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**Photochemistry and Electrochemistry in
Continuous Flow Toward Integrated
Processes**

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Doctor of Philosophy

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Dedication:

For my grandmother Barbara Gottsleben (Aug 1929 – Feb 2016) the most quietly strong woman I have ever met.

Abstract:

This Thesis describes how continuous flow photochemical and electrochemical reactions can contribute to sustainable synthesis, particularly when coupled to on-line analysis techniques or used as part of a multi-step synthetic process. Chapter 1 introduces photochemistry as a sustainable technique, the problems that have previously been associated with performing photochemical reactions in batch, and presents the potential benefits of performing photochemistry in continuous flow. Chapter 2 describes the UV photochemical reactor that was built as part of this Thesis, which uses monochromatic excimer lamps (KrCl = 222 nm, XeBr = 282 nm, and XeCl = 308 nm) as the reaction light source. Results from two initial model reactions, the [2+2] cycloaddition of maleimide with 1-hexyne and the photoisomerisation of β -ionone are presented in addition to chemical actinometry measurements of the radiant exitance of each excimer lamp.

Chapters 3 and 4 report the outcomes of two of the chemical reactions that were studied in the excimer reactor. In Chapter 3 results obtained for the photodecarboxylative cycloaddition of 4-phthalimidobutyric acid are presented, including the effects of sensitising solvent and irradiation wavelength dependence. This chapter also describes the integration of the photochemical reactor with a second acid catalysis step by performing an acid catalysed dehydration of the photoproduct. Both the photo-reaction and the dehydration were performed in flow from a single reagent stream. Chapter 4 describes the photochemical isomerisation of 2-pyridone in the continuous excimer flow reactor. Our reactor allowed for a more efficient reaction than comparable batch reactions. The conversion of starting material in this reaction was successfully monitored by in-line flow UV-Vis spectroscopy using a miniature UV-Vis spectrometer.

Chapter 5 briefly introduces electrochemistry in continuous flow, which, like photochemistry, is an under utilised “reagent-less” technique that can benefit from being performed in continuous flow reactors. Specifically, the work described in Chapter 5 involved separating the hydrogen gas produced during electrochemical reactions performed in a commercially available electrochemical flow reactor, so that on-line analysis could more easily be integrated with the reactor. The methoxylation of *N*-formylpyrrolidine was chosen as a model reaction in an attempt to incorporate in-line Raman spectroscopy with the electrochemical reactor. Secondly, the methoxylation of 4-*tert*-butyltoluene was used as the model reaction for assimilating the electrochemical reactor with on-line GC analysis. After separating the hydrogen gas from the reaction by a simple gravity separation, both techniques were capable of providing in/on-line analysis results. However, the GC experimental set-up proved to give better results as the reaction set-up had a smaller dead volume and therefore required less equilibration time.

All relevant experimental details and reactor standard operating procedures are given in Chapter 6 with supplementary information provided where necessary in the appendices. The overall conclusions for this Thesis and recommendations for future work are collected in Chapter 7.

Acknowledgement

"If you want to go fast, go alone; but if you want to go far, go together."

–African Proverb

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My lab-mates, colleagues, and friends at Nottingham, thank you for making it a pleasure to come to work everyday. I don't need to mention names you all know who you are. It was all of you who were there to celebrate with me when there were successes, and help boost my spirits when the going got tough. I've truly made friends for life and I cannot imagine what my PhD would have been like without all of you.

Finally, I want to acknowledge my parents Debra Gottsleben and Jay DeLaney and my husband Dr. Philip Auckland. Thank you all for being my biggest cheerleaders in life and always believing in me. Knowing I have your love makes me all the more determined to make you proud.

Declaration

I declare that the work presented in this Thesis is an account of my own research for the period of October 2014 until September 2017. Where any research has been carried out in collaboration, the relevant researcher or researchers have been acknowledged. This Thesis has not been accepted in part or whole for the fulfilment of any other degree or personal qualification.

Erica Noel DeLaney, July 19th 2018

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Abbreviations

ATR: Attenuated Total Reflectance

DCM: Dichloromethane

E.G.: *Exempli Grata*

EMCR : Electrochemical Micro-flow Reactor

Equiv: Equivalents

FEP: Fluorinated Ethylene Propylene

FTIR: Fourier Transform Infrared

GC: Gas Chromatography

H: Hour

HPLC: High Performance Liquid Chromatography

IR: Infrared

ISC: Inter-system Crossing

Min: Minute

N.B.: *Nota Bene*

OFAT: One-Factor-At-A-Time

PET: Photoinduced Electron Transfer

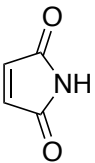
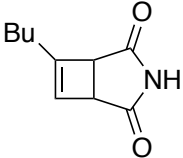
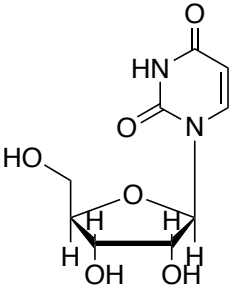
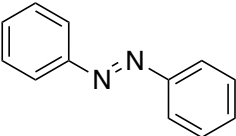
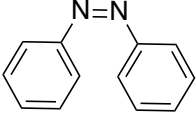
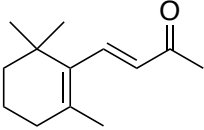
STY: Space-Time Yield

Temp: Temperature

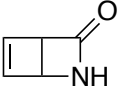
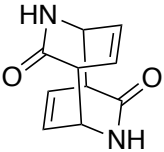
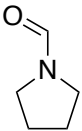
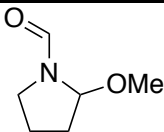
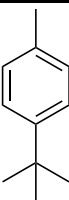
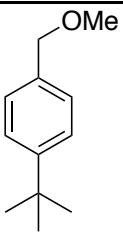
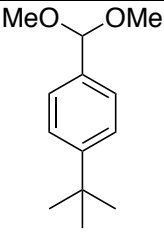
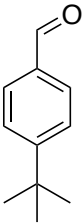
UV-Vis: Ultra-Violet- Visible

List of Compounds

Please note only the compounds that have been used as part of the experimental work in this Thesis have been given compound numbers.

Compound Number	Compound Structure	Compound Name
1		Maleimide
2	Bu—	1-Hexyne
3		6-Butyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione
4		Uridine
5		Uridine photohydrate
6		<i>trans</i> -Azobenzene
7		<i>cis</i> -Azobenzene
8		(<i>E</i>)-β-Ionone

9		2,5,5-Trimethyl-6,7,8,8a-tetrahydro-5 <i>H</i> -chromene
10		2,5,5,8a-Tetramethyl-6,7,8,8a-tetrahydro-2 <i>H</i> ,5 <i>H</i> -2,4a-epidioxychromene
11		(<i>Z</i>)-4-(2,2-Dimethyl-6-methylenecyclohexylidene)butan-2-one
12		(<i>Z</i>)-β-Ionone
13		1-(5,5,8a-Trimethyl-3,5,6,7,8,8a-hexahydrobenzo[<i>c</i>][1,2]dioxin-3-yl)ethan-1-one
14		4-Phthalimidobutyric Acid
15		9b-Hydroxy-1,2,3,9b-tetrahydro-5 <i>H</i> -pyrrolo[2,1- <i>a</i>]isoindol-5-one
16		2,3-Dihydro-5 <i>H</i> -pyrrolo[2,1- <i>a</i>]isoindol-5-one
17		2(1 <i>H</i>)-Pyridone

18		2-Azabicyclo[2.2.0]hex-5-en-3-one
19		3,7-Diazatricyclo[4.2.2.2 ^{2,5}]dodeca-9,11-diene-4,8-dione
20		N-Formylpyrrolidine
21		2-Methoxypyrrolidine-1-carbaldehyde
22		4- <i>tert</i> -Butyltoluene
23		1- <i>tert</i> -Butyl-4-methoxymethylbenzene
24		1- <i>tert</i> -Butyl-4-dimethoxymethylbenzene
25		4- <i>tert</i> -Butylbenzaldehyde

Chapter 1: Introduction

Humanity has been aware of the interaction of light with substances since ancient times.¹ However, early documented examples of “photochemistry” were limited to matters of practical importance, for example, the bleaching properties of sunlight on fibres and the negative impact light could have on the quality of beer.² Up until the turn of the 20th century, for the most part, the underlying fundamentals dictating these chemical reactions were poorly understood.³ The systematic study of the interaction of light with organic molecules, organic photochemistry as a true science, did not begin until the late 1800s and early 1900s with the work of pioneers such as Ciamician and Silber.^{3, 4} Over the course of their partnership they mainly focused on the photo-reactivity of carbonyl compounds reporting on the different reaction outcomes they observed including photoreductions, photopinicolisation, intramolecular cycloaddition and α - and β -cleavage.²⁻⁴

The period 1930-1970 saw major developments in the understanding of the photophysics governing photochemical reactions, helping to establish the basic “rules” of photochemistry.^{1, 5-9} It was during this period that the existence of the triplet excited state was confirmed.⁶ In addition to the advancements in theoretical understanding, the technique of flash photolysis was introduced by Norrish and Porter in 1949,¹⁰ which, for the first time, allowed for the spectroscopic characterisation of excited states and long lived reaction intermediates.¹ Since then spectroscopic studies have been widely exploited and developed by many researchers worldwide.¹¹⁻¹⁶ Many of the classes of organic photochemical reactions (discussed later in the Introduction to this Thesis) were discovered including intramolecular [2+2] cycloaddition of olefins,¹⁷ intermolecular [2+2] cycloaddition of enones and olefins,¹⁸ and photochemical rearrangements.¹⁹

The later half of the 20th century through the turn of the century was a period of slower development for the field of organic photochemistry, and at that time it would have appeared that the “Golden Age” of organic photochemistry had passed.²⁰ Considering the historical context, it therefore could be seen as somewhat surprising that the September 2016 issue of Chemical Reviews was entirely dedicated to photochemistry in organic synthesis.²⁰ This introduction will seek to show the factors that have resulted in what has been described as the “renaissance” for organic photochemistry.²⁰

First a general introduction to photochemical reactivity will be given, including examples of some of the different classes of photochemical reactions. This provides the fundamental explanation for why chemists might be interested in performing photochemical reactions. Following this a brief description of photochemistry in terms of Green Chemistry is given, which has provided a strong secondary motivation for looking into performing reactions photochemically. The challenges linked to photochemical synthesis, particularly with scale-up in traditional photochemical reactors, will then be described along with how the use of flow reactors for photochemistry has provided a solution that alleviates many of the drawbacks associated with photochemical synthesis. The Introduction will conclude with the specific aims for this Thesis, which define how the work presented in the next Chapters aims to contribute to the broader field of photochemistry in organic synthesis and demonstrate its applicability for multi-step and continuously monitored reactions when performed in continuous flow.

1.1 General Introduction to Photochemistry

Organic synthesis typically requires that relatively stable molecules must be induced to react in order to produce the desired product. Traditionally this has been achieved by weakening, polarizing, or cleaving a covalent bond through the use of heat, a

catalyst or an additional reactive reagent.^{21, 22} It is also possible to activate compounds photochemically generating more reactive excited states through the absorption of a photon.²¹

The rotational, vibrational, and electronic energy levels of a chemical species are quantised.²³ If the difference in energy between two energy levels is the same as the energy of a photon (Equation 1), then the photon can be absorbed by the molecule. Photons of visible light ($\lambda = 380\text{-}750\text{ nm}$) and ultra-violet (UV) light ($\lambda = 10\text{-}380\text{ nm}$) are of the correct magnitude to induce electronic excitation in organic molecules.²⁴⁻²⁶ This means that absorption of these types of photons leads to the promotion of an electron from the ground state to an excited singlet state. Vibrational relaxation to the lowest vibrational state of the singlet excited state occurs rapidly.²⁷ In certain molecules it is then possible for intersystem crossing to occur; although this is technically a forbidden transition based on the selection rules. This ISC leads to a vibrationally excited triplet state, which will rapidly decay to the lowest vibrational state of the first excited triplet state.^{25, 28, 29} These processes can be illustrated by a Jablonski diagram (Figure 1).

Equation 1: Energy of a photon, where E is energy, h is Planck's constant, and ν is frequency.

$$E = h\nu$$

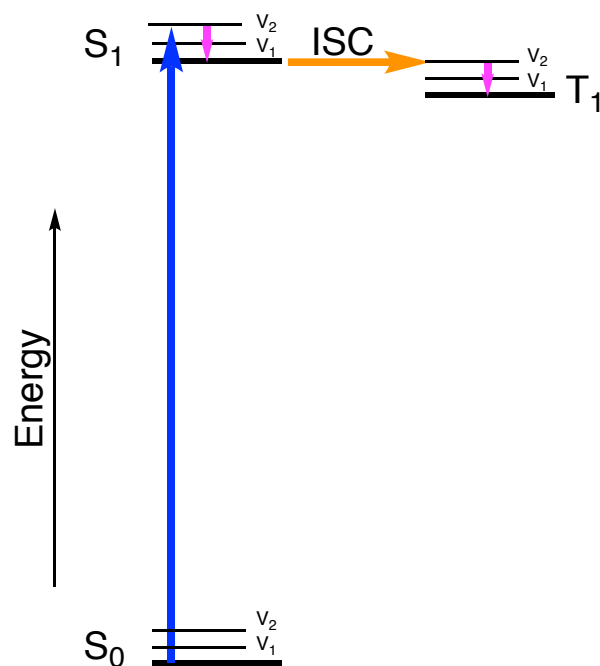


Figure 1: A simplified Jablonski diagram showing excitation from the ground electronic state to the first singlet excited state (blue) on absorption of a photon, vibrational relaxation (pink), and intersystem crossing to the excited triplet state (orange). Adapted from Frankowiak.³⁰

Once in the electronically excited state, there are many possible deactivation pathways for these species (Figure 2). From a synthetic viewpoint many of the possible outcomes, such as fluorescence/ phosphorescence, quenching and non-radiative decay, do not result in reaction and must therefore be avoided.^{24, 25} It is also possible for an electronically excited molecule to undergo processes that can be more synthetically useful such as charge transfer, isomerisation or direct reaction with another chemical species.²⁵ The relative probability that any one of these pathways is taken from a given excited state can be measured by their quantum yield (Equation 2).²⁶ More specifically in a photochemical reaction, the quantum yield is defined as the number of molecules consumed per photon absorbed.²⁴ Depending on the nature of the reactivity, this value can range from 10^{-6} up to 10^6 where absorption of a photon leads to a chain reaction mechanism for example in photopolymerisation.^{25, 26}

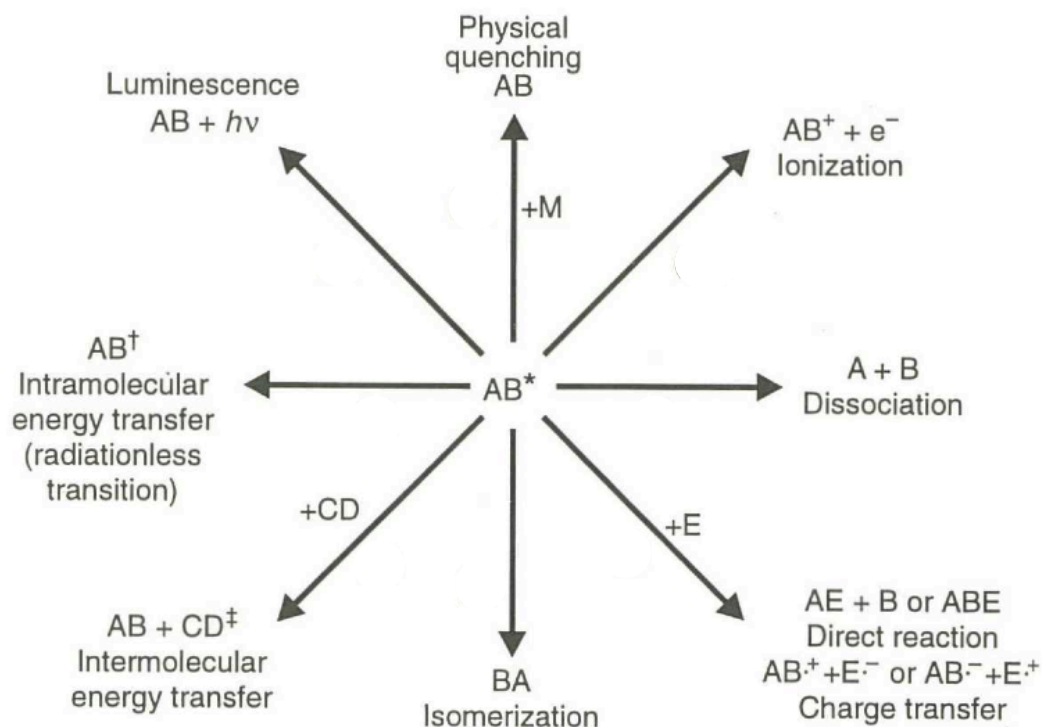


Figure 2: Fates of excited states as classically depicted by Wayne and Wayne.²⁵

Equation 2: Equation for determining the quantum yield.²⁶

$$\Phi_n = \frac{\text{number of molecules that undergo a photochemical process } n}{\text{number of photons absorbed}}$$

Since electronically excited states are higher in energy than the ground state, the necessary activation energies for the reaction can more easily be overcome. Additionally, the fact that an electron was promoted to a different orbital means that reactions that were formally forbidden in the ground state may be allowed in the excited state and can therefore proceed rapidly.^{25, 31}

1.2 Photochemical Reactions

Considering that the reaction pathway of a photochemical reaction proceeds from the excited state, it is unsurprising that photochemistry has proved to be an effective tool on the laboratory scale, allowing chemists to make products ranging from small building blocks to highly complex natural products.^{32, 33} Photochemical methods have

been useful in numerous different classes of reactions including cycloadditions,^{32, 34-36} cyclizations,³⁷ and rearrangements.³⁸ Frequently, the products generated by these reactions would otherwise require multiple synthetic steps to be made using traditional routes.³⁹ Thus photochemistry offers access to molecular structures that are difficult to achieve with classic synthetic methods.^{32, 40} Examples of some of the most common structures that can be photochemically generated by UV photochemical reactions are given in the next sections. (N.B. This is by no means a fully exhaustive review of all possible photochemical reactivities, furthermore, photochemical reactions involving visible light are not discussed here as they fall largely outside the scope of this Thesis.)

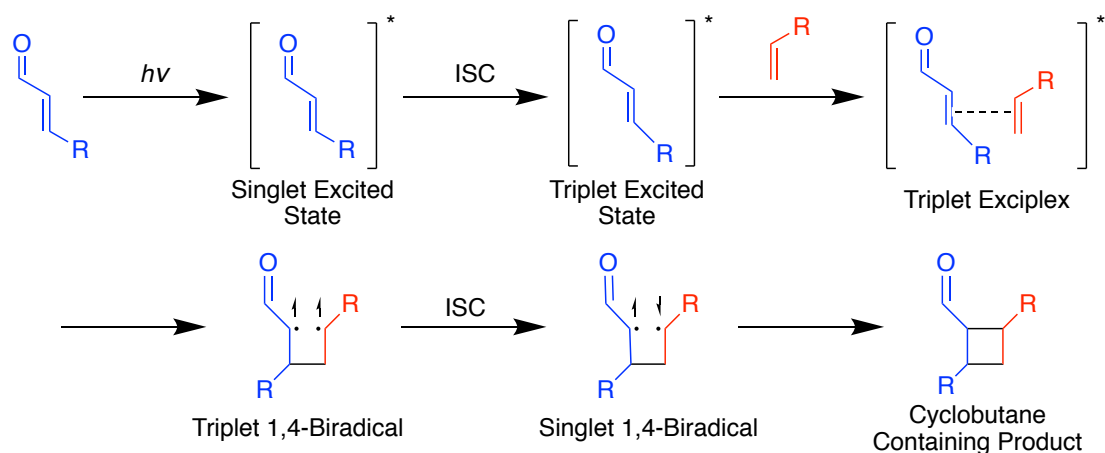
1.2.1 Photochemical Cycloadditions

Photochemical cycloaddition reactions give access to carbocyclic and heterocyclic compounds in a single step.¹⁷ Typically, in these reactions, one of the reactants is an unsaturated compound that reacts at both carbons, sacrificing a π -bond for the formation of two single bonds.^{17, 18} Examples of photochemical [4+4], [3+2] and [4+2] cycloadditions can be found in the literature,⁴¹ however only the most common [2+2] cycloaddition reaction will be discussed further in the next section.

1.2.1.1 [2+2] Cycloaddition

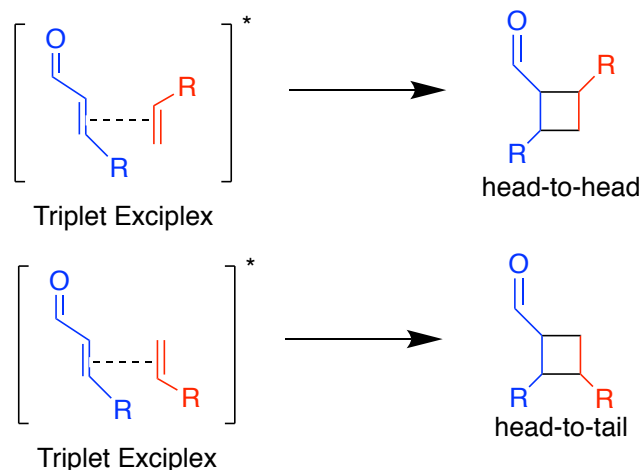
In organic synthesis, the most commonly used photochemical reaction is the [2+2] cycloaddition of an α,β -unsaturated enone to an alkene, alkyne, or allene generating a 4-membered ring which has up to four new stereocentres.^{18, 41, 42} Examples of both intra and inter-molecular [2+2] cycloadditions have been extensively studied¹⁸ and used as part of natural product total syntheses.^{41, 43} Mechanistically, the [2+2] cycloaddition of an enone with an olefin has been shown to occur via excitation of the enone to its first excited singlet state and subsequent rapid intersystem crossing to the triplet excited.^{17, 44} The excited triplet enone then forms an exciplex with the

olefin. The exciplex decays to a triplet biradical. This is followed by spin inversion to a singlet state where bond formation rapidly occurs to give the cyclobutane-containing product (Scheme 1).⁴⁴⁻⁴⁶ However, some debate still remains about the exact mechanism of this reaction.



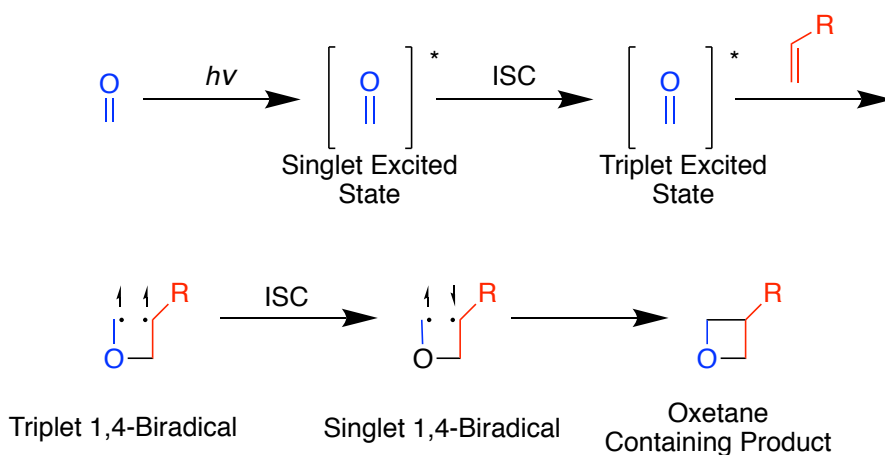
Scheme 1: Mechanistic pathway of [2+2] photo-cycloaddition between an enone and olefin. Adapted from Kärkäs *et al.*⁴⁴

When both reaction partners in the [2+2] photo-cycloaddition reaction are unsymmetrical, two regio-isomers, described as head-to-head or head-to-tail, can be formed (Scheme 2).¹⁷ The ratio of the two isomers formed is controlled by steric effects from the substituents on the double bonds, as well as the electronic interactions between the enone and olefin in the excited exciplex.¹⁸ Being able to control the regio-selectivity is key for a selective step in a synthesis.¹⁸



Scheme 2: Names given to describe the regio-isomers of the [2+2] photocycloaddition products of enones and olefins. Adapted from Poplata *et al.*¹⁷

Heterocyclic 4-membered rings can also be generated in photochemical [2+2] cycloaddition between a ketone and alkene yielding oxetanes in the Paternò-Büchi reaction. The most common reaction pathway for photochemical oxetane formation is similar to that for cyclobutane formation. The ketone is excited to the first singlet excited state by absorption of a photon, which is rapidly followed by ISC to the first triplet excited state. The triplet excited ketone reacts with the alkene to form a triplet 1,4-biradical. A second ISC occurs giving a singlet 1,4-biradical which combine to close the ring and form the oxetane, Scheme 3.⁴⁷ As the oxetane moiety can be found in many natural products, the Paternò-Büchi reaction has found synthetic utility as part of several total syntheses.^{41, 44, 47}



Scheme 3: Mechanistic pathway of the Paternò-Büchi reaction for photochemical synthesis of oxetanes. Adapted from Fréneau and Hoffman.⁴⁷

1.2.2 Photochemical Cyclisations

Like photochemical cycloaddition reactions, photochemical cyclisations also generate more complex cyclic products in a single step. Photochemical electrocyclisations and Norrish-Yang cyclisation reactions are discussed further in the next sections.

1.2.2.1 Photochemical Electro-Cyclisations

In an electro-cyclisation reaction a σ bond is formed between the ends of a linear system at the price of a π bond.^{48, 49} There are examples in the literature of photochemical electrocyclisation reactions being used to generate both carbocyclic and heterocyclic rings of various sizes.^{37, 41} The σ bond can form either by disrotatory or conrotatory motion of the end orbitals. The number of conjugations in the system will define the phase of the end orbitals, thus dictating which direction rotation must occur for bond formation. This is exemplified by Figure 3, which shows the HOMO of butadiene (left) and its LUMO (right). In order for bond formation to occur from the HOMO the end orbitals must rotate in a conrotatory manner, whereas bond formation when the LUMO is occupied requires end orbital rotation in a disrotatory manner. In a photochemical reaction an electron is promoted to LUMO and therefore, photochemical electro-cyclisation reactions will give different diastereoselectivity to thermal reactions (assuming the product can have diastereoisomers).^{48, 50} The direction of the rotation and thus the diastereoselectivity of the product is defined by the Woodward-Hoffman rules (Table 1).

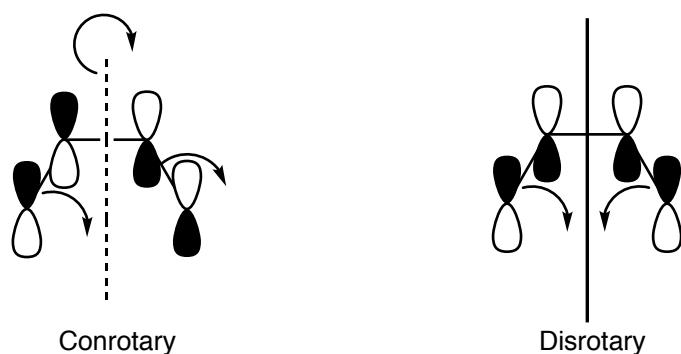


Figure 3: Frontier orbital diagrams depicting the HOMO and LUMO of butadiene and conrotatory and disrotatory manners of electrocyclization respectively. Adapted from Hoffman and Woodward.⁵⁰

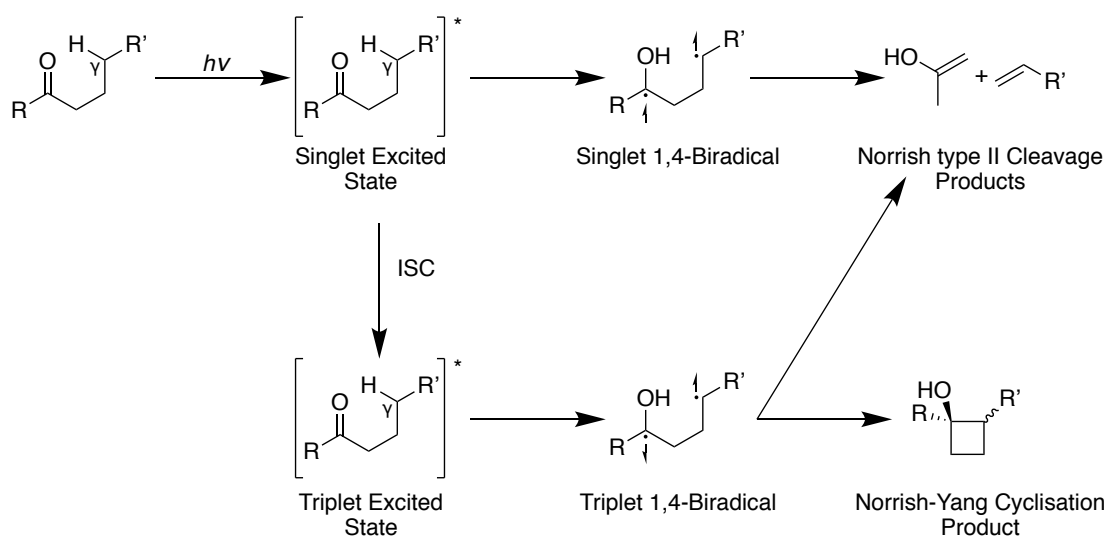
Table 1: End orbital rotation direction for bond formation according to Woodward-Hoffman Rules.⁵⁰

Number of Conjugations	Ground State (Thermal)	Excited State (Photochemical)
Even	Conrotatory	Disrotatory
Odd	Disrotatory	Conrotatory

1.2.2.2 Norrish Yang Photochemical Cyclisations

Norrish-Yang cyclisation is an intramolecular photochemical reaction that produces cyclobutanones from ketones with a γ -hydrogen, making it a reaction of interest for the synthesis of natural products, fine chemicals or novel compounds.^{41, 51, 52} The reaction begins by an $n\pi^*$ excitation of the ketone through the absorption of a photon to produce the first excited singlet state of the ketone (Scheme 4). If the ISC rate is fast, it will generate the first excited triplet state of the ketone. This is followed by γ -hydrogen abstraction giving a triplet biradical. If the ISC rate is slow, γ -hydrogen abstraction can occur directly from the excited singlet state, generating a singlet biradical. The triplet biradical will either recombine to produce the cyclobutanone ring (Norrish-Yang cyclisation) or cleave to the corresponding enone and alkene (Norrish type II cleavage).^{41, 52} The nature of the substituents on the excited triplet biradical

will influence whether the fragmentation or cyclisation pathway predominates.⁴¹ The singlet biradical will typically cleave to the enol and alkene.^{41, 52}



Scheme 4: Mechanism for Norrish type II cleavage and Norrish-Yang cyclisation. Adapted from Oelgemöller and Hoffman.⁵²

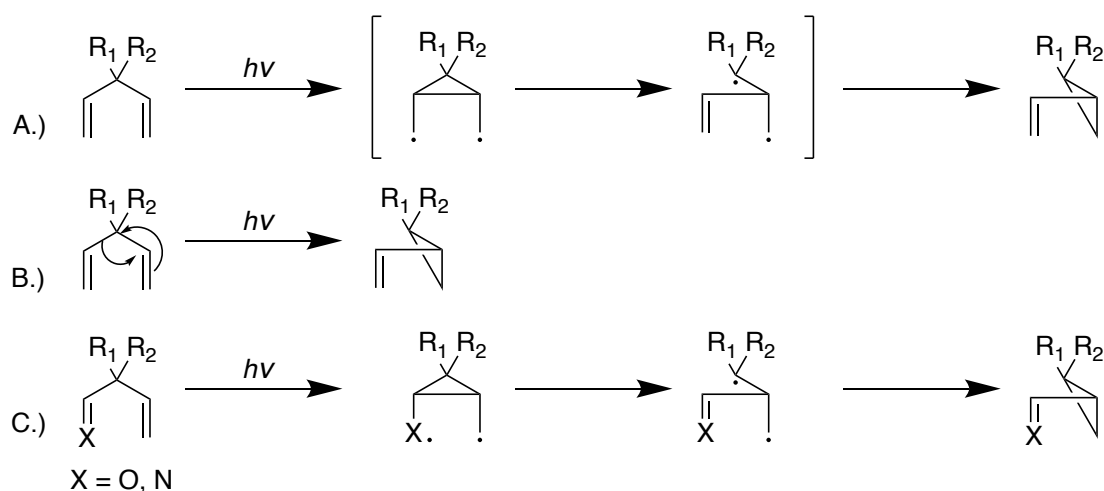
1.2.3 Photochemical Rearrangements

Photochemical rearrangements have been used to transform relatively simple starting materials into more complex products. Only the photochemical di- π -methane rearrangement will be discussed further in the next section, although examples of other photochemical rearrangements, such as the photo-Claisen rearrangement, can be found in the literature.⁵³

1.2.3.1 Photochemical Di- π -methane Rearrangement

The di- π -methane rearrangement involves the formation of a cyclopropane ring from a 1,4-diene (Scheme 5, A).^{41, 54, 55} When the starting diene moiety is part of a larger ring system, this rearrangement can be used to generate complex multi-cyclic products.⁴¹ Irradiation of the diene (frequently using a triplet sensitizer) results in a 1,4-triplet biradical containing a cyclopropane ring. One of the bonds in the cyclopropane cleaves generating a double bond and 1,3-biradical. Radical recombination then occurs to generate the singly unsaturated cyclopropane-

containing product.^{41, 54, 55} When a triplet sensitiser is not employed to excite the starting diene it is possible for the reaction to proceed directly from the singlet excited state. In this case a concerted mechanism might be considered to explain the final product (Scheme 5, B).⁴¹ The reaction will proceed in an identical manner if one of the carbon-carbon double bonds is replaced with a carbon-oxygen or carbon-nitrogen double bond (Scheme 5, C). When a heteroatom is present the carbon heteroatom double bond is the double bond reformed in the final product.^{41, 54}



Scheme 5: Mechanism of photochemical di- π -methane rearrangement. (A) When a triplet sensitiser is used the mechanism involves a 1,4-triplet bi-radical. (B) When a triplet sensitiser is not employed, the reaction may proceed via the singlet-excited state through a concerted mechanism if ISC does not occur. (C) Mechanism of oxa- and aza- di- π -methane rearrangements. Adapted from Hoffman.⁴¹

1.3 Green Chemistry

Over the last three decades, the fields of green and sustainable chemistry have emerged from the increased awareness of the impact that humanity and its chemical products have had on the environment.⁵⁶⁻⁶² Sheldon offers a clear and concise definition of Green Chemistry: "Green chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the application of chemical products."⁵⁹ These fields have never been more relevant considering that at least one chemical step is

required in the production of 95% of all goods,^{63, 64} the world's population is predicted to grow to 9.8 billion by 2050,⁶⁵ and developing nations must be entitled to a higher level of resource consumption than their current usage rates, if they are to reach the same level of development as high income countries.⁶⁶ The increasing demand for chemicals with lower environmental impact has and continues to challenge chemists to find more sustainable ways to synthesise new molecules and develop ways of making established syntheses more efficient.^{67, 68} As a result there has been a shift of focus solely from the question of "what to synthesise" to give equal consideration to the question of "how to synthesise".⁵⁶ This has led to an increased interest in less frequently used synthetic techniques such as photochemistry and electrochemistry, which have inherent green credentials because they both can be used to perform reactions in a "reagent-less" manner. The "12 Principles of Green Chemistry" (Figure 4), as proposed by Warner and Anastas⁶² can be thought of as a checklist to determine how green a particular synthesis is. They will be discussed in the next section in relation to photochemistry. (N.B. Electrochemistry is an analogous technique to photochemistry, and many similar arguments can be made for it being an inherently sustainable synthetic technique, electrochemistry will be discussed in more detail in Chapter 5.)

The 12 Principles of Green Chemistry

- 1.) It is better to prevent waste than to treat or clean up waste after it is formed.
- 2.) Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.
- 3.) Synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
- 4.) Chemical products should be designed to preserve efficacy of function while reducing toxicity.
- 5.) The use of auxiliary substrates (e.g. solvents) should be made unnecessary wherever possible.
- 6.) Energy requirements should be recognised for their environmental and economic impacts and should be minimised. Synthetic methods should be conducted at ambient temperature and pressure.
- 7.) A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
- 8.) Unnecessary derivatisation (e.g. protecting / deprotecting groups) should be avoided wherever possible.
- 9.) Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
- 10.) Chemical products should be designed so that at the end of their function they do not persist in the environment and instead break down into innocuous degradation products.
- 11.) Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
- 12.) Substances and the form of a substance used in a chemical process should be chosen so as to minimise the potential for chemical accidents.

Figure 4: The 12 Principles of Green Chemistry as stated by Warner and Anastas.⁶²

1.3.1 The 12 Principles of Green Chemistry Applied to Photochemistry

As stated in Section 1.3 photochemical reactions provided access to structures that usually require multiple steps to be produced by traditional synthetic routes.³⁹ By reducing the total number of steps in a synthetic process waste can be avoided (Principle 1).⁶⁹ Photochemistry uses photons to activate the reagent and drive the reaction. This means that it is possible to avoid the use of stoichiometric reagents and/or potentially toxic catalysts (Principles 3, 9) that would then have to be separated from the products at the end of the reaction.^{69, 70} This prevents stoichiometric waste (Principle 1) and can potentially reduce the solvent consumption of the process as the separation process is simpler without an additional reagent (Principles 1, 5). Most photochemical reactions typically proceed quickly under mild

conditions of ambient temperature and pressure (Principle 6).³⁹ The mildness of the conditions used for photochemical reactions can allow sensitive functional groups to be present without the need for protection/ deprotection (Principle 8).⁶⁹ Furthermore, photochemical reactions tend to be relatively resistant to changes in temperature and impurities, so long as they do not influence the fate of the excited species.^{21, 39} This can also help to minimise waste as less pure reagents are required (Principles 1, 5). Photochemical reactions are often highly atom economic (Principle 2),^{39, 69} indeed all of the examples of photochemical reactivity presented in Section 1.2 have the potential to be 100% atom economic.

Principles 4, 7, 10, and 11 will be specific to the particular photochemical reaction being performed and the set-up being used. While it is possible that all of these principles could apply to a particular photochemical synthesis they are not general to the technique. However, photochemistry performed in continuous flow reactors is becoming more common.^{69, 71} Continuous reactors are well suited to integration with real-time monitoring techniques (Principle 11). This will be discussed in more detail in Section 1.6.

Finally, it must be noted that many of the light sources used for photochemical reactions (discussed in Section 1.5.1) emit high-energy photons that can be hazardous to the health of anyone exposed (Principle 12).⁶⁹ Furthermore, high energy photons can produce ozone from atmospheric oxygen which is also hazardous to human health. However, photons do not persist in the environment so while local risk is high, the photons from these light sources have no global risk. Operating light sources in fume cupboards with strict safety protocols and training procedures can mitigate risk of ozone and UV exposure to those in the vicinity of the light source (Principle 12).

1.4 Drawbacks to Photochemistry

Photochemistry has remained largely under utilised both on the academic scale and in industry.⁷² However, with the dual motivation of both the synthetic potential and green credentials of photochemistry, the scene was set for chemists to re-examine the factors that had typically limited the number of chemists performing photochemistry and to begin finding solutions. There are significant issues associated with traditional photochemical reactors, discussed in the next section, which may have impeded more widespread use of photochemistry.⁷³ These reactors are particularly problematic for the scale-up of photochemistry.⁷³ The advent and adoption of new technologies such as continuous flow chemistry^{21, 56, 74-78} and increased availability of different types of light source has helped to address problems related to photochemical equipment; this will be the topic of the following section. Furthermore, Booker-Milburn and co-workers⁷¹ and Gilmore and Seeburger⁷⁹ have highlighted in their reviews on the subject of photochemistry that some of the under-use of photochemistry is simply due to a lack of knowledge about how a photochemical step might benefit a particular synthesis, how to perform photochemical experiments, as well as the appropriate safety measures that might be required for photochemical experiments. These problems can really only be addressed through the increased popularity of photochemistry, which given the breadth of recent reviews on the topic does seem to be under way.^{17, 41, 44, 71, 73, 79, 80}

1.5 Photochemical Apparatus

In order to perform a photochemical reaction both a light source and reactor are necessary. Both the choice of light source and reactor can have significant implications for the outcome of the reaction.

1.5.1 Light Sources

The most “green” of all light sources is of course the sun,^{81, 82} and there is currently significant interest in the field of solar photochemistry.⁸²⁻⁸⁴ However, the photon flux of the sun depends largely on location, weather, and time of day and year.⁸⁵ Furthermore, the position of the sun moves throughout the course of the day, meaning adjustments would frequently be needed to keep the sunlight directly focused on the reaction vessel. Therefore, it stands to be impractical as an everyday, reproducible, light source for photochemical reactions. Research in the area of visible light photochemistry has rapidly grown over the past decade, which can in part be contributed to the increasing availability of inexpensive, and long-lived, narrow-band emitting light emitting diodes (LEDs) in the visible region.^{72, 86} However, visible photochemical reactions rely upon the reaction mixture being able to absorb photons of visible light, and unfortunately only a small percentage of organic substrates are coloured and therefore able to absorb visible light.^{87, 88} In some instances, a photosensitiser can be used to absorb light and then transfer energy to excite the substrate (the process of photosensitisation is discussed further in Chapter 2).³² However, performing direct irradiation of most organic molecules requires a UV light source. This traditionally has come in the form of either a low, medium, or high pressure mercury lamp.⁸⁹ With the exception of the visible reaction presented in Chapter 2, visible light photochemistry falls largely outside the scope of this Thesis.

1.5.1.1 Mercury Lamps

Low-pressure mercury lamps are readily available with a range of powers. However, more powerful low-pressure lamps tend to be very large in size. Low-pressure lamps can convert approximately 30% of the energy put into the lamp into UV photons. Of the light emitted approximately 90% has a wavelength of 254 nm (Figure 5), making them a practical light source for high-energy excitations.^{71, 86, 90}

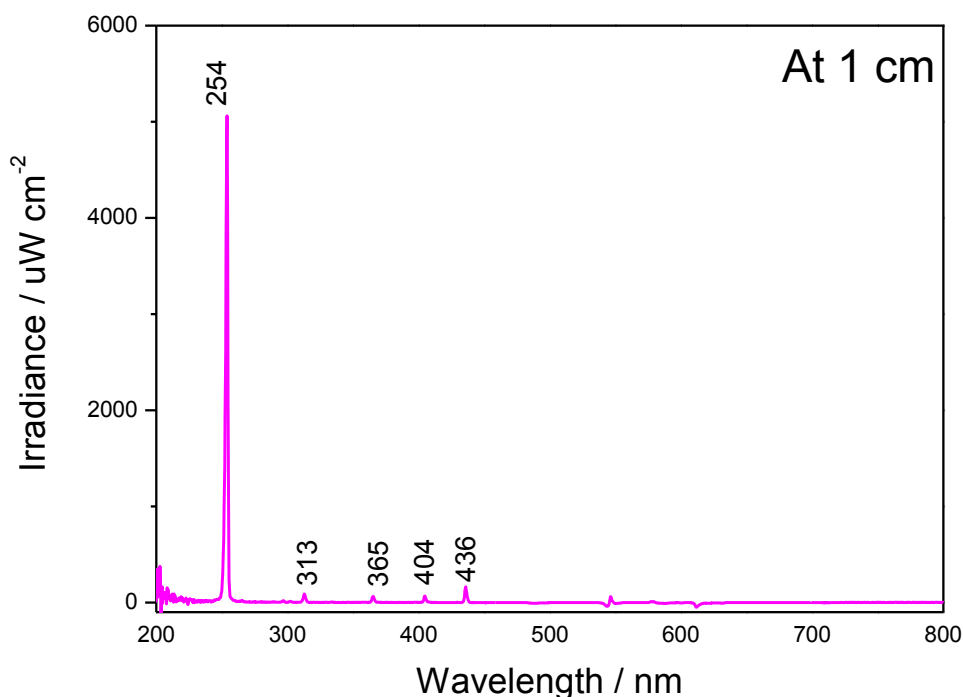


Figure 5: Emission spectrum of a Photochemical Reactors 3006 6W low-pressure mercury lamp. Recorded by Charlotte Clark using a calibrated Ocean Optics UV-Vis USB 2000+ spectrometer. Reproduced with permission.⁹¹

By contrast medium-pressure and high-pressure mercury lamps with much higher powers (125W -60kW) than low-pressure lamps are commercially available.^{71, 86} However, these lamps are broadband emitters, Figure 6. While mercury still emits strongly at 254 nm it also absorbs strongly at 254 nm. Therefore, as the pressure of the lamp is increased, more of the 254 nm photons are “re-absorbed” by excited mercury ions and re-emitted at longer wavelength photons in a phenomenon known as “imprisonment of radiation,”⁹² leading to a reduction of the intensity of the emission band at 254 nm and an increase in intensity of the longer wavelength emission bands. Practically, from a photochemistry standpoint, this means that medium and high-pressure mercury lamps will emit photons at multiple wavelengths with sufficient energy to excite multiple different absorbing chromophores within the reaction system rather than selectively exciting the appropriate chromophore. This

decreases the chance that the photochemical reaction will be selective.⁴⁰ Filters can be introduced to give monochromatic light at the necessary wavelength,^{90, 93} but, this often results in the reduction of the photon flux.

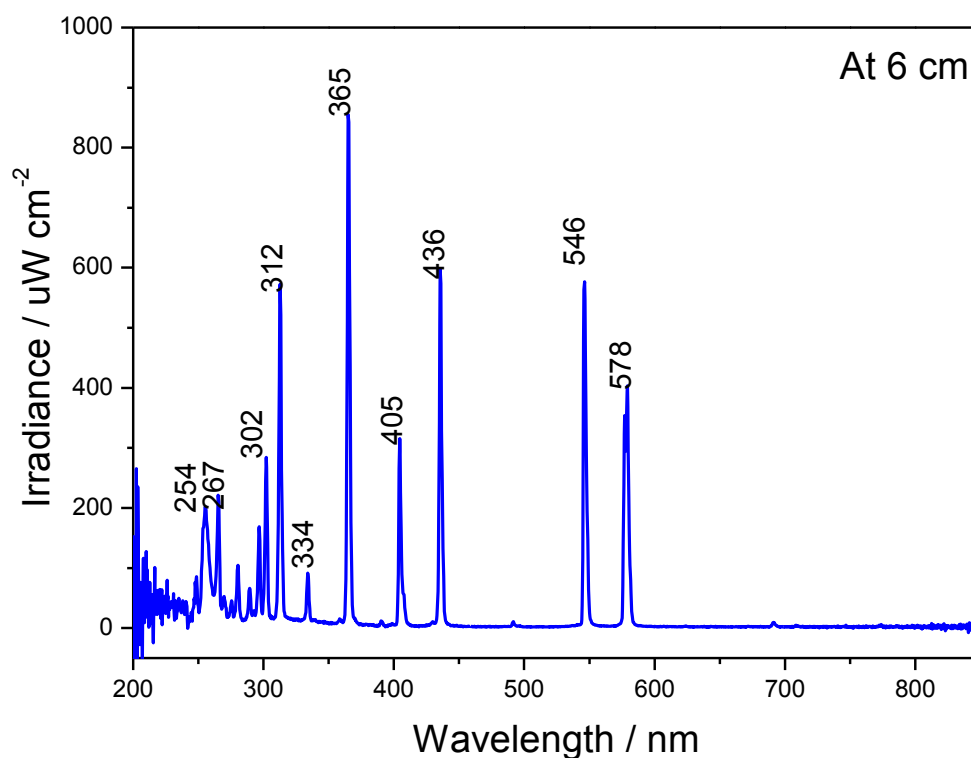


Figure 6: Emission spectra of a 125 W Heraeus Noblelight high pressure Hg lamp. Recorded by Charlotte Clark using a calibrated Ocean Optics UV-Vis USB 2000+ spectrometer. Reproduced with permission.⁹¹

Furthermore, in addition to emitting UV light in the range from 254-370 nm, Hg lamps also emit significant quantities of visible and infra-red (IR) radiation and the operating temperature of the quartz envelopes of these lamps is around 600° C. This means that the reaction vessel must be cooled properly, which both on the lab scale and industrially is an energy intensive process.^{71, 90, 94} Because of the broadband emission, a large proportion of the electrical energy put into the lamp is wasted by generating heat and photons that cannot be absorbed by the substrate.⁹⁰

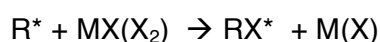
1.5.1.2 Excimer Lamps

Excimer lamps, or excilamps, by contrast stand as an interesting alternative to mercury lamps as a UV-light source. Excilamps utilise the excitations of rare gas dimers, halogen dimers, or rare gas-halogen exciplexes to generate UV light.⁹⁵ An electrical discharge is used to generate the excited state of these gases.⁹⁴ In the case where the lamp is filled only with rare gas, the excited dimers are generated by three body association reactions as shown in Equation 3. In the case of rare gas and halogen mixed lamps, exciplex molecules are formed through harpoon reactions, Equation 4, or by ion-ion recombination, Equation 5.

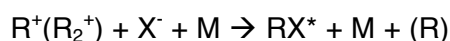
Equation 3: Where R is a rare gas atom.



Equation 4: Where R is a rare gas atom, X is a halogen atom, and M is a third atom or molecule.



Equation 5: Where R is a rare gas atom, X is a halogen atom, and M is a third atom or molecule.



In the equations above X stands for a halogen atom, R is a rare gas atom, and M is a third atom or molecule that removes excess vibrational energy.^{89, 94} Figure 7 shows that once excited, rapid non-radiative internal conversion of higher energy excited states of the excimer/exciple to the lowest energy excited state then takes place. The subsequent decay from lowest energy excited state of the excimer/exciple down to the ground state produces the intense emission band that characterises these lamps. The energy gap between the excited and ground state defines the

wavelength of light emitted, and in all cases the energy gap is large enough to produce emission in the UV region.^{89, 94}

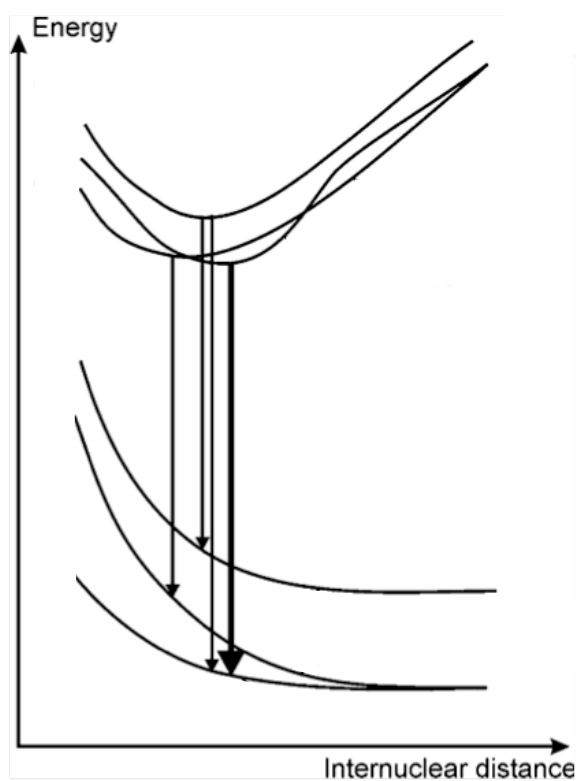


Figure 7: Schematic of the potential energy diagram showing the intersection of higher energy exciplex excited states with the lowest energy excited state. Decay from the lowest energy excited state to the ground state leads to intense emission band (shown in bold). Adapted from Sosnin *et al.*⁹⁴

This leads to narrow-band emission being produced by these lamps. Narrow-band emission not only means that all of the light generated can be useful, but it also means that far less IR radiation is produced than by a Hg lamp of similar power.⁹⁴ Therefore, excilamps operate at a far lower temperature than mercury lamps. Thus using excimer lamps in photochemical reactors requires far less cooling compared to reactors using mercury lamps. Excimer lamps have other advantages including: long lifetimes (several thousand hours),^{96, 97} simpler disposal at the end of useful life since they do not contain toxic mercury, and they can be manufactured in a variety of geometries.^{89, 94} This allows for the shape of the lamp to be tailored specifically to its application.⁹⁶

Excimer lasers are frequently used in spectroscopic studies⁹⁸ and incoherent excimer light has been used for applications such as photo-curing.^{99, 100} However, despite the advantageous properties of excimer lamps, to the best of my knowledge, there is only one example where they are used for synthetic organic photochemistry (discussed further in Section 1.6.2.1).⁹⁰

1.5.2 Batch Photochemical Reactors

Traditionally, the main way of performing photochemical experiments on a lab scale has been to use an immersion-well photo reactor (Figure 8).^{71, 101} In these batch reactors the light source, typically a mercury lamp, sits within a double walled cooling jacket that is then placed directly into the reaction flask. These systems work well for reactions up to a few grams in scale.⁷¹ However, scale-up of these types of reactors is problematic on both an industrial scale and even on laboratory scale where the overall yield of a multi-step synthetic process might require larger quantities if it is needed in an early synthetic step, due to an increase in inner-filter effects. As the size of a batch photochemical reactor increases the depth of the reagent solution will increase, increasing the optical pathlength. The longer pathlength results in fewer photons reaching the reagent solution that is furthest from the light source since the intensity of light available for the reaction decreases in a logarithmic fashion according to the Beer-Lambert law, Equation 6 because it has already been absorbed by the solution closest to the light source.

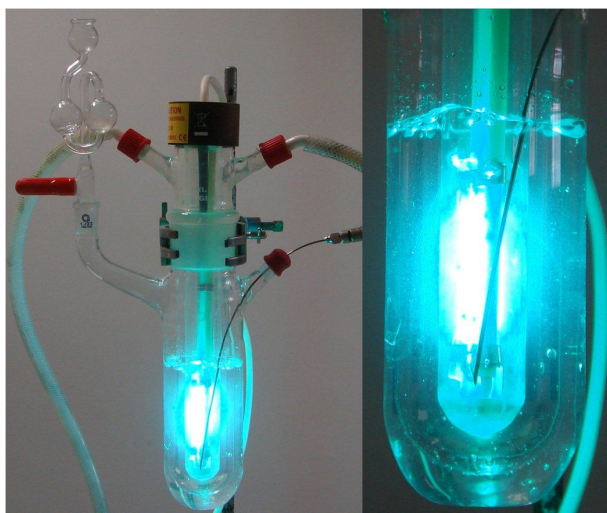


Figure 8: Immersion well reactor. Adapted from Knowles *et al.*⁷¹

Equation 6: The Beer-Lambert Law, where A is absorbance, ϵ is molar extinction coefficient, c is concentration, l is optical pathlength, I is transmitted light intensity and I_0 is incident light intensity.

$$A = \epsilon cl = -\log_{10} \frac{I}{I_0}$$

More simply, this can be thought of as the solution nearest to the lamp absorbing most of the photons and thus effectively screening the rest of the solution from the light. Therefore, as the size of the reaction vessel is increased, it becomes more and more difficult to achieve the necessary light penetration into the bulk solution in order for the reaction to reach completion.^{71, 73, 101} While at first it may seem that there are two very simple solutions to this problem, increasing the concentration of the reactants or increasing the irradiation time, neither of these is a practical on larger scales. As absorbance is linearly proportional to concentration, inner-filter effects become more pronounced as concentration is increased. Lengthening the irradiation time frequently leads to undesired side products such as oligomers, the result of over-irradiation of the reactant/product mixture.^{71, 79, 86}

Small-scale batch photochemistry can also be performed in commercially available Rayonet reactors¹⁰² (Figure 9). In these reactors, a flask, test tube, or Schlenk tube containing the reagent solution is placed at the centre of a fan-cooled drum. Between

8 and 16 (depending on model) Hg bulbs placed around the circumference of the drum irradiate the reagents. Interchangeable Hg bulbs with various coatings allow for irradiation at specific wavelengths.^{71, 86, 102} This style of batch reactor has the advantage of being completely enclosed and not needing water-cooling. However like all batch reactors Rayonet reactors suffer from inner-filter effects, making them practical for small-scale reactions but less so for scale-up.

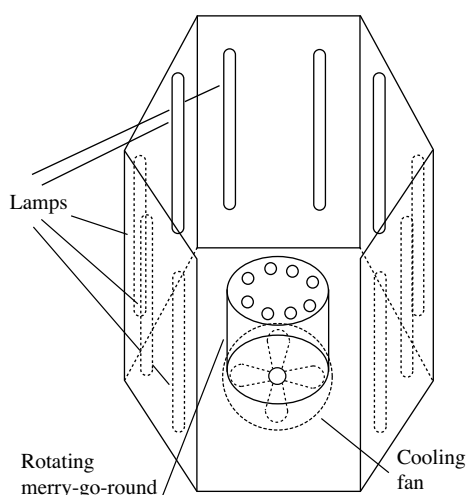


Figure 9: Schematic of a Rayonet style reactor. Adapted from Albini and Germani.⁸⁶

1.6 Continuous Flow Chemistry

Prior to describing the benefits of continuous flow chemistry for photochemistry, a brief general introduction to continuous flow chemistry is given. Chemical engineers have used continuous processing for over 100 years; however, batch processes have dominated both laboratory-scale reactions and the industrial-scale production of fine chemicals.¹⁰³⁻¹⁰⁶ It is only in the past two decades that small, continuous reactors, appropriate for the academic laboratory setting, have become relatively popular for performing organic reactions.^{103, 107, 108} With the growth of the field, the number of different types of continuous reactor has grown. Examples range from “chip” style reactors,^{108, 109} and laboratory built reactors,^{101, 110} to commercially available units.^{76, 93, 111} Continuous reactors have proved to be an enabling

technology in a variety of applications.^{76, 105} This is due to the fact that performing reactions in continuous flow can offer improvements in the mixing, heating, and scalability of the reaction.^{76, 103, 105-107, 109} Furthermore, the nature of continuous processes can make them more suited to performing multi-step synthesis and integrating reaction-monitoring systems.^{76, 105, 106, 112} The advantages of continuous flow are explained in more detail in relation to photochemistry, electrochemistry and multi-step synthesis in Section 1.6.1 of this chapter, Chapter 5 - Section 5.2, and Chapter 2 - Section 5.2 respectively.

1.6.1 Photochemistry in Continuous Flow

Flow chemistry offers an elegant solution to many of the problems encountered with batch photochemical reactors mentioned above.^{71, 79, 103, 113} Generally, in a typical flow set-up, the optical pathlength through the reagent solution in the reactor is kept as small as possible and only a fraction of the total reagent solution is exposed to the light at any given time. (Details of specific flow reactors found in the literature will be presented in the next sections). This leads to a more effective and more uniform irradiation of the solution during the course of the reaction.⁷⁹ The reduced pathlength of the light in flow systems means that often it is possible to irradiate solutions of higher concentrations without losing conversion, due to light still being transmitted through the entirety of the solution depth. This results in processes that can produce more material in a given amount of time and can reduce the volume of solvent needed.⁷¹ Furthermore, as irradiation in flow is more uniform, flow rate can be used to control for both under-irradiation and over-irradiation. This gives flow systems more tunability for each particular photochemical reaction, rather than a “one-size fits all” system.^{71, 79}

In contrast to batch reactors, scale-up of photochemical reactions in flow reactors is relatively simple because increasing the scale of a continuous reaction can be

accomplished merely by running the reactor for longer. This is particularly true when a photochemical reaction requires dilute solutions to suppress intermolecular side-reactions. By having a continuous flow process, it can still be economically practical to irradiate large volumes of very dilute solutions because even under these conditions a large apparatus is not required to generate usable quantities of product.⁷¹

Finally, and arguably most importantly, flow chemistry is likely to make photochemical processes safer. The light sources typically used to irradiate photochemical reactions generate heat close to the reaction medium, which, is likely to be flammable. In a flow system, only a small amount of the reactant mixture is next to the light source at any one time, unlike the bulk solution of a batch reactor.^{71,}

79

1.6.2 Continuous Flow Photochemical Reactors

This section describes some of the different styles of UV photochemical flow reactors that can be found in the literature.

1.6.2.1 Falling-Film Reactors

A falling film reactor is not strictly speaking a continuous flow reactor but can more accurately be classified as a batch-flow reactor. In these reactors reactant solution is contained in a reservoir tank of fixed volume. In one version, the solution is pumped from the reservoir tank to the edge of a glass barrel, where it slides down the glass wall as a thin film past the UV light source returning to the reservoir tank (Figure 10).¹¹⁴ The solution from the reservoir tank has to be cycled past the light source numerous times to achieve an acceptable level of conversion because the residence time is gravity controlled and therefore extremely short.¹⁰¹ The overall reaction time will depend on both the nature of the chemistry and the power of the light source.¹¹⁵ In theory, any appropriately sized light source could be used in conjunction with a

falling-film reactor. Low or medium-pressure mercury lamps and XeCl excimer lamps have all been previously reported as the light source for irradiating reactions in falling-film reactors.^{90, 114, 115}

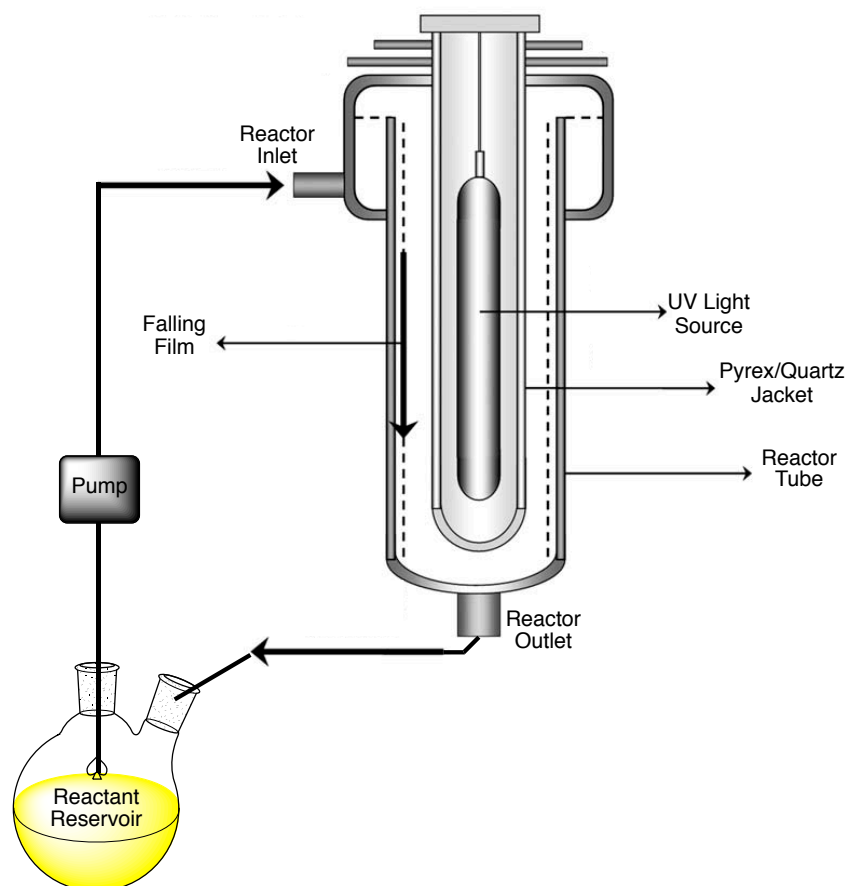


Figure 10: Schematic of one type of falling-film reactor. Adapted from Schlögl *et al.*¹¹⁴

Falling-film reactors, have significantly reduced inner filter effects compared to immersion well batch reactors because of the thinner optical path-length of the solution film.¹⁰¹ Furthermore, the fast flow rate induced by gravity helps to minimise deposition of solid by-products on the surface of the reactor.^{116 114}

1.6.2.2 Micro-reactors

Micro-reactors consist of a base plate with a small channel cut into it (1000 μm or smaller) covered by a transparent top plate (Figure 11).^{71, 86, 117, 118} Typically, the reagent flow is delivered via a syringe pump due to the extremely small volume of

solution reacting at any one time in these reactors.⁷¹ Because of the small dimensions of the micro-reactor, even highly concentrated reagent solutions are irradiated uniformly.^{71, 117, 118} Furthermore, the small scale allows for very precise control over the temperature of the reaction.^{71, 117} Micro-reactors have proved themselves to be more efficient than batch photochemical process for a wide range of reactions,¹¹⁷ including increasing the diastereoselectivity of cyclopentene to a chiral cyclohexanone derivative (Scheme 6).¹¹⁹

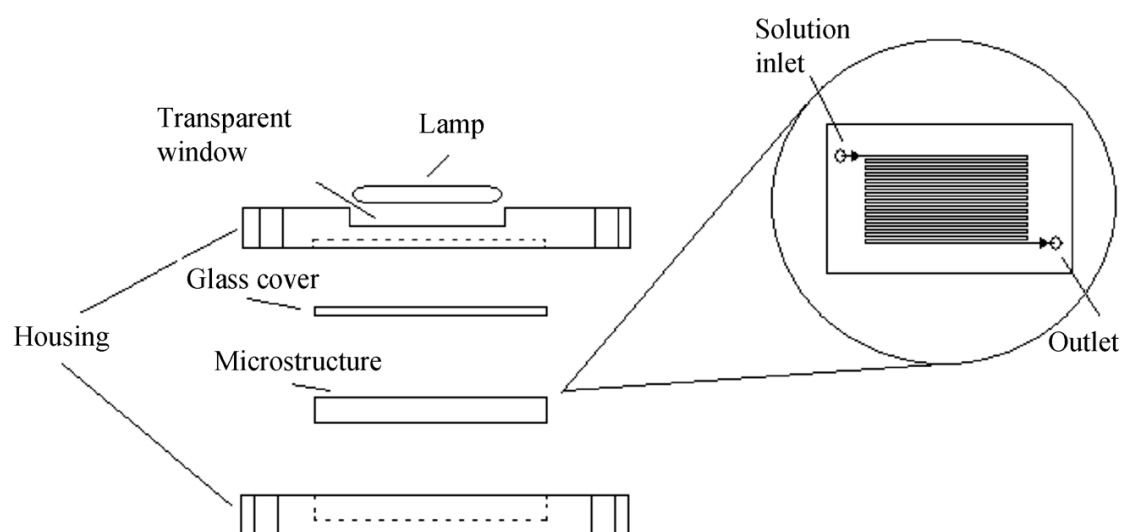
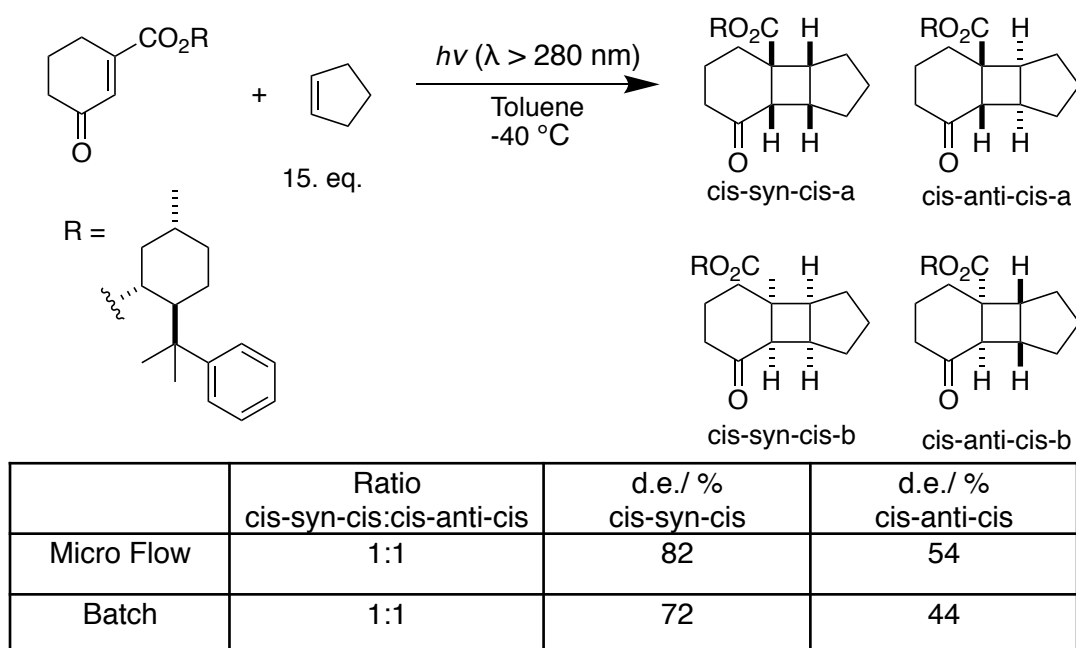


Figure 11: Schematic of a micro-reactor. Adapted from Albini and Germani.⁸⁶



Scheme 6: Photochemical [2+2] cycloaddition of cyclopentene to a chiral cyclohexanone with higher diastereoselectivity being achieved when a micro reactor was used. Adapted from Tsutsumi *et al.*¹¹⁹

However, the small size of micro-reactors limits their ability to synthesise product on larger scales.⁷¹ Additionally, most designs of micro-reactors are planar and typically feature a relatively small window through which the solution can be irradiated. This leads to inefficient capture of photons from a radial light source (e.g. a mercury lamp) and point light sources (e.g. LEDs) if the width of the beam is wider than the reactor window.⁸⁶

1.6.2.3 The FEP Reactor

The design of UV continuous flow photoreactor that has achieved the most prominence is the FEP reactor designed by Booker-Milburn and co-workers in 2005.¹⁰¹ Briefly this type of reactor consists of a water-cooled medium-pressure mercury lamp with fluorinated ethylene propylene (FEP) tubing wrapped directly around the cooling jacket of the lamp. Reagent solutions are flowed through the reactor via an HPLC pump and product is collected at the outlet. A schematic and photograph of this reactor set-up can be seen in Figure 12.

