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2 Electrochemical processes in flow

2.1 Electrochemical aspects in flow

As it would go far beyond the scope of this chapter to give a comprehensive survey on electrosynthetic chemistry, we will only give a brief overview of the key principles. A more detailed insight can be gained within the recommended literature [1–8].

2.1.1 General electrochemical aspects

Increasing ecological and economic concerns in modern society challenge chemists to develop more efficient and environmentally benign synthesis techniques. Due to the use of inexpensive electricity as terminal redox agent, electrosynthetic processes come along with a significant cut in reagent waste and, thus, offer an appealing and green alternative to classical synthetic approaches. Since the reagent is applied close to the electrode, runaway reactions can be avoided and inherent safety is given [1–5, 9, 10]. In a routine laboratory electrochemical cell, a working electrode and a counter electrode (WE and CE, respectively) are placed in a finite distance from each other. For batch-type cells, a reference electrode is optionally inserted in the cell in the close vicinity of the WE.

Importantly, the electron transfer itself, even though it is a key step, is not the only factor affecting the electrochemical conversion of a substrate (Fig. 2.1, top). The characteristics of the electrode surface, for example, surface morphology or any catalytic behavior of the material, as well as the accessible potential window and inhibiting effects like overpotentials, may promote a certain reaction path. In addition, consecutive reactions of the generated intermediates are influenced by the conditions prevalent in the electrolyte. As most electroconversions contain a cascade of electron transfers and chemical steps, the (de-)stabilization of the intermediates by the electrolyte and mixing effects (mass transfer) have high influence on the selectivity. This (de-)stabilization may happen, for example, by solvation effects (Tab. 2.1), as it can be observed in the anodic dehydrogenative phenol–phenol and phenol–arene C–C cross-coupling. Here, the solvent system is successfully used to manipulate the oxidation potential and nucleophilicity of the employed arenes [4, 9, 11]. Furthermore, the electrodegradation of the solvent may happen by evolution of hydrogen (protic solvents) or oxygen (water only). However, depending on the potential applied, the backbone of the molecule can be decomposed, too.

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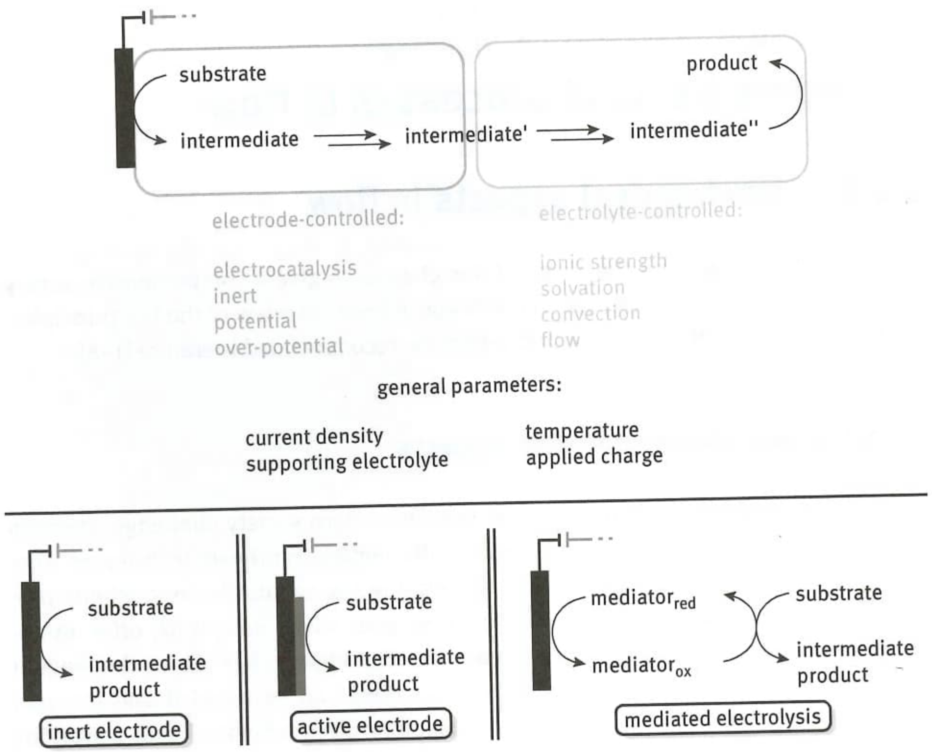


Fig. 2.1: Top: Exemplary reaction cascade in electrosynthetic processes and important parameters that influence the reaction. Bottom: Different modes of electron transfer. Adapted with permission from [9]. Copyright 2020 American Chemical Society.

Therefore, the stability of the solvent under the given conditions (electrode material, supporting electrolyte, etc.), also known as the electrochemical window (Fig. 2.2), has to be respected. Still, in some cases the degradation of an (inexpensive) solvent may be a counter reaction worth considering or can even be helpful, for example, in the case of electrogenerated bases [12]. On the other hand, the supporting electrolyte is not only an agent in ensuring sufficient conductivity of the system. By formation of a layer on the electrode surface, its accessibility can be tuned toward the wanted species and, thus, concurring reactions can be suppressed [13]. Coordinating effects of the anions may contribute to the abovementioned stabilization of intermediates and the acid–base properties of the solution can be tailored. Furthermore, the supporting electrolyte has to be inert to reduction and oxidation as well as to reactions with the electrogenerated species [14].

Since the electrode surface is the place where the (initial) electron transfer from or into the electrolyte comes to pass, the material is of high interest for controlling the electrochemical steps of the reaction. Generally speaking, any conductive material can serve as an electrode. The stability, costs, malleability, and, especially, the

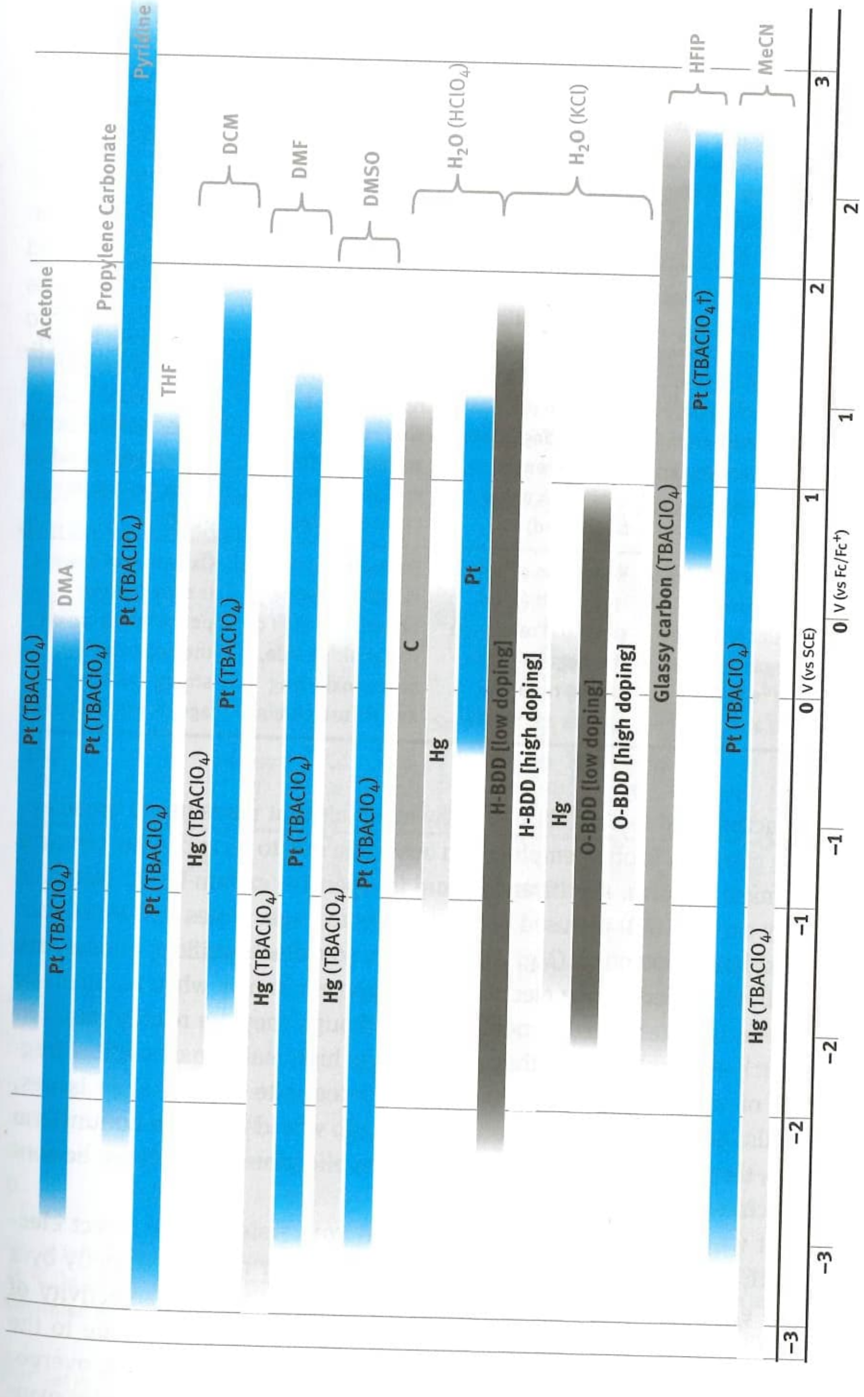


Fig. 2.2: Electrochemical window of different solvents at various electrode materials. (†current density cut-off at $j=\pm0.1$ mA/cm^2) Reprinted with permission of the authors, D.M. Heard and A.J.J. Lennox, from [12].

Tab. 2.1: Influence of the solvent's acid/base properties on ion solvation, proton transfer, and redox stability.

	Solvents with strong acidity	Solvents with weak acidity	Solvents with weak basicity	Solvents with strong basicity
Ion solvation properties	Solvation of small anions is easy (small anions are not reactive)	Solvation of small anions is difficult (small anions are reactive)	Solvation of small cations is difficult (small cations are reactive)	Solvation of small cations is easy (small cations are not reactive)
Proton donating ability	Proton donation from solvent is easy (narrow pH region on the basic side, strong bases are leveled, very weak acids cannot be titrated)	Proton donation from solvent is difficult (wide pH region on the basic side, strong bases are differentiated, very weak acids can be titrated)	Proton acceptance from solvent is difficult (wide pH region on the acidic side, strong acids are differentiated, very weak bases can be titrated)	Proton acceptance from solvent is easy (narrow pH region on the acidic side, strong acids are leveled, very weak bases cannot be titrated)
Redox properties	Reduction of solvent is easy (narrow potential region on the negative side, strong reducing agents are unstable)	Reduction of solvent is difficult (wide potential region on the negative side, strong reducing agents are stable)	Oxidation of solvent is difficult (wide potential region on the positive side, strong oxidizing agents are stable)	Oxidation of solvent is easy (narrow potential region on the positive side, strong oxidizing agents are unstable)

often unique reactivity led to a cutback to a few materials that made it into broad application. While platinum is often employed in academia due to its appealing physical and electrochemical features, significantly more inexpensive carbon-based materials (graphite, glassy carbon (GC)) are used when it comes to larger scales [12]. Metal anodes with low oxidation potentials (Mg, Al, Zn, etc.), so-called sacrificial anodes, are stoichiometrically degraded during electrolysis and come into play when an auxiliary effect of the metal ions generated is needed. Even though they are readily found in literature on batch electrochemistry, they would imply high maintenance effort (regular exchange of the electrode, variation in interelectrode gap, leakage issues, etc.) in flow cells. Additionally, the interelectrode gap would alter in a nonuniform way. Therefore, they are of no importance in flow applications and will not be considered in this chapter.

