ELECTROCHEMICAL REDUCTION
OF AMIDES AND C=C BONDS

A DISSERTATION FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
FROM IMPERIAL COLLEGE LONDON

BY
KATHRYN RIX

MARCH 2013

DEPARTMENT OF CHEMISTRY
IMPERIAL COLLEGE LONDON
DECLARATION

I confirm that this report is my own work and where reference is made to other research this is referenced in text.
Copyright Notice

Imperial College of Science, Technology and Medicine

Department of Chemistry

Electrochemical Reduction of Amides and C=C bonds

‘The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution Non-Commercial No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the licence terms of this work’

© 2013 Kathryn Rix

k.rix08@imperial.ac.uk

Published by:
Kathryn Rix
Department of Chemistry
Imperial College London
South Kensington Campus,
London,
SW7 2AZ
UK

www.imperial.ac.uk
Acknowledgements

Firstly I would like to thank my principal supervisor, Dr Mimi Hii, for her continued support, enthusiasm and patience throughout my PhD. She has not only advised me but provided a wealth of ideas and suggestions to help make the inter-disciplinary project a success, particularly providing expertise in organic chemistry.

I would like express my gratitude to my supervisor Professor Geoff Kelsall for his excellent supervision and guidance throughout the project. I am particularly grateful to him for providing support in the electrochemical aspects of the project.

I would also like to thank my supervisor Dr Klaus Helgardt for his encouragement and direction during my PhD. I am especially thankful for all advice regarding reaction engineering and for all guidance in the lab. I have developed expertise in GC-MS maintenance, thank you Klaus!

I am very grateful to Dr Barry Dillon, my Industrial Supervisor from Pfizer. Barry provided endless optimism for the project and made my time at Pfizer a challenging and enjoyable experience. I would also like to thank Dr Alan Happe from Pfizer for providing a fresh perspective on the project and all of his advice relating to the project. Thanks go to all the members of the Pharmacat Consortium for providing feedback on my project and excellent suggestions. I would like to acknowledge Pfizer, GSK, Astra Zeneca and the EPSRC for financial support.

I would like to thank Ms Patricia Carry for her assistance in the Chemical Engineering Analytical Laboratory and Paul Crudge in the Chemical Engineering Workshop for fabricating parts of my reactor and for training in SolidWorks.

Thanks goes to all members, past and present, of the Hii, Kelsall and Hellgardt groups for their friendship and assistance. In particular I would like to thank Dr Steven Dennison, Dr Candice Palmer, Melanie, Umi, Lisa, Chung-yee, Chin and Palang for some good times in the lab.

I thank my parents and my brother Steven for their love, support and encouragement throughout the PhD and my good friends Catriona Gelder and Rebecca Wilson Scott. Thanks also go to the Buchard family.
Special thanks go to my partner Antoine Buchard who has always believed in me and provided much needed reassurance during the PhD. Thank you for putting up with me throughout the seemingly never ending writing up period, dragging me to Paris and putting a roof over my head.
Abstract

Reduction of amides to amines is an important transformation in organic synthesis, which has been identified as among the ‘top ten most important reactions’ by a consortium of pharmaceutical companies. Presently achieved by hydride or borane reagents, it is both hazardous and generates excessive volumes of effluent and waste. Similarly, chemoselective reduction of C=C bonds, particularly conjugated double bonds, also presents a significant challenge in organic synthesis.

Electrochemical synthesis using a flow reactor offers an environmentally benign and energy efficient technology for producing key intermediates in the synthesis of candidate drug molecules; its benefits include: improved control of reaction parameters, reproducibility and scalability.

The first part of the thesis describes a study on the kinetics of the selective electrochemical reduction of C=C maleimide derivatives using a rotating disc electrode system. The resulting data was used to define the reactor’s operating conditions. Subsequently, the chemoselective and stereoselective reduction of maleimide derivatives were carried out in the electrochemical flow reactor with a graphite felt cathode and the rate of reactant depletion, monitored by UV-visible spectroscopy.

In the second part, amide reduction was studied in an electrochemical flow reactor using vitreous carbon and boron-doped diamond cathodes. The reduction of \( \text{N,N-dimethylbenzamide} \) produced the corresponding amine, benzaldehyde and benzyl alcohol. The selectivity of the reaction was investigated as a function of reaction conditions, and a mechanism for the reduction was proposed. Subsequently, a range of functionalised amides were subjected to electrochemical reduction under optimised conditions, to further assess the scope of the methodology as a tool for organic synthesis. The influence of electron donating and withdrawing groups incorporated in to \( \text{N-benzoilpyrroldine} \) derivatives were investigated, as well as the pattern of substitution on the amides. The result revealed observable trends in the product distribution between the corresponding amine, benzaldehyde and benzyl alcohol compounds.
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8</td>
<td>Electrochemical Reduction of C=C Bonds</td>
<td>62</td>
</tr>
<tr>
<td>1.9</td>
<td>Research Objectives</td>
<td>69</td>
</tr>
<tr>
<td>1.10</td>
<td>Thesis Structure</td>
<td>69</td>
</tr>
<tr>
<td><strong>Chapter 2</strong></td>
<td><strong>Principles of Electrochemical Systems</strong></td>
<td>71</td>
</tr>
<tr>
<td>2.1</td>
<td>Charge-Transfer Controlled Electrochemical Reactions</td>
<td>71</td>
</tr>
<tr>
<td>2.2</td>
<td>Transport Processes in Electrochemical Systems</td>
<td>71</td>
</tr>
<tr>
<td>2.3</td>
<td>Electrochemical Thermodynamics</td>
<td>72</td>
</tr>
<tr>
<td>2.4</td>
<td>Electrochemical Kinetics</td>
<td>74</td>
</tr>
<tr>
<td>2.5</td>
<td>Electrochemical Reaction Coupled to Mass Transport</td>
<td>76</td>
</tr>
<tr>
<td>2.6</td>
<td>Energy Efficiencies of Electrochemical Processes</td>
<td>78</td>
</tr>
<tr>
<td>2.7</td>
<td>Rotating Disc Electrode</td>
<td>80</td>
</tr>
<tr>
<td>2.8</td>
<td>Chapter Summary</td>
<td>81</td>
</tr>
<tr>
<td><strong>Chapter 3</strong></td>
<td><strong>Experimental Methodology</strong></td>
<td>82</td>
</tr>
<tr>
<td>3.1</td>
<td>Rotating Disc Electrode Experiments</td>
<td>82</td>
</tr>
<tr>
<td>3.2</td>
<td>Batch Electrolysis Experiments</td>
<td>83</td>
</tr>
<tr>
<td>3.3</td>
<td>Electrochemical Reactor Experiments</td>
<td>84</td>
</tr>
<tr>
<td>3.3.1</td>
<td>Reactor Modifications</td>
<td>84</td>
</tr>
<tr>
<td>3.3.2</td>
<td>Graphite Felt Electrode</td>
<td>86</td>
</tr>
<tr>
<td>3.3.3</td>
<td>Reactor Operation Conditions</td>
<td>87</td>
</tr>
<tr>
<td>3.4</td>
<td>Electrode materials: Boron Doped Diamond</td>
<td>89</td>
</tr>
<tr>
<td>3.5</td>
<td>Chapter Summary</td>
<td>90</td>
</tr>
<tr>
<td><strong>Chapter 4</strong></td>
<td><strong>Reduction of Maleimide</strong></td>
<td>91</td>
</tr>
<tr>
<td>4.1</td>
<td>Maleimide Reduction Kinetics at a Rotating Disc Electrode</td>
<td>91</td>
</tr>
<tr>
<td>4.1.1</td>
<td>Mechanism of Maleimide Reduction</td>
<td>103</td>
</tr>
<tr>
<td>4.2</td>
<td>Batch Reactor Investigations</td>
<td>104</td>
</tr>
<tr>
<td>4.3</td>
<td>Maleimide Reduction in Electrochemical Flow-through Reactor</td>
<td>106</td>
</tr>
<tr>
<td>4.3.1</td>
<td>Effect of Volumetric Surface Area</td>
<td>107</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
<td>Page</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>4.3.2</td>
<td>Effect of Flow Rate</td>
<td>113</td>
</tr>
<tr>
<td>4.3.3</td>
<td>Effect of Temperature</td>
<td>116</td>
</tr>
<tr>
<td>4.3.4</td>
<td>Effect of concentration</td>
<td>117</td>
</tr>
<tr>
<td>4.3.5</td>
<td>Effect of pH</td>
<td>119</td>
</tr>
<tr>
<td>4.4</td>
<td>Chapter Summary</td>
<td>121</td>
</tr>
<tr>
<td>5.1</td>
<td>Reduction of C=C bonds</td>
<td>123</td>
</tr>
<tr>
<td>5.1.1</td>
<td>Chemoselective C=C Bond Reduction</td>
<td>123</td>
</tr>
<tr>
<td>5.1.2</td>
<td>Kinetic Investigation with a Rotating Disc Electrode</td>
<td>124</td>
</tr>
<tr>
<td>5.2</td>
<td>Stereoselective C=C Bond Reduction</td>
<td>137</td>
</tr>
<tr>
<td>5.2.1</td>
<td>Kinetic Investigations with a Rotating Disc Electrode</td>
<td>139</td>
</tr>
<tr>
<td>5.2.2</td>
<td>Kinetic Investigations with the Flow-through Electrochemical Reactor</td>
<td>140</td>
</tr>
<tr>
<td>5.3</td>
<td>Chapter Summary</td>
<td>144</td>
</tr>
<tr>
<td>6.1</td>
<td>Reduction of C=C bonds</td>
<td>145</td>
</tr>
<tr>
<td>6.2</td>
<td>N, N-Dimethylbenzamide Reduction</td>
<td>145</td>
</tr>
<tr>
<td>6.2.1</td>
<td>Cyclic Voltammetry Experiments</td>
<td>145</td>
</tr>
<tr>
<td>6.2.2</td>
<td>Chronopotentiometry Results</td>
<td>147</td>
</tr>
<tr>
<td>6.2.3</td>
<td>Mechanism of N,N-dimethylbenzamide Reduction</td>
<td>149</td>
</tr>
<tr>
<td>6.2.4</td>
<td>Effects of Applied Current Density and Cathode Material</td>
<td>151</td>
</tr>
<tr>
<td>6.2.5</td>
<td>Effect of Temperature</td>
<td>153</td>
</tr>
<tr>
<td>6.2.6</td>
<td>Effect of Flow Rate</td>
<td>154</td>
</tr>
<tr>
<td>6.2.7</td>
<td>Effect of pH</td>
<td>156</td>
</tr>
<tr>
<td>6.2.8</td>
<td>On-line Spectroscopic Analysis</td>
<td>157</td>
</tr>
<tr>
<td>6.3</td>
<td>Chronoamperometry Experiments</td>
<td>158</td>
</tr>
<tr>
<td>6.3.1</td>
<td>Effect of Applied Potential</td>
<td>158</td>
</tr>
<tr>
<td>6.3.2</td>
<td>Effect of Temperature</td>
<td>161</td>
</tr>
<tr>
<td>6.3.3</td>
<td>Effect of pH</td>
<td>161</td>
</tr>
<tr>
<td>6.3.4</td>
<td>Effect of Volumetric Surface Area</td>
<td>162</td>
</tr>
</tbody>
</table>
6.3.5 Effect of Benzyl Alcohol ................................................................. 162
6.3.6 Reduction of Benzaldehyde ............................................................ 163
6.3.7 Effect of Solvent ........................................................................... 165
6.4 Reduction of Primary, Secondary and Tertiary benzamide derivatives .... 170
6.5 Chapter Summary ............................................................................. 173

**Chapter 7  Reduction of Tertiary Amides .............................................. 175**

7.1 Reduction of Benzamide Derivatives ............................................... 176
7.1.1 Electron-withdrawing and -donating Substituents ......................... 177
7.1.2 Aliphatic Substituents ................................................................. 182
7.2 Reduction of Additional Tertiary Amides .......................................... 185
7.3 Reduction of a Complex Amide ....................................................... 188
7.4 Chapter Summary ............................................................................. 189

**Chapter 8  Conclusions and Recommendations .................................... 191**

8.1 Chapter Conclusions ......................................................................... 191
8.1.1 Reduction of Maleimide ............................................................... 191
8.1.2 Reduction of C=C Bonds ............................................................. 192
8.1.3 N,N-Dimethylbenzamide Reduction ........................................... 193
8.1.4 Reduction of Tertiary Amides ..................................................... 193
8.2 Contribution of this Thesis .............................................................. 194
8.3 Recommendations ............................................................................ 194

**References .......................................................................................... 198**

**Appendix 1 Organic Synthesis ............................................................... 204**

General Remarks .................................................................................. 204
Compounds used in Chapter 5 ............................................................ 205
Compounds used in Chapter 7 ............................................................ 206

**Appendix 2 Characterisation of Reduction Products ............................. 211**

**Appendix 3 Parameters ...................................................................... 215**
List of Figures

Figure 1-1: Examples of CNS drugs containing amine functionality. .......................... 30
Figure 1-2: Organic electrosynthesis and its direct relationship to green chemistry principles. Figure adapted from Frontaan-Uribe et al. .................................................. 32
Figure 1-3: Structures of aluminium hydride reagents ............................................. 35
Figure 1-4: Amine-borane adduct 1-14 formed during synthesis of (S)-fluoxetine. ........ 37
Figure 1-5: Structure of diphosphine ligands DIPAMP, DIOP and BINAP. .................. 56
Figure 1-6: Structure of Crabtree’s catalyst and Pfaltz’s catalyst. .............................. 56
Figure 1-7: Outline of thesis structure. .................................................................. 69
Figure 2-1: Plot of Butler-Volmer equation for simple charge transfer reaction. ............. 75
Figure 2-2: Tafel plot of the Butler-Volmer equation. .............................................. 76
Figure 2-3: Relationship between current density and electrode potential as mass transport rates are increased. ............................................................... 77
Figure 2-4: Concentration profile for reactions at solid/liquid interfaces. .................... 77
Figure 2-5: Potential distribution in an electrochemical reactor. ............................... 79
Figure 2-6: Rotating disc electrode set up. ............................................................. 80
Figure 3-1: Schematic of the rotating disc electrode equipment. ............................... 83
Figure 3-2: Schematic of the H-cell and equipment setup for batch electrolysis experiments. ................................................................. 83
Figure 3-3: Photograph of the ElectroCell reactor with the reactor dimensions. .......... 84
Figure 3-4: Photograph of a VC electrode and the AgCl reference electrode with dimensions. ........................................................................................................ 84
Figure 3-5: Schematic diagram of the reactor indicating the flow system within the reactor. ........................................................................................................ 85
Figure 3-6: Schematic diagram of the PTFE frame designed to hold AgCl reference electrode. ......................................................................................................... 86
Figure 3-7: Photograph of the PTFE frame holding the AgCl reference electrode ........... 86
Figure 3-8: Schematic diagram of the modified electrochemical flow-through components. 86
Figure 3-9: Configuration of the graphite felt inserted into the PTFE reference electrode frame. ........................................................................................................ 86
Figure 3-10: Schematic representation of the electrochemical reactor experimental setup... 87
Figure 3-11: Flow-through quartz cuvette (1 mm wide). .......................................... 88
Figure 3-12: Fibre optic cable and flow through cuvette set-up. ................................. 88
Figure 3-13: Photograph of the gas counter. ............................................................... 88
Figure 3-14: Schematic diagram of the gas counter. .................................................. 88
Figure 3-15: $sp^3$-hybridisation of carbon atoms in diamond structure. ..................... 89
Figure 3-16: BDD electrodes: a) doped diamond film directly on the substrate material,
b) doped diamond film with an interlayer on the substrate, c) doped diamond particles implanted
in a conductive substrate with a passivation surface layer, and d) doped diamond particles.
immobilised on an insulating layer. ............................................................................... 89
Figure 4-1: Cyclic voltammogram for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M
aq. H$_2$SO$_4$ at a Pb-coated VC RDE; electrode potential swept between -0.4 V and -1.4 V
(SCE) at a scan rate of 25 mV s$^{-1}$ and at a range of rotation rates. ............................... 92
Figure 4-2: Effect of rotation rate on measured current densities for the reduction of 0.01 M
maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ using a Pb-coated VC RDE compared with those
predicted by Levich’s equation. ....................................................................................... 93
Figure 4-3: Cyclic voltammogram for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M
aq. H$_2$SO$_4$ at a VC RDE; electrode potential swept between -0.2 V and -1.5 V (SCE) at a scan
rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm. ......................................................... 95
Figure 4-4: Effect of overpotential ($E_{\text{disc}}-E_{\text{Mal}}$) on log(current density) for the reduction of
0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a VC RDE at a scan rate of 25 mV s$^{-1}$
and a rotation rate of 1000 rpm. ..................................................................................... 95
Figure 4-5: Cyclic voltammogram for the reduction of protons in 100 mL 1 M aq. H$_2$SO$_4$ at a
VC RDE; electrode potential swept between -0.2 V and -1.5 V (SCE) at a scan rate of 25 mV
s$^{-1}$ and at a range of rotation rates. ............................................................................... 96
Figure 4-6: Effect of overpotential ($E_{\text{disc}}-E_{\text{Hydrogen}}$) on log(current density) for the reduction of
protons in 100 mL 1 M aq. H$_2$SO$_4$ at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a rotation
rate of 1000 rpm. ............................................................................................................. 97
Figure 4-7: Koutecky-Levich plots at -1.1, -1.0 and -0.9 V (SCE) for the reduction of 0.01 M
maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a
rotation rate of 1000 rpm. ............................................................................................... 98
Figure 4-8: Effect of rotation rate on measured current densities for the reduction of 0.01 M
maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ using a VC RDE compared with those predicted by
Levich’s equation. ............................................................................................................. 99
Figure 4-9: Cyclic voltammograms for the reduction of 0.01 M maleimide 4-1 in 100 mL
0.01 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 2) and 100 mL 0.0001 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$
List of Figures

Figure 4-10: Effect of overpotential \((E_{\text{disc}} - E_{\text{mal}})\) on log(current density) for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.01 M aq. \(H_2SO_4\) + 0.1 M \(Na_2SO_4\) (pH 2) at a VC RDE at a scan rate of 25 mV s\(^{-1}\) and a rotation rate of 1000 rpm. 100

Figure 4-11: Effect of overpotential \((E_{\text{disc}} - E_{\text{mal}})\) on log(current density) for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.0001 M aq. \(H_2SO_4\) + 0.1 M \(Na_2SO_4\) (pH 4) at a VC RDE at a scan rate of 25 mV s\(^{-1}\) and a rotation rate of 1000 rpm. 101

Figure 4-12: Cyclic voltammogram for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.5 M aq. \(Na_2SO_4\) (pH 7) at a VC RDE; electrode potential swept between -0.2 V and -1.8 V (SCE) at a scan rate of 25 mV s\(^{-1}\) and at a range of rotation rates. 102

Figure 4-13: Effect of rotation rate on measured current densities for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.5 M aq. \(Na_2SO_4\) (pH 7) using a VC RDE compared with those predicted by Levich’s equation. 103

Figure 4-14: Current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. \(H_2SO_4\) at a VC electrode in a glass H-cell at a potential of -1.2 V (SCE). 105

Figure 4-15: Current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. \(H_2SO_4\) at a VC electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature. 107

Figure 4-16: Cross sectional current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. \(H_2SO_4\) at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature. 108

Figure 4-17: Equivalent circuit and potential distribution for porous electrodes. 109

Figure 4-18: UV spectrum of 0.01M maleimide 4-1 in 100 mL 1 M aq. \(H_2SO_4\); C=C bond absorbance at 276 nm. 109

Figure 4-19: Comparison of experimental and theoretical depletion of 0.01 M maleimide 4-1 in 100 mL 1 M aq. \(H_2SO_4\) at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature. 111

Figure 4-20: Comparison of theoretical and experimental ln[maleimide]-time relationship using 0.01 M maleimide 4-1 in 100 mL 1 M aq. \(H_2SO_4\) at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature. 112
Figure 4-21: Cross sectional current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rates of 30, 60 and 90 mL min$^{-1}$ and room temperature. ................................................................. 114

Figure 4-22: Comparison of experimental and theoretical depletion of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rates of 30, 60 and 90 mL min$^{-1}$ and room temperature. ......................................................................................................................... 115

Figure 4-23: Comparison of theoretical and experimental ln[maleimide]-time relationship using 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rates of 30, 60 and 90 mL min$^{-1}$ and room temperature. ............................................................................................................. 115

Figure 4-24: Cross sectional current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature and 50 °C. ......................................................................................................................... 115

Figure 4-25: Cross sectional current density-time relationship for the reduction of 0.01 M and 0.1 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature. ......................................................................................................................... 118

Figure 4-26: Experimental depletion of 0.1 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature. ......................................................................................................................... 118

Figure 4-27: Comparison of theoretical and experimental ln[maleimide]-time relationship using 0.1 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate 60 mL min$^{-1}$ and room temperature. ......................................................................................................................... 119

Figure 4-28: Cross sectional current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.01 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 2) and 100 mL 0.0001 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 4) at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature. ....... 120

Figure 4-29: Comparison of experimental and theoretical depletion of 0.01 M maleimide 4-1 in 100 mL 0.01 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 2) and 100 mL 0.0001 M aq. H$_2$SO$_4$ +
0.1 M Na$_2$SO$_4$ (pH 4) at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature.......................... 121

**Figure 5-1:** Maleimide derivatives investigated electrochemically.................................. 123

**Figure 5-2:** Cyclic voltammograms for the reduction of 0.01 M $N$-allylmaleimide 5-1 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a VC RDE; electrode potential swept between -0.2 V and -1.5 V (SCE) at a scan rate of 25 mV s$^{-1}$ and at a range of rotation rates. ......................................................................................................................... 125

**Figure 5-3:** Effect of overpotential ($E_{\text{disc}}$-$E_{\text{allyl}}$) on log(current density) for the reduction of 0.01 M $N$-allylmaleimide 5-1 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm. ......................... 126

**Figure 5-4:** Effect of rotation rate on measured current densities for reduction of 0.01 M $N$-allylmal..maleimide 5-1 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) using a VC RDE, compared with those predicted by Levich’s equation........................................ 126

**Figure 5-5:** Cyclic voltammograms for the reduction of 0.01 M $N$-allylmaleimide 5-1 in 100 mL of a mixture of 0.01 M aq. H$_2$SO$_4$ + MeOH (8:2 v/v) + 0.5 M Na$_2$SO$_4$ (pH 2) and 100 mL of a mixture of 0.0001 M aq. H$_2$SO$_4$ + MeOH (8:2 v/v) + 0.5 M Na$_2$SO$_4$ (pH 4) at a VC RDE; electrode potential swept between 0 V and -1.75 V (SCE) at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm. ........................................................................................................ 128

**Figure 5-6:** Cyclic voltammogram for the reduction of 0.01 M $N$-propargylmaleimide 5-2 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a VC RDE; electrode potential swept between -0.2 V and -1.2 V (SCE) at a scan rate of 25 mV s$^{-1}$ and at a range of rotation rates. ................................................................................................................................ 129

**Figure 5-7:** Effect of overpotential ($E_{\text{disc}}$-$E_{\text{propargyl}}$) on log(current density) for the reduction of 0.01 M $N$-propargylmaleimide 5-2 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm. .................. 129

**Figure 5-8:** Cyclic voltammogram for the reduction of 0.01 M $N$-propargylmaleimide 5-2 in 100 mL of a mixture of 0.0001 M aq. H$_2$SO$_4$ + MeOH (8:2 v/v) + 0.5 M Na$_2$SO$_4$ (pH 4) at a VC RDE; electrode potential swept between -0 V and -1.75 V (SCE) at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm. ................................................................................... 130

**Figure 5-9:** Current density-time relationship and charge passed for the reduction of 0.01 M $N$-allylmal..maleimide 5-1 in 500 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) and the background solution (without $N$-allylmaleimide 5-1) at a VC electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature. ................................................................................................................................. 131
Figure 5-10: Current density-time relationship for the reduction of 0.01 M \( N \)-propargylmaleimide 5-2 in 100 mL of a mixture of 1 M aq. \( \text{H}_2\text{SO}_4 \) and MeOH (8:2 v/v) and the background solution (without \( N \)-allylmaleimide 5-1) at a VC electrode using the flow-through reactor at a potential of -1.0 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature. .............................................................. 133

Figure 5-11: Current density-time relationship and charge passed for the reduction of 0.01 M \( N \)-allylmaleimide 5-1 in 500 mL of a mixture of 1 M aq. \( \text{H}_2\text{SO}_4 \) and MeOH (8:2 v/v) and the background solution (without \( N \)-allylmaleimide 5-1) at a graphite felt electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature. .............................................................. 134

Figure 5-12: Current density-time relationship and charge passed for the reduction of 0.01 M \( N \)-allylmaleimide 5-1 in 500 mL of a mixture of 1 M aq. \( \text{H}_2\text{SO}_4 \) and MeOH (8:2 v/v) and the background solution (without \( N \)-allylmaleimide 5-1) at a graphite felt electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and 50 °C. .............................................................. 136

Figure 5-13: Comparison of experimental and theoretical depletion of 0.01 M \( N \)-allylmaleimide 5-1 in 100 mL of a mixture of 1 M aq. \( \text{H}_2\text{SO}_4 \) and MeOH (8:2 v/v) at a graphite felt electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and 50 °C. .............................................................. 136

Figure 5-14: Current density-time relationship and charge passed for the reduction of 0.01 M \( N \)-allylmaleimide 5-1 in 100 mL of a mixture of 0.0001 M aq. \( \text{H}_2\text{SO}_4 \) + MeOH (8:2 v/v) + 0.5 M Na\(_2\text{SO}_4 \) (pH 4) and the background solution (without \( N \)-allylmaleimide 5-1) at a graphite felt electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature. .............................................................. 137

Figure 5-15: Biologically active succinimide derivatives. 136-139 ........................................ 138

Figure 5-16: Cyclic voltammograms for the reduction of 0.01 M 3,4-dimethylmaleimide 5-3 in 100 mL of a mixture of 1 M aq. \( \text{H}_2\text{SO}_4 \) and MeOH (8:2 v/v) at a VC RDE; electrode potential swept between -0 V and -1.75 V (SCE) at a scan rate of 25 mV s\(^{-1}\) and at a range of rotation rates. .............................................................. 139

Figure 5-17: Cyclic voltammograms for the reduction of 0.01 M \( N \)-benzyl-3,4-dimethylmaleimide 5-4 in 100 mL of a mixture of 1 M aq. \( \text{H}_2\text{SO}_4 \) and MeOH (8:2 v/v) at a VC RDE; electrode potential swept between -0 V and -1.75 V (SCE) at a scan rate of 25 mV s\(^{-1}\) and at a range of rotation rates. .............................................................. 140
**Figure 5-18:** Current density-time relationship and charge passed for the reduction of 0.01 M \(N\)-benzyl-3,4-dimethylmaleimide 5-4 in 100 mL of a mixture of 1 M aq. \(\text{H}_2\text{SO}_4\) and \(\text{MeOH}\) (8:2 v/v) and the background solution without \(N\)-benzyl-3,4-dimethylmaleimide 5-4 at a BDD electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature. ....................................................................................... 141

**Figure 5-19:** \(^1\)H NMR for the products of the reduction of \(N\)-benzyl-3,4-dimethylmaleimide 5-4. ................................ ................................................................................................... 142

**Figure 5-20:** \(^1\)H NMR for the products of the reduction of 3,4-dimethylmaleimide 5-3. .... 142

**Figure 5-21:** Current density-time relationship and charge passed for the reduction of 0.01 M \(N\),\(N\)-dimethylbenzamide 6-1 in 100 mL of a mixture of 1 M aq. \(\text{H}_2\text{SO}_4\) and \(\text{MeOH}\) (8:2 v/v) and the background solution (without 3,4-dimethylmaleimide 5-3 at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature................................................................. 143

**Figure 6-1:** Cyclic voltammogram for the reduction of protons in 100 mL 1 M aq. \(\text{H}_2\text{SO}_4\) at a BDD electrode; electrode potential swept between 3.0 V and -3.0 V (AgCl|Ag) starting at 0 V, at a scan rate of 10 mV s\(^{-1}\) and a rotation rate of 1000 rpm. .............................................. 146

**Figure 6-2:** Cyclic voltammogram for the reduction of 0.01 M \(N\),\(N\)-dimethylbenzamide 6-1 in 100 mL 1 M aq. \(\text{H}_2\text{SO}_4\) at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s\(^{-1}\) and a rotation rate of 1000 rpm. .................... 147

**Figure 6-3:** Potential-time relationship for the reduction of 0.01 M \(N\),\(N\)-dimethylbenzamide 6-1 in 100 mL 1 M aq. \(\text{H}_2\text{SO}_4\) at a BDD electrode using the flow-through reactor at a current density of -2000 A m\(^{-2}\), flow rate of 60 mL min\(^{-1}\) and room temperature................................. 148

**Figure 6-4:** Mole percentage of \(N\),\(N\)-dimethylbenzylamine 6-1a, benzaldehyde 6-2 and benzyl alcohol 6-3 formed during the reduction of 0.01 M \(N\),\(N\)-dimethylbenzamide 6-1 in 100 mL 1 M aq. \(\text{H}_2\text{SO}_4\) at a BDD electrode in the flow-through reactor at a current density of -2000 A m\(^{-2}\), a flow rate of 60 mL min\(^{-1}\) and room temperature......................................................... 149

**Figure 6-5:** Mole percentage of \(N\),\(N\)-dimethylbenzylamine 6-1a, benzaldehyde 6-2 and benzyl alcohol 6-3 formed during the reduction of 0.01 M \(N\),\(N\)-dimethylbenzamide 6-1 in 100 mL 1 M aq. \(\text{H}_2\text{SO}_4\) at a BDD electrode in the flow-through reactor at a current density of -2000 A m\(^{-2}\), a flow rate of 60 mL min\(^{-1}\) and 50 °C. .............................................................................................................. 154

**Figure 6-6:** Fractional conversion for the reduction of 0.01M \(N\),\(N\)-dimethylbenzamide in 100 mL 1 M aq. \(\text{H}_2\text{SO}_4\) at a BDD electrode in the flow-through reactor at a current density of -2000 A m\(^{-2}\), flow rates of 30, 60 and 90 mL min\(^{-1}\) and room temperature...................... 155
List of Figures

Figure 6-7: Raman spectrum of 1 M $N,N$-dimethylbenzamide 6-1 before and after 8 hours of electrolysis in 1 M aq. H$_2$SO$_4$. ................................................................. 157

Figure 6-8: Raman spectrum of 1 M $N,N$-dimethylbenzamide 6-1, $N,N$-dimethylbenzylamine 6-1a, benzaldehyde 6-2 and benzyl alcohol 6-3 in 1 M aq. H$_2$SO$_4$. ........................................ 158

Figure 6-9: Current density-time relationship and charge passed for the reduction of 0.01 M $N,N$-dimethylbenzamide 6-1 in 100 mL of 1 M aq. H$_2$SO$_4$ at a BDD electrode in the flow-through reactor at a potential of -2.8 V (AgCl|Ag), a flow rate of 60 mL min$^{-1}$ and room temperature. ...................................................................................................................... 159

Figure 6-10: Hydrogen evolved during reduction of 0.01 M $N,N$-dimethylbenzamide 6-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a BDD electrode in the flow-through reactor at a potential of -2.8 V (AgCl|Ag), a flow rate of 60 mL min$^{-1}$ and room temperature. ........................................ 160

Figure 6-11: Cyclic voltammogram for the reduction of 0.01 M benzaldehyde 6-2 in 100 mL 1 M aq. H$_2$SO$_4$ at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s$^{-1}$ and a rotation rate of 1000 rpm. ...................... 163

Figure 6-12: Current density-time relationship for the reduction of 0.01 M benzaldehyde 6-2 in 100 mL 1 M aq. H$_2$SO$_4$ (100 mL) at a BDD electrode in the flow reactor at a constant cathode potential of -2.8 V (AgCl|Ag), a flow rate of 60 mL min$^{-1}$ and room temperature. ........................................ 164

Figure 6-13: Cyclic voltammogram for the reduction of a range of solvent systems consisting of 100 mL of THF and 1 M aq. H$_2$SO$_4$ at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s$^{-1}$ and a rotation rate of 1000 rpm. ........................................ 167

Figure 6-14: Cyclic voltammogram for the reduction of 0.01 M $N,N$-dimethylbenzamide 6-1 in 100 mL of a mixture of THF, 0.5 M aq. TBAB and 1 M aq. H$_2$SO$_4$ (5:3:2 v/v) at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s$^{-1}$ and a rotation rate of 1000 rpm. ........................................ 168

Figure 6-15: Cyclic voltammogram for the reduction of 0.01 M $N,N$-dimethylbenzamide 6-1 in 100 mL of a mixture of IPA or MeOH and 1 M aq. H$_2$SO$_4$ (7:3 v/v) at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s$^{-1}$ and a rotation rate of 1000 rpm. ........................................ 169

Figure 6-16: Structure of $N$-methylbenzamide 6-9 and benzamide 6-10. ...................... 170

Figure 7-1: Amides studied in the electrochemical flow-through reactor. .................... 175

Figure 7-2: Examples of top-selling pharmaceutical products. ..................................... 178

Figure 7-3: Cyclic voltammogram for the reduction of 0.01 M $N$-(4-methoxybenzoyl)pyrrolidine 7-2 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (v/v
9:1) at a BDD electrode in the flow-through reactor; electrode potential swept between -0.5 V and -3.0 V (AgCl|Ag) at a scan rate of 25 mV s\(^{-1}\) and a rotation rate of 1000 rpm. ........ 181

**Figure 7-4:** Cyclic voltammogram for the reduction of 0.01 M \(N\)-(4-toluoybenzoyl)pyrrolidine 7-3 in 100 mL of a mixture of 1 M aq. \(\text{H}_2\text{SO}_4\) and MeOH (v/v 9:1) at a BDD electrode in the flow-through reactor; electrode potential swept between -0.5 V and -3.0 V (AgCl|Ag) at a scan rate of 25 mV s\(^{-1}\) and a rotation rate of 1000 rpm. ........ 181

**Figure 7-5:** Cyclic voltammogram for the reduction of 0.01 M \(N\)-ethyl-\(N\)-cyclohexylbenzamide 7-4 in 100 mL of a mixture of 1 M aq. \(\text{H}_2\text{SO}_4\) and MeOH (v/v 8:2) at a BDD electrode in the flow-through reactor; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 25 mV s\(^{-1}\) and a rotation rate of 1000 rpm. .......................... 184

**Figure 7-6:** Mechanism of the reduction of 7-6 after hemiaminal formation...................... 185

**Figure 7-7:** (S)-(4-Benzyl-3,6-dioxo-piperazin-2-yl)-acetic acid benzyl ester 7-29 as an example of a drug compound. .......................................................................................................................... 188

**Figure 7-8:** Possible products from the reduction of (S)-(4-benzyl-3,6-dioxo-piperazin-2-yl)-acetic acid benzyl ester 7-28.................................................................................................................. 189

**Figure 8-1:** Proposed maleimide substituents to further investigate stereoselective reduction. .................................................................................................................................. 195

**Figure 8-2:** Proposed amides for further investigation. ........................................................ 196

**Figure 8-3:** Protected hemiaminal structure 8-15. ............................................................... 196

**Figure 8-4:** Wall-jet BDD electrode based on the design by Compton *et al.* 153 .................. 197
List of Tables

Table 1.1: Examples of industrial organic electrosynthesis processes.\textsuperscript{13} .................................................. 35
Table 1.2: Electrochemical reduction of amides and imides.\textsuperscript{59,61} .......................................................... 49
Table 1.3: Electrochemical reduction of aliphatic amides to the corresponding alcohol or the aldehyde.\textsuperscript{57} .......................................................................................................................... 53
Table 1.4: Electrochemical reduction of C=C bonds.\textsuperscript{59} .................................................................................. 65
Table 1.5: Effect of the electrode material and the charge passed for the reduction of cyclcohex-2-en-l-one 1-132.\textsuperscript{103} .................................................................................................................. 67
Table 1.6: Electrochemical hydrogenation of C=C bonds at a LaNi\textsubscript{5} electrode. ................... 67
Table 4.1: Calculated kinetic and diffusion coefficients for the reduction of 0.01 M maleimide 4-1 derived from the Koutecky-Levich Plot, using a kinematic viscosity of 0.98\times10^{-6} m^{2} s^{-1}. Calculated for 1 M aq. H\textsubscript{2}SO\textsubscript{4} using NRTL thermodynamic model with Hysys\textregistered software................................................................................................................ 98
Table 5.1: Efficiencies for reduction N-allylmaleimide 5-1 using the flow through reactor. ......................................................................................................................................... 132
Table 6.1: Results for the reduction of 0.01 M N,N-dimethylbenzamide 6-1 after 8 hours of electrolysis in 100 mL 1 M aq. H\textsubscript{2}SO\textsubscript{4} at a BDD and Pb electrode in the flow-through reactor at a current density of -2000 A m\textsuperscript{-2}, a flow rates of 60 mL min\textsuperscript{-1} and room temperature. .... 152
Table 6.2: Results for the reduction of 0.01 M N,N-dimethylbenzamide 6-1 after 8 hours of electrolysis in 100 mL 1 M aq. H\textsubscript{2}SO\textsubscript{4} at a BDD electrode in the flow-through reactor at a current density of -2000 A m\textsuperscript{-2}, a flow rates of 60 mL min\textsuperscript{-1} and room temperature and 50 °C. ......................................................................................................................................... 153
Table 6.3: Results for the reduction of 0.01 M N,N-dimethylbenzamide 6-1 in 100 mL 1 M aq. H\textsubscript{2}SO\textsubscript{4} at a BDD electrode in the flow-through reactor at a current density of -2000 A m\textsuperscript{-2}, flow rates of 30, 60 and 90 mL min\textsuperscript{-1} and room temperature. .................................................. 155
Table 6.4: Results for the reduction of N,N-dimethylbenzamide 6-1 at BDD at -2000 A m\textsuperscript{-2} at pH 1 and 2 and a flow rate of 60 mL min\textsuperscript{-1}, room temperature and 1 M H\textsubscript{2}SO\textsubscript{4} anolyte.. 156
Table 6.5: Conversion and mole percentage of products formed after 4 hours of electrolysis of 0.01 M N,N-dimethylbenzamide 6-1 in 100 mL 1 M aq. H\textsubscript{2}SO\textsubscript{4} at a BDD electrode in the flow-through reactor at a range of potentials, a flow rate of 60 mL min\textsuperscript{-1} and room temperature. ...................................................................................................................... 159
**Table 6.6:** Conversion and mole percentage of products formed after 4 hours of electrolysis of 0.01 M $N,N$-dimethylbenzamide 6-1 in 100 mL 1 M aq. $\text{H}_2\text{SO}_4$ at a BDD electrode in the flow-through reactor at -2.8 V (AgCl|Ag), a flow rate of 60 mL min$^{-1}$ and 15, 25 and 50 °C. ...................................................................................................................................................... 161

**Table 6.7:** Conversion and mole percentage of products formed after 4 hours of electrolysis of 0.01 M $N,N$-dimethylbenzamide 6-1 in pH 0-4 solutions (100mL of 1-0.0001 M aq. $\text{H}_2\text{SO}_4$) at a BDD electrode in the flow-through reactor at -2.8 V (AgCl|Ag), a flow rate of 60 mL min$^{-1}$ and room temperature. ............................................................................. 162

**Table 6.8:** Pfizer solvent selection guide ........................................................................... 165

**Table 6.9:** Solvents suitable for reduction.$^{53}$ .................................................................................. 166

**Table 6.10:** Conversion of $N,N$-dimethylbenzamide 6-1, $N$-methylbenzamide 6-9, benzamide 6-10 and the products formed. ........................................................................................................ 171

**Table 7.1:** Amide to amine reduction using LiAlH$_4$ .......................................................... 177

**Table 7.2:** Results from the reduction of functionalised 4-benzoylpyrrolidine derivatives.$^{[a]}$ ...................................................................................................................................................... 179

**Table 7.3:** Results from the reduction of tertiary amides and a secondary imide. ............ 186
List of Schemes

Scheme 1.1: Paired electrosynthesis of phthalate 1-2 and 4-(tert-butyl)benzaldehyde dimethylacetal 1-4.9 .......................................................... 33
Scheme 1.2: Electrochemical reduction of carboxylic acid hydrazines to amides.10 ........ 33
Scheme 1.3: Anodic Phenol–Arene cross coupling reaction.11 .................................. 34
Scheme 1.4: Order of reactivity for the reduction of the carbonyl group..................... 35
Scheme 1.5: Amide reduction step for the synthesis of paroxetine 1-10.16 ............... 36
Scheme 1.6: Final step for the synthesis of (S)-fluoxetine 1-13.23 ..................... 37
Scheme 1.7: Rhodium catalysed reduction of amides to amines with Ph2SiH2.26 .......... 38
Scheme 1.8: Reaction of acetamide derivative 1-17 with PhMeSiH2.28 ...................... 39
Scheme 1.9: Selective reduction of secondary amides to imines 1-19, aldehydes 1-20 or amines 1-21.33 ................................................................. 40
Scheme 1.10: Diiron catalysed hydrosilylation of benzamide 1-22 to benzylamine 1-23.35 . 41
Scheme 1.11: Catalytic hydrogenation of N-substituted succinimide 1-24 and phthalimide 1-26 ............................................................ 42
Scheme 1.12: Rhenium catalysed hydrogenation of amides to amines.40, 41 ........ 42
Scheme 1.13: Catalytic hydrogenation of N-acetylpyrrolidin 1-36.43 ...................... 43
Scheme 1.14: Homogeneous hydrogenation of butanamide with a Ru-Triphos catalyst.44 ... 43
Scheme 1.15: Catalytic hydrogenation of cyclohexylcarboxamide 1-42 with Ru/Mo bimetallic catalyst. ........................................................... 44
Scheme 1.16: Catalytic hydrogenation of N-methylpyrrolidin-2-one 1-45 to N- methylpyrrolidin 1-46 at low temperature and pressure using a Pt/Re catalyst.45 .......... 44
Scheme 1.17: Proposed mechanism of biocatalytic amide reduction.46 ....................... 45
Scheme 1.18: Electrochemical reduction of amides to amines.................................. 46
Scheme 1.19: Products accessible from cathodic reduction.53 .................................. 46
Scheme 1.20: Electrochemical reduction isonicotinic amide 1-49 under different acidic conditions.55 ................................................................. 47
Scheme 1.21: Mechanism for the electrochemical reduction of nicotinamide 1-52. .... 47
Scheme 1.22: Electrochemical reduction of N-benzylbenzamide 1-54 in alcoholic solutions.54, 58 ................................................................. 48
Scheme 1.23: Electrochemical reduction of N,N-dimethylbenzamide 1-57.60 .............. 48
Scheme 1.24: Reduction of phthalimide 1-59 to 2,3-dihydro-1H-isoindoline 1-60.63 ...... 50
Scheme 1.25: Potential controlled reduction of tetrachlorophthalimide 1-61.65 .......................... 51
Scheme 1.26: Reduction of succinimide 1-64 to pyrrolidine 1-65.56 ................................. 51
Scheme 1.27: Reduction of glutarimide 1-66 to piperidone 1-67.68 ........................................... 52
Scheme 1.28: Electrochemical reduction N,N-dimethylvaleramide 1-68.69 .......................... 52
Scheme 1.29: Electrochemical reduction of aliphatic amides 1-69.57 ...................................... 53
Scheme 1.30: Homogeneous catalytic reduction of maleic acid 1-77 using a Ru (II) catalyst.76 ......................................................................................................................................................... 55
Scheme 1.31: Mechanism for the hydrogenation of alkenes using the Wilkinson’s catalyst.78 ........................................................................................................................................................................................................... 55
Scheme 1.32: Enantoiselective hydrogenation of geminal substituted alkenes.86 .................. 57
Scheme 1.33: Reversible heterolytic cleavage of H₂ using phosphine–borane species 1-79. 57
Scheme 1.34: Catalytic cycle for the reduction of imines using FLP and H₂ ......................... 58
Scheme 1.35: Heterolytic cleavage of H₂ using amine–borane species. ................................. 58
Scheme 1.36: Catalytic enone 1-88 hydrogenation using alkenylborane/DABCO FLP........... 58
Scheme 1.37: Reduction of the C=C bond in a conjugated alkene and the reduction of a chalcone using InCl₃/NaBH₄.92 ................................................................................................................................. 59
Scheme 1.38: Reduction of C=C bond of unsaturated carboxylic acid derivatives.93 ............ 59
Scheme 1.39: Reduction of 3-methyleneoxindoles 1-101 using the Hantzch ester 1-103.96. 60
Scheme 1.40: Reduction of 3-phenylpropanoate 1-99 using a ReIO₂(PPh₃)₂ catalyst and PhMe₂SiH. .............................................................................................................................................. 61
Scheme 1.41: Reduction of αβ-unsaturated ketones.98 ............................................................... 61
Scheme 1.42: Reduction of β,β-disubstituted nitroalkenes 1-103 and α,β-disubstituted nitroalkenes 1-105 by Clostridium sporogenes.99 .................................................................................. 62
Scheme 1.43: Reduction of C=C and C≡C bonds of phenyl substituted alkene and acetylene at the Dropping Mercury Electrode. A 75% dioxane/H₂O electrolyte was used with tetrabutylammonium iodide as the supporting electrolyte. ................................................................. 63
Scheme 1.44: Reduction of alkyl and aryl acetylenes at a spongy nickel electrode. .............. 64
Scheme 1.45: Asymmetric electrochemical reduction of citraconic acid 1-128 and 4-methylcoumarin 1-130 at a poly-L-valine coated graphite electrode. .................................................. 66
Scheme 1.46: Electrocatalytic hydrogenation of cyclohex-2-en-1-one 1-132 to cyclohexanone 1-133 and cyclohexanol 1-134................................................................. 66
Scheme 1.47: Mechanism of electrocatalytic hydrogenation. ................................................. 68
**Scheme 3.1:** Synthesis of p-tert-butylbenzaldehyde dimethyl acetal 3-4 at a BDD electrode in a MeOH-H₂SO₄-H₂O electrolyte. A possible competitive side reactions is possible via the intermediate dimer product 1-11.  

