THE UNIVERSITY OF HULL

Electroorganic Synthesis in Microreactors

being a thesis submitted for the degree of

Doctor of Philosophy

in the University of Hull

by

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April 2009

PAGE NUMBERING AS ORIGINAL

DECLARATION

The work described in this thesis was carried out in the Department of Chemistry, The University of Hull under the supervision of Dr Paul Watts and Prof. S. J. Haswell between September 2003 and August 2007. Except where indicated by references, this work is original and has not been submitted for any other degree.

Tamsila Nayyar Aziz

March 2009

Acknowledgements

I would like to thank my supervisors Dr Paul Watts and Stephen Haswell, for their support, guidance and encouragement during the course of this work. I would also like to thank John Whittall at Crystal Faraday for his valuable support and helpful discussions.

Special thanks to Dr Charlotte Wiles and Dr Ping He for their support and useful discussions throughout this work. I also wish to thank Mike Bailey at Hull University Glass blower workshop for making the required electrochemical glass flow cells, used in this project. I would also like to acknowledge the EPSRC for fully funding this research program.

I would like to thank my parents (late) and family for their prayers and support. Finally, I would like to thank my Husband Nayyar and my children Maaz, Moez and Hira, who stood by my side and have been a great source of support and encouragement over the last three years.

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Abbreviations

Some abbreviations that are commonly used in this work are listed below:

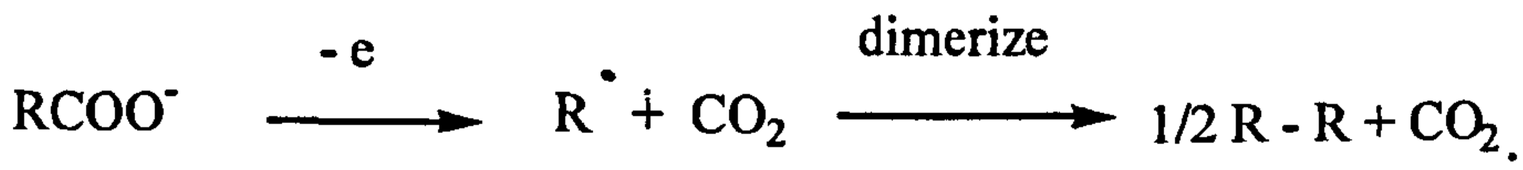
DCM	-	dichloromethane
DMF	-	1,2-dimethylformamid
DMSO	-	1,2-dimethylsulfoxide
TLC	-	thin layer chromatography
GC	-	gas chromatography
MS	-	mass spectrometry
CV	-	cyclic voltammetry
FID	-	flame ionized detector
DISP	-	Disproportionation
TB	-	NBu_4BF_4
PTFE	-	polytetrafluoroethylene (Teflon)
PEEK	-	polyetherether-Ketone
SMB	-	simulated miving bed technology
PEM	-	Polymer electrolyte membrane
Boc	-	t-butoxycarbonyl
Cbz	-	benzyloxycarbonyl
Pt	-	platinum

Abstract

At present, description of applications, using electrochemical micro reactor are rare. Such techniques are extremely desirable to pharmaceutical companies who are interested in the high throughput synthesis of combinatorial libraries for pharmaceutical evaluation. Furthermore, techniques such as electrochemical synthesis may be used to prepare chemicals, which are difficult to prepare by conventional techniques.

The main aim of this research project was to identify any unique control, over electrochemical organic synthesis, that micro reactors offer, and the modification of methods to gain chemical and practical advantages. These advantages come from the close control that exists between flow, concentration and thermal properties with a diffusion limited small volume system.

The project involved investigation of certain factors, such as concentration of reacting species, the current limitations, and process flexibility of electro organic synthesis, in micro reactors. To investigate these factors, a versatile reaction for organic synthesis Kolbe electrolysis is selected, without using an electrolyte, in order to benefit from the quick separation and purification of products. The anodic oxidation of carboxylic acids produces alkanes by dimerization of the radicals generated at the anode. (Scheme a)



Scheme a. Kolbe electrolysis

To investigate this reaction, in a micro reactor environment, several batch cell/ flow system arrangements were employed in order to achieve the optimum yields. Once a set of conditions giving optimum yield is established, the system will be applicable to the electrochemical synthesis, and to develop novel methods to optimize various reactions and prepare reactive intermediates *in situ*.

CHAPTER 1: INTRODUCTION

1.1.0 Electrochemistry

Electrochemistry plays a significant role in a number of research areas in chemistry and this is basically a consequence of a unique combination of the different features of electrochemical reactions. Electrochemical reactions for example, by the application of a potential, can overcome kinetic limitations even at very low temperatures and can be chemically and stereo chemically specific. This in turn leads to its applications in the area of chemical synthesis. Whilst being highly sensitive even to extremely small amounts of reactants, electrochemistry leads a number of analytical applications.

Early electrochemistry started in 1786 when Luigi Galvani,[1] who was an anatomist / physiologist, discovered electricity in animal muscles, and named it animal electricity. Later Alessandro Volta,[2] in 1794 invented the first practical battery "the voltaic pile", by using the potential difference between two metals. Humphry Davy,[3] in 1800 developed a much more powerful battery by improving the design of the voltaic pile. He also discovered elements such as K, Na, Sr, Ba, Ca and Mg by electrochemical methods. The discovery of the laws of electrolysis, including the proportionality between the mass of product deposited and the current passed during electrolysis, was a big achievement, made by Michael Faraday[4] between 1833-1836.

At the beginning of the twentieth century, electrochemistry was mainly dominated by studies of the transport of charged species and thermodynamic considerations. With the pioneering work, carried out by Butler, Volmer, Gerischer, Marcus and others,[5] kinetic aspects of electrochemistry have become more important in electrochemical research since the middle of the twentieth century with an increased understanding of the chemical and electronic structure of the solid/solution interface. These studies have been accelerated by the application of numerous *in-situ* and *ex-situ* spectroscopic techniques, which have been combined with electrochemical experiments over the last thirty years. More recently the introduction of *in-situ* scanning probe techniques has allowed researchers to follow electrochemical reactions at an atomic or molecular scale.

Based on theoretical and experimental results, as well as methods gathered by electrochemists for many decades, electrochemistry is now used in many fundamental fields, such as the study of new organic and inorganic compounds and biological systems. In more applied areas, it is used to shape materials from the macroscopic to the microscopic scale, to accurately analyse for chemical impurities, to understand and prevent the corrosion of materials at low and extremely high temperatures, to probe the function of living cells, and to convert chemical energy into electricity.

1.1.1 Synthetic Electrochemistry[6]

Electrochemical methods are currently used as a tool for important organic transformations (mostly industrial, such as reductive dimerization of acrylonitrile, hydrogenation of heterocycles, pinacolization, reduction of nitro aromatics, the Kolbe reaction, Simons fluorination, methoxylation, epoxidation of olefins, oxidation of aromatic hydrocarbons etc), however the use of electrochemical methods in complex organic synthesis remains much more rare. Synthetic electrochemistry however, is an expanding area of interest within the synthetic community, although it is still far from being a routine technique. Electrochemical reactions can be classified as either oxidations or reductions with the reaction being comprised of the electroactive substrates, electrodes, electrolyte, solvents and various additives. In a typical galvanic cell (two electrodes are connected by a salt bridge composed of a solution of an electrolyte), oxidations take place at the anode and reductions take place at the cathode. The primary event is the transfer of electrons from the electrode to the substrate (reduction), or from the substrate to the electrode (oxidation). The characteristic of an electrochemical reaction that makes it unique from many other reactions is that these reactions take place at the surface of the electrode and produce many highly reactive intermediates such as radical-cations (*via* oxidation) and radical-anions (*via* reduction). The electron transfer may occur before or after a chemical step (*e.g.* pre protonation of ketones). In short, these reactions can be denoted by the type of "mechanisms" involving the array of electrochemical (E) and chemical (C) steps in the proper sequence, *e.g.* EC, ECE, CEC, *etc.* Thus electrosynthesis can be considered as multi disciplinary subject and comprises an important category of reactions from cathodic or anodic reactions (when one can be synthetically useful) to

paired reactions (when both electrodes concert a synthetically useful result), whether it's the transformation of functional groups, *e.g.* $RNO_2 \rightarrow RNH_2$ and $RCH_2OH \rightarrow RCHO$, or the conversion of the nucleophillic $\leftrightarrow$ electrophillic character of the substrate. Indeed the scope of organic electrochemical synthesis has now become so wide that it has successfully adopted synthetically important reactions like coupling, cyclization, addition, cleavage, substitution, elimination, electrocatalysis, photoelectrochemistry and indirect electrolysis generating and utilising anion radicals, carbanions, dicarbanions, cation radicals, cations, dications, radicals, acids/electrophiles and bases/nucleophiles.

Electrolysis takes place in an electrochemical reactor, referred to as the cell. The term cell is used to describe any set up that consists of an electroactive species, solvent, electrolyte and at least two electrodes. The ability to choose a given potential or current to affect selective oxidation or reduction is another characteristic feature of electrochemical processes that makes them unique. There are two basic choices for the construction of the electrochemical reactors, a divided and an undivided cell. Typically, undivided cells are used for constant current experiments and divided cells for constant potential experiments. For any electrochemical reaction taking place within a cell, the potential (V) of the cell is given by Ohm's Law, (Equation 1)

$$V = IR \qquad (1)$$

Where I, is the current and R is the resistance of the cell, given in Ohms (Ω). The resistance of the cell is directly related to the concentration of the electrolytes / electroactive species in solution. As the concentration of the electroactive species decreases, the resistance increases. This accounts for a drop in current during a constant potential experiment. Similarly for a constant current experiment, as the resistance increases, the potential also increases. According to Faraday's laws, the amount of substance produced or consumed in electrolysis is proportional to the amount of electricity that passes through the cell. The electrical charge on one mole of electrons is called Faraday's constant (F) and generally expressed in Coulombs per mole of electrons (96485 Coulombs/mole of electrons). Faraday's Law (Equation 2) is one of the fundamental laws of electrochemistry, it relates the charge (Q) passed in an

electrochemical experiment to the number of electrons (n) transferred per molecule of the number of moles of the analyte electrolysed (N).

$$Q = nFN \qquad (2)$$

The differential form of this Law (Equation 3) is

$$dQ/dt = I = nF.\ dN/dt \quad (3)$$

according to which, the current is directly proportional to the rate of electrolysis. An electrode reaction always occurs in several series and parallel elementary reaction steps. Even in the simplest case there are three steps involved, these are discussed in detail below.

1.1.2 Electrode Reactions[7]

Electrode reactions are heterogeneous reactions occurring at the electrolyte-electrode interface, making them more complex than a typical thermal reaction (Figure 1). The rate at which the electrons are transferred between the electrode surface and molecules in the interfacial region is influenced by the relative values of the applied potentials and the standard redox-potential. Most importantly, once the molecules in the interfacial region have been electrolysed, they need to be transported from the electrode surface to the bulk of the solution and vice versa in order to continue the electrolysis. The electron transfer step occurs at the interface. The purely chemical reactions may precede or follow these steps. The current also critically depends on the rate of mass transport between the interfacial region and the bulk solution. In the majority of electrochemical experiments, it is the mass transport to the electrode surface that is considered rate determining and not the electron transfer process. For some experiments the mass transport behaviour continuously changes over time, with changing concentration gradient at a given potential:

1. The reactant must be transported to the electrode surface from the bulk of the electrolyte usually predominantly by diffusion and/or electromigration.

2. Then there should be a charge transfer reaction.

3. Finally the product must be transported from the electrode surfaces to the bulk of the electrolyte solution.

For a steady state, after an initial change, the rate of charge transfer should be equal to the rate of mass transport. Many electrode reactions can proceed either as oxidation or as reduction, depending on the direction of the current flowing through the electrode/electrolyte interface, where E, E' is substrate and P, P' is product. Circles indicate adsorbed molecules.

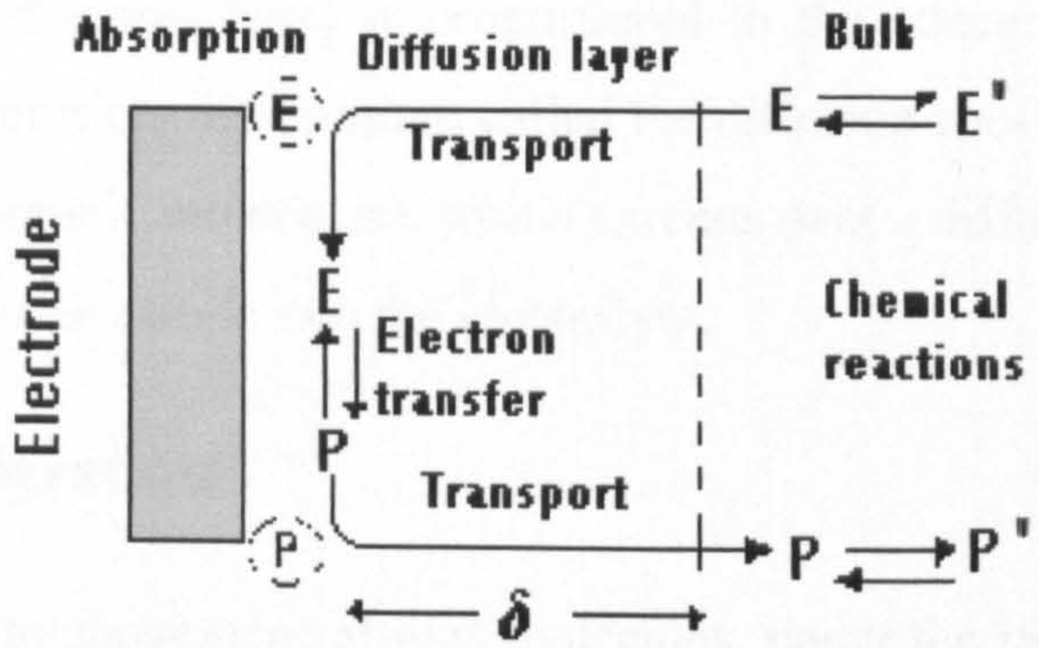


Figure 1 Steps involved in a typical organic electrode reaction

1.1.3 Mass Transport[7]

Three types of mass transport are important at an electrode surface and these are discussed below.

1.1.3.1 Diffusion

Diffusion in solutions is the most important phenomenon in electrochemistry. It is defined as the movement of chemical species (ions or molecules), under the influence of a concentration gradient. The species move from the area of higher concentration to the area of lower concentration, until the concentration is uniform in the whole phase. The rate of diffusion (diffusional flux) is proportional to the concentration gradient in the solution, and the proportionality constant called the diffusion coefficient, D (typical value $10^{-5}cm^2/s$ for small organic molecules), which extends over a diffusion layer (thickness δ) that develops from the electrode into the electrolyte.

1.1.3.2 Electromigration

Electromigration is the movement of ions/molecules, under the influence of an electrical potential difference. In most experiments the concentration of supporting electrolyte ions is much higher (100-1000) than that of other ions, suppressing the migration of the latter. Migration dominates in the regions of low electrolyte concentration and at modified electrode surfaces.

1.1.3.3 Convection

Convection is the molecular motion imposed by the bulk motion of the medium, *e.g.* vibrations or stirring/hydrodynamic transport. Convection can be natural (due to thermal effects or density gradients) .or forced (mass transport mode in hydrodynamic techniques). Nevertheless a diffusion layer characteristically develops close to the electrode surface.

1.1.4 Charge Transfer[7]

The electron transfer (ET) at the interface between the electrode and electrolyte is very important for an electrode reaction (Figure 2). Electrons pass through the interface and an electric current *I*, is observed. The transfer of an electron to R (reduction) or from the substrate A (oxidation) is an activated process, characterized by a rate constant k_s, defined as the standard (or formal) potential E^0, and the transfer coefficient α.

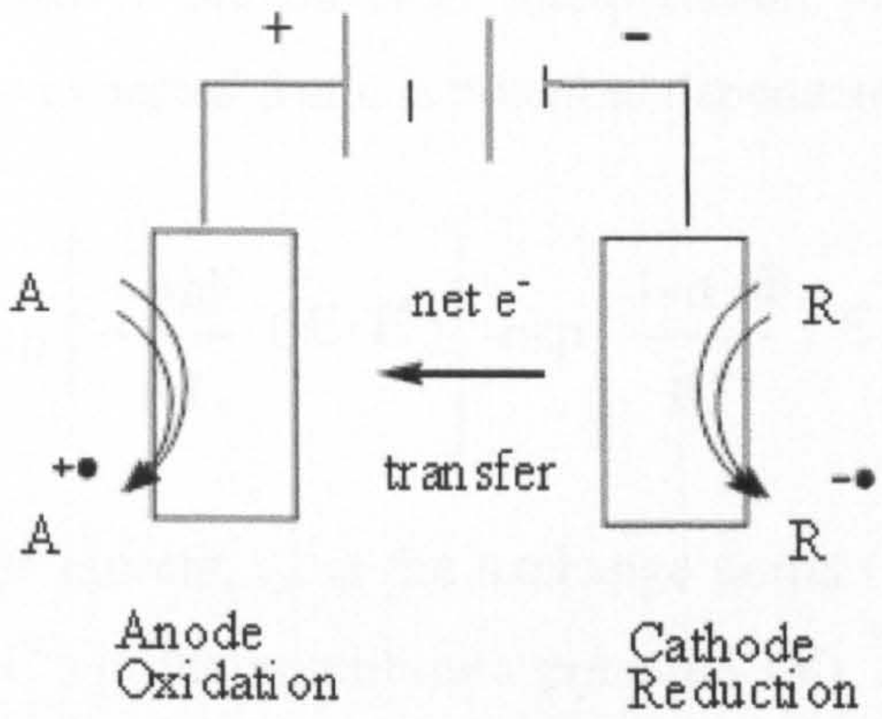


Figure 2 Flow of electrons (current) to drive oxidation/reduction

The three conditions regarding the electron transfer can be easily distinguished and are outlined below.

1.1.4.1 Reversible Reactions[7]

When the electron transfer is much faster than transport (transport control) and the electrochemical equilibrium is attained at all times at the surface of electrodes and defined by the electrode potential *E*, the concentrations of oxidized (C_{ox}) and reduced (C_{red}) forms of the redox couple follow the Nernst equation (4). For a reversible ET, where n = number of electrons transferred, F = Faraday constant, R = gas constant, T = temperature, the current is proportional to the amount of material transported to the electrode in a unit time.

$$\frac{C_{ox}}{C_{red}} = \exp\left[\frac{nF}{RT}(E - E^0)\right] \qquad (4)$$

1.1.4.2. Irreversible Reactions[7]

When electron transfer is much slower than transport (ET control), the current follows the Butler-Volmer equation (5), where i_0 defines the exchange current at E-E^0 for an irreversible reaction. However the physical interpretation of α is related to the ET transition state.[8] It is also expected that α is potential dependant.[9,10]

$$I = A.i_0\left\{\exp\left[\frac{-\alpha nF}{RT}(E-E^0)\right] - \exp\left[\frac{1-\alpha\, nF}{RT}(E-E^0)\right]\right\} \qquad (5)$$

Where I, is the electrode current, i_o, is the exchange current density (A/m^2), E, is the electrode potential (V), E^0, is the equilibrium potential (V), A, is the electrode active surface area (m^2), T, is the absolute temperature (K), n, is the number of electrons involved in the electrode reaction, F, is the Faraday constant, R, is the universal gas constant, α, is the so-called symmetry factor, dimensionless.

1.1.4.3. Quasi Reversible Reactions[7]

For a reaction where electron transfer and transport have comparable rates in a mixed control situation, an electrode reaction can correspond to either of these situations under particular experimental conditions, especially under the external control of mass transfer.

1.1.5 Chemical Kinetics[7]

Electrode reactions involve chemical reaction steps, which can be described by the usual chemical kinetic equations, such as first order and second order reactions, and may be chemically reversible or irreversible. These are often assumed to occur in homogeneous solutions, and not at the electrode surface. The chemical steps may precede (the electroactive species is formed in a pre-equilibrium) or follow the transport and ET processes (a reactive species is formed as a result of ET and undergoes a chemical

transformation to a stable product).

1.1.6 Adsorption[7]

The electrode process becomes even more complex by the involvement of specific attractive interactions of molecules with the electrode surface, a phenomenon called adsorption. Figure 3 explains the formation of a charged double layer at the solid liquid interface, which originates from the surface of the electrode extending towards the bulk of the solution. The strength of these interactions is determined by the intensity of these attractions making them weak (physisorption) to strong (adsorbate chemically bonded to the surface of electrodes). The adsorption of intermediates at the electrode surface has been discussed for the Kolbe electrolysis of carboxylates.[11,12] The choice of the electrode material can be very critical in designing a successful process because the reactions exclusively occur at the surface of electrode and not in the bulk solution.[13-16] When a positive charge is applied, a strong electrical field is generated at the surface of the anode from the high concentration of negatively charged ions being attracted to the positively charged electrode. These negatively charged ions, in turn, attract more positively charged ions from the solution and form another electrical field towards the solution side, which is significantly weaker, since the anode compensates for most of the field generated by the negative ions. This process is repeated throughout the solution and as the charged layers progress further and further away from the electrodes, the effective potential of the field diminishes. The innermost layer (the distance from electrode to x_1) is termed as the compact inner layer and is only a few Angstroms wide. The potential of this layer decreases linearly with the increasing distance from the electrode. As a result, at the end of the compact layer, or outer Helmholtz plane, most of the potential difference between the electrode and the solution is lost. Once x_1 is reached, the potential drops exponentially through the diffuse layer (x_1 to x_2). This diffuse layer can be anywhere from a few tens to hundreds of Angstroms away from the surface of electrode. Both the compact layer and the diffuse layer constitute the electrical double layer. Once the outermost region of the diffuse layer is reached, the potential is identical to the bulk of the solution. It is generally accepted that the oxidation/reduction of an electroactive species takes place at the electrode surface in the compact inner layer. Cyclization reactions are known to be

kinetically faster than diffusion through the inner layer.[13-16] This is the reason that highly reactive radical cations and radical anions can be generated in the presence of nucleophillic and protic solvents.

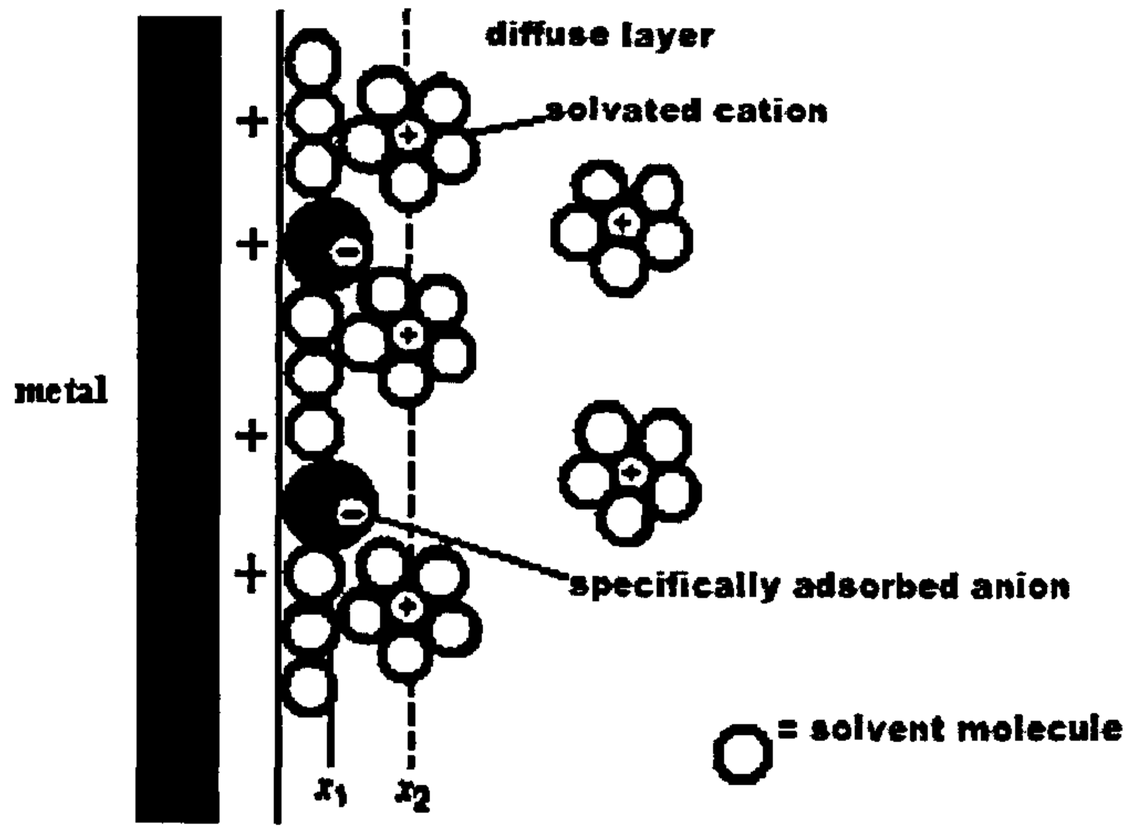


Figure 3 Double layer region where anions are specifically adsorbed

1.1.7 Organic Electrode Reaction Mechanism[17]

By connecting an electrode to an external power supply, one can electrically control the electrochemical potential of electrons in the electrode, thereby perturbing the equilibrium and driving a reaction. Applying a negative potential to an electrode increases the energy level E_f of electrons. Increasing the electrons energy above the lowest unoccupied molecular orbital (LUMO) of a species in the adjacent electrolyte will cause reduction of that species (Figure 4). This reduction current (flow of electrons into the electrode and from there into the reactant) is also called a cathodic current, and the electrode at which it occurs is called the cathode. Conversely, applying a positive potential to an electrode decreases the energy of electrons, causing electrons to be transferred from the highest occupied molecular orbital (HOMO) of reactants to the electrode. The electrode where such an oxidation reaction is occurring is called the anode. Thus, applying a positive potential relative to the equilibrium potential of the electrode will drive the reaction in the anodic direction; that is, electrons will be removed from the reactants. Applying a

negative potential relative to the equilibrium potential will drive the reaction in the cathodic direction. Anodic currents are defined as positive (flow of positive charges into the solution from the electrode) while cathodic currents are negative.

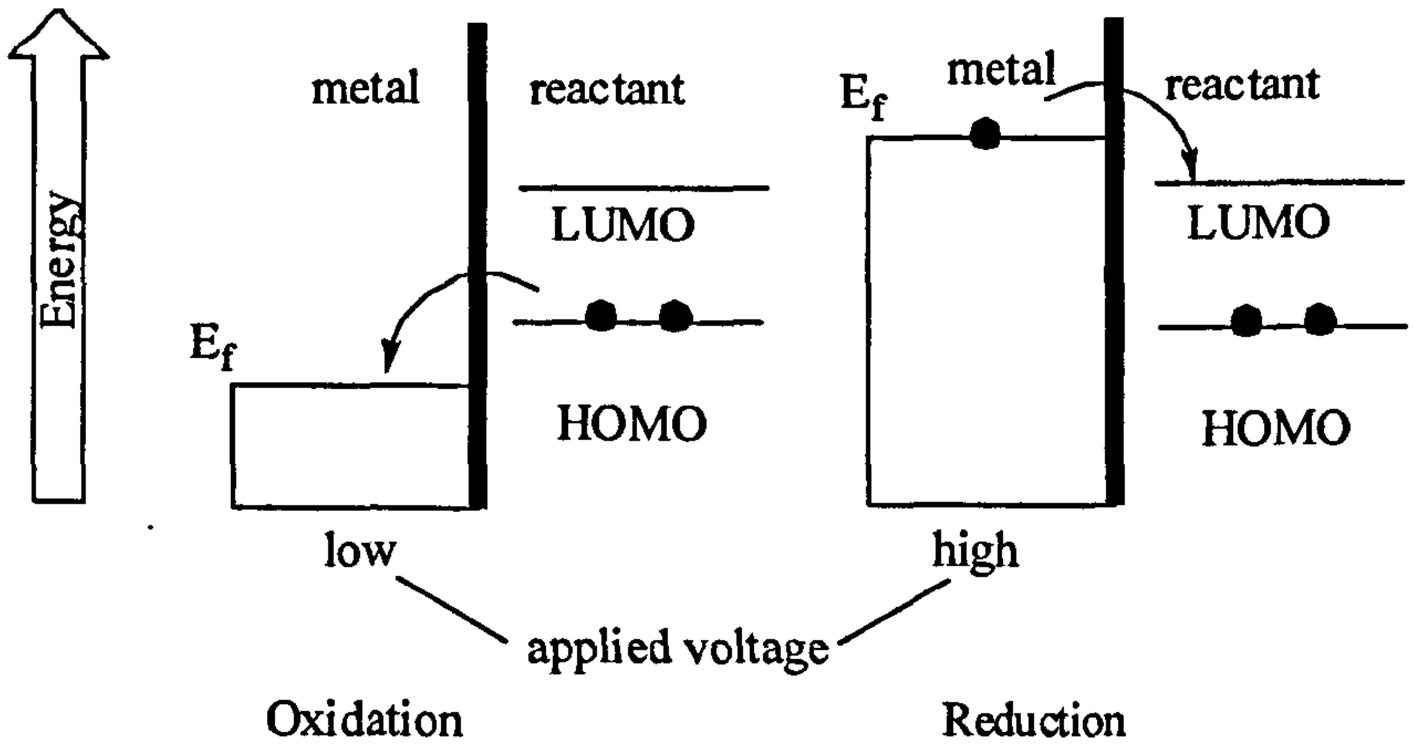
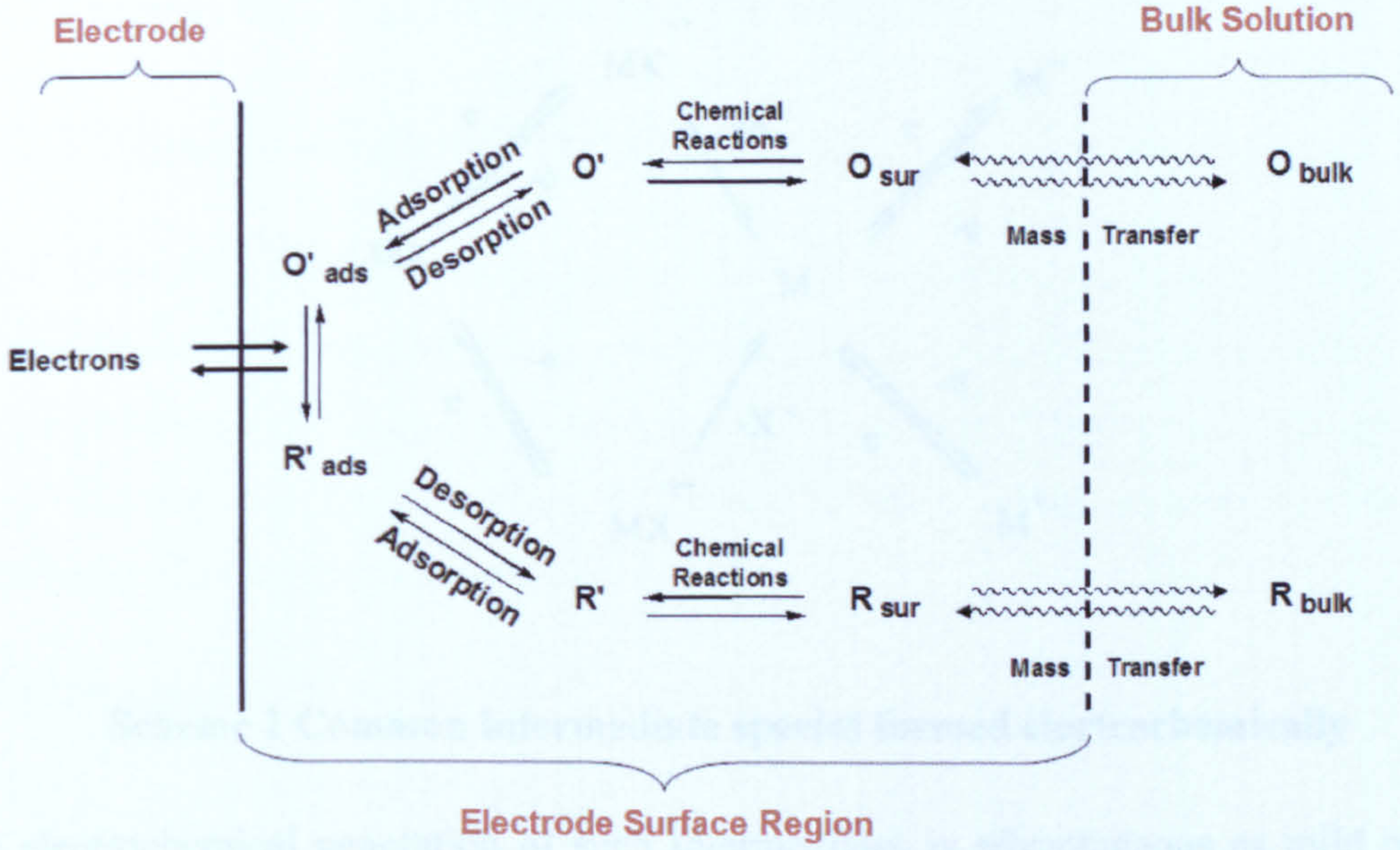


Figure 4 Varying the applied potential changes the oxidizing/reducing ability of the electrode

1.1.7.1 Electron Transfer Initiated Chemistry

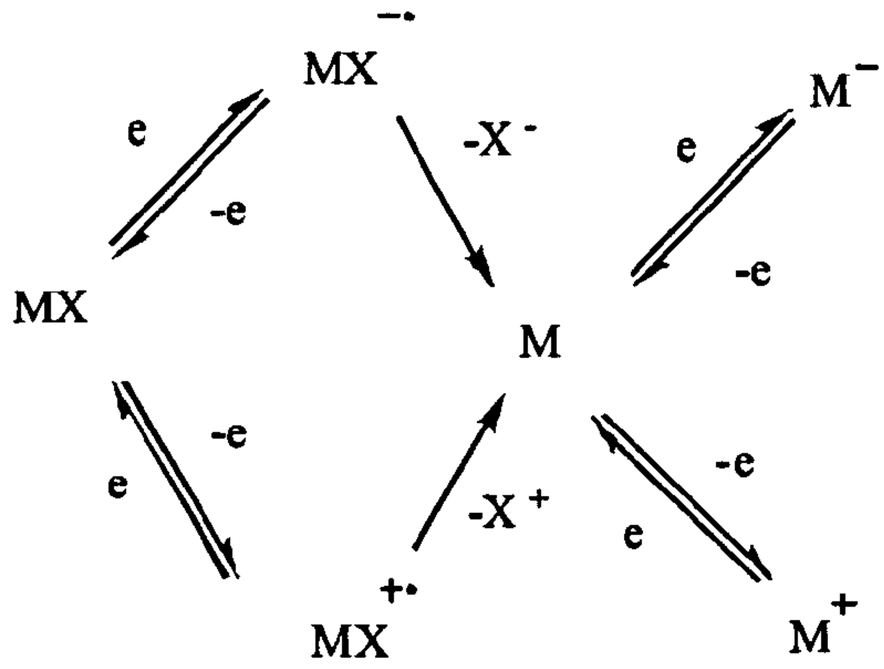
The majority of organic electrode reactions are characterized by the generation of a reactive intermediate at the electrode surface by ET and subsequent reactions typical of that species. Therefore the oxidation or reduction step infact initiates the follow-up chemistry to generate the required product.[18] Figure 5 describes the process, which occurs in simple electrode reactions. In the case of reduction, a species (O) capable of accepting an electron, diffuses to the surface of the electrode, receives an electron and diffuses away from the surface as (R). Current is generated at the surface by the transfer of electrons from the electrode to the redox species. In the solution the current is carried by the migration of ions.



where O, O' are reduced and R, R'are oxidised

Figure 5 Electrochemical system that includes electron transfer along with its equivalent circuit.

The electron deficient species such as carbocations (M^+), unpaired electrons such as radicals ($M^{\bullet}$) and radical ions ($M^{\bullet -}$ and $M^{\bullet +}$), electron rich species such as carbanions (M^-) or those of unusual oxidation states such as metal complexes with low-or high-valent central atoms are produced at the electrode. Radical ions are usually the first-formed species but fragmentation can lead typically to radicals, which may be further reduced or oxidized as illustrated in Scheme 1.[19]



Scheme 1 Common intermediate species formed electrochemically

The electrochemical generation of such intermediates is advantageous as mild reaction conditions are employed (*i.e.* room temperature; strong acids or bases are not necessary) and also additional selectivity can be introduced in the controlled–potential experiments. Electron transfer also brings about *umpolung*; electron rich compounds are oxidized to electron-deficient species (electrophiles) and reduction of electron-poor compounds gives nucleophiles. The chemical behaviour of these species is as expected, radical anions may be nucleophillic and basic, radical cations can be electrophillic and both can react to give coupling reactions.[19] Thus, the reaction mechanism of organic electrochemical reactions involves at least one ET step at the electrode as well as preceding (EC) and follow-up (CE) bond making and bond breaking, or structural rearrangement steps. These chemical steps can be concerted with the electron transfer process.[20,21]

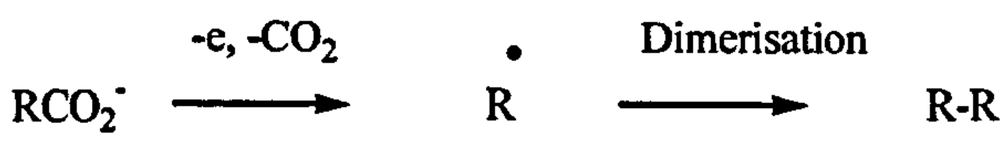
Electron transfers at the surface of electrodes, are usually denoted by "E", whereas, the chemical steps not involving the electrodes are simply denoted by "C". The ET may further be classified as "E_r","E_{qr}"or "E_i" for reversible, quasi-reversible and irreversible reactions, where it is usually not clear how transport occurs. In the case of the C-step being a dimerisation, the symbol "D" is commonly used, and for an "ET" between two species in a (homogeneous) solution, is denoted by "SET" (single electron transfer), or ECE or "DISP" for second electron transfer at the electrode.

1.1.7.2 Common Electrochemical Conversions[19]

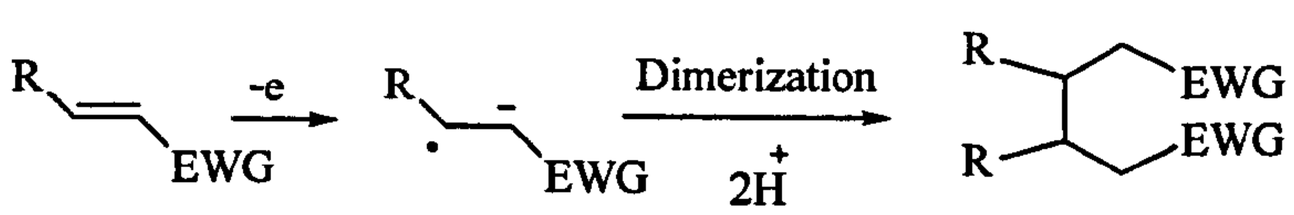
1.1.7.2.1 Carbon-Carbon Bond Formation

Kolbe electrolysis and hydrodimerization are well-established processes, which operate under relatively mild conditions and give a comparatively simple one-step carbon-carbon bond formation, difficult to match with any other process (Scheme 2). These reactions, along with the coupling reactions of alkenes to some extent have been extensively exploited in the recent developments.

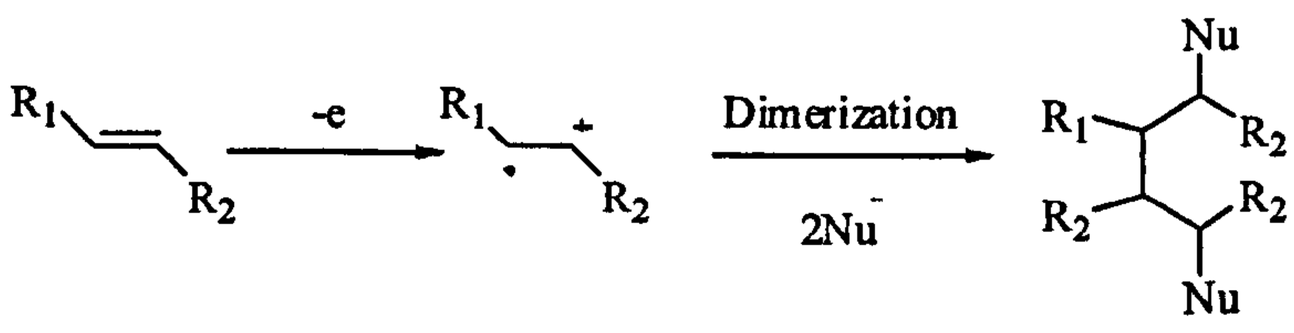
Kolbe Reaction (a)



Electrodimerization (b)



Anodic Coupling (c)



Scheme 2 (a), (b) and (c) Coupling of electrogenerated radicals and radical ions

The carbon radicals generated by the anodic oxidation of carboxylate ions by Kolbe electrolysis are known to be free, but probably, because of higher local concentrations at the electrode surface, the coupling reaction always dominates. These carbon-centred radicals are very reactive and can be added to the double bonds either inter- or intra-molecularly. The details of some examples of this reaction are discussed later in section 1.5.0.

Electrohydrodimerization (EHD) of alkenes, activated by the electron withdrawing groups is a typical example of cathodic reduction. The reaction totally depends upon the rapid combination of delocalised anion radicals, and must be formed under conditions of minimum competing protonation *i.e.* hydrogenation of the double bond. Therefore, alkenes activated by the electron withdrawing groups, such as COOR, COR, CN, NO_2, C=NR, will undergo EHD. One of the examples is the production of adiponitrile by the cathodic reduction of acrylonitrile (the Monsanto process) discussed in section 1.5.0.

1.1.8 Important Events at an Electrode[7]

1.1.8.1 Current-Potential-Time Relationship

The equations (4) and (5) given in sections 1.1.4.1 and 1.1.4.2 involve the most important quantities, current *i*, time *t* and potential *E*, in order to understand the reaction mechanism at the electrode. Most of the electroorganic techniques involve the determination of *I,* or *E* as a function of time, *t* (while the other one is kept constant) or as a function of each other (while one is varied with *t* in a defined manner). Similar *I-E-t* relationships are derived theoretically from the basic equations on the basis of hypothesis for the concerned reaction mechanism and the theoretical and experimental results are compared. This way the hypothesis can be proved or disproved to be consistent with the events taking place at the electrode.

1.1.8.2 Concentration Profile

The electrical current through the electrode is proportional to the flux of redox-active material to the surface, which, in turn is related to the concentrations '*c*' of various species near the interface.

1.1.9 Methods of Mechanistic Electroorganic Chemistry[13c]

The electrochemical methods can be classified on the basis of the quantity that can be controlled in the reaction, that is, current or potential. These are detailed below:

1.1.9.1 Controlled Current Electrolysis (Galvanostatic)[13c]

The first method is referred to as a 'constant current' reaction. In a constant current reaction, the flow of current through the electrochemical cell is held at a constant value while the potentials of the electrodes are allowed to vary. Once the current for the reaction is set, the potential of the anode climbs until it reaches a value sufficient for oxidizing the species in solution with the lowest oxidation potential. The potential then stabilizes and the species in solution is oxidised at a rate consistent with the current flow required by the cell. When the first reactive species is consumed, the potential of the electrode climbs until a second species with a higher oxidation potential is found. The potential of the electrode then stabilizes at this second potential and the rate of oxidation of the second species proceeds in a fashion consistent with the current flow set for the cell. This process repeats until either the solvent is oxidized or the current is turned off. At the cathode, an equivalent reduction process takes place. The advantage of a constant current reaction is that the reaction set up is very simple, and for this reason constant current reactions are very common. The disadvantage is that the selectivity of the initial oxidation reaction decreases as the first substrate is consumed and the potential at the electrode begins to climb. In many cases, the lack of selectivity associated with a constant current reaction is not a problem. For example, if no other electroactive species exists in solution and the reaction product oxidizes at a potential much greater than that of the starting material, then constant current reactions can be pushed to greater than 90% completion. Even in cases where selectivity is an issue, constant current reactions can often be run to a greater than 60% conversion without interference from the competing processes. As mentioned above, the potential at an electrode in a constant current reaction remains constant so long as sufficient starting material is present to satisfy the demands of the preset current. While this condition holds, the selectivity of the initial reaction is not lost.

1.1.9.2 Controlled Potential Electrolysis (Potentiostatic)[13c]

The second method is used for the type of reactions where selectivity is an issue. For a 'controlled potential' reaction, a reference electrode is added to the reaction and the potential of the working electrode (the electrode at which the desired reaction occurs) is held constant relative to the reference electrode. For an anodic reaction, these conditions ensure the oxidation of the substrates having an oxidation potential equal to or lower than that set for the anode. The reactions are selective, since the potential of the electrode cannot climb as the substrate is consumed and the selectivity is maintained for the entire course of the reaction. However the drawback of this process is that when the concentration of the initial substrate drops the current for the reaction also decreases. For this reason, the controlled potential reactions are time consuming to push the reaction to completion. In addition these reactions also require a third electrode and a potentiostat to control the potential of the working electrode relative to the reference electrode, which leads to a more complicated reaction set up.

1.1.9.3 Exhaustive Electrolysis[7]

For a typical exhaustive electrolysis the electrodes used, have a comparatively large surface area, and the electrolyte is constantly stirred to increase the mass transport. Exhaustive electrolysis can be performed under both controlled potential or controlled current mode.

In a potentiostatic exhaustive electrolysis, the potential of the working electrode is constant throughout the experiment. The substrate is transported by convection and diffusion to the working electrode surface. The current decreases with the bulk concentration of the substrate, if no further electron transfer occurs. The charge transferred is expressed by (Equation 6)

$$Q = \int_{0}^{t_{end}} it \, . \, dt \qquad (6)$$

where t_{end} denotes the time when the experiment is stopped. A unique stopping criteria which is quite frequent is the remaining current, for example 1% of the initial *i*. One

could also test for disappearance of the substrate or some intermediate, *in situ* or in samples taken from the reaction mixture. The duration of a potentiostatic electrolysis is much larger than a transient experiment. Q can be related to the amount *m* of substrate (with molecular mass *M*) consumed. From Faraday's first Law Equation 2 ($Q = nFm / M$ where $m/M = N$), n (number of electrons transferred) is available. From exhaustive potentiostatic electrolysis, the product(s) formed at the selected electrode potential can be isolated.

For a galvanostatic exhaustive electrolysis the current is kept constant through the working electrode, resulting in the constant flux of electroactive material to the surface. Consequently, the electrode potential will vary during the experiment. As a result, at different times various electrode processes may be induced. Hence, the results of galvanostatic and potentiostatic electrolysis will not necessarily be identical. The product at the electrodes can be isolated, after defining a protocol for the end point. Electroanalytical methods are now widely used to gain information about the kinetics and mechanisms of chemical reactions associated with the electron transfer at an electrode. A unique feature of these methods is that the electrode serves both as the means of generating an intermediate, for instance a radical ion, and as the means to monitor its reactions to product. The following section briefly reviews some of the electroanalytical techniques.

1.2.0 Electroanalytical Techniques[22]

In the middle of 20th century (1940-1960) electroanalytical methods, such as polarography and voltammetry at solid electrodes, were used to study organic reactions. These results were used to both analyse reactions and to study the reaction mechanism. The following section will review these techniques.

1.2.1 Polarography

Polarography produces current–voltage curves, and these are obtained at a dropping mercury electrode (DME). The main goal of polarography is to convert the analyte from one form to another by the positioning of the electrode, increasing the potential results in

a more rapid conversion. This technique was invented by Heyrovskey.[23] In general, polarography is a technique in which the electric potential (or voltage) is varied in a regular manner between two sets of electrodes (indicator and reference) while the current is monitored.

The shape of a polarogram depends on the method of analysis selected, the type of indicator electrode used and the potential ramp that is applied. Figure 6 shows five selected methods of polarography; the potential ramps are applied to a mercury indicator electrode and the shapes of the resulting polarograms are compared.

The majority of the chemical elements can be identified by polarographic analysis and the method is applicable to the analysis of alloys and to various inorganic compounds. Polarography is also used to identify and quantify numerous types of organic compounds such as fructose,[24] aromatic and halogenated carbonyl compounds,[25] acetylacetone,[26] and cystine,[27,28] and to study chemical equilibria and rates of reactions in solutions.

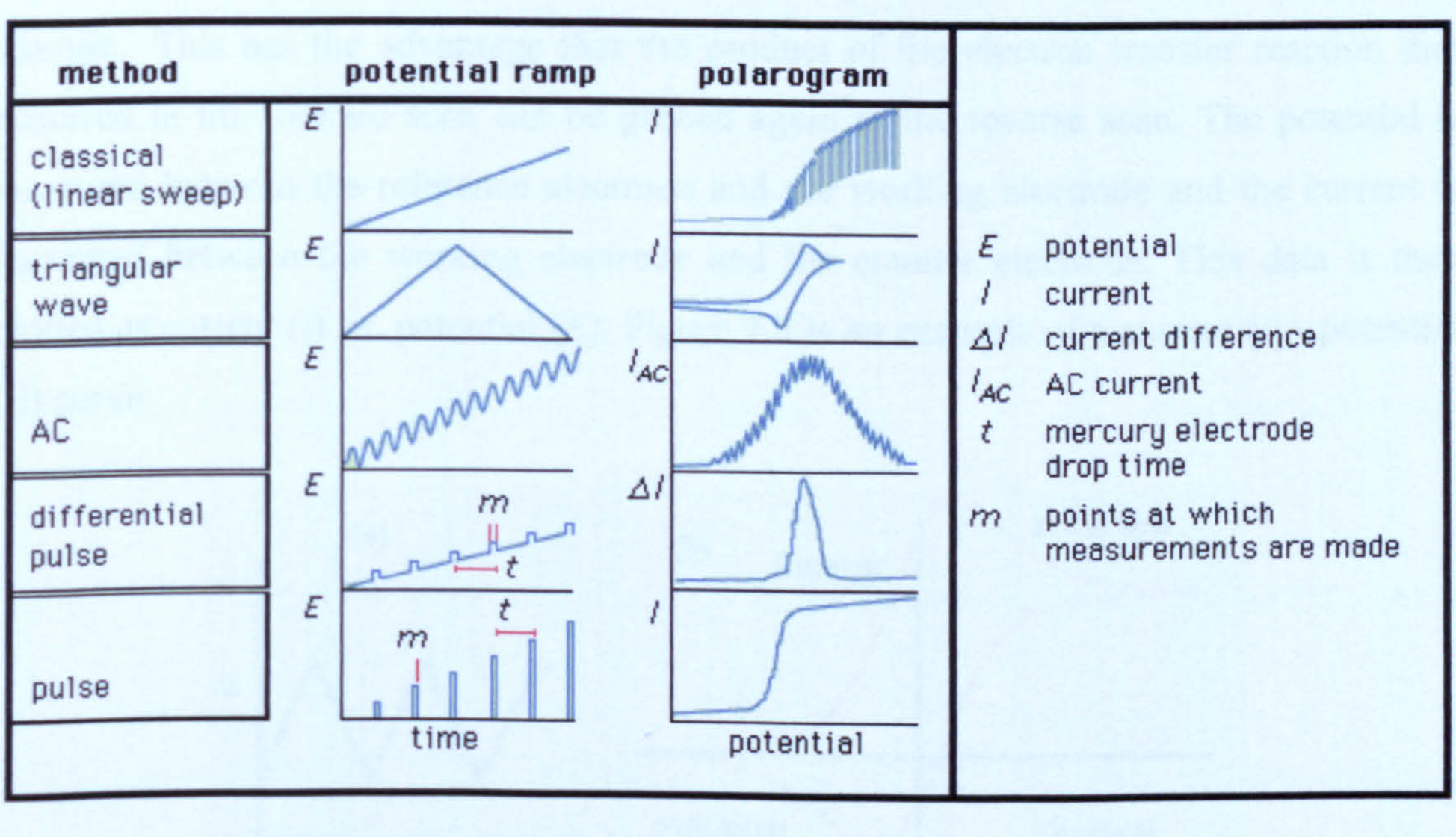


Figure 6. The figure shows various potential ramps that can be applied to a mercury indicator electrode during selected forms of polarography along with their typical corresponding polarograms.

1.2.2 Voltammetry

This is a method in which a small portion of a material is reduced or less commonly oxidized electrolytically. There are several methods, which can be employed on the basis of electrode type, how the potential is applied and how the current is measured. A simple potential wave form that is often used in electrochemical experiments is the linear wave form *i.e.*, the potential E (V), is continuously changed as a linear function of time, (t) (Figure 7 a). The rate of change of potential with time is referred to as the scan rate (*v*). The simplest technique that uses this waveform is linear sweep voltammetry. The potential range is scanned in one direction, starting at the initial potential $E_{initial}$ and finishing at the final potential E_{final}.

A more commonly used variation of the technique is cyclic voltammetry, in which the direction of the potential is reversed at the end of the first scan. The electrode potential ramps linearly versus time as shown in Figure 7(a). This ramping is known as the experiment's scan rate (V/s). Thus, the waveform is usually of the form of an isosceles triangle. This has the advantage that the product of the electron transfer reaction that occurred in the forward scan can be probed again in the reverse scan. The potential is measured between the reference electrode and the working electrode and the current is measured between the working electrode and the counter electrode. This data is then plotted as current (*i*) vs. potential (*E*). Figure 7 b is an example of a current (*i*) - potential (E) curve.

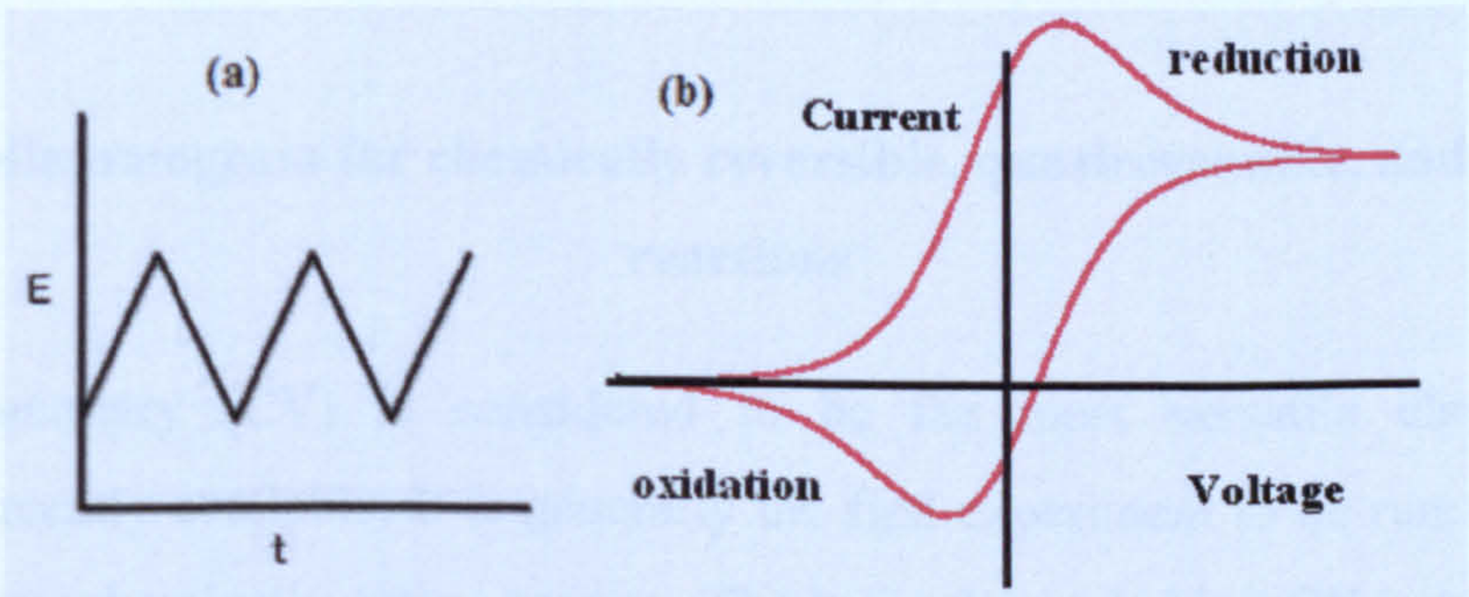


Figure 7(a). waveform for potential against time,(b). a voltammogram for chemically reversible reaction

As the waveform shows, the forward scan produces a current peak for any analytes that can be reduced (or oxidized depending on the initial scan direction) through the range of the potential scanned. The current will increase as the potential reaches the reduction potential of the analyte, but then falls off as the concentration of the analyte is depleted close to the electrode surface. If the redox couple is reversible then when the applied potential is reversed, it will reach the potential that will reoxidize the product formed in the first reduction reaction, and produce a current of reverse polarity from the forward scan. This oxidation peak will usually have a similar shape to the reduction peak. As a result, information about the redox potential and electrochemical reaction rates of the compounds are obtained.In addition, it is a powerful tool for the determination of formal redox potentials, detection of chemical reactions that precede or follow the electrochemical reaction and the evaluation of electron transfer kinetics, such as reversible, quasireversible, and irreversible reactions (Figure 8).

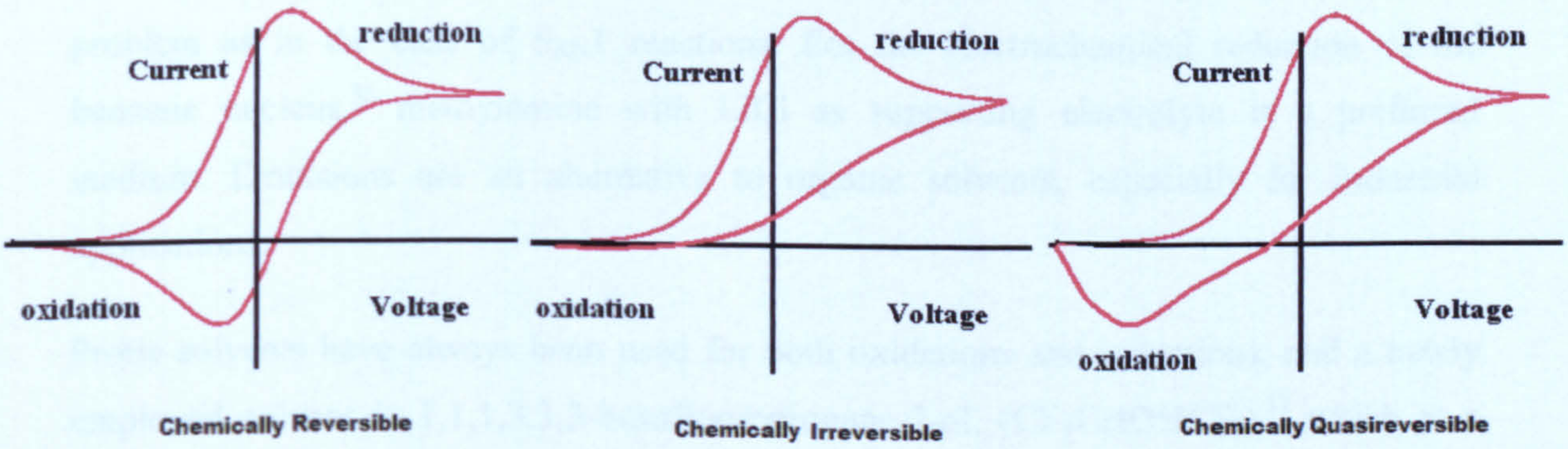


Figure 8. voltammogram for chemically reversible, quasireversible, and irreversible reactions

Cyclic voltammetry (CV) is considered to be the most versatile electroanalytical technique currently available. It is generally the first experiment to be run when dealing with any electrochemically active species. The basic theory behind CV is to measure the current response at an electrode surface at a range of potentials in an unstirred solution. DME, glassy carbon or Pt electrodes may be used. Voltage is swept in both directions in a drop (typically <1 sec). The method is used to study REDOX reactions of organic and

organometallic compounds.

1.3.0 Reaction Media and Electrodes

Aprotic media have been employed, both for electrochemical reductions[29] and oxidations.[30] For oxidations acetonitrile with sodium perchlorate is typically used as the supporting electrolyte and Ag^+/Ag-reference electrodes were first employed. Later methylene chloride,[31] sometimes with added trifluoroacetic acid and its anhydride to remove nucleophiles was used as a solvent.[32] Liquid sulphur dioxide can also be used as a solvent having low nucleophilicity,[33] and limited solubility of supporting electrolytes allows preparative electrolysis in a few cases.[34]

For reductions *N,N*-dimethylformamide (DMF), acetonitrile (MeCN) and dimethylsulfoxide (DMSO) have been most commonly used as solvent. Acetonitrile being slightly more acidic than DMF and DMSO is less likely to lose hydrogen by atom abstraction. Liquid ammonia,[35] can be used for reactions where hydrogen abstraction is a problem as in the case of $S_{RN}1$ reactions. For the electrochemical reduction of the benzene nucleus,[36] methylamine with LiCl as supporting electrolyte is a preferred medium. Emulsions are an alternative to organic solvents, especially for industrial applications.

Protic solvents have always been used for both oxidations and reductions, and a newly employed solvent is 1,1,1,3,3,3-hexafluoropropane-2-ol, $(CF_3CHOHCF_3)$,[37] which is a good solvent for cation radicals, as it has unusually low nucleophilicity, a high ionizing power and strong hydrogen bonding capability.

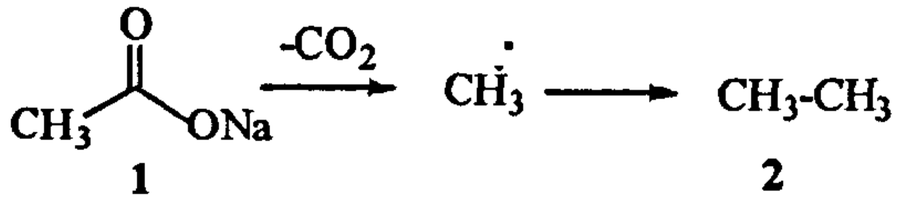
The choice of anode material and anode reaction is very important in aprotic media, using an undivided cell. Aluminium[38] and magnesium[39] can be used as sacrificial anodes, to not only solve the problem of anode reaction, but the dissolved ions also function as added supporting electrolyte, and in some cases the magnesium ions play a special role by salt formation of the product.

Electrode surfaces can be modified to get better results like catalytic effects, chiral

induction and some other desirable effects, which cannot be obtained at the "classical" electrode materials. The modified electrodes are usually not stable enough for preparative reactions using high current densities.

1.4.0 Applications of Organic Electrochemistry[22]

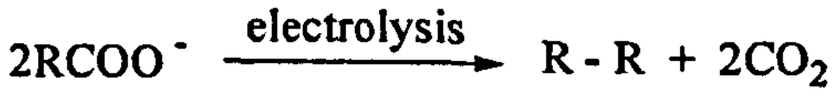
Although electrochemistry is a very well established branch of analytical chemistry, organic electrochemistry is still in development to fulfil its potential as a green and modern methodology. After the invention of the battery, the "Volta pile" in 1800,[2] no preparative electrolysis was carried until Faraday's experiments in the 1830s. Faraday[4] was the first scientist, to conduct an electroorganic synthesis by electrolysing sodium acetate **1** solution and obtaining a gaseous product, ethane **2** (Scheme 3).



1 **2**

Scheme 3. Electrolysis of sodium acetate solution

The anodic oxidation of salts of fatty acids to hydrocarbons with loss of carbon dioxide was developed by Kolbe[40] to become the first useful electroorganic synthesis, (Scheme 4) which was later extended by Brown and Walker[41] to the electrolysis of salts of mono esters of dibasic acids, resulting in dimerization to diesters (Scheme 5).



Scheme 4. Kolbe electrolysis



Scheme 5. Electrolysis of a salt of monoester

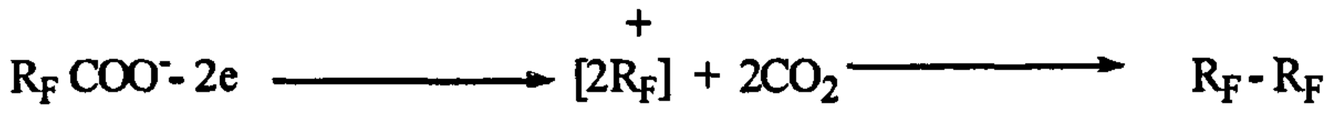
From literature, the first electrochemical reduction of an organic compound seems to be the reductive dehalogenation of trichloromethane sulphonic acid to methanesulphonic acid[42] at a zinc electrode.

During the second half of the 19thcentury preparative organic electrochemistry started to develop. In this period several oxidations and oxidative substitutions as well as reductions of nitro compounds, carbonyl derivatives and dehalogenation reactions were performed; however, in most cases mixtures of products were obtained, as initial electrochemical synthesis was not very selective. Electrochemistry has for almost 50 years made a significant contribution in the field of organic synthesis, however only a few reactions became industrial processes. Electrochemistry provides the opportunity to make and break C-C bonds and creates reactive intermediates through bonds between carbon and heteroatoms. The chemistry described in this section provides an overview of some of the creative aspects of industrial as well as synthetic organic electrochemistry that researchers have selected to synthesize molecules.