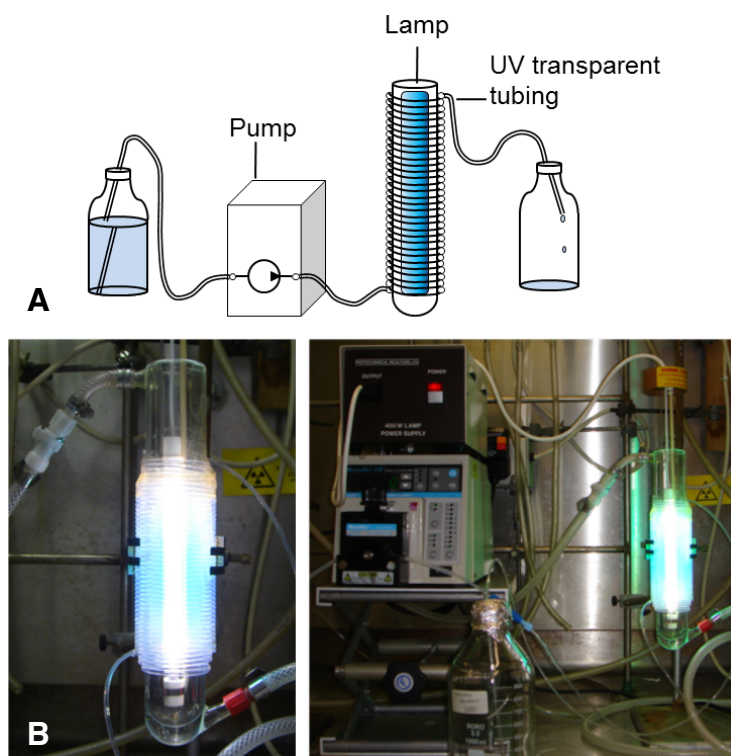


Figure 12: (A) Schematic of the Berry-Booker-Milburn FEP reactor. (B) Photographs of the FEP reactor. Adapted from Knowles *et al.*¹⁰¹

Despite its simplicity, this reactor has been shown to be efficient for a wide range of organic transformations including both inter- and intra- molecular cycloadditions.¹⁰¹ Additionally, numerous groups have adopted this reactor set-up. Aggarwal *et al.* have shown its utility in the photochemical generation of thioaldehyde.¹²⁰ Seeberger *et al.* have taken the reactor design a step further by including an oxygen dosing system for their continuous photo-oxygenation using singlet O₂ for antimalarial drug synthesis.^{121, 122}

The FEP reactor has gone on to inspire the commercially available Vaportec UV-150 photochemical reactor. Their system includes the feature of interchangeable reactor volumes, made by coiling various lengths of FEP tubing, as well as the option to change the intensity of the lamp via a dimmer function.⁹³ Despite these features, the Vaportec system at its core is essentially a more consumer minded version of the Berry-Booker-Milburn FEP reactor.^{123, 124}

Despite the success of FEP style reactors, Booker-Milburn and colleagues did point out some of the disadvantages associated with these reactors in a subsequent publication.¹²⁴ Firstly, FEP is not a completely UV-transparent material, meaning that the tubing will absorb some of the UV from the light source rather than all of the light being available for the photochemical reaction. Secondly, bending the tubing can cause weak spots that may burst under the pressure of the flowing reactants. Finally, the FEP reactor was not immune to blockages and fouling. Because a single length of tubing was used in these reactors, all of the tubing had to be replaced in the event of a small hole or when flushing with solvent did not remove the blockage or fouling. This becomes increasingly problematic if larger reactors are constructed since large quantities of FEP would be required every time the tubing needed replacement.¹²⁴

1.6.2.4 The Firefly

In 2016 Booker-Milburn and colleagues introduce their Firefly reactor, a reactor that avoided many of the issues associated with FEP.¹²⁴ The Firefly consists of parallel quartz tubes arranged around a large cylindrical central space, into which a 5 kW medium pressure mercury lamp is placed (Figure 13). The reagent solution is flowed through the quartz tubes in series. A metal screen is secured around the outside of the quartz tube assembly to reflect stray UV light back into the solution, increasing both the efficiency of the reactor and its safety profile. The large internal volume (120 mL) and powerful light source (variable power 1.5-5 kW) make this reactor particularly suited to large-scale reactions; of the seven photoreactions reported, four had productivities of over 1 kg per day (Scheme 7).¹²⁴

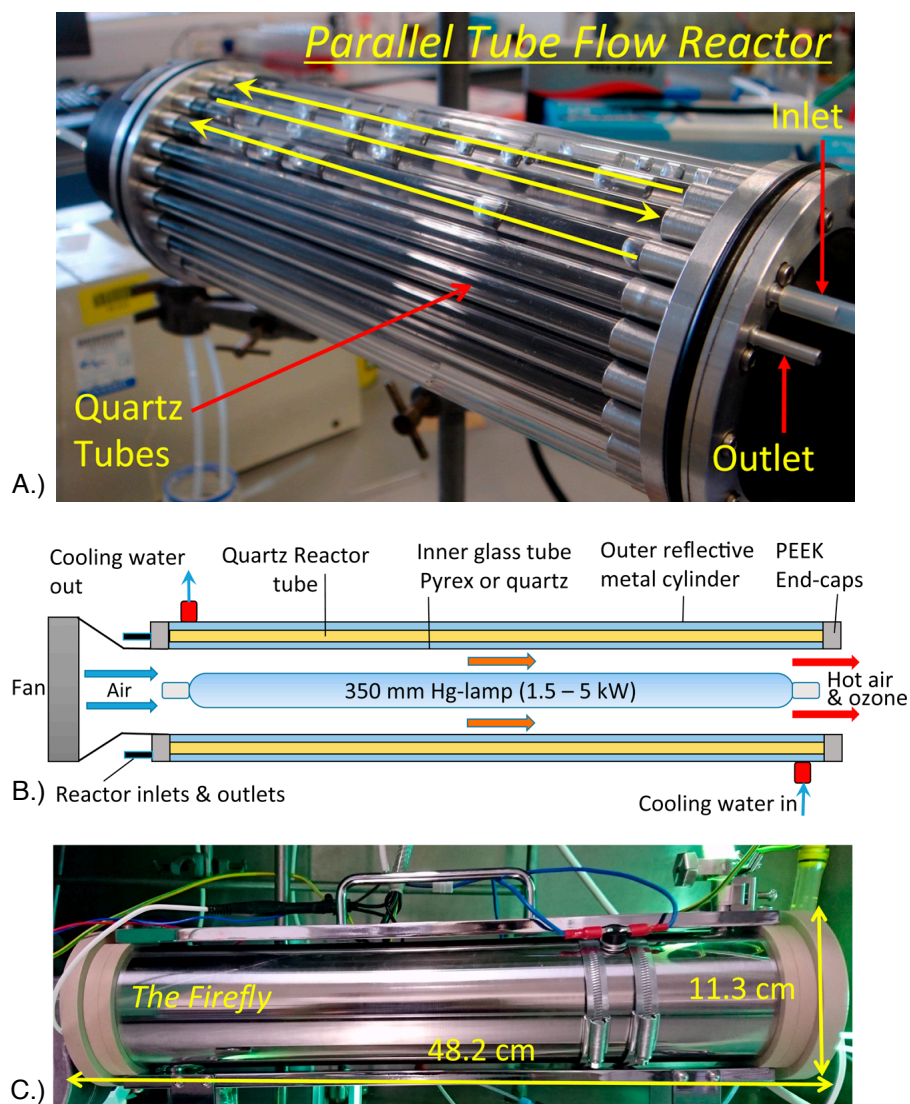
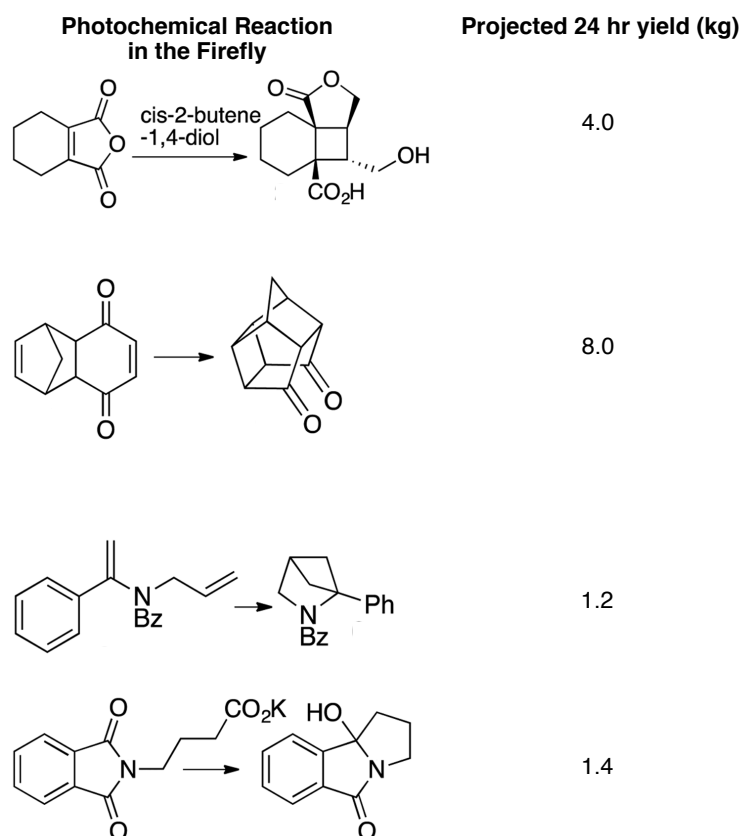


Figure 13: (A) Photograph of the Firefly reactor without its reflector, showing the concentric arrangement of the quartz tubes and alternating flow directions through quartz tubes. (B) Cross sectional schematic of the Firefly. (C) Photograph of the Firefly with the metal reflector in its operational position. Adapted from Elliot *et al.*¹²⁴



Scheme 7: Photochemical reactions in the Firefly that produce over 1 kg of product per day. The lamp was used with 3 kW of power and reaction concentrations ranged from 0.2 – 1.0 M. Adapted from Elliot *et al.*¹²⁴

1.6.2.5 Photochemical-Flow Reactors – Summary

Despite the advantages that flow reactors can offer to photochemical synthesis, none of the reactors presented in the previous sections is a “perfect” reactor. There is still scope to build better photochemical reactors that capitalise on the positive aspects of each of the reactors described, and minimise negative aspects (e.g. broad-band emitting light sources, reactor materials that absorb UV light.)

1.7 Thesis Aims

Photochemistry and electrochemistry represent “reagent-less” synthetic methods that can provide a sustainable way of obtaining compounds that are difficult to synthesise under more traditional thermal methods.^{52, 125, 126} Performing photochemistry and electrochemistry in continuous flow has addressed some of the challenges that have previously plagued these synthetic techniques.^{71, 127} However, a small uptake of

these techniques has so far resulted in chemists over-looking how these techniques might benefit a particular synthesis. The work in this Thesis aims to increase the versatility of these techniques by providing an additional photochemical reactor and demonstrating how the modular nature of flow chemistry⁷⁵ can be effectively exploited for multi-step synthesis and reaction monitoring. Therefore, the chemistry presented in this Thesis serves first mainly to test the viability of the reactor set-ups rather than to provide novel reactivity or additional photo-physical understanding of the reactions studied. Specifically the aims of this project were:

- 1.) To design and build a UV photochemical reactor that employs excimer lamps as the light source and to compare the efficiency of this reactor to other flow reactors reported in the literature.
- 2.) To study the wavelength dependence of photochemical reactions by employing three excimer lamps with different gas mixture for irradiation in the Nottingham photo-reactor.
- 3.) To integrate the Nottingham excimer photochemical reactor into a continuous multi-step process.
- 4.) To use the intense monochromatic light of excimer lamps and the Nottingham UV photochemical reactor to more efficiently perform photoreactions with low quantum yield.
- 5.) To integrate in-line analysis with the UV photochemical reactor.
- 6.) To find a simple method for incorporating in-line or on-line analysis onto a commercially available flow electrochemical reactor.

Chapter 2: Designing and Testing a Continuous Flow UV Photochemical Reactor Utilising Excimer Lamps

2.1 Chapter Summary

The continuous flow photochemical reactors that were presented in Chapter 1 represent a convenient alternative to batch reactors, frequently giving better reaction outcomes. However, many of the flow reactors described in the literature have drawbacks, the severity of which depends upon the desired scale of the reaction and the nature of the chemistry being performed. The aim of our research group has been to build upon the positive attributes of the UV flow reactors found in the literature and to minimise negative features by designing an effective small-scale continuous flow UV reactor, exploiting the monochromatic nature of the light from excimer lamps. This chapter describes the design of such a UV photochemical reactor using an excimer light source as well as benchmarking that reactor using the [2+2] cycloaddition of maleimide and 1-hexyne. Chemical actinometry using uridine and azobenzene for ensuring the long-term performance characteristics of excimer lamps is also detailed. Finally, a so far unsuccessful attempt to integrate two reactors for a multi-step synthetic reaction is described with the 6π electro-cyclisation reaction of β -ionone followed by photo-oxygenation of the electro-cyclisation product.

2.2 Excimer Lamps from the Institute of High Current Electronics

Excimer lamps are frequently used in industrial applications such as UV-curing, and UV “cleaning” in the process of display and semiconductor manufacture.¹²⁸ These industrial applications require large high-powered excimer light sources. However, as previously mentioned in the Introduction, excimer lamps are not commonly used for synthetic organic photochemistry. This may be due to the fact that excimer lamps of lower power, appropriate for academic scale reactions, are difficult to obtain. (For

example Griesbeck and co-workers used a 3 kW high power excimer lamp).⁹⁰ Therefore, our research group commissioned three custom-built excimer lamps from The Institute of High Current Electronics in Tomsk, Russia. Each lamp is filled with a different rare gas/halogen mixture leading to narrow band emissions at specific wavelengths: 222 nm for KrCl, 282 nm for XeBr and 308 nm for XeCl. The emission spectrum for each lamp is given in Figure 14.

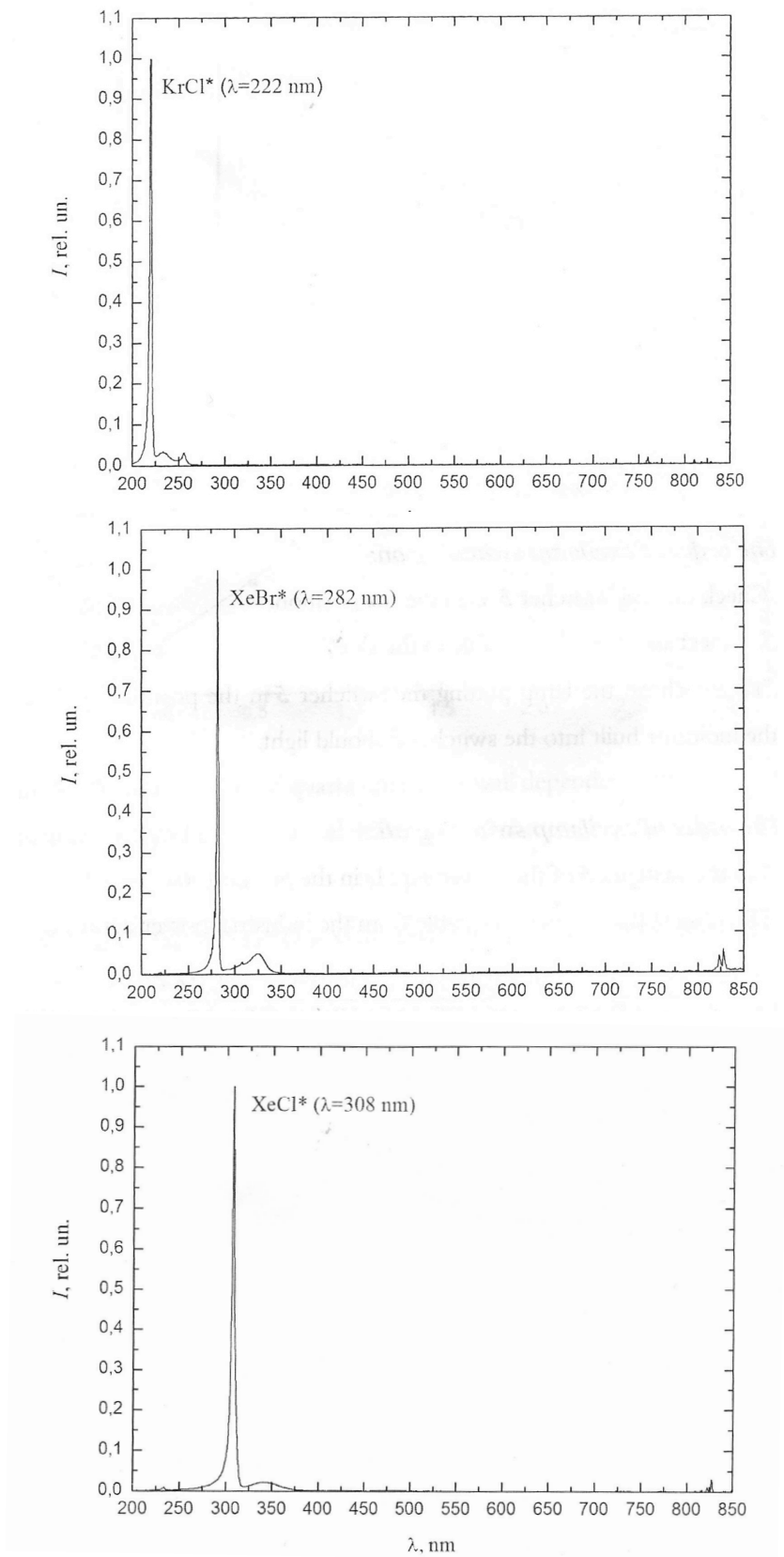


Figure 14: The emission spectrum for each of the three excimer lamps purchased, (top) KrCl $\lambda = 222 \text{ nm}$, (middle) XeBr $\lambda = 282 \text{ nm}$ and (bottom) XeCl $\lambda = 308 \text{ nm}$. Figure adapted from manufacturers specifications.¹²⁹

Additionally, our excimer lamps are annular; with a central bore of large enough diameter to accommodate a tubular reactor. The overall design of the lamps can be seen in the lamp schematic (Figure 15)¹²⁹ and photograph (Figure 16).

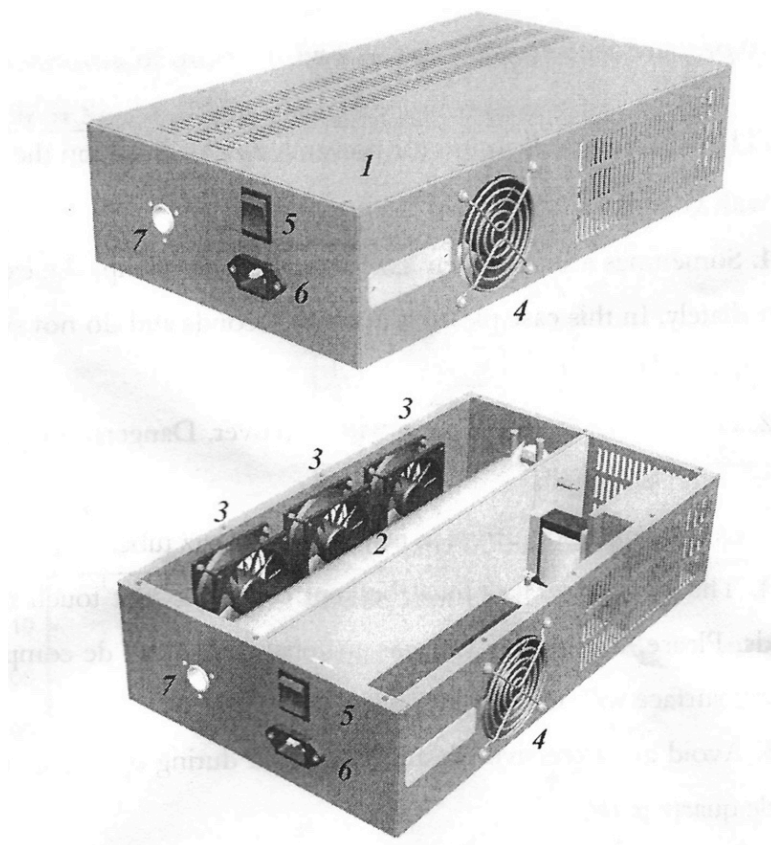


Figure 15: Schematic of the excimer lamps showing the various features, adapted from the manufacturers user manual.¹²⁹ 1: Metal box to shroud UV light. 2: Annular excimer bulb. 3: Fans for cooling outer surface of the lamp. 4: Fan for cooling the lamp electronics. 5: Power Switch. 6: Power supply. 7: Hole allowing for inserting a reactor into the lamp.



Figure 16: Photograph of the XeBr excimer lamp. All three lamps have the same dimensions, with a central lamp bore of 16 mm.

2.3 Design Constraints for the Continuous Flow Excimer System.

Building on the design of the flow reactors in the literature,^{71, 101, 118, 124} there were certain features that I felt were essential to include in a flow photochemical reactor for use with these excimer lamps that would be both efficient and would suit laboratory optimisation scale reactions aimed at generating useful quantities of product. These features were as follows:

- 1.) The reactor must be made from a material transparent to UV light at all three wavelengths of our excimer lamps.

- 2.) The reagent flow must have a short pathlength to minimise inner-filter effects.
- 3.) The system should have a volume large enough to allow for gram quantities of products to be produced but also should be small enough to be used for test reactions without necessitating lengthy equilibration times, leading to excessive waste of reagents.
- 4.) The reagent solution should be as close as possible to the UV light source.
(Ideally no cooling system should come between the lamp and the reagents).
- 5.) The design should allow for the same reactor to be used in all three lamps without disassembly.
- 6.) Ideally the reactor should be quick and relatively inexpensive to build.

2.3.1 Reactor Materials

Borosilicate (pyrex), quartz and fluorinated ethylene propylene (FEP) plastic have all been used as reaction vessels for UV photochemical reactions.⁷¹ The transmission spectrum of pyrex (Figure 17) shows that it would not be suitable for the excimer reactor. Borosilicate absorbs wavelengths of light shorter than 300 nm and would therefore be inappropriate for use with two of the three excimer lamps (222 nm and 282 nm).

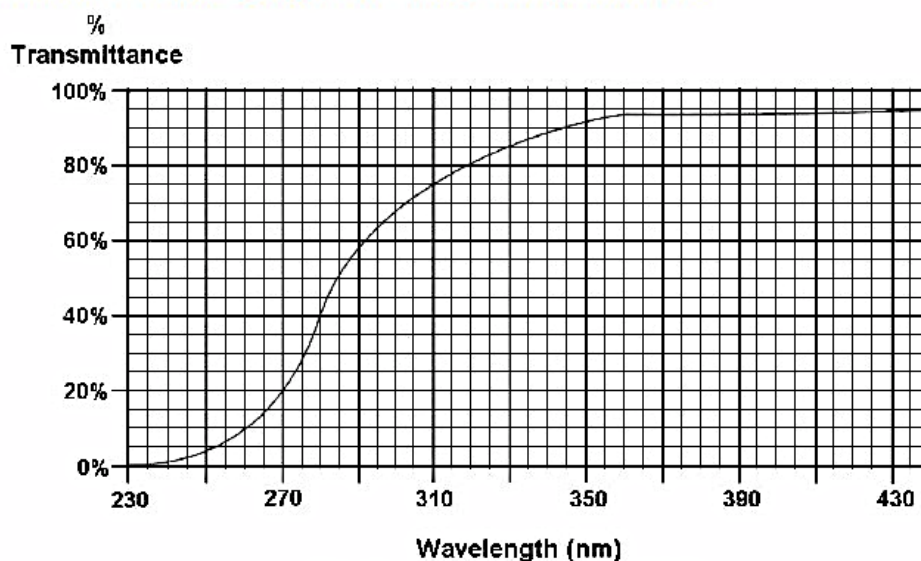


Figure 17: Transmission spectrum of 1 mm wall thickness borosilicate (Pyrex) glass. Figure adapted from the specifications given by Corning.¹³⁰

A simple experiment performed by inserting a thermocouple into one of the lamps (XeBr 282 nm), showed that temperature inside the bore of the lamp had reached 208° C after only 11 minutes (Figure 18). Therefore FEP tubing was also ruled out due to concerns about its thermal stability while in close proximity to the lamp. The maximum operating temperature of FEP plastic tubing is 200° C.¹³¹ Thus, I decided that quartz would be the best material for the excimer reactor as it is not only UV transparent at the wavelengths of our excimer lamps¹³² (Figure 19) but also it is highly resistant to thermal shock due to its low thermal expansion coefficient.¹³³ This means that there is lower risk of the quartz shattering due to a temperature gradient across its surface (i.e. hot on the outer surface due to the lamp and cold inner surface from cold reagent solutions or coolant).

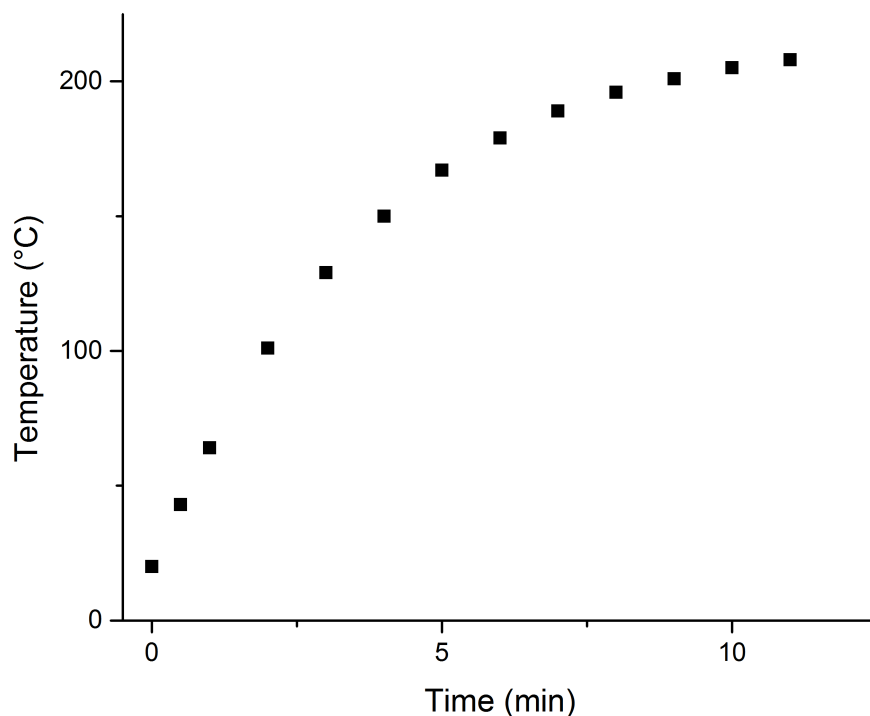


Figure 18: Temperature inside the XeBr lamp while operated without a flow down the centre of the lamp as measured by thermocouple inserted down the central bore.

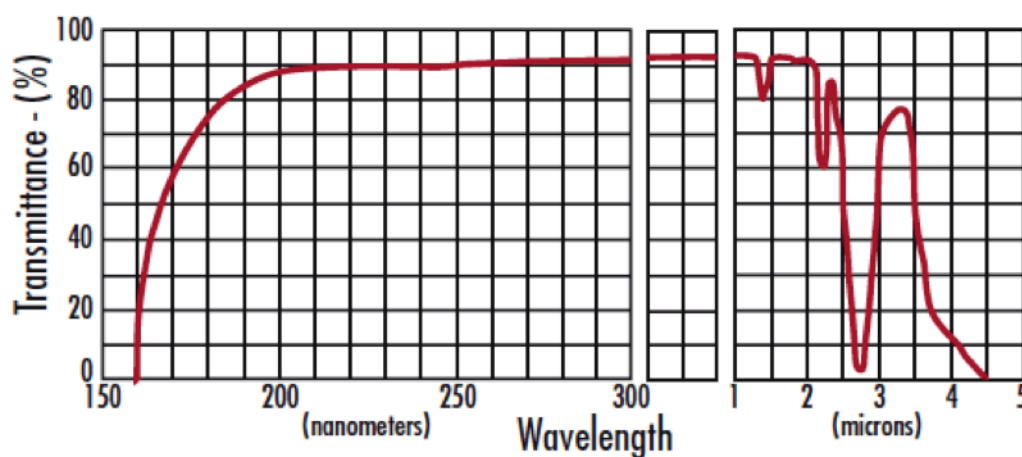


Figure 19: Transmission spectrum of 10 mm wall thickness fused silica (quartz); this is a much thicker sample than is used in the wall of our reactor. Figure adapted from the specifications given by Montana Instruments.¹³²

The temperature monitoring experiment also gave an indication of the operating conditions of the excimer lamps. The experiment was stopped after only 11 minutes to ensure that the lamp did not overheat, and the temperature increase had not fully

stabilised within this time frame. However, it did appear that the operating temperature would finally stabilise far below 600° C, the operating temperature of a typical medium pressure mercury lamp.⁷¹ Despite this, it was still clear that any reactor using these excimer lamps would need a suitable cooling system to be operated safely (well below the boiling point of conventional solvents).

2.4 The Nottingham Excimer Reactor

The final design of the reactor incorporated all of the features listed in Section 2.3. A schematic and photograph of this reactor can be found in Figure 20. The annular reactor consists of an extended quartz test tube that fits snugly over a stainless-steel cold finger. The substrate flow is delivered via a small feed tube (o.d. = $\frac{1}{16}$ "), which runs down the entire length of the cold finger to the sealed end of the quartz tube. The substrate is irradiated as it flows back through the annular gap between the inner wall of the quartz jacket and the outer wall of the cold finger. This gap is approximately 120 microns creating a desirably thin reagent film. The overall dimensions of the reactor give an irradiation volume of approximately 1.37 mL and a total system volume of 10 mL. Pathlength and reactor volume are calculated based on the open end dimensions of the quartz tube and assume that the inner diameter of the quartz tube and outer diameter of the cooling finger are uniform along the irradiation length.

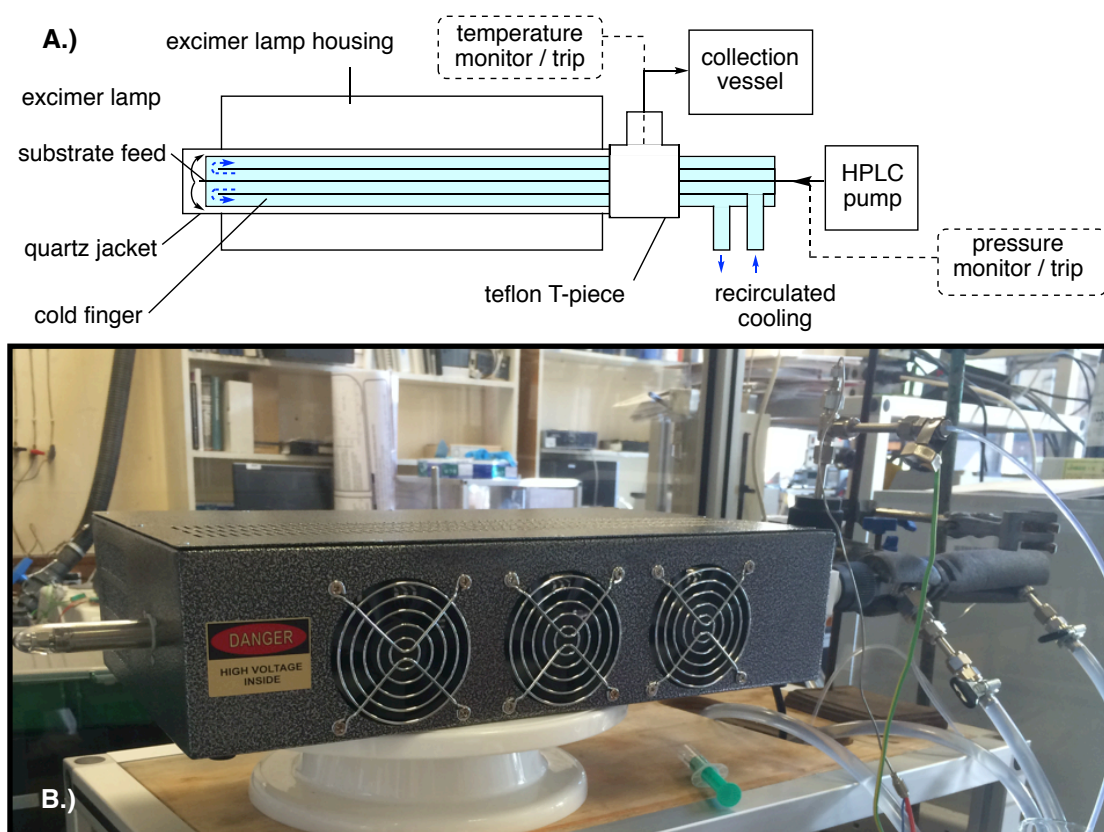


Figure 20: (A) Schematic and (B) photograph of the Nottingham excimer reactor.¹³⁴

The cooling system consists of a pipe inside pipe design (Figure 21). The fact that the cooling system is inside the reactor, rather than between the light source and the reagents, ensures that the substrate and lamp are in close proximity, meaning that the maximum intensity of light is delivered. Additionally, having the cooling media inside the reactor means that the coolant does not have to be UV transparent. This allows one to use coolants with a greater temperature range (i.e. below 0° C) and also to put additives into the coolant to prevent growth of bacteria/algae without consideration of UV transparency of the additives. The flow of the coolant in the reactor does not run in the opposite direction to the reagent flow because diameters of the tubes inside the cold finger meant that less back pressure was created by flowing the coolant in this direction. I did not observe this to negatively affect the ability of the cooling system to remove the heat from the reaction.

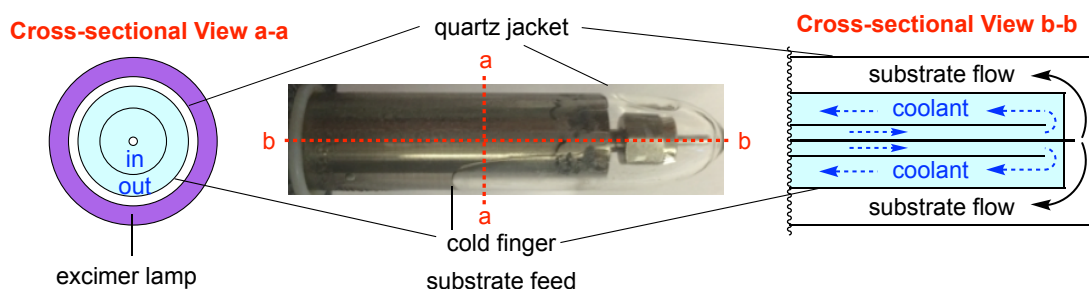


Figure 21: Photograph showing the tip of the reactor. Schematic cross sections show the directions of flow of the cooling system.¹³⁴

As can be seen in the photographs in Figure 20 and Figure 21, the closed end of the quartz tube is completely unfettered by fittings, preserving the slender profile of the quartz tube. This means that the entire reactor system can be removed from one lamp and inserted into a different wavelength lamp without the need to disconnect any fittings, and, thus, without any leakage from the system. Being able to easily remove the reactor from the lamp permitted rapid inspection of the reactor after a photochemical reaction was completed.

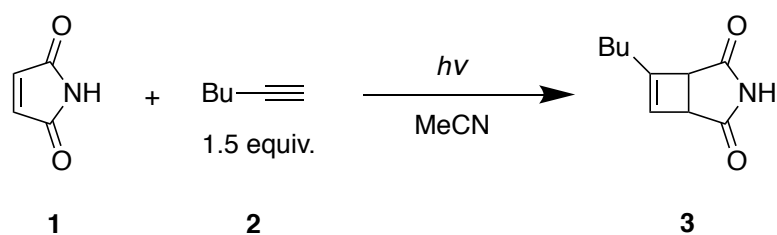
The major part of the reactor is made from standard-sized commercially available materials. The quartz tubes were supplied with the lamps from Russia, however, additional tubes of similar dimensions and quality have more recently been purchased from the UK-based quartz supplier, Robson Scientific, at low cost. The body of the reactor is constructed from Swagelok and Bola fittings and tubing. As these fittings can be redone many times without detrimental effects, in the event of reactor fouling or blockage, the reactor can be fully disassembled for cleaning and easily rebuilt. Furthermore as standard sized Bola and Swagelok fittings were used, the reactor was assembled quickly and replacement parts are simple to obtain with minimal lead-time. The only custom constructed elements of the reactor are three PTFE inserts that slot into the Bola T-piece to reduce dead volume. These were machined in house by the University of Nottingham School of Chemistry workshop. Full details of the reactor can be found in the Experimental Chapter.

2.4.1 Excimer Reactor Safety Features

In addition to making a UV reactor that was efficient, ensuring the safety of its users was of paramount importance. A temperature and pressure monitoring and trip system were incorporated into the design. In the event of run-away heating or excessive build up of pressure (i.e. in the case of a blockage), the trip system cuts off the power to the reagent pump and UV lamp. (N.B. The low clearance in the reactor system does not allow for the temperature inside the irradiation zone to be monitored, rather a thermocouple is placed immediately downstream of the quartz tube. For consistency, the temperatures reported for all reactions in this Thesis are the set-temperatures of the recirculating bath.) The design of the excimer lamps also contributes to the overall safety of the reactor. The lamps are completely enclosed within a metal housing that provides a high degree of shrouding and avoids stray UV light. Furthermore, the tight fit of the reactor inside of the lamp minimises the airflow thereby reducing the generation of potentially toxic ozone. Even so the reactor must be used behind a polycarbonate screen with adequate extraction (i.e a fume cupboard or extracted box). The standard operating procedure can be found in the Experimental Chapter and the HAZOP to ensure safe use of the reactor can be found in Appendix 1.

2.5 Reactor Testing

Once the reactor was built, the next step was to benchmark its performance against the standard reactor in the literature, the Booker-Milburn FEP reactor.¹⁰¹ The [2+2] cycloaddition of maleimide, **1**, and 1-hexyne, **2**, (Scheme 8) had been studied by Booker-Milburn in the FEP reactor^{101, 135} and involves inexpensive commercially available starting materials, making it a suitable test reaction. This reaction follows the classic mechanism for the [2+2] cycloaddition of an enone and olefin as described in Chapter 1.



Scheme 8: [2+2] photocycloaddition of maleimide with 1-hexyne.

2.5.1 Results in the Nottingham Excimer Reactor

For this reaction the crucial maleimide absorption wavelength occurs between 280-300 nm (Figure 22).¹⁰¹ Our experimental conditions were chosen to mirror those used by Booker-Milburn and co-workers in the FEP reactor.¹⁰¹ Therefore, 0.3 M solutions of maleimide in acetonitrile with 1.5 equivalents of 1-hexyne were irradiated in the Nottingham reactor using the XeBr (282 nm) lamp, with the recirculating bath set to 25 °C. (N.B. the temperature of the reaction was not stated for this reaction in the FEP reactor.)¹⁰¹

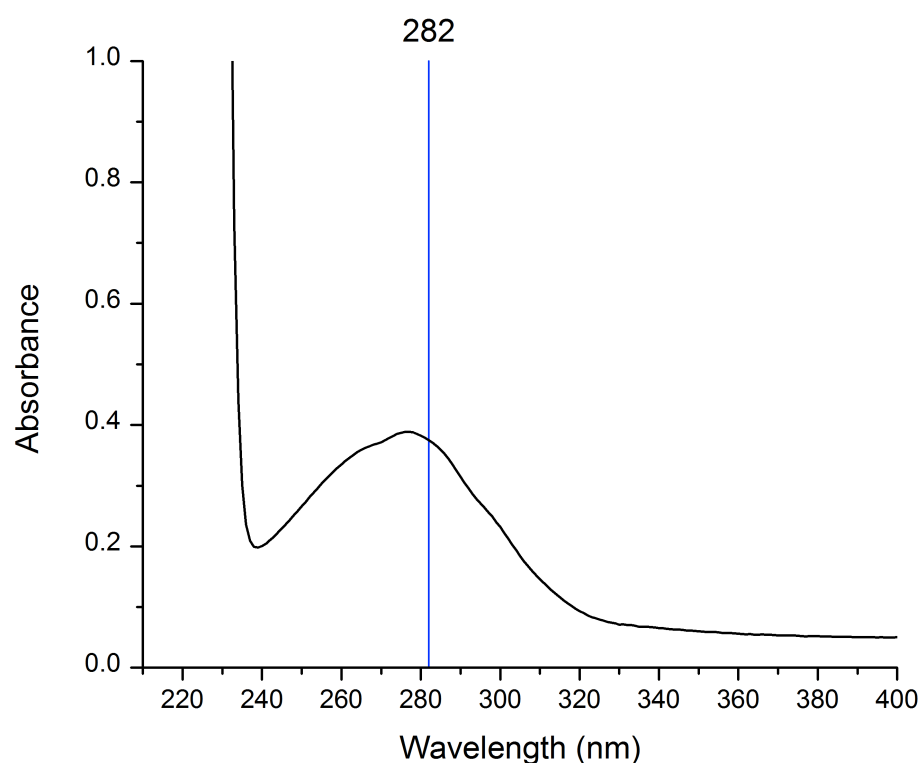


Figure 22: UV-Vis absorption spectrum of 5×10^{-3} M solution of maleimide in acetonitrile (pathlength = 1 mm).

Conversions were measured by ^1H NMR integration and are presented in Table 2, full experimental details can be found in the Chapter 6 – Section 6.3.1. As the FEP reactor and Nottingham reactor have very different volumes, adjustments must be made, to obtain a fair comparison between the two reactors. Space-time yield (STY) is a measure of the amount of product that can be generated per unit time, per unit volume of a reactor, Equation 7. As no external standard was added to the ^1H NMR samples for these initial test reactions, yield was assumed to be equal to conversion, therefore, the results obtained are qualitative rather than quantitative. The objective of this experiment was to see if full conversion in the excimer reactor was achieved, assuming to the desired product, would the STY be similar to that of the FEP reactor or would a significant redesign necessary, consequently measurement of conversion provided enough data for our purposes.

Equation 7: Equation for STY (irradiation volume for the excimer reactor is 1.37 mL)

$$STY = \frac{\text{Concentration} \times \text{Flow Rate} \times \text{Yield} \times \text{Molecular Mass of the Product}}{\text{Reactor Irradiation Volume}}$$

Table 2: Comparison of the FEP reactor to the excimer reactor for the [2+2] photocycloaddition of maleimide (0.3 M) and 1-hexyne in acetonitrile.

Reactor	Flow Rate (mL min ⁻¹)	Residence Time (min)	Conversion to 3	Space Time Yield of 3 (g mL ⁻¹ h ⁻¹) *Based on NMR Conversions
FEP Reactor (Vycor Glassware) ¹⁰¹	6.0	46.7	88% ¹⁰¹	0.061
Nottingham Excimer Reactor	0.2	10	97%	0.31

Under optimised conditions for this reaction the FEP reactor was run using a flow rate of 6 mL min⁻¹. With the 280 mL reactor volume this leads to a residence time of approximately 47 minutes and a corresponding STY of 0.061 g mL⁻¹ h⁻¹.¹⁰¹ In order for the comparison between the two reactors to be reasonable, the conditions used for both reactors should result in a similar degree of conversion, as higher throughput can lead to higher STYs but with lower overall conversion (this is discussed further in Chapter 3) In the excimer reactor, near full conversion, appropriate for comparison with the FEP reactor, was achieved when the flow rate was 0.2 mL min⁻¹. Under these conditions, the excimer reactor had a STY approximately 5 times that of the FEP reactor. This demonstrates the suitability of the reactor design and indicates that it could be used for further photochemical reactions without modification.

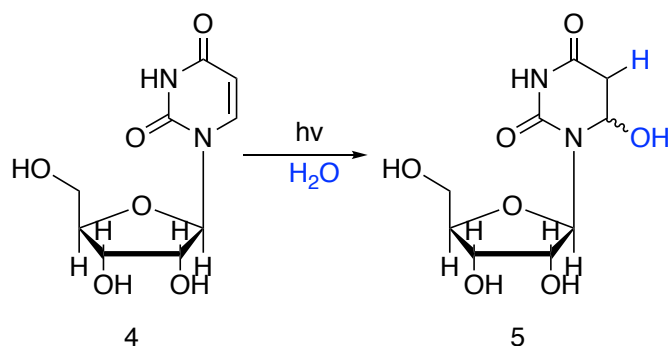
2.6 Monitoring the Spectral Irradiance of the Excimer Lamps by Chemical Actinometry

The initial test experiments revealed no serious design flaws with the excimer reactor and therefore it appeared that the design described in Section 2.4 could be used for additional photochemical studies. Although excimer lamps containing the same gas mixtures as those purchased by our research group (KrCl, XeBr and XeCl) have been shown to retain their emission performance for more than 4000 hours of use, all lamps have a finite lifetime.^{136, 137} Hence, creating a methodology for monitoring the spectral irradiance, a measure of the number of photons emitted at a given wavelength by the surface of a light source per unit area, of the excimer lamps was important. Prior to being shipped from Russia, the manufacturer's of our excimer lamps had measured the spectral irradiance by reflecting the light from a small section of the lamp onto a foil and measuring the photon flux of the reflected light with a HAMAMATSU H8025-222 photo detector. This value was then appropriately scaled to reflect the photon flux emitted by the entire surface of the excimer lamps. An appropriate photo detector to make similar measurements of spectral irradiance for the excimer lamps was not available.¹³⁸ However chemical actinometry, where a photochemical reaction induces a change (e.g. in the spectra of the compound), represents an alternative way of calculating the photon flux, since the photochemical conversion is proportional to the number of photons that enter the system.¹³⁹

2.6.1 Uridine Actinometry for Measuring the Spectral Irradiance of the KrCl (222 nm) and XeBr (282 nm) Excimer Lamps.

When aqueous solutions of uridine, **4**, are irradiated with UV light of a wavelength that can be absorbed, the photohydrate of uridine, **5**, is formed (Scheme 9).¹³⁸⁻¹⁴² The photo reaction transforms the α,β -unsaturated carbonyl moiety of **4** to an α,β -saturated carbonyl moiety in the photohydrate, **5**.¹³⁸ This results in the loss of the UV absorbance peak centred at approximately 260 nm (Figure 23) relating to the $\pi \rightarrow \pi^*$

of the uridine α,β -unsaturated carbonyl.^{138, 142} The other absorbance peak in the uridine UV-Vis absorption spectrum centred at 205 nm, is due to the overlap of transitions from the $\pi \rightarrow \sigma^*$ /Rydberg mixed orbitals and $\pi \rightarrow$ Rydberg orbital.¹⁴³



Scheme 9: Irradiation of uridine in aqueous solution results in the loss of the α,β -unsaturated carbonyl moiety by photo-degradation to compounds such as the corresponding photohydrate.

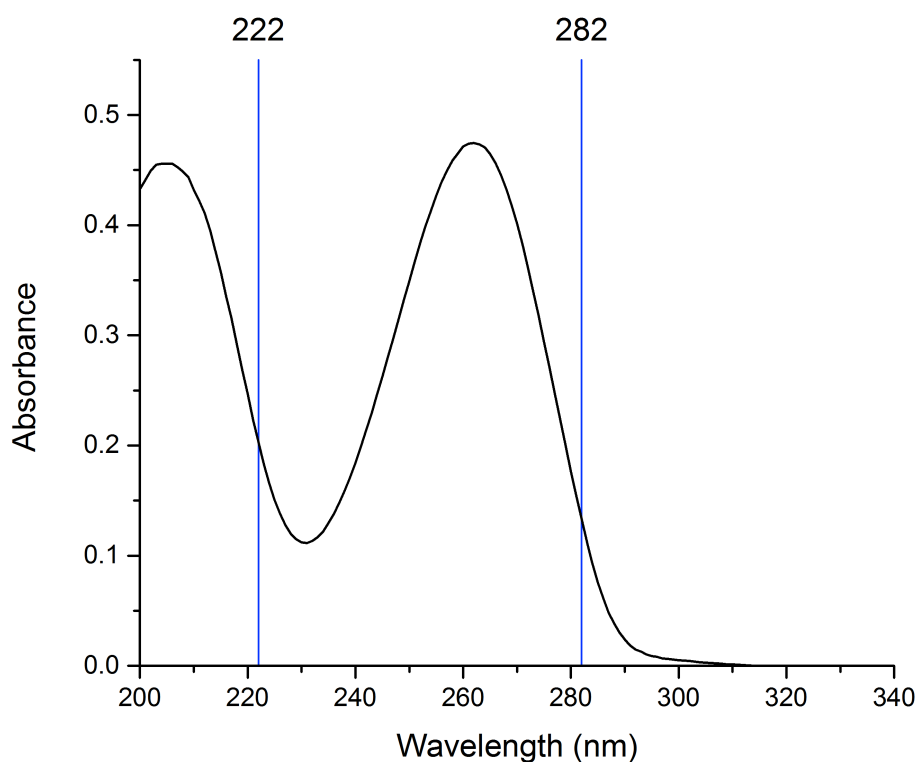


Figure 23: UV-Vis absorption spectrum of a 0.011 mM solution of uridine in water (pathlength = 4 cm).

The number of photons emitted by the lamp per unit time can be calculated using Equation 8, where the dA/dt term is the change in the absorbance of the chemical

actinometer at a given wavelength over the change in irradiation time, N_A is Avagadro's constant, V is the irradiation volume, Φ is the quantum yield of the reaction at the wavelength of lamp emission, ϵ is the extinction coefficient at the monitored absorption wavelength and l is the pathlength of absorbance.¹⁴⁴ Zhang *et al.* had successfully used uridine as a chemical actinometer for measuring the spectral irradiance of a KrCl (222 nm) excimer lamp,¹³⁸ and the literature¹³⁹ and UV-Vis absorbance spectrum of uridine (Figure 23) suggested that it would also be an appropriate chemical actinometer for the XeBr (282 nm) lamp. Using uridine as the actinometer species and plotting the change in absorbance peak at 262 nm versus irradiation time gives the dA_{262}/dt term as the slope of the line of best fit. The other values necessary to solve Equation 8 can be found in Table 3.

Equation 8: Equation for using chemical actinometry to calculate the number of photons emitted by a monochromatic light source per second, where dA/dt is the change in the absorbance of the chemical actinometer at a given wavelength over change in irradiation time, N_A is Avagadro's constant, V is the irradiation volume, Φ is the quantum yield of the reaction at the wavelength of lamp emission, ϵ is the extinction coefficient at the monitored absorption wavelength and l is the pathlength of absorbance

$$q_p = \left(\frac{dA_{\lambda_{abs}}}{dt} \right) \frac{N_A V}{\Phi_{\lambda_{lamp}} \epsilon_{\lambda_{abs}} l}$$

Table 3: Values for solving Equation 8 for uridine actinometry at 222 nm and 282 nm.

Equation Symbol	Numerical Value For Solving Equation 8
V (Irradiation Volume)	1.37 cm^3
Φ_{222} (Quantum Yield at 222 nm) ¹³⁸	0.034
Φ_{280}^* (Quantum Yield at 280 nm) ¹³⁹	0.016
ϵ_{262} (Extinction Coefficient at 262 nm) ¹⁴⁵	$9900 \text{ dm}^3 \text{ M}^{-1} \text{ cm}^{-1}$
l (Absorbance Measurement Pathlength)	4 cm

*Quantum yield at 282 nm assumed to be the same.

2.6.1.1 Results of Uridine Actinometry

All results for excimer lamp actinometry presented in the following sections were obtained in collaboration with fellow research group member Inès Penders.¹⁴⁶ A dilute aqueous solution (0.011 mM) of uridine was irradiated with either the KrCl or XeBr lamp in the excimer reactor for increasing lengths of time (between 18 and 48 seconds) by altering the flow rate of the uridine solution through the reactor. A sample was taken after irradiation at each flow rate and the UV-Vis absorption spectrum was recorded. The experiment was repeated three times for each flow rate (irradiation time). Monitoring the UV-Vis absorption spectra showed decay in the peak at 262 nm with increasing irradiation time as **4** was converted to **5** at both irradiation wavelengths (Figure 24, A and B). Further experimental details can be found in Chapter 6 – Section 6.3.2.

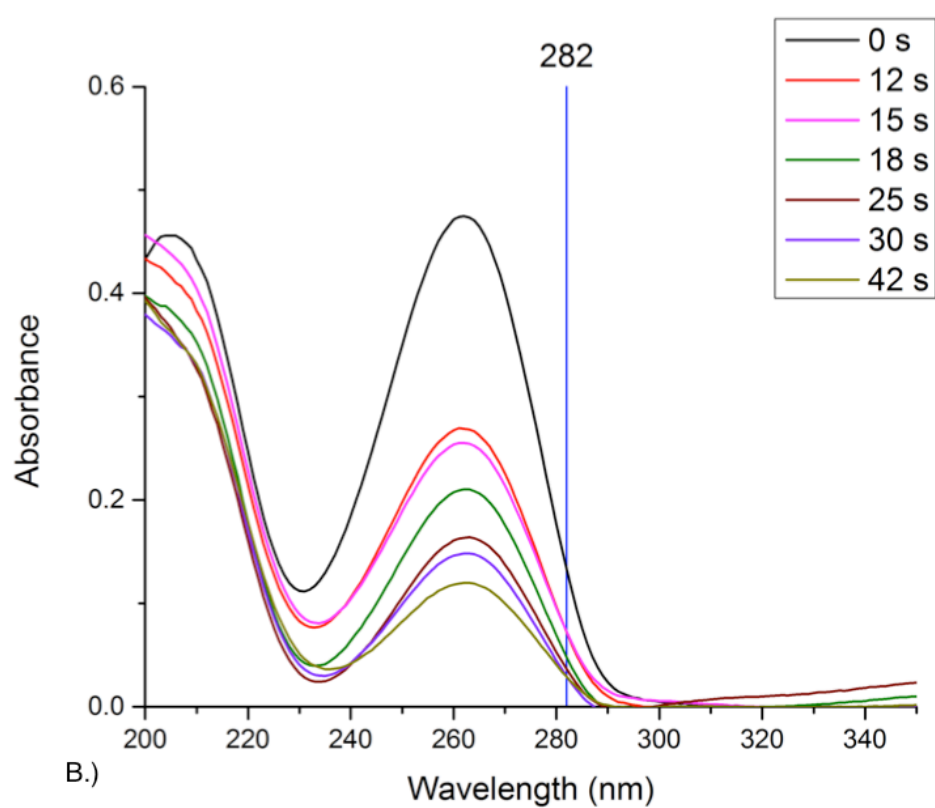
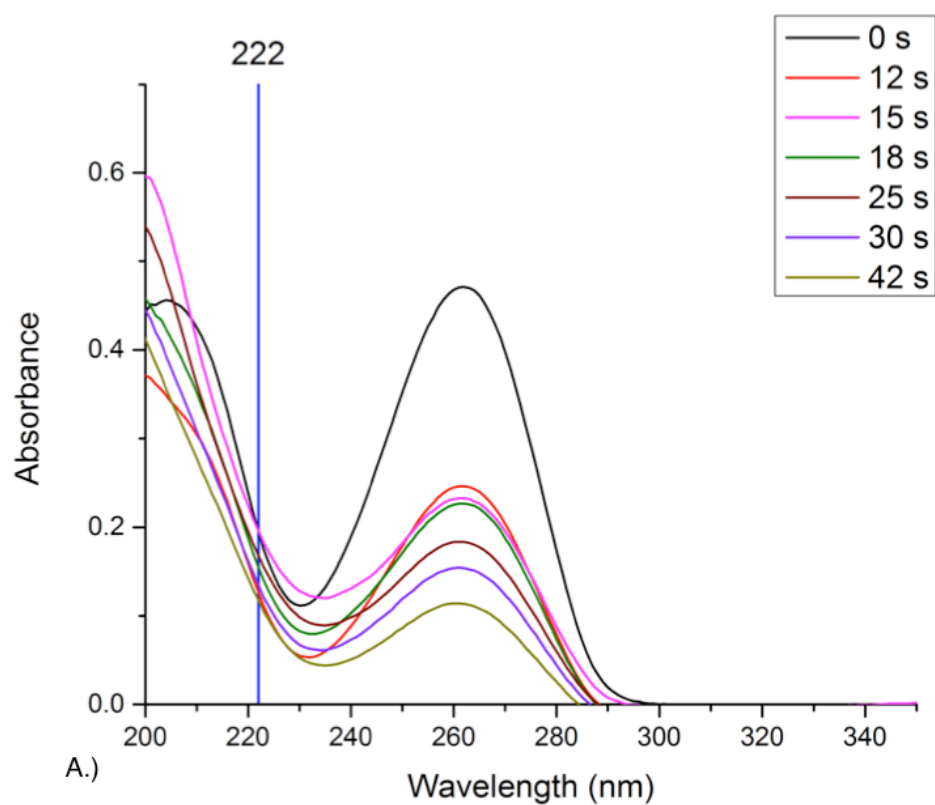


Figure 24: (A) UV-Vis absorption spectra of uridine solutions after irradiation with 222 nm light and (B) after irradiation with 282 nm light.

The change in absorbance versus the irradiation time was plotted for each of the three triplicate runs at both irradiation wavelengths (scatter plots can be found in Appendices 2.1 and 2.2). A high degree of linearity was obtained for irradiation with the 282 nm excimer lamp. Irradiation with the 222 nm excimer lamp by contrast showed some deviation from linearity with different rates of change in absorbance for short and long irradiation times. This is likely due to the fact that compound **5** also absorbs 222 nm light as evidenced by the fact that the peak at 205 nm does not decay nearly as rapidly as the absorption peak at 260 nm. Therefore, the competitive absorption of 222 nm by compound **5** would leave fewer photons available to be absorbed by **4** and therefore to induce the reaction of **4** → **5**. This in turn could result in reduced reaction rates when higher concentrations of **5** are present and would explain the results obtained.

Prior to performing the actinometry measurements the lamps had been used for less than 100 hours, far less than 4000 hours, the suggested lifetime of excimer lamps with these gas mixtures. Consequently, we were confident that the lamps were still working with the same spectral irradiance as specified by the manufacturers. Instead, the main goal of performing this actinometry was to have a method for being able to detect loss of lamp performance, rather than using it to precisely measure the spectral irradiance. Considering this, we decided that the slight deviation from linearity in the 222 nm measurements was not problematic for our calculation of spectral irradiance.

The equation for calculating the number of photons emitted by a light source (Equation 8) assumes that all of the light emitted by the lamp is absorbed by the actinometer solution. In order to absorb all of the light in the excimer reactor it would be necessary to use very concentrated uridine solutions. This can result in uridine dimerisation, which interferes with the accuracy of the actinometry.^{139, 147} Instead, the

proportion of light transmitted through the solution at the beginning of the reaction was calculated using Equation 9 and the values given in Table 4.

Equation 9: Variation of the Beer-Lambert law for calculating the light transmitted through a solution, where %T is percentage light transmitted, ϵ is the extinction coefficient at the lamp irradiation wavelength, c is actinometer concentration and l is pathlength through the actinometer solution in the excimer reactor.

$$\%T = 10^{\epsilon_{\lambda_{lamp}} c l}$$

Table 4: Values for solving Equation 9 for uridine actinometry at 222 and 282 nm.

Equation Symbol	Numerical Value For Solving Equation 9
ϵ_{222} (Extinction Coefficient at 222 nm) ¹³⁸	3150 dm ³ M ⁻¹ cm ⁻¹
ϵ_{282} (Extinction Coefficient at 282 nm)*	2650 dm ³ M ⁻¹ cm ⁻¹
c (Uridine Concentration)	0.011 mM
l (Reactor Pathlength)	0.012 cm

*Experimentally measured, calibration curve can be found in Appendix 2.3.

The number of photons emitted per second by the lamps was calculated for each of the three experiments at both irradiation wavelength using Equation 8. The values were then scaled accordingly using Equation 10. This correction assumes that the absorbance of the actinometer solution is constant at the irradiation wavelength over the course of the reaction, which of course it is not. However, considering the objective of the actinometry, we did not feel that a more accurate correction factor that accounted for the absorbance gradient of the actinometer solution was necessary.

Equation 10: Equation for the corrected photon flux where $q_{p_{total}}$ is the corrected photon flux, q_p is the uncorrected photon flux calculated by Equation 8, and T is transmittance as calculated by Equation 9.

$$q_{p_{total}} = \frac{q_p}{(1 - T)}$$

The average of the three corrected values for photon flux for each lamp obtained through uridine chemical actinometry for both lamps are similar to value given in the

manufacturer's specifications (differences $\leq 18\%$). However, the experimental values are larger than the given photon fluxes. In correcting for the light transmitted through the solution, the assumption was made that any photons not absorbed by the uridine solution were absorbed by the cold finger, and no longer available for chemical reaction. However, it is possible for a polished stainless steel-surface to reflect nearly 40% of 222 nm and 282 nm photons. Although the stainless steel cold-finger is periodically polished, at the time of the actinometry measurements the reactor had been used for approximately 100 hours without polishing, which would account for the measured values of spectral irradiance being somewhat less than 140% (100% from the lamp + up to 40% reflectance by the stainless steel) at 118% and 111% respectively for the 222 nm and 282 nm excimer lamps.

2.6.2 Azobenzene Actinometry for Measuring the Photon Flux of the XeCl (308 nm) Excimer Lamp

As uridine does not absorb at 308 nm (Figure 24) it is not an appropriate chemical actinometer for calculating the photon flux of the XeCl lamp. Azobenzene by contrast is a chemical actinometer suitable for calculating the photon flux for wavelengths between 230 and 460 nm, as it absorbs across these wavelengths (Figure 25).¹³⁹ Absorption of a photon of UV light can result in the trans-cis isomerisation of azobenzene (Scheme 10), which in turns leads to the depletion of the absorbance band at 317 nm.^{148, 149} By monitoring the decay of this band the photon flux can be calculated as described in the previous section.

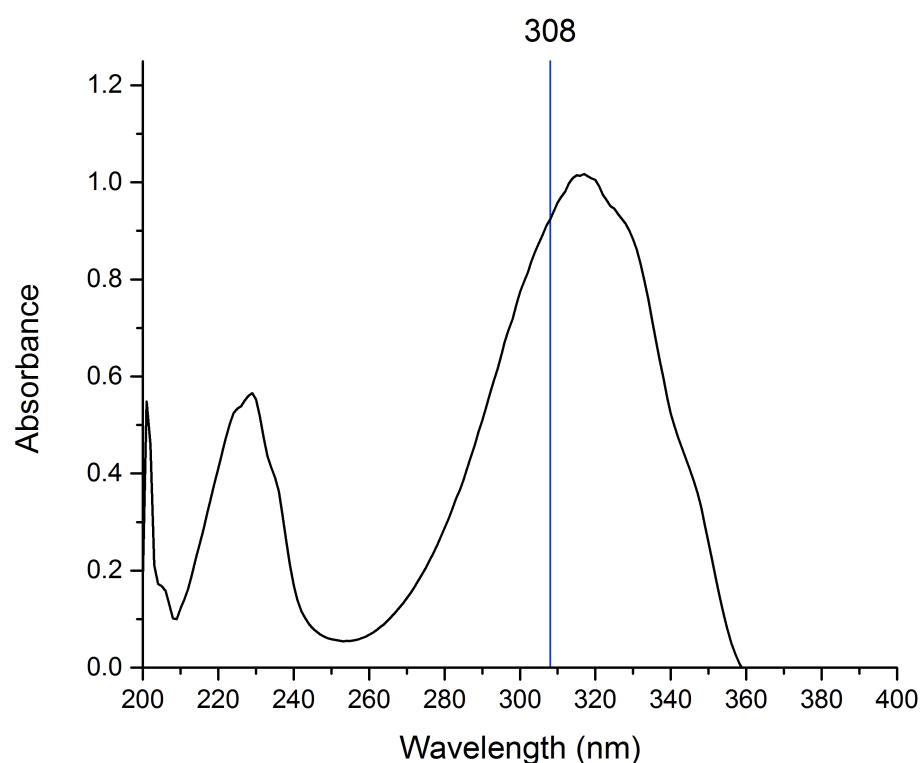
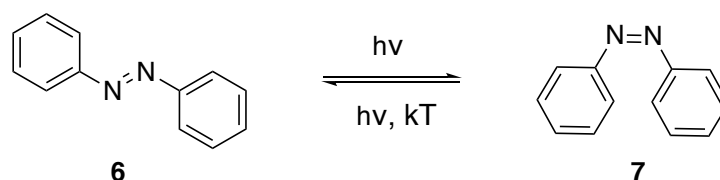


Figure 25: UV-Vis absorption spectrum of a 5×10^{-5} M solution of azobenzene in methanol (pathlength = 1 cm).



Scheme 10: Trans-cis isomerisation of azobenzene resulting from UV irradiation.¹⁵⁰

2.6.2.1 Results of Azobenzene 308 nm Actinometry

Azobenzene actinometry is more complex than uridine actinometry as cis-azobenzene, **7**, can isomerise back to trans-azobenzene, **6**, both photochemically upon continued irradiation and thermally. Our protocol was adapted from that of Gauglitz *et al.*¹⁴⁸ Concentrated (0.1 M) solutions of azobenzene in methanol were irradiated at 15 °C with fast flow rates (irradiation times between 4.5 and 6.0 seconds) to ensure the overall conversion was less than 15%. By utilising concentrated solutions where >99% of the light was absorbed, no correction of

calculated photon flux would be necessary.¹⁴⁸ A lower reaction temperature, and low overall conversion were used in an attempt to minimise the back reaction of *cis* azobenzene → *trans* azobenzene, which would interfere with the actinometry.^{148, 150}

Representative UV-Vis absorption spectra collected as a function of irradiation time collected for one of three replicate experiments is presented in Figure 26. Increased irradiation time results in the decay of the absorbance peaks at both 229 and 317 nm.

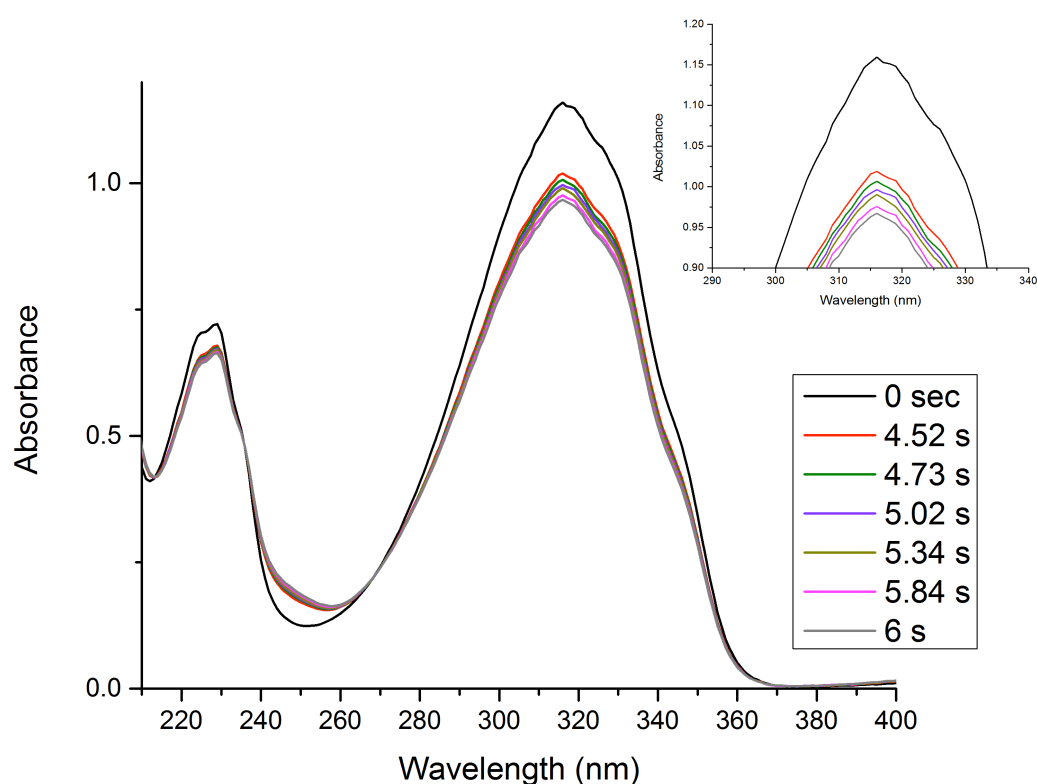


Figure 26: UV-Vis absorption spectra of methanol solutions of azobenzene as a function of irradiation time (308 nm irradiation). Inset shows a zoomed in view of the 290 to 340 nm region of the spectra.

The decay in the peak at 317 nm was used to calculate the photon flux, by plotting the change in absorbance at this wavelength versus irradiation time (plots can be found in Appendix 2.4). An acceptable degree of linearity was obtained and therefore the slope of the line of best fit was used to calculate the photon flux using Equation 8 and the values shown in Table 5.

Table 5: Values for solving Equation 8 for azobenzene actinometry at 308 nm.

Equation Symbol	Numerical Value For Solving Equation 8
V (Irradiation Volume)	1.37 cm ⁻³
Φ_{308} (Quantum Yield at 308 nm) ¹³⁹	0.14
ϵ_{317} (Extinction Coefficient at 317 nm)*	21180 dm ³ M ⁻¹ cm ⁻¹
l (Absorbance Measurement Pathlength)	50 μ m

*Calculated experimentally. Calibration curve can be found in Appendix 2.4.

Unfortunately, relative to the manufacturer's specifications, the photon flux calculated for the XeCl lamp via azobenzene actinometry was only 19.5%. Although overall conversion was less than 15% even at the longest irradiation time, it is possible that photochemical re-isomerisation was taking place. Gauglitz *et al.* kept conversion below 5% in their azobenzene actinometry experiments.¹⁴⁸ Unfortunately, in the excimer reactor, using even shorter irradiation times and thus obtaining only conversions below 5% was not possible. The fast flow rates used to keep conversion below 15% were already generating a backpressure within the excimer reactor. Using even faster-flow rates would have meant operating the excimer reactor at potentially unsafe conditions.

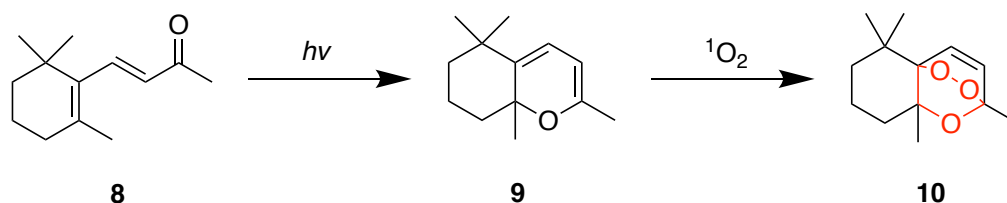
Additional error in the photon flux calculated by azobenzene actinometry might have been due to thermal cis→trans isomerisation. The temperature of the azobenzene solution was controlled whilst inside the reactor, however, it can warm to ambient temperatures in the reactor's exit tube. Despite the large discrepancy between the obtained and given value for the photon flux of the XeCl lamp, it is likely that if the same protocol was used for future calculations of photon flux, they would reflect any loss of lamp performance when compared to the value we obtained for photon flux of the 308 nm excimer lamp using azobenzene chemical actinometry. We therefore did not feel it was the best use of time to perform additional actinometry for the XeCl

lamp, and instead using the excimer reactor for other photochemical transformations would be better.

2.7 Photochemical Isomerisation of β -Ionone Toward a Multi-Step Continuous Flow Process

Traditionally, batch organic chemical processes are performed in a step-wise fashion with purification of products after each step. Performing chemistry in this way is both time consuming and can generate significant quantities of waste.^{112, 151} Instead by doing reactions in continuous flow it is possible to integrate multiple subsequent reaction steps from a single reagent stream, resulting in savings of both time and waste.^{152, 153} Reagent-less reactions, such as UV photochemical reactions, are particularly suited to this type of telescoped synthesis as they do not require additional reagents, which may be incompatible with later steps in the synthetic process.¹⁵⁴

The photochemical 6π electro-cyclisation of β -Ionone, **8**, to the α -pyran containing product **9** is a well-studied UV photochemical reaction (Scheme 11).¹⁵⁵⁻¹⁶² More recently it was demonstrated that the α -pyran moiety of compound **9** can undergo reaction with singlet oxygen¹⁶³⁻¹⁶⁶ generating the 1,2,4-trioxane functionality that is the pharmacore of the artemisinin anti-malarial molecule (Scheme 11, shown in red).^{163, 164, 167}



Scheme 11: The UV 6π electrocycloisalisation of β -Ionone, followed by reaction with singlet oxygen to give the 1,2,4-trioxane core shown in red.

2.7.1 Photochemical Generation of Singlet Oxygen

Singlet oxygen can be generated using visible light and an appropriate photosensitiser.¹⁶⁸⁻¹⁷¹ The photosensitiser absorbs the light and becomes excited to the singlet-excited state. Intersystem crossing can then occur giving the photosensitiser in its longer-lived triplet-excited state.¹⁶⁸ Once the excited triplet state of the photosensitiser is formed, there are two possible mechanisms for the generation of the reactive oxygen species. In a Type I mechanism, the excited photosensitiser interacts with an organic substrate generating free radicals, which react with ground state oxygen. In the Type II mechanism the triplet photosensitiser can then excite molecular oxygen from the triplet ground state to the singlet excited state via energy transfer (Figure 27).¹⁶⁸⁻¹⁷⁰ Other methods for producing singlet oxygen are outside the scope of this Thesis.

