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Photocatalytic Applications in Organic Synthesis

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Contents

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Abstract

As the search for new pharmaceuticals continues our understanding of their operation grows. A result of this is that design of new drugs is more often being limited only by the ability of synthesis techniques to produce them. The development of new synthesis techniques is therefore always of great interest. Among these techniques is semiconductor photocatalysis, most well known for its use in the clean-up of contaminated water; however it is capable of a wide range of reactions, from oxidation to cyclisation. This study examined some of the factors and influences involved in the applications of the technique for the oxidation of alcohols to ketones.

For the photocatalysis the steroid 6β-hydroxy-3α,5-cyclo-5α-androstan-17-one was synthesised, a compound with suspected antiprogesterone properties. A feature of the compound is the presence of a cyclopropane group within the A ring. It was synthesised easily through normal techniques; the presence of the cyclopropane group however makes the safe oxidation of the compound a difficult task.

The photocatalytic oxidation studies started with cyclohexanol as the base compound; this is the target area of the steroid without the influences of the other rings. Derivatives of cyclohexanol were used to study the effect of neighbouring groups on the reaction rate. The compounds used were 2-methylcyclohexanol, menthol, 2-chlorocyclohexanol and 1,2,3,4-tetrahydronaphthol; these being chosen to give a mixture of compounds with electron donating and electron withdrawing groups. It was found that the presence of electron donating groups gave a slower reaction rate while electron withdrawing groups gave a faster reaction rate. The reaction rate of 1.066×10^{-8} mol s^{-1} for the cyclohexanol dropped to 1.023×10^{-8} mol s^{-1} with the addition of the methyl group in 2-methylcyclohexanol. However the chloro group raised the rate to 1.689×10^{-8} mol s^{-1}. The rate increased further due to the presence of the benzene ring in 1,2,3,4-tetrahydronaphthol. These results showed the influence of induction on the compound, the groups affecting the electron density around the hydroxyl group. It was also found that the catalyst used had a large impact on the reaction rate; the anatase to rutile ratio had an effect but the major influence was the surface area of the catalyst. In cyclohexanol conversions of 41% were achieved with UV100 and 38% with PC500. The P25 gave a conversion of 43% but the Aldrich anatase just 25%. While the steroid could not eventually be oxidised photocatalytically a greater understanding was gained and a number of areas for further study found.

The study did succeed in examining the influence of vessel absorption on the UV light reaching the sample, it also synthesised a steroid containing a cyclopropane group. The study also examined the effect of electron donating and withdrawing groups on the photocatalytic oxidation of alcohols. And finally it examined the effect of the catalyst used on reaction rate.

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Abbreviations

CdS	**Cadmium sulphate**
cm^3	**Cubic centimetre**
DHEA	**Dehydroepiandrostanone**
DDT	**Dichlorodiphenylethane**
FTIR	**Fourier Transform Infrared Spectroscopy**
g	**grammes**
g/cm^3	**grammes per cubic centimetre**
GC/ECD	**Gas Chromatography with Electron Capture Detector**
GC/MS	**Gas Chromatography with Mass Spectroscopy**
h	**Hours**
HATR	**Horizontal Attenuated Total Reflectance**
HOMO	**Highest occupied molecular orbital**
$KMnO_4$	**Potassium permanganate**
$LiAlH_4$	**Lithium aluminium hydride**
LUMO	**Lowest unoccupied molecular orbital**
m^2g	**Square metres per gramme**
ml	**millilitres**
mol	**moles**
$NaIO_4$	**Sodium periodate**
nm	**nanometres**
NMR	**Nuclear Magnetic Resonance**

pH	**A measure of acidity or alkalinity**
PMMA	**Polymethyl Methacrylate**
RFE	**Rotary film evaporation**
RuO_2	**Ruthenium(IV) oxide**
$SrTiO_3$	**Strontium titanate**
TiO_2	**Titanium Dioxide**
TLC	**Thin Layer Chromatography**
UV	**Ultraviolet**
W	**Watts**
ZnO	**Zinc oxide**

Chapter One
Introduction

1.1 Background

The state of the environment is a subject of continually growing interest to the public, and as interest grows the factors influencing the health of the environment are being scrutinised. A primary source of pollution is industry, which contributes a large amount of pollution through a host of sources. Industry produces large amounts of wastes from its own processes; this can be in the form of exhaust gases, as waste streams or as waste by-products. These by-products must be disposed of in a safe manner, which represents a large cost to industry each year. An alternative approach would be to switch to techniques with a reduced waste output[1]. This would result in reduced waste disposal costs for industry and lower the environmental impact.

While semiconductor photocatalysis is not a new technique; it is only in the last 30 years that it has gained prominence. It is a catalytic technique that is obtains its energy from the absorption of photons of light (solar or artificial), potentially making its use very cheap and therefore finding new applications is a subject of much interest[2,3]. When the applications of photocatalysis were eventually examined a wide range of possible applications of the technology were found. During that initial period applications such as water splitting[4], oxidation[5], and reduction[6] were found to be possible. On the discovery of photocatalysis use in wastewater remediation however much of the scientific interest in the technique was redirected towards the newly discovered application. Photocatalytic destruction made it possible to clean up waste streams using light and a catalyst, opening up a new field in waste remediation[7].

Amongst the compounds that have been destroyed using photocatalysis are hydrocarbons, polymers, surfactants[8], herbicides[9], dyes[10], and even pesticides such as DDT[11]. The method has even been used to remove heavy metals from water[12]. This makes it an ideal technique to examine when looking at new methods for cleaning-up contaminated water.

One of the applications of photocatalysis that has only found investigation to a limited extent is the use of the technique for organic synthetic reactions. This process can induce oxidations and reductions, removing the need for expensive and dangerous solvents and chemicals[13]. Another advantage is that photocatalytic processes do not require some of the extreme conditions necessary for some processes and which again can have an effect on cost as well as safety considerations such as high temperatures and pressures. The technique is also potentially far more selective and therefore the production of by-products is reduced. However a complete understanding of the factors influencing the photocatalysis is not yet known.

1.1 Green Chemistry

Pharmaceuticals and fine chemicals are important and high value components of the synthetic chemical industry, usually produced through complex and difficult procedures, also as product yields are low they are produced in low volumes at a high cost[14,15]. Some of the techniques used in the synthesis require the use of chemicals and procedures that are hazardous and expensive, and produce hazardous by-products. This results in increased costs for the producer because of the additional safety requirements and the waste disposal needs[16].

Fine chemicals tend to be complex molecules with limited thermal stability, which are produced through multistep syntheses. They are normally produced on a small scale using batch reaction equipment, and with high purity requirements, resulting in higher value. While fine chemical production only corresponds to about 5% of chemical manufacture it accounts for around 20% of profits[17].

In the past few years there has been a push to get chemical producers to employ more environmentally friendly practices in their production. Companies that have implemented such practices have found that they can reduce their production costs which in turn results in an increase in their profits. This can be helped through the use of catalysts[1,17-22].

In the green chemistry process there are twelve points that can summarise the subject as a whole[16].

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methodologies should be designed to maximise the incorporation of all materials used in the process into the final product.
3. Whenever practical 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 achieve efficiency of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary whenever possible, and innocuous when used.
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 where possible.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically 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 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, including releases, explosions and fires.

Companies that have switched to using more environmentally friendly techniques have reduced their wastes by tens of tonnes each year, resulting in major savings as less wastes result in reduced treatment and disposal costs.

1.2 Clean Technology

Historically industry has taken the approach of treating pollution and waste at the end of the process, before it is discharged or dumped, rather than prevention or recycling. However this method has a number of disadvantages as it results in increased costs with no advantages to balance it, the wastes are not reused nor are alternative uses found for them. This results in there being no way to make any profit from the existence of the reaction by-products, and no way to balance the cost of handling them. End of stream clean-up can involve the disposal of waste by-products and the treatment of waste streams, all of which have an economic impact. The alternative to this is to use waste prevention techniques and recycling, removing or reducing the amount of treatment required. These lower the amount of energy and materials used, resulting in reduced costs. They also reduce the end-of-pipe treatment costs as fewer wastes are produced[23].

The concept of cleaner production in industry began to emerge in the mid 70's as a response to growing environmental regulations[16].

An early example of clean production was the 'Pollution Prevention Pays' (3P) program started by 3M in 1975[24,25]. This was a large scale programme that involved company-wide changes. Through this program it has been estimated that 1.2 billion pounds of pollution were eliminated from the air, land and water. In addition the savings during the first year totalled more than 750 million dollars. Subsequently similar programmes were launched by Dow and DuPont as well as others.

1.3 Photocatalysis

While it was not until the 1970s that this technique gained attention many examples of semiconductor photocatalysis had already been reported in the literature by the start of the century. In particular the semiconductor zinc oxide had been extensively reported as a photosensitiser for the decomposition of organic compounds and sensitizer for a number of inorganic photoreactions[2].

Photocatalytic reactions constitute one of the emerging technologies for chemical transformations. In the late 1970s, the initial stages of this development were boosted by very attractive proposals concerning water splitting using UV energy[4]. Initial hopes were however, not fulfilled and in the early 1980s, when enthusiasm for the technology was declining, a new possible application appeared, when it was reported that photocatalytic reactions could be utilised for environmental remediation[26]. Since then there have been a wide range of investigations on the abatement of air and water pollution; and pollution control remains as the most important target for applications and the main reason for research and development studies. The application for chemical synthesis has however only been investigated to a limited extent[27-30].

1.3.1 Basic Principles

When the atomic orbitals of atoms overlap they split to form discrete molecular orbitals, one for each atom involved. When two atoms overlap a bonding orbital and an antibonding orbital are formed, the electrons sitting in the lowest energy levels (figure 1b). If the atoms only have one electron in the atomic orbital (such as with Group 1 elements) then only half of the orbitals are filled, with the electrons existing in the bond orbital. When a third atom joins then three molecular orbitals are formed; one fully bonding, one fully antibonding, and a nonbonding orbital between them (figure 1c). The inclusion of a fourth atom results in the formation of a fourth molecular orbital (figure 1d). In metals all the atoms are tightly packed together can be thought of as one massive molecule. When N atomic orbitals overlap the number of molecular orbitals is massive, forming continuous bands rather than discrete energy levels (figure 1e).

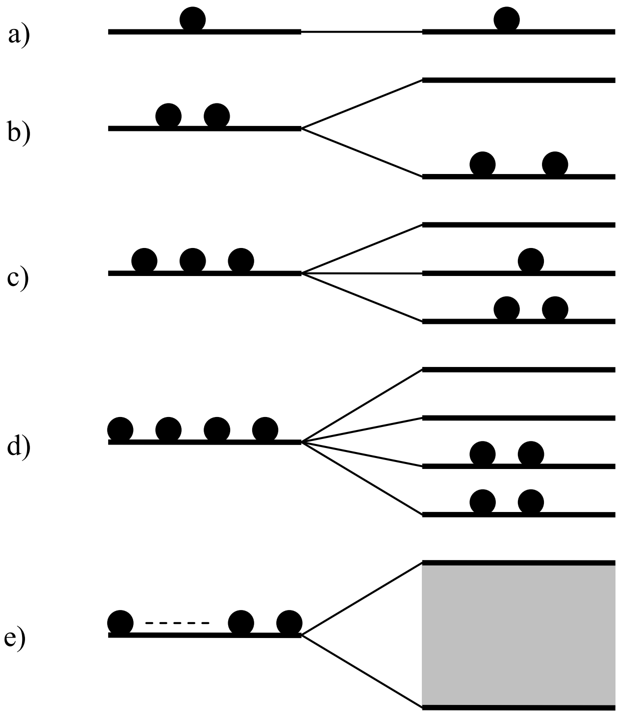


Figure 1 - Diagram of the bands created through the overlap of atomic orbitals

However as this example is with an element with only one s electron only half the band will be filled, with the electrons occupying the lower energy levels, with the rest empty. Where the electrons stop is the highest occupied molecular orbital (HOMO), with the next unoccupied level being the lowest unoccupied molecular orbital (LUMO). The Fermi level is the HOMO of the molecule at 0K, when there are no excited electrons. When the temperature of the material is raised electrons in the topmost occupied orbitals are promoted into higher energy unoccupied orbitals. This allows conduction to occur. However when the element has 2 s electrons (such as Group 2 metals) then the band is completely filled with electrons, and so cannot be promoted within the band. The instead have to jump in to the p band orbitals. With an electrical conductor the s and p bands are so close that they overlap, thus making it very easy for electrons to be promoted into a higher energy level (figure 2). With a semiconductor the s and p bands are separated by a gap, and in an insulator this gap is very large.

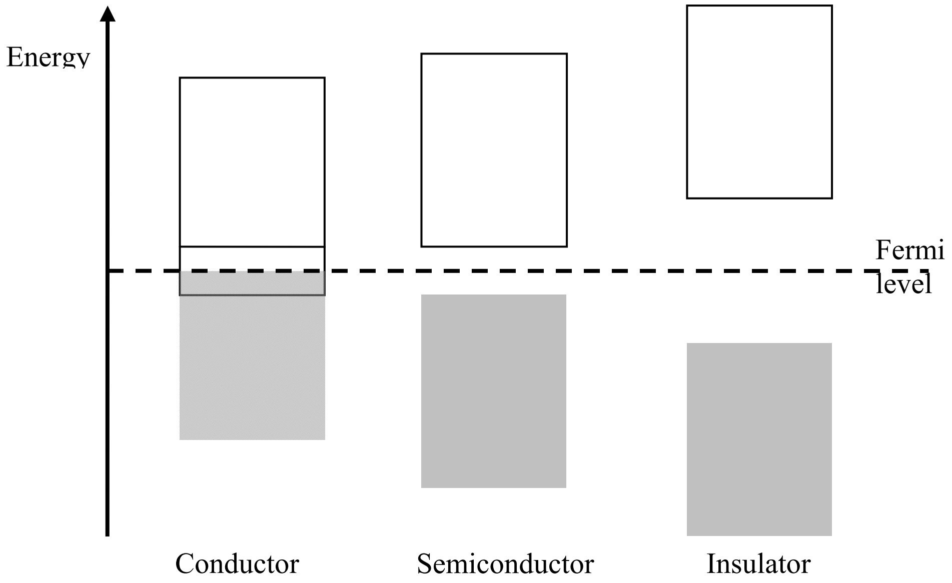


Figure 2 - Diagram of differences in band positions in different materials

In semiconductors and insulators the fully occupied lower s band is referred to as the Valence band, and the upper unoccupied band as the Conduction band. The gap between them is called the band gap. As the temperature increases it is possible for electrons to be promoted and jump across the band gap into the conduction band. This results in a positively charged hole left behind in the valence band and the excited electron in the conduction band[2,32,33]. Both hole and the electron are mobile within their band, allowing the material to conduct electricity; the conduction being determined by the number of electrons promoted across the band gap, a number that increases as the temperature increases.

There are different types of semiconductor, one of those types is called intrinsic semiconductors. Intrinsic semiconductors are generally pure materials, although compounds semiconductors such as GaN and CdS are also intrinsic semiconductors.

With these at 0K is an insulator as the Fermi level is the top of the valence band, as the band is full there is no room for the electrons to move within the bands. But as the temperature is increased the electrons are promoted across the band gap and into the conduction band, allowing the material to conduct[33] (figure 3). Intrinsic semiconductors can be thought of as pure materials as the electron levels are not altered.

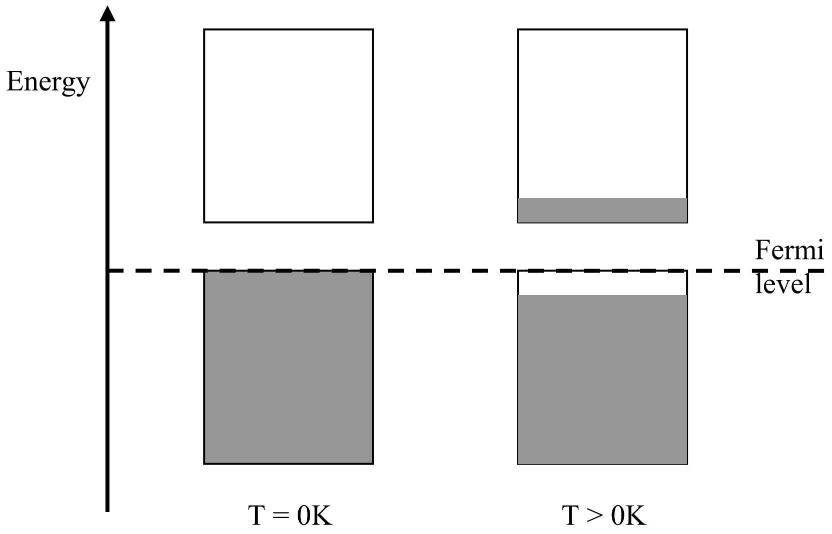


Figure 3 - Diagram of an intrinsic semiconductor at different temperatures

The other type of semiconductor is called an extrinsic semiconductor, these are materials that gain the ability to conduct through the addition of dopant atoms of another valence level to the main element. If the dopant atoms can trap electrons then electrons are drawn out of the valence band and into the dopant atoms, leaving positively charged holes in the valence band. Theses are referred to as p-type semiconductors (figure 4). However if the dopant atoms carry an excess of electrons then these electrons occupy the lowest levels of the conduction band, allowing conduction to occur. There are referred to as n-type semiconductors.

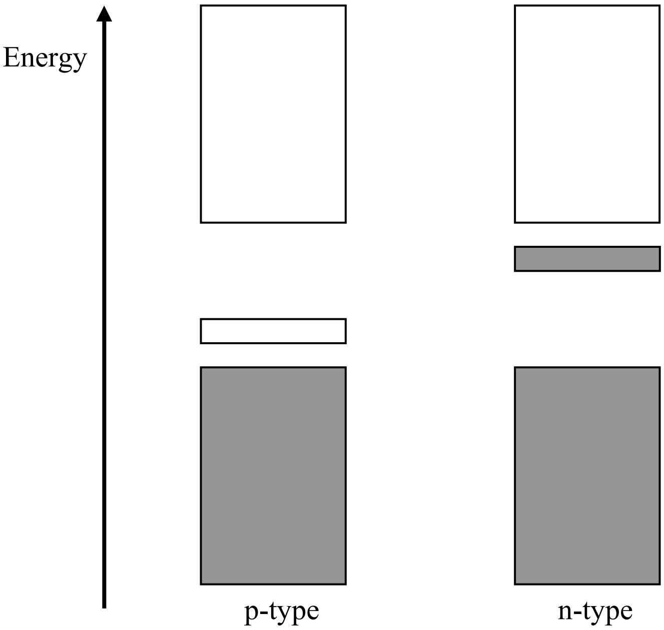


Figure 4 - Diagram of p and n type semiconductors

1.3.2 Titanium dioxide

The semiconductor TiO_2 is an example of an n-type semiconductor, this is due to the presence of the higher valence oxygen atoms adding electrons to the Ti atoms. It can be found in three different forms: anatase, rutile and brookite[35,36]. Of the three forms only anatase and rutile are photocatalytically active and therefore of commercial importance. The appearance of both is of a fine white powder, unlike brookite which is brown. Rutile has a density of 4.2 g/cm^3, while anatase has a density of 3.9 g/cm^3. This difference is explained by their different crystal structures, rutile is more tightly packed than the anatase crystal[31,35,36].

As early as 1929 it was known that the pigment "titanium white," (TiO_2) was responsible for flaking paints. The allure of TiO_2 as a pigment for the paint industry comes from its high refractive index (3.87 for rutile and 2.5-3 for anatase TiO_2, whereas the refractive index for diamond is 2.42)[35]. When its photosensitising ability was discovered at first it appeared to be unsuitable as a pigment for paint, due to the degradation of the binding constituent of the paint by the TiO_2. This problem however was largely solved by coating the pigment with a layer of inert oxide, such as silica, alumina, or zirconia[37].

Subsequently TiO_2 has been used in even more applications[2]. Due to its high refractive index, durability, dispersion, tinting, strength, chemically inert nature and non-toxicity, it is also widely used for coatings, enamels, specification paints, lacquers, inks, tanners leather finishes, shoe whiteners and ceramics[36]. It is used in electroceramics and glass (due to its high stability and property to absorb ultraviolet light), as well as a sunblock in suncreams. Due to its chemical stability and non-toxicity it can even be used as a pigment in pharmaceuticals and food colourings..

Both rutile and anatase are photoactive and photocatalysis using a number of different combinations of these have been carried out[12,38]. Through study it has been found that a material with 70/30 % anatase/rutile mix appears to demonstrate good photocatalytic activity in waste water treatment[39], a catalyst that uses this ratio is Degussa P25. Although there are many different varieties of TiO_2, Degussa P25 TiO_2 has effectively become a research standard. This is because it has a reasonably well defined nature (typically a 70:30 anatase:rutile mixture, non-porous, average particle size 30nm), and a substantially higher photocatalytic activity than most readily available samples of TiO_2. Its is also chemically stable, not suffering from the photo-decomposition or degradation that some semi-conductors can suffer from.

1.3.3 Mechanisms of Semiconductor Photocatalysis

In semiconductor photocatalysis the energy used to promote electrons comes from light, the energy normally referred to as hν. The amount of energy contained in the light can be determined through the equation:

$$E = \frac{hc}{\lambda} \qquad \text{Eqn 1}$$

Where h is Planck's constant, c is the speed of light, and λ is the wavelength of the light. When the energy of the light exceeds the bandgap of the semiconductor, an electron, e_{cb}^-, is promoted from the valence band, VB, into the conduction band, CB, leaving a hole, h_{vb}^+ behind (figure 5)[10,31,32].

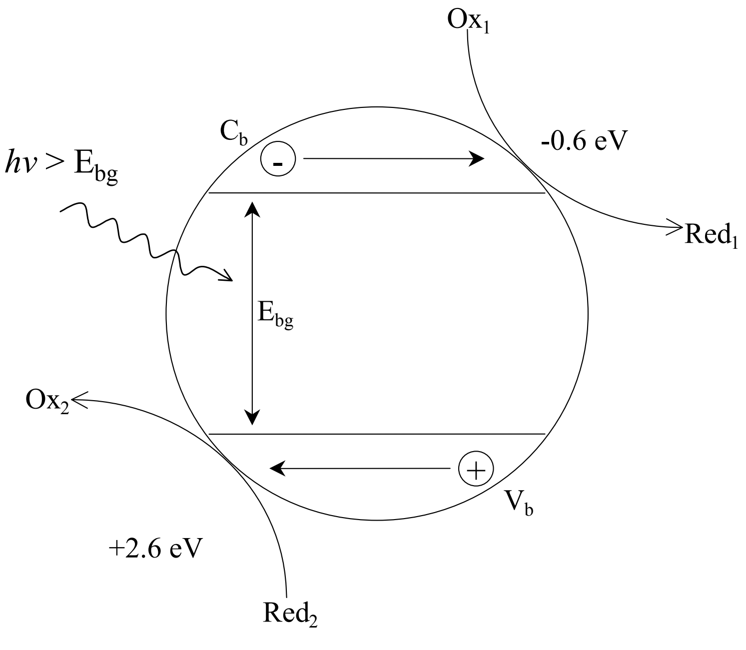


Figure 5 - Mechanism of a semiconductor

Once in this state the electron can then either drop back down into the valence band, resulting in the production of heat (eqn 2), or it can react with other species. While the hole and the electron are apart they can react with species in the solution. Such as the hole will react with compounds adsorbed to it, species such as organic compounds (eqn 6), water (eqn 4) or hydroxyl ions (eqn 5).

$$TiO_2 + h\nu \rightarrow e^- + h^+ \quad \text{Eqn 2}$$

$$e^- + h^+ \rightarrow \text{heat} \quad \text{Eqn 3}$$

$$h^+ + H_2O_{ads} \rightarrow \bullet OH + H^+ \quad \text{Eqn 4}$$

$$h^+ + OH^-_{ads} \rightarrow \bullet OH \quad \text{Eqn 5}$$

$$h^+ + RH_{ads} \rightarrow \bullet R + H^+ \quad \text{Eqn 6}$$

The electrons can also react with the compounds that are present in the solution such as oxygen and hydrogen peroxide. The electrons can be absorbed by the oxygen to form superoxide (eqn 7) or it can react with oxygen together with hydrogen to create hydrogen peroxide (eqn 8). It can then react with hydrogen peroxide to create hydroxyl radicals and hydroxyl ions (eqn 9).

$$e^- + O_{2ads} \rightarrow O_2^- \quad \text{Eqn 7}$$

$$2e^- + O_{2ads} + 2H^+ \rightarrow H_2O_2 \quad \text{Eqn 8}$$

$$e^- + H_2O_{2ads} \rightarrow \bullet OH + OH^- \quad \text{Eqn 9}$$

All of these produced species are highly reactive, capable of attacking and breaking down organic compound they come in contact with[2]. This can be further enhanced by adding additional hydrogen peroxide to the solution. This can then either react with the free electrons to form hydroxyl radicals and hydroxyl ions, or it can undergo a photolytic reaction to form two hydroxyl radicals (eqn 10).

$$H_2O_2 + h\nu \rightarrow 2\ {\bullet}OH \qquad \text{Eqn 10}$$

The reaction between electrons and oxygen serves another purpose, not just becoming a reactive species, by combining with oxygen the electrons are stopped from dropping back to the valence band where electron-hole recombination can occur. This means that the hole and the electron have more time to react with species adsorbed to the catalyst. A lack of dissolved oxygen would hinder the reaction as electron-hole recombination would occur far more readily, giving less time for the species to react.

It is all of the reactive species created that make these reactions attractive to scientists for treating pollution problems due to the wide range of contaminants that can be broken down, with the resulting products being cleaner air or water streams and the recovered catalyst[31,32] (eqn 11).

$$\text{Organic pollutant} + O_2 \xrightarrow{\overset{h\nu > E_{bg}}{\textit{semiconductor}}} CO_2 + H_2O + \text{mineral acids} \quad \text{Eqn 11}$$

Several compounds have been investigated as potential catalysts; including TiO_2, ZnO, $SrTiO_3$, RuO_2 and CdS[41-43]. However the most widely used catalyst is titanium dioxide due to a wide range of factors, it is inexpensive, it can degrade a wide range of pollutants, it is non-toxic, it can be recycled without significant loss of performance, it is chemically inert, and it has resistance to photocorrosion and decomposition.

1.3.4 Factors Influencing Photocatalytic Processes

During the photocatalytic process the organic compounds are fully mineralised and transformed into water, carbon dioxide and mineral acids; if elements other than carbon, hydrogen and oxygen are present. The rate of the reaction is dependent upon a number of factors. These include pH, the light intensity, the amount of catalyst added, temperature, oxygen, and sample concentration in the system[44-47].

The pH of the aqueous solution significantly affects TiO_2, including the charge on the particles and the size of the aggregates it forms, and the positions of the conductance and valence bands[38,48-50]. The pH can result in the catalyst having either a positive or negative charge, this effects how easily the catalysts mixes into the solvent and how easily the target compound adsorbs onto the catalyst. However the rate of reaction is not usually found to be strongly dependent upon pH, typically varying by less than an order of magnitude from pH 2 to pH 12[51]. Higher reaction rates for various TiO_2 sensitised photocatalytic mineralizations have been reported for both high and low pH[52,53]. The best pH for a reaction is generally dependent on the compound involved. The pH also effects the positions of the conductance and valence bands due to the effect of the pH on the thermodynamic stability in the oxide. This causes a shift in the bands as the TiO_2 adjusts to become more stable, this is normally by around 59mV for every 1 pH in difference.

As oxygen is an important component of the photocatalytic reaction it is not surprising that its concentration has an effect on the reaction rate[54]. The more oxygen available to take part in the process then the faster it can proceed. The maximum amount of oxygen that can take part is of course affected by its solubility in the reactant solution. If the amount of dissolved oxygen is low, the lack of oxygen will result in a reduction in the reaction rate when there are no other electron acceptors available[55-57].

The light intensity is one of the most important factors in the whole photocatalysis process; it is this which supplies the energy to the catalyst. The more intense the light then the more energy that is supplied to the catalyst and the faster the reaction will proceed[58]. The amount of photons irradiating the sample have a direct relationship with the number of molecules produced, this can be shown with the quantum yield Φ (eqn 12).

$$\Phi = {}^{N_{molec}}\!/_{n_{ph}} \quad \text{Eqn 12}$$

Where N_{molec} is the amount of product molecules formed and n_{ph} is the quantity of photons absorbed by the catalyst.

The loading rate of the photocatalyst is another factor that is of great importance to the reaction rate of the process[59]. In batch reactors the rate of photomineralisation is often found to increase with increasing TiO_2 but tends towards a limiting value at high concentrations. This is due to the catalyst concentration reaching a point where light cannot penetrate completely into the reactor but is instead absorbed and blocked by only the catalyst closest to the light source. In any commercial system it is more likely that the TiO_2 will be fixed and the sample will be passed over it[60]. Such a flow system eliminates the need for filtration or settling of the photocatalyst. This system however will not have as great a reaction rate, as the fixed catalyst system has a smaller surface area compared to the free catalyst in the batch system[51,55,61-66].

The effect of changing the operating temperature on the reaction rate is difficult to predict, but not usually found to be a big factor. On one hand increasing the reaction temperature adds more energy to the system, increasing the rate of all reactions occurring in the system, except for the photogeneration of electron-hole pairs. On the other hand, increasing the reaction temperature will lower the solubility of oxygen. A lower concentration of dissolved oxygen in the liquid will result in less electrons being captured by oxygen, and so a greater change of electron-hole recombination occurring. If this process is rate linked for the overall process, then increasing the reaction temperature will cause the rate of degradation to decrease. In practice, it appears that the effect of increasing the reaction temperature varies with the particular system under study[52,67]. The other issue with temperature is evaporation of the solvent. Evaporation of the solvent even when minimal could become a problem when a long reaction is being performed. The loss in the solvent could result in the sample being concentrated and influence the reaction performance. However evaporation can be minimised through the use of condensers.

In photocatalysis the rate depends on the ease at which the light can be absorbed onto the surface of the TiO_2, therefore the absorption spectrum of the compound can have a large effect on the reaction rate. If the sample is a strong UV absorber as the concentration increases then more UV light will be absorbed by the compound instead of the catalyst. This will cause a reduction in the photocatalytic rate. The effectiveness in the light reaching the catalyst is also affected by the loading rate of the catalyst. As the photons pass through the sample vessel they will continue until they encounter a catalyst and are absorbed, if they do not encounter a catalyst they will continue through to the other side of the vessel. The more catalyst present in the vessel the higher the likelihood of the photon being captured. The more photons captured the faster the reaction happens. This rate will continue to rise as the loading rate is increased until the catalyst reaches a concentration where all light entering the sample vessel is captured before it can reach the far side. Increasing the loading rate further will not improve the reaction but will just effect how deeply the light can penetrate the sample vessel before being absorbed by the catalyst.

1.4 Applications of Photocatalysis in Organic Synthesis

While the standard and most widely known use of semiconductor photocatalysis is the remediation of polluted waste streams, this is not the only way that this technology can be applied. In photocatalytic destruction the reaction is carried out in water so that when the reaction proceeds the water is converted into reactive species such as hydrogen peroxide, hydroxyl radicals and superoxide[3]. All of these species are extremely reactive and will attack and break down organic wastes in the water. However, if the reaction is carried out in a solvent other that water, such as acetonitrile, then these species cannot be produced. With no intermediate compound present direct valence band oxidation may be possible[68,69].

Semiconductor photocatalysis opens the possibility of performing reactions which would otherwise require complex chemicals and extreme conditions to perform[70]. To date a number of basic oxidation processes have been reported[30,71,72] and the most important will be reviewed here.

The first example is the conversion of an alcohol into an aldehyde (figure 6)[73,74].

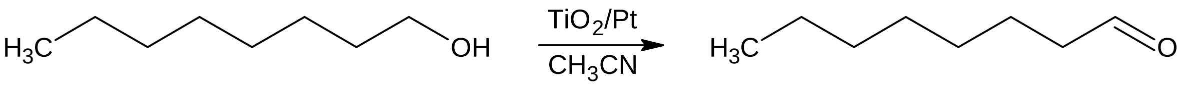
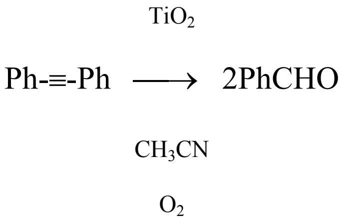


Figure 6 - Photocatalytic oxidation of an alcohol to an aldehyde

Using photocatalytic methods the conversion is a simple reaction carried out in acetonitrile with a reusable catalyst, and obtaining a high conversion yield. For the same reaction to be carried out using traditional organic synthesis techniques, the conversion would require the use of either chromic acid or hot concentrated nitric acid[75]. The use of either of these chemicals introduces handling problems, from having to use reaction vessels that can handle the acids. Also the use of acids can be a problem as they can cause the break down of the product where the compound being produced has a fragile structure, this will result in a reduced yield.

There have been a number of studies done into the oxidation of hydrocarbons using TiO_2[20,68,76-79]. One study by Hussein[80] reported the oxidation of cyclic alcohols using TiO_2, with yields of between 60 to 98% recorded. These were obtained using a 400 W mercury lamp for 8-15 hour and a benzene solvent. The use of benzene makes the results hard to replicate as the carcinogenic properties of benzene have made it a controlled substance, however the authors mention that the use of acetonitrile as a replacement solvent did not effect the yield.

The reaction displayed in figure 7 show the use of photocatalysis for oxidative cleavage of a carbon-carbon triple bond[29,30,81-83]. This is normally performed using strong oxidising agents such as acid permanganate or acid dichromate. Using these reagents, however yields are generally low, and the reaction is seldom useful. The reaction can be carried out with $KMnO_4$ dissolved in benzene containing the crown ether dicyclohexano-18-crown-6. A mixture of aqueous $KMnO_4$ and $NaIO_4$ on sand has also been applied.



$$\text{Ph-}{\equiv}\text{-Ph} \xrightarrow[\substack{\mathrm{CH_3CN} \\ \mathrm{O_2}}]{\mathrm{TiO_2}} \text{2PhCHO}$$

Figure 7 - Photocatalytic cleavage of a carbon-carbon triple bond

The reaction in figure 8 was examined by Fox[81] and Chen[68], during a study on photocatalysed oxidative cleavage. The study used TiO_2 in acetonitrile irradiated with a Rayonet photochemical reactor equipped with RPR-black lights (λ=350 ±30 nm) for 6 hours. The reaction gave an 85% conversion of the reactant, with an 84% yield of the product, the remaining 16% appearing as by-products.

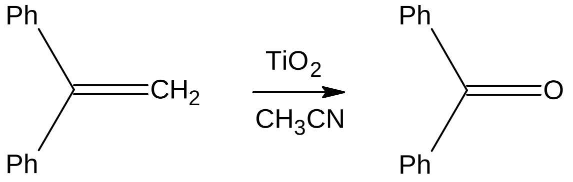


Figure 8 - Oxidative cleavage of carbon-carbon double bonds

The mechanism for the reaction proposed by the author is that the 1,1,diphenylethylene reacts with a positively charged hole to create a radical cation. This then reacts with dissolved oxygen to become dioxetane before continuing on to become benzophenone (figure 9).