**Scheme 4.1:** Electrochemical reduction of maleimide 4-1 to succinimide 4-1a.  
**Scheme 4.2:** Electrochemical reduction of protons to evolve hydrogen.  
**Scheme 4.3:** Mechanism for the formation of dimer 4-2.  
**Scheme 4.4:** Proposed mechanism for the electrochemical reduction of maleimide 4-1.  
**Scheme 5.1:** Reduction of intermediate 5-5 using a copper catalyst.  
**Scheme 5.2:** Chemoselective reduction of C=C bond of pyridine derivative 5-8.  
**Scheme 5.3:** Synthesis of N-allylmaleimide 5-1 and N-propargylmaleimide 5-2.  
**Scheme 5.4:** Proposed mechanism for the electrochemical reduction of N-allylmaleimide 5-1 to N-allylsuccinimide 5-1a.  
**Scheme 5.5:** Electrochemical reduction of N-allylmaleimide 5-1 to N-allylsuccinimide 5-1a.  
**Scheme 5.6:** Electrochemical reduction of N-propargylmaleimide 5-2 to N-propargylsuccinimide 5-2a.  
**Scheme 5.7:** Synthesis of 3,4-dimethylmaleimide 5-3 and N-benzyl-3,4-dimethylmaleimide 5-4.  
**Scheme 5.8:** Electrochemical reduction of 3,4-dimethylmaleimide 5-3 and N-benzyl-3,4-dimethylmaleimide 5-4.  
**Scheme 6-1:** Reduction of N,N-dimethylbenzamide 6-1.  
**Scheme 6-2:** Reduction products observed for the reduction of 0.01 M N,N-dimethylbenzamide 6-1 in 100 mL 1 M aq. H₂SO₄ at a BDD electrode in the flow-through reactor. A current density of -2000 A m⁻² was applied for 8 hours a flow rate of 60 mL min⁻¹ and room temperature.  
**Scheme 6-3:** Reduction pathways of N,N-dimethylbenzamide 6-1.  
**Scheme 6-4:** Mechanism for the formation of the hemiaminal intermediate 6-4.  
**Scheme 6-5:** Mechanism for the formation of N,N-dimethylbenzylamine 6-1a or benzyl alcohol 6-3 from 6-4.  
**Scheme 6-6:** Mechanism for the formation hydrobenzoin product from benzaldehyde 6-2.  
**Scheme 6-7:** Electrochemical reduction of phthalimide 6-7 to isoindoline 6-8 at a Hg electrode using an acidified acetonitrile and water electrolyte.  
**Scheme 6-8:** Formation of N-benzylidene benzylamine 6-11.
**Scheme 6-9:** Protonation of the nitrogen of hemiaminal 6-4, leading to the elimination of dimethylamine. .......................................................................................................................... 172

**Scheme 6-10:** Protonation of the oxygen of the primary hemiaminal leading to the elimination of H₂O and the formation of the iminium ion. ................................................................. 172

**Scheme 7.1:** General reaction scheme for amide synthesis. ........................................................... 176

**Scheme 7.2:** Mechanism for the formation of the dimer 1,2-bis(4-methoxyphenyl)ethane 7-18. ..................................................................................................................................... 180

**Scheme 7.3:** Mechanism for the reduction of the nitrile group of 4-cyano benzoylpyrrolidine 7-5. .......................................................................................................................... 182

**Scheme 7.4:** Reduction of N-ethyl-N-cyclohexylbenzamide 7-6. .................................................. 183

**Scheme 7.5:** Reduction of glutarimide 7-11 and the 4-electron and 8-electron reduction products. .......................................................................................................................... 187
# Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>Electrode area</td>
<td>m$^2$</td>
</tr>
<tr>
<td>$a$</td>
<td>Specific surface area of porous electrode</td>
<td>m$^2$ m$^{-3}$</td>
</tr>
<tr>
<td>$c_i$</td>
<td>Concentration of species $i$</td>
<td>mol m$^{-3}$</td>
</tr>
<tr>
<td>$c_{i,0}$</td>
<td>Inlet concentration of species $i$</td>
<td>mol m$^{-3}$</td>
</tr>
<tr>
<td>$c_{t=0}$</td>
<td>Initial concentration</td>
<td>mol m$^{-3}$</td>
</tr>
<tr>
<td>$c_t$</td>
<td>Concentration at time $t$</td>
<td>mol m$^{-3}$</td>
</tr>
<tr>
<td>$d$</td>
<td>distance</td>
<td>m</td>
</tr>
<tr>
<td>$D_i$</td>
<td>Diffusion coefficient of species $i$</td>
<td>m$^2$ s$^{-1}$</td>
</tr>
<tr>
<td>$d_f$</td>
<td>Fibre diameter</td>
<td>m</td>
</tr>
<tr>
<td>$d_{pore}$</td>
<td>Pore size</td>
<td>m</td>
</tr>
<tr>
<td>$d_h$</td>
<td>Hydraulic diameter of felt fibre</td>
<td>m</td>
</tr>
<tr>
<td>$E$</td>
<td>Electrode potential</td>
<td>V</td>
</tr>
<tr>
<td>$E^0$</td>
<td>Standard electrode potential</td>
<td>V</td>
</tr>
<tr>
<td>$E_{O/R}$</td>
<td>Reversible potential</td>
<td>V</td>
</tr>
<tr>
<td>$E_{disc}$</td>
<td>Disc potential of rotating</td>
<td>V</td>
</tr>
<tr>
<td>$e^+$</td>
<td>Electronic charge ($1.602 \times 10^{-19}$)</td>
<td>C</td>
</tr>
<tr>
<td>$F$</td>
<td>Faraday constant (96485)</td>
<td>C mol$^{-1}$</td>
</tr>
<tr>
<td>$f$</td>
<td>Rotation rate</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$\Delta G$</td>
<td>Gibbs free energy change</td>
<td>kJ mol$^{-1}$</td>
</tr>
<tr>
<td>$I$</td>
<td>Current</td>
<td>A</td>
</tr>
<tr>
<td>$j$</td>
<td>Current density</td>
<td>A m$^{-2}$</td>
</tr>
<tr>
<td>$j_L$</td>
<td>Mass transport limited current density</td>
<td>A m$^{-2}$</td>
</tr>
<tr>
<td>$j_o$</td>
<td>Exchange current density</td>
<td>A m$^{-2}$</td>
</tr>
<tr>
<td>$k_m$</td>
<td>Mass transport rate constant</td>
<td>m s$^{-1}$</td>
</tr>
<tr>
<td>$k_i$</td>
<td>Heterogeneous rate constant</td>
<td>m s$^{-1}$</td>
</tr>
<tr>
<td>$k_0$</td>
<td>Standard heterogeneous rate constant</td>
<td>m s$^{-1}$</td>
</tr>
<tr>
<td>$K$</td>
<td>Equilibrium constant</td>
<td>1</td>
</tr>
<tr>
<td>$L$</td>
<td>Length of system being modelled</td>
<td></td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
<td>Units</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
<td>-------</td>
</tr>
<tr>
<td>$M$</td>
<td>Molar mass</td>
<td>g mol$^{-1}$</td>
</tr>
<tr>
<td>$m$</td>
<td>mass</td>
<td>kg</td>
</tr>
<tr>
<td>$n$</td>
<td>Number of electrons involved in a reaction</td>
<td>1</td>
</tr>
<tr>
<td>$N_i$</td>
<td>Flux of species $i$</td>
<td>mol m$^{-2}$ s$^{-1}$</td>
</tr>
<tr>
<td>$p$</td>
<td>Partial pressure of gas</td>
<td>Pa</td>
</tr>
<tr>
<td>$Q$</td>
<td>Charge</td>
<td>C</td>
</tr>
<tr>
<td>$q$</td>
<td>Charge density</td>
<td>C m$^{-2}$</td>
</tr>
<tr>
<td>$R$</td>
<td>Universal gas constant (8.31441)</td>
<td>J K$^{-1}$ mol$^{-1}$</td>
</tr>
<tr>
<td>$R^2$</td>
<td>R-square value: the fraction of variance in the data that is explained by a regression</td>
<td>1</td>
</tr>
<tr>
<td>$r$</td>
<td>Radius of micro-disc electrode</td>
<td>m</td>
</tr>
<tr>
<td>$Re$</td>
<td>Reynolds number</td>
<td>-</td>
</tr>
<tr>
<td>$Sh$</td>
<td>Sherwood number</td>
<td>-</td>
</tr>
<tr>
<td>$t$</td>
<td>Process time</td>
<td>mol m$^{-3}$</td>
</tr>
<tr>
<td>$T$</td>
<td>Absolute temperature</td>
<td>K</td>
</tr>
<tr>
<td>$u_i$</td>
<td>Ionic mobility for species $i$</td>
<td>m$^2$ V$^{-1}$ s$^{-1}$</td>
</tr>
<tr>
<td>$U$</td>
<td>Cell voltage</td>
<td>V</td>
</tr>
<tr>
<td>$u_i$</td>
<td>Mobility of ion in an electric field</td>
<td>m s$^{-1}$</td>
</tr>
<tr>
<td>$\dot{V}$</td>
<td>Volumetric flow rate</td>
<td>m$^3$ s$^{-1}$</td>
</tr>
<tr>
<td>$v$</td>
<td>Local fluid velocity</td>
<td>m s$^{-1}$</td>
</tr>
<tr>
<td>$v_0$</td>
<td>Inlet liquid velocity</td>
<td>m s$^{-1}$</td>
</tr>
<tr>
<td>$v_{eff}$</td>
<td>Solution velocity in the empty cross section area</td>
<td>m s$^{-1}$</td>
</tr>
<tr>
<td>$v_t$</td>
<td>Terminal velocity</td>
<td>m s$^{-1}$</td>
</tr>
<tr>
<td>$V$</td>
<td>Volume</td>
<td>m$^3$</td>
</tr>
<tr>
<td>$w$</td>
<td>Specific electrical energy consumption (SEEC)</td>
<td>kW h kg$^{-1}$ product$^{-1}$</td>
</tr>
<tr>
<td>$x$</td>
<td>Horizontal distance from electrolyte inlet</td>
<td>m</td>
</tr>
<tr>
<td>$y$</td>
<td>Vertical distance from electrolyte inlet</td>
<td>m</td>
</tr>
<tr>
<td>$z_i$</td>
<td>Electron stoichiometry or charge number of reaction</td>
<td>1</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Transfer coefficient</td>
<td>1</td>
</tr>
<tr>
<td>$\beta_a$</td>
<td>Tafel coefficient for anodic reaction, $(1-\alpha) n F/(RT)$</td>
<td>V$^{-1}$</td>
</tr>
<tr>
<td>$\beta_c$</td>
<td>Tafel coefficient for cathodic reaction, $\alpha n F/(RT)$</td>
<td>V$^{-1}$</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Nernst diffusion layer thickness</td>
<td>m</td>
</tr>
</tbody>
</table>
## Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\epsilon$</td>
<td>Voidage of the graphite felt electrode</td>
<td>-</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Electrical potential</td>
<td>V</td>
</tr>
<tr>
<td>$\Phi$</td>
<td>(Fractional) current efficiency</td>
<td>-</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Overpotential (E-E_r)</td>
<td>V</td>
</tr>
<tr>
<td>$\eta_a$</td>
<td>Anode overpotential</td>
<td>V</td>
</tr>
<tr>
<td>$\eta_c$</td>
<td>Cathode overpotential</td>
<td>V</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Electrolyte conductivity, $\sum_i z_i \mu_i c_i$</td>
<td>S m$^{-1}$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Dynamic viscosity</td>
<td>kg m$^{-1}$ s$^{-1}$</td>
</tr>
<tr>
<td>$\nu$</td>
<td>Electrolyte kinematic viscosity</td>
<td>m$^2$ s$^{-1}$</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Angular frequency</td>
<td>m s$^{-1}$</td>
</tr>
<tr>
<td>$\nabla$</td>
<td>Gradient operator</td>
<td>-</td>
</tr>
</tbody>
</table>

## Sub- and superscript

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>start (t=0) (as subscript) or standard (as superscript)</td>
</tr>
<tr>
<td>a</td>
<td>Anode properties</td>
</tr>
<tr>
<td>c</td>
<td>cathode properties</td>
</tr>
<tr>
<td>e</td>
<td>electrode</td>
</tr>
<tr>
<td>i</td>
<td>species or reaction i</td>
</tr>
<tr>
<td>s</td>
<td>solid phase</td>
</tr>
<tr>
<td>k</td>
<td>reaction</td>
</tr>
<tr>
<td>l</td>
<td>liquid phase</td>
</tr>
<tr>
<td>m</td>
<td>membrane</td>
</tr>
<tr>
<td>N</td>
<td>Nernst</td>
</tr>
<tr>
<td>O</td>
<td>oxidised form</td>
</tr>
<tr>
<td>R</td>
<td>reduced form</td>
</tr>
<tr>
<td>T</td>
<td>total</td>
</tr>
</tbody>
</table>
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D</td>
<td>Two dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three dimensional</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>BDD</td>
<td>Boron Doped Diamond</td>
</tr>
<tr>
<td>C=C</td>
<td>Carbon-carbon double bond</td>
</tr>
<tr>
<td>CV</td>
<td>Cyclic Voltammogram</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier Transfer Infrared Spectroscopy</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas Chromatograph-Mass Spectroscopy</td>
</tr>
<tr>
<td>HP-LC</td>
<td>High Performance-Liquid Chromatography</td>
</tr>
<tr>
<td>IPA</td>
<td>Isopropyl alcohol</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid Chromatography-Mass Spectrometry</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>NMP</td>
<td>N-Methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>PVDF</td>
<td>Polyvinylidene difluoride</td>
</tr>
<tr>
<td>RDE</td>
<td>Rotating Disc Electrode</td>
</tr>
<tr>
<td>RDS</td>
<td>Rate Determining State</td>
</tr>
<tr>
<td>SCE</td>
<td>Saturated Calomel Electrode</td>
</tr>
<tr>
<td>SHE</td>
<td>Standard Hydrogen Electrode</td>
</tr>
<tr>
<td>TBAB</td>
<td>Tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TBAP</td>
<td>Tetrabutylammonium perchlorate</td>
</tr>
<tr>
<td>TEAP</td>
<td>Tetraethylammonium perchlorate</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra-Violet</td>
</tr>
<tr>
<td>VC</td>
<td>Vitreous Carbon</td>
</tr>
</tbody>
</table>
Chapter 1  Introduction

1.1 Background

Amines are important organic intermediates for the chemical industry; used in the production of agrochemicals, dyes, pharmaceuticals, surfactants and plastics. Amines constitute important core structures of many biologically active molecules, and are particularly prevalent in central nervous system (CNS) drugs (Figure 1-1); which make up the largest sector of pharmaceuticals sold worldwide.¹

Currently, the reduction of amides to amines accounts for only 0.6% of chemical transformations used in drug manufacture, as they require hydride and borane reagents.² These reagents are hazardous; borane reagents are air sensitive and pyrophoric while metal hydrides can ignite on contact with water.³ Further shortcomings associated with the use of these reagents include complex work up procedures and generation of excessive waste.⁴ In a seminal review published by the Process Chemistry R&D departments of GlaxoSmithKline, AstraZeneca and Pfizer, gaps were highlighted in the current technologies used to manufacture candidate drug molecules.⁴ The reduction of amides, without the use of hydride reagents, was identified as a priority research area.²

If a safer, environmentally-benign and scaleable method can be developed for the transformation, a higher percentage of amide reductions would be undertaken in pharmaceutical manufacturing. Electrochemical synthesis offers an atom efficient, environmentally sound and energy efficient solution to the problems associated with

Figure 1-1: Examples of CNS drugs containing amine functionality.¹

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fluoxetine
Eli Lilly
Anti-depressant

Venlafaxine
Wyeth
Anti-depressant

Amphetamine
Shire
Attention Deficit
Hyperactivity Disorder
chemical reduction of amides. Further exploitation of this technique to reduce other organic functional groups would support the use of electrochemical synthesis in pharmaceutical manufacturing, and the benefits can be extended to other chemical industries.

This chapter aims to provide an overview of the chemical and electrochemical processes for the reduction of amides and C=C bonds. Initially the chemical reduction reactions will be discussed followed by the electrochemical processes for the amide and C=C bond reductions respectively. The contribution of organic electrochemistry to green chemistry and industrial manufacturing will also be discussed.

1.2 Organic Electrosynthesis: A Green Technology

The sustainability of the chemical industry is a major concern due to the dependence on the petrochemical industry and the quest for green chemical processes and technologies offers a significant challenge for industry and academia. The principles of green chemistry, as defined by Anastas and Warner are:

- to prevent washes
- utilise renewable materials
- omit derivatisation steps
- produce degradable chemical products
- use safe synthetic methods
- be catalytic
- use ambient conditions
- have a low E-factor
- follow the reaction with online monitoring
- use few auxiliary substances
- have low toxicity
- be an overall safe process

A green process should aspire to achieve as many of the 12 principles as possible and have a minimal E-factor. The E-factor measures the ratio between the mass of waste generated, defined as everything but the desired product, and the mass of the product produced, a true green process will have an E-factor of zero.
E-factor = \frac{\text{kg(waste)}}{\text{kg(product)}} \quad [1.1]

In the case of the pharmaceutical industry the E-factor can be greater than 100 as candidate drug molecules are frequently complex molecules. The synthesis of complex molecules requires multiple step reactions that often involve the use of protecting groups to acquire the desired product selectivity and large volumes of solvents, for example the production of antidepressant sertraline required 250,000 litres of solvent for each 1000 kilograms produced.\textsuperscript{5}

Electrochemical synthesis is increasingly recognised as a green technology for organic chemistry for a number of reasons.\textsuperscript{8} Figure 1-2 highlights the direct relationship between organic electrochemistry and green chemistry.

A major goal of the pharmaceutical industry is to reduce the levels of solvents used in manufacturing. Water is a green solvent and can be used in electrosynthesis. Indirect and direct electrolysis can provide highly atom efficient processes and waste generation can be limited when stoichiometric reagents are prepared electrochemically within the electrochemical reactor.\textsuperscript{8} Furthermore, electrosynthesis can be carried out at ambient temperatures and pressures, making the process intrinsically safer and more energetically viable. Some examples of the benefits of organic electrosynthesis are highlighted below.

---

**Figure 1-2**: Organic electrosynthesis and its direct relationship to green chemistry principles. Figure adapted from Frontaan-Uribe et al.\textsuperscript{8}
An example of a successful green industrial electrosynthesis process was introduced by BASF in 1999. The paired electrochemical processes involved the reduction of dimethyl phthalate 1-1 to phthalide 1-2 and the simultaneous oxidation of tert-butyl-toluene 1-3 to produce 4-(tert-butyl)benzaldehyde dimethylacetal 1-4 in an undivided cell (Scheme 1.1). The process achieves 100% atom efficiency as the methanol solvent is a starting reagent and is also produced in the cathodic process which is then, in turn, consumed at the anode. The proton generated at the anode is also consumed at the cathode.

Scheme 1.1: Paired electrosynthesis of phthalate 1-2 and 4-(tert-butyl)benzaldehyde dimethylacetal 1-4.

The reduction of carboxylic acid hydrazines 1-5 to amides 1-6 was demonstrated by Breinbauer et al. in 2009 at a tin electrode, replacing the use of toxic mercury pool electrodes and pre-existing chemical reduction techniques (Scheme 1.2). Good yields of 90% were observed and C=C bond and aryl halogen groups were tolerated. This work demonstrated that electrochemical techniques can reduce the reliance on toxic materials and reagents often employed in organic synthesis.

Scheme 1.2: Electrochemical reduction of carboxylic acid hydrazines to amides.

The potential of organic electrochemistry was further demonstrated by the electro-synthesis of biaryls. Non-symmetrical biaryls are important components in organic synthesis as they are used in natural product synthesis, molecular catalysis and in materials science. Synthesis of biaryls 1-9 achieved by cross coupling mechanisms typically require leaving
functionality and complex catalysts based on toxic/precious metals; however the direct C-C cross coupling between phenols 1-7 and arenes 1-8 was achieved electrochemically at a boron doped diamond (BDD) anode. The electrolysis was carried out in an undivided cell at a constant current density of 2.8 mA cm\(^{-2}\) until a charge of 965 C (2 F mol\(^{-1}\) phenol) was passed (Scheme 1.3). The electrolyte consisted of \(N\)-methyl-\(N\),\(N\),\(N\)-triethylammonium methylsulfate (Et\(_3\)NMe\(_2\)OSMe), 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) and methanol, the electrolyte was recovered after electrolysis.

![Scheme 1.3: Anodic Phenol−Arene cross coupling reaction.](image)

The methodology is an example of a green chemistry as simple starting materials can be utilised. Activating groups (such as halides and organometallic reagents) and toxic/precious metals are not required, and no waste is generated when using stoichiometric levels of reagents.

### 1.3 Industrial Applications of Organic Electrochemistry

The industrial application of organic electrochemistry for the creation of organic commodities has generated considerable interest. Following the development of the Monsanto process for the electrochemical synthesis of acrylonitrile from adiponitrile in the 1960s numerous new processes have emerged. In a review published in 2009, it was estimated that there are approximately 70 commercialised organic electrosynthesis processes implemented globally, some of which are presented in Table 1.1. The Monsanto process is still the largest volume organic electrochemical process in operation.
Table 1.1: Examples of industrial organic electrosynthesis processes.\textsuperscript{13}

<table>
<thead>
<tr>
<th>Product</th>
<th>Starting material</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipoin dimethyl acetal</td>
<td>Cyclohexane</td>
<td>BASF</td>
</tr>
<tr>
<td>Adiponitrile</td>
<td>Acrylonitrile</td>
<td>Monsanto, BASF, Asahi Chemical</td>
</tr>
<tr>
<td>Azobenzene</td>
<td>Nitrobenzene</td>
<td>Johnson Matthey</td>
</tr>
<tr>
<td>2,5-Dimethoxy—2,5-dihydrofuran</td>
<td>Furan</td>
<td>BASF</td>
</tr>
<tr>
<td>Mucic acid</td>
<td>Galacturonic acid</td>
<td>EDF</td>
</tr>
<tr>
<td>3,4,5-Trimethoxytolyl aldehyde</td>
<td>3,4,5-Trimethoxytoluene</td>
<td>Otsuka Chemical</td>
</tr>
</tbody>
</table>

1.4 Chemical Reduction of Amides

Regarding the reactivity of the carbonyl group, the reduction of carboxylic acid derivatives, particularly amides, present a significant challenge to the organic chemist. The general reactivity for the reduction of carbonyl groups is given in Scheme 1.4. This chapter will consider, discuss and present the findings from the literature regarding chemical and electrochemical methods for amide reduction.

\[
\begin{align*}
R'\text{H} & > R\text{CH} > R\text{CO}\text{R'} > R\text{CONH}_2 > R\text{CONR'}_2 > R\text{COOH} > R\text{COOR'} > R\text{COOR'}
\end{align*}
\]

Scheme 1.4: Order of reactivity for the reduction of the carbonyl group.

1.4.1 Hydride Reagents

Nystom and Brown first reported the use of hydride reagents for the reduction of amides to amines in the 1940’s.\textsuperscript{15} Since then, much work has been carried out into the use of these reagents in organic chemistry. Currently, lithium aluminium hydride (LiAlH\textsubscript{4}), diisobutyl aluminium hydride (DIBAL) and sodium bis(2-methoxyethoxy) aluminium hydride (RedAl) are often used in the reduction of amides to amines (Figure 1-3).
LiAlH₄ is a key reagent often employed in the synthesis of drug molecules. For example, the synthesis of paroxetine 1-10, a selective serotonin reuptake inhibitor used to treat depression and post-traumatic stress disorder, was achieved using LiAlH₄ to reduce the enantio-enriched glutarimide 1-11 to a piperidine ring, and an ester to an alcohol at C-2 (Scheme 1.5).

![Scheme 1.5: Amide reduction step for the synthesis of paroxetine 1-10.](image)

Although LiAlH₄ is a useful and reactive reagent, it reacts violently with water, and therefore can only be employed under anhydrous conditions. As a result, much research has been carried out to find safer alternatives. However, improving the stability of the hydride reagent often led to a decrease in reactivity. For example, Red-Al is a non-pyrophoric reducing agent, but produces monomethoxyethanol as a by-product, which is a known teratogen.

Generally, reduction of primary and secondary amides with LiAlH₄ gives the corresponding amines in good yields, but the reduction of tertiary amides can provide a secondary amine as a by-product, particularly if the N-substituents are bulky. LiAlH₄ is an extremely powerful reducing agent, capable of reducing other organic functional groups (such as esters, ketones, aldehydes, carboxylic acids and nitriles), therefore selective reduction of amides can be challenging.

In terms of atom economy, LiAlH₄ has a molecular weight of 38 and can deliver four hydrides per molecule. Despite its high hydride density, it also generates lithium and aluminium hydroxide wastes. These by-products are difficult to separate from the product; the recommended work up is to precipitate and filter the aluminium hydroxide during which the product can be lost. The disposal of waste also exerts an unfavourable environmental impact.
1.4.2 Borane Reagents

Borane is a milder reducing reagent compared to LiAlH₄. Primary, secondary and tertiary amides (aromatic and aliphatic) can be reduced quantitatively to the corresponding amine using an excess of borane in THF.²¹ It is often employed for the reduction of amino acid derived compounds, as well as amides that contain functional groups that are prone to be attacked by LiAlH₄ reagents, namely N-benzylamides, α-fluoro or α-bromoamides, and sulfonylamides.²¹ Following the reduction, acid or base is often employed in the workup, hydrolysing the intermediate to the corresponding amine.²¹ In certain cases borane-amine adducts can be formed as a side-product during the process. Other than strong acids, palladium and Raney nickel have been used to catalyse the methanolysis of the borane-amine adduct, to liberate the product.²²

An example is the final stage of the synthesis of (S)-fluoxetine 1-13, an anti-depressant (Scheme 1.6). A solution of borane in THF proved to be very effective at reducing amide precursor 1-12, but the reaction results in an amine-borane adduct 1-14 (Figure 1-4), which required careful hydrolysis (using 6 M HCl), due to the acid sensitivity of the drug.²³

![Scheme 1.6: Final step for the synthesis of (S)-fluoxetine 1-13.²³](image)

![Figure 1-4: Amine-borane adduct 1-14 formed during synthesis of (S)-fluoxetine.](image)
1.4.3 Silane Reagents

Metal-catalysed reduction of amides in the presence of silane reagents were first demonstrated in the 1980s. In 1982 Corriu et al. reported the hydrosilylation of $N,N$-diethylphenylacetamide with Wilkinson’s catalyst and 1,2-bis(dimethylsilyl)benzene, forming the enamine product via the deoxygenation of the amide. Following this in 1985 Voronkov et al. described the reduction of DMF with a range of silanes in the presence of metal catalysts (e.g. $[\text{Me}_2\text{NH}_2]_2[\text{Rh(CO)}_2\text{Cl}_2]$) to produce the amine and a disiloxane. These preliminary studies generated substantial interest in metal catalysed amide reductions using silane reagents.

Ito et al. showed that a wide range of tertiary amides were reducible to the corresponding amines in high yields with 2 molar equivalents of diphenylsilane (which is detrimental for the E-factor) in the presence of 0.1 mol% of $[\text{RhH(CO)}(\text{PPh}_3)_3]$. Interestingly, it was demonstrated that chemoselective reduction could be achieved when the amide derivative contained ester or epoxide functionality. Scheme 1.7 shows the reduction of 1-15 to the corresponding amine 1-16 in 70% yield, with the ester group remaining intact after the reaction.

![Scheme 1.7: Rhodium catalysed reduction of amides to amines with Ph$_2$SiH$_2$.](image)

Further research by Fuchikami et al. demonstrated that the reduction of tertiary, secondary and primary amides to the corresponding amines could be achieved using monohydrosilanes and a range of transition metal catalysts such as ruthenium, platinum, palladium and rhodium in good yields.

Inexpensive titanocene catalysts (2-10 mol%) in the presence of PhMeSiH$_2$ have also been used to catalyse the reduction of a range of acetamide derivatives to the tertiary amines. Scheme 1.8 shows the reduction of acetamide 1-17 to amine 1-18 using Cp$_2$TiF$_2$. 
Scheme 1.8: Reaction of acetamide derivative 1-17 with PhMeSiH2.

It was shown that tertiary amides with bulky N-substituents can be reduced in yields of up to 87% after 20 hours under reflux using silane reagents (2 mmol) in the presence of catalytic amounts of dioxomolybdenum dichloride (10% mol). This catalyst can also be used with several silanes including hydrosilanes and polysiloxanes. On the other hand, H2PtCl6·6H2O only reduces tertiary amides in the presence of siloxanes containing two Si-H groups. Limitations have also been identified for the use of rhodium catalysts: Ph2SiH2/RhH(CO)(PPh3)3 only reduces tertiary amides and Ph2SiH2/[RhCl(PPh3)3] can only reduce secondary amides with bulky substrates.

Nagashima et al. described the efficient reduction of carboxylic acids, esters and amides using trialkylsilanes and a triruthenium carbonyl cluster bearing a bridging acenaphthylene ligand. Nagashima’s group carried out further research into the platinum catalysed silane reduction of carboxamides to tertiary amines, demonstrating that platinum catalysts are active when siloxanes contained more than two Si-H groups. High yields of up to 95% were obtained using 0.01 mol catalyst, 3.7 mmol Si-H and a reaction time of 3 hours. Using polymethylhydrosiloxane (PMHS) enhances amide reduction and also contributes to forming an insoluble siloxane resin which by encapsulates the platinum catalyst. The platinum catalytic system provided higher yields of the amine product compared to the molybdenum system. The reaction time was also greatly reduced from 20 hours to 3 hours using the platinum catalyst rather than the molybdenum catalyst.

A mechanistic and development investigation was carried out by Brookhart et al. into the use of iridium silyl complexes to reduce tertiary amides. It was found that Ir(III) complex, [(2,6-bis(di-tert-butylphosphino)phenyl)Ir(H2)(acetone)]+, catalysed the reduction of a range of tertiary amides to the corresponding amine using diethylsilane as the reducing agent under an H2 atmosphere (1 atm). Low catalysts loadings of 0.01% achieved quantitative conversion and functional groups such as alkenes, ethers, nitriles and halides were tolerated. However the system did not work for primary or secondary amide reduction. Furthermore, the
reactions were only carried out on NMR scale in chlorobenzene-$D_5$, with only one example carried out at a larger scale (< 1g). Coupled with the expense of Ir, it does not make this process particularly attractive.

Charette *et al.* reported a metal-free procedure to reduce tertiary amides to tertiary amines\(^{32}\) and has recently further developed the technique to selectively reduce secondary amides to imines, aldehydes and amines (Scheme 1.9).\(^{33}\) The secondary amide was activated with triflic anhydride which can then be reduced to the iminium ion using triethylsilane. The imine 1-19 is isolated with a basic workup and the aldehyde 1-20 obtained from an acidic workup. To isolate the amine 1-21 a further reductive amination is achieved by the addition of Hantzsch ester hydride (HEH).

![Scheme 1.9: Selective reduction of secondary amides to imines 1-19, aldehydes 1-20 or amines 1-21.\(^{33}\)](image)

The method described achieves reasonable product yields (70-95%), does not involve costly metal catalysts and is compatible with a variety of functional groups such as alkenes, external alkynes, esters and epoxides. However triflic anhydride is highly water sensitive and low temperatures and a dichloromethane are required which are not desirable conditions for the pharmaceutical industry.

The ample availability of iron and the often low toxicity makes it an attractive material for catalyst development.\(^{34}\) Beller *et al.* described the iron catalysed reduction of tertiary and secondary amides to the corresponding amines using the inexpensive silane polymethylhydrosiloxane (PMHS). \(N,N\)-dimethylbenzamide 1-22 was used as the model substrate and a high yield of 93% was obtained using a 2 mol\% [Fe\(_3\)(CO)\(_{12}\)] and 5 eq. PMHS in toluene.\(^{34}\) This work was further extended to the reduction of primary amides, however two different iron complexes in a sequential mode were required to afford the primary amine.\(^{35}\) The conditions required to reduce benzamide 1-22 are given in Scheme 1.10.\(^{35}\)
Although the iron catalyst complexes successfully reduced a range of primary, secondary and tertiary amides, the process is not atom efficient as up to 5 equivalents of the silane reagents are required as the reducing agent.

**Scheme 1.10: Diiron catalysed hydrosilylation of benzamide 1-22 to benzylamine 1-23.**

In summary, silane reagents provide an alternative method for amide reduction but they do not meet the criteria of green chemistry. On large scale applications, the cost of the silane must be considered, stoichiometric levels of silica waste is generated, often a precious or toxic metal catalyst is required to catalyse the reaction, and the reactions are carried out in solvents such as dichloromethane, toluene or chlorobenzene.

### 1.4.4 Catalytic Hydrogenation

The most atom efficient chemical reducing agent is molecular hydrogen (H\(_2\)). Catalytic hydrogenation would provide the most atom economical route for the reduction of amides to amines with ideal reaction conditions being <30 atm H\(_2\) and 70 °C.

Wojcik and Adkins first reported the catalytic hydrogenation of amides to amines using a copper-chromium oxide catalyst at high catalytic loadings (ca. 20 wt%), high temperatures of up to 250 °C and high pressures of 200-300 atm. \(^{39}\) N-substituted succinimides 1-24 were reduced to the corresponding amines 1-25 in high yields whereas N-substituted phthalimides 1-26 were hydrogenated to give 1-27 and 1-28. Under these harsh reaction conditions, the aromatic ring was also hydrogenated, and the tertiary amide reduced to the secondary amine (Scheme 1.11). \(^{39}\)
Amides can also be hydrogenated over rhenium catalysts at 185-245 °C to the corresponding amine under high pressures of H₂; examples include the reduction of acetamide 1-29⁴⁰, N-phenylacetamide 1-31⁴⁰ and N-ethyl-N-phenylacetamide 1-34⁴¹ (Scheme 1.12). The primary and tertiary amides were reduced selectively to the amine product in high yields, however the secondary amide N-phenylacetamide 1-31 was reduced to N-ethylaniline 1-32 and the side product aniline 1-33.

Further development has shown that bimetallic catalysts of groups 6-9 metals were effective at reducing amides in high yields but high temperatures and pressures were still required (160°C and 100 atm).⁴² These conditions are too harsh to use for the production of drug compounds with thermally unstable functionalities.
More recently, a new method for catalytic hydrogenation of amides to amines under milder conditions has been described. A range of bi- and tri-metallic catalysts have been screened for the reduction of N-acetylpyrrolidinone 1-36 to N-ethylpyrrolidinone 1-37. At 70 °C, the most successful catalyst was found to be Pt-Re-In supported on silica, which afforded a modest 50% yield of the amine (Scheme 1.13), with a higher yield of 80% achieved at 130 °C and 10 atm. Although these results show promise, the study was restricted to the reduction of N-acetylpyrrolidinone and therefore only have limited applications.

![Scheme 1.13: Catalytic hydrogenation of N-acetylpyrrolidinone 1-36.](image)

In 2007, a homogeneous catalytic system for the hydrogenation of butanamide 1-38 was reported by Cole-Hamilton et al. Using a [Ru(acac)₃] (1% Ru) and triphos (1,1,1-tris(diphenylphosphinomethyl)ethane) (2% triphos) catalyst at 39 atm H₂ and 164 °C for 14 hours (Scheme 1.14), the reaction produced a mixture of products, including the primary amine butylamine 1-41, the secondary amine N,N-dibutlyamine 1-39 and the tertiary amine tributylamine 1-40. The addition of aq. ammonia and using a [Ru₂(Triphos)₃Cl₃]Cl catalyst, the selectivity can be improved, leading to the formation of the primary amine butylamine 1-45 with up to an 85% yield.

![Scheme 1.14: Homogeneous hydrogenation of butanamide with a Ru-Triphos catalyst.](image)

Whyman et al. reported the catalytic hydrogenation of cyclohexylcarboxamide 1-42 to cyclohexanemethylamine 1-43 using a ruthenium/molybdenum bimetallic catalyst, generated
in situ from triruthenium dodecacarbonyl \([\text{Ru}_3(\text{CO})_{12}]\) and molybdenum hexacarbonyl \([\text{Mo}(\text{CO})_6]\) (Scheme 1.15). A side product of cyclohexylmethanol 1-44 was also formed during the hydrogenation. Interestingly, no ammonium or amine was required to suppress any side reactions. The optimum catalyst composition was found to be ca. 50% of each metal and the optimal reaction conditions were 20-100 atm \(\text{H}_2\) and 145-160 \(^\circ\text{C}\). Although amide reduction was successful at low pressures of 20 atm \(\text{H}_2\), at operational temperatures below 145 \(^\circ\text{C}\) amide hydrogenation was not achievable. In the case of the hydrogenation of benzamide, \(N\)-methylbenzamide and \(N_N\)-dimethylbenzamide, using the Ru/Mo catalyst lead to the hydrogenation of the aromatic ring.

![Scheme 1.15: Catalytic hydrogenation of cyclohexylcarboxamide 1-42 with Ru/Mo bimetallic catalyst.](image)

The first hydrogenation of a tertiary amide, \(N\)-methylpyrrolidine-2-one 1-45 to the corresponding amine 1-46 was reported by Burch et al. to occur at a relatively low temperature and pressure (100 \(^\circ\text{C}\) and 20 atm \(\text{H}_2\)) using a platinium-rhenium bimetallic catalyst (4 wt% Pt- 4 wt% Re) (Scheme 1.16). It was found that the interaction between the Pt and Re was vital to form an active catalyst and a TiO\(_2\) support further promoted the catalytic activity. A high conversion of 90% was recorded and >99% selectivity to the amine after 24 hours.

![Scheme 1.16: Catalytic hydrogenation of \(N\)-methylpyrrolidine-2-one 1-45 to \(N\)-methylpyrrolidine 1-46 at low temperature and pressure using a Pt/Re catalyst.](image)

Although much progress has been made recently in the development of catalytic systems for catalytic hydrogenation, there still remains a methodology that can successfully reduce amides to amines under ambient conditions.
1.4.5 **Biocatalytic Reduction**

There are certain enzymes that can reduce amides to amines, providing an attractive method for amine synthesis, as these processes can occur under ambient conditions in benign reaction environments.

