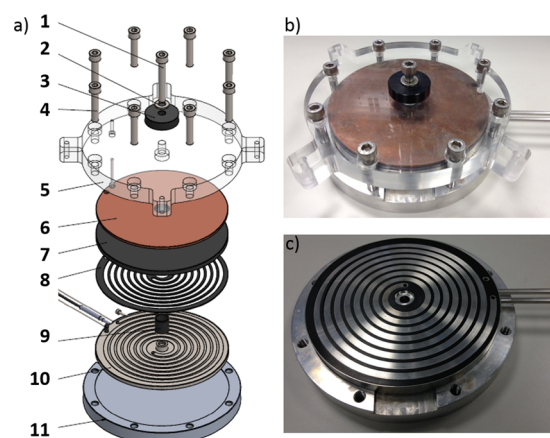
## Supporting Information

**ABSTRACT:** A large microflow electrolysis cell for laboratory synthesis on a multigram scale is described. It is based on two circular electrodes with a diameter of 149 mm and a spiral electrolyte flow channel 2000 mm long, 5 mm wide, and 0.5 mm interelectrode gap. Using the methoxylation of *N*-formylpyrrolidine as a model reaction, it is demonstrated that the cell approaches 100% conversion in a single pass, and it is possible to achieve a reaction selectivity >95% and a product formation rate of >20 g h<sup>-1</sup>.

## 1. INTRODUCTION

Usually, laboratory electrolysis cells for synthesis achieve chemical conversion at a very slow rate (for example, a full conversion may take many hours in a beaker cell), while industrial flow cells generally operate with a low conversion per pass of reactant through the cell and hence require extensive recycling of reactant solutions.<sup>1,2</sup> During the past 15 years, there has been a growing interest in the application of microflow chemistry to organic synthesis in the laboratory.<sup>3,4</sup> The introduction of electrolysis into flow synthesis required the design of systems capable of a high fractional conversion in a single pass. This has led to significant innovation in electrolysis cell design that has been reviewed recently.<sup>5,6</sup> Commonly, however, the high fractional conversion of reactant to product in a single pass has been achieved by restricting the electrolyte flow to very slow rates;<sup>7</sup> this allows novel and interesting syntheses but limits severely the amount of product that can be formed. Recently, we have demonstrated another approach to the design of microflow electrolysis cells where the electrolyte channel has an extended length.<sup>6,8,9</sup> When operated under appropriate conditions, these cells can combine a high fractional conversion and reaction selectivity with a product formation rate of multiple grams per hour.

Here we describe a cell design intended to allow the synthesis of larger amounts of product without loss of reaction selectivity or fractional conversion in a single pass of the solution through the cell. As shown in Figure 1, the cell has a parallel plate configuration with circular electrodes but the interelectrode gap is divided up into a spiral microchannel by a polymer spacer. As in previous papers,<sup>6,8,9</sup> the performance of the cell was demonstrated using the methoxylation of *N*-



**Figure 1.** (a) Components of the microflow electrolysis cell. 1. Central bolt. 2. Washer. 3. Insulating tube. 4. Peripheral bolt. 5. Perspex top plate. 6. Cu backing plate. 7. Carbon/polymer anode plate. 8. Perfluoroelastomer gasket. 9. Insulating tube around central bolt. 10. Stainless steel cathode plate with spiral groove. 11. Al base plate. (b) Photograph of reactor with perspex top. (c) Photograph of reactor with gasket fitted into cathode plate to create the spiral channel.

formylpyrrolidine (**1**) to give **2** as the test reaction in MeOH at a carbon/polymer anode (Scheme 1).<sup>10,11</sup> The cathode reaction was the reduction of MeOH to hydrogen and methoxide, so that the overall chemical change is formally a dehydrogenative coupling.

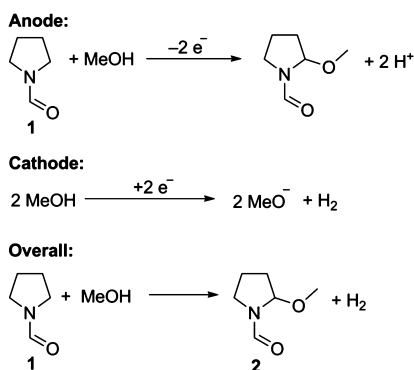
## 2. RESULTS

The electrolysis cell was based on two circular electrodes, diameter 149 mm, with the spiral electrolyte channel between; see Figure 1. The spiral channel design allows an extended channel length within a small device and maximizes the active area of the electrode plate. In addition it avoids corners that disrupt and modify the electrolyte flow regime. In fact, the channel was 2000 mm in length and 5 mm in width giving an active electrode area of 100 cm<sup>2</sup>. The machining of the spacer groove and the thickness of the spacer control the interelectrode gap, which was 0.5 mm for most of this work.