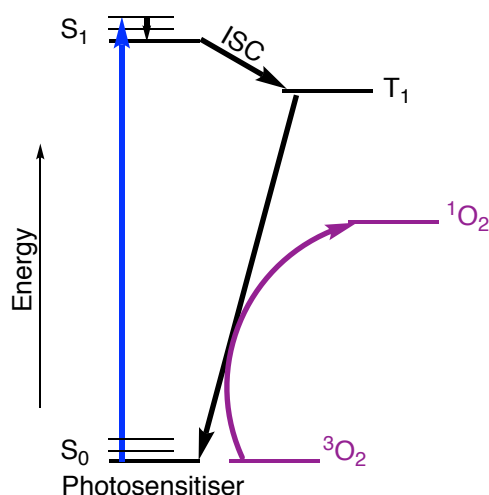


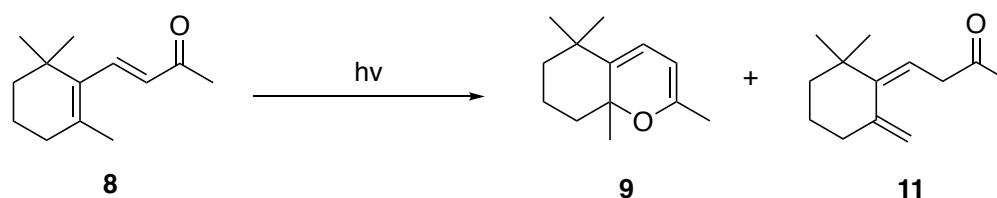
Figure 27: Jablonski diagram depicting Type II singlet oxygen photosensitisation. The photosensitiser absorbs a photon of light promoting an electron to the singlet-excited state. The triplet excited state of the sensitiser is formed through inter-system crossing, which excites ground state triplet oxygen to singlet oxygen via energy transfer. Adapted from Bonnett.¹⁷²

Prior to the start of this Thesis, our research group had designed two continuous flow reactors capable of performing photo-oxygenation with singlet oxygen generated by visible light and an appropriate photosensitiser.¹⁷³⁻¹⁷⁷ Furthermore, one of these reactors was used to perform the photo-oxygenation of dihydroartimisinic acid to give

the anti-malarial drug artemisinin.¹⁷⁶ Therefore, generating product **10** from inexpensive β -Ionone utilising the Nottingham excimer reactor, and Nottingham sapphire tube visible light singlet oxygen reactor, represented an interesting model reaction that would tie into the group's previous work. Naturally, optimising the first step, the UV photochemical 6π electro-cyclisation of β -Ionone, was key to the overall success of an integrated multi-step reaction.

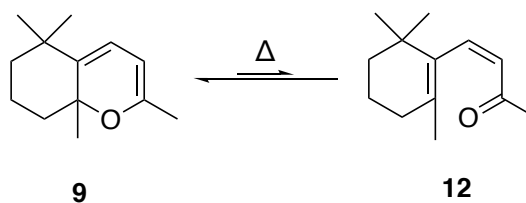
2.7.2 The Photochemical 6π Electro-cyclisation of β -Ionone

When β -Ionone is irradiated, in addition to the electro-cyclisation product **9**, a [1,5] sigmatropic hydrogen shift can also occur yielding the undesired side product compound **11** (Scheme 12).¹⁶¹ The desired photoproduct, **9**, is reported to form from the triplet excited state of β -Ionone whereas compound **11** is thought to be formed from the singlet excited state, since photolysis with a triplet sensitizer yielded only compound **9**.^{158, 178, 179}



Scheme 12: Irradiation of β -ionone gives two products, the α -pyran derivative, **9, and Z-retro- γ -ionone, **11**.**

The 6π electro-cyclization products of oxygen containing systems have low activation energies toward the back reaction; meaning that the formation of a (2*H*)-pyran is a highly reversible process.¹⁸⁰ This means that the α -pyran cyclised product **9** will be in equilibrium with the ring opened Z-isomer of β -ionone, compound **12** (Scheme 12).



Scheme 13: Photoproduct 9 is in thermal equilibrium with the ring-opened product 12.

The literature has suggested that the position of the equilibrium between products 9 and 12 is strongly temperature dependant.^{156, 179} The temperature dependence of the equilibrium was investigated further using variable temperature ¹H NMR (Figure 28). Comparing the peak area ratios for compound 9 and 12 showed that higher temperatures favour the ring-opened product, 12 (

Table 6).

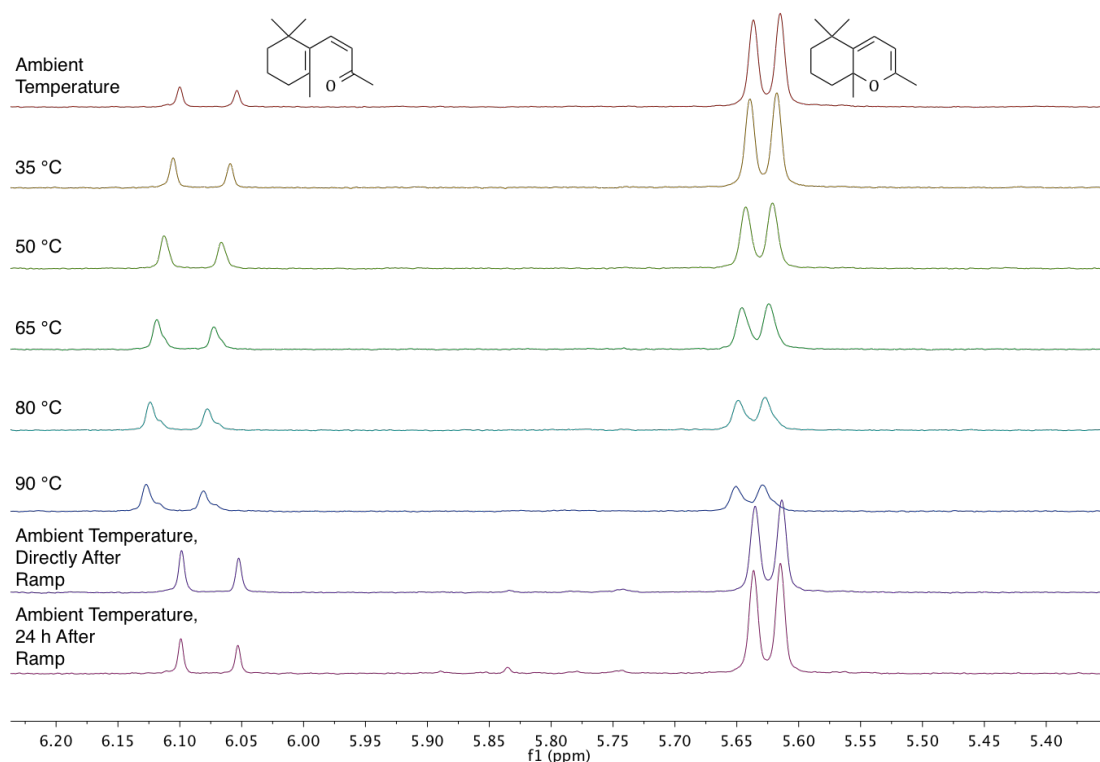


Figure 28: Comparison of a ¹H NMR peak for compound 9 to a peak for compound 12 at various temperatures in D₆-DMSO

Table 6: Comparison of the peak area ratios for 9 : 12 at different temperatures.

Temperature (°C)	Ratio 9 : 12
Ambient	1 : 0.14
35	1 : 0.22
50	1 : 0.38
65	1 : 0.51
80	1 : 0.67
90	1 : 0.87
Ambient directly after temperature ramp	1 : 0.31
Ambient 24 h later	1 : 0.21

Variable temperature ^1H NMR was recorded in D_6 -DMSO

Kurata *et al.*¹⁸¹ stated that utilising a pyrex filter ($\lambda > 300$ nm) while irradiating solutions of β -ionone led only to the formation of **9**, the α -pyran containing product. In the excimer system, rather than using a filter, irradiating with the XeCl lamp (308 nm) should achieve the same result (no photons of wavelengths shorter than 300 nm). Measuring the UV-Vis spectrum of β -ionone in ethanol (Figure 29) and measuring the extinction coefficients of β -ionone at each available excimer wavelength (Table 7), showed that although absorbance at 282 nm is the highest, absorbance at 308 nm is nearly as high (calibration curves can be found in Appendix 2.6). Ethanol was chosen as the reaction solvent as it had been used previously for this reaction and is an environmentally acceptable solvent.^{158, 182, 183}

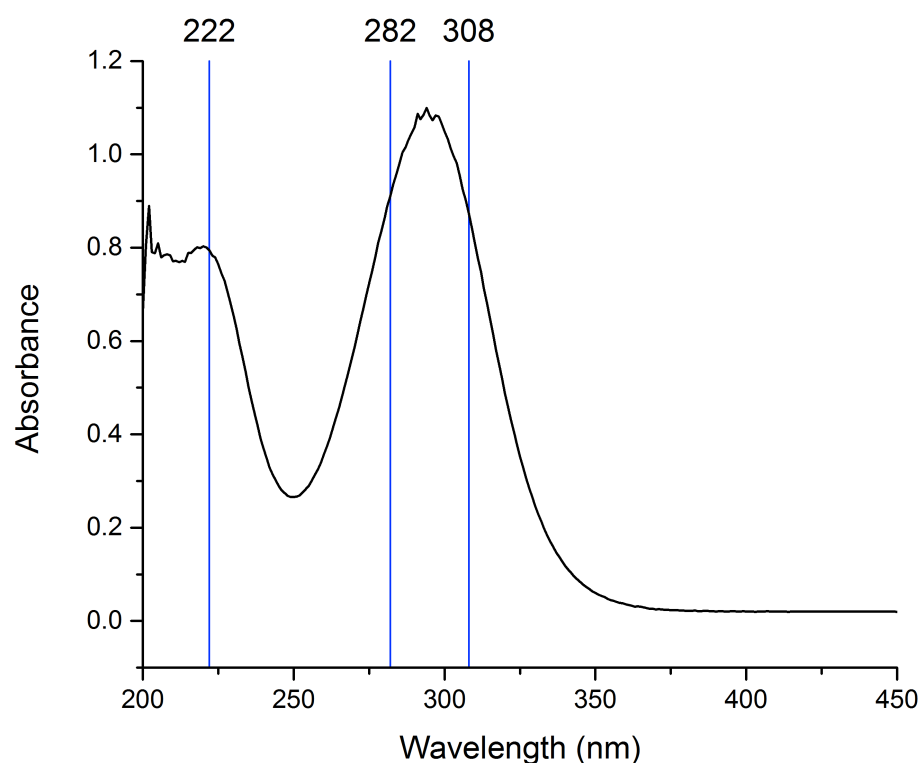


Figure 29: UV-Vis absorption spectrum of 1.1×10^{-4} M solution of β -ionone in ethanol showing the three excimer lamp wavelengths (pathlength = 1 cm).

Table 7: Extinction coefficients of β -ionone at the available excimer wavelengths.

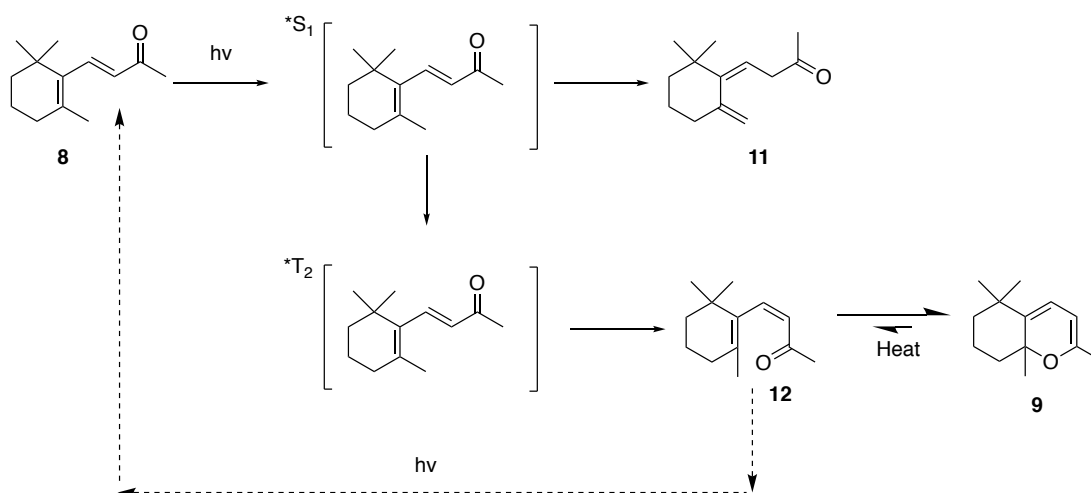
Wavelength (nm)	Extinction Coefficient ($\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$)
222	6420
282	7850
308	7760

Solutions of β -ionone in ethanol (0.1 M) were irradiated utilising the 308 nm (XeCl) excimer lamp. For each set of reaction conditions conversions were measured by ^1H proton NMR integration. As products **9** and **12** are in thermal equilibrium (Figure 28) selectivity for these two compounds are given together, to account for any changes in selectivity that might have been due to differences in the ambient temperature.

Table 8: The effect of flow rate on the irradiation of 0.1 M solutions of β -ionone in ethanol. Conversion and selectivity were measured by ^1H NMR integration.

Flow Rate (mL min ⁻¹)	Conversion	Selectivity 9 + 12	Selectivity 11
0.05	84%	27%	73%
0.1	78%	51%	49%
0.2	72%	69%	31%
0.5	68%	83%	17%
1.0	53%	86%	14%
1.2	33%	90%	10%
1.5	17%	95%	5%

The results (Table 8) showed that the combined selectivity for compounds **9** and **12** decreases as conversion increases. Furthermore even utilising a very long residence time did not result in full conversion. This can likely be explained by considering the overall reaction pathways and reactivity of the photoproducts (Scheme 14). When β -ionone is irradiated directly with UV light, the singlet-excited state will be formed and compound **11** can be formed from this excited state. However, singlet state lifetimes are short, and it is also possible for decay to occur from the singlet excited state to the triplet excited state before **11** is formed. The photoproduct, **9**, can be generated from the triplet excited state. However, photoproduct **9** is in a temperature dependent equilibrium with product **12**, *Z*- β -ionone. Under continued irradiation, *Z*- β -ionone can undergo photochemical *cis*→*trans* isomerisation to reform the starting material, **8**. Considering this, it is unsurprising that conditions that gave high overall conversion of the starting material did not give high selectivity for products **9** and **12**. The results from reactions with low conversion suggest that product **9**, is formed with a higher quantum yield than product **11** although additional studies would be necessary to confirm this hypothesis.



Scheme 14: Reaction pathways for the irradiation of β -ionone, showing the reformation of the starting material from the continued irradiation of product 12.

A temperature study at a flow rate of 0.2 mL min^{-1} showed that there was no trend in the selectivity or conversion for the reaction between -10°C and 40°C (Table 9). However, the literature suggests that high selectivity and high conversion can be obtained in batch reactions by using temperatures less than -50°C .^{161, 179} Unfortunately, the minimum temperature of the re-circulating bath connected to the cold finger, limits the lower temperature range of the Nottingham excimer reactor. With the current re-circulating bath, the minimum temperature is -10°C . It is possible to purchase a more powerful re-circulator, but we decided that this would not be cost effective.

Table 9: The effect of temperature on the selectivity and conversion for the irradiation of 0.1 M solutions of β -ionone at 308 nm in ethanol at a flow rate of 0.2 mL min^{-1} .

Temperature ($^\circ\text{C}$)	Conversion	Selectivity 9 + 12	Selectivity 11
-10	72%	69%	31%
0	68%	62%	38%
10	77.5%	74%	26%
20	76%	74%	26%
30	76%	69%	31%
40	82%	75%	25%

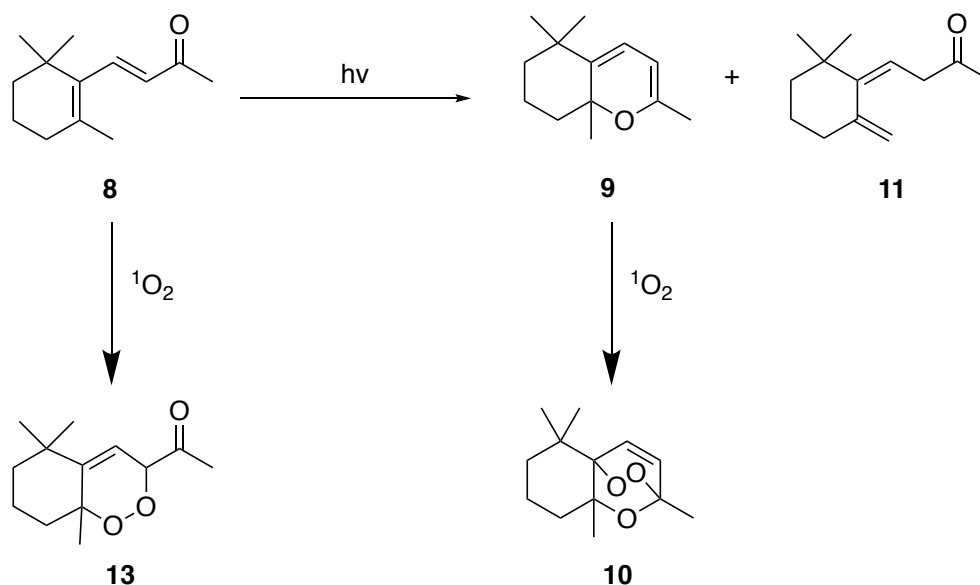
The reaction was also performed in six additional solvents (Table 10). The results showed no trend in selectivity with solvent polarity. Under all of the reaction conditions utilised, no conditions gave both high selectivity and near full or full conversion.

Table 10: The effect of solvent on the selectivity and conversion for the irradiation of 0.1 M solutions of β -ionone at 308 nm in ethanol at a flow rate of 0.2 mL min⁻¹.

Solvent	Solvent Dielectric Constant at 20 °C ¹⁸⁴	Conversion	Selectivity 9 + 12	Selectivity 11
Acetonitrile	37.5	73%	71%	29%
Ethanol	22.4	72%	69%	31%
Acetone	20.6	72%	77%	23%
Isopropyl alcohol	18.3	74%	80%	20%
Ethyl Acetate	6.02	74%	69%	31%
Toluene	2.38	82%	69%	31%
Hexane	1.9	80%	73%	26%

2.7.3 Adding Photo-oxygenation as a Second Step

To test the viability of the second step, the photo-oxygenation reaction, a small-scale batch reaction was performed. Tetraphenylporphyrin (TPP) (1 mole percent), a visible photosensitiser, was added to the crude mixture from the outlet of the excimer reactor (0.2 mL min⁻¹) after removal of the ethanol and re-dissolving in an equal quantity of dichloromethane. This was then irradiated with visible white LEDS while a stream of oxygen was bubbled through the reagents. Product **9**, successfully reacted with singlet oxygen to give the 1,3,4-trioxane product, **10**. However, the starting material, **8**, also reacted with singlet oxygen yielding compound **13** (Scheme 15).



Scheme 15: The reactions of β-ionone, **8**, and its α-pyran photoproduct, **9**, with singlet oxygen.

This meant that the starting material, **8**, could not be recycled after the photo-oxygenation step if conditions that resulted in low conversion but high selectivity for **9** were used for the UV electrocyclysis. This demonstrated the fact that in order for a multi-step continuous process without in-line purification to be viable, each step in the reaction sequence (other than the last) must be high yielding or non-reactive and non-interfering in following steps. Therefore, I decided that investigating a different UV photochemical reaction that was cleaner was more likely to be successful as part of an integrated process than making further attempts to attain higher selectivity with high conversion for the photochemical electro-cyclisation of β-ionone reaction. An example of this is given in Chapter 3.

2.8 Looking Forward: Designing a Larger Reactor

Two examples of successful photochemical studies undertaken in the excimer reactor and are presented in Chapters 3 and 4, and additional examples can be found in Inès Pender's Thesis.¹⁴⁶ Specifically, the photochemical isomerisation of 2-pyridone (Chapter 4) showed that while the excimer reactor is well sized for test-

scale reactions and the synthesis of small quantities of products, having a larger reactor would be useful for situations in which larger quantities of products are desirable.

To this end our research group purchased three additional custom excimer lamps, emitting at the same wavelengths as the original lamps, from the Institute of High Current Electronics in Russia. The newer lamps are of similar design to the original lamps, however they are more powerful (229 W, XeBr and XeCl and 268 W KrCl vs. 113 W) and are larger with a 6 cm central bore. Therefore these newer lamps can accommodate a much larger reactor.

All of the key design features identified for building a successful photochemical reactor with the smaller excimer lamps (see Section 2.3) were equally relevant to building the larger reactor. However, with the larger lamps it was desirable to have an overall larger irradiation volume so that, considering the increased power of the bigger lamps, more material could be produced in a given time period. I decided that a larger version of the current excimer reactor would be an effective design solution.

Although the design for the larger reactor mainly reused the original design, increasing the scale of the reactor in an academic laboratory setting brought additional challenges that had to be resolved before the new reactor could be built. In order to keep a tight fit of the quartz flask inside the excimer bore (for minimizing production of ozone and maximizing capture of light) and to have a thin film of reagents, a cold finger with non-standard dimensions was necessary. This meant that all but one of the fittings would be of non-standard size and instead would have to be custom-built by the University of Nottingham Workshop.

Considering the proposed dimensions of the larger reactor I became aware that this reactor would be very heavy (especially once filled with coolant). Changing between different lamps for the smaller excimer reactor is accomplished by simply sliding the

reactor out from the lamp and clamping it in place while the lamps are exchanged. It was obvious to me that it would be unwise to rely upon the physical strength of the operators to manipulate a heavy and fragile reactor. Instead, having a stand for the reactor would reduce the risk of damage to the reactor. In order to leave one end free from fittings, I suggested orienting the reactor vertically, where the stand has two legs separated by a distance large enough to accommodate the width of the large excimer lamp.

Having the larger reactor vertical rather than horizontal does however create a new challenge. Our research group's fume cupboards and extracted boxes are not tall enough to provide enough clearance for the reactor to be removed from the lamp. I considered three options:

- 1.) Situating the reactor on rails that would allow for the entire reactor to slide horizontally and create a side door to the vented cabinet. This would allow the whole reactor to be moved out onto the bench top, where the reactor could be raised on its stand and the large lamps exchanged (Figure 30).

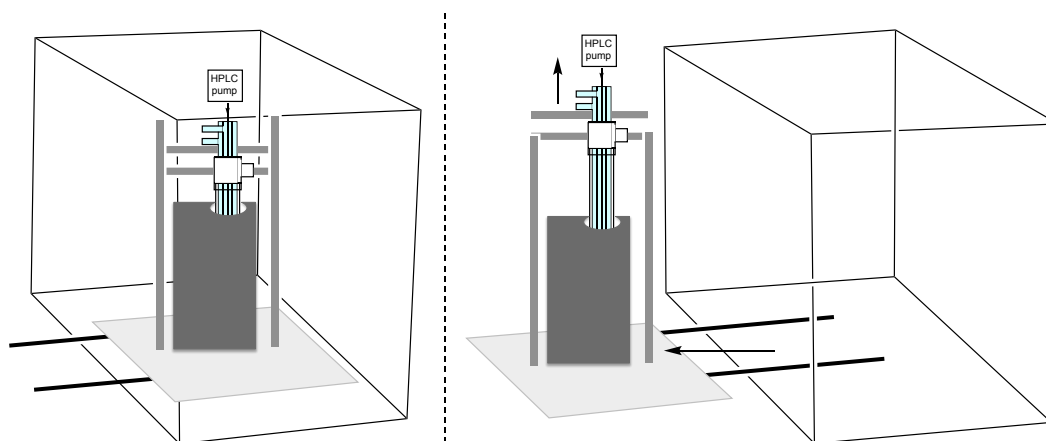


Figure 30: Large excimer reactor design where the entire reactor is moved horizontally out of the fume hood so there is enough clearance to remove the reactor from inside the lamp.

- 2.) Inverting the reactor so that the tip end was facing upward. The inverted reactor would also be situated on a horizontally sliding table that could slide

out from the vented cabinet. In this orientation the larger lamp (lighter than the reactor) would physically be lifted and lowered onto the reactor (Figure 31).

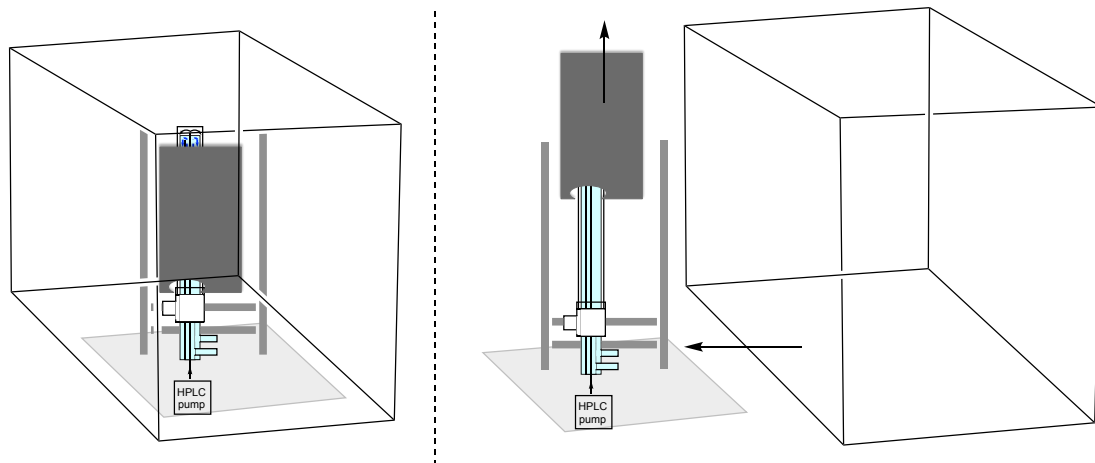


Figure 31: Large excimer reactor design where the reactor is inverted with the closed end upward. The entire reactor is moved horizontally out of the fume hood so there is enough clearance to remove the lamp from over the reactor.

- 3.) Cutting a hole in the bottom of the vented cabinet just large enough for the excimer lamp. The large excimer lamp would then be placed onto a stand that could be smoothly raised and lowered into the desired position (Figure 32).

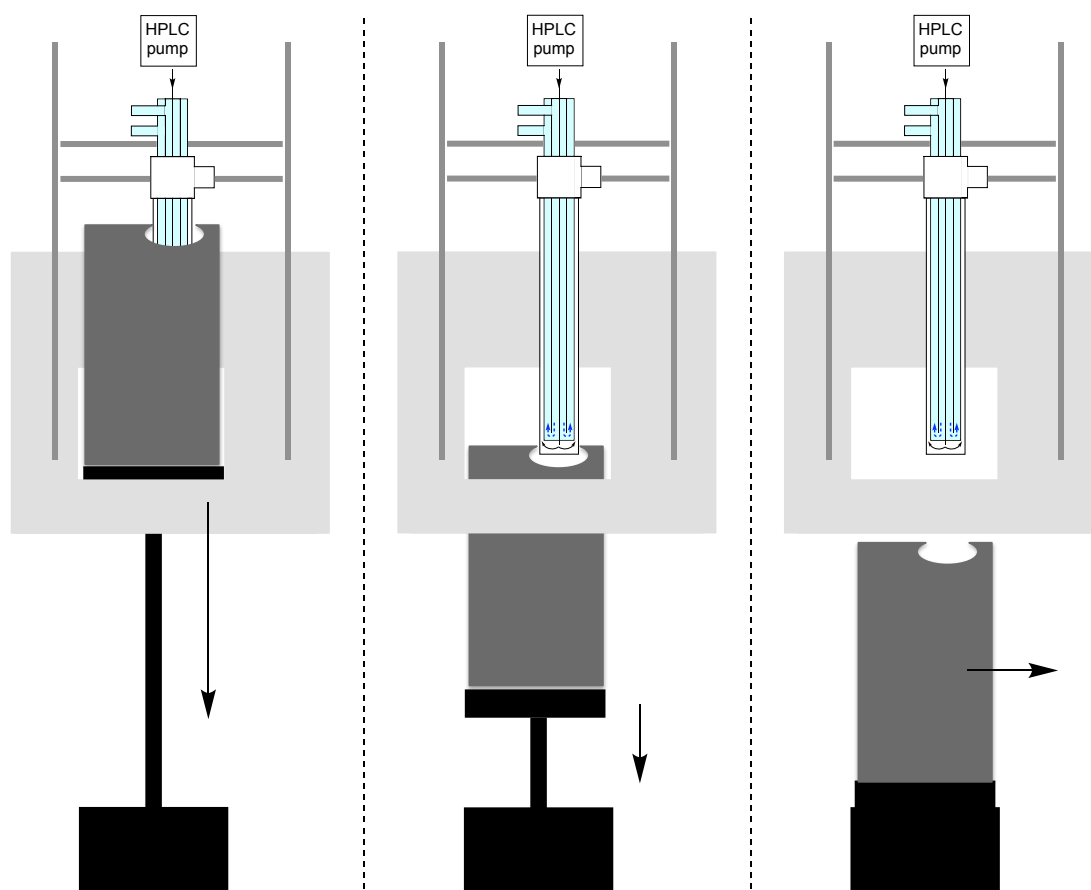


Figure 32: Large excimer reactor design where the reactor sits above a hole in the fume hood floor. The lamp is vertically lifted into place over the reactor, and lowered for lamp changes.

4.) Purchasing a walk-in fume cupboard.

In design strategy one, in order for the reactor to be lifted directly on the stand to an appropriate height the rails of the stand would have to be taller than the height of the vented cabinet. It would be possible to remove the reactor from the top of its stand but then again the weight of the reactor would become problematic, and lifting a reactor potentially full of solvent or reagents above eye-level is not safe. Design strategy two posed two potential issues. By inverting the direction of the reactor it is possible that the flow dynamics would change and gravity would effect the residence time. Additionally, although the larger excimer lamps are considerably lighter than the large reactor will be they are still cumbersome, and lifting them above head height greatly increases the potential risk of damage to both the lamps and reactor.

Solution 4 has been considered, and in the future a walk-in fume cupboard might be purchased however, these are expensive and require lab space. Therefore solution 3 seemed most viable. Richard Wilson from the University of Nottingham Workshop has confirmed that it would be possible to build a suitable lift for the larger excimer lamps. The larger reactor design has been agreed upon with the workshop and is currently awaiting construction. Although it was not completed in time for to be used for the work presented in this Thesis it will hopefully be part of our research group's pool of photochemical reactors by the end of 2018.

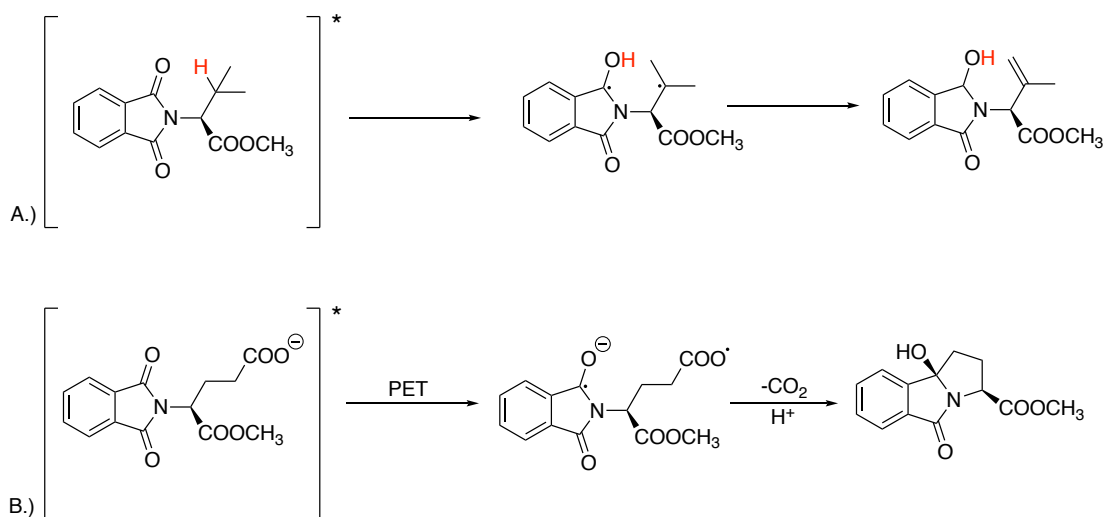
Chapter 3: The Photochemical Decarboxylation of 4-Phthalimidobutyric Acid

3.1 Chapter Summary

Carbon-carbon (C-C) bond formation is an important step in organic synthesis as these bonds form the backbone of all organic molecules.¹⁸⁵ Many C-C bond forming reactions require the use of expensive and potentially toxic transition metal catalysts and/or stoichiometric quantities of organometallic reagents such as Grignard reagents.^{134, 186, 187} Therefore finding greener routes to forming new C-C bonds is an important challenge for organic chemists. Photochemical C-C bond formation has the potential to be a greener way of performing these reactions because photochemical reaction can take place under mild conditions^{80, 188} and do not require additional reagents that must then be removed at the end of the reaction. The literature contains numerous examples of photocatalytic pathways in which visible light generates reactive intermediates that form new C-C bonds.^{80, 188, 189} However, UV light allows the substrate to be directly excited to form the reactive intermediate, avoiding the need for potentially costly photocatalysts.^{134, 190} This chapter concerns phthalimides, one class of compounds that can be photochemically excited to generate reactive intermediates for C-C bond formation.⁸⁰ Specifically, the decarboxylative photo cyclisation of 4-phthalimidobutyric acid was studied in the excimer reactor using the three different lamps, to investigate the wavelength dependence of the reaction. Furthermore, two solvent systems were used to probe the effects of sensitisation. Following optimisation of the photocyclisation step, a second step, the acid catalysed dehydration of the photoproduct, was added to give an integrated continuous two step process.

3.2 The Photochemistry of Phthalimides

The photochemistry of phthalimides has been extensively studied since the 1970s.¹⁹¹⁻²¹³ Generally, phthalimides have two UV absorption maxima, one corresponding to the $\pi \rightarrow \pi^*$ transition with a λ_{max} around 220 nm and the other ca. 290 nm for the $n \rightarrow \pi^*$ transition. Rapid intersystem crossing from the lowest singlet excited state to the $n \rightarrow \pi^*$ triplet occurs as these two levels are very close in energy, although their ordering is debated.¹⁹⁶ The photochemistry of phthalimides is similar to that of the chemically related carbonyl functionality; however, the singlet and triplet excited states of phthalimides are highly oxidising. Therefore, it is possible for phthalimides to photochemically react like carbonyls by homolytic bond cleavage inducing CH-activation (e.g. Scheme 16, A). However, if a suitable electron-donating group is present in the reaction mixture, either as part of the phthalimide molecule or as a second reagent, photoinduced electron transfer (PET) can occur, resulting in radical ions (e.g. Scheme 16, B).^{196, 209}



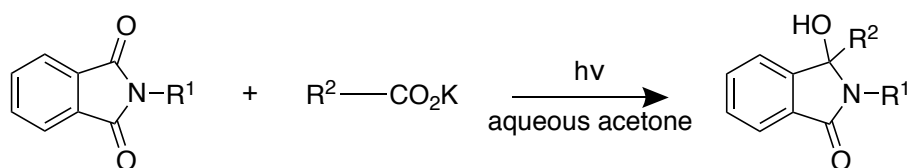
Scheme 16: Scheme showing types of reactivity of phthalimides. (A) Carbonyl like behaviour of the phthalimide system in a Norrish Type 2 reaction (λ -hydrogen abstraction). (B) PET resulting in decarboxylation.²⁰⁹

Once PET occurs, there are three main reactive pathways; deactivation back to the ground state by back-electron transfer, radical recombination, or a bond near to the

oxidised site is mesolytically broken and a carbon radical centre together with a leaving group are generated. By gaining control of these reaction pathways through various synthetic methods such as tuning the leaving group, the PET process has proven itself useful for C-C bond formation in organic reactions.^{80, 209}

3.3 Photochemical Phthalimide Decarboxylation

When strong electron donors are present phthalimides, which are *N*-functionalised with a carboxylic acid, can eliminate CO₂ after PET has taken place. This photodecarboxylation reaction of phthalimides is an important transformation in synthetic organic chemistry and it has been studied extensively.^{192, 196, 198, 203, 204, 208, 214-219} Intermolecular versions of this reaction can exploit the radical carbon centre generated from the decarboxylation as a reactive intermediate in radical coupling reactions, Scheme 17. This offers a versatile approach to Grignard-like products with CO₂ and potassium hydroxide being generated as the only waste product.^{192, 208, 220} Another sustainable feature of these reactions is that they can be performed in aqueous mixtures of acetone¹⁸³ which can act not only as a component of the solvent system but also as a triplet sensitiser, since the decarboxylation reaction proceeds via a triplet excited state of the phthalimide chromophore.^{197, 203}

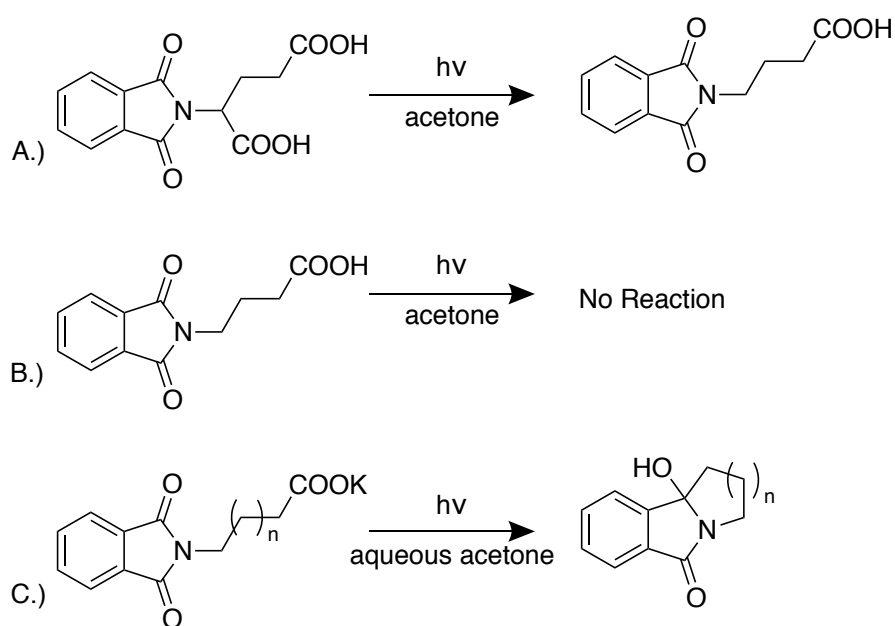


Scheme 17: Intermolecular photodecarboxylative addition. Adapted from Oelgemöller *et al.*¹⁹²

Intramolecular versions of this reaction have also been studied.^{191, 194, 196, 198, 210, 221}

When phthalimides which are *N*-functionalised with carboxylic acid groups are irradiated, decarboxylation only occurs at the α -position (Scheme 18, A). If the carboxylic acid group is not located on the alpha carbon, decarboxylation will not

occur (Scheme 18, B). However, using the potassium salts of phthalimido carboxylates it is possible to activate a “remote” carboxylate group and decarboxylation from the ω -position can occur. The phthalimide group can then behave as an electron-accepting group leading to ring closure (Scheme 18, C). This has been shown to be useful for generating molecules containing medium and large heterocyclic rings.^{198, 210, 221}

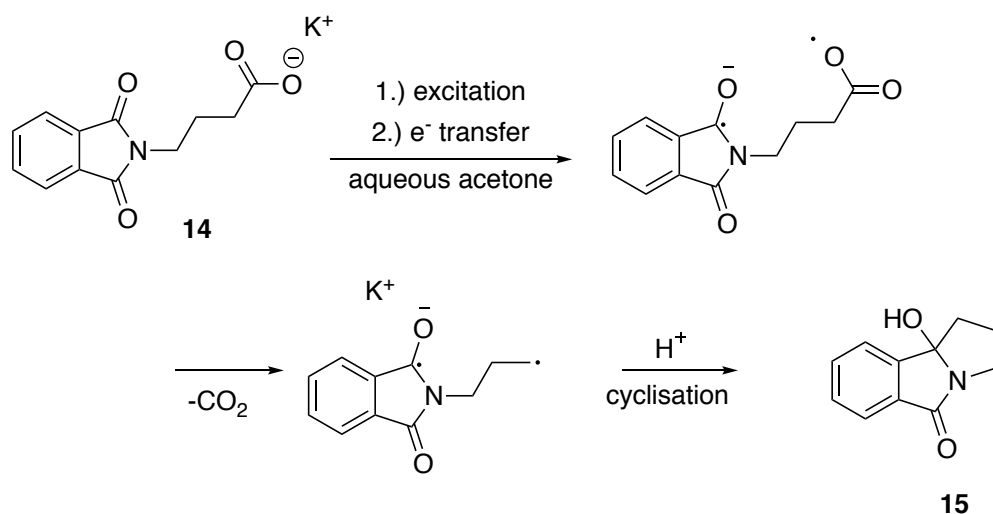


Scheme 18: Photochemical reaction pathways of carboxylic acid containing phthalimides.¹⁹⁸

3.3.1 The Photochemical Decarboxylation of 4-Phthalimidobutyric Acid

One such “remote photocyclisation” reaction is the photodecarboxylation and cyclisation of 4-phthalimidobutyric acid, **14**, to the tricyclic product, **15**, shown in Scheme 19. This reaction is often used as a test reaction for photochemical reactors because large quantities of the starting material can easily be prepared from inexpensive commercially available reagents in a single step.^{222, 223} This reaction was initially used by Griesbeck with a Rayonet photochemical reactor²¹⁰ and later with a 3 kW falling film excimer reactor.⁹⁰ Oegelmöller built on this pioneering work by comparing the efficiency of this photodecarboxylative cyclisation in microreactors

and Rayonet reactors.²²⁰ More recently a study by Booker-Milburn showed that this reaction was more productive when irradiating through quartz than through pyrex.¹²⁴ This reaction was therefore chosen as a convenient benchmark for the Nottingham excimer reactor because it not only would allow for direct comparison between various reactors and demonstrates generating molecular complexity in one clean photochemical step but also appeared to have some wavelength dependence that could be investigated using the three discrete wavelengths of the excimer lamps.



Scheme 19: Proposed mechanism for the decarboxylation of 4-phthalimidobutyric acid.

3.4 The Photochemical Decarboxylation and Cyclisation of 4-Phthalimidobutyric Acid in the Nottingham Excimer Reactor

The photochemical decarboxylation of 4-phthalimidobutyric acid was studied in the Nottingham excimer reactor. Both 1:1 acetone-water and 1:1 acetonitrile-water were studied as the reaction solvent since both had previously been reported in the literature.^{124, 201, 210, 220, 224} Both acetone and acetonitrile are miscible with water and having an organic component in the solvent mixture ensured that both starting material and product were completely dissolved. Nevertheless, the concentrations of **14** used for the reaction were always kept below 0.3 M as the mixture became biphasic and/or reagents precipitated from solution at higher concentrations.

The UV-Visible spectrum of **14**, Figure 33, shows the two absorption bands with local maxima at 220 nm and 295 nm, which is consistent with typical phthalimide UV-Vis spectra.^{196, 197, 225} By changing the excimer lamp, it was possible to excite the two chromophores individually and to determine how this affects the productivity of the reaction.

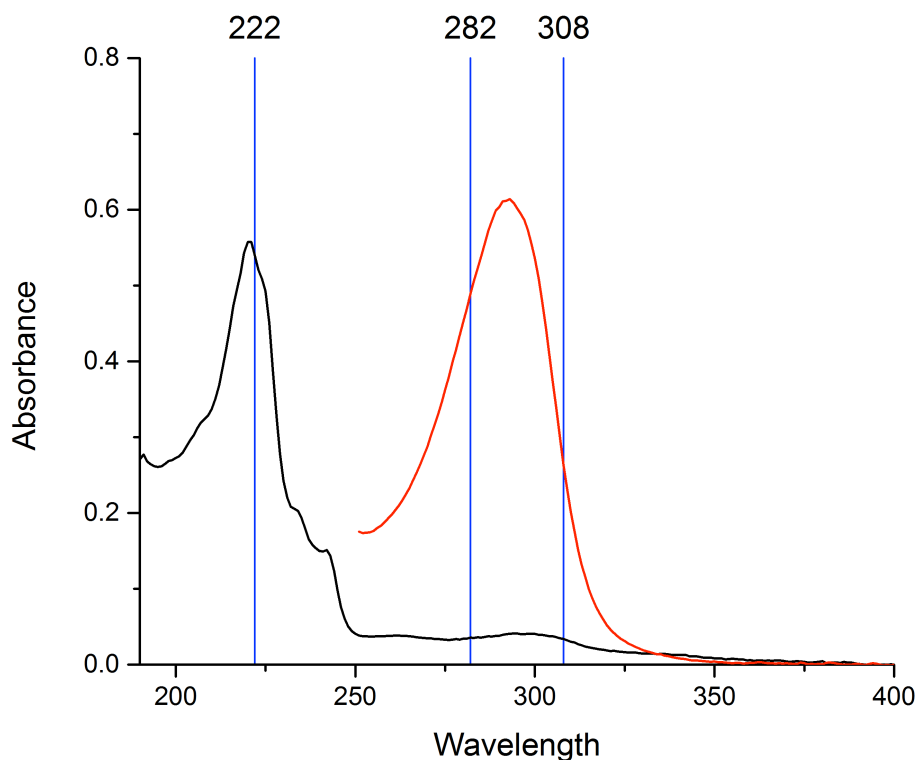


Figure 33: UV-Vis absorption spectra (pathlength = 1 cm) of compound 14 in 1:1 acetonitrile-water at concentrations of 1×10^{-5} M (black), and 2.9×10^{-4} M (red).

Unlike acetonitrile-water, the acetone-water solvent system is not UV transparent. Acetone has an absorption band centred at approximately 280 nm, Figure 34. However, by comparing the extinction coefficients of acetone at 282 nm and 308 nm to those of **14**, Table 11, it is clear that the absorption of the acetone is weak compared to that of **14**. It should also be noted that interaction of acetone with water causes a blue shift in the UV-Vis absorption peak centred at 280 nm. This causes the extinction coefficient measurement to deviate from linearity at high

concentrations. Therefore, considering that the acetone constitutes 50% of the reaction solvent, the extinction coefficients are illustrative rather than accurate. Nevertheless they indicate how much weaker the absorbance of acetone is compared to compound **14** but will have a high degree of error (see Appendix 3.2 for calibration curves). In the literature,^{201, 210} acetone has been used as a triplet sensitiser for this reaction. It is therefore possible, that it may still be acting in this role during the excimer reactions; however, additional experiments would be needed to determine the extent of possible triplet sensitisation. The results of irradiating at the three excimer wavelengths in each solvent system are presented in the next sections. (N.B. The results presented in the following sections with additional discussion have been published in our 2017 Green Chemistry paper.)¹³⁴

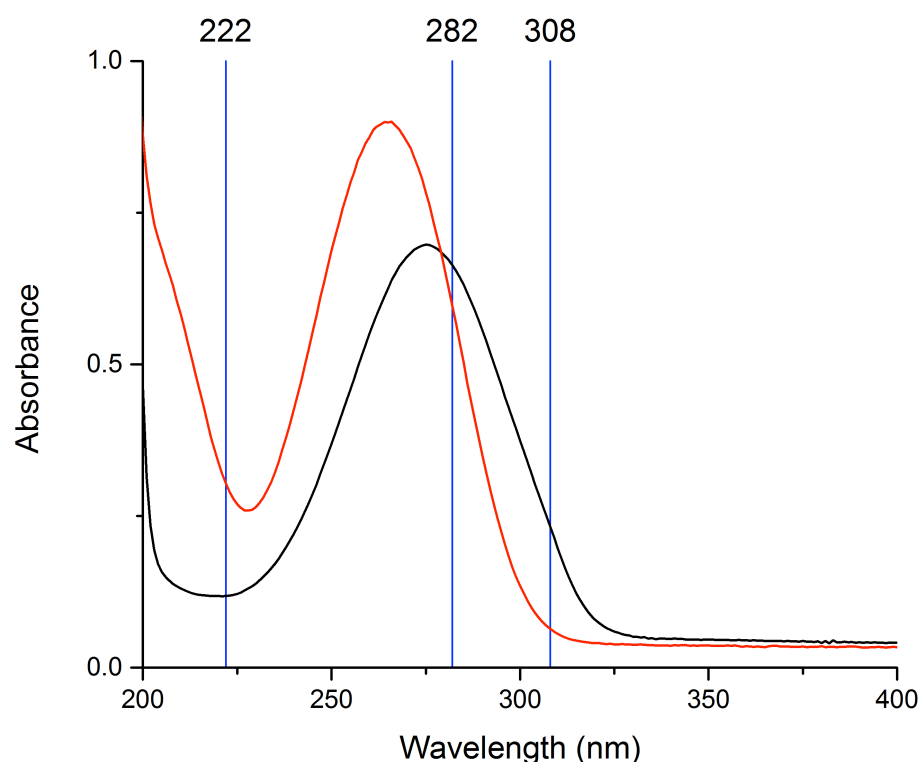


Figure 34: UV-Vis absorption spectra (black) of neat acetone (pathlength = 25 μ m) and (red) 0.05 M acetone in water (pathlength = 1.0 cm).

Table 11: Extinction coefficients of compound 14 and acetone in water at the 282 nm and 308 nm irradiation wavelengths.

Wavelength (nm)	Extinction Coefficient of 14 in Water (dm ³ mol ⁻¹ cm ⁻¹)	Extinction Coefficient of Acetone in Water (dm ³ mol ⁻¹ cm ⁻¹)
282	1180	12.1
308	1367	0.94

3.4.1 The Photochemical Decarboxylation and Cyclisation of 4-Phthalimidobutyric Acid in Acetone-Water.

The results of irradiating **14** to form product **15** at two different concentrations, four flow rates and all three excimer wavelengths in 1:1 acetone-water are presented in Table 12. The yield of the reaction was calculated by ¹H NMR proton integration against an external standard of 1,3,5-trimethoxybenzene. Three samples were taken and the average yield is presented below. From the yield both the productivity and STY were also calculated. Productivity is a measure of the quantity of product that can be made in a given period of time, Equation 11.

Equation 11: Equation for productivity. Appropriate units must be used to give productivity in the units presented in Table 12.

$$Productivity = Concentration \times Flow Rate \times Yield$$

Table 12: The effects of flow rate, concentration and irradiation wavelength on the yield, productivity and space-time yield of compound 15 in 1:1 acetone-water.¹³⁴

Entry	Conc. (M)	Flow rate (mL min ⁻¹)	Yield 15 (%) ^a	Productivity (mmol h ⁻¹)	STY (mmol h ⁻¹ mL ⁻¹)
222 nm Irradiation					
1	0.1	0.2	37	0.44	0.32
2	0.1	0.5	28	0.74	0.54
3	0.1	1.0	16	0.98	0.72
4	0.1	1.5	8	0.75	0.55
5	0.2	0.2	26	0.62	0.45
6	0.2	0.5	16	0.94	0.69
7	0.2	1.0	9	1.1	0.82
8	0.2	1.5	9	1.6	1.2
282 nm Irradiation					
9	0.1	0.2	97	1.2	0.85
10	0.1	0.5	58	1.7	1.3
11	0.1	1.0	42	2.5	1.9
12	0.1	1.5	38	3.4	2.5
13	0.2	0.2	74	1.8	1.3
14	0.2	0.5	55	3.3	2.4
15	0.2	1.0	35	4.2	3.1
16	0.2	1.5	28	5.1	3.7
308 nm Irradiation					
17	0.1	0.2	>99	1.2	0.88
18	0.1	0.5	87	2.6	1.9
19	0.1	1.0	68	4.1	3.0
20	0.1	1.5	43	3.8	2.8
21	0.2	0.2	94	2.3	1.6

22	0.2	0.5	54	3.2	2.4
23	0.2	1.0	32	3.9	2.8
24	0.2	1.5	20	3.5	2.6

a = calculated by ^1H NMR proton integration against an external standard of 1,3,5-trimethoxybenzene.

From Table 12 it can be seen that as expected at both concentrations and at all three irradiation wavelengths, the highest yields for product **15** were obtained when slower flow rates, i.e. longer irradiation times, were used. When comparing across the three wavelengths, the worst yields were always obtained when irradiating at 222 nm, where irradiation was generally accompanied by a small degree of reactor fouling (observed as a yellow film on the inner surface of the quartz jacket, which was removed by scrubbing with a test tube brush). The lower yields at 222 nm could be the result of two factors. Increased competitive absorption by product **15** at 222 nm compared to the other two wavelengths (Figure 35) may have caused fewer photons to be available for the conversion of starting material **14** and could possibly have degraded **15**. Secondly, despite having equal power input (113 W) the KrCl, 222 nm, excimer lamp has a somewhat lower spectral irradiance compared to the other two lamps, see Table 13.

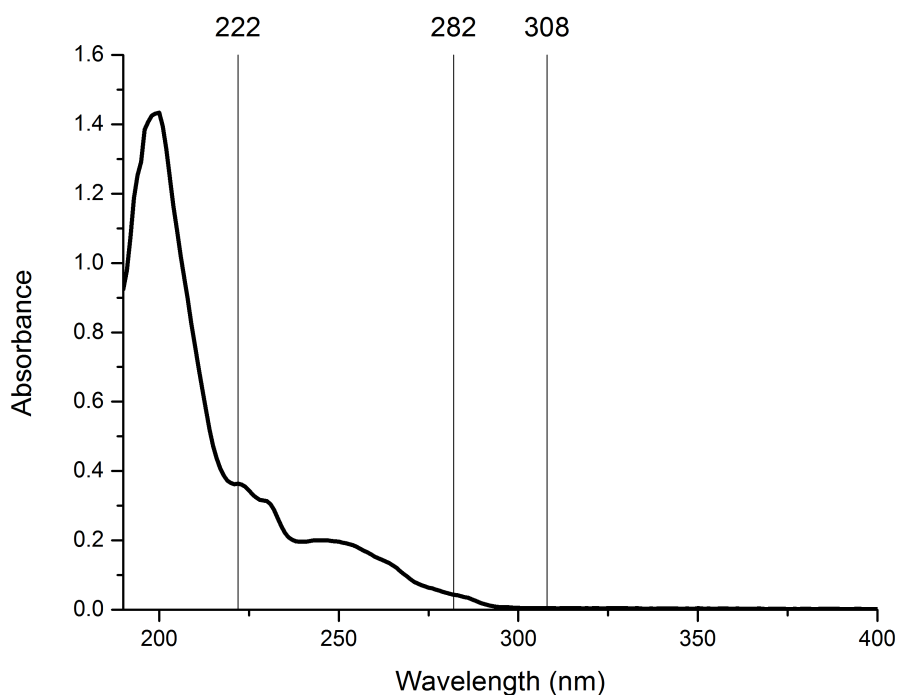


Figure 35: UV-Vis absorption spectrum of 5.0×10^{-5} M photoproduct 15 in 1:1 acetonitrile-water (pathlength = 1 cm).

Table 13: Spectral irradiances of the different excimer lamps as given by the manufacturers specifications.

Excimer Lamp	Spectral Irradiance (photons $\text{s}^{-1} \text{cm}^{-2}$)
KrCl (222 nm)	2.34×10^{16}
XeBr (282 nm)	5.11×10^{16}
XeCl (308 nm)	7.57×10^{16}

The spectral irradiance of the KrCl (222 nm) lamp is approximately half that of the XeBr (282 nm) lamp and one third that of the XeCl (308 nm). When this fact is taken into account, the STYs across all three lamps become reasonably more similar, compare Table 12 Entries 1-3 with 9-11 and 17-19. This suggests that the spectral irradiance is a more important factor than the absorption of light by product **15** in explaining the difference in yield between lamps.

The results in Table 12 also show that doubling the concentration of the reactants increases the STYs and productivities of the reaction. However, the increase in STY and productivity in all cases is less than twice. In order for STY and productivity to double with doubled concentration, at each similar flow rate the yield at the higher concentration would have to be equal to that at the lower concentration. At the start of the lower concentration reactions more than 99% of the light is absorbed at all wavelengths by the solution of **14**. Therefore, the reaction is photon limited and having more starting material does not result in more conversion of **14** to **15** to occur. However, as **14** is converted to **15**, the solution becomes less absorbing to the point where light can be transmitted through the entire thickness of the solution, and photons can be absorbed by the cooling stick rather than used for reaction. Having a higher initial concentration of starting material means that transmission of light through the solution, and wasting of photons, happens only after much longer residence times. Despite this, since the initial rates of formation of **15** at both concentrations must be similar, thus the 0.2 M STYs cannot be double those of the 0.1 M STYs.

Additionally, the results also showed that higher productivities and STYs could be obtained by increased throughput, via utilising faster flow rates, up to 1.0 mL min^{-1} . This came at the sacrifice of yield, which decreased as expected with faster flow rates. Since residence time decreases with increasing flow rate, at the faster flow rates starting material **14** is simply not in the reactor long enough to achieve high levels of conversion to product **15**. In some cases at the fastest flow rate, 1.5 mL min^{-1} , the low yield resulted in productivity dropping below that of 1.0 mL min^{-1} where increased throughput could not compensate for the reduced yield.

3.4.2 The Photochemical Decarboxylation and Cyclisation of 4-Phthalimidobutyric Acid in Acetonitrile-Water

Irradiation of **14** at similar concentration, flow rate and irradiation wavelength were performed with 1:1 acetonitrile-water as the reaction solvent rather than acetone-water. As before the yield of the reaction was calculated by ^1H NMR proton integration against an external standard of 1,3,5-trimethoxybenzene. In all cases three samples were taken and the average yield for each set of conditions is presented below.

Table 14: The effects of flow rate, concentration and irradiation wavelength on the yield, productivity and space-time yield of compound 15 in 1:1acetonitrile-water.¹³⁴

Entry	Conc. (M)	Flow rate (mL min ⁻¹)	Yield 15 (%) ^a	Productivity (mmol h ⁻¹)	STY (mmol h ⁻¹ mL ⁻¹)
222 nm Irradiation					
1	0.1	0.2	31	0.37	0.27
2	0.1	0.5	54	1.7	1.2
3	0.1	1.0	34	2.0	1.5
4	0.1	1.5	22	2.0	1.5
5	0.2	0.2	22	0.52	0.39
6	0.2	0.5	19	1.1	0.83
7	0.2	1.0	17	2.1	1.5
8	0.2	1.5	11	2.1	1.5
282 nm Irradiation					
9	0.1	0.2	82	0.98	0.72
10	0.1	0.5	74	2.2	1.6
11	0.1	1.0	61	3.7	2.7
12	0.1	1.5	35	3.2	2.3
13	0.2	0.2	77	1.9	1.4
14	0.2	0.5	63	3.7	2.8

15	0.2	1.0	39	4.7	3.4
16	0.2	1.5	26	4.6	3.4
308 nm Irradiation					
17	0.1	0.2	89	1.1	0.78
18	0.1	0.5	78	2.4	1.7
19	0.1	1.0	50	3.0	2.2
20	0.1	1.5	26	2.3	1.7
21	0.2	0.2	96	2.3	1.7
22	0.2	0.5	53	3.0	2.3
23	0.2	1.0	32	3.9	2.8
24	0.2	1.5	22	4.0	2.9

a = calculated by ^1H NMR proton integration against an external standard of 1,3,5-trimethoxybenzene.

Table 14 shows that the results of irradiation in the UV transparent acetonitrile-water solvent system gave generally similar trends to those observed in acetone-water. Yield increased with decreasing flow rate and STY and productivity both increased with the use of faster flow rates up to 1.0 mL min^{-1} . Whether or not STY and productivity were higher at 1.0 mL min^{-1} or 1.5 mL min^{-1} was once again dependent on the reaction conditions. As before, 222 nm irradiation gave the worst overall yields. However, the experiments involving prolonged 222 nm irradiation in this solvent system, flow rates of 0.2 mL min^{-1} , resulted in more significant reactor fouling and there was noticeable mass loss. This is probably the cause of the decline in observed yield for this experiment (Table 14, Entry 1).

3.4.3 Comparison of Results in Acetone-Water to Results in Acetonitrile-Water

Comparison of Table 12 and Table 14 shows that the yields obtained when a 0.2 M solution was irradiated were very similar in both solvents across all three wavelengths (Table 12 and Table 13, compare entries 5-8, 13-16, and 21-24).

However, the results of irradiating the less concentrated solutions (0.1 M) show a significant solvent dependence. With 308 nm irradiation, the yields in acetonitrile-water are lower than those in obtained when using acetone-water. This may be due to the effects of sensitisation by the acetone, which absorbs only weakly at 308 nm (see Table 11 for extinction coefficient). Therefore, acetone is unlikely to absorb the 308 nm photons competitively and to decrease production of **15** when the concentration of **14** is high at the start of the reaction. However, as the concentration of **14** decreases the acetone can absorb some the 308 photons and act as a sensitiser, resulting in fewer photons being transmitted through the solution and wasted.

Using 282 nm light gave yields of product **15** that were higher in acetonitrile-water compared to acetone-water, except at the slowest flow rate where the yield was 15% lower than with acetone-water. Again, the effects of sensitisation and the concentration gradient present inside the reactor can explain this. At the slowest flow rate, the conversion is highest, leading to a decrease in the concentration of **14**. In this case since acetone is the strongest absorber at 282 nm; it is able to absorb the light and sensitise the reaction, leading to more efficient photon utilisation than in the transparent solvent. However, since acetone does absorb more strongly at 282 nm, it will competitively absorb at this wavelength. The fact that the results were lower in acetone-water at the three faster flow rates (lower conversion) suggests that the quantum yield for the sensitised reaction is lower than for the direct reaction. However, experiments to measure the precise quantum yield of both the sensitised and unsensitised reaction would be necessary to confirm this hypothesis. Experiments to measure quantum yield are most often complicated and time consuming. Specifically, quantum yield measurements require very accurate knowledge of the light source photon-flux, typically calculated through chemical

actinometry.²²⁶ As presented in Chapter 2, the high photon flux of the excimer reactor can complicate chemical actinometry, and the values obtained for photon flux by chemical actinometry in Chapter 2 were for qualitative use to measure decrease in lamp efficiency over time, rather than for precise calculations of quantum yield. The manufacturer's specifications cannot be used as they are measurements of photon flux inside the lamp central bore, not inside the reactor quartz tube. A more accurate method of chemical actinometry would need to be developed to calculate the quantum yields of the reaction. Therefore, although these experiments would have provided photo-physical information about the reaction, they would not have provided additional information as to how this reaction is affected by being performed in the excimer reactor. Therefore, given the time that these experiments would have taken, they fall outside the scope of this thesis.

Finally, 222 nm irradiation gave results that were higher in acetonitrile-water compared to acetone-water. Acetone absorbs moderately at this wavelength. The lower overall spectral irradiance of the KrCl (222 nm) lamp meant that near full conversion was not obtained even using the lower concentration (0.1 M) and the slowest flow rate (0.2 mL min⁻¹). Therefore, the absorbance of light by **14** was high over the entire course of the reaction. This means that absorption of light by acetone was most probably detrimental to the reaction rather than beneficial by making photon capture more efficient. The one notable exception to this is the result from irradiating using a flow rate of 0.2 mL min⁻¹, where the result in acetone was higher than in acetonitrile. As already explained above, under prolonged short wavelength irradiation in the transparent solvent, significant mass loss and reactor fouling was observed. It is probable that competitive absorption from the acetone was able to protect product **15** from undergoing secondary photochemical reactions by absorbing some of the light.

3.4.4 Comparing the Productivity of the Nottingham Reactor to Reactors Described in the Literature.

As stated in Section 3.3.1 this reaction has been performed in other photochemical reactors described in the literature.^{90, 124, 220} For comparison to other reactors, two high concentration (0.2 M) data points from the Nottingham UV reactor were used; one with high yield (Table 15, Entry 6) and one with high productivity (Table 15, Entry 7). In both cases the Nottingham excimer reactor outperforms the other reactors described in the literature in terms of productivity with the exception of the 3 kW falling film reactor and the Firefly (Table 15, Entries 4 and 5). When the productivity is adjusted to account for the power of the lamp used, the Nottingham excimer reactor when operated at high yielding conditions (Table 15, Entry 6) was over 25 times more productive than the Rayonet reactor, over 6 times more productive than the μ -reactor and over 3 times more productive than the falling film reactor. Only the Bristol Firefly reactor was more productive per unit lamp power.

Table 15: Comparison of the efficiency of different photochemical reactors for the transformation of 14→15.

Entry	Reactor Type	Light Source	Yield 15 (%)	Productivity (mmol h ⁻¹)	Normalized Productivity (mmol h ⁻¹ W ⁻¹)	STY (mmol h ⁻¹ mL ⁻¹)
1 ²²⁰	Rayonet	16 x 8 W UVB	69	0.10	7.8 x 10 ⁻⁴	0.010
2 ²²⁰	Rayonet	5 x 8 W UVB	19	0.030	7.5 x 10 ⁻⁴	0.003
3 ²²⁰	micro-reactor	5 x 8 W UVB	77	0.12	3.0 x 10 ⁻³	0.069
4 ⁹⁰	Falling Film	3 kW 308 nm Excimer	82	15.9	5.3 x 10 ⁻³	.0037*-0.011*
5 ¹²⁴	Firefly	3 kW Hg	85	306	1.0 x 10 ⁻¹	2.55
6 ⁺	Nottingham UV Rig	113 W 308 nm Excimer Lamp	96	2.31	2.0 x 10 ⁻²	1.69
7 [#]	Nottingham UV Rig	113 W 308 nm Excimer Lamp	28	5.10	4.5 x 10 ⁻²	3.72

*Falling-film reservoir can hold between 1.5-5.0 L of solvent. Exact volume for this reaction was not given.⁹⁰

⁺Reaction conditions (308 nm irradiation, 0.2 M, 0.2 mL min⁻¹, acetonitrile-water; Table 14, Entry 21).

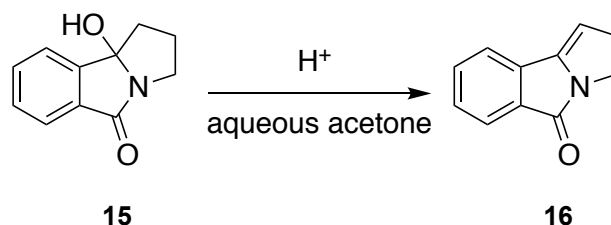
[#]Reaction conditions (282 nm irradiation 0.2 M, 1.0 mL min⁻¹, acetone:water; Table 12, Entry 7).

When STY was used at the benchmark for the reaction, and thus reactor volume was taken into consideration, the Nottingham excimer reactor once again outperformed the other reactors with the exception of the Firefly.¹²⁴ When the Nottingham excimer Reactor was run under conditions of higher yield and lower productivity, it had a STY approximately two-thirds that of the Firefly. However, when more productive lower yielding conditions were used the STY of the excimer reactor had a STY

approximately 1.5 times that of the Firefly. As no excimer reactor results were obtained that directly match the yield of the reaction in the Firefly, it is only fair to conclude that both the Firefly and excimer reactor give STYs of similar magnitude for this reaction.

3.5 Integrating the Photochemical Decarboxylation of 4-Phthalimidobutyric Acid into a Multistep Process.

As stated in Chapter 2, performing multiple reaction steps from a single reagent stream is highly desirable. However, as the photo-isomerisation β -Ionone showed, in order for this to be successful the first reaction step must achieve a high degree of conversion or the residual starting material must be unreactive in subsequent steps. Generating product **16** from **14** presents an example of a multi-step process that can be performed in a continuous integrated process as photoproduct **15** can be produced in high yield and selectivity in the initial UV photochemical step. Photoproduct **15** can then be transformed to product **16** by acid catalysed dehydration as briefly mentioned by Griesbeck *et al.*¹⁹⁸



Scheme 20: The dehydration of product 15 occurs with catalytic quantities of strong acid.

Initially, the feasibility of this second step was confirmed in small batch test reactions. Adding HCl to isolated samples of **15** in acetone-water resulted in rapid conversion to compound **16**. However, using HCl in the integrated process would be undesirable because halogens are incompatible with stainless steel, an additional pump and mixer would have been required, and the reagent stream would have been diluted complicating the work-up. Therefore, I decided that the integrated process would be

much simpler if a solid acid were used instead. As the photochemical decarboxylation requires an aqueous solvent stream to solubilise **14**, it was necessary to use a solid acid that was stable in the presence of water. Amberlyst® 15 and niobium phosphate were identified as potentially suitable acids to perform this dehydration. Niobium phosphate is a solid acid with a Brønsted acidity approaching 90% that of sulfuric acid,^{227, 228} and Lewis acidic sites that permit a range of reactions to be catalysed on its surface.²²⁹⁻²³¹ Despite this, niobium phosphate remains largely under utilised.²³² Small-scale batch tests showed that treatment of **15** with Amberlyst® 15 did not result in conversion to product **16**, probably because it was not a strong enough acid to catalyse the dehydration. Treatment with niobium phosphate by contrast led to full conversion of **15**→**16**.

Once niobium phosphate was identified as a suitable solid acid catalyst, the next step was to integrate the acid-catalysis with the photochemical step under the conditions that gave the highest conversion of **14**→**15** (308 nm, 0.1 M, 0.2 mL min⁻¹, acetone-water). Initially a column of NbOPO₄ was attached directly to the outlet stream of the excimer reactor. This was largely unsuccessful as samples taken after 10 minutes of reaction showed only 3% conversion of **15**→**16**. The low conversion was unsurprising, since one equivalent of potassium hydroxide is generated as a by-product of the photochemical step. This KOH was neutralizing the acidic sites of the acid catalyst and led to its rapid deactivation. Therefore, it was necessary to neutralise the KOH before the reagent stream encountered the NbOPO₄. This was accomplished by attaching two solid acid columns in series to the excimer reactor (Figure 36). The first was filled with Amberlyst® 15, which acted as a sacrificial quench for the KOH in order to prevent deactivation of the NbOPO₄. This strategy exploits the fact that Amberlyst® 15 costs approximately 50 times less than NbOPO₄. The second column was filled with NbOPO₄, which without deactivation by KOH, was

now capable of catalysing the dehydration of **15**→**16**. The NbOPO₄ column was placed so that the reagents were flowing upwards through the solid acid. This helped to reduce the amount of backpressure observed in the system during the course of reaction, presumably as the flow against gravity help to prevent compacting of the solid acid at the column outlet. As the excimer reactor is not pressure rated, operation at any backpressure had to be avoided. (Extra safety measures must be taken if any backpressure build up is possible).

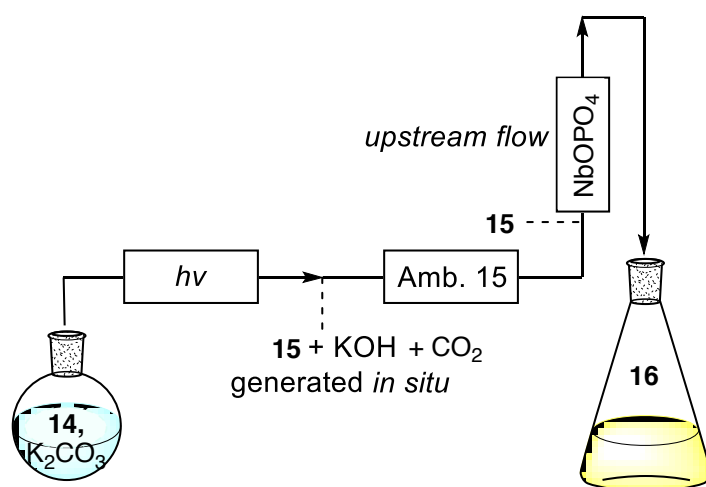


Figure 36: Rig schematic for streamlined dehydration of 15. Adapted from Delaney *et al.*¹³⁴

Obviously the sacrificial Amberlyst[®] column cannot be used indefinitely as eventually all of the acid sites will become saturated. It would in the future be a simple modification to have two Amberlyst[®] columns in parallel to each other, so that one could be used as the reaction quench while the other was being regenerated by a flow of acid. However, without changing the Amberlyst[®] column, the integrated process was run for 10 hours. Under these conditions initially 79% conversion from **15**→**16** was observed. However, the conversion had dropped to just 15% after 3 hours and remained at this lower level for the remainder of the reaction time. Initially, the drop in conversion was thought to be due once again to deactivation of the NbOPO₄. However, opening the reactor between the Amberlyst[®] and NbOPO₄

columns showed that the pH of the reagent stream was still neutral and, thus, that not all of the sacrificial acid had been consumed. Furthermore titration of both acids with NaOH using phenolphthalein as an indicator, after reaction, showed that both the Amberlyst® and NbOPO₄ were still acidic (Table 16).