1.4.1 The Industrial Applications of Electroorganic Chemistry[22]

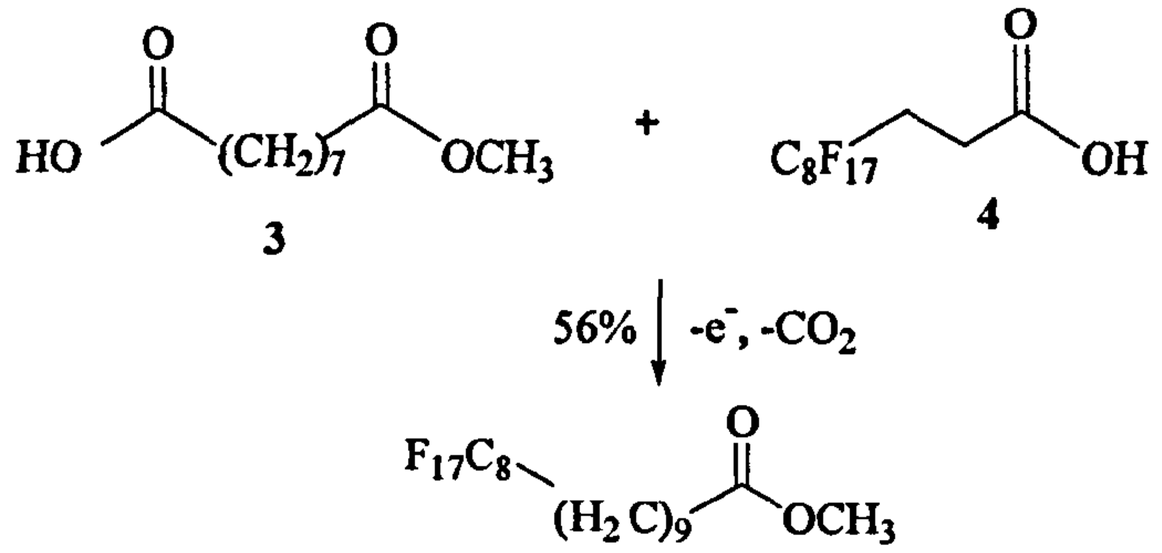
The most important industrial application of organic electrochemistry was the Simons Process,[43] for electrochemical fluorination (ECF) of organic substrates in anhydrous hydrogen fluoride at a nickle anode. By the development and commercialization of the Simons Process, it is possible to produce perfluorinated compounds (compounds in which all the hydrogen atoms are replaced by fluorine) and at the same time double bonds are saturated but some functional groups remain unaffected. Later other electrochemical partial fluorination reactions were developed.[44] In these reactions the substrate is oxidized to a radical cation or cation, which reacts with the fluoride anion; for such a reaction the selection of a medium is important in which the nucleophillic reactivity of the fluoride ion is not diminished by solvation.

The Kolbe electrolysis is one of the best-known electrosynthetic reactions. The Kolbe product 'dimers' are formed by the anodic oxidation of carboxylate ions, (Scheme 6), where R_F is a fluorinated alkyl chain. If the carboxylate is trifluoroacetate ion, CF_3COO^-, 93% yield of hexafluoroethane can be obtained.



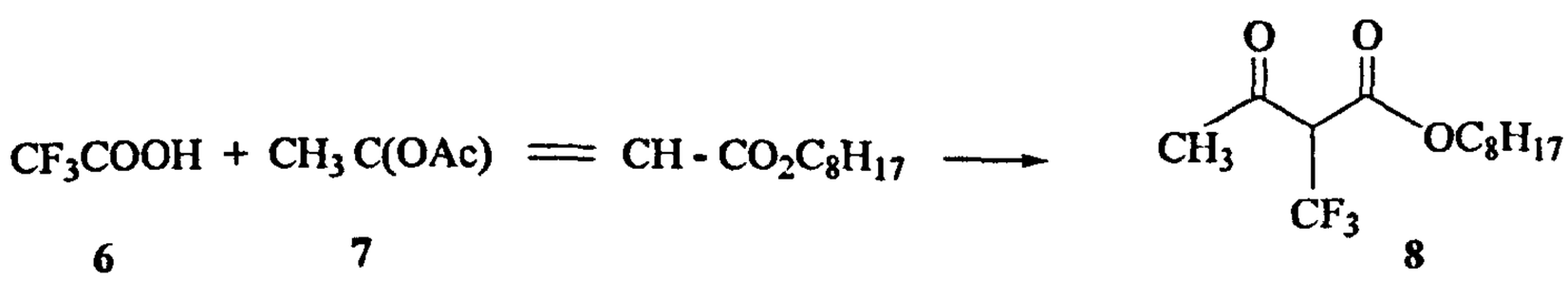
Scheme 6 Anodic oxidation of fluorinated carboxylate ions

The possibilities are numerous if 'cross-coupling', is taken into account. Partially fluorinated esters **5** can be obtained by the Kolbe reaction (cross coupling) between two different carboxylates **3** and **4** (Scheme 7).



Scheme 7 Anodic oxidation of fluorinated carboxylate ions

Kolbe radicals from carboxylic acid **6** can also be added to olefins **7** to obtain fluorinated ester **8** as shown in (Scheme 8).

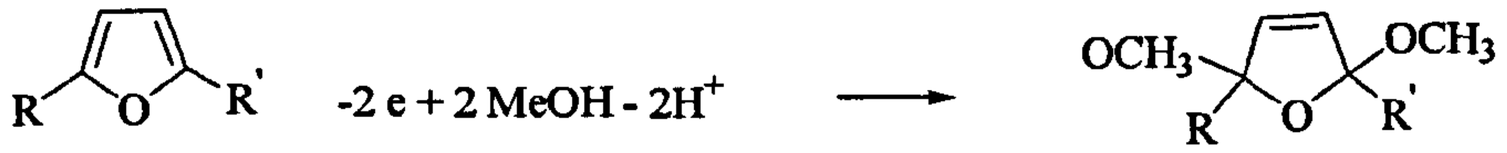


Scheme 8 Anodic oxidation of fluorinated carboxylate ions

Anodic nucleophillic substitution of aromatic compounds is a well-characterized family of reactions. Some of the examples are acyloxylations, alkoxylations and cyanations. For

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a given nucleophillic species CF_3CO_2-, fluorinated esters can be produced in high yields. Another industrial production has been the anodic methoxylation of furan **9** and furan derivatives to 2,5-dihydro-2,5-dimethoxyfurans[45] **10** (Scheme 9).



9 **10**

Scheme 9. Anodic oxidation of a furan derivative

In the last part of 20th century (1960-2001), new electroanalytical techinques made it possible to investigate the mechanism of electrode reactions. In addition, the introduction of indirect elecrolysis, using organic and organometallic mediators and electrochemisty of bioorganic systems and the development of *in situ* analytical techniques, enabled the researchers to better understand the electrosynthetic processes.

1.5.0 Cathodic Reduction (Coupling Reaction)

The mechanism of reductive coupling of ACN (acrylonitrile) to ADN (adiponitrile), where hydrodimerization of activated olefins was investigated after the discovery by Baizer[19, 46,] that on electrolysis under certain conditions (*i.e.* in the presence of quaternary ammonium salts such as tetraethylammonium *p*-toluenesulfonate as supporting electrolyte), acrylonitrile **11**, an olefin activated by an electron withdrawing group (EWG), could dimerize to adiponitrile (Scheme 10). This could be transformed to the two components, adipic acid and hexamethylenediamine **12**, used in the synthesis of Nylon66. The process is also known as Monsanto process, operated by BASF in the UK, essentially in aqueous conditions.[19]

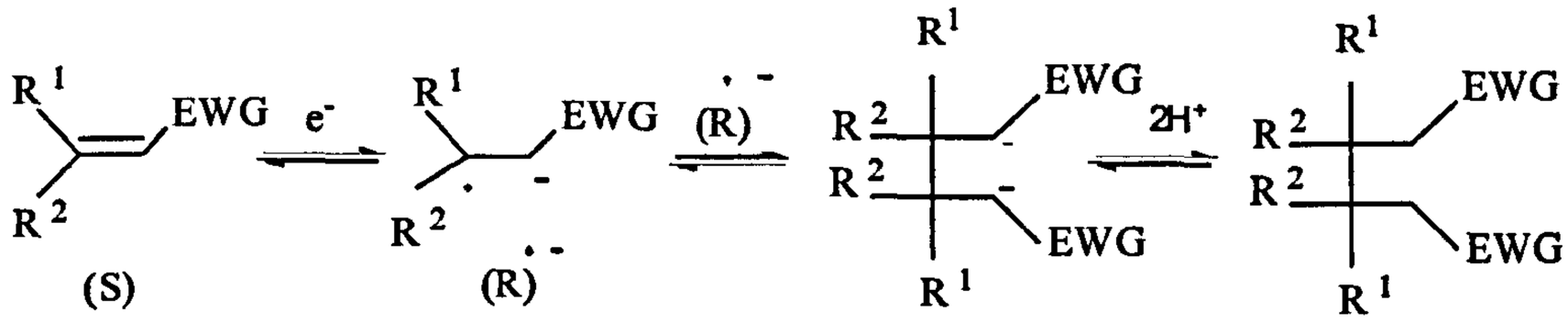


11 **12**

Scheme 10. Electrolysis of acrylonitrile

The electrolysis of an activated olefin **13** leads to a one-electron reduction to a dimer **14** or a two-electron reduction with saturation of the double bond. Several side reactions,

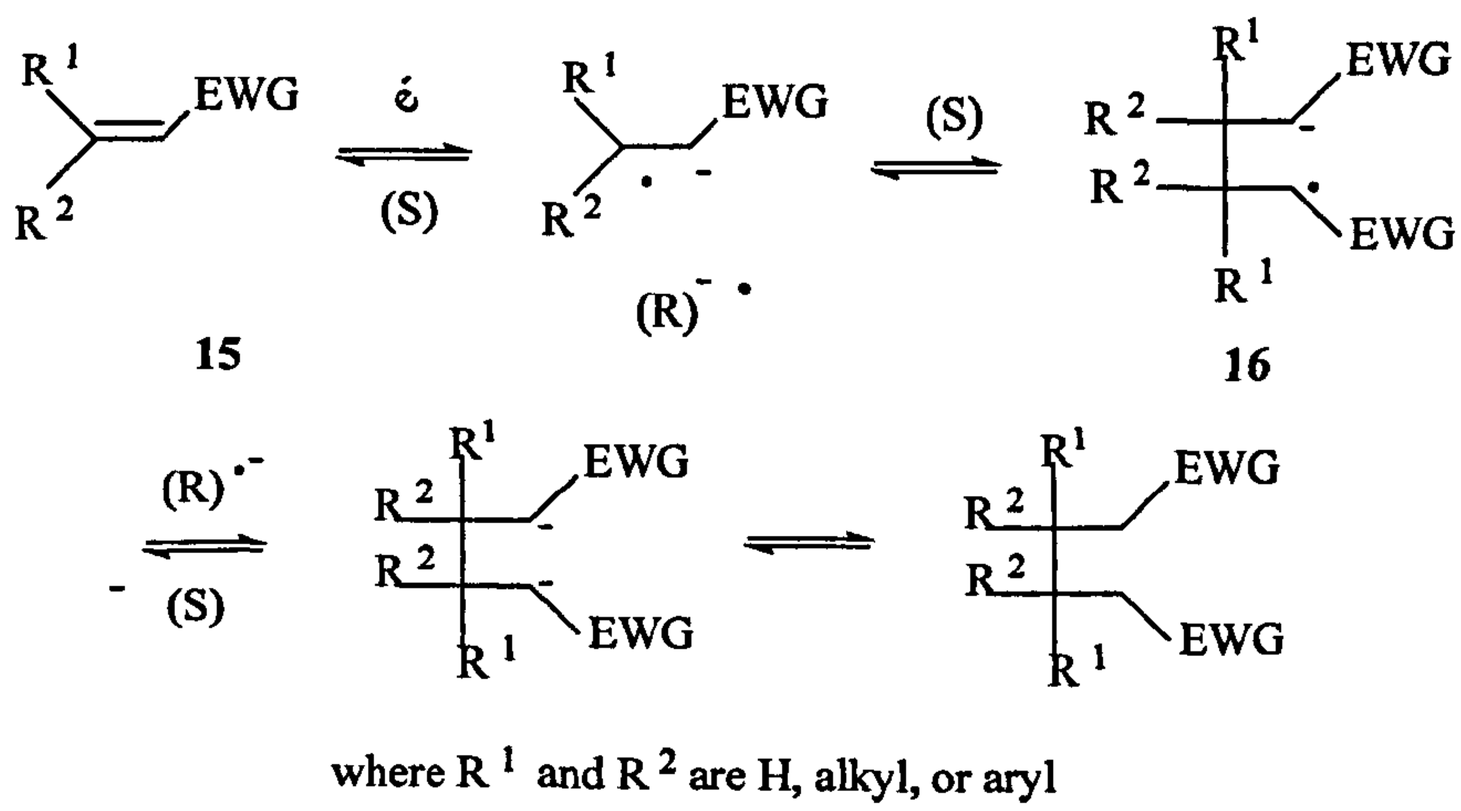
such as a Michael addition of a nucleophile to the double bond or polymerization could compete with the electrochemical reactions. There are two mechanistic possibilities for dimerization, a dimerization of two radical species (RR), (Scheme 11) or an addition of a radical species to the substrate (RS) followed by an electron transfer.[47]



where R^1 and R^2 are H, alkyl, or aryl

Scheme 11 Dimerization of two radical species

For some activated olefins **15** (*e.g.*, some ketones) a preprotonation takes place in protic solution, such that two neutral radicals dimerize **16**. The radical-substrate dimerization (RS) may be represented as follows, (Scheme 12), which is followed by product making steps. The degree of reversibility depends on the competition between the backward reaction and the forward reaction.



where R^1 and R^2 are H, alkyl, or aryl

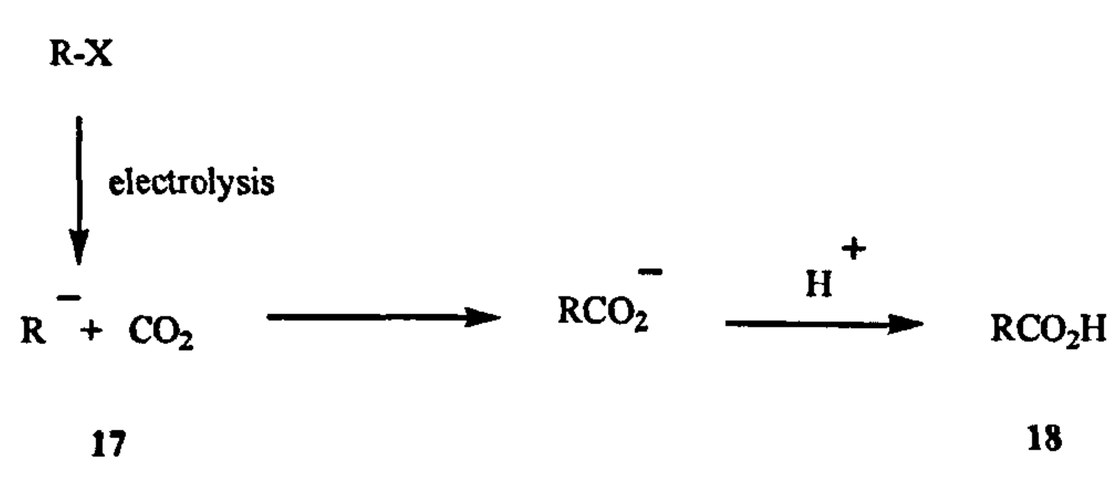
Scheme.12 Radical-Substrate dimerization

The product of an electrolysis reaction depends on the competition between different possible reactions and thus on a number of rate constants. Compounds with slower

kinetics were used for studying electrohydrodimerizations, such as activated olefins and anthracenes substituted with EWG, which could dimerize reductively.

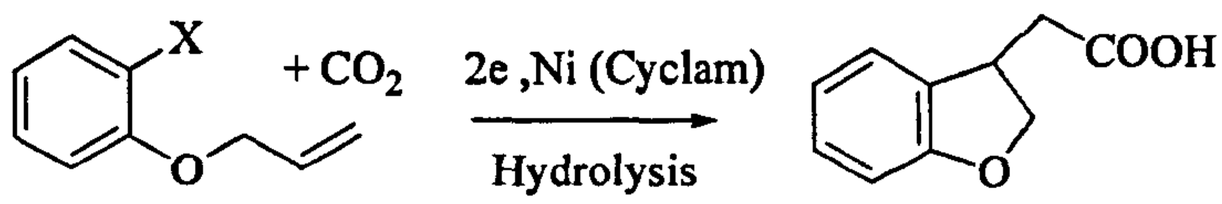
More recently there has been a lot of discussion in the literature on the correct interpretation of experimental data obtained by different research groups on the R-R *vs.* R-S problem. Accordingly the development of instrumentation and the power of simulation of theoretical curves for different electroanalytical techniques have indicated that hydrodimerization of activated alkenes proceeds through a radical anion-radical anion coupling.[48,49]

The electrolytic reduction of alkyl and benzyl halides in DMF to the respective anions **17**, in the presence of activated olefins may result in a Michael addition; where the product anion may undergo protonation or S_N2 reaction with the starting halide.[50] Furthermore carboxylic acids **18** can be formed in the presence of carbon dioxide[51] (Scheme 13).



Scheme 13. Representing the Carboxylation of alkyl or benzyl anion

Carboxylation may be catalysed by nickel complexed with Ph_3P[52] or salen.[53] Electrolysis of unsaturated haloaryl ethers **19** (Scheme 14), at a carbon fibre cathode in DMF in the presence of Ni II (cyclam) leads to dihydrobenzofuran derivative **20** in a tandem cyclization carboxylation.[54]



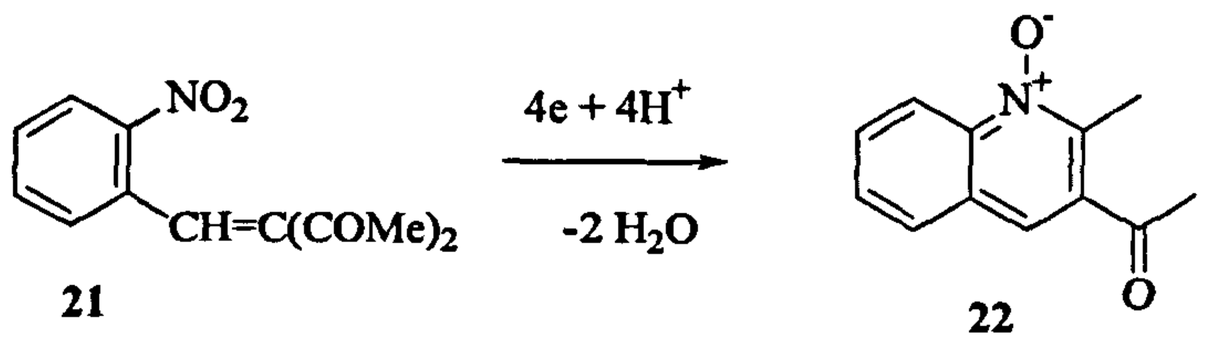
19 **20**

Where X = F, Cl, Br, I,

Scheme 14. Carboxylation of an unsaturated Haloarylether

Intramolecular coupling is further type of reductive coupling, where the ring closure results from a radical coupling or by the reaction between an electrochemically generated nucleophile and an electrophillic center. When diethylmalonate is the proton donor of an activated olefin having a carbonyl or cyano group in an α-position, the reduction in acetonitrile/Et_4NOTs results in a ring closure by the attack of the nucleophillic β-carbon on the carbonyl group.

The reductive formation of nucleophiles followed by an attack on an electrophillic centre is the basis for the synthesis of many heterocyclic compounds. The reduction of the nitro group in *ortho*–substituted nitro compounds to the hydroxylamine may lead to an *N*-oxide of an *N*-heterocyclic compound; for example the reduction of *o*-nitrobenzalacetylacetone **21** to 3-acetyl-2-methylquinoline-*N*-oxide **22**[55] (Scheme 15).



21 **22**

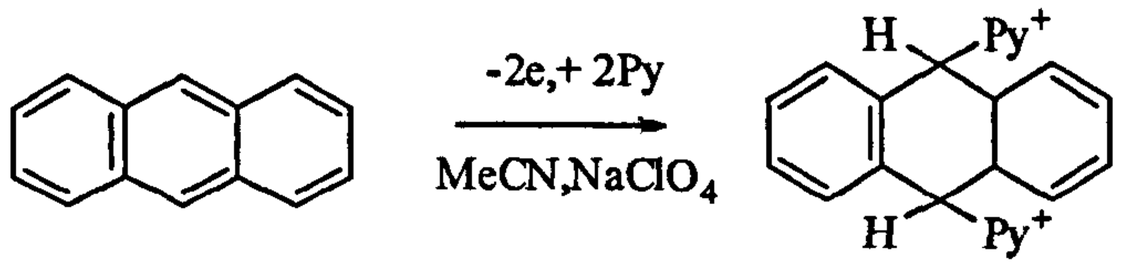
Scheme 15. The reduction of *o*-nitrobenzalacetylacetone

The reduction of aryl halides forms radical anions, which decompose to a halide ion and the aryl radical. The aryl radical is more easily reduced than the substrate so it can abstract a hydrogen atom from the solvent system. However, in suitably substituted compounds the aryl radical may attack the phenyl ring resulting in the ring closure.

1.6.0 Anodic Oxidation (Substitution and Coupling)

Synthetic applications of anodic electrochemistry have been comprehensively discussed in various reviews, however a quick overview of a number of anodic reactions, detailing the type and uses of anodic oxidation to complement the existing methodology is highlighted, in a review by Moeller.[13c] This review focuses mainly on the advantages and uses of anodic oxidation as an electrochemical tool, utilizing neutral/mild reaction conditions with a wider range of oxidation potentials for selectively oxidizing the functional groups and generating highly reactive intermediates by even reversing the polarity of nucleophiles in certain cases. For the anodic oxidation reactions discussed in the review listed above, the primary reaction of interest occurs at the anode. The anodic reactions mainly fall into one of the three categories; elimination, fragmentation and coupling reactions that trap the initial reactive intermediates generated at the anode and transform the reactive substrate to complex molecules.

Without using an added mediator, anodic reactions may involve a loss of electrons from the substrate as in the case of pyridination of anthracene **23** (Scheme 16), and methoxylation of furan, or the loss of electrons from the solvent, as in some oxidations the solvent is oxidized with a loss of an electron and a proton, forming a radical which abstracts a hydrogen atom from the substrate. Some of these issues are discussed in detail below.



23 **24**

Scheme 16. Pyridination of anthracene

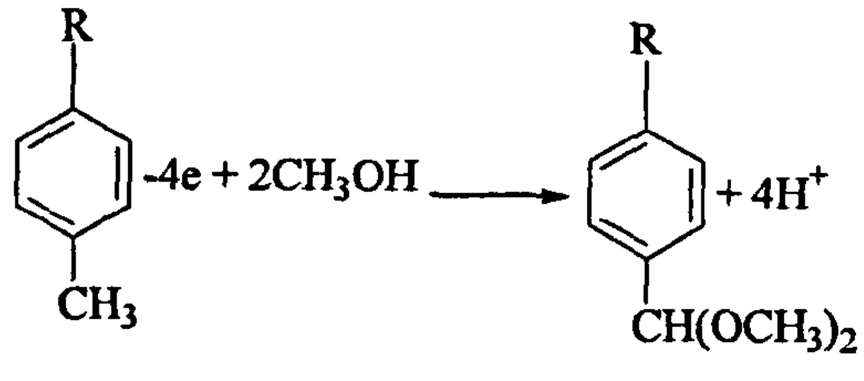
Preparative oxidations at controlled potential, using acetonitrile/$NaClO_4$ as a medium, were made by Lund,[31] some in the presence of pyridine as a base/ nucleophile. The conclusion was that the oxidation at controlled potential consisted of a loss of electrons from the aromatic system, which then, by loss of protons or the reaction with a

nucleophile, formed the product **24**.

1.6.1 Methoxylation

Methoxylation of alkylbenzenes **25** may take place in the aliphatic side chain or in the aromatic nucleus. The conversion of 4-methoxyanisole into methoxybenzylmethyl ether depends on the medium, the nuclear methoxylation can dominate under reaction conditions where methoxy radicals are formed.[56]

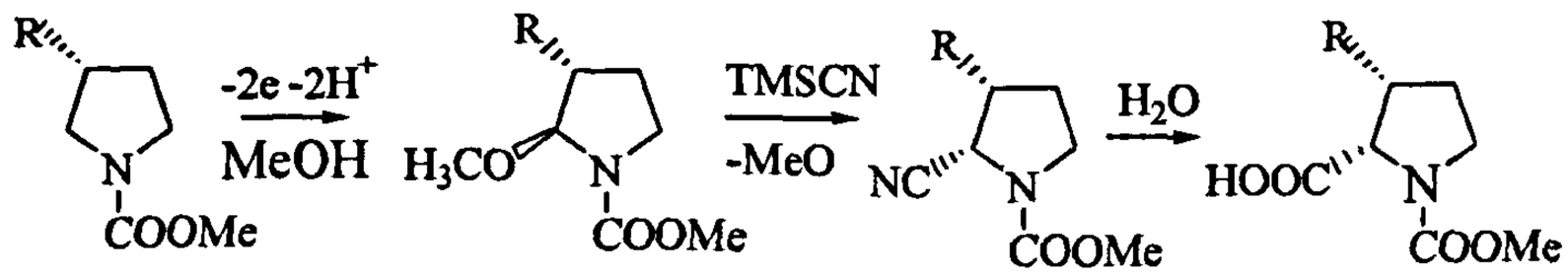
The methoxylation of methylbenzenes is of industrial importance and BASF is producing substituted benzaldehyde dimethylacetal **26** by the oxidation of methanolic solutions of substituted toluenes **25** at a carbon anode in a capillary gap cell (Scheme 17).



25 **26**

Scheme 17. Oxidation of substituted toluene

The methoxylation of *N,N*-dialkylamides is a useful reaction, an example is the oxidation of dimethylamides to *N*-alkoxy-*N*-methylamides in $MeOH/NH_4NO_3$, under these conditions the oxidation of both the amide and the nitrate ion takes place.[57] A large number of heterocyclic derivatives **28, 29** and **30** have been prepared by the anodic methoxylation of acylated heterocycles **27** [58] (Scheme 18).

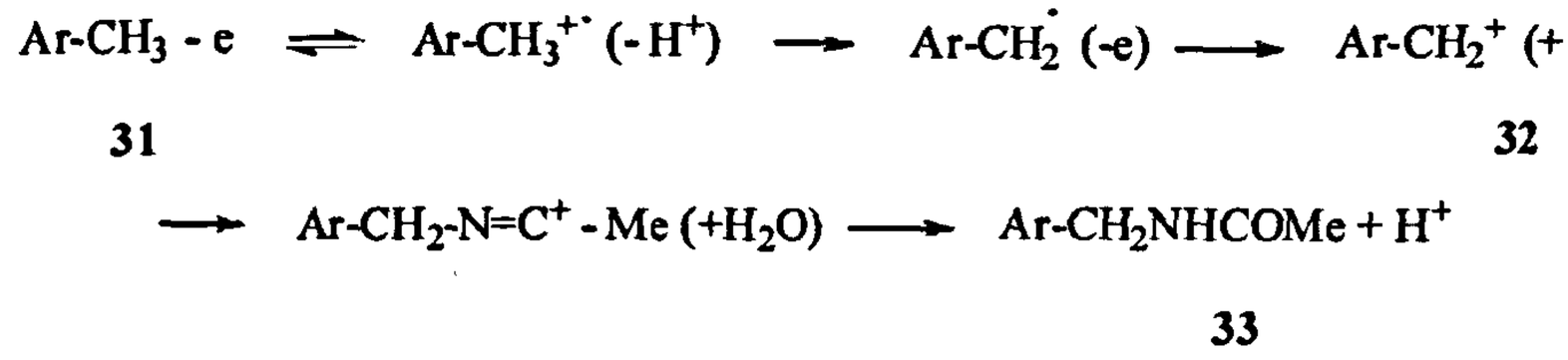


27 **28** **29** **30**

Scheme 18 Oxidation of 3-alkyl-pyrrolidine-1-carboxylic acid methyl ester

1.6.2 Acetoxylation

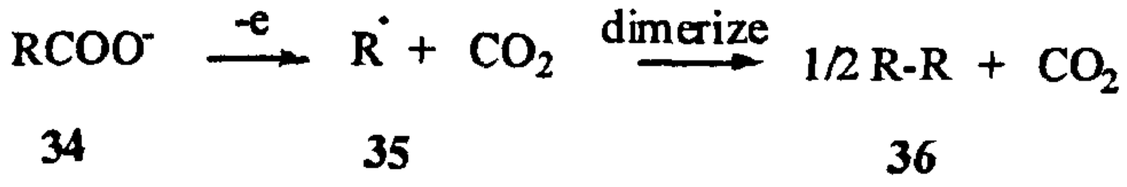
In the presence of acetic acid and acetic anhydride the oxidation of aromatic compounds results in acetoxylation. The only previous well-authenticated example of anodic alkoxylation, was reported by van der Hoek and Nauta,[59] who isolated methoxydiphenylmethane (36% yield) from the products formed by electrolysis of diphenylacetic acid in a mixture of methanol and pyridine. Anodic alkoxylations, in general, are reminiscent of the formation of alcohols on electrolysis of fatty acids in aqueous solution.[60] The Hofer-Moest reaction is promoted by various inorganic anions and can involve attack at positions both α and β to the eliminated carboxyl group.[61] The attack can occur on both the ring as well as the side chain of the alkyl arenes. The presence of acetate ions **31** leads to the substitution in the aromatic ring.[62] In the presence of acetonitrile and trifluoroacetic anhydride, the carbocation **32** (which is formed by oxidation) may attack the solvent to yield **33** (Scheme 19).



Scheme 19. The reaction of carbocation with solvent acetonitrile

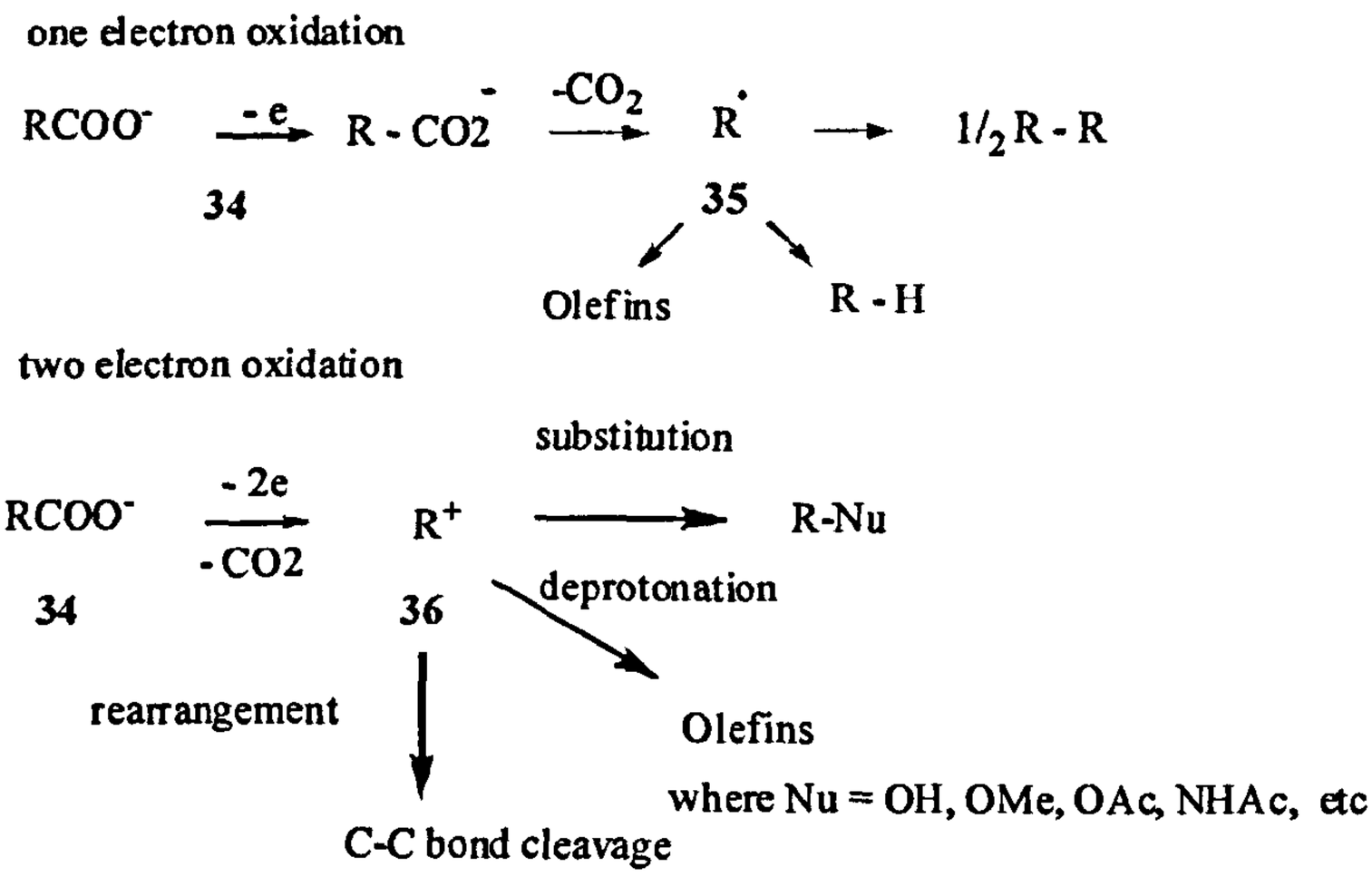
1.6.3 Kolbe Electrolysis

Kolbe[40] electrolysis is a well-established process, which operates, in relatively mild conditions. In a classical Kolbe reaction the carboxylate **34** is oxidized to a radical **35**, which dimerizes to form an alkane **36**, (Scheme 20).



Scheme 20. Kolbe Electrolysis

But under certain conditions this radical may further oxidize to a carbenium ion (in the so called non-Kolbe pathway). A more promising utility of this electrodecarboxylation was discovered in 1960s by Brown and Walker,[41] in which a carbenium ion intermediate R^+ is formed at the anode and may undergo a variety of reactions like substitution, deprotonation and rearrangement to form alcohols, ethers, esters, amides, olefins, and others. By carefully controlling the electrolysis conditions (current density, electrode material, solvent and pH), selective (*i.e.*, $R^\bullet$ radical **35** / one electron oxidation *vs* R^+ cationic **36**/ two electron oxidation pathway) transformations can be achieved (Scheme 21.



Scheme 21. Showing one electron oxidation and two electron oxidation

Weedon[63] has discussed optimal experimental procedures for the Kolbe reaction. According to which apparently, a film of absorbed intermeditates inhibits oxidation of the solvent and permits a potential to be attained where the Kolbe reaction can then occur. This feature is of interest synthetically because it results in considerable experimental simplifications. Since anodic potential control (to avoid oxidation of the solvent) is rendered unnecessary by this absorption process, one may use constant-current, rather than controlled-potential electrolysis.

1.6.4 Radical Reaction (one electron oxidation)[13a, 64-71]

Radicals can be generated in preparative amounts *via* Kolbe electrolysis, in an experimentally simple way. These radicals couple or react with olefins to give "additive" dimers and/or monomers, as will be discussed in the following section.

1.6.4.1 Kolbe Cross Coupling

In a Kolbe cross coupling reaction two carboxylates are simultaneously oxidized, both symmetrical dimers and cross coupled products are formed. This valuable extension of the Kolbe reaction was first reported by Wurtz.[72] Who found that oxidation of a mixture of two different carboxylic acids **37**, and **38** results in a mixture of three possible coupling products **39**, **40** and **41** (Scheme 22).

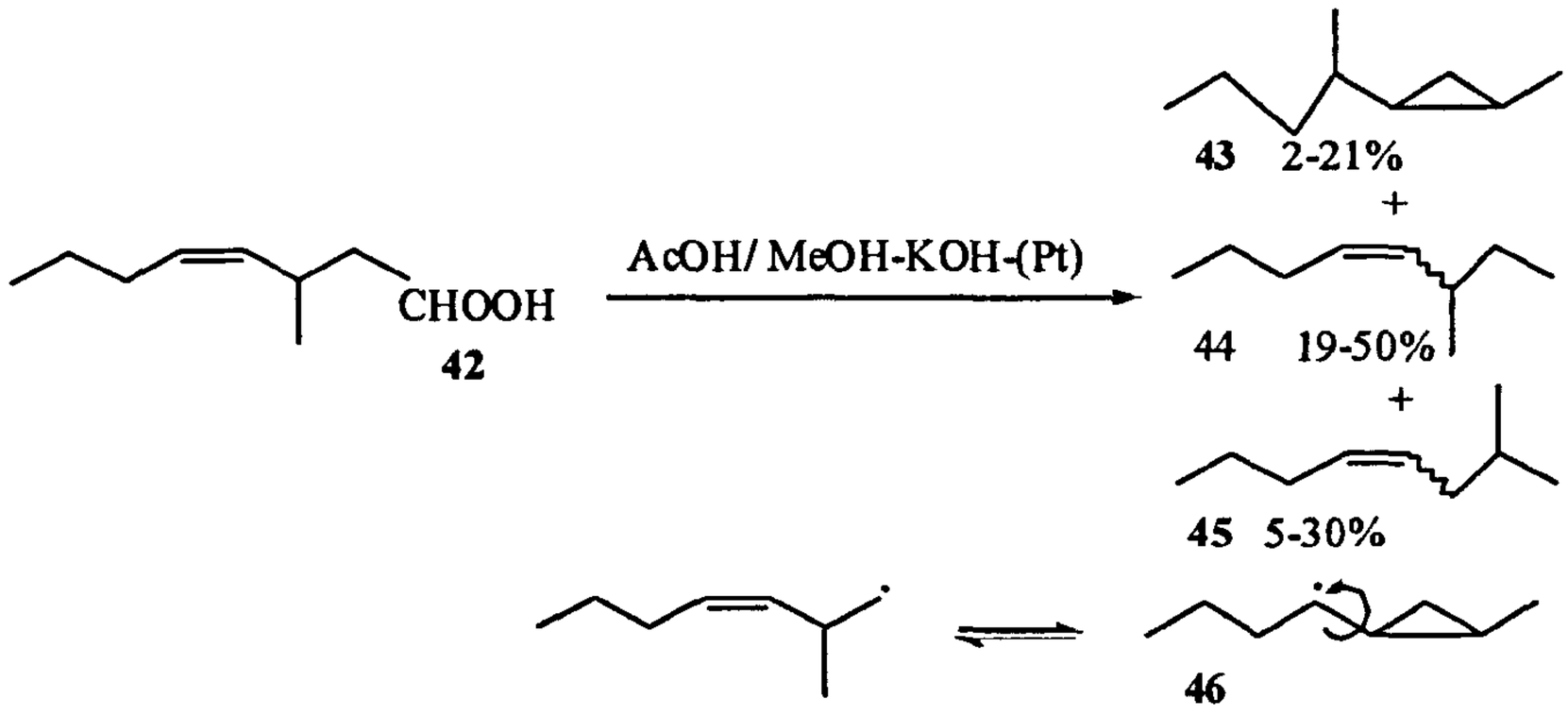
$$\underset{\mathbf{37}}{RCO_2H} + \underset{\mathbf{38}}{R'CO_2H} \xrightarrow[-2\,e]{-\,2\,CO_2} \underset{\mathbf{39}}{RR} + \underset{\mathbf{40}}{RR'} + \underset{\mathbf{41}}{R'R'}$$

Scheme 22. Kolbe cross coupling

Good yields of cross-coupled products can be obtained by using an excess of the cheaper carboxylate. The fact that the three are formed in more or less statistical ratios need not be a detterent, for the proper choice of the molecular size of R and R' the products can be made to differ substantially in physical properties, thus making separation easy, and the use of a large excess of the cheaper acid increases the relative yield of the desired mixed product RR', such kinds of reaction have been employed for the synthesis of natural products such as carotenoids, fatty acids, muscone, fumulene[66b] and pheromones.[73]

Under the cross-coupling conditions, the double bond of the unsaturated acids generally retains its configuration. Partial Z/E isomerization of olefins is also observed in the electrolysis of Z-4-enoic acids.[74] The electrolysis of Z-3-methyl-4-enoic acid **42** with acetic acid (Scheme 23), gives a mixture of Z and E isomers of the cross coupling product **43** (9:1-7:3) together with **44** and **45**. This can be well understood by assuming a Z/E

isomerization *via* a reversible ring closure to cyclo-propylcarbenyl radicals **46** (Scheme 23).

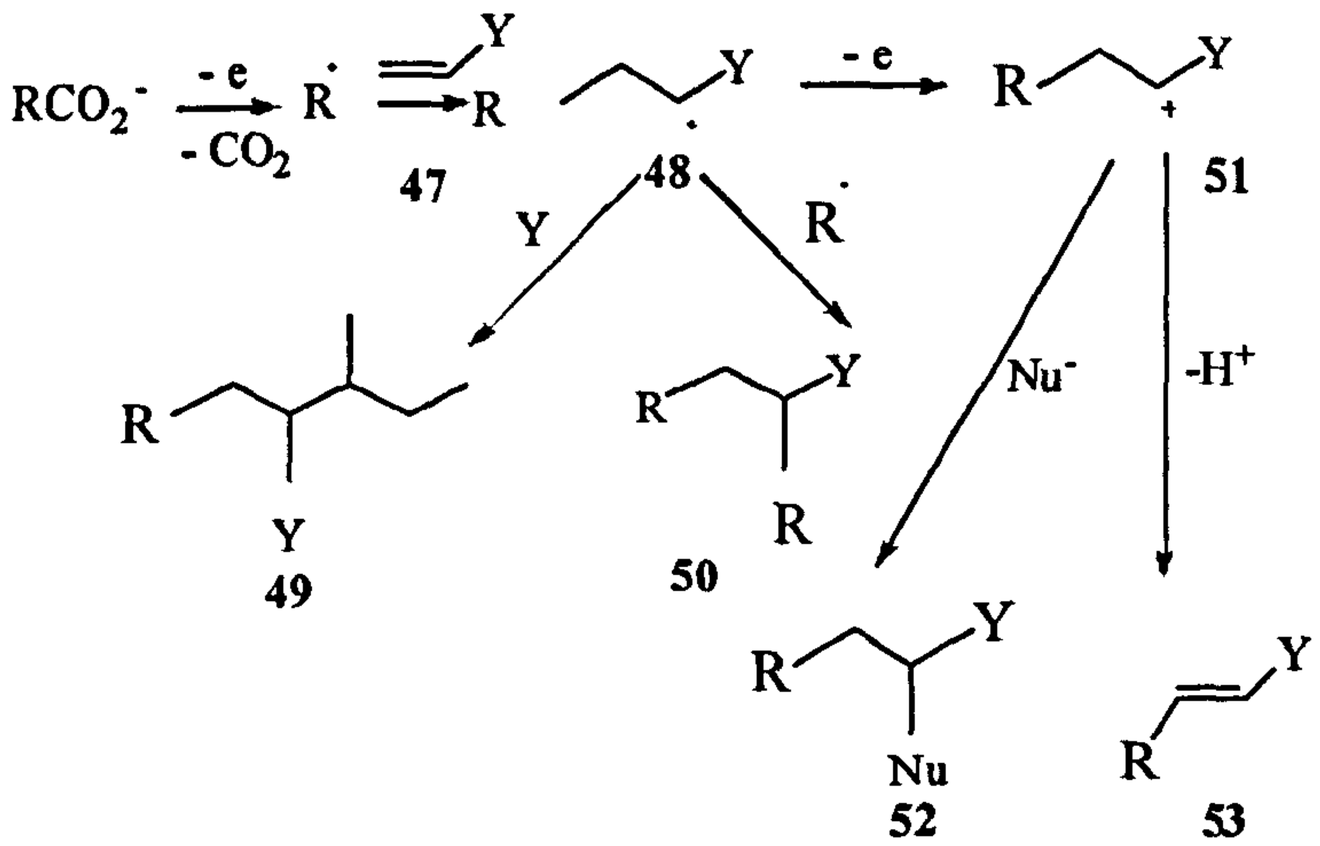


Scheme 23 A Z/E isomerization via a reversible ring closure to cyclo-propylcarbenyl radicals

One common application of this crossed Kolbe coupling is the oxidation of a carboxylic acid in the presence of a large excess of acetate ion, thus resulting in efficient conversion of the acid RCO_2H to the alkane RCH_3 in one step. The crossed Kolbe coupling reaction has the dual advantage of being able to accommodate a wide variety of functional groups and of enabling the quick assembly of molecular subunits whose coupling by other routes might be lengthy.

1.6.4.2 Radical Addition to Olefins

Radicals, which are generated in Kolbe reactions can be added to olefins **47**. The intermediate radical **48** can dimerize to give **49** and **50** or it can be further oxidized (non-Kolbe) to form a carbenium ion **51**, which can react with a nucleophile or may lose a proton to alkanes **52** and **53**, (Scheme 24). The addition of a radical to an olefin is used in ring closure reactions[75] and to introduce trifluoromethyl group in different compounds.[76, 77]



Scheme 24. The radical addition to an olefin

Depending upon the solvent, further oxidation of the radicals to carbenium ions may result in the acetoxylation, methoxylation or acetamidation. The methoxylation reaction has been used to synthesise carbohydrate[78] derivatives and oligopeptides.[79]

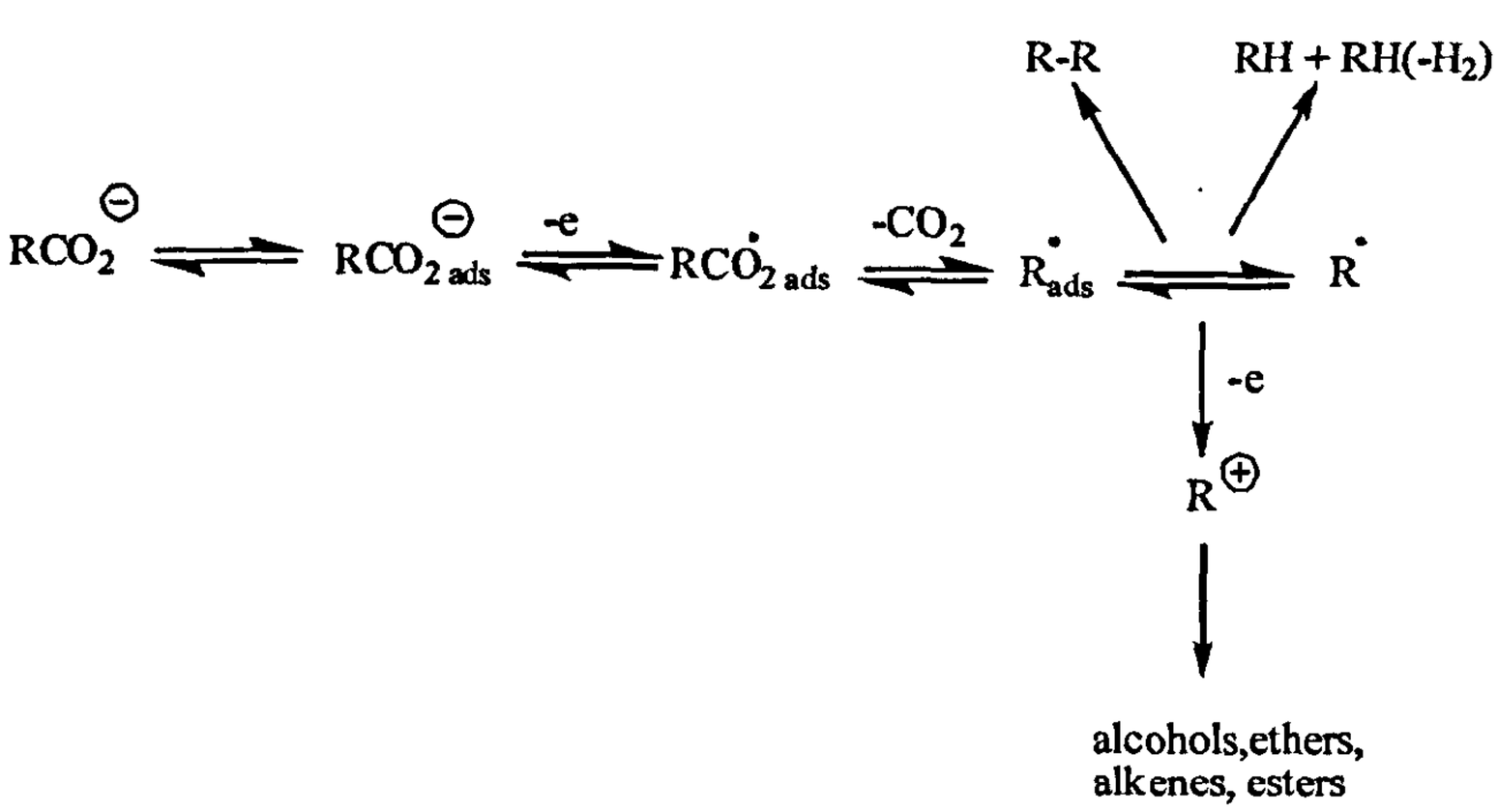
1.6.4.3 Kolbe Symmetric Coupling (Dimerization)

Kolbe electrochemical oxidation of carboxylates is one of the earliest reactions in the organic electrochemistry. The Kolbe reaction can be regarded as a chemical process, involving the control of one electron oxidation to generate $R^{\cdot}$ radicals. These radicals give rise to coupling/dimerization reactions, which have found numerous synthetic applications.[71b, 80, 81] Preparative use of the Kolbe coupling has been well established and several examples are reported in excellent reviews.[66b, 68, 70, 73, 80, 82-84]

1.6.4.4 Mechanism of Kolbe Dimerization[12, 13a, 85]

In the 1930's, different mechanisms were proposed for Kolbe electrolysis. The free radical or discharge ion theory was suggested by Crum, Brown and Walker,[86] assuming acyloxy radicals were present as intermediates. This theory comes closest to the present mechanistic ideas. According to Glasstone's and Hickling's hydrogen peroxide theory,[87] Kolbe dimers and Hoefer-Moest products (alcohols and esters) are formed by the action of $HO^{\cdot}$ and H_2O_2. According to the acyl peroxide theory by Schall and Fichter,[88] the

acyloxy radicals formed by discharge of the carboxylates couple to diacyl peroxides that decompose. The recent mechanistic proposals explain the experimental factors the most, however there is some disagreement existing between the physical and organic chemists.[85] From the physical chemist point of view[89] the following general scheme is assumed (Scheme 25).



Scheme 25 1e– oxidation generates radicals (Kolbe Electrolysis), 2e– Oxidation generates carbenium ions (non Kolbe)

The competing pathways to radical or carbenium ion derived products are determined by the ionization potential of the radical. By determining the product ratios and ionization potentials of the intermediate radicals, such conclusion can be drawn that radicals with ionization potentials higher than 8eV lead preferentially to the coupling product and radicals with ionization potential less than 8eV are further oxidized to carbenium ions.[90] By employing the rotating disc electrode experiments[91] and the radioactive tracer method with ^{14}C-labeled carboxylic acid,[92] it has been shown that carboxylates are adsorbed at the anode surface. Almost all measurements support the idea that Kolbe reaction and other reactions of this type are preceded by a substantial change in the electrode surface state due to the adsorption processes occurring at the electrode surface not only in aqueous media[93-95] but to the same extent in nonaqueous media.[96-102] A number of studies show that a direct discharge of carboxylates occurs at sufficiently high anodic potentials with the formation of radicals.[41a, 103-109] The extensive study,[110-127] into the role of

adsorbed species and the nature of intermediates at the electrode surface for the elucidation of mechanisms for Kolbe type reactions, also points to the importance of adsorption processes. According to the studies, reviewed by Vassiliev and Grinberg,[85] even the founders of the radical discharge theory, Crum-Brown and Walker[41a, 104] postulated that the electrode surface takes part in the reaction as shown in Scheme 26.

$$RCOO^- + M \longrightarrow RCOO^{\cdot}/M + e$$

$$RCOO^{\cdot}/M \longrightarrow R^{\cdot}/M + CO_2$$

$$2\,R^{\cdot}/M \longrightarrow R_2$$

Scheme 26 1e–oxidation generates radicals at the metal surface

On the basis of the analogy with the formation of adsorbed hydrogen in the reaction of hydrogen evolution, Conway and Vijh [89, 96, 128] suggested that radicals $RCOO^{\bullet}$ and $R^{\bullet}$ are formed in an adsorbed state (Figure 9), and raised criticism against the calculations performed[90, 105, 129] in deriving electrode potentials for individual stages in the Kolbe reaction.

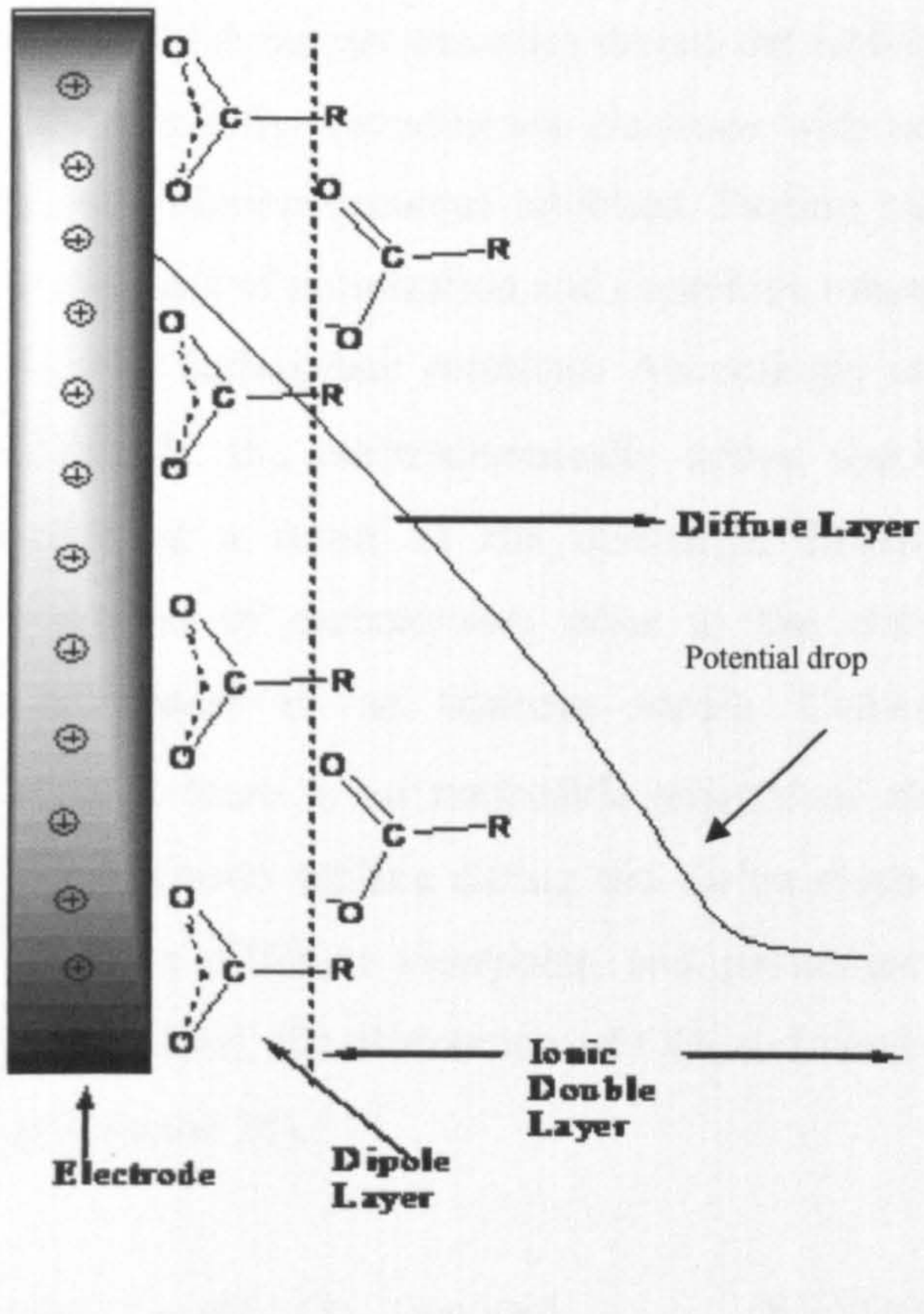


Figure 9 Schematic representation of metal-solution potential drop at an electrode with a dipole barrier type layer of adsorbed intermediates

According to Conway and his colleaguges[96-99, 128, 130-135] after $RCOO^{\bullet}$ is adsorbed at the metal surface, as a result of the discharge of $RCOO^{-}$ this radical starts to decompose heterogeneously. The decomposition leads to the formation of $R^{\bullet}$ and CO_2 adsorbed at the neighboring adsorption sites. This process is followed by either the heterogeneous recombination of the adsorbed radicals $R^{\bullet}$ according to Scheme 27, or by their electrochemical desorption.[130]

$$RCOO^{-} + R^{\bullet}/M \longrightarrow R_2 + CO_2 + e^{-}$$

Scheme 27 1e–oxidation generates radicals at the metal surface

Dickinson and Wynne-Jones[82] proposed the mechanism according to which, $HO^{\bullet}$ radicals

are preferably removed from the surface at low current densities, before the acetate radicals. As a result of which, the oxygen evolution predominates suppressing the Kolbe reaction. On the other hand high current densities favour the Kolbe reaction, discharging the acetate radicals predominantly, covering the electrode with acetoxyl radicals under steady state, and oxygen evolution becomes inhibited. Fioshin and Merkind[135-137] gave their point of view, on the basis of polarization and capacitive measurements taken on the smooth platinum in various carboxylate solutions. Accordingly at potentials below the "critical" value by 0.8-0.9V, the electrochemically active species ($RCOO^{\bullet}$ and $R^{\bullet}$) emerge at the electrode as a result of the discharge. Eberson and Nyberg[114-116] demonstrated the adsorption of carboxylates prior to the critical potential by the electrooxidation of propionate in an aqueous media. Conway and Liu[121] have experimentally proved, that there is no noticeable amount of chemisorbed $RCOO^{\bullet}_{ads}$ species at the platinum electrode surface during the Kolbe electrosynthesis. However, Eberson[90, 115, 116, 129] held a different viewpoint, and postulated that because of the instability of the $RCOO^{\bullet}$ radical, the abstraction of CO_2 and detachment of the electron takes place in one step (Scheme 28).

$$RCOO^{-} \longrightarrow [R....CO_2....e(anode)] \longrightarrow R + CO_2 + e$$

Scheme 28 1e– oxidation generates radicals at the metal surface

The $R^{\bullet}$ radical then diffuses into the bulk solution and undergoes further transformation. The radical is truly free and the homogeneous nature of the reaction has been confirmed by the stereochemistry of the products obtained. Recently results were reported[138, 139] which could be interpreted as proving the existence of the adsorption of $CH_3^{\bullet}$ radicals. All these and other assumptions and debates center around the issue of whether or not the adsorption of intermediate radicals, which are formed as a result of discharge of the carboxylate anion, is possible. The majority of literature supports the important role played by adsorption in the electrosynthesis and the necessity of knowing the nature of various species chemisorbed at the electrode, in order to elucidate the mechanism of this

reaction.The electrooxidation of the solvent, current density, degree of neutralization *i.e.* pH (which suits the electrolyte), temperature, additives, supporting electrolyte, electrode material and chain length (or most importantly the structure of the acid) are the factors influencing the selectivity of Kolbe *vs* non-Kolbe pathways.[12] A high current density and a resulting high concentration of alkyl radicals at the surface of electrodes favours the formation of dimeric products.[103]

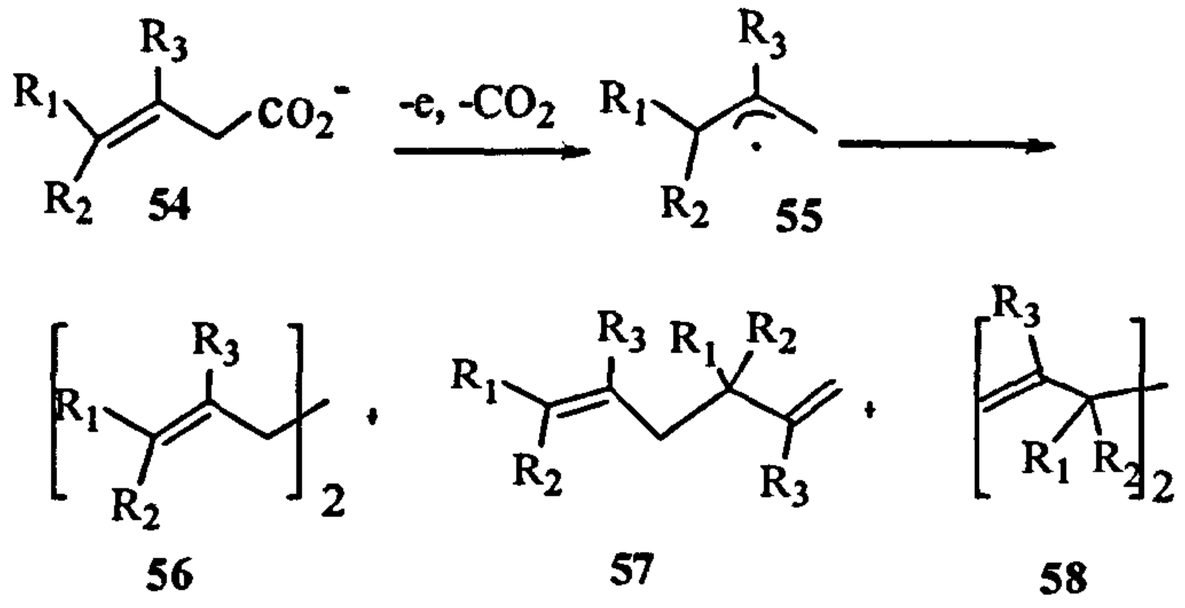
1.7.0 Factors Affecting Dimerization[12, 85]

1.7.1 Structure of the Acid

The Kolbe synthesis of compounds of the type R-R formed by electrolysis of the acids R-COOH is known to be accompanied by side reactions, a number of which were described by Kolbe himself.[140] The extent to which by-products are formed is governed both by the experimental conditions and to a degree by the structure of the acid to be electrolysed. The experimental results reported in the literature show that the influence of the carboxylic acid structure on the Kolbe electrosynthesis, manifests itself in three ways.[85] Firstly by changing the rate of destructive chemisorption and destructive oxidation of the carboxylic acid molecule, secondly by the competition between the solvent and carboxylate ion, in the range of high potentials, on the surface of platinum electrode, and thirdly by a change in the direction of radical reactions, caused by the change in the nature of the radical formed. The chain length is one of the main factors related to the Kolbe ($1e^-$oxidation)/non-Kolbe ($2e^-$oxidation) reaction.[141] The increased length of the chain increases the preference of dimer formation. This is believed to originate as a result of the packing of the substrate at the electrode surface. The carboxylates tend to stack in a mono layer, perpendicular to the surface of electrode, resulting in a close packing of the carboxylates producing a high local concentration of radicals.[11] A survey of the literature[96, 142-146] reveals that the presence of substituents α to the carboxyl group has the most pronounced influence, as would be expected, and may result in the Kolbe coupling reaction being largely or completely suppressed. For example, the electrolysis of α-halogeno acetic acids, produce poor yields of the dimeric Kolbe products, giving rise to the assumption of another reaction pathway leading through the carbene ion in the

electrochemical stage.[147, 148] Thus although normal coupling occurs with alkyl hydrogen malonates[41a] and, to a smaller extent, with α-phenyl-,[149] and α-aryloxy-acetic acids,[150] and a few α-alkyl acids, little or no coupling has been reported for α-methoxy-, α-hydroxy-, α-halogen-, α -keto, α- cyano, and α -amino- acids[151] or for di or tri-phenylacetic acid.[59, 60] Kolbe dimers are formed in 50-90% yield when the intermediate radical is either primary[66b] or is substituted by electron-withdrawing groups,[152] that is RCH_2 or RCHX or $RCHX_2$ where $X=COOR'_2$, $CONR'_2$ *etc.* When the α-position of the acid contains a substituent capable of stabilizing a carbonium ion (X = alkyl, alkoxyl, halogen, aryl, *etc.*), yields of the Kolbe dimer are very low (0-10%). In such cases, the initially formed radical is oxidized further to a carbonium ion.[138, 139]

There are a few other cases where the Kolbe yields are low, aryl[149, 153] and α, β unsaturated acids afford little or no dimer, for example the isolation of benzene from the oxidation of benzoic acid. In contrast to aliphatic acids, aromatic carboxy compounds and amino acids give poor yields of Kolbe dimerization.[85] The potential at which anions of carboxylic acids discharge[154] at the platinum electrode, increases in the order $C_2H_5COO^-$ < CH_3COO^- < $C_4H_9COO^-$ < CH_2ClCOO^- < CCl_3COO^- < $CHCl_2COO^-$ < CF_3COO^-. Many functional groups such as halogens, acetals, ketones, and acetates, and in some cases alcohols, aldehydes, and amides, survive during the Kolbe decarboxylation. Double bonds isolated from the carboxylic acid group are usually not affected by the Kolbe electrolysis conditions. The β,γ-unsaturated acids **54** (Scheme 29), give the isomeric 1,5 dienes **56-58** *via* the allylic radicals **55**.[155]

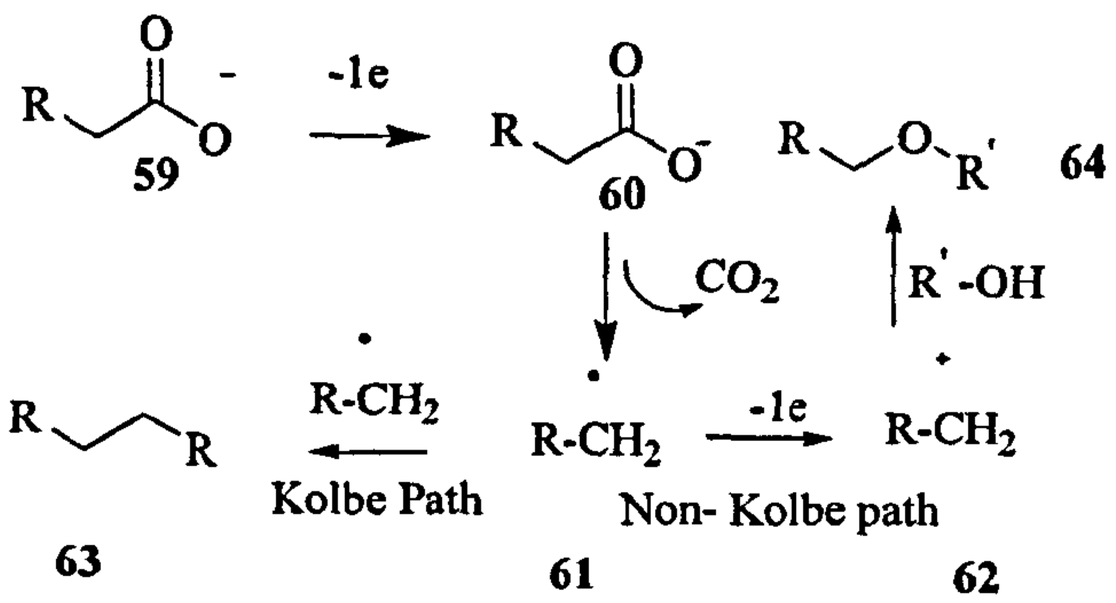


Scheme 29. The oxidation of a β,γ-unsaturated acid

Other than the above, there are really very few restrictions on the nature of the R group in a carboxylic acid (RCO_2H), to be submitted to the Kolbe reaction.