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**Scheme 1. Anodic and Cathodic Processes in the Formal Dehydrogenative Methoxylation of *N*-Formylpyrrolidine (1) to Give 2**



The narrow interelectrode gap allows electrolysis with a low electrolyte concentration. The conditions for the anodic methoxylation of *N*-formylpyrrolidine were largely established in our previous papers.<sup>6,9</sup> In the new, larger cell the experiments were limited to demonstrating the performance at higher flow rates and with larger amounts of reactant.

The percentage conversion and yield in a single pass and the product formation rate for a series of electrolyses carried out with 0.1 M solutions of **1** in MeOH with 0.05 M Et<sub>4</sub>NBF<sub>4</sub> were established (Table 1). The currents employed were generally slightly higher than the theoretical values to meet the charge input demanded by Faraday's law for a full consumption of the reactant in a single pass. This leads to a charge efficiency below 100% (in fact, varying between 50 and 90% in the experiments of Table 1), but in a laboratory cell this is not important, and high conversion and selectivity are the goals. A cell current of 1 A corresponds to an average current density of 10 mA cm<sup>-2</sup>, but current density is a parameter of limited value in a cell of this type. It is inevitable that the local current density drops strongly along the channel (in theory, the decay is exponential)<sup>9</sup> as the reactant is consumed.

A full consumption was obtained at the slowest flow rate (entry 1, Table 1), and it decreased marginally at higher flow rates. The percentage consumption was, however, always significantly higher than predicted by a simple model,<sup>9</sup> which is believed to originate from the high rate of hydrogen formation at the counter electrode leading to an increased mass transfer coefficient in the microchannel (the gas volume increases the linear flow rate, and the bubbles enhance turbulence in the flow). On the other hand, the higher flow rate permitted a higher rate of product formation; indeed, productivity is proportional to the flow rate (i.e., the weight of

**1** passing through the cell/hour). The productivities with the 0.1 M reactant solution were several g h<sup>-1</sup>, similar to those reported with the earlier cell, but these rather high productivities were achieved in a different way.<sup>6,9</sup> In the current work they resulted from the high flow rate of reactant solution, whereas in the earlier work higher productivities were achieved by increasing the *N*-formylpyrrolidine concentration to 0.75 M. In the larger cell, increased reactant concentration can be used to increase the rate of product formation further, and it was not expected to influence significantly the fractional conversion. This was confirmed by electrolysis of a 0.2 M solution of **1**. Using a flow rate of 16 mL min<sup>-1</sup> and a cell current of 12 A, the conversion was 88%, and the productivity was increased to 20.7 g h<sup>-1</sup> (equivalent to 0.5 kg or 5 mol in a day, entry 6, Table 1).

Table 2 reports data from longer time scale experiments, again with 0.1 M solutions of *N*-formylpyrrolidine. It can be

**Table 2. Electrolyses of Larger Volumes of Solution<sup>a</sup>**

entry	volume of reactant solution (mL)	flow rate (mL min <sup>-1</sup> )	cell current (A)	reactant <b>1</b> consumed <sup>b</sup>	mass of product (g) <sup>b</sup>
1	125	8	5	92%	1.4
2	480	8	5	92%	5.4 <sup>c</sup>
3	480	16	6	74%	4.1
4	2500	8	5	87%	24

<sup>a</sup>0.1 M *N*-formylpyrrolidine in MeOH with 0.05 M Et<sub>4</sub>NBF<sub>4</sub>. Interelectrode gap 0.5 mm. <sup>b</sup>Determined by calibrated GC. <sup>c</sup>Isolated product.

seen that the consumption of reactant varied little with the volume of reactant solution (hence, electrolysis time) and the weight of product formed was determined only by the weight of reactant used. The cell performance was stable with time, and with this reactant concentration and electrolyte flow rate allows the formation of >100 g of 2-methoxy-*N*-formylpyrrolidine (**2**) in a day (entries 2–3, Table 2).

A few electrolyses were carried out in a cell where the steel cathode plate had a deeper (0.75 mm) spacer groove in order to create a narrower interelectrode gap (0.25 mm). This results in a higher linear flow rate (at constant volumetric flow rate) and consequent increased mass transfer coefficient and conversion. Methoxylation of **1** (0.1 M) in the narrower interelectrode gap at a flow rate of 16 mL min<sup>-1</sup> resulted in 94% consumption of the starting material.

