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Translating Batch Organic Electrochemistry to Single-Pass Continuous Flow Conditions

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Snjezana Maljuric

Abstract

Electroorganic chemistry is considered as environmentally friendly and is gaining more and more importance in the chemical industry, demanding an extensive research in this field. In this work, a well-known electrochemical process of methoxylation is translated from batch to single-pass continuous flow conditions, under consideration of reaction parameters, such as interelectrode distance, flow rate, backpressure and the concentration of the supporting electrolyte. For this purpose, a commercially available Ion Electrochemical Reactor (Vapourtec Ltd) for a continuous flow process was used. The variation and adjustment of the process parameters in the continuous flow reactor led to a significant improvement of the conversion, selectivity and current efficiency in much shorter reaction time in comparison to the batch process. To achieve satisfactory results in continuous flow, a narrow interelectrode distance and a slow flow rate play a key role. The reduction of the interelectrode distance has a positive effect on cell resistance and the voltage. At a sufficiently small distance between electrodes, the concentration of the supporting electrolyte can be greatly reduced, without having a negative impact on the results. Very good results are achieved in a single-pass, without the need to recycle the reactant solution.

Elektroorganische Chemie gilt als umweltfreundlich und gewinnt immer mehr an Bedeutung in der chemischen Industrie. Aus diesem Grund wird eine umfangreiche Forschung in diesem Bereich betrieben. In dieser Arbeit wird der literaturbekannte elektrochemische Prozess der Methoxylierung von einem diskontinuierlichen Batchverfahren in ein kontinuierliches Durchflussverfahren übertragen, unter der Berücksichtigung der Reaktionsparameter wie Elektrodenabstand, Durchflussrate, Gegendruck und die Konzentration des Leitelektrolyten. Der kontinuierliche Prozess basiert auf nur einem Durchlauf des Reaktionsgemisches durch die Durchfluss-Zelle, ohne Mehrfachdurchlauf wie dies typischerweise in der Literatur praktiziert wird. Für den kontinuierlichen Prozess wurde ein kommerziell erhältlicher elektrochemischer Reaktor (Vapourtec Ltd) verwendet. Der Umsatz, die Selektivität, die Stromausbeute sowie die Reaktionsdauer der untersuchten Reaktion im diskontinuierlichen Reaktor konnten im kontinuierlichen Prozess deutlich verbessert werden. Außerdem konnte bei ausreichend geringem Elektrodenabstand die Konzentration des Leitelektrolyten minimiert werden, ohne dass die Ergebnisse dadurch negativ beeinflusst wurden. Es wurde festgestellt, dass ein geringer Elektrodenabstand, sowie eine geringe Durchflussrate, maßgeblich dafür verantwortlich sind optimale Ergebnisse zu erreichen.

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1. Introduction

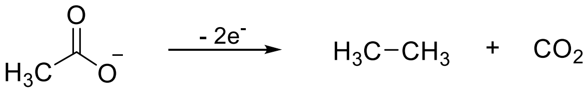
Nowadays, a great emphasis is placed on the sustainability and protection of the environment. This includes chemical manufacturing processes. Electrochemical technologies are considered as environmentally friendly methods and have been described as “inherently green”. Therefore, organic electrochemistry is becoming increasingly important. Organic electrochemistry is based on the direct interaction of the reactants with electrons, which can be considered as very clean reagents. Commonly used reducing and oxidizing agents can be avoided reducing waste generation.[1,2]

Electrosynthesis is usually performed at ambient pressure and ambient temperature.[3] The energy costs related to heating or cooling the reactor can therefore be minimized in most cases. The solvents are usually safe, cheap and easy to remove after the reaction.[3,4,5,6] Moreover, some electrode material can favour the degradation of the toxic organic compounds, e.g. boron-doped diamond electrodes.[7] Many different chemical compounds can be used as substrates in the electrosynthesis, but the renewable raw materials are particularly interesting.[8,9] A huge advantage of organic electrochemistry is that the polarity of a substrate can be changed by electron transfer.[10,11,22] This means that an electrophile can be transformed to a nucleophile at the cathode and the nucleophile can be changed to an electrophile at the anode.[3] In this way, the number of reaction steps can be reduced. Moreover, the radical reactions can be carried out on large scale without the use of protecting groups.[3]

The requirement for the substrates is to have an electroactive group or the possibility to react with electrogenerated intermediates, if the functional group interconversions or C‑C bond formations are desired.[3] Electrosynthesis is environmentally friendly, innately scalable, chemoselective and functional group tolerant.[12] Baran and coworkers summarized the benefits of electrosynthesis and compared it with the traditional reagent-based synthesis of complex molecules.[12] Electrochemistry is an environmentally friendly way to perform very important oxidative coupling reactions, such as the coupling of two nucleophilic functional groups. In the case of Moeller’s synthesis of alliacol,[13] where the coupling of the furan nucleophiles and enoxysilane was performed, exceptional selectivity was achieved under electrochemical conditions. The good selectivity was the result of the different redox potentials of the functional groups in the molecule and the possibility to control the potential of the reaction.[12] Furthermore, electrochemistry offers a sustainable way to perform allylic C-H oxidations on large scale. In conventional C-H oxidations, toxic and expensive reagents are typically utilized, which is problematic for the industrial processes.[14]

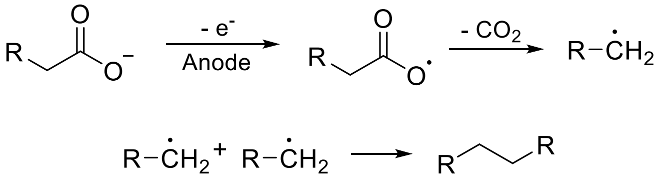
1.1. History of Organic Electrochemistry

The origins of organic chemistry date back to the beginning of the 19th century. In 1834, Michael Faraday performed the first electroorganic synthesis. It was the anodic decarboxylation of acetic acid in an aqueous medium, which resulted in the formation of ethane and carbon dioxide.[15]



Scheme 1. First organic electrosynthesis by Faraday.

The first useful organic electrosynthesis was discovered by Henry Kolbe in 1849. He demonstrated the basis of electroorganic synthesis by electrolyzing the fatty acids and half-esters of dicarboxylic acids. This reaction was called Kolbe reaction or Kolbe electrolysis.[15]



Scheme 2. Kolbe electrolysis.

Besides Kolbe, also Haber, Fichter, and Tafel made early contributions to the field.[15] In 1898, Haber found out that for a good reaction selectivity the potential at the working electrode needs to be kept constant.[17] At the beginning of the 20th century, only a few groups were doing research in the field of organic electrochemistry. Some of them were groups of F. Fichter, S. Swann, and H. D. Law. By 1940, the research had progressed and several electrochemical reactions were carried out on the industrial scale.[17]

The cathodic reduction of glucose to mannitol and sorbitol in 1937 was the first electroorganic reaction, carried out on a large-scale by Atlas Powder Co.[16] During the decades of the 1940s to 1960s, several electroanalytical methods for the detection of organic compounds were developed.[17] The commercial production of tetraethyl lead by Nalco,[18] as well as the demonstration of a large-scale manufacturing plant for production of adiponitrile by Monsanto,[19] were some of the greatest achievements in the 1960s'.

The first elucidation of the reaction mechanism of electroorganic reactions could also be done in 1960'. Better knowledge in the theory of organic electrosynthesis and the improvement of the equipment for measurements made it possible.[20] Until 1970', organic electrochemistry was an unknown field for most organic chemists, but afterwards the society recognized the need for environmentally friendly methods for the synthesis of organic compounds. Therefore, electrochemistry was recognized as a "green" method and attracted much attention in the organic synthesis community. In the 1980', the methods and technologies for the electrosynthesis have been extensively developed.[20]

In the 21st century, significant progress has been made in the field of organic electrosynthesis, since it is considered as the most promising green synthetic process. A number of successful electroorganic systems have been developed to date. In addition to the electroorganic chemistry in batch, great efforts have been made to develop and improve the continuous flow reactors for the organic electrosynthesis.[21]

1.2. Basic Principles in Organic Electrochemistry

Electroorganic synthesis is carried out in an electrolytic cell and consists of two half-cell reactions. A reduction takes places on the cathode and an oxidation occurs simultaneously on the anode. The electrode in which the target transformation takes place is called "working electrode" while the other transformation happens on the "counter electrode" surface. The working electrode can be either cathode or anode, depending on the reaction. The same applies to the counter electrode.[15] The electrodes are immersed in an electrolyte solution, consisting of a solvent, supporting electrolyte and the substrate, and in some cases a catalyst.

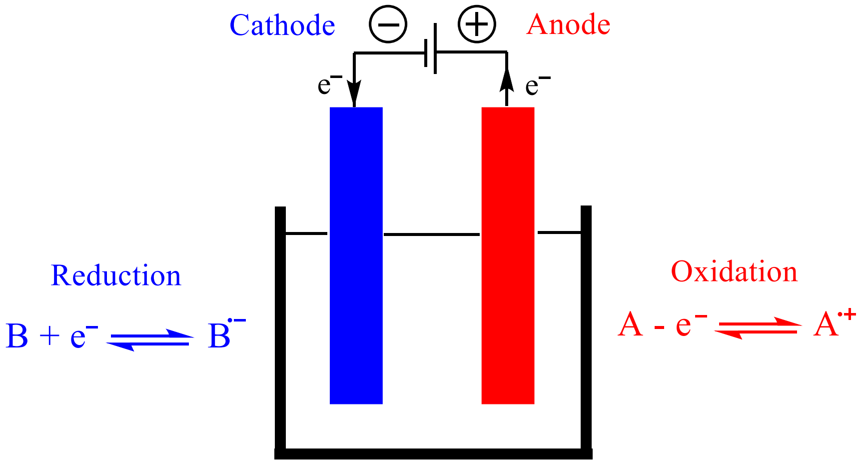


Figure 1. Electron transfer in the electrolytic cell.

Organic electrosynthesis consists of two main processes: electron transfer on the electrode surface leading to the formation of a reactive intermediate and the chemical reaction in solution. The reactive intermediate can be formed either via anodic oxidation or via cathodic reduction.[1,22,23,24] During electrooxidation, the electrons are transferred from the substrate to the anode. The resulting intermediate can be a radical $[R]^{\cdot}$, cation $[R]^{+}$ or cation radical $[R]^{+\cdot}$. During cathodic reductions, radicals $[R]^{\cdot}$, anions $[R]^{-}$ or anions radicals $[S]^{-\cdot}$ are formed.[15] In general, the electrons removed on the anode are transported to the cathode where they are used to reduce the organic compound. The electron transfer on the electrode surface is a heterogeneous process.[22,23] The potential of the electrodes determines the energy of the electron transfer process.[23]

The transfer of electrons between the inert electrode surface and the substrate and the resulting formation of the reactive intermediate is called direct electrolysis.[20,22] In direct electrolysis (Figure 2a), the reactive intermediate is formed on the electrode surface and diffuses afterwards into the solution. Subsequently, it undergoes a chemical reaction forming the desired product. The reactive intermediate can also be formed using a mediator,[24,22] which is a homogenous process (Figure 2b). In the case of anodic oxidation, the discharge of the mediator on the anode occurs in order to be able to accept the electrons transferred from the substrate.[20,24] An advantage of this type of system is the possibility to use milder potentials.[25] Francke and Little [25] have investigated the mediated electrolysis in more detail. Another possibility is to use active electrodes with electrically conductive coatings of immobilized redox-active reagents. An unique reactivity is achieved with this type of electrodes.[24]

In contrast to the conventional electrosynthesis, in which the main reaction takes place only on one of the electrodes (working electrode), in a paired electrosynthesis the products are formed on both electrodes.[22] Different types of paired electrosynthesis can be distinguished: parallel, convergent, divergent, and linear paired electrosynthesis.[22] In Figure 2c, the general process of a parallel paired electrochemical reaction is shown. In this system, different starting materials are used. Each starting material reacts at one of the electrodes and leads to the formation of different products.[22] In a convergent paired electrosynthesis the two starting materials give the same product, whereas in the divergent organic electrosynthesis a single starting material is used.[22,58]

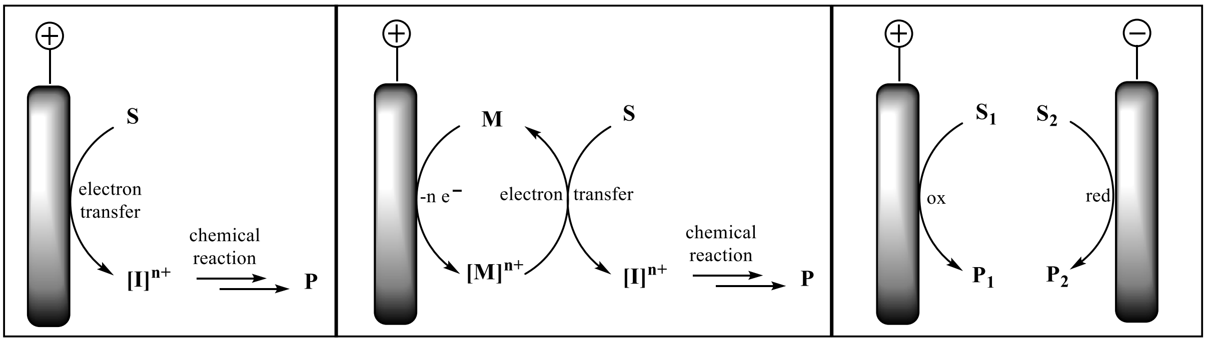


Figure 2. Different types of organic electrosynthesis: (a) direct electrosynthesis, (b) mediated electrosynthesis (c) parallel paired electrosynthesis.

The chemical behaviour of the substrate depends on the stereochemistry and on the types and arrangement of functional groups.[20] The possible chemical reactions are elimination, substitution, addition, degradation, recombination, and rearrangement.[20] Schäfer and coworkers demonstrated that electrolysis can be used for converting oleochemicals, carbohydrates and trimethyl aconitate to higher-value compounds by the formation of C-C bond and interconversion of functional groups.[26]

The understanding of the chemical process is very important because it can be influenced by many factors, such as the type of supporting electrolyte, solvent, and additives, leading to different results. A change of some of these electrolyte constituents could lead to completely different products, having a great effect on the selectivity.[20] However, not only the constituents of the electrolyte but also the electrolysis conditions, such as current density, potential, pH, etc. determine the outcome of the chemical reaction. For the optimization of the conditions, it is necessary to understand the function and behaviour of each constituent in the electrolyte solution.[20]

Baran and coworkers [27] succeeded in performing an electrochemically enabled nickel-catalysed amination, which is one of the most important reactions in modern medicinal chemistry. They presented the electrochemical method to achieve the cross-coupling between alkyl amines and aryl halides at room temperature, without an external base and in a very simple experimental setup. Cardoso et al.[28] reported in a review of some applications of electroorganic chemistry from the laboratory to the industrial scale. They described the suitable operating conditions and the electrochemical equipment, as well as the principles and examples of paired electrochemical reactions, indirect electrosynthesis, and electrochemical microreactors. Moreover, the production of adiponitrile, substituted benzaldehydes, anthraquinone, fluorinated products, and succinic acid was described. J. Utley [29] presented another review explaining the basis of organic electrosynthesis, the common electrochemical conversations, the direct, indirect, and mediated approach of electrosynthesis as well as the mechanistic aspects.