Clostridium sporogenes had been used to successfully reduce benzamide 1-47 to benzylamine 1-48 in 73% yield using 10 g L\(^{-1}\) of the biocatalyst (Scheme 1.17).\(^{46,47}\)

\[\begin{align*}
\text{1-47} & \xrightarrow{\text{H}_2\text{O}} \text{COOH} \\
\text{1-47} & \xrightarrow{\text{H}_2\text{O}} \text{NH}_2 \\
\text{1-47} & \xrightarrow{\text{H}_2\text{O}} \text{CHO} \\
\text{1-47} & \xrightarrow{\text{H}_2\text{O}} \text{NH} \\
\text{1-48} & \xrightarrow{\text{NAD(P)}{H} + H^+} \text{NAD(P)}^+ \\
\text{1-48} & \xrightarrow{\text{NAD(P)}{H} + H^+} \text{NAD(P)}^+ \\
\text{1-48} & \xrightarrow{\text{NH}_3^+} \\
\end{align*}\]

**Scheme 1.17: Proposed mechanism of biocatalytic amide reduction.**\(^{46}\)

Under anaerobic conditions, C. sporogenes uses amino acids as respiratory electron acceptors to metabolise an amide to the amine. Competitive hydrolysis of the amide could lead to the acid product, however this pathway is not favoured, as benzoic acid is not a widely used energy source in anaerobic respiration. Although this method would provide an environmentally benign process there are major challenges to be overcome before this technology can be employed on an industrial scale.\(^{46}\)

1.5 **Electrochemical Reduction of Amides**

Oxidation and reduction of functional groups are important transformations in organic synthesis and electrochemical synthesis offers a greener approach to these transformations.\(^{48}\)

Although it is not a widely applied technique, synthetic electrochemistry is a growing research area and there have been a number of reviews that highlight its applications.\(^{49,50,51,52}\)

Theoretically, the reduction of amides to amines can be effected electrochemically by a route summarised in Scheme 1.18.
Chapter 1  Introduction

Scheme 1.18: Electrochemical reduction of amides to amines.

The carbonyl group of amides, lactams and imides has been reported to be reduced electrochemically using lead and mercury cathodes in acidic catholytes.\textsuperscript{53, 54} Depending on the structure of the starting material, reaction conditions and the acidity of the catholyte, the reduction can lead to different products (outlined in Scheme 1.19).

\[
\text{Cathode: } \quad \text{RCONH}_2 + 4\text{H}^+ + 4\text{e}^- \xrightarrow{\text{reduction}} \text{RCH}_2\text{NH}_2 + \text{H}_2\text{O} \quad [1-1]
\]

\[
\text{Nafion membrane: } \quad \text{H}^+ \text{ (anolyte)} \xrightarrow{\text{oxidation}} \text{H}^+ \text{ (catholyte)} \quad [1-2]
\]

\[
\text{Anode: } \quad 2\text{H}_2\text{O} \xrightarrow{\text{oxidation}} \text{O}_2 + 4\text{H}^+ + 4\text{e}^- \quad [1-3]
\]

\[
\text{Overall reaction: } \quad \text{RCONH}_2 + \text{H}_2\text{O} \xrightarrow{\text{reduction}} \text{RCH}_2\text{NH}_2 + \text{O}_2 \quad [1-4]
\]

Scheme 1.19: Products accessible from cathodic reduction.\textsuperscript{53}

The most common competitive processes are the formation of aldehydes and alcohols, which can be dependent on pH. For example, Lund demonstrated that isonicotinic amide 1-49 was reduced to the aldehyde 1-50 in strong acidic solutions (pH <1), while the alcohol 1-51 was formed in a less acidic (pH 3.5) solution (Scheme 1.20).\textsuperscript{55}
On the other hand, the reduction of nicotinamide 1-52 under aqueous acidic conditions (< pH 3) was carried out by Mellado et al. and they found that the product of the 2-electron, 2-proton transfer reaction provided the hydrated form of the aldehyde 1-53 (Scheme 1.21).56

Scheme 1.21: Mechanism for the electrochemical reduction of nicotinamide 1-52.

Aliphatic amides were also reduced to the aldehyde with electrochemically generated solvated electrons in methylamine, using lithium chloride as the supporting electrolyte.57 Aromatic amides in neutral or basic alcoholic catholytes provides the alcohol; N-benzylbenzamide 1-54 in alcoholic media gave either benzylalcohol 1-55 and ammonia or benzylamine 1-56 from the cleavage reaction (Scheme 1.22).54, 58 The product afforded in this case is dependent on the electrolyte used (the potential is not quoted for the reduction).
Thus, reaction conditions have to be carefully controlled for optimum selectivity. Generally, amides were reduced electrochemically to the corresponding amine in acid catholytes using lead cathodes.\textsuperscript{59} Imides were also reduced in acid catholytes, largely at Pb cathodes. As early as 1899, Tafel demonstrated that N,N-dimethylbenzamide 1-57 can be reduced to N,N-dimethylbenzylamine 1-58 using 50% H\textsubscript{2}SO\textsubscript{4} at 35 °C and a lead cathode (Scheme 1.23).\textsuperscript{60} A current efficiency of 11% was recorded and a yield of 63% achieved.

Table 1.2 shows the structures of some amides and imides that have been reduced electrochemically; it is worth noting that most of these reports are old, with many dating from the 1940’s-1960’s. It is clear from the results that more substituted the N-groups afford greater yields of the amine products, suggesting that reduction is easier as the electron donating character of the N-substituent’s or α–carbon atom is increased.\textsuperscript{59}
Table 1.2: Electrochemical reduction of amides and imides.\textsuperscript{59,61}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Cathode material</th>
<th>Amine Yield / %</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] |
|       | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Pb | 39 |
| 2     | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Hg | 92 |
| 3     | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Pb, Hg | 100 |
| 4     | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Zn, Hg | 100 |
| 5     | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Pb | 56 |
| 6     | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Hg | 93 |
| 7     | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Pb, Hg | 97 |
| 8     | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Hg | 97 |
| 9     | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Hg, Pb, Cd | 97 |
| 10    | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\] | Zn, Cd, Pb | 61 |
Swann et al., successfully reduced anisamide to 4-methoxybenzylamine at etched zinc, cadmium and lead cathodes in H$_2$SO$_4$ catholytes. A lead cathode provided the best yield of 4-methoxybenzylamine (61%) with a cathode area of 100 cm$^2$, current density 0.05 A cm$^{-2}$ between 30-37 °C.

Several studies have reported the electrochemical reduction of phthalimide derivatives; Sakurai reduced phthalimide, $N$-methylphthalimide, and $N$-ethylphthalimide at zinc amalgam cathodes using acid electrolytes.

Much more recently, Fechete and Jouikov reported a cathodic reduction of phthalimide 1-59 to 2,3-dihydro-1H-isoindoline 1-60 (Scheme 1.24).

![Scheme 1.24: Reduction of phthalimide 1-59 to 2,3-dihydro-1H-isoindoline 1-60.](image)

In this work, the reduction was performed in a water-acetonitrile electrolyte acidified with H$_2$SO$_4$ using a range of cathodes. In an acidic media, hydrogen evolution was a competitive process with carbonyl reductions. Thus, to achieve improved current efficiency for the reaction, cathode materials with high hydrogen evolution over-potentials (Pb, Hg, Cd) were chosen. The potential window used to maintain high current efficiency at pH 2 was $-0.9 \text{ V} < E < -1.1 \text{ V (SCE)}$, where yields of 1-60 achieved at Hg, Cd and Pb were 97%, 95% and 82% respectively, comparing very favourably with a 50% reported yield of 1-60 obtained via chemical reduction of phthalimide (using BH$_3$/THF). Furthermore there are no side products, and complex workup procedures are not required.

The reduction of the tetrachlorophthalimide 1-61 provides an example of how potential controlled electrolysis can direct the selectivity of the product formed (Scheme 1.25).
Scheme 1.25: Potential controlled reduction of tetrachlorophthalimide 1-61.\textsuperscript{65}  
As shown in Scheme 1.25, it is clear that the alcohol 1-62 is formed at a less negative potential (-0.68 V) than the reduction potential required to form the isoindoline derivative 1-63 (-1.1 V).

The complete reduction of succinimide 1-64 to pyrrolidine 1-65 was achieved at a zinc amalgam cathode in a 50% (w/v) H\textsubscript{2}SO\textsubscript{4} electrolyte (Scheme 1.26).\textsuperscript{66} When succinimide 1-64 was electrolysed at a current density of 1 A m\textsuperscript{-2} for 6 hours, a 14% yield of the pyrrolidine 1-65 hydrochloride salt was recovered, increasing to 28% when the reaction time was doubled. If the concentration of the H\textsubscript{2}SO\textsubscript{4} electrolyte exceeded 50% (w/v) the succinimide decomposed to succinic acid and ammonia. In contrast, no decomposition of the starting material was found if a concentration of less than 30% was used. N-methylsuccinimide and N-ethylsuccinimide were also fully reduced to the corresponding pyrrolidine using a zinc cathode and H\textsubscript{2}SO\textsubscript{4} electrolyte.\textsuperscript{67}

Scheme 1.26: Reduction of succinimide 1-64 to pyrrolidine 1-65.\textsuperscript{66}  
The reduction of glutarimide 1-66 to piperidine 1-67 was carried out in two steps (Scheme 1.27): the first reduction to piperidone was achieved using a zinc amalgam cathode in a 20-30% solution of H\textsubscript{2}SO\textsubscript{4}, the second reduction utilised the same cathode material, but the
concentration of the electrolyte was increased to 50% H$_2$SO$_4$. The current density for the reduction was 88.6 A cm$^{-2}$, the cathode area was 15.8 cm$^2$ and the temperature was 25 °C. Under these conditions, 47% of the piperidine hydrochloride can be recovered. A zinc amalgam cathode was chosen for the global reduction to the amine, as it was found to suppress the level of decomposition of the starting material. In the case of N-phenyl glutarimide, a lead cathode and 90% H$_2$SO$_4$ electrolyte was used for the first carbonyl reduction. For the second reduction, the lead cathode was replaced with a zinc amalgam cathode in a 50% H$_2$SO$_4$ electrolyte solution.

Scheme 1.27: Reduction of glutarimide 1-66 to piperidone 1-67.

Electrolytic reductions of acyclic amines have also been reported. These include the transformation of N,N-dimethylvaleramide 1-68 to N,N-dimethylamylamine 1-69 and acetanilide to ethylaniline, which were conducted in H$_2$SO$_4$ at cadmium, tin, lead, mercury and zinc electrodes; lead provided the highest yield of both amines, around 50%. The conditions for the reduction of 1-68 were 30 % H$_2$SO$_4$ cathode area of 100 cm$^2$, current density 0.05 A cm$^{-2}$ and a temperature of 30 °C (Scheme 1.28). Lead was the only cathode that showed marked activity although zinc and cadmium showed some activity.

Scheme 1.28: Electrochemical reduction N,N-dimethylvaleramide 1-68.

Further examples of the electrochemical reduction of aliphatic amides 1-69 was demonstrated by Sabol et al. in the 1960’s, however the products of the reaction were the corresponding alcohol 1-70 or aldehyde 1-71 (Scheme 1.29). The reduction was carried out at a Pt electrode using monomethylamine and lithium chloride as the electrolyte and when ethanol was used as the proton source, the product of the reaction was the aldehyde. Table 1.3 displays the results obtained for the electrochemical reduction of a range of aliphatic amides to alcohols or aldehyde.
Scheme 1.29: Electrochemical reduction of aliphatic amides 1-69.\textsuperscript{57}

Table 1.3: Electrochemical reduction of aliphatic amides to the corresponding alcohol or the aldehyde.\textsuperscript{57}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Alcohol Yield / %</th>
<th>Aldehyde Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{amide} )</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>( \text{amide} )</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>( \text{amide} )</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>( \text{amide} )</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>( \text{amide} )</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>( \text{amide} )</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>( \text{amide} )</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>( \text{amide} )</td>
<td>93</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>( \text{amide} )</td>
<td>0</td>
<td>45</td>
</tr>
</tbody>
</table>
It is clear from this literature survey that amides and imides can be reduced electrochemically, but much of the work discussed above pre-dates the advent of modern spectroscopic techniques for accurate product characterisation. Most of the reductions were carried out in H$_2$SO$_4$ electrolytes and generally at lead cathodes, due to its high overpotential for hydrogen evolution. Lead also showed higher activity over other cathode material for the reduction of amides.

### 1.6 Chemical Reduction of C=C bonds

The utility of alkenes and alkynes in synthetic and natural products chemistry and the petroleum, pharmaceutical and agrochemical industries prompted the development of their chemistry. In particular, the reduction of alkenes has become an essential process for the synthesis of bulk and fine chemicals. Typically, C=C bond reduction is achieved by catalytic hydrogenation using homogenous or heterogeneous catalysts (Pd or Pt catalyst) and high pressures of molecular hydrogen.

In 2001 the Nobel Prize in Chemistry was awarded to S. Knowles and R. Noyori for their contribution to asymmetric catalysed hydrogenation reactions. Although there are numerous techniques that have been developed in organic synthesis to achieve C=C bond reduction, selective and asymmetric reduction still provides a real challenge to the organic chemist. A great deal of work has been undertaken over the last 50 years into the development of hydrogenation catalysts for the reduction of alkenes. In this literature review the methodologies to reduce C=C bonds and conjugated C=C bonds will be reviewed.

#### 1.6.1 Catalytic Hydrogenation of C=C Bonds

##### 1.6.1.1 Metallic catalysts

The first examples of heterogeneous catalytic hydrogenation of ethene and other C=C systems were first described in the 1890’s by Sabatier. However, it was the pioneering work carried out in the 1960’s by Halpern and Wilkinson that led to the first homogeneous catalysts for alkene hydrogenation.

Halpern et al. reported the successful hydrogenation of maleic, fumaric and acrylic acids using a Ru(II) catalyst, Scheme 1.30 shows the hydrogenation of maleic acid 1-72 to succinic acid 1-73. The Ru(II) catalyst was prepared by the reduction of (NH$_4$)$_2$RuCl$_6$ with TiCl$_3$. 

---

54
Scheme 1.30: Homogeneous catalytic reduction of maleic acid 1-77 using a Ru (II) catalyst.\textsuperscript{76}

In 1965 Wilkinson described a rhodium-based catalyst that was capable of reducing alkenes and acetylenes under homogeneous catalysis conditions.\textsuperscript{77} The catalyst used was \textit{tris}(triphenylphosphine)chlororhodium(I) and have since become known as Wilkinson’s catalyst. The mechanism of alkene hydrogenation using the Wilkinson catalyst is given in Scheme 1.31.

Scheme 1.31: Mechanism for the hydrogenation of alkenes using the Wilkinson’s catalyst.\textsuperscript{78}

Early asymmetric hydrogenation catalysts were based on rhodium and ruthenium centres with chiral diphospine ligands such as DIPAMP, DIOP and BINAP (Figure 1-5), some are still commonly used today.\textsuperscript{79} Since the 1970s an impressive number of rhodium and ruthenium catalysts with chiral phoshine ligands have been developed, which induce very high enantioselective hydrogenation products.\textsuperscript{80} However rhodium and ruthenium catalysts require a coordinating group next to the C=C bond to achieve hydrogenation in high enantiomeric excess.
The field of iridium-catalyzed hydrogenation began with the discovery of Crabtree’s catalyst, [Ir(pyridine)(Cy3P)(COD)] PF6 (COD: 1,4-cyclooctadiene) in 1977.81, 82 Iridium catalysts were further developed by the Pfaltz group, in 1998 they discovered an iridium complex with chiral P, N ligands, developed to hydrogenate unfunctionalised alkenes with high enantioselective excess (Figure 1-6).80, 83, 84 Over the past decades, a range of iridium catalysts have been developed to hydrogenate a wide range of alkenes to provide excellent enantioselectivities.79, 85

Very recently, Chirik et al. described the asymmetric hydrogenation of alkenes using enantiopure C_1-symmetric bis(imino)-pyridine cobalt complex catalysts.86 Using this catalyst, enantioselective hydrogenation of geminal substituted alkenes 1-76 to 1-78 can be achieved (Scheme 1.32). High conversions to the alkane products were found with high enantiomeric excess (>90% ee). The transformations were carried out at ambient temperature, low pressure and low catalytic loading but the reaction time was long, and benzene (toxic) was used as the solvent.
1.6.1.2 Non-metallic catalysts

In 2006, Stephan et al. introduced the concept of “frustrated Lewis pairs” (FLPs), combinations of bulky Lewis acids (e.g. boranes or aluminum compounds) and bases (e.g. phosphines or amines), which are prevented from the formation of Lewis adducts by steric hindrance. These FLPs could heterolytically cleave $\text{H}_2$, forming phosphonium borates of the form $[\text{R}_3\text{PH}][\text{BHR}_3]$ (Scheme 1.33). They further reported the first non-metal system known to reversibly activate and liberate $\text{H}_2$.

For example, the phosphonium borate $(2,4,6-\text{Me}_3\text{C}_6\text{H}_2)_2\text{PH}(\text{C}_6\text{F}_4)\text{BH}(\text{C}_6\text{F}_5)_2$ 1-82 was formed by reaction of the phosphine–borane species $(2,4,6-\text{Me}_3\text{C}_6\text{H}_2)_2\text{P}(\text{C}_6\text{F}_4)\text{B}(\text{C}_6\text{F}_5)_2$ 1-81 with $\text{H}_2$ while heating of the zwitterion above 100 °C liberated hydrogen and regenerated the original FLP species (Scheme 1.34). This system provided the first metal-free catalyst for the hydrogenation of imines, nitriles, and aziridines to produce primary and secondary amines in high yields under relatively mild reaction conditions (5% mol. catalyst, 80°C, 5 atm. $\text{H}_2$).
Scheme 1.34: Catalytic cycle for the reduction of imines using FLP and H₂.

In the following years, several other FLP systems and applications were developed. Several examples of alkenylboranes were shown to undergo reactions with H₂, heterolytically splitting dihydrogen in the presence of the Lewis base DABCO while retaining the C=C double bond (Scheme 1.35). They were also reported to act as catalysts for the hydrogenation of imines under relatively mild reaction conditions (5% mol. catalyst, 120°C, 5 atm H₂).

Scheme 1.35: Heterolytic cleavage of H₂ using amine–borane species.

Interestingly, some of these alkenylboranes also catalysed the selective hydrogenation of the electron-poor C=C double bonds of diaryl-substituted enones 1-88 (Scheme 1.36).

Scheme 1.36: Catalytic enone 1-88 hydrogenation using alkenylborane/DABCO FLP
1.7 Alternative C=C Bond Reduction Techniques

1.7.1 Sodium Borohydride and Metal Salt Systems

The selective reduction of the C=C bond in conjugated alkenes has been demonstrated by Ranu et al. using an indium (III) chloride catalyst and sodium borohydride as the hydride source in acetonitrile.\textsuperscript{92} Alkenes substrates such as \(\alpha,\alpha\)-dicyano olefins, cyanoesters, cyanophosphates, \(\alpha,\beta\)-unsaturated nitriles and dicarboxylic esters were all successfully reduced to the alkane product \textit{1-91} in high yields and fast reaction times. However, it was found that for the reduction of chalcones \textit{1-92}, both the C=C bond and the carbonyl group could both be reduced. If the reaction was quenched with water, a mixture of the saturated ketone and the alcohol was formed, whereas quenching with MeOH lead to the sole formation of the alcohol. Scheme 1.37 presents the conditions required for the reduction of the C=C bond of a conjugated alkene and the reduction of a chalcone to the alcohol \textit{1-93} product.

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Et} \\
\text{H} & \\
\text{CN} & \\
\text{PhCN} & \\
\text{CO}_2\text{Et} & \\
\text{Ph} & \\
\text{H} & \\
\text{H} & \\
\text{1-91} & \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \\
\text{H} & \\
\text{1-91} & 88\%
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{CO} \quad \text{Ph} \\
\text{1-92} & \\
\text{PhCN} & \\
\text{CO}_2\text{Et} & \\
\text{Ph} & \\
\text{H} & \\
\text{H} & \\
\text{1-91} & \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \\
\text{H} & \\
\text{1-91} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{CO} \quad \text{Ph} \\
\text{1-92} & \\
\text{PhCN} & \\
\text{CO}_2\text{Et} & \\
\text{Ph} & \\
\text{H} & \\
\text{H} & \\
\text{1-91} & \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \\
\text{H} & \\
\text{1-91} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{CO} \quad \text{Ph} \\
\text{1-92} & \\
\text{PhCN} & \\
\text{CO}_2\text{Et} & \\
\text{Ph} & \\
\text{H} & \\
\text{H} & \\
\text{1-91} & \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \\
\text{H} & \\
\text{1-91} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{CO} \quad \text{Ph} \\
\text{1-92} & \\
\text{PhCN} & \\
\text{CO}_2\text{Et} & \\
\text{Ph} & \\
\text{H} & \\
\text{H} & \\
\text{1-91} & \\
\end{align*}
\]
Alternative methodologies for C=C reduction include using solvents to provide a source of hydrogen such as 2-propanol and hydroxylamine (NH$_2$OH) in the presence of a catalyst.$^{94,95}$

### 1.7.2 Non-metallic Reagents

The Hantzch ester (1,4-dihydropyridine ester 1-98) was reported as an effective reducing agent for the reduction of C=C bonds conjugated to electron withdrawing groups. Garden et al. described the reduction of 3-methyleneoxindoles 1-96 using the Hantzch ester to the saturated product 1-97 (Scheme 1.39).$^{96}$ Good yields were observed and it was found that the reaction rate was dependent on the substituent groups. Chemoselective reduction was observed but the solvent system used for the reaction incorporated benzene, which is not an acceptable solvent in green chemistry.

![Scheme 1.39: Reduction of 3-methyleneoxindoles 1-101 using the Hantzch ester 1-103.\textsuperscript{96}](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-96a</td>
<td>H</td>
<td>CO$_2$Et</td>
<td>CO$_2$Et</td>
<td>92</td>
</tr>
<tr>
<td>1-96b</td>
<td>H</td>
<td>CN</td>
<td>CN</td>
<td>80</td>
</tr>
<tr>
<td>1-96c</td>
<td>Me</td>
<td>CN</td>
<td>CN</td>
<td>70</td>
</tr>
<tr>
<td>1-96d</td>
<td>H</td>
<td>CN</td>
<td>CO$_2$Me</td>
<td>89</td>
</tr>
<tr>
<td>1-96e</td>
<td>H</td>
<td>CN</td>
<td>CO$_2$Et</td>
<td>85</td>
</tr>
</tbody>
</table>

### 1.7.3 Silane Reagents

Silanes have also found utility for the reduction of conjugated C=C bonds in the presence of an oxo-rhenium catalyst.$^{97}$ The reduction of 3-phenylpropanoate 1-99 using a ReIO$_2$(PPh$_3$)$_2$ catalyst and the silane PhMe$_2$SiH (Scheme 1.40). The reaction was carried out under solvent free conditions and at 45 °C, however the reaction required 24 hours to afford only a moderate yield of the saturated product.$^{97}$
Scheme 1.40: Reduction of 3-phenylpropanoate 1-99 using a ReIO₂(PPh₃)₂ catalyst and PhMe₂SiH.

Xu et al. recently described the use of PMHS, combined with a malononitrile, for the reduction of the C=C bond of α,β-unsaturated ketones, catalysed by bismuth triflate (Scheme 1.41). High yields were recorded for the reaction and no hydrosilylation of the carbonyl group was observed. However, the reaction progressed at a slow rate (50 hours), 7 equivalents of the silane PMHS was required and the solvent used was dichloromethane, making this process undesirable as a green process.

Scheme 1.41: Reduction of αβ-unsaturated ketones.

1.7.4 Biological Techniques

Clostridium sporogenes (previously described for the reduction of amides, section 1.4.5) has been used for the reduction of the C=C bond of β,β-disubstituted nitroalkenes 1-103 and α,β-disubstituted nitroalkenes 1-105 (Scheme 1.42), under a H₂ atmosphere. In the case of the reduction of β,β-disubstituted nitroalkenes 1-103, high enantioselective reduction was achieved with >97% ee and relatively good yields of up to 86%. However for the reduction of α,β-disubstituted nitroalkenes 1-105 with C. sporogenes, high yields were not observed.
Interest in the electrochemical reduction of C=C bonds began in the 1940’s with the pioneering work of Wawzonek and Laitinen.\textsuperscript{100} They reported that it was challenging to reduce isolated ethylenic bonds that were not conjugated to a carbonyl group or a nitro group. However, they demonstrated that phenyl-substituted alkene and acetylene groups were reducible at the dropping mercury electrode (DME).\textsuperscript{100} Scheme 1.43 displays the compounds that were reduced in Wawzonek and Laitinen’s study.

Considering the reduction of the C=C bonds presented in Scheme 1.43, it was found that all of the groups were reducible and the hydrogenated products were obtained. Interestingly, increasing the substitution of the C=C bond facilitated the reduction process, as the reduction potential became less cathodic with the addition of each phenyl ring. This is potentially interesting, as these sterically bulky substrates are generally challenging for metal surface-catalysed processes.

In the case of C≡C reduction it was found that phenylacetylene 1-115 was fully reduced in a 4-electron process, to provide the fully saturated product ethyl benzene 1-116. The reduction potentials of styrene 1-113 and phenylacetylene 1-115 were comparable at -2.34 V and -2.37 V (vs. SCE).
Scheme 1.43: Reduction of C=O and C≡O bonds of phenyl substituted alkene and acetylene at the Dropping Mercury Electrode. A 75% dioxane/H₂O electrolyte was used with tetrabutylammonium iodide as the supporting electrolyte.

The reductions of 4-allylanisole and 1-heptyne however were not successful at the DME, suggesting that isolated C=C and C≡C bonds were difficult to reduce electrochemically. However, Campbell and Young demonstrated that alkyl and aryl acetylenes could be reduced easily to alkenes at a spongy nickel cathodes (Scheme 1.44). A current of 2 A was applied during the electrolysis, using an electrolyte of ethanol and H₂SO₄.
Scheme 1.44: Reduction of alkyl and aryl acetylenes at a spongy nickel electrode.

Under these conditions, other C≡C bonds were reducible (Scheme 1.44). Moderate to good yields were obtained of the products and in the case of the 4-octyne \textit{1-119}, 5-decyne \textit{1-121} and diphenylacetylene \textit{1-126} the \textit{cis}-products were obtained. In the case of phenylacteylene \textit{1-123}, the C≡C bond underwent a 2-electron reduction to provide the alkene product and a 4-electron reduction to provide the alkane product. Experiments were also carried out using lead, cadmium and platinum electrodes but were unsuccessful.

The electrochemical reduction of a range of C=C bonds are presented in Table 1.4.\textsuperscript{59} Interestingly, the reduction of the aliphatic C=C bond of ethyl acrylate (entry 1) at a mercury electrode led to the formation of a dimer product in a moderate yield. Considering the reduction of entry 2 and entry 3, the C=C bond was selectively reduced at a mercury electrode. In the case of benzoic acid and phenyl acetic acid (entry 4 and 5 respectively) a platinum electrode was used to reduce the C=C bonds and also the aromatic rings, to provide the cyclohexane acid products.
Table 1.4: Electrochemical reduction of C=C bonds.\textsuperscript{59}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Cathode material</th>
<th>Yield /</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>Hg</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>Hg</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="structure5.png" alt="Structure" /></td>
<td><img src="structure6.png" alt="Structure" /></td>
<td>Hg</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="structure7.png" alt="Structure" /></td>
<td><img src="structure8.png" alt="Structure" /></td>
<td>Pt</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="structure9.png" alt="Structure" /></td>
<td><img src="structure10.png" alt="Structure" /></td>
<td>Pt</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="structure11.png" alt="Structure" /></td>
<td><img src="structure12.png" alt="Structure" /></td>
<td>Pb, Cd, Sn</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

In 1983, an example of asymmetric electrochemical reduction was reported by Nonaka \textit{et al.} by utilising a poly-L-valine coated graphite electrode (Scheme 1.45).\textsuperscript{102} Poly-L-valine was coated on the graphite electrode due to its high optical rotatory capability. Citraconic acid \textsuperscript{128} and 4-methylcoumarin \textsuperscript{130} were reduced at the modified electrode but poor yields and enantio excess was observed.\textsuperscript{102} Modifying the electrode surfaces with a prochiral reagent would provide an asymmetric reduction technique that required low levels of prochiral reagents and remove the requirement of recovering the prochiral reagent during product purification.
Scheme 1.45: Asymmetric electrochemical reduction of citraconic acid 1-128 and 4-methylcoumarin 1-130 at a poly-L-valine coated graphite electrode.

Mahdavi et al. studied the electrocatalytic hydrogenation of cyclohex-2-en-1-one 1-132 at nickel boride, nickel and Raney nickel electrodes. The reduction process is outlined in Scheme 1.46 and the desired product cyclohexanone 1-133 was obtained as well as cyclohexanol 1-134 in which both the C=C bond and the carbonyl group was reduced.

Scheme 1.46: Electrocatalytic hydrogenation of cyclohex-2-en-1-one 1-132 to cyclohexanone 1-133 and cyclohexanol 1-134.

It was reported that the selectivity of C=C bond reduction (to provide the ketone product 1-133) could be improved by decreasing the applied current density (Table 1.5). The greatest selectivity was observed at the nickel electrode and the lowest selectivity at the Raney Nickel electrode. It was also found that increasing the initial concentration of the starting material improved the selectivity of C=C bond reduction.
Table 1.5: Effect of the electrode material and the charge passed for the reduction of cyclohex-2-en-1-one 1-132.103

<table>
<thead>
<tr>
<th>Electrode / %</th>
<th>Conversion / %</th>
<th>Selectivity (1-140) / %</th>
<th>Current efficiency/ %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 F mol⁻¹</td>
<td>4 F mol⁻¹</td>
<td>2 F mol⁻¹</td>
</tr>
<tr>
<td>Ni₂B</td>
<td>68</td>
<td>91</td>
<td>74</td>
</tr>
<tr>
<td>Ni</td>
<td>62</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Raney Nickel</td>
<td>79</td>
<td>95</td>
<td>20</td>
</tr>
</tbody>
</table>

However, lanthanum-nickel (LaNi₅) was used as a selective electrode material for the electrochemical hydrogenation of C=C bonds.104 The electrochemical reduction of methyl vinyl ketone, 1-decene and 5-hexen-2-one were carried out on a preparative scale, in all cases only the C=C bond was reduced and there was no evidence of carbonyl reduction. The LaNi₅ was supported on an Al, Ni or Fe grid and presents the current efficiencies that were recorded for the reduction of C=C bonds (Table 1.6). It was found that the grid support for the LaNi₅ electrode had a significant effect on the current efficiency observed. Unsurprisingly, the current efficiency was diminished when the iron was the support due to the overpotential of hydrogen evolution at iron electrodes.105, 106 Although Al gave the best current efficiencies, over time a deposit formed on the Al surface, which hindered the hydrogenation reaction.

Table 1.6: Electrochemical hydrogenation of C=C bonds at a LaNi₅ electrode.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Grid</th>
<th>Electrolyte</th>
<th>Potential / V (SCE)</th>
<th>Current efficiency / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl vinyl ketone</td>
<td>Al</td>
<td>H₂O</td>
<td>-0.6</td>
<td>90-100</td>
</tr>
<tr>
<td>Methyl vinyl ketone</td>
<td>Fe</td>
<td>H₂O</td>
<td>-0.9</td>
<td>65</td>
</tr>
<tr>
<td>Methyl vinyl ketone</td>
<td>Ni</td>
<td>H₂O</td>
<td>-0.9</td>
<td>95</td>
</tr>
<tr>
<td>1-decene</td>
<td>Al</td>
<td>EtOH</td>
<td>-0.8</td>
<td>100</td>
</tr>
<tr>
<td>1-decene</td>
<td>Fe</td>
<td>EtOH</td>
<td>-0.8</td>
<td>10-15</td>
</tr>
<tr>
<td>1-decene</td>
<td>Ni</td>
<td>EtOH</td>
<td>-0.8</td>
<td>50-65</td>
</tr>
<tr>
<td>5-hexen-2-one</td>
<td>Ni</td>
<td>EtOH</td>
<td>-1.0</td>
<td>45-70</td>
</tr>
</tbody>
</table>
Electrocatalytic hydrogenation is based on two mechanisms that included the electrochemical generation of hydrogen (adsorbed proton) followed by catalytic hydrogenation. Hydrogen is formed according to equations [1-5] to [1-7] on the surface of the electrode material. The alkene bond is then adsorbed onto the metal (electrode) surface [1-8] and is hydrogenated [1-9], desorption then provides the hydrogenated alkane product [1-10] (Scheme 1.47). It has been reported that electrocatalytic hydrogenation can be affected by the solvent system used and the supporting electrolyte. 

\[
\begin{align*}
H_+^{(ad)} + e^- & \rightarrow H_0^{(ads)} \quad [1-5] \\
H_0^{(ads)} + H_0^{(ads)} & \rightarrow H_2 \quad [1-6] \\
H_0^{(ads)} + H_0^{(ads)} & \rightarrow H_2 \quad [1-7] \\
R=R' & \xrightarrow{\text{metal}} (R=R')_{(ads)} \quad [1-8] \\
(R-R')_{(ads)} + 2H_0^{(ads)} & \rightarrow (RH-R'H)_{(ads)} \quad [1-9] \\
(RH-R'H)_{(ads)} & \xrightarrow{\text{metal}} (RH-R'H) \quad [1-10]
\end{align*}
\]

Scheme 1.47: Mechanism of electrocatalytic hydrogenation.

Navarro et al. described the electrocatalytic hydrogenation of organic compounds using a sacrificial anode and an iron cathode deposited with nickel. They demonstrated that conjugated C=C bonds were reducible in good yields and selectivity but also highlighted that non-conjugated C=C bonds in compounds such as geraniol and cyclohexane were not reducible.

The electrochemical hydrogenation of soybean oil in an electrochemical reactor with a proton exchange membrane (PEM), a Pd-powder cathode and hydrogen gas as the source of hydrogen was reported by Pintauro et al. The process partially hydrogenated the soybean oil with a low proportion of trans-fatty acid isomers. Compared to the traditional catalytic hydrogenation methods, the electrochemical hydrogenation technique resulted in 20-40% less of the undesirable trans-isomer products. Factors that influenced the selectivity of the reaction included the use of a turbulence promoter and high flow rate and using a bimetallic cathode (Pd/Co or Pd/Fe).
1.9 Research Objectives

The project aims to develop an electrochemical process for an environmentally benign, atom and energy efficient method for reducing amides to amines.

The research objectives of the project are as follows:

- Design, construction and characterisation of the performance of an electrochemical flow reactor with 2D and 3D cathodes, operated in batch recycle mode with reservoirs.
- Develop an experimental methodology to investigate the reduction of amides and C=C bonds using the electrochemical flow reactor.
- Determine reduction kinetics of functionalised amides and substrates containing C=C bonds.
- Determination of product yields in batch electrolyses as functions of electrode potential, solvent, reactant initial concentration, conversion, pH and temperature.
- Design suitable on-line spectroscopic methods to monitor the progress of the electrochemical reduction.
- Evaluation of organic solvents as electrolytes for electrosynthesis, suitable for pharmaceutical manufacturing.

1.10 Thesis Structure

To satisfactorily achieve and explore the research objectives proposed by this thesis, the structure of the thesis is outlined in Figure 1-7.
• Chapter 2: The principles of electrochemical systems will be described.

• Chapter 3: The design of the electrochemical flow reactor will be presented and the experimental methodologies used to obtain results and measurements.

• Chapter 4: The results obtained for the reduction of maleimide will be presented and discussed. In particular the reduction at a vitreous carbon rotating disc and using the electrochemical flow reactor at both 2D and 3D electrodes.

• Chapter 5: The results for the reduction of C=C bonds will be discussed, including the determination of the reduction kinetics, the use of 3D graphite electrodes in the electrochemical flow reactor and incorporating an on-line UV spectrometer into the experimental set-up. Chemoselective and stereoselective C=C bond reduction will be presented.

• Chapter 6: The experimental results for the reduction of \(N,N\)-dimethylbenzamide in the electrochemical flow reactor at a boron doped diamond electrode will be discussed. The use of organic solvents will be evaluated to identify an ideal solvent for electrolysis.

• Chapter 7: The reduction of a range of functionalised tertiary amides and candidate drug molecules are explored.

• Chapter 8: The conclusions and recommendations are evaluated.
Chapter 2  Principles of Electrochemical Systems

2.1 Charge-Transfer Controlled Electrochemical Reactions

Electrochemical reactions are heterogeneous chemical reactions in which charge is transferred between an electronically conductive electrode and an ionically conducting electrolyte, represented by equation [2.1].

\[ O + ne^- \rightleftharpoons R \]  \hspace{1cm} [2.1]

The oxidised or reduced species may be in solution and therefore must be transported to, and from, the electrode surface if the reaction is to be sustained. Thus, the reaction rate may be limited by the transport of the electro-active species and/or products in the overall electrode process.

2.2 Transport Processes in Electrochemical Systems

The Nernst-Planck equation [2.2] relates the flux \( N_i \) of charged (infinitely dilute) electro-active solute species \( i \) with mobility \( u_i \) \((u_i = 0 \text{ for uncharged species})\) to an electrode surface, to the vectorial sum of:111

i) migration in an electric field \( \nabla \phi \);

ii) diffusion in a concentration gradient \( \nabla c \);

iii) convection due to local fluid velocity \( v \);

\[ N_i = -u_i c_i \nabla \phi - D_i \nabla c_i + c_i v \]  \hspace{1cm} [2.2]

where the (electrical) ionic mobility \( u_i \) is related to the diffusion coefficient by the Nernst-Einstein equation for electro-active species with \( n \) elementary charges:

\[ u_i = D_i \frac{nF}{RT} \]  \hspace{1cm} [2.3]

The current density, according to Faraday’s Law is then given by:
Chapter 2  Principles of Electrochemical Systems

\[ i = F \sum_i n_i N_i \]  \hspace{1cm} [2.4]

Where the current densities at an electrode of area, A, are related to the current I by:

\[ i = \frac{I}{A} \]  \hspace{1cm} [2.5]

Discounting concentration gradients, substitution of equation [2.4] into equation [2.2] provides Ohm’s law:

\[ j = -\sigma \cdot \nabla \phi \]  \hspace{1cm} [2.6]

2.3 Electrochemical Thermodynamics

The standard equilibrium potential, \( E^0 \) for the half-reaction [2.1] can be expressed in terms of the standard Gibbs free energy (\( \Delta G^0 \)) when the reactants and the products have activities of unity:\(^\text{112}\)

\[ \Delta G^0 = -nFE^0 \]  \hspace{1cm} [2.7]

\( \Delta G^0 \) can also be used to calculate the equilibrium constant for the half-reaction [2.1], when the activity of the electrons is unity.

\[ -\Delta G^0 = RT \ln K \]  \hspace{1cm} [2.8]

When [2.1] reaches a state of dynamic equilibrium, the Nernst equation describes the electrode potential:

\[ E_{O/R} / V = E_{O/R}^0 + \frac{RT}{nF} \ln \left[ \frac{[O]}{[R]} \right] \]  \hspace{1cm} [2.9]

At electrode potentials more positive than the equilibrium potential, given by the Nernst Equation [2.9], species R is oxidised and species O is reduced, and an oxidation or reduction current is measured for the case of non-standard conditions.
Chapter 2  Principles of Electrochemical Systems

For the generalised charge transfer reaction [2.10]:

\[ pA^q + rH^+ + ne^- \rightarrow qB^p + cH_2O \]  \[2.10\]

Thermodynamics predicts the likelihood of a reaction to occur under specific conditions. Considering charge transfer reactions the determining factor is the electrode potential. This potential is given by the Nernst equation [2.11]:

\[ E_{B/A}^\circ / V = E_{B/A}^\circ + \frac{RT}{nF} \ln \left( \frac{(A_q)^p(H^+)^r}{(B_p)^q(H_2O)^c} \right) \]  \[2.11\]

where the subscripts \( p \) and \( q \) in reaction [2.10] define the number of atoms associated with each species. Parentheses denote activities, whereas brackets indicate concentrations.

At 298.15 K, the quotient:

\[ \frac{2.303RT}{F} = 0.0591 \text{  V} \]  \[2.12\]

Hence equation can be derived as:

\[ E_{B/A}^\circ / V = E_{B/A}^\circ - \frac{0.0591 \cdot r \cdot pH}{n} + \frac{0.0591}{n} \log \left( \frac{(A_q)^p}{(B_p)^q} \right) \]  \[2.13\]

The overpotential (\( \eta \)) is defined as the driving force at an electrode potential; it is the difference between the actual potential \( E \) and the equilibrium potential \( (E_{O/R}) \) for the charge transfer reaction:

\[ \eta = E - E_{O/R} \]  \[2.14\]

Thus, positive overpotentials provide positive currents and conversely negative overpotentials give rise to negative currents.
2.4 Electrochemical Kinetics

The Nernst equation applies only under equilibrium conditions and is a thermodynamic expression that provides no information about the rate of the charge transfer reaction.

To understand the kinetics of a charge transfer reaction, a simple model can be developed using the following assumptions:

- the electron transfer step is the rate-determining step
- the reaction does not involve phase transitions

The net current density ($j$) is composed of the partial oxidation current ($j_o$) and the partial reduction current ($j_r$), and is equal to zero:

$$ j = j_r + j_o = 0 \quad [2.15] $$

Net current will flow at potentials other than the reversible potential; these net current densities ($j$) can be described by assuming that the reaction rate is linearly dependent on reactant concentration.

The exchange current density ($j_0$) is a measure of the rate of the reaction under dynamic equilibrium conditions. The Butler-Volmer equation [2.16] describes the kinetics of simple redox reactions. The Butler-Volmer equation is plotted in Figure 2-1 for a simple charge transfer reaction.

$$ j = j_0 \left[ \exp \left( \frac{(1-\alpha)n_F}{RT} \eta \right) - \exp \left( -\alpha n_F \frac{F}{RT} \eta \right) \right] \quad [2.16] $$
The Butler-Volmer equation is commonly used in a limiting case as a convenient approximation. Considering equation [2.16], the first exponential term corresponds to the contribution of the reverse reaction (anodic) to the net current. This term may be neglected at high negative (cathodic) overpotentials, as the net current density is dominated by the partial current density for the cathodic reaction and the Butler-Volmer equation [2.16] simplifies to:

$$-j_c = j_0 \exp \left( \frac{-\alpha n F}{RT} \eta \right)$$  \[2.17\]

$$\log(-j_c) = \log(j_0) - \frac{\alpha n F}{2.303RT} \eta$$  \[2.18\]

At high positive (anodic) overpotentials, the exponential term corresponding to the forward reaction (cathodic) can be neglected and equation [2.16] simplifies to:

$$j_a = j_0 \exp \left( \frac{(1-\alpha) n F}{RT} \eta \right)$$  \[2.19\]

$$\log(j_a) = \log(j_0) + \frac{(1-\alpha) n F}{2.303RT} \eta$$  \[2.20\]

Equations [2.17] and [2.19] are the Tafel equations and Figure 2-2 presents the Tafel plot for the Butler-Volmer equation. There is a linear relationship between $\log j$ and $\eta$ at positive and negative overpotentials, the lines should extrapolate to $\log j_0$ at $\eta = 0$, and the gradients of the
slopes allow the transfer coefficient to be determined. However, this is only true when electron transfer is the sole rate-determining step and the surface and bulk concentrations are in equilibrium. The Tafel plots are only observable when the exchange current density ($j_0$) is small compared to the mass transport limited current density. For fast charge transfer reactions, the reaction is always at equilibrium and the current densities are governed by mass transport only.