### 3. DISCUSSION

A microflow electrolysis cell for multigram synthesis is described. It is easily set up and operates with inexpensive

**Table 1. Electrolyses of 0.1 M *N*-Formylpyrrolidine (**1**) in MeOH with 0.05 M Et<sub>4</sub>NBF<sub>4</sub><sup>a</sup>**

entry	flow rate/cm <sup>3</sup> min <sup>-1</sup>	volume of solution/cm <sup>3</sup>	cell current/A	charge passed/C	reactant <b>1</b> consumed <sup>b</sup>	yield of <b>2</b> <sup>b</sup>	product <b>2</b> rate of formation (g h <sup>-1</sup> ) <sup>c</sup>
1	2.0	10	1	300	100%	73%	1.1
2	3.0	10	1	200	84%	84%	2.0
3	5.0	10	2	240	84%	84%	3.3
4	8.0	10	3	225	83%	69%	4.3
5	16.0	128	6	2880	77%	77%	8.7
6	16.0 <sup>d</sup>	240	12	10800	88%	84%	20.7

<sup>a</sup>Interelectrode gap of 0.5 mm. The theoretical charge for full conversion of 10 cm<sup>3</sup> of 0.1 M of the reactant solution is 200 C. <sup>b</sup>Determined by calibrated GC. <sup>c</sup>Calculated from the yield, which was determined by calibrated GC. <sup>d</sup>Using a 0.2 M solution of reactant.

auxiliary equipment. It is particularly convenient to use for extended electrolysis where the objective is the synthesis of larger quantity of product. When operated under appropriate conditions,<sup>9</sup> it allows high conversions in a single pass and the synthesis of tens of grams of product. The cell is also straightforward and rapid to dismantle, clean, and reassemble.

This design of microflow electrolysis cell also has the advantage of a low residence time (150–19 s for flow rates of 2–16 mL min<sup>-1</sup>) in the reactor for high conversion. This minimizes competing reactions in homogeneous solution (often a problem during lengthy electrolyses in beaker cells) and aids high selectivity. The high conversion also greatly simplifies pure product isolation.

With high flow rates, a high conversion in a single pass demands a high current (the charge/unit volume demanded by Faraday's law must be passed during the residence time of the reactant within the cell). In fact, the performance is limited by the current density that can be used with the present anode material. When operated with a cell current above 10 A (an average current density of 0.1 A cm<sup>-2</sup>), high conversions were still obtained although the carbon/PVDF composite was found to undergo some pitting with black powder appearing in the product reservoir. In the case of the cell possessing a narrower interelectrode gap (0.25 mm), electrical shorting was observed at the higher current densities, although this was not observed when the interelectrode gap was 0.5 mm. Despite the observed pitting, the anode material was reused multiple times (after polishing between reactions) without observed detriment to conversion or productivity. Clearly, alternative more stable anode materials would be attractive and are being investigated. Nonetheless, the larger cell reported here with the carbon/polymer composite anode is an effective tool for multigram laboratory electrosynthesis. It is particularly advantageous compared to our earlier cell design for the electrolysis of substrates with limited solubility or when the electrolysis target is a large weight of product.

#### 4. EXPERIMENTAL SECTION

**Microflow Electrolysis Cell.** The cell was manufactured by Cambridge reactor Design Ltd. It was designed to allow the conversion of larger amounts of product with high selectivity and conversion in a single pass. The cell design is based on two circular plate electrodes, diameter 149 mm and a spiral solution channel, width 5 mm where the electrolyte flows from the center of the discs to their perimeter (Figure 1). The spiral solution channel was created by machining a spiral groove (2 mm in width and 0.5 mm in depth) into one of the electrodes so that there was a 5 mm spacing between neighboring sections of the groove. A polymer gasket/spacer, thickness 1 mm, was laser cut so that it fitted into the groove. When compressed against a flat plate electrode, this creates a channel 2 m long, 5 mm wide with an interelectrode gap of 0.5 mm. The interelectrode gap may be adjusted via the depth of the groove and/or the thickness of the gasket/spacer.

In the particular cell used in this paper, the groove was machined into the stainless steel (grade 316L, Castle Metals UK Ltd.) cathode plate, and the anode plate was carbon filled polyvinylidene fluoride (C/PVDF, type BMA5, Wilhelm Eisenhuth GmbH, Germany) sheet, thickness 3 mm or 5 mm. The gasket/spacer was cut from a sheet of KALREZ perfluoroelastomer (James Walker Ltd., 1 mm thick). The carbon/polymer composite electrode had a copper backing plate to improve the potential distribution. The cell was

compressed between an aluminum base plate and a perspex top each of diameter 180 mm via a central bolt (tightened to 20 N m) and 8 bolts around the perimeter (each tightened to 4 N m). The reaction solution entered and exited the cell via steel tubing, 3/16th inch diameter to which connection could be made with standard fittings. There were separate reservoirs for reactant and product solutions, and the solution was pumped with an Ismatec Reglo digital peristaltic pump, with flow rates generally in the range 1–20 mL min<sup>-1</sup>. Electrolyses were carried out with constant currents controlled by either a TTi 35 V/10A power supply (type TSX3510P) or a Farnell AP60-150 regulated power supply. The cell is straightforward to dismantle, clean, and reassemble.