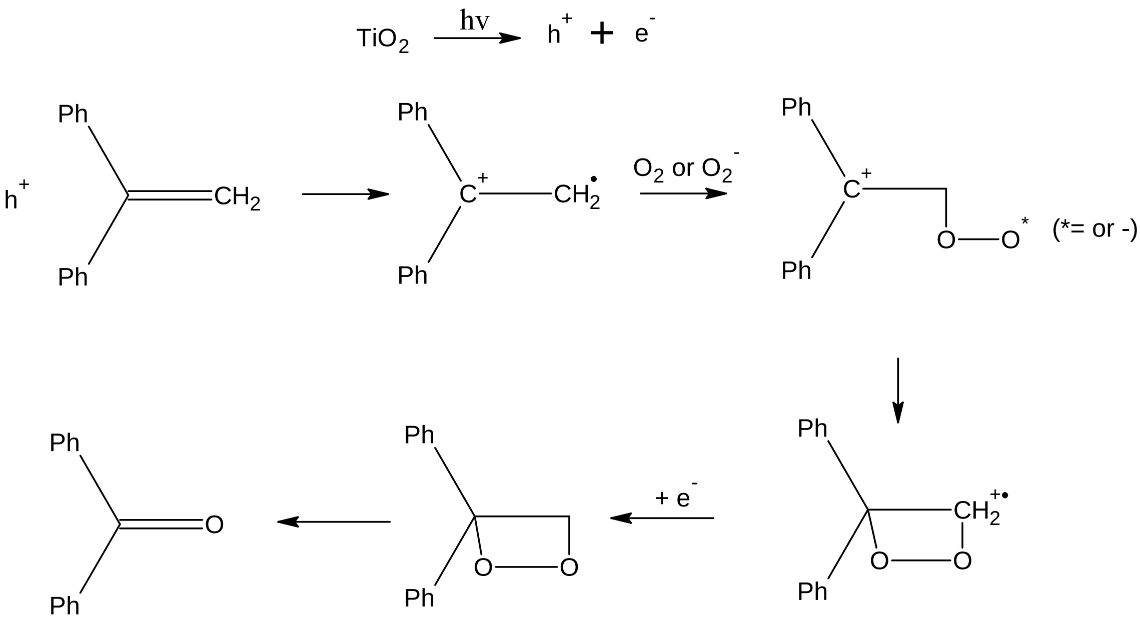


Figure 9 - Expanded reaction of the oxidative cleavage of carbon carbon bonds

Figure 10 shows the reduction of an amide to an aldehyde, a conversion normally carried out using $LiAlH_4$, (semiconductor reduction is not very common due to the low reduction potential of the Conduction band of most semiconductors). Using this reagent, however it is not always possible to prevent further reduction and primary alcohols are frequently obtained. It can however be carried out using semiconductor photocatalysis[6,76,84,85].

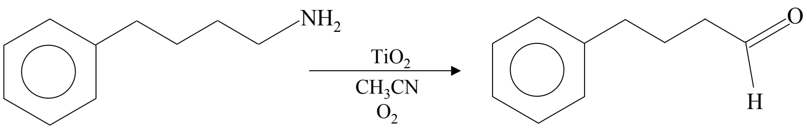


Figure 10 - Photocatalytic reduction of an amide to an aldehyde

In 1983 Fox et al. reported on the use of photocatalysis for the synthesis of primary and secondary amines. They looked at two compounds, N-methyl-4-phenylbutylamine and its demethylated analogue. These were in an oxygenated acetonitrile solution containing platinized TiO_2 powder and irradiated at 350 nm for 4 hours. They found that on oxidation the N-formylation (30% yield) and the oxidative cleavage product (25% yield) were produced.

Joyce-Pruden et al.[6] examined the use of photocatalysis for the reduction of benzaldehyde, benzyl alcohol and hydro-benzoin. The samples in the study were exposed to 350 nm light and anatase TiO_2 in ethanol that had been purged with nitrogen. They reported that reduction only occurred with the electron-deficient aldehydes. They also stated that the reduction potentials for electron-deficient aldehydes such as benzaldehydes were near the conduction band energy of TiO_2 (-0.85 eV vs SCE), resulting in them being easily reduced by the semiconductor. The reduction potentials of electron-rich aldehydes are significantly lower; as a result they are far less reducible due to their poor ability to accept an electron from TiO_2. This was because order to photoreduce a chemical species the conduction band of the semiconductor must be more negative than the reduction potential of the chemical species. Conversions of up to 82% were reported for the conversion of benzaldehyde to benzyl alcohol.

Photocatalysis has also been used in a number of other reactions such as hydrogenation[86], the preparation of aldehydes, cyclisation processes, carbon-carbon bond formation, and simple oxidations[5,87-90].

The conversion of toluene to benzaldehyde was studied by Fujihira[91] in 1982 (figure 11). The reaction was the oxidation of an aromatic compound; this was as part of an examination of the possibility of using TiO_2 to produce valuable compounds from cheap raw materials. The catalysts used were Aerosil, P25 and a 99.99% anatase catalyst. These were used together with double distilled water and either a 500 W Xe-lamp or a 500 W high-pressure mercury arc lamp. The authors looked at the effects for using additives such as H_2O_2 and Cu(II) to improve the reaction performance, together with the adjustment of the pH of the reaction. By adjusting the conditions the authors were able to obtain yields of either 77% cresol or 61% benzaldehyde from toluene.

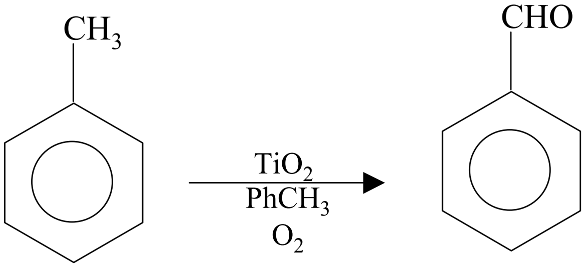


Figure 11 - Conversion of toluene to benzaldehyde

In 1983 Nishimoto et al[92] reported on the use of photocatalysis for the conversion of primary amines to secondary amines as well as cyclisation (figure 12). This study used anatase TiO_2 with Ar-purged distilled water and a 500 W high-pressure mercury lamp with an irradiation time of 20 hours. The study reported yields of between 7% (dipropylamine) and 67% (pyrrolidine), depending on the reactant, along with a number of minor products. Among these products were 1-propanol and propionaldehyde, the appearance of these oxygenated products indicates that the water has taken part in the reaction.

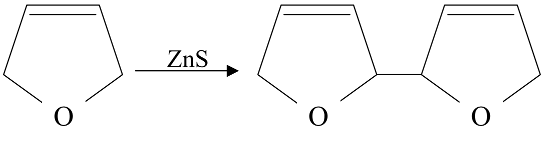


Figure 12 - Production of carbon-carbon bonds

The oxidation of N-acetyl-3-pyrroline was reported by Pavlik et al.[28] in 1981 (figure 13). The study was carried out using anatase TiO_2 in aqueous suspensions of the amines, and investigated a number of factors involved in the reaction. Pavlik reported that the reaction required light, TiO_2 and oxygen, with no reaction being observed when the reaction was carried out with a nitrogen purged solution. However it was found that Cu(II) could also be used as an oxidant in the reaction. When the reaction was carried out with copper sulphate added to the solution it was observed that the Cu(II) was reduced to copper metal. The study gave good results with yields of up to 90% reported.

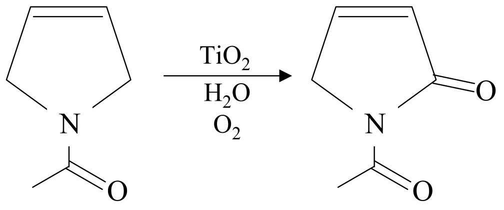


Figure 13 - Oxidation of N-acetyl-3-pyrroline into a lactam

A wide range of different chemical reactions can be initiated by the photocatalysts providing in some cases new synthetic routes for generating otherwise inaccessible products. The photocatalysts also have the advantage of providing greater reaction control as the reaction can be stopped instantly by switching the light source off. The problems of reactor design for scale up of the process, improved product yield for some reactions still have to be addressed; however these difficulties may be surmountable in the future.

1.5 Steroids

Steroids are a group of organic compounds essential for healthy living. They are normally biologically derived and can be found in both plants and animals[93]. They can be characterised by a carbon skeleton of four fused rings, three six-membered rings and a five-membered ring (figure 14). Their structural variations are primarily due to differences in the side chains attached at carbons 10, 13 and 17[94] (10 and 13 normally being methyl groups) as well as the saturation of the bonds within the rings.

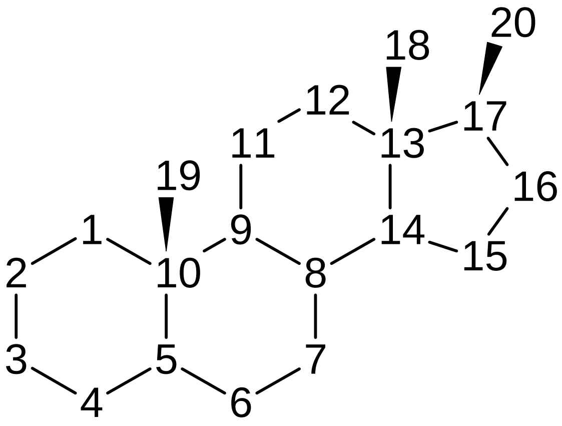


Figure 14 - General structure of a steroid showing the numbering used for naming

The structure of a steroid is determined by its rings, the structure of these being effected by things such as double bonds, however the main ring found within a steroid is cyclohexane. With the cyclohexane ring the compound can assume a number of different structural conformations. Among these are the chair, half-chair, twist-boat and boat (figure 15). The group is free to switch between the different conformations although it spends most of its time in the chair conformation. This arrangement gives the greatest distance between all of the carbons and so has the lowest energy. Roughly 99.9% of cyclohexane molecules are in the chair arrangement at any time. The half-chair has the highest energy, with much of the structure being almost planar.

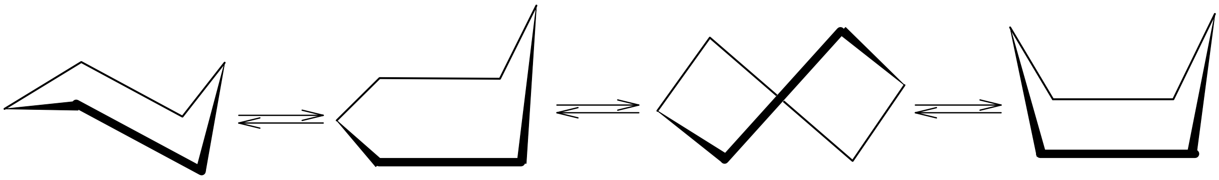


Figure 15 - Conformation structures of cyclohexane in the chair (far left), half-chair (left), twist-boat (right) and boat (far right)[93]

In steroids the chair is the conformation most commonly found although this can be affected by the presence of doubled bonds. The presence of a double bond in a six-membered ring results in a flattening of the chair conformation in the region of the double bond, this results in the molecule adopting the half-chair conformation (figure 16). However in steroids the interlocking of the rings locks the conformation, stopping the structure from freely switching between conformations.

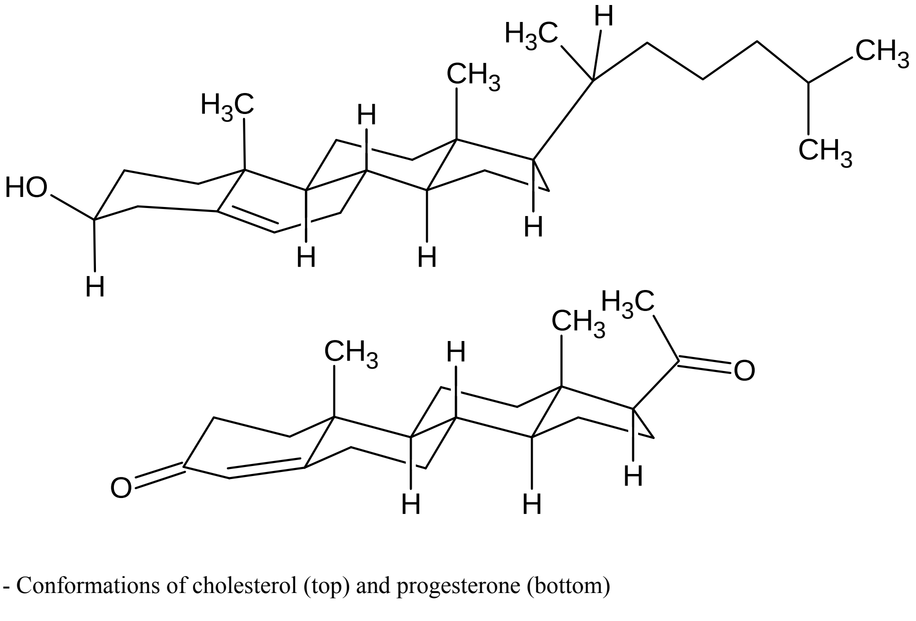


Figure 16 - Conformations of cholesterol (top) and progesterone (bottom)

The most common steroid is cholesterol (figure 17), serving as a structural component in cell membranes. The other function of cholesterol is as a precursor to many other steroids through biosynthesis. The body obtains cholesterol through the diet as well has being able to syntheses it from smaller molecules.

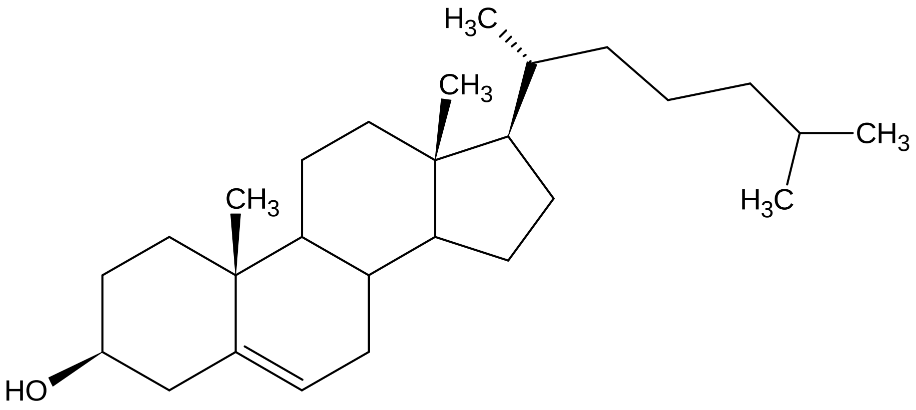


Figure 17 - Molecular structure of cholesterol

Most cholesterol is metabolised in the liver to bile acid, the rest is used in the synthesis of other steroids. Humans derive all their steroid hormones from cholesterol. Two classes are synthesised in the adrenal gland; mineralocorticoids and glucocorticoids, while sex hormones are produced in the male and female gonads. Figure 18 shows a chart of some of the steroids synthesised from cholesterol.

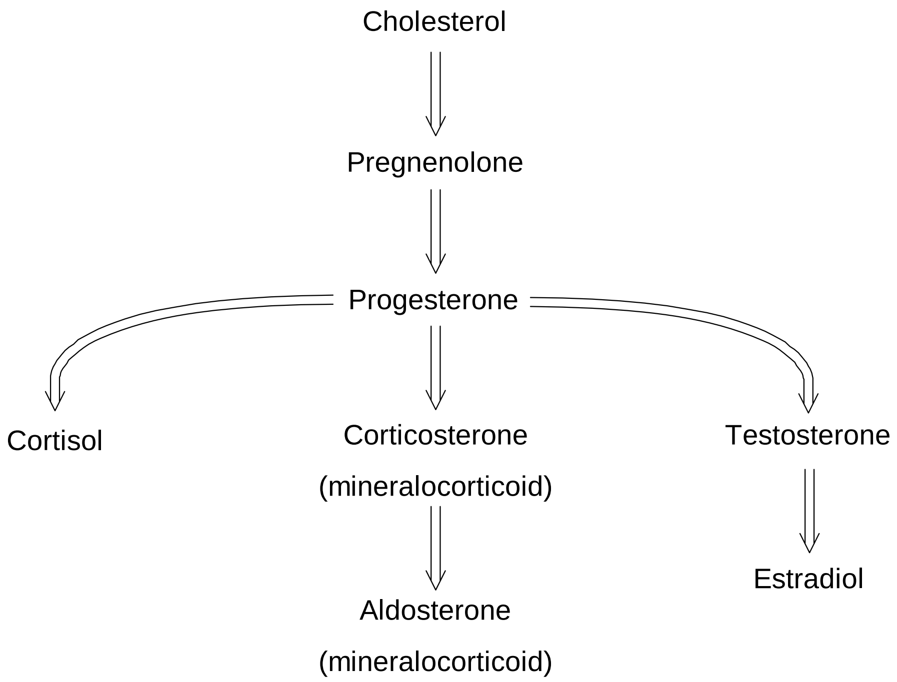


Figure 18 - Chart of the metabolism of cholesterol[96]

Synthetic steroids (those not obtained from the human body) for pharmaceuticals are obtained from a wide variety of sources. Some are totally synthetic; being produced totally through laboratory procedures. Others steroids are obtained from plants; progesterone can be derived from wild yams and soy. And other steroids are obtained from other biological sources; the estrogens found in one of the most common hormone replacement treatments are extracted from pregnant mare’s urine. All these sources are used and more continue to be found. This search continues as steroids have a number of useful functions.

1.6 Steroid Hormones

Steroids serve as hormones in the body. Hormones are chemical messengers, serving to regulate functions within the body. These processes include maintenance of blood pressure, blood volume, electrolyte balance, sexual development and reproduction, hunger and digestion. Steroid hormones move through the bloodstream from their site of production to the target tissues. Once there they bind to highly specific receptor proteins and trigger changes. With peptide, amine and eicosanoid hormones they act from outside the target cell via surface receptors, while steroid, vitamin D, retinoid, and thyroid hormones enter the cell and act through receptors in the nucleus. Because of the high affinity of hormones for their receptors only very low concentrations are needed.

Steroids work by binding to receptor proteins, causing changes in gene transcription and cell function. As they have the ability to easily effect the functions of the body they are extremely useful as medicinal drugs, replicating, blocking or even enhancing the effects of naturally occurring steroids in the body.

Of the steroids synthesised in the body there are several classes of steroids, each performing a different vital function within the body. Androgen and oestrogen effect sexual development and the function of the body (androgen in males, oestrogen in females). They regulate sexual differentiation and sexual behaviour patterns. Another steroid is progestin which mediates the menstrual cycle and pregnancy. Mineralocorticoids regulate the excretion of salt and water by the kidneys, whereas glucocorticoids affect carbohydrate, protein and lipid metabolism in addition to affecting a wide variety of other functions including inflammatory reactions and the capacity to cope with stress. One of the most important steroids found in the body is cholesterol[93]. It is very common within the body, being the compound from which the body synthesises all other steroids.

As is the case with all chemicals there are dangers when even beneficial drugs are present in the body in excess, potentially resulting in a number of problems. Oestrogen for example has been found to be important in the development of breast cancer[95], while testosterone in excess can be involved in the development of prostate cancer. However the development of new steroids for pharmaceutical purposes offers an important area for the development of new drugs.

Among the most important steroids derived from cholesterol are the sex hormones. One of the female sex hormones is progesterone (figure 19). Progesterone plays an important role in pregnancy, performing a large number of vital roles. Those include suppressing ovulation during pregnancy and causing an increase in the growing of uterine tissue at the site of egg implantation. If pregnancy does not occur progesterone levels decrease leading to menstruation. Its important role in controlling pregnancy has made it a source of great interest in the development of new drugs. Its ability to stop ovulation makes it of use in the creation of chemical contraceptives, stopping egg production and so preventing the possibility of pregnancy. Progesterone itself is not used as an oral contraceptive as it is not absorbed into the body well through the stomach. In oral contraceptives synthetic progesterones (progestins) are used.

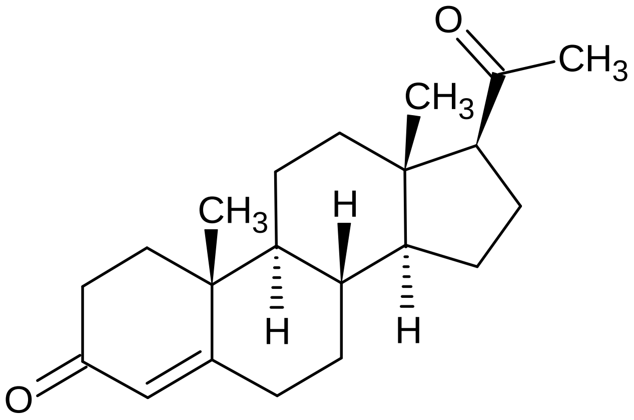


Figure 19 - Molecular structure of progesterone

Its role in pregnancy has also made it of interest in the development of drugs for uses other than contraceptive. While the presence of progesterone can prevent pregnancy from occurring, the blocking of progesterone can terminate pregnancy. This is done through the use of anti-progesterones, compounds with a higher affinity to progesterone receptor sites than progesterone. When both the progesterone and anti-progestins reach the receptor site the anti-progestins competitively bind to the sites. This blocks the progesterone from being able to bind and so no message is sent (figure 20).

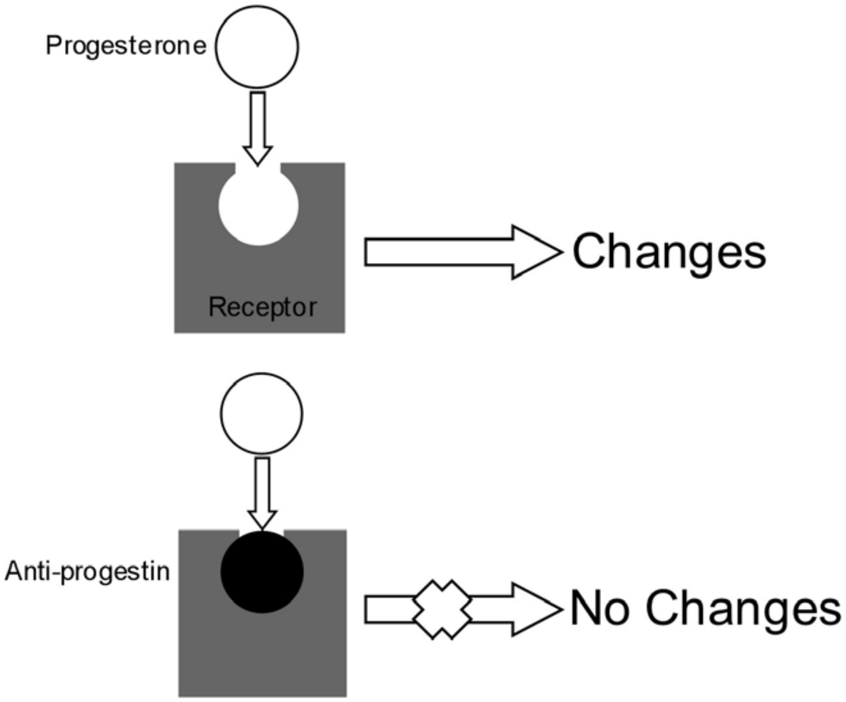


Figure 20 - Effect of anti-progestins on the ability of progesterone to bind to progesterone receptors

One anti-progestin is Mifepristone (also known as RU 486). It has the chemical name 11β-(4-dimethylaminophenyl)-17β-hydroxy-17-(prop-1-ynyl)-estra-4,9-dien-3-one (figure 21). In the presence of progesterone Mifepristone competitively binds to the progesterone receptor. It has been found to have an affinity 2-10 times greater than progesterone.

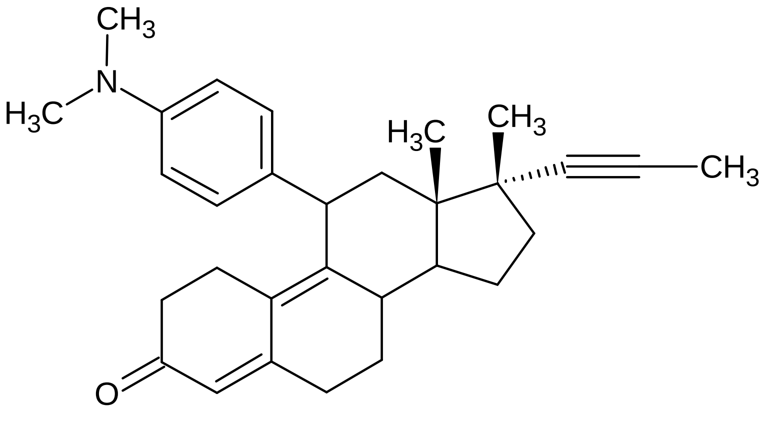


Figure 21 - Molecular structure of Mifepristone

Mifepristone is one example of a synthetic steroid, however there are many more. By manipulating and controlling hormones within the body a range of functions can be controlled. Therefore new and better drugs are always being developed, what is created only being limited by the ability of the synthesis techniques to produce the compounds. Because of this chemical synthesis techniques are always being examined for potential applications in the synthesis of new pharmaceutical drugs.

1.5 Aims and Objectives

It is clear that there is a growing demand for greener chemical production techniques in chemical synthesis. Photocatalysis has been shown in the past to be a method which allows chemical reactions to be performed without many of the harmful chemicals normally required. However it is an area of photocatalysis that has not been examined as deeply as some of the other applications of the technique. It opens up the possibility of synthesising new pharmaceuticals. This is the aim of this research project, to examine some of the influences effecting photocatalytic oxidation and attempt to synthesis a new steroid aided by the technique.

Therefore the objectives are:

- ⇒ Synthesis of a steroid.
- ⇒ Photocatalytic oxidations of a range of compounds with structural similarities to the steroid; to examine the influence of neighbouring groups on the ability of the compound to be oxidised.
- ⇒ Photocatalytic oxidation of the synthesised steroid.

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Chapter Two

Materials and Methods

2.1 Materials

All chemicals used were purchased from Sigma Aldrich or Fischer Scientific and were of general purpose grade or better.

2.1.1 Chemicals

Chemical		Supplier
2-Chlorocyclohexanol		Aldrich
Copper sulphate, anhydrous		Fischer
Cyclohexane		Aldrich
Cyclohexanol		Aldrich
Dehydroepiandrostanone (DHEA)		Aldrich
Dichloromethane		Fischer
Ferric chloride		Aldrich
Ferric sulphate		Fischer
Magnesium sulphate		Fischer
-Menthol		Aldrich
2-Methylcyclohexanol		Aldrich
1,10-Phenanthroline		Fischer
Potassium acetate		Fischer
Potassium oxalate		Fischer
Pyridine, anhydrous		Fischer
Sodium acetate		Fischer
Sulphuric acid		Fischer
1,2,3,4-Tetrahydronapthol		Aldrich
p-Toluene sulphonyl chloride		Aldrich

2.1.2 Titanium dioxide

Type	**Particle size/ nm**	**Purity**	**Source**
P25	30	99%	Degussa
Anatase	150	Min 99%	Aldrich
UV100	<10	99%	Sachtleben Chemie
PC500	5-10	82-86%	Millenium

2.1.3 Solvents

Solvent	**Detail**	**Supplier**
Acetone	Bench grade	Fischer
Acetonitrile	HPLC grade	Fischer

2.2 Equipment

2.2.1 Lamps

2.2.1.1 Coil reactor lamp

The coil lamp was a 15 W General electric black light, this was normally used as the light source of a photocatalytic coil flow reactor but was removed for use in this experiment. Figure 22 shows the emission spectrum of a black light.

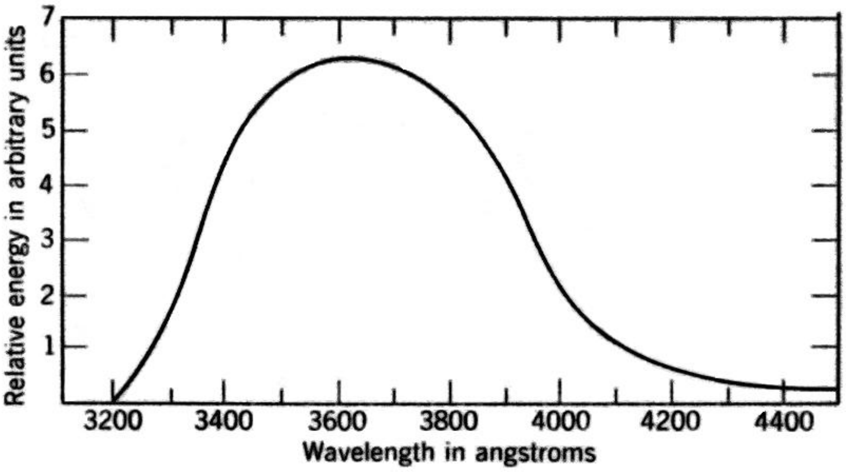

Figure 22 - Emission spectra of a UV Blacklight source[5]

2.2.1.2 Striplight

The lamp used was a 120 cm 40 W black light, this was placed parallel to the sample so that the centre of the lamp was the closest point to the sample.

2.2.1.3 Half moon lamp

The half-moon lamp consists of six 8 W Philips blacklight UV bulbs arranged in a curve.

2.2.1.4 Box lamp

The UV source used here was a Dr Hönle UVA Spot 400/T, a 450 W mercury lamp. This was a high powered lamp that required a separate power adapter and was fan cooled. Figure 23 shows the emission spectra of the lamp.

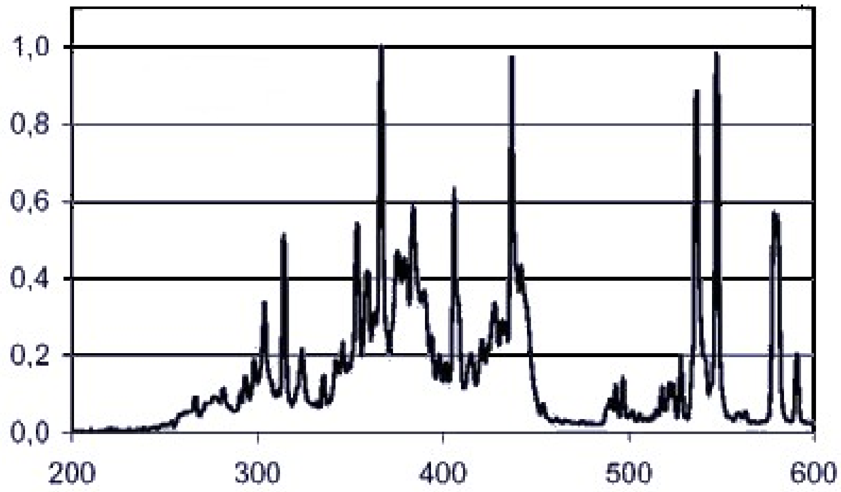

Figure 23 - Emission spectra of 450 W box lamp

2.3 Analytical equipment

2.3.1 UV/Vis Spectroscopy

The UV spectra were obtained with a Perkin Elmer UV/Vis spectrometer Lambda 2.

2.3.2 FTIR

FTIR analysis was performed using a Perkin Elmer Spectrum GX FTIR system with an HATR set-up.

2.3.3 GCMS

The GCMS data was obtained with a Hewlett Packard 5890 series II GCMS fitted with a ZB-5 column. The thermal program used by the GCMS over the duration of the analysis was as follows: The oven temperature increased to 70 °C where it remained for 1 min, it was then ramped 15 °C per min for 15 min taking the oven temperature to 230 °C where it remained for 1 min.

2.3.4 Thin Layer chromatography (TLC)

The TLC was performed using an acetate/cyclohexane mixture (1:3) as a mobile phase on a silica plate.

2.3.5 Ferric Chloride analysis of samples

The ferric chloride test is a traditional colorimetric test for the detection of phenolic compounds, using a 1% solution neutralised with sodium hydroxide. A small amount of the sample solution was placed in a test tube, to this was added several drops of Ferric chloride indicator, on reaction with a phenolic compound a blue/black colour would develop[7]. Where problems occurred due to the immiscibility of the indicator with acetonitrile several drops of ethanol was added to help the indicator to dissolve into the solution.

2.4 Methodology

2.4.1 Preparation of Potassium ferrioxalate[4]

Ferric chloride (40.45 g, 0.15 mol) was dissolved in distilled water (100 ml) by heating in a water bath, Solution A. Potassium oxalate (82.9 g, 0.45 mol) was dissolved in distilled water (300 ml) by heating in a water bath, Solution B. Following dissolution of both samples, Solution A was added to Solution B forming a green coloured solution. All of this work was carried out in darkroom conditions. The green coloured solution was stirred vigorously prior to placing the flask in ice to cool the solution and promote the formation of potassium ferrioxalate crystals. The flask was left for 10 min until the solution was as cold as possible. The solution was then poured through a Buchner funnel to collect the precipitate, which was dried under suction. The precipitate was recrystallised in distilled water twice before being dried in a vacuum oven.

2.4.2 Preparation of Calibration Graph

2.4.2.1 Calibration Solutions

0.4x10^{-6} mol of Fe^{2+} in Sulphuric acid[6].

Ferric sulphate (1.52 g, 0.01 mol l^{-1}) was dissolved in sulphuric acid (100 ml, 0.1 mol l^{-1}) to prepare a standardised 0.1 mol l^{-1} $FeSO_4$ solution. A 0.4x10^{-6} mol l^{-1} solution was prepared by diluting with sulphuric acid (0.1 mol l^{-1}).

1g per litre of 1,10 phenanthroline in water[6].

1,10 phenanthroline (0.25 g) was added to a 250 ml volumetric flask. This flask was filled to the mark with distilled water. The flask was shaken until all solids have been dissolved.

pH 3.5 Buffer solution[6].

Sodium acetate (300 ml, 1 mol l^{-1}) was added to sulphuric acid (180 ml, 0.5 mol l^{-1}). The solution was diluted to 500 ml with distilled water.

2.4.2.2 Procedure[6]

Into a series of 20 ml flasks the following volumes of Fe^{2+} (0.4x10^{-6} mol) 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 ml were added. A sufficient volume of sulphuric acid (0.5 mol l^{-1}) was added to adjust the volume to 10 ml. Phenanthroline solution (2 ml) was added to this, and the flasks were filled up to the mark with buffer. The flask was shaken vigorously before being poured into a plastic centrifuge tube and placed in the dark. The samples were left over night before being transferred to a PMMA cell with a 1 cm path length, and the absorbance at 510 nm recorded.

2.4.3 Actinometric Solutions

Potassium ferrioxalate soln.

Potassium ferrioxalate (2.947 g) was added to a 1 litre volumetric flask and the flask filled to the mark with distilled water. The flask was shaken until all of the solids had dissolved.

2.4.3.1 Procedure

Ferrioxalate solution (4 ml) was placed in a cell with a 10 mm path length, and placed at a distances of 20, 40, 60, 80, 100 and 120 cm from the UV source. The cell had a small magnetic follower added to stir the solution. The preparation was performed under red light conditions (the light being turned off during the experiment). The cell was exposed to the UV light for a set amount of time (this varied depending on the power of the lamp used as well as the lamp to cuvette distance) before the room was returned to red light conditions. Due to the differing times it took the different lamps to warm up the sample was kept covered until the source had warmed up. The solution was transferred from the cell to a 20 ml volumetric flask, to this was added of phenanthroline solution (2 ml) (as section 2.2.2), and buffer (2 ml) (as section 2.2.2), following the procedure outlined in section 2.2.2.2. The flask was made up to the mark with distilled water, and the flask shaken. The contents of the flask were transferred to a plastic centrifuge tube and left in the dark overnight. About 4 ml of the solution was transferred into a PMMA cell and the absorbance at 510 nm recorded. This was repeated so that three readings were taken at each distance for all of the cell types: PMMA, quartz, and glass.

2.4.4 Synthesis of 6β-Hydroxy-3α,5-cyclo-5α-androstan-17-one[8,9]

Dehydroepiandrosterone(DHEA), (1 g, 3.47 mmol, Aldrich) was dissolved in 10 ml of anhydrous pyridine. To this stirring solution was added p-toluenesulfonyl chloride (0.67 g, 3.52 mmol, Aldrich). During dissolution and for a period thereafter of 30 min, an increase in the solution temperature was noted. The reaction mixture was then allowed to stand at room temperature for 16 hours. After this period the pyridine hydrochloride salt had precipitated out of solution. 10 ml of cold (0 ˚C) distilled water was added to allow dissolution of the salt and cause complete precipitation of the steroid product. The slightly off white solid was then filtered, washed further with cold distilled water and dried by vacuum. (1.4 g, 92%)

Then to a solution of the tosylated DHEA (1 g, 2.26 mmol) in 100 ml acetone was added 30 ml of distilled water containing 1g of potassium acetate (KOAc). This mixture was then heated under reflux for 6 hours. After cooling, the solution was extracted with 5x 50 ml portions of dichloromethane (CH_2Cl_2). The organic layer was then dried with magnesium sulphate and the solvent removed using RFE (Rotary Film Evaporation). The product, a white solid was recrystalised from 70% acetone. (0.53 g, 75.8%).

2.4.5 Photocatalytic oxidation of Cyclic alcohols

1×10^{-3} mol l^{-1} of the reactant compound was prepared in 170 ml of acetonitrile in a 250 ml beaker. The resulting solution was air-sparged for an hour. After the hour 50 ml of the solution was poured into three round bottomed flasks and air condensers were fitted, the remaining solution was then poured into a sample bottle and kept for comparison. The air condensers were attached to prevent the solvent evaporating over the duration of the experiment from heat generated by the UV lamp. In order to determine if the results obtained were the result of the photocatalytic reaction and not produced through another mechanism, such as photolysis due to the UV light or a reaction with the catalyst, the three flasks were each treated under differing conditions during the reaction.

