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Organic electrosynthesis – A road to greater application. A mini review

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ABSTRACT

Despite a long history, electrosynthesis has never become a routine procedure in organic synthesis laboratories or for the manufacture of organic compounds within industry. One major reason is the nature of the literature. This review highlights the need for electrosyntheses to meet the demands of the user and for papers to make this clear. To be attractive to synthetic chemists, papers need to demonstrate a high conversion of reactant to product as well as the isolation of pure product on a scale of interest and in high yield. In addition, it is absolutely essential that papers include a detailed description of the procedure, especially the electrolysis cell (geometry, dimensions, component materials and sources, mass transfer regime etc.) and all the control parameters (solvent, concentration of reactants(s) and electrolyte, pH, cell current, temperature etc.) used for the electrolysis.

1. Introduction

Organic electrosynthesis has a history dating back almost 200 years and has led to a very extensive literature. Over the years, many books and reviews (recent examples [1–8]) have regularly lauded the diversity of chemistry possible at electrodes but electrolysis remains a very under-used procedure for the preparation of organic compounds both in the laboratory and in industry. Why? One reason is the nature of the literature. Organic electrosynthesis presents itself very badly to the synthetic organic chemist.

It needs to be recognised that the electrolyses of organic compounds are carried out with several distinct goals:

- to assist the interpretation of voltammetry.
- to propose a route for the laboratory synthesis of an organic molecule.
- to develop a commercial route for the manufacture of an organic compound.

The experiments required for each are significantly different and the authors of many papers do not state clearly their objectives and reasons for reporting an electrolysis. For example, there is a major difference between demonstrating that an electrode reaction can take place and establishing that an electrolysis is a useful laboratory synthesis. To make matters worse, books and reviews often fail totally to make the distinction and this leads to a literature that is misleading and confusing, especially to non-electrochemists.

Moreover, too often an attempt to repeat an electrosynthesis in a different laboratory leads to a much degraded selectivity and/or yield.

All too frequently, this results from insufficient detail in the description of the electrolysis cell (geometry, dimensions, materials of components, mass transfer regime etc.) and the electrolysis conditions (solvent, concentration of reactants(s) and electrolyte, pH, cell current, temperature etc.). Of course, it is also critical that the information in the paper is followed precisely.

Hence, this review sets out the experimental consequences of the different goals and suggests the changes that will lead to electrolysis becoming a more widely used synthetic method.

2. The interpretation of voltammetry

The voltammetry of organic molecules may be studied for the purposes of developing a method of analysis, understanding the influence of solution conditions or electrode materials on the rate and/or selectivity of an electrode reaction or defining the mechanism and/or kinetics of homogeneous chemical reactions. Electrolysis is then an aid to the interpretation of the voltammetry as it is the only definitive way to verify the product and hence the overall chemical change leading to a voltammetric peak. Clearly, it is advantageous for the electrolysis to be carried out in the same conditions as the voltammetry. Hence, electrolyses can usually employ a low concentration of reactant leading to a low cell current and a high concentration of electrolyte making possible the use of a three electrode cell and the potentiostatic control of the potential of the working electrode. Also, it is reasonable to limit the electrolysis time equivalent to only a small consumption of reactant and minimal changes to the solution environment since this will also be the case in voltammetric experiments.

3. Laboratory synthesis

In the laboratory, an electrosynthesis will compete with other methods of carrying out the conversion of starting material to desired product and, indeed, other syntheses of the desired product from other starting materials. It should be stressed that the mere demonstration of some conversion of reactant to product does not constitute a "synthesis"; a synthesis is a procedure for producing a desired quantity of pure product.

The organic chemist will be aware of the quantity of product required (commonly 10 mg–100 g) and will select their approach based on the availability of the starting material, convenience of the synthesis conditions (including the availability of appropriate equipment) and selectivity with a growing importance of "green" factors. There can be no doubt that electrolysis can be a 'green' procedure. It permits oxidation/reduction without the use of stoichiometric quantities of redox reagents and/or toxic or hazardous reagents and the conversion is generally carried out close to ambient temperature and pressure. But the synthetic chemist will be expecting a high conversion of reactant to product as well as good selectivity so that the fractional yield approaches 1.0. Also a simple isolation of pure product increases the attractiveness of the procedure. Necessarily in a synthesis, there will be a significant decrease in the reactant concentration with time along with the build-up of product. In many electrolyses, the desired conversion is accompanied by other large changes in the electrolysis medium, most commonly the accumulation of protons or hydroxide. Hence for a successful synthesis, the conversion must be unaffected by the changes in solution composition or the synthesis must include steps to minimise the changes.