Table 16: Acidity of solid acids before and after

Solid Acid Type	As Purchased (meq. H ⁺ g ⁻¹)	Post Reaction (meq. H ⁺ g ⁻¹)
Amberlyst® 15 Wet Form	2.50	1.60
NbOPO ₄	2.40	1.65

The drop in conversion was probably due to channeling through the acid catalyst bed. As stated above the Nottingham excimer reactor is not pressure rated, and therefore, it was necessary to pack the NbOPO₄ column only loosely with the powdered niobium phosphate so that no backpressure could be created. Because of this it is probable that a flow channel was created through the catalyst bed resulting in reduced contact between the catalyst and **15**. This is consistent with the fact that when the NbOPO₄ column was opened after the reaction, a channel could be clearly seen near the outlet. However, there is another possible explanation. Niobium phosphate has two different types of acid sites, Lewis and Brønsted acid sites. The titration of the new and used NbOPO₄ catalyst did show a slight drop in acidity of NbOPO₄ (Table 16). Therefore, it is possible that the type of acidic sites necessary for this dehydration reaction had been quenched or that compound **15** was sticking to some of the acid sites rather than being converted and flushed through to the bulk collection.

3.6 Conclusions and Future Work

The Nottingham excimer reactor has shown itself to be a useful tool to determine the most efficient wavelength and conditions for the photoinduced decarboxylation

reaction of 4-phthalimidobutyric acid. Once these conditions had been established, comparison of this reactor to those described in the literature confirmed that, for this reaction, the Nottingham excimer reactor was more efficient than most other reactors except for the Bristol Firefly. Furthermore, by studying the reaction at different wavelengths, we observed that it was possible to suppress undesirable side-reactions by utilising longer wavelength irradiation.

Although the integrated process to generate **16** was run for 10 hours and demonstrated the value of NbOPO₄ as a solid acid catalyst capable of replacing strong liquid acids such as trifluoroacetic acid, it was far from perfect. Over the course of the reaction, conversion dropped considerably. We believe that this is due to the flow channelling through the acid catalyst, because the column could not be fully packed to avoid backpressure build-up. Clearly an understanding of the pressure limits would be beneficial for the Nottingham excimer reactor to flexibly be integrated into future reactions. It would be particularly advantageous to know the weakest point in the system, whether that is the quartz tube or the O-ring seal onto the quartz tube. A leak at the O-ring would be far less catastrophic as this is outside the lamp, whereas pressure cracking the quartz tube would result in it being necessary to at a minimum replace a relatively expensive quartz tube. However this would also result in reagents being leaked directly onto the excimer lamp potentially ruining it, considering the cost and custom nature of the excimer lamps it is crucial to prevent this happening.

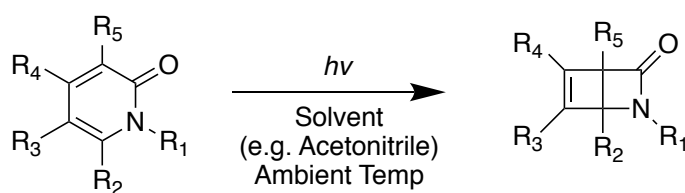
Chapter 4: Photochemical Isomerisation of 2-Pyridone

4.1 Chapter Summary

This chapter describes performing the photochemical isomerisation of 2-pyridone in continuous flow in the excimer reactor. The precipitation of the photo-dimer of 2-pyridone meant that it was necessary to perform the reaction in aqueous rather than organic solvent. This resulted in a complication of reaction analysis by quantitative ^1H NMR spectroscopy as the photoproduct was subliming while the solvent was removed. FTIR, UV-Vis, and HPLC were all investigated as alternative methods for reaction analysis, with HPLC giving both a fast and effective way to determine the success of the photochemical reaction.

4.2 Introduction to the Photochemical Isomerisation of 2-Pyridone

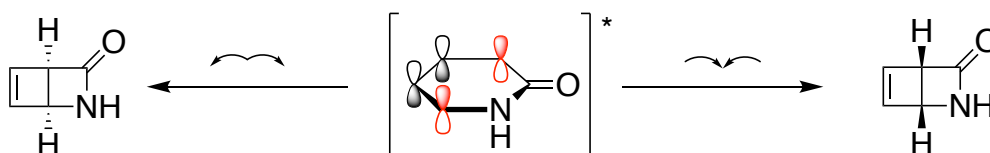
Our research group aims to build new reactors that allow sustainable chemical transformations to be performed in a more efficient way, and also to use these reactors to generate useful molecules or synthetic building blocks. These aims are as exemplified by group's work^{176, 233} on improving the semi-synthetic route to the antimalarial artemisinin. This chapter concerns photochemical isomerisation of 2-pyridone to a bicyclic compound, containing cyclobutene and β -lactam rings, Scheme 21. This reaction generates desirable molecular complexity in one clean, atom economical step. These photo-2(1*H*)-pyridones have the potential to be used as synthons for a β -lactam based antibiotics.²³⁴⁻²⁴¹ Since this reaction was discovered in the early sixties by Corey and Streith,²⁴² it has been extensively studied because of its synthetic potential,^{234-241, 243-256} but has proved difficult to scale-up.



Scheme 21: The photochemical isomerisation of 2-pyridone to 3-oxo-2-azabicyclo[2.2.0]hex-5-enes.

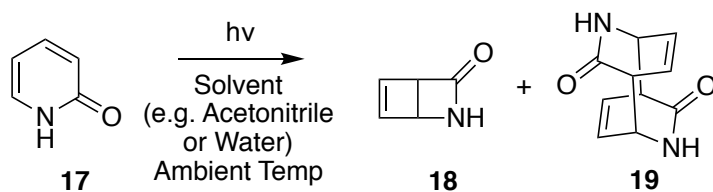
4.2.1 Mechanism of the Photochemical Reaction

The photochemical isomerisation reaction takes place from the S_1 singlet excited state of the 2-pyridone. While the pyridone is in this excited state, the 1,4 bond is formed via the disrotatory motion of the p-orbitals and a concerted 4-electron cyclisation, as shown Scheme 22. Since the rotation of the p-orbitals can be either inward or outward, prochiral 2-pyridones give rise to two enantiomeric photoproducts shown in Scheme 22.^{251, 253} As antibiotics must be enantiomerically pure it is unsurprising that there has been interest in performing this photoreaction enantioselectively, both in solution,^{249, 251-254} and in the solid state.^{241, 250, 251}



Scheme 22: Disrotatory 1,4 bond formation, giving rise to two enantiomers of photo-pyridone. The 1 and 4 p-orbitals are shown in red for clarity. Adapted from Sivasubramanian et al.²⁵¹

This reaction has been extensively studied, but surprisingly the majority of the literature focuses on substituted 2-pyridones, rather than the completely unsubstituted 2-pyridone, compound **17**, Scheme 23. This can be attributed to the fact that the many of the substituted 2-pyridones give higher yields of the corresponding photo-pyridones than the unsubstituted 2-pyridone does.^{243, 245, 256}



Scheme 23: Photochemical reaction of 2(1*H*)-pyridone, **17, to its photoisomer, **18**, and the [4+4] cycloaddition product, dimer **19**.**

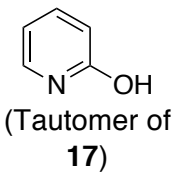
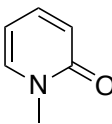
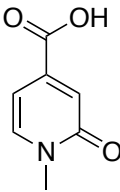
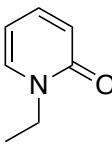
Upon irradiation **17** will form photo-pyridone **18**; however, there is a competing [4+4] dimerisation leading to compound **19**. In order to suppress this dimerisation, the reaction must be run under extremely dilute conditions,²⁵⁶ to prevent two molecules of **17** from meeting on the timescale of the excited state lifetime. The dimerisation occurs less readily in many of the substituted 2-pyridones and does not occur at all in 2-pyridones with an oxygen-based functional group at the 4-position,²⁵⁵ or when irradiating 1-alkenyl-2-pyridones.²⁵⁶

In addition to the competing reaction pathway, the quantum yield for the photochemical isomerisation of **17** is extremely low.²⁵⁶ This is consistent with the fact that the reaction takes place from a singlet excited state of the molecule, which is known to be very short lived both from the literature²⁵⁷ and from unpublished experimental results performed by our group (see Appendix 4.1). Because the excited state is so short lived there is only a small probability that the 1-4 bond will form before the excited state decays back to the ground state, via other more efficient intramolecular deactivation pathways.²⁵⁶

Despite the challenges associated with the photochemical isomerisation of unsubstituted 2(1*H*)-pyridone, compound **17**, the reaction does still provide an atom economic route to a valuable synthetic building block, **18**. The unfunctionalised photo-pyridone does not have any additional functional groups that may later require removal, which would add more steps to a synthetic route. Furthermore, there is a commercial motivation to study the photo-isomerisation reaction of **17** instead of a

functionalised pyridone; it is a very inexpensive starting material. The price of **1** and some examples of functionalised pyridones are compared in Table 17.

Table 17: Prices of 2-pyridone compounds. Prices taken from Sigma Aldrich (Merck) website 9th of Nov. 2017. Where the price for a 1g quantity was not given, the price was scaled as required.

Compound	 (Tautomer of 17)			
Price (£ / g)	0.71	2.68	47.20	908.0

4.3 Utilising the Excimer Flow Reactor for the Photochemical Isomerisation of 2(1*H*)-Pyridone

As stated in Section 4.2, the photoisomerisation of **17** → **18** is plagued by a low quantum yield, and a competing dimerisation reaction that requires low concentrations of **17** to be employed. One of the advantages of flow chemistry is that dilute solutions can be processed practically, since extremely large volume vessels are not necessary to generate product on a reasonable scale.⁷¹ This avoids impractically large set-ups for a research laboratory setting. Excimer lamps, as described in Chapter 1 - Section 1.5.1.2, emit light at a precise wavelength. We hypothesised that, because of the high intensity of monochromatic light and the nature of flow photochemistry, the low quantum yield of the reaction and need for dilute concentration could be partially offset by using the Nottingham excimer UV flow reactor. Thus, not only would the photochemical reaction be improved but also **18** would be produced in usable quantities. This was a major goal of the project, as **18** is a desirable material for both research groups at the University of Nottingham and potentially for customers outside the University.

4.3.1 Initial Results in Acetonitrile

To the best of our knowledge there are no previous examples of the photoisomerisation reaction from **17**→**18** performed in continuous flow in the literature. Therefore, appropriate conditions and irradiation wavelength had to be chosen as an initial starting point for the reaction. The concentration (0.01 M) and solvent (acetonitrile) were chosen to mirror those used by Adamo *et al.*²³⁶ To determine which UV lamp should be used, UV spectra were recorded for a series of dilutions of **17** in acetonitrile to determine the extinction coefficient of **17** at each excimer wavelength, see Figure 37 and Table 18 (see Appendix 4.2 for calibration curves, and Chapter 6 - Section 6.3.6 for further details). Figure 37 shows that **17** absorbs strongly at all three excimer wavelengths, 222 nm, 282 nm, and 308 nm, with a maximum absorption for the $n\rightarrow\pi^*$ transition occurring at 303 nm and a maximum absorption of the $\pi\rightarrow\pi^*$ transition occurring at 229 nm. Of the available excimer wavelengths, the molar extinction coefficient of **17** is highest at 222 nm. However, the spectral irradiance of the KrCl (222 nm) excimer lamp is the lowest of the three, see Table 13 in Chapter 3 – Section 3.4.1. Because the overall aim of the project was to generate **17** on a usable scale, it was deemed that irradiation with the 308 nm lamp would be the best starting point, as irradiation at this wavelength would combine the highest spectral irradiance with the second highest extinction coefficient. The 308 nm XeCl lamp was used for initial tests as this would compare most readily with previous work, where 2-pyridone solutions were irradiated with a 300 or 310 nm monochromatic light source^{236, 240, 255} or a mercury lamp with a pyrex filter^{234, 235, 237, 238, 243, 245, 251, 255} (wavelengths > 300 nm).⁷¹

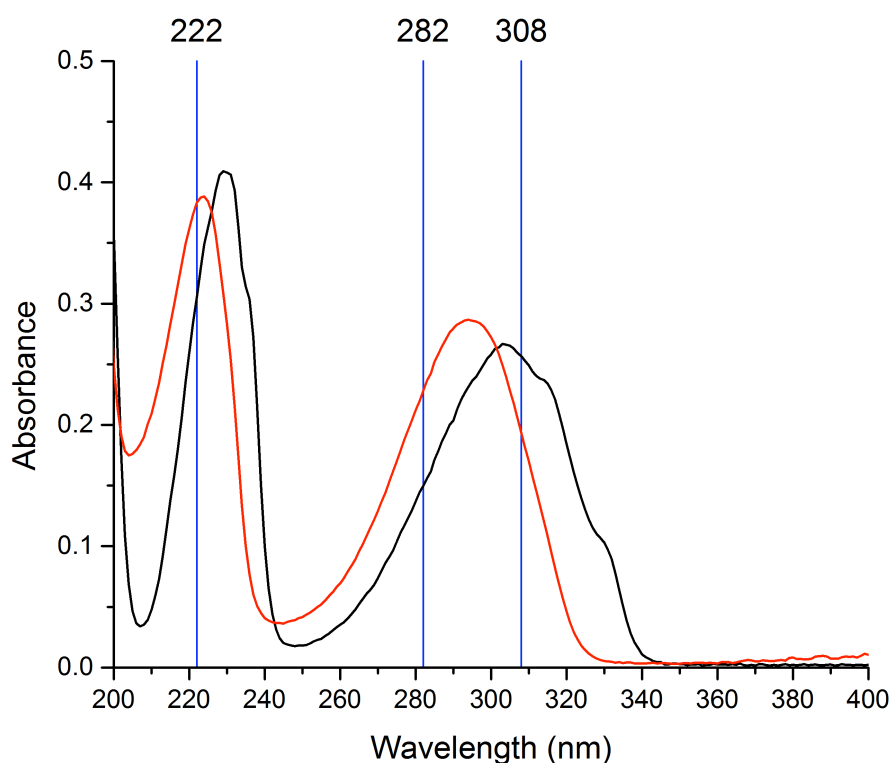


Figure 37: (Black) UV-Vis absorption spectrum of 5.0×10^{-4} M solution of 17 in acetonitrile (pathlength = 1 mm). (Red) UV-Vis absorption spectrum of a 5×10^{-5} M solution of 17 in water (pathlength = 1 cm). Excimer wavelengths marked with vertical lines for reference.

Table 18: Comparison of the molar extinction coefficients of 17 in acetonitrile and water at the wavelengths of the excimer lamps.

Wavelength (nm)	Solvent	Extinction Coefficient of 17 ($\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$)
222	Acetonitrile	5600
	Water	7110
282	Acetonitrile	2900
	Water	4700
308	Acetonitrile	4840
	Water	4090

When the initial experiment was performed, using a flow rate of 0.2 mL min^{-1} , significant reactor fouling occurred. Quantities of white powder was stuck inside the

reactor and tubing. This white powder was identified as **19** by ^1H and ^{13}C NMR spectroscopy and later by crystallography. Compound **18** was isolated from the solution that exiting the reactor and its identity was confirmed by ^1H and ^{13}C NMR spectroscopy, GC-MS, and X-ray crystallography (see Chapter 6 – Section 6.3.6). It was, however, nearly impossible to estimate the yield for this reaction, as the precipitation of solid resulted in the reaction being inhomogeneous. The white precipitate, dimer **19**, blocked off a portion of the reactor, thereby changing its volume and hence the residence time. Washing the precipitate out into the bulk collection would also not have given an accurate sample, as it had been irradiated for far longer than the expected residence time based on the flow rate.

Although no increase in pressure was observed during the course of this run, generating solids in flow reactors can result in a blockage to the flow system that could lead to the build-up of backpressure. As the excimer system is not pressure rated, one must avoid all reactions that can generate an increase in pressure for safety reasons. Additionally, reactor fouling will result in less light being able to penetrate into the reaction solution, reducing the efficiency of the irradiation and thus diminishing the yield of the reaction at a given flow rate. In an attempt to reduce the build up of precipitate, **19**, inside the reactor, it was decided to perform the reaction in a different solvent where the solubility of dimer **19** is higher. Water is capable of dissolving low concentrations of **19** and therefore kept the reaction stream homogeneous when used as the reaction solvent.

4.3.2 Initial Results in Water

Prior to irradiation in continuous flow, the UV-Vis spectrum of **17** in water was recorded to ensure that irradiating at 308 nm would still be appropriate (Figure 37). The molar extinction coefficients of **17** in water were calculated for each excimer wavelength, these can be found in Table 18 (calibration curves for the molar

extinction coefficient can be found in Appendix 4.2.2). Comparing the UV absorbance of **17** in water to the absorbance in acetonitrile, shows that in water the absorption maximum for the $n \rightarrow \pi^*$ transition is blue shifted from 303 nm in acetonitrile to 294 nm in water. The result of this blue shift meant that in water the molar extinction coefficients of compound **17** at 282 nm and 308 nm were much closer than they were in acetonitrile, with 282 nm actually having a larger extinction coefficient in water, see Table 18. It was therefore decided to conduct experiments at both 308 nm and 282 nm.

The reaction was run at the same conditions as described above (0.2 mL min⁻¹, 0.01 M, 308 nm irradiation) with DI water as the solvent rather than acetonitrile. Using water as the solvent did not result in any reactor fouling, and no precipitate was observed inside of the reactor. Therefore, subsequent reactions were performed at additional flow rates, and irradiating at 282 nm.

To assess the success of these experiments, three samples of a known volume (between 1 and 5 mL) were taken for each set of reaction conditions and the water was sublimed or evaporated to dryness, either by freeze drying or by rotary evaporation. In order to determine the yields of **18** and **19** and conversion of **17**, quantitative ¹H NMR spectra were recorded in d₆-DMSO against an external standard of 1,3,5-trimethoxybenzene. The ¹H NMR results from the three samples were averaged to give the conversion of **17** as well as the yields of **18** and **19**. The results of irradiation of 0.01 M 2-pyridone solution in DI water are presented in Table 19.

As expected in photochemical reactions longer residence times (slower flow rates) led to a higher degree of conversion. However, as can be seen in Table 19, higher conversion did not result in a higher yield of **18**. By comparing the yield of **18** when 308 nm irradiation was used, Entries 1, 2, and 3, there was no clear trend in yield vs.

flow rate (irradiation time). The most striking feature of the data was the poor mass balance with up to 87% “missing mass” in an experiment of slower flow rate, see Table 19 mass balance column.

Table 19: Results of the irradiation of 0.01 M 2-pyridone in DI water at 1°C.

Entry	Irradiation Wavelength	Flow Rate (mL min ⁻¹)	17 Unconverted (%)	Yield 18 (%)	Yield 19 (%)	Mass Balance* (%)
1	308	0.2	15	2	5	22
2	308	0.5	41	9	4	54
3	308	1.0	64	6	3	73
4	282	0.2	5	1	7	13

* Mass balance is given by the sum of unconverted **17**, yield of **18**, and yield of **19**.

Degradation in photochemical experiments is commonly due to photoproducts undergoing secondary photolysis.²⁵⁸ However, in order for these processes to occur, the primary photoproducts must absorb the UV light.²⁵⁹ As can be seen from the UV-Vis spectra of **18** and **19**, Figure 38, these two compounds have only minimal UV absorption at 308 nm and 282 nm. Although a large mass loss was present both when irradiating at 308 nm and 282 nm, the mass balance is slightly worse with the shorter wavelength UV irradiation, Table 19 compare Entries 1 and 4. However, there was also a higher degree of conversion when irradiating at 282 nm, and higher conversion generally resulted in a larger mass loss. When the fact that compounds **18** and **19** absorb very little light at 282 nm and 308 nm is added to little evidence for any photodegradation products detected by ¹H NMR, it seemed unlikely that the large mass loss was due to photochemical degradation and must, therefore, have another explanation.

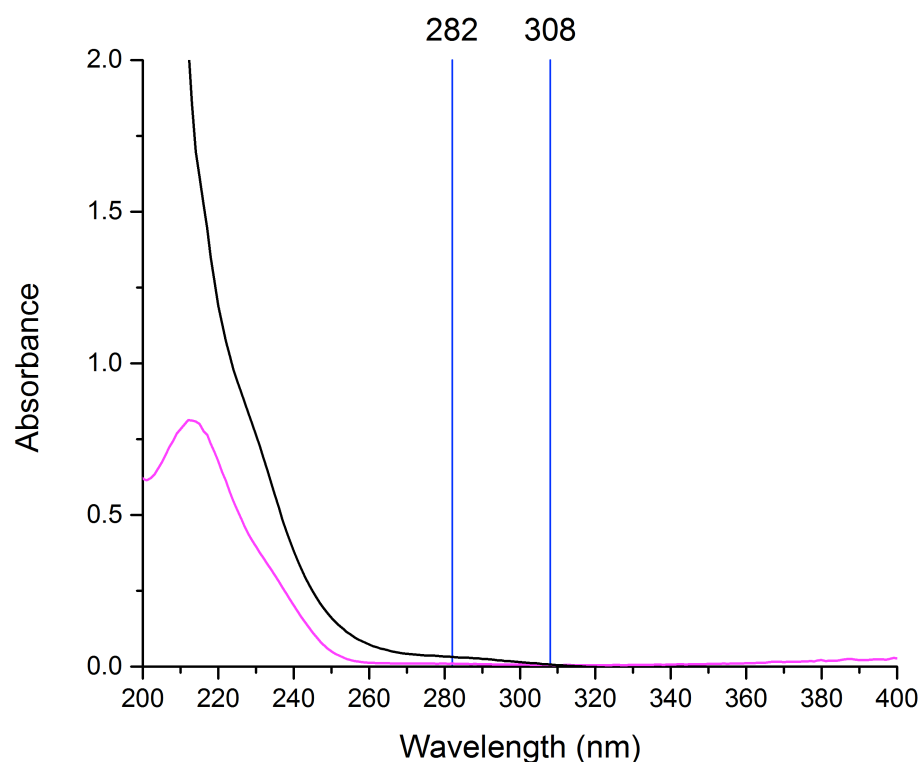


Figure 38: (Pink) UV-Vis absorption spectra of a 5×10^{-4} M solutions of product 18 and (black) dimer 19 in water (pathlength = 1 cm).

Since the reaction had such a high degree of unexplained mass loss when analysed by ^1H NMR, it was decided to use a different analytical technique, which might provide additional information to explain poor mass balance and lack of trend in yield of **18** with increasing conversion. Additionally, since the reaction was run in water, evaporation of the samples prior to running NMR analysis was the slowest step in generating results, with evaporation (for all samples together) taking a minimum of 12 hours in the freeze drier. It was therefore highly desirable to introduce a faster analytical method.

4.4 In-line Photochemical Reaction Analysis

The importance of fast analysis is discussed further in Chapter 5. In-line Fourier transform infrared (FTIR) spectroscopy and in-line UV-Vis analysis were proposed as

two potential ways of analysing the reaction, and instruments were available to perform these spectroscopic techniques in-line.

4.4.1 In-line FTIR

The Bruker Alpha-P attenuated total reflectance (ATR) FTIR spectrometer has a cell that allows the reaction output stream to continually run through the spectrometer, delivering real-time reaction feedback, highly desirable for the 2-pyridone isomerisation reaction. Therefore test ATR spectra were recorded for 0.05 M aqueous solutions of compounds **17**, **18**, and **19**. Unfortunately none of the characteristic peaks for each compound, that were present in the solid state, were detectable even at 0.05 M, a concentration higher than used in our initial photochemical experiments. Only the IR bands of water were detectable. The solid state, solution and water subtracted spectra for compound **17** are shown in Figure 39, and similar spectra for compounds **18** and **19** can be found in Appendix 4.3. Difference ATR spectra, were obtained by subtracting the spectrum of pure water from spectra of **17**, **18**, or **19** but even these difference spectra showed no distinct bands due to the solutes. Therefore, it was clear that in-line ATR was not appropriate for analysing this reaction.

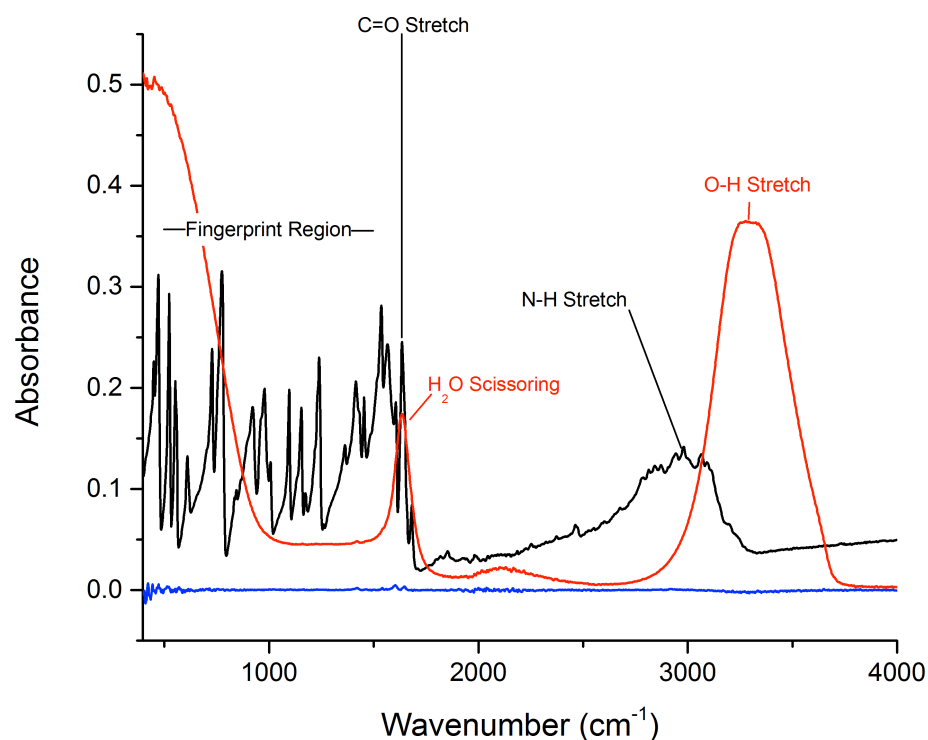


Figure 39: ATR spectra of compound **17** in the solid state (black), ATR spectra of **17** as a 0.05 M solution in water (red), and ATR spectra of **17** as 0.05 M solution in water with a background spectrum of water subtracted (blue).

4.4.2 In-line UV-Vis Analysis

UV-Vis was another real-time spectroscopic technique that had the potential to give fast feedback during the photochemical isomerisation of **17**→**18**. By utilising the Ocean Optics Fibre optic probes, Ocean Optics Flame miniature UV-Vis spectrometer, DH-mini light source and spectra suite software, in conjunction with a Harrick flow cell and appropriate spacers, it was possible to obtain continuous UV-Vis data from the excimer reactor flow stream.

4.4.2.1 In-line UV-Vis Flow Set-Up

The outflow tube from the excimer reactor was connected to the bottom fitting of a Harrick cell that had either 150 μm or 100 μm PTFE spacers between the calcium fluoride windows (transparent to wavelengths between 130 nm and 10 μm).²⁶⁰ An

additional tube was connected to the top fitting of the Harrick cell that fed to the bulk collection. Orienting the tubing so that the flow was against gravity (up-flow) helped to minimise the time that bubbles spend in the Harrick cell. Gas bubbles can potentially lead to a “dead spectrum”, where nothing is seen. Fortunately, the excimer system does not generate gas and if any bubbles do appear in the outlet tubing they are typically very small, coming only from small quantities of gas dissolved in the solvent or trapped inside the reactor. Figure 40 shows a schematic of the in-line UV-Vis setup. The light source, Harrick cell, and spectrometer are all small enough to be conveniently placed downstream of the reactor inside the fume hood.

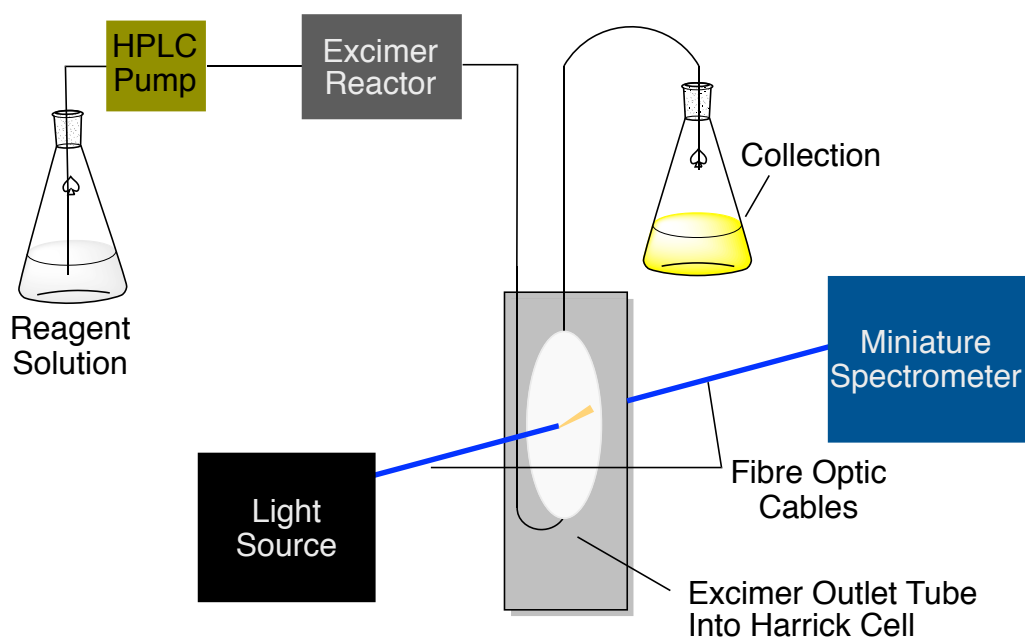


Figure 40: Schematic of in-line UV-Vis set-up connected to the excimer reactor.

The time interval between successive spectra can be set by the operator using the Spectra Suite software anywhere from milliseconds to hours. In the case of this reaction, a spectrum was collected every five minutes; this provided a compromise between obtaining excessive amounts of data and having insufficient data to see how the reaction was changing over time. After recording a background spectrum

when the reactor and Harrick cell only contained solvent (water), some of the reagent solution of **17** was pumped through the reactor and Harrick cell while the lamp was off. Once equilibrium was reached (the on-screen spectrum was no longer changing) the recording of spectra was started and the lamp switched on to begin the reaction. The pre-irradiation spectrum was used to give a starting concentration rather than relying on the concentrated calculation from mass of starting material and volume of reagent solution.

4.4.2.2 In-line UV-Vis Limitations and Calibration

Unfortunately only compound **17** has a unique peak in its UV-Vis spectrum (peak maximum 294 nm) that can be used to measure conversion. Compound **18** has a peak absorption at 213 nm which overlaps with absorption by compounds **17** and **19**. Compound **19** has a weak absorption peak at 266 nm, but this peak has a degree of overlap with the absorption peak of **17** at 294 nm. The UV-Vis spectra of these compounds have been reprinted below for clarity, Figure 41.

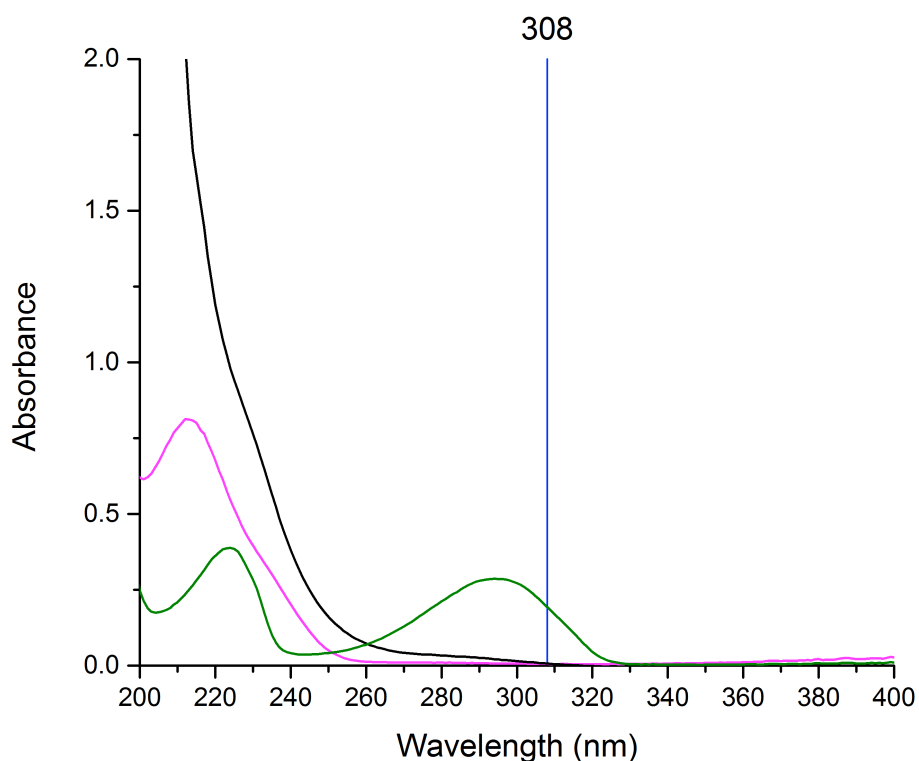


Figure 41: (Green) UV-Vis absorption spectra of a 5×10^{-5} M solution of starting material **17 in water and 5×10^{-4} M solutions of (pink) product **18** and (black) dimer **19** in water (pathlength = 1 cm).**

Calibration curves for absorption vs. concentration of **17** in water had already been performed for each of the three excimer lamp wavelengths, 222 nm, 282 nm, and 308 nm, to calculate the molar extinction coefficient of **17** at each of these wavelengths. Since compounds **18** and **19** have almost no absorbance at longer wavelengths, the absorbance of **17** at 308 nm and the corresponding extinction coefficient were used to calculate the conversion of **17**. At 308 nm no overlap should be present so all measured UV absorbance should be due to absorption by starting-material **17**.

4.4.2.3 In-line UV-Vis Results

Using the Beer-Lambert law,²⁶¹ the molar extinction coefficient from the calibration curve and the measured absorbance at 308 nm it was possible to determine the

concentration of **17** before and after the reaction. From these concentrations the conversion and proportion of starting material remaining after the reaction could be calculated.

Table 20: Results of irradiation of 0.01 M solutions of **17 in water at 0.2 mL min⁻¹ and 1°C.**

Irradiation Wavelength (nm)	Flow Rate (mL min ⁻¹)	17 Unconverted (%) by UV-Vis	17 Unconverted (%) by ¹ H NMR	Yield 18 (%) by ¹ H NMR	Yield 19 (%) by ¹ H NMR	Mass Balance (%)	
						17 by ¹ H NMR	17 by UV-Vis
308	0.2	19	15	2	5	22	26
308	0.5	50	41	9	4	54	63
308	1.0	73	64	6	3	73	82
282	0.2	8	5	1	7	13	16

When compared to the ¹H NMR results, the percentage of **17** remaining as given by UV-Vis was only slightly higher, and within error of the result as given by quantitative ¹H NMR, see Table 20. Even with the slightly higher quantities of **17** given by UV-Vis, the mass balances of the reaction were still far from 100 percent (Table 20). The UV-Vis results did not provide clear evidence that there was a problem with analysing the reaction by ¹H NMR. However, they also did not help to explain why the mass balances were so far from 100 percent as the yields of both **18** and **19** could not be measured by UV-Vis. Therefore, it was clear that yet another analytical technique would be necessary to help discover why the mass balance was so poor when analysed by ¹H NMR.

4.4.2.4 Additional Information Provided by In-Line UV-Vis Analysis

Despite not being able to analyse the photochemical reaction by UV-Vis, it did provide additional information about the excimer reactor system, particularly validating our decision on equilibration times, namely to allow two system volumes (defined Chapter 2 - Section 2.4) to flow through the reactor at the reaction conditions before samples were taken. While there is some precedent for allowing this amount of equilibration time,^{134, 262} it had not specifically been tested in the excimer system.

Solutions of **17** were pumped through the reactor that was initially full of pure solvent while the lamp was off (no reaction taking place). During this time it was possible to monitor the growth of the UV peak at 294 nm for compound **17**. At a flow rate of 1.0 mL min⁻¹ the peak at 294 nm had reached a consistent absorbance value after 20 minutes, or after the equivalent of 1.7 system volumes had been flowed through the reactor (N.B. the additional tubing to the UV-Vis spectrometer added approximately 2 mL to the system volume, meaning the overall system volume was 12 mL). This can be seen in Figure 42 where the peak at 294 nm reached full height after 20 minutes (shown in green). By decreasing the time period between spectra to less than five minutes it would be possible to obtain an ever more precise equilibration time if it were desired.

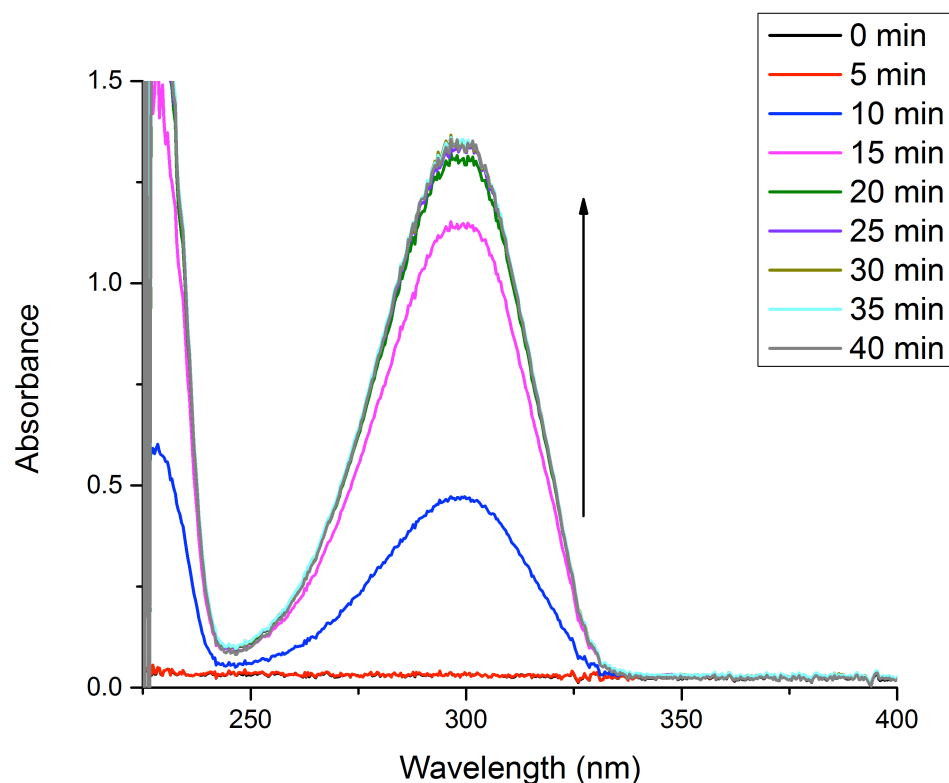
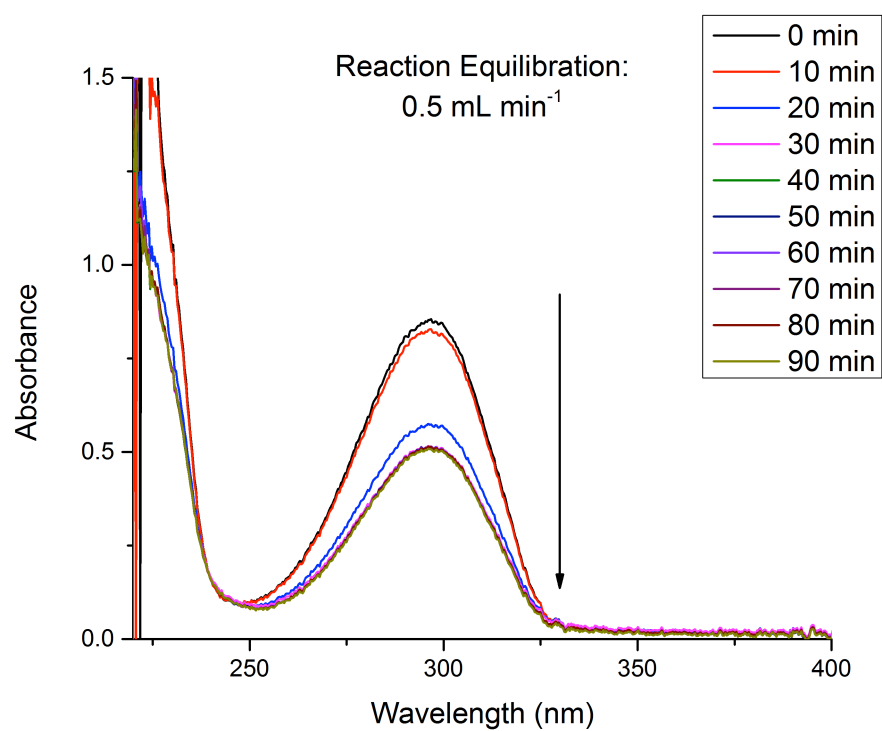
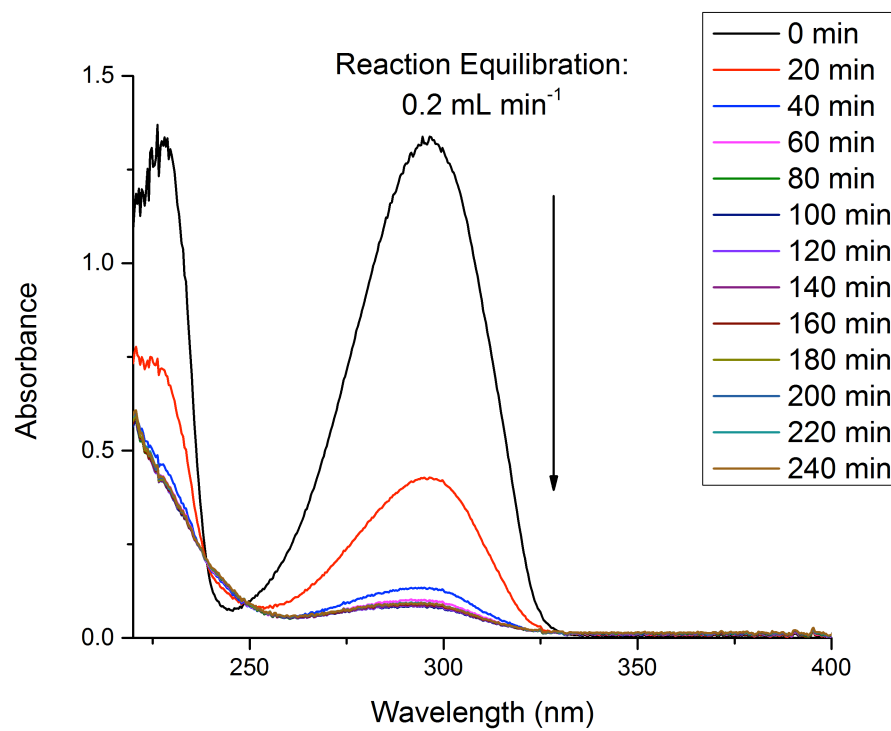


Figure 42: Ocean Optics in-line UV-Vis spectra of the pre-reaction equilibration of starting material **17 solution at 1.0 mL min^{-1} .**

After the lamp was switched on, the peak at 294 nm decayed due to the conversion of **17** to products **18** and **19** until it reached a steady constant absorbance when an equilibrium was reached. This occurred after 80 minutes when flowing at 0.2 mL min^{-1} (Figure 43, top), 30 minutes for a flow rate of 0.5 mL min^{-1} (Figure 43, middle) and 20 minutes for a reaction at 1.0 mL min^{-1} (Figure 43, bottom). These equilibration times correspond to 1.3, 1.2 and 1.7 system volumes respectively. As when allowing the reactor to equilibrate pre-reaction, a more accurate equilibration time can be obtained by taking more frequent spectra. This is particularly true when the faster flow rate, 1.0 mL min^{-1} is used.



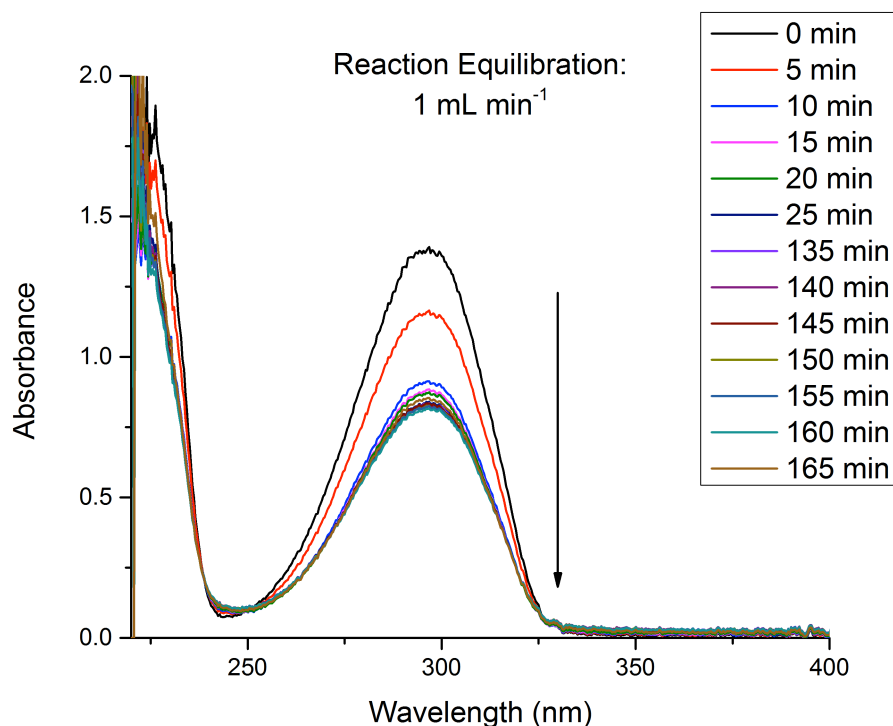


Figure 43: UV-Vis spectra showing the decay of compound 17 to a steady absorbance as the reactor equilibrates at (top) 0.2 mL min⁻¹, (middle) 0.5 mL min⁻¹, (bottom) 1.0 mL min⁻¹.

This gave clear evidence that the system had reached equilibrium conditions in previous experiments, when two system volumes had been allowed to flow through the reactor before samples were collected. However, moving forward it became possible to take samples after only 1.7 system volumes had passed through the reactor and to have confidence that these samples accurately represented the set experimental conditions. In future excimer reactor experiments this will allow for both less waste of reagents, and faster sampling, meaning that more results can be obtained in a shorter period of time.

The in-line UV-Vis results also gave an indication of the maximum fluctuation in yield during a continuous UV flow experiment. Once the system had reached equilibrium, there was only a small fluctuation in the absorbance at 294 nm, with no trend over time. This fluctuation is the combination of the error due to fluctuation in the intensity of the light source, the error due to slight changes in the composition of the reagent

stream leaving the reactor, and the error associated with pump flow rate. The differences in absorption of **17** at 308 nm, for equilibrium conditions pre-reaction and after irradiation at 0.2, 0.5, and 1.0 mL min⁻¹, can be seen in Table 21. At all flow rates tested the fluctuation in absorbance gave rise to an error in absorbance of **17** of less than 4%. A more detailed discussion of the errors can be found in Appendix 4.4.

Table 21: Errors in absorbance at 308 nm at different flow rates.

Entry	Flow Rate (mL min ⁻¹)	Error in Absorbance at Equilibrium (%)	Error in Absorbance at Equilibrium (AU)
1	1.0 (no irradiation)	0.49	5.6 x 10 ⁻³
2	1.0	1.3	8.7 x 10 ⁻³
3	0.5	0.82	3.2 x 10 ⁻³
4	0.2	3.3	1.9 x 10 ⁻³

4.5 Results by HPLC

Although UV-Vis was able to corroborate the conversion given by ¹H NMR and give near-real time feedback about the photoisomerisation reaction, it failed to suggest why the mass balance of the reaction was so low. Therefore it was decided to attempt to analyse the reaction by HPLC, which combines separation with quantification of the components of the product mixture. Compounds **17**, **18**, and **19** are highly polar, therefore reverse phase HPLC, where the eluent is more polar than the stationary phase, seemed most likely to achieve separation.²⁶³

4.5.1 Method Development

The Agilent Technologies 1200 series HPLC was fitted with a Waters C₁₈ (3.9 x 150 mm) reverse phase column. Using an isocratic mixture of 98% water and 2% acetonitrile at a flow rate of 1.0 mL min⁻¹, compounds **17**, **18**, and **19** separated well, see Figure 44 for an example chromatogram and Table 22 for the retention time of

the three compounds. This method was able to separate the compounds in less than 3 minutes (the overall run time including column flush and re-equilibration was slightly longer at 7 minutes). This short processing time meant that reaction analysis would no longer be the rate-limiting step in generating results.

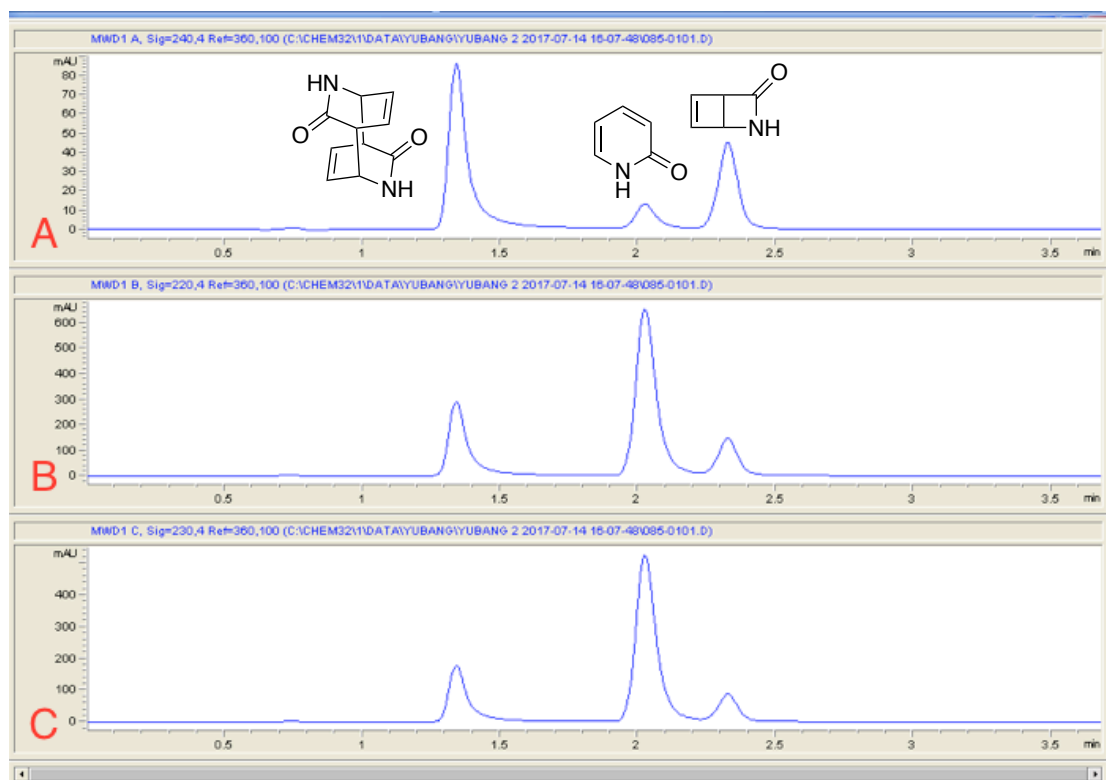


Figure 44: Representative HPLC chromatograms with UV detection at (A) 240 nm, (B) 220 nm, and (C) 230 nm.

Table 22: HPLC retention times of products and starting material in the photochemical reaction of 2(1*H*)-pyridone.

Compound	Retention Time (min)
17	2.39
18	2.79
19	1.56

4.5.2 Calibration

Compounds were detected by the Agilent 1200 series multiple wavelength detector that is capable of monitoring up to four different wavelengths simultaneously. Three

wavelengths, 220 nm, 230 nm, and 240 nm were used to build calibration curves of peak area vs. concentration for compounds **17**, **18**, and **19**. These wavelengths were chosen as all three compounds absorb at these wavelengths, Figure 45.

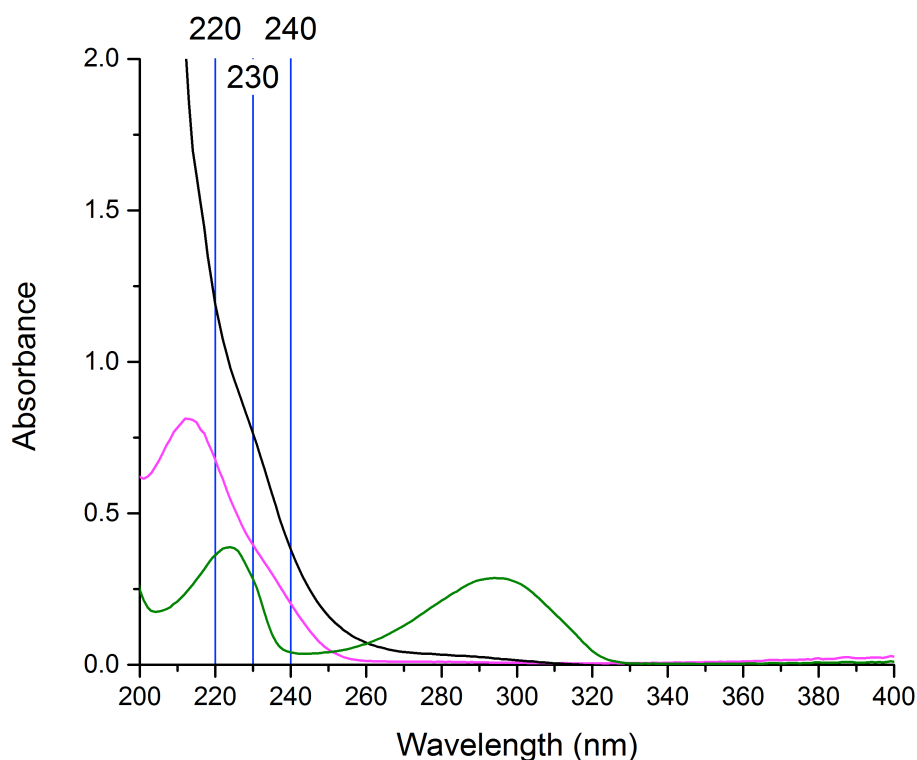


Figure 45: UV-spectra marked with HPLC detection wavelengths of (green) 5×10^{-5} M solution of **17, (pink) 5×10^{-4} M solution of **18** and (black) 5×10^{-4} M solution of **19** (pathlength = 1 cm).**

For each compound, the absorbance is highest at 220 nm and lowest at 240 nm. Because the compounds absorb strongly at 220 nm, detection of compounds is possible even when they are present in only very low concentrations. By detecting at 240 nm, where the three compounds absorb less strongly, it is possible to measure much higher concentrations of the compounds without the signal being saturated. By using multiple wavelength detection it is possible to cover a much larger dynamic range of concentrations with the method, without the need for changing the injection volume or pre-dilution of samples.

Calibration curves with a high degree of linearity were obtained for all three compounds at each of the three detection wavelengths. Calibration curves can be found in Appendix 4.5.

4.5.3 HPLC Method Testing Results

An experiment was repeated at one of the sets of conditions that had previously been tested when the experiment was analysed by ^1H NMR and UV-Vis, (0.01 M, 1°C , 0.2 mL min^{-1} , 282 nm irradiation). However, this time an additional sample was taken and analysed by reverse phase HPLC. The proportion of unconverted compound **17** and yields of compounds **18** and **19**, at each detection wavelength are given in Table 23.

Table 23: Results by HPLC at three detection wavelengths of 282 nm irradiation of 0.01M solution of 17 in water at a flow rate of 0.2 mL min^{-1} and 1°C .

Detection Wavelength (nm)	Unconverted 17 (%)	Yield 18 (%)	Yield 19 (%)
220	9	78	13
230	7	79	11
240	6	78	12

All detection wavelengths gave similar yields for each of the three compounds. The concentrations of **17**, **18**, and **19** were within the linear region of each calibration curve and well below the saturation limit of the detector. Therefore, in this case it was appropriate to average the results of the three detector wavelengths to get overall results by HPLC. When compared with the results given by ^1H NMR, it immediately became apparent that the two analytical techniques for the same experiment gave vastly different results, Table 24.

Table 24: Comparison of results when analysing the reaction results for the photo-isomerisation 17→18 by HPLC and ¹H NMR (0.01 M aqueous solution of 17 irradiated at 282 nm at 0.2 mL min⁻¹ and 1 °C).

Analytical Technique	Unconverted 17 (%)	Yield 18 (%)	Yield 19 (%)	Mass Balance (%)
HPLC	7	79	12	98
¹ H NMR	10	5	6	21

Although there is a slight difference in the values obtained for the conversion of **17** and the yield of **19** between the two techniques, the discrepancy between the values is within experimental error. However, the 72% difference in yield of **18** between the two analytical techniques clearly shows that one of the analytical techniques was giving incorrect results. Since, the mass balance by HPLC was very near to 100%, it seemed most probable that the NMR results were unreliable, and that the manner in which quantitative ¹H NMR was being performed was not appropriate for this reaction.

4.5.3.1 Control Experiments to Test Compound 18 for Volatility

NMR spectroscopy is generally thought of as a non-invasive, non-destructive technique.²⁶⁴ However, it does typically require that samples are prepared in deuterated solvents.²⁶⁵ This normally means that the non-deuterated reaction solvent is evaporated from a sample prior to being redissolved in a deuterated solvent for NMR spectroscopy.

In the literature compound **18** is isolated by removing the solvent at reduced pressure.^{236, 247, 256} However, in all of these cases lower boiling point organic solvents such as acetonitrile (81.6 °C),¹⁸⁴ ethyl acetate (77.0 °C),¹⁸⁴ benzene (80.0 °C),¹⁸⁴ and diethyl ether (34.5 °C)¹⁸⁴ were used for the reaction and work-up. The volatility of **18** was not initially considered, as it is a solid at ambient temperature and pressure. However, as the reactions described in this chapter were carried out in water, a

higher boiling solvent, it was a likely explanation for the large degree of mass loss in samples that had been prepared by reduced pressure evaporation/sublimation (NMR samples) compared with those that had no pre-analysis solvent removal (HPLC). To elucidate whether this was indeed the case, a control experiment was necessary.

A 0.01 M solution of **18** was made and divided into six 1 mL samples and three 4 mL samples. Three of the smaller samples (1 mL) were run directly on the HPLC. The other six samples were freeze dried over-night to dryness. The three 1 mL samples were re-dissolved in water to a volume of 1 mL and submitted for HPLC analysis. An external standard, (1,3,5-trimethoxybenzene), was added to the three 4 mL freeze dried samples and they were dissolved in d_6 -DMSO and submitted for ^1H NMR analysis. The average recovery of **18** was taken for each set of samples, since samples with similar treatment produced similar results. The percentage recovery of **2** for each type of sample treatment is presented in Table 25.

Table 25: Recovery of 18 before after freeze drying.

Analytical Technique and Treatment	Recovery (%)
HPLC – No sample preparation	94
HPLC – Freeze dried overnight	1
NMR – Freeze dried overnight	1

The results of this control experiment clearly show that compound **18** is volatile and is lost during reduced pressure solvent removal when high boiling water is used as the solvent. Analysing the reaction without solvent removal by pre-saturated ^1H NMR would also be possible (results were similar for a selected experiment by both pre-saturated ^1H NMR and HPLC, see Appendix 4.7). Obtaining results by reverse phase HPLC method was faster than obtaining results by ^1H NMR spectroscopy. Furthermore running pre-saturated ^1H NMR required more careful sample preparation as samples had to be spiked with a known quantity of deuterium oxide

and a known quantity of external standard had to be added. By contrast reverse phase HPLC could be performed with samples directly from the outlet of the reactor. Therefore, HPLC was deemed the better way of analysing the reaction and used to obtain the results presented in the next section.

4.5.4 The Photochemical Isomerisation of 2-Pyridone in the UV-Flow Reactor, Results by HPLC.

After determining that HPLC was the best technique for analysing the photochemical isomerisation of **17**→**18**, it was possible to begin identifying conditions that would give **18** in the highest yields and that would be the most productive. The effects of flow rate on yield and productivity are shown in Table 26.

Table 26: Yield and productivity for the photochemical isomerisation of **17→**18** as a function of flow rate, 282 nm irradiation of 0.01 M aqueous solution at 1°C.**

Flow Rate (mL min ⁻¹)	Unconverted 17 (%)	Yield 18 (%)	Yield 19 (%)	Productivity 18 (mmol h ⁻¹)
0.2	7	79	12	0.095
0.5	48	40	10	0.12
0.8	60	29	7	0.14
1.0	63	25	6	0.15

As expected the slower the flow rate (the longer the residence time), the higher the product conversion and thus the yield. However, productivity decreased with decreasing flow rate (and conversion) due to less substrate passing through the reactor and loss of efficiency of photon capture. At the start of the reaction when the concentration of **17** is highest more photons are absorbed by the solution and are used to generate **18**. As the reaction proceeds along the reactor there are fewer molecules of **17** present to capture the UV light. Therefore, more UV light is transmitted through the solution where it can be absorbed by the cooling stick of the reactor rather than used for photochemical reaction. As a result the reaction

becomes less efficient with longer irradiation time (higher degree of conversion), leading to an overall decrease in productivity with slower flow rate.

4.5.4.1 Concentration Study

In theory, by increasing the concentration of the reagent solution the efficiency of the photon capture should also increase, up to the point where no light is transmitted through the solution over the entire irradiation volume of the reactor. This in turn would lead to the highest productivity for the reaction but also mean that overall conversion would be low. In practical terms, however, choosing between high yielding and highly productive reactions will come down to the nature of a particular reaction, i.e. the cost of the starting materials, value of products, the ease of purification, and ability to recycle starting material. This is discussed further in Chapter 5.

In the case of the photo-isomerisation of **17**→**18**, increasing productivity by using a more concentrated reagent solution is slightly more complex; as higher concentration also increases the likelihood that dimer **19** will form. It was important to see how much the concentration could be increased without detrimental effects to the yield of **18** in an attempt to increase productivity. To achieve the theoretical limit of productivity where the solution exiting the reactor absorbs a minimum of 99% of the light, the solution exiting the reactor after the reaction would have to have starting material **17** at a concentration 0.035 M when irradiating at 282 nm.

The results presented so far were carried out at 0.01 M, well below the theoretical limit of productivity. Therefore, additional photochemical experiments at concentrations of 0.02, 0.05, 0.1, and 0.5 M were performed at the four flow rates that had previously been used. However, when the 0.5 M solution was irradiated, a significant quantity of precipitate, confirmed to be dimer **19** by ¹H NMR spectroscopy, was formed and the reaction could not be analysed for the reasons previously

described in Section 4.3.1, Figure 46, making it clear that it would not be possible to analyse reactions at 0.5 M or above. Results from the irradiation of 0.02, 0.05 and 0.1 M solutions as well as the previously shown 0.01 M results are presented in Table 27.



Figure 46: Quartz tube after 0.5 M solution of 17 had been irradiated.

Table 27: Yield and productivity from irradiating aqueous solutions of **17 at 282 nm as a function of concentration and flow rate, with 282 nm irradiation at 1°C.**

Concentration (M)	Flow Rate (mL min ⁻¹)	Unconverted 17 (%)	Yield 18 (%)	Yield 19 (%)	Productivity 18 (mmol h ⁻¹)
0.01	0.2	7	79	12	0.095
	0.5	48	40	10	0.12
	0.8	60	29	7	0.14
	1.0	63	25	6	0.15
0.02	0.2	28	55	20	0.13
	0.5	61	30	12	0.18
	0.8	69	22	8	0.21
	1.0	73	18	7	0.22
0.05	0.2	43	25	19	0.15
	0.5	63	13	12	0.20
	0.8	66	10	8	0.24
	1.0	70	8	7	0.24
0.1	0.2	39	15	23	0.18
	0.5	56	7	11	0.21
	0.8	60	5	8	0.24
	1.0	64	5	7	0.30

As expected, increasing the concentration did increase the productivity of the reaction, for a given flow rate. However, the increase in productivity was not proportional to the increase in concentration i.e. a two fold increase in concentration did not result in a two fold increase in productivity for compound **18**. This can at least partially be attributed to the fact that more dimer was produced when higher concentrations were used, meaning that more photons were being used for the

production of **19**. This is not immediately clear from the yields of **19** because higher concentration solutions resulted in lower conversion. However, when selectivity for compound **19** was compared across the concentrations, it became immediately evident that the selectivity for **19** increased with increasing concentration, Table 28. This large change in selectivity is also most likely the reason that conversion was actually higher at all four flow rates when the concentration was raised from 0.05 M to 0.1 M. This result provides some evidence that if the concentration of **17** is high enough for molecules of **17** to meet on the time scale of the lifetime of the excited state, then the quantum yield of the dimerisation reaction is higher than the isomerisation reaction. However accurate quantum yield calculations would be necessary to definitively make this claim, and these were not made for the same reasons as stated in Chapter 3.

Table 28: Selectivity for compounds **18 and **19** as a function of flow rate and concentration when irradiating aqueous solutions of **17** at 282 nm and 1°C.**

Concentration (M)	Flow Rate (mL min ⁻¹)	Selectivity 18 (%)	Selectivity 19 (%)
0.01	0.2	87	13
	0.5	80	20
	0.8	81	19
	1.0	81	19
0.02	0.2	73	27
	0.5	71	29
	0.8	73	27
	1.0	72	28
0.05	0.2	57	43
	0.5	52	48
	0.8	56	44
	1.0	53	47
0.1	0.2	39	61
	0.5	39	61
	0.8	38	62
	1.0	42	58

One would expect that the selectivity for **19** would have been higher when faster flow rates at given concentration were used, due to the concentration gradient present inside the reactor. The concentration gradient means that the concentration of **17** gets lower along the length of the reactor as **17** is converted to **18** and **19**. With faster flow rates, the irradiation time is shorter, and therefore less conversion of **17** occurs. Therefore, the concentration gradient is larger with slower flow rates, so more of the conversion of **17**→**18** takes place when the effective concentration inside

the reactor is lower. However, the results showed that selectivity for **19** did not display a trend to increase with flow rate at a given concentration. Rather selectivity for **19** was more or less consistent for a given concentration.

With increasing concentration, the mass balance also became increasingly lower than 100%, Table 28. The calculation for mass balance in this table only includes compounds **17**, **18**, and **19**. As the concentration was increased a peak at a retention time of 1.6 minutes began to grow in in the HPLC traces. The peak area of this peak when detected at 220 nm, as a ratio to the peak area of compound **19** is given in Table 29 below. It must be noted that some of the mass balances are slightly over the maximum 100%. This is probably the result of rounding of the percentages (ie uncertainty in the final digit). Additionally the calibration curves used to calculate yield do have a small degree of error. In all cases the mass balances do not exceed 100% by more than 3%, which is within the error of the measurement.

Table 29: Reaction mass balance and peak area at 1.6 min as a function of concentration and flow rate when irradiating aqueous solutions of **17 at 282 nm and 1°C.**

Concentration (M)	Flow Rate (mL min ⁻¹)	Mass Balance	Peak Area at 1.6 min (220 nm detection)	Ratio of Peak Area at 1.6 min to Peak Area of 19 (220 nm detection)
0.01	0.2	94	No peak detected	-
	0.5	98	No peak detected	-
	0.8	96	No peak detected	-
	1.0	95	No peak detected	-
0.02	0.2	103	No peak detected	-
	0.5	103	293	0.64 : 1
	0.8	99	267	0.84 : 1
	1.0	98	252	0.95 : 1
0.05	0.2	87	1002	0.53 : 1
	0.5	88	1079	0.91 : 1
	0.8	84	888	1.1 : 1
	1.0	85	682	1.2 : 1
0.1	0.2	77	2801	.62 : 1
	0.5	74	2361	1.1 : 1
	0.8	73	2019	1.2 : 1
	1.0	76	1668	1.3 : 1

Compound **19** has been identified as the trans-anti dimer. There are three other conformations that [4+4] cycloaddition dimers of 2-pyridones can theoretically take (Figure 47). However, the trans-anti dimer, **19**, appears to be the most favored.^{256, 266,}

²⁶⁷ Without a calibration curve and hence a response factor for the compound giving rise to the peak at 1.6 min, from here on referred to as **D1.6**, it is impossible to obtain a yield for this compound. However, by comparing the area of the peak at 1.6 minutes to the peak area of dimer **19**, it is possible to see a pattern appearing in terms of both concentration and conversion (flow rate). With increasing concentration, the ratio of **D1.6:19** increases. Furthermore at a given concentration the ratio of **D1.6:19** is also higher when faster flow rates are used and thus conversion is lower. When conversion is lower (faster flow rates are used) the effective concentration over the entire reaction is higher because of the concentration gradient inside the reactor. This gives support to the hypothesis that **D1.6** is another dimer of **17**, with regiochemistry that results from a less favoured pre-association of molecules of **17** compared to **19**, and thus is only formed at higher concentrations. Further work would be necessary to purify and identify this compound. After doing so it would be possible to perform a calibration curve for this compound, which could be used to calculate yields of **D1.6** and overall mass balances for the results presented above.

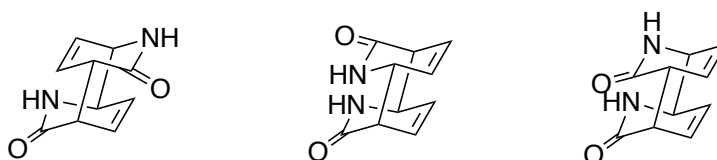


Figure 47: Alternative regioisomers of [4+4] dimers of 2(1*H*)-pyridone, (left) trans-syn, (middle) cis-anti, and (right) cis-syn.

4.5.4.2 Irradiation Wavelength Comparison

As previously shown in Table 19, preliminary experiments, performed whilst using ^1H NMR (with solvent evaporation) as the only analysis technique suggested that irradiation with 282 nm light resulted in higher conversions. This was consistent with the knowledge that the molar extinction coefficient of **17** in water is larger at 282 nm

than at 308 nm. However, since **17** also absorbs strongly at 308 nm, and the 308 nm (XeCl) lamp has the highest spectral irradiance, it was important to see how the yield and productivity of **18** would compare across the two wavelengths. A concentration of 0.01 M, where selectivity for **18** was highest, was used. The results are presented in Table 30.

Table 30: Yield and productivity for the photochemical isomerisation of 17→18 as a function of flow rate, 308 nm irradiation of 0.01 M aqueous solutions of 17 at 1°C.