1.3. Electrode Materials in General

The electrodes are the most important components of the electrolytic cell, since the electron exchange take place on their surface. The outcome of the chemical reaction is strongly affected by the chemical composition and morphology of the electrode surface. Porosity is also an important aspect, since the presences as well as the size and dimensions of pores affect the surface and the effective current density. Electrodes usually consist of homogenous materials. However, in some cases, a carrier material with an active coating is used.[31]

The change of the electrode material can lead to the formation of a completely different product in some cases and in this way influence the selectivity. However, not only the electrode materials but also the chemical nature of the same type of electrodes play a significant role in the electrochemical reactions. A good example are the carbon electrodes, which can vary depending on the source, additives, furnace temperature, soaker, graphite grade, treatment period, etc.[20]

In addition to the composition of electrodes and their chemical properties, also the mechanical properties such as strength, hardness, elasticity, brittleness, etc. need to be considered when choosing the electrode material for a particular electroorganic synthesis. Moreover, the stability of the electrodes in the electrolyte solution plays an important role.[31]

As mentioned in chapter 1.2, the electrolysis process consists of two half-cell reactions. Although the desired reaction takes place on the working electrode, the electrode material of both electrodes and the combination of those electrodes needs to be considered, since they can affect each other during an electrolysis.[30] Couper at al.[30] reported about electrode materials for small-scale electrosynthetic processes. They discussed, amongst other things, the physical properties, stability, surface chemistry and adsorption, electrocatalysis and economic factors of the electrode materials. Generally speaking, there are many different types of electrodes. Some of them are a smooth or porous electrode, gas evolving electrodes, gas diffusion electrodes, and sacrificial electrodes. Sacrificial electrodes are consumed during reactions.[31]

In some cases, during the electrochemical reactions, precipitation occurs leading to the passivation of the electrode surface, which consequently results in smaller effective surface and increase in current density. The problem of passivation of the electrode surface can be solved by periodical alternating the cell polarity.

1.3.1. Anode Materials

A very common problem typical for the anode is corrosion. This problem must be considered when choosing the electrode material for a particular reaction. Temperature and pH value are some of the factors which influence the stability of the anode. The oxygen evolution overpotential is an important factor when a reaction is carried out in aqueous electrolytes.[31] Usually, special materials with high oxygen overpotential are preferable, especially if the anode is a working electrode. In this way oxygen production can be minimized. However, the unwanted oxidation reactions can hardly be avoided, if anode is the oxygen-evolving counter electrode.[31]

Very common anode materials for nonaqueous media are Pt, Pt/Ti or carbon. Nickel is an exceptional anode material for aqueous alkaline solutions. Pt has very high oxygen overpotential and is very stable to corrosions, but it is also very expensive.[30]

1.3.2. Cathode Materials

Cathode materials are typically not affected by corrosion. However, if the cathode is a working electrode, the hydrogen evolution overpotential needs to be considered when choosing the material. For instance, platinum-group metals, Ni and Au have very low hydrogen overpotential, whereas Cd, Hg, Pb, Sn, Zn, and graphite have high hydrogen overpotential.[31] The hydrogen overpotential of the cathode is decreased if the pure cathode material is contaminated with other metals. These metals can be dissolved from the anode. Therefore, the suitable combination of the cathode material with the anode materials plays a significant role.[31]

1.4. Supporting Electrolyte

Electrochemical reactions can be performed only in the electrolyte solution which can conduct electricity. Due to the poor conductivity of the organic solvents, supporting electrolyte needs to be used.[31]

The conductivity of the electrolyte solution can be improved in several ways. One of them is the use of an inorganic salt, such as tetrabutylammonium tetrafluoroborate, lithium perchlorate or tetraethylammonium tetrafluoroborate as supporting electrolyte.[22] The choice of supporting electrolyte usually depends on its solubility in the desired solvent. The supporting electrolyte must be chemically inert under the reaction conditions and should be well soluble in the solvent. Furthermore, it must be stable against oxidation and reduction. Low toxicity and low price are also very important criteria when choosing the supporting electrolyte.

Another possibility to increase the conductivity is the use of bases or acids as additives.[31] Reactions requiring acid or basic conditions typically have sufficient conductivity and an additional supporting electrolyte is not needed. This is a very inexpensive method to increase conductivity. The conductivity can also be improved by reducing the distance between the electrodes, which is discussed in chapter 2.4.2.

1.5. Solvents in Organic Electrochemistry

Solvents play a very important role in the electrolysis and there are several selection criteria which need to be considered. First of all, they should be nontoxic, inexpensive, and easy to handle. Furthermore, they must be able to dissolve the organic compounds and the supporting electrolyte, which in most cases is an inorganic salt.[31]

In general, one can distinguish between one-phase and two-phase systems. Regarding one-phase systems, the most common solvents used are the dipolar aprotic solvent (acetonitrile, dimethylformamide or dimethyl sulfoxide) and hydroxylic solvents (water and other protic solvents).[20] Bard[32] investigated the electrochemistry of organic compounds in aprotic solvent. He presented a general mechanism describing the oxidation and reduction process of aromatic hydrocarbons and related compounds. In addition to above-mentioned solvents, the typical solvents used in electroorganic synthesis are methanol, dichloromethane, or tetrahydrofuran.[22]

In the optimal case, organic and inorganic compounds are soluble in the desired organic solvent. However, since the poor solubility of some inorganic salts in organic solvents can be a problem, the two-phase system consisting of an organic solvent and water were developed.[33] A two-phase system usually consists of protic solvent and water, dipolar aprotic-protic or dipolar aprotic-water.[20]

The choice of the solvent has a significant influence on the chemical reaction and the results. One of the criteria for choosing the solvent is the polarity. It influences the capability of the solvent to solvate ions, and in this way improves the conductivity of the electrolyte. A further criterion is the usable potential window of the solvent. The solvent must be inert and the potential window should be large enough in order to avoid reaction of the solvent on the electrode surface. Furthermore, the dielectric constant is also an important characteristic of the solvent, because it influences the ohmic resistance of the solution.[31]

When choosing the solvent, not only the characteristics of a single solvent are important but the combination of solvent, supporting electrolyte, electrode materials, and additives needs to be taken into account.[20]

1.6. Galvanostatic Operation

Under galvanostatic conditions or constant current operation, the current between the electrodes is kept constant and the voltage is recorded. Voltage is the difference between the electrode potentials. The potential of the electrodes changes depending on reactions occurring on them.[22] Constant current operation is very simple and usually used in the industrial scale electrolysis.[31]

When anodic oxidations are performed, it is necessary to know the oxidation potential of the electroactive species. When the current is applied, the potential increases until it meets that required to oxidize electroactive species at the initial concentration. As the concentration of the electroactive species decreases, the voltage increases further.[23] The voltage of an electrochemical cell depends on the concentration of the chemical species undergoing reduction and oxidation on the electrodes, as described by the Nernst Equation,[34] in addition to other factors such as overpotentials due to the electrode material or cell resistance.[40] At high potentials, a second electroactive compound may start to oxidize or even the solvent.[23]

The advantage of galvanostatic operation is that the charge transferred during a reaction, can be determined by simply applying the Faraday’s law. In contrast, during potentiostatic operation, which is discussed in the next chapter, calculation of the amount of charged applied is more complex.

A very common problem of galvanostatic operation is that the limiting current density decreases with the time, as the concentration of the substrate decreases. At these conditions the voltage increases. Due to the increase in voltage, the side reactions occur and might lead to poor selectivity. Therefore, a galvanostatic operation is suitable for systems where no problematic side reactions occur which could negatively influence the reaction selectivity.[31] A good example of unproblematic side reactions is solvent decomposition or water electrolysis.[31] When side reactions strongly influence the selectivity of the reaction, potentiostatic methods are preferred.

1.7. Potentiostatic Operation

During potentiostatic or constant potential operation two- or three-electrode configurations are commonly used. Four-electrode setups are rare in organic electrochemistry.[35] Under constant potential conditions in a three-electrode setup, the potential difference between the working and the reference electrode is controlled. A reference electrode is an electrode with constant and known potential. The current flows between the working electrode and the counter electrode to close the electric circuit.[22]

In a two-electrode setup, the potential across the cell is measured (i.e. the potential difference between the working and the counter electrode), including the interface between counter electrode and electrolyte and the electrolyte solution itself. With this method the whole cell can be investigated.[35] To calculate the transferred charge during a potentiostatic operation, the current must be monitored and then integrated with respected to the electrolysis time. However, it has to be considered that the potentials of the working and the counter electrode and the voltage drop of the electrolyte solution are included.[31]

The selectivity of a reaction can be improved by conducting a reaction at controlled potential. The potential is set at a certain value and only species which are electroactive under such conditions will be oxidized or reduced. In the course of a reaction the electroactive species is consumed, which leads to a decrease of the current. At lower currents, the oxidation or reduction of the substrate requires longer time and it gets difficult to complete the reaction.[23]

1.8. Cyclic Voltammetry

Cyclic voltammetry is used in electrochemistry to determine the oxidation and reduction potential of the substrate. The experimental set up consists of three electrodes: working electrode (usually glassy carbon or platinum), a counter electrode (platinum wires) and a reference electrode (e.g. Ag/AgCl). The results are presented in a current-potential curve, so-called voltammogram. The voltammogram shows if the oxidation (or reduction) of the substrate is a reversible or irreversible process. Most organic compounds are oxidized or reduced in an irreversible fashion because the species formed (cations, anions or radicals) are unstable and undergo further transformation in solution.[23]

1.9. Divided and Undivided Cells

In general, one can distinguish between batch and flow cells. The electrolytic cell for batch experiments is very simple. It consists of a glass beaker, two electrodes (anode and cathode) and a reference electrode, if needed. Moreover, a power supply or potentiostat is required.[15] Continuous flow cells are discussed in chapter 1.10.

Both types of cells can be classified into divided and undivided cells. In divided cells two electrode compartments are separated. Undivided cells are preferable, due to the simple construction.[31] However, undivided cells are not suitable for the reaction in which the intermediate or product produced at one electrode can interfere with the reactions on the opposite electrode.[20] Moreover, the side products generated on the counter electrode during the electrochemical reaction can affect non-reacted substrate or the products and, in this way, influence the selectivity.[23] Since the catholyte and anolyte are not separated in an undivided cell, suitable conditions need to be found in order to prevent the unwanted reactions on the counter electrode. If this is not possible, divided cells are used.[31]

The construction and operation of divided cells are more complex. The anodic and cathodic compartments are separated by a separator. When using a divided cell, the effectiveness of separation and ion conductivity, as well as the chemical, thermal and mechanical stability of the separator must be considered. Although the separator is used to separate the two electrode reactions, a complete separation is not possible.[31] To keep the charge balance cation or anion exchange membranes are required to enable the transport of charged species (e.g. protons) from one compartment to the other. The membranes or frits utilized should avoid the undesired transport of the organic substrates or products.[31] Regarding the cell separators, one can distinguish two different types: the selective and unselective. As the name suggests, the selective separators allow selective transport of either cations or anions, whereas the unselective separator provides ion transport without selection.[31] Usually, a microporous separator such as fritted glass or porous ceramics, or ion-exchange membranes are used.[20] In many cases, the undivided cells are used for experiments operated at galvanostatic conditions, whereas the divided cells are preferable for potentiostatic experiments.[22] However, there are some exceptions. The separator can be omitted if the chemical reactions on the two electrodes do not interfere with each another, e.g. in paired electrolysis.[22,36]

1.10. Organic Electrochemistry in Continuous Flow

Although it took a long time for organic electrochemistry to become accepted in synthetic methodology, extensive research has been done in the past decades. The lab scale research was mostly based on the electrosynthesis in the conventional batch reactors such as glass beakers, pot cells or H cells.[36] The construction of batch cells is very simple and they are readily used in the laboratory. However, batch processes in general suffer from various drawbacks such as high ohmic drop due to the large distance between electrodes and the consequent requirement of the large amounts of supporting electrolyte. Moreover, the surface-to-volume ratio, an important parameter determining the reaction rate, depends on the scale. Mass transfer is limited on larger scale batch reactions and they are more difficult to reproduce. These problems can usually be overcome by conducting the reactions in continuous flow microreactors, which have a narrow interelectrode gap and a high and scale-independent surface-to-volume ratio. The continuous flow process in a microreactor is well reproducible and easily scalable. The scale-up is usually achieved by increasing the electrode area or by using multiple cells in parallel.

1.10.1. Basic Principles of Electrosynthesis in Continuous Flow

This chapter describes the basic principles of parallel plate flow reactors, since this type of setup was used for the experimental study of this work. As in the conventional batch processes, also in the continuous flow process the aim is to achieve a full conversion of the substrate to the desired product, with high efficiency in the shortest possible reaction time. In industry, electrosynthesis is often conducted with recycling of the reactants solution between the reactor and the reservoir. In this way, an acceptable conversion is reached, but the resulting electrolysis time is very long.[36] In addition, real continuous processing cannot be achieved using solution recycling, as the electrochemical step cannot be telescoped to subsequent reaction of workup steps. Therefore, a great effort has been made to improve the single-pass high conversion electrosynthesis. The high conversion in short time is achieved by applying a sufficiently high current to the cell, which corresponds to a certain amount of the charge. In contrast to batch experiments, during continuous flow operation calculation of the current applied takes into account the flow rate of the electrolyte and the reactor volume if high conversion in a single-pass is desired. The theoretical current, required to reach the desired charge, can be calculated using Faraday’s law:

$$I_{cell} = \frac{n\,F\,z}{t}$$

In this equation, *n* is the initial number of moles of the substrate in the solution, *F* is the Faraday constant (C mol^{-1}), *z* is the number of electrons involved in the chemical reaction and *t* is the residence time of the electrolyte solution containing *n* moles of the substrate in the reactor. The calculated current is applied to the cell, resulting in a specific current density. However, it must be mentioned that the current density distribution in a parallel plate reactor is not uniform. The current density is very high at the inlet of the reactor due to the high concentration of the substrate. Since the concentration of the substrate decreases along the reactor channel, the current density is higher at the beginning of the flow reactor than near the outlet (where high conversion is achieved, should be near zero). When high conversions in a single pass are aimed, high currents are typically required. Such current should only be applied when the reactor reaches steady-state conditions. Otherwise overoxidations will occur due to a lack of starting materials at the beginning of the run with the cell to match the current applied. One possibility to overcome this problem is to perform the reaction under constant voltage conditions.

A very important parameter for the description of the cell performance is the current efficiency. Current efficiency is defined as the amount of the charge which is effectively used in a reaction and is calculated as follows:

$$Current\ efficiency = \frac{Q_{experimental}}{Q_{theory}} \cdot 100\ \%$$

1.10.2. Cell Designs and Operation

Due to the numerous advantages of the continuous flow process, extensive research has been done in this field in recent years. Many different flow reactor designs have been developed.[36,37,38,41,45,49,53,54] Most of them are used in the laboratory scale, some of them are commercially available whereas the others are “home-made” cells, developed for particular investigations.