![Tafel plot of the Butler-Volmer equation.](image)

**Figure 2-2: Tafel plot of the Butler-Volmer equation.**

### 2.5 Electrochemical Reaction Coupled to Mass Transport

Electron transfer and mass transport processes are intrinsically coupled in an electrochemical reaction, *i.e.* the transport of the electro-active species must occur prior to any charge transfer reaction. At low overpotentials, the transport rates are typically fast in comparison to the electron transfer process, and therefore the kinetic process is the rate determining step. As the overpotential is increased, an exponential increase in the current density often occurs, the electro-active species is increasingly depleted at the interface and a concentration gradient is established in the boundary layer. The rate of the reaction is under mixed control as the kinetic and mass transport processes are comparable. The surface concentration of the electro-active species tends to zero as the overpotential is increased further and a limit is reached where the current density is independent of the applied potential and the rate of the reaction is governed by mass transport (Figure 2-3).
When mass transport is governed by diffusion, the flux can be directly related to the concentration gradient by Fick’s First Law:

\[
|j_i| = nF N_i = nF \frac{D_i}{\delta_N} c_i = nF k_m c_i \tag{2.21}
\]

where \(k_m\) is the mass transport rate coefficient in the bulk solution.\(^{111}\)

The reactant concentration at the electrode surface depleting to zero is shown in Figure 2-4.

Figure 2-3: Relationship between current density and electrode potential as mass transport rates are increased.\(^{113}\)

Figure 2-4: Concentration profile for reactions at solid/liquid interfaces.\(^{113}\)
2.6 Energy Efficiencies of Electrochemical Processes

The charge \( Q \) passed during an electrochemical process is calculated from the current \( I \) passed with time:

\[
Q = \int I(t) dt
\]  

[2.22]

The charge yield \( (\Phi_p) \) is the ratio of the theoretical charge \( (Q_p) \) passed to form product to the total charge \( (Q) \) passed during electrolysis:

\[
\Phi_p = \frac{Q_p}{Q}
\]  

[2.23]

The theoretical charge is calculated from the stoichiometry of the half-cell reaction using Faraday’s Law:

\[
Q_p = \frac{m_p v_e F}{v_e M_p}
\]  

[2.24]

where \( m_p \) is the mass of the product \( P \) formed during the electrolysis, \( M_p \) is the molar mass of \( P \) and \( v_e \) represents the electron stoichiometry of the electrode reaction. A low charge yield indicates that a large fraction of the total charge is due to loss reactions.

The charge yield can then be used to calculate the specific electrical energy consumption \( (w_p^e) \) which is the electrical energy required to form unit mass of the product \( P \) in an electrochemical cell. It is required for the estimation of operational costs of an electrochemical process or reactor.

\[
w_p^e = \left( \frac{nF}{\phi_p^e} \right) \frac{U}{3.6 M_p}
\]  

[2.25]
Chapter 2  Principles of Electrochemical Systems

U is the overall cell voltage and in a cell in which current is passed and the reaction is not in thermodynamic equilibrium. U is comprised of the following components which are depicted in Figure 2-5.

i) The thermodynamic potential $E_a$, requirement for the anode reaction,

ii) The anode overpotential, $\eta_a$, which provides the driving force for the anode reaction to depart from thermodynamic equilibrium,

iii) The thermodynamic potential $E_c$, requirement for the cathode reaction,

iv) The cathode overpotential, $\eta_c$,

v) ohmic potential drop $IR$, due to resistance in the electrolytes and membrane

Therefore:

$$U = -(E_a + \eta_a - E_c + \eta_c + IR) = -(E_a + \eta_a - E_c - \eta_c - \sum_i \frac{j_i d_i}{\kappa_i})$$ \[2.26\]

For which negative sign represents the cell voltage for an electrolytic reactor where $d_i$ is the current path length and $\kappa$ is the effective conductivity of phase $i$. 

Figure 2-5: Potential distribution in an electrochemical reactor.\[113\]
2.7 Rotating Disc Electrode

Rotating disc electrode (RDE) experiments provide a convenient method of studying the kinetics of electrochemical reactions, while being able to vary the mass transport rate coefficient predictably by varying the disc rotation rate.

The working electrode consists of a disc of electrode material that is inserted into a cylindrical insulating sheath, usually made from PTFE. The electrode is rotated in the electrolyte solution of interest to establish a well-defined flow pattern; the rotating motion acts as a pump that pulls the solution axially upwards toward the disc, and spins the solution out from the disc radially (Figure 2-6). This maintains a steady supply of the electro-active material to the electrode.

![Rotating Disc Electrode Cell](image)

The RDE is an example of a hydrodynamic electrode in which rotation forces convection to dominate transport to the electrode under laminar flow conditions. The solution near to the RDE is separated into two regions: a well stirred bulk region and the other a diffusion layer.
of thickness $\delta_d$. The diffusion layer thickness for a RDE decreases with the inverse square root of the rotation frequency ($f$):

$$\delta_d = 0.643D^{1/3}v^{1/6}f^{-1/2}$$

[2.27]

So that the mass transport coefficient ($k_m$) is defined by equation [2.30]:

$$k_m = D/\delta_d = 1.554D^{2/3}v^{-1/6}f^{1/2}$$

[2.28]

showing that the mass transport coefficient is dependent on the electrolyte properties and the rotation rate.

Substituting $k_m = I_L/nFcA$ into equation [2.28] provides the Levich equation [2.29] for a RDE and predicts the transport limited current as a function of rotation speed. Where $I_L$ is the limiting current, $n$ is the electron stoichiometry, $D$ is the diffusion coefficient of the electro-active species and $c$ is the concentration.

$$I_L = 1.554nFAD^{2/3}v^{-1/6}\omega^{1/2}c$$

[2.29]

The Levich equation [2.29] is extremely useful as it predicts the variation in the transport limited current against the square root of the rotation rate, producing a straight line which passes through the origin.\textsuperscript{114,115} If the rotation rate is increased, transport of the electro-active species is enhanced as the velocity of the solution being drawn to the electrode is increased, this in turn compresses the diffusion layer\textsuperscript{114}, enabling electro-active species to diffuse through this layer to the electrode at a faster rate. This results in proportionately higher current densities, provided the reaction is transport controlled, when a current plateau may be evident in voltammogram, provided it is not masked by secondary reactions such as solvent decomposition.

### 2.8 Chapter Summary

This chapter has described the theoretical principles of electrochemical systems which supplement the experimental work discussed in the following chapters.
Chapter 3  Experimental Methodology

This chapter describes the experimental procedures and materials used to obtain the results described in this thesis, including rotating disc experiments, batch electrolysis and reactor experiments. The fabrication and properties of Boron doped diamond (BDD) electrode materials will also be discussed. The synthesis and characterisation of organic compounds are given in Appendix 1.

3.1 Rotating Disc Electrode Experiments

Rotating disc experiments were carried out using a Pine Electrode Rotator AFMSRCE (Pine Research Instruments) at a range of scan rates (10 mV s\(^{-1}\) to 25 mV s\(^{-1}\)) and at disc rotation rates between 3-50 Hz. An Autolab PGSTAT302N Potentiostat (Metrohm Autolab) was used to control the cyclic voltammetry and constant potential experiments. A vitreous carbon RDE (Pine Instrument Company) was used to investigate the kinetics of the charge transfer reactions. The disc area was 1.97x10\(^5\) m\(^2\) and the diameter was 5 mm. A three-compartment glass cell was used for the rotating disc experiments, incorporating a vitreous disc electrode, a saturated calomel reference electrode (Monocrystaly), assumed to have a potential of 0.244 V (SHE), and a platinum flag counter electrode (Figure 3-1).

The vitreous carbon (VC) disc electrode was mechanically polished prior to each experiment using 300 nm and 0.5 \(\mu\)m silica (Sigma Aldrich) wetted with ultra-pure water (18 M\(\Omega\)). To remove any silica adhered to the electrode surface, the electrode was immersed in ultra-pure water and placed in an ultrasonic bath (Thermo Scientific). Nitrogen was bubbled through the solution before experimentation for 15 minutes to remove dissolved oxygen, which could be reduced at the working electrode. All experiments were carried out a room temperature and pressure.
3.2 Batch Electrolysis Experiments

A glass H-cell was used to carry out batch electrolysis, providing results to compare to electrolysis carried out in the electrochemical flow-through reactor. A Nafion ion-permeable membrane was used to separate the two compartments, a vitreous carbon electrode (0.001 m$^2$) was used as the cathode and a platinised titanium mesh was used as the anode; a saturated calomel electrode (Monocrystally) was the reference electrode (Figure 3-2).
The volume of the anode and the cathode compartments was 270 mL; the anolyte consisted of 1 M aq. H$_2$SO$_4$ and the catholyte consisted of 0.01 M of the amide substrate with 1 M aq. H$_2$SO$_4$ as the supporting electrolyte. Nitrogen was bubbled through the system to remove dissolved oxygen and the cathode was polished prior to each experiment. The catholyte was continuously stirred throughout the experiment to enhance mass transport. The potentiostat was used to carry out chronoamperometry experiments, holding the cathode at a fixed potential with respect to the reference electrode and the current measured for a period of time.

### 3.3 Electrochemical Reactor Experiments

#### 3.3.1 Reactor Modifications

An ElectroCell Micro Flow Cell® (ElectroCell) was modified for electrosynthesis. Electrodes and membrane were purchased from ElectroCell. Vitreous carbon and BDD electrodes were used as the cathode materials and the electrode area was 0.001 m$^2$. An IrO$_2$ (Dimensionally stable anode for O$_2$) was used as the anode and a Nafion 117 ion permeable membrane separated the anode and the cathode compartment. The AgCl reference electrode was custom made to be 5 mm in diameter and 45 mm in length (Monocrystal). Figure 3-3 and Figure 3-4 display photographs of the flow-through reactor, the VC electrode and the AgCl reference electrode, including dimensions.

![Figure 3-3: Photograph of the ElectroCell reactor with the reactor dimensions.](image1)

![Figure 3-4: Photograph of a VC electrode and the AgCl reference electrode with dimensions.](image2)

A schematic diagram of the flow-through reactor assembly is given in Figure 3-5 and displays the flow configuration within the reactor. The reactor was assembled to allow two or
Chapter 3  Experimental Methodology

four separate compartment flows, one for the anolyte, one for the catholyte and a further two for heating/cooling water.

![Schematic diagram of the reactor indicating the flow system within the reactor.](image)

Figure 3-5: Schematic diagram of the reactor indicating the flow system within the reactor.

The reactor was modified with a PTFE frame to accommodate the AgCl reference electrode, schematic diagrams and photographs are given in Figure 3-6 and Figure 3-7, respectively. The PTFE frame design was based upon the original frames used in the reactor and provided a cathode compartment volume of 0.0189 L. An extension was designed into the frame to hold the reference electrode at a close proximity to the cathode surface. The reference electrode was inserted into the extension to be a tight fit to prevent the sealant contaminating the reactor, however this limited the maximum flow rate achievable to 90 mL min$^{-1}$ (leakage observed beyond this flow rate).

PTFE gaskets (Polyflon) were machined for use with the flow-through reactor, to provide chemical resistivity and prevent contamination. Chem-Durance tubing (Masterflex L/S-17, Cole-Parmer) was used to provide high chemical resistivity and flexibility for use with a peristaltic pump; the fittings (Masterflex Barbed Fittings, Cole-Parmer) were made from PVDF. Masterflex peristaltic pump (Model 07524-40) was used to circulate the catholyte and Williamson’s pumps (Series 200CM) were used to deliver the anolyte and heating/cooling water. Figure 3-8 displays the configuration of the modified electrochemical flow-through reactor used in the experiments.
Figure 3-6: Schematic diagram of the PTFE frame designed to hold AgCl reference electrode.

Figure 3-7: Photograph of the PTFE frame holding the AgCl reference electrode.

Figure 3-8: Schematic diagram of the modified electrochemical flow-through components.

3.3.2 Graphite Felt Electrode

To increase the electrode surface area, graphite felt (RVC 4002, Le Carbone Lorraine) was inserted into the PTFE frame holding the AgCl reference electrode. The graphite felt filled the void of the frame and was in contact with a graphite feeder electrode (Figure 3-9).

Figure 3-9: Configuration of the graphite felt inserted into the PTFE reference electrode frame.
3.3.3 Reactor Operation Conditions

The reactor was operated under batch recycle mode with a continuously stirred reservoir, Figure 3-10 shows the schematic representation of the experimental set up used for the electrochemical reactor investigations. Chronoamperometry and chronopotentiometry experiments were carried out using the potentiostat. An Agilent digital multimeter was used to measure and record the cell voltage.

The catholyte consisted of 0.01 M amide and 1 M aq. H$_2$SO$_4$ electrolyte (unless otherwise stated) and the anolyte consisted of 1 M aq. H$_2$SO$_4$, the volume of the catholyte and anolyte reservoirs were 100 mL. The majority of the experiments were carried out at room temperature; however some experiments were carried out at 15 °C and 50 °C by immersing the catholyte and anolyte reservoirs into a re-circulatory waterbath (T100R, Grant). The reactor was cleaned by flushing methanol and ultra-pure water through the reactor and tubing to remove any organic compounds and salts from the system.

1 mL aliquots were extracted from the catholyte solution for analysis. After each experiment the resulting solution was neutralised to pH 10 by the addition of 1 M aq. NaOH, extracted with dichloromethane and the solvent evaporated under vacuum.

![Schematic representation of the electrochemical reactor experimental setup.](image)

To follow the progress of some reactions a UV-visible spectrophotometer (Agilent 8453) was used to measure the concentration of organic compounds in solution. Online measurements were taken by incorporating a quartz flow-through cuvette (1 mm wide) into the reactor outlet tubing (Figure 3-11). The fibre optic cables (Hellma) were inserted into the cuvette and were
connected to the UV-visible spectrophotometer (Agilent 8453); the set-up of the fibre optic cables and the quartz cuvette is shown in Figure 3-12.

![Fibre optic cables](image)

Figure 3-11: Flow-through quartz cuvette (1 mm wide).\textsuperscript{116,117}

Figure 3-12: Fibre optic cable and flow through cuvette set-up.\textsuperscript{118}

The formation of hydrogen gas is a competing reaction observed at the cathode, during electrochemical reduction experiments performed in strongly acidic media (pH 0). To quantify the level of hydrogen gas produced during the experiments, a gas counter (MGC-1, Ritter) was fitted to the catholyte reservoir, which was sealed during these experiments. A photograph and schematic diagram of the gas counter are given in Figure 3-13 and Figure 3-14 respectively.

![Photograph of the gas counter](image)

Figure 3-13: Photograph of the gas counter.\textsuperscript{119}

![Schematic diagram of the gas counter](image)

Figure 3-14: Schematic diagram of the gas counter.\textsuperscript{119}
3.4 Electrode materials: Boron Doped Diamond

Conductive diamond has generated significant interest as an electrode material from the mid-1980’s due to its unique characteristics of extreme hardness, chemical stability, low capacitance and high thermal conductivity.\textsuperscript{120} Pure diamond is a natural insulator due to the complete sp\textsuperscript{3}-hybridisation of the carbon atoms (Figure 3-15) and has a band gap of 5.47 eV.\textsuperscript{121} However, doping the diamond with boron can transform diamond into an efficient electrical conductor.\textsuperscript{121,122} Boron has an empty p-orbital in its outer shell making it an electron acceptor, providing p-type semiconductor properties and lowering the Fermi level to enable electrical conductivity in the BDD electrode. A boron doping level of 10\textsuperscript{20} cm\textsuperscript{-3} (ca. one boron atom per 1000 carbon atoms) affords good electrochemical properties.\textsuperscript{122}

Boron doped diamond electrodes are fabricated in one of four assemblies outlined in Figure 3-16.\textsuperscript{121} The successful growth of diamond at low pressures can be achieved by chemical vapour deposition (CVD) of doped diamond onto a substrate material.\textsuperscript{123} Substrate materials include silicon, titaniaum, niobium, vitreous carbon and molybdenum.\textsuperscript{124}

Boron doped diamond is a particularly attractive electrode material for organic electrosynthesis as it offers a wide potential window of ca. 3-3.5 V in aqueous solutions and an even wider window of ca. 5-7.5 V in non-aqueous solutions such as acetonitrile, methanol and N,N-dimethylformamide.\textsuperscript{121,123} Pleskov et al. demonstrated that BDD has a high overpotential for hydrogen and oxygen evolution; using 0.5 M aq. H\textsubscript{2}SO\textsubscript{4} as the electrolyte it was found that the potential window was ca. -0.75-2.35 V.\textsuperscript{121,125}
Organic electro-synthesis was also demonstrated at a BDD electrode for the methoxylation of p-tert-butyltoluene 3-1 in a methanol-H$_2$SO$_4$-H$_2$O electrolyte, to form p-tert-butylbenzaldehyde dimethyl acetal 3-4 selectively, Scheme 3.1. It was found that the mechanism involved the formation of methoxyl radicals which abstract the hydrogen atom from p-tert-butyltoluene 3-1 to give the dimer product 3-2 which is then cleaved at the C-C bond electrochemically to provide 3-3 and p-tert-butylbenzaldehyde dimethyl acetal 3-4.

**Scheme 3.1: Synthesis of p-tert-butylbenzaldehyde dimethyl acetal 3-4 at a BDD electrode in a MeOH-H$_2$SO$_4$-H$_2$O electrolyte. A possible competitive side reaction is possible via the intermediate dimer product 1-11.**

BDD is an attractive electrode material as it offers the widest potential window compared to other electrode materials, exhibits a high overpotential for hydrogen evolution and is a chemically inert material. Other electrodes such as Pb, Hg and Cd provide high overpotentials for hydrogen evolution however toxicity issues associated with these materials make them undesirable. However, BDD electrodes are currently expensive to fabricate and materials such as VC electrode materials can provide a more economical alternative.

### 3.5 Chapter Summary

The chapter describes the modifications made to the commercially available ElectroCell Micro Flow Cell® (ElectroCell) and the experimental procedures performed using it. The experimental set-up and conditions were also provided for rotating disc and batch electrolysis experiments.
Chapter 4 Reduction of Maleimide

This chapter discusses the reduction of maleimide 4-1 using the electrochemical flow-through reactor. Maleimide 4-1 was chosen as the model substrate as it displays a well understood electrochemical reduction mechanism, established by experiments with a rotating disc electrode over a wide pH range. Herein, results obtained with these compounds will be presented and discussed; the detailed experimental procedure is presented in Chapter 3.

4.1 Maleimide Reduction Kinetics at a Rotating Disc Electrode

To understand the kinetics and mass transport properties of the reduction process, rotating disc electrode (RDE) experiments were carried out. The overall electrochemical reduction of maleimide 4-1 is given in Scheme 4.1.

Scheme 4.1: Electrochemical reduction of maleimide 4-1 to succinimide 4-1a.

Lead was reported previously to be a suitable cathode material for the reduction of amides and was therefore deposited onto a VC RDE. The VC disc electrode was rotated at 3000 rpm in a solution of 0.1 M aq. NaOH containing 100 ppm Pb (II) at a fixed potential of -1.0 V (SCE) for 900 s. The total charge passed was of 0.11 C (5583 C m⁻²) which equates to ca. 2000 monolayers of Pb on the VC surface.

Figure 4-1 shows the cyclic voltammogram (CV) for the reduction of 0.01 M maleimide 4-1 in 1 M aq. H₂SO₄ using the Pb-coated VC RDE; the potential was scanned between -0.4 and -1.4 V (SCE) at a scan rate of 25 mV s⁻¹ and at a range of rotation frequencies. Interestingly the CV curves show plateau regions around -1.2 V, suggesting that the reduction process is operating under mass transport control. The rotation frequency was changed to monitor the effect on the current density; it is clear from the graph that increasing the rotation frequency increased the current density, due to an increase in the flux of the electro-active species to the electrode surface.
Figure 4-1: Cyclic voltammogram for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H₂SO₄ at a Pb-coated VC RDE; electrode potential swept between -0.4 V and -1.4 V (SCE) at a scan rate of 25 mV s⁻¹ and at a range of rotation rates.

Mass transport controlled current densities are defined by equation [4.1], in which δ is the (mean) Nernst diffusion layer thickness. The hydrodynamic regime at downward-facing rotating disc electrodes was solved by Levich, enabling mass transport rates to be varied predictably, as they increase linearly with the square root of rotation rate. When the electron transfer reaction is mass transport controlled, the limiting current density can be given by the Levich equation [4.2].

\[
I_L = \frac{nFDC}{\delta_d}
\]  
\[\text{[4.1]}\]

\[
I_L = -1.554nFD^{2/3}\omega^{1/2}v^{-1/6}c
\]  
\[\text{[4.2]}\]

To confirm that the reduction process was mass transport controlled a Levich plot of the square root of the rotation frequency against the limited current density should be linear and pass through the origin. The limiting current density for maleimide 4-1 was calculated using equation [4.2] when \( n = 2, D = 1 \times 10^{-9} \text{ m}^2 \text{ s}^{-1} \) and \( c = 10 \text{ mol m}^{-3} \) and the Levich plot is given in Figure 4-2. The plot shows a linear trend line can be fitted to the measured data which passes through the origin, confirming that the reaction was mass transport controlled.
The product of this 2-electron reduction was subsequently found to be succinimide 4-1a, i.e. the reduction had occurred at the C=C bond rather than at the C=O; this has been previously reported by Fletcher et al.\textsuperscript{127}

![Graph showing effect of rotation rate on measured current densities for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H\textsubscript{2}SO\textsubscript{4} using a Pb-coated VC RDE compared with those predicted by Levich's equation.]

Pb was deposited onto the VC RDE prior to each amide RDE reduction experiment. However, the surface of the Pb deposited VC RDE varied in appearance after each deposition experiment. In some cases the Pb was deposited in patches on the surface and at other times the Pb coated the whole surface, i.e. it was difficult to reproduce a fully coated surface. In addition, the toxicity of Pb was a particularly unattractive property as an electrode material for the prospective use in pharmaceutical manufacturing. Therefore the electrochemical flow-through reactor incorporated a VC, BDD or a graphite felt cathode in contact with a graphite plate feeder electrode for the reduction of C=C bonds. As a surrogate for these materials, a VC RDE was employed to obtain kinetic data, i.e. the relationship between the current and electrode potential as functions of experimental variables for these reductions; difficulty was experienced fabricating a BDD RDE.
Figure 4-3 shows the CV recorded for the reduction of 0.01M maleimide 4-1 in 1M H\textsubscript{2}SO\textsubscript{4} at the VC disc electrode between -0.2 and -1.5 V (SCE) at a rotation rate of 1000 rpm and a scan rate of 25 mV s\textsuperscript{-1}.

In the negative-going potential sweep, maleimide 4-1 reduction began at -0.6 V (SCE), below which current densities increased exponentially, then reached the mass transport limited current density at -1.2 V (SCE). The further exponential increase in current densities between -1.2 and -1.5 V (SCE) was attributed to the evolution of H\textsubscript{2} (Scheme 4.2).

Scheme 4.2: Electrochemical reduction of protons to evolve hydrogen.

$$2\text{H}^+ + 2\text{e}^- \rightarrow \text{H}_2$$

In the positive-going potential sweep between -1.5 and -0.2 V (SCE), there was no evidence in the cyclic voltammogram that the reverse reaction of Scheme 4.1 occurred. Figure 4-4 shows the semi-log plot of the current densities-overpotential relationship for the reduction of 0.01 M maleimide 4-1 in 1M H\textsubscript{2}SO\textsubscript{4}. The equilibrium potential for maleimide (E\textsubscript{mal}) was measured by recording the potential between the VC RDE and the SCE reference electrode in a 1M H\textsubscript{2}SO\textsubscript{4} solution containing 0.01M maleimide 4-1 and 0.01M succinimide 4-1a, as no value was reported in the literature. The E\textsubscript{mal} was measured to be -0.12 V (SCE) (Appendix 3). The Tafel slope was calculated as 119 ± 7% mV decade\textsuperscript{-1} and j\textsubscript{0} as 1.8x10\textsuperscript{-3} ± 5% A m\textsuperscript{2}, which represents the potential region of -0.4 to -0.55 V (SCE) in the cyclic voltammogram shown in Figure 4-3. The small exchange current density j\textsubscript{0}, indicates that a high overpotential is required to reach a high current flow.
Figure 4-3: Cyclic voltammogram for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a VC RDE; electrode potential swept between -0.2 V and -1.5 V (SCE) at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.

Log(jmal) = -5.3799(E$_{disc}$-E$_{mal}$) - 2.7455
R$^2$ = 0.9972

Figure 4-4: Effect of overpotential (E$_{disc}$-E$_{mal}$) on log(current density) for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.
The CV for the reduction of protons to hydrogen (Scheme 4.2) is shown in Figure 4-5 to demonstrate the background current density measured for the reduction of 1 M aq. H₂SO₄ at the VC RDE. The onset of hydrogen evolution was detected at ca. -1.2 V (SCE) and current densities increased with increasing rotation rate. The semi-log plot of the current density-overpotential relationship is shown in Figure 4-6. The Tafel slope was derived as 361 mV decade⁻¹ and j₀ as 0.05 A m⁻².

![Cyclic voltammogram for the reduction of protons in 100 mL 1 M aq. H₂SO₄ at a VC RDE; electrode potential swept between -0.2 V and -1.5 V (SCE) at a scan rate of 25 mV s⁻¹ and at a range of rotation rates.](image)

Figure 4-5: Cyclic voltammogram for the reduction of protons in 100 mL 1 M aq. H₂SO₄ at a VC RDE; electrode potential swept between -0.2 V and -1.5 V (SCE) at a scan rate of 25 mV s⁻¹ and at a range of rotation rates.
The kinetics of electron transfer reactions under mixed control can be determined using the Koutecky-Levich equation [4.3]; the left term relating to kinetic control and the second term relating to diffusion control. A plot of $1/j_L$ against $1/\omega^{1/2}$ is shown in Figure 4-7 for the reduction of 0.01 M maleimide 4-1 in 1 M aq. H$_2$SO$_4$ at a range of potentials. Extrapolating $1/\omega^{1/2} \rightarrow 0$ removes diffusion limitations and the kinetic rate coefficient can be calculated. From Figure 4-7 at each potential, the plots are linear and the calculated kinetic coefficient and diffusion coefficient are given in Table 4.1. The Levich plot of $j_L$ against $f^{1/2}$ is shown in Figure 4-8. The experimental plot is linear ($R^2=0.98$) and passes through the origin, indicating that the reduction of maleimide was mass transport controlled.

\[
\frac{1}{j} = \frac{1}{nFkc} + \frac{1.61v^{1/6}}{nFD^{2/3}c \omega^{1/2}}
\]  

[4.3]
Figure 4-7: Koutecky-Levich plots at -1.1, -1.0 and -0.9 V (SCE) for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.

Table 4.1: Calculated kinetic and diffusion coefficients for the reduction of 0.01 M maleimide 4-1 derived from the Koutecky-Levich Plot, using a kinematic viscosity of 0.98x10$^{-6}$ m$^2$ s$^{-1}$. Calculated for 1 M aq. H$_2$SO$_4$ using NRTL thermodynamic model with Hysys© software.

<table>
<thead>
<tr>
<th>Potential / V (SCE)</th>
<th>k / m s$^{-1}$</th>
<th>D / m$^2$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.9</td>
<td>8.84x10$^{-5}$</td>
<td>1.85x10$^{-9}$</td>
</tr>
<tr>
<td>-1.0</td>
<td>3.73x10$^{-4}$</td>
<td>9.89x10$^{-10}$</td>
</tr>
<tr>
<td>-1.1</td>
<td>7.36x10$^{-4}$</td>
<td>8.016x10$^{-10}$</td>
</tr>
</tbody>
</table>
The reduction of 0.01 M maleimide 4-1 was also carried out at pH 2 and pH 4 using 0.01 M aq. H$_2$SO$_4$ and 0.0001 M aq. H$_2$SO$_4$ electrolyte solutions respectively, a supporting electrolyte of 0.1 M Na$_2$SO$_4$ was used to increase the conductivity of the solution. The pH was measured using a pH probe (Hanna Instruments Ltd., UK) to ensure the desired pH had been achieved. The negative-going sweep for the reduction of 0.01 M maleimide 4-1 at pH 2 and pH 4 are given in Figure 4-9. In both cases, the current onset for reduction of maleimide 4-1 was at -0.6 V (SCE) and the current density increased until limiting current densities of 53.64 and 43.03 A m$^{-2}$ at pH 2 and pH 4, respectively, were achieved. The lower limiting current density at pH 4 may have been limited by the concentration of protons in the electrolyte. It should also be noted that the reduction potentials measured for the evolution of hydrogen and maleimide 4-1 reduction will shift by 59 mV per pH unit as defined by the Nernst equation [2.13] (Chapter 2). This is observable in Figure 4-9 for the reduction of maleimide 4-1 at pH 2 and pH 4.
Chapter 4  Reduction of Maleimide

Figure 4-9: Cyclic voltammograms for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.01 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 2) and 100 mL 0.0001 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 4) at a VC RDE; electrode potential swept between -0.2 V and -1.5 V (SCE) at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.

The log current density-overpotential relationships are given in Figure 4-10 and Figure 4-11 for maleimide 4-1 reduction at pH 2 and pH 4 respectively. The Tafel slope was calculated to be 115 ± 9% mV decade$^{-1}$ and $j_0$ as 9 x10$^{-5}$ ± 10% A m$^{-2}$ at pH 2 and at pH 4 the Tafel slope was 161 ± 4 % mV decade$^{-1}$ and $j_0$ was 6.5x10$^{-4}$ ± 3.5% A m$^{-2}$. The potential region used to calculate the Tafel slopes were -0.5 to -0.68 V (SCE) and -0.6 to -0.75 V (SCE) for pH 2 and pH 4 respectively. The estimated Tafel slopes suggest that as the pH is increased (lower proton concentration); the rate of the kinetic electrode reaction becomes slower.
Figure 4-10: Effect of overpotential ($E_{\text{disc}} - E_{\text{mal}}$) on log(current density) for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.01 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 2) at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.

Figure 4-11: Effect of overpotential ($E_{\text{disc}} - E_{\text{mal}}$) on log(current density) for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.0001 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 4) at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.
In order to simplify the workup procedure and to use less corrosive electrolytes, tests were carried out using 0.5 M aq. Na$_2$SO$_4$ (pH 7) as the electrolyte solution. Considering Figure 4-12, two reduction waves were observed in the CV at ca. -1 V (SCE) and ca. -1.3 V (SCE).

To establish if two 1-electron processes occurred, the Levich plot for the reduction of maleimide 4-1 in 0.5M Na$_2$SO$_4$ was predicted (Figure 4-13). Two predictions were made for the limiting current density when n = 1 and when n = 2 and D = 1 x 10$^{-9}$ m$^2$ s$^{-1}$. From the graph, it is clear that the prediction when n = 1 is a better fit to the measured limiting current density, suggesting that two 1-electron reduction processes occurred. This is in good agreement with the findings of Barradas et al. who suggested in the pH range of 7-10 the dimer product 4-2 is formed (Scheme 4.3), via a 1-electron transfer to form the radical species.$^{127}$

Figure 4-12: Cyclic voltammogram for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.5 M aq. Na$_2$SO$_4$ (pH 7) at a VC RDE; electrode potential swept between -0.2 V and -1.8 V (SCE) at a scan rate of 25 mV s$^{-1}$ and at a range of rotation rates.

Scheme 4.3: Mechanism for the formation of dimer 4-2.
4.1.1 Mechanism of Maleimide Reduction

The mechanism of maleimide 4-1 reduction at pH 1 proposed by Barradas et al. is given in Scheme 4.4.\(^{127}\)

Scheme 4.4: Proposed mechanism for the electrochemical reduction of maleimide 4-1.
This mechanism is an example of an electron-transfer chemical electron-transfer (ECE) process:

$$O + ne^- \xrightarrow{\text{red}} \text{ox} \xrightarrow{\text{ne}^-} R$$ \[4.4\]

In an ECE mechanism, the second reduction step often occurs at a potential less negative than the first reduction process, resulting in a single irreversible peak in the CV.\textsuperscript{114} At high potential scan rates, the chemical reaction of the second electron transfer can be concealed,\textsuperscript{114} as was the case for the reduction of the C=C bond of maleimide 4-1. Although the Levich plot and the current density suggested that a 2-electron process had occurred, only a single irreversible wave was present in the voltammogram (Figure 4-1).

### 4.2 Batch Reactor Investigations

In order to perform reduction on a preparative scale, batch electrolyses were carried out in a glass H-cell with the compartments separated by a Nafion 417 cation-permeable membrane (DuPont Inc.). The reduction of maleimide 4-1 was carried out using a vitreous carbon cathode with an area of 0.001 m\(^2\) and an electrolyte volume of 100 mL.

The theoretical charge passed in a charge transfer reaction to convert reactant to product is given in [4.5]; for the reduction of 0.01M maleimide 4-1 the theoretical charge required for a two electron transfer is 192 C.

$$Q = mnF$$ \[4.5\]

Figure 4-14 shows the plot for the reduction of maleimide 4-1 in the batch cell using a vitreous carbon electrode; the current density decayed with time as expected for a single transport controlled reaction. The potential was held at -1.2 V for 15000 seconds, during which the total charge passed was 467 C. The current efficiency was calculated with [4.6] to be 41%, suggesting that most of the charge being passed during electrolysis was due to the evolution of hydrogen.

$$\Phi^e = \frac{Q}{Q_e}$$ \[4.6\]
Figure 4-14: Current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a VC electrode in a glass H-cell at a potential of -1.2 V (SCE).

To confirm product formation, the catholyte was neutralised to pH 7 (by the addition of 1 M aq. NaOH), and extracted with dichloromethane. Following evaporation of the solvent, the residue was analysed by $^1$H NMR, which indicated a 40% conversion of maleimide 4-1 to succinimide 4-1a, calculated by the comparison of their methylene resonance signals at 6.71 and 2.79 ppm, respectively. The low conversion is attributed to the poor current efficiency observed.
4.3 Maleimide Reduction in Electrochemical Flow-through Reactor

Following successful reduction of maleimide 4-1 to succinimide 4-1a in the batch cell, experiments were repeated in the flow-through reactor operated in batch recycle mode at constant cathode potential. The construction of the reactor is described in Chapter 3.

There is growing interest in the use of continuous flow reactors in organic synthesis for several reasons. The main advantages of using flow reactors include high reproducibility, improved safety and process reliability as constant parameters can be easily controlled.\textsuperscript{128, 129} Utilising the flow-through reactor to carry out electrochemical reduction also improves mass transport of the electro-active species to the electrode.

Chronoamperometry experiments under batch recycle mode with a continuously stirred tank were carried out for the reduction of maleimide 4-1. The RDE experiments indicated that the limiting current for maleimide 4-1 reduction occurred at a potential of -1.2 V (SCE) therefore a CV was recorded using the electrochemical reactor with the AgCl|Ag reference electrode to determine the reduction potential in relation to the AgCl|Ag electrode. It was found that the reduction potential was -1.2 V (AgCl|Ag) and this potential was applied to the reactor.

The reduction of 0.01 M maleimide 4-1 in a solution of 1 M aq. H\textsubscript{2}SO\textsubscript{4} was carried out initially at a VC electrode at a cathode potential of -1.2 V (AgCl|Ag) and a flow rate of 60 mL min\textsuperscript{-1} for 5 hours; the current density-time relationship is given in Figure 4-15. The catholyte was neutralised to pH 7 (by the addition of 1 M aq. NaOH) and extracted with dichloromethane. The product was identified by \textsuperscript{1}H NMR to be succinimide 4-1a. Succinimide 4-1a was the only product of the reaction and a conversion of 60 % and a current efficiency of 62 % observed.
To further investigate the reduction of maleimide 4-1 using the electrochemical flow-through reactor, experiments were conducted with BDD as the cathode material, with the same conditions outlined above. After 5 hours of electrolysis at -1.2 V (AgCl|Ag), complete conversion was achieved with a current efficiency of 96%. It is thought the process was more efficient with the BDD electrode due to the high overpotential for hydrogen evolution compared to VC.

4.3.1 Effect of Volumetric Surface Area

To scale up the (volumetric) surface area of the cathode, the graphite feeder electrode was contacted with graphite felt of specific surface area $a \approx 10^4 \text{ m}^2 \text{ m}^{-3}$ and 11 mm thick in the direction of current flow.

0.01 M maleimide 4-1 in 1 M aq. H$_2$SO$_4$ was reduced at the graphite felt electrode at a fixed potential of -1.2 V (AgCl|Ag); the resulting time dependence of the cross sectional current density is shown in Figure 4-16.
In the direction of current flow, three dimensional electrodes have potential distributions, which depend on current density so change with time in batch (recycle) depletion experiments. Hence, added complexity is to be expected to the behaviour described by equation [4.7] and [4.8] below. The AgCl|Ag reference electrode was situated at a distance of 1 mm from the graphite felt electrode surface, perpendicular to the electrolyte flow direction (see Chapter 3 Figures 3.5-3.8). The potential in the electrolyte solution and of the graphite felt electrode is dependent on the cross-sectional current density, which depends on the reactant concentration. Figure 4-17 displays the equivalent circuit and potential distribution for a porous electrode.
To follow the progress of the reaction, an UV absorption cell was incorporated into the reactor outlet tubing. The C=C bond of maleimide 4-1 has an absorbance maximum at 276 nm, as shown in the UV spectrum in Figure 4-18; the absorbance at < 240 nm was due to the carbonyl groups.
The experimental concentration depletion of maleimide 4-1 was calculated from the time dependence of the maximum absorbance at a wavelength of 276 nm in the UV spectra.

For a single reaction operating under complete mass transport control in a plug flow electrochemical reactor operating under batch recycle mode with a continuously stirred tank reservoir, reactant concentrations and current densities are predicted to decay (approximately) exponentially with time\(^{131}\), according to equations [4.7] and [4.8], respectively.

\[
c_r = c_0 \exp \left\{ -\frac{Q t}{V} \left[ 1 - \exp \left( -\frac{k_m a AL}{Q} \right) \right] \right\} \tag{4.7}
\]

\[
I_L = n F Q c_0 \left[ 1 - \exp \left( -\frac{k_m a AL}{Q} \right) \right] \exp \left\{ -\frac{Q t}{V} \left[ 1 - \exp \left( \frac{k_m a AL}{Q} \right) \right] \right\} \tag{4.8}
\]

The theoretical concentration depletion was calculated using equation [4.7], estimating the mass transport coefficient from the correlation developed by Carta \textit{et al.} at a porous felt electrode, equation [4.9]:\(^{132}\)

\[
k_m = 3.19 \left( \frac{D}{d_h} \right) \left( \frac{v_{eff} d_h}{v} \right)^{0.69} \tag{4.9}
\]

The mass transport coefficient \((k_m)\) was estimated to be 1.76\(\times10^{-6}\) m s\(^{-1}\) at a volumetric flow rate of 1.0\(\times10^{-6}\) m\(^3\) s\(^{-1}\) and using a diffusion coefficient of 1.85\(\times10^{-9}\) m\(^2\) s\(^{-1}\), estimated from the rotating disc experiments for the reduction of maleimide 4-1 at pH 0. Figure 4-19 shows the experimental and theoretical concentration depletions with time for the reduction of maleimide 4-1.
Chapter 4

Reduction of Maleimide

Figure 4-19: Comparison of experimental and theoretical depletion of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H₂SO₄ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min⁻¹ and room temperature.

The theoretical concentration depletion of maleimide 4-1 was predicted to occur at a faster rate than the experimental data obtained; however, the experimental results show that a conversion of ca. 99% after 400 seconds; the theoretical data predicted complete conversion after 600 seconds. The discrepancy between the data sets is likely to be due to the theoretical data being based on estimated kinetic parameters of $k_m = 1.76 \times 10^{-6} \text{ m s}^{-1}$ and $D = 1.85 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$.

The ln[maleimide]-time relationship, according to equation [4.7], is plotted in Figure 4-20. It is clear from this plot that the experimental data has a number of outlying points beyond 800 seconds, indicating a poor fit to equation [4.7]. Again the plot highlights that the experimental depletion of maleimide 4-1 was slower compared to the theoretical prediction.

The charge passed after 400 seconds of electrolysis was 181 C, whereas the theoretical charge required to reduce 0.01 M maleimide 4-1 was calculated to be 192 C, suggesting that after 400 seconds only ca. 95% of the maleimide 4-1 was converted to succinimide 4-1a. The UV may not have been able to detect very low levels of maleimide 4-1 that had not been reduced, or the unreacted maleimide 4-1 may have been adsorbed onto the surface of the graphite felt and not in the bulk solution.
Chapter 4  
Reduction of Maleimide

Figure 4-20: Comparison of theoretical and experimental ln[maleimide]-time relationship using 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature.

Considering the current-time relationship in Figure 4-15, current densities had not decayed to the plateau after 400 seconds, also suggesting that there was some unreacted maleimide 4-1 present in the reactor; after 600 seconds, current densities reached a plateau value due to hydrogen evolution. The experimental charge passed after 600 seconds of electrolysis was 212 C; using this charge for complete conversion of maleimide 4-1 a cumulative current efficiency was calculated using [4.6] to be 91 %. Current efficiencies improved significantly using the flow reactor compared to the efficiency calculated for maleimide 4-1 reduction in the batch H-cell (41%), due to improved mass transport rates.

