

MASTER

Towards a modular design for an electrochemical micro reactor

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Abstract

Conventional production of many organic molecules on an industrial scale involves harsh conditions, multiple toxic or hazardous reagents, and long reaction times. An electrochemical approach for organic synthesis could eliminate the need for hazardous reagents, as it offers a clean route to forming radical species. Moreover, the selectivity can easily be controlled by applying an electric potential similar to the oxidation potential of the desired reaction.

Major drawbacks of electrochemical processes in batch, however, are limiting mass transfer due to the distance between the electrodes and saturation of the electrode surface (*i.e.* electrodeposition). These drawbacks can be overcome with the use of a continuous microreactor, due to the small dimensions and continuous flow.

During this project a fully modular and simple electrochemical microreactor was developed (**Figure 1**). The oxidation of thioanisole was chosen as benchmark reaction and operation parameters such as gasket thickness, flowrate, and the applied potential and current were investigated.

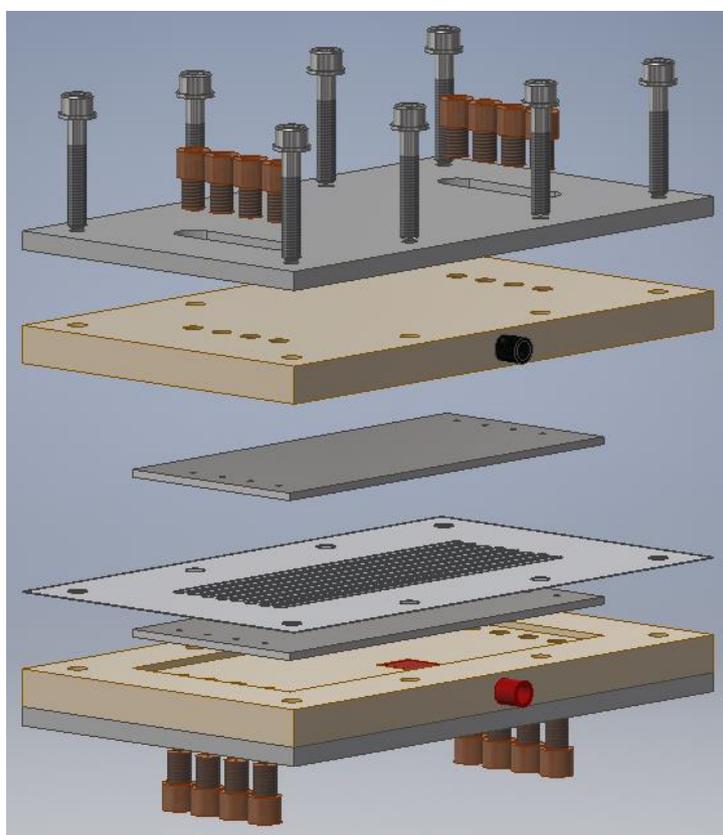


Figure 1: Exploded view of the reactor design

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Introduction

Many organic reactions are driven by electron-transfer processes, but in order to achieve the production of organic compounds by transfer of electrons, often harsh conditions and toxic reagents are required. Moreover, conventional organic synthesis routes often suffer from selectivity issues. Electrochemically synthesizing organic compounds would be an attractive method, as transformations requiring electron-transfer, *e.g.* oxidation of functional groups and C-C coupling, are achievable without having to deal with the disadvantages of these conventional processes.^{1,2,3,4} The use of electrons as traceless reagents offers a sustainable alternative, while also adding the advantages of mild reaction conditions, good functional group tolerance, and high chemoselectivity.⁵

Electrochemistry

Electrochemical reactions revolve around the use of electrons to transfer energy and initiate reactions. An external power source supplies a current, which donates electrons to the mixture. Due to the supply of electrons at the cathode, reduction reactions can occur near the electrode surface. The anode extracts electrons from the mixture, resulting in oxidation reactions to take place. In order to have a closed electrical circuit, however, it is necessary for the reaction mixture to conduct the current. As organic solvents generally have a low conductivity, conduction through the reaction mixture can occur due to the presence of other compounds in solution, which are called electron carrying species. Examples of electron carrying species are electrolytes, acids or bases. Intermediate ionic radicals formed by electrochemical reactions act as electro-active species as well.⁶

This formation of ionic radicals via electrochemical reaction can only take place in close proximity of the electrode surface, in the so-called Helmholtz layer.⁶ This layer is only a few nanometers wide and therefore transport of reactive species towards this region is of great importance. Transfer of an electron to an organic compound in this layer can create an intermediate ionic radical, which can react further towards the desired product.

Because the electrons in electrochemical synthesis partake in the reactions, they act as reagents whose reactivity is easily tuneable by changing the current or potential on the system. Therefore it is unnecessary to operate at elevated temperatures, use expensive catalysts, or use hazardous and toxic reagents. Moreover, the electrodes can often be made using cheap materials, making electrochemical synthesis green and inexpensive.⁷

In an electrochemical system, the applied potential can be seen as the energy of the electrons, while the current is the amount of electrons flowing through the system per second. Two methods of operation can be used to perform electrochemical reactions, by either fixing the potential or the current on the system (called potentiostatic and galvanostatic operation respectively). Provided that the energy of the electrons is high enough to initiate a reaction, the current determines the reaction rate. Fixing the potential on the other hand, determines the species that are able to react at the electrode surface, as different reactions need a different amount of energy from the electrons. Both the reductive and oxidative reaction determine the total necessary energy, and thus the potential that needs to be applied for reaction to occur. Therefore, the selectivity towards a certain product can be tuned with the potential in a system where multiple reactions are possible. To achieve the highest yield of a desired compound, the potential should be fixed accordingly and voltammetry is a method to find this optimal potential.

Voltammetry

Voltammetry is an analytical method, which helps find the relation between the potential and the current on a system. Applying a range of potentials and measuring the current corresponding to each potential is called single sweep voltammetry. When the two parameters are plotted against each other, the resulting graph is called a polarogram. An example of a polarogram of the oxidation of thioanisole is given in **Figure 2**.⁵ At potentials below 1 V the system does not conduct electricity and there is no current measured. By increasing the potential the energy of the electrons will increase and at some point reaction of the substrate at the electrode surface is possible. At that point the system will start to conduct electricity. Transfer of the reactive compound to the electrode surface by diffusion becomes the limiting step for reaction and thus conduction. The current will therefore flatten off and a plateau can be observed (2.2 – 2.6 V). If multiple oxidation steps are possible (as is the case with thioanisole), a second plateau can be observed at higher potentials (3.4 – 3.7 V). Each plateau can be attributed to one of the two oxidized products, as can be seen in **Figure 2**. At very high potentials the current will increase exponentially, which indicates the anodic limit of the system. At this point over-oxidation of the system is possible which can damage the electrodes. It is possible for a plateau to disappear in the exponential growth of the current, if the corresponding reaction occurs at potentials near the anodic limit.

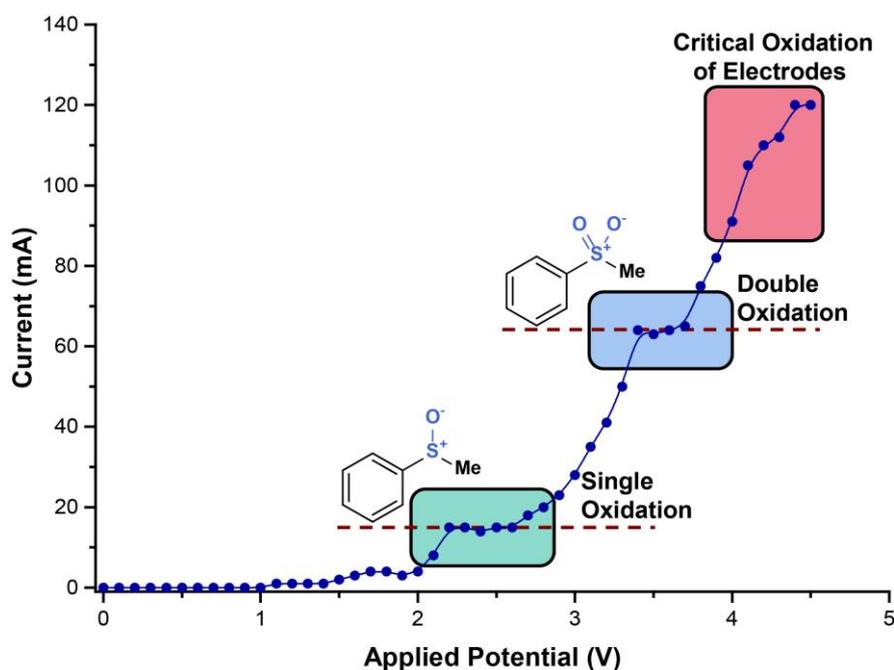


Figure 2: Polarogram of the oxidation of thioanisole

Organic electrochemical synthesis in batch

There are several examples of electrochemical processes on a multi-ton scale, such as the production of ammonia, aluminium, and caustic soda.⁸ However, electrochemical synthesis of organic compounds on a big scale suffers from several disadvantages and is therefore much less developed. This is mainly due to the big dimensions of the reactor vessels used for large scale production, as transport of reactants from the bulk of the mixture towards the electrodes is limiting. A general representation of an electrochemical batch setup is given in **Figure 3**. A power source supplies electrons to the system via the cathode and anode and reactions take place at the electrode surfaces. The electrodes, however, only take up a small portion of the volume in the vessel. As most of the vessel is filled with the bulk of the reaction mixture, which does not facilitate reactions. The active volume fraction, as well as the surface-to-volume ratio of batch setups is therefore low.

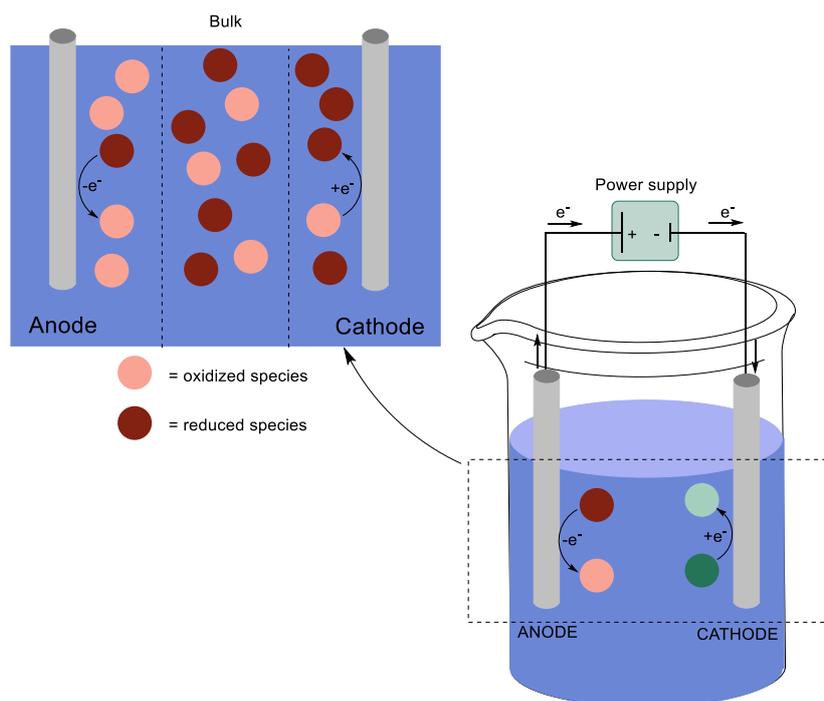


Figure 3: Typical electrochemical batch setup

Because the electrodes are stationary and reaction only takes place in close proximity of the electrodes, transfer of mass to the electrodes is a very important aspect of electrochemistry. This does not only hold for the reagents, but also for other electron carrying species in solution that are necessary to stabilize the formed intermediate ionic radicals. For systems with a low surface-to-volume ratio, such as electrochemical batch setups, the transfer of mass to the reactive sites is the rate limiting step of the process.

Another issue with the a surface-to-volume ratio is that heat created by exothermic reactions at the electrode surface is difficult to remove, which can result in the formation of hotspots. These hotspots, in turn, can lead to side reactions to take place, reducing one of the advantages of electrochemistry: high selectivities.⁹

On top of these problems with mass- and heat transfer, another disadvantage of electrochemical batch setups is the distance between the two electrodes. The further away from one another, the higher the resistance over the bulk of the mixture, resulting in conductivity problems. Moreover, the electrical field will be less homogeneous with increasing inter-electrode spacing, which could result in hotspot formation. Lastly, organic compounds can deposit on the electrode surface during reaction. As organic compounds generally do not conduct a current, this saturation of the electrode surface with organic compounds inhibits further reaction.

An overview of the most important advantages and disadvantages of organic electrochemistry in batch is given in **Table 1**.