Some examples of the flow reactor used in the industry are the *filter press cell* and the *capillary gap cell*.[31] The FM01-LC electrolyser [39] is a filter press cell and is one of the commercially available laboratory-scale electrolysers. It is based on a larger FM21-SP electrolyser designed for the chlor-alkali industry. The FM21-SP electrolyser offers good potential distribution due to the parallel-plate configuration but the space-time yield and the energy efficiency suffer due to the difficulties to reduce the interelectrode gap.[40] Another flow reactor, used for the large scale electrosynthesis, is the capillary gap flow cell with sub-millimetre gap and disk electrodes.[40] This flow reactor provides high productivity but due to the low conversion per pass, the recycling of the reactant solution is required. All these problems have led to the development of the new reactor constructions. The aim of the current investigations is to develop single-pass flow cells, which provide both high conversion and high productivity.

Green et al.[41] developed laboratory-scale microfluidic cells with extended channel lengths. In these flow reactors, high conversions can be achieved even at flow rates above 1 mL min^{-1} (> 1 g h^{-1} product formation). This is not the case in conventional microflow cells with short channel lengths, where a very slow flow rate has to be applied in order to reach a good conversion, leading to the low rate of product formation. In 1995, Matlosz [42] reported in a theoretical study about the flow-through porous electrodes and their performance. The electrodes consisted of alternating insulating and conducting sections. Several years later, Rode et al.[43,44] performed a theoretical study based on model calculations of the influence of segmented working electrodes on the reaction. Afterwards, a thin-gap, single-pass, high-conversion reactor was developed and the influence of the kinetic parameters on the cell performance was investigated.[45,46,47,48] Using this flow reactor, a space-time yield 5-10 times higher than current industrial processes could be achieved.[48] Watts at al.[49] manufactured a simple microreactor with a very small interelectrode gap (100-250 µm), which was successfully used for the synthesis of several organic compounds.[49,50,51] Afterwards, they developed a much-improved electrochemical reactor with easily exchangeable electrodes (25 cm^2 each) with secure and robust electrode-wire connection. Thus, the flexibility, productivity and current efficiency could be improved.[52] Very recently, Amri et al.[53] from the same research group reported about methoxylation of pyrrolidine-1-carbaldehyde in the commercially available Ion Electrochemical Reactor. For this particular reaction, high efficiency in performing the reaction regioselectively could be achieved. The same reactor was used for the experimental study of this work and is going to be discussed in the following chapters.

As mentioned in the previous chapters, one of the advantages of a flow reactor in contrast to conventional batch equipment is the possibility of the reduction of the amount of supporting electrolyte. Therefore, besides the research of the different cell designs, the supporting electrolyte was also a subject of various investigations. Successful reactions conducted in microreactors with a reduced amount or even without the use of the supporting electrolyte have been reported in the literature. Yoshida and coworkers [54] investigated the anodic methoxylation of 4-methylanisole in a divided microflow reactor without using a supporting electrolyte. However, they reported that most likely the protons contributed to the conductivity of the solution, because they flow from the anodic to the cathodic chamber. Wirth and coworkers [52] investigated the reaction in a microflow reactor without the use of supporting electrolyte. However, in this case the base used in the reaction acted as supporting electrolyte, with the advantage that the removal of the base is much easier than the removal of supporting electrolyte during work-up. Haswell and coworkers [55] reported the self-supported electro-reductive coupling of benzyl bromide derivates and activated olefins in a micro flow reactor. They found out that the conversion strongly depends on the electrode gap. The same group investigated the cathodic dimerization of 4-nitrobenzylbromide in a continuous flow microreactor, in presence and in absence of supporting electrolyte.[56] Excellent yields for the dimer were achieved without using a supporting electrolyte. A self-propagation mechanism was proposed to explain the results. Such self-supported systems can be successful only if the residual intrinsic conductivity of the organic solvents is high enough and the thickness of the diffusion layer is similar to the gap between electrodes.[56] Paddon et al.[57] performed an electrochemical reaction without supporting electrolyte in a flow-through mode. The electrolyte-free electrosynthesis was possible only at sufficiently small electrode distance, due to the overlapping of electrode diffusion layers. The same group investigated also the paired and coupled electrode reactions in a flow microreactor.[58] Laudadio at al.[59] performed selective electrochemical oxidation of thiols and sulphides in a commercially available continuous flow reactor with the use of supporting electrolyte and under controlled potential conditions. An undivided cell electrochemical reactor with adjustable reactor volume was used, with the possibility to be used in serial or parallel mode.[60]

2. Results and Discussion

2.1. Project Aims

The aim of this research is to investigate the translation of a model electrochemical batch reaction to single-pass continuous flow mode. The effect of all reaction parameters, namely interelectrode distance, flow rate, backpressure and the concentration of the supporting electrolyte on the reaction outcome have been investigated in detail. Moreover, the behaviour of the electrochemical reaction under constant current and constant voltage conditions has been examined. The target was to optimize the continuous flow process in terms of conversion, selectivity and current efficiency, based on the results obtained in the batch reactions.

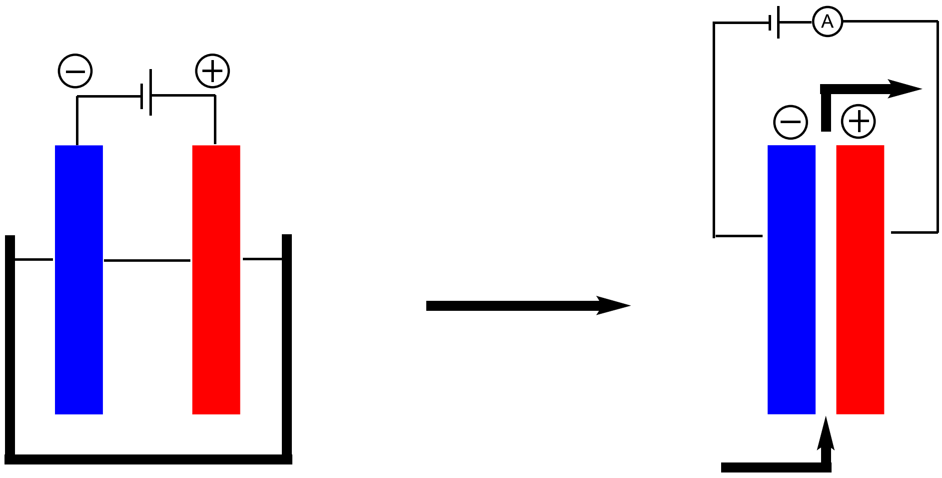
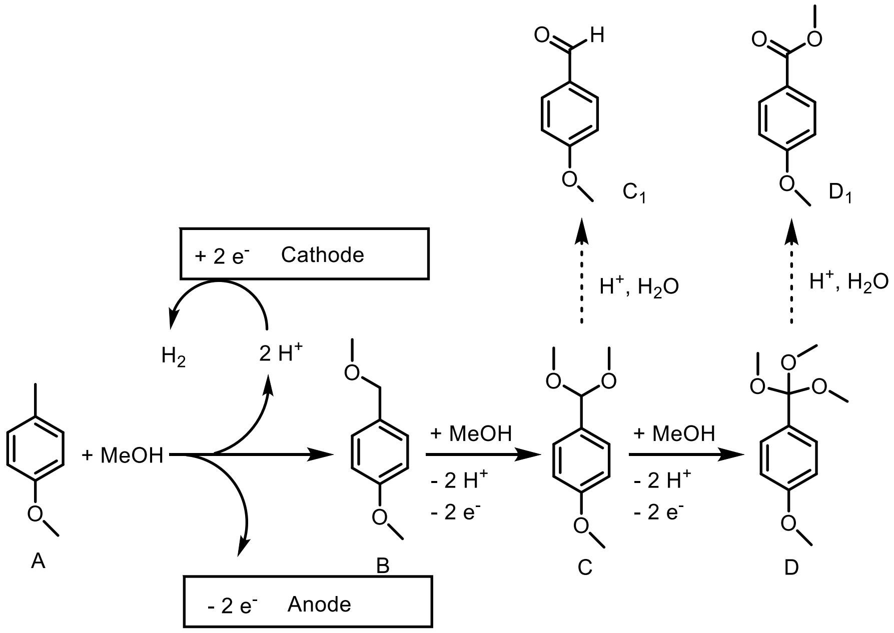


Figure 3. The aim of this work is translating batch electrochemistry to single-pass continuous flow conditions.

2.2. Model Reaction

For this study, the methoxylation of 4-methylanisole was chosen as a model reaction. The methoxylation of 4-methylanisole to 4-anisaldehyde is a very important industrial process, patented by BASF and currently carried out on a large scale in a narrow gap cell.[61] The mechanism of this reaction is well known (Scheme 3). It is a four-electron reaction, meaning that 4 F mol^{-1} are theoretically needed for the full conversion of the substrate (A) to the desired product C. First, the intermediate B is formed (two-electron reaction), which further reacts to form the main product C. If overoxidation of the product occurs, the side product D is formed (six-electron reaction). However, in most cases, the formation of the intermediate and the side product occurs simultaneously to the formation of the product and in this way affects the selectivity. For the calculation of the current efficiency the intermediate B, product C, and the side product D were included. Besides the side product D, very small amounts of other side products were formed but they were not considered for the calculation of the current efficiency. Hydrogen gas bubbles, which are formed on the cathode, have a negative impact on the current efficiency.

$$Q_{\text{experimental}} = 2 \cdot \frac{\%\,intermediate}{100} + 4 \cdot \frac{\%\,product}{100}\ 6 \cdot \frac{\%\,side\ product}{100}$$



Scheme 3. Reaction mechanism of the methoxylation of 4-methylanisole.

2.2.1. Experimental Procedures

Batch

The model reaction was initially investigated in a commercial batch reactor (IKA *ElectraSyn 2.0*). The anode material was graphite, whereas graphite and stainless steel were used as the cathode materials. Both cathode materials provided very similar results. First, the supporting electrolyte Et_4NBF_4 was dissolved in methanol (variable amounts from 0.1 to 0.01 M). Afterwards, 4-methylanisole (0.1 M) was added. The reaction mixture was stirred and 1-6 F mol^{-1} of charge at a constant current of 20 mA were applied. The distance between electrodes in the batch reactor was 5 mm.

Continuous Flow

Design of the Flow Reactor

This work describes the translation of an electroorganic process from a conventional electrochemical beaker cell to a continuous flow conditions in a single-pass procedure. The continuous flow Ion Electrochemical Reactor fabricated by Vapourtec Ltd [1] was used for this study. It is a very simple rectangular parallel plate reactor with easily replaceable electrodes separated by a FEP (0.1-0.5 mm) or PTFE spacer (1 mm) (see Table 1). The interelectrode gap can by adjusted exchanging the spacer. The interelectrode gap spacer contains the reaction channel (Figure 4). It can be utilized in undivided and divided configuration.

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[1] https://www.vapourtec.com/products/flow-reactors/ion-electrochemical-reactor-features/

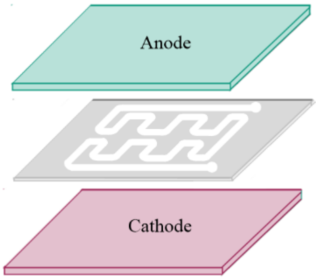

Figure 4. Schematic representation of the electrodes with the spacer between them.

Table 1. The four different spacers used in the flow reactor with a corresponding channel area and the volume.

Spacer thickness [mm]	Electrode area (channel) [mm^2]	Flow channel volume [µL]
0.1	1250	125
025		313
0.5		625
1.0		1250

General procedure

First, the supporting electrolyte Et_4NBF_4 was dissolved in methanol (variable amounts from 0.1 to 0 M). Afterwards, 4-methylanisole (0.1 M) was added. The solution was stirred until the supporting electrolyte was dissolved. The reactor was connected to a power supply (*DC Power Supply 6070*) and a multimeter (*PeakTech® 2025*). The reaction mixture was introduced in the reactor using a sample-loop (1.5 mL), and injected by a 6-port valve. Solvent was continuous pumped through the system using a syringe pump (Syrris Asia). The desired flow rate and the current/voltage were manually set. The current and the voltage were recorded with the *PeakTech DMM Tool.* Samples of the crude reaction mixture were collected at the reactor outlet and analyzed with GC-MS and GC-FID.

2.2.2. Analytics

Crude reaction mixtures were analysed using a ThermoFisher Focus GC-MS (TR-5MS column 30 m × 0.25 mm × 0.25 µm) in order to identify the retention times of the species. The injector temperature was set at 280 °C. After 1 min at 50 °C, the temperature was increased to 300 °C (25 °C min^{-1}) and kept constant at 300 °C for 3 min. Helium was used as a carrier gas with a flow rate of 1.0 mL min^{-1}. Quantitative analysis was performed on a ThermoFisher Focus GC-FID (TR-5MS column 30 m × 0.25 mm ID × 0.25 µm). The injector temperature was set at 280 °C. After 1 min at 50 °C, the temperature was increased to 300 °C (25 °C min^{-1}) and kept constant at 300 °C for 4 min. Helium was used as a carrier gas with a flow rate of 1.0 mL min^{-1}. The chemicals used for this research were purchased from commercial sources and were used without further purification. Methanol (HPLC grade, Lot: 19E234009) was purchased by VWR Chemicals, 4-methylanisole (99%, Lot: MKBW6448V) was purchased from Aldrich and the supporting electrolyte Et_4NBF_4 (99%, Lot: BCBV4670) was purchased from Aldrich as well.

2.3. Batch Process

The results of the batch experiments are shown in Table 2. The results shown in the first section of the table (entries 1-5) were obtained with a stainless steel cathode, whereas in the second section of the table (entries 6-10) graphite was used as cathode. As expected, the conversion increased with increased charge, whereas the current efficiency remained fairly constant. After 4 F mol^{-1} of charge, a conversion of 69 % and a current efficiency of 62 % were achieved. To obtain high conversions (>90%) an excess of charge (6 F mol^{-1}) was required[2]. The reaction time required to apply 6 F mol^{-1} was 144 min at 20 mA. Formation of the side product D was observed, even if not all the substrate was consumed. When graphite was used as cathode, even lower conversion and lower current efficiency were obtained.

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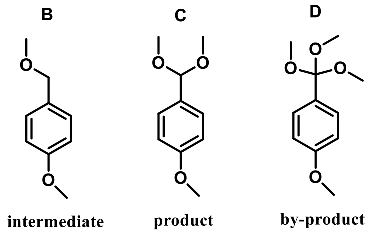
[2] Since the charge > 6 F mol^{-1} did not contribute to the improvement of the conversion, only charges ≤ 6 F mol^{-1} were considered.

Table 2. Conversion, current efficiency, and composition of the crude reaction mixtures obtained in batch mode.[a]



Entry	rpm	I [mA]	Q [F mol $^{-1}$]	Conversion/ Current Efficiency [%]	Products B [%], C [%], D [%]
1	800	20	1	21/63	10, 11, 0
2			2	38/61	15, 23, 0
3			3	53/61	15, 38, 0
4			4	69/62	14, 55, 0
5			6	91/60	5, 84, 2
6	800	20	1	20/59	10, 10, 0
7			2	37/58	14, 22, 0
8			3	52/57	16, 35, 0
9			4	64/55	15, 47, 0
10			6	81/48	11, 64, 2

[a] Reaction conditions: 0.1 M 4-methylanisole and 0.1 M Et_4NBF_4 in 3 mL methanol, graphite (+)/stainless steel (-) (entry 1-5) and graphite (+)/graphite (-) (entry 6-10), constant current operation, B=intermediate, C=product, D=side product.