The easiest way to obtain an electrochemical conversion is the direct electrolysis (Fig. 2.1, bottom left). The substrate is oxidized or reduced directly by a heterogeneous electron transfer at the electrode surface, and the selectivity of the electroconversion is dominated by the applied potential [9, 15]. Due to the simple setup, this method is often used [3–5, 12]. As mentioned above, overpotentials may still have high impact on the reaction outcome. This includes overpotential of the substrate as well as overpotentials of concurring reactions like hydrogen or oxygen evolution reaction (HER/OER). However, the complex nature of the processes on the electrode surface often obliges to rely on empirical experience. While there are standardized, tabulated values for HER/OER overpotentials at diverse electrode materials (Fig. 2.3) and in different media as a basis of estimation, a targeted trial-and-error approach is usually the most promising procedure for most other conversions [16]. An introduction to statistically driven optimization approaches is given in the *reaction optimization* section of this chapter (Section 2.4). Which reaction has to be promoted or suppressed at the respective electrode is a matter of consideration. For example, discharging of protons is a common counter reaction for anodic processes in protic media. Thus, cathodes with low HER overpotential are usually employed in those systems. Vice versa, a cathodic reduction in a protic medium requires a WE with high overpotential for HER to avoid charge dissipation [12]. In this context, boron-doped diamond (BDD) has drawn increasing attention as a commercially available and sustainable high-performance material over the last years, due to its extraordinary high overpotential for both HER and OER, thus enabling a broad electrochemical window for various solvents [16–19].

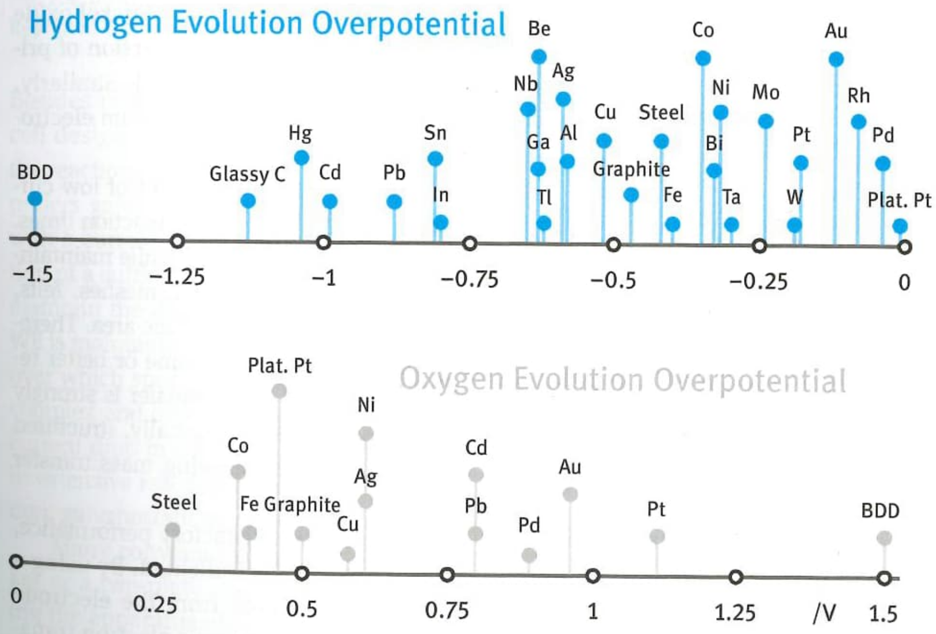


Fig. 2.3: HER and OER overpotential at various electrodes. HER overpotential recorded at 1 mA cm^{-2}, 25 °C, in 1 M aqueous HCl. OER overpotential recorded at 1 mA cm^{-2}, 25 °C, in 1 M aqueous KOH. Reprinted with permission of the authors, D.M. Heard and A.J.J. Lennox, from [12].

For larger molecules, the ad-/desorption behavior of intermediates on the electrode surface largely influences the selectivity of the reaction. This was observed for Kolbe and Hofer-Most electrolysis on platinum or graphite electrodes, where the stronger adsorption of the radicals formed in the first step is assumed to facilitate a second electron abstraction, thus leading to cationic species instead of radicals. Furthermore, the electrode may even be catalytically involved in the reaction, whereby certain intermediates are preferably stabilized in relation to others, or promote a concerted or step-wise process of electron abstraction/addition and stabilization of the radical ion by fragmentation [12].

Nevertheless, the reactivity of some substrates may demand more sophisticated systems to achieve the desired conversion or fine-tune the selectivity of the reaction. Speaking of the electrode, this can be realized by active electrode reactions (Fig. 2.1, bottom center). The selectivity of active electrodes originates in the redox potential and the reactivity of an active layer on the electrode surface. This layer can be understood to be a redox filter. It is usually prepared beforehand to provide a uniform electrode surface and is regenerated in situ during the electrolysis. The big advantage of an active electrode is the introduction of high selectivity without contamination of the electrolyte. Thus, no additional workup effort or reagents are needed. Often, stoichiometric reagents can be replaced by similar immobilized species electro(re)generated in this technique. The most prominent example is the nickel oxide hydroxide anode, which is widely employed, for example, in the conversion of primary and secondary alcohols to carboxylic acids and ketones [20–23]. Similarly, molybdenum(V) reagents can be mimicked by employment of molybdenum electrodes with extraordinary selectivity in arene coupling reactions [24, 25].

A frequent challenge of electrosynthetic chemistry is the requirement of low current densities to achieve efficient conversions and, therefore, prolonged reaction times. Using three-dimensional structured electrodes can mitigate this effect. While maintaining the same geometrical dimensions, these porous materials (foams, meshes, felts, fabrics, etc.) feature a significantly higher electrochemically active surface area. Therefore, a higher geometrical current density may be applied with the same or better results. Especially in flow electrochemistry, where the internal mass transfer is strongly connected to the flow rate, this setup enables new possibilities. Additionally, structured electrodes here may serve as a retention mixing unit, hence, boosting mass transfer within the cell [11, 20].

If neither direct electrolysis nor active electrodes show satisfactory performance, the use of a dissolved electron transfer catalyst (mediator) is indicated. By using a mediator, the conversion of the substrate itself is decoupled from the electrode (Fig. 2.1, bottom right). The mediator is activated by heterogeneous electron transfer at the electrode; however, the substrate transformation usually occurs as a homogenous reaction in the bulk electrolyte. Mediated electrolysis is mostly employed in case of substrates with high overpotential, or, when the reactivity of a mediator offers a unique reaction pathway or selectivity [4, 5, 7, 15]. These properties were successfully used, for example, in various electrochemical fluorination techniques, including *gem*-difluorinations and the synthesis of fluoromethyl substituted heterocycles [4, 7, 26–29]

or selective oxidation of a primary alcohol to an aldehyde in the presence of a secondary alcohol [7, 23, 30].

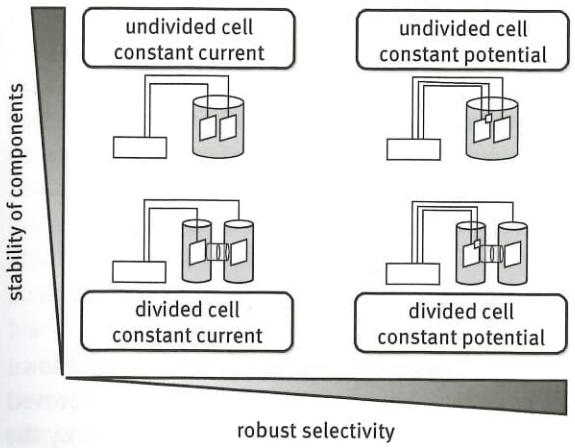


Fig. 2.4: Different cell designs and modes of operation versus their impact on the reaction. Reprinted with permission from [31]. Copyright 2018 American Chemical Society.

Besides manipulating the mechanisms at the electrode and in the electrolyte, the cell design and the mode of operation may be changed to influence the outcome of the reaction (Fig. 2.4). For ease in use, nowadays, electrosynthetic chemistry commonly prefers galvanostatic conditions. Here, a simple two electrode setup in combination with a current source can be used. The electrolysis time is determined by the application of a sufficient amount of charge, which is enforced by adjusting the cell voltage to maintain the desired current. Contrary to the galvanostatic setup, the potential of the WE is maintained as a constant in potentiostatic electrolysis. This allows precise control over which species is converted. However, this mode suffers from a significantly more complex and expensive setup with WE, CE, and a reference electrode. Additionally, a current drop in proceeding conversion due to a decrease in available substrate results in extensive reaction times. Therefore, with regard to scalability and technical application, galvanostatic electrosynthesis is often the technique of choice [2, 4, 5, 10, 15, 31].

Many conversions can be done in undivided cells – for example, a simple beaker or a two-plate electrode arrangement in an electrochemical flow cell, minimizing the apparatus effort. Consecutive or concurring transformations of the substrate and the product at the CE may, however, interfere with the selectivity and efficiency of the reaction. This can be circumvented by switching to divided cells. The cell is split into an anode and a cathode compartment by a separator. Suitable separator materials range from simple glass, ceramic, or polymer (PE/PP) frits to functionalized materials like Nafion® or Thomapor®. While the former only slow down the mixing of the two compartments, the latter bear ionic groups and, thus, can discriminate between differently charged species. It has to be noted, that the employment of a separator results in a severe increase in the cell voltage due to the additional internal resistance. Inexpensive glass and ceramic frits show lower voltage drops than unfunctionalized polymers; however, their brittleness and inflexibility might raise challenges during scale-up. Nafion®, Thomapor®, and similar materials represent a suitable intermediate option, but come with the drawback of comparatively high cost. If a separator is needed, a careful balance must be reached between increased cell voltage, selectivity, scalability, material costs, and recyclability [15, 31].