1.7.2 Current Density[64]

Kolbe electrolysis has been thoroughly discussed in the literature[11, 140, 156] and it is well-known for its versatility, as far as various reaction conditions are concerned. The result of a typical 1e $^-$ oxidation (Scheme 30), of the salt of a carboxylic acid **59** leads to the formation of carboxyl radical **60**, from where the loss of CO_2 affords an alkyl radical **61**. In addition to giving a dimer **63**, the radical may also lose another electron leading to the formation of a carbocation **62**. This cation is intercepted by an alcoholic solvent, Hofer-Moest[157] reaction, to give rise to a so-called non-Kolbe product **64**. The non-Kolbe pathway is favoured by low current density, the use of graphite electrodes, salt additives and an alkaline medium.[11] Whereas, Kolbe products are favoured by a high current density, the use of platinum electrodes, an acidic media, and electron releasing groups.[158]



Scheme 30. Kolbe/Non Kolbe pathway

High current densities around 0.25 - 1.0 A / cm^2 and high carboxylate concentrations favour the formation of dimers.[82] This is due to a high radical concentration at the electrode surface that promotes dimerization. Furthermore, at high current densities the so called *critical potential* of about 2.0 - 2.8 V (*vs* normal hydrogen electrode, NHE)[159] is reached, above which the decarboxylation and Kolbe dimerization proceeds smoothly. As the electrolysis operates at constant current density, there is, however, no need for potential control in Kolbe electrolysis because the critical potential is already exceeded at 1 to 10 m A /cm^2. This is much below the usually applied current density, which should be as high as possible, normally equal to or greater than 250 m A /cm^2.

1.7.3 Electrolytic Media (solvent, pH)[64]

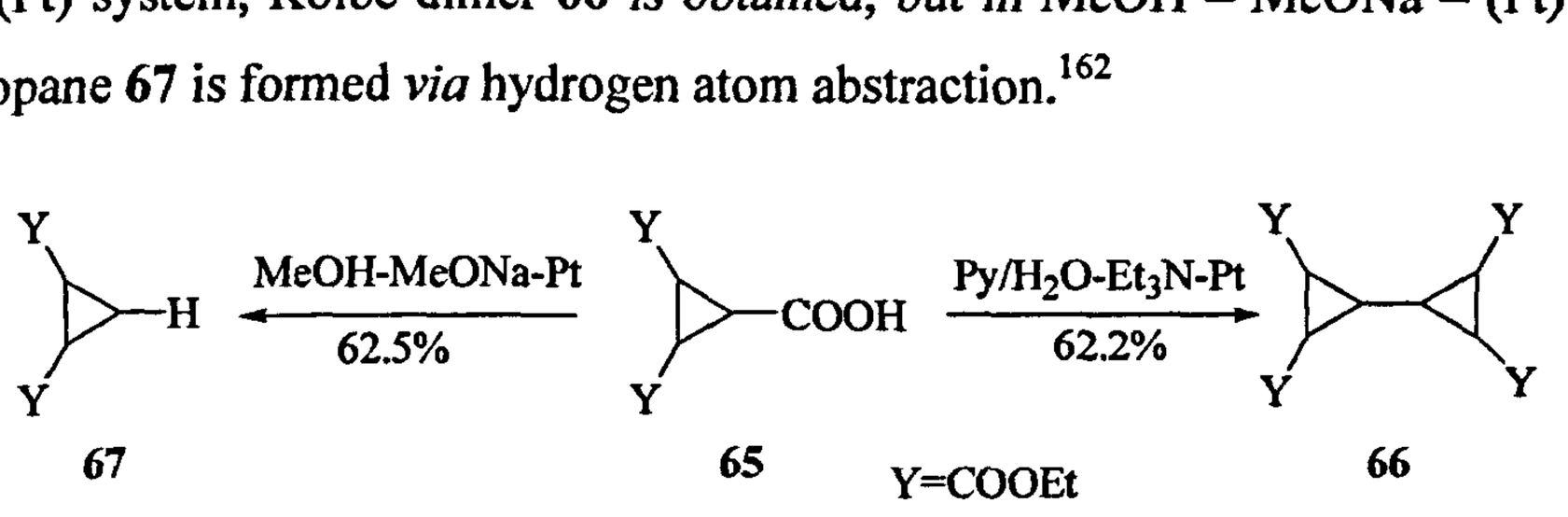
In the Kolbe reaction all the radical processes take place near the surface of the electrode in the electric double layer. This is not only influenced by changing the solvent structure but also by the influence of the potential jump in the double layer[85]. Along with high current density, a carboxylate layer at the electrode surface and resulting high concentration of radicals is necessary for the higher dimer yields, this carboxylate layer can be supported by a suitable solvent, and methanol is the best suited solvent for Kolbe electrolysis.[160] Common solvents are methanol or methanol/water, but sometimes dioxane, dimethylacetamide, acetonitrile/water or dimethylsulfoxide is used.[161]

A neutral medium, or even better a weakly acidic solution, with partial neutralization of the acid, seems more favourable for the Kolbe reaction.[13a] This is achieved by

neutralizing the carboxylic acid to an extent of 2 to 5%, in some cases up to 30%, by an alkali metal hydroxide or alkoxide or trialkyl amine. Since the hydroxyl ions are formed at the cathode at the same rate as the carboxylate ions are consumed at the anode, the concentration of carboxylate ions remains approximately constant throughout the whole run. As the electrolyte is kept acidic during electrolysis, the endpoint of the electrolysis is indicated by a change of the electrolyte to an alkaline pH.[64]

Most frequently alkaline protic solvent (Pt electrodes) system,[64] such as MeOH-MeONa, MeOH-H_2O-NaOH, MeOH-KOH, MeOH-Py–Et_3N, and MeOH-Py–Na salt systems are used as electrolysis media. Aprotic media, such as DMF–KOH, MeCN–Et_3N, MeCN–Et_4NBF_4, and Py–H_2O–Et_3N, are also used and in particular cases, acetone–H_2O–NaOH.[64]

The choice of medium may provide significant selectivity of product for each reaction. As in the electrolysis of cyclopropane carboxylic acid **65**, (Scheme 31), in a Py – H_2O – Et_3N – (Pt) system, Kolbe dimer **66** is obtained, but in MeOH – MeONa – (Pt) system cyclopropane **67** is formed *via* hydrogen atom abstraction.[162]



Scheme 31 Selective dimerization of cyclopropane carboxylic acid

1.7.4 Temperature and Pressure[64]

In aqueous solution an elevated pressure favours the Kolbe-coupling against non-Kolbe products. At high pressure, volatile species such as hydrogen, carbon dioxide and olefins or alkanes get accumulated on the anode surfaces and affect the product distribution.[163]

Temperature has some effect on Kolbe electrolysis. Increase in temperature, generally increases the yield of Kolbe dimers, but increasing it over 50°C causes a total change in products *i.e* forms non Kolbe products. Very high temperatures seem to support

disproportionation against the coupling reaction and intramolecular additions to double bonds against a competing inter- molecular coupling.[164]

1.7.5 Additives[64]

Additives can strongly influence the Kolbe-reaction. Foreign anions should be definitively excluded, because they seem to disturb the formation of the necessary carboxylate layer at the anode. Their negative effect increases with the charge of the anion. Foreign cations can increasingly lower the yield in the order of Fe^{2+}, $Co^{2+} < Ca^{2+}$. Alkali and alkaline earth metal ions, alkyl ammonium ions and also zinc or nickel cations do not affect the Kolbe reaction, and therefore, work as supporting electrolytes and counterions of choice in preparative applications.[13a]

Pyridine, also used as aprotic solvent and a strong base is the conventional additive for methanol solutions in Kolbe electrolysis.[165] It does improve the yield of dimerization considerably, as well as preventing the fouling of electrodes, yet the mechanism of pyridine action is not quite clear.[166]

1.7.6 Electrode Material[13a, 64]

The formation of Kolbe radicals is favoured by platinum electrodes and also by those of vitereous or baked carbon[167] or glass like hard carbon.[13a] Preparative electrolysis of triethylammonium heptanoate using different types of carbon as the anode material was investigated by Brennan and Brettle.[167] It was found that in protic solvents the Kolbe dimer dodecane, was the major product at vitreous or baked carbon anodes, but the formation of hexyl heptanoates dominantes at graphite electrodes. The product distribution, using edges and face surfaces of pyrolytic graphite, lead to the view that these differences in products from different carbon electrodes, are due to the different adsorptive properties of these electrode surfaces. The results of electrolysis of heptanoic acid (0.02M) neutralized to the extent of 20% by triethylamine at an apparent current density of 110-65mAcm^{-2} for (baked carbon and graphite) are given in Table 1.

Solvent	Graphite	Vitreous Carbon	Baked Carbon	Platinum
MeOH	1	24-33	30	52
EtOH	5-9	45-53	39	62
H_2O	2	47-50	-	45
$Me(CH_2)_5CO_2H$	1	33	-	-
$HCONMe_2$	0	1-3.5	-	66

Table 1[167] Electrolysis of heptanoic acid showing chemical yields (%) of dodecane

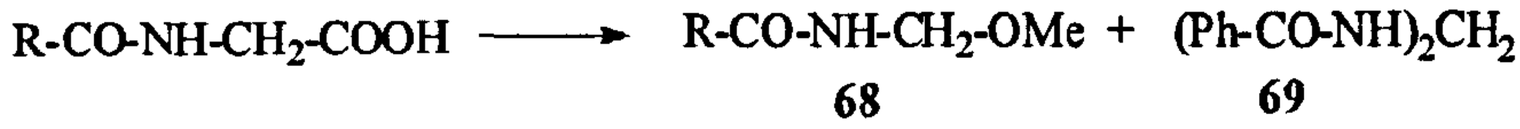
As anode material, smooth platinum in the form of a foil or mesh seems to be most universally applicable.[168, 169] However in aqueous solutions anode materials, such as platinum, iridium and vitreous carbon electrodes favour the coupling reactions, whereas graphite and porous carbon anodes facilitate the two electron transfer and cation intermediates.[168-171] In the non aqueous medium a variety of electrode materials can be employed, however platinum is again the best for one-electron process, and carbon for two-electron process.[13a, 71, 172] The nature of the cathode material is not critical in the Kolbe reaction.[13a] The reduction of protons from the carboxylic acid is the main process, so that the electrolysis can normally be conducted in an undivided cell. For substrates with double or triple bonds, however the use of a platinum cathode should be avoided to minimise the hydrogenation of the unsaturated substrate.

1.8.0 Dimerization of Amino Acids

Kolbe electrolysis serves as an experimentally simple way of generating radicals in preparative amounts.[11, 13a] The dependence of the yield on certain factors like solvent, temperature and concentration of the carboxylate anion, and protecting group has been extensively investigated.[173] For the preparation of 2,7-diaminosubaric acid by Kolbe coupling of *N*-protected α-glutamic acid esters, the highest yield of protected dimer is obtained with Boc-Glu-OMe as starting material and MeOH/pyridine/NaOMe as electrolyte.[174]

1.8.1 Kolbe Electrolysis of *N*-Acylaminoacids [173]

Electrolysis of *N*-acyl-glycines and DL-α-alanines in methanol gives *N*-methoxymethyl- and *N*-methoxyethyl-amides respectively in good yields. Analogous reactions occur in both ethanol and isopropanol. Under similar conditions *N*-acyl derivatives of 6-aminohexanoic acid, γ-aminobutyric acid and β-alanine undergo the normal Kolbe reaction giving the corresponding derivatives of polymethylenediamines in 20-40% yields. The results with *N*-acylamino acids are reported in a communication by Linstead and Schaffer.[173] These have yielded results quite different from those reported by Fichter and Schmidt[175] according to which, electrolysis of α-amino acids or their *N*-acyl or *N*-sulphonyl derivatives in aqueous solutions, led to complete destruction of the molecule and not to coupling of the Kolbe type. In the Kolbe electrolysis of fatty acids the use of methanolic rather than aqueous solutions has frequently been found advantageous. The electrolysis of *N*-benzoylglycine in methanol (Scheme 32) also furnished the neutral product in good yield (61%) which was formulated as *N*-methoxymethyl-benzamide **68** where (R = Ph). The product was confirmed on the basis of the analytical results and the formation of bisbenzamidomethane **69** and formaldehyde on treatment with mineral acid.



Scheme 32 Electrolysis of N-Benzoylglycine in methanol

In this electrolysis, the anodic methoxylation also took place readily with *N*-acetyl- and *N*-carbobenzyloxyglycine, giving *N*-methoxymethylacetamide **68** (where R = Me) and benzylurethane **68** (where R = $PhCH_2O$) in 78 and 74% yield respectively. Similarly *N*-acetyl- and *N*-benzoyl-DL-α-alanine gave *N*-methoxyethylamides **70** (where R = Me and Ph) in 85% and 91% yield respectively.

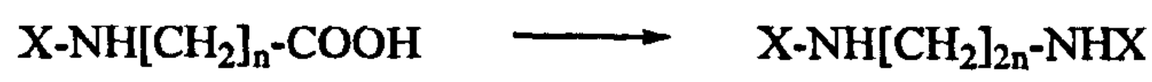
The use of solvents other than methanol was also briefly investigated,[173] and by electrolysis of *N*-benzoylglycine **71** in ethanol and isopropanol, and of *N*- benzoyl-DL-α-alanine **71** in ethanol, the corresponding ethoxy- and isopropoxy-alkylamides **72** were obtained (56-70%). These reactions can be generalised as (Scheme 33).



Scheme 33 Electrolysis of *N*-Benzoylglycine in ethanol and Isopropanol

Where X is acyl, R hydrogen or methyl, and R' is an alkyl group. The alkoxyalkyl-amides (acylaminoethers) so produced were of a rare type hard to prepare in other ways. The yields were high and the products obtained were crystalline solids or colourless distillable liquids. Electrolysis of *N*-phenylacetylglycine in acetic acid solution yielded *N*-acetoxymethyl-phenylacetamide ($Ph\text{-}CH_2\text{-}CONH\text{-}CH_2\text{-}OAc$), in 38% yield. From a few of the electrolyses in alcohols described above, small amounts (<15%) of α-diamine derivatives, the products of normal coupling, were also isolated. After the study of derivatives of α-amino-acids, attention was directed to acids with the amino- and carboxyl groups separated from one another. Fichter and Schmidt, were unable to detect

the normal Kolbe reaction on electrolysis of β-alanine or its *N*-benzoyl derivative in aqueous solution, but Offe[6] has stated that electrolysis in methanol of *N*-acyl or *N*-alkyl sulphonyl derivatives of amino-acids other than those of the α-series leads to the corresponding derivatives of diamines by normal coupling. This conclusion was based on the results of electrolysing γ-phthalimido-butyric acid and derivatives of 6-aminohexanoic acid but yields were given in one case only. However, Linstead and Shaffer's[173] work details the normal Kolbe coupling, in the electrolysis in methanol of a considerable range of acylamino-acids **73** other than those of the α-series. The general reaction (scheme 34), proceeds in about 30% yield of **74**, where n is 2, 4, or 6. Thus 6-acetamido-, 6-benzamido-, and 6-carbobenzyloxyamino-hexanoic acids yielded the corresponding derivatives of 1:10-diamino-decane (31, 23, and 38% respectively). 1:6-Biscarbobenzyloxyaminohexane was similarly prepared (35%) from γ-carbobenzyloxyaminobutyric acid. Electrolysis of *N*-benzoyl and *N*-carbobenzyloxy-β-alanine furnished the derivatives of 1:4-diaminobutane in 20 and 33 % yield. From *N*-benzoyl-β-alanine a small amount of 2-phenyloxazoline was isolated (in the form of its picrate) as by-product. In general, however, the nature of the side products in these reactions remained to be determined.



73 **74**

Scheme 34 Electrolysis of *N*- Acylamino acids in methanol

1.9.0 Microreactors[171]

Microreactors are defined as miniaturized reaction systems fabricated using methods of micro technology and precision engineering. The characteristic dimensions of the internal structures of microreactors, such as fluid channels, typically range from the sub-micrometer to the sub-millimeter range. There are two classes of miniaturized reaction systems, referring to their applications in analysis or chemical synthesis.

A vast majority of microfluidic devices refer to continuous flow systems, which were developed for analytical purposes starting in the late 1980s. If a series of processes such as filtration, mixing, separation and analysis is combined within one unit the resulting microsystem is termed as a micro total analysis system (μTAS).[176]

With regard to chemical synthesis, there are many fundamental advantages of micro-reactors compared to lab-scale equipments, as the smaller devices need less space, materials, energy and often shorter response time. Microreactors are flow-through systems that are made from a solid matrix with typical channels or cell widths of 50–500 μm, however there are examples where channels can go up to several mm in size. They are made by appropriate means of micro fabrication, *e.g.* structuring of photosensitive glass, anisotropically etching of silicon, or using the LIGA process.[177]

Micro reactors designed for the synthesis of chemicals have attracted the most attention. Because of the small amount of injected chemicals and the high rate of heat transfer, the systems are especially suited for reactions with highly toxic, flammable and explosive chemical compounds. Heat control and heat transfer play an important role in most chemical reaction processes, and because of the large surface area to volume ratios the removal of heat can be optimised in microreactors. Microreactor technology increases the safety, reliability and quality of chemical processes. Up to now most studies concentrated on microreactors for the efficient micro mixing, and heat exchanging to enable chemical reactions to be efficiently conducted.

Heat exchangers, static mixers, pumps and other components can be fabricated in configurations measured in millimetres, and embedded with micrometer-sized pores or channels. As a result of larger relative surface areas, devices with these small dimensions are more efficient for mass and heat transfer. This results in greater selectivity and a higher yield for chemical reactions. Such small devices are used in high-throughput screening and combinatorial chemistry.

Microreactors have now created a new approach for performing reactions. Instead of a traditional electrochemical cell with macroscopic electrodes, the cell composed of a large number of thinly sliced porous electrodes separated by thin insulators can also do the same job. Besides electrochemical reactions, thermal and photochemical reactions can be made smarter by controlled periodic processing. In addition reactions can be carried out at room temperature within the micro reactors when batch reactions often need elevated temperatures.

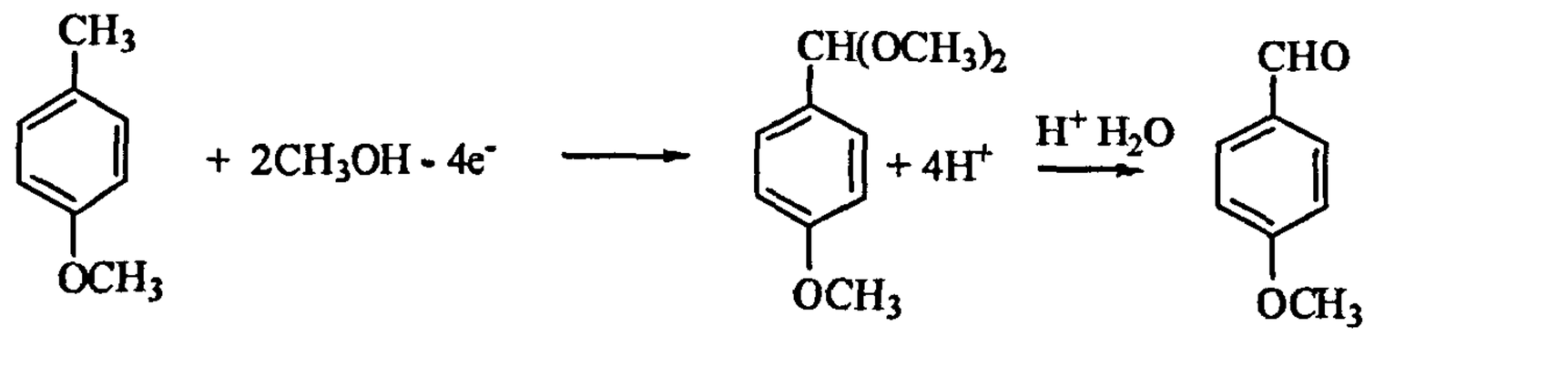
1.9.1 Electroorganic Synthesis in Microreactors[176]

Electrochemical processes which use current as the reactive agent have a number of advantages and disadvantages when compared with conventional liquid phase processes, based on the utilization of various chemical compounds. In particular, oxidation and reduction processes, benefit from continuous variation of reactivity by means of regulation of electric potential, and has a clear advantage in terms of product separation and process flexibility.

However, there are several limitations of current electrochemical process technology which hinder its wide spread use in synthetic industry. One of the drawbacks is that current cells suffer from in-homogeneities of the electric field. Some of these limitations can be overcome by precisely fabricated microreaction systems. Apart from field homogeneity, such electrochemical microreactors should have a uniform flow distribution, *i.e.* without any dead zones, and efficient heat transfer.

One of the examples of such an electrochemical microreactor is the plate-to-plate electrode microreactor, developed by researchers at the Institut fur Mikrotechnik Mainz (Germany),[178, 179] based on the the micro structuring techniques for thin layer technology.[180] The main component of this microreactor is a micro-channel layer of 800 μm width, 25μm depth and 64μm length, embedded between a working and a counter-electrode, referred to as a plate-to-plate configurations (Figure 10). The reaction temperature is controlled by an integrated cooling element.

The electrosynthesis of 4-methoxy benzaldehyde **77** from 4-methoxytoluene **75** by direct anodic oxidation, (Scheme 35) is performed on an industrial scale.[176] *Via* an intermediate methyl ether derivative **76** the corresponding diacetal is obtained which can be hydrolysed to the target product.[181]



4-Methoxy-Toluene	4-Methoxy-benzaldehyde-dimethyl acetal	4-Methoxy-benzaldehyde
75	**76**	**77**

Scheme 35. Electrosynthesis of 4-methoxybenzaldehyde

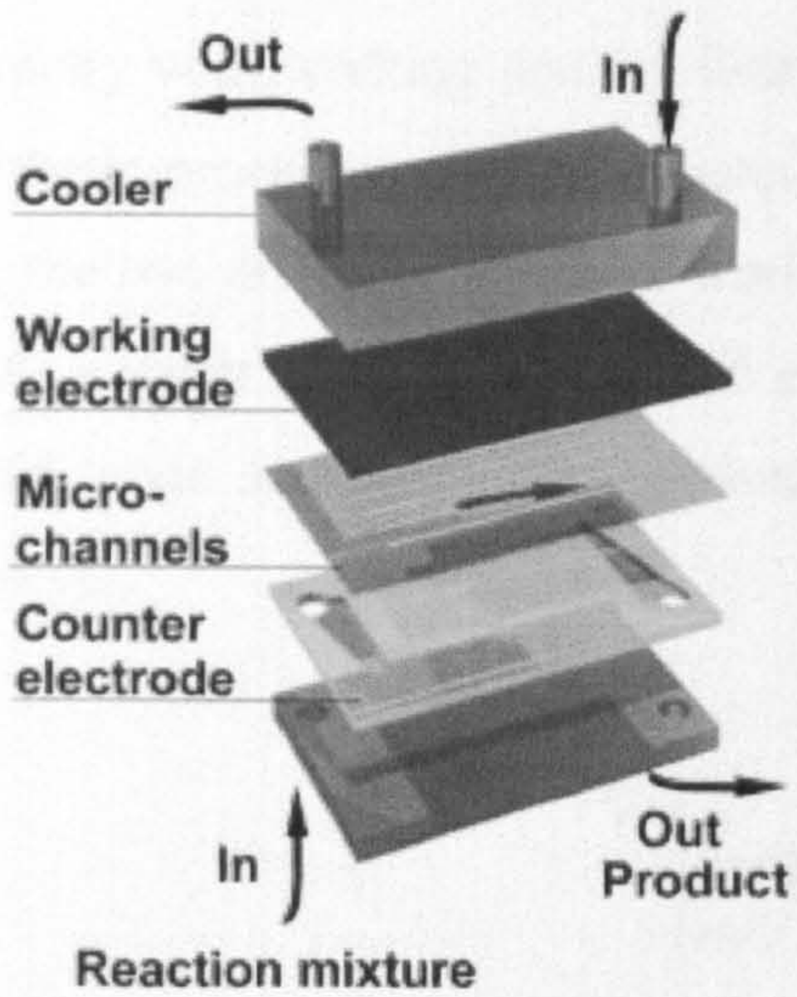


Figure 10. A mounted Plate- to -Plate Electrode Microreactor

The three types of products ether, diacetal, and aldehyde correspond to three distinct single oxidation steps. By means of HPLC analysis, it was shown that all three types of products were formed during the reaction in the microreactor.

The oxidation of 4-methoxytoluene was carried out at a current density of 79 mA/cm^2, using 0.1 M KF as conducting salt. The conversion and selectivity of this reaction increased rapidly at low values of electric potential. A potential of 4.5 V provided the best results, of 86% selectivity and 88% conversion. At higher potentials, conversion slightly increases, whereas selectivity decreases due to side reactions. A new type of reaction, can be realized by omitting the conductive salt to simplify the separation of the product and reducing the operational cost.

The micro flow cell [182] (Figure 11), represents a very good example of paired electro-synthesis, it was constructed by gluing a suitable metal film Pt or Ni of 25 μm thickness, onto glass slides of 1 cm width, 5 cm length, applying a spacer (one or several layers of tape of 50 μm thickness), to leave a rectangular channel exposed, and sandwiching the two electrodes together. The electrical contact to the outside of the channel flow cell was made with conducting copper tape. After connecting the silicon tubing to inlet and outlet,

the cell was sealed at 60-100 ^{0}C.

The thin layer flow cell geometry with working and auxiliary electrodes directly facing each other, allows electrosynthetic processes to be conducted in flow-through mode. At sufficiently small cell height, the two diffusion layers of working and auxiliary electrode overlap or become coupled. As a result the electrogenerated acids and bases are instantly neutralised, products from the anode and cathode can interact, and bulk electrolysis is possible without added electrolyte.

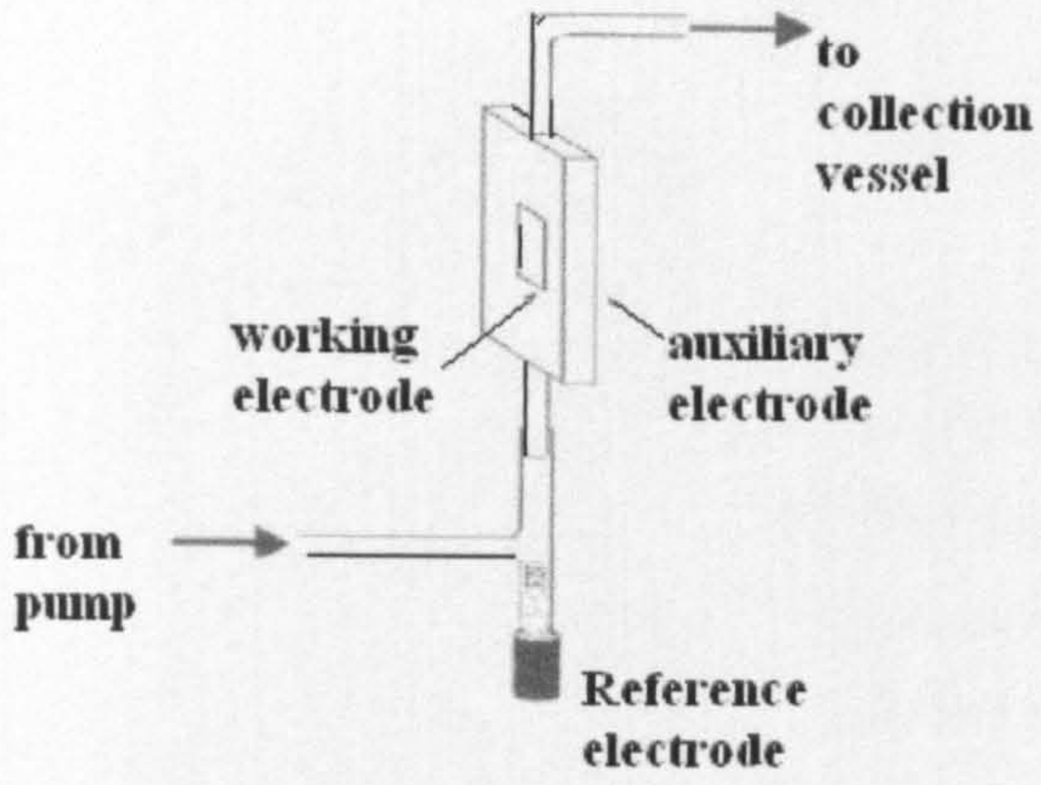


Figure11. Schematic representation of the flow system with pump inlet, external reference, micro-flow cell, and outlet[182]

The operation of a micro flow cell with coupled diffusion layers was studied for the one electron oxidation of ferrocene and two electron two proton reduction of tetraethylenetetracarboxylate dissolved in ethanol. High yields (up to 90%) of tetraethyl ethanetetracarboxylate were obtained (by increasing the electrode length and in general at a low volume flow rate) without intentionally added electrolyte at a Ni working electrode, as a sufficient concentration of electrolyte is generated locally *in situ* between working and auxiliary electrode.

The electrochemical TLC microreactor[183] (Figure 12) used for the synthesis of D-arabinose in the SMB- environment (simulated-moving-bed technology) was developed using an electrode area of 114 cm^2 carrying 75 parallel micro channels with a channel length of 189 mm on a graphite anode of 189 × 98 mm^2. The reactor design allows the

use of either divided or combined cells operated in bipolar or monopolar mode. The design consists of layered independent cell-modules and is therefore highly extendible and versatile in the choice of electrode material. In practical tests, it shows pressure resistivity up to 35 bar at a flow rate of 10 ml min^{-1} per plane.

Electrolysis under standard pressure suffers from the evolution of CO_2 gas which turns the flow of electrolyte into a two phase system, theoretical description of which is complicated, however under a pressure of 30 bar, the disturbing effect of gas bubbles diminishes, as the CO_2 dissolves in the solution.

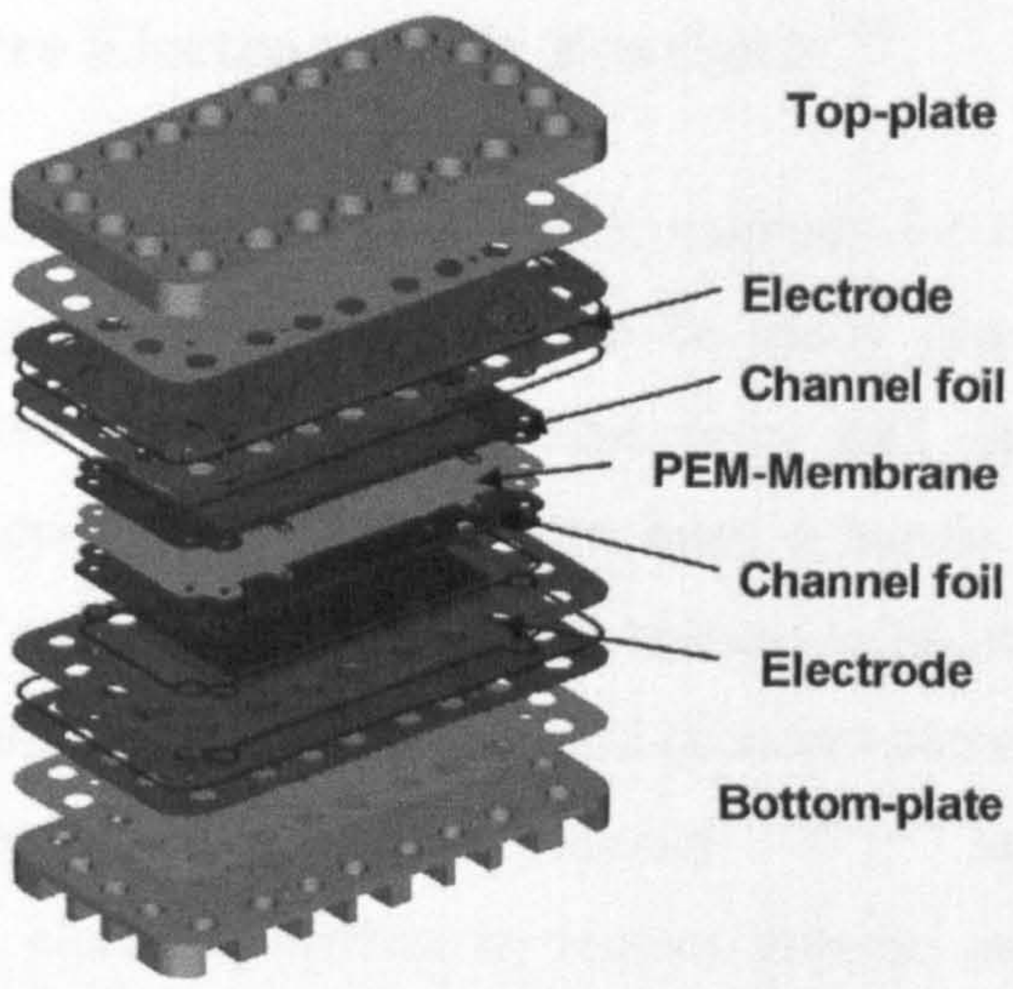


Figure 12. An explosion view of the TLC electrochemical microreactor[183]

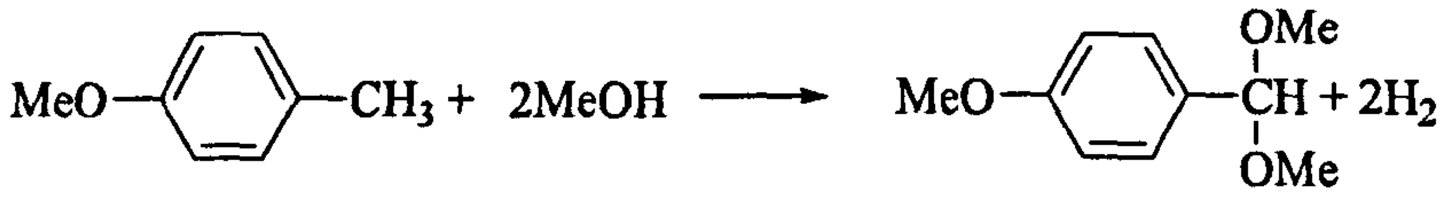
The cell consists of stainless steel, Ni, Pb, glassy carbon or graphite (that may be catalyst plated) electrodes. For the micro-channels, foil PEEK was used for making it more resistant to oxygen, chlorine and strong pH shifts. The tempering elements (cooler/heater) consist of stainless steel with channels of 100μm height that run parallel to the micro channels in the PEEK foils. The reactor is sealed by two sets of gaskets, an inner one, to guide the fluids through and an outer one to prevent any leakage, caused from a high pressure. The cell stack is pressed between massive top and bottom stainless steel plates, which allow the stacking of at least five complete electrolysis cells. The cell stack is insulated from top and bottom by Teflon-insulation foil. Next follows a tempering unit, on to which an electrode frame (cathode) is placed. On top of the cathode is the micro

structured foil, which forms the micro channels, which are closed at the top by the PEM (polymer electrolyte membrane). The half-cell described so far is mirrored in the plane of the PEM to give one full electrochemical cell.

So far the reactor has only performed stand-alone synthesis of D-arabinose, as a step prior to the integration into the SMB plant. This allows the characterization, which is essential for the digital modelling of the whole SMB synthesis process. Further improvement of the controllability of the electrochemistry inside the microreactor will come with the use of miniaturised solid-state reference electrodes.

1.9.2 Electrolyte Free Electroorganic Synthesis[184]

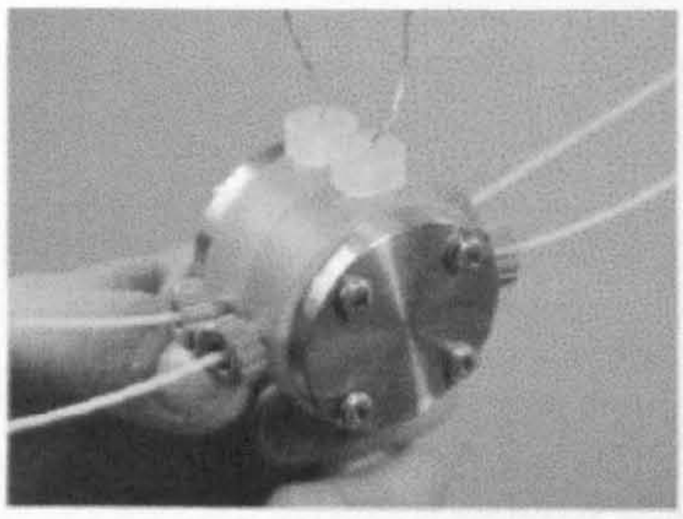
The electrochemical reactions serve as powerful methods for the synthesis of organic compounds because highly reactive species can be easily generated under very mild conditions. The electrochemical reactions have been well known for many years, however the use of supporting electrolytes has been a hurdle for synthetic chemists. Although SPE[185] (solid polymer electrolyte membranes) technology has been developed for electrolyte-free electrolysis, an approach based on micro chemical systems also seems to be attractive. Electrochemical microflow reactors[179, 183, 186] have received significant research interest. High electrode surface to reactor volume ratios and short distance between electrodes are advantageous from viewpoints of reaction efficiency and conductivity. Effective temperature control and short residence time are also favorable when highly reactive species generated by the electrochemical processes are involved. Recently, Marken and coworkers reported an electrochemical micro flow process without adding supporting electrolyte.[182] In their system, two electrodes are placed facing each other in a distance of millimeter order and the substrate solution flows through the chamber between them. Therefore, they design a system where the liquid flow and the current flow are perpendicular. Yoshida and coworkers have successfully showed (Scheme 36) the anodic methoxylation of several organic compounds including **78** in the absence of intentionally added supporting electrolyte using an electrochemical microflow system.[184]



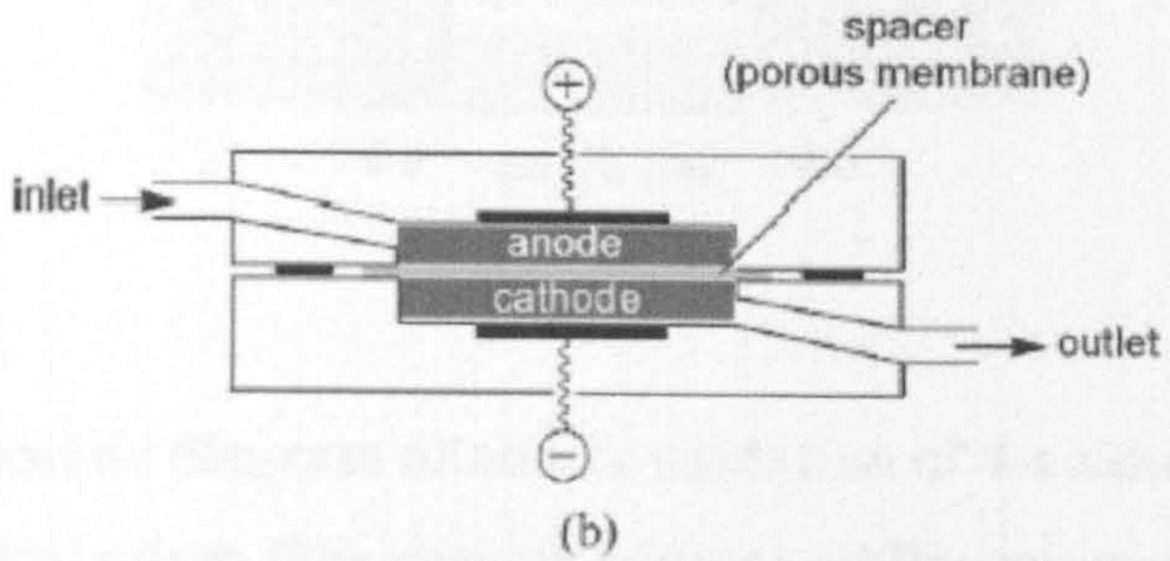
78 79

Scheme 36 Anodic oxidation of 4-methoxytoluene

The Yoshida group developed a micro system, shown in Figure 13, to achieve electrolyte-free electrosynthesis. In this system, two carbon fiber electrodes, were separated by a spacer in a distance of the micrometer order. A substrate solution is fed in the anodic chamber, flows through the spacer and the cathode, and leaves the cell from the cathodic chamber as products. As a spacer, a hydrophobic porous PTFE membrane (ADVANTEC T010A, pore size: 3 mm, thickness: 75 mm) was found to be suitable for the purpose. In this system, the electric current flow and the liquid flow are parallel, whereas they are in perpendicular orientation in the Marken system.[182] In this system the whole electrochemical chamber is filled with the carbon felt electrode, in contrast with the Marken reactor that has an empty space between the cathode and anode, therefore, the electrode surface area is greater in this system. Furthermore, this electrochemical micro system allows higher flow rate and higher current, which could be an advantage for future scaling up. The focus was the anodic methoxylation of *p*-methoxytoluene **78** (Scheme 33) because this process is well-known and industrially important.[185C, 187] A solution of *p*-methoxytoluene in methanol (0.05 M, 2 mL/h) was fed into the electrochemical microflow system. The reaction was carried out under the constant current condition (11 mA at room temperature, 4 F/mol, based on p-methoxytoluene, cell voltage: 21–25 V) to obtain the desired product **79**, in more than 90% yield based on consumed starting material (30% conversion).



(a)



(b)

Figure 13. Electrochemical microflow system: (a) outside, (b) system diagram.

It was difficult, however, to increase the current. The application of 22 mA of current gave rise to breaking of the membrane. Although the conversion of the starting material was low, the success of the present reaction can be interpreted in terms of the following scheme (Figure 14). The anodic methoxylation of compound **78** accompanied proton generation. Protons and acetal[179, 183, 186] thus formed were immediately transferred to the cathodic chamber through the porous spacer membrane. At the cathode, protons were reduced to hydrogen. Thus, acetal **79** and hydrogen gas came out at the outlet of the system. It is assumed that the flow of protons from the anodic to the cathodic chamber should be responsible for the conductivity in the solution. Some more results of compounds **80-84** are given in Table 2.

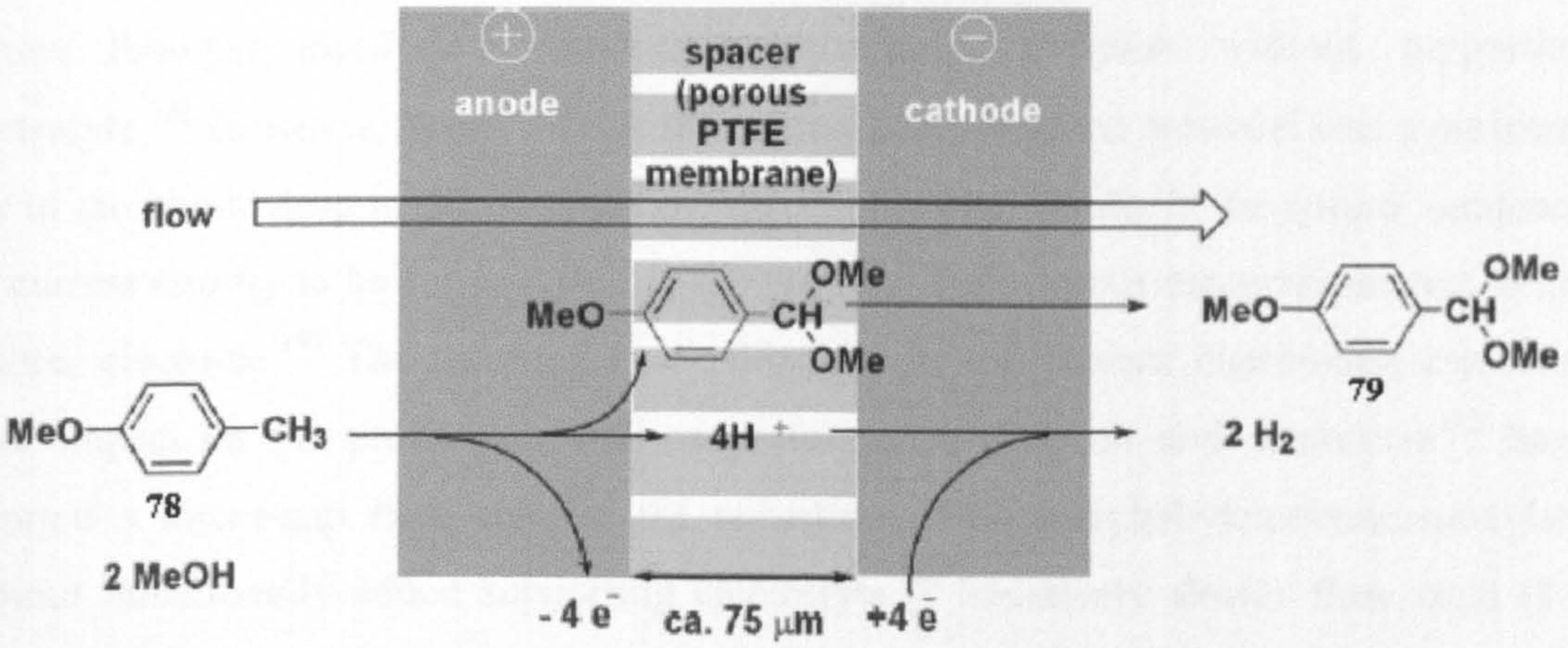
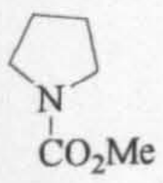
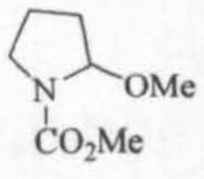


Figure 14[184] Schematic diagram of anodic oxidation of 4-methoxytoluene using the electrochemical micro flow reactor without adding supporting electrolyte

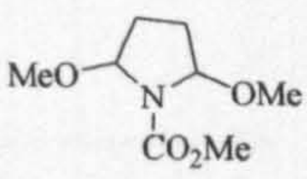
Starting material	Current/mA	Conversion/%	Product	Conversion Yield/%
80	11	77	**81** and **82**	57(26),40[b](27)
80	22	86	**82** and **83**	46(26),47[b](27)
81	11	25	**84**	56[b]
81	11	75	**84**	65[b]



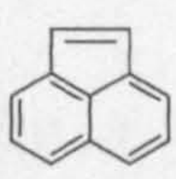
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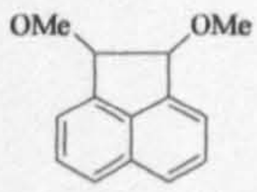
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82



83



84

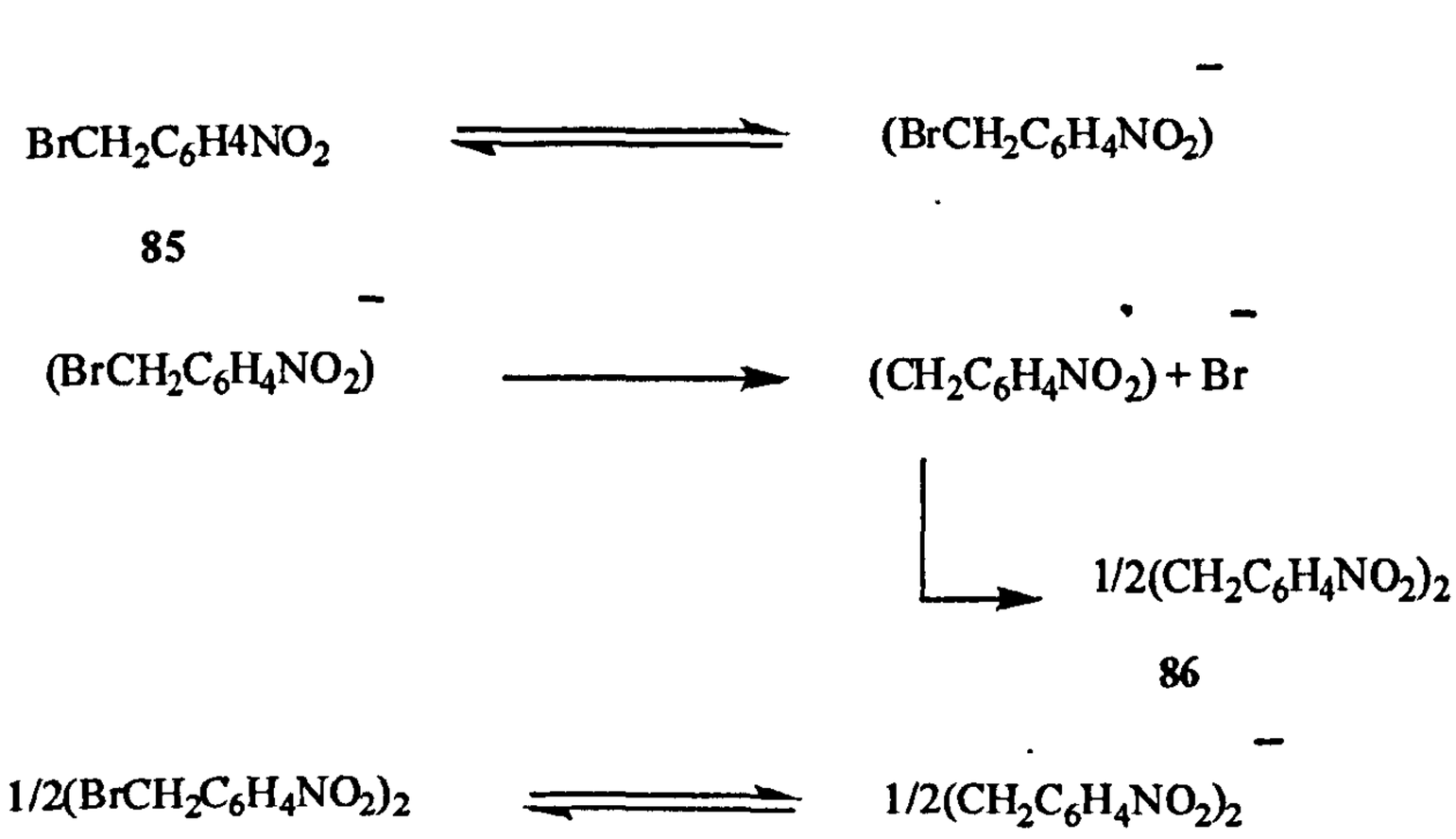
[a] Flow rate2mL h^{-1}.[b] A mixture of *cis* and *trans* isomers. [c] 50° C.

Table 2[184] Electrochemical methoxylation of organic compounds without supporting electrolyte[a]

1.9.3 Self Supported Electroorganic Synthesis in Microgap Flow Cell[188]

Recently, many types of thin-gap flow cells have been employed for the electroorganic synthesis namely the segmented thin-gap flow cell,[189] multisectioned porous electrode flow through cell, [190-193] the coplanar interdigitated micro-band electrode cell[194], and the miniaturised parallel channel electrochemical reactor.[183, 188] All of these approaches however, involve the use of supporting electrolytes or relatively low conversion without

intentionally added electrolyte.[182, 195] Yoshida and coworkers[184] reported a flow-through porous thin-gap electrode microreactor permitting operation without supporting electrolyte.[183] However, in this reactor the control of the applied potential was a problem, due to the ohmic drop in the current flow direction which results in the natural tendency for current density to be concentrated in the portion of the porous electrode nearest to the counter electrode.[191] The resulting non-uniformity in the current distribution can have great impact on the process as well as performance. Marken and coworkers[182] have reported a micro-gap flow cell for the reduction of tetraethylethylenetetracarboxylate without intentionally added supporting electrolyte.[182] Relatively slower flow rates (1.9 μl/min) were employed to obtain the high yields. Although the electrolyte free electro synthetic approach has received limited attention to date, its ability to offer a cleaner electrosynthesis still attracts the exploration of a green methodology in micro reactor synthesis. Haswell[188] and coworkers have characterised a micro-gap flow cell for the cathodic dimerisation of 4-nitrobenzylbromide **85**, without intentionally added supporting electrolyte (Scheme 37).



Scheme 37 Cathodic reduction of 4-nitrobenzyl bromide[188]

The cell consists of two glass plates (3 cm long, 2 cm wide, 6 mm thick) forming a top and a bottom. The top plate has two holes connected to PEEK tubes (I.D 0.24 mm), which acted as the flow inlet and outlet. Two equally sized Pt foils (squares of 5 mm width and length, and 0.05 mm thickness) were used for the working and counter electrodes. The flow cell is built by clamping all components together with a PTFE

spacer having a rectangular window (3mm wide and 19 mm long) cut through its center, as shown in Figure 15. A small amount of silicone sealant is used to seal the edges. The results of preparative electrolysis are given in Table 4.

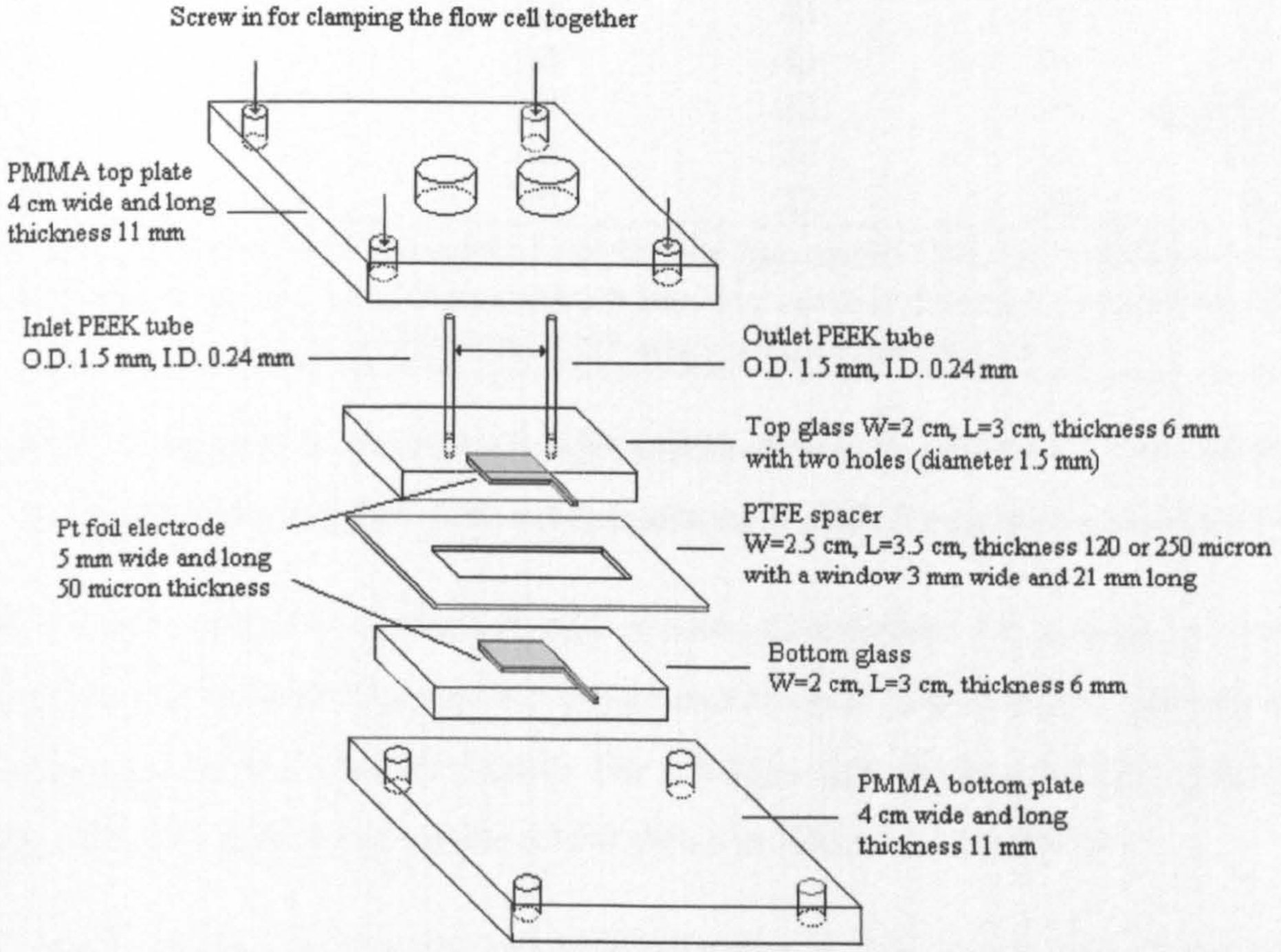


Figure 15 Construction of flow-through micro-gap cell

Electrode Gap/μm	Current/mA	Flowrate /μL/min	Residence Time/sec	Conversion /%	Product Distribution	
					R-R	R-H
160	0.8	20	22	99	68	32
160	1.3	40	11	95	69	31
320	0.6	20	43	70	93	07
320	1.2	20	43	91	91	09
320	0.6	40	22	58	94	06
320	2.5	40	22	92	91	09
320[b]	2.5	40	22	100	76	24

[a] Preparative electrolysis was carried out in thin-gap micro-flow cells with two electrode geometry with a current set to the optimum limiting current detected voltammtrically. [b] Co-solvents DMF and THF were used in the ratio of 3:1

Table 3[188] Preparative electrolysis with micro-flow cell systems for the reduction of 10 mM 4-NBB in DMF without intentionally added supporting electrolyte[a]

Table 3 summarizes the conversion and product distribution for a range of conditions. The results clearly show that the conversion and product distribution is dependent on the electrode gap and the applied current. For a bigger gap, higher voltages giving higher current, will give higher conversion of the dimer product 4, 4'-DNBB **86**.

While some of the designs for microreactors are in the developing stages, they are believed to have the potential for industrial use. Currently there are no microreactors in commercial use for electrochemistry, however researchers are focusing on, various ways of implementing micro reactors into the chemical industry. One possibility would be to run tens of thousands of the tiny reactors in parallel, creating a continuous flow micro reactor. This would allow the network of the reactors to behave like a conventional, large-scale reactor, but still have the specialized capabilities of the microreactor.

1.9.4 Initial Considerations into Microreactor cell designs

The micro reactor cell designs developed throughout the thesis were reoptimised based on experimental results obtained. However from the outset the overall aim was to develop reactors which would enable high volume production; we acknowledged that this could be affected by pumping the chemical solution very fast through the reactors. In order to achieve this it was imperative to enable very high electrode surface area to volume ratios to be achieved such that the chemical reaction happened very fast. Furthermore we considered that without electrolyte the resistance would be very high and consequently it would be necessary to design the cells in such a way that the electrodes were as close to each other as possible to minimize the energy losses.

The spacing of the electrodes for cell designs with parallel electrodes is critical, since there is a direct relationship between the current and separation of electrodes. The smaller electrode gap reduces the resistance and gives higher current and higher efficiency. However if the inter electrode distance is not equal throughout the length the current will not be homogeneous hence will significantly affect the efficiency reducing the product production due to energy losses.

To enable rapid prototyping of different designs, initial reactors were very simply made from PTFE tubing, however once preliminary experiments had been conducted optimised designs were made from glass as this would provide stronger more durable devices for long term use.

References

1. J. C. Kotz, P. Treichel, Jr. *Chemistry and Chemical Reactivity.*, Third Edition, New York , NY, 1990, 950.
2. A. G. Volta, *J. Nat. Phil. Chem.Arts.*, 1800, **4**, 179.
3. D. Abbot, *Biographical Dictionary of Scientists-Chemists.*, Peter Bedrich Books, New York, NY, 1983, 35-36.
4. M. Faraday, *Ann. Phys.*, (Leipzig), 1834, **47**,438.
5. J.O'M.Bockris, A.K.N.Reddy, M.Gamboa–Aldeco, *Modern Electrochemistry.*, Second Edition, *Fundamentals of Electrodics.*, Kluwer Acad., 2000, **2A**, 1048.
6. (a) M. M. Baizer, *Tetrahedron.*, 1984, **40**, 6, 935-969. (b) D. Pletcher, F. C. Walsh, *Industrial Electrochemistry.* 3rd Edition, Blackie Academic & Professional, London-New York, 1993.
7. B. Speiser, A. J. Bard, M. Stratmann, H. J. Schafer, *Encyclopedia of Electrochemistry.*, Vol 8. *Methods to Investigate Mechanisms of Electroorganic Reactions*, Wiley-VCH, Weinheim, 2004, 1-23.
8. J. O'M. Bockris, Z. Nagy, *J. Chem. Educ.*, 1973, **50**, 839-843.
9. J. M. Saveant, D. Tessier, *Faraday Discuss. Chem.Soc.*, 1982, **74**, 57-72.
10. S. Antonello, F. Maran, *J. Am. Chem. Soc.*, 1990, **121**, 9668-9676.
11. E. Klocke, A. Matzeit, M. Gockeln., *Chem. Ber.*, 1993, **126**, 1623-1630.
12. V. A. Grinberg. Yu. B. Vassiliev, *Russian Journal of Electrochemistry.*, 1996, **32**, 3, 281.
13. (a) H. J. Schafer, *Top, Curr. Chem.*, 1990, **152**, 91; (b) T. Shono, *Top. Curr. Chem.*, 1988, **148**, 131; (c) K. D. Moeller, *Tetrahedron.*, 2000, **56**, 9527; (d) R. D. Little, K. D. Moeller, *Electrochem. Soc. Interface.*, 2002, **11**, 4, 28; (e) M. M. Baizer, H. Lund, *Organic Electrochemistry.*; An Introduction and a Guide, 2nd Edn, Dekker, New York, NY, 1983.
14. A. J. Fry, *Synthetic Organic Electrochemistry.*, Harper& Row, New York, NY, 1972.
15. K. Yoshida, *Elecrtooxidation in Organic Chemistry.*, John Wiley & Sons, Inc, New York, NY, 1984.

16. M. R. Rifi, F. H. Covitz, *Introduction to Organic Electrochemistry.*, Marcel Dekker, Inc., New York, NY, 1974.
17. J. Newman, E. Karen, A. Thomas, *Electrochemical Synthesis.*, 3rd Edition John Wiley& Sons. Inc, 2004.
18. D. H. Evans, *Acc. Chem. Res.*, 1977, **10**, 313-319.
19. James Utley, *Chemical Society Reviews.*, 1997, **26**, 157.
20. J. M. Saveant, *Adv. Electron Transfer Chem.*, 1994, **4**, 53-116.
21. B. Speiser, *Angew. Chem.*, 1996, **35**, 2471-2474.
22. H. Lund, *Journal of The Electrochemical Society.*, 2002, **4**, 194, S21-S33.
23. J. Heyrovsky, *Chem Listy.*, 1992, **16**, 256; J. Heyrovsky, *Philos. Mag*, 1923, **45**, 303.
24. J. Heyrovsky, I. Smoler, *Collect. Czech. Chem. Commun.*,1932, **4**, 521.
25. A. Winkel, G.. Proske, *Ber. Dtsch. Chem.Ges. B.*,1936, **69**, 693, 1917.
26. G.. Semerano, A.Chisine, *Gazz. Chim. Ital.*, 1936, **66**, 504.
27. R. Brdicka, *Collect.Czech.Chem.Commun.*, 1933, **5**, 238., R. Brdicka, *Collect.Crech. Chem. Commun.*, R. Brdicka, *Collect. Crech.Chem. Commun.*, 1936, **8**, 366.
28. I. M. Kolthoff , S. C. M. ller, *J. Am. Chem. Soc.*, 1940, **62**, 2171.
29. I. M. Kolthoff , J. F. Coctzec, *J. Am. Chem. Soc.*, 1957, **79**, 870, 1852.
30. H. Lund, *Acta Chem. Scand.*, 1957, **11**, 491, 1323.
31. J. Phelps, K. S. V. Santhanam, A. J. Bard, *J. Am. Chem. Soc.*, 196, **89**, 1752.
32. O. Hammerich, V. D. Parker, *Electrochim Acta.*, 1973, **18**, 537.
33. E. Garcia, A. J. Bard, *J. Electrochem. Soc.*, 1990,**137**, 2752.
34. R. S Glass, V. V. Jouikov, *Tetrahedron Let.*, 1990, **40**, 6357.
35. C. Amatore, M. A. Oturan, J. Pinson, J. M. Saveant, A..Thicbault, *J. Am. Chem. Soc.*, 1985, **107**, 3451; C. Combellas, F. Kanoufi, A. Thicbault, *J. Electroanal. Chem.*, 1996, **407**, 195.
36. R. A. Benkeser and E. M. Kaiser, *J. Electroanal. Chem. Soc.*, 1963, **85**, 2858.
37. L. Eberson, M. P. Hartshorn, J. J. McCullough, O. Persson, and F.Radner, *Acta Chem. Scand.*, 1998, **52**, 1024; L. Eberson, M. P. Hartshorn, F. Radner, and O. Persson, *J. Chem.Soc. Perkin Trans.*, 1998, **2**, 59.