2.4. Continuous Flow Process

During the experiments, the reactor was positioned vertically with the inlet at the bottom and outlet at the top. Graphite was used as a cathode and anode material for most the experiments, except the experiments with backpressure. For these experiments, a stainless steel cathode was used instead of graphite. In general, the cell voltage is greatly influenced by the interelectrode gap and the flow rate (Figure 5). The interelectrode gap is determined by the thickness of the spacer, resulting in different reactor volumes and different residence time depending on the flow rate applied. Different flow rates in the range from 200 µL min^{-1} to 1600 µL min^{-1} were investigated. Constant current and constant voltage experiments were performed.

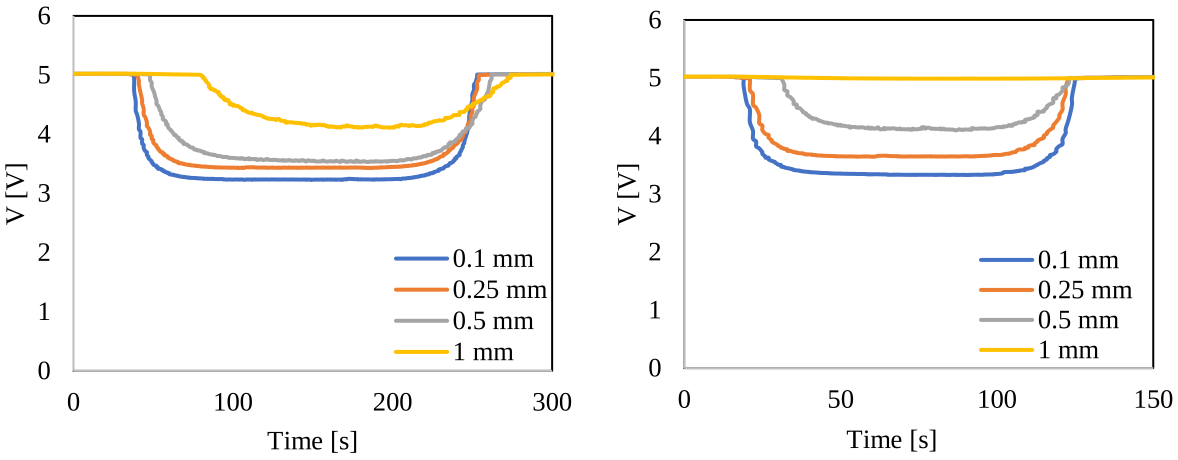


Figure 5. Influence of the interelectrode distance on the voltage. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), constant current operation, 4 F mol^{-1}, (a) 400 µL min^{-1}, 257 mA, (b) 800 µL min^{-1}, 515 mA.

In addition to the optimization of the parameters mentioned above, the concentration of the supporting electrolyte was reduced stepwise from 0.1 M to 0 M in order to find the lowest concentration possible for a reaction to be performed without a significant increase in voltage or change in conversion. Besides that, a well-known problem of the gas evolution was considered too. Therefore, experiments with applied backpressure up to 5 bars were performed and the influence on the voltage, conversion, and the current efficiency were examined. In each experiment, 1.5 mL of the electrolyte solution, containing methanol with the substrate 4-methylanisole (0.1 M) and the supporting electrolyte Et_4NBF_4 (0.1 M), was continuously pumped through the cell. The product samples were collected at the outlet of the reactor and were measured by GC-FID for determination of the conversion. All reactions were performed at ambient temperature and ambient pressure unless otherwise stated.

The flow reactor discussed in this work was operated at constant current and constant voltage conditions. For the constant current mode, the required current (Faraday’s law) was applied and the voltage was measured and recorded. The maximum voltage of the power supply was set at 5 V. At the beginning, the reactor was flushed and filled with the pure solvent. Since the resistance of a pure solvent is high, the maximum voltage of 5 V was reached at this moment in the reactor.

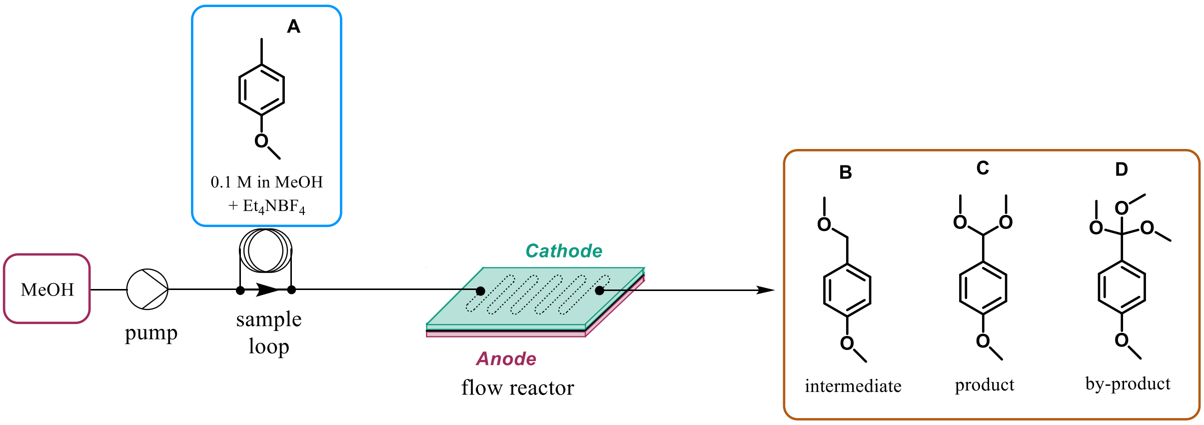


Figure 6. Schematic representation of the continuous flow process.

The voltage drops when the electrolyte solution enters the reactor (transient region X in Figure 7). In this area, overoxidations take place and influence the selectivity. The same situation was observed during the last stage of the reaction processing (transient region Z), when most of the electrolyte solution had left the reactor and the voltage increased again. This experiment stressed the importance of working under steady-state conditions when constant current is applied. Only during steady-state the cell voltage and reaction conversion and selectivity are representative of the electrochemical process. As can be seen in Figure 7b, at the large interelectrode distance (large reactor volume), the steady-state was very short and the voltage was very high. Accordingly, more side products were formed.

The side reactions can be avoided or reduced by performing a reaction at a constant voltage. In general, during constant voltage operation, the voltage is applied and the current is recorded. The current increases when the electrolyte solution enters the reactor and drops when the electrolyte leaves the reactor. In between, the steady-state is attained. The major advantage of the constant voltage experiments is that no or little overoxidation occurs, in comparison to the constant current operation, at the initial and final stage. The detailed comparison of the constant current and constant voltage experiments is described in chapter 2.4.4.

It is important to mention that as soon as the electrolyte solution enters the reactor and the chemical reaction occurs, gas evolution at the cathode leads to the formation of a liquid-gas mixture. Due to the gas bubbles in the flow channel, the actual residence time of the gas-liquid mixture in the reactor is shorter than the theoretical residence time calculated for the particular flow rate and the reactor volume. At higher currents, more bubbles are formed and the residence time in the reactor is shorter compared to lower currents using the same flow rate (see Figure 8).

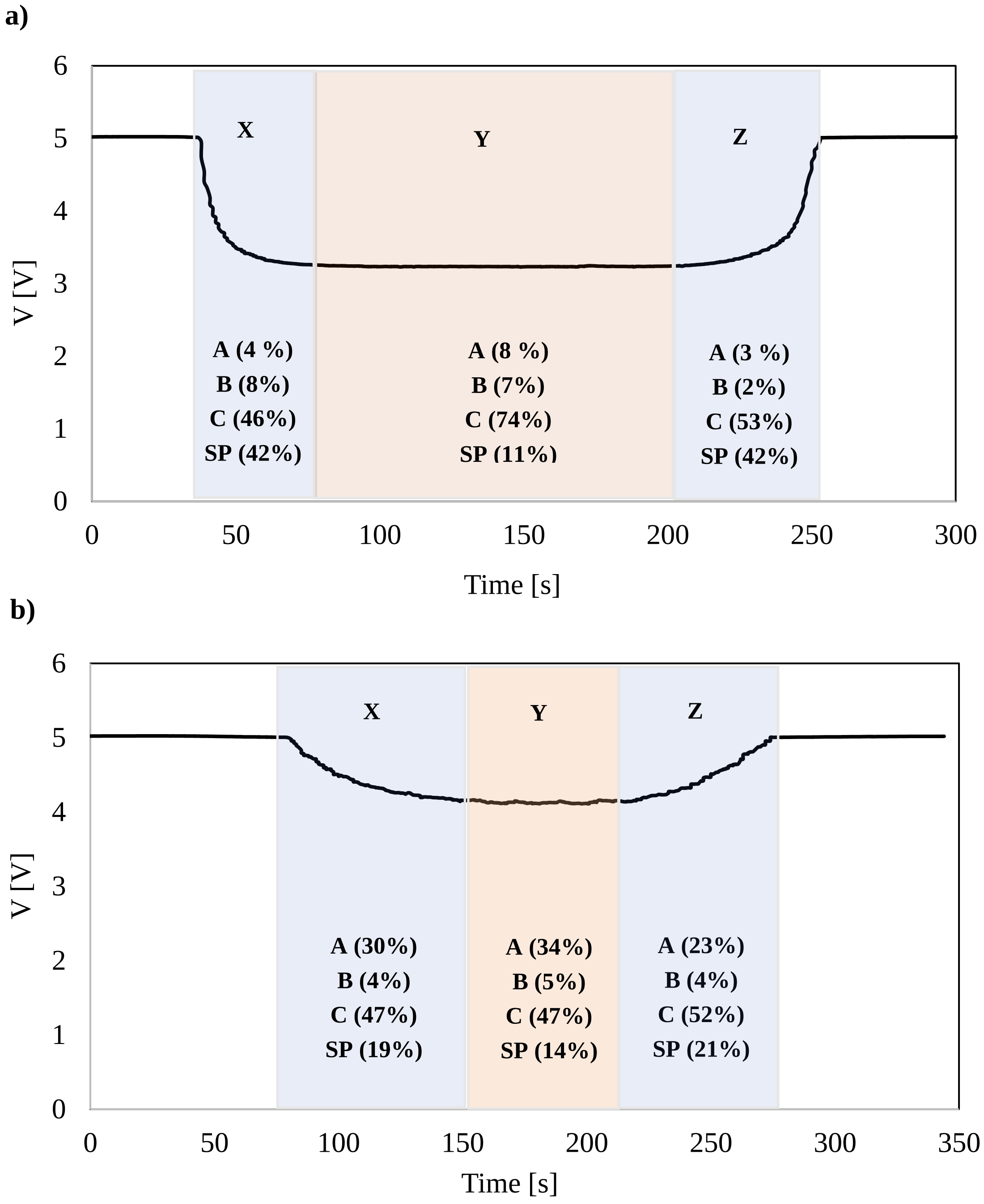


Figure 7. The transient regions shown on the curve recorded during constant current operation. (a) 0.1 mm spacer = 0.125 mL reactor volume (b) 1 mm spacer = 1.25 mL reactor volume. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), constant current operation, 400 µL min^{-1}, 257 mA (4 F), A=substrate, B=intermediate, C=product, SP= all side products including the side product D.

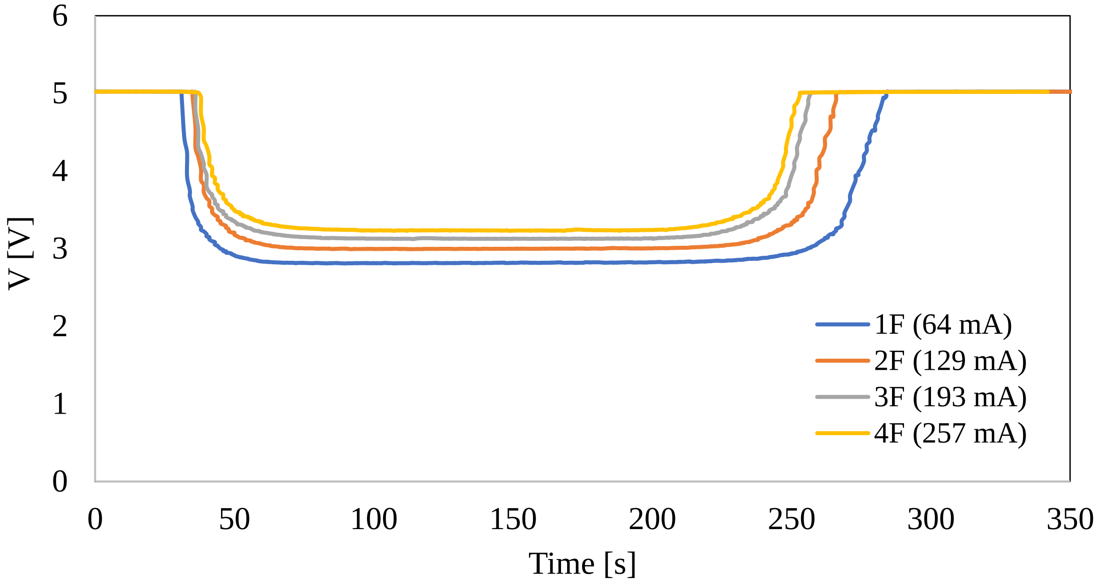


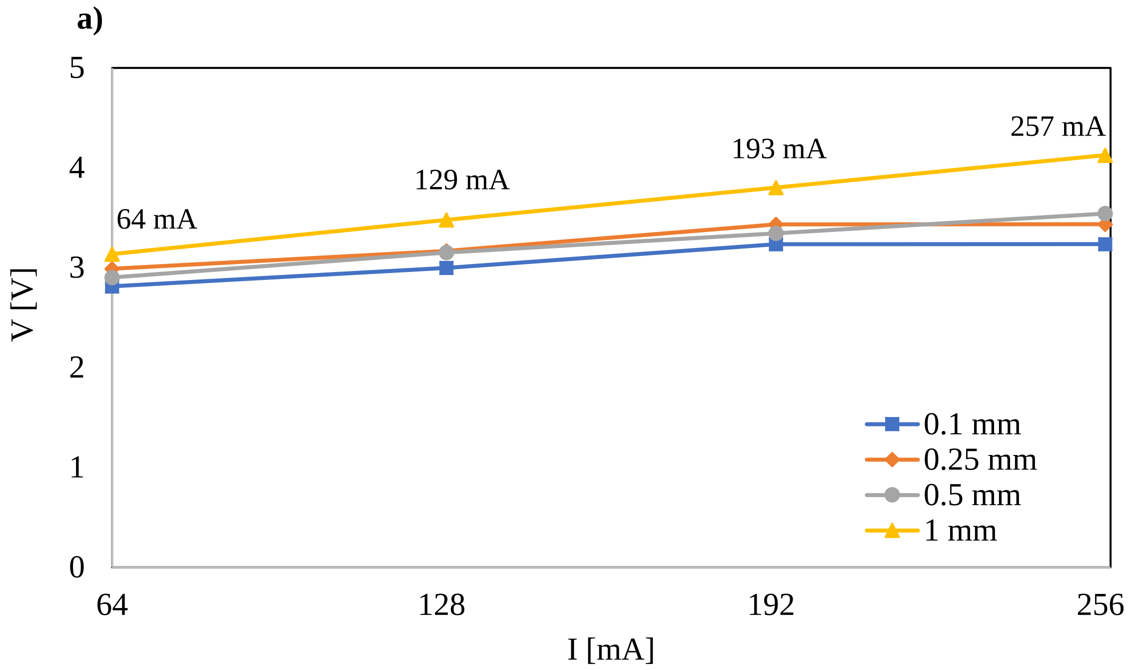
Figure 8. Influence of the gas bubbles on the residence time distribution. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, 0.1 mm spacer, graphite (+)/graphite (-), constant current operation, 400 µL min^{-1}.

