Chapter - III
EXPERIMENTAL

3.1 Introduction

Many chemists not familiar with electrochemistry are put off by the technique because of a feeling that it is complicated and requires the use of specialised equipment. This feeling is exacerbated by summaries of electrochemical reactions that describe a variety of reaction setups and electrochemical equipment that are not common to most synthetic laboratories. However, utilising an electrochemical reaction for synthesis is not necessarily difficult. With even a basic understanding of electrochemistry, many reaction setups can be simplified so that a transformation of interest can be attempted using a simple battery as a power supply and glassware common to any synthetic laboratory [193]. In most cases, an understanding of even this very simplistic view of electrochemistry is sufficient for beginning to successfully pursue the reactions.
To begin electrochemical reactions, two electrodes are to be inserted into the solution, a voltage is applied to across the gap between the electrodes. This initiates two separate processes. At one electrode (the anode), molecules are oxidised leading to a transfer of electrons from the reaction mixture to the electrode. At the other electrode (the cathode), molecules are reduced leading to a transfer of electrons from the electrode to the reaction mixture. The net result of these two processes is the transfer of electrons from cathode to anode. This electron transfer completes the circuit and allows current to flow through the cell.

Electrochemical reaction can be controlled in a way 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 oxidising the species in solution with the lowest oxidation potential. The potential is stabilised and species in solution is oxidised at a rate consistent with the current flow required by the cell. This process repeats until the current is turned off. At the cathode, an equivalent reduction takes place. The advantage of a constant current reaction is that the reaction setup is very simple and very common.

Electrochemistry deals with electron transfer processes, the structure of interfaces and the process at electrodes. Electroanalytical techniques play an important role in almost all fields of activity in electrochemistry.

The classes of techniques that study the solution composition through current-potential relationship are termed as “electrochemical techniques”. Electrochemical
techniques can be used to illustrate mass transport (diffusion, convection, migration), thermodynamics (Nernst relationship), kinetics (homogeneous and heterogeneous rates) and surface chemistry (adsorption and chemically modified electrodes). The applicability of electrochemical techniques is diverse. There are numerous different kinds of advanced electrochemical techniques and each technique has its own advantages.

Polarography has contributed to the understanding of processes involved in the electrolysis of organic substances more than any other method. It can be used in the determination of reaction mechanisms, in studies of equilibrium and rate constants, in search of optimal conditions for some preparative reactions, in studies of composition of organic compounds and in correlation of structure with polarographic data.

Among the various electrochemical methods of analysis, the name polarography is associated with the names of Heyrovsky and Shikata. Heyrovsky introduced the polarographic technique in 1922 [194] and the latter has helped in the introduction of automatic recording of polarogram on a photographic plate [195]. Kolthoff and Lattpen [196] advocated a more descriptive general name voltammetry to indicate that the voltage and current are the two quantities measured, in which the former one can provide qualitative information on the nature of the electroactive substance and the latter one is indication of its concentration.

In the present investigation, electrochemical hydrogenation and carboxylation were carried out using Potentiostat in an undivided cell. Cyclic voltammetric determination has been carried out to investigate the mechanism for α-aryl acrylic acids.
and α-methyl benzyl bromides. Differential pulse polarography is used for the determination of bond cleavage and analysis of α-aryl acrylic acids and α-methyl benzyl bromides. For identification of the products, Mel-temp apparatus is used for the determination of melting points. $^1\text{H NMR}$ is recorded on a Varian EM-360 spectrometer in CDCl$_3$ in the presence of SiMe$_4$ as an internal standard and IR spectra are obtained with a Perkin-Elmer 1600 spectrophotometer. The precursors of non-steroidal anti-inflammatory drugs are prepared according to the published procedure.

3.2 General electrolysis procedure

For the preparative electrolysis of hydrogenation, the electrochemical cell of capacity 100 ml volume was equipped with Raney nickel cathode (3x4 cm$^2$) and lead anode (3x4 cm$^2$). The two electrodes were connected to a DC power supply. The electrolyses measurements for cell voltage were carried out by using a potentiostat (Model. PS-603, Techno Potentiostat, Lucknow, India) in an undivided cell.