0.1 g of catalyst was added to two of the flasks. One of those flasks was kept in the dark and stirred magnetically at room temperature. The remaining flasks, one with TiO_2 added and the other without, were placed 25 cm in front of the UV light source with a magnetic stirrer used to keep the catalyst suspended within the solution. The flasks were irradiated for twelve hours with samples taken every hour. In order to perform optical analysis some of the samples were passed through an acrodisc syringe filter to remove any catalyst present.

2.5 Actinometric analysis

2.5.1 Actinometry

Actinometry is a chemical method for that can be utilised in determining the light output of a light source. When an actinometric solution is irradiated it undergoes a photochemical transformation which can be easily measured. By measuring this change it is possible to determine the number of photons the solution has absorbed. Theoretically any substance when exposed to irradiation undergoes a photochemical transformation and if its quantum yield is known it can be used as a chemical actinometer. One commonly used actinometric compound is Potassium ferrioxalate[1], although there are others available such as 3,4-dimethoxynitrobenzene[2] and benzophenone-4-carboxylic acid[3], as well as others, each absorbing light over a slightly different range.

When a solution of ferrioxalate is exposed to UV light the Fe^{3+} ions are reduced to Fe^{2+} ions (eqn 1).

$$2\,Fe^{3+} + C_2O_4^{2-} \xrightarrow{hv} 2\,Fe^{2+} + 2\,CO_2 \qquad \text{Eqn 1}$$

This change can be determined by adding phenanthroline to the solution; this is a complexing agent which complexes with Fe^{2+} (figure 24).

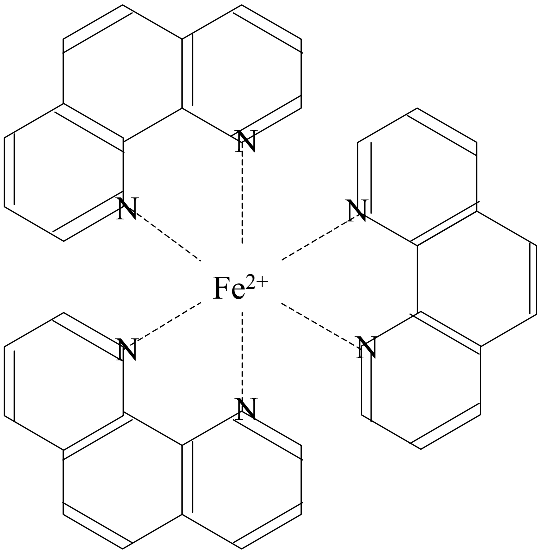

Figure 24 - Structure of Fe^{2+} complexed to phenanthroline

The complex, which has a red/orange colour, can be measured by recording its absorbance at 510 nm. Figure 25 illustrates the colour change of the Fe^{2+}-phenanthroline complex with increasing concentration.

Figure 25 - Photo of the colour range of Fe-Phenanthroline from weakest (left) to strongest (right)

Actinometry allows the analysis of the UV output of lamps, this is useful as it makes it possible to determine how much energy a sample absorbs during an experiment. By looking at the energy absorbed it is possible to see the effect of the different cuvette materials on the quantity of light absorbed by the sample.

Figure 26 shows the light absorption spectra of potassium ferrioxalate, the grey area shows the absorption, this is the light absorbed by the ferrioxalate under the conditions used.

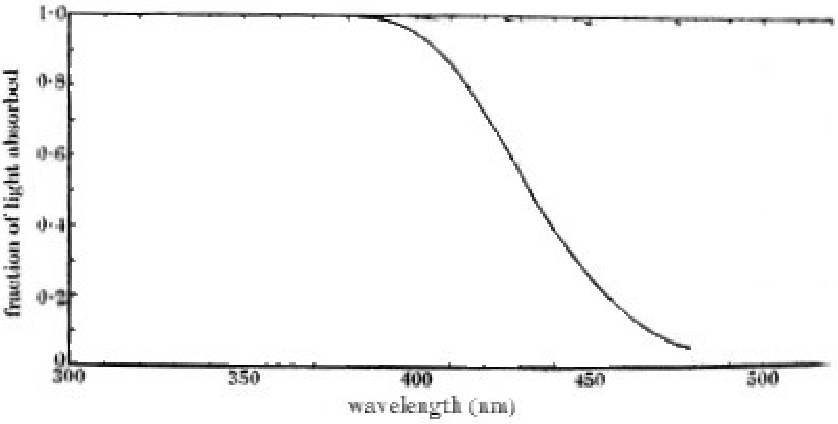

Figure 26 - Absorption spectrum of potassium ferrioxalate[4]

The experiment investigated four different lamps; a 15 W and 40 W striplight, a lamp composed of six 8 W bar lights, and a 450 W box lamp. All of these lamps are UV blacklights apart from the Box Lamp which is a mercury lamp. Figure 24 shows the emission spectrum of a Blacklight UV source. When the emission spectrum of black light is compared to the light absorption spectrum of potassium ferrioxalate it can be seen that virtually all of the light emitted by the lamps will be absorbed.

Figure 27 illustrates the UV absorbance spectra of PMMA, Quartz and glass cuvettes between 200 and 500 nm. When the absorption spectrum of cuvettes are compared with blacklight emission, figure 24, it can be clearly seen that the cuvette material should have little effect on the results obtained.

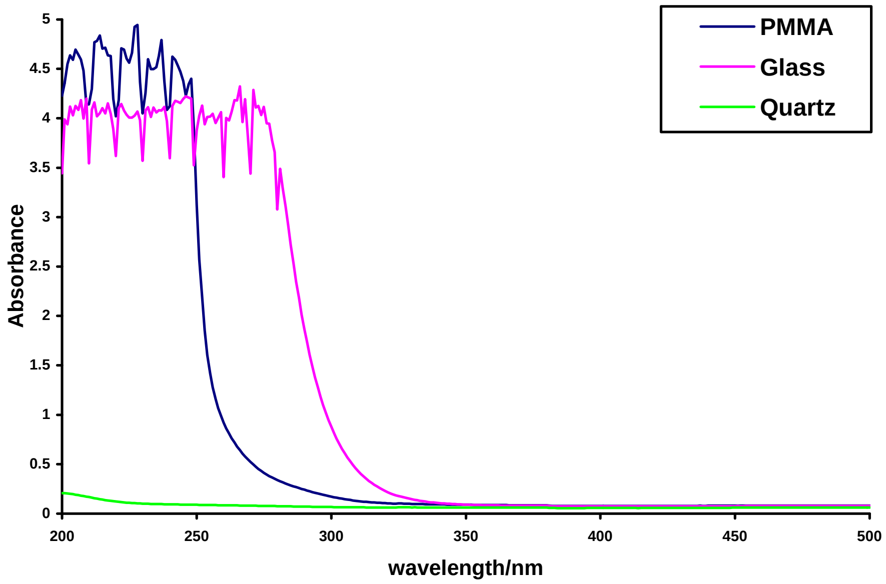

Figure 27 - UV absorbance spectra of cuvettes of PMMA, glass and quartz

The materials the cuvettes are made from have a variety of UV absorbances, some absorb more of the UV spectrum than others. If these materials are absorbing the UV light themselves then it will mean that the light can not pass through to the solution inside. This means that depending on the wavelength of the light source and the absorbance spectra of the sample then the cuvette could have a large effect of the amount of photons reaching the sample.

2.5.2 Calibration

A calibration chart was produced using solutions of known Fe^{2+} concentrations, measuring the absorbance of the complexed Fe^{2+}. Figure 28 illustrates the calibration chart of the UV absorbance of a group of solutions of known Fe^{2+} concentration.

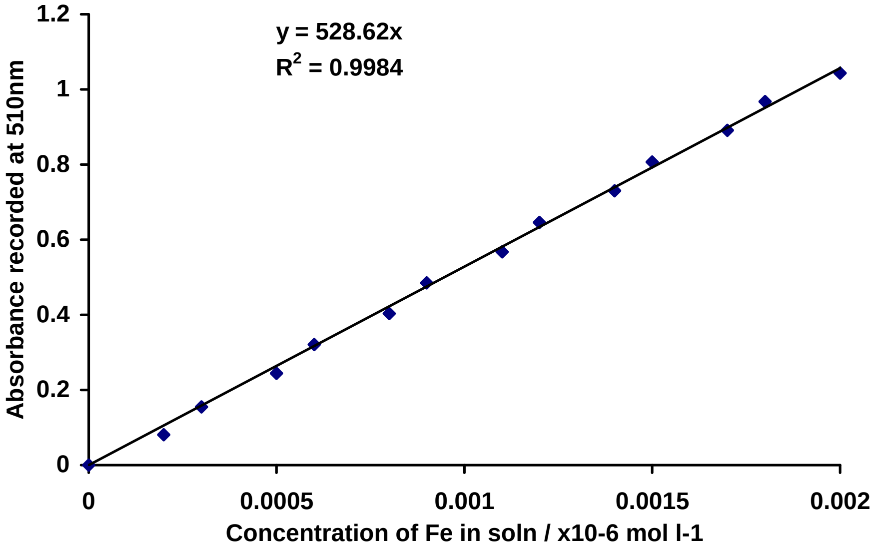

Figure 28 – Calibration chart of potassium ferrioxalate at 510nm

The calibration chart uses the absorbance at 510 nm of a range of solutions of a range of Fe^{2+} concentration. When plotted the increase in absorbance with concentration is linear. The equation of the line was calculated, and by using the equation it was possible to determine the concentration of Fe^{2+} in a solution from the recorded absorbance of the complex at 510 nm.

The relationship between the absorbance and concentration can be expressed as:

$$D_{AC,\lambda}(t) = \varepsilon_{AC,\lambda}\, l[Ac]$$

Where $D_{AC,\lambda}$ is the absorbance of the solution at wavelength λ.

t is the time

$\varepsilon_{AC,\lambda}$ is the molecular coefficient of the actinometer at the wavelength of irradiation ($mol^{-1}cm^{-1}$)

l is the optical path length of the irradiation cell (cm)

Ac is the concentration of the actinometer ($mol\ l^{-1}$)

2.5.3 Summarised Absorbance Data with Fe^{2+}

The actinometry was performed using the four UV lamps at distances of 20, 40, 60, 80, 100, 120 cm from the lamp to the actinometric solution. In addition the effect of glass, PMMA (Perspex) and quartz cuvettes was examined. Experiments were performed in triplicate to minimise experimental error.

2.5.3.1 Coil Lamp

Figure 29 illustrates a graph of the data obtained from the experiments with the 15 W coil lamp showing the data for all three cuvette materials. The coil lamp gave slightly different results to the other lamps as at 20 cm distance from the lamp there was no difference observed in the rates obtained from the different materials, which continued at 40 cm. A small jump was recorded in the PMMA at 60 cm but this is likely due to an abnormal reading among the data, this however was minimised through the use of multiple runs. Ignoring the anomalous reading at 60 cm the rate reacted as expected for the rest of the experiment, dropping by a half from 40 to 60 cm before becoming more linear.

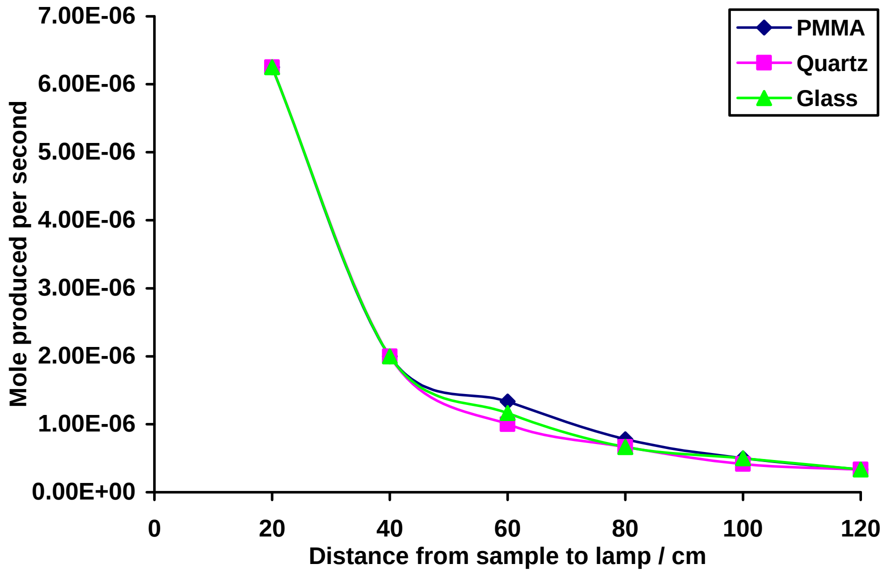

Figure 29 - Moles of Fe^{2+} produced per second at varying distances from the 15W coil lamp

2.5.3.2 Striplight

Figure 30 illustrates the chart of the data obtained from the 40 W black light, showing the reduction in the rate of moles produced per second as the sample to lamp distance is increased. The data from the 40 W black light shows a curving line, between 20 to 40 cm the rate dropped very rapidly, halving over the 20 cm distance. From 40 to 60 cm the rate dropped from 7x10^{-6} mol s^{-1} down to 4x10^{-6} mol s^{-1}, not quite halved. The rate continued to drop beyond 60 cm but at a far slower rate. A small difference could be detected in the rates, with the PMMA with a rate of 1.44x10^{-5} mol s^{-1} ±0.07x10^{-5} showing a slight lead over the quartz at 1.40x10^{-5} mol s^{-1} ±0.017x10^{-5}, and the glass giving the poorest rate at 1.37x10^{-5} mol s^{-1} ±0.059x10^{-5}. This trend continued at distances of 20 to 40 cm, with the differences slowly decreasing. As the distance from the lamp increased the differences in the rates between the three materials became increasingly smaller. At 60 cm distance and greater all three materials gave rates that were almost identical to one another.

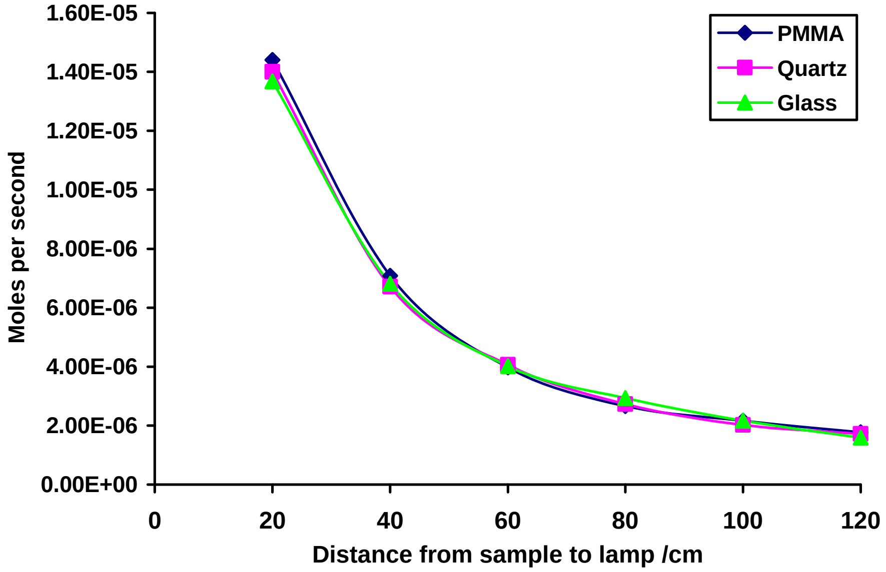

Figure 30 - Moles of Fe^{2+} produced per second at varying distances from the 40W black light

This indicates that the effect of the different cuvette materials on the absorption of light by the potassium ferrioxalate is small enough that it is only distinguishable at high light intensities and even the differences here can be explained by standard deviation. As the sample gets further from the light source the scattering of the light as it moves away from the source reduced the amount of light falling on any one area, therefore as the light source to cuvette distance is increased the number of photons falling on the sample decreases.

2.5.3.3 Half-Moon Lamp

Figure 31 illustrates the chart of the data obtained from the experiments using the half-moon lamp. The results for the 6x8 W half-moon lamp were similar to that obtained for the 40 W black light, the differences in rates between the different cuvette materials being most noticeable closer to the light source. With the strip lamp the quartz cuvette gave the best rate at a distance of 20 cm of 3.7×10^{-5} mol s^{-1} with PMMA second with a rate of 3.5×10^{-5} mol s^{-1}. The differences in materials decreased as the distance from the lamp, the only anomaly observed was a small jump in the rate of the glass cuvette at 80 cm, due to an inconsistent reading. The other two sample runs performed at that distance with the glass cuvette gave results which followed the trend for the data already taken.

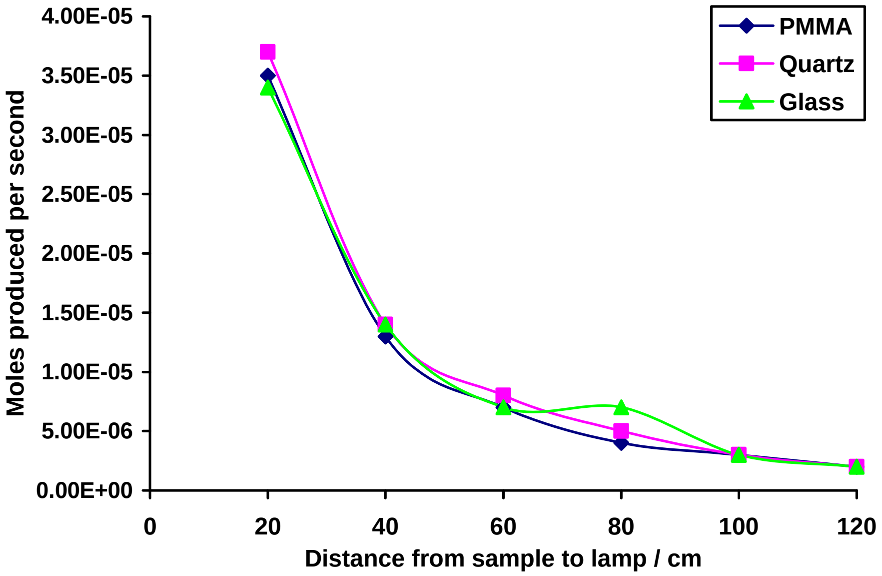

Figure 31 - Moles of Fe^{2+} produced per second at varying distances from the 6x8 W half-moon lamp

2.5.3.4 Box Lamp

Figure 33 illustrates a chart of the data obtained from the 450 W box lamp, showing the rate of moles produced per second against the sample to lamp distance. The box lamp showed the same trend to that of the less powerful lamps, some small differences in the rates at 20 cm which decreased as the cuvette to light source distance increased. The rates were considerably greater than that of the other lamps as would be expected. The strongest of the other lamps gives around 48 W in comparison to the 450 W of the box lamp. There was little difference observed at distances of 60 cm and greater. In this case the PMMA cuvette gave the best rate at 20 cm with the quartz second. The reduction of the rate followed that of the other lamps, from 20 to 40 cm the rate halved, from 40 to 60 cm it halved again, before becoming more linear.

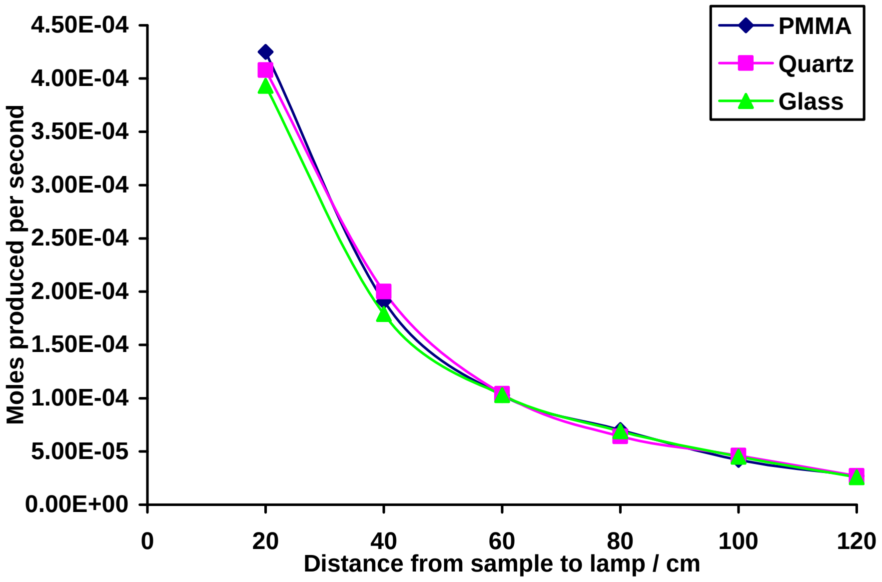

Figure 32 - Moles of Fe^{2+} produced per second at varying distances from the 450 W box lamp

2.5.4 Incident Photon rate

The incident photon rates recorded from the four different lamps did not show any great difference between the three cuvette materials investigated. This was not entirely unexpected as the absorbances of the cuvettes do not greatly overlap with the absorbance of the potassium ferrioxalate.

Table 1 - Incident photon rates at 20 cm distance with differing UV sources and cuvettes

Cuvette type	Striplight 40 W (mol s^{-1})	Half-moon 6x8W (mol s^{-1})	Box lamp 450 W (mol s^{-1})	Coil reactor lamp 15 W (mol s^{-1})
Glass	1.10E-05 ±0.057E-05	2.73E-05 ±0.05E-05	3.17E-04 ±0.16E-04	5.07E-06 ±0.04E-04
PMMA	1.16E-05 ±0.059E-05	2.81E-05 ±0.11E-05	3.43E-04 ±0.10E-04	5.00E-06 ±0.06E-06
Quartz	1.13E-05 ±0.014E-05	2.95E-05 ±0.02E-05	3.29E-04 ±0.14E-04	5.18E-06 ±0.04E-04

Table 1 illustrates a chart of the incident photon rate of the three cuvettes at 20 cm distance between the sample and the UV source. In the study the highest rate was at distance of 20 cm, decreasing as the distance increased. The data shows that the differences between the different cuvettes are small, and that none of the materials show any clear advantage over the others. When the standard deviation is included it is clear that this has more to do with the differences observed between the different samples than the materials the cuvettes are constructed from. The data from the 40W striplight shows that the difference between highest to lowest was only 0.06×10^{-5} mol

s^{-1} but the error levels are as high as $0.059\text{x}10^{-5}$ mol s^{-1}. This deviation is enough that no material can be determined to have performed better than the others as a shift in data that is within the calculated standard deviation could result in any of the samples giving greater performance.

The data from the half-moon lamp is again interesting, the difference from highest to lowest is $0.22\text{x}10^{-5}$ mol $s^{-1}$with a maximum error of $0.11\text{x}10^{-5}$ mol s^{-1}. The error on the glass and quartz are small but that on the PMMA is enough that while the data indicates that the quartz is best and glass worst, the PMMA could switch places with the glass and have a rate very close to that of the quartz. Therefore again the standard deviation is enough that no sample can be clearly said to perform best.

The boxlamp gave data with a range of $0.26\text{x}10^{-4}$ mol s^{-1} with a maximum error of $0.16\text{x}10^{-4}$ mol s^{-1}on the glass. If the error is included on the glass it is possible to reach $3.33\text{x}10^{-4}$ mol s^{-1}which is the lowest the PMMA can reach if the error is included. So again when errors and are included there is no significant difference between samples. The coil reactor lamp gave a range of $0.18\text{x}10^{-6}$ mol $s^{-1}$with a maximum error of $0.06\text{x}10^{-6}$ mol s^{-1}. The errors are small and as a result the quartz sample is ahead of the others. The errors on the glass and PMMA are enough that neither can be said to give better performance.

The data clearly shows that while the data does appear to show some samples performing better than others, when the errors are included the differences between samples disappear. In addition even if the error is ignored no sample can be shown to be consistently better, even when it is just the three blacklights are examined. Therefore it is clear that the differences in data are just due to standard deviation.

2.5.5 Actinometry summary

This experiment did an actinometric study examining a range of UV sources of varying power as well several cuvettes of varying material. These would be used for an actinometric examination of the effect of lamp power, lamp to sample distance, and the effect of the absorbance of light by the cuvette on the total light reaching the sample.

The results were used to produce a straight line graph which could then be used to convert absorbance data into concentration of Fe^{2+}. It was possible to use this information to determine the mole production rate by dividing the total number of moles produced by the irradiation time. Then using the following formula[6]:

$$IncidentPhotonRate = \frac{\Delta n_{Ac}}{\Phi t}$$

It was possible to determine the incident photon rate where Δn is the number of moles reacted, t is the irradiation time in seconds, and Φ is the quantum yield. Quantum yield is normally specific to a particular wavelength and reference tables of these can be found within most books on actinometry, such as Rabek[6].

In this experiment polychromatic light was used and therefore these tables are not a useful reference as they give only the quantum yields of potassium ferrioxalate under monochromatic light. The standard technique for determining quantum yield is comparative by using another solution of known quantum yield. There are no tables of data for quantum yields of potassium ferrioxalate under polychromic light. However quantum yields of materials do not fluctuate greatly as the wavelength is changed so it is possible to use 1.24 which is an average quantum yield value for potassium ferrioxalate[6], this is because potassium ferrioxalate is a stable actinometric solution, making it a good solution to use. This can therefore be used to determine the incident photon rate.

However, when greater than 99% of the rate at which light is absorbed by the solution is equal to the incident photon rate. Using a 1 cm path length greater than 99% of the UV light should have been absorbed and as a result the above rule can be applied.

The charts of the data show that the rate dropped in a similar way for all of the lamps tested. There were some differences between the lamps but these were in scale, due to the differences in lamp power, rather than differences in shape. The variations in shape were mostly due to the presence of anomalous readings, however these could be reduced by using averages of all three runs for each point. The graphs also show similar results for all of the cells used so as was predicted there did not seem to be a difference in incident photon rate when different cell materials were used. Although this would be different if the absorption went below 300 nm as the differences in the UV absorbances of the materials start to vary below that.

From the data it is clear that while some differences could be observed in the different materials, once taking the standard deviation into consideration illustrates that the differences are not significant. Study of the data shows that the influence of the wattage of the lamps used is far greater. The use of a material such as quartz will be very minimal in the UV region being used. A powerful lamp will make much more effect. This is useful to know as using quartz containers in experiments would add to experimental costs.

2.5 References

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Chapter Three

Synthesis of a Cyclo Steroid

3.1 Introduction

At the beginning of the twentieth century the world population was estimated at 1.65 billion people. By the end of the century this figure had risen to over six billion[1]. This ever growing population places greater and greater demands on fuel, food and water supplies.

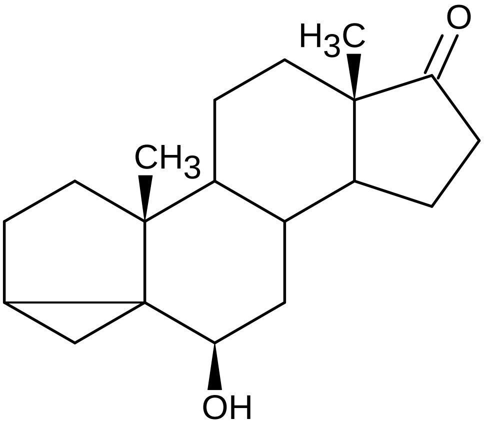

Figure 33 - Structure of 6β-hydroxy-3α,5-cyclo-5α -androstan-17-one

6β-Hydroxy-3α,5-cyclo-5α-androstan-17-one (figure 34) is one compound that has been examined in the search for new drugs. Its effects on male rats have been examined[2] but its effect on the female reproductive system have not. However previous RGU studies have indicated that it possesses progestational or anti-progestational activity. The biological activity generated by the presence of the cyclopropane ring is not known however it appears to have a structural effect. The structural requirements of compounds to fit progesterone receptors are known[3]. It has been found that the progesterone ring A is key to binding, with binding only occurring with the ring in the 1β,2α half-chair conformation rather than the more common 1α,2β half-chair conformation. The conformation of the structure created by the presence of the cyclopropane ring is similar to that of the 1β,2α half-chair conformation. Figure 35 shows the conformational structures of the 1β,2α half-chair and cyclosteroid cyclopropane ring.

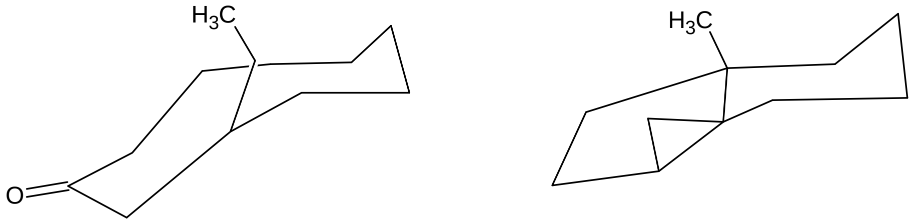

Figure 34 - Conformation structures of the 1β,2α half-chair and cyclosteroid cyclopropane ring

However the cyclosteroid will not have the ability to form hydrogen bonds in the 2C (β-face) area of the molecule; a general requirement for good progesterone receptor affinity. As such it would be a weak progestin. The cyclopropane ring also has interesting chemical properties, despite the 60° angles of the bonds it is more stable than it should be. This appears to be due to σ-aromatisation which aids in the stabilisation of the ring. The group while saturated exhibits reactivity similar to that of an unsaturated compound. One effect of the presence of the cyclopropane ring is that it would exclude it from oral administration as the ring would be easily destroyed in the stomach.

The goal of this project was the synthesis of a steroid through normal chemical synthesis techniques. This compound would then be ready to be oxidised photocatalytically. This oxidation is possible with Jones[4] (CrO_3 in concentrated sulphuric acid) or Collins' reagent[5] (dipyridine CrO_3 complex in dichloromethane). The problem with these methods are the use hexavalent chromium, an extremely dangerous substance that is highly toxic, carcinogenic and genotoxic. Therefore a less harmful oxidation technique would be necessary if the steroid were to be produced on a large scale. An examination of its oxidation by photocatalysis might offer an alternative oxidation method for the synthesis.

3.2 Synthetic Pathways

The reactions used in the synthesis were relatively straight forward to perform experimentally, and are considered as standard methods[6]. The first stage is the tosylation of the DHEA (dehydroepiandrostanone), this is performed through the addition of toluenesulphonylchloride. Figure 36 illustrates the tosylation reaction. The toluenesulphonylchloride reacts with the hydroxyl group in the DHEA, this results in the formation of the tosyl group and a hydrochloric acid molecule. This is a standard method for the attachment of a leaving group at 3-C[7,8].

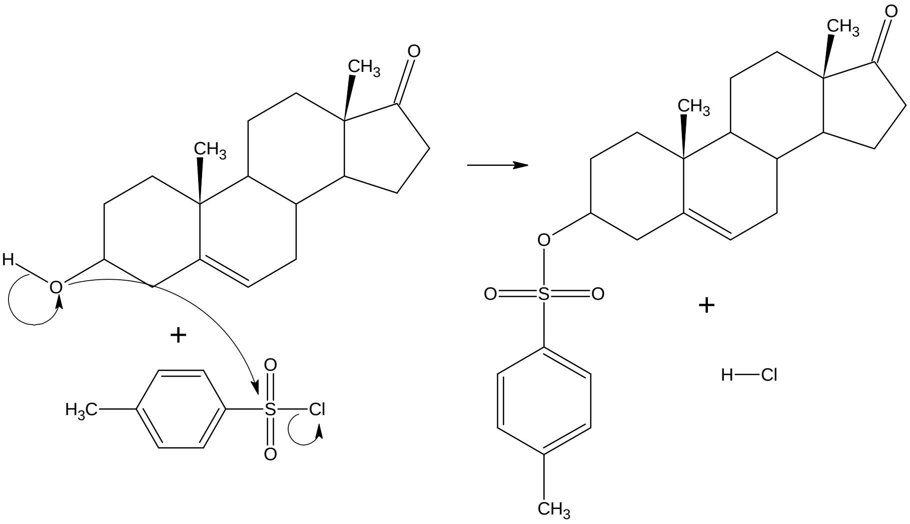

Figure 35 - Diagram of the tosylation reaction

The next reaction to be performed is the creation of the three-membered ring, this is best demonstrated through a two stage diagram. The first stage is the removal of the tosyl group from the steroid through the reflux reaction, this loss leaves a positive charge on carbon 3. Figure 37 shows the diagram of the reaction, with the loss of the tosyl group from the steroid and the production of a cationic species.

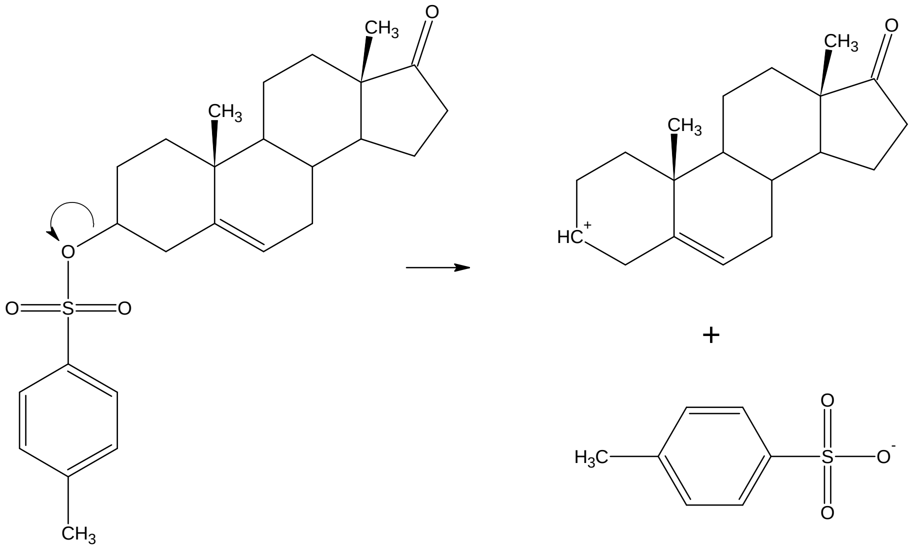

Figure 36 - Diagram of the reflux of the tosylated steroid

Figure 38 shows the second stage of the reaction. This occurs due to the positive charge, it allows a re-arrangement reaction to occur in the presence of acetate. One of the bonds between carbon 5 and 6 moves creating a new bond between carbon 3 and 5. This turns a six-membered ring into a six-membered ring containing a three-membered ring.

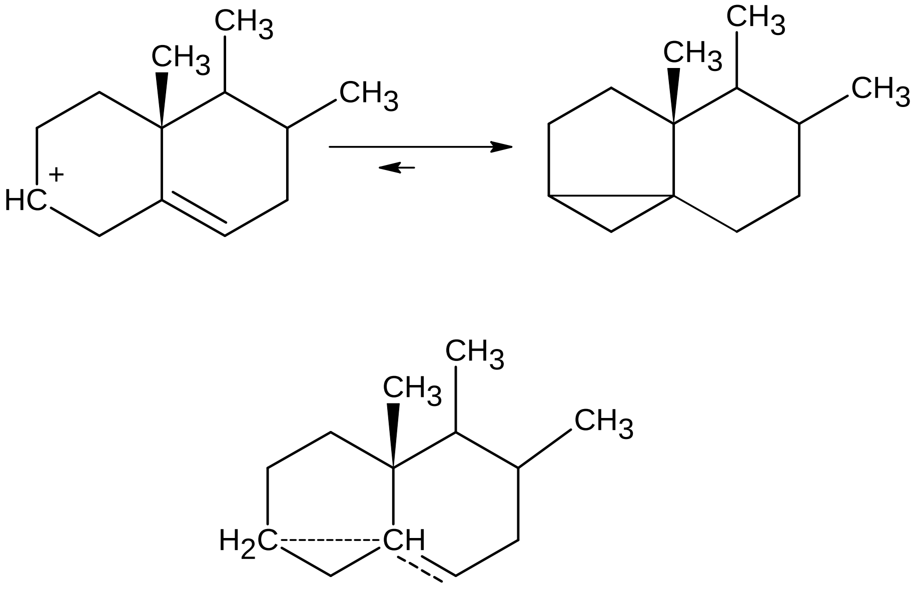

Figure 37 - Diagram of the molecular re-arrangement

Figure 39 shows the last stage of the reaction. This is a reaction between the steroid and water, a hydroxyl group attaches to the steroid at the site of the positive charge, producing the final compound.