2.1.2 Electrolysis in flow

The main advantage of flow electrolysis compared to batch processes is, as known from other applications, the high surface-to-volume ratio. Besides the improved heat exchange, which is beneficial for the management of the heat produced by the internal resistance of a cell, the contact area between reactant solution and electrode features the possibility of fast conversion and, thus, high productivity of the cell. Moreover, the short residence time within the actual cell facilitates precise control over the charge applied to each small fraction of the substrate solution. In addition, a prolonged exposure to an electrode material can be avoided and slow degradation reactions efficiently suppressed. This way, reactions of substrates prone to over-oxidation/-reduction can be realized and controlled much more easily, since the product is removed from the cell [10, 11, 32–36].

In the context of continuous manufacturing and multistep reactions in flow, a single pass of the electrolyte through the cell is of high interest [10, 11]. However, in contrast to classical chemistry, where an added reagent can be consumed later on, in electrochemical processes, the charge provided has to be consumed right away while the substrate (or the mediator) is at the electrode, hence, establishing a flow setup, within the cell. Therefore, a short residence time in the interelectrode gap may be challenging if low current densities have to be applied [11, 37]. If substrate and product are easily separated from the mixture and the overall conversion is of minor importance, one might consider using a flow cell with a high throughput to synthesize the desired amount of product and reuse the unconverted substrate. If this approach cannot be pursued, the residence time and, thus, the applied charge may be increased by decreasing the flow rate or using a longer channel for electrolysis. However, a decreased flow rate results in an inferior mass transfer regime, which may have a negative influence on conversion and selectivity. Electrolysis cells with long channels (meandering, serpentine, ammonite cell) can address this problem, but to some extent, at the cost of a more complex setup [11]. They will be discussed in more detail in Section 2.1.4 of this chapter. Instead of extending the channel length within one cell, a cascade of cells can be employed, or the electrolyte can be pumped through a single cell, multiple times. While passing the electrolyte through multiple electrolysis cycles, a proportional fraction of charge is applied in each passage [10, 35, 37]. In a single cell with one long channel, the local current density fluctuates along the channel with the changing concentrations of the electrochemically active species. Hence, the electrolysis conditions change significantly [11, 34]. In the cascading mode, the current density can be controlled in each cell or pass-through independently, and more controlled reaction conditions can be ensured. Additionally, higher flow rates and better heat control can be realized [37]. Just like pumping from one vessel to another and reusing the electrolyte in cascading mode, the electrolyte can be stored in one reservoir and cycled through one cell. Instead of having a defined composition before/after every pass-through, the electrolyte constitution changes gradually during the process. However, this gradual change leads to very mild conditions and high energy efficiency.

Both cycling and cascading modes can be employed for the handling of suspensions and emulsions. The high flow rates possible in these systems, combined with stirring and/or sonication of the reservoir, provide, in most cases, sufficient mixing of the phases and prevent separation. In addition, electrolysis in segmented flow offers the possibility of enhanced mass transfer from and to the electrode surface and in between the phases by toroidal vortices at the phase boundaries between the segments (Fig. 2.5). Such systems have also been successfully employed in single pass mode [32].

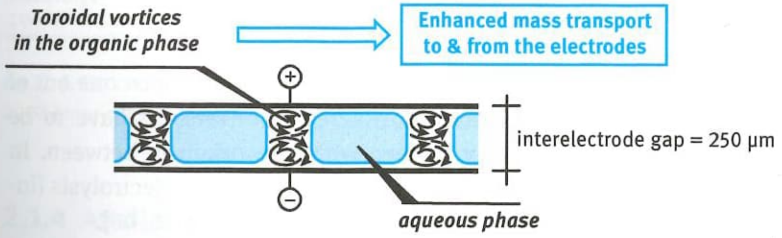


Fig. 2.5: Enhanced mass transfer in segmented flow by vortices at the phase boundary. Reprinted with permission from [32]. Copyright 2019 American Chemical Society.

As mentioned in Section 2.1.1, the evolution of hydrogen is a widespread and convenient counter reaction for anodic processes. This and other gas-evolving reactions are a major issue in flow electrochemistry. While the evolution of gas bubbles may enhance the mass transfer, the gas can block a significant part of the electrode, if it is not removed from the surface properly. The insulating properties of the gas, therefore, lead to a nonuniform and irreproducible distribution of the local current densities [10, 11, 32]. In cascading or cycling mode, this problem is readily solved. The high applicable flow rates ensure efficient removal of the gas from the electrode, which is, in turn, removed from the system via the headspace of the reservoir [20, 37]. In single pass flow electrolysis – if the system is not robust enough to tolerate the effects of the gas – the bubbles may be (partially) removed by pressurizing the whole system. The higher pressure causes smaller gas segments and, thus, a more uniform current distribution and decreased internal resistance. On the other hand, more gas is dissolved in the electrolyte at elevated pressure. Therefore, conversion, yield, and current efficiency decrease due to reoxidation of the dissolved hydrogen at catalytically active anodes [10].

Other issues in electrochemistry involve fouling and corrosion of the electrodes. Corrosion can usually only be prevented by using an appropriate electrode material. Some applications have been published with electrodes unstable within the electrolyte itself; however, they are stabilized by the applied potential [38, 39]. Other examples are known, where electrode corrosion is prevented by the supporting electrolyte [40–42]. Fouling is a common process in electrochemistry. Side reactions like polymerization form an insoluble layer on the electrode surface. This passivation of the electrode may compromise the performance of the reactor (nonuniform current distribution, increased resistance, etc.), but may be needed if the layer provides an enhanced selectivity. Unwanted fouling can be prevented by use of self-cleaning materials like BDD [17, 19, 43, 44]. However, the highly reactive species formed in this internal cleaning process (e.g., hydroxyl radicals for aqueous media at BDD anodes) limits the application of these systems to conversions with robust substrates and products [45].

2.1.3 Follow-up conversions

Just like other transformations, an electrosynthetic process, often, is just one out of many steps in a synthetic route. Therefore, downstream conversions have to be done. Directly consecutive reactions may happen without workup in between. In electrochemistry, these may be performed either directly during the electrolysis (in-cell) or after the application of charge is finished (ex-cell) [10, 11, 32, 36, 46].

For in-cell synthesis, the reaction partner for the follow-up conversion needs to be stable under the electrolytic conditions. On the other hand, in-cell reactions can be used to generate and directly consume unstable reagents. Many electrosynthetic processes can be understood as in-cell conversions. As mentioned above (Section 2.1.1), the electrogenerated species usually undergoes chemical steps like trapping of a generated cation by a nucleophile (e.g., solvent) or reprotonation of an electrogenerated base. Example reactions are the methoxylation of furanes, *N*-protected pyrrolidines or toluenes, the synthesis of diaryliodonium salts, and non-Kolbe reactions [4, 11, 32, 33, 47]. Further, oxidations of cyanhydrines and the addition products of aldehydes and *N*-heterocyclic carbenes (*Breslow* intermediates) [46, 48] and carboxylations of electrogenerated carbanions have been published [33]. If the reaction partner is not stable for electrolysis, ex-cell processing can be employed. Especially in flow, the ex-cell approach offers appealing possibilities due to the opportunity for processing unstable electrogenerated species right away. Consequently, a lot of work has been done on this field [11, 32, 33]. The most prominent examples of these processes are electrogenerated high performance oxidizers like peroxodicarbonate [19, 49], periodate [50], and hypervalent organic iodine species [19, 32, 36] with corresponding follow-up conversions. Another prominent example of an ex-cell approach is the cation flow method. Metastable carbocations are produced electrochemically at low temperatures and may be stored under inert conditions for further reactions or processed right away in flow. Examples range from allylation and arylation reactions to cationic polymerization. Additionally, more recent developments enabled similar reactions as an in-cell version (Fig. 2.6). In a highly laminar flow, a solution of the cation precursor is fed from the anode side, while the nucleophile is contained in the cathode feed. Due to the absence of turbulences, mixing of the two streams solely relies on diffusion. Thus, the cation can be generated in the presence of the nucleophile without the latter being oxidized [11, 32, 33, 36].

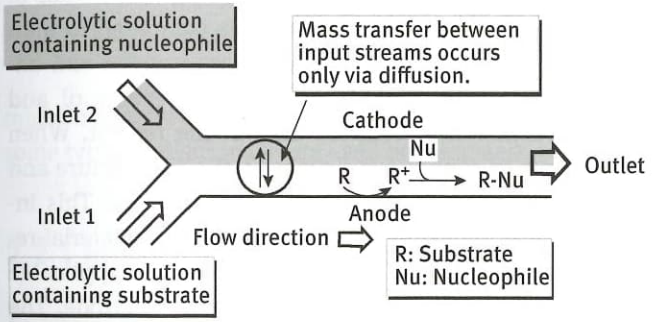


Fig. 2.6: Cation flow method as an in-cell approach. Reprinted with permission from [51]. Copyright 2007 American Chemical Society.

2.1.4 Availability of lab-scale flow electrolyzers

The majority of narrow gap flow cells in academia are self-made, mostly in cooperation with the departments' machine shop. The widespread emergence of possibilities such as CNC machining and 3D-supported planning allows the precise machining of flow cells [32, 34, 35, 52]. In the plate-frame approach, especially (see Section 2.2.2), the cell is easily built by screwing together two half cells with a spacer in between. For a divided setup, a membrane and a second spacer may be employed. If the spacer is structured, even serpentine channels can be realized [53]. In some cases, the flow setup was made commercially available [34, 54]. Common suppliers are IKA (IKA ElectraSyn Flow, flow cell and related equipment) [55], Vapourtec (Vapourtec Ion Electrochemical Reactor, flow cell and related equipment) [56], Cambridge Reactor Design (ammonite cells) [57], and CONDIAS (diamond-based electrodes) [58]. The IKA flow cells come along with a modular design, enabling easy and fast exchange of different electrode materials, since several half cells of different materials are included in the packages.

They are among the less expensive devices, allowing an easy entry in this field. The Ammonite Electrolysis cell offers a very long pathway for the reaction to take place. This ensures high single-pass conversion and/or driving multistep processes. For gas diffusion electrode (GDE) containing electrolyzer cells, among others, Electrocell GmbH [59], Dioxide Materials [60], and ThalesNanoEnergy [61] have their products in the market. These cells allow standardized comparison of components (catalysts, membranes, and gas diffusion layers (GDLs)) in different industrially relevant processes (e.g., water splitting, CO_2 reduction).