It is important to recognise that even with a fractional current efficiency of 1.0, the formation of product at the rates required for convenient synthesis necessitates a substantial cell current (e.g. 5.5 A to generate 10 g/h of a product with a molecular weight of 100 Da in an electrode reaction involving $2e^-$ per reactant molecule). The use of such cell currents is likely to require cells with electrodes of a significant size. The electrode dimensions will depend on the current density and, to minimise equipment size, the target should be a current density $> 50\,mA\,cm^{-2}$. Since the current density depends on the reactant concentrations and mass transport regime, a reasonable solubility of the reactant (> 0.1 M) and efficient stirring or solution flow are required [9,10]. Cell designs need to consider electrode geometry and the potential distribution over the working electrode surface, the influence of the counter electrode chemistry and the mass transport regime. Such cell currents are also beyond the capability of commercial potentiostats. This is not, however, important since current and potential are not independent parameters and laboratory electrolyses are conveniently controlled with cheap constant current power supplies although it can be advantageous to decrease periodically the cell current during the electrolysis.

Selectivity of the reaction to give a high yield of single product is essential in a successful laboratory synthesis. Hence, it is critical for the electrolysis to be carried out in conditions where the electrode reaction leads cleanly to a single reactive intermediate and this intermediate decays by a very dominant pathway to the desired product. The structure of the reactant, electrode material, solution composition and temperature can all influence the selectivity of the reaction. It is important to recognise that organic synthesis is likely to involve polyfunctional substrates and hence the consequences of the other functional groups in the reactant molecule need to be understood. The literature is presently too dominated by studies of simple model compounds with a single active functional group.

Water is the ideal solvent for electrolysis. Electrolytes are highly soluble and such aqueous solutions have a high conductivity. Moreover, the electrochemical oxidation/reduction of water (as may occur as a competing reaction at the working electrode or as the main reaction at the counter electrode) leads only to gas and a change of pH. Organic solvents are more attractive for synthesis (higher solubility of organics etc.). Unfortunately, the conductivity of electrolyte solutions in organic solvents vary significantly but seldom approaches that of aqueous solution. This increases cell voltages (not necessarily a problem) but leads to a more variable potential distribution over the surface of the working electrode; for example, the latter restricts the use of three-dimensional electrodes to increase the cell current. Furthermore, the electrode reactions of organic solvents are generally complex and particularly aprotic solvents can be subject to acid/base catalysed, homogeneous degradation. These factors can lead to a contaminated product solution hindering the isolation of pure product. A possible compromise is the use of aqueous/organic mixtures or an alcohol or carboxylic acid as solvent for oxidations. Soluble anodes can assist syntheses that involve cathodic reduction in aprotic solvents [11,12]. Platinum is widely used for anodic oxidations in the literature but is very expensive for electrodes with the dimensions required for synthesis; graphite or a carbon polymer composite are a more reasonable choice. A wider range of materials is available for cathodic reductions, e.g. carbons, lead, steel, nickel and copper. Many of these materials are available as meshes and foams as well as plates, opening possibilities for cell design.

Convenience implies that the equipment required (cells, electrodes, control electronics) is readily available. This immediately brings beaker cells to the fore; all laboratories have beakers of several volumes and it is attractive to believe that electrolysis only requires dipping two electrodes into a beaker perhaps with a lid to maintain an oxygen free environment. Unfortunately, beaker cells generally perform badly [10]. It is difficult to achieve the high ratio of active electrode area to solution volume and efficient mass transport to give both high selectivity and conversion as well as a high cell current to allow a reasonable synthesis time. Completion of the electrolysis within minutes is attractive and a few hours should be regarded as a maximum. In addition, longer electrolysis times can lead to homogeneous chemistry (especially hydrolysis or solvolysis) competing with the electrode reaction. Another approach to home-built cells is based on microscope plates [10,13–15] but such cells are only suitable for syntheses on a scale of a few mg. The alternative is to purchase a commercial cell and a number of flow cells [9] are available both with recycle of the reactant solution (e.g. the Electrocell family [16], the ElectraSyn cell [17,18], the C-Flow cell [19]) or with an extended electrolysis channel to allow a high conversion of reactant to product in a single pass of the reactant solution through the cell [20] (e.g. the Syrris cell [21,22], the Ammonite family [23–25]). It is important to recognise, however, that any design of electrolysis cell will only form product at a rate within a defined range; for example, the Ammonite cells are designed to permit syntheses at a rate of 0.1–50 g/h. A further significant scale up may well necessitate a change in cell design. Hence, before the purchase of a cell, it is important to consider the rate of product formation required and the importance of a high conversion of reactant to product. Of course, the performance of commercial flow cells can be replicated by laboratory designed equipment but the design and fabrication of electrolysis cells takes time and effort. A number of cell designs with different geometries have been described [10].