In addition, increasing the volumetric surface area of the electrode by using the graphite felt had a significant impact on the rate of maleimide 4-1 reduction. After 400 seconds 99 % conversion of maleimide 4-1 was achieved using graphite felt compared to 60 % and 100 % conversion after 5 hours using the vitreous carbon and BDD electrode respectively.
4.3.2 Effect of Flow Rate

To determine if the reactor was operating under mass transport control and to evaluate the effect of residence time on the reaction progress, experiments were carried out at three different flow rates, namely 30, 60 and 90 mL min$^{-1}$, with residence times in the reactor of 37.8 s, 18.9 s and 12.6 s, respectively. A Masterflex peristaltic pump (Model 07524-40) was used to control the flow rate and was limited using $\frac{1}{4}''$ tubing to a minimum flow rate of 30 mL min$^{-1}$, which was therefore the minimum flow rate obtainable in the experiments. The AgCl|Ag reference electrode was inserted into a PTFE frame so that it was a tight fit, due to the difficulty of sealing onto PTFE. It was also not desirable to use sealant materials that may have come into contact with the catholyte, potentially contaminating the solution with organic material. Due to the design of the PTFE frame, it was found that flow rates beyond 90 mL min$^{-1}$ resulted in the catholyte solution leaking around the AgCl|Ag electrode.

Figure 4-21 shows the results for the experiments carried out at 30, 60 mL and 90 mL min$^{-1}$. It appears from the current-time relationship that the flow rate had little influence on the rate of the reaction with all of the experiments reaching a constant current after ca. 500 seconds. However, there was a marginal difference between the reaction times shown, at the fastest flow rate the current decayed at a faster rate compared to the slowest flow rate. It is interesting that the highest cathodic current was not recorded for the fastest flow rate as expected if the reaction was under complete mass transport control.

As in Figure 4-16, Figure 4-21 exhibits a more complex behaviour than mere exponential decay. Here again, this could have been due to a complex reaction mechanism and/or spatial distribution of potential, current densities and concentrations in the graphite felt cathode.
Chapter 4   Reduction of Maleimide

Figure 4-21: Cross sectional current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl/Ag), flow rates of 30, 60 and 90 mL min$^{-1}$ and room temperature.

The concentration depletion-time relationship is given in Figure 4-22 for the experimental and theoretical data for the reduction of 0.01 M maleimide 4-1 in 1 M aq. H$_2$SO$_4$; a $k_m$ value of $1.76 \times 10^{-6}$ m s$^{-1}$ and a diffusion coefficient of $1.85 \times 10^{-9}$ m$^2$ s$^{-1}$ were used to calculate the theoretical data. The calculated data indicate that the flow rate had a more pronounced effect on the concentration depletion compared to the experimental data, the theoretical reaction time being ca. 400 seconds at a flow rate of 90 mL min$^{-1}$ compared to ca. 1000 seconds at a flow rate of 30 mL min$^{-1}$. The experimental data for 90 mL min$^{-1}$ shows that the reaction was completed after ca. 400 seconds, in good agreement with the current decay displayed in the current-time plots in Figure 4-21.
Figure 4-22: Comparison of experimental and theoretical depletion of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl/Ag), flow rates of 30, 60 and 90 mL min$^{-1}$ and room temperature.

Figure 4-23: Comparison of theoretical and experimental ln[maleimide]-time relationship using 0.01 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl/Ag), flow rates of 30, 60 and 90 mL min$^{-1}$ and room temperature.
4.3.3 Effect of Temperature

Considering the proposed mechanism of maleimide 4-1 reduction given in Scheme 4.4, it is suggested that after the initial electron and proton transfers, the radical species formed undergoes a rearrangement and a keto-enol tautomerisation, the chemical rate determining step of the reaction mechanism. Increasing the temperature of the catholyte to 50 °C could enhance the rate of the rearrangement and tautomerisation, overall improving the rate of the reaction. To increase the reaction temperature, the catholyte and anolyte reservoirs were immersed in a water bath. Figure 4-24 shows the current-time relationship for the reduction of 0.01 M maleimide 4-1 at room temperature and 50 °C at the graphite felt electrode at a potential of -1.2 V (AgCl|Ag).

![Graph showing current-time relationship](image)

Figure 4-24: Cross sectional current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 1 M aq. H₂SO₄ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min⁻¹ and room temperature and 50 °C.

Unfortunately, the results for the experiments carried out at 50 °C were always noisy. However, the cross sectional current density-time relationship suggests that the maleimide 4-1 had been converted after ca. 350 seconds, in good agreement with the UV data showing that the maleimide 4-1 was completely depleted in 300 seconds. At room temperature complete conversion was obtained after 400 seconds. These results suggest that elevated temperatures may increase the rate of the chemical steps occurring in the bulk solution, and/or increase the rate of diffusion of the organic from the bulk solution to active sites on the graphite felt
electrode surface, improving conversion of the starting material. Further experiments should be carried out at higher temperatures to determine if the reaction time could be improved for the reduction of maleimide 4-1.

### 4.3.4 Effect of concentration

Gratifyingly, the reduction of 0.01 M maleimide 4-1 to succinimide 4-1a was competed after 400 seconds of electrolysis at -1.2 V (AgCl|Ag) using a three dimensional graphite felt electrode. To determine if high efficiency could be achieved at a higher concentration, experiments were carried out using 0.1 M maleimide 4-1 solution. Figure 4-25 compares the current-time relationship for the reduction of 0.01 M and 0.1 M maleimide 4-1 in 1 M aq. H₂SO₄. As expected, cathodic current densities increased with increased reactant concentration and reaction times. As the concentration of the reactant is increased this increases the limiting diffusion current density and therefore higher current densities were observed. However, the reaction was completed within 2400 seconds as indicated in Figure 4-26. Figure 4-27 shows the semi-log plot of maleimide 4-1 depletion compared to the theoretical depletion, a slower rate of depletion was observed for the experimental data. The charge passed during the reaction was 3645 C whereas the theoretical charge required to reduce 0.1 M maleimide 4-1 was 1929 C. Again a poor charge yield was obtained due to the competing reaction of hydrogen evolution. Nevertheless, the conversion of a high quantity of starting material could be achieved by this method within a reasonable time.
Figure 4-25: Cross sectional current density-time relationship for the reduction of 0.01 M and 0.1 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature.

Figure 4-26: Experimental depletion of 0.1 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature.
Figure 4-27: Comparison of theoretical and experimental ln[maleimide]-time relationship using 0.1 M maleimide 4-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate 60 mL min$^{-1}$ and room temperature.

4.3.5 Effect of pH

The proton concentration of electrolyte solutions plays an important role in the reduction of organic compounds. To determine the effect of proton concentration on the reduction of maleimide 4-1 in the flow-through reactor experiments were carried out at pH 0, 2 and 4, using 1 M aq. H$_2$SO$_4$, 0.01 M aq. H$_2$SO$_4$ and 0.0001 M aq. H$_2$SO$_4$ electrolyte solutions, respectively. To improve the conductivity of the electrolytes 0.1 M Na$_2$SO$_4$ was used as a supporting electrolyte. Decreasing the proton concentration of the electrolyte would have decreased the rate of hydrogen evolution and so could potentially have increased current efficiencies of the reaction.

Figure 4-28 displays the current-time relationship for 0.01 M maleimide 4-1 reduction at pH 2 and pH 4; currents did not decay exponentially with time as expected, but the current decay also did not behave as previously observed for reduction at pH 0 (Figure 4-15). The progress of the reactions was much slower at pH 2 and 4; complete conversion of maleimide 4-1 was achieved after 3300 seconds at pH 2, whereas at pH 4 complete conversion was not observed within 3600 seconds (Figure 4-29). This suggests that a high proton concentration is essential
to achieve efficient reduction of maleimide 4-1. The only product of the reduction at pH 2 and pH 4 was succinimide 4-1a, as expected in this pH range.

The reaction order with respect to protons was calculated from the initial rate of reaction using [4.10]. Plotting the log of the initial rate of the reaction versus pH using [4.11], a reaction order of 0.3 (with respect to protons) was calculated suggesting that the reaction was not solely kinetically controlled in the flow-through reactor.

\[
V_0 = k[\text{maleimide}]_0[H^+]_0^m = A[H^+]_0^n
\]

\[
\log(V_0) = \log(A) + n \log([H^+]_0) = \log(A) - n \cdot p\text{H}
\]  

![Graph showing cross sectional current density-time relationship](image)

Figure 4-28: Cross sectional current density-time relationship for the reduction of 0.01 M maleimide 4-1 in 100 mL 0.01 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 2) and 100 mL 0.0001 M aq. H$_2$SO$_4$ + 0.1 M Na$_2$SO$_4$ (pH 4) at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and room temperature.
Figure 4-29: Comparison of experimental and theoretical depletion of 0.01 M maleimide 4-1 in 100 mL 0.01 M aq. H\textsubscript{2}SO\textsubscript{4} + 0.1 M Na\textsubscript{2}SO\textsubscript{4} (pH 2) and 100 mL 0.0001 M aq. H\textsubscript{2}SO\textsubscript{4} + 0.1 M Na\textsubscript{2}SO\textsubscript{4} (pH 4) at a graphite felt electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min\textsuperscript{-1} and room temperature.

### 4.4 Chapter Summary

Maleimide 4-1 was reduced electrochemically to succinimide 4-1a using the modified electrochemical flow-through reactor operated in batch recycle mode. Complete conversion of 0.01 M maleimide 4-1 was achieved after 5 hours of electrolysis at -1.2 V (AgCl|Ag) at a BDD cathode. Increasing the volumetric surface area of the electrode by incorporating graphite felt as the working electrode resulted in 99 % conversion of 0.01 M maleimide 4-1 in 400 seconds.

pH 0 was required to achieve the fastest conversion, due to the high concentration of protons and beyond pH 7 the desired product, succinimide 4-1a, was not obtained due to a switch in the reaction mechanism. Higher initial concentrations starting material were converted within a 1 hour period.

The chapter has demonstrated that the reduction of maleimide 4-1 to succinimide 4-1a was achieved successfully at a graphite felt electrode in an aqueous system at high conversions and short reaction times. Furthermore, the electrolysis was carried out at ambient temperature.
and pressure at non-toxic electrode materials; solvents were not required during the electrolysis and no waste material was generated in the process. The process qualifies as a green chemical technology as it meets a number of the 12 principles of green chemistry.\(^5\) However, to develop the overall process an improvement is required for the isolation of the product as in this work dichloromethane was used to extract the product from the aqueous solution.
Chapter 5  Reduction of C=C bonds

The experimental results in this chapter describe the electrochemical reduction of maleimide derivatives (Figure 5-1) to understand the selectivity of the reduction of C=C bonds using the electrochemical flow-through reactor system.

![Maleimide derivatives investigated electrochemically.](image)

Figure 5-1: Maleimide derivatives investigated electrochemically.

5.1 Chemoselective C=C Bond Reduction

Chemoselective reduction of C=C bonds, particularly conjugated double bonds presents a significant challenge in organic synthesis. Several reagents, such as Raney nickel, silanes in the presence of catalytic rhodium(bisoxazolinylphenyl), $H_2$ gas and trialkylammonium formates, are available for the reduction of unsaturated carbonyl compounds. However, these reagents and the conditions used in some cases do not offer high selectivity. These limitations often occur in the presence of other double bonds. For example, the reduction of the enone group of intermediate 5-5 using a copper catalyst and a silane reagent (Scheme 5.1).

![Scheme 5.1: Reduction of intermediate 5-5 using a copper catalyst.](image)

Scheme 5.1: Reduction of intermediate 5-5 using a copper catalyst.

Previously, Korotaeva et al demonstrated selective electrochemical reduction of the cyclic double bond of the pyridine derivative 5-8 into 5-9, using a mercury pool electrode, anhydrous DMF and 0.1 M $Bu_4$NClO$_4$ as a supporting electrolyte (Scheme 5.2). However, the process also caused racemisation of a stereogenic centre, leading to a mixture of the cis- and trans- diastereoisomers in a ratio of 5:7 (Scheme 5.2).
Scheme 5.2: Chemoselective reduction of C=C bond of pyridine derivative 5-8.

To investigate the capability of the electrochemical flow-through reactor as an atom efficient and clean technology for chemoselective reduction, N-allylmaleimide 5-1 and N-propargylmaleimide 5-2 were synthesised to examine whether the C=C bond and/or the allyl/propargyl groups would be reduced. Scheme 5.3 shows the synthesis of N-allylmaleimide 5-1 and N-propargylmaleimide 5-2 via reflux of maleic anhydride 5-10 with allylamine 5-11 and propargylamine 5-12 respectively, in acetic acid.

Scheme 5.3: Synthesis of N-allylmaleimide 5-1 and N-propargylmaleimide 5-2.

5.1.1 Kinetic Investigation with a Rotating Disc Electrode

A VC RDE was used to investigate the electrochemical reduction of N-allylmaleimide 5-1 and N-propargylmaleimide 5-2, to establish kinetic parameters not available in the literature and the reduction potential of each substrate for application to the electrochemical flow-through reactor.

The substrates were not soluble in 1 M aq. H$_2$SO$_4$, so methanol (MeOH) was added to the electrolyte solution to dissolve them. The reduction of N-allylmaleimide 5-1 will be considered initially before discussing the reduction of N-propargylmaleimide 5-2 at the RDE.

Figure 5-2 shows the CV recorded for the reduction of 0.01 M N-allylmaleimide 5-1 in 100 mL of a mixture of 1 M aq H$_2$SO$_4$ and MeOH (8:2 v/v), at the VC RDE between 0 and -1.5 V (SCE) at a range of rotation frequencies and a scan rate of 25 mV s$^{-1}$. In the negative-going
sweep, reduction began at -0.6 V (SCE), below which current densities increased until the mass transport limited current density was reached at -1.1 V (SCE). There was no evidence of an oxidative process occurring on the subsequent positive-going potential sweep between -1.5 and -0.2 V (SCE). The potential at which the limiting current was observed was ca. -1.1 V (SCE). The exponential increase in current densities between -1.2 and -1.5 V (SCE) was due to the evolution of H$_2$.

Figure 5-3 shows a semi-log plot of the current density-overpotential relationship for the reduction of 0.01 M $N$-allylmaleimide 5-1 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v), at the VC RDE at a rotation of 1000 rpm. The $E_{allyl}$ was measured experimentally to be -0.19 V (SCE) (Appendix 3). The Tafel slope was calculated to be 140 ± 10 % mV decade$^{-1}$ and $j_0$ as 2.2x10$^{-3}$ ± 9 % A m$^{-2}$ which represents potentials between -0.6 and -0.75 V (SCE) in the CV shown in Figure 5-2. The Tafel slope measured was slightly higher than that measure for maleimide 4-1 (119 ± 7% mV decade$^{-1}$) suggesting that the electrode reaction kinetics were slower for the reduction of $N$-allylmaleimide 5-1.

![Figure 5-2: Cyclic voltammograms for the reduction of 0.01 M $N$-allylmaleimide 5-1 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a VC RDE; electrode potential swept between -0.2 V and -1.5 V (SCE) at a scan rate of 25 mV s$^{-1}$ and at a range of rotation rates.](image-url)
Figure 5-3: Effect of overpotential $(E_{\text{disc}}-E_{\text{allyl}})$ on log(current density) for the reduction of 0.01 M $N$-allylmaleimide 5-1 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.

The Levich plot is shown in Figure 5-4 for the reduction of $N$-allylmaleimide 5-1, calculated from the Levich equation (Chapter 4, equation [4.2]). To determine if the process was mass transport controlled, and whether it was a one 2-electron reduction or a two 1-electron process, when the diffusion coefficient is estimated to be $D= 1 \times 10^{-9}$ m$^2$s$^{-1}$, $c=10$ mol m$^{-3}$, n=1 or n=2.

Figure 5-4: Effect of rotation rate on measured current densities for reduction of 0.01 M $N$-allylmaleimide 5-1 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) using a VC RDE, compared with those predicted by Levich’s equation.
The result showed that the measured limiting current density fits the predicted limited current density when \( n = 2 \), suggesting that the process is an overall 2-electron reduction, as for reduction of maleimide 4-1 (Chapter 4). As increasing rotation rate did not decrease the apparent electron stoichiometry from two towards one, these data imply the intermediate was adsorbed, so could not be dispersed to the bulk solution before the second electron transfer occurred. The proposed mechanism is given in Scheme 5.4, which parallels that for maleimide 4-1 reduction. An initial proton transfer is followed by an electron transfer, the resulting intermediate then undergoes a keto-enol tautomerisation RDS and a further proton and electron transfer to provide the product.

A reduction potential of -1.1 V (SCE) was required to achieve transport controlled reduction of \( N \)-allylmaleimide 5-1. This is thought to be due to the allyl group on the N-atom stabilising the radical intermediate formed during the reduction process (Scheme 5.4).

![Scheme 5.4: Proposed mechanism for the electrochemical reduction of \( N \)-allylmaleimide 5-1 to \( N \)-allylsuccinimide 5-1a.](image)

Experiments were carried out at pH 2 and pH 4 for the reduction of 0.01 M \( N \)-allylmaleimide 5-1 at the VC RDE; the CV is shown in Figure 5-5. At pH 2, the reduction of \( N \)-allylmaleimide 5-1 began at -0.6 V (SCE) and a limiting current of ca. 80 A m\(^{-2}\) at -1.1 to -1.4 V (SCE) was measured. Whereas at pH 4, the reduction began at -0.8 V (SCE) and a limiting current of ca. 40 A m\(^{-2}\) was measured between -1.0 and -1.4 V (SCE). At pH 0 a limiting current of ca. 110 A m\(^{-2}\) was observed at -1.2 V (SCE). In both cases (pH 2 and 4), a shift to a more negative potential at the limiting current was observed compared to the CV recorded for the reduction at pH 0 as predicted by the Nernst equation (Chapter 2, equation [2.13]).
Figure 5-5: Cyclic voltammograms for the reduction of 0.01 M $N$-allylmaleimide 5-1 in 100 mL of a mixture of 0.01 M aq. $\text{H}_2\text{SO}_4 + \text{MeOH}$ (8:2 v/v) + 0.5 M $\text{Na}_2\text{SO}_4$ (pH 2) and 100 mL of a mixture of 0.0001 M aq. $\text{H}_2\text{SO}_4 + \text{MeOH}$ (8:2 v/v) + 0.5 M $\text{Na}_2\text{SO}_4$ (pH 4) at a VC RDE; electrode potential swept between 0 V and -1.75 V (SCE) at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.

Figure 5-6 shows the CV for the reduction of 0.01 M $N$-propargylmaleimide 5-2 in 100 mL of a mixture of 1 M aq. $\text{H}_2\text{SO}_4$ and MeOH (8:2 v/v), at a VC RDE between -0.2 and -1.2 V (SCE) at a range of rotation frequencies and a scan rate of 25 mV s$^{-1}$. Reduction began at -0.6 V (SCE) and the limiting current density was achieved at -1 V (SCE), below which the onset of hydrogen evolution was evident. The semi-log plot of current density-overpotential is shown in Figure 5-7; the $E_{prop}$ was measured experimentally to be -0.18 V (SCE) (Appendix 3). From the plot a Tafel slope of 117 ± 9 % mV decade$^{-1}$ and the exchange current density $j_0$ 3.5x10$^{-3}$ ± 6% A m$^{-2}$ were calculated between -0.5 and -0.6 V (SCE) in the CV shown in Figure 5-6. The Tafel slope is in good agreement with the Tafel slope measure for maleimide 4-1.
Chapter 5   Reduction of C=C Bonds

Figure 5-6: Cyclic voltammogram for the reduction of 0.01 M N-propargylmaleimide 5-2 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a VC RDE; electrode potential swept between -0.2 V and -1.2 V (SCE) at a scan rate of 25 mV s$^{-1}$ and at a range of rotation rates.

Figure 5-7: Effect of overpotential (E$_{\text{disc}}$-E$_{\text{propargyl}}$) on log(current density) for the reduction of 0.01 M N-propargylmaleimide 5-2 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a VC RDE at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.

Figure 5-8 shows the reduction of N-propargylmaleimide 5-2 in 100 mL of a mixture of 0.0001 M aq H$_2$SO$_4$ and MeOH (8:2 v/v) and 0.1 M Na$_2$SO$_4$, to provide pH 4. The limiting current density of ca. 40 A m$^{-2}$ for the reduction of N-propargylmaleimide 5-2 was measured between -1.0 and -1.4 V (SCE).
The results obtained from the RDE experiments suggest that the reduction of \( N\text{-}allyl\text{maleimide} \ 5\text{-}1 \) and \( N\text{-}propargyl\text{maleimide} \ 5\text{-}2 \) undergo a 2-electron process resembling the reduction mechanism of maleimide \( 4\text{-}1 \) (Chapter 4). Again it is thought that an ECE mechanism occurs to reduce the cyclic C=C bond, with only one of the electron transfers detected in the voltammograms (Figure 5-2, Figure 5-5 and Figure 5-6). This implies that the second electron transfer is limited, possibly by its equilibrium potential \( E_2 < E_1 \) and buried in hydrogen evolution.

However, for the case of \( N\text{-}propargyl\text{maleimide} \ 5\text{-}2 \) reduction at pH4 (Figure 5-8) indicated an initial electron transfer occurring at ca. -0.7 V (SCE) which suggests under these conditions a different reaction mechanism was operative (e.g. disproportionation of a radical anion intermediate into \( N\text{-}propargyl\text{succinimide} \ 5\text{-}2a \) and starting material \( 5\text{-}2 \)).
5.1.2 Kinetic Investigations with the Flow-through Electrochemical Reactor

Preparative electrolysis was carried out in the electrochemical flow-through reactor operating in batch recycle mode with a continuously stirred tank reservoir to determine the products of \(N\)-allylmaleimide 5-1 and \(N\)-propargylmaleimide 5-2 reduction.

Based on the data obtained in the rotating disc experiments, initial experiments were carried out for the reduction of 0.01 M \(N\)-allylmaleimide 5-1 in 500 mL of a mixture of 1 M aq. \(\text{H}_2\text{SO}_4\) and MeOH (8:2 v/v), using the flow-through reactor at both VC and BDD electrode materials. A constant potential of \(-1.1\) V (AgCl|Ag) was applied for 5 hours and at a flow rate of 60 mL min\(^{-1}\). The aim of these experiments was to determine if one of the C=C bonds of \(N\)-allylmaleimide 5-1 would be reduced selectively on a preparative scale. Figure 5-9 displays the current density-time relationship for the reduction of 0.01 M \(N\)-allylmaleimide 5-1 at a VC electrode. The current density recorded started at \(ca.\) -60 A m\(^{-2}\) and decayed to \(ca.\) -35 A m\(^{-2}\). A charge of 725 C was passed during electrolysis at the VC electrode and a conversion of 59% and current efficiency of 79% was achieved.

![Figure 5-9: Current density-time relationship and charge passed for the reduction of 0.01 M \(N\)-allylmaleimide 5-1 in 500 mL of a mixture of 1 M aq. \(\text{H}_2\text{SO}_4\) and MeOH (8:2 v/v) and the background solution (without \(N\)-allylmaleimide 5-1) at a VC electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature.](image)

After neutralisation and extraction with \(\text{CH}_2\text{Cl}_2\), the \(^1\text{H}\) NMR indicated that gratifyingly the cyclic C=C bond of \(N\)-allylmaleimide 5-1 had been reduced while the allyl group remained intact, providing \(N\)-allylsuccinimide 5-1a as the only product (Scheme 5.5). As the cyclic...
The C=C bond is more electron deficient, the addition of two electrons and two protons to the conjugated C=C bond is more favourable than addition to the allyl group.

\[
\text{Scheme 5.5: Electrochemical reduction of } N\text{-allylmaleimide 5-1 to } N\text{-allylsuccinimide 5-1a.}
\]

The highest rate of conversion and the greatest current efficiency were recorded when BDD was used as the cathode material; after 5 hours of electrolysis a conversion of >99% and a current efficiency of 85% were attained.

Table 5.1 presents the current efficiencies, conversion, specific energy consumption and costs for the reduction of \(N\)-allylmaleimide 5-1 to \(N\)-allylsuccinimide 5-1a using the flow reactor. The specific electrical energy consumption \(w_p^e\) was calculated using equation [5.1].

\[
w_p^e = \frac{vF}{\Phi_p^x} \frac{U}{3.6M_p}
\]  

[5.1]

<table>
<thead>
<tr>
<th>Electrode</th>
<th>VC</th>
<th>BDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion / %</td>
<td>59</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Current efficiency (\Phi_p^x)</td>
<td>0.79</td>
<td>0.85</td>
</tr>
<tr>
<td>Specific electrical energy consumption / kWh tonne(^{-1})</td>
<td>1353</td>
<td>1257</td>
</tr>
<tr>
<td>Cost / £ tonne(^{-1})</td>
<td>135</td>
<td>125</td>
</tr>
</tbody>
</table>

Based on these figures, the cost to produce a tonne of the product was calculated from the specific electrical energy consumption (equation [2.25] Chapter 2), assuming that the price for a kWh of energy was £ 0.1. It is clear that the cost to produce a tonne of product is low, indicating that the flow-through reactor is energy efficient.
Figure 5-10 displays the current density-time relationship data for the reduction of 0.01 M \( N \)-propargylmaleimide \( 5-2 \) at a BDD electrode at a constant potential of -1 V (AgCl|Ag) in 100 mL of a mixture of 1 M aq. \( \text{H}_2\text{SO}_4 \) and MeOH (8:2 v/v).

![Current density-time relationship](image)

**Figure 5-10:** Current density-time relationship for the reduction of 0.01 M \( N \)-propargylmaleimide \( 5-2 \) in 100 mL of a mixture of 1 M aq. \( \text{H}_2\text{SO}_4 \) and MeOH (8:2 v/v) and the background solution (without \( N \)-allylmaleimide \( 5-1 \)) at a VC electrode using the flow-through reactor at a potential of -1.0 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature.

The reaction solution was analysed according to the previous method at the end of the experiment and \(^1\)H NMR analysis indicated that the cyclic C=C bond was selectively reduced, while the propargyl and the C=O groups remained intact. \( N \)-propargylmaleimide \( 5-2 \) was electrochemically reduced to \( N \)-propargylsuccinimide \( 5-2a \) as shown in Scheme 5.6.

\[ \begin{align*}
\text{5-2} & \quad + 2\text{H}^+ + 2\text{e}^- \\
\text{5-2a} & \\
\end{align*} \]

**Scheme 5.6:** Electrochemical reduction of \( N \)-propargylmaleimide \( 5-2 \) to \( N \)-propargylsuccinimide \( 5-2a \).
5.1.2.1 Effect of Volumetric Surface Area

As in the case of maleimide 4-1 reduction, the volumetric surface area of the cathode was increased by incorporating graphite felt and a feeder electrode into the electrochemical flow-through reactor in order to decrease the reaction time. An in-situ UV cell was incorporated into the reactor outlet tubing to follow the progress of the reaction. Indeed, the cyclic C=C bond of \( N \)-allylmaleimide 5-1 displays an absorbance peak at a wavelength of 299 nm and in the case of the cyclic C=C bond of \( N \)-propargylmaleimide 5-2 the absorbance peak was observed at 292 nm.

As expected, the increase in electrode surface area dramatically diminished the reaction time for the reduction of \( N \)-allylmaleimide 5-1 and \( N \)-propargylmaleimide 5-2. Figure 5-11 displays the cross sectional current density-time relationship for the reduction of \( N \)-allylmaleimide 5-1 at -1.1 V (AgCl|Ag). 92 % conversion was achieved after 30 minutes, compared with 80% after 5 hours for the reactor with the BDD cathode. Similarly the reduction of \( N \)-propargylmaleimide 5-2 at -1.1 V (AgCl|Ag) provided a high conversion of 95% after 30 minutes. For both experiments, \(^1\)H NMR analysis was carried out to verify that the only products of the reactions were \( N \)-allylsuccinimide 5-1a and \( N \)-propargylsuccinimide 5-2a and that the reduction was chemoselective.

![Figure 5-11: Current density-time relationship and charge passed for the reduction of 0.01 M \( N \)-allylmaleimide 5-1 in 500 mL of a mixture of 1 M aq. \( \text{H}_2\text{SO}_4 \) and MeOH (8:2 v/v) and the background solution (without \( N \)-allylmaleimide 5-1) at a graphite felt electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature.](image-url)
5.1.2.2 Effect of Temperature

The effect of elevated temperature was investigated for the reduction of \(N\text{-allylmaleimide 5-1}\) by immersion of the catholyte and anolyte reservoirs in a water bath at 50 °C, to determine if the temperature had an effect on the chemoselectivity of the reaction.

Figure 5-12 shows the cross sectional current density-time relationship for the reduction of \(N\text{-allylmaleimide 5-1}\) at -1.1 V (AgCl|Ag) at 50 °C. Interestingly, cross sectional current densities were increased compared with those at room temperature. Based on this data, the reaction appeared to reach its end after 15 minutes, suggesting that the elevated temperature increased the rate of the reaction.

The reaction was also monitored by UV spectroscopy. Figure 5-13 shows the experimental concentration depletion of \(N\text{-allylmaleimide 5-1}\) (experimental concentration according to UV absorbance and theoretical concentration calculated from equation [4.7] Chapter 4), compared with the theoretical depletion for a single transport controlled reaction \((k_m =1.76 \times 10^{-6} \text{ m s}^{-1})\). The plot shows that the concentration of \(N\text{-allylmaleimide 5-1}\) was not depleted to zero, but was reaching after 30 minutes a plateau value of \(10^{-3} \text{ M (1 mol m}^{-3}\)), \textit{i.e.}\ 93\%\ conversion. It would be interesting to carry out an experiment for a longer time period to determine if complete conversion could be achieved.

The product of the reaction was nonetheless \(N\text{-allylsuccinimide 5-1a}\) and the reaction temperature did not appear to affect the chemoselectivity of the reaction. Due to synthesis difficulty, \(N\text{-propargylmaleimide 5-2}\) experiments were not carried out at elevated temperature.
Figure 5-12: Current density-time relationship and charge passed for the reduction of 0.01 M N-allylmaleimide 5-1 in 500 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) and the background solution (without N-allylmaleimide 5-1) at a graphite felt electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and 50 °C.

Figure 5-13: Comparison of experimental and theoretical depletion of 0.01 M N-allylmaleimide 5-1 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a graphite felt electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min$^{-1}$ and 50 °C.
5.1.2.3 Effect of pH

The reduction of \(N\)-allylmaleimide 5-1 and \(N\)-propargyImaleimide 5-2 was studied at pH 4 at a graphite electrode in the electrochemical flow-through reactor. In the case of the reduction of \(N\)-allylmaleimide 5-1 at -1.1 V (AgCl|Ag), shown in Figure 5-14, a conversion of 94 % to \(N\)-allylsuccinimide 5-1a was achieved after 1 hour. However, a conversion of only 85 % was achieved for the reduction of \(N\)-propargyImaleimide 5-2 at the same potential at pH 4 after 1 hour. This suggests that the reduction of \(N\)-propargyImaleimide 5-2 was hindered at pH 4, though chemoselective reduction remained and only the cyclic C=C bond was reduced. This could suggest that the mechanism of the reduction is not affected by pH variation.

![Figure 5-14: Current density-time relationship and charge passed for the reduction of 0.01 M \(N\)-allylmaleimide 5-1 in 100 mL of a mixture of 0.0001 M aq. H\(_2\)SO\(_4\) + MeOH (8:2 v/v) + 0.5 M Na\(_2\)SO\(_4\) (pH 4) and the background solution (without \(N\)-allylmaleimide 5-1) at a graphite felt electrode using the flow-through reactor at a potential of -1.1 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature.](image)

5.2 Stereoselective C=C Bond Reduction

Catalytic hydrogenation of cyclic C=C bonds using H\(_2\) and metal catalysts provide \textit{cis}-addition products. The electrochemical reduction of C=C bond proceeds via sequential electron transfer and H\(^+\) addition, and therefore could potentially offer \textit{trans}-addition of H\(_2\), which can be achieved using chemical means only via dissolved metal reduction.\(^{136}\) \textit{Trans}-addition of H\(_2\) to maleimide derivatives is interesting, as it can be used potentially for the
synthesis of a range of biologically active natural products and candidate drug molecules that contain succinimide functionality (Figure 5-15).\textsuperscript{136, 137, 138, 139}

\textbf{Figure 5-15: Biologically active succinimide derivatives.}\textsuperscript{136-139}

To test the stereochemistry of the electrochemical reduction methodology, 3,4-dimethylmaleimide 5-3 and \(N\)-benzyl-3,4-dimethylmaleimide 5-4 were synthesised (Scheme 5.7). These syntheses were carried out by refluxing maleic anhydride 5-13 with ammonium acetate 5-14 and benzylamine 5-15 respectively in acetic acid.\textsuperscript{135}

\textbf{Scheme 5.7: Synthesis of 3,4-dimethylmaleimide 5-3 and \(N\)-benzyl-3,4-dimethylmaleimide 5-4.}
5.2.1 Kinetic Investigations with a Rotating Disc Electrode

Rotating disc electrode experiments were carried out to determine the reduction potential of each substrate for application with the flow-through reactor. The reduction of 3,4-dimethylmaleimide 5-3 and N-benzyl-3,4-dimethylmaleimide 5-4 was studied using a VC RDE. Figure 5-16 shows the CV for the reduction of 0.01 M 3,4-dimethylmaleimide 5-3 in 100 mL of a mixture of 1 M aq. H₂SO₄ and MeOH (8:2 v/v), between 0 V and -1.75 V (SCE) at a range of rotation frequencies. It is clear from the plot that no reduction wave was evident in the CV, possibly due to the current density associated with hydrogen evolution. Similarly, the CV for the reduction of N-benzyl-3,4-dimethylmaleimide 5-4 (Figure 5-17) did not show any reduction waves, again likely masked by the evolution of hydrogen.

Figure 5-16: Cyclic voltammograms for the reduction of 0.01 M 3,4-dimethylmaleimide 5-3 in 100 mL of a mixture of 1 M aq. H₂SO₄ and MeOH (8:2 v/v) at a VC RDE; electrode potential swept between -0 V and -1.75 V (SCE) at a scan rate of 25 mV s⁻¹ and at a range of rotation rates.
Figure 5-17: Cyclic voltammograms for the reduction of 0.01 M N-benzyl-3,4-dimethylmaleimide 5-4 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (8:2 v/v) at a VC RDE; electrode potential swept between -0 V and -1.75 V (SCE) at a scan rate of 25 mV s$^{-1}$ and at a range of rotation rates.

As no information for the reduction was derived from the CV, the reduction potential of -1.2 V (AgCl|Ag) was applied for the electrochemical flow-through reactor experiments. This potential was chosen as it was the reduction potential required to successfully reduce maleimide 4-1.

5.2.2 Kinetic Investigations with the Flow-through Electrochemical Reactor

The reduction of 3,4-dimethylmaleimide 5-3 and N-benzyl-3,4-dimethylmaleimide 5-4 was performed subsequently using the electrochemical flow-through reactor with a BDD cathode (Scheme 5.8).

Scheme 5.8: Electrochemical reduction of 3,4-dimethylmaleimide 5-3 and N-benzyl-3,4-dimethylmaleimide 5-4.
Figure 5-18 shows that current densities decayed with time during the reduction of \(N\)-benzyl-3,4-dimethylmaleimide 5-4 using a BDD cathode when the potential was fixed at -1.2 V for 5 hours. Following extraction of products with CH\(_2\)Cl\(_2\), \(^1\)H NMR indicated that a mixture of diastereomers was produced. The \(^1\)H NMR data of the \textit{cis} and \textit{trans}- products had been previously reported.\(^{140-142}\) Thus, a ratio of 2:3 of the \textit{cis}- and \textit{trans}-products was identified by comparing the relative integrals of the new C-H group signals at 2.95 and 2.45 ppm for the \textit{cis}- and \textit{trans}- products respectively (Figure 5-19).

![Figure 5-18: Current density-time relationship and charge passed for the reduction of 0.01 M \(N\)-benzyl-3,4-dimethylmaleimide 5-4 in 100 mL of a mixture of 1 M aq. H\(_2\)SO\(_4\) and MeOH (8:2 v/v) and the background solution without \(N\)-benzyl-3,4-dimethylmaleimide 5-4 at a BDD electrode using the flow-through reactor at a potential of -1.2 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature.](image-url)
Figure 5-19: $^1$H NMR for the products of the reduction of $N$-benzyl-3,4-dimethylmaleimide 5-4.

Similarly, by applying a constant potential at -1.2 V to a solution of 3,4-dimethylmaleimide 5-3 for 5 hours using BDD, a mixture of diastereomeric products was also obtained in a ratio of 2:3, as indicated by $^1$H NMR (Figure 5-20).

Figure 5-20: $^1$H NMR for the products of the reduction of 3,4-dimethylmaleimide 5-3.
5.2.2.1 Effect of Volumetric Surface Area

To see if the increase in volumetric surface area could increase the stereochemistry of the products observed for the reduction of 3,4-dimethylmaleimide \( \text{5-3} \) and \( N \)-benzyl-3,4-dimethylmaleimide \( \text{5-4} \). The graphite felt electrode could provide more stereoselective adsorption sites on the surface of the electrode compared to the 2-dimensional VC or BDD electrodes.

Figure 5-21 displays the cross sectional current density-time relationship for the reduction of 3,4-dimethylmaleimide \( \text{5-3} \) at the graphite felt electrode at a fixed potential of \(-1.2\) V (AgCl|Ag). After 30 minutes of electrolysis, a 94 % conversion was achieved and a mixture of diastereomeric products was obtained in a ratio of 2:3 of the \( \text{cis} \)- and \( \text{trans} \)- products. The graphite felt electrode appeared to have no effect on the selectivity of the reduction process.

![Figure 5-21: Current density-time relationship and charge passed for the reduction of 0.01 M \( N \)-3,4-dimethymaleimide \( \text{5-3} \) in 100 mL of a mixture of 1 M aq. H\(_2\)SO\(_4\) and MeOH (8:2 v/v) and the background solution (without 3,4-dimethylemaleimide \( \text{5-3} \) at a graphite felt electrode using the flow-through reactor at a potential of \(-1.2\) V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature.]

However, a shift in the selectivity was observed for the reduction of \( N \)-benzyl-3,4-dimethylmaleimide \( \text{5-4} \) at the graphite felt cathode at \(-1.2\) V (AgCl|Ag). After 30 minutes of electrolysis, it was found that the ratio of the \( \text{cis} \)- and \( \text{trans} \)-products was 1:3. This suggests that the benzyl group influences the selectivity and favours the \( \text{trans} \)- product.
5.3 Chapter Summary

The electrochemical reductions of a range of maleimide derivatives were investigated to determine if chemoselective or stereoselective reduction could be achieved using the flow-through reactor. After rotating disc electrode experiments were used to determine the reduction potential of \( N \)-allylmaleimide 5-1 and \( N \)-propargylmaleimide 5-2, the cyclic C=C bonds in both substrates were successfully reduced chemoselectively using the electrochemical reactor. This process is particularly interesting to synthetic organic chemistry as it demonstrates an environmentally benign method of reducing a conjugated C=C bond which is usually achieved using metal catalysts. Utilising graphite felt as the cathode and increasing the temperature to 50 °C decreased the reaction time and had no effect on the chemoselectivity of the reaction.

The electrochemical reduction of 3,4-dimethylmaleimide 5-3 and \( N \)-benzyl-3,4-dimethylmaleimide 5-4 produced a mixture of diastereomeric products, with a slight bias towards the formation of the \textit{trans}-product (2:3 ratio \textit{cis}- to \textit{trans}-). Furthermore, by increasing the volumetric surface of the cathode with graphite felt, the stereochemistry of the reduction of \( N \)-benzyl-3,4-dimethylmaleimide 5-4 was slightly enhanced, producing the \textit{trans}-product at 75% (1:3 ratio \textit{cis}- to \textit{trans}-).

Again, the methodology developed demonstrated that the electrochemical flow-through reactor can be employed as an environmentally benign technology for the chemoselective reduction of conjugated cyclic C=C bonds and a slight bias towards the stereoselective reduction of cyclic C=C bonds.
Chapter 6  

*N, N*-Dimethylbenzamide Reduction

The reduction of an amide to provide an amine was highlighted as a key transformation for pharmaceutical manufacturing requiring urgent attention. The results discussed in this chapter focus on the reduction of *N*,*N*-dimethylbenzamide 6-1, this amide was chosen for study as Tafel demonstrated in 1899 that *N*,*N*-dimethylbenzamide 6-1 was reduced to *N*,*N*-dimethylbenzylamine 6-1a (63% yield) using a current of 2 A, a 50% H\textsubscript{2}SO\textsubscript{4} electrolyte at 35 °C and a lead cathode (Scheme 6-1).

Scheme 6-1: Reduction of *N*,*N*-dimethylbenzamide 6-1.

Using *N*,*N*-dimethylbenzamide 6-1 as the model compound this chapter aimed at establishing an improved understanding of the electrochemical reduction mechanism and determine the factors that influence the process. A number of conditions were investigated using the electrochemical flow-through reactor, including current density, electrode potential, electrode material, flow rate, pH, temperature and solvent. The results of these experiments will be presented and discussed in this chapter.

6.1  Cyclic Voltammetry Experiments

The electrochemical reduction of *N*,*N*-dimethylbenzamide 6-1 was carried out in the modified electrochemical flow-through reactor. To date, amide reductions have not been reported in a flow reactor operating in batch recycle mode with a continuously stirred tank reservoir. The reactor design and experimental details are given in Chapter 3.

Successful amide reductions were described when a highly concentrated H\textsubscript{2}SO\textsubscript{4} electrolyte was utilised; up to 50% H\textsubscript{2}SO\textsubscript{4} was required. \textsuperscript{59} In this work, H\textsubscript{2}SO\textsubscript{4} was used as the electrolyte solution, but at a concentration of 1 M, making the process considerably safer.

Due to the experimental conditions, it was difficult to utilise a VC RDE, as hydrogen was evolved at ca. -1.2 V (SCE) and at potentials beyond -1.8 V (SCE) a bubble was formed on
the VC RDE which blocked the electrode surface. Boron doped diamond was chosen as the cathode material for amide reduction due to the high overpotential for hydrogen evolution, wide potential window, chemical inertness and mechanical stability. The BDD electrodes were sourced from Electrocell, USA, and consisted of a doped diamond film on a niobium support. Difficulty was experienced fabricating a BDD RDE system. Therefore CVs were recorded using the electrochemical flow-through reactor at the BDD electrode.