Table 1: Most important advantages and disadvantages of organic electrochemical synthesis

Organic electrochemical synthesis	
Advantages	Disadvantages
Selectivity	Mass-transfer
Low costs	Energy-transfer
Environmentally benign	Deposition on the electrodes

Organic electrochemical synthesis in microflow

Most of the disadvantages of organic electrochemistry in batch can easily be overcome by performing the reactions in a continuous-flow microreactor. Microreactors in general have the advantage of scale, due to the increased surface-to-volume ratio and decrease in inactive volume. By decreasing the reactor dimensions, mass transfer limitations can be overcome, efficiency and selectivity can be increased, and safe operation is ensured due to the low quantities of reagents in the reactor. An added advantage is that, by bringing both electrodes closer together, a more evenly distributed electrical field can be achieved, making hot-spot formation and consecutive side reactions less pronounced.³

The last notable advantages of microflow are caused by the continuous flow through the reactor. Because of this flow, the heat produced by reaction can be removed efficiently and organic deposition on the electrode surface is inhibited.¹⁰

Reactor design

Due to the advantages that organic electrochemistry in microflow has to offer, this has become an area of interest for researchers. For this research however, specialized equipment is often necessary. Research groups often fabricate their own setups, but there are also several commercially available electrochemical reactors. Most of these setups, both self-made and commercially available, have parallel plates with the reactants flowing between the electrodes, as the use of parallel plate cells has a number of advantages:¹¹

- Due to the parallel alignment of the electrodes, an homogeneous electrical field is formed
- A constant narrow interelectrode gap can be achieved using a simple polymer spacer
- Uniform flow between the electrodes can be achieved due to the small dimensions of the setup
- Scaling of the setup can easily be achieved by increasing the electrode surface or by external numbering up

Three examples of commercially available electrochemical reactors are displayed in **Figure 4**.

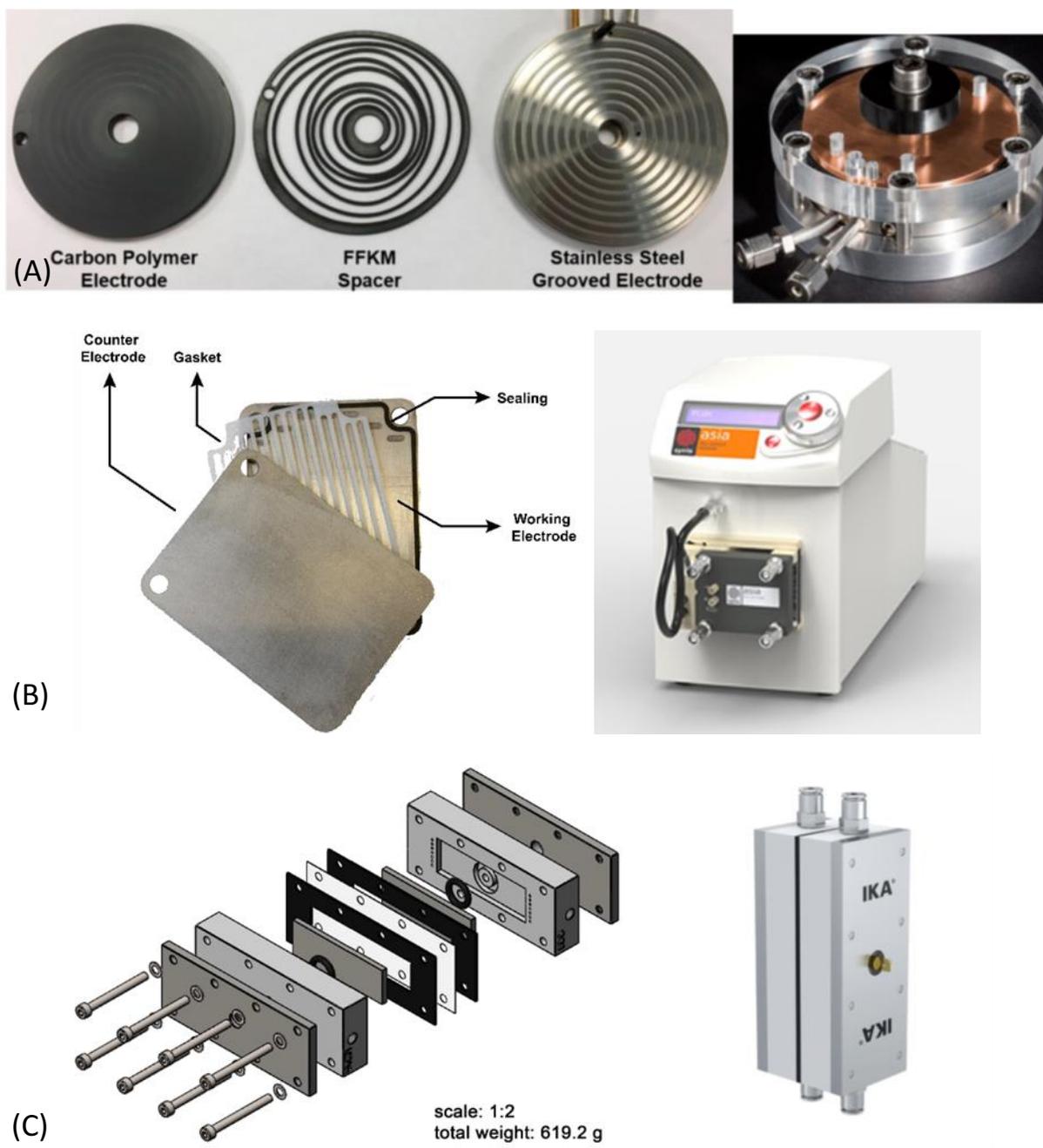


Figure 4: Commercially available electrochemical microreactors (A) Ammonite 8, (B) Syrris Asia Flux, and (C) ElectraSyn Flow

Each of these three designs has their own distinctive feature. Ammonite 8, for instance, has a circular design with a spiralling channel between the electrodes. While ElectraSyn Flow opts for an open gasket design without any channels. Features of these three designs are summarized in **Table 2**.¹²⁻¹⁴

Table 2: Features of commercially available electrochemical microreactors

	Ammonite 8	Syrris Asia Flux	ElectraSyn Flow
Reactor volume (mL)	1.0	0.3	1.2
Gasket thickness (mm)	0.5	0.25	1.0
Flow range (mL/min)	> 1.0	> 0.05	> 1.0
Residence time (min)	< 1	< 15	< 1
Gasket material	FFKM	PTFE	EPDM
Gasket type	spiralling channel	linear channels	no channels
Electrode material	carbon and stainless steel	stainless steel	variable
Electrode design	circular and machined	complex and machined	simple
Modular	except for machined electrode	no	yes*
Sealing ring	no	yes	no
Cell type	undivided	undivided	divided and undivided
Power supply	excluded	included	included
Pump	excluded	excluded	included
Easy assemblage	no	no	yes
Cost	€ 9,047.00	€ 18,824.00	€ 9,200.00

*Each electrode does, however, needs its own Teflon piece.

Previous research within this group on the oxidation of sulfides was done using the Syrris Asia Flux module.^{5,15}

Previous work

In previous research performed in the NRG group, a general procedure for electrochemical synthesis of sulfoxides and sulfones was developed and a basic reaction scope was carried out using Syrris Asia Flux (**Figure 5**).^{5,15}

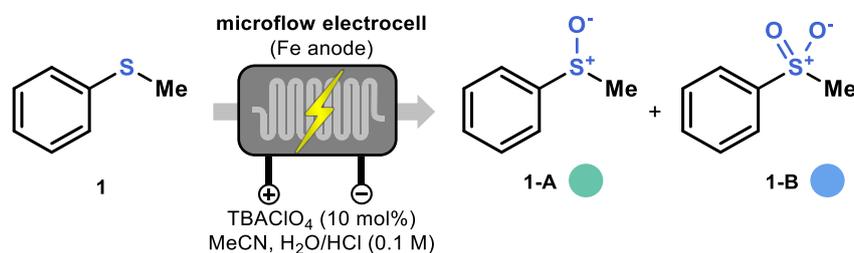


Figure 5: General procedure for the electrochemical synthesis of sulfoxides and sulfones using Syrris Asia Flux

In this generalized method, 0.15M of substrate was dissolved in acetonitrile. In order for the mixture to conduct a current, 10 mol% of tetrabutylammonium perchlorate was necessary as supporting electrolyte. Lastly, an aqueous acidic solution was necessary to supply the oxygen for reaction, as well as to lower the pH. The lowered pH was necessary to increase the redox potential of the electrodes. The stabilizing property of acid on the electrodes is shown in **Figure 6**, as the oxidizing potential of iron is higher at lower pH.¹⁶ Rust (Fe^{3+}) formation could clog the microchannels, therefore a 0.1M HCl solution in water was necessary. The aqueous acidic solution mixed with acetonitrile in a 1:3 v/v ratio.

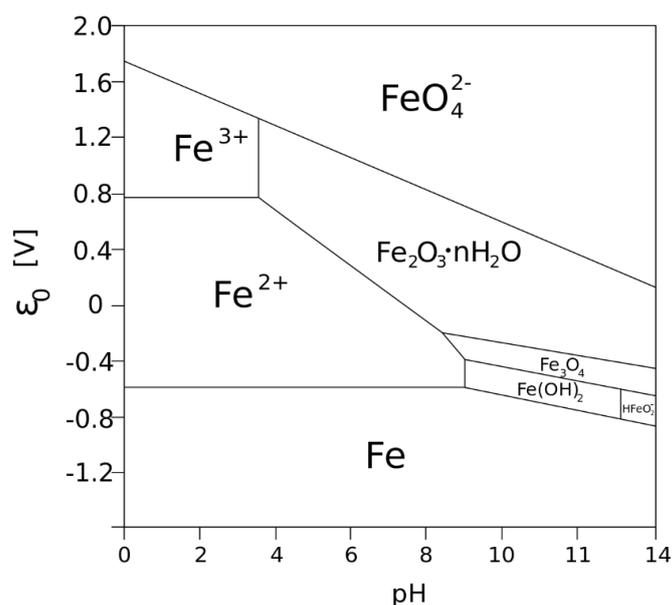


Figure 6: The Pourbaix diagram for iron at 25°C

The Syrris Asia Flux module used in previous research has several limitations, which limits further research. One of these limitations is the small reactor volume of 300 μL , which, for many compounds, results in having to enter the reaction mixture into the flow cell multiple times, in order to achieve full conversion. Moreover, because one of the electrodes has been machined to facilitate flow from one channel to the next, alignment of the gasket to these machined indents is difficult, while also making replacement parts expensive. Because of the vulnerability of the small gasket, and the difficulty to align it to the indents in the electrode, experiments often fail due to improper assemblage. Lastly, monitoring the reaction inside of the flow cell is impossible, as the reaction mixture is inaccessible due to the casing.

Project aim

The aim of this project is to come up with a design for an electrochemical microreactor, which is simple, modular and cheap. Compared to Syrris Asia Flux, this design should have a bigger reactor volume to accommodate a broader residence time range. It should be easier to assemble, without having excessive points of alignment (such as the indents in the Syrris Asia Flux electrode visible in **Figure 7**). Machining of one of the electrodes would complicate the design and make it more expensive. Other improvements to the new reactor design would be to have as little unique components as possible to achieve a modular design, and to add an option for intermediate sampling.