The electrochemical hydrogenation was carried only by dissolving the starting compound in ethanol containing 10% sulphuric acid at a constant current density of 100 A/m$^2$. The cell was kept under an atmosphere of nitrogen and the contents were stirred at 50 °C. The extent of the reaction was followed by regular sampling by thin layer chromatography. At the end of the reaction, the electrolyte solution was diluted with water, the product was extracted into ether, washed with water, and dried over magnesium sulphate and the evaporation of solvents gave the final product. $^1\text{HNMR}$, IR, and melting point determinations were used in the identification of the product.
For the preparative electrolysis of carboxylation, the electrochemical cell of capacity 100 ml volume was equipped with a platinum cathode (20 cm²) and magnesium anode (20 cm²) arranged with the carbon dioxide inlet outlet tubes. The two electrodes were separated by 1 cm and connected to a DC power supply. The electrolyses were carried out using potentiostat (Model PS-603, Techno Potentiostat, Lucknow, India) in an undivided cell.

The cell was charged with solvent (DMF) containing the supporting electrolyte (Bu₄NI) and the starting halide was added to the cell. Then, the cell was immersed in cold water to dissipate the heat evolved by the electrolysis and to keep the temperature near 5 °C. Before electrolysis, the O₂ in the system was removed by passing N₂ gas through the solution. After that, the stirred mixture was saturated by bubbling CO₂. In this saturated state, the system was electrolysed by supplying regulated dc power supply at 10 mA/cm² until 2 F/mol had been passed through the cell. Usual workup of the electrolyzed solution afforded desired product. ¹H NMR, IR and its melting point determination were used in the identification of the product.

3.3 Cyclic Voltammetry (CV)

Cyclic voltammetry is one of the modern electrochemical techniques, which provides the means to examine the nature of an electrochemical reaction in detail. From the investigation of an electrochemical reaction, one obtains information which not only provides a firmer basis for control of the reaction but also opens the door to studies of reactive intermediates and the fundamental chemistry that underlies the reaction system of interest.
The technique was apparently first practiced by Sevcik [197] in which an isosceles-triangular waveform was employed. An excellent series of contributions by Ceramak [198,199] and Kemula and co-workers [200-204] employing the hanging mercury drop electrode pointed the way to studies of electrode mechanism. Adams [205] gave a good account of this technique. Neurenberg [206,207] reviewed the triangular wave method employing oscilloscopic recording. Koufman et al. [208] described the triangular wave generation and its application at mercury electrode. Sham and co-workers [209-212] developed the theory of this technique. Some authors have developed new methods in cyclic voltammetry in recent years [213,214]. Jayarama Reddy et al. [215-256] used cyclic voltammetry in association with other electroanalytical techniques very extensively in the determination of electrochemical reaction mechanisms of many organic substrates.

In the present study, cyclic voltammetry is used to elucidate the mechanism for the cathodic reaction of α-aryl acrylic acids and α-methyl benzyl bromides in presence of sulphuric acid and carbon dioxide by taking α-phenyl propenoic acid and α-phenyl ethyl bromide as model compounds for synthesis of non-steroidal anti-inflammatory drugs.

3.4 Differential Pulse Polarography (DPP)

Differential pulse polarography (DPP) was originally introduced by Barker and Gardiner [257] and Bond [258] and Keller [259] developed the theory. This technique has been widely used for the study of reversible reactions [260-263]. Several scientists...
have studied widely analytical performance of differential pulse polarography in many reactions [264-283]

Unlike in direct current polarography, the potential is applied periodically during the short time intervals in pulse polarography. There are two different ways of applying the potential to the working electrode. A series of pulses, each of greater amplitude than the previous one by the same amount is applied to the working electrode and the resulting potential - time curve is a linear potential scan and the technique gets the name normal pulse polarography. If pulses of constant amplitude are superimposed on a steadily increasing d.c voltage, the technique is referred to as differential pulse polarography.

Differential pulse polarographic technique has been used in several analytical applications in organic and inorganic chemistry. This technique was successfully used for the determination of proguanil [284], analysis of corticosteroids [285], cephalosporins [286] and in the reduction behaviour of nitrofurantoin, chloramphenicol and related compounds [287]. Jayarama Reddy et al [232, 236-239, 243, 251, 288-299] studied reduction behaviour and analysis of many kinds of pesticides, drugs and pharmaceuticals including trace metal analysis employing differential pulse polarography.