Figure 6-1 displays the CV of 1 M aq. H$_2$SO$_4$ at a BDD electrode. The potential was swept between 3.0 V (AgCl|Ag) and -3.0 V (AgCl|Ag), initially with a positive-going potential from 0 V (AgCl|Ag) and at a scan rate of 10 mV s$^{-1}$. The potential window determined in 1 M aq. H$_2$SO$_4$ using the Electrocell BDD electrode was found to be ca. 3.5 V, comparable to that with other BDD electrodes. In the negative-going potential sweep, current attributed to hydrogen evolution started around -1.4 V (AgCl|Ag); the noise observed between -2.0 V (AgCl|Ag) and -3.0 V (AgCl|Ag) was due to hydrogen gas bubbles in the cathode compartment, blocking sites on the electrode surface.

![Figure 6-1: Cyclic voltammogram for the reduction of protons in 100 mL 1 M aq. H$_2$SO$_4$ at a BDD electrode; electrode potential swept between 3.0 V and -3.0 V (AgCl|Ag) starting at 0 V, at a scan rate of 10 mV s$^{-1}$ and a rotation rate of 1000 rpm.](image)

The CV for the reduction of 0.01 M $N,N$-dimethylbenzamide 6-1 at the BDD electrode in 1 M aq. H$_2$SO$_4$ is shown in Figure 6-2. The potential was swept between 0 V (AgCl|Ag) and -3.0 (AgCl|Ag) at a scan rate of 10 mV s$^{-1}$. It is clear from the plot that no distinctive reduction features were observable in the CV and it was difficult to deduce the exact reduction potential.
of N,N-dimethylbenzamide 6-1. Therefore, it was decided to begin reactor investigations under constant current conditions to verify claims from the early literature that N,N-dimethylbenzamide 6-1 could be reduced to the corresponding amine N,N-dimethylbenzylamine 6-1a.

![Cyclic voltammogram for the reduction of 0.01 M N,N-dimethylbenzamide 6-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s$^{-1}$ and a rotation rate of 1000 rpm.](image)

Figure 6-2: Cyclic voltammogram for the reduction of 0.01 M N,N-dimethylbenzamide 6-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s$^{-1}$ and a rotation rate of 1000 rpm.

### 6.2 Chronopotentiometry Results

Initial investigations were carried out with the reactor operating at constant current density, as reported previously to be successful for the reduction of N,N-dimethylbenzamide 6-1 to N,N-dimethylbenzylamine 6-1a. An experiment was carried out at a current density of -2000 A m$^{-2}$ and the reactor was operated under batch recycle mode with a continuously stirred tank reservoir containing 0.01 M N,N-dimethylbenzamide 6-1 and 1 M aq. H$_2$SO$_4$ (100 mL) (Figure 6-3). At this current density, a potential of ca. -2.8 $\pm$ 0.2 V was measured, the fluctuations being due to hydrogen bubbles forming and detaching from the electrode surface. The charge passed after 8 hours of electrolysis at -2000 A m$^{-2}$ was 57 600 C. The theoretical charge required to reduce 0.01 M N,N-dimethylbenzamide 6-1 to N,N-dimethylbenzylamine 6-1a is only 385.94 C; hence, assuming that all the amide was reduced, the overall fractional charge yield was poor.
Figure 6-3: Potential-time relationship for the reduction of 0.01 M \(N,N\)-dimethylbenzamide 6-1 in 100 mL 1 M aq. \(\text{H}_2\text{SO}_4\) at a BDD electrode using the flow-through reactor at a current density of \(-2000\ \text{A m}^{-2}\), flow rate of 60 mL min\(^{-1}\) and room temperature.

A current density of \(-2000\ \text{A m}^{-2}\) was applied due to previous reports of successful amide reduction at this current density.\(^{60}\) Furthermore difficulty calculating the limiting current density was experienced due to the design of the commercial electrochemical flow-through reactor. Mass transport rate predictions apply to developed laminar flow; in the case of the commercial reactor the hydrodynamics at the cathode would have been strongly perturbed by the design of the fluid entry point.\(^{143}\) The mass transport rate would have also been influenced by the rate of hydrogen gas bubble generation.\(^{144}\)

The reaction progress was monitored by GC-MS analysis and the reduction products were found to be \(N,N\)-dimethylbenzylamine 6-1a, benzaldehyde 6-2 and benzyl alcohol 6-3, Scheme 6-2.

Scheme 6-2: Reduction products observed for the reduction of 0.01 M \(N,N\)-dimethylbenzamide 6-1 in 100 mL 1 M aq. \(\text{H}_2\text{SO}_4\) at a BDD electrode in the flow-through reactor. A current density of \(-2000\ \text{A m}^{-2}\) was applied for 8 hours a flow rate of 60 mL min\(^{-1}\) and room temperature.
Figure 6-4 displays the mole percentage of the products formed during the course of \(N,N\)-dimethylbenzamide 6-1 reduction. Satisfyingly, 100% of the 0.01 M \(N,N\)-dimethylbenzamide 6-1 was converted to products after 5 hours of electrolysis, equating to a charge of 36 000 C being passed.

![Figure 6-4: Mole percentage of \(N,N\)-dimethylbenzylamine 6-1a, benzaldehyde 6-2 and benzyl alcohol 6-3 formed during the reduction of 0.01 M \(N,N\)-dimethylbenzamide 6-1 in 100 mL 1 M aq. \(H_2SO_4\) at a BDD electrode in the flow-through reactor at a current density of -2000 A m\(^{-2}\), a flow rate of 60 mL min\(^{-1}\) and room temperature.](image)

After 8 hours of electrolysis, only two products were identified as remaining in the catholyte reservoir: \(N,N\)-dimethylbenzylamine 6-1a (32.8%) and benzyl alcohol 6-3 (67.2%). Benzaldehyde 6-2 was detected during only the first 3 hours of electrolysis and was reduced further to benzyl alcohol 6-3, the major product.

### 6.2.1 Mechanism of \(N,N\)-dimethylbenzamide Reduction

The formation of \(N,N\)-dimethylbenzylamine 6-1a, benzaldehyde 6-2 and benzyl alcohol 6-3 is thought to result from the operation of two competitive pathways, Scheme 6-3. Both of these pathways require 4 electrons and 4 protons.\(^{53}\)
An initial 2 electron, 2 proton transfer to the precursor was thought to produce an unstable hemiaminal intermediate \textit{6-4} (Scheme 6-4). The hemiaminal could then undergo elimination of either water or dimethylamine, to produce \textit{N,N}-dimethylbenzylamine \textit{6-1a} or benzyl alcohol \textit{6-3}, following successive 2-electron, 2 H\(^{+}\) reduction processes (Scheme 6-5). The product distribution appears dependent on the equilibrium between the elimination of water and dimethylamine.

Scheme 6-4: Mechanism for the formation of the hemiaminal intermediate \textit{6-4}.
From the initial experiment carried out at a constant current density, it was found the major product was benzyl alcohol 6-3 and the minor product, the desired product, was N,N-dimethylbenzylamine 6-1a in a ratio of ca. 2.3:1. Experiments were carried out to determine the effects of applied current density, cathode material, flow rate, temperature and pH on the product yield and product distribution.

6.2.2 Effects of Applied Current Density and Cathode Material

To determine whether cathode material or applied current density could affect the selectivity of the reduction process, BDD and Pb cathodes were employed. Boron doped diamond and Pb electrodes were selected as cathode materials because of their high overpotentials for hydrogen evolution, the competing reduction process. However, materials have different overpotentials for hydrogen evolution therefore applying the same current density to the BDD and the Pb electrodes could give rise to different reduction potentials. Therefore the experiments were carried out at current densities of -1000 and -2000 A m⁻² at the BDD and Pb electrodes to determine if the current density affected the results.

Table 6.1 displays the results for the reduction of 0.01 M N,N-dimethylbenzamide 6-1 in 1 M aq. H₂SO₄ (100 mL) at BDD and Pb electrodes at applied current densities of -1000 or -2000 A m⁻².
Each experiment was carried out at a flow rate of 60 mL min\(^{-1}\) and room temperature for 8 hours.

**Table 6.1:** Results for the reduction of 0.01 M \(N,N\)-dimethylbenzamide 6-1 after 8 hours of electrolysis in 100 mL 1 M aq. \(\text{H}_2\text{SO}_4\) at a BDD and Pb electrode in the flow-through reactor at a current density of -2000 A m\(^{-2}\), a flow rates of 60 mL min\(^{-1}\) and room temperature.

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Current density / A m(^{-2})</th>
<th>Conversion amide / %</th>
<th>Amine / %</th>
<th>Alcohol / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDD</td>
<td>-1000</td>
<td>100</td>
<td>30.5</td>
<td>69.5</td>
</tr>
<tr>
<td>BDD</td>
<td>-2000</td>
<td>100</td>
<td>32.8</td>
<td>67.2</td>
</tr>
<tr>
<td>Pb</td>
<td>-1000</td>
<td>100</td>
<td>29.8</td>
<td>70.2</td>
</tr>
<tr>
<td>Pb</td>
<td>-2000</td>
<td>100</td>
<td>22.3</td>
<td>77.7</td>
</tr>
</tbody>
</table>

Conversion and yield calculated from GC-MS analysis using an internal standard method, diethylene glycol was used as the standard material.

There was no significant difference in the product ratio and full conversion of the starting material was achieved after 5 hours of electrolysis with the BDD cathode at current densities of -1000 and -2000 A m\(^{-2}\). In both cases, the ratio of products was ca. 2.3:1 benzyl alcohol 6-3 to \(N,N\)-dimethylbenzylamine 6-1a. As shown in Figure 6-4, benzaldehyde 6-2 was produced as an intermediate during the reduction process but underwent a further 2 electron, 2 proton reduction process to form benzyl alcohol 6-3. This was also the case for the Pb cathode, for which full conversion was observed after 7 hours of electrolysis. The product ratios at -1000 A m\(^{-2}\) and -2000 A m\(^{-2}\) were 2.35:1 and 3.48:1 respectively.

These results suggests that the selectivity of \(N,N\)-dimethylbenzamide 6-1 reduction was independent of the electrode material and the applied current density. The product ratio achieved was dependent on the chemical process that occurred after the hemiaminal intermediate 6-5 was produced (Scheme 6-5), when control of the selectivity could be achieved.
6.2.3 Effect of Temperature

Kinetically controlled electrochemical reactions are not very temperature sensitive, but increasing temperatures for diffusion controlled processes increases diffusion rates of the organic material from the bulk solution to the electrode surface, improving conversion of the starting material. The rate of any subsequent chemical processes coupled to the charge transfer reactions may then also be enhanced at elevated temperature.

Experiments were carried out at 25 and 50 °C to establish whether a higher temperature could improve the rate of conversion and if the selectivity of the reaction could be altered. Due to the tubing used to pump the catholyte, a maximum temperature of just 50 °C was achievable using 1 M aq. H₂SO₄ as the electrolyte. Beyond this temperature, the tubing manufacturer (Cole-Parmer) advised that the tubing was not stable.

0.01 M N,N-dimethylbenzamide 6-1 in 1 M aq. H₂SO₄ (100 mL) was reduced at BDD and Pb electrodes at constant current density (-1000 or -2000 A m⁻²), a flow rate of 60 mL min⁻¹ and at 25 or 50 °C for 8 hours. The results of these experiments are given in Table 6.2

Table 6.2: Results for the reduction of 0.01 M N,N-dimethylbenzamide 6-1 after 8 hours of electrolysis in 100 mL 1 M aq. H₂SO₄ at a BDD electrode in the flow-through reactor at a current density of -2000 A m⁻², a flow rates of 60 mL min⁻¹ and room temperature and 50 °C.

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Current density / A m⁻²</th>
<th>Temperature / °C</th>
<th>Conversion / %</th>
<th>Amine / %</th>
<th>Alcohol / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDD</td>
<td>-1000</td>
<td>25</td>
<td>100</td>
<td>30.5</td>
<td>69.5</td>
</tr>
<tr>
<td>BDD</td>
<td>-1000</td>
<td>50</td>
<td>100</td>
<td>30.7</td>
<td>69.3</td>
</tr>
<tr>
<td>BDD</td>
<td>-2000</td>
<td>25</td>
<td>100</td>
<td>32.8</td>
<td>67.2</td>
</tr>
<tr>
<td>BDD</td>
<td>-2000</td>
<td>50</td>
<td>100</td>
<td>31.2</td>
<td>68.8</td>
</tr>
<tr>
<td>Pb</td>
<td>-1000</td>
<td>25</td>
<td>100</td>
<td>29.8</td>
<td>70.2</td>
</tr>
<tr>
<td>Pb</td>
<td>-1000</td>
<td>50</td>
<td>100</td>
<td>35.4</td>
<td>64.6</td>
</tr>
</tbody>
</table>

Conversion and yield calculated from GC-MS analysis using an internal standard method, diethylene glycol was used as the standard material.

Considering the data in Table 6.2, all conditions studied provided complete conversion of 6-1 in 8 hours, but again the ratio of products observed were ca. 2.3:1 benzyl alcohol 6-3 to N,N-dimethylbenzylamine 6-1a. Experiments carried out at room temperature and 50 °C indicated that the temperature of the catholyte appeared to have little effect on the selectivity, but the overall reaction rate increased at the higher temperature. The conversion of the starting material reached completion after 5 hours using a Pb cathode and 4 hours using the BDD
cathode at 50 °C (Figure 6-5), whereas complete conversion at room temperature took 7 hours on Pb and 5 hours for BDD.

![Figure 6-5: Mole percentage of N,N-dimethylbenzylamine 6-1a, benzaldehyde 6-2 and benzyl alcohol 6-3 formed during the reduction of 0.01 M N,N-dimethylbenzamide 6-1 in 100 mL 1 M aq. H₂SO₄ at a BDD electrode in the flow-through reactor at a current density of -2000 A m⁻², a flow rate of 60 mL min⁻¹ and 50 °C.]

These results suggest that increased temperature may have increased the rate of chemical steps occurring in the bulk solution, and/or increases the rate of diffusion of the organic from the bulk solution to the electrode surface, increasing the reactant conversion. However, the product ratio at both room temperature and 50 °C remained comparable, although at 50 °C using Pb and -1000 A m⁻², there was a slight shift in the product distribution with the conditions favouring the formation of N,N-dimethylbenzylamine 6-1a with a ratio of 2.35:1 of alcohol to amine.

### 6.2.4 Effect of Flow Rate

To determine if the process was mass transport controlled, the effects of increasing flow rates were investigated: 30 mL min⁻¹, 60 mL min⁻¹ and 90 mL min⁻¹, at room temperature. Complete conversion of the starting material was achieved at all flow rates after 8 hours of reduction using BDD at -2000 A m⁻² (Figure 6-6, Table 6.3).
At the slowest of these flow rates (30 mL min\(^{-1}\)), almost 80\% of the starting material was converted to the products after 1 hour. Complete conversion was achieved after 6 hours. (21600 C passed) and 33.3\% of \(N,N\)-dimethylbenzylamine 6-1a and 66.7 \% of benzyl alcohol 6-3 were obtained. The conversion after 1 hour using 60 mL min\(^{-1}\) was 75\%, full conversion achieved after 5 hours and the proportion of \(N,N\)-dimethylbenzylamine 6-1a and benzyl alcohol 6-3 at the end of electrolysis was 31.2\% and 68.8\%, respectively. Using a flow rate of 90 mL min\(^{-1}\), the conversion of \(N,N\)-dimethylbenzamide 6-1 after 1 hour was 50\% and full conversion was reached after 6 hours; 29.4 \% of the \(N,N\)-dimethylbenzylamine 6-1a and 70.6\% of the benzyl alcohol 6-3 were attained. This suggests that increasing the flow rate could affect the rate of hydrogen evolution and bubbles formed in the reactor, hindering the reduction of \(N,N\)-dimethylbenzamide 6-1.

Figure 6-6: Fractional conversion for the reduction of 0.01M \(N,N\)-dimethylbenzamide in 100 mL 1 M aq. H\(_2\)SO\(_4\) at a BDD electrode in the flow-through reactor at a current density of -2000 A m\(^{-2}\), flow rates of 30, 60 and 90 mL min\(^{-1}\) and room temperature.

Table 6.3: Results for the reduction of 0.01 M \(N,N\)-dimethylbenzamide 6-1 in 100 mL 1 M aq. H\(_2\)SO\(_4\) at a BDD electrode in the flow-through reactor at a current density of -2000 A m\(^{-2}\), flow rates of 30, 60 and 90 mL min\(^{-1}\) and room temperature.

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Flow rate / mL min(^{-1})</th>
<th>Conversion / %</th>
<th>Amine / %</th>
<th>Alcohol / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDD</td>
<td>30</td>
<td>100</td>
<td>33.3</td>
<td>66.7</td>
</tr>
<tr>
<td>BDD</td>
<td>60</td>
<td>100</td>
<td>31.2</td>
<td>68.8</td>
</tr>
<tr>
<td>BDD</td>
<td>90</td>
<td>100</td>
<td>29.4</td>
<td>70.6</td>
</tr>
</tbody>
</table>

Conversion and yield calculated from GC-MS analysis using an internal standard method, diethylene glycol was used as the standard material.
These results suggest that the residence time had a significant effect on the rate of the reduction process, but not product selectivity. The residence times for 30 mL min$^{-1}$, 60 mL min$^{-1}$ and 90 mL min$^{-1}$ flow rates were 37.8 s, 18.9 s and 12.6 s, respectively. At slower flow rates and longer residence times, it is postulated that there is significant absorption of $N,N$-dimethylbenzamide 6-1 onto the electrode surface, blocking sites for hydrogen evolution, the rate of which is consequently decreased, thus facilitating electron transfer to amide, whereas at high flow rates, the proportion of $N,N$-dimethylbenzamide 6-1 adsorbed onto the electrode surface would have been lower and there would be more available sites for hydrogen evolution, decreasing the rate of $N,N$-dimethylbenzamide 6-1 reduction. It would be interesting to further decrease the flow rate to 15 mL min$^{-1}$ and to determine the conversion after 1 hour.

### 6.2.5 Effect of pH

A source of protons is required for the reduction of $N,N$-dimethylbenzamide 6-1, so 1 M aq. $\text{H}_2\text{SO}_4$ (pH 0) was used initially as the electrolyte, as electrochemical reduction of amides has reported to be achieved in aq. $\text{H}_2\text{SO}_4$.\textsuperscript{59} Experiments carried out in this solution produced a molar ratio of ca. 2.3:1 benzyl alcohol 6-3 to $N,N$-dimethylbenzylamine 6-1a. To determine whether the pH influenced the selectivity of the reduction, experiments were also carried out at pH 1 (0.1 M aq. $\text{H}_2\text{SO}_4$) and pH 2 (0.01 M aq. $\text{H}_2\text{SO}_4$) (Table 6.4).

<table>
<thead>
<tr>
<th>Electrode</th>
<th>pH</th>
<th>Conversion / %</th>
<th>Amine / %</th>
<th>Alcohol / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDD</td>
<td>1</td>
<td>92.8</td>
<td>0</td>
<td>82.1</td>
</tr>
<tr>
<td>BDD</td>
<td>2</td>
<td>91.4</td>
<td>0</td>
<td>82.3</td>
</tr>
</tbody>
</table>

Conversion and yield calculated from GC-MS analysis using an internal standard method, diethylene glycol was used as the standard material.

To improve the conductivity of the electrolyte at pH 1 and 2, 0.5 M $\text{Na}_2\text{SO}_4$ was used as a supporting electrolyte; the conductivity of the resulting solutions were 2.68 and 1.32 S m$^{-1}$, respectively. The process did not proceed to complete conversion using these solutions. Furthermore, no $N,N$-dimethylbenzylamine 6-1a was produced; instead, only benzyl alcohol 6-3 was formed. It is thought that the sodium cations may promote the protonation of the nitrogen atom, forming a good leaving group, and as dimethylamine is eliminated, benzaldehyde 6-2 is subsequently formed and reduced electrochemically to benzyl alcohol 6-3. It would be interesting to investigate the effect on the selectivity of the reduction of sodium...
cations at pH 0 and to identify an additive salt that hinders dimethylamine elimination by complexing to the nitrogen.

### 6.2.6 On-line Spectroscopic Analysis

On-line FT-IR and on-line Raman were used to determine if on-line spectroscopic techniques could be used to follow the progress of the reaction. Experiments using the FT-IR were not successful as the aqueous based electrolyte was so strongly absorbing in the infrared that no bands could be identified for the amide, amine, alcohol or aldehyde.

Although water does not absorb in the Raman spectra, the concentration of the compounds to be analysed must be high enough for detection, so the experiments were carried out at 1 M \(N,N\)-dimethylbenzamide 6-1. Unfortunately after 8 hours of electrolysis (Figure 6-7) there appeared to be only starting material evident in the spectrum, benzaldehyde 6-2 was the only product identified in the LC-MS. The spectra recorded for amide, amine, alcohol and aldehyde are given in Figure 6-8, there were only limited differences between all spectra.

![Figure 6-7: Raman spectrum of 1 M \(N,N\)-dimethylbenzamide 6-1 before and after 8 hours of electrolysis in 1 M aq. H\(_2\)SO\(_4\).](image-url)
6.3 Chronoamperometry Experiments

6.3.1 Effect of Applied Potential

The applied electrode potential determines what electrochemical reactions can occur, as well as their rates, and can be used to control the selectivity of electron transfer reactions. Earlier attempts to determine the reduction potential of \( \text{N,N-dimethylbenzamide 6-1} \) by cyclic voltammetry was hampered by competitive hydrogen evolution (Figure 6-2). Hence, \( \text{N,N-dimethylbenzamide 6-1} \) was reduced for 4 hours each at \(-2.2\), \(-2.4\), \(-2.6\) and \(-2.8\) V (\(\text{AgCl|Ag}\)), from which reduction of the amide was found to be optimally achieved at \(-2.8\) V (\(\text{AgCl|Ag}\)). These potentials were not corrected for uncompensated ohmic potential losses.

Table 6.5 shows the effect of cathode potential on the conversion of \( \text{N,N-dimethylbenzamide 6-1} \) and the distributions of products after 4 hours of electrolysis. The results indicate that the potential controls the selectivity of the reaction; \(\text{e.g.}\) at a potential of \(-2.2\) V (\(\text{AgCl|Ag}\)), no amine product was obtained, whereas at \(-2.4\), \(-2.6\) and \(-2.8\) V (\(\text{AgCl|Ag}\)), amine product was detectable, but reaching only 5.5 % at \(-2.8\) V. This was accompanied by an increase in yield of benzyl alcohol \(6-3\), which remained the dominant product.
Table 6.5: Conversion and mole percentage of products formed after 4 hours of electrolysis of 0.01 M \(N,N\)-dimethylbenzamide 6-1 in 100 mL of 1 M H\(_2\)SO\(_4\) at a BDD electrode in the flow-through reactor at a range of potentials, a flow rate of 60 mL min\(^{-1}\) and room temperature.

| Potential (AgCl|Ag) / V | Conversion / % | Amine / % | Aldehyde / % | Alcohol / % | \(H_2 \) / L |
|-----------------|---------------|-----------|--------------|-------------|-------------|
| -2.2            | 5.6           | 0         | 0.7          | 4.9         | 2.6         |
| -2.4            | 35.9          | 4.3       | 6.1          | 25.5        | 2.9         |
| -2.6            | 37.4          | 1.3       | 7.8          | 28.3        | 3.2         |
| -2.8            | 74.7          | 5.5       | 6.3          | 62.9        | 4.9         |

Conversion and yield calculated from GC-MS analysis using an internal standard method, diethylene glycol was used as the standard material.

Figure 6-9 shows current density-time and charge passed for the reduction of 0.01 M \(N,N\)-dimethylbenzamide 6-1 at -2.8 V (AgCl|Ag), at which 45 023 C of charge was passed, resulting in a charge yield of 0.047% for the \(4F\) (mol amine\(^{-1}\) process in the Figure 6-9. The poor charge yield can be attributed to the competitive process of hydrogen evolution occurring; indeed, 4.9 L of hydrogen was collected over the course of the electrolysis, which production alone accounts for 87% of the charge passed.

![Figure 6-9: Current density-time relationship and charge passed for the reduction of 0.01 M \(N,N\)-dimethylbenzamide 6-1 in 100 mL of 1 M H\(_2\)SO\(_4\) at a BDD electrode in the flow-through reactor at a potential of -2.8 V (AgCl|Ag), a flow rate of 60 mL min\(^{-1}\) and room temperature.](image)

Had the reduction occurred by a single first order chemical or transport controlled process, reactant concentrations and current densities would have decayed exponentially with time. However, in this case current densities increased initially to a maximum of -3500 A m\(^{-2}\)
before decaying. Concurrently, the reaction progress was followed by GC-MS analysis, which revealed the presence of the three products identified in previous experiments with benzyl alcohol 6-3 as the major constituent.

The maximum exhibited in the current density-time data confirms that the reaction pathway to form the alcohol occurs in two steps, the first step to form benzaldehyde 6-2 being the rate limiting step. According to the reaction profile, the initial increase in current densities during the first hour of electrolysis was associated with benzaldehyde 6-2 formation, and the subsequent decay of current densities was related to the conversion of benzaldehyde 6-2 to benzyl alcohol 6-3.

Figure 6-10 displays the time dependence of the volume of hydrogen evolved during electrolysis at -2.8 V (AgCl|Ag), with a total of 4.9 L formed during 4 hours. This demonstrates the extent of the competing side reaction occurring in the reactor and the difficulty in suppressing this reaction. The charge yield for the reduction of $N,N$-dimethylbenzamide 6-1 was extremely poor and decreased over time as the evolution of hydrogen increased with time.

![Graph showing the volume of hydrogen evolved during electrolysis](image)

**Figure 6-10:** Hydrogen evolved during reduction of 0.01 M $N,N$-dimethylbenzamide 6-1 in 100 mL 1 M aq. H$_2$SO$_4$ at a BDD electrode in the flow-through reactor at a potential of -2.8 V (AgCl|Ag), a flow rate of 60 mL min$^{-1}$ and room temperature.
A poor conversion of just 5.6% was determined at -2.2 V (AgCl|Ag). The results suggest that forcing electrochemical conditions are required to attain satisfactory conversion and the greatest yield of \( N, N \)-dimethylbenzylamine 6-1a.

### 6.3.2 Effect of Temperature

Chronoamperometric experiments at constant potential were carried out at 15, 25 and 50 °C, by immersing the catholyte and anolyte reservoirs into a thermostated water bath. From Table 6.6, it is clear that the conversion of \( N, N \)-dimethylbenzamide 6-1 to \( N, N \)-dimethylbenzylamine 6-1a, benzaldehyde 6-2 and benzyl alcohol 6-3 was obtained at all temperatures after 4 hours. The highest yield of \( N, N \)-dimethylbenzylamine 6-1a was obtained at 15 °C, suggesting that low reaction temperature may slow down the reduction to alcohol. At 50 °C, there appeared to be increased selectivity towards the alcohol product. This suggests the alcohol formation could be thermodynamically favoured and the amine formation kinetically controlled.

<table>
<thead>
<tr>
<th>Temperature / °C</th>
<th>Conversion / %</th>
<th>Amine / %</th>
<th>Aldehyde / %</th>
<th>Alcohol / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>72.8</td>
<td>8.6</td>
<td>5.7</td>
<td>58.5</td>
</tr>
<tr>
<td>25</td>
<td>74.7</td>
<td>5.5</td>
<td>6.3</td>
<td>62.9</td>
</tr>
<tr>
<td>50</td>
<td>83.1</td>
<td>6.5</td>
<td>5.8</td>
<td>70.8</td>
</tr>
</tbody>
</table>

### 6.3.3 Effect of pH

The proton concentration of electrolyte solutions plays an important role in the reduction of organic compounds.\(^5\) To determine the effect of proton concentration on the reduction of \( N, N \)-dimethylbenzamide 6-1 in the flow-through reactor, experiments were carried out at pH 0, 2 and 4, using 1, 0.01 and 0.001 M aq. \( \text{H}_2\text{SO}_4 \) electrolyte solutions, respectively. To improve the conductivity of the electrolyte solutions, 0.1 M \( \text{Na}_2\text{SO}_4 \) was also added as a supporting electrolyte. Decreasing the proton concentration of the electrolyte would decrease the rate of hydrogen evolution, potentially increasing current efficiencies of the required reaction. A change in the proton concentration would also shift the reduction potential for hydrogen evolution by 59 mV per pH unit and there by affecting the reduction potential of \( N, N \)-dimethylbenzamide 6-1.
It is clear from the data in Table 6.7 that proton concentrations greatly affected not only the reaction rate but also the selectivity of the amide reduction process. At pH 0, 74.7% of the $N,N$-dimethylbenzamide 6-1 was reduced to three products: $N,N$-dimethylbenzylamine 6-1a, benzaldehyde 6-2 and benzyl alcohol 6-3. Reduction at pH 1 provided just two products: benzaldehyde 6-2 and benzyl alcohol 6-3. At pH 2 and pH 4, no reduction occurred and only starting material was recovered. The results clearly highlight the importance of proton concentration on the selectivity of the reduction process; pH 0 being optimal for the reduction process.

Table 6.7: Conversion and mole percentage of products formed after 4 hours of electrolysis of 0.01 M $N,N$-dimethylbenzamide 6-1 in pH 0-4 solutions (100mL of 1-0.0001 M aq. $H_2SO_4$) at a BDD electrode in the flow-through reactor at -2.8 V (AgCl|Ag), a flow rate of 60 mL min$^{-1}$ and room temperature.

<table>
<thead>
<tr>
<th>pH</th>
<th>Conversion / %</th>
<th>Amine / %</th>
<th>Aldehyde / %</th>
<th>Alcohol / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>74.7</td>
<td>5.5</td>
<td>6.3</td>
<td>62.9</td>
</tr>
<tr>
<td>1</td>
<td>7.2</td>
<td>0</td>
<td>0.5</td>
<td>6.7</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

6.3.4 Effect of Volumetric Surface Area

To scale up the (volumetric) surface area of the cathode, the BDD cathode was used as a feeder electrode to contact graphite felt of specific surface area $a \approx 10^4$ m$^2$ m$^{-3}$ and 11 mm thick in the direction of current flow. Chronoamperometry experiments were carried out for the reduction of $N,N$-dimethylbenzamide 6-1 at -2.8 V (AgCl|Ag) for 4 hours in 1 M aq. $H_2SO_4$. Unfortunately, graphite has a lower overpotential for hydrogen evolution compared to BDD, resulting in increased rates of hydrogen production and causing bubbles to be trapped within the felt.

6.3.5 Effect of Benzyl Alcohol

The reduction of $N,N$-dimethylbenzamide 6-1 was carried out at -2.8 V (AgCl|Ag) in 1 M $H_2SO_4$ for 4 hours with benzyl alcohol 6-3 present in the catholyte, in an attempt to perturb the equilibrium in Scheme 6-5 towards the formation of $N,N$-dimethylbenzylamine 6-1a. A concentration of only 0.01 M was used, due to the low solubility of benzyl alcohol 6-3 in aqueous solutions. Nevertheless, the added alcohol did not have the desired effect on the selectivity of the reaction and only 2% of amine was obtained; 75% of the amide being
converted. It is thought that the benzyl alcohol may have been adsorbed onto the electrode surface, blocking active sites and hindering the formation of the amine.

### 6.3.6 Reduction of Benzaldehyde

The reduction of benzaldehyde 6-2 was carried out to determine whether benzyl alcohol 6-3 was the only product of the reduction process. Figure 6-11 shows the CV for the reduction of 0.01 M benzaldehyde 6-2 at a BDD electrode in 1 M aq. H₂SO₄ using the electrochemical flow-through reactor. The potential was swept between 0 and -3 V (AgCl|Ag) at a scan rate of 25 mV s⁻¹. On the negative-going potential sweep, the current density began to increase at ca. -0.75 V (AgCl|Ag) and reduction waves were observable at ca. -1.4 V (AgCl|Ag) and ca. -2 V (AgCl|Ag). The exponential increase in current density between -2.5 and -3 V (AgCl|Ag) was due to hydrogen evolution. In the positive-going potential sweep, there was no evidence of an oxidation of the reduction product formed on the prior negative-going sweep.

![Cyclic voltammogram for the reduction of 0.01 M benzaldehyde 6-2 in 100 mL 1 M aq. H₂SO₄ at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s⁻¹ and a rotation rate of 1000 rpm.](image)

To determine the reduction products, benzaldehyde 6-2 was reduced at -2.8 V (AgCl|Ag) at a BDD electrode in the flow-through reactor, resulting in the current density-time data shown in Figure 6-12. The current density decayed exponentially with time and after 2.5 hours and 10 298 C of charge passed, the reaction was complete, but the current density achieved a steady state value of ca. 500 A m⁻² due to hydrogen evolution. GC-MS and ^1^H NMR analysis
confirmed that the reaction had gone to completion and that benzyl alcohol 6-3 was the only product of the reaction.

Figure 6-12: Current density-time relationship for the reduction of 0.01 M benzaldehyde 6-2 in 100 mL 1 M aq. H₂SO₄ (100 mL) at a BDD electrode in the flow reactor at a constant cathode potential of -2.8 V (AgCl|Ag), a flow rate of 60 mL min⁻¹ and room temperature.

Interestingly the electrochemical reduction of 0.01 M benzaldehyde 6-2 in 100 mL of 1M H₂SO₄ at -2.8V (AgCl|Ag) at a BDD electrode using the electrochemical flow reactor has been shown to form hydrobenzoin product shown in Scheme 6-6.¹⁴⁶ However, this product was not identified in ¹H or ¹³C NMR using N,N-dimethylbenzamide 6-1 as the starting material.

Scheme 6-6: Mechanism for the formation hydrobenzoin product from benzaldehyde 6-2.
6.3.7 Effect of Solvent

Identification of a suitable solvent and electrolyte was required to carry out electrolysis, since most pharmaceutical compounds are insoluble in water. Table 6.8 indicates which solvents are recommended for use in medicinal chemistry and those which are undesirable.\(^{147}\)

Table 6.8: Pfizer solvent selection guide

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Usable</th>
<th>Undesirable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Cyclohexane</td>
<td>Pentane</td>
</tr>
<tr>
<td>Acetone</td>
<td>Heptane</td>
<td>Hexane</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Toluene</td>
<td>Di-isopropylether</td>
</tr>
<tr>
<td>2-propanol</td>
<td>Isooctane</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>1-propanol</td>
<td>Acetonitrile</td>
<td>Chloroform</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>2-methyl THF</td>
<td>Dimethyl formamide</td>
</tr>
<tr>
<td>Isopropyl acetate</td>
<td>Tetrahydrofuran</td>
<td>(N)-methylpyrrrolidinone</td>
</tr>
<tr>
<td>Methanol</td>
<td>Xylenes</td>
<td>Pyridine</td>
</tr>
<tr>
<td>Methyl ethyl ketone</td>
<td>Dimethyl sulfoxide</td>
<td>Dioxane</td>
</tr>
<tr>
<td>1-butanol</td>
<td>Acetic acid</td>
<td>Benzene</td>
</tr>
<tr>
<td>t-butanol</td>
<td>Ethylene glycol</td>
<td>Diethyl ether</td>
</tr>
</tbody>
</table>

It was also necessary to remove water from the electrolyte system to drive the equilibrium towards the formation of the iminium ion 6-5 (Scheme 6-5). However, water is essential in the electrolyte solution to provide a source of protons; therefore suitable solvents must therefore be miscible with water and meet pharmaceutical manufacturing criteria. Furthermore

Table 6.9 shows water miscible solvents and supporting electrolyte combinations and their cathodic potential limit. The solvents that were identified as suitable for reduction based on these criteria were acetonitrile, THF, DMSO, methanol and IPA.
Table 6.9: Solvents suitable for reduction.\textsuperscript{63}

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric constant</th>
<th>Reference electrode</th>
<th>Supporting electrolyte</th>
<th>Negative potential limit vs. Ag ref. / V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>80</td>
<td>SCE</td>
<td>TBAP</td>
<td>-2.7</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>37.5</td>
<td>Ag/Ag(^+)</td>
<td>LiClO(_4)</td>
<td>-3.5</td>
</tr>
<tr>
<td>DMSO</td>
<td>46.7</td>
<td>SCE</td>
<td>TEAP</td>
<td>-2.8</td>
</tr>
<tr>
<td>THF</td>
<td>7.4</td>
<td>Ag/Ag(^+)</td>
<td>LiClO(_4)</td>
<td>-3.6</td>
</tr>
<tr>
<td>DMF</td>
<td>36.7</td>
<td>SCE</td>
<td>TEAP</td>
<td>-3.5</td>
</tr>
<tr>
<td>NMP</td>
<td>32</td>
<td>SCE</td>
<td>TEAP</td>
<td>-3.3</td>
</tr>
</tbody>
</table>

TBAP = tetrabutylammonium perchlorate, TEAP = tetraethylammonium perchlorate

Fechete \textit{et al.} demonstrated the reduction of carbonyl groups of phthalimide \textbf{6-7} to isoindoline \textbf{6-8} at a Hg electrode between -0.9 and -1.2 V (SCE) using acetonitrile (20 mL), water (12 mL) and several drops of HCl or H\(_2\)SO\(_4\) until pH 2 (Scheme 6-7).\textsuperscript{63}

Scheme 6-7: Electrochemical reduction of phthalimide \textbf{6-7} to isoindoline \textbf{6-8} at a Hg electrode using an acidified acetonitrile and water electrolyte.

Due to the successful report of the double decarbonylation of phthalimide \textbf{6-7} by Fechete \textit{et al.} in aqueous acidified acetonitrile, preliminary experiments were carried out for the reduction of 0.01 M \(N,N\)-dimethylbenzamide \textbf{6-1}. Acetonitrile was acidified to pH 0.5 with H\(_2\)SO\(_4\) and a constant potential of -2.8 V (Ag/AgCl) was applied; however, no reduction occurred. It was found that the solution was unstable and the acetonitrile was reduced to ethylamine under the reaction conditions, as confirmed by GC-MS. A further attempt to reduce \(N,N\)-dimethylbenzamide \textbf{6-1} was attempted at -2.4 V (Ag/AgCl); however, the acetonitrile was still not stable. The reduction of acetonitrile was also found to occur when NaClO\(_4\) was employed as the supporting electrolyte at bulk pH 6.96 and -2.8 V (Ag/AgCl).

To test the feasibility of using THF as a suitable solvent system, the potential window for a range of THF and H\(_2\)SO\(_4\) solutions were recorded between 0 and -3 V (AgCl|Ag) at a BDD electrode in the electrochemical reactor; 0.1 M \(N,N\)-dimethylbenzamide \textbf{6-1} reduction was also recorded in these solutions (Figure 6-13). On the positive-going potential sweep, current
densities increased at ca. -1.2 V (AgCl|Ag) to -3 V (AgCl|Ag) and there were no reduction peaks observed for any of the THF/H$_2$SO$_4$ solutions. As expected, the greatest current densities were detected for the solution containing 70 mL 1 M aq. H$_2$SO$_4$ and the lowest current densities for the solution containing 30 mL 1 M aq. H$_2$SO$_4$, for which current density were assigned to hydrogen evolution.

Figure 6-13: Cyclic voltammogram for the reduction of a range of solvent systems consisting of 100 mL of THF and 1 M aq. H$_2$SO$_4$ at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s$^{-1}$ and a rotation rate of 1000 rpm.

Using an electrolyte solution of THF and 1 M aq. H$_2$SO$_4$ (7:3 v/v), the conductivity of which was measured as 1.013 S m$^{-1}$, and an applied potential of -2.8 V (AgCl|Ag), resulted in a blue coating on the BDD cathode, possibly due to polymerisation of THF.

As the THF and 1 M aq. H$_2$SO$_4$ (7:3 v/v) solution did not appear to be stable under these conditions, further experiments were carried out using alternative supporting electrolytes. It has been reported that polymerisation of THF can be achieved with fuming H$_2$SO$_4$. Hence, some acid was removed and a TBAB and tetrabutylammonium hydrogenosulfate supporting electrolytes added to maintain the conductivity. However, pH has been reported to influence the selectivity of the reduction and at pH > 1, the detected product was benzyl alcohol 6-3. Therefore, it is believed that acid must be present in the electrolyte solution for amine formation. Typical supporting electrolytes used for electrolysis in organic solvents such as perchlorates and tetrafluoroborates were not chosen as they have been shown to act as co-catalysts with H$_2$SO$_4$ for the polymerisation of THF.
Figure 6-14 shows the voltammogram for the reduction of 0.1 M \( N,N \)-dimethylbenzamide 6-1 at a BDD cathode between 0 and -3 V (AgCl|Ag) at a scan rate of 25 mV s\(^{-1}\) and at 60 mL min\(^{-1}\). An electrolyte solution consisting of THF, 0.5 M aq. TBAB and 1 M aq. H\(_2\)SO\(_4\) (5:3:2 v/v), was utilised; addition of TBAB as the supporting electrolyte provided a conductivity 2.369 S m\(^{-1}\).

The background scan recorded in Figure 6-14 shows that at potentials of ca. -1.2 V (AgCl|Ag), current densities increased exponentially, due to proton reduction. Considering the scan incorporating \( N,N \)-dimethylbenzamide 6-1, a plateau is observed at ca. -2 V (AgCl|Ag) (absent in the background scan) which suggests that \( N,N \)-dimethylbenzamide 6-1 was reducible in this electrolyte system. However the addition of reactant decreased the current densities so it may have adsorbed onto the electrode surface inhibiting hydrogen evolution.

A potential of -2.8 V was applied to the BDD cathode in the flow-through reactor at a flow rate of 60 mL min\(^{-1}\) and room temperature, to determine whether \( N,N \)-dimethylbenzylamine 6-1a synthesis could be achieved in this THF electrolyte system. After 5 hours of electrolysis 3.44% \( N,N \)-dimethylbenzylamine 6-1a, 4.55% benzyl alcohol 6-2 and 3.07% benzaldehyde 6-3 were determined to have been formed. Although this was a promising result, at the end of electrolysis the membrane was contaminated with a brown film, probably polymerised THF.
Difficulty was experienced gaining control over the reactor using the contaminated membrane; it is believed that the brown film hindered the conductivity of the membrane.