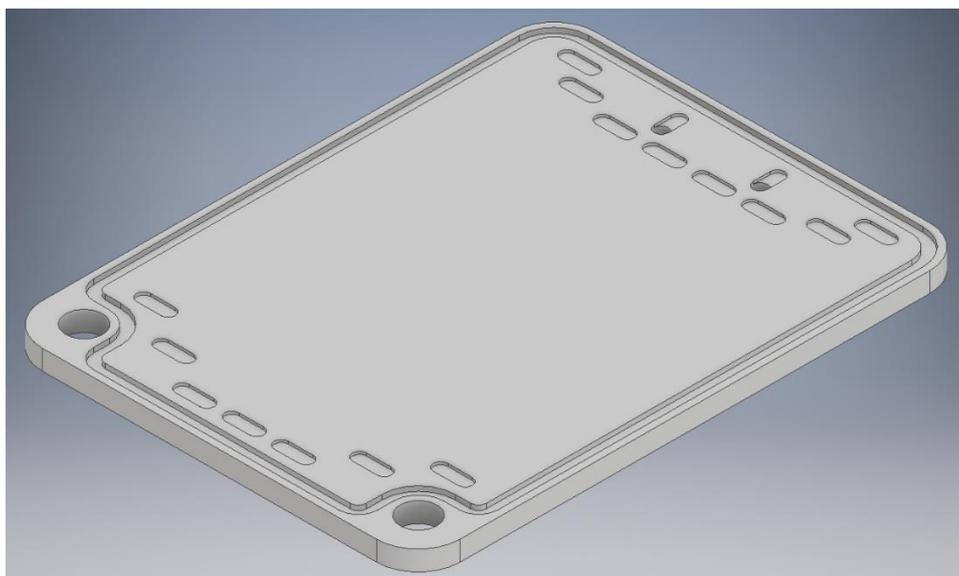


Figure 7: Machined electrode of Syrris Asia Flux with indents so facilitate flow between channels

After designing, the new reactor will be characterized for the volume and the range of possible flowrates. Using the method shown in **Figure 5**, the oxidation of thioanisole will be the benchmark reaction to test the new reactor. Previous experiments by Menno Lanting MSc. and Benny Knoops MSc., involving linear sweep voltammetry for thiol oxidation and the dependence of the residence time on product yields (**Figure 8**), will be repeated and compared to the results using Syrris Asia Flux.^{15,17}

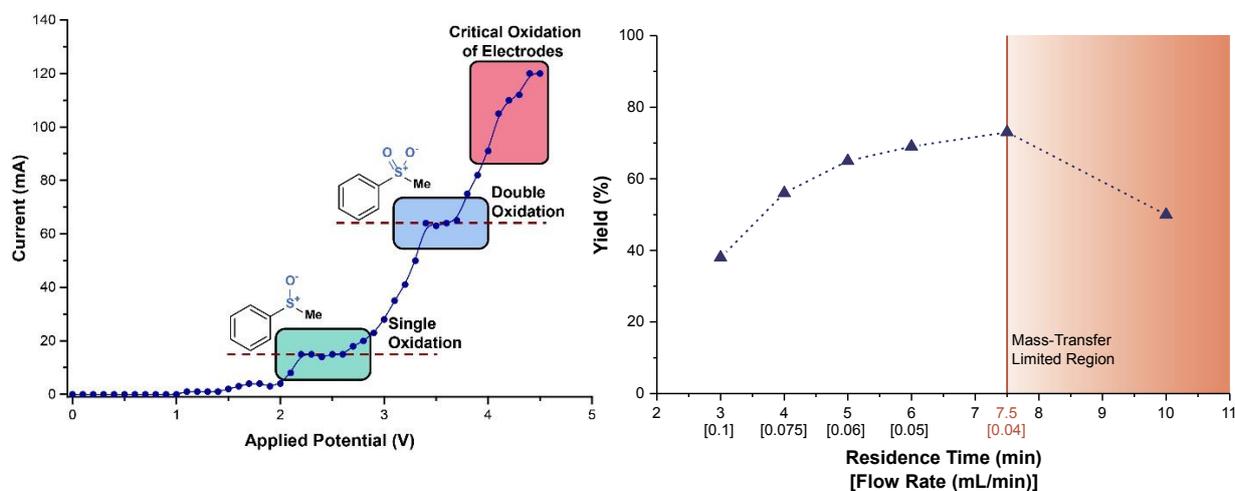


Figure 8: Previous results using Syrris Asia Flux. Left) polarogram of the oxidation of thioanisole Right) dependency of the sulfoxide yield on the residence time

Reactor design

A new parallel plate reactor was designed, improving on the design of Syrris Asia Flux used in previous research.¹³ Main limitations of this setup were the limited reactor volume and difficulties with assemblage. ElectraSyn Flow was a second reactor the new reactor design was based on.¹⁴ Some features of these two designs were previously mentioned in **Table 2**. Based on these characteristics, the following criteria were set for the new reactor design:

- Increased reactor volume
- Variable spacing between electrodes
- Simple electrode design
- Fully modular
- Possibility for intermediate sampling
- Cheap materials

ElectraSyn Flow uses a simple electrode, whose surface is fully used for electrochemical reaction by using an open gasket design. **Figure 9b** shows the electrode being embedded in a Teflon piece, with its top surface aligned to the Teflon surface. In order to align the electrode surface precisely with the in- and outlets of the Teflon piece, the Teflon piece is heated to 200 °C, and the electrode is pressed inside it. Heating of this piece could damage the integrity of the material over time. Moreover, one unique Teflon piece is needed per electrode, because of the exact fit that is necessary for operation. The reaction mixture is added via the Teflon piece, which requires this piece to be chemically resistant and able to distribute the reaction mixture over the width of the electrode.

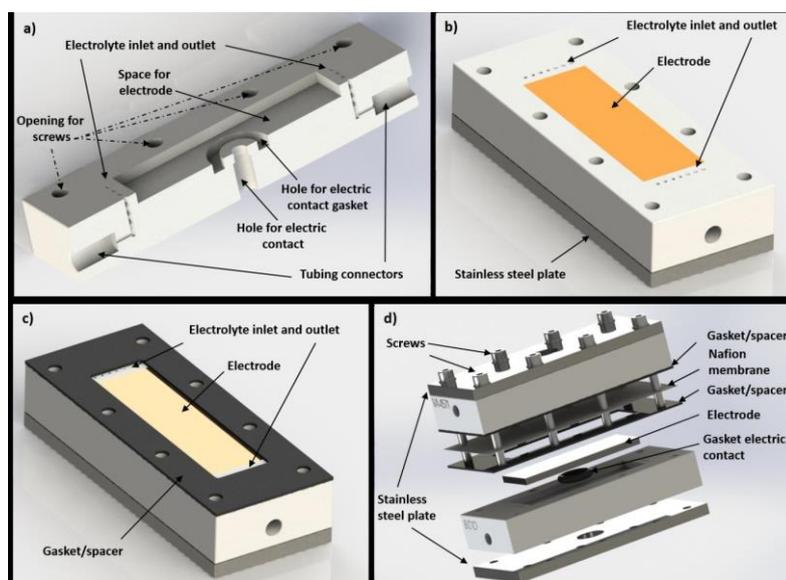


Figure 9: ElectraSyn Flow design. a) cross-section of the Teflon piece. b) complete half-cell with Teflon piece, electrode and back plate. c) complete half-cell with gasket. d) exploded view of total reactor

In order to lower the machining and material costs of the Teflon piece embedding the electrode, the new design was simplified and the material was changed to polyoxymethylene (POM), a polymer material with a high stiffness and excellent stability. Instead of using this piece to transport and distribute the reaction mixture, the mixture would directly be added between the electrodes by locating the in- and outlet into the electrode design, simplifying the casing piece while not adding complexity to the electrodes. **Figure 10** shows the new design for both the electrode and the POM casing to hold the electrode in place. The electrode fits in the indent of the POM piece, but unlike ElectraSyn Flow's design, the top surface does not need to align perfectly to the POM surface.

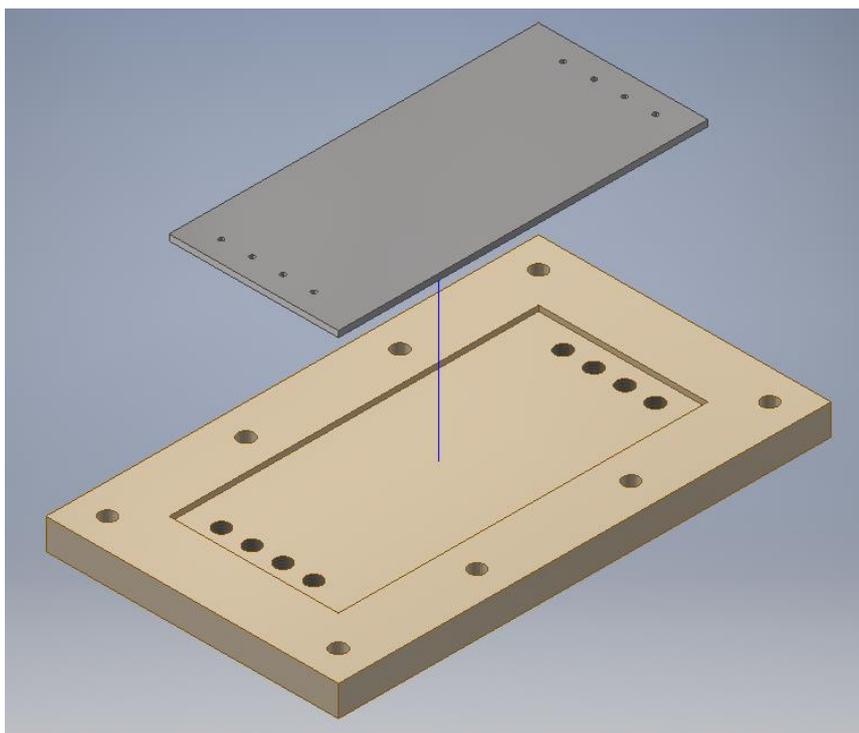


Figure 10: Design of the electrode with in- and outlet holes, and a POM piece to hold the electrode in place

In order to supply the reaction mixture directly between the two electrodes, Super Flangeless Fittings (**Figure 11**) need to be pressed against the outside surface of the electrodes, without coming in contact with the POM piece. Therefore, threaded holes were added to the POM piece, that are aligned to the in- and outlet holes of the electrode.



Figure 11: Super Flangeless Fitting, including PFA tubing

The electrode was made big enough, for eight channels of 100 x 3 mm to fit on its surface. With a interelectrode spacing of 0.25 mm, this would result in a total reactor volume of 600 μL , which is twice the volume of Syrris Asia Flux. Each electrode would have one inlet hole for each channel, the outlet hole would be located in the other electrode. By designing it like this, a symmetry axes perpendicular to the electrode surface is created (the blue line in **Figure 10**), which results in the two electrodes being exactly the same. This also holds for the POM piece, resulting in the top and bottom part of the reactor to be the same, and thus interchangeable. This greatly lowers the complexity of the design and makes the device easy to assemble. Moreover, because of the simplicity of the electrode design, the electrodes can easily be made of different materials.

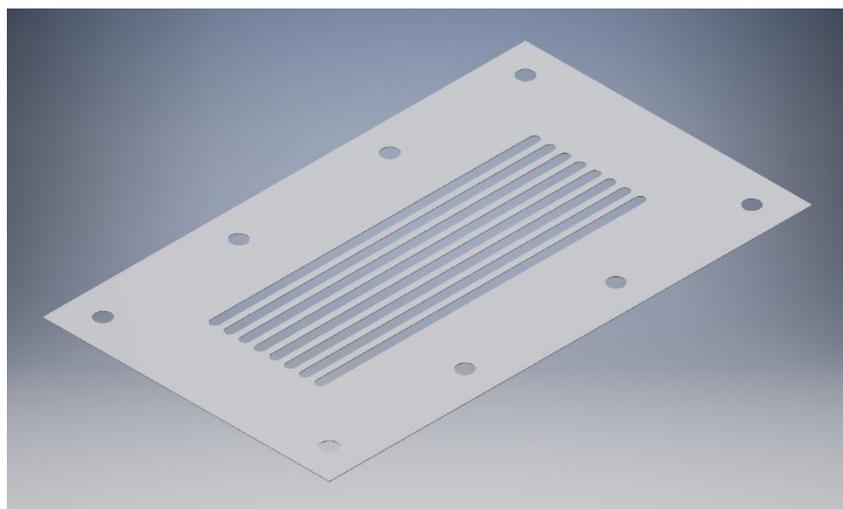


Figure 12: Gasket design with eight channels

In order to facilitate the channels as mentioned above, a gasket was designed as shown in **Figure 12**. The gasket has eight channels, aligned to the holes in the electrode. This gasket serves as a spacer between the two parallel electrodes and is made of Teflon. As Teflon sheets of different thicknesses can be bought, the interelectrode spacing can be chosen by varying the sheet thickness. This sheet of Teflon has the same surface dimensions as the POM piece, to simplify alignment of all parts.

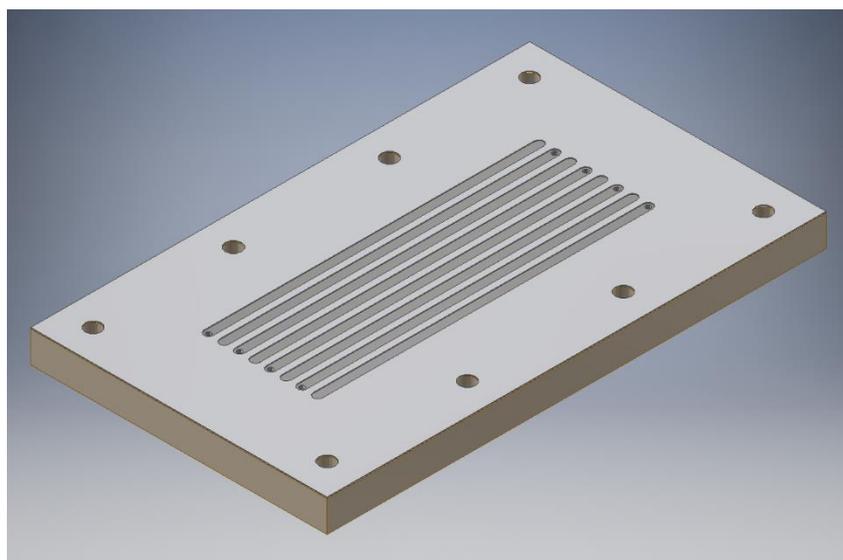


Figure 13: Gasket aligned to the POM piece and the inlet holes of the electrode

Figure 13 shows the gasket on top of the electrode to create eight channels. As can be seen in this figure, each channel only has one inlet hole, the outlet of the channel is through the other electrode. In order for the reaction mixture to be transported from one channel to the next, a piece of tubing loops outside of the reactor to the next channel. Because of this external loop, the reaction mixture is brought outside of the reactor, making it possible to monitor the reaction by taking samples after each channel.