2.2 Design of flow electrolyzers

Whether we consider technology scale-up or reliable rapid screening of materials in the laboratory, continuous-flow reactors have multiple benefits compared to their batch counterparts. Among others, these include increased mass transfer and improved mixing of different phases, better temperature and heat transfer control, and more precise influence on reaction mixture residence time in the reactor. When moving from batch-type experiments to continuous-flow cells, the architecture and design of the reactor (electrochemical cell) must first be clearly defined. This includes features such as the type of electrolyte used (liquid/gas), reactor material-reaction mixture compatibility, whether it can be pressurized or not, the applicable temperature and flow rate, and the possibility of using a reference electrode. The design of flow electrolyzers has developed continuously, over the past decades. As a major flag carrier, the chlor-alkali process went through several evolutionary steps, starting from diaphragm-separated cells, through using asbestos separator and mercury cells, to the currently dominantly applied membrane-separated cells [62]. The most important driver in this case was the energy efficiency of the process, hence the production cost of chlorine and NaOH. As for the energy efficiency of an electrochemical process, the most straightforward definition is the voltage efficiency of the cell. This is the ratio of the thermodynamic voltage and the total voltage applied to the electrolysis cell (V_{cell}) to drive the electrochemical reactions at a given rate. Note that the thermoneutral voltage is not only sufficient for driving the reactions, but also to produce enough heat to maintain constant temperature. Beyond the thermodynamic requirements, V_{cell} also includes losses related to the anodic and cathodic electrochemical processes (activation losses, overpotentials), to the cell components (ohmic losses, IR drop), and to mass transport. In aiming for high energy efficiency, each of these effects should be minimized (see Fig. 2.7 for details) [63].

It is important to distinguish between the large-quantity production of commodity chemicals, where large current densities are of prime importance, and the continuous-flow electrochemical production of fine chemicals (e.g., pharmaceutical compounds). In the latter case, the purity of the product stream, and hence, the process selectivity might be an even more important parameter than the reaction rate. In what follows, some typical cell arrangements will be discussed.

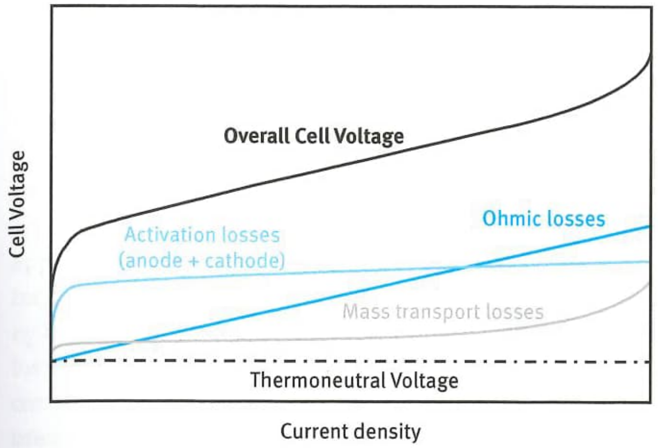


Fig. 2.7: Voltage loss mechanisms in electrochemical cells. Reproduced with permission by Elsevier [63].

2.2.1 Industrial narrow gap cells

To minimize the energy input and to avoid the use of large solution volumes, the electrodes are generally placed very close to each other (narrow gap). A typical example of this is the production of sodium chlorate, where the electrodes are positioned at 2–3 mm distance from each other, in an interdigitated manner. This way, the IR-drop is minimized, and the reactions are driven on both sides of the electrodes, hence increasing the surface area. Narrow gap cells offer a inexpensive and easy design. On the other hand, such cells have a few clear drawbacks. One important issue is the cross-talk of the electrode processes. Products formed on one electrode can be re-converted on the other, hence decreasing the Faraday efficiency (FE) of the product formation [64]. Such narrow gap cells have been found to allow the use of less conductive media (lower supporting electrolyte concentration), but this, eventually, still limits the maximum current density (typically in the range of a few hundred mA cm^{-2}). At higher current densities, the insufficient removal of the products or byproducts, for example, hydrogen, from the electrodes becomes a major obstacle. Using concentrated electrolytes complicates the product separation process and invokes extra costs related to the handling of high density/viscosity solutions.

While some robust reactions are performed in flow cells with large electrode gap, the output of reactions with oxidation-sensitive intermediates or products can be strongly dependent on the electrode gap. The interaction between the liquid phase and the solid electrode results in the formation of a rather immobile stagnant

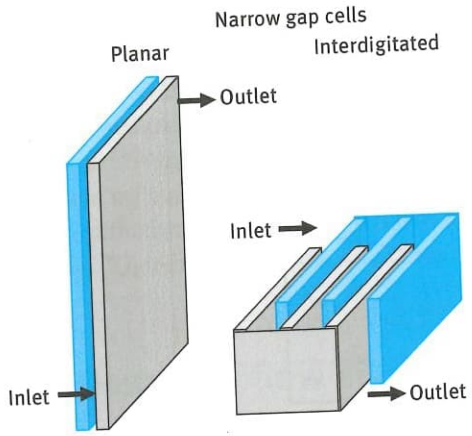
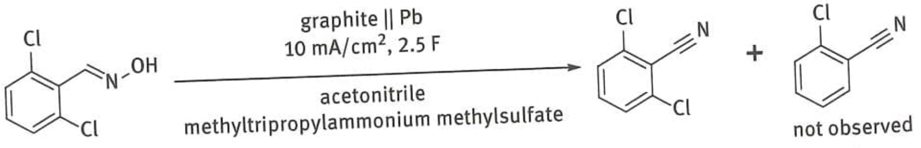


Fig. 2.8: Two typical arrangements of industrial narrow gap electrolyzer cells.

layer with a thickness in the µm range [65]. Within this layer, mass transport takes place only by diffusion, in contrast to convection within the bulk. The size of the stagnant layer, besides other properties, depends on the speed of motion for the bulk, whereby faster movement reduces the thickness of the stagnant layers. This leads to smaller diffusion paths. The corresponding diffusion coefficient is first-order dependent on the temperature [66]. With constant current density and transferred amount of charge, a smaller electrode gap leads to higher flow rates in the cell and thus also to a smaller stagnant layer. In addition, the required amount of supporting electrolyte can be reduced or completely avoided by narrow gaps. This was demonstrated well by *Waldvogel* and coworkers [34]. They investigated the domino-oxidation-reduction sequence for synthesis of nitriles from aldoximes. The batch process suffered from dehalogenation of the starting material; flow electrolysis with an electrode gap of 1 mm showed similar behavior or bad conversion. Since dehalogenation, in this case, is a slow chemical follow-up reaction, it is not directly evident from CV experiments. A smaller gap size of 0.12 mm allows for supporting electrolyte-free electrolysis and allows a short residence time, which suppresses dehalogenation. By optimizing the ratios of the solvent mixture, the reaction achieved a yield of 80%. Dehalogenated species could only be detected in traces.



2.2.2 Membrane/diaphragm-separated electrolyzer cells and plate-frame approach

Physically separating the electrodes circumvents product mixing, hence the back-transformation of anodic/cathodic products on the other electrode. A typical historical example for such separator is a glass or asbestos diaphragm, which was successfully applied in the early years of the chlor-alkali process [62]. A more current and widely applied technology that uses a diaphragm separator is alkaline water electrolysis [67]. Including such a separator between the electrodes increases the product formation FE by avoiding product mixing. On the other hand, the extra cell element induces extra losses due the increased cell resistance (*R*). To minimize the IR drop in the cell, the concept of zero-gap cells was developed. In such electrolyzer cells, the electrodes are pressed directly to the separator with the catalyst layers facing each other (Fig. 2.9). This way, the resistance of the electrolyzer is minimized. In addition, the electrolysis is conducted at elevated temperatures to achieve maximum conductive performance of the separator, for example, in chlor-alkali electrolysis at 85–90 °C.

Instead of further increasing the lateral dimension of the electrodes, the electrolysis area can be increased by building electrolyzer stacks. In this method, several cells are built on top of each other, applying bipolar plates (acting as anode on one side and as cathode on the other) between the cells. A serial electrical connection is established between the cells, while the reactant is typically fed in parallel. In industrial applications, such electrolyzer stacks are built on large frames (Fig. 2.9). In such application, the electrodes (and other cell components, e.g., gaskets, membranes) are first secured on the frame and are subsequently pressed together with the rest of the cell [68].

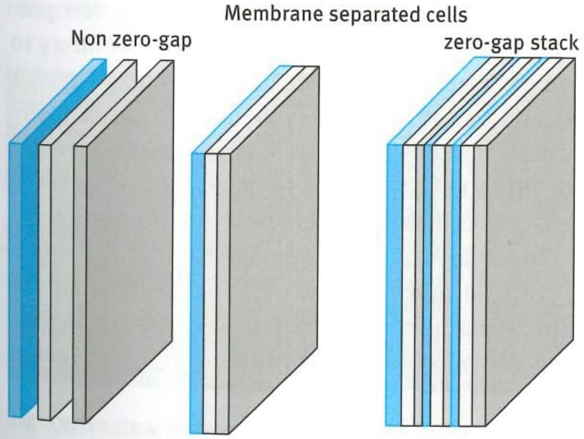


Fig. 2.9: Possible embodiments of membrane-separated electrolyzers and electrolyzer stacks.

To further decrease the cell resistance, polymer-based ion exchange membranes are typically used in zero-gap electrolyzers. As there is no liquid electrolyte between the electrodes, the ion conduction is determined by the chemical nature of the used membrane. Hence, these electrolyzer cells can be categorized by the ion-exchange properties of the membrane as follows: cation exchange membrane (CEM), anion exchange membrane (AEM), or bipolar membrane (BPM)-based electrolyzers (Fig. 2.10) [69].

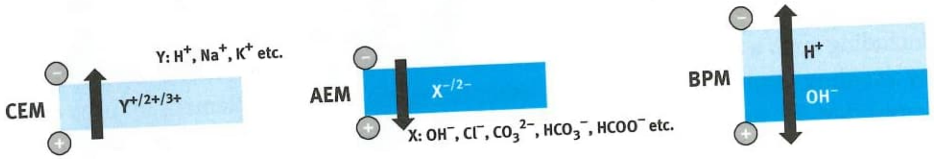


Fig. 2.10: Working principle of different ion exchange membrane types in electrolyzer cells. CEM – cation exchange membrane, AEM – anion exchange membrane, BPM – bipolar membrane.