A further experiment was carried out using 0.1 M $N,N$-dimethylbenzamide 6-1 in THF (50 mL), 0.5 M aq. tetrabutylammonium hydrogenosulfate aq (30 mL) and 1 M aq. $H_2SO_4$ (20 mL); the conductivity of the solution was 2.848 S m$^{-1}$. A constant potential experiment was carried out at -2.8 V (AgCl|Ag) at a BDD electrode using the electrochemical reactor. The experiment was abandoned after 2 hours as peroxides were detected in the electrolyte solution, however, traces of benzyl alcohol and benzaldehyde were determined by LC-MS.

Experiments were carried out to determine the potential windows of methanol and iso-propyl alcohol (IPA) with $H_2SO_4$. Figure 6-15 shows the potential windows for 70 mL of the solvent and 30 mL 1 M aq. $H_2SO_4$ solutions, with and without 0.1 M $N,N$-dimethylbenzamide 6-1. It is clear from the plot that no waves were observed during the background solvent scans or for the electrolytes containing 0.1 M $N,N$-dimethylbenzamide 6-1. The only process evident in the voltammograms was hydrogen evolution, which may have masked any amide reduction.

![Cyclic voltammogram for the reduction of 0.01 M $N,N$-dimethylbenzamide 6-1 in 100 mL of a mixture of IPA or MeOH and 1 M aq. $H_2SO_4$ (7:3 v/v) at a BDD electrode; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 10 mV s$^{-1}$ and a rotation rate of 1000 rpm.](image)

Constant potential experiments were carried out at -2.8 V for IPA and 1 M aq. $H_2SO_4$ (7:3 v/v) and for MeOH and 1 M aq. $H_2SO_4$ (7:3 v/v), each during 2 hours to determine if any amine was formed. In both cases, no amide reduction was achieved. A further experiment using MeOH and 1 M aq. $H_2SO_4$ (5:5 v/v) at -2.8 V for 2 hours was carried out and amide
conversion was observed, providing 11.31% \( \text{N,N-dimethylbenzylamine 6-1a} \), 7.08% benzyl alcohol 6-3 and 9.80% benzaldehyde 6-2. Electrolysis at -2.8 V after 2 hours in 100% 1 M aq. \( \text{H}_2\text{SO}_4 \) provided a lower conversion of amide to amine (4.55% \( \text{N,N-dimethylbenzylamine 6-1a} \), 3.93% benzyl alcohol 6-3 and 3.65% benzaldehyde 6-2) suggesting that the 1:1 ratio of MeOH to 1 M aq. \( \text{H}_2\text{SO}_4 \) solvent system was most efficient for \( \text{N,N-dimethylbenzamide 6-1} \) reduction.

### 6.4 Reduction of Primary, Secondary and Tertiary benzamide derivatives

Investigations were carried out into the reduction of \( \text{N-methylbenzamide 6-9} \) and benzamide 6-10 (Figure 6-16) to determine whether it was possible achieve their reduction to the corresponding amines in the electrochemical flow reactor. It has also been reported that the more substituted the amide nitrogen group, the greater the yield of amine attained\(^{59}\); therefore, it was expected that the tertiary amide would produce the greatest yield of amine, followed by the secondary amide and then the primary amide.

![Figure 6-16: Structure of N-methylbenzamide 6-9 and benzamide 6-10.](image)

To test this hypothesis, \( \text{N,N-dimethylbenzamide 6-1, N-methylbenzamide 6-9} \) and benzamide 6-10 were subjected to 4 hours of electrolysis at a BDD cathode at a potential of -2.8 V (AgCl|Ag), flow rate of 60 mL min\(^{-1}\) and room temperature. After electrolysis, the pH of the electrolyte solution was adjusted to pH 10 (with 1 M aq. \( \text{NaOH} \)) and \( \text{CH}_2\text{Cl}_2 \) used to extract the organic products, which were analysed by GC-MS and \( ^1\text{H} \) NMR spectroscopy. The results of the experiments are presented in Table 6.10.
Table 6.10: Conversion of \( N,N \)-dimethylbenzamide 6-1, \( N \)-methylbenzamide 6-9, benzamide 6-10 and the products formed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide conversion / %</th>
<th>Product yields / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74.7% 6-1</td>
<td>5.5% 6-1a 6.3% 6-2</td>
</tr>
<tr>
<td>2</td>
<td>35% 6-9</td>
<td>25% 6-9a 1% 6-2</td>
</tr>
<tr>
<td>3</td>
<td>82% 6-10</td>
<td>54% 6-10a 0% 6-2</td>
</tr>
</tbody>
</table>

The conversion of \( N \)-methylbenzamide 6-9 and benzamide 6-10 and the product yields for these compounds were estimated by \(^1\)H NMR spectroscopy. The results show that the tertiary, secondary and primary amide were all successfully reduced to the corresponding amine and the side products benzaldehyde 6-2 and benzyl alcohol 6-3. The reduction of benzamide 6-10 provided the highest conversion to the amine product, benzylamine 6-10a; however, \( N \)-benzyldiene benzylamine 6-11 was formed via the coupling of the 6-11 with benzaldehyde 6-2 (Scheme 6-8).

Scheme 6-8: Formation of \( N \)-benzyldiene benzylamine 6-11.
These results are contrary to results reported in the literature which suggests that electrochemical reduction of tertiary amides provides the highest yield of amine and that primary amides gave the lowest yield of amine.\textsuperscript{59}

It is postulated that the reduction of the tertiary \textit{N},\textit{N}-dimethylbenzamide 6-1 provides the lowest yield of the desired amine product as the amine moiety of the hemiaminal formed during electrochemical reduction is more basic (donor effect of the methyl substituents) compared to the hemiaminals generated from the secondary and primary benzamides. This results in the nitrogen of the hemiaminal 6-4 being protonated easily to eliminate dimethylamine, which is also volatile and helps to drive the reaction (Scheme 6-9). Therefore the selectivity towards the elimination of dimethylamine and the formation of benzyl alcohol as the major product is observed for the reduction of \textit{N},\textit{N}-dimethylbenzamide 6-1.

\begin{center}
\textbf{Scheme 6-9: Protonation of the nitrogen of hemiaminal 6-4, leading to the elimination of dimethylamine.}
\end{center}

For the case of reduction of \textit{N}-methylbenzamide 6-9 and benzamide 6-10, the amine moiety of the hemiaminals formed are less basic and more difficult to protonate (compared to tertiary), hence the elimination of water is favoured forming the iminium ion and then the desired amine products. Scheme 6-10 provides the mechanism for the protonation of the oxygen for the primary hemiaminal formed from the initial reduction of benzamide 6-10.

\begin{center}
\textbf{Scheme 6-10: Protonation of the oxygen of the primary hemiaminal leading to the elimination of H\textsubscript{2}O and the formation of the iminium ion.}
\end{center}

However the lone pair of the nitrogen of the hemiaminal also needs to be available to aid the elimination of water to form the iminium ion and subsequently the desired amine product. Therefore the amine moiety of the hemiaminal generated should not be too basic to promote the protonation of the nitrogen and elimination of the undesired amine leading to the alcohol.
product, but the lone pair of the nitrogen should still be available to facilitate the elimination of water via the formation of the iminium ion.

It would be interesting to investigate the reduction of tertiary amides that could favour the elimination of water from the hemiaminal species by incorporating the nitrogen atom into a cyclic aromatic make the nitrogen lone pair less available for protonation. This could also be achieved by using strongly withdrawing groups such as CF$_3$ as the nitrogen substituents.

### 6.5 Chapter Summary

Selectivity for $N,N$-dimethylbenzylamine 6-1a formation in the electrochemical reduction of $N,N$-dimethylbenzamide 6-1 at BDD was found to be governed by the cathode potential and the pH of the electrolyte solution. The fastest reduction was achieved at -2.8 V (AgCl|Ag), uncorrected for uncompensated ohmic potential losses, below which the rate of hydrogen evolution resulted in unacceptably low charge yields. Experiments carried out at pH 0 resulted in the formation of the amine product, whereas at pH 1 only aldehyde and alcohol products were identified.

Incorporating benzyl alcohol 6-3 into the electrolyte solution with the starting material did not have any effect on the selectivity of the process. Decreasing the concentration of water in the electrolyte also did not improve the selectivity of the reaction.

A range of solvents were examined under electrolysis conditions to establish if amide reduction was possible and whether the selectivity for amine could be improved with the removal of water. It was found that in THF and 1 M aq. H$_2$SO$_4$, amide reduction was possible; however, polymerisation of the THF coated the electrode surface. Using TBAB as a supporting electrolyte prevented the formation of the polymer, but the membrane was coated in a brown solution and using teterabutylammonium hydrogenosulfate generated peroxides and the only products of reduction were benzaldehyde 6-2 and benzyl alcohol 6-3.

Chronopotentiometric experiments for the reduction of $N,N$-dimethylbenzamide 6-1 were carried out at current densities of -1000 and -2000 A m$^{-2}$ successfully to benzyl alcohol 6-3 and $N,N$-dimethylbenzylamine 6-1a in the ratio of ca. 2.3:1. Investigations of effects of reaction parameters found that the applied current density, electrode material, flow rate, and temperature had little effect on the product distribution. Only for the case of Pb at -2000 A m$^{-2}$
2, room temperature and a flow rate of 90 mL min\(^{-1}\) was the product distribution affected, with a ratio of 3.48:1 benzyl alcohol 6-3 to \(N,N\)-dimethylbenzylamine 6-1a being formed.

The lowest flow rate tested provided the highest initial conversion of the starting material, suggesting that flow rates probably did not disperse intermediates, facilitating their further reduction may improve the rate of the reduction of \(N,N\)-dimethylbenzamide 6-1 compared to the evolution of hydrogen.
Chapter 7  Reduction of Tertiary Amides

This Chapter explores the application of the electrochemical reactor as a tool for amide reduction:

i) to determine whether functionalised amides can be reduced to the corresponding amine;
ii) to correlate structural parameters of the substrate with the selectivity of the reaction;
iii) to determine whether a complex amide compound can be reduced.

Encouraged by the successful reduction of the tertiary amide \( N,N \)-dimethylbenzamide 6-1 (Chapter 6), a series of functionalised benzamide derivatives and other tertiary amides were synthesised and subjected to reduction with the electrochemical reactor (Figure 7-1).

![Figure 7-1: Amides studied in the electrochemical flow-through reactor.](image)

With the exception of 1-ethyl-2-pyrrolidone 7-10, 1-benzyl-2-piperidone 7-11, and glutarimide 7-13, which are commercially available, all other substrates were synthesised via a Schotten-Baumann reaction (Scheme 7.1). Experimental details and characterisation can be found in Appendix 1.
The study focussed on the reduction of a range of tertiary amides, to define the structural factors that influence the reduction process. The results obtained for the reduction of benzamide derivatives will be discussed; starting with the reduction of functionalised derivatives of \(N\)-benzoylpyrrolidine (7-1 to 7-5), followed by the reduction of \(N\)-ethyl-\(N\)-cyclohexylbenzamide 7-6.

### 7.1 Reduction of Benzamide Derivatives

Micovic and Mihailovic described the reduction of amides to amines with LiAlH\(_4\) with the aim of developing a protocol for the transformation.\(^{150}\) A range of amides were reduced to the corresponding amines in good yields and are outlined in Table 7.1.

Interestingly Micovic and Mihailovic found that for the reduction of \(N,N\)-diethylbenzamide (entry 3, Table 7.1) to the corresponding \(N,N\)-diethylbenzylamine product was obtained in a good yield, but carrying out the reaction at 0 °C provided the amine product as well as benzyl alcohol (15% yield). This suggested that the temperature of the reaction influences the selectivity of the reaction.
Table 7.1: Amide to amine reduction using LiAlH₄

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Starting Material 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Starting Material 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Starting Material 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Starting Material 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Starting Material 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Starting Material 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>91</td>
</tr>
</tbody>
</table>

7.1.1 Electron-withdrawing and -donating Substituents

A range of functional groups were incorporated into the phenyl ring of N-benzoylpyrrolidine 7-1 to establish the effect of electron withdrawing group (EWG) and electron donating group (EDG) substituents on the reduction of amides. The EWG’s and EDG’s were located on the para position of the phenyl ring of the amide. Previously, only the effects of the N-atom substituents were investigated, where it was found that EDG substituents are beneficial for the reduction of the amide to the corresponding amine.⁵⁹

A complex drug compound can contain a number of functionalities; Figure 7-2 displays the structures of some top selling pharmaceutical products.¹⁵¹ For electrochemical techniques to have a real application for these molecules, the reduction process must be selective.
Therefore, it was desirable to establish the stability of the EWG and EDG substituents during electrochemical reduction to confirm the selectivity of the process.

\[ \text{Figure 7-2: Examples of top-selling pharmaceutical products.} \]

The synthesised amides \(N\)-benzoylpyrrolidine 7-1, \(N\)-(4-methoxybenzoyl)pyrrolidine 7-2, \(N\)-(4-toluoylbenzoyl)pyrrolidine 7-3, \(N\)-(4-fluorobenzoyl)pyrrolidine 7-4 and \(N\)-(4-cyanobenzoyl)pyrrolidine 7-5 were first examined. Using the reaction conditions optimised for the reduction of \(N\),\(N\)-dimethylbenzamide 6-1 (Chapter 6) each compound was subjected to the electrochemical reduction for 8 hours at a BDD electrode in the flow-through reactor at a potential of -2.8 V (AgCl|Ag), a flow rate of 60 mL min\(^{-1}\) and at room temperature. The electrolyte used consisted of 100 mL of a mixture of 1 M aq. H\(_2\)SO\(_4\) and MeOH (9:1 v/v), and a concentration of 0.01 M of the amide compound was used. At the end of the electrolysis process, the pH of the electrolyte was adjusted to pH 10 using 1 M aq. NaOH and dichloromethane was used to extract the organic products, which were analysed by GC-MS and \(^1\)H NMR spectroscopy. The results of the experiments are presented in Table 7.2.

It is clear that all of the amides were reduced, except \(N\)-(4-fluorobenzoyl)pyrrolidine 7-8 (entry 4). \(N\)-Benzoylpyrrolidine 7-1 was reduced to \(N\)-benzylpyrrolidine 7-1a, benzaldehyde 7-14 and benzyl alcohol 7-15, with a reasonable conversion of 66%. The predominant product observed was benzyl alcohol 7-15 at 53%, accompanied by 42% of \(N\)-benzylpyrrolidine 7-1a. Constraining the N-atom into a ring did not appear to improve the selectivity of the reduction reaction towards the formation of the amine product, compared to the reduction of \(N\),\(N\)-dimethylbenzamide 6-1; the product distribution suggests that the reduction mechanism is comparable to the mechanism postulated for the reduction of \(N\),\(N\)-dimethylbenzamide 6-1 in Chapter 6, although the formation of pyrrolidine was not observed.
Table 7.2: Results from the reduction of functionalised 4-benzoylpyrrolidine derivatives.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide conversion / %</th>
<th>Recovered product ratio / %[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7-1 66%</td>
<td>7-1a 42% 7-14 5% 7-15 53%</td>
</tr>
<tr>
<td>2</td>
<td>7-2 46%</td>
<td>7-2a 48% 7-16 2% 7-17 46% 7-18 4%</td>
</tr>
<tr>
<td>3</td>
<td>7-3 72%</td>
<td>7-3a 46% 7-19 4% 7-20 50%</td>
</tr>
<tr>
<td>4</td>
<td>7-4 0%</td>
<td>7-4a 0% 7-21 0% 7-22 0%</td>
</tr>
<tr>
<td>5</td>
<td>7-5 12%</td>
<td>7-5a 66% 7-23 17% 7-24 17%</td>
</tr>
</tbody>
</table>

[a] 0.01 M of each amide was reduced for 8 hours at a BDD electrode in the flow-through reactor, at a potential of -2.8 V (AgCl|Ag), a flow rate of 60 mL min⁻¹ and at room temperature. The electrolyte consisted of 100 mL of a mixture of 1 M aq H₂SO₄ and MeOH (9:1 v/v).[b] Conversions and the product ratios were estimated by 1H NMR spectroscopy by comparing the integrals of methylene and methyl groups: 7-1 (δ: 3.39 ppm), 7-1a (δ: 3.15 ppm), 7-14 (δ: 9.99 ppm), 7-15 (δ: 4.62 ppm), 7-2 (δ: 3.57 ppm), 7-2a (δ: 1.75-1.68 ppm), 7-16 (δ: 9.82 ppm), 7-17 (δ: 4.52 ppm), 7-18 (δ: 3.82 ppm), 7-3 (δ: 2.40 ppm) 7-3a (δ: 1.81-1.74 ppm), 7-19 (δ: 9.96 ppm), 7-20 (δ: 4.62 ppm), 7-5 (δ: 3.56 ppm), 7-5a (δ: 1.75-1.68 ppm), 7-22 (δ: 10.03 ppm) and 7-23 (δ: 4.65 ppm).
However, pyrrolidine is soluble in water, so it may not have been extracted by CH$_2$Cl$_2$, or it may have evaporated due to its low boiling point (87 °C).

The incorporation of EDG’s at the para position of the phenyl ring could possibly facilitate the reduction of amide by increasing the electron density on the oxygen atom. In this study, a strongly activating methoxy group and a weakly activating methyl group were chosen to establish the effect of EDG’s on the reduction reaction.

After subjecting N-(4-methoxybenzoyl)pyrrolidine 7-2 to 8 hours of electrolysis at -2.8 V (AgCl|Ag), the product mixture were found to contain the corresponding amine N-(4-methoxybenzyl)pyrrolidine 7-2a, 4-methoxybenzaldehyde 7-16, 4-methoxybenzyl alcohol 7-17 and 1,2-bis(4-methoxyphenyl)ethane 7-18 in recovered product yields of 48%, 2%, 46% and 2%, respectively.

Interestingly, the formation of a dimer 1,2-bis(4-methoxyphenyl)ethane 7-18 was observed as a minor product from the reduction of 4-(methoxybenzoyl)pyrrolidine 7-2. Formation of corresponding dimers was not observed in the reduction of other 4-benzoylpyrrolidine derivatives examined in this work. The proposed mechanism for the formation of the dimer is outlined in Scheme 7.2. It is thought that the protonated form of 4-methoxybenzaldehyde 7-16 can undergo an electron transfer to form a radical species which self-condenses to give the diol species 1,2-bis(4-methoxyphenyl)-1,2-ethanediol 7-25. Dehydration of 7-25, followed by an electron and proton transfers provided the product 1,2-bis(4-methoxyphenyl)ethane 7-18. The dimer is only observable for the reduction of 4-(methoxybenzoyl)pyrrolidine 7-2, as the methoxy group can strongly stabilise the dehydrated species.

Scheme 7.2: Mechanism for the formation of the dimer 1,2-bis(4-methoxyphenyl)ethane 7-18.
The CV of \(N\)-(4-methoxybenzoyl)pyrrolidine \(7-2\) is given in Figure 7-3. In the negative sweep, the reduction began at -1 V (AgCl|Ag) and the current density increased exponentially until a reduction wave was observed between -2 and -2.5 V (AgCl|Ag). A further exponential increase in the current density was seen between -2.5 and -3 V (AgCl|Ag), accounting for the reduction of protons and \(H_2\) evolution. In the positive sweep there was no evidence of a reversible reaction. The reduction of the \(C=\)C bonds in the dehydrated species could be responsible for the reduction wave observed at -1 V in the CV.

In comparison, the reduction of \(N\)-(4-toluoylbenzoyl)pyrrolidine \(7-3\) provided the products 4-toluoylbenzylpyrrolidine \(7-3a\), 4-toluoylbenzaldehyde \(7-19\), and 4-toluoylbenzyl alcohol \(7-20\); the formation of a dimer was not observed. The CV for 4-(toluoylbenzoyl)pyrrolidine \(7-3\) was also recorded (Figure 7-4). In sharp contrast to the CV of \(7-2\), no reduction peak was observed. In the negative potential sweep the current density increases exponentially between -1 V and -3 V (AgCl|Ag), representing the reduction of protons to gaseous \(H_2\). In the positive sweep there was no evidence of a reversible reaction.

Comparing the product ratios obtained from the reduction of \(N\)-(4-methoxybenzoyl)pyrrolidine \(7-2\) and \(N\)-(4-toluoylbenzoyl)pyrrolidine \(7-3\), it will appear that the nature of the EDG had no influence on the selectivity. The overall conversion of \(7-2\) and \(7-3\) was 46% and 72%, respectively, in comparison to 66% obtained for \(7-1\). As observed previously with the reduction of \(N\)-benzoylpyrrolidine \(7-1\), the major products of the
reactions were the alcohols 4-methoxybenzyl alcohol 7-17 (46%) and 4-methylbenzyl alcohol 7-20 (50%).

In contrast, \(N\)-benzoylpyrrolidine derivatives containing EWG’s had a negative effect on the reduction process. In the case of \(N\)-(4-fluorobenzoyl)pyrrolidine 7-4, no reduction can be achieved, and only the starting material was recovered. A limited conversion (12%) of \(N\)-(4-cyanobenzoyl)pyrrolidine 7-5 can be observed, however, with an interesting increase in the amine ratio; 4-(cyanobenzyl)pyrrolidine 7-5a was formed as the predominant product (66%), with equivalent amounts of 4-cyanobenzaldehyde 7-23 and 4-cyanobenzyl alcohol 7-24 constituting the rest of the product mixture. The switch of selectivity of the reaction for the amine production is likely due to the stabilisation of the reduced species by the C≡N group, at the expense of a poor level of conversion. Nevertheless, it is pleasing to observed that the nitrile group is not reduced as might be expected (Scheme 7.3).

![Scheme 7.3: Mechanism for the reduction of the nitrile group of 4-cyanobenzoylpyrrolidine 7-5.](image)

In conclusion, the incorporation of an EWG at the para position of the benzene ring hindered the level of conversion of the amide, whereas EDG’s had little influence. Interestingly, the inclusion of a nitrile group appeared to improve the selectivity of the reduction to the amine product, whereas EDG’s had no effect on the selectivity. In this study, all of the EWG’s and EDG’s were stable to electrolysis, which is promising with respect to its potential applications in the pharmaceutical industry.

### 7.1.2 Aliphatic Substituents

To further understand the role of aliphatic substituents on the nitrogen atom, \(N\)-ethyl-\(N\)-cyclohexylbenzamide 7-6 was prepared and studied using the electrochemical flow-through reactor. Due to poor solubility of this substrate, the amount of MeOH in the electrolyte solution was increased to 20 mL (\(i.e.\) 8:2 \(v/v\) 1 M aq. \(\text{H}_2\text{SO}_4\):MeOH) to ensure its complete dissolution. Figure 7-5 shows the cyclic voltammogram recorded for the reduction of 0.01M \(N\)-ethyl-\(N\)-cyclohexylbenzamide 7-6 in 1 M aq. \(\text{H}_2\text{SO}_4\) and MeOH (8:2 \(v/v\)) at the BDD electrode in the flow-through reactor at a flow rate of 60 mL min\(^{-1}\) and a scan rate of 25 mV
The reaction was carried out using the electrochemical reactor with a BDD electrode as a BDD RDE was not available. In the negative potential sweep, the reduction began at a small negative potential of -0.002 V (AgCl|Ag) was applied, the current density increased exponentially, then reached a limited current density at -1.5 V (AgCl|Ag). A further exponential increase in current densities between -2 and -3 V (AgCl|Ag) was attributed to proton reduction resulting in the evolution of H₂. In the positive- potential sweep between -3 and 0 V (AgCl|Ag), there was no evidence that the reduction is reversible.

Based on the CV, there appears to be potential independent current densities in the range of –1.5 and -2 V (AgCl|Ag). To examine this further, a potential of -1.5 V (AgCl|Ag) was applied to the BDD electrode for 8 hours. It was found that this was not sufficient to provide an efficient conversion of N-ethyl-N-cyclohexylbenzamide 7-6 to the corresponding amine: GCMS and ¹H NMR analysis of the products indicated only trace levels of N-benzyl-N-cyclohexylethylamine 7-6a, benzyl alcohol 7-15 and N-ethyl-N-cyclohexylamine 7-26, the major compound being recovered starting material. Hence, a further experiment was carried out at a fixed potential of -2.8 V (AgCl|Ag) for 8 hours; the results from this experiment are shown in Scheme 7.4.

Scheme 7.4: Reduction of N-ethyl-N-cyclohexylbenzamide 7-6.
Figure 7-5: Cyclic voltammogram for the reduction of 0.01 M N-ethyl-N-cyclohexylbenzamide 7-4 in 100 mL of a mixture of 1 M aq. H$_2$SO$_4$ and MeOH (v/v 8:2) at a BDD electrode in the flow-through reactor; electrode potential swept between 0 V and -3.0 V (AgCl|Ag) at a scan rate of 25 mV s$^{-1}$ and a rotation rate of 1000 rpm.

In this case, an overall conversion of 58% was achieved. The desired amine product N-benzyl-N-cyclohexylethylamine 7-6a constitute 17% of the product mixture, with the side products benzaldehyde 7-14, benzyl alcohol 7-15 and N-ethyl-N-cyclohexylamine 7-26 ratios making up the remaining 3%, 60% and 20%, respectively. The lower amount of amine 7-26 recovered suggests that it was not completely recovered from the aqueous layer. The amine yield was disappointing low but the side products formed provides further evidence for the mechanism of their formation. It is thought that the reaction mechanism follows the same pathways as proposed for N,N-dimethylbenzamide 6-1 reduction (Chapter 6); involving the formation of a hemiaminal substituent followed by cleavage of the C-N bond to eliminate an amine, in this case N-ethyl-N-cyclohexylamine 7-26. Figure 7-6 displays the proposed mechanism for the reduction of 7-6 and the formation of side products 7-14, 7-15 and 7-27 (after the initial charge transfer reaction to form the hemiaminal).
Figure 7-6: Mechanism of the reduction of 7-6 after hemiaminal formation.

Here, the elimination of N-ethyl-N-cyclohexylamine 7-26 from the hemiaminal may have been favoured, skewing the selectivity towards aldehyde and alcohol formation. This may have also been the case for the elimination of pyrrolidine (for reduction of 4-benzylpyrrolidine derivatives), although pyrrolidine was not isolated. From this work, it is clear that the aliphatic substituent on the nitrogen atom had little impact on the conversion of the amide compound. The result also suggests that bulky N-substituents drive the selectivity of the reaction towards the formation of benzaldehyde 7-14 and benzyl alcohol 7-15.

7.2 Reduction of Additional Tertiary Amides

To fully appreciate the scope and limitations of the flow-through reactor for amide reduction, a series of tertiary amides (Figure 7-1) were investigated. Examples of tertiary amides containing aliphatic substituents, acetanilide derivatives, an acetamide, an imide and cyclic amides were subjected to 8 hours of electrolysis at -2.8 V (AgCl|Ag) at a BDD electrode. Table 7.3 displays the results for the reduction of these tertiary amides.

Reduction of the amides proved difficult and levels of conversion were low. In particular N-cyclohexyl-N-ethyl-1,2,2-dimethylpropanamide 7-7 containing only aliphatic substituents was not reducible at -2.8 V (AgCl|Ag) (entry 1). In this respect, it is interesting to compare this with the reduction of N-ethyl-N-cyclohexylbenzamide 7-6, which only differs by the substituent at the carbonyl group. The results suggest that bulky substituent like the tert-butyl group hinders the reduction of the carbonyl group while that a phenyl ring conjugated to the carbonyl group facilitated reduction.
Next, the aromaticity of the nitrogen substituent was restored in the acetanilide derivative \( N\)-methyl-\( N\)-phenylpivalamide 7-8, retaining the \textit{tert}-butyl group on the \( \alpha \)-carbon. This did not improve the reducibility of the amide group and no conversion of the starting material was recorded after 8 hours of electrolysis at -2.8 V (AgCl|Ag) (entry 2). Hence, the presence of the \textit{tert}-butyl group could have prevented the reduction. Next, the \textit{tert}-butyl group was replaced with a methyl group.

Table 7.3: Results from the reduction of tertiary amides and a secondary imide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide conversion(^a) / ( % )</th>
<th>Recovered product ratio(^b) / ( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="7-7_0%25" alt="Image" /></td>
<td><img src="7-7a_0%25" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="7-8_0%25" alt="Image" /></td>
<td><img src="7-8a_0%25" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="7-9_4%25" alt="Image" /></td>
<td><img src="7-9a_50%25" alt="Image" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="7-10_4%25" alt="Image" /></td>
<td><img src="7-10a_100%25" alt="Image" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="7-11" alt="Image" /></td>
<td><img src="7-11a_Traces" alt="Image" /></td>
</tr>
<tr>
<td>6</td>
<td><img src="7-12_36%25" alt="Image" /></td>
<td><img src="7-12a_100%25" alt="Image" /></td>
</tr>
<tr>
<td>7</td>
<td><img src="7-13_0%25" alt="Image" /></td>
<td><img src="7-13a_0%25" alt="Image" /></td>
</tr>
</tbody>
</table>

\(^a\) From the normalised integrals in the \(^1\)H NMR spectra of the methylene and methyl groups: 7-9 (\( \delta \): 1.87 ppm), 7-9a (\( \delta \): 2.83 ppm), 7-27 (\( \delta \): 2.90 ppm), 7-10 (\( \delta \): 3.47 ppm), 7-10a (\( \delta \): 2.47-2.39 ppm), 7-12 (\( \delta \): 1.83-1.73 ppm), 7-12a (\( \delta \): 3.48 ppm).
Indeed, N-methyl-N-phenylacetamide 7-9 can be reduced for 8 hours at -2.8 V (AgCl|Ag). Formation of N-methyl-N-phenylethylamine 7-9a and N-methylaniline 7-27 can be observed, however the conversion was still very poor, at just 4% (entry 3). Therefore, the removal of the tertiary butyl group appeared to aid the reduction process, but the level of conversion was low. Hence, it will appear that steric hindrance of the substituent on the α-carbon is less important than its electronic properties on the reduction process.

The next structure to be examined was the acetamide N-acetylpiperidine 7-10. The reduction of N-acetylpiperidine 7-10 was carried out at -2.8 V (AgCl|Ag) for 8 hours. A poor conversion of only 4% was achieved, and only 1-ethylpiperidine 7-10a can be observed as a product (entry 4).

Successful reduction of the C=C bond of maleimide 4-1 and derivatives was discussed in chapter 4 and 5. To determine the efficiency of reduction of imides, glutarimide 7-11 was reduced electrochemically (entry 5), where a 4-electron or 8-electron reduction process was possible (Scheme 7.5). After 8 hours of electrolysis at -2.8 V (AgCl|Ag), an 8-electron reduction to the product piperidine 7-11a was recorded, but only in trace levels, so a more prolonged period of electrolysis would be required to determine a level of conversion of the product formed. Interestingly, 2-piperidinone 7-28, the intermediate of the reduction process, was not observed in the resultant reaction mixture, Scheme 7.5.

![Scheme 7.5: Reduction of glutarimide 7-11 and the 4-electron and 8-electron reduction products.](image)

Next, the reduction of 1-benzyl-2-piperidone 7-12 and 1-ethyl-2-pyrrolidone 7-13 were studied to determine the reducibility of cyclic amides. 1-benzyl-2-piperidone 7-12, a six-membered cyclic amide containing a benzyl group on the nitrogen, was studied to further understand the structural limitations of amide reduction (entry 6). Gratifyingly, the conversion to 1-benzylpiperidine 7-12a was successful, a 36% conversion of 1-benzyl-2-piperidone 7-12 was observed after 8 hours of electrolysis at -2.8 V (AgCl|Ag). Although the level of conversion was relatively low in comparison to the other tertiary amides (excluding benzamide derivatives) it was a promising result.
In comparison, the reduction of 1-ethyl-2-pyrrolidone 7-13 to 1-ethylpyrrolidine 7-13a was not successful and only starting material was recovered after electrolysis (entry 7).

Recently, the chemical reduction of 1-benzyl-2-piperidone 7-12 and 1-methyl-2-pyrrolidone to the amine product in the presence of a homogeneous iridium hydride catalyst has been reported, on an NMR scale in deuterated benzene, at 60°C. However, the procedure required the use of 3 equivalents of silanes Me$_2$EtSiH or Et$_2$SiH$_2$. The reduction of 1-methyl-2-pyrrolidone required 27 hours to provide a conversion of 91% to the corresponding amine product. This result suggests that γ-lactams require an extensive reaction time to undergo reduction. Therefore the electrochemical reduction of the γ-lactam 1-ethyl-2-pyrrolidone 7-13 should be increased beyond a reaction time of 8 hours, in order for a direct comparison to be made.

### 7.3 Reduction of a Complex Amide

Although a series of tertiary amides have been investigated in this chapter the compounds investigated were relatively simple structures and therefore it was of interest to reduce a drug-like compound. (S)-(4-Benzyl-3,6-dioxo-piperazin-2-yl)-acetic acid benzyl ester 7-29, a complex molecule that could represent a candidate drug molecule containing a range of functionality (Figure 7-7). This compound contains two amide functional groups in a six-membered ring, one is a secondary amide and the other is a tertiary amide bearing an aliphatic ester side chain. Interestingly, the tertiary amide group resembles the amide group of 1-benzyl-2-piperidone 7-12 and the secondary amide group can be compared to glutarimide 7-11. Based on the results obtained in this chapter it was anticipated that the carbonyl group of the tertiary amide would be reduced preferentially to the secondary amide.

![Figure 7-7: (S)-(4-Benzyl-3,6-dioxo-piperazin-2-yl)-acetic acid benzyl ester 7-29 as an example of a drug compound.](image-url)
Compound 7-29 was subjected to 8 hours of electrolysis at -2.8 V (AgCl|Ag). The electrolyte solution comprised of 100 mL of a mixture of 1 M aq. H₂SO₄ and MeOH (8:2 v/v). Disappointingly, neither of the amide groups were reduced; instead, the GC-MS results indicated that a phenyl ring had been cleaved from 7-29, although it was difficult to identify the product from the ^1H NMR spectra. Cleavage of a phenyl group could lead to the formation of two products, (S)-(4-benzyl-3,6-dioxopiperazin-2-yl)acetic acid methyl ester 7-30 and (S)-(4-methyl-3,6-dioxopiperazin-2-yl)acetic acid benzyl ester 7-31 (Figure 7-8).

![Figure 7-8: Possible products from the reduction of (S)-(4-benzyl-3,6-dioxo-piperazin-2-yl)-acetic acid benzyl ester 7-28.](image)

To resolve this, it would be interesting to attempt the reduction of 7-29 in a different electrolyte medium between the pH range of 1-4. Furthermore, it would be advantageous to gain a better understanding of the stability of ester groups to electrolysis, and future work would involve synthesis of a range of amide compounds that include the ester functionality.

### 7.4 Chapter Summary

The results presented in this chapter describe the reduction products achieved from the reduction of a range of tertiary amides. The reduction of N-benzoylpyrrolidine 7-1 derivatives successfully demonstrated that tertiary amides can be reduced to the corresponding amine product. However the C-N bond was also cleaved, providing the aldehyde and alcohol products. From the results, it is believed that the reduction mechanism is comparable to the reduction of N,N-dimethylbenzamide 6-1 (Chapter 6). Incorporating EWG’s into the para position of the phenyl ring appeared to hamper the level of conversion where as EDG’s had little impact on the level of conversion. The nitrile group was the only substituent to improve the selectivity of the reaction towards amine formation, whereas EDG’s had no detectable effect on the selectivity of the reaction. More importantly, the EDG’s and EWG’s were stable to electrolysis which demonstrates that electrochemical reduction can be selective and that the technique could have potential applications in the pharmaceutical industry.
Limited success was observed for the reduction of other tertiary amides that were not benzamide derivatives. The reduction of 1-benzyl-2-piperidone 7-12 provided the highest level of conversion for a non-benzamide derivative; the benzyl group on the nitrogen atom was important for successful reduction. Interestingly, tertiary amides containing aliphatic substituents were not reducible, and it appeared that tert-butyl groups on the α-carbon hindered reduction of the carbonyl group.

Finally, the reduction of (S)-(4-benzyl-3,6-dioxo-piperazin-2-yl)-acetic acid benzyl ester 7-29 did not result in the formation of the amine product, but a phenyl group appeared to have been cleaved from the compound.
Chapter 8  Conclusions and Recommendations

This chapter provides a summary of the work carried out in this thesis to develop an electrochemical process for an environmentally benign, atom- and energy-efficient method for application in organic synthesis. In particular, the reduction of amides to amines and the reduction of C=C bonds.

Experiments were carried out using a VC RDE to determine kinetic parameters and a commercially available Electrocell Micro Flow Cell® was successfully modified to perform reactor investigations. Batch electrolysis was also carried out in a two compartment H-cell using a VC electrode.

8.1  Chapter Conclusions

8.1.1  Reduction of Maleimide

The reduction of maleimide 4-1 to succinimide 4-1a was achieved using the electrochemical flow-through reactor operating in batch recycle mode, demonstrating the chemoselective reduction of the C=C bond rather than the carbonyl groups. Complete conversion of maleimide 4-1 was obtained after 5 hours of electrolysis at both BDD and VC cathodes at a fixed potential of -1.2 V (AgCl|Ag).

For comparison, batch electrolyses were carried out using maleimide 4-1 in a two compartment batch cell using a VC electrode. Using a VC electrode 40% of maleimide 4-1 was converted to succinimide 4-1a. This indicates that batch electrolysis is not as efficient as the flow-through reactor to carry out electrochemical synthesis.

The volumetric surface area of the cathode in the flow-through reactor was increased by incorporating a three dimensional graphite felt electrode. This had a dramatic effect on the reaction time, affording a 99% conversion of the maleimide 4-1 to succinimide 4-1a after ca. 400 seconds. The combination of a short reaction time and a high conversion makes this a highly efficient process for the chemoselective reduction of the C=C bond of maleimide 4-1, with a current efficiency of 95%.

Further reaction parameters were investigated and it was found that pH 0 provided the optimal reaction conditions to achieve the fastest conversion to succinimide 4-1a. Reduction
at pH 2 and pH 4 progressed slower compared to pH 0; at pH 7 no succinimide 4-1a was formed. This suggests that the H⁺ concentration is essential for efficient and selective reduction of maleimide 4-1.

It was therefore demonstrated that the reduction of maleimide 4-1 to succinimide 4-1a could be attained in high conversion and short reaction times at a graphite felt electrode. The use of the electrochemical flow-through reactor and the conditions used for the electrolysis satisfied many of the criteria required for a green chemical technology.

8.1.2 Reduction of C=C Bonds

Following the successful reduction of maleimide 4-1 a range of maleimide derivatives were synthesised to determine whether chemoselective and stereoselective reduction of C=C bonds could be achieved using the electrochemical flow-through reactor.

Using N-allylmaleimide 5-1 and N-propargylmaleimide 5-2 as substrates, it was shown that the flow-through reactor was effective for the chemoselective reduction of the cyclic C=C bond of in the presence of allyl, propargyl and imide groups. As observed for the reduction of maleimide 4-1, the use of a 3D graphite felt electrode decreased the reaction time but did not affect the chemoselectivity of the reduction.

Stereoselective reduction was investigated using 3,4-dimethylmaleimide 5-3 and N-benzyl-3,4-dimethylmaleimide 5-4; where mixtures of diastereomeric products were obtained. Reduction carried out at a 2D BDD electrode resulted in a 2:3 mixture of the cis- and trans-isomers respectively, showing a bias towards the formation of the trans- product. Incorporating the 3D graphite felt electrode slightly enhanced the stereochemical reduction of N-benzyl-3,4-dimethylmaleimide 5-4 where a 1:3 mixture of cis- and trans- isomers was obtained.

The ability to chemoselectively reduce a conjugated C=C bond is particularly interesting to organic synthesis as it offers an environmentally benign technology. Such chemoselective and stereoselective reduction using the electrochemical flow-through reactor provided a further example of a green technology that could be applied to organic synthesis.
8.1.3 \textit{N,N-Dimethylbenzamide Reduction}

Chemical methods to reduce amides to amines are not desirable processes as they suffer from poor atom-economy, and are also hazardous and are not environmentally benign. In this work, it has been demonstrated that \textit{N,N-dimethylbenzamide 6-1} can be reduced electrochemically at a BDD electrode using the flow-through reactor in 1 M aq. H$_2$SO$_4$.

Difficulty measuring the limiting current density and the reduction potential of \textit{N,N-dimethylbenzamide 6-1} from CV experiments was observed due to the competing reaction of hydrogen evolution dominating the CV. This led to the use of forcing current densities (suggested from the early literature) of 2000 A m$^{-2}$ and highly cathodic potentials of -2.8 V (AgCl|Ag), therefore low charge yields were measured due to competitive reduction of water to hydrogen.

Reduction carried out at a constant current density (1000 and 2000 A m$^{-2}$) reduced the amide to benzyl alcohol 6-3 and \textit{N,N-dimethylbenzylamine 6-1a} in a ratio of \textit{ca.} 2.3:1. The selectivity of the reaction under constant current density conditions could not be improved. However the reduction of \textit{N,N-dimethylbenzamide 6-1} was found to be governed by cathode potential and pH of the electrolyte solution. The fastest reduction was achieved at -2.8 V (AgCl|Ag) and at pH $\geq$ 1 the only products of the reduction were benzaldehyde 6-2 and benzyl alcohol 6-3.

A reduction mechanism was proposed for the reduction of the amide and it was proposed that the removal of water from the electrolyte solution could hypothetically shift the equilibrium towards the production of the amine product. To test this, a range of organic solvents were incorporated into the electrolyte system (Scheme 6.5, Chapter 6). Unfortunately the organic solvent-electrolyte systems were not very successful and did not have the desired effect. However the work carried out in this Chapter described a method for the reduction of \textit{N,N-dimethylbenzamide 6-1} to a mixture of products, containing the desired amine.

8.1.4 Reduction of Tertiary Amides

The reduction of \textit{N,N-dimethylbenzamide 6-1} demonstrated that tertiary amides were reducible using the electrochemical flow-through reactor, therefore a range of tertiary amides were synthesised for investigation. \textit{N-benzoxylypyrrolidine 7-1} derivatives were reduced to the corresponding amines but the aldehyde and alcohol products were also recovered. Electron
withdrawing and donating groups incorporated into the phenyl ring of the \( N \)-benzoylpyrroloidine 7-1 derivatives had no effect on the selectivity of the reaction as mixtures of the amine, aldehyde and alcohol products were still obtained. However these EWG and EDG functionality were stable to electrolysis, which shows that the electrochemical flow-through reactor retains its selectivity towards the amide functional group under these conditions. This was a promising result as candidate drug molecules often contain a range of functional groups and for the electrochemical technique to be applied to the pharmaceutical industry the method would have to be highly chemoselective.