Two thick steel plates are added to press all components together with bolts. The resulting pressure on the gasket seals off the cell and prevents leakage. Finally, the design is completed by creating space for spring contacts into the POM pieces with banana cable connections. An exploded view of the final

design and a picture of the assembled reactor with tubing loops are shown in **Figure 14** (left and right picture respectively).

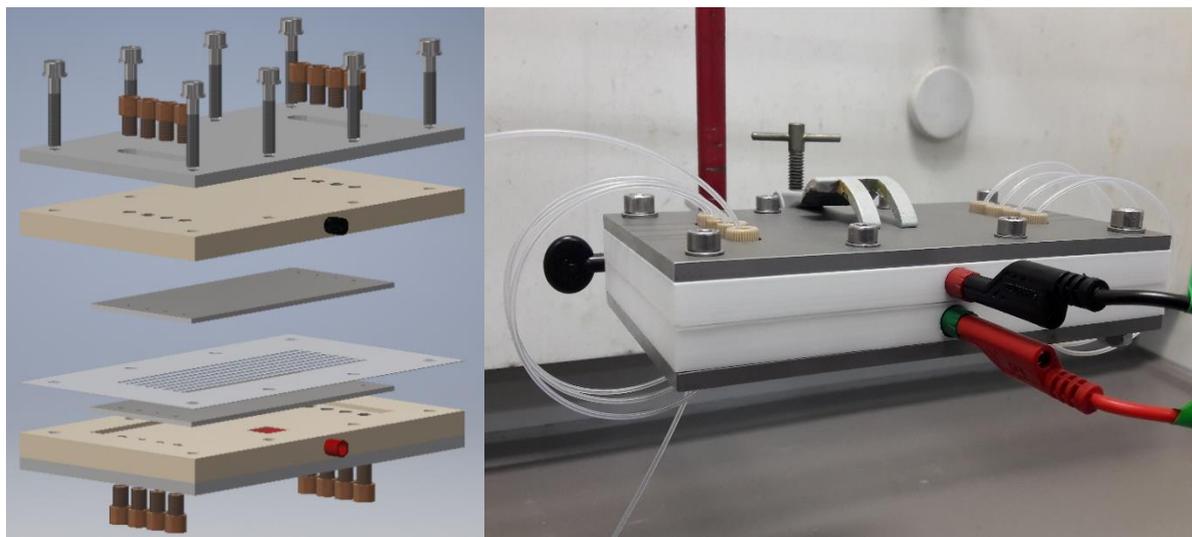


Figure 14: Left) exploded view of the reactor design. Right) assembled electrochemical reactor

In summary, **Table 3** shows the designed features of the new reactor, compared to Syrris Asia Flux and ElectraSyn Flow.

Table 3: Features of the new reactor design, compared to Syrris Asia Flux an ElectraSyn Flow

	New reactor design	Syrris Asia Flux	ElectraSyn Flow
Reactor volume (mL)	0.6-1.2	0.3	1.2
Gasket thickness (mm)	variable	0.25	1.0
Flow range (mL/min)	> 0.05	> 0.05	> 1.0
Residence time (min)	1-15	< 15	< 1
Gasket material	PTFE	PTFE	EPDM
Gasket type	linear channels	linear channels	no channels
Electrode material	variable	stainless steel	variable
Electrode design	simple	complex and machined	simple
Modular	fully	no	yes*
Sealing ring	no	yes	no
Cell type	divided and undivided	undivided	divided and undivided
Power supply	excluded (+ € 120.00)	included	included
Pump	excluded	excluded	included
Easy assemblage	yes	no	yes
Cost	€ 902.00 (+ € 120.00)	€ 18,824.00	€ 9,200.00

*Each electrode does, however, needs its own Teflon piece.

With the new reactor design, the setup is not limited to a certain type of pump or power supply. For this research syringe pumps were used, but HPLC or peristaltic pumps are also an option. Any power supply can also be connected to the setup, as long as a banana plug cable is used.

Results and discussion

Reactor characterization

Prior to testing the new flow cell with reaction, first the reactor volume had to be determined. By marking the time the fluid front inside the tubing entered and exited each channel, the time spent in each channel and intermediate tube piece was determined. By multiplying with the flowrate of the syringe pump, the channel and tube volumes were calculated.

A visual representation of the reactor volume is given in **Figure 15**. The red bodies indicate the channels on the electrode surface. Each channels has two fittings (brown), one below the electrode for the inlet and one on top for the outlet. The red arrows in **Figure 15** indicate the in- and outlet of the first channel.

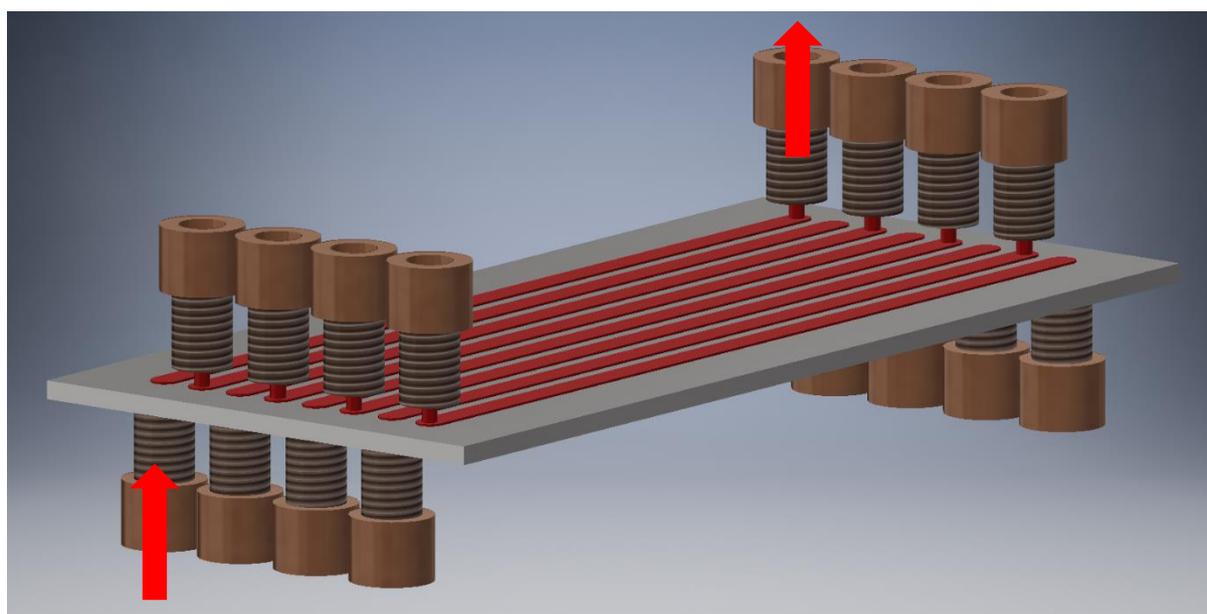


Figure 15: Visual representation of the reactor volume inside the flow cell

In order to get a reliable average on the volumes, volume measurements were carried out at four different flowrates. The calculated channel volume is given in microliters for each of the eight channels for flowrates ranging from 0.1 mL/min up to 1.0 mL/min. The results using the 0.25 mm thick gasket are given in **Figure 16**.

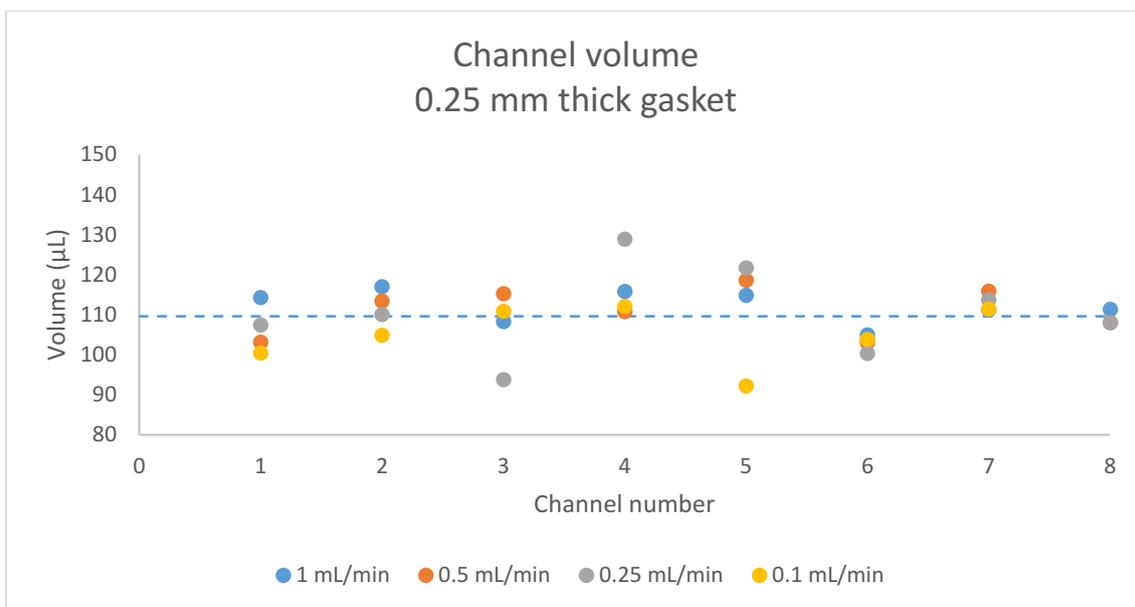


Figure 16: Reactor volume measurements at different flowrates for the 0.25 mm thick gasket

The average volume per channel was calculated to be 110 µL for all flowrates. However, within the same measurement, large deviations in channel volume are notable. An example of this deviation between channels is given in **Figure 17**. This figure shows the results using a 0.25 mL/min flowrate. Most points are in line with the average, with exception of channel 3, 4, 5, and 6, which deviate substantially.

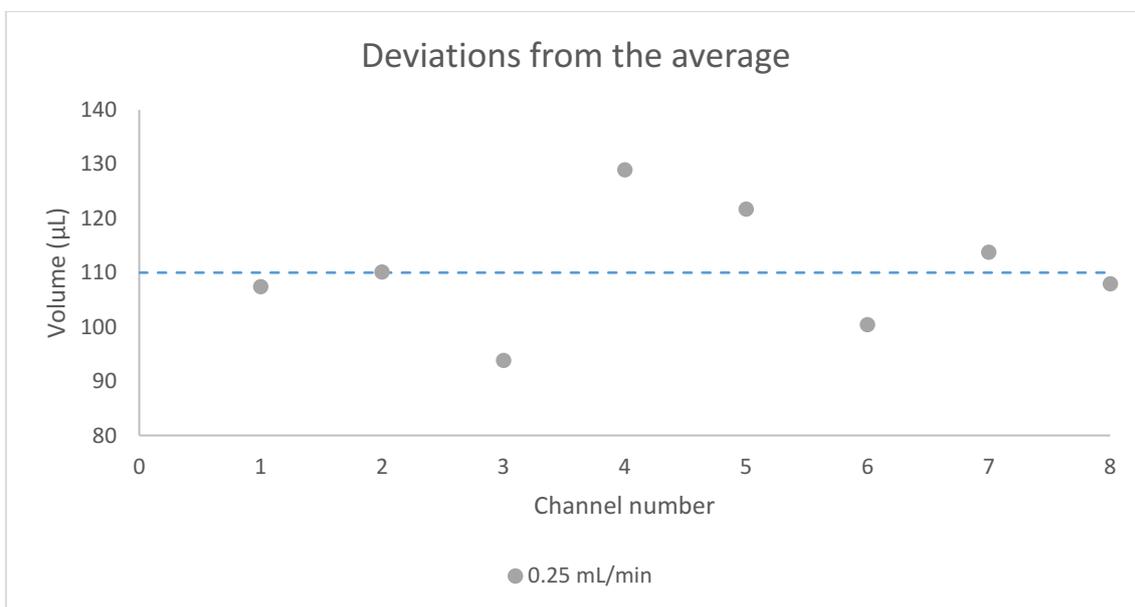


Figure 17: Measurement deviations from the average channel volume

This effect can be attributed to the flexibility of the Teflon gasket. The interchannel spacing can move around slightly during assemblage of the reactor, resulting in some channels being smaller or larger than average, on account of their neighbouring channels. Channel 4 and 5 in **Figure 17** are most likely larger than average on account of channel 3 and 6 being slightly smaller than average. The calculated standard deviation for the volume measurement was 7.5 µL (6.9%), with a standard deviation below 10% being acceptable.

The tubing between two channels was made to be 0.2m long. The resulting tube volume from this measurements was determined to be 82.8 μL using the same method as for the channel volume.