Flow Rate (mL min ⁻¹)	Unconverted 17 (%)		Yield 18 (%)		Yield 19 (%)		Productivity 18 (mmol h ⁻¹)	
Irradiation wavelength (nm)	308	282	308	282	308	282	308	282
0.2	8	7	78	79	8	12	0.094	0.095
0.5	31	48	65	40	9	10	0.19	0.12
0.8	41	60	56	29	9	7	0.27	0.14
1.0	63	63	36	25	7	6	0.22	0.15

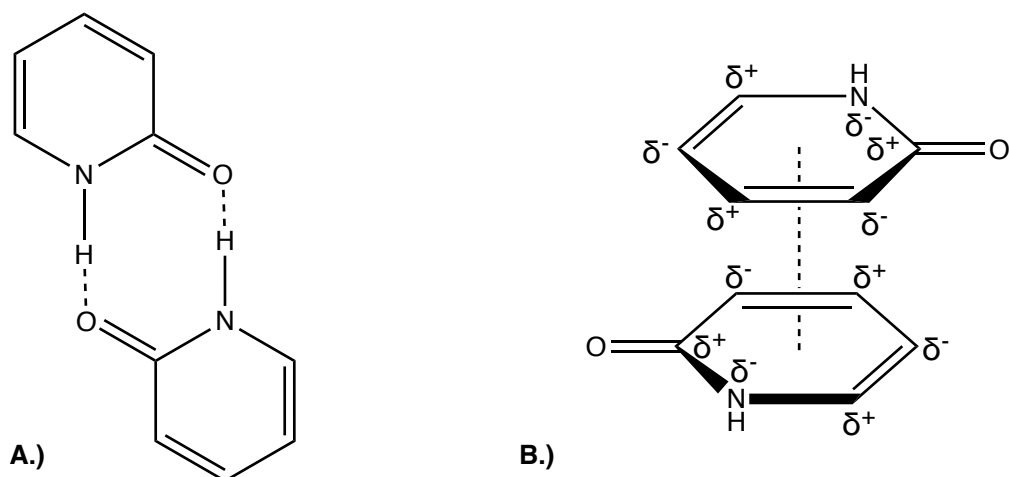
The results show that the yields of dimer **19** are not significantly different at the two irradiation wavelengths, but that there are differences in the yield of **18** and degree of conversion. Despite the starting material **17**, having a higher molar extinction coefficient at 282 nm, the results display that 308 nm irradiation gives higher yield of **18**, except when flowing very slowly and approaching near full conversion (0.2 mL min⁻¹ flow rate). This is probably the result of the spectral irradiance of the 308 nm (XeCl) lamp being higher than that of the 282 nm (XeBr) lamp. At low conversions, when **17** is present in higher concentrations (faster flow rates) the most important factor is having more total photons per unit area, as light of both 282 nm and 308 nm can be absorbed by **17**. However, as conversion increases (slower flow rates) and a

lower concentration of **17** is present to absorb the light, having a larger number of photons is less important.

Considering that the difference in yield of **18** is more pronounced at conditions that do not approach full conversion (Table 30, flow rates of 0.5, 0.8 and 1.0 mL min⁻¹), where the concentration of **17** is higher over the course of the reaction, a concentration study at 308 nm should be performed in the future. If 308 nm irradiation also gives higher yields when a higher initial concentration of **17** is used, in theory the best overall productivities should result from 308 nm irradiation.

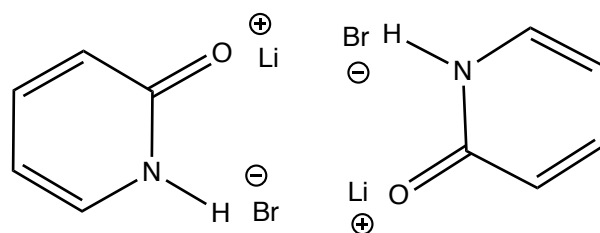
4.5.5 Attempts to Reduce Formation of 2-Pyridone Dimer with LiBr

Even at the lowest concentration tested for the reaction, 0.01 M, dimer **19** was still being formed. It was therefore highly desirable to attempt to prevent this dimerisation to give a cleaner reaction from **17**→**18**. Studies in the literature suggest that hydrogen bonded dimers of 2-pyridones form in solution,^{268, 269} as shown in Scheme 24, A. This is supported by unpublished experimental results of the ground state FTIR performed by our group, which show a large degree of solvent dependence (see Appendix 4.8). Other studies suggest that the molecules of 2-pyridone form dipole-dipole associations, Scheme 24, B, in solution rather than hydrogen bonds.²⁵⁶ In either case if the molecules are pre-associated before irradiation takes place, they will then be close enough in solution to meet on the time scale of the excited state and to dimerise upon irradiation.



Scheme 24: A.) Hydrogen bonding of two molecules of 2(1H)-pyridone and B.) dipole-dipole associated molecules of 2(1H)-pyridone.

It was hypothesised that if the molecules of 2-pyridone are hydrogen bonded in solution than the addition of a mild Lewis acid such as lithium bromide should help to break-up the hydrogen bonds, Scheme 25, and therefore reduce the amount of dimer **19** formed during the photo reaction.



Scheme 25: Dissociation of 2-(1H)-pyridone H-bonded dimers with LiBr.

To test this hypothesis, 0.01 M solutions of **17** were irradiated with between 2.5 and 10 equivalents of LiBr. Results are presented in Table 31, with comparable results without LiBr shown in red for comparison.

Table 31: Yields of the photoisomerisation of 2-pyridone with LiBr as an additive, 282 nm irradiation of 0.01 M solution at 1°C. Results in brackets shown in red are results of similar irradiation conditions without LiBr for comparison.

Entry	Equivalents LiBr	Flow Rate (mL min ⁻¹)	Unconverted 17 (%)	Yield 18 (%)	Yield 19 (%)
1	2.5	0.5	47 (48)	46 (40)	8 (10)
2	5	0.2	8 (7)	81 (79)	11 (12)
3		0.5	40 (48)	53 (40)	8 (10)
4		0.8	54 (60)	41 (29)	7 (7)
5	10	0.5	40 (48)	52 (40)	8 (10)

The yields of **19** were not significantly smaller when LiBr was used as an additive compared to when it was not present. However, if the differences in yield are due to random error it would be expected that the yields of **19** with LiBr would sometimes be higher and sometimes be lower than those without (i.e. normal distribution).²⁷⁰ However, the yields of **19** with LiBr are always less than or equal to the yields of **19** without LiBr. This suggests either that LiBr is reducing the amount of dimer formed, albeit only slightly, or that there is systematic error²⁷¹ present between the two sets of results. Additionally, these results show a trend that having LiBr present in the reaction solution does increase the yield of product **18**.

The effect of LiBr on the reaction was only tested with a small number of reaction conditions, a small range of equivalents of LiBr and at the lowest concentration (0.01 M). For the conditions tested the results were somewhat inconclusive but do suggest that LiBr may be having a role in the reaction. If LiBr is truly having an effect on the yields of **18** and **19** by reducing the pre-association of **17** in solution, than this might be more pronounced at higher concentration where the selectivity for **19** is higher. Looking at the effects of LiBr over the full range of reaction conditions and

number of equivalents LiBr is worth investigating further to determine if this is indeed the case.

4.6 Comparison of the Photoisomerisation of 2(1*H*)-pyridone in the Nottingham Excimer Reactor to Literature Results

One of the initial hypotheses of this project was that the excimer reactor system would be able to generate **18** more productively because of its intense monochromatic irradiation. In order to see if this is true, the productivities from the excimer system were compared to those stated in the literature. Although generally the photoisomerisation of 2-pyridones has been extensively studied only two examples were found that both used the unfunctionalised 2-pyridone and provided irradiation times so that productivities could be calculated. In order to keep the comparisons fair, the conditions from the excimer system used for comparison had to give a yield of **18** that was either greater than or equal to the literature yield. In this way the excimer system productivities are not artificially high due to higher throughput, while only achieving low conversion and wasting more of starting material **17**. Results are presented in Table 32 below.

Table 32: Comparison of productivities for the formation of compound 18 between batch and our flow reactions.

Entry	Light Source	Concentration (M)	Irradiation Time	Yield (%)	Productivity (mmol h ⁻¹)
1 ²⁴⁷	Not stated	0.004	24 h	46	0.0767
2	308 nm excimer flow reactor	0.01	1.71 min (0.8 mL min ⁻¹)	56	0.269
3 ²³⁶	Hanovia Chamber (300 nm)	0.01	65 h	65	0.1
4	308 nm excimer flow reactor	0.01	2.74 min (0.5 mL min ⁻¹)	65	0.195

In comparison to both literature reactions the excimer system is more productive, compare Table 32 Entry 1 with 2 and 3 with 4. In the case where the yield of the reaction need only be over 46%, the excimer system is over 3.5 times more productive. Even when the yield of the reaction is higher, 65%, the excimer system is still almost twice as productive.

4.7 Conclusions and Future Scope for the Reaction

Utilising the excimer system for the photoisomerisation of **17**→**18** has proven to be far more productive than comparably yielding batch conditions presented in the literature.^{236, 247} However, the on-going goal of this project is to produce as much of compound **18** in the minimum amount of time with the minimum amount of waste. One of the unfortunate trade-offs in the flow reactor is that the efficiency of photon capture decreases with increasing conversion. This in practical terms means that typically the productivity of a reaction decreases with increasing conversion. In an ideal system productivity, conversion and selectivity would all be high, meaning that the reaction is efficiently using the photons generated by the lamp, and that there is minimal waste due to unconverted starting material or producing unwanted side products. A reaction with high selectivity and low conversion is far less wasteful if the starting material can be recycled through a simple purification process.

In order to purify **18** from the crude reaction stream, brine is added to the crude mixture. This is then extracted with ethyl acetate. In the extraction process dimer **19** stays in the aqueous phase, product **18** extracts into the organic phase, and the starting material **17**, partitions at a ratio of approximately 1:1 organic: aqueous phase. Compound **18** can then be isolated by removal of the ethyl acetate at reduced pressure, followed by a flash silica chromatography using ethyl acetate as the eluent. Removal of ethyl acetate by reduced pressure evaporation can be performed without evaporating compound **18**. A simple test showed that 98% of the mass of **18** was still

present after a solution of **18** in ethyl acetate was evaporated to dryness on the rotary evaporator.

Although it was inconclusive as to whether the addition of LiBr decreases the yield of **19** and increases the yield of **18**, it definitely did not appear to have deleterious effects upon the yield of **18**, see Table 31 in Section 4.5.5. LiBr can be used instead of NaCl in the extraction process of **18**, with as efficient partitioning. Combining all of these factors makes this reaction a prime candidate for in-line extraction and recycling of the starting material. Recently the our research group has purchased a Zaiput SEP-10 that is capable of separating immiscible solvent streams in flow such as brine and ethyl acetate.²⁷² By using a second pump to deliver ethyl acetate and the Zaiput it would be possible to remove product **18** from the aqueous stream and then recycle it through the reactor. A schematic showing this process is presented in Figure 48.

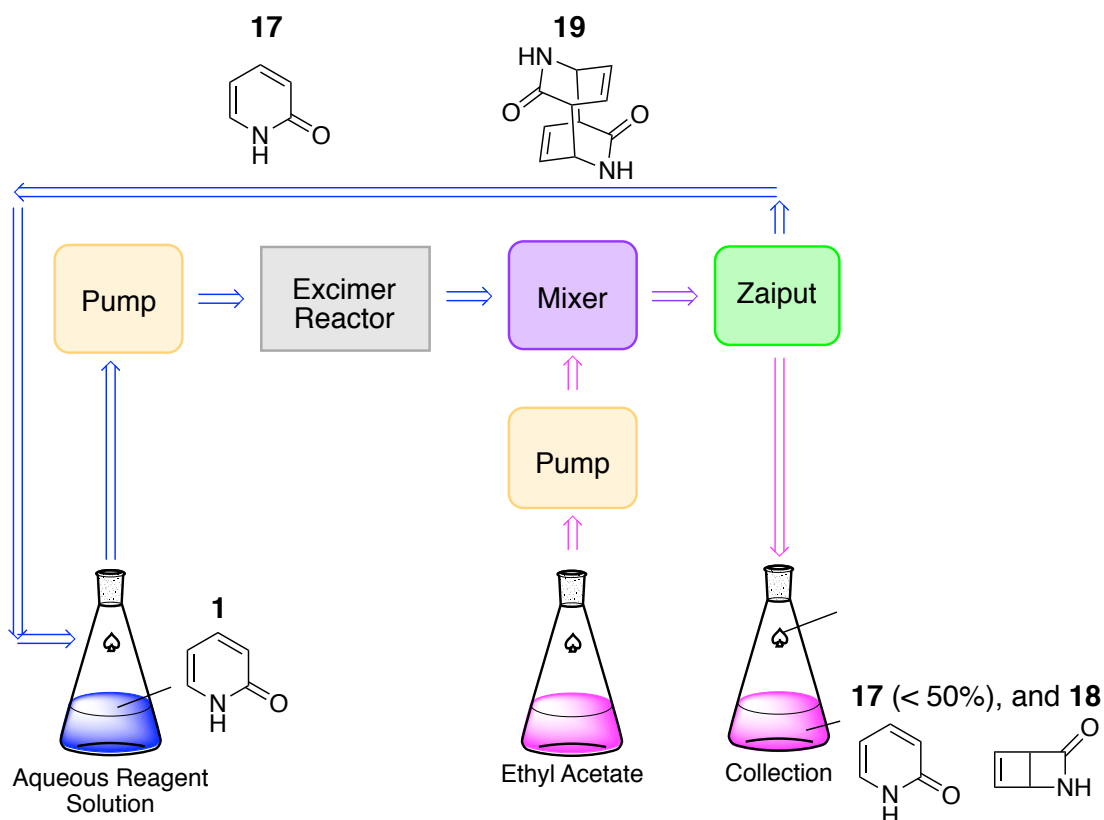


Figure 48: Schematic showing a theoretical in-line extraction set-up for starting material recycling.

As the partitioning of **17** into the aqueous phase is not perfect, some of the starting material will be lost to the organic stream. However, a significant proportion could be recycled meaning that more productive, higher flow rates, could be used with far less waste of the starting material. Furthermore there is also scope to improve the extraction process. To date only ethyl acetate has been used to extract **18**, as it achieved the main goal of removing **18** from the aqueous phase. A slightly less polar solvent might have higher separation efficiency and leave a larger proportion of **17** in the aqueous stream that could then be recycled through the reactor.

Although a recycling process does seem likely to work, there is still the potential to improve the yield or selectivity of the photochemical reaction. To date the majority of this work has focused on performing the reaction in water as this did not result in

dimer **19** precipitating from the solution. It is possible however, that other solvents or solvent mixtures may give higher yields of **18**. Tests of this reaction in other solvent systems should be performed with careful attention being paid to the extinction coefficients of **17** in each solvent system so that the correct irradiation wavelength is chosen. In scenarios where **17** absorbs more strongly at 282 nm, experiments at 308 nm should still be conducted as the larger number of photons emitted from this lamp can result in overall higher productivity. Furthermore, additional experiments should be performed to test whether the addition of LiBr, particularly when higher concentrations of **1** are irradiated, could result in higher selectivity for **18**.

Chapter 5: Toward Self-Optimised Continuous Flow Electrochemistry

5.1 Chapter Summary

Electrochemistry, like photochemistry, is a less frequently used synthetic technique that can benefit from being performed in continuous flow. This chapter begins with a brief introduction to organic electrochemistry. The advantages of performing organic electrochemistry in continuous flow and the disadvantages of batch electrochemical reactors are described. A method for in-line Raman analysis coupled to the Ammonite 8 electrochemical flow cell using the methoxylation of *N*-formylpyrrolidine as a model reaction is described. Following this a method for integrating on-line GC analysis with the Ammonite 8 using the methoxylation of 4-*tert*-butyltoluene is given.

5.2 Introduction to Organic Electrochemistry

As previously discussed in Chapter 1, there is a drive for synthetic organic chemists to synthesise ever more complex molecules and to do so in more efficient²⁷³ and more sustainable, atom-economic ways.^{57, 125, 274} In electrochemical reactions, the desired chemical reaction proceeds through the decay of reactive intermediates (e.g. radical anions and radical cations) that are generated via oxidation/reduction of reagents at the surface of the electrodes.²⁷⁵⁻²⁸⁰ By adding or removing electrons electrochemically rather than employing a chemical oxidant or reductant, organic electrochemistry offers a unique way of performing reagent-less synthesis, avoiding the generation of stoichiometric waste, and therefore has inherent green credentials.^{74, 77, 125, 276, 279, 281-285} Utilising electrons as the “reagent” to replace an additional chemical reagent can be more cost effective, particularly since electrochemical reactions typically take place under mild conditions.^{74, 77, 125, 279-282} Furthermore, these reactions can be more selective if the correct potential is applied, which only allows for the selective oxidation or reduction of a specific moiety.^{125, 275,}

²⁷⁶ Although currently the majority of the world's electricity comes from combustion of non-sustainable fuels, there are many sustainable technologies being developed for the generation of electricity, which in the future could be used to power electrochemical reactions.^{74, 284}

Organic electrochemistry has been in existence since the mid 1800s^{277, 278, 286} and is therefore quite a mature field. However, with the increasing interest in green chemistry over the last two decades, there has been renewed interest in synthetic electrochemistry.^{77, 125, 276, 287, 288} Electrochemical reactions have a wide scope and large synthetic potential as they can be used for carbon-carbon bond formation, functional group inter-conversion, and adding heteroatoms into molecules,^{279, 284} all of which are key steps in organic synthesis. The progress in the field has been summarised in numerous recent reviews on the subject.^{275, 277, 279, 282, 283, 289, 290}

Despite the large body of literature, synthetic electrochemistry has been, and continues to be widely under utilised²⁸⁴ with the majority of organic electrochemical reactions being performed by groups with a particular interest in electrochemistry.²⁷⁸

Pletcher *et al.* blame this under utilisation of synthetic electrochemistry on, “the absence of equipment and support designed specifically for convenient laboratory synthesis by non-electrochemists.”²⁷⁸ Baran goes further stating that the lack of standard electrochemical equipment means that, “electrochemistry is widely feared by practicing organic chemists”¹²⁵ many of whom hold, “the common misconception that only aqueous solvents may be employed and that product separation is difficult.”¹²⁵

5.3 Electrochemistry in Batch Cells

It is easy to see how these misconceptions may have arisen in the context of electrochemistry being performed in batch cells. These types of cells are common in the electrochemical transformations found in the literature and can be made without

difficulty from the typical glassware found in organic chemistry laboratories.^{275, 276, 278}

However, batch electrochemical cells suffer from significant drawbacks.^{275, 276, 278, 291-}

293

In an electrochemical cell, the oxidations and/or reductions that generate the reactive intermediates can only occur at the surface of the electrode.^{74, 275, 277, 278} Therefore, in order for a high degree of conversion to be achieved in a given period of time, it is desirable to have a high ratio of electrode surface area to volume of reagent solution.^{278, 279, 294} The degree of conversion can be expressed by Equation 12, where X is conversion, k_m is the mass transfer coefficient, A is the electrode surface area, t is reaction time and V is the volume of reactant solution. (N.B. This equation is only correct for mass transfer controlled reactions where the rate limiting step is diffusion of reagents to the electrode surface.)²⁷⁸

Equation 12: Conversion of a mass transfer controlled reaction, where X is conversion k_m is the mass transfer coefficient, A is the electrode surface area, t is reaction time and V is the volume of reactant solution.²⁷⁸

$$X = 1 - \exp \frac{-k_m A t}{V}$$

In the typical batch cell set-up, the ratio of the surface area of the electrode to the volume of the reagent solution is low.^{276, 278, 295} This means that in a given time period the overall conversion will be lower. Furthermore, if the solution in the batch cell is not adequately stirred the mass transport at the electrodes will be inefficient, further reducing the conversion.^{278, 279} It is because of these two factors that obtaining full or near full conversion in a batch cell can require reaction times of many hours.^{278, 292, 296}

The design of a batch cell typically has the two electrodes separated by a large distance. This means that in order for the solvent to conduct well enough for the reaction to occur, a supporting electrolyte must be added to the solution.^{276, 297, 298}

This requires that the supporting electrolyte be soluble in the reaction solvent and the

electrolyte must be removed from the products later, complicating the downstream work up and generating additional waste.^{74, 276, 294}

In addition to the extended reaction times, the design of batch cells make them very susceptible to irreproducibility.²⁷⁸ Selectivity in electrochemical reactions is maintained by controlling the electrode potential so that only the desired reactive intermediates are generated at homogeneous concentration across the surface of the electrode.²⁷⁸ In order for this to occur the mass transport regime must be consistent over the surface of the working electrode.^{278, 279} The high sensitivity of both conversion and selectivity to mass transport means that even small differences in how batch cells are stirred or the placement of the electrodes, can cause irreproducibility.^{278, 284} Additionally, the current density must be uniform over the entire cell (achieved by points on the working electrode being geometrically equivalent with those of the counter electrode). This ensures that no local “hot-spots” are generated which could influence the reaction and change the selectivity.^{276, 278, 299}

5.4 Electrochemistry in Micro-flow Reactors

Utilising micro-flow reactors for electrochemical reactions can help to overcome many of the issues associated with batch electrochemical processes.^{276, 278, 279, 287, 291}

In the simplest micro-flow set-up, the reagent solution is pumped through a small gap between the working and counter electrode, Figure 49.²⁷⁶ Reactions performed in this way are more efficient due to the fact that there is a high electrode surface area, compared to the volume of solution, on which the reaction can take place. The parallel geometry of the electrodes means that it is much easier to achieve the uniform current distribution needed to obtain high selectivity in reactions.^{276, 278} Additionally, because the electrodes only have a small gap between them, ions generated at the surface of one electrode are within the diffusion layer of the surface of the other electrode.²⁹⁷ This means that either no supporting electrolyte or very

small quantities are needed, making for an easier downstream separation.^{74, 276, 297,}

300

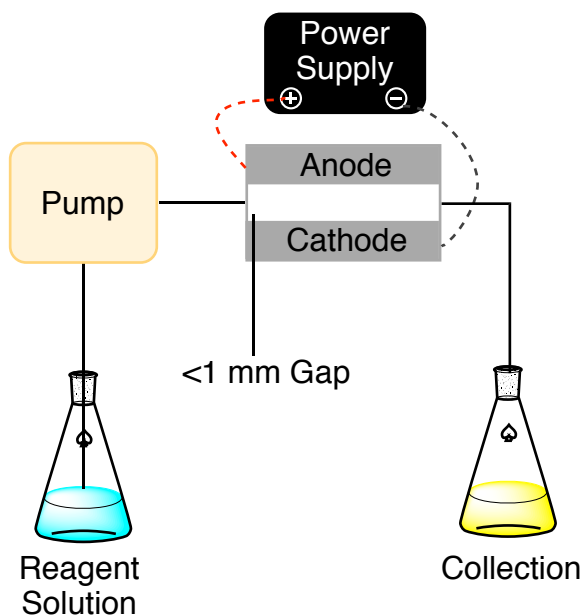


Figure 49: Simplified schematic of a typical micro-flow electrochemical cell adapted from Watts *et. al* and Green *et. al*.^{276, 296}

5.4.1 Types of Electrochemical Flow Reactors

It should now be clear why researchers are keen to perform electrochemical reactions in flow but methodologies often differ between them. This is exemplified by the numerous different electrochemical micro-flow reactors (ECMRs) that can be found in the literature.^{276, 278, 280, 291, 294, 295, 300-308} However, for preparative synthetic electrochemistry the reactors fit broadly into two subgroups, divided and undivided ECMRs.²⁷⁶

5.4.2 Divided EMCRs

In an electrochemical cell, reactions occur at both electrodes.^{275, 278} Therefore, the solution reacting at the anode and the solution reacting at the cathode must be physically separated from one and other during the reaction if the reaction products from one electrode will react undesirably at the other electrode or with the compounds generated there.^{275, 276, 278} For electrochemical reactions where this is

indeed the case, it is possible to divide the ECMR with a separator, keeping the chemistries at each electrode from negatively impacting each other.^{276, 296} Separators are typically made from porous polymer sheets or ion-selective membranes.²⁷⁸ However, utilising a divided cell is not without significant disadvantages. Firstly, divided cells are more complex to design.^{276, 278} Secondly, although a separator will greatly reduce the amount of mixing between the anolyte and catholyte movement of all species through the separator is possible and therefore a certain degree of mixing is unavoidable.²⁷⁸ Consequently, there have been numerous different approaches to circumvent the need for divided cells such as generating the same product at both electrodes or pairing two different chemical reactions where the products of one reaction are not reactive at the other electrode and vice versa.^{278, 309, 310}

5.4.3 Undivided EMCR

Not only are undivided cells easier to fabricate but they can also be beneficial to the electrochemical reactions, for example by helping to maintain neutral pH of the reacting solution.^{275, 278, 293} This prevents desired products from degradation by acid or base catalysed reactions.^{275, 278} Undivided electrochemical cells have been shown to be highly useful in a wide number of reactions including trifluoromethylations of olefins,³⁰¹ methoxylations of furan and toluene derivatives,^{296, 300, 302} couplings of activated olefins with benzyl bromides,³¹¹ as well as many others.^{280, 294, 303-307, 312, 313}

5.4.3.1 Undivided EMCR with Extended Channel Length

Many EMCRs that have been published in the literature have a short channel length, where the reaction takes place.²⁸⁷ In practice this means that either very slow flow rates must be used to allow for a long enough reaction time, or if faster flow rate are used the reaction will not reach full conversion.^{287, 292} Employing slow flow rates means that only a limited quantity of product can be made in a given period of time.²⁹⁶ Reactions with low conversion can complicate the downstream work-up.²⁹³

To rectify these problems ECMRs with extended channel length have been designed. The longer channel means that faster flow rates can be utilised while maintaining high conversion.^{287, 293, 296} This allows for reasonable quantities (10 mg - 100g) of products to be generated in a day, without complicating the work-up due to the presence of large quantities of starting material.^{278, 292, 293, 296} Examples of this type reactor in the literature include the Syrris micro-flow cell,²⁸⁷ the Ammonite 8²⁹³ and the Ammonite 15.²⁹³

5.4.4 The Ammonite 8 Electrochemical Flow Reactor

The Ammonite 8 is an undivided extended channel microfluidic electrolysis cell designed by the Brown group²⁹³ at the University of Southampton and is now commercially available through Cambridge Reactor Design Ltd. This cell comprises a carbon anode (Pt is also available), a stainless steel cathode with a spiral groove cut into it, and a Kalrez polymer spacer that fits into the groove creating a 0.5 mm channel through which reagent solution can flow. The anode, cathode, and spacer are sandwiched between an aluminium plate at the bottom and a copper contact plate and Perspex plate at the top via 7 bolts ensuring a liquid-tight seal.²⁹³ An expanded schematic can be seen in Figure 50. Additional details about the Ammonite 8 can be found in the Experimental Chapter.

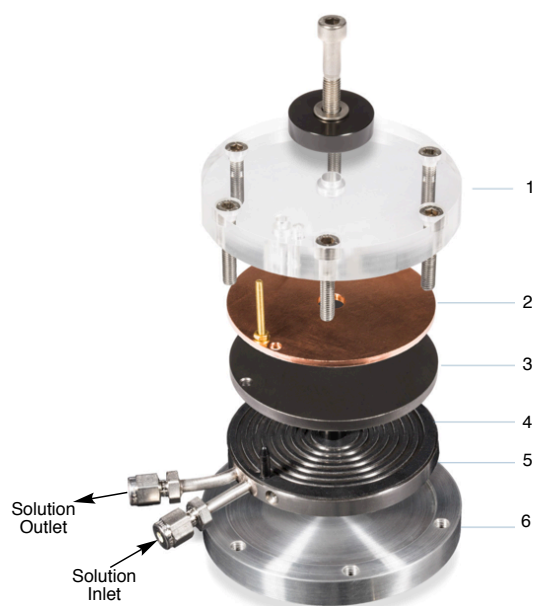


Figure 50: Expanded schematic showing the components of the Ammonite 8 reprinted from manufacturers product specifications.¹¹¹ (1) Perspex top plate (2) copper electrical contact plate (3) carbon/ polymer anode plate (4) Kalrez gasket (5) stainless steel cathode with groove (6) aluminium base plate.²⁹²

The Ammonite 8 capitalises upon all of the strengths of performing electrochemistry in micro-flow cells. It can be run with very low electrolyte concentration, and its narrow channel gap and large electrode surface area mean that high conversion of starting material to product is possible in a single pass through the reactor.²⁹⁶ However, its extended channel length allows faster flow rates to be used while still maintaining short residence times, on the scale of minutes.^{293, 296} This means that these cells can be used to generate products on a multi-gram scale in a single day, rather than being limited to only screening scale reactions.^{292, 293, 296} Because the cell is designed to give full conversion in a single pass, it must be noted that the current across the working electrode must as a consequence be inhomogeneous across the electrode surface i.e. high current near the inlet and low current near the outlet as the concentration of reactant decreases along the reactor path as it is converted.²⁹⁶

Our research group purchased an Ammonite 8 reactor, as part of their collaborative Photo-Electro project with the Universities of Bristol and Southampton. This added

an electrochemical reactor to the numerous, photochemical, thermal, high-pressure, and supercritical reactors already in the group's possession, expanding the available continuous flow synthetic toolbox.

5.4.4.1 Achieving Full Conversion in the Ammonite 8

One of the main goals when designing the Ammonite 8 was to design an electrochemical flow cell that would achieve full conversion in a single pass as this can simplify the purification process and maximise product yields.²⁹³ Rather intuitively, in order for full conversion to be possible enough charge must be passed through the cell during the residence time of the reagents so that the mass balance of the reaction is satisfied. If there are no competing reactions, the minimum current necessary to obtain full conversion is given by Equation 13, where m is the number of moles of reactant, n is the number of electrons involved in the reaction, F is the Faraday constant and t is the residence time inside the reactor.²⁹⁶

Equation 13: Equation for minimum current to achieve full conversion in the Ammonite 8.^{293, 296}

$$I_{cell,minimum} = mnF/t$$

Using a current less than $I_{cell,minimum}$ means that full conversion is not possible and using a current above $I_{cell,minimum}$ requires that a competing reaction must be taking place at the working electrode. This reaction can either be the degradation of reaction products or the oxidation of the solvent or electrolyte if one is being used. Furthermore in order for the reaction to proceed cleanly the desired electrochemical reaction must take place quickly so that it is the main or only reaction occurring at the electrode surface. In order for the desired reaction to take place instead of competing reactions, enough reagents must be present at the surface of the electrode at any given time to support $I_{cell,minimum}$. If not a competing reaction must take place.^{287, 296}

5.5 Integrating In-line or On-line Analysis with the Ammonite 8

It is highly desirable to have on-line or in-line analysis as part of a continuous flow process. This allows for real-time or near real-time reaction feedback, which is beneficial because a reaction can be stopped as soon as something goes wrong in the system before large quantities of reagents and time are wasted. When a reaction is being studied to find the optimal conditions, real-time feedback allows the operator to make an informed decision about which conditions to change without losing valuable time waiting for analytical information.^{61, 314-316}

In order for many analytical techniques e.g. GC, UV-Vis spectroscopy, Raman spectroscopy, IR spectroscopy, HPLC, etc. to continuously give accurate information about the reaction, the output stream from the reactor must be homogeneous. Electrochemistry presents a challenge because frequently the reaction at the counter-electrode produces H₂ gas.^{287, 292, 293, 296} In a flow electrochemical reactor, this results in a slug-flow of gas and liquid exiting the reactor from the outlet tube (Figure 51). For techniques such as GC to give quantitative results, it is crucial that an identical volume of liquid is injected for each assay so that any changes in peak area will represent a true yield or selectivity change in the reaction. With the set-up that uses UV-Vis flow spectroscopy (described in Chapter 4 – Section 4.4.2) measuring a spectrum while a bubble of gas is passing through the cell would result in a “dead spectrum” where nothing was observed. Having an occasional “dead spectrum” is not problematic if the data are manually processed and in fact the Ley group has recently successfully used in-line UV-Vis spectroscopy to monitor an electrochemical reaction in the Ammonite 8.³¹⁷ However, having a dead spectrum is far more problematic if computer controlled analysis is performed as in the case of self-optimisation. This is discussed further later on in this chapter.

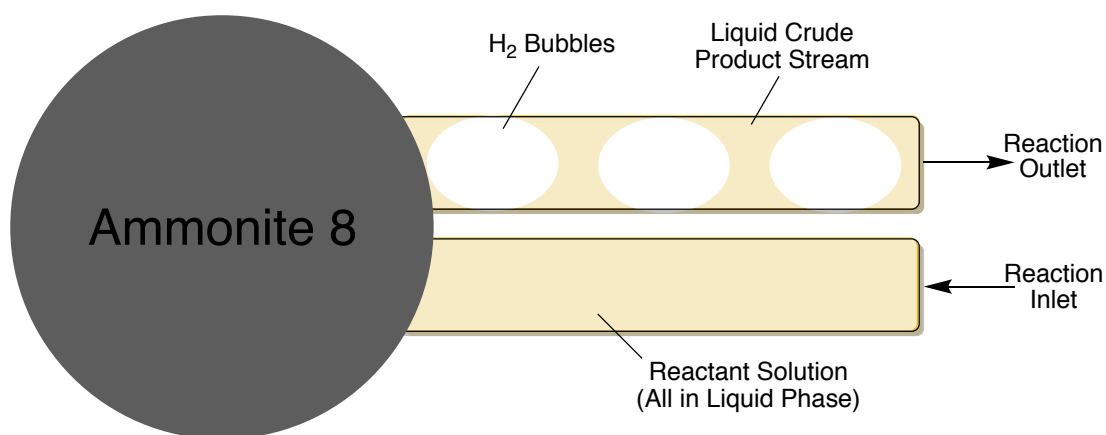


Figure 51: Slug-flow at the outlet of the Ammonite after the reaction has produced H₂.

One of the over-arching goals of our research group is to have a pool of reactors, all with in-line or on-line analysis, which can be linked together for the telescoped synthesis of a desired compound. Therefore, it is not worthwhile to design in-line analysis for the Ammonite simply using reactions that do not produce gas, as gas might be unavoidable in the future. Rather, designing a way of separating the gas from the liquid stream was imperative.

5.5.1 Methods of Gas Separation from The Reaction Stream

When confronted with the challenge of having a slug-flow of gas and liquid leaving the reactor, three ways of coping with the gas appeared to be viable solutions for addressing this problem; homogenise the reaction stream into one phase, utilise a gas permeable membrane, or employ a physical separation by gravity. An experimental set-up for each of these methods of gas/ liquid separation was designed. After consideration of the designs for homogenising the reaction stream and removing the gas via a gas permeable membrane (described below), I decided that both of these designs were too time and cost intensive to be practical for initial experiments that required gas/ liquid separation from the outlet of the Ammonite 8.

It was proposed that by adding a backpressure regulator and increasing the pressure on the system it might be possible to dissolve the hydrogen into the liquid phase.

However, the Ammonite comes with no official pressure rating, although contact with the supplier indicated that it might be able to withstand pressures between 0.2 and 0.5 bar. The set pressure on the backpressure regulator could therefore not be increased indefinitely and still be deemed safe. As Hydrogen solubility is dependant on pressure, temperature, and solvent³¹⁸ this would present further issues if the reaction concentration or conversion was increased leading to an increase in gas production. Therefore, this way of dealing with the hydrogen would be quite susceptible to changes in reaction conditions or reaction, making it far from ideal for the more universal “plug and play” research strategy that the group is trying to achieve. Furthermore, there is some evidence to suggest that the production of gas bubbles within the reactor increases the turbulence of the flow leading to better mass transport and overall higher product conversion,²⁸⁷ so homogenising the stream may have detrimental effects to conversion.

The Ley group has published examples³¹⁹⁻³²² of tube-inside-tube reactors where the inner tube is made from a gas permeable material such as Teflon AF-2400, and the outer tube is made of a standard impermeable material, typically PTFE (Figure 52, A). Teflon AF 2400 is a polymer that combines the high chemical resistivity characteristic of most fluoropolymers with very high gas permeability and almost no liquid permeability. Therefore, a stream of gas can be flowed around the outside of a Teflon-AF 2400 tube containing the organic reagent stream. The gas is able to permeate through the tube where the reaction can efficiently take place due to the large gas to liquid surface area. Recently this type of system was used in reverse where gaseous diazomethane was generated in-situ in the inner Teflon AF-2400 tube and then diffused to the outer tube PTFE where it reacted with various organic substrates.³²³

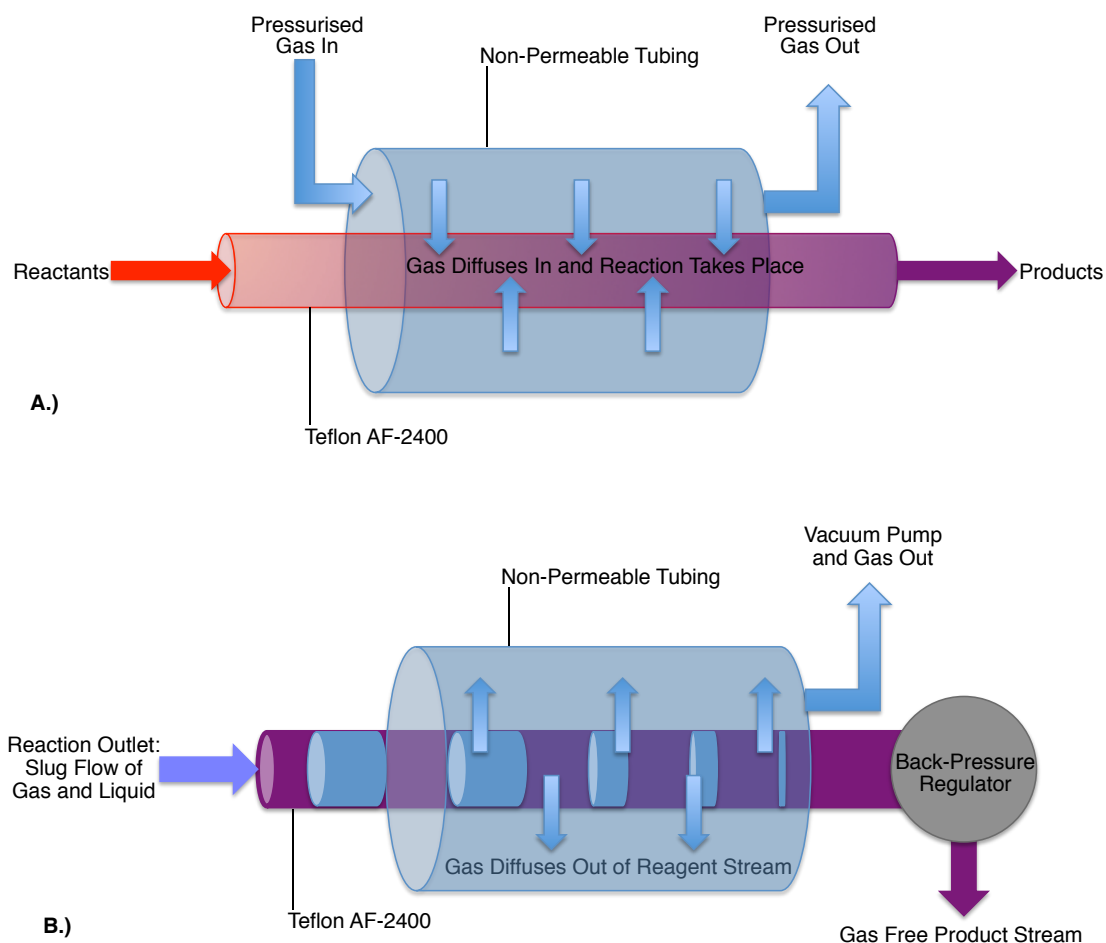


Figure 52: Schematics showing A.) gas diffusing into reagent stream through Teflon AF-2400 where the reaction takes place. and B.) slug-flow stream of gas and liquid, where the gas diffuses out of the liquid phase through a Teflon AF 2400-membrane.

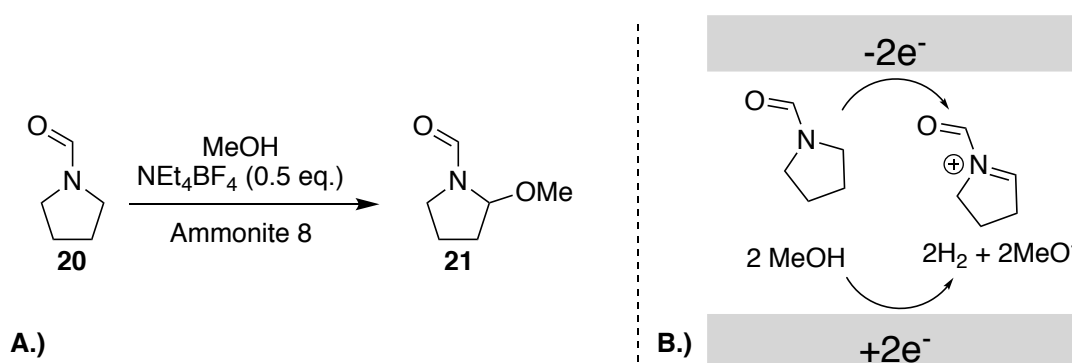
It was proposed that running this type of system in reverse, with the reagent stream exiting the Ammonite into an AF-2400 tube surrounded by lower pressure, may provide a viable solution to removing the gas from the liquid stream (Figure 52, B). In fact the Ley group used this type of design to remove all of the H_2 dissolved in the solvent (DCM) after a reaction pressurised with H_2 was completed. In order to fully remove the dissolved gas, a length of Teflon AF-2400 had to have an internal back-pressure of 5 bar and external vacuum applied.³²⁰ A backpressure of 5 bar is well above the pressure that the Ammonite is thought to be able to safely operate at and this system was only removing H_2 dissolved in a reaction solvent not the larger amounts that would be generated by a high concentration reaction in the Ammonite.

Teflon AF-2400 is very expensive, with a resin price over \$30,000 per kg (Price quoted by Biogeneral 6th July 2017), and an additional vacuum pump would also be required in order to implement this type of gas/liquid separation method. In the initial phases of integrating in-line analysis with the Ammonite, utilising a semi-permeable membrane to remove the gas, though an elegant solution, seemed to be too costly and time intensive considering there was no guarantee of it working.

Therefore it was decided that a simple physical separation of the gas from the liquid stream was the best starting point for the initial trials.

5.6 The Continuous Electrochemical Methoxylation of *N*-Formylpyrrolidine with In-line Raman Spectroscopy

In-line spectroscopy where the reaction sample continuously flows through or past the analytical device represents the only way of getting true real-time reaction feedback.³¹⁶ Using a Raman probe, the electrochemical methoxylation of *N*-formylpyrrolidine, Scheme 26, in the Ammonite 8 was studied. This reaction was an ideal model reaction for developing the in-line spectroscopic set-up as it is a robust electrochemical reaction that has been extensively studied, including in the Ammonite 8.^{287, 292, 293, 296}



Scheme 26: A.) The electrochemical methoxylation of *N*-formylpyrrolidine by B.) oxidation of *N*-formylpyrrolidine at the anode and reduction of methanol at the cathode.

5.6.1 Reaction Set-Up

As stated above it was necessary to physically separate the H_2 gas from the liquid reagent stream, in order to consistently produce reliable Raman spectra. The reaction set-up shown in Figure 53 was used in these experiments. The reagents were pumped via HPLC pump through the Ammonite 8 between the carbon and stainless steel electrodes where a current was supplied and the reaction took place. The outlet pipe from the Ammonite was placed into a secondary collection flask where gas separation occurred. A 25 mL measuring cylinder that also contained the Raman probe was used for this purpose. The outlet pipe was situated above the Raman probe so that the rising gas bubbles did not interfere with the spectra being taken. The inlet pipe of the peristaltic pump was placed at the 5 mL mark. The peristaltic pump flow rate was set to compensate for the HPLC flow rate and H_2 production in such a way that the liquid level was maintained constantly at the 5 mL mark (N. B. the actual volume of solution was closer to 4 mL due to the volumes of the Raman probe and outlet pipe). The flow rate of the peristaltic pump results in air as well as reagent solution being drawn through the peristaltic pump. This is not problematic as the introduction of air takes place after the spectroscopy has taken place and unlike HPLC pumps, peristaltic pumps do not become air-locked.

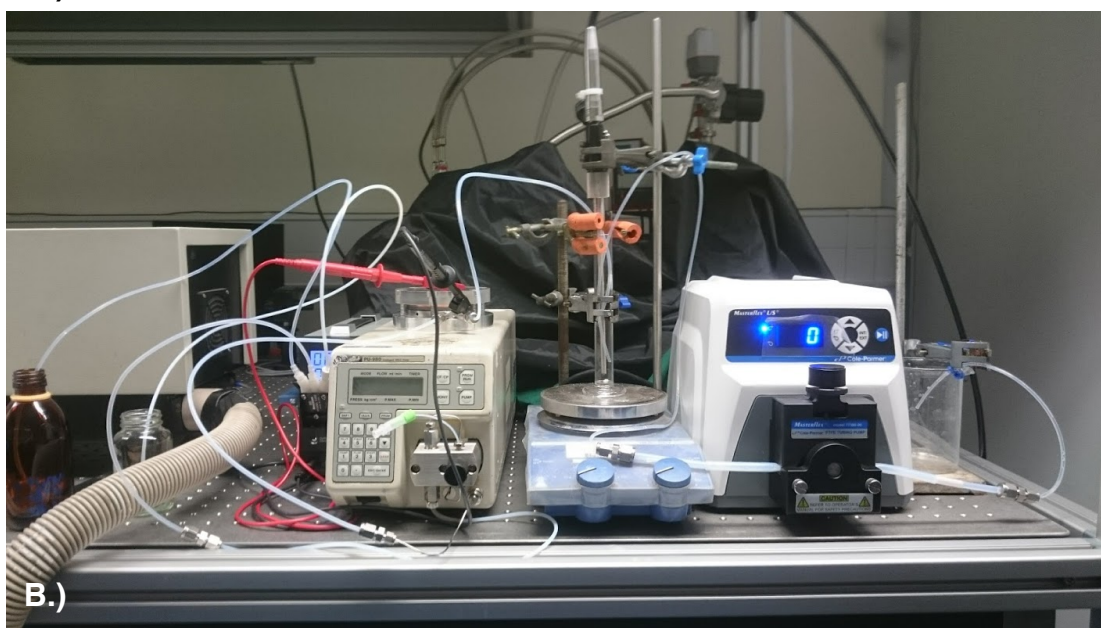
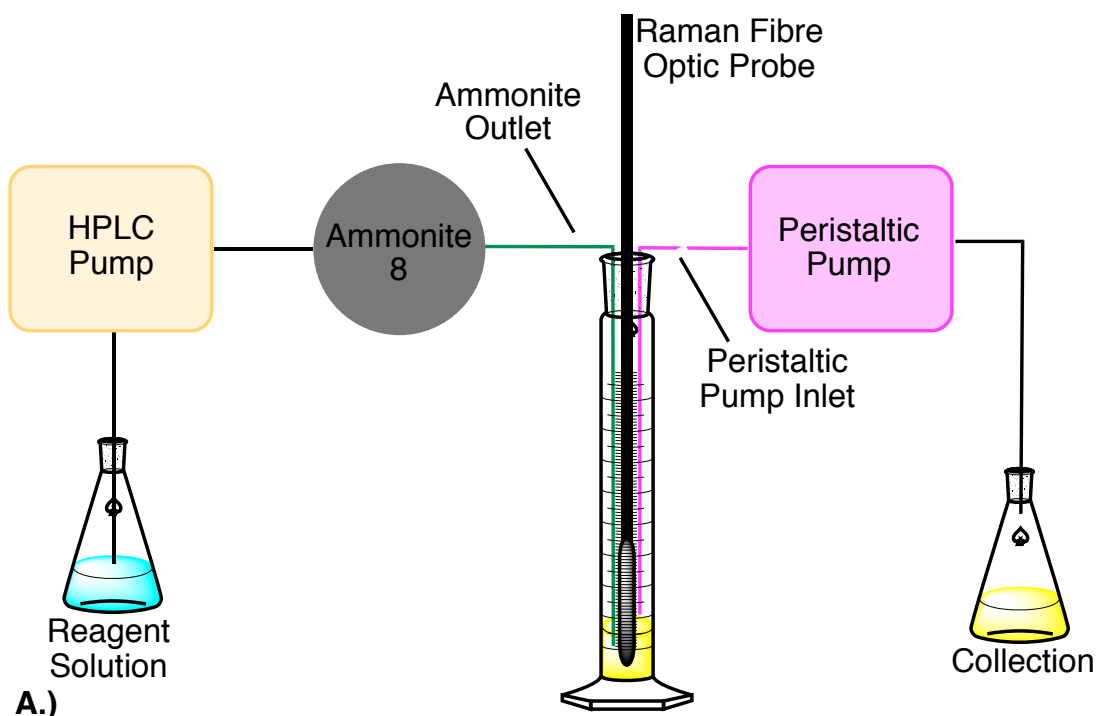


Figure 53: (A) Reaction set-up for Ammonite 8 electrochemical flow reactions with in-line Raman spectroscopy. (B) Photo of the in-line Raman spectroscopy rig.

It must be noted that the Raman probe was operated in a laser safety area. As these experiments were intended to be quick initial tests and I was not laser safety trained, once the reaction was set-up, it was performed by Dr. Ashley Love who had the appropriate laser safety training.

5.6.2 Results

The Raman spectra of a 0.1 M solution of starting material **20** and a 0.1 M solution of product **20** in methanol were recorded. The major differences between the spectra of the two compounds were found in the finger print region (Figure 54).

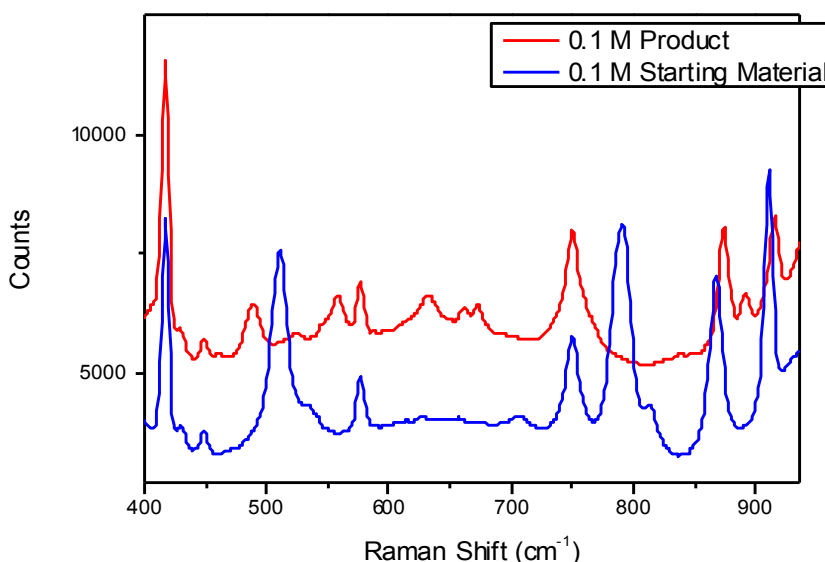


Figure 54: Fingerprint region of the Raman spectra of 0.1 M solutions of **20 and **21** in methanol.**

After the voltage was applied the starting material bands decayed and the product bands grew in (Figure 55), showing that in-line monitoring of the reaction was indeed feasible. However by monitoring the decay of the starting material band at 511 cm⁻¹ and the growth of the product peak at 489 cm⁻¹ for an experiment where 500 mA were applied and a flow rate of 0.5 mL min⁻¹ was used, showed that equilibration was not reached until the reaction had been running for 40 minutes (Figure 56). This is an unacceptably long time to say that this reactor set-up gives real time monitoring. Furthermore this long equilibration delay would lead to large quantities of waste being produced.

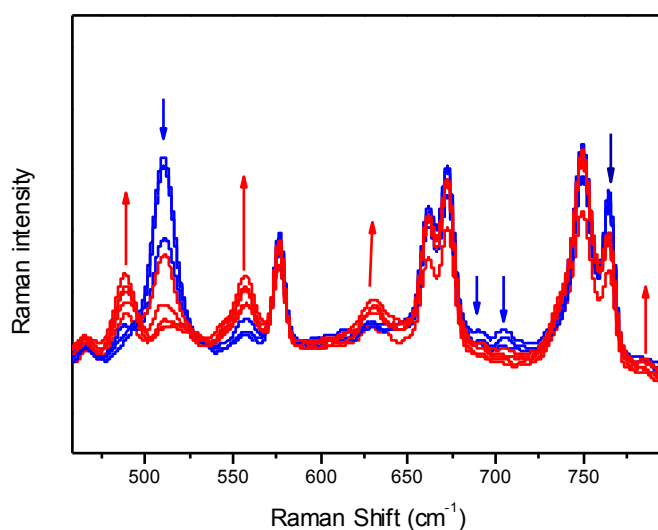


Figure 55: Raman spectra taken every 5 minutes showing the decay of band for the starting material (blue), and growth of bands for the product (red).

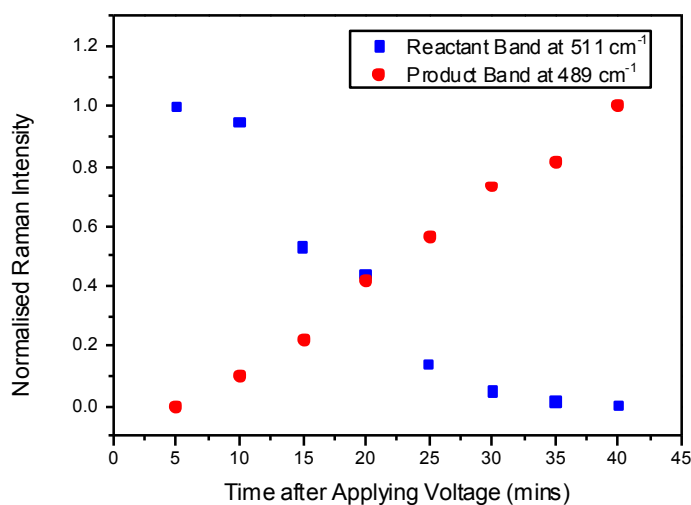


Figure 56: Decay of the reactant band (blue) and growth the product band (red) after voltage was applied to the reaction.

5.6.3 In-line Raman Spectroscopy of The Methoxylation of *N*-Formylpyrrolidine in the Ammonite 8 Conclusions

In-line Raman results for this reaction show that the experimental set-up described above does allow for monitoring of the conversion of this reaction. However, the large volume (~4 mL) of the secondary collection flask meant that a lengthy

equilibration period was necessary before the spectra being taken by the probe were an accurate reflection of the set reaction conditions. In order to fully exploit the potential that in-line Raman can offer to reaction monitoring, with its true real-time reaction feedback, the reaction set-up needs to be redesigned so that the equilibration time is minimised.

In order to analyse a reaction by Raman the reactants and products must be Raman active, and reactions that will be studied in the future may not have Raman active species. This makes Raman less than ideal for the “plug and play” strategy that our research group is working towards. Furthermore, the set-up described above must currently be utilised by laser trained individuals in a laser safety area, limiting its generally applicability.

Despite these limitations, it is possible that with some simple design changes the size of the collection flask could be reduced improving the reaction set-up. Reducing the size of the collection flask can be accomplished by reducing the size of the tubes coming into the collection flask from the Ammonite and peristaltic pump, designing a collection flask that integrates these tubes directly into the side wall of the collection flask and/or reducing the size of the Raman probe, though this would have more significant cost implications. In addition the development of other methods for near/real-time analysis is also key in achieving the “universal reactor strategy” that is so strongly desired.

5.7 The Continuous Electrochemical Methoxylation of 4-*tert*-Butyltoluene with In-line GC-Analysis Toward Self-Optimisation

By combining on-line or in-line analysis techniques with computer controllable lab equipment e.g. pumps, heater controls, backpressure regulators etc. and using a suitable computer algorithm, it is possible for a self-optimised chemical process to be implemented.^{315, 324-326}

In a self-optimised continuous flow process the reagent solution is pumped through the reactor and, subsequent to the reaction, an appropriate analysis technique obtains real-time or near real-time information about the reaction outcome. The analytical data is then fed back to a computer, with an appropriate algorithm capable of interpreting the analytical data. The software then suggests new parameters that the algorithm has predicted to give a better result for the reaction. The computer then adjusts the set parameters of the hardware (pumps, heaters, etc.) accordingly. This loop is repeated until an optimum point is met e.g. highest yield or full conversion.^{315,}

324, 325, 327-330

By utilising the analysis feedback, fewer data points that are far away from the optimum point are generated than in a more traditional fully exhaustive high-throughput optimisation. This results in an optimisation that is not only much faster but that is also less wasteful, since fewer reactions need to be performed. Therefore, smaller quantities of reagents are used and smaller quantities of waste products needing to be disposed of are generated, meaning that these optimisations are also more cost effective. Furthermore, as parameters are not optimised individually, as is the case in more traditional optimisation, the interaction between reaction variables does not get ignored.³²⁸

Our research group has a proven track record of performing self-optimisation on reactions that are analysed by GC.^{324, 325, 328-330} Although GC does come at the cost of increased analysis time compared to an in-line analysis technique like Raman spectroscopy, it is important to have more than one way of performing in-line or on-line analysis for a range of reactions. This increases the probability that for any reaction that is chosen to be studied in the future there is an established method to give real-time or near real time analysis of the results (i.e. the compounds do not have to be Raman active). For our research group, GC is the most “mature”

analytical technique utilised with self-optimisation software. Therefore I thought that it was the best analytical technique, most likely to accomplish a self-optimised electrochemical reaction using the Ammonite 8. Even so, in order for self-optimisation of Ammonite reactions to be possible with GC, it was first necessary to develop a way of linking the Ammonite 8 with on-line GC analysis.

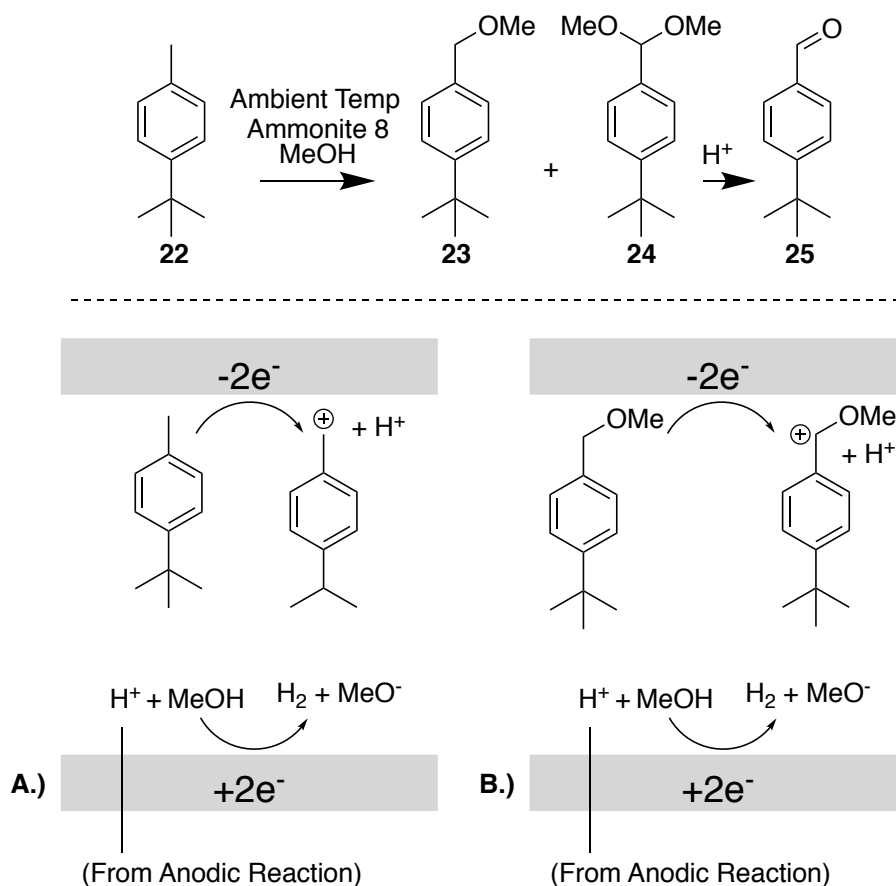
5.7.1 Ammonite Reaction Parameters That Could Be Self-Optimised.

As stated in Section 5.7 in order for self-optimisation to be possible the hardware that controls the reaction parameter to be varied must be able to be controlled by a computer e.g. via USB, RS232 etc.³¹⁵ It is therefore key to decide which parameters are going to be varied not only so that the correct hardware is utilised but also so that control for this equipment is included into the self-optimisation program.

In the case of the Ammonite 8 the most obvious reaction parameters to change are, electric current, reagent flow rate, reagent concentration, and electrolyte concentration. This would require the power supply and all pumps to be computer controllable. A change in reagent concentration and electrolyte concentration could be achieved by utilising a high concentration starting solution and a secondary dilution pump, so that the operator would not have to be present in order to change the solution.

5.7.2 Methoxylation of 4-*tert*-Butyltoluene

To validate the on-line analysis a known, robust electrochemical reaction was needed. The electrochemical methoxylation of 4-*tert*-butyltoluene in methanol, Scheme 27, was chosen as the initial test reaction for on-line GC analysis for the Ammonite 8. This is a reaction involving inexpensive starting materials and has been shown to work well in the Ammonite 8.²⁹⁶ As the reaction makes more than one product, it provides enough complexity such that there will be enough scope for a demonstration of self-optimisation in the future.



Scheme 27: Top.) Schematic of the electrochemical methoxylation of 4-*tert*-butyltoluene. A.) The 1st oxidation reaction, oxidation of 4-*tert*-butyltoluene at the anode and reduction of methanol at the cathode. B.) The 2nd oxidation reaction, oxidation of 4-*tert*-butylbenzyl methyl ether at the anode and reduction of methanol at the cathode.

5.7.3 Ammonite 8 with On-line GLC Analysis Reaction Set-Up

As stated in Sections 5.6 and 5.6.1 it was necessary to physically separate the hydrogen gas from the liquid phase at the outlet of the Ammonite in order for on-line GC analysis to give consistent results. A secondary collection and additional pump was employed to do this. A schematic of the on-line GC monitoring set-up from the Ammonite 8 can be seen in Figure 57.

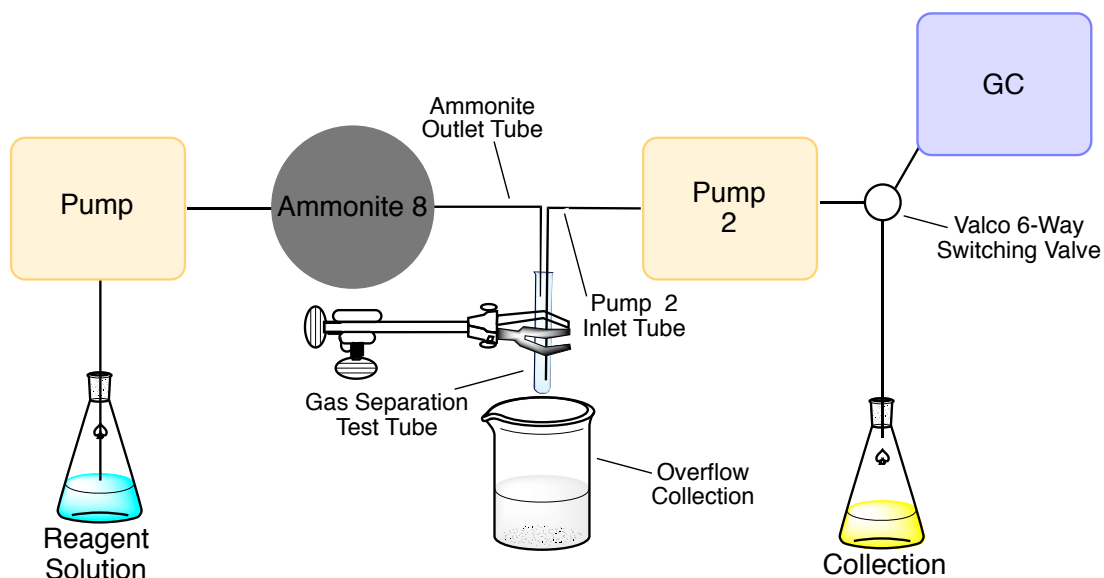


Figure 57: Schematic showing the set-up for on-line GC analysis of Ammonite 8 reactions.

The reagent solution is pumped via HPLC pump into the Ammonite where the electrochemical reaction takes place. The outflow pipe sits at the top of a small vial (max volume 0.5 mL). The inlet pipe of the second pump sits at the bottom of the small vial. The second pump, pumps the reagent solution through a Valco 6-way switching valve capable of dosing a sample into the GC when prompted via the GC Solutions software, see Figure 58 showing the 2 positions of the 6-way switching valve.

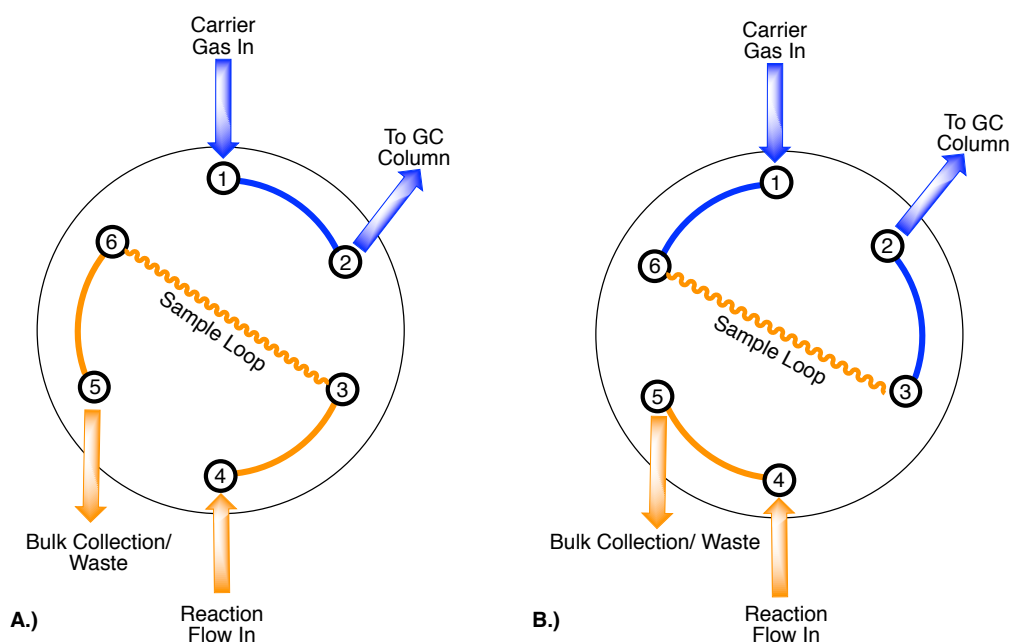


Figure 58: Schematic of the Valco 6-Way switching valve. A.) The rest position where the reactor is filling the sample loop. B.) The load position where the sample loop contents are flushed by the carrier gas onto the column.

In many ways this reaction set-up is very similar to the set-up used for the in-line Raman spectroscopy presented in Section 5.6.1. However, it does differ in a two key ways. Firstly, the secondary collection for the on-line GC was much smaller than that for the Raman, and secondly an HPLC pump was used as the second pump for the on-line GLC analysis rather than a peristaltic pump.

In the GC set-up the secondary collection flask is used simply to separate the gas. In the Raman set-up the secondary collection vessel had to be large enough to accommodate the outlet and inlet pipes to the 1st and 2nd pumps respectively as well as the Raman probe. In practice this meant that the secondary vessel for the in-line Raman had a volume of 5 mL. This large volume led to a long equilibration time after reaction parameters were changed. When designing the on-line GC system it was therefore highly desirable to make the volume of the secondary collection as small as possible. The vial used for this has a maximum volume of 0.5 mL not including the inlet and outlet pipes. When in operation the vial was typically approximately half full. Determining the volume inside the vial during the course of the reaction is

exceptionally difficult as the liquid level rises and falls in a “breathing like” motion since the in-flow from the first pump does not occur exactly at the same moment that the second pump withdraws liquid. However, even with the worst-case scenario volume of 0.5 mL this is still a 8-fold reduction in volume giving a similar reduction in equilibration time.

In Section 5.6, with the in-line Raman analysis, a peristaltic pump was used to remove the solution from the second collection flask to the bulk collection flask. In this set-up the peristaltic pump inlet tube was set just above the maximum desirable volume (5 mL mark on the measuring cylinder) and pumped away any liquid that rose above this point, as well as sucking in air when no excess liquid was present. Having air in the secondary line was not problematic in this case, as the analysis had already taken place. For the on-line GC, no air could be present in the pump line going into the GC dosing unit. Firstly, air in the line could cause an airlock in the HPLC pump resulting in the pump being air-locked and ceasing to pump efficiently or at all. Secondly, to get consistent GC results, the same volume of liquid must be injected onto the column each time and having air would lead to inconsistent results. A pump head calibration was performed for both pumps used for the on-line GC set-up to make sure the flow rates matched (see Appendix 5.1 for pump head calibration). However, if the system was to be left unwatched for an extended period of time (i.e. more than ten minutes), it was better to place an overflow collection beneath the small vial, and slightly lower the flow rate of pump 2 so that only liquid would be pumped into the GC line and consistent results were sure to be obtained. It must also be noted that the secondary collection must be placed below pump 2. When placed above, capillary action drew the liquid from the vial out faster than the set pump flow rate, leading to air being drawn into the line.

5.7.4 On-line GC Method Development for GC Separation the Reaction Mixture From Electrochemical Methoxylation of 4-*tert*-Butyltoluene

Initially, a method of separating the products **23**, and **24** and starting material **22** was developed on a Shimadzu GC-2014 Gas Chromatograph utilising a SPB-1701 column and a 4 μ L auto-injection from a Shimadzu AOC-20i. In addition to fully resolving the compound peaks it was desirable to have a fast GC method so that a greater number of reaction conditions could be analysed in a short space of time. This would in theory lead to a faster optimisation and less waste being generated.³²⁷ As can be seen in Figure 59, a method that gave good separation of the peaks was devised. Full method details are presented in Table 33.

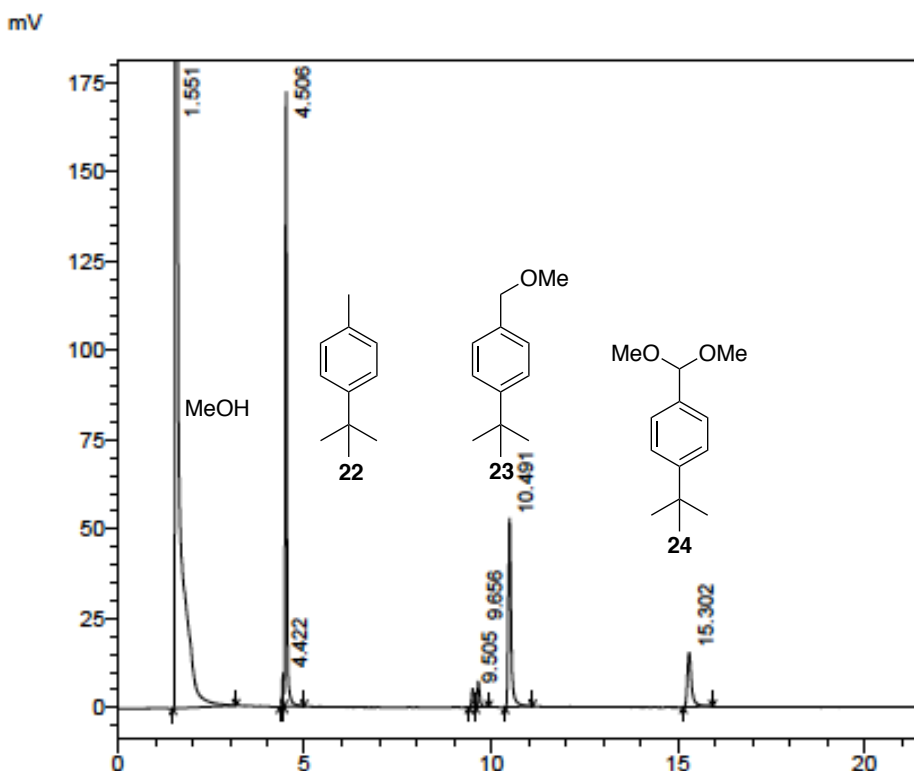


Figure 59: Initial GC separation of compounds **22**, **23**, and **24** using auto injection.