When applying a CEM to separate the cell, the ion conduction is maintained by the migration of cations from the anode to the cathode. These are either cations from the applied electrolyte (e.g., Na^+ ions in case of Na_2SO_4 electrolysis or the chlor-alkali process in a CEM cell), or protons, either from the electrolyte solution, or formed as anodic by-products. A typical example for the latter is CEM water electrolysis, where H^+ is the by-product during oxygen evolution ($2H_2O \rightarrow O_2 + 4H^+ + 4e^-$) [70]. H^+ ions form on the anode, and as they are the charge carriers crossing the membrane, they are also present on the cathode side of the membrane in high local concentration. This results in a highly acidic pH on both electrodes. Using AEMs, on the other hand, leads to reversed direction ion conduction – in this case, anions cross the membrane from the cathode to the anode [71, 72]. In typical electrochemical reduction processes, such as water, CO_2 or O_2 reduction, OH^- ions are formed. This –contrary to the CEM membrane case – results in an alkaline local pH on both electrodes. In recent years, BPMs are being applied in electrolysis processes to avoid product crossing. The typical operation of BPMs is based on water dissociation at the interface between the AEM and the CEM, and consequent OH^- and H^+ migration to the anode and cathode, respectively [73–75]. This results in acidic cathode and alkaline anode pH. A reversed combination of an AEM and a CEM would lead to alkaline cathode and acidic anode pH. In this case, OH^- (or CO_3^{2-}/HCO_3^-) and H^+ ions (or other cations) would move toward the interface of the two membranes and recombine there. The formed product must be removed from the space between the two membranes, necessitating the inclusion of a buffer layer.

Notably, ion conduction is always associated with the transport of water through the membrane. As an example, when applying a Nafion® membrane (CEM), two to three water molecules are carried from the anode to the cathode with each H^+ ion transported. This changes the electrolyte composition (if any) on both electrodes, which must be considered during continuous operation. Also note that a free space is required in both the anode and the cathode compartments to deliver the reactants to the catalyst surface and to allow the products to leave the cell. Accordingly, porous electrodes are generally used as catalyst supports. This includes frits, meshes, foams, or other porous structures made of conducting materials, typically (electro)chemically resistant metals or carbon.

2.2.3 Gas diffusion electrodes

Supplying reactants to the electrodes in gas phase boosts the reaction rate by circumventing the rate limitations related to transport processes in liquids [76, 77]. In such cases, the reaction occurs on a triple phase boundary, where the solid catalyst particle, the gas reactant, and a liquid phase (or solid electrolyte) are mutually present [78]. The most recent understanding of the reaction conditions within the triple phase boundary is that a thin liquid layer forms on the catalyst surface. The reactant is dissolved in this liquid layer, leading to a very thin diffusion layer that ensures high mass transport rate to the catalyst particles.

When designing GDEs, several requirements should be simultaneously fulfilled [79]. The most important of these are the high electrical conductivity of the electrode, the gas permeation properties of the structure, the catalyst layer composition, and the hydrophilicity of the different components and the GDE, as a whole. The first of these is somewhat trivial, as high electrical conductivity of the electrodes is a prerequisite in any electrochemical process. To achieve this, metal foams, meshes, or other porous structures might be used. Carbon-based structures (carbon felts, carbon papers, etc.), however, offer higher flexibility, lower price, and easier processability, hence these are the most typically used GDLs in GDEs.

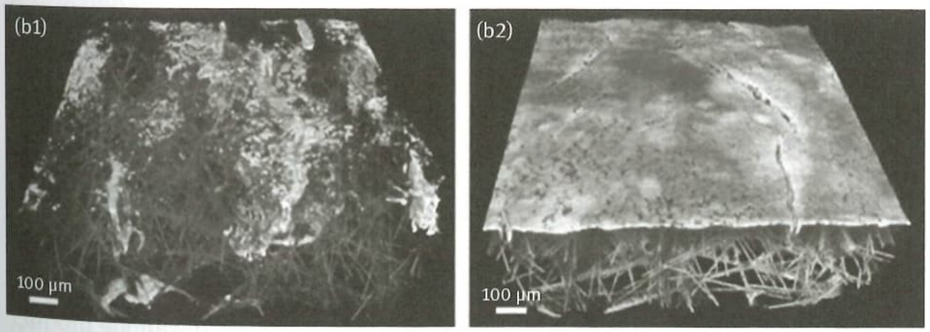


Fig. 2.11: Three-dimensional microtomographic models of a GDE, showing the structure of the microporous layer (b1) and the microporous layer with the catalyst. Copyright 2013 Wiley-VCH [80].

Carbon-based GDEs are usually formed of multiple layers with specific functionality (Fig. 2.11). A macroporous layer ensures that the reactant gas can enter the structure easily, and the products can exit the cell. A microporous layer on the other side serves as support for the catalyst and is also responsible for good electrical connection between the GDL and the catalyst particles. To avoid water accumulation in the GDE (flooding of the structure, increased diffusion layer thickness, and the consequent reaction rate decrease), the carbon GDL is most usually infused by a hydrophobic material such as PTFE.

The structure of the catalyst layer is of prime importance in achieving high reaction rate. Large electrochemically active surface area (ECSA), proper electrical conductivity, high ion conductivity, porosity, and homogeneity are all crucial properties of GDEs that define the electrochemical performance of an electrolyzer cell. Without going into too much detail regarding the specific function of each constituents, the chemical nature, physical dimensions, and morphological features of the catalyst particles, the chemical quality, the amount of binder used, and the total layer thickness must be tailored for the specific application. As for the catalyst layer formation on a GDL, multiple methods are widely applied. These include physical methods, such as brush-, spray-, or drop-coating or physical vapor deposition, and chemical methods such as electrodeposition, chemical deposition, or chemical vapor deposition. Note that even the catalyst layer preparation method can have a significant effect on the electrochemical properties of the GDE [80].

2.2.4 Electrochemical system design

While most studies focus on the electrochemical cell itself, there are many other components which together enable electrochemical processes. Beyond the obvious potentiostat/galvanostat (or power supply in simple cases), depending on the cell configuration, up to two liquid and gas inlets, product stream processing parts (including liquid/gas separators and product collection units), pressure and temperature sensors and controllers, a gas- and liquid flow meter, and often complex in-line analytical systems, are utilized. To have a controlled electrolysis process (yielding reproducible results), all these units need to function together smoothly. Here, we show one specific example of CO_2 electroreduction as the cathodic process, which is coupled with a liquid phase oxidation process [81]. In this particular process, one or two (peristaltic) pumps are used to deliver the liquid electrolytes (depending on the cell configuration). Optionally, gas phase reactants can also be fed to the anode of the cell, just like in the cathodic CO_2 feed. These fluids are tempered before entering the cell to maintain constant operational conditions. Subsequently, the anode product stream leaves the cell through a pressure regulating valve to be processed further. First, the gas products are removed, and then, the dissolved/liquid phase products are separated from the anolyte. The composition of the anode product stream shall be analyzed continuously to ensure proper operation. This should include online and offline methods both for the liquid and gas phases. These generally encompass gas/liquid chromatography (coupled with mass spectrometry), NMR, FTIR, and Raman spectroscopies, but other product specific spectroscopic methods can also be applied. Another engineering challenge will be to isolate the valuable products from the anolyte, which can be subsequently recirculated in the process.

2.3 Electrochemical processes in flow

2.3.1 Industrial electrochemical processes in flow

Performing electrolysis in flow cells is an easy way to continuously refresh the reactant solution/gas mixture around the electrodes, thus providing constant and precisely controlled reaction conditions. This is one of the most important differences when compared to batch processes, where the continuous reactant depletion causes dynamically varying conditions. Another important difference is the continuous removal of products to avoid their accumulation. This way, unwanted consecutive chemical/electrochemical reactions are avoided. When discussing industrial flow-electrochemical processes, one must distinguish between the mass production of commodity chemicals and the production of specialty chemicals, which is performed on a significantly smaller scale. From the first class, the chlor-alkali, the chlorate, water-, and CO_2 electrolysis processes are discussed here briefly.

The chlor-alkali process is one of the largest electrochemical industrial processes in terms of both annual production and energy consumption [62]. During the process, a concentrated NaCl solution (brine) is continuously fed to the anode, and diluted caustic soda (30%) is supplied to the cathode of a divided electrolyzer cell. The separator is typically a combination of two cation exchange membranes (perfluorosulfonic acid/perfluorocarboxylic acids) in the currently used cells. At the anode, which is typically a dimensionally stable anode (DSA), chlorine is formed and is extracted from the cell in gaseous state. The exhausted brine solution exits the cell and is recirculated in the inlet line. At the cathode, water is reduced to form hydrogen (being responsible for about 4% of the global H_2 production) and hydroxide ions. These ions, together with the Na^+ ions crossing the cation exchange membrane to maintain the ion conduction between the electrodes, form the other important product of the process, a concentrated caustic soda. An alternative that is gaining traction is the use of oxygen depolarized cathodes (ODC) [82]. In the ODC technology, the cathode is a porous GDE that is fed by pure oxygen gas. The reduction of oxygen occurs at a significantly less negative electrode potential compared to water reduction; hence the cell voltage is decreased.

Industrial water electrolysis cells are of similar design as the chlor-alkali cell, whether we consider alkaline water electrolysis or PEM water electrolysis processes [83]. In both cases, hydrogen is produced on the cathode, while oxygen forms on the anode. The two compartments are separated by means of a diaphragm (or