Something else to take into account is that the marked time is not in fact the time the fluid enters and leaves the actual channel. Instead, the time is marked when the fluid front enters and exits the fittings (as can be seen in **Figure 15**, the fittings block the view on the actual channel entrance and exit). The volume of the tubing inside the fitting, as well as the volume of the in- and outlet holes in the electrodes need to be subtracted from the measured values. Based on the inner tube diameter and the length of the fittings, as well as the inlet diameter and thickness of the electrodes, a value of 23.2 μL needs to be subtracted from the channel volume, and added to the tube volume. The average results of the volume measurements are given in **Table 4**.

Table 4: Average results of the volume measurements for the 0.25 mm thick gasket

	Volume (μL)
Channel volume (8x)	88
Tube volume (7x)	106
Total active reactor volume	702
Total tube volume	744
Total reactor volume	1446

During the characterization of the reactor volume, it was found that a flowrate below 0.05 mL/min resulted in leakage between channels. Therefore, 0.05 mL/min was determined to be the lower limit of the system.

The same measurement was carried out using the thicker 0.5 mm thick gasket. Results of this measurement are given in **Figure 18** for flowrates ranging from 0.1 mL/min up to 1.0 mL/min.

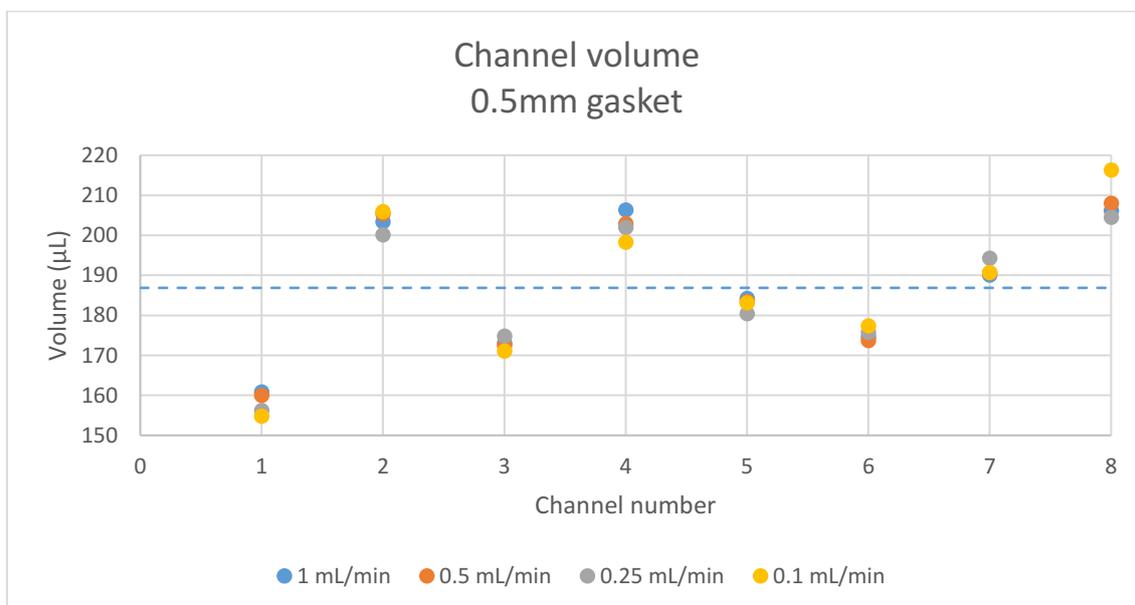


Figure 18: Reactor volume measurements at different flowrates for the 0.5 mm thick gasket

The average channel volume of these measurements resulted in 187 μL . Similar to the measurements using the 0.25 mm thick gasket, large deviations between channels are notable. The calculated standard deviation is 16.8 μL (9.0%). As this value lies below 10%, the deviation is acceptable. Again, a correction factor of 23.2 μL needs to be subtracted from the average channel volumes and added to the average tube volumes. The resulting volume values are given in **Table 5**.

Table 5: Average results of the volume measurements for the 0.5 mm thick gasket

	Volume (μL)
Channel volume (8x)	164
Tube volume (7x)	106
Total active reactor volume	1310
Total tube volume	744
Total reactor volume	2054

Linear sweep voltammetry of thioanisole oxidation

The benchmark reaction to test the new reactor is the oxidation of thioanisole, as given in **Figure 19**.

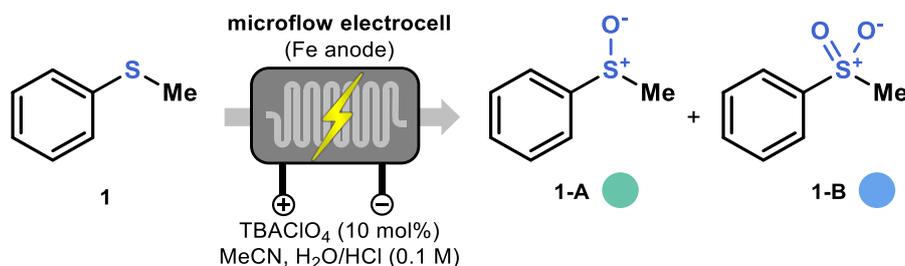


Figure 19: Benchmark reaction method for the oxidation of thioanisole

The general protocol to screen for the electrochemical oxidation of thiols is given in the Experimental section. Using this general protocol, the polarogram of the oxidation of thioanisole was determined using the 0.25 mm thick gasket, and a flowrate of 0.15 mL/min resulting in 5 minutes of residence time. The resulting polarogram is given in **Figure 20** and is compared to the polarogram measured in previous research, using Syrris Asia Flux.⁵

During this experiment, the temperature of the fluid at the end of the reactor was measured. A picture of the used setup is shown in **Figure 21**. Over the course of the experiment, which took multiple hours, no increase of the temperature was measured. Therefore it was concluded that there is no significant heat accumulation over time.

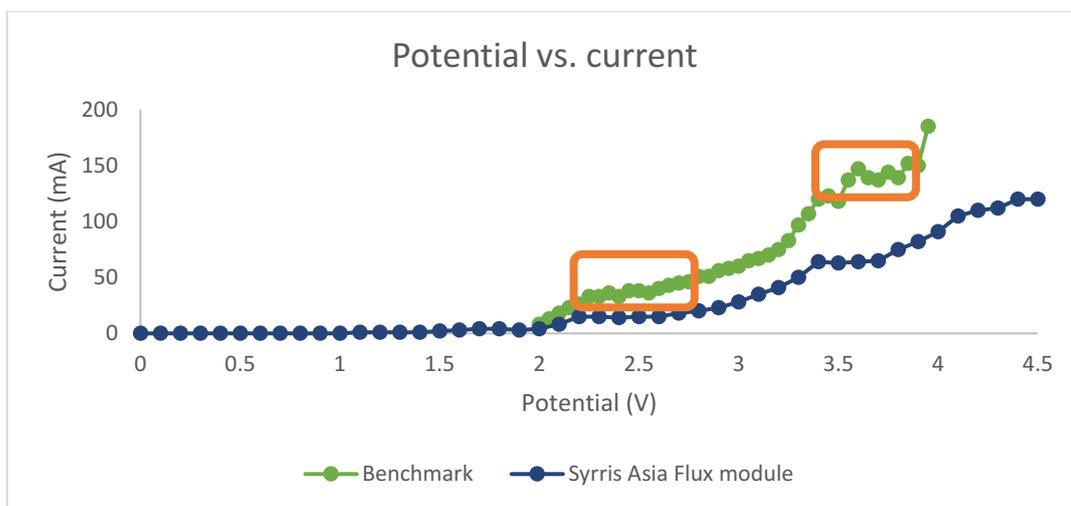


Figure 20: Polarogram of the oxidation of thioanisole in the new reactor, compared to the polarogram using Syrris Asia Flux

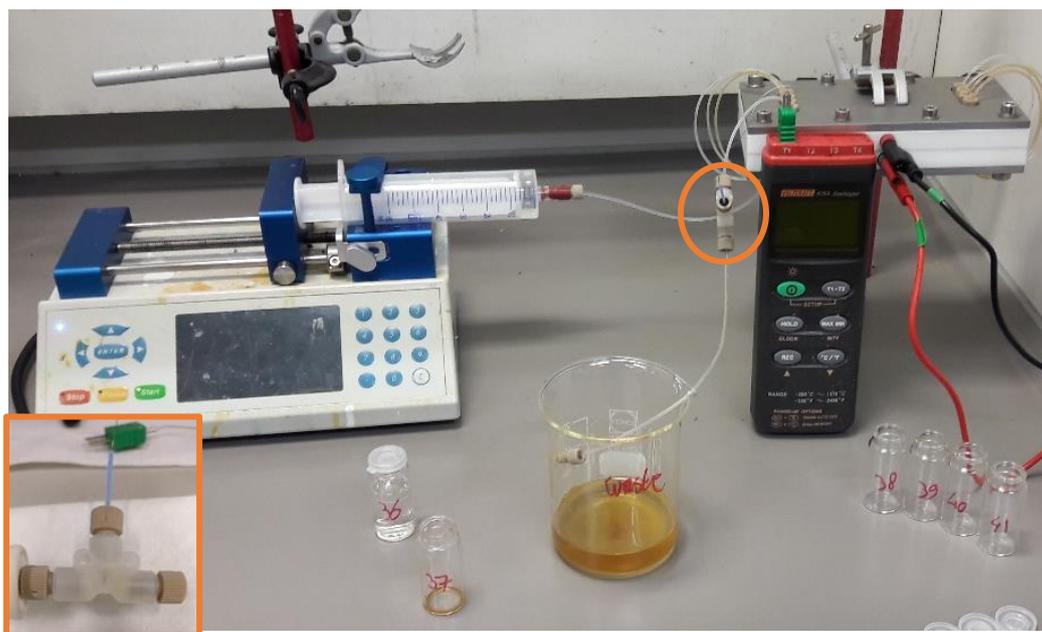


Figure 21: The experimental setup. Highlighted in the bottom left corner is a T-piece with a thermocouple inserted into it. This was used to measure the temperature of the fluid exiting the reactor

The resulting polarogram for the new reactor shows two plateaus, although not completely levelled off. These two plateaus indicate the oxidation towards sulfoxide and sulfone respectively. Similar to previous results using Syrris Asia Flux, the sulfoxide plateau is located between 2.2 and 2.6V, while the sulfone plateau is located around 3.5V. Due to the anodic limit of the system being close to the second plateau, the second plateau shows more noise and is less visible.

An expected difference between the two results is that the measured current for the new reactor is about twice as high, as opposed to the Syrris Asia Flux module. This can be attributed to the larger electrode area of the new reactor, which is approximately four times as large as Syrris Asia Flux.

In order to test the influence of several tuneable parameters on the system, linear sweep voltammetry experiments were repeated and compared to the benchmark case. The three manipulated variables are the residence time, the gasket thickness, and the electrolyte concentration. **Table 6** shows the parameter values for each of the experiments.

Table 6: Overview of parameters per experiment

	Residence time	Gasket thickness	Electrolyte
Benchmark	5 min	0.25 mm	10 mol% eq.
Experiment A	<u>10 min</u>	0.25 mm	10 mol% eq.
Experiment B	5 min	<u>0.5 mm</u>	10 mol% eq.
Experiment C	5 min	0.25 mm	<u>100 mol% eq.</u>

The results of these experiments are show in **Figure 22**. All four experiments follow the same trend and the two plateaus indicating the oxidation reactions are visible for experiments A and B. Experiment C seems to have an elevated current at higher potentials compared to the other experiments, and no visible second plateau. The exponential growth of the current near the anodic limit of the system is probably the reason that the second plateau is less visible for experiment C. The elevated current as opposed to the benchmark reaction could be attributed to the increased electrolyte concentration, but the use of different electrical contacts inside the POM pieces could also cause this effect.