Convenience also implies a straightforward isolation of pure product. This is aided by a full conversion of reactant to product and the absence of a high concentration of electrolyte in the reaction medium. Such performance is aided by extended channel length cells and cells with a narrow interelectrode gap [10,20]. Current (charge) efficiency is only important in laboratory synthesis when competing reactions (oxidation/reduction of the reactant to alternative products or of solvent/electrolyte) lead to loss of reaction selectivity or complicates the isolation of pure product; energy efficiency is never relevant on the laboratory scale.

A convenient synthesis also needs to take account of the chemistry at the other electrode. In terms of charge, the same amount of chemical change will occur at the counter electrode as at the working electrode and it is important that the counter electrode chemistry does not

degrade the performance of the working electrode. Moreover, passage of 2F of charge at the working electrode will lead to significant changes in the composition of the electrolysis solution, most commonly the formation of acid at an anode or base at the cathode (typically to a concentration of > 1 M). This can promote competing chemistry and, as a result, a common strategy is to use an undivided cell where the counter electrode chemistry maintains a constant pH in the electrolysis solution [10,20]. Other strategies for the counter electrode in an undivided cell include 'paired synthesis' [26,27] and 'dissolving metal anodes' [11,12,28]. Alternatively, the anode and cathode chemistries can be separated by an ion permeable membrane or porous separator but it must be recognised that ion transport between anode and cathode is a prerequisite of electrolysis in the cell and some transfer of reactant and product between compartments will occur whenever there is a concentration gradient. Moreover, suitable separator materials can be difficult to source and, in practice, separators/membranes always behave imperfectly as well as complicating cell design.

An absolute necessity for a paper proposing a laboratory synthesis is a detailed description of the method, especially the electrolysis equipment. This must include a full description of the cell design, cell dimensions, electrodes (materials, pre-treatment, geometry, position and dimensions), separator if used, solution volumes, concentration of both reactant and electrolyte, temperature, mass transfer regime and cell current as well as product isolation and characterisation. Defining the mass transfer regime in a stirred solution will require a statement of rotation rate and position and shape of the stirrer while in a flow cell, the flow rate, channel dimensions, solution inlet and outlet design and presence/design of turbulence promoters must be stated. Without such detailed information, a synthesis cannot be successfully transferred from one laboratory to another.

4. Commercial production

While electrolysis has been used for the hydrodimerisation of acrylonitrile to adiponitrile on a scale of > 100,000 tons/year [9], the market for most organic compounds is much smaller. In the pharmaceutical, agrochemical, food and fine chemicals industries the required scale of production is more likely to be in the range 1–100 kg/day. This will require cell currents in the range 20–5000 A and electrode areas in the range 200 cm^2–50 m^2. The most likely cell design is a parallel plate, flow electrolyser [9] although other designs, e.g. the BASF bipolar disc stack cell [9,27,29–31] have been used commercially. The lower scale is achievable with a single pair of electrodes in a parallel plate flow cell while the upper scale can be achieved with a number of such cells in a stack [9].

There are several drivers for the development of industrial electroorganic processes. These include (a) to lower the cost of the product (b) to reduce the number of steps in a multistep synthesis and (c) to reduce the hazards associated with its production. The latter implies the displacement of toxic/hazardous reagents including many organic solvents, the avoidance of spent reagent effluent streams and operation at ambient temperatures/pressures. Also, another possible outcome of introducing an electrolytic process is a reduction in the quantity of byproducts for disposal. Recycle of solvents and/or electrolytes will be an advantage.