2.4.1. Influences on the Cell Voltage

The Ohm’s law describes the dependence of the voltage on the current and resistance. It states that the current is directly proportional to the voltage across the two points in the cell ($V=RI$).[62] As previously mentioned, the ohmic resistance is minimized when the interelectrode distance is short, which can be easily achieved in a microflow reactor. Low resistance means that even when the current is increased, the cell voltage does not changes substantially (Figure 9a, 0.1 mm), in contrast to the large interelectrode distance where the resistance is higher and thus the voltage increases significantly with the increasing current at the constant flow rate (Figure 9a, 1 mm).

Figure 9b shows how the voltage changes when the flow rate is increased from 200 µL min^{-1} to 800 µL min^{-1} at a constant charge (4 F mol $^{-1}$), depending on the distance between the electrodes. In order to keep the charge constant, the current was increased with increasing flow rate. It is obvious that the voltage increases when the flow rate and the current are increased. Notably, while for the larger interelectrode gap the voltage increases nearly linearly with the current, for the narrower spacers (0.1 mm and 0.25 mm) the voltage flattens at above 400 µL min^{-1}. Thus, increased current does not translate to increase voltage. This interesting effect could be ascribed to a larger improvement of the mass transfer with increased flow rates for the narrow spacers.

At high currents, more gas bubbles are formed, which leads to an increase in resistance and results in high voltage. In general, the resistance and the voltage are the highest at the large interelectrode gap and the lowest at the small interelectrode gap. The larger the distance between electrodes, the stronger is the effect of the current on the voltage.



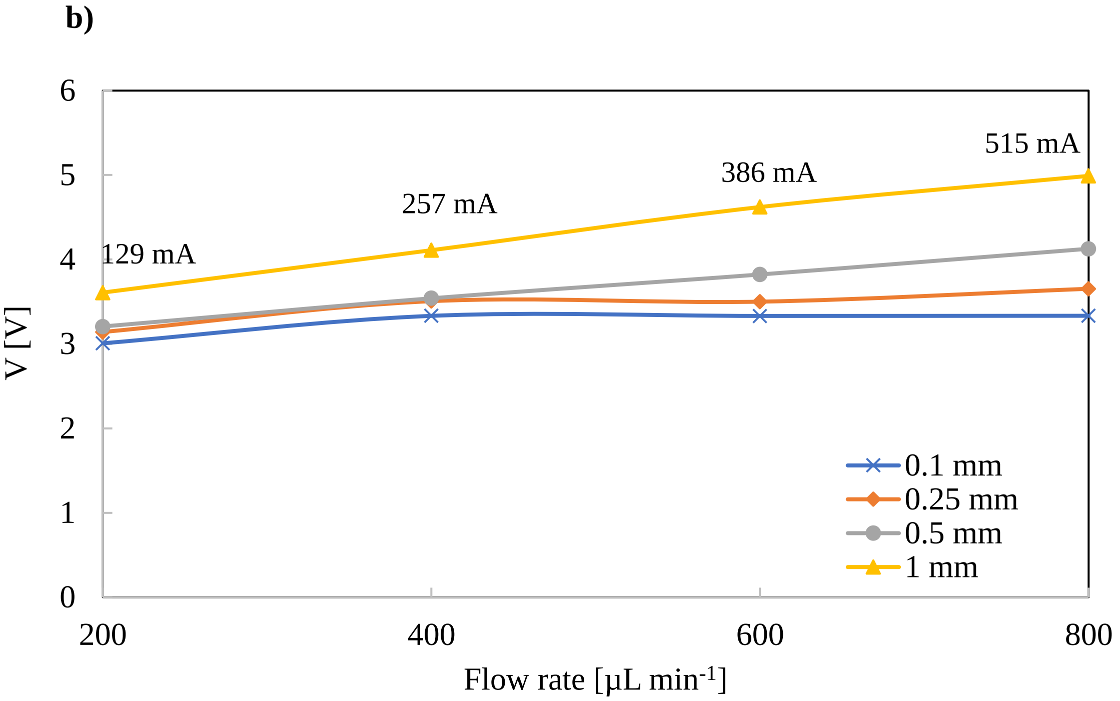


Figure 9 Comparison of the voltage recorded at different electrode distances (a) influence of the charge on the voltage at constant flow rate (400 µL min^{-1}) (b) influence of the flow rate/current on the voltage at constant charge (4 F). Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), constant current operation.

Besides the experiments at constant flow rate (400 µL min^{-1}) and constant charge (4 F mol^{-1}), also experiments at constant current (257 mA) were performed. Therefore, the current was kept constant and the flow rate was increased, leading to decreasing charge. In this way, the effect of the flow rate on the voltage, possibly by influencing the mass transfer, could be directly evaluated. Notably, increased flow rates led to lower voltages in all cases, confirming that higher flow rates improve the mass transfer of the liquid. This is not surprising, as the Reynolds number of the system is proportional to the flow velocity of the liquid stream.

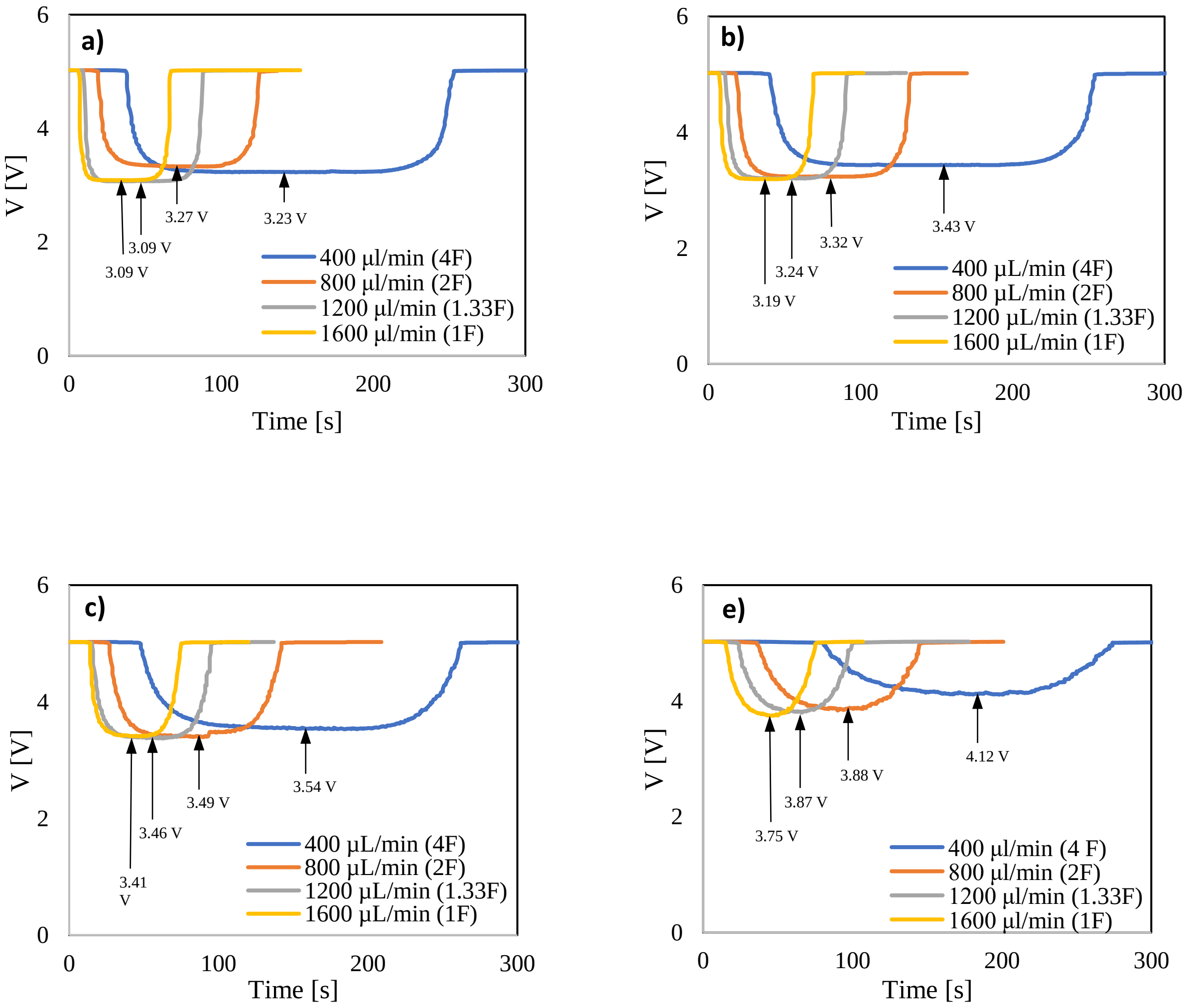


Figure 10. Influence of the flow rate/charge on the voltage at constant current and different interelectrode gaps: (a) 0.1 mm (b) 0.25 mm (c) 0.5 mm (d) 1 mm. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), constant current operation.

2.4.2. Concentration of Supporting Electrolyte

Supporting electrolytes are used in the organic electrochemistry to increase the conductivity of the electrolyte solution, and thus lower the ohmic resistance and the voltage of the cell (see chapter 1.4). However, the ohmic resistance and the voltage of the cell can also be lowered by the reduction of the distance between the electrodes, allowing the concentration of the supporting electrolyte to be significantly reduced. The reduction of the concentration or the removal of the supporting electrolyte is very important due to their cost and the potential simplification of the workup procedures.[52]

In this study the changes in voltage and conversion when the concentration of supporting electrolyte was reduced stepwise from 0.1 mol L^{-1} down to 0 mol L^{-1} was investigated for all available interelectrode gaps (0.1 to 1 mm). Additionally, the batch experiments were performed with reduced amounts of supporting electrolyte. As shown in Figure 11, with the smallest interelectrode gap (0.1 mm), the concentration of the supporting electrolyte could be reduced down to 0.02 mol L^{-1} without a significant increase in voltage or change in conversion. The best conversion was achieved at an interelectrode gap of 0.1 mm and a concentration of supporting electrolyte of 0.015 mol L^{-1}. The current efficiency for these conditions could be determined as 99%, whereas for the same concentration of supporting and large interelectrode gap, the maximum voltage was reached and the system switched to the constant voltage operation. In such cases, the conversion and current efficiency could not be determined since the charge of 4 F mol^{-1} was not reached. At the large distances between the electrodes (1 mm), the voltage was generally very high, even if a high concentration of the supporting electrolyte was used. The limit of 5 V was usually reached at the concentrations lower than 0.02 mol L^{-1}, depending on the interelectrode gap. For this particular reaction in this reactor, the complete removal of the supporting electrolyte was not possible.

In the batch experiments, the concentration of supporting electrolyte was reduced from 0.1 mol L^{-1} to 0.01 mol L^{-1}. For these reactions no voltage limit was set and the voltage increased to 7.6 V when the lowest amount of supporting electrolyte (0.01 mol L^{-1}) was used. Interestingly, the conversion remained fairly constant even at high voltages. This indicates that the voltage does not have a significant impact on the conversion of this reaction.

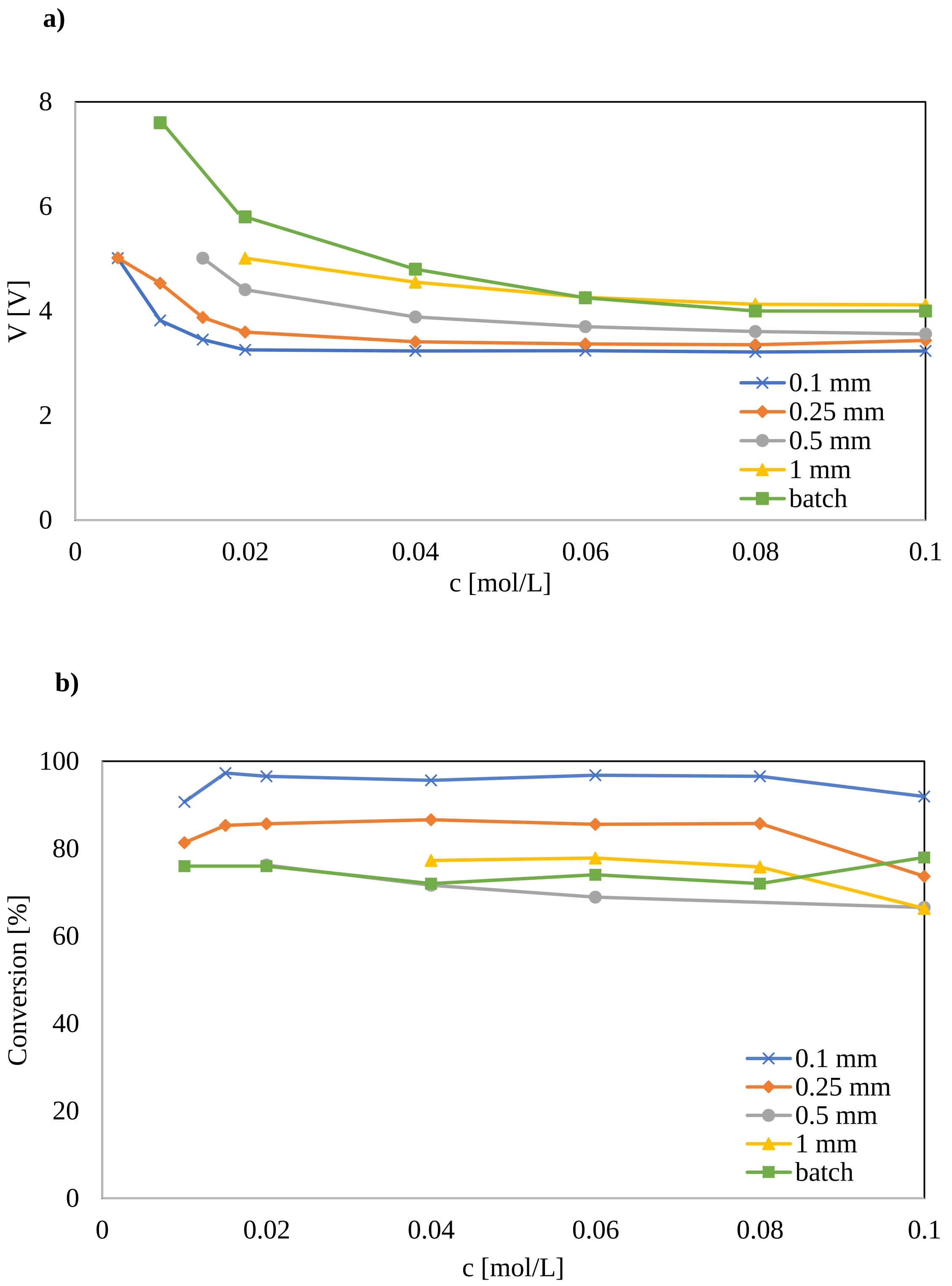


Figure 11 (a) Comparison of the voltage recorded in a flow reactor at different electrode distances and in a batch reactor when different concentrations of supporting electrolyte are used, (b) Comparison of the resulting conversions. Reaction conditions: 0.1 M 4-methylanisole with 0.005-0.1 M Et_4NBF_4 in 1.5 mL methanol (flow) or 3 mL methanol (batch), graphite (+)/graphite (-), constant current operation, 400 µL min^{-1}, 257 mA (4 F).