The SPB-1701 column was then moved to a Shimadzu GC-2010 Gas Chromatograph, which was already fitted with the Valco 6-way switching valve system that is controlled through a relay using the GC Solutions software (see

Chapter 6 – Section 6.4.2 for additional experimental details). The switching valve fitted to the GC injection port can be seen in Figure 60.

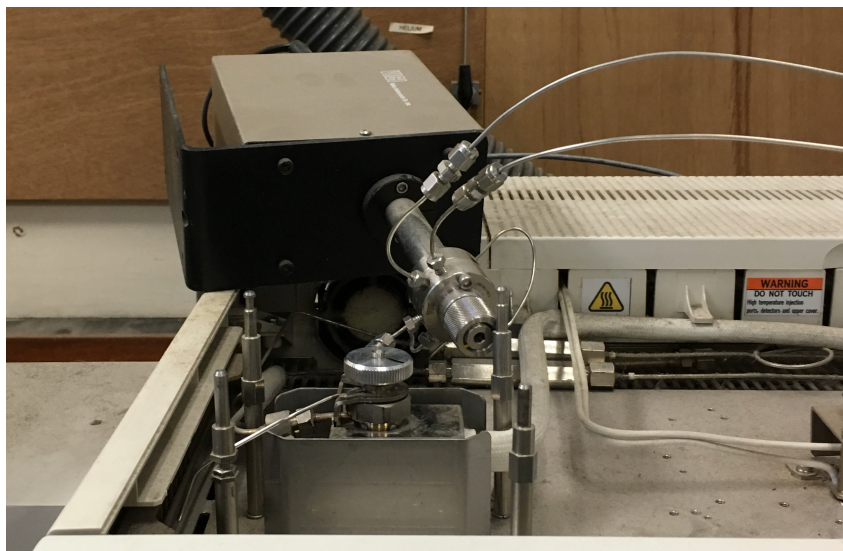


Figure 60: Valco 6-way switching valve connected to the GC injection port for on-line sample dosing.

Table 33: Comparison of GC method parameters that gave separation via auto-injection, that did not separate when modified for Valco injections and the parameters that did give separation using a Valco injection.

Setting	Auto-Injection Method 1			Method 1 Modified for Valco Injection			Final Valco Injection Method		
Injection Port Temp (°C)	250			250			250		
Split Ratio	50			2.0			50		
Flow Control Mode	Pressure			Pressure			Pressure		
Pressure (kPa)	103.1			103.1			170.3		
Total Flow (mL min ⁻¹)	12.4			4.1			107.6		
Column Flow (mL min ⁻¹)	1.04			1.04			2.09		
Linear Velocity (cm sec ⁻¹)	28.3			28.3			45.3		
Purge Flow (mL min ⁻¹)	1.0			1.0			1.0		
Method	Rate	Temp (°C)	Hold Time (min)	Rate	Temp (°C)	Hold Time (min)	Rate	Temp (°C)	Hold Time (min)
	-	100.0	0.0	-	100.0	0.0	-	100.0	0.0
	5.00	200.0	0.0	5.00	200.0	0.0	2.00	110.0	0.0
	25.00	250.0	0.0	25.00	250.0	0.0	5.00	125.00	0.0
							0.75	135.0	0.0
							10.0	200.0	0.0

Initially, it was attempted to utilise essentially the same method as developed using the GC-2014 and 4 µL auto-injection. The relay on the GC solutions software allows the sample loop to be flushed onto the GC column by the carrier gas for 1.2 seconds.

Since the sample loop in the Valco switching valve was 0.06 μL a split ratio of 2.0 was used, as this should have resulted in a relatively similar, though slightly smaller, amount of material being injected onto the column as in the auto-injection method that gave good separation.

However, when a solution of compound **22** was loaded onto the column via the Valco injection port using this method there was significant overlap of the solvent (methanol) peak and compound **22** peak, shown in Figure 61, A. By comparing Figure 59 and Figure 61 A, it is clear that with the same method and similar sample volume the Valco injection resulted in much more peak tailing than the auto-injection. To confirm that the peak tailing was in fact a result of the Valco injection and not due to differences between the two different GCs a manual injection by-passing the switching valve was also performed with the method utilising a 4 μL injection via syringe and a split ratio of 50. The manual injection, like the auto-injection on the GC-2014 also gave good peak resolution with minimal peak tailing, see Figure 61 B.

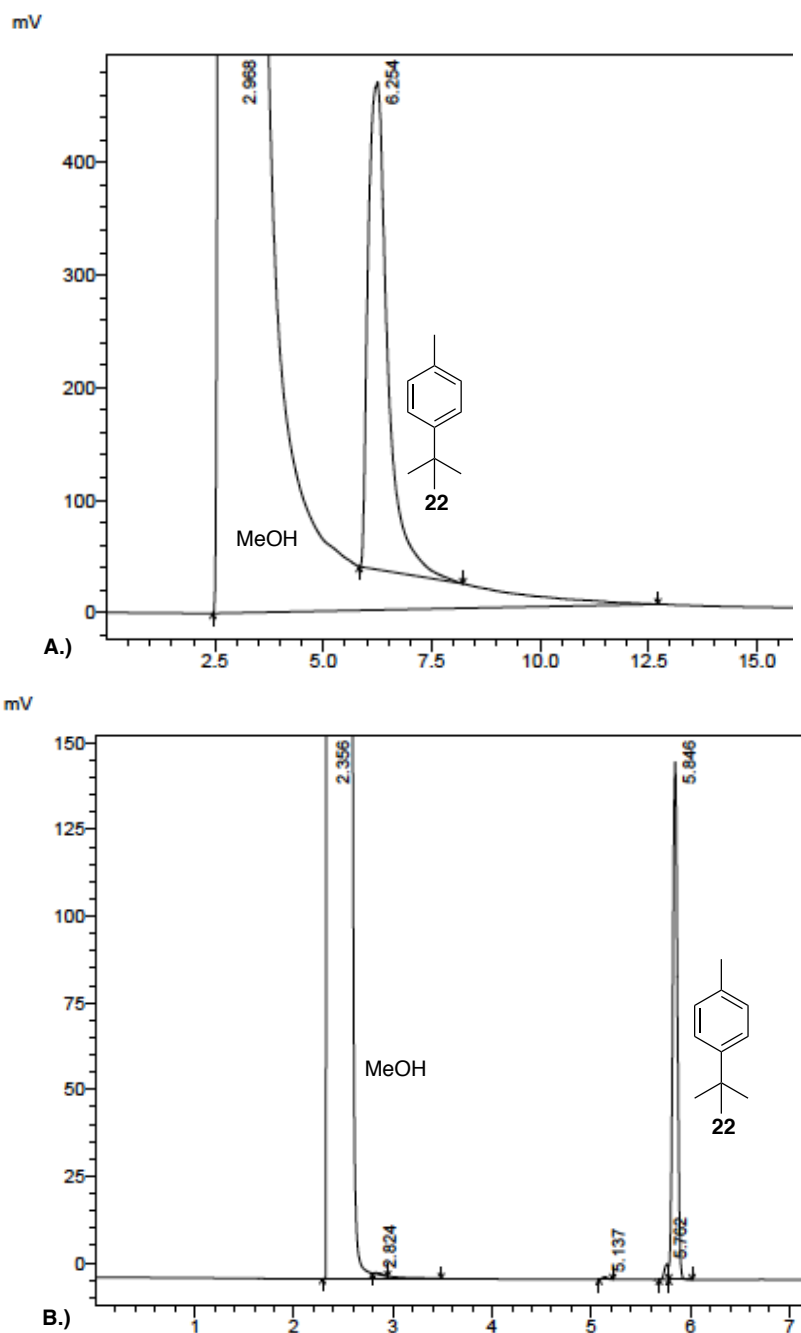


Figure 61: A.) Valco injection of compound 22 in methanol. Methanol peak tails onto the peak for compound 22. B.) Manual injection of compound 22 in methanol utilising GC-2010 with the same method used on the GC-2014 using auto injection.

Since a manual injection also gave good separation, it indicated that the poor separation was due to the Valco injection rather than utilising a different GC. This is probably due to the fact that the Valco injection is slower than an auto or manual injection, and that the Valco injection system may increase overall dead volume.

Both of these factors can lead to poorer GC resolution.^{331, 332} It was clear that a different method was necessary in order to resolve the peaks when the Valco injection was being utilised. The final working method, shown in Table 33, utilises a faster carrier gas flow rate in attempt to reduce peak tailing as well as a longer method time with a slower temperature ramp to increase the gap in retention time between peaks so that peak tailing is less detrimental to peak resolution. Additionally the split ratio was increased so that less total sample is injected onto the column further reducing the peak tailing. As can be seen in Figure 62, in the Valco method that gives separation there is still some peak tailing but this does not result in peak overlap. Unfortunately the trade-off for good peak resolution with the on-line GC is time. Since the method is longer fewer reaction conditions can be analysed in a given period of time, and an optimisation would therefore take longer. Looking into different ways to deliver the sample to the GC, so that the peak tailing is minimised would be advantageous in the future.

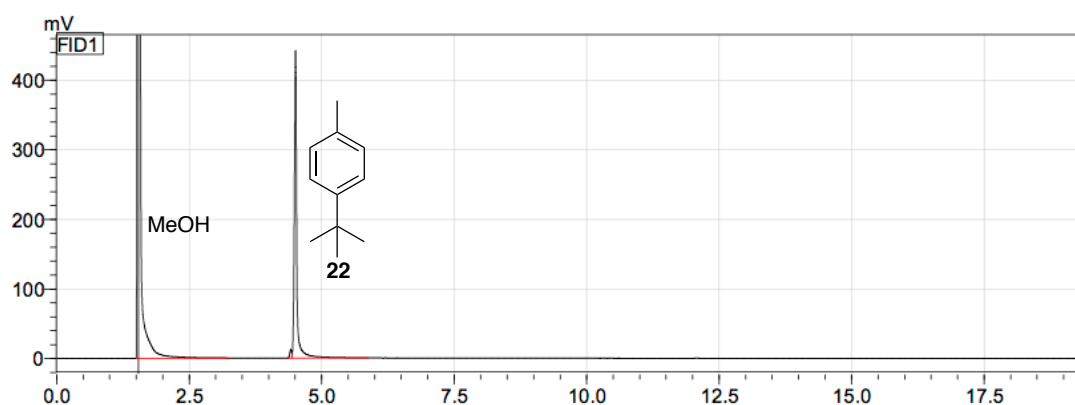


Figure 62: Final Valco injection method GC chromatogram. A faster carrier gas flow rate and higher sample split ratio reduced the solvent peak tailing.

5.7.4.1 GC Method Calibration Curves

Once a method for separating the reaction peaks with Valco injection was established, it was necessary to establish calibration curves for the starting material and three potential products so that the GC analysis could be quantitative. The

calibration curves for compounds **22** and **25** were produced by serial dilution of the commercially available compounds. Compounds **23** and **24** were synthesised and purified before calibration curves were produced by serial dilution (see Chapter 6 – Section 6.4.2.2 for details).

For each calibration curve a series of different concentration solutions were made up in methanol, the reaction solvent, for each compound. Each solution was pumped through pump 2 into the Valco 6- way switching valve. Using the GC Lab Solutions software, GC analysis was performed on three samples from each solution. Samples were taken consecutively without additional operator input. The GC Lab Solutions software automatically picked the peak areas, however each reported peak area was manually checked to ensure the software had picked accurately. The peak areas for each of the three samples were then averaged and a calibration curve of concentration vs. average peak area was established for each of the 4 compounds. A list of compounds vs. retention times can be found in Table 34. The GC calibration curves for compounds **22-25** can be found in Appendix 5.2. All four calibration curves showed a high degree of linearity with R^2 values greater than 0.99. The calibration curve for compound **25** was performed, in case trace quantities of acid in the reactor converted **24** to **25**. In this way it would have been possible to combine the yields for **24** and **25** to see what proportion of the material had undergone the second methoxylation. This was however not necessary as analysis of the GC results presented in Section 5.7.5.3 showed that even at higher concentrations of **24** no more than trace quantities of **25** were present.

Table 34: Compounds 1-4 vs. GC retention time.

Compound	Retention Time (min)
22	4.48
23	10.44
24	15.26
25	12.09

It was clear from the error bars on the points of the calibration curves (Appendix 5.2) that there is some spread on the peak areas on data points that should give identical results. This is probably due to some inconsistency in the injection from the Valco switching valve as well as small fluctuations in the FID between samples. Both of these variations could be removed by doing a calibration against an internal standard. However, an initial set of data was necessary. In the future it will now be possible to compare results with an internal standard to those without and it will be clear if the internal standard interferes with the electrochemical reaction.

5.7.5 Ammonite 8 Continuous Electrochemical Methoxylation of 4-*tert*-Butyltoluene with On-line GC Analysis

It was not possible to utilise the self-optimisation software once the on-line GC experimental set-up was established, due to lack of computer controllable hardware and appropriate computer code capable of controlling the reaction parameters. However, it was still desirable to prove that the on-line GC set-up integrated with the Ammonite 8 functioned properly in test experiments

5.7.5.1 Experimental Design for Electrochemical Methoxylation of 4-*tert*-Butyltoluene

Electrochemical reactions in the Ammonite are sensitive to the current applied, the residence time in the reactor, controlled by flow rate, and the concentration of reagents being passed through the reactor. These were the 3 factors varied to

achieve different degrees of conversion and selectivity for the reaction, assuring that the in-line GC method was capable of analysing the reaction over an appropriate reaction space. Each of these reaction parameters then needed an upper and lower level. Chemical knowledge, typical values used in the literature,^{287, 296} and equipment limitations (leads to power supply have 500 mA fuses), were used to set the upper and lower levels, these values can be found in Table 35.

Table 35: Reaction space limits for the electrochemical methoxylation of 4-*tert*-butyltoluene.

Reaction Parameter	Starting Material Concentration (M)	Flow Rate (mL min ⁻¹)	Current (mA)
Lower Level	0.1	0.1	100
Upper Level	0.15	1.0	400

Three GC samples were taken for each set of reaction conditions. Using the equations for the calibration lines presented in the previous section it was possible to determine the concentration of the products and remaining starting material. An average concentration for each product was obtained by taking the average calculated concentration from the three GC samples. These resulting concentrations were used to calculate percentage yield, conversion, selectivity, and productivity for each experiment.

5.7.5.2 Results

The results from the test reactions for the electrochemical methoxylation of 4-*tert*-butyltoluene analysed by in-line GC are presented below. The conversion of **22** and selectivity's for compounds **23** and **24** are given in Table 36. As expected high conversion was achieved when slow flow rate were used. Lower concentration and higher current also contributed to higher conversions. Also as expected conditions of

lower conversion resulted in higher selectivity for **23** as it was less likely to undergo the second methoxylation reaction.

Table 36: Conversion and selectivity results from the electrochemical methoxylation of 4-*tert*-butyltoluene.

Entry	Flow Rate (mL min ⁻¹)	Current (mA)	Concentration (M)	Conversion (%)	Selectivity 23 (%)	Selectivity 24 (%)
1	0.55	250	0.125	63	75	25
2	0.1	100	0.10	97	15	80
3	1.0	400	0.15	46	75	25
4	0.1	100	0.15	91	57	43
5	1	100	0.1	44	72	28
6	1	100	0.15	30	67	33
7	1	400	0.1	70	65	35
8	0.1	400	0.15	99	30	70
9	0.1	400	0.1	95	40	60

The yields and productivities from the electrochemical methoxylation of 4-*tert*-butyltoluene are presented in Table 37. Conditions of high conversion resulted in higher yield of **24** (Table 37, Entries 2 and 4) except when low flow rate and high current were used (Table 37, Entries 8 and 9), due to degradation of **24** under prolonged exposure to high current. The highest yield for **23** was found when the mid-point value was used as this provided enough current for the reaction to occur without the reaction being pushed toward product **24** by continued exposure to current. The highest productivities were found at the fastest flow rate (Table 37, Entries 3, 5, 6 and 7). Although productivity is influenced by reaction yield, the throughput of material has a large effect on overall productivity.

Table 37: Yield and productivity results from the electrochemical methoxylation of 4-*tert*-butyltoluene.

Entry	Flow Rate (mL min ⁻¹)	Current (mA)	Concentration (M)	Yield 23 (%)	Yield 24 (%)	Productivity 23 (mmol h ⁻¹)	Productivity 24 (mmol h ⁻¹)
1	0.55	250	0.125	37	12	1.5	0.495
2	0.1	100	0.10	9	49	0.057	0.292
3	1.0	400	0.15	25	8	2.22	0.739
4	0.1	100	0.15	33	25	0.292	0.223
5	1	100	0.1	12	5	0.722	0.280
6	1	100	0.15	9	7	0.784	0.604
7	1	400	0.1	24	13	1.43	0.767
8	0.1	400	0.15	2	4	0.016	0.037
9	0.1	400	0.1	6	8	0.034	0.045

Most importantly these results show is that the highest yields, conversions, selectivities and productivities do not all occur under the same reaction conditions. Simply, optimising for full conversion as has been done in the literature^{287, 292, 293, 296} but this does not always mean that the desired outcome for the chemist is also optimised. Finding the reaction “optimum” really depends on the nature of a particular reaction. For example having a more productive reaction might be more important than the yield if the resulting product is much more valuable than the starting material, or a simple purification can allow for the starting material to be recycled easily. For this reaction when purifying by silica, separating **22** from **23** or **24** is easily done, while separating **23** from **24** is far more difficult. It would might be in the chemist’s best interest to choose reaction conditions that might be very low in conversion but highly selective for compound **23**. Similarly reactions conditions that

might degrade compound **24** might be more favourable than slightly more productive conditions that leave some of compound **23** unreacted. Moving forward, it is imperative that computer code is written so that multiple parameters such as yield, selectivity, conversion, and productivity can all be optimised for individually at the click of a button. This would allow the self-optimised Ammonite reactions to truly be the enabling technology that the group is aiming to produce, capable of generating the desired outcome for as many unique reactions as possible.

5.7.6 Conclusions and Future Directions Self-Optimised Electrochemistry Utilising On-line GC Analysis

As was said in Section 5.7, having a functioning self-optimisation system requires two things: (1) a suitable computer algorithm with computer controllable hardware and (2) an experimental set-up that gives real or near real-time analysis without operator intervention. In Section 5.7.4 it was shown that point two was successfully accomplished with on-line GC analysis. Now, in order to get self-optimisation fully integrated with the Ammonite 8, a computer controllable power supply and pumps must be purchased and appropriate computer code needs to be written. The challenges associated with the chemistry and experimental set-up have mostly been overcome and a computational obstacle remains the largest hurdle to a self-optimised system. It is also clear from the experimental results that in order for the self-optimisation system to really be as powerful as possible the code must be written so that there is a choice in which results can be optimised.

Although the experimental set-up was able to perform on-line GC analysis there is of course some room for improvement. The GC method has to be quite long in order to fully resolve compound peaks from the solvent peaks due to dead volume and slow injection. In the future, reducing the dead volume of the Valco switching valve set-up by utilising smaller tubing might be able to reduce peak tailing. This would allow for a

faster method to be used and therefore more samples being able to be run in a given amount of time.

Chapter 6: Experimental

The experimental equipment, methods, and compound characterisations for this Thesis are described in this chapter. In Section 6.1 full details of the excimer reactor are given, including the standard operating procedures for the excimer reactor. In Section 6.3 a general procedure is given for each of reactions performed in the excimer reactor as part of this Thesis, along with relevant compound characterisation. Section 6.4 provides details of the experimental set-ups and standard operating procedures used for reactions in the Ammonite 8 with in/on-line analysis. The general reaction procedure and compound characterisation for the electrochemical reactions performed for this Thesis can also be found in Section 6.4.

6.1 The Excimer Reactor: Full Details

An abridged version of the following description of the excimer reactor can be found in Delaney *et al.*¹³⁴ A cross-section of the excimer reactor is given in Figure 63, showing a schematic of the components as will be described below. The cold finger of the reactor (shown in grey and blue, Figure 63) consists of a ¼" stainless steel tube (wall thickness – 0.049") inside of a 12 mm stainless steel tube (wall thickness = 1 mm) that is closed at one end. The ¼" tube sits approximately 1 cm back from the closed end of the 12 mm tube. Each of these two tubes is connected to an asymmetric Swagelok stainless steel T-piece (or symmetrical T-piece with appropriately sized Swagelok reducers). The side arm of the ¼" T-piece (small SS T-piece) is connected to the in-flow of a Julabo F250 circulating bath filled with a 50-50 mix of ethylene glycol and water. The side arm of the 12 mm T-piece (large SS T-piece) is connected to the out-flow of the cooling bath. The two joints of the 12 mm T-piece that are parallel to the reactor seal to the 12 mm tube and ¼" tube respectively. The two joints of the ¼" T-piece that are parallel to the reactor seal to the ¼" tube and a 1/16" tube respectively. The 1/16" stainless steel tube runs down the length of the

1/4" tube and is welded through the closed end of the 12 mm tube and protrudes approximately 1 cm. The other end of this tube is connected to a Jasco PU-980 HPLC pump and serves as the input of organics into the reactor. The cold finger / organic in-flow set-up is placed inside of a 15.6 mm OD standard grade quartz tube (214 grade quartz, wall thickness = 1.5 mm) that has been modified in house such that one end is sealed. The joint of a Bola GL 32 PTFE T-piece closest to the sealed end of the reactor seals to the quartz tube using a Bola GL 32 thread cap and 16 mm PTFE gasket. The joint of the Bola T-piece furthest from the sealed end of the reactor seals to the 12 mm tube, and the tube connected to the side arm acts as the organic out-flow. Standard Bola GL 32 HT screw joints (12 mm and 1/4" respectively) were used to seal the top and side arm of the Bola T-piece. Inserts for these joints were machined in-house to reduce the dead volume as shown in Chapter 2.

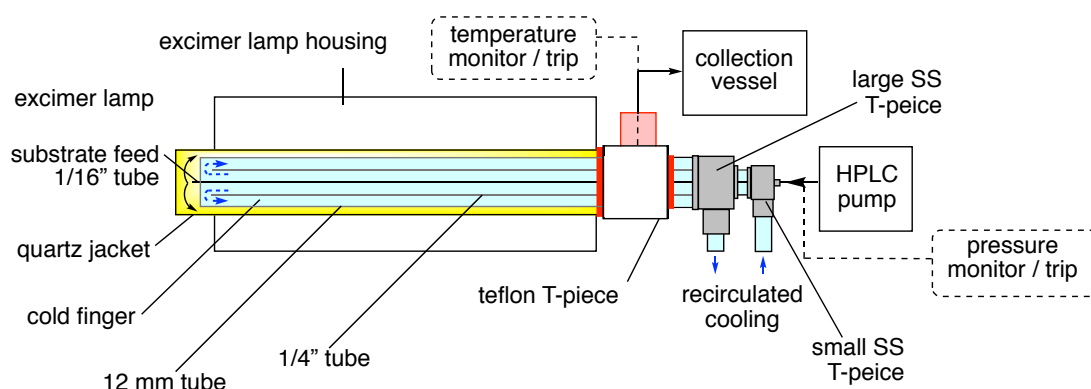


Figure 63: Schematic of a cross section of the excimer reactor. Adapted from DeLaney et al.¹³⁴

The reactor is then posted down the 16 mm bore of one of the three excimer lamps described in Chapter 2, a schematic and a photograph of the lamps has been duplicated here for clarity (Figure 64). The reactor is relatively long (~ 90 cm). The length of the reactor is greater than the depth of the vented cabinet in which it is housed. To facilitate the removal of the reactor from one lamp and insertion into an excimer lamp filled with a different gas mixture (different emission wavelength), the lamp and reactor sit on a turntable (Figure 64, C). This allows for the reactor to be

turned toward the open doors of the vented cabinet during withdrawal from/ insertion into the lamp, which provides the necessary space for this process. After the lamps have been changed the reactor and lamp can turn on the turntable so that the reactors longest dimension is parallel with the length of the vented cabinet, allowing the doors of the vented cabinet to be closed fully.

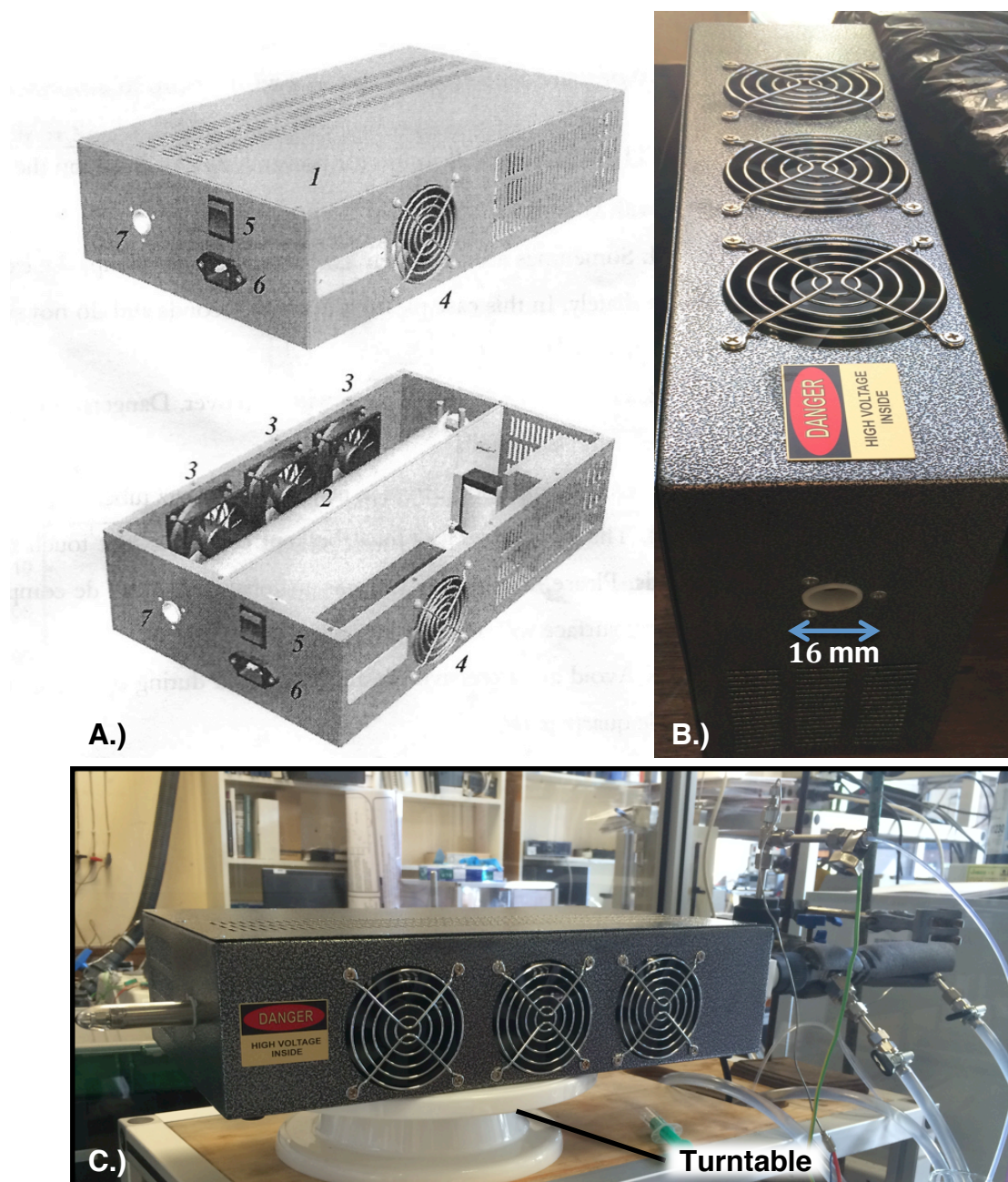


Figure 64: A.) Schematic of the excimer lamps showing the various features, adapted from the manufacturers user manual.¹²⁹ 1: Metal box to shroud UV light. 2: Annular excimer bulb. 3: Fans for cooling outer surface of the lamp. 4: Fan for cooling the lamp electronics. 5: Power Switch. 6: Power supply. 7: Hole allowing for inserting a reactor into the lamp. B.) Photograph of the XeBr excimer lamp. All three lamps have the same dimensions, with a bore of 16 mm. C.) Photograph of the excimer reactor showing the turntable it sits on.

The inner diameter of the quartz tube and outer diameter of the metal cold finger, result in an optical pathlength of 120 microns. The total reactor volume is 1.37 mL and the overall system volume is 10.0 mL.

6.1.1 Standard Operating Procedure for the Excimer Reactor

The standard operating procedure (SOP) for the excimer reactor is presented below. Care must be taken when working with ultraviolet light; therefore the safety procedures detailed below must be strictly followed.

Start up

- Prepare the reagent solution and de-gas by bubbling Argon through the solution for at least 10 minutes.
- Ensure that the excimer lamp switch is in the off position.
- Switch on the power to the system at the trip box and reset the trip.
- Pump 200 mL of degassed solvent through the rig at a rate of at least 5.00 ml min⁻¹ to clean the reactor.
- At the same time, check all joints and fittings for leaks.
- Turn on and set the cooling bath to the desired temperature (Between -10°C and 40°C depending on the freezing point of the solvent). Allow the reactor to reach within 2° C of the set temperature. (N.B. Do not set the cooling bath temperature below the freezing point of the reaction solvent.)

Reaction

- Prime the reaction mixture into the organic pump.
- Set the desired flow rate and start pump.
- Switch on the UV lamp using the power switch on the lamp box.
- Allow for equilibration time (typically 2 full system volumes, ~20 mL).
- Take samples or collect reaction output.

Shut-down

- Stop the lamp and the organic pump using the emergency trip box.
- Set the lamp power switch to the off position.
- Turn the organic pump back on using the reset button on the trip box.

- Pump 200 mL of clean solvent through the rig at a rate of 5.0 mL min⁻¹. Turn off the pump.
- Turn off the cooling bath.
- Partially withdraw the reactor from the lamp and check for fouling of the inner quartz surface. If the quartz appears dirty, proceed with the cleaning procedure.

Cleaning Reactor/ Changing Lamp

- With lamp, pump, and cooling bath off, unclamp the reactor.
- Turn the turntable so that the end of the reactor with the T-pieces is facing out of the fume cupboard.
- Carefully, slide the reactor completely out of the lamp and securely clamp the reactor in the vertical position with the T-pieces pointed upward.
- Visually inspect for fouling.
- If necessary, flush the reactor with DMSO at 5.0 mL min⁻¹ until fouling is visibly removed. Then pump 200 mL of clean solvent at a rate of at least 5.0 mL min⁻¹ to remove residual DMSO from the system. Turn off the pump.
- If flushing with DMSO does not clean the quartz tube, carefully unscrew the Bola fitting and remove quartz jacket from cold finger. Clean by scrubbing with an appropriately sized test tube brush and acetone. Once clean, replace the quartz tube over the cold finger and tighten the Bola fitting.
- If it is necessary to switch lamps, be sure that the new lamp is positioned evenly on the turntable such that it is well balanced.
- Slide the reactor back into the lamp. Rotate the turntable such that the fume cupboard door can be closed. Then, clamp the reactor securely into position.

Safety

The excimer lamps are contained within a metal box. However, adequate protection against UV light should still be taken. The University of Nottingham School of Chemistry standard operating procedures for the use of UV lamps for chemical reactions should be strictly adhered to. While the lamp is in operation, the Lexan doors of the vented cabinet should remain closed unless absolutely necessary. Samples should be taken as rapidly as possible and all skin must be covered to ensure the minimum of exposure.

Emergency Shut-down

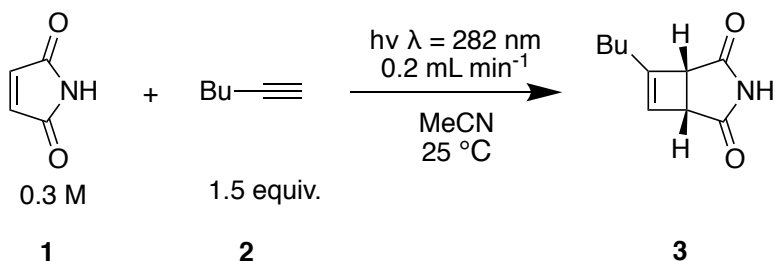
Stop power to the UV lamp and organic pump by pressing the emergency stop button. The cooling bath, temperature and pressure monitors should be left switched on. In the case of a solvent or coolant leak, all electronics should be immediately switched off.

6.2 General Methods and Materials

Reagents were commercially sourced unless otherwise specified. All solvents and reagents were used directly without further purification. NMR spectra (^1H , ^{13}C) were recorded on a JEOL EX270, Bruker AV400, DPX300 or AV(III)400 spectrometer at ambient temperature unless stated otherwise. Chemical shifts are reported in ppm and coupling constants (J) are given in Hz. UV-Vis spectra were recorded with an Agilent 8453 Diode Array Spectrophotometer unless otherwise stated. High-resolution mass spectra were recorded using a Bruker Apex IV FT-ICRMS instrument with electrospray ionisation.

6.3 Reaction Procedures and Characterisation of Compounds Made in the Excimer Reactor

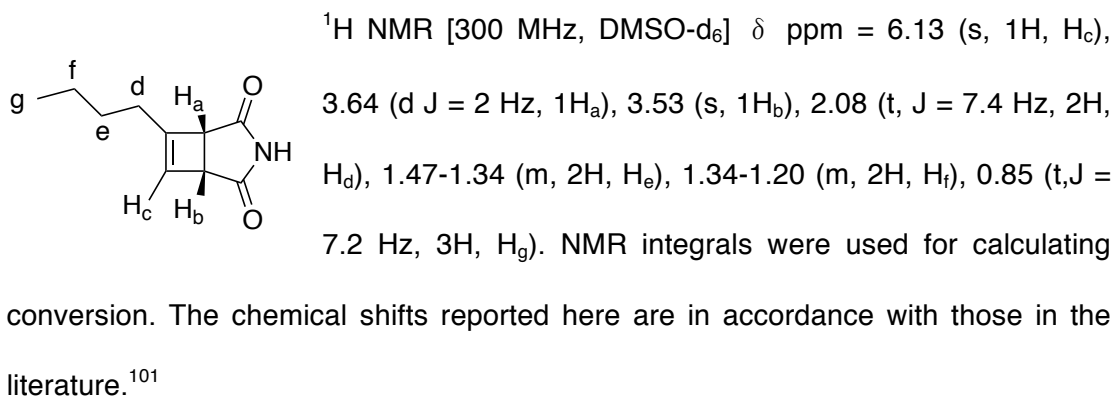
6.3.1 [2+2] Cycloaddition of Maleimide and 1-Hexyne (Results Presented in Chapter 2 - Section 2.5)



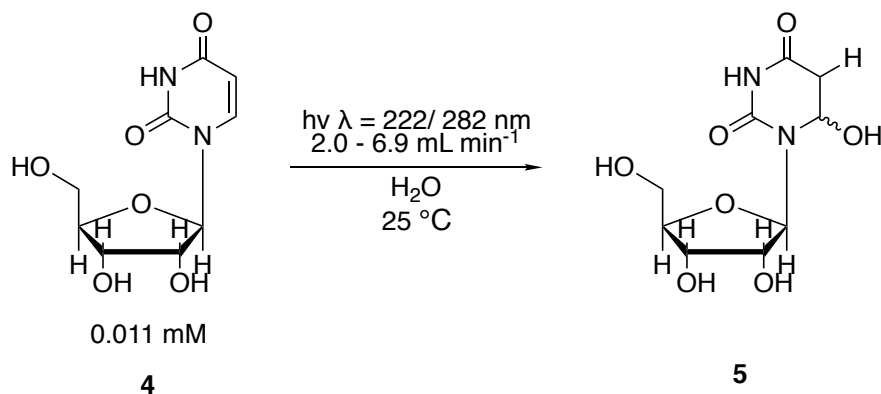
Scheme 28: Reaction scheme for the [2+2] cycloaddition of maleimide and 1-hexyne in the excimer reactor.

The procedure for this reaction was adapted from Booker-Milburn and co-workers.¹⁰¹ Maleimide, **1** (2.9 g, 30 mmol, 1 equiv.), and 1-hexyne, **2** (5.2 mL, 45 mmol, 1.5 equiv.), were added to acetonitrile (100 mL). The resulting solution was stirred until the maleimide had fully dissolved (approximately 10 minutes). This solution was irradiated in the Nottingham excimer reactor at 25°C using the 282 nm lamp and the standard operating procedure for the reactor. After the reaction had reached equilibrium, three (1 mL) samples were taken. Conversions were calculated by ^1H NMR from the crude mixture without further purification, and were the average of three samples. The ratio of the integration of the ^1H NMR peaks of maleimide ^1H NMR [300 MHz, CDCl_3] δ ppm = 6.70 (2H, s) was used for calculating conversion.

6-butyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (3)



6.3.2 Uridine Actinometry (Results Presented Chapter 2 – Section 2.6.1)

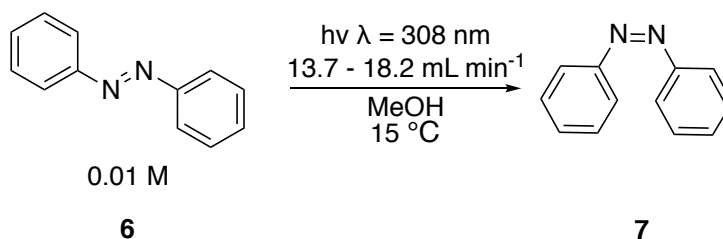


Scheme 29: Reaction scheme for the hydration of uridine, used for 222 nm and 282 nm actinometry in the excimer reactor.

The procedure for uridine actinometry was adapted from the method used by Zhang *et al.*¹³⁸ and a description can also be found in Inès Penders' PhD Thesis.¹⁴⁶ Uridine, **4** (30 mg, 0.12 mmol), was dissolved in water (100 mL). From the resulting stock solution, 1 mL was diluted 1000-fold. This diluted solution was pumped through the excimer reactor at 25 °C in accordance with the standard operating procedure. A single sample (5 mL) was collected for each of the six flow rates used. A UV-Vis spectrum of each sample was recorded using a 4 cm pathlength cuvette and a background of deionised water. (N.B. The same starting solution must be used for all six flow rates to avoid any error induced by discrepancy in the dilution process.) This

process was repeated three times for irradiation using both the 222 nm and 282 nm lamps.

6.3.3 Azobenzene Actinometry (Results Presented in Chapter 2 -Section 2.6.2)

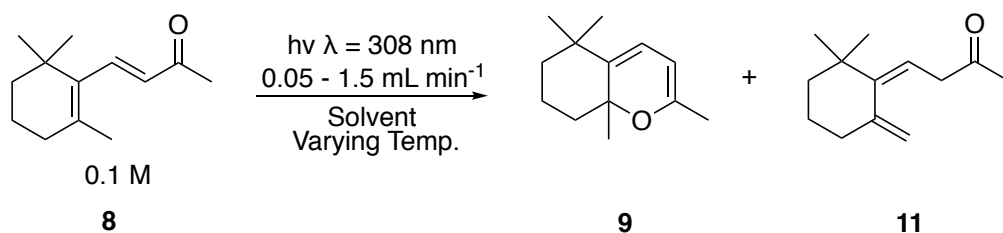


Scheme 30: Reaction scheme for the isomerisation of azobenzene, used for 308 nm actinometry in the excimer reactor.

The procedure for azobenzene actinometry was adapted from the method used by Gauglitz *et al.*¹⁴⁸ and a description can also be found in Inès Penders' PhD Thesis.¹⁴⁶

To accommodate the fast flow rates necessary for the azobenzene actinometry, the Jasco™ PU-986 HPLC pump, which was normally used with the excimer reactor, was temporarily replaced with a Gilson 305 HPLC pump with 50 SC pump head. A Harrick cell containing CaF₂ windows, separated by a 50 μm PTFE spacer, was connected directly to the outlet of the excimer reactor using approximately 20 cm of 1/8" FEP tubing (adding ca. 0.5 mL to the system volume). Azobenzene, **6** (1.83 g, 10.0 mmol), was dissolved in methanol (1 L). The resulting solution was pumped through the excimer reactor at 15 °C and irradiated with the 308 nm excimer lamp following the standard operating procedure. After the appropriate equilibration time for each flow rate a UV-Vis measurement was taken. This process was repeated three times. (N.B. The same starting solution must be used for all the flow rates in a given run to avoid any error induced by discrepancy in the dilution process.)

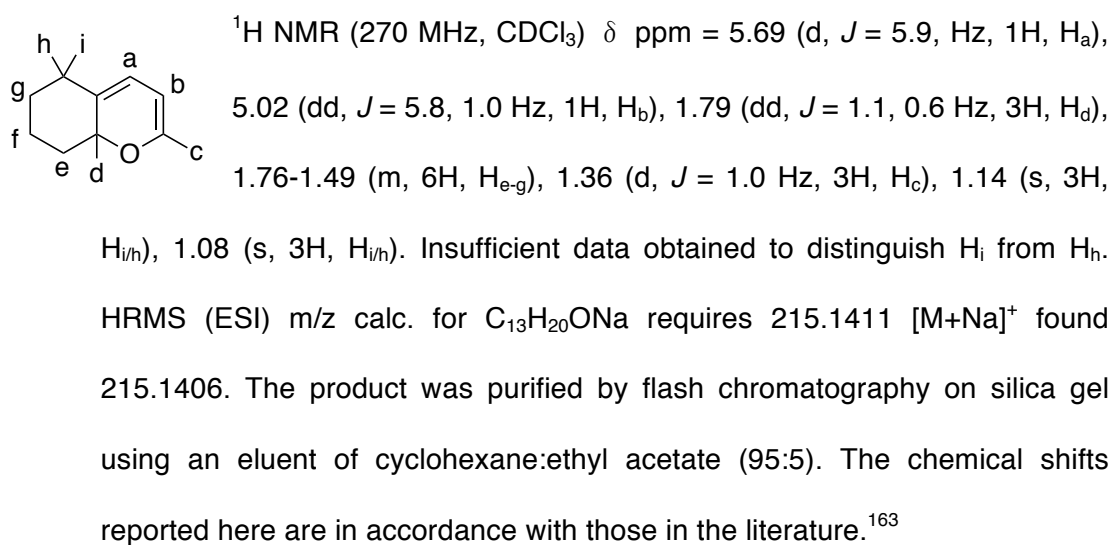
6.3.4 The Photo-isomerisation of β -Ionone (Results Presented Chapter 2 – Section 2.7)



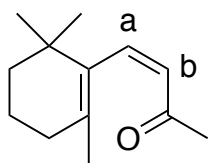
Scheme 31: Reaction scheme for the photo-isomerisation of β -ionone in the excimer reactor.

The general procedure for the isomerisation reactions of β -ionone is given, a range of solvents and reaction temperatures were used. β -ionone, **8** (2.03 mL, 10.0 mmol), was added to the reaction solvent (100 mL). The solution was stirred to ensure homogeneity. The resulting solution was irradiated in the excimer reactor using the 308 nm lamp following the standard operating procedure. Conversions were calculated by ^1H NMR from the crude mixture against β -ionone peaks at ^1H NMR [300 MHz, CDCl_3] δ ppm = 7.27 (d, J = 16.4 Hz, 1H), 6.11 (d, J = 16.4 Hz, 1H) without further purification, and were the average of three samples.

2,5,5,8a-tetramethyl-6,7,8,8a-tetrahydro-5H-chromene (9)



(Z)-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-2-one (12)



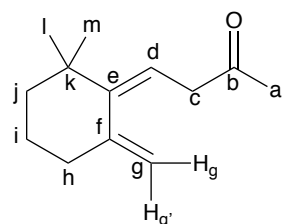
Compound **12** cannot be isolated as it is in equilibrium with **9**.

The peaks for protons H_a and H_b were found in the spectrum of **12**

well separated from other peaks. ¹H NMR (270 MHz, CDCl₃) δ

ppm = 6.57 (1H, ds, *J* = 12.6, 1.3 Hz, H_a), 6.08 (1H, d, *J* = 12.5 Hz, H_b).

(Z)-4-(2,2-dimethyl-6-methylenecyclohexylidene)butan-2-one (11)



¹H NMR (300 MHz, CDCl₃) δ ppm = 5.39 (1H, t, *J* = 7.2 Hz,

H_d), 5.02 (1H, dt, *J* = 2.6, 1.3 Hz, H_{g'}), 4.55 (1H, d, *J* = 2.6

Hz, H_g), 3.30, (2H d, *J* = 7.2, H_c), 2.14 (3H, s, H_a), 1.07 (6H,

s, H_l & m). Signals for protons H_{h-j} apparently overlap with

impurity peaks of starting material **8** and product **9** and cannot be resolved. ¹³C NMR

(300 MHz, CDCl₃) δ ppm = 208.1 (CO, C_b), 129.0 (C, C_e), 128.2 (CH, C_d), 125.3 (C,

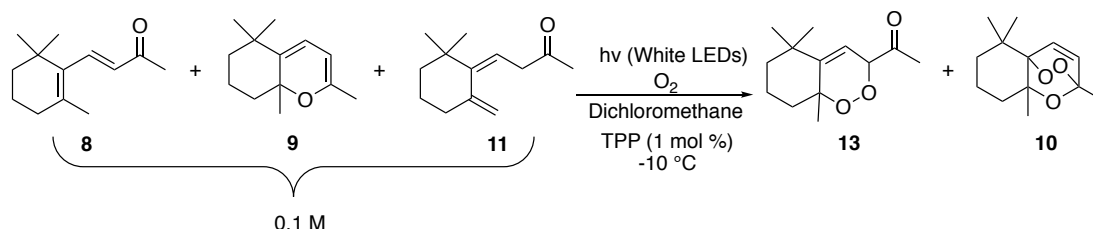
C_e), 111.8 (CH₂, C_g), 44.0 (CH₂, C_c), 41.4 (CH₂, C_{j/h}), 38.2 (C, C_k), 37.2 (CH₂, C_{j/h}),

29.6 (CH₃, C_{a/l}), 28.8 (CH₃, C_{l/m}), 27.4 (CH₃, C_{l/m}), 23.4 (CH₂, C_i). Insufficient data to

distinguish the quaternary carbon e from f, the CH₂ carbon j from h, and the CH₃

carbons, l, and m.

6.3.4.1 Batch Photochemical Oxygenation of the Crude Mixture from UV Irradiation of β-Ionone (Results presented in Chapter 2 - Section 2.7.3)



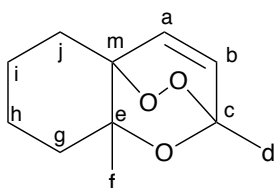
Scheme 32: Reaction scheme for the photo-oxygenation of the products from the photo-isomerisation of β-ionone in the excimer reactor.

The resultant solution from the irradiation of β-ionone (0.2 mL min, 308 nm, -10 °C)

was evaporated to dryness by rotary evaporation to give a crude mixture of isomers

(0.17 g). Tetraphenylporphyrin (5.7 mg, 0.0092 mmol) and dichloromethane (8.8 mL) were added and the solution was stirred. The resulting solution was irradiated with visible white LEDS (1000 lumen, 5 diode array) in an acetone/ice bath, with a steady stream of oxygen bubbled through the solution (ca. 1 bubble per second) for 7 hours. Yields were not calculated for the reaction.

2,5,5,8a-tetramethyl-6,7,8,8a-tetrahydro-2*H*,5*H*-2,4a-epidioxychromene (10)

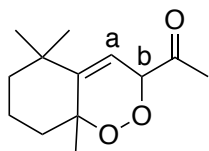


^1H NMR (300 MHz, CDCl_3) δ ppm = 6.53 (1H, d, J = 8.5 Hz, H_a), 6.43 (1H, d, J = 8.5 Hz, H_b), 1.87 – 1.51 (4H, m, $\text{H}_{i,g}$), 1.49 (3H, s, H_d), 1.29 – 1.16 (2H, m, H_h), 1.14 (3H, s, $\text{H}_{k/l}$), 1.11 (3H, s, $\text{H}_{k/l}$), 1.01 (3H, s, H_f). Insufficient data were obtained to distinguish H_k from H_l and significant peak overlap did not allow for the assignment of the peaks for H_{g-i} . ^{13}C NMR (300 MHz, CDCl_3) δ ppm = 133.6 (CH, C_a), 128.8 (CH, C_b), 94.9 (C, C_c), 82.4 (C, C_m), 78.3 (C, C_e), 35.8 (C, C_j), 34.8 (CH_2 , $\text{C}_{g/i}$), 27.1 (CH_2 , $\text{C}_{g/i}$), 26.8 (CH_3 , C_f), 25.7 (CH_3 , $\text{C}_{k/l}$), 24.6 (CH_3 , $\text{C}_{k/l}$), 21.1 (CH_3 , C_d), 19.5 (CH_2 , C_h). Insufficient spectral data were obtained to distinguish the CH_2 carbons g from i and the CH_3 carbons k from l. Nevertheless, the chemical shifts reported here are in accordance with those in the literature.¹⁶³ HRMS (ESI) m/z calc. for $\text{C}_{13}\text{H}_{20}\text{O}_3\text{Na}$ requires 247.1310 $[\text{M}+\text{Na}]^+$ found 247.1307. Product was purified by column chromatography using silica gel with an eluent of cyclohexane:ethyl acetate (80:20).

1-(5,5,8a-trimethyl-3,5,6,7,8,8a-hexahydrobenzo[*c*][1,2]dioxin-3-yl)ethan-1-one

(13)

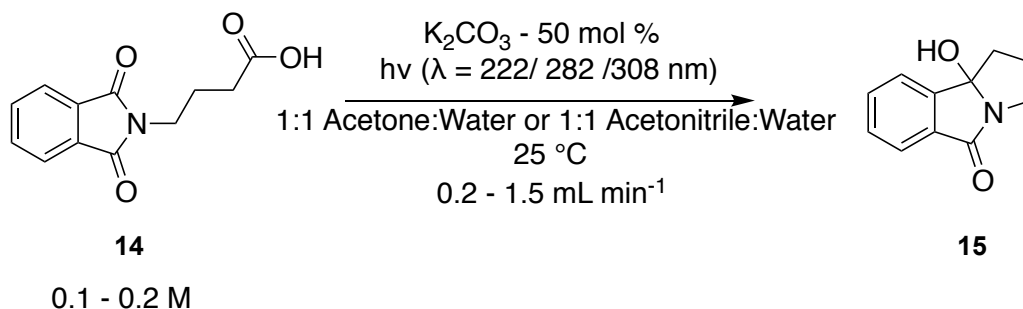
The endo-peroxide product is highly unstable,¹⁶³ a pure sample was not obtained.



The peaks for protons H_a and H_b (in accordance with those reported in the literature)¹⁶⁵ were observed in the ¹H spectra

obtained for the crude material; they were well separated from other peaks. ¹H NMR (300 MHz, CDCl₃) δ ppm = 5.75 (1H, d, *J* = 5.9 Hz, H_a), 4.59 (1H, d, *J* = 5.9 Hz, H_b).

6.3.5 The Photochemical Decarboxylation of 4-Phthalimido Butyric Acid (Results Presented in Chapter 3 – Section 3.4)

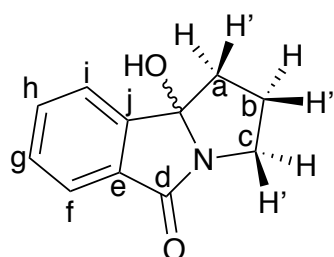


Scheme 33: Reaction scheme for the photo-decarboxylative cyclisation of 4-phthalimidobutyric acid.

A representative procedure is given below for the irradiation of 4-phthalimidobutyric acid; concentration, solvent and irradiation wavelength were varied as described in Chapter 3. 4-Phthalimidobutyric acid was prepared as reported in the literature²²² from phthalic anhydride and 4-aminobutanoic acid. 4-Phthalimidobutyric acid, **14** (7.00 g, 30.0 mmol) was suspended in deionised water (75 mL). Then K₂CO₃ (2.08 g, 15.0 mmol) was added and the resulting mixture was stirred until completely dissolved. Acetone (75 mL) was added and stirred for 10 minutes, giving a 0.2 M solution with respect to **14**. The solution was irradiated at 25 °C with one of the three excimer lamps using the standard operating procedure.

Samples (0.5 mL) were collected in triplicate for each set of experimental conditions. The product yield was determined by comparison of ^1H NMR integrations in d_6 -DMSO of the external standard (1,3,5-trimethoxybenzene) and signal corresponding to **15** (^1H signal at 1.43 ppm). The yields reported are the averaged values from the triplicate samples taken for each flow rate, wavelength and concentration. The product was isolated from the bulk when desired by removal of the organic solvent by rotary evaporation, followed by extraction with chloroform. Drying of the organic layer over MgSO_4 and removing the solvent by rotary evaporation afforded **15**, as a white solid.

9b-hydroxy-1,2,3,9b-tetrahydro-5H-pyrrolo[2,1-a]isoindol-5-one (15)



^1H NMR (300 MHz, DMSO-d_6) δ ppm = 7.75 – 7.44 (4H, m, $\text{H}_f\text{-H}_i$), 6.35 (OH, s, H_j), 3.52 (1H, dt, $J = 11.2, 8.4$ Hz, H_c), 3.38– 3.19 (1H, m, H_c'), 2.64 – 2.35 (1H, m, H_a'), 2.30 – 2.09 (2H, m, H_a and H_b'), 1.43 (1H, m, H_b). ^{13}C NMR (300 MHz, DMSO) δ ppm = 169.1 (CO, C_c), 148.3 (C_j), 132.5 (C_e), 131.5 (CH, C_h), 129.3 (CH, C_g), 122.8 (CH, C_f), 122.7 (CH, C_i), 95.6 (C_k), 41.1 (CH_2 , C_c), 35.2 (CH_2 , C_a), 27.4 (CH_2 , C_b). HRMS (ESI) m/z calc. for $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{Na}$ requires 212.0682 $[\text{M}+\text{Na}]^+$ found 212.0688. ^1H and ^{13}C NMR peaks correspond well with those reported in the literature.²²⁴

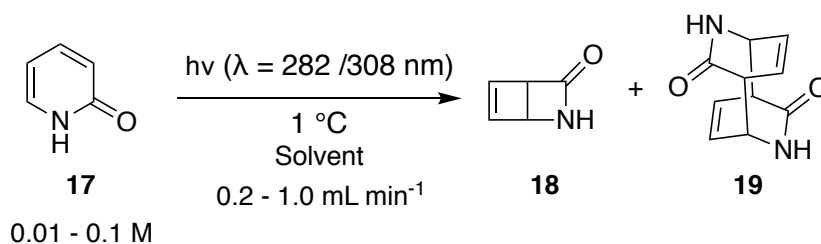
The outlet from the excimer reactor was connected to a stainless steel reactor (reactor OD = ½”) containing Amberlyst 15® (wet form, 5.0 g). The outlet from this reactor was connected to another stainless steel reactor (reactor OD = ½”), this reactor had been loosely packed with NbOPO₄ (1.0 g) and glass beads. The reagents were flowed through the final column upflow to minimise backpressure. The integrated reaction was performed at 0.2 mL min⁻¹ using 0.1 M solution of **14** in 1:1 acetone:water at 25 °C and irradiating with the 308 nm excimer lamp.

The chemical structure shows a phenyl ring (atoms g, h, i, j, e, f) connected to an imidazole ring (atoms a, b, c, d, k). The nitrogen atom in the imidazole ring is labeled 'N'. The methyl group is represented by atom 'c' bonded to atom 'd'. The carbonyl group is represented by atom 'd' double-bonded to an oxygen atom 'O'. The labels a through k identify the following atoms: a (C2), b (C3), c (N1), d (C4), e (C5), f (C6), g (C7), h (C8), i (C9), j (C10), k (C11).

¹H NMR (400 MHz, CDCl₃) δ ppm = 7.82 (1H, d, *J* = 7.5 Hz, H_f), 7.65 (1H, d, *J* = 7.5 Hz, H_i), 7.54 – 7.48 (2H, m, H_g and H_h), 5.76 (1H, t, *J* = 3.1 Hz, H_a), 3.94 (2H, t, *J* = 7.4 Hz, H_c), 3.21 (2H, td, *J* = 7.4, 3.1 Hz, H_b). ¹³C NMR

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6.3.6 The Photochemical Isomerisation of 2-Pyridone (Results Presented in Chapter 4)



Scheme 35: Reaction scheme for the photo-isomerisation of 2(1H)-pyridone.

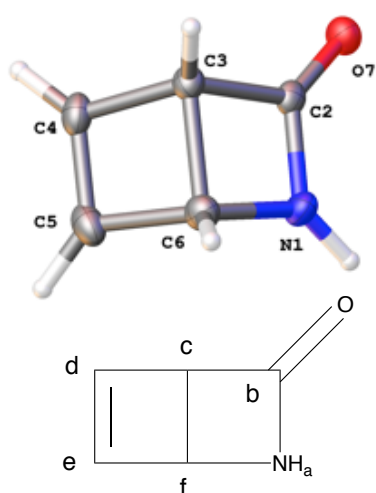
A representative procedure for the photochemical isomerisation of 2-pyridone is given below; concentration, solvent, irradiation wavelength and the addition of LiBr were varied as described in Chapter 4. 2(1H)-Pyridone, **17** (0.095 g, 1.0 mmol), was added to water (100 mL) and stirred until completely dissolved. The resulting solution was pumped through the excimer reactor at 1°C and irradiated with 308 nm light according to the standard operating procedure.

Samples (5.0 mL) were collected in triplicate for each set of experimental conditions. The solvent was removed from the samples by freeze-drying or rotary evaporation to dryness. Initially the product and dimer yields were determined by comparison of ^1H NMR integrations in d_6 -DMSO of the external standard (1,3,5-trimethoxybenzene) and signals corresponding to **18** and **19** (^1H signals at 4.36 ppm and 7.63 ppm respectively). The yields reported are the averaged values from the triplicate samples taken for each flow rate, wavelength and concentration.

Conversion was also determined by in-line UV-Vis. A Harrick cell containing CaF_2 windows, separated by either a 150 or 200 μm PTFE spacer, was connected directly to the outlet of the excimer reactor using approximately 20 cm of $\frac{1}{8}$ " FEP tubing (adding ca. 0.5 mL to the system volume). Conversion of the starting material was determined using absorbance from the absorption spectrum obtained at each set of experimental condition and the Beer-Lambert law. Calibration curves for the extinction coefficient of starting material **17** can be found in Appendix 4.2.

The most accurate yields were determined by HPLC using the Agilent Technologies 1200 series HPLC fitted with a Waters C₁₈ (3.9 x 150 mm) reverse phase column with compounds detected by an Agilent 1200 series multiple wavelength detector. A sample (0.5 mL) was taken for each experimental condition. From the sample 25 μ L was injected onto the column and separated using the method described in Appendix 4.6. The yields for individual flow experiments were determined based upon the calibration curves for the response factor of the purified compounds. The calibration curves can be found in Appendix 4.5.

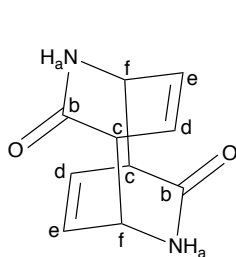
2-Azabicyclo[2.2.0]hex-5-en-3-one (**18**)



¹H NMR (300 MHz, DMSO-D₆) δ ppm = 8.16 (1H, s, broad, H_a), 6.67 (1H, m, H_e), 6.61 (1H, dd, J = 2.4, 1.3 Hz H_d), 4.35 (1H, ddd, J = 2.7, 2.1, 0.5 Hz, H_f), 4.09 (1H, dq, J = 2.2, 1.1 Hz, H_c). ¹³C NMR (400 MHz, CDCl₃) δ = 172.2 (CO, C_b), 142.5 (CH, sp², C_d), 140.5 (CH, sp², C_e), 59.5 (CH, sp³, C_e), 50.8 (CH, sp³, C_f). Carbon NMR peaks correspond well with those reported in the literature.²³⁶ Product **18**

was isolated from the bulk when desired by saturating with NaCl and extracting three times with an equal volume of ethyl acetate. The organic layer was dried over magnesium sulfate and the solvent was removed. Flash column chromatography on silica gel, using ethyl acetate as the eluent, gave **18**, as a pale yellow solid, after the solvent was removed.

3.7-Diazatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione (**19**)



^1H NMR (300 MHz, DMSO- D_6) δ ppm = 7.63 (2H, d, J = 5.3 Hz,

H_a), 6.58 (2H, m, H_e), 6.05 (2H, ddd, J = 8.3, 7.1, 1.5 Hz, H_d),

4.04 (2H, m, H_f) 3.27 (2H, ddt, J = 10.4, 7.1, 1.8 Hz, H_c). ^{13}C

NMR (400 MHz, CDCl_3) δ ppm = 177.2 (CO, C_b), 135.4 (CH,

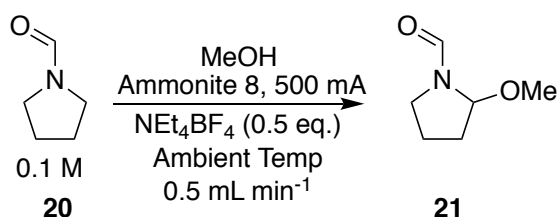
C_e), 131.1 (CH, C_d), 52.2 (CH, C_c), 49.9 (CH, C_f). HRMS (ESI) m/z calc. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2\text{Na}$ requires 213.0640 $[\text{M}+\text{Na}]^+$ found 213.0638. Dimer **19** can be isolated from the bulk by removal of the aqueous solvent by freeze drying or rotary evaporation, followed by washing of the resulting solid with copious ethyl acetate. A final wash with a minimal quantity of water gives **19** as a white solid.

6.4 The Ammonite 8 Reaction Set-Ups and Compound Characterisation (Results Presented in Chapter 5)

6.4.1 Ammonite 8 Reactions with In-line FTIR, Experimental Set-up (Results Presented in Chapter 5 - Section 5.5.2)

The Ammonite 8 was connected to the Voltcraft® –LRP1205 power supply. The inlet of the Ammonite was connected to a Jasco PU 4180 HPLC pump using 10 cm of 1/8" FEP tubing. The outlet from the Ammonite 8 was connected to approximately 20 cm of 1/8" FEP tubing. The outlet tube was secured into the top third of standard sized 25 mL graduated measuring cylinder. The inlet tube (ca. 20 cm of 1/8" FEP tubing) leading to the peristaltic pump (Cole-Palmer Master-Flew L/S PTFE Tubing Peristaltic Pump) was secured at the 5 mL graduation inside the measuring cylinder. The Raman fibre optic probe was placed into the measuring cylinder approximately 0.5 cm from the bottom.

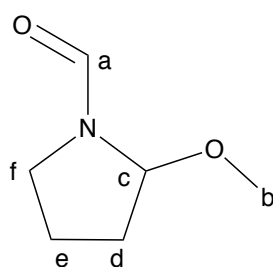
6.4.1.1 Reaction Details and Compound Characterisation



Scheme 36: Reaction scheme for the methoxylation of *N*-formylpyrrolidine in the Ammonite 8 with in-line Raman monitoring.

N-formylpyrrolidine, **20** (0.99 g, 10 mmol), and tetraethylammonium tetrafluoroborate (1.1 g, 5.0 mmol) were added to methanol (100 mL) and stirred to ensure the reagents were fully dissolved. The solution was primed into the HPLC pump of the previously described reaction set-up. The electrochemical reaction was performed with a flow rate of 0.5 mL min⁻¹ using a current on 500 mA. The peristaltic pump was set to 50 rpm. Raman spectra were recorded using a Kaiser Optical Raman Rxn2 probe with a wavelength of 785 nm. (N.B. An authorised laser user must operate the Raman probe in a laser safety area.) Details for the general set-up and cleaning of the Ammonite 8 can be found in the next section.

2-Methoxypyrrolidine-1-carbaldehyde (**21**)



¹H NMR (300 MHz, CDCl₃) δ ppm = 8.42 (1H, s, H_a), 4.95 (1H, d, *J* = 4.7 Hz, H_c), 3.52-3.39 (2H, m, H_f), 3.28 (3H, s, H_b), 2.24-1.79 (4H, m, H_{e-d}). Product was purified by evaporating the solvent from the crude (full conversion reaction), adding

ethyl acetate, and filtering to remove the insoluble electrolyte. This gave **21** as a yellow oil. ¹H NMR chemical shifts reported here are in accordance with those presented in the literature.²⁹²

6.4.2 Ammonite 8 Reactions with On-line GC Analysis (Results Presented in Chapter 5 - Section 5.7.5.3)

The Ammonite 8 was connected to the Voltcraft® LRP-1205 power supply. The inlet of the Ammonite was connected to a Jasco PU 4180 HPLC pump using 10 cm of 1/8" FEP tubing. The outlet from the Ammonite 8 was connected to approximately 20 cm of 1/16" FEP tubing. The outlet tube was secured into the top third of a small (0.5 mL) vial. The inlet tube (ca. 10 cm of 1/16" FEP tubing) to the second pump (Jasco PU-986) was secured at the bottom of the small vial. The small vial was placed below the second pump. The outlet from the second pump was connected to the Valco 6-way switching valve on the GC using approximately 20 cm of 1/16" SS tubing. The Valco 6-way switching valve was fitted with a 0.06 µL sample loop.

6.4.2.1 Standard Operating Procedure: Electrochemical Reactions in the Ammonite 8 with On-line GC Analysis

The standard operating procedure (SOP) for the Ammonite Reactor with on-line GC analysis is presented below. Care must be taken when working with electrically live equipment; therefore the safety procedures detailed below must be strictly followed.

Start-Up

- Start the GC, light the FID, and load the appropriate method file.
- Prepare the reagent solution.
- Tighten the bolts on the Ammonite 8.
- Pump clean solvent through the reactor at 2.0 mL min⁻¹; check for solvent leaks.
- Ensure the GC has equilibrated and the baseline is steady.
- Clip the Ammonite power supply clamps together while the circuit is open, close the circuit using the button on the power supply and set the desired current and maximum voltage (12 V). Re-open the circuit.

- Connect the leads from the power supply to the appropriate pins on the Ammonite 8 (black to bottom pin, red to top pin).
- Place an over-flow collection below the small test-tube.

Reaction

- Prime the reagent solution into pump 1.
- Set the desired reaction flow rate on pump 1.
- Set the flow rate of the second pump to match the flow rate pump 1. (A calibration for the efficiency of these two pumps and can be found in Appendix 5.1)
- Start pumps 1 and 2.
- Turn on the power supply and close the circuit. (The Ammonite is now live!)
- Allow 2 system volumes (10 mL total) to flow through the Ammonite.
- Start the GC sampling program to take the desired number of consecutive samples. (N.B. The conditions can be changed after the final GC run has started, it is not necessary to wait for the run to finish.)

Shut-Down

- Open the circuit and then turn off the power supply.
- Stop both pumps. Prime pure solvent into both pumps.
- Flush pure solvent through both pumps individually at 3.0 mL min^{-1} until 150 mL have passed through both pumps, and then stop both pumps.
- Clean the small vial with acetone.
- Disconnect the inlet and outlet of the Ammonite 8 and follow the cleaning procedure.

Cleaning Procedure

- Open the Ammonite 8.

- Wipe all surfaces and both sides of the gasket with methanol and cotton wool.
- Polish the carbon electrode with a spatula full of silica, a polishing cloth and methanol.
- Remove the silica completely by washing with methanol.
- Reassemble the Ammonite, leaving the fittings only finger tight to prevent the top plate from sticking.
- Reconnect the inlet and outlet tubes.

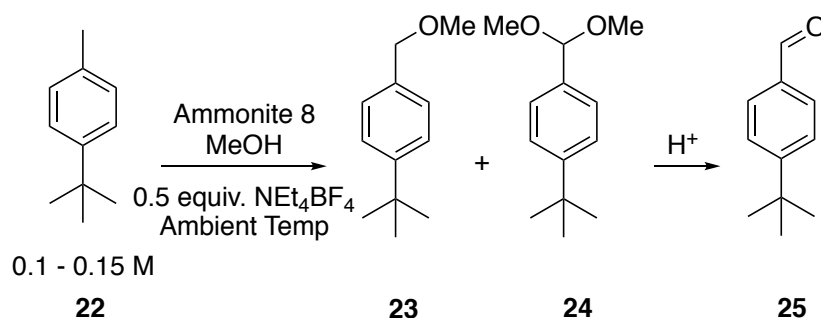
Safety

Many reactions in the Ammonite 8 produce H_2 . Ensure that the Ammonite is used in a fume cupboard with adequate ventilation without any possible sources of ignition in the vicinity. During the reaction the Ammonite base plate will be live, do not touch it.

Emergency Shut-Down

Stop power to the power supply and both pumps. In the case of a leak all electrical equipment should be immediately shut off.

6.4.2.2 Procedures and Compound Characterisation

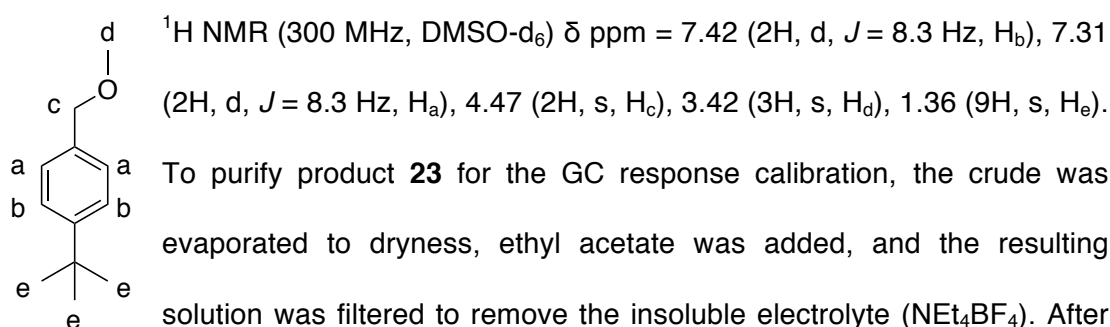


Scheme 37: Reaction scheme for the electrochemical methoxylation of 4-tert-butyltoluene performed in the Ammonite 8.

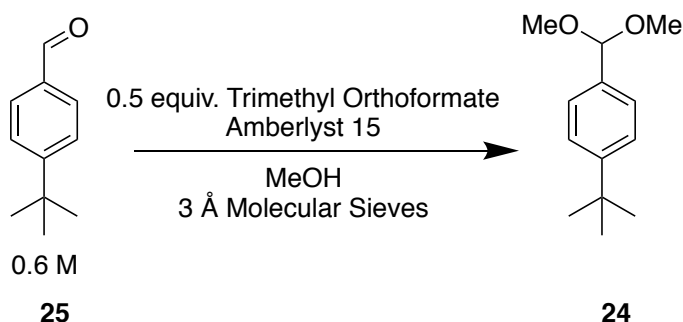
A representative procedure is given for the electrochemical methoxylation of 4-tert-butyltoluene, concentration was varied as described in Chapter 5. 4-tert-Butyltoluene, **22** (1.72 mL, 10.0 mmol), and tetraethylammonium tetrafluoroborate

(1.08 g, 5.00 mmol) were added to methanol (100 mL) and sonicated for 10 minutes to ensure the reagents were fully dissolved. The reaction was performed as described in the standard operating procedure given above. Yields were calculated from the area of the GC peaks compared to the response factor calibration curve for obtained each compound using a Shimadzu GC-2010 and SPB-1701 column. The calibration curves for the GC response factors can be found in Appendix 5.2.

***p*-(Methoxymethyl)(*tert*-butyl)benzene (**23**)**



To purify product **23** for the GC response calibration, the crude was evaporated to dryness, ethyl acetate was added, and the resulting solution was filtered to remove the insoluble electrolyte (NEt_4BF_4). After removal of the ethyl acetate by rotary evaporation, column chromatography on silica gel with an eluent of pentane:diethyl ether 95:5 afforded **23** as a colourless oil.