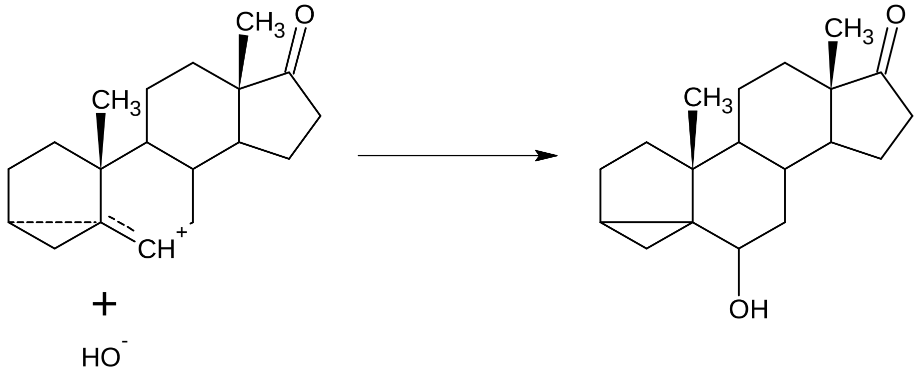

Figure 38 - Diagram of the reaction with water

3.3 Results and Discussion

The synthesis was to first convert the DHEA to a tosylated form before it was converted to the cycloandrostanone. The tosyl group is a very good leaving group, when it was removed it would allow the formation of the three membered ring. Once the synthesis had been performed the initial analysis was carried out using thin layer chromatography (TLC) to determine whether any change in the sample had occurred. On testing the TLC indicated the presence of new compounds within the sample.

The next analysis was performed using FTIR fitted with a horizontal attenuated total reflectance (HATR) setup. In this system the light beam is bounced off mirrors into a long flat crystal. Once inside the crystal the beam undergoes total internal reflectance, bouncing off the walls of the crystal repeatedly before leaving the crystal and being directed to the detector. However when total internal reflectance occurs a small amount of the light passes beyond the walls of the crystal. These are called evanescent waves. If the sample is present on the crystal then the evanescent waves can pass across the boundary of the crystal, and absorbed by the sample. The light absorbed by the sample can be detected and used to build up an absorption spectrum of the sample. This system is useful as it can be used on a wide range of samples, from liquids to solids without any sample preparation.

The first sample to be analysed was the starting compound, DHEA; this would serve as a baseline to help in highlighting changes. Unsurprisingly most of the IR spectrum of DHEA is due to C-C and C-H bonds (figure 40), however there are a number of groups within the structure that can be used to aid in the analysis. The peaks at 3465 cm^{-1} were due to the presence of the hydroxyl group attached at carbon 3, while the peak at 1731 cm^{-1} was due to the carbon-oxygen double bond at carbon 17. The peaks at around 2800-3000 cm^{-1} were due to the various C-H bonds.

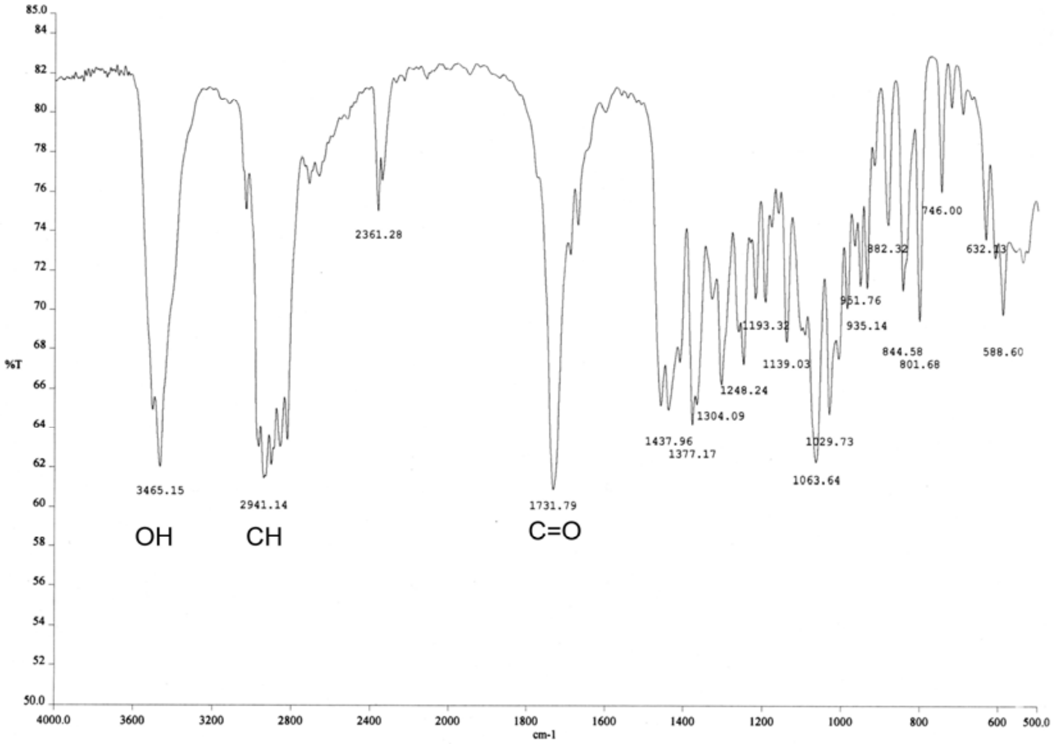

Figure 39 - IR spectrum of DHEA

With a baseline established the analysis of the product of the tosylation reaction could be carried out. The expected product of this was 3β-tosyl-5-androstan-17-one. If the reaction occurred as expected then this would be seen easily. In the tosylation the hydroxyl group on the DHEA at carbon 3 should be replaced by a tosyl group. The addition of this new group would be expected to generate several new peaks on the IR spectrum at around 1350-1400 cm^{-1} and 1150-1200 cm^{-1} due to the R-O-SO$_2$-R.

Examination of the FTIR spectrum of the product showed that the reaction had occurred as planned (figure 41). Comparing the product spectrum with that obtained from the DHEA showed a large reduction in the size of the hydroxyl peak at 3448 cm^{-1}, as expected. This showed a change had occurred at the hydroxyl group, with the hydroxyl being lost in the reaction. The presence of the hydroxyl peak in the tosylated DHEA spectrum was most likely due to the presence of unreacted DHEA within the sample. The new peak at 1599 cm^{-1} was caused by the C=C bonds of the aromatic ring of the tosyl group. The other new important peaks were those at 1333 cm^{-1} and 1173 cm^{-1}; both corresponding to the S=O bond of the tosyl group. When brought together the analysis showed the loss of the hydroxyl from the DHEA, and the appearance of a SO_2 and an aromatic ring. This proved that the reaction had occurred as planned and DHEA successfully tosylated.

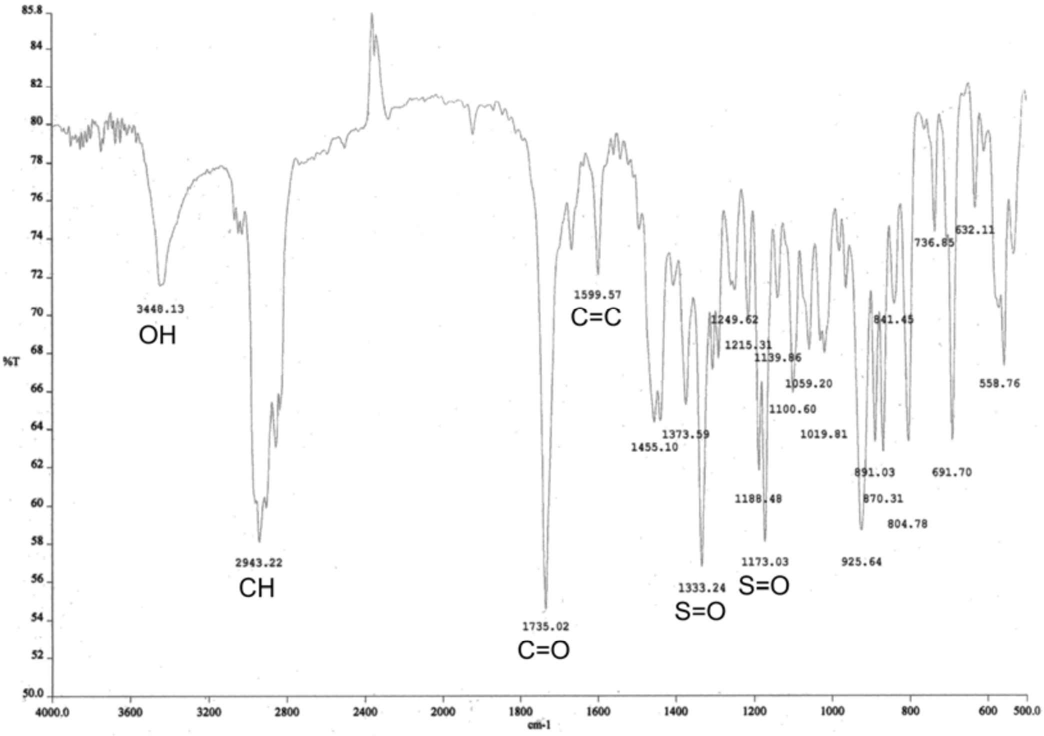

Figure 40 - IR spectrum of 3β-tosyl-5-androstan-17-one

The confirmation of the successful reaction allowed the synthesis to continue with the tosylated DHEA being used as the starting material for the final stage, the synthesis of the 6β-hydroxy-3α,5-cyclo-5α-androstan-17-one.

On completing the reaction the sample was tested using TLC to detect the presence of any new compounds (figure 42). For comparative purposes the FTIR spectrum of the tosylated DHEA was used to aid in the detection of changes. However even before examining the spectrum it was possible to say what changes would be seen in the spectrum if the reaction had proceeded as expected. When examining the chemistry of the reaction the most obvious change was the loss of the tosyl group. This would be seen as a loss of the peaks caused by the SO_2 and C=C in the tosyl. Also there would be the appearance of a hydroxyl group and the cyclopropane ring; both of which would be detected quite easily.

Analysis of the FTIR spectrum of the product showed that the peaks at 1599, 1333, and 1173 cm^{-1} which were present in the spectrum of the tosylated DHEA, and due to the tosyl group, were gone. The spectrum showed a large increase in the OH peak as 3491 cm^{-1}, which showed the appearance of a hydroxyl group in the structure. An important new peak is that at 3061 cm^{-1}, this peak is usually associated with the C-H bond of a cyclopropane group; the presence of the peak was a strong indicator that the reaction had succeeded. When the analysis was taken together it showed that during the reaction the tosyl group had been removed and a hydroxyl and cyclopropane had joined the structure.

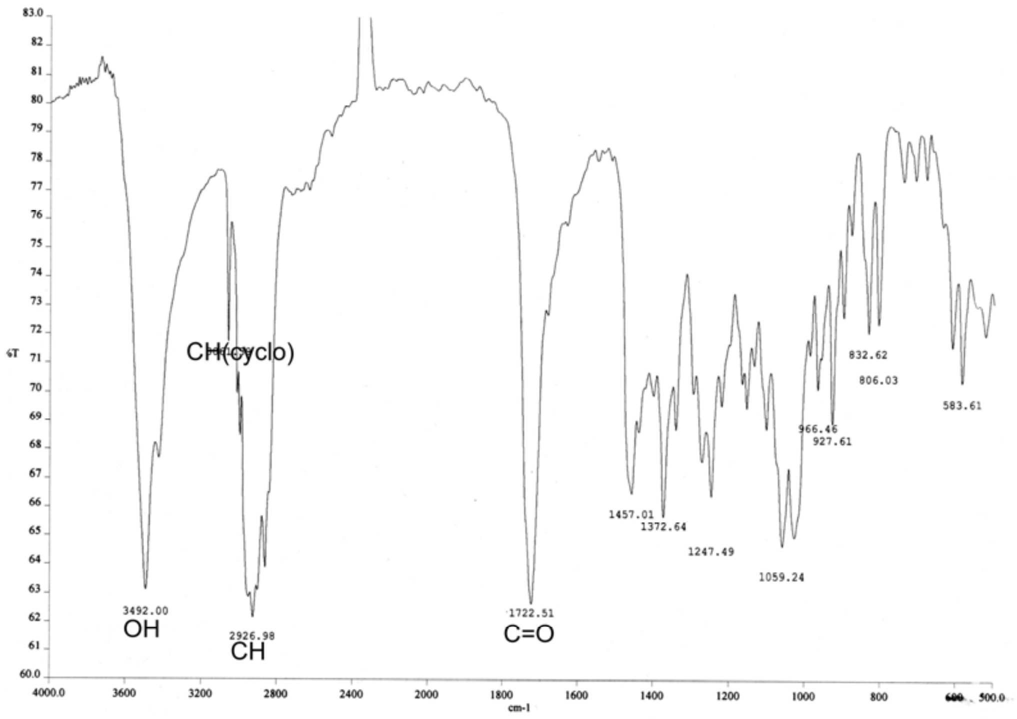

Figure 41 - IR spectrum of cycloandrostanone

The FTIR gave strong evidence that the reaction had occurred correctly, but that this would need to be checked through other techniques to confirm..

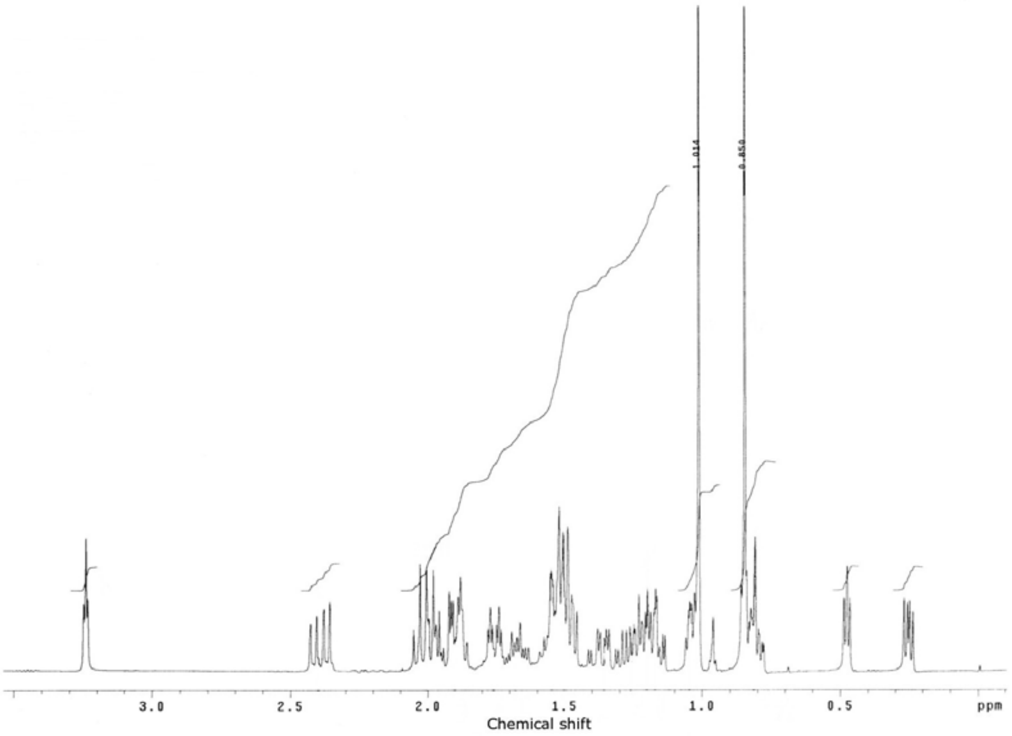

Figure 42 - ^{1}H NMR spectrum of 6β-hydro-3α,5-cyclo-5α-androstan-17-one

NMR is a powerful analytical technique that works by analysing how nuclei resonate within a powerful magnetic field, enabling accurate readings on the chemical environment around the nuclei. This data can give both the functional group the atom is within as well as the groups near it. ^{1}H NMR is a useful technique as it uses the resonance of the hydrogens in the compound to perform the analysis (figure 43).

In nmr the resonance of the atoms are affected by the other atoms near them. The presence of an electronegative atom such as oxygen will tend to unshield the atom, causing it to resonate more. This is observed as a shift in the peaks from the right to the left of the spectra. The actual number of peaks produced by each group is affected by the number of hydrogen atoms attached to adjacent atoms. If there are no hydrogens on any of the adjacent atoms then only a single peak is produced, but if one is present a doublet peak is produced, two hydrogens produce a triplet etc. The last part of the analysis is the area of the peaks of each group, this is affected by the number of hydrogens in the group. If the total number of hydrogens is known then the peak area can be used to determine how many atoms each group contains by using the percentage of the total peak area that the groups have as the percentage of the total hydrogens in the molecule. Put together the analysis can be used to determine the number of hydrogens in each group as well as showing what groups are nearby. This can be used to construct the molecular structure of the sample.

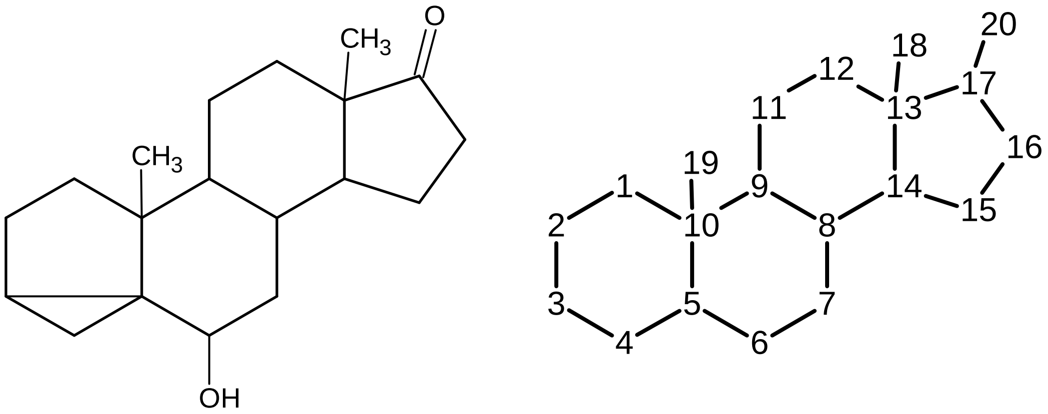

Figure 43 - Structure of 6β-Hydroxy-3α,5-cyclo-5α-androstan-17-one (left with ^{1}H analysis guide)

With the ^{1}H NMR spectrum it was possible to build up an image of the structure of the molecule. The data gives all the groups which contain H in the molecule as well as indicating which groups are neighbouring it.

The NMR analysis helped to confirm the identity of the reaction product. The analysis could be compared with the structure of the expected product to check that all the groups identified were consistent with the expected product (figure 44).

The key feature of the expected product structure was the cyclopropyl group, the identification of this in the ^{1}H NMR data would be very significant. But while the cyclopropyl ring is composed of three carbons, however as only two have hydrogens attached only those two will be detected. Therefore only carbon groups at C-3 and C-4 would be detected from the ring. Those were detected as a triplet group at 0.48 ppm and a pair of doublets at 0.25 ppm. The triplet was due to the hydrogen attached to C-3 while the peaks at 0.25 ppm were due to the hydrogen attached to C-4. The detection of these showed that the cyclisation had occurred successfully. Further NMR analysis would determine if the rest of the compound was correct and that no groups had been lost unexpectedly from the structure in the reaction. The singlet peaks at 0.85 and 1.014 ppm are due to the methyl groups at C-18 and C-19 respectively. Each bonded to a carbon to which no hydrogens are bonded. The triplet at 3.24 ppm is due to the C-5 carbon, the position being due to the presence of an OH group.

With this analysis it was possible to show that the synthesis had proceeded as expected with the correct compound produced.

3.4 Conclusion

The aim of the synthesis was to produce the cycloandrostanone from DHEA (figure 45). This was achieved adding a tosyl group to the DHEA before removing it to create a cyclopropane ring. The purpose of this was to produce a compound that could be used for a photocatalytic oxidation study.

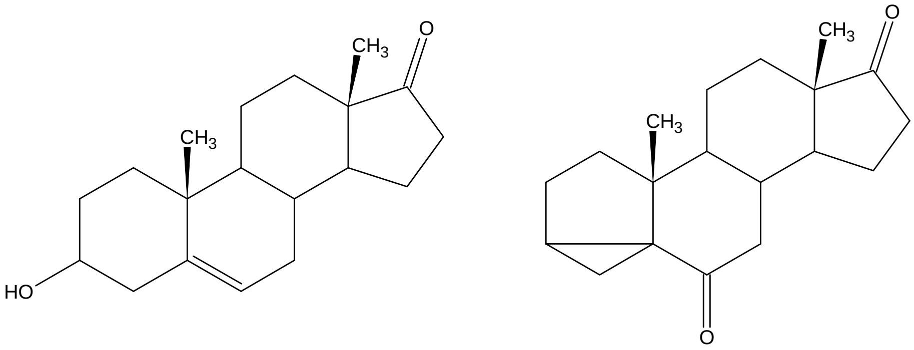

Figure 44 - Structures of DHEA (left) and the cyclosteroid ketone (right)

On completing the reaction the product was identified through the use of both FTIR and ^{1}H NMR.

The most common technique for the chemical oxidation of an alcohol is a Jones oxidation[8]. There are a number of problems with this method however, such as that most of the chemicals used are highly toxic; CrO_3 in particular is extremely toxic and carcinogenic. Also this is an aggressive reaction and tends to break bonds such as those of the cyclopropane ring, resulting in poor yields.

If the cyclosteroid were to be oxidised on any commercial scale it would be necessary to find a technique that was both safer to perform (and therefore cheaper to perform) and produced less waste compounds as by-products. Photocatalytic oxidation may offer such a technique. However it is a technique that is not fully understood and so would require that some study was made to gain a greater understanding of some of the influences on the reaction.

3.5 References

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Chapter Four

Photocatalytic oxidation of Alcohols

4.1 Introduction

4.1.1 Oxidation

While the most widely known application of semiconductor photocatalysis is the remediation of polluted waste streams[1] it is not the only application for this technology[2]. The oxidising and reducing power of semiconductor can also be used to perform other reactions than destroying compounds. That energy can be used to drive chemical synthesis. Semiconductor photocatalysis opens the possibility of performing reactions which would otherwise require dangerous chemicals to perform[5,6].

In the photocatalytic oxidation of an alcohol the reaction is carried out using a catalyst such as TiO_2 in a solvent such as acetonitrile[7-10]. For the same reaction to be carried out using traditional organic synthesis techniques, the conversion would require the use of a chemical such as chromic acid or hot concentrated HNO_3. This is an aggressive reaction that can damage weak bonds destroying the desired product, and can result in poor yields where particularly complex compounds are being oxidised. Photocatalysis offers the possibility of a less destructive reaction occurring, something that could make it a useful process in the development of new compounds for pharmaceutical use.

4.1.2 Mechanisms of the reaction

The exact mechanism of photocatalytic oxidation is something which while a number of suggestions have been put forward a definitive answer has not yet been found. However with photocatalysis there are some facts that are known.

The reaction begins when the catalyst is irradiated by light, this generates an electron in the conduction band and a positively charged hole in the valence band[2] (eqn. 1).

$$TiO_2 \xrightarrow{\lambda\nu} TiO_2\,(e_{cb}^- + h_{vb}^+) \quad \text{eqn 1}$$

Also oxygen, when present serves as an electron scavenger, mopping up free electrons and preventing immediate electron-hole recombination from occurring. This increases the length of time the electron is free to interact with compounds in the system. The product of this is the superoxide molecule (eqn 2).

$$e^- + O_2 \rightarrow O_2^{\cdot -} \quad \text{Eqn 2}$$

In photocatalytic remediation of waste streams the solvent used it the water itself, the presence of this allows the production of reactive species such as hydroxyl radicals[6] (eqn 3 and 4), and hydrogen peroxide. It is the presence of these species along with superoxide that makes photocatalysis so useful.

$$H_2O + h^+ \rightarrow \bullet OH + H^+ \quad \text{Eqn 3}$$

$$OH^- + h^+ \rightarrow OH\bullet \quad \text{Eqn 4}$$

In photocatalysis for chemical synthesis a very commonly used solvent is acetonitrile, a non-aqueous solvent. As a result of the use of this solvent the hydroxyl groups and hydrogen peroxide are not produced, and so there is less chance of further oxidation occurring beyond the initial reaction. Acetonitrile has some other uses, it has been shown that in acetonitrile primary alcohols can be oxidised in preference to secondary alcohols[8,11]. It has also been found that in acetonitrile hetroatomic sites (e.g. –OH, -NH etc) are oxidised more efficiently than are the C-C or C-H of hydrocarbons[11].

In this study the reaction that is of most interest is the photocatalytic oxidation of alcohols. When determining the mechanism it is important to remember that unlike water remediation there are no intermediate molecules such as hydroxyl or hydrogen peroxide being produced. Therefore any reaction that occurs is likely due to direct reaction between the semiconductor and the adsorbed compound rather than due to a reaction with an intermediate species such as $\bullet OH$ or OH^-. When the compound is adsorbed to the catalyst it is most likely to undergo oxidation due to the strong oxidation potential of the valence band. Infrared spectroscopic studies have found that alcohols are chemisorbed onto TiO_2 through their OH moieties[10,13]. As a result it is likely that any charge transfer from the catalyst will happen on the hydroxyl group.

A last important fact in the determination of the mechanism is the presence of oxygen dissolved in the solvent. Most authors have reported that the presence of oxygen is vital to the operation of the reaction. Some have even found, through the use of nitrogen purged systems, that the reaction can not proceed without the presence of oxygen. This evidence is interesting as even without an electron scavenger present electrons will be promoted, however their life before electron-hole recombination occurs will be far shorter. That no reaction occurred when no oxygen was present could indicate that the oxygen serves a purpose in the reaction beyond acting as an electron scavenger. It could be that the oxygen takes part in the reaction, either as O_2 or O_2^-. This could be tested by performing the reaction with a nitrogen purged system to remove oxygen and an alternative electron scavenger present. If oxygen's only duty in the reaction is as an electron scavenger then the reaction will proceed normally with the alternative scavenger, however if the reaction does not occur then it would indicate that the oxygen takes a direct role in the reaction.

One suggested mechanism is rather simplistic[6]. In this mechanism, using ethanol on ZnS, the generated hole transfers a positive charge to the alcohol, with a hydrogen being thrown off (eqn 5). This would then be followed by a second hole transfer to the alcohol, with another hydrogen ejected (eqn 6).

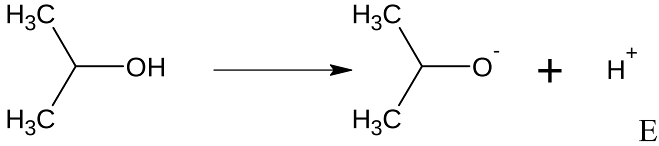
$$CH_3CH_2OH + h^+ \rightarrow CH_3CHOH + H^+ \quad \text{Eqn 5}$$

$$CH_3CHOH + h^+ \rightarrow CH_3CHO + H^+ \quad \text{Eqn 6}$$

Kisch theorises that the time between the successive absorption of two photons is extremely small, short enough that other reactions will not occur between.

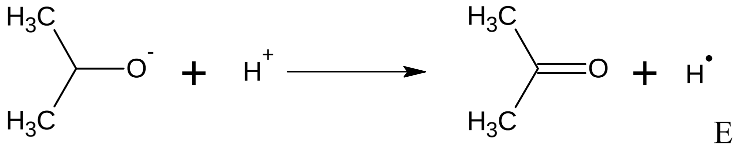
The main problem with the mechanism is its overly simplistic nature; all the events occur quickly on the surface of the catalyst with no other species taking part in the reaction. If that were so then with this mechanism the rate of the reaction should not be greatly affected by the dissolved oxygen in the solvent. But without the electron scavenging effect of oxygen, electron-hole recombination will occur more quickly. So while the reaction may be slowed, the reaction should still work. Yet it has been found that a lack of oxygen can stop the reaction from occurring[14].

A mechanism was suggested by Pichat[15] for TiO_2 photocatalytic dehydrogenation of 2-propanol. With this mechanism the electron-positive hole pairs are created as normal. The alcohol first undergoes dissociative adsorption at the semiconductor (eqn 7).



Eqn 7

The alcohol then undergoes abstraction of a second hydrogen through reaction with a positive hole (eqn 8).



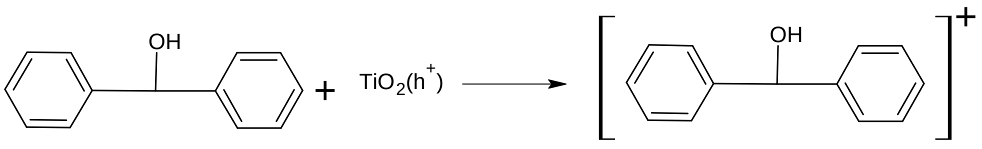
Eqn 8

One problem with this mechanism is that again oxygen appears to serve no purpose in the reaction, not even as an electron scavenger. The experiment used solvents that had been purged with nitrogen and hydrogen, which would indicate that the authors do not believe that oxygen has a purpose in the reaction. This is interesting as oxygen's role as an electron scavenger would be important to the success of the reaction. While the authors did show that a reaction had occurred no yield was given so the success of the method used is not known. Another problem with the mechanism is the dissociative adsorption. If the alcohol dissociates on adsorption then it is unlikely that the presence of any neighbouring groups would have an effect. Inductive effect works to affect the strength of the hydrogen-oxygen bond of the alcohol, something that would have little meaning if the bond was simply dissociating.

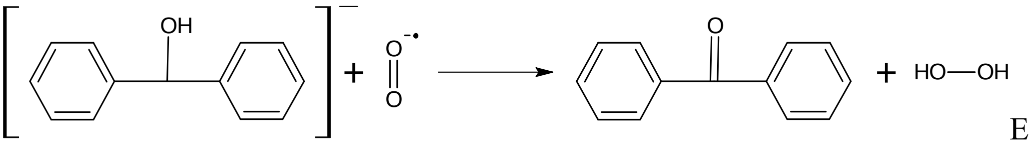
An alternative proposed mechanism was modelled on benzaldehyde oxidation with TiO_2[4]. In this mechanism the electron and hole are generated at the catalyst (eqn 9). The electron then reacts with the dissolved molecular oxygen to produce superoxide (eqn 10). While that occurs the positive charge of the hole is transferred to the alcohol producing a radical cation (eqn 11). The alcohol then reacts with the superoxide producing the ketone and hydrogen peroxide (eqn 12).

$$TiO_2 \xrightarrow{hv} TiO_2(h^+) + e^- \quad \text{Eqn 9}$$

$$e^- + O_2 \longrightarrow O_2^{\cdot -} \quad \text{Eqn 10}$$

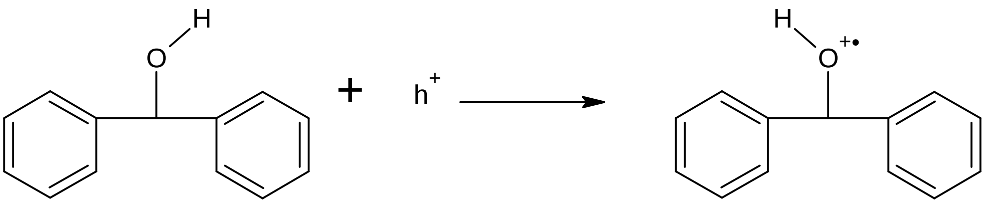


Eqn 11



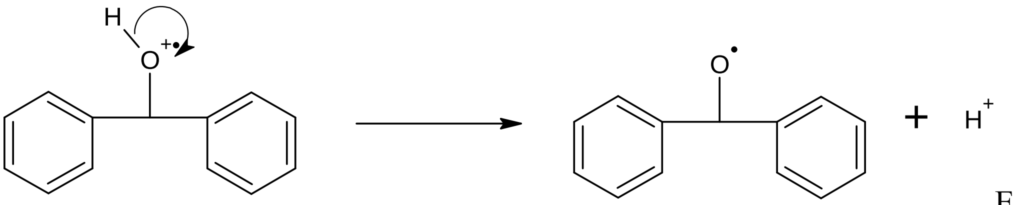
Eqn 12

With this mechanism the facts do appear to match the evidence. With this system the presence of oxygen is important to the reaction, playing an active role in the reaction. However the author does not try to look at the reaction any further than that show above. The reaction may work first though the reaction of the alcohol with the catalyst to produce a positively charge radical. The evidence that alcohols adsorb to the catalyst at the hydroxyl group would indicate that the charge would be transferred to this group rather than to another part of the structure (eqn 13).



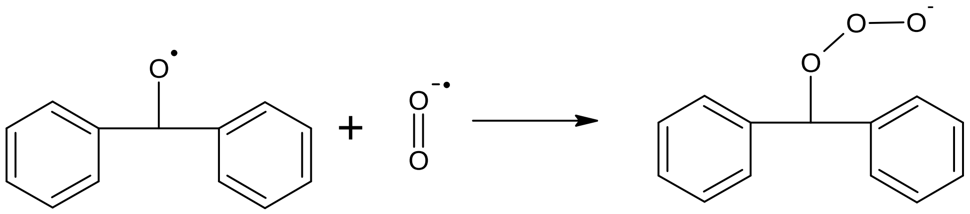
Eqn 13

This positively charged radical can stabilise itself by the removal of a positively charged hydrogen (eqn 14). This radical however can also react with an electron in an electron recombination reaction, returning the reaction to the start. Under induction theory the electrons drawn towards the oxygen serve to stabilise the O-H bond, if more electrons are drawn to the oxygen then the bond should be more stable. The effect of this should be that the presence of a nearby electron donating group should make the bond harder to break while the presence of a nearby electron withdrawing group should make it easier. If the bond is more stable then it will be less likely to eject a hydrogen atom before recombination can occur. These changes in stability would be apparent because of differences in the rate at which the alcohol reacts; a more stable compound would react more slowly while a less stable compound would react more quickly. This stage would also be affected by the presence of oxygen in the solution, dissolved oxygen serves as an electron scavenger, moping up free electrons and serving to lengthen the time before recombination can occur.



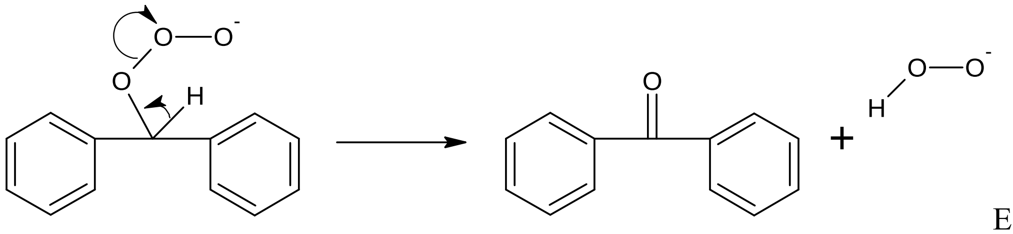
Eqn 14

The compound could then react with the superoxide through the combination of the radicals of each, eqn 15.



Eqn 15

A rearrangement could then occur with the oxygens from the superoxide taking an additional hydrogen before breaking free, leaving the compound with a carbon-oxygen double bond, eqn 16.



Eqn 16

Another possible factor in the rate of the reaction is steric hindrance. As the alcohol is adsorbed at the hydroxyl group there is the possibility of neighbouring groups interfering with the hydroxyl making contact with the catalyst. If the hydroxyl is hindered from adsorbing to the catalyst then there is the possibility of the rate being reduced. If the group is large enough to actually block adsorption from occurring then this could stop the reaction or result in adsorption occurring at another point in the compound and a different reaction occurring.

4.1.3 Cyclic alcohols

One of the key structures in the cyclosteroid is the cyclopropyl group (as discussed in Chapter 3.) It is believed that this ring will have an effect on both the chemical and structural properties of the steroid. Therefore when studying photocatalytic oxidation for possible applications it is important that the samples chosen include groups that can show the effect of a group at an α position to the hydroxyl group of the base compound. Cyclohexanol was chosen as the base compound along with a number of derivatives 2-chlorocyclohexanol, 2-methylcyclohexanol, menthol, and 1,2,3,4-tetrahydronaphthol. Cyclohexanol was chosen as when the 6β-Hydroxy-3α,5-cyclo-5α-androstan-17-one is stripped down then the simplest structure is cyclohexanol with an attached group. Figure 46 shows the molecular structures of the compounds selected for use in the photocatalysis.