To test the application of the electrochemical flow-through reactor to the pharmaceutical industry, (S)-(4-benzyl-3,6-dioxo-piperazin-2-yl) was used to represent a candidate drug molecule. The reduction did not lead to the formation of the amine product in this case.

### 8.2 Contribution of this Thesis

The work presented in this thesis has provided insight into the utility of flow electrochemistry to the field of organic synthesis. A commercial electrochemical reactor was modified to enable chronoamperometry experiments to be carried out on a preparative scale. In particular this work has provided a methodology for chemoselective reduction of conjugated C=C bonds using an electrochemical flow-through reaction under conditions that are environmentally benign and safe. Amide reduction was significantly more challenging but a mixture of products, including the desired amine product, was achieved in the flow-through reactor. This has provided the basis for further work into the electrochemical reduction of amides to amines.

### 8.3 Recommendations

Future work and recommendations that could be explored to improve upon the work presented in this thesis are discussed below.

To gain improved control of the electrochemical flow reactor, the AgCl reference electrode could be relocated within the reactor to improve the accuracy of the results; a luggin probe system could be explored to enable closer contact with the working electrode.

The synthesis and reduction of maleimide derivatives with bulky substituents across the C=C bond would provide an insight into the stereoselective mechanism of the electrochemical
reduction. The stereochemical reductions could also be carried out chemically to determine if there is a natural bias towards a particular stereoisomer. The proposed structures for synthesis are shown in Figure 8-1.

![Figure 8-1: Proposed maleimide substituents to further investigate stereoselective reduction.](image)

Synthesising a more thorough range of amides to study would broaden the outlook of the work, Figure 8-2 shows some structures that could be synthesised. The ester functionality incorporated into the benzamide derivative could also be investigated to determine if it is stable to electrochemical reduction ([8-10](figure), Figure 8-2). This functionality was not explored in this thesis but many candidate drug molecules incorporate ester functionality therefore determining their stability to electrochemical reduction would be beneficial.

It would be interesting to explore the reduction of primary and secondary amides after the successful reduction of N-methylbenzamide [6-9] and benzamide [6-10]. To complete the work on the reduction of benzamide derivatives, it is proposed to use strongly electron withdrawing substituents on the amide nitrogen and to incorporate the nitrogen lone pair into an aromatic ring to promote water elimination and the production of the desired amine product ([8-11](figure) and [8-12](figure), Figure 8-2). Aliphatic amides could be synthesised to determine if they are reducible and a range of structures similar to candidate drug molecules ([8-13](figure) and [8-14](figure), Figure 8-2) could be investigated.
Finding a synthetic technique to test the reduction of a hemiaminal would validate the proposed amide reduction mechanism. Hemiaminals are very unstable but using protecting groups such as an ether group would enable synthesis of a compound that could be stable enough to study. Melika synthesised the protected hemiaminal \(8-15\) as shown in Figure 8-3 by the use of a protecting ether group.\(^{152}\)

Developing a wall-jet BDD electrode would enable the electro-kinetics for the reduction of \(N,N\)-dimethylbenzamide \(6-1\) to be defined in the absence of hydrogen gas bubbles to gain a better understanding of the reduction mechanism. A design proposed by Compton et al. could be implemented with a BDD electrode as shown in Figure 8-4.\(^{153}\) Establishing a better understanding of the reduction mechanism would provide a powerful insight into developing an optimised methodology for amide reduction. This would also enable a kinetic model to be developed which would strengthen the results and enable the electrochemical reactor to be studied computationally.
Further work should be carried out to identify a suitable solvent system and supporting electrolyte to carry out the reduction and improve the scope of electrochemical reduction of organic compounds. Dimethyl sulfoxide (DMSO) would provide good solubility for a range of organics, is a usable solvent for the pharmaceutical industry and has a reduction potential limit of -2.8 V (Ag reference) when using TEAP as a supporting electrolyte. Although DMSO would not be a suitable solvent for the reduction of N,N-dimethylbenzamide 6-1 as the reduction potential is -2.8 V (Ag|AgCl) it could be useful for the reduction of other compounds.

The work-up procedure described in this thesis used dichloromethane to isolate the products, this is not desirable for a green process and an alternative should be found. Ethyl acetate is a polar aprotic solvent like dichloromethane and is usable by pharmaceutical standards. Therefore experiments with ethyl acetate should be carried out to improve product isolation.

Finally to further improve the work the reactor conditions should be further optimised and amide and C=C reductions should all be followed online with UV-visible spectrometer and GC-MS analysis.

Figure 8-4: Wall-jet BDD electrode based on the design by Compton et al. 153

*References*

53. While DMSO would not be a suitable solvent for the reduction of N,N-dimethylbenzamide 6-1 as the reduction potential is -2.8 V (Ag|AgCl) it could be useful for the reduction of other compounds.
References

References

References

Appendix 1 Organic Synthesis

General Remarks

Commercial reagents were used as received and purchased from Sigma-Aldrich or Alfa Aesar. High purity water was prepared by reverse osmosis (Elga Elgastat) and de-ionisation (Elga prima) to give a resistivity of $1.6 \times 10^5$ $\Omega$ m. Solvents were dried over molecular sieve columns in a solvent purification system. Commercial reagents were used as received and purchased from Sigma-Aldrich or Alfa Aesar. Column chromatography was performed on flash silica gel (Kieselgel 60, 63-200 $\mu$m).

$^1$H and $^{13}$C NMR spectra were obtained using a Bruker Avance 400 MHz instrument ($^1$H at 400 MHz and $^{13}$C at 100 MHz). The chemical shifts are reported in $\delta$ (ppm) and referenced to residual protons and $^{13}$C signals in deuterated chloroform. The coupling constants ($J$) are expressed in Hertz (Hz). Multiplicities are indicated as below: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m).

Mass spectra (MS) were recorded on a Micromass Autospec-Q Mass spectrometer (EI and CI sources). Melting points (uncorrected) were determined using an Electrothermal Gallenhamp apparatus and a calibrated thermometer ($\pm$ 2º C). Infra-red (IR) data was recorded using a Perkin Elmer FT-IR spectrometer fitted with an ATR accessory Gas Chromatography Mass Spectroscopy (GCMS) were recorded using an HP GCD C GCMS and a Zebron Wax Plus column (Phenomenex).

High Performance Liquid Chromatography (HPLC) was obtained using a HP 1050 HPLC instrument and a Gemini NX C-18 column (Phenomenex).

UV-visible spectra were recorded using an Aglient 8453 spectrophotometer and HELLMAs fibre optic cables and flow-through cuvette.

Hydrogen gas evolution was measured using a Ritter MGC-1 gas counter.
Compounds used in Chapter 5

**N-Allylmaleimide (5-1).**\(^{154, 155}\) Allyl alcohol (1.65 g, 28.4 mmol) was dissolved in 225 mL of THF. To this solution Ph\(_3\)P (7.98 g, 30.6 mmol), maleimide (3.00 g, 31.2 mmol) and DIAD (6.9 g, 34.2 mmol) were added, and the reaction mixture was left to stir overnight. The solvent was then evaporated and the product was isolated by column chromatography (SiO\(_2\), 5:1 hexane:EtOAc, \(R_f = 0.5\)) to give **N-allylmaleimide 5-1** as a yellow solid (1.72 g, 44%). M.p. 41-43 °C (lit. 42-44 °C) \(^{61}\); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3100, 3058, 2985, 1720, 1600, 1475, 1430, 1206, 900, 862, 635; \(\delta_H\) (400 MHz, CDCl\(_3\)) 6.71 (2H, s, CH), 5.82-5.72 (1H, m, CH), 5.17-5.11 (2H, m, C=CH\(_2\)), 4.12-4.06 (2H, m, NCH\(_2\)) \(\delta_C\) (100 MHz, CDCl\(_3\)) 170.3 (2C, C=O), 134.2 (2C, CH), 131.5 (1C, CH=CH\(_2\)), 117.6 (1C, CH=CH\(_2\)), 39.8 (1C, CH\(_2\)); \(m/z\) (EI) 138 (M\(^+\), 7%), 137 (100), 109 (15), 95 (23), 55 (40), 43 (78).

**N-Propargylmaleimide (5-2).**\(^{135, 155}\) To a solution of maleic anhydride (2 g, 20.40 mmol) in acetic acid (50 mL), propargylamine (1.69 g, 30.59 mmol) was added and the reaction mixture was refluxed for 16 hours. After cooling to room temperature, the acetic acid was evaporated. The crude product was dissolved in CH\(_2\)Cl\(_2\) and neutralised with 1 M KOH. The solvent was evaporated and the product purified by column chromatography (SiO\(_2\), 7:3 hexane:EtOAc, \(R_f = 0.4\)) to give the product as a yellow oil (0.53 g). \(\nu_{\text{max}}/\text{cm}^{-1}\) 3280, 3100, 2961, 1775, 1600 (C=O), 1485, 1106, 805, 643; \(\delta_H\) (400 MHz, CDCl\(_3\)) 6.73 (2H, s, C=CH), 4.21 (2H, d, J 2 Hz CH\(_2\)), 5.17-5.11 (1H, t, J 2 Hz, C≡CH); \(\delta_C\) (100 MHz, CDCl\(_3\)) 169.31 (2C, C=O), 134.48 (2C, CH), 76.89 (1C, C≡CH), 71.62 (1C, C≡CH), 26.70 (1C, CH\(_2\)); \(m/z\) (EI) 136 (M\(^+\), 7%), 135 (82), 107 (100), 79 (30), 54 (75), 52 (48).

**3,4-Dimethylmaleimide (5-3).**\(^{135, 156}\) To a solution of dimethylmaleic anhydride (2 g, 15.63 mmol) in acetic acid (50 mL), ammonium acetate (1.81 g, 23.44 mmol) was added and the reaction mixture was refluxed for 16 hours. After cooling to room temperature, the solvent was evaporated and the product purified by column chromatography (SiO\(_2\), CH\(_2\)Cl\(_2\), \(R_f = 0.4\)) to give 3,4-dimethylmaleimide 5-3 as a white solid (1.62 g, 83%). M.p. 109-112 °C (lit.\(^{156}\) 111-113 °C); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3242, 2961, 1723, 1654, 1453, 1256, 1038, 904, 695, 650; \(\delta_H\) (400 MHz, CDCl\(_3\)) 8.15 (1H, s, NH), 1.96 (6H, s, CH\(_3\)); \(\delta_C\) (100...
MHz, CDCl$_3$) 172.1 (C=O), 138.3 (=C), 8.6 (CH$_3$); m/z (EI) 126 (M$^+$, 12%), 125 (100), 82 (10), 54 (68), 53 (30).

$N$-Benzyl-3,4-dimethylmaleimide (5-4). $^{135, 157}$ Benzylamine (2.51 g, 23.44 mmol) was added to a solution of dimethylmaleic anhydride (2 g, 15.63 mmol) in acetic acid (50 mL), and the reaction mixture was refluxed for 16 hours. The solvent was removed under vacuum and the product purified by column chromatography (SiO$_2$, 7:3 hexane:EtOAc, R$_f$ = 0.4) to give $N$-benzyl-3,4-dimethylmaleimide 5-4 as a yellow solid (2.23g, 66%). M.p. 43-46 $^\circ$C (lit.$^{157}$ 44-45 $^\circ$C); $\nu$$_{max}$/cm$^{-1}$ 3026, 1650 (C=O), 1584, 1452, 1418, 1390, 1035, 963, 706, 650; $\delta$$_H$ (400 MHz, CDCl$_3$) 7.35 (5H, m, H-Ar), 4.66 (2H, s, CH$_2$), 1.97 (6H, s, CH$_3$); $\delta$$_C$ (100 MHz, CDCl$_3$) 171.8 (C=O), 137.3 (CH), 136.7 (CH), 129.3 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 127.7 (C-Ar), 41.5 (CH$_2$), 8.7 (CH$_3$); m/z (EI) 217 (M$^+$, 2%), 216 (25), 215 (100), 187 (28), 172 (35), 104 (35), 91 (32), 77 (15), 54 (17).

Compounds used in Chapter 7

$N$-Benzoylpyrrolidine (7-1) Benzoyl chloride (2.6 mL, 22.42 mmol) was dissolved in CH$_2$Cl$_2$ (30 mL) and the solution was cooled to 0$^\circ$C with stirring. Pyrrolidine (5.98 mL, 71.74 mmol) was added dropwise, and the resulting mixture was stirred for 30 minutes before quenching with H$_2$O (30 mL). The organic layer was washed with 0.5M HCl (2 x 30 mL), saturated aq. NaHCO$_3$ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO$_4$ and concentrated under vacuum to give the product as a colourless oil (3.80 g, 96.7%). $\nu$$_{max}$/cm$^{-1}$ 2950, 2800, 1650 (C=O), 1445, 1210, 1094, 1003, 675; $\delta$$_H$ (400 MHz, CDCl$_3$) 7.55-7.51 (2H, m, Ar), 7.43-7.40 (3H, m, Ar), 3.67 (2H, t, $J$ 7 Hz, NCH$_2$), 3.45 (2H, t, $J$ 7 Hz, NCH$_2$), 1.96-1.91 (4H, m, CH$_2$); $\delta$$_C$ (100 MHz, CDCl$_3$) 169.57 (1C, C=O), 137.21 (1C, CC=O), 129.66 (1C, Ar), 128.15 (2C, Ar), 127.19 (2C, Ar), 49.50 (1C, CH$_2$), 46.05 (1C, CH$_2$), 26.31 (1C, CH$_2$), 24.37 (1C, CH$_2$); m/z (EI) 176 (M$^+$, 12%), 175 (64), 146 (25), 105 (100), 77 (68), 51 (30).

$N$-(4-Methoxybenzoyl)pyrrolidine (7-2) A solution of 4-methoxybenzoic acid chloride (3 g, 17.59 mmol) in CH$_2$Cl$_2$ (10 mL) was added dropwise to a stirred solution of pyrrolidine (1.38 g, 19.34 mmol) and triethylamine (2.22 g, 21.98 mmol) in CH$_2$Cl$_2$ (30 mL) at 0$^\circ$C. The resulting mixture was stirred for 30 minutes before quenching with H$_2$O (30 mL). The organic layer
was washed with 1M HCl (2 x 30 mL), saturated aq. NaHCO₃ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO₄ and concentrated under vacuum to give N-(4-methoxybenzoyl)pyrrolidine 7-2 as a white solid (1.77 g, 49% yield). M.p 79-81 °C (lit. 158 78-79 °C); \( \nu_{\text{max}}/\text{cm}^{-1} \) 2990, 2843, 1620 (C=O), 1472, 1225, 1182, 1008, 790, 700; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 7.54 (2H, d, J 6 Hz, Ar), 6.92 (2H, d, J 6 Hz, Ar), 3.86 (3H, s, OCH₃), 3.59 (4H, brs, CH₂); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 169.45 (1C, C=O), 160.79 (1C, C(OCH₃)), 132.14 (1C, C(=O)), 129.16 (2C, Ar), 113.61 (2C, Ar), 55.32 (1C, OCH₃), 49.75 (2C, CH₂), 46.30, (2C, CH₂); m/z (EI) 206 (M⁺, 8%), 205 (52), 204 (12), 135 (100), 108 (8), 92 (15), 77 (19).

N-(4-Toluoyl) pyrrolidine (7-3) 4-Toluyl chloride (3.00 g, 19.41 mmol) was added dropwise to a stirred solution of pyrrolidine (1.52g, 21.35 mmol) and triethylamine (2.45g, 24.26 mmol) in CH₂Cl₂ (30 mL) at 0°C. The resulting mixture was stirred for 30 minutes before it was quenched by the addition of H₂O (30 mL). The organic layer was washed with 1M HCl (2 x 30 mL), saturated aq. NaHCO₃ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO₄ and concentrated under vacuum to give N-(4-toluoyl)pyrrolidine 7-3 as an orange solid (2.26 g; 61.5%) M.p 89-90 °C (lit. 158 90-91 °C); \( \nu_{\text{max}}/\text{cm}^{-1} \) 2987, 2806, 1590 (C=O), 1475, 1192, 810, 702; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 7.46 (2H, d, J 10 Hz, Ar), 7.22 (2H, d, J 10 Hz, Ar), 3.62 (2H, brs, CH₂), 3.50 (2H, brs, CH₂), 2.40 (3H, s, CH₃), 1.93 (4H, d, J 10 Hz, CH₂); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 169.81 (1C, C=O), 139.87 (1C, C(CH₃)), 134.35 (1C, C(CH₃)), 128.11 (2C, Ar), 127.22 (2C, Ar), 49.52 (1C, CH₂), 49.16 (1C, CH₂), 26.38 (1C, CH₂), 24.54 (1C, CH₂), 21.38 (CH₃); m/z (EI) 190 (M⁺, 8%), 189 (59), 188 (22), 146 (15), 119 (100), 91 (42), 65 (15).

N-(4-Fluorobenzoyl) pyrrolidine (7-4) 4-Fluorobenzoyl chloride (3.00 g, 19.42 mmol) was added dropwise to a stirred solution of pyrrolidine (1.48 g, 20.81 mmol) and triethylamine (2.39 g, 23.65 mmol) in CH₂Cl₂ (30 mL) at 0°C. The resulting mixture was stirred for 30 minutes before it was quenched by the addition of H₂O (30 mL). The organic layer was washed with 1M HCl (2 x 30 mL), saturated aq. NaHCO₃ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO₄ and concentrated under vacuum to give N-(4-fluorobenzoyl) pyrrolidine 7-4 as a white solid (3.19 g, 87.3%). M.p 88-90 °C (lit. 159 89-90 °C); \( \nu_{\text{max}}/\text{cm}^{-1} \) 3025, 2997, 2900, 1687 (C=O), 1450, 1215 (C-F), 1152, 800, 707; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 7.58-7.54 (2H, m, Ar), 7.10 (2H, t,
3.45 (2H, brs, NCH₂), 1.94 (2H, brs, CH₂), 1.92 (2H, brs, CH₂) δC (100 MHz, CDCl₃) 168.70 (1C, C=O), 164.70 (1C, CF), 133.27 (1C, C(C=O)), 129.48 (1C, Ar), 129.40 (1C, Ar), 115.37 (1C, Ar), 115.16 (1C, Ar), 49.71 (1C, CH₂), 46.32 (1C, CH₂), 26.45 (1C, CH₂), 24.45 (1C, CH₂); m/z (EI) 194 (M⁺, 7%), 193 (53), 164 (11), 123 (100), 95 (35), 75 (9).

N-(4-Cyanobenzoyl)pyrrolidine (7-5) 4-Cyanobenzoyl chloride (3.00 g, 18.12 mmol) in CH₂Cl₂ (5 mL) was added dropwise to a stirred solution of pyrrolidine (1.42 g, 19.93 mmol) and triethylamine (2.29 g, 22.65 mmol) in CH₂Cl₂ (30 mL) at 0°C. The resulting mixture was stirred for 30 minutes before it was quenched by the addition of H₂O (30 mL). The organic layer was washed with 1M HCl (2 x 30 mL), saturated aq. NaHCO₃ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO₄ and concentrated under vacuum to give N-(4-cyanobenzoyl) pyrrolidine 7-5 as a white solid (1.81 g; 50%). M.p 83-85 °C (lit. 86-88 °C); υmax/cm⁻¹ 2990, 2850, 2212 (C≡N), 1623 (C=O), 1430, 870, 720; δH (400 MHz, CDCl₃) 7.74 (2H, d, J 8 Hz, Ar), 7.64 (2H, d, J 8 Hz, Ar), 3.68 (2H, t, J 7 Hz, CH₂), 3.40 (2H, t, J 7 Hz, CH₂), 2.05-1.90 (4H, m, CH₂); δC (100 MHz, CDCl₃) 167.63 (1C, C=O), 146.41 (1C, CN), 132.27 (1C, C(C=O)), 127.81 (1C, C(CN)), 118.21 (2C, Ar), 113.56 (2C, Ar), 49.44 (1C, CH₂), 36.44 (1C, CH₂), 24.37 (1C, CH₂); m/z (EI) 201 (M⁺, 10%), 200 (70), 171 (30), 130 (100), 102 (66), 75 (10).

N-Cyclohexyl-N-ethylbenzamide (7-6) Benzoyl chloride (3.00 g, 21.34 mmol) was added dropwise to a stirred solution of N-ethyl-cyclohexylamine (2.99 g, 23.48 mmol) and triethylamine (2.70 g, 26.68 mmol) in CH₂Cl₂ (30 mL) at 0°C. The resulting mixture was stirred for 30 minutes before it was quenched by the addition of H₂O (30 mL). The organic layer was washed with 1M HCl (2 x 30 mL), saturated aq. NaHCO₃ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO₄ and concentrated under vacuum to give N-cyclohexyl-N-ethylbenzamide 7-6 as a clear oil (4.25 g; 86%). υmax/cm⁻¹ 2950, 2810, 1590 (C=O), 1475, 1320, 1046, 625; δH (400 MHz, CDCl₃) 7.43-7.30 (5H, m, Ar), 4.38 (1H, m, CH₂), 3.45 (2H, brs, CH₂CH₃), 1.86-1.83 (3H, m, CH₂CH₃), 1.74-1.03 (10H, m, CH₂); δC (100 MHz, CDCl₃) 171.24 (1C, C=O), 137.77 (1C, C(C=O)), 128.88 (1C, Ar), 128.41 (2C, Ar), 125.98 (2C, Ar), 58.79 (1C, NCH), 36.44 (1C, CH₂CH₃), 31.77 (2C, CH₂), 25.66 (2C, CH₂), 25.19 (1C, CH₂), 14.91 (1C,
$\text{CH}_2\text{CH}_3$; \textit{m/z} (EI) 232 (M$^+$, 9%), 231 (49), 230 (11), 202 (25), 174 (23), 150 (25), 134 (12), 105 (100), 77 (53), 41 (8).

\textit{N-Cyclohexyl-N-ethyl-2,2-dimethylproponamide} (7-7) Pivaloyl chloride (3.00 g, 24.88 mmol) was added dropwise to a stirred solution of \textit{N}-ethyl-cyclohexanamine (3.48 g, 27.37 mmol) and triethylamine (3.15 g, 31.10 mmol) in CH$_2$Cl$_2$ (30 mL) at 0°C. The resulting mixture was stirred for 30 minutes before it was quenched by the addition of H$_2$O (30 mL). The organic layer was washed with 1M HCl (2 x 30 mL), saturated aq. NaHCO$_3$ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO$_4$ and concentrated under vacuum to give \textit{N-cyclohexyl-N-ethyl-2,2-dimethylpropanamide} 7-7 as a clear oil (4.37 g; 83%). $\nu_{\text{max}}$/cm$^{-1}$: 2923, 2830, 1605 (C=O), 1410, 1334, 1200, 1090, 1045, 800; $\delta_\text{H}$ (400 MHz, CDCl$_3$): 3.75-3.65 (1H, m, C=H), 3.13-3.04 (2H, m, CH$_2$CH$_3$), 1.73-1.65 (2H, m, CH$_2$), 1.60-1.48 (2H, m, CH$_2$), 1.47-1.34 (2H, m, CH$_2$), 1.21-1.13 (2H, m, CH$_2$), 1.13 (3H, m, CH$_2$CH$_3$), 1.10 (9H, s, CH$_3$), 0.98-0.90 (2H, m, CH$_2$); $\delta_C$ (100 MHz, CDCl$_3$): 176.42 (1C, C=O), 56.82 (1C, NCH), 38.95 (1C, CHC=O), 31.56 (1C, CH$_2$CH$_3$), 28.50 (2C, CH$_2$), 27.19 (3C, CH$_3$), 26.02 (2C, CH$_2$), 25.38 (1C, CH$_2$), 14.78 (1C, CH$_2$CH$_3$); \textit{m/z} (EI) 212 (M$^+$, 8%), 211 (7), 182 (35), 154 (78), 126 (18), 83 (95), 57 (100), 41 (40).

\textit{N-Methyl-N-phenylpivalamide} (7-8) Pivaloyl chloride (3.00 g, 24.88 mmol) was added dropwise to a stirred solution of \textit{N}-methylaniline (2.93 g, 27.37 mmol) and triethylamine (3.15 g, 31.10 mmol) in CH$_2$Cl$_2$ (30 mL) at 0°C. The resulting mixture was stirred for 30 minutes before it was quenched by the addition of H$_2$O (30 mL). The organic layer was washed with 1M HCl (2 x 30 mL), saturated NaHCO$_3$ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO$_4$ and concentrated under vacuum to give \textit{N-methyl-N-phenylpivalamide} 7-8 as an orange solid (3.66 g; 77%). M.p 75-76 °C (lit.$^{160}$ 79 °C); $\nu_{\text{max}}$/cm$^{-1}$ 2990, 1625 (C=O), 1600 (HC=CH), 1490, 1400, 1250, 1100, 800, 650; $\delta_\text{H}$ (400 MHz, CDCl$_3$): 7.43-7.33 (3H, m, Ar), 7.43-7.33 (3H, m, Ar), 7.27-7.22 (1H, m, Ar), 3.23 (3H, s, NCH$_3$), 1.06 (9H, s, CH$_3$); $\delta_C$ (100 MHz, CDCl$_3$): 178.14 (1C, C=O), 145.33 (1C, Ar), 129.22 (2C, Ar), 128.81 (2C, Ar), 127.77 (1C, Ar), 41.37 (1C, CH$_3$N), 40.82 (1C, C(CH$_3$)), 29.56 (3C, C(CH$_3$)). $\textit{m/z}$ (EI) 193 (M$^+$, 2%), 192 (7), 191 (47), 149 (15), 134 (15), 107 (77), 106 (54), 57 (100), 41 (15).
**N-Methyl-N-phenylacetamide (7-9)** Acetyl chloride (3.00 g, 38.22 mmol) was added dropwise to a stirred solution of N-methylaniline (4.50 g, 42.04 mmol) and triethylamine (4.83 g, 47.77 mmol) in CH$_2$Cl$_2$ (30 mL) at 0 °C. The resulting mixture was stirred for 30 minutes before it was quenched by the addition of H$_2$O (30 mL). The organic layer was washed with 1M HCl (2 x 30 mL), saturated aq. NaHCO$_3$ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO$_4$ and concentrated under vacuum to give N-methyl-N-phenyl-acetamide 7-9 as a white solid (3.97 g, 69.6%). M.p 95-97 °C (lit. 161 98-100 °C); $\nu_{\text{max}}$/cm$^{-1}$ 3050, 1676 (C=O), 1562, 1450, 1407, 1250, 1105, 1064, 750, 712; $\delta_H$ (400 MHz, CDCl$_3$) 7.47-7.41 (2H, m, Ar), 7.39-7.33 (2H, m, Ar), 7.24-7.19 (1H, m, Ar), 3.29 (3H, s, NCH$_3$), 1.90 (3H, s, CH$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 170.58 (1C, C=O), 144.64 (1C, Ar), 129.74 (2C, Ar), 127.72 (2C, Ar), 127.20 (1C, Ar), 37.16 (1C, (NCH$_3$)), 29.56 (1C, C=O(CH$_3$)); m/z (EI) 150 (M$^+$, 7%), 149 (98), 107 (100), 106 (90), 77 (30), 43 (32).

**N-Acetylpiperidine (7-10)** Acetyl chloride (3.00 g, 38.22 mmol) was added dropwise to a stirred solution of piperidine (3.58 g, 42.04 mmol) and triethylamine (4.83 g, 47.77 mmol) in CH$_2$Cl$_2$ (30 mL) at 0°C. The resulting mixture was stirred for 30 minutes before it was quenched by the addition of H$_2$O (30 mL). The organic layer was washed with 1M HCl (2 x 30 mL), saturated aq. NaHCO$_3$ (2 x 30 mL) and brine (30 mL). The organic extract was dried over MgSO$_4$ and concentrated under vacuum to give N-acetylpiperidine 8-10 as a yellow oil (1.49 g, 30.65%). $\nu_{\text{max}}$/cm$^{-1}$ 2980, 2875, 1620 (C=O), 1430, 1250, 980, 750; $\delta_H$ (400 MHz, CDCl$_3$) 3.53 (2H, t, J 2 Hz, CH$_2$), 3.38 (2H, t, J 2 Hz, CH$_2$), 2.05 (3H, s, CH$_3$), 1.68-1.58 (4H, m, CH$_2$), 1.56-1.51 (2H, m, CH$_2$), $\delta_C$ (100 MHz, CDCl$_3$) 168.77 (1C, C=O), 47.42 (1C, NCH$_3$), 42.45(1C, NCH$_3$), 26.39 (1C, (CH$_2$), 25.47 (1C, (CH$_2$), 24.45 (1C, (CH$_2$), 21.45 (1C, (CH$_3$); m/z (EI) 128 (M$^+$, 8%), 127 (98), 84 (100), 70 (35), 56 (38), 43 (57).
Appendix 2 Characterisation of Reduction Products

The characterisation of the products obtained after electrochemical reduction using the flow-reactor.

**Electrochemical reduction of maleimide (4-1).** The reduction of maleimide 4-1 led to the formation of succinimide 4-1a; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 8.05 (1H, s, NH), 2.79 (4H, s, CH₂).

**Electrochemical reduction of N-allylmaleimide (5-1).** The reduction of N-allylmaleimide 5-1 led to the formation of N-allylsuccinimide 5-1a<sup>162</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 5.82-5.72 (1H, m, CH), 5.17 (2H, dt, J 16, 2 Hz, C=CH₂), 4.10 (2H, d, J 6.0 Hz, NCH₂), 2.71 (4H, s, CH₂).

**Electrochemical reduction of N-propargylmaleimide (5-2).** The reduction of N-propargylmaleimide 5-2 led to the formation of N-propargylsuccinimide 5-2a<sup>163</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 4.31 (1H, d, J 2 Hz, CH₂), 4.28 (1H, d, J 2 Hz, CH₂), 2.78 (4H, s, CH₂CO), 2.20 (1H, t, J 2 Hz, C≡CH).

**Electrochemical reduction of 3,4-dimethylmaleimide (5-3).** The reduction of 3,4-dimethylmaleimide 5-3 led to the formation of 3,4-dimethylsuccinimide 5-3a as a mixture of diastereoisomers<sup>141,142</sup>; cis-isomer δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 8.52 (1H, s, NH), 3.00-2.90 (2H, m, CH), 1.18 (6H, d, J 7.0 Hz, CH₃); trans-isomer δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 9.35 (1H, s, NH), 2.49-2.41 (2H, m, CH), 1.31 (6H, d, J 7.0 Hz, CH₃).

**Electrochemical reduction of N-benzyl-3,4-dimethylmaleimide (5-4).** The reduction of N-benzyl-3,4-dimethylmaleimide 5-4 led to the formation of N-benzyl-3,4-dimethylsuccinimide 5-4a as a mixture of diastereoisomers<sup>140,164</sup>; cis-isomer δ<sub>H</sub> (400 MHz,CDCl<sub>3</sub>) 7.34-7.21 (5H, m, H-Ar), 4.59 (2H, s, CH₂), 2.99-2.91 (2H, m, CH), 1.16 (6H, d, J 7.0, CH₃); trans-isomer 7.34-7.21 (5H, m, H-Ar), 4.59 (2H, s, CH₂), 2.49-2.40 (2H, m, CH), 1.29 (6H, d, J 7.0, CH₃).
Electrochemical reduction of \( N,N \)-dimethylbenzamide (6-1). The reduction of \( N,N \)-Dimethylbenzamide 6-1 led to the formation of a mixture of products which were identified using the \(^1\)H NMR spectroscopy and mass spectrometry: \( N,N \)-dimethylbenzylamine \( 6-1a \) \( ^{31} \delta_H \) (400 MHz, CDCl\(_3\)) 7.35-7.28 (5H, m, H-Ar), 4.66 (2H, s, CH\(_2\)), 3.49 (6H, s, CH\(_3\)); m/z (EI) 135 (M\(^+\), 48), 118 (5), 91 (58), 77 (5), 65 (20), 58 (100), 42 (22); benzaldehyde 6-2 \(^{165},^{166} \delta_H \) (400 MHz, CDCl\(_3\)) 10.0 (1H, s), 7.88-7.85 (2H, m), 7.64-7.60 (1H, m), 7.54-7.46 (2H, m); m/z (EI) 106 (M\(^+\), 33), 105 (100), 77(89), 51 (30); benzyl alcohol 6-3 \(^{167},^{168} \delta_H \) (400 MHz, CDCl\(_3\)) 7.42-7.35 (5H, m), 4.66 (1H, s), 3.03 (1H, br s); m/z 108 (M\(^+\), 60), 107 (66), 79 (68), 77 (100).

Electrochemical reduction of \( N \)-benzoylpyrrolidine (7-1). The reduction of \( N \)-benzoylpyrrolidine 7-1 led to the formation of a mixture of products which were identified using the \(^1\)H NMR spectroscopy: \( N \)-benzylpyrrolidine 7-1a \(^{169} \delta_H \) (400 MHz, CDCl\(_3\)) 7.47-7.19 (5H, m), 3.73 (2H, s), 2.73-2.51 (4H, m), 1.94-1.73 (4H, m); benzaldehyde 7-14 \(^{165} \delta_H \) (400 MHz, CDCl\(_3\)) 10.0 (1H, s), 7.88-7.85 (2H, m), 7.64-7.60 (1H, m), 7.54-7.46 (2H, m); benzyl alcohol 7-15 \(^{167} \delta_H \) (400 MHz, CDCl\(_3\)) 7.42-7.35 (5H, m), 4.66 (1H, s), 3.03 (1H, br s).

Electrochemical reduction of \( N \)-(4-methoxybenzoyl)pyrrolidine (7-2). The reduction of \( N \)-(4-methoxybenzoyl)pyrrolidine 7-2 led to the formation of a mixture of products which were identified using \(^1\)H NMR spectroscopy: \( N \)-(4-methoxybenzyl)pyrrolidine 7-2a \(^{170} \delta_H \) (400 MHz, CDCl\(_3\)) 7.22 (2H, d, \( J \) 8.6 Hz), 6.84 (2H, d, \( J \) 8.6 Hz), 3.79 (3H, s), 3.55 (2H, s), 2.49-2.47 (4H, m), 1.78-1.75 (4H, m); 4-methoxybenzyl alcohol 7-16 \(^{171} \delta_H \) (400 MHz, CDCl\(_3\)) 9.89 (1H, s), 7.84 (2H, d, \( J \) 6.8 Hz), 7.00 (3H, d, \( J \) 6.8 Hz), 3.89 (3H, s); 4-methoxybenzyl alcohol 7-17 \(^{172} \delta_H \) (400 MHz, CDCl\(_3\)) 7.28 (2H, d), 6.89 (2H, d), 4.61 (2H, s), 3.81 (3H, s); 1,2-bis-(4-methoxyphenyl)ethane 7-18 \(^{173} \delta_H \) (400 MHz, CDCl\(_3\)) 7.09 (4H, d, \( J \) 8.4 Hz), 6.82 (4H, d, \( J \) 8.7 Hz), 3.79 (6H, s), 2.83 (4H, s).
Electrochemical reduction of \(N\)-(4-toluoyl)pyrrolidine (7-3). The reduction of 1-(4-methylbenzoyl)pyrrolidine 7-3 led to the formation of a mixture of products which were identified using \(^1\)H NMR spectroscopy: 1-(4-methylbenzyl)pyrrolidine 7-3\(\text{a}^{174}\) \(\delta\text{H} (400 MHz, CDCl}_3\) 7.19 (2H, d, J 8.0 Hz), 7.09 (2H, d, J 8.0 Hz), 3.38 (2H, s), 2.34 (4H, t, J 7.4 Hz), 2.31 (3H, s), 1.55 (4H, m), and 1.41 (2H, m); 4-methylbenzaldehyde 7-19 \(\delta\text{H} (400 MHz, CDCl}_3\) 9.96 (1H, s), 7.77 (2H, d, J 8.0 Hz), 7.33 (2H, d, J 8.0 Hz), 2.44 (3H, s); 4-toluoylbenzyl alcohol 7-20 \(\delta\text{H} (400 MHz, CDCl}_3\) 7.26 (2H, d, J 7.6 Hz), 7.17 (2H, d, J 7.6 Hz), 4.64 (2H, s), 2.35 (3H, s).

Electrochemical reduction of \(N\)-(4-cyanobenzoyl)pyrrolidine (7-5). The reduction of \(N\)-(4-cyanobenzoyl)pyrrolidine 7-5 led to the formation of a mixture of products which were identified using \(^1\)H NMR spectroscopy: 4-(cyanobenzyl)pyrrolidine 7-5\(\text{a}^{177}\) \(\delta\text{H} (400 MHz, CDCl}_3\) 7.6 (2H, d, J 8.0 Hz), 7.4 (2H, d, J 8.0 Hz), 3.55 (2H, s), 2.55 (2H, t, J 8.0 Hz), 1.7 (2H, t, J 8.0 Hz); 4-cyanobenzaldehyde 7-23 \(\delta\text{H} (400 MHz, CDCl}_3\) 10.11 (1H, s), 8.01 (2H, d, J 8.0 Hz), 7.86 (2H, d, J 8.0 Hz); 4-cyanobenzyl alcohol 7-24 \(\delta\text{H} (400 MHz, CDCl}_3\) 7.64-7.60 (2H, m), 7.47-7.44 (2H, m), 4.76 (2H, s), 2.16 (1H, br s).

Electrochemical reduction of \(N\)-ethyl-\(N\)-cyclohexylbenzamide (7-6). The reduction of \(N\)-ethyl-\(N\)-cyclohexylbenzamide 7-6 led to the formation of a mixture of products which were identified using \(^1\)H NMR spectroscopy: \(N\)-benzyl-\(N\)-cyclohexylamine 7-6\(\text{a}^{178}\) \(\delta\text{H} (400 MHz, CDCl}_3\) 7.40-7.20 (5H, m), 3.60 (2H, s), 2.52 (2H, q, 6.0 Hz), 1.00-1.90 (11H, m), 0.97 (3H, t, J 7.8 Hz); benzaldehyde 7-14 \(\delta\text{H} (400 MHz, CDCl}_3\) 10.0 (1H, s), 7.88-7.85 (2H, m), 7.64-7.60 (1H, m), 7.54-7.46 (2H, m); benzyl alcohol 7-15 \(\delta\text{H} (400 MHz, CDCl}_3\) 7.42-7.35 (5H, m), 4.66 (1H, s), 3.03 (1H, br s); \(N\)-ethyl-\(N\)-cyclohexylamine 7-26 \(\delta\text{H} (400 MHz, CDCl}_3\) 3.03 (2H, q, J 8.0 Hz), 2.97-2.89 (1H, m), 2.24-2.21 (2H, m), 1.90-1.80 (2H, m), 1.66-1.56 (3H, m), 1.48 (3H, t, J 7.2 Hz), 1.23-1.27 (3H, m).
Appendix 2  Characterisation of Reduction Products

Electrochemical reduction of N-methyl-N-phenylacetamide (7-9). The reduction of N-methyl-N-phenylacetamide 7-9 led to the formation of a mixture of products which were identified using $^1$H NMR spectroscopy: N-methyl-N-phenylethylamine 7-9a $^{180}$ $\delta_H$ (400 MHz, CDCl$_3$) 7.26 (3H, m), 6.70 (2H, m), 3.42 (2H, q, $J$ 7.2 Hz), 2.91 (3H, s), 1.13 (3H, t, $J$ 7.2 Hz); N-methylaniline 7-27 $^{181}$ $\delta_H$ (400 MHz, CDCl$_3$) 7.42 (2H, dd, $J$ 7.2, 8.0 Hz), 6.95 (1H, t, $J$ 7.2 Hz), 6.79 (2H, d, $J$ 8.0 Hz), 3.78 (1H, br s), 2.96 (3H, s).

Electrochemical reduction of 1-benzyl-2-piperidone (7-12). The reduction of 1-benzyl-2-piperidone 7-12 led to the formation of 1-benzylpiperidine 7-12a $^{169}$ $\delta_H$ (400 MHz, CDCl$_3$) 7.47-7.12 (5H, m), 3.53 (2H, s), 2.43 (4H, br s), 1.63 (4H, q, $J$ 5.6 Hz), 1.53-1.41 (2H, m).
Appendix 3  Parameters

Parameters used in this thesis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>96485</td>
<td>C mol⁻¹</td>
</tr>
<tr>
<td>T</td>
<td>298</td>
<td>K</td>
</tr>
<tr>
<td>R</td>
<td>8.31441</td>
<td>J mol⁻¹ K⁻¹</td>
</tr>
<tr>
<td>a</td>
<td>10⁴</td>
<td>m² m⁻³</td>
</tr>
<tr>
<td>E_{H₂}⁰</td>
<td>0</td>
<td>V</td>
</tr>
<tr>
<td>E_{mal}⁰</td>
<td>-0.12</td>
<td>V</td>
</tr>
<tr>
<td>E_{allyl}⁰</td>
<td>-0.19</td>
<td>V</td>
</tr>
<tr>
<td>E_{prop}⁰</td>
<td>-0.18</td>
<td>V</td>
</tr>
<tr>
<td>d_h</td>
<td>3.61E-04</td>
<td>m</td>
</tr>
<tr>
<td>d_r</td>
<td>1.90E-05</td>
<td>m</td>
</tr>
<tr>
<td>d_pores</td>
<td>1.90E-05</td>
<td>m</td>
</tr>
<tr>
<td>ε</td>
<td>0.94</td>
<td>-</td>
</tr>
<tr>
<td>c</td>
<td>10</td>
<td>mol m⁻³</td>
</tr>
<tr>
<td>D</td>
<td>1.00E-09</td>
<td>m² s⁻¹</td>
</tr>
<tr>
<td>υ</td>
<td>1.00E-05</td>
<td>m² s⁻¹</td>
</tr>
<tr>
<td>RDE Area</td>
<td>1.97E-05</td>
<td>m²</td>
</tr>
<tr>
<td>Cathode compartment volume</td>
<td>1.90-05</td>
<td>m³</td>
</tr>
<tr>
<td>Graphite cross sectional area</td>
<td>0.0003</td>
<td>m²</td>
</tr>
<tr>
<td>Graphite felt electrode length</td>
<td>6.35E-02</td>
<td>m</td>
</tr>
<tr>
<td>Graphite felt electrode width</td>
<td>3.00E-02</td>
<td>m</td>
</tr>
<tr>
<td>Graphite felt electrode depth</td>
<td>1.1E-02</td>
<td>m</td>
</tr>
</tbody>
</table>