Clearly, an essential for the development of a new industrial process is the prospect of a profit. The product must have a stable or expanding market and be saleable at a price significantly higher than the reactant. The reactant must also be readily available. Selectivity and a high conversion (although not necessarily in a single pass of the reactant solution through the cell) as well as a facile procedure for the isolation of pure product remain important. Indeed, the electrolysis conditions are often strongly influenced by the need to match those needed for the product isolation procedure. For example, an electrolyte with specific properties (e.g. readily extracted or distillable) can be chosen. Processes may be operated in batches when a complete conversion of reactant to

desired product will be advantageous or continuously where a fraction of the reservoir solution is continuously removed for product isolation. A complete conversion can be achieved in a single pass by using a three dimensional electrode or a cell with an extended channel length or in a recycle system by extending the electrolysis time preferably with a programmed decrease in cell current as the reactant concentration drops.

Experience (or a Faraday's law calculation) shows that the electricity consumption will be well below the level when its cost is critical to process economics. More likely, the investment cost for the electrolysis cell(s) is dominant. Since the size/number of cells is determined by the current density, a goal must be to operate in conditions where the current density is as high as possible, ideally above or close to 100 mA cm^{-2}. In addition, it is advisable to avoid expensive electrode materials and separators; platinum is a non-starter and carbon, lead and steel electrodes are attractive. Undivided cells not only avoid a separator but also reduce the number of cell components and auxiliary equipment (e.g. pumps and pipework). Stable operation of the technology over an extended period (preferably months) without replacement of electrodes or separators is essential. Electrodes are prone to corrosion and erosion and their stability is always an issue to be addressed.

While the development of a commercial process is likely to follow a successful laboratory synthesis, a successful laboratory synthesis cannot always be scaled up; different challenges are met. Hence, laboratory synthesis and industrial electrolysis should be regarded as related but separate activities. Inevitably, the cell technology will be different. It is particularly advantageous in the development of industrial processes to select cells that are available on the open market and will scale to the dimensions essential for the demand of the product. Again, parallel plate cell designs most easily meet these demands. As soon as possible, process trials should be carried out in the selected cell. The design of a new process is an opportunity to design a new total package from reactant to product and to re-examine the choice of solvent, electrolyte, electrode materials etc. and also to seek to combine unit processes. The form of reactant available and that desired for the product (pure or a solution suitable for further chemistry) will be known, as will their properties. Stability of performance is essential (and stability of electrodes and other cell components are issue that must be addressed) and combining unit processes will be highly desirable.

In selecting reactions for development, the emphasis should be on (a) conversions with a significant increase in value (b) products with stable and perhaps expanding markets and (c) products currently manufactured by a technology with significant drawbacks, e.g. based on toxic/hazardous reagents or generating substantial byproduct streams. Too often in the past, targets have been selected predominantly on the basis of difficulty in finding redox reagents and conditions suitable for a highly selective conversion; if a reaction is impossible with chemical reagents, it is unlikely to be highly selective at an electrode.

5. Conclusions

While many electrochemical oxidations and reductions of organic molecules have been reported, only a few papers can claim to report a "synthesis". Commonly, authors are satisfied to demonstrate the formation of some product (often still in the electrolysis solution) without moving on to demonstrating the isolation of a useful quantity of pure product.

A "synthesis" is a plea to other chemists to prepare the product by the procedure described. This necessitates a detailed description of all steps. When the procedure involves electrolysis, a detailed description of the cell used is essential; the design of cell, both geometry and dimensions, influences reaction performance at least as much as electrode material and solution conditions but is largely overlooked for systematic study in the literature. A statement of cell type and electrode

materials is insufficient; a full definition of the electrolysis cell and operating conditions will include the cell type, cell dimensions, electrodes (materials, pre-treatment, geometry and dimensions), solution volumes, concentration of both reactant and electrolyte, temperature, as well as the cell current and all parameters determining the mass transfer regime (rotation rate and position of stirrer or flow rate, cell inlet and outlet design, presence of turbulence promoters). Papers also need to highlight the ways in which the electrosynthesis is advantageous compared to competing procedures.

Unfortunately, the "synthesis" will be suited only to a particular rate of product formation. Increasing the quantity of product by increasing the cell size, concentration of reactor or electrolysis time will have only a limited impact. A major increase in quantity of product will require a redesign of the electrolysis cell and operating conditions.

It would be very helpful if all papers reporting electrolyses of organic compounds had a clear vision as to the purposes of the electrolyses. If the goal is a "synthesis" then it should describe the preparation of a significant quantity of product and include a full and detailed description including the cell and electrolysis conditions. The future of electrosynthesis would be much enhanced by the publication of more papers directly targeting the needs and interests of organic chemists and a more critical assessment of the existing literature. Authors of books/reviews need to be clear as to which papers truly report a 'synthesis'.

Conflict of interest statement

The author declares no conflict of interest.

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