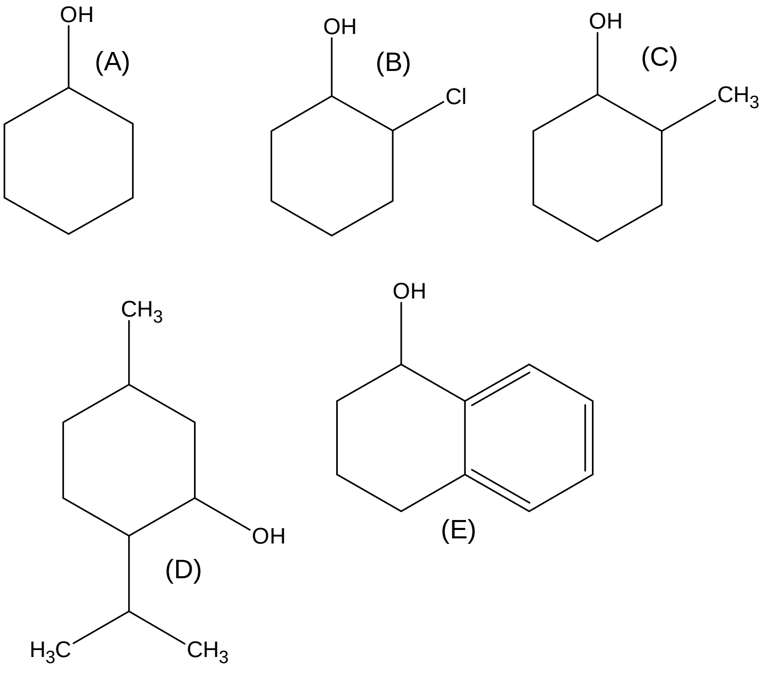


Figure 45 - Structures of cyclohexanol (A), 2-chlorocyclohexanol (B), 2-methylcyclohexanol (C), Menthol (D) and 1,2,3,4-tetrahydronaphthol (E)

By including both modified and unmodified cyclohexanol compounds it was possible to observe the effects of a neighbouring electron withdrawing and electron donating group on the reaction kinetics and product distribution. This would provide some insight into the impact on the reaction generated by neighbouring functional groups. The composition of the compound could determine how well it would react. The inclusion of chloro and methyl moieties would help to gain a better understanding, and aid in making predictions on the success of more complex systems. The chloro group is an electron withdrawing, while the methyl group is electron donating. The menthol and the 1,2,3,4-tetrahydronaphthol are a continuation of that, the menthol containing multiple electron donating groups, and the aromatic ring of 1,2,3,4-tetrahydronaphthol being strongly electron withdrawing.

In a molecule the electrons are not wholly attached to their parent atom. Instead they tend to be effected by electronegativity within the molecule, more electronegative atoms holding onto their bonding electrons more tightly than less electronegative atoms. As a result the electrons instead tend to be displaced towards the most electronegative part of the molecule[16]. The result of this process is that electronegative atoms tend to form more stable bonds, and are so are less willing to react. In cyclohexanol this results in the greatest density of electron being found around the oxygen atom. This should benefit the hydroxyl group by stabilising the bonds of the oxygen atom.

However the presence of nearby groups can affect this stability. The presence of an electron withdrawing group such as a chloro group on a α carbon will have a destabilising effect on the hydroxyl group. This is due to the electron withdrawing ability of the chloro group, while before all the electrons were drawn towards the oxygen of the hydroxyl group they are now drawn towards both the chloro and hydroxyl groups. The electrons are now shared between them, the distribution being affected by the electronegative strength of each, the more electronegative getting the most electrons. When the α group is an electron donating group then this will add to the total electrons in the system; more electrons to be drawn towards the oxygen of the hydroxyl. The increase in electron density serves to increase the stability of the group, making it harder to react. This is for groups in the α position to the hydroxyl, the groups will also have an effect if they are in other positions around the ring but the effects of these groups diminishes as the number of carbons between the groups increases

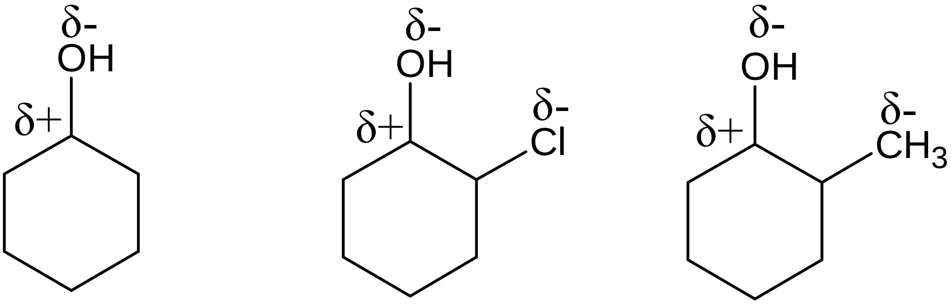


Figure 46 - Electron distribution through a cyclohexanol molecule with (middle) and without (right) the presence of an electron withdrawing group

The compounds chosen were structurally similar to cyclohexanol, one with additional electron donating groups and the other with additional electron withdrawing groups. As a result of the inductive effect the electron withdrawing halogenated and aromatic groups should increase reactivity while the compounds containing electron donating alkyl groups should exhibit decreased reactivity over unmodified cyclohexanol[16].

The aims of this study were:

- ⇒ perform catalytic oxidations on a range of compounds structurally similar to cyclohexanol
- ⇒ study the effect of neighbouring groups on the reactivity of the hydroxyl group
- ⇒ examine the effect of catalyst particle size on reaction rate to examine if the total surface of the catalyst is important to the reaction.
- ⇒ examine the effect of catalyst composition on reaction rate

4.2 Results and Discussion

4.2.1 Cyclohexanol

The initial photocatalytic oxidation reaction examined was that of cyclohexanol with TiO_2 under UV illumination. The structure of cyclohexanol is shown in figure 51, a saturated six membered ring with a hydroxyl group attached. With this compound the hydroxyl group was converted to a ketone to produce cyclohexanone. This could be used as a baseline for the analysis of the later compounds which had additional groups added to the basic cyclohexanol structure. Their results could then be compared to that of cyclohexanol to show if the presence of the additional groups had a positive or negative effect on the rate at which the alcohol could be converted to the ketone.

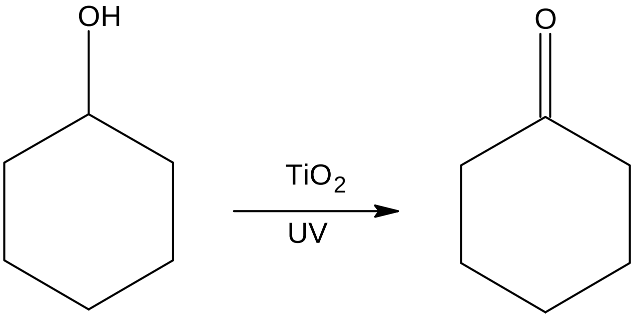


Figure 47 - Molecular structure of cyclohexanol

When the reaction was performed the solution was a suspension of the white TiO_2 in a colourless solution; however after the reaction was complete a yellow colouration could be observed within the solution. This change in colour could only be observed in the sample which contained catalyst and had been irradiated with UV light. Neither the dark control (catalyst added but no light exposure) nor the UV control (UV irradiated but no catalyst) showed any apparent change in colouration. This would indicate that the colour change was due to the photocatalyst and the UV light together, rather than due to photolysis or some reaction between the sample and the TiO_2 catalyst. The appearance of the colour change was a good indication that the ketone had been formed as cyclohexanone has a yellow colouration to it.

The samples were first analysed using UV spectroscopy. These would give a clearer image of any changes that had occurred within the samples. It is also useful with this reaction as the carbonyl group will absorb UV in the 200-400 nm range whereas the hydroxyl group will not. This means that the appearance of a ketone in the solution will be easily seen. When the dark control sample was analysed and compared with the spectrum of the starting solution it showed that nothing had occurred. Figure 49 shows the UV spectra of the three samples after 12 hours as well as the starting sample. The UV spectrum of the dark control was virtually identical to that of the starting sample, there were some small differences but those may have been due to some loss of the sample from the solution due to adsorption to the catalyst which was then removed when the catalyst was filtered out. The control sample which had been exposed to the UV light showed a slightly different spectrum when compared with the starting solution. The UV control was the same shape as the starting sample but had a slightly higher absorption. However in the starting sample and both the controls all that appeared to have been detected was the acetonitrile solvent which gave a peak at 190nm.

When the photocatalysed sample was compared with the starting sample it showed a number of changes. At lower wavelengths the photocatalysed sample grew increasingly different. Peaks could be observed at 280 nm, 230 nm, 205 nm and 195 nm in the cyclohexanol. The peak at 205 nm was due to the acetonitrile solvent and could be ignored. These peaks were not present in the spectra of the initial sample, indicating that these peaks were due to a compound created during the photocatalytic reaction. The fact that these peaks were not detected in the spectra from the other samples indicates strongly that these were from something that was produced by the reaction. The reaction was designed to turn an alcohol into a ketone, so if the reaction occurred correctly then a C=O bond will have been created. The absorbance of a C=O bond is at around 195 and 275 nm, and when the spectra is examined peaks can be found at 195 and 280 nm. These would indicate that it is likely that the reaction did occur correctly.

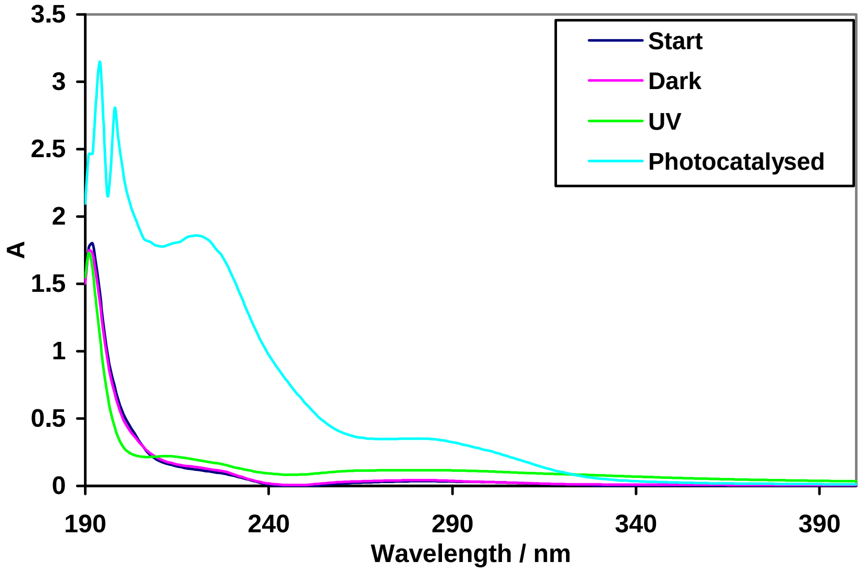


Figure 48 - UV/Vis spectra of cyclohexanol samples

The sample was examined using GCMS analysis, the data obtained from the starting solution and the photocatalysed sample is shown in figure 50. The starting solution was first examined; this showed a large peak at 3.32 min. This was then checked comparatively by performing the GC run using a sample solution of cyclohexanol in acetonitrile. In addition the peak was run against the mass spectra database of the instrument.

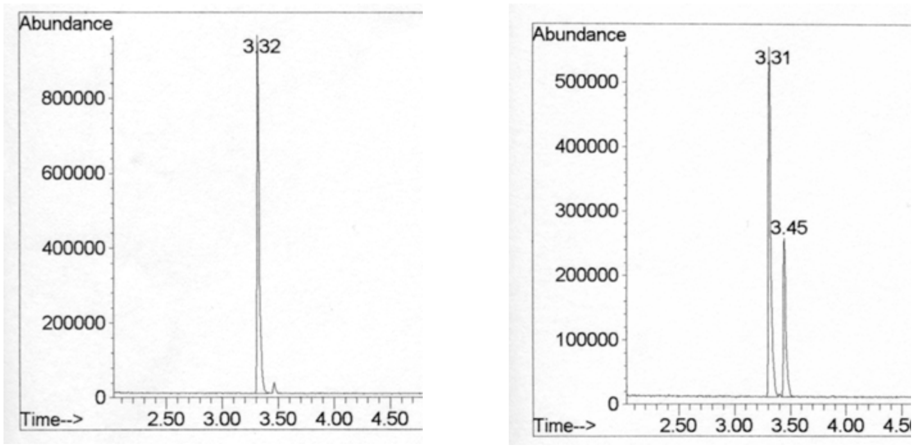


Figure 49 - GCMS data of the cyclohexanol starting solution (left) and the photocatalysed solution (right)

Both identified the peak as belonging to cyclohexanol as expected. A small peak was noticed at around 3.45 min that was identified as cyclohexanone. The mass spectra clearly showed the molecular ion at 98. The presence of this peak may be due to light having reached the sample where it was stored which allowed a small amount of cyclohexanone to be produced. When the photocatalysed sample was analysed, it showed that the area of the reactant peak at 3.32 min had diminished by a third over the 12 hours of the reaction and that the small peak at 3.45 min had grown considerably.

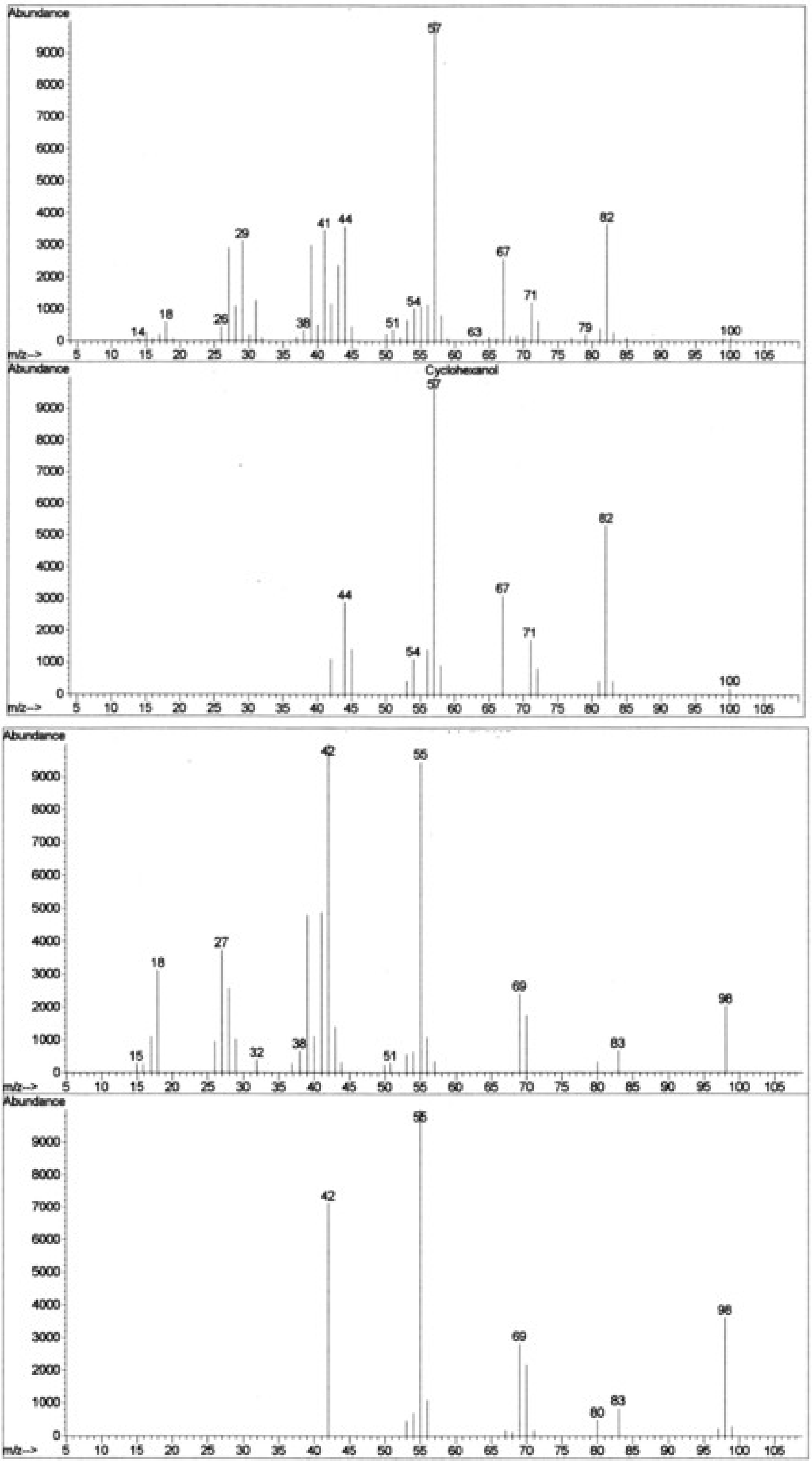


Figure 50 - Mass spectra of the cyclohexanol (left) and the product (right), (reference top, recorded bottom)

The mass spectra of the reactant showed the molecular ion of 100, this is the weight of cyclohexanol. The next signal was 82, this is a drop of 18 from the molecular ion and was likely due to the loss of the hydroxyl group and a hydrogen. Figure 51 shows the mass spectra of reactant peak and the product peak, with both the mass spectrum and the library spectrum of the expected compounds. The molecular peak of the product was 98 which correspond with the weight of cyclohexanone with a drop to 83 as the ion fragments CH_3.

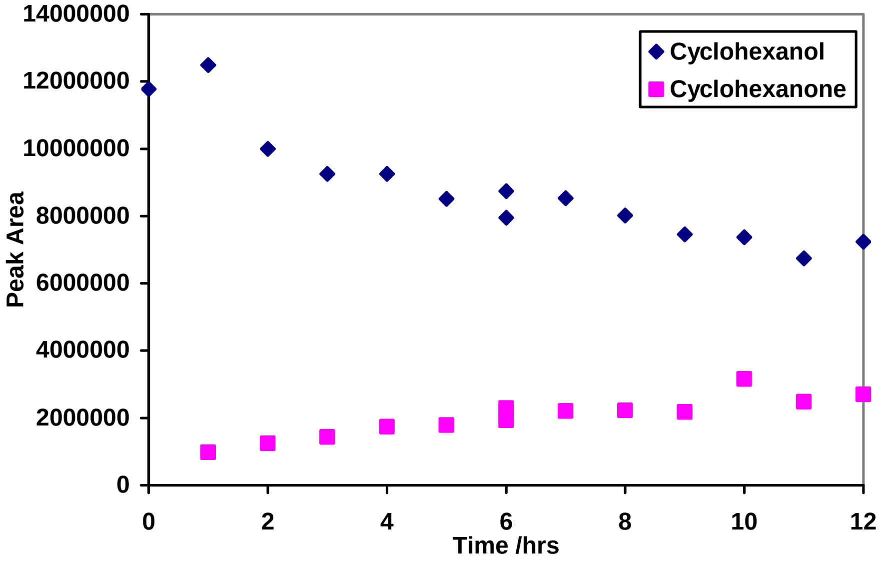


Figure 51 - Photocatalysis of cyclohexanol using Aldrich TiO_2

The samples were subsequently analysed using FTIR, with a Horizontal Attenuated Total Reflectance (HATR) set-up, this technique is useful in detecting the presence of new functional groups in products. The HATR set-up was used as it does not send the light beam directly through the sample so it is not affected by the presence of suspended solids in the samples which would otherwise block or impede the light beam if it had to pass through the sample. Any interference to the light beam could make it impossible to obtain a spectra of the sample. The presence of the acetonitrile solvent was addressed by creating a difference spectra composed of the scans of the sample solution and pure distilled acetonitrile.

Figure 53 shows the comparison between the starting and photocatalysed samples, with the appearance of a C=O peak. In all of the solutions the main differences observed was a peak at about 1700 cm^{-1} which indicates the presence of a C=O group. Therefore the results indicate that in all of the solutions a C=O group has appeared in the sample structure, suggesting oxidation of the hydroxyl group to a ketone.

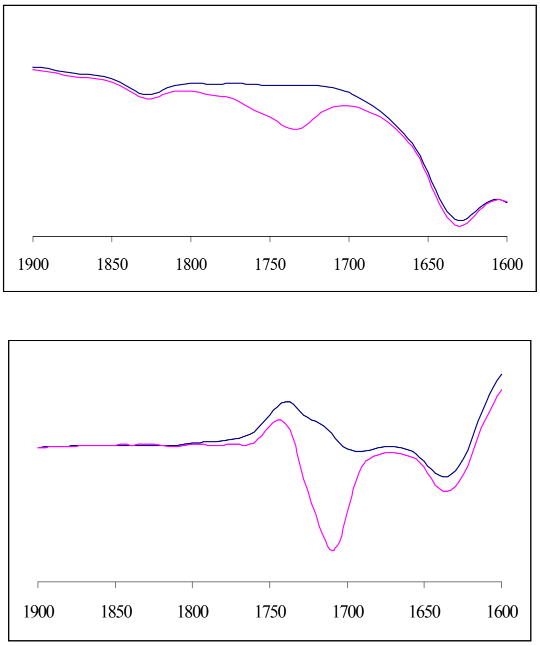


Figure 52 - FTIR of the reaction samples showing the appearance of the C=O peak

The analysis clearly showed that the reaction had occurred as expected with the cyclohexanol being photocatalysed to cyclohexanone. The experiment was then repeated using a number of different TiO_2 photocatalysts. Figure 54 shows a chart of the photocatalytic oxidation of cyclohexanol using PC500, UV100 and Aldrich anatase TiO_2. While P25, which was chosen for the initial reaction due to the popularity of the catalyst, is composed of a mixture of rutile and anatase TiO_2, the other catalysts investigated are composed of just anatase. These three catalysts differ in their particle size, with both PC500 and UV100 having far smaller particle sizes than Aldrich at under 10 nm compared to the 150 nm of Aldrich. The effect of this is that the smaller particle size of these catalysts will give them a far greater surface area per gramme. In fact PC500 and UV100 have a surface area per gramme of greater then 250 m^2/g. This is considerably larger than Aldrich with just 10.2 m^2/g. Therefore it was to be expected that PC500 and UV100 would give greater reaction rates as their larger surface area will allow more of the reactant to adsorb and so allow the reaction to proceed more quickly. Table 2 shows a comparison of the TiO_2 catalysts examined.

Table 2 - Table of the properties of the TiO_2 catalysts

CATALYST NAME	SURFACE AREA m^2/g	RATIO ANATASE/RUTILE	PARTICLE SIZE nm
DEGUSSA P25	50	70/30	30
ALDRICH ANATASE	10.2	100/0	150
UV100	>250	99/1	<10
PC500	>250	100/0	5-10

When the data was analysed this was indeed what was found, both PC500 and UV100 gave similar results with a yield of 38% of reactant with the PC500 and 41% with UV100. Aldrich however with its smaller surface area had a yield of just 25%. This clearly showed that the amount of surface area is an important factor in the rate at which the reaction occurs. P25 however gave the best performance with a yield of 51%, which is interesting as it shows that the particle size is not the dominant factor in the reaction.

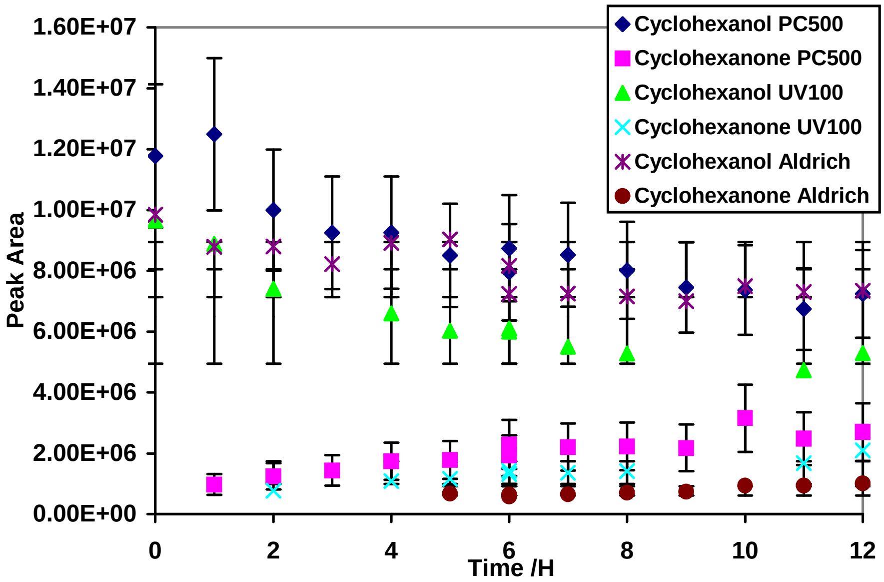


Figure 53 - Chart of the generation of cyclohexanone

The oxidation of cyclohexanol is a reaction that has also been performed using chemical oxidation techniques. Nwauka[18] used a simple chemical oxidation with calcium hypochlorite and sodium hypochlorite as the oxidation agents. Using these yields of 91% cyclohexanone were obtained with calcium hypochlorite and 98% yield with sodium hypochlorite. This was with a reaction time of around an hour although the paper does not give exact times for the duration of the reactions. This serves to show that even simple chemical oxidation techniques are capable of giving very good yields in the oxidation of reasonably simple alcohols. Photocatalysis even now can not reach the yields or reaction rates of chemical oxidation. However the speed of the chemical oxidations may be where they have problems. When the reaction is performed on compounds containing fragile components there is the possibility of these being damaged by the vigorous reaction, photocatalytic oxidation may be able to perform these without causing damage. This would give photocatalysis an area where it could find commercial use. Industrially photocatalysis would have problems matching chemical oxidation, but it could find use with the oxidation of complex alcohols where damage caused in chemical oxidation results in very poor yields.

Martin[19] used a catalytic oxidation technique with $Fe(NO_3)_3$-$FeBr_3$ as the catalyst. They reported an 80% yield following a 24 hour reaction time. One interesting feature of the method is that the authors found that only secondary alcohols were oxidised, primary alcohols were not oxidised even where compounds contained both a primary and secondary hydroxyl groups. The paper achieved a yield of 80%, but that was with a very long reaction time.

4.2.2 2-Methylcyclohexanol

The next molecule to be examined was 2-methylcyclohexanol; this replaced the electron withdrawing chloro group with an electron donating methyl group. This difference in the functional group attached at the 2 carbon should have an effect on the reaction rate. Figure 55 shows the molecular structure of 2-methylcyclohexanol.

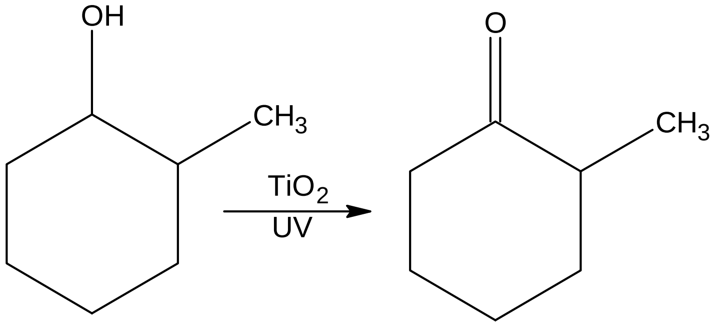


Figure 54 - Photocatalysis of 2-methylcyclohexanol

With this reaction a racemic mixture was used, this is a mixture of both cis and trans isomers of the compound. These geometric isomers where in the cis 2-methylcyclohexanol both the hydroxyl and methyl groups are on the same side of the plane of the ring, whereas in trans 2-chlorocyclohexanol the groups are on opposite side of the plane of the ring and therefore further apart. Figure 56 shows the structure of both cis and trans 2-methyl cyclohexanol. The use of this mixture will make it possible to determine if there are any possible steric influences in the reaction. The methyl group when close to the hydroxyl group could interfere with the hydroxyl's ability to adsorb to the catalyst and so be reacted. If this is the case then while it is not possible to determine which peak was generated by the cis and which by the trans, it would be shown through a difference in the rate at which the two isomers react, with one peak showing a slower reaction rate than the other. Testing of the racemic mixture found one isomer to be present at higher concentration than the other, however the instruments were not able to distinguish between them enough to obtain identification as their mass spectra are identical.

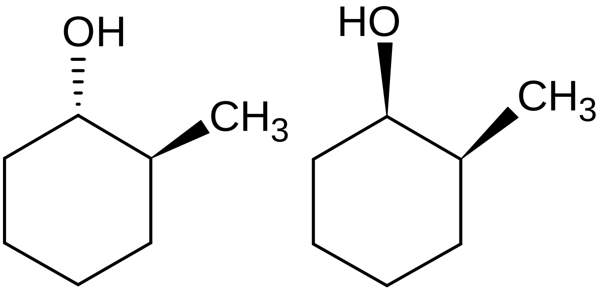


Figure 55 - Molecular structure of cis (right) and trans (left) 2-methylcyclohexanol

Once the reaction had been performed the initial analysis was UV absorbance spectroscopy. Figure 57 shows the UV absorbance spectra of the photocatalysed 2-methylcyclohexanol sample and both controls. Analysis of this data showed identical absorbances for the UV and dark controls. These two spectra only showed the acetonitrile peak at 190 nm. This is not unusual as 2-methylcyclohexanol would be expected to absorb in the 100-200 nm range, however most instruments are not designed to operate in this region as absorption of the light beam by atmospheric CO_2 becomes a hindrance and any analysis would have to be performed in an atmosphere composed of something other than air. UV absorbance spectroscopy in the 200-400 nm range is mainly due to double bonds. The result of this is that while an alcohol may not be detected by the instrument a ketone would. This is one of the reasons this analysis is useful for the analysis of the oxidation being carried out. The spectrum of the photocatalysed sample was considerably stronger that that of the control samples with absorbance bands at 280 nm and 230 nm. This established quickly that a reaction had occurred; the next step was therefore to identify the product.

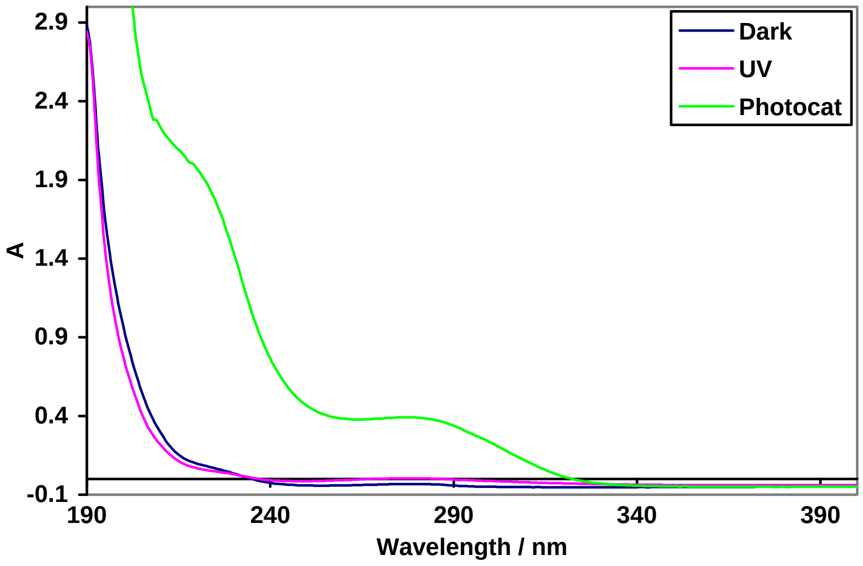


Figure 56 - UV/Vis spectra of methylcyclohexanol reaction samples

The GCMS analysis of the starting solution showed two peaks, one at 3.86 min and another smaller peak at 3.95 min. The GC/MS data can be seen in figure 58, with both the starting sample and photocatalysed sample showing clear peaks.

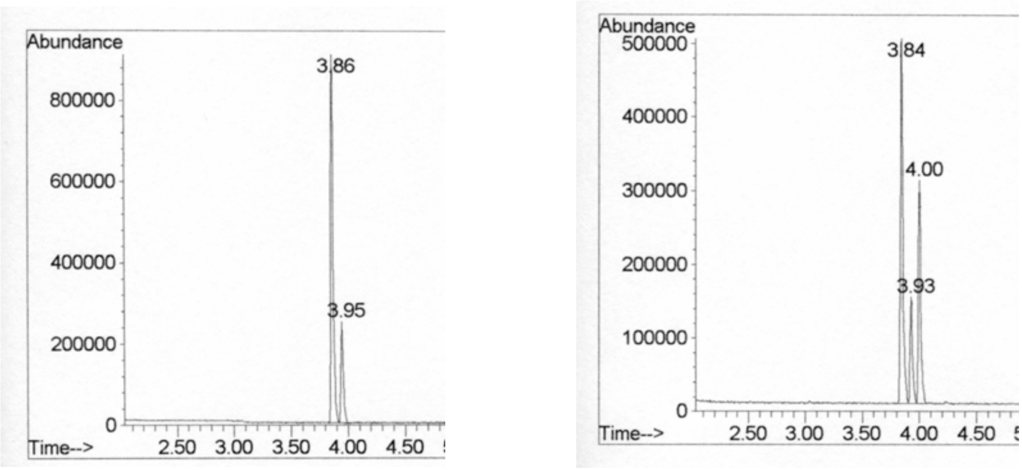


Figure 57 - GCMS data of the 2-methylcyclohexanol starting solution (left) and the photocatalysed solution (right)

These two peaks were identified as both being 2-methylcyclohexanol, although it was not possible to determine which peak was generated by the cis and which by the trans isomers. The photocatalysed sample showed a reduction in the starting compound as well as the appearance of a new peak at 4 min, this new peak was identified from its mass spectra as 2-methylcyclohexanone. This was checked by examining the mass spectra of the peaks. Figure 59 shows the mass spectrum of the product as well as a library spectrum of 2-methylcyclohexanone. The spectrum showed the molecular ion at 112 which matches the molecular weight of 2-methylcyclohexanone, the expected product. The signal at 97 is due to the loss of the methyl group from the molecular ion, the peak at 84 then being due to the loss of a C-H as the ring breaks. The peak at 68 is then due to the fragmentation of the molecule resulting in the loss of the oxygen. The peaks at 55 and 41 are then caused as the molecule undergoes further fragmentation with first the loss of a C-H before the loss of a CH_2. The loss of a further CH_2 gives the signal at 27. The mass spectrum confirms the analysis of the instrument that the product was 2-methylcyclohexanone as expected.

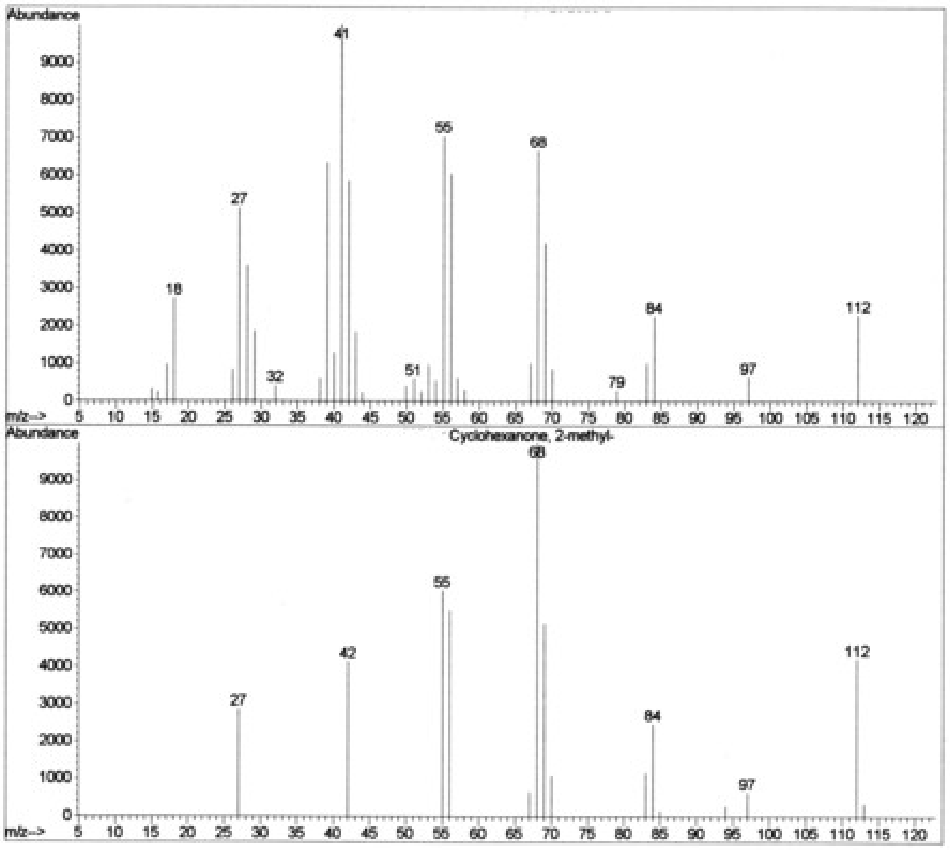


Figure 58 - Mass spectrum of 2-methylcyclohexanone (reference top, recorded bottom)

A plot of the GCMS data showed that the reaction proceeded as expected with the 2-methylcyclohexanol being consumed during the reaction and the production of 2-methylcyclohexanone as the sole detectable product. Figure 60 shows the chart of the peak areas from the GCMS, showing the two peaks of the 2-methylcyclohexanol isomers and the 2-methylcyclohexanone produced by the reaction. From the data the reaction appeared to proceed at a similar rate to the unmodified cyclohexanol, with a 55% loss of the reactant. This loss was found in both 2-methylcyclohexanol isomers. This data shows that the difference in distance between the methyl and hydroxyl group in these isomers did not affect the rate at which the compound reacted. Therefore there is no evidence of any steric influence from the methyl group, if there had then that would have been difference between the rates of the cis and trans isomers. In the cis conformation the methyl group is closer to the hydroxyl group therefore if there were any steric effects then it would have been exhibited with a slower reaction rate in the cis compared to the trans. The fact that no difference was observed would seem to indicate that conformation was not a factor in the reaction. However that does not mean that steric effects could not play a part in other photocatalytic oxidations, with a compound as large as a steroid there is a strong possibility that the large structure could sterically influence the ability of the hydroxyl group to be oxidised.