38. G. Silvestri, S. Gambino, G. Filardo, *Adv. Polym. Sci.*, 1981, **38**, 28; G. Silvestri, S.Gambino, G. Filardo, *Acta Chem. Scand.*, 1991, **45**, 987.

39. O. Sock, M. Troupel, J. Perichon, *Tetrahedron Lett.*, 1985, **26**, 1509; C. Saboureaum, M. Troupel, J. Perichon, *J. Appl. Electrochem.*, 1990, **20**, 97.

40. J. Kolbe, *J. Prakt. Chem.*, 1847, **41**, 138.

41. (a) A. Crum Brown, J. Walker, *Leibigs Ann.Chem.*,1891, **261**,107; (b) A. Crum Brown and J. Walker, *Leibigs Ann.Chem.*,1893 , **41**, 274.

42. C. F. Schoenbein, *Leibigs Ann. Chem.*, 1845, **54**, 164.

43. J. H. Simons, *J. Electrochem. Soc.*, 1949, **95**, 47.

44. (a) K. Uneyama, *Tetrahedron.*, 1991, **47**, 4/5, 555. (b) G. D. Zappi, Selective Electrochemcal Fluorinations, Electrosynthesis Company, Watts New™,. 1996, **2**, 2, 1-7.

45. N. Clauson-Kaas, F. Limborg, K. Glens, *Acta Chem.Scand.*, 1952, **6**, 531; N. Clauson-Kaas, Z. Tyle, *Acta Chem. Scand.*, 1952, **6**, 962.

46. M. M. Baizer. *J. Electrochem. Soc.*, 1964, **111**, 215.

47. M. M. Baizer, in '*Organic Electrochemistry',ed.*, H. Lund, M. M. Baizer, Marcel Dekker, New York, 1991, 908.

48. J.-M. Saveant, *Acta Chem. Scand.,B.*, 1983, **37**, 365; C. Amatore,J. Pinson, J. M. Saveant, *J. Electroanal. Chem.*, 1982, **137**, 143.

49. V. D. Parker, *Acta Chem. Scand. B.*, 1981, **35**, 147, 149; V. D. Parker, *Acta Chem Scand.*, *B.*,1983, **37**, 393;O. Hammerich and V. D. Parker, *Acta Chem. Scand.*, *B.* 1983, **37**, 379.

50. M. M. Baizer and J. L. Cruma, *J. Org. Chem.*, 1972, **37**, 1951.

51. J. H. Wagenknecht, *J.Electroanal. Chem.*, 1974, **52**, 489.

52. M. Troupel, Y. Rollin, J. Perichon, J. Fauvarque, Nuov. *J. Chem.*, 1981, **5**, 621.

53. A. Gennaro, A, A, Issc, and F. Maran, *J. Electroanal.Chem.*, 2001, **507**, 124.

54. S. Olivero and E. Dunach, *Eur. J. Org. Chem.*, 1999, 1885.

55. H. Lund and L. G. Feoktistov, *Acta. Chem. Scand.*, 1969, **23**, 3482.

56. A. Nilsson, U. Palmquist, T. Petterson, A. Ronlan, *J. Am. Chem. Soc.*, *Perkin Trans. I*, 1978, 708.

57. S. D. Ross, M. Finkelstein, R. C. Petersen, *J. Am. Chem. Soc.*, 1966, **88**, 4657; E.

J. Rudd, M. Finlelstein, S. D. Ross, *J. Org. Chem.*, 1972, **37**, 1763.

58. T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S. Yamane, T. Kanazawa, and T. Aoki, *J. Am. Chem. Soc.*, 1982, **104**, 6697; T. Shono, Y. Matsumura, K. Tsubuta, K. Uchida, *J. Org. Chem.*, 1986, **51**, 2590.
59. Vander Hoek and Nauta, *Rec. Trav. Mm*, 1942, **51**, 845. *Riccoboni, Gazzetta.*, 1940, **70**, 748.
60. Kruis and Schanzer, Z. *Physical. Chem.*, 1942, **191**, A301.
61. R. P. Linstead, B. R. Shephard, B. C. L.Weedon, Part vii, *J.*, 1952, 3624.
62. T. Siu, W. Li, A. K. Yudin, *J. Comb. Chem.*, 200, **2**, 545; A. K.Yudin, T. Siu, *Curr. Opin. Chem. Biol.*, 2001, **5**, 269.
63. B. C. L. Weedon, *Advan. Org. Chem.*, 1960, **1**, 1.
64. H. Lund, O. Hammerich, *Organic Electrochemistry*, Fourth Edition, 2001, NY, Marcel Dekker, Inc.
65. J. H. P. Utley, Technique of Electroorganic Synthesis, Part I, New York, Wiley Interscience, 1974, 793.
66. (a) G. E. Sadkovaskaya, S. A. Voitkevich, *Russian. Chem. Rev.*, 29, **161**, 1960; (b) B. C. L. Weedon, *Adv. Org. Chem. I.*, 1963, 1.
67. L. Eberson, (S. Patai. ed,) The Chemistry of Carboxylic Acids and Esters, New York, Wiley Interscience, 1974, Chapter 2.
68. F. Beck, Elektroorganische Chemie. Weinheim, Verlag Chemie, 1974, 201.
69. E. H. Pride. Fatty Acids (E. H. Pryde, ed,) Champaign, 1L, American Oil Chemist's Society, 1979, 478.
70. S. D. Ross, M. Finkelstien, E. J. Hudd, Anodic Oxidation. New York, Acadaemic Press, 1975, 134.
71. (a) H. J. Schafer, *Chem Phys Lipids*, 1979, **24**, 321.(b) H. J. Schafer, B. M. Trost, I. Flemming, Comprehnsive Organic Synthesis (eds.). New York,

Pergamon Press, 1991, **3**, 633. (c) K. D. Moeller. *Top. Curr. Chem*., 1997, 185, **49**, 55.

72. A. Wurtz, *Ann. Chim.et Phys*., 1855, **44**, 291; A. Wurtz, *Jahresberichte*, 1855, 575.
73. H. J Schafer. *Angew. Chem. Int. Ed. Engl*., 1981, **20**, 911.
74. M. Huhtasaari, H. J. Schafer, H. Luftmann. *Acta Chem Scand*, 1983, **37**, 537.
75. L. Becking, H.J. Schafer, *Tetrahedron Lett*., 1988, **29**, 2797, 2801.
76. R. N. Renaud, P. J. Champagne, M.Savard, *Can. J. Chem*., 1979, **57**, 2627.
77. N. Muller, *J. Org. Chem*., 1983, **48**, 1370; N. Muller, *J. Org. Chem*., 1984, **49**, 2826, 4559; N. Muller, *J. Org.Chem*., 1986, **51**, 263.
78. M. Yoshikawa, T. Kamigauchi,Y. Iked , I. Kitagawa, *Chem. Pharm. Bull.* (Tokyo). 1981, **29**, 2582.
79. D. Seebach, R.Charezuk, C. Gerber, P. Renaud, H. Berner, H. Schneider, *Helv. Chim. Acta,* 1989, **72**, 419.
80. L. Eberson, *Organic Electrochemistry*, Baizer, Ed., New York, Marcel Dekker, 1973.
81. A. Weiper-Idelmann, M. Kahmen, H. J. Schafer, M. Gockeln., *Acta. Chem. Scand*., 1998, **52**, 672.
82. T. Dickenson, W. F. K. Wynne Jones, *Trans Faraday Soc*., 1962, **58**, 382, 388, 400.
83. S. Tori, T. Okamoto, H. Tanaka, *J. Org. Chem.,* 1974, **39**, 2486.
84. N. L. Weinberg. *Technique of Electroorganic synthesis*, Paris I and II, New York: Wiley. Interscience, 1974.
85. Yu. B. Vassiliev, V. A. Grinberg, *J. Electroanal. Chem.,* 1991, **308**, 1.
86. O. J. Walker, J. Weiss, *Trans. Faraday Soc*., 1935, **31**, 1011.
87. a) S. Glasstone, A. Hickling, Chem. Rev., 1939, **25**, 407. b) A. Hickling, *Quart. Rev*. London, 1949, **3**, 95.
88. C. Schall, *Z. Elektrochem*., 1896, **3**, 83.
89. B. E. Conway, A. K. Vigh, *Electrochim. Acta*, 1967, **12**, 102.
90. L. Eberson, *Acta. Chem. Scand*., 1963, **17**, 2004.

91. J. W. Shaw, T. Nonaka, T. C. Chou, J. Chin. *Inst. Chem. Eng.*, 1986, **16**, 245.

92. a) A. G. Dubinin, L. A. Mirkind, V. E. Kazarinov, M. Y. Fioshin, *Electrokhimiya* 1979, **15**, 1337. b) A. A. Yakovicva, S. N. Kaidalova, Y. B. Veselovskii VI, *Electrokhimiya*, 1973, **8**, 1799.

93. M. R. Fleischmann, J. R. Mansfield, W. F. K. Wynne Jones, *Electroanal. Chem.*, 1965,**10**, 511.

94. M. R. Fleischmann, J. R. Mansfield, W. F. K. Wynne Jones, *Electroanal. Chem.*, 1965, **10**, 522.

95. M. R. Fleischmann, J. R. Mansfield, H. R.Thirsk, H. G. E. Wilson, Lord Wynne Jones, *Electrochim. Acta*, 1967, **12**, 967.

96. A. K. Vijh, B. E. Conway., *Chem. Rev.*, 1967, **67**, 623.

97. B. E. Conway, M. Dzieciuch, *Can. J. Chem.*, 1963, **41**, 21.

98. B. E. Conway, M. Dzieciuch, *Can. J. Chem.*, 1963, **41**, 38.

99. B. E. Conway, M. Dzieciuch, *Can. J. Chem.*, 1963, **41**, 55.

100. L. A. Mirkind, M. Ya. Fioshin, V. I. Romanov, *Zh. Fiz. Khim.*, 1964, **38**, 2840.

101. L. A. Mirkind, L. A. Sibirev., Abstracts of Papers, Trudy VII simposiuma"Dvoinoi sloi I adsorptsiya na tverdykh electrodakh"(Proc. VII Symp. DoubleLayer and Adsorption at solid Electrodes", Tartu, 1985, 233.

102. B. E. Conway, Modern Aspects of Electrochemistry, J. O'M. Bockris, B. E. Conway., Eds., London: Butterworths, 1964, 3. Translated under the title Sovremennye aspekty electrokhimii, Moscow: Mir, 1067.

103. N. Sato, T. Sekino, K. Sugino., *J. Electrochem. Soc.*, 1968, **115**, 242.

104. S. Shukla, O. J. Walker., *Trans. Faraday Society.*, 1931, **27**, 722.

105. K. Sasaki, K. Uneuma, S. Nagaura., *Electrochim. Acta*, 1966, **11**, 891.

106. L. Eberson, K. Nyberg., *Tetrahedron*, 1976, **32**, 2185.

107. B. E. Conway, E. Gileadi, M. Dzieciuch., *Electrochim. Acta,* 1963, **8**, 143.

108. A. Matzeit, H. J. Schafer., Abstracts of Papers, Proc. 2nd Int. Symp. On Electroorganic Synthesis, Kurashiki, Japan, 1994, 69.

109. H. J. Schafer, N. Schoo, U. Howeler, C. Zielinski, B. Koltz-Berendes., Abstracts of Papers, Proc. 2nd Int. Symp. On Electroorganic Synthesis, Kurashiki, Japan, 1994, 1.

110. A. G. Kornienko, L. A. Mirkind, M. Ya. Fioshin, and A. A. Karabanov, *Elektrokhimiya*, 1974, **10**, 350.

111. S. Torii, H. Tanaka, T. Fukuoka, and E. Hirai, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 2534.

112. L. A. Mirkind, M. A. Khrizolitova, and L. V. Aniskova, in *Novosti elektrokhimii organicheskikh soedinenii* (News in the Electrochemistry of Organic Compounds), Kazan, 1970, 81.

113. Y. Fukumoto, K. Tamura, T. Hayashi, and I. Ihida, *Bull. Univ. Osaka Prefect., Ser. A*, 1964, **13**, 125.

114. L. Eberson, and K. Nyberg, *J. Am. Chem. Soc.*, 1966, **88**, 1686.

115. L. Eberson, *J. Am. Chem. Soc.*, 1969, **81**, 2402.

116. L. Eberson, *Chemistry of Carboxyl Groups*, S. Patai, Ed., New York: Wiley, 1969, chapter 6.

117. B. E. Conway, *Discuss. Faraday Soc.*, 1968, **45**, 271.

118. M. Leung, J. Herz, and H. W. Salzberg, *J. Org. Chem.*, 1965, **30**, 310.

119. H. W. Salzberg, and M. Leung, *J. Org. Chem.*, 1965, **30**, 2873.

120. R. M. Cervino, W. E. Triaca, and A. J. Arvia, *J. Electroanal. Chem.*, 1984, **172**, 255.

121. B. E. Conway, and T. C. Liu, *J. Electroanal. Chem.*, 1988, **242**, 317.

122. D. S. Corrigan, E. K. Krauskopf, L. M. Rice, A. Wieckowski, and M. J. Weaver, *J. Phys. Chem.,* 1988, **92**, 1597.

123. A. Takeda, T. Moriwake, S. Toru, and T. Takaki, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 3718.

124. P. H. Reichenbacher, M. Y. C. Liu, and P. S. skell, *J. Am. Chem. Soc.*, 1968, **90**, 1816.

125. P. H. Reichenbacher, M. D. Morris, and P. S. skell, *J. Am. Chem. Soc.*, 1968, **90**, 3432.

126. W. Smit, *Electrochim. Acta,* 1971, **16**, 653.

127. H. W. Salzberg, A. Barnett, and S. Kandler, *J. Electrochem. Soc.*, 1969, **116**, 1198.

128. B. E. Conway, and A.K. Vijh, *J. Phys. Chem.*, 1967, **71**, 3637.

129. L. Eberson, *Electrochim. Acta,* 1967, **12**, 1473.

130. B. E. Conway, and M. Dzieciuch, *Pro. Chem. Soc.,* 1962, 121.

131. B. E. Conway, and A.K. Vijh, *J. Phys. Chem.*, 1967, **71**, 3655.

132. A.K. Vijh, and B. E. Conway, *Z. Anal. Chem.*, 1967, **224**, 160.

133. B. E. Conway, and A.K. Vijh, *Z. Anal. Chem.*, 1967, **224**, 149.

134. B. E. Conway, and A.K. Vijh, *J. Org. Chem.,* 1966, **31**, 4283.

135. L. A. Mirkind, M. Ya. Fioshin, and D. Konstantinesku, *Elektrokhimiya*, 1966, **2**, 193.

136. M. Ya. Fioshin and L. A. Mirkind, *Itogi Nauki Tekh., Ser.: Elektrokhimiya,* Moscow: VINITI, 1966, 114.

137. L. A. Mirkind, M. Ya. Fioshin, and D. Konstantinesku, *Elektrokhimiya*, 1966, **2**,

1095.

138. E. L. Vasini and M. Giordano, *Electrochim. Acta*, 1989, **34**, 577.

139. A. A. Yakovleva, S. N. Kaidalova, Ya. B. Skuratnik and V. I. Veselovskii, *Elektrokhimiya,* 1972, **8**, 1799.

140. H. Kolbe, *Ann.* 1849, **69**, 257.

141. D. L. Muck, E. R. Wilson. *J. Am. Chem. Soc.*, 1970, **177**, 1358.

142. G. P. Girina, M.Ya. Fioshin, and V. E. Kazarinov, *Elektrokhimiya*, 1965, **1**, 478.

143. G. S. Pande and S. N. Shukla, *Electrochim. Acta*, 1961, **4**, 215.

144. M. Ya. Fioshin, and Yu. B. Vassiliev, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1963, 3, 437.

145. M. J. Allen, *Organic Electrode Processes,* New York: Reinhold, 1958.

146. J. P. Coleman, R. Lines, J. H. P. Utley, B. C. L. Weedon. *J. Chem. Soc. Perkin Trans. II.*, 1974, 1064.

147. E. J. Corey, N. L. Bauld, R. T. La Londe, Jr. J. Casanova and E. T. Kaiser, *J. Am. Chem. Soc.,* 1960, **82**, 2645.

148. R. G. Woolford, J. Soong and W. S. Lin, *Can. J. Chem.,* 1967, **45**, 1837.

149. Fichter and Stenzl, *Helv. Chim. Ada*, 1939, **22**, 970.

150. Fichter and Kesten-Holz, *Ibid.*, 1942, **25**, 785.

151. Brockman, "Electro-Organic Chemistry", New York, 1926.

152. L. Eberson. *Acta Chem. Scand.*, 1963, **17**, 1196; L. Eberson and B. Sandberg, *Acta Chem., Scad.*, 1966, **20**, 739; L. Eberson and S. Nilsson, *Acta Chem. Scand.*, 1968, **22**, 2453.

153. (a) F. Ficher and R. E. Myer, *Helv. Chim. Acta*, 1934, **17**, 535; (b) F. Ficher and

H. Stenzl, *Helv. Chim. Acta*, 1939, **22**, 970.

154. Yu. B. Vassiliev, and V. A. Grinberg, *J.Electroanal. Chem.*, 1991, **336**, 281.

155. R. F. Garwood, n Vd Din, C. J. Scott, B. C. L. Weedon. *J. Chem Soc Perkin, Trans.*, 1973, **1**, 2714.

156. A. J. Fry, Synthetic Organic Electrochemistry, 2nd ed, New York, John Wiley& Sons, 1989, 238.

157. H. Hofer and M. Moest, *Ann.* 1902, **232**, 248.

158. B. Giese, Radicals in Organic Synthesis. Formation of Radical Reactions. New York. VCH, 1996.

159. L. Eberson. *Chemistry of carboxyl Group* (S. Patei, ed.), London; Wiley, 1969, Chapter 2.

160. R. N. Renaud, O. E. Sullivan. *Can. J. Chem.*, 1973, **51**, 772.

161. G Nuding, F. Vogtle,K. Danielmeier, E. Steckhan, *Synthesis.*, 1996,71.

162. K. Kimura, S. Horie, I. Minato, Y. Odaira, *Chem Lett.*, 1973, 1209.

163. J. E. Sanderson, P. F. Levy, L. K. Cheng, G W. Bernard, *J. Electrochem So .*, 1983, **130**, 1844.

164. R. G Woolford, W. Arbic, A. Rosser. *Can. J. Chem.*, 1964, **42**; 1788.

165. S. D. Ross, and M. Finkelstein, *J. Org. Chem*, 1969, **34**, 2923.

166. N. V. Smirnova, O. A. Petrii, I. P. Beletskaya, E. G. Neganova, *Russian Journal of Electrochemistry.*, 2001, **37**, 9,893.

167. M. P. J. Brennan, H. Brettle, *J. Chem. Soc. Perkin Trans.*, 1973, **I**, 257.

168. J. Haufe, F. Beck, *Chem. Ing. Techn.*, 1970, **42**, 170.

169. F. Beck, H. Nohe, J. Haufe, DOS 1802865 (1968) BASF; (1971) CA74:37822, 34.

170. T. Ohno, T. Fukumoto, T. Hirashima, I. Nishiuchi Chem Lett., 1991, 1085.

171. W. Ehrfeld, V. Hessel, H. Lowe, *Microreactors New Technology for Modern Chemistry*., First Edition, 2000, Wiley-VCH, Wienheim ,Germany.

172. W. J. Koehl, JR, *J. Am. Chem. Soc*., 1964, **86**, 21, 4686.

173. Johann Hiebl, Michael Blanka, Andras Guttman, Hermann Kollmann, Kornelia Leitner, Gunter Mayrhofer, Franz Rovenszky and Karin Winnkler, *Tetrahedron*., 1998, **54**, 2059.

174. R. P. Linstead, B. R. Shephard, B. C. L. Weedon, *J. Chem. Soc*., 1951, **1130**, 2854.

175. Fichter and Schmidt, *Helv. Chim. Acta*, 1920, **3**, 704.

176. W. Ehrfeld, V. Hessel, V. Haverkamp; "*Microreactors*", *Ullmann's Encyclopedia of Industrial Chemistry*., Wiley-VCH, Weinheim, 1999.

177. J. Arnold, U. Dasbach, W. Ehrfeld, K. Hesch, H. Lowe; *Appl. Surf. Sci*., 1995, **86**, 251.

178. H. Lowe, W. Ehrfeld, M. Kupper, A. Ziogas, Microreaction Technology: 3rd International Conference on Microreaction Technology, ed. W. Ehrfeld, Proceedings of IMRET 3, Springer-Verlag, Berlin, 2000, 136-156.

179. H. Lowe, W. Ehrfeld; *Electrochim. Acta*., 1999, **44**, 3679-3689.

180. F. E. Woodard, C. N. Reilly; "*Thin Layer Cell Techniques*", in Yeager, V., Bockris, J. O. M.,Conway, P. P., Sarangabani, S. T. (Eds) *Comprehensive Treatise of Electrochemistry*., 1984, 9, 353-392, Plenum Press, New York.

181. H. Wendt, S. Bitterlich, *Electrochim. Acta.*, 1992, **37**, 1951, 11.

182. C. A. Paddon , G J. Pritchard , T. Thiemann , F. Marken , *Electrochemistry Communications.*, 2002, **4**, 825-831.

183. M. Kuppur , V. Hessel , H. Lowe ,W. Stark, J. Kinkel, M. Michel, H. Schmidt-Traub ,*Electrochimica Acta.*, 2003, **48** , 2889- 2896.

184. R. Horcajada, M. Okajima, S. Suga, J. Yoshida, *Chem. Commun.*, 2005, 1303.

185. (a) J. Jorissen, *J. Appl. Electrochem.*, 2003, **33**, 969; (b) S. S. Vaghela, G. Ramachandraiah, P. K. Ghosh, D. Vasudevan, *J. Appl. Electochem.*, 2002, **32**, 1189; (c) D. Hoorman, C. Kubon, J. Jorrisen, J. Kroner, H. Putter, *J. Electroanal. Chem.*, 2001, **507**, 215; (d) J. Jorissen, *Electrochim. Acta.*, 1996, **41**, 553; (e) Z. Ogumi, K. Inatomi, J. T. Hinatsu, Z. Takehara, *Electrochim. Acta.*, 1992, **37**, 1295; (f) Z. Ogumi, M. Inaba, S. Ohashi, Z. Takehara, *Electrochim. Acta.*, 1988, **33**, 365; (g) E. Raoult, J. Sarrazin, A. Tallec, *J. Membr. Sci.*, 1987, **30**, 23; (h) Z. Ogumi, S. Ohashi, Z. Takehara, *Electrochim. Acta.*, 1985, **30**, 121; (i) Z. Ogumi, K. Nishio, Z. Yoshizawa, *Electrochim. Acta.*, 1981, **26**, 1779.

186. For example of flow and microflow electrochemical reactors: see (a) J. Heo, K. J. Thomas, G. H. Seong and R. M. Crooks, *Anal. Chem.*, 2003, **75**, 22; (b) W. Zhan, J. Alvarez and R. M. Crooks, *Ana.Chem.*, 2003, **75**, 313: (c) W. Zhan, J. Alvarez, L. Sun and R. M. Crooks, *Anal. Chem.*, 2003, **75**, 1233; (d) M. Kupper, V. Hessel, H. Lowe, W. Stark, J. Kinkel, M. Michel and H. Schmidt-Traub, *Electrochim. Acta.*, 2003, **48**, 2889; (e) W. Zhan and R. M. Crooks, *J. Am.Chem. Soc.*, 2003, **125**, 9934; (f) V. Mengeaud, O. Bagel, R. Ferringno, H.

H. Girault and A. Haider, *Lab, Chip.*, 2002, **2**, 39; (g) J. Yoshida and S. Suga, *Chem. Eur. J.*, 2002, **8**, 2650; (h) H. Ernst, B. Rob and M. Knoll, *Electrochim. Acta.*, 2002, **47**, 1795; (i) S. Suga, M Okajima, K. Fujiwara and J.Yoshida, *J. Am. Chem. Soc.*, 2001, **123**, 7941; (j) H. Lõwe and W. Ehrfeld, *Electrochim. Acta.*, 1999, **44**, 3679; (k) C. Karakus and P. J. Zuman, *J. Electrochem. Soc.*, 1995, **142**, 4018.

187. BASF Information 15.10.98, company brochure, BASF, Ludwigshafen.

188. P. He, P. Watts, F. Marken, S. J. Haswell, *Electrochemistry Communications.*, 2005, **7**, 918.

189. D. Horii, M. Atobe, T. Fuchigami, F. Marken, *Eelectrochem. Commun.*, 2005, **7** 35.

190. T. Bechtold, A. Turcanu, *J. Electrochem. Soc.*, 2002, **149**, D 7.

191. C. Vallieres, M. Matlosz, *J. Electrochem.* Soc., 1999, **146**, 2933.

192. T. Bechtold, E. Burts, A. Turcanu, O. Bobleter, *J. Appl. Electrochem.*, 1997, **27**, 1021.

193. M. Matlosz, *J. Electrochem. Soc.*, 1995, **142**, 1915.

194. C. Belmont, H.H. Girault, *J. Appl. Electrochem.*, 1994, **24**, 719.

195. A. Ziogas, M. Kupper, H. Lowe, W. Ehrfeld, in: IMRET3: Micro-reaction Technology: Industrial Processes, Springer, Berlin. 1998, 136.

CHAPTER 2: AIMS OF THE PROPOSED RESEARCH

2.0 Aims of the Research

Microreactor methodology enables multi-step reactions to be conducted in such a way that it is not necessary to isolate intermediates and reactants during reactions. At present, reports on applications based on electrochemical microreactors are limited. But we cannot deny the fact that notable benefits due to miniaturization makes this an attractive approach. The use of such techniques is extremely desirable to pharmaceutical companies who are interested in the high throughput synthesis of combinatorial libraries for pharmaceutical evaluation. Furthermore, techniques such as electrochemical synthesis may be used to prepare chemicals, which are difficult to prepare by conventional techniques.

The main aim of this project will be to identify the presence of any unique control, over electrochemical organic synthesis, that micro reactors offer, and the modification of methods to gain chemical and practical advantages. These advantages come from the close control that exists between flow, concentration and thermal properties with a diffusion limited small volume system.

The project will start initially, with an investigation into the current limitations, and process flexibility of electroorganic synthesis, without using an electrolyte, in order to benefit from the quick separation and purification of products. Ultimately the aim will be to investigate the scope of electrochemical synthesis. The advantage of low cost and quick purification will also be evaluated to identify the opportunities to develop novel methods to optimize various reactions and prepare reactive intermediates *in situ*.

This work includes the study of various reactor designs and parameters affecting the Kolbe electrolysis in a flow cell and to exploit the desirable conditions under which aliphatic acids can be electrolysed to give alkanes. In order to establish a comprehensive electrochemical microreactor for organic synthesis, certain factors like residence time, flow rate, concentrations of reacting species, electrode surfaces and current/voltage efficiencies

need to be investigated. As more results will be gathered from the experiments using conductive salts/bases, the basis for the optimum conditions for such electrochemical microreactor can be formulated for an electrolyte free electroorganic synthesis.

CHAPTER 3: EXPERIMENTAL SECTION

3.1.0 Starting Materials, Reagents and Reaction Solvents

Starting materials were obtained from Aldrich, Fluka, Acros or Lancaster Synthesis or were available internally from other research programmes. All solvents and reagents that were purchased were used without further purification unless otherwise stated. Solvents, such as methanol and dimethyl fomamide (99.0%) (Fisher, UK), were pre-dried over molecular sieves. Methanol HPLC grade (absolute, Fisher, UK), triethylamine (99.0%) (Aldrich), sodium-*tert*-butoxide (99.0%) (Aldrich), ferrocene (99.0%) (Aldrich), and tetraethyl ammonium tetrafluoro borate (99.0%) (Aldrich) were used as purchased. All batch reactions were carried out using a dry nitrogen atmosphere.

3.2.0 Analytical methods

3.2.1 Power Supply

The power supply used was Advance Highvolt - 2A (UK), which is capable of providing a direct current of 0 – 2 A, with a TTi 1906 Computing Multimeter (Thurlby Thandar Instrument) working at the ammeter mode (Figure 16), which enabled the current passed through the reaction mixture to be measured.

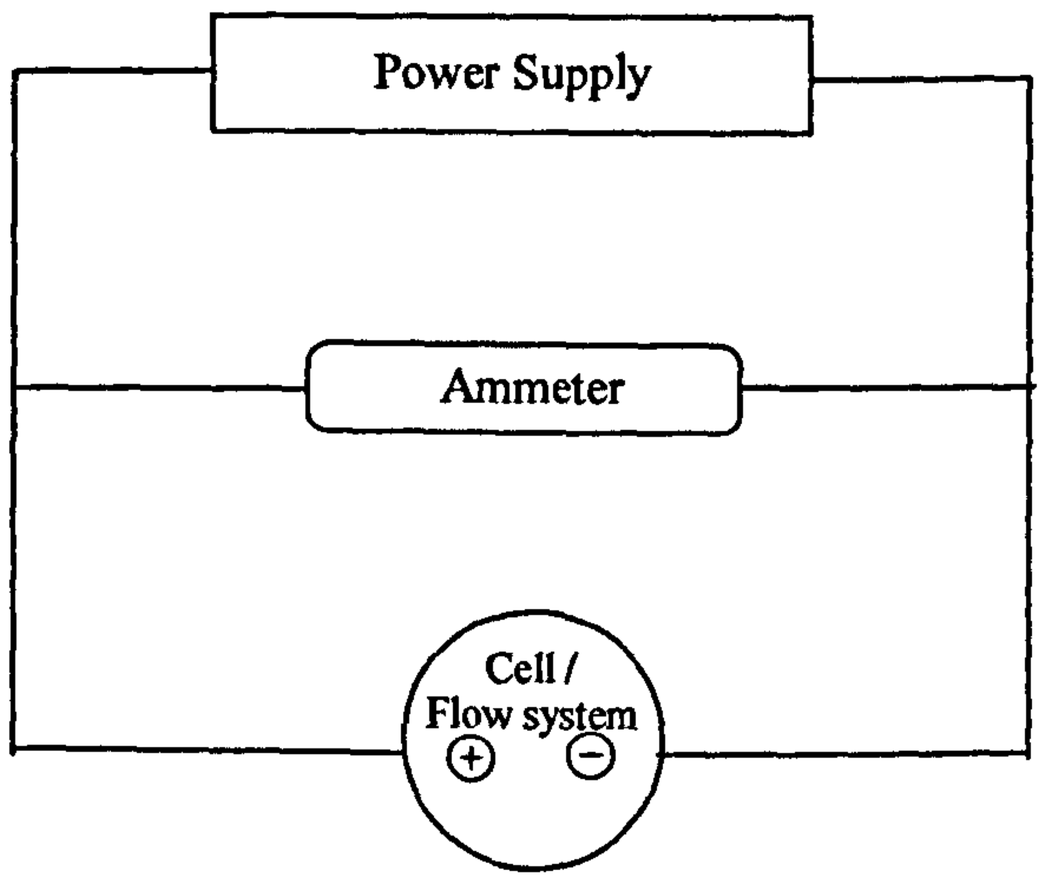


Figure 16 The arrangement of power supply

3.2.2 Gas Chromatography

The reaction mixtures were analysed by an internal standard method, a set of standard mixtures containing known concentrations of the analytes was analysed and their peak areas recorded. A calibration graph of area vurses concentration was constructed for each analyte to confirm a linear detector response from which the amount (% conversion) of the analytes in the reactions were determined.

The compounds used as an internal standard were octane (99.0%), decane (99.0%), dodecane (99.0%), tetradecane (99.0%), and hexadecane (99.0%) which were commercially available materials (Aldrich). The compounds electrolysed such as hexanoic acid (99.0%), octanoic acid (99.0%), pentanoic acid (99.0%), hexanoic acid (99.0%), heptanoic acid (99.0%), octanoic acid (99.0%), nonanoic acid (99.0%), ethyl propiolate (99.0%), ethyl crotonate (99.0%), styrene (99.0%) β-alanine (99.0%), Fmoc-β-alanine (99.0%), Z-β-alanine (99.0%), *N*-benzoyl-β-alanine (99.0%), *N*-acetyl-β-alanine (99.0%), Boc-β-alanine (99.0%), *N*-acetyl-β-alanine (99.0%) and pyridine (used as base) (99.8%) were also commercially available materials (Aldrich/ Fluka).

The compounds obtained as products were decane, dodecane, tetradecane, hexadecane and the dimers of amino acids such as *N*-acetyl-β-alanine dimer and Boc-β-alanine dimer. The reaction mixtures were analysed using GC/FID (Shimadzu GC-17A) and/ or GC / MS (Varian Saturn 2100 T), using the following methods.

3.2.2.1 Method A (GC/FID)

The GC/FID (Shimadzu GC-17A) injector was set to 250 °C, the detector was set to 250 °C, the column (ZB-5 Phenomenex, 30 m x 0.25 mm x 0.25 μm) temperature was initially at 50°C, held for 4 minutes, then raised to 250 °C at 30°C / min. The total time for the whole program was 10.7 min. The calibration was carried out using known pure compounds. The Method A, Table 4 was used to analyse the reaction mixture for the electrolysis of octanoic acid and its addition reactions to the double and triple bonds. The electrolysis was carried out in the batch cell A and flow cells B, C and D.

Compound	R_t(min)
Decane*	7.2
Ethyl propiolate	3.7
Ethyl crotonate	5.4
Diethyl amine	4.2
Diisopropylethylamine	6.5
Hexanoic acid	7.6
Octanoic acid	9.5
Pyridine	3.8
Styrene	6.0
Tetradecane*	9.8
Triethyl amine	5.8

*Compounds used as internal standard

Table 4 The R_t of compounds Method A

3.2.2.2 Method B (GC/MS)

The GC3800 injector of the GC / MS (Varian Saturn 2100 T) was set to 250 °C, the detector was set to 250 °C, the column (ZB-5 Phenomenex, 30 m x 0.25 mm x 0.25 μm) temperature was initially at 50 °C, held for 4 minutes, then raised to 250 °C at 30 °C / min. The total time for the whole program was 25 min. The calibration was carried out using known pure compounds. The method was used to analyse the reaction mixtures from the electrolysis of amino acids as well as the coupling reactions of octanoic acid with hexanoic acid and the addition reactions of octanoic acid to the double and triple bonds. The Method B, Table 5 was also used to analyse the reaction mixtures from the electrolyses of pentanoic acid, hexanoic

acid, heptanoic acid and nonanoic acid. The electrolysis was carried out in the batch cell A and flow cells A, B, C, D, E, F and G.

Compound	R_t(min)
β-alanine	3.2
Boc-β-alanine	10.7
Boc-β-alanine dimer	13.7
Decane*	7.1
Dodecane*	9.3
Ethyl propiolate	3.7
Ethyl crotonate	5.4
Fmoc-β-alanine	11.6
Heptanoic acid	7.8
Hexadecane*	11.1
Hexanoic acid	7.6
N-acetyl-β-alanine	9.8
N-acetyl-β-alanine dimer	10.9
N-benzoyl-β-alanine	10.8
Nonanoic acid	9.1
Octane*	5.1
Octanoic acid	9.3
Pentanoic acid	6.7
Pyridine	4.0
Styrene	6.2
Tetradecane*	10.1
Z-β-alanine	12.9

*Compounds used as internal standard

Table 5 The R_t of compounds Method B

3.2.2.3 Method C GC/FID

The GC/FID (Shimadzu GC-17A) injector was set to 250 °C, the detector was set to 250 °C, the column (ZB-5 Phenomenex 30 m x 0.25 mm x 0.25 μm) temperature was initially at 50 °C, held for 4 minutes, then risen to 250 °C at 30 °C / min. The total time for the whole program was 13 -17 min. The calibration was done with known pure compounds. The Method C, Table 6 was used to analyse the reaction mixtures from the electrolysis of octanoic acid and the addition reactions of octanoic acid to the double and triple bonds. The method was also used to analyse the reaction mixtures from the electrolyses of hexanoic acid and nonanoic acid. The electrolysis was carried out in the batch cell A and flow cells E, F and G.

Compound	R_t(min)
Decane*	6.9
Dodecane*	8.5
Ethyl propiolate	3.7
Ethyl crotonate	5.4
Hexadecane*	10.8
Hexanoic acid	7.6
Nonanoic acid	9.3
Octane*	5.1
Octanoic acid	9.3
Pyridine	4.0
Styrene	6.2
Tetradecane*	9.8

*Compounds used as internal standard

Table 6 The R_t of compounds Method C

3.2.2.4 Method D GC/FID

The GC/FID (Shimadzu GC-17A) injector was set to 250 °C, the detector was set to 250 °C, the column (ZB-5 Phenomenex 30 m x 0.25 mm x 0.25 μm) temperature was initially at 50 °C, held for 4 minutes, then raised to 250 °C at 30 °C / min. The total time for the whole program was 14 min. The calibration was carried out using known pure compounds. The Method D, Table 7 was used to analyse the reaction mixtures from the electrolysis of amino acids as well as the coupling reactions of octanoic acid with hexanoic acid and the addition reactions of octanoic acid to the double and triple bonds. The method was also used to analyse the reaction mixtures from the electrolyses of pentanoic acid, hexanoic acid and heptanoic acid. The electrolysis was carried out in the batch cell A and flow cells E, F and G.

Compound	R_t(min)
Decane*	6.9
Dodecane*	8.5
Ethyl propiolate	3.6
Ethyl crotonate	5.5
Heptanoic acid	7.4
Hexadecane*	11.0
Hexanoic acid	7.5
Nonanoic acid	9.3
Octane*	4.1
Octanoic acid	9.0
Pentanoic acid	6.0
Pyridine	3.5
Styrene	6.3
Tetradecane*	10.0

*Compounds used as internal standard

Table 7 The R_t of compounds Method D

3.2.2.5 Method E GC/MS

The GC3800 injector was set to 250 °C, the detector was set to 250 °C, the column (ZB-5 Phenomenex 30 m x 0.25 mm x 0.25 μm) temperature was initially at 50 °C, held for 4 minutes, then raised to 250 °C at 25 °C / min. The total time for the whole program was 22 min. The calibration was carried out using known pure compounds. The Method E, Table 8 was used to analyse the reaction mixtures from the electrolysis of octanoic acid as well as the coupling reactions of octanoic acid with hexanoic acid and the addition reactions of octanoic acid to the double and triple bonds. The electrolysis was carried out in the batch cell A and flow cells E, F and G.

Compound	R_t(min)
Decane*	7.2
Dodecane*	9.5
Ethyl propiolate	3.7
Ethyl crotonate	5.4
Heptanoic acid	8.0
Hexadecane*	11.2
Hexanoic acid	7.8
Nonanoic acid	9.4
Octane*	5.3
Octanoic acid	9.5
Pentanoic acid	6.4
Pyridine	4.1
Styrene	6.2
Tetradecane*	10.2

*Compounds used as internal standard

Table 8 The R_t of compounds Method E

3.2.2.6 Method F GC/FID

The GC/FID (Shimadzu GC-17A) injector was set to 250 °C, the detector was set to 250 °C, the column (ZB-5 Phenomenex 30 m x 0.25 mm x 0.25 μm) temperature was initially at 50 °C, held for 6 minutes, then raised to 250 °C at 30 °C/ min. The total time for the whole program was 17 min. The calibration was carried out using known pure compounds. The Method F, Table 9 was used to analyse the reaction mixtures from the electrolysis of amino acids such as Boc-β-alanine. The electrolysis was carried out in the batch cell A and flow cells E, F and G.

Compound	R_t(min)
Boc-β-alanine	10.7
Boc-β-alanine dimer	13.7
Decane*	7.9

*Compound used as internal standard

Table 9 The R_t of compounds Method F

3.3.0 Batch Cell

3.3.1 Batch Cell A

Batch reactor (Cell A Figure 17, 18) consisted of a small glass HPLC screw cap (Thames Restek UK) vial with internal diameter of 0.8 mm, sealed with a rubber seal screw cap, with a nitrogen gas balloon fitted on a syringe back with the needle inserted through the rubber seal. A magnetic stirrer and a pair of platinum wire electrodes (Alfa Aesar) with 0.5 mm diameter, 5 mm apart, and 5 mm inserted in the solution.

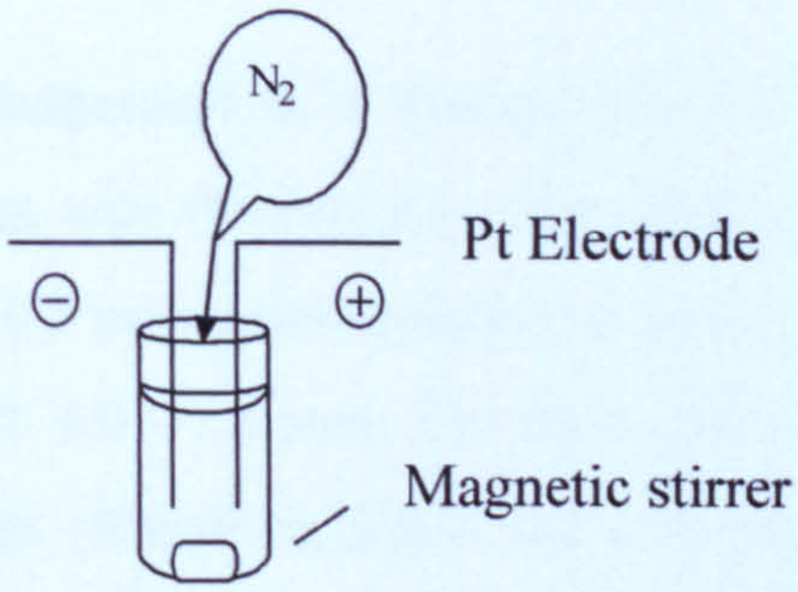


Figure 17 The arrangement of electrodes in batch Cell A

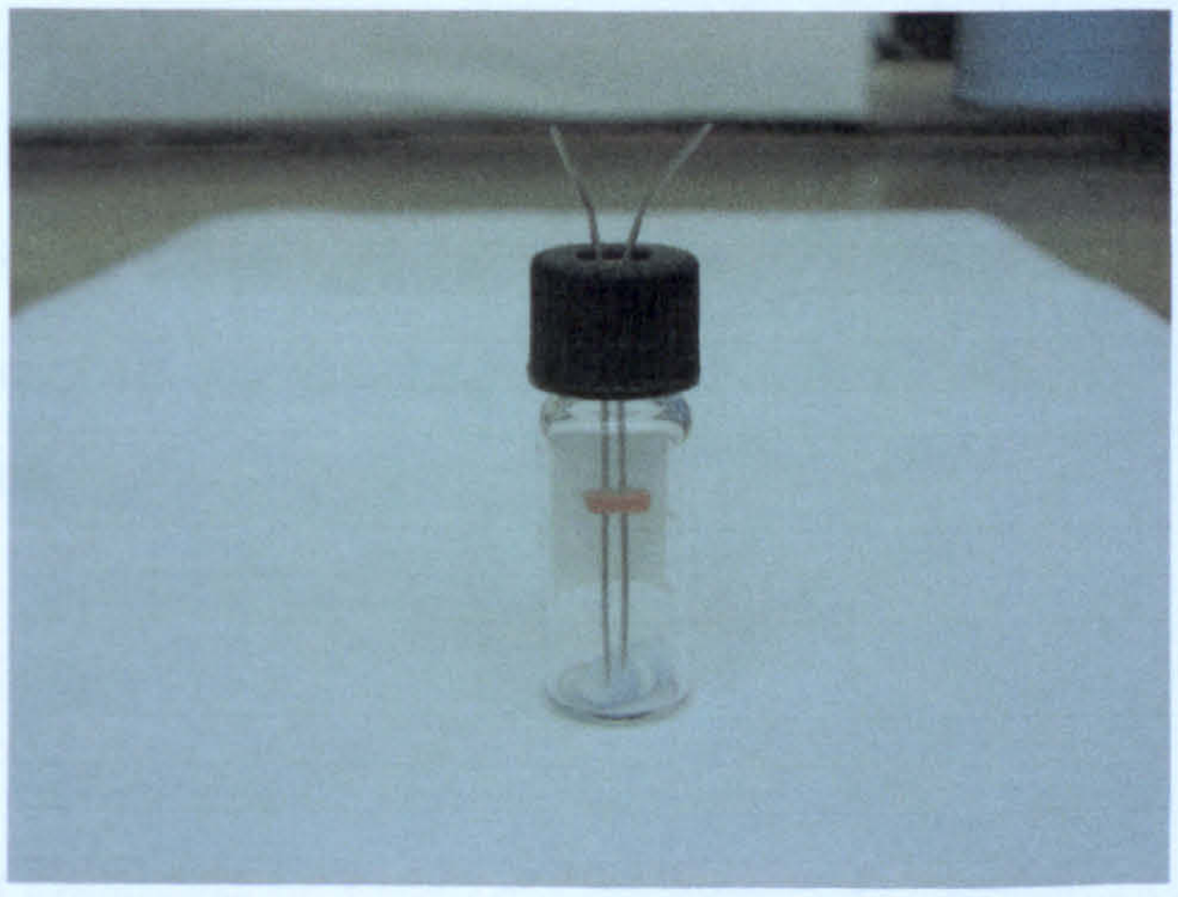


Figure 18 The arrangement of electrodes in batch Cell A

3.4.0 Flow Cells

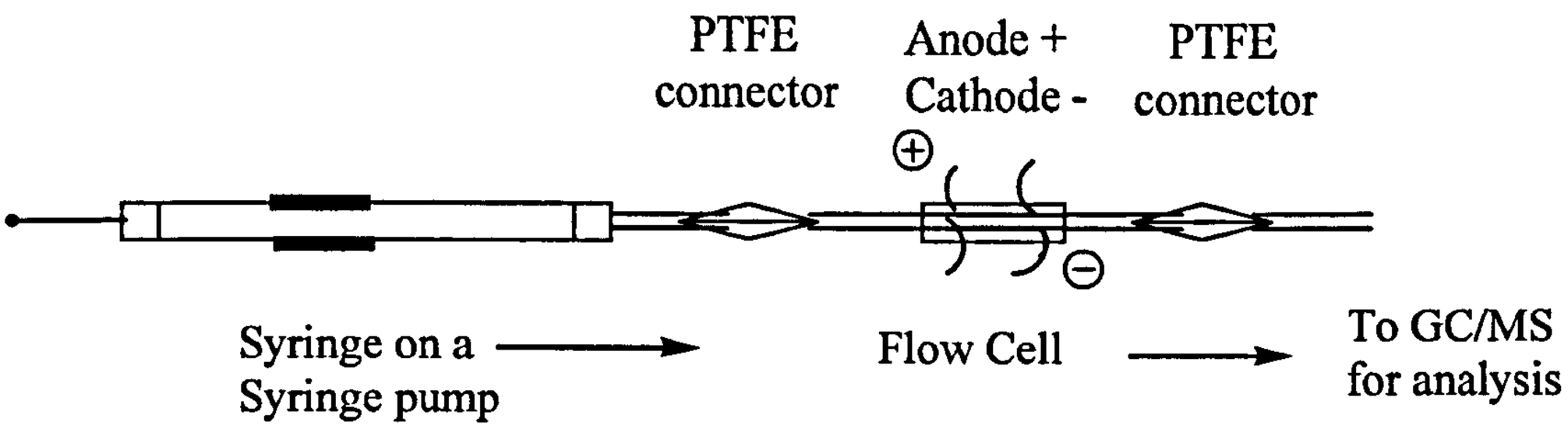


Figure 19 The arrangement of Flow Cell Set Up

Figure 19, shows the typical arrangement of a syringe and a flow cell. The flow cell was fabricated from a pair of platinum wire (Goodfellow Cambridge Limited) electrodes, 0.18 – 1.0 mm diameter, sealed (0.35 – 0.7 mm apart) parallel or across, through a length of 2.5 cm of a glass capillary (Supelco) I.D. 1.0 - 1.5 mm. The flow cell was connected to a luer lock 250 μL - 5 ml gas tight syringe (Hamilton/SGE) *via* a female luer finger tight adoptor (Thames Restek UK) and a HPLC union (Thames Restek UK) to a luer lock glass syringe. All designs described below were made using the above maerials. The acid solutions containing varying concentrations of acid and pyridine were pumped through the syringe by a syringe pump (Bioanalytical Systems, Inc), at different flow rates. Flow cells E, F and G were mounted vertically (held by a clamp on a retort stand) in order to give an easy escape for the gas bubbles formed during the electrolysis. The electrolysis was controlled by a power supply through an ammeter (Figure 16) at different voltages / currents. The current potential values kept declining over time with deteriorating electrode surface, and therefore mean values are taken for each conversion.

3.4.1 Flow Cell B

Flow cell B (Figure 20) consisted of a pair of platinum wire electrodes, 0.5 mm diameter, 0.8 mm long (spaced approximately 5 - 7 mm apart), sealed across into a PTFE tube (I.D. 0.8 mm). The reactor was connected to the pump as described above.

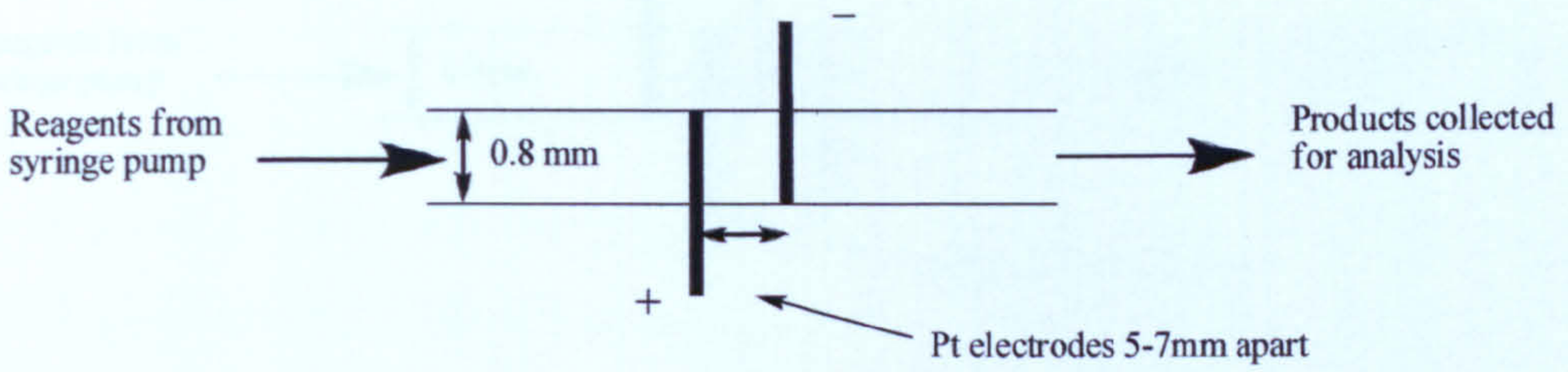


Figure 20 The arrangement of electrodes in Flow cell B

3.4.2 Flow Cell C

Flow cell C (Figure 21, 22) consisted of two pairs of platinum wire electrodes, 0.5 mm diameter, 0.8 mm long, (spaced approximately 5.0 - 7.0 mm apart) sealed across into a PTFE tube (I.D 0.8 mm). The PTFE tube was connected to the pump as described above.

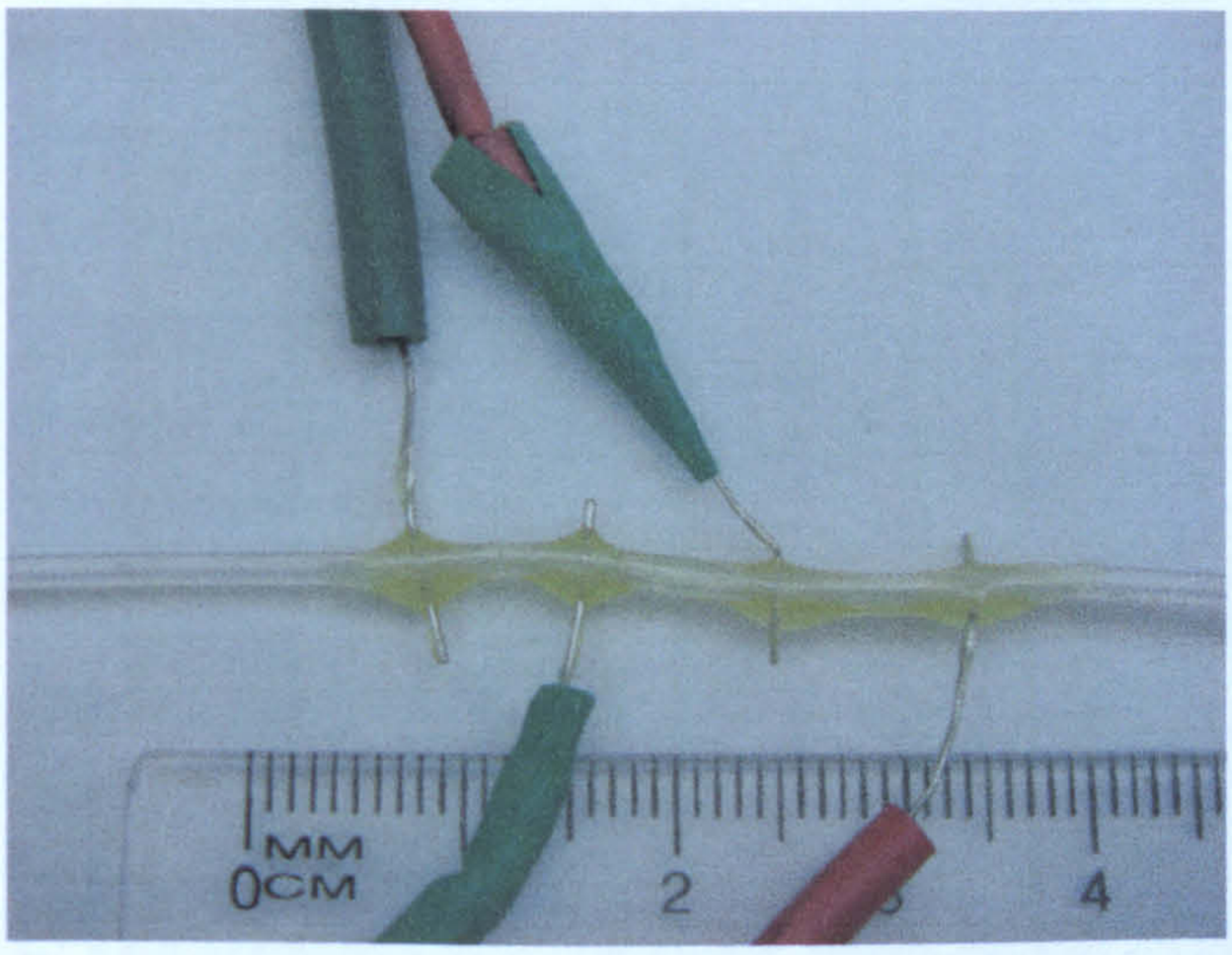


Figure 21 The arrangement of electrodes in Flow cell C

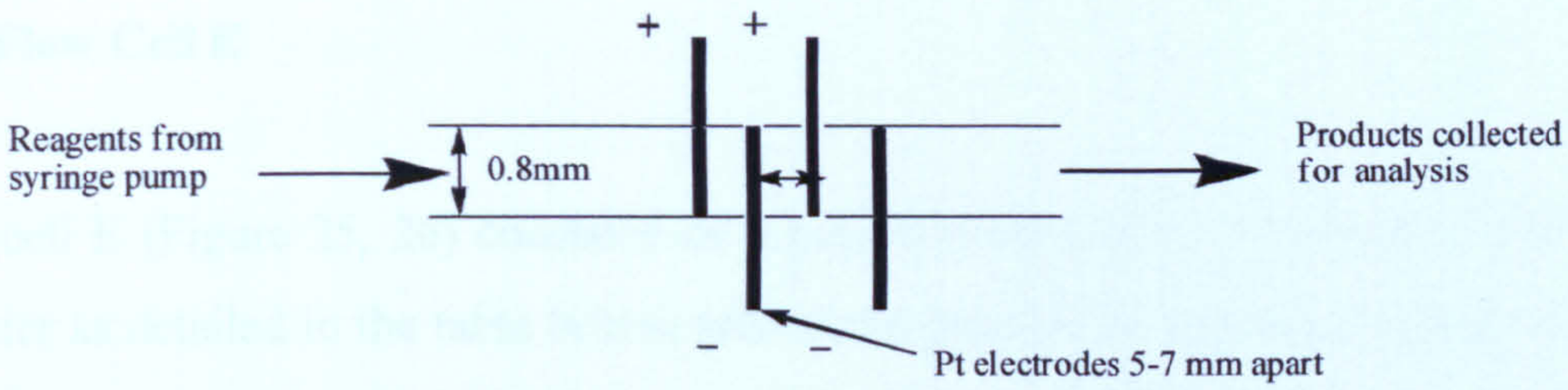


Figure 22 The arrangement of electrodes in Flow cell C

3.4.3 Flow Cell D

Flow cell D (Figure 23, 24) consisted of a pair of platinum wire electrodes, 0.36 mm diameter, and sealed parallel to each other, along a length of 2.5 cm (spaced approximately 0.5 - 0.7 mm apart) of a PTFE tube (I.D 1.5 mm). The PTFE tube was connected to the pump as described above.

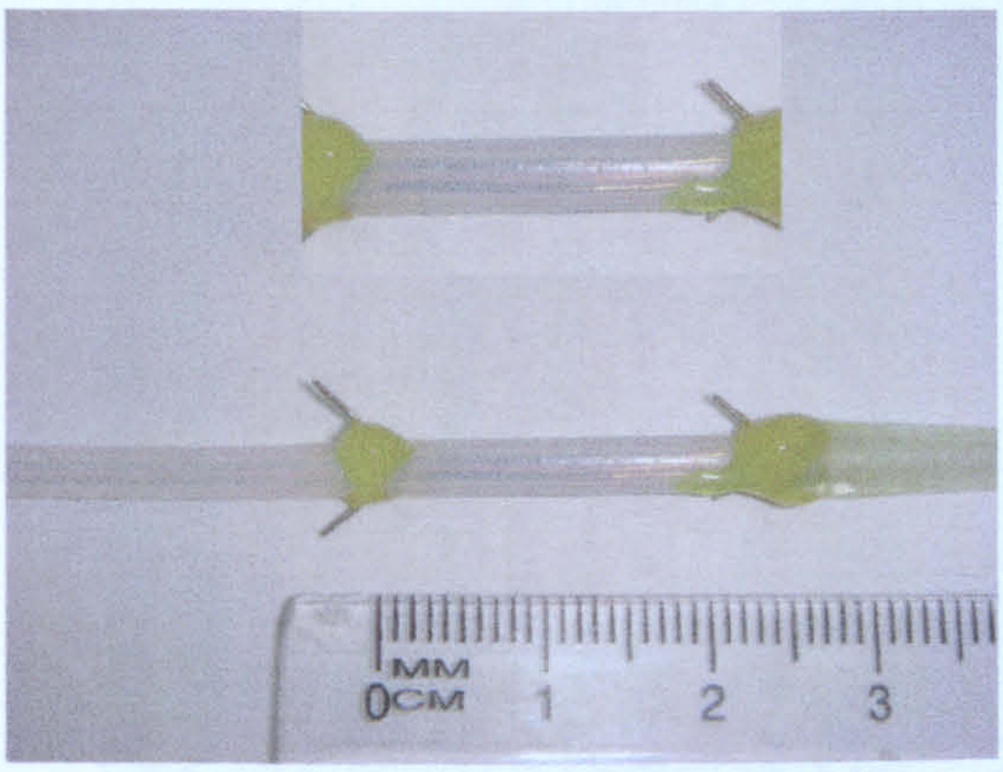


Figure 23 The arrangement of parallel electrodes in Flow cell D

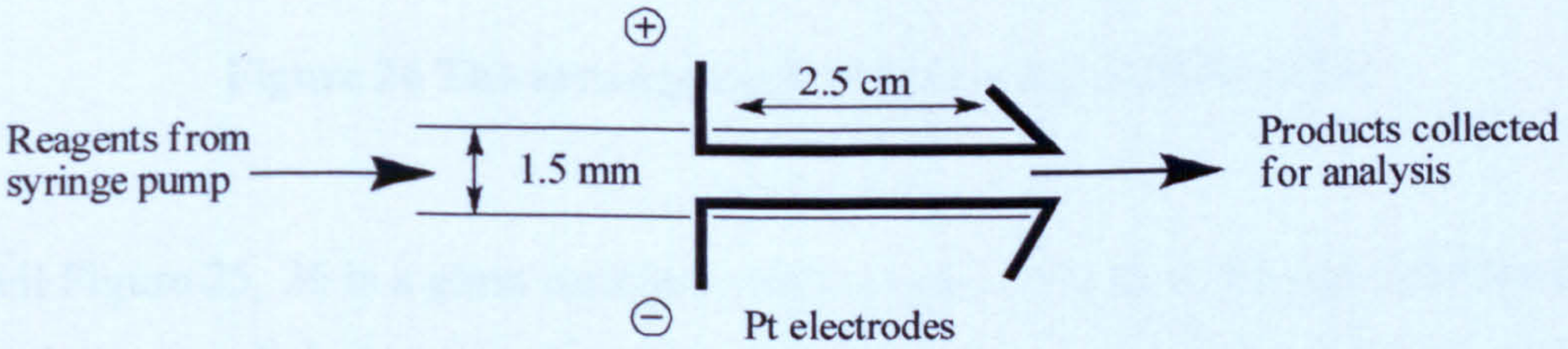


Figure 24 The arrangement of parallel electrodes in Flow cell D

3.4.4 Flow Cell E

Flow cell E (Figure 25, 26) consisted of a pair of platinum wire electrodes, 0.17 - 0.36 mm diameter as detailed in the table below, and sealed parallel to each other, along a length of 2.5 cm (spaced approximately 0.38 - 0.7 mm apart) of a glass capillary (I.D 1.0/1.5 mm). The glass tube was connected to the pump and mounted vertically as described above.

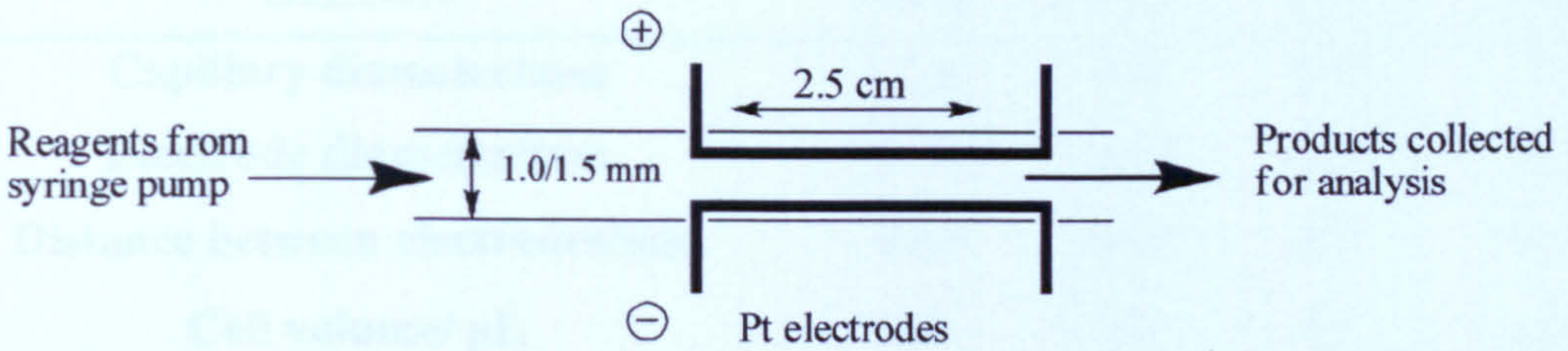


Figure 25 The arrangement of electrodes in Flow cell E

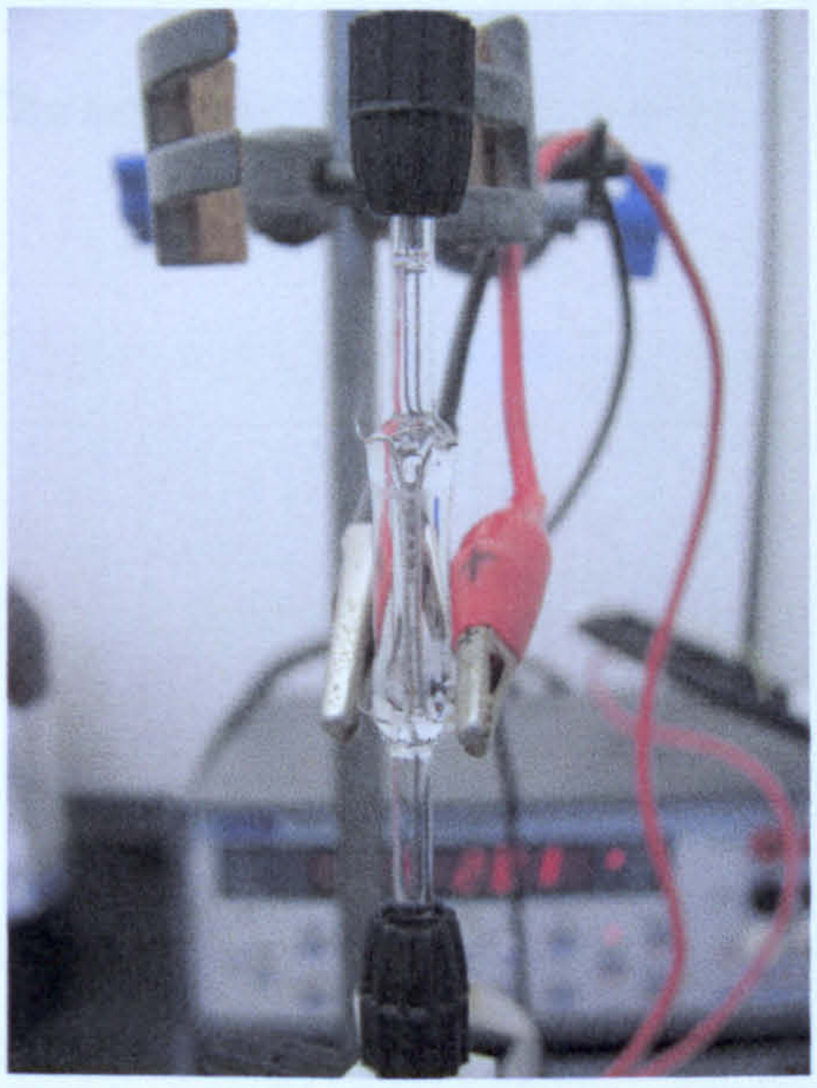


Figure 26 The arrangement of electrodes in Flow cell E

Flow cell Figure 25, 26 is a glass capillary, with a 1mm wide flow through reaction chamber, fitted with two parallel platinum wire electrodes. The electrode surface area and gap between the two electrodes could be varied, by varying the thickness of wire. The gap between the anode and cathode was 0.36 – 0.7mm depending upon the thickness of the wire, which was between 0.18mm – 1.0 mm (Table 5) in various designs. The solution was continuously

supplied into the chamber with the aid of an electric syringe pump holding a 2.5ml/5ml plastic syringe, to give flow rates of 3 – 216 μL/min, in order to identify the optimum conditions for highest conversion for each cell. The cell was working all the time under constant potential mode at 100 V where current values were measured over time and average values were calculated for each conversion.