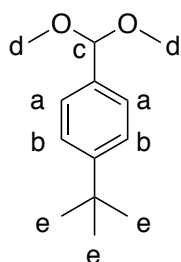


Scheme 38: Reaction scheme for the conversion of 4-*tert*-butylbenzaldehyde to *p*-(methoxymethyl)(*tert*-butyl)benzene (24**).**

As product **24** was more difficult to purify from the crude mixture obtained from the electrochemical reactions it was synthesised for the GC calibration as follows: 4-*tert*-butylbenzaldehyde, **25** (1.0 mL, 6.0 mmol), and trimethyl orthoformate (0.97 mL, 9.0 mmol) were added to methanol (10 mL). Amberlyst[®] 15 (ca. 1 g) and 3 Å molecular

sieves (ca. 1 g) were also added, and the mixture was stirred for 4 hours. The mixture was filtered through Celite and purified by column chromatography on silica gel using an eluent of pentane:ethyl acetate (90:10). This gave compound **24** as a colourless oil in 55% yield.

1-*tert*-Butyl-4-(dimethoxymethyl)benzene (24)



^1H NMR (300 MHz, DMSO- d_6) δ ppm = 7.39 (2H, d, J = 8.4 Hz, H_b),
 7.30 (2H, d, J = 8.4 Hz, H_a), 5.33 (1H, s, H_c), 3.21 (6H, s, H_d), 1.26
 (9H, s, H_e).

Chapter 7: Conclusions and Future Directions

This Thesis aimed to help to increase the versatility of photochemistry by providing an additional photochemical flow reactor and demonstrating how the modular nature of flow chemistry⁷⁵ can be effectively exploited for multi-step synthesis and reaction monitoring for both photochemistry and electrochemistry. As detailed in Chapter 1, the specific aims of the work presented in this Thesis were:

- 1.) To design and build a UV photochemical reactor that employs excimer lamps as the light source and to compare the efficiency of this reactor to other reactors reported in the literature.
- 2.) To study the wavelength dependence of photochemical reactions by employing three excimer lamps with different gas mixture for irradiation in the Nottingham excimer reactor.
- 3.) To integrate the Nottingham excimer photochemical reactor into a continuous multi-step process.
- 4.) To use the intense monochromatic light of excimer lamps and the Nottingham UV photochemical reactor to more efficiently perform photoreactions with low quantum yield.
- 5.) To integrate in-line analysis with the UV photochemical reactor.
- 6.) To find a simple method for incorporating in-line or on-line analysis with a commercially available flow electrochemical reactor.

In the next sections the motivation for each aim, results obtained toward each aim, and future work that could be performed to further each aim, are described.

Aim 1: To design and build a UV photochemical reactor that employs excimer lamps as the light source and to compare the efficiency of this reactor to other reactors reported in the literature.

Motivation

Performing photochemistry in continuous flow can have significant benefits to the overall reaction outcome including minimising inner-filter effects and reducing the formation of secondary photoproducts.⁷¹ However, the majority of UV flow photochemical reactors utilise broadband emitting mercury lamps. This results in the reaction being unable to absorb a considerable proportion of the photons generated by the lamp. Excimer lamps by contrast are a source of monochromatic light.⁹⁰ Therefore, they have the potential to be more efficient since, in theory, all of the photons emitted by the lamp can be of an appropriate wavelength for performing a given photochemical reaction.

Developments

The Nottingham excimer reactor was designed for both efficient photochemistry and for facile laboratory use. The outer jacket of the reactor is made from highly UV transparent quartz, and the cooling system is at the centre of the reactor rather than between the reagents and light source. This allows for the maximum number of photons emitted from the lamp to be absorbed by the reagents without competitive absorption by the reactor or cooling media. The reactor was designed to include a small optical pathlength (120 μm) to avoid inner-filter effects.

This reactor was then used to study the photo-isomerisations of β -ionone and 2-pyridone, as well as the [2+2] cycloaddition of maleimide and 1-hexyne, and the photo-decarboxylation of 4-phthalimidobutyric acid. Using space-time yield as the metric for reactor efficiency, the Nottingham excimer reactor gave a STY approximately 5 times greater than the FEP reactor¹⁰¹ for the [2+2] cycloaddition of

maleimide and 1-hexyne. For the decarboxylation of 4-phthalimidobutric acid, the STY of the Nottingham reactor was 25 times greater than the Rayonet batch reactor, 6 times greater than the micro-reactor,²²⁰ and 3 times greater than a falling-film reactor⁹⁰ also employing an excimer light source. Only the Firefly¹²⁴ was more efficient for this reaction with a STY approximately 1.5 times greater than the Nottingham excimer reactor.

Future Work

The Nottingham excimer reactor is efficient for synthesising products on a scale from milligrams up to about 10 grams, depending on the nature of the particular reaction. However, to synthesise larger quantities of product and to obtain STY closer to the Firefly¹²⁴ a more powerful light source and larger reactor are necessary. The design for a larger excimer reactor using similarly shaped lamps that can accommodate a reactor with a diameter more than three times as large as the smaller excimer reactor, and that are more than twice as powerful, was presented in Chapter 2.

Aim 2: To study the wavelength dependence of photochemical reactions by employing excimer lamps with three different gas mixture for irradiation in the Nottingham excimer photo-reactor.

Motivation

Since the Nottingham UV excimer reactor can use three different excimer lamps with emission wavelengths of 308 nm, 282 nm and 222 nm, it provides an opportunity to investigate the wavelength dependence of photochemical reactions. Elliot *et al.*¹²⁴ showed that the photo-decarboxylative cyclisation of 4-phthalimidobutyric acid was more efficient when irradiating through quartz rather than borosilicate. It is expected that with the increased photon flux through quartz (borosilicate will absorb photons with wavelengths less than 300 nm) the productivity of a photochemical reaction will increase. However, the productivity increase for this reaction was approximately

twice what is typically observed with other photochemical reactions. The three different irradiation wavelengths from our lamps meant that it was possible to study the productivity of the reaction at each of these wavelengths to determine whether the increased productivity seen by Elliot *et al.*¹²⁴ was a result of the reaction being wavelength dependant.

Developments

Irradiation using each of the three excimer lamps showed that the productivity of the reaction was largely unaffected by the irradiation wavelength. Rather, the most important factor for affecting the overall productivity of the reaction was the number of photons produced in a given time period by each lamp (radiant exitance). Although some product breakdown was observed when the reaction was performed with the 222 nm lamp, the photoproduct proved to be relatively robust. This may account for why the productivity for this reaction was observed to be higher through quartz than other photochemical reactions.¹³⁴

Irradiation wavelength was important to the overall productivity of the reaction when a sensitising solvent mixture (acetone:water) was used. It appeared that the sensitizer was able to improve the productivity of the reaction under conditions of high conversion where the concentration of reagents able to absorb light is reduced. However, at higher concentrations (or lower conversions) the sensitizer competitively absorbs the light decreasing the overall productivity.¹³⁴

Future Work

The comparison of the results from non-sensitising solvent (MeCN:water) to sensitising solvent (acetone:water), suggest that the quantum yield of the sensitised reaction is lower than the quantum yield of the direct reaction. Measuring the quantum yield of both the sensitised and direct reactions would make it possible to determine if this is indeed the case.

Although this reaction did not prove to be significantly wavelength dependant, it did show that irradiation wavelength can have an influence on photochemical reactions (e.g. additional secondary photoproducts were only observed under 222 nm irradiation), particularly if a sensitiser is employed. It is therefore worth continuing to study other photochemical reactions at different irradiation wavelengths, particularly those reactions with multiple photoproducts, as the irradiation wavelength may alter the major reaction pathway.

Aim 3: To integrate the Nottingham Excimer UV photochemical reactor into a continuous multi-step process.

Motivation

Most organic syntheses require multiple-steps in order to generate the desired product. Linking these steps together into a single continuous process can result in savings of both time and waste.^{152, 153} Flow reactors have been described as modular,^{75, 334} and one of claimed advantages of flow is the relative ease with which flow “modules” can be linked together to generate a desired compound.⁷⁶ It was therefore of interest to see if the excimer reactor could be integrated into a multi-step process.

Developments

The photoproduct from the photochemical decarboxylation of 4-phthalimidobutyric acid will undergo dehydration in the presence of catalytic quantities of strong acid. The excimer reactor was integrated with the acid dehydration step with the addition of two acid columns downstream of the photochemical reactor. The first acid column contained Amberlyst 15® to quench the potassium hydroxide generated in the photochemical step and the second column contained NbOPO₄, a solid acid that catalysed the dehydration reaction. The initial high yields of the process (79%) dropped to just 15% after 10 hours of running the reaction due to channelling through

the second acid column.¹³⁴ The channelling through the NbOPO₄ bed could perhaps be minimised by packing the catalyst bed more tightly or running the reaction at a backpressure. However, the photochemical reactor, with its quartz outer jacket, cannot currently be operated safely at elevated pressures.

Future Work

Integrating the acid catalysis with the photochemical reactor demonstrated the clear challenge when linking reactors together; the system becomes limited by the lowest maximum operating conditions of any of the reactor modules that are linked together. Understanding how the excimer reactor would respond to elevated pressures is of vital importance to future integrated processes. Specifically, it would be useful to know whether a pressure failure of the excimer reactor would lead to the quartz jacket exploding and leaking reagents in to the lamp or if it would cause a leak at the O-ring seal outside of the lamp. To further develop the modular “plug-and-play” strategy with the excimer reactor, developing a way of decoupling the pressures between reactor modules would be desirable.

Aim 4: To use the intense monochromatic light of excimer lamps and the Nottingham UV photochemical reactor to more efficiently perform photoreactions with low quantum yield.

Motivation:

A photochemical reaction with low quantum yield will require more photons to reach full conversion. This translates to long irradiation times, making the overall process inefficient. However, using a more intense light source, where all of the photons emitted can be absorbed by the substrate (e.g. an excimer lamp), should increase the overall efficiency of the reaction. The photochemical isomerisation of inexpensive 2-pyridone generates a bicyclic β -lactam that is of higher value than the starting material, having significant potential as a synthon for pharmaceutically active

products.^{236, 247} However, the low quantum yield and a competing [4+4] dimerisation reaction have previously meant that the reaction mixture must be irradiated for long periods of time at high dilutions.²⁵⁶ Considering the synthetic potential of the photo-pyridone product, the isomerisation of 2-pyridone provided an interesting model reaction for testing whether the excimer reactor could increase the efficiency of low quantum yield reactions.

Developments:

Prior to this Thesis, to the best of my knowledge, the photochemical isomerisation of 2-pyridone had only been performed in batch. In organic solvents, including polar organic solvents such as acetonitrile, the photo-dimer of 2-pyridone will precipitate from solution. As solids can create blockages in flow reactors, the reaction was instead performed in aqueous solution. Due to the relatively low boiling point of the photo-pyridone product (despite its being a solid), we discovered that the reaction yield could only accurately be determined by techniques that did not require the evaporation of the high-boiling aqueous solvent. Therefore reverse phase HPLC with UV-Vis detection was used to quantify the yield of the reaction. Comparison with results in the literature showed that the excimer reactor was able to produce the photo-pyridone product at almost twice the rate as the most productive batch reaction previously reported.²³⁶

Although using aqueous solvent does improve the solubility of the pyridone-dimer, when concentrations above 0.1 M are used for the reaction, precipitation of the dimer does become problematic. Being limited to low concentrations means that many of the photons generated by the excimer lamp will be transmitted through the reagent solution to be absorbed by the reactor cold finger, rather than being used to perform the photochemical reaction. This decreases the possible efficiency of the overall reaction. Higher concentrations of starting material could be used if it were possible

to reduce the formation of the dimer. Some investigation into using a mild Lewis acid (LiBr) to reduce dimer formation by reducing the pre-association of the starting material was performed. The LiBr did not change the overall yield of the photopyridone, and while there was a slight trend toward lowered dimer formation with the additive, the results remain inconclusive.

Future Work

As the results with LiBr did show a slight trend toward reducing dimer formation, this trend should be explored further. The addition of other additives should also be investigated.

As previously mentioned in Chapter 4, the photon utilisation for a given reaction is always highest at the beginning of the reaction before conversion to a UV transparent product occurs. Therefore for this reaction, where the product can be separated from the starting material and impurities (dimer) by extraction, it would be worth investigating in-line flow extraction so that the unconverted starting material could be recycled. This would allow for faster flow rates with lower conversion to be used, where the productivity is highest, without wasting excessive quantities of unconverted starting material.

Aim 5: To integrate in-line analysis with the UV photochemical reactor.

Motivation

In-line analysis techniques can allow for continuous reaction monitoring, which can provide invaluable information about the reaction in real-time/near real-time.^{314, 315}

This allows for more informed decisions to be made when changing reaction conditions as part of the optimisation process. Additionally, issues with the reaction can be detected more quickly, potentially saving the waste of large quantities of valuable reagents.^{314, 316, 335} Obtaining near real-time reaction feedback became

pertinent to this Thesis when the use of high-boiling aqueous solvents made it time consuming to obtain results by NMR, where the solvent had to be removed.

Developments:

In-line UV-Vis spectroscopy using the Ocean-Optics miniature spectrometer was successfully integrated with the excimer reactor to monitor the photo-isomerisation reaction of 2-pyridone. From the in-line UV-Vis spectrum it was possible to establish in real-time when the reaction had reached its equilibrium at the set conditions, reducing the wait-time necessary before samples were collected. Furthermore, it was possible to monitor the conversion of the starting material via the decay in its UV-Vis absorption band at 294 nm. However, lack of distinct UV-Vis absorption peaks for either the photo-pyridone product or the dimer, meant that in-line UV-Vis could not provide full analysis of the reaction. However, as a proof of concept, the Ocean-Optics spectrometer seamlessly integrated with the excimer reactor without any major modifications to the reactor. In future reactions, where products and starting materials have distinct absorption bands, it may be possible to monitor the reaction fully and in near-real time by UV-Vis spectroscopy using the set-up described in Chapter 4.

Additionally, integration of in-line FTIR was also attempted for monitoring the photo-isomerisation of 2-pyridone. Unfortunately, the peaks due to the starting material and products were not intense enough to be observed in the presence of solvent peaks, at the low concentrations used for the photochemical reaction (< 0.1 M). Therefore, no further attempts were made to incorporate in-line FTIR monitoring with the excimer reactor.

Future Work

The inability of all products and starting materials to be detected by both FTIR and UV-Vis spectroscopy highlights the importance of having multiple analytical

techniques available so that they can be integrated as part of the reactor system depending on the reaction being studied. On-line chromatography, such as GC and HPLC, do not usually provide useful data as rapidly as spectroscopic analysis. However, by separating the compounds prior to detection, chromatography can provide a greater amount of information about the outcome of a given reaction.³²⁷ Furthermore, sampling can be automated to reduce the amount of direct operator time necessary to obtain reaction analysis. Therefore, developing a method to include on-line HPLC or GC with the excimer reactor would be a logical next step.

Aim 6: To find a simple method for incorporating in-line or on-line analysis with a commercially available flow electrochemical reactor.

Motivation

On-line analysis techniques can reduce the human interaction time necessary for acquiring reaction data, meaning that optimisation can be performed more rapidly.³¹⁵ Furthermore, our research group has previously used in-line and on-line analysis with self-optimisation software to optimise continuous flow reactions without the need for additional operator input after the reaction was started.^{324, 325, 328, 330} Overall, this has led to faster and less laborious reaction optimisation. In order for the in-line or on-line analysis to provide quantitative and reproducible results (particularly when analysed by computer), the sample stream must be homogeneous. Electrochemical reactions in the Ammonite 8 continuous flow electrochemical cell²⁹³ frequently generate hydrogen gas, leading to a liquid-gas plug-flow exiting the reactor. The gas has to be homogenised into or separated from the liquid stream prior to analysis in order to avoid “dead spectra” or irreproducible results. (The motivation for performing electrochemical reactions in the Ammonite 8 was described in Chapter 5, and is not repeated here).

Developments

By running the outlet from the Ammonite 8 into a secondary collection it was possible to remove the hydrogen gas before analysis took place. This physical separation strategy was employed with both in-line Raman spectroscopy and on-line GC analysis.

In-line Raman analysis was used to monitor the electrochemical methoxylation of *N*-formylpyrrolidine. The in-line Raman set-up had a secondary collection (also containing the Raman probe) that was relatively large (~4 mL). This led to long equilibration times meaning that real-time or “near real-time” reaction feedback could not be obtained as was hoped.

For on-line GC analysis a small vial (< 0.5 mL) was used as the secondary collection of the reaction mixture, where the hydrogen was physically separated from the reagent stream while the integrity of the liquid stream was preserved. A second pump was used to fill the GC sample loop from the small vial. This method was used to analyse the electrochemical methoxylation of 4-*tert*-butyltoluene. The dose response calibration curve using automated sample loop injection was determined for the major reaction products and the starting material. Using the calibration curves and the gas separation method previously described, quantitative GC results were obtained for the electrochemical methoxylation of 4-*tert*-butyltoluene.

Injections made onto the GC column via the sample loop showed significant peak broadening compared to injection made manually by syringe or by auto-injection. It is likely that, since injecting onto the column via the sample loop requires the GC carrier gas to flush the contents of the sample loop onto the GC column, the resulting injection is slower compared to a manual or auto-injection. Additionally, it is also possible that the sample-loop set-up has some dead volume, which might also contribute to peak broadening. Therefore, in order to achieve the separation

necessary for quantitative analysis using the sample loop, the GC method using the sample loop had to employ a slower temperature ramp (longer method time).

Future Work

The in-line Raman set-up was able to collect data in real-time from the reaction. However, the reaction set-up was far from perfect. The large volume of the secondary collection meant that the equilibration time for the spectra to represent the set reaction conditions was unsatisfactorily long. Redesigning the reaction set-up using a smaller secondary collection might allow for in-line Raman spectroscopy with electrochemical reactions to provide more timely results.

In an attempt to make reactions in the Ammonite 8²⁹² with on-line GC analysis compatible with self-optimisation, the most reasonable next steps would be to replace the currently used power supply and pumps with those that can be controlled by computer so that the reaction variables (flow rate, concentration, and current) can be controlled by the self optimisation software. After which, it would be possible to begin to test a self-optimising reaction in the Ammonite 8.

In such a self-optimisation process, the time necessary to optimise the reaction would depend upon the GC method time. The on-line analysis of the methoxylation of 4-*tert*-butyltoluene showed that a slower GC method had to be used when injecting via the sample loop in its current set-up. To reduce the time taken by the GC analysis it would be worth investigating using different sampling set-ups. A different sample-loop with a smaller dead volume might help to reduce the peak broadening observed in the sample loop injections. Additionally, developing GC methods using the highest possible carrier gas flow rates might help to increase the speed of the injection onto the column reducing peak broadening and should therefore be investigated as part of the method development process.

Closing Remarks

This Thesis has presented a new UV flow photochemical reactor based on an excimer light source. Progress has been made toward integrating this continuous flow photochemical reactor with other reactors to perform a multi-step synthesis. Furthermore, developments have been made for linking analytical techniques to both the excimer continuous flow photochemical reactor and the commercially available Ammonite 8 electrochemical reactor. However, in order to fully exploit continuous flow photochemistry and continuous flow electrochemistry, reactors with appropriate analytical tools must be designed in such a way as to allow them to be easily coupled together as the reaction sequence and conditions require. Therefore, it is highly desirable that chemists and chemical engineers work together in the future if the true potential of these techniques is to be realised.

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Appendix 1: UV Reactor “Hazop”

Rig 37 is for continuous flow UV irradiation of organic compounds using excimer lamps and has been designed accordingly.

Maximum Operating Conditions

The maximum operating conditions are as outlined below. All safety trips should be set according to the desired experimental conditions but to ensure the system remains within the following limits.

Maximum temperature of 100 °C.

Maximum pressure is ambient pressure.

HAZOP – Rig 37

Before starting any reaction with “**rig 37**” you must:

- Be an authorised user.
- Ensure COSHH assessment is completed and signed.
- Log any changes/repairs in the log book.
- Leak Test
- Following maintenance, modification or replacement of parts, a leak test should be conducted using clean reaction solvent and blue roll to ensure the rig is not leaking before carrying out experiments.

Safety Shield

Due to use of UV light the continuous flow synthesis rig should only be operated inside a polycarbonate box. Extraction must always be used as the UV excimer lamps have the potential to produce ozone. Extraction is also necessary if ethanol or other flammable solvents are to be used, due to the potential for the release and accumulation of highly flammable gasses; or if there is the possibility of the reaction or reagents to produce noxious gas.

Power Supply and Safety Trip

The power supply for the lamp and pump (Jasco PU-980) should be powered via an extension lead connected to the trip box. The trip box, pressure and temperature monitors are powered directly from the fumehood. The trip box is connected to the pressure monitor, which must be connected to the pressure transducer. The trip system should also be connected to the temperature trip, connected in turn to the thermocouple located inside of the largest reactor T-piece. The over pressure trip value should be set to 3.5 bar (50 psi), such that the system will power off in the event of a blockage but not shut-off due to slight drift in the trip box value. The P. Max trip on the Jasco PU-980 pump should also be set to this value.

Cooling

Cooling for this rig is provided by a recirculating cooling bath (Julabo F250) feeding a pipe in pipe cooling stick. The coolant is a 50:50 mixture of ethylene glycol and water and is suitable for use between the min. and max operating temperatures of the Julabo F250, -10°C and 40°C. Care should be taken when maintaining the cooling system, as ethylene glycol is toxic. If a cooling bath temperature is set lower than the freezing point of the reaction solvent, the cooling bath should be turned off and the flow through the rig must also be stopped to avoid the solvent within the rig freezing and causing blockages.

System Temperature

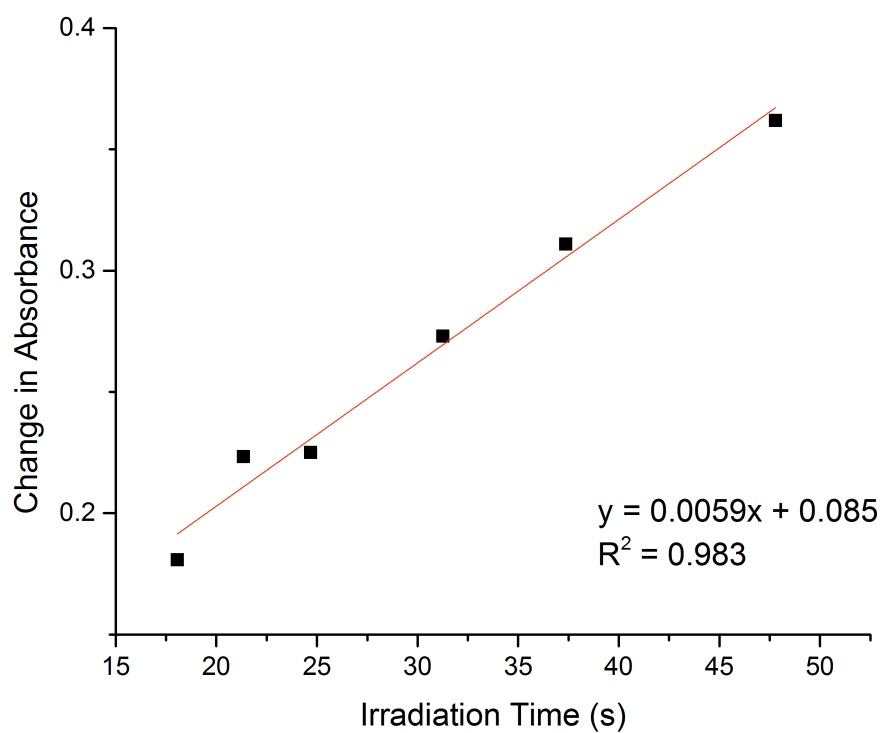
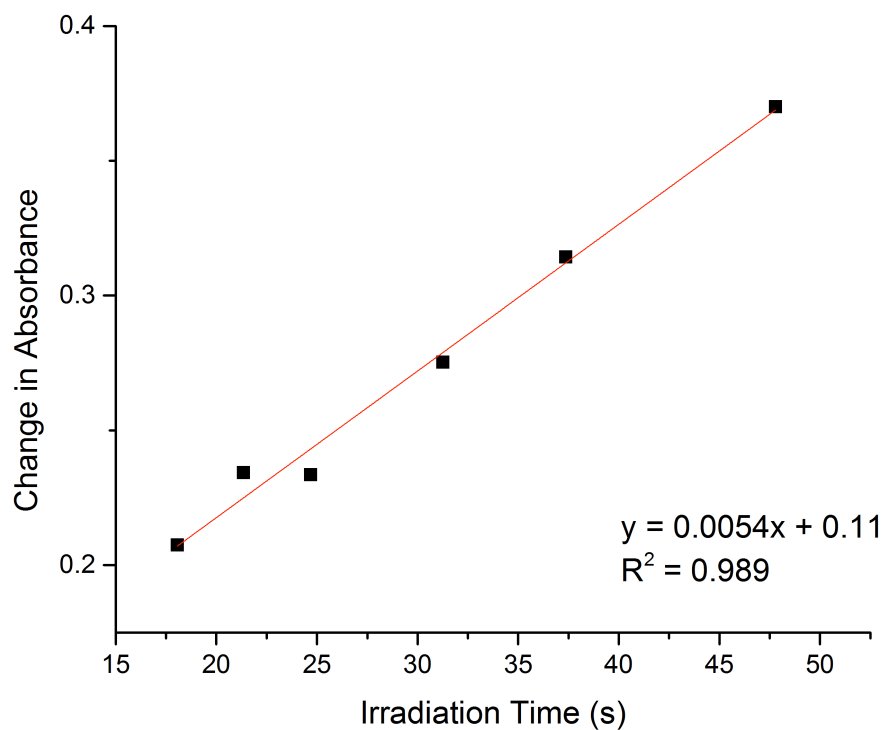
The cooling system and the heat generated by the UV lamp controls the temperature of the reactor. A thermocouple has been placed in the organic flow just after the irradiation zone and is connected to an external temperature monitor/trip, which will interrupt power to the lamp and pump if the temperature exceeds a set limit. The temperature trip point for TM1 should be set according to the desired operating conditions and solvent but must not exceed the boiling point of the reaction solvent.

Checklist

- Prior to reaction check that the trip box is working correctly, including:
 - Pressure trips
 - Temperature trips
 - Emergency stop button
- Ensure all thermocouples and heater power cables are properly connected.
- Leak testing should be carried out using blue paper.
- Ensure that the cooling bath tubing is well insulated so that condensation will not drip.

Appendix 2: Chapter 2 Reactions Additional Details

2.1 222 nm Actinometry: Change in Absorbance vs. Irradiation Time



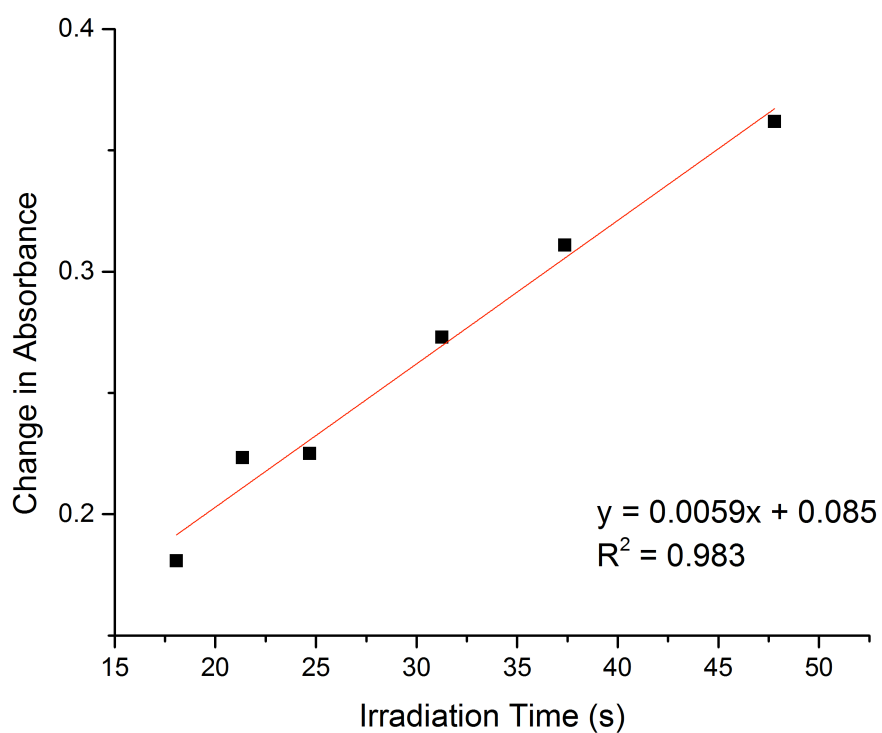
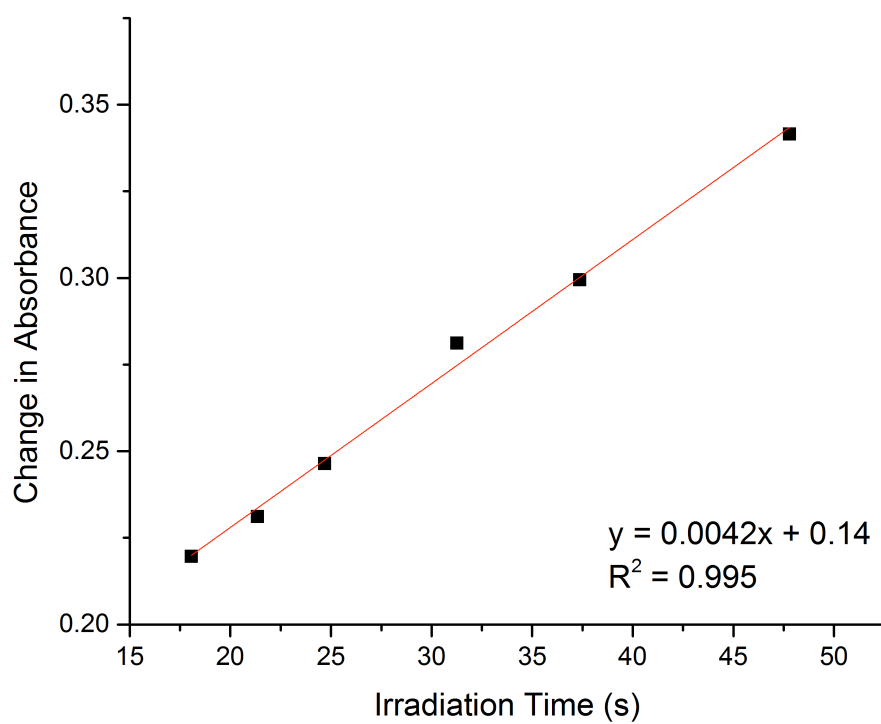


Figure 65: Change in uridine, 4, absorbance at 262 nm vs. irradiation time using 222 nm light.

2.2 282 nm Actinometry: Change in Absorbance vs. Irradiation Time



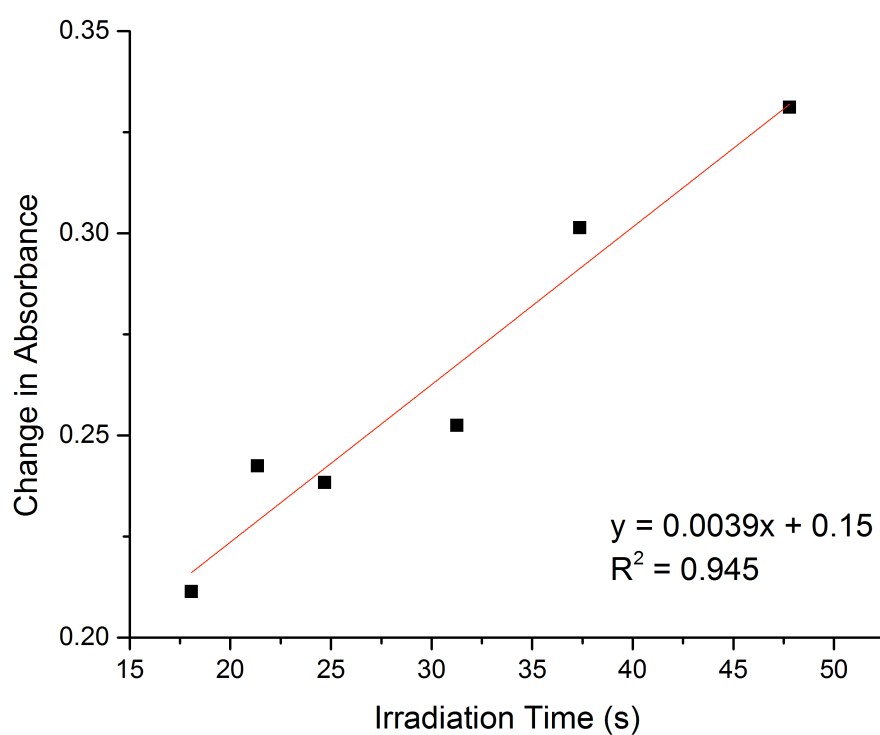
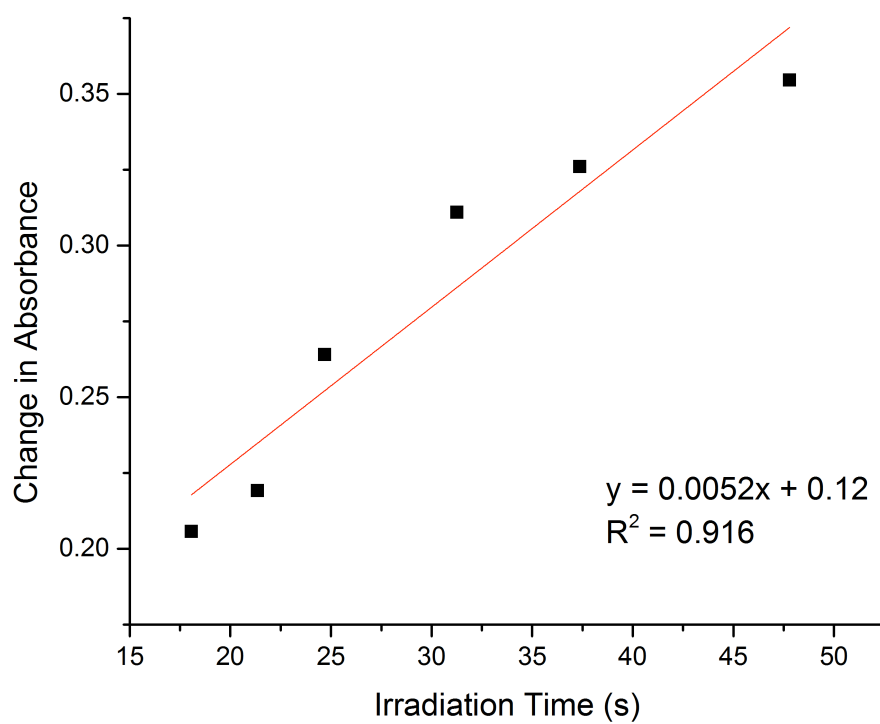


Figure 66: Change in uridine, 4, absorbance at 262 nm vs. irradiation time using 282 nm light.

2.3 Uridine Molar Extinction Coefficient Calibration Curve

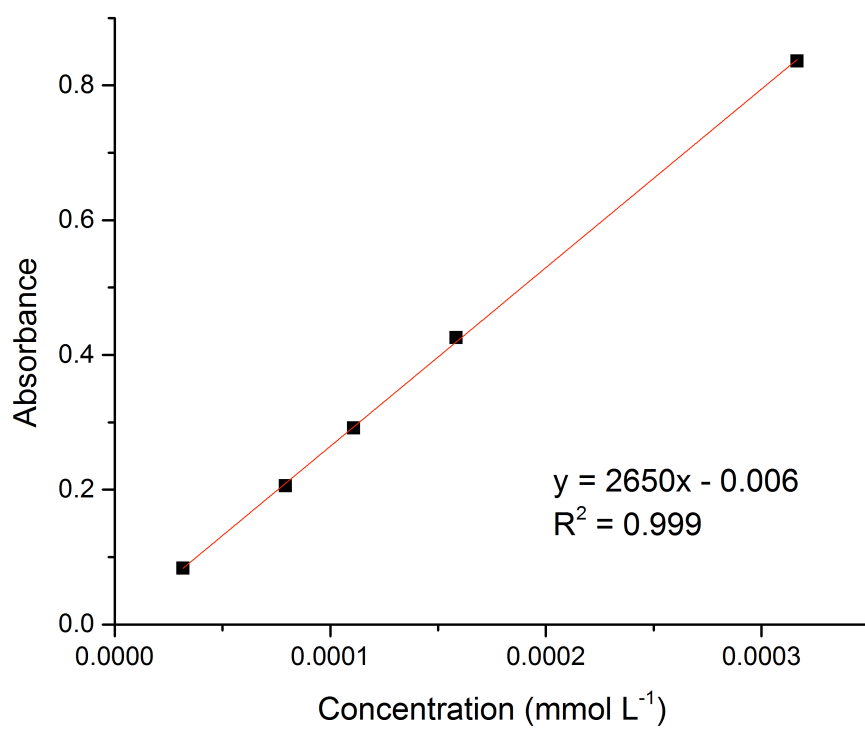
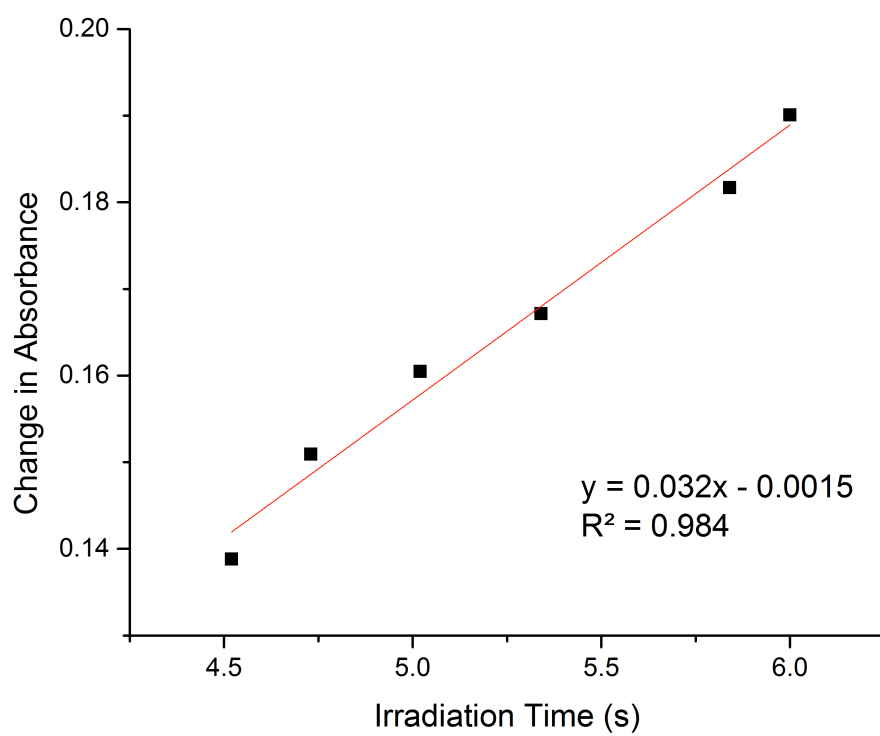


Figure 67: Calibration curve for determining the molar extinction coefficient of uridine, 4, in water at 282 nm (absorbance pathlength = 1 cm).

2.4 308 nm Actinometry: Change in Absorbance vs. Irradiation Time



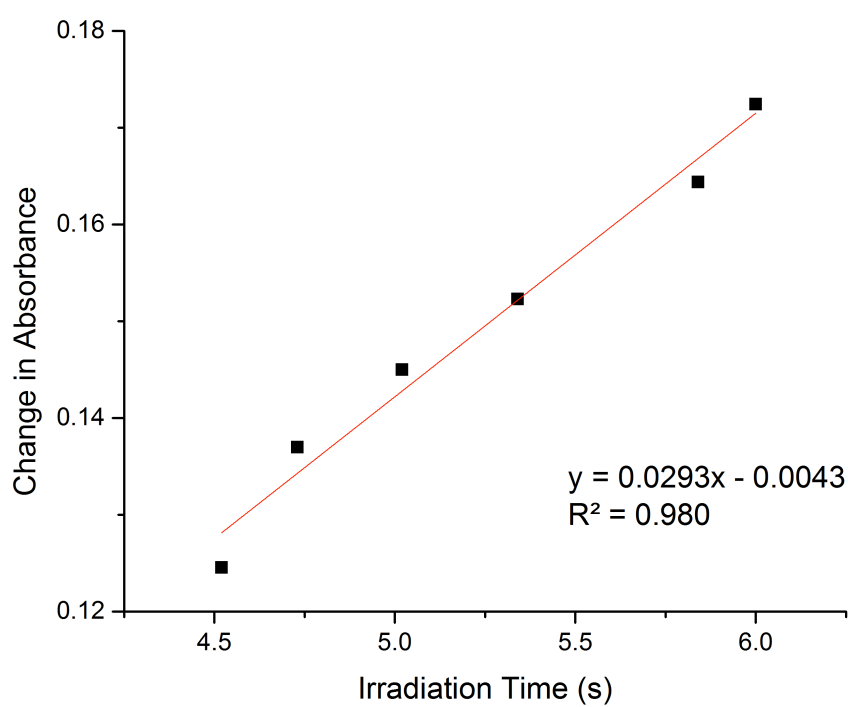
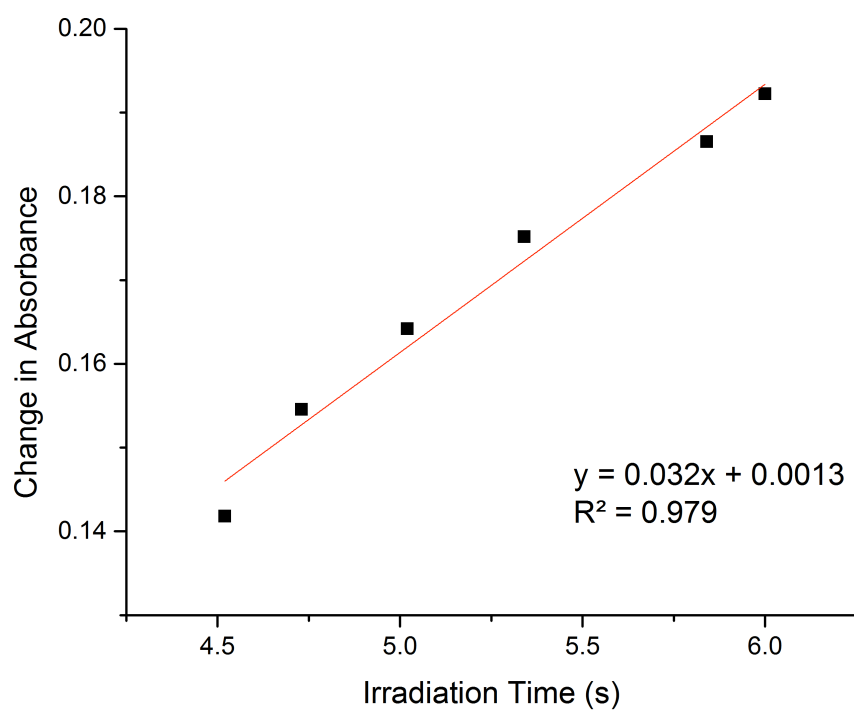


Figure 68: Change in azobenzene, 6, absorbance at 317 nm vs. irradiation time using 308 nm light.

2.5 Azobenzene Extinction Coefficient Calibration Curve

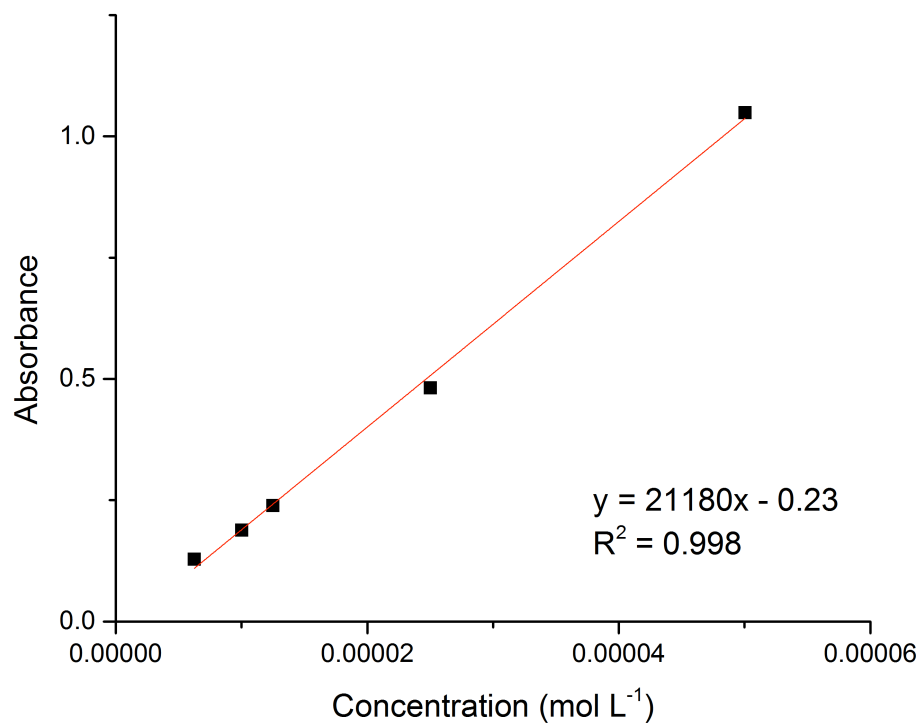


Figure 69: Calibration curve for determining the molar extinction coefficient of azobenzene, 6, in methanol at 317 nm (absorbance pathlength = 1 cm).

2.6 β -Ionone Extinction Coefficient Calibration Curves

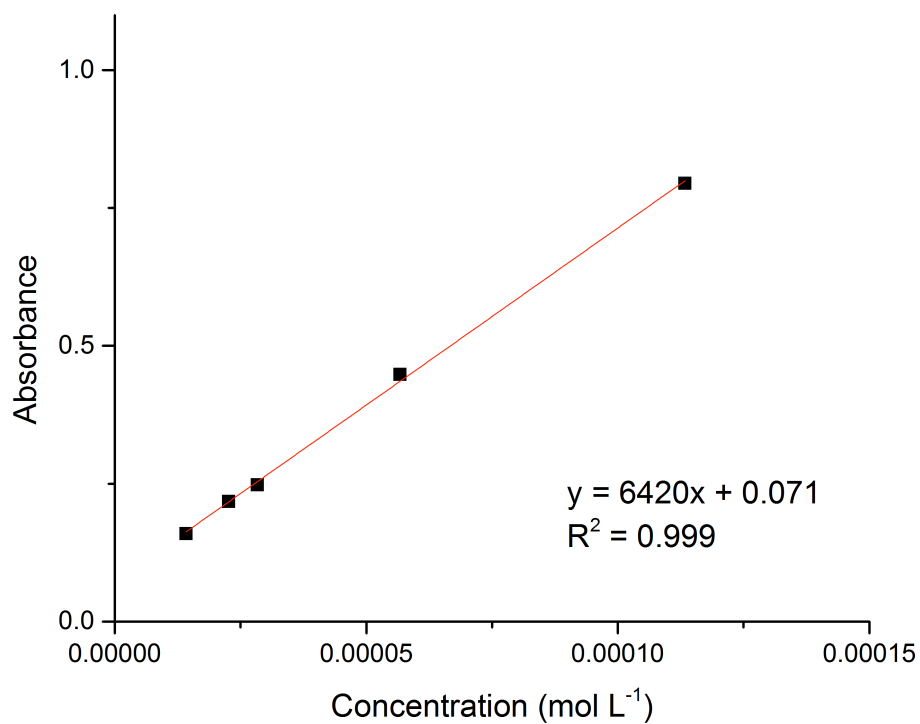


Figure 70: Calibration curve for determining the molar extinction of β -ionone, 8, in ethanol at 222 nm (absorbance pathlength = 1 cm).

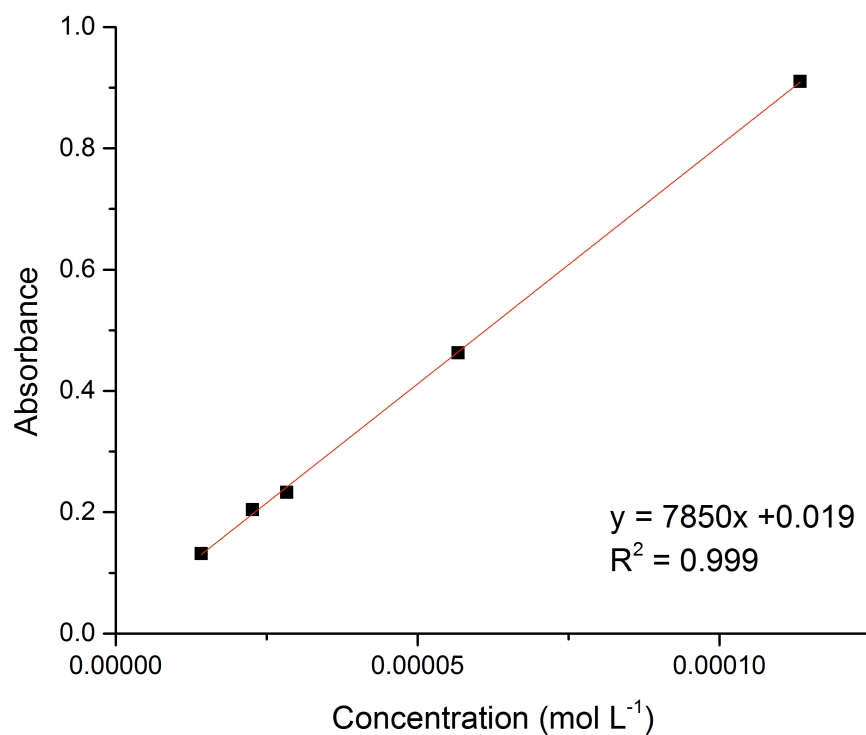


Figure 71: Calibration curve for determining the molar extinction of β -ionone, 8, in ethanol at 282 nm (absorbance pathlength = 1 cm).

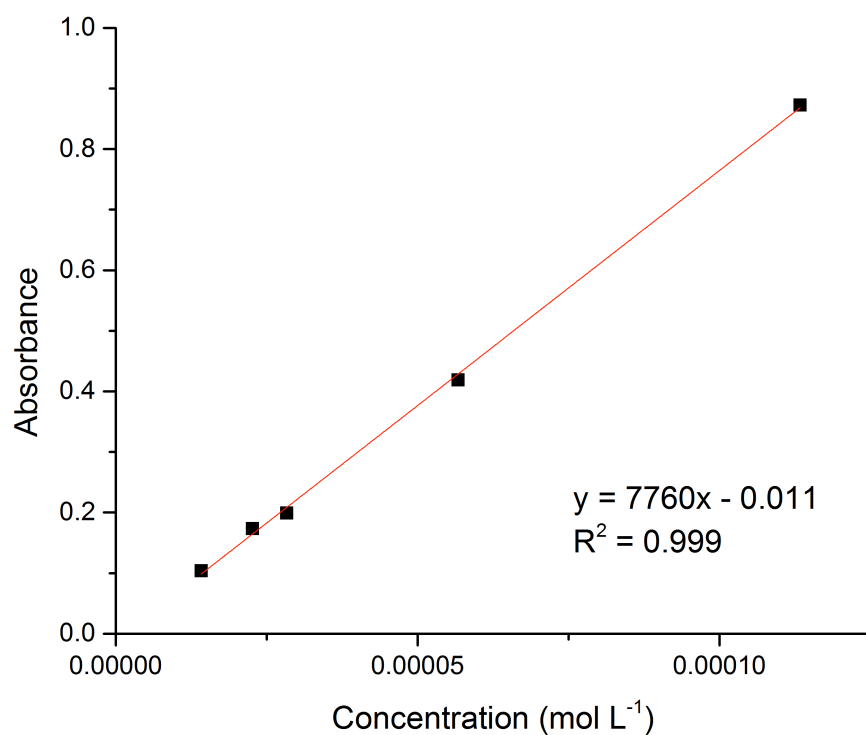


Figure 72: Calibration curve for determining the molar extinction of β -ionone, 8, in ethanol at 308 nm (absorbance pathlength = 1 cm).

Appendix 3: Chapter 3 Additional Details

3.1 4-Phthalimidobutyric Acid Molar Extinction Coefficient Calibration Curves

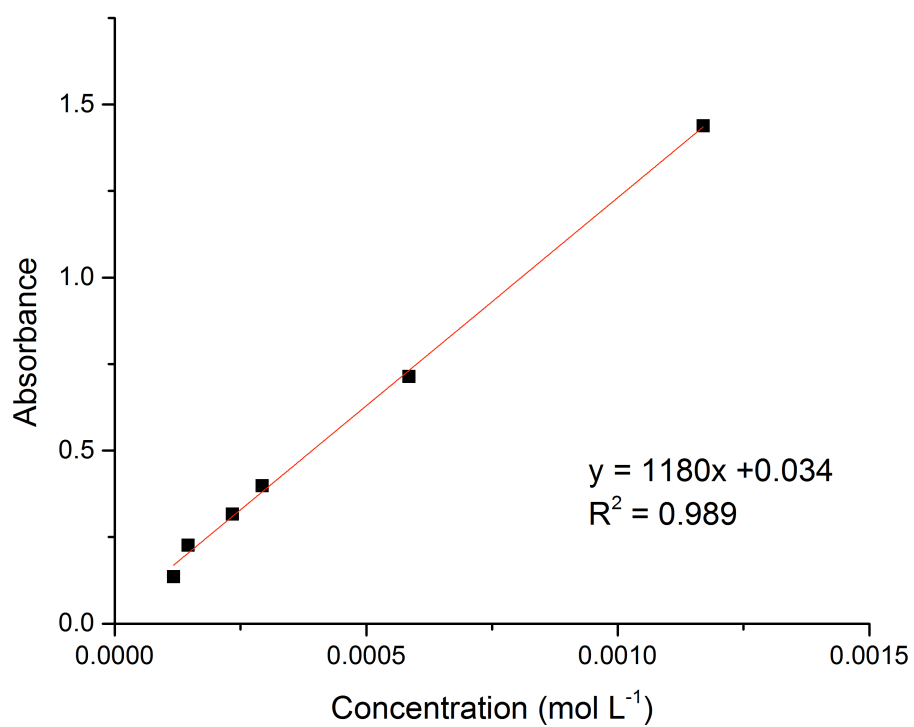


Figure 73: Calibration curve for determining the molar extinction of 4-phthalimido butyric acid, 14, in a 1:1 mixture of acetonitrile and water at 282 nm (absorbance pathlength = 1 cm).

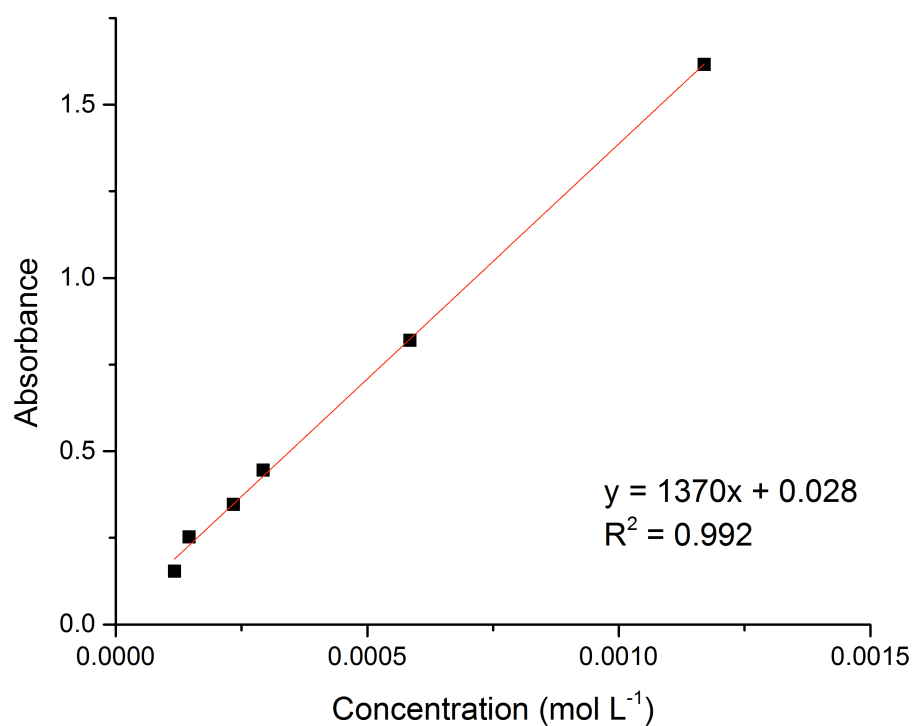


Figure 74: Calibration curve for determining the molar extinction of 4-phthalimido butyric acid, 14 in a 1:1 mixture of acetonitrile and water at 308 nm (absorbance pathlength = 1 cm).

3.2 Acetone Molar Extinction Coefficient Calibration Curves

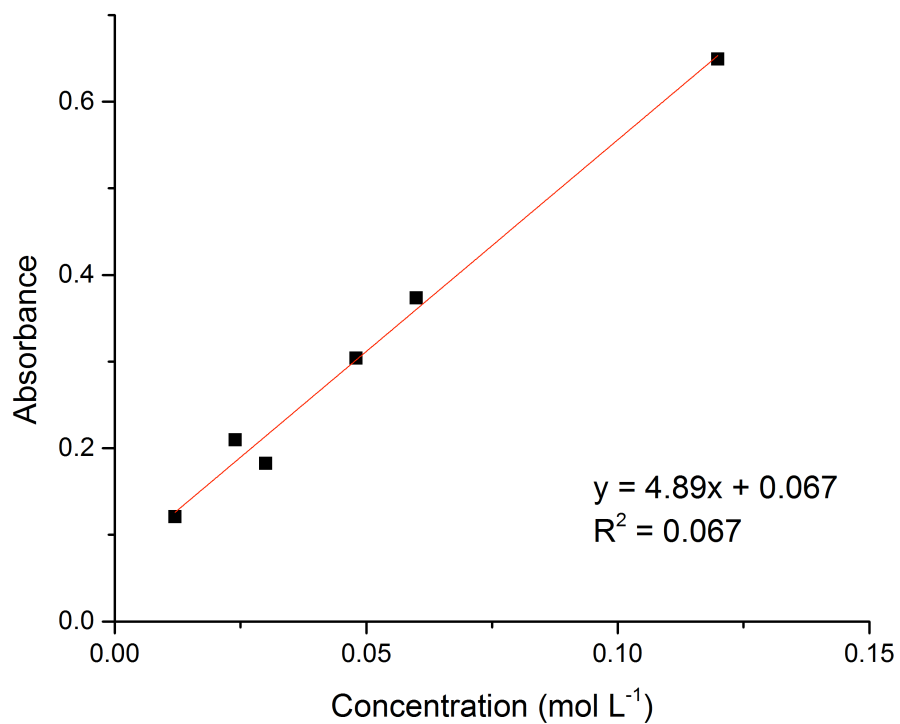


Figure 75: Calibration curve for determining the molar extinction of acetone in water at 222 nm (absorbance pathlength = 1 cm).

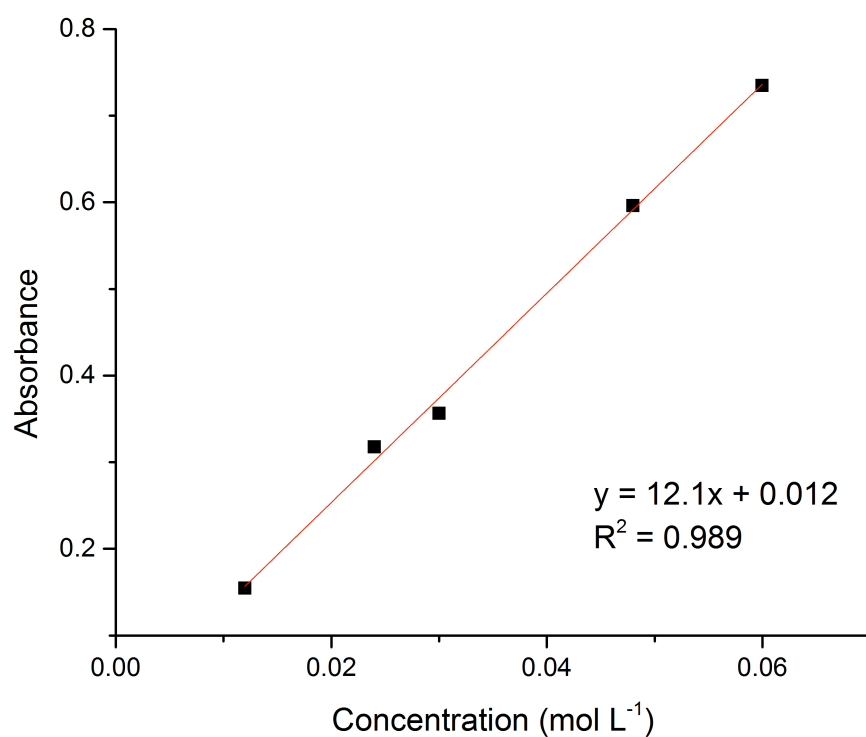


Figure 76: Calibration curve for determining the molar extinction of acetone in water at 282 nm (absorbance pathlength = 1 cm).

Figure 77: Calibration curve for determining the molar extinction of acetone in water at 308 nm (absorbance pathlength = 1 cm).

Appendix 4: Chapter 4 Additional Details

4.1 Time-Resolved Infrared Spectroscopy of 2(1*H*)-Pyridone

Picosecond TRIR measurements of 2(1*H*)-pyridone were performed by Charlotte Clark at the Rutherford Appleton Laboratory using the ULTRA instrument (complete details of which can be found in the literature)¹⁵ and a pump probe technique.

An in-house built re-circulating flow system comprising of a single reservoir that is connected to an Harrick flowing solution IR cell by a pair of PTFE pipes was used for the TRIR measurements. The Harrick IR cell contains two CaF₂ windows separated by two PTFE spacers (100 microns in thickness). The system reservoir was connected to the Schlenk line during sample preparation, degassing and was afterward placed under a pressure of Ar. The solution was flowed during the experiment using a peristaltic pump (Masterflex, PTFE Tubing) and rastering of the cell in the X and Y dimensions was undertaken to minimise sample degradation by ensuring that a fresh portion of the solution was irradiated each time.

TRIR measurements were taken in four different solvent systems (CD₃CN, DCM, EtOH and 1:1 EtOH:D₂O). Each TRIR spectrum shows loss of the parent band corresponding to the ground state of the 2(1*H*)-pyridone and a growth of a new band corresponding to 2(1*H*)-pyridone in the excited state (Figure 78, A – Figure 81, A). Plotting the decay of the excited state band and the recovery of the parent band allow for calculation of the lifetime of the excited state. The kinetics plots are given below the TRIR for each solvent system Figure 78, B –Figure 81, B. A summary of the results from the four solvent systems is given in Table 38.

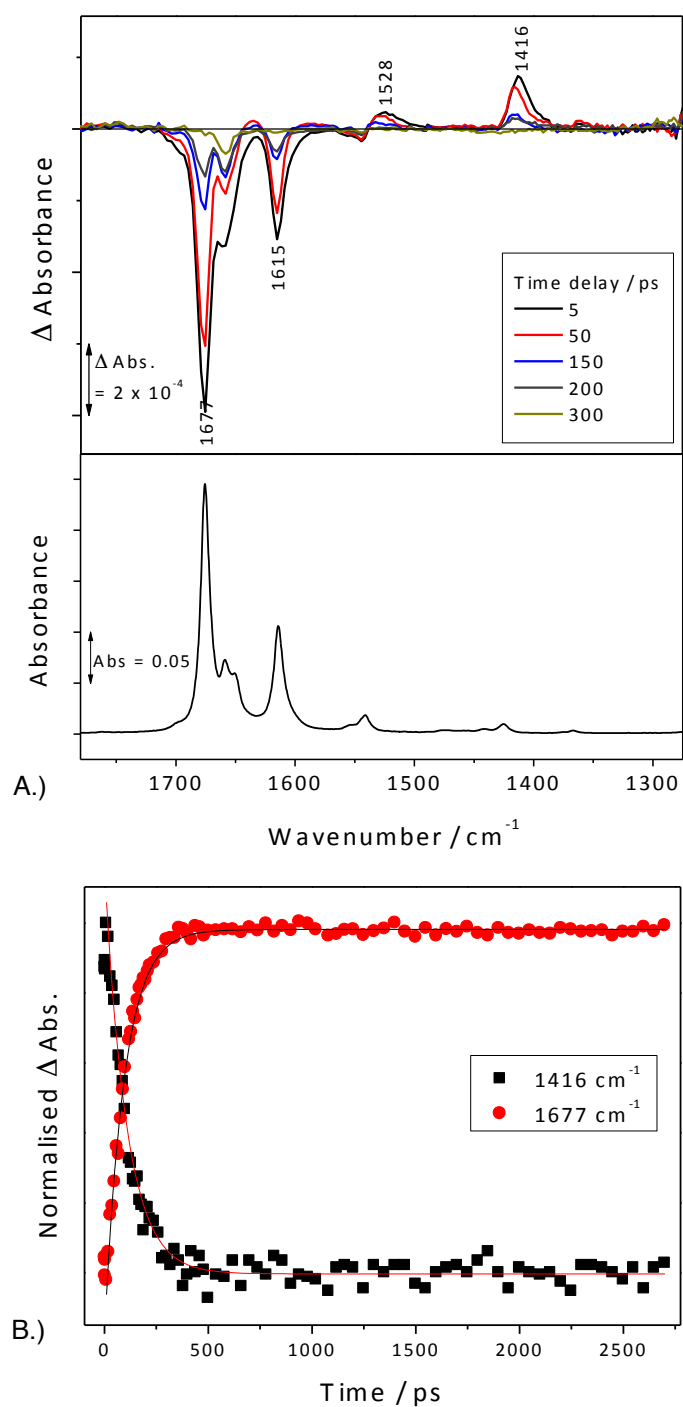


Figure 78: (A) TRIR spectrum of 2(1*H*)-pyridone, 17, in CD_3CN relative to the ground state IR spectrum (middle), showing initial bleaching of the parent band at 1677 cm^{-1} and growth of the excited state band at 1416 cm^{-1} . (B) Kinetics band fitting for the regrowth of the parent band at 1677 cm^{-1} over time and decay of the excited state band at 1416 cm^{-1} .

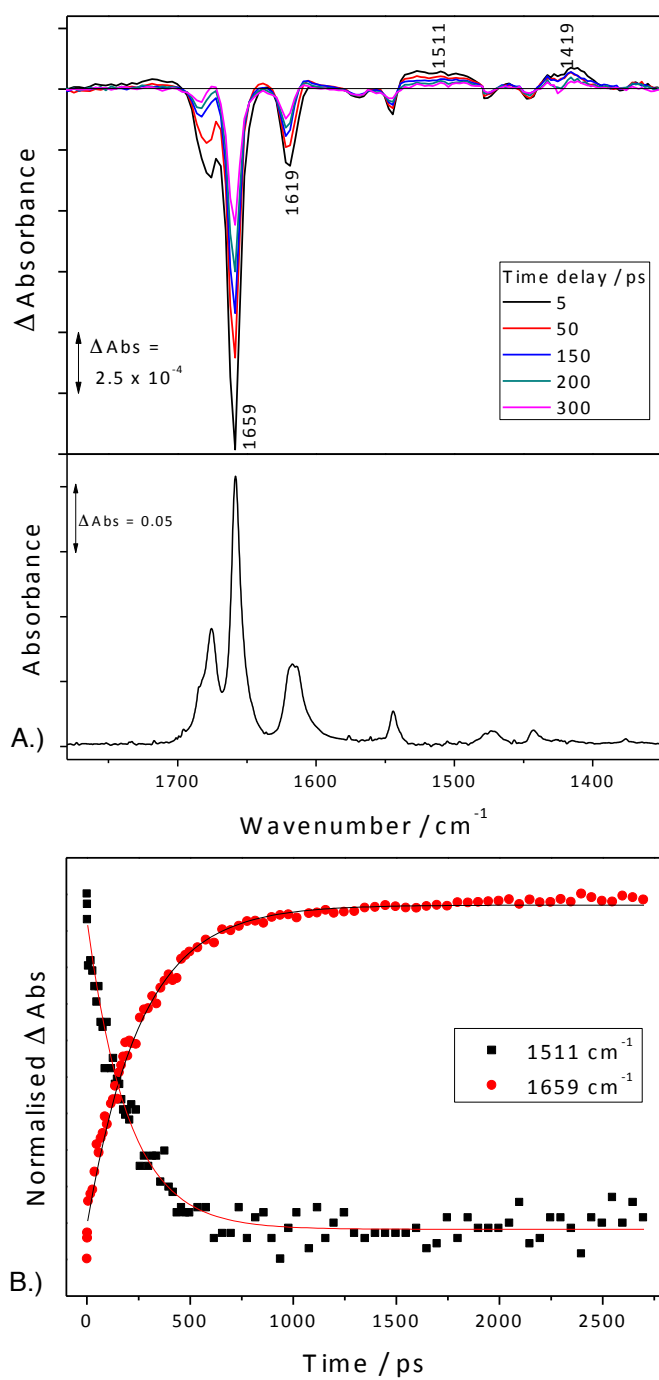


Figure 79: (A) TRIR spectrum of 2(1*H*)-pyridone, 17, in DCM relative to the ground state IR spectrum (middle), showing initial bleaching of the parent band at 1659 cm^{-1} and growth of the excited state band at 1511 cm^{-1} . (B) Kinetics band fitting for the regrowth of the parent band at 1659 cm^{-1} over time and decay of the excited state band at 1511 cm^{-1} .

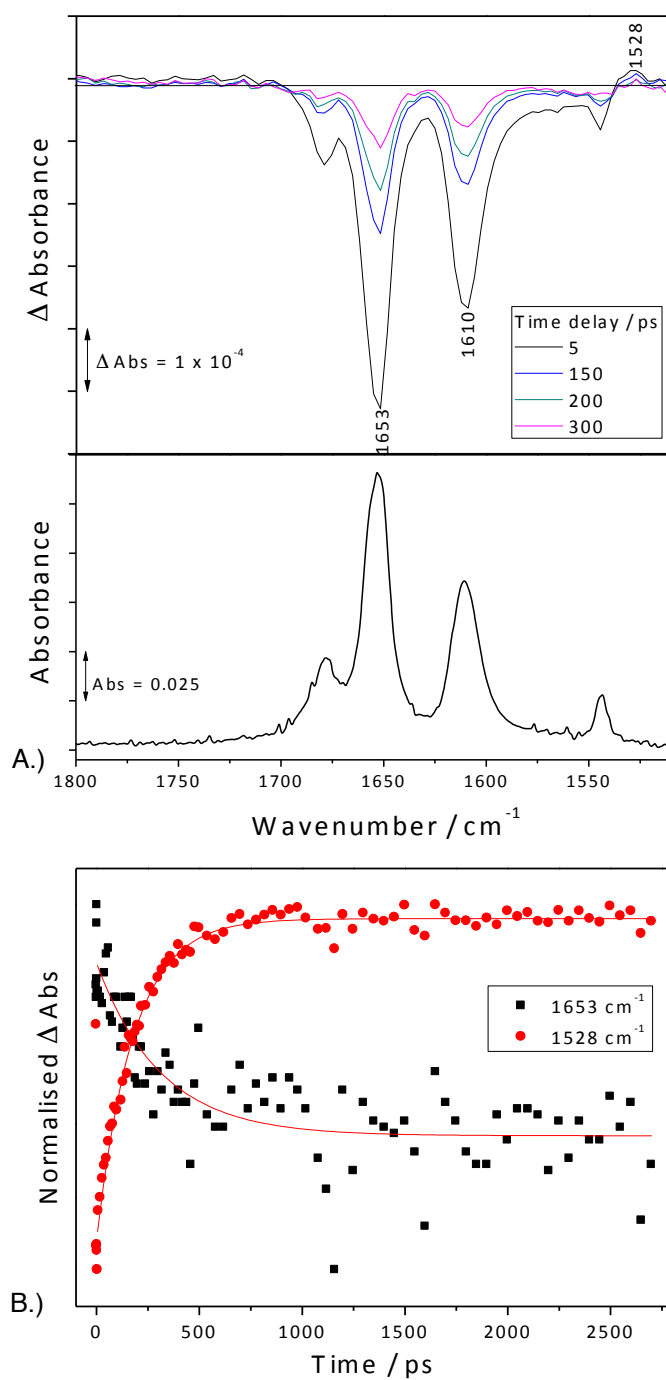


Figure 80: (A) TRIR spectrum of 2(1*H*)-pyridone, 17, in EtOH relative to the ground state IR spectrum (middle), showing initial bleaching of the parent band at 1653 cm^{-1} and growth of the excited state band at 1528 cm^{-1} . (B) Kinetics band fitting for the regrowth of the parent band at 1653 cm^{-1} over time and decay of the excited state band at 1528 cm^{-1} .