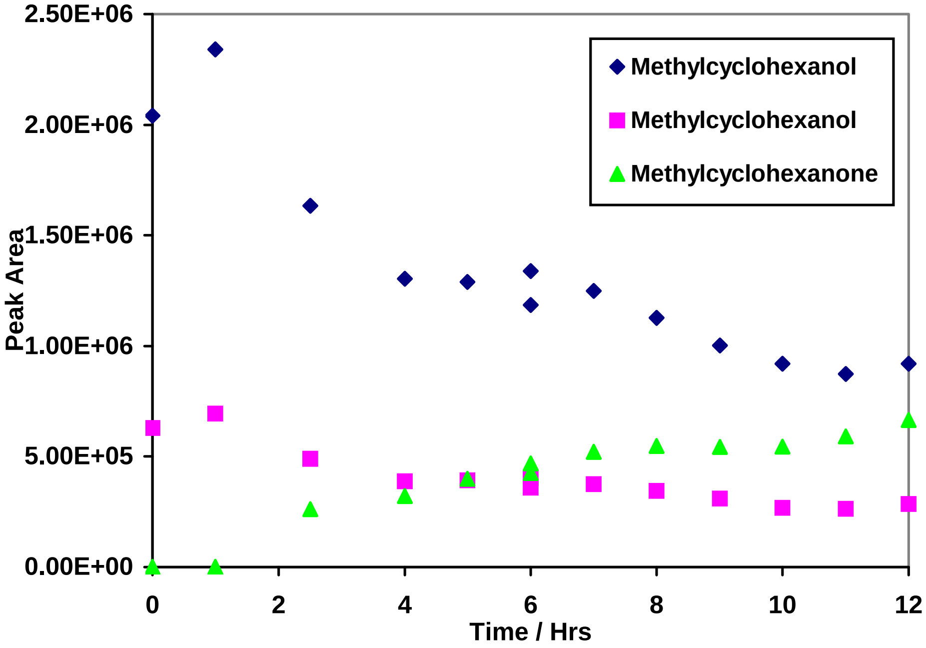


Figure 59 - Chart of the photocatalysis of methylcyclohexanol

Hussein[8] also examined the photocatalytic oxidation of 2-methylcyclohexanol, as well as several aliphatic alcohols. However their method used a platinized titanium dioxide as the catalyst. The paper reports that a yield of 11% was obtained. Much of the method is similar to that used in this thesis, making it an interesting study to examine. The UV source used was of a similar type and power, and the solvent used was also the same. The paper only gives the reaction time as 8-15 hours but that is of a similar length as the 12 hours used in this thesis. In this thesis a yield of 45% was achieved, showing that something about the two studies had a large difference in the yield obtained. The most likely reason is the differences in the level of dissolved oxygen in the solvents. Hussein purged the solvent with nitrogen to remove dissolved oxygen whereas this thesis bubbled air through the solvent prior to the photocatalysis reaction. Dissolved oxygen acts as an electron scavenger, moping up free electrons. This serves to prolong the life of the electrons ejected by the catalyst, and preventing electron recombination from occurring. The loss of oxygen from the sample should result in recombination more quickly, giving the catalytic products a far shorter lifespan. This should make the oxidation harder to perform and would explain the poor yield reported. The authors give no reason for their decision to purge the solvent but it does serve to show the effect of dissolved oxygen on the reaction performance. They also focus purely on the method, taking no consideration of the compounds chosen to test it. No mention is made of the isomers of 2-methylcyclohexanol, so it is not known which was used. No mention was made of the effect that the methyl group would have on the results obtained, and even though it is a paper on the method no attempt is made to try to give a mechanism.

4.2.3 -Menthol

The next compound to be studied was -menthol, this molecule is similar to 2-methylcyclohexanol but with a propyl group replacing the methyl group and the appearance of a new methyl group on the 5 carbon. Figure 61 shows the molecular structure of menthol. The addition of the electron donating groups should add some stability to the compound compared to unmodified cyclohexanol, therefore it would be expected that the reaction would proceed more slowly than observed for 2-methylcyclohexanol.

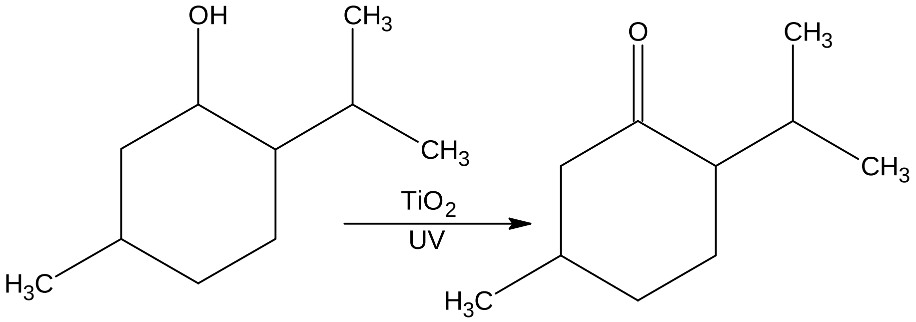


Figure 60 - Photocatalysis of menthol

Menthol is a good example of a compound that could benefit from the use of photocatalytic oxidation, it can be oxidised currently using a strong oxidising agent such as chromic acid but this is a highly toxic material and requires very careful handling. A less toxic oxidation such as photocatalysis is therefore far more preferable.

While menthol occurs as a number of different isomers only one was used in the experiment. -Menthol (2R,2S,5R) is the most common configuration of menthol due to its high stability compared to the other isomers. -Menthol is the trans form of the molecule with the functional groups positioned as to have the greatest distance between them. Figure 62 shows the structural arrangement of -menthol.

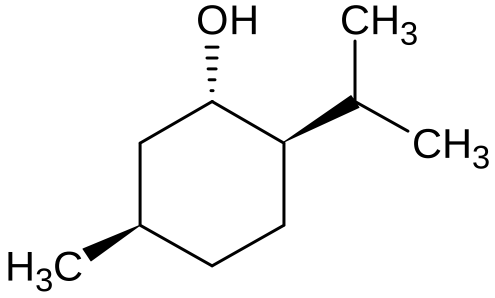


Figure 61 - Structure of -menthol

In addition, while this molecule is in a trans conformation the propyl group is larger that the methyl group of 2-methylcyclohexanol. This could raise the possibility of the propyl group interfering with the ability of the molecule to adsorb to the catalyst at the hydroxyl group.

The GCMS analysis was carried out on the reaction samples; these gave a strong peak at 6.59 min due to the menthol. This was initially identified by the use of the instruments spectra database before being checked through examination of the mass spectrum, figure 63. A signal at 156, the molecular weight of menthol, was not present. The first signal was at 138 and will be due to the loss of the hydroxyl group. The signal at 123 will then be due to the fragmentation of a methyl group off the molecule. The ring structure then appears to break as the signal begins to drop by 14 to 109 then 95, then 81, then 67 as it fragments CH_2 groups. From this it can be identified as the spectra of menthol.

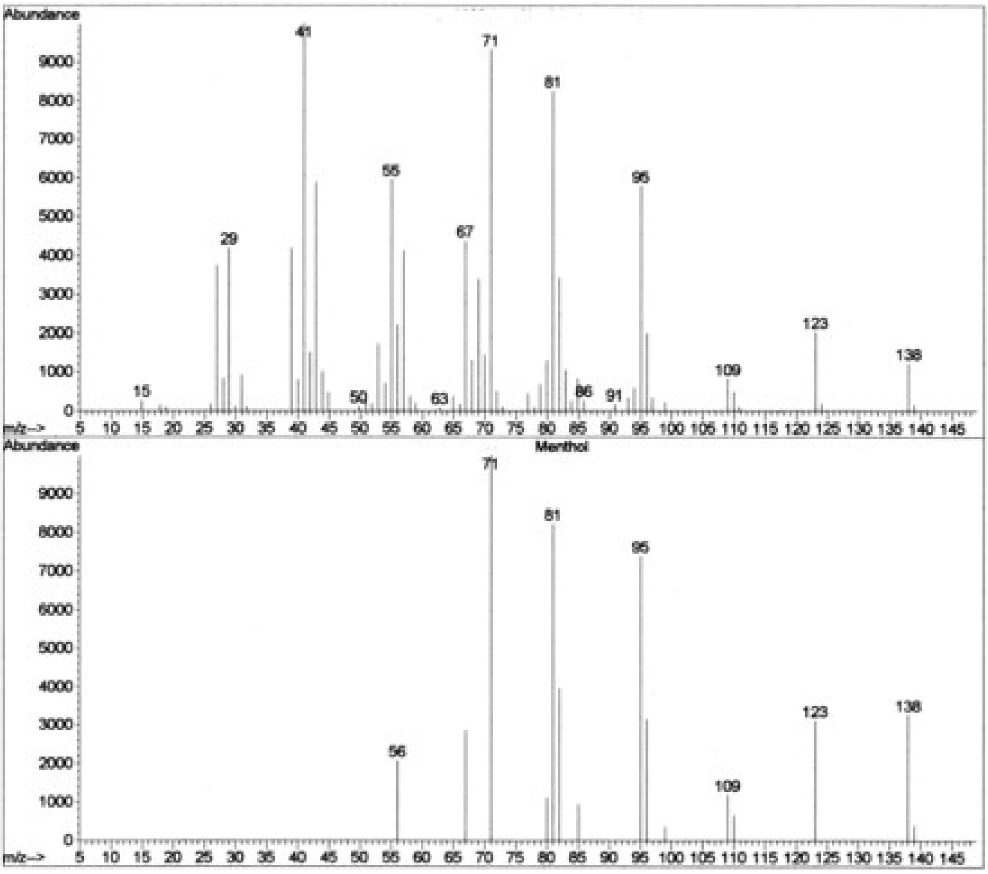


Figure 62 - Mass spectrum of menthol sample (reference top, recorded bottom)

The GCMS analysis showed only a small reduction in the menthol peak at 6.59 during the reaction, and a small peak appeared at around 6.39 min that was likely to be a product of the reaction. It was possible to obtain a reasonable mass spectrum of this peak which indicated that menthone had been produced. Figure 64 shows the mass spectrum of the product. The mass spectrum gave the first signal at 154, the molecular weight of menthone, followed by a signal at 139 which is likely the loss of a methyl group. The signal at 112 was a loss of 27, likely the loss of C_2H_3. This loss of 27 matched the presence of an ion at 27, likely the fragment that had broken off. This made it possible to confirm the library identification of the peak as menthone. This manual checking of the spectrum is important as while the library is useful it is not always correct.

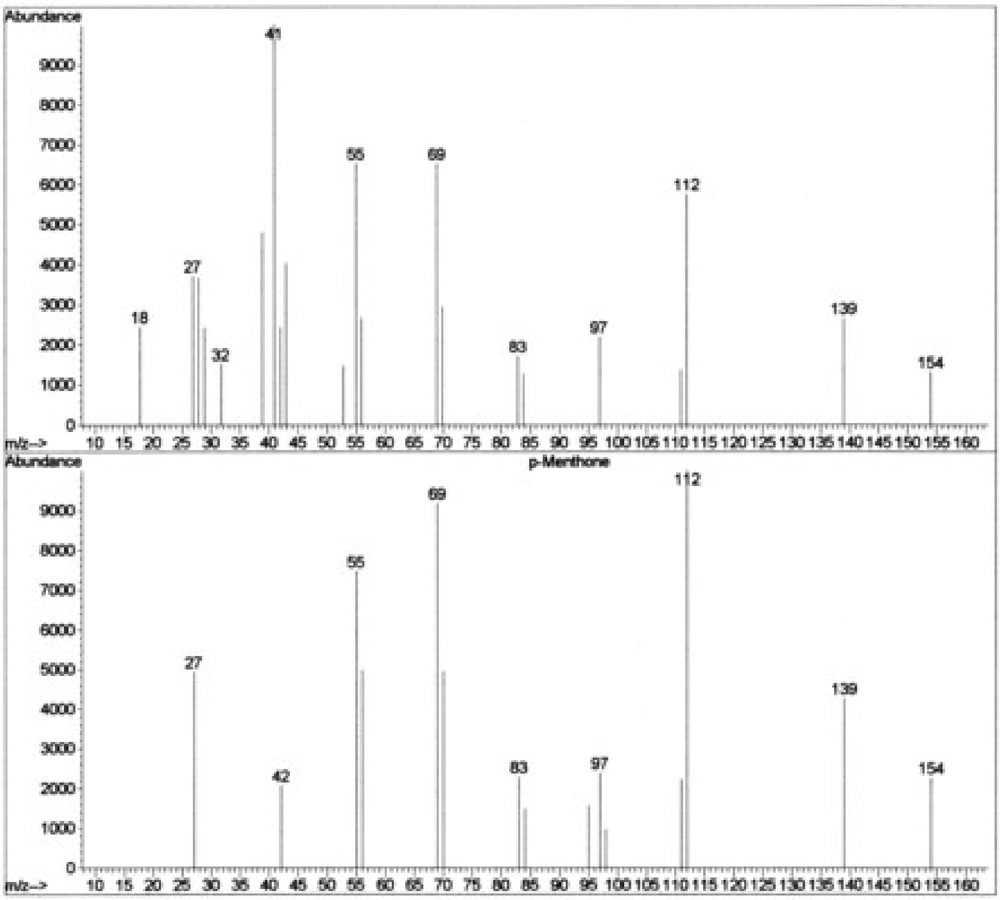


Figure 63 - Mass spectrum of menthone (reference top, recorded bottom)

Figure 65 shows the menthol samples before and after the photocatalysis, with a small second peak evident in the photocatalysed sample.

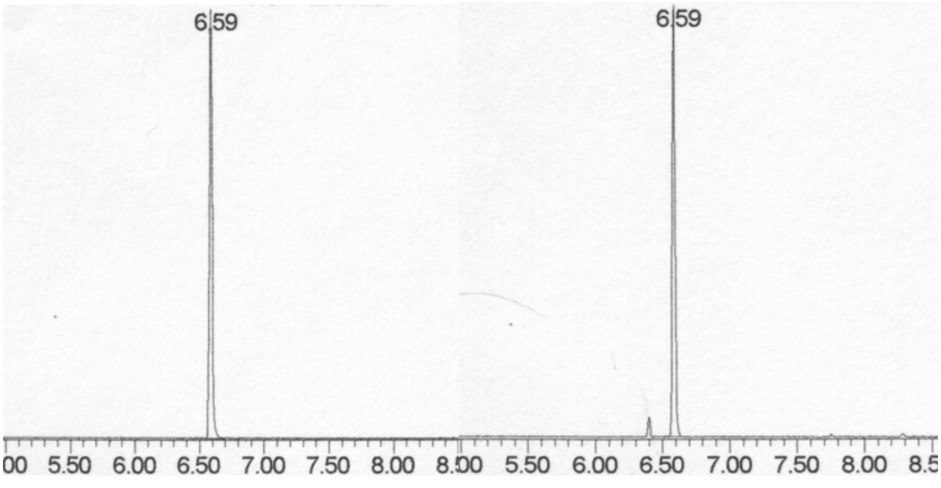


Figure 64 - GCMS data of the menthol before (left) and after (right) photocatalysis

The reaction was tested using several different catalysts, as can be seen in figure 66. The data did not show a great deal of reactivity in the menthol, although there was some differences across the catalysts examined, ranging from 30% loss of menthol with P25 to just 8% with Aldrich anatase.

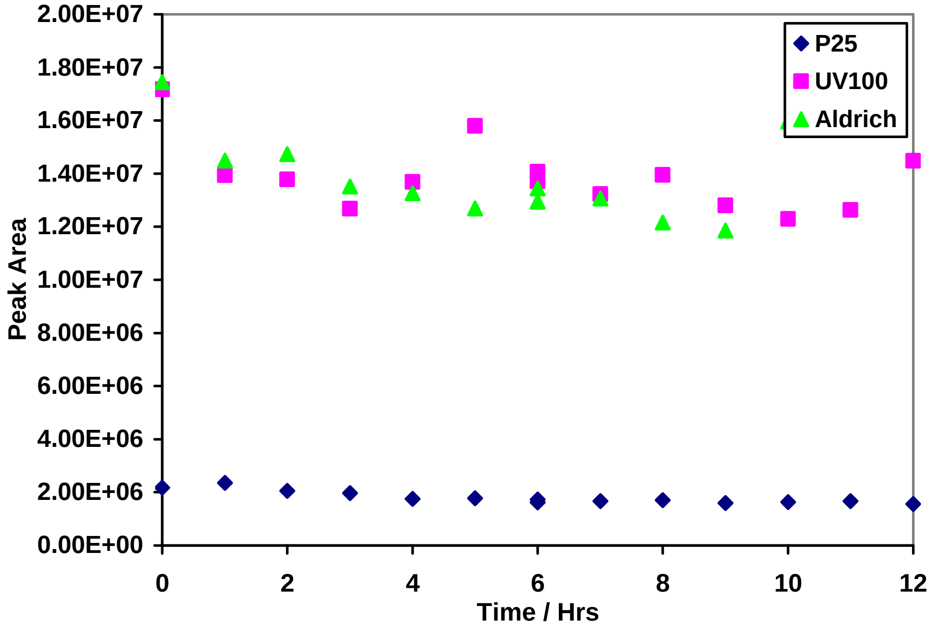


Figure 65 - Photocatalysis of -menthol using different catalysts

The oxidation of menthol has also been examined by Nwauka[18]. In this paper the oxidation was performed using calcium hypochlorite as an oxidation agent. The paper reports a yield of 98, this large yield is interesting as it shows that the chemical oxidation technique could not have been affected by the induction effect of the structure, or by any steric influences. In photocatalysis a drop in the yield was observed between the oxidation of cyclohexanol and that of menthol. This showed that the presence of the groups had influenced the ability of the alcohol to become a ketone. Yet with calcium hypochlorite an almost complete conversion was reported, giving little evidence that the reaction was slowed in any way. This would suggest that the chemical oxidation used a mechanism which did not have problems breaking the O-H bond. That steric hindrance did not occur did not was to be expected as it was not observed in the photocatalytic oxidation of the menthol. If steric influence was to occur then it would be more likely to be seen in the photocatalytic oxidation of menthol as the catalyst is far larger than the calcium hypochlorite. If the photocatalysis has no problems then it is unlikely calcium hypochlorite would have problems.

4.2.4 2-Chlorocyclohexanol

The first of the cyclohexanol derivatives studied was 2-chlorocyclohexanol. This is a cyclohexane ring with a hydroxyl group attached and a chloride group attached to the 2 carbon. Figure 67 shows the molecular structure of the 2-chlorocyclohexanol.

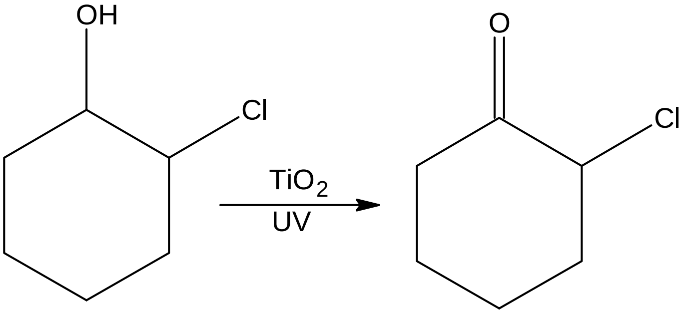


Figure 66 - Photocatalysis of 2-chlorocyclohexanol

The reaction was performed using the same method as had been performed on cyclohexanol. As had been observed with cyclohexanol a colour change was apparent in the sample that had been photocatalysed while the dark and UV controls remained colourless. When the samples were analysed using UV spectroscopy it was clear that something had occurred. The UV and dark controls both gave identical spectra that only appeared to show the presence of the acetonitrile solvent. However the photocatalysed sample gave a very large absorbance. It was such that it was required that the sample be diluted down to get the spectra within the detection limits of the UV spectrometer. Figure 68 shows the UV spectrum of the two controls and the diluted photocatalysed sample. The photocatalysed spectrum appears to show absorbances at 250 nm and 280 nm that were not present in the controls. The extremely strong absorbance is unusual as while a strong absorbance was expected due to the formation of the carbonyl group, the absorbance from cyclohexanone was not as intense.

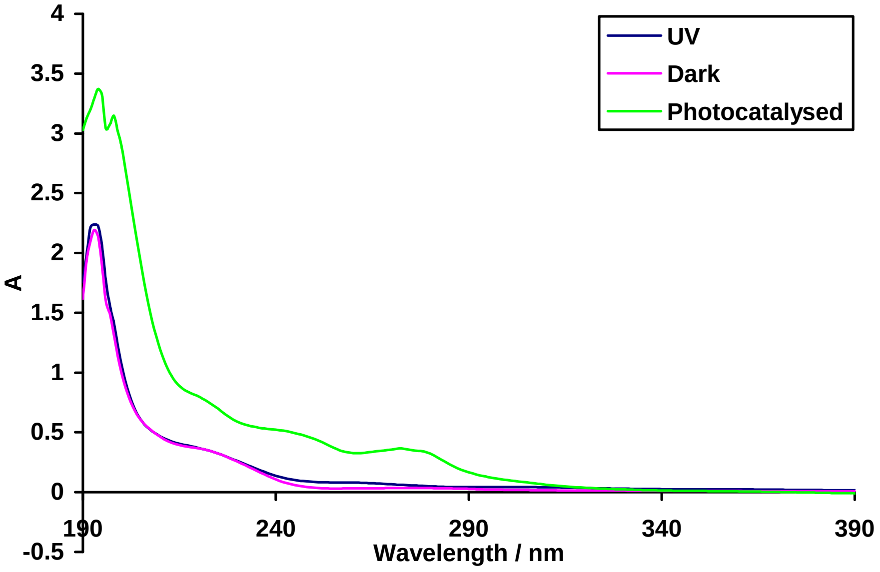


Figure 67 - UV/Vis spectra of the 2-chlorocyclohexanol reaction samples

Analysis of the compound using GCMS would give a better understanding of the product formed. The GCMS of the 2-chlorocyclohexanol showed two peaks from the starting solution, one at 4.93 min and the second smaller peak at 5.41 min (figure 69). The first peak was assigned to 2-chlorocyclohexanol, the smaller peak was assigned as dichlorocyclohexane.

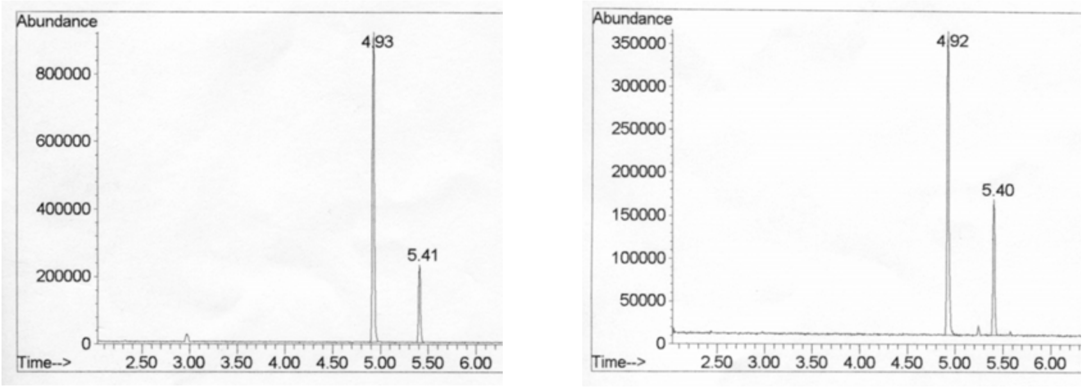


Figure 68 - GCMS data of the 2-chlorocyclohexanol starting solution (left) and the photocatalysed solution (right)

Figure 70 shows the mass spectra of the two peaks present in the starting solution as well as the library spectrum of the expected compounds. The mass spectrum of the larger peak showed a molecular ion at 134 which is the molecular mass of 2-chlorocyclohexanol. The signals 116 are due to the loss of the hydroxyl group with a hydrogen atom from the molecular ion and the signal at 98 would be due to the loss of the chloride group from the molecular ion. The signal at 80 is due to the carbon ring with both functional groups fragmented off. This would give a strong indication that this sample was indeed 2-chlorocyclohexanol. The mass spectrum of the second smaller peak in the starting solution gave a molecular ion of 152 where 1,2-dichlorocyclohexane has a formula mass of 153. The signal at 116 is due to the loss of a chloride from the molecular ion. The signal at 80 is due to the cyclohexane ring.

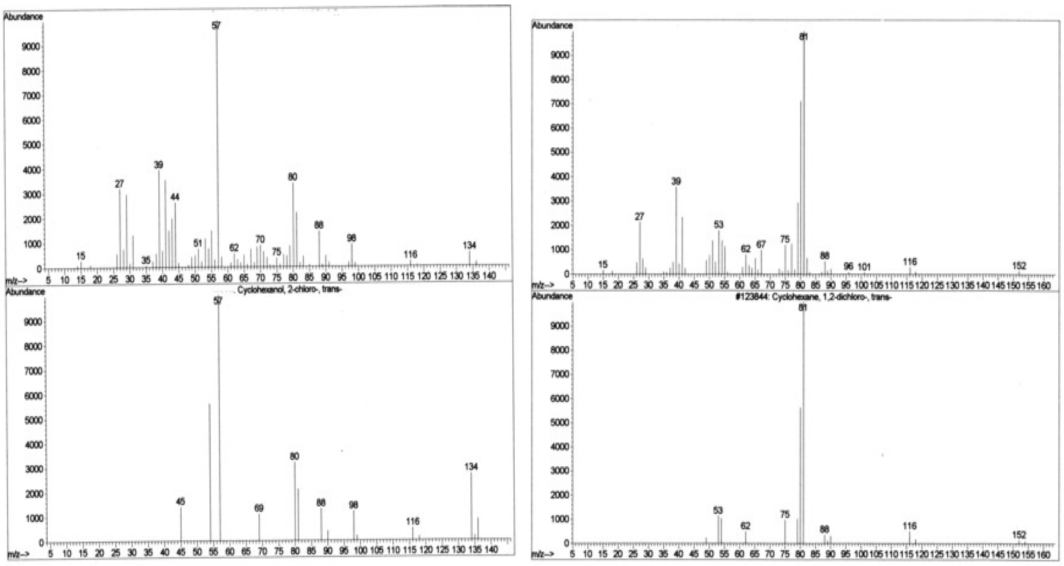


Figure 69 - Mass spectra of 2-chlorocyclohexanol and 1,2-dichlorocyclohexane (reference top, recorded bottom)

The presence of the dichlorocyclohexane is not unexpected, this is a by-product of the 2-chlorocyclohexanol production process and is a common impurity in 2-chlorocyclohexanol. When the photocatalysed sample was analysed it showed a drop in the peak at 4.92 min, but little change in the dichlorocyclohexane peak at 5.40 min. The most significant feature was that despite the drop in the reactant no product peak was detected.

The GCMS data was of the 2-chlorocyclohexanol and 1,2-dichlorocyclohexanol plotted into a scatter chart to show the effect of the reaction on the reactant. Figure 71 illustrates the decrease in the peak area of 2-chlorocyclohexanol over the 12 hours of the reaction. The chart shows that the 2-chlorocyclohexanol was being consumed during the reaction and that the dichlorocyclohexane was not. This was to be expected as the reaction took place at the hydroxyl group, which is not present in dichlorocyclohexane. The question to be answered was why no product was detected.

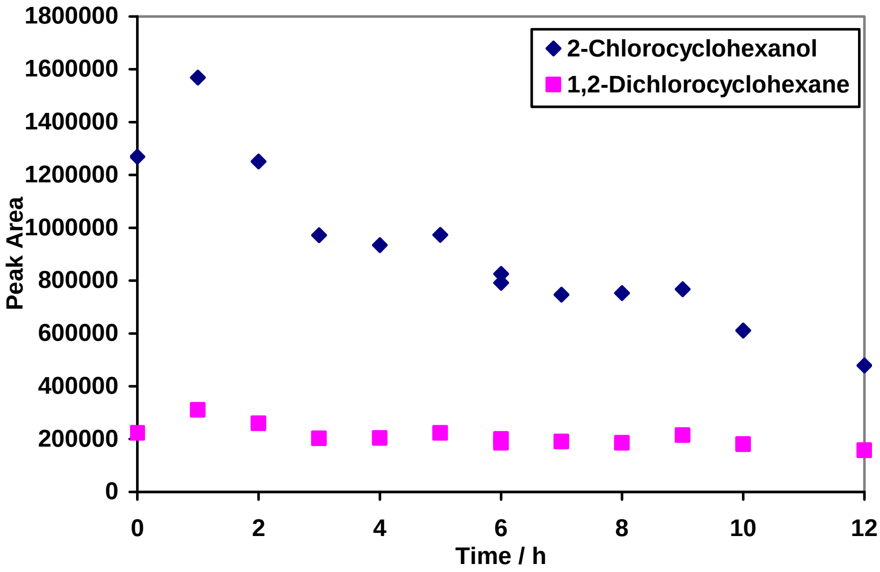


Figure 70 - Photocatalysis of 2-chlorocyclohexanol

The first check was the GCMS of a solution of 2-chlorocyclohexanone in acetonitrile. The purpose of this was to identify if there was anything about the compound that may result in the instrument having difficulty detecting it. Since it was found to be easily detected by the instrument it would seem likely that the reaction had not proceeded as expected and 2-chlorocyclohexanone had not been produced.

The reaction was repeated several times to determine if the results obtained in the first run were normal for the reaction or an anomaly. The results showed an extremely effective reaction with, in some cases, 90% loss of the 2-chlorocyclohexanol; however no corresponding product could be found. With the repetition of the experiment one thing became apparent, while the reaction was occurring which resulted in the loss of the reactant the product did not appear to be consistent. In the samples a colour change was normally observed, from colourless to yellow and in some cases brown, although the exact colour differed from run to run. This went with the GCMS data which also gave inconsistent results,

With one sample an odour change was also noticed. A number of tests were carried out on the samples to determine what had occurred. The first was a simple odour test, and on smelling the sample there was a distinct phenolic odour. This was followed by a ferric chloride test of the sample; this is a simple test to determine the presence of phenolic compounds. The ferric chloride solution was added to a test tube containing a small amount of the sample. With this test if a phenolic compound is present then the solution will turn black. When this was performed on the sample the solution did turn black. However when this was performed on some of the photocatalysed samples from the other runs of the experiment it was found that only a couple contained phenolics. This raised the question of why in some cases the reaction was giving a phenolic compound and not in others, as well as how the mechanism through which the phenolic compounds were being produced through photocatalysis.

When the sample was examined by GCMS a number of small peaks were observed on the chromatograph but were too small for an identifiable mass spectra to be obtained. In many cases the mass spectrum obtained composed of just a few fragments. Identification of the peaks by the instruments library of spectra gave a few possible products but in all cases the poor mass spectra resulted in the accuracy of the matches being low.

A UV spectrum of the sample was compared to that of benzaldehyde, phenol and 2-chlorophenol, some of the compounds that could have been produced (figure 72). These are all aromatic compounds that have a similar general structure to 2-chlorocyclohexanol. Theoretically these could have been produced, although the mechanism for this reaction would be challenging. The generation of the 2-chlorophenol in particular is an exciting prospect as it would mean that a photocatalytic aromatisation had occurred, something that had previously been unknown, and that has huge commercial potential.

The UV comparison of the samples was interesting. The phenolic sample showed a small absorbance at around 360 and 310 nm which none of the other samples exhibited although that could have been due to the presence of other compounds within the photocatalysed sample. The absorbance at 269 nm was observed in all four of the samples. This band is normal in phenolic compounds and often used for the quantitative analysis of phenol. The appearance of the peak in the photocatalysed sample again proves that a phenolic compound had been produced in the reaction. The band at around 245 nm was found in just the phenol and benzaldehyde, the 2-

chlorophenol showed no adsorption at that wavelength while the photocatalysed sample showed a little. Between 200 and 230 nm around three peaks could be observed in the spectrum of the photocatalysed sample, these could also be seen in the spectra of phenol and 2-chlorophenol. The absorbance of the benzaldehyde was quite different in this region. When the samples are compared with the photocatalysed sample it is quite clear the benzaldehyde is not a match, the spectrum differs in a number of places. Of the compounds examined benzaldehyde was the spectrum with the most differences to that from the 2-chlorocyclohexanol. The pure phenol does not match in that it had a strong absorbance at 250 nm which the photocatalysed samples did not. The closest match is between the photocatalysed sample and 2-chlorocyclohexanol. While they are not exactly identical there are no significant differences between them that could not have been caused by differences in solution concentration or the presence of other compounds within the photocatalysed sample.

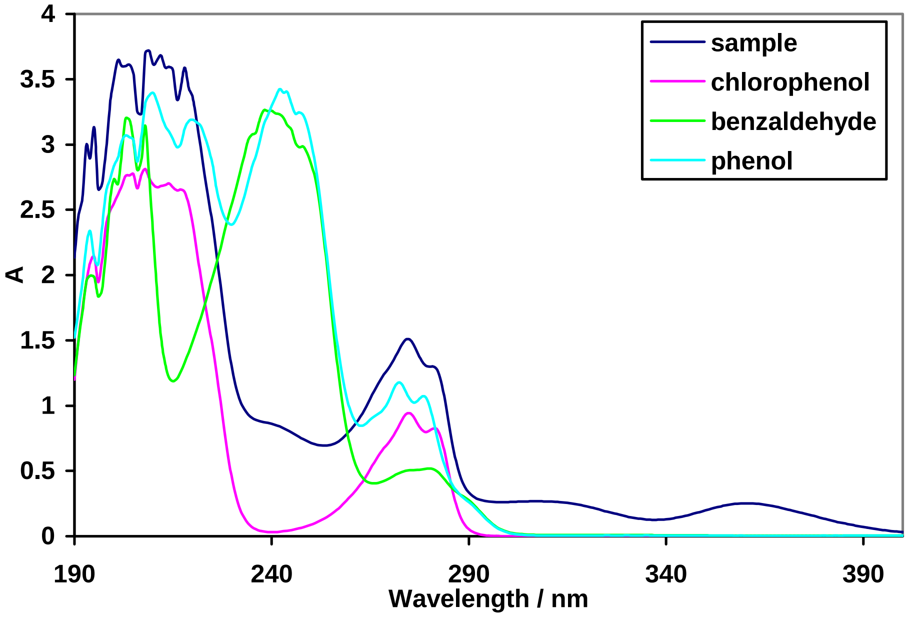


Figure 71 - UV/Vis spectrum of 2-chlorocyclohexanol product and reference samples of possible products

The samples were also analysed using a gas chromatograph with an electron capture detector (ECD), this is an instrument that is sensitive towards halogenated compounds and therefore is ideal for the analysis of the 2-chlorocyclohexanol reaction samples.

