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Introducing new reactions and technologies in industrial synthesis: Challenges, hurdles and opportunities for start-up initiatives for sustainable chemistry

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A B S T R A C T

Following up on the UNEP/UNIDO/ISC3-workshop in Berlin in September 2017, the context of the French start-up initiative INNOVERDA is presented, and its anticipated contribution to mainstreaming the practice of green and sustainable chemistry highlighted. INNOVERDA is dedicated to implement electrochemical flow methods for sustainable production processes in the chemical and pharmaceutical industry. Challenges and hurdles encountered during the first phase of this start-up as also experiences from a previous one, TETRAHEDRON, are summarized, and potential solutions proposed.

1. Introduction: The ideas behind the start-up

The recent creation of INNOVERDA, a French start-up dedicated to implement green and sustainable chemistry solutions in industry, was inspired by key experiences and insights which we gained with our first start-up in the chemical sector, TETRAHEDRON (www.tetrahedron.fr), created in 2003 together with J. C. Yadan and M. Moutet. TETRAHEDRON set up to develop safe and natural or nature-derived novel antioxidants for nutrition, cosmetics and pharmaceutical applications. In several years of research and development, we succeeded to bring Ergothioneine, a fascinating amino acid, (Cheah and Halliwell, 2012) from the lab to the market.[1] (Fig. 1).

Essential steps on the long way to the market were (i) the development of an industrial production process, for which we invented a new green and biomimetic synthesis in water (Erdelmeier et al., 2012) and (ii) obtaining a regulatory status for our product as Novel Food, (Statement on the safety of synthetic l-ergothioneine as a novel food, 2017) thus overcoming the final barrier to broad commercialisation.

During the process development phase, we faced technical challenges of purification and separation from salts, due to the extremely high polarity and water solubility of this unusual zwitterionic amino acid. While others circumvent this by using protecting group chemistry to gain on lipophilicity with the goal to work in organic solvents, playing the high price of adding several steps, (Xu and Yadan, 1995; Trampota) we searched an appropriate purification technology. The solution was the implementation of a desalination-purification method based on electrochemical principles, called electrodialysis.

The simplicity and efficacy of this method is striking, contrasting with the fact that it is only rarely used in organic synthesis in the laboratory, and even less in industrial productions.

This observation led us to take a broader look in the current use of electrochemical methods such as electrodialysis (ED) and electrosynthesis in chemical research, development and production. Quite surprisingly, the results showed that there seems to be a huge unused potential for such a potentially sustainable production technology, particularly in organic synthesis. This is perhaps simply due to the historical separation in the chemistry curriculum assigning electrochemistry to the physical chemistry, not being specifically addressed in the training of organic synthetic chemists. Another explanation could be the lack of convenient equipment for the synthetic organic chemist, as highlighted recently by Baran et al. (Yan et al., 2018).[2,3]

Therefore, at the time when TETRAHEDRON concentrated on marketing and sales of its key product ergothioneine (under the brand name Ergoneine®), I decided to launch a new company in 2017. The goal of this start-up initiative, INNOVERDA, is to focus on the implementation of electrochemical methods and in particular flow

[1] Under the trade name Ergoneine®.

[2] Interestingly, some equipment suppliers start to supply convenient lab equipments: see for example: https://www.ika.com/laboratory-equipment/products/electrochemistry-kit/ and http://www.pccell.de/.

[3] See for example the following statement: Electrochemistry and photochemistry are not really new technologies, but they are certainly technologies that have been largely viewed as curiosities by most of the fine chemical and pharmaceutical community. Some companies are looking at or even using both these techniques, but the two reasons listed for having low interest in this area is a lack of in house expertise and perhaps more importantly a lack of suppliers/vendors with expertise and/or equipment in this area. in Watson W. J. W., “How do the fine chemical, pharmaceutical, and related industries approach green chemistry and sustainability?” Green Chem., 2012,14, 251–259, DOI:10.1039/c1gc15904f.

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Fig. 1. TETRAHEDRON's key product L-Ergothioneine, commercialised under the trade name Ergoneine®.

electrosynthesis in organic synthesis from the research lab to industrial productions.

2. Anticipated contribution to green and sustainable chemistry

While we should be very careful and selective to introduce further new chemicals into the environment, we nevertheless need new sustainable materials, and sustainable production processes to provide essential chemical intermediates, final products and drugs.

At INNOVERDA, we design and develop continuous flow electrochemistry and biomimetic processes. This technology will contribute to green and sustainable chemistry by two means:

Firstly, by significantly changing and/or improving industrial production processes by not only replacing corrosive and/or toxic agents, but also by increasing selectivity, efficiency and safety, using electrical energy (i.e. renewable energy), thereby offering ecological and economic advantages.