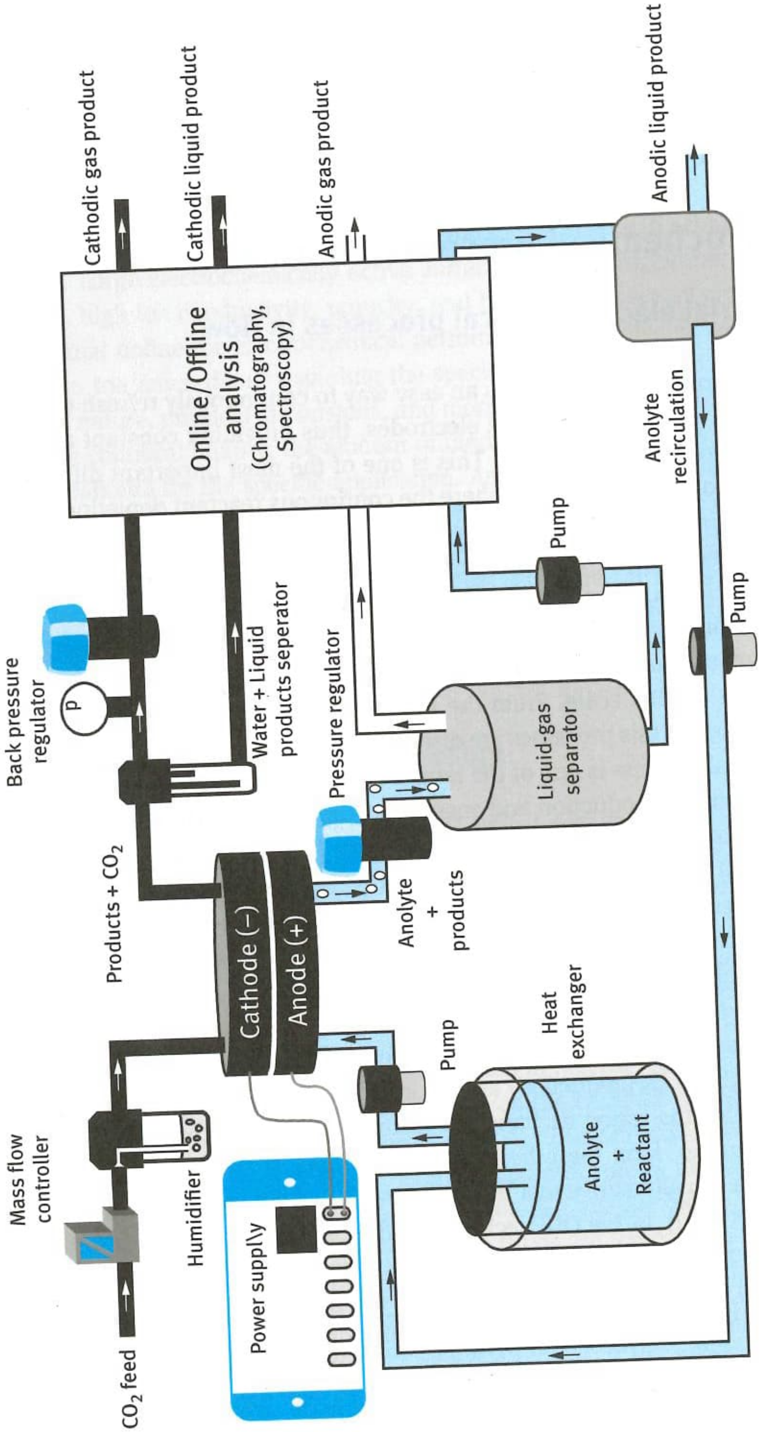


Fig. 2.12: Exemplary operational framework for CO_2R paired with a value-added anode process in a zero-gap design. It can be extended to cells using liquid catholyte, by adding an extra pump to the cathode circuit [77]. Copyright 2020 Elsevier.

alkaline membrane) in case of alkaline cells; while a PEM membrane is inserted between the two electrodes in PEM electrolyzer cell. Alkaline water electrolysis is a mature technology with large plants installed worldwide already. Using alkaline electrolyte allows the use of non-noble metal electrodes that significantly reduce capital costs of this technology. However, with the rapid membrane development, PEM water electrolyzers allow operation at higher current densities and lower cell voltages, hence result in higher energy efficiency and production rate. This technology is in the industrialization phase, with several large plants (MW range) installed already.

Of late, significant R&D resources are being dedicated to finding active catalysts and suitable cell designs for the industrial-scale electroreduction of carbon dioxide, thus turning a harmful greenhouse gas into useful chemicals. Solid oxide electrolysis cells (SOEC) offer very high process efficiencies in the direct electrochemical conversion of CO_2 to CO or water to H_2 [84]. Due to the high operating temperatures, the kinetics and thermodynamics of these processes are both very favorable. The SOEC technology is approaching maturity, with larger pilot plants already installed worldwide. This technology necessitates the application of heat tolerant structural materials and high reaction temperatures, which results in high operational and capital investment cost. This is expected to decrease with the mass production of these cells; hence, SOECs are envisaged to compete with low temperature cells in the future – a battle, which will eventually be decided by the cost and the nature of the given application.

Among the low temperature cells, two types have emerged over the years: (i) microfluidic cells, in which thin liquid layer(s) flow between the electrodes, and (ii) zero-gap designs, in which only the anode is fed with liquid electrolyte, but all the cell constituents are pressed together [63]. In both cases, CO_2 is fed in gas phase through a GDE cathode. This technology is still in the R&D phase, but larger and/or multilayer cells have already been operating at sufficiently high current densities, although the lifetime of such devices has to be improved.

The cells used for sodium chlorate production represent another class with no separator placed between the electrodes. Instead, the cathodes and anodes of these cells are arranged in an interdigitated manner with a few mm thick solution layer between them. The chemistry of the cell is similar to that of the chlor-alkali process: H_2 evolves on the cathode, and chlorine forms on the anode. The solution pH is however significantly different, which leads to the dissolution of chlorine and its subsequent chemical transformation to sodium chlorate in an external reaction vessel [85].

Synthesis of different organic molecules (e.g., adiponitrile, *p*-aminophenol, or anthraquinone) constitutes another important group of industrial flow-electrochemical processes [53, 86]. No general cell structure, process conditions, or electrode type can be defined for this group; these parameters must always be tailored to the given reaction.

2.3.2 Electroconversion of small molecules

Using the earlier described modular flow cell, *Waldvogel* and coworkers demonstrated the synthesis of nitriles from the corresponding aldoximes in a direct domino oxidation–reduction sequence [34]. Conventional approaches depend on harsh reagents like thionyl chloride or acetic anhydride. While the batch electrolysis faced the challenge of additional dehalogenation reaction, the optimization of flow electrolysis allows a supporting electrolyte-free electrolysis with excellent selectivity. The aldoxime is oxidized at a graphite anode, giving nitrile oxide, which is subsequently reductively deoxygenated at a lead cathode. During optimization, an acetonitrile water mixture of 11:1 (v/v) sufficiently suppressed dehalogenation. The solvent was recovered by evaporation, and the product was obtained by simple crystallization with 63% yield.

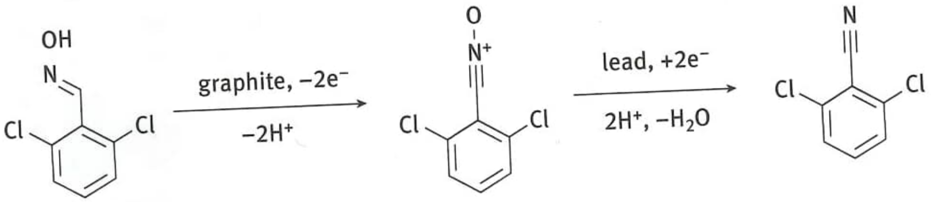


Fig. 2.13: Domino-oxidation–reduction sequence for the synthesis of nitriles from aldoximes in a narrow-gap cell.

Using a separator, they were able to trap the nitrile oxide with methyl acetoacetate in a 1,3-dipolar cycloaddition, yielding isoxazole with 60% as building block, for example, dicloxacillin synthesis. *Waldvogel* and coworkers used the same type of cell to investigate phenol-phenol cross-coupling at BDD anodes [35]. In combination with fluorinated alcohols like 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), especially, a wide electrochemical window and good stabilization of the generated phenoxyl radicals is achieved. Established approaches use transition metal catalysts in a reductive fashion for the synthesis of such compounds. Additionally, leaving functionalities are required to be initially installed at the coupling partners. The direct electrochemical dehydrodimerization reaction overcomes these economical drawbacks and makes them sustainable. They showed efficient cross-coupling of different phenols and naphthol derivatives in yields up to 86%. Additionally, scale up to a flow cell with an anodic surface of 4 cm × 12 cm resulted in stable yields, showing the high robustness and scalability of this reaction.

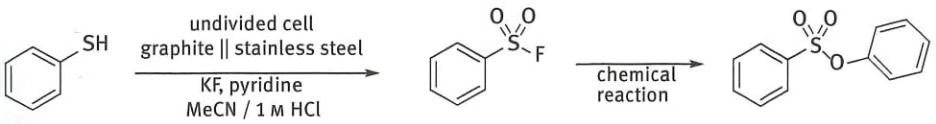


Fig. 2.14: Electrochemical oxidation of thiols in the presence of potassium fluoride toward sulfonyl fluorides. Chemical follow-up reaction toward phenyl sulfonate derivatives.

Noel and coworkers reported a series of transformations starting from thioethers and thiols, and starting with the oxidation of sulfides to sulfoxides at iron anodes [87]. Using polarography, they identified the necessary cell voltages for selective oxidation to the corresponding sulfoxides or sulfones. They then expanded the protocol with the preparation of sulfonamides from amines and thiols at a graphite anode [88]. The thiol is oxidized to the disulfide, which is then attacked by the generated aminium radical, under formation of a sulfenamide. The sulfenamide is then oxidized via the sulfinamide to the sulfonamide. They reported the electrochemical oxidation of thiols in the presence of potassium fluoride to obtain sulfonyl fluorides usable in the popular sulfur(VI)-fluoride exchange (SuFEx) click chemistry reactions [89]. The reaction is carried out in a biphasic system with 1 M HCl and acetonitrile, using an undivided, self-made flow cell with a graphite anode and stainless steel cathode with yields up to 81%. Since the corresponding sulfonyl fluorides are, sometimes, volatile compounds, they circumvent the isolation by an uninterrupted flow protocol for the SuFEx click reaction toward phenyl sulfonate derivatives, with up to 73% isolated yield.

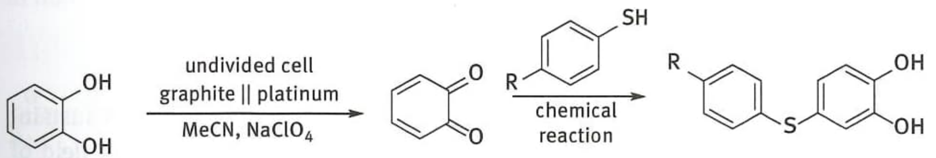


Fig. 2.15: Anodic oxidation of *o*-quinones toward unstable *o*-benzoquinone. Follow-up Michael addition.

In a similar fashion, *Atobe* and coworkers successfully synthesized diphenyl sulfides via unstable *o*-benzoquinone, which they generated electrochemically and later trapped in a Michael addition reaction with benzenethiols [90]. *o*-Quinones are versatile building blocks but need to be generated in situ, since they tend to decompose, isomerize, or polymerize upon storage. Due to this high reactivity and the competing oxidation due to similar oxidation potentials, batch-type electrolysis (in- and ex-cell) ended up with low yields. A direct oxidation of the dihydroquinones in flow is carried out at a graphite anode, and the stream is immediately joined with the thiol one, resulting in the corresponding Michael addition product, with yields up to 88%.

2.3.3 Electrosynthesis with high value addition

Besides new pathways for classical synthesis with an improved atom economy and an inherent safety, electrosynthesis can be utilized in a variety of redox-based transformations. The over-stoichiometric use of terminal oxidizers or reduction agents can be circumvented, with carbon-based electrode materials allowing metal-free synthesis that is useful for later drug synthesis.

Waldvogel and coworkers have lately optimized the electrochemical synthesis of periodate at a BDD anode [50]. Periodate is used in a broad scope of the synthesis of active pharmaceutical ingredients. Previous approaches suffer from toxic anode materials like lead dioxide or expensive starting materials. By using a Nafion® membrane, they avoided the otherwise-necessary toxic anti-reducing agents. The synthesis was optimized by design of experiments (DoE), resulting in a highly efficient conversion with yields up to 98%. The use of BDD electrodes makes this synthesis heavy metal free, which drastically lowers the costs for the purification of the product.

$$\text{NaI (0.4 M)} \xrightarrow[\substack{\text{aqueous NaOH (4 M), rt} \\ \text{up to 98\% yield, 84\% CE}}]{\substack{\text{BDD anode, } j = 100\ \text{mA/cm}^2 \\ \text{divided cell (Nafion membrane)}}} \text{Na}_3\text{H}_2\text{IO}_6$$

Fig. 2.16: Oxidation of sodium iodide to periodate at a BDD anode.