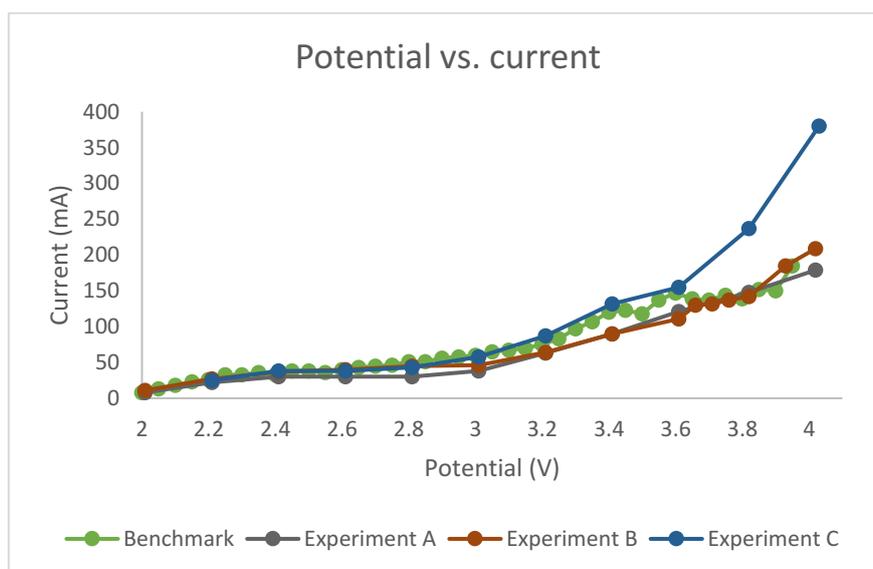


Figure 22: Polarograms of experiment A ($\tau_R=10\text{min}$), B (0.5 mm thick gasket) and C (100 mol% electrolyte), compared to the benchmark

Every sample taken at each potential was analysed using GC-FID. Conversion plots towards sulfoxide and sulfone are given in **Figure 23** and the reaction schemes are listed below:

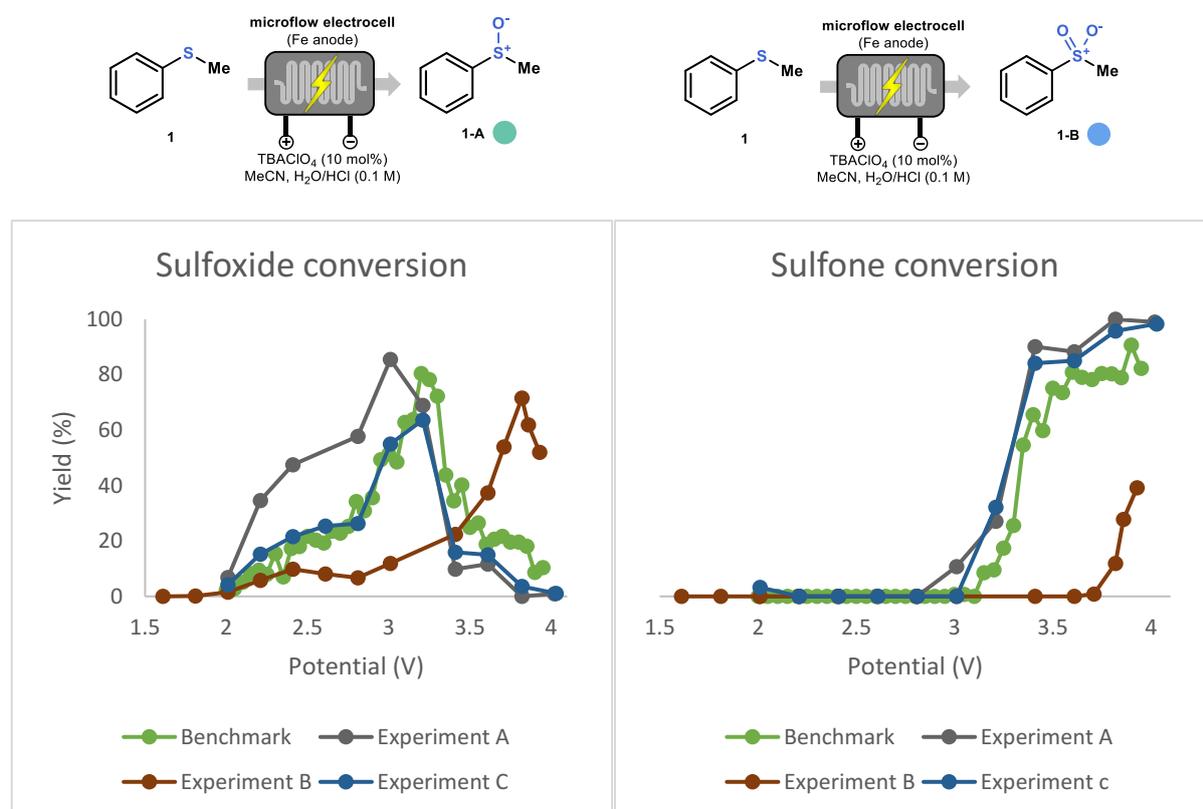


Figure 23: Conversion towards sulfoxide (left) and sulfone (right) for experiment A ($\tau_R=10\text{min}$), B (0.5 mm thick gasket) and C (100 mol% electrolyte), compared to the benchmark

From **Figure 23** can be seen that the sulfoxide production starts directly at 2.0 V. An increase in current at this point is also directly visible in **Figure 22**. The sulfoxide yield increases with increasing potential and, for the benchmark reaction, peaks at 3.2 V with a sulfoxide yield of 80%. Starting from 3.1 V, however, the electrons have sufficient energy to start conversion towards sulfone. Above 3.1 V, sulfone yield is increasing exponentially, on account of the sulfoxide yield decreasing.

For the benchmark experiment, highest conversion towards sulfoxide was found to be 80% at 3.1V and conversion towards sulfone levelled off at 80%.

For experiment A, the residence time was increased to 10 minutes by lowering the flowrate to 0.07 mL/min. **Figure 23** shows that, because of the longer residence time, more thioanisole is converted to sulfoxide, as the increase in yield is steeper up to 3.1 V. Beyond 3.1V, however, sulfone is produced again, and sulfoxide conversion decreases rapidly. Although less noticeable, the increase in sulfone yield, as opposed to the benchmark experiment, is also steeper due to the longer residence time. Using a residence time of 10 minutes, full conversion towards sulfone is achieved beyond 3.8 V.

By increasing the thickness of the gasket (experiment B) the conversion plots seem to be shifted to higher potentials. Although the polarogram is similar for experiment B and the benchmark, conversion towards sulfoxide and sulfone start much later. For this experiment the sulfoxide yield peaks at 3.8 V instead of 3.1, and also the start of the sulfone production is shifted. Because of the thicker gasket, the distance between the electrodes is increased and the path for the electrons through the fluid is longer. Because organic solvents generally have a low conductivity, the longer the pathway through

the solvent is, the higher the resistance. Electrons therefore seem to lose part of their energy to the increased resistance and all reactions start at elevated potentials.

Increasing the amount of electrolyte in the solution does not seem to have a noticeable effect on the conversion plots, as the results of experiment C follow the same trends as the benchmark reaction. The resistance over the system, as well as the diffusion of ions that stabilize the formed intermediate ionic radicals, are not limiting the reaction rates at 10 mol% equivalents of electrolyte. Therefore, there is no effect when increasing the electrolyte concentration.

Influence of residence time on thioanisole conversion

Previous research in this group found an optimal residence time for highest yields of sulfoxide. Increasing the residence time beyond the optimum resulted in lower yields, as can be seen in **Figure 24**. The optimal sulfoxide yield was 73% after 7.5 minutes of residence time. The effect of decreasing yield beyond this optimal residence time was attributed to flow induced mixing that decreased at very low flowrates.⁵ This flow induced mixing was believed to enhance mass transfer towards the electrodes at higher flowrates. To check whether this phenomena also occurs in the new reactor, the influence of the residence time on the conversion towards sulfoxide was measured.

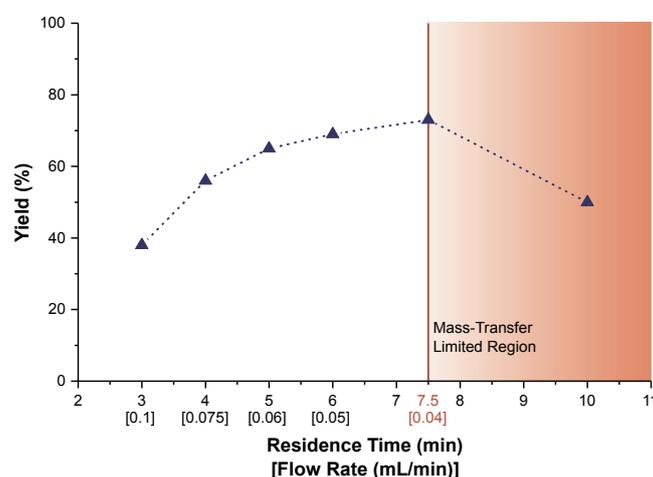


Figure 24: Sulfoxide yield vs. residence time for the oxidation of thioanisole in Syrris Asia Flux

The highest sulfoxide yield found in the linear sweep voltammetry experiment was 80% yield at 3.1 V for the benchmark case. This potential was chosen as optimal in order to test the influence of the residence time on the sulfoxide yield. The result of this experiment can be seen in **Figure 25**.

At a residence time of 5 minutes, the expected sulfoxide yield of about 80% was indeed found, but at longer residence times the amount started to decrease, as sulfone was also formed at this potential. As sulfoxide is the desired product, the potential had to be adjusted to prevent the formation of sulfone. Therefore, 2.8 V was chosen as the optimal potential for sulfoxide production in next experiments.

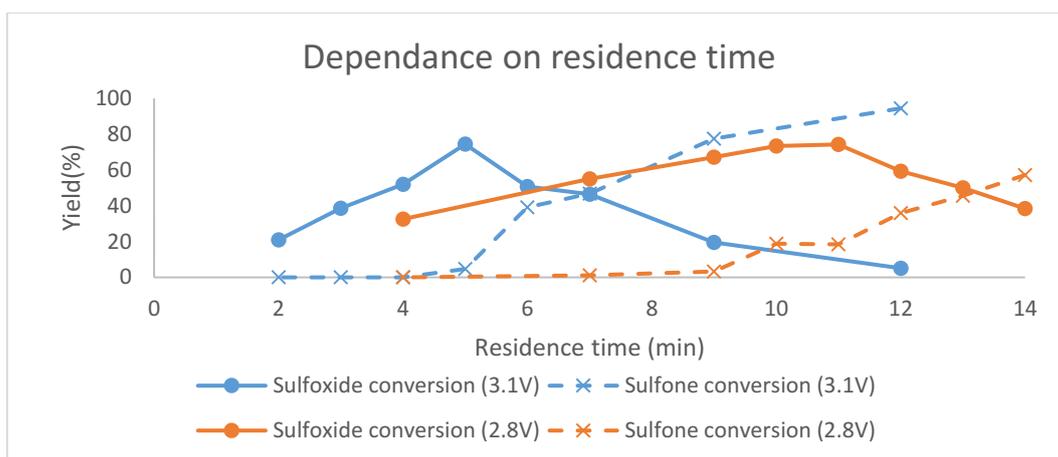


Figure 25: Influence of the residence time on the thioanisole conversion towards sulfoxide and sulfone

The results of the residence time experiment at 2.8 V is also shown in **Figure 25**. At this potential the screening experiment yielded a sulfoxide yield of 34% after 5 minutes of residence time. The results of the residence time experiment at 2.8V yielded a similar value of 33% after 4 minutes. For the measurement at 2.8 V, the production of sulfone does not start at residence times below 9 minutes, as opposed to the measurement at 3.1 V. Increasing the residence time above 9 minutes has a negative impact on the selectivity. Due to the slight sulfone production, longer residence times result in more time for the sulfoxide to react towards sulfone. For these measurements, an optimum is also found for the residence times. For the 2.8 V measurement, the sulfoxide yield increases up to 74% at a residence time of 11 minutes.

Above 11 minutes of residence time, however, a drop in yield is observed, similar to the measurement done using Syrris Asia Flux. An optimum of 10 minutes of residence time was chosen for highest sulfoxide yields. The flowrate probably induces some mixing in the channels that promote diffusion to the electrode surface and thus increases the reaction rates. Similar to the Syrris Asia Flux measurement, there seems to be a trade-off between longer residence times for higher yields and mixing induced by the flowrate.

Preparative scale of sulfoxide and sulfone

The optimal parameters for both sulfoxide and sulfone production were determined in the previous set of experiments and are given in **Table 7**.

Table 7: Optimal parameters for sulfoxide and sulfone production

	Residence time	Potential
Sulfoxide	10 min*	2.8V
Sulfone	5 min	3.8V

* Run through the reactor twice at 5 minutes residence time per run.

The results of this gram scale production of both sulfoxide and sulfone is given in **Table 8**.

Table 8: Preparative scale results

	Sulfoxide	Sulfone
Starting material	0.7474 g 6 mmol	0.6522 g 5.25 mmol
Product	0.83 g 5.9 mmol	0.64 g 4.1 mmol
Yield	98%	78%

Based on the results of these preparative scales, it was concluded that the reactor has stable performance over several hours and yields production of both sulfoxide and sulfone. Reported isolated yields using Syrris Asia Flux were 65% for sulfoxide after 5 minutes of residence time, and 92% for sulfone after 10 minutes of residence time.⁵ Sulfoxide yields were improved using the new reactor, but for sulfone the isolated yield was lower. The residence time for sulfone, however, was only 5 minutes instead of 10 for the new reactor.

Conversion per channel

The sulfoxide yield over each single channel was measured, in order to test for possible uneven electron flow over the surface of the electrodes. Each channel was connected to a single syringe containing reaction mixture and the yield over each channel was measured. **Figure 26** shows a picture of the setup and **Figure 27** shows the sulfoxide yield after 14 minutes of residence time at 2.8 V. Small outliers for channel 3 and 4 aside, all channels perform similar and it can thus be concluded that the electron flow over the electrode surface is not location dependent.