DESIGN	E(1)	E(2)	E(3)	E(4)
Capillary diameter/mm	1.5	1.0	1.0	1.0
Electrode diameter/mm	0.38	0.18	0.18	0.26
Distance between electrodes/mm	0.65	0.56	0.7	0.38
Cell volume/ μL	50	20	70	15
Surface area of electrodes($2x2\pi rh$)/cm^2	2x0.298	2x0.141	2x0.142	2x0.204
Cell Volume(πr^2h)/cm^3	0.044	0.02	0.02	0.02
Surface /Volume ratio/cm	14	14	14	20
Surface/Volume ratio cm^2/ μL	0.0119	0.0141	0.004	0.03

Table 10 The arrangement of electrodes in Flow cell E



Figure 27 The arrangement of electrodes in Flow cell E

Flow cell E 3 was a 3.0 cm glass capillary (I.D 1.0 mm) with removable Pt electrodes of diameter 0.18 mm which were approx 0.5mm apart (by placing a PTFE spacer at both edges between the electrode wires) Figure 28. The capillary was sealed on both sides by silicone sealant (Ambersil, UK).

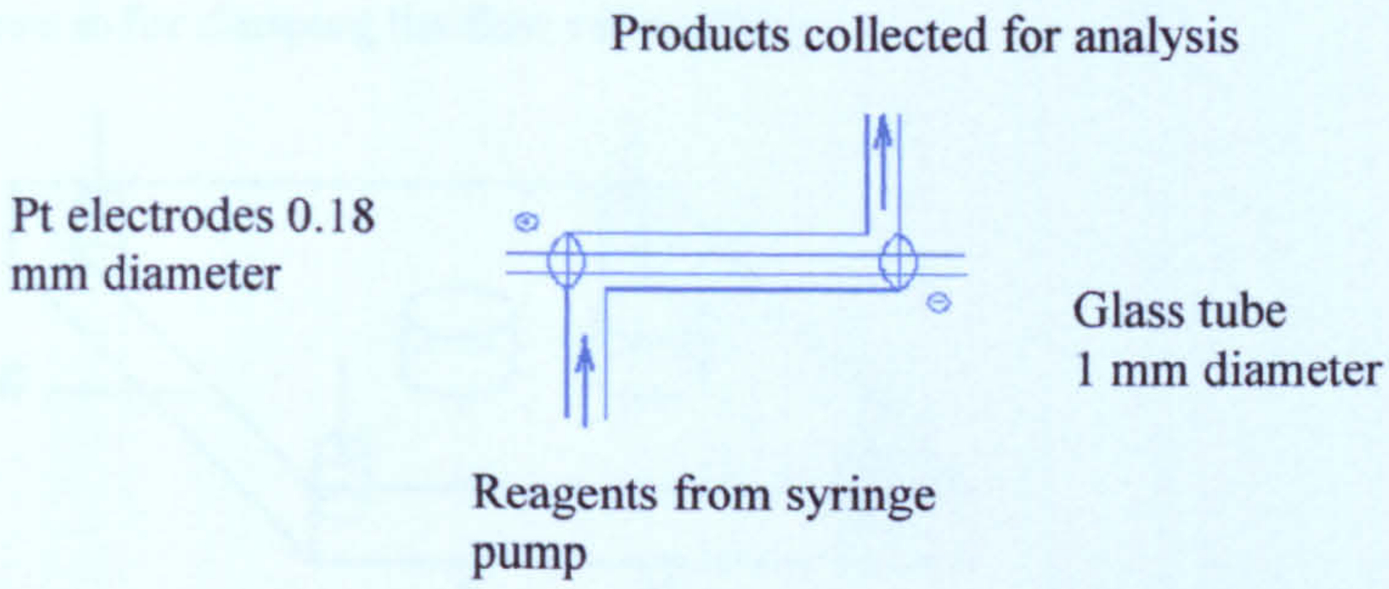


Figure 28 The arrangement of removable electrodes in Flow cell E 3

3.4.5 Flow Cell F

Construction of flow-through micro-gap cell



Figure 29 Flow-through micro-gap cell F

Flow cell F, Figure 29, consists of two glass plates (3 cm long, 2 cm wide, 6 mm thick) forming a top and a bottom. The top plate contained two holes which were connected to the PEEK tubes (I.D 0.24 mm), which acted as the flow inlet and outlet. Two equally sized Pt foils (squares of 5mm width and length, and 50μm thickness, Good fellow Cambridge Limited, purity 99.99%) were used for the working and counter electrodes. The flow cell was formed by clamping all

components together with a PTFE spacer (BOHLENDER GmbH, Germany) having a rectangular window (3 mm wide and 19 mm long) cut through its centre, as shown in Figure 30. A small amount of silicone sealant (Ambersil, UK) was used to seal the edges around glass and the Pt foil to avoid leakage. PTFE spacers with thickness of 120μm and 250μm were employed. The cell was mounted vertically as described above.

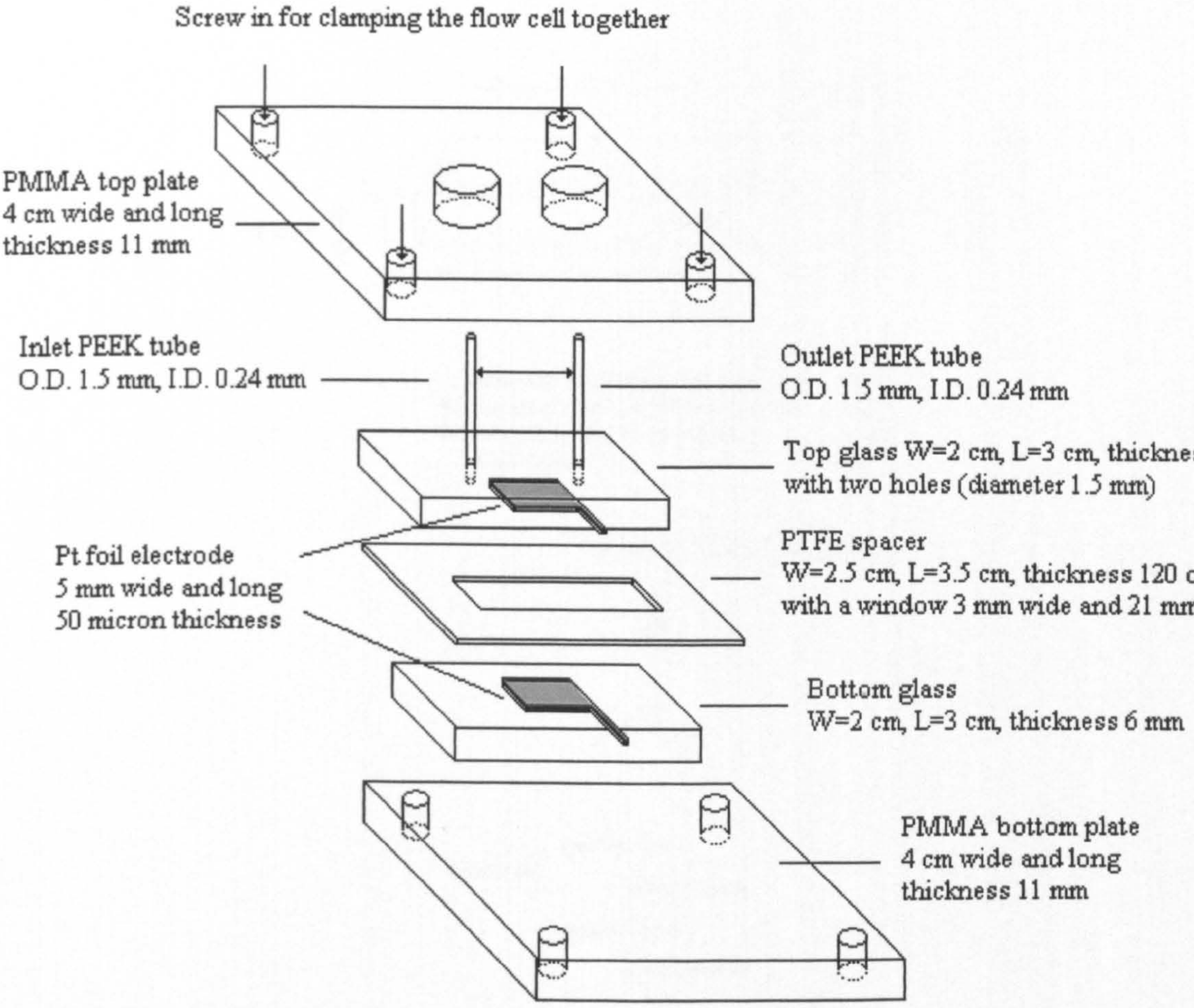
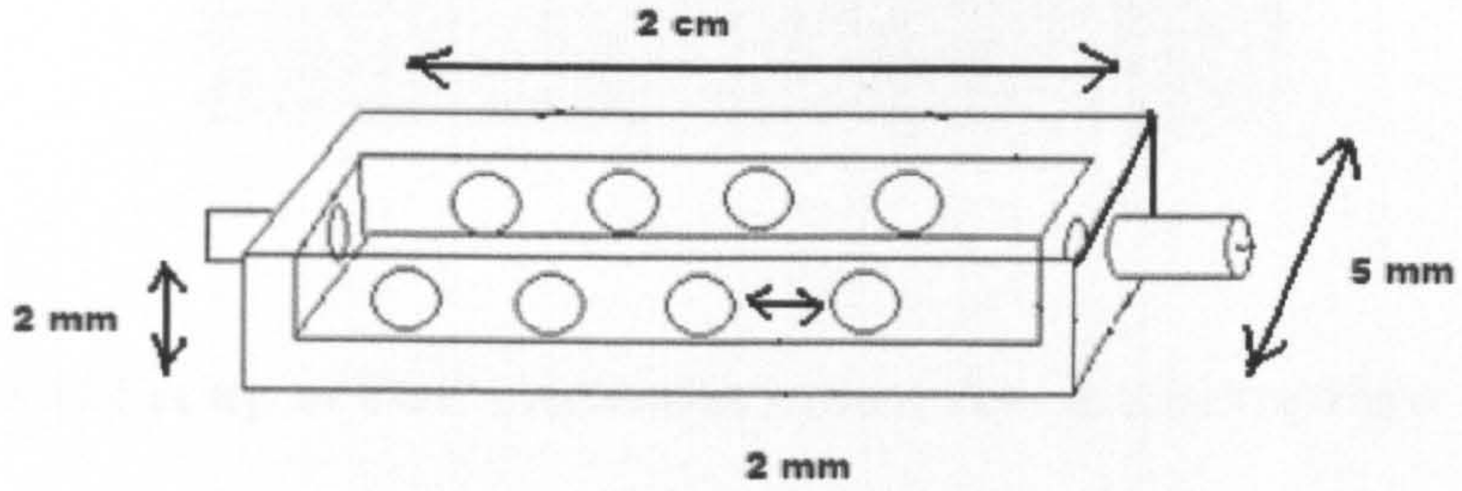


Figure 30 Set up of electrodes across the channel in Flow Cell F

3.4.6 Flow Cell G

Flow cell G (Figure 31 and 32) was constructed from synthetic silica plates, to give a rectangular channel, with a 5 mm wide and 2.5 cm long flow through reaction chamber, fitted with two pairs of electrodes glassy C anode (C rod type 2, Alfa Aesar) and Pt cathode (1 mm diameter, Alfa Aesar) across it. The gap between the two electrodes was 2mm.



Electrode diameter C /mm (anode)	**1.0**
Electrode diameter Pt/mm (cathode)	**1.0**
Distance between electrodes/mm	**1.0**
Cell volume/ µL	**100**

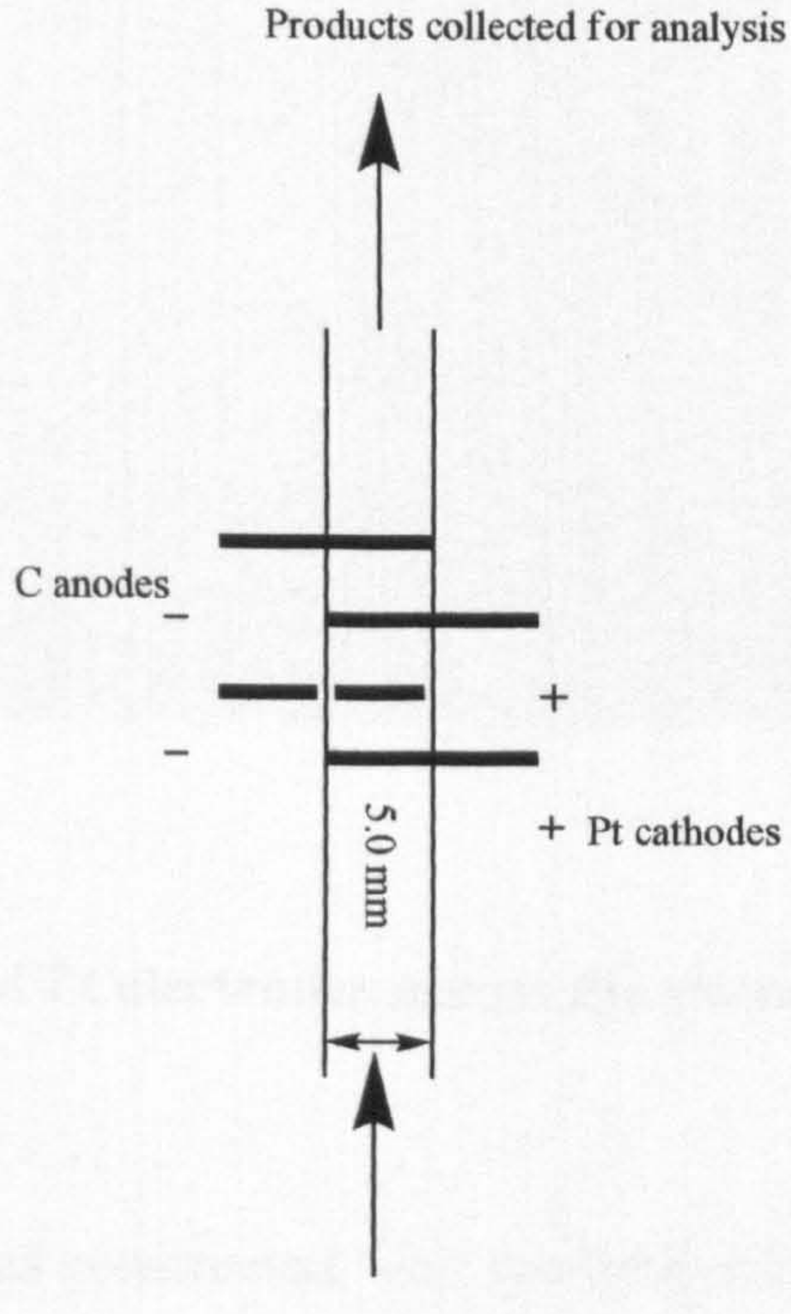


Figure 31 Set up of electrodes across the channel in Flow Cell G

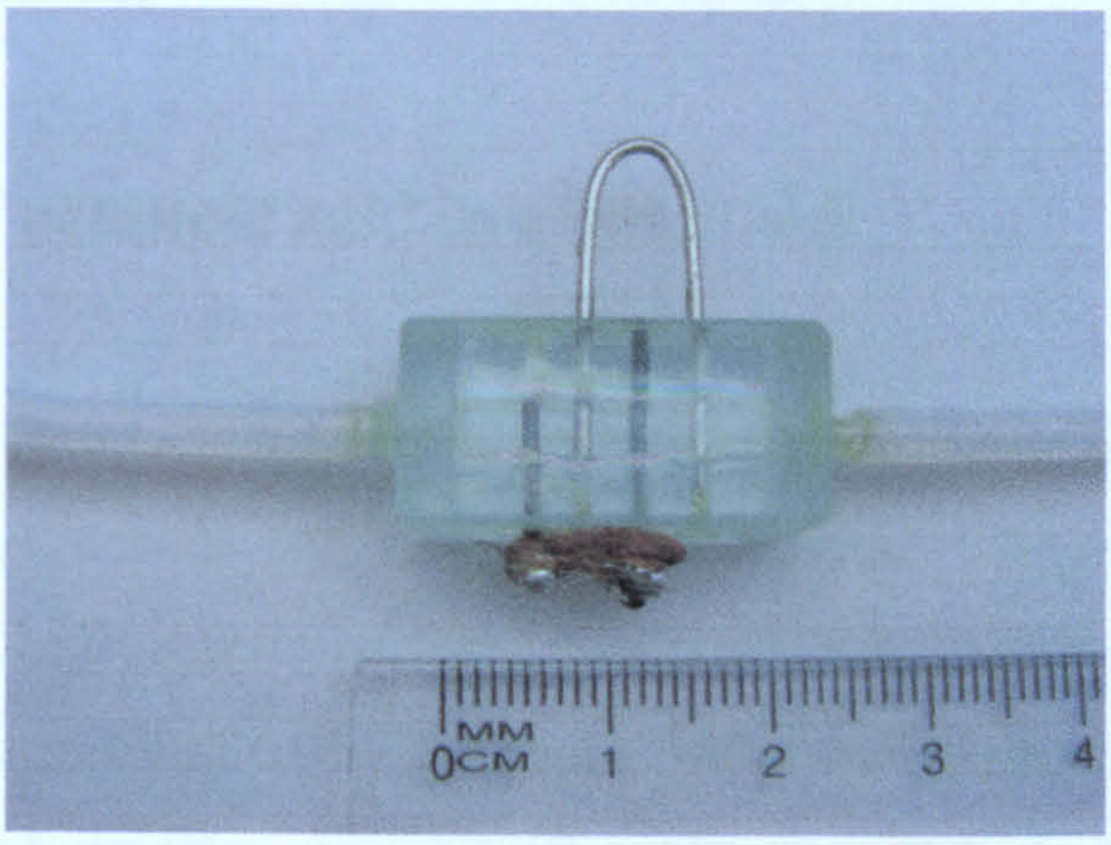


Figure 32 Set up of Pt/C electrodes across the channel in Flow Cell G

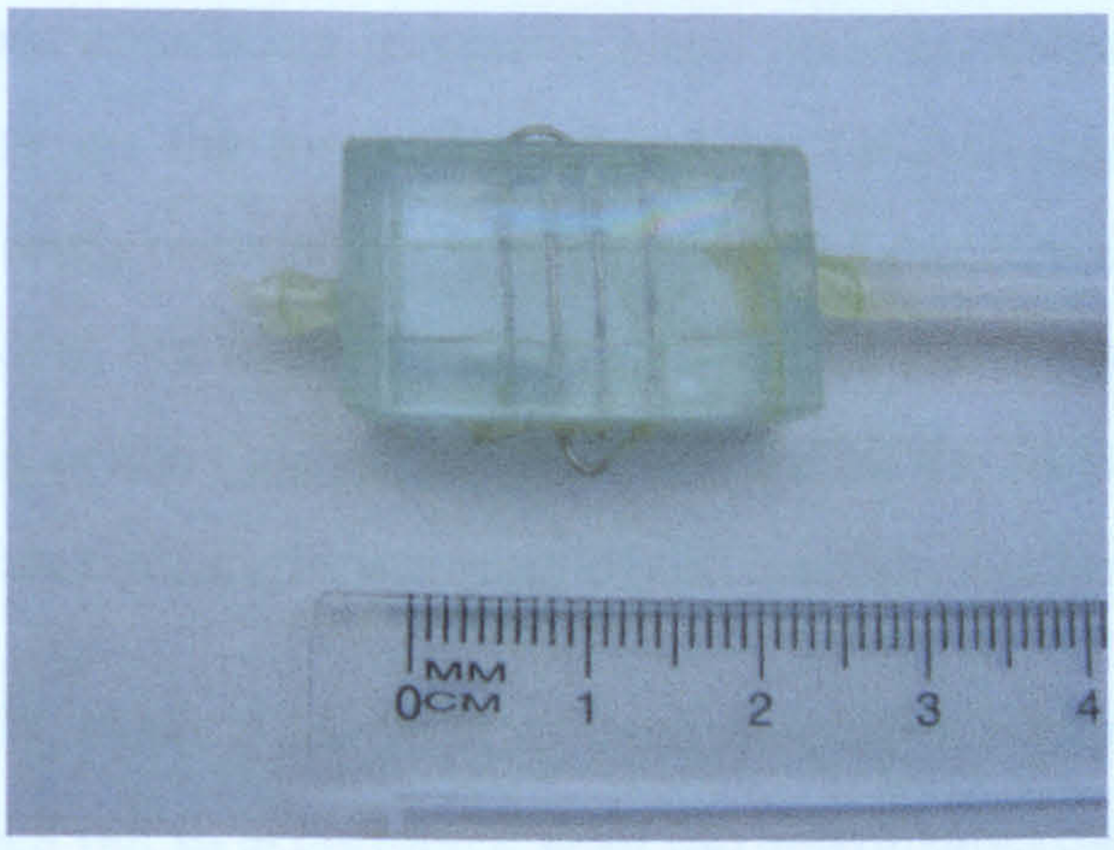


Figure 33 Set up of Pt electrodes across the channel in Flow Cell G

The flow cell G (Figure 33) was constructed with synthetic silica plates, to give a rectangular channel, with a 5mm wide and 2.0 cm long flow through reaction chamber, fitted with two pairs of Pt electrodes (1 mm diameter Alfa Aesar). The gap between the anode and cathode was 2.0 mm. The solution was continuously supplied into the chamber with the aid of an electric syringe pump connected to the cell as described above.

3.5.0 Synthetic Protocols

3.5.1 Electrolysis of octanoic acid in a batch cell

The electrolysis of 0.05 mol L^{-1} - 0.1 mol L^{-1} octanoic acid solution in methanol, was carried out with internal standard decane and varying concentrations 0.05 mol L^{-1} - 0.25 mol L^{-1} of bases such as diethylamine, triethylamine, diisopropylethylamine, pyridine, sodium *tert*-butoxide, sodium methoxide, and 0.05 - 0.2 mol $L^{-1}$of potassium hydroxide, sodium chloride, potassium iodide, tetrabutylammoniumtetrafluoroborate and ammonium chloride were employed. A 2 ml aliquot of each solution having 0.1 mmol of acid and 0.2 mmol of the base for most of the reactions was divided into two halves, storing each vial under N_2. To one of the vials 100 - 600V was applied using BioRad/Advance High volt – 2 A power supply from 10 minutes to 180 minutes depending upon how the reactions behaved for different bases. While the other vial (blank) was kept at room temperature for 10 - 180 minutes. After 10 - 180 minutes the solutions containing inorganic bases and electrolytes were filtered through silica with a celite layer on the top and analysed by GC/MS and GC/FID, whereas the reaction mixtures containing organic bases were analysed directly by GC/FID and GC/MS. The electrolysis was carried out under nitrogen, in a sealed vial Figure 18 Cell A. The pH of the solutions was slightly acidic / almost neutral 5 – 6 for all the reactions. No drastic change, apart from the temperature rise, slight warming of the reaction mixture / vial was observed.

The electrolysis of all the other acids such as pentanoic acid, hexanoic acid heptanoic acid nonanoic acid was carried out in accordance with the above procedure using octane, decane, dodecane, tetradecane and hexadecane as internal standard. The electrolysis of amino acids was carried out using decane as internal standard. For the addition reactions 0.05 - 0.1 mol L^{-1} of the substrates such as styrene, ethyl propiolate and ethyl crotonate were electrolysed with the above acids in the presence of 0.05 - 0.2 mol $L^{-1}$of pyridine.

3.5.2 Electrolysis of octanoic acid in a flow cell

The electrolysis of 0.05 – 0.1 mol L^{-1} octanoic acid solution in methanol, was carried out in flow cells B, C, D, E, F and G, with internal standard decane and varying concentrations of bases 0.05 – 0.5 mol L^{-1} such as diethylamine, triethylamine, diisopropylethylamine, pyridine, sodium *tert*-butoxide, sodium methoxide, and salts such as potassium hydroxide, sodium chloride, potassium iodide and ammonium chloride were employed in a similar way as described above for the Batch Cell A. A 2 ml aliquot of each solution having 0.1mmol of acid and 0.2 mmol of the base for most of the reactions was electrolysed. The acid solutions before electrolysis were stored under N_2. The solutions were flown through the various designs of flow cells as described in the flow cell set up. A voltage of 100 – 600 V was applied using BioRad/Advance High volt – 2 A power supply. The samples were collected after every three to five minutes over a certain time depending upon the reactions. The solutions containing the inorganic salts and bases were filtered through silica with a celite layer on the top and analysed by GC/MS and GC/FID. As mentioned above for the pH of the solutions was slightly acidic / almost neutral 5 – 6. The only change observed for the flow cells was also the temperature rise and warming of the flow cell was observed.

The electrolysis of all other acids along with amino acids and addition reactions of styrene, ethyl propiolate and ethyl crotonate to octanoic acid and hexanoic acid was carried out in the same way as described above for the batch cell.

CHAPTER: 4 RESULTS AND DISCUSSION

4.1.0 Results of constant potential electrolysis in a batch cell

Radical chemistry provides mild reaction conditions for the formation of C-C bonds and the anodic decarboxylation of carboxylic acids offer a useful method for the generation of such radicals. The generated radicals can be used in homo - and hetero coupling or in addition reactions involving double bonds. It is important however to keep in mind the fact that the yields and selectivity of Kolbe reactions are strongly dependent on the reaction conditions. In this work a Kolbe reaction using octanoic acid was investigated in the first instance under a variety of conditions in order to define the most favourable conditions for the formation of the product tetradecane, based on a batch reaction. As discussed in the introduction, the literature[1] suggests that electrolysis can be conducted in flow reactors without the use of an added electrolyte. Consequently a study was conducted to see if the Kolbe reaction could be performed in this way as all literature based batch Kolbe reactions always use an added electrolyte. Literature[1] also suggests that dimer formation is not only favoured by high current densities, high carboxylate concentrations, and weakly acidic/neutral media, but also the electrode material best suited for this kind of synthesis. Furthermore the literature[1] indicates that methanol is the solvent of choice, as the oxidation of methanol is inhibited by the formation of the carboxylate layer at the electrode surface. Therefore, the reaction was carried out initially using a platinum electrodes and different solvents, in order to define an appropriate solvent without using a supporting electrolyte. Platinum electrodes were used because preliminary studies showed that nickel and copper electrodes turned black and the solution became very hot leading to the discontinuation of the reaction. The arrangement of electrodes in a batch cell can be seen from Cell-A, Figure 17. The reaction mixtures for the batch reactions were analysed by GC/MS method B and GC FID method A.

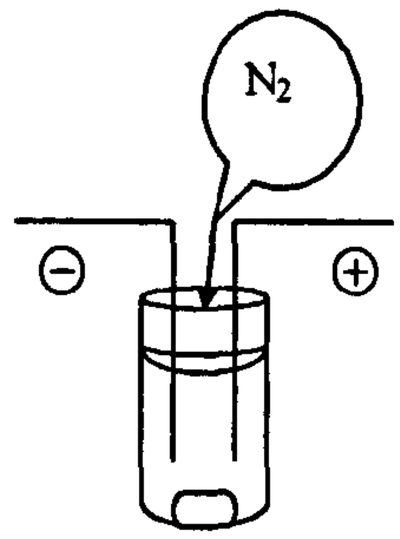


Figure 17 The arrangement of electrodes in batch Cell – A

4.1.1 Concentration study

The literature[1] supports methanol as the best solvent for Kolbe electrolysis. To study the optimum conditions for the formation of tetradecane in a batch reaction, without using an electrolyte, the electrolysis of octanoic acid was conducted at different concentrations. It was found that higher concentrations of the acid was required to achieve higher currents, as lower concentration of the acid solution (0.025 mol L^{-1}) was found less conducting (Table 11), and hence gave lower yields of the product. However when the concentration of the acid was too high (0.1mol L^{-1}) excessive CO_2 bubbles were generated (along with H_2) and the electrodes became coated with black carbon resulting in a lower yield. Therefore at this stage it was evident that the optimised acid concentration was 0.05 mol L^{-1}, without using any electrolyte.

Acid Concentration/ mol L^{-1}	Voltage/ kV	Time/min	Current/ mA	Product Yield/%
0.025	0.2	10	1-3	0
0.05	0.2	10	2-7	8
0.1	0.2	10	4-10	6

Table 11 The results of electrolysis of octanoic acid using methanol in Cell-A Figure 17

4.1.2 Solvent Study

Using 0.05 mol L^{-1}as the optimised concentration, the effect of solvent on the electrolysis of octanoic acid was studied using other solvents such as DMF, THF, DMSO and acetonitrile, using the Set up – A (Figure 16) with Cell–A (Figure 17). However as expected none of the above mentioned solvents worked except methanol as can be seen from the results in Table 12.

Solvent	Voltage/ kV	Time/min	Current/ mA	Product Yield/%
THF	0.2	10	2-3	0
DMF	0.2	10	1-2	0
DMSO	0.2	10	1-1	0
Acetonitrile	0.2	10	3-5	0
Methanol	0.2	10	2-7	8

Table 12 The results of electrolysis of 0.05 mol L^{-1} octanoic acid from different solvents in Cell-A Figure 17

The results above (Table 12), showed that methanol was the best solvent for Kolbe electrolysis and this was in agreement with the literature.[1] Methanol supports the electrolysis, as a higher current was obtained as shown in Table 7 resulting in a higher yield of tetradecane as compared to all other solvents. These results also suggest that the electrolysis can only be conducted at a high voltage (200 V) without using a base/electrolyte, which was still not giving significant dimer yields. All reported work using Kolbe electrolysis supports the use of a base and electrolyte as the base decarboxylates the acid and electrolyte helps in the conduction of current.[1] Therefore it was assumed that Kolbe electrolysis of octanoic acid could be carried out at a lower voltage when a base was added which would also work as an electrolyte. In order to determine the best suited base which can also work as an electrolyte for the electrolysis of octanoic acid a study was conducted using different bases.

4.1.3 Base study in batch cell

The experiments were conducted to define an appropriate base for Kolbe electrolysis of octanoic acid in methanol as solvent, using different base (also acting as an electrolyte) concentrations. Assuming that under these conditions the reaction mixtures would be more conducting to give higher currents hence the experiments were initially conducted at lower voltage (50 V). The set of results for 0.05 mol L^{-1} octanoic acid with 0.1 mol L^{-1} of base, (Table 13) showed that these concentrations of acid and base did not work effectively in the above setup at 50 Volts. However it was found that increasing the time for the reaction from 10 minutes to 20 minutes for constant potential electrolysis gave better dimer yield, from 10 to 18% respectively in case of diethylamine. The idea of using an inorganic base was also introduced however as can be seen from the results (Table 13) the addition of an inorganic base does not affect the process at all as it did not dissolve in methanol and hence could not conduct.

Base/electrolyte	Current / mA	Voltage/ kV	Yield/ %After 10 min	Yield/%After 20 min
Diethylamine	2-4	0.05	10	18
Triethylamine	2-5	0.05	7	7
N,N-Diisopropylethylamine	1-4	0.05	-	14
Pyridine	1-3	0.05	-	-
Sodium *t*-butoxide	1-2	0.05	-	1
Sodium methoxide	1-3	0.05	1	1
Potassium hydroxide	1-2	0.05	1	5

Table 13 Results of constant potential electrolysis of 0.05 mol L^{-1} octanoic acid with 0.1 mol L^{-1} base/base and electrolyte at 50V

The results from Table 13 show that the electrolysis of octanoic acid with different organic and inorganic bases also acting as electrolytes gave very low (10% after 10 min)

or no dimer product at all, and the use of these bases also poses the difficulty in separation of products from the reaction mixture. The organic bases in organic solvent methanol seemed more effective, as the inorganic bases did not seem to dissolve completely and the solution needed continuous stirring. Therefore to increase the conductivity in order to achieve a higher current without using an electrolyte, the concentration of the acid and organic base was increased by two fold.

4.1.4 Acid base concentration effect

The constant potential electrolysis of 0.1 mol L^{-1} octanoic acid with 0.2 mol L^{-1} base also gives almost the same results (Table 14), as increasing the concentration of the acid to base does not significantly increase the percentage (%) yield even after 20 minutes and the anode got coated with a black mass giving more CO_2 bubbles. The current was observed to fluctuate between very high (9 mA) and very low (0 mA) values giving an average of 1- 4 mA therefore these results (Table 14) could not be repeated in the batch cell, however the data did indicate that triethylamine and *N,N*-diisopropylethylamine (although electrodes were coated with polymeric films) would be more promising for further investigation in the Kolbe electrolysis.

Base/electrolyte	Current/ mA	Voltage/ kV	Time/min	Yield/ %
Diethylamine	2-3	0.05	20	6
Triethylamine	2-4	0.05	20	16
N,N-Diisopropylethylamine	1-4	0.05	20	21
Pyridine	1-3	0.05	20	0

Table 14 Results of constant potential electrolysis of 0.1 mol L^{-1} octanoic acid with 0.2 mol L^{-1} of a base

Whilst an electrolyte free electrolysis was considered ideal for clean reactions, the fact remained that using a supporting electrolyte enhances the conductance of current, therefore a small study was conducted at higher voltage (100V) using different bases and

additionally added electrolytes, the results of these experiments are reported in the next two sections.

4.1.5 Voltage study in batch cell

The electrolysis was carried out in solutions of 0.05 mol L^{-1} octanoic acid with 0.1 mol L^{-1} bases (the optimum concentration without electrolyte) at 100 V for 20 – 120 min. The current values fluctuated between the range of 1-8 mA for theses bases, however the values varied between individual reaction mixtures. The current was recorded throughout the electrolysis and the average current was used to calculate the current density. The results (Table 15) show that different bases have different conductivity and when compared to bases such as diethylamine, triethylamine, and *N,N*-diisopropylethylamine, pyridine did not give any significant dimer yield under the above set of conditions. The electrolysis using all these bases except pyridine could be conducted for a comparatively longer period at this voltage. In case of triethylamine the electrolysis was conducted for 1 hour to give 46% yield and for diethylamine and *N,N*-diisopropylethylamine the electrolysis was carried out for 80 minutes and 120 minutes respectively to get a significant yield (57% and 36%) under the above conditions. The experiments were conducted for a range of times for different bases however this was necessary due to the conductance of these reaction mixtures. As can be seen (Table 15) reaction mixture containing pyridine could not conduct for a long period of time and the reaction stopped after 20 minutes, whereas the reaction mixtures for diethylamine, triethylamine and *N, N*-Diisopropylethylamine could conduct longer at 100 Volts.

Base/ Electrolyte	Current/ mA	Time/min	Yield/%
Diethylamine	3-8	80	57
Pyridine	1-4	20	1
Triethylamine	2-5	60	46
N,N-Diisopropylethylamine	1-3	120	36

Table 15 Results of electrolysis of 0.05 mol L^{-1} of octanoic acid with 0.1 mol L^{-1} of bases at 100 V

Although the yield was significant, the reaction mixtures turned brown (giving olefin byproducts) and the anode turned black whereas the cathode was covered with a brown film and the current was not consistent giving very low (0 mA) and very high (10 mA) current values which was monitored by an ammeter connected to the power supply. On the other hand pyridine gave a steady current, however the dimer yield was not significant but the electrodes remained clean and the reaction mixture did not turn brown under these conditions. The effect of supporting electrolyte was studied next to improve the optimum conditions for these bases.

4.1.6 Base and supporting electrolyte study in batch cell

In order to achieve the optimum conditions for the above bases like triethylamine (for giving comparatively better yield in less time) and pyridine (for giving steady current), the electrolysis was carried out in the solutions of 0.05 mol L^{-1} octanoic acid with 0.1 mol L^{-1} of these bases and 0.01 mol L^{-1} of the electrolyte (various). The results (Table 16) show that in the presence of a conducting salt the base triethylamine lost the acid deprotonating effect and did not give dimer yield as good as when it was used without electrolyte (Table 15). The electrolysis was carried out for up to 100 minutes yet poor conversions (1%) were obtained (Table 16) and the electrodes (especially anode) turned black suppressing the Kolbe electrolysis. Whereas the use of pyridine 0.1 mol L^{-1} gave some interesting results (61 % yield) when used in combination with 0.01 mol L^{-1} KOH, although the electrodes turned black with the current fluctuating and reaction mixture turning brown consequently the electrolysis had to be stopped. As the literature suggests pyridine is one of the most commonly used base (also used with KOH for some reactions) for the Kolbe electrolysis,[1] because it not only enhances the neuteralization/deprotonation of the acid but also helps cleaning the electrodes from the polymeric films formed on the electrodes at high current/potentials,[2] hence it can be used more effectively in combination with an inorganic base such as KOH which also acts as an electrolyte. The reaction conditions although optimum for a batch cell could not be investigated further to be applied to the flow cell for there would be more chances of blocking the channels and loosing the product while trying to separate it from the reaction mixture in order to perform GC and GC/MS analysis.

Base/ Electrolyte	Current/ mA	Time/min	Yield/%
Pyridine+KOH	1-4	90	61
Triethylamine + NH_4 Cl	1-2	100	2
Triethylamine + NaCl	1-2	100	1
Triethylamine + KI	1-2	60	2
Triethylamine + But_4NBF_4	2-8	20	3

Table 16 Results of electrolysis of 0.05 mol L^{-1} of octanoic acid with 0.1 mol $L^{-1}$of bases / bases and electrolytes

The results (Table 16) showed that the use of triethylamine 0.1 mol L^{-1} and conducting salts 0.01 mol L^{-1} did not improve the reaction conditions and one of the reasons for not having a higher yield (46%) could have been the current fluctuating between very high (10 mA) and very low (0 mA) values at all times. As the temperature of the cell contents also rose to 35-40°C the electrolysis had to be stopped. The anode also turned black in all of the above experiments using triethylamine as the base in spite of the continuous stirring, therefore the use of pyridine acting as a base as well as an electrolyte was identified as being ideal for generating a significant dimer yield with cleaner electrodes and reaction mixture at a steady current. It was also suggested to investigate the effect of a higher voltage to generate radicals in the presence of pyridine as a base.

4.1.6.1 Pyridine study in batch cell

As already described (Table 14) increasing the concentration of the acid and base did not show any significant effect on the dimer formation, instead it increased the electrode fouling, leading to current fluctuations. Therefore it was also suggested that to minimize the electrode fouling 0.05 mol L^{-1} of the acid and 0.1 mol L^{-1} of the base pyridine (giving a steady current Table 15) should be electrolysed at higher voltages (200V). The voltage was increased from 100 to 200 Volts to investigate the effect of higher voltage and as suggested by the electrolysis results reported above all the bases and base electrolyte combinations could not give a steady current except pyridine (although gave significant yields up to

57%). Interestingly for pyridine solutions the electrolysis was established at 200 Volts. The results (Table 17) show that pyridine alone works better for the Kolbe electrolysis of octanoic acid to produce tetradecane, although it only works at a higher voltage, which needed to be investigated further to make the process cost effective.

Base/ Electrolyte	Current/ mA	Time/min	Yield/%
Pyridine	2-5	50	71

Table 17 Results of electrolysis of 0.05 mol $L^{-1}$of octanoic acid with 0.1 mol $L^{-1}$of pyridine at 200V

The use of pyridine suggested that at the above mentioned concentrations it could only work better at higher voltage, and increasing the concentration of pyridine could be investigated in order to enable its use at lower voltage because it was assumed that at higher concentrations it will behave more as an electrolyte as well as a base. In order to investigate the effect of pyridine concentration, 0.05 mol L^{-1}, 0.25 mol L^{-1} and 0.5 mol L^{-1} pyridine was employed. The results Table 18 show that when pyridine is used in excess the Kolbe electrolysis of octanoic acid was not favoured and gave a poor dimer yield (16%). However the presence of 0.25 mol L^{-1} pyridine gave higher yield (72%) and showed that by increasing the concentration of pyridine by approximately two folds (up to 0.25 mol L^{-1}) affected the reaction and gave a higher yield as can be seen from the results given in Table 18.

Octanoic acid/ mol L-1	Pyridine/ mol L-1	Voltage/ kV	Current density/ mA/ cm2	Yield /%
0.05	0.000	0.2	1	8
0.05	0.25	0.2	38	72
0.05	0.5	0.2	30	16

Table 18 The results of electrolysis of 0.05 mol L^{-1} octanoic acid with pyridine at 200V for 30 min in methanol

Most of the above reactions using different bases as well as bases and electrolytes could not give a steady current at 100 – 200 V, although some reactions gave significant dimer yield (57%) suggesting an investigation based on the use of organic bases (without a supporting electrolyte) for batch reactions to be conducted at lower voltages (up to 50 – 100 V).

4.1.6.2 Organic bases combinations

The results in Table 15 showed that diethylamine and triethylamine gave higher currents (3-8 and 2-5mA) and higher dimer yields (57 % and 46 %) respectively at 100 Volts, it was also observed that the current values were not steady and fluctuated between very high (10 mA) and very low (0 mA) and the anode also turned black. On the other hand the use of pyridine gave a steady current but less dimer yield at 100 Volts, however when higher voltage was applied pyridine gave higher dimer yield with (72 % at 100V) and without (71 % at 200V) a supporting electrolyte. In order to investigate further the effect of organic bases pyridine, diethylamine and triethylamine (without a supporting electrolyte) in different concentrations and different combinations were applied, the results are given in (Table 19). These results suggested that organic bases work best in anhydrous methanol compared to when they were used with an inorganic base or conducting salt. However using pairs of bases gave more byproducts (olefins). In the batch cell pyridine was not found effective for the Kolbe reaction at 50 or 100V. Therefore pyridine was used in combination with the bases giving higher dimer yield at 100V, in order to achieve steady currents. Different concentrations of pyridine (giving steady current)/triethylamine (46% yield at 100V in 1 hr) were employed, and as can be seen from the following results (Table 19) that by pairing triethylamine with pyridine in the ratio of 2:1 respectively gave a higher current (13 – 31 mA) giving a higher yield (34 %) at lower voltage (100 V). However more byproducts (olefins) were formed with less reproducibility RSD (24-39 %). Therefore it was suggested that the use of one base pyridine which acted as a base as well as an electrolyte should be investigated in more detail in order to avoid the formation of byproducts (keeping in mind the accurate means of separation of products from the reaction mixture) to define the optimum conditions.

Bases/ mol L^{-1}/ mol L^{-1}	Voltage/ kV	Current/ mA	Average Yield%	n	Time/min	RSD
A) 0.1/0.1 triethylamine/pyridine	0.1	13-24	16	6	20	39
B) 0.2/0.1 triethylamine/pyridine	0.1	13-31	34	5	20	32
C) 0.1/0.2 triethylamine/pyridine	0.1	14-47	19	6	20	38
D) 0.1/0.1 diethylamine/pyridine	0.1	15-33	10	5	20	24
E) 0.2/0.1 diethylamine/pyridine	0.1	11-44	14	5	20	27

Table 19 Results of batch electrolysis of 0.05 mol L^{-1} octanoic acid using different organic bases in methanol

The results (Tables 13-19), suggested that using pyridine alone (0.25 mol L^{-1}) in methanol as a solvent gives higher conversions (71 %), at 200V. The data in these experiments suggested that Kolbe electrolysis can be carried out in the presence of organic bases, because once the acid is deprotonated it can be easily decarboxylated to give radicals. The base not only deprotonates the acid but also increases the conductivity of the solution for the electrolysis. The use of conducting salts does improve the system conductivity but hinders the decarboxylation of the acid and dimerisation, and also makes the process more complicated in terms of separating the products from the reaction mixture. However these results suggested some optimum conditions for the Kolbe electrolysis of octanoic acid in a batch cell which could be transferred to a flow cell later, although the reproducibility was poor. On the other hand flow reactors are reported to give highly reproducible yields of products as discussed in the introduction.[3] Consequently we wished to investigate the reproducibility of the batch reactors such that we could later compare the results with those obtained in the flow reactors.

4.1.7 Reproducibility of batch cell results

In order to best exploit the use of organic bases for Kolbe electrolysis of 0.05 mol L^{-1} of octanoic acid a set of experiments were conducted to define the reproducibility of a batch cell using a base (0.1 mol L^{-1}) giving higher yields of dimer product on its own and in combination with a conducting salt. When the electrolyses were repeated at 100 Volts for

twenty minutes, for different base and electrolyte combinations, it was seen that the batch reactions do not give reproducible results (2 % yield) with a very high RSD up to 85% using triethylamine in combination with NH_4Cl (Table 20). The results also suggested that organic bases could affect the Kolbe electrolysis of octanoic acid and among diethylamine (27 % yield), triethylamine (35 % yield) and *N,N*-diisopropylethylamine (28 % yield), *N,N*-diisopropylethylamine gave better reproducibility with an RSD of 21%. These results clearly showed the effect of triethylamine giving comparatively better yield (35%) as compared to when it was used in combination with different electrolytes (0.01 mol L^{-1}) (NaCl, NH_4Cl, KI and But_4NBF_4) where it could not give more than 3 % yield.

Base/ Electrolyte	Voltage/ kV	Current/ mA	Average Yield/%	n	RSD
Diethylamine	0.1	2-4	27	8	55
Triethylamine	0.1	2-8	35	6	26
N,N-Diisopropylethylamine	0.1	1-4	28	12	21
Triethylamine + NH_4Cl	0.1	0-2	2	10	85
Triethylamine + NaCl	0.1	0-1	1	10	29
Triethylamine + KI	0.1	0-1	2	6	36
Triethylamine + But_4NBF_4	0.1	2-8	3	2	0

Table 20 Results of repeated electrolysis of 0.05 mol L^{-1} octanoic acid with different bases 0.1 mol L^{-1} and electrolytes 0.01 mol L^{-1}

The use of electrolytes did not improve the RSD and could not give any significant yield (1 – 3%) for the batch cell. However these results do give an insight into the effect of bases and how they could be best employed for use in an organic solvent in a flow cell set up. It was suggested that the effect of pyridine should be investigated to achieve reproducible results in the batch cell. Pyridine could not be used under the same conditions as its acid (0.05 mol L^{-1}) / base reaction mixture required higher concentrations of pyridine (0.2 - 0.25 mol L^{-1}) to conduct. The solution was electrolysed at 200 Volts instead of 100 Volts (Table 21). It was seen that 0.2 mol L^{-1} pyridine at 200 Volts gave an optimum yield (71 %) and improved the RSD greatly (2 %).

Base	Voltage/ kV	Current / mA	Time/min	Average Yield/%	n	RSD
Pyridine	0.1	1-4	20	6	2	13
Pyridine	0.2	3-6	20	71	3	2
Pyridine	0.25	1-15	20	16	3	67

Table 21 Results of repeated electrolysis of 0.05 mol L^{-1} of octanoic acid with pyridine 0.1- 0.25 mol L^{-1}

The results (Table 20) and (Table 19 discussed earlier) were as expected initially from the batch cell, however these results were improved by using pyridine (Table 21). All the above results could be used to illustrate the possible optimum conditions under which dimers could be formed from octanoic acid using different bases in a batch cell. The effect of pyridine on establishing the appropriate current density at 3 - 6 mA to increase the dimer yield (71 %) explains how a base (pyridine) which can also act as an electrolyte affects the formation of radicals. It affects in establishing equilibrium to support the diffusion layer formation and mass transport at the surface of the electrodes.

In spite of the fact that Kolbe electrolysis of octanoic acid in a batch reaction was greatly affected by pyridine, it did so only under a high concentration (0.2 mol L^{-1}) and high voltage (200 Volts). It was suggested that the effect of triethylamine on the Kolbe electrolysis of octanoic acid in aqueous medium (which is also supported by the literature)[1] should be investigated in order to exploit an optimum set of conditions with better reproducibility. The experiments given below were conducted to establish the best anhydrous experimental conditions using triethylamine in aqueous medium.

4.1.8 Aqueous medium in Batch cell

All previous experiments were conducted in dry methanol hence we were also interested to investigate the reactions carried out under aqueous conditions. The experiments were conducted in such a way that it introduced 2 - 20% of water. The results (Table 22), clearly show the negative effect of aqueous methanol on triethylamine, which gave a significant

dimer yield (46 %) (Table 10) at comparatively low voltage 100V as compared to pyridine which gave the product (71 %) at 200V (Table 17). Increasing the water content decreased the dimer yield and the electrolysis in 8%, 10% and 20% aqueous methanol did not give any dimer yield at all. We propose that the reason for this observation is that organic acids such as octanoic acid are less soluble in aqueous medium therefore could not be electrolysed under the above conditions.

Methanol %	Current / mA	Voltage/ kV	Average Yield/%	n	RSD
2%aq	13-39	0.1	14	11	79
4%aq	19-41	0.1	8	10	71
6%aq	13-47	0.1	5	10	88
8%aq	15-52	0.1	0	6	n/a
10%aq	17-53	0.1	0	6	n/a
20%aq	15-57	0.1	0	5	n/a

Table 22 Results of electrolysis of 0.05 mol L^{-1} octanoic acid with 0.1 mol L^{-1} triethylamine in aq methanol

However no complete conversion (only 65% on the average) was observed, even after adding upto 20 vol % excess pyridine. On the basis of these results it was concluded that although aqueous medium is best for giving high current, however it is not suited for the Kolbe electrolysis of octanoic acid in a batch cell and the %RSD for these experiments was also very high showing the poor reproducibility.

4.1.9 Summary of batch reactions

It was observed that dimer formation by Kolbe electrolysis of octanoic acid in a batch cell depends upon the concentration of the acid/base 0.05-0.1/ 0.1-0.2 mol L^{-1}(especially for pyridine) at which the acid is partially neutralized to generate carboxylate ions, and the potential 100V (200V especially for pyridine) at which an optimum current (different for different bases) is attained to generate radicals from the carboxylate ions. It was also found that at a higher current (Table 19) does not necessarily generate radicals, and the formation

of dimers is purely depending on the radical formation from the carboxylate ions at the electrode surface, it was also observed that increasing the voltage or concentrations of acid/base increased the electrode fouling considerably. As mentioned above one of the factors that affects the radical generation in the case of pyridine is the electrode potential (200V) and an optimum concentration (0.2-0.25 mol L^{-1}) and it was clearly seen that increasing the potential considerably increased the product yield, reducing byproducts (not identified), whereas increasing the concentration of pyridine up to 0.25 mol L^{-1} hindered the Kolbe electrolysis under the same conditions (at 200V with 0.05 mol L^{-1} of the acid). Organic bases such as diethylamine, triethylamine and *N,N*-diisopropylethylamine favoured the decarboxylation to produce dimer and also added to the conductivity of the reaction mixture although failed to produce steady current and reproducible results. One of the drawbacks in adding the organic bases to the reaction mixture was, the formation of byproducts, whereas when the organic bases were used in combination with the inorganic bases (sodium methoxide and sodium tertbutoxide) alkenes were formed. In all the above electrolysis reactions it was difficult to control the fouling of electrodes and temperature of the cell for an electrolysis which was carried out for a longer period of time in the batch cell and therefore the reaction had to be stopped. As indicated in the literature[1] introducing triethylamine in aqueous methanol (2 - 20 %) did not improve the radical formation, and electrode fouling was observed in all reactions including pyridine reactions (longer period of time at 200 V), in spite of a continuous stirring. The results obtained from all batch reactions, suggested that methanol was the best solvent to use with pyridine as a base at platinum electrodes (becauase electrode material and surface area is also important) for Kolbe electrolysis of octanoic acid. In general the concentration of the acid and base along with the potential is critical to attain a current at which the decarboxylation and electron transfer is facilitated to generate radicals.

4.2.0 Results of constant potential electrolysis in a flow cell

For illustrative studies the Kolbe electrolysis of octanoic acid was selected to determine the best operating parameters such as cell potential, inlet solution velocity/ flow rates, composition of the reaction mixtures and the inter electrode spacing for a flow cell. The optimum conditions for a batch cell provided a framework to demonstrate the Kolbe electrolysis of octanoic acid using different bases as well as bases and electrolytes in a flow cell. The above parameters were investigated starting with the optimum conditions of 0.05 mol L^{-1} of octanoic acid, 0.05-0.2 mol $L^{-1}$of pyridine using methanol as solvent and platinum electrodes. Various flow cell designs were employed to investigate and determine the optimum conditions for Kolbe electrolysis. The final design of the flow through reactor was selected on the basis of preliminary results gathered from the experiments using PTFE flow through reactors.

A series of flow cell experiments were conducted using the different flow cells B - G (Figures 20-27) to establish a set of conditions best suited to Kolbe electrolysis in a flow system. For all the designs it was found that a change in the dimension and arrangement of electrodes could be accounted for in the cell performance in terms of dimer yield and that each design had to be optimised for its own set of conditions. The current values fluctuated between acertain ranges and varied between individual reaction mixtures. The current was recorded throughout the electrolysis and the average current was used to calculate the current density. The following sections describe the results gathered, the problems associated and the optimum conditions attained for each cell in chronological order.

4.2.1 Results of PTFE flow cell B

Flow cell B was a PTFE (0.8 mm I.D) flow cell (Figure 20) with one pair of electrodes across the channel. In order to investigate the effect of acid/base concentration and flow rate on the product formation the optimum concentration (from the batch cell results) of the acid (0.05 mol L^{-1}) and pyridine (0.25 mol L^{-1}) was employed at a variety of flow rates (5μL/min - 25μL/min) using flow cell B (Figure 20). The two sets of results obtained are discussed in the following sections. Bearing in mind that CO_2 is also produced as one of the main products, the acid concentration was not increased in the first instance in order to prevent the extensive CO_2 bubble formation and fouling of the electrodes, which could cause disruption in the flow as well as electrolysis.

4.2.1.1 Effect of potential using flow cell B

Table 23 shows that with a lower concentration of the acid 0.05 mol L^{-1} and base 0.25 mol L^{-1} the reaction mixture did not give high currents in flow cell conditions at lower potential (200 V) and that higher potentials (600 V) gave higher current hence producing better product yields (7 %) along with more CO_2 and H_2 bubbles and more fouling of electrodes. The current values fluctuated between the range of 1-8 mA for theses bases, however the values varied between individual reaction mixtures. The current was recorded throughout the electrolysis and the average current was used to calculate the current density. The reaction mixture was analysed by GC/MS method B and GC/FID method A.

Flow rate/μL/min	Voltage/ kV	Current/ mA	Current density mA/ cm2	Product yield/%
5	0.6	0.06-0.2	16	7
5	0.4	0.04-0.12	9	5
5	0.2	0.01-0.04	3	1

Table 23 The results of electrolysis of 0.05 mol L^{-1} octanoic acid 0.25 mol L^{-1} pyridine in flow cell B (0.8 mm I.D), Figure 20

In order to make the reaction mixture to conduct at lower voltage hence generating more radicals it was suggested that the acid concentration could be increased to make the reaction mixture more conducting. However considering the fact that increasing the concentration of the acid could increase the CO_2 formation and the fouling of electrodes simultaneously, the effect of flow rate was investigated which could affect the electrolysis and also keep the carbon dioxide bubbles moving. The effect of flow rate using flow cell B is discussed in the following section.

4.2.1.2 Flow rate study using flow cell B

As the results in Table 24 indicate, slower flow rates give greater product yields owing to the fact that slower flow rates offer longer residence time in the flow cell. Although slower flow rate (5μL/min) gives a lower current but gives a comparatively better dimer yield (7 %) whereas a faster flow rate (25μL/min) gives higher current yet less dimer yield (1 %). At a slower flow rate and high voltage the electrodes became coated with polymeric films and required cleaning for better performance (conducting 0.5 – 1.0 mA current) in spite of the fact that pyridine would be expected to remove these films. It was also observed that the flow cell (0.8 mm I.D) did not conduct at lower voltages (200 V) and the electrolysis was carried out at very high voltages (600V) yet no significant dimer yield (7 %) was obtained.

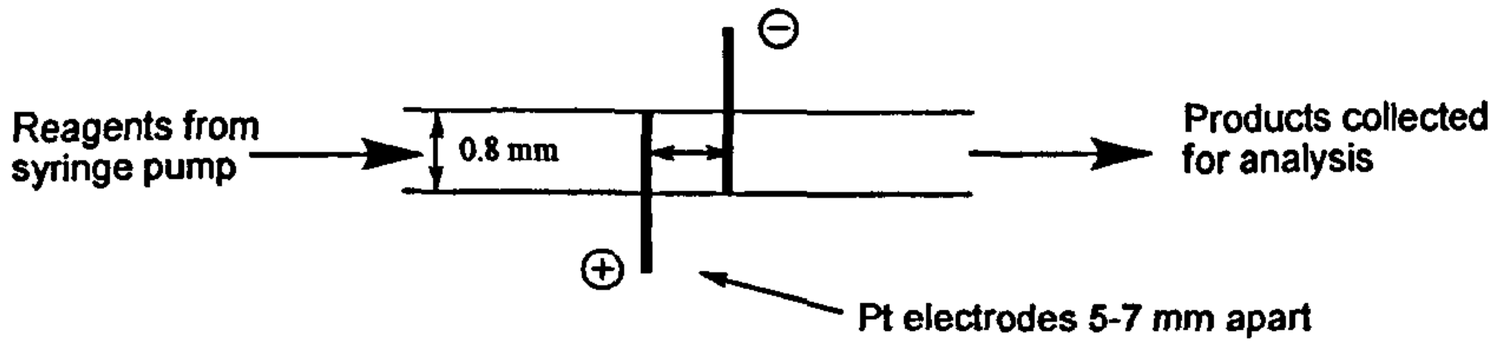


Figure 20 The arrangement of electrodes flow cell B

Flow rate/μL/min	Voltage/ kV	Current/ mA	Current density mA/ cm2	Product yield /%
25	0.6	0.005-0.8	32	1
12.5	0.6	0.012-1.0	43	4
5	0.6	0.005-0.5	19	7

Table 24 The results for the electrolysis of 0.05 mol L^{-1} octanoic acid with 0.25 mol L^{-1} pyridine in methanol with different flow rates in flow cell B (0.8 mm I.D) (Figure 20)

In the above flow cell B the product was formed but a very low yield (7 %) and this was obtained even at a higher voltage (600 V), therefore in order to attain a higher current with lower voltage and to optimise the electrolysis conditions in a flow cell, it was suggested that the electrode surface area should be increased. Flow cell C was employed introducing another pair of electrodes in order to improve the product yield by increasing the electrode surface area.

4.2.2 Results of PTFE flow cell C

Flow cell C was also a PTFE flow cell (0.8mm I.D) (Figure 22) with two pairs of electrodes across the channel. In order to investigate the effect of flow rate on the product formation keeping the optimum concentration of the acid (0.05 mol L^{-1}) and pyridine (0.25 mol L^{-1}) constant, a variety of flow rates were employed. The fact is that increasing the electrode surface area should increase the product yield. Hence the results in Table 25 also show an increase in the dimer yield when two pairs of electrodes were used. However the CO_2 gas bubbles generated at the anode got trapped between the electrodes (put 5-7 mm apart across the channel), which hindered the flow as well as electrolysis at the electrode surface. The reaction mixture was analysed by GC/MS method B and GC/FID method A.

4.2.2.1 Flow rate study using flow cell C

On the basis of the observations made while investigating the effect of flow rate using flow cell C, it was suggested that although the slower flow rate of 5 μL/min, was giving a better yield (9 %) as compared to the faster flow rate 25 μL/min which gave up to 6 % yield yet the CO_2 bubbles were interfering with the flow as well as electrolysis because the equilibrium could not be established at the surface of electrodes hence there was no significant radicals generated to give dimers and even at 12.5μL/min flow rate the product yield was almost the same (8 %). However the results (Table 25) still show that two pairs of electrodes provided greater surface area therefore gave higher product yield even at a higher flow rate.

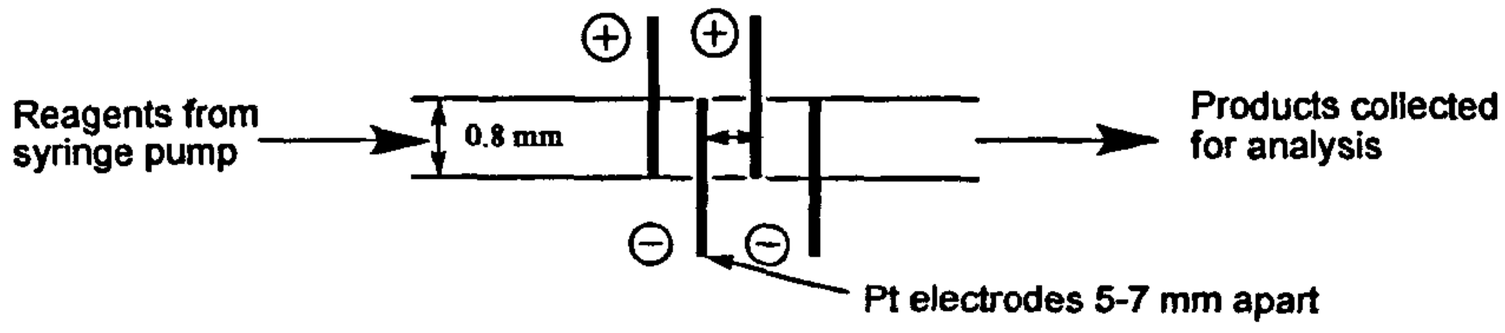


Figure 22 The arrangement of electrodes in flow cell C

Flow rate/μL/min	Voltage/ kV	Current/ mA	Current density mA/ cm2	Product yield %
25	0.6	0.003-0.368	15	6
12.5	0.6	0.010-0.268	11	8
5	0.6	0.011-0.478	19	9

Table 25 The results from the electrolysis of 0.05 mol L^{-1} octanoic acid with 0.25 mol L^{-1} pyridine in methanol using different flow rates in flow cell C (0.8 mm I.D), Figure 22

The fact that the anode is the means of generating radicals, the position of electrodes in the flow systems (flow cell B and flow cell C) was quite critical. The electrodes were connected to the power supply such that the anode comes before cathode in the direction of flow for flow cells B and C (Figures 20 and 22). The reproducibility of the flow cell C was investigated by repeating some of the experiments giving optimum yields (9 %).

4.2.2.2 Reproducibility of the flow cell C

Table 26, shows that although increasing the surface area gives a higher current even with a 0.05 mol L^{-1} of the acid and with two pairs of electrodes gave greater product yields still the CO_2 bubbles were interrupting the flow as well as electrolysis. It was also clear from the results (Table 26) of experiments repeated under the optimum conditions of 0.05 mol L^{-1} octanoic acid 0.25 mol L^{-1} pyridine at 5 μL/min at 600 V that the flow cell C did not give reproducible results (n = 6, sample collected every 5 minutes over 30 minutes of electrolysis) with 18 % optimum yield. One of the reasons which may be accounted for the

system not giving reproducible results, could be the formation of bubbles of CO_2 between the electrodes, breaking up the liquid flow and interrupting the electrolysis, as a result the reaction proceeded with fluctuating values of current therefore even though the electrolysis was repeated under the same optimum conditions as above, which did not give reproducible results generating an RSD of 47% (where n=6).

Flow rate/μ L/min	Voltage/ kV	Current/ mA	Current density mA/ cm2	Average yield %
5	0.6	0.13-0.23	7	15
5	0.6	0.12-0.20	6	18
5	0.6	0.19-0.23	8	11
5	0.6	0.20-0.30	10	7
5	0.6	0.22-0.30	10	4
5	0.6	0.13-0.19	6	11

Table 26 The results for the repeated electrolysis of 0.05 mol L^{-1} octanoic acid with 0.25 mol L^{-1} pyridine in flow cell C, Figure 22

The results of the repeated experiments were not consistent and showed that in PTFE flow cell C, when two pairs of electrodes which were put across the channel the gas bubbles were more likely to be and block the channel, which eventually hindered the flow as well as electrolysis. In addition the polymeric films were continuously formed at the surface of electrodes and the anode was also turning black under these conditions. Although at times the polymeric films which were trapped between the electrodes were removed with the flow, the cell was still unable to show any better results with respect to reproducibility. As the literature[1, 2] suggested and batch results supported the effect of pyridine to give better results for the batch cell (although at 600V), in order to improve the dimer yield for flow cell C, the effect of pyridine concentration at different voltages was investigated and the results from these experiments are following in the next section.