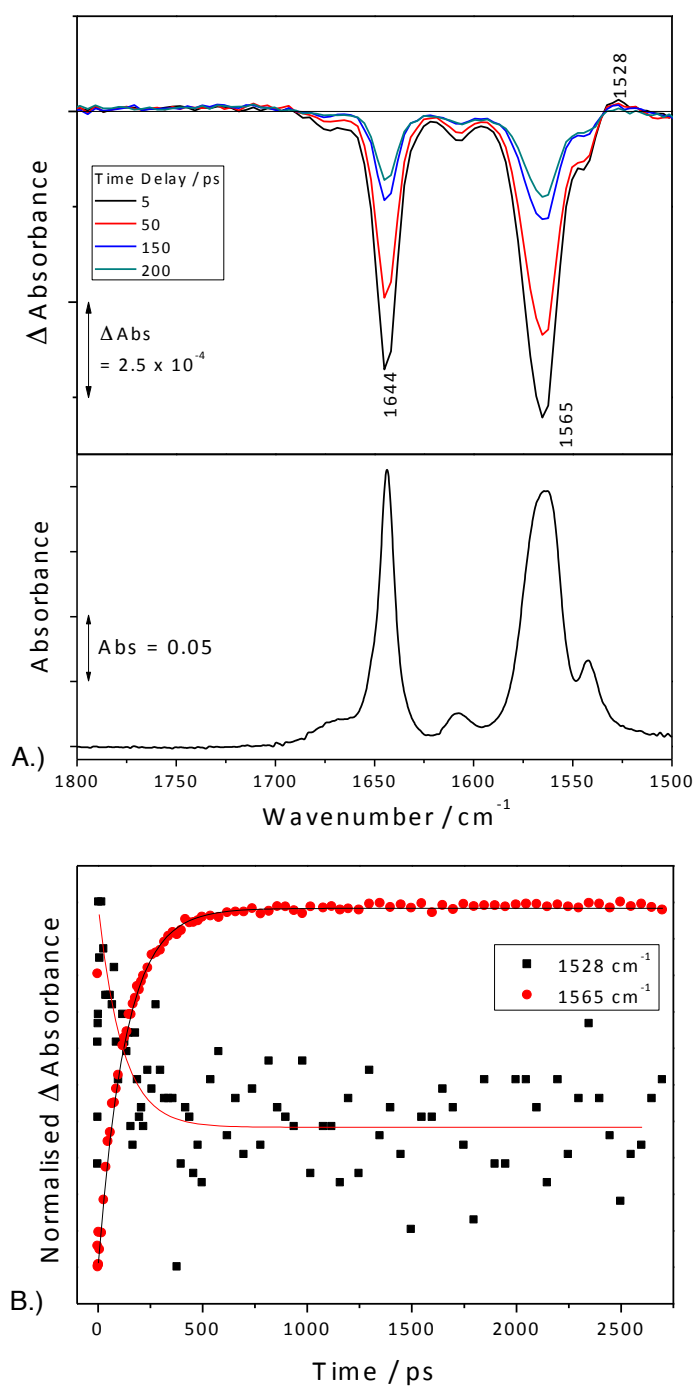


Figure 81: (A) TRIR spectrum of 2(1*H*)-pyridone, 17 in 1:1 EtOH: D₂O relative to the ground state IR spectrum (middle), showing initial bleaching of the parent band at 1565 cm^{-1} and growth of the excited state band at 1528 cm^{-1} . (B) Kinetics band fitting for the regrowth of the parent band at 1565 cm^{-1} over time and decay of the excited state band at 1528 cm^{-1} .

Table 38: Summary of the lifetimes of the 2(1*H*)-pyridone excited state in four different solvent systems.

Solvent	Band Type	Peak (cm ⁻¹)	Lifetime (ps)
CD ₃ CN	Excited State	1416	106 (± 3)
	Ground State	1677	95 (± 2)
DCM	Excited State	1511	200 (± 8)
	Ground State	1659	260 (± 6)
EtOH	Excited State	1528	300 (± 50)
	Ground State	1653	180 (± 5)
EtOH:D ₂ O	Excited State	1528	114 (± 23)
	Ground State	1565	130 (± 2)

These results show that the 2(1*H*)-pyridone excited state is short lived in all of the solvent systems tested. This is consistent with the literature,²⁵⁶ which states that the isomerisation of 2-pyridone proceeds from the singlet excited state. Furthermore in three of the four solvents (except EtOH) the decay in the excited state band correlates well with the growth in the parent band. This suggests that there is not an intermediate between these two states (e.g. a triplet excited state) and further supports that the reaction must proceed directly from the singlet excited state, as no triplet state has been detected.

4.2 2(1*H*)-Pyridone Molar Extinction Coefficient Calibration Curves

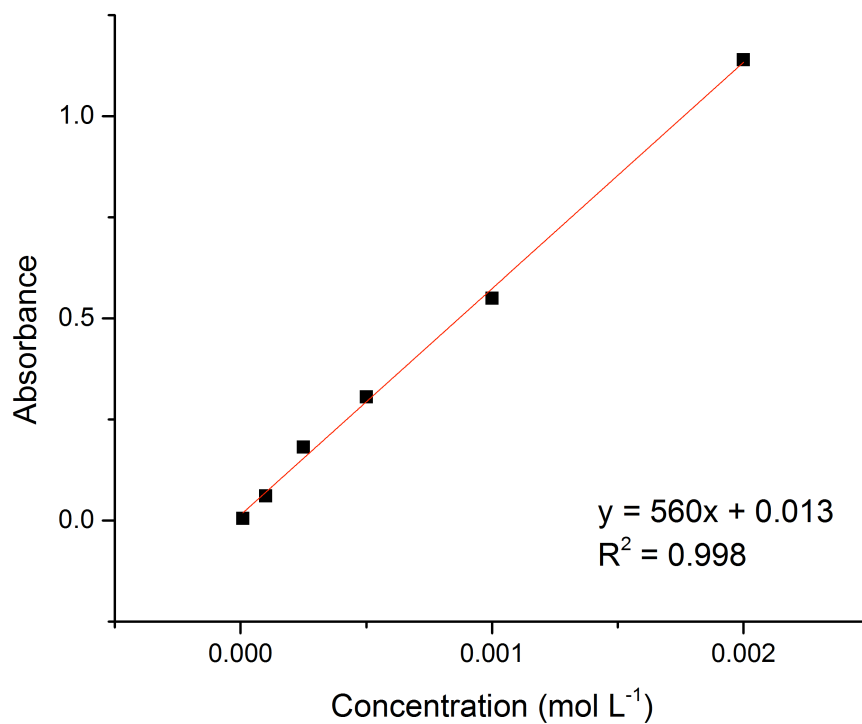


Figure 82: Calibration curve for determining the molar extinction of 2(1*H*)-pyridone, 17, in acetonitrile at 222 nm (absorbance pathlength = 1 mm).

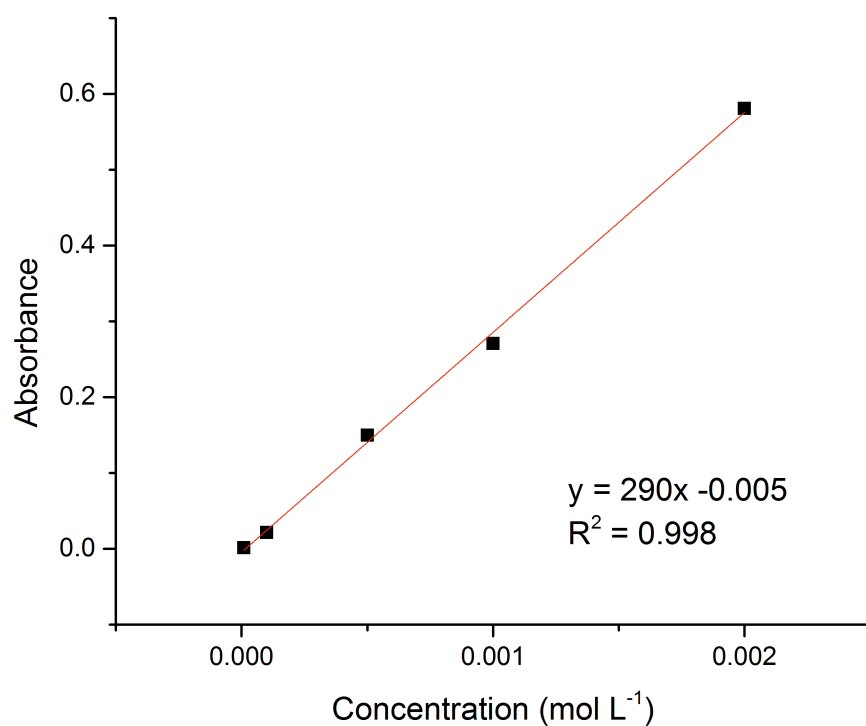


Figure 83: Calibration curve for determining the molar extinction of 2(1*H*)-pyridone, 17, in acetonitrile at 282 nm (absorbance pathlength = 1 mm).

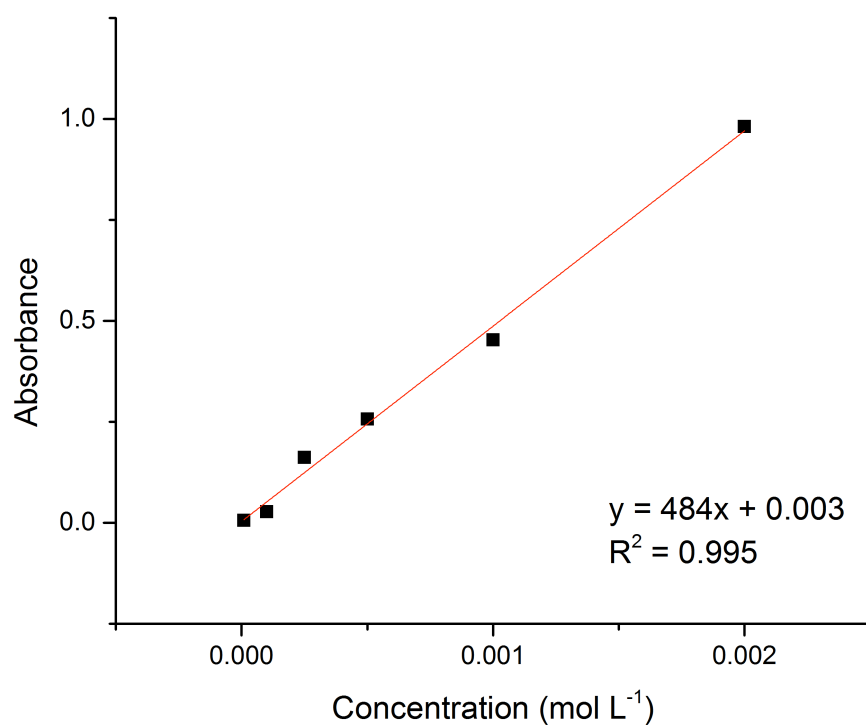


Figure 84: Calibration curve for determining the molar extinction of 2(1*H*)-pyridone in acetonitrile at 308 nm (absorbance pathlength = 1 mm).

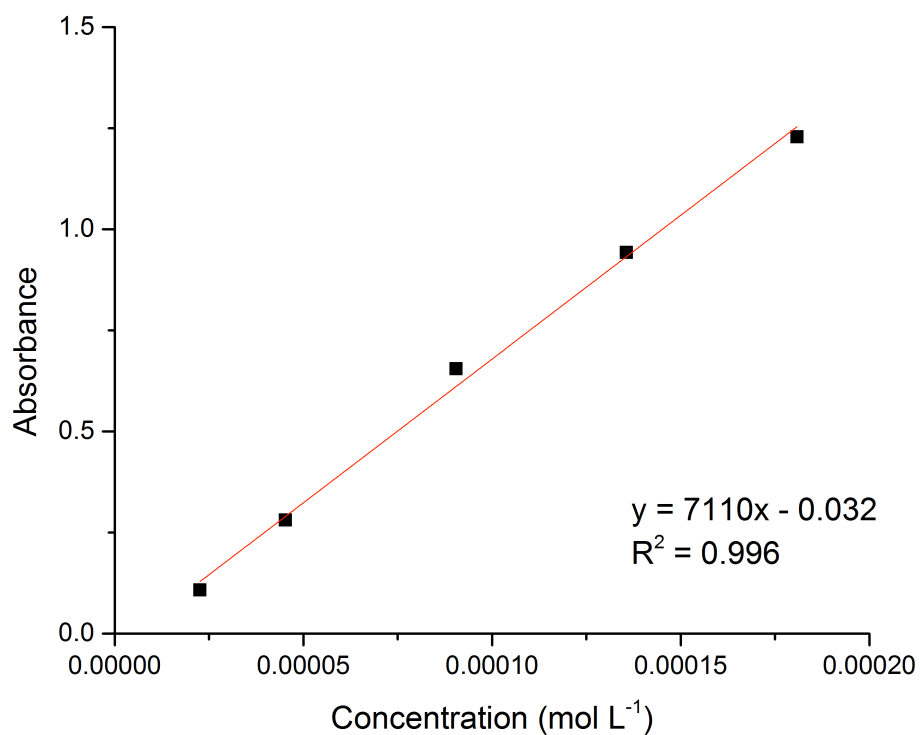


Figure 85: Calibration curve for determining the molar extinction of 2(1H)-pyridone, 17, in water at 222 nm (absorbance pathlength = 1 cm).

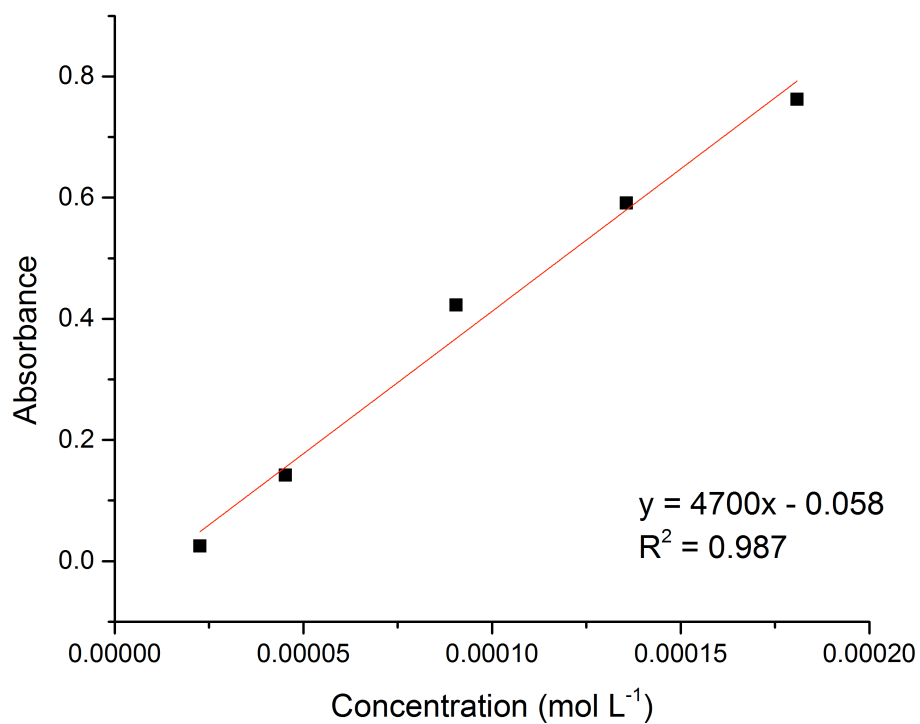


Figure 86: Calibration curve for determining the molar extinction of 2(1H)-pyridone, 17, in water at 282 nm (absorbance pathlength = 1 cm).

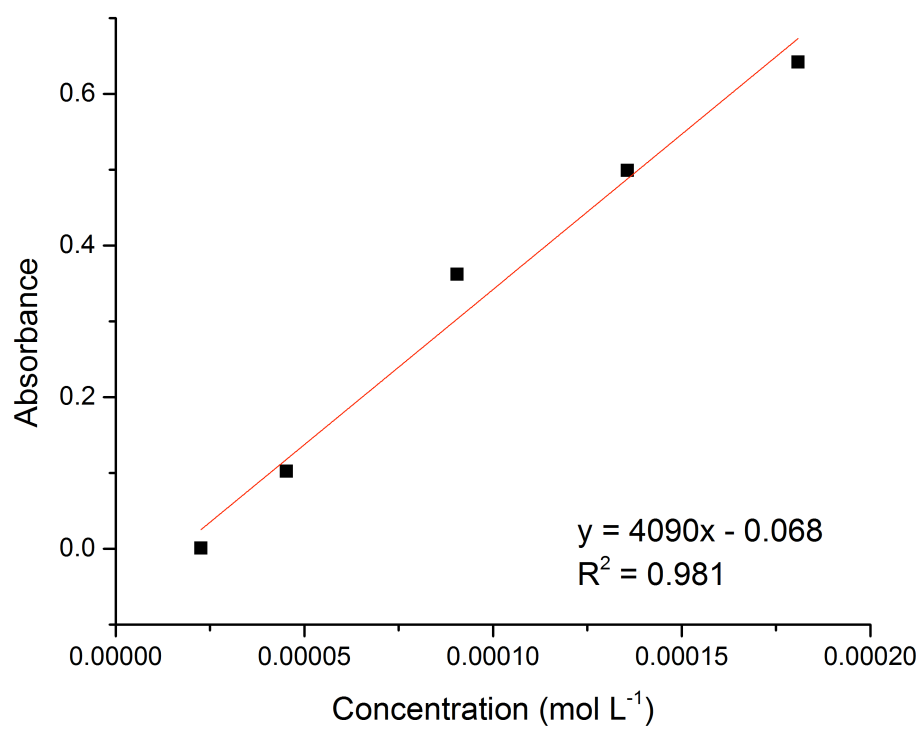


Figure 87: Calibration curve for determining the molar extinction of 2(1*H*)-pyridone, 17, in water at 308 nm (absorbance pathlength = 1 cm).

4.3 ATIR of the Photoproducts From the Irradiation of 2(1*H*)-Pyridone

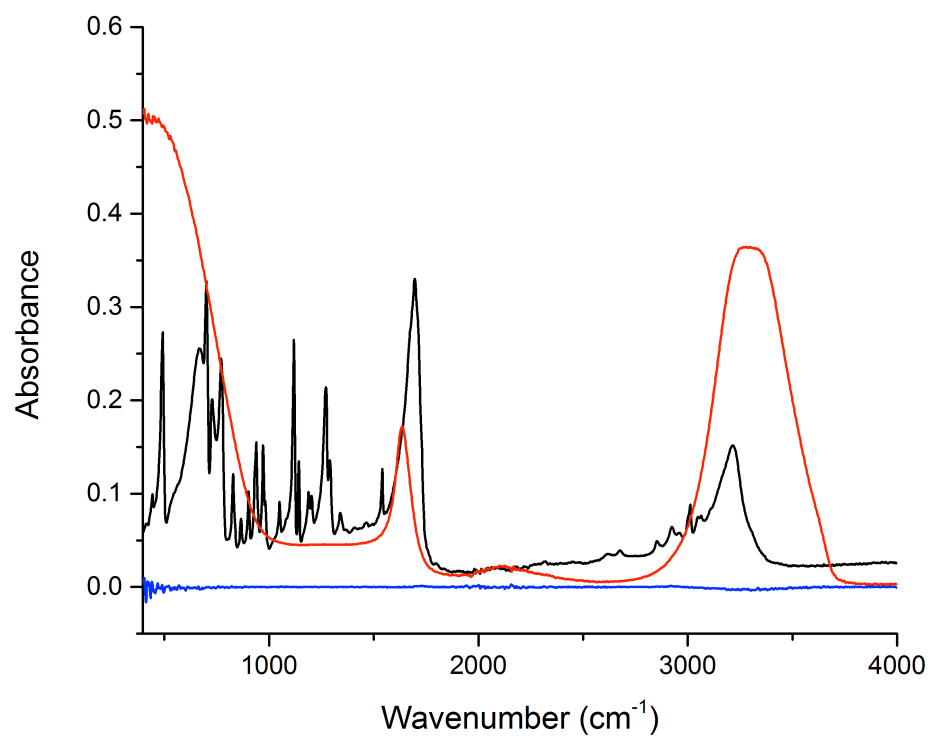


Figure 88: ATR spectra of photoproduct 18 in the solid state (black), ATR spectra of 18 as a 0.05 M solution in water (red), and ATR spectra of 18 as 0.05 M solution in water with a background spectrum of water subtracted (blue).

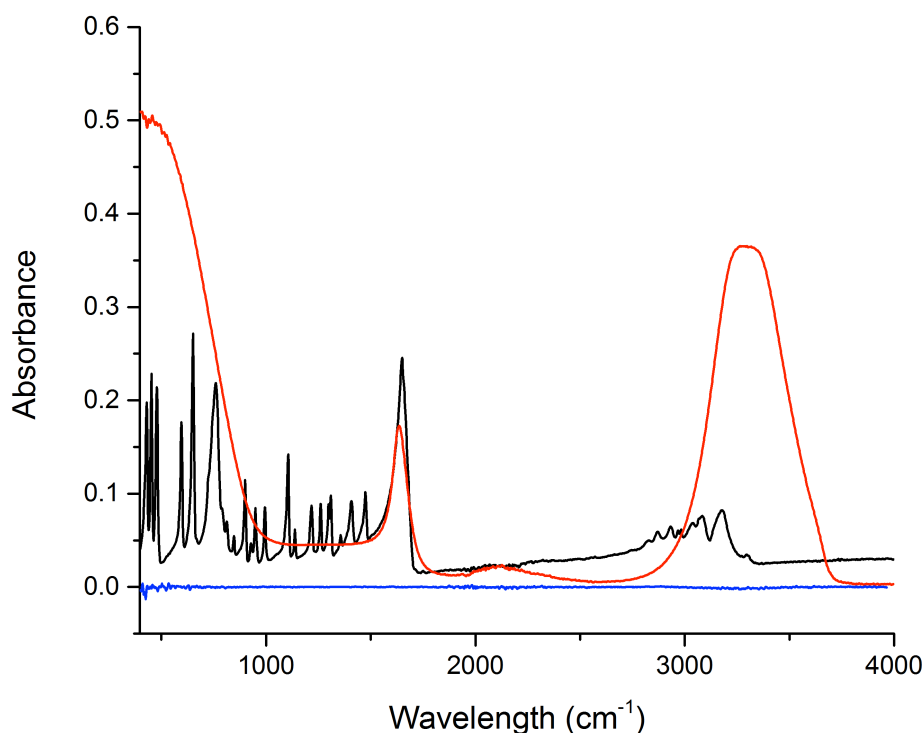


Figure 89: ATR spectra of dimer 19 in the solid state (black), ATR spectra of 19 as a 0.05 M solution in water (red), and ATR spectra of 19 as 0.05 M solution in water with a background spectrum of water subtracted (blue).

4.4 In-line UV-Vis Analysis: Further Discussion of Errors

Unlike more sophisticated spectrometers that utilise a reference cell to give the value of I_0 , the intensity of the light entering the sample, the I_0 value in the Ocean Optics spectrometer is fixed by taking a “light spectrum” when the cell is filled with solvent at the beginning of the experiment. Fluctuations of the intensity of the light coming from the probe or even changes to the intensity of background light (intensity of the light in the laboratory) will change the true value of I_0 . However, the value of I used to calculate absorbance will not express this change. This will induce a small degree of error in the measured value of absorbance, represented in the UV-Vis results of the experiment, where even at equilibrium conditions the absorbance value fluctuates slightly.

When the reaction is started, the fluctuation in absorbance also includes error induced by errors in solution concentration and irradiation time. These could, for example, be due to incomplete mixing inside the reactor or inconsistencies in pump flow rate. It is also possible that the intensity of the UV light coming from excimer lamp may fluctuate slightly. The differences in absorption of **17** at 308 nm, for equilibrium conditions pre-reaction and after irradiation at 0.2, 0.5, and 1.0 mL min⁻¹, can be seen in Table 39.

Table 39: Errors in absorbance of **17 at 262 nm when 0.01 M aqueous solution of **17** are irradiated at 308 nm and 1 °C at different flow rates.**

Entry	Flow Rate (mL min ⁻¹)	Error in Absorbance at Equilibrium (%)	Error in Absorbance at Equilibrium (AU)
1	1.0 (no irradiation)	0.49	5.6 x 10 ⁻³
2	1.0	1.3	8.7 x 10 ⁻³
3	0.5	0.82	3.2 x 10 ⁻³
4	0.2	3.3	1.9 x 10 ⁻³

At all flow rates the fluctuation in absorbance gave rise to an error in absorbance of **17** of less than 4%. The percentage error of the absorbance of **17** is smallest when no reaction was taking place. However, when absolute values of the error in absorbance units were examined, the error when no reaction is taking place is larger than reactions at 0.5 and 0.2 mL min⁻¹. Only the reaction at 1.0 mL min⁻¹ had a higher absolute error. Once the reaction was started the percentage error did follow a trend with flow rate. However the absolute error for the three investigated flow rates decreased with decreasing flow rate (increasing conversion). This suggests that the percentage errors may be misleading because very small changes in absorbance will look proportionally higher when lower concentrations of **17** are present and the peak absorbance at 294 nm is accordingly smaller. This could be tested by flowing lower concentrations of **17**, similar to the concentrations of **17** after the reaction at the three

flow rates, through the reactor without irradiation. By comparing these non-irradiated errors to those of similar resultant concentration, it would be possible to determine if error truly does increase with decreasing flow rate, or if error simply increases with decreasing concentration of **17**. Although it is not possible to say definitively how concentration and flow rate affect error, all flow rates showed only a small degree of error. This means that samples can be collected more confidently knowing that the variation between samples should be small.

4.5 Calibration Curves for HPLC Response Factors for the Photo Reaction of 2(1*H*)-Pyridone

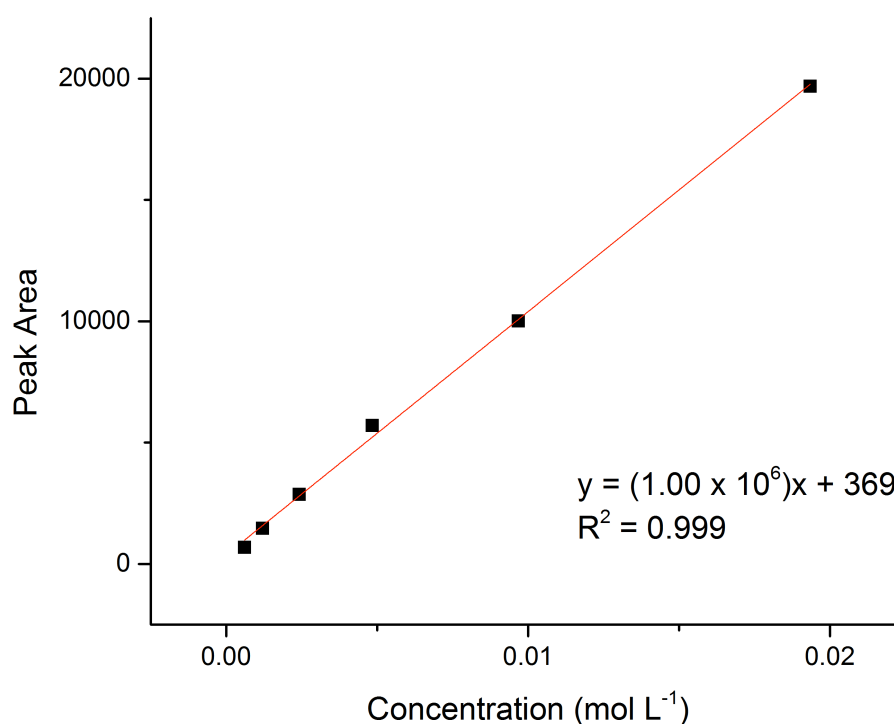


Figure 90: Calibration curve for the UV-Vis response factor of solutions of 2(1*H*)-pyridone, **17**, in water when analysing at 220 nm.

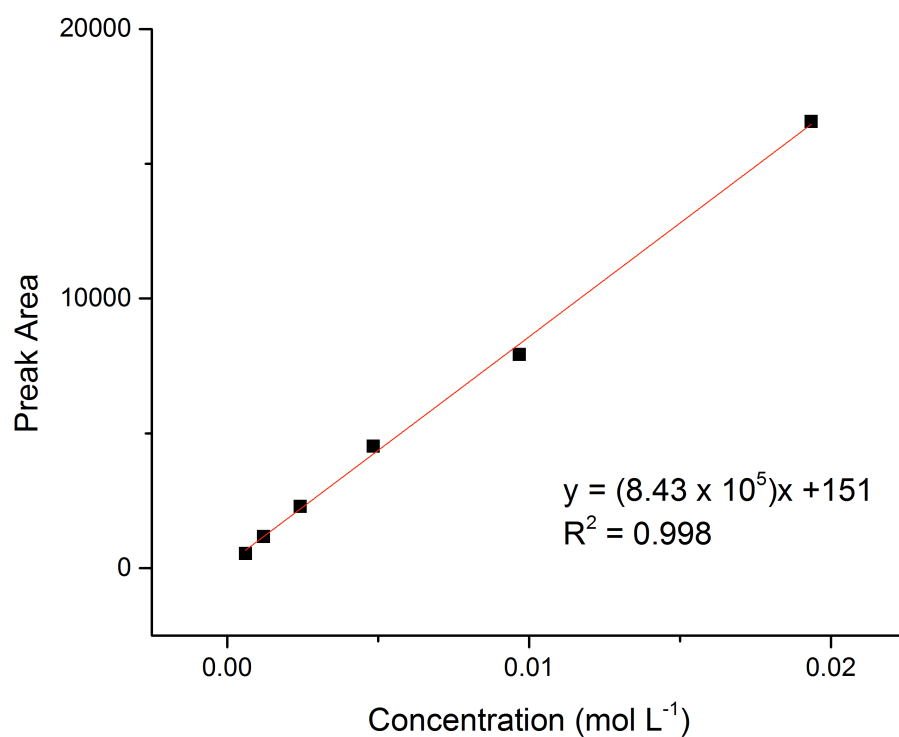


Figure 91: Calibration curve for the UV-Vis response factor of solutions of 2(1H)-pyridone, 17, in water when analysing at 230 nm.

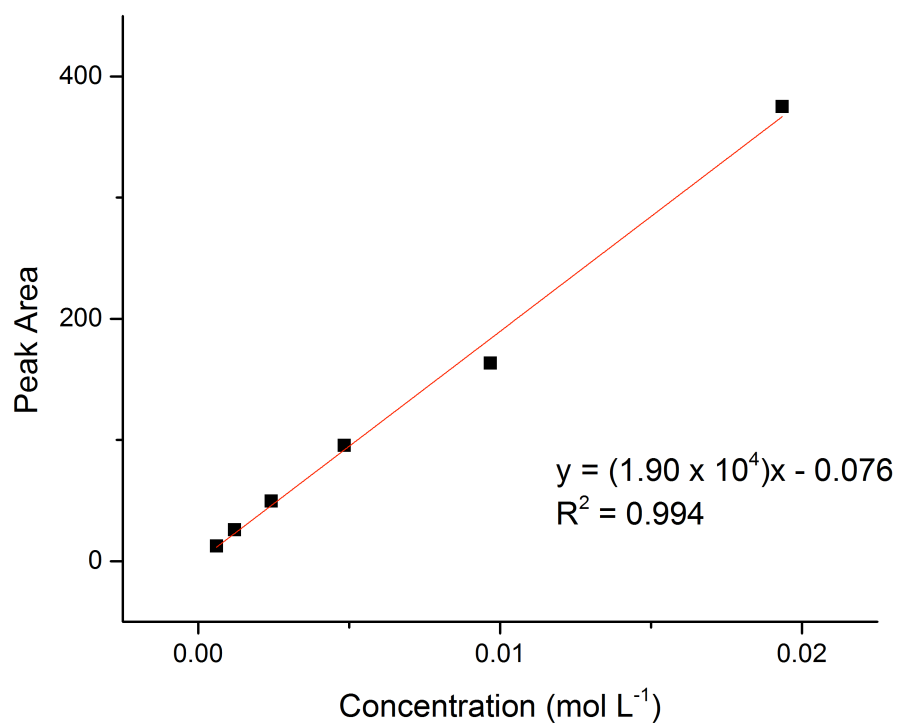


Figure 92: Calibration curve for the UV-Vis response factor of solutions of 2(1H)-pyridone, 17, in water when analysing at 240 nm.

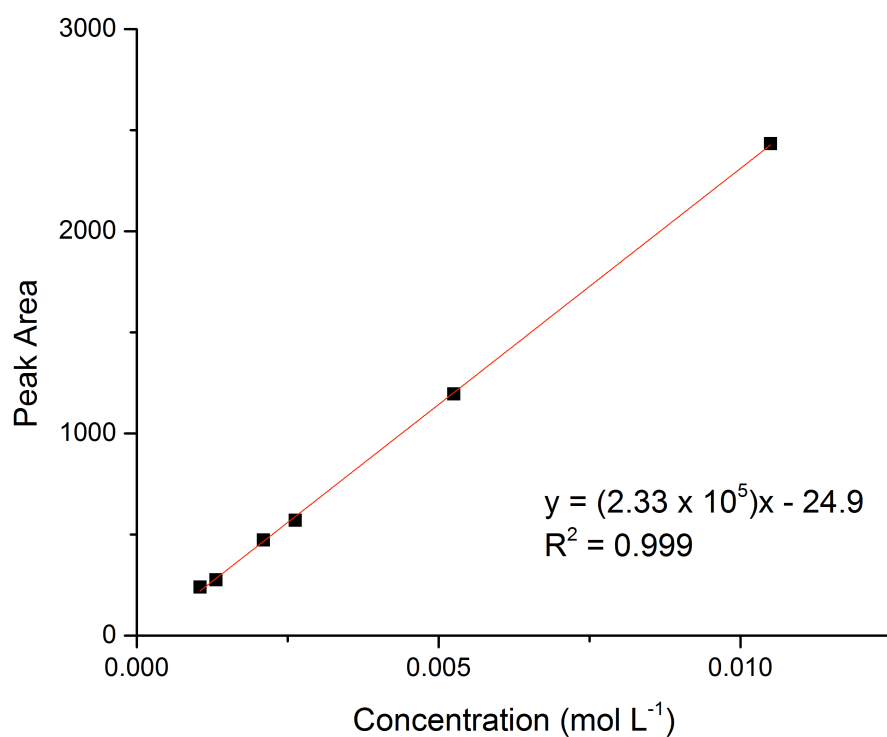


Figure 93: Calibration curve for the UV-Vis response factor of solutions of photoproduct 18 in water when analysing at 220 nm.

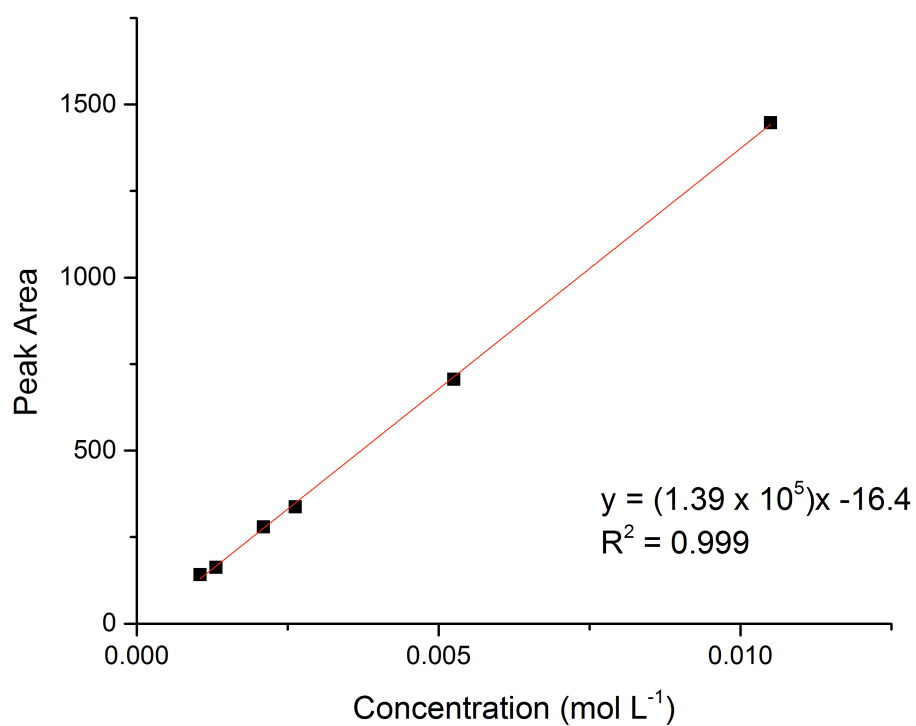


Figure 94: Calibration curve for the UV-Vis response factor of solutions of photoproduct 18 in water when analysing at 230 nm.

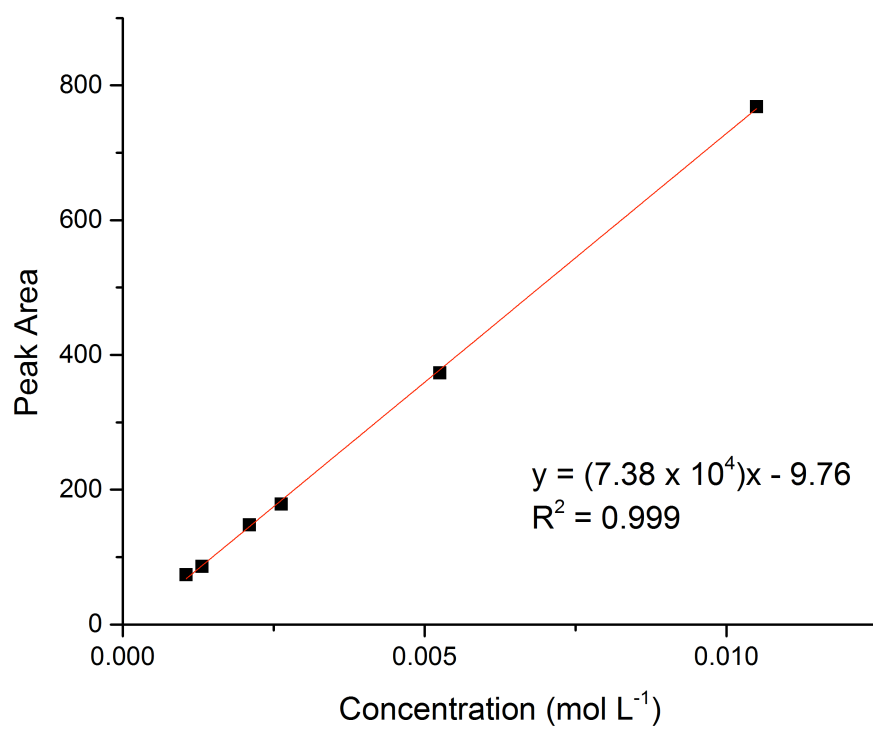


Figure 95: Calibration curve for the UV-Vis response factor of solutions of photoproduct 18 in water when analysing at 240 nm.

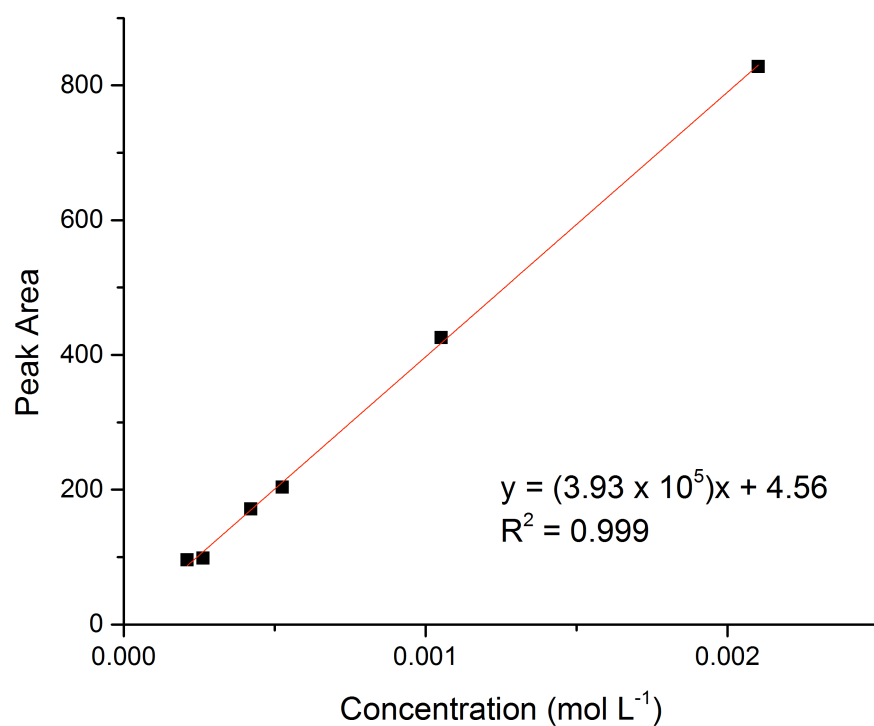


Figure 96: Calibration curve for the UV-Vis response factor of solutions of dimer 19 in water when analysing at 220 nm.

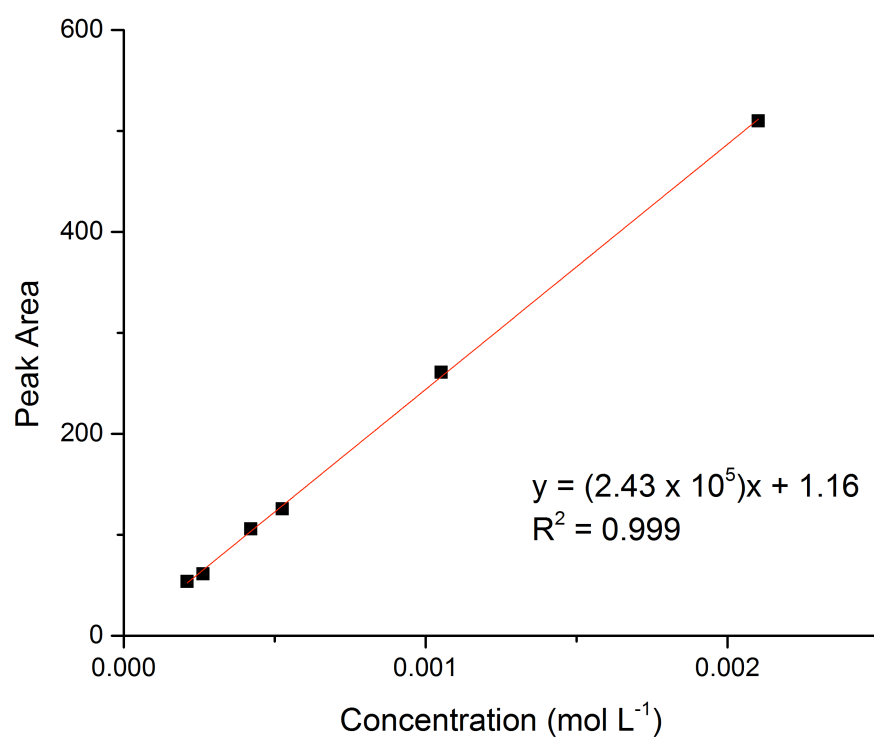


Figure 97: Calibration curve for the UV-Vis response factor of solutions of dimer 19 in water when analysing at 230 nm.

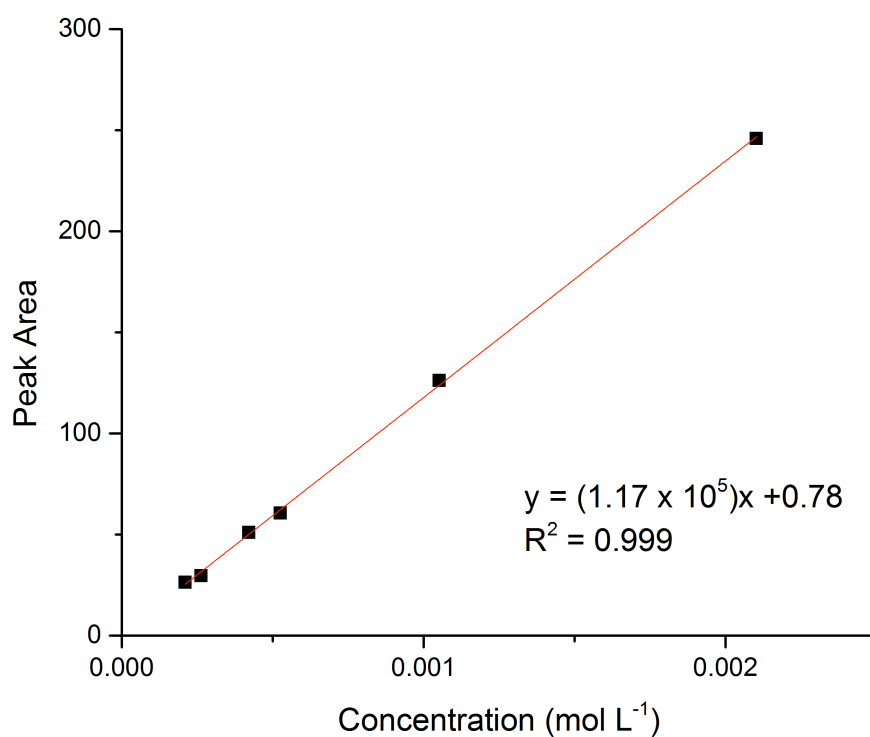


Figure 98: Calibration curve for the UV-Vis response factor of solutions of dimer 19 in water when analysing at 240 nm.

4.6 HPLC Method Sequence Parameters

Table 40: HPLC method parameters for separating the reaction mixture from the irradiation of 2(1*H*)-pyridone.

Column	Waters C ₁₈ (3.9 x 150 mm)
Flow Rate	1 mL min ⁻¹
Method Stop Time	4 min
Re-Equilibration Time	3 min
Solvent System	98% H ₂ O, 2% MeCN
Max. Pressure	400 bar
Min. Pressure	0 bar
Injection Volume	25 µL

4.7 Pre-Saturated NMR Results for the Irradiation of 2(1*H*)-Pyridone

Pre-saturation of solvent peaks allow for a ^1H NMR spectrum to be obtained in undeuterated solvents.³³⁶ In the case of the isomerisation of 2(1*H*)-pyridone, pre-saturated NMR meant that a ^1H NMR yield for the reaction could be obtained without first removing the reaction solvent. A sample for water pre-saturated ^1H NMR was prepared by diluting 0.5 mL of solution from the outlet of the reactor with 5 mL of D_2O . A known quantity of the sodium acetate was added as an external standard. The results of the reaction as analysed by pre-saturated ^1H NMR are compared with those acquired by HPLC in Table 41.

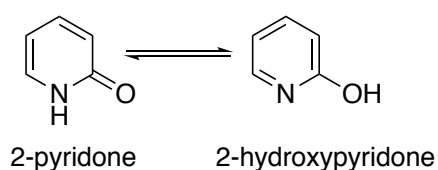
Table 41: Comparison of results analysed by water pre-saturated NMR and HPLC for 0.1 M solution of 2(1*H*)-pyridone, **17, in water irradiated at 282 nm at 0.2 mL min^{-1} and 1°C .**

Analysis Technique	17 Unconverted (%)	Yield 18 (%)	Yield 19 (%)	Mass Balance* (%)
Pre-Saturated NMR	41	8	11	60
HPLC	39	15	23	77

The two analysis techniques give yields of photoproduct **18** that are relatively close in value. This provides additional evidence that evaporation/ sublimation of product **18** was the main reason for the large discrepancy seen previously between results obtained by HPLC and NMR requiring solvent removal. In this example there is a discrepancy in the yield of dimer between the two techniques. However, these results are at higher concentration and precipitation of the dimer was increasing. It is likely that this discrepancy is due to inconsistency in samples of from the reactor outlet due to dimer precipitation.

4.8 Comparison of the Ground State FTIR of 2(1H)-Pyridone in Different Solvents

Solutions of 2-pyridone will contain a mixture of both 2-pyridone and its tautomer 2-hydroxypyridone (Scheme 39) as the energy difference between the two species is small. The equilibrium between the two species is dependant on the properties of the solvent, with polar protic solvents favouring the 2-pyridone (Scheme 39, left) and non-polar solvents favouring the 2-hydroxypyridine species (Scheme 39, right).³³⁷



Scheme 39: In solution 2-pyridone (right) will be in equilibrium with its tautomer 2-hydroxypyridone.

Both tautomers can form homodimers (Figure 99, A and B) and a mixed dimer can also form (Figure 99, C). Furthermore, in solvents that can form hydrogen bonds, it is possible for both tautomers to form hydrogen bonds with the solvent leading to pyridone-solvent complexes. The equilibria between the possible structures is reflected in the differences in the ground state IR spectra of 2-pyridone in different solvent systems.³³⁷

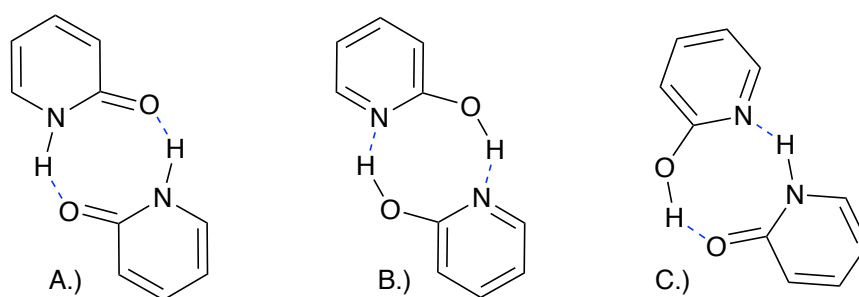


Figure 99: Structures of 2-pyridone and 2-hydroxypyridone hydrogen bonded dimers (hydrogen bonds shown in blue for clarity). (A) 2-Pyridone homodimer, (B) 2-hydroxypyridone homodimer, (C) 2-pyridone and 2-hydroxypyridone mixed dimer.

Ground state FTIR spectra of 2(1*H*)-pyridone solutions were recorded by Charlotte Clark using a Thermo Nicolet Avatar 360 FTIR spectrometer. Spectra in DCM, CD₃CN, EtOH, and 1:1 EtOH: D₂O are shown below in Figure 100 - Figure 103.

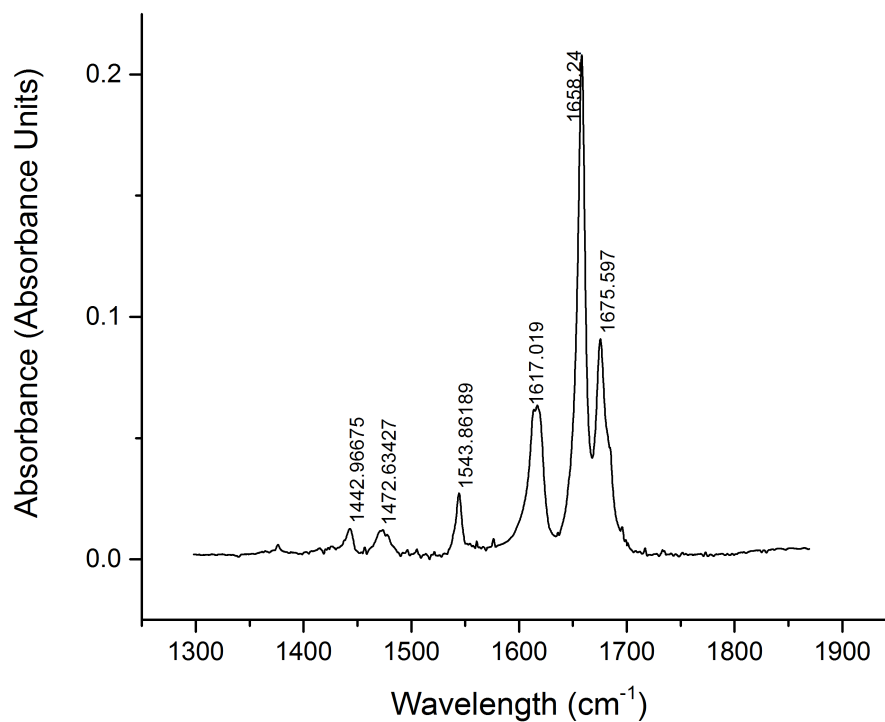


Figure 100: Ground state FTIR spectrum of 2(1*H*)-pyridone in DCM.

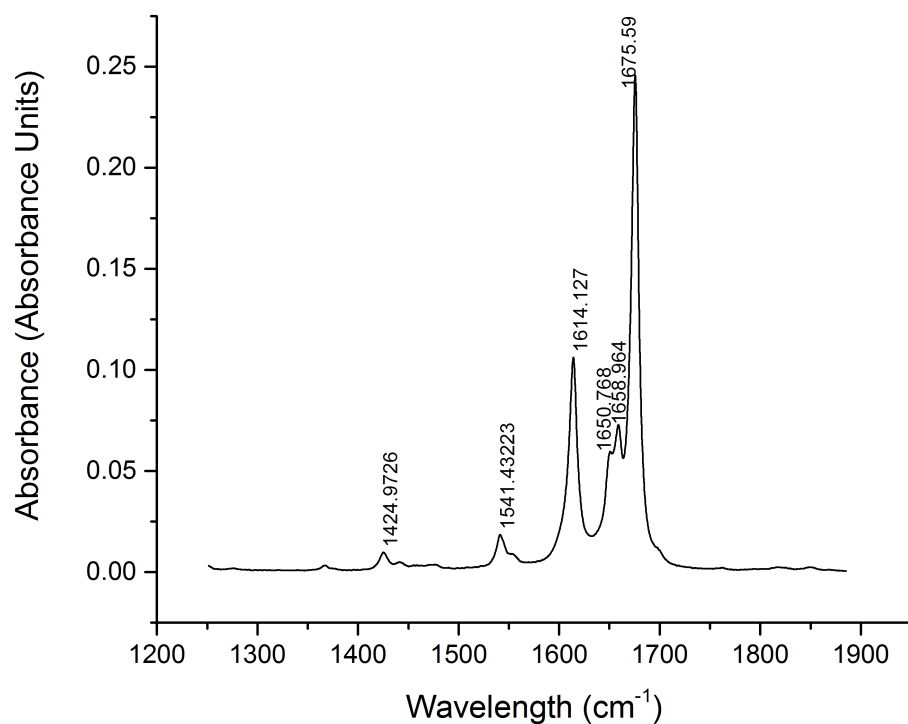


Figure 101: Ground state FTIR spectrum of 2(1H)-pyridone in CD₃CN.

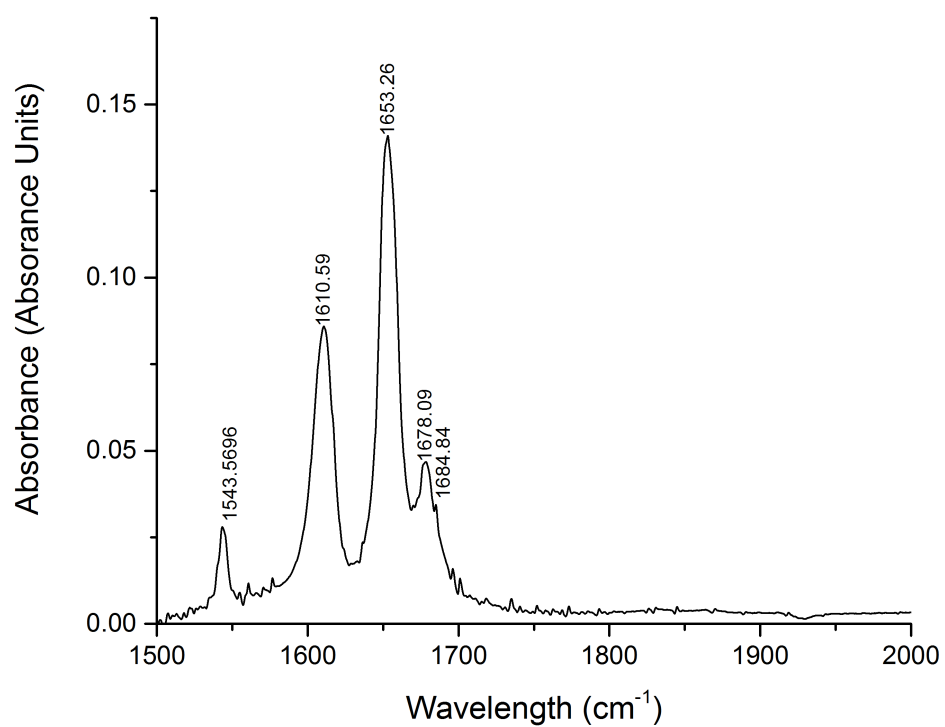


Figure 102: Ground state FTIR spectrum of 2(1H)-pyridone in EtOH.

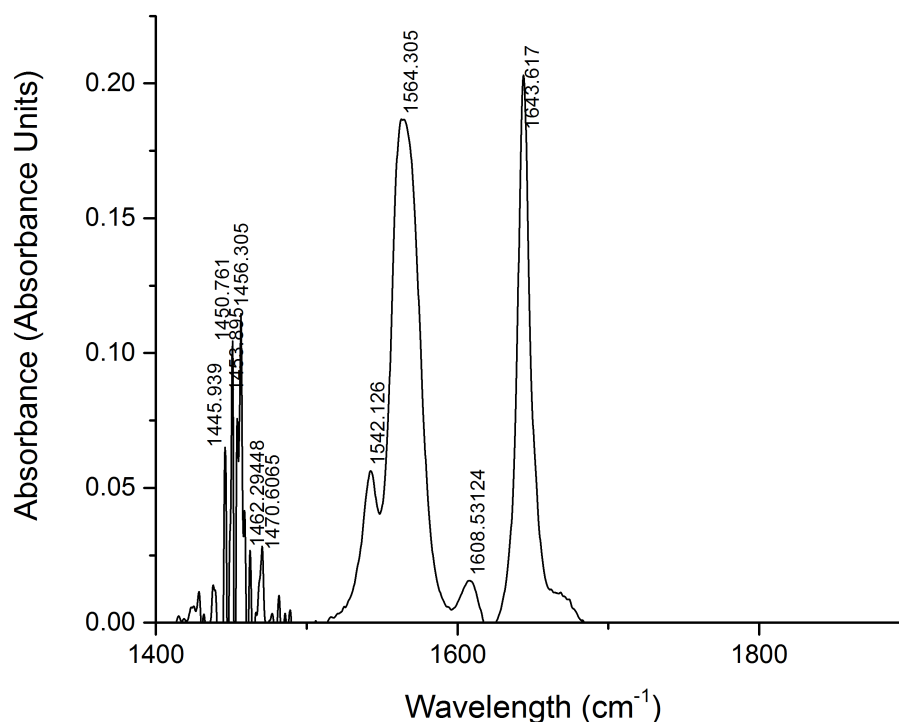


Figure 103: Ground state FTIR spectrum of 2(1*H*)-pyridone in a 1:1 mixture of EtOH:D₂O.

Appendix 5: Chapter 5 Additional Details

5.1 Paired Flow Rate Pump Head Calibration

When performing in-line GC measurements it was necessary to pair the flow rates of pumps 1 and 2 as accurately as possible to avoid either an air-lock in pump 2 or the small collection test-tube overflowing. A pump head calibration (Figure 104) was performed so that the correct flow could be set on pump 2, which was less efficient than pump 1.

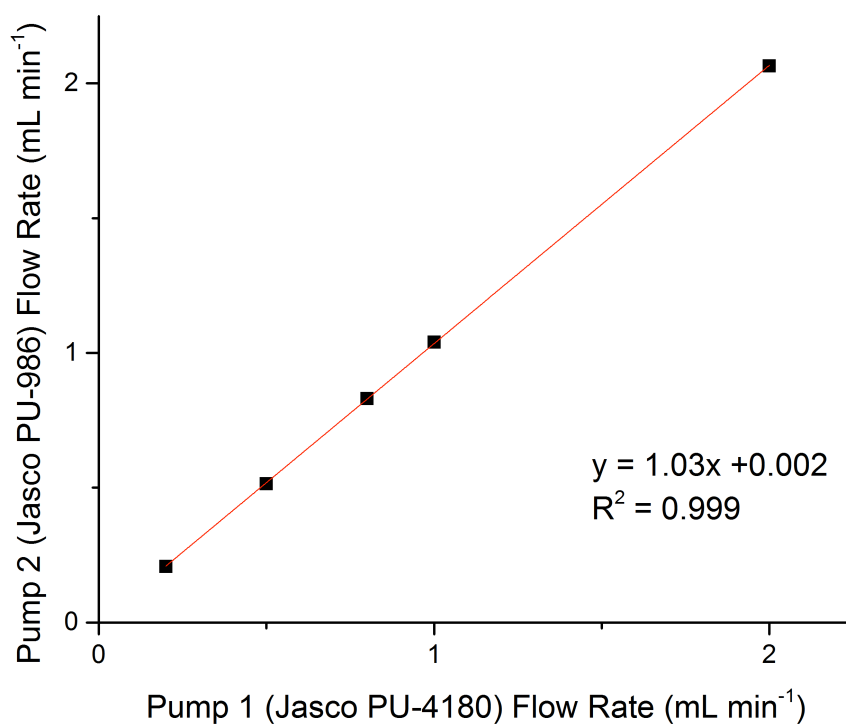


Figure 104: Calibration curve for determining the flow rate that must be set on pump 2 such that it pumps at the same rate as pump 1.

5.2 Calibration Curves for GC Response Factors for the Electrochemical Methoxylation of 4-*tert*-Butyltoluene

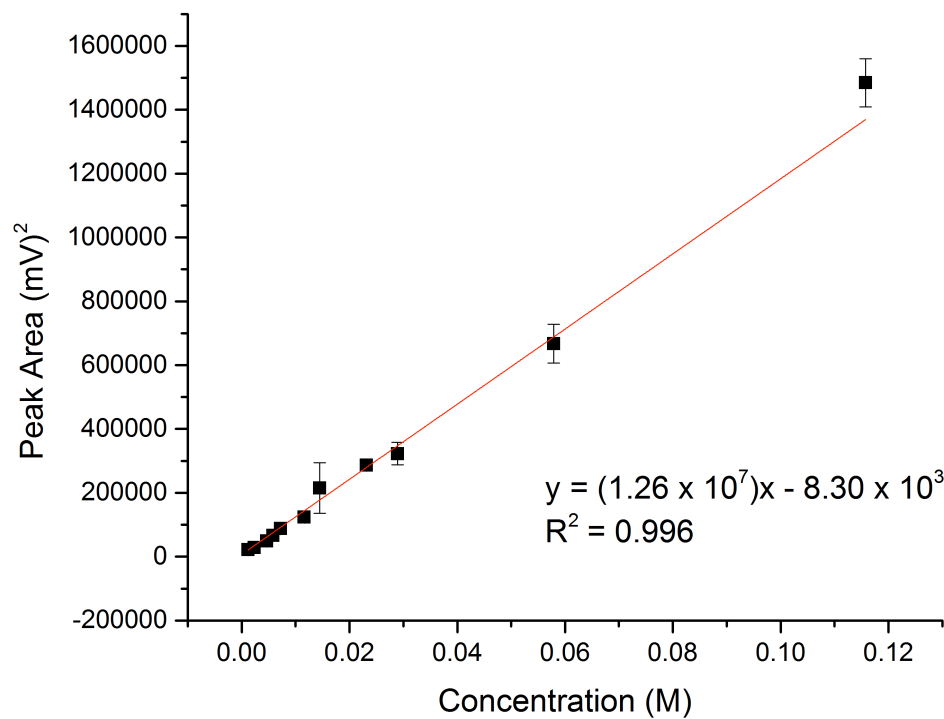


Figure 105: Calibration curve for the GC response factor of solutions of 4-*tert*-butyltoluene 22 in methanol. Peak areas are the average of three injections from the same solution.

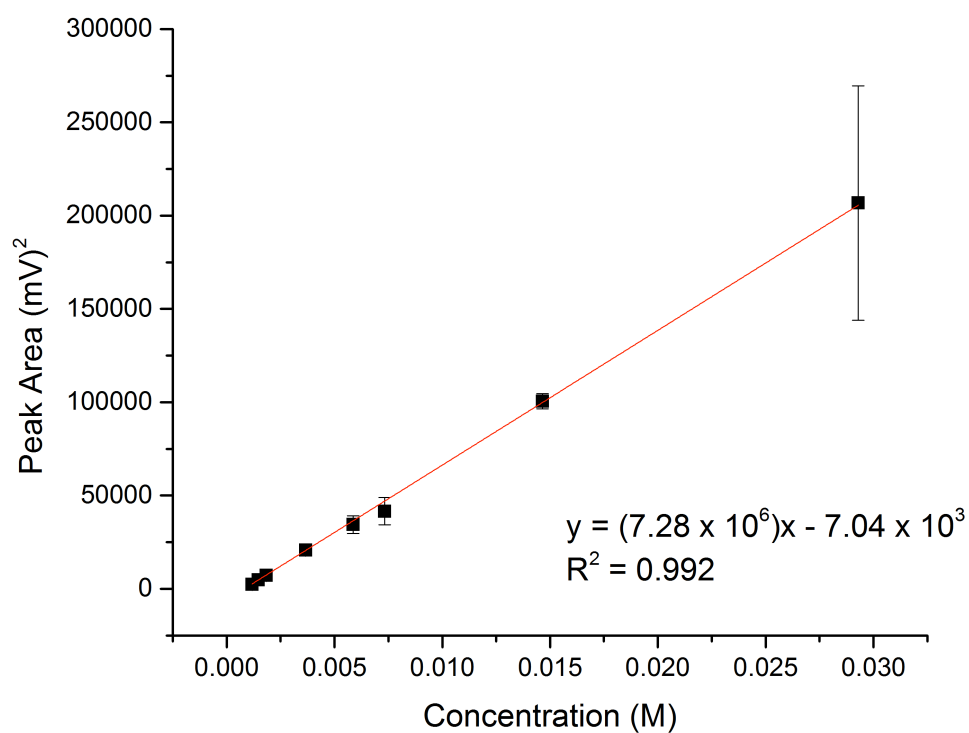


Figure 106: Calibration curve for the GC response factor of solutions of compound 23 in methanol. Peak areas are the average of three injections from the same solution.

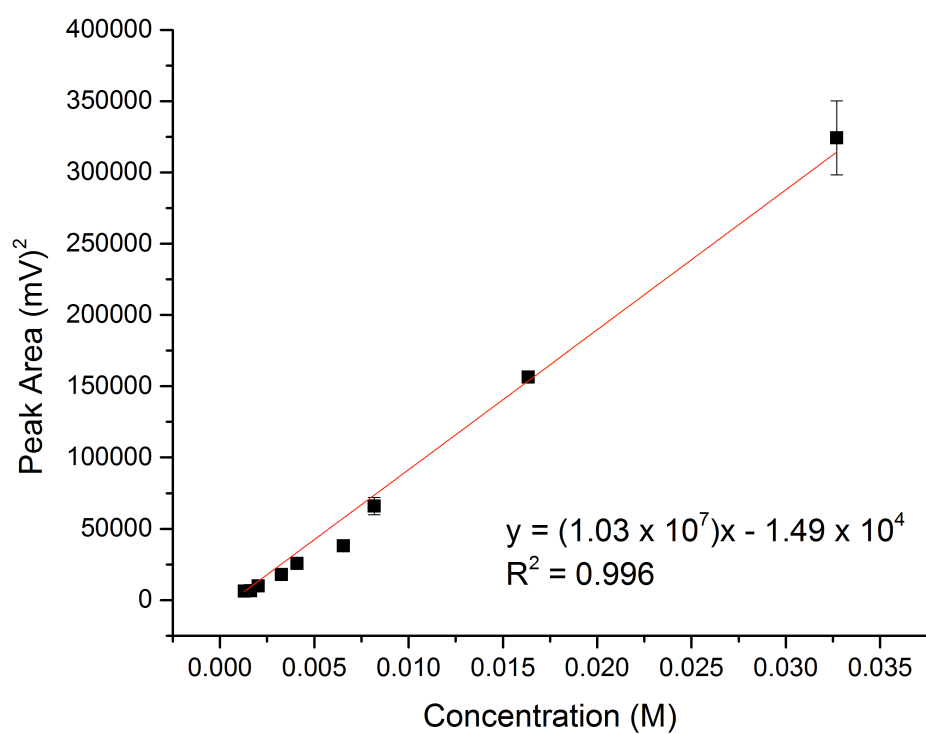


Figure 107: Calibration curve for the GC response factor of solutions of compound 24 in methanol. Peak areas are the average of three injections from the same solution.

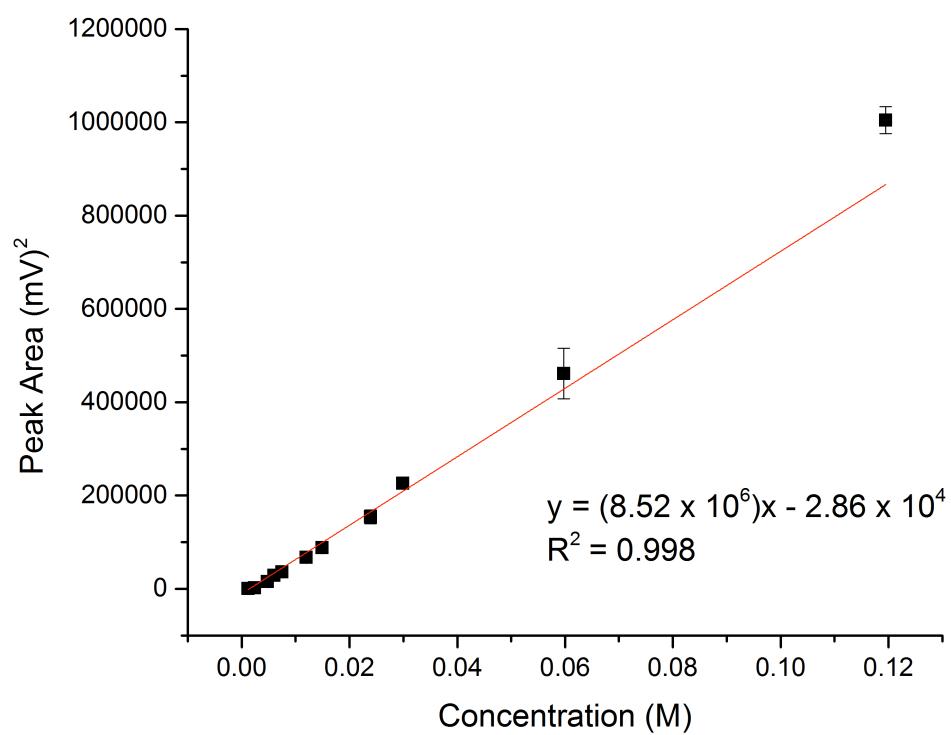


Figure 108: Calibration curve for the GC response factor of solutions of compound 25 in methanol. Peak areas are the average of three injections from the same solution.