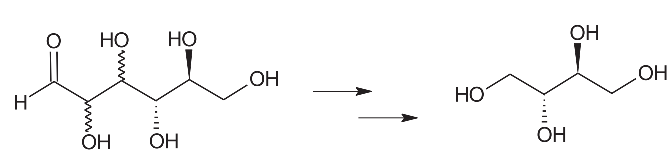
Obviously, oxidative and reductive transformations, which are defined by adding or removing electrons (and protons) are excellent candidate reactions for electrosynthesis, using electrons (and occasionally water to deliver protons) as *sole* reagent. In traditional chemical oxidoreductions, stoichiometric quantities of oxidants or reductants are required to deliver or remove electrons, with the concomitant generation of at least (molar) equivalent quantities of waste. In electrosynthesis, electrons are added at the cathode and removed at the anode, if appropriate reaction conditions are identified. By choosing the appropriate parameters for electrode materials, distance between electrodes, solvents, pH, temperature and flow rates, these synthetic transformations are reduced to its essential feature. Impressive examples are the industrial production of Erythritol (vide infra), but also innovative electrochemical oxidations of non-activated C-H-bonds, (Kawamata et al., 2017) or NH-bonds, as illustrated recently by the group of Baran in the synthesis of Dixiamycin (Rosen et al., 2014). Electrochemical reduction can also be used to afford smooth dehalogenation without the need for chemical reagents, as illustrated by the group of Waldvogel in the synthesis of a Cyclosporin analogue (Gutz et al., 2015a; 2015b). A broad diversity of other chemical transformations may be improved or enabled by electrochemical activation or mediation (Atobe et al., 2018; Möhle et al., 2018). Interestingly, some of those new electrosynthetically feasible transformations had been highlighted a decade before as “key green chemistry research areas from the Pharmaceutical Manufacturers perspective”, for which “greener” solutions were needed (Constable et al., 2007).

Most recently developed electrochemical reactions respect several principles of Green Chemistry, such as prevention of waste, less hazardous processes, higher energy efficiency, reduction of derivatives, catalysis (often plays the electrode material also a catalytic role or catalytic mediators are involved), and inherently safer chemistry. Electrochemical processes can move chemical production to more sustainability, if additional aspects are considered such as (i) sourcing of renewable energy for electricity, (ii) sustainable electrode materials, as for example stainless steel or graphite, avoiding further depletion of rare elements, and (iii) use of renewable raw materials.

INNOVERDA wants to contribute with its second business focus to this movement to more sustainable chemistry, by developing new processes for the transformation and valorisation of biomass (in preference waste) to supply in an economic and ecological way starting materials for the chemical industry, replacing petrochemical feed stocks by biomass. In this context electrosynthesis is a particularly powerful and promising tool for the biorefinery concept, as bioderived feedstocks are inherently highly oxygenated and functionalised. To obtain platform molecules or fine chemicals and ingredients from biomass, reductive transformations are essential. Therefore, a broader application of electrosynthesis using “electrons as sole reagents” wherever possible is a promising goal and economically feasible, as exemplified with the industrial scale production of erythritol by an American Company (Dynamic Food Ingredient, http://dficorp.com/). In this process, C6-sugars are first electrochemically oxidized and decarboxylated at an anode, followed by electrochemical reduction at the cathode to erythritol (see Scheme 1) (Stapley et al.).

Key features of flow electrochemical methods are the possibility to use water but also organic solvents if required, modularity, efficiency and selectivity. Moreover, they can be conveniently upscaled and easily replicated in other regions, as flow processes can be implemented with mobile units. These aspects are important, not only to avoid the transportation of dangerous goods (as shown for example in the “on demand” generation of ammonium persulfate (Zhu et al., 2016)), but also in the perspective of waste transformation.

Besides working with flow electrosynthesis, INNOVERDA thrives to explore also the potential of electrodialysis as sustainable process technology for treatment and purifications. ED is a high-throughput membrane-based technique which is easily adaptable on an industrial scale, and commonly used in water treatment for (solar-driven) desalination of seawater, (Wright and Winter, 2014; Strathmann, 2010) or removal of inorganic trace contaminants from bore water sources (Banasiak and Schäfer, 2009). Its sustainability depends on membrane material, efficiency and water consumption, but also on the source of energy. Contrary to ion-exchange column chromatography, where the ions are absorbed on a resin, ions are migrating in ED through the membranes and collected in a “concentrate”. The membranes can be



Erythritol

Scheme 1. Industrial electrosynthesis of erythritol (Ref. Stapley et al.).