4.2.2.3 Pyridine Study at different potential in flow cell C

To investigate the effect of pyridine concentration on the electrolysis of 0.05 mol L^{-1} octanoic acid at 5μL/min flow rate, a set of experiments were repeated at different voltages in flow cell C. Two sets of results were obtained without pyridine and with varying concentrations of pyridine by keeping the concentration of the acid, and the flow rate 5 μL/min constant. The results in Table 27 show that pyridine is very important for the Kolbe electrolysis of octanoic acid in a flow cell, as it enables the reaction mixture conducting the potential under present conditions to give a suitable current (up to 10 mA) to assist the dimer yield up to 22 %. Therefore it was suggested that the concentration of pyridine which could conduct the potential to an optimum and give a better dimer yield should be defined. Table 27 clearly reflected the effect of pyridine concentration under a range of potentials, and as can be seen from these results increasing the concentration of pyridine to 0.5 mol L^{-1} compared to the acid 0.05 mol L^{-1}, gave higher conversion of 22 %, at 600V, however very high concentrations of pyridine 2.0 mol L^{-1} did not show any significant effect on the dimer yield even at high voltage 600V and high current 6 mA. The results also showed that the concentration of pyridine 0.5 mol L^{-1} was critical along with the optimum current (5 mA) under these conditions for the formation of radicals to produce dimers.

Pyridine/ mol L^{-1}	Voltage/ kV	Current/ mA	Current density mA/ cm2	AverageYield/ %
0.00	0.2	0.02-0.03	2	0.5
	0.4	0.02-0.03	1	0.5
	0.6	0.03-0.05	1	1
0.06	0.2	0.03-0.05	2	3
	0.4	0.03-0.05	2	3
	0.6	0.07-0.09	4	2
0.12	0.2	0.01-0.05	2	3
	0.4	0.03-0.07	3	8
	0.6	0.09-0.13	5	6
0.25	0.2	0.02-0.04	2	2
	0.4	0.07-0.09	3	19
	0.6	0.07-0.15	6	11
0.5	0.2	0.05-0.07	3	7
	0.4	0.06-0.11	4	6
	0.6	0.06-0.14	5	22
1.0	0.2	0.08-0.2	7	7
	0.4	0.12-0.2	7	5
2.0	0.2	0.05-0.08	2	6
	0.4	0.10-0.13	5	8
	0.6	0.12-0.15	6	9

Table 27 The results of electrolysis of 0.05 mol L^{-1} octanoic acid with varying concentrations of pyridine in methanol using flow cell C, Figure 22

The above results showed that pyridine concentration is critical and does affect the radical generation and dimer formation. As stated above one of the reasons accounted for the system not giving significant yields and reproducible results, could be the formation of bubbles of CO_2 between the electrodes, breaking up the liquid flow and interrupting the electrolysis, as a result the reaction proceeded with fluctuating values of current. To improve the efficiency of the flow system by controlling the gas bubbles from getting trapped between the electrodes also providing a greater electrode surface area, a flow cell with parallel Pt electrodes (0.36 mm diameter) through a certain length (2.5 cm) of a PTFE tube (I.D 1.5 mm) flow cell D, was designed (Figure 24). The next section comprises the results obtained from flow cell D.

4.2.3 Results of PTFE flow cell D

The flow cell D (1.5 mm I.D) was employed for the Kolbe electrolysis of octanoic acid using the optimum conditions for the flow cell C (0.05 mol L^{-1} octanoic acid and 0.25 mol L^{-1} pyiridine) except the potential was decreased from 600 V to 100 V with the understanding that the improved design (a parallel arrangement of Pt electrodes with a larger diameter 0.36 mm and a longer length 2.5 cm) would be conducting more current at a lower potential as a result of the increased electrode surface area. It was also assumed that the bigger diameter of the cell would help to remove the CO_2 bubbles more easily posing less interruption. The results (Table 28) showed some improvement in the dimer yield (28 %) with an RSD of 11% where n = 5. Samples were collected after every five minutes and each experiment was conducted over twenty to thirty minutes. However the optimum conditions (0.05 mol L^{-1} octanoic acid and 0.25 mol L^{-1} pyiridine, at 100 V) could not be benchmarked unless they were varied with respect to each other and investigated and evaluated for flow cell D. The reaction mixture was analysed by GC/MS method B and GC/FID method A.

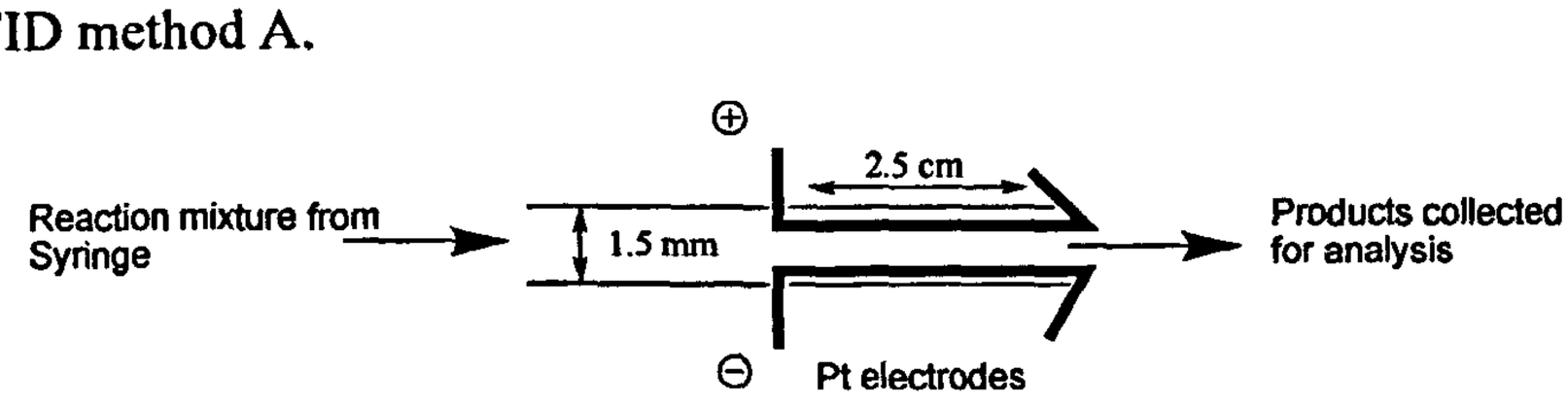


Figure 24 The arrangement of parallel electrodes in flow cell D

Flow rate/ μL/min	Voltage/ kV	Current/ mA	Current density mA/ cm2	Average yield/%
5	0.1	0.7-1.8	4	27
5	0.1	1.4-1.7	5	26
5	0.1	1.4-2.1	6	28
5	0.1	1.0-0.9	3	25
5	0.1	0.7-2.2	5	33

Table 28 The results of electrolysis of 0.05 mol L^{-1} octanoic acid with 0.25 mol L^{-1} pyridine using flow cell D Figure 24

The results showed reproducibility with an improved RSD from 47 % (flow cell C) to 11 (flow cell D), which indicated that the flow cell D was a better design with a continuous channel and parallel electrodes with an increased surface area, however it still needed more investigation to improve further. Results from the above experiments showed that with a larger I.D of the PTFE tube (1.5 mm) it was possible to overcome some of the disruption of the flow, associated with the bubbles from the CO_2 gas (which were removed along the flow), and did not affect the electrolysis significantly. It was also suggested that at 5μL/min flow rate the reacting species get enough contact with the electrodes, having more residence-time although the dimer yield still remains less than 50%. Omitting a conductive salt seemed to have simplified the product separation, and also optimised the selectivity of the reaction, as less/no byproducts (such as alkyl esters and alkenes) were found.

4.2.3.1 Reproducibility of the flow cell D

As the above results (Table 28) for flow cell D showed improved reproducibility (RSD 11 %) it was proposed that a greater surface area of the electrodes might enhance the dimer formation although more CO_2 bubbles will be generated but may not become trapped between the electrodes because of the bigger diameter of the PTFE tube (1.5 mm). Hence there was less hindrance in the radical formation giving more product yield (28 %) with less RSD 11% (n = 5) as compared to the results (Table 26) from flow cell C which gave 18 % yield with 47 % RSD (n = 6). The results also showed that increasing the surface area of the electrode for flow cell D gave more product yield 28 % at 100V and at a current of up to 2mA (which was steady) as compared to flow cell C which gave the product 18% at 600V. The electrolysis was carried out in flow cell D for 20 minutes. When the cell was put into prolonged use (e.g. 5 hours) the electrodes became coated with thick polymeric layers (not identified). In order to improve this condition it was suggested that the effect of pyridine and other organic bases should be investigated. Bearing in mind the better performance of the flow cell D different parameters like flow rates and the use of organic bases, which had not worked in the flow cells B and C were employed. The use of different bases was another option to increase the product yield, therefore the experiments described under the next heading were designed to investigate the effect of organic bases in the flow cell D, which was found to have given better yield with pyridine.

4.2.3.2 Base study and the effect of flow rate for flow cell D

The use of bases like diethylamine and triethylamine along with pyridine was investigated for the Kolbe electrolysis in flow cell D, however the effect of different flow rates was also explored to some extent. Using the varying flow rate of 5 μL/min - 50 μL/min and keeping the concentration of octanoic acid at 0.05 mol L^{-1} experiments were conducted with varying concentrations of pyridine and triethylamine (initially) in order to identify the effect of different flow rates and concentration of a base for flow cell D. To improve the dimer yield it was also suggested that the electrolysis should be carried out at 600 V instead of 100 V because when faster flow rates would be applied the residence time for the reaction mixture would be shortened and there will be less time for electrolysis.

Table 29 shows that using 0.2 mol L^{-1} pyridine at a slightly higher flow rate of 10μL/min gives more conversion 26% as compared to the slower flow rate of 5μL/min which gives 20% yield, because at a slower flow rate the electrodes became coated by the formation of polymeric films (less in case of pyridine) which did not come off easily at a slower flow rate. It was also observed that the higher voltage 600 V enhanced the radical generation giving more CO_2 bubbles which were slowly moved by a slower flow rate and partially getting trapped between the electrodes hence there was less reproducibility under the above conditions. The results also indicate poor reproducibility with % RSD of 37 and 38 respectively, where n= 3 (samples were collected after every two minutes for faster flow rates of 20 and 50 μL/min), the acid was left unreacted and very low/no significant by products (if any) were formed. The reaction mixture was analysed by GC/MS method B and GC/FID method A.

Flow rate µl/min	Acid/base mol L^{-1}	current/ mA	Voltage/ kV	Average yield/%	n	RSD
50	0.05/0.2 pyridine	2-4	0.6	25	3	6
20	0.05/0.2 pyridine	1-5	0.6	24	3	13
10	0.05/0.2 pyridine	1-3	0.6	26	3	38
5	0.05/0.2 pyridine	0-1	0.6	20	3	37

Table 29 Result of electrolysis of 0.05mol L^{-1} octanoic acid using flow cell D Figure 24, with 0.2 mol L^{-1} at different flow rates

The results (Table 30) suggested that although triethylamine gave higher yield 51% with less RSD = 2 % (where n = 3) however more by products were generated. Furthermore with prolonged use the electrodes got coated and the polymeric films started giving sparks where ever they started touching along the length of the electrodes. Therefore the use of diethylamine and triethylamine was discontinued as diethylamine gave even more sparks between the electrodes at slower flow rates. The use of diethylamine and triethylamine did not suit the flow cell environment specially the flow cell D, at slower flow rates. In this case increasing the flow rate to avoid the sparks decreases the yield. It was observed that although more CO_2 bubbles were formed at higher voltage 600 V however they did not affect the reproducibility under the above conditions. On the contrary although pyridine gave lower yield (26%) at 600 V with a higher RSD (38 %), it was thought that varying flow rates and the concentration of pyridine could work at a range of lower – higher voltage (100-600V) to define the best conditions to optimize the dimer % yield in flow cell D.

Flow rate µl/min	Acid/base mol L^{-1}	current/ mA	Voltage/ kV	Average yield/%	n	RSD
50	0.05/0.1 triethylamine	5-13	0.6	47	3	12
20	0.05/0.1 triethylamine	3-12	0.6	51	3	2
10	0.05/0.1 triethylamine	3-9	0.6	42	3	23
5	0.05/0.1 triethylamine	0-2	0.6	19	4	35

Table 30 Result of electrolysis of 0.05mol L^{-1} octanoic acid using flow cell D Figure 24, with triethylamine and at different flow rates

The use of different bases, supports the fact that electrolyte free electrolysis can be attained with a significant yield using a flow cell, and the presence of these bases increases the conductivity. The comparison of results of electrolysis using triethylamine and pyridine as a base and electrolyte, showed that triethylamine was a better electrolyte base giving higher current therefore higher conversion but with more byproducts. The flow cell could not be put into use for a long period however, as the electrodes became coated, turned black and the cell needed cleaning because polymeric films caused the sparks at the electrodes. Pyridine on the other hand did not give byproducts and could be used at a higher voltage 600 V, the electrodes did not become coated with polymeric films. Accordingly considering the above results, it was decided to concentrate on improving the product yield by using pyridine. The effect of pyridine concentration was investigated and is reported in Table 26 keeping the flow rate at 5µL/min the electrolysis was conducted at 0.6 KV which was not giving reproducible results. Table 31, the optimum concentration 0.25 mol L^{-1} of pyridine at 600 V gave 41 % yield for 0.05mol $L^{-1}$of octanoic acid at 5µL/min. The results showed very poor reproducibility with up to 70 % RSD (n = 8), suggesting that the design needed further improvement as the electrodes were getting coated and losing the surface area to conduct. It was not possible to observe the state of electrodes as they were sealed in the PTFE tube, and every time they were

cleaned the arrangement had to be fixed and adjusted to keep the electrodes straight and not touching along the length.

Concentration of pyridine/mol L^{-1}	Voltage/ kV	Current/ mA	Current density mA/ cm2	Product Yield/%	n	%RSD
0.015	0.6	0-1	2	20	7	46
0.03	0.6	0-1	3	37	6	48
0.06	0.6	0-1	2	20	7	28
0.125	0.6	0-1	3	33	8	40
0.25	0.6	0-1	3	41	8	70
0.5	0.6	0-2	5	20	6	60

Table 31 Results of electrolysis of 0.05 mol L^{-1} octanoic acid with pyridine using flow cell D Figure 24

In summary, comparison of results for flow cell C and D showed an improvement in the reproducibility (33 % yield with 0.2 mol L^{-1} pyridine at 100 V and 5μL/min with 11 % RSD) and dimer yield (41% for 0.2 mol L^{-1} pyridine at 600 V and 5μL/min with 70% RSD) for flow cell D, (Tables 28 and 31 respectively). As can be seen there was an improvement of design for flow cell D, which produced dimer in double the yield (41%) as compared to that of flow cell C (18 %) as shown in Table 26. Increasing the electrode length and diameter gave more surface area compared to cell volume, and enhanced the radical formation. The results also showed that pyridine could be used to improve the yield as well as reproducibility of a PTFE flow cell. By increasing the concentration of pyridine the cell could be used longer before cleaning was required. The PTFE cell design was a preliminary design and needed more care while handling and cleaning. In order to further improve the flow cell design, a glass tube was introduced in place of a PTFE tube, because glass is transparent and chemically and mechanically resistant and could withstand the electrochemical conditions better. The next section comprises the results gathered from glass flow cells.

4.2.4. Results of glass flow cell E 1

Based on the preliminary results gained from the PTFE flow cells, a glass flow cell E 1 having similar dimensions to flow cell D, was designed with electrodes (0.36 mm diameter x 2.5 cm long) sealed parallel in a glass tube (1.5 mm diameter). In order to compare the performance and evaluate flow cell E 1 (Figure 25), the electrolysis of octanoic acid with varying concentrations of bases and flow rates was carried out. In addition to remove the CO_2 bubbles (which interrupts the flow and the formation of the kinetically stable diffusion layer around the electrodes and changes the diffusion as well as concentration profile of the electrode surface) the flow cell was mounted vertically with the solution entering from the bottom and flowing upwards in order to allow the easy escape of gas bubbles. The advantage of using a transparent glass tube was that the condition of electrodes could be observed as the electrolysis progressed. Therefore it was suggested that the effect of cleaning the electrodes should also be studied based on the previous results from flow cells C and D it was necessary to clean and restore the electrode surface because the electrodes got coated and needed cleaning after electrolysis. The next two sections state the effect of different conditions and the results from flow cell E 1. The reaction mixture was analysed by GC/MS method B and GC/FID method A.

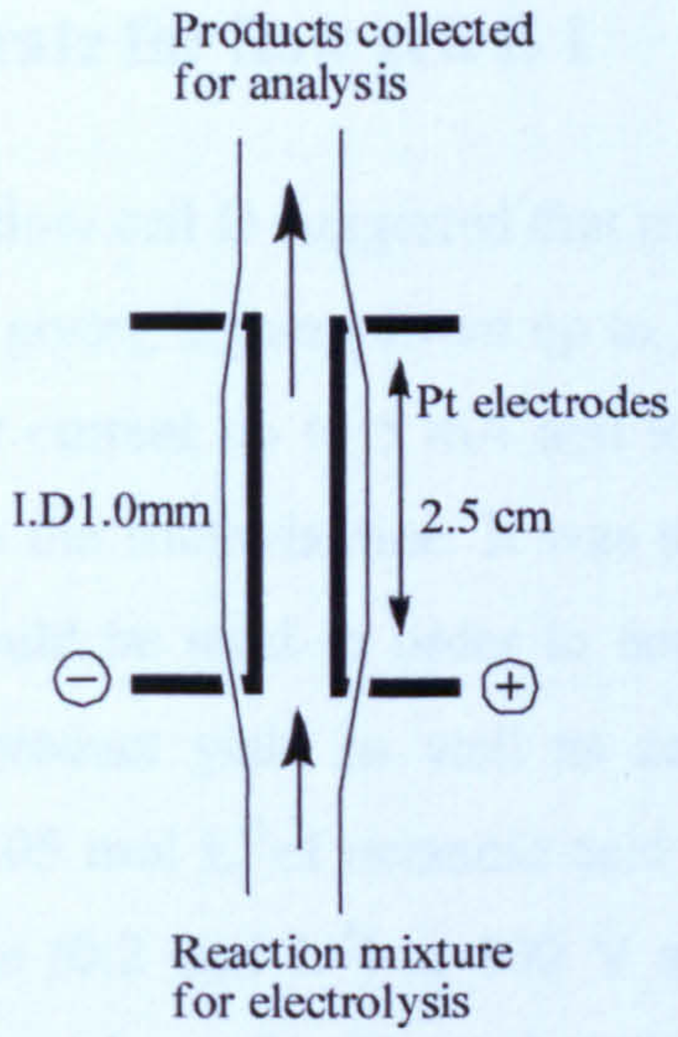


Figure 25 The vertically mounted flow cell E 1

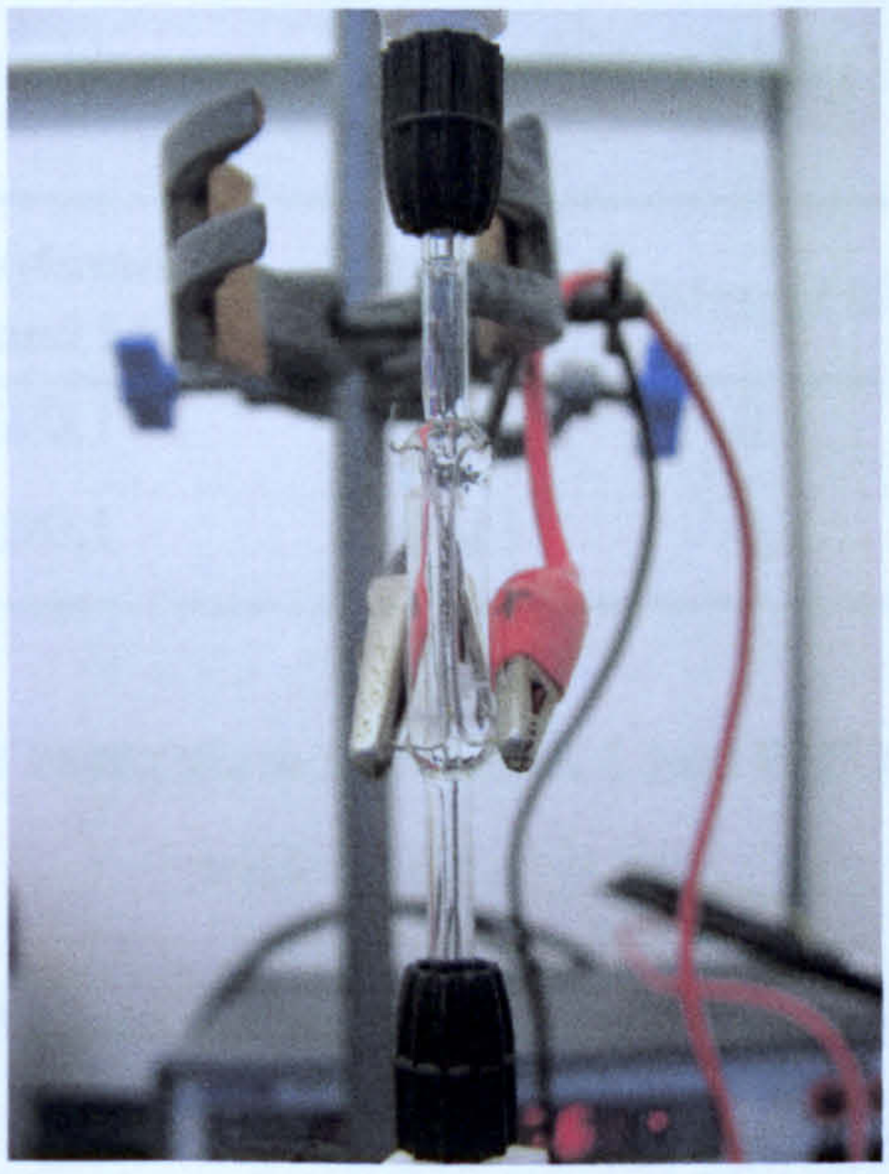


Figure 26 The vertically mounted flow cell E 1

4.2.4.1 The effect of flow rate for flow cell E 1

As the results (Table 30) from flow cell D suggested that triethylamine performed better as a base as well as an electrolyte giving higher current up to 13 mA and higher yield (51 %), whereas pyridine gave a lower current up to 5 mA and lower yield (41 %) but kept the electrodes cleaner compared to the triethylamine. It was suggested that the pair of bases triethylamine and pyridine should be used in order to acquire a higher current at lower voltage (100 V) and higher product yield as well as easy cleaning of the electrodes. Therefore the electrolysis of 0.05 mol $L^{-1}$of octanoic acid was carried out using pyridine (0.1 mol L^{-1}) and triethylamine (0.2 mol L^{-1}) at 100 V and a faster flow rate up to 50 µL/min (in order to avoid the sparks at the electrodes). Table 32, shows the preliminary results from flow cell E 1 using triethylamine and pyridine. A faster flow rate up to 50µL/min clearly increased the current (17 mA) however decreased the residence time hence decreased the yield (5 %) with an RSD (10 %). The flow rate of up to 10 µL/min increased the residence time as well as a higher current (13 mA) resulting in a significant increase in the yield (40 %) with a comparatively higher RSD (15 %).

Flow rate µl/min	Acid/ triethylamine/ pyridin/mol L^{-1}	Current/ mA	Voltage/ kV	Average yield/%	n	RSD
50	0.05/0.2/0.1	01- 17	0.1	5	5	10
10	0.05/0.2/0.1	10 -13	0.1	40	6	15

Table 32 Electrolysis using glass flow cell E 1 and 0.05 mol L^{-1} octanoic acid with a pair of bases

The slower flow rate could cause the fouling of electrodes in the presence of pyridine as was seen in flow cell D. It was suggested that the flow cell should be cleaned in order to achieve consistent results.

4.2.4.2 The effect of cleaning flow cell E 1

It was easy to view the condition of the electrodes in the glass flow cell E 1 hence it was possible to clean the electrodes when they became coated with the polymeric films during

the electrolysis (although the films were partially removed by pyridine), as cleaning of the electrodes was necessary for reproducible results. The cell was sonicated in (50:50) ethanol : water solution for twenty minutes before subsequent experiments. The results (Table 33) at 10μL/min show that after cleaning the electrodes the yield increased from 40 to 43 % and the current increased from 13 to 16 mA with an improved RSD of 7%.

Flow rate μl/min	Acid/ triethylamine/ Pyridin/mol L^{-1}	Current/ mA	Voltage/ kV	Average yield/%	n	RSD
10	0.05/0.2/0.1	10 -13	0.1	40	6	15
After cleaning						
10	0.05/0.2/0.1	4 -16	0.1	43	5	7

Table 33 Electrolysis using glass flow cell E 1 and 0.05 mol L^{-1} octanoic acid with a pair of bases after cleaning

The results also showed that the pair of bases was not giving optimum yield and the electrodes were also getting coated. Therefore it was suggested that the effect of these bases should be investigated independent of each other. The next section comprises of the results from the electrolysis conducted using pyridine and triethylamine in separate experiments.

4.2.4.3 Base study and the effect of flow rate using the flow cell E 1

In order to investigate the individual effect of pyridine and triethylamine as electrolytic bases in the Kolbe electrolysis of octanoic acid, the acid was electrolysed with and without these bases at 10μL/min flow rate giving up to 48 % yield (Table 34). These results suggested a better reproducibility (3 % RSD) for pyridine as a base in flow cell E 1. Results also showed the effect of pyridine concentration (0.05 mol L^{-1}) as a base on improving the dimer yield (48 %) at 100 V with a better reproducibility (RSD 3%).

Flow rate µl/min	Acid/ Base mol L^{-1}	current/ mA	Voltage/ kV	Average yield%	n	RSD
10	0.05/0.0 pyridine	1.0 – 4.0	0.1	3	6	0
10	0.05/0.05 pyridine	1.0 - 3.0	0.1	48	6	3
10	0.05/0.1 pyridine	1.0 - 4.0	0.1	44	6	3

Table 34 Results of electrolysis of 0.05 mol L^{-1} octanoic acid using glass flow cell E 1 with and without pyridine

The results also showed that electrolysis of octanoic acid without pyridine did not give any significant yield and that 0.05mol L^{-1} octanoic acid was best electrolysed by 0.05mol $L^{-1}$of pyridine at 10µL/min flow rate using flow cell E 1. In order to investigate the effect of triethylamine as an electrolytic base, octanoic acid (0.05µL^{-1}) was electrolysed with 0.2 mol $L^{-1}$of triethylamine at 10 µL/min flow rate at 100 Volts, as was established in flow cell D (Table 30). However results using triethylamine (Table 35) did show a similar effect (43 % yield) as pyridine (44 % yield) however with less reproducibility (RSD 14%).

Flow rate µl/min	Acid/ Base mol L^{-1}	current/ mA	Voltage/ kV	Average yield%	n	RSD
10	0.05/0.2 triethylamine	1.0 – 2.0	0.1	43	5	14

Table 35 Results of electrolysis of 0.05 mol L^{-1} octanoic acid using glass flow cell E 1 with 0.2 mol L^{-1} of triethylamine

As triethylamine could not be used for further study because of inconsistent results it was suggested that pyridine should be used as an electrolytic base for the Kolbe electrolysis of octanoic acid. In order to determine the optimum conditions for Kolbe electrolysis in a glass flow cell and improve the product yield further, it was suggested to investigate the effect of the inter electrode distance. A flow cell E 2 with a smaller diameter of the glass tube 1.0 mm diameter with 0.18 mm diameter x 2.5 cm long electrodes sealed along the

length was put into use for the electrolysis of octanoic acid under a set of optimum conditions already established for flow cell E 1.

4.2.5 Results of glass flow cell E 2

The use of pyridine (0.05 mol L^{-1}) at a potential of 100 V and slower flow rates (10 μL/min), had already been established as optimum conditions for 0.05 mol L^{-1} of octanoic acid in the flow cell E 1. The optimum conditions for flow cell E 1 suggested that the cell design could be improved in terms of inter electrode distance. The inter electrode distance and the electrode surface area would both play an important role in a way by establishing equilibrium between the electro active species diffusing towards the electrodes and the diffusion of products away from the electrodes, once this equilibrium was established the radical formation was favoured. In an attempt to improve the design further, the electrolysis was carried out in flow cell E 2 (0.18 mm x 2.5 cm electrodes, Figure 27) with a smaller inter electrode distance (0.56 mm) having a smaller surface (electrode) to volume ratio. The next section details the results gathered from flow cell E 2. The reaction mixture was analysed by GC/MS method B and GC/FID method A.

4.2.5.1 Effect of flow rate using the flow cell E 2

The use of pyridine and slower flow rates had already been established as optimum under certain conditions in the PTFE flow cell D and glass flow cell E 1. The effect of flow rates was studied starting from 100 μL/min to 10 μL/min based on the observation that faster flow rate gave higher current. At a faster flow rate (100μL/min) samples were collected after every two minutes from an electrolysis carried out for twenty minutes and for a slower flow rate (10μL/min) the samples were collected after every five minutes from an electrolysis over thirty minutes. The results (Table 36) showed that the optimum conditions for flow cell E 1 (0.05 mol L^{-1} of octanoic acid, 0.05 mol L^{-1} at 100 V giving 3-4 mA and a slower flow rate 10μL/min) also gave an optimum yield (63 %) for flow cell E 2 Figure 27. The results were more reproducible with an improved RSD (3 %) at a slower flow rate 10 μL/min as compared to higher flow rate 100 μ L/min.

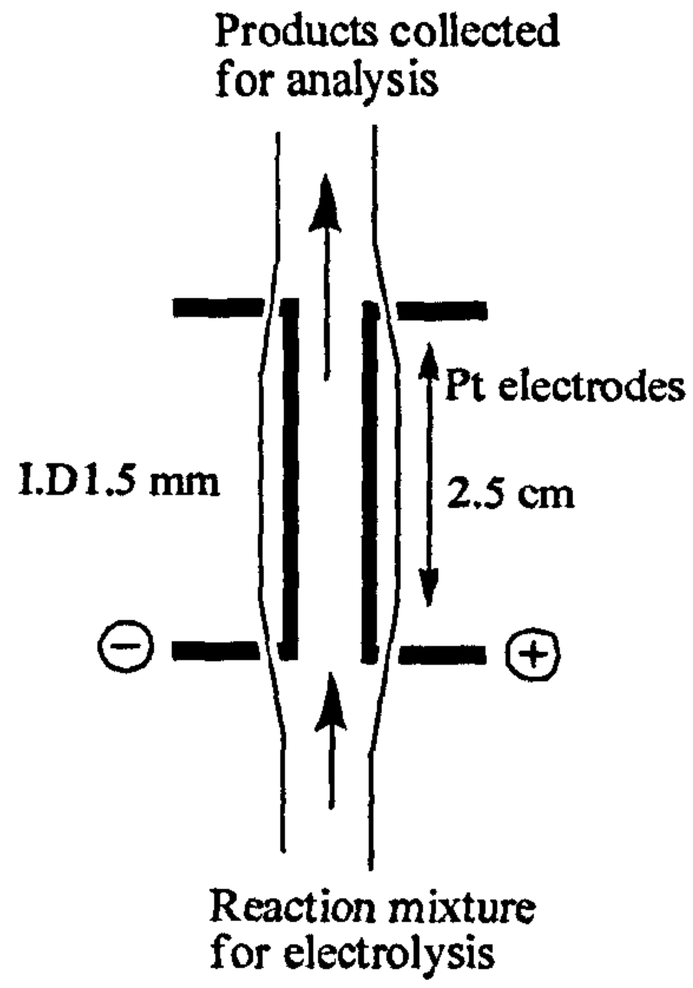


Figure 27 The vertically mounted flow cell E 2

Flow rate µl/min	Acid/ Base mol L^{-1}	current/ mA	Voltage/ kV	Average yield/%	n	RSD
100	0.05/0.05 pyridine	6 – 7	0.1	36	7	3
50	0.05/0.05 pyridine	4 – 5	0.1	34	7	7
20	0.05/0.05 pyridine	3 – 4	0.1	50	7	3
10	0.05/0.05 pyridine	3 – 4	0.1	63	6	3

Table 36 Results of electrolysis of 0.05 mol L^{-1} octanoic acid using glass flow cell E 2 with pyridine showing the effect of flow rate

The results showed clearly that the surface to volume ratio and the inter electrode distance also influences the product yield with an improved RSD (3 – 7 %). Flow cell E 2 with smaller inter electrode gap and a smaller surface to volume ratio showed better conversion than E 1. A set of electrolysis experiments was conducted in order to investigate the reproducibility of flow cell E 2 using the above optimum conditions and the next section describes the results in detail.

4.2.5.2 Reproducibility of the flow cell E 2 after cleaning with ethanol : water (50:50)

Experiments for the electrolysis of 0.05 mol L^{-1} octanoic acid using 0.05 mol L^{-1} pyridine at 10μL/min flow rate giving optimum yield (63 %) were repeated using flow cell E 2. These experiments gave reproducible results (Table 37) over time with cleaning RSD (3 - 8%). Each individual experiment was conducted for 30 minutes to collect samples after every five minutes. The optimum conditions for flow cell E 2 were also found to be 0.05 mol L^{-1} of octanoic acid with 0.05 mol L^{-1} of pyridine at 10μL/min and 100 Volts. The flow rate was reduced further however as the cell was designed with the electrodes with a smaller inter electrode gap the polymeric films which were formed at the surface of the electrodes were sticking out before coming off completely.

In addition the smaller inter electrode gap posed more risk of sparks at the electrodes where these films touched along the length (would not come off completely with the flow and would be hanging out still attached on the other end) causing sparks. The results suggested that although pyridine was effective in cleaning the electrodes however in this case it was not as effective as it was for flow cell E 1 (with a bigger inter electrode gap). Therefore it was proposed that some other method was also required for the cleaning of electrodes. Literature[4] suggested the cleaning of electrodes by sonicating the cell in ethanol : water (50:50) mixture to be employed for the cell after use. The results (Table 37) were gathered from a series of experiments after cleaning and without cleaning the electrodes, which showed that the average product yield dropped by 17 % without cleaning, and the results after cleaning were reproducible (61%, 62%, 63% with an RSD of 4%, 3% and 5% respectively).

Flow rate µl/min	Acid/base mol L^{-1}	Current/ mA	Voltage/ kV	Average yield/%	n	RSD
10	0.05/0.05 pyridine	1 – 7	0.1	63	6	5
10	0.05/0.05 pyridine	3 – 4	0.1	61	7	4
10 without cleaning	0.05/0.05 pyridine	2 – 5	0.1	50	7	5
10	0.05/0.05 pyridine	3 – 4	0.1	62	6	3
10 without cleaning	0.05/0.05 pyridine	2 – 3	0.1	52	5	8

Table 37 Results of electrolysis of 0.05 mol L^{-1} octanoic acid with pyridine using glass flow cell E 2, showing change in results every time after cleaning the electrodes

The results show that a glass flow cell E 2 could be employed for better product yield (63 %) and reproducibility (% RSD = 5) compared to a batch cell and a PTFE flow cell, and that the cell could be put into prolonged use with effective cleaning. The method of cleaning the electrodes was however very important and needed to be established for further use.

4.2.5.3 Effect of pyridine and cleaning the electrodes for flow cell E 2 using 0.5 mol $L^{-1}HNO_3$ and 0.5 mol $L^{-1}H_2SO_4$

In order to retain the surface properties, the cleaning of sealed electrodes of a flow cell was of great concern because if the electrodes were not cleaned after a prolonged use, it altered the surface properties of the electrodes affecting the electrolysis greatly affecting the radical generation and the dimer yield. A series of experiments were conducted to evaluate the use of HNO_3 and H_2SO_4 for electrode cleaning. In the first part of the cleaning process, cleaning of electrodes was carried out by rinsing with 0.5 mol L^{-1} HNO_3, and later sonicating with ethanol/water 50:50. It was observed that after cleaning the electrodes with the above acid solutions the electrodes took longer to equilibrate (stabilizing to give consistent current).

In order to enhance the cleaning action within the cell during the electrolysis and achieve a consistent current, it was suggested that the pyridine concentration should also be increased

so that the electrodes could retain the surface longer before it needed cleaning. As the optimum conditions for flow cell E 2 suggested pyridine gave smooth and consistent current (3 - 4 m A) therefore the cleaning of electrodes within the cell was enhanced by increasing the pyridine concentration to 0.1 mol L^{-1} in the reaction mixture, which would be expected to give a consistent current as well as higher product yield with reproducibility. Table 38 showed the results of experiments repeated for the electrolysis of 0.05mol L^{-1}octanoic acid using 0.1mol L^{-1} of pyridine at 10μL/min, giving the optimum yield (74 %) with a % RSD of 6 % at 100 V and 4 - 5 m A. The electrolysis was conducted after cleaning the cell which changed the results every time (from 60 % yield – 74 % yield) although the % RSD was not affected much. The results without cleaning the electrodes clearly showed that the yield (44 %) and RSD (21 %) both were affected without cleaning even under the optimum conditions. The reaction mixture was analyzed by GC/MS method B and GC/FID method A.

Flow rate μl/min	Acid/Pyridine /mol L^{-1}	Current/ mA	Voltage/ kV	Average Yield/%	n	RSD
10	0.05/0.1 pyridine	4-5	0.1	71	7	5
10	0.05/0.1 pyridine	7-8	0.1	74	6	6
10	0.05/0.1 pyridine	4-7	0.1	60	6	5
10	0.05/0.1 pyridine	4- 6	0.1	66	6	4
Without cleaning						
10	0.05/0.1 pyridine	3-5	0.1	44	6	21

Table 38 Results of electrolysis of 0.05 mol L^{-1} octanoic acid with 0.1 mol L^{-1} pyridine using glass flow cell E 2, showing change in results every time after cleaning the electrodes using 0.05 mol L^{-1} HNO_3

In the second step the cleaning of electrodes with 0.5 mol L^{-1} H_2SO_4 followed by sonicating in 50:50 ethanol/water mixture was employed, and it was observed that cleaning with sulphuric acid took even longer to equilibrate for the cell (giving a fluctuating current between 0.0 m A – 8 m A) than when cleaned with 0.5 mol L^{-1} HNO_3 for the electrodes to give a consistent current (3 – 5 m A). Therefore it was suggested that the pyridine concentration should be increased and the experiments were conducted using 0.2 mol $L^{-1}$of

pyridine in order to achieve a smooth and consistent current. The results (Table 39) showed the effect of 0.2 mol $L^{-1}$of pyridine at 10μL/min on the dimer yield (69 %) with a poor reproducibility % RSD (17) after cleaning the electrodes with sulphuric acid.

Flow rate μl/min	Acid/Pyridine/mol L^{-1}	current/ mA	Voltage/ kV	Average Yield/%	n	RSD
10	0.05/0.2 pyridine	3-4	0.1	67	6	17
10	0.05/0.2 pyridine	2-3	0.1	64	6	6
10	0.05/0.2 pyridine	4-6	0.1	69	6	13

Table 39 Results of electrolysis of 0.05 mol L^{-1} octanoic acid with pyridine using glass flow cell E 2 after cleaning the electrodes with 0.05 mol L^{-1} H_2SO_4

Clearly the cleaning of electrodes with 0.5 mol L^{-1} HNO_3 and sonicating with ethanol/water 50:50 gave better reproducibility with 0.1mol L^{-1} of pyridine. And the electrolysis of 0.05 mol L^{-1} of octanoic acid gave better dimer yield (up to 74 %) and reproducible results (RSD 6 %).

4.2.5.4 Effect of flow rate on the flow cell E 2

In order to determine the optimum flow rate under the above conditions (cleaning with 0.5 % HNO_3 and sonicating with 50:50 ethanol : water) to further improve the dimer yield, the effect of flow rate was investigated. The results (Table 40) show that for the Kolbe electrolysis of 0.05 mol L^{-1} octanoic acid at a slower flow rate 10μL /min gave better conversion (77 % yield), using 0.1 mol L^{-1} of pyridine with reproducible results (% RSD = 6).

Flow rate µl/min	Acid/Pyridine/ mol L^{-1}	current/ mA	Voltage/ kV	Average Yield/%	n	RSD
50	0.05/0.1	6 – 7	0.1	28	6	30
20	0.05/0.1	5 – 6	0.1	36	6	2
10	0.05/0.1	5 – 7	0.1	77	7	6

Table 40 Results of electrolysis of 0.05 mol L^{-1} octanoic acid with pyridine using glass flow cell E 2 showing the effect of flow rate after cleaning the electrodes

The formation of CO_2 bubbles was also affecting the dimer yield by disturbing the flow and diffusion layer at the surface of electrodes the effect was minimized by mounting the cell vertically to allow the easy escape of the gas bubbles as can be seen from the enlarged image of flow cell E 2 in Figure 27. The gas bubbles could easily escape with the upwards flow even at a slower flow rate of 10µL/min allowing a constant flow of the reaction mixture and product towards and away from the electrode surface.



Figure 27 Enlarged view of vertically mounted flow cell E 2

The above conditions (0.05 mol $L^{-1}$of octanoic acid with 0.1 mol $L^{-1}$of pyridine at 10μL/min flow rate and at 100 Volts) gave up to 77 % yield with RSD of 6 %. However in order to improve the conditions further for Kolbe electrolysis of octanoic acid in the flow cell E 2 it was considered that the cleaning of electrodes could be carried out more effectively if the cell was designed by employing removable electrodes. The next section comprises of some of the results from the flow cell E 3 with removable electrodes. The electrolysis was carried out using the above optimum conditions (0.05 mol L^{-1} octanoic acid and 0.1 mol L^{-1} pyridine).

4.2.6 Results of glass flow cell E 3

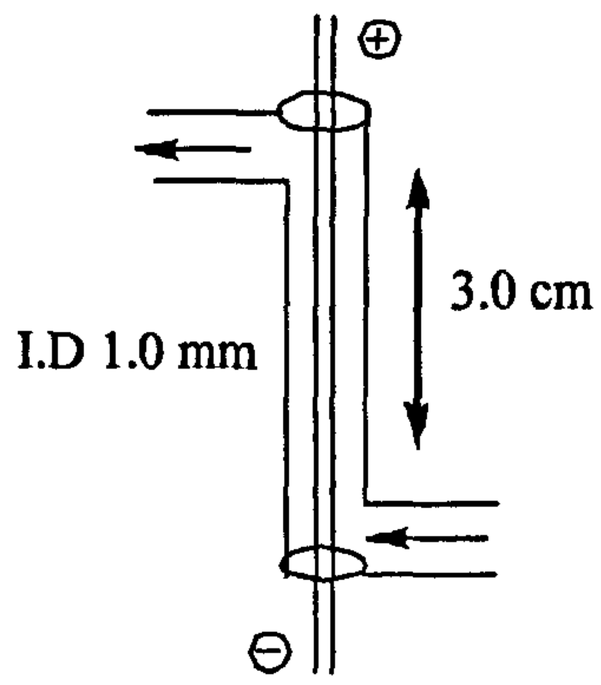


Figure 28 The arrangement of parallel removable electrodes in flow cell E 3

As the cleaning of sealed electrodes in the cell E 2 in the above section was a challenge, a flow cell E 3 (Figure 28) with removable electrodes (0.18 mm diameter x 3.0cm) sealed in a glass tube (1.0 mm diameter) was used for the electrolysis of 0.05 mol L^{-1}octanoic acid with varying concentration of pyridine (0.05-0.2 mol L^{-1}) in order to determine the optimum conditions. The electrodes were removed and cleaned after every use. The reaction mixture was analyzed by GC/MS method B and GC/FID method A.

4.2.6.1 Effect of pyridine concentration and flow rate in flow cell E 3

The effect of pyridine concentration was investigated using flow cell E 3. The cell could not be used at slower flow rates than 10 µL/min, as the CO_2 bubbles were formed at the inlet end causing back pressure hence made it difficult for the flow rate to be established. The cell worked better at higher flow rates 100 µL/min and gave reproducible results (Table 41) however a dimer yield only 48 % could be achieved due to lower residence time. The use of two and four equivalents of pyridine (0.1 and 0.2 mol L^{-1}) gave significant conversion (48 %) and (47 %) respectively, however two equivalents of pyridine gave better reproducibility (RSD 0.0%).

Flow rate µl/min	Acid/Pyridine/mol L^{-1}	current/ mA	Voltage/ kV	Average Yield/%	n	RSD
100	0.05/0.05 pyridine	8 -12	0.1	44	6	12
100	0.05/0.1pyridine	8 -14	0.1	48	6	0
100	0.05/0.2 pyridine	7-14	0.1	47	4	5

Table 41 Results of electrolysis of 0.05 mol L^{-1} octanoic acid with pyridine using glass flow cell E 3 with removable electrodes, after cleaning the electrodes

The results of electrolysis of octanoic acid with two equivalents of pyridine which gave better reproducibility were repeated using flow cell E 3. Results in (Table 42) show reproducibility (RSD 0 - 4 %) with comparatively low dimer yield (up to 29 %). The cell design was not used further because fixing the electrodes after cleaning changed the inter electrode distance changing the diffusion layer profile every time the electrodes were assembled after cleaning.

Flow rate µl/min	Acid/Pyridine/ mol L^{-1}	current/ mA	Voltage/ kV	Average Yield/%	n	RSD
100	0.05/0.1pyridine	6 – 11	0.1	29	8	3
100	0.05/0.1pyridine	9 – 14	0.1	40	6	0
100	0.05/0.1pyridine	7 – 9	0.1	38	6	4
100	0.05/0.1pyridine	8 – 14	0.1	33	6	3

Table 42 Results of electrolysis of 0.05 mol L^{-1} octanoic acid with pyridine using glass flow cell E 3 with removable electrodes, after cleaning the electrodes

4.2.7 Summary of results from flow cells E1 – E3

The design of the glass flow cell was selected on the basis of preliminary results gathered from the experiments using PTFE flow cells B, C and D which helped in selecting the better arrangement E 1 and E 2 as well as glass flow cells with parallel electrodes along the channel (platinum wire 2.5 cm long, 0.36 and 0.18 mm diameter respectively) in a glass tube with internal diameter 1.5 mm (flow cell E 1) and 1.0 mm (flow cell E 2).

As detailed in the results in the above sections for flow cells E 1, E 2 and E 3, it was observed that higher currents up to 7 mA gave better dimer yields, however higher currents (14 mA) originating because of faster flow rates (100 μL^{-1}/min) gave poor dimer yields (29 %). It was also observed that the dimer yield could be increased by introducing two to four equivalents of pyridine into methanol solutions. During the electrochemical oxidation of octanoic acid in a flow cell under the above conditions the dimerization predominantly occured with even higher yields than expected initially from a flow cell. However the results from flow cells E 1- E 3 suggested that glass flow cell E 2 was better design giving better yields (74 %) as compared to E 1 (64 %) and E 3 (48 % with removable electrodes), therefore the further work was carried out using glass flow cell E 2.

4.2.8 Further Results from prolonged use of flow cell E 2

On the basis of the results reported in the previous section it was suggested that cell design E 2 should be put into prolonged use (up to 5 hours) in order to investigate and establish the conditions for optimum dimer yield for Kolbe electrolysis of octanoic acid. As described earlier the acid solution (with or without pyridine) was continuously supplied into the upright flow cell chamber, with the aid of a syringe pump at a varying flow rate. The cell was working under constant potential mode at 100 V. In order to investigate if the current values decline over time with deteriorating electrode surface, mean values of current were taken and reported for each conversion. The samples were taken after every six and four minutes for slower flow rates (4 and 11μL/min respectively), and every one to two minutes for faster flow rates (21 and 43μL/min respectively). The reaction mixture was analyzed by GC/MS method B and GC/FID method A.

4.2.8.1 Effect of flow rate from prolonged use of flow cell E 2

The effect of flow rate over the prolonged use was investigated for the optimum conditions (0.05 mol L^{-1}octanoic acid and 0.1mol L^{-1} pyridine) in flow cell E 2. The results (Table 43), suggested that prolonged use of flow cell E 2 at a flow rate 4μL/min gave significant dimer yield (53 %) with a good reproducibility (RSD 6 %) showing a consistent diffusion of carboxylate ions towards the electrodes. In this case it was observed that at faster flow rates (43 μL/min with the reproducibility of 8 %) and slower flow rates (4 μL/min with the reproducibility of 6%) the product yield was affected because of a less consistent diffusion layer. At a faster rate the factors affecting the dimer yield was, the reactants getting less residence time and for slower flow rate it was assisted with the gas bubbles accumulating around the electrodes interrupting the reactants. However it was also observed that at slower flow rate (4μL/min) the cell could not be used for a longer time and the electrodes became coated with the polymeric films and current dropped considerably, which would have lead to the lowering of the dimer yield

from 77% (where n = 6) to 53% where n = 16, for prolonged use. Therefore the cell could not be used for long at a slower flow rate of 4μL/min.

Flow rate/μL/min	Acid/Pyridine/mol L^{-1}	Current / mA	Average Yield/%	n	%RSD
43	0.05/0.1	3	42	36	8
21	0.05/0.1	4	38	35	13
11	0.05/0.1	4	43	33	7
4	0.05/0.1	3	53	16	6

Table 43 0.05 mol L^{-1} octanoic acid with 0.1 mol L^{-1} pyridine at 0.1KV
Effect of flow rate Flow cell E 2

In order to further improve the dimer yield for the prolonged use of flow cell E 2 at slower flow rate of 4 μL/min an investigation into the effect of four equivalents of pyridine (0.2 molL^{-1}) was carried out to establish if the electrodes could be kept clean and more effectively electrolyze the octanoic acid.

4.2.8.2 Effect of pyridine concentration on prolonged use of flow cell E 2

The effect of pyridine concentration for cleaning the electrodes was investigated and a higher concentration of pyridine (0.2 mol L^{-1}) was employed to improve the dimer yield and reproducibility by effectively cleaning the electrodes. Table 44 showed that increasing the concentration of pyridine for the optimum conditions of 4μL/min at 100 Volts gave 30 % yield in flow cell E 2.

Flow rate/μL/min	Acid/Pyridine/mol L^{-1}	Current / mA	Average Yield/%	n	%RSD
4	0.05/0.2	4	30	37	62

Table 44 0.05 mol L^{-1} octanoic acid with 0.2 mol L^{-1} pyridine at 0.1KV
Effect of four equivalents of pyridine in flow cell E 2

The results from prolonged use of flow cell E 2 (Table 44) suggested no significant effect on improving the dimer yield in this arrangement of electrodes even with higher concentration of pyridine. Furthermore the cell did not give reproducible results for 4μL/min flow rate over prolonged use. The reproducibility of the reaction after prolonged use was affected because of the fact that the electrodes became coated at the slower flow rate. The average percentage (%) dimer yield declined before the polymer films come off from the surface and electrodes become active again.

The next section comprises of the results from flow cell E 4 with thicker electrodes (0.26mm diameter) and an average inter electrode distance 0.38 mm (instead of 0.56 mm as was in flow cell E 2). In order to acquire an optimum product yield the electrode surface area was also an important factor. The cell takes some time to equilibrate and the dimer yield drops after a prolonged use. The time an electrode takes to reach a steady state after its "switched on" depends on its size – longer for a larger electrode. Assuming that the electrode surface area being critical in determining the dimer yield, the surface area of electrodes was increased by designing flow cell E 4 with thicker electrodes.

4.3.0 Results from prolonged use of flow cell E 4

In order to investigate the effect of electrode surface area on the dimer yield the electrolysis of octanoic acid was carried out in flow cell E 4. Flow cell E 4 was of a similar design to flow cell E 2 with thicker electrodes (0.26 mm diameter, 2.5 cm long) and a smaller inter electrode gap (0.38 mm) fitted parallel within 1.0 mm diameter glass tube. The following section comprises of results from the prolonged use of flow cell E 4. At the slower flow rate of 4μL/min makes a slower removal of the bubbles because of a smaller inter electrode gap in flow cell E 4 (smaller inter electrode gap gave poor yield) therefore the faster flow rate of 11μL/min was employed for the next set of experiments. The cell was mounted vertically for the gas bubbles to escape easily and samples were collected after every three minutes for experiments carried out for up to two hours (for a faster flow rate of up to 21 - 86 μL/min), and after five minutes for an experiment carried out for up to five hours, (for a slower flow rate of 4 - 11 μL/min). The reaction mixture was analyzed by GC/MS method B and GC/FID method A.

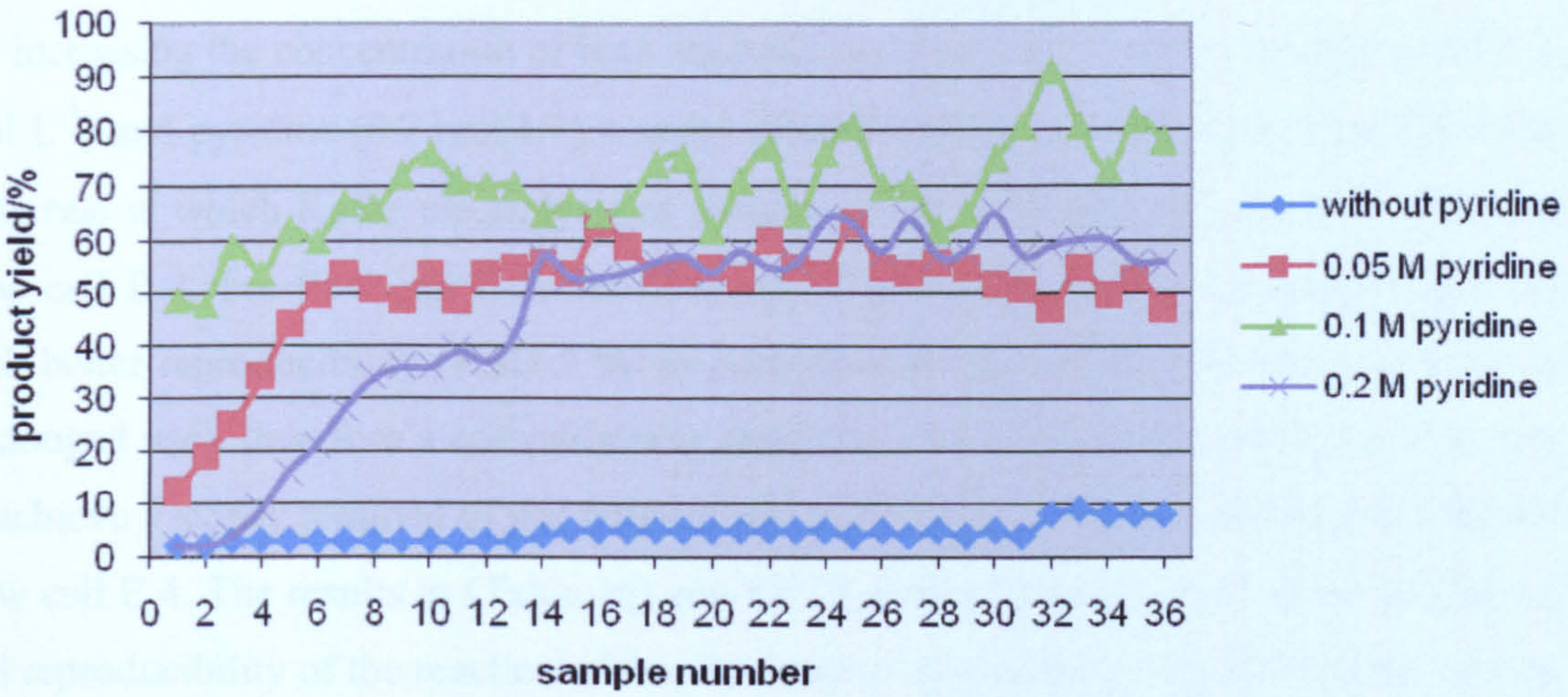
4.3.1 Effect of pyridine concentration and flow rate in flow cell E 4

The results (Table 45) suggested that the optimum conditions (0.05mol L^{-1}octanoic acid 0.1 mol L^{-1} pyridine at 100 Volts) at 11µL/min, flow cell E 4 gave a yield of 65 %. The RSD (14 %) suggested the interruption of flow rate and gas evolution as a result of CO_2 bubbles which were not moving fast because of smaller inter electrode gap and possibly as a result of a fast reaction at the electrode surface disturbing the diffusion layer and the mass transport. The Plot 1 showed a steady equilibrium setup after few minutes of the start of the flow, which establishes the diffusion profile at that flow rate (11µL/min as optimum from the above results).

The effect of pyridine (2 equivalents) was very obvious not only in affecting the product yield (65 %) but also the reproducibility of the results (RSD 14 %) and the system in terms of conductivity (4 mA). The results (Table 40) indicated that for a very high and low concentration of pyridine the cell took longer to equilibrate (giving very high 8 mA and very low 0.0 mA current values), Plot 1 clearly suggested that 0.1 mol L^{-1} pyridine had a pronounced effect on the Kolbe electrolysis of octanoic acid giving 65 % yield in a flow cell with thicker electrodes and with a smaller gap, however the reproducibility in terms of RSD (14 %) needed to be addressed. Hence this factor was investigated further by a series of reactions considering the acid concentration also important factor in establishing a steady diffusion layer at the surface of the electrodes.

Flow rate/µL/min	Acid/Pyridine/ mol L^{-1}	Current / mA	Average Yield/%	n	%RSD
11	0.05/0.0	1	5	36	39
11	0.05/0.05	3	50	36	22
11	0.05/0.1	4	65	35	14
11	0.05/0.2	6	45	36	42

Table 45 Flow cell E 4, Effect of pyridine concentration on the conversion of 0.05 mol L^{-1} octanoic acid at 0.1KV



Plot 1 Flow cell E 4, Effect of pyridine concentration on tetradecane yield and stabilization with 0.05 mol L^{-1} octanoic acid at 0.1KV

Considering the RSD (14 %) for the optimum yield (65 %) it was thought that the bubbles which were formed at the surface of the electrodes disturbed the diffusion layer to a greater extent because of a smaller inter electrode distance. For the larger surface area of thicker electrodes with a smaller inter electrode gap, it was assumed that the reaction at the electrode surface was enhanced (dimer formation) and it took a while before the CO_2 bubbles and alkane molecules were removed. Hence the diffusion layer established again lacking a steady flux of carboxylate ions because of fast declining concentration of carboxylate ions at and around the surface of electrodes. In order to establish a continuous supply of carboxylate ions a higher concentration of acid (0.1 mol L^{-1}) and pyridine (0.2 mol L^{-1}) was employed and the effect of flow rate was investigated, however the rate of the two reagents was kept constant.

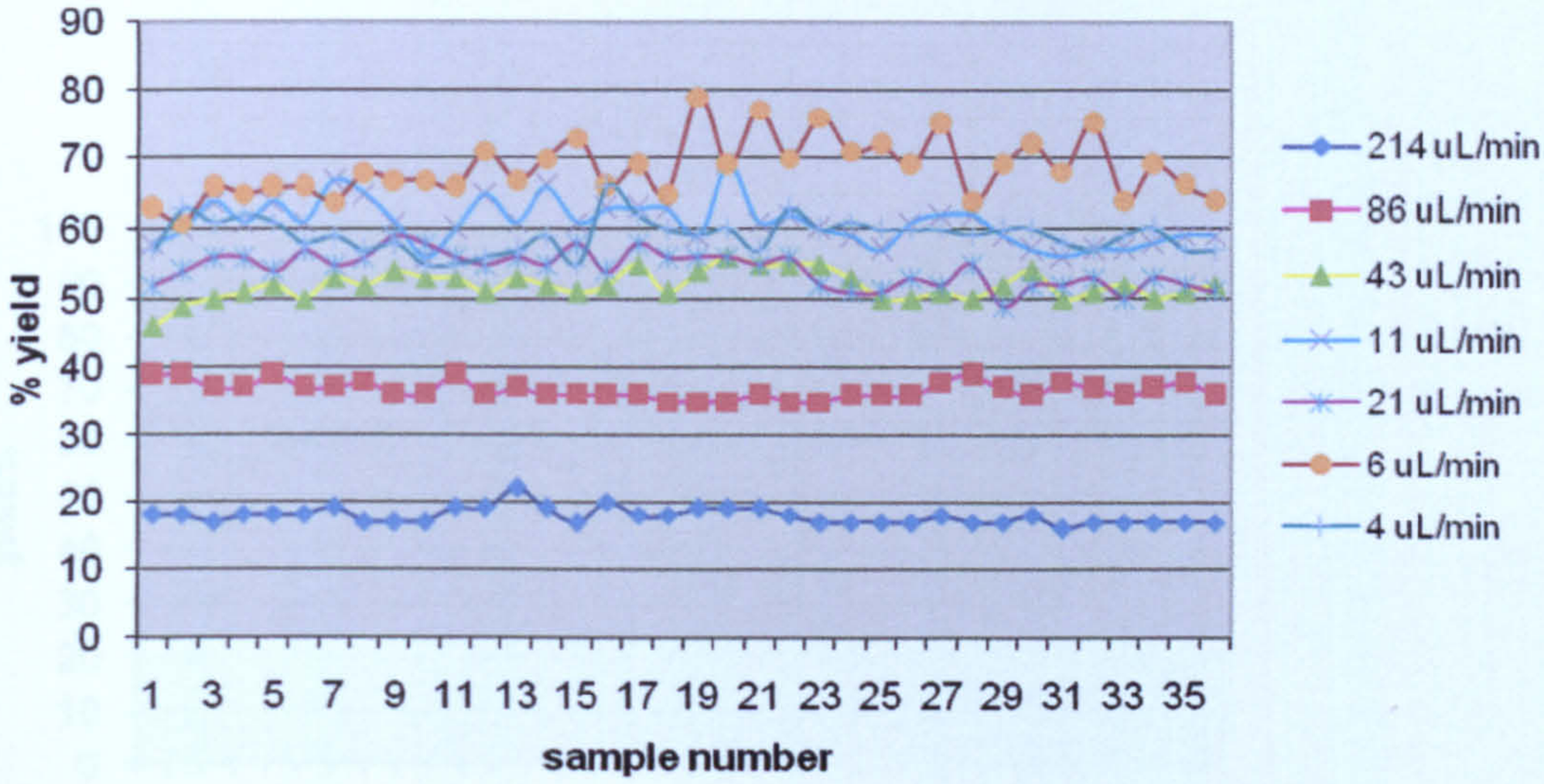
4.3.2 Effect of acid/base concentration and flow rate in flow cell E 4

By increasing the concentration of both acid and pyridine by two folds, octanoic acid (0.1 mol L^{-1}) and pyridine (0.2 mol L^{-1}) a series of experiments were performed to define the flow rate at which Kolbe electrolysis of octanoic acid could give reproducible results in flow cell E 4. For flow cell E 2, the flow rate 11μL/min gave good conversion (61 %) with better reproducibility (RSD 5 %) as compared to 4μL/min (could not be put into a prolonged use), therefore a comparatively faster flow rate was employed in the first step to achieve a steady removal of gas bubbles and continuous supply of carboxylate ions for flow cell E 4. The results in (Table 46) and Plot 2 showed this effect on dimer formation and reproducibility of the reaction with a flow rate of 6 μL/min giving 69 % yield with an acceptable RSD (6 %). The results also suggested that although faster flow rates gave higher current however the dimers were not formed, supporting the fact that dimers were only formed when a diffusion layer was established in such a way that there was an active and effective mass transport at the surface of electrodes.

Flow rate/μL/min	Acid/Pyridine/mol L^{-1}	Current / mA	Average Yield/%	n	%RSD
214	0.1/0.2	10	18	36	6
86	0.1/0.2	9	37	36	3
43	0.1/0.2	7	52	36	4
21	0.1/0.2	5	54	36	5
11	0.1/0.2	4	61	36	5
6	0.1/0.2	5	69	36	6
4	0.1/0.2	2	59	36	4

Table 46 Flow cell E 4, effect of flow rate on conversion

0.1mol L^{-1} octanoic acid at 0.1KV

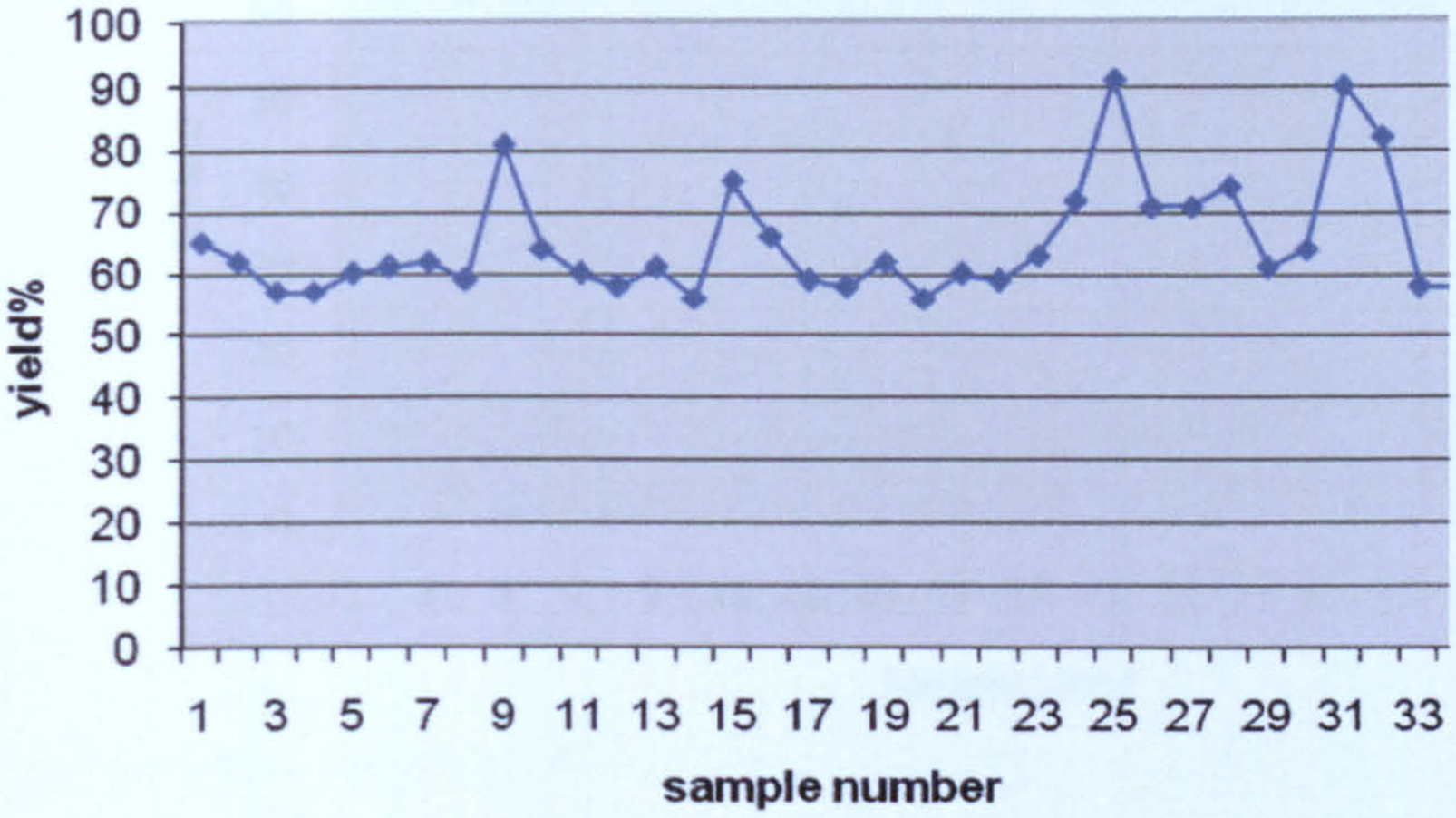


Plot 2 Flow cell E 4, 0.1mol L^{-1} octanoic acid and 0.2 mol L^{-1} pyridine, effect of flow rate on conversion at 0.1KV

The effect of flow rate determined the dimer yield in the above conditions and Plot 2 clearly showed that although at the slower flow rate of 4μL/min gave a higher residence time occurred, still less product yield (59 %) was produced whereas a faster flow rate of 6μL/min with comparatively less residence time gave better product yield (69 %). It was also clear that the effect of concentration of acid / pyridine in the reaction mixture improved reproducibility (RSD 5 % as compared to 14 %).