On the analysis of the samples under ECD it was obvious that something significant had occurred. Figure 73 shows the GC spectrum produced from the analysis of the photocatalysed 2-chlorocyclohexanol sample. In the first sample the primary peaks were at 0.752, 1.004, 1.533, 2.559, 2.724 and 3.853. By looking at the reference scans it was clear that the peak at 0.752 was the solvent peak, acetonitrile, and so was excluded. When the photocatalysed sample was examined then it was clear that there had been a change in the sample. The peaks at 1.004, 1.533 and 2.724 showed little change in their peak area, so these compounds were not influenced by the photocatalysis. A number of new peaks however appeared together with increases in existing peaks. The peaks at 3.553 and 3.848 showed a large increase in peak area, and new peaks were observed at 2.161, 2.913 and 5.279. When these peaks were compared to the standards then it was clear that a trace level of 2-chlorocyclohexanone was produced which was not detected by GCMS. The peaks at 2.553 and 3.847 could be identified as 2-chlorocyclohexanone through the use of standards. These peaks can be seen although diminished in the starting sample; this may be due to bad sample storage where the sample may have been exposed to some light allowing a small amount of product to be formed.

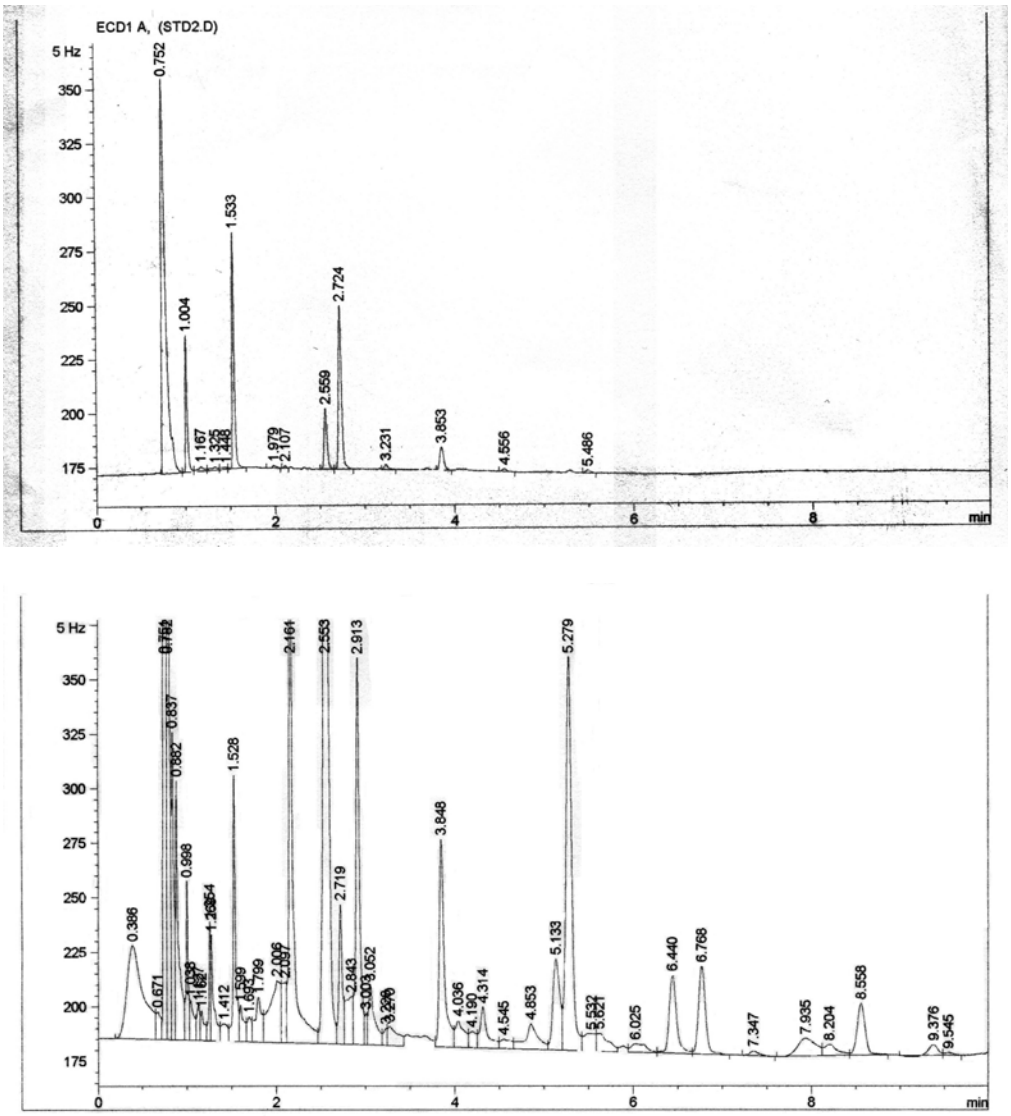


Figure 72 - GC/ECD data of 2-chlorocyclohexanol (top) and the photocatalysis product (bottom)

When the second set of spectra were analysed it was clear that 2-chlorocyclohexanone had been formed, indicated by the peaks at 2.557 and 3.851, figure 74.

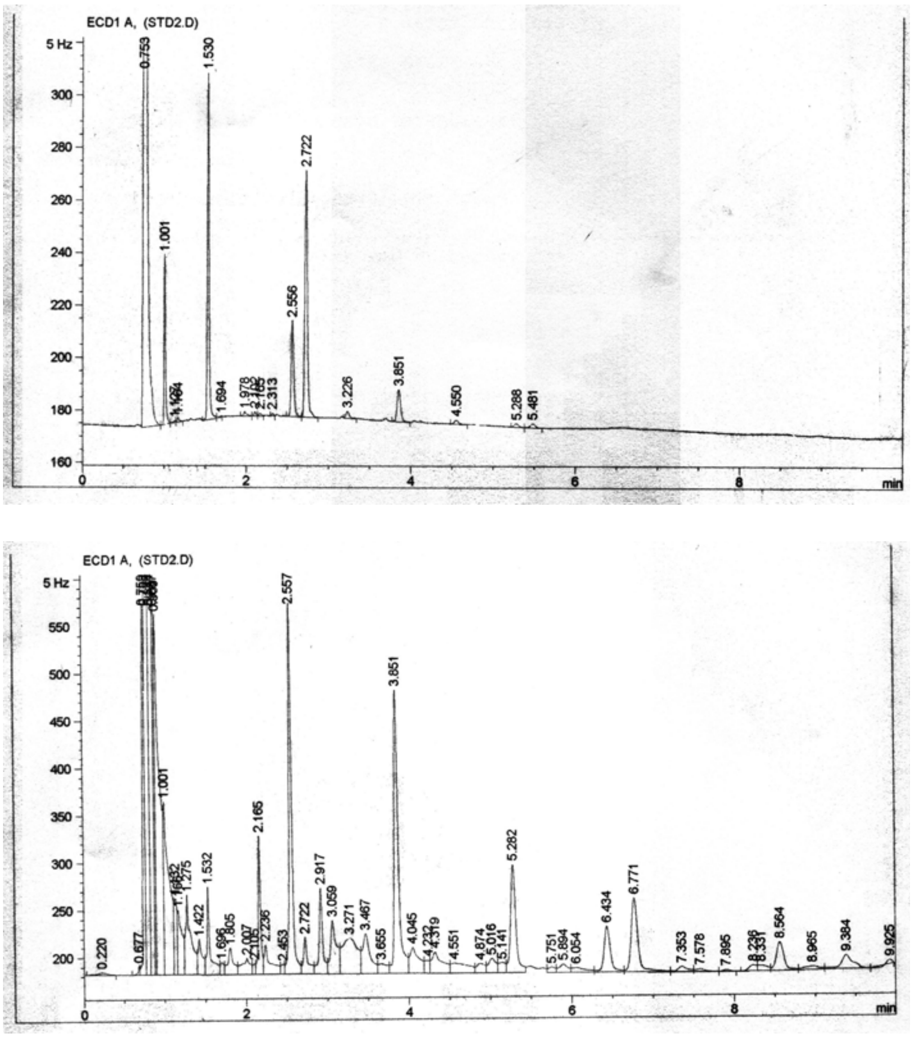


Figure 73 - GC/ECD data of the 2-chlorocyclohexanol (above) and the solution after photocatalysis (bottom)

The analysis was also performed on a number of different test samples, figure 75. These are the GC/ECD data from acetonitrile, a photocatalysed 2-chlorocyclohexanol sample, phenol and 2-chlorophenol. The purpose of this was to look for any similarities in the data that might indicate if one of the compounds had been synthesised.

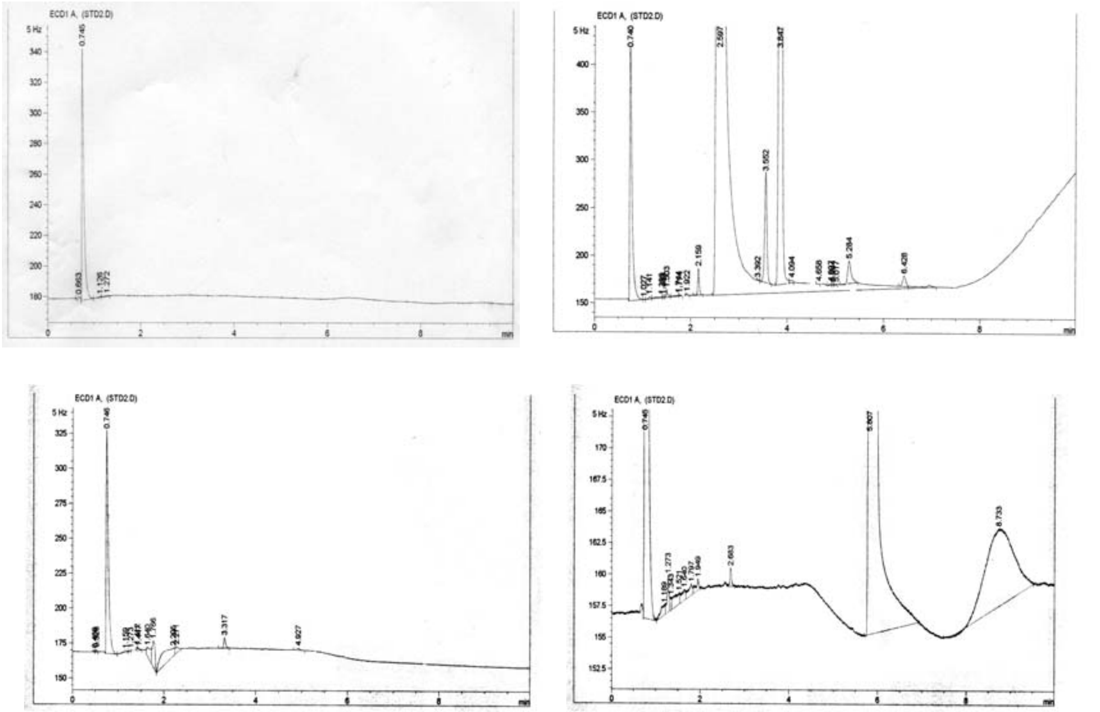


Figure 74 - GC/ECD analysis of acetonitrile (top left), 2-chlorocyclohexanol (top right), phenol (bottom right) and 2-chlorophenol (bottom right)

The reaction rate was faster than that of the unmodified cyclohexanol, indicating that the presence of the chloro group was having an influence on the structure. The problem however is that the results obtained are inconsistent, when the reaction was performed the products detected were often different from those of the previous run. It is possible that this reaction is highly sensitive to small changes in the reaction conditions. Possible factors could be water contamination, as while a lot of effort was taken to ensure that the acetonitrile was as dry as possible, it can occur, perhaps through the use of glassware that was not completely dry. The reaction could also be sensitive to the amount of dissolved oxygen in the solvent. A final factor that could be examined is the effect of heat on the reaction. The UV lamp used in this study is high powered and as such produces a lot of hot air and some heating of the sample did occur despite the use of an extractor fan. It is possible that small variations in temperature could effect how the reaction proceeds. Even if it is not the presence of the heating directly that is a factor, heating has an effect on the ability of the solvent to absorb oxygen.

Giving a mechanism for the aromatisation is hard as it is not known what is causing the reaction to be changed, nor the exact compound produced. If this was known then it would be far easier to determine. The GC/ECD analysis showed a number of peaks in the aromatic sample, it is possible that some of these were caused by by-products of the reaction. One possibility is that oxidation did occur and that the ketone was produced, but that the compound continued reacting, figure 76. Photocatalytic oxidation is a dehydrogenation reaction, that is during the reaction hydrogen is removed; therefore it is not impossible that the dehydrogenation could continue until the sample was aromatic. However this would seem to be a big change in the photocatalytic oxidation, and raises the question of why it was never observed to have occurred in the other samples, only 2-chlorocyclohexanol.

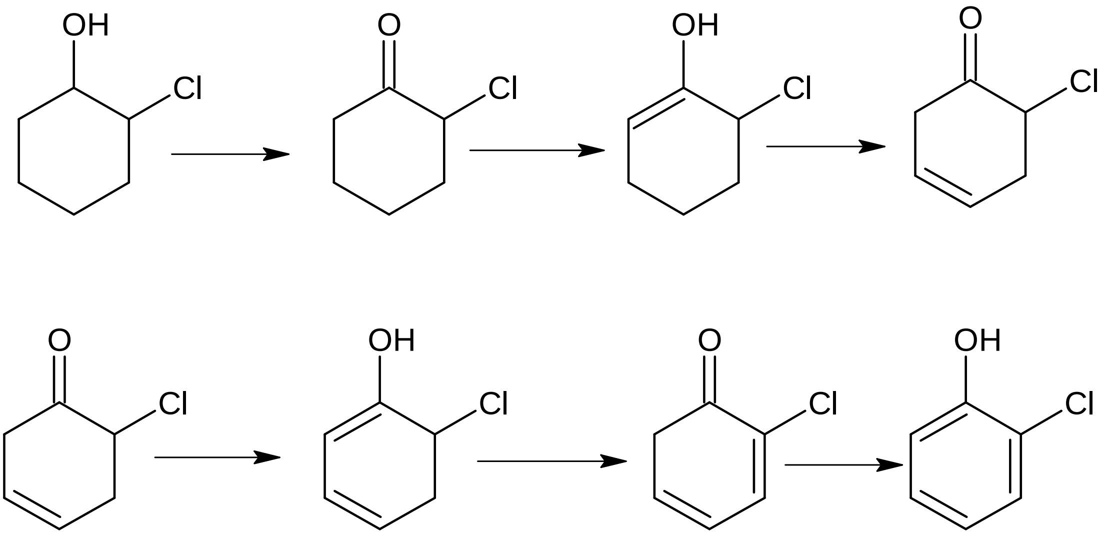


Figure 75 - Possible mechanism for the aromatisation of 2-chlorocyclohexanol

Aromatisation is not an unknown reaction, it can be performed in a number of different ways although in most the actual mechanisms of the reaction are not known. It can be performed using a hydrogenation catalyst such as platinum, palladium, or nickel heated to 300-350 °C. Another chemical technique for the creation of aromatic compounds is transfer hydrogenation[20]. This technique works by using a catalyst to transfer hydrogen from the reactant to an unsaturated compound. This is often done using an aromatic compound so that the overall effect is to transfer the aromaticity from one compound to the other. A common effect of the reaction is that halides are often removed, which did not occur in this case.

Among the reagents that have been used in aromatisation reactions are atmospheric oxygen, MnO_2, SeO_2, strong bases, chromic acid, and activated charcoal. Of the possible causes of aromatisation only one was present in the solution; oxygen. If it is possible for atmospheric oxygen to act as a reagent in the aromatisation then it would seem possible that the more reactive superoxide, produced in photocatalysis, could do the same. This could work with the superoxide pulling off hydrogens to become hydrogen peroxide. This would be similar to transfer hydrogenation. Again the question is raised that if this was the mechanism through which the aromatisation occurred then why was it only observed with 2-chlorocyclohexanol.

There are a number of possible reasons for the results found. One is that a variation or contamination of the reaction mixture occurred, such as the presence of water. The problem with this though is why the contamination only occurred in the 2-chlorocyclohexanol samples, it never happened in any of the others. If it was simply an experimental error then it should have occurred at least once in the other reactants.

That it did not would indicate that it was something particular to 2-chlorocyclohexanol that caused the aromatisation.

If the reaction was due to 2-chlorocyclohexanol then there are several areas that could be involved. The first would be that the 1,2-dichlorocyclohexane, which was present as a by-product of the 2-chlorocyclohexanol manufacturing process, somehow affected the photocatalytic oxidation. The analysis of the samples however showed no evidence of the dichlorocyclohexane being consumed, which would mean that if this was occurring then the dichlorocyclohexane was acting catalytically. This would seem unlikely although this could be checked through the use of a pure sample of 2-chlorocyclohexanol, one which did not contain 1,2-dichlorocyclohexane.

The next possibility is that the reaction was due to a chemical effect of the chloro group. One possible way of testing this would be to use compounds where the chloro group is replaced by other halides such as bromine or fluorine. They all have similar chemical properties so the use of a compound such as 2-bromocyclohexanol would give a material with similar chemical properties as 2-chlorocyclohexanol.

Another possibility, and one of most interest to this research is that it was due to the inductive influence of the chloro group. All compounds so far have had electron donating groups attached. The effect of these is that the reaction occurs more slowly than that of cyclohexanol. 2-chlorocyclohexanol however contains an electron withdrawing chloro group, the effect of this being to increase the rate of reaction. It could be possible that the aromatisation was due to this, if the hydroxyl is weakened enough through the inductive effect then the aromatisation could occur. This is unlikely as if this was possible other researchers would have observed and reported it. A way to test this would be by using another cyclohexanol compound, one which contains a group which has a strong inductive influence. This would have to be something other than a halide to avoid the possibility of the chemical effect of the halide taking part in the reaction. In addition the presence of an unsaturated area would be useful. While the mechanisms of many aromatisations are unknown, some of the factors influencing them are. One is that the presence of one or two double bonds, or even a benzene ring fused to the main ring, can make the aromatisation easier to perform[21]. By using an unsaturated group with a strong inductive influence a compound could be used to test the possibility of the reaction being due to inductive influence. The group would offer inductive influence and the lack of saturation would make the compound easier to aromatise, ensuring that the reaction can occur then.

An alternative to aromatisation is the possibility of an enol having been synthesised. Enols are alkenes with a hydroxyl group attached to one of the carbons in the double bond. These are isomers of ketones and aldehydes, with a chemical equilibrium occurring between the two forms (figure 77).

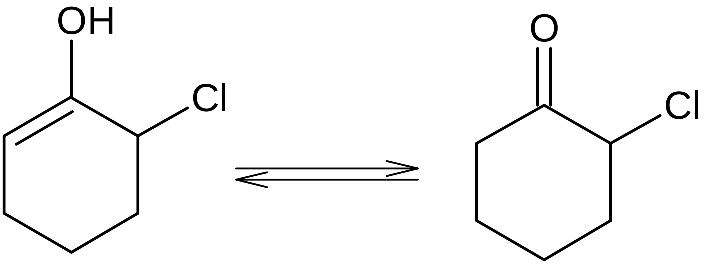


Figure 76 - Keto-enol tautomerism

They are however unstable and the keto form is normally far more common. But the equilibrium is affected by the conditions such as pH and temperature.

It is possible that the reason that the chloro oxidation was rather random with its results was that the reaction was producing an enol. Variations in the reaction conditions would then affect the equilibrium, so that under different conditions different compounds were being produced. The presence of enols can also explain the ferric chloride results as enols are the other chemicals that give a positive result with the test. However stable enols are rare so the possibility of this having occurred, while not impossible is unlikely.

4.2.5 1,2,3,4-Tetrahydronaphthol

The next of the test compounds to be examined was 1,2,3,4-Tetrahydronaphthol. This compound is like that of unmodified cyclohexanol but with a conjoined benzene ring. Figure 78 shows the chemical structure of 1,2,3,4-tetrahydronaphthol. The unsaturated ring has a large inductive influence[21] and should therefore have a strong destabilising effect on the oxygen of the hydroxyl group.

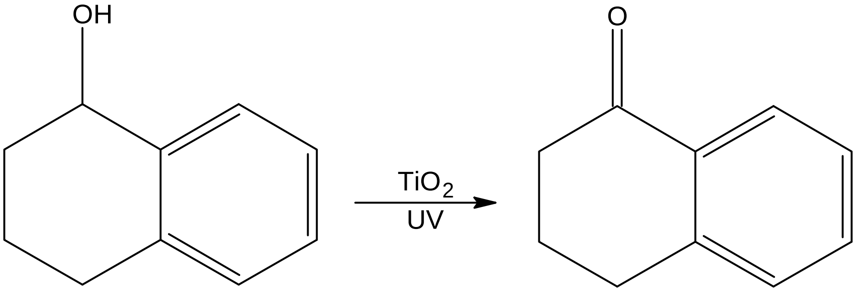


Figure 77 - Molecular structure of 1,2,3,4-tetrahydronaphthol

Figure 79 shows the GCMS data from the analysis of the starting and photocatalysed samples, with just the reactant peak evident in the first sample but a second peak in the photocatalysed sample. The initial peak was easily detected as 8.5 min; over the duration of the reaction this peak rapidly diminished to a fraction of its original size. With the disappearance of the initial peak came the appearance of a new peak at 8.74 min, this rapidly grew in size approaching the size of that of the original size of the starting peak.

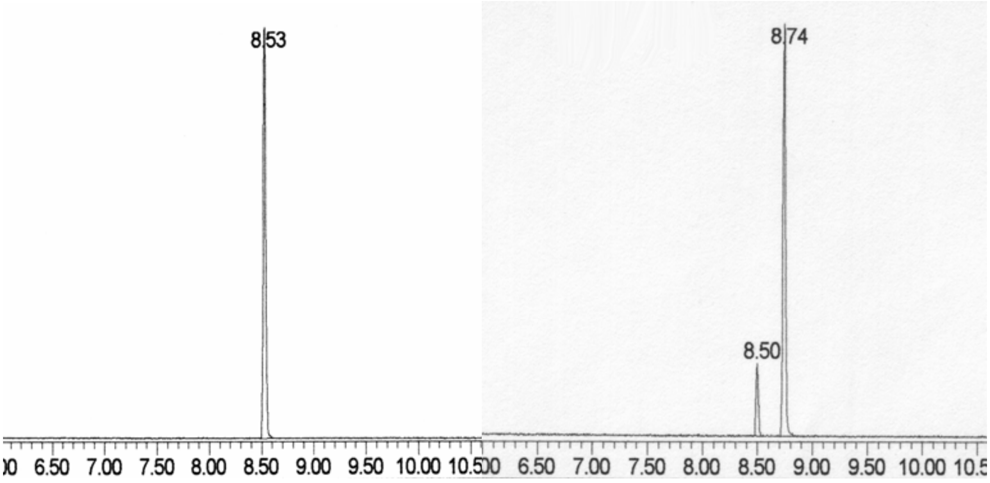


Figure 78 - GCMS data from the analysis of 1,2,3,4-tetrahydronaphthol before (left) and after (right) photocatalysis

The initial peak was identified from its mass spectrum as 1,2,3,4-Tetrahydronaphthol. Examination of the mass spectra showed the molecular ion at 148 corresponding to the molecular weight of tetrahydronaphthol. Figure 80 shows the mass spectra obtained from the peak in the starting sample. The 130 signal is due to the molecular ion minus the hydroxyl group. The 120 fragment however is due to the molecular ion minus C_2H_4. The peaks at 105 and 115 would then be due to the fragmentation of a CH_3 group from the 120 and 130 fragments respectively.

The product peak in the photocatalysed sample was identified as 3,4-dihydro-1(2H)-naphthalenone by use of the GCMS library of spectra. A more commonly used name for this compound is tetralone, and was the expected product. The mass spectrum of the peak showed a mass ion at 146 which is the structural weight of tetralone. Ions at 118 and 131 were detected, the 131 due to the molecular ion minus a CH_3 group. The 118 ion is a drop of 28 from the molecular ion which is equal to C_2H_4. This drop of 28 was followed by another to 90. This confirmed the identity of the product as tetralone.

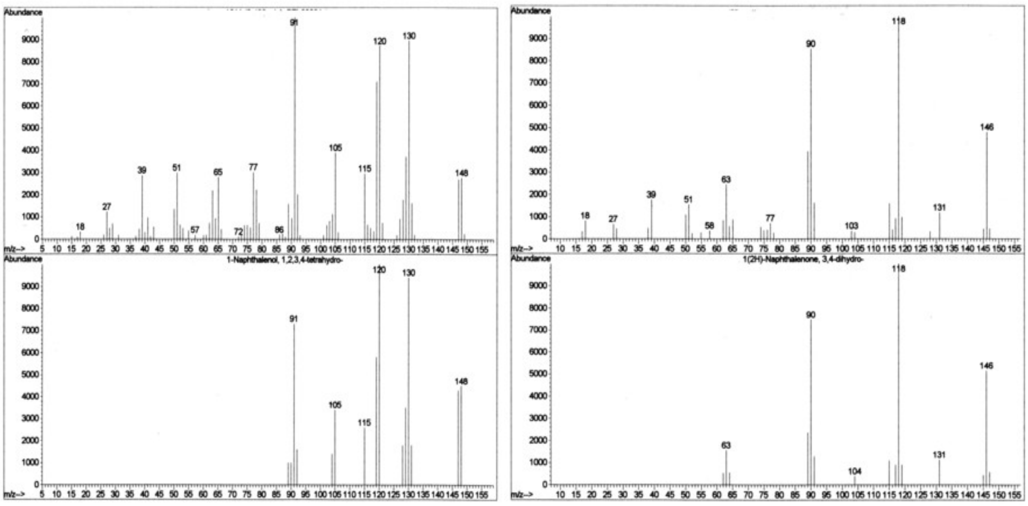


Figure 79 - Mass spectra of the initial sample and product (reference top, recorded bottom)

Figure 81 shows a chart of the photocatalysis of 1,2,3,4-tetrahydronaphthol using P25, UV100 and Aldrich anatase TiO_2. As observed with the other compounds some catalysts perform better than others. The Aldrich again gave a low performance with only a 27% yield whereas the P25 gave a 45% yield. The best results were from the UV100 with a 90% yield of the 1,2,3,4-tetrahydronaphthol over the duration of the reaction. These results show that in this photocatalysis the rate is influenced by both the catalyst composition and the surface area. The P25, which is a mixture of anatase and rutile TiO_2, gave a better performance than that of Aldrich which is pure anatase. Also the UV100 gave a far greater result than that of the Aldrich despite both catalysts being composed of just anatase TiO_2. As they are both anatase the difference in results must be due to the larger surface area per gramme of the UV100. When compared the data shows that the P25 was almost twice as effective as the Aldrich anatase, but that the UV100 was twice as effective as the P25. This would indicate that while both catalyst composition and surface area play an important part in the reaction rate, the surface area has the greatest effect. This is not of great surprise as in photocatalysis the compound has to adsorb onto the surface of the catalyst for the reaction to occur.

A greater surface area would allow more to be adsorbed at any time, and therefore the reaction to occur more quickly.

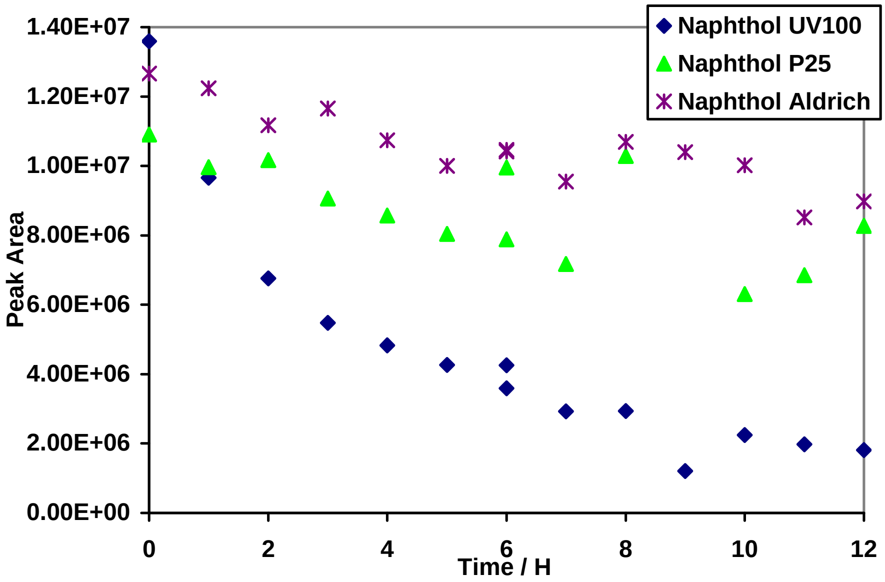


Figure 80 - Photocatalysis of 1,2,3,4-tetrahydronaphthol

The data obtained is interesting as apart from the data on the catalysts it also shows that this compound can be photocatalysed easily. This would seem to prove the initial belief that 1,2,3,4-tetrahydronaphthol photocatalyses more readily than unmodified cyclohexanol. This is due to a number of factors; the benzene ring generates a large inductive influence and so will have weakened the hydroxyl making it more willing to react. Also the presence of the benzene means that resonance stabilisation will occur between the carboxyl group and the benzene, this stabilisation will have aided the reaction. Also of note is that no aromatisation was observed, indicating that it was not being caused by inductive effect.

Among the compounds oxidised by Stoltz[22] is Tetrahydronaphthol. The oxidation used Pd(norbornadiene)Cl_2 and sparteine in $CHCl_3$. The reactions were performed in air at atmospheric pressure and room temperature just as in photocatalysis. The paper reported a conversion of 60% after 16 hours, considerably lower than the yield obtained with photocatalysis. This shows that photocatalysis is the better technique. The palladium catalysed method has a number of disadvantages when compared to photocatalysis, one of the main ones being its complexity. While the Tetrahydronaphthol was oxidised at room temperature and in an open vessel, the reaction is normally performed at 60-80 °C in a pure oxygen atmosphere. These reaction conditions make the technique a lot more expensive than photocatalysis which only requires adding the catalyst to the reaction solvent and irradiating it. This method also appears to require larger reaction times than photocatalysis. While the Tetrahydronaphthol was reacted for 16 hours, which is longer than that used in the photocatalysis, this is shorter than many of the other compounds tested, some being reacted for as much as 192 hours. When compared with photocatalysis the palladium catalysed technique has no apparent advantages, it is harder to perform and gives a poorer performance. One unusual thing is that, in the paper, the authors despite using a number of aromatic compounds, make no mention of the fact that the resonance induced stability would have had an effect on the results.

4.2.6 Oxidation of the cyclosteroid

Once the cyclohexanol derivatives were studied a photocatalytic oxidation was performed on the cyclosteroid synthesised in chapter 3. Figure 82 shows the photocatalytic oxidation of the cyclosteroid.

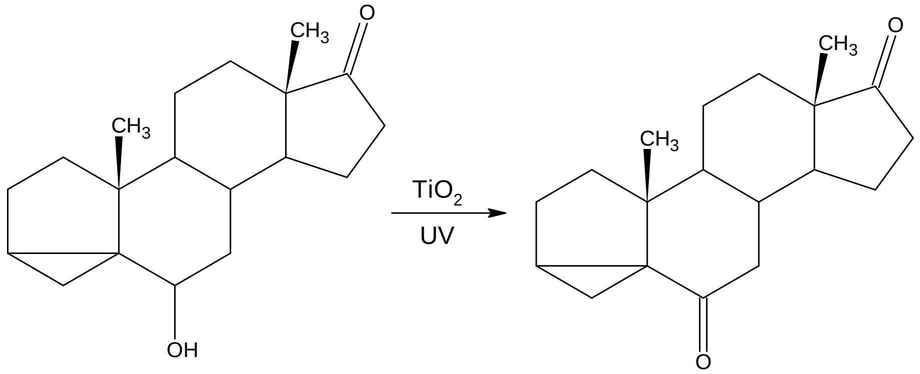


Figure 81 - Oxidation of the cyclosteroid

Steroids are complex structures that can be susceptible to bond breakage during chemical oxidation. Unsaturated bonds in particular are prone to attack during chemical oxidation. With a structure such as the steroid the problems associated with the use of chemical oxidation are increased. The three membered ring created during the synthesis adds a major point of stress to the structure, one that could be easily broken during oxidation. The ideal angle for a carbon bond is 109.5°, when molecules are unable to achieve that angle (as is found in ring structures containing less than six-members) then strain is placed on the bond. The further from 109.5° the greater the strain. A three-membered ring has a bond angle of 60° and also due to the small size of the group the ring is not able to twist itself in order to move the bond angle closer to 109.5° to decrease the strain on the bonds[16].

The three-membered cyclopropyl ring is considered to be a reactively electronegative group. From the previous studies it has been seen that the presence of an electron withdrawing group on a 2 carbon affects the density of electrons around the oxygen of the hydroxyl group. This should result in a drop in stability at the oxygen, resulting in it being more willing to react. However the effect of the presence of the other rings within the steroid is unknown.

There is also the possibility of the structural conformation of the steroid having an effect. The conformation generated by the presence of the cyclopropane is similar to that of the half chair conformation, figure 83. The presence of this conformation creates a bend in the structure. It is possible that if the hydroxyl group was positioned on the inside of the bend rather than the outside, then the bend could hinder the hydroxyl's ability to adsorb to the catalyst. If the bend was large enough then the ends of the steroid could make contact with the surface of the catalyst but the bend would hold hydroxyl up, out of reach of the catalyst. This is due to the large differences in size between the steroid and catalyst, but this size difference does not occur in chemical oxidation techniques. Steric influence such as this would not affect chemical oxidation techniques as the oxidation agents would be small enough that the structural bend would have no influence. The possibility of this occurring in photocatalytic oxidation however may be small, in the photocatalytic oxidation of 2-methylcyclohexanol no steric influence was observed. Both cis and trans conformations were equally effected by the reaction. If photocatalysis was sensitive to steric influence then something would have been observed, the cis 2-methylcyclohexanol where the methyl and hydroxyl groups are in closer proximity would have reacted at a slower rate if steric hindrance had any influence. An alternative to that would be that the reaction of both the cis and trans was sterically hindered. Again however this is unlikely, the 2-methylcyclohexanol had a reaction rate not much slower than that of cyclohexanol. If steric hindrance was affecting both cis and trans then that would have been recorded as a slower reaction rate that that actually observed.

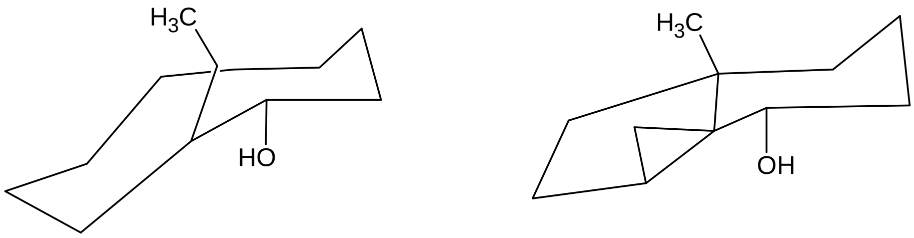


Figure 82 - Structures of the half-chair arrangement and the 3α,5,cyclo-5α of the cyclosteroid

The GCMS data showed a single peak at 33 minutes but when the samples were tested, no reduction in the peak area could be seen when comparing the spectra from the starting solution to the photocatalysed solution. This is shown in figure 84 with the sample of the starting solution and the sample of the photocatalysed sample.