The cell was always operated in the single pass mode. The volume of the electrolyte solution channel in the microflow cell was 5 mL. Hence, with a flow rate of 10 mL min<sup>-1</sup> the residence time of reactant in the cell was only 30 s (excluding the increased flow rate as a consequence of bubble formation) necessitating a cell current of 3.3 A for full conversion with 0.1 M reactant undergoing a 2e<sup>-</sup> oxidation.

**Chemicals and Analysis.** Methanol (Fisher Scientific, HPLC grade), tetraethylammonium tetrafluoroborate (Alfa Aesar, 99%), and *N*-formylpyrrolidine (Sigma-Aldrich 98%+) were used without purification.

In general, conversions were determined by gas chromatography of the cell effluent. A Shimadzu GC-2014 equipped with an autosampler, FID detector, and an Agilent technologies HP5 column (length 30 m, I.D. 0.32 mm, film thickness 0.25 μm) was used. The results were processed using GC Solution Lite software. Separations were carried out using He as a carrier gas with a flow rate of 2.48 mL min<sup>-1</sup> through the column. A split injection was conducted using a split ratio of 100:1. The injection and detector temperatures were maintained at 280 and 295 °C, respectively. The oven temperature was initially held at 60 °C and then programmed to increase at 10 °C min<sup>-1</sup> to 180 °C, where it was held for 1 min. 1 and 2 were observed at 5.2 and 6.2 min, respectively. The GC was calibrated using serial dilutions of a known concentration of both the starting material and the product.

**Electrochemical Synthesis of 2-Methoxy-*N*-formylpyrrolidine.** A solution containing 0.10 M of 1 (4.95 g, 0.05 mol, 1.00 equiv) in MeOH (500 mL) with 0.05 M of Et<sub>4</sub>NBF<sub>4</sub> (5.42 g, 0.025 mol, 0.5 equiv) present as electrolyte was sonicated prior to the electrolysis to ensure complete dissolution. Before assembly of the reactor, the working electrode (carbon filled PVDF) was polished with cotton wool. The cell was filled with MeOH at a flow rate of 8 mL min<sup>-1</sup> and the power supply set to a constant current of 5 A (a constant voltage limit was also set at 12 V). The cell feed was then switched to the reactant solution (note: the cell current does not actually reach the set value until the MeOH in the channel is displaced by electrolyte solution). The reaction was continued for 1 h, by which point 480 mL of reaction solution has passed, whereupon the cell feed was switched back to the MeOH reservoir. The product reservoir solution was analyzed by GC to determine the conversion (92%), the yield (89%) and the charge efficiency (49%). The MeOH was removed under reduced pressure, and the resultant oil was treated with EtOAc causing the Et<sub>4</sub>NBF<sub>4</sub> to precipitate. The solid was removed by filtration (and could be reused after recrystallization from a minimum amount of hot MeOH, and drying overnight in a vacuum oven at 90 °C, ~10 mbar). EtOAc was removed to give a yellow oil, which was purified by vacuum distillation (100 °C at 15 mbar to remove

starting materials, then 170 °C at 15 mbar), to give **2** as a colorless oil (5.4 g, 0.042 mol, 88%).

<sup>1</sup>H NMR data are consistent with reported values.<sup>12</sup> FT-IR (cm<sup>-1</sup>) neat; 3499, 2892, 1671, 1588. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm; Spectra presented as a mixture of rotamers (~5:1). 8.40<sub>maj</sub> and 8.29<sub>min</sub> (1H, s), 5.37<sub>min</sub> and 4.92<sub>maj</sub> (1H, d, *J* = 4.8 Hz), 3.58–3.40 (2H, m), 3.37<sub>min</sub> and 3.26<sub>maj</sub> (3H, s), 2.13–1.79 (4H, m). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ ppm; Spectra presented as a mixture of rotamers. 162.5<sub>min</sub> and 161.2<sub>maj</sub>, 89.5<sub>maj</sub> and 85.4<sub>min</sub>, 56.5<sub>min</sub> and 54.2<sub>maj</sub>, 45.0<sub>min</sub> and 42.5<sub>maj</sub>, 31.8<sub>min</sub> and 31.7<sub>maj</sub>, 22.0<sub>min</sub> and 21.2<sub>maj</sub>. LRMS (ESI) *m/z* 130.1 [M + H]<sup>+</sup>.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00260.

<sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **2** (PDF)

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### Notes

The authors declare no competing financial interest.

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