The processing of natural feedstock from abundant sources in the sense of sustainable production of base chemicals will become an increasingly important field of research, in the near future. The US Department of Energy identified 12 high interest sugar-based chemicals to produce value-added chemicals from biomass that is derived from, for example, hemicellulose, cellulose, and lignin. Latest research shows that flow electrolysis is a precious platform for a sustainable transformation of biomass feedstock.

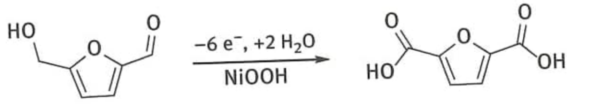


Fig. 2.17: Two-step oxidation sequence of (HMF) toward (FDCA) at activated nickel hydroxide electrode.

Giling and coworkers developed a two-cell reactor rig for the two-step oxidation sequence of 5-(hydroxymethyl)furfural (HMF) to obtain 2,5-furandicarboxylic acid (FDCA) [91]. During the optimization, different noble anode materials (Au, Au_3Pd_2, and Pt) were tested; finally, nickel with deposited active NiOOH layer gave outstanding yields of up to 90% with high faradaic efficiencies of 80%. They were able to scale up the reaction using nickel foam electrodes in a continuous setup with integrated product separation and a production of about 30 g FDCA per hour. The input stream with 15 wt% HMF is oxidized under basic conditions, resulting in a 5 wt% FDCA stream that is acidified, resulting in direct product crystallization.

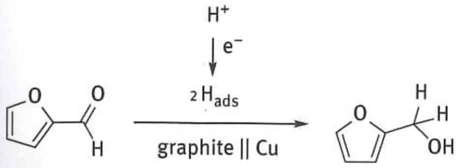


Fig. 2.18: Electrocatalytic hydrogenation of furfural to furfuryl alcohol. *Noel* and coworkers exploited the Volmer reaction to generate furfuryl alcohol from furfural in an electrocatalytic hydrogenation fashion [92].

Furfuryl alcohol is used as a monomer in furan resin synthesis [93]. During the reduction, the dimerization of the neutral radical needs to be suppressed. The optimization showed that under basic conditions, using a copper-graphite electrode setup yields furfuryl alcohol of 90%. The use of small amounts of potassium ethanolate (0.05 M) as base and supporting electrolyte was beneficial for the reaction, resulting in high faradaic efficiency of 90%.

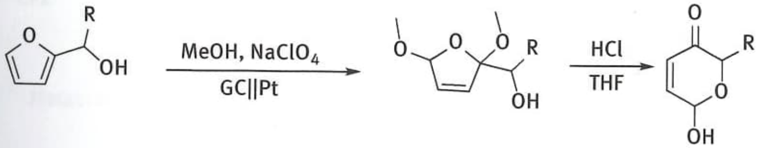


Fig. 2.19: Anodic conversion of furfuryl alcohol in presence of MeOH toward 2,5-dimethoxy-dihydrofurfuryl alcohols. Subsequent Achmatowicz reaction yields hydroxypyrones.

Starting from furfuryl alcohols, *Robertson* and coworkers developed an flow oxidation protocol for the 2,5-dimethoxy-dihydrofurfuryl alcohols [94]. A subsequent acidic hydrolysis in Achmatowicz reaction fashion yields the corresponding hydroxypyrones like maltol. Maltol and derivatives are widely used as flavor enhancers. For the electrolysis, they used a self-designed cell made from PEEK as mounting material. A GC anode and a platinum cathode were used and fixed with Araldite® epoxy resin glue. With optimized electrolysis conditions, they yielded dimethoxy derivatives of up to 71% isolated yield.

Hammond and coworkers investigated the electrochemical depolymerization of lignosulfonate in a technical-scale reactor [95]. Lignosulfonate is an abundant by-product of the pulping industry. In oxidative conditions, a variety of phenolic monomers like vanillin can be obtained. They used a FM01-LC reactor commercially available from ICI, which can be equipped with different electrode materials. The optimization of reaction allowed electrolysis of 150 g at up to 12 A, 145 °C/500 kPa/3 M NaOH. The yield of vanillin was similar to that of terminal oxidizers in batch processes of about 5–7% w/w.

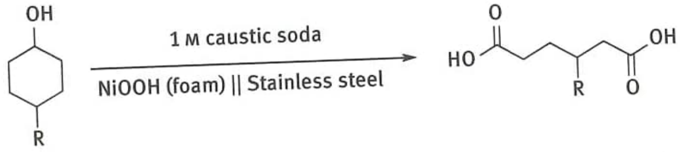


Fig. 2.20: Electrochemical oxidation of alkylated cyclohexanols to alkylated adipic acid derivatives at NiOOH foam electrodes.

Catalytic reductive fractionation of lignin gives rise to a broad scope of alkylated cyclohexanols. Lately, *Waldvogel* and coworkers have developed a protocol for the electrochemical oxidation of alkylated cyclohexanols to alkylated adipic acid derivatives at NiOOH foam electrodes in batch and flow electrolyzers [20]. The 3-methyladipic acid was obtained in yields up to 64% in a cycling electrolysis, providing efficient removal of the developing hydrogen. Sodium hydroxide was employed as a base as well as supporting electrolyte, making this an elegant and cost efficient pathway to obtain dicarboxylic acids, which can be later employed as monomer in polyester and polyamide synthesis.

2.3.4 Electrochemical synthesis of drug metabolites

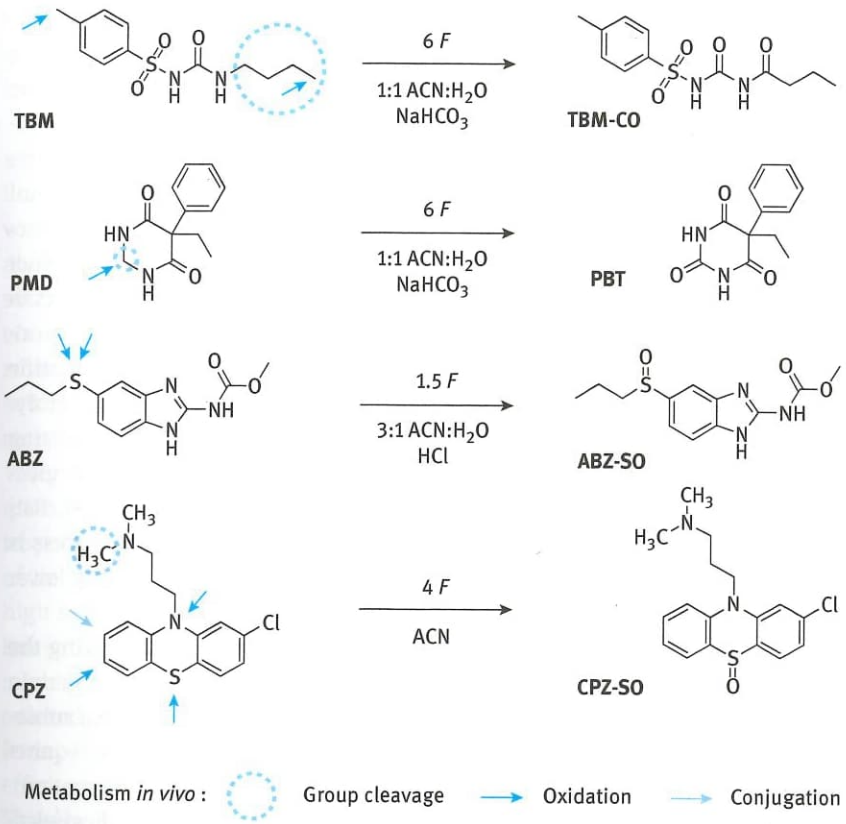


Fig. 2.21: Oxidation products of the flow electrolysis of tolbutamide (TBM), primidone (PMD), albendazole (ABZ), and chlorpromazine (CPZ). Reprinted with permission from [96]. Copyright 2013 American Chemical Society.

Electrochemical synthesis offers a low-cost approach for synthesizing and studying drug metabolites [97]. Importantly, this way, the use of expensive enzymes is avoided. Furthermore, electrochemical flow cells offer an easy way of continuously producing such metabolites, which can be analyzed by a connected in-line analytical system. Also, such a system allows the detection and characterization of unstable (or reactive) metabolites that, in a biological matrix, would otherwise rapidly bind covalently to proteins [98]. Not all metabolic pathways can be mimicked by electrochemical methods. Therefore, these studies cannot fully circumvent biological studies. Furthermore, some electrochemically induced metabolic pathways lack their counterpart in biological systems, which could, therefore, be somewhat misleading. In addition, most of such electroconversions only provide traces for analysis but not enough material for extensive studies. A valid approach is the installation of stabilizing groups [99].

2.3.5 Paired and consecutive electrolysis

To increase process efficiency and decrease production costs in any electrochemical process, it is desired to form valuable products on both electrodes, while applying as the lowest possible cell voltage. When it comes to industrially relevant cathodic reactions such as H_2 production or CO_2 electroreduction, water oxidation (i.e., oxygen evolution) reaction is the most often used green anodic pair. This requires high energy input (i.e., large cell voltage), and generates a product of little commercial value (i.e., oxygen). Pairing appropriate alternative anode processes with these reductions is of major interest, as it might result in a significantly increased total product value. On the other hand, this significantly increases the system complexity, necessitating the continuous composition monitoring of both the anodic and cathodic product streams, and the multistep separation of these products. This implies scientific and engineering challenges, but a properly designed and optimized paired electrolysis process offers the possibility of direct industrial implementation. As a promising example, either CO_2 reduction or H_2 production might be coupled with anodic glycerol oxidation to glyceraldehyde, a product that is more valuable than O_2 [100, 101] by orders of magnitude. Furthermore, the standard redox potential of this process is almost 1 V lower than that in water oxidation, offering operation at significantly lower cell voltages when compared to the case of anodic water oxidation.

Finding suitable catalysts for multistep electrochemical processes involving the transfer of multiple electrons (and multiple protons) could be challenging. In certain cases, forming an intermediate in one electrolysis cell and further reacting it in a subsequent setup applying different catalyst material is favorable in terms of energy requirements (including process selectivity, hence the costs related to product separation). Reducing CO_2 to an intermediate and further reacting it in a subsequent chemical/electrochemical step offers a way to synthesize a large variety of functional chemicals that serve as building blocks for organic synthetic chemistry. An example is the production of ethylene oxide in a two-step electrochemical method – first reducing CO_2 to C_2H_4, and subsequently, selectively oxidizing the product in a separate cell [102]. This is a green alternative for ethylene oxide production, which is an important bulk chemical that is produced in large quantities – ~20 million metric tons per year.