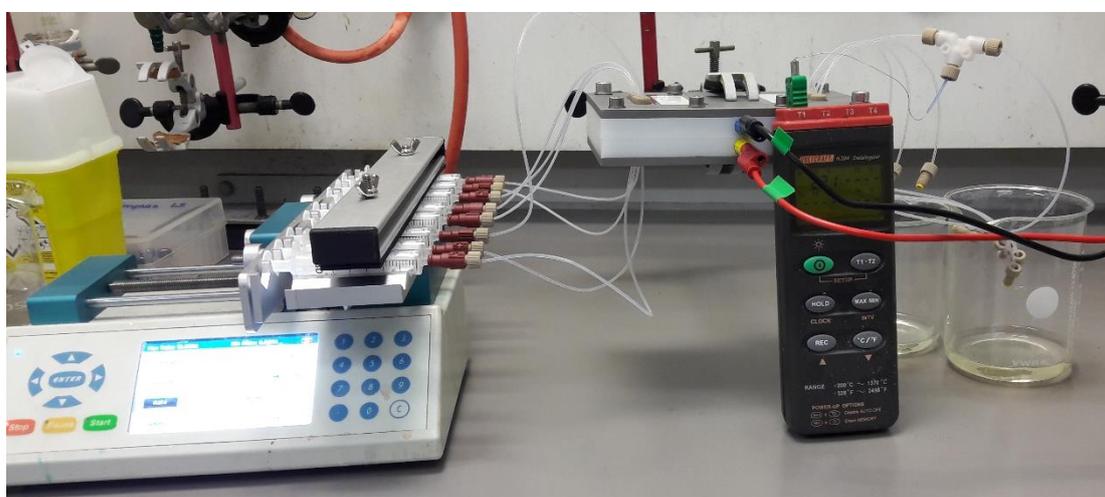


Figure 26: Experimental setup to measure yield per single channel

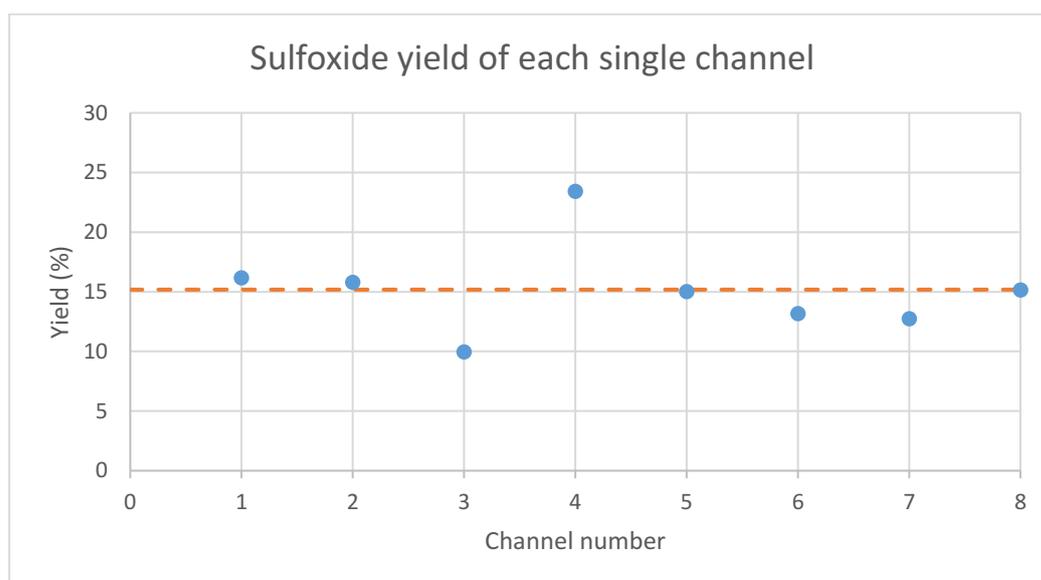


Figure 27: Sulfoxide yield of each single channel and the average over all channels

In order to test the conversion for different amounts of channels, the reactor was rebuilt to have two different in- and outlets. Using two syringes, a variable amount of channels in the reactor could be filled with reaction mixture. The leftover channels could either be filled with reaction mixture as well, or be filled with solvent (acetonitrile), without reactants or electrolyte. As acetonitrile does not conduct a current, the part of the electrode surface able to conduct scaled with the amount of channels used. As this could have an influence on the thioanisole conversion, both cases were tested at a potential of 2.8V. **Figure 28** shows the sulfoxide yield for different amounts of channels, for both 5 and 10 minutes of residence time, when all channels were filled with reaction mixture, as well as with the leftover channels being filled with acetonitrile.

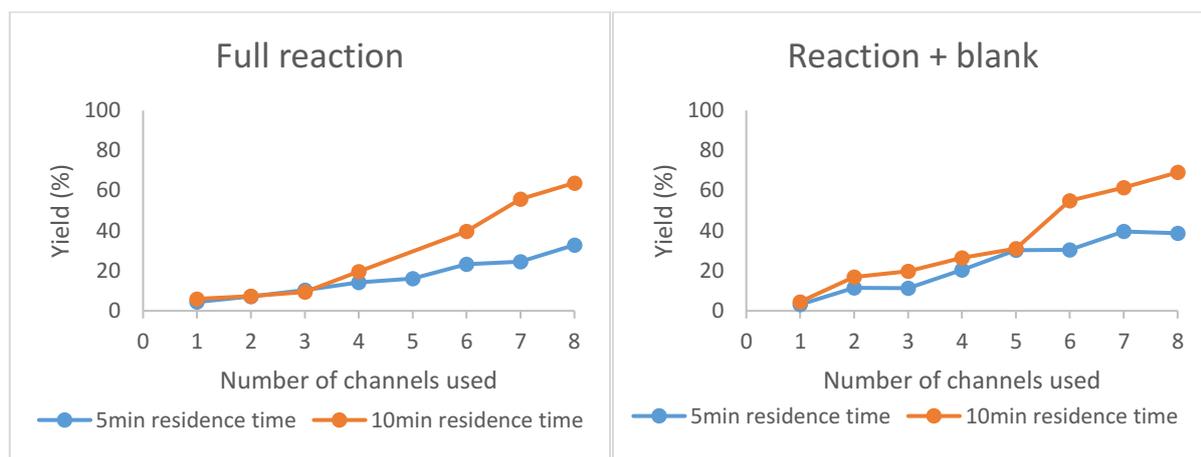


Figure 28: Conversion for different amounts of channels. Left) all channels are filled with reaction mixture
Right) channels that are measured are filled with reaction mixture, the leftover channels are filled with acetonitrile

The final sulfoxide yield for both cases reaches approximately 40% and 70% after 5 and 10 minutes of residence time respectively. The leftover channels being filled with either reaction mixture or solvent does not seem to have an influence on the yields.

The measured current, however, does vary between these two experiments, as can be seen in **Figure 29**. When all channels are filled with reaction mixture, they can all conduct a current. Therefore, the measured current is constant, regardless of the amount of channels that are measured. When the leftover channels are filled with acetonitrile, however, these cannot conduct a current. Therefore, there is a linear trend between the current and the amount of channels containing reaction mixture.

Another visible trend in this figure is the difference in current between 5 and 10 minutes of residence time. A higher current is reported at 5 minutes of residence time. Due to the higher flowrate to achieve 5 minutes of residence time, more substrate is supplied to the reactor per second, which increases the reaction rates and therefore the consumption of electrons per second.

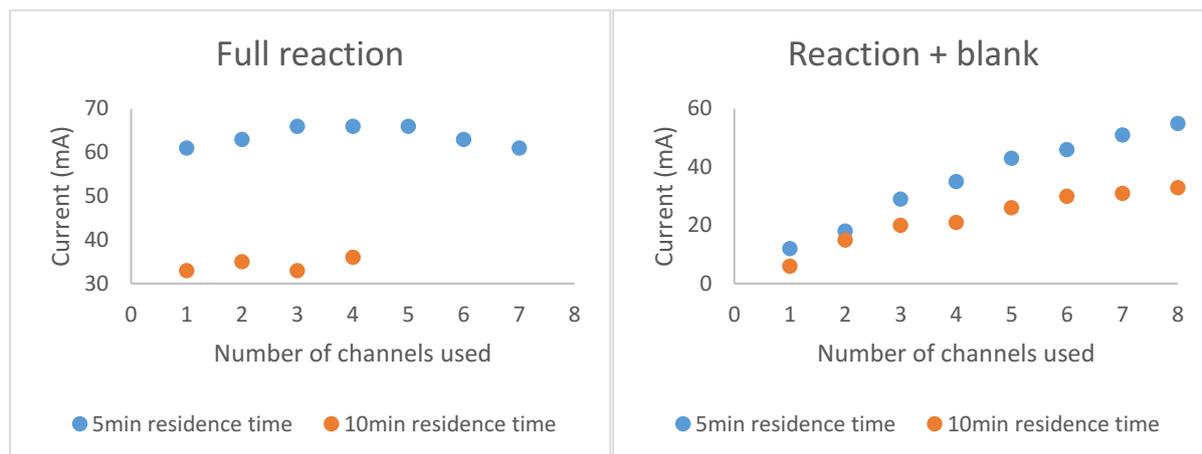


Figure 29: Measured current for different amounts of channels. Left) all channels are filled with reaction mixture. Right) Channels that are measured are filled with reaction mixture, the leftover channels are filled with acetonitrile

Linear sweep voltammetry of methionine oxidation

In order to validate the reactor for other electrochemical transformations, a second substrate that was tested was methionine. A linear sweep voltammetry screening was performed using the same protocol as for thioanisole. Two measurements were carried out from 2.0 to 4.5V and the results are shown in **Figure 30**, together with the reaction scheme of the oxidation of methionine.

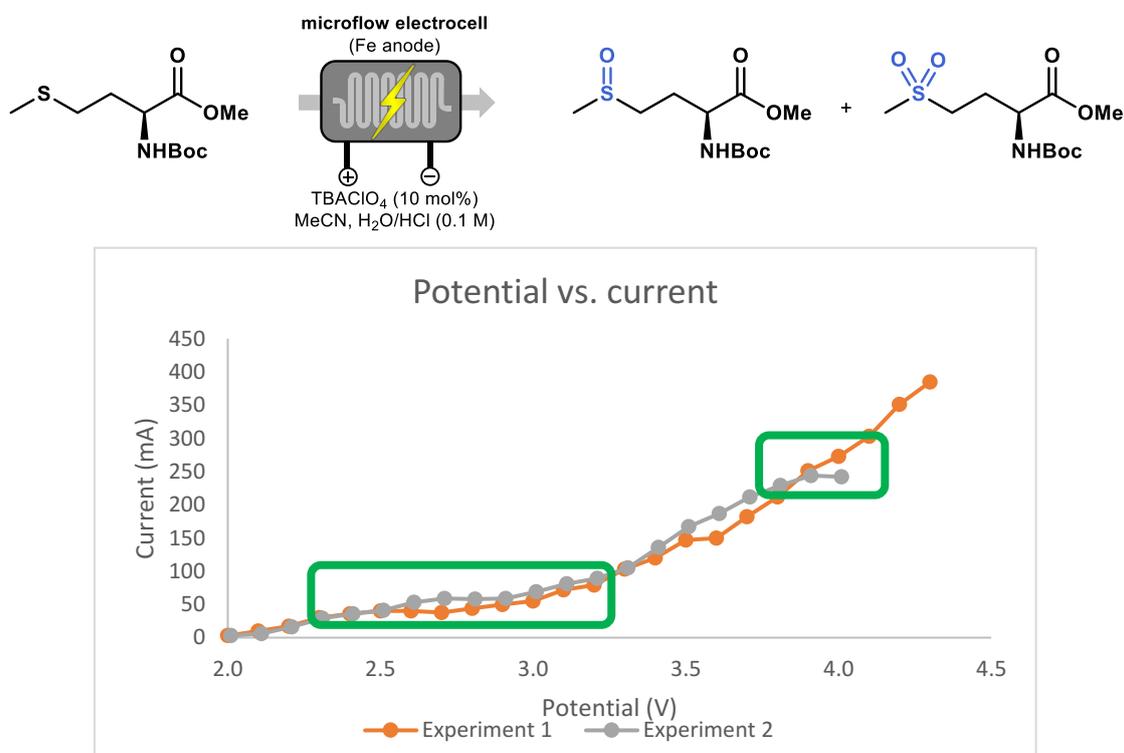


Figure 30: Polarogram of the oxidation of methionine

The plateau of the first oxidation step towards sulfoxide is clearly visible between 2.5 and 2.8 V. The second plateau, however, is not as visible, but is most likely located between 3.9 and 4.0 V. Furthermore, the current could not be measured up until 4.5 V, as rust formation started to clog the reactor beyond 4.3V. **Figure 31** shows the sulfoxide yield at different potentials. A yield of 95% was achieved above 3.4 V. Sulfone production was negligible during this measurement.