The comparison of individual results from Table 47 plot 3, Table 48 plot 4 and Table 49 plot 5 explain the difference. Table 47 plot 3, a previous optimum result from flow cell E 4 for 0.05 mol L^{-1}acid and 0.1 mol L^{-1} pyridine that gave 65 % yield with 14 % RSD at 11 μL/min flow rate, and Table 48 and plot 4 showing a steady equilibrium set up by increasing the acid/base concentration to 0.1 mol L^{-1} acid/0.2 mol L^{-1} pyridine that gave 61 % yield with an improved reproducibility (5 % RSD at 11 μL/min flow rate). The

effect of acid/pyridine concentration was very obvious as it improved the reproducibility of the results (improved to 5 % RSD).



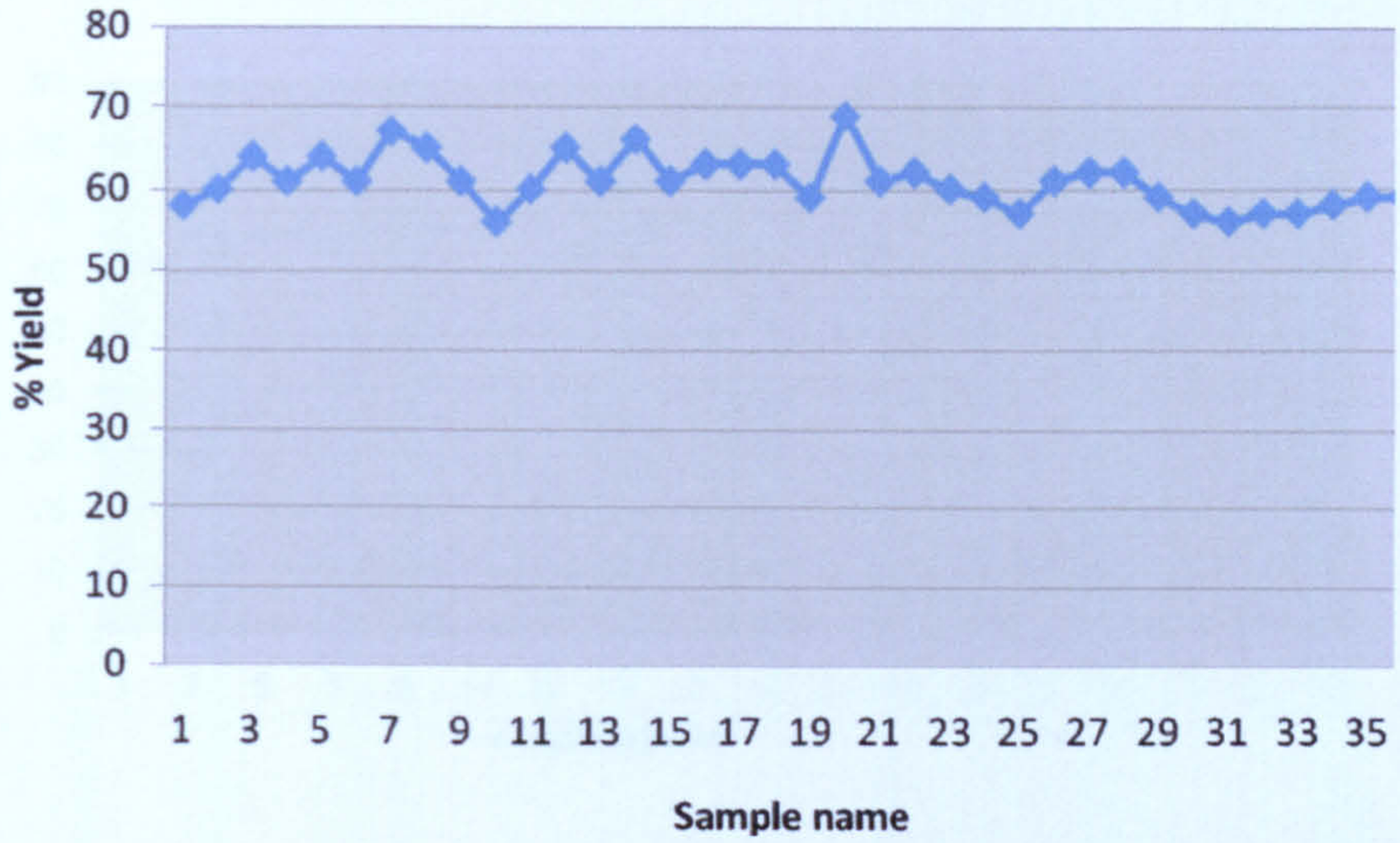
Plot 3 Flow cell E 4 presents the stability of the results 0.1 mol L^{-1} octanoic acid at 0.1KV

Flow rate µL/min	Acid/Pyridine/ mol L^{-1}	Current/ mA	Average Yield/%	n	%RSD
11	0.05/0.1	4	65	34	14

Table 47 Flow cell E 4, effect of acid concentration on conversion 0.1 mol L^{-1} octanoic acid at 0.1KV

To establish the effect of flow rate on the formation of a steady diffusion layer the comparison of (Tables 47, 48 and 49) explains the effect of flow rate, without greatly affecting the RSD (6 %) for the Kolbe electrolysis of octanoic acid. It was assumed that the diffusion layer was established in such a way that formation of alkane product and carbon dioxide within the diffusion layer would not have greatly affected the radical

formation resulting a steady flux of carboxylate ions and Plot 4 describes the effect of concentration, clearly.



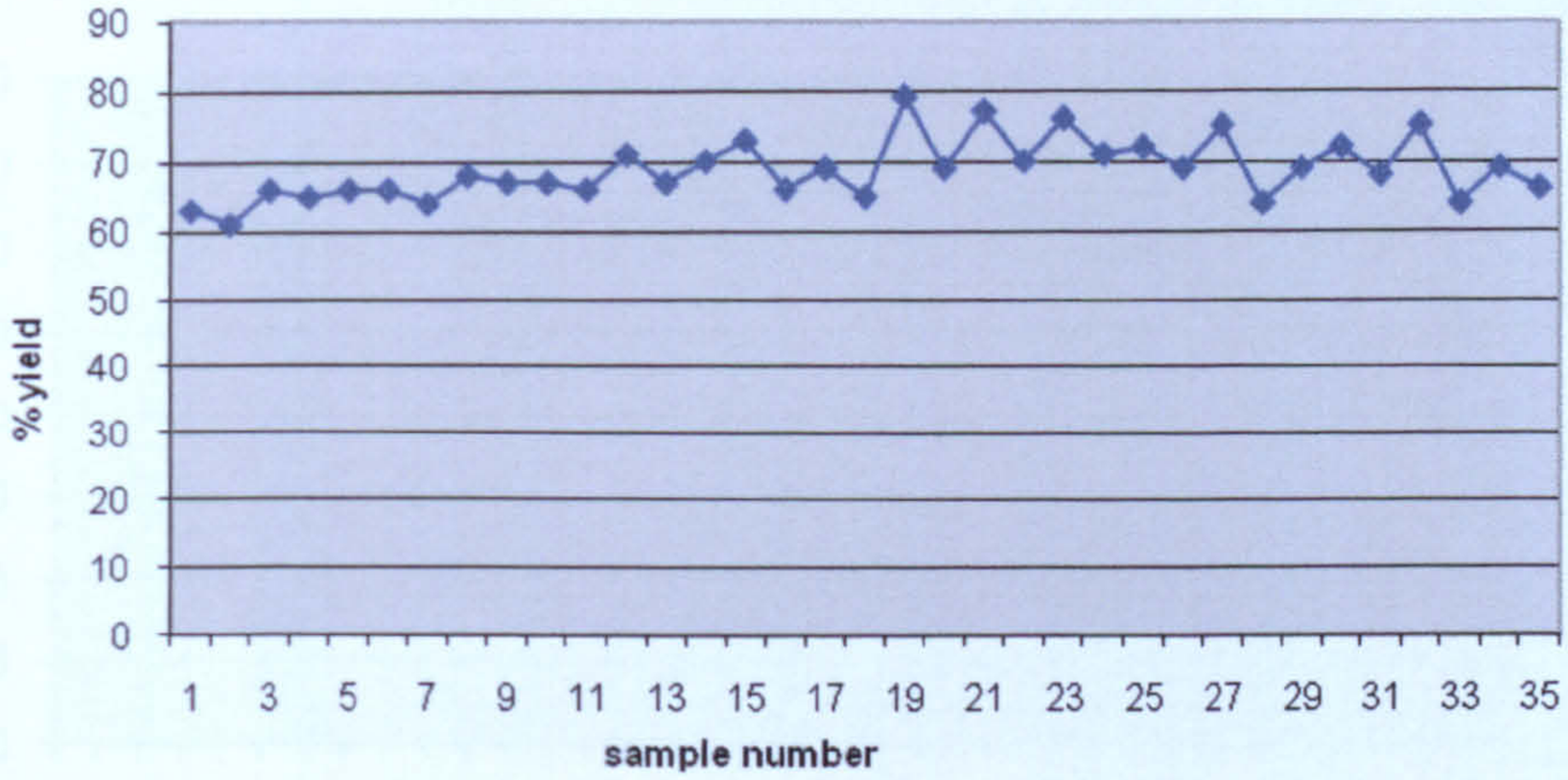
Plot 4 presents the stability of the results, Flow cell E 4, 0.1 mol L^{-1} octanoic acid at 0.1KV

Flow rate/μL/min	Acid/Pyridine/ mol L^{-1}	Current/ mA	Average Yield/%	n	%RSD
11	0.1/0.2	4	61	36	5

Table 48 Flow cell design E 4, effect of acid base concentration 0.1 mol L^{-1} octanoic acid at 0.1KV

It was suggested that assuming an increase in acid/base concentration aided the diffusion layer formation and steady mass transfer, the flow rate would have also contributed to it. This phenomenon was more pronounced at the lower flow rate and the electrolysis at a flow rate of 6 μL/min for 0.1mol L^{-1} acid/0.2mol L^{-1}pyridine gave 68 % yield with good reproducibility (RSD 6 %). These results Table 49 plot 5, established that higher concentration affects the diffusion profile at 6 μL/min flow rate, to behave as a static

system giving a steady reproducibility (RSD 6 %) as well as an improved average dimer yield (69 %).



Plot 5 presents the stability of the results, flow cell E 4 0.1 mol L^{-1} octanoic acid 0.2 mol L^{-1} pyridine at 0.1KV

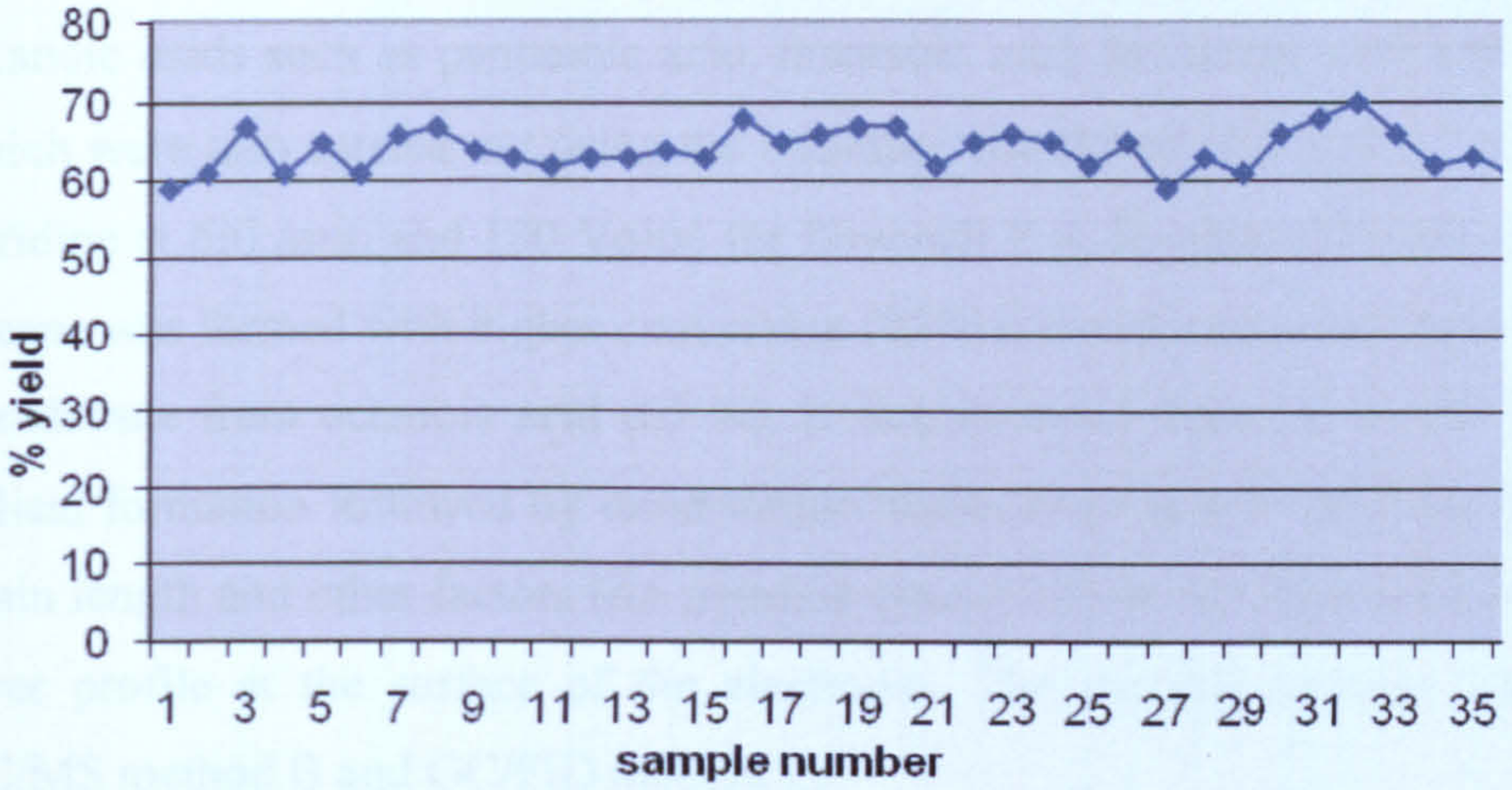
Flow rate/μL/min	Acid/Pyridine/ mol L^{-1}	Current / mA	Average Yield /%	n	%RSD
6	0.1/0.2	5	69	36	6

Table 49 Flow cell E 4, Effect of acid base concentration 0.1mol L^{-1} octanoic acid at 0.1KV

4.3.3 Effect of acid/base concentration and flow rate at higher voltage in flow cell E 4

In an attempt to improve the dimer yield an investigation into the effect of higher voltage giving higher current/current density on the electrolysis of octanoic acid was carried out. The experiments were conducted at a higher voltage (150 V) using the optimum conditions 0.1mol L^{-1} of acid 0.2 mol L^{-1} of pyridine at 6 μL/min flow rate and it was observed that there was no increase in the average current as a result of this high voltage.

Hence the results Table 50 and Plot 6 showed no significant improvement in the dimer yield (64 %) or the RSD (5 %) at higher potential.



Plot 6 presents the stability of the results, flow cell E 4 0.1mol L^{-1} octanoic acid 0.2 mol L^{-1} pyridine at 0.15KV

Flow rate µL/min	Acid/Pyridine /mol L^{-1}	Current / mA	Voltage /V	Average Yield /%	n	RSD %
6	0.1/0.2	4	150	64	36	5

Table 50 Flow cell E 4, effect of higher voltage, 0.1 mol L^{-1} octanoic acid 0.2 mol L^{-1} pyridine at 0.15 KV

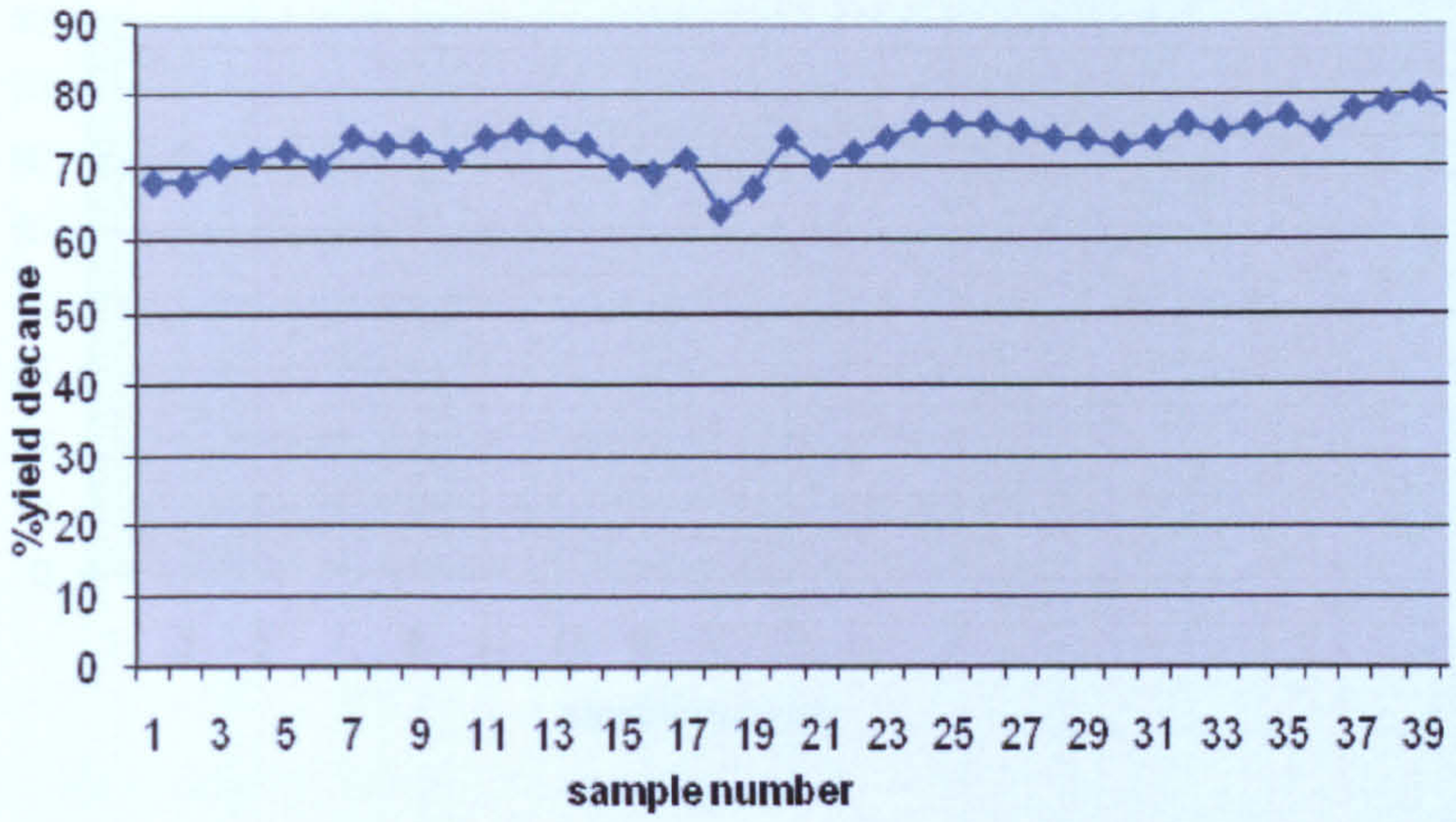
The optimum conditions (giving 69 % dimer yield with RSD of 6 %) for Kolbe electrolysis of octanoic acid were determined to be 0.1 mol L^{-1} of acid with 0.2 mol L^{-1} of pyridine, when electrolysed at 100 Volts at a flow rate of 6 µL/min. In order to investigate the effect of acid chain length, the next set of experiments were conducted to further improve the dimer yield for the Kolbe electrolysis of some other common straight chain alkanoic acids. The next section comprises of comparative results from these acids in detail.

4.4.0 Effect of acid chain length in flow cell E 4

As part of an investigation regarding the effect of structure of the acid, the effect of chain length on the ease of radical formation was investigated by the electrolysis of other alkanoic acids such as pentanoic acid, hexanoic acid, heptanoic acid and nonanoic acid, which were also carried out using the optimum conditions (0.1 mol L^{-1} acid, 0.2 mol L^{-1} pyridine at 6μL/min and 100 Volts) for flow cell E 4. Results of (Table 51) showed that decane was formed with higher conversion (73 %) from the hexanoic acid as compared to tetradecane from octanoic acid (65 %). It was assumed from the results that the ease of radical formation followed by dimerisation varies from acid to acid depending upon the chain length and other factors like pyridine concentration for deprotonation and diffusion layer profile at the surface of the electrodes. The reaction mixture was analyzed by GC/MS method B and GC/FID method C.

4.4.1 Effect of hexanoic acid chain length in flow cell E 4

In order to determine the optimum conditions for hexanoic acid a series of experiments were conducted to draw some relation between the chain length and dimer yield, (Table 51). As expected the results showed that the conditions favourable for dimerisation of octanoic acid would not necessarily suit the dimerisation of hexanoic acid. However, the results (Table 51) showed that 0.05 mol $L^{-1}$of hexanoic acid and 0.1 mol L^{-1} pyridine at 6 μL/min gave the optimum yield (73 %) with a better reproducibility unlike octanoic acid (which although gave a better yield of 65 % but with less reproducibility of RSD 14%) .

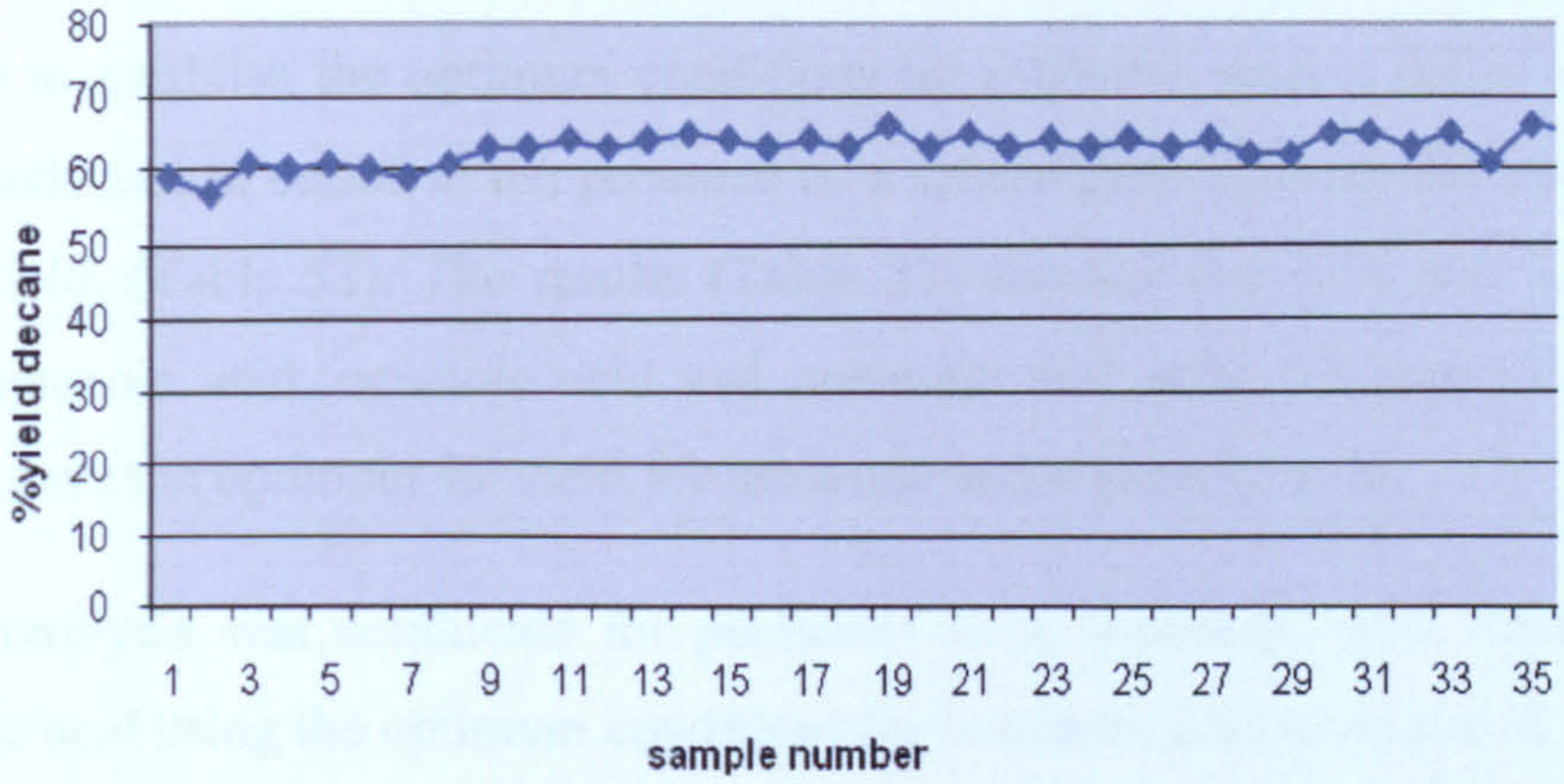


Plot 7 presents the stability of the results, 0.05 mol L^{-1} hexanoic acid at 0.1KV

Flow rateμL/min	Acid/Pyridine/mol L^{-1}	Current / mA	Average Yield/%	n	%RSD
6	0.05/0.1	5	73	40	5

Table 51 Flow cell E 4 0.05 mol L^{-1} hexanoic acid 0.1mol L^{-1} pyridine at 0.1KV

The electrolysis was repeated with 0.1 mol L^{-1} of hexanoic acid and 0.2 mol $L^{-1}$of pyridine under the above conditions of 6 μL/min at 100 Volts. It was observed (Table 52 plot 8) that increasing the acid/base concentration slightly decreased the average dimer yield to 63 % although the reproducibility was improved (RSD 3 %).



Plot 8 presents the stability of the results, 0.2 mol L^{-1} hexanoic acid at 0.1KV

Flow rate µL /min	Acid/Pyridine /mol L^{-1}	Current / mA	Average Yield /%	n	RSD %
6	0.1/0.2	5	63	40	3

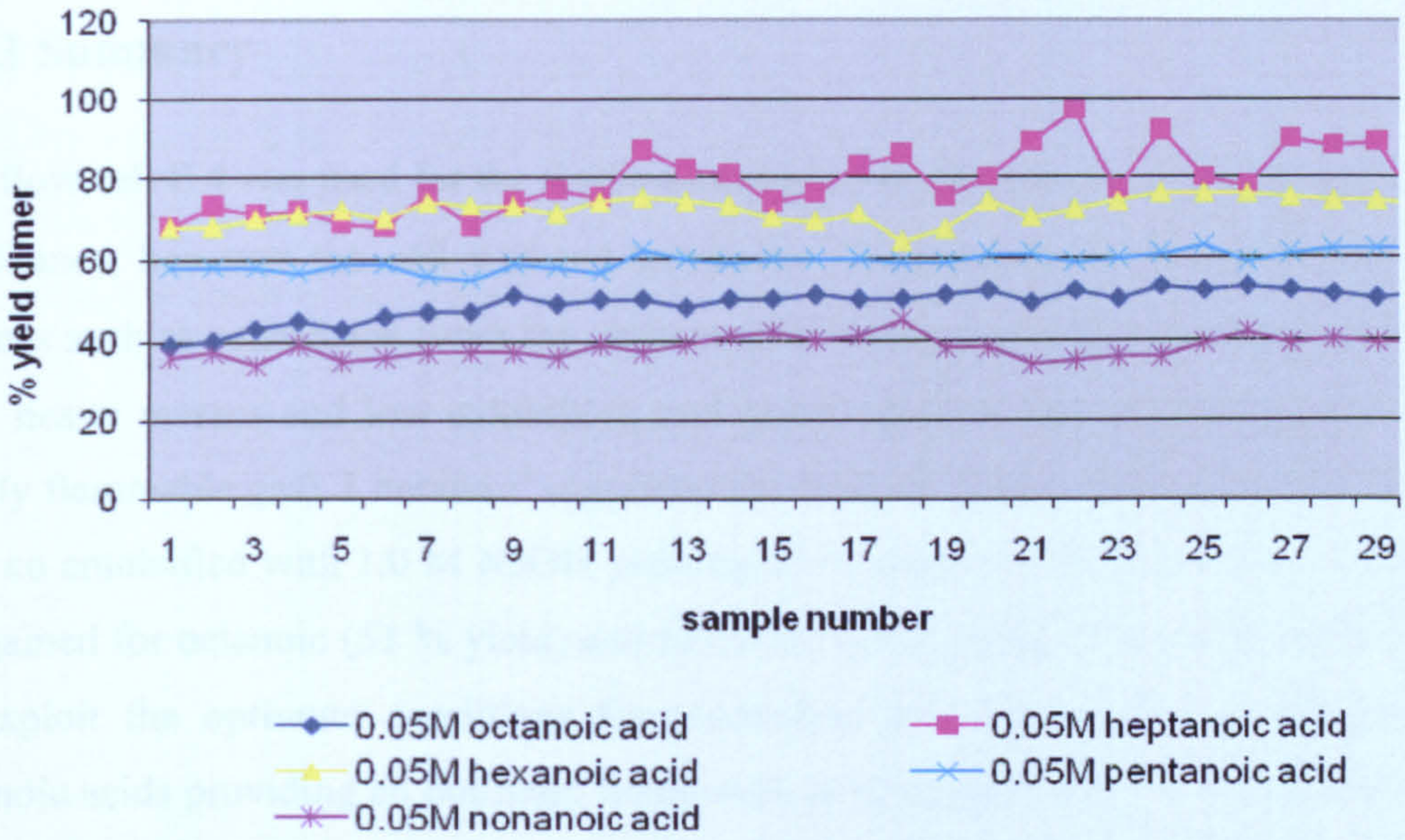
Table 52 Flow cell E 4 0.1 mol L^{-1} hexanoic acid 0.2 mol L^{-1} pyridine at 0.1KV

It was assumed that the conditions favourable for octanoic acid and hexanoic acid would not be favourable for other straight chain alkanoic acids like pentanoic, heptanoic and nonanoic acid. Therefore the electrolysis of these acids was conducted under the conditions giving optimum average product % yield for hexanoic acid that was 0.05 mol L^{-1} of the acid with 0.1 mol $L^{-1}$of pyridine 6 µL/min at 100Volts.

4.4.2 The effect of acid chain length for pentanoic, heptanoic and nonanoic acid in flow cell E 4

In order to establish the optimum conditions for different acids a series of experiments were conducted to establish the presence of a relationship between the chain length and dimer yield, (Table 53). The results (Table 53) showed that 0.05 mol $L^{-1}$of pentanoic acid, heptanoic acid, octanoic acid and nonanoic acid with 0.1 mol L^{-1} pyridine at 6 μL/min gave the optimum % yield for hexanoic and heptanoic acid .

The electrolysis was conducted for pentanoic acid, heptanoic acid, octanoic acid and nonanoic acid using the optimum conditions for hexanoic acid as above. A comparison of results including results from hexanoic acid (Table 53, Plot 9) clearly explained that different acids depending upon the chain length would exhibit different optimum conditions. Hence the electrolysis of acids with different chain lengths such as pentanoic acid gave 59 % yield with 3 % RSD, heptanoic acid gave 80 % yield with 5 % RSD, octanoic acid under the above conditions gave 51 % yield with 8 % RSD and nonanoic acid gave 38 % yield with 6 % RSD using the optimum conditions established for hexanoic acid. These results however could not be used to establish any relation between the chain length of the acid and dimer yield. However the reproducibility of these reactions from the RSD values (3 - 9 %) showed the validity of the capillary glass flow cell E 4 for the electrolysis of a range of acids.



Plot 9 presents the stability of the results, 0.05 mol L^{-1} pentanoic, hexanoic, heptanoic, octanoic and nonanoic acid with 0.1 mol L^{-1} of pyridine at 0.1KV

Flowrate/uL/min	acid/pyridine /mol L^{-1}	Current/ mA	n	Average Yield/%	%RSD
6	C_8H_{17} COOH/0.05/0.1	5	36	38	6
6	C_7H_{15} COOH/0.05/0.1	3	36	51	8
6	C_6H_{13} COOH/0.05/0.1	4	33	80	9
6	C_5H_{11} COOH/0.05/0.1	5	40	73	5
6	C_4H_9 COOH/0.05/0.1	5	36	59	3

Table 53 Flow cell E 4, effect of chain length, 0.05 mol L^{-1} of an acid 0.1 mol L^{-1} of pyridine at 0.1KV

4.4.3 Summary

The flow cell E 4 was used for the Kolbe electrolysis of alkanoic acids giving oily masses of alkanes, however the cell was not tested for the acids giving products like higher alkanes such as octadecane (with the chances of blocking the channels for being wax like with heavy masses and low solubility), and lower alkanes such as butane (for being a highly flammable gas). Literature[5] suggested the biphasic Kolbe dimerisation of hexanoic acid co emulsified with 1.0 M NaOH yielding 45 % decane at Pt electrodes. The data so far gained for octanoic (51 % yield) and hexanoic acid (giving 77% yield) could be used to exploit the optimum conditions for electrolyte free electrolysis of straight chain alkanoic acids providing an optimum framework to demonstrate the Kolbe electrolysis of other carboxylic acids such as amino acids in microreactors. It was thought that under the optimum electrolyte free conditions generating radicals from the alkanoic acids, the flow cell E 4 could be used for some other reactions such as addition of radicals at the double and triple bonds. One of the most commonly used olefin suggested for this purpose was styrene, therefore was used for the addition of radicals to a double bond (results to be discussed later).

4.5.0 Kolbe electrolysis in a parallel plate flow-through micro-gap cell F

In this work the micro-gap flow cell was also evaluated to investigate the optimum conditions for the Kolbe electrolysis of alkanoic acids. The standard optimum conditions for Kolbe electrolysis in flow cell E 4 were applied in the micro-gap cell F (Figure 29 and 30), with an understanding that a larger electrode surface area and a smaller inter electrode distance under these conditions will give more conversion. The cell was mounted vertically providing an easy escape of the CO_2 gas bubbles as a result of the Kolbe electrolysis of alkanoic acids. The reaction mixture was analyzed by GC/MS method B, and GC/FID method C.

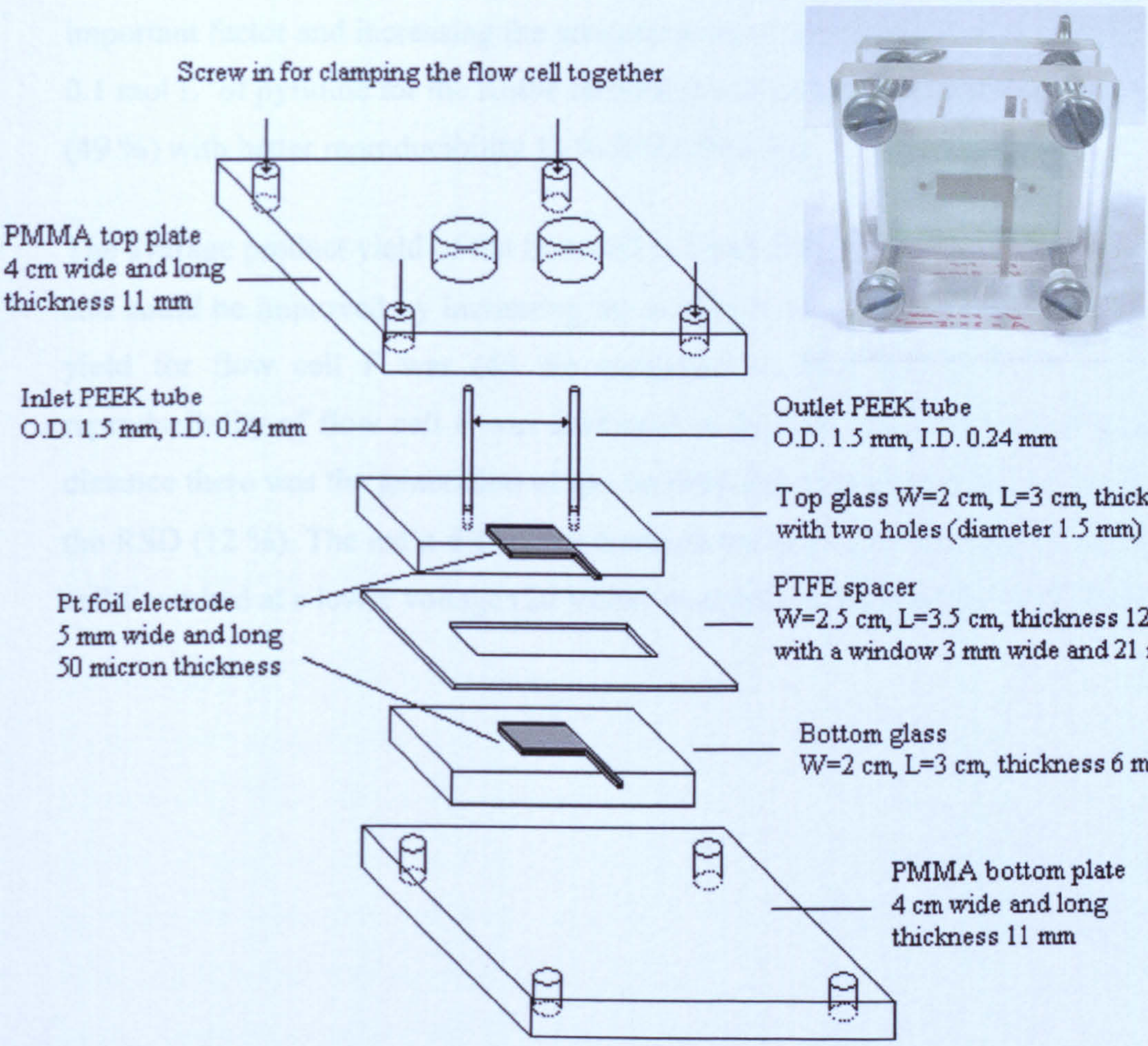
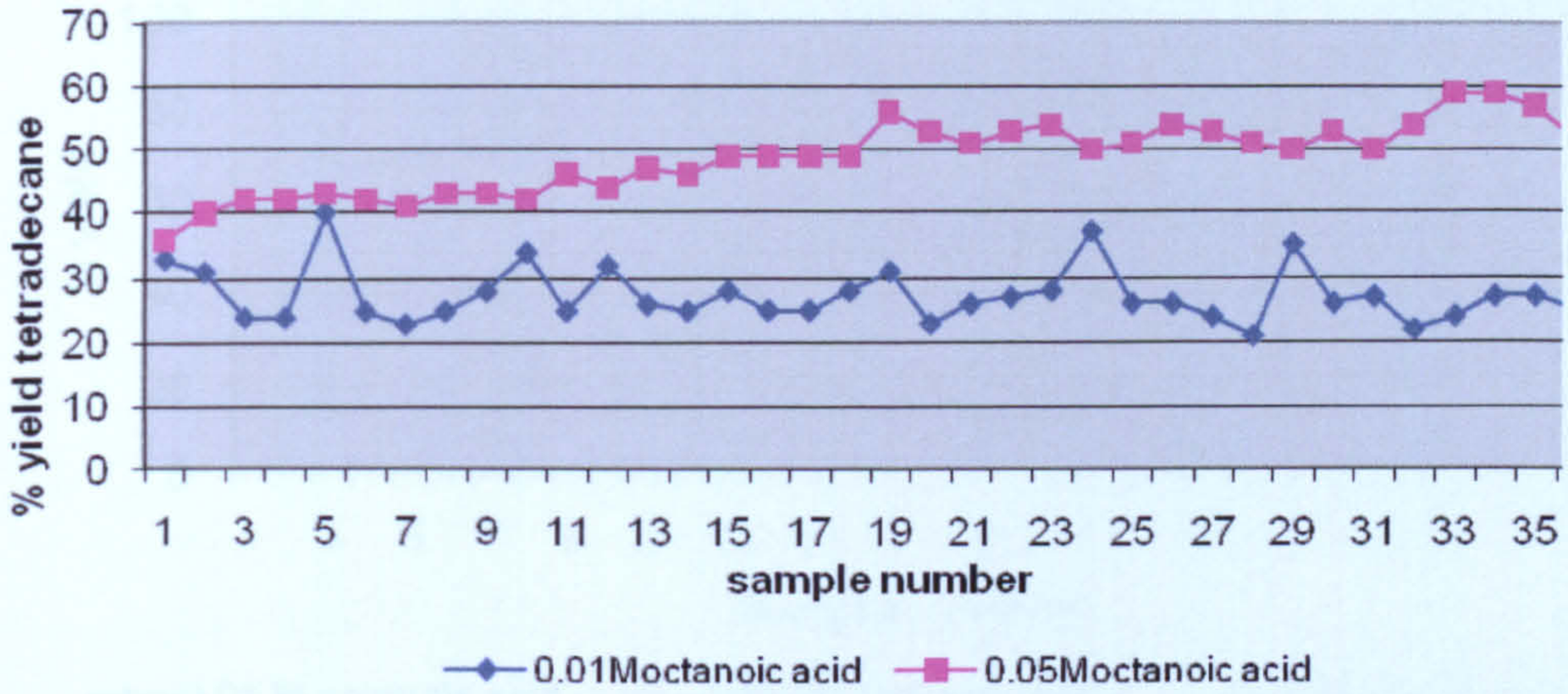


Figure 29 and 30 Construction of parallel plate flow-through micro-gap cell F

4.5.1 Results from parallel plate flow cell F

In order to evaluate the microgap flow cell for the Kolbe electrolysis, octanoic acid was electrolysed to establish the best acid/base concentration as determined for flow cell E 4. The electrolysis was conducted in two sets and the effect of acid concentration was investigated, for the first set 0.05 mol $L^{-1}$of the octanoic acid and 0.1 mol L^{-1} of pyridine was electrolysed and for the second set 0.01 mol L^{-1} of the acid with 0.02 mol $L^{-1}$of pyridine was electrolysed. Considering the small inter electrode gap in the flow cell F it was thought that the cell would be able to give better conversion for lower acid/base concentration, hence 0.01 mol L^{-1} of the acid was electrolysed with 0.02 mol L^{-1} of pyridine. The results (Table 54), showed that acid/pyridine concentration was an important factor and increasing the concentration to 0.05 mol L^{-1} of the octanoic acid and 0.1 mol $L^{-1}$of pyridine for the Kolbe electrolysis of octanoic acid gave more product yield (49 %) with better reproducibility 12 % RSD (Plot 10).

The average product yield of the flow cell E 4 and flow cell F was somewhat comparable and could be improved by increasing the acid/base concentration. The optimum product yield for flow cell F was (49 %) compared to flow cell E 4 (51 %). The poor reproducibility of flow cell F was attributed to the fact that with a small inter electrode distance there was the generation of gas bubbles disturbing the diffusion layer increasing the RSD (12 %). The main difference between the two cells was that the micro-gap flow cell F worked at a lower voltage (20 Volts) than that of flow cell E 4 (100 Volts).



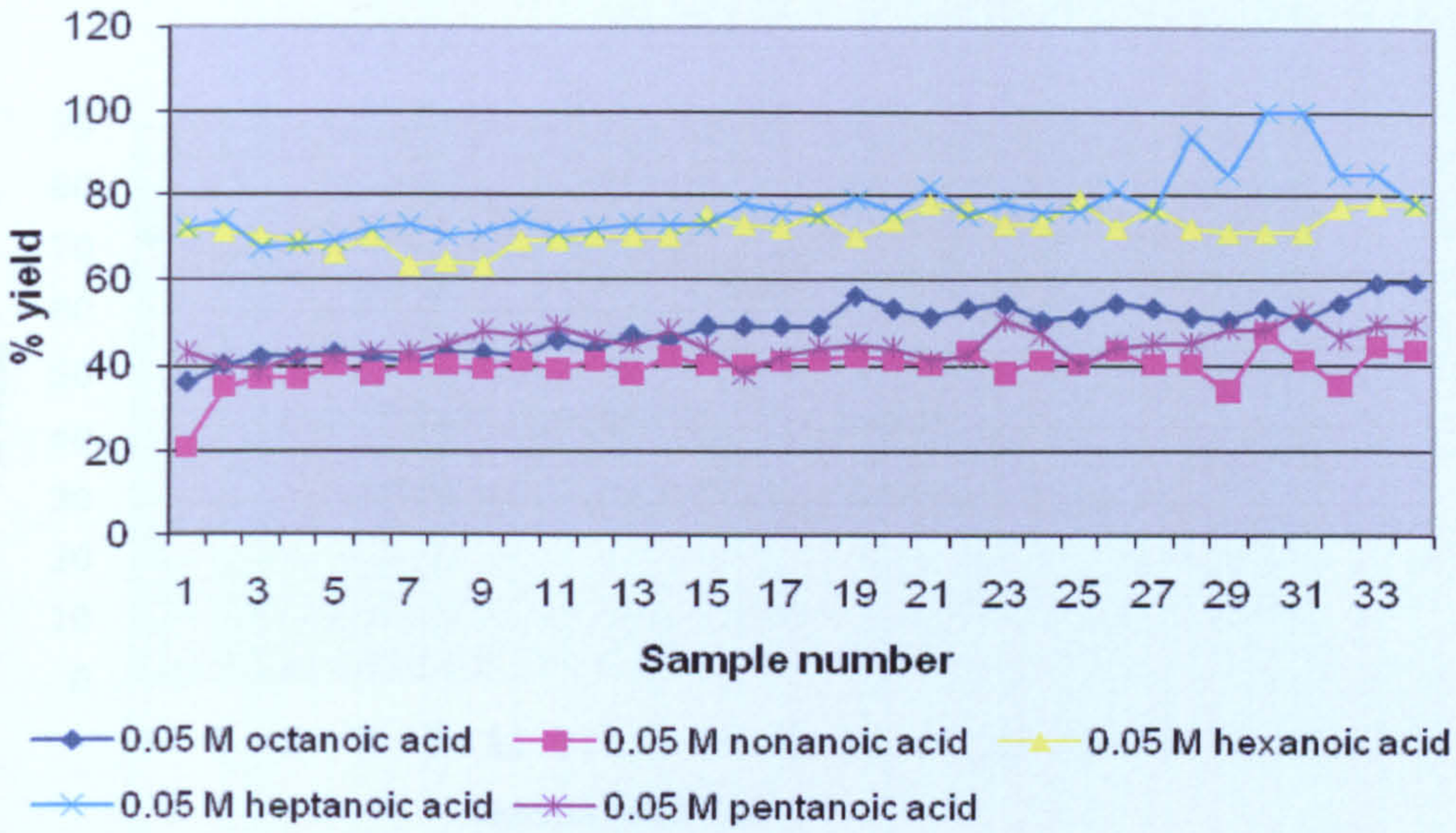
Plot 10 Effect of acid concentration on dimer yield in a parallel plate cell F

Flow rate µl/min	Acid/Pyridine/ mol L^{-1}	current/ mA	Voltage/V	Average Yield/%	n	%RSD
6	0.01/0.02 pyridine	8	20	27	36	16
6	0.05/0.1 pyridine	7	20	49	36	12

Table 54 Microgap flow cell design F, effect of pyridine, 0.01 and 0.05 mol L^{-1} of an acid at 0.1KV

4.5.2 Effect of acid chain length in parallel plate flow cell F

To compare the performance in terms of results and reproducibility in flow cell E 4 and F, for Kolbe electrolysis of octanoic and other alkanoic acids, a series of reactions were carried out. The results of reactions of electrolysis of pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid and nonanoic acid are given in (Table 55). The effect of pyridine concentration was also investigated to mark any difference, between the glass flow cell E 4 and micro-gap flow cell F in order to investigate the effect of composition of the reaction mixture on the diffusion profile at the electrode surface.

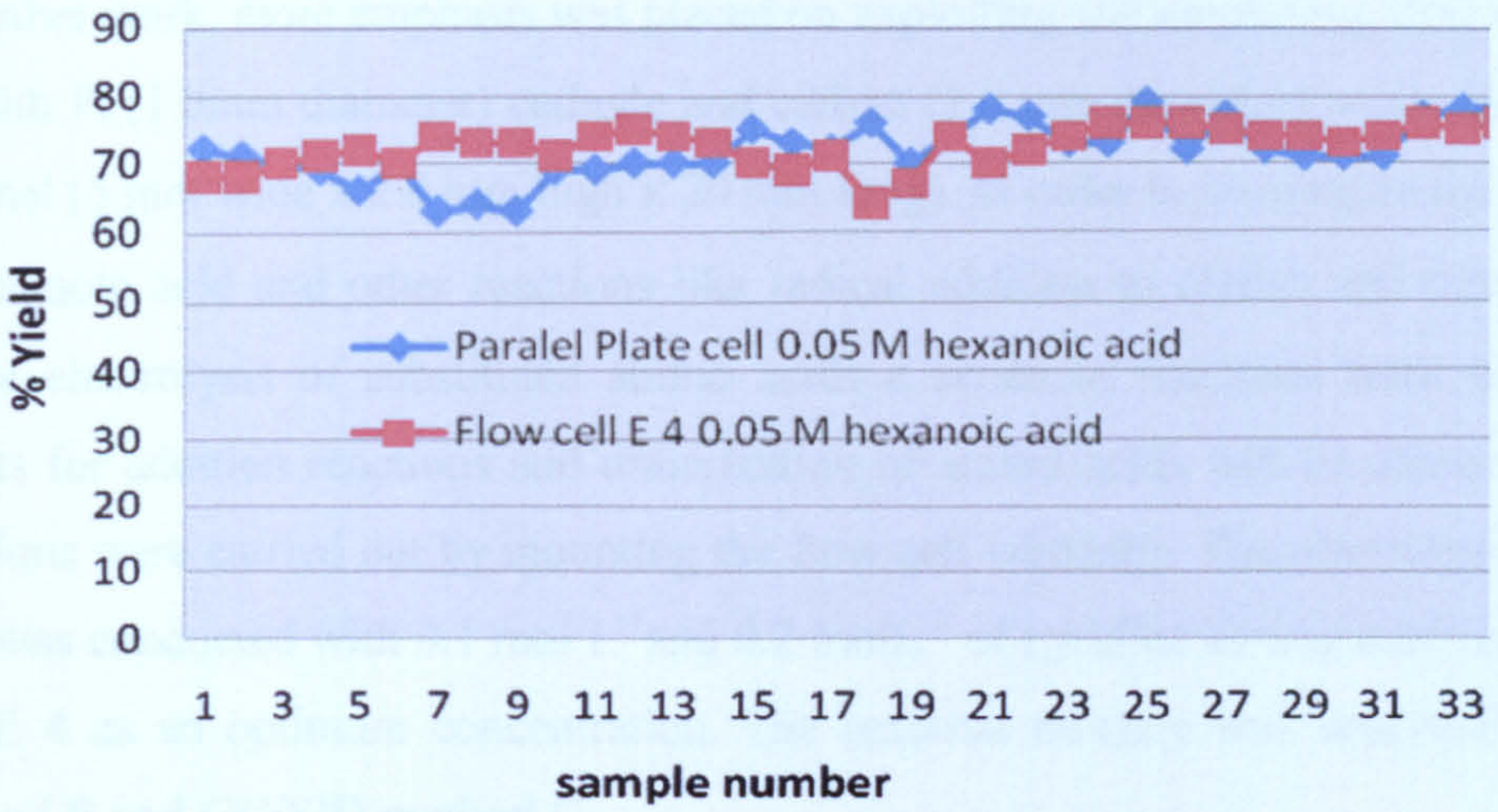


Plot 11 Parallel plate flow cell F at 20V, effect of chain length on dimer yield

Flow rate/µL/min	Acid/Pyridine/mol L^{-1}	Current/ mA	Average Yield/%	n	%RSD
6	$C_8H_{17}COOH$/0.05/0.1	6	37	36	11
6	$C_7H_{15}COOH$/0.05/0.1	7	49	36	12
6	$C_6H_{13}COOH$/0.05/0.1	7	77	35	10
6	$C_5H_{11}COOH$/0.05/0.1	7	72	34	6
6	C_4H_9COOH/0.05/0.1	8	44	36	15

Table 55 Micro gap flow cell design F, effect of chain length, 0.05 mol L^{-1} of an acid at 0.1KV

The comparison Plot 11, of product yield and (%) RSD of the results for hexanoic acid only, from both the cells (Table 53 and 55) reveal that the only advantage in case of parallel plate cell was that it works at a lower voltage, however, there was not much difference in the percentage (%) yield of products or the (%) RSD of flow cell E 4.

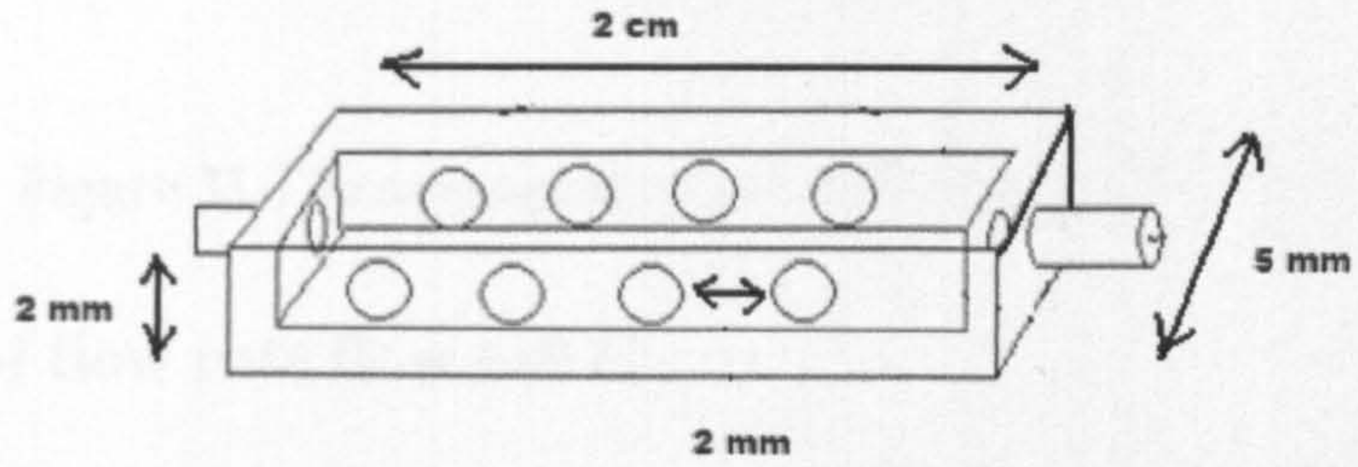


Plot 12 Comparison of flow cell E 4 / parallel plate cell F performance

Kolbe electrolysis, which operates in relatively mild conditions, usually requires a supporting electrolyte.[1] The results show that such a reaction in which gases are produced at the anode/cathode, as one of the major products of the electrochemical reaction, a strategy can be formulated by carefully controlling the electrolysis conditions. The results also suggested that by adjusting the inter electrode distance, current density (electrode surface area) and electrode material, the alkane transformations can be achieved with less or no side products at all, without using an electrolyte. In addition various conditions were studied further to optimize the electrochemical synthesis of alkanes and olefins in an electrochemical flow through reactor with carbon anodes. The next section comprises of results from flow cell G using carbon electrodes.

4.6.0 Results from flow cell G

In further work, more emphasis was placed on exploiting and employing flow cell G Figure 31 with Pt (1.0mm diameter) cathode and carbon (1.0 mm diameter) anode (put across the channel (5 mm wide x 2.0 mm high x 20 mm long). In order to investigate the dimerisation of octanoic acid and other reactions like radical addition to olefins and dimerisation *via* Kolbe electrolysis of substituted amino acids a series of reactions were designed. The results for addition reactions and dimerization of amino acids will be discussed later. All reactions were carried out by mounting the flow cell vertically. The electrolysis of octanoic acid was conducted with 0.1 mol $L^{-1}$and 0.2 molL^{-1} of pyridine as was established for flow cell E 4 as an optimum concentration. The reaction mixture was analyzed by GC/MS method B and GC/FID method C.



Electrode diameter C /mm (anode)	**1.0**
Electrode diameter Pt/mm (cathode)	**1.0**
Distance between electrodes/mm	**1.0**
Cell volume/ µL	**100**

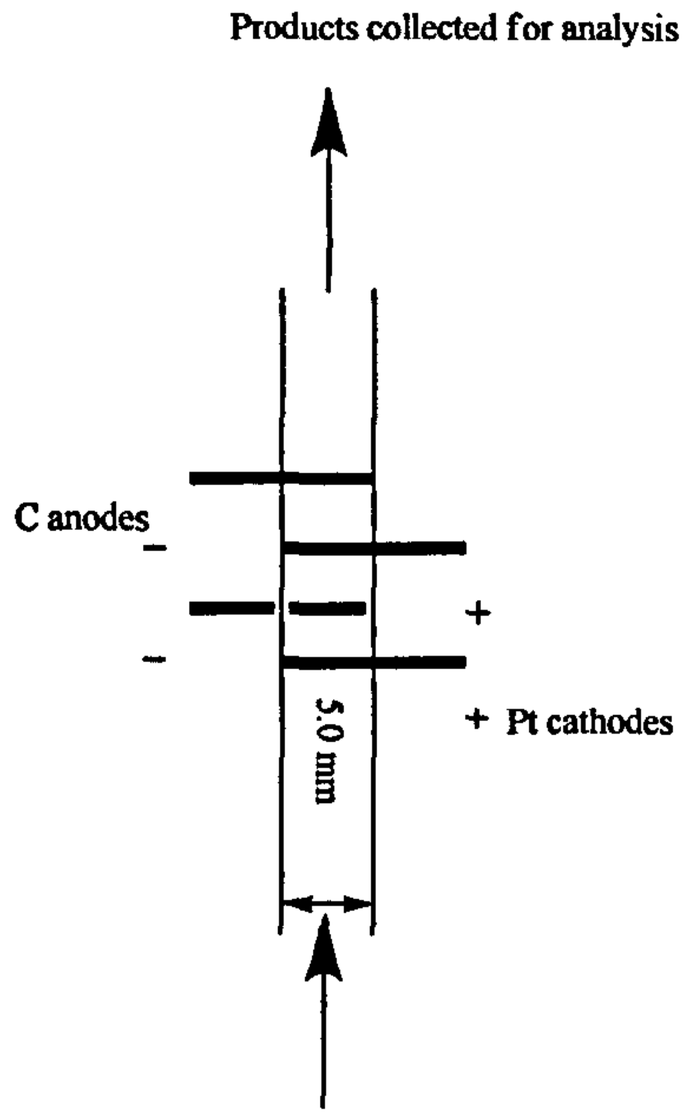


Figure 31 The arrangement of electrodes in flow cell G

4.6.1 Effect of flow rate flow cell G

Table 56, comprises the set of results for the electrolysis of 0.1 mol L^{-1} octanoic acid and 0.2 mol $L^{-1}$of pyridine for flow cell G (with Pt cathode/Carbon anode). The results showed a similar trend as seen for flow cell E 4 for octanoic acid which gave 69 % yield at 6 μL/min. However flow cell G gave 70 % yield at a slower flow rate of 4 μL/min. The (%) RSD (16 and 6 gave reproducible yield 59 % and 57 % respectively) for the experiments repeated at 6 μL/min showed that this arrangement of electrodes poses more negative effects because of the gas bubbles being trapped within the electrodes that were put across the channels. The results did not show any difference in terms of product yield with carbenium ions instead of radicals and the dimer formation still dominated. In addition a large number of impurities were seen. However all peaks were so small that it was not possible to identify each compound. The cell was not used further for the posed complications in its assembly and maintenance.

Flow rate/μL/min	Acid/Pyridine/mol L^{-1}	Current / mA	Average Yield/%	n	%RSD
150	0.1/0.2	1	8	21	29
75	0.1/0.2	2	13	20	20
60	0.1/0.2	2	19	20	14
30	0.1/0.2	2	31	20	16
15	0.1/0.2	2	34	18	6
6	0.1/0.2	2	59	20	16
Repeated					
6	0.1/0.2	4	57	12	4
4	0.1/0.2	3	70	12	13

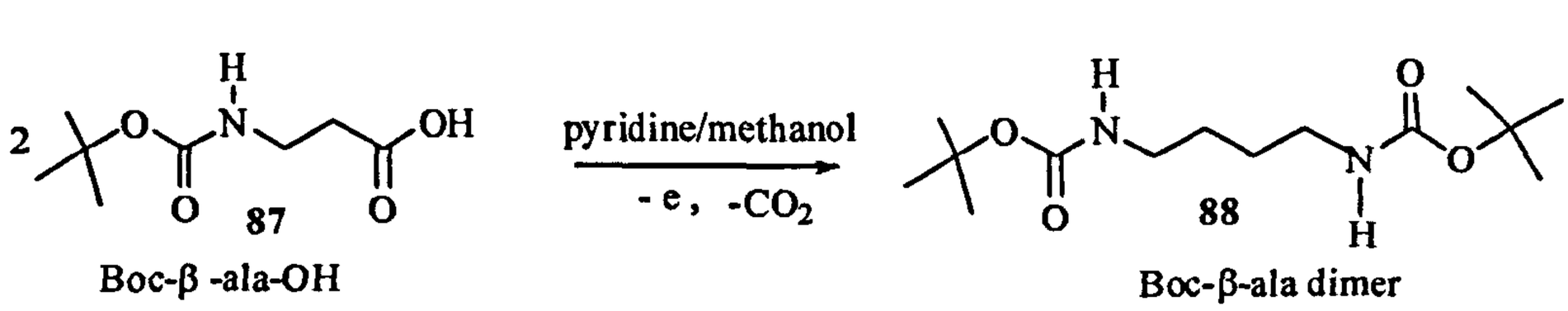
Table 56 Flow cell G 0.1 mol L^{-1} octanoic acid effect of flow rate on the electrolysis of octanoic acid

The results show low reproducibility with more byproducts as compared to the results from flow cell E 4 and F. The production of gas bubbles causes disruption in the flow and when the bubbles were trapped between the electrodes the current dropped considerably. The bubble was hard to move even in the upright position and the flow was stopped. For a slower flow rate of 4 – 6 μ L/min samples took up to 12 minutes to come through to the outlet end to be collected for analysis. The C electrodes got coated with the polymeric films which did not come off even after sonicating the cell in ethanol /water solution, and also sonicating the cell loosened the glass glue causing the leackage. The cell with Pt electrodes also posed similar challenges, therefore was not further used for any other reaction.

4.7.0 Kolbe electrolysis of amino acids

The results of Kolbe electrolysis of alkanoic acids from flow cell E 4, parallel plate cell F and flow cell G (with carbon anodes), suggested the use of these flow cells for the Kolbe electrolysis of amino acids. Literature [2, 6] supports the anodic decarboxylative oxidation of protected amino acids giving symmetric dimers. However as the experimental conditions employed in much of the early work in this thesis could now be regarded as the most suitable for coupling, still further study seemed desirable. Moreover an investigation of the coupling reactions of protected amino acids might well reveal new and valuable synthetic processes for biologically significant entities such as putrescine derivatives (1,2- and 1,4-diamines). With these considerations in mind an exploratory investigation of the electrolysis of a number of substituted amino acids has been employed.