2.4 Strategies for screening and optimization

The optimization of reactions in electrochemical flow cells can present a challenge due to the high number of parameters involved. Classic optimization strategies, like one variable at a time (OVAT), often fail to reach the global maximum (or minimum) of a system response, since they cannot resolve interactions between the parameters. An interaction is the influence of one parameter setting on the system response when changing the value of a second parameter. This can result in a high number of experiments needed for optimization, as well as unnecessary allocation of resources and time. Statistically driven approaches like DoE provide a remedy. We do not want to describe the theory in detail in this chapter, since it is covered in literature [103, 104], but we want to provide a guide and a jump start with a few real-life examples.

The basic idea is to treat a reaction as a black box process, if no deeper understanding of the mechanisms is available prior to the optimization. The process is influenced by reaction parameters – both controllable like the current density as well as probably not controllable like the humidity in the lab. If possible, one should always record data on these so-called covariates. The setting of these parameters results in system responses like yield or selectivity, once the process is carried out. In contrast to OVAT, the influence of all parameters on the system response is analyzed at once; therefore each parameter is investigated at two levels (high (+) and low (–) setting), resulting in a balanced experimental design. These so-called full factorial designs require a total number of 2^n experiments, where n is the number of parameters. When the experimental plan is carried out, one can start with the calculation of the main effects. A main effect of a parameter represents the mean change of a system response when the setting is changed from low to high, calculated by the difference of the two subsets, one containing all experimental results with the parameter on high setting, and the second containing experimental results with the parameter on low setting. An interaction causes a different system response when changing one parameter from low to high depending on the setting of a second parameter and is calculated as the difference of the two effects at both levels of the second parameter. It needs to be noted that main effects are usually dominating in contrast to the effect sizes of the interactions; they decrease with increasing order of interaction. This acted as motivation for fractional factorial designs, which include only a subset of the full design, resulting in lower numbers of experiments needed, but for the price of the confounding of main effects and interactions [105]. Based on the amount of reduction, the models are classified into three ascending resolution levels: III–V.

Besides the calculation of the main effects, the balanced fashion of the design allows a linear regression to yield a predictive model within the investigated space. Furthermore, the calculated effect sizes can be probed by using analysis of variance (ANOVA). The working assumption is the normal distribution of the model error over the whole design, justified by the central limit theorem. In the case of fractional designs, nonsignificant parameters can be excluded from the model, resulting in a stronger design (projection property).

Within the range of a maximum (or minimum) of a system response, a linear regression is no longer sufficient to fit the resulting curvature of the responses hyperplane in the parameter space. This can be checked by a center point experiment. The result is compared with the predicted value from the linear regression. In case of a large residuum, the design needs to be extended by additional experiments to fulfill the needs of a second order regression. Typical designs are the central composite design or Box–Behnken design [106, 107].

DoE needs to be understood as a recursive procedure. In the early stage of an optimization, a fractional design or screening design should be carried out to measure the main effect sizes and exclude all parameters that show no influence on the system response. With a reduced number of parameters, designs of higher resolution can be used. Within the range of a maximum (or minimum), a second order model can be used to fine-tune the parameter settings [108]. If more than one system response is of interest, the desirability functions offer multitarget optimization. For each response, its desirability function scales between 0 (if the predicted response is outside the acceptable range) and 1 (if it matches to desired value). The individual desirability functions are then multiplied to get an overall desirability that needs to be maximized. Most statistical software suites provide an algorithm to solve this optimization problem, resulting in optimized parameter settings.

Wirth and coworkers recently showed an elegant combination of their electrochemical flow cell with online 2D HPLC analysis [54]. They used the memory effect of chirality in *N*-aryl carbonylated amino acid derivatives under Kolbe electrolysis to generate enantiomerically enriched alkoxylated amides, via an acyliminium ion intermediate. Due to the supporting electrolyte (SE)-free conditions, they were able to measure yield and enantioselectivity as system responses directly, via (chiral) HPLC. Initial experiments in batch type cells resulted in poor yields and selectivities due to the unstable acyliminium intermediate. They started by pre-screening of electrode materials, substrate concentrations, and flow rates ending up with graphite and GC as promising anode materials. Afterward, using a 2^{5-1} fractional design, they investigated the influence of the concentration of starting material, flow rate, applied charge, temperature, and – as a category parameter – the anode material (graphite and GC). In the case of yield, the amount of charge and the anode material were dominating parameters, whereas, in the case of enantioselectivity, the anode material was mainly influential together with a second order interaction involving the temperature. They finally investigated the influence of the flow rate, amount of charge, and temperature in a full factorial 2^3 design, using GC as anode material ending up with optimized conditions with yield up to 100% and enantioselectivities up to 70 % *ee*.

Waldvogel and coworkers investigated the anodic C–C cross-coupling of 2-methoxy-4-methylphenol and 2,4-dimethylphenol as a model system [109]. This cross-coupling reaction was a subject of research for a longer period; linear optimization strategies yielded 44% of the corresponding biphenol. Based on this primary research, they used a 2^{7-3} design to investigate the influence of the electrode gap, temperature, current density, amount of charge, concentration of SE, and concentration as well as ratio of the substrates. In 35 experiments, they found the electrode gap as the dominating parameter, where a small gap was beneficial for the yield. Due to DoE-based investigation, an isolated yield of 85% was easily achieved. Furthermore, the main effect

analysis revealed no significant influence of the substrate concentration or current density; therefore, a near-threefold increase in space–time yield was reached.

2.5 Options for industrialization and scale-up

Industrialization of electrochemical reactions give rise to different challenges in the various processes. Many conversions discussed in this chapter are industrially relevant, even at a relatively small scale. Synthesis of drug molecules or selective redox transformation of key intermediates can be readily performed in microfluidic cells, in up to kilogram scale. In these cases, the consecutive reactions and the cross-talk between the two electrodes are the most important challenges during scale-up. Interdigitated electrodes, as well as special long-path designs can help increasing the conversion. In strong contrast, large units and systems are needed in the chlor-alkali electrolysis, water splitting, and CO_2 conversion processes, to have industrially relevant size. Moreover, while product selectivity is the key driver in the first category, energy efficiency, conversion rate, and materials cost become dominant for large-scale technologies. This is something that has to be kept in mind even at the research stage, because electrolysis cells shall be developed, which operate (i) at high current density (conversion rate), (ii) at low cell voltage (i.e., high energy efficiency), (iii) with high Faradaic efficiency (selectivity), and (iv) with high conversion efficiency. Notably, even though these four parameters together describe the overall performance of an electrolysis cell, very seldom are all of these reported in the scientific literature [71].

Another important concept to highlight is the scale-out approach. This means that the result of the scale-up process is not a giant cell, but, rather, multiple cell stacks. One stack is made of several (up to over 100) electrochemical cells, where the key component is a bipolar plate (acting as cathode in one cell and anode in the subsequent cell). This approach overcomes the need for manufacturing very large electrodes and cell components, as also difficulties related to the management of the electrochemical process itself. Stack cells enabled the industrialization of both water splitting and the chlor-alkali process, and the concept has been recently extended to new processes. For example, *Endrődi* and *Janáky* published on the implementation of this strategy to CO_2 electrolyzers, which can accelerate technology development to scale up electrochemical CO_2 reduction to an industrially relevant level. A zero-gap CO_2-stacked cell which consists of multiple layers and can operate with a pressurized CO_2 gas feed without the need for any liquid catholyte was demonstrated. The flexibility of the presented design allows different connections between the layers of the electrolyzer based on the distribution of the reactant CO_2 gas. Connecting the cells in parallel (Fig. 2.22A), the gas is equally distributed among them; hence, pure CO_2 is fed to each cathode. On the other hand, when connecting the gas channels in series (Fig. 2.22B), the total gas flux enters the first layer, and

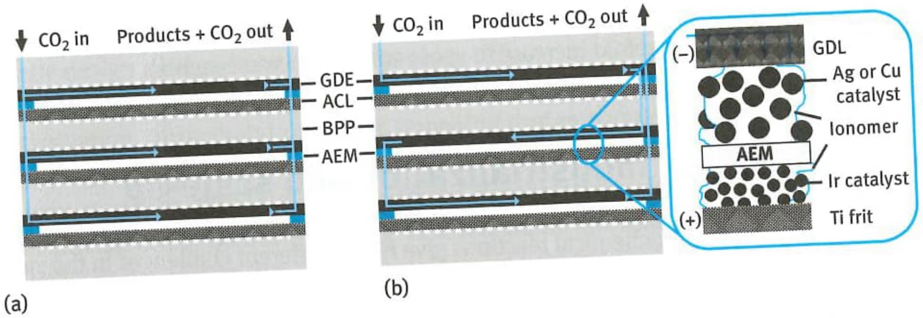


Fig. 2.22: CO$_2$ gas channel structure in an electrolyzer stack consisting of three layers in the (A) parallel and (B) serial connection configurations. BPP, bipolar plate; ACL, anode catalyst layer; GDE, gas diffusion electrode; GDL, gas diffusion layer; AEM, anion exchange membrane. Copyright 2019 American Chemical Society [110].

the off-gas (remnant CO$_2$ + products) continues to the subsequent layer(s), thus allowing very high conversion efficiencies.

Further readings

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Study questions

2.1 Electrochemical processes are widely used. Please provide some examples.

2.2 Please describe the principle of an electrochemical cell, indicate electrodes, and explain physical and chemical processes at the individual electrode surfaces. Use water as electroactive species in acidic and alkaline solution to evolve hydrogen and oxygen.

2.3 Why is it necessary to add a so-called supporting electrolyte into an electrolyte to perform a conventional electrolysis? Is it possible to reduce the amount of supporting electrolyte when a narrow-gap cell is used?

2.4 Please make a suggestion for avoiding or suppressing undesired electrode reactions.

2.5 Please describe strategies for handling gas evolution within the flow electrolyzers.

2.6 What are suitable electrodes for anodic conversions of organic compounds?

2.7 Carbon electrodes can be considered as essentially metal free. Which materials do you know and what are the specific features, thereof?

2.8 Platinum is often used in lab electrolyzers. Why should chloride-containing electrolytes be avoided?

2.9 What is a paired electrolysis? Please provide examples.

2.10 Please calculate the necessary applied charge for a homo-coupling reaction in dependence of the molar quantity of the substrate A. How does this change when considering a cross-coupling of components A and B? Which criterion is used to decide which of the substance quantities is used in the calculation? How is the flow rate calculated for a given charge quantity and current density, in relation to the volume of the reactor chamber (for a single pass)?

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