The purpose of differential pulse polarography used in this study is for the determination of bond cleavage and also to develop analytical procedure for the determination of α-aryl acrylic acids and α-methyl benzyl bromides present in the electrolyte solution during the electrosynthesis of NSAIDs.
3.5 Electrolytic cell

Electrochemical determination is carried out using Metrohm Unit 757VA Computrace Metrohm Herisau, Switzerland, supplied the Teflon coated electrolytic cell used in the investigation. The cell consisted of three electrodes: (1) the working electrode whose potential is controlled at desired values, (2) the reference electrode with reference to which the potential of the working electrode is measured, and (3) the counter or auxiliary electrode which completed the electrolytic circuit. Nearly 10-15 ml of the electrolytic solution was sufficient to make the electrodes dip in the solution. The cell was designed in such a way that it has the provision for inserting working electrode, reference electrode, an auxiliary electrode and an inlet and outlet for passing nitrogen gas.

The dropping mercury electrode (DME) was used as the working electrode for DPP and the hanging mercury drop electrode (HMDE) for CV with an area of 0.15 mm² respectively. Double distilled mercury was used for the working electrode, Ag/AgCl as reference electrode and Pt electrode as an auxiliary electrode in both techniques.

3.6 Experimental procedure

The test solution was prepared by dissolving required quantity of the substance under investigation with the solvent making up with supporting electrolyte to get the desired concentration. Nearly 10-15 ml of the solution was taken into the electrolytic cell and deoxygenated by passing nitrogen gas for about 15 min. A test run with blank was taken to confirm that there was no reducible species in the supporting electrolyte.
3.7 PREPARATION OF PRECURSORS OF NON-Steroidal ANTI-INFLAMMATORY DRUGS

3.7.1 2-(4-Chlorophenyl)-α-methyl-5-benzoxazole ethene-1-oic acid (precursor of benoxaprofen) [300]

40 g of 2-amino-3-hydroxyphenyl propionic acid in 20 ml of ether was added to the 50 g of Benzoyl chloride and refluxed for 3 hrs. After refluxion, it was hydrolysed by successive addition of 50 ml of 15 % aq sodium hydroxide at 0°C. The hydrolysed solution was heated with 150 ml of concentrated sulphuric acid at 170°C. At the end of reaction, this solution was diluted with water, the product was extracted into ether, dried over magnesium sulphate and the evaporation of solvents gave 2-(4-chlorophenyl)-α-methyl-5-benzoxazole ethene-1-oic acid.

3.7.2 6-Chloro-α-methyl-9H-carbazole-2-ethene-1-oic acid (precursor of carprofen) [301]

The 50 ml of ethanol was added the drop wise to the mixture of 45 g of carbazole propionyl chloride and 50 g of chloranil and the contents were stirred at room temperature for 7 hrs, then heated with 150 ml of concentrated sulphuric acid at 145°C. After completion of the reaction, the resulting solution was diluted with water, the residue was distilled to give 6-chloro-α-methyl-9H-carbazole-2-ethene-1-oic acid.

3.7.3 2-(5H-[1]benzopyrino[2,3-b]pyridin-7-yl)propene-1-oic acid (precursor of pranoprofen) [302]

A three-necked round-bottomed flask fitted with a mechanical stirrer was charged with 200 ml of dry nitrobenzene followed by 13 g of anhydrous aluminium.
chloride. The stirrer was started after adding of 6.0 g of 2-phenoxy nicotinic acid in the presence of phosphoric acid. One neck of the flask was fitted a thermometer with the bulb in the solution and the third neck of the flask was fitted with a 50 ml pressure-equalising addition funnel. After the addition of phosphoric acid, the flask was immersed in ice water while stirring was continued for 2 h and the mixture was allowed to stand at room temperature for 12 h.