2.4.3. Conversion and Current Efficiency (Galvanostatic Operation)

For a better understanding of the influence of different parameters on the conversion, current efficiency and the amount of intermediate, product and side product, the parameters (flow rate, current/charge, and interelectrode gap) were varied in different combinations and the results were summarized and shown in Table 3.

In the first section of the table (entries 1-4), one can observe the progress of the reaction from 1 F mol $^{-1}$ to 4 F mol $^{-1}$ at a constant flow rate of 400 µL min^{-1}. Increase in conversion with increasing current/charge was observed for all four spacers. The current efficiency, however, does not show a clear trend in this case, especially with the larger interelectrode gaps. The best results were obtained at the narrow interelectrode gap (0.1 mm). At the flow rate of 400 µL min $^{-1}$ the reaction was almost complete after 4 F mol $^{-1}$ (92 % conversion) with the current efficiency of 91 % and the amount of intermediate, product and side product of 7 %, 74 % and 9 % respectively. This ratio indicates that after 4 F mol $^{-1}$ there was still a small amount of unreacted intermediate observable and at the same time the formation of the side product occurred.

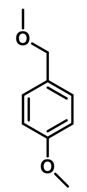
In the second section of the table (entries 5-8), the influence of different flow rates on the results is demonstrated. For these experiments, a charge of 4 F mol $^{-1}$ was applied in all cases. The reduction of the flow rate from 400 µL min $^{-1}$ to 200 µL min $^{-1}$ resulted in a significant increase in conversion and current efficiency for all spacers. This improvement could be specially noticed for larger interelectrode gap (1 mm), where the high flow rate leads to drastic drop in the conversion and current efficiency. The best results were achieved at a small interelectrode distance of 0.1 mm and low flow rate of 200 µL min $^{-1}$ leading to 96 % conversion, 96 % current efficiency and the amount of intermediate, product and side product of 3 %, 87 %, and 5 %. To reach 4 F mol^{-1} at low flow rate also lower current needs to be applied, resulting in lower current density and consequently higher current efficiency. If the flow rate and the distance are increased at the same time, the conversion and the current efficiency decrease correspondingly.

In the last section of the table (entries 9-12) the results are shown, which were obtained with variable flow rates and constant current (257 mA) resulting in different amount of charge being applied. High flow rates are unfavourable in this case as well. High flow rates result in very poor conversion and low current efficiency for narrow and large interelectrode distances.

Considering the amount of intermediate, product and side product, a significant amount of intermediate could be observed, which indicates the uncomplete reaction.

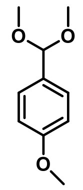
Table 3. Conversion, current efficiency, and composition of the crude reaction mixtures of the reactions performed in the flow reactor at different electrode distances.[a]

B



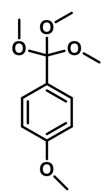
intermediate

C



product

D



by-product

Entry	**Flow rate [μL min $^{-1}$]**	**I [mA]**	**Q [F mol $^{-1}$]**	**Conversion [%]/Current efficiency [%] Products B [%], C [%], D [%]**			
				0.1 mm	**0.25 mm**	**0.5 mm**	**1 mm**
1	400	64	1	25/74 (12, 13, 0)	20/64 (6, 13, 0)	18/55 (9, 9, 0)	25/84 (8, 17, 0)
2	400	129	2	42/71 (12, 30, 0)	42/71 (12, 30, 0)	38/63 (11, 26, 0)	50/92 (7, 39, 2)
3	400	193	3	71/85 (11, 57, 0)	60/72 (11, 46, 1)	52/61 (7, 42, 0)	60/77 (7, 46, 6)
4	400	257	4	92/91 (7, 74, 9)	74/73 (10, 52, 11)	67/63 (9, 49, 6)	66/68 (5, 47, 12)
5	200	129	4	96/96 (3, 87, 5)	89/93 (5, 71, 13)	84/81 (6, 71, 4)	89/97 (2, 65, 20)
6(4)	400	257	4	92/91 (7, 74, 9)	74/73 (10, 52, 11)	67/63 (9, 49, 6)	66/68 (5, 47, 12)
7	600	386	4	90/87 (9, 72, 7)	72/69 (10, 48, 11)	67/58 (3, 48, 5)	59/58 (5, 39, 11)
8	800	515	4	88/84 (10, 64, 10)	68/61 (9, 43, 8)	47/38 (10, 28, 3)	44/39 [b] (5, 29, 5)
9(4)	400	257	4	92/91 (7, 74, 9)	74/73 (10, 52, 11)	67/63 (9, 49, 6)	66/68 (5, 47, 12)
10	800	257	2	43/68 (15, 26, 0)	39/62 (12, 25, 0)	28/48 (5, 21, 1)	35/60 (6, 25, 1)
11	1200	257	1.33	31/70 (13, 16, 0)	24/54 (9, 13, 0)	19/44 (7, 11, 0)	20/52 (5, 14, 0)
12	1600	257	1	21/55 (11, 8, 0)	17/49 (8, 8, 0)	13/37 (6, 6, 0)	12/36 (5, 6, 0)

[a] Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), constant current operation, B=intermediate, C=product, D=side product.

[b] Max. voltage was reached. Thus, less than 4 F mol^{-1} were applied.

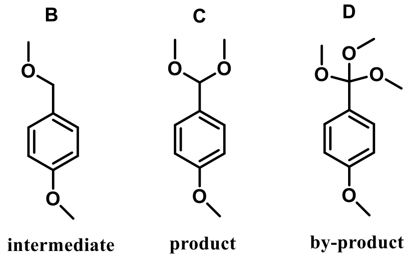
2.4.4. Conversion and Current Efficiency (Potentiostatic Operation)

As discussed in chapter 2.4, during constant current operation the overoxidations in the transient regions occur and lead to the formation of undesired side products. In some cases, the overoxidations can be avoided by conducting the reactions at a constant voltage. In contrast to constant current operation, no steady-state conditions are required for the operations at constant voltage. However, the potentiostatic operation suffer from several drawbacks which are discussed in this chapter.

In Table 4 the conversion, current efficiency, and the amount of intermediate, product, and side product during constant current and constant voltage operations are compared. Three sets of experiments with increasing flow rates under galvanostatic and potentiostatic conditions were performed, aiming for an amount of charge of 4 F mol^{-1}. This charge was easily attained at galvanostatic conditions, by calculating the required current using Faraday’s law. At potentiostatic conditions, a voltage slightly higher to that required to achieve the desired transformation is applied. When the voltage was set to the values observed during galvanostatic operation, significant deviations from the expected current were obtained, especially at high currents (see entry 5 and 6). This is a well-known phenomenon due to the fact that the cell voltage is susceptible of significant deviations due to parameters such as ambient temperature, small amounts of impurities in the reaction mixture or electrodes surface, or even the connections to the power supply.[40]

The conversion and the current efficiency, as well as the amounts of intermediate, product and side product obtained at constant current and constant voltage conditions at constant flow rate were similar and no trend could be recognized (see Table 4). Since no improvement of the results could be achieved and due to the complexity of this process, the potentiostatic operation is considered as an unsuitable method for carrying out these experiments.

Table 4. Comparison of the conversion, current efficiency, and composition of the crude reaction mixtures obtained at constant current and constant voltage operation.[a]



Entry	Operation	Flow rate [μL min $^{-1}$]	V [V]	Q [F mol $^{-1}$]	I [mA]	Conversion/Current Efficiency [%]	Products B [%], C [%], D [%]
1	galvanostatic	200	3.00	4	129	96/96	3, 87, 5
2	potentiostatic		3.29	3.93	127	97/92	3, 89, 0
3	galvanostatic	600	3.34	4	386	90/87	9, 72, 7
4	potentiostatic		3.74	3.36	324	83/92	7, 70, 3
5	galvanostatic	800	3.33	4	515	88/84	10, 64, 10
6	potentiostatic		4.31	3.91	503	89/75	5, 65, 4

[a] Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), 0.1 mm spacer, B=intermediate, C=product, D=side product.

2.4.5. Handling Gas Evolution in a Continuous Flow Reactor

The reactor performance is greatly affected by the hydrogen gas bubbles which are formed in the channel of the reactor and act as an insulator on the electrode surface. As mentioned previously, the gas evolution on the cathode is a very common issue in the continuous flow electrochemistry because the reduction of water or other protic solvents is often used for the counter electrode.

Taqieddin et al.[63] investigated the gas bubbles hydrodynamics and behaviour in electrochemical cells, including the interaction of the bubbles with the electrode surface and the solution, as well as interactions between bubbles itself. They divided the gas bubbles evolving mechanism into four stages: nucleation, growth, departure, and rise (buoyancy and flow). Gas nucleation occurs on the electrode surface. The formed gas bubbles grow during electrolysis and coalescence with other gas bubbles on the electrode surface, forming large bubbles. After the bubble size reaches the critical radius, they detach from the electrode surface and move into the bulk flow.[63]

The effects of the gas bubbles are very complicated. The bubbles are non-conducting, they decrease electrolyte conductivity and thus increase the resistance in the cell.[64] Consequently, the energy efficiency of the process is lowered. Moreover, the mass transfer is affected by the gas bubble behaviour.[65]

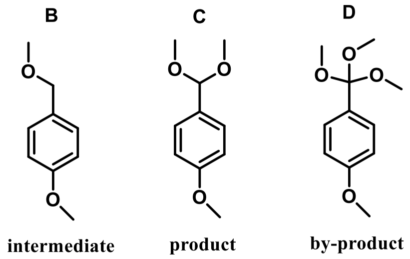
Křišťál et al.[66] reported a very detailed investigation of the influence of the gas bubbles on the local current density control of a segmented electrochemical cell. Moreover, they investigated the size distribution of the bubbles for different electrolyte flow rates and current densities. The conclusion was that the bubble size increases with a lower flow rate at the constant current density and at increasing current at constant flow rate. The explanation was that the higher current activates more nucleation centres on surface of the electrode and increase the bubble growth rate. At lower flow rate the gas bubbles tend to conglomerate to form larger bubbles, due to long residence time in the cell. Higher flow rate results in narrow bubble size distribution.[66]

Sillen [65] stated that the average density of the bubbles decreases and the bubble radius increases by increasing the electrolysis time. This results in a decrease in the volume of attached bubbles per unit surface area. The bubbles have shielding effect on the electrode and thus reduce the active surface area, which consequently results in increase of the local current density. Besides that, he reported about the influence of the pressure on the gas bubbles. The radius of the bubbles decreases and the density increases if the pressure is applied.[65]

In the literature, two main approaches can be found to solve the problem of the gas bubbles. One of them is the operation at elevated pressure, as reported by Rode and coworkers.[44] Another possibility is the periodical removal of the gas phase from the interelectrode space.[67] Bouzek et al. performed investigations based on the processes in the microstructured electrochemical reactor with the electrolyte which contains hydrogen bubbles.[67]

In the present study, backpressure was applied in order to compress the hydrogen gas bubbles and thus improve the cell performance. As it can be seen in Table 5, the voltage decreased when the pressure was applied, which indicates improved conductivity. However, conversion and the current efficiency slightly decreased. A possible explanation for this effect is that the concentration of hydrogen in solution increases with the pressure and influences cell performance.[48]

Table 5. Influence of the backpressure on the conversion, current efficiency, and composition of the crude reaction mixtures. [a]



Entry	**Flow rate [μL min^{-1}]**	**I [mA]**	**Q [F mol $^{-1}$]**	**Backpressure [bar]**	**V [V]**	**Conversion/Current Efficiency [%]**	**Products B [%], C [%], D [%]**
1	400	257	4	0	3.543	76/81	1, 60, 14
2				1	3.491	75/77	2, 61, 10
3				2	3.481	74/75	1, 60, 9
4				3	3.426	74/72	1, 57, 10
5				4	3.422	70/70	2, 54, 11
6				5	3.295	71/72	0, 55, 11

[a] Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/stainless steel (-), constant current operation, 0.5 mm spacer, B=intermediate, C=product, D=side product.

Figure 12 and Figure 13 show the influence of the backpressure on the cell current observed during constant voltage operation and the cell voltage during constant current operation, respectively. When a backpressure of 5 bar is applied, fluctuations of the cell voltage (Figure 13) and the cell current (Figure 12) could be clearly observed. The fluctuations are stronger at the lower flow rate. At 0 bar (Figure 12a and Figure 13a) slight oscillations were noticeable as well, probably because the backpressure regulator was not completely removed and the regulator itself causes slight pressure. When pressure is applied, the fluctuations occur due to the release of gas bubbles through the backpressure regulator, which causes pressure oscillations in the system and changes in the size of the bubbles. Drop of the gas coverage of the electrodes when gas bubbles are released have also been suggested in the literature.[68]. Thus, high voltage indicates momentary higher resistance due to the coverage of the electrode with gas bubbles (Figure 13). At constant voltage conditions, however, low currents indicate high resistance due to the bubble presence (Figure 12).