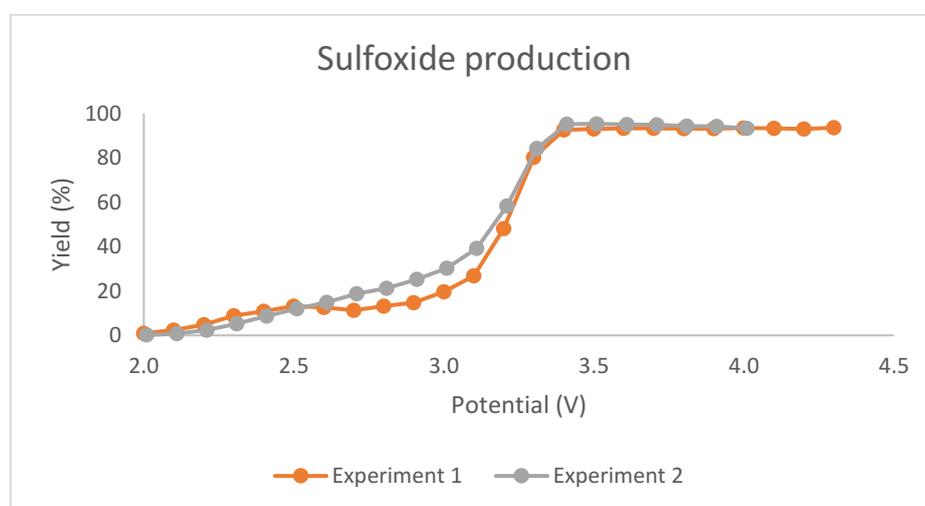


Figure 31: Conversion towards the sulfoxide of methionine

Conclusions and outlook

To conclude, a new design for an electrochemical microreactor was successfully developed. The new design is fully modular, easy to assemble and versatile. Moreover, the total cost of the setup is only € 902.00, making it a cheap alternative to the commercially available Syrris Asia Flux module, while improving on its performance.

The volume and operating limitations were characterized and a benchmark oxidation of thioanisole was carried out. Results previously found with Syrris Asia Flux, were recreated using the new reactor and the general performance was improved.

For further research, validation of the new reactor through more electrochemical reactions should be tested. Moreover, electrodes of different materials could be tested. For this research, only stainless steel electrodes have been used, but copper and graphite electrodes have also been made (**Figure 32**). These different electrode materials could enhance yields for certain reaction types and are currently tested for other electrochemical transformations.

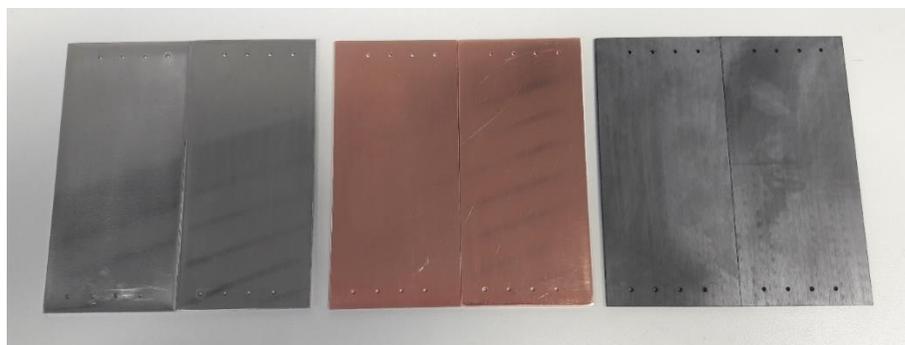


Figure 32: Stainless steel electrodes on the left, copper in the middle, and graphite on the right

The design is capable of being turned into a divided electrochemical cell with only small alterations. Using two slightly altered gaskets and a membrane, reactions needing a separated cathodic and anodic reaction mixture could be tested. **Figure 33** shows an altered design for the gaskets in order to make divided cell operation possible. In this design each channel has both the inlet and outlet hole in the same electrode. Therefore, when separated via a membrane, two different reaction mixtures can be added to the reactor, without coming into contact with each other, creating a divided cell.

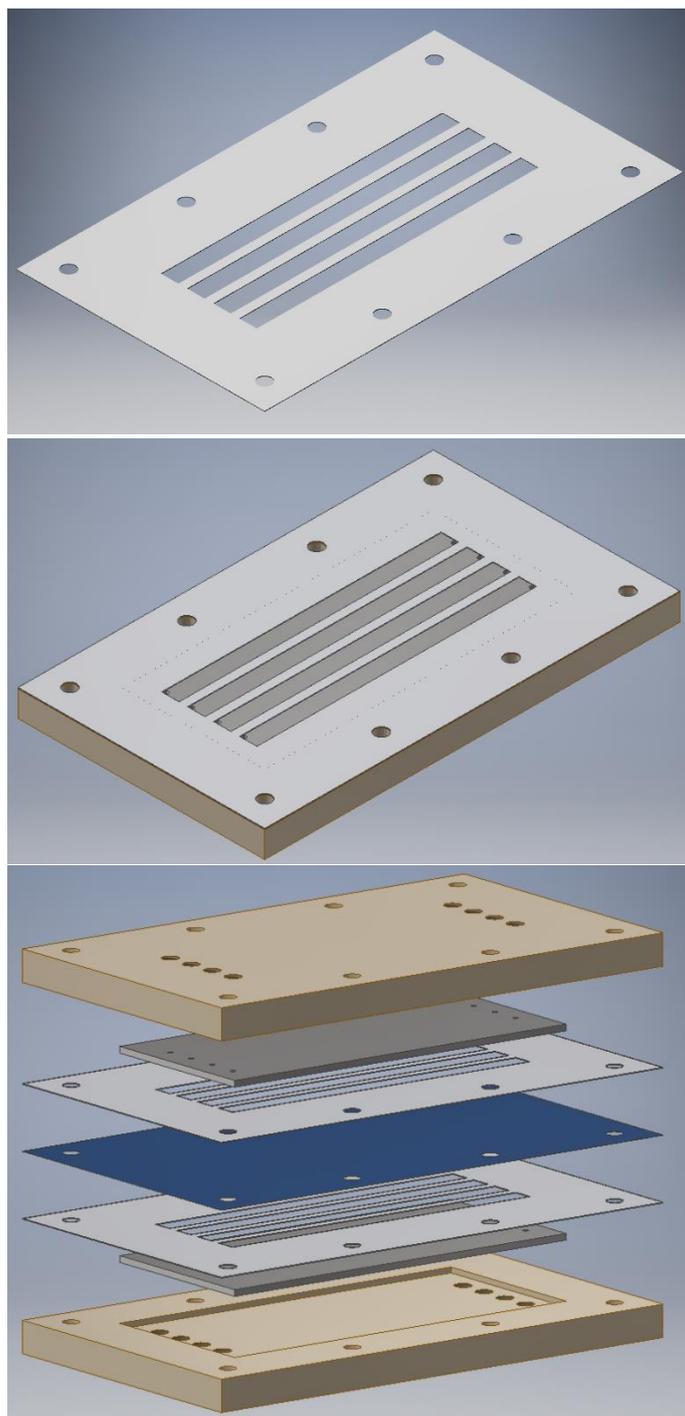


Figure 33: Top) gasket design for divided operation. Middle) gasket laid over the electrode, each channel has an in- and outlet hole in the same electrode. Bottom) exploded view of the assembled reactor, including a membrane (blue)

Lastly, it could be interesting to look into consecutive reactions of a single substrate, where one substrate undergoes two different electrochemical transformations in continuous flow, which could be carried out in two different electrochemical reactors in series.

Experimental section

Electrochemical synthesis setup

For all electrochemical reactions, the newly designed flow cell was used, together with a Velleman LABPS3005D power supply that is connected to the flow cell. The cell consists of a working electrode and a counter electrode, both made of stainless steel, with a PTFE (Polytetrafluoroethylene) gasket containing micro-channels in between. Depending on whether a 0.25 mm or 0.5 mm thick gasket is used, the active reactor volume is either 700 μ L or 1300 μ L. This results in an undivided electrochemical cell. In the cell, direct contact between the electrode surface and the reaction mixture is established. The reaction mixture is pumped through the system via syringe pump, and is collected in a glass vial. Both electrodes can be set to be the anode or the cathode at any time.

General protocol for the screening of electrochemical oxidation of thiols

The concerning thioether was dissolved in the corresponding amount of stock solution (3:1 v/v acetonitrile/0.1 M HCl (aq) and 10 mol% tetrabutylammonium perchlorate) to yield a 0.15M solution of thioether in stock solution. The solution was flown through the electrochemical setup with a fixed flowrate of 0.15 mL/min to give a residence time of 5 minutes in the active part of the reactor, using the 0.25mm thick gasket. During the experiment, the potential was varied between 2.0 V – 4.0 V. Samples were taken at the corresponding potential after the total residence time had elapsed (10min at 0.15 mL/min). For each fraction, the current was determined. The fraction was washed with ethyl acetate and water. The ethyl acetate fraction was analysed without further purification using GC-MS or GC-FID.

General protocol to optimize residence time for the electrochemical oxidation of thiols

The concerning thioether was dissolved in the corresponding amount of stock solution (3:1 v/v acetonitrile/0.1 M HCl (aq) and 10 mol% tetrabutylammonium perchlorate) to yield a 0.15M solution of thioether in stock solution. The solution was flown through the electrochemical setup at a flowrate ranging from 0.05 mL/min up to 0.35 mL/min to give a residence time of 2 to 14 minutes in the active part of the reactor. A gasket thickness of either 0.25mm or 0.5mm was used. During the experiment, the potential was set at the optimal potential found in the screening experiment. Samples were taken for each flowrate after the total residence time had elapsed. For each fraction, the current was determined. The fraction was washed with ethyl acetate and water. The ethyl acetate fraction was analysed without further purification using GC-MS or GC-FID.

General protocol to change the amount of channels for the electrochemical oxidation of thiols

The concerning thioether was dissolved in the corresponding amount of stock solution (3:1 v/v acetonitrile/0.1 M HCl (aq) and 10 mol% tetrabutylammonium perchlorate) to yield a 0.15M solution of thioether in stock solution. The solution was flown through the electrochemical setup with a flowrate of 0.15 mL/min to give a residence time of 5 minutes in the active part of the reactor. A gasket thickness of 0.25mm was used. During the experiment, the potential was set at the optimal potential found in the screening experiment. Two syringes were connected to the reactor and the amount of channels per syringe was varied by changing the tube loops around. For the full reaction test both syringes would be filled with reaction mixture. For the reaction + blank test, one of the syringes would be filled with just acetonitrile. Samples were taken for each amount of channels (ranging for just one channel to all eight channel) after the total residence time had elapsed. The fraction was washed with ethyl acetate and water. The ethyl acetate fraction was analysed without further purification using GC-MS or GC-FID.

General protocol for the electrochemical oxidation of sulfides

The concerning thioether was dissolved in the corresponding amount of stock solution (3:1 v/v acetonitrile/0.1 M HCl (aq) and 10 mol% tetrabutylammonium perchlorate) to yield a 0.15M solution of thioether in stock solution. The solution was flown through the electrochemical setup with a fixed flowrate of 0.15 mL/min to give a residence time of 5 minutes. During the experiment, the potential was set at the optimal potential determined in the screening experiment. All of the solution was collected in a vial, covered by a parafilm tape. If the conversion was found to be sufficiently high after collecting, the solution was diluted with saturated bicarb solution (15 mL) and transferred to a separation funnel. The water phase was extracted with ethyl acetate (three times 25 mL). The resulting organic fractions were washed with brine, dried over MgSO₄ and concentrated in vacuo. The product was then purified using flash chromatography (PE/EtOAc, CyHex/EtOAc or DCM/MeOH) and analysed by H-NMR, C-NMR, GC-MS, FT-IR, HR-MS and TLC. The electrode surface was cleaned after every experiment by sonicating the electrodes and gasket acetone for 5 minutes. The plates were dried, scrubbed with an abrasive sponge, and polished with paper towels drenched in 1 M HCl (aq) and acetone.

Acknowledgements

During this project I was able to work on a reactor design, starting from scratch. The satisfaction of seeing your work go from a design to a real product is priceless. Therefore, I would like to thank Timothy Noël for giving me the opportunity to work on this project and to trust me with this task.

During the designing phase, several people were of great importance to the final product. I would especially like to thank Koen Kuijpers, Gabriele Laudadio, Erik van Herk and Rick Huisman. Without their help and the discussions we had, I would not have been able to come up with the finalized design. For creating the reactor, I want to thank Wouter Kuip. Who did not just create all parts, but was also genuinely interested in the actual function and performance of the reactor.

Above all, I would like to thank Gabriele Laudadio. As my daily supervisor he helped me all the way from the designing phase, up until the characterization and testing of the actual reactor. He was always available for questions and I enjoyed all the discussions we had during the project. I really appreciate his enthusiasm on my work and the trust he put into my work during the characterization and testing of the reactor. This really made me feel appreciated and that my contribution to his research was valued.

Lastly, I would like to thank my girlfriend, Patricia, for helping me whenever I struggled during the project. Especially during the writing of the final report, her help to push me through was invaluable.

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