The reaction mixture was cooled in an ice bath and poured with manual stirring into a 600 ml beaker containing 200 g of crushed ice, then treated with 100 ml of concentrated sulphuric acid. The resulting two-phase mixture was transferred to a separator funnel containing 50 ml of chloroform. The chloroform-nitrobenzene layer was separated and washed with three 100 ml portions of water. The organic layer was transferred to a round-bottomed flask, the flask was heated on oil bath at about 120 °C. After 3 hrs, the distillation was stopped and the residue in the flask was allowed to cool. Residual water in the flask was decanted from the solid organic material, extracted with chloroform and dried over magnesium sulfate to give the 2-(5H-[1] benzopyrino[2,3-b]pyridin-7-y1)propene-1-oic acid.

3.7.4 2-(7-Methoxy-10-methyl-2-phenothiszinyl)propene-1-oic acid (precursor of protizinic acid) [303]

A mixture of 6.5 g of acetylphenothazine and 4.2 g of methyl iodide was heated at 140-145 °C for 50 min in 150 ml ether. The resulting compound was triturated with water (50 ml), washed with 10% sodium hydroxide (50 ml) and filtered. The suspension of phenothazine acetic acid was heated with concentrated sulphuric acid at 170-175 °C and
then refluxed for 10 hrs. The precipitate was collected by filtration, the filtrate was washed with water and dried over magnesium sulphate to give 2-(7-methoxy-10-methyl-2-phenothiazinyl) propene-1-oic acid.

3.7.5 2-(2-Fluoro-4-biphenyl) propene-1-oic acid (precursor of flurbiprofen) [304]

The solution of 40 g of fluorobenzene and 50 g of phenyl propionic acid in 150 ml carbon disulphide and it was kept under stirring at room temperature for 7 hrs and poured upon crushed ice. The product was extracted with ether and it was dried over calcium chloride and evaporates of the solution gave 4-fluorobenzene propionic acid.

4-fluorobenzene propionic acid was diluted with water and hydrolysed by using 50 ml of aqueous sodium hydroxide then refluxed for 3 hrs. After refluxion, the solution was transferred into a separator funnel and heated with concentrated sulphuric acid at 140-145° C. The residue was distilled to give 2-(2-fluoro-4-biphenyl) propene-1-oic acid.

3.7.6 3-Chloro-4-(2,5-dihydro-1H-pyrrol-1-yl)-α-methyl benzyl bromide (precursor of pirprofen) [305]

A three-necked round-bottomed flask was fitted with a dropping funnel and reflux condenser. The flask was placed 64 g of 1,3-dichloro-4-nitrobenzene and 54 g of ethyl acetate in 100 ml of sodium hydride and stirred for 7 hrs. After stirring 60 g of 4-amino-phenylpropionic ester was added then refluxes gently with sodium hydride.

The refluxed solution was diluted with water and adding the 1,4-dibromobutene in the presence of potassium hydroxide and concentrated sulphuric acid. At the end of reaction, the solution was diluted with water and the product was extracted into ether,
washed with water, dried over magnesium sulphate and evaporation of the solvents gave 3-chloro-4-(2,5-dihydro-1H-pyrrol-1-yl)-α-methyl benzyl bromide

3.7.7 2-(4-Fluorophenyl)-α-methyl-5-benzoxazole bromide (precursor of flunoxaprofen) [306]

The precursor of flunoxaprofen was prepared from 5.4 g of 4-fluorobenzene by the addition of 6.2 g of α-methyl-5-benzoxazole bromide in dry ether. This solution was refluxed for 2 hrs and 150 ml aq sodium hydroxide was added. The solution was heated with 100 ml of concentrated sulphuric acid at 170 °C and the residue was distilled to give 2-(4-fluorophenyl)-α-methyl-5-benzoxazole bromide

3.7.8 2-Isopropyl-α-methylene-5-indan acetic acid (precursor of isoprofen) [307]

To a stirred solution of sodium ethoxide (EtONa) in ethyl alcohol was added to the 4.4 g of methyl iodide and 6.2 g of indan-5-acetic acid and stirring continued for 30 min. This mixture was refluxed for 3 hrs after adding the 2.5 N sodium hydroxide in ethyl alcohol. This solution was diluted with water and the neutral product was taken in ether. The aqueous layer was acidified with diluted hydrochloric acid and then heated with concentrated sulphuric acid at 140 °C. After heating, recrystallisation of the solution from hexane afforded 2-isopropyl-α-methylene-5-indan acetic acid.