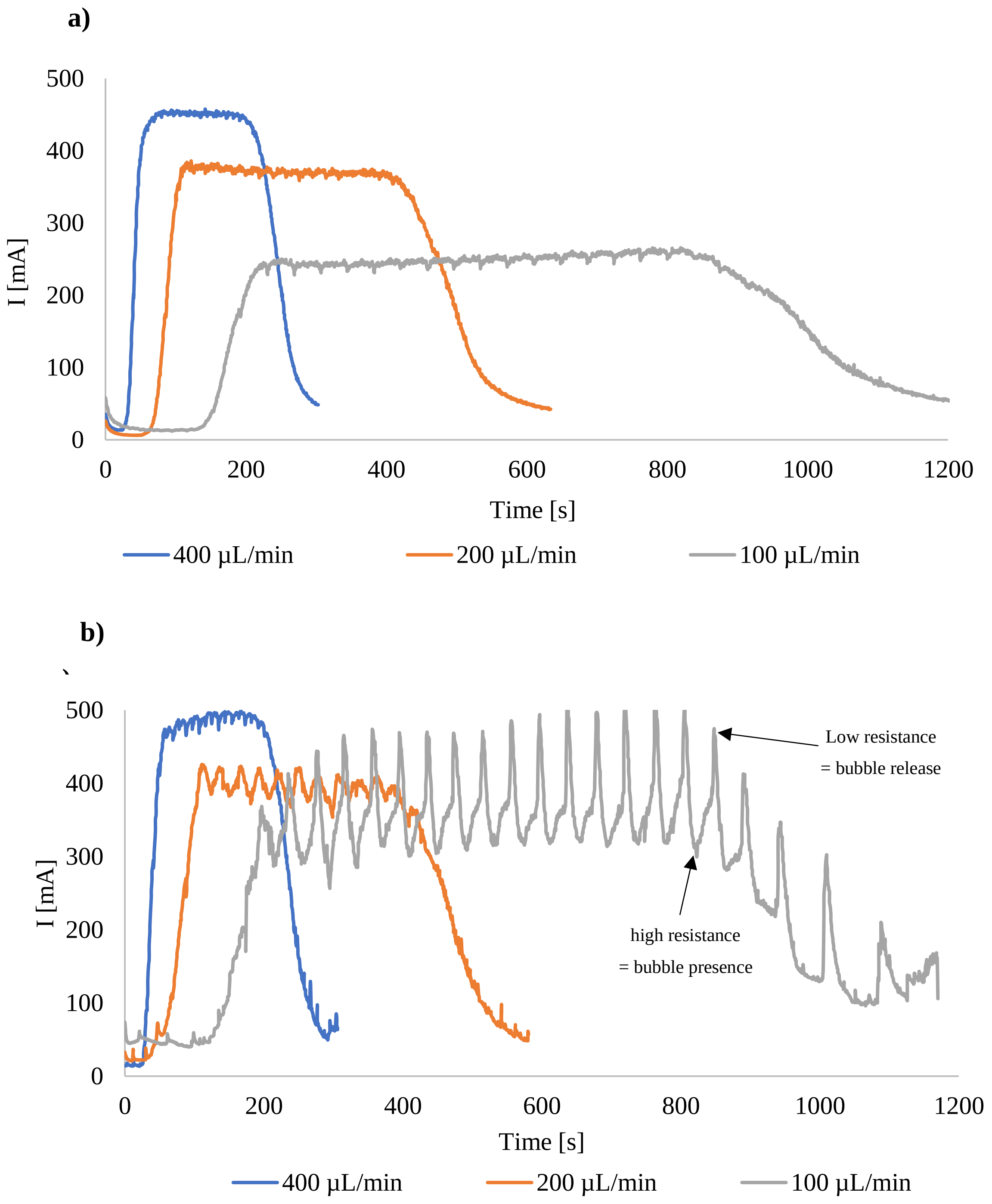


Figure 12. Influence of the backpressure on the current during the constant voltage operation at different flow rates. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/stainless steel (-), constant voltage operation, 4 V, 0.1 mm spacer (a) 0 bar (b) 5 bar.

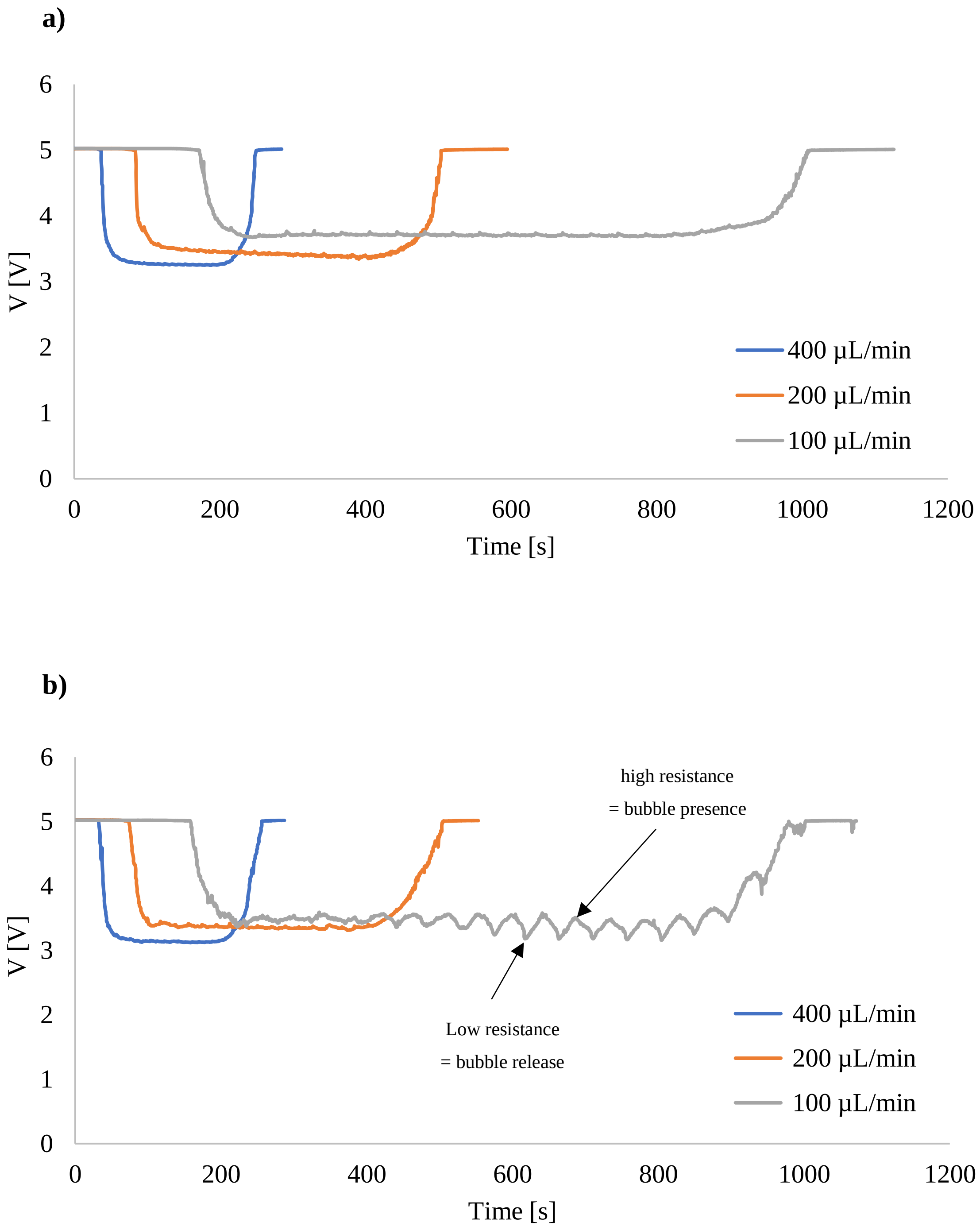


Figure 13. Influence of the backpressure on the voltage during the constant current operation at different flow rates. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/stainless steel (-), constant current operation, 257 mA, 0.1 mm spacer (a) 0 bar (b) 5 bar.

2.5. Comparison of the Batch and Continuous Flow Process

In order to show the advantages of the continuous flow process in terms of conversion and current efficiency, the direct comparison with the batch process is shown in Table 6. During batch experiments, the current of 20 mA was applied, whereas in the continuous flow experiments the flow rate was kept constant (400 µL min $^{-1}$) and the desired current was applied (see Table 6) in order to reach the desired charge. In the batch reaction, the conversion increases with time, whereas the current efficiency remains fairly constant. After 4 F mol $^{-1}$ in the batch reactor (96 min reaction time), only 64 % conversion and 55 % current efficiency were attained.

In the continuous flow experiments, the conversion and current efficiency could be significantly improved to 92 % and 91 % respectively (19 s residence time and around 7 min 30 s total processing time[3] at 400 µL min $^{-1}$), if the reaction was carried out at the smallest interelectrode gap of 0.1 mm. Additionally, if the concentration of the supporting electrolyte was reduced to 0.015 mol L $^{-1}$, the resulting conversion was 97 % with the current efficiency of 99 %. The reactions in the microreactor were conducted only until a charge of 4 F mol $^{-1}$ was reached. Higher charges led to very low selectivity, most likely due to the overoxidations. In the batch reaction, however, the best results were obtained after 6 F mol $^{-1}$ (144 min reaction time) and even then, the conversion and current efficiency (81% and 48 % respectively) were significantly lower than those obtained after 4 F mol $^{-1}$ in a flow reactor with narrow interelectrode gap. Hence, it can be concluded that the reaction in continuous flow mode is faster and more efficient than the reaction conducted in a conventional batch reactor.

In Figure 14, one can compare the course of the reaction in the batch reactor (5 mm interelectrode distance) and in a flow reactor (0.1 mm interelectrode distance) until a charge of 4 F mol $^{-1}$. It is clear that the reaction in a flow reactor is much faster and leads to a high amount of the product already after 4 F mol $^{-1}$. However, the amount of side product increases as well.

Regarding the space-time yield, at the flow rate of 400 µL min $^{-1}$, 125 µL reactor volume, a substrate concentration of 0.1 mol L $^{-1}$ and 74% GC yield of desired product, a space-time yield of 1.7 kg L $^{-1}$ h $^{-1}$ could be achieved. The best results in continuous flow were achieved at a flow rate of 200 µL min $^{-1}$ with 87 % of desired product. The productivity for this very low volume reactor (125 µL) was 1.27 g h $^{-1}$, with a 38 s residence time and 15 min total processing time for 3 mL of electrolyte solution. The space-time yield was 1.0 kg L $^{-1}$ h $^{-1}$. The flow rate of

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[3] Refers to the 3 mL of the electrolyte solution.

800 µL min^{-1} provides higher productivity (3.75 g h^{-1} with a 10 s residence time and 3 min 45 s total processing time for 3 mL of electrolyte solution), with 64% of desired product and a space-time yield of 2.9 kg L^{-1} h^{-1}. In contrast, in a batch reactor the space-time yield was only 3.3 g L^{-1} h^{-1} (after 6 F mol^{-1} and 64% of desired product), which is around 300-800 times (depending on the flow rate) less than the space-time yield obtained in a continuous flow reactor.

Table 6. Comparison of the conversion and current efficiency obtained in batch and flow reactor.[a]

Entry	**Flow rate [µL min $^{-1}$]**	**I flow (batch) [mA]**	**Q [F mol $^{-1}$]**	**Conversion/Current Efficiency [%]**				
				0.1 mm	**0.25 mm**	**0.5 mm**	**1 mm**	**batch (0.5 mm)**
1	400	64 (20)	1	25/74	20/64	18/55	25/84	20/59
2		129 (20)	2	42/71	42/71	38/63	50/92	37/58
3		193 (20)	3	71/85	60/72	52/61	60/77	52/57
4		257 (20)	4	92/91	74/73	67/63	66/68	64/55
5	-	(20)	6	-	-	-	-	81/48

[a] Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 3 mL methanol (batch) and 1.5 mL methanol (flow), graphite (+)/graphite (-), constant current operation.

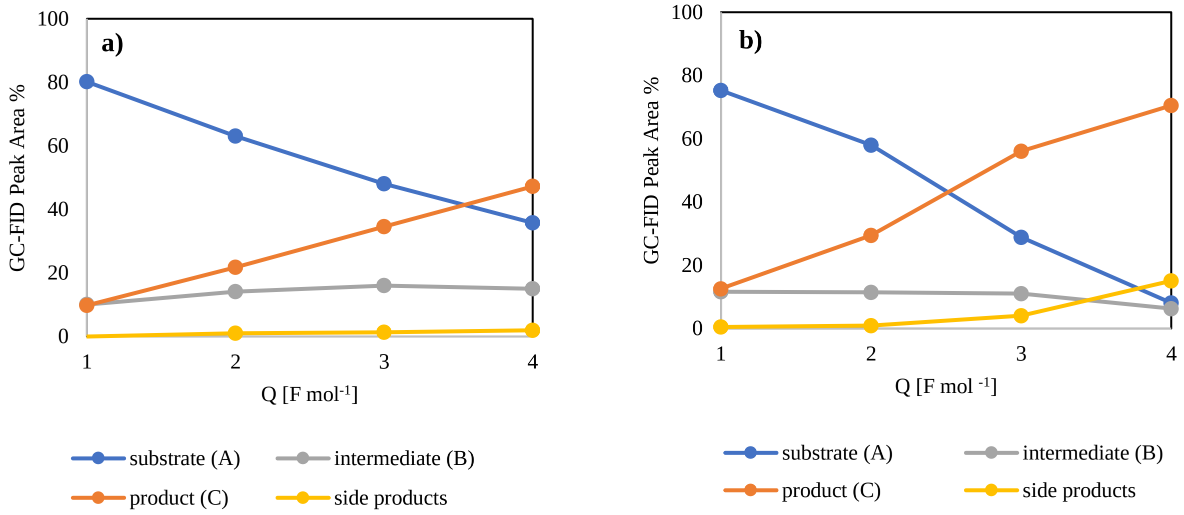

Figure 14. Course of the reaction in the batch (a) and flow (b) reactor. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 3 mL methanol (batch) and 1.5 mL methanol (flow), graphite (+)/graphite (-), constant current operation. (a) 5 mm distance between electrodes, 20 mA, 4 F mol^{-1}, 800 rpm (b) 0.1 mm spacer, 400 µL min^{-1},1 F = 129 mA, 2 F = 129 mA, 3 F = 193 mA, 4 F = 257 mA.

3. Conclusions

In this study, an electrochemical process was successfully translated from batch to single-pass continuous flow conditions. The reaction in the flow reactor was more than 20 times faster and provided much higher conversion and better current efficiency than the reaction in the batch reactor. In the flow reactor, a very good conversion could be achieved already after 4 F mol^{-1} whereas the reaction in batch needed 6 F mol^{-1} and even then, the conversion and the current efficiency were lower than in the flow reactor. However, the best results in the flow reactor were obtained at the small interelectrode distance (0.1 mm) and a slow flow rate (200 µL min^{-1}), which is disadvantageous for the productivity of the reaction. The space-time yield obtained in a flow reactor was around 300-800 times (depending on the flow rate) higher than the space-time yield achieved in the batch reactor. The increase of the flow rate and the distance between electrodes at the same time led to a significant decrease in the conversion and current efficiency. Regarding the voltage of the cell, it could be lowered by decreasing the distance between electrodes. Moreover, with very narrow interelectrode distances, the voltage remained fairly constant, even when the current and the flow rate were increased. This is one of the most important advantages of a microflow reactor. Due to the small resistance at the small interelectrode distance, the concentration of the supporting electrolyte could be significantly reduced without increase in voltage or decrease in conversion. The lowest investigated concentration of supporting electrolyte at which the reaction was possible and the conversion was high for all spacers, was 0.02 mol L^{-1}. The issue of the gas evolution within the reactor channel has been shown as problematic for reaction control and reproducibility. Applying pressure resulted in a decrease in the cell voltage but the conversion and the current efficiency decreased as well. Therefore, more research on this topic is required.