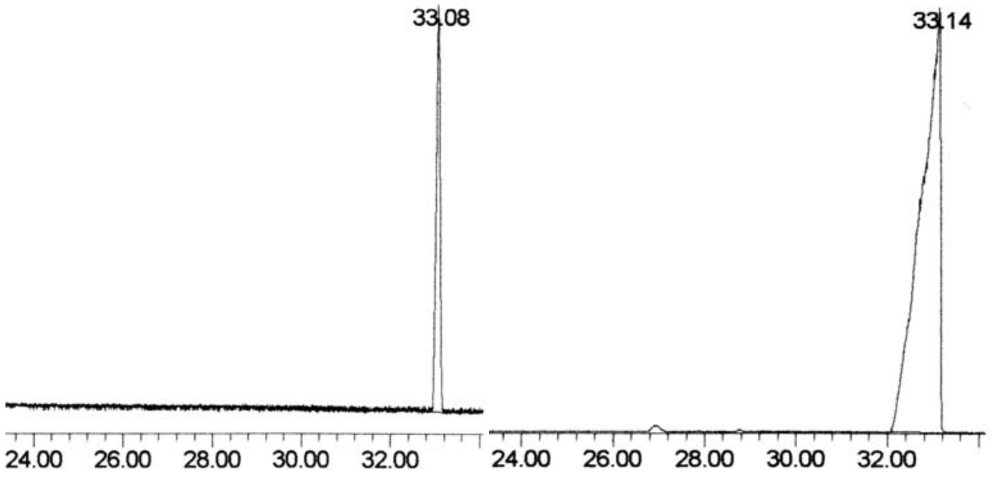


Figure 83 – GCMS data of the cyclosteroid sample before (left) and after (right) oxidation

Both the starting solution and the photocatalysed solution were analysed using FTIR spectroscopy. Figure 85 shows the FTIR spectrum of the starting and photocatalysed samples. When the spectra were compared they showed peak disappearances at 2400, 1700 and 1200 cm^{-1}. The losses of these peaks could be the result of the loss of a carbonyl group. The starting steroid contained two carbonyl groups, a hydroxyl group attached to the body of the steroid, and a carbonyl in the ketone group. If the hydroxyl group had been oxidised then a loss of OH bonds around 3600 cm^{-1} would be observed with an increase around 1700 cm^{-1} corresponding to the carbonyl formed by the oxidation of the hydroxyl group to the ketone. Therefore there is the possibility that any reaction that has occurred happened at the existing ketone group in the steroid rather than at the hydroxyl group as intended.

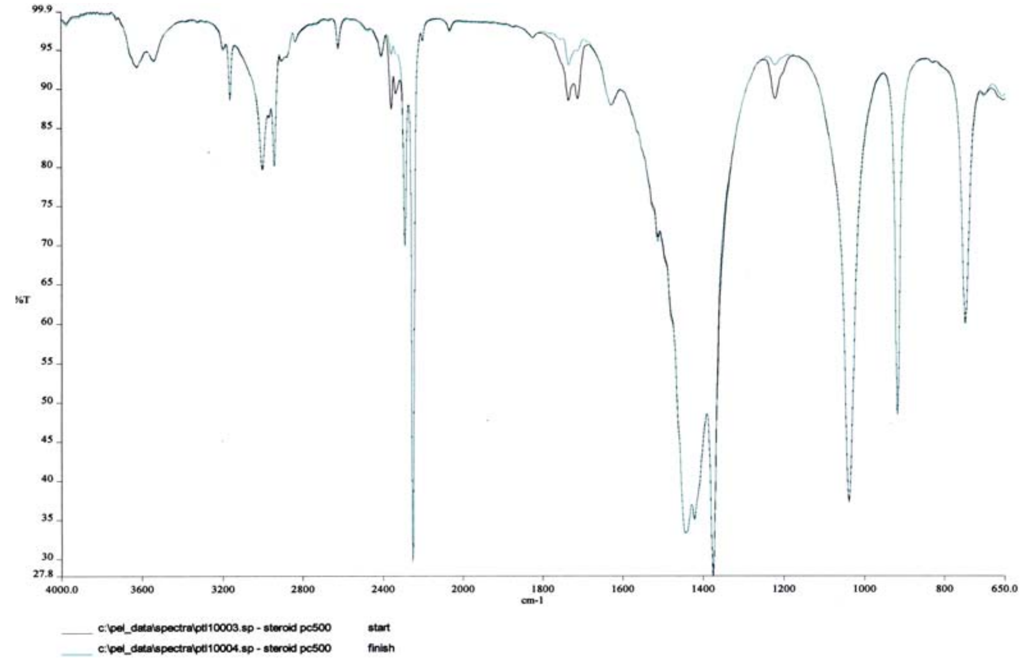


Figure 84 - FTIR spectrum of the cyclosteroid sample

This is however unlikely as while the oxidation of ketones can be performed there is no evidence from past experimentation to suggest that photocatalysis has any selectivity towards the oxidation of ketones. The data from the other cyclic alcohol oxidations did not show any evidence that the ketone product was being further oxidised during the reactions. In addition the ketone group present in the steroid is next to a methyl group which has been shown to retard oxidation.

However the FTIR spectra showed only small differences so it is hard to conclusively determine from them if the reaction has occurred.

The results do not however mean that the oxidation of the hydroxyl group cannot be done using photocatalysis. Photocatalytic studies using reactants as large steroids are not common so there are many factors that are not fully understood. Steroids are complex structures containing many functional groups, all of which will have an effect on the reaction.

In further studies the possibility of steric hindrance could be examined more closely. While there was no obvious evidence of steric hindrance in the test compounds used in the study it is possible that with compounds as large as steroids steric effects could become a factor.

A useful study would be an examination of the photo-oxidation of cyclohexanol conjoined with a saturated ring rather than the unsaturated ring of 1,2,3,4-tetrahydronaphthol. This study would show the effect of this group on the ability of the hydroxyl group to be oxidised and give insight into the effect of the other rings present in the steroid.

Additionally it has been shown that electron withdrawing groups have a destabilising effect on the oxygen atom of the hydroxyl group, causing it to react more readily. Also it is possible that the destabilising effect could extend to not just the hydroxyl group but to the entire molecule, particularly the already fragile three-membered ring[16].

These studies show how photocatalysis is still a technique in development. While photocatalytic oxidation is a rather simple reaction the details of the reaction can vary between papers. These can even give contradictory methods, where one paper can report that aerating the solution gives the best results while another paper may report that the best results were obtained when the solution was purged with nitrogen to remove the oxygen from the solution. Photocatalysis is a technique that is still being refined and optimised, the number of different forms of TiO_2 gives evidence to the fact that a method has been developed that gives the best performance. The fact that the steroid was not oxidised does not mean that it can not be done but merely that the techniques requires further developing.

4.2.7 Comparisons of rates of oxidation of the Cyclic alcohols and influence of substituent groups

When the rates of oxidation of each derivative were compared some interesting results became apparent. The results show that the chloro compound reacted faster than the unmodified cyclohexanol (figure 86). The methyl form however did not show much difference, and only a limited oxidation of menthol to menthone was observed. As the main differences between each of these compounds are the functional groups attached any differences in reaction rate should be due to the effect of these groups.

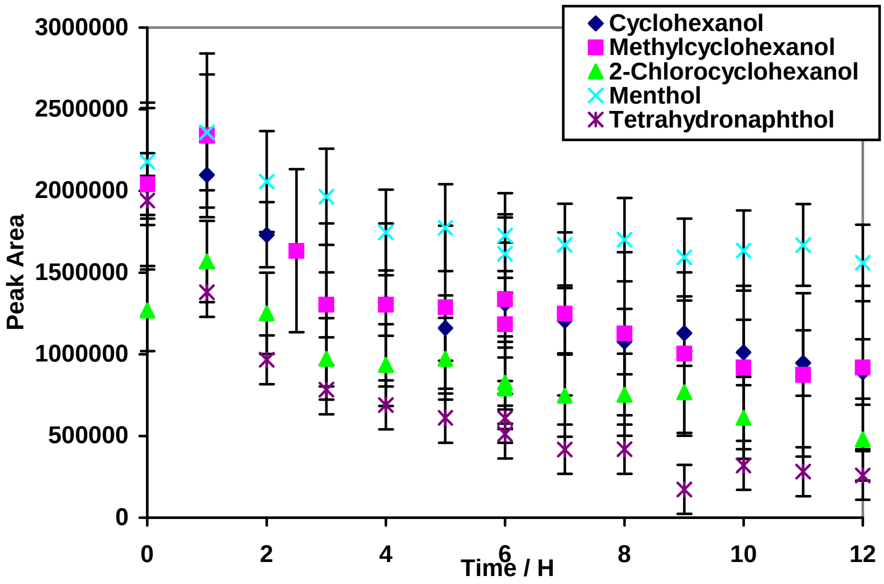


Figure 85 - Chart of the photocatalysis of different compounds

Under induction theory electrons are drawn towards the electronegative points in a molecule, with an alcohol one of these is the hydroxyl group. These additional electrons near the hydroxyl group serve to stabilise the bond between the hydrogen and the oxygen. The effect of this should be to make the bond harder to break. If an electron donating group is present in the molecule then the number of electrons should be increased, this should result in more electrons near the hydroxyl group and a further increase in the stability of the O-H bond. However if an electron withdrawing group is present then this adds another electronegative point in the compound, the electrons will then be drawn towards the electronegative points, the electrons being shared based on which group is most electronegative. The more electronegative points will receive the largest share of the electrons. This sharing of the electrons will reduce the electrons at the hydroxyl group and reduce the stability of the O-H bond. The differences in stability between the different compounds should be observed as differences in their ability to react, the more stable compounds being harder to react and therefore slower to react while the less stable are easier and faster.

Functional groups such as methyl are electron donating; therefore their presence has a stabilising effect on the structure decreasing the ease of the reaction by adding electron to the structure. Electron withdrawing groups such the chloro group and benzene draw electrons away from the hydroxyl group, this results in the structure becoming less stable and allows the reaction to proceed more easily. Table 3 shows the reaction rates of the samples photocatalysed with PC500 TiO_2.

Table 3 - Table of recorded reaction rates

REACTANT	RATE OF REACTION / X10^{-8} mol s^{-1}
CYCLOHEXANOL	0.91 ±0.02
2-METHYLCYCLOHEXANOL	0.41 ±0.08
2-CHLOROCYCLOHEXANOL	1.17 ±0.07
MENTHOL	0.22 ±0.03
1,2,3,4-TETRAHYDRONAPHTHOL	1.74 ±0.33

The calculated rates of reaction showed the effects of the neighbouring functional groups more clearly. The reaction rate of the methylcyclohexanol at 0.41x10^{-8}mol s^{-1} was slightly slower than that of the cyclohexanol at 0.91x10^{-8} mol s^{-1}, this was to be expected as the methyl group is an electron donator and should have had a stabilising effect. The menthol was even slower again than 2-methylcyclohexanol, with the slowest recorded rate at 0.22x10^{-8} mol s^{-1}. Again this is not surprising; menthol has two electron donating groups attached, a methyl group and a propyl group. Most of the donating effect will be from the propyl group which is more electron donating that the methyl of 2-methylcyclohexanol. The methyl present in the menthol however will have less effect than the methyl of 2-methylcyclohexanol, the donating effect of the menthol methyl group being severely reduced by the additional distance between the group and the hydroxyl.

With 2-chlorocyclohexanol and 1,2,3,4-tetrahydronaphthol the functional groups attached served to increase the rate at which the hydroxyl group of the alcohol reacted. Both of these compounds contain strong electron withdrawing groups, 2-chlorocyclohexanol with a rate of 1.17×10^{-8} mol s^{-1} reacted faster than cyclohexanol, not unexpected with the presence of the electron withdrawing chloro group. The fastest rate however was 1.74×10^{-8} mol s^{-1} observed for 1,2,3,4-tetrahydronaphthol. This group has an electron withdrawing benzene ring conjoined to the ring of the cyclohexanol. The high rate shows the electron withdrawing abilities of the group which stabilise itself using resonance. This is interesting as under resonance laws the hydroxyl group would switch from being electron withdrawing to electron donating, something which would result in a large destabilisation of the hydroxyl. However in tetrahydronaphthol the benzene and hydroxyl group are sufficiently separated that only induction applies.

4.2.8 Effect of Catalyst

The results were analysed to determine which catalyst was the most efficient for the photooxidation of cycloalcohols.

The samples were photocatalysed using four different Titanium dioxide semiconductor photocatalysts; these were Aldrich Anatase, P25, UV100 and PC500. These catalysts gave a range of titanium dioxide phase mixtures as well as different surface areas, allowing for the effect of catalyst variations to be examined. The rates of reaction were compared.

Of the catalysts chosen the most commonly used is Degussa P25, this is an extremely popular catalyst, used particularly in photocatalytic remediation. Its ratio of 70% anatase to 30% rutile has been found to be ideal for photocatalytic destruction[2]. Another standard is the pure anatase; this is also a commonly used catalyst with many photocatalytic applications. The other two catalysts are both high surface area forms of anatase, their greater surface areas allowing more of the reactant to be adsorbed to the catalyst surface where it can react. One issue with titanium dioxide is that a batch reaction as was used here requires that the catalyst be suspended in the solution; this then creates a problem of removing the catalyst afterwards. This could be done through techniques such as filtering or centrifuging, but the small particle size of the catalyst does not make this easy. Catalysts with a high surface area normally achieve this through smaller particle size which can make removal harder. One solution is to use an immobilised catalyst but this normally results in a large loss of surface area.

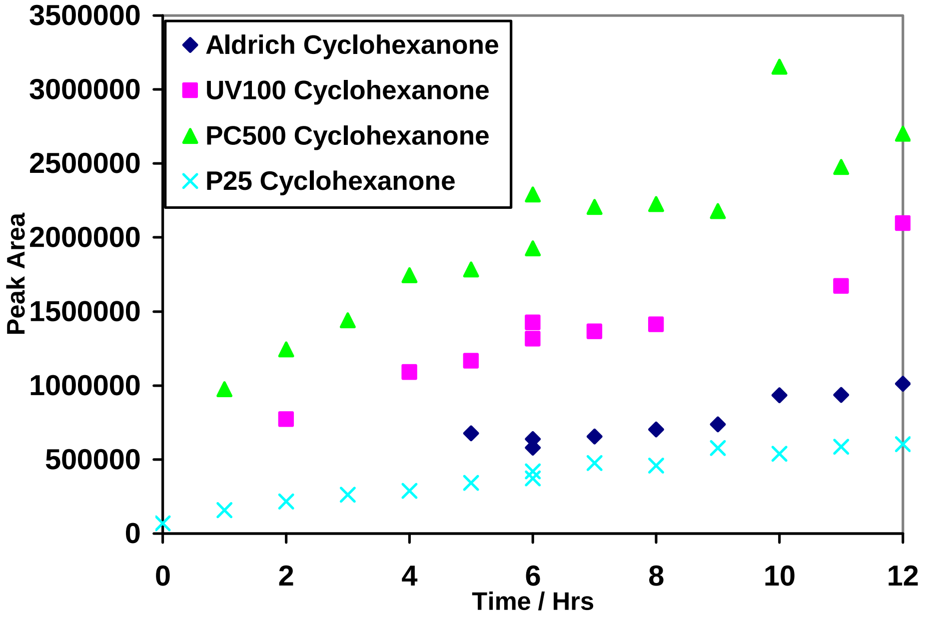


Figure 86 - Photocatalysis of cyclohexanol using different catalysts

The best yields were obtained from the UV100, PC500, and P25. The UV100 gave 41%, the PC500 38% and the P25 43% (figure 87). This fits with the data obtained from the photocatalysis of the other compounds. This is interesting that UV100 and PC500 are there as they have the smallest particle size and so have the greatest surface area. The poorest yield was from the Aldrich anatase with only 25%.

These results show that the surface area is very important to the rate of reaction, as would be expected. Greater surface area gives a greater are for the reactant to adsorb to and react. The composition of the catalyst is also clearly an important factor in the reaction rate; the P25 gave as good a yield as the UV100 and PC500 even though it has a particulate size at least three times that of UV100 and PC500. Therefore the mixture of anatase and rutile in P25 work better than would be obtained from a catalyst, of similar particle size, composed of anatase alone.

A number of different forms of TiO_2 catalyst have been used in photocatalytic reactions, from pure rutile to pure anatase, from gold doped to platinized. Ohno et.al[23] examined the photocatalytic oxidation of naphthalene using a range of TiO_2 catalysts. They found that for the reaction rutile had far higher activity than anatase. The best results however were not obtained from pure rutile; they found that activity was greatly enhanced by a small quantity of anatase. They believed that while the naphthalene was mainly oxidised on the rutile, that the oxygen was mainly reduced on the anatase. These two working together gave the best performance.

4.3 Conclusion

This chapter demonstrates the photocatalysis of cyclic alcohols in acetonitrile by TiO_2 catalysts. It also shows how variations in the structure can have an effect on the ability of the compound to react. By varying the functional groups attached at a single point in the parent compound it has been possible to see the effect of electron donating and withdrawing groups on the reactivity of the parent compound. By doing so it may be possible to gain the ability to quickly gauge the difficulty of photocatalytic oxidation reactions.

The experimental data showed that changes to a base compound such as cyclohexanol can either make the oxidation rate increase or decrease. This was tested through the use of a functional group on a 2 carbon of cyclohexanol. A faster reaction was obtained with 2-chlorocyclohexanol and 1,2,3,4-tetrahydronaphthol. The addition of an electron withdrawing group such as the chloro group has a destabilising effect on the oxygen atom, making the compound more willing to be oxidised, and thus a faster reaction was observed. The data also showed that a compound such as 2-methylcyclohexanol which contains an electron donating group was more stable than cyclohexanol.

The effects of electronegativity on bond stability are well known but the results obtained helped to prove that their effects on structural stability holds true for the oxidation of cyclic alcohols by TiO_2 photocatalysis.

The data obtained from the analysis of the catalyst types showed that the best reaction rate was observed in the samples using PC500; this was the catalyst with the smallest particulate size and therefore had the greatest surface area per gramme of catalyst when compared to the other catalysts. The larger the surface area of a catalyst the larger the area a compound has to adsorb to and be catalysed, so the fact that this catalyst gave the fastest rate was not surprising. It did however help to show that different catalysts are better for different reactions; some catalysts have more affinity to certain reactions than others. For example one of the poorest catalysts tested was Degussa P25, one of the most popular commercially available catalysts.

This set of experiments has helped to gain a better understanding of the effects that determine how quickly a reaction proceeds and the factors affecting it. It also helps to show where problem areas may occur and how they may be resolved. Where a person was trying to synthesise a compound and having problems with their yields then they may find that the groups within the compound cause sufficient retardation of the reaction that it would be better to try the reaction using an alternative compound.

The one area left that still requires further study is that of the photocatalysis of 2-chlorocyclohexanol, this is the one area that has left the most unanswered questions. The data obtained showed that the compound produced by the reaction could vary quite widely from experiment to experiment; this indicates that the reaction may be very sensitive to variations in the reaction conditions outside of the reaction controls. It is possible that the reaction is sensitive to air temperature, small variations in dissolved oxygen concentrations, or even the presence of water in the acetonitrile. These being the actual cause are unlikely however as the fact that the aromatisation only occurred in 2-chlorocyclohexanol would make it unlikely that contamination was the cause. If contamination occurred multiple times with 2-chlorocyclohexanol then it would be likely to also occur with the other compounds. The Tetrahydronaphthol helped to put further doubt on the inductive effect as the cause of the aromatisation, as it would be likely to occur with tetrahydronaphthol. However the aromatic ring of tetralone would undergo resonance stabilisation with the carbonyl group. This stabilisation would make further reaction of the compound difficult. It does however show that inductive effect only increases the reaction rate of the oxidation to the ketone, not cause the reaction to occur differently.

This would indicate that the aromatisation is likely to occur after the ketone has been produced. This aromatisation is most likely due to a chemical effect of the chloro group, probably as a result of the chloro group leaving the ring. The carbonyl then takes a hydrogen from the ring, generating a double bond on the ring. If the reaction were to continue it would result in the aromatisation of the ring.

The very limited experimentation on the cyclosteroid due to the short amount of time gave no opportunity for conclusions to be made on how successful the reaction would have been. The interactions studied while giving insight into the reaction are simpler than those occurring in the cyclosteroid. The cyclosteroid is affected by a combination of the rings, the methyl groups and the cyclopropane group; these will all affect the oxidation of the hydroxyl in different ways and to different extents. There is also the question of how the cyclopropane group will effect the reaction; it is a complex compound that is not fully understood.

Further examination would be aided by looking at compounds containing more complex interactions to investigate how the influences of the different groups interact.

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Chapter Five

Conclusion

5.0 Introduction

The goal of the project was to examine the possibility of using semiconductor photocatalytic oxidation to aid in the synthesis of a steroid, containing a cyclopropane ring. As a result of the presence of this ring the compound is fragile and could be damaged by standard chemical oxidation techniques. Photocatalytic oxidation offered the possibility of oxidising the compound without causing the cyclopropane to be broken.

The first stage of the study was to perform an organic synthesis, this involved generating a three membered ring in the A ring of a steroid. The photocatalytic study involved an examination of some of the structural influences that can affect the performance of a photocatalytic reaction reaction. This was carried out by using cyclohexanol as the base compound; this would give a simplified form of the groups within the steroid involved in the photocatalysis, the hydroxyl group and the cyclohexane ring. By examining the effect attached groups have on the oxidation of the hydroxyl group it is possible to gain some understanding of the effect of neighbouring groups on reaction rate. This would allow some understanding of the influences inside the synthesised steroid.

Chapter 5 - Conclusion

5.1 Steroidal Synthesis

The first stage of the study focused on the chemical synthesis of the steroid Dehydroepiandrostanone (DHEA) changing it to the steroid to be used in the photocatalytic oxidation. This was a two stage process; the first stage involved the addition of a tosyl group to the DHEA at carbon 3 on the steroid. The second stage was the removal of the tosyl group leaving a positive charge on carbon 3. This allows a rearrangement of the steroid that creates a cyclopropane ring.

The first stage was a tosylation, a simple reaction where the product was confirmed by FTIR analysis, which clearly showed the appearance in the sample of functional groups consistent with the presence of a tosyl group. The next stage was equally simple with the tosyl group being removed to allow a rearrangement to occur and create a cyclopropane group. This product was analysed by FTIR, GCMS and ^{1}H NMR analysis. The FTIR spectrum showed the loss of the tosyl group from the structure, as well as the addition of a hydroxyl group. It also showed a peak among the C-H peaks at 3000cm^{-1} consistent with the presence of a cyclopropane group. The ^{1}H NMR and GCMS also showed that the reaction had proceeded as expected and that the cyclosteroid had been synthesised correctly.

5.2 Photocatalytic Oxidation

An initial examination of the use of semiconductor photocatalysis for oxidation showed a general lack of understanding of the mechanisms through which it operates, with different mechanisms being offered by different people. A greater understanding of the factors influencing the reaction was needed; an understanding of what determines the success of the reaction. Initial testing of the photocatalytic oxidation was done using cyclohexanol as the test compound. Cyclohexanol is composed of a six-membered ring and a hydroxyl group; this gives a simplified version of the oxidation target area of the cyclosteroid but without as many interactions from other groups. By simplifying the structure for oxidation it was easier to determine what influences were effecting the reaction. This could be used to predict the chances of a compound being oxidised photocatalytically and could make the oxidation of the steroid easier to understand.

The analysis examined a number of factors that could effect the reaction. One of these was the effect the catalyst had on the rate of the reaction. Experimental studies demonstrated that certain catalysts showed greater affinity towards certain reactions over others. The catalysts investigated were all TiO_2 catalysts, with variations in surface area, and the ratio of rutile to anatase. In catalysis the larger the surface area of the catalyst under investigation the larger the area for the reactant to adsorb to and react. Therefore it was expected that the greatest reaction rates would occur with the catalysts with the greatest surface area. The results did show this, among the pure anatase catalysts the fastest reactions were obtained by the PC500 and UV100 catalysts which had the smallest particulate size and so the largest surface area per gramme of catalyst. The results for the effect of the ratio of anatase to rutile were less conclusive, some differences were seen in the rates of reaction among these catalysts but as they all had different surface areas it is more likely that it was the surface area that had the greatest influence.

The other factor that was examined was the influence that neighbouring functional groups had on the reactivity of the hydroxyl group to be oxidised. Inductance theory indicates that the area with the greatest induction power will draw electrons towards it, resulting in an increase in electron density around that point. If more than one inductive group are present then the electrons will be drawn to both, with the strongest group receiving the greatest amount. In cyclohexanol the electronegative hydroxyl group is an inductive group, the increase in electron density serving to increase the stability of the hydroxyl group. The stabilisation of the group should serve to make the group harder to oxidise. If an electron donating group was added to the cyclohexanol then this should serve to increase the number of electrons and so increase the electron density around the hydroxyl group further increasing the stability. The presence of a group with a strong inductive influence would result in the electrons drawn to the hydroxyl group being divided between the two groups; this would result in a lowering of the stability of the hydroxyl group and an increase in the susceptibility to oxidation.

By studying cyclohexanol with different groups attached in adjacent positions to the hydroxyl it was possible to learn about some of the factors that affect the hydroxyl group, and through it affect the rate at which the compound was photocatalytically oxidised.

The first compound investigated was cyclohexanol, through it a baseline could be created. By comparing the rates for cyclohexanol it would be possible to quickly determine if an adjacent group was having a positive or negative influence on the rate of the reaction. Visual observation of the sample showed a colour change in the sample, with a yellow colouration appearing. The production of the cyclohexanone was confirmed through the use of GCMS, UV absorbance spectroscopy and FTIR analysis.

Examination of the GCMS data made it possible to plot the loss of the cyclohexanol and the production of the cyclohexanone using the area of the peaks. The data showed that there was differences between the different catalysts used; UV100 showed a conversion of 41%, PC500 38% and P25 43%. The Aldrich anatase showed a conversion of just 25%. The similar yields of the UV100 and PC500 were not surprising as they are both pure anatase catalysts and both have similar particle sizes and surface areas. The low rate of the Aldrich is due to its smaller surface area, a smaller surface area gives the reactant less sites to adsorb to and react. The results obtained from the P25 are of interest as it has a larger particle size than PC500 or UV100. If surface area alone was the only important factor in the success of the photocatalysis then it should have given results, which while better than those of the Aldrich TiO_2, were not as good as PC500 or UV100. P25 unlike the other catalysts used is not a pure anatase TiO_2, but a 70/30 anatase/rutile mixture. Some TiO_2 mixtures have been found to perform better in some reaction than in others so it is possible that the good performance is due to the reaction having a preference to an anatase/rutile catalyst over a pure anatase catalyst.

Next was 2-Methylcyclohexanol, this compound is similar to cyclohexanol expect for the addition of a methyl group in the 2 position to the hydroxyl group. The methyl group is electron donating, therefore induction theory states that this would result in an increase in the stability of the hydroxyl group and therefore this compound would be harder to oxidise than cyclohexanol. When the sample was photocatalysed there was an indication that a reaction had occurred. The UV spectra showed that the photocatalysed sample was different from the starting sample, with a larger absorbance recorded.

The plots of the GCMS data was interesting, it showed a conversion of 17% with UV100, 21% with PC500 and 16% with Aldrich. This is interesting as all these results are lower than those observed with cyclohexanol, which would indicate that the addition of the methyl group to the structure had resulted in the compound reacting at a slower rate. This was an expected result, the presence of an electron donating group causing the compound to be harder to react. The differences in the rates of the catalysts were not great which is different from what was seen in the cyclohexanol where the PC500 and UV100 reacted at a higher rate than the Aldrich. A possible reason for this would be that the adsorption of the catalysts was not the rate determining step, that all the anatase catalysts were adsorbing the reactant but that the rate was being inhibited elsewhere. One possibility would be steric hindrance; the presence of the methyl group interfering with the ability of the catalyst to adsorb the reactant. However if this was the case then evidence would have been seen in the data. The reactant used was a racemic mixture so both cis and trans isomers of methylcyclohexanol were present. Steric effects would have shown themselves through differences in the rates of the two isomers. The cis isomer where the groups are closer together would have experienced more interference and so would have had a slower reaction rate than that of the trans isomer. However when the data was examined it showed that both 2-methylcyclohexanol peaks were converted by the same percentage; if steric hindrance occurred then they would have been converted by different amounts.

The presence of the steric hindrance could also be disproved through the results obtained from the P25 samples. With this catalyst a 55% loss was observed. This is far higher than that obtained with the other catalysts, if it was physical interference as in steric hindrance then this rate should not have been obtained. These results could indicate that the compound is oxidised more easily with an anatase/rutile catalyst.

This was followed by the oxidation of –Menthol, a compound containing both a methyl and propyl group. This should have the effect of stabilising the hydroxyl group, which was what the results showed. The rates obtained were lower again than those seen with methylcyclohexanol, ranging from a 30% conversion with P25 to 8% with Aldrich. These demonstrate that the presence of the additional electron donating group further stabilises the structure, resulting in a slower reaction rate. It is interesting also that again the anatase/rutile catalyst gave better results than the pure anatase.

The next compound investigated was 2-chlorocyclohexanol, a compound constructed of cyclohexanol with a chloro group attached. Unlike the electron donating groups found in the previous compounds examined the chloro group is electron withdrawing. Its presence in the structure should result in a lowering of the electron density around the hydroxyl group which should result in a loss in stability and therefore greater ease in initiating oxidation.

When the reacted samples were analysed they showed that a reaction had occurred in the solution. This was already apparent due to the colour change that had occurred in the sample. The UV absorption spectra showed a very large increase in the absorption from the photocatalysed sample requiring the sample to be diluted before a clear spectrum could be obtained.

Initial analysis proceeded well with the presence of the 2-chlorocyclohexanol and 1,2-dichlorocyclohexanol being detected. Analysis of the photocatalysed sample showed a large reduction in the chlorocyclohexanol compared to the starting sample, greater than that seen in cyclohexanol. However while the chlorocyclohexanol was being lost there was no indication of any product being formed. The reaction was repeated to confirm the results and at this point a problem was identified, the reaction did not appear to give consistent results. The destruction of the 2-chlorocyclohexanol was identified each time but no clear product was observed. In some cases a number of small peaks were seen while in others no product peaks could be detected. Testing a range of samples of possible products found that all would be detected by GCMS analysis if they were present. Many of the compounds detected were not what had been expected, in a couple of runs the presence of phenolic compounds was detected, both through odour and ferric chloride indicator tests. The results indicated that one of the reactions that were occurring was an aromatisation.

While the data showed that the reaction was occurring at a higher rate than that of pure cyclohexanol, the reason for the inconsistent results does not appear to have an obvious solution. One obvious cause would be experimental error, a procedural mistake that resulted in the experiment occurring differently. This however could be ruled out by the fact that it only occurred with 2-chlorocyclohexanol, never in any of the other compounds tested. This would also rule out contamination as again there is the question of why it would happen repeatedly in chlorocyclohexanol but never in any of the other compounds. So if it was not experimental then the likely cause would be the 2-chlorocyclohexanol itself. That could be due to the 1,2-dichlorocyclohexane present as a by-product of the 2-chlorocyclohexanol production process, it could be influencing the reaction in some unknown way, there was no apparent loss of dichlorocyclohexane which would indicate that it was a chemical effect of the chloro group. Halides are reactive so it is possible that its presence could result in the reaction being altered. The last is the inductive effect; it could be possible that the inductive influence of the chloro group on the hydroxyl resulted in the oxidation reaction going further than it had in previous compounds. All the previous compounds used electron donating groups so to test this another compound would have to be used that also generated a strong inductive influence.

The next sample was 1,2,3,4-tetrahydronaphthol, this is a cyclohexanol group with a conjoined benzene ring. The benzene ring has a strong inductive influence so a high reaction rate was expected. Also, if the aromatisation was due to the inductive influence then it should also occur in this compound as in chlorocyclohexanol. The tetrahydronaphthol gave some very good results, a 27% conversion with Aldrich, a 45% conversion with P25 and a 90% conversion with UV100. The difference between the pure anatase catalysts clearly shows that the surface area is a very important factor in the rate of reaction. The more surface area for the reactant to adsorb to the faster the reaction can proceed. The rate of the P25 is interesting as in the photocatalysis of the methylcyclohexanol and menthol the P25 usually performed better than the pure anatase catalysts, yet with tetrahydronaphthol the high surface area pure anatase catalysts were clearly faster.

A possibility could be that P25 is less affected by inhibiting effects. When electron donating groups are present and the hydroxyl group harder to catalyse the P25 may be less sensitive to this effect and so give a better performance. However with a compound like Tetrahydronaphthol where there is no inhibition to the reaction the limiting factor for the photocatalysis becomes the surface area and so the high surface area catalysts perform better. This could explain the small variation seen in the results from P25 in the different compounds tested.

The results proved that the groups present were determining the rate of reaction, those with the greatest inductive influence increasing the reaction rate by lowering the stability of the hydroxyl group. This should work by affecting how quickly the hydroxyl can stabilise the charge from the catalyst by losing hydrogen. If the hydrogen is stable this should take longer and should give more time for electron-hole recombination to occur. But while understanding was gained from these compounds the influences in a steroid are far more complex.

The steroid was the final sample to be examined; this had been attempted previously without success. The compound was reacted using some of the experience gained from the oxidations of the other samples. The steroid had been confirmed through analysis. When the sample that had been through photocatalysis was examined it showed that there had been no apparent effect on the steroid during the reaction; the GCMS peaks showing only the reactant in the photocatalysed sample with no apparent reduction from the starting solution. No evidence of any reaction product could be seen. When examined by FTIR some small differences could be noted between the reactant and product samples but not enough for any conclusion to be made on the success of the reaction.

While the examination of the effect of neighbouring groups on reaction rate gave some insight into their influence they did not replicate all the influences present within the steroid. The steroid skeleton will have an effect on the stability of the hydroxyl group. The hydroxyl stability will also have been affected by the cyclopropane ring that had been added to the steroid; a group of which a lot is not known. It is a group for which a number of contradictory theories have been given. As such its influence on the reaction are unknown. It is also possible that there was some steric hindrance due to the body of the steroid affecting the ease at which the hydroxyl group could absorb to the catalyst. Chemical oxidation has been able to oxidise this oxidise this compound but this is performed using materials with a far smaller size that a particle of TiO_2.

It is also possible that the photocatalysis was not an aggressive enough reaction for the steroid was opposed to the chemical oxidation; which is strong enough but also breaks the bonds of the cyclopropane. It is even possible that the oxidation of the hydroxyl group can not be done without using a reaction strong enough to break the cyclopropane.

5.3 Future Work

The project ended with a number of areas that could be looked at in the future as well as questions that had not been answered.

One of the obvious applications of the technique is to adapt it for use on an industrial scale. The experiments performed during the study were simple batch reactions in beakers; at an industrial scale a continuous flow reactor would be more desirable. A simple effect of that would be that rather than use the catalyst as a fine powder in a suspension it would instead be immobilised. By having the catalysts immobilised for example in thin film reactor the additional difficulty and expense of removing the catalyst from a suspension is avoided. It would be useful to study this problem and find a technique for the reaction that would work industrially and give the best rate of reaction.

A second factor in the adaptation of the technique to industrialisation is the use of acetonitrile as the solvent; acetonitrile is both flammable and toxic so limiting its use would be useful. The solvent also has a low boiling point with evaporation occurring just from the heat from the UV lamps. An area that could be studied for the adaptation to industrialisation is the study of alternative solvents that could be used for photocatalytic oxidation.

The oxidation of the cyclosteroid is an area that could be studied further. This study chose cyclohexanol as the base compound for study as it contained the main functional groups involved with the oxidation of the hydroxyl in the steroid. This base compound could then be examined to observe the influence that neighbouring functional groups could have on the hydroxyl group. One possible study would be to look at the oxidation of alcohols with two or even three rings in their structures; this would act as a stepping stone from cyclohexanol to steroids. This could also look at the effect of distance on the inductive effect; as the distance between the hydroxyl group and the neighbouring group grows the influence should decrease. This would be useful information to have to understand induction more.

Of all the reactions in the study the one that left the most unanswered questions was that of the oxidation of 2-chlorocyclohexanol. This reaction had a number of problems, the first being the inconsistent results found. The products produced by the reactions varied between runs. It would be worth studying this reaction in more detail to determine the factors that were effecting the reaction so greatly. If the conditions influencing the reaction were determined then it would offer the possibility to control those factors. The problem of the varying products for the reaction demonstrates some of the possible reactions that can be performed with the right conditions. The phenolic product is of particular interest as the reaction would be of great commercial value. The manipulation of the reaction conditions to deliberately rather than accidentally produce phenolic compounds is a goal worth attempting. Part of this could be the investigation of trends; looking at the differences in very similar groups such as chloro, bromo, and the fluoro group. These are all from the same family and so are chemically similar, as such it would be interesting to see just how much difference would occur between these. And while those three are the compounds that are most obvious there are other families that could be examined.

To conclude, future work should consider the following:

- A study of the adaption of photocatalytic techniques to use on an industrial scale through the use of immobilised catalyst reactors.
- An investigation into alternative, less toxic, reaction solvents.
- Examination of the influences exerted by electron donating and electron withdrawing groups on the oxidation of two and three ringed alcohols.
- An in-depth study into the influences effecting the photocatalytic oxidation of 2-chlorocyclohexanol.