4.7.1 Results of flow cell E 4



Boc-β -ala-OH

Boc-β-ala dimer

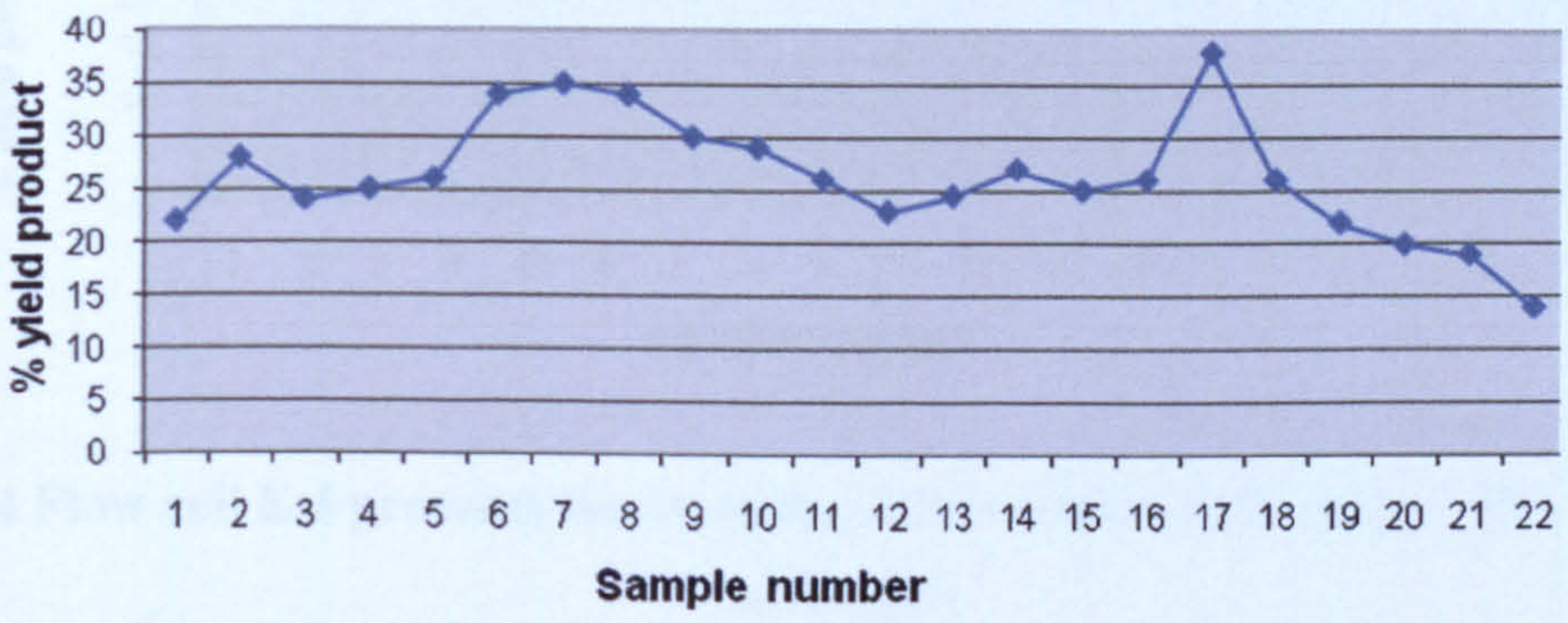
Scheme 38 Kolbe dimerization of Boc-β-Ala-OH

The study of dimerization reaction in case of α-amino acids was not successful and could not be carried out because the α-amino acid degraded and could not withstand the electrochemical oxidation. Therefore an attempt was made to carry out the electrolysis of β-amino acids, in flow cell conditions, that although proved to be challenging later, but revealed some interesting facts. The dimerization of β-alanine and phenyl alanine was not possible even after changing the optimum conditions (established earlier for octanoic acid), however some of the protected forms of these acids were suggested to be employed for the Kolbe electrolysis. The reaction mixture was analyzed by GC/MS method B, E and GC/FID method C, F.

The dimerization of protected β-alanine, with different protecting groups, was tried under the optimum conditions (0.1 mol L^{-1} of the acid and 0.2 mol L^{-1} of pyridine). Interestingly the protecting groups showed a clear difference in the dimer yields as far as the flow cell conditions were concerned, and Boc-β-Ala_OH and *N*-acetyl-β-Ala_OH gave dimers (putrescine derivetives), whereas the Fmoc-β-Ala-OH, Cbz-β-Ala-OH, *N*-benzyloxy-β-Ala_OH could not be dimerized even after changing the established optimum conditions for octanoic acid. The next section includes the results from the series of experiments conducted to evaluate the optimum conditions for Boc-β-Ala-OH.

4.7.1.1 Effect of pyridine on the electrolysis of Boc-β-Ala-OH

In order to investigate the optimum conditions for the dimerization of Boc-β-Ala-OH, 0.05 mol L^{-1} of the acid was electrolysed without pyridine. The results given in (Table 57), Plot 13 showed good product yield 26 % without using pyridine, when compared with alkanoic acids although with less reproducibility (21 % RSD).



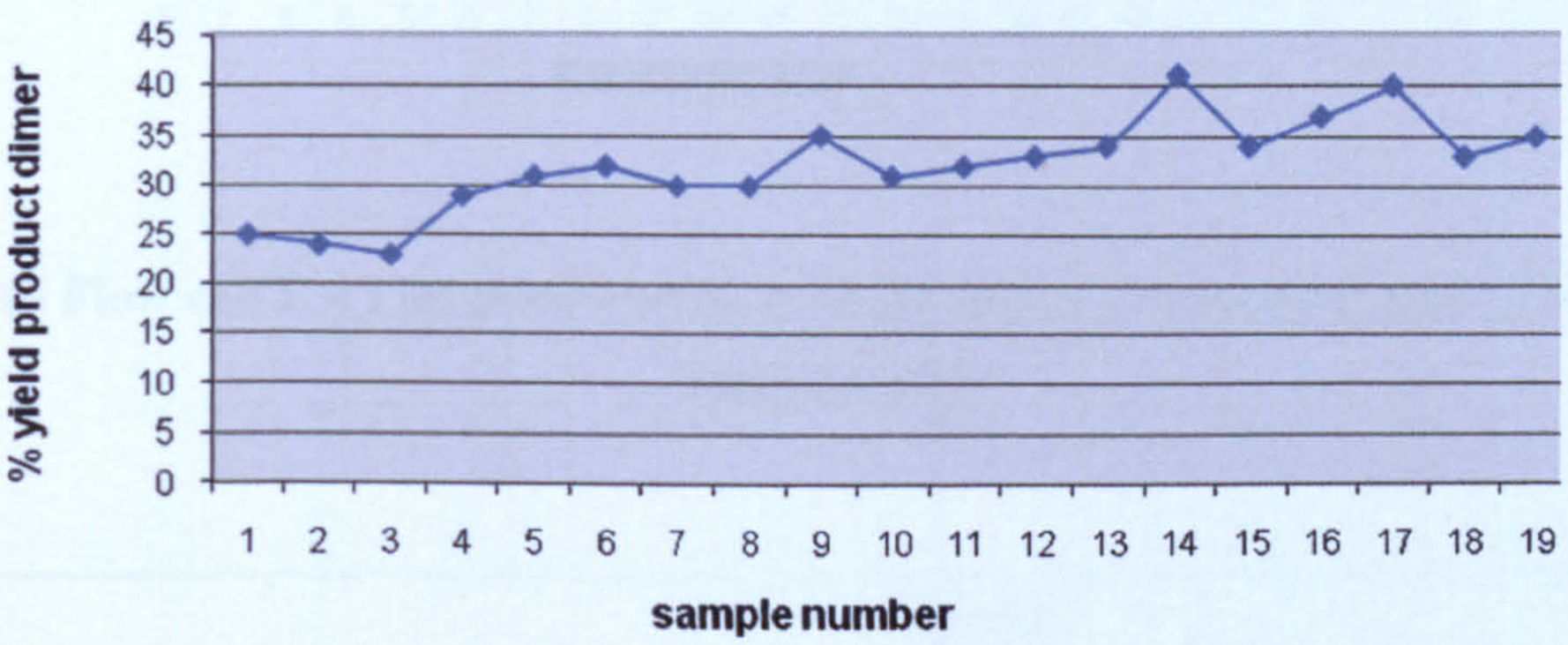
Plot 13 Flow cell E 4 presents the stability of the results

0.05 mol L^{-1} Boc-β-Ala-OH at 0.1KV

Flow rateμL/min	Acid/Pyridine/ mol L^{-1}	Current/ mA	Average Yield/%	n	%RSD
6	0.05/0.0	7	26	22	21

Table 57 Flow cell E 4, Plot presents the stability of the results 0.05 mol L^{-1} Boc-β-Ala-OH at 0.1KV

The effect of pyridine was investigated further and the results (Table 58, Plot 14) showed that when 0.05 mol L^{-1} Boc-β-alanine was electrolysed with 0.05 mol L^{-1} pyridine, gave the dimer yield (32 %). The (%) RSD was improved (15 % RSD) by using pyridine as a base/electrolyte as already established in the electrolysis of octanoic acid.

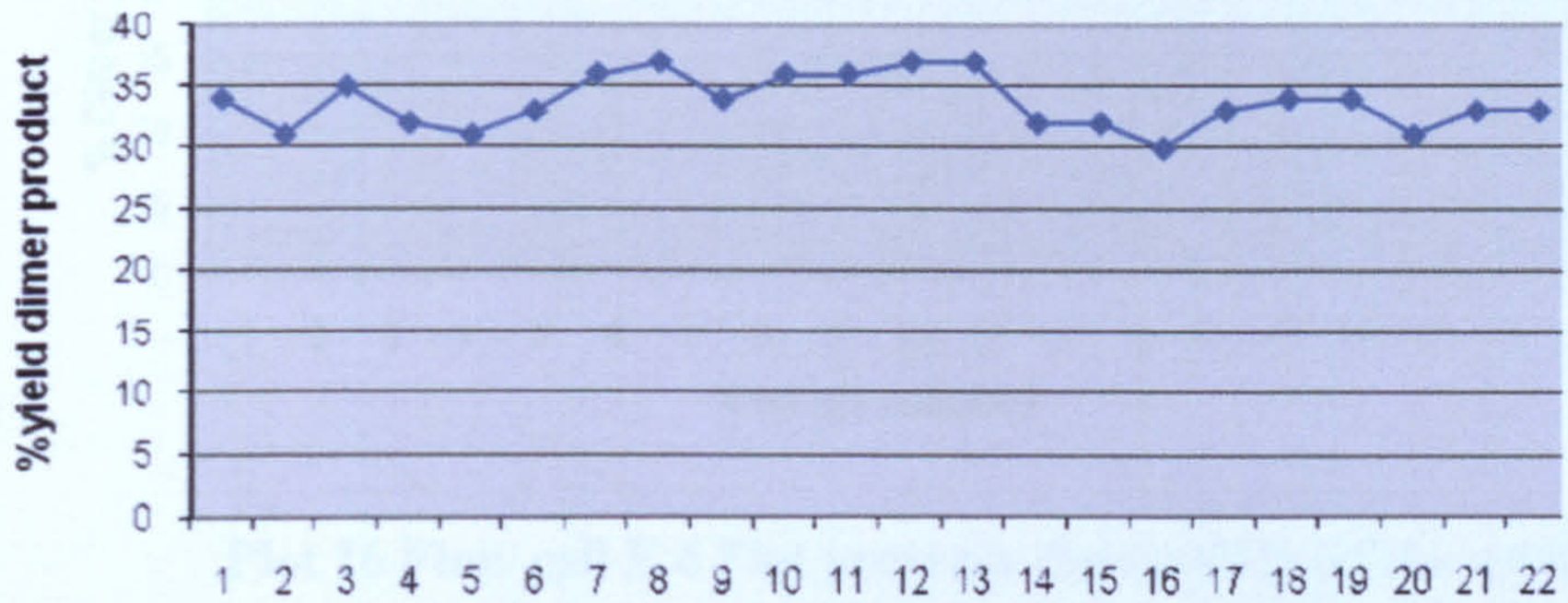


Plot 14 Flow cell E 4 presents the stability of the results, 0.05 mol L^{-1} Boc-β-Ala-OH at 0.1KV

Flow rateμL/min	Acid/Pyridine/mol L^{-1}	Current/ mA	Average Yield/%	n	%RSD
6	0.05/0.05	5	32	19	15

Table 58 Flow cell E 4 Plot presents the stability of the results, 0.05 mol L^{-} Boc-β-Ala-OH at 0.1KV

When the optimum conditions for the electrolysis of octanoic acid (0.1 mol L^{-1} of acid 0.2 mol L^{-1} of pyridine at 100 Volts and 6 μL/min) that was 2 equivalents of pyridine to acid concentration were employed for the electrolysis of Boc-β-alanine, the reproducibility of the results was further improved (RSD 6 %) and the dimer yield improved (34 %). The results, (Table 59), Plot 15, showed the effect of excess of pyridine in the optimum conditions.



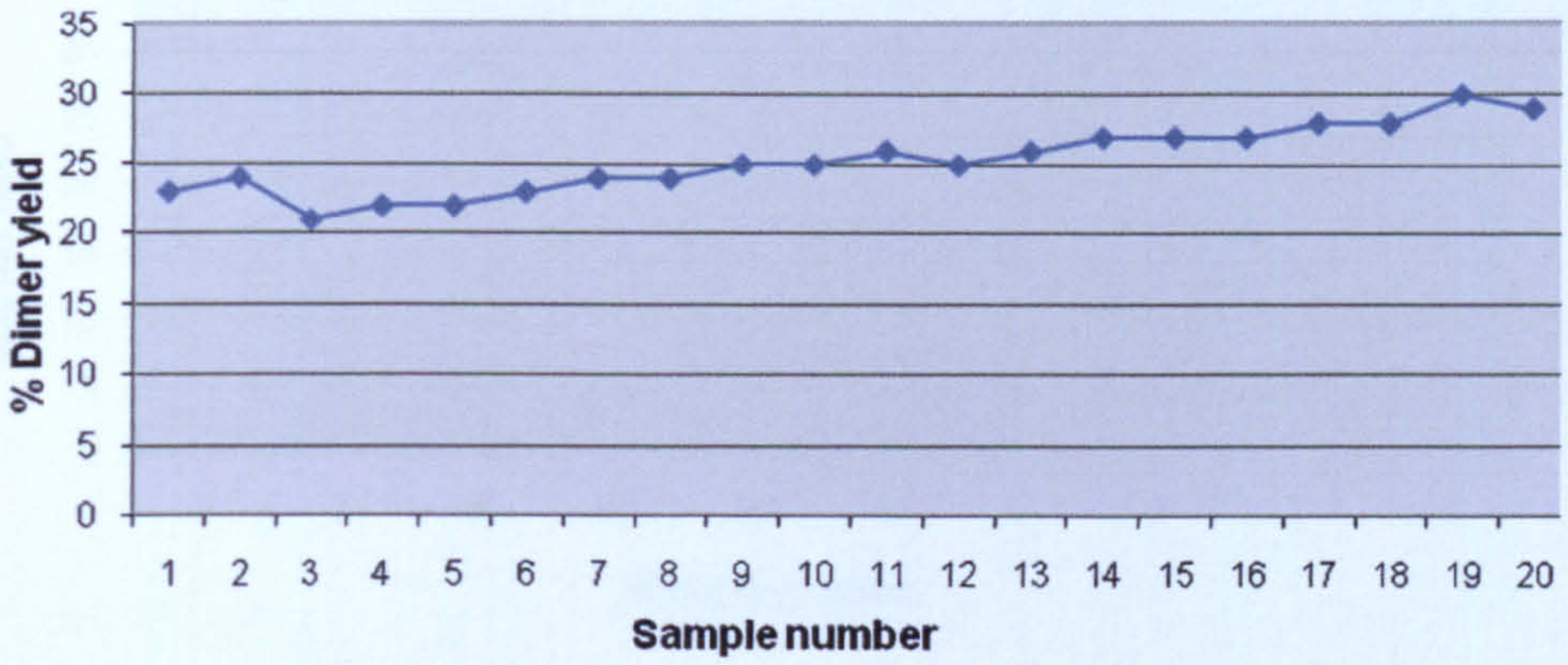
Plot 15 Flow cell E 4 Plot presents the stability of the results, 0.05 mol L^{-} Boc-*β*-Ala-OH at 0.1KV

Flow rate/μL/min	Acid/Pyridine/ mol L^{-1}	Current/ mA	Average Yield/%	n	%RSD
6	0.05/0.1	6	34	22	6

Table 59 Flow cell E 4 Plot presents the stability of the results, 0.2 mol L^{-1} Boc-β-Ala-OH at 0.1KV

The excess of pyridine (4 equivalents) gave a similar result (as electrolysis without pyridine), however the % RSD was 10 %. Increasing the pyridine to 4 equivalents gave poor yield (25 %) still with reproducible results (Table 60) Plot 16. The Kolbe

electrolysis of Boc-β-Alanine using flow cell E 4 could not be carried out for longer sessions because the electrodes became coated with polymeric films and therefore needed cleaning after every experiment.



Plot 16 Flow cell E 4 Plot presents the stability of the results 0. mol L^{-1} Boc-*β*-Ala-OH at 0.1 KV

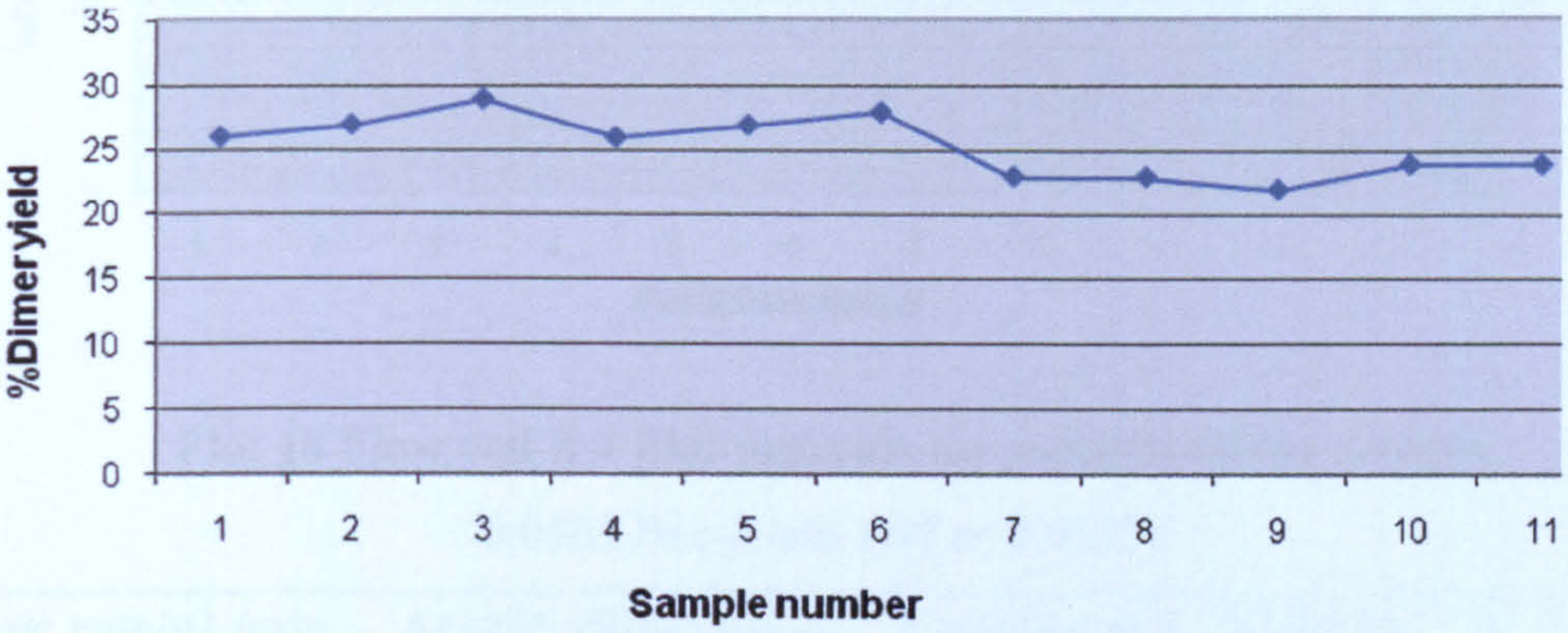
Flow rate/µL/min	Acid/Pyridine/ mol L^{-1}	Current/ mA	Average Yield/%	n	%RSD
6	0.05/0.2	7	25	20	10

Table 60 Flow cell E 4 Plot presents the stability of the results, 0.1 mol L^{-1} Boc-*β*-Ala-OH at 0.1KV

In order to investigate the effect of voltage and improve the dimer yield further, the following set of experiments was conducted.

4.7.1.2 Effect of Voltage on the electrolysis of Boc-*β*-Ala-OH

The effect of voltage was also investigated for the electrolysis of Boc-β-alanine and it was found (Table 61), Plot 17 that the optimum conditions for octanoic acid (100 Volts) were the optimum conditions for Boc-β-alanine and lower voltage (50 Volts) did not increase the dimer yield (26 %) with a poor reproducibility (15 % RSD).

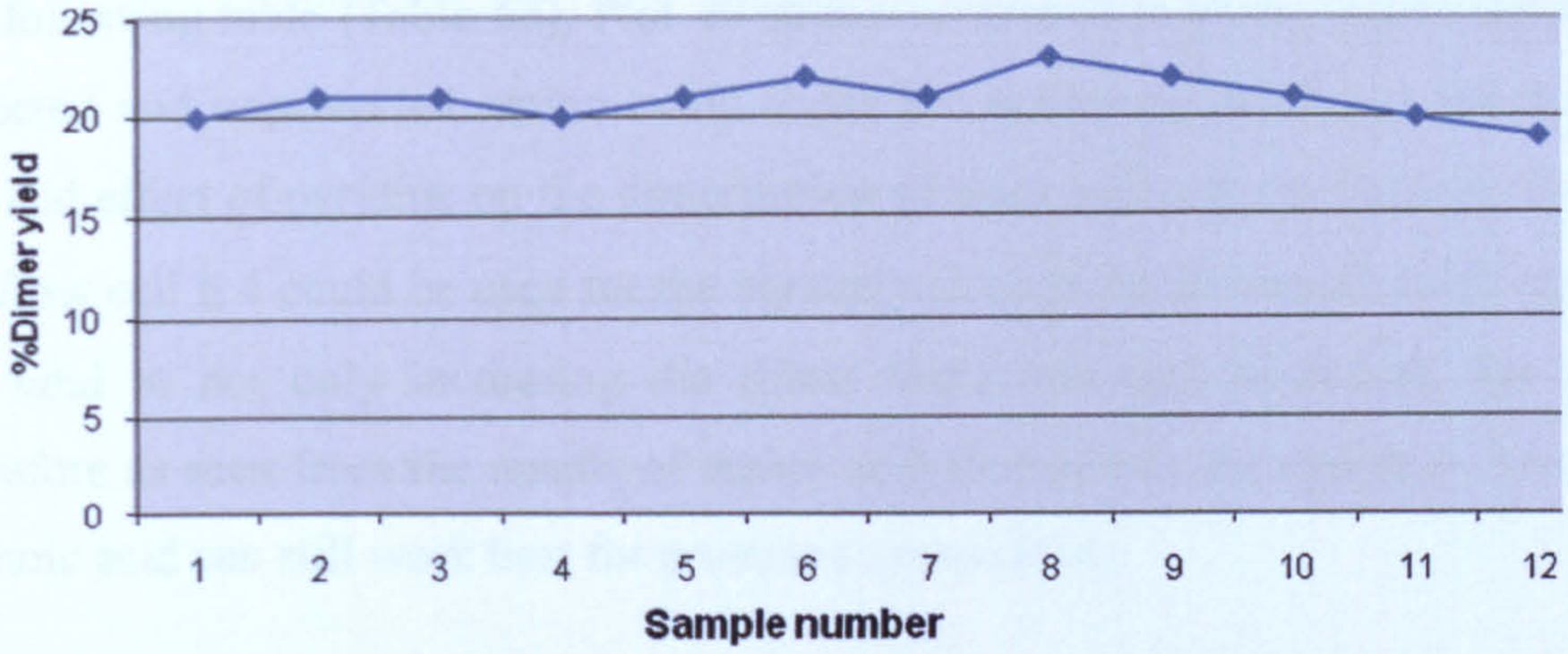


Plot 17 Flow cell E 4,Plot presents the stability of the results 0.05 mol L^{-1} Boc-β-Ala-OH at 0.05KV

Flow rate/µL/min	Acid/Pyridine/mmol	Current/ mA	Average Yield/%	n	%RSD
6	0.05/0.1	6	26	12	15

Table 61 Flow cell E 4 Plot presents the stability of the results, 0.05 mol L^{-1} Boc-β-Ala-OH at 0.05KV

The effect of voltage was investigated by changing the acid/pyridine concentration and for the electrolysis of 0.05 mol L^{-1} Boc-β-alanine with 0.2 mol $L^{-1}$of pyridine and the results (Table 62), Plot 18 showed that the lower voltage (50 Volts) did not increase the dimer yield (21 %) for this concentration still with a poor reproducibility (14 % RSD).



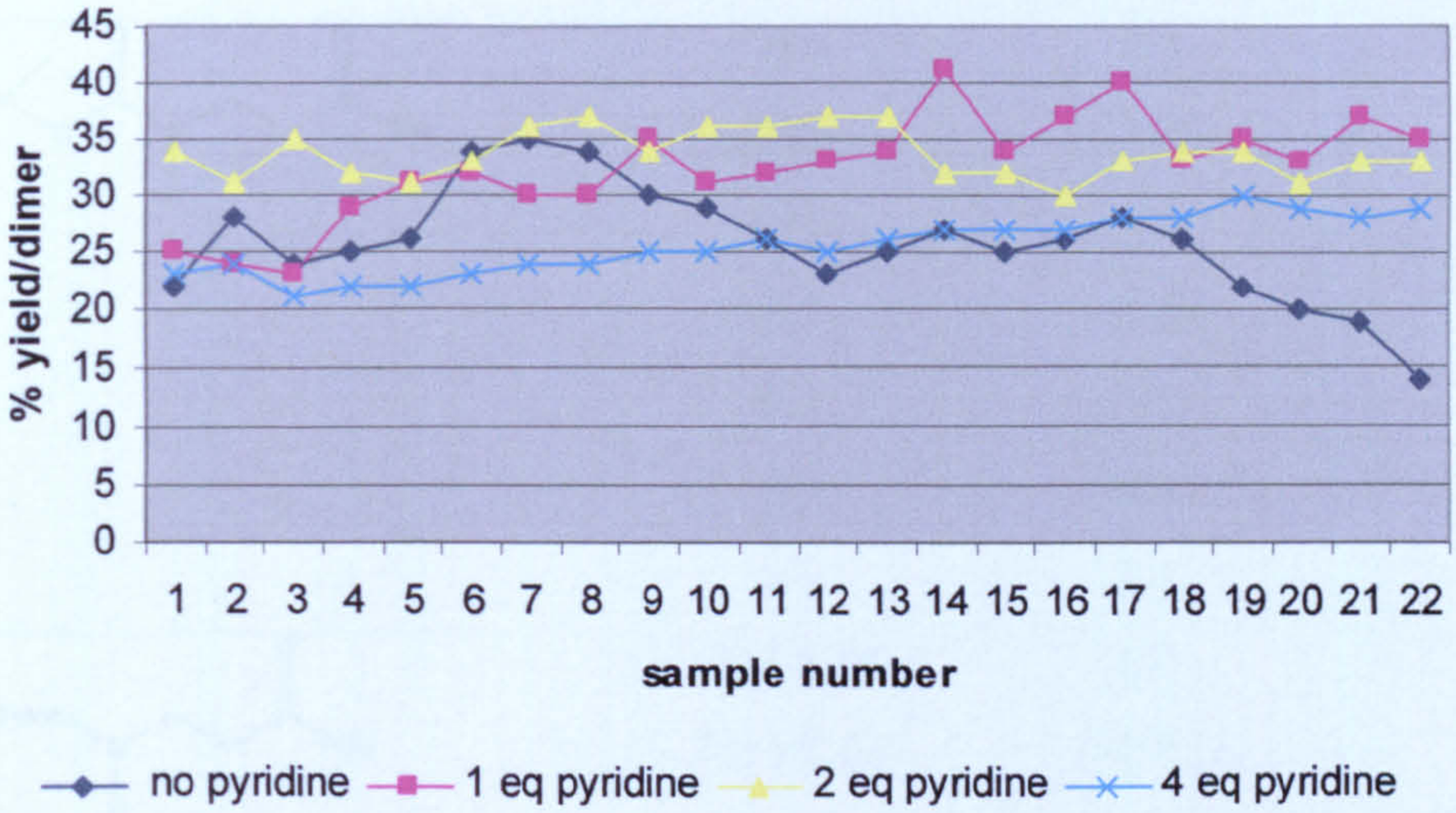
Plot 18 Flow cell E 4 Plot presents the stability of the results 0.05M Boc-β-ala-OH at 0.05KV

Flow rate/μL/min	Acid/Pyridine/mmol	Current/ mA	Yield/%	n	%RSD
6	0.05/0.2	6	21	12	14

Table 62 Flow cell E 4 Plot presents the stability of the results, 0.05 mol L^{-1} Boc-β-Ala-OH at 0.05KV

4.7.2 Summary

The following table (Table 63), Plot 19 shows an overview of the Kolbe electrolysis of protected and unprotected amino acids under the optimum conditions for the octanoic acid and effect of pyridine on the dimerisation of these acids. It can be seen from Plot 19 that flow cell E 4 could be used for the electrolysis of protected amino acids and pyridine was vital in not only increasing the dimer yield but also improving the (%) RSD. Therefore as seen from the results of amino acid electrolysis the optimum conditions for octanoic acid can still work best for protected amino acids.



Plot 19 Flow cell E 4 the effect of pyridine on the results

0.05 mol L^{-1} Boc-β-Ala-OH

A series of experiments were conducted for a set of protected amino acids. The Kolbe electrolysis of *N*-acetyl-β-alanine (Table 63) also gave dimer although the yield was not good (17 %), however the results from the electrolysis of Boc-β-alanine and *N*-acetyl-β-alanine were in agreement with the results already reported in literature for these acids.[5c]

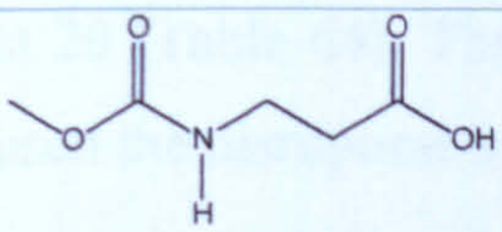
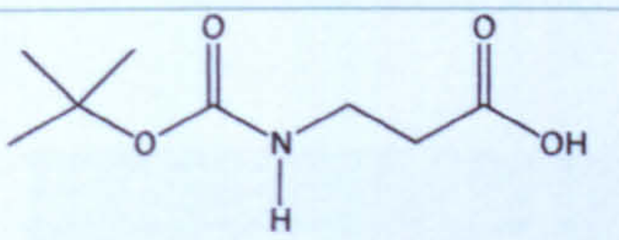
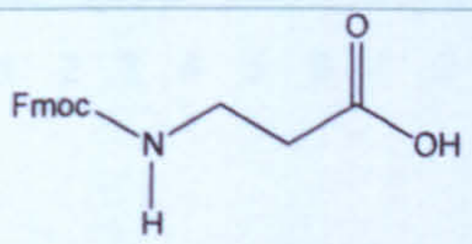
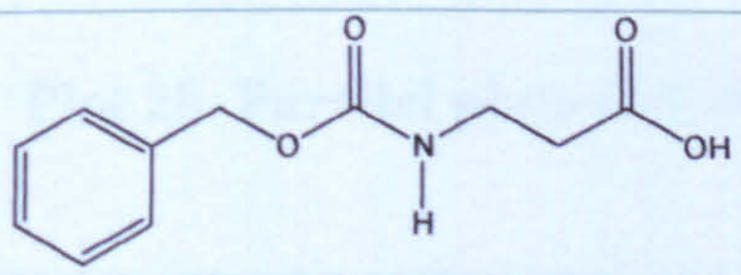
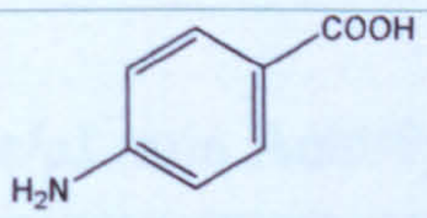
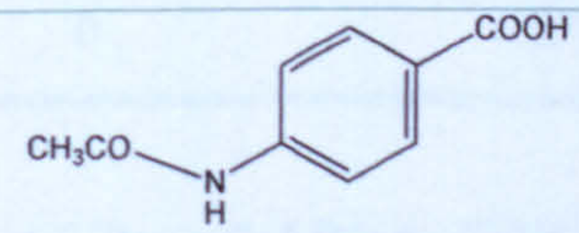
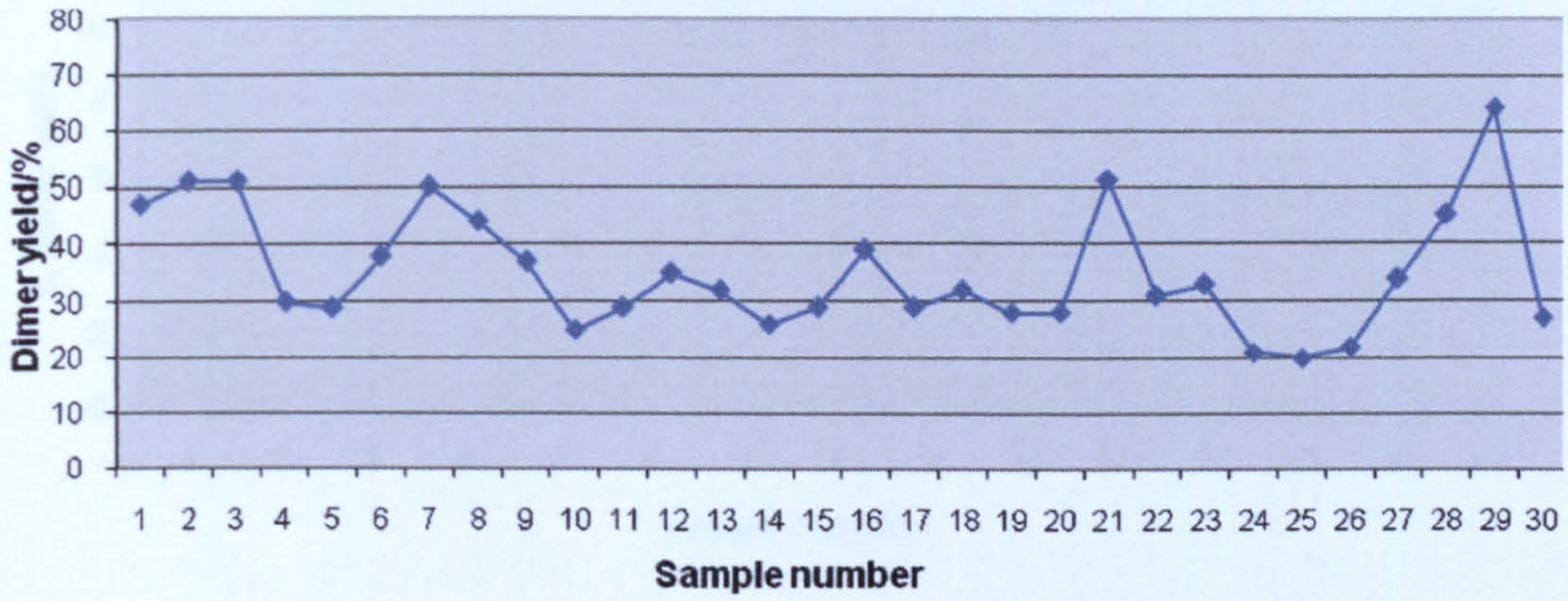
Amino acid/2mmol	Pyridine/ mol L^{-1}	Voltage/ kV	Dimer Yield%
$NH_2(CH_2)_5COOH$	0.0	0.05/0.1	-
	0.05	0.05/0.1	-
$CH_3CONH(CH_2)_5COOH$	0.0	0.05/0.1	-
	0.05	0.05/0.1	-
	0.0	0.05/0.1	-
	0.05	0.1	17
	0.0	0.1	26
	0.05	0.05	26
	0.05	0.1	32
	0.2	0.05	21
	0.1	0.1	34
	0.1	0.05	12
	0.2	0.1	25
	0.0/0.05	0.1	-
	0.05/0.05	0.05/0.1	
	0.0/0.05	0.1	-
	0.0/0.05	0.05/0.1	
	0.0/0.05	0.05/0.1	-
	0.0/0.05	0.05/0.1	-

Table 63 Flow cell E 4 the summary of the results, 0.05 mol L^{-1} Boc-β-Ala-OH at 0.05/0.1KV with /without pyridine

4.7.3 Results of flow cell F

The Kolbe electrolysis of 0.05 mol L^{-1} Boc-β-alanine was carried out with 0.1 mol L^{-1} pyridine using parallel plate flow cell F. The results (Table 64, Plot 20) showed that although the electrolysis was conducted at 0.02 KV, gave the dimer yield of (35 %). The reaction was carried out in a parallel plate cell giving almost similar results as far as the conversion was concerned, but a higher RSD (30 %) showing poor reproducibility over time Plot 20 (Table 64). The poor RSD could be related to the gas bubbles which could have caused the disruption in the flow.



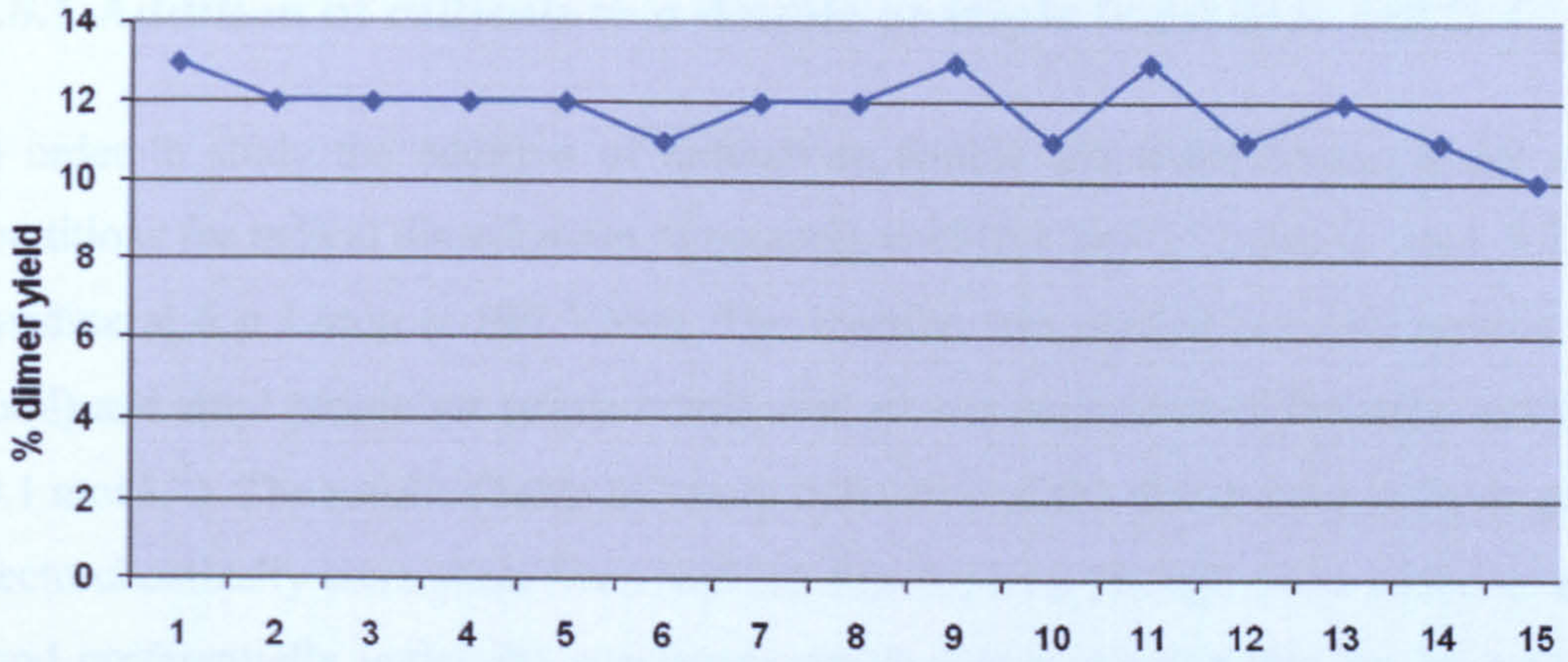
Plot 20. Parallel plate Cell F, 0.05M Boc-β-Ala-OH 0.1M Pyridine at 0.02 KV

Flow rate/µL/min	Acid/Pyridine/ mol L^{-1}	Current/ mA	Average Yield/%	n	% RSD
6	0.05/0.1	5	35	30	30

Table 64 Parallel Plate F Plot presents the stability of the results, 0.05 mol L^{-1} Boc-β-Ala-OH at 0.02 KV

4.7.4 Results of flow cell G

The Kolbe electrolysis of 0.05 mol L^{-1} Boc-β-alanine was also carried out with 0.1 mol L^{-1} pyridine using flow cell G (using graphite electrodes). The results (Table 65, Plot 21) showed that although the electrolysis was conducted at 0.1 KV, it gave a poor dimer yield of (15 %). The results show less dimer yield (12 %) with a reproducibility (7 % RSD).



Plot 21 Flow cell G Plot presents the stability of the results0.05 mol L^{-1} Boc-β-Ala-OH at 0.1KV

Flow rate/µL/min	Acid/Pyridine/ mol L^{-1}	Current/ mA	Average Yield/%	n	%RSD
6	0.05/0.1	2	12	15	7

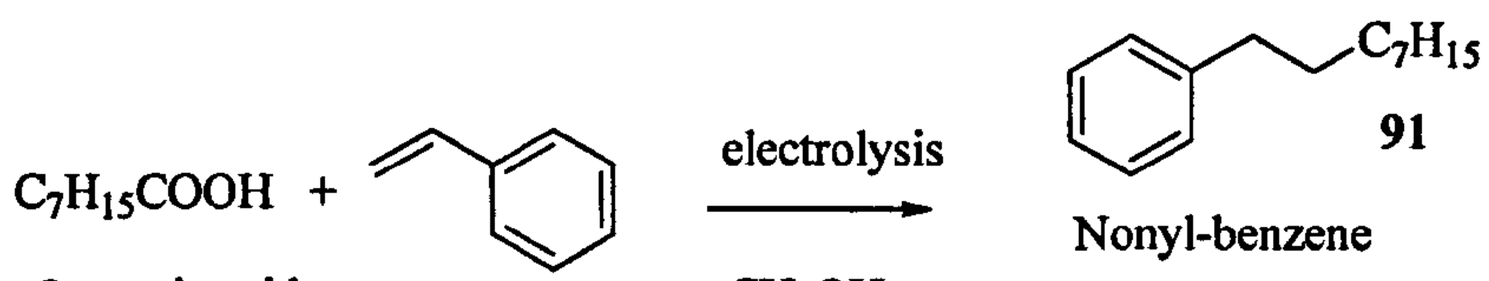
Table 65 Flow cell G (graphite anode) 0.05 mol L^{-1} Boc-β-Ala-OH at 0.1 KV

4.8.0 Anodic addition of radicals to olefins

Another interesting feature of Kolbe electrolysis to be investigated using a flow cell was the addition of radicals generated at the anode to the double bond of an olefin to give an addition product as suggested by the literature.[1, 7] The next section comprises of the results generated by flow cells E 4, F and G. More over the addition of radicals to a triple bond was also investigated.

4.8.1 Addition of radicals to a double or triple bond flow cell E 4

In order to study the addition of radicals to double and triple bonds, under optimum conditions for radical dimerisation of octanoic acid (0.1 mol L^{-1} octanoic acid, 0.2 mol L^{-1} pyridine at 6 μ L/min at 100 Volts). The reaction was carried out with styrene (double bond) and ethyl propiolate (triple bond) used as one equivalent of the acid concentration (0.1 mol L^{-1}). The results (Table 66) were indicative of the fact that the radicals generated electrochemically were short lived and not free for long enough to be added to a double bond preferentially under the conditions which favour dimerisation (to give alkane) in any flow cell set up. The addition of styrene **90** interfered with the deprotonation effect of pyridine, and changed the diffusion layer profile and ionic equilibrium at the surface of electrodes in such a way that radical generation and dimerisation were suppressed altogether. The reaction gave very low dimer yield (3 % teteradecane **92**) with no addition product (nonyl benzene **91**), instead gave some addition products of polymeric nature containing ring structures, which could not be identified exactly. The polymeric films covered the electrode surface and made it inactive affecting the addition product/dimer formation further. The reaction mixture was analyzed by GC/MS method B and GC/FID method C. The reaction mixture was analyzed by GC/MS method B, E and GC/FID method C and D.

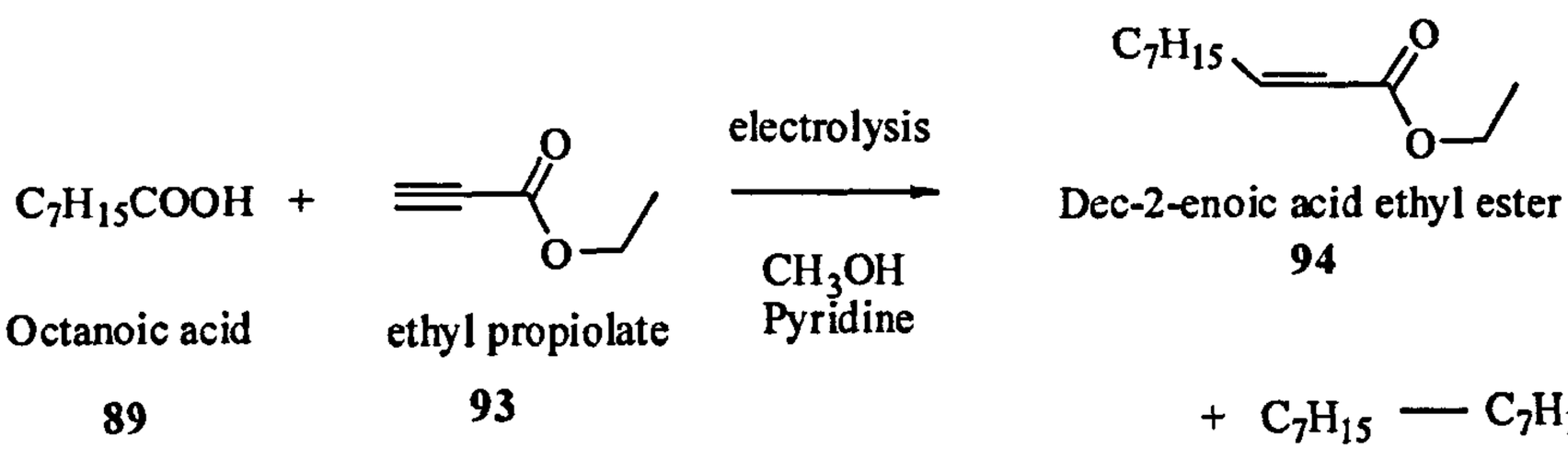


Scheme 39 Radical addition to a double bond

Flow rate/μL/min	Acid/Pyridine/styrene / mol L^{-1}	Current / mA	Voltage/V	Addition product	Dimer yield /%
6	0.1/0.2/0.1	4	100	traces	3

Table 66 Flow cell E 4, radical addition to olefins, 0.1mol L^{-1} octanoic acid at 0.1KV

On the other hand the results (Table 67) showed that the addition of ethyl propiolate did not affect the dimerisation when electrolysed with octanoic acid under the above conditions which favour dimerisation. As apparent from the results the addition of ethyl propiolate **93** did not considerably change the radical formation, diffusion layer profile and ionic equilibrium at the surface of electrodes, and the radical generation and dimerisation were not suppressed altogether, and gave more dimer yield (47 % tetradecane **92**) compared to the addition product (not **94**) which was again of the polymeric nature and could not be identified.



Scheme 40 Radical addition to a triple bond

Flow rate/μL/min	Acid/pyridine/Ethyl propiolate/mmol	Current / mA	Voltage/V	Addition product	Dimer Yield/%
6	0.1/0.2/0.1	4	100	traces	47

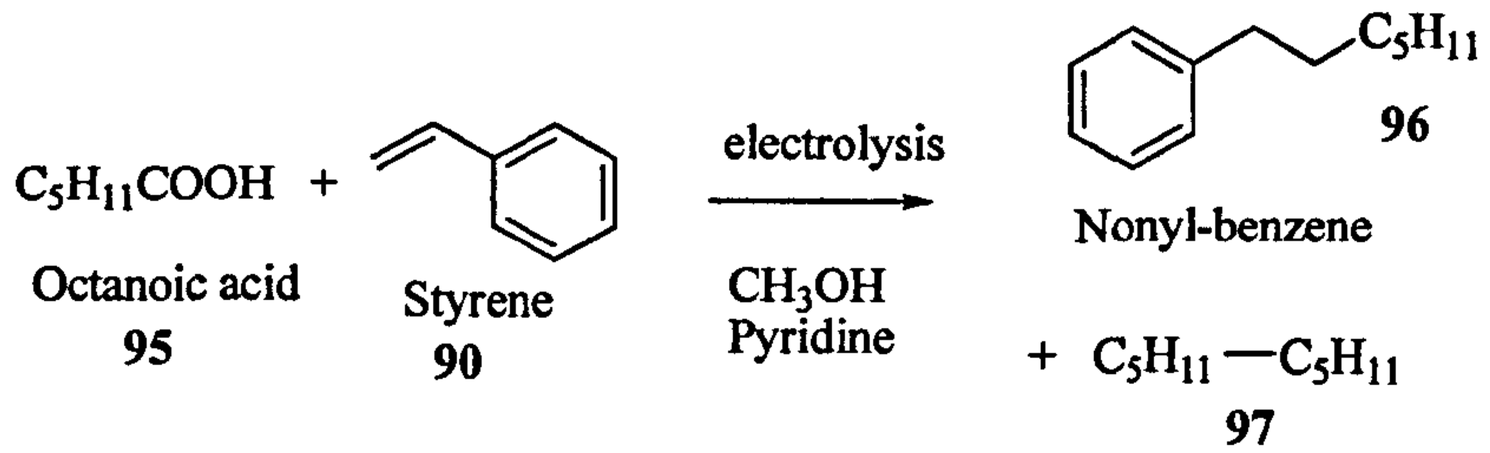
Table 67 Flow cell E 4, radical addition to a triple bond, 0.1mol L^{-1} octanoic acid at 0.1KV

The results suggested that the optimum conditions for dimerization of octanoic acid were not favourable for the addition of radicals to the double or triple bonds of styrene and ethylpropiolate respectively. The next set of results was obtained as an effort to investigate the effect of acid chain length on the addition of radicals to double or triple bond.

4.8.2 Addition of radicals to a double bond flow cell E 4 effect of chain length and voltage

In order to investigate the effect of chain length on the ease of radical addition to the double bond the electrolysis of hexanoic acid was conducted using flow cell E 4 under the optimum conditions of 0.1 mol L^{-1}hexanoic acid, 0.2 mol L^{-1}pyridine at 6 μ L/min. In addition the effect of voltage was also investigated. Results (Table 68) showed that although the dimer (decane **97**) was formed in a higher yield (67 %) at a higher voltage (150 Volts) however with no addition product (heptyl benzene). On the basis of these

results it was suggested that addition of pentyl radicals to the styrene **90** double bond (Scheme 41), was not favoured by the optimum conditions established so far for the dimerization of octanoic or hexanoic acid therefore could not necessarily suit the radical addition to a double or triple bond. The reaction mixture was analyzed by GC/MS method B and GC/FID method C and D.



Scheme 41 Radical addition to a double bond

Flow rate/μL /min	Acid/Pyridine/styrene /mol L^{-1}	Current / mA	Voltage/V	Addition product	Dimer Yield/%
6	0.1/0.2/0.1	3	50	none	58
6	0.1/0.2/0.1	5	100	none	64
6	0.1/0.2/0.1	5	150	none	67

Table 68 Flow cell E 4, radical addition to a double bond, 0.1mol L^{-1} hexanoic acid

From the above results it could be seen that flow cell E 4 giving the highest conversion for radical dimerization, however the optimum conditions for other reactions could be studied further using flow cell E 4. It was suggested that the above addition reactions should be investigated using parallel plate flow cell (the advantage of small inter electrode gap and bigger electrode surface area) which works at a lower voltage (20 Volts). The next section comprises of the results for the above reactions carried out in parallel plate cell F, using the same set of optimum conditions for the flow cell E 4, for octanoic acid dimerization.

4.8.3 Effect of pyridine on the addition of radicals to a double or triple bond flow cell F

The addition of radicals to a double (Scheme 41) or triple bond (Scheme 40) was investigated using parallel plate cell. Hence the advantage of parallel plate cell F working at a lower voltage was exploited to investigate the ability of this cell to generate radicals and add them to the double and triple bonds. To investigate this reaction a set of electrolysis reactions under optimum conditions of radical formation (0.1 mol $L^{-1}$of octanoic acid and 0.2 mol L^{-1} of pyridine) were carried out. The addition of alkyl radicals generated from hexanoic acid to the double bond of styrene (Table 69) and octanoic acid to the triple bond of ethylpropiolate (Table 70) respectively was investigated. The effect of pyridine could also be seen from these results, as there was comparatively low dimer yield for the experiments carried out in the absence of pyridine (14 % with styrene and 10 % with ethyl propiolate). The reaction mixture was analyzed by GC/MS method B and GC/FID method C and D.

Flow rate/μL/min	Acid/pyridine/styrene /mol L^{-1}	Current / mA	Voltage /V	Addition product	Dimer Yield/%
6	0.1/0.0/0.1	3	20	Traces	14
6	0.1/0.2/0.1	8	20	Traces	40

Table 69 Anodic addition of radicals to styrene, 0.1 mol L^{-1} hexanoic acid parallel plate cell F

Flow rate/μL/min	Acid/pyridine/ethyl propiolate / mol L^{-1}	Current / mA	Voltage/V	Addition product	Dimer Yield/%
6	0.1/0.0/0.1	2	20	traces	10
6	0.1/0.2/0.1	5	20	traces	43

Table 70 Anodic addition of radicals to ethyl propiolate 0.1 mol L^{-1} octanoic acid parallel plate cell F

4.9.0 Cross coupling reaction[1, 7]

In order to investigate the cross coupling reactions in flow cell E 4, for hexanoic acid 0.1 mol $L^{-1}$and octanoic acid 0.1 mol L^{-1} it was observed (Table 71), that the cross coupled product dodecane (39 %) was formed as three folds to the coupling product decane (13 %) of the acid with smaller chain (hexanoic acid). The selectivity of this reaction to give the coupling product was as expected and the two symmetrical dimers (tetradecane 24 % and decane 13 %) were also formed. The reaction mixture was analyzed by GC/MS method B, E and GC/FID method C and D. The formation of three higher alkanes in the reaction mixture made it difficult to separate the three products and the oily drops of the product made the electro active layer inactive and disturbed the diffusion layer.

Flow rate/uL/min	Voltage/V	Current/ mA	Dodecane/%	Tetradecane/%	Decane/%
6	50	3	39	24	13
6	100	7	39	24	13
6	150	6	48	30	15

Table 71 Cross coupling reaction between octanoic acid and hexanoic acid flow cell E 4

The effect of potential was also investigated (Table 71), and it was found to have a significant effect on dodecane and tetradecane yield and the selectivity of the reaction for the formation of decane was not affected much.

References

1. H. Lund, O. Hammerich, *Organic Electrochemistry*, Fourth Edition, 2001, NY, Marcel Dekker, Inc.
2. (a) S. D. Ross, and M. Finkelstein, *J. Org. Chem*, 1969, **34**, 2923. (b) N. V. Smirnova, O. A. Petrii, I. P. Beletskaya, E. G. Neganova, *Russian Journal of Electrochemistry*., 2001, **37** (9),893.
3. (a) Christopher A. Paddon ,Gareth J. Pritchard , Thies Thiemann , Frank Marken , *Electrochemistry Communications*., 2002, **4**, 825-831. (b) M. Kuppur , V. Hessel , H.Lowe ,W. Stark ,J. Kinkel , M. Michel , H. Schmidt-Traub ,*Electrochimica Acta*., 2003, **48** , 2889- 2896. (c) R. Horcajada, M. Okajima, S. Suga, J. Yoshida, *Chem. Commun*., 2005, 1303. (d) Ping He, Pual Watts, Frank Marken, Stephen J. Haswell, *Electrochemistry Communications*., 2005, **7**, 918.
4. P. T. Kissinger, W. R. Heineman, *Laboratory Techniques in Electroanalytical Chemistry*, Second Edition, 2003, NY, Marcel Dekker, Inc.
5. J. D. Wadhawan, F. Marken, R. G. Compton, S. D. Bull, S. G. Davies, *Chem. Commun*., 2001, 87.
6. (a) Johann Hiebl, Michael Blanka, Andras Guttman, Hermann Kollmann, Kornelia Leitner, Gunter Mayrhofer, Franz Rovenszky and Karin Winnkler, *Tetrahedron*., 1998, **54**, 2059. (b) R. P. Linstead, B. R. Shephard, B. C. L. Weedon, *J. Chem. Soc*., 1951, **1130**, 2854. (c) Fichter and Schmidt, *Helv. Chim. Acta*., 1920, **3**, 704.
7. H. Schafer, A. Alazrak, *Angew. Chem. Int. Ed. Engl*., 1968, **7**, 474.
8. R. P. Linstead, B. R. Shephard, B. C. L. Weedon; *J. chem. Soc*., 1951, **5**, 2854.

CHAPTER 5: CONCLUSION

5.1.0 Conclusion

The results from different flow cell designs show that for each cell there is a different set of optimum conditions for a specific reaction. The optimum conditions for a particular reaction in one cell do not necessarily favour the same reaction in another cell, and are directly affected by the factors such as flow rates, acid to base concentrations, surface area inter electrode distance and arrangement of electrodes. There are still some important challenges to be addressed in order to improve the flow system to design an electrochemical micro reactor for organic synthesis, where a new type of process could be realized, by omitting the conductive salt hence simplifying the product separation and reducing the operational costs. The feasibility of this approach seems likely from the results obtained in the study, as the selectivity of the reaction increases without a conductive salt, though the product yield drops. In contrast, a temperature rise in salt free process brings about more conversion, by means of which selectivity is maintained, however very high temperatures also halt the process.

The current efficiency, which is very high within the electrolyte, needs to be improved in the above conditions, by decreasing the resistance. Further investigations are required to obtain a control over certain factors, such as an optimum flow rate, current density, current efficiency, and concentrations of both, the acid and pyridine. Perhaps most important of all is the use of an electrolytic base to improve the current efficiency, to carryout electrolytic reaction more efficiently without blocking the channels.

While competitive designs like flow cell F (parallel plate microgap flow cell) usually work at lower voltages (20 V) showing a higher current efficiency due to less resistance (smaller electrode gap), flow cell E 4 shows reduced efficiency and produces almost similar product yield at voltages five folds higher (100 V) as compared to flow cell F. In addition it was also observed, that in E type glass flow cells with electrodes further apart (flow cell E 2) although allowed less time for stabilization but resulted in comparatively less conversion even at higher voltages (100 V), showing the effect of inter electrode distance in terms of resistance offered by the electrolyte free system. The product yield was increased by reducing the inter

electrode gap with increased surface area in flow cell E 4, hence reducing the resistance offered by an electrolyte free system to improve the product yield.

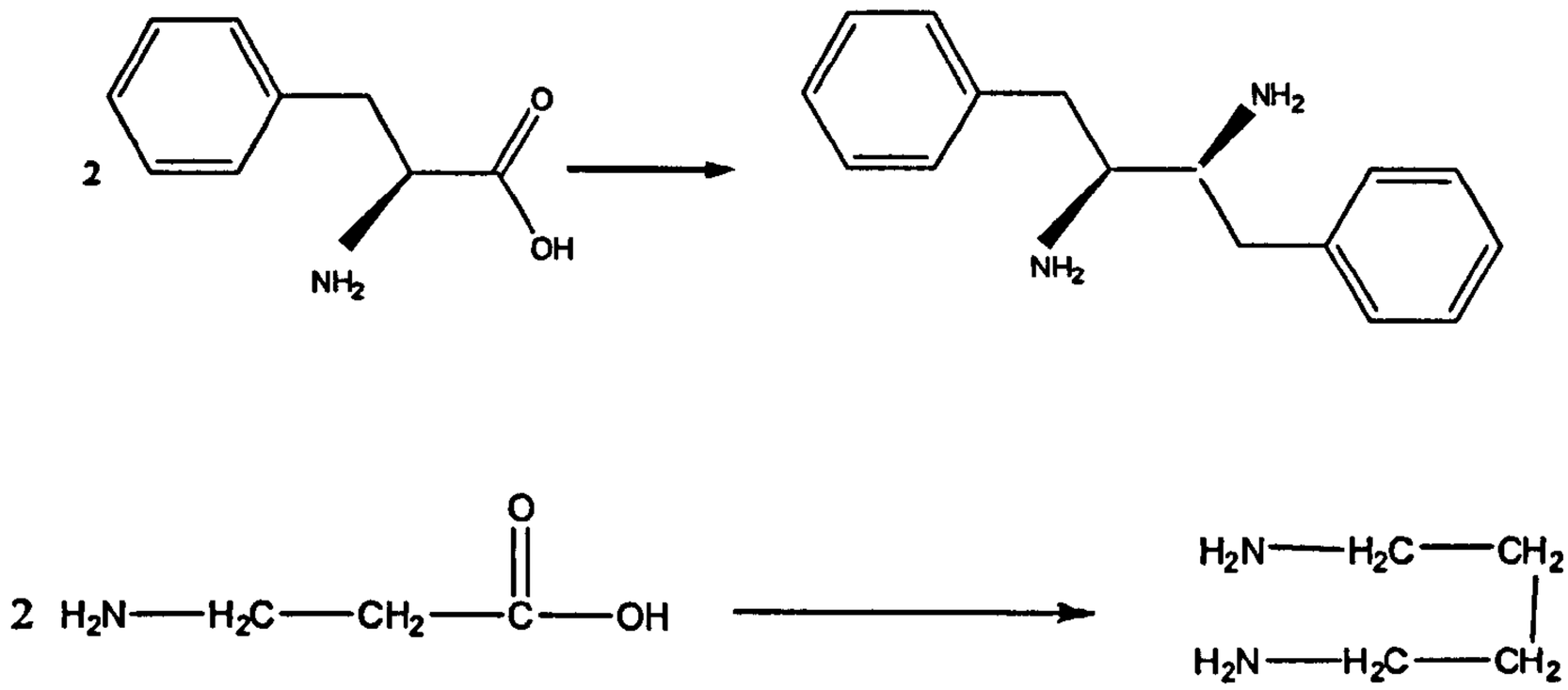
However the electrode surface in both cells deteriorates during prolonged use with higher concentrations of reacting species. A cleaning method for the type of cell E 4, once established, could solve the problem for prolonged use with even higher concentrations of reacting species. In addition, it was found that apart from the flow rates, other factors such as composition and pH of the acid solution to be electrolysed, the electrode materials, quality and the surface properties of the electrodes in the flow cell were also decisive factors for a consistent performance. As carbon dioxide and hydrogen was produced and needed to be removed from the surface of the electrodes, if gas bubbles (carbon dioxide and hydrogen) cannot be removed efficiently from the electrode surface, they remain covering the surface area and hence decrease the effective mass transport, also resulting in flow blockage particularly in channels of small dimensions, making a laminar flow into turbulent flow.

When the addition reactions were carried out in parallel plate cell F, using the same set of optimum conditions for the flow cell E 4, for octanoic acid dimerization, although radicals were generated from styrene (giving traces of addition products) and from octanoic acid (giving dimer), but successful addition of radicals from the acid to a double or triple bond does not seem to have occurred in both the cases. It was also seen for the Kolbe electrolysis of aromatic acids or olefins that the ease with which dimerisation occurs for the acids with alkyl chains does not exist for aromatic acids/olefins. The said reaction might occur under another set of conditions which can be achieved by changing the solvent or electrode material in a flow cell set up.

CHAPTER 6: FUTURE WORK

6.1.0 Future Work

The work presented in this thesis is based mainly on the electrolyte free Kolbe electrolysis of aliphatic nonsubstituted acids and substituted amino acids in flow through microreactors. Kolbe electrolysis is one of the earliest reactions in the organic chemistry but has rarely been conducted without an electrolyte, however as a result of extensive study over the years this reaction has found numerous synthetic applications. Therefore it seems worthwhile to extend this method of dimerization of organic compounds to a range of functionally substituted carboxylic acids using flow through electrochemical microreactors. In order to estimate the possibilities of optimizing electrolyte free Kolbe synthesis for an important group of reactants, specifically the amino acids. The reaction can be exploited in the electrolyte free, microreactor environment and formulate the possibilities and limitations of electrosynthesis of corresponding 1,2- and 1,4-diamines *via* reactions of the type given below.[1]



Scheme Kolbe dimerization of *β* alanine to putrescine

Another application of mixed Kolbe electrolysis using the electrochemical microreactor in an electrolyte free environment is the selective generation of molecules with two chiral centres and bearing up to four different protecting groups. Orthogonally protected 2,5-diaminoadipic, 2,6-diaminopimelic, and 2,7-diaminosuberic acid derivatives bearing up to four different protecting groups are prepared in one step by mixed Kolbe electrolysis.[2] This one step synthesis provides versatile starting materials of medicinal value. The diamino dicarboxylic acids having two amino and two carboxylic functionalities provide unique building blocks for combinatorial chemistry.

References

1. J. Hiebl , M. Blanka, A. Guttman, H. Kollmann, K. Leitner, G. Mayrhofer, F. Rovenszky and K. Winkler, *Tetrahedron*, 1998, **54**, 2059.

2. N. V. Smirnova, O. A. Petrii, I. P. Beletskaya, E. G. Neganova, *Russian Journal of Electrochemistry*, 2001, **37**, 9, 893.