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5. Appendix

Appendix 1

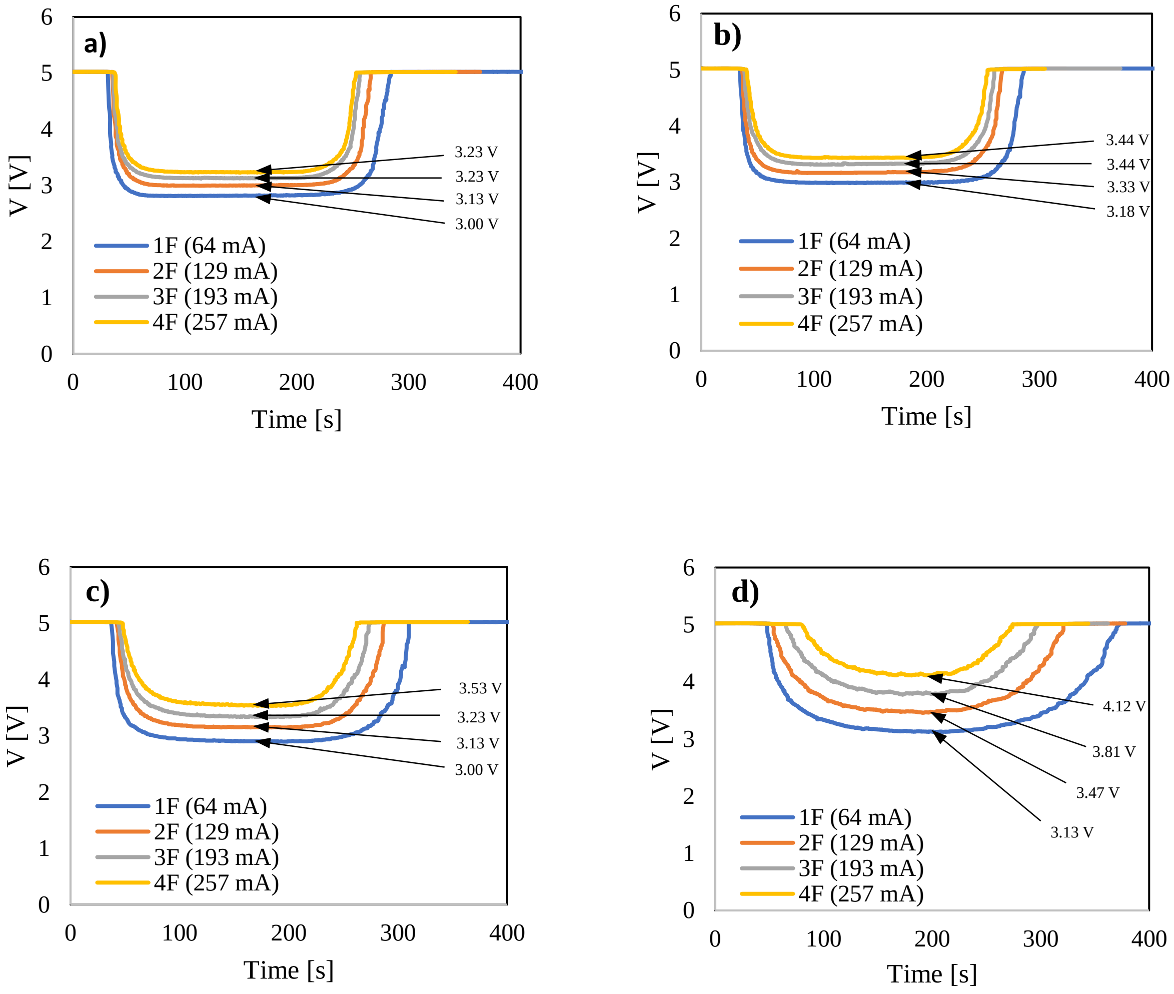

Figure 15. Influence of the current/charge on the voltage at constant flow rates and different interelectrode gaps: (a) 0.1 mm (b) 0.25 mm (c) 0.5 mm (d) 1 mm. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), constant current operation.

Appendix 2

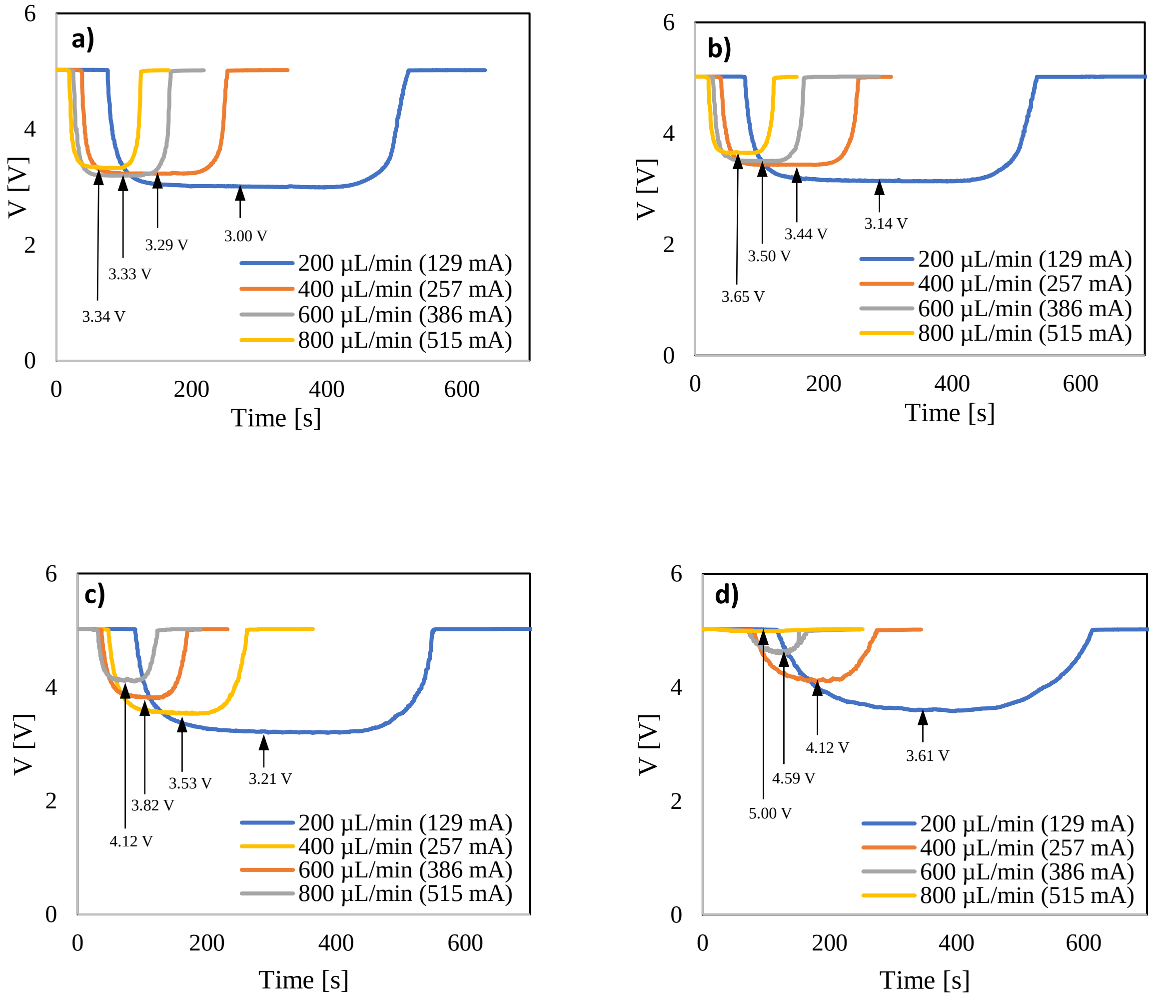

Figure 16. Influence of the current on the voltage at different flow rates and different interelectrode gaps: (a) 0.1 mm (b) 0.25 mm (c) 0.5 mm (d) 1 mm. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), constant current operation.

Appendix 3

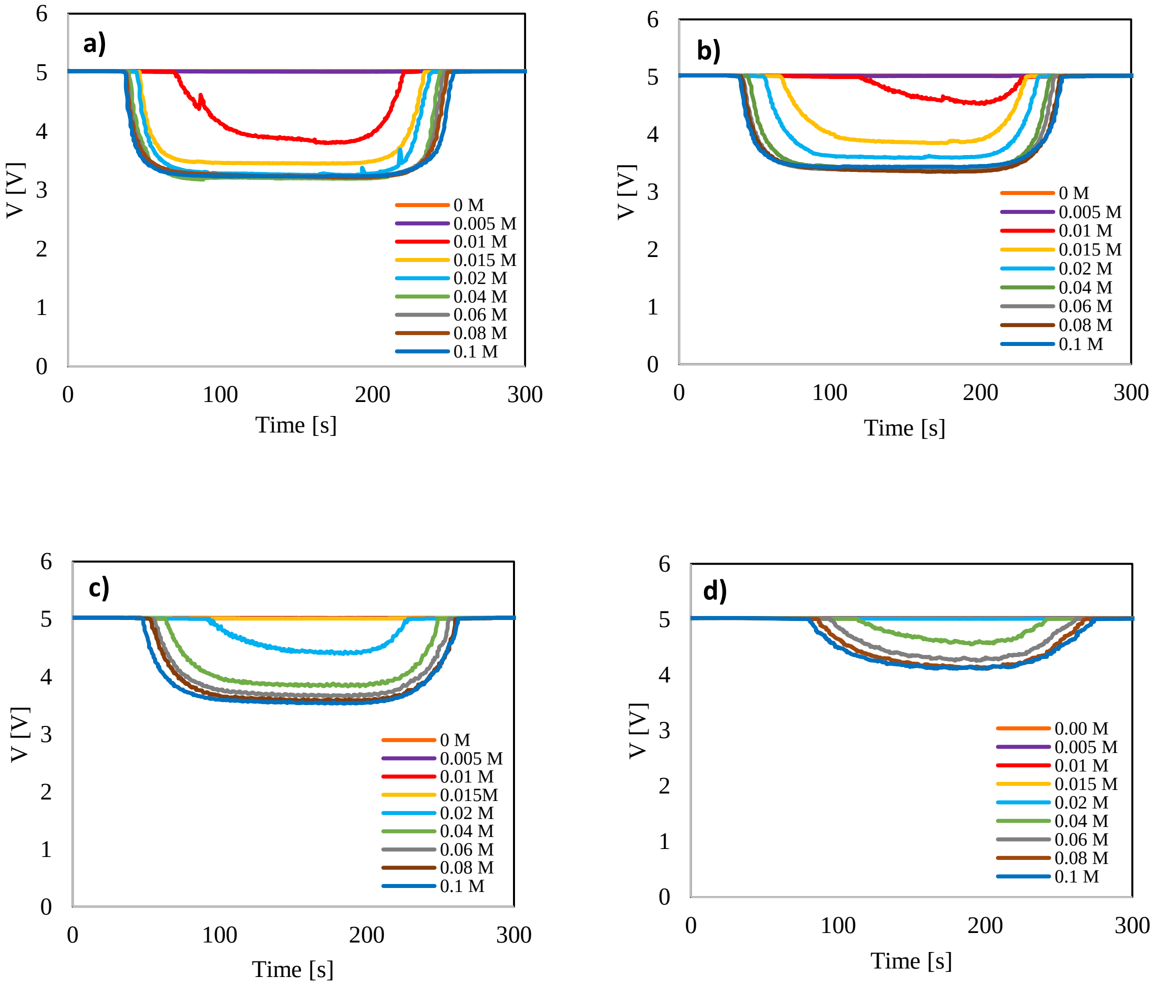

Figure 17. Influence of the concentration of the supporting electrolyte on the voltage at constant flow rate of 400 µL min^{-1} and a current of 257 mA, at different interelectrode gaps: (a) 0.1 mm (b) 0.25 mm (c) 0.5 mm (d) 1 mm. Reaction conditions: 0.1 mm spacer, 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), constant current operation.

Appendix 4

Calibration for the constant voltage experiments

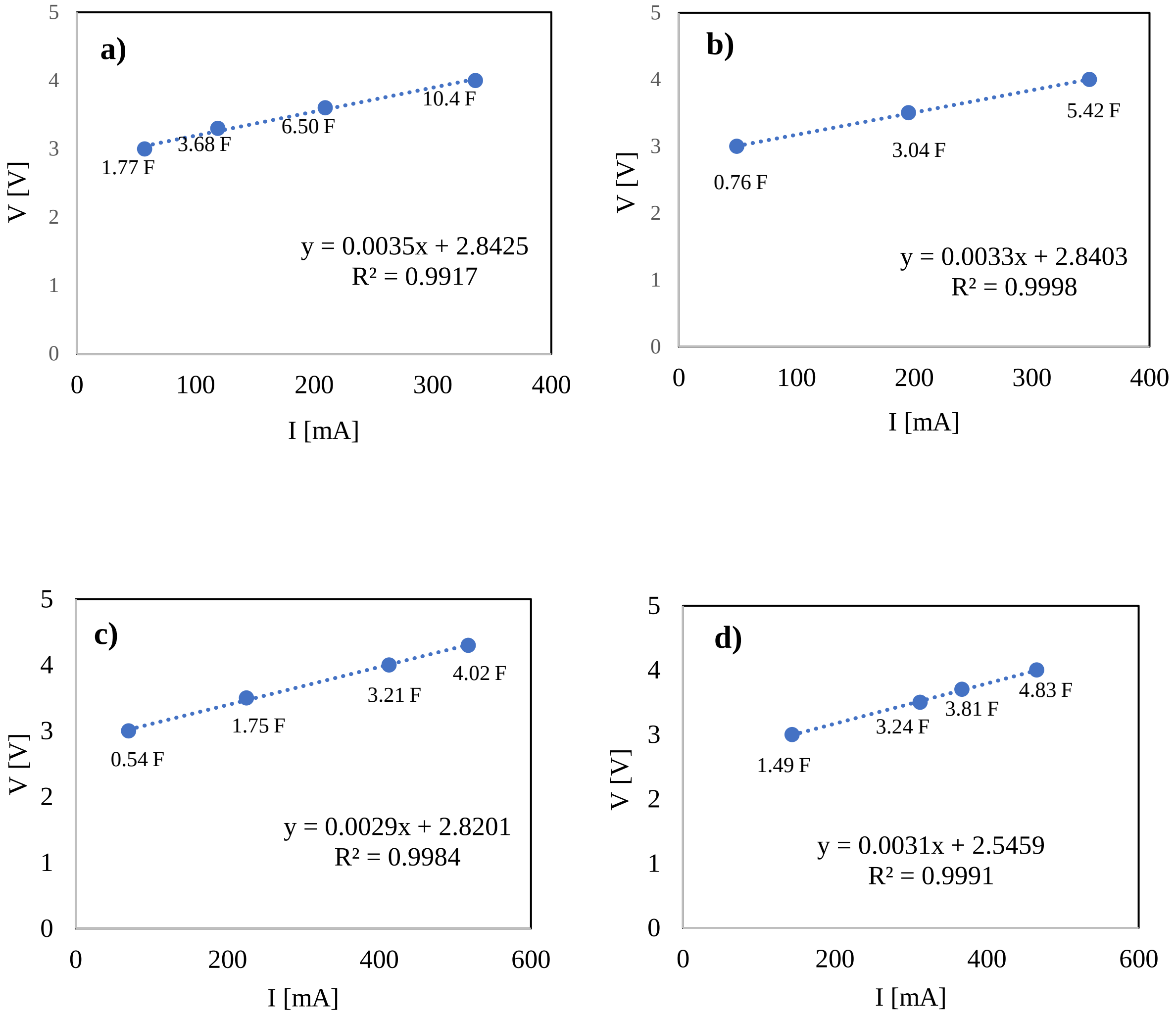

Figure 18. Calibration for the constant voltage experiments. Reaction conditions: 0.1 M 4-methylanisole with 0.1 M Et_4NBF_4 in 1.5 mL methanol, graphite (+)/graphite (-), 0.1 mm spacer, constant voltage operation (a) 200 µL min^{-1} (b) 400 µL min^{-1} (c) 600 µL min^{-1} (d) 800 µL min^{-1}.